INHIBITORS OF BETA-SECRETASE

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/210,146 , filed March 13, 2009 and U.S. Provisional Application No. 61/307,542, filed February 24, 2010. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

β-Amyloid deposits and neurofibrillary tangles are two major pathologic characterizations associated with Alzheimer's disease (AD). Clinically, AD is characterized by the loss of memory, cognition, reasoning, judgment, and orientation. Also affected, as the disease progresses, are motor, sensory and linguistic ablities until global impairment of multiple cognitive functions occurs. These cognitive losses take place gradually, but typically lead to severe impairment and eventual death in 4-12 years.

β-Amyloid deposits are predominantly an aggregate of Aß peptide, which in turn is a product of the proteolysis of amyloid precursor protein (APP). More specifically, Aβ peptide results from the cleavage of APP at the C-terminals by one or more γ-secretases, and at the N-terminus by β-secretase enzyme (BACE), also known as aspartyl protease, as part of the β-amyloidogenic pathway.

BACE activity is correlated directly to the generation of Aβ peptide from APP, and studies increasingly indicate that the inhibition of BACE inhibits the production of Aβ peptide.

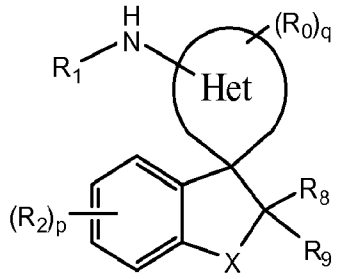
Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of patients with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders. Neurofibrillary tangles also occur in other neurodegenerative disorders including dementia-inducing disorders.

Recently, Amyloid-β (Aß) has been reported to be implicated in the development of RGC apotosis in glaucoma, with evidence of caspase-3-mediated abnormal amyloid precursor protein processing, increased expression of Aß in RGCs in experimental glaucoma and decreased vitreous Aβ levels (consistent with retinal Aβ deposition) in patients with glaucoma.

The present invention provides compounds that are BACE inhibitors and are useful as therapeutic agents in the treatment, prevention and amelioration of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is directed to a compound represented by the following Structural Formula:



(A),

or a pharmaceutically acceptable salt thereof, wherein:

ring Het is a 5 membered monocyclic heterocycle or a 6 membered monocyclic heterocycle;

R_a and R_b are each independently –H, -halogen, (C_1-C_4)alkyl, methoxy, fluoromethoxy, methoxy(C_1-C_4)alkyl and fluoro(C_1-C_4)alkyl;

each R_0 is independent selected from –H, =O, =S, =NR_{15}, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -CN, -NO_2, halogen, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$NR_{11}S(O)_iR_5$,

-C(=O)OR_5, -OC(=O)OR_5, -C(=S)OR_5, -O(C=S)R_5, -C(=O)$NR_{12}R_{13}$, -NR_{11}C(=O)R_5, -C(=S)$NR_{12}R_{13}$, -NR_{11}C(=S)R_5, -NR_{11}(C=O)OR_5, -O(C=O)$NR_{12}R_{13}$, -NR_{11}(C=S)OR_5, -O(C=S)$NR_{12}R_{13}$, -NR_{11}(C=O)$NR_{12}R_{13}$, -NR_{11}(C=S)$NR_{12}R_{13}$, -C(=S)R_5, -C(=O)R_5, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, each of the (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl group represented by R_0 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_3)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl, heteroaryl, -NR_6R_7, -NR_{11}S(O)$_i$$R_5$, -C(=O)$NR_{12}R_{13}$, -$NR_{11}$C(=O)$R_5$, -S(O)$_i$$R_5$-, -S(O)$_i$$NR_{12}R_{13}$, -$OR_5$, -C(=O)$R_5$, -C(=S)$NR_{12}R_{13}$, -$NR_{11}$C(=S)$R_5$, -C(O)$OR_5$, -OC(=O)$OR_5$, -C(=S)$OR_5$, -O(C=S)$R_5$, -O(C=O)$NR_{12}R_{13}$, -$NR_{11}$(C=O)$OR_5$, -$NR_{11}$(C=S)$OR_5$, -O(C=S)$NR_{12}R_{13}$, -$NR_{11}$(C=O)$NR_{12}R_{13}$, -$NR_{11}$(C=S)$NR_{12}R_{13}$ and -C(=S)R_5, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_0 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_1 is -H, -OH, -(C_1-C_4)alkoxy, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, or heteroaryl(C_1-C_6)alkyl; wherein each alkyl, aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from halogen, -CN, -OH, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_3)alkoxy and halo(C_1-C_3)alkoxy;

each R_2 is independently selected from a) -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -S(O)$_i$$R_5$, -$NR_{11}$S(O)$_i$$R_5$, -S(O)$_i$$NR_{12}R_{13}$, C(=O)$OR_5$, -OC(=O)$OR_5$, -C(=S)$OR_5$, -O(C=S)$R_5$, -C(=O)$NR_{12}R_{13}$, -$NR_{11}$C(=O)$R_5$, -C(=S)$NR_{12}R_{13}$, -$NR_{11}$C(=S)$R_5$, -$NR_{11}$(C=O)$OR_5$, -O(C=O)$NR_{12}R_{13}$, -$NR_{11}$(C=S)$OR_5$, -O(C=S)$NR_{12}R_{13}$, -$NR_{11}$(C=O)$NR_{12}R_{13}$, -$NR_{11}$(C=S)$NR_{12}R_{13}$, -C(=S)$R_5$, and -C(=O)$R_5$,; and b) ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkyl($C_1$-

C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_4-C_8)cycloalkenyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, and heteroaryl(C_2-C_6)alkynyl, wherein each of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_4-C_8)cycloalkenyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, and heteroaryl(C_2-C_6)alkynyl groups represented by R_2 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, -NO_2, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)R_5$, -$C(=S)OR_5$, -$OC(=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$C(=O)R_5$, -$C(=S)R_5$, -$OC(=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=O)OR_5$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=O)R_5$, -$C(=S)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_3 and R_4 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkyl($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl($C_2$-$C_6$)alkynyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_3$-$C_9$)heterocycloalkyl($C_1$-

C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl represented by R_3 and R_4 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_3 and R_4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

or R_3 and R_4, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A optionally contains 1 to 3 heteroatoms independently selected from O, N, and S and when the heteroatom is nitrogen, the nitrogens is substituted with -H, (C_1-C_3)alkyl or halo(C_1-C_3)alkyl, and when the heteroatom is sulfur, the sulfurs is optionally mono or di-oxygenated; and ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, $-C(=O)R_5$,

(C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylamino(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, and heteroaryl(C_2-C_6)alkynyl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on ring A are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_5 is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl in the groups represented by R_5 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, =O, $-NR_6C(=NH)NR_6R_7$, $-C(=O)OR_c$, $-OR_c$, $-SR_c$, $-C(=O)NR_6R_7$, $-C(=O)R_c$, $-S(O)_iR_c$, $-NO_2$, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and $-NR_6R_7$;

R_c is –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl;

R_6 and R_7 are each independently -H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl, or heteroaryl(C_1-C_6)alkyl , all of which groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_8 and R_9, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A optionally contains 1 to 3 heteroatoms

independently selected from O, N, and S and when the heteroatom is nitrogen, the nitrogen is substituted with -H, $(C_1$-$C_3)$alkyl or halo$(C_1$-$C_3)$alkyl, and when the heteroatom is sulfur, the sulfur is optionally mono or di-oxygenated; and ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of from halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, and heteroaryl$(C_2$-$C_6)$alkynyl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on ring A are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl,or two substituents attached to the same ring atom of ring A can together with the ring atom to which they are attached form a 3 to 6 membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring optionally substituted with 1 to 3 substituents independently selected from -halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, heterocycloalkyl, heterocycloalkyl$(C_1$-$C_6)$alkyl, heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl,and heteroaryl$(C_2$-$C_6)$alkynyl; or

when R_3 and R_4, together with the carbon to which they are attached, form a ring A, R_8 and R_9 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$NR_{11}S(O)_iR_5$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, and -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkyl($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl($C_2$-$C_6$)alkynyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_3$-$C_9$)heterocycloalkyl($C_1$-$C_6$)alkyl, ($C_3$-$C_9$)heterocycloalkyl($C_2$-$C_6$)alkynyl, aryl, aryl($C_1$-$C_6$)alkyl, aryl($C_2$-$C_6$)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl group represented by R_8 and R_9 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$NR_{11}S(O)_iR_5$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_8 and R_9 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_{11} is –H or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with 1 to 5 substituents independently selected from halogen, CN, (C_1-C_6)alkoxy, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl, wherein

the (C_1-C_6)alkoxy, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl groups are each optionally substituted with 1 to 3 substitutes independently selected from the group consisting of halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_{12} and R_{13} are each independently -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_3)alkylamino(C_1-C_6)alkyl, di(C_1-C_3)alkylamino(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, wherein the (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

or R_{12} and R_{13}, together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$NR_{11}S(O)_iR_5$, -C(=O)OR_5, -OC(=O)OR_5, -C(=S)OR_5, -O(C=S)R_5, -C(=O)NR_6R_7, -NR_{11}C(=O)R_5, -C(=S)NR_6R_7, -NR_{11}C(=S)R_5, -NR_{11}(C=O)OR_5, -O(C=O)NR_6R_7, -NR_{11}(C=S)OR_5, -O(C=S)NR_6R_7, -NR_{11}(C=O)NR_6R_7, -NR_{11}(C=S)NR_6R_7, -C(=S)R_5, -C(=O)R_5, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_6)alkoxy(C_1-C_3)alkyl, wherein the 3-8 membered ring optionally contains 1 to 3 additional heteroatoms, which are independently selected from O, N and S, wherein when the additional heteroatom is nitrogen, the nitrogen is substituted with -H, (C_1-C_3)alkyl or halo(C_1-C_3)alkyl, and when the additional heteroatom is sulfur, the sulfur is optionally mono or di-oxygenated;

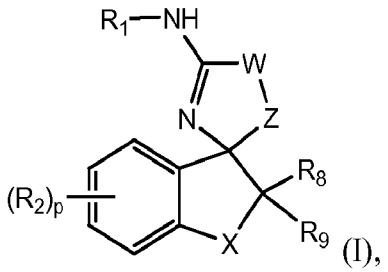
R_{15} is -H or (C_1-C_6)alkyl optionally substituted with 1 to 5 –F.

i is 0, 1 or 2;

p is 1, 2 3 or 4; and

q is 1, 2 or 3.

In another embodiment, the compound of the present invention is represented by the following Structural Formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

W is -N(R_{14})-, -S- or -O-;

Z is -C(=O)-, -C(=S)-, -C(=NR_{15})-, -O-, -C(=O)C($R_{16}R_{17}$)-, -C($R_{16}R_{17}$)C(=O)-, -C(=S)C($R_{16}R_{17}$)-, -C($R_{16}R_{17}$)C(=S)-, -N(R_{18})-, -(C$R_{16}R_{17}$)$_m$-, -O-C($R_{16}R_{17}$)- or –C($R_{16}R_{17}$)-O-; provided when W is –S- or –O-, Z is not –O-;

R_{14} is independent selected from –H, =O, =S, -NR_6R_7, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, each (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl represented by R_{14} is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, -OR_5, -NR_6R_7, -S(O)$_i$$R_5$, -S(O)$_iNR_{12}R_{13}$, -N$R_{11}$S(O)$_i$$R_5$, -C(=O)O$R_5$, -OC(=O)O$R_5$, -C(=S)O$R_5$, -O(C=S)$R_5$, -C(=O)N$R_{12}R_{13}$, -N$R_{11}$C(=O)$R_5$, -C(=S)N$R_{12}R_{13}$, -N$R_{11}$C(=S)$R_5$, -N$R_{11}$(C=O)O$R_5$, -O(C=O)N$R_{12}R_{13}$, -N$R_{11}$(C=S)O$R_5$, -O(C=S)N$R_{12}R_{13}$, -N$R_{11}$(C=O)N$R_{12}R_{13}$, -N$R_{11}$(C=S)N$R_{12}R_{13}$, -C(=S)$R_5$ and -C(=O)R_5;

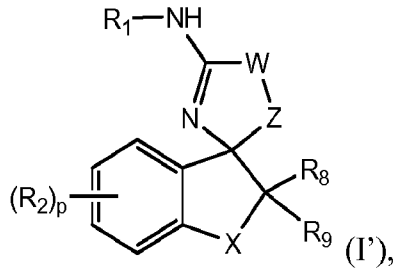
R_{16} and R_{17} are each independently -H or (C_1-C_3)alkyl optionally substituted with 1 to 5 -F;

R_{18} is -H or (C_1-C_3)alkyl optionally substituted with 1 to 5 -F; and

m is 1 or 2.

The remainder of the variables are as described above for Structural Formula (A).

In another embodiment, the compound of the present invention is represented by Structural Formula (I'), wherein:



(I'),

or a pharmaceutically acceptable salt thereof, wherein:

X is -O-, -CH_2-$C(R_3R_4)$-, or -$C(R_3R_4)$-;

W is -$N(R_{14})$-, -S-, -O-;

Z is -C(=O)-, -C(=S)-, -$C(=NR_{15})$-, -O-, -$C(=O)C(R_{16}R_{17})$-, -$C(=S)C(R_{16}R_{17})$-, -$C(=NR_{15})C(R_{16}R_{17})$-, -$N(R_{18})$-, -$(CR_{16}R_{17})_m$- or -O-$(CR_{16}R_{17})$-; provided when W is –S- or –O-, Z is not –O-;

R_1 is -H, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, or heteroaryl$(C_1$-$C_6)$alkyl;

each R_2 is independently selected from a) -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, and -C(=O)R_5; and b) $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, heteroaryl, phenoxy, and benzyloxy, each optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -C(=S)$NR_{12}R_{13}$, -C(=O)R_5, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy ,$(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl;

R_3 and R_4 are each idependently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, -C(=O)R_5, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, or heteroaryl, wherein each $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, or heteroaryl is optionally

substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

or R_3 and R_4, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

R_5 is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_7) cycloheteroalkyl, aryl, heteroaryl or benzyl, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_6 and R_7 are each independently -H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_8 and R_9, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring, wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo$(C_1-$

C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl; or

when R_3 and R_4, together with the carbon to which they are attached, form a ring A, R_8 and R_9 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

R_{11} is -H, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

R_{12} and R_{13} are each independently -H, (C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_3)alkylamino(C_1-C_6)alkyl, or di(C_1-C_3)alkylamino(C_1-C_6)alkyl;

or R_{12} and R_{13}, together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_6)alkoxy(C_1-C_3)alkyl, wherein the 3-8 membered ring optionally contains 1 to 3 additional heteroatoms, which are independently selected from O, N and S, wherein when the additional heteroatom is nitrogen, the nitrogens is substituted with -H, (C_1-C_3)alkyl or halo(C_1-C_3)alkyl, and when the additional heteroatom is sulfur, the sulfurs is optionally mono or di-oxygenated;

R_{14} is -H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, cycloheteroalkyl$(C_1\text{-}C_3)$alkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_3)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_3)$alkoxy;

R_{15} is -H or $(C_1\text{-}C_6)$alkyl;

R_{16} and R_{17} are each independently -H or $(C_1\text{-}C_3)$alkyl;

R_{18} is -H or $(C_1\text{-}C_3)$alkyl;

i is 0, 1 or 2;

p is 1 or 2; and

m is 1 or 2.

One embodiment of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof).

Another embodiment of the invention is a method of inhibiting BACE activity in a subject in need of such treatment. The method comprises administering to the subject an effective amount of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof).

Another embodiment of the invention is a method of treating a BACE mediated disorder in a subject. The method comprises administering to the subject an effective amount of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof).

Another embodiment of the invention is the use of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof) for the manufacture of a medicament for inhibiting BACE activity in a subject.

Another embodiment of the invention is the use of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a

pharmaceutically acceptable salt thereof) for the manufacture of a medicament for treating a BACE mediated disorder in a subject.

Another embodiment of the invention is the use of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof for inhibiting BACE activity in a subject in need of such treatment.

Another embodiment of the invention is the use of a BACE inhibitor disclosed herein (e.g., a compound represented by Structural Formula (A), (I) or (I'), or a pharmaceutically acceptable salt thereof for treating a BACE mediated disorder in a subject.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds represented by the Structural Formula (A), (I) or (I'), or a phamaceutically acceptable salt thereof. Values and alternative values for the variables used in the Structural Formulas described herein are provided in the following paragraphs. It is understood that the invention encompasses all combinations of the substituent variables (i.e., R^1, R^2, R^3, etc.) defined herein. - Values and alternative values for the variables are as follows:

1. R_1:

In one embodiment, R_1 is as described above for Structural Formula (A). In another embodiment, R_1 is as described above for Structural Formula (I').

Alternatively, R_1 is -H, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, or heteroaryl$(C_1$-$C_6)$alkyl. In another embodiment, R_1 is -H, $(C_1$-$C_6)$alkyl or benzyl. Alternatively, R_1 is –H or –C(O)-$(C_1$-$C_3)$alkyl (e.g., acetyl). In another embodiment, R_1 is -H.

2. R_2:

In one embodiment, R_2 is as described above for Structural Formula (A). In another embodiment, R_2 is as described above for Structural Formula (I').

Alternatively, each R_2 is –H, halogen, -CN, -OR_5, -C(=O)$NR_{12}R_{13}$, -C(=O)OR_5, -C(O)R_5, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-

C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl, (C_5-C_6)heterocycloalky(C_1-C_3)alkyl. The heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl, triazole and thiophenyl, the heterocycloalkyl is selected from oxetanyl, tretrahydrafuran, tetrapyran, piperidine, pyrrolidinyl and pyrrolidinonyl. Each of (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl and (C_5-C_6)heterocycloalky(C_1-C_3)alkyl groups represented by R_2 is optionally substituted with 1 to 5 substituents independently selected from halogen, -CN, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_2-C_6)alkynyl, -NR_6R_7, -$S(O)_iR_5$, -$C(O)R_5$, -OH, (C_3-C_6)cycloalkyl, (C_1-C_3)alkoxy and halo(C_1-C_3)alkoxy.

In another alternative, each R_2 is independently selected from the group consisting of –H, -F, –Br, -Cl, -I, -OH, -CN, cyclopropylethyl, 5-propynyl-3-pyridyl, 2-fluoro-3-pyridyl, N,N-dimethylaminoethoxy, cyclopentoxy, cyclopropylmethoxy, 3-methoxypropyl, 3-methoxypropynyl, cyclopropylethynyl, 3-cyanophenyl, trifluoromethoxy, 2-chloro-4-pyridyl, 1-methanesulfonyl-4-piperidinylmethyl, 1-acetyl-4-piperidinylmethyl, 3-methanesulfonylphenyl, 5-trifluoromethyl-3-pyridyl, 2-methoxyethoxy, 2-methyl-5-pyridazin-3-onyl, 1-cyclopropyl-4-pyridin-2-onyl, 1-methyl-2,2,2-trifluoroethyl, 2-cyclopropyl-5-thiazolyl, trifluoromethyl, 2,2,2-trifluoroethyl, methoxy, 3-chloro-5-fluorophenyl, N-methyl-4-pyridin-2-onyl, 4-methylpentyl, 3-methoxyphenoxy, dimethylaminocabonyl, cyclopropyl, 1-hydroxy-2,2,2-trifluoroethyl, pyrrolidinylcarbonyl, 3,3,3-trifluoropropyl, difluoromethoxy, 1,1-dihydroxy-2,2,2-trifluoroethyl, 3-methoxyphenyl, 2,2,2-trifluoroethoxy, phenoxy, 2-methoxy-4-pyridyl, 2-methyl-5-thiazolyl, 3,3,3-trifluoroprop-1-en-2-yl, 5-thiazolyl, 2-thiazolyl, thiophen-3-ylethynyl, 1-hydroxycyclopentan-1-ylethynyl, 5-fluoro-3-pyridyl, pyrrolidinyl, 5-chloro-3-pyridyl, 3,3-dimethylbutyn-1-yl, phenylethynyl, cyclopentylethynyl, 2-pyrazinyl, 3-chlorophenyl, 3-hydroxycyclopent-1-enyl, 3-fluoro-5-trifluoromethylphenyl, 3,5-dicyanophenyl, 3-fluoro-5-cyanophenyl, 3-chloro-4-fluorophenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3-chloro-5-cyanophenyl, 3-

pyridazinyl, 3-pyridyl, 3-cyano-4-fluorophenyl, 3-cyano-5-fluorophenyl 6-methoxypyrazin-2-yl, 6-indolyl, 3-chloro-5-methoxyphenyl, 3-trifluoromethoxyphenyl, 3,5-dimethylphenyl, 2-methyl-5-fluorophenyl, 3-trifluoromethylphenyl, phenyl, cyclopentylmethyl, 1-propyl, 2-propyl, 2-methylpropyl, phenylethyl, 1-pentyl, 2-methylbutyl, ethyl, 4-methoxyphenylmethoxy, 1-methylethoxy, methoxycarbonyl, cyclopropyloxy, 5-cyano-3-pyridyl, 4-(propyn-1-yl)-2-thiophenyl, 4-bromo-2-thiazolyl, ethenyl, ethynyl, 4-methylpentyn-1-yl, dimethylaminopropyl, N-methylpyrrolidin-3-ylmethyl, 2,2-difluorocyclopropylmethoxy, 4-bromo-2-thiophenyl, methoxy, methyl, carboxy, 5-propyl-3-pyridyl, 2-methyl-5-fluorophenyl, 2-oxazolyl, propylthio, phenylthio, 2,2-dimethylpropyl, butyl, cyclobutylmethoxy, 2-methyl-5-pyrimidyl, pyrrolidin-2-onyl, 3,3-difluoropyrrolidin-1-yl, cyclopropylethyl, 2-propyloxy, 4-cyano-2-thiophenyl, ethoxymethyl, 4-methoxybenzyloxy, 1-methylethyl, cyclohexylmethyl, 5-chloro-3-pyridyl, 5-methyl-3-pyridyl, 2-methylpropyloxy and 2-chloro-4-pyridyl.

In one embodiment, each R_2 is independently selected from a) -H, -halogen, -CN, $-NO_2$, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, and $-C(=O)R_5$; and b) $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, aryl, heteroaryl, phenoxy, and benzyloxy, each optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, cyano$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylcarbonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy, halo$(C_1\text{-}C_3)$alkoxy ,$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_3)$alkyl, aryl and heteroaryl.

In one embodiment, R_2 is -H, -Br, -F,–Cl or -CN.

In another embodiment, R_2 is $(C_1\text{-}C_6)$alkyl. In an alternative, R_2 is a $(C_1\text{-}C_3)$alkyl.

In another embodiment, R_2 is a $(C_2\text{-}C_6)$alkynyl optionally substituted with -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylsulfonylaminoalkyl,

hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl or heteroaryl. Alternatively, R_2 is a (C_2-C_6)alkynyl optionally substituted with a (C_1-C_6)alkyl or a (C_3-C_8)cycloalkyl. In another alternative, R_2 is a (C_2-C_6)alkynyl optionally substituted with a cyclopropyl. In yet another alternative, R_2 is cyclopropylethynyl. Alternatively, R_2 is a (C_2-C_6)alkynyl optionally substituted with -F, -Cl, -Br, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl.

In another embodiment, R_2 is a phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. Alternatively, R_2 is a phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl and halo(C_1-C_6)alkoxy. In another alternative, R_2 is phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -Me, -Et, -OMe, $-CF_3$ and $-OCF_3$.

In another embodiment, R_2 is a 5-6 membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consiting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl and a heteroaryl group. In an alternative, R_2 is a pyridinyl, thiophenyl, pyrrolyl, pyrimidinyl, each optionally substituted with 1 to 3 substituents independently selected from the group consiting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_6)alkoxy(C_1-C_3)alkyl.

In another embodiment, R_2 is an indolyl, pyridinyl, thiophenyl, pyrrolyl, pyrimidinyl, cyclohexyl, or thiozolyl, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, cyano$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkylcarbonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy, halo$(C_1\text{-}C_3)$alkoxy ,$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_3)$alkyl, aryl and heteroaryl. Alternatively, R_2 is an indolyl or pyridinyl optionally substituted with -F, -Cl, -Br, -CN, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy or halo$(C_1\text{-}C_3)$alkoxy. In another alternative, R_2 is 2-pyridinyl or 6-indolyl.

In another embodiment, R_2 is $-OR_5$, wherein R_5 is –H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_3)$alkyl, phenyl or phenyl$(C_1\text{-}C_3)$alkyl, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_3)$alkyl, phenyl or phenyl$(C_1\text{-}C_3)$alkyl groups is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy, halo$(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkyl and $-NR_6R_7$. More specifically, R_6 and R_7 are each independently selected from –H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkyl.

3. R_3 and R_4

In one embodiment, R_3 and R_4 are as described above for Structural Formula (A). In another embodiment, R_3 and R_4 are as described above for Structural Formula (I')

Alternatively, R_3 and R_4 are each idependently -H, -halogen, -CN, $-NO_2$, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, aryl, or heteroaryl, wherein each $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, aryl, or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}$

C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. In one embodiment, R_3 and R_4 are each independently -H, -F, -Cl, -Br or a (C_1-C_6)alkyl. In another embodiment, R_3 and R_4 are both -H.

In another embodiment, R_3 and R_4, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl.

4. R_5:

In one embodiment, R_5 is as described above for Structural Formula (A). In another embodiment, R_5 is as described above for Structural Formula (I')

Alternatively, R_5 is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_7) cycloheteroalkyl, aryl, heteroaryl, or benzyl, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl. In a another alternative, R_5 is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_1-C_3)alkoxy(C_1-C_6)alkyl. Alternatively, R_5 is methyl, ethyl, propyl, butyl, or trifluoromethyl.

In another embodiment, R_5 is selected from the group consisting of –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, phenyl and phenyl(C_1-C_3)alkyl, wherein the phenyl group in the groups represented by R_5 is optionally substituted with 1 to 3 substituents

independently selected from -F, -Cl, -Br, -CN, =O, -NR_6R_7, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl.

In another alternative embodiment, R_5 is selected from the group consisting of of –H, methyl, ethyl, 2-propyl, 2-methylpropyl, cyclopentyl, -CHF_2, -CF_2CHF_2, -CH_2CF_3, -CF_3, cyclopropylmethyl, 2,2-difluorocyclopropylmethyl, methoxyethyl, phenyl, 3-methoxyphenyl, (1-amino-2-(4-hydroxyphenyl))ethylcarbonyl, dimethylaminoethyl, cyclobutylmethyl, and 4-methoxybenzyl.

5. R_6 and R_7:

In one embodiment, R_6 and R_7 are as described above for Structural Formula (A). In another embodiment, R_6 and R_7 are as described above for Structural Formula (I')

Alternatively, R_6 and R_7 are each independently -H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl and (C_1-C_3)alkoxy(C_1-C_6)alkyl. In a alternative embodiment, R_6 and R_7 are each independently -H or (C_1-C_6)alkyl. In another alternative embodiment, R_6 and R_7 are both -H. Alternatively, R_6 is –H or (C_1-C_3)alkyl and R_7 is –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl.

In another alternative embodiment, R_6 is –H or methyl and R_7 is –H, methyl or -CH_2CF_3.

6. R_8 and R_9:

In one embodiment, R_8 and R_9 are as described above for Structural Formula (A). In another embodiment, R_8 and R_9 are as described above for Structural Formula (I').

Alternatively, R_8 and R_9, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$,

$-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. In one embodiment, ring A is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy.

Alternatively, when R_3 and R_4, together with the carbon to which they are attached, form a ring A, R_8 and R_9 are each independently -H, -halogen, -CN, $-NO_2$, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. In an alternative embodiment, R_8 and R_9 are both -H.

7. Ring A:

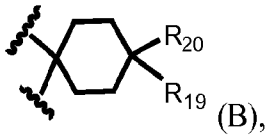
In one embodiment, ring A is as described above for Structural Formula (A). In another embodiment, ring A is as described above for Structural Formula (I')

Alternatively, ring A is a 5-7 membered monocyclic ring or a 9-14 membered bicyclic or tricyclic fused ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, $(C_1-$

C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein ring A contains 0 to 2 heteroatoms, which are independently selected from O, N and S. Alternatively, the substituents are selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy.

In another alternative embodiment, ring A is selected from tetrahydrofuran, tetrahydropyran, cyclopentane, cyclohexane, cyclohexene, cycloheptane, oxepane, 1,3-dioxane, piperidine, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, tetrahydronaphthalene, decahydronaphthalene, 5,6,7,8-tetrahydroquinoline, 5,6,7,8-tetrahydroisoquinoline, 2,3,4,5-tetrahydrobenzo[b]oxepine, and 2,3-dihydro-1H-phenalene, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy. Alternatively, the substituents are selected from the group consisting of -F, -OMe, -OEt and -Ph.

In another embodiment, ring A is represented by the following Structural Formula:



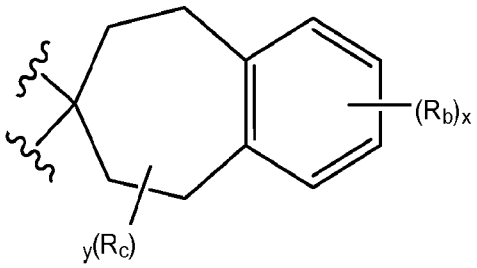
(B),

wherein:

R_{19} and R_{20} are each independently selected from -H, halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl, wherein each of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl,

aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl groups represented by R_{19} and R_{20} is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -CN, -OH, -$NR_{11}SO_2$(C_1-C_3)alkyl, -$NR_{11}C(=O)$-(C_1-C_3)alkyl, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl. Alternatively, R_{20} is –H and R_{19} is –OH, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy or (C_1-C_3)alkoxy(C_1-C_3)alkoxy. In another alternative embodiment, R_{19} and R_{20} are each independently –H or –NR_6R_7, wherein R_6 and R_7 are each independently selected from the group consisting of –H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, and (C_1-C_3)alkoxy(C_1-C_3)alkyl.

In another embodiment, ring A is represented by the following Structural formula:



(C),

wherein:

R_g and R_h, for each occurrence, are independently –H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl, heteroaryl, each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl represented by R_b is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, , hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

x is an integer from 1 to 4; and

y is an integer from 1 to 6.

In one embodiment, for structural formula (C), each R_g is independently selected from –H, Me and F and each R_h is independently –H, halogen, -CN, -NO_2, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy. Alternatively, for structural formula (C), R_g is –H and each R_h is independently –H, halogen, -CN, -NO_2, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy. In another alternative embodiment, for structural formula (C), R_g and R_h are both –H.

8. R_{11}:

In one embodiment, R_{11} is as described above for Structural Formula (A).

Alternatively, R_{11} is -H, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl. In another alternative embodiment, R_{11} is -H. Alternatively, R_{11} is –H or (C_1-C_3)alkyl (e.g., methyl).

9. R_{12} and R_{13}:

In one embodiment, R_{12} and R_{13} are as described above for Structural Formula (A).

Alternatively, R_{12} and R_{13} are each independently -H, (C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_3)alkylamino(C_1-C_6)alkyl, or di(C_1-C_3)alkylamino(C_1-C_6)alkyl. In a alternative embodiment, R_{12} and R_{13} are independently -H, (C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, cyano(C_1-C_3)alkyl, or di(C_1-C_3)alkylamino(C_1-C_3)alkyl. Alternatively, R_{12} and R_{13} are independently -H, methyl, ethyl, propyl, butyl, methoxyethyl, cyanoethyl, or dimethylaminoethyl.

In another alternative embodiment, R_{12} and R_{13} together with the nitrogen atom to which they are attached forms a pyrrolidine or piperidine ring, optionally substituted with 1 to 3 substituents selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl. In another alternative embodiment, R_{12} and R_{13} together with the nitrogen atom to which they are attached forms an unsubstituted pyrrolidine or piperidine ring.

10. R_{14}:

In one embodiment, R_{14} is as described above for Structural Formula (I).

Alternatively, R_{14} is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, cycloheteroalkyl(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, aryl(C_1-C_6)alkyl,

heteroaryl(C_1-C_6)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl and (C_1-C_3)alkoxy. In another alternative embodiment, R_{14} is (C_1-C_6)alkyl, halo(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl or benzyl. In yet another alternative embodiment, R_{14} is ethyl, propyl, cyclohexylmethyl, cyclopropylethyl, trifluoroethyl, or benzyl. In another alternative embodiment, R_{14} is methyl.

In another alternative embodiment, R_{14} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_7)heterocycloalkyl and (C_3-C_7)heterocycloalkyl(C_1-C_3)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, -NR_6R_7, -$NR_{11}S(O)_iR_5$, -$S(O)_iR_5$-, -OH and –$C(O)OR_5$.

In another alternative embodiment, R_{14} is selected from (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_7)heterocycloalkyl, (C_3-C_7)heterocycloalkyl(C_1-C_3)alkyl, wherein each of the group represented by R_{14} is optionally substituted with a substituent selected from (C_1-C_3)alkyl, -CO_2H, -SO_2-(C_1-C_3)alkyl, -CN, -OH and –(C_1-C_3)alkoxy and the (C_3-C_7)heterocycloalkyl is selected from oxepane, tetrahydrapyran and *N*-(C_1-C_3)alkylpiperidine.

In another alternative embodiment, R_{14} is –H, -OR_5, -NR_6R_7, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl, wherein the heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl and thiophenyl and triazolyl, the (C_3-C_5)heterocycloalkyl is selected from oxetanyl, tetrahydrofuran, tetrahydropyran, piperidinyl and pyrrolidinyl, and each of the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl groups represented by R_{14} is optionally substituted with 1 to 3 substituents independently selected from halogen, (C_1-

C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}SO_2R_5$, -OH, -$COOR_5$, -$C(=O)R_5$, -$C(=O)NR_{12}R_{13}$ and thiazolyl.

In another alternative embodiment, R_{14}, when present, is selected from the group consisting of –H, methyl, ethyl, 2-propyl, 1-propyl, 1-butyl, benzyl, 2-pyridylmethyl, methoxyethyl, 1-methoxypropan-2-yl, N,N-dimethylaminoethyl, 4-cyanobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 2-thiazolylethyl, 2-thiazolylmethyl, 6-quinoxalinylmethyl, 1-phenylethyl, 2-propyl, *tert*-butyl, 3-dimethylaminobenzyl, 3-methanesulfonamidobenzyl, 3-methanesulfonylbenzyl, 2-oxazolylmethyl, 1,1,2,2-tetrafluoroethoxy, 2-oxetanylmethyl, 2-ethylbutyl, 5-fluoro-2-pyridyl, 3-fluorobenzyl, 4-thiazolylmethyl, 2,2-difluoroethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydrofuranyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-fluorobenzyl, 4-methanesulfonylbenzyl, 2-tetrahydrafuranylmethyl, 2,2,2-trifluoroethyl, 5-trifluoromethyl-2-pyridylmethyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 2-chlorobenzyl, 2-methoxyethyl, cyclobutylmethyl, 4-tetrahydropyranylmethyl, 2-methylpropyl, phenylethyl, cyclopropyl, cyclobutyl, 1-methylpropyl, 5-pyrimidylmethyl, 2-carboxyethyl, dimethylamino, 4-tetrahydropyranyl, 1-methylpiperidin-4-yl, 2-fluoroethyl, 2-butyl, dimethylaminoethyl, 1-(3-pyridazinyl)ethyl, 1-methoxy-2-propyl, (4-methyl-1,2,4-triazol-3-yl)methyl, (2-methoxy-2-phenyl)ethyl, (1,3,4-oxadiazol-2-yl)methyl, (quinoxalin-2-yl)methyl, 1-phenylethyl, methanesulfonylaminoethyl, aminocarbonylethyl, aminocarbonylmethyl, 3-methoxypropyl and (3-(2-thiazolyl))benzyl, carboxymethyl, 1-methylethoxycarbonylmethyl, 5-methyl-1,3,4-thiadizolyl, 4-pyridazinyl, 5-methyl-2-oxazolylethyl, 2-hydroxyl-2-methylpropyl, 2-hydroxy-1-methylethyl and 2-pyrazinylmethyl.

11. R_{15}, R_{16}, R_{17} and R_{18}:

In one embodiment, R_{15} is as described above for Structural Formula (A). Alternatively, R_{15} is -H or (C_1-C_6)alkyl. In another embodiment, R_{15} is -H.

In one embodiment, R_{16} and R_{17} are as described above for Structural Formula (I). Alternatively, R_{16} and R_{17} are each independently -H or (C_1-C_3)alkyl. In another embodiment, R_{16} and R_{17} are both -H.

In one embodiment, R_{18} is as described above for Structural Formula (I). Alternatively, R_{18} is -H or (C_1-C_3)alkyl. In another embodiment, R_{18} is -H.

12. X, W, Z, i, p, m and q:

In one embodiment, X is as described above for Structural Formula (A). Alternatively, X is -O-, -CH_2-C(R_3R_4)-, or -C(R_3R_4)-. In one embodiment, X is -O-. In another embodiment, X is -CH_2-CH_2-. In another embodiment, X is -CH_2-.

In one embodiment, W is as described above for Structural Formula (I). Alternatively, W is -N(R_{14})-, -S-, -O-. In one embodiment, W is -N(CH_3)-.

In one embodiment, Z is as described above for Structural Formula (I). Alternatively, Z is -C(=O)-, -C(=S)-, -C(=NR_{15})-, -O-, -C(=O)C($R_{16}R_{17}$)-, -C(=S)C($R_{16}R_{17}$)-, -C(=NR_{15})C($R_{16}R_{17}$)-, -N(R_{18})-, -($CR_{16}R_{17}$)$_m$- or -O-($CR_{16}R_{17}$)-. In one embodiment, Z is -C(=O)-. In another embodiment, Z is -O-. In another embodiment, Z is -C(=O)CH_2-.

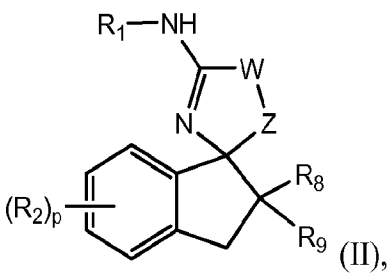
i is 0, 1 or 2;

p is 1 or 2. In one embodiment, p is 1.

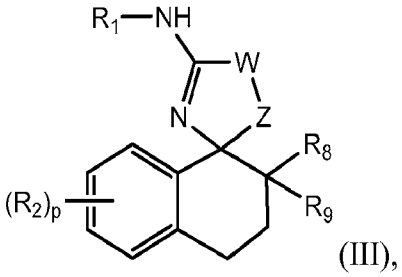
m is 1 or 2.

q is 1, 2 or 3.

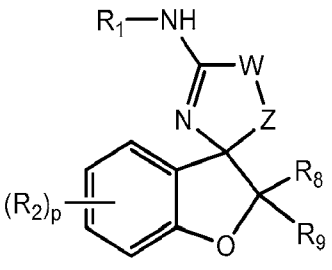
In a 1st embodiment, the compound of the present invention is represented by Structural Formula (II), (III) or (IV):



(II),



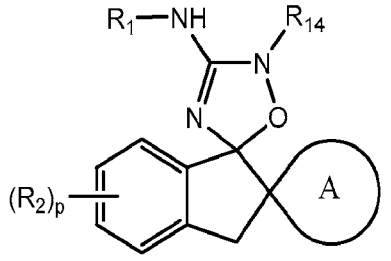
(III),



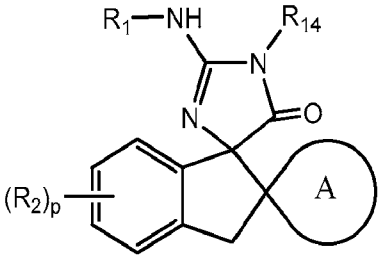
(IV),

or a pharmaceutically acceptable salt thereof. Values and alternative values for Structural Formulas (II), (III) and (IV) are as described above for Structural Formula (I) or (I').

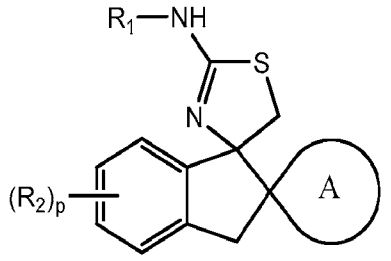
In a 2nd embodiment, the compound of the present invention is represented by Structural Formulas (V)-(XXV):



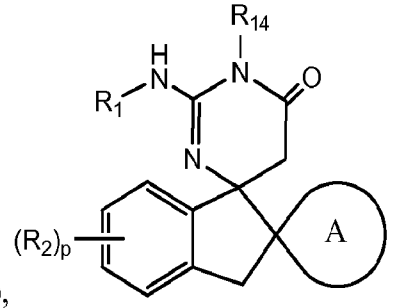
(V),



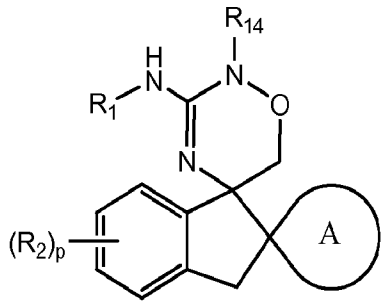
(VI),



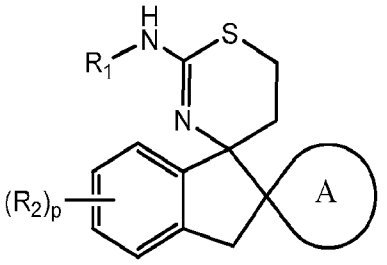
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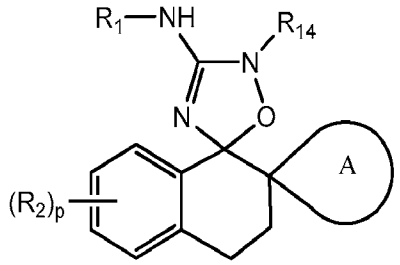
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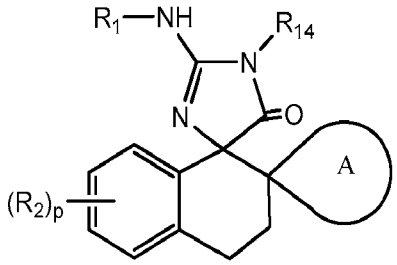
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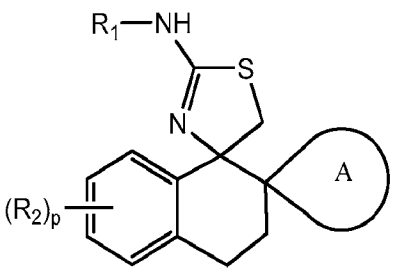
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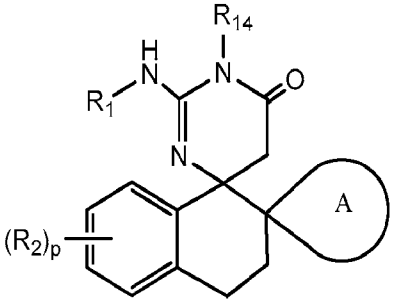
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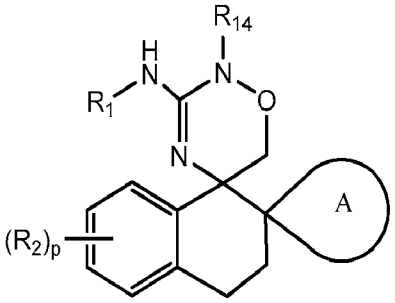
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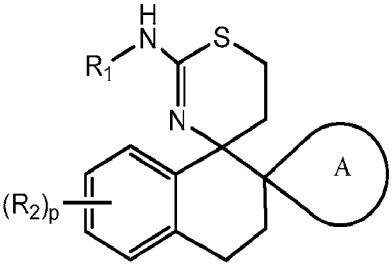
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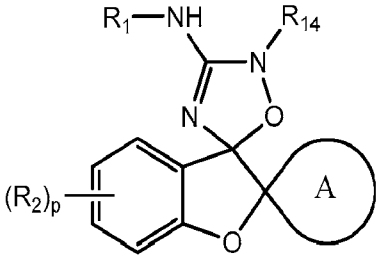
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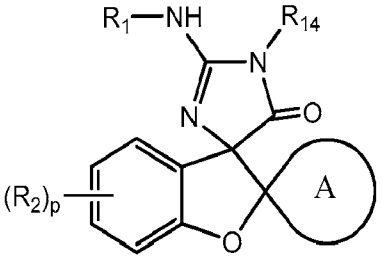
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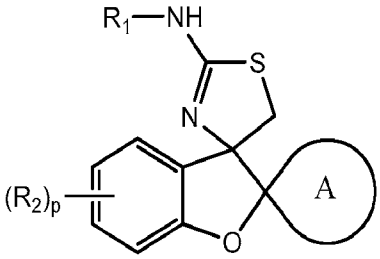
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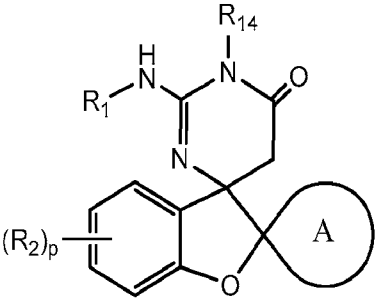
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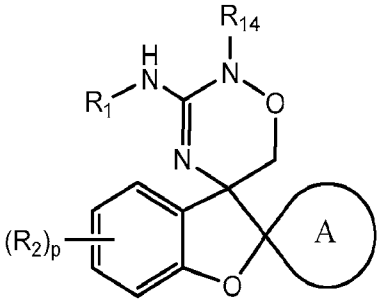
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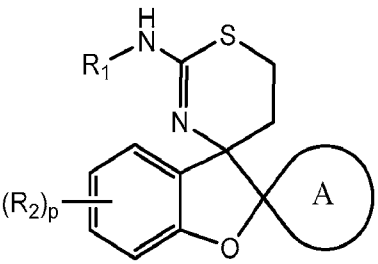
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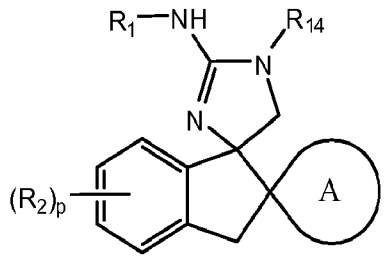
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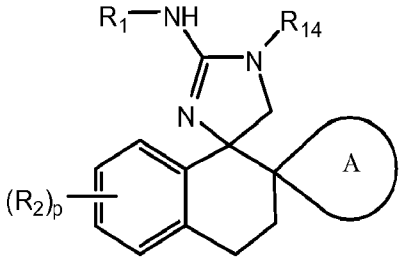
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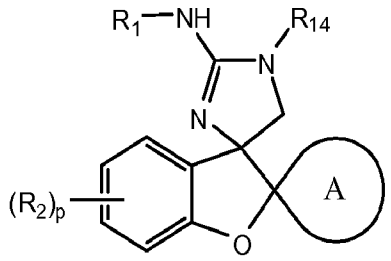
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(XXIII),



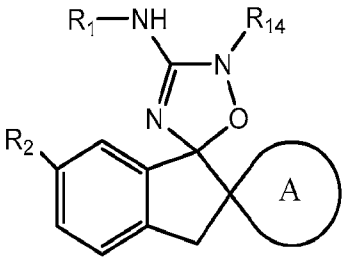
(XXIV), or



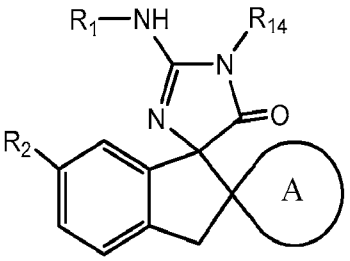
(XXV),

or a pharmaceutically acceptable salt thereof. Vaules or alternative values for the variables in Structural Formulas (V)-(XXV) are as described above for Structural Formula (I) or (I').

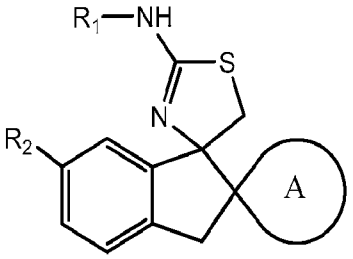
In a 3rd embodiment, the compound of the present invention is represented by Structural Formulas (Va)-(XXVa):



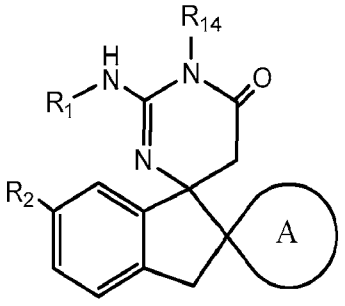
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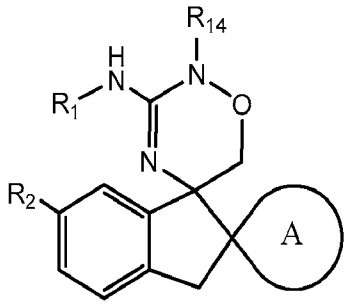
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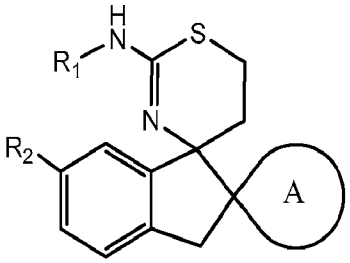
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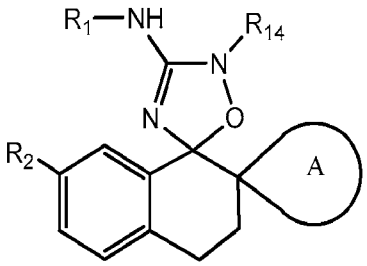
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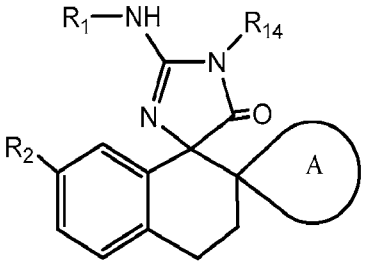
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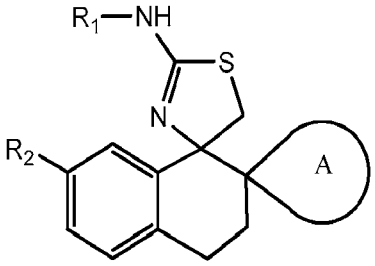
(Xa)



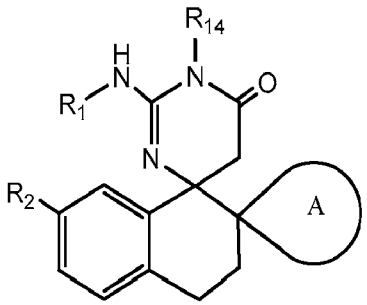
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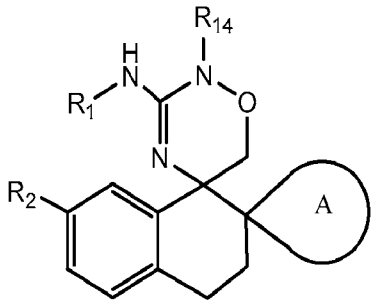
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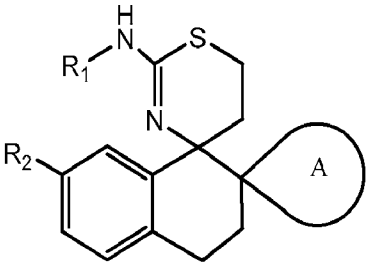
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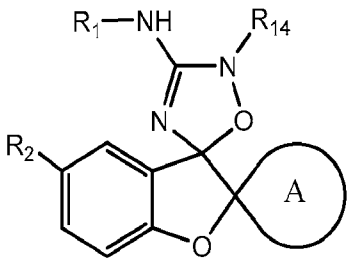
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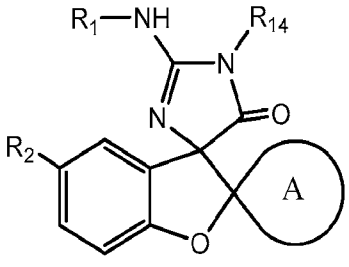
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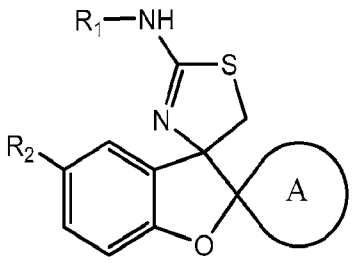
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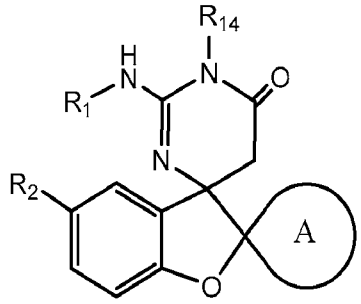


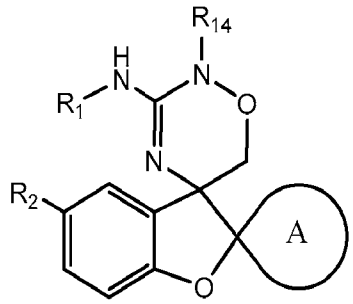
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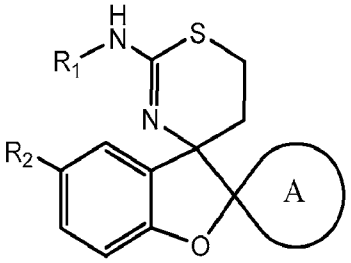


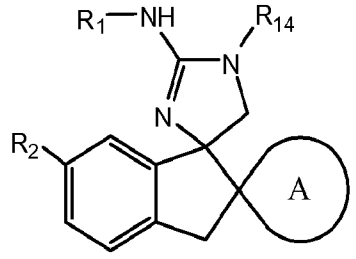
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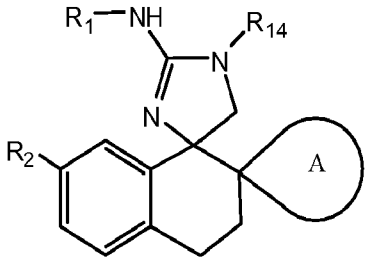

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(XXa),

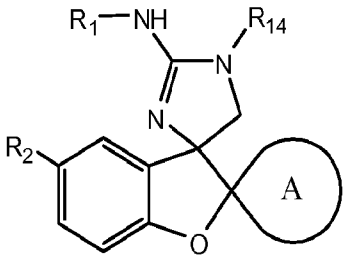

(XXIa),


(XXIIa),


(XXIIIa),


(XXIVa),

or


(XXVa), or a pharmaceutically acceptable salt thereof.

Values and alternative values for variables in Structural Formulas (Va)-(XXVa) are as described above for Structural Formula (I) or (I').

In one embodiment, ring A is a 5-7 membered monocyclic ring or a 9-14 membered bicyclic or tricyclic fused ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$,

$-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein ring A contains 0 to 2 heteroatoms, which are independently selected from O, N and S. Values and alternative values for the remainder of the variables are as described above for Structural Formula (I) or (I'). More specifically, the substituents are selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy. Even more specifically, R_1 is -H and R_{14} is -Me.

In another embodiment, ring A is selected from tetrahydrofuran, tetrahydropyran, cyclopentane, cyclohexane, cyclohexene, cycloheptane, oxepane, 1,3-dioxane, piperidine, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, tetrahydronaphthalene, decahydronaphthalene, 5,6,7,8-tetrahydroquinoline, 5,6,7,8-tetrahydroisoquinoline, 2,3,4,5-tetrahydrobenzo[b]oxepine and 2,3-dihydro-1H-phenalene, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with halogen (e.g., -F, -Cl or -Br), -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy. Values and alternative values for the remainder of the variables are as described above for Structural Formula (I) or (I'). More specifically, the substituents are selected from the group consisting of -F, -OMe, -OEt and -Ph. Even more specifically, R_1 is -H and R_{14} is -Me.

In a 4th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is -H, -Br, -F, (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl or heteroaryl, each of the (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl and heteroaryl represented by R_2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$,

-C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, -NR_{11}C(=O)R_5, -C(=S)$NR_{12}R_{13}$, -C(=O)R_5, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl and a heteroaryl group. Values and alternative values for the remainder of the variables are as described above for Structural Formula (I) or (I').

In a 5th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is -H, -Br, -F, –Cl or -CN. Values and alternative values for the remainder of the variables in Structural Formulas (Va)-(XXVa) are as described above in the 3rd embodiment.

In a 6th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is (C_1-C_6)alkyl optionally substituted with -F, -Cl, -Br, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl. Values and alternative values for the remainder of the variables in Structural Formulas (Va)-(XXIIa) are as described above in the 3rd embodiment. Alternatively, R_2 is a (C_1-C_3)alkyl.

In a 7th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is a (C_2-C_6)alkynyl optionally substituted with halogen (e.g., -F, -Cl or –Br), (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl with halogen (e.g., -F, -Cl or -Br), (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl. Values and values for the remainder of the variables in Structural Formulas (Va)-(XXVa) are as described above in the 3rd embodiment. Alternatively, R_2 is a (C_2-C_6)alkynyl optionally substituted with a cyclopropyl. In another alternative, R_2 is cyclopropylethynyl.

In a 8th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is a phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, -OR_5, -SR_5, -NR_6R_7, -S(O)$_i$$R_5$, -$NR_{11}$S(=O)$_i$$R_5$, -C(=O)$OR_5$, -C(=O)$NR_{12}R_{13}$, -$NR_{11}$C(=O)$R_5$, -C(=S)$NR_{12}R_{13}$, -C(=O)$R_5$, ($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. with halogen (e.g., -F, -Cl or -Br), (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl. Values and alternative

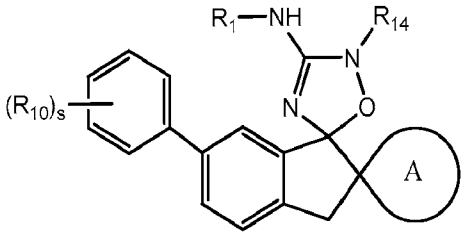
values for the remainder of the variables in Structural Formulas (Va)-(XXVa) are as described above in the 3rd embodiment. Alternatively, R_2 is a phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl and halo$(C_1$-$C_6)$alkoxy. In another alternative, R_2 is phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, -Me, -Et, -OMe, $-CF_3$ and $-OCF_3$.

In a 9th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is a 5-6 membered heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or –Br), -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy ,$(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl. Values and values for the remainder of the variables in Structural Formulas (Va)-(XXVa) are as described above in the 3rd embodiment. Alternatively, the substitents are independently selected from the group consisting of halogen (e.g.,-F, -Cl or –Br), -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_3)$alkoxy,halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl. In another alternative, R_2 is a pyridinyl, thiophenyl, pyrrolyl or pyrimidinyl, each optionally substituted with 1 to 3 substituents independently selected from the group consiting of halogen, -CN, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl.

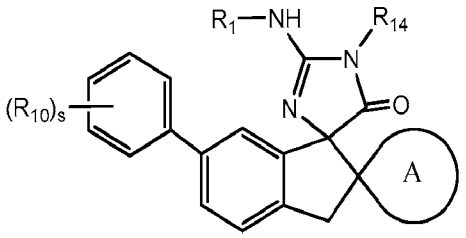
In a 10th embodiment, for Structural Formulas (Va)-(XXVa), R_2 is an indolyl, pyridinyl, thiophenyl, pyrrolyl, pyrimidinyl, cyclohexyl, or thiozolyl, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-

C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl. Values and alternative values for the remainder of the variables in Structural Formulas (Va)-(XXVa) are as described above in the 3rd embodiment. Alternatively, R_2 is an indolyl or pyridinyl optionally substituted with -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy or halo(C_1-C_3)alkoxy. In another alternative, R_2 is 2-pyridinyl or 6-indolyl.

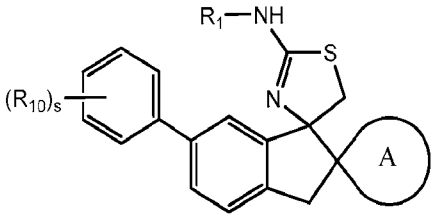
In a 11th embodiment, the compound of the present invention is represented by the following Structural Formulas:



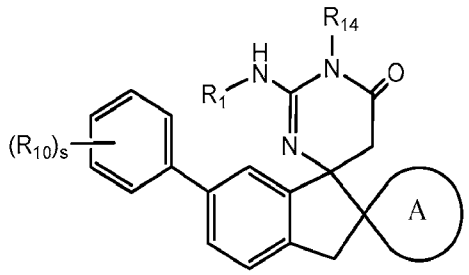
(Vb),



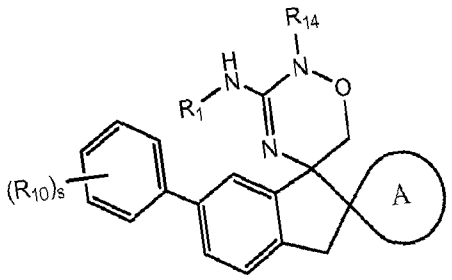
(VIb)

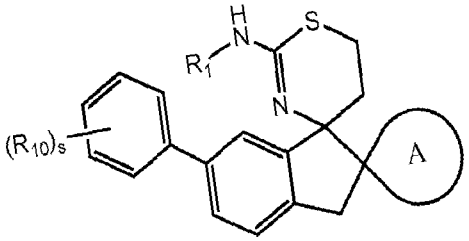


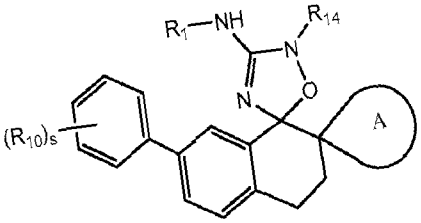
(VIIb),

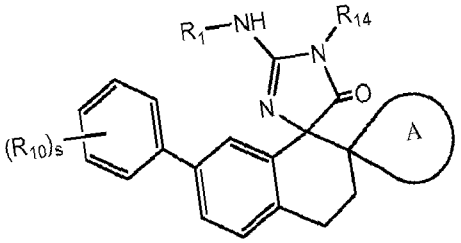


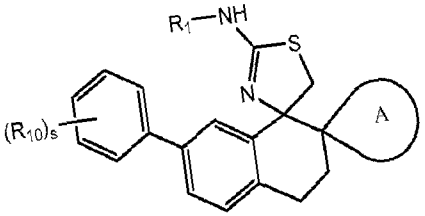
(VIIIb),

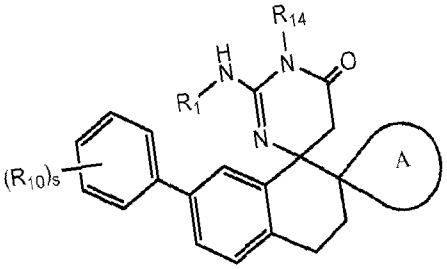

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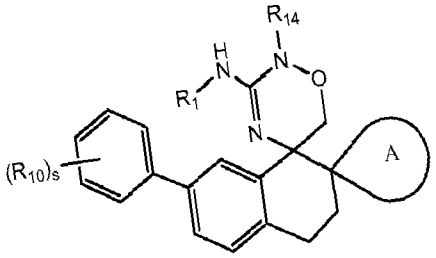

(Xb)

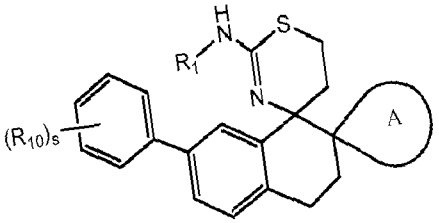

(XIb),

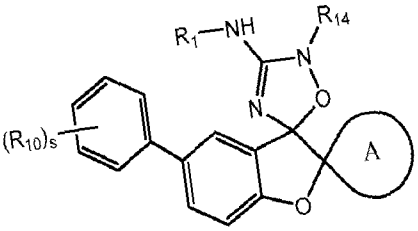

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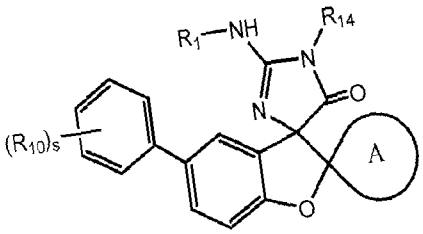

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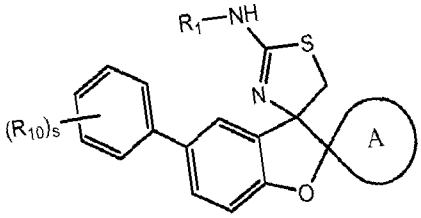

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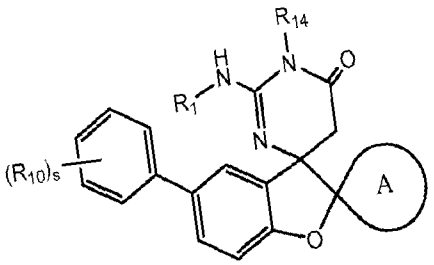

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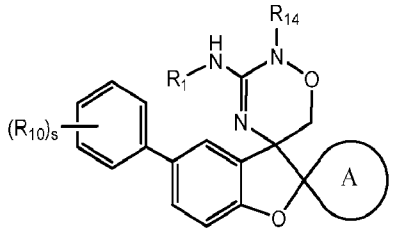

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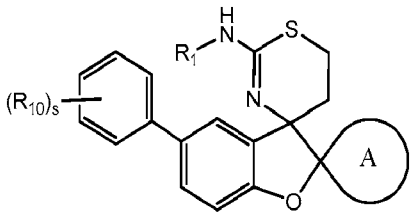

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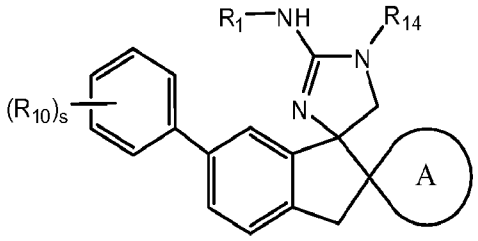

(XVIIIb)

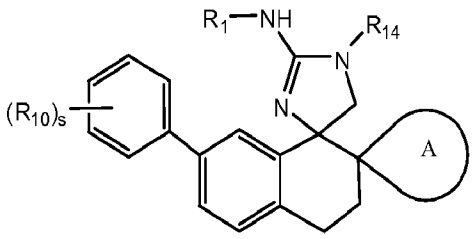

(XIXb),

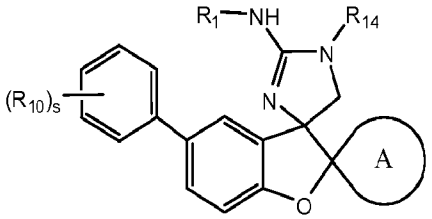

(XXb),


(XXIb),


(XXIIb),


(XXIIIb),




(XXIVb), or

(XXVb),

or a pharmceutically acceptable salt thereof, wherein R_{10} is independently selected from the group consisting of halogen, -CN, -NO_2, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)R_5$, -$C(=S)OR_5$, -$OC(=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$C(=O)R_5$, -$C(=S)R_5$, -$OC(=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=O)OR_5$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=O)R_5$, -$C(=S)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the groups represented by R_{10} are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl and s is 0, 1, 2 or 3 . Values and alternativel values for the remainder of the variables in Structural Formulas (Vb)-(XXVb) are as descrbed above in Structural

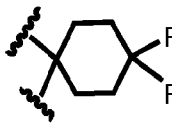
Formula (I) or (I'). In one embodiment, s is 1 or 2. Alternatively, R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy and $-SO_2(C_1$-$C_3)$alkyl; and s is 0, 1, 2 or 3. In another alternative, R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, and halo$(C_1$-$C_6)$alkoxy; and s is 0, 1, 2 or 3. In yet another alternative, R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, -Me, -Et, -OMe, $-CF_3$, $-OCF_3$. In another alternative embodiment, R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, -Me, -Et, -OMe, $-CF_3$, $-OCF_3$ and $-SO_2CH_3$.

In one embodiment, ring A is a 5-7 membered monocyclic ring or a 9-14 membered bicyclic or tricyclic fused ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl, wherein ring A contains 0 to 2 heteroatoms, which are independently selected from O, N and S. Values and alternative values for the remainder of the variables are as described in the 11th embodiment. More specifically, the substituents are selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and phenyl, wherein the phenyl is optionally substituted with halogen (e.g., -F, -Clor -Br), -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy. Even more specifically, R_1 is -H and R_{14} is -Me.

In another embodiment, for Structural Formulas (Vb)-(XXVb), ring A is selected from tetrahydrofuran, tetrahydropyran, cyclopentane, cyclohexane, cyclohexene, cycloheptane, oxepane, 1,3-dioxane, piperidine, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, tetrahydronaphthalene, decahydronaphthalene, 5,6,7,8-tetrahydroquinoline, 5,6,7,8-tetrahydroisoquinoline, 2,3,4,5-tetrahydrobenzo[b]oxepine, and 2,3-dihydro-1H-phenalene, each of which is

optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen (e.g., -F, -Cl or -Br), -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and phenyl, wherein the phenyl is optionally substituted with halogen (e.g., -F, -Cl or -Br), -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy. Values and alternative values for the remainder of the variables are as described in the 11th embodiment. More specifically, the substituents are selected from the group consisting of -F, -OMe, -OEt and -Ph. Even more specifically, R_1 is -H and R_{14} is -Me.

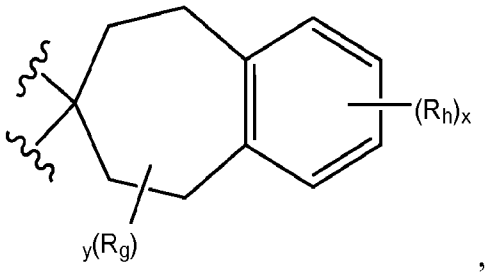
In a 12th embodiment, for compounds represented by Structural Formulas (A), (I), (I'), (II)-(XXV), (IIa)-(XXVa), (IIb)-(XXVb), ring A is represented by the following structural formula:



(B),

wherein R_{19} and R_{20} are each independently selected from -H, halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl, wherein each of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl groups represented by R_{19} and R_{20} is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -CN, -OH, -$NR_{11}SO_2$(C_1-C_3)alkyl, -$NR_{11}C(=O)$-(C_1-C_3)alkyl, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl. The remainder of the variables are as described above in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th or 11th embodiment. Alternatively, R_{20} is –H and R_{19} is -OH, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy or (C_1-C_3)alkoxy(C_1-C_3)alkoxy. In another alternative, R_{19} and R_{20} are each independently –H or –NR_6R_7, wherein R_6 and R_7 are each independently selected from the group consisting of –H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, and (C_1-C_3)alkoxy(C_1-C_3)alkyl.

In a 13th embodiment, for compounds represented by Structural Formulas (A), (I), (I'), (II)-(XXV), (IIa)-(XXVa), (IIb)-(XXVb), ring A is represented by the following structural formula:



,

wherein:

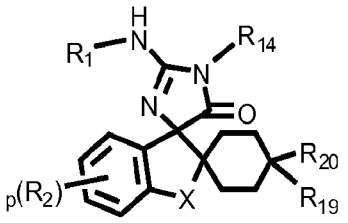
R_g and R_h, for each occurrence, are independently –H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, -C(=O)R_5, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl, heteroaryl, each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl represented by R_b is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -C(=O)OR_5, -C(=O)$NR_{12}R_{13}$, -NR_{11}C(=O)R_5, -C(=S)$NR_{12}R_{13}$, -C(=O)R_5, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, , hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

x is an integer from 1 to 4; and

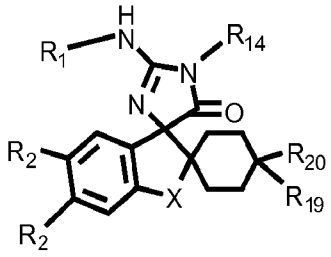
y is an integer from 1 to 6.

The remainder of the variables are as described above in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th or 11th embodiment. Alternatively, each R_g is independently selected from –H, Me and F and each R_h is independently –H, halogen, -CN, -NO_2, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy. Alternatively, each R_g is independently selected from –H, Me and F and each R_h is independently –H, halogen, -CN, -NO_2, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy. In another alternative embodiment, R_g is –H and each R_h is independently –H, halogen, -CN, -NO_2, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, and halo(C_1-C_3)alkoxy. In yet another alternative, R_g and R_h are both –H.

In a 14th embodiment, the compounds of the present invention are represented by the following structural formula:



(D), or



(E),

or a pharmaceutically acceptable salt thereof, wherein: R_{19} and R_{20} are each independently selected from -H, halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl and heteroaryl$(C_1\text{-}C_6)$alkyl, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl and heteroaryl$(C_1\text{-}C_6)$alkyl groups represented by R_{19} and R_{20} is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -CN, -OH, $-NR_{11}SO_2(C_1\text{-}C_3)$alkyl, $-NR_{11}C(=O)\text{-}(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy and $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_6)$alkyl; and the remainder of the variables are as described in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th,10th or 11th embodiment.

In one embodiment, for compounds represented by Structural Formula (D) or (E): each R_2 is independently selected from the group consisting of -H, halogen, -CN, $-OR_5$, $-S(O)_iR_5$, $-NR_6R_7$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocycloalkyl, $(C_3\text{-}C_7)$heterocycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl and heteroaryl$(C_1\text{-}C_6)$alkyl, each of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$heterocycloalkyl,

(C_3-C_7)heterocycloalkyl(C_1-C_6)alkyl, (C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the aryl and heteroaryl groups in the substituents on the groups represented by R_2 are each independently optionally substituted with 1 to 3 substituents selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_{14} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_7)heterocycloalkyl and (C_3-C_7)heterocycloalkyl(C_1-C_3)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, -NR_6R_7, -$NR_{11}S(O)_iR_5$, -$S(O)_iR_5$-, -OH and –$C(O)OR_5$; and

R_{20} is –H and R_{19} is –OH, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy or (C_1-C_3)alkoxy(C_1-C_6)alkoxy.

In a 15th embodiment, for compounds represented by Structural Formulas (I)-(XXV), (Va)-(XXVa) and (Vb)-(XXVb):

R_1 is –H or –C(=O)(C_1-C_3)alkyl;

for Structural Formulas (I)-(XXV) and (Va)-(XXVa), R_2 is –H, halogen, -CN, -OR_5, -$C(=O)NR_{12}R_{13}$, -$C(=O)OR_5$, -$C(O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl, (C_5-C_6)heterocycloalky(C_1-C_3)alkyl, wherein the heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl, triazole and thiophenyl, the heterocycloalkyl is selected from oxetanyl, tretrahydrafuran, tetrapyran,

piperidine, pyrrolidinyl and pyrrolidinonyl, and each of (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl and (C_5-C_6)heterocycloalky(C_1-C_3)alkyl groups represented by R_2 is optionally substituted with 1 to 5 substituents independently selected from halogen, -CN, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_2-C_6)alkynyl, -NR_6R_7, -$S(O)_iR_5$, -$C(O)R_5$, -OH, (C_3-C_6)cycloalkyl, (C_1-C_3)alkoxy and halo(C_1-C_3)alkoxy; and

R_{14}, when present, is –H, -OR_5, -NR_6R_7, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl, wherein the heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl and thiophenyl and triazolyl, the (C_3-C_5)heterocycloalkyl is selected from oxetanyl, tetrahydrofuran, tetrahydropyran, piperidinyl and pyrrolidinyl, and each of the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl groups represented by R_{14} is optionally substituted with 1 to 3 substituents independently selected from halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}SO_2R_5$, -OH, -$COOR_5$, -$C(=O)R_5$, -$C(=O)NR_{12}R_{13}$ and thiazolyl; and

for Structural Formulas (Vb)-(XXVb), each R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy and –SO_2(C_1-C_3)alkyl; and s is 0, 1, 2 or 3.

The remainder of the variables are as described above in the 1st, 2nd, 3rd, 11th, 12th or 13th embodiment.

In a 16th embodiment, for compounds represented by Structural Formulas (I)-(XXV), (Va)-(XXVa) and (Vb)-(XXVb):

R_1 is –H or –$C(=O)CH_3$.

for Structural Formulas (Va)-(XXVa) each R_2 is independently selected from the group consisting of –H, -F, –Br, -Cl, -I, -OH, -CN, cyclopropylethyl, 5-propynyl-3-

pyridyl, 2-fluoro-3-pyridyl, N,N-dimethylaminoethoxy, cyclopentoxy, cyclopropylmethoxy, 3-methoxypropyl, 3-methoxypropynyl, cyclopropylethynyl, 3-cyanophenyl, trifluoromethoxy, 2-chloro-4-pyridyl, 1-methanesulfonyl-4-piperidinylmethyl, 1-acetyl-4-piperidinylmethyl, 3-methanesulfonylphenyl, 5-trifluoromethyl-3-pyridyl, 2-methoxyethoxy, 2-methyl-5-pyridazin-3-onyl, 1-cyclopropyl-4-pyridin-2-onyl, 1-methyl-2,2,2-trifluoroethyl, 2-cyclopropyl-5-thiazolyl, trifluoromethyl, 2,2,2-trifluoroethyl, methoxy, 3-chloro-5-fluorophenyl, N-methyl-4-pyridin-2-onyl, 4-methylpentyl, 3-methoxyphenoxy, dimethylaminocabonyl, cyclopropyl, 1-hydroxy-2,2,2-trifluoroethyl, pyrrolidinylcarbonyl, 3,3,3-trifluoropropyl, difluoromethoxy, 1,1-dihydroxy-2,2,2-trifluoroethyl, 3-methoxyphenyl, 2,2,2-trifluoroethoxy, phenoxy, 2-methoxy-4-pyridyl, 2-methyl-5-thiazolyl, 3,3,3-trifluoroprop-1-en-2-yl, 5-thiazolyl, 2-thiazolyl, thiophen-3-ylethynyl, 1-hydroxycyclopentan-1-ylethynyl, 5-fluoro-3-pyridyl, pyrrolidinyl, 5-chloro-3-pyridyl, 3,3-dimethylbutyn-1-yl, phenylethynyl, cyclopentylethynyl, 2-pyrazinyl, 3-chlorophenyl, 3-hydroxycyclopent-1-enyl, 3-fluoro-5-trifluoromethylphenyl, 3,5-dicyanophenyl, 3-fluoro-5-cyanophenyl, 3-chloro-4-fluorophenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3-chloro-5-cyanophenyl, 3-pyridazinyl, 3-pyridyl, 3-cyano-4-fluorophenyl, 3-cyano-5-fluorophenyl 6-methoxypyrazin-2-yl, 6-indolyl, 3-chloro-5-methoxyphenyl, 3-trifluoromethoxyphenyl, 3,5-dimethylphenyl, 2-methyl-5-fluorophenyl, 3-trifluoromethylphenyl, phenyl, cyclopentylmethyl, 1-propyl, 2-propyl, 2-methylpropyl, phenylethyl, 1-pentyl, 2-methylbutyl, ethyl, 4-methoxyphenylmethoxy, 1-methylethoxy, methoxycarbonyl, cyclopropyloxy, 5-cyano-3-pyridyl, 4-(propyn-1-yl)-2-thiophenyl, 4-bromo-2-thiazolyl, ethenyl, ethynyl, 4-methylpentyn-1-yl, dimethylaminopropyl, N-methylpyrrolidin-3-ylmethyl, 2,2-difluorocyclopropylmethoxy, 4-bromo-2-thiophenyl, methoxy, methyl, carboxy, 5-propyl-3-pyridyl, 2-methyl-5-fluorophenyl, 2-oxazolyl, propylthio, phenylthio, 2,2-dimethylpropyl, butyl, cyclobutylmethoxy, 2-methyl-5-pyrimidyl, pyrrolidin-2-onyl, 3,3-difluoropyrrolidin-1-yl, cyclopropylethyl, 2-propyloxy, 4-cyano-2-thiophenyl, ethoxymethyl, 4-methoxybenzyloxy, 1-methylethyl, cyclohexylmethyl, 5-chloro-3-pyridyl, 5-methyl-3-pyridyl, 2-methylpropyloxy and 2-chloro-4-pyridyl; and

R_{14}, when present, is selected from the group consisting of –H, methyl, ethyl, 2-propyl, 1-propyl, 1-butyl, benzyl, 2-pyridylmethyl, methoxyethyl, 1-methoxypropan-2-yl, N,N-dimethylaminoethyl, 4-cyanobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 2-thiazolylethyl, 2-thiazolylmethyl, 6-quinoxalinylmethyl, 1-phenylethyl, 2-propyl, *tert*-butyl, 3-dimethylaminobenzyl, 3-methanesulfonamidobenzyl, 3-methanesulfonylbenzyl, 2-oxazolylmethyl, 1,1,2,2-tetrafluoroethoxy, 2-oxetanylmethyl, 2-ethylbutyl, 5-fluoro-2-pyridyl, 3-fluorobenzyl, 4-thiazolylmethyl, 2,2-difluoroethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydrofuranyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-fluorobenzyl, 4-methanesulfonylbenzyl, 2-tetrahydrafuranylmethyl, 2,2,2-trifluoroethyl, 5-trifluoromethyl-2-pyridylmethyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 2-chlorobenzyl, 2-methoxyethyl, cyclobutylmethyl, 4-tetrahydropyranylmethyl, 2-methylpropyl, phenylethyl, cyclopropyl, cyclobutyl, 1-methylpropyl, 5-pyrimidylmethyl, 2-carboxyethyl, dimethylamino, 4-tetrahydropyranyl, 1-methylpiperidin-4-yl, 2-fluoroethyl, 2-butyl, dimethylaminoethyl, 1-(3-pyridazinyl)ethyl, 1-methoxy-2-propyl, (4-methyl-1,2,4-triazol-3-yl)methyl, (2-methoxy-2-phenyl)ethyl, (1,3,4-oxadiazol-2-yl)methyl, (quinoxalin-2-yl)methyl, 1-phenylethyl, methanesulfonylaminoethyl, aminocarbonylethyl, aminocarbonylmethyl, 3-methoxypropyl and (3-(2-thiazolyl))benzyl, carboxymethyl, 1-methylethoxycarbonylmethyl, 5-methyl-1,3,4-thiadizolyl, 4-pyridazinyl, 5-methyl-2-oxazolylethyl, 2-hydroxyl-2-methylpropyl, 2-hydroxy-1-methylethyl and 2-pyrazinylmethyl;

for Structural Formula (Vb)-(XXVb), each R_{10} is independently selected from the group consisting of –H, -F, -Cl, -Br, -CN, -Me, -Et, -OMe, $-CF_3$, $-OCF_3$ and $-SO_2CH_3$.

The remainder of the variables are as described above in the 1st, 2nd, 3rd, 11th, 12th or 13th embodiment.

In a 17th embodiment, for compounds described in the 1st to 16th embodiment:

R_5 is selected from the group consisting of –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, phenyl and phenyl(C_1-C_3)alkyl, wherein the phenyl group in the groups represented by R_5 is

optionally substituted with 1 to 3 substituents independently selected from -F, -Cl, -Br, -CN, =O, $-NR_6R_7$, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl;

R_6 is –H or (C_1-C_3)alkyl;

R_7 is –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl;

R_{11} is –H or (C_1-C_3)alkyl;

R_{12} is –H or (C_1-C_3)alkyl; and

R_{13} is –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl, or R_{12} and R_{13} together with the nitrogen atom to which they are attached forms a pyrrolidine or piperidine ring.In a 18th embodiment, for compounds described in the 1st to 16th embodiments:

R_5 is selected from the group consisting of –H, methyl, ethyl, 2-propyl, 2-methylpropyl, cyclopentyl, $-CHF_2$, $-CF_2CHF_2$, $-CH_2CF_3$, $-CF_3$, cyclopropylmethyl, 2,2-difluorocyclopropylmethyl, methoxyethyl, phenyl, 3-methoxyphenyl, (1-amino-2-(4-hydroxyphenyl))ethylcarbonyl, dimethylaminoethyl, cyclobutylmethyl, and 4-methoxybenzyl;

R_6 is –H or methyl,

R_7 is –H, methyl or $-CH_2CF_3$,

R_{11} is –H or methyl,

R_{12} and R_{13} are each independently –H or methyl, or R_{12} and R_{13} together with the nitrogen atom to which they are attached form a pyrrolidine ring.

General definitions:

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group. For example, (C_1-C_6)alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more

subgroups, the last named subgroup is the radical attachment point. For example, the substituent "aryl(C_1-C_3)alkyl" means an aryl group which is bound to a (C_1-C_3)alkyl group, the latter of which is bound to the core or to the group to which the substituent is attached.

When a compound of the present invention is depicted in form of a chemical name and as a formula, in case of any discrepancy, the formula shall prevail.

When any variable (e.g. aryl, heterocyclyl, R^1, R^2 etc.) occurs more than once in a compound, its definition on each occurrence is independent of any other occurrence.

"Alkyl" means a saturated aliphatic branched or straight-chain monovalent hydrocarbon radical having the specified number of carbon atoms. For example, "(C_1-C_6)alkyl" means a radical having from 1-6 carbon atoms in a linear or branched arrangement. "(C_1-C_6)alkyl" includes methyl, ethyl, propyl, butyl, pentyl, and hexyl.

"Alkenyl" means branched or straight-chain monovalent hydrocarbon radical containing at least one double bond and having specified number of carbon atoms. Alkenyl may be mono or polyunsaturated, and may exist in the E or Z onfiguration. For example, "(C_2-C_6)alkenyl" means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

"Alkynyl" means branched or straight-chain monovalent hydrocarbon radical containing at least one triple bond and having specified number of carbon atoms. For example, "(C_2-C_6)alkynyl" means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

"Cycloalkyl" means a saturated aliphatic cyclic hydrocarbon radical having the specified number of carbon atoms. It can be monocyclic, bicyclic, polycyclic (e.g., tricyclic), fused, bridged, or spiro. For example, monocyclic (C_3-C_8)cycloalkyl means a radical having from 3-8 carbon atoms arranged in a monocyclic ring. Monocyclic (C_3-C_8)cycloalkyl includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctane.

Monocyclic ring systems have a single ring structure. They include saturated or unsaturated aliphatic cyclic hydrocarbon rings or aromatic hydrocarbon ring having the specified number of carbon atoms. The monocyclic ring system can optionally contain

1 to 3 heteroatoms in the ring structure and each heteroatom is independently selected from the group consisting O, N and S. When the heteroatom is a ring nitrogen atom connected to other ring atoms only by single bonds, it can be substituted. Exemplary substituents, unless otherwise indicated, include -H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl (preferrably, -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_1-C_3)alkylcarbonyl), each of which can be optionally substituted with halogen, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-). Examples of monocyclic ring system include, but are not limited to, monocyclic cycloalkyls (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctane), partially unsaturated cycloalkyls; monocyclic heterocycloalkyls (e.g., azetidine, pyrrolidine, piperidine, piperazine, hexahydropyrimidine, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine, tetrahydro-2H-1,2-thiazine 1,1-dioxide, and isothiazolidine 1,1-dioxide, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, and isothiazolidine 1,1-dioxide, pyrrolidin-2-one, piperidin-2-one, piperazin-2-one, and morpholin-2-one); monocyclic aryls (e.g., phenyl) and monocyclic heteroaryls (see descriptions below).

Bicyclic ring systems have two rings that have at least one ring atom in common. Bicyclic ring systems include fused, bridged and spiro ring systems. The two rings can both be aliphatic (e.g., cycloalkyl or cycloheteroalkyl), both be aromatic (e.g., aryl or heteroaryl), or a combination thereof. The bicyclic ring sytems can optionally contain 1 to 3 heteroatoms in the ring structure and each heteroatom is independently selected from the group consisting O, N and S. When the heteroatom is a ring nitrogen atom connected to other ring atoms only by single bonds, it can be substituted. Exemplary substituents, unless otherwise indicated, include H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl (preferrably, -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_1-C_3)alkylcarbonyl), each of which can be optionally

substituted with halogen, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-).

A fused bicyclic ring system has two rings which have two adjacent ring atoms in common. The two rings can both be aliphatic (e.g., cycloalkyl or cycloheteroalkyl), both be aromatic (e.g., aryl or heteroaryl), or a combination thereof. For example, the first ring can be monocyclic cycloalkyl or moncyclic cycloheteroalkyl, and the second ring can a cycloalkyl, partially unsaturated carbocycle, aryl, heteroaryl or a monocyclic cycloheteroalkyl. For example, the second ring can be a (C_3-C_6)cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Alternatively, the second ring can be an aryl ring, e.g., phenyl. Examples of fused bicyclic ring systems include, but not limited to, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, octahydro-1H-indene, tetrahydronaphthalene, decahydronaphthalene, indoline, isoindoline, 2,3-dihydro-1H-benzo[d]imidazole, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydrobenzo[d]thiazole, octahydrobenzo[d]oxazole, octahydro-1H-benzo[d]imidazole, octahydrobenzo[d]thiazole, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 5,6,7,8-tetrahydroquinoline and 5,6,7,8-tetrahydroisoquinoline and 2,3,4,5-tetrahydrobenzo[b]oxepine.

A spiro bicyclic ring system has two rings which have only one ring atom in common. The two rings can both be aliphatic (e.g., cycloalkyl or cycloheteroalkyl). For example, the first ring can be a monocyclic cycloalkyl or a monocyclic cycloheteroalkyl and the second ring can be a cycloalkyl, partially unsaturated carbocycle, or a monocyclic cycloheteroalkyl. Examples of sprial bicyclic ring system include, but are not limited to, spiro[2.2]pentane, spiro[2.3]hexane, spiro[3.3]heptane, spiro[2.4]heptane, spiro[3.4]octane, spiro[2.5]octane, azaspiro[4.4]nonane, 7-azaspiro[4.4]nonane, azasprio[4.5]decane, 8-azaspiro[4.5]decane, azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane and 3,9-diazaspiro[5.5]undecane.

A bridged bicyclic ring system has two rings which have three or more adjacent ring atoms in common. For example, the first ring can be a monocyclic cycloalkyl or a monocyclic cycloheteroalkyl and the other ring is a cycloalkyl, partially unsaturated carbocycle, or a monocyclic cycloheteroalkyl. Examples of bridged bicyclic ring

system include, but are not limited to, bicyclo[1.1.0]butane, bicyclo[1.2.0]pentane, bicyclo[2.2.0]hexane, bicyclo[3.2.0]heptane, bicyclo[3.3.0]octane, bicyclo[4.2.0]octane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[3.3.2]decane bicyclo[3.3.3]undecane, azabicyclo[3.3.1]nonane, 3-azabicyclo[3.3.1]nonane, azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 6-azabicyclo[3.2.1]octane and azabicyclo[2.2.2]octane, 2-azabicyclo[2.2.2]octane and 2-oxabicyclo[2.2.2]octane.

Polycyclic ring systems have more than two rings (e.g., three rings resulting in a tricyclic ring system) and adjacent rings having at least one ring atom in common. Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common. Examples of polycyclic ring system include, but not limited to, tricyclo[3.3.1.$0^{3,7}$]nonane (noradamantane) and tricyclo[3.3.1.$1^{3,7}$]decane (adamantane) and 2,3-dihydro-1H-phenalene

"Heterocycle" means a saturated, unsaturated, or aromatic mono- or polycyclic-ring systems containing one or more heteroatoms independently selected from N, O or S. When the heteroatom is N, unless otherwise indicated, it can be substituted. Exemplary substituents include H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl (preferrably, -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_1-C_3)alkylcarbonyl), each of which can be optionally substituted with halogen, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, unless otherwise indicated, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-). A heterocycle can be a heteroaryl ring or heterocycloalkyl ring.

"Cycloheteroalkyl" or "heterocycloalkyl" means a saturated or partially saturated 4-12 membered ring radical having specified number of ring carbon atoms. The cycloheteroalkyl or heterocycloalkyl contains 1 to 4 ring heteroatoms, which may be the same or different, selected from N, O or S. The cycloheteroalkyl or heterocycloalkyl ring optionally contains one or more double bonds. It can be

monocyclic, bicyclic, tricyclic, fused, bridged, or spiro. For example, (C_3-C_9)heterocycloalkyl means a ring radical containing 3-9 ring carbon atoms. The term "cycloheteroalkyl" or "heterocycloalkyl" is intended to include all the possible isomeric forms. When the heteroatom is a ring nitrogen atom connected to other ring atoms only by single bonds, it can be substituted. Exemplary substituents, unless otherwise indicated, include H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl (preferrably, -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_1-C_3)alkylcarbonyl), each of which can be optionally substituted with halogen, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-).

Haloalkyl and halocycloalkyl include mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, and bromine.

"Heteroaryl", "heteroaryl group", "heteroaryl ring", "heteroaromatic", "heteroaromatic group" and "heteroaromatic ring" are used interchangeably herein. "Heteroaryl" means a monovalent heteroaromatic monocyclic or polycylic ring radical. Monocyclic heteroaryl rings are 5- and 6-membered aromatic heterocyclic rings containing 1 to 4 heteroatoms independently selected from N, O, and S, and include, but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole 1,1-dioxide, 1,3,4-thiadiazole, pyridine, pyridine-N-oxide, pyrazine, pyrimidine, pyridazine, 1,2,4-triazine, 1,3,5-triazine, and tetrazole. Bicyclic heteroaryl rings are bicyclo[4.4.0] and bicyclo[4,3.0] fused ring systems containing 1 to 4 heteroatoms independently selected from N, O, and S, and include indolizine, indole, isoindole, benzo[b]furan, benzo[b]thiophene, indazole, benzimidazole, benzthiazole, purine, 4H-quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. "Alkoxy" means an alkyl radical attached through an oxygen linking atom. "(C_1-C_4)-alkoxy" includes methoxy, ethoxy, propoxy, and butoxy.

"Aromatic", "aromatic group", "aromatic ring", "aryl", "aryl group" and "aryl ring" are used interchangeable herein..

"Aryl" means an aromatic monocyclic, or polycyclic hydrocarbon ring system. Aryl systems include, but limited to, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, and anthracenyl.

"Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. A hetero ring may have 1, 2, 3, or 4 carbon atom members replaced by a heteroatom.

"Halogen" used herein refers to fluorine, chlorine, bromine, or iodine.

"Carbocycle" means 3-14 membered saturated or unsaturated aliphatic cyclic hydrocarbon ring.

"Cycloalkene" an unsaturated and non-aromatic aliphatic cyclic hydrocarbon radical having the specified number of carbon atoms. It can be monocyclic, bicyclic, tricyclic, fused, bridged, or spiro. Thus, $(C_3\text{-}C_8)$cycloalkene means a radical having from 3-8 carbon atoms arranged in a ring. $(C_3\text{-}C_8)$cycloalkene includes cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

The compounds of the invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of the invention refer to non-toxic "pharmaceutically acceptable salts." The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

For example, such salts include, the acetate, ascorbate, benzenesulfonate, benzoate, bezylate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, ethane disulfonate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, methanesulfonate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oxalate, pamoate, pantothenate, phenylacetate, phosphate/diphospate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamide, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide, ammonium, benzathine, chloroprocaine, colline, diethanolamine, ethylenediamine, meglumine and procaine salts. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an

isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses one enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s).

When compounds having one or more stereocenters and are depicted with particular stereochemistry for at least one stereocenter, the present invention also include compounds that have the opposite stereochemistry at the corresponding stereocenter(s) and compounds that has no specific stereochemistry at the corresponding stereocenter(s).

The disclosed compounds of the invention are BACE inhibitors for treating, preventing or ameliorating disorders or diseases characterized by elevated β-amyloid deposits or β-amyloid levels in a subject. The present invention also provides a method for the treatment of a disorder related to or associated with excessive BACE activity in a patient in need thereof which comprises administering to said patient an effective amount of a disclosed compound or a pharmaceutically acceptable salt thereof. The present invention also provides methods for inhibiting the activity of BACE in a subject in need thereof, comprising administering to a subject and/or contacting a receptor thereof with an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof. The present invention also provides methods of ameliorating β-amyloid deposits in a subject in need thereof, comprising administering to said subject an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof.

As such, the disclosed BACE inhibitors can be used to treat neurodegenerative disorders, disorders characterized by cognitive decline, cognitive impairment, dementia and diseases characterized by production of β-amyloid deposits or neurofibrillary tangles.

Exemplary diseases or disorders that can be treated by the disclosed BACE inhibitors include Alzheimer's disease, Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-typle (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy and dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and glaucoma.

Accordingly, the present invention relates to a compound described herein or a pharmaceutically acceptable salt thereof as a medicament.

In a further embodiment, the present invention relates to methods for the treatment or prevention of above-mentioned diseases and conditions, which method

comprises the administration of an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof.

The invention includes a therapeutic method for treating or ameliorating an BACE mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of Formula I or any other formulas of the invention described herein, or pharmaceutically acceptable salts thereof or composition thereof.

Administration methods include administering an effective amount (i.e., an effective amount) of a compound or composition of the invention at different times during the course of therapy or concurrently in a combination form. The methods of the invention include all known therapeutic treatment regimens.

As used herein, the term "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses, sheep, goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

As used herein, the term "treating" or 'treatment" refers to obtaining desired pharmacological and/or physiological effect. The effect can be prophylactic or therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome; or partially or totally delaying, inhibiting or reducing the likelihood of the onset or development of disease, disorder or syndrome.

"Effective amount" means that amount of active compound agent that elicits the desired biological response in a subject. Such response includes alleviation of the symptoms of the disease or disorder being treated. The effective amount of a compound of the invention in such a therapeutic method is from about 0.01 mg/kg/day to about 1000 mg/kg/day, from about 0.1 mg/kg/day to about 100 mg/kg/day.

"Pharmaceutically acceptable carrier" means compounds and compositions that are of sufficient purity and quality for use in the formulation of a composition of the invention and that, when appropriately administered to an animal or human, do not produce an adverse reaction.

In one embodiment, the present invention includes combination therapy for treating or ameliorating a disease or a disorder described herein. The combination therapy comprises administering a combination of at least one compound represented by structural formula (A), (I) or (I') with another compound selected from the group of, for example, gamma-secretase inhibitors; amyloid aggregation inhibitors (e.g. ELND-005); directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants (e.g. vitamin E or ginkolide); anti-inflammatory substances (e.g. Cox inhibitors,NSAIDs additionally or exclusively having Abeta lowering properties); HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, tacrine, galantamine, memantine; tacrine); NMDA receptor antagonists (e.g. memantine); AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone (e.g., ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotics (e.g., minocyclin or rifampicin); PDE2, PDE4, PDE5, PDE9, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline and trazodone; anxiolytics, such as lorazepam and oxazepam; antiphychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and

ziprasidone, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced. The compounds according to the invention may also be used in combination with immunotherapies (e.g., active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or nanobodies) for the treatment of the above-mentioned diseases and conditions.

Combination therapy includes co-administration of the compound of the invention and said other agent, sequential administration of the compound and the other agent, administration of a composition containing the compound and the other agent, or simultaneous administration of separate compositions containing of the compound and the other agent.

Suitable preparations for administering the compounds of formula will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc. The content of the pharmaceutically active compound(s) should be in the range from 0.005 to 10% wt.-% of the composition as a whole.

The dosage form containing the composition of the invention contains an effective amount of the active ingredient necessary to provide a therapeutic effect. The composition may contain from about 5,000 mg to about 0.5 mg (preferably, from about 1,000 mg to about 0.5 mg) of a compound of the invention or salt form thereof and may be constituted into any form suitable for the selected mode of administration.

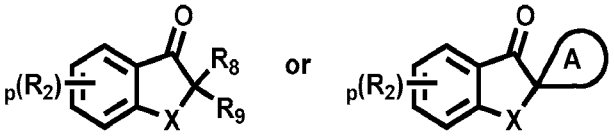
Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants . The tablets may also consist of several layers.

METHODS OF PREPARATION

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily

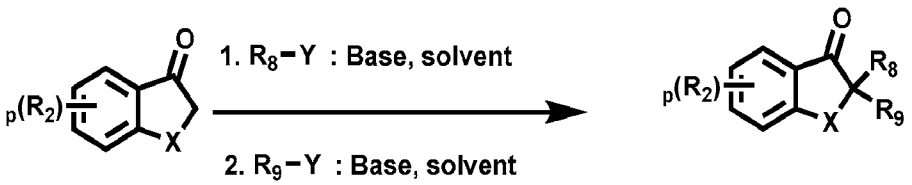
available starting materials, reagents and conventional synthesis procedures. Many of the reactions can also be carried out under microwave conditions or using conventional heating or utilizing other technologies such as solid phase reagents/scavengers or flow chemistry. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to a person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined below. The abbreviations used in these experimental details are listed below and additional ones should be known to a person skilled in the art of synthesis. In addition one can refer to the following references for suitable methods of synthesis as described in March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985 or Greene and Wuts Protective groups in organic synthesis 2nd edition, John Wiley & sons 1991 and as in Richard Larock, comprehensive organic transformations, 4th edition, VCH publishers Inc, 1989.

Scheme 1: Synthesis of key intermediate A



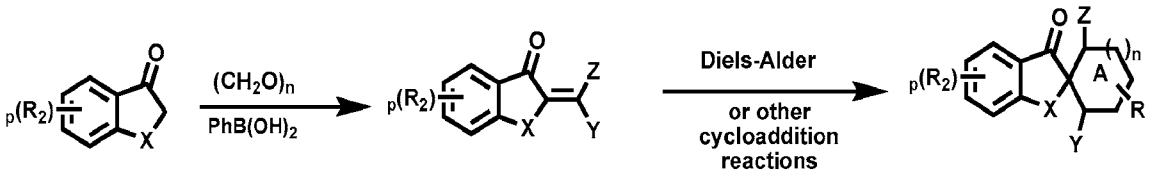
The above shown intermediate can be synthesized by the following methods or by any other methods not detailed here by anyone who is well versed in the art of synthesis.

Method 1



Method 1. Starting with the appropriate ketone one can sequentially alkylate with alkyl halides, triflates and mesylates utilizing bases such as LDA, NaH in various solvents such as THF, DME etc at temperatures varying from -78 °C to 50 °C. Each alkylation can be carried out in a sequential fashion with each intermediate being isolated and purified or in one pot in a stepwise fashion. In the event the final product from the above reactions yields a substituent on the alkyl group such as an olefin, sulfone, cyano etc, they can be further manipulated by Dieckman cyclization, RCM or other known reaction such as cycloaddition, nuecleophilic substitution etc. to yield highly functionalized spirocyclic intermediates.

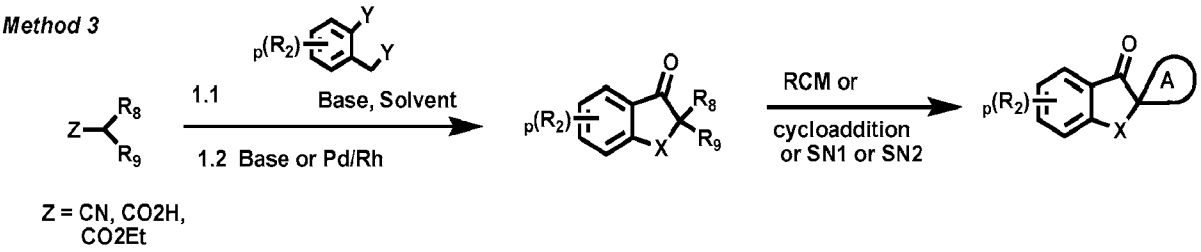
Method 2



Method 2 represents a specific method for the synthesis of spirocyclic compounds through the Diels Alder reaction or through other cycloaddition reaction such as 1,3-dipolar cycloaddition. The first step involves condensation of ketone with formaldehyde, aldehydes and ketones in presence of any protic acid or boronic acid in solvents such as benzene or toluene at temperatures varying from room temperature to 80 °C. The dienophile (or enone) intermediate then can be reacted with various dienes utilizing the Diels-Alder reaction. This reaction can be carried out neat or in presence of non-protic solvents such as benzene, THF in a sealed tube at temperature 30-220 °C. In addition one can utilize Lewis acids or any other agents that may assist in the reaction to yield pure enantiomers or diastereomers. The resulting spirocyclic cyclohexyl product may optionally contain one or more alkyl/aryl substituent or functional groups such as a ketone aldehyde, cyano etc. These functional groups can be further elaborated by known functional group transformations. For example the reaction of the dienophile with the Danishefsky diene in refluxing solvents such as benzene or toluene under nitrogen atmosphere yields spirocyclohexanone. The spirocyclohexanone can be further elaborated by reactions such as reduction with hydrides like NaBH4, LAH, DiBAL etc.

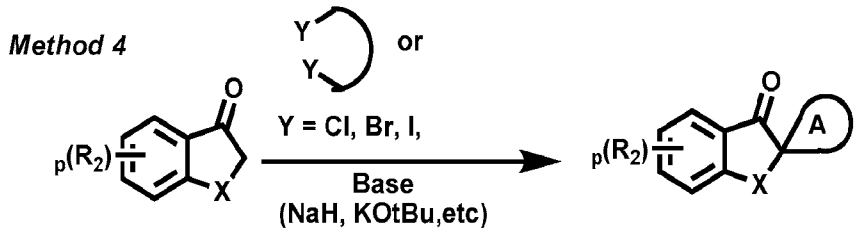
to yield an alcohol. This alcohol can be further alkylated with various alkyl groups by employing base such as NaH or LiHMDS in solvents such as DMF, THF etc. at room temperature to yield spirocyclic alkyl ethers. The alcohol can also be reacted with aryl/heteroarylhalides in the presence of palladium or copper catalyst along with appropriate bases such as $Cs_2CO_3$to yield aryl ethers.

Alternatively the ketone functional group can be further modified by known procedures in literature to yield heterocycles or other bicyclic ring systems. In addition the dienophile intermediate can also be reacted with 1,3 ylides to yield 5-membered spirocyclic heterocycles or carbocyles. The utility of these cycloaddition reaction are well documented in literature and are exemplified in these references: Synthesis of heterocycles via cycloadditions, Volume 1 By Alfred Hassner, Topic in heterocyclic chemistry volume 12, 1st edition, springer, 2008 and Cycloaddition reactions in organic synthesis; Kobayashi and Jørgensen, 1st edition, Wiley-VCH, 2002



In method 3, starting with alkyl or cycloalkyl or heterocycloalkyl derivatives containing electron withdrawing groups such as cyano or esters, the alkyl/cycloalkyl/ heterocycloalkyl groups can be alklylated with optionally substituted ortho-halo benzyl bromides or chlorides utilizing base such as LDA, NaH, or LiHMDS in solvents such as benzene, THF etc. at temperatures ranging from -78 °C to 80 °C. The alkylated intermediate can be isolated and further subjected to base such as n-BuLi or LDA in aprotic solvents such as THF, Hexane etc. to effect ring cyclization towards the final intermediate A. Alternatively one can also utilize transition metal based chemistry such as Pd/Cu or Rh containing chelating agents such as phosphine derivatives or amines in solvents such as DMF, DMA, THF and toluene in presence of base (TEA, or K_2CO_3) at

temperatures varying from room temperature to 80 °C. In the event where the final product from the above reactions yields substituent on the alkyl group such as olefins or sulfones, cyano etc, they can be further manipulated by Dieckman cyclization, RCM or other known reactions such as cycloaddition, nucleophilic substitution etc to yield highly functionalized spirocyclic intermediates.



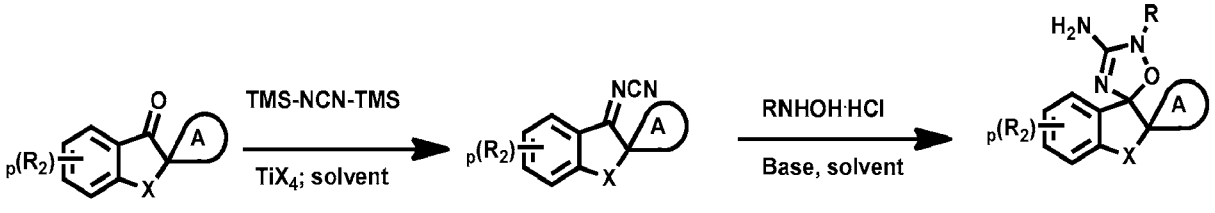
Method 4 represents a one pot reaction towards the synthesis of spirocyclic ketone intermediate A. Starting with appropriate ketone one can utilize alkylation chemistry of internally tethered bis alkyl halides/triflates or mesylates in presence of base such as LDA, LiHMDS and in aprotic solvents such as THF, dioxane, ether etc. at temperature varying from 0 °C to 80 °C to yield spirocyclic intermediate A.

Alternatively ketones can be reacted with acrylates in presence of base such as KOtBu and solvents such as tert-butanol with subsequent decarboxylation of β-keto ester to yield spirocyclic ketone intermediate A.

Scheme 2: Synthesis of monocyclic heterocyclic amines

The ketone intermediate A can be further functionalized and cyclized to yield various monocyclic heterocycles as described in "Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds" by Katritzky and Rees, Wiley and sons, 3rd edition 1991, or as described in Heterocyclic Chemistry by Joule Keith Mills, 5th edition by Wiley. Alternatively the methods outlined in WO 2008/103351 can also be utilized in the synthesis of various monocyclic heterocycles. Representative examples of some monocyclic amino heterocycles are shown below.

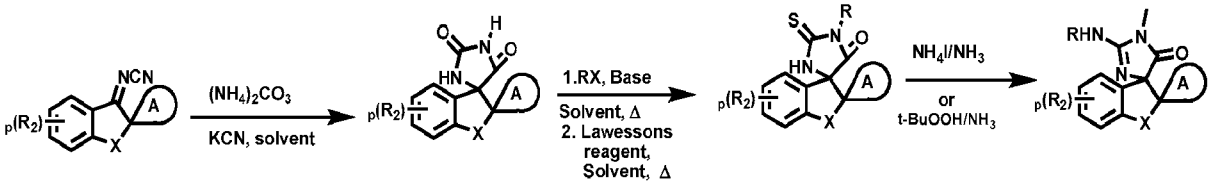
Scheme 2a: Synthesis of 2,5-dihydro-1,2,4-oxadiazol-3-amine heterocycle.



The ketone intermediate is condensed with bis trimethylsilyl carbodimide in presence of Lewis acids such as titanium isoporpoxide in solvents such as DCM or THF at room temperature to yield the N-cyanoimine product. The imine is subsequently condensed with hydroxylamine derivative in presence of base such as sodium methoxide in protic solvent such as methanol, t-Butanol etc. at room temperature to yield the desired 1,2,4-oxadiazol-3-amine heterocycle.

Scheme 2b. Synthesis of 2-amino-1H-imidazol-5(4H)-one

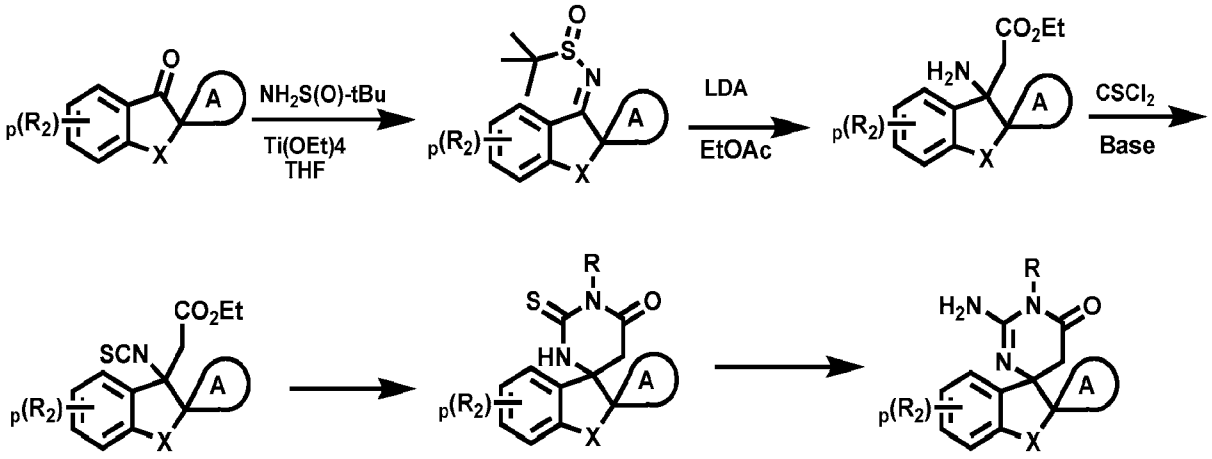
1.



The N-cyano intermediate as described in scheme 2a is reacted with ammonium carbonate and KCN in protic solvent mixture such as ethanol/water and heated to 50-150 °C in a sealed tube overnight. The resulting hydantoin can be alkylated with various alkylating agents in the presence of inorganic bases such as Cs_2CO_3 or K_2CO_3 or organic bases such as TEA or DBU in various solvents such as ethanol, DMF or dioxane at temperatures ranging from room temperature to 120 °C. The resulting alkylated product is reacted with thionating reagents such as Lawesson's reagent or P_2S_5 in a solvent such as THF, Dioxane, toluene etc. at temperatures ranging from 50-150 °C. The thioimide is then converted to a 2-amino imidazalinone by reacting with tert butyl hydroperoxide in presence of ammonia or alkylamines.

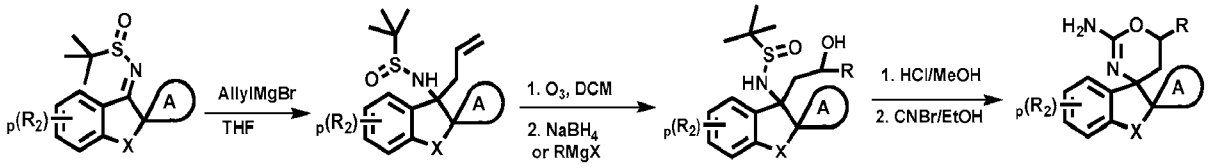
Alternatively the synthesis of 2-amino imidazolinone can be realized from the hydantoin by converting it to a thioimide, followed by bis-alkylation of the thioamide and imide functions in a one pot procedure. Such a bis-alkylated reagent can be reacted with ammonium hydroxide and ammonium iodide in various solvents such as DMF, ethanol, dioxane etc. at temperatures ranging from room temperature to 150 °C in a sealed tube to yield 2-amino-1H-imidazol-5(4H)-one. Similar procedure can also be employed starting with ketone intermediate A.

Scheme 2c. Synthesis of 2-amino-5,6-dihydropyrimidin-4(3H)-one



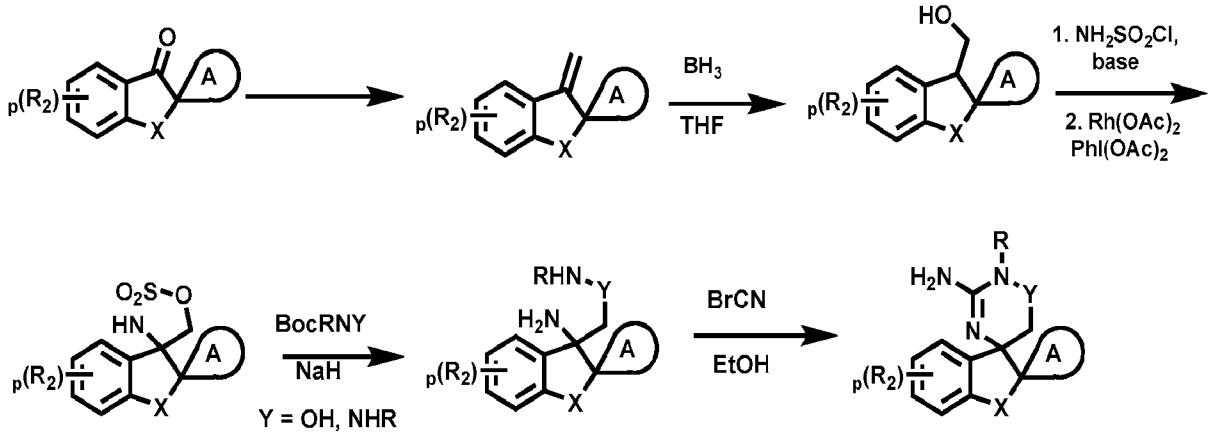
The intermediate ketone A can be condensed with t-butyl sulfonylamine or any other amine such as a-methylbenzylamine under dehydrating conditions as exemplified by use of titanium alkoxide reagents or under a Dean Stark apparatus. The imine is reacted with various nucleophiles as illustrated by lithiated ethylacetate. The deprotection of t-butyl sulfonamide is achieved by reacting with acids such as HCl in protic solvents such as methanol etc. The amino ester intermediate product is then condensed with thiophosgene or its equivalent reagent to convert the amino ester to the thioisocyanate ester. Condensation of thioisocyanate intermediate with various primary/secondary amines yielded thiodihydropyrimidinone. The thiodiydropyrimidnone can be converted to 2-amino dihydropyrimidinone by utilizing methods as described in method 2b.

Scheme 2d Synthesis of 5,6-dihydro-4H-1,3-oxazin-2-amine



The imine intermediate form above example can also be reacted with carbon neucleophiles such as allylmagnesium bromide to yield sulfonamide. The olefin is subsequently oxidized to aldehyde by ozonolysis or any of its equivalent protocol. The alcohol is obtained from the reaction of aldehyde with reducing agents such as sodium borohydride or utilizing Grignard reagents to yield primary or secondary alcohols. The resulting amino alcohol can be reacted with cyanogen bromide in protic solvents at room temperature to yield 5,6-dihydro-4H-1,3-oxazin-2-amine derivatives.

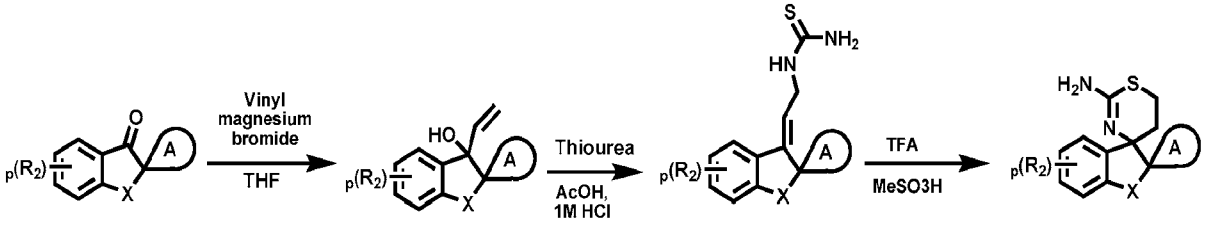
Scheme 2e. Synthesis of 5,6-dihydro-2H-1,2,4-oxadiazin-3-amine or 1,2,5,6-tetrahydro-1,2,4-triazin-3-amine



The ketone intermediate A can be converted to an olefin by utilizing the Wittig reaction or any derivation thereof or by other known literature methods. The olefin is hydroborated with borane or equivalent thereof in aprotic solvents such as THF, DCM, diethyl ether etc. at room temperature. The alcohol is condensed with sulfamoyl

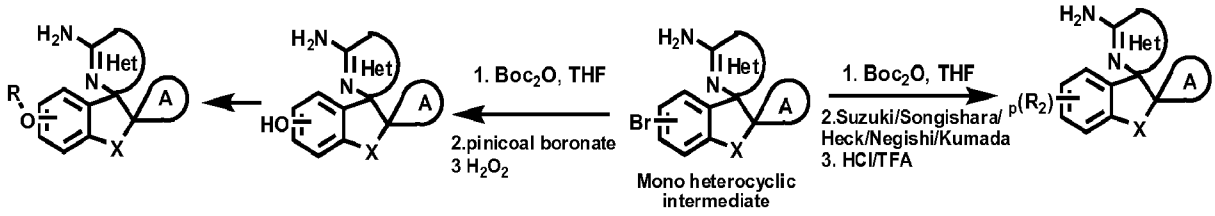
chloride in presence of base such as NMM, TEA in solvents such as DCM at room temperature. The cyclization of the methylsulfamate can be affected by rhodium catalyst in presence of oxidizing agent such as phenyliodoacetate in solvents such as toluene, acetonitrile, dichloromethane at room temperature to refluxing temperature of the solvent. The cyclic sulfamate is then activated towards neuclophillic attack by reacting with chloroformates followed by addition of a nucleophile such as alkoxide as illustrated by boc protected-N-substituted hydroxyl amine. The protecting group such as t-butyl carbamate can be removed and the resulting amino alcohol condensed with cyanogen bromide in solvents such as ethanol to yield 2,4-oxadiazin-3-amine or 1,2,5,6-tetrahydro-1,2,4-triazin-3-amine heterocycles.

Scheme 2f. Synthesis of 5,6-dihydro-4H-1,3-thiazin-2-amine



The ketone intermediate A is reacted with a vinyl magnesium derivative or substituted vinyl lithium at room temperature in solvents such as THF, ether, toluene or in hexane to yield a vinylic alcohol. The vinylic alcohol undergoes electrophilic substitution under acidic conditions (such as AcOH/1M HCl or $MeSO_3H$) in presence of thiourea to yield a vinylogous thiourea derivative. This intermediate can be cyclized to 1, 3 thiazine-2-amine when exposed to strong acidic conditions as in TFA/$MeSO_3H$ at room temperature overnight.

Scheme 3. Elaboration of monoheteocyclic intermediate



The monoheterocyclic intermediate A containing halogens on the benzene ring can be further elaborated by known organic transformations such as Suzuki couplings of boronates or trifluorborates or with pinacol boronates using various palladium catalyst such as $Pd[P(Ph_3)_3]$ or $Pd(dppf)_2Cl_2$ or any such similar catalyst in presence of inorganic bases such as K_2CO_3, $CsCO_3$ in variety of solvents either as single solvent or as combination comprising of Toluene, DMF, Ethanol, water etc. at temperature ranging from 50-100 °C. One can utilize copper mediated Sonogashira coupling to introduce alkyne substituent's on the scaffold. Alternatively one can utilize additional transition metal chemistry to introduce alkyne, alkenes, aryls, heterocycles and additional functional groups. Number of such chemical transformations are exemplified in following references: Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, by Beller and Bolm, 2nd Edition by Wiley-VCH, 2002 and in Modern Arylation Methods by Lutz Ackermann, 1st edition, 2009.

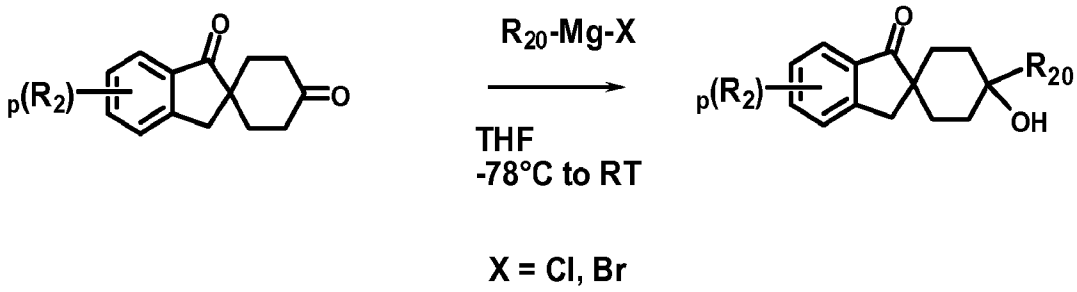
For example, the amino heterocycle of the bromo intermediate is protected as its Boc derivative utilizing Boc anhydride in solvents such as THF, DCM at room temperature. This allows conversion of the bromo to the corresponding pinacolboronate derivative as described in literature. Peroxide oxidation of the pinacolboronate to yield the alcohol is then an available option. The alcohol can be further alkylated with various alkyl/cycloalkyl/heteroalkyl halides in presence of bases such as Cs_2CO_3, KOtBu or TEA in solvents such as DMF or dioxane. In addition the alcohol can be arylated under variety of coupling conditions to yield aryl/heteroaryl ethers. The Boc group is further deprotected to yield final compound.

Scheme 4. Synthesis of key intermediate with ring A being cyclohexyl group substituted with -OR_5



Exemplary reagents and reaction conditions are described in Example 410G.

Scheme 5. Synthesis of key intermediate with ring A being cyclohexyl group substituted with -OH



Suitable reagents and reaction conditions for Grignard reaction can be used for the reaction depicted in Scheme. Exemplary reagents and reaction conditions are described in Example 410I.

In cases where the synthetic intermediates and final products of Formula (A), (I') or (I) described below contain potentially reactive functional groups, for example amino, hydroxy, thiol and carboxylic acid groups, that may interfere with the desired reaction, it may be advantageous to employ protected forms of the intermediate. Methods for the selection, introduction and subsequent removal of protecting groups are well known to those skilled in the art. (T.W. Greene and P. G. M. Wuts "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc., New York 1999). Such protecting group manipulations are assumed in the discussion below and not usually described explicitly. Generally, reagents in the reaction schemes are used in equimolar

amounts; however, in certain cases it may be desirable to use an excess of one reagent to drive a reaction to completion. This is especially the case when the excess reagent can be readily removed by evaporation or extraction. Bases employed to neutralize HCl in reaction mixtures are generally used in slight to substantial excess (1.05 – 5 equivalents).

Abbreviation	***Meaning***
AcCl	acetyl chloride
ACN or CH_3CN	acetonitrile
$AlCl_3$	aluminum chloride
Ar	argon
B_2H_6	diborane
Boc	*tert*-butoxy carbonyl or *t*-butoxy carbonyl
borax	sodium borate
brine	saturated aqueous NaCl
CH	cyclohexane
CH_2N_2	carbodiimide
Cs_2CO_3	cesium carbonate
CuBr-SMe_2	cuprous bromide methylsulfide complex
CuI	cuprous iodide
d	days
DCM or CH_2Cl_2	methylene chloride
DEA	diethylamine
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
EtI	ethyl iodide
Et	ethyl
Et_2O	ethyl ether
EtOAc or EA	ethyl acetate

EtOH	ethanol
$Et_3O^+BF_4^-$	triethyloxonium tetrafluoroborate
h or hr	hour
HCl	hydrochloric acid
H_2O	water
H_2O_2	hydrogen peroxide
$HCONH_2$	formamide
HMPA	hexamethylphosphoric triamide
HOAc or AcOH	acetic acid
HPLC	high performance liquid chromatography
HPLC-MS	High performance liquid chromatography with mass detection
K_2CO_3	potassium carbonate
KCN	potassium cyanide
LAH	$LiAlH_4$ = lithium aluminium hydride
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide
LC-MS	Liquid chromatography with mass detection
LDA	lithium diisopropylamide
min	minute
MeOH	methanol
MeI	methyl iodide
Me	methyl
MeNHOH	methylhydroxylamine
MPLC	Medium pressure liquid chromatography
MTBA	4-(methylthio)benzoic acid
Me_2S	methyl sulfide
NaOH	sodium hydroxid

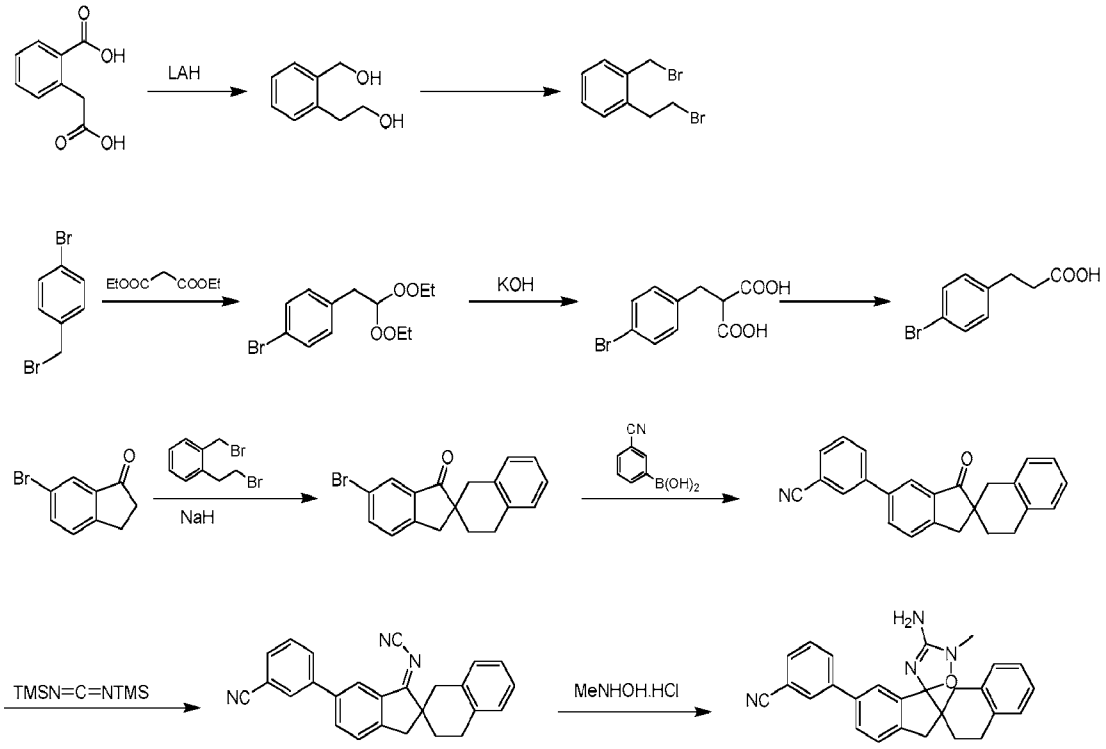
NaOMe	sodium methoxide
$Na_2S_2O_3$	sodium thiosulfate
Na_2SO_4	sodium sulfate
NHMDS	Sodium bis(trimethylsilyl)amide
NH_4OH	ammonium hydroxide
$(NH_4)_2CO_3$	ammonium carbonate
NH_4I	ammonium iodide
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaH	sodium hydride
$PdCl_2dppf$	[1,1-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd(OH)_2$	palladium hydroxide
$Pd(PPh_3)_2Cl_2$	bis(triphenylphosphine)palladium (II) dichloride
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PrBr	propyl bromide
PBr_3	phosphorous tribromide
PCC	pyridinium chlorochromate
PE	petroleum ether
PPA	polyphosphoric acid
PPh_3	triphenyl phosphine
RF	heated to reflux
Rt	Retention time
RT or r.t.	room temperature
Selectfluor™	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
$SOCl_2$	thionyl chloride
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
$TiCl_4$	titanium chloride
TMSCl	trimethylsilyl chloride
Triton B	Benzyltrimethylammonium hydroxinde in water

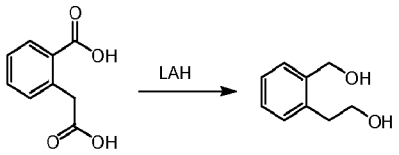
Compounds of the invention can be prepared employing conventional methods that utilize readily available reagents and starting materials. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. Representative compounds of the present invention can be prepared using the following synthetic schemes.

SYNTHETIC METHODS

Example 1. Preparation of 3-(spiro[spiro[2,3-dihydro-indene-2,2'-tetrahydronaphthalene]-1,5'-(3-amino-2-methyl-2*H*-[1,2,4]oxadiazole)]-6-yl)benzonitrile (compound 45)

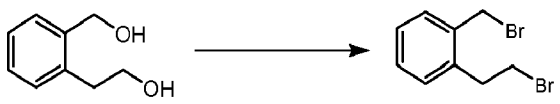


Experimental data:



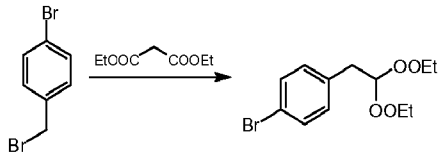
Step 1. 2-(2-(hydroxymethyl)phenyl)ethanol

To a solution of 2-(carboxymethyl)benzoic acid (9 g, 0.05 mol) in THF (200 mL) was added to LAH in THF (250 mL) dropwise, the mixture was refluxed for 18 hours. The mixture was cooled in ice bath and carefully added water dropwise, followed by 50% NaOH (150 mL), then removed the ice bath and added water slowly with stirring until the gray precipitate turns white. The mixture was filtrated and the filtrate was concentrated to give crude 2-(2-(hdroxymethyl)phenyl)ethanol (6 g, 80%).



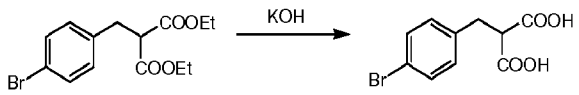
Step 2. 1-(2-Bromoethyl)-2-(bromomethyl)benzene

To a solution of 2-(2-(hydroxymethyl)phenyl)ethanol (2.6 g, 17 mmol), perbromo methane (13.7 g, 41.8 mmol) in DCM (100 mL) was added triphenylphosphine (10.95 g, 41.8 mmol) at 0 ℃, the mixture was stirred at room temperature for 18 hours. The mixture was concentrated, redissolved by Et_2O, filtered, the organic layer was concentrated to give crude 1-(2-bromoethyl)-2-(bromomethyl)benzene (4.2 g, 89%). **^{1}H-NMR** (CD_3OD): 3.69 (m, 2H), 4.05 (m, 2H), 4.97 (m, 2H), 7.64-7.77 (m, 4H).



Step 3. Diethyl 2-(4-bromobenzyl)malonate

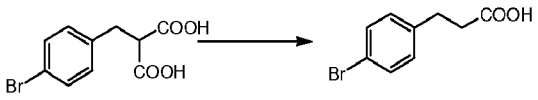
To a solution of CH_3CH_2OH (240 mL) was added Na (5.82 g, 0.25 mol), the mixture was stirred until Na was disappeared, then 1-bromo-4-bromomethyl-benzenein (37.35 g, 0.15 mol), malonic acid diethyl ester(78 g, 0.49 mol) was added slowly, the mixture was refluxed overnight. The solvent was removed in *vacuo*, the residue was dissolved with H_2O, extracted with ether, the organic layer was washed with 0.5N HCl aqueous, then washed with brine, dried over Na_2SO_4, concentrated to give diethyl 2-(4-bromobenzyl)malonate (40 g, 85%).



Step 4. 2-(4-Bromobenzyl)malonic acid

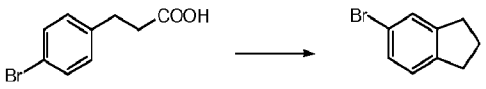
Diethyl 2-(4-bromobenzyl)malonate (40 g, 13 mmol) and KOH (42.8 g, 76 mmol) was dissolved in a mixture of HOAc-H_2O-THF (1:2:3,200 mL), the mixture was refluxed for 12 hours. The solvent was removed in *vacuo*, the residue was added HCl

aqueous ,.then extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated to give 2-(4-bromobenzyl)malonic acid (31 g, 95%).



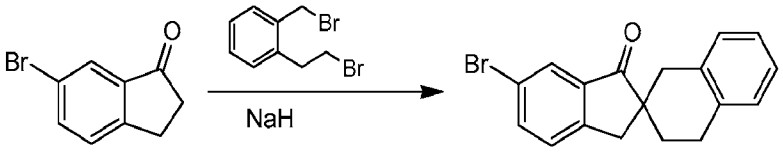
Step 5. 3-(4-Bromophenyl)propanoic acid

2-(4-Bromophenyl)malonic acid (36 g, 11 mmol) was heated at 165 ℃ until evolution of CO_2. the production was crystallized from petrol ether to give 2-(4-bromophenyl)acetic acid (26 g, 87%).



Step 6. 6-Bromo-indan-1-one

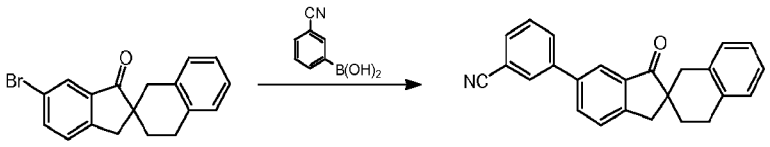
A mixture of 3-(4-bromophenyl)propanoic acid (26 g, 12 mmol) in $SOCl_2$ (50 mL) was refluxed overnight, the mixture was concentrated, then added to $AlCl_3$ (80 g, 61 mmol) in DCM (100 mL), the mixture was stirred at room temperature overnight. The mixture was quenched with HCl aqueous, extracted with DCM, washed with brine, dried over Na_2SO_4, concentrated to give 6-bromo-indan-1-one (12 g, 48%). **^{1}H-NMR** (CD_3OD): 2.65 (m, 2H), 3.06 (m, 2H), 7.31 (m, 1H), 7.62 (m, 1H), 7.80 (m, 1H).



Step 7. 6-Bromo-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one

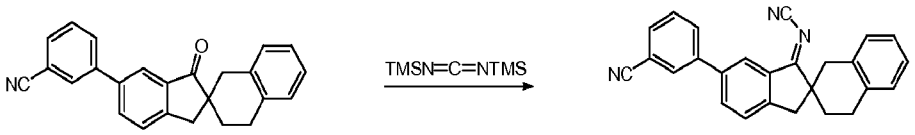
A mixture of 6-bromo-indan-1-one (3.57 g, 17 mmol), 1-(2-bromo-ethyl)-2-bromomethyl-benzene (4.7 g, 17 mmol) in THF (50 mL) was added NaH (816 mg, 34 mmol) at room temperature, the mixture was refluxed for 2 hours. The mixture was quenched with water, concentrated, then extracted with DCM, washed with brine, dried

over Na_2SO_4, concentrated to 6-bromo-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one (1.8 g, 33%).



Step 8. 3-(1-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'-naphthalene]-6-yl) benzonitrile

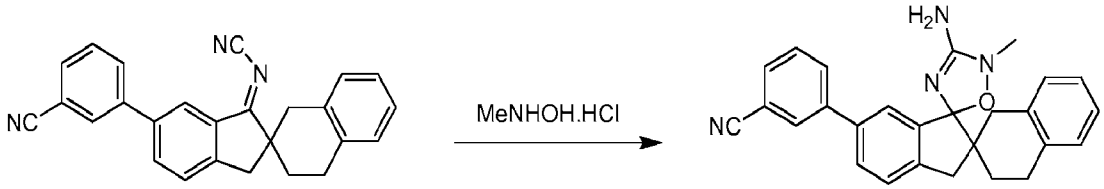
6-Bromo-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one (163 mg, 0.5 mmol), 3-cyanophenylboronic acid (147 g, 1 mmol) in [1,4]-dioxane (12 mL), Cs_2CO_3 (2 N, 3.2 mL), then $Pd(PPh_3)_2Cl_2$ (5 mg, 0.01 mmol) was added under Ar_2, the mixture was refluxed for 30 minutes. The reaction mixture was concentrated in *vacuo* to give the residue, which was purified by TLC to give 3-(1-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'- naphthalene]-6-yl)benzonitrile (35 mg, 6%).



Step 9. (*Z*)-*N*-(5-(3-cyanophenyl)-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*) -ylidene)cyanamide

To a solution of 3-(1-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'-naphthalene]-6- yl)benzonitrile (35 mg, 0.1 mmol) in DCM (5 mL) was added $TiCl_4$ (76 mg, 0.4 mmol) dropwise, the mixture was stirred at 50 ℃ at Ar_2 under microwave for 5 minutes, *N*,*N*'-methanediylidenebis(1,1,1-trimethylsilanamine) (74 mg, 0.4 mmol) was added dropwise. The mixture was stirred at 60 ℃ at Ar_2 under microwave for 10 minutes and poured into ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2, which was combined with the organic layer. The organic layer was dried and

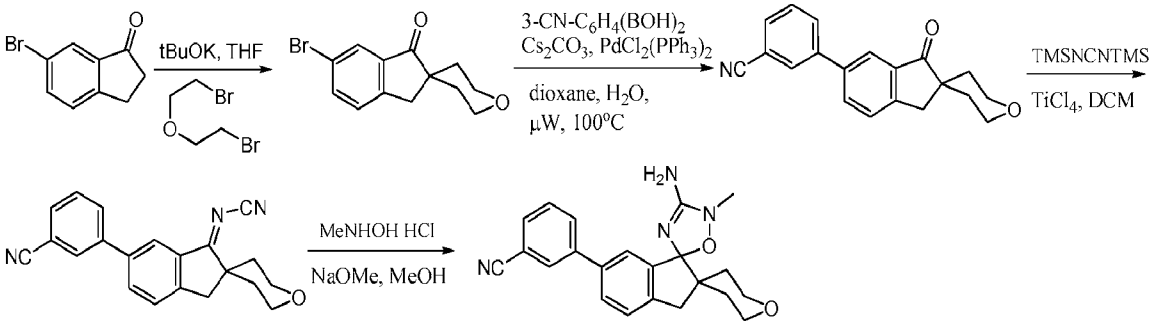
concentrated to give crude (*Z*)-*N*-(5-(3-cyanophenyl)-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)–ylidene)cyanamide (50 mg, 93%).



Step 10. **Compound 45**

To a solution of *N*-methyl-hydroxylamine hydrochloride (11. mg, 0.134 mmol) in MeOH (5 mL) was added MeONa (0.026 mL, 25% (Wt.) in MeOH), followed by (*Z*)-*N*-(5-(3-cyanophenyl)-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)–ylidene)cyanamide (50 mg, 0.13 mmol). After stirred for 10 minutes, the solvent was removed in *vacuo*. The crude product was purified by preparative HPLC to give the title compound as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.05 (m, 1H), 7.99 (m, 2H), 7.84 (m, 1H), 7.79-7.62 (m, 4H), 7.66 (m, 1H), 7.43 (m, 1H), 7.18-7.07 (m, 2H), 3.34 (s, 3H); MS ESI +ve m/z 421 $(M+H)^+$.

Example 2. Preparation of 3-(spiro[spiro[2,3-dihydro-indene-2,1'-(4-oxacyclohexane)]-1,5'-(3-amino-2-methyl-2*H*-[1,2,4]oxadiazole)]-6-yl)benzonitrile (compound 51)



Step 1: Preparation of 6-bromo-2',3',5',6'-tetrahydrospiro[indene-2,4'-pyran]-1(3H)-one

To a solution of 6-bromo-1-indanone (1.033 g, 4.89 mmol) in anhydrous THF (100 mL) under N_2 atmosphere at room temperature was added a solution of tBuOK in tBuOH (1 M, 10.3 mL, 10.3 mmol) within 30 min (the color turned to deep black upon a drop of tBuOK solution was added), followed by 1-bromo-2-(2-bromoethoxy)ethane (1.134 g, 0.62 mL, 4.89 mmol). The reaction was quenched with saturated aqueous NH_4Cl, and extracted with ether two times. The combined organic phases were washed with H_2O, brine, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to give black tar. It was purified by flash chromatography on silica gel yield 300 mg of the desired product. MS ESI +ve m/z 281 $(M+H)^+$.

Step 2: Preparation of 3-(1-oxo-1,2',3,3',5',6'-hexahydrospiro[indene-2,4'-pyran]-6-yl)benzonitrile

To a 10 mL CEM microwave test tube was charged with Cs_2CO_3 (232 mg, 0.712 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), 6-bromo-2',3',5',6'-tetrahydrospiro[indene-2,4'-pyran]-1(3H)-one (100 mg, 0.356 mmol), 3-cyanophenylboronic acid (78 mg, 0.534 mmol), dioxane (4 mL) and H_2O (0.4 mL), the system was swept with N_2 and capped, and heated in a CEM microwave reactor at 100°C for 10 min. The reaction mixture was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with EA in hexane (0-30%) to give 42 mg of 3-(1-oxo-1,2',3,3',5',6'-hexahydrospiro[indene-2,4'-pyran]-6-yl)benzonitrile. MS ESI +ve m/z 304 $(M+H)^+$.

Step 3: Preparation of N-(5-(3-cyanophenyl)-2',3',5',6'-tetrahydrospiro[indene-2,4'-pyran]-3(1H)-ylidene)cyanamide

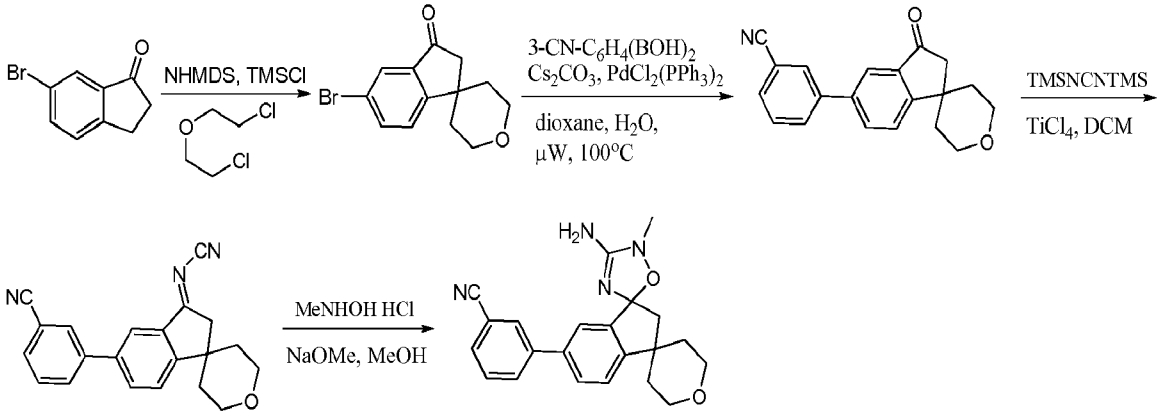
To a solution of 3-(1-oxo-1,2',3,3',5',6'-hexahydrospiro[indene-2,4'-pyran]-6-yl)benzonitrile (42 mg, 0.139 mmol) in anhydrous DCM (10 mL) under N_2 atmosphere was added 1 M $TiCl_4$ (in DCM, 0.28 mL, 0.28 mmol) dropwise within 15 min at room temperature. It was stirred another 1 h after the addition. To this mixture was added Bis-trimethylsilylcarbodiimide (0.1 mL, 0.427 mmol) dropwise. The resulting mixture was stirred overnight. The reaction mixture was quenched with ice-water (20 g), and stirred for 20 min, then it was transferred to a separating funnel, the separated aqueous phase

was extracted 2 times with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered, and concentrated to give 44 mg of *N*-(5-(3-cyanophenyl)-2',3',5',6'-tetrahydrospiro[indene-2,4'-pyran]-3(1H)-ylidene)cyanamide as light brown solid which was used for next step without further purification. MS ESI +ve m/z 328 $(M+H)^+$.

Step 4: 3-(spiro[spiro[2,3-dihydro-indene-2,1'-(4-oxacyclohexane)]-1,5'-(3-amino-2-methyl-2H-[1,2,4]oxadiazole)]-6-yl)benzonitrile

To a suspension of the crude product obtained from previous step in MeOH (5 mL) was added a solution of *N*-methylhydroxylamine in MeOH (0.373 M, 0.40 mL, prepared from *N*-methylhydroxylamine HCl salt and 0.9 eq 25wt% NaOMe/MeOH in MeOH). The mixture was stirred at room temperature for 20 min, followed by adding another portion of *N*-methylhydroxylamine in MeOH (0.373 M, 1 mL). Solvent was removed under reduced pressure after stirred another 20 min. The residue was purified by preparative PHLC to yield 16.5 mg of the title compound as TFA salt. ^1H NMR (400 MHz, CD_3OD) δ: 8.02-7.90 (m, 3H), 7.79-7.62 (m, 3H), 7.48 (d, J = 7.6 Hz, 1H), 4.05-3.92 (m, 2H), 3.72-3.60 (m, 2H), 3.37(s, 3H), 3.21 (d, J = 16.0 Hz, 1H), 3.11 (d, J = 16.0 Hz, 1H), 1.99 (td, J = 13.2, 4.8 Hz, 1H), 1.86 (td, J = 13.2, 4.8 Hz, 1H), 1.56 (m, 1H), 1.28 (dd, J = 13.2, 2.4 Hz, 1H); MS ESI +ve m/z 375 $(M+H)^+$.

Example 3 Preparation of 3-(spiro[spiro[2,3-dihydro-indene-3,1'-(4-oxacyclohexane)]-1,5'-(3-amino-2-methyl-2*H*-[1,2,4]oxadiazole)]-6-yl)benzonitrile (compound 69)



Step 1: Preparation of 5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3(2H)-one

To a solution of 6-bromo-1-indanone (0.50 g, 2.35 mmol) in anhydrous THF (40 mL) under N_2 atmosphere at -78°C was added a solution of NHMDS (1 M in THF, 2.5 mL, 2.5 mmol) within 30 min, followed by TMSCl (0.281 g, 0.327 mL2.59 mmol) after stirred 30 min. To this reaction mixture was added NHMDS (1 M in THF, 6.0 mL, 6.0 mmol) within 30 min at this temperature. The temperature was allowed to warm to -30 to -20°C, after stirred another 30 min, 2,2-eichlorodiethyl ether (336 mg, 0.275 mL, 2.35 mmol) was added. Then the reaction temperature was allowed to warm to room temperature without removing cooling bath, and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with EA two times. The combined organic phases were washed with 1 M HCl, H_2O, brine successively, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to give black oil. It was purified by flash chromatography on silica gel yield 103 mg of the desired product. MS ESI +ve m/z 281 $(M+H)^+$.

Step 2: 3-(3-oxo-2,2',3,3',5',6'-hexahydrospiro[indene-1,4'-pyran]-5-yl)benzonitrile

To a 10 mL CEM microwave test tube was charged with Cs_2CO_3 (147 mg, 0.45 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), 5-bromo-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3(2H)-one (51 mg, 0.18 mmol), 3-cyanophenylboronic acid (35 mg, 0.24 mmol), dioxane (3 mL) and H_2O (0.1 mL), the system was swept with N_2 and capped, and heated in a CEM microwave reactor at 100°C for 10 min. The reaction mixture was

diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with EA in hexane (0-30%) to give 42 mg of 3-(3-oxo-2,2',3,3',5',6'-hexahydrospiro[indene-1,4'-pyran]-5-yl)benzonitrile as white solid. MS ESI +ve m/z 304 $(M+H)^+$.

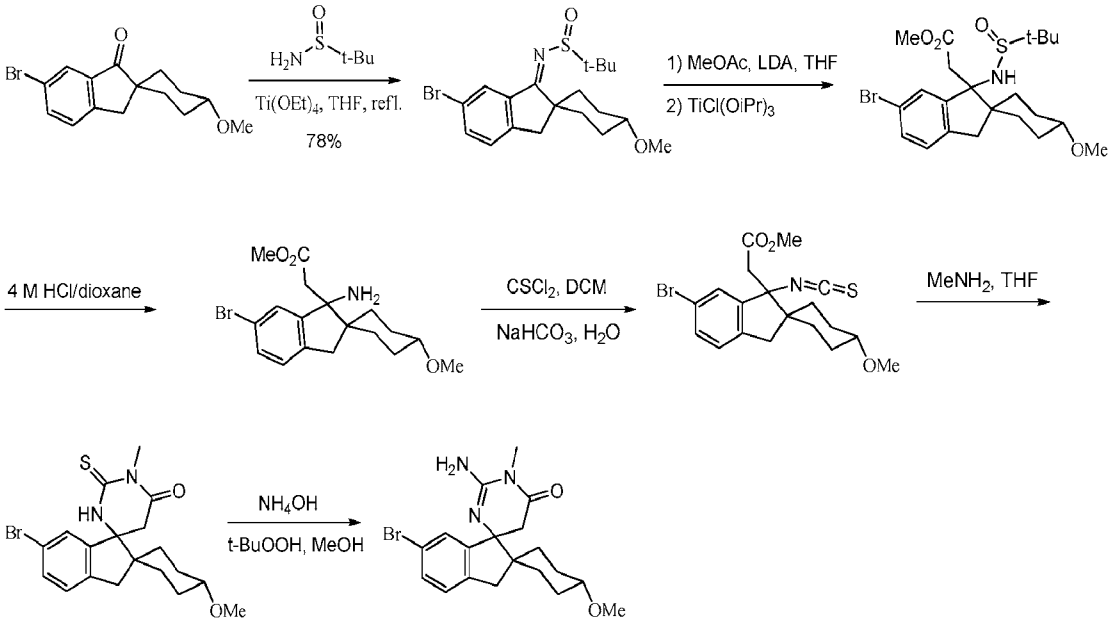
Step 3: Preparation of N-(5-(3-cyanophenyl)-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3(2H)-ylidene)cyanamide

To a solution of 3-(3-oxo-2,2',3,3',5',6'-hexahydrospiro[indene-1,4'-pyran]-5-yl)benzonitrile (42 mg, 0.139 mmol) in anhydrous DCM (10 mL) under N_2 atmosphere was added 1 M $TiCl_4$ (in DCM, 0.28 mL, 0.28 mmol) dropwise within 15 min at room temperature. It was stirred another 1 h after the addition. To this mixture was added Bis-trimethylsilylcarbodiimide (0.1 mL, 0.427 mmol) dropwise. The resulting mixture was stirred overnight. The reaction mixture was quenched with ice-water (15 g), and stirred for 30 min, then it was transferred to a separating funnel, the separated aqueous phase was extracted 2 times with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered, and concentrated to give the desired product as white solid, which was used for next step without further purification. MS ESI +ve m/z 328 $(M+H)^+$.

Step 4: Preparation of 3-(spiro[spiro[2,3-dihydro-indene-3,1'-(4-oxacyclohexane)]-1,5'-(3-amino-2-methyl-2H-[1,2,4]oxadiazole)]-6-yl)benzonitrile

To s suspension of the crude product obtained from previous step in MeOH (6 mL) was added a solution of *N*-methylhydroxylamine in MeOH (prepared from *N*-methylhydroxylamine HCl salt (13 mg, 0.153 mmol) inanhydrous MeOH (4 mL) and 25wt% NaOMe/MeOH (31 μL, 0.138 mmol), stirred 5 min). The mixture was stirred at room temperature for 60 min. Solvent was removed under reduced pressure. The residue was purified by preparative PHLC to yield 2.1 mg of the title compound as TFA salt. ^1H NMR (400 MHz, CD_3OD) δ: 8.14-7.84 (m, 4H), 7.74 (m, 1H), 7.65 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 4.06-3.96 (m, 2H), 3.74-3.59 (m, 2H), 3.39 (s, 3H), 2.34-1.48 (m, 6H); MS ESI +ve m/z 375 $(M+H)^+$.

Example 4. Preparation of 2''-amino-6-bromo-1'''-methyl-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''*H*)-one (compound 64)



Step 1: Preparation of N-(trans-5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)-2-methylpropane-2-sulfinamide

To a solution of *trans*-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (923 mg, 2.99 mmol) and 2-methyl-2-propane sulfonamide (1.450 g, 11.96 mmol) in anhydrous THF (75 mL) was added $Ti(OEt)_4$ (5.46 g, 4.96 mL, 23.92 mmol). The resulting mixture heated to reflux for 24 h. To this reaction mixture was added 2-methyl-2-propane sulfonamide (0.725 g, 5.98mmol) and $Ti(OEt)_4$ (2.73 g, 2.48 mL, 11.96 mmol), then reflux another 14 h. After this period of time, 2-methyl-2-propane sulfonamide (0.725 g, 5.98mmol) and $Ti(OEt)_4$ (2.73 g, 2.48 mL, 11.96 mmol) was added, the mixture was refluxed for another 48h. The reaction mixture was cooled to room temperature and quenched with brine (3 mL), and stirred vigorously for 30 min. The mixture was filtered through a pad of Celite®, and washed with ethyl acetate (50 mL). The filtrate was concentrated, and the residue was dissolved in DCM, filtered again. The filtrated was concentrated, the residue was purified by flash chromatography

on silica gel to afford 0.968 g of the desired product as a light yellow solid. MS ESI +ve m/z 412 $(M+H)^+$

Step 2: Preparation of methyl 2-(trans-6'-bromo-1'-(1,1-dimethylethylsulfinamido)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)acetate

To a flame dried 50 mL of round bottom flask was charged with of methyl acetate (0.088 mL, 1.11 mmol) and anhydrous THF (10 mL) under N_2 atmosphere. The solution was cooled to -78°C with stirring, 2 M LDA solution in THF (0.551 mL, 1.112 mmol) was added dropwise. The mixture was stirred for another 30 min at the same temperature after the addition. To this mixture was added 1 M solution of $TiCl(OiPr)_3$ in hexane (1.2 mL, 1.2 mmol) dropwise, then stirred another 30 min at -78°C. To this mixture was added a solution of *N*-(*trans*-5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)-2-methylpropane-2-sulfinamide (227.6 mg, 0.55 mmol) in anhydrous THF (10 mL) dropwise within 30 min. The reaction mixture was stirred another 1 h at -78°C. LC-MS shows 10% conversion. Keep this temperature and stirred another 2 h, no improvement in conversion.

In another flame dried 50 mL round bottom, enolate anion was prepared again using the same procedure with bigger scale and higher concentration: methyl acetate (0.44 mL, 1.11 mmol) in anhydrous THF (4 mL); 2 M LDA solution in THF (2.77 mL, 5.55 mmol); 1 M solution of $TiCl(OiPr)_3$ in hexane (6.1 mL, 6.1 mmol). Part of this enolate anion solution (6 mL) was transferred to above reaction flask with a syringe quickly. 70% conversion was achieved after 30 min. More of this Enolate anion solution (2 mL) was added to the reaction system in the same maner. The reaction was quenched after stirred another 30 min. 85% conversion was achieved at this point. The reaction mixture was filtered through a pad of Celite, and washed with EA. The separated aqueous phase was extracted with EA once. The combined organic phases were washed with brine, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to dryness. The residue was purified by flash chromatography on silica gel to yield 210 mg of the desired product as white foam. MS ESI +ve m/z 486 $(M+H)^+$.

Step 3: Preparation of methyl 2-(trans-1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)acetate

The solution of methyl 2-(*trans*-6'-bromo-1'-(1,1-dimethylethylsulfinamido)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)acetate (190 mg, 0.89 mmol) in MeOH (4 mL) and 4 M HCl solution in 1,4-dioxane (8 mL) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to give the desired HCl salt as a white foam. It was used for next step without further purification. MS ESI +ve m/z 382 $(M+H)^+$.

Step 4: Preparation of methyl 2-(trans-6'-bromo-1'-isothiocyanato-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)acetate

Above crude product was added to a solution of $NaHCO_3$ (328 mg, 3.9 mmol) in H_2O (10 mL) and DCM (1 mL) which was chilled at °C, to this stirred mixture was added thiophosgene (33 μL, 49.5 mg, 0.93 mmol) and stirred for 1 h at °C. Thiophosgene (22 μL, 33 mg, 0.62 mmol) was added to the reaction and stirred another 30 min. The reaction was diluted with DCM and brine, and the separated organic phase was washed with saturated brine and dried over anhydrous Na_2SO_4, and filtered, and concentrated to produce the desired product as oil. It is used for next step without further purification. MS ESI +ve m/z 365 $(M-NCS)^+$.

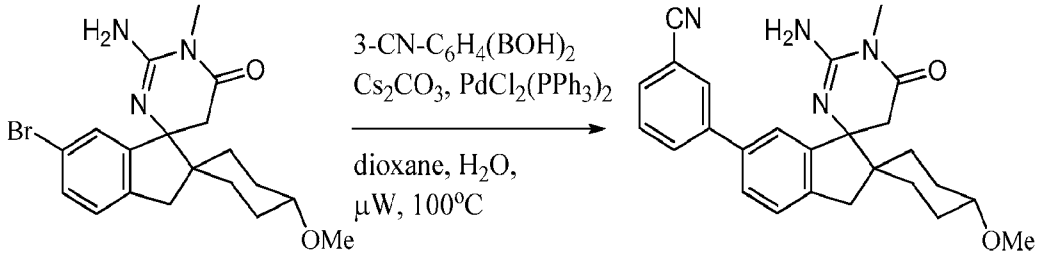
Step 5: Preparation of 6-bromo-1'''-methyl-2''-thioxo-2'',3''-dihydro-1''H-spiro[spiro[2,3-dihydro-indene-2,1'-(trans-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''H)-one

To a solution of above crude product in DCM (3 mL) was added a solution of 2 M $MeNH_2$ in THF (3 mL). The mixture was stirred for 20 min at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in DCM (2 mL) and hexane (2 mL) and evaporated to afford 179 mg of crude product as off-white solid. This product was used for next without further purification. MS ESI +ve m/z 423 $(M+H)^+$.

Step 6: Preparation of 2"-amino-6-bromo-1'"-methyl-1"H-spiro[spiro[2,3-dihydro-indene-2,1'-(trans-4-methoxycyclohexane)]-1,4'-pyrimidin]-6"(5"H)-one

To a solution of above crude product in MeOH (9 mL) was added concentrated aqueous NH_4OH (4.5 mL), followed by *tert*-butyl hydroperoxide solution (ca. 5.5 M in nonane, 1 mL). The resulting suspension was stirred overnight. The resulting clear solution was concentrated in vacuum to produc the crude product. 10 mg of the crude product was purified through preparative HPLC to give the desired product as TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.54 (d, J = 1.6, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 3.20-3.07 (m, 3H), 3.01 (d, J = 16.8 Hz, 1H), 2.83 (d, J = 16.8 Hz, 1H), 2.03 (m, 2H), 1.74 (m, 1H), 1.44-1.27 (m, 5H); MS ESI +ve m/z 406 $(M+H)^+$.

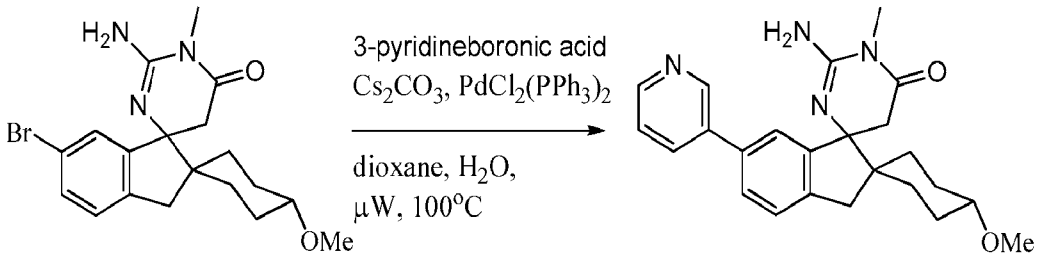
Example 5. Preparation of 3-(2"-amino-1'"-methyl-6"-oxo-5",6"-dihydro-1"*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidine]-6-yl)benzonitrile (compound 58)



To a solution of crude product of 2"-amino-6-bromo-1'"-methyl-1"*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6"(5"*H*)-one (15 mg, purity 70%, 0.026 mmol), 3-cyanophenylboronic acid (8 mg, 0.055 mmol) and Cs_2CO_3 (40 mg, 0.12 mmol) in 1,4-dioxane (2.5 mL) and H_2O (0.2 mL) charged in a 10 mL CEM microwave test tube was added $PdCl_2(PPh_3)_2$ (3 mg, 0.004 mmol), then the system was degassed by sweeping N_2. The tube was sealed and heated to 110°C for 10 min in a CEM microwave reactor. Solvent was removed in vacuum and the residue was purified by preparative HPLC to yield 4 mg of the desired product as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.00 (d, J = 1.6 Hz, 1H), 7.95

(m, 1H), 7.71 (m, 1H), 7.66-7.61 (m, 3H), 7.42 (d, J = 8.4, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.21-3.17 (m, 3H), 3.10 (d, J = 16.8 Hz, 1H), 2.93 (d, J = 16.8 Hz, 1H), 2.04 (m, 2H), 1.79 (m, 1H), 1.48-1.31 (m, 5H); MS ESI +ve m/z 429 $(M+H)^+$.

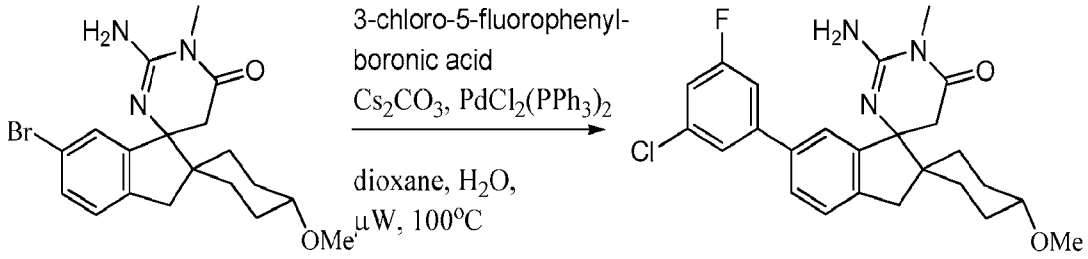
Example 6. Preparation of 2''-amino-1'''-methyl-6-(pyridin-3-yl)-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''*H*)-one (compound 59)



To a solution of crude product of 2''-amino-6-bromo-1'''-methyl-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''H)-one (25 mg, purity 70%, 0.043 mmol), 3-pyridineboronic acid (10 mg, 0.08 mmol) and Cs_2CO_3 (40 mg, 0.12 mmol) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) charged in a 10 mL CEM microwave test tube was added $PdCl_2(PPh_3)_2$ (4 mg, 0.005 mmol), then the system was degassed by sweeping N_2. The tube was sealed and heated to 110°C for 10 min in a CEM microwave reactor. Solvent was removed in vacuum and the residue was purified by preparative HPLC to yield 7 mg of the desired product as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 9.14 (s, 1H), 8.82 (m, 2H), 8.10 (dd, J = 8.0, 1.6 Hz, 1H), 7.80 (s, 1H), 7.77 (dd, J = 9.2, 1.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.25-3.17 (m, 3H), 3.08 (d, J = 17.2 Hz, 1H), 2.96 (d, J = 17.2 Hz, 1H), 2.05 (m, 2H), 1.81 (dd, J = 12.0, 2.8 Hz, 1H), 1.50-1.28 (m, 5H); MS ESI +ve m/z 405 $(M+H)^+$.

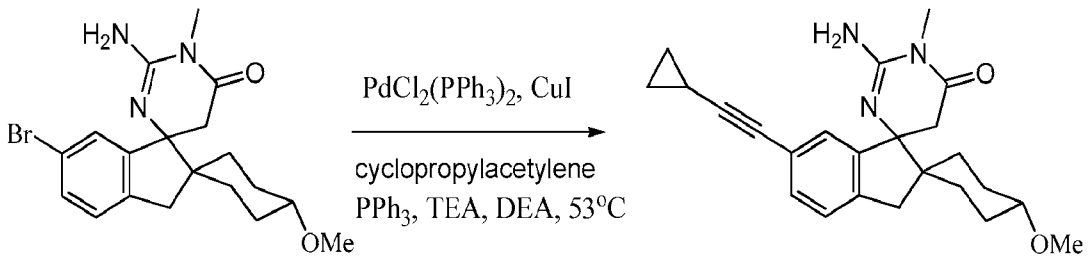
Example 7. Preparation of 2''-amino-1'''-methyl-6-(3-chloro-5-fluorophenyl)-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-

pyrimidin]-6''(5''*H*)-one (Compound 42)



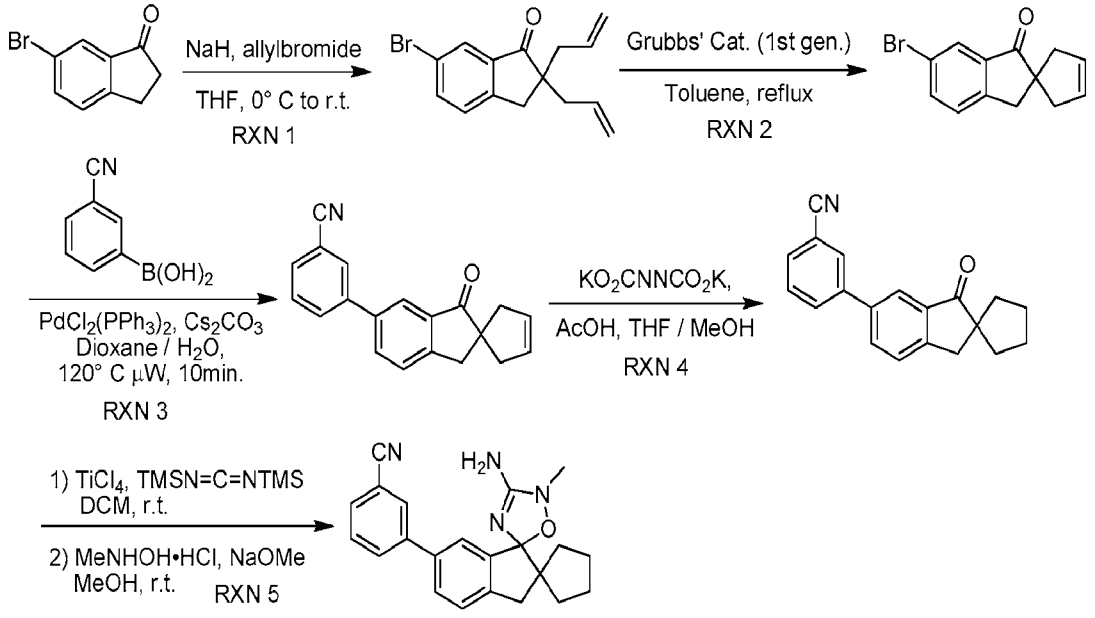
To a solution of crude product of 2''-amino-6-bromo-1'''-methyl-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''H)-one (25 mg, purity 70%, 0.043 mmol), 3-chloro-5-fluorophenylboronic acid (13 mg, 0.07 mmol) and Cs_2CO_3 (40 mg, 0.12 mmol) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) charged in a 10 mL CEM microwave test tube was added $PdCl_2(PPh_3)_2$ (4 mg, 0.005 mmol), then the system was degassed by sweeping N_2. The tube was sealed and heated to 110°C for 10 min in a CEM microwave reactor. Solvent was removed in vacuum and the residue was purified by preparative HPLC to yield 6 mg of the desired product as a TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.63 (m, 2H), 7.51 (d, J = 1.6 Hz, 1H), 7.40 (m, 1H), 7.36 (m, 1H), 7.19 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.20-3.16 (m, 3H), 3.09 (d, J = 17.2 Hz, 1H), 2.92 (d, J = 16.4 Hz, 1H), 2.03 (m, 2H), 1.79 (m, 1H), 1.48-1.28 (m, 5H); MS ESI +ve m/z 456 $(M+H)^+$.

Example 8. Preparation of 2''-amino-1'''-methyl-6-(cyclopropylethynyl)-1''*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6''(5''*H*)-one (compound 55)



An oven dried 3-necked round bottom flask equipped with condenser was charged with crude product of 2"-amino-6-bromo-1'"-methyl-1"*H*-spiro[spiro[2,3-dihydro-indene-2,1'-(*trans*-4-methoxycyclohexane)]-1,4'-pyrimidin]-6"(5"H)-one (25 mg, purity 70%, 0.043 mmol), TEA (3 mL), DEA (0.3 mL) and DMF (1 mL) under N_2 atmosphere. To this solution was added CuI (5.7 mg, 0.026 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and PPh_3 (4 mg, 0.015 mmol). The system was degas once again, then cyclopropyl acetylene (0.3 mL, excess) added and the mixture was heated to 53°C (oil bath) with stirring. The reaction was evaporated after 12 h and the residue was filtered and purified by preparative HPLC to yield 3 mg of the desired product as TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.33 (s, 1H), 7.30 (dd, J = 7.6, 1.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 3.33 (s, 3H), 3.32(s, 3H), 3.21-3.07 (m, 3H), 2.99 (d, J = 17.2 Hz, 1H), 2.86 (d, J = 16.4 Hz, 1H), 2.04 (m, 2H), 1.71 (m, 1H), 1.46-1.27 (m, 6H), 0.88 (m, 2H), 0.69 (m, 2H); MS ESI +ve m/z 392 $(M+H)^+$.

Example 9. Preparation of compound 50



Step 1. Preparation of 2,2-diallyl-6-bromo-2,3-dihydro-1H-inden-1-one (RXN1)

In a heat gun dried 50 mL round bottom flask was placed 6-bromo-1-indanone (500 mg, 2.37 mmol), and it was dissolved in THF (7.9 mL). To this solution was added allylbromide (513 μL, 5.93 mmol) and the solution was cooled down to 0° C. After stirring for 5 minutes, sodium hydride (237 mg, 5.93 mmol, 60% dispersion in mineral oil) was slowly added. The reaction mixture was allowed to stir for 2 hours at 0° C, warmed to room temperature, and stirred for another 2 hours. At that time it was quenched with ethyl acetate (10 mL) and water (10 mL). The phases were separated and the aqueous phase was back-extracted twice with ethyl acetate (5 mL / each). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding the diallyl product (493 mg, 1.70 mmol, 72% yield) as a light yellow oil.

M+H = 291.4

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.85 (dd, J = 2.0, 0.4 Hz, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.30 (dd, J = 8.0, 0.4 Hz, 1H), 5.62 – 5.51 (m, 2H), 5.07 (ddd, J = 16.8, 3.2, 1.2 Hz, 2H), 4.99 (ddd, J = 10.0, 2.0, 0.8 Hz, 2H), 2.97 (s, 2H), 2.45 (m, 2H), 2.30 (m, 2H) ppm.

Step 2. Preparation of 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'H)-one (RXN2)

In a heat gun dried 50 mL round bottom flask was placed 2,2-diallyl-6-bromo-2,3-dihydro-1H-inden-1-one (95 mg, 0.328 mmol) and it was dissolved in toluene (15 mL). To this solution was added Grubbs Catalyst 1st generation (40 mg, 0.049 mmol). This solution was purged with a stream of nitrogen for 2 minutes. A condenser was attached to the flask and reaction was heated to reflux overnight (~ 14 hours). After that time, the reaction was concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12 g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce

pressure yielding 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'H)-one (72 mg, 0.275 mmol, 84% yield) as a white solid.

M+H = 262.9, 264.8

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.89 (dd, J = 2.4, 0.4 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (dd, J = 8.0, 0.4 Hz, 1H), 5.71 (s, 2H), 3.10 (s, 2H), 2.87 (m, 2H), 2.33 (m, 2H) ppm.

Step 3. Preparation of 3-(1'-oxo-1',3'-dihydrospiro[cyclopent[3]ene-1,2'-indene]-6'-yl)benzonitrile (RXN3)

In a microwave vial was placed 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'H)-one (72 mg, 0.275 mmol), 3-cyanobenzeneboronic acid (52 mg, 0.354 mmol), $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol) and cesium carbonate (224 mg, 0.687 mmol). This solid mixture was dissolved in a Dioxane / water mixture (2.7 mL, 6 : 1 ratio, respectively). The solution was purged with a N_2 stream for 1 minute. The vessel was placed in the microwave and heated to 120° C for 10 minutes. After that time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (20 mL) and water (20 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (5 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(1'-oxo-1',3'-dihydrospiro[cyclopent[3]ene-1,2'-indene]-6'-yl)benzonitrile (45 mg, 0.158 mmol, 57% yield) as white crystals.

M+H = 286.5

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.97 (bd, J = 1.6 Hz, 1H), 7.88 (m, 1H), 7.84 (dt, J = 6.4, 1.6 Hz, 1H), 7.81 (ddd, J = 8.0, 1.6, 1.2 Hz, 1H), 7.67 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 2H), 5.75 (s, 2H), 3.23 (s, 2H), 2.93 (d, J = 14.8 Hz, 2H), 2.39 (d, J = 14.4 Hz, 2H) ppm.

Step 4. Preparation of 3-(1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile (RXN4)

In a 25 mL round bottom flask was placed 3-(1'-oxo-1',3'-dihydrospiro[cyclopent[3]ene-1,2'-indene]-6'-yl)benzonitrile (37 mg, 0.130 mmol) and it was dissolved in THF / MeOH (2.5 mL, 1:1). To this solution was added KO_2CNNCO_2K (378 mg, 1.95 mmol) followed by the dropwise addition of AcOH (334 μL, 5.83 mmol). After 1 hour, more KO_2CNNCO_2K (378 mg, 1.95 mmol) and AcOH (334 μL, 5.83 mmol) were added and this was repeated until complete consumption of the alkene. When the reaction was completed, it was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with ethyl acetate (10 mL). The phases were separated. The aqueous phase was back-extracted with ethyl acetate twice (5 mL / each). The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12 g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile (17 mg, 0.059 mmol, 45% yield).

M+H = 288.4

^1H NMR = ($CDCl_3$, 400 MHz) δ 7.95 (bs, 1H), 7.88 (bs, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 8.0, 1.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.56 (m, 2H), 3.10 (s, 2H), 2.00 (m, 2H), 1.82 (m, 1H), 1.65 (m, 1H) ppm.

Step 5. Preparation of compound 50 (RXN5)

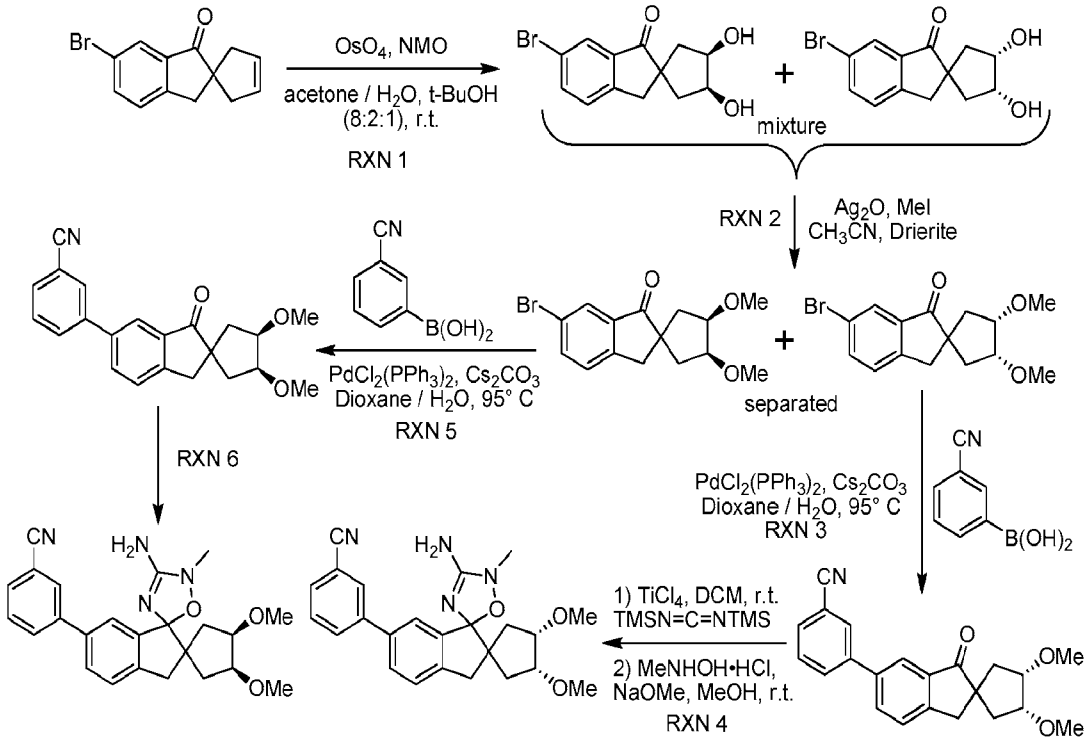
In a 20 mL vial was placed 3-(1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile (20 mg, 0.070 mmol), and it was azeotroped twice with toluene (2 mL / each). Dichloromethane (4 mL) was added followed by $TiCl_4$ (139 μL, 0.139 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (50 μL, 0.223

mmol) was added and the solution was allowed to stir overnight (14 hours) at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (5 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (7 mg, 0.084 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (15 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 3 hours. After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated yielding the final product (6.5 mg, 0.018 mmol, 26% yield) as a white solid.

M+H = 359.1

^1H NMR = (CD_3OD, 400 MHz) δ 8.02 (bs, 1H), 7.92 (m, 1H), 7.78 – 7.61 (m, 4H), 7.42 (d, 1H), 3.36 (s, 3H), 2.97 (d, 2H), 2.07 – 1.51 (m, 4H) ppm.

Example 10. Preparation of compounds 57 and 62



Step 1. Preparation of 6'-bromo-3,4-dihydroxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one (RXN1)

In a 20 mL vial was placed 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'H)-one (100 mg, 0.382 mmol) and it was dissolved in a mixture of acetone, H_2O and *t*-BuOH (3.8 mL, 8:2:1). To this solution was added NMO (89 mg, 0.760 mmol) and was followed by the addition of aqueous OsO_4 (50 μL, 0.153 M in H_2O). The reaction was allowed to stir overnight (~ 14 hours). At that time, the reaction was cooled down to 0° C and sodium sulfite (50 mg) was added and the mix was stirred for 30 minutes. After that time, water (5 mL) and ethyl acetate (5 mL) were added. The phases were separated and the aqueous phase was back-extracted with ethyl acetate three times (5 mL / each). The combined organic phases were washed with 1M HCl, water, brine, dried over Na_2SO_4, filtered and concentrated under reduce pressure. ^1H NMR of this crude showed ~1:1 mixture of 6'-bromo-3,4-dihydroxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one cis-isomers. This crude mixture of isomers was used as it is for the next reaction. 100 mg of crude were obtained.

M+H = 296.9, 298.9

Step 2. Preparation of 6'-bromo-3,4-dimethoxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one (RXN 2)

In a 50 mL round bottom flask was placed 6'-bromo-3,4-dihydroxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one (100 mg, 0.338 mmol) and it was dissolved in acetonitrile (2 mL). To this heterogenous solution was added Ag_2O (470 mg, 2.028 mmol) followed by freshly grounded Drierite (500 mg). Then MeI (843 μL, 2.97 mmol) was added, the round bottom flask was capped with a plastic cap and it was parafilmed. The reaction was allowed to stir at room temperature. After 2 days stirring the alcohol was consumed. The reaction mixture was filtered through a plug of Celite and the cake was rinsed with ethyl acetate three times (5 mL / each). The filtrate was concentrated under reduce pressure. This crude material was purified by flash chromatography (ISCO, 12g SiO2 cartridge, using ethyl acetate / hexanes as the eluents). The mixture of cis-isomers was easily separated in the chromatography. The corresponding fractions for each isomer were combined and concentrated under reduce pressure yielding the two cis-isomers of 6'-bromo-3,4-dimethoxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one (51 mg 1st isomer, 23 mg 2nd isomer).

M+H = 324.9, 327.0 (for both isomers)

1st isomer (51 mg)

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 3.96 (m, 2H), 3.42 (s, 6H), 3.20 (s, 2H), 2.15 (m, 2H), 1.86 (dd, J = 14.0, 5.2 Hz, 2H) ppm.

2nd isomer (23 mg)

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 1.6 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.29 (d, J = 8.0 Hz), 3.87 (m, 2H), 3.42 (s, 6H), 3.01 (s, 2H), 2.30 (dd, J = 13.2, 6.4 Hz, 2H), 1.80 (dd, J = 13.2, 6.0 Hz, 2H) ppm.

Step 3. Preparation of 3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile (RXN 3) 1st isomer

In a microwave vial was placed 6'-bromo-3,4-dimethoxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one 1st isomer (51 mg, 0.157 mmol), 3-cyanobenzeneboronic acid (30 mg, 0.204 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.016 mmol) and cesium carbonate (128 mg, 0.393 mmol). This solid mixture was dissolved in a Dioxane / water mixture (2.0 mL, 6:1 ratio, respectively). The solution was purged with a N_2 stream for 30 seconds. The vessel was placed in the μwave and heated to 110° C for 30 minutes. After that time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (4 mL) and water (4 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (2 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile 1st isomer (40 mg, 0.115 mmol, 73% yield).

M+H = 347.9

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 1.2, 1.2 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.65 (ddd, J = 8.0, 1.2, 1.2 Hz, 1H), 7.58 – 7.53 (m, 2H), 4.00 (m, 2H), 3.44 (s, 6H), 3.33 (s, 2H), 2.24 – 2.19 (m, 2H), 1.92 (dd, J = 14.0, 5.2 Hz, 2H) ppm.

3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile (RXN 5) 2nd isomer

In a microwave vial was placed 6'-bromo-3,4-dimethoxyspiro[cyclopentane-1,2'-inden]-1'(3'H)-one 1st isomer (23 mg, 0.071 mmol), 3-cyanobenzeneboronic acid (14 mg, 0.095 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and cesium carbonate (58 mg, 0.178 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.0 mL, 6:1 ratio,

respectively). The solution was purged with a N_2 stream for 30 seconds. The vessel was placed in the microwave and heated to 110° C for 30 minutes. After that time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (2 mL) and water (2 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (2 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile 2nd isomer (24 mg, 0.069 mmol, 97% yield).

M+H = 347.9

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 2.0 Hz, 1H), 7.86 (m, 1H), 7.83 – 7.78 (2H), 7.67 – 7.64 (m, 1H), 7.59 – 7.52 (m, 2H), 3.91 (m, 2H), 3.44 (s, 6H), 3.13 (s, 2H), 2.34 (dd, J = 13.2, 6.8 Hz, 2H), 1.85 (dd, J = 13.2, 5.6 Hz, 2H) ppm.

Step 4. Preparation of compound 62 (RXN 4)

In a 20 mL vial was placed 3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile 1st isomer (40 mg, 0.115 mmol), and it was azeotroped with toluene twice (2 mL / each). Dichloromethane (3 mL) was added followed by $TiCl_4$ (231 µL, 0.231 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (83 µL, 0.370 mmol) was added and the solution was allowed to stir 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (2 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (11 mg, 0.132 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (26

μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the reaction mixture was concentrated under reduce pressure. Attempts to purify by HPLC failed due to poor solubility in acetonitrile / water. The white solid was collected and LC/MS analysis showed the desired final compound (9.6 mg, 0.023 mmol, 20% yield) >95% pure. 1H NMR confirmed purity.

M+H = 419.0

^{1}H NMR = (d_6-DMSO, 400 MHz) δ 8.03 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0, 1.6 Hz, 1H), 7.35 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 3.67 – 3.62 (m, 2H), 3.25 (s, 3H), 3.20 (s, 3H), 2.88 (s, 3H), 2.91 – 2.78 (m, 2H), 2.08 – 1.96 (m, 2H), 1.62 (dd, J = 13.6, 4.0 Hz, 1H), 1.30 (dd, J = 13.2, 6.4 Hz, 1H) ppm.

Preparation of compound 57 (RXN 6)

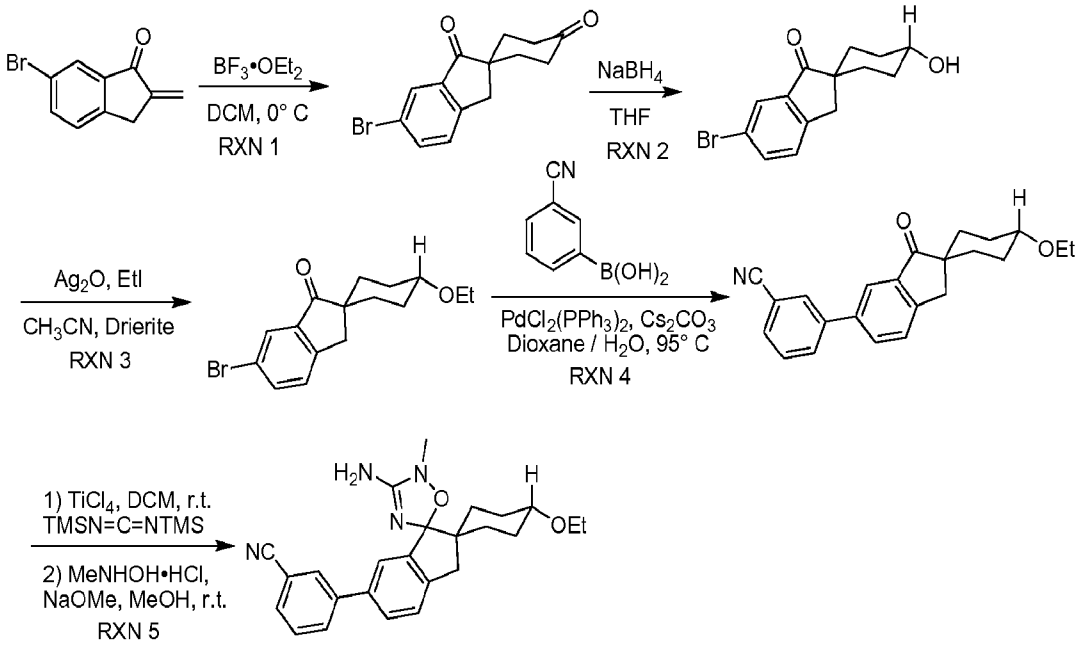
In a 20 mL vial was placed 3-(3,4-dimethoxy-1'-oxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-6'-yl)benzonitrile 2nd isomer (24 mg, 0.069 mmol), and it was azeotroped with toluene twice (2 mL / each). Dichloromethane (2 mL) was added followed by $TiCl_4$ (138 μL, 0.138 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (50 μL, 0.223 mmol) was added and the solution was allowed to stir 1 hour at room temperature. Only 50% conversion was observed. The reaction was not forced to completion and it was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (2 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (6 mg, 0.072 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (16 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution

was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated yielding the final product (4.17 mg, 0.010 mmol, 14% yield) as a colorless oil.

M+H = 419.0

^{1}H NMR = (CD_3OD, 400 MHz) δ 8.02 (bs, 1H), 7.97 – 7.94 (m, 1H), 7.76 – 7.72 (m, 3H), 7.64 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 3.90 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 3.10 – 2.99 (m, 2H), 2.48 (dd, J = 14.8, 4.0 Hz, 1H), 2.06 (m, 1H), 1.83 (dd, J = 14.4, 4.8 Hz, 1H), 1.63 (dd, J = 12.8, 6.0 Hz, 1H) ppm.

Example 11. Preparation of compound 49



Step 1. Preparation of 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (RXN 1)

In a flame dried 20 mL vial was placed 6-bromo-2-methylene-2,3-dihydro-1H-inden-1-one (98 mg, 0.441 mmol) and it was dissolved in dichloromethane (4.5 mL). To this solution was added 2-trimethylsilyloxy-1,3-butadiene (98 μL, 0.565 mmol) and the solution was cooled down to -78° C. After stirring for 5 minutes, BF_3•OEt_2 (27 mL, 0.219 mmol) was slowly added. After 5 minutes of the BF_3•OEt_2 addition, TLC indicated consumption of the dienophile. The reaction was quenched with MeOH (300 μL), allowed to stir for 5 minutes at -78° C and then warmed up to room temperature. Once at room temperature, 2M HCl (7 mL) was added. The phases were separated and the aqueous phase was back-extracted with dichloromethane twice (5 mL / each). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (62 mg, 0.212 mmol, 48% yield).
^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 8.0, 2.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 2.94 (s, 2H), 2.48 (dt, J = 15.2, 5.6 Hz, 2H), 2.22 (ddd, J = 15.2, 10.8, 5.6 Hz, 2H), 1.98 (ddd, J = 13.6, 11.2, 5.2 Hz, 2H), 1.65 (m, 2H) ppm.

Step 2. Preparation (trans-6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (RXN 2)

To a 20 mL vial was added 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (102 mg, 0.349 mmol) and it was dissolved in THF (3.49 mL). This solution was cooled down to -78° C and stirred for 5 minutes at that temperature. Then, $NaBH_4$ (7 mg, 0.184 mmol) were added at -78° C. After 10 minutes more $NaBH_4$ (7 mg, 0.184 mmol) was added. After 5 minutes, LC/MS showed ~ 70% conversion. Finally, a final portion of $NaBH_4$ (10 mg, 0.263 mmol) was added. After 5 minutes, TLC showed total consumption of the diketone. The excess $NaBH_4$ was quenched immediately with

acetone (300 μL). After stirring for 15 minutes at -78° C, the reaction was warmed to room temperature and ethyl acetate (7 mL) and water (7 mL) were added. The phases were separated and the aqueous phase was back-extracted with ethyl acetate twice (5 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The fractions corresponding to the isomer shown in the scheme were combined and concentrated under reduce pressure yielding *trans*-6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (71 mg, 0.241 mmol, 69% yield) as a colorless oil.

M+H = 294.9, 296.9

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.84 (bs, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 3.73 (m, 1H), 2.96 (s, 2H), 2.04 (m, 2H), 1.94 (s, 1H), 1.77 (m, 2H), 1.47 – 1.40 (m, 4H) ppm.

Step 3. Preparation of trans-6'-bromo-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (RXN 3)

In a 20 mL vial was placed *trans*-6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (295 mg, 1.00 mmol) and it was dissolved in acetonitrile (3 mL). To this heterogenous solution was added Ag_2O (690 mg, 2.98 mmol) followed by freshly grounded Drierite (1 g). Then EtI (1.58 mL, 19.75 mmol) was added, the round bottom flask was capped with a plastic cap and it was parafilmed. The reaction was allowed to stir at 40° C overnight (~ 14 hours). The reaction mixture was filtered through a plug of Celite and the cake was rinsed with dichloromethane (15 mL). The filtrate was concentrated under reduce pressure. This crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, using ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding *trans*-6'-bromo-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (200 mg, 0.621 mmol, 62% yield).

M+H = 322.9, 324.9

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.79 (bs, 1H), 7.61 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 3.49 (quart., J = 7.2 Hz, 2H), 3.28 (m, 1H), 2.90 (s, 2H), 2.05 (m, 2H), 1.69 (ddd, J = 13.6, 3.6 Hz, 2H), 1.44 – 1.27 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H) ppm.

Step 4. Preparation of 3-trans-4-ethoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (RXN 4)

In a 20 mL vial was placed *trans*-6'-bromo-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (56 mg, 0.174 mmol), 3-cyanobenzeneboronic acid (33 mg, 0.225 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) and cesium carbonate (142 mg, 0.436 mmol). This solid mixture was dissolved in a Dioxane / water mixture (2 mL, 6 : 1 ratio, respectively). The solution was purged with a N_2 stream for 20 seconds. The reaction vial was capped and allowed to stir at 95° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (10 mL) and water (10 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane twice (5 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(*trans*-4-ethoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (51 mg, 0.148 mmol, 66% yield) as a yellow solid.

M+H = 346.0

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 1.6 Hz, 1H), 7.86 (dd, J = 1.6, 1.6 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.65 (dt, J = 7.6, 1.6 Hz, 1H), 7.58 – 7.54 (m, 2H), 3.57 (quart., J = 6.8 Hz, 2H), 3.37 (m, 1H), 3.08 (s, 2H), 2.14 (m, 2H), 1.80 (ddd, J = 14.0, 3.6 Hz, 2H), 1.54 – 1.37 (m, 4H), 1.22 (t, J = 6.8 Hz, 3H) ppm.

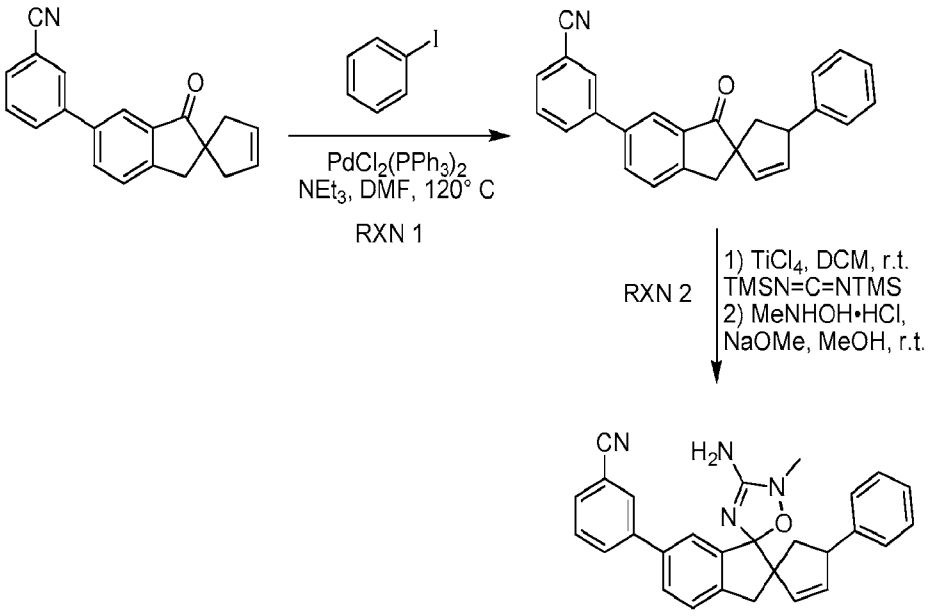
Step 5. Preparation of compound 11 (RXN 5)

In a 20 mL vial was placed 3-(*trans*-4-ethoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (51 mg, 0.148 mmol), and it was azeotroped with toluene (2 mL). Dichloromethane (4 mL) was added followed by $TiCl_4$ (296 μL, 0.296 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (106 μL, 0.472 mmol) was added and the solution was allowed to stir for 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (2 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (14 mg, 0.167 mmol) and it was dissolved in MeOH (3 mL). To this solution was added NaOMe (33 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature overnight (~ 14 hours). After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 5 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The oil obtained was liophilized yielding the final product (14 mg, 0.034 mmol, 23% yield) as white solid.

M+H = 417.1

^{1}H NMR = (CD_3OD, 400 MHz) δ 8.00 (bs, 1H), 7.95 – 7.93 (m, 1H), 7.78 – 7.61 (m, 4H), 7.45 (m, 1H), 3.57 (quart., J = 7.2 Hz, 2H), 3.34 (s, 3H), 3.09 – 2.97 (m, 2H), 2.17 – 2.03 (m, 2H), 1.82 – 1.67 (m, 2H), 1.57 – 1.37 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H) ppm.

Example 12. **Preparation of compouds 47 and 53**



Step 1. Preparation of 3-(1'-oxo-4-phenyl-1',3'-dihydrospiro[cyclopent[2]ene-1,2'-indene]-6'-yl)benzonitrile (RXN 1)

In to a 4 mL vial was placed 3-(1'-oxo-1',3'-dihydrospiro[cyclopent[3]ene-1,2'-indene]-6'-yl)benzonitrile (99 mg, 0.347 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol). They were dissolved in DMF (1 mL). To this solution was added NEt_3 (72 μL, 0.518 mmol) followed by iodobenzene (47 μL, 0.420 mmol). The vial was capped and heated in an oil bath at 120° C overnight (~ 14 hours). After that time, the mixture was filtered through a Celite plug and rinsed with dichloromethane twice (5 mL / each). To the filtrate was added water (5 mL). The phases were separated and the aqueous phase was back-extracted with dichloromethane twice (2 mL / each). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(1'-oxo-4-phenyl-1',3'-dihydrospiro[cyclopent[2]ene-1,2'-indene]-6'-yl)benzonitrile (43 mg, 0.119 mmol, 34% yield).

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.96 (bs, 1H), 7.87 (bs, 1H), 7.84 – 7.80 (m, 2H), 7.66 (dd, J = 7.6, 1.2 Hz, 1H) 7.60 – 7.54 (m, 2H), 7.43 – 7.30 (m, 3H), 7.26 – 7.21 (2H), 6.10 (ddd, J = 5.6, 2.4, 0.8 Hz, 1H), 5.69 (dd, J = 5.6, 2.4 Hz, 1H), 4.37 (m, 1H), 3.45 (d, $J_{A,B}$ = 17.6 Hz, 1H), 3.15 (d, $J_{A,B}$ = 17.6 Hz, 1H), 2.92 (dd, J = 12.8, 8.4 Hz, 1H), 1.85 (dd, J = 12.8, 6.4 Hz, 1H) ppm.

Step 2. Preparation and separation of compounds 47 and 53

In a 20 mL vial was placed 3-(1'-oxo-4-phenyl-1',3'-dihydrospiro[cyclopent[2]ene-1,2'-indene]-6'-yl)benzonitrile (43 mg, 0.119 mmol), and it was azeotroped with toluene twice (2 mL / each). Dichloromethane (4 mL) was added followed by $TiCl_4$ (238 μL, 0.238 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (86 μL, 0.383 mmol) was added and the solution was allowed to stir for 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (2 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (11 mg, 0.167 mmol) and it was dissolved in MeOH (3 mL). To this solution was added NaOMe (26 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature overnight (~ 14 hours). After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). Two diastereomers were separated by the HPLC. The corresponding fractions for each respective diastereomer were combined and concentrated yielding two final diastereomeric products (1.1 mg, 0.034 mmol, FRACTION A, 1.64 mg, 0.000 mmol, FRACTION B, 23% yield).

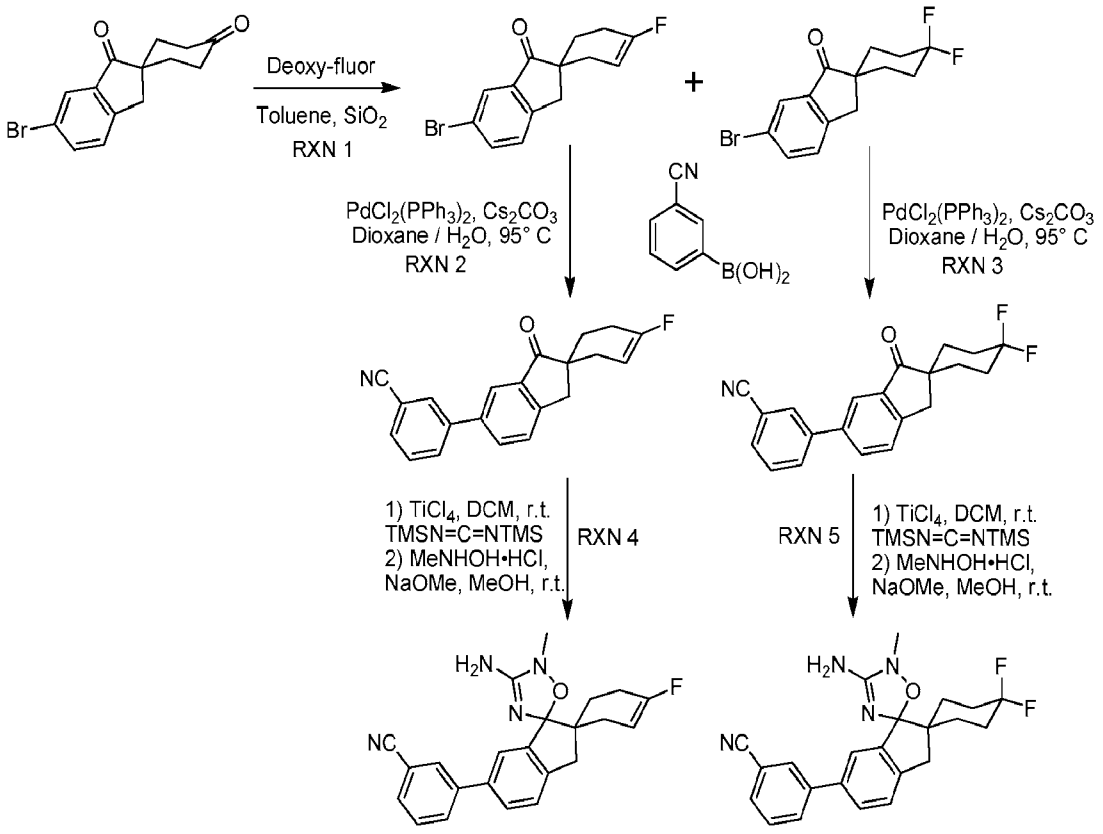
M+H = 433.0 (ISOMER A)

M+H = 433.0 (ISOMER B)

FRACTION A ^{1}H NMR = (CD_3OD, 400 MHz) δ 8.03 (bs, 1H), 7.98 – 7.95 (m, 1H), 7.82 – 7.72 (m, 3H), 7.65 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 6.10 (dd, J = 5.6, 1.6 Hz, 1H), 5.71 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.12 (m, 1H), 3.41 (s, 3H), 3.25 (d, $J_{A,B}$ = 16.4 Hz, 1H), 3.09 (d, $J_{A,B}$ = 16.4 Hz, 1H), 3.05 (dd, J = 14.0, 7.6 Hz, 1H), 1.78 (dd, J = 14.0, 7.6 Hz, 1H) ppm.

FRACTION B ^{1}H NMR = (CD_3OD, 400 MHz) δ 8.03 (m, 1H), 7.98 – 7.95 (m, 1H), 7.82 – 7.72 (m, 3H), 7.64 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 6.08 (m, 2H), 4.12 (t, J = 4.0 Hz, 1H), 3.46 (d, $J_{A,B}$ = 16.0 Hz, 1H), 3.34 (s, 3H), 2.91 (d, $J_{A,B}$ = 16.0 Hz, 1H), 2.65 (dd, J = 14.0, 8.4 Hz, 1H), 1.63 (dd, J = 14.0, 7.6 Hz) ppm.

Example 13. Preparation of compounds 34 and 44



Step 1: Preparation of 6'-bromo-4-fluorospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one and 6'-bromo-4,4-difluorospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (RXN 1)

In a 15 mL plastic tube was placed 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (100 mg, 0.340 mmol) and dry silica gel (50 mg). To the mixture was slowly added Deoxy-fluor (2 mL, 50% in toluene). The reaction was allowed to stir for 2 hours. LC/MS analysis indicated formation of the vinyl fluoride adduct along with the geminal difluoro analog. The reaction mixture was directly transferred to a 12g SiO2 cartridge packed in 100% hexanes and purified by flash chromatography (ISCO, using ethyl acetate / hexanes as the eluents. The corresponding fractions for each individual compound were combined and concentrated under reduce pressure yielding 6'-bromo-4-fluorospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one (14 mg, 0.048 mmol) as a white solid, and 6'-bromo-4,4-difluorospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (37 mg, 0.118 mmol) as a white solid.

M+H = 294.9 and 296.9 (VINYL FLUORIDE)

M+H = 314.9 and 316.9 (GEMINAL DIFLUORIDE)

<u>6'-bromo-4-fluorospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one</u>

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 1.6 Hz, 1H), 7.70 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 5.25 (m, 1H), 3.00 (d, $J_{A,B}$ = 17.2 Hz, 1H) 2.90 (d, $J_{A,B}$ = 17.2 Hz, 1H), 2.52 (m, 1H), 2.39 – 2.35 (m, 2H), 2.09 – 2.02 (m, 1H), 1.87 – 1.81 (m, 1H), 1.63 – 1.58 (m, 1H) ppm.

<u>6'-bromo-4,4-difluorospiro[cyclohexane-1,2'-inden]-1'(3'H)-one</u>

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 2.0 Hz), 7.70 (dd, J = 8.0 Hz, 2.0 Hz), 7.33 (d, J = 8.0 Hz, 1H), 2.99 (s, 2H), 2.34 – 2.25 (m, 2H), 2.06 – 1.99 (m, 2H), 1.96 – 1.81 (m, 2H), 1.63 – 1.58 (m, 2H) ppm.

Step 2. Preparation of 3-(4-fluoro-1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (RXN 2)

In a 20 mL vial was placed 6'-bromo-4-fluorospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one (11 mg, 0.037 mmol), 3-cyanobenzeneboronic acid (7 mg, 0.048 mmol),

$PdCl_2(PPh_3)_2$ (3 mg, 0.004 mmol) and cesium carbonate (30 mg, 0.092 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1 mL, 6 : 1 ratio, respectively). The reaction vial was capped and allowed to stir at 95° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (1 mL) and water (1 mL). The filtrate was diluted with dichloromethane (2 mL) and water (2 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane twice (2 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 4g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(4-fluoro-1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (15 mg, 0.047 mmol, quantitative).

M+H = 318.0

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.95 (bs, 1H), 7.87 (bs, 1H), 7.84 – 7.80 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.59 – 7.55 (m, 2H), 5.31 – 5.25 (m, 1H), 3.12 (d, $J_{A,B}$ = 17.6 Hz, 1H), 3.03 (d, $J_{A,B}$ = 17.6 Hz, 1H), 2.60 – 2.54 (m, 1H), 2.40 (m, 2H), 2.14 – 2.06 (m, 1H), 1.91 – 1.87 (m, 1H), 1.68 – 1.63 (m, 1H) ppm.

Preparation of 3-(4,4-difluoro-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (RXN 3)

In a 20 mL vial was placed 6'-bromo-4,4-difluorospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (35 mg, 0.111 mmol), 3-cyanobenzeneboronic acid (23 mg, 0.157 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.011 mmol) and cesium carbonate (91 mg, 0.279 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.1 mL, 6 : 1 ratio, respectively). The reaction vial was capped and allowed to stir at 90° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (5 mL) and water (5 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane twice (3 mL / each). The

combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(4,4-difluoro-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (30 mg, 0.089 mmol, 80% yield) as a white solid.

M+H = 338.0

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.94 (d, J = 2.0 Hz, 1H), 7.87 (m, 1H), 7.84 – 7.80 (m, 2H), 7.72 – 7.66 (m, 1H), 7.61 – 7.55 (m, 2H), 3.11 (s, 2H), 2.34 – 2.28 (m, 2H), 2.12 – 2.04 (m, 2H), 1.99 – 1.89 (m, 2H), 1.64 (m, 2H) ppm.

Step 3. Preparation of compound 34

In a 20 mL vial was placed 3-(4-fluoro-1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (15 mg, 0.047 mmol), and it was azeotroped with toluene (2 mL). Dichloromethane (3 mL) was added followed by $TiCl_4$ (94 μL, 0.094 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (34 μL, 0.151 mmol) was added and the solution was allowed to stirvfor 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (3 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (4.3 mg, 0.051 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (11 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature overnight (~ 14 hours). After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 5 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). The corresponding

fractions were combined and concentrated yielding the final product (0.78 mg, 0.002 mmol, 4% yield).

M+H = 389.0

^{1}H NMR = (CD_3OD, 400 MHz) δ 8.02 (m, 1H), 7.97 – 7.95 (m, 1H), 7.80 – 7.77 (m, 2H), 7.75 – 7.72 (m, 1H), 7.68 – 7.63 (m, 1H), 7.48 – 7.45 (m, 1H), 5.28 – 5.16 (m, 1H), 3.35 (s, 3H), 3.07 (d, $J_{A,B}$ = 16.4 Hz, 1H), 2.93 (d, $J_{A,B}$ = 16.4 Hz, 1H), 2.57 – 2.32 (m, 3H), 2.10 – 1.81 (m, 3H) ppm.

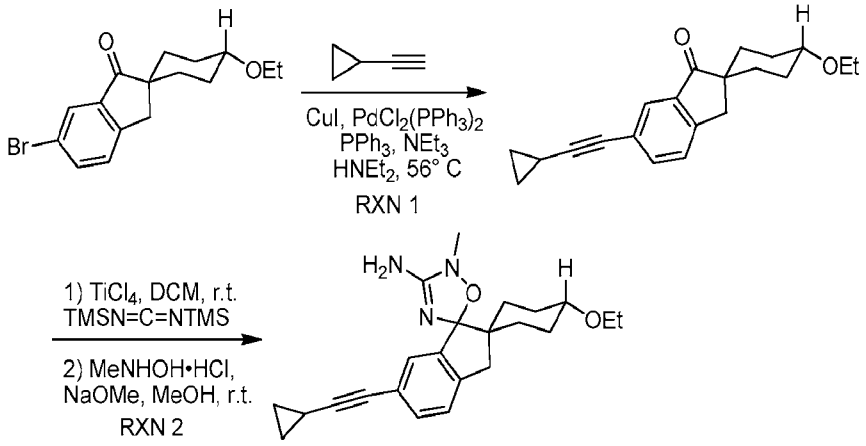
Preparation of compound 44 (RXN 5)

In a 20 mL vial was placed 3-(4,4-difluoro-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (30 mg, 0.089 mmol), and it was azeotroped with toluene (2 mL). Dichloromethane (3 mL) was added followed by $TiCl_4$ (178 μL, 0.178 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (64 μL, 0.285 mmol) was added and the solution was allowed to stir for 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL) and diluted with dichloromethane (3 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (3 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (8 mg, 0.096 mmol) and it was dissolved in MeOH (2.5 mL). To this solution was added NaOMe (20 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature overnight (~ 14 hours). After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% CH_3CN / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The glace product was liophilized yielding the final product (3.01 mg, 0.007 mmol, 8% yield).

M+H = 409.0

^{1}H NMR = (CD_3OD, 400 MHz) δ 8.01 (bs, 1H), 7.96 – 7.94 (m, 1H), 7.79 – 7.76 (m, 2H), 7.73 – 7.71 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 3.36 (s, 3H), 3.14 (d, $J_{A,B}$ = 16.0 Hz, 1H), 3.06 (d, $J_{A,B}$ = 16.0 Hz, 1H), 2.13 – 2.07 (m, 3H), 2.00 – 1.76 (m, 4H), 1.52 (m, 1H) ppm.

Example 14. **Preparation of compound 24**



Step 1. Preparation of 6'-(cyclopropylethynyl)-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (RXN 1)

In a 25 mL round bottom flask was placed 6'-bromo-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (200 mg, 0.621 mmol) and it was azeotroped twice with toluene (5 mL / each). Triethylamine (3.0 mL) and diethylamine (0.8 mL) were added and this solution was bubbled with a nitrogen stream for 1 minute. Then $PdCl_2(PPh_3)_2$ (22 mg, 0.031 mmol) and CuI (6 mg, 0.032 mmol) were added and again the solution was bubbled with a stream of nitrogen for 1 minute. Then, PPh_3 (16 mg, 0.061 mmol) was added followed by the addition of cyclopropyl acetylene (600 μL, excess) and one more time the solution was bubbled with a stream of nitrogen for 1 minute. The flask was capped with a septum and allowed to stir overnight (~14 hours) at 56° C. At that time, the solvent was removed under reduce pressure and the crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, using ethyl acetate / hexanes as the

eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 6'-(cyclopropylethynyl)-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (180 mg, 0.584 mmol, 94% yield).

M+H = 309.0

^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 3.55 (quart., J = 7.2 Hz, 2H), 3.34 (m, 1H), 2.99 (s, 2H), 2.11 (m, 2H), 1.75 (ddd, J = 13.6, 13.6, 2.8 Hz, 2H), 1.48 – 1.33 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H), 0.90 – 0.83 (m, 2H), 0.82 – 0.77 (m, 2H) ppm.

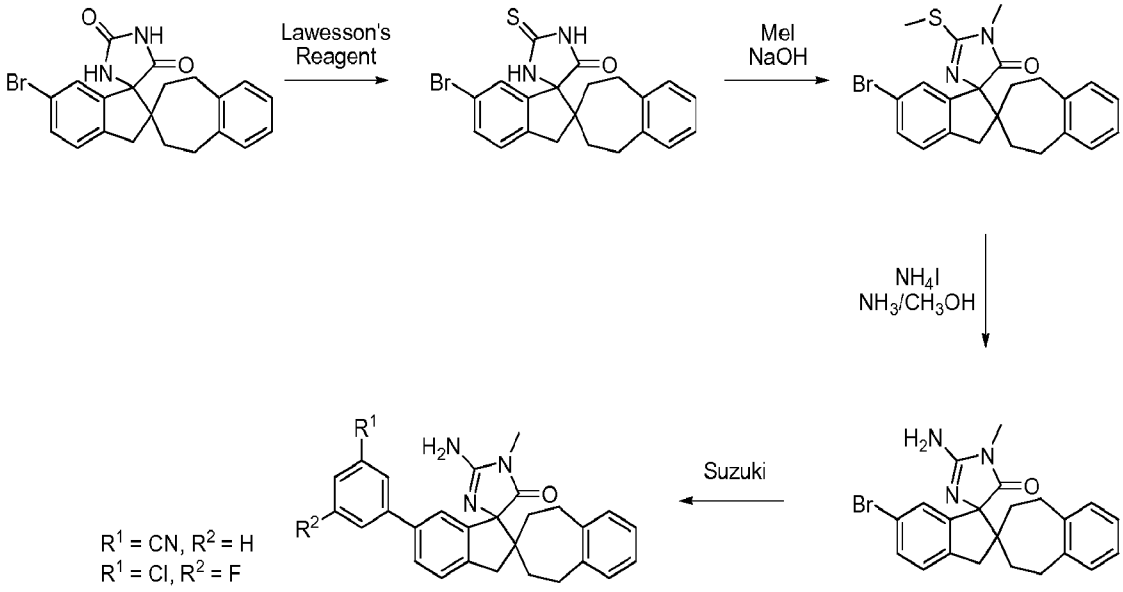
Step 2. Preparation of compound 24 (RXN 2)

In a 50 mL round bottom flask was placed 6'-(cyclopropylethynyl)-4-ethoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (180 mg, 0.584 mmol), and it was azeotroped with toluene twice (2 mL / each). Dichloromethane (20 mL) was added followed by $TiCl_4$ (1.17 mL, 1.17 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (420 μL, 1.87 mmol) was added and the solution was allowed stir overnight (~ 14 hours). The reaction was quenched with ice cold water (20 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane (10 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 20 mL vial was placed MeNH(OH)·HCl (54 mg, 0.647 mmol) and it was dissolved in MeOH (15 mL). To this solution was added NaOMe (118 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The concetrated product was lyophilized yielding the final product (90 mg, 0.237 mmol, 41% yield).

M+H = 380.1

^{1}H NMR (CD_3OD, 400 MHz): δ 7.41 (bs, 1H), 7.38 (m, 1H), 7.26 (d, J = 7.6 Hz, 1H), 3.57 (m, 2H), 3.27 (s, 3H), 2.99 (d, $J_{A,B}$ = 16.0 Hz, 1H), 2.93 (d, $J_{A,B}$ = 16.0 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.71 – 1.62 (m, 2H), 1.51 – 1.34 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H), 0.92 – 0.85 (m, 2H), 0.75 – 0.71 (m, 2H) ppm.

Example 15. Preparation of compounds 26, 29 and 56



Step 1.

A 10 mL microwave tube was charged with Lawesson's reagent (0.0745 g, 0.184 mmol), hydantoin (0.0758 g, 0.184 mmol), and 1,4-dioxane (3 mL). The tube was heated in a CEM microwave reactor for three times, at 110 °C for 30 min, 140 °C for 30 min, and 140 °C for 30 min, respectively. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.0339 g (43%) of 2-thiohydantoin as a solid. LC-MS t_R = 1.88 min in 3 min chromatography, *m/z* 427, 429 (MH^+).

Step 2.

A 10 mL microwave tube was charged with 2-thiohydantoin (0.0339 g), MeOH (3 mL), and 1 *N* NaOH (0.5 mL). After stirring at room temperature for 10 min, MeI (0.5 mL) was added. The reaction mixture was heated in a CEM microwave reactor at 60 °C for 10 min and then purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% CH_3CN/H_2O, 0.1% CF_3COOH over 8 min and then 90% CH_3CN/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0180 g (50%) of 3-methyl-2-(methylthio)-3,5-dihydroimidazole-4-one. LC-MS t_R = 2.17 min in 3 min chromatography, *m/z* 455, 457 (MH^+).

Step 3. Preparation of compoud 56

A 10 mL microwave tube was charged with 3-methyl-2-(methylthio)-3,5-dihydroimidazole-4-one (0.0180 g), NH_4I (0.600 g), 1,4-dioxane (1 mL), and 7 *M* NH_3 in MeOH (4 mL). The tube was heated in a CEM microwave reactor at 120 °C for 1 h. The reaction mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% CH_3CN/H_2O, 0.1% CF_3COOH over 8 min and then 90% CH_3CN/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford TFA salt of compound 56. LC-MS t_R = 1.80 min in 3 min chromatography, *m/z* 424, 426 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.46-6.89 (m, 7H), 5.62-5.56 (m, 1H), 5.26-5.22 (m, 1H), 3.11 (s, 3H), 2.90-2.58 (m, 6H), 1.74-1.67 (m, 2H).

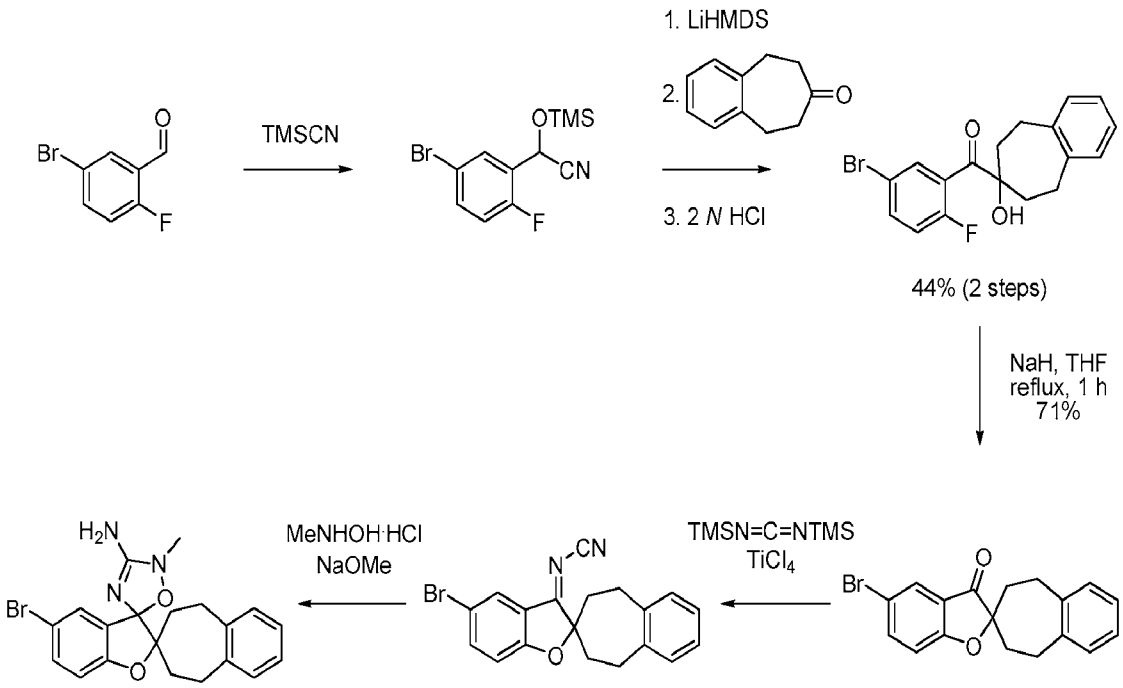
Step 4. Preparation of compounds 26 and 29

A 10 mL microwave tube was charged with compound 56 (0.0040 g), 3-cyanophenylboronic acid (0.0462 g), Cs_2CO_3 (0.2225 g), $PdCl_2(PPh_3)_2$ (0.0142 g), 1,4-dioxane (4 mL), and H_2O (0.5 mL). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% CH_3CN/H_2O, 0.1% CF_3COOH over 8 min and then 90% CH_3CN/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford TFA salt of compound 29. LC-MS t_R = 1.86 min in 3

min chromatography, *m/z* 447 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.93-6.92 (m, 11H), 5.63-5.58 (m, 1H), 5.28-5.24 (m, 1H), 3.13 (s, 3H), 3.02-2.59 (m, 6H), 1.82-1.70 (m, 2H).

A 10 mL microwave tube was charged with compound 56 (0.0068 g), 3-chloro-5-fluorophenylboronic acid (0.0782 g), Cs_2CO_3 (0.2277 g), $PdCl_2(PPh_3)_2$ (0.0127 g), 1,4-dioxane (4 mL), and H_2O (0.5 mL). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% CH_3CN/H_2O, 0.1% CF_3COOH over 8 min and then 90% CH_3CN/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford TFA salt of compound 26. LC-MS t_R = 2.27 min in 3 min chromatography, *m/z* 474, 476 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.62-6.75 (m, 10H), 5.62-5.56 (m, 1H), 5.27-5.23 (m, 1H), 3.12 (s, 3H), 3.00-2.56 (m, 6H), 1.77-1.68 (m, 2H); ^{19}F NMR (376 MHz, CD_3OD) δ -113.11 (m).

Example 16. Preparation of compound 67



Step 1. 2-(5-bromo-2-fluorophenyl)-2-(trimethylsilyloxy)acetonitrile

To a solution of 5-bromo-2-fluorobenzaldehyde (2.1385 g, 10.53 mmol) and DMAP (0.0146 g, 0.12 mmol, 0.011 equiv) in CH_3CN (20 mL) was added TMSCN (1.4086 g, 14.20 mmol, 1.35 equiv) dropwise via a syringe under nitrogen at room temperature. After 4 h, the solvent was removed under reduced pressure. The crude product was directly used in the next step without further purification.

Step 2. (5-bromo-2-fluorophenyl)(7-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-7-yl)methanone

To a solution of 2-(5-bromo-2-fluorophenyl)-2-(trimethylsilyloxy)acetonitrile (10.53 mmol), obtained as described above, in THF (10 mL) was added LiHMDS (1.0 *M* in THF, 11 mL, 11 mmol, 1.05 equiv) via a syringe under nitrogen at -78 °C. After 1.25 h, a solution of 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one (1.6550 g, 10.33 mmol, 0.98 equiv) in THF (16 mL) was added dropwise via a cannula. The resulting mixture was allowed to slowly warm to 7 °C over 16 h. The mixture was then treated with 2 *N* HCl (25 mL) and MeOH (75 mL). The resulting solution was vigorously stirred at room temperature for 22 h and the solvents were removed under reduced pressure. The residue was extracted twice with CH_2Cl_2, dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 1.6570 g (44% in two steps) of (5-bromo-2-fluorophenyl)(7-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)methanone as a solid. LC-MS t_R = 2.02 min in 3 min chromatography, *m/z* 345, 347 $(M-H_2O)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (m, 1H), 7.41-7.38 (m, 1H), 7.13 (m, 4H), 7.01-6.97 (m, 1H), 3.43-3.36 (m, 2H), 3.31 (s, 1H), 2.64-2.59 (m, 2H), 2.00-1.88 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.01; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.59, 157.47 (d, J = 249.2 Hz), 142.18, 134.95 (d, J = 8.4 Hz), 131.18 (d, J = 3.8 Hz), 128.93, 128.24 (d, J = 19.9 Hz), 126.40, 117.89 (d, J = 24.5 Hz), 116.81 (d, J = 3.1 Hz), 81.65, 35.21, 35.19, 29.25.

Step 3. 5'-bromo-5,6,8,9-tetrahydro-3'H-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one

A mixture of (5-bromo-2-fluorophenyl)(7-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)methanone (1.3739 g, 3.78 mmol) and 60% NaH (0.5900 g, 14.75 mmol) in THF (20 mL) was heated at 100 °C for 1 h. The reaction mixture was then cooled with an ice bath and quenched with 2 *N* HCl (5 mL), extracted with ethyl acetate, dried over Na_2SO_4. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.9170 g (71%) of 5'-bromo-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one as a solid. LC-MS t_R = 2.31 min in 3 min chromatography, *m/z* 343, 345 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.78 (m, 1H), 7.73-7.71 (m, 1H), 7.17 (m, 4H), 7.11-7.09 (m, 1H), 3.41-3.35 (m, 2H), 2.78-2.75 (m, 2H), 1.95-1.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.53, 169.46, 141.50, 140.56, 128.93, 127.47, 126.62, 121.63, 115.61, 114.15, 92.58, 32.98, 29.67.

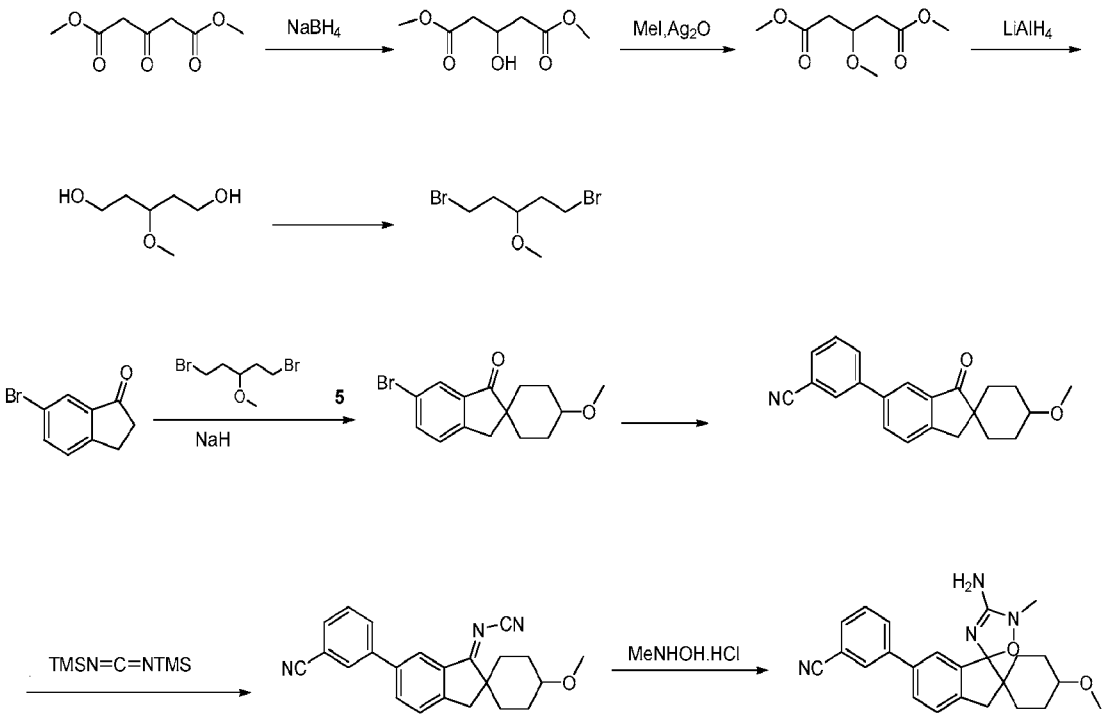
Step 4. N-(5'-bromo-5,6,8,9-tetrahydro-3'H-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-ylidene)cyanamide

To a solution of 5'-bromo-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one (0.1660 g, 0.48 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.0 *M* in CH_2Cl_2, 1.0 mL, 1.0 mmol) dropwise at room temperature. The reaction mixture was turned into orange precipitates in a few minutes. After 1 h, 1,3-bis(trimethylsilyl)carbodiimide (0.30 mL, 1.32 mmol) was added via a syringe. The precipitates were disappeared and the reaction mixture was turned into a red solution. The mixture was stirred at room temperature for 15 h and then quenched with ice, extracted with CH_2Cl_2, dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was directly used in the next step without further purification. LC-MS t_R = 2.27 min in 3 min chromatography, *m/z* 367, 369 (MH^+).

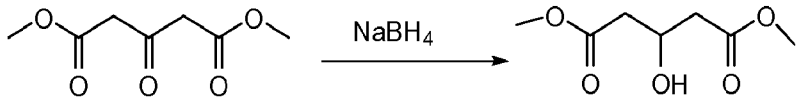
Step 5. Preparation of compound 67

To a suspension of *N*-(5'-bromo-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-ylidene)cyanamide (0.48 mmol), obtained as described above, in EtOH (20 mL) was added a mixture of methylhydroxyamine·HCl salt (0.0986 g, 1.18 mmol) and CH_3ONa (25 wt. % in MeOH, 0.25 mL, 1.10 mmol) in MeOH (10 mL). After 16 h, the reaction mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% CH_3CN/H_2O, 0.1% CF_3COOH over 8 min and then 90% CH_3CN/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford TFA salt of compound 67. LC-MS t_R = 1.43, 1.58 min in 3 min chromatography, *m/z* 414, 416 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.81-6.83 (m, 7H), 3.37-3.30 (m, 2H), 2.70-2.64 (m, 2H), 2.07-2.02 (m, 2H), 1.78-1.72 (m, 2H).

Example 17. Preparation of compound 25

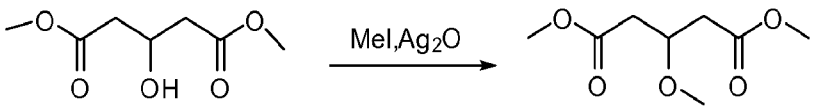


Experimental data:



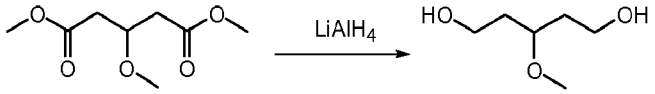
Step 1. dimethyl 3-hydroxypentanedioate

To a mixture of dimethyl 3-oxopentanedioate (20 g, 115 mmol) in anhydrous MeOH (140 mL) was added $NaBH_4$ (2.33 g, 63.18 mmol) in small portions over 10 minutes. The mixture was stirred for 1 h at room temperature and concentrated. Water and EtOAc was added and the organic phase was separated and dried. The combined organic layer was concentrated to give the crude product, which was purified by column chromatography to give dimethyl 3-hydroxypentanedioate (9 g, 44%). **^{1}H-NMR** ($CDCl_3$): 2.51 (m, 4H), 3.43 (m, 1H), 3.70 (m, 6H), 4.45 (m, 1H).



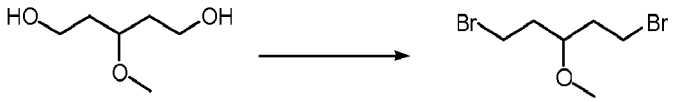
Step 2. dimethyl 3-methoxypentanedioate

To a solution of dimethyl 3-hydroxypentanedioate (9 g, 51.1 mmol) in DMF (70 mL) was added Ag_2O (35.5 g, 154.3 mmol) and iodomethane (48.2 g, 339.2 mmol) under ice-cooling. The mixture was stirred at room temperature overnight. The mixture was filtrated and the filtrate was washed with water. Ether was added and the organic layer was dried and concentrated to give the crude product, which was purified by column chromatography to give dimethyl 3-methoxypentanedioate (8 g, 82%). **^{1}H-NMR** ($CDCl_3$): 2.48 (m, 4H), 3.21 (m, 3H), 3.50 (m, 6H), 3.85 (s, 1H).



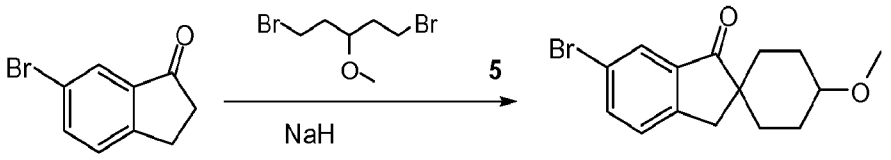
Step 3. 3-methoxypentane-1,5-diol

To a stirred suspension of LAH (1.77 g, 46.6 mmol) in THF (40 mL) under N_2 was cooled to 0 ℃ and was added dimethyl 3-methoxypentanedioate (3.7 g, 19.5 mmol). The mixture was stirred overnight. Aqueous NaOH (1 N, 12 mL) was added at 0 ℃. The mixture was filtered and the cake was washed with EtOAc 3 times. The filtrate was dried and concentrated to give 3-methoxypentane-1,5-diol (1 g, 38%). **^{1}H-NMR** ($CDCl_3$): 1.75 (m, 4H), 2.62 (s, 2H), 3.37 (m, 3H), 3.6 (m, 2H), 3.7 (m, 4H).



Step 4. 1,5-dibromo-3-methoxypentane

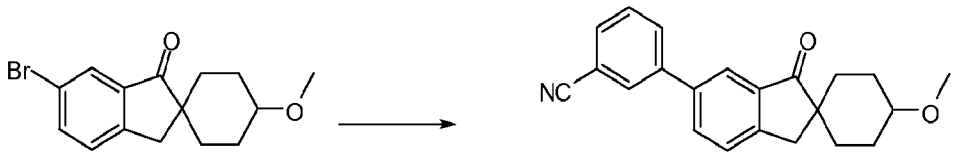
To a solution of 3-methoxypentane-1,5-diol (1 g, 7.46 mmol) in DCM (10 mL) was added PPh_3 (5.77 g, 22.05 mmol) and CBr_4 (4.87 g, 14.7 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 2 h. The mixture was filtrated and the filtrate was concentrated to give the residue, which was purified by column chromatography to give 1,5-dibromo-3-methoxypentane (1.2 g, 62%). **^{1}H-NMR** ($CDCl_3$): 2.0 (m, 4H), 3.3 (m, 3H), 3.37 (m, 4H), 3.5 (m, 1H), 3.7 (m, 4H).



Step 5. 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one

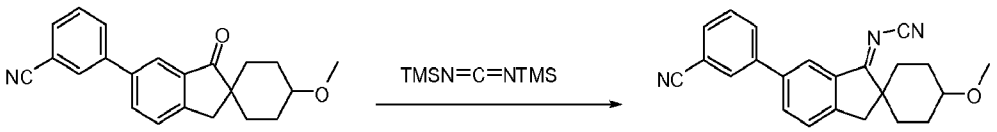
A mixture of 6-bromo-2,3-dihydro-1*H*-inden-1-one (1.037 g, 4.94 mmol) and 1,5-dibromo-3-methoxypentane (1.2 g, 4.94 mmol) in THF (16 mL) was added NaH (237.12 mg, 60%, 9.88 mmol) at room temperature. The mixture was refluxes for 3 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was dried and concentrated to give the residue, which was purified by column

chromatography to give 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (60 mg, 4%).



Step 6. 3-(4-methoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile

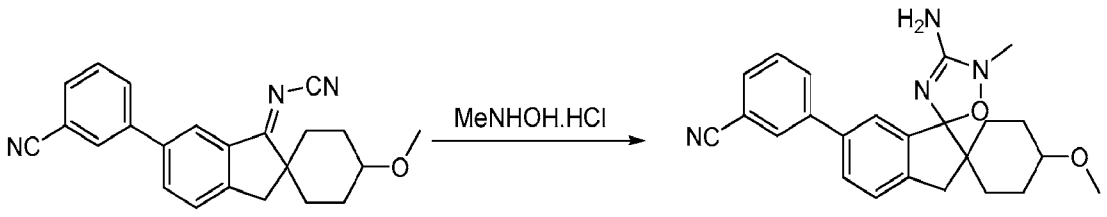
To a solution of 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (40 mg, 0.130 mmol) and 3-cyanophenylboronic acid (30.5 mg, 0.208 mmol) in Cs_2CO_3 (2 M, 0.247mL) and 1,4-dioxane (1.2 mL) under N_2 was added $Pd(PPh_3)_2Cl_2$ (7.5 mg). The mixture was stirred at 100 ℃ for 6 mimutes. After cooled to room temperature, the organic layer was dried and concentrated to give the residue, which was purified by TLC to give 3-(4-methoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (20 mg, 46%).



Step7. (*E*)-*N*-(5'-(3-cyanophenyl)-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)–yli dene) cyanamide

To a solution of 3-(4-methoxy-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl) benzonitrile (30 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was added $TiCl_4$ (0.2 mL). It was stirred in microwave at 50 ℃ for 5 minutes. Then bis-trimethylsilylcarbodiimide (0.2 mL, 0.146 mmol) was added. The resulting mixture was stirred in microwave at 60 ℃ for 10 minutes. The reaction mixture was poured into ice-water, extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to give (*E*)-*N*-(5'-(3-

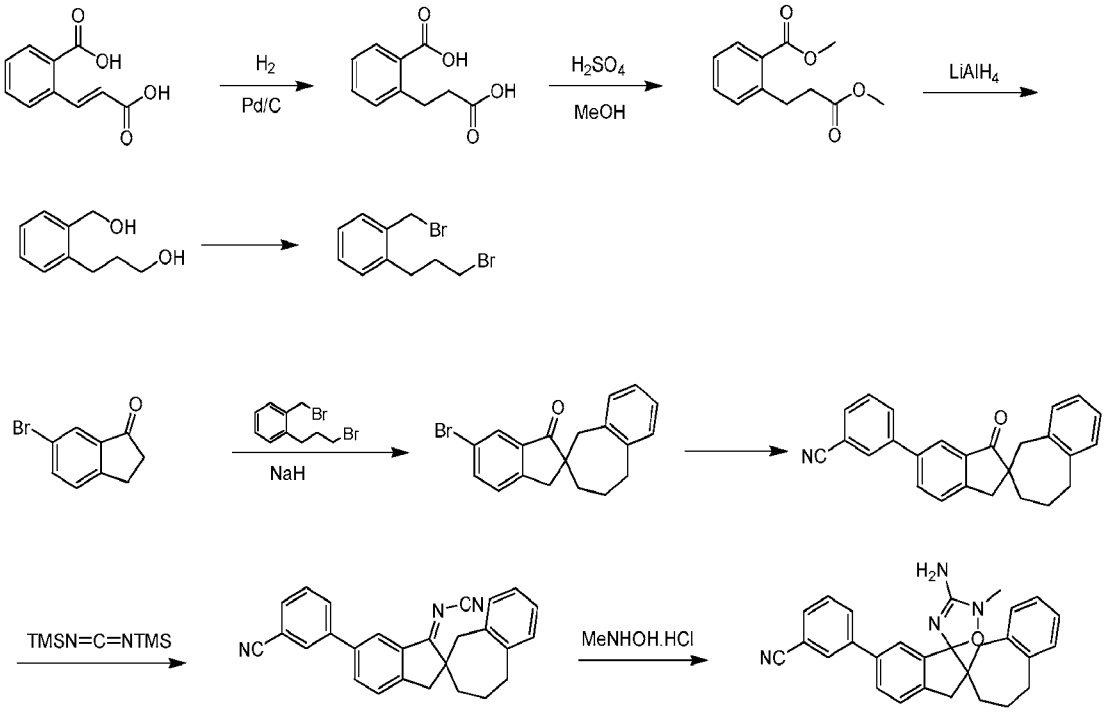
cyanophenyl)-4-methoxyspiro[cyclohexane-1,2'-indene]- 3'(1'*H*)–ylidene) cyanamide (30 mg, crude).



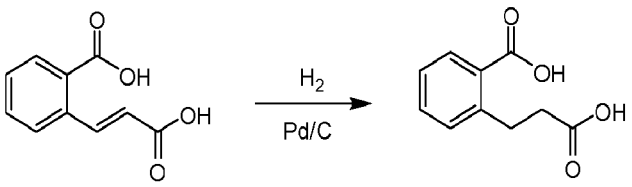
Step 8. Preparation of **Compound 25**

To a solution of methylhydroxylamine HCl salt (7 mg, 0.085 mmol) in anhydrous MeOH (1 mL) was added NaOMe (25% in MeOH (Wt%), 0.017 mL), followed by (*E*)-*N*-(5'-(3-cyanophenyl)-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)–ylidene)cyanamide (30 mg, 0.085 mmol). After stirred for 15 minutes, the solvent was removed in *vacuo*. The residue was redissolved in DCM (5 mL). The mixture was filtered, and the solvent was removed to give the residue, which was purified by preparative HPLC to give **compound 25** (2.35 mg, 7%). **^{1}H-NMR** (MeOD): 1.37 (m, 4H), 1.77 (m, 3H), 2.09 (m, 2H), 3.03 (m, 1H), 3.23 (m, 1H), 3.32 (m, 3H), 3.45(m, 3H), 7.45 (m, 1H), 7.75 (m, 4H), 8.0 (m, 2H).

Example 18. Preparation of compound 46

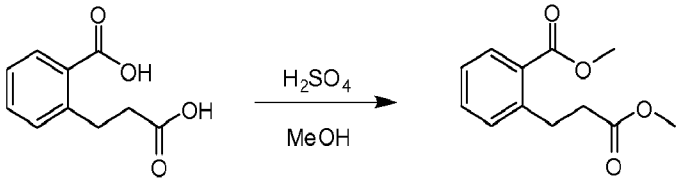


Experimental data:



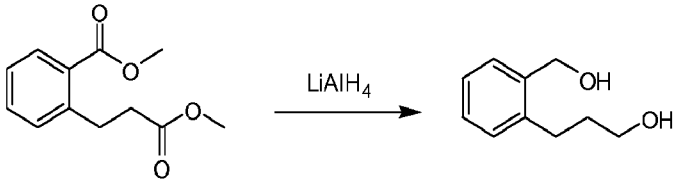
Step 1. 2-(2-carboxyethyl)benzoic acid

A mixture of 2-(2-carboxyvinyl)benzoic acid (5 g, 26 mmol) in MeOH (45 mL) was bubbled with H_2 (10 psi) at room temperature overnight. The mixture was filtered and the filtrate was concentrated to give 2-(2-carboxyethyl)benzoic acid (5.2 g, 100%). **^{1}H-NMR** ($CDCl_3$): 2.61 (m, 2H), 3.21 (m, 2H), 7.22 (m, 2H), 7.38 (m, 1H), 7.88 (m, 1H).



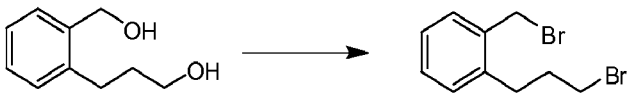
Step 2. methyl 2-(3-methoxy-3-oxopropyl)benzoate

Concentrated H_2SO_4 (1.7 mL) was added dropped into a mixture of 2-(2-carboxyethyl)benzoic acid (5 g, 25.9 mmol) in MeOH (21 mL) under ice-cooling. The mixture was refluxed overnight. The mixture was concentrated and EtOAc was added. The organic layer was dried and concentrated to give methyl 2-(3-methoxy-3-oxopropyl)benzoate (5.75 g, 100%). **^{1}H-NMR** ($CDCl_3$): 2.67 (m, 2H), 3.28 (m, 2H), 3.57 (s, 3H), 3.91 (s, 3H), 7.27 (m, 2H), 7.44 (m, 1H), 7.92 (m, 1H).



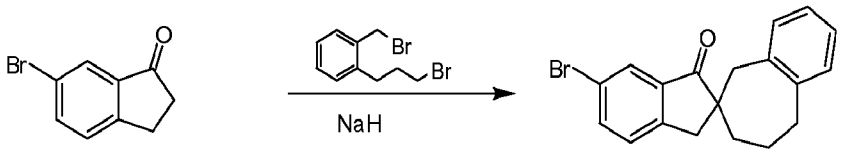
Step 3. 3-(2-(hydroxymethyl)phenyl)propan-1-ol

To a stirred solution of LAH (1.89 g, 49.77 mmol) in Et_2O (40 mL) under N_2 was cooled to 0 ℃ and was added $AlCl_3$ (1.6 g, 11.8 mmol). The mixture was allowed to warm to room temperature and stirred for 30 minutes. A mixture of methyl 2-(3-methoxy-3-oxopropyl)benzoate (2 g, 9 mmol) in Et_2O was added dropwise. The mixture was stirred overnight. Aqueous NaOH (1 N, 12 mL) was added at 0 ℃. The mixture was filtered and the cake was washed with EtOAc 3 times. The filtrate was dried and concentrated to give 3-(2-(hydroxymethyl)phenyl)propan-1-ol (1.46 g, 98%). **^{1}H-NMR** ($CDCl_3$): 1.85 (m, 2H), 2.77 (m, 2H), 3.52 (m, 2H), 4.62 (s, 2H), 7.23 (m, 2H), 7.27 (m, 2H).



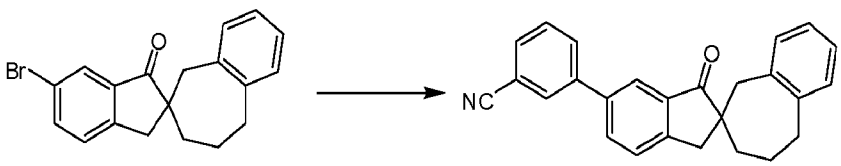
Step 4. 1-(bromomethyl)-2-(3-bromopropyl)benzene

To a solution of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (1.46 g, 8.85 mmol) in DCM (40 mL) was added PPh_3 (6.95 g, 26.5 mmol) and CBr_4 (5.86 g, 17.7 mmol) at 0 ℃. The mixture was stirred at room temperature overnight. The mixture was concentrated to give the residue, which was purified by column chromatography to give 1-(bromomethyl)-2- (3-bromopropyl)benzene (2.27 g, 88 %).



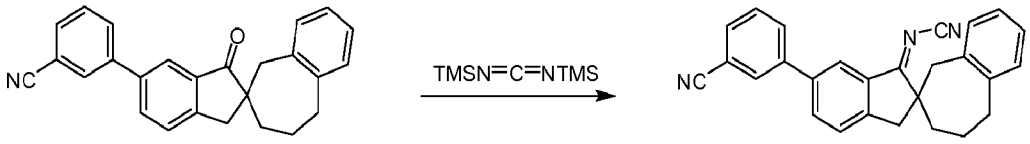
Step 5. 6'-bromo-5,7,8,9-tetrahydrospiro[benzo[7]annulene-6,2'-inden]-1'(3'*H*)-one

A mixture of 6-bromo-2,3-dihydro-1*H*-inden-1-one (1.2 g, 5.71 mmol) and 1-(bromomethyl)-2-(3-bromopropyl)benzene (1.66 g, 5.71 mmol) in THF (40 mL) was added NaH (457 mg, 60%, 11.42 mmol) at room temperature. The mixture was refluxes for 2 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was dried and concentrated to give the residue, which was purified by column chromatography to give 6'-bromo-5,7,8,9-tetrahydrospiro[benzo[7]annulene-6,2'-inden]-1'(3'*H*)-one (420 mg, 22%).



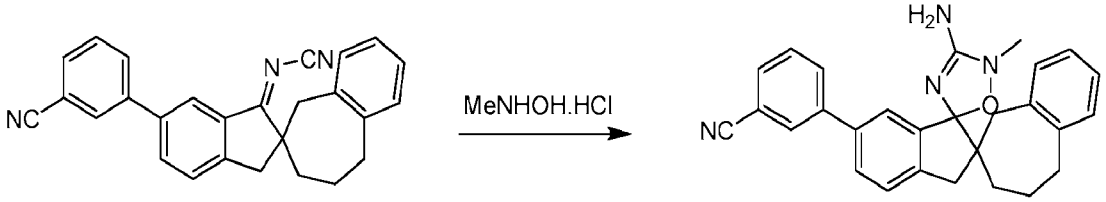
Step 6. 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[benzo[7]annulene-6,2'-indene]-6'-yl) benzonitrile

To a solution of 6'-bromo-5,7,8,9-tetrahydrospiro[benzo[7]annulene-6,2'-inden]-1'(3'*H*)-one (200 mg, 0.59 mmol) and 3-cyanophenylboronic acid (130 mg, 0.885 mmol) in Cs_2CO_3 (2 M, 1 mL) and 1,4-dioxane (4.2 mL) under N_2 was added $Pd(PPh_3)_2Cl_2$ (20 mg). The mixture was stirred at 100 ℃ for 0.7 h. After cooled to room temperature, the organic layer was dried and concentrated to give the residue, which was purified by TLC to give 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[benzo[7]annulene-6,2'-indene]-6'-yl) benzonitrile (120 mg, 56%).



Step 7. *N*-(5'-(3-cyanophenyl)-5,7,8,9-tetrahydrospiro[benzo[7]annulene-6,2'-indene]-3'(1'*H*)-ylidene)cyanamide

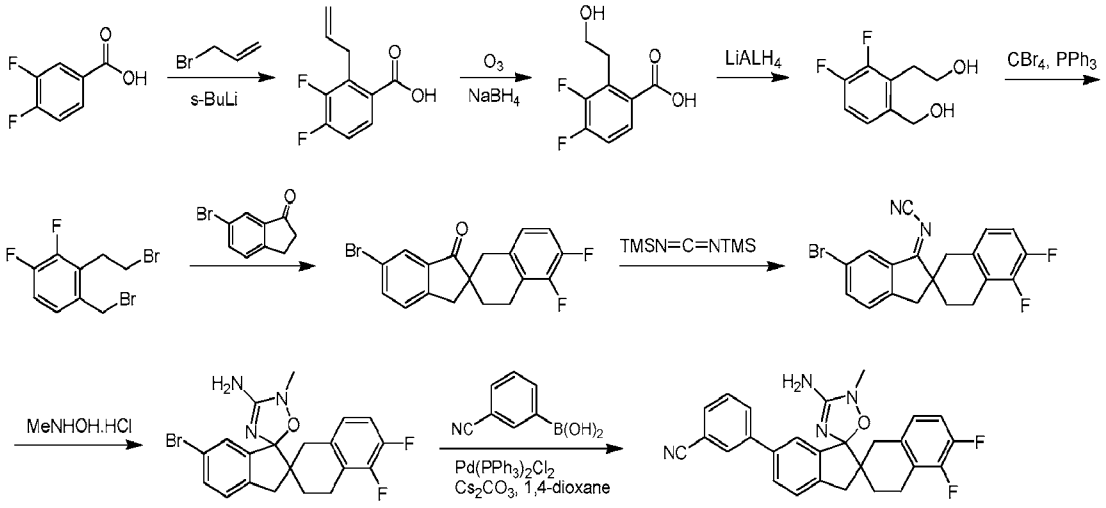
To a solution of 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[benzo[7]annulene-6,2'-indene]- 6'-yl) benzonitrile (31 mg, 0.086 mmol) in CH2Cl2 (2mL) was added $TiCl_4$ (66 mg). It was stirred in microwave at 50 ℃ for 5 minutes. Then bis-trimethylsilylcarbodiimide (112 mg, 0.6 mmol) was added. The resulting mixture was stirred in microwave at 60 ℃ for 10 minutes. The reaction mixture was poured into ice-water, extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to give *N*-(5'-(3-cyanophenyl)-5,7,8,9-tetrahydrospiro[benzo[7]annulene- 6,2'-indene]-3'(1'*H*)-ylidene)cyanamide (50 mg, crude).



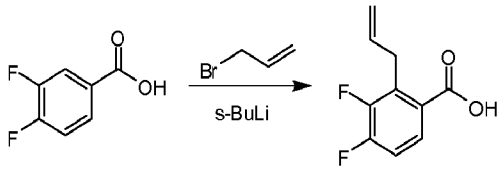
Step 8. Preparation of **Compound 46**

To a solution of methylhydroxylamine HCl salt (13 mg, 0.13 mmol) in anhydrous MeOH (2 mL) was added NaOMe (25% in MeOH (Wt.%), 5 drops), followed by *N*-(5'-(3-cyanophenyl)-5,7,8,9-tetrahydrospiro[benzo[7]annulene-6,2'-indene]-3'(1'*H*)-ylidene)cyanamide (50 mg, 0.13 mmol). After stirred for 10 minutes, the solvent was removed in *vacuo*. The residue was redissolved in DCM (5 mL). The mixture was filtered, and the solvent was removed to give the residue, which was purified by preparative HPLC to give **compound 46** (2.38 mg, 4%). **^{1}H-NMR** (MeOD): 1.41 (m, 1H), 1.72-2.23 (m, 3H), 2.46 (m, 2H), 2.81 (m, 3H), 3.08 (m, 1H), 3.32 (m, 3H), 6.62 (m, 1H), 7.02 (m, 3H), 7.21 (m, 1H), 7.62 (m, 4H), 7.92 (m, 2H).

Example 19. **Preparation of compound 48**

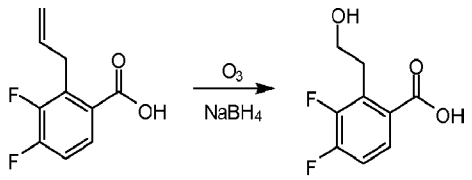


Experimental data:



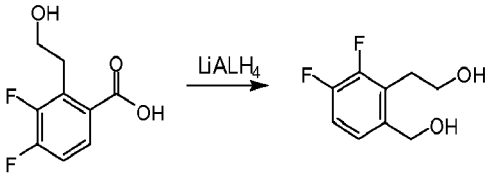
Step 1. 2-allyl-3,4-difluorobenzoic acid

To a solution of TMEDA (32.2 g, 0.278 mol) in dry THF (150 mL) was added *s*-BuLi (1.3 M, 0. 278 mol, 214 mL) at -78 ℃. The mixture was stirred at this temperature for 0.5 hour, and then a solution of 3,4-difluorobenzoic acid (20 g, 0.127 mol) in THF (100 mL) was added dropwise. After stirring for 1 hour, CuBr.DMS (3.9 g, 0.019 mol, 15% mol) was added, followed by 3-bromoprop-1-ene (46 g, 0.38 mol) in 50 mL of THF. The reaction mixture was allowed to warm to room temperature and was quenched with water. The aqueous layer was washed with Et_2O, and acidified with 4 N HCl. The mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 2-allyl-3,4-difluorobenzoic acid (22 g, 55%). **^{1}H NMR** ($CDCl_3$): 3.91 (d, 2H), 5.06 (m, 2H), 6.01 (m, 1H), 7.12 (m, 1H), 7.90 (m, 1H).



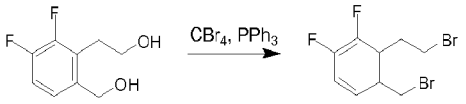
Step 2. 3,4-difluoro-2-(2-hydroxyethyl)benzoic acid

A steam of O_3 was bubbled through a solution of 2-allyl-3,4-difluorobenzoic acid (13 g, 0.065 mol) in absolute CH_2Cl_2 (200 mL) at -78 ℃ until the mixture was turned blue. Then $NaBH_4$ (7.25 g, 0.196 mol) in was added to the above mixture, and the final mixture was stirred at room temperature overnight. The solution was concentrated. Water was added at 0 ℃, and the mixture was acidified by adding 6 N HCl, and was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 3,4-difluoro-2-(2-hydroxyethyl)benzoic acid (8.2 g, crude).



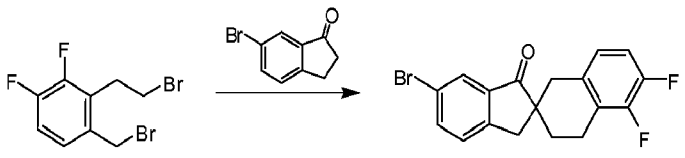
Step 3. 2-(2,3-difluoro-6-(hydroxymethyl)phenyl)ethanol

To a solution of $LiAlH_4$ (2.45 g, 0.065 mol) in THF (30 mL) was added 3,4-difluoro- 2-(2-hydroxyethyl)benzoic acid (8.7 g, 0.043 mol) in THF (60 mL) at 0 ℃. The mixture was stirred at aoom temperature overnight. The reaction was quenched with 3 mL of H_2O, followed by aqueous NaOH solution (3 mL, 10%). The solution was filtered and the filtrated was concentrated to give the residue, which was purified by chromatography to give 2-(2,3-difluoro-6-(hydroxymethyl)phenyl)ethanol (2.5 g, 31%). **^{1}H NMR** ($CDCl_3$): 2.99 (m, 2H), 3.58 (s, 2H), 3.83 (t, 2H), 4.52 (s, 2H), 7.03 (m, 2H).



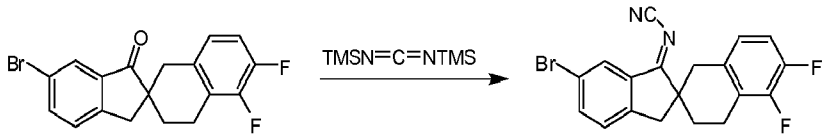
Step 4. 2-(2-bromoethyl)-1-(bromomethyl)-3,4-difluorobenzene

To a solution of 2-(2,3-difluoro-6-(hydroxymethyl)phenyl)ethanol (2.5 g, 13.3 mmol) and CBr_4 (10.9 g, 33 mmol) in DCM (100 mL) was added PPh_3 (8.65 g, 33 mmol) at 0 ℃ in portions. The mixture was stirred at room temperature overnight. The solution was concentrated. The residue was re-dissolved in Et_2O and filtered. The filtrated was concentrated to give the crude product, which was purified by chromatography to afford 2-(2-bromoethyl)-1-(bromomethyl)-3,4-difluorobenzene (3.2 g, 77%). **^{1}H NMR** ($CDCl_3$): 3.37 (t, 2H), 3.63 (t, 2H), 4.53 (s, 2H), 7.11 (m, 2H).



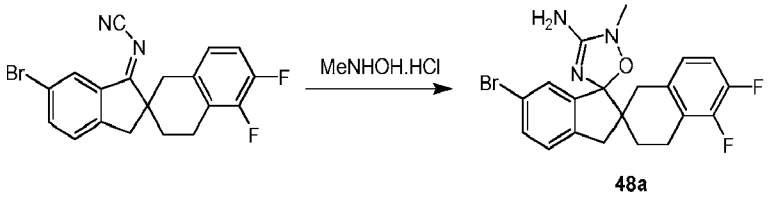
Step.5 6-bromo-5',6'-difluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one

To a solution of 2-(2-bromoethyl)-1-(bromomethyl)-3,4-difluorobenzene (3 g, 9.62 mmol) and 6-bromo-2,3-dihydro-1*H*-inden-1-one (2.03 mg, 9.62 mmol) in THF (20 mL) was added NaH (0.58 mg, 14.43 mmol), and the mixture was refluxed for 2 hour. The reaction was cooled and quenched with ice-water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give the residue, which was purified by preparative TLC to afford 6-bromo-5',6'-difluoro-3',4'- dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one (1.6 g, 46%). **^{1}H NMR** ($CDCl_3$): 1.68 (m, 1H), 2.01 (m, 1H), 2.47 (d, 1H), 2.72 (m, 2H), 2.89 (d, 1H), 3.07 (m, 2H), 6.71 (m, 1H), 6.86 (m, 1H), 7.22 (d, 1H), 7.63 (d, 1H), 7.92 (s, 1H).



Step 6. (*Z*)-*N*-(5-bromo-5',6'-difluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)-ylidene)cyanamide

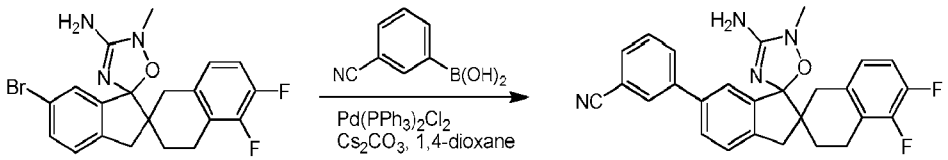
To a solution of 6-bromo-5',6'-difluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one (150 mg, 0.41 mmol) in dried CH_2Cl_2 (1 mL) was added $TiCl_4$ (1 M solution in DCM, 0.1.24 mmol) dropwise within 15 minutes, and stirred for 1 h. Then to this mixture was added *bis*-trimehtlysilylcarbodiimide (234 mg, 1.24 mmol) dropwise. The resulting mixture was stirred overnight. The reaction mixture was poured into ice-water, extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give (*Z*)-*N*-(5-bromo-5',6'-difluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)-ylidene)cyanamide (180 mg, crude), which was used for the next step without further purification.



48a

Step 7. Compound 48a

To a solution of MeNHOH.HCl (39 mg, 0.47 mmol) in anhydrous MeOH (5 mL) was added NaOMe (25 *wt*% in MeOH, 91 mg, 0.42 mmol), followed by (*Z*)-*N*-(5-bromo-5',6'-difluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)-ylidene)cyanamide (180 mg, 0.47 mmol). After stirring for 5 minutes, the solvent was removed in vacuum. The residue was re-dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated to give the residue, which was purified by preparative TLC to afford the compound **48a** (50 mg, 24%). **^{1}H NMR** (MeOD): 1.72 (m, 1H), 2.09 (m, 1H), 2.32 (d, 1H), 2.53 (m, 1H), 2.69 (m, 2H), 2.97 (m, 2H), 3.06 (d, 3H), 6.76 (m, 1H), 6.88 (m, 1H), 6.98 (m, 1H), 7.37 (d, 1H), 7.43 (m, 1H).

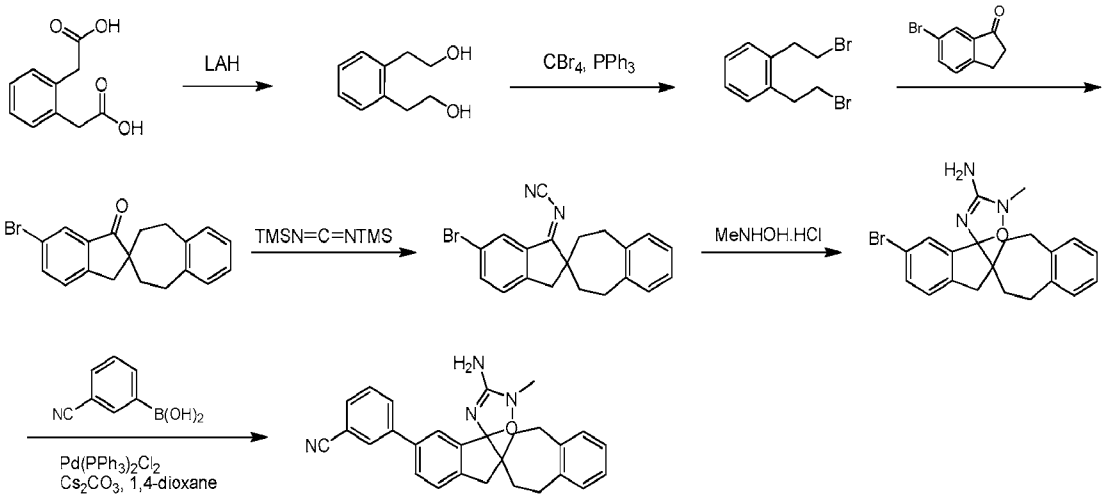


48a

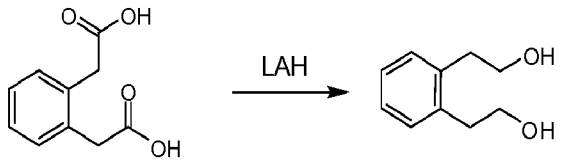
Step 8. **Compound 48**

$Pd(PPh_3)_2Cl_2$ (10 mg) in a 10 mL of flask under N_2 was treated sequentially with the compound 48a (50 mg, 0.146 mmol) in 1,4-dioxane (1 mL), Cs_2CO_3 (2 N, 0.2 mL) and 3-cyanophenylboronic acid (43 mg, 0.29 mmol). The mixture was heated under 110 ℃ at N_2 under microwave for 20 minutes. The reaction mixture was concentrated in *vacuo* to give the residue, which was purified by preparative TLC and HPLC to give **compound 48** (6.73 mg, 10%). **^{1}H NMR** (MeOD): 1.48 (m, 1H), 2.03 (m, 1H), 2.51 (d, 1H), 2.77 (m, 2H), 2.93-3.13 (m, 3H), 3.37 (m, 3H), 6.88 (m, 1H), 7.03 (m, 1H), 7.39 (m, 1H), 7.62-7.83 (m, 4H), 7.97 (m, 2H).

Example 20. Preparation of compound 22

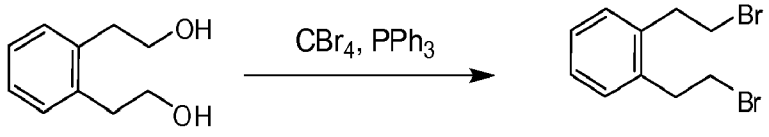


Experimental data:



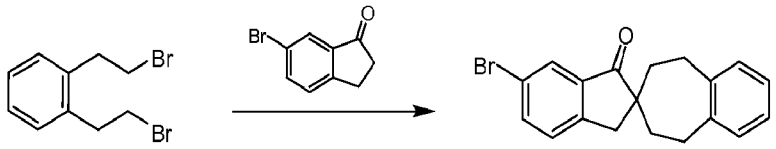
Step 1. 2,2'-(1,2-phenylene)diethanol

To a solution of 2,2'-(1,2-phenylene)diacetic acid (10 g, 51.5 mmol) in THF (100 mL) was added to LAH in THF (90 mL) dropwise, the mixture was refluxed for 18 hours. The mixture was cooled in ice bath and carefully added water (8 mL) dropwise, followed by 1 N NaOH (8 mL), then removed the ice bath added water slowly with stirring until the gray precipitate turns white. The mixture was filtrated and the filtrate was concentrated to give crude 2,2'-(1,2-phenylene)diethanol (8 g, 94%). **^{1}H-NMR** ($CDCl_3$): 2.02 (s, 3H), 2.97 (m, 4H), 3.83 (m, 2H), 4.12 (m, 1H), 4.24 (t, 1H), 7.19 (m, 4H).



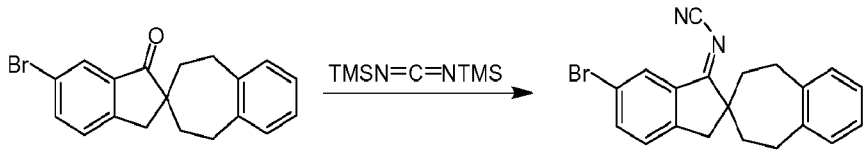
Step 2. 1,2-bis(2-bromoethyl)benzene

To a solution of 2,2'-(1,2-phenylene)diethanol (5 g, 30.1 mmol), perbromo methane (24.7 g, 75.3 mmol) in DCM (200 mL) was added triphenylphosphine (19.73 g, 75.3 mmol) at 0 ℃, the mixture was stirred at room temperature for 18 hours. The mixture was concentrated, redissolved by Et_2O, filtered, the organic layer was concentrated to give crude product, which was purified by column chromatography to give 1,2-bis(2-bromoethyl)- benzene (2.3 g, 26%). **^{1}H-NMR** ($CDCl_3$): 3.12 (t, 4H), 3.47 (t, 4H), 7.16 (m, 4H).



Step 3. 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'*H*)-one

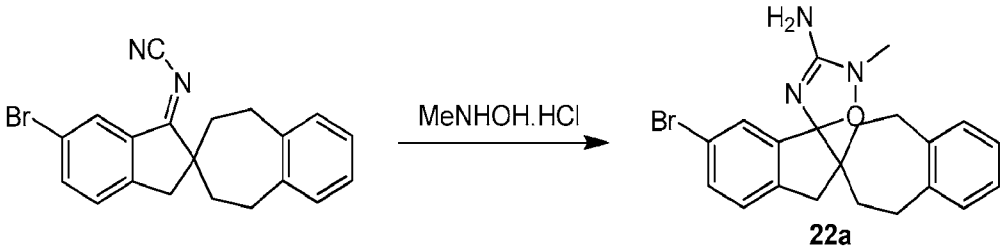
A mixture of 6-bromo-indan-1-one (300 mg, 1.43 mmol), 1,2-bis(2-bromoethyl)- benzene (414.3 mg, 1.43 mmol) in THF (10 mL) was added NaH (114 mg, 2.86 mmol) at room temperature, the mixture was refluxed for 2 hours. The mixture was quenched with water, concentrated, then extracted with DCM, washed with brine, dried over Na_2SO_4, concentrated to 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'*H*)-one (20 mg, 5%).



Step 4. (*Z*)-*N*-(5'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-indene]-3'(1'*H*)-ylidene)cyanamide

To a solution of 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'*H*)-one (20 mg, 0.059 mmol) in DCM (2 mL) was added $TiCl_4$ (44.7 mg, 0.235 mmol) dropwise, the mixture was stirred at 50 ℃ at Ar_2 under microwave for 20 minutes, *N*,*N*'-methanediylidenebis(1,1,1-trimethylsilanamine) (43.8 mg, 0.235 mmol)

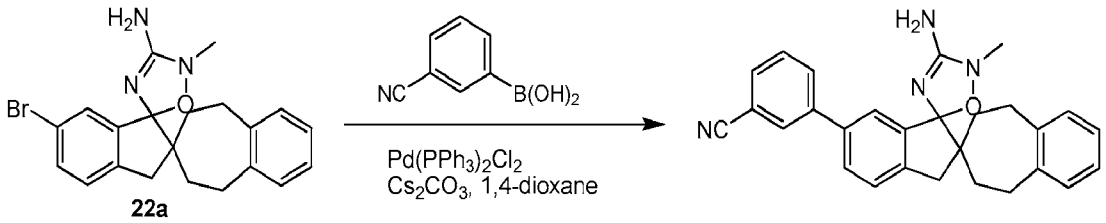
was added dropwise. The mixture was stirred at 60 ℃ at Ar_2 under microwave for 10 minutes and repeated the same operation for one time and then poured into ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2, which was combined with the organic layer. The organic layer was dried and concentrated to give crude (*Z*)-*N*-(5'-bromo-5,6,8,9- tetrahydrospiro[benzo[7]annulene-7,2'-indene]-3'(1'*H*)-ylidene)cyanamide (20 mg, 4%).



22a

Step 5. The compound 22a

To a solution of *N*-methyl-hydroxylamine hydrochloride (4.59 mg, 0.055 mmol) in MeOH (3 mL) was added MeONa (0.02 mL, 25% (Wt.) in MeOH), followed by (*Z*)-*N*-(5'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-indene]-3'(1'*H*)-ylidene)cyanamide (20 mg, 0.055 mmol). After stiring for 10 minutes, the solvent was removed in *vacuo* to give the crude compound **22a** (20 mg).



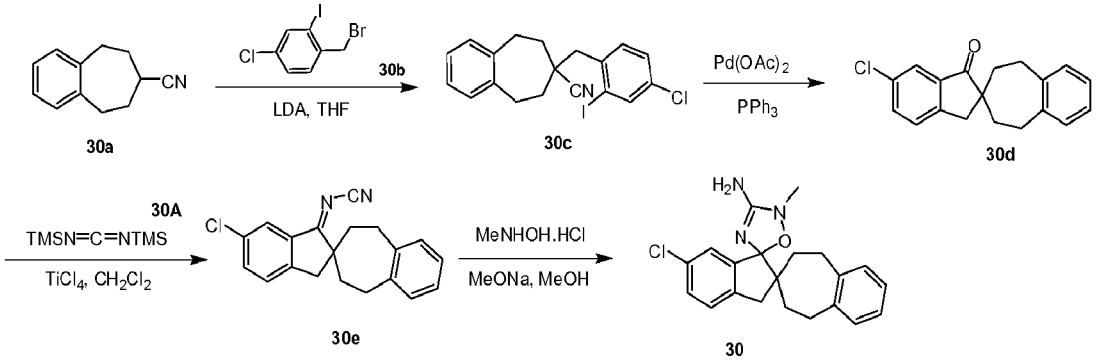
22a

Step 6. **Compound 22**

$Pd(PPh_3)_2Cl_2$ (10 mg) in a 10 mL of tube under Ar_2 was treated sequentially with compound 1 (20 mg, 0.049 mmol) in 1,4-dioxane (1 mL), Cs_2CO_3 (2 N, 0.3 mL) and 3-cyanophenylboronic acid (14.4 mg, 0.097 mmol). The mixture was heated under microwave at 120℃ for 25 minutes. The reaction mixture was concentrated in *vacuo* to give the residue, which was purified by preparative TLC and then by preparative HPLC

to give pure **compound 22** (1.12 mg, 5%). **^{1}H-NMR** (MeOD): 1.53 (t, 0.7H), 1.71 (m, 1H), 1.89 (m, 1.5H), 2.16 (m, 0.6H), 2.79 (m, 2H), 3.12 (m, 3H), 3.27 (m, 3H), 3.49 (m, 1H), 3.63 (s, 1H), 7.12 (m, 4H), 7.52 (d, 0.6H), 7.71 (m, 1.5H), 7.79 (m, 2H), 7.97 (m, 1H), 8.03 (m, 1H).

Example 21. Preparation of compound 30



Step 1: Preparation compound 30c

To a solution of LDA (5.2 mL, 9.36 mmol, 1.8 M in THF) in THF (10 mL) was added the solution of compound **30a** (800 mg, 4.68 mmol) in THF (15 mL) slowly at -60 °C. It was stirred at -60 °C for 30 min. To the resulting mixture the solution of compound **30b** (1.38 g, 4.21 mmol) in THF (4 mL) was added slowly. The resulting mixture was stirred at -60 °C for 1.5 h. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to dryness to give the crude product, which was purified by chromatography to give compound **30c** (750 mg, yield 38%) as yellow solid.

^{1}H NMR ($CDCl_3$ 400 MHz): δ 7.74 (s, 1H), 7.58-7.73 (m, 1H), 7.43 (m, 1H), 7.11 (m, 4H), 2.99-3.13 (m, 2H), 2.97 (s, 2H), 2.66 (m, 2H), 2.04-2.10 (m, 2H), 1.52-1.61 (m, 2H).

Step 2: Preparation of compound 30d

An 100 mL flask was charged with compound **30c** (0.75 g, 1.78 mmol), $Pd(OAc)_2$ (0.0523 g, 0.23 mmol), Ph_3P (0.136 g, 0.52 mmol), DMF (28 mL) and H_2O (3.13 mL). The resulting mixture was degassed and then Et_3N (0.216 g, 2.14 mmol) was added under nitrogen. The reaction mixture was stirred at 130 °C for 4 h. Then the mixture was cooled to room temperature, diluted with water (10 mL). The solution was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness to give the crude product, which was purified by chromatography to give compound **30d** (30 mg, yield 8%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.74 (s, 1H), 7.58-7.73 (m, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.14 (m, 4H), 3.16 (s, 2H), 3.04-2.97 (m, 2H), 2.89 (br s, 2H), 1.91-1.85 (m, 2H), 1.69-1.63 (m, 2H).

Step 3: Preparation of compound 30e

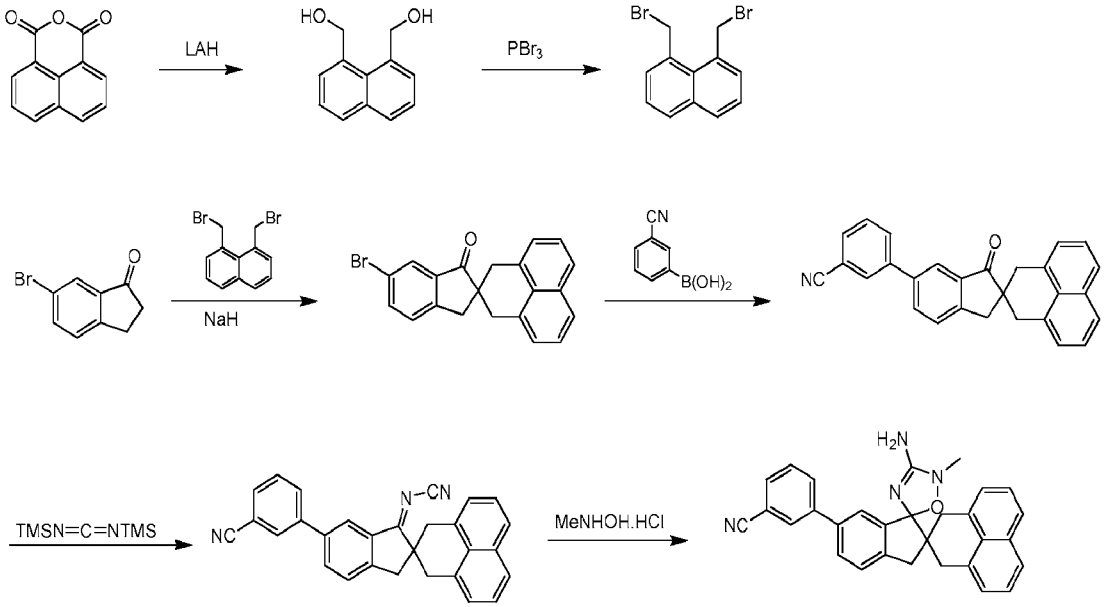
To a solution of compound **30d** (30 mg, 0.102 mmol) in CH_2Cl_2 (2mL) was added $TiCl_4$ (0.408mL, 0.408 mmol). It was stirred at 50 °C for 6 min in microwave. To the resulting mixture bis-trimethylsilylcarbodiimide (0.05mL, 0.224 mmol) was added. The resulting mixture was stirred at 60 °C for 12 min in microwave. TLC showed that the reaction was completed. The reaction mixture was poured into ice-water (10 mL). The solution was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness to give compound **30e** (30 mg, 93% crude yield) as yellow solid, which was used directly for the next step without purification.

Step 4: Preparation of Compound 30

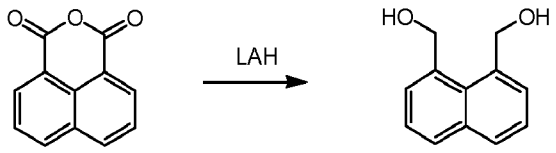
To a solution of methylhydroxylamine HCl salt (7.9 mg, 0.094 mmol) in anhydrous MeOH (2 mL) was added a solution of NaOMe (10 wt%, 0.048 mL, 0.0846 mmol) in methanol followed by compound **30e** (30 mg, 0.094 mmol). After being stirred for 20 min, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL). The mixture was filtered, and the solvent was removed under reduce

pressure to give the residue, which was purified by HPLC to give compound **30** (4.9 mg, yield 14%) as a white solid. **LC-MS** t_R = 1.017 min and 1.078 min in 2 min chromatography, MS (ESI) *m/z* 368[M+H]$^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.63-7.77 (m, 1H), 7.51 (m, 1H),7.40-7.48 (m, 1H), 7.10-7.14 (m, 4H) 3.32 (s, 3H), 2.97-3.12 (m, 3H), 2.77-2.84 (s, 2H), 2.05 (m, 1H), 1.83-1.92 (m, 2H), 1.55-1.69 (m, 2H).

Example 22. Preparation of compound 61



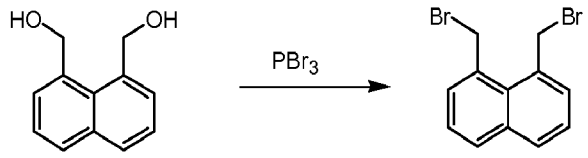
Experimental data:



Step 1. (8-hydroxymethyl-naphthalen-1-yl)-methanol

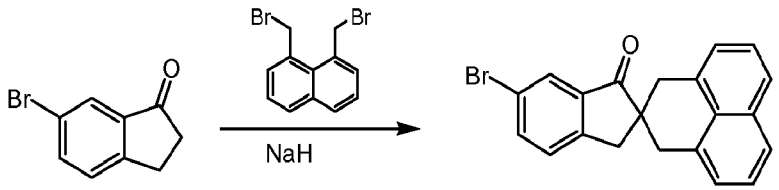
Benzo[de]isochromene-1,3-dione (30 g, 0.15 mol) in anhydrous THF (300 mL) was added dropwise to a solution of LAH (10 g, 0.38 mol) in anhydrous THF (200 mL). The result reaction mixture was refluxed for 3 h, then allowed to cool and stand overnight at room temperature. Water and 10% aq. NaOH was added dropwise, filtered. The filtrate was concentrated in vacuum to give the crude product, which was

used directly without purification (1.15 g, crude). **^{1}H-NMR ($CDCl_3$)**: 5.06 (m, 4H), 5.23 (m, 2H), 7.42 (m, 2H), 7.60 (m, 2H), 7.82 (m, 2H).



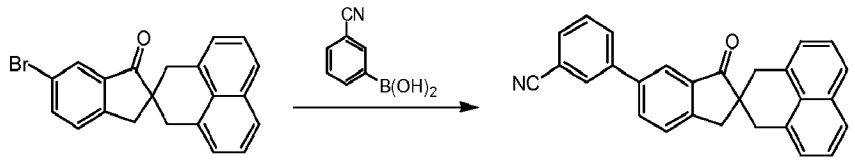
Step 2. 1,8-bis-bromomethyl-naphthalene

A mixture of naphthalene-1,8-diyldimethanol (1.15 g, 6 mmol) and CH_2Cl_2 (10 mL) was stirred mechanically and PBr_3 (1.2 mL) added dropwise over 20 mins. During the first half of the addition the solution refluxed spontaneously. After stirring overnight at room temperature, water was added dropwise with stirring over 20 min, which again caused refluxing and evolution of much HBr. After stirring for an additional 2 h, water was added and the layers separated and the organic layer washed with water. The organic layer was evaporated in vacuum to give the crude product, which was used directly without purification (1.6 g, 84%). **^{1}H-NMR** ($CDCl_3$): 5.30 (s, 4H), 7.44 (m, 2H), 7.62 (m, 2H), 7.87 (m, 2H).



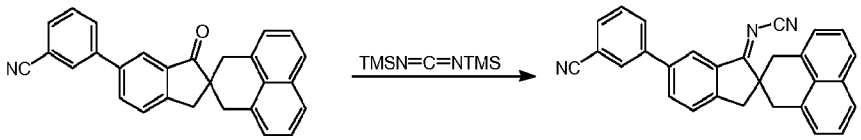
Step 3. 6-bromo-1',3'-dihydrospiro[indene-2,2'-phenalen]-1(3*H*)-one

A mixture of 6-bromo-2,3-dihydro-1*H*-inden-1-one (400 mg, 1.9 mmol) and 1,8-bis(bromomethyl)naphthalene (596 mg, 1.9 mmol) in THF (20 mL) was added NaH (152 mg, 3.8 mmol) at room temperature, the mixture was heated under reflux for 2 h. The mixture was quenched with water, concentrated, then extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated to give 6-bromo-1',3'-dihydrospiro[indene-2,2'- phenalen]-1(3*H*)-one (386 mg, 56%). **^{1}H-NMR** ($CDCl_3$): 2.79 (d, 2H), 3.50 (d, 2H), 7.12 (m, 1H), 7.18 (m, 2H), 7.36 (m, 2H), 7.60 (m, 1H), 7.71 (m, 1H), 7.92 (m, 1H).



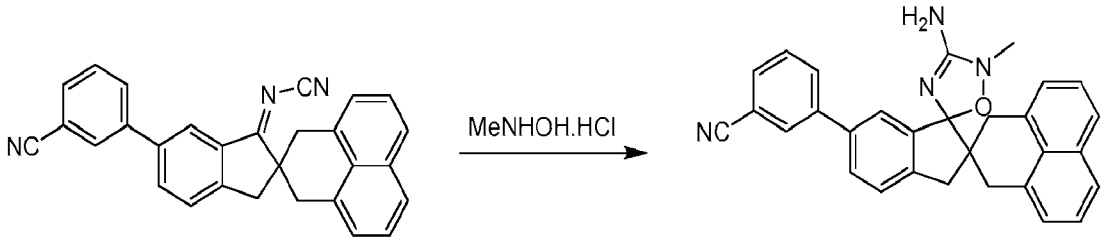
Step 4. 3-(1-oxo-1,1',3,3'-tetrahydrospiro[indene-2,2'-phenalene]-6-yl)benzonitrile

6-Bromo-1',3'-dihydrospiro[indene-2,2'-phenalen]-1(3*H*)-one (200 mg, 0.57 mmol) and 3-cyanophenylboronic acid (168 mg, 1.17 mmol) was dissolved in 1,4-dioxane (5 mL), Cs_2CO_3 (0.6 mL, 2 M) was added. Then $Pd(PPh_3)_2Cl_2$ (10 mg) was added under N_2. The mixture was heated at 100 ℃ for 10 minutes under microwave. The solvent was removed in vacuum. The crude product was purified by preparative TLC to give 3-(1-oxo-1,1',3,3'- tetrahydrospiro[indene-2,2'-phenalene]-6-yl)benzonitrile (130 mg, 60%).



Step 5. (*E*)-*N*-(5-(3-cyanophenyl)-1',3'-dihydrospiro[indene-2,2'-phenalene]-3(1H)-ylidene) cyanamide

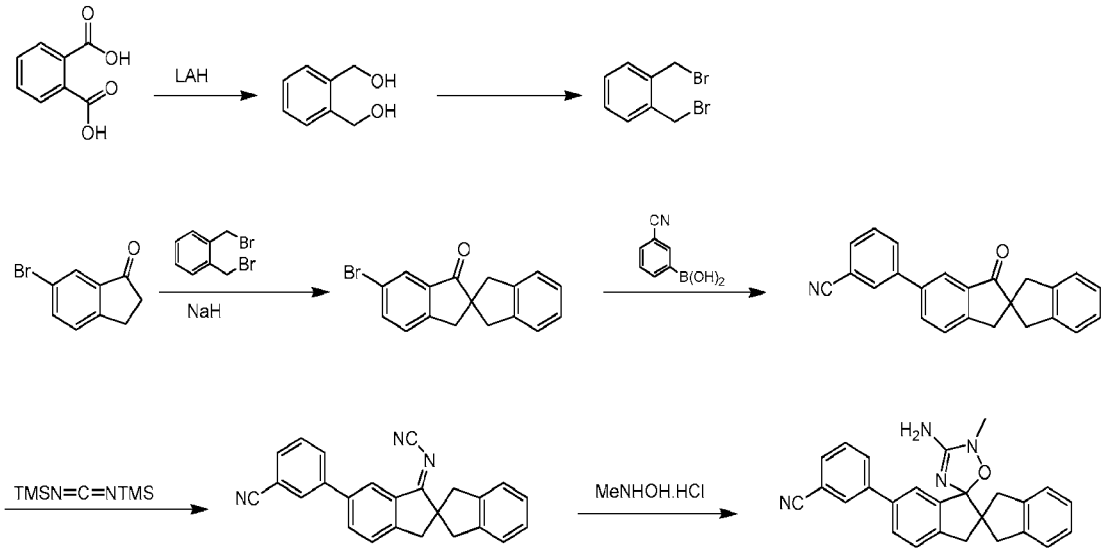
To a solution of 3-(1-oxo-1,1',3,3'-tetrahydrospiro[indene-2,2'-phenalene]-6-yl) benzonitrile (130 mg, 0.34 mmol) in DCM (2 mL) was $TiCl_4$ (257 mg, 1.35 mmol), then the mixture was heated at 50 ℃ for 5 minutes under microwave. Then the reagent was added, and it was heated at 60 ℃ for 10 minutes. The reaction mixture was poured into ice-water, and then extracted with DCM. The organic layer was washed with brine, dried and concentrated to give the crude product. The crude product was used directly without purification (70 mg, crude).



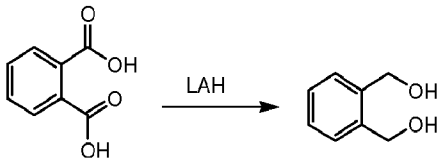
Step 6. **Compound 61**

To a solution of MeNHOH.HCl in anhydrous MeOH was added NaOMe (25% in MeOH) followed by (*E*)-*N*-(5-(3-cyanophenyl)-1',3'-dihydrospiro[indene-2,2'-phenalene]- 3(1*H*)-ylidene)cyanamide (35 mg, 0.085 mmol). After stirring for 10 minutes, the solvent was removed in vacuum. The residue was dissolved in DCM. The mixture was filtered and the solvent was removed in vacuum. The crude product was purified by preparative HPLC to give **compound 61** (1.02 mg, 3%). **^{1}H-NMR** (MeOD): 2.76 (m, 1H), 2.97 (m, 1H), 3.06 (s, 2H), 3.28 (m, 3H), 3.41 (m, 1H), 3.58 (m, 1H), 7.18 (m, 1H), 7.26 (m, 1H), 7.36 (m, 2H), 7.58 (m, 1H), 7.68 (m, 2H), 7.72 (m, 1H), 7.81 (m, 1H), 7.90 (m, 1H), 7.98 (m, 1H)

Example 23. **Preparation of compound 40**

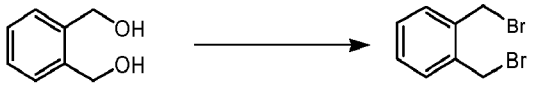


Experimental data:



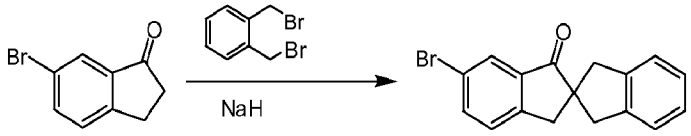
Step 1. 1,2-phenylenedimethanol

A solution of phthalic acid (9 g, 0.05 mol) in anhydrous THF (200 mL) was added to LAH (7.6 g, 0.2 mol) in THF (250 mL) dropwise, and the mixture was refluxed for 18 hours. The mixture was cooled in ice bath and carefully added water dropwise, followed by 50% NaOH (150 mL), and then removed the ice bath added water slowly with stirring until the gray precipitate turns white. The mixture was filtrated and the filtrate was concentrated to give crude 1,2-phenylenedimethanol (7 g, 92%).



Step 2. 1,2-bis(bromomethyl)benzene

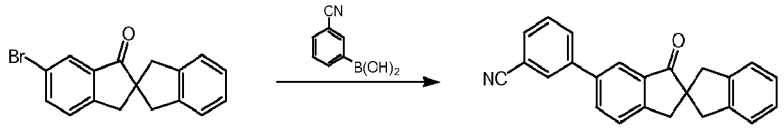
To a solution of 1,2-phenylenedimethanol (2.6 g, 17 mmol), perbromo methane (13.7 g, 41.8 mmol) in DCM (100 mL) was added triphenylphosphine (10.95 g, 41.8 mmol) at 0 ℃, the mixture was stirred at room temperature for 18 hours. The mixture was concentrated, redissolved by Et_2O, filtered, the organic layer was concentrated to give crude 1,2-bis(bromomethyl)benzene (4.2 g, 89%).



Step 3. 6-bromo-1',3'-dihydro-2,2'-spirobi[inden]-1(3*H*)-one

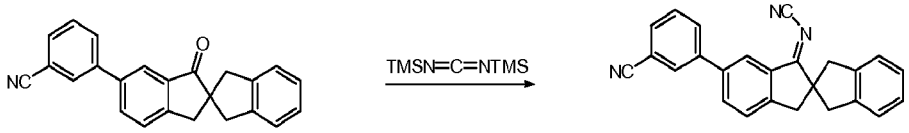
A mixture of 6-bromo-indan-1-one (1.05 g, 5 mmol), 1,2-bis(bromomethyl)benzene (1.31 g, 5 mmol) in THF (50 mL) was added NaH (240 mg, 10 mmol) at room temperature, the mixture was refluxed for 2 hours. The mixture was

quenched with water, concentrated, then extracted with DCM, washed with brine, dried over Na_2SO_4, concentrated to 6-bromo-1',3'-dihydro-2,2'-spirobi[inden]-1(3*H*)-one (1.8 g, 33%).



Step 4. 3-(1-oxo-1,1',3,3'-tetrahydro-2,2'-spirobi[indene]-6-yl)benzonitrile

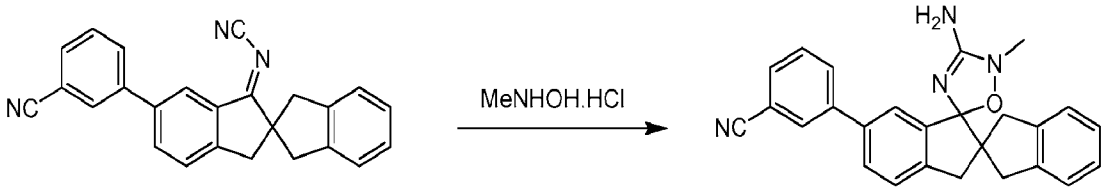
6-Bromo-1',3'-dihydro-2,2'-spirobi[inden]-1(3*H*)-one (314 mg, 1 mmol), 3-cyanophenylboronic acid (294 g, 2 mmol) in [1,4]-dioxane (12 mL), Cs_2CO_3 (2 N, 3.2 mL), then $Pd(PPh_3)_2Cl_2$ (5 mg, 0.01 mmol) was added under Ar_2, the mixture was stirred at 100 ℃ for 5 minutes under microwave. The reaction mixture was concentrated in *vacuo* to give the residue, which was purified by TLC to give 3-(1-oxo-1,1',3,3'-tetrahydro-2,2'-spirobi[indene]- 6-yl)benzonitrile (34 mg, 10%). **^{1}H-NMR** ($CDCl_3$):3.00 (d, 2H), 3.33 (s, 2H), 3.62 (d, 2H), 7.31 (m, 3H), 7.67 (m, 2H), 7.78 (m, 1H), 7.96 (m, 2H), 8.02 (m, 1H), 8.11 (m, 1H).



Step 5. (*Z*)-*N*-(5-(3-cyanophenyl)-1',3'-dihydro-2,2'-spirobi[indene]-3(1*H*)-ylidene) cyana mide

To a solution of 3-(1-oxo-1,1',3,3'-tetrahydro-2,2'-spirobi[indene]- 6-yl)benzonitrile (34 mg, 0.1 mmol) in DCM (5 mL) was added $TiCl_4$ (76 mg, 0.4 mmol) dropwise, the mixture was stirred at 50 ℃ at Ar_2 under microwave for 5 minutes, *N*,*N*'-methanediylidenebis(1,1, 1-trimethylsilanamine) (74 mg, 0.4 mmol) was added dropwise. The mixture was stirred at 60 ℃ at Ar_2 under microwave for 10 minutes and poured into ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2, which was combined with the organic layer. The organic layer was dried and concentrated to

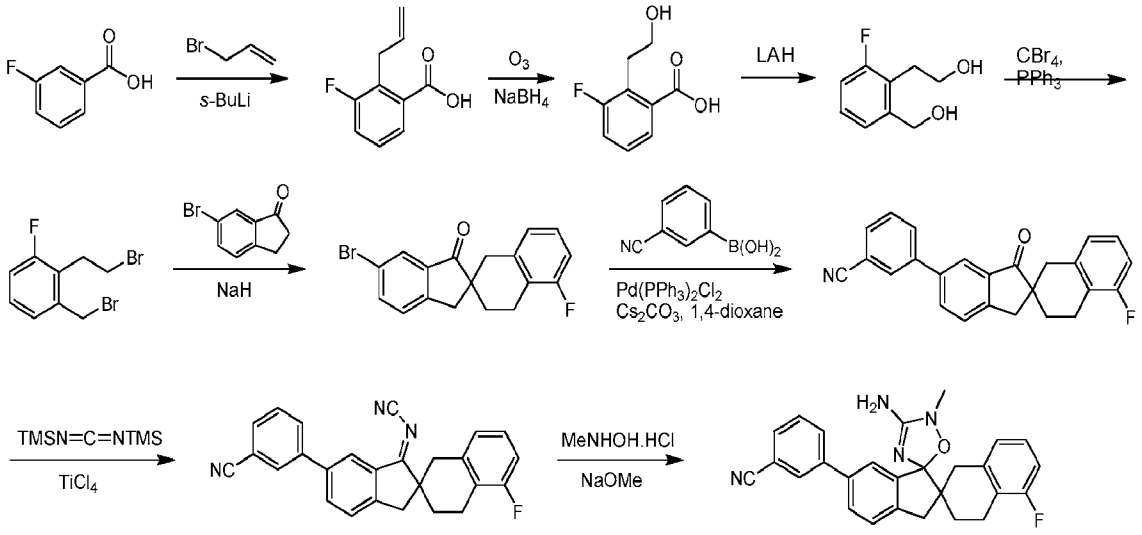
give crude ((*Z*)-*N*-(5-(3-cyanophenyl)-1',3'- dihydro-2,2'-spirobi[indene]-3(1*H*)-ylidene) cyana mide (36 mg, 99%).



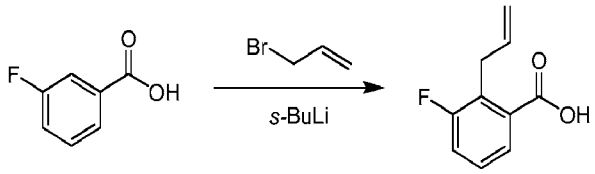
Step 10. **Compound 40**

To a solution of *N*-methyl-hydroxylamine hydrochloride (11. mg, 0.134 mmol) in MeOH (5 mL) was added MeONa (0.026 mL, 25% (Wt.) in MeOH), followed by (*Z*)-*N*-(5-(3-cyanophenyl)-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)–ylidene)cyanamide (50 mg, 0.13 mmol). After stirred for 10 minutes, the solvent was removed in *vacuo*. The residue was purified by preparative TLC, and then HPLC to give **compound 40** (2.19 mg, 5%). **^{1}H-NMR** (MeOD): 2.79 (m, 1H), 2.91 (m, 1H), 3.02-3.19 (m, 3H), 3.25 (s, 3H), 3.48 (m, 1H), 7.17 (m, 4H), 7.45 (m, 1H), 7.63 (m, 1H), 7.75 (m, 3H), 8.02 (m, 2H).

Example 24. Preparation of Compoud 54



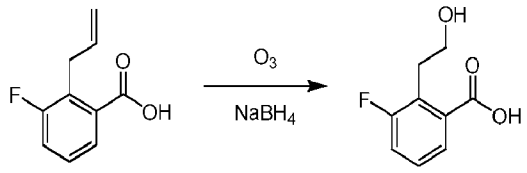
Experimental data:



54a

Preparation of compound 54a

To a solution of TMEDA (25.5 g, 0.22 mol) in dry THF (150 mL) was added *s*-BuLi (1.3 M, 0.22 mol, 169 mL) at -78°C. The mixture was stirred at this temperature for 0.5 hour, and a solution of 3-fluorobenzoic acid (14 g, 0.1 mol) in THF (50 mL) was added dropwise. After being stirred for 1 hour, CuBr/DMS (3.09 g, 0.015 mol, 15%mol) was added, followed by addition of 3-bromoprop-1-ene (36 g, 0.3 mol) in 50 mL of THF. The reaction mixture was warmed to room temperature, and quenched with water. The aqueous layer was washed with Et_2O, and acidified with 4 N HCl. The mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give compound **54a** (14.2 g, 79%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.87 (d, 1H), 7.35 (m, 2H), 6.03 (m, 1H), 5.06 (d, 1H), 5.03 (s, 1H), 3.87 (d, 2H).

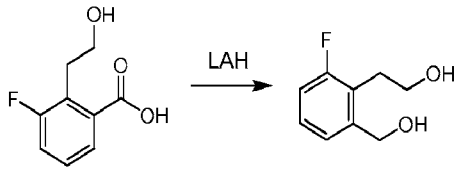


54b

Preparation of compound 54b

A steam of O_3 was bubbled through a solution of 2-allyl-3-fluorobenzoic acid (8.0 g, 0.044 mol) in absolute methanol (50 mL) at -78°C until the mixture was turned to blue. The ozonide solution was added dropwise to an ice-cold solution of NaOH (0.066 mol, 2.64 g) and $NaBH_4$ (0.22 mol, 8.2 g) in 50% aqueous ethanol (50 mL). The mixture was stirred at room temperature overnight, and concentrated. Water was added

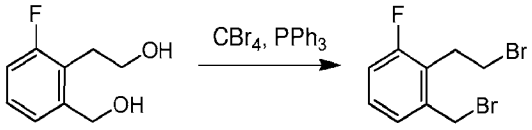
at 0 ℃, and the mixture was acidified by adding 6 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the compound **54b** (6 g, crude).



54c

Preparation of compound 54c

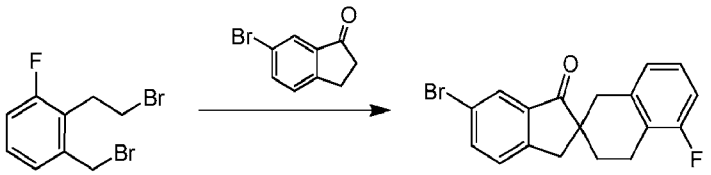
To a solution of $LiAlH_4$ (2.76 g, 0.072 mol) in THF (50 mL) was added 3-fluoro-2- (2-hydroxyethyl)-benzoic acid (6 g, 0.036 mol) in THF (30 mL) at 0°C. The mixture was stirred at aoom temperature overnight, quenched with 3 mL of H_2O, followed by addition of 3 mL of 10% aqueous NaOH solution. The solution was filtered, and the filtrate was concentrated, the residue was purified by chromatography to give the compound **54c** (2.5 g, 41%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.24 (m, 1H), 7.13 (m, 1H), 7.03 (m, 1H), 4.59 (s, 2H), 3.86 (t, 2H), 3.02 (m, 4H).



54d

Preparation of compound 54d

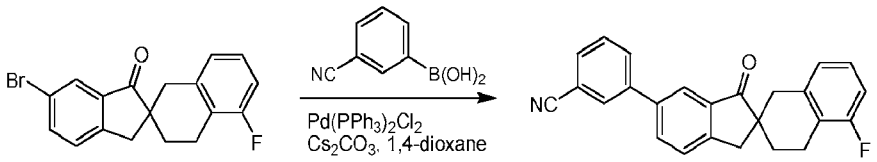
To a solution of 2-(2-fluoro-6-(hydroxymethyl)phenyl)ethanol (3 g, 17.5 mmol) and CBr_4 (14.4 g, 43.9 mmol) in DCM (10 mL) was added PPh_3 (11.5 g, 43.9 mmol) at 0°C in portions. The mixture was stirred at room temperature overnight, and concentrated. The residue was dissolved in Et_2O and filtered. The filtrate was concentrated to give the crude product, which was purified by chromatography to afford the compound **54d** (2.5 g, 48%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.23 (m, 1H), 7.17 (m, 1H), 7.04 (m, 1H), 4.58 (s, 2H), 3.62 (t, 2H), 3.33 (t, 2H).



54e

Preparation of compound 54e

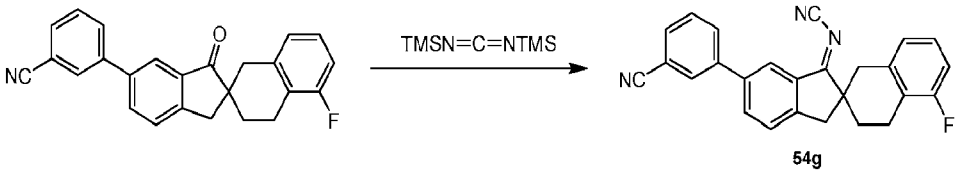
To a solution of 2-(2-bromoethyl)-1-(bromomethyl)-3-fluorobenzene (500 mg, 1.69 mmol) and 6-bromo-2,3-dihydro-1*H*-inden-1-one (356 mg, 1.69 mmol) in THF (20 mL) was added NaH (102 mg, 2.54 mmol), and the mixture was refluxed for 2 hour. The reaction was cooled, and quenched with ice-water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated, the residue was purified by preparative TLC to afford the compound **54e** (210 mg, 36%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.79 (s, 1H), 7.62 (d, 1H), 7.24 (m, 1H), 7.03 (m, 1H), 6.79 (m, 2H), 2.95-3.13 (m, 3H), 2.76 (m, 2H), 2.49 (d, 1H), 2.02 (m, 1H), 1.71 (m, 1H).



54f

Preparation of compound 54f

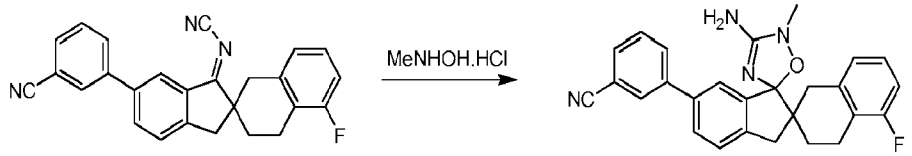
$Pd(PPh_3)_2Cl_2$ (10 mg) in a 10 mL of flask under N_2 was treated sequentially with a solution 6-bromo-5'-fluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1(3*H*)-one (100 mg, 0.29 mmol) in 1,4-dioxane (1 mL), Cs_2CO_3 (2 N, 0.3 mL), and 3-cyanophenylboronic acid (64 mg, 0.43 mmol). The mixture was heated at 100°C under N_2 in microwave for 10 minutes, concentrated in *vacuo*, and purified by preparative TLC to give the compound **54f** (100 mg, 94%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.94 (s, 1H), 7.82 (m, 1H), 7.77 (m, 2H), 7.63 (m, 1H), 7.51 (m, 2H), 7.04 (m, 1H), 6.82 (m, 2H), 3.11 (m, 3H), 2.88 (d, 1H), 2.76 (m, 1H), 2.52 (d, 1H), 2.08 (m, 1H), 1.73 (m, 1H).



54g

Preparation of compound 54g

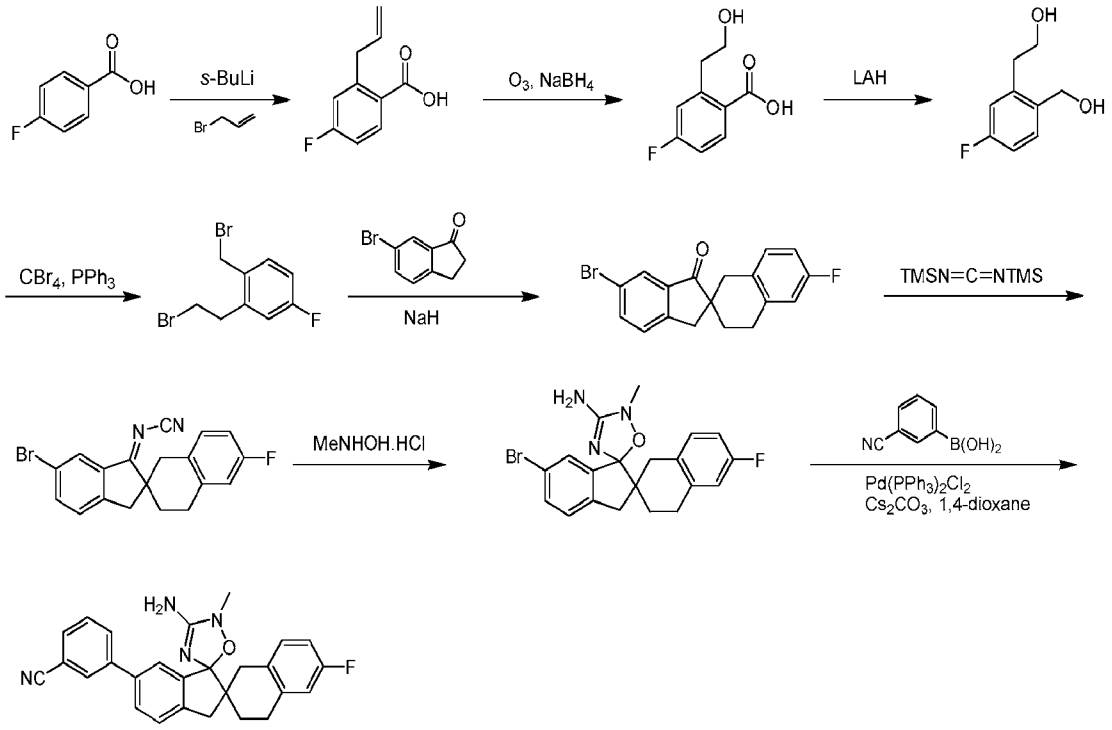
To a solution of 3-(5'-fluoro-1-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'-naphthalene]-6-yl)benzonitrile (100 mg, 0.29 mmol) in dried CH_2Cl_2 (1 mL) was added $TiCl_4$ (1 M solution in DCM, 0.817 mmol) dropwise within 15 minutes. This mixture was heated at 50°C under N_2 in microwave for 10 minutes, added *bis*-trimehtlysilylcarbodiimide (206 mg, 1.09 mmol) dropwise, heated at 60°C under N_2 in microwave for another 10 minutes, poured into ice-water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the compound **54g** (105 mg, crude), which was used for the next step without further purification.



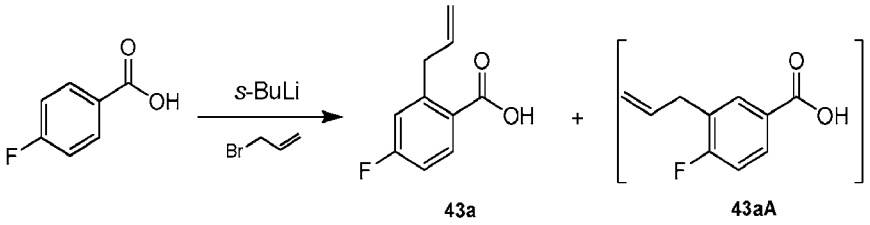
Preparation of compound 54

To a solution of MeNHOH.HCl (22.5 mg, 0.269 mmol) in anhydrous MeOH (5 mL) was added NaOMe (25 *wt*% in MeOH, 53 mg, 0.242 mmol) and (*Z*)-*N*-(5-(3-cyanophenyl)-5'-fluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)-ylidene)cyanamide (105 mg, 0.269 mmol). After being stirred for 20 minutes, the solvent was removed in vacuum, and the residue was dissolved in CH_2Cl_2. After filteration, the filtrate was concentrated, and the residue was purified by preparative TLC and preparative HPLC to afford **compound 54** (25 mg, 21%). **^{1}H NMR** (400 MHz CD_3OD): δ7.92-8.01 (m, 2H), 7.62-7.83 (m, 4H), 7.39 (m, 1H), 7.14 (m, 1H), 6.88 (m, 2H), 3.38 (d, 3H), 3.28 (m, 1H), 3.02 (m, 2H), 2.48-2.84 (m, 3H), 1.89-2.23 (m, 2H); ESI MS: m/z 439 $[M+H]^+$.

Example 25. Preparation of Compound 43



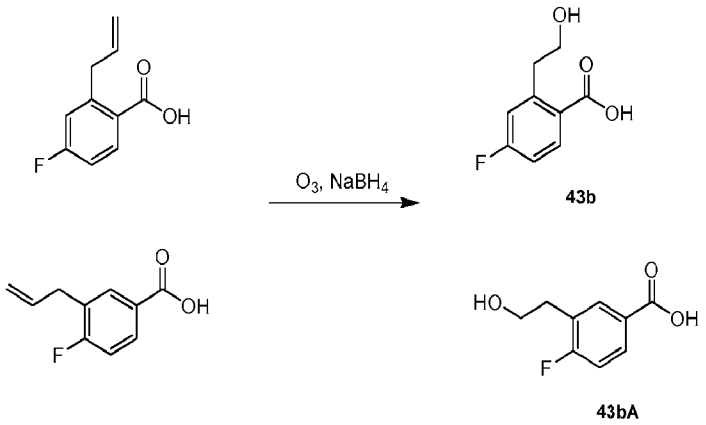
Experimental data:



Preparation of compound 43a

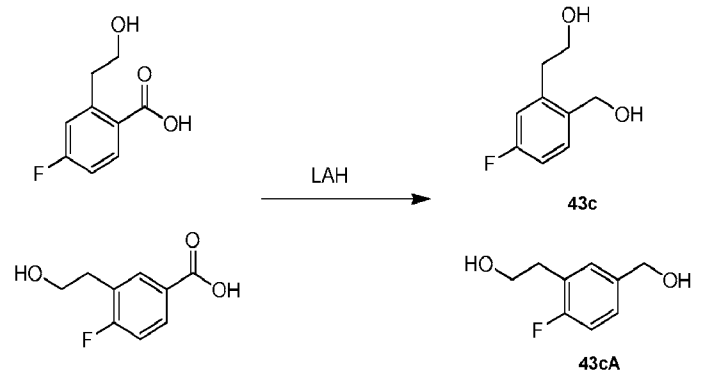
To a solution of TMEDA (33 mL, 0.22 mol) in dry THF (150 mL) was added *s*-BuLi (1.3 M, 0.22 mol, 169 mL) at -78°C. The mixture was stirred at this temperature for 0.5 hour, and a solution of 4-fluorobenzoic acid (14 g, 0.1 mol) in THF (50 mL) was added dropwise. After being stirred for 1 hour, CuBr.DMS (3.09 g, 0.015 mol, 15%mol) was added, followed addition of 3-bromoprop-1-ene (36 g, 0.3 mol) in 50 mL of THF. The reaction mixture was warmed to room temperature, and quenched with water. The aqueous layer was washed with Et_2O, acidified with 4 N HCl, and extracted

with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the mixture of compound **43a** and compound **43aA** (10 g, 55%).



Preparation of compound 43b

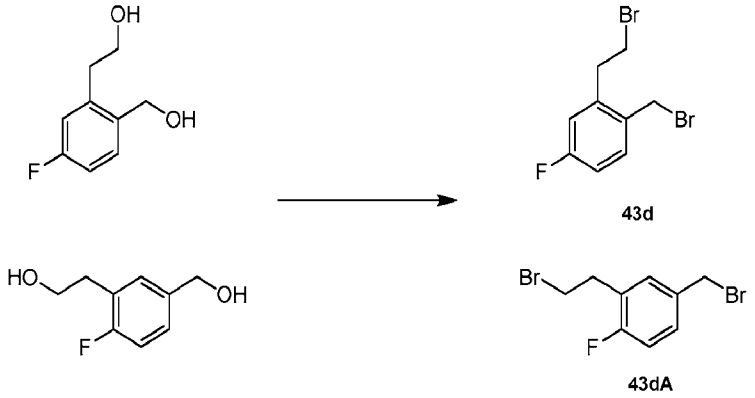
A steam of O_3 was bubbled through a solution of 2-allyl-4-fluoro-benzoic acid (5.0 g, 27.6 mmol) in absolute methanol (30 mL) at -78°C until the mixture was turned to blue. $NaBH_4$ (3 g, 82.9 mmol) was added, and the mixture was stirred at room temperature overnight. The solution was concentrated, water was added at 0°C, and the mixture was acidified by adding 6 N HCl. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the mixture of compounds **43b** and **43bA** (3.8 g, crude).



Preparation of compound 43c

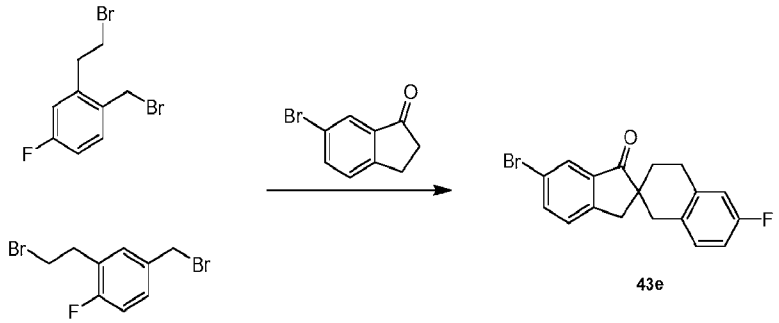
To a solution of $LiAlH_4$ (1.2 g, 31 mmol) in THF (15 mL) was added 4-fluoro-2-(2-hydroxy-ethyl)-benzoic acid (3.8 g, 20.7 mmol) in THF (30 mL) at 0°C. The

mixture was stirred at aoom temperature overnight, quenched with 1.2 mL of H_2O, followed by addition of 1.2 mL of 10% aqueous NaOH solution. The solution was filtered, and the filtrate was concentrated, the residue was purified by chromatography to give the mixture of compounds **43c** and **43cA** (1.1 g, 31%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.21 (m, 0.5H), 7.12 (m, 1H), 6.94 (m, 0.5H), 6.84 (m, 2H), 4.53 (m, 1H), 4.51 (m, 2H), 3.77 (m, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.81 (m, 1H).



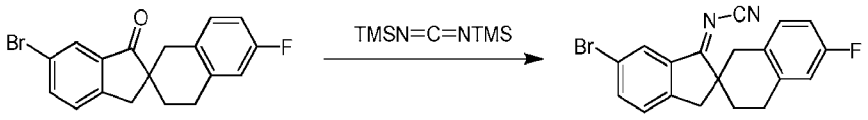
Preparation of compound 43d

To a solution of 2-(5-fluoro-2-hydroxymethyl-phenyl)-ethanol (1.1 g, 6.5 mmol) and CBr_4 (5.3 g, 16.2 mmol) in DCM (30 mL) was added PPh_3 (4.2 g, 16.2 mmol) at 0°C in portions. The mixture was stirred at room temperature overnight, and concentrated. The residue was dissolved in Et_2O, and filtered. The filtrate was concentrated to give the crude product, which was purified by chromatography to afford the mixture of compounds **43d** and **43dA** (2.5 g, 48%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.36 (m, 1H), 7.26 (m, 1H), 7.04 (m, 0.5H), 6.98 (m, 2H), 4.54 (s, 2H), 4.46 (s, 1H), 3.66 (t, 2H), 3.58 (t, 1H), 3.29 (t, 2H), 3.20 (t, 1H).



Preparation of compound 43e

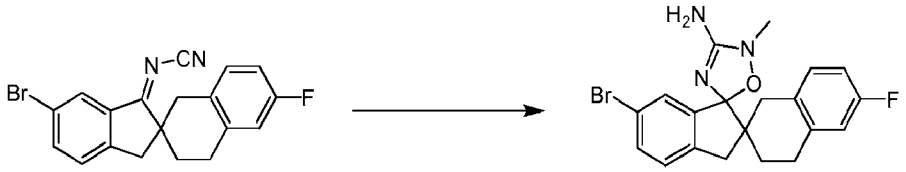
To a solution of 2-(2-bromo-ethyl)-1-bromomethyl-4-fluoro-benzene (500 mg, 1.7 mmol) and 6-bromo-2,3-dihydro-1*H*-inden-1-one (360 mg, 1.7 mmol) in THF (60 mL) was added NaH (102 mg, 2.6 mmol), and the mixture was refluxed for 1.5 hour. The reaction was cooled, quenched with ice-water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated, the residue was purified by preparative TLC to afford the compound **43e** (280 mg, 47%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.89 (s, 1H), 7.62 (d, 1H), 7.23 (m, 1H), 6.95 (m, 1H), 6.76 (m, 2H), 3.04 (m, 2H), 2.90 (m, 3H), 2.77 (m, 1H), 2.42 (m, 1H), 2.04 (m, 1H), 1.64 (m, 1H).



43f

Preparation of compound 43f

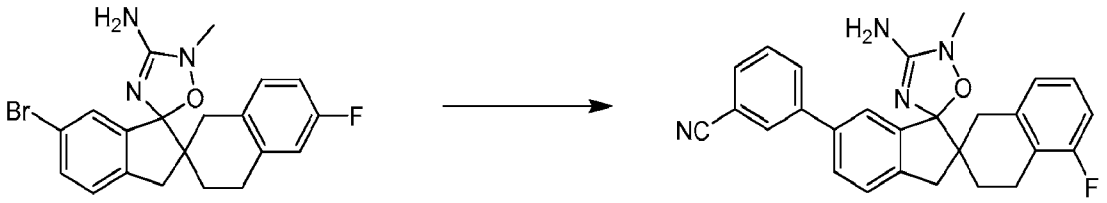
To a solution of 6-bromo-6'-fluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalen]-1 (3*H*)-one (100 mg, 0.29 mmol) in dried CH_2Cl_2 (3 mL) was added $TiCl_4$ (0.87 mL, 1 M solution in DCM, 0.87 mmol) dropwise within 15 minutes at room temperature. After the mixture was stirred for another 1h, *bis*-trimehtlysilylcarbodiimide (220 mg, 1.16 mmol) was added dropwise. The resulting mixture was stirred overnight, poured into ice-water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the compound **43f** (170 mg, crude), which was used for the next step without further purification.



43g

Preparation of compound 43g

To a solution of MeNHOH.HCl (19.5 mg, 0.23 mmol) in anhydrous MeOH (5 mL) was added NaOMe (25 *wt*% in MeOH, 45 μL, 0.21 mmol) and (*E*)-*N*-(5-bromo-6'-fluoro-3',4'-dihydro-1'*H*-spiro[indene-2,2'-naphthalene]-3(1*H*)-ylidene)cyanamide (85 mg, 0.23 mmol). After being stirred for 10 minutes, the solvent was removed in vacuum. The residue was dissolved in CH_2Cl_2. After filteration, the filtrate was concentrated, and the residue was purified by preparative TLC and preparative HPLC to afford the compound **43g** (30 mg, 32%). **^{1}H NMR** (400 MHz CD_3OD): δ7.92-8.01 (m, 2H), 7.62-7.83 (m, 4H), 7.39 (m, 1H), 7.14 (m, 1H), 6.88 (m, 2H), 3.38 (d, 3H), 3.28 (m, 1H), 3.02 (m, 2H), 2.48-2.84 (m, 3H), 1.89-2.23 (m, 2H).

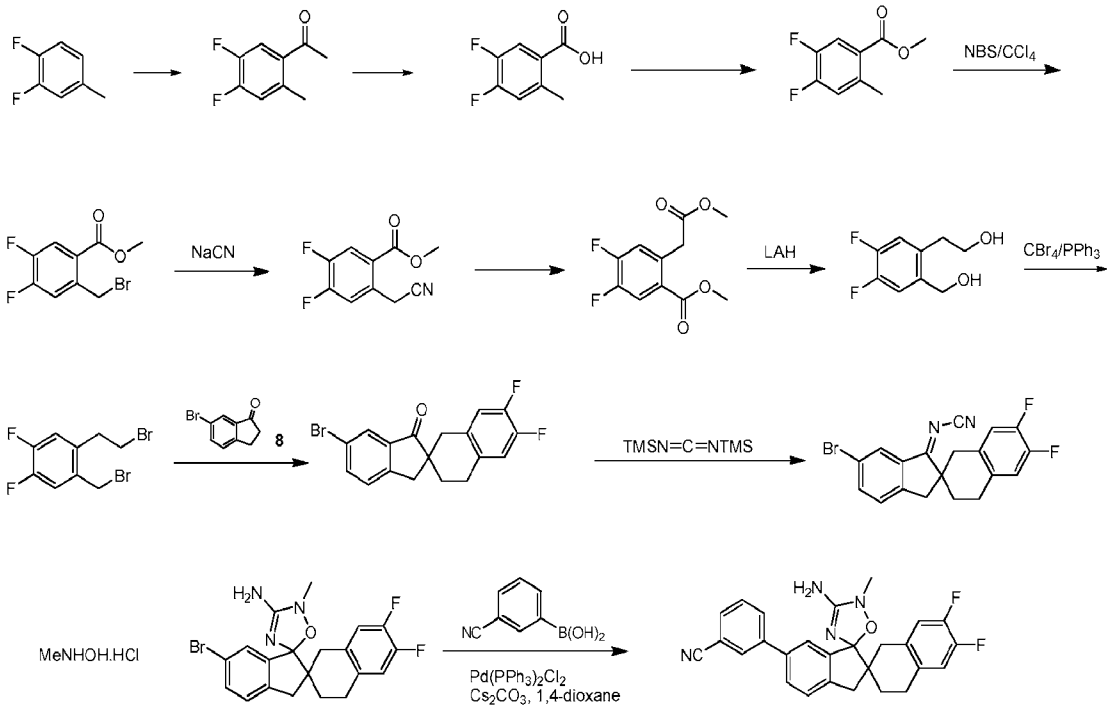


43g

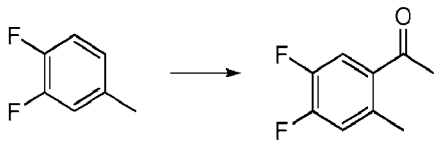
Preparation of compound 43

$Pd(PPh_3)_2Cl_2$ (10 mg) in a 10 mL of flask under N_2 was treated sequentially with the solution of compound **43g** (30 mg, 0.07 mmol) in dioxane (1 mL), Cs_2CO_3 (2 N, 0.09 mL), and 3-cyanophenylboronic acid (18 mg, 0.12 mmol). The mixture was heated at 100°C under N_2 in microwave for 10 minutes, concentrated, and purified by preparative TLC to give **compound 43** (4.69 mg, 15%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.94 (m, 2H), 7.62-7.81 (m, 4H), 7.41 (m, 1H), 7.04 (m, 1H), 6.86 (m, 2H), 3.46 (m, 3H), 3.08 (m, 1H), 3.01 (m, 2H), 2.67-2.81 (m, 2H), 2.45 (m, 0.5H), 2.12 (m, 0.5H), 2.00 (m, 1H), 1.84 (m, 1H); ESI MS: m/z 439 $[M+H]^+$.

Example 26. Preparation of Compound 33



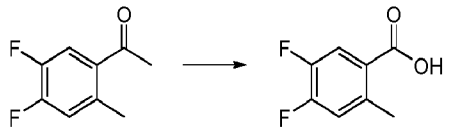
Experimental data:



33a

Preparation of compound 33a

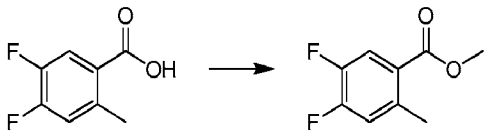
To a solution of $AlCl_3$ (195 g, 1.48 mol) in dichloroethane (200 mL) was added acetyl chloride (103 g, 1.56 mol) and 1,2-difluoro-4-methylbenzene (100 g, 0.78 mol) dropwise in cooling ice bath. After the completion of the addition, the mixture was stirred at room temperature for 5 hours, added to ice water, extracted with DCM, washed with aqueous 5% HCl and saturated $NaHCO_3$ aqueous solution, dried with Na_2SO_4, and concentrated to give the crude compound **33a** (80 g, crude). **^{1}H-NMR** (400 MHz CD_3OD): δ7.50 (m, 1H), 6.91 (m, 1H), 2.51 (s, 3H), 2.48 (s, 3H).



33b

Preparation of compound 33b

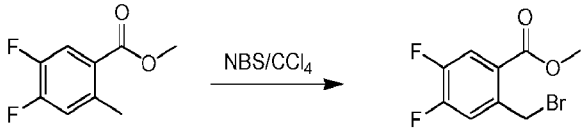
To a solution of 1-(4,5-difluoro-2-methylphenyl)ethanone (44 g, 256 mmol) in dioxane (500 mL) was added NaOCl (63%, 7.3 mmol) at 5°C, and the mixture was stirred in iced water bath for 2 hours. Na_2SO_3 was added, and the reaction mixture was extracted with DCM, washed with 20% HCl, dried over Na_2SO_4, and filtered. The organic layer was concentrated to give the crude compound **33b** (40 g, 90%). **^{1}H-NMR** (400 MHz CD_3OD): δ7.86 (m, 1H), 7.08 (m, 1H), 2.56 (s, 3H), 2.11 (s, 3H).



33c

Preparation of compound 33c

To a solution of 4,5-difluoro-2-methylbenzoic acid (10 g, 0.1 mol) in MeOH (30 mL) was added H_2SO_4 (5 mL) dropwise at 0°C, and the mixture was stirred at room temperature overnight. The mixture was acidified to PH=8 with $NaHCO_3$, and the residue was extracted with EA. The organic layer was washed brine, dried over Na_2SO_4, and concentrated to give the compound **33c** (8.9 g, 82%).

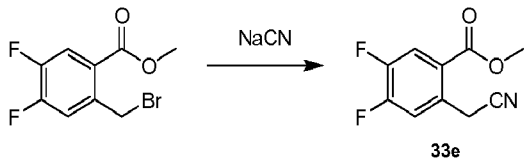


33d

Preparation of compound 33d

The mixture of methyl 4,5-difluoro-2-methylbenzoate (8.9 g, 48 mmol), NBS (9.35 g, 52.8 mmol) and AIBN (790 mg, 4.8 mmol) in CCl_4 (100 mL) was stirred at 80°C for overnight, and filtrated. The filtrate was extracted with $CHCl_3$, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give the compound

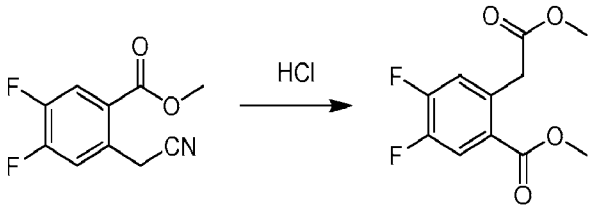
33d (12.8 g, crude). **^{1}H-NMR** (400 MHz CD_3OD): δ7.84 (m, 1H), 7.32 (m, 1H), 4.91 (s, 2H), 3.95 (s, 3H).



33e

Preparation of compound 33e

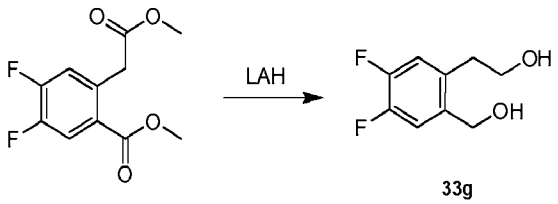
To a solution of methyl 2-(bromomethyl)-4,5-difluorobenzoate (12.8 g, 48 mmol) in MeOH (100 mL) was added NaCN (4.2 N, 11.4 mL) dropwise, and the mixture was stirred at 50°C for 2 hours. After concentration, the residue was dissolved in EA. The solution was washed with H_2O and brine, dried over Na_2SO_4, and concentrated to give the compound **33e** (5 g, 50%). **^{1}H-NMR** (400 MHz CD_3OD): δ7.95 (m, 1H), 7.48 (m, 1H), 4.21 (s, 2H), 3.91 (s, 3H).



33f

Preparation of compound 33f

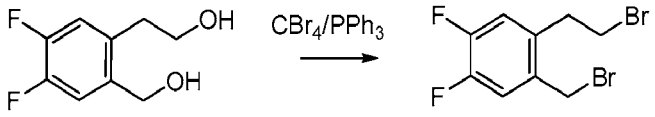
A mixture of methyl 2-(cyanomethyl)-4,5-difluorobenzoate (5 g, 24 mmol) in H_2SO_4 (50 mL) was stirred at 100°C under N_2 overnight, cooled to 65°C, added MeOH (50 mL), and stirred for 4 hours. The mixture was cooled, acidified to PH 7-8 with $NaHCO_3$, extracted with EA, washed brine, dried over Na_2SO_4, and concentrated to give the compound **33f** (5 g, 87%).



33g

Preparation of compound 33g

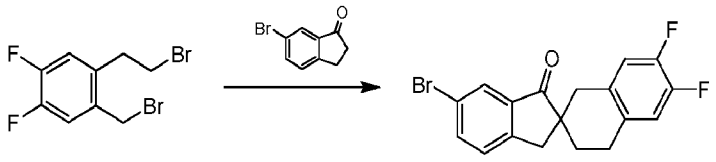
To a solution of 2-(carboxymethyl)-4,5-difluorobenzoic acid (5 g, 20 mmol) in ether (250 mL) was added LAH (3.04 g, 82 mmol), and the mixture was refluxed overnight. The mixture was cooled in ice bath, added water (3 mL) carefully, and followed by addition of 2N NaOH (3 mL). The mixture was filtrated, and the filtrate was concentrated to give the crude compound **33g** (3.5 g, 90%).



33h

Preparation of compound 33h

To a solution of 2-(4,5-difluoro-2-(hydroxymethyl)phenyl)ethanol (3.5 g, 18.5 mmol) and tetrabromomethane (15 g, 46.3 mmol) in DCM (100 mL) was added triphenylphosphine (12 g, 46.3 mmol) at 0°C, and the mixture was stirred at room temperature for 18 hours. After concentration, the residue was dissolved in Et_2O, the organic layer was concentrated to give the crude compound **33h** (2.3 g, 40%). **^{1}H-NMR** (400 MHz CD_3OD): δ7.19 (m, 1H), 7.05 (m, 1H), 4.46 (s, 2H), 3.62 (t, 2H), 3.21 (t, 2H).

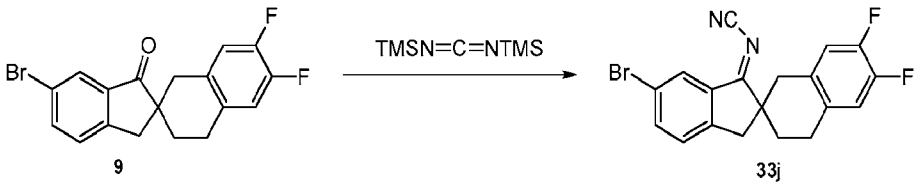


33i

Preparation of compound 33i

A mixture of 6-bromo-indan-1-one (1.6 g, 7.4 mmol), 1-(2-bromoethyl)-2-(bromomethyl)-4,5-difluorobenzene (2.3 g, 7.4 mmol) in THF (50 mL) was added NaH (360 mg, 15 mmol) at room temperature, and the mixture was refluxed for 2 hours. The mixture was quenched with water, concentrated, extracted with DCM, washed with brine, dried over Na_2SO_4, and concentrated to give the compound **33i** (600 mg, 22%). **^{1}H-NMR** (400 MHz CD_3OD): δ7.88 (s, 1H), 7.63 (s, 1H), 7.30 (m, 1H), 7.21 (m, 1H),

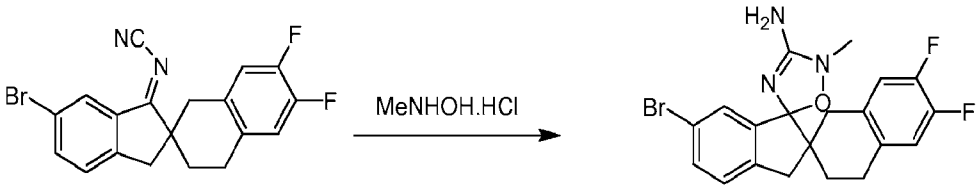
6.87 (m, 1H), 6.75 (m, 1H), 3.03 (m, 2H), 2.85 (m, 2H), 2.38 (m, 1H), 2.00 (m, 1H), 1.66 (m, 1H), 1.55 (m, 1H).



9 33j

Preparation of compound 33j

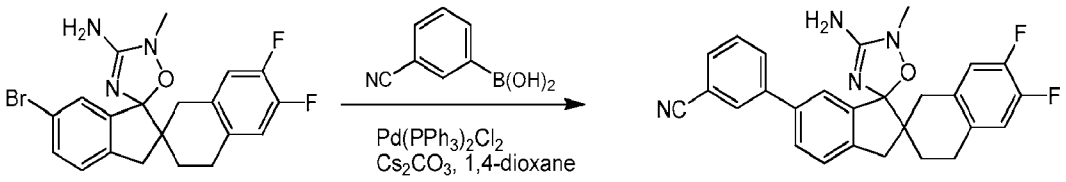
To a solution of 3-(6',7'-difluoro-1-oxo-1,3,3',4'-tetrahydro-1'*H*-spiro[indene-2,2'-naphthalene]-6-yl)benzonitrile (150 mg, 0.41 mmol) in DCM (2 mL) was added $TiCl_4$ (151 mg, 0.83 mmol) dropwise. After the mixture was stirred at 50°C under Ar_2 under microwave for 10 minutes, *N*,*N*'-methanediylidenebis(1,1,1-trimethylsilanamine) (157 mg, 0.83 mmol) was added dropwise. After being stirred at 60°C under Ar_2 in microwave for 10 minutes, the mixture was poured into ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2, the organic layer was dried and concentrated to give the crude compound **33j** (100 mg, 63%).



33j 33k

Preparation of compound 33k

To a solution of *N*-methyl-hydroxylamine hydrochloride (19 mg, 0.23 mmol) in MeOH (5 mL) was added MeONa (0.05 mL, 25% (Wt.) in MeOH) and compound **33j** (100 mg, 0.26 mmol). After being stirred for 10 minutes, the mixture was concerntrated in *vacuo*. The residue was dissolved with DCM, after filitration and concentration, the crude product was purified by preparative TLC to give the compound **33k** (58 mg, 52%).

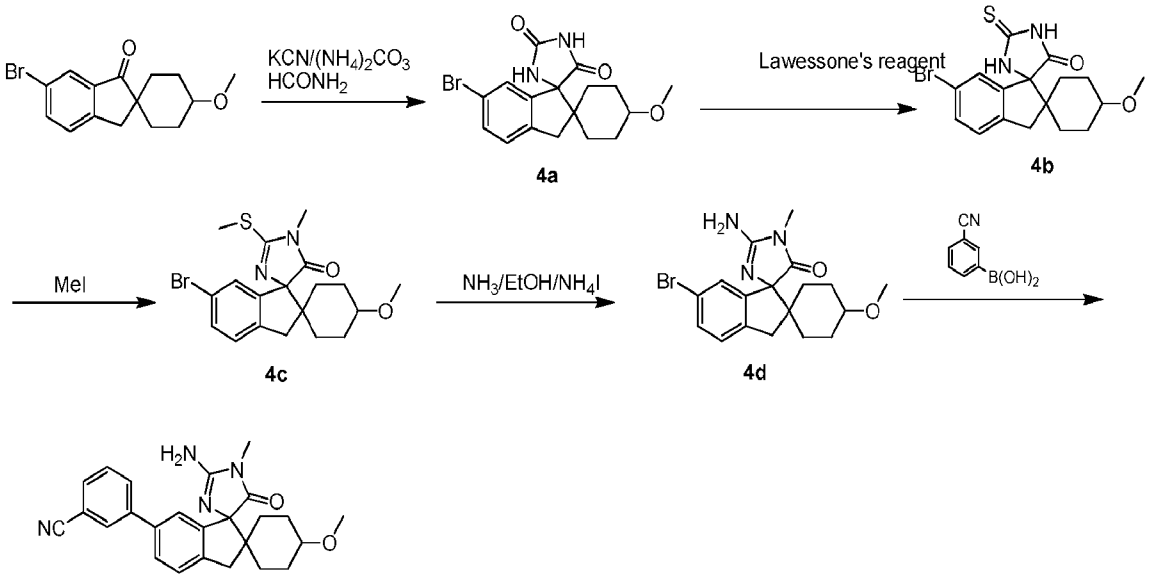


33k

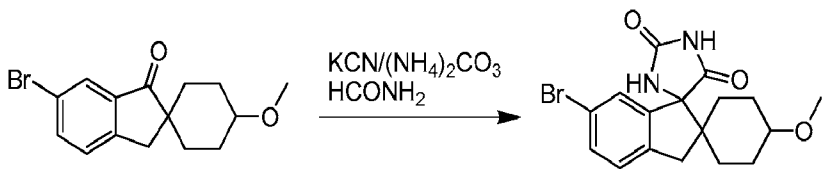
Preparation of compound 33

The mixture of compound **33k** (58 mg, 0.13 mmol), 3-cyanophenylboronic acid (39 mg, 0.26 mmol), Cs_2CO_3 (2 N, 0.5 mL), $Pd(PPh_3)_2Cl_2$ (5 mg, 0.01 mmol) in dioxane (2 mL) was refluxed under Ar_2 for 30 minutes. After concentration in *vacuo*, the residue was purified by TLC and HPLC to give **compound 33** (2.53 mg, 4.15%). **^{1}H-NMR** (400 MHz CD_3OD): δ7.98 (m, 2H), 7.63-7.82 (m, 4H), 7.40 (m, 1H), 6.89-7.12 (m, 2H), 3.33 (s, 3H), 3.08 (m, 2H), 2.96 (m, 2H), 2.68-2.87 (m, 1.7H), 2.44 (m, 0.6H), 1.75-2.16 (m, 2H); ESI MS: m/z 457 $[M+H]^+$.

Example 27. **Preparation of Compound 4**



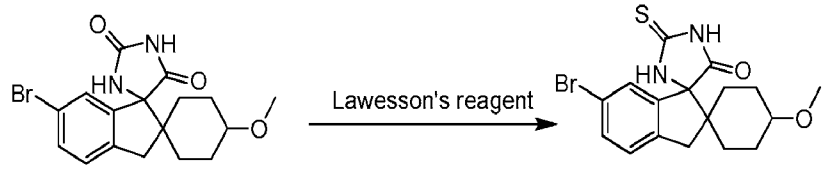
Experimental data:



4a

Preparation of compound 4a

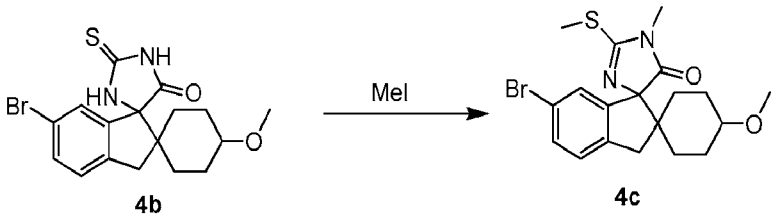
A steel clave was charged with 6'-bromo-4-methoxyspiro [cyclohexane-1, 2'-inden]-1'(3'*H*)-one (500 mg, 1.62 mmol), KCN (211 mg, 3.25 mol), and $(NH_4)_2CO_3$ (1.67 g, 12.15 mol). Formamide (25 mL) was added to fill the tube completely. The mixture was heated at 80°C for 72 h, cooled, and poured into ice. After acidification with concentrated HCl solution, the mixture was filtrated, the solid was dissolved in ethyl acetate, and washed with water for 2 times. The combined organic phases were dried, and concentrated to give compound **4a** (500 mg, 81%), which was used for the next step without purification. **^{1}H-NMR** ($CDCl_3$): δ7.32 (m, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 3.33 (m, 3H), 3.00 (m, 3H), 2.00 (m, 3H), 1.21-1.41 (m, 5H).



4a **4b**

Preparation of compound 4b

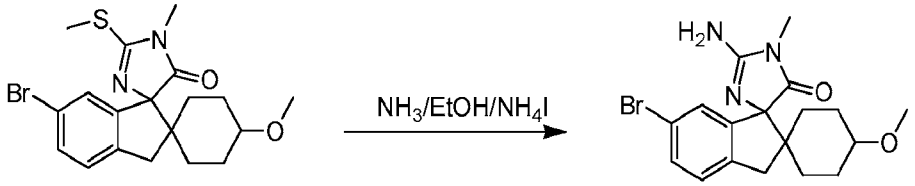
A suspension of compound **4a** (450 mg, 1.19 mmol) and Lawesson's Reagent (481 mg, 1.19 mmol) in dry 1,4-dioxane (9 mL) was heated under 120°C for 35 minutes in CEM microwave reactor. The mixture was concentrated in *vacuo*, and the residue was purified by column to give the compound **4b** (220 mg, 47%).



4b 4c

Preparation of compound 4c

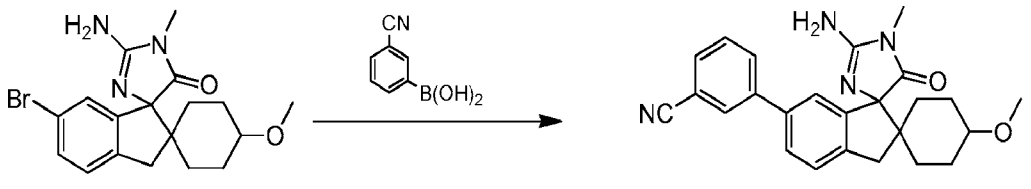
To a solution of compound **4b** (150 mg, 0.381 mmol) in MeOH (9 mL) was added a solution of NaOH (1.143 mL, 0.6 N). After being stirred for 5 min., MeI (0.27 mL) was added, and the reaction mixture was heated at 60°C for 15 minutes in microwave. The mixture was concentrated in *vacuo*, and the residue was purified by preparative TLC to give the compound **4c** (50 mg, 31%).



4c 4d

Preparation of compound 4d

A solution of compound **4c** (70 mg, 0.166 mmol), NH_4I (60 mg, 0.415 mmol) in a solution of NH_3/EtOH (6 mL, 5 N) was heated at 120°C in a CEM tube in a microwave reactor for 3 h. After being cooled, the mixture was concentrated in vacuum. The residue was dissolved in DCM, filtrated, and the filtrate was concentrated in vacuum to give the compound **4d** (20 mg, 31%), which was used for the next step without purification. **^{1}H-NMR** ($CDCl_3$): δ7.42 (m, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.22 (m, 1H), 3.33 (m, 3H), 3.20 (m, 3H), 3.01 (m, 3H), 2.00 (m, 3H), 1.51-1.70 (m, 3H), 1.32 (m, 2H).

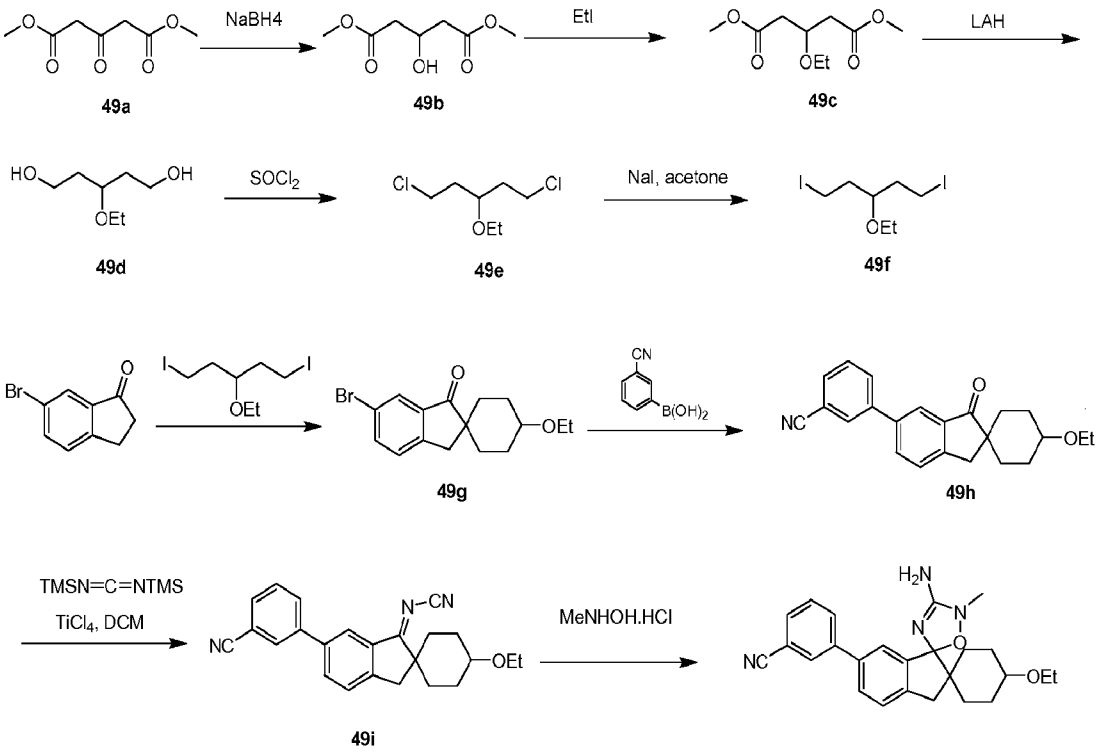


4d

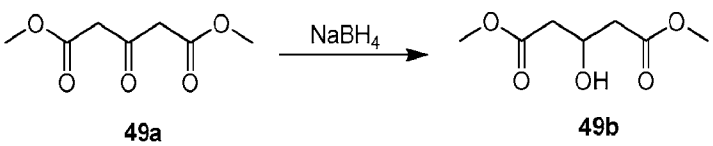
Preparation of compound 4

A mixture of compound **4d** (20 mg, 0.051 mmol), 3-cyanophenylboronic acid (15 mg, 0.102 mmol), Cs_2CO_3 (2 M, 0.30 mL) and $Pd(PPh_3)_2Cl_2$ (5 mg) in 1,4-dioxane (1 mL) under Ar_2 was stirred in microwave at 120°C for 35 minutes. The reaction mixture was concentrated in vacuum, the residue was purified by preparative TLC and HPLC to give **compound 4** (2.81 mg, 13%). **^{1}H-NMR** (CD_3OD): δ8.00(m, 2H), 7.61-7.71 (m, 4H), 7.50 (m, 1H), 3.33-3.41(m, 4H), 3.25 (m, 3H), 3.21(m, 2H), 2.04 (m, 2H), 1.92 (m, 1H), 1.50 (m, 2H), 1.30 (m, 3H); ESI MS: m/z= 415 $[M+H]^+$.

Example 28. Preparation of Compound 49

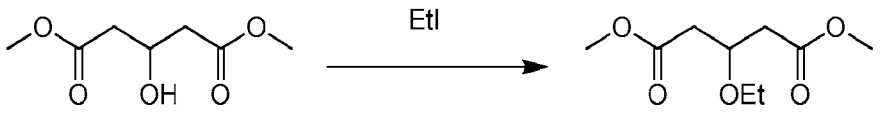


Experimental data:



Preparation of compound 49b

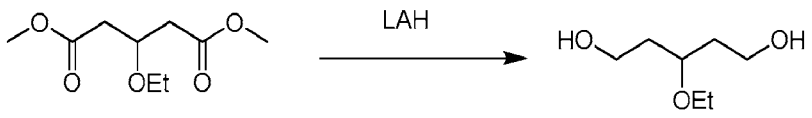
To a solution of dimethyl compound **49a** (240 g, 1.37mol) in anhydrous MeOH (1000 mL) was added $NaBH_4$ (28 g, 0.73 mmol) 0°C. The temperature was rised to room temperature, and the mixture was stirred at this temperature for 1.5 hr. The solvent was removed in *vacuo*, the crude product was purified by silica gel column to give the compound **49b** (150 g, 60%). **^{1}H NMR** ($CDCl_3$, 400MHz): δ4.55-4.96 (m. 1H), 3.70-3.74 (s, 6H), 2.60-2.55 (m, 4H).



49b **49c**

Preparation of compound 49c

A solution of dimethyl compound **49b** (20 g, 106 mmol), Ag_2O (40 g, 169 mmol) and EtI (40 g, 254 mmol) in MeCN (15 mL) was refluxed overnight. The mixture was filtered, and concentrated in *vacuo*, and purified by silica gel column to give the compound **49c** (20.6 g, 30%).

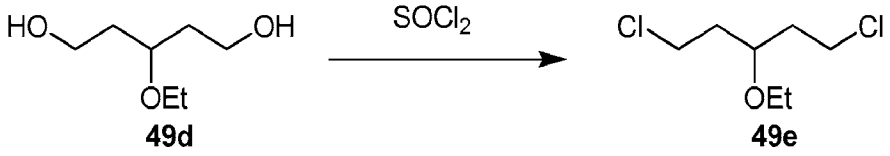


49c 49d

Preparation of compound 49d

To a solution of LAH (13.7 g, 404 mmol) in anhydrous THF (150 mL) was added dropwise a solution of dimethyl compound **49c** (20.6 g, 101 mmol) in anhydrous THF (50 mL) under N_2 at 0°C. The temperature was rised to room temperature, and the mixture was stirred overnight. 2 N NaOH (100mL) was added dropwise, and the mixture was extracted with ethyl acetate (100mL×3). The organic layer was dried over Na_2SO_4 and concentrated in *vacuo* to give the compound **49d** (10.6 g, 71%). **^{1}H NMR**

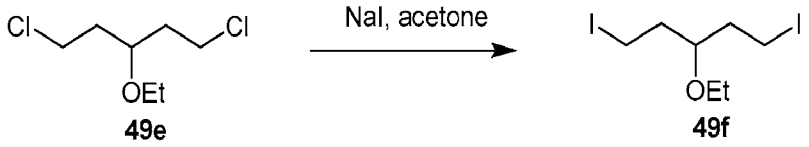
($CDCl_3$, 400MHz): δ3.71-3.82 (m, 4H), 3.52-3.60 (m, 2H), 2.11-2.21 (s, 1H), 1.69-1.75 (m, 4H), 1.11-1.22 (m, 3H).



49d **49e**

Preparation of compound 5

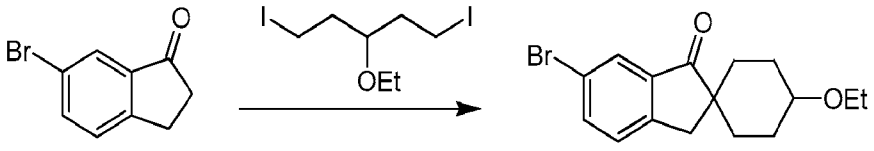
A solution of compound **49d** (10.6 g, 71.6 mmol) in DCM (6 mL) was added $SOCl_2$ (34.1 g, 296.4 mmol) at 0°C. The mixture was refluxed overnight, and the solvent was removed in *vacuo* to give the compound **49e** (13 g, 100%). **^{1}H NMR** ($CDCl_3$, 400MHz): δ3.39-3.65 (m, 6H), 1.70-1.95 (m, 4H), 1.05-1.12 (m, 3H).



49e **49f**

Preparation of compound 49f

A solution of compound **49e** (13 g, 70.6 mmol) and NaI (42.3 g, 282.4 mmol) in acetone (130 mL) was refluxed overnight. The mixture was filtered, and concentrated to give the compound **49f** (crude 28 g), which was used for the next step directly.

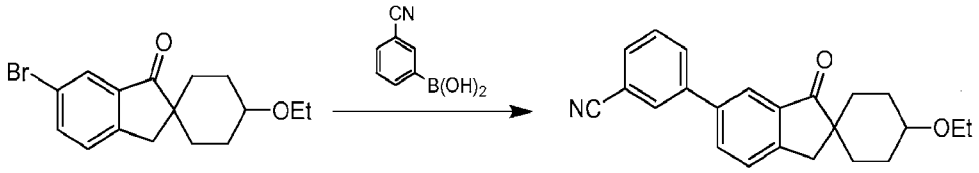


49g

Preparation of compound 49g

To a solutin of 6-bromo-2,3-dihydro-1*H*-inden-1-one (3.5 g, 16.7 mmol) in DMF (15 mL) was added NaH (1.2 g, 50.1 mmol) at 0°C. After being stirred for 15 minutes, the mixture was added 3-ethoxy-1,5 -diiodopentane (8.8 g, 16.7 mmol) 0°C, and stirred at room temperature overnight. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (150 mL×3). The organic layer was washed by water

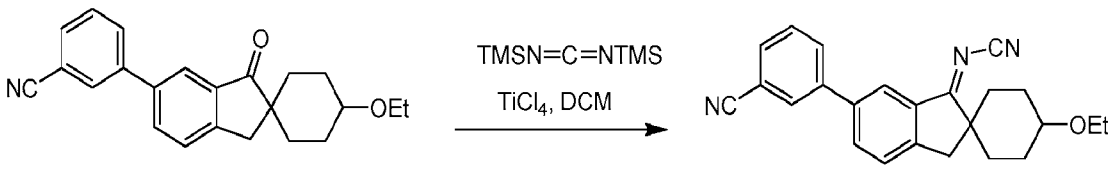
(50 mL×3), and organic layer was dried over Na_2SO_4, and concentrated in *vacuo*, and purified by silica gel column to give the compound **49g** (700 mg, 10%). **^{1}H NMR** ($CDCl_3$, 400MHz): δ7.78-7.82 (s, 1H), 7.55-7.67 (t, 1H), 7.25-7.29 (d, 1H), 3.50-3.55 (s, 1H), 3.35-3.40 (m, 2H), 2.85-2.95 (s, 2H), 1.89-2.15 (m, 4H).



49g **49h**

Preparation of compound 49g

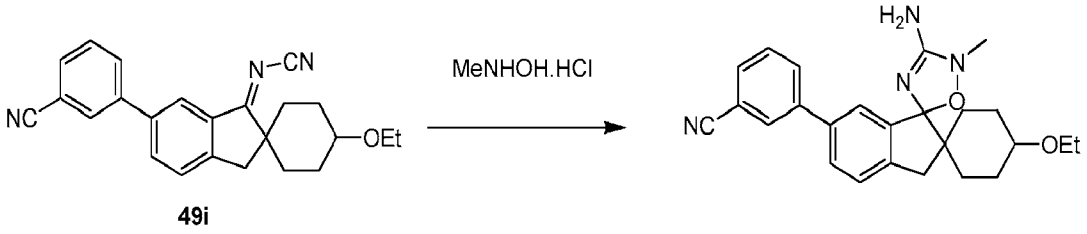
A mixture of compound **49g** (120 mg, 0.37 mmol), 3,5-dicyanophenylboronic acid (110 mg, 0.75 mmol), Cs_2CO_3 (0.5 mL) and $Pd(dppf)Cl_2$ (25 mg) in 1,4-dioxane (2 mL) was heated at 110°C for 20 minutes. The separated organic layer was concentrated in *vacuo* and purified by prepare TLC to give the compound **49h** (108 mg, 84%). **^{1}H NMR** ($CDCl_3$, 400MHz): δ7.50-7.95 (m, 7H), 3.50-3.55 (1, H), 3.39-3.45 (m, 2H), 2.85-2.95 (s, 2H), 1.90-2.20 (m, 4H).



49h **49i**

Preparation of compound 49i

To a solution of compound **49h** (100 mg, 0.3 mmol) in anhydrous DCM (2 mL) was added $TiCl_4$ (0.6 mL, 1mol/L) dropwise in 15 minutes at room temperature. The mixture was stirred for 1 h, added *N,N'*-methanediylidenebis(1,1,1-trimethylsilanamine) (123 mg, 0.6 mmol), and stirred at room temperature for another 18 hr. Ethyl acetate (2 mL) was added, and the mixture was filtered and purified by prep TLC to give the crude compound **49i** (90 mg, 84%).

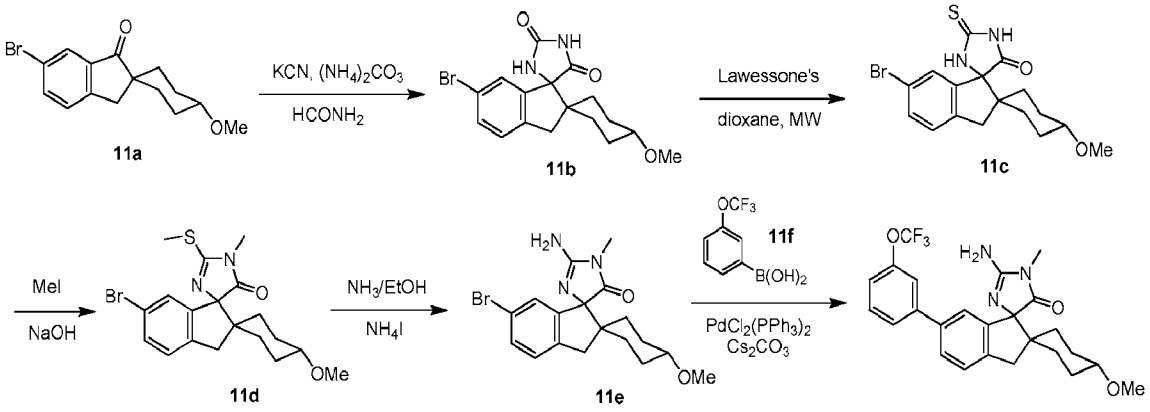


49i

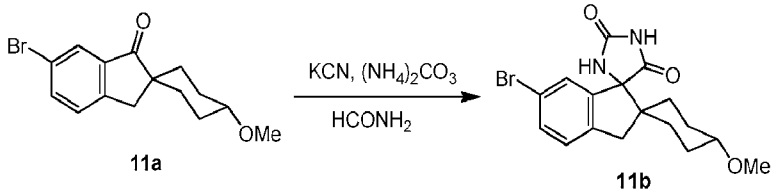
Preparation of compound 49

To a solution of MeNHOH.HCl (19 mg 0.23 mmol) in anhydrous MeOH (1ml) was added NaOMe (0.21 mmol) and compound **9** (84 mg, 0.23 mmol). The mixture was stirred for 5 minutes and purified by preparative TLC and HPLC to give **compound 49** (2.52 mg, 3%). **^{1}H NMR** (400MHz CD_3OD): δ7.91-8.15 (m, 2H), 7.62-7.80 (m, 4H), 7.42-7.48 (m, 1H), 3.60-3.63 (s, 1H), 3.45-3.54 (m, 2H), 3.30-3.35 (s, 3H), 1.40-2.25 (m, 7H); ESI MS: m/z=417 $[M+H]^+$.

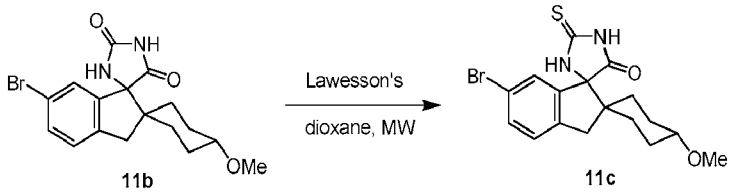
Example 29. **Preparation of Compound 11**



Experimental data

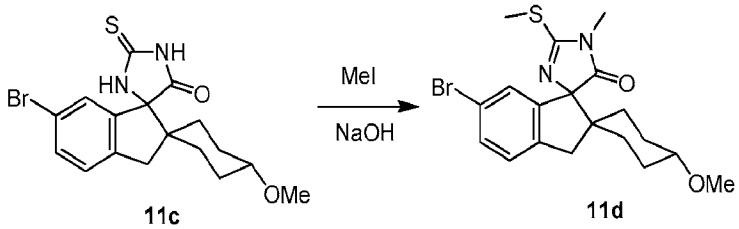


A steel autoclave was charged with compound **11a** (700 mg, 2.27 mmol), KCN (294 mg, 4.53 mmol), and $(NH_4)_2CO_3$ (1.63 g, 16.98 mmol). Formamide (25 mL) was added to fill the tube completely. The mixture was heated at 80°C for 72 h, cooled, and poured into ice. After acidification with concentrated HCl solution (30 mL), the mixture was filtrated. The solid was dissolved in ethyl acetate (600 mL), and washed with water (2×150 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the compound **11b** (550 mg, yield 61%) as a white solid, which was used for the next step directly without purification. **^{1}H NMR** ($CDCl_3$ 300MHz): δ7.80 (s, 1H), 7.62 (m, 1H), 7.25 (m, 1H), 3.33 (m, 3H), 3.05-3.21 (m, 2H), 2.92 (s, 1H), 1.91-2.26 (m, 3H), 1.67 (m, 2H), 1.43 (m, 1H), 1.33 (m, 2H), 1.21 (m, 3H), 0.80 (m, 1H).



11b 11c

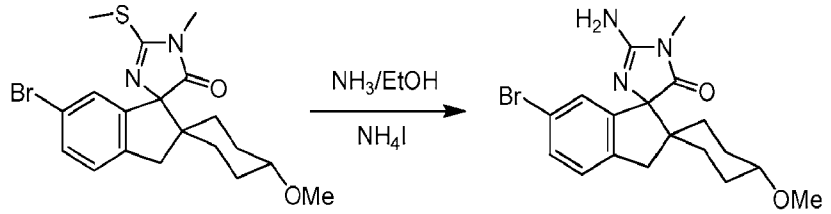
A suspension of compound **11b** (1 g, 2.64 mmol) and Lawesson's Reagent (1.68 g, 2.64 mmol) in dry 1,4-dioxane (18 mL) was heated at 120°C for 35 min. in a CEM microwave reactor. The mixture was concentrated in *vacuo*, and purified by column (petroleum ether/EA=8/1-5/1) to give the compound **11c** as a yellow solid (390 mg, yield 37%).



11c 11d

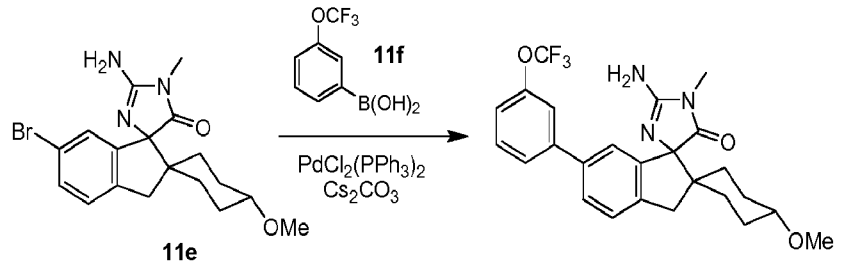
To a solution of compound **11c** (200 mg, 0.51 mmol) in MeOH (20 mL) was added NaOH solution (1.5 mL, 0.6 N). After being stirred for 5 min., the mixture was added MeI (0.36 mL), and stirred at room temperature for another 10 minutes and at 60°C for 15 minutes in a CEM microwave reactor. The mixture was concentrated in *vacuo*, and purified by preparative TLC (petroleum ether/EA=5/1) to give the

compound **11d** (80 mg, yield 37%) as a white solid. **^{1}H-NMR** ($CDCl_3$ 300MHz): δ7.31 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.88 (s, 1H), 3.29 (s, 3H), 3.13-2.92 (m, 6H), 2.61 (s, 3H), 1.94-1.78 (m, 3H), 1.69 (t, 1H), 1.51 (m, 1H), 1.39-1.26 (m, 3H), 1.08 (m, 1H).



11d **11e**

A solution of compound **11d** (45 mg, 0.107 mmol) and NH_4I (78 mg, 0.535 mmol) in NH_3/EtOH (5 mL, 5 N) was heated at 120°C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated in vacuum, and the residue was dissolved in CH_2Cl_2. After filtration, the filtrate was concentrated in *vacuo* to give the compound **11e** (25 mg, 60%) as a white solid, which was used for the next step directly without purification. **^{1}H-NMR** ($CDCl_3$ 400MHz): δ7.51 (d, 1H), 7.22 (m, 2H), 3.39 (m, 5H), 3.15 (4, 2H), 2.96 (s, 3H), 2.11 (m, 2H), 1.93 (m, 1H), 1.55 (m, 2H), 1.42 (m, 3H).

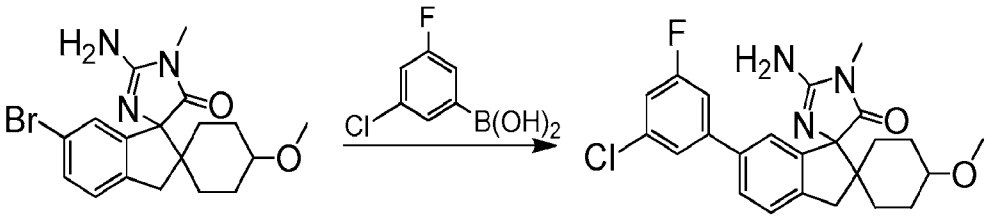


11e

A 10 mL flask was charged with a solution of compound **11e** (20 mg, 0.051 mmol) in 1, 4-dioxane (1 mL), Cs_2CO_3 solution (2 N, 0.1 mL), 3-(trifluoromethoxy)phenylboronic acid (21 mg, 0.102 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mg) under N_2 atmosphere. The mixture was heated at 120°C in a CEM microwave reactor for 15 minutes, and concentrated in *vacuo*. The residue was purified by preparative TLC (CH_2Cl_2/MeOH=10/1) and HPLC to give **compound 11** (2.25 mg, yield 9%). **^{1}H-NMR** (CD_3OD, 400MHz): δ7.66 (m, 2H), 7.54 (m, 4H), 7.27 (m, 1H), 3.41 (s, 3H),

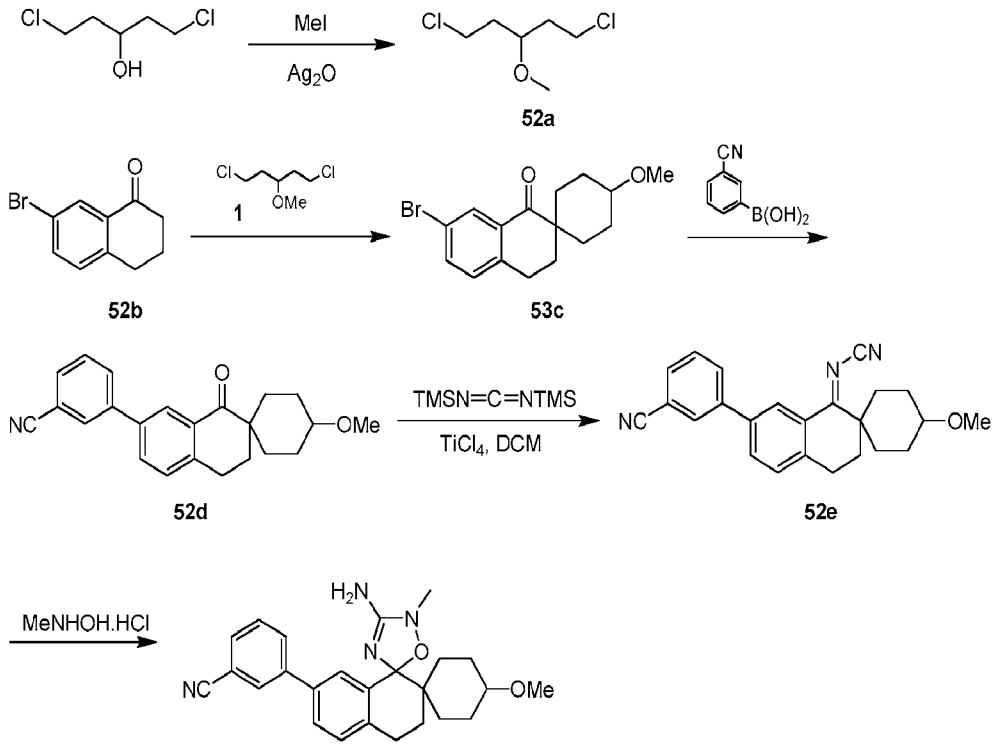
3.29-3.11 (m, 6H), 2.09 (m, 2H), 1.94 (m, 1H), 1.54-1.31 (m, 5H); ESI MS: m/z 474 $[M+H]^+$.

Example 30. Preparation of Compound 14

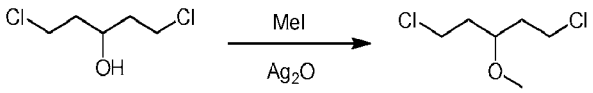


By using the same synthetic strategy as **compound 4** described in example 27, **compound 14** (3.5 mg, yield 13%) was obtained. **^{1}H NMR** (CD_3OD 400MHz): δ7.68 (m, 1H), 7.60-7.45 (m, 3H), 7.48 (m, 1H), 7.21 (m, 1H), 3.49 (s, 3H), 3.32-3.14 (m, 6H), 2.21 (m, 2H), 1.89 (m, 1H), 1.53-1.26 (m, 5H); ESI MS: m/z=441 $[M+H]^+$.

Example 31. Preparation of Compound 52



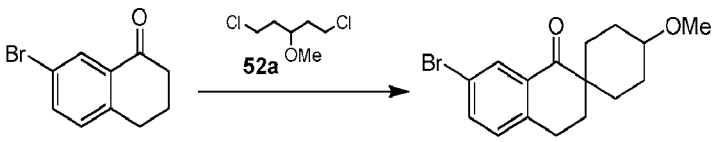
Experimental data:



52a

Preparation of compound 52a

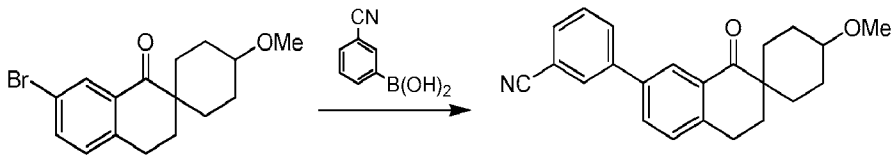
MeI (4.46 mL, 71.6 mmol) was added to a solution of 1, 5-dichloropentan-3-ol (1.9 g, 12.2 mmol) and Ag_2O (7.5 g, 32.3 mmol) in DMF (25 mL) at 20-30°C. The mixture was stirred at room temperature overnight, and filtered. The filtrate was extracted with Et_2O for 3 times, and the combined organic layers were washed with H_2O, dried, and concentrated to give the crude compound **52a** (1.3 g, 63%), which was used directly without further purification.



52b **52c**

Preparation of compound 52c

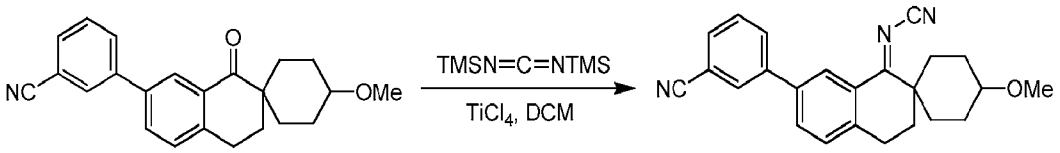
To a solution of compound **52b** (336 mg, 1.5 mmol) in DMF was added NaH (150 mg, 60%, 3.75 mmol) at 0°C, and the mixture was stirred for 1 h at the same temperature. Compound **52a** (510 mg, 3 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was quenched with ice water, and extracted with EtOAc. The organic layer was concentrated, the residue was purified with preparative TLC to give the compound **52c** (50 mg, 10%).



52c **52d**

Preparation of compound 52d

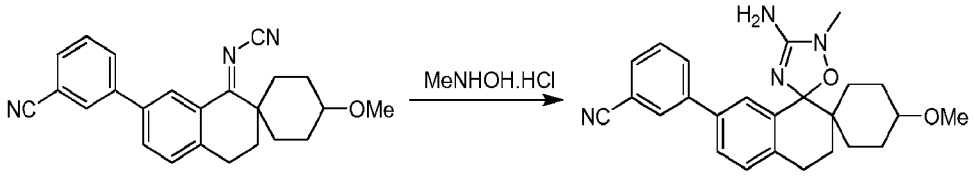
To a solution of compound **52c** (34 mg, 0.23 mmol) and Cs_2CO_3 (2 M, 0.8 mL) in 1,4-dioxane (1.5 mL) under N_2 was added $Pd(PPh_3)_2Cl_2$ (15 mg). The mixture was stirred at 100°C for 6 h. After being cooled to room temperature, the organic layer was dried, and concentrated. The residue was purified by TLC to give the compound **52d** (25 mg, 47%).



52d **52e**

Preparation of compound 52e

To a solution of compound **52d** (25 mg, 0.07 mmol) in CH_2Cl_2 (1.5 mL) was added $TiCl_4$ (28 mg). The mixture was stirred at 50°C in a microwave reactor for 6 minutes, and bis-trimethylsilylcarbodiimide (30 mg, 0.16 mmol) was added. The resulting mixture was stirred at 60°C in a microwave reactor for 10 minutes. The reaction mixture was poured into ice-water, and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to give the crude compound **52e** (30 mg, 116% crude).



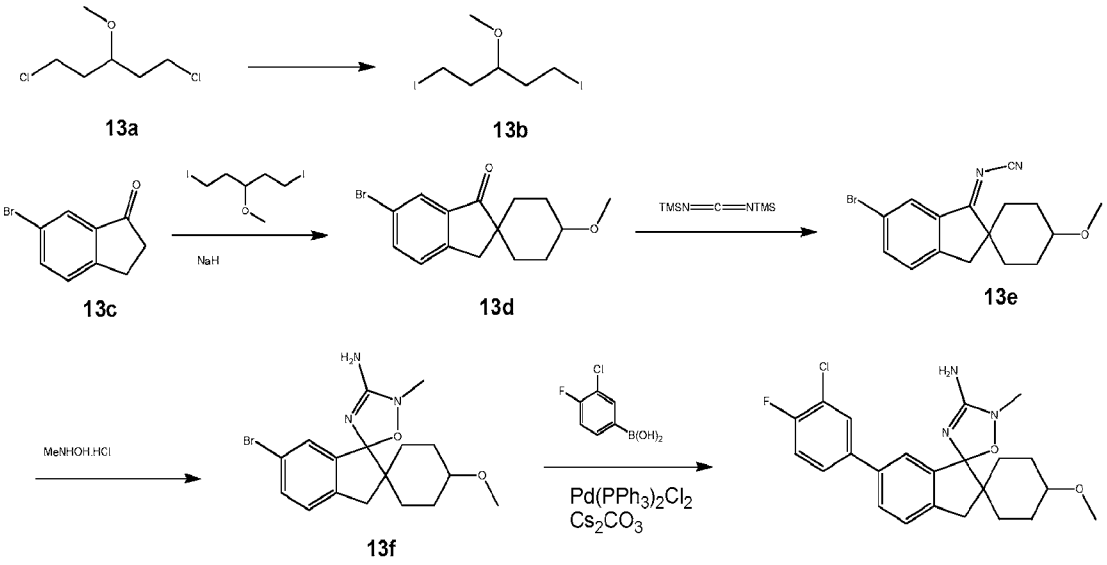
52e

Preparation of compound 52

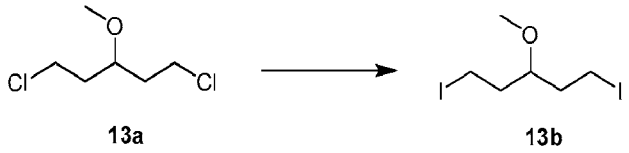
To a solution of methylhydroxylamine HCl salt (7 mg, 0.08 mmol) in anhydrous MeOH (1 mL) was added NaOMe (25% in MeOH, 6 drops) and compound **52e** (30 mg, 0.08 mmol). After being stirred for 10 minutes, the solvent was removed in *vacuo*. The residue was purified by preparative HPLC to give **compound 52** (1.07 mg, 3%). **^{1}H-**

NMR (400MHz CD_3OD): δ7.95 (m, 2H), 7.74 (m, 2H), 7.64 (m, 2H), 7.35 (m, 1H), 3.45 (d, 6H), 2.92 (m, 1H), 2.13 (m, 1H), 2.03 (m, 3H), 1.63 (m, 1H), 1.52 (m, 3H), 1.43 (m, 1H), 1.35 (m, 1H); ESI MS: m/z=417 $[M+H]^+$.

Example 32. Preparation of compound 13

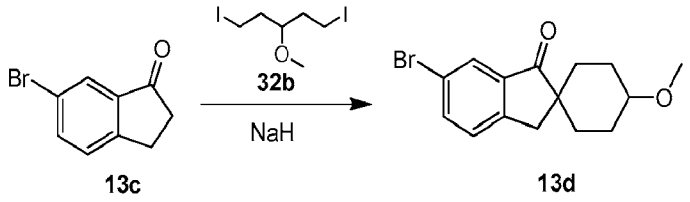


Experimental data:



Preparation of compound 13a

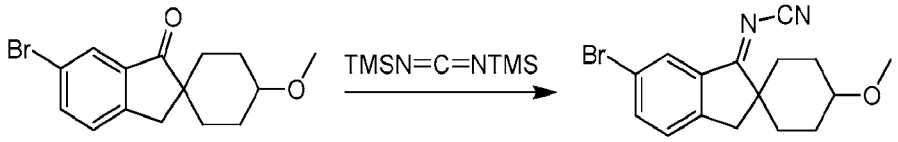
To the solution of compound **13a** (5 g, 29.4 mmol) in acetone (62.5 mL) was added sodium iodide (17.64 g, 117.6 mmol). The mixture was refluxed overnight, and filtrated. The filtrate was concentrated, and the residue was dissolved in DCM (100 mL). After filtration, the filtrate was concentrated to give the compound **13b** (9.6 g, 93%). **^{1}H-NMR** (400 Hz $CDCl_3$): δ3.39 (m, 3H), 3.22-3.30 (m, 5H), 1.95-2.00 (m, 4H).



13c 13d

Preparation of compound 13d

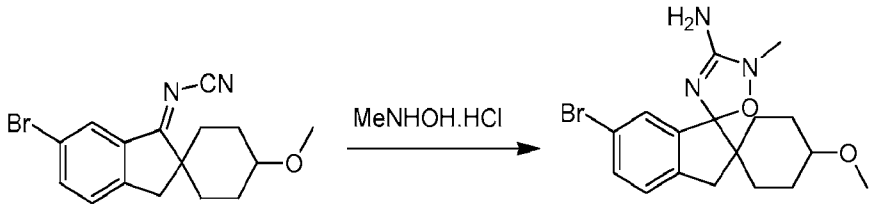
A solution of compound **13c**(4.75 g, 22.6 mmol) and compound **13b** (9.6 g, 27.1 mmol) in DMF (80 mL) was added NaH (2.71 g, 60%, 67.8 mmol) at 0°C. The mixture was stirred at room temperature for 2 h, quenched with water, and extracted with EtOAc. The organic layer was dried, and concentrated. The residue was purified by column chromatography to give the compound **13d** (900 mg, 12%). **^{1}H-NMR** ($CDCl_3$): δ7.80 (m, 1H), 7.62 (m, 1H), 7.25 (m, 1H), 3.34(m, 3H), 3.22 (m, 1H), 2.91 (m, 2H), 2.10 (m, 2H), 1.75 (m, 2H), 1.44 (m, 2H), 1.20-1.30 (m, 2H).



13d 13e

Preparation of compound 13e

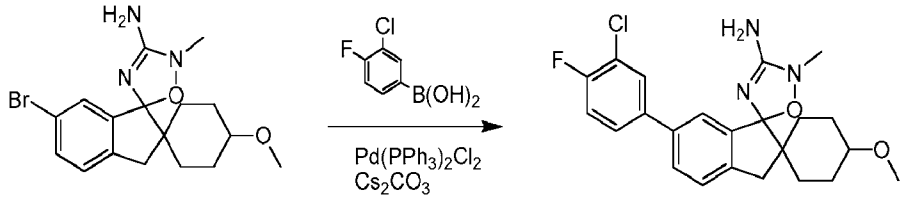
To a solution of compound **13d** (700 mg, 2.27 mmol) in CH_2Cl_2 (18mL) was added $TiCl_4$ (4.55 mL, 4.55 mmol). The mixture was stirred for 1 h at room temperature, and bis-trimethylsilylcarbodiimide (1.12 mL, 5.00 mmol) was added. The resulting mixture was stirred overnight, poured into ice-water, and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to give the crude compound **13e** (700 mg, 93%).



13e 13f

Preparation of compound 13f

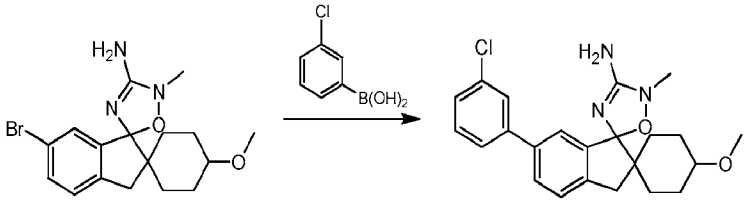
To a solution of methylhydroxylamine HCl salt (177 mg, 2.11 mmol) in anhydrous MeOH 35 mL) was added NaOMe (10% in MeOH, 1.05 mL) and compound **13e** (700 mg, 2.11 mmol). After being stirred for 25 minutes, the solvent was removed, and the residue was dispended in DCM (50 mL), and the precipitate was filtered off. The solvent was removed, and the residue was purified by TLC to give the compound **13f** (1 g, 125% crude). **^{1}H-NMR** (400 Hz $CDCl_3$): δ7.45 (m, 2H), 7.10 (m, 1H), 3.40 (m, 3H), 3.20 (m, 1H), 3.00 (m, 3H), 2.70-2.88 (m, 2H), 2.00 (m, 2H), 1.75 (m, 1H), 1.45-1.62 (m, 3H), 1.35 (m, 2H).



Preparation of compound 13

A mixture of compound **13f** (20mg, 0.053 mmol), 3-chloro-4-fluorophenylboronic acid (14 mg, 0.08 mmol), Cs_2CO_3 (2 M, 0.300 mL) and $Pd(PPh_3)_2Cl_2$ (5 mg) in 1,4-dioxane (1 mL) under Ar_2 was stirred in a microwave reactor at 120°C for 18 minutes. The reaction mixture was concentrated under vacuum, and the residue was purified by preparative TLC and HPLC to give the compound **compound 13** (2.67 mg, 12%). **^{1}H-NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.3H), 7.55-7.65 (m, 3H), 7.50-7.60 (m, 1H), 7.30-7.45 (m, 2H), 3.35-3.40 (m, 6H), 3.30-3.35 (m, 1H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 1H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=430 $[M+H]^+$.

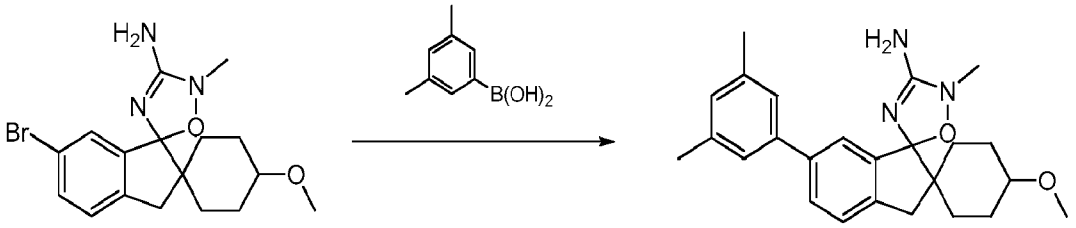
Example 33. Preparation of Compound 5



13f

By using the same synthetic strategy as **compound 13** described in Example 32, **compound 5** (1.79 mg, 8%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 1H), 7.65-7.75 (m, 2H), 7.50-7.65 (m, 4H), 7.35-7.50 (m, 1H), 3.35-3.45 (m, 6H), 3.15-3.30 (m, 2H), 3.00-3.10 (d, 1H), 2.00-2.20 (m, 2H), 1.60-1.90 (m, 3H), 1.35-1.55 (m, 3H); ESI MS: m/z=412 $[M+H]^+$.

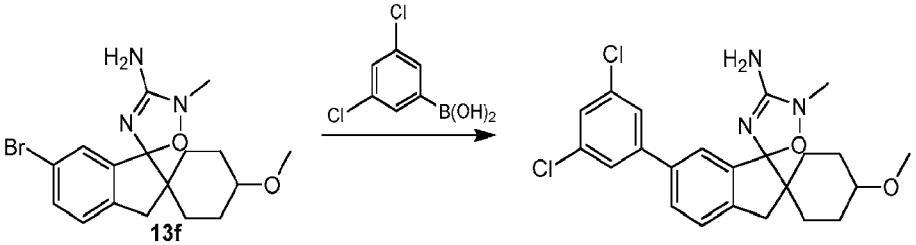
Example 34. Preparation of Compound 19



13f

By using the same synthetic strategy as **compound 13** described in Example 32, **compound 19** (2.16 mg, 10%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 1H), 7.60-7.75 (m, 2H), 7.30-7.40 (m, 1H), 7.10-7.20 (m, 2H), 6.95-7.05 (m, 1H), 3.35-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.30-2.45 (d, 6H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=406 $[M+H]^+$.

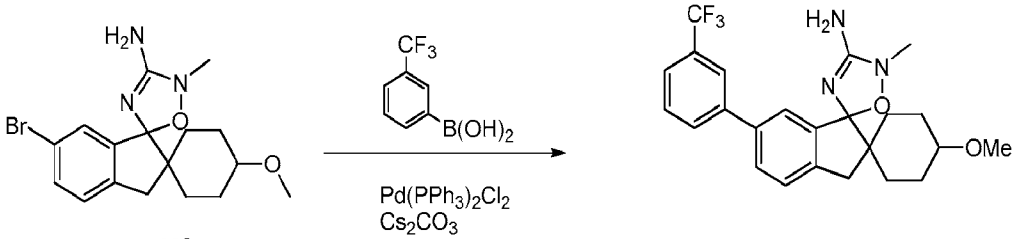
Example 35. Prepation of Compound 6



13f

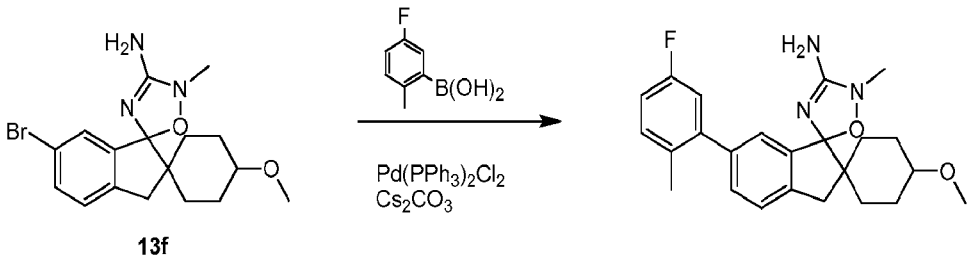
By using the same synthetic strategy as **compound 13** described in Example 32, **compound 6** (1.82 mg, 8%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ7.65-7.75 (m, 2H), 7.50-7.65 (m, 2H), 7.40-7.50 (m, 2H), 3.35-3.45 (m, 6H), 3.15-3.25 (m, 2H), 2.95-3.05 (m, 2H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=446 $[M+H]^+$.

Example 36. Preparation of Compound 20



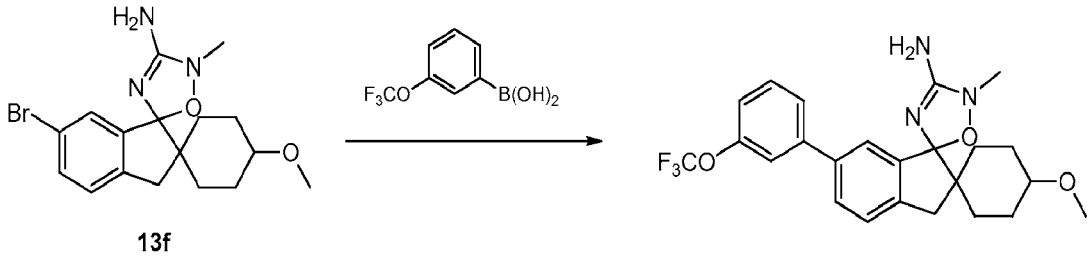
By using the same synthetic strategy as **compound 13** described in Example 32, **compound 20** (2.06 mg, 10%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ 7.80-8.00 (m, 2H), 7.60-7.80 (m, 4H), 7.40-7.50 (m, 1H), 3.35-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=446 $[M+H]^+$.

Example 36a. Preparation of Compound 32



By using the same synthetic strategy as **compound 13** described in Example 35, compound 32 (9.28 mg, 42%) was . **^{1}H-NMR** (400 Hz CD_3OD): δ7.60-7.70 (m, 1H), 7.30-7.40 (m, 2H), 7.20-7.30 (m, 1H), 6.85-7.05 (m, 2H), 3.23-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.10-2.18 (m, 4.3H), 2.00-2.10 (m, 1H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=410 $[M+H]^+$.

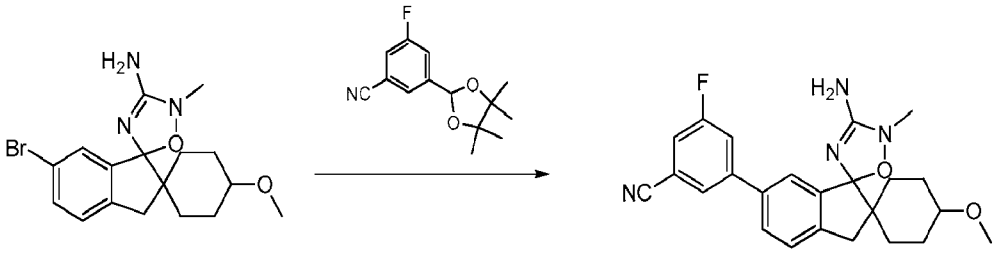
Example 37. Preparation of Compound 9



13f

By using the same synthetic strategy as **compound 13** described in Example 32, **compound 9** (2.46 mg, 10%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ7.65-8.00 (m, 1H), 7.50-7.65 (m, 2H), 7.40-7.50 (m, 2H), 7.20-7.40 (m, 1H), 3.23-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.10-2.18 (m, 4.3H), 2.00-2.10 (m, 1H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=462 $[M+H]^+$.

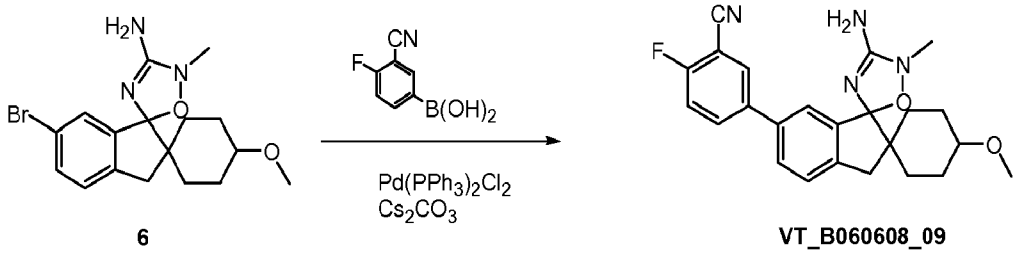
Example 38. Preparation of Compound 8



13f

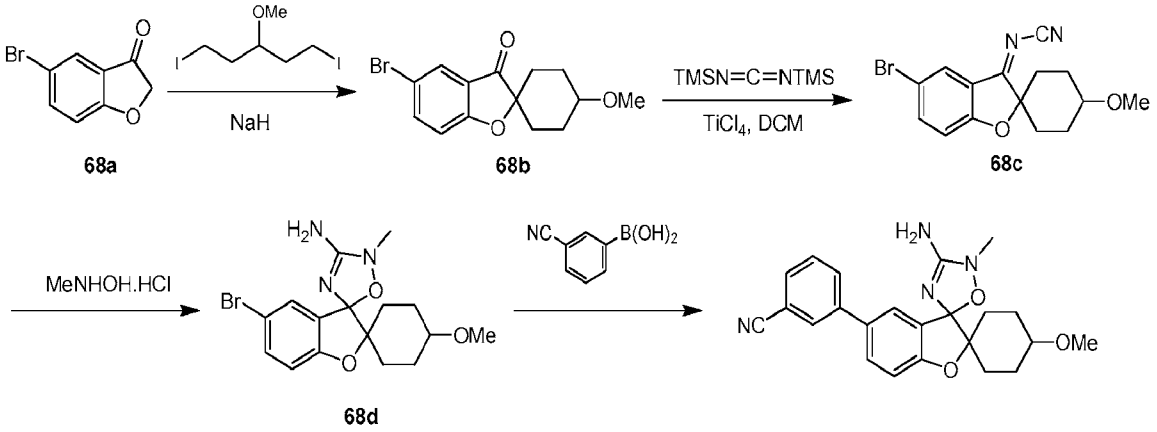
A mixture of compound **13f** (20 mg, 0.053 mmol), 3-fluoro-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl) benzonitrile (20 mg, 0.08 mmol), Cs_2CO_3 (2 M, 0.300 mL), and $Pd(PPh_3)_2Cl_2$ (5 mg) in 1,4-dioxane (1 mL) under Ar_2 was stirred at 100°C for 90 minutes. The reaction mixture was concentrated in vacuum, the residue was purified by preparative TLC and HPLC to give **compound 8** (1.85 mg, 8%). **^{1}H-NMR** (400 Hz CD_3OD): δ 7.85-8.00 (m, 1H), 7.70-7.85 (m, 3H), 7.50-7.65 (m, 1H), 7.40-7.50 (m, 1H), 3.23-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 2H), 1.30-1.55 (m, 4H); ESI MS: m/z=421 $[M+H]^+$.

Example 39. Preparation of Compound 12

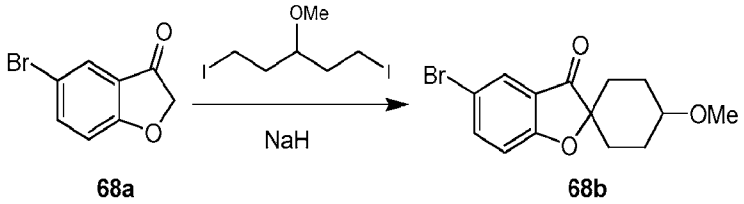


By using the same synthetic strategy as **compound 13** described in Example 35, **compound 12** (2.73 mg, 12%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ7.90-8.10 (m, 2H), 7.70-7.80 (m, 2H), 7.40-7.50 (m, 2H), 3.23-3.45 (m, 6H), 3.15-3.25 (m, 1H), 2.95-3.05 (m, 2H), 2.00-2.20 (m, 2H), 1.64-1.95 (m, 3H), 1.30-1.55 (m, 3H); ESI MS: m/z=421 $[M+H]^+$.

Example 40. **Preparation of Compound 68**



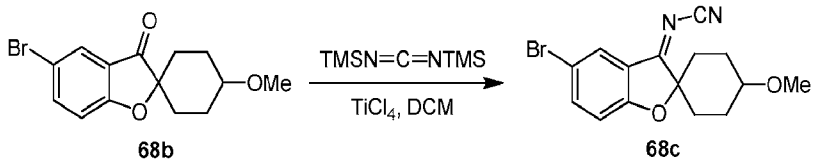
Experimental data:



Preparation of copound 68b

To a solution of NaH (5.4 g, 0.135 mol) in dry THF (150 mL) was added dropwise a solution of compound **68a** (9.48 g, 0.045mol) in THF (20 mL) at –30°C. The mixture was stirred at –30°C for 0.5 h, 1,5-diiodo-3-methoxypentane (15.8 g, 0.045

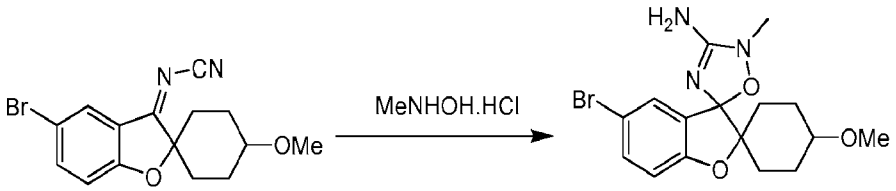
mol) was added dropwise, and the mixture was stirred at ambient temperature overnight. The mixture was concentrated in *vacuo*, and purified by preparative TLC and HPLC to give the compound **68b** (220 mg, 2%).



68b 68c

Preparation of compound 68c

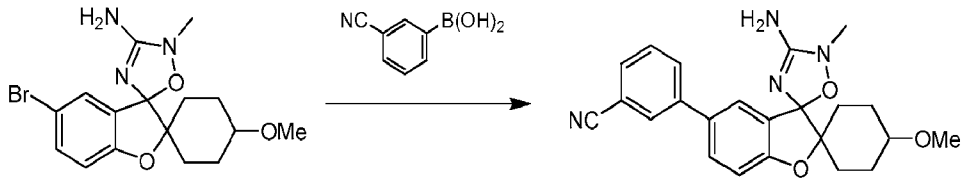
To a solution of compound **68b** (100mg, 0.32mmol) in DCM (10 ml) was added $TiCl_4$ (0.8 mL, 0.8 mmol) dropwise. The mixture was stirred for 1h, $(TMSN)_2C$ (150 mg, 0.8 mmol) was added, and the mixture was stirred at ambient temperature overnight. The mixture was quenched with water, extracted by DCM, dried over Na_2SO_4, and concentrated *in vacuo* to give the compound **68c** (96 mg, 95%).



68c 68d

Preparation of compound 68d

To a solution of MeNHOH.HCl (24 mg, 0.284mmol) in anhydrous MeOH (10 ml) was added NaOMe (138 mg) and compound **68c** (95 mg, 0.284 mol). The mixture was stirred at ambient temperature for 1 h, quenched with water, extracted by DCM, and concentrated *in vacuo* to give the compound **68d** without other purification (60 mg, 50%).

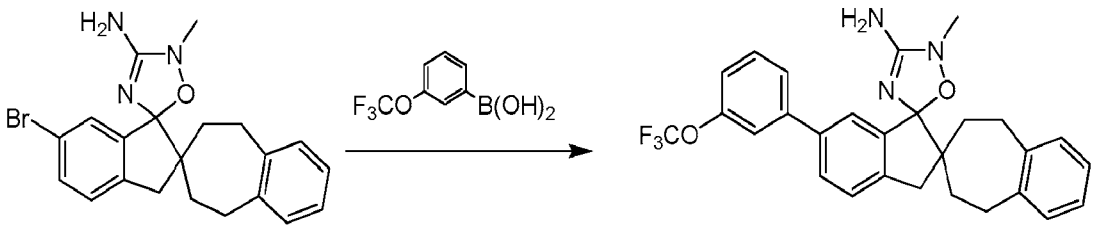


68d

Preparation of compound 68

By using the same synthetic strategy as **compound 13** described in Example 35, **compound 68** (2.11 mg, 3%) was obtained. **^{1}H-NMR** (400 Hz CD_3OD): δ8.00-8.10 (m, 1H), 7.85-8.00 (m, 2H), 7.70-7.80 (m, 2H), 7.60-7.70 (m, 1H), 7.30-7.40 (m, 1H), 3.50-3.70 (m, 1H), 3.30-3.40 (m, 6H), 2.10-2.25 (m, 2H), 2.00-2.10 (m, 2H), 1.85-2.00 (m, 2H), 1.65-1.75 (m, 2H); ESI MS: m/z=405 $[M+H]^+$.

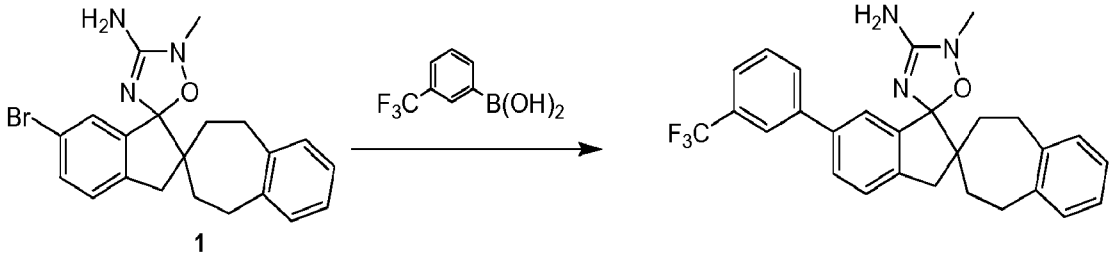
Example 41. Preparation of Compound 38



38a

$Pd(PPh_3)_2Cl_2$ (10 mg, 0.014 mmol), Cs_2CO_3 (2 N, 0.3 mL) and 3-(trifluoromethoxy)phenylboronic acid (15 mg, 0.073 mmol) were added to a solution of compound **1** (15 mg, 0.036 mmol) in 1,4-dioxane (2 mL) in a 10 mL tube under Ar_2. The mixture was heated at 120°C in a microwave reactor for 20 min. The reaction mixture was concentrated in *vacuo*, and the residue was purified by preparative TLC and HPLC to give **compound 38** (4.59 mg, 28%). **^{1}H NMR** (400 Hz CD_3OD): δ7.95-8.05 (m, 0.4H), 7.70-7.80 (m, 2H), 7.60-7.65 (m, 0.6H), 7.45-7.60 (m, 3H), 7.25-7.40 (m, 1H), 7.05-7.15 (m, 4H), 3.35-3.50 (m, 2H), 3.20-3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.90 (m, 2H), 1.75-2.20 (m, 2H), 1.50-1.75 (m, 2H); ESI MS: m/z=494 $[M+H]^+$.

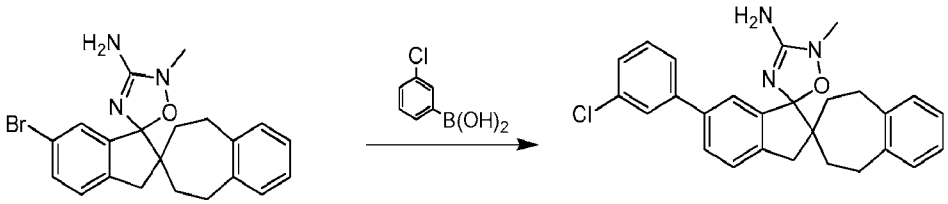
Example 42. Preparation of Compound 39



1

By using the same synthetic strategy as compound 38 described in Example 41, **compound 39** (1.40 mg, 27%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.95-8.05 (m, 0.4H), 7.75-7.90 (m, 2H), 7.60-7.75 (m, 4H), 7.40-7.50 (m, 0.6H), 7.05-7.15 (m, 4H), 3.30-3.50 (m, 2H), 3.15-3.25 (m, 3H), 2.95-3.15 (m, 2H), 2.65-2.85 (m, 2H), 1.75-2.20 (m, 2H), 1.40-1.70 (m, 2H); ESI MS: m/z=478 $[M+H]^+$.

Example 43. Preparation of Compound 17



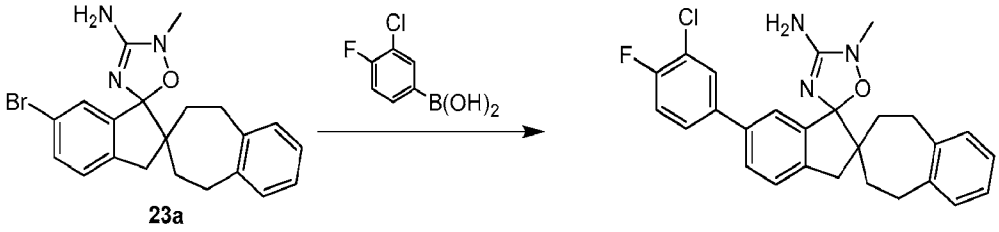
17a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 17** (2.78 mg, 8%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.70-8.00 (m, 2H), 7.50-7.70 (m, 2H), 7.35-7.50 (m, 3H), 7.05-7.15 (m, 4H), 3.40-3.50 (m, 2H), 3.20-3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.75-2.20 (m, 2.5H), 1.45-1.70 (m, 1.6H); ESI MS: m/z=444 $[M+H]^+$.

Alternatively, a solution containing compound **17a** (105 mg, 0.255 mmol) and compound 1A (60 mg, 0.384 mmol) in dioxane (5 mL), and aqueous Cs2CO3 (2 M, 1.8 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, PdCl2(PPh3)2 (18 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a

short Celite pad. The solution was concentrated in vacuo and the residue was purified by preparative TLC and HPLC to give compound 17 (48.2 mg, 42%) as a white solid. LC-MS tR = 1.178, 1.241 min in 2 min chromatography, MS (ESI) m/z 444 [M+H]+; 1H-NMR (CD3OD 400 MHz): δ 7.62-7.90 (m, 2H), 7.47-7.55 (m, 2H), 7.27-7.45 (m, 3H), 7.00-7.27 (m, 4H), 3.27 (s, 3H), 2.90-3.10 (m, 3H), 2.61-2.75 (m, 2H), 1.77-2.08 (m, 3H), 1.41-1.84 (m, 2H).

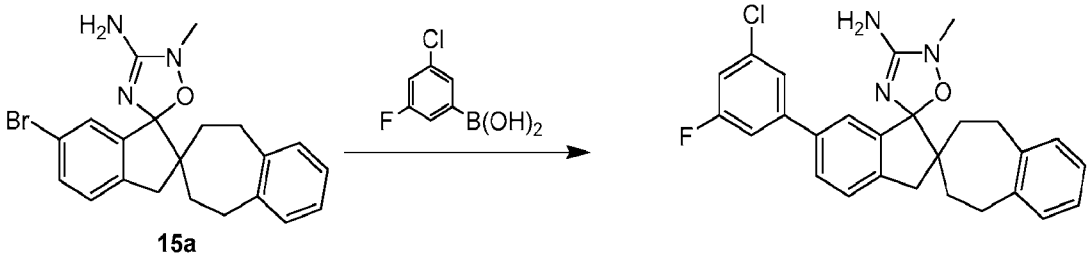
Example 44. Preparation of Compound 23



23a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 23** (1.57 mg, 10%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.4H), 7.65-7.80 (m, 2H), 7.45-7.60 (m, 1.6H), 7.30-7.40 (m, 1H), 7.05-7.15 (m, 4H), 3.40-3.50 (m, 2H), 3.20-3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.80-2.20 (m, 2H), 1.45-1.75 (m, 2H); ESI MS: m/z=462 $[M+H]^+$.

Example 45. Preparation of Compound 15

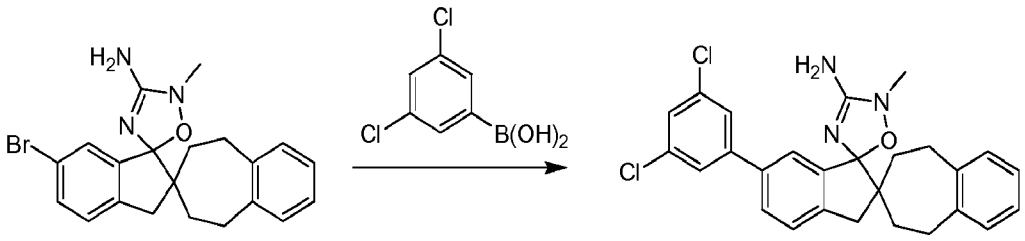


15a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 15** (1.51 mg, 10%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.3H), 7.70-7.80 (m, 2H), 7.45-7.55 (m, 1.6H), 7.20-7.40 (m, 2H), 7.05-7.15 (m,

4H), 3.40-3.50 (m, 2H), 3.20-3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.80-2.20 (m, 2H), 1.50-1.75 (m, 2H); ESI MS: m/z=462 $[M+H]^+$.

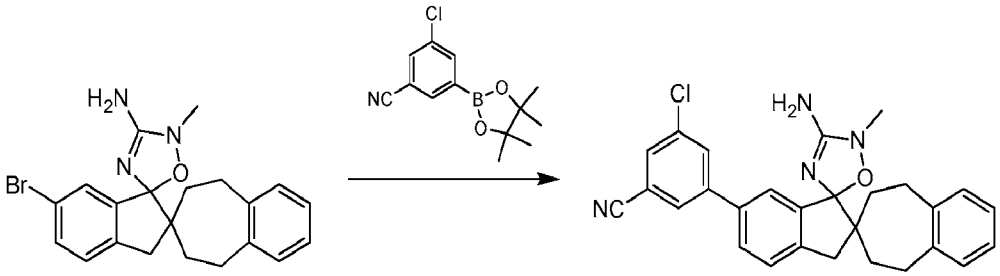
Example 46. Preparation of Compound 21



21a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 21** (1.51 mg, 10%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.3H), 7.70-7.80 (m, 1.7H), 7.55-7.65 (s, 1H), 7.45-7.55 (m, 2H), 7.05-7.15 (m, 4H), 3.40-3.50 (m, 1H), 3.20-3.30 (m, 4H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.80-2.20 (m, 2H), 1.50-1.75 (m, 2H); ESI MS: m/z=478 $[M+H]^+$.

Example 47. Preparation of Compound 10

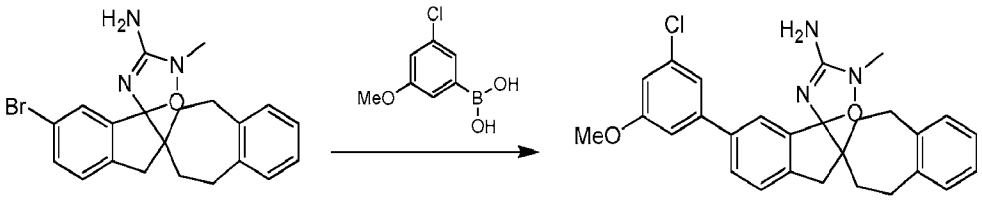


10a

A mixture of compound **10a** (20mg, 0.049 mmol), 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl) benzonitrile (19.20 mg, 0.073 mmol), Cs_2CO_3 (2 M, 0.300 mL) and $Pd(PPh_3)_2Cl_2$ (5 mg) in 1,4-dioxane (1 mL) under Ar_2 was stirred at 120°C in a microwave reactor for 20 minutes. The reaction mixture was concentrated in *vacuum*, the residue was purified by preparative TLC and HPLC to give **compound 10** (2.10 mg, 9%). **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.3H), 7.85-8.10 (m, 2.6H), 7.75-7.85 (m, 2H), 7.45-7.55 (m, 0.7H), 7.05-7.15 (m, 4H), 3.40-3.50 (m, 2H), 3.20-

3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.80-2.20 (m, 2H), 1.50-1.75 (m, 2H); ESI MS: m/z=469 $[M+H]^+$.

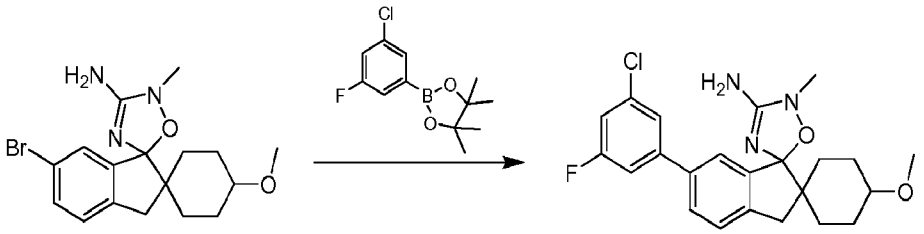
Example 48. Preparation of Compound 27



27a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 27** (1.08 mg, 3%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.85-7.95 (m, 0.5H), 7.55-7.75 (m, 2H), 7.35-7.45 (m, 0.6H), 6.85-7.20 (m, 7H), 3.75-3.80 (s, 3H), 3.40-3.50 (m, 2H), 3.20-3.30 (m, 3H), 2.95-3.20 (m, 2H), 2.65-2.85 (m, 2H), 1.80-2.20 (m, 2H), 1.50-1.75 (m, 2H); ESI MS: m/z=474 $[M+H]^+$.

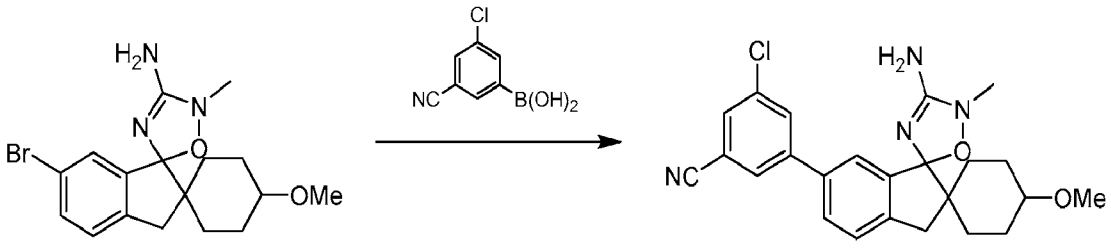
Example 49. Preparation of Compound 1



1a

By using the same synthetic strategy as compound 10 described in Example 47, **compound 1** (2.8 mg, 14%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.85-7.95 (m, 0.3H), 7.65-7.75 (m, 2H), 7.20-7.55 (m, 3.5H), 3.30-3.40 (m, 6H), 3.15-3.25 (m, 1H), 3.20-3.30 (m, 3H), 2.95-3.10 (m, 2H), 2.00-2.20 (m, 2H), 1.65-1.95 (m, 2H), 1.30-1.60 (m, 4H); ESI MS: m/z=430 $[M+H]^+$.

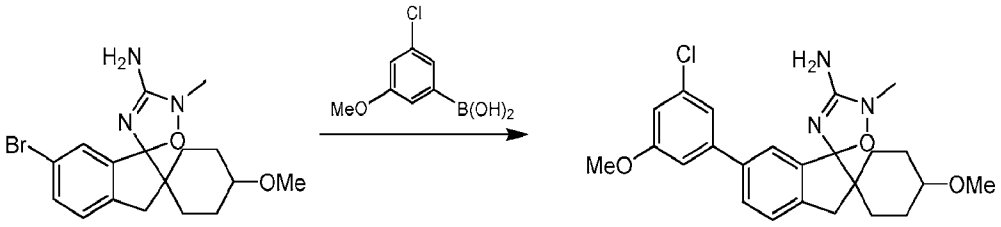
Example 50. Preparation of Compound 2



2a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 2** (2.8 mg, 14%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.85-7.95 (m, 0.3H), 7.65-7.75 (m, 2H), 7.20-7.55 (m, 3.5H), 3.30-3.40 (m, 6H), 3.15-3.25 (m, 1H), 3.20-3.30 (m, 3H), 2.95-3.10 (m, 2H), 2.00-2.20 (m, 2H), 1.65-1.95 (m, 2H), 1.30-1.60 (m, 4H); ESI MS: m/z=430 $[M+H]^+$.

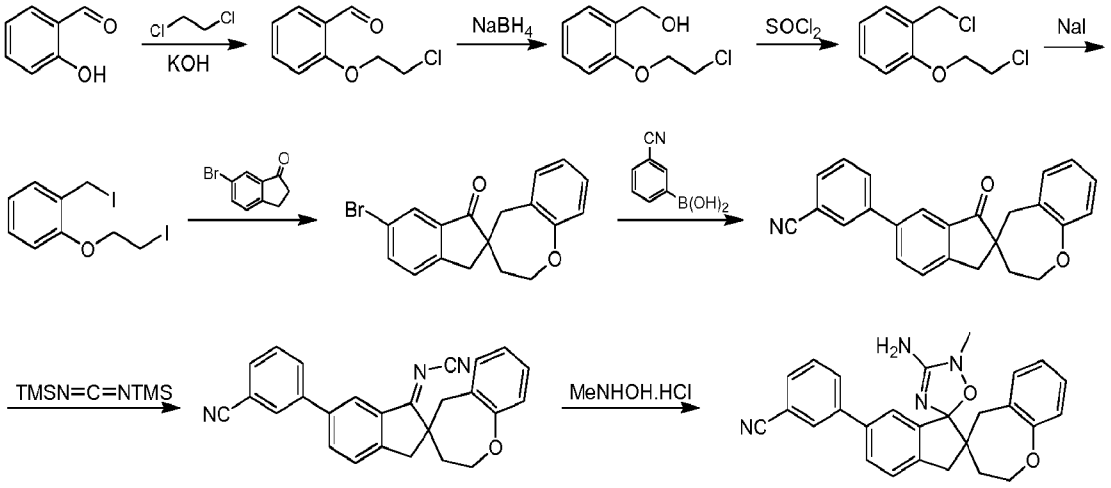
Example 51. Preparation of Compound 7



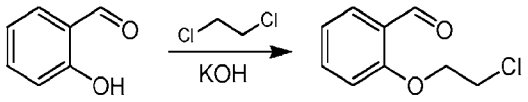
7a

By using the same synthetic strategy as compound 38 described in Example 41, **compound 7** (1.23 mg, 4.1%) was obtained. **^{1}H NMR** (400 Hz CD_3OD): δ7.90-8.00 (m, 0.5H), 7.65-7.75 (m, 2H), 7.35-7.45 (m, 0.6H), 7.10-7.20 (m, 1H), 6.95-7.05 (m, 2H), 3.80-3.90 (s, 3H), 3.30-3.45 (m, 6H), 3.00-3.25 (m, 3H), 2.00-2.20 (m, 2H), 1.65-1.95 (m, 3H), 1.35-1.55 (m, 3H); ESI MS: m/z=442 $[M+H]^+$.

Example 52. Preparation of Compound 36



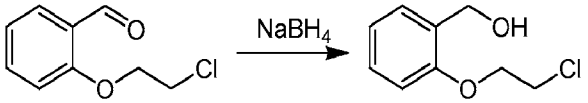
Experimental data:



36a **36b**

Preparation of compound 36b

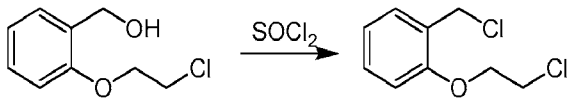
A mixture of compound **36a** (50 g, 410 mmol), 1,2-dichloroethane (50 mL), and KOH (25 g, 445 mmol) in H_2O (50 mL) was refluxed for three days. The organic layer was separated, diluted with CH_2Cl_2, washed with aqueous NaOH solution and with water, and concentrated to give the compound **36b** (47 g, 63%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.82 (m, 1H), 7.53 (m, 1H), 7.06 (m, 1H) 6.94 (d, 1H), 4.33 (t, 2H), 3.87 (t, 2H).



36b **36c**

Preparation of compound 36c

To a solution of compound **36b** (10 mg, 54.3 mmol) in MeOH (50 mL) was added $NaBH_4$ (3.0 g, 81.5 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h, and concentrated. Water (100 mL) was added at 0°C, and the mixture was extracted with EtOAc (100 mL×3). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the compound **36c** (10 g, 99%). **^{1}H NMR** ($CDCl_3$): δ7.28 (m, 2H), 6.98 (m, 1H), 6.83 (m, 1H), 4.69 (m, 2H), 4.38 (t, 2H), 3.83 (t, 2H).



36c **36d**

Preparation of compound 36d

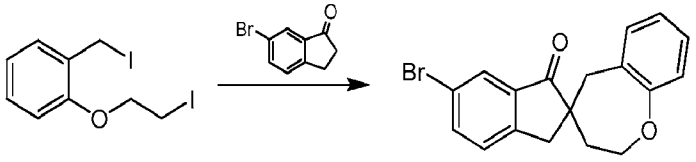
To a solution of compound **36c** (10 g, 53.7 mmol) in DCM (30 mL) was added $SOCl_2$ (51g, 430 mmol) dropwise at 0°C, and the reaction mixture was refluxed overnight. The solution was concentrated, and the residue was diluted NH_4OH and extracted with EtOAc. The organic layer was dried, and concentrated. The residue was purified by flash chromatography to afford the compound **36d** (3.8 g, 35%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.73 (m, 1H), 7.36 (m, 1H), 7.06 (t, 1H), 6.88 (d, 1H), 4.72 (s, 2H), 4.33 (t, 2H), 3.89 (t, 2H).



36d **36e**

Preparation of compound 36e

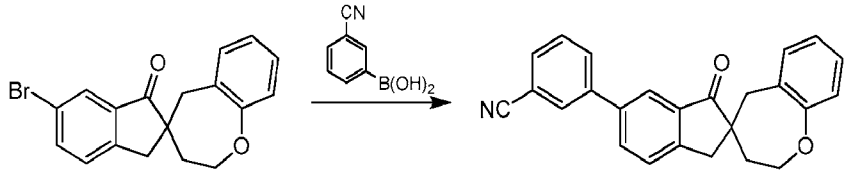
To a solution of compound **36d** (1 g, 4.88 ooml) in propan-2-one (25 mL) was added NaI (2.2 g, 14.63 mmol), and the mixture was refluxed for 2 hour. The mixture was filtered, and concentrated. The residue was dissolved in EtOAc (50 mL), and the solution was washed with water (30 mL). The organic layer was dried, and concentrated to give the compound **36e** (1.5 g, 79%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.34 (d, 1H), 7.25 (m, 1H), 6.93 (t, 1H), 6.81 (d, 1H), 4.51 (s, 2H), 4.31 (m, 2H), 3.92 (t, 2H).



36e **36f**

Preparation of compound 36f

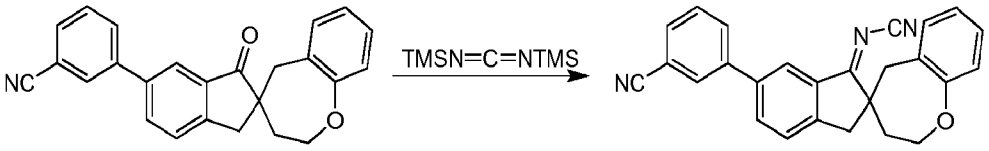
To a solution of 6-bromo-indan-1-one (500 mg, 2.37 mmol) in DMF (15 mL) was added NaH (190 mg, 4.74 mmol) at 0°C. After being stirred for 30 minutes, compound **36e** (919 mg, 2.37 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with water, and extracted with TBME. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC to afford the compound **36f** (145 mg 18%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.88 (s, 1H), 7.64 (m, 1H), 7.16 (m, 1H), 7.01 (d, 4H), 6.88 (m, 1H), 4.48 (m, 2H), 4.07 (m, 1H), 3.69 (m, 2H), 3.38 (d, 1H), 3.22 (m, 1H), 2.68-2.92 (m, 3H), 2.51 (t, 1H), 2.36 (d, 1H), 1.61 (d, 1H).



36f **36g**

Preparation of compound 36g

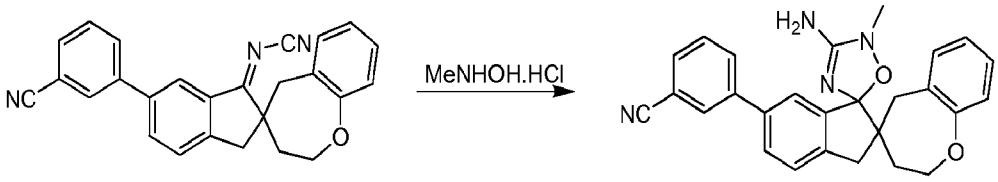
$Pd(PPh_3)_2Cl_2$ (10 mg) in a 10 mL of flask under N_2 was treated sequentially with the solution of the compound **36f** (105 mg, 0.305 mmol) in 1,4-dioxane (2 mL), Cs_2CO_3 solution (2 N, 0.3 mL), and 3-cyanophenylboronic acid (90 mg, 0.61 mmol). The mixture was heated at 100°C under N_2 in microwave for 10 minutes. The organic layer was concentrated in vacuo, and the residue was purified by preparative TLC to give the compound **36g** (98 mg, 96%). **^{1}H NMR** (400 MHz $CDCl_3$): δ7.95 (s, 1H), 7.80 (m, 4H), 7.63 (m, 1H), 7.51 (m, 3H), 7.16 (m, 1H), 6.98 (m, 4H), 4.48 (m, 1H), 3.72 (m, 1H), 3.43 (d, 2H), 3.21 (m, 1H), 2.88 (m, 2H), 2.53 (t, 1H), 2.41 (d, 1H).



36g **36h**

Preparation of compound 36h

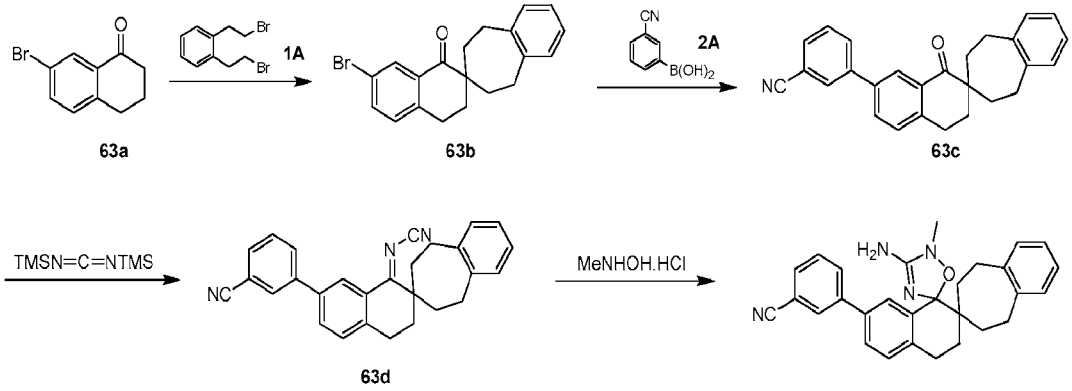
To a solution of compound **36g** (70 mg, 0.19 mmol) in drying CH_2Cl_2 (3 mL) was added $TiCl_4$ (1 M solution in DCM, 0.38 mL) at room temperature dropwise within 15 minutes. The mixture was stirred for 1 h, added *bis*-trimehtlysilylcarbodiimide (109 mg, 0.58 mmol) dropwise, stirred overnight, poured into ice-water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the compound **36h** (80 mg, crude), which was used for the next step without further purification.



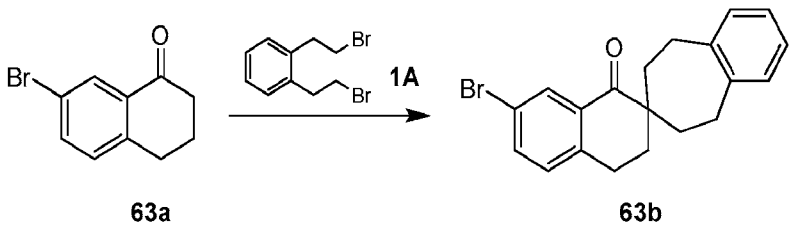
Preparation of compound 36

To a solution of MeNHOH.HCl (17 mg, 0.206 mmol) in anhydrous MeOH (3 mL) was added NaOMe (10% in MeOH, 100 mg, 0.185 mmol) and compound **36h** (80 mg, 0.206 mmol) at room temperature. After being stirred for 10 minutes, the solvent was removed in vacuum, the residue was dissolved in CH_2Cl_2. After filtration, the filtrate was concentrated, and the residue was purified by preparative TLC and HPLC to afford the **compound 36** (5.08 mg, 6%). **^{1}H NMR** (400 MHz CD_3OD): δ8.02 (m, 2H), 7.52-7.93 (m, 4H), 7.38 (m, 1H), 7.21(m, 1H), 7.03 (m, 3H), 4.48 (m, 1H), 3.7 (m, 1H), 3.48 (m, 3H), 3.19 (m, 2H), 2.52-2.78 (m, 2H), 2.46 (m, 1H), 1.73-2.11 (m, 1H); ESI MS: m/z 437 $[M+H]^+$.

Example 53. **Preparation of Compound 63**



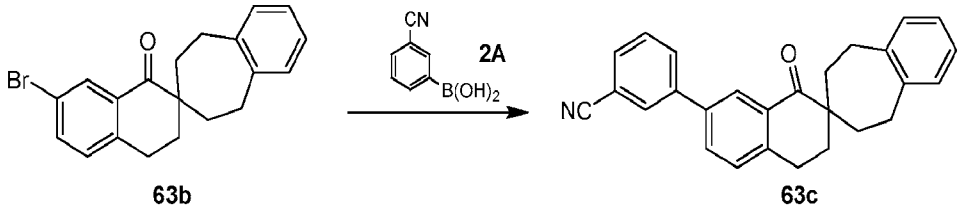
Experimental data:



Preparation of compound 63b

A solution of compound **63a** (1 g, 4.46 mmol) in DMF (20 mL) was added NaH (393 mg, 9.81 mmol) in ice water bath, and the mixture was stirred at room temperature for 30 min., and compound **1A** was added dropwise. The mixture was stirred overnight,

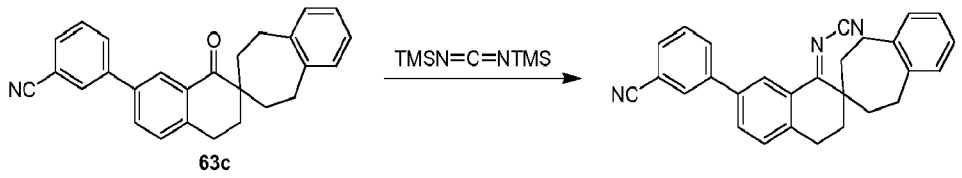
quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the compound **63b** (100 mg, 5%).



63b 63c

Preparation of compound 63c

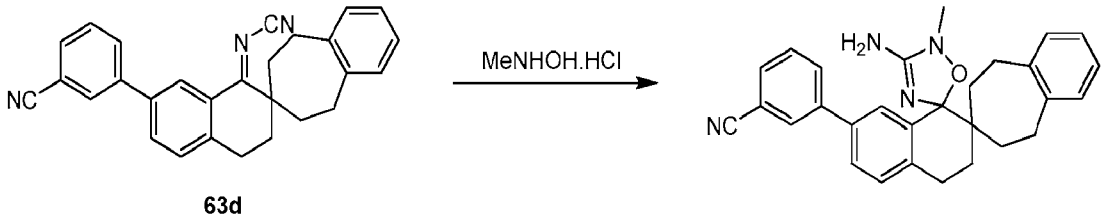
$Pd(PPh_3)_2Cl_2$ (30 mg) in a 10 mL of tube was treated sequentially with a solution of compound **63b** (100 mg, 354 mmol) in 1,4-dioxane (3 mL), Cs_2CO_3 solution (2 N, 0.6 mL), and 3-cyanophenylboronic acid (83 mg, 147 mmol) under Ar_2 atmosphere. The mixture was heated in microwave at 120°C for 25 min. The reaction mixture was concentrated in *vacuo*, the residue was purified by preparative TLC to give the compound **63c** (20 mg, 18%).



63c 63d

Preparation of compound 63d

To a solution of compound **63c** (20 mg, 0.053 mmol) in CH_2Cl_2, (3 mL) was added $TiCl_4$ (39.5 mg, 0.2 mmol) dropwise, and the mixture was stirred at 50°C at Ar_2 in microwave for 20 minutes, *N*, *N*'-methanediylidenebis (1, 1, 1-trimethylsilanamine) (18 mg, 0.096 mmol) was added dropwise. The mixture was stirred at 60°C under Ar_2 in microwave for 10 minutes, and poured into ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried, and concentrated to give the crude compound **63d** (20 mg), which was used for the next step directly without purification.

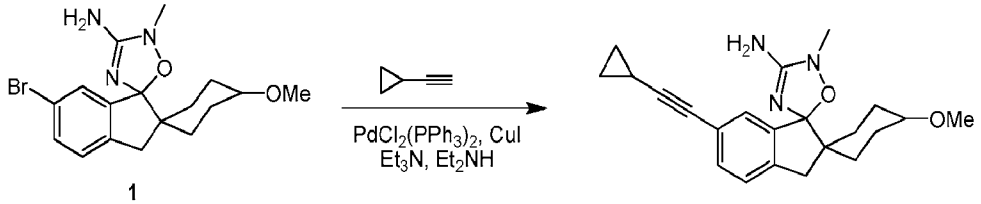


63d

Preparation of compound 63

To a solution of *N*-methyl-hydroxylamine hydrochloride (4.2 mg, 0.05 mmol) in MeOH (5 mL) was added MeONa (2.43 mg, 25% in MeOH) and (*E*)-*N*-(7'-(3-cyanophenyl)- 3',4',5,6,8,9-hexahydro-1'*H*-spiro[benzo[7]annulene-7,2'-naphtha- lene]-1'-ylidene)cyanamide (20 mg, 0.053 mmol). After being stirred for 10 minutes, the solvent was removed in *vacuo* to give the crude compound, which was purified by preparative TLC and HPLC to give **compound 63** (0.41 mg, 2%). **^{1}H-NMR** (CD_3OD 400 MHz): 7.92 (t, 2H), 7.60-7.74 (m, 4H), 7.41 (t, 1H), 7.09 (m, 4H), 3.33 (d, 3H), 3.12 (m, 2H), 3.00 (t, 2H), 2.69 (d, 2H), 2.32 (t, 2H), 1.58 (t, 2H), 1.47 (d, 2H); ESI MS: m/z 449 $[M+H]^+$.

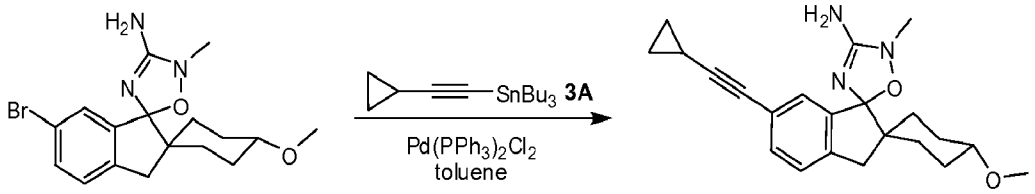
Example 54. Preparation of Compound 3



1

By using the same synthetic procedure as compound 76a in Example 56, **compound 3** (4.5 mg, 12%) was obtained as a white solid. **^{1}H-NMR** (400MHz CD_3OD): δ7.59 (m, 1H), 7.42 (d, J = 9.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 3.38 (d, J = 12.0 Hz, 3H), 3.31 (m, 3H), 3.17 (m, 1H), 2.97 (m, 1H), 2.16 (m, 2H), 1.72 (m, 3H), 1.46 (m, 4H), 0.91 (m, 2H), 0.76 (m, 2H); ESI MS: 366 $[M+H]^+$.

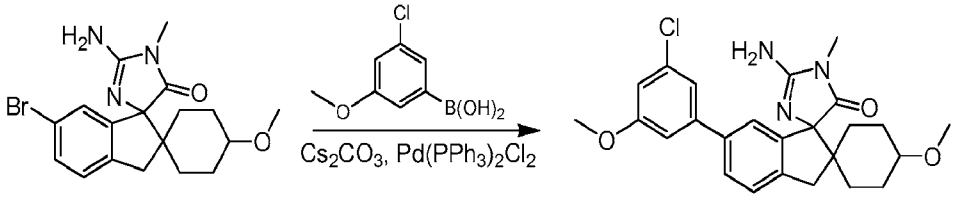
Alternatively, compound 3 can be prepared according to the following scheme:



3a 3

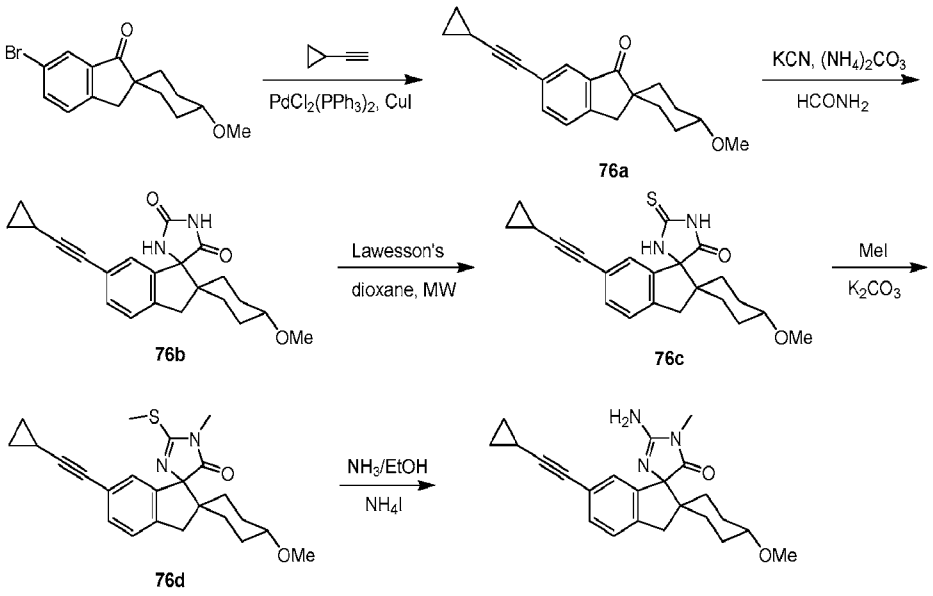
A solution containing compound **3a** (300 mg, 0.789 mmol) and compound **3A** (560 mg, 1.58 mmol) in toluene (20 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (5 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 30 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (50 mL) and aqueous CsF (4.0 M, 50 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative HPLC to afforded compound **3** (93 mg, 31%) as a white solid. **LC-MS** t_R = 1.084 min and 1.143 min in 2 min chromatography, MS (ESI) *m/z* 366.2 $[M+H]^+$. **^{1}H NMR (CD_3OD, 400 MHz)**: δ 7.22-7.26 (t, J = 7.6 Hz, 2H), 7.13-7.15 (d, J = 7.6 Hz, 1H), 3.37 (s, 3H), 3.12-3.20 (m, 1H), 3.03 (s, 3H), 2.78-2.88 (q, J = 16.0 Hz, J = 10.4 Hz, 2H), 1.99-2.06 (m, 2H), 1.65-1.68 (m, 1H), 1.52-1.60 (m, 2H), 1.41-1.49 (m, 2H), 1.27-1.37 (m, 2H), 0.86-0.92 (m, 2H), 0.70-0.75 (m, 2H).

Example 55. **Preparation of Compound 16**

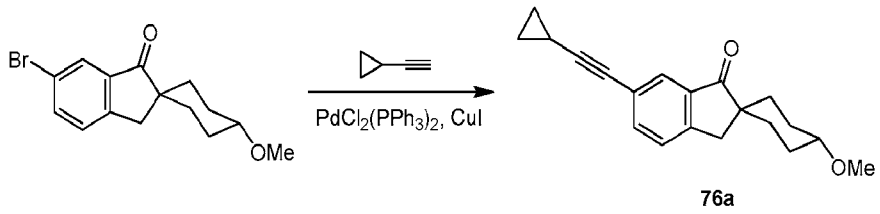


By using the same synthetic procedure as **compound 4** described in Example 27, **compound 16** (2.3 mg, yield 8%) was obtained. **^{1}H-NMR** (CD_3OD, 400MHz): δ7.53 (d, 1H), 7.38 (m, 2H), 7.12 (m, 1H), 6.99 (m, 1H), 6.83 (m, 1H), 3.72 (s, 3H), 3.26 (m, 3H), 3.05-3.12 (m, 6H), 1.88-2.06 (m, 2H), 1.76 (d, 1H), 1.38 (m, 3H), 1.22 (m, 2H); ESI MS: m/z 454 $[M+H]^+$.

Example 56. Preparation of Compound 76



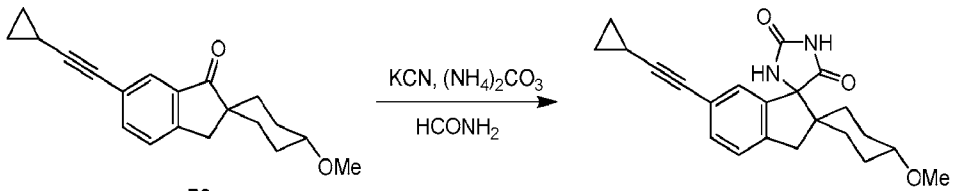
Procedure for preparation of the compound 76a



A dry three-necked round bottom flask equipped with a condenser was charged with 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (1.8 g, 5.8 mmol), TEA (30 mL) and DEA (6 mL) under N_2 atmosphere. To this solution was added CuI (60 mg, 0.3 mmol), and $PdCl_2(PPh_3)_2$ (210 mg, 0.3 mmol). After being degassed once again, the cyclopropyl acetylene (3 mL, excess) was added, and the mixture was heated at 50°C (oil bath) with stirring for 15 hours. After evaporation, the residue was partitioned with EtOAC (50 mL) and water (30 mL), and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel eluting with

5%~20% EtOAc in hexane to afford the compound **76a** (1.55 g, 87% purity), which was purified by preparative HPLC to yield give the pure compound **1** (0.88 g, 51%) as a white solid. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ7.66 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 3.32 (s, 3H), 3.18 (m, 1H), 2.93 (s, 2H), 2.08 (m, 2H), 1.69 (m, 2H), 1.52 (s, 1H), 1.38 (m, 5H), 0.82 (m, 2H), 0.71 (m, 2H).

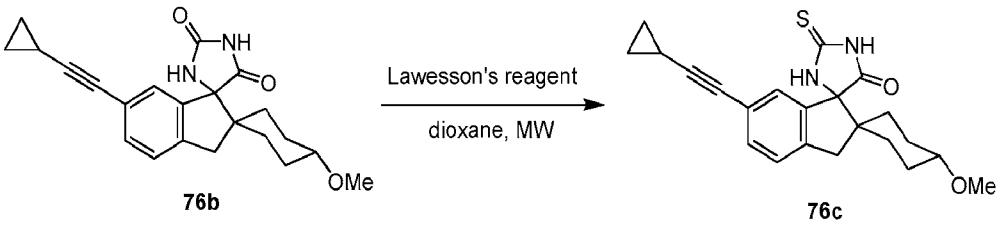
Procedure for preparation of the compound 76b



76a 76b

A steel clave was charged with a mixture of 6'-(cyclopropylethynyl)-4-methoxyspiro [cyclohexane-1,2'-inden]-1'(3'*H*)-one (600 mg, 2.04 mmol), KCN (266 mg, 4.08 mmol), and $(NH_4)_2CO_3$ (689 mg, 15.29 mmol). Formamide (20 mL) was added to fill tube completely. The mixture was heated at 100°C for 72 h, and the reaction mixture was cooled, and poured into ice. After acidification with concentrated aqueous HCl solution (20 mL), the mixture was filtrated to give the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (150 mL×2). The organic phase was dried over Na_2SO_4 and concentrated to give the compound **76b** (660 mg, 80%) as a white solid, which was used for the next step directly without purification. **^{1}H-NMR** ($CDCl_3$ 400MHz): δ7.59 (s, 1H), 7.23 (m, 1H), 7.16 (m, 2H), 3.29 (s, 3H), 2.92-3.11 (m, 3H), 2.06 (m, 1H), 1.88-1.97 (m, 2H), 1.59 (m, 1H), 1.43 (m, 1H), 1.32-1.38 (m, 2H), 1.25 (m, 2H), 0.82 (m, 2H), 0.73 (m, 2H).

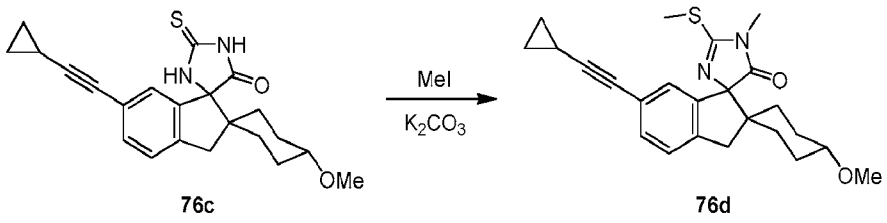
Procedure for preparation of the compound 76c



76b **76c**

A suspension of compound **76b** (660 mg, 1.81 mmol) and Lawesson's Reagent (730 mg, 1.81 mmol) in dry 1,4-dioxane (60 mL) was heated at 120°C for 35 minutes in a CEM microwave reactor. The mixture was concentrated in *vacuo*, and the residue was purified by column chromatography on silica gel eluting with PE/EA=5/1 to give the compound **76c** as a yellow solid (330 mg, 47%). **^{1}H-NMR** ($CDCl_3$ 400MHz): δ7.96 (s, 1H), 7.27 (m, 1H), 7.08-7.14 (m, 2H), 6.92 (m, 1H), 3.63-3.79 (m, 1H), 3.28 (s, 3H), 2.92-3.11 (m, 3H), 2.04 (m, 1H), 1.97 (m, 1H), 1.35 (m, 5H), 1.26 (m, 1H), 0.81 (m, 2H), 0.72 (m, 2H).

2. Procedure for preparation of compound 76d

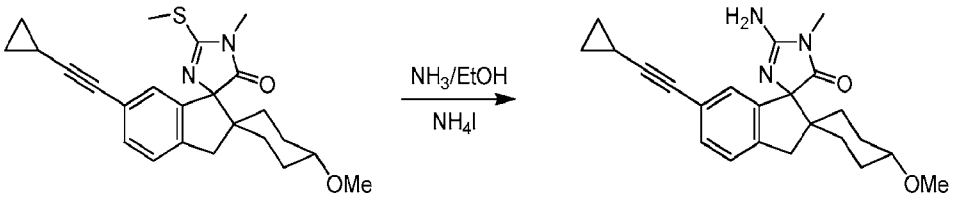


76c **76d**

To a solution of compound **76c** (300 mg, 0.786 mmol) in CH_3CN (30 mL) was added K_2CO_3 (434 mg, 3.14 mmol). After being stirred for 5 minutes, MeI (462 mg, 3.14 mmol) was added, and the reaction mixture was heated at 60°C for 10 minutes in microwave, and at 100°C for another 10 minutes. The mixture was filtered, and the

filtrate was concentrated in *vacuo*. The residue was purified by preparative TLC (PE/EA=5/1) to give the compound **76d** (150 mg, 47%) as a white solid. **^{1}H-NMR** ($CDCl_3$ 400MHz): δ7.18 (m, 1H), 7.16 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 3.27 (s, 3H), 3.14 (m, 1H), 2.98-3.04 (m, 2H), 2.92 (s, 3H), 2.58 (s, 3H), 1.78-1.92 (m, 3H), 1.65 (t, 1H), 1.46 (m, 1H), 1.22-1.36 (m, 3H), 1.08 (m, 1H), 0.74 (m, 2H), 0.67 (m, 2H).

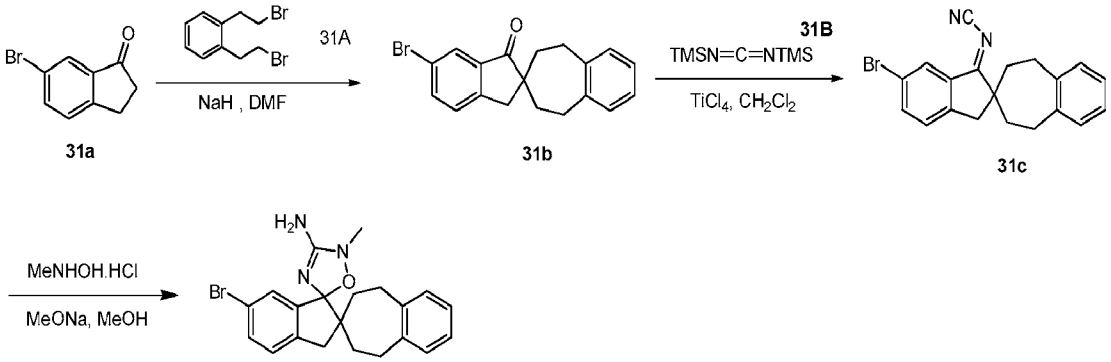
3. ***Procedure for preparation of compound 76***



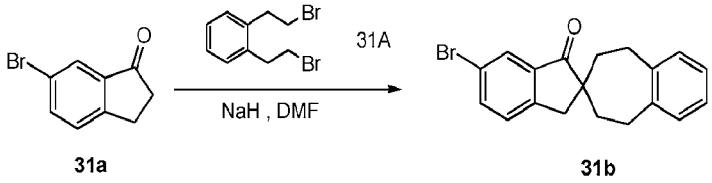
76d

A solution of compound **76d** (150 mg, 0.37 mmol), NH_4I (531 mg, 3.7 mmol) in NH_3/EtOH (15 mL, 5 N) was heated at 120°C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated in vacuum, and the residue was purified by preparative TLC (DCM/MeOH=10/1) and preparative HPLC to give **compound 76** (92 mg, 66%) as a white solid. **^{1}H-NMR** (CD_3OD 400 MHz): δ7.19 (m, 2H), 6.88 (s, 1H), 3.32 (s, 3H), 3.2.98-3.12 (m, 6H), 1.91-2.04 (m, 2H), 1.82 (m, 1H), 1.57 (m, 1H), 1.21-1.43 (m, 5H), 0.82 (m, 2H), 0.68 (m, 2H); ESI MS: m/z 378 $[M+H]^+$.

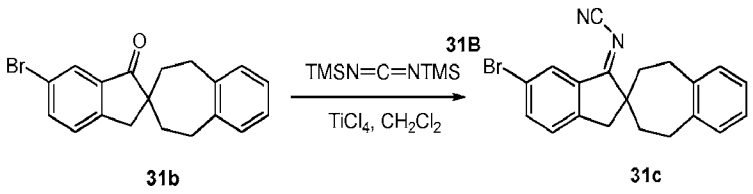
Example 57. Preparation of Compound 31



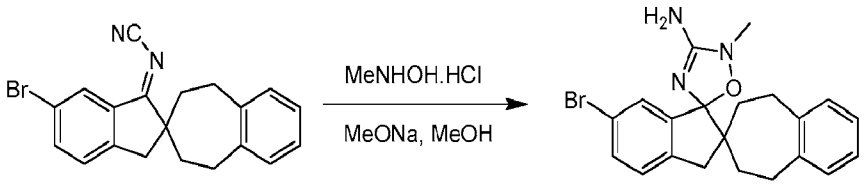
Experimental data



A mixture of compound **31a** (2.17 g, 10.35 mmol) and compound **31A** (6 g, 20.7 mmol) in DMF (17.5 mL) was added NaH (910 mg, 60%, 22.75 mmol) at 0°C. The mixture was stirred at room temperature overnight, quenched with water (5 mL), and extracted with EtOAc (3×50 mL). The organic layer was dried, and concentrated. The residue was purified by column chromatography to give the compound **31b** (250 mg, yield 7%) as a yellow solid.



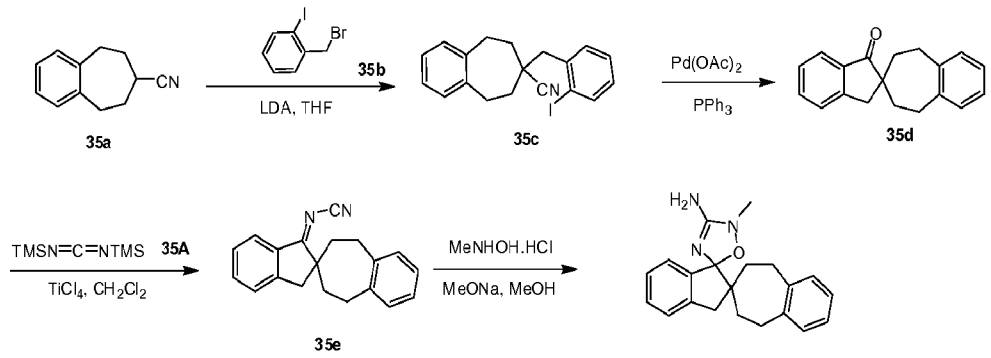
To a solution of compound **31b** (200 mg, 0.59 mmol) in CH_2Cl_2 (26 mL) was added $TiCl_4$ (2.35 mL, 2.35 mmol). The mixture was stirred at room temperature for 1 h, and compound **31B** (245.7 mg, 1.3 mmol) was added. The mixture was stirred at room temperature overnight, poured into ice-water (5 mL), and extracted with CH_2C1_2 (2×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the compound **31c** (200 mg, crude) as a yellow solid.



31c

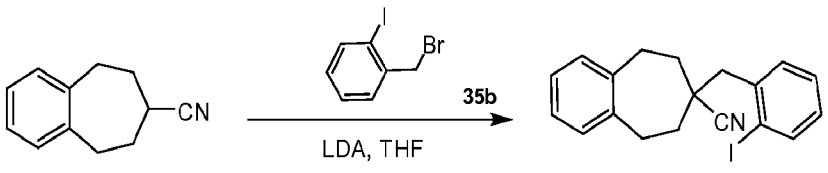
To a solution of methylhydroxylamine HCl salt (11.5 mg, 0.137mmol) in anhydrous MeOH (2.5 mL) was added NaOMe (10% in MeOH, 0.07 mL) and compound **31c** (50 mg, 0.137 mmol). After being stirred for 20 minutes, the solvent was removed in *vacuo*, and the residue was dissolved in CH_2Cl_2 (10 mL). The mixture was filtered, concerntrated, and purified by pre-TLC and HPLC to give the compound **31** (4.99 mg, yield 9%) as a white solid. **^{1}H-NMR** (CD_3OD 400 MHz): δ7.60-7.87 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.10-7.13 (m, 4H), 3.32 (m, 3H), 2.97-3.11(m, 3H), 2.70-2.78 (m, 2H), 2.05-2.10 (m, 1H), 1.67-1.70 (m, 1H), 1.47-1.68 (m, 3H); ESI MS: m/z 412 $[M+H]^+$.

Example 58. **Preparation of Compound 35**



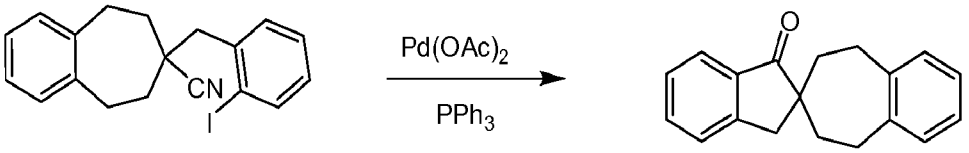
35a 35c 35d 35e

Experimental data



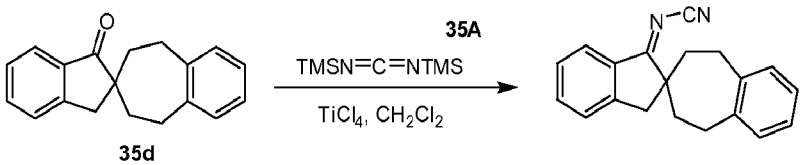
35a 35c

The solution of LDA (6.5 mL, 11.7 mmol, 1.8M in THF) in THF (12.5mL) was added the solution of compound **35a** (1 g, 5.85 mmol) in THF (6mL) slowly at -60°C. The mixture was stirred at -60°C for 30 min., the solution of compound **35b** (1.55 g, 5.26 mmol)) in THF (5mL) was added slowly. The resulting mixture was stirred at -60°C for 1.5 h, quenched with water (10 mL), and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated, and purified by chromatography to give the compound **35c** (1.85 g, yield 82%) as a yellow solid. **^{1}H-NMR** ($CDCl_3$ 400 MHz): δ7.81 (m, 1H), 7.52 (m, 1H), 7.26-7.49 (m, 1H), 7.19 (m, 4H), 6.92 (m, 1H), 2.99-3.13 (m, 2H), 2.97 (s, 2H), 2.66 (m, 2H), 2.04-2.10 (m, 2H), 1.52-1.61 (m, 2H).



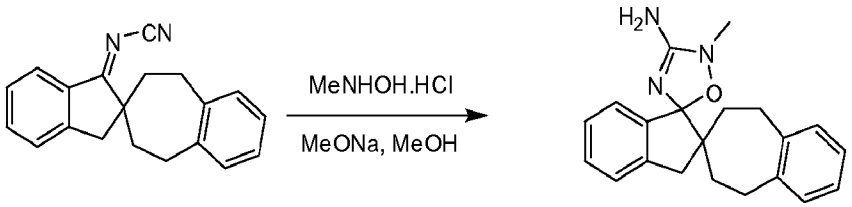
35c **35d**

A 100 mL flask was charged with compound **35c** (1.85 g, 4.77 mmol), $Pd(OAc)_2$ (0.140 g, 0.62 mmol), Ph_3P (0.363 g, 1.38 mmol), DMF (75 mL) and H_2O (8.33 mL). The resulting mixture was degassed, and Et_3N (0.578 g, 5.72 mmol) was added under nitrogen. The reaction mixture was stirred at 130°C for 4 h, cooled to room temperature, diluted with water (20 mL), and extracted with EtOAc (2×40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated, and purified by chromatography to give the compound **35d** (650 mg, yield 52%) as a white solid. **^{1}H-NMR** ($CDCl_3$ 400 MHz): δ7.74 (m, J = 8.2 Hz, 1H), 7.58-7.73 (m, 1H), 7.41-7.43 (m, 1H), 7.31-7.33 (m, 1H), 7.03-7.09 (m, 4H), 3.15 (s, 2H), 2.93-3.00 (m, 2H), 2.80 (br s, 2H), 1.79-1.86 (m, 2H), 1.57-1.62 (m, 2H).



35d **35e**

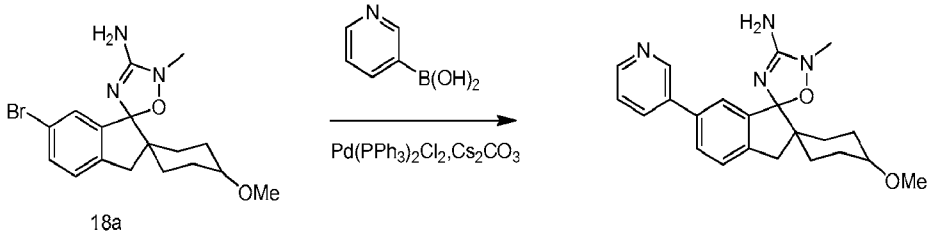
To a solution of compound **35d** (100 mg, 0.38 mmol) in CH_2Cl_2 (7mL) was added $TiCl_4$ (1.53mL, 1.53 mmol). This mixture was stirred at 50°C for 10 min in microwave, and added bis-trimethylsilylcarbodiimide (0.187mL, 0.836 mmol). The resulting mixture was stirred at 60°C for 12 min. in microwave, TLC showed that the reaction was completed, the mixture was poured into the ice-water (20 mL). The solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give the compound **35e** (100 mg, yield 93%) as a yellow solid, which was used directly for the next step without purification.



35e

To a solution of methylhydroxylamine HCl salt (14.5 mg, 0.175 mmol) in anhydrous MeOH (3 mL) was added NaOMe (10% in MeOH, 0.090 mL, 0.157 mmol) and compound **35e** (50 mg, 0.175 mmol). After being stirred for 25 minutes, the solvent was removed in *vacuo*, and residue was dissolved in CH_2Cl_2 (20 mL). The mixture was filtered, and the solvent was removed, the residue was purified by HPLC to give the compound **35** (3.4 mg, yield 6%) as a white solid. **^{1}H-NMR** (CD_3OD 400 MHz): δ7.51-7.77 (m, 2H), 7.47 (m, 1H),7.40 (m, 1H), 7.11-7.17 (m, 4H) 3.34 (s, 3H), 2.97-3.12 (m, 3H), 2.73-2.85 (s, 2H), 2.09-2.67 (m, 3H), 1.66-1.69 (m, 1H), 1.49-1.56 (m, 1H); ESI MS: 515 $[M+H]^+$.

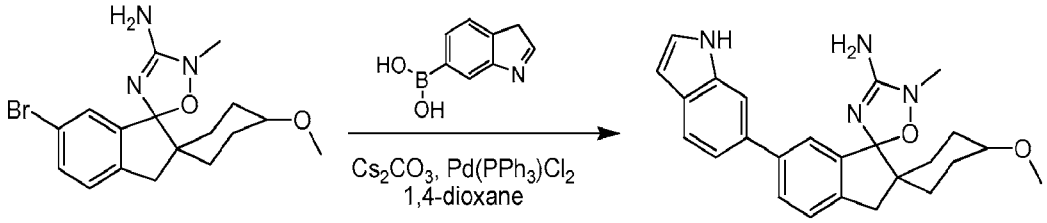
Example 59. **Preparation of Compound 18**



18a

A solution of compound **18a** (25 mg,0.065 mmol) in 1,4-dioxane(2 mL) was added 3-pyridinylboronic acid (12 mg,0.098 mmol), Cs_2CO_3 (2N, 0.5 mL), and $Pd(PPh_3)_2Cl_2$(4.3 mg, 0.00065 mmol, under nitrogen atmosphere. The mixture was stirred in microwave at 120°C for 15 min., TLC showed the reaction was completed, and the reaction mixture was concentrated, and purified by Prep-TLC and Prep-HPLC to give **compound 18** (5 mg, 20%) as a white solid. **^{1}H-NMR**: δ8.78 (s, 1H), 8.51 (d, 1H), 8.10 (m,1H), 7.61 (m,1H), 7.54 (m, 2H), 7.39 (m,1H), 3.51 (s, 3H), 3.15 (s, 3H), 2.94 (m, 2H), 2.09 (m, 2H), 1.76 (m, 1H),1.64 (m, 2H), 1.32-1.49 (m, 4H); ESI MS: 379 $[M+H]^+$.

Example 60. Preparation of Compound 37



By using the same synthetic strategy as **compound 18** described in Example 59, compound 37 (3.9 mg, yield 11%) was obtained as a white solid. **^{1}H-NMR** (CD_3OD 400 MHz): δ7.71-7.92 (m, 1H), 7.30-7.69 (m, 4H), 7.11-7.29 (m, 2H), 3.25-3.36 (m, 6H), 3.11-3.15 (m, 2H), 2.88-2.90 (d, 1H), 1.95-2.15 (m, 2H),1.57-1.85 (m, 3H), 1.26-1.50 (m, 3H); ESI MS: 417 $[M+H]^+$.

Specific stereochemistry shown in Examples 1-60 was determined based on spectroscopic data and/or computer modeling study.

LCMS method for Examples 61-409 and 411-433:

LCMS Chromatographic method: (**2 min**)

Column: Welch Xtimate C18 2.1*30 mm, 3 um

<table>
<tr><td>Mobile Phase</td><td>A 4L H_2O（1.5 mL TFA）
B 4L MeCN（0.75 mL TFA）
<table>
<tr><th>TIME(min)</th><th>A%</th><th>B%</th></tr>
<tr><td>0</td><td>90</td><td>10</td></tr>
<tr><td>1.5</td><td>20</td><td>80</td></tr>
<tr><td>1.51</td><td>20</td><td>80</td></tr>
<tr><td>2</td><td>90</td><td>10</td></tr>
</table></td></tr>
<tr><td>Flow Rate</td><td>1.2 mL/min</td></tr>
<tr><td>Wavelength</td><td>UV220</td></tr>
<tr><td>Oven Tem.</td><td>50 °C</td></tr>
<tr><td>MS</td><td>ESI</td></tr>
</table>

LCMS Chromatographic method: (**3min**)

Column: Welch Xtimate C18 2.1*30 mm, 3 um

<table>
<tr><td>Mobile Phase</td><td>A 4L H_2O（1.5 mL TFA）
B 4L MeCN（0.75 mL TFA）
<table>
<tr><th>TIME(min)</th><th>A%</th><th>B%</th></tr>
<tr><td>0</td><td>90</td><td>10</td></tr>
<tr><td>1.35</td><td>20</td><td>80</td></tr>
<tr><td>2.25</td><td>20</td><td>80</td></tr>
<tr><td>2.26</td><td>90</td><td>10</td></tr>
<tr><td>3.00</td><td>90</td><td>10</td></tr>
</table></td></tr>
<tr><td>Flow Rate</td><td>0.8 mL/min</td></tr>
<tr><td>Wavelength</td><td>UV220</td></tr>
<tr><td>Oven Tem.</td><td>50 °C</td></tr>
<tr><td>MS</td><td>ESI</td></tr>
</table>

LCMS Chromatographic method: (**7min**)

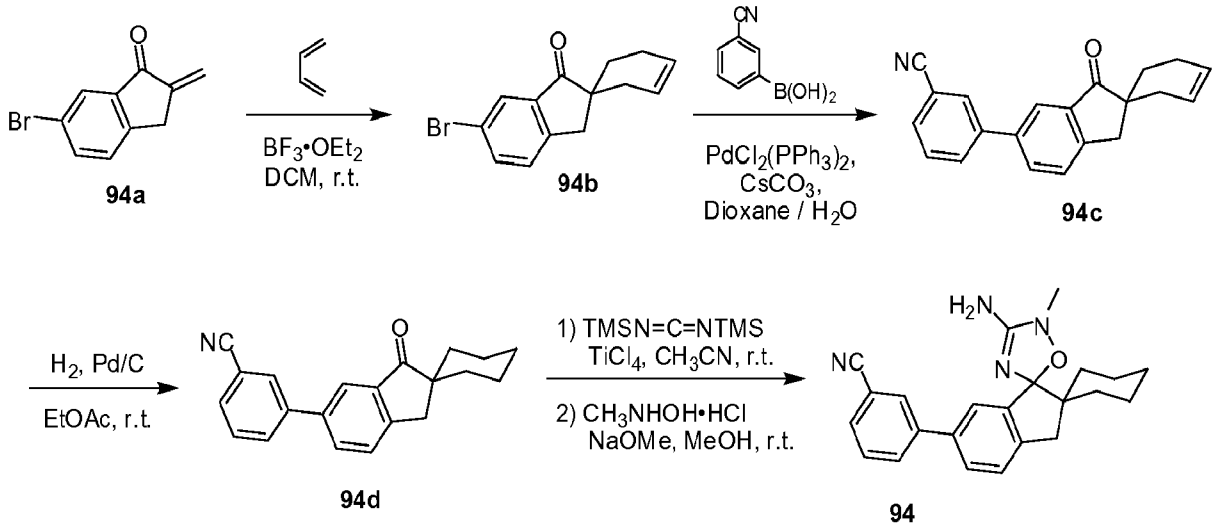
Column: Welch Xtimate C18 2.1*30 mm, 3 um

Mobile Phase	A 4L H_2O（1.5 mLTFA） B 4L MeCN（0.75 mL TFA）

TIME(min)	A%	B%
0	90	10
6	20	80
6.5	20	80
6.51	90	10
7	90	10

Flow Rate	0.8 mL/min
Wavelength	UV220
Oven Tem.	50 °C
MS	ESI

Example 61 Preparation of compound 94



Step 1: preparation of 6'-bromospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one (94b)

In a flame dried 50 mL round bottom flask was placed 6-bromo-2-methylene-2,3-dihydro-1H-inden-1-one (500 mg, 2.252 mmol) and it was dissolved in dichloromethane (7.5 mL). To this solution was bubbled 1,3-butadiene (excess). After stirring for 5 minutes, BF_3•OEt_2 (414 μL, 3.377 mmol) was slowly added and the 1,3-butadiene still bubbling (2-3 bubbles per second,; for 2 minutes). After the 2 minutes, the reaction was quenched with saturated $NaHCO_3$ aq. (10 mL), and diluted with DCM

(10 mL). The phases were separated and the aqueous phase was back-extracted with dichloromethane (10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 6'-bromospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one (317 mg, 1.149 mmol, 51% yield). M+H = 276.9, 278.9 (bromine ion effect). ^1H NMR = ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 5.81 – 5.72 (m, 2H), 2.98 (d, $J_{A,B}$ = 17.6 Hz, 1H), 2.86 (d, $J_{A,B}$ = 17.2 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.28 – 2.16 (m, 2H), 1.93 – 1.85 (m, 1H), 1.81 – 1.75 (m, 1H), 1.51 – 1.46 (m, 1H).

Step 2: Preparation of 3-(1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (94c)

In a 20 mL vial was placed 6'-bromospiro[cyclohex[3]ene-1,2'-inden]-1'(3'H)-one (155 mg, 0.562 mmol), 3-cyanobenzeneboronic acid (107 mg, 0.728 mmol), $PdCl_2(PPh_3)_2$ (39 mg, 0.056 mmol) and cesium carbonate (457 mg, 1.403 mmol). This solid mixture was dissolved in a Dioxane / water mixture (5.6 mL, 6 : 1 ratio, respectively). The reaction vial was capped and allowed to stir at 90° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (15 mL) and water (15 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 3-(1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (125 mg, 0.418 mmol, 74% yield). M+H = 299.9 ^1H NMR = ($CDCl_3$, 400 MHz) δ 7.94 (d, J = 1.6 Hz, 1H), 7.87 (s, 1H), 7.83 – 7.78 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.58 – 7.54 (m, 2H), 5.83 – 5.75 (m,

2H), 3.10 (d, $J_{A,B}$ = 17.6 Hz, 1H), 2.97 (d, $J_{A,B}$ = 17.6 Hz, 1H), 2.49 (d, J = 9.2 Hz, 1H), 2.25 – 2.20 (m, 2H), 1.97 – 1.89 (m, 1H), 1. 84 – 1.79 (m, 1H), 1.55 – 1.50 (m, 1H)

Step 3: Preparation of 3-(1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (94d)

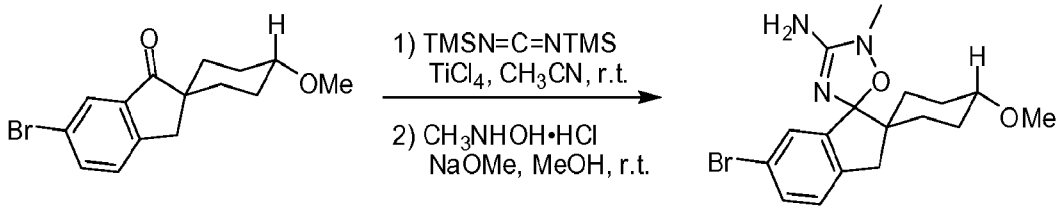
To a 100 mL round bottom flask was placed 3-(1'-oxo-1',3'-dihydrospiro[cyclohex[3]ene-1,2'-indene]-6'-yl)benzonitrile (52 mg, 0.174 mmol) and it was dissolved in Ethyl Acetate (5 mL). To this solution was added Pearlmann's catalyst (10 mg, Pd/C). A three way adapter was attached and one of the lines had a H_2 filled balloon attached. The system was flushed with H_2 and evacuated under vacuum for 3 cycles. After 1 hour stirring at room temeratures, the starting alkene was consumed. The reaction was filtered through a celite cake and the cake was rinsed with ethyl acetate (5 mL). The filtrate was concentrated yielding 3-(1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (49 mg, 0.163 mmol, 94% yield) and use as it is for the next reaction. M+H = 302.1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 1H), 7.87 (s, 1H), 7.84 – 7.78 (m, 2H), 7.65 (dd, J = 7.6, 1.2 Hz, 1H), 7.59 – 7.55 (m, 2H), 3.08 (s, 2H), 1.85 – 1.80 (m, 2H), 1.77 – 1.71 (m, 3H), 1.50 – 1.36 (m, 5H).

Step 4: Preparation of compound 94

In a 20 mL vial was placed 3-(1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (49 mg, 0.163 mmol), and it was azeotroped with toluene (2 mL). Dichloromethane (3 mL) was added followed by $TiCl_4$ (326 μL, 0.326 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (117 μL, 0.521 mmol) was added and the solution was allowed to stir overnight (~14 hours) at room temperature. The reaction was quenched with ice cold water (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (3 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (15 mg, 0.180 mmol) and it was dissolved in MeOH (3 mL). To this solution was added NaOMe (35 μL, 25% in MeOH) and the solution was stirred

for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The obtained oil was lyophilized yielding the final product (1.65 mg, 0.004 mmol, 2% yield) as white solid. M+H = 373.1. ^{1}H NMR = (CD_3OD, 400 MHz) δ 8.01 – 7.90 (m, 2H), 7.80 – 7.62 (m, 4H), 7.45 (d, J = 8.4 Hz, 1H), 3.35 (s, 3H), 3.09 – 2.96 (m, 2H), 1.83 – 1.42 (m, 10 H).

Example 62 Preparation of compound 95

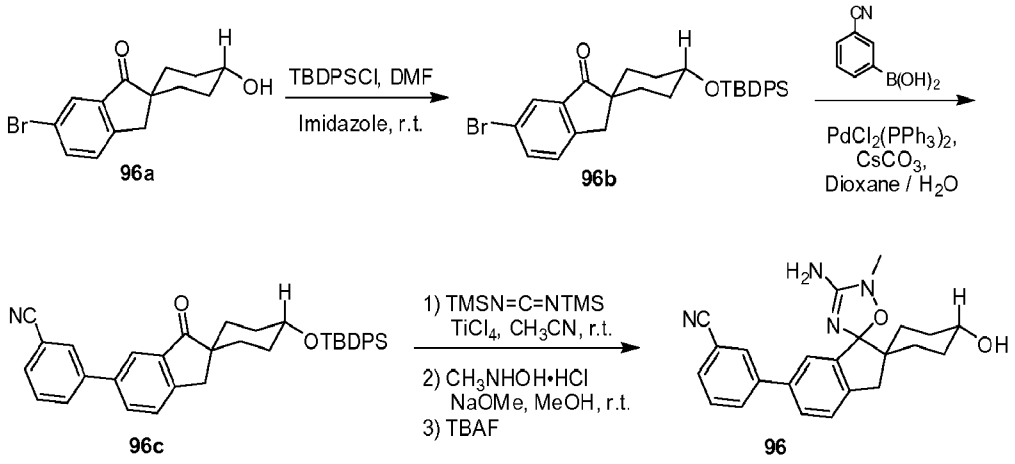


95

In a 4 mL vial was placed 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (26 mg, 0.084 mmol), and it was azeotroped with toluene twice (1 mL / each). Dichloromethane (3 mL) was added followed by $TiCl_4$ (177 μL, 0.177 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (61 μL, 0.272 mmol) was added. The solution was allowed to stir 2 hours at room temperature. The reaction was quenched with ice cold water (5 mL) and diluted with DCM (5 mL). The two phases were separated and the aqueous phase was back-extracted twice with dichloromethane (3 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (8 mg, 0.096 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (22 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room

temperature for 1 hour. After that time, the reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The obtained oil was lyophilized yielding the final product (1.05 mg, 0.003 mmol, 3% yield) as white solid. M+H = 381.9. ^1H NMR = (CD_3OD, 400 MHz) δ 7.64 – 7.54 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 3.17 (m, 1H), 2.94 (m, 2H), 2.18 – 2.05 (m, 2H), 1.73 – 1.33 (m, 6H).

Example 63 Preparation of compound 96



Step 1: Preparation of 6'-bromo-4-(tert-butyldiphenylsilyloxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (96b)

To a 4 mL vial was placed 6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (41 mg, 0.139 mmol) and it was azeotroped with toluene twice (1 mL /each). The solid was dissolved in DMF (1.5 mL). To this solution was added TBDPS-Cl (40 μL, 0.154 mmol) followed by imidazole (24 mg, 0.353 mmol). The reaction was allowed to stir overnight (~14 hours) at room temperature. The reaction was quenched with H_2O (1 mL) and diluted with diethyl ether (1 mL). The phases were separated and the aqueous phase was back extracted twice with diethyl ether (2 mL / each). The combined organic phases were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were

combined and concentrated under reduce pressure yielding 6'-bromo-4-(tert-butyldiphenylsilyloxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (58 mg, 0.109 mmol, 78% yield). M+H = did not ionized. ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 1.6 Hz 1H), 7.69 – 7.66 (m, 5H), 7.45 – 7.32 (m, 7H), 3.73 (m, 1H), 2.98 (s, 2H), 1.93 – 1.89 (m, 2H), 1.62 – 1.47 (m, 4H), 1.37 (m, 2H), 1.08 (s, 9H).

Step 2: 4-(tert-butyldiphenylsilyloxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (96c)

In a 50 mL round bottom flask was placed 6'-bromo-4-(tert-butyldiphenylsilyloxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (58 mg, 0.109 mmol), 3-cyanobenzeneboronic acid (21 mg, 0.143 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.011 mmol) and cesium carbonate (89 mg, 0.273 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.1 mL, 6 : 1 ratio, respectively). The flask was capped and allowed to stir at 90° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (5 mL) and water (5 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane twice (2 mL / each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 4-(tert-butyldiphenylsilyloxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (24 mg, 0.043 mmol, 39% yield).

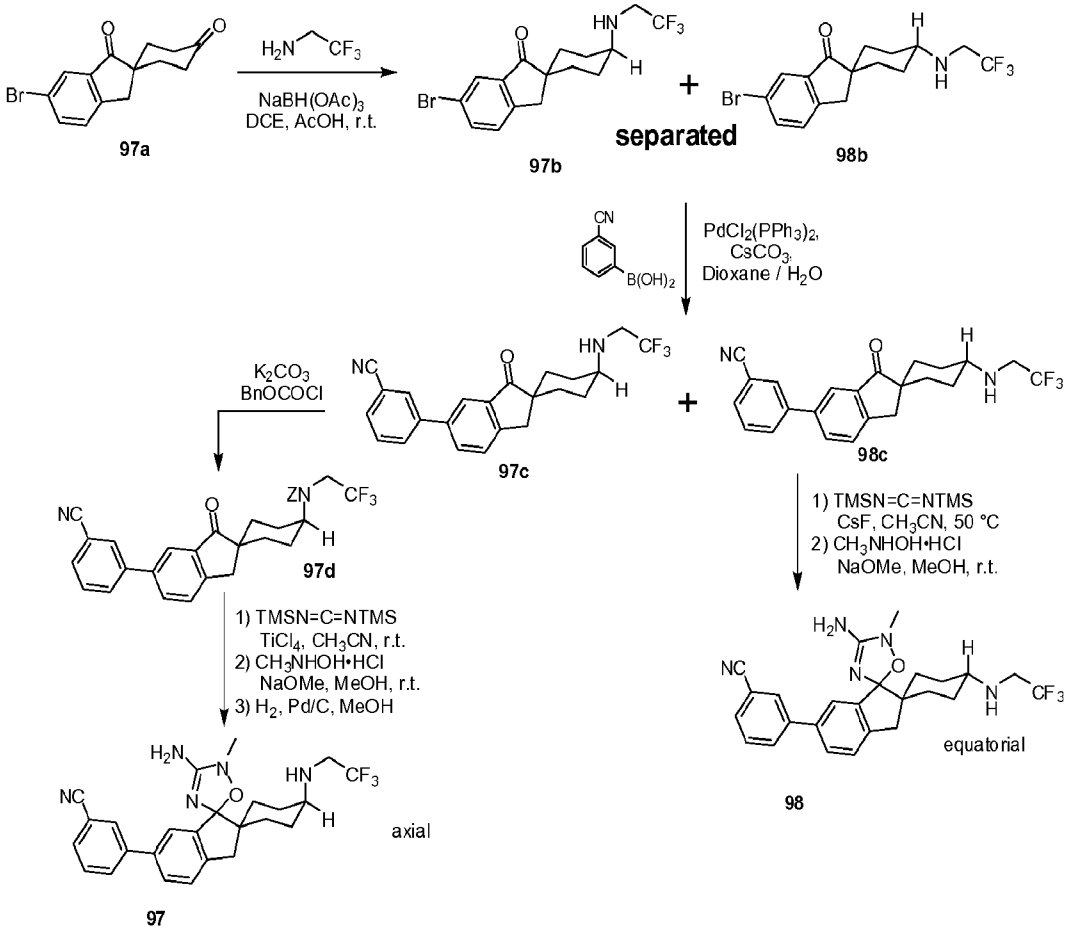
M+H = 556.0. ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.90 – 7.78 (m, 4H), 7.71 – 7.64 (m, 5H), 7.58 – 7.54 (m, 2H), 7.46 – 7.36 (m, 5H), 3.75 (m, 1H), 3.10 (s, 2H), 1.94 (m, 2H), 1.67 – 1.51 (m, 4H), 1.41 (m, 2H), 1.08 (s, 9H).

Step 3: Preparation of compound 96

In a 20 mL vial was placed 4-(tert-butyldiphenylsilyloxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (24 mg, 0.043 mmol), and it was azeotroped with toluene twice (1 mL / each). Dichloromethane (2 mL) was added

followed by $TiCl_4$ (86 μL, 0.086 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (31 μL, 0.138 mmol) was added. The solution was allowed to stir 1 hour at room temperature. The reaction was quenched with ice cold water (5 mL) and diluted with DCM (5 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane (5 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (4 mg, 0.048 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (10 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the solvent was removed under reduced pressure. TBAF (1 mL of a 1M THF sol'n) was added and the reaction was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduce pressure and the crude material was purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated. The obtained material was lyophilized yielding the final product (2.1 mg, 0.005 mmol, 12% yield) as white solid. M+H = 389.0. ^1H NMR = (CD_3OD, 400 MHz) δ 8.01 – 7.90 (m, 2H), 7.77 – 7.62 (m, 4H), 7.47 (m, 1H), 3.57 (m, 1H), 3.45 (s, 3H), 3.04 (m, 2H), 2.06 – 1.96 (m, 2H), 1.80 – 1.68 (m, 2H), 1.61 – 1.44 (m, 4H).

Example 64 Preparation of compounds 97 and 98



Step 1: Preparation of compound 97b and 98b

In a 25 mL round bottom flask was placed 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (501 mg, 1.716 mmol) and it was dissolved in dichloroethane (5.7 mL). To this solution was added the trifluoro ethylamine (162 μL, 2.059 mmol), AcOH (124 μL, 2.059 mmol), and $NaBH(OAc)_3$ (582 mg, 2.746 mmol) at last. The reaction was stirred at room temperature. When the reaction was completed it was quenched with saturated $NaHCO_3$ (aq) (20 mL) and diluted with ethyl acetate (20 mL). The phases were separated and the aqueous phase was back-extracted with ethyl acetate twice (5 mL / each). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). At the end, two isomers were obtained and their corresponding fractions were combined

separately and concentrated under reduce pressure yielding 6'-bromo-4-(2,2,2-trifluoroethylamino)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (axial, **97b**) (420 mg, 1.120 mmol) and 6'-bromo-4-(2,2,2-trifluoroethylamino)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (equatorial, **98b**) (108 mg, 0.288 mmol) (82% yield). Compound **97b**: M+H = 375.9, ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 1.6 Hz, 1H), 7.67 (dd, J = 8.0, 1.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 3.21 (q, J = 9.2 Hz, 2H), 2.93 (s, 2H), 2.90 (m, 1H), 2.01 – 1.94 (m, 2H), 1.87 – 1.81 (m, 2H), 1.75 – 1.68 (m, 2H), 1.38 – 1.29 (m, 2H). Compound **98b**: M+H = 375.8, ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 1.6 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 3.24 (q, J = 9.6 Hz, 2H), 2.95 (s, 2H), 2.68 (m, 1H), 2.03 – 1.97 (m, 2H), 1.81 – 1.74 (ddd, J = 14.0, 14.0, 3.6 Hz, 2H), 1.46 (m, 2H), 1.31 – 1.21 (m, 2H).

Step 2: Preparation of compound 97c and 98c

To a microwave vial was placed was placed 6'-bromo-4-(2,2,2-trifluoroethylamino)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (axial) (50 mg, 0.133 mmol), 3-cyanobenzeneboronic acid (25 mg, 0.170 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and cesium carbonate (109 mg, 0.335 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.5 mL, 6 : 1 ratio, respectively). The vial was capped and heated in the microwave at 110° C for 10 minutes. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (5 mL) and water (5 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (2 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 1'-oxo-4-(2,2,2-trifluoroethylamino)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (axial, **97c**) (50 mg, 0.126 mmol, 74% yield). M+H = 399.0

In a 20 mL vial was placed 6'-bromo-4-(2,2,2-trifluoroethylamino)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (axial) (43 mg, 0.115 mmol), 3-cyanobenzeneboronic acid (22 mg, 0.150 mmol), $PdCl_2(PPh_3)_2$ (4 mg, 0.006

mmol) and cesium carbonate (93 mg, 0.285 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.2 mL, 6 : 1 ratio, respectively). The vial was capped and allowed to stir at 95° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (10 mL) and water (10 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane twice (3 mL / each). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 1'-oxo-4-(2,2,2-trifluoroethylamino)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (equatorial, **98c**) (48 mg, 0.121 mmol, quantitative). M+H = 399.0

Step 3: Preparation of benzyl 6'-(3-cyanophenyl)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-4-yl(2,2,2-trifluoroethyl)carbamate (axial) (97d)

To two separate 4 mL vials were placed 1'-oxo-4-(2,2,2-trifluoroethylamino)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (axial) (25 mg / each, 0.063 mmol / each). To vial #1 was added NaOH (100 mg of a cruch pellet, excess), DCM (1 mL) and H_2O (1 mL). To vial #2 was added K_2CO_3 (270 mgs, excess), DCM (1 mL) and H_2O (1 mL). To each vial was added benzyl chloroformate (50 μL, 1.5 equivalents) and they were allowed to stir overnight (~14 hours) at room temperature. At that time, both reactions were completed. The K_2CO_3 was cleaner than the NaOH one (judge by LC/MS). The reactions were combined and diluted with H_2O (5 mL) and DCM (5 mL). The phases were separated and the aqueous phase was back-extracted with dichloromethane (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding benzyl 6'-(3-cyanophenyl)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-

4-yl(2,2,2-trifluoroethyl)carbamate (axial, **97d**) (50 mg, 0.094 mmol, 75% yield). M+H = 533.0, ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.86 – 7.75 (m, 4H), 7.66 – 7.48 (m, 3H), 7.36 – 7.31 (m, 5H), 5.18 (bs, 2H), 4.19 (bs, 1H), 3.96 (bs, 2H), 2.97 (s, 2H), 2.31 (m, 2H), 1.94 (d, J = 14.0 Hz, 2H), 1.75 (m, 2H), 1.65 (d, J = 10.4 Hz, 2H).

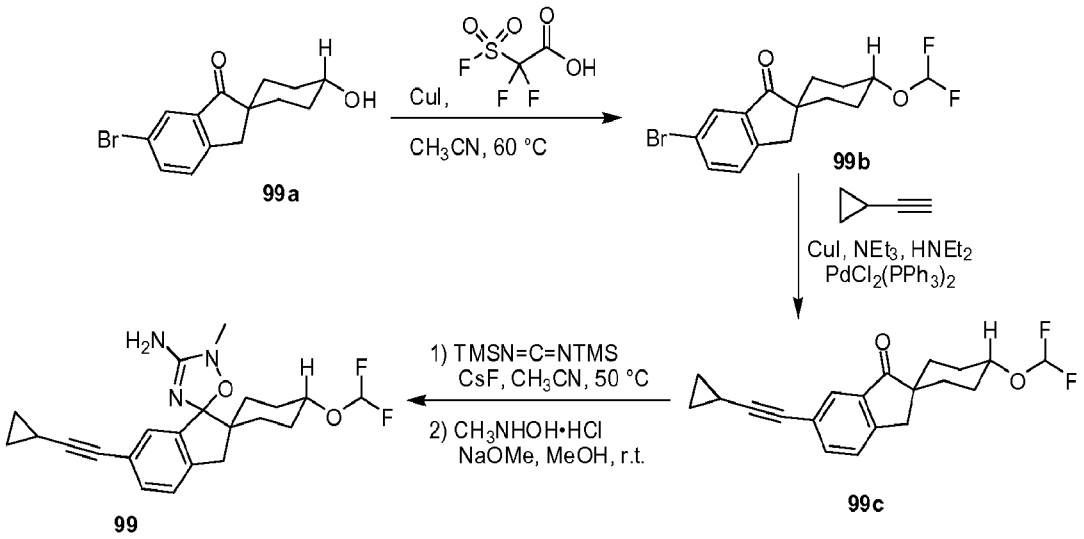
Step 4: Preparation of compound 97

In a 20 mL vial was placed benzyl 6'-(3-cyanophenyl)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-4-yl(2,2,2-trifluoroethyl)carbamate (axial) (50 mg, 0.094 mmol), and it was azeotroped with toluene twice (2 mL / each). Dichloromethane (3 mL) was added followed by $TiCl_4$ (188 μL, 0.188 mmol, 1M in DCM). The reaction mixture was allowed to stir at room temperature for 1 hour. At that time bis-trimethylsilylcarbodiimide (68 μL, 0.303 mmol) was added. The solution was allowed to stir 20 minutes at room temperature. The reaction was quenched with ice cold water (7 mL) and diluted with DCM (7 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane twice (3 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (1 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (9 mg, 0.108 mmol) and it was dissolved in MeOH (3 mL). To this solution was added NaOMe (24 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 20 minutes. After that time, the solvent was removed under reduced pressure. The crude was dissolved in MeOH (2 mL) and Pd/C (< 1 mg) was added. A balloon filled with H_2 was attached to the flask and the mixture was stirred for 5 minutes. The reaction mixture was filtered through Celite and the filtrate was directly purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated yielding the final product (0.5 mg, 0.001 mmol, 11% yield). M+H = 470.1; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.00 – 7.89 (m, 2H), 7.80 – 7.62 (m, 4H), 7.43 (d, J = 7.6 Hz, 1H), 3.78 (m, 1H), 3.63 (m, 2H), 3.40 (s, 3H), 3.06 – 2.90 (m, 2H), 2.19 – 2.10 (m, 2H), 2.00 – 1.89 (m, 4H), 1.78 (m, 2H) ppm.

Step 4: Preparation of compound 98

In a 20 mL vial was placed 1'-oxo-4-(2,2,2-trifluoroethylamino)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (equatorial) (48 mg, 0.121 mmol) and it was azeotroped with acetonitrile twice (2 mL / each). Acetonitrile (2.5 mL) was added. To this solution was added bis-trimethylsilylcarbodiimide (111 μL, 0.494 mmol) was added followed by cesium fluoride (75 mg, 0.494 mmol). The vial was tightly capped and heated overnight (~14 hours) at 50° C. The reaction was quenched with water (5 mL) and diluted with DCM (10 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane twice (3 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (11 mg, 0.132 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (20 μL, 25% in MeOH) and the solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the solvent was removed under reduced pressure. The crude was dissolved in MeOH (2 mL), the solution filtered and purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated under reduced pressure. The material was lyophilized yielding the final product (1.4 mg, 0.003 mmol, 2% yield) as a white fluffy solid. M+H = 470.1, ^{1}H NMR = (CD_3OD, 400 MHz) δ 8.03 – 7.90 (m, 2H), 7.80 – 7.62 (m, 4H), 7.47 (d, J = 7.6 Hz, 1H), 3.93 (m, 2H), 3.36 (s, 3H), 3.30 – 3.20 (m, 2H), 3.06 (m, 1H), 2.25 – 2.18 (m, 2H), 1.94 – 1.80 (m, 2H), 1.66 – 1.58 (m, 2H).

Example 65 Preparation of compound 99



Step 1: Preparation of 6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (99b)

In a 25 mL round bottom flask was placed 6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (368 mg, 1.252 mmol) and it was azeotroped twice with acetonitrile (2 mL / each). CuI (24 mg, 0.126 mmol) was added followed by acetonitrile (2.5 mL). This solution was purged under a stream of N_2 for 30 seconds. The solution was heated to 60 °C under a nitrogen atmosphere. After being 5 minutes at 60 °C, $FSO_2CF_2CO_2H$ (136 µL, 1.316 mmol) was added dropwise. After 1 hour, the reaction was quenched with H2O (10 mL) and diluted with diethyl ether (10 mL). The phases were separated and the aqueous phase was back-extracted with diethyl ether (5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 40g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding benzyl 6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (137 mg, 0.398 mmol, 32% yield).

M+H = 344.9, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 1.2 Hz, 1H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.26 (t, J = 75.2 Hz, 1H), 4.20 (m, 1H), 2.98 (s, 2H), 2.14 (m, 2H), 1.80 (m, 2H), 1.65 – 1.52 (m, 4H).

Step 2: Preparation of 6'-(cyclopropylethynyl)-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (99c)

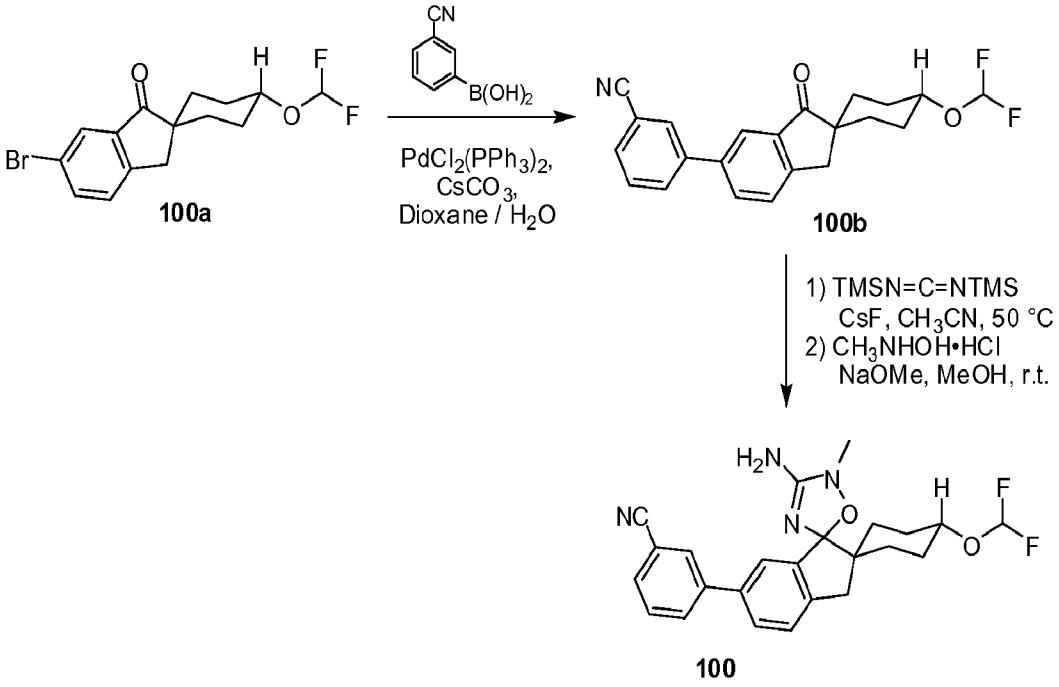
In a 20 mL vial was placed 6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (51 mg, 0.148 mmol) and it was azeotroped twice with toluene (2 mL / each). Triethylamine (1.5 mL) and diethylamine (0.4 mL) were added and this solution was bubbled with a nitrogen stream for 1 minute. Then $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and CuI (1.5 mg, 0.008 mmol) were added and again the solution was bubbled with a stream of nitrogen for 1 minute. Then, PPh_3 (4 mg, 0.015 mmol) was added followed by the addition of cyclopropyl acetylene (300 μL, excess, 70% toluene solution) and one more time the solution was bubbled with a stream of nitrogen for 1 minute. The vial was capped and allowed to stir overnight (~14 hours) at 56° C. At that time, the solvent was removed under reduce pressure and the crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, using ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 6'-(cyclopropylethynyl)-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (44 mg, 0.133 mmol, 90% yield) as an off-white solid. M+H = 331.0, ^{1}H NMR = ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.25 (t, J = 75.6 Hz, 1H), 4.18 (m, 1H), 3.00 (s, 2H), 2.12 (m, 2H), 1.78 (m, 2H), 1.64 – 1.41 (m, 5H), 0.89 – 0.77 (m, 4H).

Step 3: Preparation of compound 99

In a 20 mL vial was placed 6'-(cyclopropylethynyl)-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (44 mg, 0.133 mmol) and it was azeotroped with acetonitrile twice (2 mL / each). Acetonitrile (2 mL) was added. To this solution was added bis-trimethylsilylcarbodiimide (120 μL, 0.534 mmol) was added followed by cesium fluoride (81 mg, 0.533 mmol). The vial was tightly capped and heated for 3 hours at 50 °C. The reaction was quenched with water (7 mL) and diluted with DCM (10 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane twice (5 mL / each). The combined organic phases

were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (12 mg, 0.144 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (21 μL, 25% in MeOH) and the solution was stirred for 3 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 30 minutes. After that time, the solvent was removed under reduced pressure. The crude was dissolved in MeOH (2 mL) and H_2O (500 μL). The solution was filtered and purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated under reduced pressure. The obtained material was lyophilized yielding the final product (1.24 mg, 0.003 mmol, 2% yield). M+H = 402.0; ^{1}H NMR = (CD_3OD, 400 MHz) δ 7.66 – 7.26 (m, 3H), 6.41 (t, J = 75.6 Hz, 1H), 4.08 (m, 1H), 3.33 (s, 3H), 2.99 (m, 2H), 2.12 – 1.91 (m, 3H), 1.75 – 1.43 (m, 6H), 0.93 – 0.86 (m, 2H), 0.77 – 0.71 (m, 2H).

Example 66 Preparation of compound 100



Step 1: Preparation of 4-(difluoromethoxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (100b)

In a 20 mL vial was placed 6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (51 mg, 0.148 mmol), 3-cyanobenzeneboronic acid (28 mg, 0.1910 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and cesium carbonate (121 mg, 0.371 mmol). This solid mixture was dissolved in a Dioxane / water mixture (1.5 mL, 6 : 1 ratio, respectively). The vial was capped and allowed to stir at 95° C for 1 hour. At this time, the mixture was filtered through a Celite plug. The plug was rinsed with dichloromethane (10 mL) and water (5 mL). The phases in the filtrate were separated. The aqueous phase was back-extracted with dichloromethane (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude material was purified by flash chromatography (ISCO, 12g SiO_2 cartridge, ethyl acetate / hexanes as the eluents). The corresponding fractions were combined and concentrated under reduce pressure yielding 4-(difluoromethoxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (equatorial) (48 mg, 0.131 mmol, 88% yield). M+H = 368.0

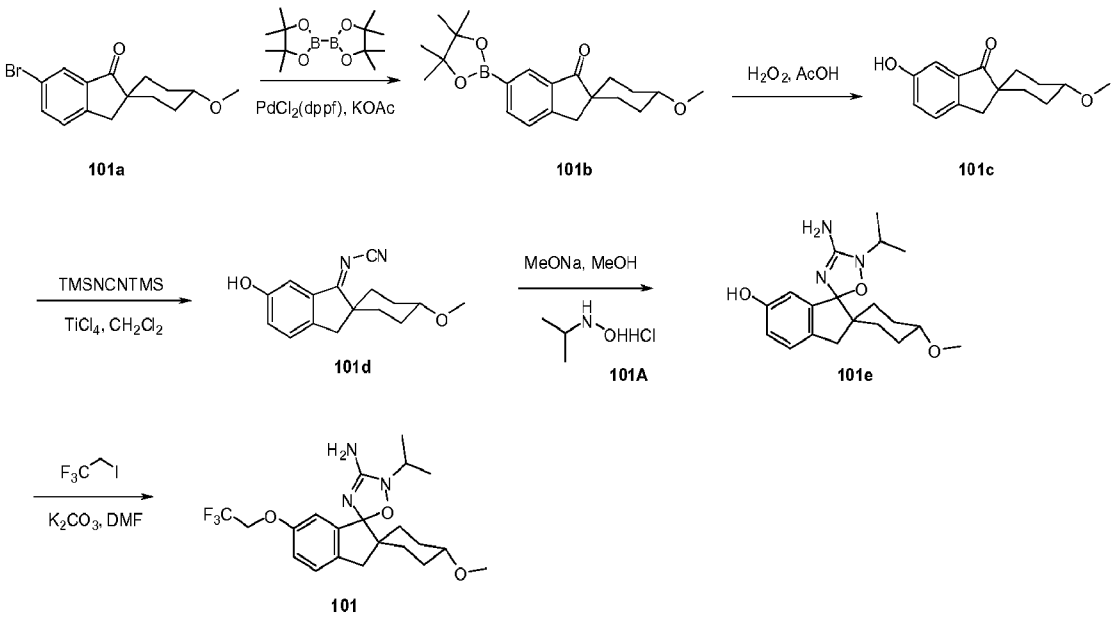
Step 2: Preparation of compound 100

In a 20 mL vial was placed 4-(difluoromethoxy)-1'-oxo-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-6'-yl)benzonitrile (equatorial) (48 mg, 0.131 mmol) and it was azeotroped with acetonitrile twice (1 mL / each). Acetonitrile (1.3 mL) was added. To this solution was added bis-trimethylsilylcarbodiimide (118 µL, 0.525 mmol) was added followed by cesium fluoride (80 mg, 0.526 mmol). The vial was tightly capped and heated overnight (~14 hours) at 50 °C. The reaction was quenched with water (5 mL) and diluted with DCM (5 mL). The two phases were separated and the aqueous phase was back-extracted with dichloromethane twice (3 mL / each). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduce pressure and azeotroped with toluene (2 mL). In a separate flame dried 4 mL vial was placed MeNH(OH)·HCl (12 mg, 0.144 mmol) and it was dissolved in MeOH (2 mL). To this solution was added NaOMe (21 µL, 25% in MeOH) and the

solution was stirred for 5 minutes at room temperature. This solution was transferred, via syringe, to the cyanoimine prepared above and stirred at room temperature for 1 hour. After that time, the solvent was removed under reduced pressure. The crude was dissolved in MeOH (2 mL) and H_2O (500 μL). The solution was filtered and purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated under reduced pressure. The obtained material was lyophilized yielding the final product (5 mg, 0.011 mmol, 9% yield). M+H = 439.1

^{1}H NMR = (CD_3OD, 400 MHz) δ 8.00 (m, 2H), 7.76 – 7.60 (m, 3H), 7.45 (d, J = 8.8 Hz, 1H), 6.40 (t, J =75.6 Hz, 1H), 4.09 (m, 1H), 3.33 (s, 3H), 3.09 (d, $J_{A,B}$ = 16.0 Hz, 1H), 3.02 (d, $J_{A,B}$ = 16.4 Hz, 1H), 2.12 – 1.92 (m, 2H), 1.79 – 1.51 (m, 6H).

Example 67 Synthesis of compound 101



Step 1: Preparation of Compound 101b

To a solution of compound **101a** (4 g, 12.9 mmol) in 1, 4-dioxane (40 mL), was added KOAc (3.67g, 37.4mmol), bis(pinacolato)diboron (3.6 g, 14.2mmol) and $Pd(dppf)Cl_2$ (1.2 g, 1.8 mmol) under nitrogen, the mixture was stirred at 100 °C in a CEM microwave reactor for 1 h, LCMS showed the complete consumption of

compound **101a**. Water (20 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (20 mL × 3). The combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give compound **101b** (4.1 g, crude 90%) which was used in the next step without further purification as a black solid. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 8.15 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.45 (s, 3H), 3.26-3.19 (m, 1H), 3.07 (s, 2H), 2.08 (m, 2H), 1.73-1.96 (m, 2H), 1.65-1.70 (m, 2H), 1.42- 1.65 (m, 2H), 1.26 (s, 12H).

Step 2: Ppreparation of Compound 101c

To a solution of compound **101b** (4 g, 11.5 mmol) in THF (40 mL) was added HOAc (4 mL) and H_2O_2 (20 mL) under nitrogen, the mixture was stirred at room temperature overnight. The mixture was quenched with $NaHSO_3$ solution (20 mL), and then was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography on silica gel eluting with hexane: EtOAc (100: 10 to 30: 10) to give compound **101c** (2 g, 71%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ:7.31 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 3.33 (s, 3H), 3.23-3.27 (m, 1H), 2.86 (s, 2H), 2.05-2.09 (m, 2H), 1.85-1.94 (m, 2H), 1.39-1.47 (m, 2H), 1.28-1.34 (m, 2H).

Step 3: Preparation of Compound 101d

To a solution of compound **101c** (100 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $TiCl_4$ (1.2 mL) under nitrogen, the mixture was stirred at 50 °C in a CEM microwave reactor for 15 min, then bis-trimethylsilylcarbodiimide (189 mg, 1.0 mmol) was added. The mixture was stirred at 60 °C in a CEM microwave reactor for 15 min. The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give compound **101d** (90 mg, crude, 83%)

as a yellow solid which was used directly for the next step without purification. **LCMS**: t_R = 1.198 min in 2 min chromatography, MS (ESI) *m/z* = 271.1 $[M+H]^+$.

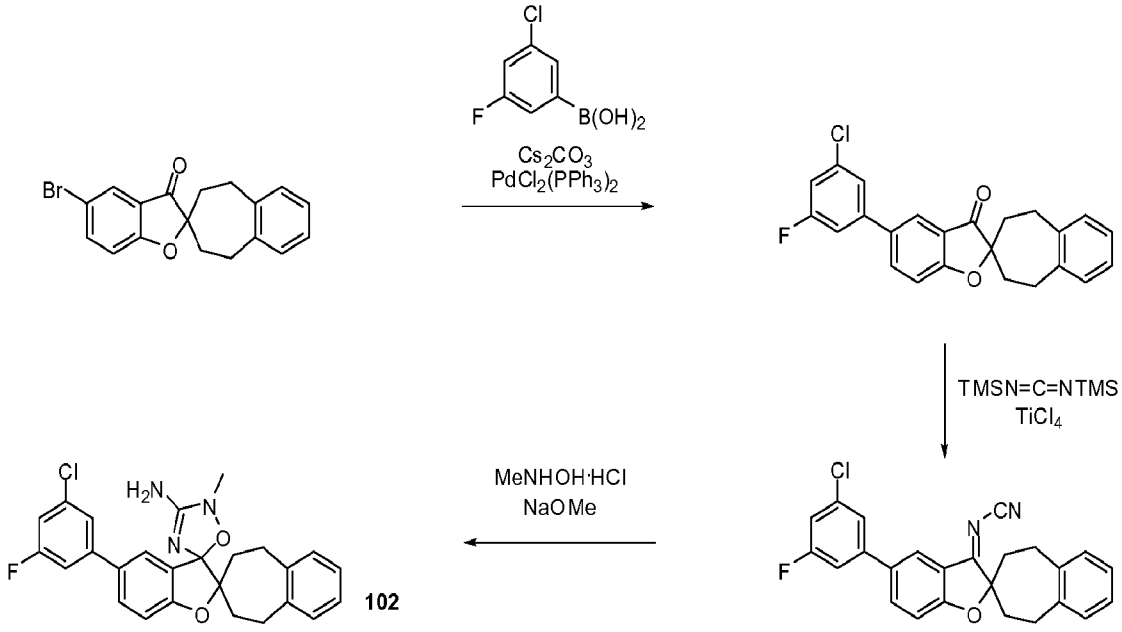
Step 4:Preparation of Compound 101e

To a solution of compound **101A** (20.6 mg, 0.19 mmol) in MeOH (2 mL) was added MeONa (99.9 mg, 0.19 mmol, 10% (Wt.) in MeOH, followed by compound **101d** (50 mg, 0.185 mmol). After stirring for 10 min, LCMS showed the complete consumption of compound **101d. T**he solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc =1: 1 to afford compound **101e** (26 mg, 41%) as a yellow solid.
LCMS: t_R = 1.016 min in 2 min chromatography, MS (ESI) *m/z* = 346.2 $[M+H]^+$.

Step5: Preparation of compound 101

To a solution of compound **101e** (26 mg, 0.075 mmol) in DMF (2 mL) was added K_2CO_3 (20.7 mg, 0.15 mmol), and 1,1,1-trifluoro-2-iodo-ethane (19.2 mg, 0.082 mmol), the mixture was stirred at room temperature overnight. The reaction was added brine (5 mL), and was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 101** (2.0 mg, 6.2%) as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 6.0 Hz, 1H), 6.94 (s , 1H), 4.52 (dd, *J* = 8.4, 16.4 Hz, 2H), 3.50-3.60 (m, 1H), 3.37 (s, 3H), 3.09-3.19 (m, 1H), 2.87 (dd, *J* = 15.2, 31.2 Hz, 2H), 1.97-2.15 (m, 2H), 1.70-1.97 (m, 1H), 1.56-1.70 (m, 2H), 1.56-1.20 (m, 3H), 1.20-1.16 (d, *J* = 7.2 Hz, 6H).
LCMS: t_R = 2.053 min in 3 min chromatography, MS (ESI) *m/z* = 428.2 $[M+H]^+$.
^{19}F NMR (CD_3OD 400 MHz) δ -75.784

Example 68 Preparation of compound 102



Step 1. 5'-(3-chloro-5-fluorophenyl)-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one

A 10 mL microwave tube was charged with 5'-bromo-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one (0.0573 g, 0.167 mmol), 3-chloro-5-fluorophenylboronic acid (0.0930 g, 0.53 mmol), Cs_2CO_3 (0.2537 g, 0.78 mmol), 1,4-dioxane (4 mL), water (1 mL), and $PdCl_2(PPh_3)_2$ (0.0118 g, 0.0168 mmol). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.0607 g (92%) of 5'-(3-chloro-5-fluorophenyl)-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one. LC-MS t_R = 2.55 min in 3 min chromatography, *m/z* 393, 395 (MH^+).

Step 2. *N*-(5'-(3-chloro-5-fluorophenyl)-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-ylidene)cyanamide

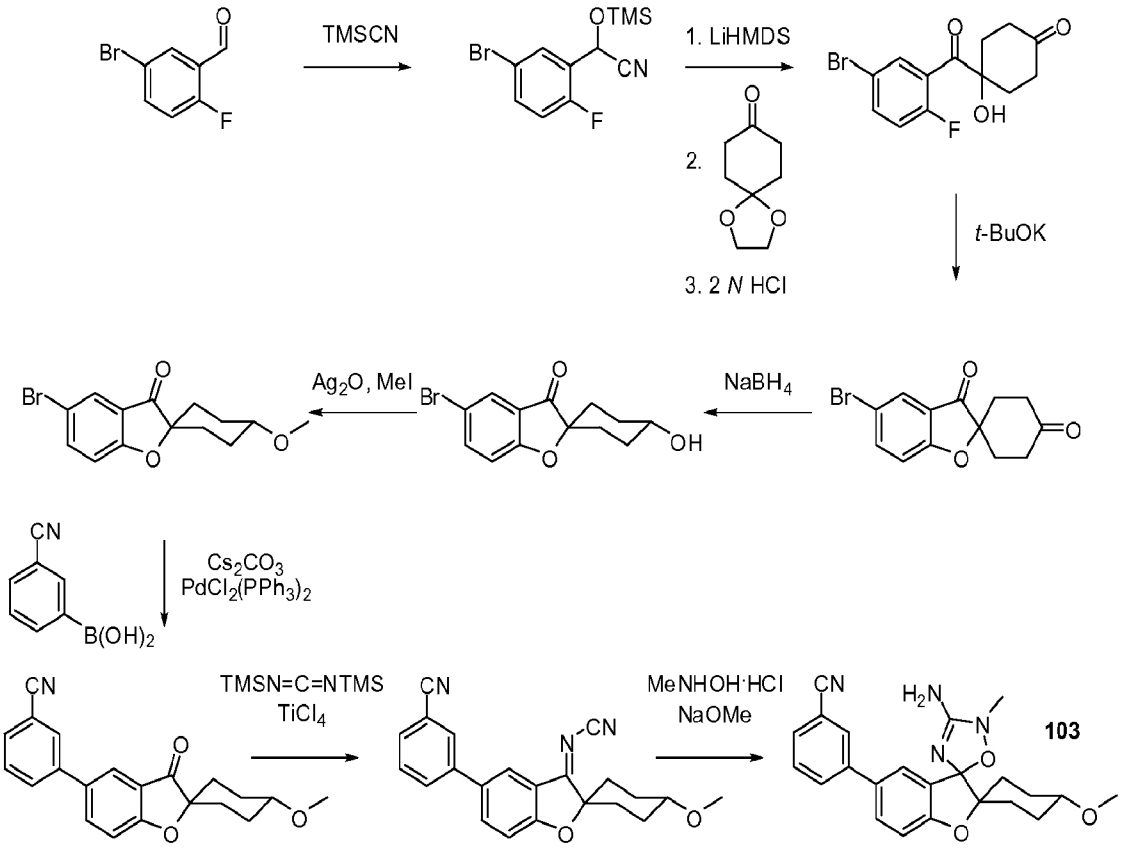
To a solution of 5'-(3-chloro-5-fluorophenyl)-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-one (0.0607 g, 0.155 mmol) in CH_2Cl_2 (5 mL) was added 0.7 mL of 1.0 *M* $TiCl_4$ in CH_2Cl_2 at room temperature. After 1 h, 0.28

mL of bis(trimethylsilyl)carbodiimide was added to the red solution. The resulting mixture was then stirred at room temperature for 18 h. The mixture was quenched with ice, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was directly used in the next step without further purification.

Step 3. Preparation of compound 102

A 50 mL flask was charged with 10 mL of EtOH, 0.2365 g of sodium methoxide (25 wt. % solution in MeOH), and 0.1050 g of *N*-methylhydroxylamine hydrochloride. The suspension was filtered through HPLC filter and the filtrate was added to *N*-(5'-(3-chloro-5-fluorophenyl)-5,6,8,9-tetrahydro-3'*H*-spiro[benzo[7]annulene-7,2'-benzofuran]-3'-ylidene)cyanamide, obtained as described above. The resulting mixture was stirred at room temperature overnight. The mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford **compound 102** as a TFA salt. LC-MS t_R = 1.72, 2.00 min in 3 min chromatography, *m/z* 464, 466 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.07-7.75 (m, 2H), 7.48-7.08 (m, 8H), 3.48 (t, *J* = 13.6 Hz, 2H), 2.80 (dd, *J* = 14.6, 6.1 Hz, 2H), 2.18 (dd, *J* = 14.5, 6.0 Hz, 2H), 1.90 (t, *J* = 13.5 Hz, 2H); ^{19}F NMR (376 MHz, CD_3OD) δ -112.40 (t, *J* = 9.2 Hz), -112.97 (t, *J* = 9.2 Hz).

Example 69 Preparation of compound 103



Step 1. 2-(5-bromo-2-fluorophenyl)-2-(trimethylsilyloxy)acetonitrile

To a solution of 5-bromo-2-fluorobenzaldehyde (3.4160 g, 16.8 mmol) and DMAP (0.0256 g, 0.21 mmol, 0.012 equiv) in CH_3CN (35 mL) was added TMSCN (1.8885 g, 19.0 mmol, 1.13 equiv) dropwise via a syringe under nitrogen at room temperature. After 3.75 h, the solvent was removed under reduced pressure. The crude product was directly used in the next step without further purification.

Step 2. 4-(5-bromo-2-fluorobenzoyl)-4-hydroxycyclohexanone

To a solution of 2-(5-bromo-2-fluorophenyl)-2-(trimethylsilyloxy)acetonitrile (16.8 mmol), obtained as described above, in THF (10 mL) was added LiHMDS (1.0 *M* in THF, 18 mL, 18 mmol, 1.07 equiv) via a syringe under nitrogen at -78 °C. After 1.25 h, a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (2.6310 g, 16.8 mmol, 1.0 equiv) in THF (20 mL) was added dropwise via a cannula. The resulting mixture was allowed to slowly warm to 10 °C over 16 h. The mixture was then quenched with

saturated NH_4Cl (10 mL) and H_2O (10 mL), extracted twice with ethyl acetate, and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was treated with MeOH (120 mL) and 2 *N* HCl (40 mL). The resulting solution was vigorously stirred at room temperature for 24 h and the solvents were removed under reduced pressure. The residue was extracted twice with CH_2Cl_2, dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 2.9319 g (55% in two steps) of 4-(5-bromo-2-fluorobenzoyl)-4-hydroxycyclohexanone. LC-MS t_R = 1.39 min in 3 min chromatography, *m/z* 315, 317 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 1H), 7.50-7.47 (m, 1H), 7.08-7.03 (m, 1H), 3.41 (s, 1H), 2.83-2.74 (m, 2H), 2.42-2.36 (m, 2H), 2.31-2.23 (m, 2H), 2.14-2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.51, 204.88 (d, J = 2.30 Hz), 157.68 (d, J = 248.44 Hz), 135.66 (d, J = 8.44 Hz), 131.55 (d, J = 3.83 Hz), 127.54 (d, J = 19.17 Hz), 118.07 (d, J = 24.53 Hz), 117.19 (d, J = 3.84 Hz), 78.07, 36.37, 33.89, 33.87; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.90.

Step 3. 5-bromo-3*H*-spiro[benzofuran-2,1'-cyclohexane]-3,4'-dione

To a solution of 4-(5-bromo-2-fluorobenzoyl)-4-hydroxycyclohexanone (1.0055 g, 3.19 mmol, 1.0 equiv) in THF (30 mL) was added 95% *t*-BuOK (0.3440 g, 2.91 mmol, 0.9 equiv) portionwise. The resulting mixture was heated at 100 °C for 1 h. The reaction mixture was then cooled with an ice bath and quenched with H_2O, extracted with ethyl acetate, dried over Na_2SO_4. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.3889 g (41%) of 5-bromo-3*H*-spiro[benzofuran-2,1'-cyclohexane]-3,4'-dione as a white solid. LC-MS t_R = 1.58 min in 3 min chromatography, *m/z* 295, 297 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.81 (m, 1H), 7.76-7.73 (m, 1H), 7.10-7.07 (m, 1H), 2.81-2.72 (m, 2H), 2.60-2.55 (m, 2H), 2.29-2.21 (m, 2H), 2.08-2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.25, 200.80, 169.71, 140.99, 127.47, 121.58, 115.55, 114.81, 88.10, 36.68, 31.86.

Step 4. *cis*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one and *trans*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one

To a solution of 5-bromo-3*H*-spiro[benzofuran-2,1'-cyclohexane]-3,4'-dione (0.2281 g, 0.77 mmol) in THF (15 mL) was added $NaBH_4$ (0.0266 g, 0.70 mmol) portionwise at -78 °C. After 15 min, additional $NaBH_4$ (0.0138 g, 0.36 mmol) was added at -78 °C. After 25 min, the reaction mixture was quenched with acetone and stirred at room temperature for 1 h. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.0108 g (5%) of *trans*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one and 0.1424 g (62%) of *cis*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one.

For *trans*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one, LC-MS t_R = 1.56 min in 3 min chromatography, *m/z* 297, 299 (MH^+), 279, 281; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.77 (m, 1H), 7.70-7.66 (m, 1H), 7.02-6.99 (m, 1H), 4.18-4.17 (m, 1H), 2.23-2.14 (m, 2H), 2.03-1.87 (m, 4H), 1.53-1.49 (m, 2H).

For *cis*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one, LC-MS t_R = 1.47 min in 3 min chromatography, *m/z* 297, 299 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77-7.76 (m, 1H), 7.70-7.67 (m, 1H), 7.05-7.02 (m, 1H), 3.83-3.78 (m, 1H), 2.08-2.03 (m, 2H), 1.88-1.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.30, 169.84, 140.60, 127.21, 121.81, 115.54, 114.20, 89.12, 68.73, 30.67, 30.37.

Step 5. *cis*-5-bromo-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one

A mixture of *cis*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one (0.1424 g, 0.48 mmol), Ag_2O (0.3800 g, 1.64 mmol), MeI (0.85 mL, 13.6 mmol), and Drierite® (0.78 g) in CH_3CN (5 mL) was vigorously stirred at room temperature for 66 h. The reaction mixture was filtered. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.1232 g (83%) of *cis*-5-bromo-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one and recover 0.0220 g (15%) of *cis*-5-bromo-4'-hydroxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one.

For *cis*-5-bromo-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one, LC-MS t_R = 1.86 min in 3 min chromatography, *m/z* 311, 313 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.67 (m, 1H), 7.63-7.60 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 3.33 (s, 3H), 3.29-3.22 (m, 1H), 2.08-2.04 (m, 2H), 1.77-1.57 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.15, 169.74, 140.44, 127.07, 121.77, 115.48, 114.04, 89.32, 55.70, 30.09, 26.95.

Step 6. 3-(*cis*-4'-methoxy-3-oxo-3*H*-spiro[benzofuran-2,1'-cyclohexan]-5-yl)benzonitrile

A 10 mL microwave tube was charged with *cis*-5-bromo-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one (0.0446 g, 0.143 mmol), 3-cyanophenylboronic acid (0.1239 g, 0.84 mmol), Cs_2CO_3 (0.4314 g, 1.3 mmol), 1,4-dioxane (4 mL), water (1 mL), and $PdCl_2(PPh_3)_2$ (0.0286 g, 0.04 mmol). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.0400 g (84%) of 3-(*cis*-4'-methoxy-3-oxo-3*H*-spiro[benzofuran-2,1'-cyclohexan]-5-yl)benzonitrile. LC-MS t_R = 1.86 min in 3 min chromatography, *m/z* 334 (MH^+).

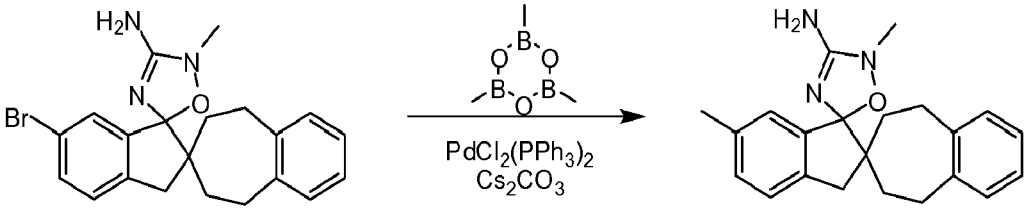
Step 7. *N*-(*cis*-5-(3-cyanophenyl)-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-ylidene)cyanamide

To a solution of 3-(*cis*-4'-methoxy-3-oxo-3*H*-spiro[benzofuran-2,1'-cyclohexan]-5-yl)benzonitrile (0.0400 g, 0.12 mmol) in CH_2Cl_2 (5 mL) was added 0.5 mL of 1.0 *M* $TiCl_4$ in CH_2Cl_2 at room temperature. After 1.5 h, 0.2 mL of bis(trimethylsilyl)carbodiimide was added to the red solution. The resulting mixture was then stirred at room temperature for 21 h. The mixture was quenched with ice, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product (0.0584 g) was directly used in the next step without further purification. LC-MS t_R = 1.90 min in 3 min chromatography, *m/z* 358 (MH^+).

Step 8. Preparation of compound 103

A 50 mL flask was charged with 10 mL of EtOH, 0.2552 g of sodium methoxide (25 wt. % solution in MeOH), and 0.1314 g of *N*-methylhydroxylamine hydrochloride. The suspension was filtered through HPLC filter and the filtrate was added to *N*-(*cis*-5-(3-cyanophenyl)-4'-methoxy-3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-ylidene)cyanamide, obtained as described above. The resulting mixture was stirred at room temperature for 2 h. The mixture was purified by reversed-phase HPLC (SunFire^{TM} Prep C_{18} OBD^{TM} 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford **compound 103** as a TFA salt. LC-MS t_R = 1.25, 1.41 min in 3 min chromatography, *m/z* 405 (MH^+); ^{1}H NMR (400 MHz, CD_3OD) δ 8.08-7.03 (m, 7H), 3.43-3.35 (m, 7H), 2.22-1.65 (m, 8H).

Example 70 Synthesis of compound 104

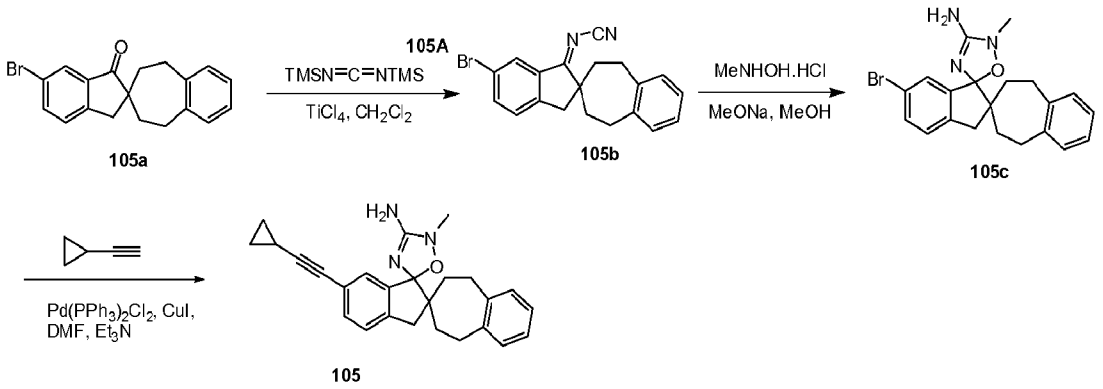


104a **104**

A solution containing compound **104a** (50 mg, 0.12 mmol) and 2,4,6-trimethyl-cyclotriboroxane (153 mg, 1.2 mmol) in dioxane (3 mL), and aqueous Cs_2CO_3 (2 M, 0.85 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (8.5 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative TLC (CH_2Cl_2: MeOH, 10:1) and HPLC to give **compound 104** (1.5 mg, yield 4%) as a white solid. **LC-MS** t_R = 1.016 min and 1.066 min in 2 min chromatography, MS (ESI) *m/z* 348 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): *δ* 7.46 (m, 1H), 7.39 (m, 1H), 7.18 (m, 1H), 7.02 (m, 4H), 3.17 (s, 3H), 2.94-2.99 (m, 3H), 3.65

(m, 2H), 2.56-2.70 (m, 2H); 2.28-2.31 (m, 3H), 1.73-1.84 (m, 3H), 1.56-1.70 (m, 1H); 1.19-1.60 (m, 1H).

Example 71 Synthesis of compound 105



Step 1: Preparation of compound 105b

To a solution of compound **105a** (200 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (14 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 2.36 mL, 2.36 mmol) at room temperature. After being stirred in microwave at 50 °C for 15 min., bis(trimethylsilyl)carbodiimide (236 mg, 1.28 mmol) was added, and the mixture was stirred in microwave at 60 °C for another 22 min. TLC showed the reaction was completed, and the mixture was poured into ice-water (20 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure to give compound **105b** (200 mg, yield 93%) as a yellow solid.

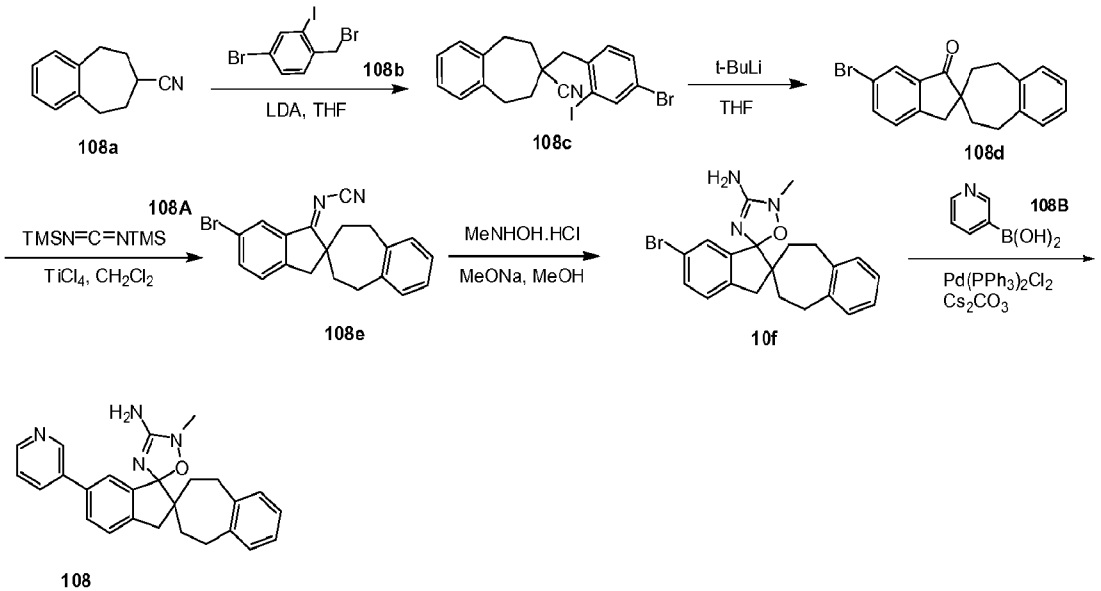
Step 2: Preparation of Compound 105c

To a solution of N-methylhydroxylamine hydrochloride (92 mg, 1.08 mmol) in anhydrous MeOH (28 mL) was added a solution of NaOMe (10 wt%, 0.56 mL, 0.972 mmol) in methanol followed by compound **105b** (400 mg, 1.08 mmol). After being stirred at room temperature for 50 min., the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). The mixture was filtered, concentrated under reduced pressure. The residue was purified by chromatograph sillica gel (CH_2Cl_2: MeOH, 10:1) to give compound **105c** (80 mg, yield 18%) as a yellow solid.

Step 3: Preparation of Compound 105

To a stirred solution of compound **105c** (30 mg, 0.073 mmol) and CuI (10 mg, 0.05) in anhydrous Et_3N (0.5 mL) and DMF (2 mL) was added cyclopropane acetylene (0.5 mL) and $Pd(PPh_3)_2Cl_2$ (10 mg, 0.011 mmol) under a N_2 atmosphere. The mixture was stirred at 55 °C overnight. The mixture was concentrated under reduced pressure to dryness. The residue was dissolved in CH_2Cl_2 (10 mL) and then filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by preparative TLC (CH_2Cl_2: MeOH, 10:1) and preparative HPLC (basic) in sequence to give compound **105** (3.5 mg, yield 12%) as a white solid. **LC-MS** t_R = 1.075 min and 1.142 min in 2 min chromatography, MS (ESI) *m/z* 398 $[M+H]^+$; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.25 (d, J = 6.4 Hz, 1H), 7.18 (m, 2H), 7.05 (d, J = 10 Hz, 2H), 3.16 (m, 3H), 2.91 (m, 3H), 2.66 (m, 2H), 1.94 (m, 2H), 1.68 (m, 1H), 1.55 (t, J = 26.4 Hz, 2H), 1.45 (m, 1H), 0.88 (m, 2H) , 0.73 (m, 1H).

Example 72 Synthesis of Compound 106



Step 1: Preparation of compound 108c

To a solution of LDA (23.4 mL, 42.1mmol, 1.8 M in THF) in THF (150 mL) was added slowly a solution of compound **108a** (3.6 g, 21.05 mmol) in THF (77 mL) at -60 °C under a N_2 atmosphere. After being stirred at -60 °C for 1 h, a solution of compound **108b** (7.05 g, 18.9 mmol)) in THF (23mL) was added slowly to the above

solution. The resulting mixture was stirred at -60 °C for 2 h. The reaction mixture was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel (petroleum: ethyl acetate, 10:1) to give compound **108c** (2.5 g, yield 26%) as a yellow solid.

Step 2: Preparation of compound 108d

A flame dried 100 mL RBF was charged with compound **108c** (2.11 g, 4.5 mmol) and anhydrous THF (80 mL) under N_2 atmosphere. The resulting solution was stirred and chilled to -70°C, and *t*-BuLi (1.3 M, in hexane 6.95 mL, 9 mmol, 2 eq.) was added dropwise. Deep red was observed during the addition. The reaction was stirred another 1 h after the addition. The reaction was quenched with MeOH (0.4 mL), and followed by *aq*. HCl solution (2 M, 8 mL). The resulting solution was concentrated to remove organic solvent. The residue was stirred in 0.5 M aq. HCl solution (40 mL). The suspension was heated to reflux (oil bath 105 °C). The reaction was cooled down to room temperature and filter. The cake was washed with H_2O. The light yellow solid was collected and co-evaporated with MeOH two times to remove water to give crude product, which was purified by chromatography to give compound **108d** (450 mg, yield 35%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.80-8.01 (m, 1H), 7.63-7.66 (m, 1H), 7.30-7.32 (m, 1H), 7.00-7.18 (m, 4H), 3.10 (s, 2H), 2.91-2.97 (m, 2H), 2.81 (brs, 2H), 1.78-1.85 (m, 2H), 1.57-1.62 (m, 2H).

Step 3: Preparation of compound 108e

To a solution of compound **108d** (100 mg, 0.29 mmol) in CH_2Cl_2 (7 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 1.18 mL, 1.18 mmol). After being stirred at 50 °C for 15 min in microwave, bis-trimethylsilylcarbodiimide (0.143mL, 0.638 mmol) was added to above solution. The resulting mixture was stirred at 60 °C for 22 min in microwave. TLC showed that the reaction was completed. The reaction mixture was poured into ice-water (20 mL). The solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined

organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dcrude compound **108e** (100 mg, yield 93%) as a yellow solid, which was used directly for the next step without purification.

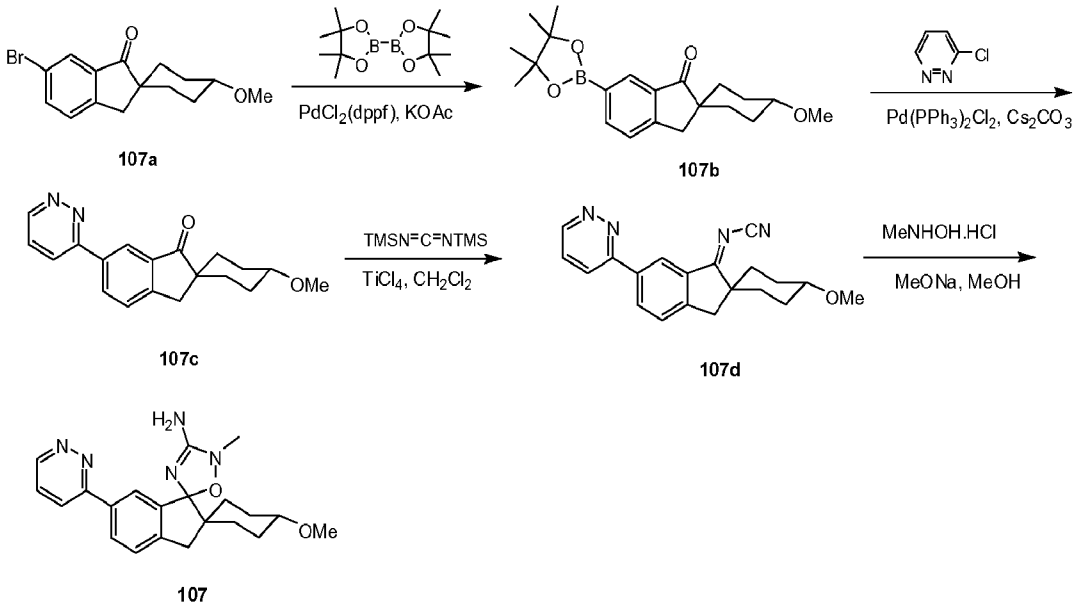
Step 4: Preparation of compound 108f

To a solution of methylhydroxylamine HCl salt (46 mg, 0.55 mmol) in anhydrous MeOH (14 mL) was added a solution of NaOMe (10 wt%, 0.280 mL, 0.5 mmol) in methanol followed by compound **108e** (200 mg, 0.55 mmol). After addition, the reaction mixture was stirred for 30 min, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL). The mixture was filtered, and the solvent was removed under reduced pressure to give the residue, which was purified by chromatography to give compound **108f** (50 mg, yield 22%) as a yellow solid.

Step 5: Preparation of Compound 108

A solution containing compound **108f** (25 mg, 0.061 mmol) and compound **108B** (11.2 mg, 0.091 mmol) in dioxane (1.5 mL), and aqueous Cs_2CO_3 (2 M, 0.43 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (4.3 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative TLC and HPLC to give compound **108** (1.5 mg, yield 6%) as a white solid. **LC-MS** t_R = 0.943 min in 2 min chromatography, MS (ESI) *m/z* 411 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.68 (s, 1H), 8.40-8.68 (m, 1H), 7.97-8.00 (m, 1H), 7.52-7.54 (m, 1H), 7.40-7.46 (m, 2H), 7.31-7.40 (m, 1H) , 6.96-7.05 (m, 4H), 3.10-3.22 (m, 2H), 2.97 (s, 3H), 2.92-2.95 (m, 2H), 2.53-2.65 (m, 2H), 1.87-1.96 (m, 2H), 1.53-1.64 (m, 1H), 1.46-1.50 (m, 2H).

Example 73. Synthesis of Compound 107



Step 1: Preparation of Compound 107b

To a solution of compound **107a** (500 mg, 1.61 mmol) in 1,4-dioxane (10 mL), was added KOAc (0.46 g, 4.69 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2 –yl)-1,3,2-dioxaborolane (450 mg, 1.77 mmol) and $PdCl_2$(dppf) (150 mg, 0.18 mmol) under nitrogen, the mixture was stirred at 100 °C in a CEM microwave reactor for 1 h, LCMS showed the complete consumption of compound **107a**. Water (5 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (10 mL × 3). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **107b** (284 mg, 50%) as a black solid, which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 8.16 (s, 1H), 7.92 (d, J = 6.4 Hz,, 1H), 7.39 (d, J = 7.6 Hz, 1H), 3.32 (s, 3H), 3.20 (m, 1H), 2.97 (m, 2H), 2.08 (m, 2H), 1.67 (m, 2H), 1.58 (m, 2H), 1.42 (m, 2H), 1.33 (s, 12H).

Step 2: Preparation of Compound 107c

To a solution of compound **107b** (400 mg, 1.1 mmol) in dioxane (10 mL) was added 3-chloropyridazine (193 mg, 1.65 mmol), Cs_2CO_3 (2 N, 8 mL) and $Pd(PPh_3)_2Cl_2$ (7.4 mg, 0.011 mmol) under nitrogen, the mixture was stirred at 120 °C in a CEM microwave reactor for 15 min. Water (5 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (10 mL × 3). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 1: 1 to give compound **109c** (100 mg, 29%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 9.11 (d, *J* = 4.8 Hz,, 1H), 8.49 (d, *J* = 7.2 Hz,, 1H), 8.21 (s, 1H), 7.87 (d, *J* = 7.2 Hz,, 1H), 7.84 (d, *J* = 4.4 Hz, 1H), 7.84 (m, 1H) 3.41 (s, 3H), 3.29 (m, 1H), 3.05 (s, 2H), 1.78 (m, 2H), 1.72 (m, 2H), 1.51 (m, 2H). 1.41-1.21 (m, 2H).

Step 3: Preparation of Compound 107d

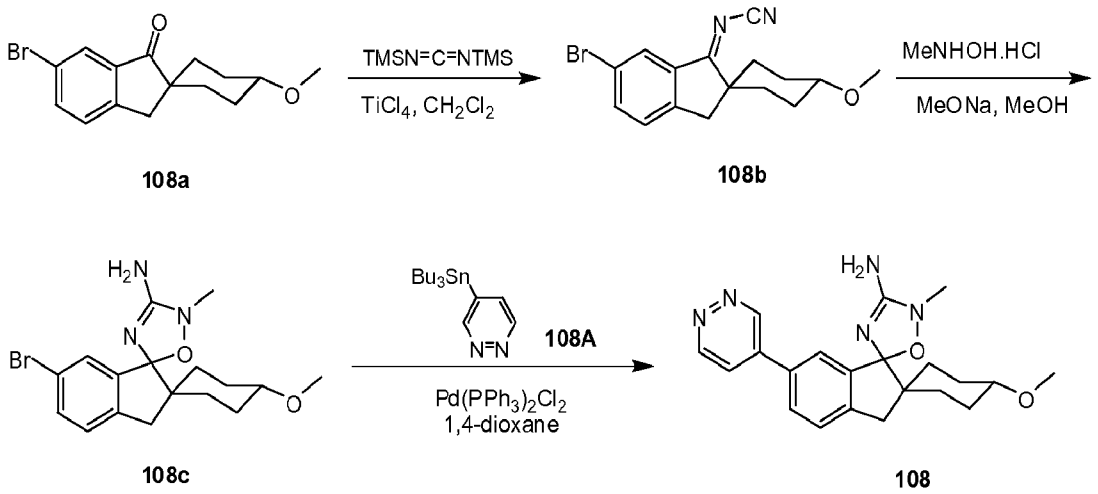
To a solution of compound **107c** (80 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $TiCl_4$ (2.5 mL) under N_2, the mixture was stirred at 50 °C in a CEM microwave reactor for 15 min, then bistrimethylsilylcarbodiimide (105.3 mg, 0.56 mmol) was added. The mixture was stirred at 60 °C in a CEM microwave reactor for 15 min. TLC (hexane: EtOAc = 3: 1) showed the complete consumption of compound **107c.** The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give compound **107d** (82 mg, crude 95%) as a yellow solid which was used directly in the next step without purification.

Step 4: Preparation of compound 107

To a solution of N-methylhydroxylamine hydrochloride (12.6 mg, 0.15mmol) in MeOH (4 mL) was added MeONa (81 mg, 0.15 mmol, 10 wt% in MeOH), followed by compound **109d** (50 mg, 0.15 mmol). The mixture was stirred at room temperature for

10 min, LCMS showed the complete consumption of compound **107d**. The solvent was removed *in vacuo* to give the crude product, which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 107** (5.6 mg, 10% for 2 steps) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.13 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.81 (m, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 3.43 (s, 3H), 3.23 (m, 1H), 3.15 (s, 3H), 3.0 (m, 2H), 2.09 (m, 2H), 1.75 (m, 1H) 1.65 (m, 2H), 1.52 (m, 1H), 1.38 (m, 2H). **LCMS:** 663-148-1, t_R = 0.810 min in 2 min chromatography, MS (ESI) *m/z* 380.1 $[M+H]^+$.

Example 74 Synthesis of Compound 108



Step 1: Preparation of compound 108b

To a solution of compound **108a** (2 g, 6.5 mmol) in anhydrous CH_2Cl_2 (70 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 14.3 mL, 14.3 mol). After stirring at room temperature for 1 h under nitrogen, bis-trimethylsilylcarbodiimide (2.47 g, 3.0 mL, 13.3 mmol) was added. After addition, the mixture was stirred at room temperature overnight. TLC showed that the reaction was completed. The reaction mixture was poured into ice-water (100 g) and stirred 30 min. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with

brine (2 × 100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give compound **108b** (2.3 g, crude, 100%) as a white solid, which was used for the next step directly without purification.

Step 2: Preparation of compound 108c

To a solution of methylhydroxylamine HCl salt (0.546 g, 6.5 mmol) in anhydrous MeOH (300 mL) was added NaOMe (10 wt% in MeOH, 3.16 g, 5.85 mmol), followed by compound **108b** (2.15 g, 6.5 mmol). After stirring at room temperature for 40 min, the solvent was removed *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (100 mL). The mixture was filtered and the solvent was removed to give the residue, which was purified by column chromatography (CH_2Cl_2: MeOH = 20:1 to 5:1) to give compound **108c** (1.7 g, 69%) as a white solid.

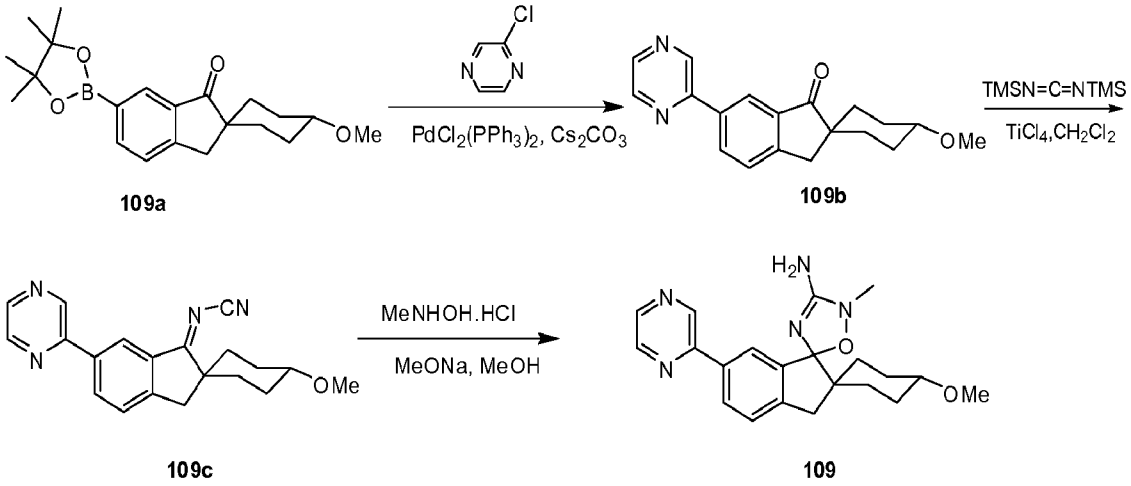
Step 3: Preparation of Compound 108

A solution containing compound **108A** (97 mg, 0.26 mmol) and compound **108c** (40 mg, 0.105 mmol) in 1, 4-dioxane (3 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (4 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC to afford product **compound 108** (7.3 mg, 18%) as a white solid.

LC-MS t_R = 0.843 min in 2 min chromatography, MS (ESI) *m/z* 380.0 $[M+H]^+$

^{1}H NMR (CD_3OD 300 MHz): δ 9.55-9.68 (d, J = 50.8 Hz, 1H), 9.32 (s, 1H), 8.18-8.23 (m, 1H), 7.96-8.07 (m, 2H), 7.58-7.61 (d, J = 10.8 Hz, 1H), 3.35-3.42 (m, 7H), 3.03-3.17 (q, 2H), 2.01-2.22 (m, 2H), 1.65-1.84 (m, 2H), 1.33-1.64 (m, 4H).

Example 75 Synthesis of Compound 109



Step 1: Preparation of Compound 109b

To a solution of compound **109a** (400 mg, 1.1 mmol) in dioxane (10 mL) were added 2-chloropyrazine (135 mg, 1.17 mmol), Cs_2CO_3 (2 N, 8 mL) and $PdCl_2(PPh_3)_2$ (5.2 mg, 0.0078 mmol) under nitrogen, the mixture was stirred at 120 °C in a CEM microwave reactor for 15 min. Water (5 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (10 mL × 3). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 1: 1 to give compound **109b** (100 mg, 41%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 9.10 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H), 7.63 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 3.43 (s, 3H), 3.37 (m, 1H), 3.13 (s, 2H), 2.2 (m, 2H), 1.87 (m, 2H), 1.56 (m, 2H), 1.47 (m, 2H).

Step 2: Preparation of Compound 109c

To a solution of compound **109b** (66 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $TiCl_4$ (2 mL, 1 M in CH_2Cl_2, 2 mmol) under nitrogen, the mixture was stirred at 50 °C in a CEM microwave reactor for 15 min, then

bistrimethylsilylcarbodiimide (87.6 mg, 0.45 mmol) was added. The mixture was stirred at 60 °C in a CEM microwave reactor for 15 min, TLC (hexane: EtOAc = 1:1) showed the complete consumption of compound **109b**. The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **109c** (47 mg, 66%) as a yellow solid which was used directly in the next step without purification.

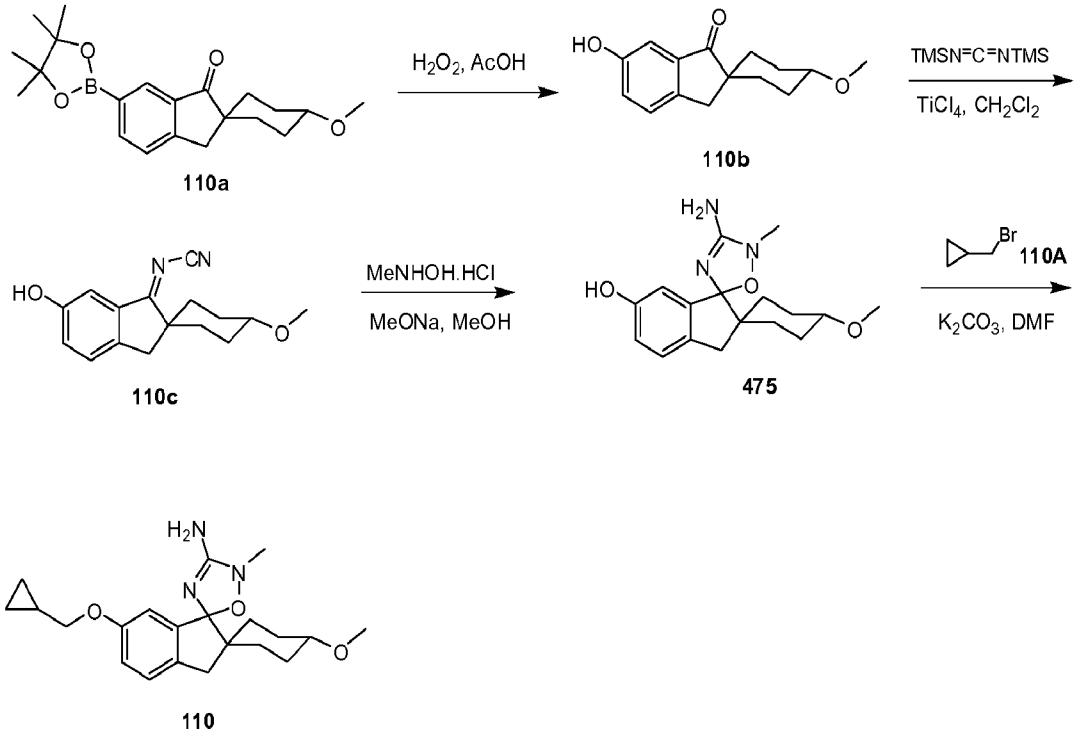
Step 3: Preparation of Compound 109

To a solution of N-methylhydroxylamine hydrochloride (11.8 mg, 0.14 mmol) in MeOH (2 mL) was added MeONa (76.4mg, 0.14 mmol, 10 wt % in MeOH), followed by compound **111c** (47 mg, 0.14 mmol), the mixture was stirred for 10 min. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 109** (1.2 mg, 2.2%) as a white solid.

^{1}H NMR ($CDCl_3$ 400 MHz): δ 9.09 (s, 1H), 8.67 (d, J = 8.0 Hz,, 1H), 8.52 (s, 1H), 8.02 (d, J = 7.6 Hz,, 2H), 7.42 (d, J = 7.6 Hz, 1H), 3.49 (s, 3H), 3.2 (m, 1H), 3.14 (s, 3H), 2.95 (m, 2H), 2.17 (m, 2H), 1.71 (m, 1H), 1.61 (m, 2H), 1.58 (m, 1H), 1.37 (m, 2H).

***LCMS*:** t_R = 0.855 min in 2 min chromatography, MS (ESI) *m/z* 380.1 $[M+H]^+$.

Example 76 Synthesis of Compound 110



Step 1: Preparation of Compound 110b

To a soltoion of compound **110a** (150 mg, 0.42 mmol) in THF (10 mL) was added HOAc (0.2 mL) and H_2O_2 (1 mL) under nitrogen, the mixture was stirred at room temperature overnight. The mixture was quenched with $NaHSO_3$ solution (10 mL), and then was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography on silica gel eluting with hexane: EtOAc (100: 10~30: 10) to give compound **110b** (100 mg, 97%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 7.31 (s, 1H), 6.91-7.15 (d, J = 8.0 Hz, 2H), 3.43 (s, 3H), 3.26 (m, 1H), 2.97 (s, 2H), 1.98-2.09 (m, 2H), 1.86-1.98 (m, 2H), 1.41-1.65 (m, 2H), 1.20-1.41 (m, 2H).

Step 2: Preparation of Compound 110c

To a solution of compound **110b** (100 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $TiCl_4$ (1.2 mL, 1.0 M in CH_2Cl_2, 1.2 mmol) under nitrogen, the mixture

was stirred at 50 °C in a CEM microwave reactor for 15 min, then bistrimethylsilylcarbodiimide (187.8 mg, 1.01 mmol) was added. The mixture was stirred at 60 °C in a CEM microwave reactor for 15 min, TLC (hexane: EtOAc = 1: 1) analysis showed the complete consumption of compound **110b**. The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated to give compound **110c** (85 mg, 77%) as a yellow solid which was used directly in the next step without purification.

Step 3: Preparation of Compound 475

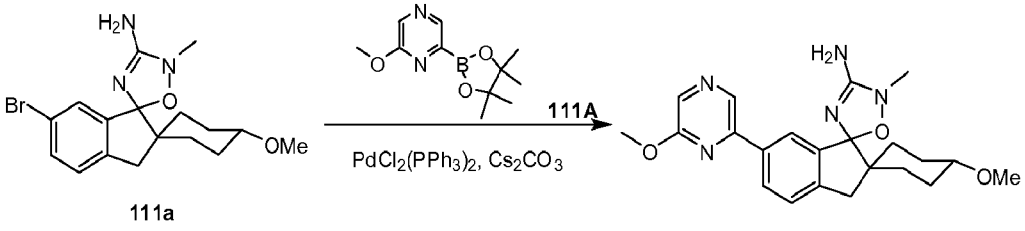
To a solution of N-methylhydroxylamine hydrochloride (26.4 mg, 0.31 mmol) in MeOH (2 mL) was added MeONa (169 mg, 0.31 mmol, 10 wt% in MeOH), followed by compound **110c** (85 mg, 0.31 mmol), the mixture was stirred for 10 min at room temperature, TLC (dichloromethane: methanol = 10: 1) analysis showed the complete consumption of compound **110c**. the solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 to afford compound **475** (50 mg, 51%) as a white solid.

Step 4: Preparation of Compound 110

To a solution of compound **475** (21 mg, 0.066 mmol) in DMF (2 mL) were added K_2CO_3 (36.5 mg, 0.26 mmol), and compound **110A** (17.8 mg, 0.132 mmol), the mixture was stirred at 50 °C for 3h, LCMS showed the complete consumption of compound **475**. The reaction was added with H_2O (5 mL), and the aqueous layer was extracted with EtOAC (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 110** (1.7 mg, 5%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 6.93 (s, 1H), 6.71-6.93 (d, J = 8.4 Hz, 2H), 3.73 (d, J = 6.8 Hz,, 2H), 3.38 (s, 3H), 3.09 (m, 1H), 2.95 (s, 3H), 2.62-2.72 (m, 2H), 1.94-

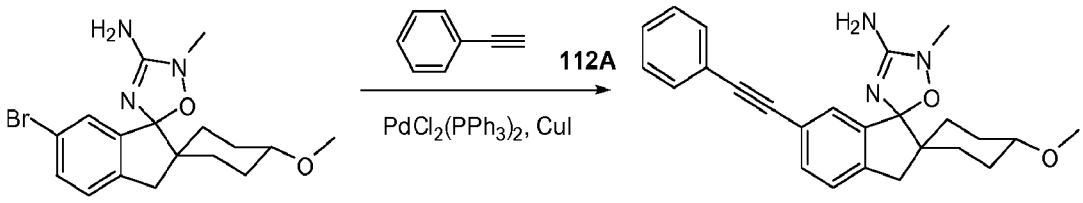
2.07 (m, 2H), 1.78 (m, 1H), 1.59 (m, 1H), 1.39-1.56 (m, 2H), 1.19-1.31 (m, 1H), 1.13-1.19 (m, 2H), 0.47-0.53 (m, 2H), 0.23-0.43 (m, 2H). **LCMS**: t_R = 0.967 min in 2 min chromatography, MS (ESI) *m/z* 372 $[M+H]^+$.

Example 77. Synthesis of Compound 111



A mixture of compound **111a** (30 mg, 0.0792 mmol), compound **111A** (28 mg, 0.1196 mmol), Cs_2CO_3 (0.567 mL, 1.134 mmol, 2 M in water) and $PdCl_2(PPh_3)_2$ (8 mg) in 1,4-dioxane (2.0 mL) was irradiated in microwave at 120°C for 15 min under nitrogen . The mixture was concentrated to give crude **compound 111**, which was purified by preparative HPLC to afford **compound 111**(1.8 mg, 5%) as a white solid. **LCMS**: t_R = 0.953 min in 2 min chromatography, MS (ESI) *m/z* 410.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz TMS): δ 8.59 (s, 1H), 8.32 (s, 1H), 8.10-8.12 (m, 2H), 7.38-7.67 (m, 1H), 3.08-4.92 (m, 3H), 3.31-3.32 (m, 6H), 3.14-3.17 (m, 1H), 2.95-2.98 (m, 2H), 1.91-2.22 (m, 2H), 1.61-1.85 (m, 2H), 1.22-1.48 (m, 4H).

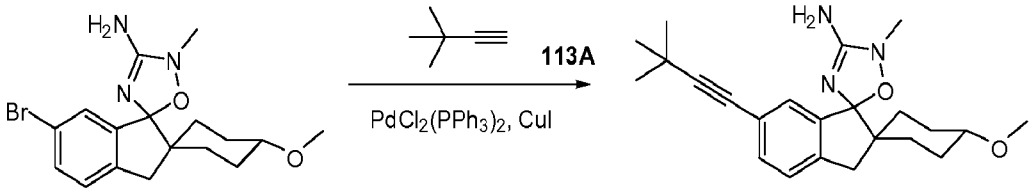
Example 78. Synthesis of Compound 112



112a 112

Compound **112a** (50 mg, 0.13 mmol) was dissolved in Et_3N (5 mL) and Et_2NH (1 mL), the resulting mixture was degassed and purged with N_2 for three times. $Pd(PPh_3)_2Cl_2$ (5 mg) and CuI (4 mg) were added under N_2 atmosphere and the system was degassed again. Ethynylbenzene (0.3 mL, excess) was added by syringe. The system was degassed one more time. The reaction was heated to 75~85 °C for 12 h. LCMS showed that the reaction was completed; the solvent was removed under reduced pressure. The residue was partitioned by CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 5:1) and RP-HPLC (basic) afforded compound **112** (4.6 mg, 9%) as a white solid. **LC-MS** t_R = 1.168 min in 2 min chromatography, MS (ESI) *m/z* 402.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.51-7.53 (m, J = 7.2 Hz, 2H), 7.37-7.45 (m, J = 8.0 Hz, 5H), 7.24-7.26 (d, J = 7.6 Hz, 1H), 3.38 (s, 3H), 3.15-3.25 (m, 1H), 3.06 (s, 3H), 2.83-2.94 (q, 2H), 2.02-2.08 (t, J = 12.8 Hz, 2H), 1.68-1.71 (d, J = 11.6 Hz, 1H), 1.56-1.63 (t, J = 14.0 Hz, 2H), 1.18-1.48 (m, 3H).

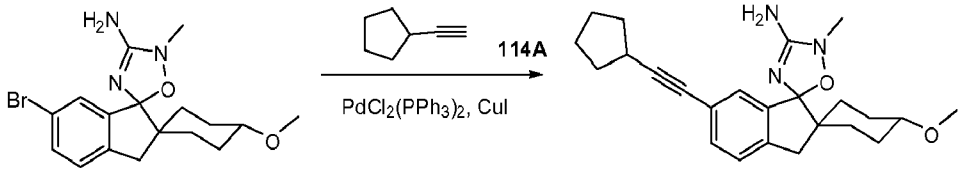
Example 79. Synthesis of Compound 113



113a **113**

The compound **113a** (50 mg, 0.13 mmol) was dissolved in Et_3N (106 mg, 1.05 mmol l) and DMF (4 mL), the resulting mixture was degassed and purged with N_2 for three times. $Pd(PPh_3)_2Cl_2$ (5 mg) and CuI (4 mg) were added under a N_2 atmosphere and the system was degassed again. 3, 3-dimethylbut-1-yne (0.5 mL, excess) was added by syringe. The system was degassed one more time. The reaction was heated to 90~100 °C for 12 h. LCMS showed that the reaction was completed. The solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL); the combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 5:1) and pre-HPLC (basic) afforded compound **113** (6.7 mg, 13%) as a white solid. **LC-MS** t_R = 1.184 min in 2 min chromatography, MS (ESI) *m/z* 382.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.10-7.14 (t, J = 7.6 Hz, 2H), 7.03-7.04 (d, J = 7.6 Hz, 1H), 3.26 (s, 3H), 3.01-3.09 (m, 1H), 2.91 (s, 3H), 2.67-2.77 (m, 2H), 1.88-1.94 (m, 3H), 1.54-1.57 (d, J = 14.0 Hz, 1H), 1.25-1.48 (m, 4H), 1.25 (s, 9H).

Example 80 Synthesis of compound 114

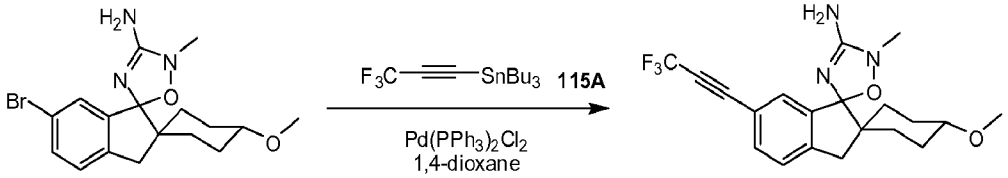


114a 114

The titled compound was synthesized as described in example 77, **compound 114** in 7% yield starting from compound **114a** and Ethynylcyclopentane. **LC-MS** t_R = 1.078 min in 2 min chromatography, MS (ESI) *m/z* 394.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.20-7.24 (t, J = 8.0 Hz, 2H), 7.12-7.14 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 3.13-3.20 (m, 1H), 3.01 (s, 3H), 2.80-2.83 (m, 3H), 1.96-2.03 (m, 4H), 1.76-1.79 (m, 2H), 1.61-1.69 (m, 5H), 1.50-1.58 (m, 2H), 1.24-1.43 (m, 3H).

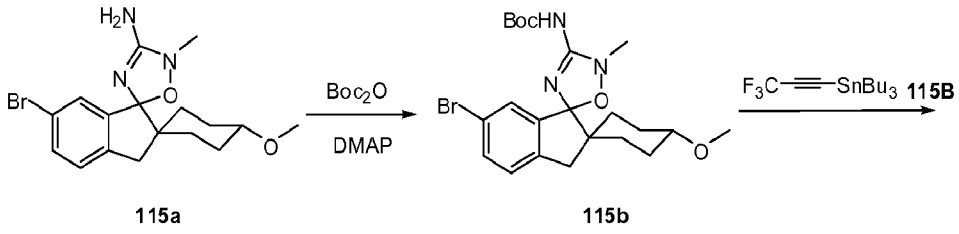
Example 81 Synthesis of Compound 115

Method 1

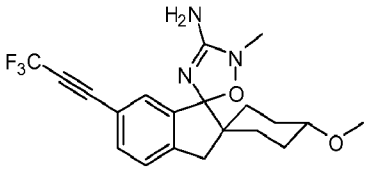


115a 115

Method 2



115a 115b



115

Method 1

A solution containing compound **115A** (126 mg, 0.33 mmol) and compound **115a** (50 mg, 0.13 mmol) in 1, 4-dioxane (4 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $Pd(PPh_3)_2Cl_2$ (5 mg) was added. The reaction vial was sealed and placed into a CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC (basic) to afford product **compound 115** (3 mg, 6%) as a white solid. **LC-MS** t_R = 1.140 min in 2 min chromatography, MS (ESI) *m/z* 394.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.42-7.44 (d, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.22-7.24 (d, J = 7.6 Hz, 1H), 3.26 (s, 3H), 3.02-3.10 (m, 1H), 2.93 (s, 3H), 2.75-2.85 (q, 2H), 1.87-1.96 (m, 2H), 1.43-1.59 (m, 3H), 1.16-1.36 (m, 3H).

Method 2 step 1: Preparation of Compound 115b

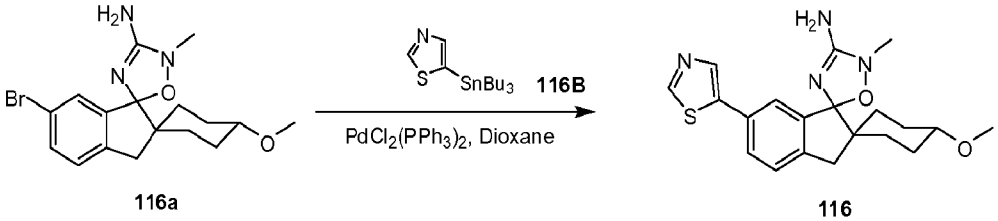
Compound **115a** (280 mg, 0.74 mmol) and $(Boc)_2O$ (241 mg, 1.1 mmol) was dissolved in THF (8 mL), this solution was added DMAP (135 mg, 1.1 mmol) and Et_3N (0.2 mL, 1.47 mmol), the reaction mixture was stirred at room temperature overnight.

LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by preparative TLC (petroleum ether: ethyl acetate = 5:1) to give **115b** (300 mg, 85%) as a white solid.

Method 2 step 2: *Preparation of Compound 115*

A solution containing compound **115B** (120 mg, 0.312 mmol) and compound **115b** (100 mg, 0.208 mmol) in in toluene (5 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (7 mg, 0.010 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC (basic) to afford product **compound 115** (9.3 mg, 6%) as a white solid. **LC-MS** t_R = 1.011 min in 2 min chromatography, MS (ESI) *m/z* 394.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.41-7.43 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 7.22-7.24 (d, J = 7.6 Hz, 1H), 3.30 (s, 3H), 3.04-3.10 (m, 1H), 2.93 (s, 3H), 2.75-2.85 (q, 2H), 1.89-1.95 (m, 2H), 1.42-1.56 (m, 3H), 1.17-1.34 (m, 3H).

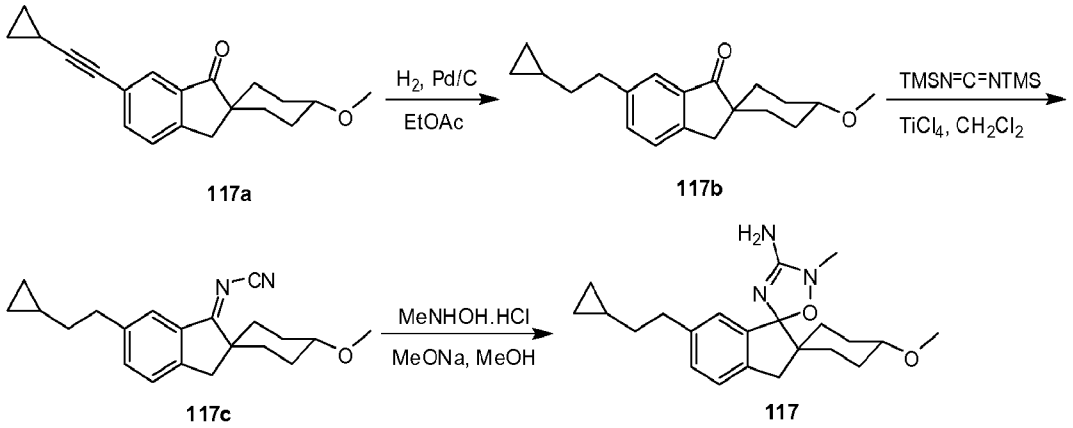
Example 82. Synthesis of Compound 116



A solution containing compound **116B** (124 mg, 0.33 mmol) and compound **116a** (50 mg, 0.13 mmol) in anhydrous 1,4-dioxane (10 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (4 mg) was added. The reaction vial was sealed and placed into CEM

microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC (basic) to afford product **compound 116** (2.2 mg, 4.3%) as a white solid. **LC-MS** t_R = 0.996 min in 2 min chromatography, MS (ESI) *m/z* 384.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 8.83 (s, 1H), 8.03 (s, 1H), 7.49-7.51 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.20-7.22 (d, J = 10.4 Hz, 1H), 3.26 (s, 3H), 3.21 (m, 1H), 2.95 (s, 3H), 2.78 (m, 2H), 1.92 (s, 2H), 1.21-1.47 (m, 6H).

Example 83. Synthesis of Compound 117



Procedure for preparation of Compound 117b

To a solution of compound **117a** (0.15 g, 0.51 mmol) in EtOAc (10 mL) was added Pd/C (15 mg, 10 wt%). The resulting mixture was stirred at room temperature under H_2 atmosphere (30 Psi) for 1 h, LC-MS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated to give compound **117b** (0.14 g, 92% crude yield) as a red oil, which was used for next step directly without purification without purification.

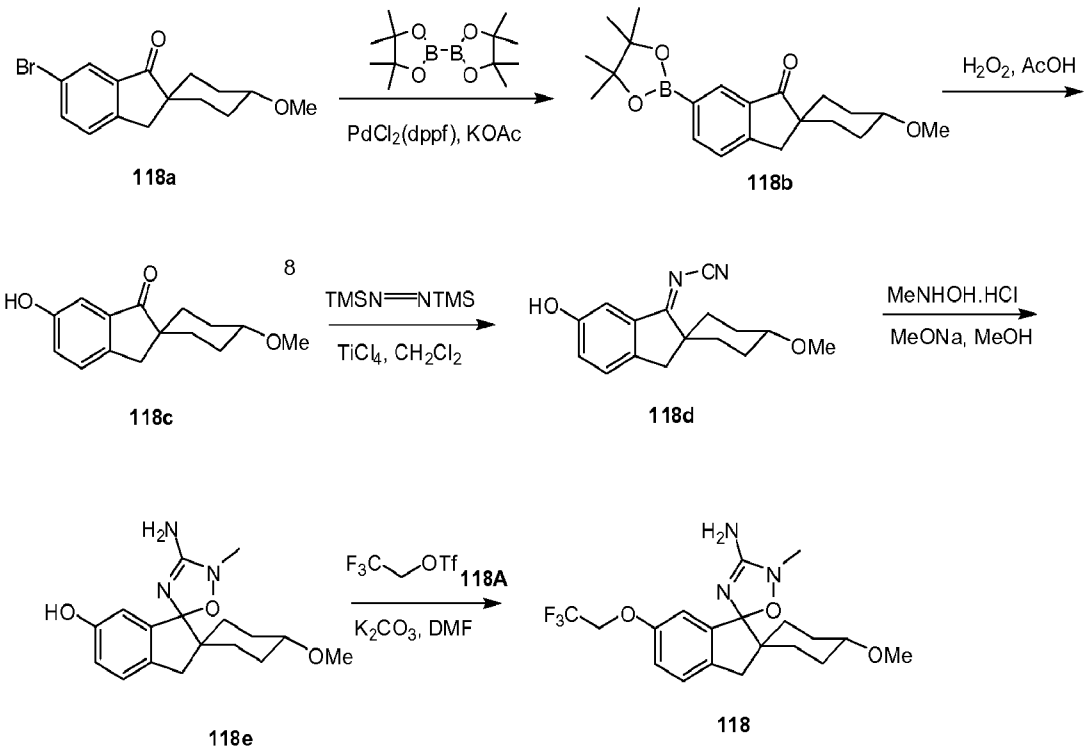
Procedure for preparation of Compound 117c

To a solution of compound **117b** (50 mg, 0.167 mmol) in anhydrous CH_2Cl_2 (4 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 0.4 mL, 0.4 mmol). The resulting mixture was stirred at room temperature for 1 h under a nitrogen atmosphere, and then bis-trimethylsilylcarbodiimide (64 mg/ 0.076 mL, 0.34 mmol) was added. After addition, the mixture was stirred at room temperature overnight. LC-MS showed that the reaction was completed. The reaction mixture was poured into ice-water (10 g) and stirred for 30 min. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give compound **117c** (54 mg, 100% crude yield) as a white solid, which was used directly for the next step without purification.

Procedure for preparation of Compound 117

To a solution of methylhydroxylamine HCl salt (14 mg, 0.167 mmol) in anhydrous MeOH (5 mL) was added NaOMe (10 wt% in MeOH, 0.08 g, 0.15 mmol), followed by compound **117c** (54 mg, 0.17 mmol). After stirred for 40 min, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and preparative RP-HPLC to give compound **117** (4.8 mg, 8%) as a white solid. **LC-MS** t_R = 1.109 min and 1.175 min in 2 min chromatography, MS (ESI) *m/z* 370.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.48-7.56 (d, J = 8.4 Hz, 1.4H), 7.38 (s, 0.6H), 7.18-7.27 (m, 1H), 3.66 (s, 1H), 3.37 (s, 2H), 3.34 (s, 1H), 3.24 (s, 3H), 3.11 (s, 1H), 2.90 (s, 1H), 2.70-2.80 (m, 2H), 2.05-2.15 (m, 2H), 1.75-1.88 (m, 1H), 1.57-1.73 (m, 2H), 1.30-1.51 (m, 5H), 0.60-0.68 (m, 1H), 0.37-0.42 (m, 2H), 0.02-0.03 (m, 2H).

Example 84. Synthesis of Compound 118



Procedure for preparation of Compound 118b

To a solution of compound **118a** (500 mg, 1.61 mmol) in 1,4-dioxane (10 mL), was added KOAc (0.46 g, 4.69 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2 –yl)-1,3,2- dioxaborolane (450 mg, 1.77 mmol) and $PdCl_2$(dppf) (150 mg, 0.18 mmol) under a nitrogen atmosphere, the mixture was stirred at 100 °C in a CEM microwave reactor for 1 h. LCMS showed the complete consumption of compound **118a**. Water (5 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **118b** (284 mg, 50%) as a black solid which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 8.20 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 3.41 (s, 3H), 3.21 (m, 1H), 2.96 (s, 2H), 2.06 (m, 2H), 1.64 (m, 2H), 1.56 (m, 2H), 1.44 (m, 2H), 1.31 (s, 12H).

Procedure for preparation of Compound 118c

To a soltoion of compound **118b** (100 mg, 0.28 mmol) in THF (10 mL) was added HOAc (0.2 mL) and H_2O_2 (1 mL) under a nitrogen atmosphere, the mixture was stirred at room temperature overnight. The mixture was quenched by addition of $NaHSO_3$ solution (10 mL), and then was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30mL), dried over Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography on silica gel eluting with hexane: EtOAc (100: 10 to 30: 10) to afford compound **118c** (50 mg, 72%) as a yellow oil. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.24 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 3.33 (s, 3H), 3.26 (m, 1H), 2.86 (s, 2H), 2.20-2.21 (m, 2H), 1.68-1.69 (m, 2H), 1.44-1.65 (m, 2H), 1.20-1.40 (m, 2H).

Procedure for preparation of Compound 118d

To a solution of compound **118c** (50 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $TiCl_4$ (1.2 mL, 1.2 mmol, 1 M in CH_2Cl_2) under a nitrogen atmosphere, the mixture was stirred at 50 °C in a CEM microwave reactor for 15 min, then bis-trimethylsilylcarbodiimide (15.1 mg, 0.40 mmol) was added. The mixture was stirred at 60 °C in a CEM microwave reactor for 15 min. The mixture was poured into ice-water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated to give compound **118d** (40 mg, 73%) as a yellow solid which was used directly for the next step without purification.

Procedure for preparation of Compound 118e

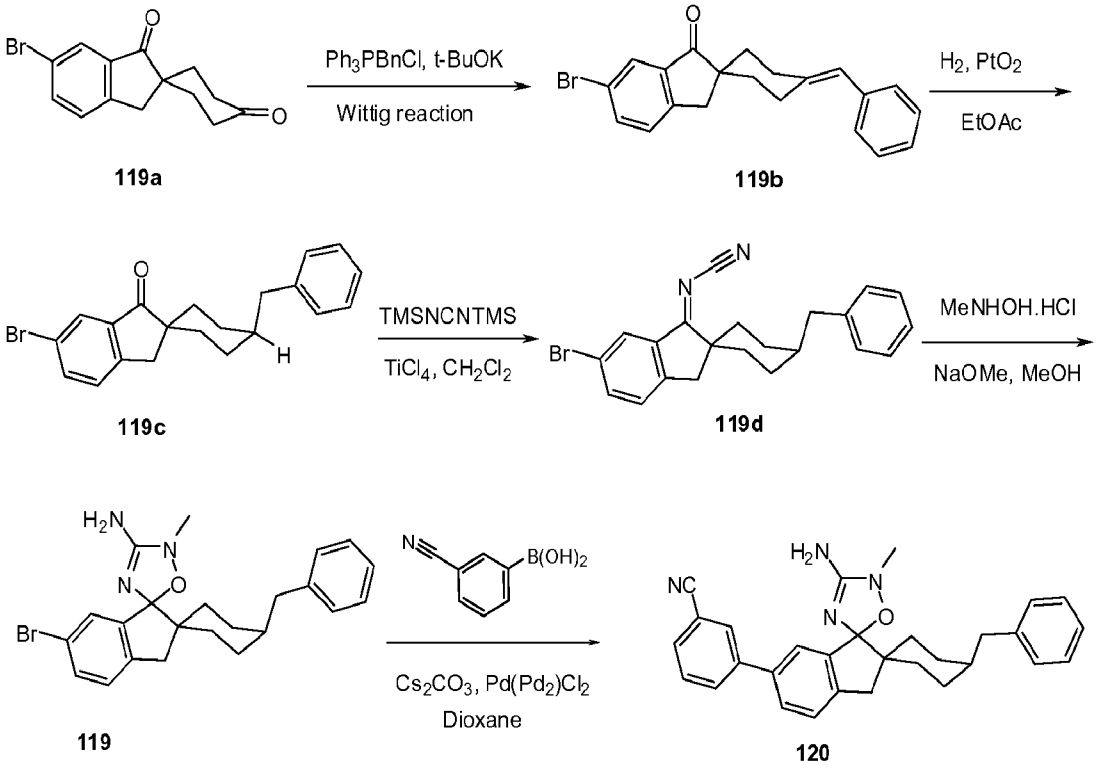
To a solution of MeNHOH.HCl (12.4 mg, 0.14 mmol) in MeOH (2 mL) was added MeONa (80 mg, 0.14 mmol, 10 wt% in MeOH), followed by compound **118d** (40 mg, 0.14 mmol). The mixture was stirred for 10 min at room temperature, LCMS analysis showed the complete consumption of compound **118d**. The solvent was removed by evaporation *in vacuo* to give the crude product, which was purified by preparative TLC eluting with dichloromethane: methanol = 10:1 to afford compound

118e (10 mg, 22%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 6.99 (s, 1H), 6.80 (d, J = 6.4 Hz, 2H), 3.41 (s, 3H), 3.25 (m, 1H), 2.94 (s, 3H), 1.92-2.08 (m, 2H), 1.86-1.93 (m, 2H), 1.58-1.75(m, 2H), 1.42-1.59 (m, 2H), 1.21-1.41(m, 2H).

Procedure for preparation of compound 118

To a solution of compound **118e** (10 mg, 0.031 mmol) in DMF (2 mL) was added K_2CO_3 (8.5 mg, 0.062 mmol) and compound **118A** (8.0 mg, 0.034 mmol), the mixture was stirred at 50 °C for 3h, LCMS analysis showed the complete consumption of compound **118e**. The reaction was added with H_2O (5 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC eluting with dichloromethane: methanol = 10: 1 followed by preparative RP-HPLC to afford **compound 118** (2 mg, 14%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15 (d, J = 8.0 Hz, 1H), 6.95 (dd, J = 2.4, 8.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 4.53 (m, 2H), 3.40 (s, 3H), 3.24 (m, 1H), 3.04 (s, 3H), 2.80-2.84 (d, J = 15.2 Hz, 1H), 2.75-2.80 (d, J = 15.2, Hz, 1H), 1.98-2.01 (m, 2H), 1.70 (m, 1H), 1.66-1.70 (m, 2H), 1.46 (m, 1H), 1.36-1.46 (m, 2H). **LCMS**: t_R = 1.80 min in 2 min chromatography, MS (ESI) *m/z* 400.2 $[M+H]^+$.

Example 85. Synthesis of Compound 119



Procedure for preparation of compound 119b

To a solution of potassium *tert*-butoxide (0.89 g, 7.7 mmol) in *tert*-butyl alchol (30 mL) was added benzyl triphenyl phosphonium chloride (2.4 g, 6.1 mmol). The mixture was stirred at ambient temperature for 3 h. Compound **1** (1.5 g, 5.1 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature overnight. The solvent was removed by evaporation *in vacuo*. The residue was added H_2O (100 mL) and then was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were washed with brine (2 × 50 mL). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with petroleum ether: ethyl acetate = 100: 1 to 10: 1 to give compound **119b** (1.0 g, 53%) as a yellow solid. **LC-MS**: t_R = 2.83 min in 3 min chromatography, MS (ESI) *m/z* 367.28 $[M+H]^+$.

Procedure for preparation of compound 119c

A mixture of compound **119b** (1.0 g, 2.7 mmol), ethyl acetate (100 mL) and PtO_2 (0.10 g, 0. 44 mmol) was stirred at temperature under hydrogen (1 atm) atmosphere overnight. The precipitate was filtered off and washed with ethyl acetate (2 × 50 mL). The filtrate and washings were concentrated by evaporation *in vacuo*. The residue was purified by column chromatography over silica gel eluting with petroleum ether: ethyl acetate = 100: 1 to 10: 1 to give compound **119c** (0.35 g, 35%) as a white solid. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.60-7.70 (m, 2H), 7.30-7.35 (d, J = 8.0 Hz, 1H), 7.10-7.20 (m, 2H), 7.00-7.10 (m, 3H), 2.80-2.90 (s, 2H), 2.50-2.60 (d, J = 7.2 Hz, 2H), 1.75-1.85 (m, 2H), 1.65-1.75 (m, 1H), 1.55-1.65 (m, 2H), 1.35-1.45 (m, 2H). **LC-MS**: t_R = 2.46 min in 3 min chromatography, MS (ESI) *m/z* 369.29 $[M+H]^+$.

Procedure for preparation of compound 119d

A sealed tube was charged with compound **119c** (0.15 g, 0.41 mmol), anhydrous dichloromethane (3 mL) and $TiCl_4$ (0.82 mL, 0.82 mmol, 1 M in CH_2Cl_2). The tube was heated at 50 °C in a CEM microwave reactor for 15 min. After cooling down, N, N'-methanediylidene bis (1,1,1-trimethylsilianamine) (0.15 g, 0.82 mmol) was added. The tube was heated at 60 °C in a CEM reactor for 15 min again. After cooling down, the mixture was quenched by addition of ice-water (2 mL) carefully with stirring. Brine (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL). The separated organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **119d** (0.17 g, 106% crude yield) as a pale yellow solid, which was used directly in next step without further purification.

Procedure for preparation of compound 119

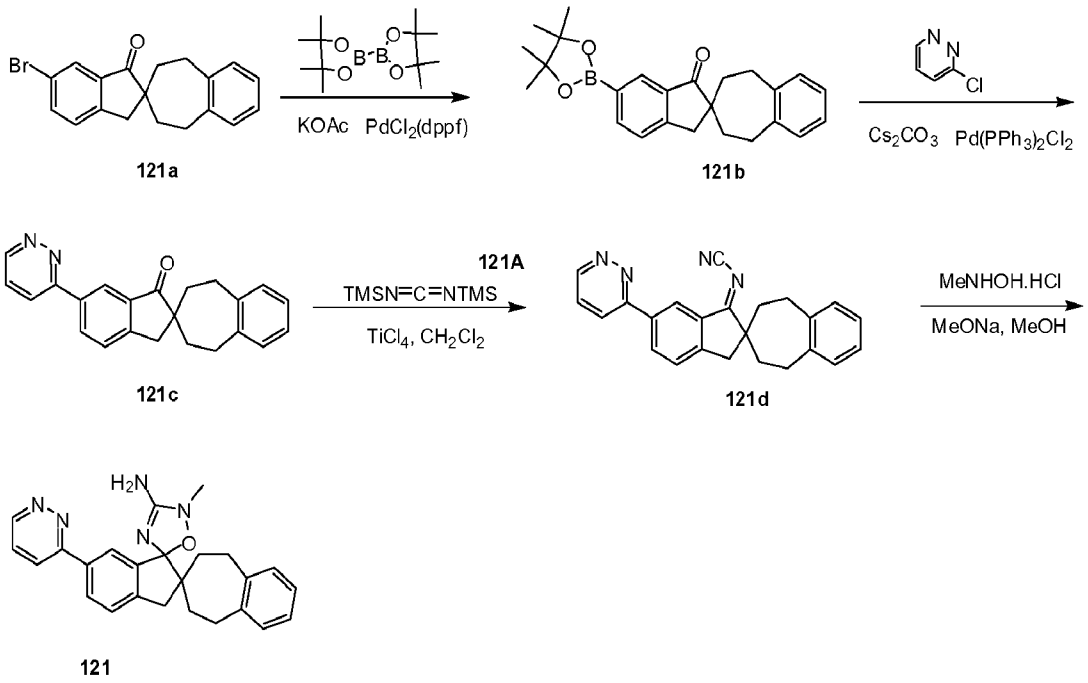
A solution of sodium methanolate in methanol (0.4 mL, 0.74 mmol, 10% in MeOH) was added to a flask was charged with compound **119d** (0.17 g, 0.41 mmol, crude), anhydrous methanol (10 mL) and N-methyl hydroxylamine hydrochloride (41 mg, 0.49 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed by evaporation *in vacuo*. Brine (20 mL) was added and the mixture was extracted with ethyl acetate (contained 10% methanol) (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL). The separated organic

phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* and the resulting residue was purified by preparative RP-HPLC to give **compound 119** (60 mg, 33%) with 99% purity based on LC-MS as a pale yellow solid. **^{1}H NMR**: (CD_3OD, 300 MHz): δ 7.35-7.40 (m, 2H), 7.20-7.30 (m, 2H), 7.05-7.20 (m, 4H), 3.00-3.10 (s, 3H), 2.70-2.80 (d, J = 20.8 Hz, 1H), 2.65-2.70 (d, J = 20.8 Hz, 1H), 2.60-2.65 (d, J = 10.0 Hz, 2H), 1.85-2.00 (m, 2H), 1.75-1.85 (m, 1H), 1.50-1.60 (m, 4H), 1.30-1.40 (m, 1H), 1.15-1.25 (m, 1H). **LC-MS**: t_R = 2.54 min in 3 min chromatography, MS (ESI) *m/z* 439.13 $[M+H]^+$.

Procedure for preparation of compound 120

A mixture of **compound 119** (30 mg, 0.053 mmol), 3-cyanophenylboronic acid (10 mg, 0.068 mmol), Cs_2CO_3 (0.2 mL, 0.40 mmol, 2M in water) and $Pd(PPh_3)_2Cl_2$ (1 mg, 0.0014 mmol) in 1,4-dioxane (5 mL) was stirred in at 80 °C for 3 h under a nitrogen atmosphere. After cooling down, brine (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*, the resulting crude product was purified by preparative TLC eluting with petroleum ether: ethyl acetate = 2:1 and then by preparative RP-HPLC to give **compound 120** (10.2 mg, 42%) with 99% purity based on LC-MS as a pale yellow solid. **^{1}H NMR**: (CD_3OD 300 MHz): δ 7.90-8.00 (m, 2H), 7.50-7.75 (m, 4H), 7.10-7.45 (m, 6H), 3.05-3.10 (s, 3H), 2.84-2.90 (d, J = 20.8 Hz, 1H), 2.65-2.82 (d, J = 20.8 Hz, 1H), 2.60-2.70 (d, J = 10.0 Hz, 2H), 1.90-2.00 (m, 2H), 1.80-1.90 (m, 1H), 1.50-1.70 (m, 4H), 1.35-1.45 (m, 1H), 1.20-1.30 (m, 1H). **LC-MS**: t_R = 2.53 min in 3 min chromatography, MS (ESI) *m/z* 463.3 $[M+H]^+$.

Example 86. Synthesis of Compound 121



Procedure for preparation of compound 121b

The mixture of $Pd(dppf)Cl_2$ (54 mg), compound **121a** (200 mg, 0.588 mmol), bispinacolatodiboron (164.3 mg, 0.647 mmol) and KOAc (167.1 mg, 1.71 mmol) in dioxane (3.5 mL) was placed into CEM microwave reactor and irradiated at 100 °C for 1 h under nitrogen. The solution was concentrated *in vacuo*, and the residue was purified by preparative TLC (petroleum: ethyl acetate, 10:1) to give compound **121b** (120 mg, 53%) as a white solid. **^{1}H-NMR** ($CDCl_3$ 400 MHz): δ 8.17 (s, 1H), 7.64-7.97 (m, 1H), 7.41-7.43 (m, 1H), 7.06 (d, J = 3.6 Hz, 4H), 3.10-3.16 (m, 2H), 2.93-2.99 (m, 2H), 2.80 (s, 2H), 1.79-1.87 (m, 4H), 1.55-1.61 (m, 2H); 1.17-1.23 (m, 12H).

Procedure for preparation of compound 121c

A solution containing compound **121b** (60 mg, 0.155 mmol), 3-chloro-pyridazine (27 mg, 0.233 mmol) in dioxane (4 mL), and aqueous Cs_2CO_3 (2 M, 1.1 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then $PdCl_2(PPh_3)_2$ (11 mg) was added. The reaction vial was sealed and placed

into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative HPLC (acidic) to afford compound **121c** (15 mg, 29%) as a yellow solid.

Procedure for preparation of compound 121d

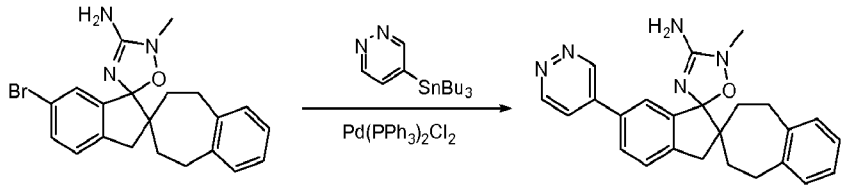
To a solution of compound **121c** (15 mg, 0.044 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a solution of $TiCl_4$ in CH_2Cl_2 (1 M, 0.44 mL, 0.44 mmol) at room temperature. The mixture placed into CEM microwave reactor and irradiated at 50 °C for 15 min, bistrimethylsilylcarbodiimide (18 mg, 0.10 mmol) was added. The resulting mixture was irradiated in microwave at 60 °C for 15 min and 70 °C for 1 h. After being cooled to room temperature, the mixture was poured into ice-water (2 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated to give compound **121d** (20 mg, 100%) as a yellow solid, which was used for next step without purification.

Procedure for preparation of Compound 121

To a solution of N-methylhydroxylamine hydrochloride (4.6 mg, 0.055 mmol) in anhydrous MeOH (1.5 mL) was added NaOMe (10 wt% in MeOH, 0.028 mL, 0.05 mmol), and compound **121d** (20 mg, 0.055 mmol). After being stirred at room temperature for 30 min, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). The mixture was filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by preparative HPLC (basic) to give **compound 121** (1.7 mg, 8%) as a white solid.

LC-MS t_R = 1.086 min in 2 min chromatography, MS (ESI) *m/z* 412 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 9.02 (d, J = 4.4 Hz, 4H), 8.06 (d, J = 9.2 Hz, 1H), 7.92-7.94 (m, 2H), 7.67-7.71 (m, 1H), 7.36-7.38 (m, 1H), 6.97-7.04 (m, 4H) ,3.03-3.11 (m, 3H), 2.91 (s, 3H), 2.60-2.65 (m, 2H), 1.89-1.91 (m, 2H), 1.64 (m, 1H), 1.48-1.54 (m, 2H).

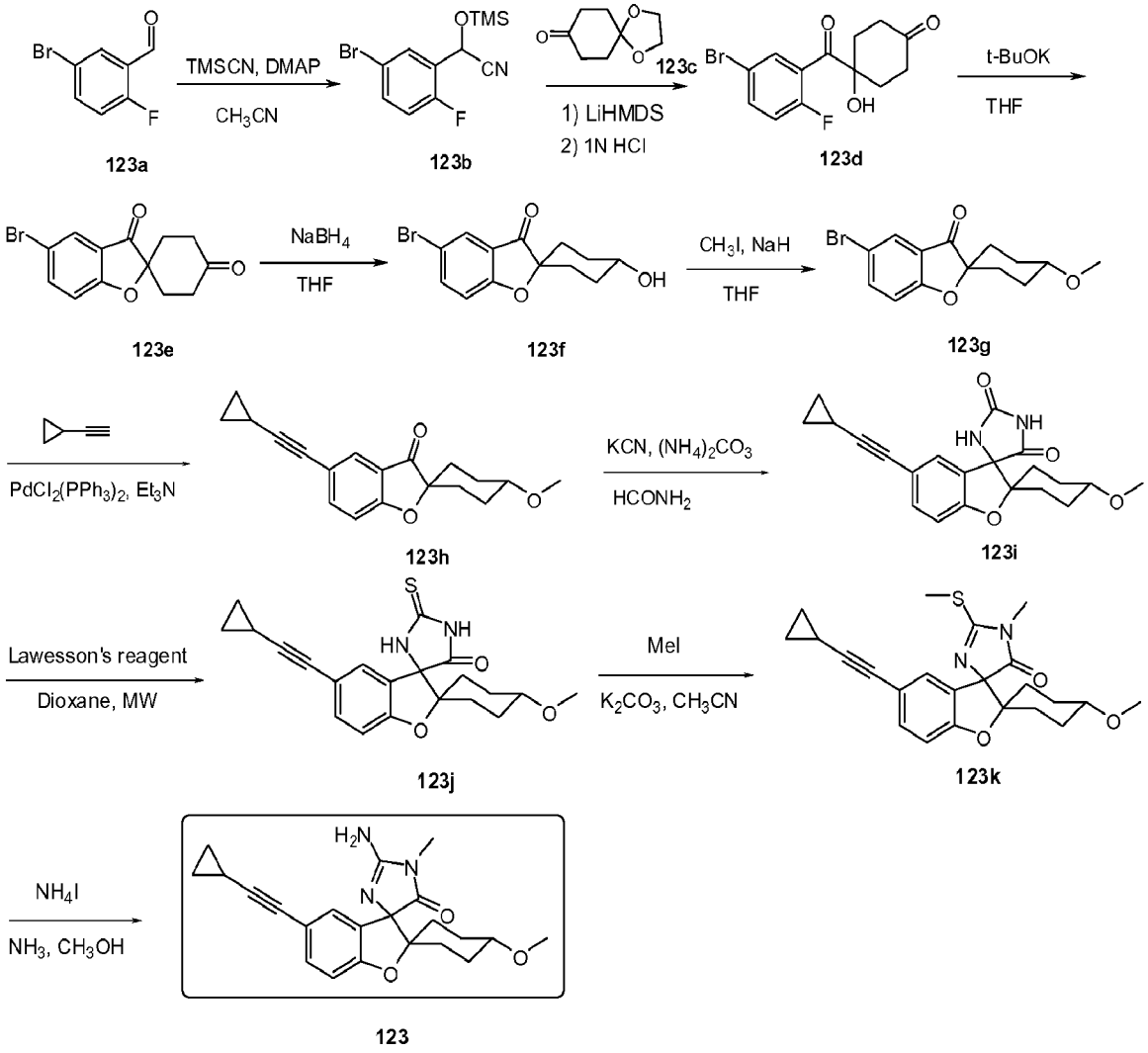
Example 87. Synthesis of Compound 122



122a 122

A solution containing 4-tributylstannanyl-pyridazine (78 mg, 0.213 mmol) and compound **1** (35 mg, 0.085 mmol) in dioxane (2 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then $PdCl_2(PPh_3)_2$ (6.1 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (20 mL) and aqueous CsF (4 M, 20 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by RP-HPLC (basic) to yield **compound 122** (3.4 mg, 10%) as a white solid.**LC-MS** t_R = 1.009 min in 2 min chromatography, MS (ESI) *m/z* 412 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 9.54-9.63 (m, 1H), 9.27-9.32 (m, 1H), 7.95-8.11 (m, 3H), 7.64-7.66 (m, 1H), 7.13-7.17 (m, 4H), 3.27(s, 3H), 3.12-3.25 (m, 3H), 2.72-3.06 (m, 2H), 2.11-2.20 (m, 1H), 1.87-2.05 (m, 1H), 1.58-1.74 (m, 3H).

Example 88. Synthesis of Compound 123



Procedure for preparation of compound 123b

A flask was charged with compound **123a** (30 g, 147.7 mmol), CH_3CN (250 mL), TMSCN (18 g, 181.5 mmol) and DMAP (0.20 g, 1.7 mmol) in turn. The reaction mixture was stirred at ambient temperature for 4 h. The solvent was removed by evaporation *in vacuo* (lower than 25 °C) to give crude compound **123b** (48.5 g, 101% crude yield) as a yellow oil, which was used directly in next step without further purification.

Procedure for preparation of compound 123d

To a solution of compound **123b** (23.7 g, 78.48 mmol) in anhydrous THF (150 mL) was added LiHMDS (1.0 M in THF, 86.3 mL, 86.3 mmol) dropwise via an addition funnel at -78 °C under a nitrogen atmosphere. After 1.5 h, a solution of compound **123c** (13.5 g, 86.3 mmol) in anhydrous THF was added dropwise *via* an addition funnel at -78 °C under a nitrogen atmosphere. After addition, the reaction mixture was stirred at -78 °C for 3 h. 1 N HCl (200 mL) was added via an addition funnel at -78 °C carefully. After that, the reaction mixture was allowed to warm to ambient temperature and kept at this temperature overnight. The mixture was separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (2 × 200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluent: petroleum ether: EtOAc = 50: 1 to 3: 1) to give pure compound **123d** (7.8 g, 31.6%) as a white solid. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.55-7.65 (m, 1H), 7.50-7.55 (m, 1H), 7.05-7.15 (m, 1H), 2.70-2.90 (m, 2H), 2.20-2.50 (m, 4H), 2.05-2.15 (m, 2H).

Procedure for preparation of compound 123e

A suspension of compound **123d** (14.5 g, 46 mmol) and *t*-BuOK (5.6 mg, 50 mmol) in THF (150 mL) was heated at 70 °C for 30 min in a CEM microwave reactor. The mixture was partitioned between EtOAc (150 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combained organic layer was washed with brine (100 mL) and concentrated *in vacuo*. The residue was purified by chromatography column on silica gel (eluent: petroleum ether: ethyl acetate from 50: 1 to 20: 1) to afford compound **123e** (2.5 g, 20%) as a yellow solid.

Procedure for preparation of compound 123f

To a mixture of compound **123e** (2.5 g, 8.47 mmol) in THF (70 mL) was added $NaBH_4$ (0.35 g, 9.3 mmol) at -78 °C under a nitrogen atmosphere. The mixture kept stirring at -78 °C for 15 min. The mixture was quenched by addition of MeOH (1 mL). The solvent was removed to afford crude compound **123f** (2.5 g, 100% crude yield) as a yellow solid, which was used directly to the next step.

Procedure for preparation of compound 123g

To a round bottle flask were added compound **123f** (2.5 g, 8.4 mmol) and NaH (0.40 g, 16.5 mmol) in THF (70 mL) at 0 °C, and then CH_3I (2.4 g, 6.5 mmol) was added. The mixture was warmed to 60 °C and stirred for 5 h. The mixture was cooled to 0 °C and quenched by addition of water (1 mL). The mixture was concentrated, the residue was purified by column chromatography on silica gel (eluent: petroleum ether: ethyl acetate = 30: 1) to afford compound **123g** (1.6 g, 62%) as a yellow solid.

Procedure for preparation of compound 123h

An oven dried three-necked round bottom flask equipped with a condenser was charged with compound **123f** (1.45 g, 4.7 mmol), Et_3N (30 mL) and Et_2NH (30 mL) under a nitrogen atmosphere. To this solution was added CuI (35 mg, 0.2 mmol), $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) under a nitrogen atmosphere. The system was degassed once again, then cyclopropyl acetylene (5 mL, excess) was added and the mixture was heated at 60 °C for 15 h. The solvent was evaporated and the residue was separated between EtOAc (50 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether: ethyl acetate = 50: 1 to 20: 1) to afford compound **123h** (630 mg, 40% purity) as a white solid.

Procedure for preparation of compound 123i

A steel autoclave was charged with a mixture of compound **123h** (300 mg, 1 mmol), KCN (130 mg, 2 mmol), $(NH_4)_2CO_3$ (700 mg, 7 mmol) and formamide (20 mL). The mixture was heated at 100 °C for 72 h. The reaction mixture was then cooled and poured over ice. After acidification with concentrated HCl (20 mL), the mixture was filtered to collect the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (2 × 150 mL). The separated organic phase was dried over Na_2SO_4 and concentrated to give compound **123i** (170 mg, 35%) as a grey solid, which was used in next step without purification.

Procedure for preparation of compound 123j

A suspension of compound **123i** (50 mg, 0.14 mmol) and Lawesson's Reagent (60 mg, 0.15 mmol) in anhydrous toluene (60 mL) was heated at 120 °C for one hour in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **123j** (22 mg, 40%) as a white solid.

Procedure for preparation of compound 123k

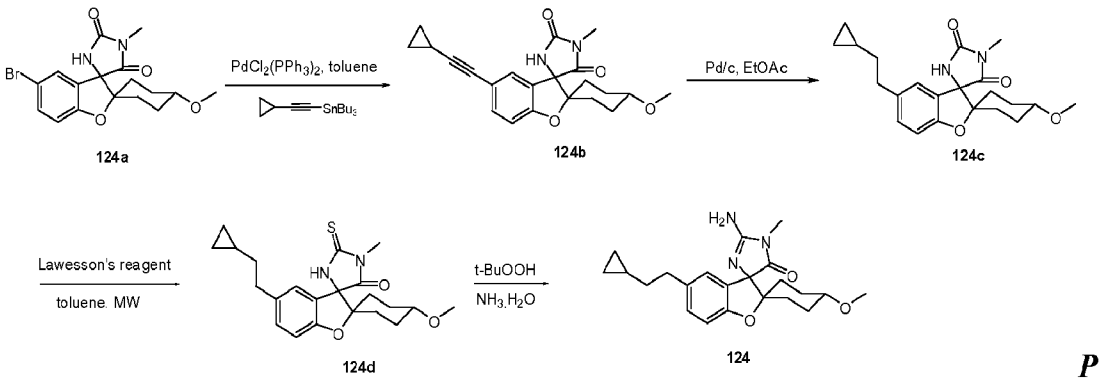
To a solution of compound **123j** (22 mg, 0.058 mmol) in DMF (3 mL) was added K_2CO_3 (15 mg, 0.1 mmol). After stirring for 5 min, MeI (10 mg, 0.11 mmol) was added and the reaction mixture was heated at 30 °C for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **123k** (10 mg, 40%) as a white solid.

Procedure for preparation of compound 123

A solution of compound **123k** (10 mg, 0.024 mmol), NH_4I (75 mg, 0.66 mmol) in a solution of NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 2 h. After cooling, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative RP-HPLC to give **compound 123** (0.9 mg, 10%) as a

white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35-7.37 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 6.88-6.90 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H), 3.25 (m, 4H), 2.24-2.27 (m, 1H), 1.99-2.08 (m, 3H), 1.51-1.68 (m, 4H), 1.42-1.46 (m, 1H), 0.86-0.87 (m, 2H), 0.68-0.69 (m, 2H).**LCMS**: t_R = 1.62 min in 3 min chromatography, MS (ESI) *m/z* 380.2 $[M+H]^+$.

Example 89. Synthesis of Compound 124



***P*rocedure for preparation of the compound 124b**

A suspension of compound **124a** (250 mg, 0.6 mmol), tributyl-cyclopropylethynyl-stannane (1.3 g, 3 mmol) and $PdCl_2(PPh_3)_2$ (40 mg, 0.06 mmol) in anhydrous toluene (5 mL) was heated at 130 °C for 30 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 2: 1) to give compound **124b** (99 mg, 40%) as a yellow oil.

Procedure for preparation of the compound 124c

A solution of compound **124b** (95 mg, 0.25 mmol) and Pd/C (10 mg) in EtOAc (10 mL) was stirred at 25 °C under H_2 (10 psi) atmosphere for 5 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue which was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate =2: 1) to give compound **124c** (77 mg, 80%) as a white solid.

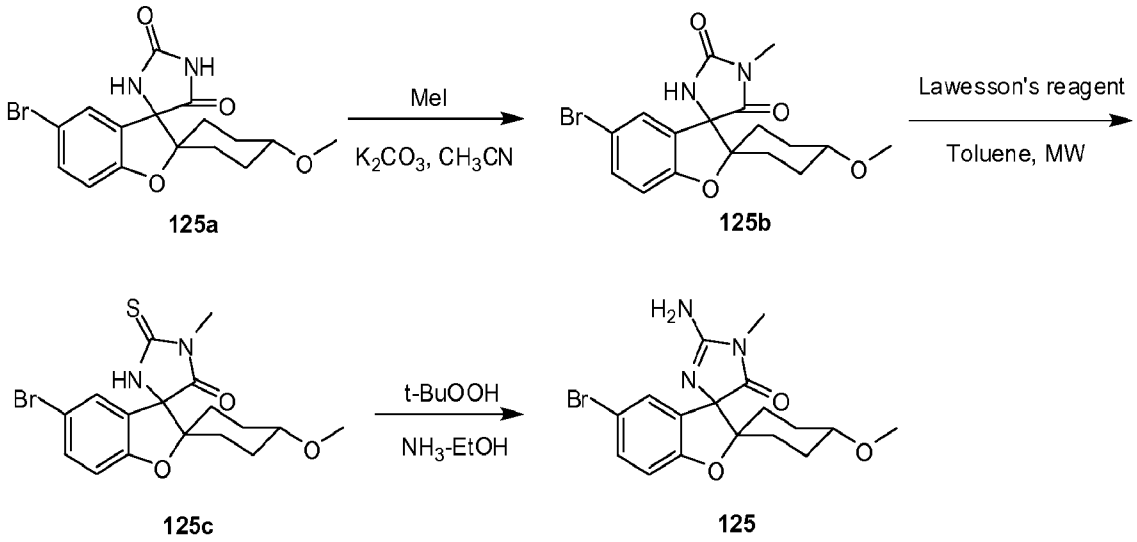
Procedure for preparation of the compound 124d

A suspension of compound **124c** (30 mg, 0.078 mmol) and Lawesson's Reagent (30 mg, 0.085 mmol) in anhydrous toluene (1 mL) was heated under 130 °C for 30 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 2: 1) to give compound **124d** (16 mg, 50%) as a white solid.

Procedure for preparation of compound 124

A solution of compound **124d** (16 mg, 0.04 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (2 mL) was stirred at 25 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 124** (9 mg, 60%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15-7.20 (d, J = 8.4 Hz, 1H), 7.05-7.10 (s, 1H), 6.80-6.85 (d, J = 8.4 Hz, 1H), 3.35-3.40 (s, 3H), 3.20-3.25 (m, 1H), 3.15-3.20 (s, 3H), 2.60-2.70 (m, 2H), 2.20-2.30 (m, 1H), 1.90-2.10 (m, 3H), 1.60-1.70 (m, 3H), 1.40-1.55 (m, 3H), 0.60-0.70 (m, 1H), 0.35-0.45 (m, 2H), 0.05-0.10 (m, 2H). **LCMS**: t_R = 1.86 min in 3 min chromatography, MS (ESI) *m/z* =384.2 $[M+H]^+$.

Example 90. Synthesis of Compound 125



Procedure for preparation of Compound 125b

To a solution of compound **125a** (190 mg, 0.5 mmol) in DMF (5 mL) was added K_2CO_3 (138 mg, 1.0 mmol) and MeI (73.5 mg, 0.5 mmol), the mixture was stirred at room temperature for 3 h. H_2O (10 mL) was added and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **125b** (170 mg, 86%) as a yellow solid. which was used in next step without further purification. **LCMS**: t_R = 1.215 min in 2 min chromatography, MS (ESI) *m/z* = 397 $[M+H]^+$.

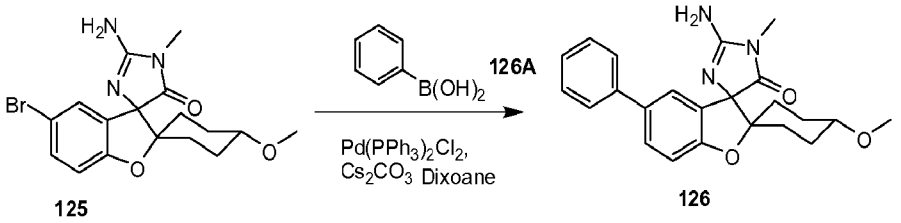
Procedure for preparation of Compound 125c

To a solution of compound **125b** (170 mg, 0.43 mmol) in anhydrous toluene (5 mL) was added Lawesson's Reagent (173.8 mg, 0.43 mmol) under N_2, the mixture was stirred at 130 °C for 30 min in microwave, the solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to afford compound **125c** (110 mg, 62%) as a white solid. **LCMS**: t_R = 1.345 min in 2 min chromatography, MS (ESI) *m/z* = 411 $[M+H]^+$.

Procedure for preparation of compound 125

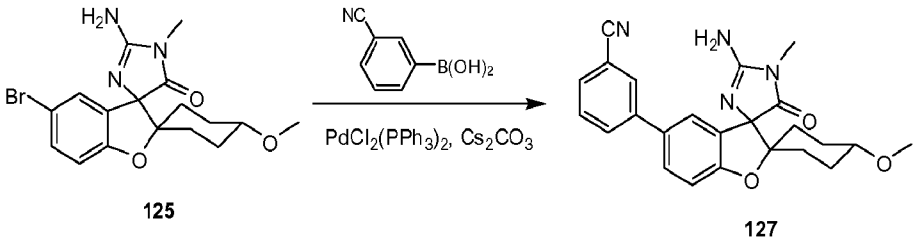
To a solution of compound **125c** (110 mg, 0.26 mmol) in EtOH (10 mL) was added *t*-BuOOH (1 mL) and NH_3-H_2O (3 mL) under N_2, the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 to afford compound **125** (60 mg, 57%) as a white solid. **LCMS**: t_R = 1.018 min in 2 min chromatography, MS (ESI) *m/z* = 394.0 $[M+H]^+$.

Example 91. Synthesis of Compound 126



To a solution of ***compound 125*** (20 mg, 0.05 mmol) in 1,4-dioxane (2 mL) was added compound **126A** (11.1 mg, 0.076 mmol), Cs_2CO_3 (2 N, 0.2 mL) and $Pd(PPh_3)_2Cl_2$ (5 mg) under nitrogen, the mixture was stirred at 120 °C in a CEM microwave reactor for 15 min, LCMS showed the complete consumption of compound **125**. Water (2 mL) was added and the precipitate was filtered off through a pad of celite, and was washed with EtOAc (10 mL × 3). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 126** (3.0 mg, 15%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H) 3.40 (s, 3H), 3.33-3.27 (m, 1H), 3.25-3.15 (s, 3H), 2.32-2.29 (m, 1H), 2.29-2.05 (m, 3H), 1.71-1.56 (m, 4H). **LCMS**: t_R = 1.018 min in 2 min chromatography, MS (ESI) *m/z* = 394.0 $[M+H]^+$.

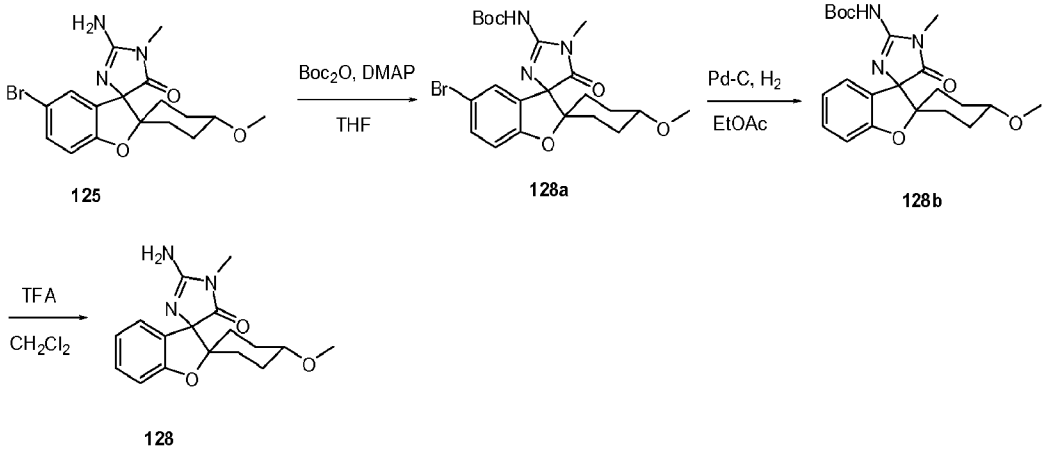
Example 92. Synthesis of Compound 127



125 127

A suspension of **compound 125** (10 mg, 0.03 mmol), 3-cyanophenylboronic acid (7 mg, 0.03 mmol), $PdCl_2(PPh_3)_2$ (1 mg, 0.003 mmol) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (2 mL) was heated under 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative HPLC to give **compound 127** (5.8 mg, 60%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.98-8.05 (s, 1H), 7.95-8.00 (d, J = 2.0 Hz, 1H), 7.55-7.80 (m, 4H), 7.05-7.10 (s, 1H), 3.40 (s, 3H), 3.20-3.35 (m, 4H), 2.20-2.30 (m, 1H), 2.00-2.10 (m, 3H), 1.55-1.80 (m, 4H). **LCMS**: t_R = 1.60 min in 3 min chromatography, MS (ESI) m/z = 416 $[M+H]^+$.

Example 93. Synthesis of Compound 128



125 128a 128b 128

Procedure for preparation of the compound 128a

To a solution of **compound 125** (45 mg, 0.11 mmol) in THF (3 mL) was added $(Boc)_2O$ (50 mg, 0.23 mmol) and DMAP (2 mg, 0.011 mmol). The reaction mixture was stirred at 30 °C for 1 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 2: 1) to give compound **128a** (46 mg, 70%) as a colorless oil.

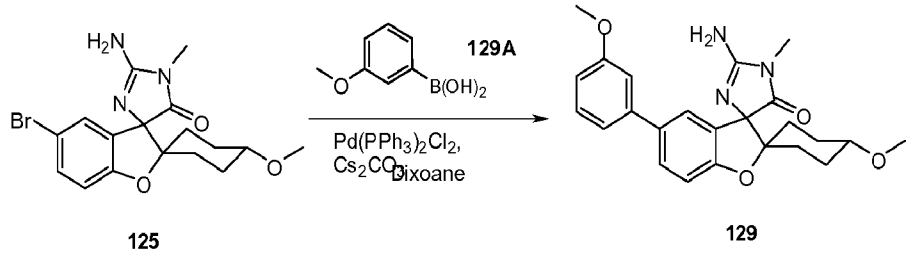
Procedure for preparation of the compound 128b

To a solution of compound **128a** (10 mg, 0.02 mmol) in EtOAc (3 mL) was added Pd/C (2 mg). The reaction mixture was stirred at 30 °C at H_2 atmosphere (1 atm) condition overnight. The mixture was filtered and concentrated *in vacuo* to give compound **128b** (10 mg, 100% crude yield) as a colorless oil.

Procedure for preparation of compound 128

To a solution of compound **128b** (10 mg, 0.024 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL). After stirring for 10 min, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 128** (1.6 mg, 20%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35-7.40 (t, J = 9.2 Hz, 1H), 7.25-7.30 (d, J = 10.4 Hz, 1H), 7.40-7.55 (m, 2H), 3.35-3.40 (s, 3H), 3.20-3.30 (m, 4H), 2.20-2.30 (m, 1H), 1.95-2.05 (m, 3H), 1.50-1.75 (m, 4H). **LCMS**: t_R = 0.792 min in 2 min chromatography, MS (ESI) m/z = 316.1 $[M+H]^+$

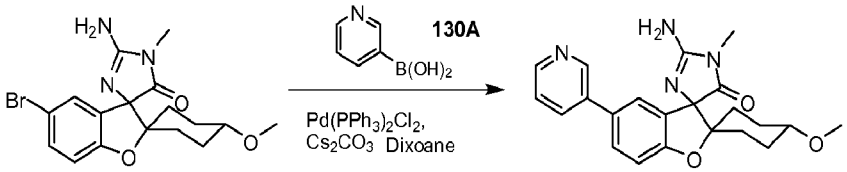
Example 94. Synthesis fo Compound 129



Synthesized by a route analogously to **compound 126** from compound **125** (20 mg, 0.05 mol) and purified by preparative TLC on silica gel eluting with petroleum

ether: ethyl acetate = 1: 1 to give **compound 129** (2.5 mg, 11%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.67 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H), 3.40 (s, 3H), 3.33-3.27 (m, 1H), 3.27-3.15 (s, 3H), 2.40-2.29 (m, 1H), 2.27-2.05 (m, 3H), 1.70-1.56 (m, 4H) .**LCMS**: t_R = 1.116 min in 2 min chromatography, MS (ESI) m/z = 422.1 $[M+H]^+$.

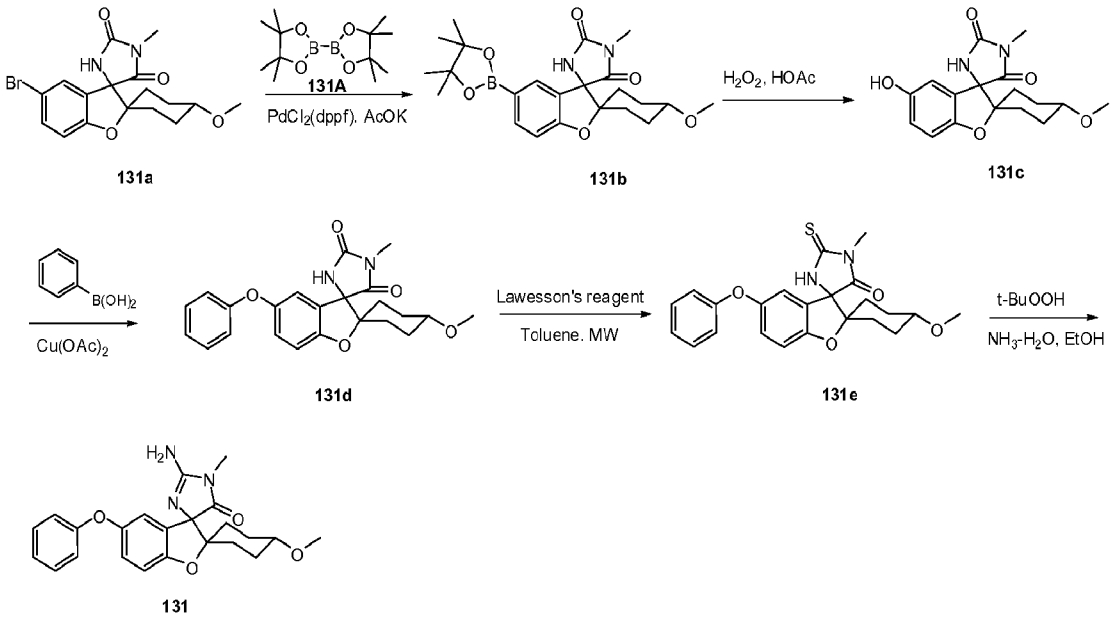
Example 95. Synthesis of Compound 130



Synthesized by a route analogously to **compound 126** from compound **125** (20 mg, 0.05 mol) and purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 130** (2.1 mg, 11%) as a white solid.

^{1}H NMR (CD_3OD 400 MHz): δ 8.91 (s, 1H), 8.70 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.2 Hz, 3H), 7.16 (d, J = 8.8 Hz, 1H), 3.40 (s, 3H), 3.34-3.27 (m, 1H), 3.28-3.15 (s, 3H), 2.45-2.24 (m, 1H), 2.25-2.06 (m, 3H), 1.72-1.57 (m, 4H); **LCMS**: t_R = 0.846 min in 2 min chromatography, MS (ESI) m/z = 393.1 $[M+H]^+$.

Example 96. Synthesis of Compound 131



Procedure for preparation of compound 131b

A suspension of compound **131a** (270 mg, 0.68 mmol), compound **131A** (190 mg, 0.75 mmol), $PdCl_2$(dppf) (60 mg, 0.08 mmol) and KOAc (200 mg, 2 mmol) in anhydrous 1,4-dioxane (5 mL) was heated at 100 °C for 60 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column on silica gel (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **131b** (300 mg, yield 88%, 67% purity) as a yellow solid.

Procedure for preparation of compound 131c

To a solution of compound **131b** (300 mg, 0.7 mmol) in THF (10 mL) was added AcOH (1 mL) and H_2O_2 (3 mL). The reaction mixture was stirred at 30 °C for 10 h. The mixture was quenched with saturated $NaHSO_3$ (6 mL) and then balanced between EtOAc (20 mL × 2) and water (10 mL). The organic layers were collected and concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 1: 2) to give compound **131c** (123 mg, 40% for two steps) as a colorless oil.

Procedure for preparation of compound 131d

To a solution of compound **131c** (30 mg, 0.09 mmol) in CH_2Cl_2 (8 mL) was added phenl boronic acid (14 mg, 0.11 mmol), $Cu(OAc)_2$ (36 mg, 0.18 mmol) and EtN_3 (18 mg, 0.18 mmol). The reaction mixture was stirred in the open air at 30 °C for 10 h. The precipitate was filtered off and washed with ethyl acetate (10 mL × 2), the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **131d** (15 mg, 50%) as a white solid.

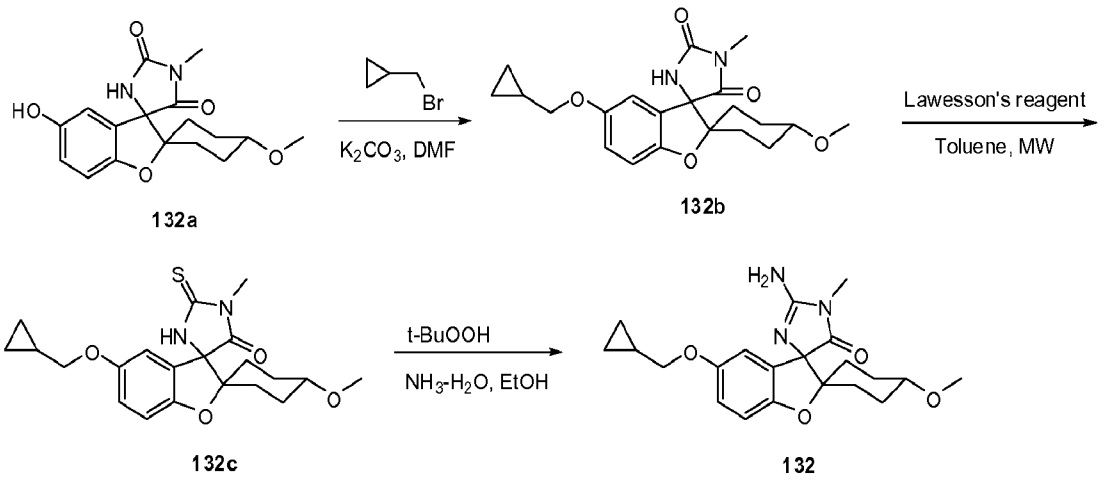
Procedure for preparation of compound 131e

A suspension of compound **131d** (13 mg, 0.03 mmol) and Lawesson's Reagent (14 mg, 0.03 mmol) in anhydrous toluene (1 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 5: 1) to give compound **131e** (8 mg, 65%) as a white solid.

Procedure for preparation of compound 131

A solution of compound **131e** (8 mg, 0.02 mmol), *t*-BuOOH (0.2 mL), NH_3-H_2O (0.3 mL) in EtOH (2 mL) was stirred at 30 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 131** (2.0 mg, 25%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35-7.45 (m, 2H,), 7.00-7.10 (m, 1H), 6.85-6.95 (m, 4H), 6.63 (s, 1H), 3.35 (s, 3H), 3.20-3.30 (m, 1H), 3.08 (s, 3H), 2.25-2.30 (m, 1H), 1.90-2.10 (m, 3H), 1.45-1.70 (m, 3H), 1.30-1.45 (m, 1H). **LCMS**: t_R = 1.66 min in 3 min chromatography, MS (ESI) *m/z* = 408.2 $[M+H]^+$.

Example 97. Synthesis of Compound 132



Procedure for preparation of compound 132b

To a solution of compound **132a**(35 mg, 0.1 mmol) in DMF (3 mL) was added K_2CO_3 (40 mg, 0.3 mmol). After stirring for 5 min, bromomethyl-cyclopropane (20 mg, 0.12 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **132b** (13 mg, 35%) as a white solid.

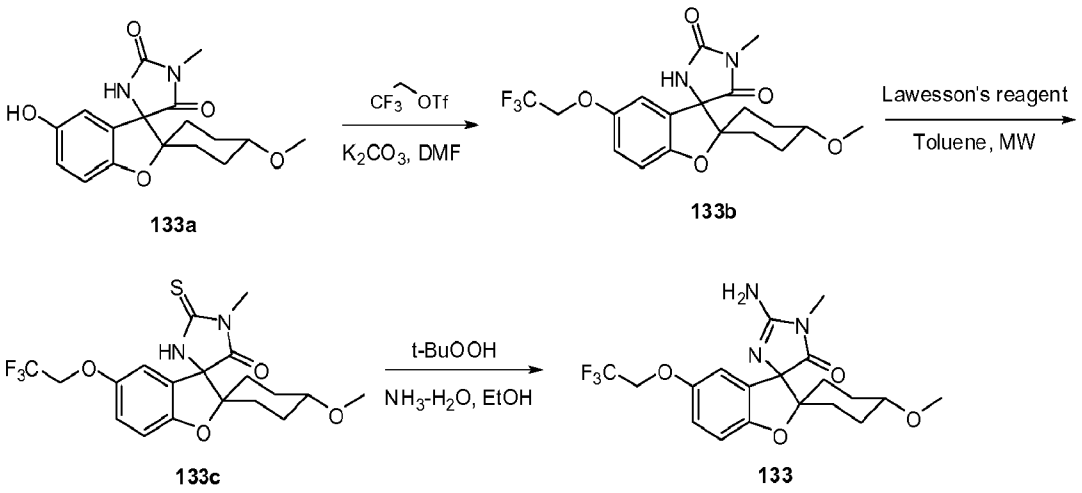
Procedure for preparation of compound 132c

A suspension of compound **132b** (13 mg, 0.03 mmol) and Lawesson's Reagent (13 mg, 0.04 mmol) in anhydrous toluene (1 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **132c** (7 mg, 45%) as a white solid.

Procedure for preparation of compound 132

A solution of compound **132c** (7 mg, 0.017 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (2 mL) was stirred at 30 °C for 10 h. The mixture was concentrated in vacuum to give the residue, which was purified by preparative HPLC to give **compound 132** (2.9 mg, 40%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 6.60-6.75 (m, 2H), 6.40-6.45 (s, 1H), 3.50-3.55 (d, J = 6.9 Hz, 2H), 3.20-3.30 (s, 3H), 3.05-3.15 (m,1H), 2.95-3.00 (s, 3H), 2.05-2.10 (d, J = 13.8 Hz, 1H), 1.80-1.90 (m, 3H), 1.40-1.60 (m, 2H), 1.15-1.30 (m, 2H), 1.00-1.10 (m, 1H), 0.40-0.50 (m, 2H), 0.15-0.25 (m, 2H). **LCMS**: t_R = 1.56 min in 3 min chromatography, MS (ESI) m/z = 386.1 $[M+H]^+$.

Example 98. Synthesis of Compound 133



Procedure for preparation of compound 133b

To a solution of compound **133a** (35 mg, 0.1 mmol) in DMF (3 mL) was added K_2CO_3 (40 mg, 0.3 mmol). After stirring for 5 min, trifluoro-methanesulfonic acid 2,2,2-trifluoro-ethyl ester (23 mg, 0.13 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered and filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (eluent:

petroleum ether: ethyl acetate = 2: 1) to give compound **133b** (14 mg, 35%) as a white solid.

Procedure for preparation of compound 133c

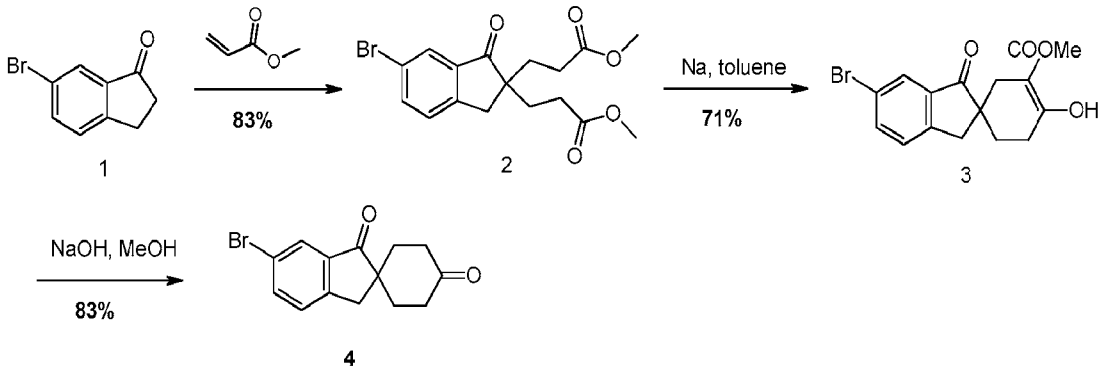
A suspension of compound **133b** (14 mg, 0.03 mmol) and Lawesson's Reagent (14 mg, 0.03 mmol) in anhydrous toluene (1 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **133c** (8 mg, 55%) as a white solid.

Procedure for preparation of compound 133

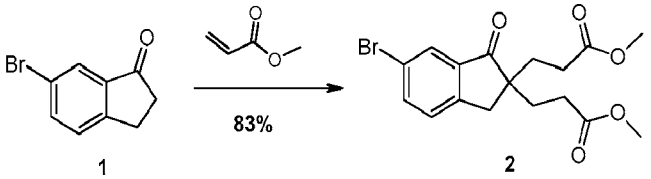
A solution of compound **133c** (8 mg, 0.018 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (1 mL) was stirred at 30 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 133** (7.0 mg, 75%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 6.75-6.85 (d, J = 8.2 Hz, 1H), 6.65-6.70 (d, J = 8.8 Hz, 1H), 6.55-6.60 (s, 1H), 4.25-4.35 (m, 2H), 3.20-3.30 (s, 3H), 3.05-3.15 (m, 1H), 2.95-3.00 (s, 3H), 2.05-2.10 (d, J = 13.8 Hz, 1H), 1.80-1.95 (m, 3H), 1.40-1.60 (m, 3H), 1.15-1.30 (m, 1H). **LCMS**: t_R = 1.57 min in 3 min chromatography, MS (ESI) m/z = 415.1 $[M+H]^+$.

Example I-0. Synthesis of *(1r,4r)-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one*

A. Synthesis of 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (4)-Method 1

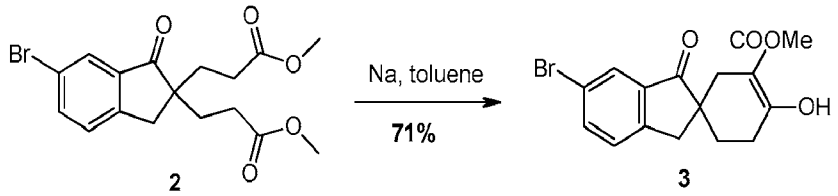


Procedure for preparation of compound 2



Under N_2, triton *B* (benzyl(tri-methyl)-ammonium hydroxide, 40% in MeOH, 2.48 mL) was added to a solution of 6-bromo-indan-1-one (**1**) (26.1 g, 0.124 mol) in toluene (200 mL), and the mixture was stirred at 50°C for 10 minutes. Acrylic methyl ester (31 mL, 0.286 mol) was added at 50°C, and the mixture was stirred at 50°C overnight. After being cooled to room temperature, the mixture was poured into water (150 mL), and extracted with DCM (100 mL×4). The combined organic phases were dried over Na_2SO_4, and evaporated, and purified by column chromatography on silica gel (PE/EA=10:1) to give compound **2** (39 g, 83%) as a yellow oil. **^{1}H NMR** ($CDCl_3$ 400MHz): δ 7.75-7.81 (s, 1H), 7.55-7.58 (d, 1H), 7.22-7.28 (d, 1H), 3.51-3.55 (s, 3H), 2.85-2.99 (s, 2H), 2.10-2.25 (m, 4H), 1.80-1.95 (m, 4H).

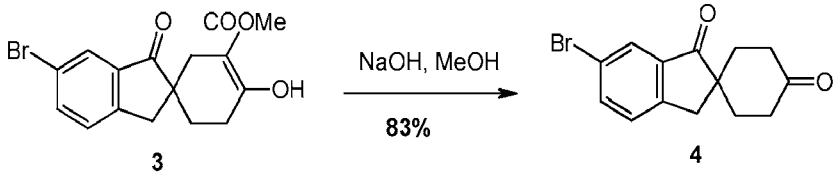
Procedure for preparation of compound 3



2 3

A solution of compound **2** (34 g, 88.7 mmol) in toluene (400 mL) was added dropwise to a flask containing Na (2.24 g, 97.6 mmol) and dry toluene (100 mL) at refluxing at 120°C. The reaction mixture was heated at 120°C for 28 hours, cooled to room temperature, and poured into a mixture H_2O (370 mL) and 4N HCl solution (37 mL) to afford a white suspension. This mixture was extracted with AcOEt (100 mL×4), evaporated, and purified by column chromatography on silica gel (PE/EA=10:1) to give compound **3** (22.11 g, 71%) as white solid. **^{1}H NMR**: ($CDCl_3$ 400MHZ): δ12.1 (s, 1H), 7.82-7.85 (s, 1H), 7.61-7.65 (d, 1H), 7.22-7.25 (d, 1H), 3.60-3.65 (s, 3H), 2.91-2.85 (d, 2H), 2.35-2.50 (m, 3H), 2.10-2.15 (d, 1H), 1.90-2.01 (m, 1H), 1.50-1.52 (m,1H).

Procedure for preparation of compound 4



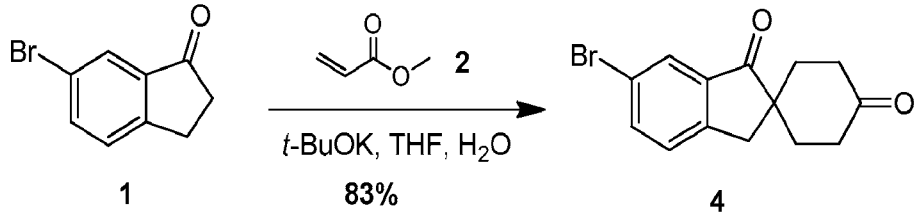
3 4

To a suspension of compound **3** (22.1 g, 63.0 mmol) in MeOH (221 mL) was added a solution of NaOH (10.20 g, 0.255 mol) in H_2O (331 mL) at room temperature. The reaction mixture was heated at 60°C overnight. The solvent was removed in *vacuo*, and extracted with DCM (250 mL×3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford compound **4** (15.33 g, 83%) as a white solid, which was used for the next step directly without purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.60-7.71 (d, 1H), 7.25-7.36 (d, 1H), 3.11 (s, 2H), 2.60-2.71 (m, 2H), 2.35-2.46 (m, 2H), 2.10-2.23 (m, 2H), 1.75-1.87 (m, 2H).

Note: 1. this reaction was completed under reflux at 120°C (oil bath) for 2 h.

2. Compound **3** couldn't be dissolved in MeOH completely, which didn't affect the reaction. After the reaction was completed, the reaction mixture was a suspension.

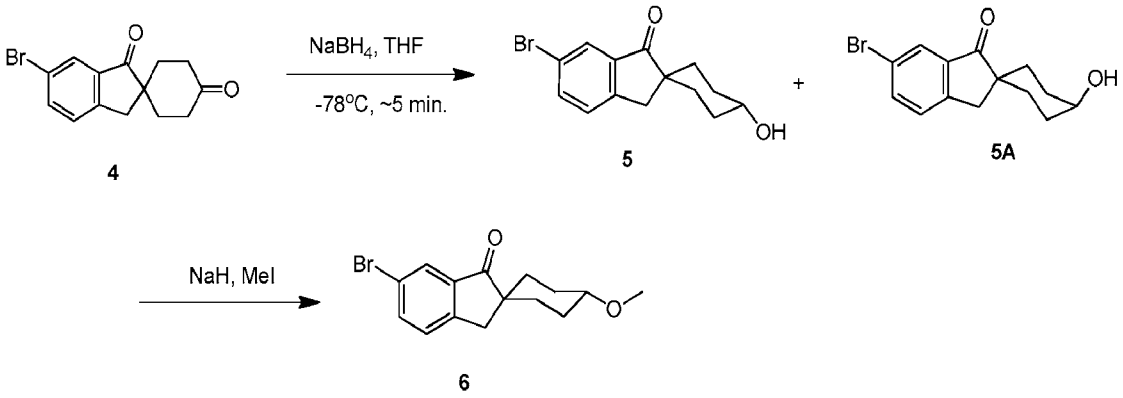
B. Synthesis of 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (4)-Method 2



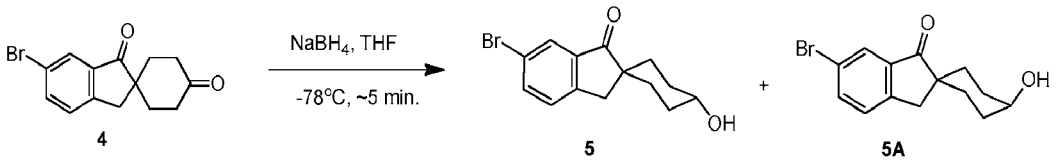
1 83% 4

To a solution of compound **1** (20 g, 95 mmol) and methyl acrylate (18 g, 201 mmol) in anhydrous THF (200 mL) was added *t*-BuOK (16 g, 114 mmol) portionwise at room temperature. The reaction mixture was stirred at room temperature for 1 hour. Water (400 mL) and KOH (5.32 g, 95 mmol) were added. The resulting mixture was heated to reflux overnight. 3 N HCl (150 mL) was added and extracted with CH_2Cl_2 (500 mL×2). The organic layers were washed with $NaHCO_3$ (150 mL), brine (150 mL) and dried over Na_2SO_4, concentrated in *vacuo* to give compound **4** as a grey solid (23 g, 83% yield), which was used for next step without purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.60-7.71 (d, 1H), 7.25-7.36 (d, 1H), 3.11 (s, 2H), 2.60-2.71 (m, 2H), 2.35-2.46 (m, 2H), 2.10-2.23 (m, 2H), 1.75-1.87 (m, 2H).

C. Synthesis of (1r,4r)-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (6)

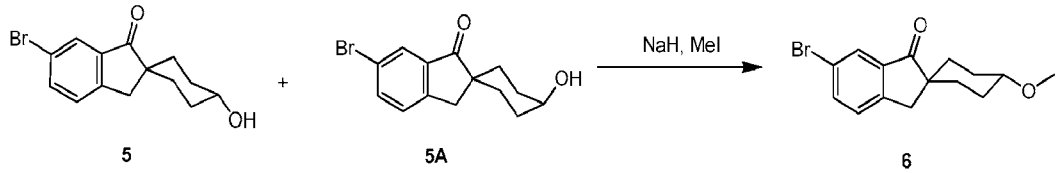


Procedure for preparation of compound 5



6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione **(4)** (19 g, 62.9 mmol, 97% purity in HPLC) was dissolved in anhydrous THF (600 mL) and was cooled to -78 °C. $NaBH_4$ (0.951 g, 25.1 mmol) was added portionwise to the reaction mixture at -78 °C. No more than 5 min, TLC (Hexane: EtOAc = 1: 1) showed the starting material **4** was consumed. CH_3OH (140 mL) and EtOAc (280 mL) was added and the resulting mixture was allowed to warm to room temperature. Water (280 mL) was added and the solution was concentrated *in vacuo* to remove THF and CH_3OH. EtOAc (200 mL) was added to dissolve the residue. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (600 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the mixture of compound **5** and compound **5A** (21 g), which was used for the next step without purification.

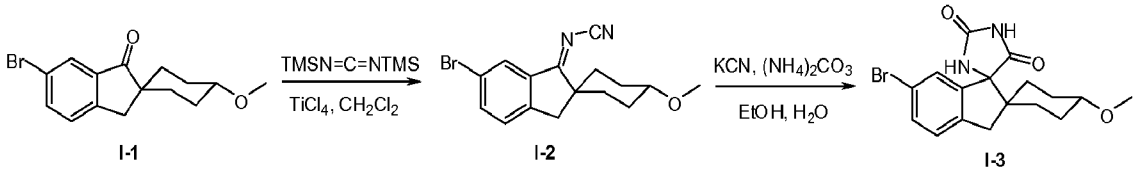
Procedure for preparation of (1r,4r)-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one



5 5A 6

The mixture of compound **5** and compound **5A** (21 g, 71.1 mmol) was dissolved in anhydrous THF (300 mL) and was cooled to 0 °C. NaH (11.38 g, 474 mmol, 60% in mineral oil) was added portionwise to the reaction mixture at 0 °C. After being stirred for 15 min at the same temperature, MeI (121.2 g, 854 mmol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and stirred at room temperature overnight. TLC (Hexane: EtOAc = 5: 1) showed the starting material was consumed. EtOH (200 mL) and brine (400 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude product (31 g), which was purified by column chromatography on silica gel (Hexane: EtOAc = 100: 1~30: 1) to give pure 1r,4r)-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**6**) (9.43 g, 62%) as a yellowish solid. **LCMS**: t_R = 4.749 min in 7 min chromatography MS (ESI) *m/z* 309.1 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.87 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 3.39 (s, 3H), 3.27 (m, 1H), 2.97 (s, 2H), 2.16 (m, 2H), 1.76 (m, 2H), 1.52 (m, 2H), 1.36 (m, 2H).

Example I-1. Synthesis of hydantoin-Method 1



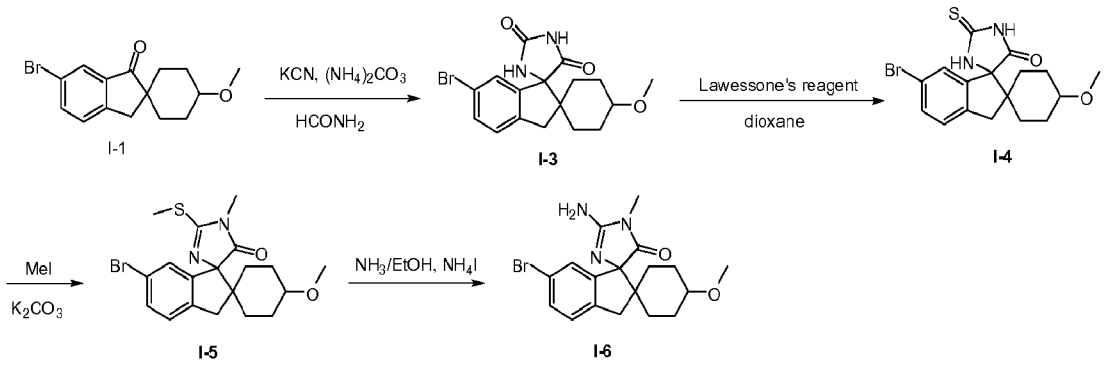
I-1 I-2 I-3

To a solution of compound I-1 (3.1 g, 10 mmol) in CH_2Cl_2 (100 mL) was added $TiCl_4$ (22 mL, 22 mmol, 1 M in CH_2Cl_2) under a nitrogen atmosphere. After stirring at room temperature for 1 h, bis-trimethylsilylcarbodiimide (4.5 mL, 20 mmol) was added.

After addition, the reaction mixture was stirred at room temperature overnight. Then the mixture was poured into ~200 g crashed ice, the organic layer was seperated and the aqueous layer was extracted with CH2Cl2, the combined organic layers were dried over anhydrous MgSO4, filtered and evaporated, the crude product was used directly for the next step without purification.

The crude product of compound I-2 (3.3 g, 10 mmol), KCN (2.6 g, 40 mmol), $(NH_4)_2CO_3$ (9.7 g, 100 mmol) were dissolved in EtOH (20 mL) and H_2O (20 mL). After heated at 75 °C in a steel autoclave overnight, the reaction mixture was cooled to room temperature and poured into H_2O. The precipitate was collected by filtration then washed with H_2O and EtOH. The yellow solid obtained was dried under vacumm and used in next step directly without purification.

Example I-2. Synthesis of Acylguanidine I-6



Procedure for preparation of hydantoin I-3-method 2

A steel autoclave was charged with a mixture of 6'-bromo-4-methoxyspiro [cyclohexane-1,2'-inden]-1'(3'*H*)-one (700 mg, 2.27 mmol), KCN (294 mg, 4.53 mmol), $(NH_4)_2CO_3$ (1.63 g, 16.98 mmol) and formamide (25 mL). The mixture was heated at 80 °C for 72 h. The reaction mixture was then cooled and poured over ice. After acidification with concentrated HCl (30 mL), the mixture was filtrated to collect the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (2 × 150 mL). The combined organic phase was dried and concentrated to give compound **I-3** (550 mg, 61%) as a white solid, which was used for the next step without purification. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.80 (s, 1H), 7.62 (m, 1H), 7.25 (m, 1H), 3.33 (m, 3H),

3.05-3.21 (m, 2H), 2.92 (s, 1H), 1.91-2.26 (m, 3H), 1.67 (m, 2H), 1.43 (m, 1H), 1.33 (m, 2H), 1.21 (m, 3H), 0.80 (m, 1H).

Procedure for preparation of compound I-4

A suspension of compound **I-3** (1 g, 2.64 mmol) and Lawesson's Reagent (1.68 g, 2.64 mmol) in anhydrous 1,4-dioxane (18 mL) was heated at 150 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column (petroleum ether: EtOAc = 8: 1 to 5: 1) to give compound **I-4** as a yellow solid (390 mg, 37%).

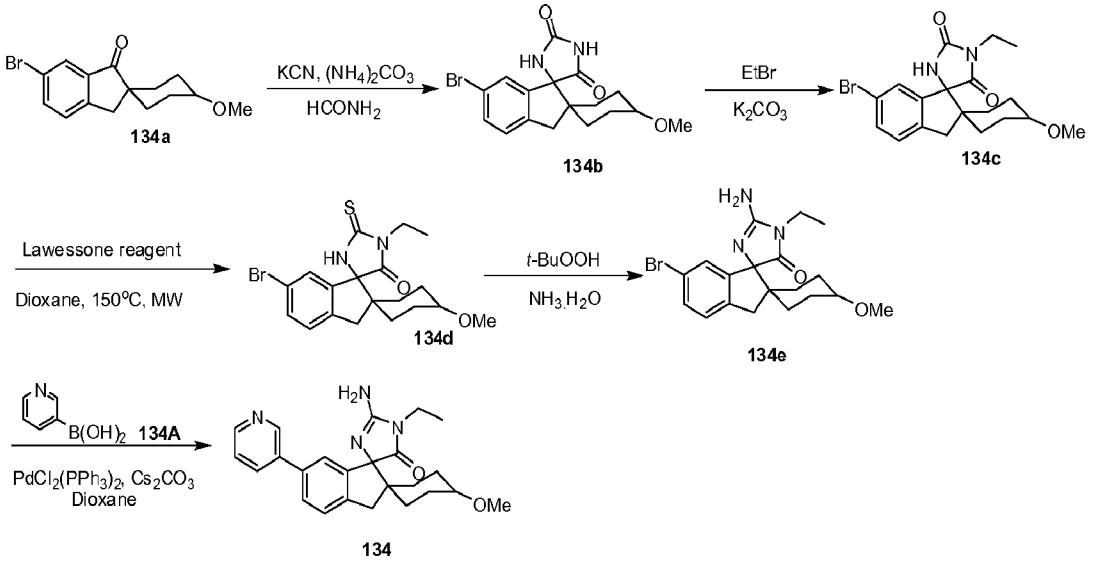
Procedure for preparation of compound I-5

To a solution of compound **I-4** (300 mg, 0.76 mmol) in CH_3CN (20 mL) was added a solution of K_2CO_3 (423 mg, 3.04 mmol) and MeI (447 mg, 3.04 mmol). The reaction mixture was heated at 60 °C for 10 min in a CEM microwave reactor. Then MeI (447 mg, 3.04 mmol) was added and the reaction mixture was heated at 60 °C for another 10 min. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by chromatography on silica gel (petroleum ether: EtOAc = 10: 1) to afford compound **I-5** (151 mg, 47%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.28 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 3.26 (s, 3H), 3.16-2.91 (m, 6H), 2.59 (s, 3H), 1.99-1.78 (m, 3H), 1.67 (t, 1H), 1.49 (m, 1H), 1.38-1.27 (m, 1H), 1.08 (m, 1H).

Procedure for preparation of compound I-6

A solution of compound **I-5** (45 mg, 0.10 mmol), NH_4I (78 mg, 0.53 mmol) in a solution of NH_3/EtOH (5 mL, 5 N) was heated at 120 °C in a CEM tube in a microwave reactor reactor for 3 h. After cooling, the mixture was concentrated *in vacuo* to give the residue, which was dissolved in CH_2Cl_2, filtrated and the filtrate was concentrated *in vacuo* to give compound **I-6** (25 mg, 60%) as a white solid, which was used for the next step without purification. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.53 (m, 1H), 7.22 (m, 2H), 3.39 (m, 6H), 3.15 (4, 2H), 2.96 (s, 3H), 2.55 (s, 2H), 2.11 (m, 4H), 1.93 (m, 2H), 1.55 (m, 3H), 1.42 (m, 4H).

Example 99. Synthesis of Compound 134



Procedure for preparation of compound 134b

To a solution of compound **134a** (1.2 g, 3.88 mmol) in $HCONH_2$ (15 mL) was added KCN (0.52 g, 7.76 mmol), $(NH_4)_2CO_3$ (3.68g, 38.8 mmol) at room temperature. The mixture was stirred in a steel autoclave at 90 °C for 72 h. TLC showed that the reaction was completed. The reaction mixture was then cooled and poured into ice water (25 mL). After acidification with concentrated HCl (5 mL), the mixture was filtrated to give the solid product (0.9 g yield 62%), which was used for the next step without purification. **^{1}H NMR** (DMSO-d_6 400 MHz): δ 10.75 (s, 1H), 8.43 (s, 1H), 7.48 (d, 1H), 7.25 (dd, J = 8.4 Hz, 2H), 3.25 (s, 3H), 3.09 (s, 1H), 2.95(s, 1H), 2.81 (d, 1H), 1.97 (d, 1H), 1.80 (m, 2H), 1.42 (m, 3H) , 1.15(m, 2H).

Procedure for preparation of compound 134c

To a solution of compound **134b** (200 mg, 0.52 mmol) in DMF (10 mL) was added ethyl bromide (60 mg, 0.56 mmol) and K_2CO_3 (72 mg, 0.8 mmol). The reaction mixture was stirred at room temperature overnight. TLC showed that the reaction was completed. The solution was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by preparative TLC to give compound **134c** (140 mg, 66%) as a yellow solid.

Procedure for preparation of compound 134d

To a solution of compound **134c** (40 mg, 0.10 mmol) and Lawesson's reagent (40 mg, 0.10 mmol) in anhydrous dioxane (5 mL) was stirred in microwave at 150 °C for 50 min. TLC showed that the reaction was completed. The mixture was concentrated under reduced pressure. The residue was purified by preparative TLC to give compound **134d** (12 mg, 29%). **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.39 (d, 1H), 7.15 (d, 1H), 6.95 (s, 1H), 3.75 (m, 3H), 3.30 (s, 3H), 3.08(s, 1H), 2.95 (s, 1H), 1.97 (m, 3H), 1.25 (m, 8H).

Procedure for preparation of compound 134e

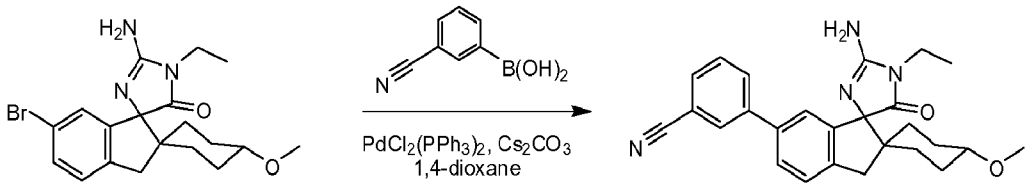
To a solution of compound **134d** (20 mg, 0.047 mmol) in MeOH (5 mL) and $NH_3.H_2O$(1 mL) was added *t*-BuOOH (0.4 g, 65 wt% in water). The reaction mixture was stirred at room temperature overnight. TLC showed that the reaction was completed. The solution was concentrated under reduced pressure and water was added. The mixture was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give compound **134e** (15.3 mg, 80%) as solid, which was used for the next step without purification.

Procedure for preparation of compound 134

To a solution of compound **134e** (36 mg, 0.089 mmol) and compound **134A** (16.4 mg, 0.133 mmol) in anhydrous dioxane (5 mL) was added CS_2CO_3 (0.7 mL, 2 mol/L) and $PdCl_2(PPh_3)_2$ (0.36 mg) under nitrogen. The mixture was stirred in microwave at 120 °C for 15 min. TLC showed that the reaction was completed. The mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH=10:1) and RP-HPLC to give **compound 134** (4.7 mg, 13%) as a white solid.**LC-MS** t_R = 0.866 min in 2 min chromatography, MS (ESI) *m/z* 405.2 [MH+]; **^{1}H NMR** (CD_3OD 400 MHz): δ 9.1 (s, 1H), 8.75 (s, 1H), 8.62 (d, 1H),

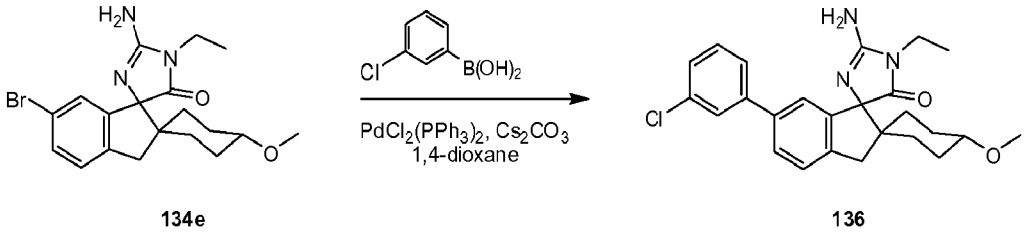
7.95 (t, 1H), 7.81 (d, 1H), 7.69 (s, 1H), 7.60 (d, 1H), 3.75 (m, 2H), 3.42 (s, 3H), 3.31(s, 1H), 3.25 (m, 2H), 2.12 (m, 2H), 1.95 (d, 1H), 1.48 (m, 5H), 1.25 (t, 3H).

Example 100. Synthesis of Compound 135



According to a similar synthesis of **compound 134**, compound **134e** (25 mg, 0.06 mmol) was reacted with 3-cyanophenylboronic acid (10 mg, 0.08 mmol) to give **compound 135** (7.6 mg, 30%) as a white solid. **LCMS** : t_R = 1.63 min in 3 min chromatography, MS (ESI) *m/z* 429 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.9 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.6 (m, 2H), 7.55 (m, 1H), 7.47 (s, 1H), 7.40 (m, 2H), 3.55-3.70 (m, 2H), 3.30 (s, 3H), 3.05-3.20 (m, 3H), 1.95-2.04 (m, 2H), 1.85 (m, 1H), 1.15-1.55 (m, 8H).

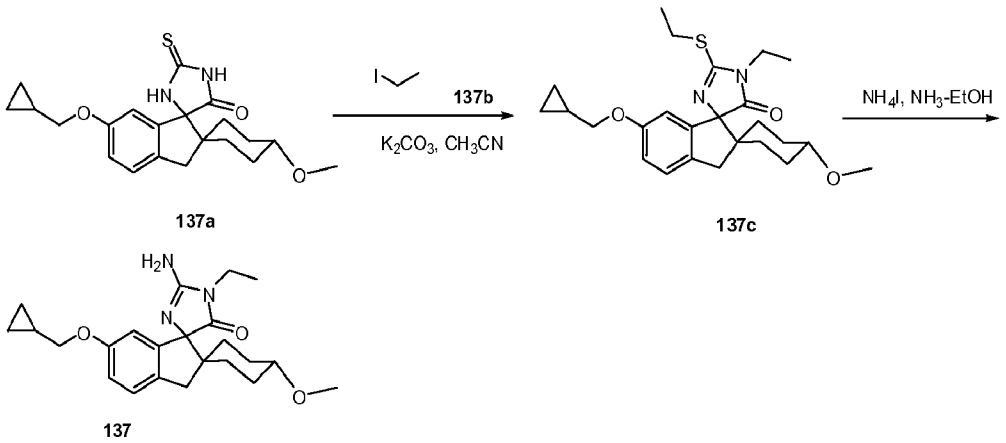
Example 101. Synthesis of Compound 136



134e 136

According to a similar synthesis of **compound 134**, compound **134e** (25 mg, 0.06 mmol) was coupled with 3-chlorophenylboronic acid (10 mg, 0.08 mmol) to give **compound 136** (7.1 mg, 28%) as a white solid. **LCMS** : t_R = 1.73 min in 3 min chromatography, MS (ESI) *m/z* 439.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400MHZ): δ 7.55-7.72 (m, 2H), 7.43-7.45 (d, J = 7.6 Hz, 1H), 7.36-7.38 (d, J = 6.8 Hz, 2H), 7.31-7.33 (m, 1H), 7.20-7.25 (d, J = 8.0 Hz, 1H), 3.70-3.80 (m, 1H), 3.60-3.70 (m, 1H), 3.26 (s, 3H), 3.10-3.20 (m, 3H), 1.93-2.05 (m, 2H), 1.79-1.82 (m, 1H), 1.21-1.38 (m, 5H), 1.12-1.19 (m, 3H).

Example 102. Synthesis of Compound 137



137a 137c 137

Procedure for preparation of Compound 137c

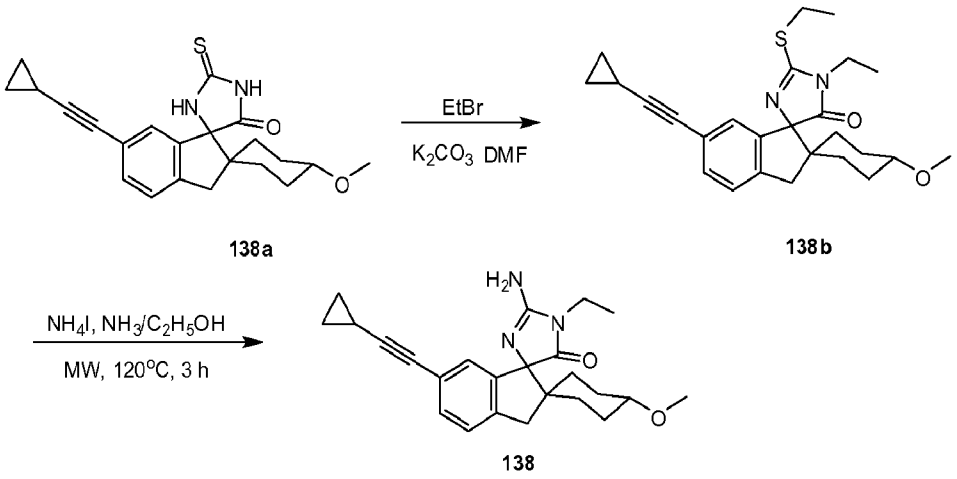
To a solution of compound **137a** (30 mg, 0.077 mmol) in CH_3CN (5 mL) was added K_2CO_3 (42.9 mg, 0.31 mmol) and compound **137b**(48.4 mg, 0.31 mmol), the reaction mixture was stirred at 60 °C for 10 min and at 100 °C for another 10 min in a CEM microwave reactor. The precipitate was filtered off and the filtrate was concentrated to give the crude product which was purified by preparative TLC on silica

gel eluting with hexane: EtOAc = 3: 1 to give compound **137c** (20 mg, 59%) as a white solid. **LC-MS** t_R = 1.511 min in 2 min chromatography, MS (ESI) *m/z* = 442.3 $[M+H]^+$.

Procedure for preparation of Compound 137

A solution of compound **137c** (20 mg, 0.045 mmol), NH_4I (54.9 mg, 0.45 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and preparative HPLC to give **compound 137** (4.60 mg 25%) as a white solid. **LC-MS** t_R = 0.864 min in 2 min chromatography, MS (ESI) *m/z* 398.1 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.6 (s, 1H), 3.79 (d, *J* = 8.0 Hz, 2H), 3.63 (d, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 3.20-3.11 (m, 1H), 3.10-2.92 (m, 2H), 2.1-1.9 (m, 2H), 1.9-1.8 (m, 1H), 1.74-1.56 (m, 1H), 1.51-1.32 (m, 2H), 1.32-1.25 (m, 3H), 1.22-1.15 (t, *J* = 8.0 Hz, 3H), 0.70-0.50 (m, 2H), 0.41-0.22 (m, 2H).

Example 103 Synthesis of Compound 138



138a 138b 138

Procedure for preparation of the compound 138b

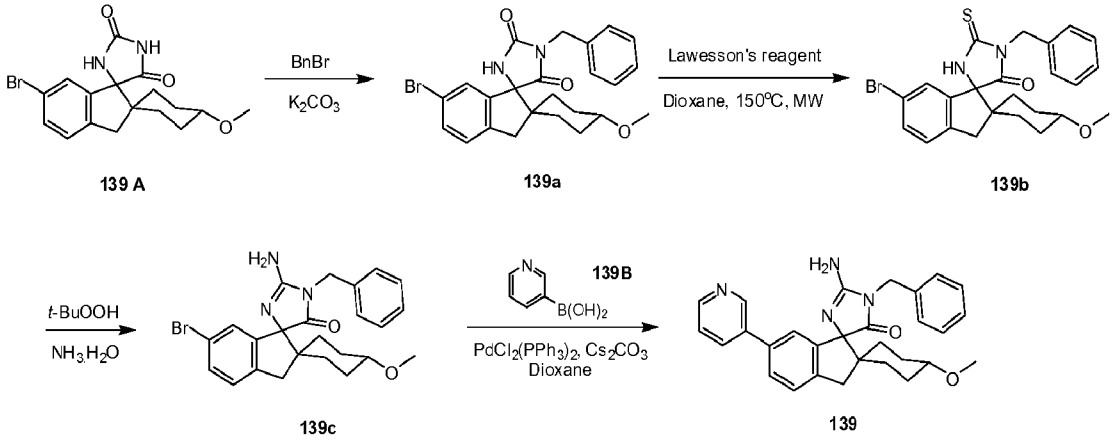
To a solution of compound **138a** (45 mg, 0.12 mmol) in DMF (3 mL) was added K_2CO_3 (50 mg, 0.36 mmol) and EtBr (33 mg, 0.3 mmol). The reaction mixture was stirred at 20 °C for 10 h. The mixture was filtered and filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel

(petroleum ether: ethyl acetate = 4: 1) to give compound **138b** (40 mg, 80%) as a white solid.

Procedure for preparation of compound 138

A suspension of compound **138b** (40 mg, 0.09 mmol) and NH_4I (100 mg, 0.7 mmol) in NH_3/EtOH (3 mL) was heated under 120 °C for 3 h in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (CH_2Cl_2: CH_3OH = 20: 1) to give **compound 138** (29 mg, 70%) as a white solid. **LCMS** : t_R = 1.65 min in 3 min chromatography, MS (ESI) *m/z* 392.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400MHZ): δ 7.11-7.18 (m, 2H), 6.87 (s, 1H), 3.48-3.55 (m, 2H), 3.21-3.28 (m, 3H), 3.02-3.06 (m, 1H), 2.93 (m, 1H), 1.81-1.97 (m, 2H), 1.70-1.80 (m, 1H), 1.41-1.49 (m, 1H), 1.15-1.40 (m, 5H), 1.05-1.10 (m, 3H), 0.72-0.78 (m, 2H), 0.54-0.61 (m, 2H).

Example 104. Synthesis of Compound 139



Procedure for preparation of the compound 139a

To a solution of compound **139A** (300 mg, 0.8 mmol) in DMF (5 mL) was added K_2CO_3 (140 mg, 1 mmol) and BnBr (150 mg, 0.9 mmol). The reaction mixture was stirred at 20 °C for 10 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel

(petroleum ether: ethyl acetate = 2: 1) to give compound **139a** (270 mg, 73%) as a white solid.

Procedure for preparation of the compound 2

A suspension of compound **139a** (260 mg, 0.55 mmol) and Lawesson's Reagent (250 mg, 0.61 mmol) in anhydrous 1, 4-dioxane (6 mL) was heated at 150 °C for 180 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel (CH_2Cl_2: CH_3OH = 15: 1) to give compound **139b** (122 mg, 46%) as a yellow solid.

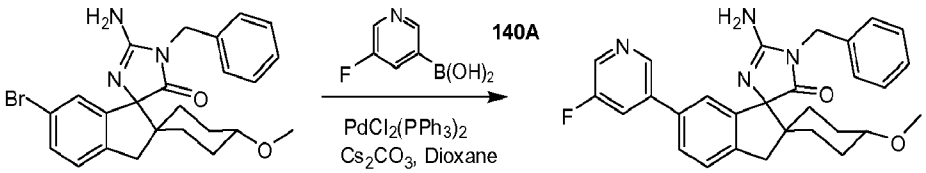
Procedure for preparation of the compound 139c

A solution of compound **139b** (120 mg, 0.25 mmol), *t*-BuOOH (450 mg, 5 mmol), $NH_3.H_2O$ (1 mL) in EtOH (4 mL) was stirred at 20 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (CH_2Cl_2: CH_3OH = 12: 1) to give compound **139c** (37 mg, 31%) as a white solid.

Procedure for preparation of compound 139

A suspension of compound **139c** (35 mg, 0.07 mmol), pyridine-3-boronic acid (10 mg, 0.09 mmol), $PdCl_2(PPh_3)_2$ (5 mg) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (2 mL) was heated under 120 °C for 15 min in CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative HPLC to give **compound 139** (11 mg, 31%) as a white solid. **LCMS**: t_R = 1.42 min in 3 min chromatography, MS (ESI) *m/z* 467 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400MHz): δ 8.85 (s, 1H), 8.58 (s, 1H), 8.30-8.40 (m, 1H), 7.66 (s, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.20-7.35 (m, 5H), 4.84-4.90 (m, 2H), 3.29-3.37 (m, 3H), 3.02-3.19 (m, 3H), 1.85-1.95 (m, 2H), 1.65 (m, 2H), 1.30-1.42 (m, 3H), 1.10-1.30 (m, 2H).

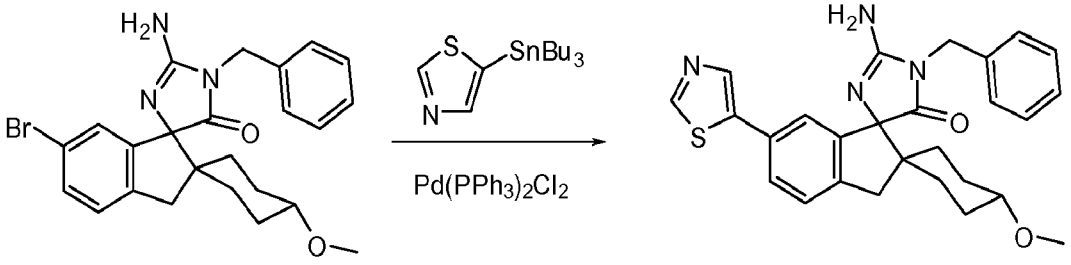
Example 105. Synthesis of Compound 140



139c 140

According to a similar synthesis of **compound 139**, compound **139c** (15 mg, 0.032 mmol) was coupled with compound **140A** (10 mg, 0.064 mmol) to give **compound 140** (4.5 mg, 30%) as a white solid. **LC-MS**: t_R = 0.997 min in 2 min chromatography, MS (ESI) *m/z* = 485 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.68 (s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 7.93 (m, 1H), 7.76 (dd, J = 2.4, 8.0 Hz, 1H), 7.56 (m, 2H), 7.38 (m, 5H), 4.96 (m, 2H), 3.36 (s, 3H), 3.29 (m, 2H), 3.23 (m, 1H), 2.01 (m, 3H), 1.79 (m, 1H), 1.46 (m, 3H), 1.31 (m, 2H).

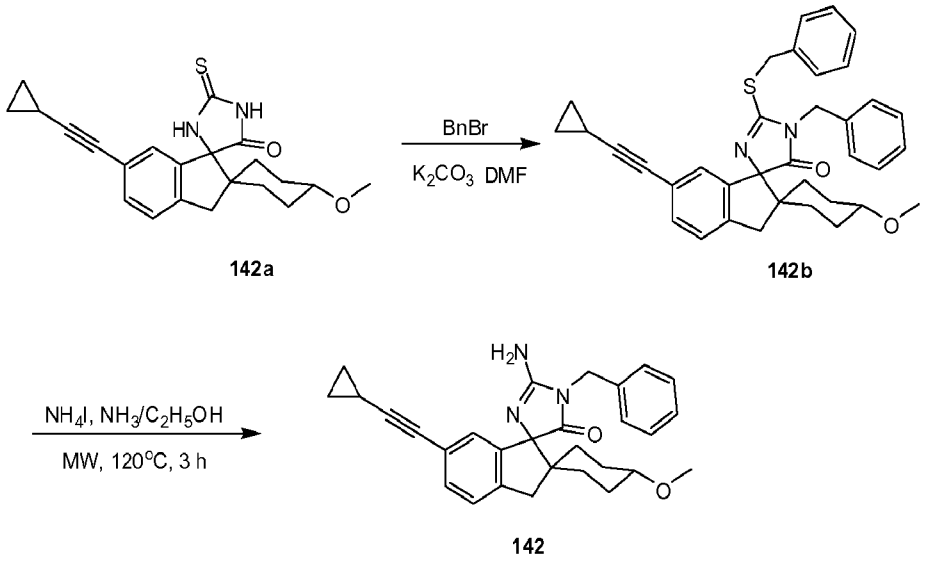
Example 106. Synthesis of Compound 141



139c 141

A suspension of compound **139c** (10 mg, 0.02 mmol), 5-tributylstannanyl-thiazole (4 mg, 0.1mmol), $PdCl_2(PPh_3)_2$ (2 mg, 0.003 mmol) in 1,4-dioxane (3 mL) was heated at 130 °C for 30 min in a CEM microwave reactor. The mixture was concentrated *in vacuo,* the residue was purified by preparative RP-HPLC to give **compound 141** (2.5 mg, 25%) as a white solid. **LCMS**: t_R = 1.79 min in 3 min chromatography, MS (ESI) *m/z* 473 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.0 (s, 1H), 8.22 (s, 1H), 7.70-7.72 (dd, J = 1.6, 9.2 Hz, 1H), 7.50-7.52 (m, 2H), 7.36-7.43 (m, 5H), 4.95 (m, 2H), 3.36 (s, 3H), 3.14-3.26 (m, 3H), 1.96 (m, 2H), 1.73-1.78 (m, 1H), 1.45-1.48 (m, 3H), 1.25-1.33 (m, 2H).

Example 107. Synthesis of Compound 142



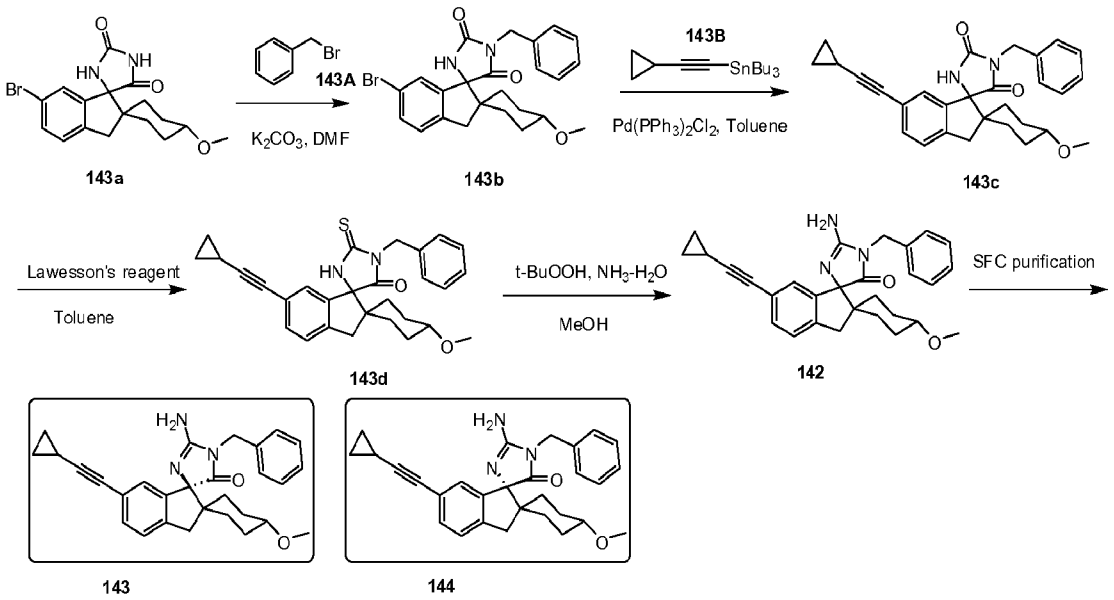
Procedure for preparation of the compound 142b

To a solution of compound **142a** (45 mg, 0.12 mmol) in DMF (3 mL) was added K_2CO_3 (50 mg, 0.36 mmol) and BnBr (50 mg, 0.3 mmol). The reaction mixture was stirred at room temperature for 10 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 5: 1) to give compound **142b** (70 mg, 95%) as a white solid.

Procedure for preparation of compound 142

A suspension of compound **142b** (70 mg, 0.125 mmol) and NH_4I (145 mg, 1 mmol) in NH_3/EtOH (4 mL) was heated under 120 °C for 3 h in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative HPLC to give **compound 142** (15.4 mg, 45%) as a white solid. **LCMS**: t_R = 1.72 min in 3 min chromatography, MS (ESI) *m/z* 454.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.30-7.44 (m 7H), 7.16 (s, 1H), 4.92 (s, 2H), 3.32-3.39 (m, 3H), 3.08-3.19 (m, 3H), 1.99 (m, 2H), 2.76 (m, 1H), 1.41-1.49 (m, 4H), 1.25-1.35 (m, 2H), 0.85-0.94 (m, 2H), 0.69-0.74 (m, 2H).

Example 108. Synthesis of Compounds 142, 143 and 144



Procedure for preparation of compound 143b

To a solution of compound **143a** (1.5 g, 2.74 mmol) in DMF (20 mL) was added K_2CO_3 (756 mg, 5.48 mmol) and compound **143A** (465 mg, 2.74 mmol). The mixture was stirred at room temperature for 3 h. The solution was added water (100 mL), the mixture was filtered to collect the solid and dried *in vacuo* to give compound **143b** (0.7 g, 38%) as a white solid, which was used in next step directly.

Procedure for preparation of compound 143c

To a solution of compound **143b** (470 mg, 1.0 mmol) in toluene (16 mL) was added compound **143B** (1.0 mL, 2.0 mmol) and $Pd(PPh_3)_2Cl_2$ (20 mg) under nitrogen. The mixture was stirred at 135 °C for 45 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was partitioned by EtOAc (50 mL) and aqueous CsF (4M, 50 mL). The separated aqueous layer was extracted with EtOAc (2 × 50 mL), the combined

organic layers were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC on silica gel (petroleum ether: ethyl acetate = 3: 1) afforded compound **143c** (400 mg, 61.4%).

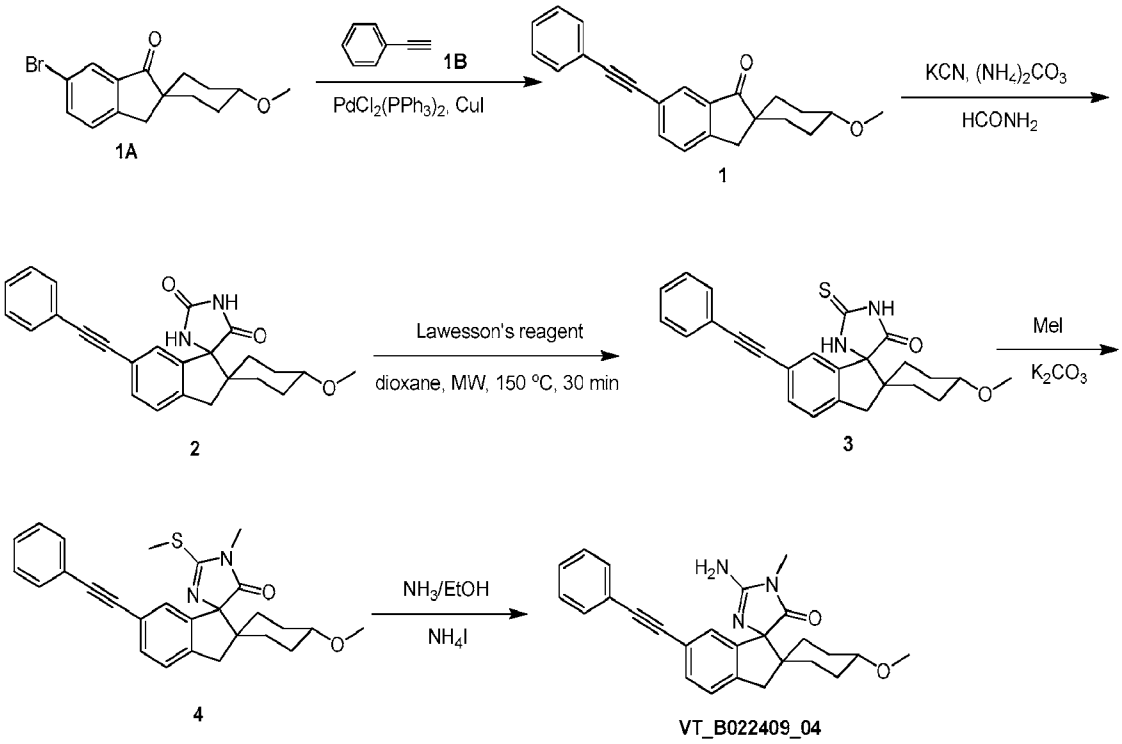
Procedure for preparation of compound 143d

To solution of compound **143c** (400 mg, 0.88 mmol) and Lawesson'reagent (356 mg, 0.88 mmol) in toluene (20 mL) was heated under 130 °C for 30 min in a CEM microwave reactor. The mixture was cooled, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 3: 1 to give compound **143d** (180 mg, 43.4%).

Procedure for preparation of compound 142

To a solution of compound **143d** (180 mg, 0.382 mmol) in a mixture of MeOH (25 mL) and NH_4OH (5 mL) was added *t*-BuOOH (690 mg, 7.65 mmol, 65% in water). The mixture was stirred at room temperature overnight, and was concentrated *in vacuo*. Water (15 mL) was added, the mixture was extracted with EtOAc (20 mL × 3). The combined organic layer were dried over Na_2SO_4 and concentrated to give the residue which was purified by HPLC to give **compound 142** (120 mg, 68%) as a white solid, which was purified by prep-SFC to give **compound 143** (25 mg, 21%); **LC-MS**: t_R = 1.102 min in 2 min chromatography, MS (ESI) *m/z* 453, 454 $[M+H]^+$; **SFC :ee** = 99.7%; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35 (m, 7H), 6.92 (s, 1H), 4.74 (s, 2H), 4.62 (s, 2H), 3.32 (s, 3H), 3.09 (m, 3H), 1.96 (m, 2H), 1.82 (m, 1H), 1.60 (m, 1H), 1.45 (m, 1H), 1.38 (m, 2H), 1.24 (m, 2H), 0.88 (m, 2H), 0.72 (m, 2H). And **compound 144** (40 mg, 33%); **LC-MS** : t_R = 1.104 min in 2 min chromatography, MS (ESI) *m/z* 453, 454 $[M+H]^+$; **SFC ee** = 99.0%; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.21 (m, 7H), 6.98 (s, 1H), 4.75 (m, 2H), 3.23 (s, 3H), 3.01 (m, 3H), 1.86 (m, 2H), 1.65 (m, 1H), 1.33 (m, 4H), 1.18 (m, 2H), 0.77 (m, 2H), 0.60 (m, 2H).

Example 109. Synthesis of Compound 145



Procedure for preparation of compound 145a

An oven dried three-necked round bottom flask equipped with condenser was charged with 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (**145A**) (500 mg, 1.62 mmol), Et_3N (40 mL) and Et_2NH (8 mL) under N_2 atmosphere. To this solution was added CuI (60 mg, 0.3 mmol), $PdCl_2(PPh_3)_2$ (115 mg, 0.16 mmol). The system was degassed once again, then ethynylbenzene (**145B**) (1.65 g, excess) was added and the mixture was heated to 80 °C (oil bath) for 12 h. The reaction was evaporated under reduced pressure and the residue was partitioned between EtOAc (50 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel eluting with 5%~20% EtOAc in hexane to afford compound **145a** (0.5 g, 93%) as a brown oil.

Procedure for preparation of compound 145b

A steel autoclave was charged with a mixture of compound **145a** (500 mg, 1.5 mmol), KCN (200 mg, 3.0 mmol), and $(NH_4)_2CO_3$ (1.1 g, 11.3 mmol), formamide (15 mL) was added. The mixture was heated at 100 °C for 72 h. The reaction mixture was then cooled and poured over ice. After acidification with concentrated HCl (20 mL), the mixture was filtrated to give the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (150 mL) for 2 times. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel eluting with 10%~33% EtOAc in hexane to afford compound **145b** (0.1 g, 82%) as a white solid.

Procedure for preparation of the compound 145c

A suspension of compound **145b** (100 mg, 0.25 mmol) and Lawesson's Reagent (101 mg, 0.25 mmol) in dry 1, 4-dioxane (10 mL) was heated under 150 °C for 35 min in CEM microwave reactor. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3:1) to give compound **145c** (50 mg, 80%) as a yellow solid.

Procedure for preparation of compound 145d

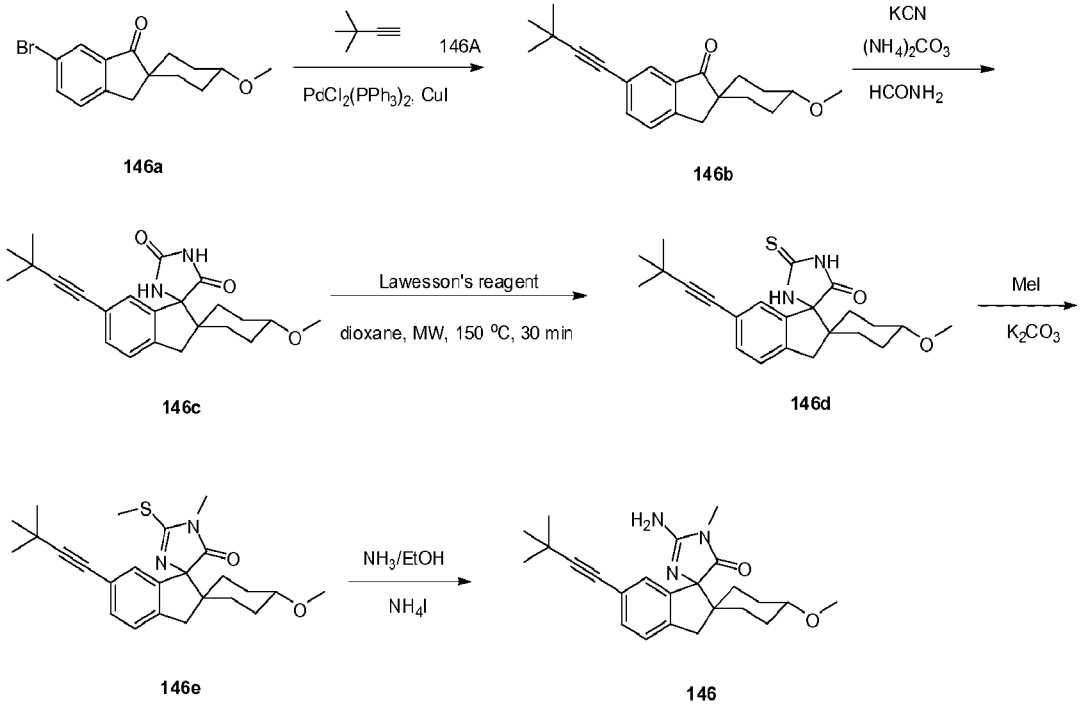
To a solution of compound **145c** (50 mg, 0.12 mmol) in CH_3CN (3.0 mL) was added K_2CO_3 (67 mg, 0.48 mmol). After stirring for 5 min, MeI (68 mg, 0.48 mmol) was added and the reaction mixture was heated at 60 °C for 10 min in microwave and then at 100 °C for another 10 min. The mixture was filtered and filtrate was concentrated under reduced pressure to give compound **145d** (50 mg, 80%) as a brown oil, which was used for the next step directly without further purification.

Procedure for preparation of compound 145

A solution of compound **145d** (50 mg, 0.113 mmol), NH_4I (164 mg, 1.13 mmol) in a solution of NH_3/EtOH (5 mL, 5 N) was heated at 120 °C in a CEM tube under microwave reactor for 3.5 h. After cooling, the mixture was concentrated under vacuum

to give the residue, which was purified by pre-HPLC (basic) to give **compound 145** (3.7 mg, 3%) as a white solid. **LC-MS** t_R = 1.162 min in 2 min chromatography, MS (ESI) *m/z* 414.2 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.51-7.55 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.35 (m, 3H), 7.30 (m, 2H), 3.39 (s, 3H), 3.3 (d, J = 16.0 Hz, 1H), 3.2-3.15 (m, 1H), 3.14 (s, 3H), 3.1 (s, 1H), 1.86-2.1 (m, 3H), 1.3-1.5 (m, 3H).

Example 110. Synthesis of Compound 146



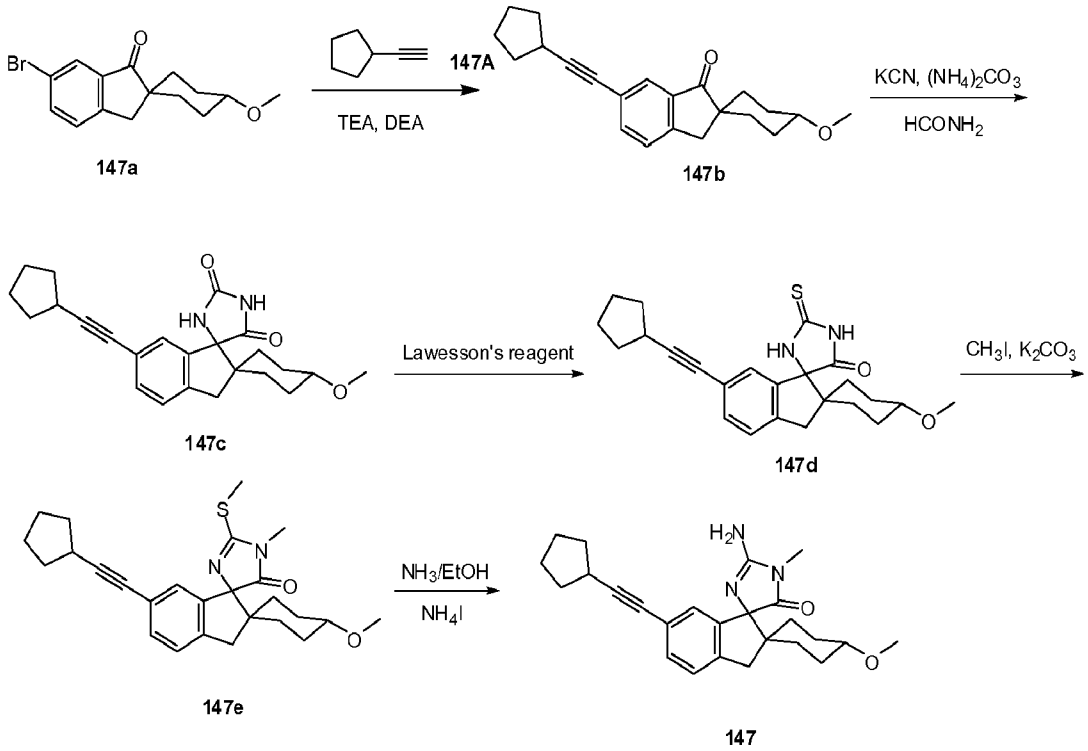
Applying the same reaction sequence as **compound 145**, compound **146a** (0.5 g, 1.61 mmol) was coupled with 3,3-Dimethyl-but-1-yne (**146A**) (3 mL, excess) to afford compound **146b** (300 mg, 50%) as a yellow oil. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 7.68 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 3.42 (s, 3H), 3.28 (m, 1H), 2.95 (s, 2H), 2.07 (m, 2H), 1.68 (m, 2H), 1.43 (m, 2H), 1.33 (m, 2H), 1.24 (s, 9H).

Compound **146b** (300 mg, 0.96 mmol) then condensed to hydantoin **146c** (100 mg, 27%) as a white solid, **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.27 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 3.29 (s, 3H), 3.07 (m, 1H), 2.95 (s, 2H), 2.07 (m, 2H), 1.86 (m, 2H), 1.68 (m, 2H), 1.35 (m, 2H), 1.24 (s, 9H).

Hydantoin **146c** (80 mg, 0.21mmol) reacted with Lawesson's Reagent (85mg, 0.21 mmol) in dry 1, 4-dioxane (10 mL) to afford compound **146d** (42 mg, 50%) as a white solid, which was methylated to give compound **146e** (30 mg, 66%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.31 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 3.43 (s, 3H), 3.26 (m, 1H), 3.21 (m, 2H), 2.94 (s, 3H), 2.59 (s, 3H), 1.77-1.81 (m, 2H), 1.81-1.99 (m, 2H), 1.26-1.31 (m, 2H), 1.31-1.41 (m, 2H), 1.26 (s, 9H).

Finally, compound **146e** (30 mg, 0.073 mmol) was converted to **compound 146** (1.7 mg, 6%) as a white solid. ***LCMS*:** t_R = 1.271 min in 2 min chromatography, MS (ESI) *m/z* 394 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.14 (d, J = 8 Hz, 2H), 6.87 (s, 1H), 3.38 (s, 3H), 3.24 (m, 1H), , 2.96 (s, 3H), 2.78 (s, 2H) 1.83-1.91 (m, 2H), 1.72-1.83 (m, 2H), 1.45-1.72 (m, 2H), 1.28-1.45 (m, 2H), 1.18 (s, 9H).

Example 111. Synthesis of Compound 147



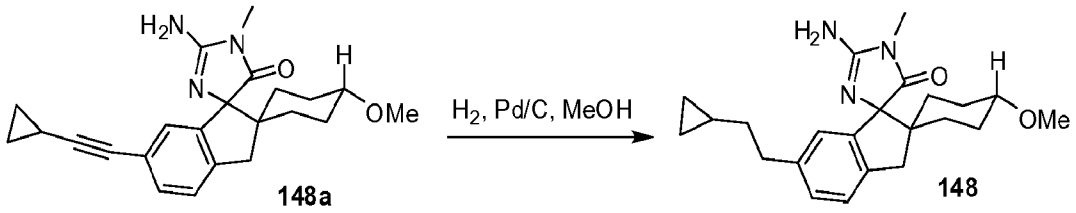
According to a similar synthesis of **compound 145**, compound **147a** (500 mg, 1.6234 mmol) was coupled with compound **147A** (11.2 g, 56.08 mmol) to afford

compound **147b** (370 mg, 71%) as a white solid. Compound **147b** (370 mg, 1.1491 mmol) was then condensed to hydantoin **147c** (100 mg, 23%) as a white solid.

Hydantoin **147c** (50 mg, 0.1276 mmol) then was reacted with Lawessons reagent (58 mg, 0.1531 mmol) to give compound **147d** (35 mg, 34%), which was methylated to give compound **147e** (27 mg, 72%) as a white solid.

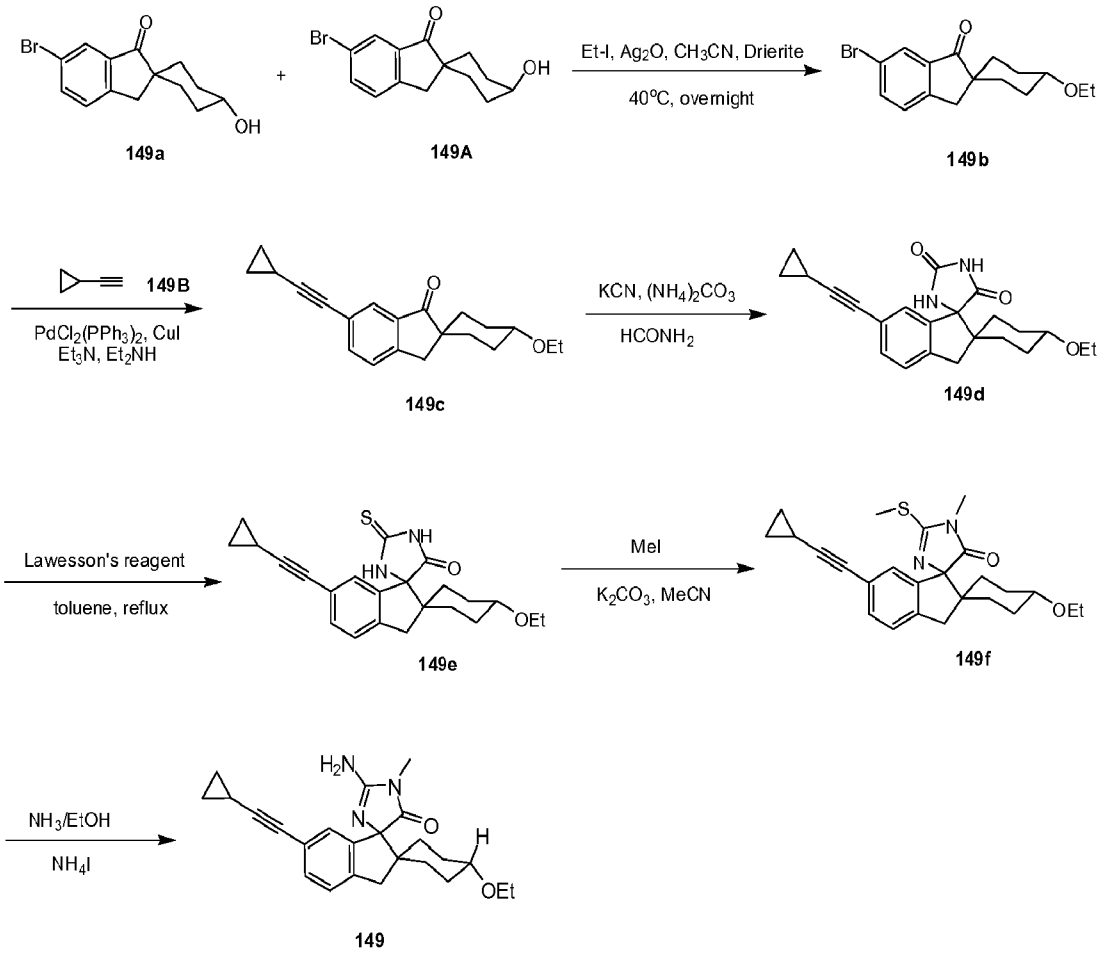
Finally, compound **147e** (27 mg, 0.06193 mmol) was converted to **compound 147** (13.0 mg, 52%) as a white solid. **LC-MS** t_R = 1.036 min in 2 min chromatography, MS (ESI) *m/z* 405.9 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.36 (m, 2H), 7.23 (s, 1H), 8.11 (m, 1H), 3.38 (s, 3H), 3.23-3.07 (m, 6H), 3.79-3.88 (m, 1H), 1.94-2.14 (m, 4H), 1.56-1.93 (m, 7H), 1.23-1.55 (m, 5H).

Example 112. Synthesis of Compound 148



To a 25 mL round bottom flask was placed the alkyne **148a** (6 mg, 0.016 mmol) and it was dissolved in MeOH (2 mL). To this solution was added Pd/C (< 1 mg) and a ballon containing H_2 was attached to the flask. The reaction atmosphere was flushed twice with H_2 and then allowed to stir at room temperature for 20 minutes. The reaction was filtered through Celite and the filtrate concentrated under reduce pressure. The crude material was purified on a HPLC (Gilson, 10 – 90% MeOH / H_2O with 0.1% TFA as the eluent). The corresponding fractions were combined and concentrated yielding the final product **compound 148** (2.7 mg, 0.007 mmol, 44% yield). **LCMS**: M+H = 382.1; **^{1}H NMR**(CD_3OD, 400 MHz) δ 7.26 – 7.21 (m, 2H), 7.02 (s, 1H), 3.34 (s, 3H), 3.19 (s, 3H), 3.12 (m, 2H), 2.70 (m, 2H), 1.99 – 1.83 (m, 3H), 1.47 – 1.28 (m, 9H), 0.67 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H) ppm.

Example 113. Synthesis of Compound 149



Procedure for preparation of compound 149b

A mixture containing compound **149a** and compound **149A** (4 g, 13.6 mmol, 60% purity) in CH_3CN (40 mL) was added Ag_2O (9.5 g, 40.8 mmol) and $MgSO_4$ (10 g) at room temperature. After the mixture was stirred for 10 min at room temperature, EtI (42 g, 172 mmol) was added dropwise to the former solution. The reaction mixture was heated overnight at 40 °C. The mixture was filtered and the filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to afford crude compound **2**, which was purified by column chromatography on silica gel eluting with Hexane: EtOAc = 30: 1 to 5: 1 to give compound **149b** (0.81 g, 40%) as yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.75-7.81 (s, 1H), 7.50-7.55 (d, 1H), 7.25-7.28 (m, 1H), 3.46-3.54 (m, 2H), 3.20-3.30

(m, 1H), 2.85-2.90 (s, 2H), 2.00-2.09 (m, 2H), 1.55-1.62 (m, 2H), 1.20-1.40 (m, 4H), 1.10-1.19 (t, 3H).

Procedure for preparation of compound 149

According to a similar synthesis of **compound 145**, compound **149b** (0.8 g, 2.48 mmol)was coupled compound **149B** (2 mL, excessive) under a nitrogen atmosphere to give compound **149c** (0.51 g, 67%) as a brown solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.67 (s, 1H), 7.52-7.49 (d, J = 8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 3.53-3.45 (m, 2H), 3.32-3.25 (m, 1H), 2.93 (s, 2H), 2.11-2.03 (m, 2H), 1.73-1.65 (m, 2H), 1.42-1.27 (m, 5H), 1.17-1.12 (m,3H), 0.83 (m, 2H), 0.74 (m, 2H).

Compound **149c** (0.51 g, 1.65 mmol) was then condensed to hydantoin **149d** (160 mg, 25%) as a gray solid. **^{1}H NMR**: (DMSO-d_6 400 MHz): δ 10.75 (s, 1H), 8.39 (s, 1H), 7.24 (m, 2H), 6.99 (s, 1H), 3.43-3.39 (m, 2H), 3.15 (m, 1H), 2.99-2.86 (m, 2H), 1.97 (m, 1H), 1.78 (m, 2H), 1.49 (m, 1H), 1.36-1.14 (m, 5H), 1.07-1.02 (m, 3H), 0.87-0.82 (m, 2H), 0.73-0.68 (m, 2H).

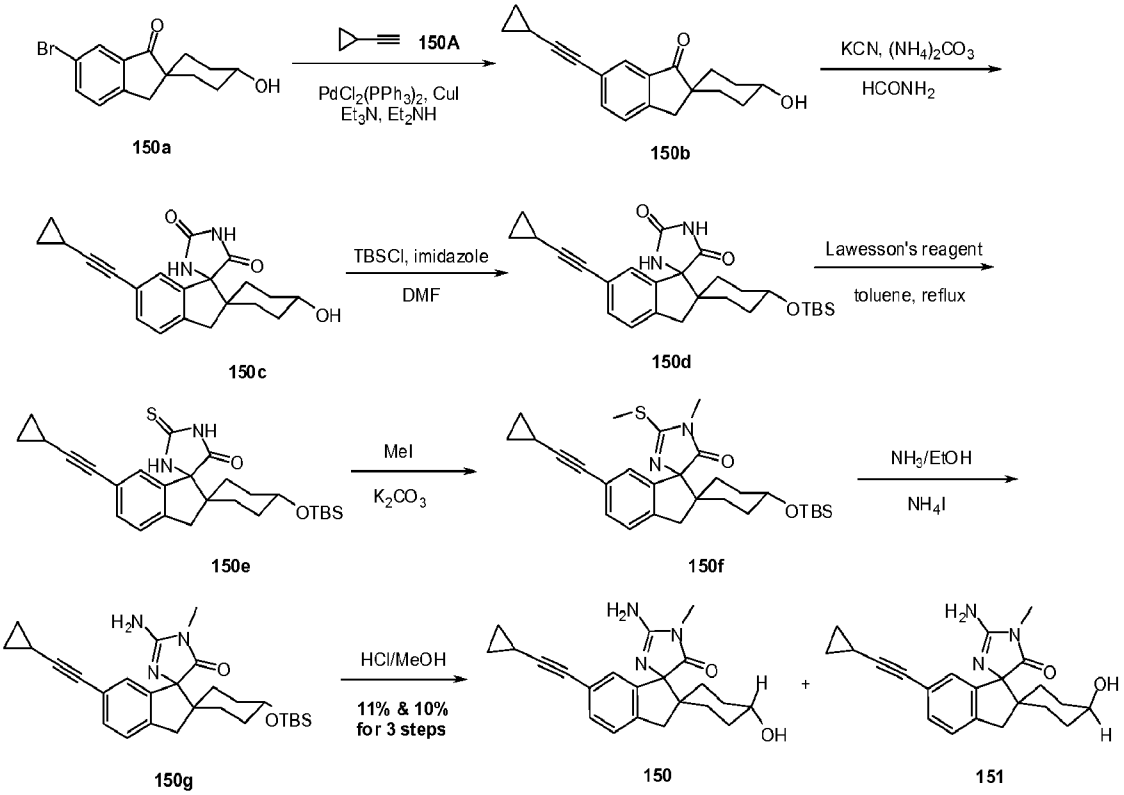
And Compound **149d** (130 mg, 0.34 mmol) was reacted with Lawesson's reagent (139 mg, 0.34 mmol) in toluene (8 mL) to give compound **149e** (100 mg, 74%) as a white solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 8.03 (s, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.09 (s, 1H), 3.48-3.43 (m, 2H), 3.18-3.13 (m, 1H), 3.09-2.96 (m, 2H), 2.10 (s, 1H), 2.01-1.89 (m, 3H), 1.40-1.23 (m, 5H), 1.13 (m, 3H), 0.80 (m, 2H), 0.72 (m, 2H).

Compound **149e** (100 mg, 0.25 mmol) was dimethylated with MeI (2 mL, excessive) to give compound **149f** (85 mg, 79%) as a white solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.18 (d, J = 10 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 3.46-3.40 (m, 2H), 3.16-3.09 (m, 2H), 2.99-2.95 (m, 1H), 2.93 (s, 3H), 2.58 (s, 3H), 1.92-1.78 (m, 3H), 1.65 (m, 1H), 1.50 (m, 1H), 1.38-1.17 (m, 4H), 1.13-1.06 (m, 4H), 0.77-0.74 (m, 2H), 0.72-0.66 (m, 2H).

Finally, compound **149f** (30 mg, 0.071 mmol) was converted to **compound 149** (8 mg, 29%) as a white solid. **LC-MS**: t_R = 1.124 min in 2 min chromatography, MS

(ESI) *m/z* 392.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.13 (m, 2H), 6.82 (s, 1H), 3.48-3.43 (m, 2H), 3.15-3.12 (m, 1H), 3.03-2.96 (m, 2H), 2.93 (s, 3H), 1.91-1.82 (m, 2H), 1.74-1.71 (m, 1H), 1.55-1.45 (m, 1H), 1.36-1.15 (m, 5H), 1.12-1.06 (m, 3H), 0.79-0.76 (m, 2H), 0.63-0.57 (m, 2H).

Example 114. Synthesis of Compounds 150 and 151



According to a similar synthesis of **compound 145**, compound **150a** (0.7 g, 2.38 mmol) was coupled with compound **150A** (2 mL, excessive) to give compound **150b** (0.53 g, 79%) as a brown solid. **^{1}H NMR**: (CDCl3 400 MHz): δ 7.67 (s, 1H), 7.52-7.49 (dd, J = 8 Hz, 1H), 7.38-7.26 (m, 1H), 3.69 (m, 1H), 2.94 (s, 2H), 2.00-1.90 (m, 2H), 1.76-1.65 (m, 2H), 1.50-1.47 (m, 1H), 1.44-1.31 (m, 5H), 0.86-0.77 (m, 2H), 0.76-0.71 (m, 2H).

Compound **150b** (0.53 g, 1.89 mmol) was then condensed to hydantoin **150c** (0.27 g, 41%) as a gray solid.**^{1}H NMR**: (DMSO-d_6 400 MHz): δ 10.74 (s, 1H), 8.39 (s, 1H), 7.27 (m, 2H), 7.01 (s, 1H), 4.58 (m, 1H), 2.99-2.88 (m, 2H), 1.84-1.63 (m, 3H),

1.57-1.45 (m, 1H), 1.38-1.16 (m, 5H), 1.06-0.98 (m, 1H), 0.87-0.86 (m, 2H), 0.77-0.69 (m, 2H).

A mixture of compound **150c** (160 mg, 0.46 mmol), TBSCl (104 mg, 0.69 mmol) and imidazol (78 mg, 1.15 mmol) in DMF (2 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by prep-TLC (petroleum ether: EtOAc = 2:1) to give compound **150d** (94 mg, 44%) as a white solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.36-7.34 (d, J = 9.2 Hz, 1H), 7.28-7.19 (m, 2H), 3.64-3.51 (m, 1H), 3.20-3.02 (m, 2H), 2.05-1.86 (m, 2H), 1.86-1.57 (m, 2H), 1.55-1.42 (m, 3H), 1.41-1.21 (m, 2H), 0.91 (s, 9H), 0.88-0.86 (m, 2H), 0.85-0.79 (m, 2H), 0.09 (s, 6H).

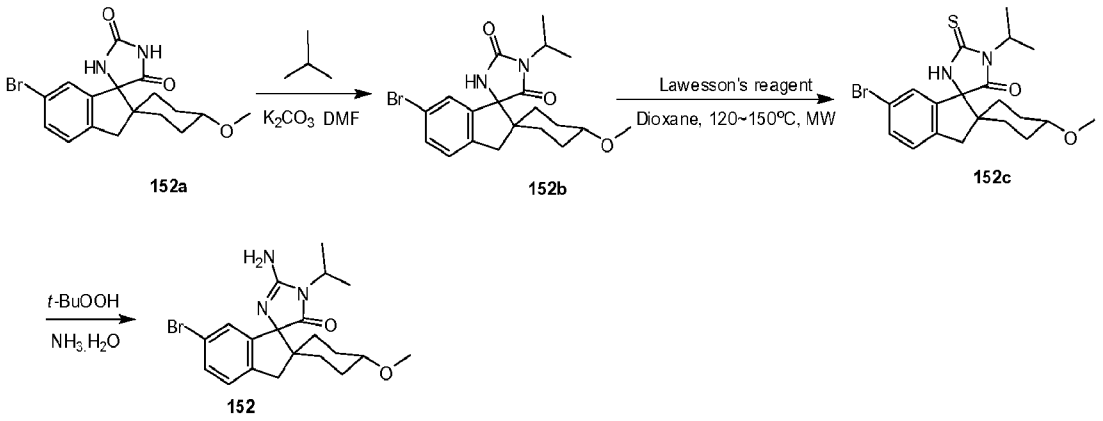
Then compound **150d** (60 mg, 0.129 mmol) was reacted with Lawesson's reagent (52 mg, 0.129 mmol) in toluene (5 mL) to give compound **150e** (38 mg, 61%) as a yellow solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.29-7.26 (m, 1H), 7.17-7.09 (m, 2H), 3.49 (m, 1H), 3.06-2.93 (m, 2H), 1.95-1.29 (m, 10H), 0.88-0.76 (m, 11H), 0.75-0.70 (m, 2H), 0.01 (s, 6H).

Compound **150e** (40 mg, 0.083 mmol) was dimethylated with MeI (1 mL, excessive) and K_2CO_3 (46 mg, 0.33 mmol) in MeCN (2 mL) to give compound **150f** (25 mg, impure), which was converted to compound **150g** (20 mg), which was used in next step directly without purification.

Finally, compound **150g** (20 mg, 0.042 mmol) in HCl/MeOH (5 N, 5 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by prep-HPLC (basic) to give **compound 150** (2.4 mg, 11% for 3 steps), **LC-MS**: t_R = 1.025 min in 2 min chromatography, MS (ESI) m/z 364.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.27-7.21 (m, 2H), 6.95 (s, 1H), 3.49-3.41 (m, 1H), 3.09 (s, 2H), 3.06 (s, 3H), 1.94-1.77 (m, 3H), 1.62-1.24 (m, 7H), 0.91-0.83 (m, 2H), 0.73-0.67 (m, 2H); and **compound 151** (2.3 mg, 10% for 3 steps), **LC-MS**: t_R = 1.073 min in 2 min chromatography, MS (ESI) m/z 364.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHZ): δ 7.28-7.21 (m, 2H), 6.98 (s, 1H), 3.95

(m, 1H), 3.15-3.03 (m, 5H), 1.98-1.89 (m, 1H), 1.82-1.60 (m, 5H), 1.57-1.39 (m, 2H), 1.12-1.04 (m, 1H), 0.91-0.81 (m, 2H), 0.73-0.68 (m, 2H).

Example 115. Synthesis of Compound 152



152a 152b 152c 152

Procedure for preparation of compound 152b

To a solution of compound **152a** (300 mg, 0.8 mmol) in DMF (6 mL) was added K_2CO_3 (220 mg, 0.95 mmol) and 2-iodo-propane (160 mg, 0.9 mmol). The reaction mixture was stirred at 20 °C for 10 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 2: 1) to give compound **152b** (300 mg, 90%) as a white solid.

Procedure for preparation of compound 152c

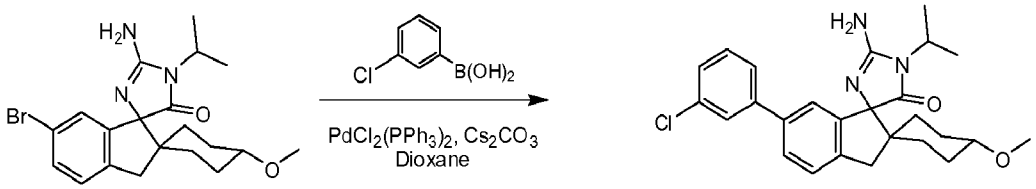
A suspension of compound **152b** (120 mg, 0.3 mmol) and Lawesson's Reagent (240 mg, 0.6 mmol) in anhydrous 1,4-dioxane (5 mL) was heated at 150 °C for 60 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 3: 1) to give compound **152c** as a yellow solid (63 mg, 50%).

Procedure for preparation of compound 152

A solution of compound **152c** (40 mg, 0.09 mmol), *t*-BuOOH (180 mg, 1.9 mmol) and $NH_3.H_2O$ (1 mL) in EtOH (4 mL) was stirred at 20 °C for 10 h. The mixture

was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (CH_2Cl_2: CH_3OH = 15: 1) to give compound **152** (23 mg, 60%) as a white solid.

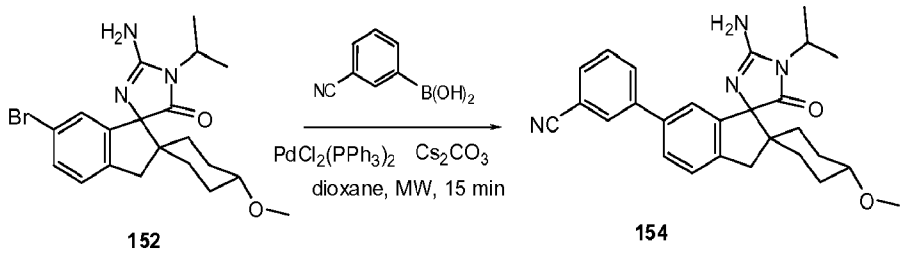
Example 116. Synthesis of Compound 153



152 153

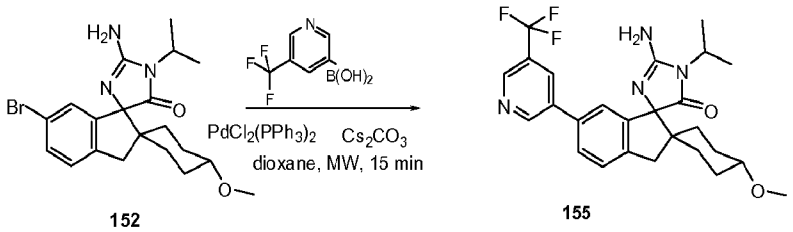
A suspension of compound **152** (20 mg, 0.05 mmol), 3-chrolophenylboronic acid (10 mg, 0.06 mmol), $PdCl_2(PPh_3)_2$ (5 mg) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (3 mL) was heated under 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo,* the residue was purified by preparative HPLC to give **compound 153** (7.9 mg, 55%) as a white solid. **LCMS**: t_R = 1.79 min in 3 min chromatography, MS (ESI) *m/z* 452.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.60-7.67 (d, 2H), 7.50-7.56 (d, 1H), 7.45-7.50 (d, 2H), 7.43-7.48 (m, 1H), 7.35-7.38 (s, 1H), 4.27-4.35 (m, 1H), 3.38 (s, 3H), 3.14-3.25 (m, 3H), 1.94-2.13 (m, 3H), 1.33-1.53 (m, 11H).

Example 117. Synthesis of Compound 154



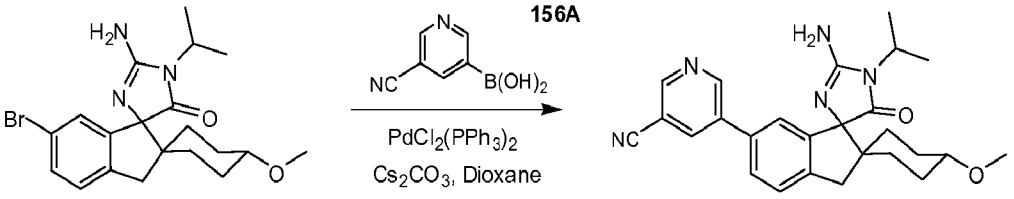
According to a similar synthesis of **compound 153**, compound **152** (10 mg, 0.024 mmol) was coupled with 3-cycnophenylboronic acid (4 mg, 0.024 mmol) to give **compound 154** (4.3 mg, 45%) as a white solid. **LCMS**: t_R = 1.71 min in 3 min chromatography, MS (ESI) *m/z* 443 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.94 (s, 1H), 7.88-7.90 (m, 2H), 7.66-7.70 (m, 1H), 7.57-7.63 (m, 2H), 7.42-7.45 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 4.20-4.28 (m, 1H), 3.37 (s, 3H), 3.08-3.20 (m, 3H), 1.91-2.08 (m, 3H), 1.64-1.66 (m, 1H), 1.30- 1.45 (m, 10H).

Example 118. Synthesis of Compound 155



According to a similar synthesis of **compound 153**, compound **152** (10 mg, 0.024 mmol) was coupled with 3-trifluromethyl-5-pyridineboronic acid (6 mg, 0.024 mmol) to give **compound 155** (5.3 mg, 52%) as a white solid. **LCMS**: t_R = 1.71 min in 3 min chromatography, MS (ESI) *m/z* 487 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.04 (s, 1H), 8.86 (s, 1H), 8.55 (s, 2H), 7.66-7.68 (m, 1H), 7.50-7.52 (d, J = 7.2 Hz, 1H), 7.15 (s, 1H), 4.21-4.26 (m, 1H), 3.37 (s, 3H), 3.11-3.22 (m, 3H), 1.94-2.10 (m, 3H), 1.61-1.70 (m, 1H), 1.31-1.47 (m, 10H).

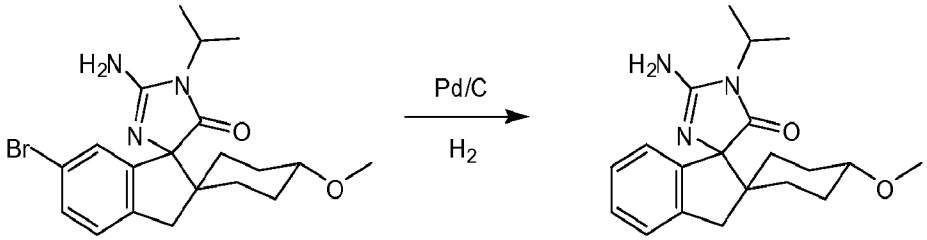
Example 119. Synthesis of Compound 156



152 156

According to a similar synthesis of **compound 153**, compound **152** (10 mg, 0.024 mmol) was coupled with compound **156A** (17 mg, 0.0714 mmol) to give product **compound 156** (6 mg, 29%) as a white solid. **LC-MS** t_R = 0.977 min in 2 min chromatography, MS (ESI) *m/z* 444 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 9.06 (s, 1H), 8.87 (s, 1H), 8.46 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 4.28 (m, 1H), 3.34 (s, 3H), 3.17 (m, 3H), 2.01 (m, 1H), 2.89 (m, 2H), 1.52 (m, 3H), 1.46 (m, 6H), 1.33 (m, 2H).

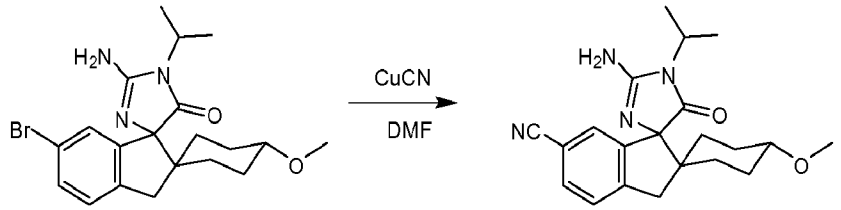
Example 120. Synthesis of Compound 157



152 157

To a solution of compound **152** (20 mg, 0.048 mmol) in MeOH (2 mL) was added Pd/C (10 mg). The reaction mixture was stirred at room temperature for 2 h. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by preparative HPLC to give **compound 157** (3.0 mg, 19%) as a white solid. **LC-MS** t_R = 0.935 min in 2 min chromatography, MS (ESI) *m/z* 342 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.41 (s, 2H), 7.38 (m, 1H), 7.17 (d, J = 7.5 Hz, 1H), 4.29 (m, 1H), 3.38 (s, 3H), 3.15 (m, 3H), 2.17-1.99 (m ,2H), 1.82 (m, 1H), 1.58 (m, 3H), 1.48-1.23 (m, 8H).

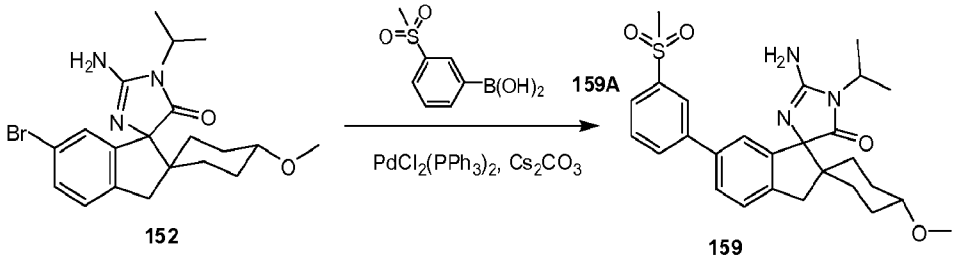
Example 121. Synthesis of Compound 158



152 158

A suspension of compound **152** (20 mg, 0.048 mmol), CuCN (30 mg, excess) and $Pd(PPh_3)_4$ (8 mg) in dry DMF (2 mL) was heated under 180 °C for 45 min in a CEM microwave reactor. Water (10 mL) was added and the mixture was extracted with EtOAc (10 mL*3). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC to give **compound 158** (8.0 mg, 51%) as a white solid. **LC-MS** t_R = 0.916 min in 2 min chromatography, MS (ESI) *m/z* 367 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.65 (d, J = 8.0 Hz,1H), 7.51 (d, J = 7.6 Hz,1H), 7.32 (s, 1H), 4.21 (m, 1H), 3.39 (s, 3H), 3.16 (m, 3H), 2.07 (m ,1H), 2.01-1.89 (m, 2H), 1.66 (m, 1H), 1.43 (m, 3H), 1.38 (m, 4H), 1.34-1.22 (m, 3H).

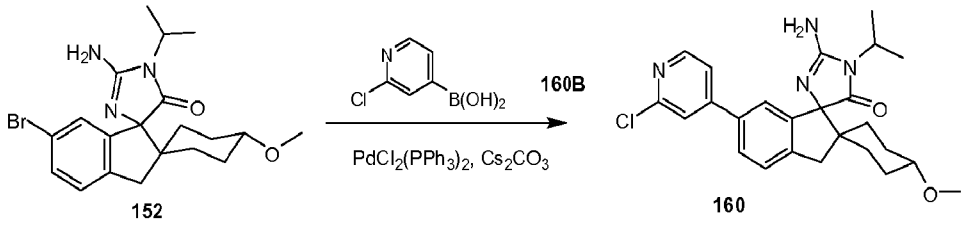
Example 122. Synthesis of Compound 159



152 159

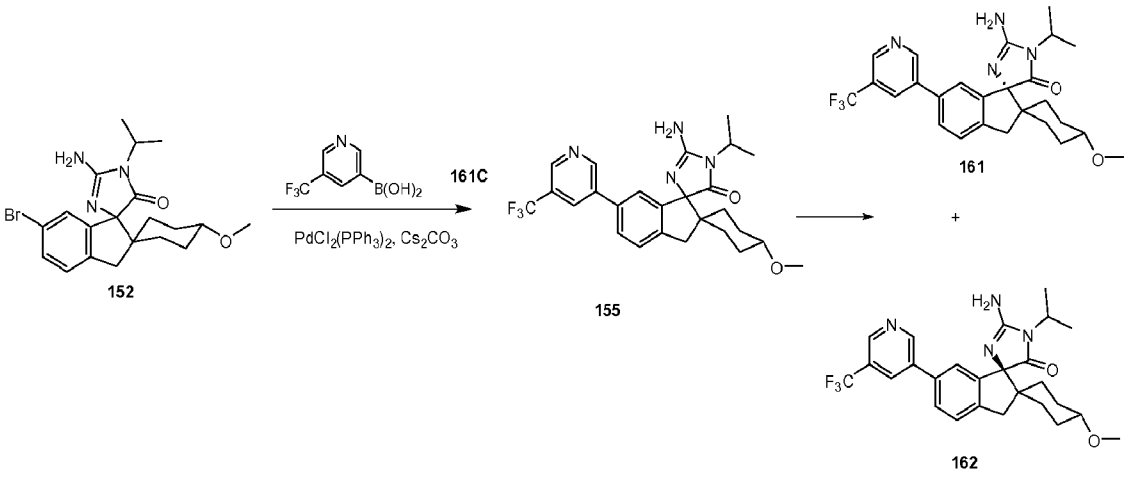
According to a similar synthesis of **153**, compound **152** (20 mg, 0.047 mmol) was coupled with compound **159A** (12 mg, 0.094 mmol) to give **compound 159** (10.6 mg, 30%) as a white solid. **LC-MS** t_R = 1.118 min in 2 min chromatography, MS (ESI) *m/z* 496 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.16 (s, 1H), 7.95-8.00 (m, 2H), 7.72-7.75 (m, 2H), 7.53-7.57 (m, 2H), 4.29-4.36 (m, 1H), 3.38 (s, 3H) 3.26-3.27 (m, 1H), 3.20-3.23 (d, 2H), 3.19 (s, 3H), 2.11-2.14 (m, 1H), 2.04 (m, 1H), 1.94-1.97 (m, 1H), 1.49-1.54 (m, 3H), 1.45-1.49 (m, 6H), 1.31-1.41 (m, 2H).

Example 123. Synthesis of Compound 160



According to a similar synthesis of **153**, compound **152** (40 mg, 0.095 mmol) was coupled with compound **160A** (30 mg, 0.19 mmol) to give **compound 160** (15.0 mg, 35%) as a white solid. **LC-MS** t_R = 1.026 min in 2 min chromatography, MS (ESI) *m/z* 453 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.41 (d, J = 5.2. Hz, 1H), 7.82 (d, J = 10.0 Hz, 2H), 7.69 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 4.33 (m, 1H), 3.38 (s, 3H), 3.22 (m, 3H), 2.23 (m, 1H), 2.04 (m, 1H), 1.96 (m, 1H), 1.49 (m, 10H), 1.37 (m, 1H).

Example 124. Synthesis of Compounds 161 and 162



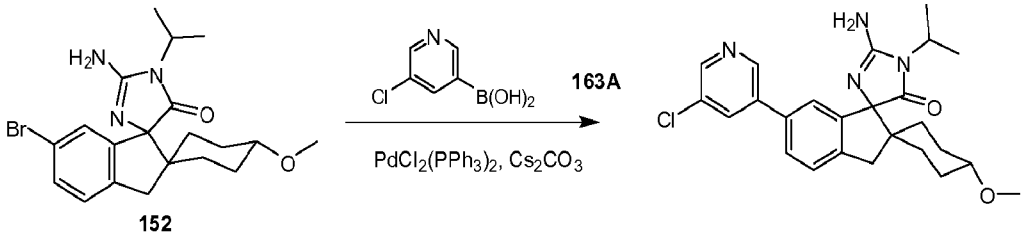
According to a similar synthesis of **compound 153**, compound **152** (200 mg, 0.476 mmol) was coupled with compound **161C** (137 mg, 0.714 mmol) to give **compound 155** (105 mg, 47%) as a white solid. **LC-MS** t_R = 1.164 min in 2 min chromatography, MS (ESI) *m/z* 487 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.01 (s, 1H), 8.88 (s, 1H), 8.39 (s, 1H), 7.82-7.58 (m, 3H), 4.33 (m, 1H), 3.38 (s, 3H), 3.21 (m,

3H), 2.17-1.94 (m, 3H), 1.57 (m, 10H), 1.37 (m, 1H).^{19}**F NMR** (CD_3OD 19F 400 MHz): δ -63.915

Compound 155 (50 mg) was separaed by SFC to give **compound 162** (10.30 mg) **LC-MS** t_R = 1.169 min in 2 min chromatography, MS (ESI) *m/z* 487 $[M+H]^+$. **SFC:** t_R = 5.16 min in 15 min chromatography, ee = 100%; ^{1}**H NMR** (CD_3OD 400 MHz): δ 9.04 (s, 1H), 8.86 (s, 1H), 8.32 (s, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.34 (s, 1H), 4.25 (m, 1H), 3.38 (s, 3H), 3.17 (m, 3H), 2.09 (m, 1H), 1.95 (m, 2H), 1.66 (m, 1H), 1.47 (m, 4H), 1.38 (m, 4H), 1.31 (m, 2H). ^{19}**F NMR** (CD_3OD 19F 400 MHz): δ -63.96.

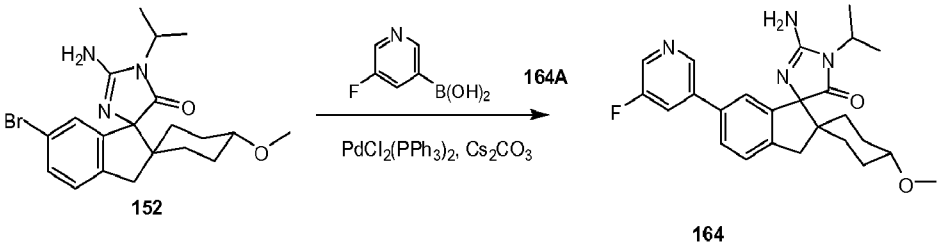
and **compound 161** (11.30 mg) as a white solid; **LC-MS** t_R = 1.169 min in 2 min chromatography, MS (ESI) *m/z* 487 $[M+H]^+$. **SFC:** t_R = 6.77 min in 15 min chromatography, ee = 100%; ^{1}**H NMR** (CD_3OD 400 MHz): δ 9.06 (s, 1H), 8.87 (s, 1H), 8.32 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.35 (s, 1H), 4.23 (m, 1H), 3.38 (s, 3H), 3.18 (m, 3H), 2.10 (m, 1H), 1.95 (m, 2H), 1.67 (m, 1H), 1.46 (m, 4H), 1.39 (m, 4H), 1.30 (m, 2H). ^{19}**F NMR** (CD_3OD 19F 400 MHz): δ -63.96.

Example 125. Synthesis of Compound 163



According to a similar synthesis of **compound 153**, compound **152** (20 mg, 0.048 mmol) was coupled with compound **163A** (12 mg, 0.071 mmol) to give **compound 163** (10.0 mg, 47%) as a white solid. **LC-MS** t_R = 0.973 min in 2 min chromatography, MS (ESI) *m/z* 453 $[M+H]^+$. ^{1}**H NMR** (CD_3OD 400 MHz): δ 8.77 (s, 1H), 8.56 (s, 1H), 8.19 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 4.33 (m, 1H), 3.38 (s, 3H), 3.24 (m, 3H), 2.17 (m, 1H), 2.08 (m, 1H), 1.97 (m, 1H), 1.53-1.45 (m, 10H), 1.38 (m, 1H).

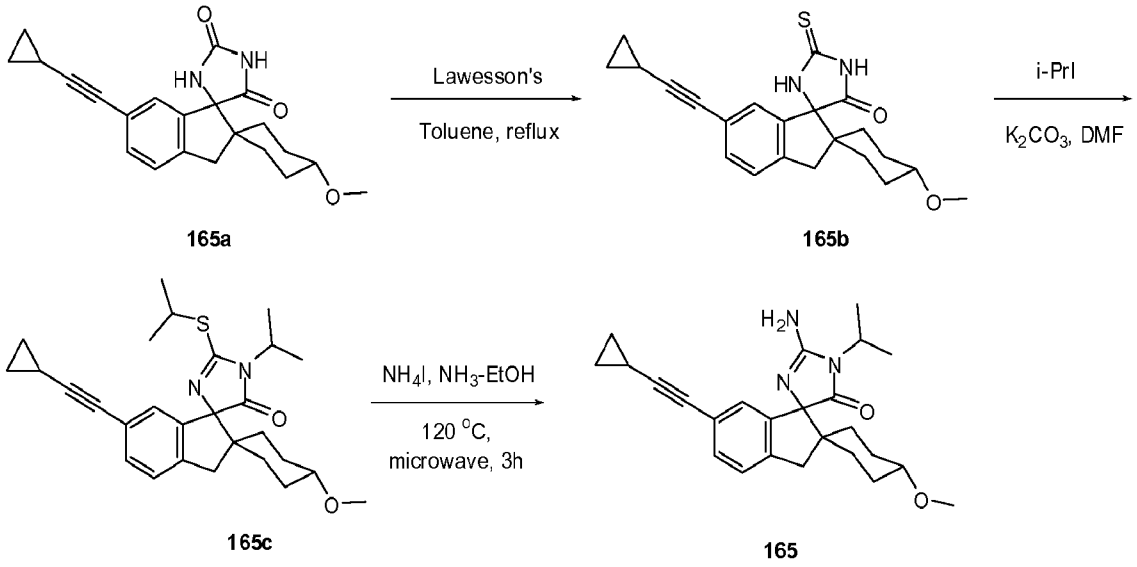
Example 126. Synthesis of Compound 164



152 164

According to a similar synthesis of **compound 153**, compound **152** (20 mg, 0.048 mmol) was coupled with compound **164A** (14 mg, 0.095 mmol) to give **compound 164** (5.1 mg, 31%) as a white solid. **LC-MS** t_R = 0.990 min in 2 min chromatography, MS (ESI) *m/z* 437 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 8.69 (s, 1H), 8.47 (s, 1H), 7.96 (d, J = 10.2 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 4.32 (m, 1H), 3.39 (s, 3H), 3.19 (m, 3H), 2.13 (m, 1H), 2.08-1.91 (m, 2H), 1.58-1.45 (m, 10H), 1.36 (m, 1H).**^{19}F NMR** (CD_3OD 19F 400 MHz): δ -128.30.

Example 127. Synthesis of Compound 165



165a 165b 165c 165

Procedure for preparation of compound 165b

A flask equipped with a condenser and a nitrogen balloon was charged with a mixture of compound **165a** (0.50 g, 1.4 mmol), Lawesson's reagent (0.60 g, 1.5 mmol) in toluene (30 mL) was heated at 130 °C for 4 h. After cooling down, the precipitate was filtered off and washed with ethyl acetate (2 × 40 mL). The filtrate and the washing were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with petroleum ether: EtOAc (20:1 to 5:1) to give compound **165b** (0.34 g, 64%) with 80% purity as a pale brown solid.

LC-MS: t_R = 1.94 min in 3 min chromatography, MS (ESI) *m/z* 381.1 $[M+H]^+$.

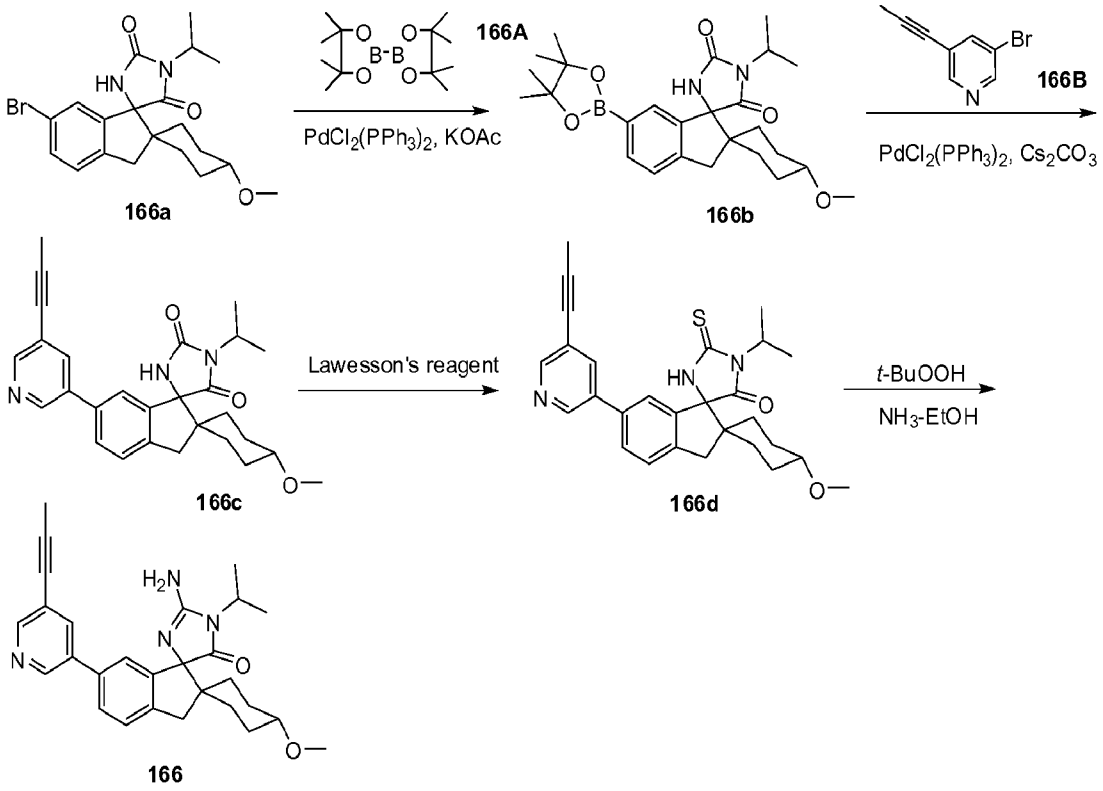
Procedure for preparation of compound 165c

A flask was charged with compound **165b** (40 mg, 0.11 mmol), 2-iodopropane (75 mg, 0.44 mmol), K_2CO_3 (0.10 g, 0.72 mmol) and DMF (2 mL). The reaction mixture was stirred at ambient temperature overnight. The precipitate was filtered of and washed with CH_2Cl_2 (10 mL), and the filtrate and washings were concentrated under vacuum and the residue was dissolved in CH_2Cl_2 (50 mL). The mixture was washed with brine (2 × 20 mL). The separated organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **165c** (40 mg, 78% crude yield) as a yellow oil, which was used directly in next step without purification.

Procedure for preparation of compound 165

A sealed tube was charged with a mixture of compound **165c** (40 mg, 0.086 mmol), NH_4I (0.10 g, 0.69 mmol) and a solution of NH_3 in ethanol (2 mL). The mixture was heated at 120 °C in a CEM microwave reactor for 3 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by preparative RP-HPLC to give **compound 165** (19.0 mg, 54.3%) with the purity of 99% as a white solid. **LC-MS**: t_R = 1.75 min in 3 min chromatography, MS (ESI) *m/z* 406.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.30-7.35 (d, J = 8.0 Hz, 1H), 7.25-7.30 (d, J = 8.0 Hz, 1H), 7.10-7.15 (s, 1H), 4.20-4.30 (m, 1H), 3.30-3.35 (s, 3H), 3.10-3.20 (m, 2H), 3.00-3.10 (d, J = 16.0 Hz, 1H), 2.00-2.10 (m, 1H), 1.90-2.00 (m, 1H), 1.80-1.90 (m, 1H), 1.20-1.50 (m, 11H), 0.80-0.90 (m, 2H), 0.60-0.70 (m, 2H).

Example 128. Synthesis of Compound 166



Procedure for preparation of Compound 166b

To a solution of compound **166a** (263 mg, 0.62 mmol) in 1,4-dioxane (10 mL) was added compound **166A** (190 mg, 0.75 mmol), $PdCl_2$(dppf) (79 mg), KOAc (182.3 mg, 1.86 mmol), the mixture was carried under microwave at 100 °C for 1 h under N_2. Then filtered, the filtrate was concentrated to give the residue which was purified by preparative TLC (hexanes: EtOAc = 1: 1) to give compound **166b** (238.9 mg, 95%) as a white solid.

Procedure for preparation of Compound 166c

Compound **166b** (238.9 mg, 0.51 mmol) in a 10 mL of flask under N_2 was treated sequentially with compound **3A** (50 mg, 0.255 mmol) in 1,4-dioxane (2 mL), Cs_2CO_3 (2 N, 0.38 mL, 0.765 mmol) and $Pd(PPh_3)_2Cl_2$ (10 mg). The mixture was heated under 120 °C under N_2 in a CEM microwave for 15 min. The reaction mixture

was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (hexanes: EtOAc = 1: 1) to give compound **166c** (100 mg, 97%) as a white solid.

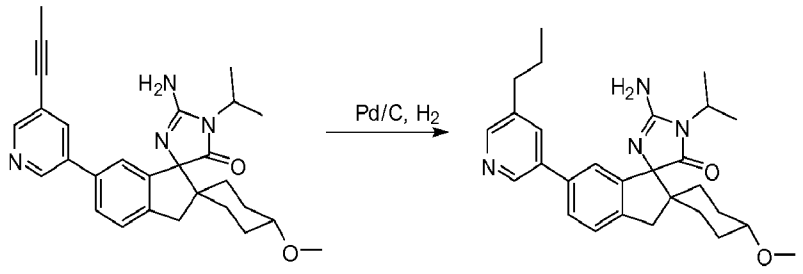
Procedure for preparation of Compound 166d

A suspension of compound **166c** (100 mg, 0.22 mmol) and Lawesson's reagent (88 mg, 0.22 mmol) in anhydrous toluene (2 mL) was heated 130 °C for 60 minis in a CEM microwave reactor. The reaction mixture was concentrated under reduced pressure, and purified by preparative TLC with petroleum ether: EtOAc=1:1 to give compound **166d** (56 mg, 54%) as a yellow solid.

Procedure for preparation of compound 166

To a solution of compound **166d** (56 mg, 0.12 mmol) in a mixture of MeOH (3 mL) and NH_4OH (0.6 mL) was added *t*-BuOOH (346 mg, 2.4 mmol, 65% in water). The mixture was stirred at room temperature overnight, and concentrated. Water (15 mL) and EtOAc (3 × 10 mL) were added, and the organic layer was dried over Na_2SO_4 and concentrated to give the residue which was purified by HPLC to give **compound 166** (5.8 mg, 11%) as a white solid. **LC-MS** t_R = 1.014 min in 2 min chromatography, MS (ESI) *m/z* 457 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.60 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 8.00 (t, J = 1.6 Hz, 1H), 7.60 (m, 1H), 7.45 (m, 2H), 4.20 (m, 2H), 3.26 (s, 3H), 3.20 (m, 1H), 3.15 (m, 2H), 1.99 (m, 4H), 1.85 (m, 2H), 1.40 (m, 3H), 1.36 (m, 7H), 1.21 (m, 1H).

Example 129. Synthesis of Compound 167

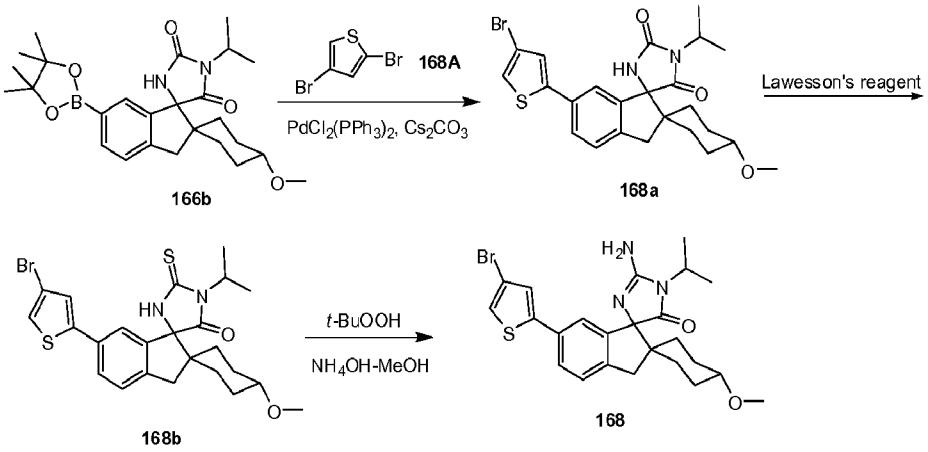


166 **167**

A solution of **compound 166** (14 mg, 0.03 mmol) and Pd/C (3 mg) in MeOH (5mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated, added CH_2Cl_2 (20 mL), filtered, concentrated, and purified by preparative HPLC (0.1% TFA as additive) to give **compound 167** (3.0 mg, 21%) as a TFA salt. **LC-MS** t_R =

0.917 min in 2 min chromatography, MS (ESI) *m/z* 461 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.82 (s, 1H), 8.57 (s, 1H), 8.38 (s, 1H), 7.80 (m, 1H), 7.66 (m, 1H), 7.57 (m, 1H), 4.36 (m, 2H), 3.46 (s, 3H), 3.20 (m, 1H), 3.15 (m, 2H), 2.86 (m, 2H), 2.14 (m, 1H), 2.05 (m, 1H), 1.97 (m, 1H), 1.79 (m, 2H), 1.54 (m, 4H), 1.48 (m, 6H), 1.37 (m, 1H), 1.05 (m, 3H).

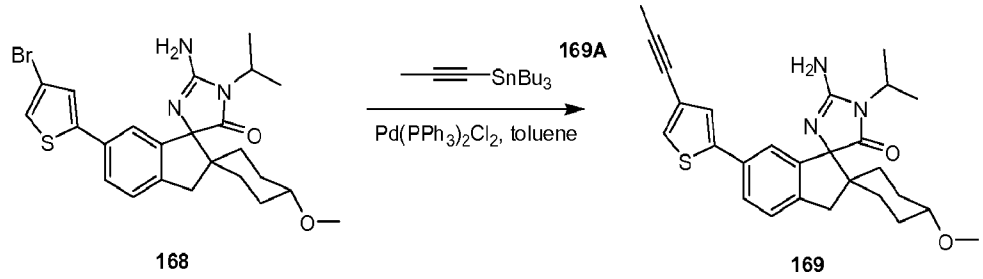
Example 130. Synthesis of Compound 168



According to a similar synthesis of **compound 166**, compound **166b** (100 mg, 0.213 mmol) was coupled with compound **168A** (103 mg, 0.426 mmol) to give compound **168a** (60 mg, 56%) as a white solid. **LC-MS:** t_R = 1.326 min in 2 min chromatography, MS (ESI) *m/z* = 503.1, 506.0 $[M+H]^-$. **^{1}H NMR** (CD_3CN 400 MHz): δ 7.45-7.48 (m, 1H), 7.28-7.29 (m, 1H), 7.20-7.26 (m, 2H), 4.07-4.15 (m, 1H), 3.18 (s, 3H), 2.97-3.05 (m, 3H), 2.07-2.10 (m, 2H),1.74-1.83(m, 6H), 1.23-1.27 (m, 6H).

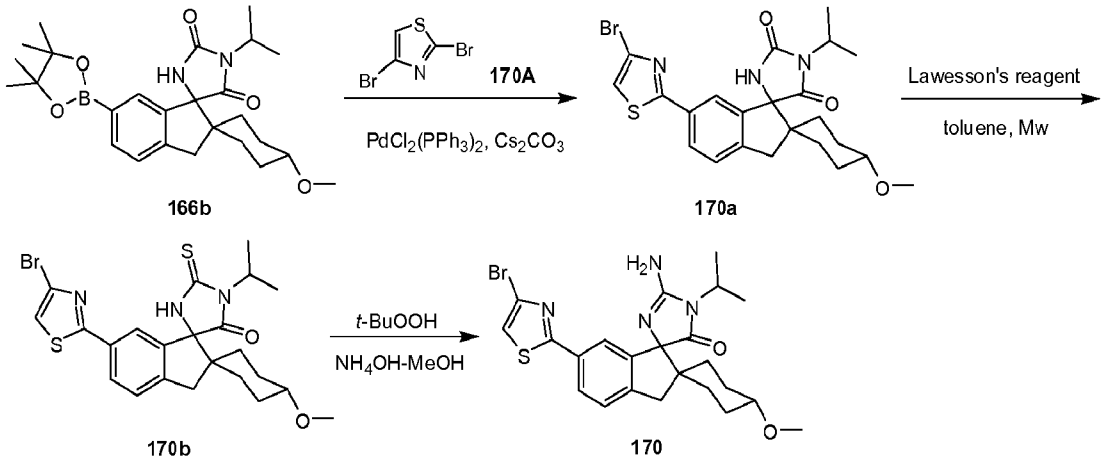
Compound **168a** (114 mg, 0.227 mmol) was reacted with Lawesson's reagent (92 mg, 0.227 mmol) to give compound **168b** (80 mg, 68%) as a yellow solid. **LC-MS:** t_R = 1.401 min in 2 min chromatography, MS (ESI) *m/z* = 519.0, 521.0 $[M+H]^+$. Compound **168b** (80 mg, 0.154 mmol) was then converted to **compound 168** (3.4 mg, 34%) as a white solid. **LC-MS:** t_R = 1.070 min in 2 min chromatography, MS (ESI) *m/z* = 502.0 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.53-7.56 (dd, J = 1.6, 8.0 Hz, 1H), 7.41-7.41 (d, J = 1.2 Hz, 1H), 7.32-7.34 (d, J = 8.0 Hz, 1H), 7.29-7.30 (d, J = 1.6 Hz, 2H), 4.19-4.25 (m, 1H), 3.27 (s, 3H), 3.01-3.12 (m, 3H), 1.99-2.02 (m, 1H), 1.81-1.93 (m, 2H), 1.38-1.43 (m, 6H), 1.18-1.36 (m, 5H).

Example 131. Synthesis of Compound 169



A solution containing **compound 168** (45 mg, 0.09 mmol) and compound **169A** (89 mg, 0.27 mmol) in toluene (1 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $Pd(PPh_3)_2Cl_2$ (5 mg) was added. The mixture was stirred at 135 °C for 45 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was partitioned by EtOAc (50 mL) and aqueous of CsF (4M, 50 mL). The aqueous layer was extracted by EtOAc (2 × 50 mL), the combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC afforded compound **169** (3.4 mg, 8%) as a white solid. **LC-MS:** t_R = 1.114 min in 2 min chromatography, MS (ESI) *m/z* = 462.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.91-7.93 (dd, J = 1.6, 8.0 Hz, 1H), 7.83 (s, 1H), 7.12 (s, 1H), 7.51-7.53 (d, J = 7.6 Hz, 1H), 4.30-4.37 (m, 1H), 3.38 (s, 3H), 3.19-3.28 (m, 3H), 2.03-2.13 (m, 4H), 1.94-1.98 (m, 2H), 1.48-1.54 (m, 3H), 1.33-1.42 (m, 8H).

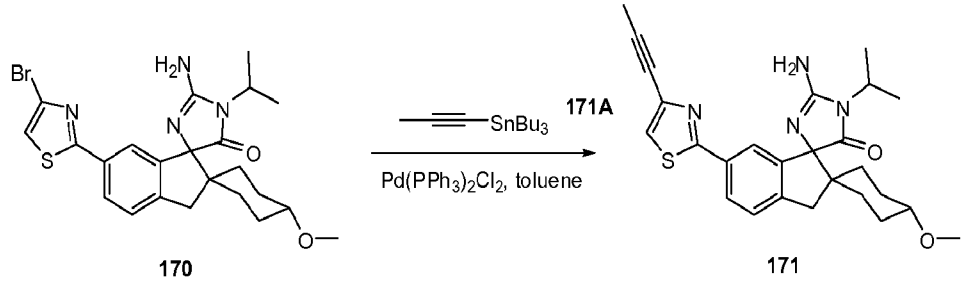
Example 132. Synthesis of Compound 170



According to a similar synthesis of **compound 166**, compound **166b** (50 mg, 0.107 mmol) was coupled with compound **170A** (52 mg, 0.213 mmol) to give compound **170a** (40 mg, 74%) as a white solid. **LC-MS:** t_R = 1.260 min in 2 min chromatography, MS (ESI) *m/z* = 504.1, 506.1 $[M+H]^+$.

Compound **170a** (100 mg, 0.20 mmol) was reacted with Lawesson's reagent (81 mg, 0.20 mmol) to give compound **170b** (80 mg, 78%) as a yellow solid. **LC-MS:** t_R = 1.593 min in 2 min chromatography, MS (ESI) *m/z* = 522.2 $[M+H]^+$. Compound **170b** (80 mg, 0.154 mmol) was then converted to **compound 170** with 60% purity (60 mg, 46%) as a white solid. 15 mg of the product was further purified by preparative HPLC to give **compound 170** (5.3 mg, 58%) as a white solid. **LC-MS:** t_R = 1.044 min in 2 min chromatography, MS (ESI) *m/z* = 503.1, 505.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.93-7.95 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.86 (s, 1H), 7.60 (s, 1H), 7.52-7.54 (d, *J* = 8.0 Hz, 1H), 4.29-4.35 (m, 1H), 3.37 (s, 3H), 3.20-3.27 (m, 3H), 2.10-2.13 (m, 1H), 1.94-2.03 (m, 2H), 1.52-1.54 (m, 3H), 1.47-1.50 (m, 3H), 1.32-1.39(m, 5H).

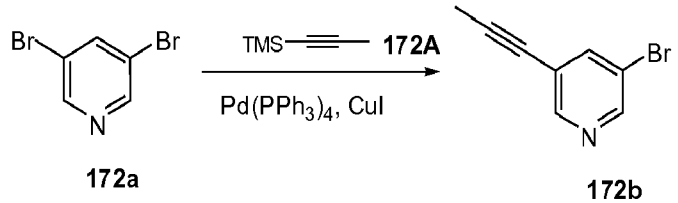
Example 133. Synthesis of Compound 171



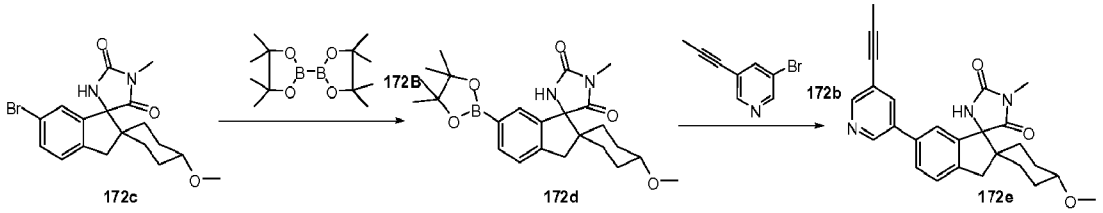
170 171

According to a similar synthesis of **compound 169**, compound **compound 170** (50 mg, 0.1 mmol) was coupled with compound **171A** (99 mg, 0.3 mmol) to give compound **171** (9.4 mg, 20%) as a white solid. **LC-MS:** t_R = 1.158 min in 2 min chromatography, MS (ESI) *m/z* = 463.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.40-7.42 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.20-7.22 (d, *J* = 9.6 Hz, 2H), 7.12 (s, 1H), 7.06 (s, 1H), 4.10-4.14 (m, 1H), 3.24 (s, 3H), 3.01-3.06(m, 1H), 2.91-2.99 (m, 2H),1.92-1.94 (m, 1H), 1.87-1.89 (m, 3H), 1.80-1.83 (m, 2H), 1.45-1.52 (m, 1H), 1.29-1.33 (m, 3H), 1.19-1.27 (m, 5H), 1.13-1.17 (m, 2H).

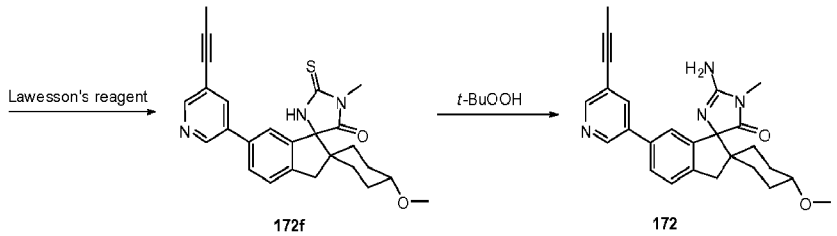
Example 134. Synthesis of Compound 172



172a 172b



172c 172d 172e



172f 172

Procedure for preparation of Compound 172b

A mixture of compound **172a** (1 g, 4.22 mmol), compound **172A** (474 mg, 4.22 mmol), CuI (241 mg, 1.27 mmol), Et_3N (1.4 g, 13.9 mmol), $Pd(PPh_3)_4$ (244 mg, 0.21 mmol) in toluene (200 mL) was stirred at room temperature for 3 h before it was extracted with CH_2Cl_2 (3 × 100 mL) and water (200 mL). The organic layer was dried, evaporated and the residue was purified by column chromatography (hexanes: EtOAc = 100: 1) to give compound **172b** (200 mg, 24%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.48 (d, J = 12.4 Hz, 2H), 7.74 (t, J = 2.0 Hz, 1H), 2.00 (s, 3H).

Procedure for preparation of Compound 172d

To a solution of compound **172c** (120 mg, 0.31 mmol) in 1,4-dioxane (3 mL) was added compound **172B** (93.3 mg, 0.37 mmol), $PdCl_2$(dppf) (36 mg), KOAc (91.1 mg, 0.93 mmol), the mixture was carried under microwave at 100 °C for 1 h under N_2. Then filtered, the filtrate was concentrated to give the residue which was purified by preparative TLC (hexanes: EtOAc = 3: 1) to give compound **172d** (100 mg, 74%) as a white solid.

Procedure for preparation of Compound 172e

$PdCl_2(PPh_3)_2$ (10 mg) in a 10 mL of flask under N_2 was treated sequentially with compound **172d** (224.6 mg, 0.51 mmol), in 1,4-dioxane (2 mL), and compound **172b** (50 mg, 0.225 mmol), Cs_2CO_3 (2 N, 0.38 mL, 0.765 mmol). The mixture was heated under 120 °C at N_2 under microwave for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (hexanes: EtOAc = 1: 1) to give compound **172e** (100 mg, 91%) as a white solid.

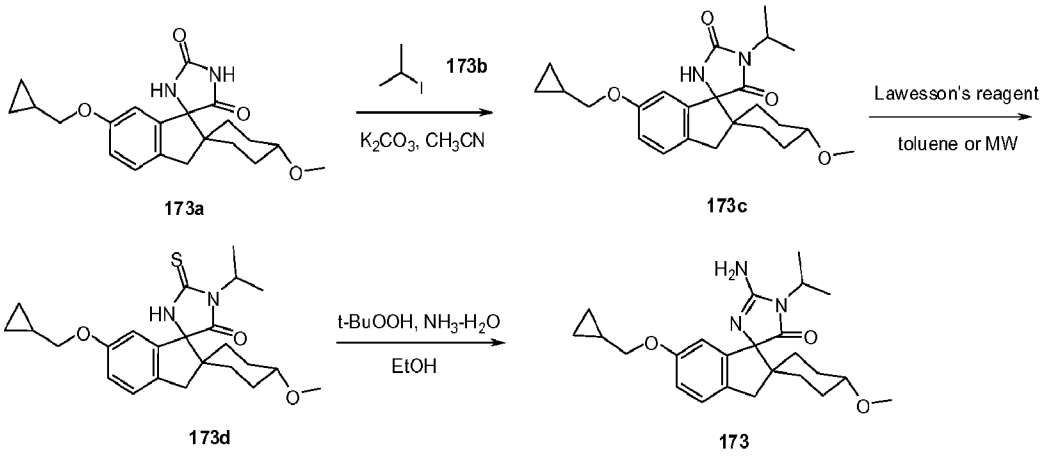
Procedure for preparation of Compound 172f

A suspension of compound **172e** (49 mg, 0.11 mmol) and Lawesson's reagent (46 mg, 0.11 mmol) in anhydrous toluene (2 mL) was heated 140 °C for 40 min in a CEM microwave reactor. The reaction mixture was concentrated under reduced pressure, and purified by preparative TLC (hexanes: EtOAc = 3: 1) to give compound **172f** (30 mg, 59%) as a white solid.

Procedure for preparation of Compound 172

To a solution of compound **172f** (30 mg, 0.067 mmol) in a mixture of MeOH (3 mL) and NH_4OH (0.6 mL) was added *t*-BuOOH (128 mg, 1.35 mmol, 65% in water). The mixture was stirred at room temperature overnight, and concentrated. Water (15 mL) and EtOAc (3 × 10 mL) were added, and the organic layer was dried over Na_2SO_4 and concentrated to give the residue which was purified by HPLC to give **compound 172** (13.4 mg, 46%) as a white solid. **LC-MS**: t_R = 0.894 min in 2 min chromatography, MS (ESI) *m/z* 429 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.72 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.13 (s, 1H), 7.71 (m, 1H), 7.55 (m, 2H), 3.50 (s, 3H), 3.25 (m, 1H), 3.22 (s, 3H), 3.15 (m, 2H), 2.11 (s, 3H), 2.04 (m, 1H), 1.89 (m, 1H), 1.43 (m, 6H).

Example 135. Synthesis of Compound 173



Procedure for preparation of Compound 173c

To a solution of compound **173a** (30 mg, 0.08 mmol) in CH_3CN (2 mL) was added K_2CO_3 (22.3 mg, 0.16 mmol), and compound **173b** (9.6 mg, 0.08 mmol), the mixture was stirred at 80 °C for 15 min in microwave, the precipitate was filtered off, the filtrate was concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to afford compound **173c** (23 mg, 68%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.19 (d, J = 8.0 Hz, 1H), 6.75 (m, J = 8.4 Hz, 1H), 6.54 (s, 1H), 4.25-4.22 (m, 1H), 3.67-3.65 (d, J = 6.8 Hz, 2H), 3.44 (s, 3H), 3.04-2.91 (m, 2H), 2.91-2.87 (m, 1H), 2.0-1.90 (m, 2H), 1.49-1.39 (m, 6H), 1.39-1.32 (m, 1H), 1.26-1.18 (d, J = 6.0 Hz, 6H), 0.68-0.58 (m, 2H), 0.38-0.27 (m, 2H).

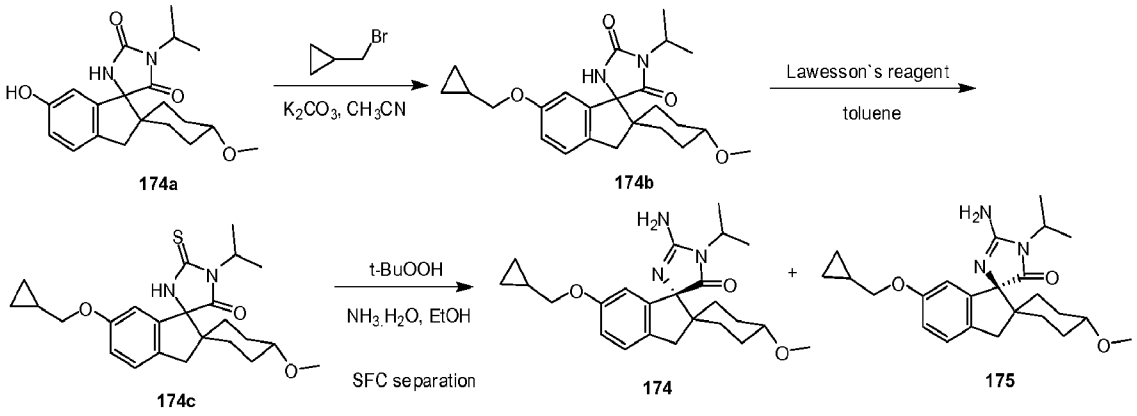
Procedure for preparation of Compound 173d

To a solution of compound **173c** (23 mg, 0.055 mmol) in anhydrous toluene (2 mL) was added Lawesson's Reagent (24.7 mg, 0.06 mmol) under N_2, the mixture was stirred at 130 °C in a CEM microwave reactor for 40 min. After cooling, the solvent was removed by evaporation *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to afford compound **173d** (15 mg, 63%) as a white solid. ***LCMS :*** t_R=1.504 min in 2 min chromatography, MS (ESI) m/z = 429.2 $[M+H]^+$.

Procedure for preparation of compound 173

To a solution of compound **173d** (15 mg, 0.035mmol) in EtOH (5 mL) was added *t*-BuOOH (0.5 mL) and $NH_3.H_2O$ (1.5 mL), the mixture was stirred at room temperature overnight, the reaction was completed detecting by LCMS. The mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and then by preparative HPLC to give **compound 173** (3.0 mg, 20%) as a white solid. ***LCMS*:** t_R = 1.867 min in 2 min chromatography, MS (ESI) *m/z* = 412.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.18 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.51(s, 1H), 4.24 (m, 1H), 3.78 (d, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 3.15-3.04 (m, 1H), 3.04-2.93 (m, 2H), 2.10-1.90 (m, 3H), 1.56-1.53 (m, 1H), 1.53-1.44 (d, *J* = 6.8 Hz,, 3H), 1.44-1.39 (d, *J* = 8.0 Hz, 3H), 1.39-1.37 (m, 1H), 1.37-1.22 (m, 4H), 0.60-0.58 (m, 2H), 0.33-0.32 (m, 2H)

Example 136. Synthesis of Compounds 174 and 175



Procedure for preparation of compound 174b

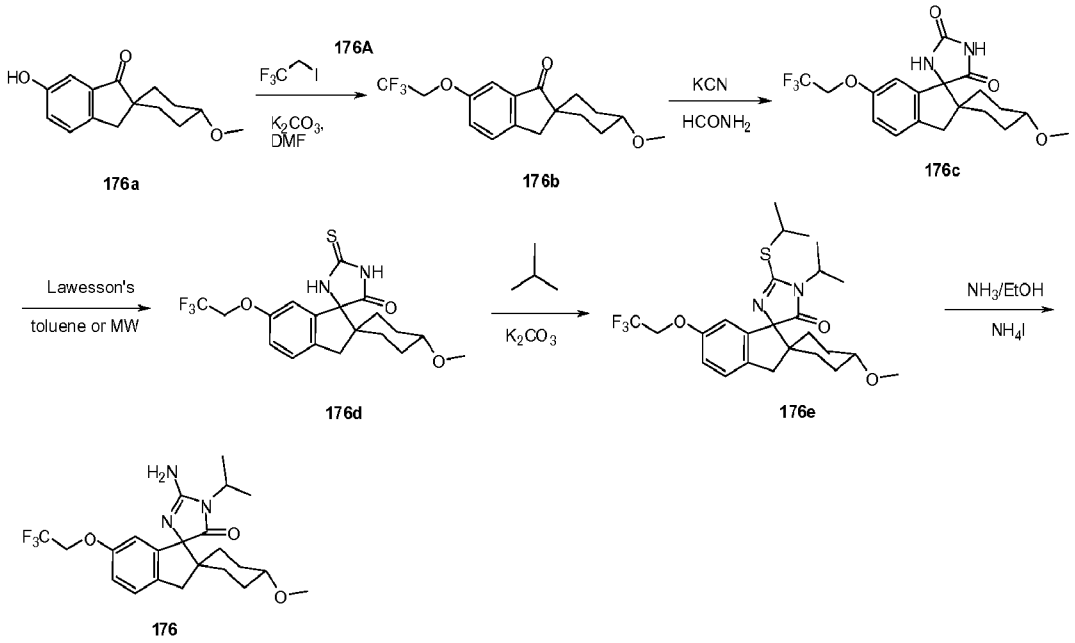
To a solution of compound **174a** (150 mg, 0.41 mmol) in anhydrous CH_3CN (10 mL) was added K_2CO_3 (115.6 mg, 0.82 mmol) and bromomethyl-cyclopropane (62.6 mg, 0.46 mmol). The resulting suspension was stirred at 60 °C for 5 h. The precipitate was filtered off and the filtrate was concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 3:

1 to give compound **174b** (100 mg, 55%); **LC-MS**: t_R = 1.216 min in 2 min chromatography, MS (ESI) *m/z* = 413.2 $[M+H]^+$.

Procedure for preparation of compounds 174 and 175

The same synthesis for compound **173** was applied for this synthesis, and compound **174b** (100 mg, 0.24 mmol) gave compound **174c** (67 mg, 65%), which was converted to **compound 173**. Preparative SFC to give **compound 174** (12.8 mg, 11%); **LC-MS**: t_R = 0.988 min in 2 min chromatography, MS (ESI) *m/z* = 412.1 $[M+H]^+$. **SFC**: t_R = 6.26 min in 16 min chromatography, ee% = 100%. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.25-7.08 (d, *J* = 8.4 Hz, 1H), 6.90-6.82 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.46 (s, 1H), 4.40-4.10 (m, 1H), 3.80-3.74 (d, *J* = 6.8 Hz, 2H), 3.35 (s, 3H), 3.14 (m, 1H), 3.10-2.90 (m, 2H), 2.10-2.01 (m, 1H), 2.01-1.85 (m, 2H), 1.60-1.50 (m, 1H), 1.50-1.40 (d, *J* = 6.8 Hz, 3H), 1.40-1.35 (d, *J* = 6.8 Hz, 3H), 1.35-1.15 (m, 5H), 0.70-0.50 (m, 2H), 0.40-0.30 (m, 2H); and **compound 175** (10.0 mg, 15%), **LC-MS**: t_R = 0.992 min in 2 min chromatography, MS (ESI) *m/z* = 412.1 $[M+H]^+$. **SFC**: t_R = 7.76 min in 16 min chromatography, ee% = 98%. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.13-7.06 (d, *J* = 8.4 Hz, 1H), 6.83-6.74 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.44 (s, 1H), 4.20-4.00 (m, 1H), 3.70-3.60 (d, *J* = 6.8 Hz, 2H), 3.36 (s, 3H), 3.10-3.01 (m, 1H), 3.00-2.81 (m, 2H), 2.00-1.91 (m, 1H), 1.90-1.75 (m, 2H), 1.50-1.35 (m, 1H), 1.35-1.30 (d, *J* = 6.4 Hz, 3H), 1.30-1.25 (d, *J* = 6.8 Hz, 3H), 1.25-1.05 (m, 1H), 1.10-1.00 (m, 4H), 0.60-0.40 (m, 2H), 0.30-0.11 (m, 2H).

Example 137. Synthesis of Compound 176



Procedure for preparation of Compound 176b

To a solution of compound **176a** (500 mg, 2.02 mmol) in DMF (2 mL) was added K_2CO_3 (559 mg, 4.04 mmol), and compound **176A** (516.6 mg, 2.22 mmol), the mixture was stirred at ambient temperature overnight. The reaction was added with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **176b** (400 mg, 60%) as a white solid, which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.34 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 4.33 (dd, J = 8.0, 40.4 Hz, 2H), 3.43 (s, 3H), 3.18-3.22 (m, 1H), 2.96 (s, 2H), 1.97-2.06 (m, 2H), 1.73-1.85 (m, 2H), 1.45-1.52 (m, 2H), 1.34-1.45 (m, 2H).

Procedure for preparation of compound 176

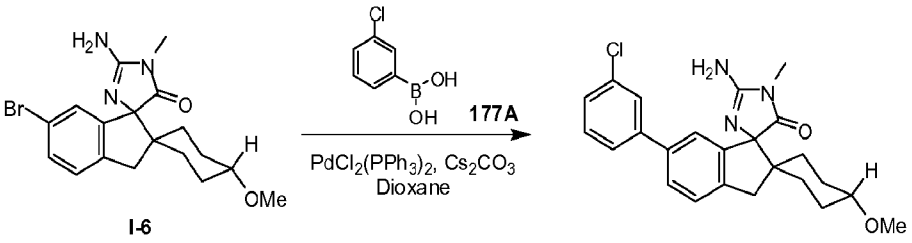
According to a similar synthesis for **Acylguanidine I-6** described in Example I-2, compound **176b** (400 mg, 1.21 mmol), was condensed to hydantoin **176c** (80 mg, 16%) as a white solid. **LCMS** : t_R = 1.080 min in 2 min chromatography, MS (ESI) *m/z* = 399.1$[M+H]^+$.

Compound **176c** (50 mg, 0.12 mmol) was reacted with Lawesson's Reagent (50.7 mg, 0.12 mmol) to afford compound **176d** (25 mg, 50%) as a white solid. **LCMS** : t_R = 1.250 min in 2 min chromatography, MS (ESI) *m/z* = 415.1$[M+H]^+$.

Compound **176d** (25 mg, 0.06 mmol) was then dialkylated with 2-iodo-propane (40.7 mg, 0.24 mmol) to give compound **176e** (15 mg, 50%) as a white solid. **LCMS**: t_R = 1.726 min in 2 min chromatography, MS (ESI) *m/z* = 499.2 $[M+H]^+$.

Finally, compound **176e** (15 mg, 0.03 mmol) was converted to **compound 176** (0.8 mg, 6%) as a white solid. **LCMS**: 694-139-1 t_R = 1.936 min in 3 min chromatography, MS (ESI) *m/z* = 440.2 $[M+H]^+$. **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.27 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 6.0 Hz, 1H), 6.65(s, 1H), 4.50 (dd, *J* = 6.4, 8.4 Hz, 2H), 4.46 (m, 1H), 3.36 (s, 3H), 3.07-3.15 (m, 1H), 2.98-3.03 (m, 2H), 1.98-2.05 (m, 4H), 1.89 (m, 2H), 1.54 (d, *J* = 11.2 Hz, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.27-1.32 (m, 2H) .**^{19}FNMR**: (CD_3OD 400 MHz): δ -75.806

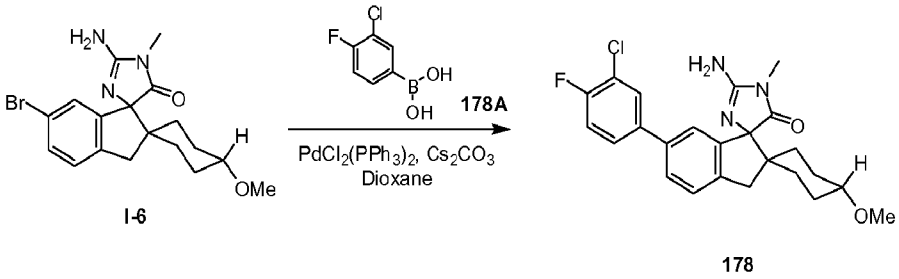
Example 138. Synthesis of Compound 177



According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (30 mg, 0.076 mmol) was coupled with compound **177A** (24 mg, 0.153 mmol) to give **compound 177** (15 mg, yield 47%). **LC-MS** t_R = 1.025 min in 2 min

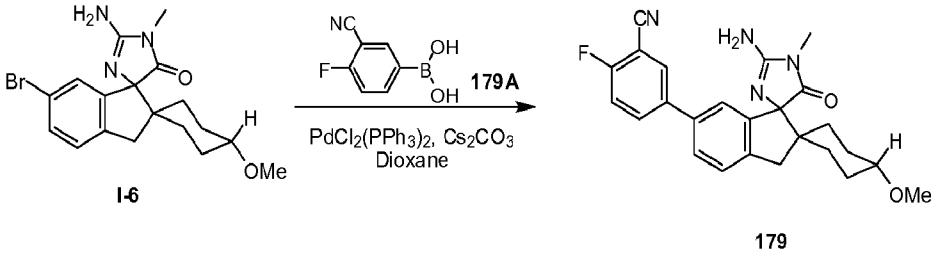
chromatography, MS (ESI) *m/z* 424.0.1 $[M+H]^{+}$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.58 (s, 2H), 7.47 (m, 2H), 7.13-7.39 (m, 3H), 3.28 (s, 3H), 3.05-3.17 (m, 6H), 1.92-2.07 (m, 2H), 1.81 (d, 1H), 1.19-1.45 (m, 5H).

Example 139. Synthesis of Compound 178



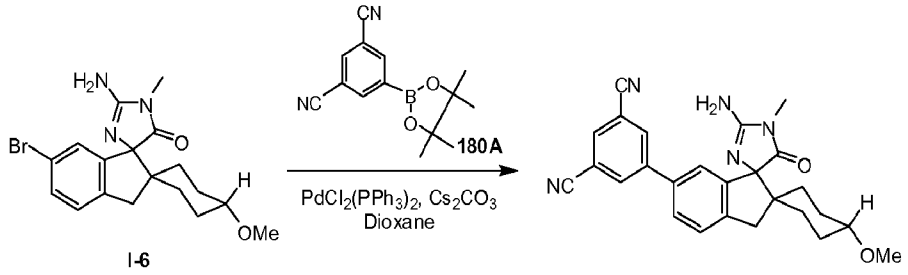
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (25 mg, 0.06 mmol) was coupled with compound **178A** (21 mg, 0.12 mmol) to give **compound 178** (9.1 mg, 32%) as a white solid. **LC-MS** t_R = 1.012 min in 2 min chromatography, MS (ESI) *m/z* 442.1 $[M+H]^{-}$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.56 (m, 1H), 7.37-7.43 (m, 2H), 7.27 (m, 1H), 7.17 (m, 1H), 7.05 (m, 1H), 3.24 (s, 3H), 2.96-3.07 (m, 3H), 2.93 (s, 3H), 1.74-1.93 (m, 3H), 1.51 (m, 1H), 1.17-1.30 (m, 4H).

Example 140. Synthesis of Compound 179



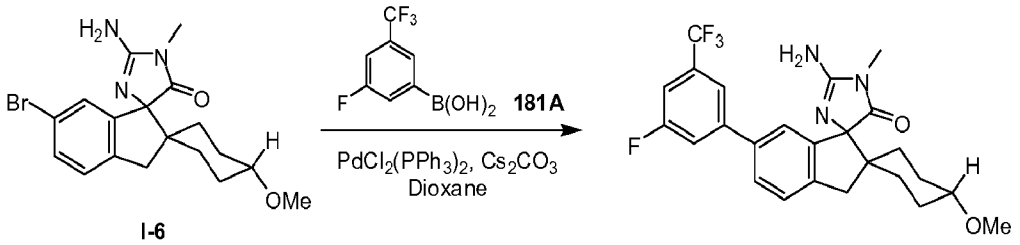
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** was coupled with compound **179A** (17 mg, 0.103 mmol) to give **compound 179** (5.6 mg, yield 25%). **LC-MS** t_R = 0.956 min in 2 min chromatography, MS (ESI) *m/z* 433.1 $[M+H]^{+}$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.91 (m, 1H), 7.83 (m, 1H), 7.44 (m, 1H), 7.32 (m, 2H), 7.13 (s, 1H), 3.28 (s, 3H), 3.17 (m, 3H), 2.94 (s, 3H), 2.01-1.84 (m, 2H), 1.78 (m, 1H), 1.57 (m, 1H), 1.42-1.17 (m, 4H)

Example 141. Synthesis of Compound 180



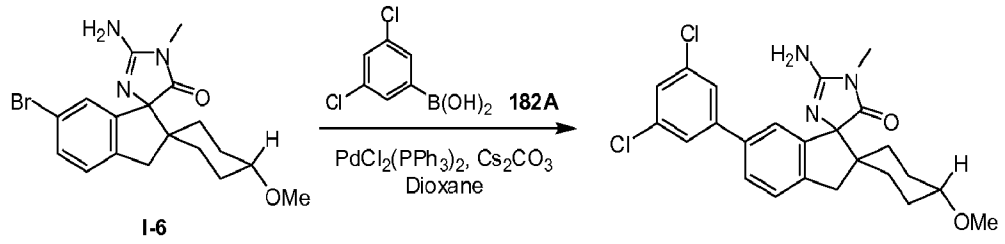
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** was coupled with compound **180A** (32 mg, 0.128 mmol) to give **compound 180** (4.4 mg, yield 20%). **LC-MS** t_R = 1.056 min in 2 min chromatography, MS (ESI) *m/z* 440.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 8.19 (s, 2H), 8.02 (s, 1H), 7.55-7.53 (m, 1H), 7.38-7.36 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H), 3.43-3.32 (m, 3H), 3.26-3.22 (m, 2H), 3.08-3.05 (m, 1H), 2.97 (s, 3H), 1.95-1.87 (m, 2H), 1.76 (m, 1H), 1.56-1.52 (m, 1H), 1.35-1.29 (m, 2H), 1.23-1.20 (m, 2H).

Example 142. Synthesis of Compound 181



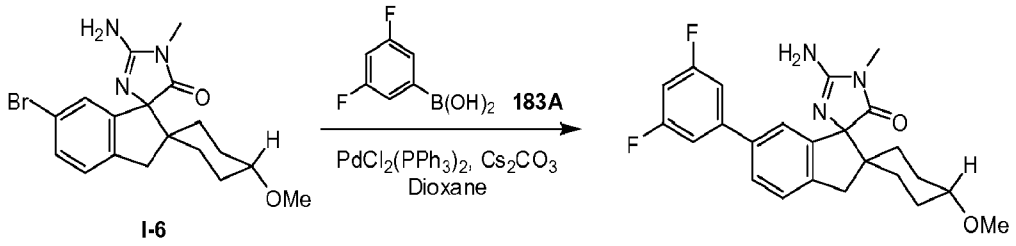
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.051 mmol) was coupled with compound **181A** (21.2 mg, 0.102 mmol) to give **compound 181** (5.6 mg, yield 25%). **LC-MS** t_R = 1.035 min in 2 min chromatography, MS (ESI) *m/z* 476.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 7.69-7.57 (m, 3H), 7.46-7.40 (m, 2H), 7.25 (s, 1H), 3.36 (s, 3H), 3.22-3.08 (m, 3H), 3.05 (s, 3H), 2.04-1.85 (m, 3H), 1.72-1.63 (m, 1H), 1.46-1.18 (m, 4H).

Example 143. Synthesis of Compound 182



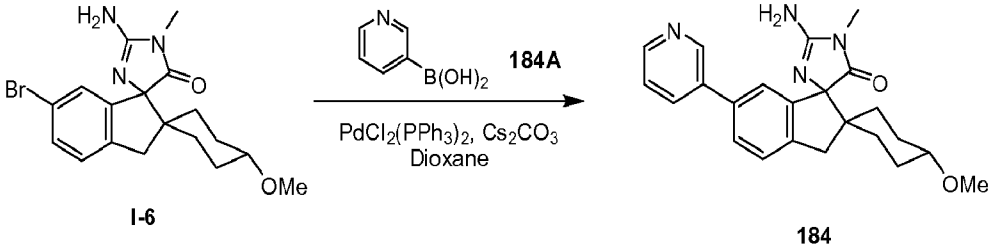
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.051 mmol) was coupled with compound **182A** (19 mg, 0.102 mmol) to give **compound 182** (1.56 mg, yield 7%). **LC-MS** t_R = 1.071 min in 2 min chromatography, MS (ESI) *m/z* 458.0 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.38-7.31 (m, 4H), 7.23 (s, 1H), 7.11 (s, 1H), 3.29 (s, 3H), 3.18 (d, J = 15.6 Hz, 1H), 3.04 (m, 5H), 1.85-1.98 (m, 3H), 1.45 (m, 1H), 1.34 (m, 2H), 1.27 (m, 2H).

Example 144. Synthesis of Compound 183



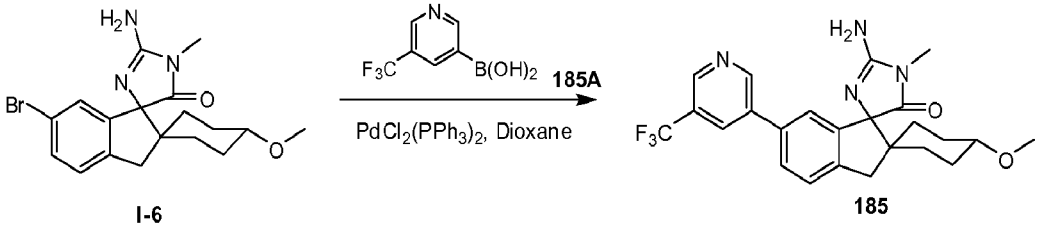
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.051 mmol) was coupled with compound **183A** (16 mg, 0.102 mmol) to give **compound 183** (3.8 mg, yield 18%). **LC-MS** t_R = 0.989 min in 2 min chromatography, MS (ESI) *m/z* 426.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.58 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.21 (m, 3H), 6.90 (m, 1H), 3.39 (s, 3H), 3.16 (m, 3H), 3.08 (s, 3H), 2.12 (m, 2H), 1.88 (m, 1H), 1.69 (m, 1H), 1.29-1.45 (m, 4H).

Example 145. Synthesis of Compound 184



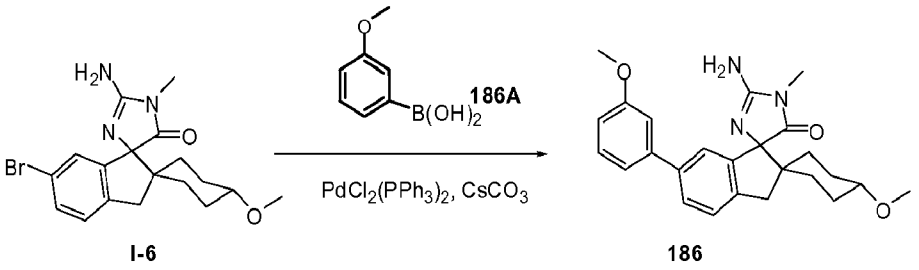
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.051 mmol) was coupled with compound **184A** (13 mg, 0.102 mmol) to give **compound 184** (3.9 mg, yield 20%). **LC-MS** t_R = 0.737 min in 2 min chromatography, MS (ESI) *m/z* 391.0 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 8.76 (s, 1H), 7.49 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.59-7.44 (m, 3H), 7.25 (s, 1H), 3.37 (s, 3H), 3.11-3.22 (m, 3H), 3.05 (s, 3H), 1.95-2.09 (m, 2H), 1.86 (m, 1H), 1.68 (m, 1H), 1.29-1.42 (m, 4H).

Example 146. Synthesis of Compound 185



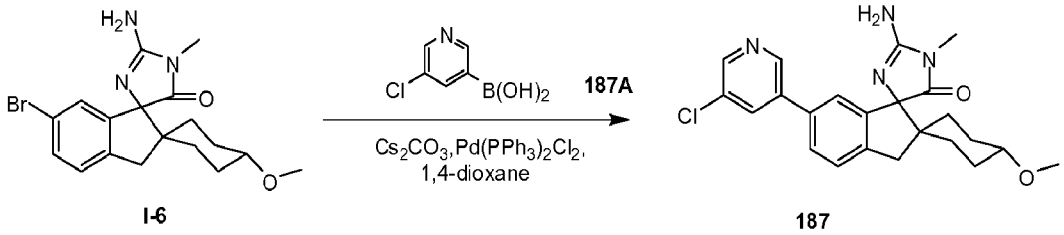
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (25 mg, 0.064 mmol) was coupled with compound **185A** (24 mg, 0.13 mmol) in 1,4-dioxane (1 mL) to give **compound 185** (15 mg, 51%) as a white solid. **LC-MS** t_R = 1.072 min in 2 min chromatography, MS (ESI) *m/z* 459.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.10 (s, 1H), 8.88 (s, 1H), 8.39 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 3.12-3.29 (m, 6H), 2.11 (m, 2H), 1.92 (m, 1H), 1.33-1.50 (m, 5H).

Example 147. Synthesis of Compound 186



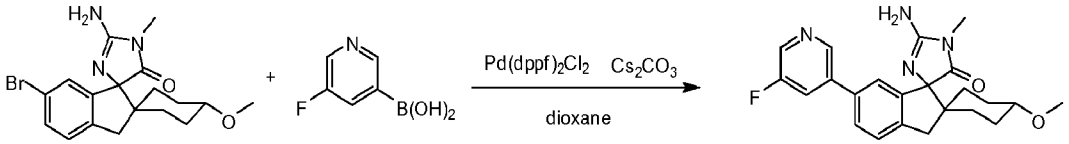
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (25 mg, 0.064 mmol) was couple with compound **186A** (15 mg, 0.095 mmol) to afford **compound 186** (7.2 mg, 28%) as a white solid. **LC-MS** t_R = 0.969 min in 2 min chromatography, MS (ESI) *m/z* 419.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.65-7.62 (d, J = 7.5 Hz, 1H), 7.46-7.43 (d, J = 9.0 Hz, 2H), 7.34 (t, J = 8.1 Hz, 1H), 7.16 (t, J = 8.1 Hz, 2H), 6.90 (d, J = 8.7 Hz, 1H), 3.84 (s, 3H), 3.52 (s, 3H), 3.20 (s, 6H), 3.06-1.82 (m, 3H), 1.49-1.39 (m, 5H).

Example 148. Synthesis of Compound 187



According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.05 mmol) was coupled with compound **187A** (15.7 mg, 0.10 mmol) to afford **compound 187** (2 mg, 10%) as a white solid. **LC-MS** t_R = 1.047 min in 2 min chromatography, MS (ESI) *m/z* 425.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.70 (s, 1H), 7.48-8.49 (s, 1H), 8.09 (s, 1H), 7.61-7.63 (m, 1H), 7.52-7.60 (m, 1H), 7.42-7.44 (m, 1H), 3.32 (s, 3H), 3.05-3.10 (m, 1H), 1.90-2.05 (m, 2H), 1.75-1.80 (m, 1H), 1.30-1.42 (m, 4H), 1.15-1.25 (m, 1H).

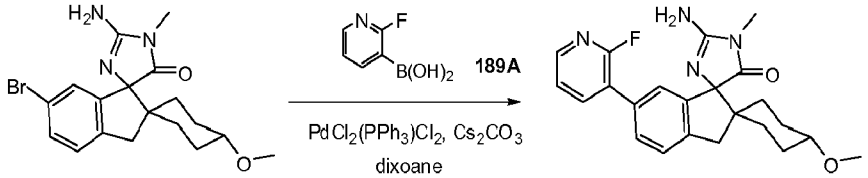
Example 149. Synthesis of Compound 188



I-6 188A 188

According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.052 mmol) was coupled with compound **188A** (7 mg, 0.052 mmol) to afford product **compound 188** (10.0 mg, 48%) as a white solid. **LC-MS** t_R = 3.580 min in 7 min chromatography, MS (ESI) *m/z* 409.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.72 (s, 1H), 8.48 (d, J = 1.6 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.75 (dd, J = 1.2, 7.6 Hz, 1H), 7.69 (s, 1H), 7.56 (m, 1H), 3.8043 (s, 3H), 3.26-3.38 (m, 6H), 2.00-2.15 (m, 2H), 1.90 (m, 1H), 1.32-1.52 (m, 5H).

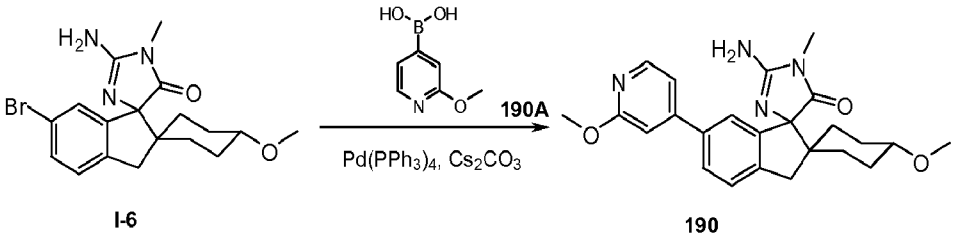
Example 150. Synthesis of Compound 189



I-6 189

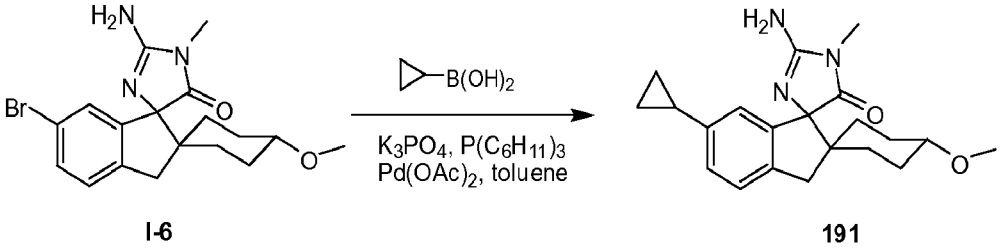
According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.051 mmol) was coupled with compound **189A** (18 mg, 0.13 mmol) to give **compound 189** (2.9 mg, 14%). **LC-MS**: t_R = 0.922 min min in 2 min chromatography, MS (ESI) *m/z* 409.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.07-8.06 (d, J = 4.4 Hz, 1H), 7.94-7.90 (m, 1H), 7.43-7.41 (d, J = 8.0 Hz, 1H), 7.36-7.28 (d, J = 7.6 Hz, 2H), 7.12 (s, 1H), 3.26-3.23 (s, 3H), 3.12-3.05 (m, 3H), 3.02-2.96 (s, 3H), 1.95-1.76 (m, 4H), 1.58-1.51 (t, 1H), 1.37-1.27 (m, 1.5H), 1.21-1.16 (m, 1.7H).

Example 151. Synthesis of Compound 190



According to a similar synthesis of **compound 4** descirbed in Example 27, compound **I-6** (20 mg, 0.05 mmol) was coupled with compound **190A** (12 mg, 0.08 mmol) to give **compound 190** (8 mg, 37%) as a white solid. **LC-MS** t_R = 0.846 min in 2 min chromatography, MS (ESI) *m/z* 421.1 $[M+H]^+$. **^{1}H NMR** (methanol-d_4 400 MHz TMS): δ 8.20 (d, J = 4.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.32 (br, 1H), 7.17 (br, 1H), 4.00 (s, 3H), 3.37 (s, 3H), 3.25-3.23 (m, 4H), 3.01 (s, 1H), 2.88 (s, 1H), 2.11-2.05 (m, 2H), 1.91-1.88 (m, 1H), 1.53-1.31 (m, 5H).

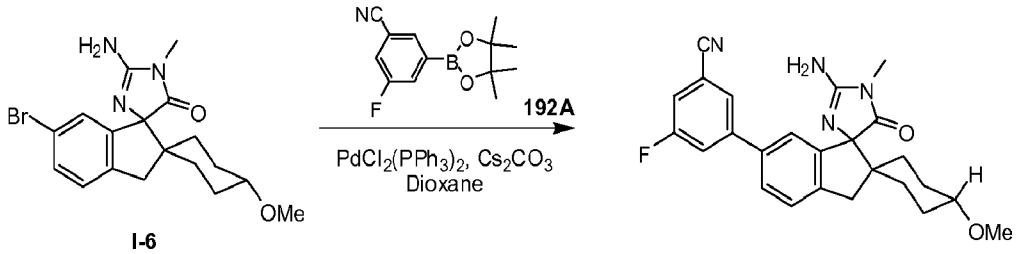
Example 152. Synthesis of Compound 191



To a suspension of compound **I-6** (39.1 mg, 0.1 mmol), cyclopropylboronic acid (11.2 mg, 0.13 mmol), K_3PO_4 (75 mg, 0.35 mmol) and tricyclohexylphosphine (5.6 mg, 0.02 mmol) in toluene and water (3 mL/100 uL) was added $Pd(OAc)_2$ (3.0 mg, 0.01 mmol) under a N_2 atmosphere, the resulting mixture was heated in a sealed tube at 100 °C for 1 day. After cooling to room temperature, the mixture was extracted with ethyl acetate (3 × 10 mL) and washed with brine (10 mL). The separated organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (basic) to give compound **compound 191** (2.3 mg, 6%) as a white solid. **LC-MS** t_R = 0.925 min in 2 min chromatography, MS

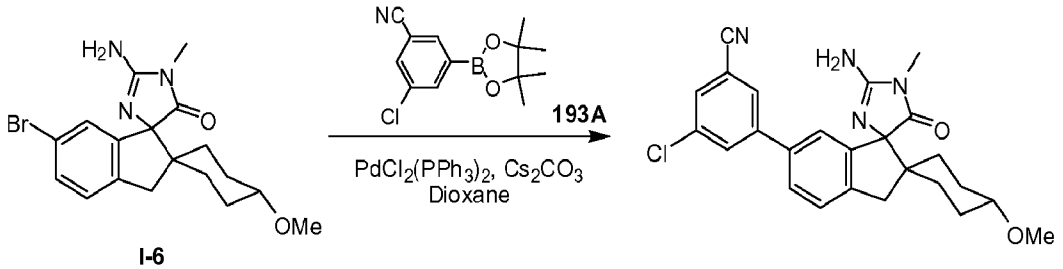
(ESI) *m/z* 354.0 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.07-7.09 (d, J = 8.0 Hz, 1H), 6.88-6.90 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 3.36 (s, 3H), 3.11 (t, J = 10.8 Hz, 2H), 3.05 (s, 3H), 2.90-2.92 (d, J = 9.2 Hz, 1H), 1.95-1.72 (m, 3H), 1.75 (m, 2H), 1.32 (m, 3H), 1.26 (m, 3H), 0.85 (q, 2H), 0.55 (q, 2H).

Example 153. Synthesis of Compound 192



$Pd(PPh_3)_2Cl_2$ (5 mg) in a 10 mL of flask under a nitrogen atmosphere was treated sequentially with compound **I-6** (25 mg, 0.06 mmol) in 1,4-dioxane (2 mL), Cs_2CO_3 (2 N, 0.09 mL, 0.18 mmol) and compound **192A** (31.5 mg, 0.12 mmol). The mixture was heated at 120 °C in a CEM microwave reactor under a nitrogen atmosphere for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC to give **compound 192** (5.6 mg, 20%) as a white solid. **LC-MS** t_R = 0.958 min in 2 min chromatography, MS (ESI) m/z 433.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400MH): δ 7.83 (s, 1H), 7.70-7.77 (m, 1H), 7.59 (m, 1H), 7.50 (m, 1H), 7.43 (m, 1H), 7.27 (s, 1H), 3.26 (s, 3H), 3.13 (m, 3H), 3.05 (s, 3H), 1.81-2.04 (m, 3H), 1.64 (m, 1H), 1.25-1.46 (m, 4H)

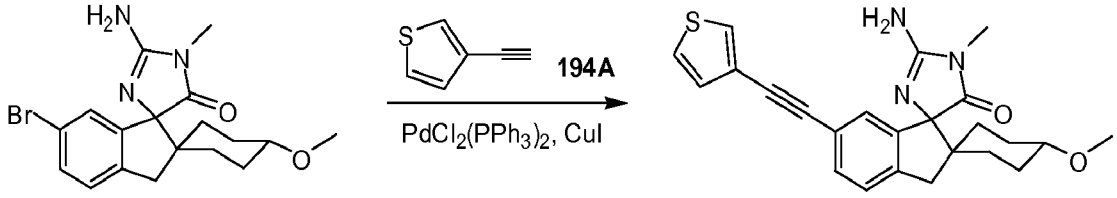
Example 154. Synthesis of Compound 193



I-6 193

According to a similar synthesis of **compound 192**, compound **I-6** (20 mg, 0.051 mmol) was comound with boronic ester **193A** (40 mg, 0.153 mmol) to give **compound 193** (1.8 mg, yield 8%) as a white solid. **LC-MS** t_R = 0.999 min in 2 min chromatography, MS (ESI) *m/z* 449.0 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.66 (d, J = 14.4 Hz, 2H), 7.51 (s, 1H), 7.37 (m, 2H), 7.12 (s, 1H), 3.28 (s, 3H), 3.21-3.01 (m, 6H), 1.95 (m, 3H), 1.48 (m, 1H), 1.36 (m, 2H), 1.24 (m, 2H).

Example 155. Synthesis of Compound 194

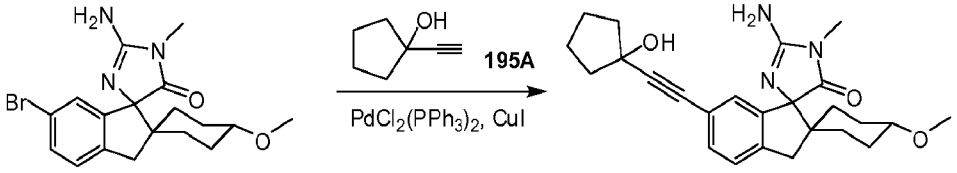


I-6 194

Compound **I-6** (16 mg, 0.041 mmol) was dissolved in Et_3N (5 ml) and Et_2NH (1 ml), the resulting mixture was degassed and purged with nitrogen for three times. $Pd(PPh_3)_2Cl_2$ (2 mg, 0.003 mmol) and CuI (0.57 mg, 0.003 mmol) were added under a nitrogen atmosphere and the system was degassed again. 3-ethynylthiophene (**194A**) (11 mg, 0.10 mmol) was added by syringe. The system was degassed one more time, then was heated at 50~60 °C for 12 h. LCMS showed that the reaction was completed and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (petroleum ether: ethyl acetate = 5: 1) and preparative RP-HPLC to afford compound **194** (1.9 mg, 11%) as a white solid. **LC-MS** t_R = 0.995 min in 2 min

chromatography, MS (ESI) *m/z* 420.0 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.60 (s, 1H), 7.40-7.46 (m, J = 7.6 Hz, 2H), 7.31-7.33 (d, J = 8.0 Hz, 1H), 7.17-7.18 (d, J = 4.8 Hz, 1H), 7.10 (s, 1H), 3.36 (s, 3H), 3.11-3.17 (m, 3H), 3.06 (s, 3H), 1.93-2.04 (m, 2H), 1.82-1.88 (m, 1H), 1.60-1.63 (m, 1H), 1.30-1.38 (m, 2H), 1.24-1.29 (m, 2H).

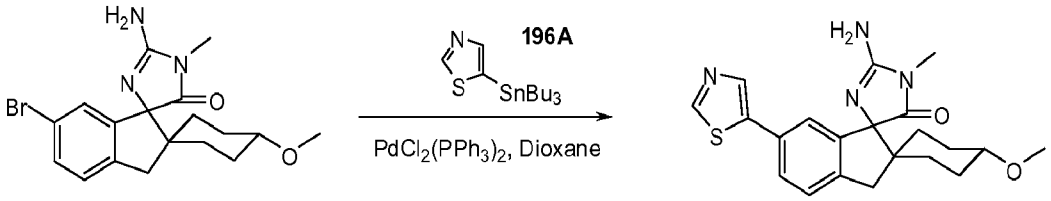
Example 156. Synthesis of Compound 195



I-6 **195**

According to a similar synthesis of compound 194, compound **I-6** (16 mg, 0.041 mmol) was coupled with 1-ethynylcyclopentanol (**195A**) (23 mg, 0.204 mmol) to afford compound **195** (3.7 mg, 22%) as a white solid. **LC-MS** t_R = 1.057 min in 2 min chromatography, MS (ESI) *m/z* 422.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.29-7.30 (m, 2H), 7.02 (s, 1H), 3.33 (s, 3H), 3.14-3.27 (m, 1H), 3.07-3.11 (m, 2H), 3.06 (s, 3H), 1.94-2.03 (m, 6H), 1.78-1.86 (m, 5H), 1.55-1.65 (m, 1H), 1.27-1.43 (m, 4H).

Example 157. Synthesis of Compound 196

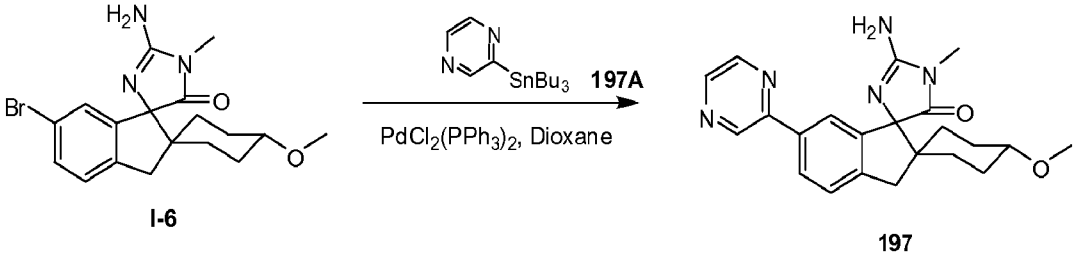


I-6 **196**

To a solution of compound **I-6** (50 mg, 0.127 mmol) in 1,4-dioxane (2 mL) was added compound **196A** (120 mg, 0.314 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol). The reaction mixture was heated at 125 °C in a CEM microwave reactor for 45 min. The solvents were removed under reduced pressure, and the residue was purified by preparative HPLC to give **compound 196** (3.4 mg, 6.7%). **LC-MS**: t_R = 0.894 min in 2 min chromatography, MS (ESI) *m/z* 397.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ

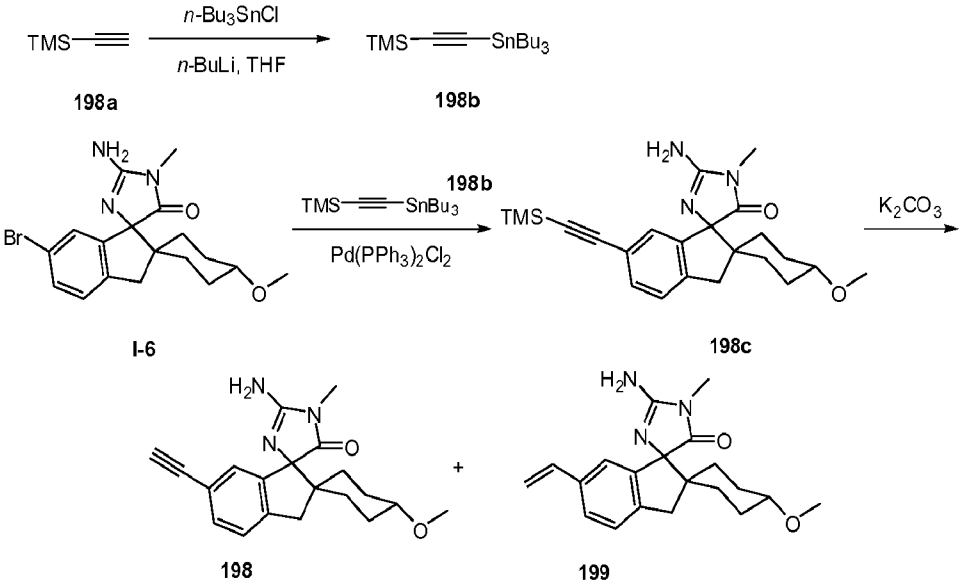
8.87 (s, 1H), 8.08 (s, 1H), 7.56-7.58 (dd, J = 1.6, 7.6 Hz, 1H), 7.49-7.50 (s, 1H), 7.34-7.36 (d, J = 8.0 Hz, 1H), 3.21 (s, 3H), 3.13 (s, 3H), 3.09-3.11 (m, 1H), 3.02-3.06 (m, 1H), 1.89-1.99 (m, 2H), 1.75-1.78 (m, 1H), 1.16-1.36 (m, 6H).

Example 158. Synthesis of Compound 197



According to a similar synthesis of **compound 196**, compound **I-6** (25 mg, 0.064 mmol) was coupled with compound **197A** (59 mg, 0.16 mmol) to give **compound 197** (1.3 mg, 5%) as a white solid. **LC-MS** t_R = 0.948 min in 2 min chromatography, MS (ESI) *m/z* 392.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 9.03 (s, 1H), 8.56 (s, 1H), 8.44 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.23 (m, 1H), 3.25 (s, 3H), 3.17-3.03 (m, 6H), 1.97 (m, 2H), 1.78 (m, 1H), 1.38-1.19 (m, 5H).

Example 159. Synthesis of Compounds 198 and 199



Procedure for preparation of compound 198b

To a solution of compound **198a** (2.65 g, 27 mmol) in THF (80 mL) was added *n*-BuLi (2.5 M in hexanes, 11.88 mL, 29.7 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min and at 0 °C 30 min. After being cooled to -78 °C, the reaction mixture was treated with *n*-Bu_3SnCl (9.67 g, 8 mL, 29.7 mmol), and allowed to warm to room temperature over 5 h. The solvent was removed under vacuum, and the residue was partitioned between diethyl ether (100 mL) and H_2O (80 mL). The diethyl ether layer was washed with brine (80mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude (Al_2O_3, petroleum) afforded compound **198b** as a colorless oil (9.4 g, 90%).

Procedure for preparation of compound 198c

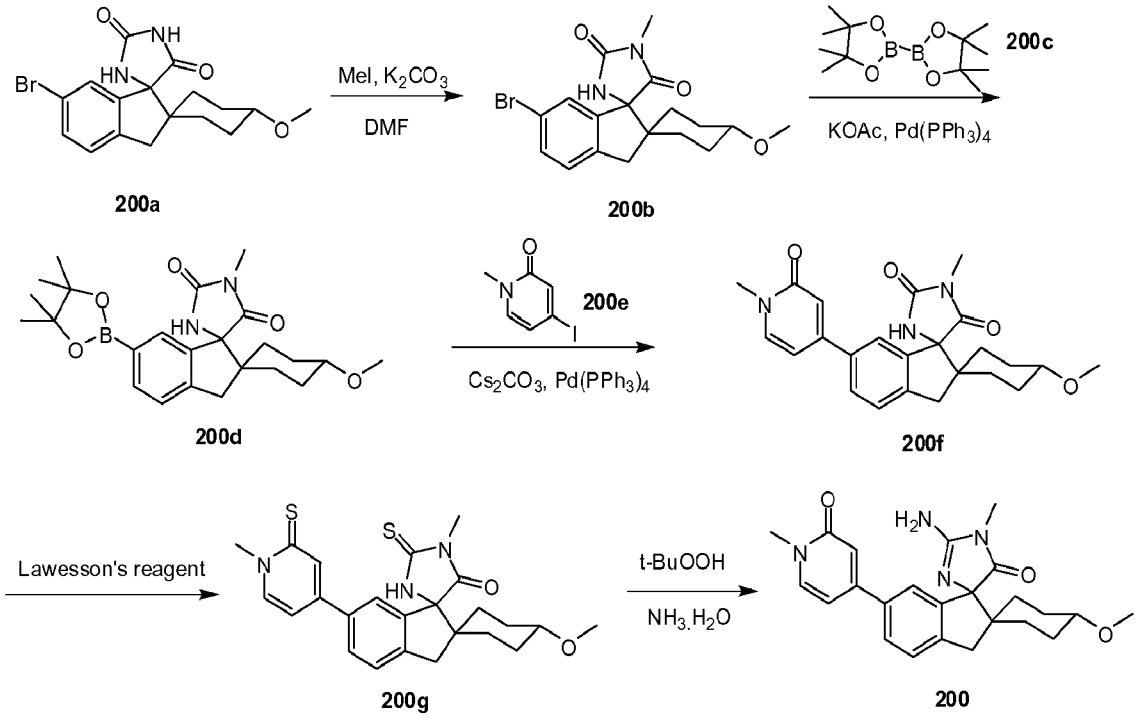
A solution containing compound **I-6** (50 mg, 0.13 mmol) and compound **198b** (246 mg, 0.635 mmol) in toluene (4 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (5 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 30 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous of CsF (4M, 8 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (petroleum/ethyl acetate = 1:1) to give compound **198c** (30 mg, 58%) as a white solid.

Procedure for preparation of compounds 198 and 199

Anhydrous K_2CO_3 (100 mg, 0.7 mmol) and compound **198c** (30 mg, 0.07 mmol) were suspended in MeOH (2 mL) and stirred at room temperature for 1 h. LCMS showed that the reaction was completed. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL), washed with brine (2 × 10 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative HPLC (basic) afforded **compound 198** (6.80 mg, 29%), **LC-MS** t_R = 0.890 min in 2 min chromatography, MS (ESI) *m/z* 338.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.38-7.40 (d, J = 8.0 Hz, 1H), 7.29-

7.31 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 3.44 (s, 1H), 3.36 (s, 3H), 3.10-3.18 (m, 3H), 3.06 (s, 3H), 1.96-2.03 (m, 2H), 1.80-1.85 (m, 1H), 1.57-1.65 (m, 1H). 1.23-1.44 (m, 4H); and by-product **compound 199** (8.20 mg, 35%) as a white solid, **LC-MS** t_R = 0.815 min in 2 min chromatography, MS (ESI) m/z 340.1 $[M+H]^+$.**^{1}H NMR** (CD_3OD, 400 MHz): δ 7.21-7.23 (d, J = 8.0 Hz, 1H), 7.14-7.16 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.56-6.63 (q, 1H), 5.58-5.62 (d, J = 17.6 Hz, 1H), 5.05-6.07 (d, J = 11.2 Hz, 1H), 3.24 (s, 3H), 2.88-3.07 (m, 6H), 1.84-1.94 (m, 2H), 1.72-1.75 (m, 1H), 1.47-1.54 (m, 1H). 1.12-1.35 (m, 4H).

Example 160. Synthesis of Compound 200



Procedure for preparation of compound 200b

To a solution of compound **200a** (200 mg, 0.53 mmol) in DMF (2 mL), K_2CO_3 (116 mg, 1.06 mmol) and MeI (60 mg, 0.53 mmol) was added subsequently. After stirring for 3 h, the reaction mixture was diluted with water (3 mL), the precipitate was collected by filtration, washed with water, dried *in vacuo* to give compound **200b** (160 mg, 77% crude yield) as a white solid, which was used directly in next step.

Procedure for preparation of compound 200d

The crude product of compound **200b** (160 mg 0.41 mmol), compound **200c** (155 mg, 0.6 mmol), KOAc (120 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (94 mg, 0.08 mmol) were suspended in anhydrous dioxane (2 mL) under a nitrogen atmosphere and then was heated at 90 °C for 4 h. The mixture was diluted with water (5 mL), extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the crude product **200d**, which was used for next step without further purification.

Procedure for preparation of compound 200f

The crude product of compound **200d** was dissolved in dioxane (2 mL) under a nitrogen atmosphere. Compound **200e** (96 mg, 0.41 mmol), $Pd(PPh_3)_4$ (90 mg, 0.08 mmol) and Cs_2CO_3 (2.0 M *aq*. 0.5 mL) were added subsequently under a nitrogen atmosphere. The reaction mixture was heated at 90 °C overnight. The solvent was evaporated and the residue was purified on preparative TLC eluting with EtOAc to give compound **200f** (50 mg, 30% yield for two steps) as a white solid.

Procedure for preparation of compound 200g

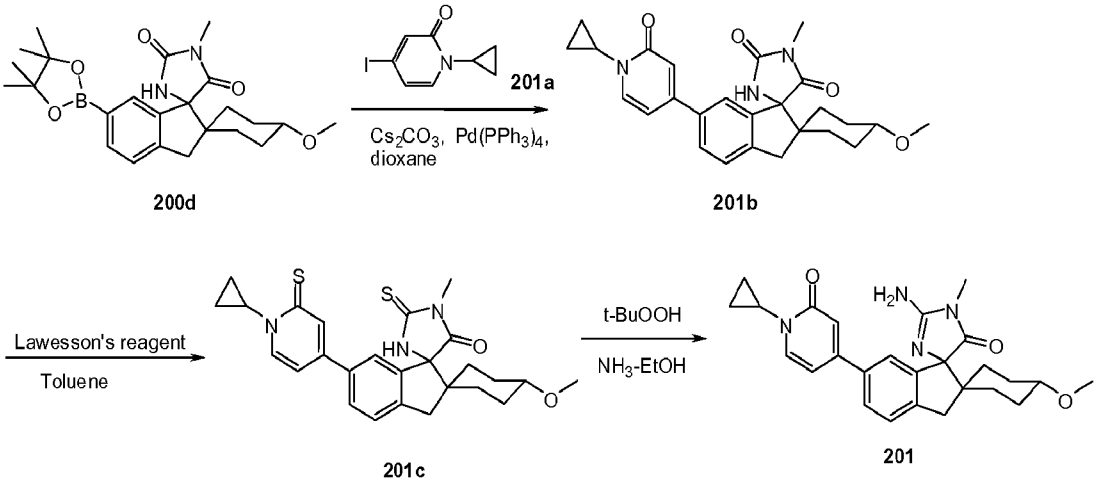
A solution of compound **200f** (28 mg, 0.066mmol) and Lawesson's Reagent (67 mg, 0.166 mmol) in anhydrous toluene (2 mL) was stirred at 140 °C for 30 min in a microwave reactor. LCMS showed that the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 2: 1) to give compound **200g** (20 mg, 66%) as a white solid.

***Procedure for preparation of* compound 200**

A mixture of compound **200g** (20 mg, 0.044 mmol) and *t*-butyl hydroperoxide (122 mg, ca. 65% solution in water, 0.88 mmol) in ammonia (1 mL) and MeOH (5 mL) was stirred at room temperature overnight, LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure to dryness, which was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and preparative RP-

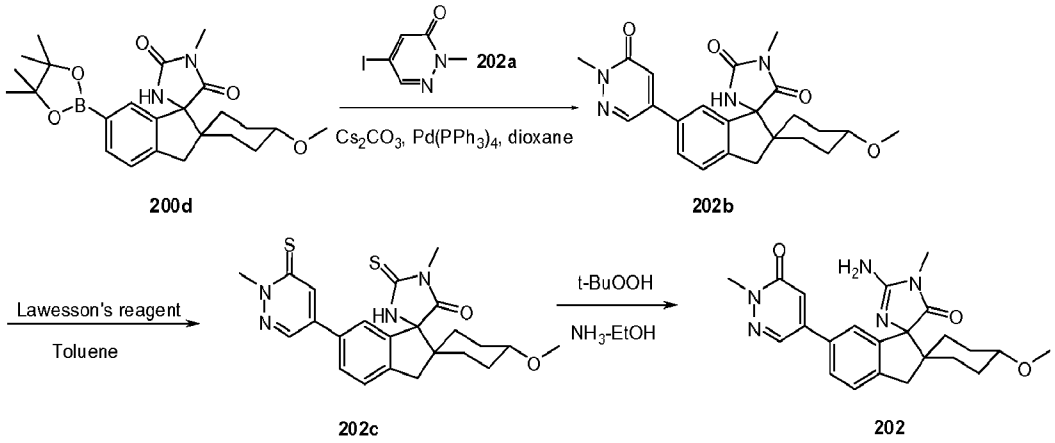
HPLC to give **compound 200** (5.6 mg, 25%) as a white solid. **LC-MS** t_R = 0.826 min in 2 min chromatography, MS (ESI) *m/z* 421.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.69-7.71 (d, J = 7.2 Hz, 1H), 7.60-7.62 (d, J = 7.6 Hz, 1H), 7.43-7.45 (d, J = 7.6 Hz, 1H), 7.30 (s, 1H), 6.75 (s, 1H), 6.68-6.70 (d, J = 7.2 Hz, 1H), 3.60 (s, 3H), 3.33 (s, 3H), 3.11-3.21 (q, 3H), 3.07 (s, 3H), 1.93-2.05 (m, 2H), 1.85-1.88 (m, 1H), 1.61-1.65 (m, 1H), 1.36-1.45 (m, 2H), 1.30-1.33 (m, 2H).

Example 161. Synthesis of Compound 201



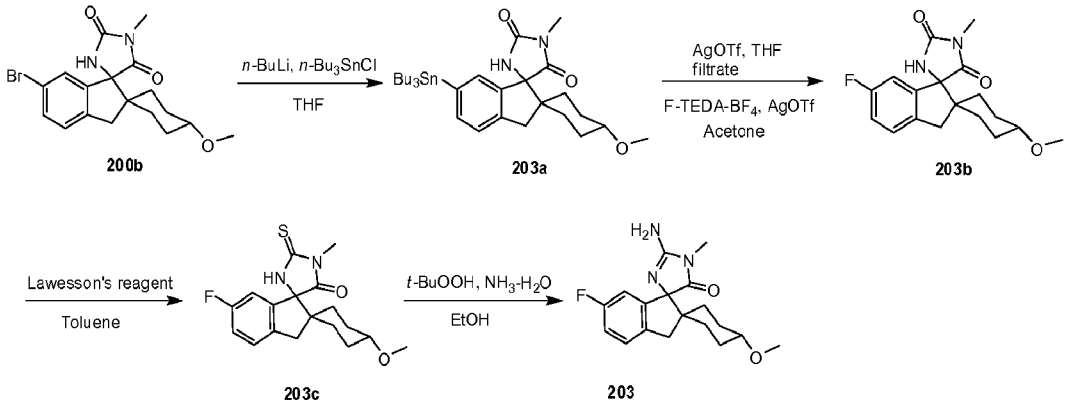
According to a similar synthesis of **compound 200**, compound **200d** was coupled with compound **201a** (99 mg, 0.38 mmol) to give compound **201b (**70 mg, 59% yield). Compound **201b** (70 mg, 0.16 mmol) was reacted with Lawesson's reagent (64 mg, 0.16 mmol) to give compound **201c (**20 mg, 26%), which was converted to final product **compound 201** (3.5 mg, 18%) as a white solid. **LC-MS** t_R = 0.887 min in 2 min chromatography, MS (ESI) *m/z* 447.3 $[M+H]^+$. **^{1}H NMR** (methanol-d_4 400 MHz TMS): δ 7.70-7.73 (m, 2H), 7.60 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 6.79 (s, 1H), 6.72 (d, J = 7.2 Hz, 1H), 3.38 (s, 3H), 3.28-3.14 (m, 7H), 2.11-2.04 (m, 2H), 1.91-1.88 (m, 1H), 1.48-1.31 (m, 5H), 1.20-1.15 (m, 2H), 0.97-0.95 (m, 2H).

Example 162. Synthesis of Compound 202



According to a similar synthesis of **compound 200**, compound **200d** was coupled with compound **202a** (89 mg, 0.38 mmol) to give compound **202b** (70 mg, 65% yield). Compound **202b** (70 mg, 0.17 mmol) was then reacted with Lawesson's reagent (67 mg, 0.17 mmol) to give compound **202c** (25 mg, 33%), which was converted to the final product **compound 202** (3.5 mg, 14.5%). **LC-MS** t_R = 0.828 min in 2 min chromatography, MS (ESI) *m/z* 422.1 $[M+H]^+$. **^{1}H NMR** (methanol-d_4 400 MHz TMS): δ 8.32 (s, 1H), 7.81-7.79 (m, 1H), 7.68 (s, 1H), 7.58-7.56 (m, 1H), 7.18 (s, 1H), 3.82 (s, 3H), 3.38 (s, 3H), 3.26-3.19 (m, 6H), 2.12-2.05 (m, 2H), 1.91-1.88 (m, 1H), 1.52-1.43 (m, 3H), 1.36-1.25 (m, 2H).

Example 163. Synthesis of Compound 203



Procedure for preparation of compound 203a

To a solution of compound **200b** (150 mg, 0.38 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (2.5 M, 0.48 mL). The reaction mixture was stirred at -78 °C for 2 h. Then, Bu_3SnCl (150 mg, 0.45 mmol) was added and stirred at -78 °C for 2 h more. The mixture was warmed up to 10 °C and quenched by addition with saturated NH_4Cl (5 mL). The mixture was extracted with ethyl acetate (2 × 30 mL). The organic fractions were concentrated to give crude compound **203a** (230 mg, 100% crude) as a yellow oil, which was used directly in the next step without further purification.

Procedure for preparation of compound 203b

A suspension of compound **203a** (230 mg, 0.4 mmol), F-TEDA-BF_4 (170 mg, 0.48 mmol) and AgOTf (200 mg, 0.8 mmol) in anhydrous acetone (5 mL) was stirred at 15 °C for 20 min. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC eluting with petroleum ether: ethyl acetate (1: 1) to give compound **203b** (62 mg, 50%) as a white solid.

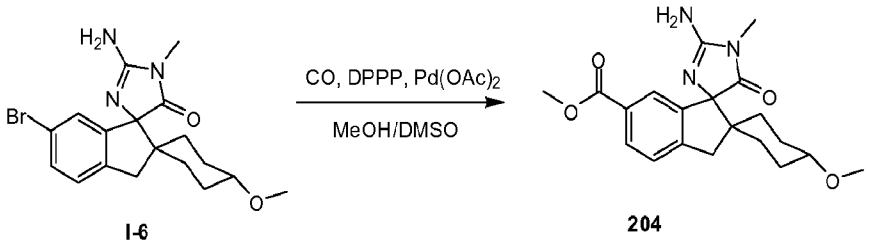
Procedure for preparation of compound 203c

A suspension of compound **203c** (60 mg, 0.18 mmol) and Lawesson's Reagent (77 mg, 0.19 mmol) in anhydrous toluene (2 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative preparative HPLC to give compound **203d** (33 mg, 45%) as a white solid.

Procedure for preparation of compound 203

A solution of compound **203c** (30 mg, 0.085 mmol), *t*-BuOOH (0.5 mL), NH_3-H_2O (0.5 mL) in EtOH (2 mL) was stirred at 10 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative preparative HPLC to give **compound 203** (22 mg, 50%) as a white solid. **LCMS**: t_R = 1.243 min in 3 min chromatography, MS ESI *m/z* 332.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.20-7.30 (m, 1H), 6.90-7.00 (m, 1H), 6.65-6.75 (d, J = 8.4 Hz, 1H), 3.35-3.40 (s, 3H), 2.90-3.15 (m, 6H), 1.90-2.10 (m, 2H), 1.75-1.85 (m, 1H), 1.50-1.65 (m, 1H), 1.20-1.45 (m, 4H). **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -118.00.

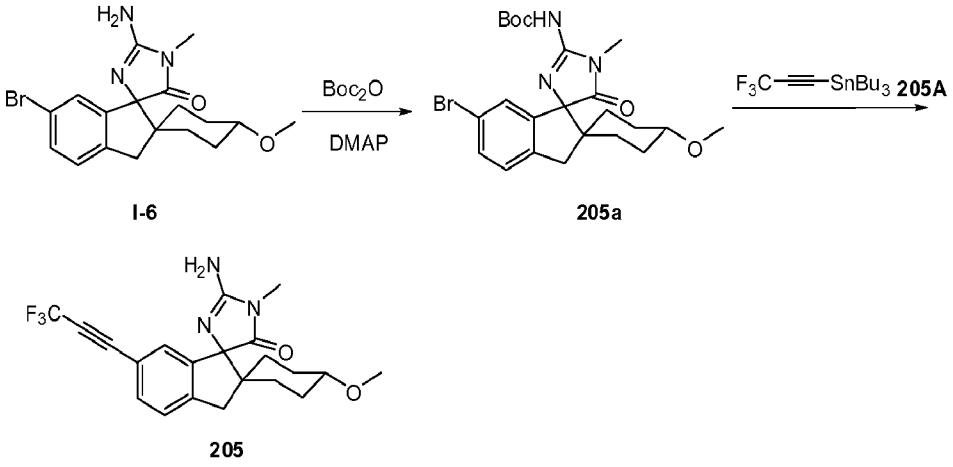
Example 164. Synthesis of Compound 204



I-6 204

To a solution of compound **I-6** (100 mg, 0.255 mmol) in MeOH (2 mL) and DMSO (6 mL) was added DPPP (52 mg, 0.127), $Pd(OAc)_2$ (31 mg, 0.127 mmol) and Et_3N (2 mL). The reaction was heated at 80 °C under CO at 40 psi for 24 h. The mixture was filtered and the filtrated was concentrated to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and acidic preparative HPLC to give **compound 204** (5.0 mg, 5%) as a white solid. **LC-MS** t_R = 0.859 min in 2 min chromatography, MS (ESI) *m/z* 372 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.07 (d, J = 7.6 Hz, 1H), 7.89 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 3.37 (s, 3H), 3.29-3.18 (m, 6H), 2.07 (m, 2H), 1.87 (m, 1H), 1.46 (m, 4H), 1.34 (m, 1H).

Example 165. Synthesis of Compound 205



I-6 205a 205

Procedure for preparation of Compound 205a

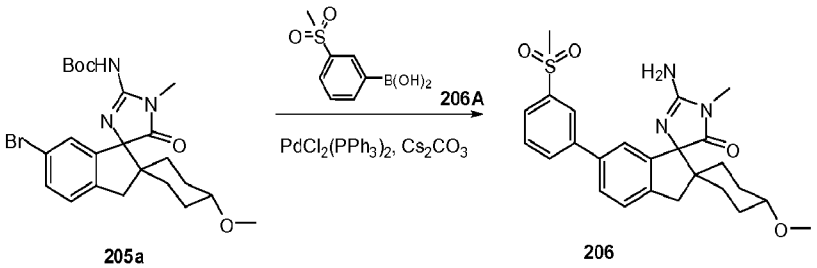
Compound **I-6** (50 mg, 0.127 mmol) and Boc_2O (42 mg, 0.19 mmol) was dissolved in THF (5 mL), this solution was added DMAP (23 mg, 0.19 mmol) and Et_3N (0.04 mL, 0.25 mmol), the reaction mixture was stirred at room temperature overnight.

LCMS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (petroleum ether: ethyl acetate = 5:1) to give **205a** (30 mg, 48%) as a white solid.

Procedure for preparation of compound 205

A solution containing compound **205a** (47 mg, 0.122 mmol) and compound **205A** (40 mg, 0.081 mmol) in toluene (5 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (4 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) and preparative HPLC to afford product **compound 205** (0.6 mg, 1%) as a white solid. **LC-MS** t_R = 1.130 min in 2 min chromatography, MS (ESI) *m/z* 406.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.57-7.60 (d, J = 10.4 Hz, 1H), 7.44-7.47 (d, J = 10.4 Hz, 1H), 7.36 (s, 1H), 3.36 (s, 3H), 3.18-3.32 (m, 3H), 3.11 (s, 3H), 1.96-2.07 (m, 2H), 1.83-1.89 (m, 1H), 1.52-1.59 (m, 1H), 1.26-1.40 (m, 4H).

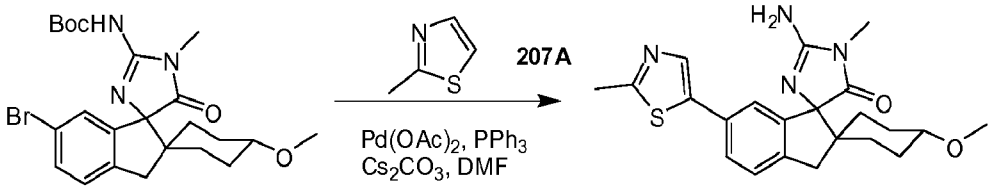
Example 166. Synthesis of Compound 206



$Pd(PPh_3)_2Cl_2$ (4 mg) was treated sequentially with compound **205a** (30 mg, 0.06 mmol) in 1,4-dioxane (2 mL), Cs_2CO_3 (2 M in water, 0.15 mL, 0.3 mmol)) and compound **206A** (24 mg, 0.12 mmol) under N_2 atmosphere. The mixture was stirred at 120 °C for 15 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the residue, which

was purified by preparative TLC (CH_2Cl_2/MeOH = 5:1) and preparative HPLC to give compound **206** (15.0 mg, 54%) as a white solid. **LC-MS** t_R = 0.942 min in 2 min chromatography, MS (ESI) *m/z* 468.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.12 (s, 1H), 7.90-7.95 (t, J = 8.4, 9.2 Hz, 2H), 7.67-7.71 (t, J = 8.0 Hz, 1H), 7.59-7.61 (d, J = 8.0 Hz, 1H), 7.43-7.45 (d, J = 7.6 Hz, 1H), 7.28 (s, 1H), 3.36 (s, 3H), 3.08-3.21 (m, 6H), 3.05 (s, 3H), 1.96-2.04 (m, 2H), 1.85-1.87 (m, 1H), 1.63-1.67 (t, J = 14.0 Hz, 1H), 1.36-1.42 (m, 2H), 1.29-1.33 (m, 2H).

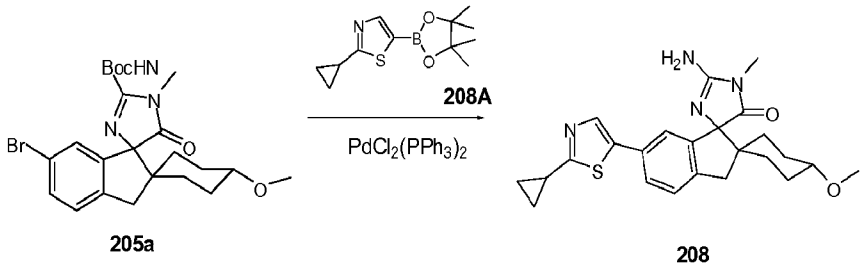
Example 167. Synthesis of Compound 207



205a **207**

The compound **205a** (25 mg, 0.051 mmol) and Cs_2CO_3 (33 mg, 0.10 mmol) was dissolved in DMF (4 ml), the resulting mixture was degassed and purged with nitrogen for three times. $Pd(OAc)_2$ (2 mg, 0.008 mmol) and PPh_3 (2 mg, 0.005 mmol) were added under a nitrogen atmosphere and the system was degassed again. 2-methyl-thiazole(**207A**) (100 mg, 1.0 mmol) was added by syringe. The system was degassed one more time. The reaction was heated to 168 °C for 45 min in a microwave reactor. LCMS showed that the reaction was completed, and the solvent was removed by evaporation under reduced pressure. The residue was purified by preparative TLC (petroleum ether: ethyl acetate = 5:1) and preparative RP-HPLC to afford compound **207** (1.9 mg, 8%) as a white solid. **LC-MS** t_R = 1.009 min in 2 min chromatography, MS (ESI) *m/z* 411.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.84 (s, 1H), 7.51-7.53 (d, J = 8.0 Hz, 1H), 7.36-7.38 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 3.36 (s, 3H), 3.11-3.18 (m, 3H), 3.07 (s, 3H), 2.71 (s, 3H), 1.96-2.04 (m, 2H), 1.84-1.91 (m, 1H), 1.60-1.64 (m, 1H), 127-1.41 (m, 4H).

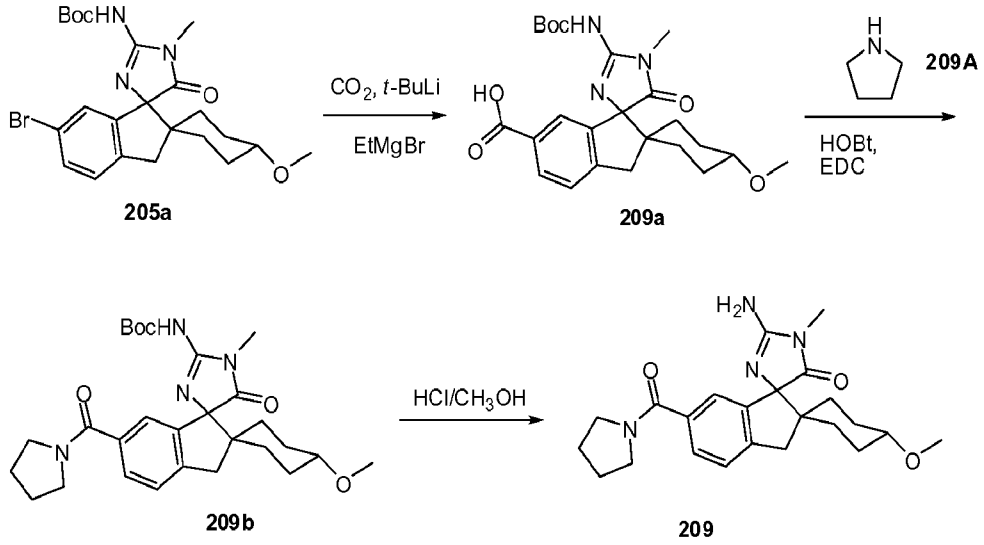
Example 168. Synthesis of Compound 208



205a 208

According to a similar synthesis of **compound 206**, compound **205a** (20 mg, 0.051 mmol) was coupled with compound **208A** (20 mg, 0.077 mmol) to give compound **208** (4.3 mg, 15%) as a white solid. **LC-MS** t_R = 0.951 min in 2 min chromatography, MS (ESI) *m/z* 437 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.58 (s, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.05 (s, 1H), 3.27 (s, 3H), 3.11 (d, J = 15.2 Hz, 1H), 3.04 (m, 1H), 2.99 (s, 3H), 2.95 (d, J = 15.2 Hz, 1H), 2.22 (m, 2H), 1.9 (m, 2H), 1.38 (m, 5H), 1.0 (m, 4H).

Example 169. Synthesis of Compound 209



205a 209a 209b 209

Procedure for preparation of compound 209a

A solution of compound **205a** (100 mg, 0.203 mmol) in dry THF (5 mL) was added dropwise EtMgBr (0.3 mL, 1.0 mmol) at -78 °C under a N_2 atmosphere. After stirring for 15 min, *t*-BuLi (0.8 mL, 1.1 mmol) was added dropwise and stirred for 20

min. CO_2 was bubbled through the reaction mixture for 25 min. he reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to give compound **209a** (0.1 g, 85%) as a brown oil.

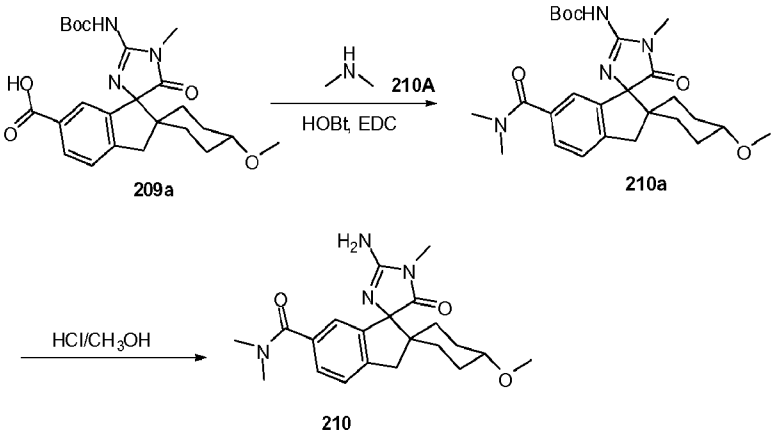
Procedure for preparation of compound 209b

A mixture of compound **209a** (50 mg, 6 mmol), **209A** (5 mg, 60 mmol), HOBt (2.7 mg, 18 mmol) and EDC-HCl (4 mg, 18 mmol) in Et_3N (2 mg, 18 mmol) and CH_2Cl_2 was stirred at room temperature overnight. The solvent was removed by evaporation to give the residue, which was purified by preparative TLC (petroleum: ethyl acetate = 1: 1) to give compound **209b** (18 mg, 50%) as a yellow solid.

Procedure for preparation of compound 209

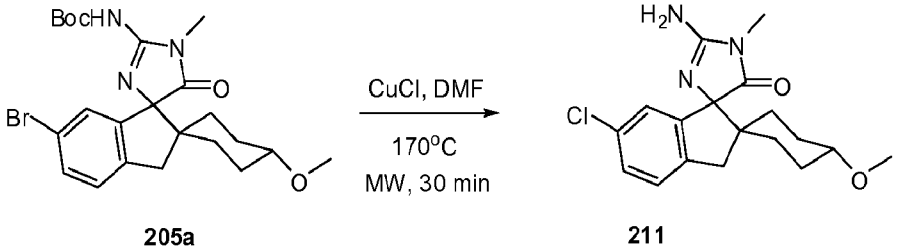
A solution of compound **209b** (18 mg, 0.035 mmol) in HCl/dioxane (5 mL, 4 N) was stirred at room temperature for 15 min. The solvent was removed to give the residue and which was purified by preparative HPLC (acidic) to afford **compound 209** (3.1 mg, 10%) as a white solid. **LC-MS** t_R = 1.316 min in 2 min chromatography, MS (ESI) *m/z* 410.23 $[M+H]^+$.**^{1}H NMR** (CD_3OD 300 MHz): δ 7.54-7.36 (m, 3H), 3.60 (m, 2H), 3.45 (m, 2H), 3.36 (s, 3H), 3.2 (s, 3H), 3.07 (s, 1H), 1.9-1.8 (m, 7H), 1.5-1.3 (m, 5H).

Example 170. Synthesis of Compound 210



According to a similar synthesis of **compound 210**, compound **209a** (30 mg, 6 mmol) was coupled with compound **210A** (5 mg, 60 mmol) to give crude compound **210a** (22 mg, 70%) as a yellow solid, which was removed the protecting group in HCl/dioxane (5 mL, 4N) to afford **compound 210** (trifluroacetic salt) (1.7 mg, 10%) as a white solid. **LC-MS** t_R = 0.807 min in 2 min chromatography, MS (ESI) *m/z* 384.22 $[M+H]^+$. ^1H NMR (CD_3OD 400 MHz): δ 7.35 (q, 2H), 7.18 (s, 1H), 3.25 (s, 3H), 3.09 (m, 3H), 3.12 (s, 1H), 2.9 (s, 3H), 2.8 (s, 3H), 1.9-1.7 (m, 3H), 1.3-1.2 (m, 5H).

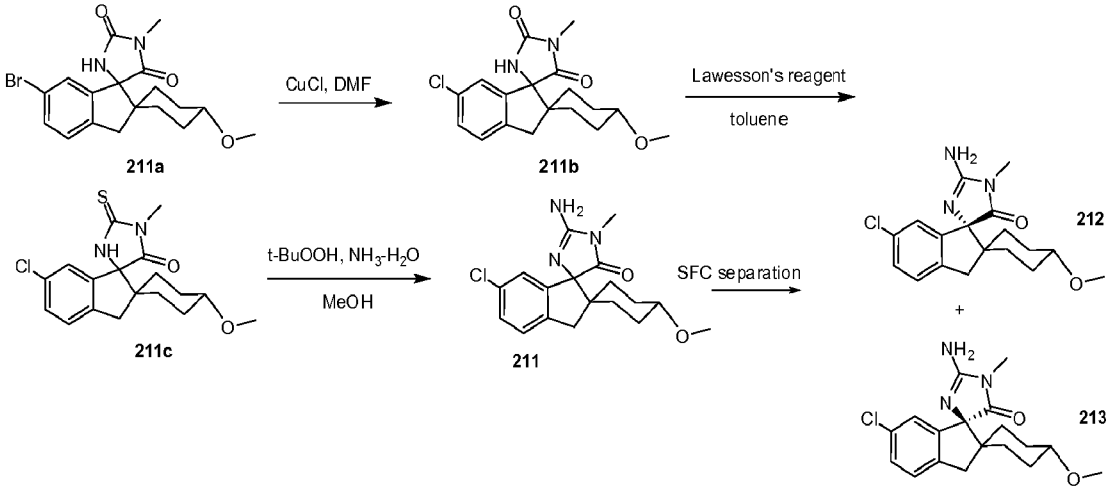
Example 171. Synthesis of Compound 211



Compound **205a** (25 mg, 0.051 mmol) and CuCl (60 mg, 0.61 mmol) was dissolved in DMF (3 mL), the resulting mixture was degassed and purged with N_2 for three times. The reaction was heated at 170 °C for 30 min in microwave. LCMS showed that the reaction was completed and solvent was removed under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 5: 1) and preparative HPLC to afford compound **211** (14.1 mg, 80%) as a white solid. **LC-MS** t_R = 1.014 min in 2

min chromatography, MS (ESI) *m/z* 348.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.26-7.32 (m, 2H), 7.01 (s, 1H), 3.33 (s, 3H), 3.12-3.18 (m, 1H), 3.02-3.09 (m, 5H), 1.96-2.07 (m, 2H), 1.82-1.84 (m, 1H), 1.59-1.67 (m, 1H), 1.32-1.44 (m, 2H), 1.27-1.30 (m, 2H)

Example 172. Synthesis of Compounds 212 and 213



Procedure for preparation of compound 211b

A suspension of compound **211a** (600 mg, 1.5 mmol), CuCl (600 mg, 6.1 mmol) in anhydrous DMF (15 mL) was heated at 180 °C for 45 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 1: 1 to give compound **211b** (510 mg, 90%) as a yellow solid.

Procedure for preparation of compound 211c

A suspension of compound **211b** (510 mg, 1.47 mmol) and Lawesson's Reagent (650 mg, 1.6 mmol) in anhydrous toluene (15 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by prep HPLC to give compound **211c** (316 mg, 60%) as a white solid.

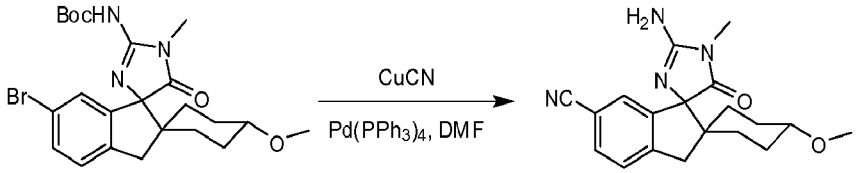
Procedure for preparation of compound 211, 212 and 213

A solution of compound **211c** (310 mg, 0.85 mmol), *t*-BuOOH (3 mL), NH_3-H_2O (3 mL) in EtOH (10 mL) was stirred at 10 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to

give **compound 211** (150 mg, 50%) as a white solid. **LCMS**: 728-054-1B, t_R = 1.310 min in 3 min chromatography, MS (ESI) *m/z* = 348.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.20-7.35 (m, 2H), 6.90-7.00 (s, 1H), 3.35-3.40 (s, 3H), 3.00-3.20 (m, 6H), 1.90-2.10 (m, 1H), 1.75-1.85 (s, 1H), 1.55-1.70 (m, 1H), 1.20-1.45 (m, 4H).

Compound 211 (40 mg, 0.12 mmol) was separated by preparative SFC to give **compound 212** (8.2 mg, 20%), **LCMS**: t_R = 0.899 min in 2 min chromatography, MS (ESI) *m/z* = 348.1 $[M+H]^+$. **SFC**: t_R = 6.29 min in 15 min chromatography, ee = 99.6%. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.20-7.35 (m, 2H), 6.90-7.00 (s, 1H), 3.35-3.40 (s, 3H), 3.00-3.20 (m, 6H), 1.90-2.10 (m, 1H), 1.75-1.85 (s, 1H), 1.55-1.70 (m, 1H), 1.20-1.45 (m, 4H); and **compound 212** (8.3 mg, 21%). **LCMS**: t_R = 0.893 min in 2 min chromatography, MS (ESI) *m/z* = 348.1 $[M+H]^+$. **SFC**: t_R = 8.39 min in 15 min chromatography, ee = 99.8%. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.20-7.35 (m, 2H), 6.90-7.00 (s, 1H), 3.35-3.40 (s, 3H), 3.00-3.20 (m, 6H), 1.90-2.10 (m, 1H), 1.75-1.85 (s, 1H), 1.55-1.70 (m, 1H), 1.20-1.45 (m, 4H).

Example 173. Synthesis of Compound 214

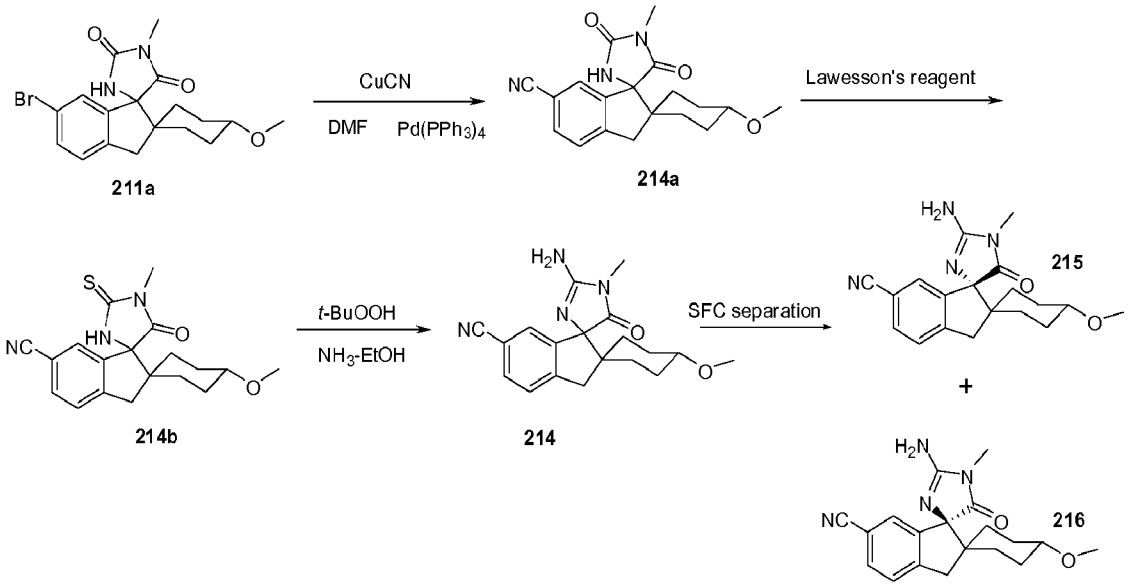


205a **214**

To a suspension of compound **205a** (40 mg, 0.08 mmol) and cyanocopper (18 mg, 0.2 mmol) in DMF (5 mL) was added $Pd(PPh_3)_4$ (5.5 mg, 0.0048 mmol) at room temperature under a nitrogen atmosphere atmosphere. After addition, the resulting mixture was heated at 120 °C in a sealed tube for 30 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and washed with brine (10 mL). The separated organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by basic preparative HPLC (basic) to give compound **214** (8.4 mg, 30%) as a white solid. **LC-MS** t_R = 0.820 min in 2 min chromatography, MS (ESI) *m/z* 338.9 $[M+H]^+$. **^{1}H NMR** (CD_3OD varian 400): δ 7.62

(d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 3.32 (s, 3H), 3.29-3.10 (m, 2H), 3.11 (m, 1H), 2.99 (s, 3H), 2.0-1.93 (m, 2H), 1.80 (m, 1H), 1.64 (m, 1H), 1.40 (m, 1H), 1.30-1.23 (m, 3H).

Example 174. Synthesis of Compounds 215 and 216



Procedure for preparation of Compound 214a

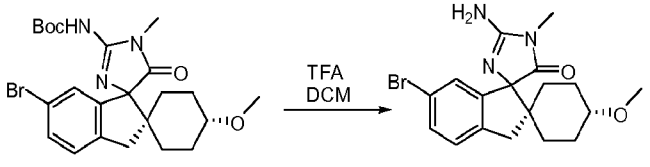
To a solution of compound **211a** (1.5 g, 3.3 mmol) in DMF (15mL) was added CuCN (682.5 mg, 6.6 mmol), and $Pd(PPh_3)_4$ (205.5 mg, 0.17 mmol) under nitrogen, the mixture was stirred at 180 °C in a CEM microwave reactor for 30min. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by column chromatography on silica gel eluting with hexane: EtOAc (20: 1 to 5: 1) to give compound **214a** (0.75 g, 58%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.55 (s, 1H), 7.44 (d, J = 7.2 Hz, 2H), 6.05 (s, 1H), 3.41 (s, 3H), 3.38-3.41 (m, 1H), 3.15-3.21 (d, J = 14 Hz, 2H), 2.94-2.97 (s, 3H), 1.89-2.10 (m, 3H), 1.18-1.47 (m, 5H).

Procedure for preparation of compounds 214, 215 and 216

According to a similar synthesis of **compound 211** described in Example 172, compound **214a** (750 mg, 2.21 mmol) was reacted with Lawesson's Reagent (893.6 mg, 2.21 mmol) under a nitrogen atmosphere to give compound **214b** (500 mg, 63%) as a white solid. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.57 (d, J = 8.4 Hz, 1H), 7.35-7.44 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 3.41 (s, 3H), 3.28-3.37 (m, 1H), 3.19 (s, 3H), 3.09-3.23 (m, 2H), 1.87-2.12 (m, 3H), 1.18-1.37 (m, 5H).

Compound **214b** (500 mg, 1.40 mmol) was converted to **compound 214**, which was separated by preparative SFC to give **compound 215 (**85.6 mg), **LCMS**: t_R = 0.937 min in 2 min chromatography, MS (ESI) m/z 339.1 $[M+H]^+$. **SFC**: t_R = 5.26 min in 16 min chromatography, ee% = 99.7%. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.65-7.63 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 3.34 (s, 3H), 3.23-3.32 (m, 1H), 3.13-3.19 (m, 2H), 3.06 (s, 3H), 1.98-2.03 (m, 2H), 1.84-1.98 (m, 1H), 1.62-1.69 (m, 1H), 1.38-1.42 (m, 2H), 1.29-1.38 (m, 2H); and **compound 216** (100 mg, totally 38%) as white solid, **LCMS**: t_R = 0.943 min in 2 min chromatography, MS (ESI) m/z 339.1 $[M+H]^+$. **SFC**: t_R = 5.92 min in 16 min chromatography, ee% = 100%.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.53 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.21 (s, 1H), 3.40 (s, 3H), 3.26-3.38 (m, 1H), 2.95-3.07 (m, 2H), 3.06 (s, 3H), 1.86-1.94 (m, 2H), 1.82-1.86 (m, 1H), 1.54-1.67 (m, 1H), 1.29-1.44 (m, 2H), 1.10-1.27 (m, 2H).

Example 175. Synthesis of Compound 217



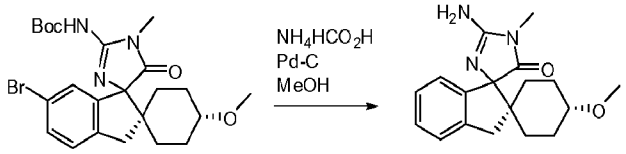
217a 217

To a solution of compound **217a** (8.0 mg, 0.016 mmol) in DCM there was added TFA (10 drops), and the solution was stirred at room temperature for 1 hour, solvent was removed in vacuum, and the residue was purified by HPLC to give **compound 217**

(6.7 mg, 81%) as a TFA salt. **LC-MS** t_R = 1.17 min in 3 min chromatography, MS (ESI) *m/z* 393.0 $[M+H]^+$

^{1}H NMR (CD_3OD, 400 MHz): δ 7.48 (dd, J = 1.2, 7.8 Hz, 1H), 7.42 (d, J = 1.2 Hz,1H), 7.26 (d, J = 7.8 Hz, 1H), 3.34 (s, 3H), 3.18 (s, 3H), 3.16-3.04 (m, 3H), 2.02 (m, 2H), 1.84 (m, 1H), 1.44-1.24 (m, 5H).

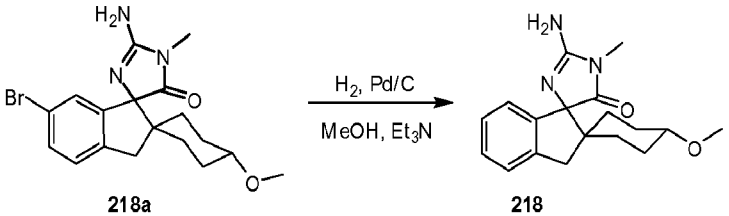
Example 176. Synthesis of Compound 218



217a 218

To a solution of compound **217a** (7.5 mg, 0.015 mmol) in MeOH (0.2 mL) was added ammonium formate (2.8 mg, 0.045 mmol) followed by Pd-C (1 mg). The resulting mixture was heated at 120 °C in a CEM microwave reactor for 10 min. The reaction mixture was filtered and the filtrate was purified by revised phase HPLC to give **compound 218** (3.8 mg, 59%) as a TFA salt. **LC-MS** t_R = 1.07 min in 3 min chromatography, MS (ESI) *m/z* 314.0 $[M+H]^+$; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.38 (m, 2H), 7.24 (m, 1H), 7.18 (m, 1H), 3.34 (s, 3H), 3.18 (s, 3H), 3.14 (m, 3H), 2.02 (m, 2H), 1.84 (m, 1H), 1.44-1.24 (m, 5H).

Alternatively, **compound 218** can be prepared according to the following scheme:

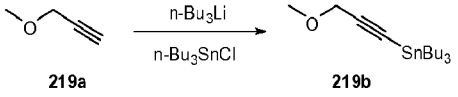


218a 218

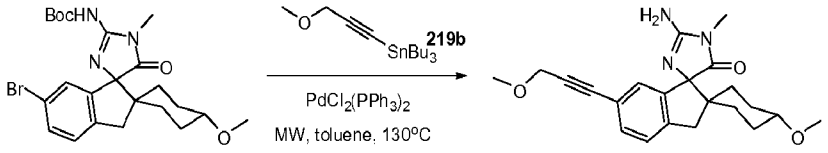
To a solution of compound **218a** (20 mg, 0.051 mmol) in MeOH (3 mL) was added Et_3N (0.1 mL) and Pd/C (10 mg, 10 wt%). The resulting mixture was stirred at

room temperature for 15 h under H_2 (15 psi), LC-MS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by pre-TLC (CH_2Cl_2: MeOH = 10: 1) and pre-HPLC to give compound **218** (5.2 mg, 33%) as a white solid. **LC-MS** t_R = 0.940 min in 2 min chromatography, MS (ESI) *m/z* 314.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25-7.31 (m, 2H), 7.16-7.20 (t, J = 7.2 Hz, 1H), 6.99-7.00 (d, J = 7.6 Hz, 1H), 3.36 (s, 3H), 3.08-3.18 (m, 3H), 3.04 (s, 3H), 1.96-2.03 (m, 2H), 1.84-1.87 (m, 1H), 1.57-1.65 (m, 1H), 1.32-1.45 (m, 2H), 1.28-1.32 (m, 2H).

Example 177. Synthesis of Compound 219



219a 219b



205a 219

Procedure for preparation of compound 219b

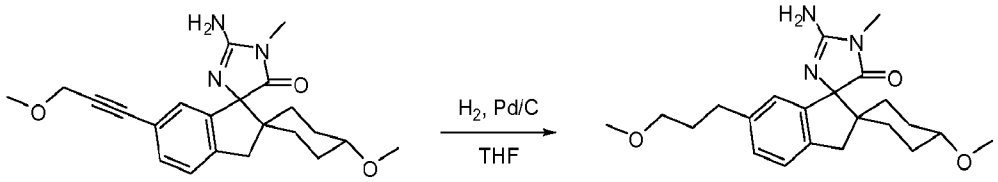
n-BuLi (2.5 M in hexane, 10.8 mL, 27 mmol) was added to a solution of compound **219a** (1.7 g, 2 mL, 24 mmol) in THF (50 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. After cooled to -78 °C, the reaction mixture was treated with *n*-Bu_3SnCl (8.68 g, 7.3 mL, 27 mmol), and allowed to warm to room temperature over 5 h. The solvent was removed under vacuum, and the residue was partitioned between diethyl ether (50 mL) and H_2O (30 mL). The diethyl ether layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude (Al_2O_3, PE) afforded compound **219b** as colorless oil (6.5 g, 75%).

Procedure for preparation of compound 219

To a solution of compound **205a** (50 mg, 0.1 mmol) and compound **219b** (73 mg, 0.2 mmol) in toluene (4 mL) was added $Pd(PPh_3)_2Cl_2$ (4 mg) under N_2 atmosphere. The mixture was stirred at 135 °C for 45 min in microwave. LCMS showed that the

reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was partitioned by EtOAc (10 mL) and aqueous of CsF (4 M, 8 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 10: 1) afforded **compound 219** (25 mg, 66%) , **LC-MS** t_R = 0.926 min in 2 min chromatography, MS (ESI) *m/z* 382.2 $[M+H]^+$. **^{1}H NMR (CD_3OD, 400 MHz)**: δ 7.34-7.36 (d, J = 8.8 Hz, 1H), 7.28-7.30 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 4.31 (s, 2H), 3.42 (s, 3H), 3.37 (s, 3H), 3.09-3.16 (m, 3H), 3.04 (s, 3H), 1.96-2.03 (m, 2H), 1.83-1.85 (m, 1H), 1.26-1.39 (m, 5H).

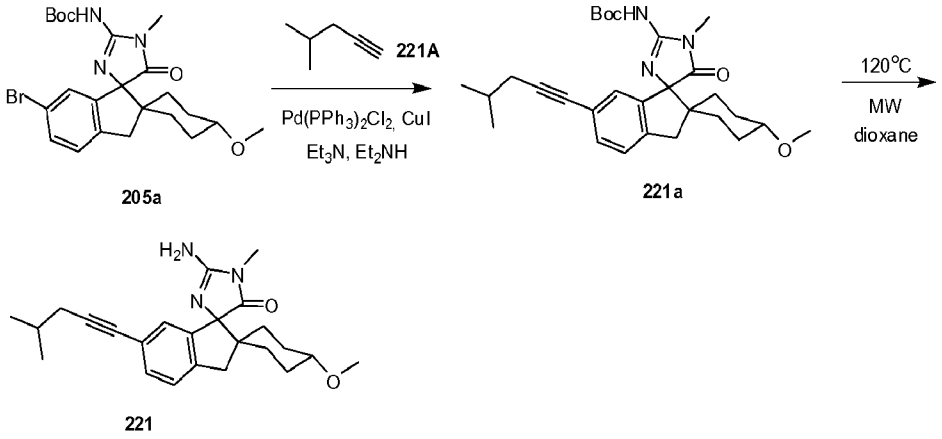
Example 178. Synthesis of Compound 220



219 **220**

To a solution of **compound 219** (30 mg, 0.079 mmol) in THF (5 mL) was added Pd/C (3 mg, 10 wt%). The resulting mixture was stirred under H_2 atmosphere at room temperature for 1 h, LC-MS showed that the reaction was completed. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated to give the residue, which was purified by preparative HPLC to afford **compound 220** (3.6 mg, 12%) as a white solid.**LC-MS** t_R = 0.893 min in 2 min chromatography, MS (ESI) *m/z* 386.0 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.17-7.19 (d, J = 8.0 Hz, 1H), 7.06-7.08 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 3.34-3.36 (m, 5H), 3.32 (s, 3H), 3.07-3.12 (m, 1H), 2.97-3.03 (m, 5H), 2.58-2.60 (t, J = 7.6 Hz, 2H), 1.90-2.00 (m, 2H), 1.74-1.82 (m, 3H), 1.52-1.56 (m, 1H), 1.23-1.37 (m, 4H).

Example 179. Synthesis of Compound 221



Procedure for preparation of compound 221a

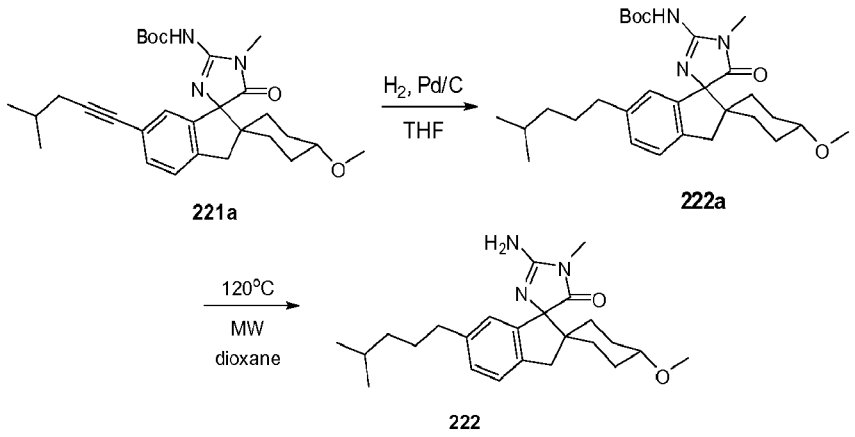
A dry three-necked round bottom flask equipped with a condenser was charged with compound **205a** (50 mg, 0.1 mmol), Et_3N (5 mL) and DEA (1 mL) under N_2 atmosphere. To this solution was added CuI (1 mg, 0.005 mmol), and $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol). After being degassed once again, compound **221A** (0.057 mL, 0.5 mmol) was added, and the mixture was heated at 50 °C (oil bath) with stirring for 12 h. LCMS showed that the reaction was completed. After evaporation, the residue was partitioned with EtOAc (15 mL) and water (10 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by preparative TLC (petroleum ether: ethyl acetate = 5: 1) to give compound **221a** (40 mg, 80%) as a white solid.

Procedure for preparation of compound 221

Compound **221a** (20 mg, 0.04 mmol) was dissolved in 1, 4-dioxane (3 mL). The mixture was stirred at 125 °C for 20 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (basic) to afford **compound 221** (5.1 mg, 32%) as a white solid. **LC-MS** t_R = 1.195 min in 2 min chromatography, MS (ESI) *m/z* 394.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.21-7.28 (q, 2H), 6.96 (s, 1H), 3.35 (s, 3H), 3.04-3.17 (m, 3H), 3.01 (s, 3H), 2.27-2.34 (d, J = 8.8 Hz, 2H), 1.93-2.02 (m, 2H),

1.82-1.91 (m, 1H), 1.56-1.61 (m, 1H), 1.35-1.43 (m, 2H), 1.25-1.33 (m, 2H), 1.02-1.05 (d, J = 8.8 Hz, 6H).

Example 180. Synthesis of Compound 222



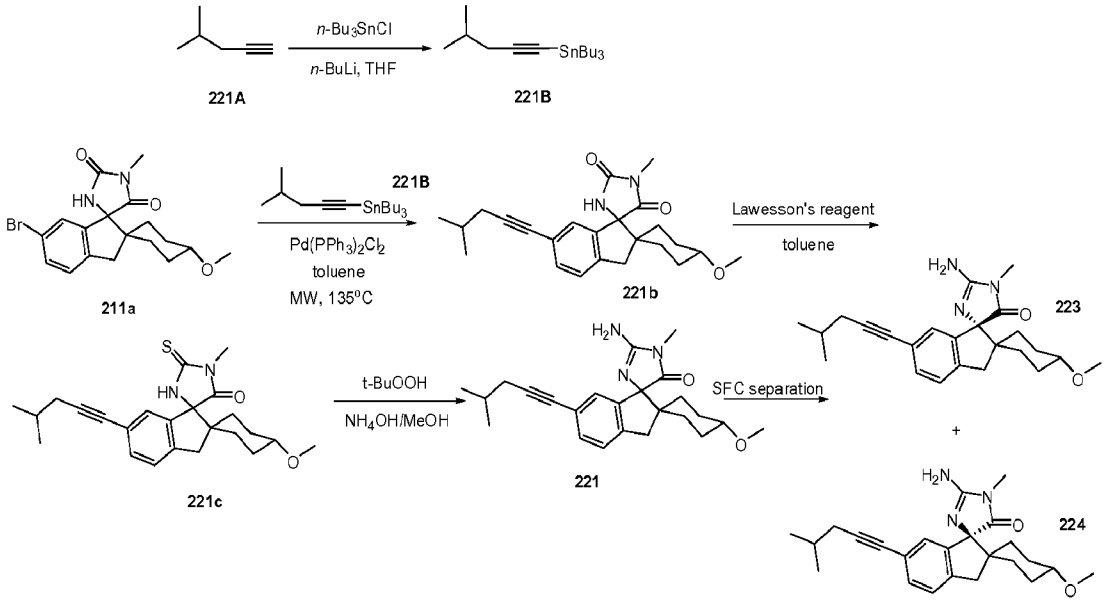
Procedure for preparation of compound 222a

To a solution of compound **221a** (20 mg, 0.04 mmol) in THF (3 mL) was added Pd/C (10 mg, 10 wt%). The reaction mixture was stirred at room temperature under H_2 atmosphere for 1 h, LC-MS showed that the reaction was completed. The reaction mixture was filtered though a pad of celite, and the filtrate was concentrated to the residue, which was purified by preparative TLC (petroleum ether: ethyl acetate = 5: 1) to afford compound **222a** (18 mg, 91%) as a white solid.

Procedure for preparation of compound 222

Compound **222a** (18 mg, 0.036 mmol) was dissolved in 1, 4-dioxane (3 mL). The mixture was stirred at 125 °C for 20 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (basic) to afford **compound 222** (3.1 mg, 22%) as a white solid. **LC-MS** t_R = 1.243 min in 2 min chromatography, MS (ESI) *m/z* 398.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.16-7.18 (d, J = 7.6 Hz, 1H), 7.06-7.08 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 3.32 (s, 3H), 3.08-3.13 (m, 1H), 3.03 (s, 3H), 2.97-3.02 (m, 2H), 2.50-2.54 (t, J = 7.6 Hz, 2H), 1.92-2.03 (m, 2H), 1.78-1.82 (m, 1H), 1.50-1.57 (m, 4H), 1.32-1.39 (m, 2H), 1.22-1.27 (m, 2H), 1.12-1.19 (m, 2H), 0.84-0.85 (d, J = 6.4 Hz, 6H).

Example 181. Synthesis of Compound 223



Procedure for preparation of compound 221B

n-BuLi (2.5 M in hexane, 11.88 mL, 29.7 mmol) was added to a solution of compound **221A** (2.216 g, 3.175 mL, 27 mmol) in THF (80 mL) at -78 °C, and the reaction mixture was stirred at -78°C for 30 min and at 0 °C for 30 min. After cooled to -78 °C, the reaction mixture was treated with *n*-Bu_3SnCl (9.67 g, 8 mL, 29.7 mmol), and allowed to warm to room temperature over 5 h. The solvent was removed under reduced pressure, and the residue was partitioned between diethyl ether (100 mL) and H_2O (3 × 80 mL). The diethyl ether layer was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated. Flash chromatography of the crude product on Al_2O_3 eluting with petroleum ether afforded compound **221B** (9 g, 90%) as a colorless oil.

Procedure for preparation of compound 221b

To a solution of compound **211a** (800 mg, 2.04 mmol) and compound **221B** (3.79 mg, 10.18 mmol) in toluene (25 mL) was added $Pd(PPh_3)_2Cl_2$ (72 mg) under N_2 atmosphere. The mixture was stirred at 135 °C for 45 min in microwave. LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the residue. The residue was partitioned by EtOAc (100 mL)

and aqueous of CsF (4M, 80 mL). The aqueous layer was extracted by EtOAc (2 × 100 mL), the combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of this residue by preparative TLC (petroleum: ethyl acetate = 2: 1) afforded compound **221b** (600 mg, 75%) as a white solid.

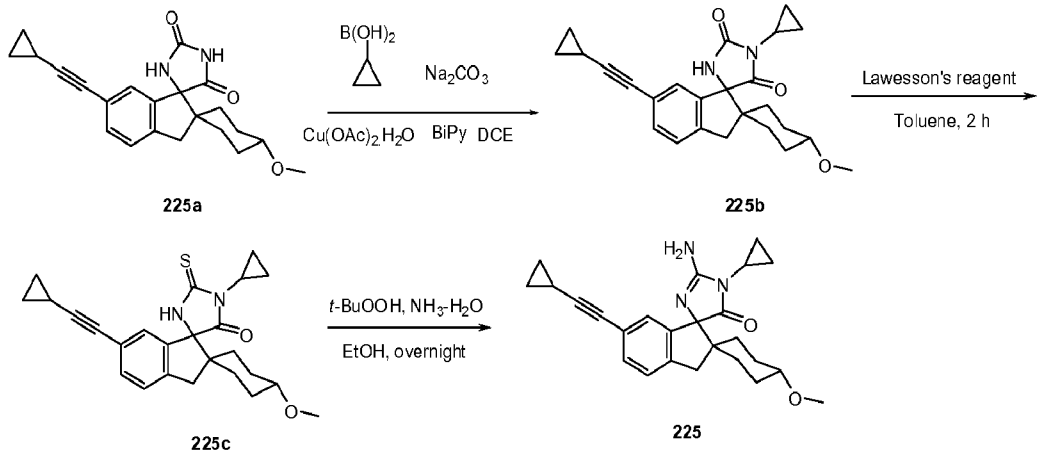
Procedure for preparation of compound 221c

A solution of compound **221b** (600 mg, 1.52 mmol) and Lawesson's Reagent (677 mg, 1.68 mmol) in dry toluene (50 mL) was refluxed for 5 h. LCMS showed that the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 2: 1) to give compound **221c** (500 mg, 81%) as a white solid.

Procedure for preparation of compounds 221, 223 and 224

A mixture of compound **221c** (0.5 g, 1.23 mmol) and *t*-butyl hydroperoxide (3.4 g, ca. 65% solution in water, 24.6 mmol) in NH_4OH/MeOH (10/50 mL) was stirred overnight at room temperature, LCMS showed that the reaction was completed, the reaction mixture was concentrated under reduced pressure to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and preparative HPLC (basic) afforded **compound 221** (60 mg, 12%, 18.50 mg delivered) and then further separated by SFC to afford compound **compound 223** (12.5 mg), **LC-MS** t_R = 1.069 min in 2 min chromatography, MS (ESI) *m/z* 394.2 $[M+H]^+$. **ee:** 98 %; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.23-7.28 (q, J = 7.6 Hz, 2H), 6.95 (s, 1H), 3.35 (s, 3H), 3.02-3.14 (m, 6H), 2.28-2.29 (d, J = 6.4 Hz, 2H), 1.83-2.08 (m, 4H), 1.58-1.66 (m, 1H), 1.26-1.42 (m, 4H), 1.03-1.06 (d, J = 6.8 Hz, 6H); and **compound 224** (11.50 mg) as a white solid; **LC-MS** t_R = 1.064 min in 2 min chromatography, MS (ESI) *m/z* 394.2 $[M+H]^+$; **ee:** 98%; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.12-7.17 (m, 2H), 6.85 (s, 1H), 3.23 (s, 3H), 2.87-3.06 (m, 6H), 2.16-2.17(d, J = 6.4 Hz, 2H), 1.71-1.90 (m, 4H), 1.45-1.49 (m, 1H), 1.14-1.30 (m, 4H), 0.87-0.93 (d, J = 6.4 Hz, 6H).

Example 182. Synthesis of Compound 225



Procedure for preparation of compound 225b

To a solution of compound **225a** (80 mg, 0.22 mmol) in $ClCH_2CH_2Cl$ (8 mL) was added $Cu(OAc)_2.H_2O$ (90 mg, 0.45 mmol), BiPy (70 mg, 0.45 mmol), Na_2CO_3 (60 mg, 0.45 mmol) and cyclopropylboronic (20 mg, 0.23 mmol). The reaction mixture was stirred at 70 °C in the open air for 6 h. The mixture was quenched by saturated NH_4Cl (3 mL). The mixture was partitioned with CH_2Cl_2 (20 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to anhydrousness. The residue was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **225b** (31 mg, 31%) as a white solid.

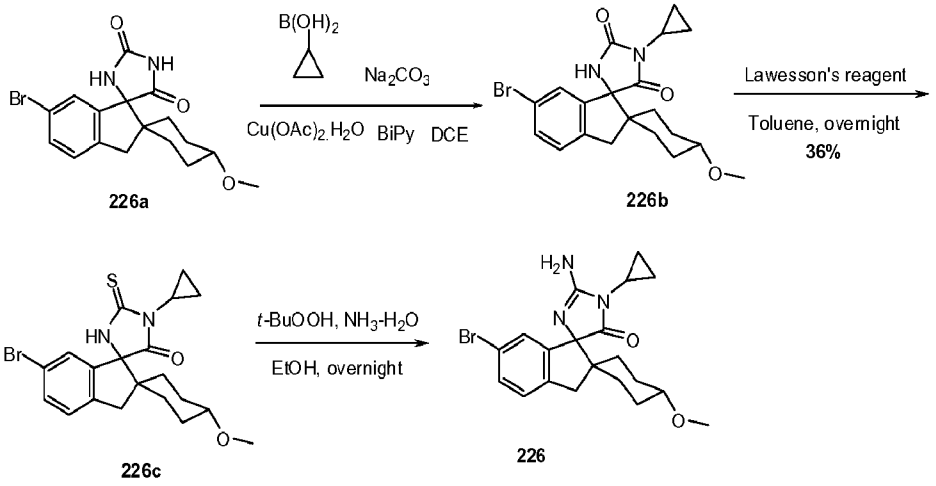
Procedure for preparation of compound 225c

A suspension of compound **225b** (28 mg, 0.07 mmol) and Lawesson's Reagent (35 mg, 0.08mol) in anhydrous toluene (10 mL) was heated at reflux for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **225c** (13 mg, 45%) as a white solid.

Procedure for preparation of compound 225

A solution of compound **225c** (13 mg, 0.03 mmol), *t*-BuOOH (60 mg, 0.6 mmol), NH_3-H_2O (0.5 mL) in EtOH (2 mL) was stirred at 20 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (eluent: CH_2Cl_2: CH_3OH = 15: 1) to give **compound 225** (4.2 mg, 30%) as a white solid. **LCMS**: t_R = 1.06 min in 2 min chromatography, MS (ESI) *m/z* 404 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.05-7.11 (m, 2H), 6.76 (s, 1H), 3.20 (s, 3H), 2.86-3.09 (m, 3H), 2.42-2.46 (m, 1H), 1.80-1.96 (m, 2H), 1.65-1.67 (m, 1H), 1.47-1.54 (m, 1H), 1.30-1.36 (m, 1H), 1.02-1.28 (m, 4H), 0.85-0.95 (m, 2H), 0.70-0.80 (m, 3H), 0.61- 0.68 (m, 3H).

Example 183. Synthesis of Compound 226

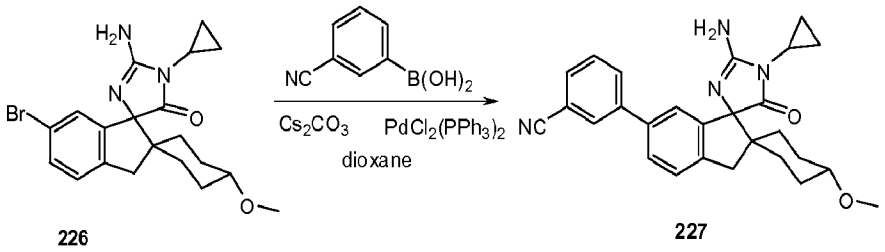


According to a similar synthesis of **compound 225**, compound **226a**(100 mg, 0.28 mmol) was coupled with cyclopropylboronic (25 mg, 0.3 mmol) to give compound **226b** (57 mg, 50%) as a white solid.

Compound **226b** (55 mg, 0.13 mmol) wad then reacted with Lawesson's Reagent (65 mg, 0.716mol) to give compound 226c (26 mg, 36%) as a yellow solid, which was converted to compound 226 as a white solid (16 mg, 62%). **LCMS**: t_R = 1.55 min in 3 min chromatography, MS (ESI) *m/z* 420 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.37-7.40 (m, 1H), 7.21-7.23 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 3.34 (s 3H), 2.95-3.15 (m, 3H), 2.54-2.58 (m, 1H), 1.92-2.02 (m, 2H), 1.72-1.80 (d, 1H), 1.58-1.70

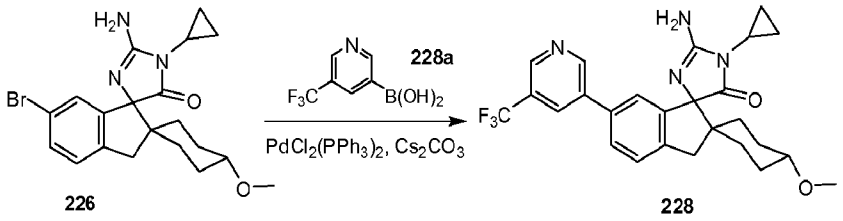
(m, 1H), 1.15-1.40 (m, 4H), 0.98-2.05 (m, 2H), 0.84-0.91 (m, 2H), 0.85-0.92 (m, 1H), 0.75-0.81 (m, 1H).

Example 184. Synthesis of Compound 227



A suspension of **compound 226** (13 mg, 0.03 mmol), 3-cyanophenylboronic acid (5 mg, 0.03 mmol), $Pd(PPh_3)_2Cl_2$ (1 mg, 0.003 mmol) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (2 mL) was heated at 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 227** (0.7 mg, 5%) as a white solid. **LCMS**: t_R = 1.82 min in 3 min chromatography, MS (ESI) *m/z* 439 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.89-7.95 (m, 2H), 7.56-7.69 (m, 3H), 7.41-7.43 (m, 1H), 7.23 (s, 1H), 3.36 (s, 3H), 3.07-3.18 (m, 3H), 2.57-2.62 (m, 1H), 1.96-2.04 (m, 2H), 1.80-1.83 (m, 1H), 1.60-1.75 (m, 1H), 1.21-1.41 (m, 5H), 1.00-1.10 (m, 2H), 0.75-0.96 (m, 2H)

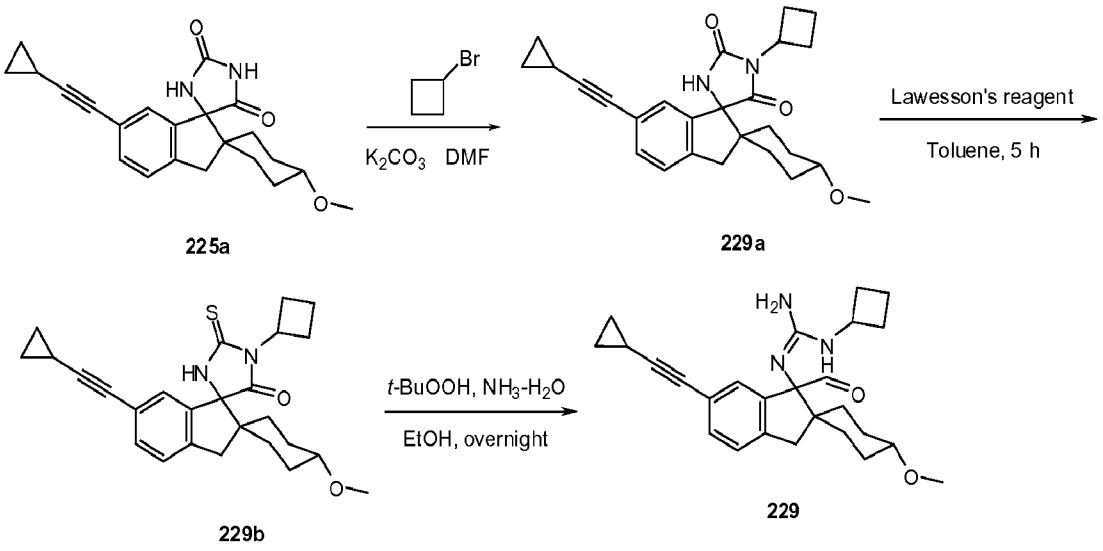
Example 185. Synthesis of Compound 228



According to a similar synthesis of **compound 227**, compound **226** (7 mg, 0.017 mmol) was coupled wirh compound **228a** (3.8 mg, 0.02 mmol) to give compound **228** (8.7 mg, 30%) as a white trifluroacetic salt solid. **LC-MS** t_R = 0.973 min in 2 min chromatography, MS (ESI) *m/z* 485.1 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 8.98 (s, 1H), 8.76 (s, 1H), 8.26 (s, 1H), 7.66-7.64 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.45-7.43

(d, J = 8.0 Hz, 1H), 3.15-3.04 (d, J = 15.6 Hz, 2H), 2.63 (s, 1H), 1.925 (m, 2H), 1.71 (m, 1H), 1.32 (s, 3H), 1.28-1.25 (m, 3H), 1.03 (m, 2H), 0.91 (m, 1H), 0.81 (s, 1H).

Example 186. Synthesis of Compound 229



Procedure for preparation of compound 229a

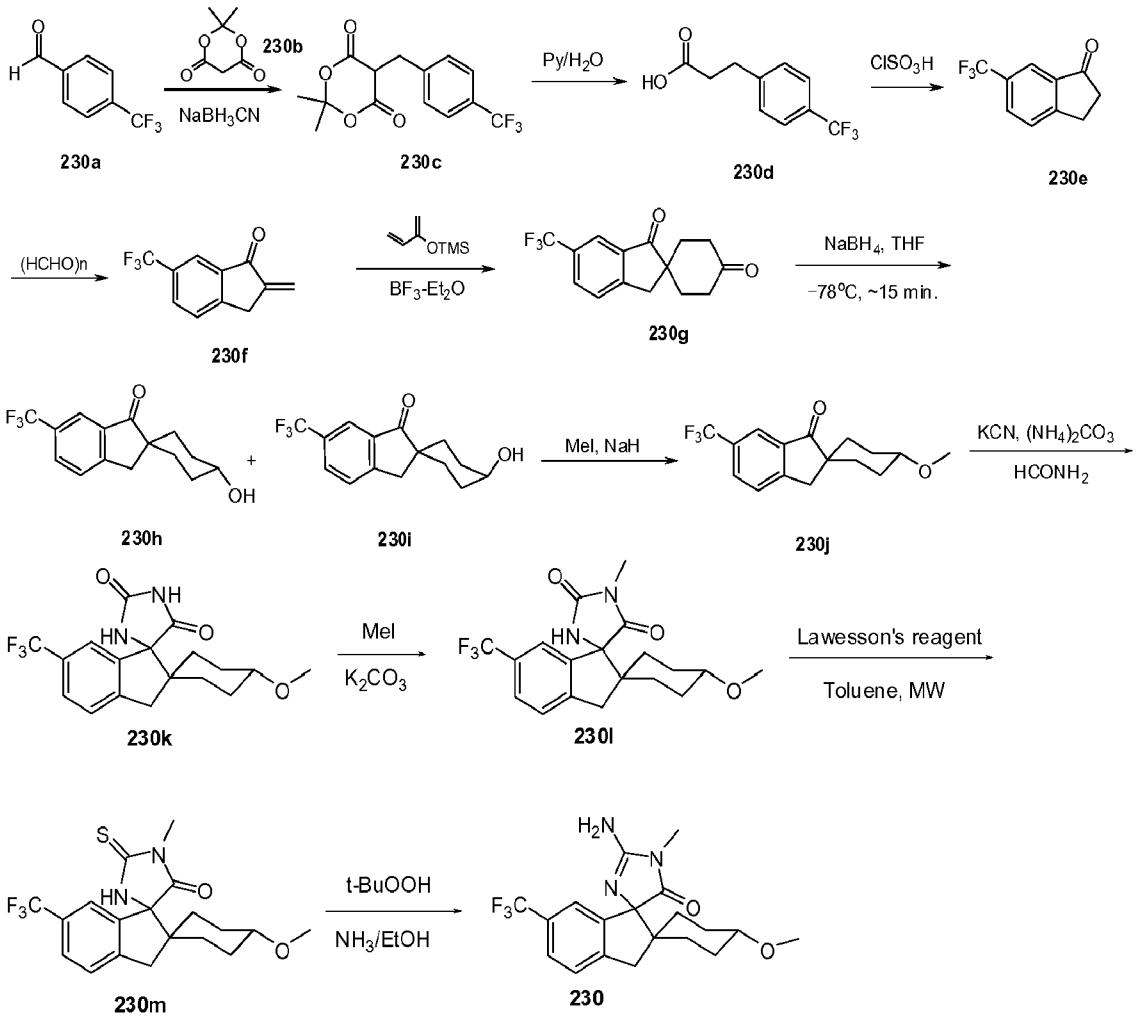
To a solution of compound **225a** (100 mg, 0.27 mmol) in DMF (5 mL) was added K_2CO_3 (120 mg, 0.8 mmol) and bromo-cyclobutane (75 mg, 0.55 mmol). The reaction mixture was stirred at 20 °C for 20 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **229a** (81 mg, 73%) as a white solid.

Procedure for preparation of compound 229

According to a similar synthesis of **compound 225,** compound **229a** (80 mg, 0.19 mmol) was reacted with Lawesson's Reagent (82 mg, 0.2mol) to give compound **229b** (33 mg, 40%) as a white solid. Compound **229b** (30 mg, 0.07 mmol) was then converted to **compound 229** (3.5 mg, 10%) as a white solid. **LCMS**: t_R = 2.00 min in 3 min chromatography, MS (ESI) *m/z* 418 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.42-7.48 (m, 2H), 7.25-7.29 (d, J = 8.4 Hz, 1H), 3.45 (s, 3H), 3.20-3.32 (m, 3H), 2.54-

2.56 (m, 1H), 2.02-2.19 (m, 3H), 1.30-1.60 (m, 7H), 0.99-1.02 (m, 2H), 0.82-0.84 (m, 2H), 0.50-0.73 (m, 3H).

Example 187. Synthesis of Compound 230



Procedure for preparation of compound 230c

To a solution of compound **230a** (17 g, 0.1 mol) and compound **230b** (14.4 g, 0.1 mol) in EtOH (100 mL), piperidium acetate (1.45 g, 0.01 mol) was added. After addition, the reaction mixture was stirred at room temperature for 30 min and then cooled to 0 °C, $NaBH_3CN$ (9.45 g, 0.15 mol) was added portionwise upon cooling. After addition, the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched with 1 M HCl till gas evolution ceased. The mixture was extracted with EtOAc (3 × 100 mL), the combined

organic layers were evaporated and the residue was recrystallized from MeOH to give a white solid 230c, which was used in the next step directly. **^{1}H NMR** ($CDCl_3$ 400 MHz TMS): δ 7.48 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 3.71 (t, J = 5.2 Hz, 1H), 3.47 (d, J = 3.2 Hz, 2H), 1.70 (s, 3H), 1.55 (s, 3H).

Procedure for preparation of compound 230d

The crude product of compound **230c** was dissolved in pyridine (45 mL) and water (15 mL). The mixture was heated at reflux for 2 h and then diluted with water (100 mL), acidified with *conc.* HCl till pH = 2. The mixture was extracted with EtOAc (3 × 100 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to give of compound **230d** (11 g, 50% yield for two steps) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz TMS): δ 7.48 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.64 (d, J = 8.0 Hz, 2H).

Procedure for preparation of compound 230e

Compound **230d** (9 g, 0.04 mol) was added portionwise to $ClSO_3H$ (100 mL) while cooling with ice-water bath. After addition, the reaction mixture was stirred at 0 ^oC for 1.5 h and then poured into ice water carefully. The mixture was extracted with EtOAc (3 × 200 mL), the combined organic layers were evaporated and the residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 10:1) to give compound **230e** (4.44 g, 55% yield) as a clear oil. **^{1}H NMR** ($CDCl_3$ 400 MHz TMS): δ 7.95 (s, 1H), 7.77-7.75 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 3.17-3.14 (m, 2H), 2.72-2.68 (m, 2H).

Procedure for preparation of compound 230f

Compound **230e** (4.44g, 22 mmol), $(CH_2O)_n$ (3 g, 0.1 mol) and *N*-methyl-aniline trifluoroacetate (7.15 g, 35 mmol) were dissolved in anhydrous THF (50 mL) under a nitrogen atmosphere. The mixture was heated at reflux overnight and then diluted with water (~100 mL), extracted with EtOAc (3 × 100 mL), the combined organic layers were evaporated and the residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1) to give compound **230f** (2.5 g, 54%) as a yellow liquid.

^{1}H NMR ($CDCl_3$ 400 MHz TMS): δ 8.16 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 6.47-6.46 (m, 1H), 5.76 (s, 1H), 3.85 (s, 2H).

Procedure for preparation of compound 230g

Compound **230f** (2.5 g, 11 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL), the solution was cooled in acetone/dry ice bath. Trimethyl-(1-methylene-allyloxy)-silane (1.85 g, 12 mmol) and $BF_3.Et_2O$ (0.84 g, 5 mmol) were added subsequently. The reaction mixture was stirred at -78 °C for 20 min and then diluted with MeOH (20 mL), after warmed to room temperature, the mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated, the residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 3:1) to give compound **230g** (400 mg, 13%) as a white solid.

Procedure for preparation of compound 230h and 230i

Compound **230g** (400 mg, 1.4 mmol) was dissolved in anhydrous THF (4 mL) under a nitrogen atmosphere, cooled in acetone-dry ice bath, $NaBH_4$ (32 mg, 0.84 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 5 min and then quenched with MeOH, after warmed to 0 °C, the mixture was diluted with EtOAc, washed with water, the aqueous layer was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered and evaporated, the crude product containing compound **230h** and compound **230i** was used in the next step without further purification.

Procedure for preparation of compound 230j

The crude product containing compound **230h** and compound **230i** was dissolved in anhydrous THF (5 mL) under a nitrogen atmosphere and cooled to 0 °C, NaH (168 mg, 2.1 mmol) was added in one portion, after 10 min MeI (986 mg, 7 mmol) was added in one portion. After addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched by addition of water at 0 °C and extracted with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated, and the residue was purified by prep. TLC

(petroleum ether: EtOAc = 4:1) to give compound **230j** (100 mg, 24% yield for 2 steps) as a white solid.

Procedure for preparation of compound 230k

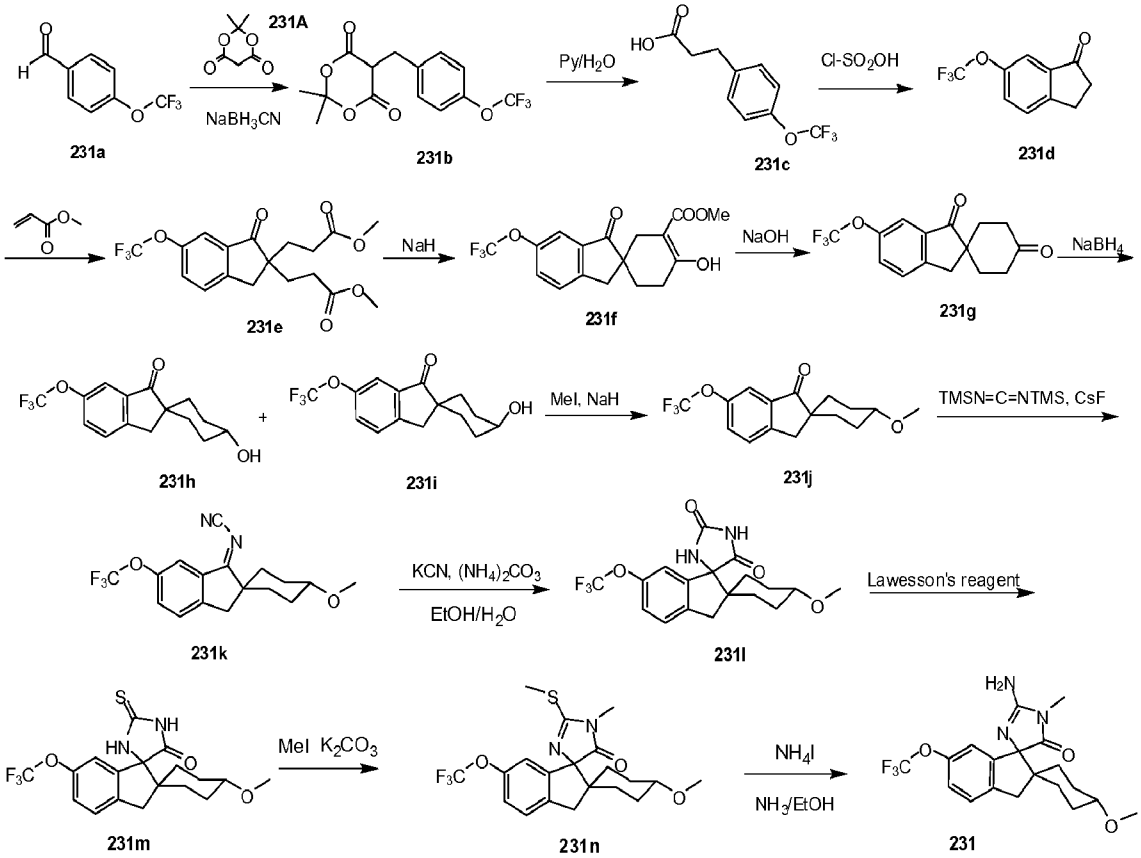
Compound **230j** (50 mg, 0.17 mmol), KCN (33 mg, 0.51 mmol) and $(NH_4)_2CO_3$ (121 mg, 1.26 mmol) was suspended in $HCONH_2$ (1.5 mL) and the mixture was heated at 90 °C in a steel autoclave for 3 days. After cooling to room temperature, the mixture was poured onto crashed ice and stirred for 20 min, and then acidified with conc. HCl till pH = 2. The solid precipitated out was collected by filtration and washed with water, and then the solid was dissolved in EtOAc and washed with water, dried over Na_2SO_4, filtered and evaporated to give compound **230k** (35 mg, 59%) as a yellow solid.

Procedure for preparation of compound 230

According to a similar synthesis of **compound 229,** compound **230k** (35 mg, 0.1 mmol) was methylated with MeI (14 mg, 0.1 mmol) to give compound **230l** (27 mg, 70%) as a yellow solid.

Compound **230l** (27 mg, 0.07 mmol) was reacted with Lawesson's reagent (40 mg, 0.1 mmol) to give compound **230m** (15 mg, 57%), which was converted to **compound 230** (1.8 mg, 12%) as a white solid. **LC-MS** t_R = 0.925 min in 2 min chromatography, MS (ESI) *m/z* 382.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.59 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 3.25 (s, 3H), 3.10-3.03 (m, 6H), 2.00-1.89 (m, 2H), 1.79-1.74 (m, 1H), 1.38-1.28 (m, 5H). **^{19}F NMR** (690-190-1C7 CD_3OD 19F): δ -63.57

Example 188. Synthesis of Compound 231



Procedure for preparation of compound 231d

According to a similar synthesis of compound 230e in **compound 230**, compound **231a** (1.0 g, 5.26 mmol) was reacted compound **231A** (75 mg, 0.53 mmol) to give compound **231b** (0.8 g, 47%) as a white solid, which was used directly in next step without purification.

Compound **231b** (5.0 g, 15.72 mmol) was heated in pyridine/H_2O (15 mL/5 mL) to give compound **231c** (3.0 g, 82%) as a colorless oil. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.17 (m, 2H), 7.07 (m, 2H), 2.89 (m, 2H), 2.61 (m, 2H).

Compound **231c** (4.0 g, 17.09 mmol) was converted to compound **231d** (1.1 g, 30%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.49 (s, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 3.07 (m, 2H), 2.67 (m, 2H).

Procedure for preparation of compound 231e

To a refluxed solution of compound **231d** (4.7 g, 21.76 mmol) in anhydrous toluene (40 mL) was added Trition B (2.45 mL, 13.49 mmol) under a nitrogen atmosphere. The reflux solution was kept stirring for 30 min, then methyl acrylate (25 mL, 281.7 mmol) was added and the resulting solution was stirred at reflux overnight. The reaction solution was poured into water and extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel to give compound **231e** (4.0 g, 48%) as a colorless oil.

Procedure for preparation of compound 231f

To a solution of compound **231e** (2.6 g, 6.70 mmol) in 50 mL of anhydrous toluene was added NaH (1.07 g, 26.80 mmol) portionwise under a nitrogen atmosphere. The mixture was heated to reflux overnight. Brine (10 mL) was added to quench the reaction, and the mixrure was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel to give compound **231f** (1.2 g, 52%) as a colorless oil.

Procedure for preparation of compound 231g

To a solution of compound **231f** (1.2 g, 3.37 mmol) in MeOH/H_2O (2.4 mL/7.6 mL) was added NaOH (0.92 g, 23.02 mmol). The mixture was heated at reflux for 1 h. Then the reaction solution was cooled to room temperature and extracted with EtOAc (2 × 50 mL). The combined organic layer was dried, evaporated under reduced pressure to give crude compound **231g** (0.6 g, crude), which was used in next step without further purification.

Procedure for preparation of compound 231h and 231i

To a solution of compound **231g** (0.6 g, 2.01 mmol) in 10 mL of anhydrous THF was added $NaBH_4$ (22.8 mg, 0.60 mmol) at -78 °C. The mixture was stirred at -78 °C for 5 min, and MeOH (5 mL) and EtOAc (5 mL) were added. The resulting mixture was allowed to warm to room temperature. Water (5 mL) was added, and the organic layer was separated, dried and evaporated under reduced pressure to give the crude procut

containing compound **231h** and compound **231i** (0.3 g, crude), which was used for next step without further purification.

Procedure for preparation of compound 231j

A crude mixture containing compound **231h** and compound **231i** (0.3 g, 1.00 mmol) in anhydrous THF (10 mL) was added NaH (160 mg, 4.0 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 30 min at room temperature, and then MeI (1.54 g, 10.0 mmol) was added. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched by addition of brine (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrour sodium sulfate and evaporated under reduced pressure to give crude compound **231j** (0.3 g, 96%) as a white solid.

Procedure for preparation of compound 231k

To a solution of compound **231j** (0.3 g, 0.96 mmol) in 10 mL of acetonitrile was added CsF (580 mg, 3.83 mmol) under a nitrogen atmosphere. The mixture was stirred at 50 °C for 30 min, then bis-trimethylsilylcarbodiimide (712 mg, 3.827 mmol) was added. The resulting mixture was stirred at 50 °C for 1 h. 5 mL of water was added to quench the reaction and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude compound **231k** (0.28 g, crude), which was used for the next step without further purification.

Procedure for preparation of compound 231l

To a solution of compound **231k** (0.28 g, 0.85 mmol) in EtOH/H_2O (10 mL/10 mL) was added KCN (0.22 g, 3.42 mmol), $(NH_4)_2CO_3$ (1.2 g, 11.95 mmol). The mixture was heated to 75 °C overnight in a sealed tube. Then the reaction was cooled to room temperature, water (10 mL) and EtOAc (10 mL) were added. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by preparative TLC to give compound **231l** (0.1 g, 30%) as a white solid.

Procedure for preparation of compound 231m

To a solution of compound **231l** (40 mg, 0.10 mmol) in anhydrous toluene was added Lawesson's reagent (46 mg, 0.12 mmol). The mixture was heated to 120 °C in a microwave reactor for 30 min. Then the solvent was evaporated under reduced pressure and the residue was purified by preparative TLC to give compound **231m** (30 mg, 70%) as a white solid.

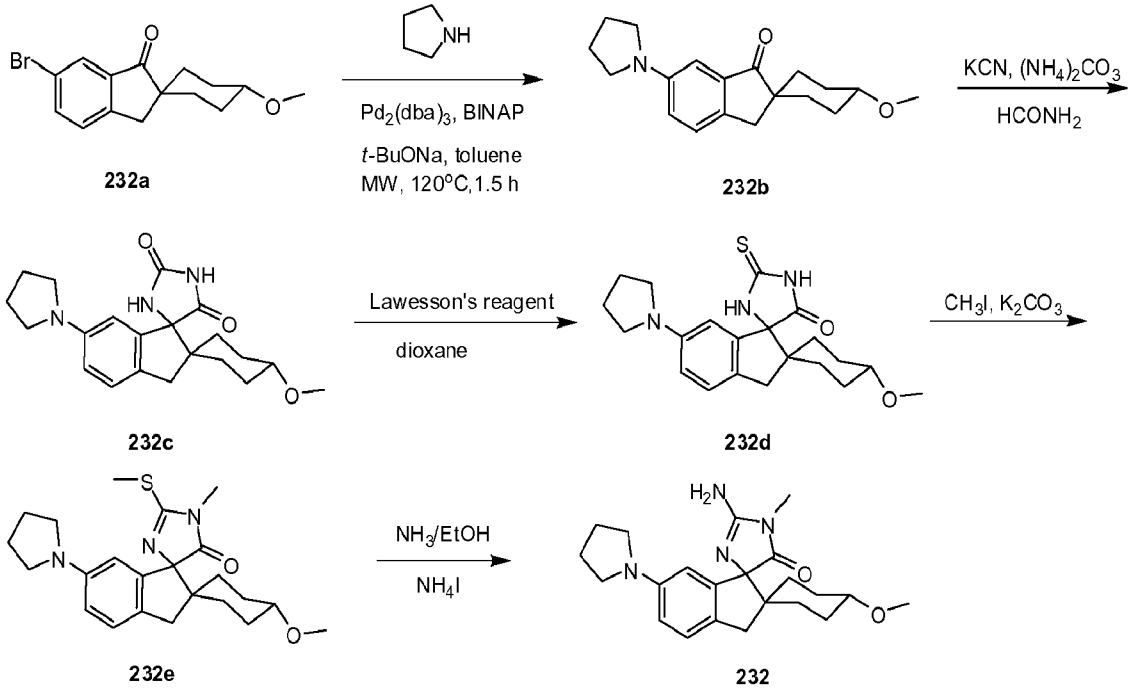
Procedure for preparation of compound 231n

To a solution of compound **231m** (50 mg, 0.13 mmol) in 3 mL of DMF was added K_2CO_3 (86 mg, 0.63 mmol). The mixture was stirred for 10 min at room temperature, then MeI (48 mg, 0.31 mmol) was added. The final mixture was stirred at room temperature and monitored by preparative TLC. When compound **231m** was consumed, brine (50 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, evaporated under reduced pressure. The residue was purified by preparative TLC to give compound **231n** (36 mg, 67%) as a white solid.

Procedure for preparation of compound 231

To a solution of compound **231n** (16 mg, 0.037 mmol) in NH_3/EtOH (3 mL) was added NH_4I (59 mg, 0.37 mmol). The mixture was heated to 120 °C for 2.5 h in a microwave reactor. The solvent was evaporated under reduced pressure and the residue was purified by preparative RP-HPLC to give **compound 231** (13 mg, 87%) as a gray solid. **LC-MS** t_R = 1.579 min in 3 min chromatography, MS (ESI) *m/z* 398 $[M+H]^+$. **^{1}H NMR** (CD_3OD): δ 7.45 (d, J = 8.0 Hz, 1H), 7.26 (m, 2H), 3.34 (s, 3H), 3.12-3.21 (m, 6H), 1.97-2.10 (m, 2H), 1.82 (m, 1H), 1.39-1.50 (m, 4H), 1.28-1.35 (m, 1H).**^{19}F NMR** (CD_3OD): δ -59.57.

Example 189. Synthesis of Compound 232



Procedure for preparation of compound 232b

To a solution of pyrrolidine (138 mg, 1.94 mmol) in toluene (15 mL) was added *t*-BuONa (186 mg, 1.94 mmol). After stirring at room temperature for 5 min under a N_2 atmosphere, compound **232a** (400 mg, 1.29 mmol), $Pd_2(dba)_3$ (135 mg, 0.13 mmol) and BINAP (121 mg, 0.19 mmol) was added under a nitrogen atmosphere, the mixture was heated at 120 °C with stirring for 1.5 h in a microwave reactor. LCMS showed that the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the residue, which was purified by preparative TLC (petroleum/ethyl acetate = 3:1) to give compound **232b** (370 mg, 91%) as a yellow solid.

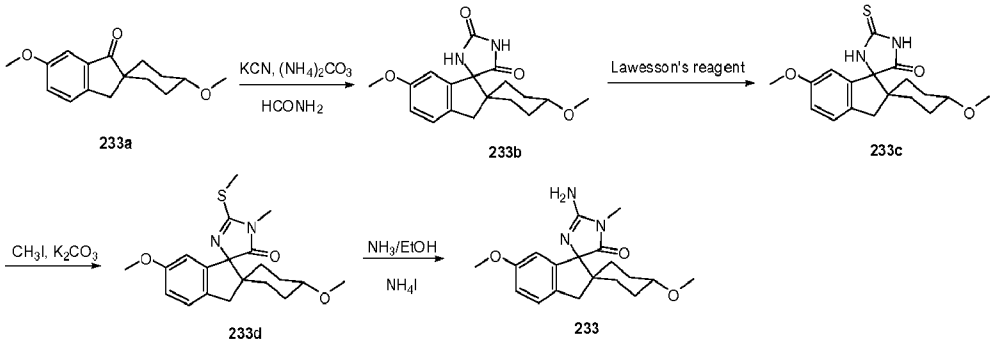
Procedure for preparation of compound 232

According to a similar synthesis for **I-6** described in Example I-2, compound **232b** (300 mg, 1.00 mmol) was condensed to form hydantoin **232c** (100 mg, 27%) as a white solid.

Compound **232c** (100 mg, 0.27 mmol) was reacted with Lawesson's Reagent (109 mg, 0.27 mmol) to give compound **232d** (50 mg, 48%) as a white solid.

Then compound **232d** (20 mg, 0.052 mmol) was dimethylated with MeI (30 mg, 0.21 mmol) to give compound **232e** (15 mg, 72%) as a white solid, which was converted to **compound 232** (2.1 mg, 14%) as a white solid. **LC-MS** t_R = 0.882 min in 2 min chromatography, MS (ESI) *m/z* 383 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.09-7.11 (d, J = 8.4 Hz, 1H), 6.50-6.52 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 3.36 (s, 3H), 3.27 (s, 1H), 3.21 (s, 3H), 3.15 (m, 1H), 3.05 (s, 3H), 2.91-3.02 (m, 2H), 1.92-2.00 (m, 5H), 1.83 (m, 1H), 1.53-1.59 (m, 1H), 1.35-1.42 (m, 2H), 1.22-1.35 (m, 3H).

Example 190. Synthesis of Compound 233



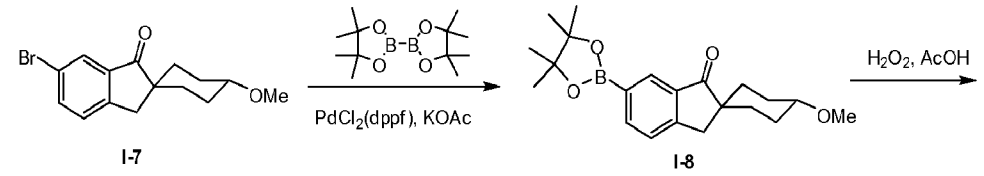
According to a similar synthesis for **I-4** described in Example I-2, compound **233a** (300 mg, 1.15 mmol) was condensed to give compound **233b** (150 mg, 39%) as a white solid.

Compound **233b** (50 mg, 0.152 mmol) was reacted with Lawessons reagent (73.5 mg, 0.182 mmol) to give compound **233c** (30 mg, 58%) as a white solid.

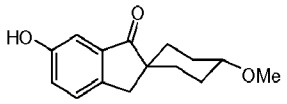
Compound **233c** (30 mg, 0.0867 mmol) was dimethylated with iodomethane (18.5 mg, 0.130 mmol) in DMF (1 mL) to give crude compound **233d** (26 mg, 80%) as a white solid, which was converted to **compound 233** (2.8 mg, 15%) as a white solid. **LC-MS** t_R = 0.884 min in 2 min chromatography, MS (ESI) *m/z* 344.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 2.4, 8.4 Hz, 1H),

6.75 (d, J = 2.4 Hz, 1H), 3.77 (s, 3H), 3.35 (s, 3H), 3.19 (s, 3H), 3.15 (m, 1H), 3.01-3.08 (m, 2H), 1.96-2.10 (m, 2H), 1.84 (d, 1H), 1.27-1.49 (m, 5H).

Example I-3 Synthesis of (1r,4r)-6'-hydroxy-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (I-9)



I-7 I-8



I-9

Procedure for preparation of Compound I-8

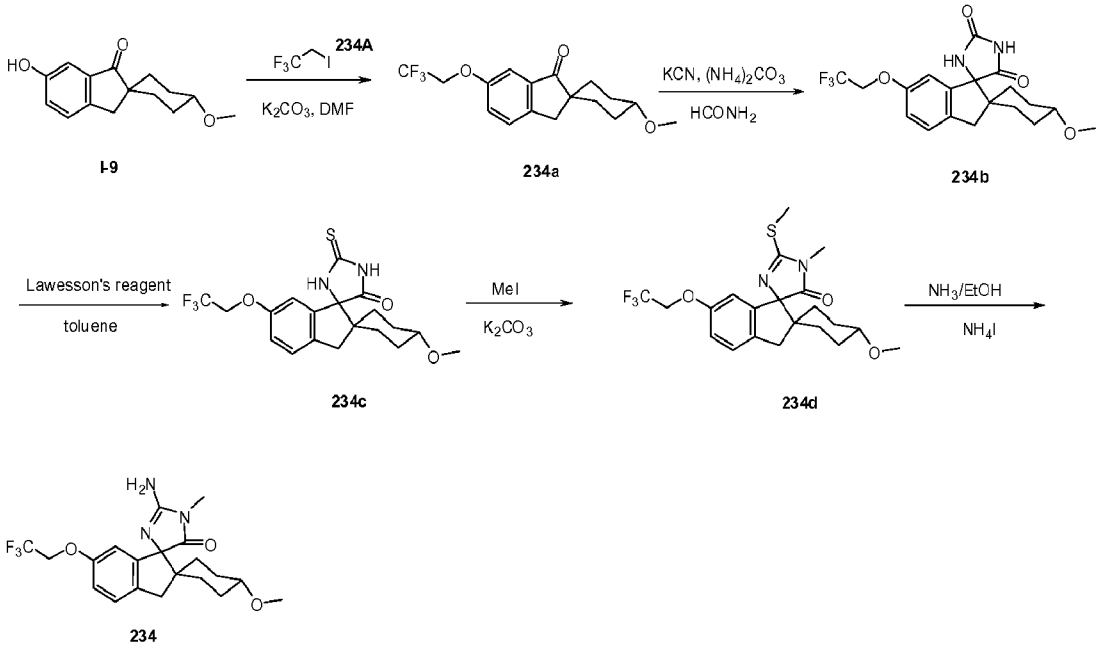
To a solution of compound **I-7** (500 mg, 1.61 mmol) in 1,4-dioxane (10 mL), was added KOAc (0.46 g, 4.69 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2 –yl)-1,3,2- dioxaborolane (450 mg, 1.77 mmol) and $PdCl_2$(dppf) (150 mg, 0.18 mmol) under a nitrogen atmosphere, the mixture was stirred at 100 °C in a CEM microwave reactor for 1 h. LCMS showed the complete consumption of compound **I-7**. Water (5 mL) was added to the mixture, and the precipitate was filtered off through a pad of celite, and then was washed with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **I-8** (284 mg, 50%) as a black solid which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz) : δ 8.20 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 3.41 (s, 3H), 3.21 (m, 1H), 2.96 (s, 2H), 2.06 (m, 2H), 1.64 (m, 2H), 1.56 (m, 2H), 1.44 (m, 2H), 1.31 (s, 12H).

Procedure for preparation of Compound I-9

To a soltoion of compound **I-8** (100 mg, 0.28 mmol) in THF (10 mL) was added HOAc (0.2 mL) and H_2O_2 (1 mL) under a nitrogen atmosphere, the mixture was stirred at room temperature overnight. The mixture was quenched by addition of $NaHSO_3$

solution (10 mL), and then was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30mL), dried over Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography on silica gel eluting with hexane: EtOAc (100: 10 to 30: 10) to afford (1r,4r)-6'-hydroxy-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**I-9**) (50 mg, 72%) as a yellow oil. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.24 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 3.33 (s, 3H), 3.26 (m, 1H), 2.86 (s, 2H), 2.20-2.21 (m, 2H), 1.68-1.69 (m, 2H), 1.44-1.65 (m, 2H), 1.20-1.40 (m, 2H).

Example 191. Synthesis of Compound 134



Procedure for preparation of Compound 234a

To a solution of compound **I-9** (360 mg, 1.46 mmol) in DMF (2 mL) was added K_2CO_3 (403.5 mg, 2.92 mmol), and compound **234A** (373.6 mg, 1.60 mmol), the mixture was stirred at ambient temperature overnight. The reaction was added with H_2O (5 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30mL), dried over Na_2SO_4 and concentrated to give compound **234a** (320 mg, 66%) as a white solid, which was used

in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.35 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 4.26 (dd, J = 8.1, 16.2 Hz, 2H), 3.41 (s, 3H), 3.25-3.29 (m, 1H), 2.91(s, 2H), 1.97-2.28 (m, 2H), 1.66-1.89 (m, 2H), 1.32-1.45 (m, 2H), 1.23-1.35 (m, 2H).

Procedure for preparation of Compound 234b

A steel autoclave was charged with a mixture of compound **234a** (320 mg, 0.97 mmol), KCN (126.8 mg, 1.95 mmol), $(NH_4)_2CO_3$ (702.4 mg, 7.31 mmol) and formamide (20 mL). The mixture was heated at 100 °C for 72 h. The reaction mixture was cooled and poured into ice. The mixture was filtrated to collect the solid, which was dissolved in ethyl acetate (100 mL), and was washed with water (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product, which was purified by preparative TLC eluting with hexane: EtOAc = 1: 1 to afford compound **234b** (90 mg, 23%) as a white solid. **LCMS**: t_R = 1.080 min in 2 min chromatography, MS (ESI) *m/z* 399.1$[M+H]^+$.

Procedure for preparation of Compound 234c

To a solution of compound **234b** (70 mg, 0.17 mmol) in anhydrous toluene (2 mL) was added Lawesson's Reagent (71 mg, 0.17 mmol) under a nitrogen atmosphere, the mixture was stirred at 110 °C for 3h. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC eluting with hexane: EtOAc = 3: 1 to afford compound **234c** (40 mg, 57%) as a white solid. **LCMS**: t_R = 1.165 min in 2 min chromatography, MS (ESI) *m/z* 415.1$[M+H]^+$.

Procedure for preparation of Compound 234d

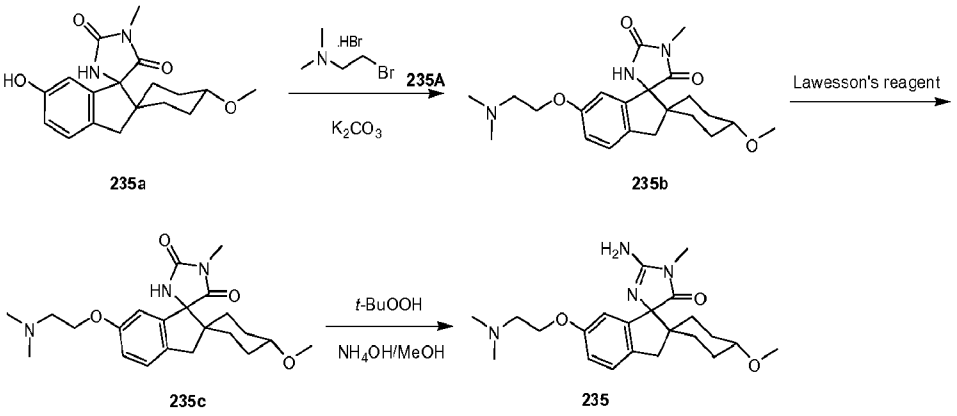
To a solution of compound **234c** (40 mg, 0.096 mmol) in CH_3CN (2 mL) was added K_2CO_3 (53.2 mg, 0.39 mmol). After being stirred for 5 min, MeI (56.8 mg, 0.39 mmol) was added, and the reaction mixture was heated at 60 °C for 10 min and at 100 °C for another 10 min in a CEM microwave reactor. The mixture was filtered through pad of celite, and the filtrate was concentrated *in vacuo*, the residue was purified by preparative TLC eluting with hexane: EtOAc = 3: 1 to give compound **234d** (30 mg,

70%) as a white solid. **LCMS**: t_R = 1.397 min in 2 min chromatography, MS (ESI) *m/z* 443.1 $[M+H]^+$.

Procedure for preparation of compound 234

A solution of compound **234d** (30 mg, 0.067 mmol), NH_4I (97.3 mg, 0.67 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC eluting with dichloromethane: methanol = 10: 1 and by preparative RP-HPLC to give **compound 234** (2.4 mg, 8%) as a white solid. **LCMS**: t_R = 1.406 min in 2 min chromatography, MS (ESI) *m/z* 412.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.39 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 6.4 Hz, 1H), 6.90 (s, 1H), 4.50 (dd, J = 8.4, 15.6 Hz, 2H), 3.40 (s, 3H), 3.35 (m, 1H), 3.14-3.27 (m, 2H), 3.03 (s, 3H), 1.97-2.16 (m, 2H), 1.62-1.84 (m, 2H), 1.36-1.42 (m, 2H), 1.27-1.36 (m, 2H).

Example 192. Synthesis of Compound 235



Procedure for preparation of compound 235b

To a solution of compound **235a** (100 mg, 0.3 mmol) in DMF (5 mL) were added compound **235A** (104.8 mg, 0.45 mmol) and K_2CO_3 (117 mg, 0.45 mol). After addition, the mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to give compound **235b** with 49% purity (10.0 mg, 28%) as a white solid. **LC-MS** t_R= 0.80 min in 2 min chromatography, MS (ESI) *m/z* 402.2 $[M+H]^+$

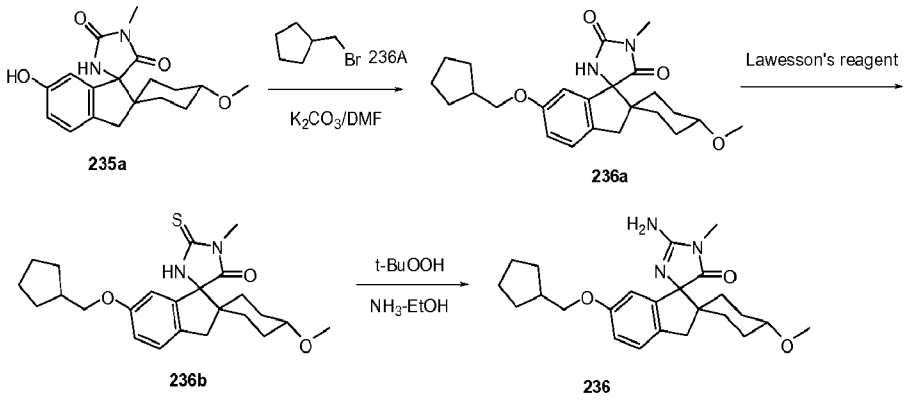
Procedure for preparation of compound 235c

To a mixture of compound **235b** (30.0 mg, 0.07 mmol) in toluene (2 mL) was added Lawesson's reagent (30.0 mg, 0.07 mmol). The mixture was heated to 130 °C in a CEM microwave reactor for 1 h. After cooling down, the precipitate was filtered off and washed with ethyl acetate (40 mL × 2). The filtrate and the washing were concentrated *in vacuo* and the residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10:1) to give compound **235c** with 80% purity (10.0 mg, 33%) as a pale yellow solid. **LC-MS** t_R= 0.888 min in 2 min chromatography, MS (ESI) *m/z* 418.2 $[M+H]^+$

Procedure for preparation of compound 235

To a solution of compound **235c** (10 mg, 0.023 mmol) in EtOH (4 mL) was added NH_3H_2O (1 mL) and *tert*-butyl hydroperoxide (0.20 g, 2.22 mol). After addition, the mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give compound **235** with 93% purity (8.0 mg, 74%) as a white solid. **LC-MS** t_R= 0.823 min in 2 min chromatography, MS (ESI) *m/z* 401.2 $[M+H]^+$; **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.35-7.33 (d, J = 8.0 Hz, 1H), 7.07-7.04 (m, 1H), 6.909-6.904 (d, J = 2.4 Hz, 1H), 4.35-4.31 (m, 2H), 3.60-3.58 (m, 2H), 3.36 (s, 3H), 3.21 (s, 3H), 3.18-3.08 (m, 3H), 2.98 (s, 6H), 2.09-2.03 (m, 2H), 1.89-1.83 (m, 1H), 1.47-1.26 (m, 5H).

Example 193. Synthesis of Compound 236



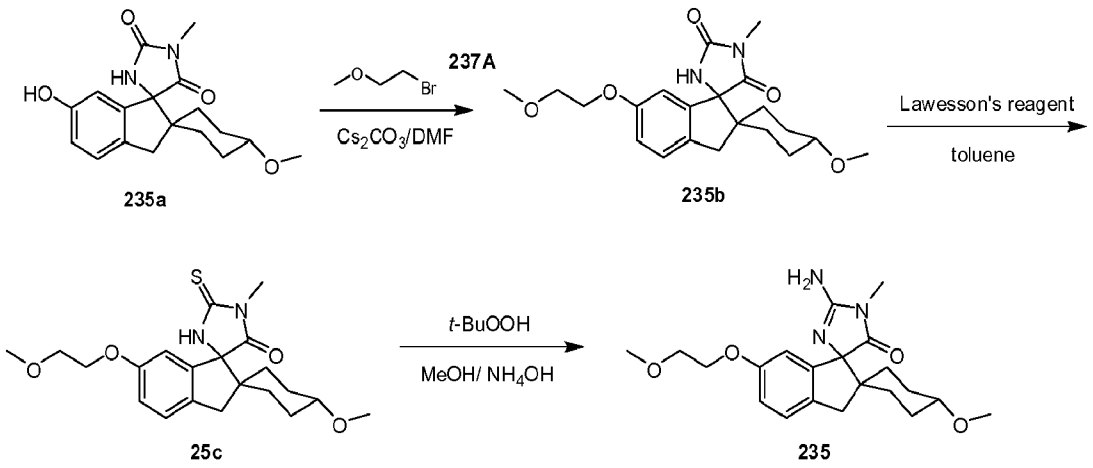
According to a similar synthesis of **compound 235**, compound **235a** (50 mg, 0.15 mmol) was alkylated with compound **236A** (33.5 mg, 0.225 mmol) to give

compound **236a** with 84% purity (60.0 mg, 94%) as a white solid. **LC-MS** t_R= 1.113 min in 2 min chromatography, MS (ESI) *m/z* 399.2 $[M+H]^+$

Compound **236a** (60 mg, 0.15 mmol) was then reacted with Lawesson's reagent (60.0 g, 0.15 mmol) to give compound **236b** with 80% purity (38.0 mg, 62%) as a pale yellow solid. **LC-MS** t_R= 1.416 min in 2 min chromatography, MS (ESI) *m/z* 415.1 $[M+H]^+$.

Compound **236b** (38 mg, 0.09 mmol) was finally converted to **compound 236** (6.3 mg, 16%) as a white solid. **LC-MS** t_R= 1.117 min in 2 min chromatography, MS (ESI) *m/z* 398.2 $[M+H]^+$; **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.16-7.14 (d, J = 8.0 Hz, 1H), 7.071-7.045 (m, 1H), 6.90 (m, 1H), 4.73 (s, 1H), 3.34 (s, 3H), 3.14 (m, 1H), 3.02 (s, 3H), 2.97 (m, 2H), 2.03-1.80 (m, 5H), 1.61 (m, 3H), 1.39-1.23 (m, 4H).

Example 194. Synthesis of Compound 237

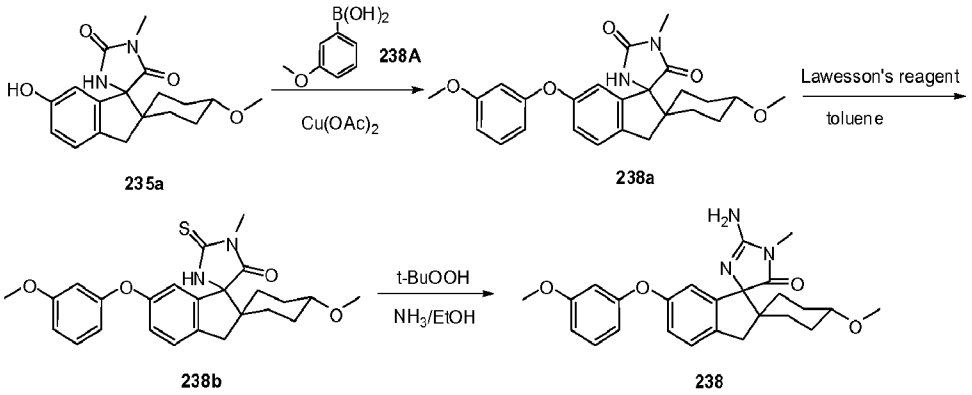


According to a similar synthesis of **compound 235**, compound **235a** (57 mg, 0.172 mmol) was alkylated with compound **237A** (34 mg, 0.258 mmol) in Cs_2CO_3 (84 mg, 0.258 mmol) to afford compound **235b** (32 mg, 48%).

And compound **235b** (32 mg, 0.082 mmol) was reacted with Lawesson's reagent (50 mg, 0.124 mmol) to give compound **235c** (32 mg, 94%), which was converted to **compound 235** (2.9 mg, 10%) as a white solid. **LC-MS** t_R = 0.994 min in 2 min chromatography, MS (ESI) *m/z* 388 $[M+H]^+$; **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.28 (d, J = 9.0 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 6.80 (s, 1H), 4.09 (s, 2H), 3.73 (m,

2H), 3.41 (s, 3H), 3.31-3.35 (m 3H), 3.19 (s, 4H), 3.01-3.13 (m, 2H), 2.01-2.03 (m, 2H), 1.86 (m, 2H), 1.27-1.44 (m, 5H).

Example 195. Synthesis of Compound 238



Procedure for preparation of compound 238a

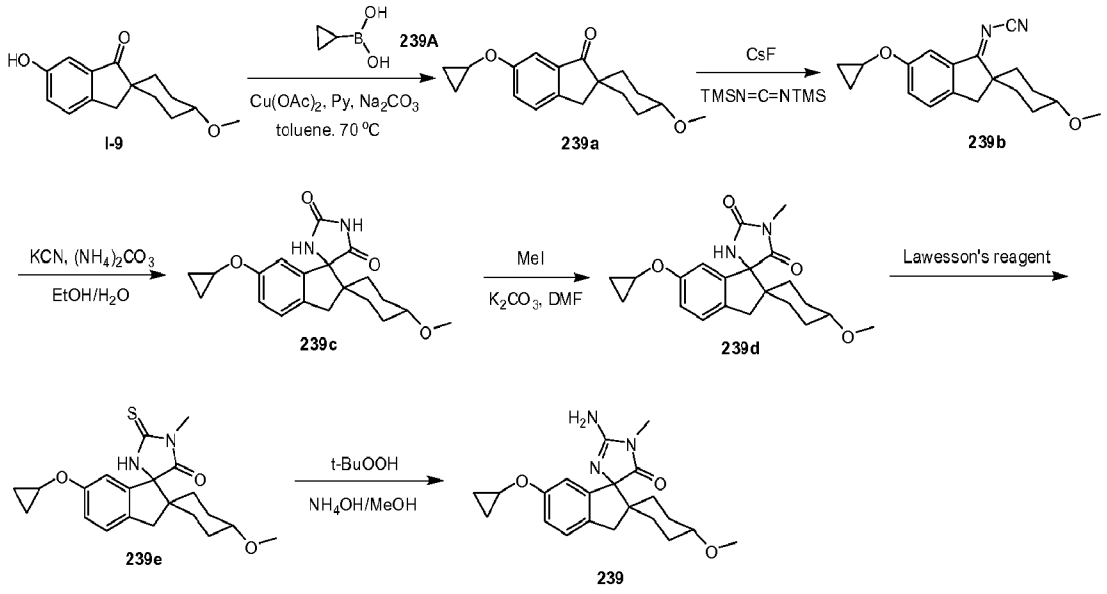
To a mixture of compound **235a** (40 mg, 0.12 mmol), compound **238A** (40 mg, 0.24 mmol), Et_3N (0.1 mL, 0.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was added molecular sieves (40 mg) and $Cu(OAc)_2$ (44 mg, 0.24 mmol) at room temperature. The resulting suspension was stirred at room temperature under O_2 atmosphere overnight. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the residue, which was purified by preparative TLC with petroleum ether: ethyl acetate (3:1) to give compound **238a** (20 mg, 45%) as a white solid. **LC-MS** t_R = 1.321 min in 2 min chromatography, MS (ESI) *m/z* 437 $[M+H]^+$.

Procedure for preparation of compound 238

A suspension of compound **238a** (30 mg, 0.068 mmol) and Lawesson's Reagent (31 mg, 0.075 mmol) in dry toluene (3 mL) was heated under 120 °C for 45 min in a CEM microwave reactor. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (petroleum: ethyl acetate = 5: 1) to give compound **238b** (15 mg, 50% purity) as a yellow solid. **LC-MS** t_R = 1.435 min in 2 min chromatography, MS (ESI) *m/z* 453.1 $[M+H]^+$.

The mixture of compound **238b** (15 mg, 0.033 mmol), *t*-BuOOH (80 mg, 0.887 mmol) in ammonia (3 mL) and methanol (1 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to the residue, which was purified by acidic preparative HPLC to give compound **238** (3.5 mg, 30%) as a white solid. **LC-MS** t_R = 1.000 min in 2 min chromatography, MS (ESI) *m/z* 436 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.28 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.6 Hz, 1H), 6.92 (dd, J = 8.4 Hz, 2.8, 1H), 6.66 (d, J = 7.2 Hz, 1H), 6.59 (s, 1H), 6.50 (s, 1H), 6.48 (s, 1H), 3.75 (s, 3H), 3.36 (s, 3H), 3.14 (d, J = 9.6 Hz, 1H), 3.08 (s, 1H), 3.05 (s, 1H), 3.01 (s, 1H), 2.01 (m, 2H), 1.85 (m, 1H), 1.62 (m, 1H), 1.39 (m, 4H).

Example 196. Synthesis of Compoudn 239



Procedure for preparation of compound 239a

To a suspension of compound **239A** (70 mg, 0.816 mmol), compound **I-9** (100 mg, 0.408 mmol), and Na_2CO_3 (71 mg, 0.816 mmol) in toluene (2 mL) was added a suspension of $Cu(OAc)_2$ (74 mg, 0.408 mmol) and pyridine (33 mg, 0.408 mmol) in hot toluene (4 mL). The reaction mixture was warmed to 70 °C and stirred overnight under air. The result mixture was cooled to room temperature, and a saturated aqueous NH_4Cl solution was added, followed by water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combine organic layers were washed

with brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum: EtOAc = 3: 1) to afford compound **239a** (15 mg, 13%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.38 (s, 1H), 7.26 (d, J = 8.8 Hz 1H), 7.14 (m, 1H), 3.69 (m, 1H), 3.33 (s, 3H), 3.21 (m, 1H), 2.89 (s ,2H), 2.09 (m, 2H), 1.70 (m, 2H), 1.44 (m, 2H), 1.28 (m, 3H), 0.73 (m, 2H), 0.68 (m, 2H).

Procedure for preparation of compound 239b

To a solution of compound **239a** (150 mg, 0.524 mmol) in dry CH_3CN (2 mL) was added CsF (239 mg, 1.573 mmol) under N_2. The reaction mixture was heated at 50 °C for 15 min, and bis-trimethylsilylcarbodiimide (0.59 mL, 2.62 mmol) was added. The final reaction mixture was stirred at 50 °C overnight. The reaction was cooled to room temperature and quenched with water (10 mL), extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give compound **239b** (120 mg, crude), which was used for the next step.

Procedure for preparation of compound 239c

In a 30 mL sealed tube was added compound **239b** (120 mg, 0.387 mmol), KCN (101 mg, 1.548 mmol) and $(NH_4)_2CO_3$ (376 mg, 3.87 mmol). To this solid was added H_2O (2 mL) and EtOH (2mL). The sealed tube was capped and heated in an oil bath at 75 °C overnight. The reaction was cooled to room temperature and water was added. The mixture was extracted with EtOAc (20 mL × 3). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give compound **239c** (138 mg, 100%) as a yellow solid.

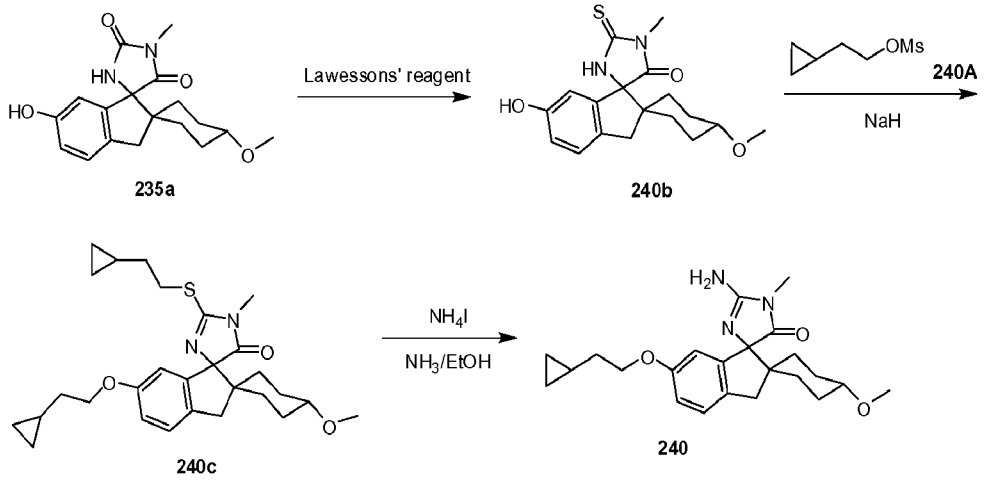
Procedure for preparation of compound 239

According to a similar synthesis of **compound 229,** compound **239c** (138 mg, 0.387 mmol) was methylated with MeI (55 mg, 0.387 mmol) to give compound **239d** (100 mg, 70%) as a white solid.

Compound **239d** (100 mg, 0.27 mmol) in dry toluene (3 mL) was reacted with Lawesson's reagent (164 mg, 0.405 mmol) to give compound **239e** (60 mg, 58%) as a white solid, which was converted to **compound 239** (8.5 mg, 15%) as a white solid. **LC-MS** t_R = 1.040 min in 2 min chromatography, MS (ESI) *m/z* 370 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 7.25 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H),

3.74 (m, 1H), 3.33 (s, 1H), 3.11 (m, 4H), 3.04 (m, 3H), 2.04 (m, 2H), 1.83 (m, 1H), 1.42-1.25 (m, 3H), 0.75-0.58 (m, 4H).

Example 197. Synthesis of Compoud 240



Procedure for preparation of compound 240b

To a solution of compound **235a** (80 mg, 0.242 mmol) in dry toluene (2 mL) was added Lawesson's reagent (118 mg, 0.291 mmol) under N_2. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 60 min. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) to give compound **240b** (20 mg, 24%) as a white solid.

Procedure for preparation of compound 240c

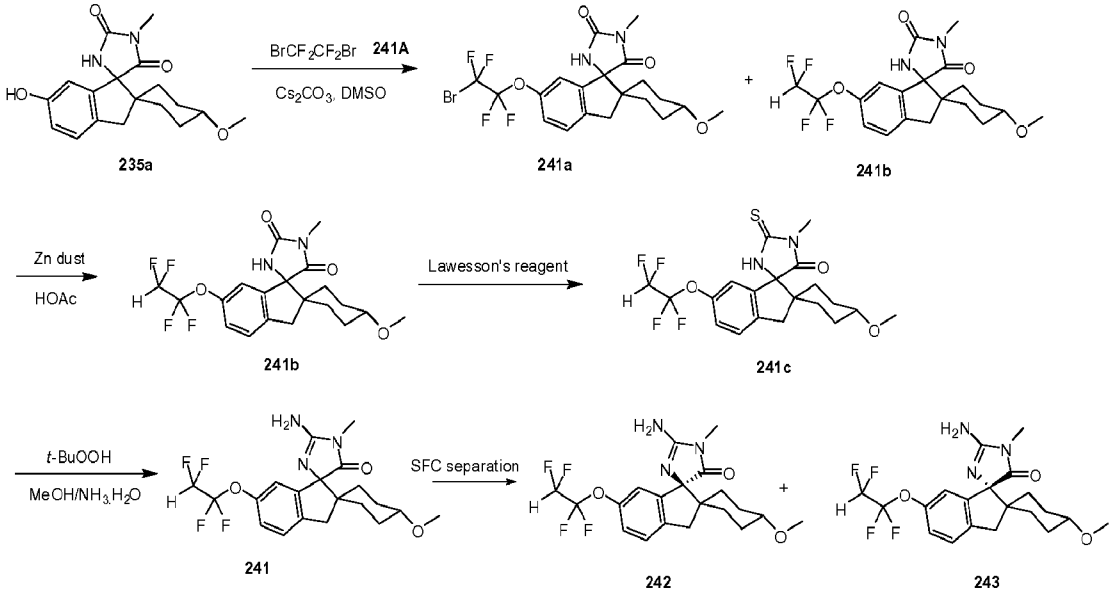
To a solution of compound **240b** (30 mg, 0.0865 mmol) in DMF (2 mL) was added NaH (13 mg, 0.346 mmol) at 0 °C. After stirring for 1 h, compound **240A** (43 mg, 0.259 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with water (15 mL), extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to afford compound **240c** (30 mg, impure) as an oil.

Procedure for preparation of compound 240

To a solution of compound **240c** (15 mg, 0.031 mmol) in NH_3/EtOH (2 mL) was added NH_4I (46 mg, 0.31 mmol). The reaction mixture was heated in a CEM

microwave reactor at 120 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by preparative HPLC to give **compound 240** (2.0 mg, 17%) as a white solid. **LC-MS** t_R = 1.017 min in 2 min chromatography, MS (ESI) *m/z* 498 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 6.0 Hz, 1H), 6.68 (s, 1H), 3.92 (m, 2H), 3.23 (s, 3H), 3.09 (s, 3H), 2.97 (m, 3H), 1.95 (m, 2H), 1.73 (m, 1H), 1.54 (m, 2H), 1.38-1.23 (m, 4H), 1.27 (m, 1H), 0.75 (m, 1H), 0.36 (m, 2H), 0.05 (m, 2H).

Example 198. Synthesis of Compounds 241, 242 and 243



Procedure for preparation of compounds 241a and 241b

A mixture of compound **235a** (80 mg, 0.19 mmol), compound **241A** (98 mg, 0.38 mmol), and Cs_2CO_3 (93 mg, 0.29 mmol) in dry DMSO (1.5 mL) was heated at 50 °C overnight. LCMS showed the reaction was completed. After cooling to room temperature, water (10 mL) and CH_2Cl_2 (10 mL) were added and the mixture was stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was

purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to afford a mixture of compounds **241a** and **241b** (70 mg, 60%) as a white solid.

Procedure for preparation of compound 241b

A solution of compounds **241a** and **241b** (70 mg, 0.157 mmol) in HOAc (2 mL) was heated to 50 °C. To the solution was added Zn dust (31 mg, 0.0.471 mmol) under N_2 in portions. After stirring at 70 °C overnight, water (10 mL) and CH_2C1_2 (10 mL) were added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2C1_2 (10 mL*3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to afford compound **241b** (20 mg, 29%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 5.96-5.68 (m, 1H), 5.51 (d, 1H), 3.29 (s, 3H), 3.12 (m, 3H), 2.96 (s, 3H), 2.04 (m, 1H), 1.93 (m, 2H), 1.38 (m, 1H), 1.27 (m, 4H), 1.19 (m, 1H).

Procedure for preparation of compound 241c

To a solution of compound **241b** (40 mg, 0.093 mmol) in dry toluene (2.5 mL) was added Lawesson's reagent (56mg, 0.140 mmol) under N_2. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 1 h. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **241c** (30 mg, 71%) as a white solid.

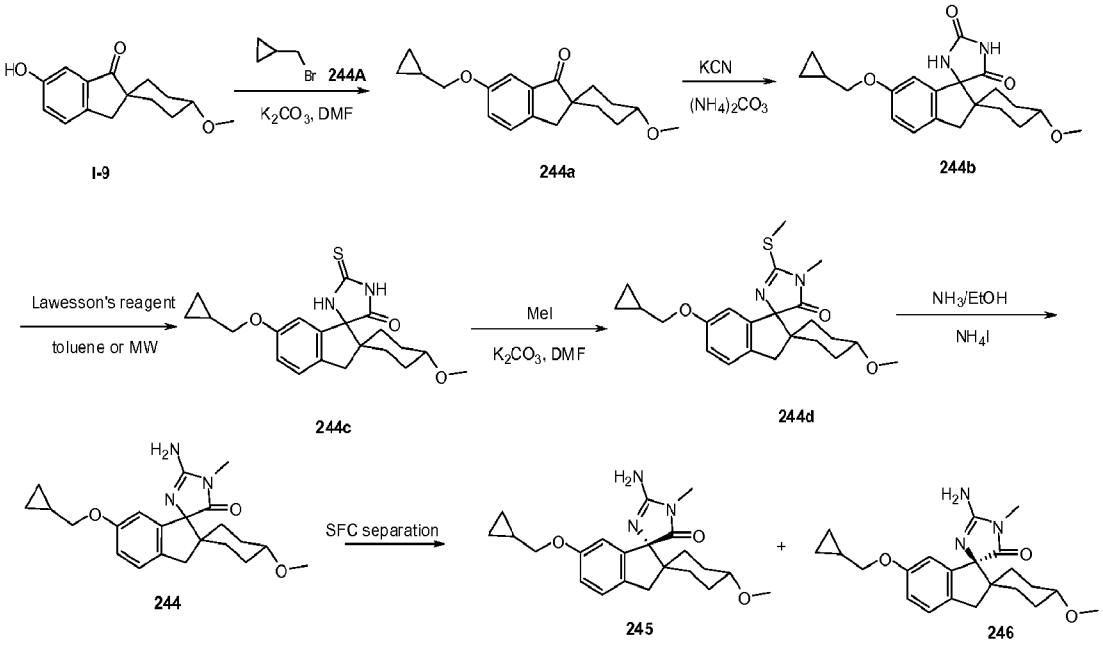
Procedure for preparation of compound 241

To a solution of compound **241c** (30 mg, 0.067 mmol) in MeOH (3 mL) and $NH_3.H_2O$ (0.6 mL) was added *t*-BuOOH (197 mg, 13.5 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by preparative HPLC to give **compound 241** (9 mg, 31%) as a white solid. **LC-MS** t_R = 1.063 min in 2 min chromatography, MS (ESI) *m/z* 430 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.43 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 6.42-6.06 (tt, 1H), 3.43 (s, 3H), 3.22-3.13 (m, 6H), 2.15 (m, 2H), 1.84 (m, 1H), 1.48 (m, 3H), 1.41-1.22 (m, 2H). **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -89.826, -139.278

Procedure for preparation of compounds 242 and 243

Compound 241 (80 mg, 0.186 mmol) was separated by SFC to give **compound 243** (15 mg, 19%), **LC-MS** t_{RA} = 0.899 min in 2 min chromatography, MS (ESI) *m/z* 430 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.36 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 6.41-6.15 (t, J = 52.8 Hz 1H), 3.36 (s, 3H), 3.15-3.13 (m, 3H), 3.06 (s, 3H), 2.02 (m, 2H), 1.86 (m, 1H), 1.66 (m, 1H), 1.41 (m, 2H), 1.29 (m, 2H). **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -89.925, -139.348; **ee%:**100%; and **compound 242** (30 mg, 38%) as white solids. **LC-MS** t_{RB} = 0.893 min in 2 min chromatography, MS (ESI) *m/z* 430 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 6.17-6.03 (t, J = 52.8 Hz, 1H), 3.27 (s, 3H), 3.05-3.98 (m, 3H), 2.95 (s, 3H), 1.89 (m, 2H), 1.71 (m, 1H), 1.51 (m, 1H), 1.27 (m, 2H), 1.16 (m, 2H).**^{19}F NMR** (CD_3OD 19F 400 MHz): δ -89.918, -139.343; **ee%:**100%.

Example 199. Synthesis of Compounds 244, 245 and 246



Procedure for preparation of Compound 244a

To a solution of compound **I-9** (380 mg, 1.53 mmol in DMF (5 mL) was added K_2CO_3 (422.2 mg, 3.06 mmol), and compound **244A** (249.2 mg, 1.84 mmol), the mixture was stirred at ambient temperature overnight. The reaction was added with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **244a** (380 mg, 67%) as a white solid which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.27 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.19 (s, 1H), 3.69 (d, J = 6.8 Hz, 2H), 3.42 (s, 3H), 3.27-3.37 (m, 1H), 2.90 (s, 2H), 1.97-2.09 (m, 2H), 1.65-1.72 (m, 2H), 1.48-1.55 (m, 2H), 1.34-1.43 (m, 2H), 1.27-1.34 (m, 1H), 0.79-0.80 (m, 2H), 0.28-0.32 (m, 2H).

Procedure for preparation of compound 244

According to a similar synthesis for **I-6** described in Example I-2, compound **244a** (380 mg, 1.26 mmol) was condensed to hydantoin **244b** (70 mg, 18%) as white

solid. **LCMS** : t_R = 1.191 min in 2 min chromatography, MS (ESI) *m/z* = 371.2 $[M+H]^+$.

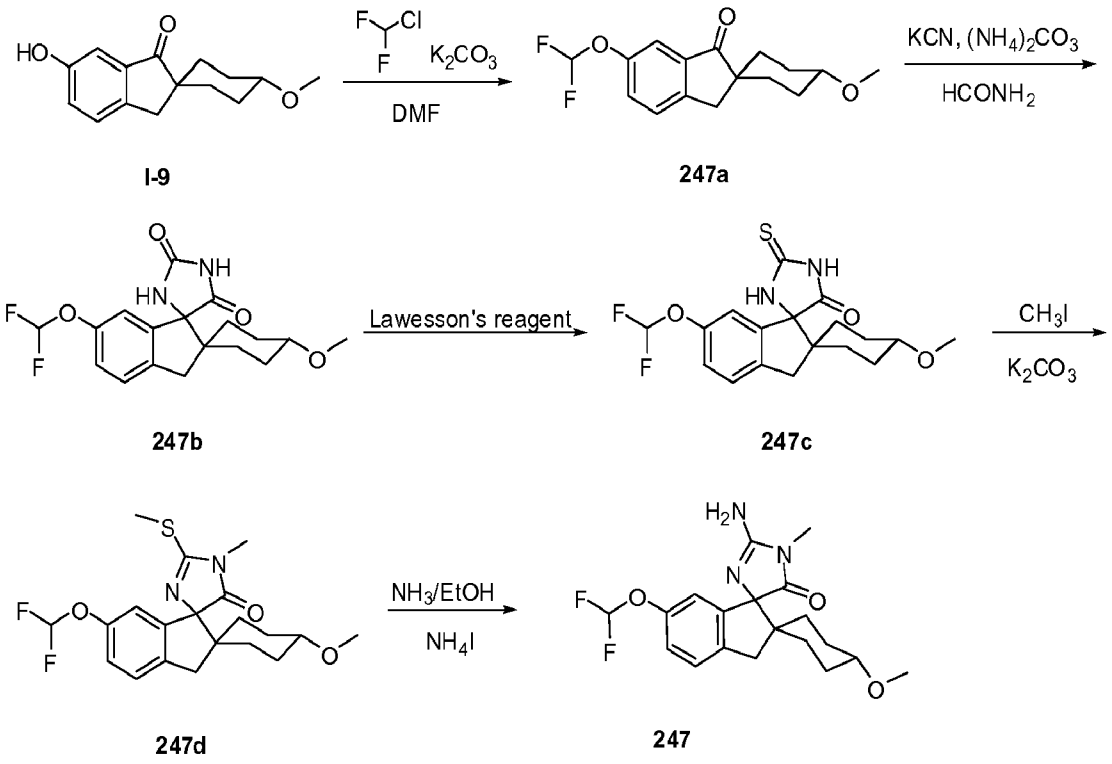
Compound **244b** (50 mg, 0.13 mmol) was reacted with Lawesson's Reagent (60 mg, 0.14 mmol) under N_2 to afford compound **244c** (30 mg, 57%) as a white solid, which was methylated with MeI (45.6mg, 0.31mmol) to give compound **244d** (20 mg, 65%) as a white solid. **LCMS** : t_R = 1.412 min in 2 min chromatography, MS (ESI) *m/z* = 415.2 $[M+H]^+$.

Finally, compound **244d** (20 mg, 0.046 mmol) was converted to **compound 244** (2.4 mg, 5%) as a white solid. **LCMS**: t_R = 1.678 min in 3 min chromatography, MS (ESI) *m/z* = 384.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.18 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.51 (s, 1H), 3.77 (d, *J* = 6.8 Hz, 2H), 3.35 (s, 3H), 3.27 (m, 1H), 3.27-3.15 (m, 2H), 3.06 (s, 3H), 2.01-1.94 (m, 2H), 1.94-1.84 (m, 2H),1.59-1.50 (m, 1H), 1.50-1.39 (m, 2H), 1.39-1.29 (m, 2H), 0.61-0.60 (m, 2H), 0.34-0.31 (m, 2H).

Compound 244 (~400 mg) was purified by SFC to give **compound 245** (133.7 mg, 27%), **LCMS**: t_R = 0.833 min in 2 min chromatography, MS (ESI) *m/z* = 384.1 $[M+H]^+$. **SFC**: t_R = 5.82 min in 16 min chromatography, ee%=100%.**^{1}H NMR** (CD_3OD 400 MHz): *δ* 7.17-7.15 (d, *J* = 8.0 Hz, 1H), 6.81-6.79 (dd, *J* = 2.4, 8.0 Hz,, 1H), 6.50 (s, 1H), 3.78 (d, *J* = 8.0 Hz, 2H), 3.34 (s, 3H), 3.27-3.12 (m, 1H), 3.04 (m, 4H), 2.97-2.93(d, *J* = 15.6 Hz, 1H), 2.01-1.96 (m, 2H), 1.93-1.82(m, 1H), 1.70-1.50(m, 1H), 1.35-1.31 (m, 2H), 1.31-1.28 (m, 3H), 0.61-0.60 (m, 2H), 0.36-0.35 (m, 2H).

& **compound 246** (144 mg, 29%) as white solids; **LCMS**: t_R = 1.080 min in 2 min chromatography, MS (ESI) *m/z* = 384.3 $[M+H]^+$. **SFC**: t_R = 9.28 min in 16 min chromatography, ee%=99%. **^{1}H NMR** (CD_3OD 400 MHz): *δ* 7.17-7.15 (d, *J* = 8.0 Hz, 1H), 6.81-6.79 (dd, *J* = 2.4, 8.0 Hz,, 1H), 6.50 (s, 1H), 3.78 (d, *J* = 8.0 Hz, 2H), 3.34 (s, 3H), 3.27-3.12 (m, 1H), 3.04 (m, 4H), 2.97-2.93(d, *J* = 15.6 Hz, 1H), 2.01-1.96 (m, 2H), 1.93-1.82 (m, 1H), 1.70-1.50(m, 1H), 1.35-1.31 (m, 2H), 1.31-1.28 (m, 3H), 0.61-0.60 (m, 2H), 0.36-0.35 (m, 2H).

Example 200. Synthesis of Compound 247



Procedure for preparation of compound 247a

To a solution of compound **I-9** (1.0 g, 4.06 mmol) in DMF (15 mL) was added K_2CO_3 (0.62 g, 4.47 mol). The mixture was bubbled with a flow of chloro-difluoro-methane at 85 °C for 6 h. Water (10 mL) was added and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with a1. sat. NH_4Cl (2 × 10 mL), dried over Na_2SO_4 and evaporated under vacuum to give the crude. The crude was purified by preparative TLC (hexane: EtOAc = 5:1) to afford compound **247a** (420 mg, 35%) as a white solid.

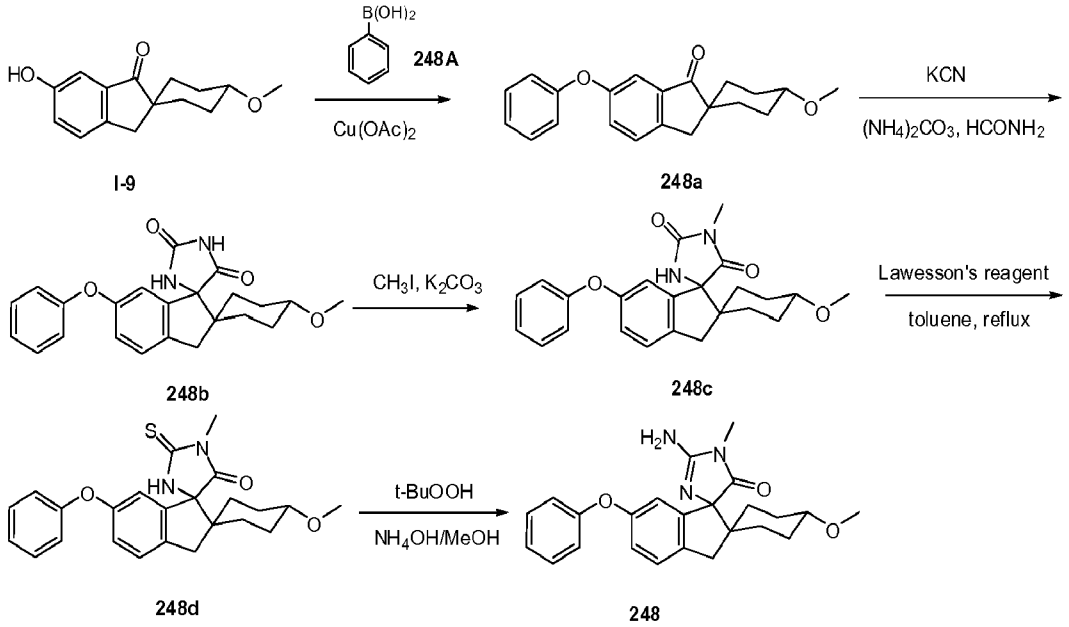
Procedure for preparation of compound 247

According to a similar synthesis for **compound I-6** described in Example I-2, compound **247a** (420 mg, 1.42 mmol) was condensed to hydantoin **247b** (45 mg, 8%) as a white solid. And compound **247b** (40 mg, 0.11 mmol) was reacted with

Lawesson's reagent (53 mg, 0.13 mmol) to give compound **247c** (36 mg, 85%) as a whit solid.

Compound **247c** (36 mg, 0.094 mmol) was then dimethylated with iodomethane (20 mg, 0.14 mmol) in DMF (1 mL) to afford compound **247d** (21 mg, 54%) as a white solid, which was converted to **compound 247** (6.1 mg, 31%) as a white solid. **LC-MS** t_R = 1.008 min in 2 min chromatography, MS (ESI) *m/z* 380 $[M+H]^+$.**^{1}H NMR** (CD_3OD 1H): δ 7.32 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 2.4, 8.0 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.52-6.89 (m, 1H), 3.28 (s, 3H), 3.12 (s, 3H), 3.09 (m, 1H), 3.00-3.07 (m, 2H), 1.92-2.01 (m, 2H), 1.77 (m, 1H), 1.20-1.42 (m, 5H). **^{19}F NMR** (CD_3OD 19F): δ -83.426

Example 201. Synthesis of Compound 248



Procedure for preparation of compound 248a

A suspension of compound **I-9** (247 mg, 2.03 mmol), 248A (500 mg, 2.03 mmol), $Cu(OAc)_2$ (737 mg, 4.06 mmol), Et_3N (1.42 mL, 10.05 mmol) and molecular sieves (200 mg) in anhydrous CH_2Cl_2 (20 mL) was stirred under open air at room temperature overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 10: 1) to give compound **248a** (0.45 g, 85%) as a brown oil.

Procedure for preparation of compound 248b

A steel autoclave were charged with a mixture of compound **248a** (450 mg, 1.4 mmol), KCN (180 mg, 2.8 mmol), $(NH_4)_2CO_3$ (1.1 g, 11.3 mmol) and formamide (15 mL). The mixture was heated at 120 °C for 72 h. The reaction mixture was then cooled and poured into ice. After acidification with concentrated HCl (20 mL), the mixture was filtrated to give the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (2 × 150 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to dryness. The crude product was purified by re-crystallization from ethyl acetate to afford compound **248b** (0.18 g, 33%) as a black solid.

Procedure for preparation of compound 248c

To a solution of compound **248b** (180 mg, 0.46 mmol) in CH_3CN (3.0 mL) was added K_2CO_3 (100 mg, 0.69 mmol). After stirring for 5 min, MeI (98 mg, 0.60 mmol) was added and the reaction mixture was heated at 80 °C for 35 min in a microwave reactor. The mixture was filtered and the filtrate was concentrated under reduced pressure to give compound **248c** (120 mg, 87%) as a yellow solid, which was used for the next step directly without purification.

Procedure for preparation of compound 248d

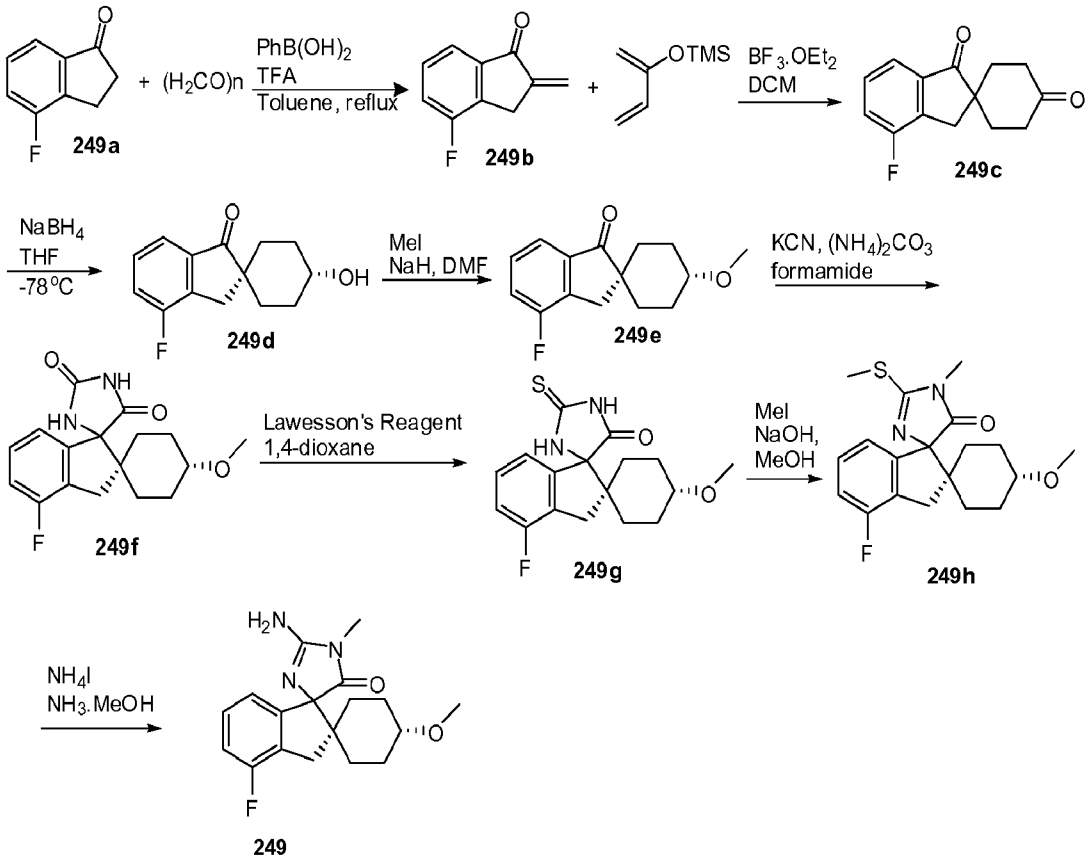
A suspension of compound **248c** (120 mg, 0.29 mmol) and Lawesson's Reagent (143 mg, 0.35 mmol) in anhydrous toluene (3 mL) was heated at 120 °C for 45 min in a CEM microwave reactor. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 3: 1) to give compound **248d** (60 mg, 90%) as a yellow solid.

Procedure for preparation of compound 248

A solution of compound **248d** (60 mg, 0.14 mmol), *t*-BuOOH (255 mg, 2.84 mmol) in a solution of NH_4OH/MeOH (2 mL/5 mL) was stirred at room temperature overnight. The solvent was removed by evaporation to give the residue, which was purified by preparative RP-HPLC (acid) to give **compound 248** (17.2 mg, 30%) (TFA

salt) as a white solid. **LC-MS** t_R = 0.967 min in 2 min chromatography, MS (ESI) *m/z* 406.0 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.37-7.30 (t, J = 5.7 Hz, 3H), 7.14-7.09 (t, J = 6.3 Hz, 1H), 7.01-6.91 (m, 4H), 3.42 (s, 3H), 3.19 (s, 4H), 3.15-3.12 (d, J = 6.3 Hz, 2H), 2.09-2.04 (m, 2H), 1.88-1.84 (m, 1H), 1.51-1.29 (m, 5H).

Example 202. Synthesis of Compound 249



Procedure for preparation of compound 249b

To a 1000 mL round bottle flask were charged 4-fluoro-2,3-dihydro-1H-inden-1-one (**249a**) (5.04 g, 33.6 mmol), paraformaldehyde (10.08 g, 336 mmol), phenylboronic acid (4.92 g, 40.3 mmol) followed by toluene (235 mL), to the suspension was added TFA 2.6 mL, 33.6 mmol), and the resulting suspension was refluxed for 4 hrs, which resulted a clear yellowish solution. The solution was cooled to room temperature, and the pH was adjusted to 7-8 by adding saturated $NaHCO_3$. After extracting with ethyl acetate, the organic layers were combined, and evaporated. The residue was purified by flash chromatography (0 to 30%EtOAc/Hexane) to give 4-fluoro-2-methylene-2,3-dihydro-1H-inden-1-one (**249b**) (3.91 g, 72%). **LC-MS** t_R = 1.49 min in 3 min chromatography, MS (ESI) *m/z* 163 $[M+H]^+$

Procedure for preparation of compound 249c

To a solution of 4-fluoro-2-methylene-2,3-dihydro-1H-inden-1-one (**249b**) (3.71 g, 22.9 mmol) and (buta-1,3-dien-2-yloxy)trimethylsilane (5.2 mL, 29.8 mmol) in DCM (200 mL) at 0°C, there was added $BF_3.Et_2O$ (0.5 mL dropwise. The resulting solution was stirred at 0oC for another 30 min, quenched with MeOH (0.3 mL), warmed to room temperature, acidified with 2N HCl aqueous solution (15 mL) and extracted with DCM (10 mLx4). The combined organic layers were dried over Na2SO4, filtered and evaporated, and the residue was purified by flash chromatography (0 to 50% EtOAc/Hexane) to give 4'-fluorospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (**249c**) (2.77 g, 49%). **LC-MS** t_R = 1.41 min in 3 min chromatography, MS (ESI) *m/z* 233 $[M+H]^+$.

Procedure for preparation of compound 249d

To a solution of 4'-fluorospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (**249c**) (2.77 g, 11.9 mmol) in THF (40 mL) at -78 °C, there was added $NaBH_4$ (0.45 g, 11.9 mmol) portion by portion (control the temperature below -70oC). The resulting solution was stirred at -78 oC for another 30 min, and -78oC acetone was added to quench the extra NaBH4. The reaction mixture was then allowed to warm to room temperature, water (10 mL) was added, and the mixture was extracted with EtOAc (10 mL X 4), combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and

evaporated to dryness. The residue was purified by flash chromatography (0 to 60% EtOAc/Hexane) to give (1r,4r)-4'-fluoro-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**249d**) and its isomer as a 3:1 mixture (2.35 g, 84%), which could not be separated by normal phase chromatography. **LC-MS** t_R = 1.29 min in 3 min chromatography, MS (ESI) *m/z* 235 $[M+H]^+$. For its ismoer, **LC-MS** t_R = 1.37 min in 3 min chromatography, MS (ESI) *m/z* 235 $[M+H]^+$.

***Procedure for preparation of compound* 249e**

To a solution of (1r,4r)-4'-fluoro-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**249d**) (2.11 g, 9.0 mmol) in anhydrous DMF (30 mL) there was added NaH (60% in mineral oil, 1.80 g, 27.0 mmol) slurry in DMF (5mL) dropwise. The resulting mixture was stirred at room temperature for 30 min, the completion of reaction was confirmed by LC-MS. The reaction was quenched by adding MeOH slowly followed by water, after extraction with DCM, the organic layer was evaporated, and the residue was purified by flash chromatography (20% EtOAc/Hexane) to give (1r,4r)-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**5**) (1.50 g, 67%), the two isomer still could not be separated. The product was recrystallized with Hexane to give pure isomer **249e** (0.94 g, 63%).

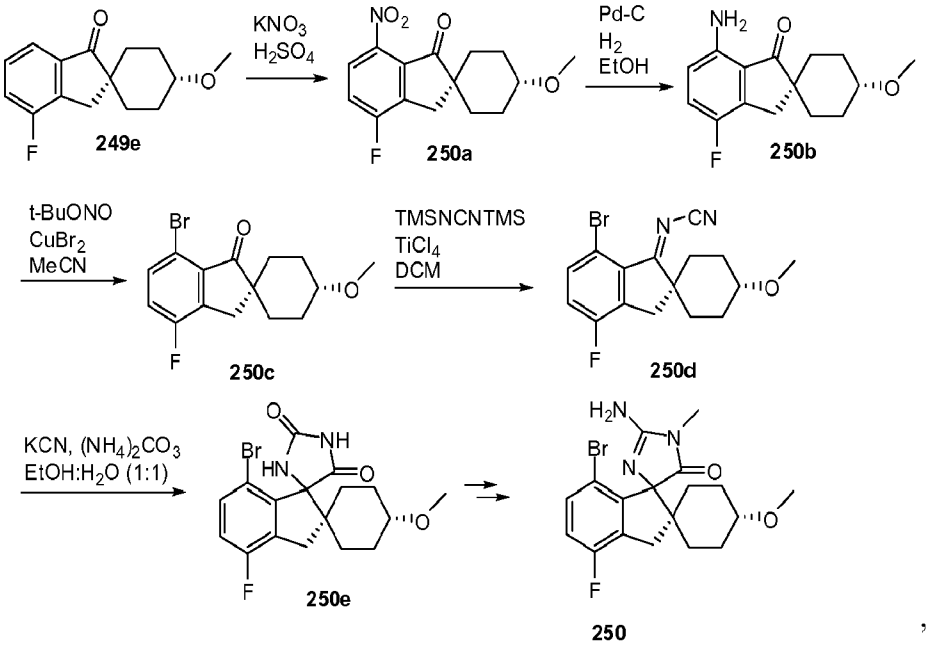
***Procedure for preparation of compound* 249f**

According to a similar synthesis of compound **I-6** described in Example I-2, (1r,4r)-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**249e**) (0.22 g, 0.89 mmol) was condensed to hydantoin **249f** (100 mg, 64% corrected yield, 99 mg of starting material **249e** was recovered). **LC-MS** t_R = .23 min in 3 min chromatography, MS (ESI) *m/z* 319 $[M+H]^+$.

Hydantoin **249f** (100 mg, 0.31 mmol) was reacted with Lawesson's Reagent (125 mg, 0.31 mmol) to afford thiohydantoin **249g** (91.3 mg, 88%). **LC-MS** t_R = 1.37 min in 3 min chromatography, MS (ESI) *m/z* 335 $[M+H]^+$. This thiohydantoin **7** (91.3 mg, 0.27 mmol) was further dimethylated MeI (0.2 mL, excess) to give thioether **249h** (79.7 mg, 80%). **LC-MS** t_R = 1.74 min in 3 min chromatography, MS (ESI) *m/z* 363 $[M+H]^+$.

Finally, thioether **249h** (40 mg, 0.11 mmol) was converted to **compound 249** as a TFA salt (25.6 mg, 70%). **LC-MS** t_R = 1.09 min in 3 min chromatography, MS (ESI) *m/z* 332 $[M+H]^+$; **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.26 (m, 1H), 7.14-7.00 (m, 2H), 3.36 (s, 3H), 3.22 (m, 2H), 3.18 (s, 3H), 3.04 (m, 1H), 2.08-1.94 (m, 2H), 1.82 (m, 1H), 1.44-1.22 (m, 5H).

Example 203. Synthesis of Compound 250



Procedure for preparation of compound 250a

To a solution of (1r,4r)-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**249e**) (1.17 g, 4.7 mmol) in concentrate H_2SO_4 (6.0 mL) at 0 °C, there was added KNO_3 (0.48 g, 4.7 mmol) in concentrate H_2SO_4 (1.5 mL) dropwise, the resulting solution was stirred at 0 °C for 2 hours, ice was added to stop the reaction, and the mixture was extracted with EtOAc (10 mL x 4), combined organics were washed with sat. $NaHCO_3$ (10 mL), brine (10 mL) dried over Na_2SO_4, and the solvent was removed in vacuum to give (1r,4r)-4'-fluoro-4-methoxy-7'-nitrospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250a**) (1.31 g, 95%), which was used for the next step without purification. **LC-MS** t_R = 1.68 min in 3 min chromatography, MS (ESI) *m/z* 294 $[M+H]^+$.

Procedure for preparation of compound 250b

A solution of 1r,4r)-4'-fluoro-4-methoxy-7'-nitrospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250a**) (1.31 g, 4.5 mmol) and Pd-C (100 mg) in EtOH (60 mL) was stirred with the connection of a H_2 balloon at room temperature for 5 hours. Reaction completion was confirmed by LC-MS, and the solution was filtered, and removed in vacuum to give (1r,4r)-7'-amino-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250b**) (1.18 g, 100 %) , which was used for the next step without purification. **LC-MS** t_R = 1.58 min in 3 min chromatography, MS (ESI) *m/z* 264 $[M+H]^+$.

Procedure for preparation of compound 250c

To a solution of $CuBr_2$ (1.25 g, 5.55 mmol) and tert-butyl nitrite (1.48 mL, 11.1 mmol) in anhydrous MeCN (15 mL) at 0°C there was added 1r,4r)-7'-amino-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250b**) (1.17 g, 4.44 mmol) in anhydrous MeCN (5 mL) dropwise to keep the temperature lower than 5 °C. After adding, the resulting solution was warmed up slowly to room temperature, and stirred for another 1 hour, quenched with 1N HCl, and extracted with EtOAc (10 mL x 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by flash chromatography (0 to 50% EtOAc/Hexane) to give (1r,4r)-7'-bromo-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250c**) (1.15 g, 79%). **LC-MS** t_R = 1.84 min in 3 min chromatography, MS (ESI) *m/z* 327 $[M+H]^+$.

Procedure for preparation of compound 250d

To a solution of 1r,4r)-7'-bromo-4'-fluoro-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**250c**) (1.14 g, 3.48 mmol) in anhydrous DCM (35 mL) there was added $TiCl_4$ (1 M in DCM, 7.0 mL, 7.0 mmol), the resulting solution was stirred at room temperature, then N,N'-methanediylidenebis(1,1,1-trimethylsilanamine) (1.74 mL, 7.6 mmol) was added dropwise. The solution was stirred at room temperature overnight. Water was added, and the mixture was extracted with DCM (10 mLx4). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. The solvent was removed in vacuum to give crude (E)-N-((1r,4r)-4'-bromo-7'-fluoro-4-

methoxyspiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)cyanamide (**250d**) (1.22 g, 100 %), which was used for the next step without purification. **LC-MS** t_R = 1.82 min in 3 min chromatography, MS (ESI) *m/z* 351 $[M+H]^-$.

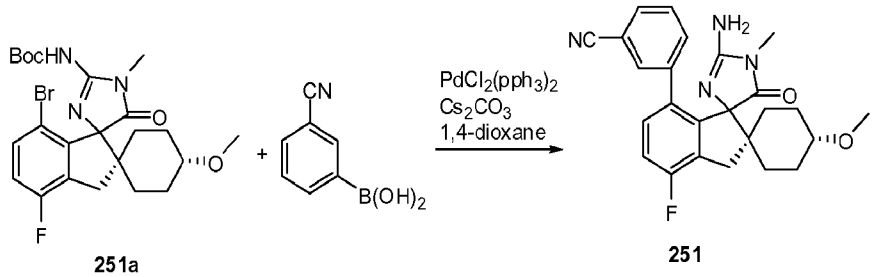
Procedure for preparation of compound 250e

To a 50 mL sealed tube there was charged (E)-N-((1r,4r)-4'-bromo-7'-fluoro-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)cyanamide (**250d**) (1.22 g, 3.48 mmol), KCN (0.47 g, 7.0 mmol), $(NH_4)_2CO_3$ (2.34 g, 24.4 mmol), and EtOH (10 mL) and water (10 mL). The tube was sealed, and heated at 75 °C overnight. The solution was cooled to room temperature, and water (15 mL) was added, filtered to give solid product **6** (0.70 g), the filtration was extracted with DCM, after removal of solvent, the residue was purified by flash chromatography to give another 0.24 product **250e** (total 68%).

Procedure for synthesis of compound 250

Using the similiar synthesis of **compound 249**, **compound 250** was synthesized as a TFA salt. **LC-MS** t_R = 1.21 min in 3 min chromatography, MS (ESI) *m/z* 410 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.48 (m, 1H), 7.14 (m, 1H), 3.38 (s, 3H), 3.26 (m, 1H), 3.24 (s, 3H), 3.20 (m, 1H), 3.00 (m, 1H), 2.06 (m, 2H), 1.82 (m ,1H), 1.56-1.26 (m, 5 H); **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.8, -121.0.

Example 204. Synthesis of Compoud 251

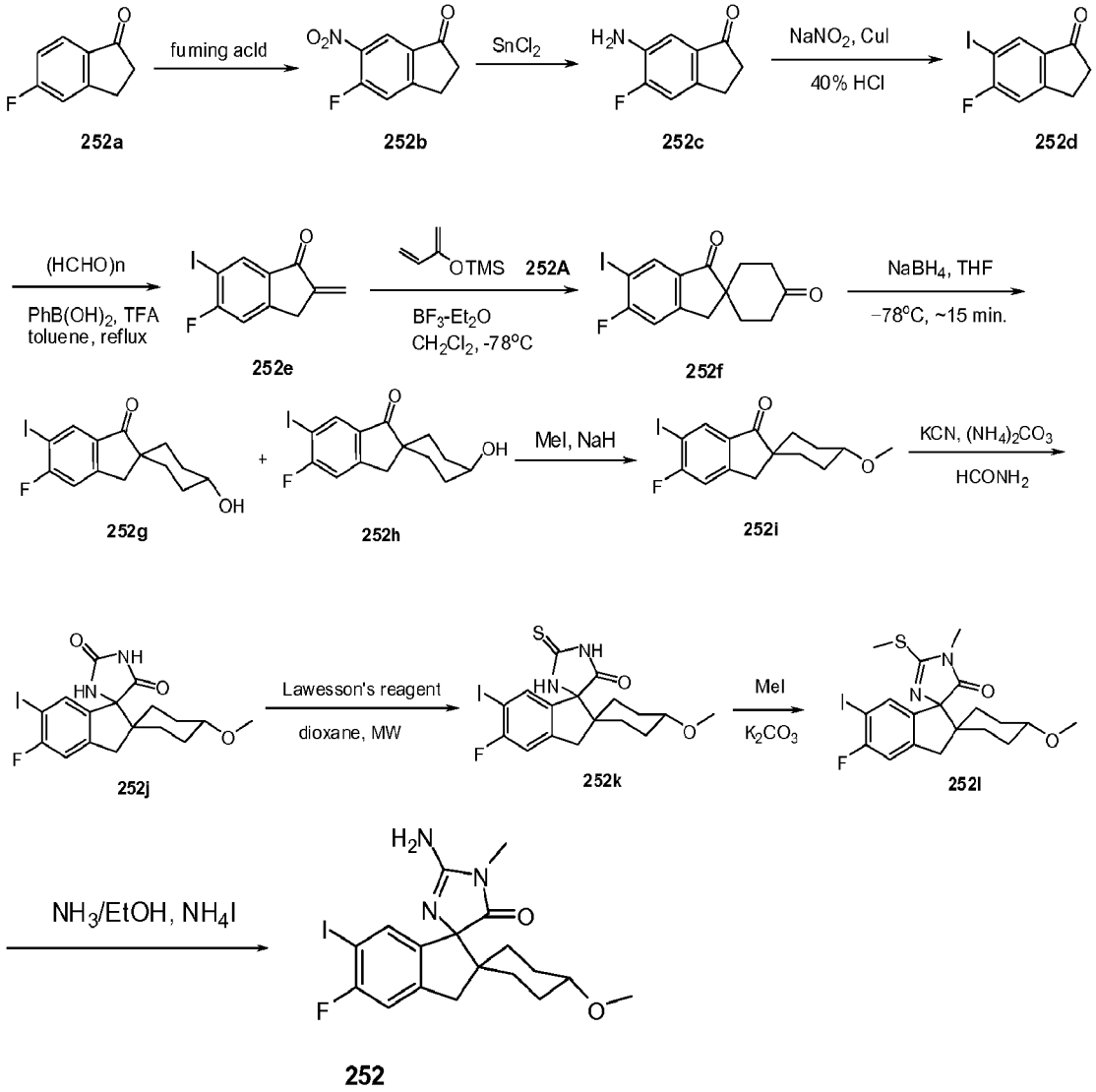


251a **251**

To a 10 mL CEM tube there was charged compound **251a** (102 mg, 0.2 mmol), $PdCl_2(pph_3)_2$ (7.0 mg), Cs_2CO_3 (130 mg. 0.4 mmol), 1,4-dioxane (1 mL) and water (0.2 mL). The tube was heated in a CEM microwave reactor at 120 °C for 30 min. The solution was filtered, solvent was removed in vacuum, and the residue was purified with HPLC to give compound **compound 251** (5.5 mg, 6%). **LC-MS** t_R = 1.31 min in 3 min

chromatography, MS (ESI) *m/z* 433 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.80 (m, 1H), 7.62 (m, 1H), 7.60-7.24 (m, 2 H), 7.22 (m, 1H), 7.14 (m, 1H), 3.36 (s, 3 H), 3.30 (m, 1H), 3.20-3.-02 (m, 5H), 2.04 (m, 2H), 1.80 (m, 1H), 1.52-1.24 (m, 5H); **^{19}F NMR** (CD_3OD, 376 MHz): δ -77, -120.

Example 205. Synthesis of Compound 252



Procedure for preparation of compound 252b

To a well-stirred solution of fuming nitric acid (92 mL) was added compound **252a** (20 g, 133 mmol) at 0 °C slowly. The resulting mixture was stirred at 0 °C for 3 h. TLC showed the reaction was completed, and the reaction mixture was poured into ice (100 g) to give the yellow solid. The resulting mixture was filtered, and the filter cake was dissolved in ethyl acetate (200 mL) and washed with water (2 × 500 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give compound **252b** (8.5 g, 33%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.36-8.44 (m, 1H), 7.33-7.42 (m, 1H), 3.18-3.30 (m, 2H), 2.73-2.81 (m, 2H).

Procedure for preparation of compound 252c

To a solution of $SnCl_2$ (39.35 g, 174 mmol) in concentrated aqurous HCl (33 mL) was added a solution of compound **252b** (8.5 g, 43.6 mmol) in 95% ethanol (16 mL). The resulting mixture was stirred at room temperature for 2 h. TLC showed the reaction was completed, and the mixture was treated with 50% aqueous NaOH solution (100 mL) to give the yellow solid. The resulting mixture was filtered, and the filter cake was dissolved in CH_2Cl_2 (200 mL). The mixture was filtered, and the filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **252c** (5.5 g, 77%) as a yellow solid. **^{1}H NMR** (CDCl3 400 MHz): δ 6.99-7.20 (m, 2H), 3.79 (s, 2H), 2.93-2.96 (m, 2H), 2.58-2.60 (m, 2H).

Procedure for preparation of compound 252d

A mixture of compound **252c** (5.5 g, 33.3 mmol) in concentrated HCl (19 mL) was stirred at room temperature. Then to the mixture was added ice (10 g) and stirred for a few min. Then to the above mixture was added a solution of $NaNO_2$ (2.59 g, 36.7 mmol) in H_2O (13 mL) slowly while keeping temperature between -5 °C~0 °C, and stirred for 30 min. Then to the mixture was added a solution of KI (55.24 g, 333 mmol) in H_2O (70 mL) slowly and stirred for another 3 h. The resulting mixture was filtered, and the filtrate was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give compound

252d (5 g, 54%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.10 (d, J = 6.0 Hz, 1H), 7.12 (d, J = 9.2 Hz, 1H), 3.02-3.05 (m, 2H), 2.65-2.68 (m, 2H).

Procedure for preparation of compound 252e

A solution of compound **252d** (10 g, 36.2 mmol), paraformaldehyde (5.1 g, 163 mol), N-methylaniline TFA salt (12 g, 54.3 mmol) in anhydrous THF (120 mL) was refluxed for 8 h. When starting material was totally consumed, the crude mixture was cooled to room temperature, concentrated to give the residue, extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 10:1) to give compound **252e** (6.7 g, 65%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.22 (d, J = 6.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.30 (s, 1H), 5.60 (s, 1H), 3.66 (s, 2H).

Procedure for preparation of compound 252f

To a solution of compound **252e** (1.6 g, 5.56 mmol, 1 equivalent) in dichloromethane (20 mL) was added 2-trimethylsilyloxy-1,3-butadiene (1.05 mL, 6.11mmol, 1.1 equivalents) and the reaction was cooled down to -78 °C. After stirring for 15 min at -78 °C, $BF_3{\cdot}Et_2O$ (0.36 mL, 2.78 mmol, 0.5 equivalents) was slowly added and the reaction was allowed to stir at -78 °C. During the addition, the color of the solution changed from colorless to light yellow. After 25 min of the $BF_3{\cdot}Et_2O$ addition, the TLC indicated total consumption of the dienophile, formation of the silyl enol ether Diels Alders adduct and the desired ketone. The reaction was rapidly quenched with MeOH (3.5 mL), allowed to stir 5 min at -78 °C and warmed up to room temperature. Once at room temperature, an aqueous diluted HCl solution (2 M, 25 mL) was added and the biphasic solution was allowed to stir no more than 5 min. The two phases were separated and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. At this point, the TLC indicated mostly the desired ketone along with other minor side products. The crude material was purified by column chromatography on

silica gel (petroleum ether: ethyl acetate = 10:1). The corresponding fractions were combined and concentrated under reduced pressure yielding compound **252f** (0.72 g, 37%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.14 (d, J = 6.0 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 3.10 (s, 2H), 2.61-2.65 (m, 2H), 2.32-2.37 (m, 2H), 2.09-2.13 (m, 2H), 1.77-1.83 (m, 2H).

Procedure for preparation of compounds 252g and 252h

To a solution of compound **252f** (720 mg, 2.01 mmol) in THF (8 mL) was cooled down to -78 °C. After 5 min, $NaBH_4$ (76 mgs, 2.01 mmol) was added, and the reaction mixture was stirred at -78 °C no more than 5 min. When TLC indicated the consumption of the diketone, the reaction was quenched by addition of MeOH (2 mL). The mixture was diluted with ethyl acetate (50 mL). Water was added (25 mL), and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure to afford the mixture containing compound **252g** and compound **252h** (750 mg, 90% crude yield) as a yellow oil.

Procedure for preparation of compound 252i

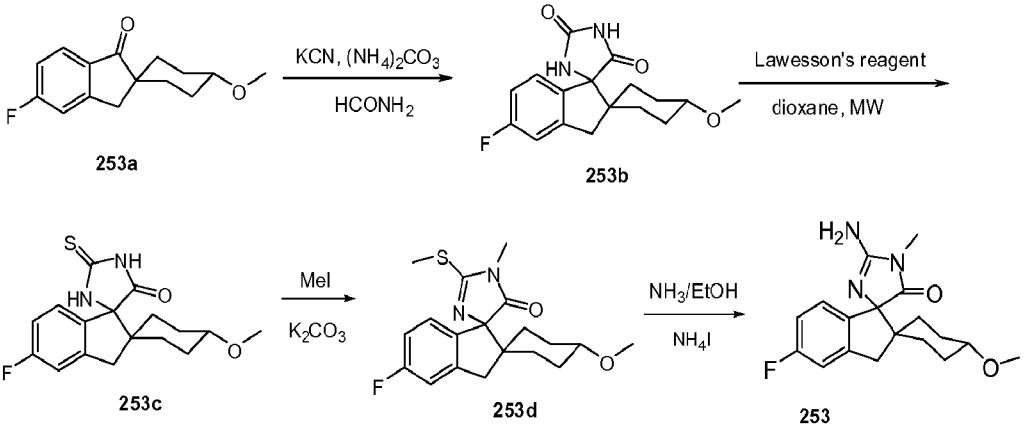
To a solution of compound **252g** (800 mg, 2.22 mmol) in THF (12 mL) was added NaH (267 mg, 6.66 mmol) and the mixture was stirred at 0 °C for 15 min. Then to the above mixture was added methyl iodide (1.39 mL, 22.2 mmol). The reaction was stirred at room temperature overnight, and TLC showed the reaction was completed. The reaction mixture was filtered through a pad of celite, and washed with ethyl acetate (40 mL). The filtrate was concentrated under reduced pressure, and purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 40:1) to afford compound **252i** (200 mg, 23%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.10 (d, J = 5.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 3.30 (s, 3H), 3.16-3.22 (m, 1H), 2.82 (s, 2H), 1.90-2.10 (m, 2H), 1.66-1.73 (m, 2H), 1.42-1.50 (m, 2H), 1.30-1.41 (m, 2H).

Procedure for preparation of compound 252

According to a similar synthesis of **compound I-6** described in Example I-2, compound **252i** (617 mg, 2.0 mmol) was condensed to hydantoin **252j** (50 mg, 6%) as a white solid. Hydantoin **252j** (20 mg, 0.045 mmol) was then reacted with Lawesson's Reagent (18 mg, 0.045 mmol) to give compound **252k** (10 mg, 50%) as a yellow solid.

Compound **252k** (15 mg, 0.033mmol) was then dimethylated with MeI (9 mg, 0.063 mmol) to give compound **252l** (8 mg, 50% crude yield) as a yellow solid, which was converted to **compound 252** (1 mg, 15%). **LC-MS** t_R = 0.937 min in 2 min chromatography, MS (ESI) *m/z* 458 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.70 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 3.23-3.33 (s, 3H), 3.15-3.18 (m, 3H), 3.05 (m, 1H), 2.67-2.70 (m, 1H), 2.08-2.17 (m, 1H), 1.95-2.05 (m, 2H), 1.83-1.86 (m, 1H) ; 1.34-1.45 (m, 3H), 1.20-1.28 (m, 2H)

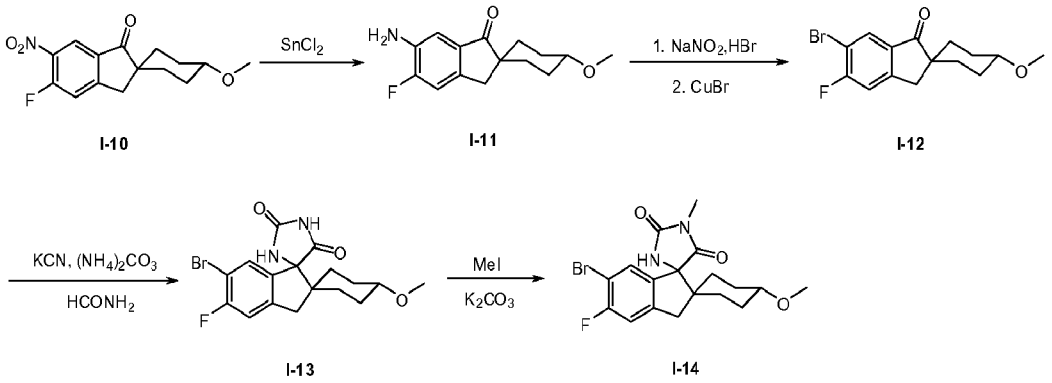
Example 206. Synthesis of Compound 253



According to a similar synthesis of **compound I-6** described in Example I-2, compound **253a** (800 mg, 2.45 mmol) was condensed to hydantoin **253b** (500 mg, 49%) as a white solid. Then compound **253b** (200 mg, 0.47 mmol) was reacted with Lawesson's Reagent (254 mg, 0.47 mmol) in anhydrous toluene (6 mL) to give compound **253c** (70 mg, 33%) as a yellow solid, which was dimethylated with MeI (118 mg, 0.42 mmol) and K_2CO_3 (116 mg, 0.84 mmol to give compound **253d** (70 mg, 90%) as a yellow solid, which was used directly in next step without purification.

Finally, compound **253d** (75 mg, 0.21 mmol) was converted to **compound 253** (6.0 mg, 8%). **LC-MS** t_R = 0.854 min in 2 min chromatography, MS (ESI) *m/z* 432 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.10-7.15 (m, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.93 (t, J = 12.0 Hz, 1H), 3.23-3.33 (s, 3H), 3.15-3.18 (s, 3H), 3.05 (m, 1H), 2.97-3.04 (m, 2H), 1.91-2.05 (m, 2H), 1.73-1.77 (m, 1H), 1.26-1.34 (m, 3H), 1.14-1.22 (m, 2H)

Example I-4. Synthesis of hydantoin I-14



Procedure for preparation of compound I-11

To a solution of $SnCl_2$ (9.25 g, 41 mmol) in concentrated HCl (7.5 mL) was added a solution of compound **I-10** (3 g, 10.24 mmol) in 95% ethanol (3.6 mL). The resulting mixture was stirred at room temperature for 2 h. TLC showed the reaction was completed; the mixture was treated with 50% aqueous NaOH solution (50 mL) to give the yellow solid. The resulting mixture was filtered, and the filtered cake was dissolved in CH_2Cl_2 (100 mL). The mixture was filtered, and the filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **I-11** (2 g, 67%) as a yellow solid.

Procedure for preparation of compound I-12

A mixture of compound **I-11** (2 g, 7.60 mmol) in concentrated HBr (13.3 mL) was stirred at room temperature. Then to the mixture was added ice (10 g) and stirred for a few min. Then to the above mixture was added a solution of $NaNO_2$ (585 mg, 8.36 mmol) in H_2O (2.28 mL) slowly while keeping temperature between -5 °C~0 °C, and stirred for 30 min. Then to the mixture was added a solution of CuBr (1.21 g, 8.36

mmol) in concentrated HBr (13.3 mL) slowly and stirred for another 30 min. The resulting mixture was filtered, and the filtrate was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to give compound **I-12** (0.85 g, 41%) as a yellow solid.

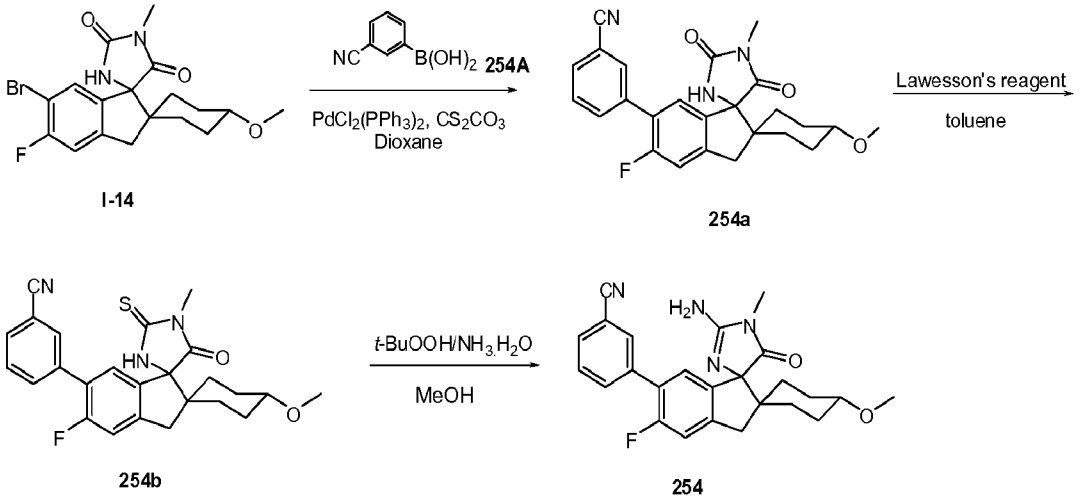
Procedure for preparation of compound I-13

A steel autoclave was charged with a mixture of compound **I-12** (850 mg, 2.60 mmol), KCN (338 mg, 5.20 mmol) and $(NH_4)_2CO_3$ (1.87 g, 19.5 mmol) in formamide (25 mL). The mixture was stirred at 110 °C for 72 h, cooled to room temperature, and poured into ice (10 g). After acidification with *conc.* HCl solution (10 mL), the resulting mixture was filtered, and the filter cake was dissolved in ethyl acetate (100 mL) and washed with water (2 × 200 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give compound **I-13** (650 mg, 63%) as a white solid, which was used in the next step without purification.

Procedure for preparation of compound I-14

To a solution of compound **I-13** (140mg, 0.354mmol) in CH_3CN (7 mL) was added MeI (77 mg, 0.53 mmol) and K_2CO_3 (77 mg, 0.53mmol). After being stirred at 80 °C for 15 min in microware, the mixture was filtrated and the filtrate was concentrated *in vacuo* to give the residue, which was dissolved in CH_2Cl_2, filtered and the filtrate was concentrated under vacuum to give the crude product, which was purified by preparative TLC (petroleum ether: ethyl acetate = 2:1) to give compound **I-14** (70 mg, 50%) as a yellow solid.

Example 207. Synthesis of Compound 254



Procedure for preparation of compound 254a

A solution containing compound **254A** (48 mg, 0.329 mmol) and compound **I-14** (90 mg, 0.220 mmol) in dioxane (6 mL), and aqueous Cs_2CO_3 (2 M, 1.56 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (15.6 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative TLC (CH_2Cl_2: MeOH = 15:1) to give compound **254a** (65 mg, 73%).

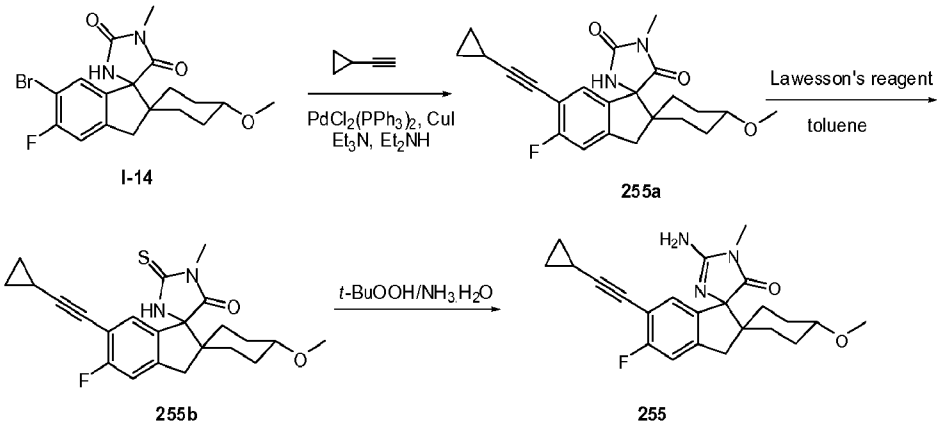
Procedure for preparation of compound 254b

A suspension of compound **254a** (65 mg, 0.15 mmol) and Lawesson's Reagent (61 mg, 0.15 mmol) in anhydrous toluene (4 mL) was heated at reflux overnight. The mixture was concentrated *in vacuo*, and the residue was purified by prep-TLC (petroleum ether: ethyl acetate = 3:1) to give compound **254b** (26 mg, 40%) as a yellow solid.

Procedure for preparation of compound 254

A solution of compound **254b** (26 mg, 0.058 mmol) and *t*-BuOOH (104mg, 1.158 mmol) in NH_4OH (0.8 mL) and MeOH (1.5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and purified by HPLC to give **compound 254** (3.2 mg, 12%). **LC-MS** t_R = 0.970 min in 2 min chromatography, MS (ESI) *m/z* 433 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ7.70-7.81 (m, 2H), 7.65-7.70 (m, 1H), 7.51-7.60 (m, 1H), 7.20-7.27 (m, 1H), 7.20 (d, J = 14.4 Hz, 4H), 3.23-3.33 (s, 3H), 3.05-3.10 (m, 1H), 3.05(s, 2H), 3.01 (s, 3H), 1.85-2.00 (m, 2H), 1.71-1.78 (m, 1H), 1.35-1.42 (m, 2H), 1.21-1.32 (m, 1H), 1.18-1.25(m, 2H)

Example 208. Synthesis of Compound 255

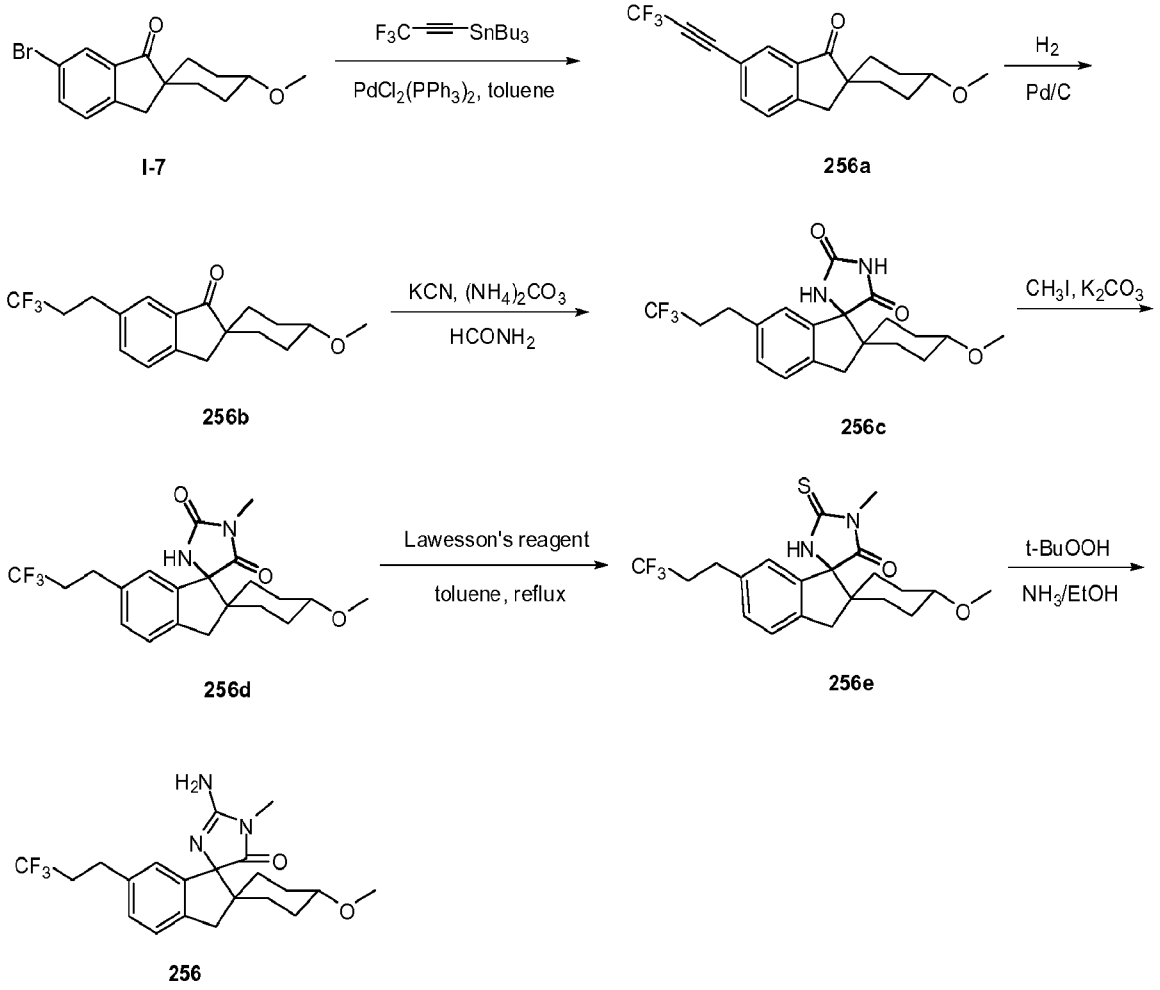


According to a similar synthesis of **compound 254**, compound **I-14** (20 mg, 0.049 mmol) was coupled with cyclopropyl acetylene (0.2 mL, excess) in the present of CuI (0.5 mg, 0.00245 mmol) and $PdCl_2(PPh_3)_2$ (1.7 mg, 0.00245 mmol) to give compound **255a** (18 mg, 96%) as white solid.

Compound **255a** (20 mg, 0.051 mmol) was then reacted with Lawesson's Reagent (20.4 mg, 0.051 mmol) to give compound **255b** (7 mg, 34%) as a yellow solid, which was conveted to **compound 255** (2.2 mg, 31%). **LC-MS** t_R = 1.001 min in 2 min chromatography, MS (ESI) *m/z* 396 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 6.95-7.01 (m, 1H), 6.88-6.93 (m, 1H), 3.23-3.33 (s, 3H), 3.05-3.10 (m, 1H), 3.05(s, 2H), 3.01 (s,

3H), 1.80-1.92 (m, 2H), 1.71-1.74 (m, 1H), 1.42-1.45 (m, 1H), 1.34-1.39 (m, 1H), 1.20-1.28 (m, 2H), 1.10-1.18(m, 2H), 0.75-0.85 (m, 2H), 0.60-0.66 (m, 2H).

Example 209. Synthesis of Compound 256



Procedure for preparation of compound 256a

A solution containing the tributyl (3,3,3-trifluoroprop-1-ynyl)stannane (1.166 g, 2.91 mmol) and compound **I-7** (600 mg, 1.94 mmol) in toluene (10 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then $PdCl_2(PPh_3)_2$ (68 mg, 0.097 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10

mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the residue, which was purified preparative TLC (petroleum/ethyl acetate = 3:1) to give compound **256a** (400 mg, 64%) as a white solid.

Procedure for preparation of compound 256b

To a solution of compound **256a** (5 mg, 0.016 mmol) in THF (5 mL) was added Pd/C (2 mg, 10 % in w.t.). The reaction mixture was stirred at room temperature for 1 h under H_2 atmosphere (1 atm), LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated to give compound **256b** (4 mg, crude, 80%) as a white solid, which was used directly for next step without further purification.

Procedure for preparation of compound 256c

A steel autoclave was charged with a mixture of compound **256b** (100 mg, 0.307 mmol), KCN (40 mg, 0.614 mmol), and $(NH_4)_2CO_3$ (221 mg, 2.3 mmol). Formamide (25 mL) was added. The mixture was heated at 100 °C for 72 h, and the reaction mixture was cooled, and poured into ice. After acidification with concentrated aqueous HCl solution (3 mL), the mixture was filtrated to give the solid, which was dissolved in ethyl acetate (100 mL) and washed with water (2 × 25 mL). The organic phase was dried over Na_2SO_4 and concentrated to give the crude compound **256c,** which was purified by preparative TLC (petroleum: ethyl acetate = 1: 1) to give compound **4** (68 mg, 56%) as a white solid.

Procedure for preparation of compound 256d

To a solution of compound **256c** (50 mg, 0.126 mmol) in CH_3CN (4 mL) was added K_2CO_3 (52 mg, 0.378 mmol). After being stirred for 5 min, MeI (20 mg, 0.139 mmol) was added, and the reaction mixture was heated at 60 °C for 10 min in microwave, and at 100 °C for another 10 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give compound **256d** (30 mg, 55%) as a white solid, which was used for the next step directly without purification.

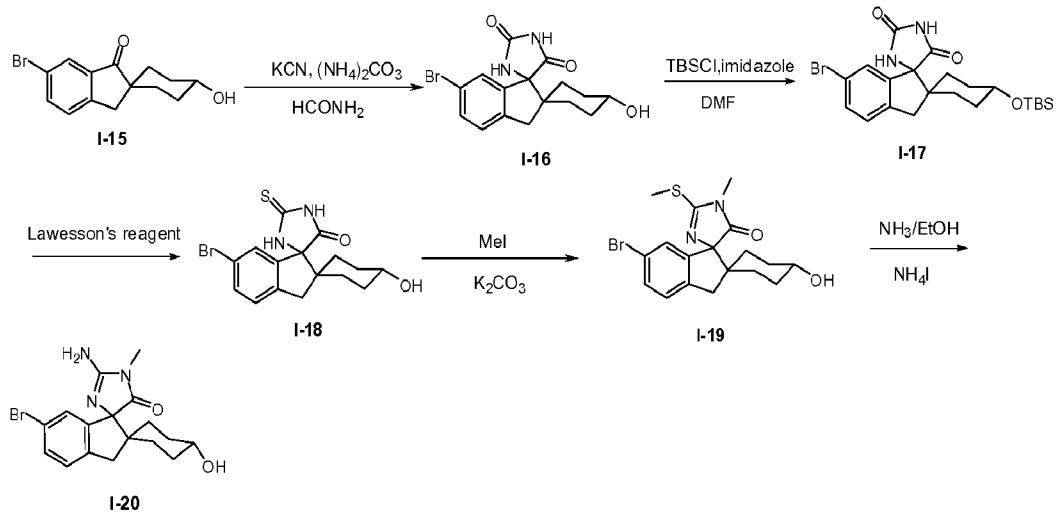
Procedure for preparation of compound 256e

A solution of compound **256d** (16 mg, 0.039 mmol) and Lawesson's Reagent (16 mg, 0.039 mmol) in dry toluene (1.5 mL) was heated at 140 °C for 30 min in a CEM microwave reactor. LCMS showed that the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (petroleum: ethyl acetate = 2:1) to give compound **256e** (14 mg, 84%) as a white solid.

Procedure for preparation of compound 256

A mixture of compound **256e** (30 mg, 0.07 mmol) and *t*-butyl hydroperoxide (127 mg of a 65% solution in water, 1.41 mmol) in NH_3/EtOH (10 mL, 5 N) was stirred at room temperature overnight, LCMS showed that the reaction was completed, then reaction mixture was concentrated under reduced pressure to dryness. Purification of this residue by preparative TLC (CH_2Cl_2: MeOH = 5:1) and preparative HPLC gave compound **256** (5.7 mg, 22%) as a white solid. **LC-MS** t_R = 1.097 min in 2 min chromatography, MS (ESI) *m/z* 410.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.23-7.26 (d, J = 7.6 Hz, 1H), 7.15-7.18 (d, J = 8.0 Hz, 1H), 6.87 (s, 1H), 3.36 (s, 3H), 3.08-3.18 (m, 2H), 3.04-3.06 (m, 1H), 3.03 (s, 3H), 2.81-2.85 (t, J = 9.6 Hz, 2H), 2.36-2.49 (m, 2H), 1.95-2.02 (m, 2H), 1.83-1.85 (m, 1H), 1.57-1.65 (t, J = 14.0 Hz, 1H), 1.34-1.44 (m, 2H), 1.25-1.32 (m, 2H). **^{19}F NMR** (CD_3OD): δ -58.90, -64.78, -68.17.

Example I-5. Synthesis of Intermediate I-20



Procedure for preparation of compound I-16

A steel autoclave was charged with a mixture of compound **I-15** (4.33 g, 14.67 mmol), KCN (1.9 g, 29.36 mmol) and $(NH_4)_2CO_3$ (10.57 g, 110.03 mmol) in formamide (80 mL). The mixture was stirred at 110 °C for 72 h, cooled to room temperature, and poured into ice (20 g). After acidification with *conc.* HCl solution (25 mL), the resulting mixture was filtered, and the filter cake was dissolved in ethyl acetate (100 mL) and washed with water (2 × 500 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **I-16** (2.78 g, 52%) as a brown solid.

Procedure for preparation of compound I-17

A solution of compound **I-16** (1.8 g, 4.95 mmol), TBSCl (0.89 g, 5.93 mmol) and imidazole (674 mg, 9.9 mmol) in DMF (18 mL) was stirred at room temperature overnight. Water (15 mL) and EtOAc (3 × 10 mL) were added, and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **I-17** (1.3 g, 60%) as a white solid.

Procedure for preparation of compound I-18

A suspension of compound **I-17** (1.3 g, 2.73 mmol) and Lawesson's Reagent (1.1 g, 2.73 mmol) in anhydrous toluene (52 mL) was heated at reflux overnight. The mixture was concentrated *in vacuo,* and the residue was purified by column chromatography on silica gel (CH_2Cl_2: MeOH = 10:1) to give compound **I-18** (750 mg, 71%) as a yellow solid.

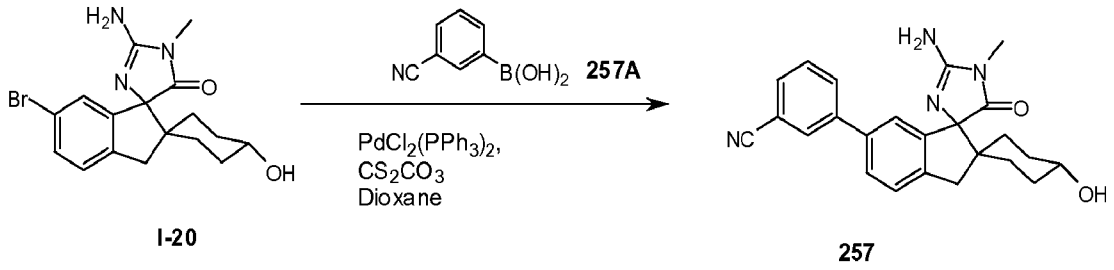
Procedure for preparation of compound I-19

To a solution of compound **I-18** (50 mg, 0.132 mmol) in CH_3CN (4 mL) was added MeI (37 mg, 0.263 mmol) and K_2CO_3 (73 mg, 0.53 mmol). After being stirred at 60 °C for 10 min in microware, additional MeI (37 mg, 0.263 mmol) was added. The reaction mixture was stirred at 100 °C for another 10 min in microware, concentrated *in vacuo* to give compound **I-19** (40 mg, 80%) as a yellow solid.

Procedure for preparation of Compound I-20

A solution of compound **I-19** (80 mg, 0.196 mmol) and NH_4I (284 mg, 1.96 mmol) in NH_3/EtOH (5.0 N, 3.5mL) was irradiated at 120 °C in a microwave reactor for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was added CH_2Cl_2 (15 mL), and stirred for 30 min. The mixture was filtered, concentrated *in vacuo* to give compound **I-20** (30 mg, 38%) as a yellow solid.

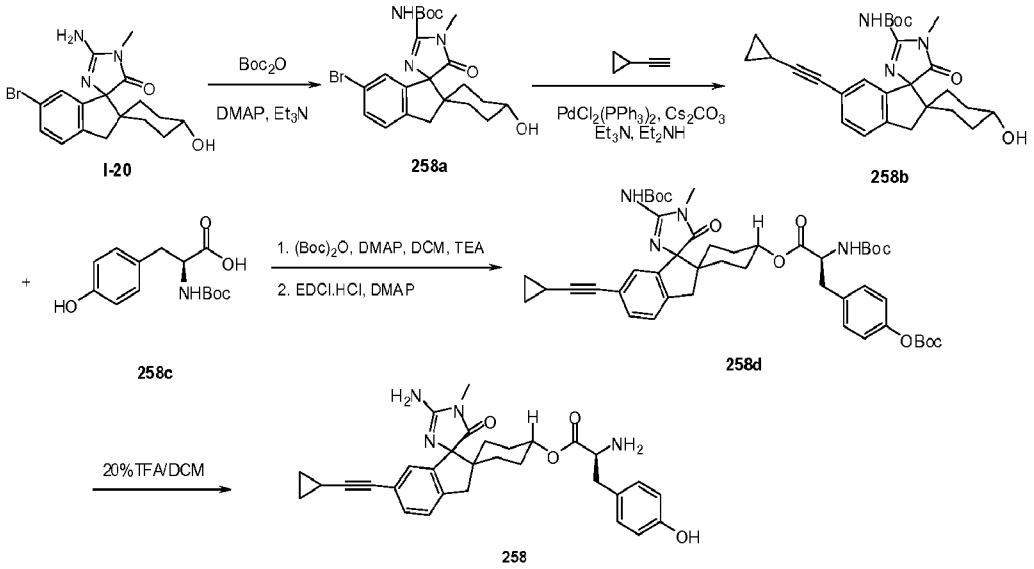
Example 210. Synthesis of Compound 257



I-20 **257**

A solution containing compound **I-20** (30 mg, 0.080 mmol) and compound **257A** (17.5 mg, 0.119 mmol) in dioxane (2 mL), and aqueous Cs_2CO_3 (2 M, 0.56 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (5.6 mg, 0.008 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative HPLC to afford **compound 257** (2.4 mg, 7%) as a white solid. **LC-MS** t_R = 0.846 min in 2 min chromatography, MS (ESI) *m/z* 401 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.96 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58-7.68 (m, 2H), 7.45(d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 3.47-3.52 (m, 1H), 3.18 (m, 2H), 3.10(s, 3H), 1.83-1.95 (m, 3H), 1.66 (m, 1H), 1.40-1.51 (m, 1H), 1.30-1.48 (m, 3H).

Example 211. Synthesis of Compoudn 258



Procedure for preparation of Compound 258a

To a solution of compound **I-20** (400 mg, 1.06 mmol) in anhydrous THF (16 mL) was added DMAP (194 mg, 1.59 mmol), Boc_2O (347 mg, 1.59 mmol) and Et_3N

(214 mg, 2.12 mmol), the reaction mixture was stirred at ambient temperature overnight. The solvent was removed by evaporation *in vacuo* to yield the crude compound **258a**, which was purified by preparative TLC (petroleum ether: ethyl acetate = 1: 1) to give compound **258a** (100 mg, 25%) as a white solid.

Procedure for preparation of Compound 258b

An oven dried three-necked round bottom flask equipped with condenser was charged with compound **258a** (80 mg, 0.17 mmol), Et_3N (5 mL) and Et_2NH (1 mL) under a nitrogen atmosphere. To this solution was added CuI (3.2 mg, 0.017 mmol) and $PdCl_2(PPh_3)_2$ (11.8 mg, 0.017 mmol). The system was degassed once again, then cyclopropyl acetylene (0.7 mL, excess) was added and the mixture was stirred at 60 °C in an oil bath for 15 h. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (20 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dryness. The crude product was purified by preparative TLC eluting with petroleum ether: ethyl acetate (1: 1) to give compound **258b** (54 mg, 70%) as a white solid.

Procedure for preparation of Compound 258d

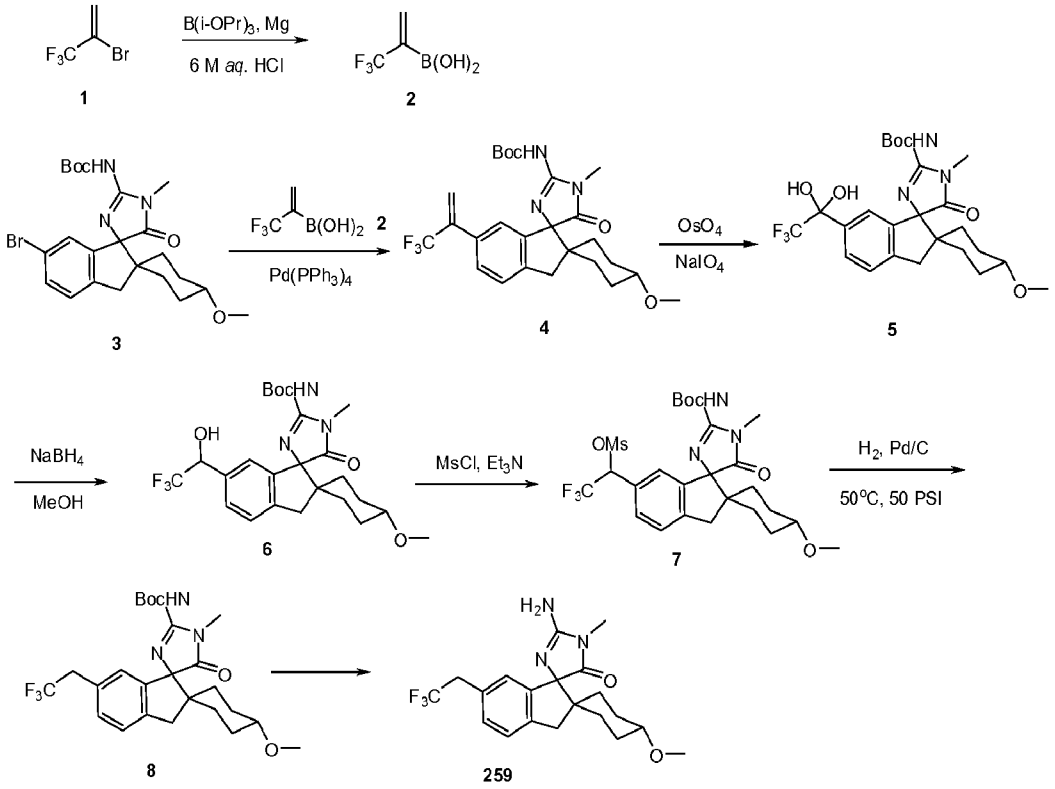
To a solution of compound **258c** (44 mg, 0.16 mmol), DMAP (0.2 mg, 0.0016 mmol) and Et_3N (0.02 mL, 0.16 mmol) in anhydrous dichloromethane (3 mL) was added Boc_2O (44 mg, 0.202 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was added compound **258b** (60 mg, 0.13 mmol), DMAP (4 mg, 0.032 mmol) and EDCI.HCl (38 mg, 0.20 mmol). Then the mixture was stirred at room temperature for 24 h. The reaction mixture was purified by preparative TLC (prtroleum ether: EtOAc = 2: 1) to give compound **258d** (32 mg, 25%) as a white solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 8.65 (s, 1H), 7.24 (d, J = 6.8 Hz, 1H), 7.13 (d, J = 6.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.02 (m, 3H), 4.90 (m, 1H), 4.59 (m, 1H), 4.43 (m, 1H), 3.13-3.09 (d, J = 16.4 Hz, 1H), 3.00 (s, 3H), 3.01-2.93 (m, 3H), 1.87-1.79 (m, 2H), 1.78-1.68

(m, 1H), 1.51 (s, 9H), 1.48 (s, 9H), 1.35 (s, 9H), 1.49-1.15 (m, 6H), 0.83-0.74 (m, 2H), 0.72-0.67 (m, 2H).

Procedure for preparation of compound 258

To a solution of compound **258d** (15 mg, 0.018 mmol) in dichloromethane (0.5 mL) was added a solution of TFA in dichloromethane (20%, 2 mL) at ~0 °C and then stirred for 1 h. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by preparative RP-HPLC (neutral) to give **compound 258** (4.5 mg, 47%) as a white solid. **LC-MS**: t_R = 0.85 min in 2 min chromatography, MS (ESI) *m/z* 527.2 $[M+H]^+$. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.22 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 8 Hz, 1H), 7.00 (s, 1H), 6.96-6.93 (dd, J = 8.4 Hz, 2H), 6.68-6.64 (dd, J = 8.4 Hz, 2H), 4.62-4.52 (m, 1H), 3.60-3.56 (m, 1H), 3.10 (d, J = 15.6 Hz, 1H), 2.97 (s, 3H), 2.93 (d, J = 16 Hz, 1H), 2.89-2.84 (m, 1H), 2.80-2.74 (m, 1H), 1.89-1.75 (m, 3H), 1.75-1.67 (m, 1H), 1.49-1.41 (m, 2H), 1.40-1.24 (m, 4H), 0.81-0.72 (m, 2H), 0.71-0.68 (m, 2H).

Example 212. Synthesis of Compound 259



Procedure for preparation of compound 2

To a solution of magnesium turning (0.7 g, 24 mmol) and trimethoxyborane (8.1 mL, 72.5 mmol) in anhydrous THF (50 mL) was added 2-bromo-3, 3, 3-trifluoropropene (2.5 mL, 29 mmol) in THF (5 mL) over 20 min at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 3 h. Most of magnesium turning was disappeared. The reaction was quenched by addition of *aq.* HCl solution (30 mL, 6 M), extracted with Et_2O (3 × 50 mL), washed with brine (30 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product (200 mg) as a gray solid, which was used for next step directly without purification without purification. **^{1}H NMR** (DMSO-d_6 400 MHz): δ 8.33 (br, 2H), 6.32 (s, 2H)

Procedure for preparation of compound 4

To a solution of compound **3** (100 mg, 0.2 mmol) in toluene/methanol (3 mL, 5:1) was added compound **2**, *aq*. Na_2CO_3 solution (0.5 mL, 1.0 M), and $Pd(PPh_3)_4$ (10 mg, 0.01 mmol) successively under a nitrogen atmosphere. The reaction mixture was heated at 70°C for 12 h. The mixture was separated between EtOAc and water. The aqueous layer was extracted with EtOAc (3 × 25 mL), washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to the crude product, which was purified by preparative TLC (prtroleum ether: EtOAc = 3: 1) to give compound **4** (45 mg, 45%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.69 (s, 1H), 7.32 (m, 1H), 7.25 (m, 1H), 6.91 (s, 1H), 5.87 (s, 1H), 5.64 (s, 1H), 3.24 (m, 1H), 3.05 (m, 5H), 1.97 (m, 3H), 1.85 (m, 1H), 1.50 (m, 10H), 1.34 (m, 5H), 1.25 (m, 5H)

Procedure for preparation of compound 5

To a solution of compound **4** (25 mg, 0.05 mmol) in *t*-BuOH/H_2O (2 mL, 4:1) was added OsO_4 (1.0 mg) and $NaIO_4$ (30 mg, 0.15 mmol). The reaction mixture was stirred at room temperature overnight, then quenched by saturate aqueous $Na_2S_2O_3$ solution, extracted with EtOAc (3 × 35 mL), washed with brine (20 mL), dried over Na_2SO_4, concentrated *in vacuo* to give the crude product (50 mg), which was purified by preparative TLC (petroleum ether: EtOAc = 3:1) to give crude compound **5** (25 mg, 100% crude yield) as a white solid, which was used for next step without purification.

Procedure for preparation of compound 6

To a solution of compound **5** (30 mg, 0.057 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (11 mg, 0.285 mmol), the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by water, precipitate was filtered off, and redissolved in EtOAc (10 mL), extracted with EtOAc (3 × 20 mL), washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to give the crude product (30 mg, 100% crude yield) as a light yellow oil, which was used for next step without purification.

Procedure for preparation of compound 7

To a solution of compound **6** (30 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (25 uL, 0.18 mmol) followed by MsCl (9 mg, 0.072 mmol). The reaction mixture was stirred at room temperature for 1 h. Water (10 mL) was added, the aqueous layer was extracted with EtOAc (3 × 15 mL), washed with brine (10 mL), dried over Na_2SO_4, concentrated *in vacuo* to give the crude product (30 mg, 100% crude yield) as a light yellow oil, which was used for next step without purification.

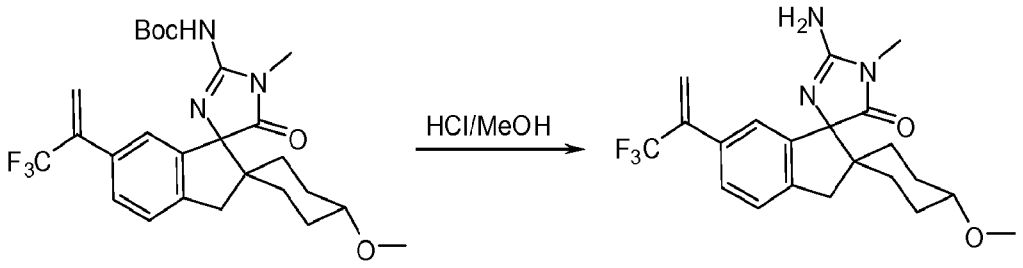
Procedure for preparation of compound 8

To a solution of compound **7** (10 mg, 0.017 mmol) in EtOH (3 mL) was added Pd/C (5 mg), the reaction mixture was hydrogenated at 50 °C under 50 PSI overnight. The catalyst was filtered, and the filtrate was concentrated under reduced pressure to give the crude product (10 mg), which was used for next step without purification.

Procedure for preparation of compound 259

To a solution of compound **8** (8 mg, 0.016 mmol) in dixoane was heated at 120°C in a microwave reactor reactor for 30 min. The solvent was removed under reduced pressure to give the residue, which was purified by preparative RP-HPLC to give **compound 259** (0.5 mg, 8%) as a white solid. **LC-MS** t_R = 1.068 min in 2 min chromatography, MS (ESI) *m/z* 396 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.44-7.25 (m, 2H), 7.02 (s, 1H), 3.50 (m, 5H), 3.11 (m, 6H), 2.04 (m, 2H), 1.83 (m, 1H), 1.58 (m, 1H), 1.43-1.27 (m, 4H); **^{19}F NMR** (CD_3OD 400 MHz) δ -62.3

Example 213. Synthesis of Compound 260

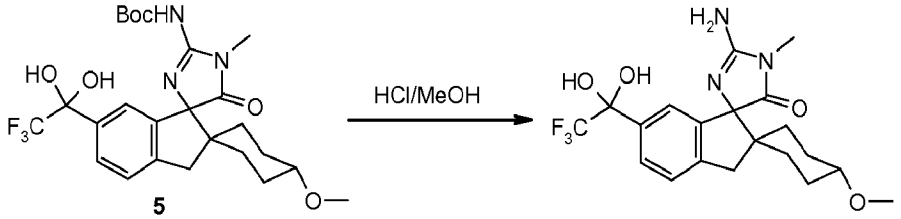


4 **260**

Compound **4** in Example 212 (14 mg, 0.076 mmol) was dissolved in 4 M HCl/MeOH solution, the reaction mixture was stirred at room temperature for 3 h.

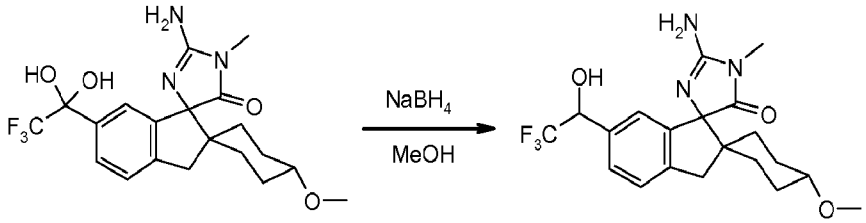
After completion, the solvent was removed under reduced pressure, and the residue was purified by acidic preparative RP-HPLC to give **compound 260** (3.1 mg, 28%) as a white solid. **LC-MS** t_R = 1.089 min in 2 min chromatography, MS (ESI) *m/z* 408 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.51-7.44 (m, 2H), 7.36 (s, 1H), 6.03 (s, 1H), 5.91 (s, 1H), 3.50 (m, 4H), 3.18 (m, 5H), 2.08 (m, 2H), 1.86 (m, 1H), 1.38 (m, 5H)

Example 214. Synthesis of Compound 261



Compound **5** in Example 212 was dissolved in 2 M HCl/MeOH (1 mL), and the resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure to the residue, which was purified by preparative RP-HPLC to afford **compound 261** (7.0 mg, 35%) as a white solid. **LC-MS** t_R = 0.964 min in 2 min chromatography, MS (ESI) *m/z* 428 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.62 (m, 1H), 7.45 (m, 2H), 3.55 (s, 3H), 3.22 (m, 6H), 2.10 (m, 2H), 1.86 (m, 1H), 1.45-1.27 (m, 5H); **^{19}F NMR** δ -84.4

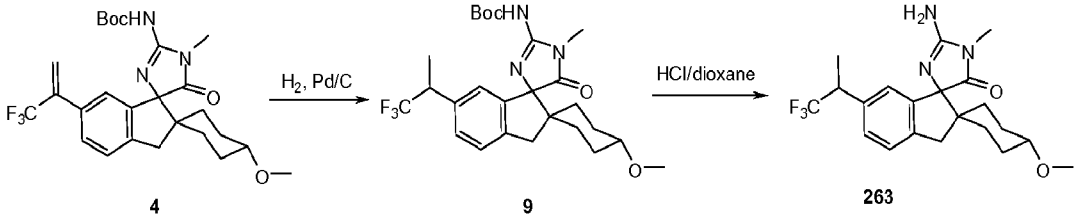
Example 215. Synthesis of Compoud 262



To a solution of compound **261** (5 mg, 0.012 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (2 mg, 0.06 mmol), the reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by preparative RP-HPLC to give **compound 262** (1.9 mg, 40%) as a white solid. **LC-MS** t_R = 0.993 min in

2 min chromatography, MS (ESI) *m/z* 412 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.53-7.33 (m, 3H), 5.04 (m, 1H), 3.34 (s, 3H), 3.19 (m, 6H), 2.04 (m, 2H), 1.85 (m, 1H), 1.43-1.29 (m, 5H); **^{19}F NMR** ($CDCl_3$ 400 MHz) δ -71.3.

Example 216. Synthesis of Compound 263

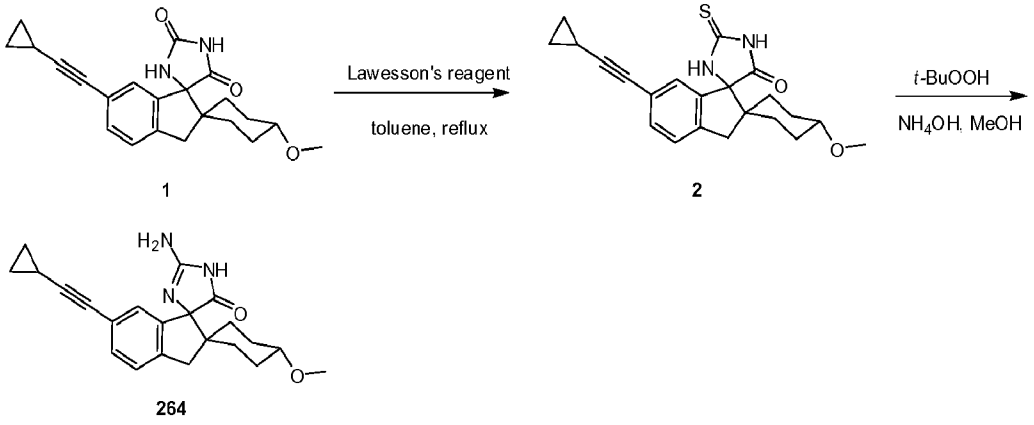


4 9 263

To a solution of compound **4** described in Example 212 (15 mg, 0.03 mmol) in MeOH (2 mL) was added Pd/C (10 mg), the reaction mixture was stirred at room temperature with H_2 balloon for overnight. The catalyst was filtered, and the filtrate was concentrated under reduced pressure to give the crude product (10 mg, 66%) compound 9 as a colorless oil, which was used for next step without purification.

To a solution of compound **9** (10 mg, 0.02 mmol) was added 4 M HCl/dioxane solution (1 mL), the reaction mixture was stirred at room temperature overnight, the solvent was removed under reduced pressure to give the residue, which was purified by preparative RP-HPLC to give **compound 263** (1.5 mg, 18%) as a white solid. **LC-MS** t_R = 1.108 min in 2 min chromatography, MS (ESI) *m/z* 410 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.30 (m, 2H), 6.99 (s, 1H), 3.56 (m, 1H), 3.31 (s, 3H), 3.17-3.04 (m, 6H), 2.00 (m, 2H), 1.84 (m, 1H), 1.63 (m, 1H), 1.46 (m, 3H), 1.40-1.29 (m, 4H); **^{19}F NMR** (CD_3OD 400 MHz): δ -62.3.

Example 217. Synthesis of Compound 264



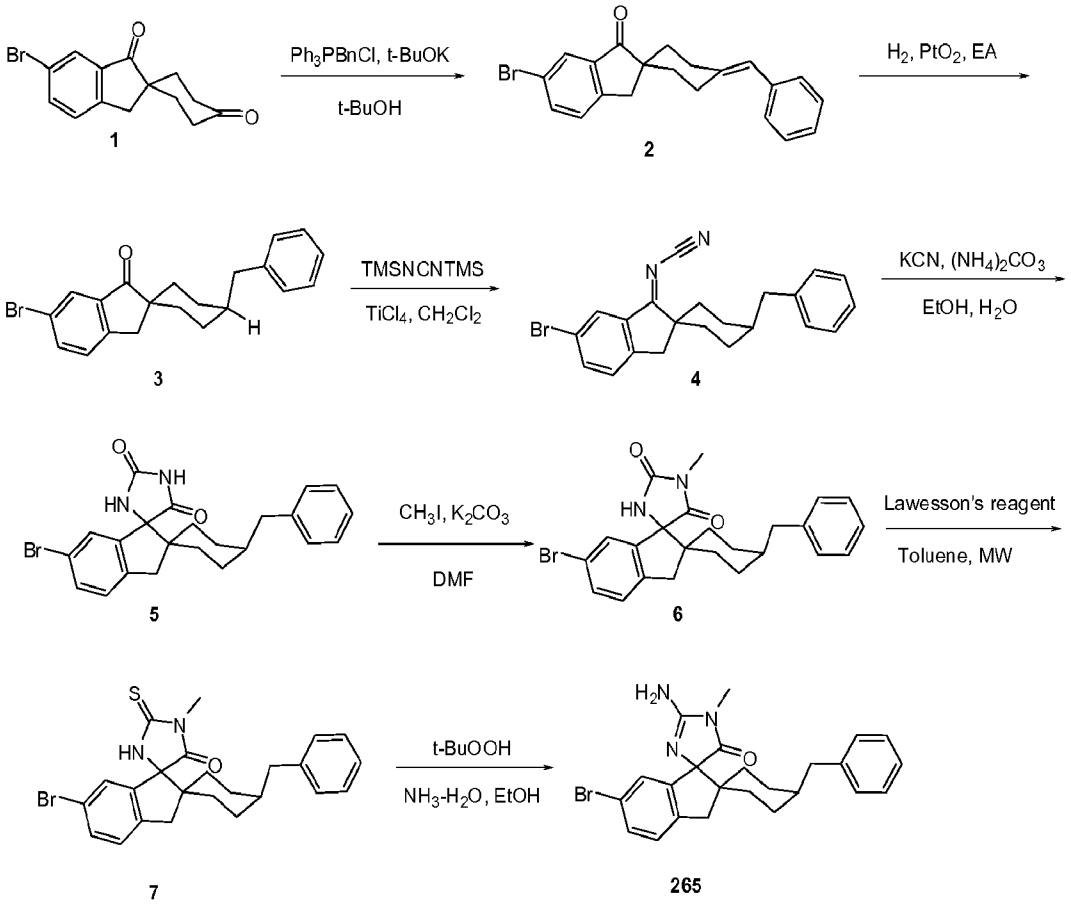
Procedure for preparation of compound 2

A suspension of compound **1** (70 mg, 0.192 mmol) and Lawesson's Reagent (85 mg, 0.212 mmol) in anhydrous toluene (10 mL) was heated to reflux overnight. LCMS showed that the reaction was completed. The mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 1: 1) to give compound **2** as a white solid (30 mg, 41%).

Procedure for preparation of compound 264

A mixture of compound **2** (15 mg, 0.04 mmol) and *t*-butyl hydroperoxide (0.11 g of a 65% solution in water, 0.8 mmol) in methanol (5 mL) was added aqueous ammonium hydroxide (1 mL), the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to dryness. The residue was purified by preparative TLC (CH_2Cl_2: MeOH = 5: 1) and preparative RP-HPLC to give compound **264** (5.8 mg, 40%) as a white solid. **LC-MS** t_R = 1.068 min in 2 min chromatography, MS (ESI) *m/z* 364.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.23 (s, 2H), 6.95 (s, 1H), 3.36 (s, 3H), 3.11-3.15 (d, J = 15.6 Hz, 2H), 3.01-3.05 (d, J = 15.2 Hz, 1H), 1.96-2.07 (m, 3H), 1.24-1.48 (m, 6H), 0.85-0.89 (m, 2H), 0.69-0.73 (m, 2H).

Example 218. Synthesis of Compound 265



Procedure for preparation of compound 2

To a solution of potassium *tert*-butoxide (1.8 g, 15.5 mmol) in *tert*-butyl alchol (60 mL) was added benzyl triphenyl phosphonium chloride (4.8 g, 12.2 mmol). The mixture was stirred at ambient temperature for 1 h. Compound **1** (3.0 g, 10.2 mmol) was added under nitrogen. The reaction mixture was stirred at ambient temperature for 5 h. The solvent was removed by evaporation *in vacuo*. The residue was added H_2O (100 mL) and then was extracted with ethyl acetate (50 mL × 3), the combined organic layers were washed with saturated brine (50 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to yield crude product, which was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 100: 1 to 10: 1 to give compound **2** (2.8 g, 75%) as a white solid.

Procedure for preparation of compound 3

A mixture of compound **2** (2.8 g, 7.6 mmol), ethyl acetate (150 mL) and PtO_2 (0.20 g, 0. 88 mmol) was stirred at ambient temperature under 1 atm hydrogen atmosphere overnight. The precipitate was filtered off and washed with ethyl acetate (50 mL × 2). The filtrate and the washings were concentrated by evaporation *in vacuo*. The residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 100: 1 to 10: 1 and then by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 10: 1 to give **compound 3** (0.70 g, 24%) as a white solid. **LC-MS**: t_R = 2.41 min in 3 min chromatography, MS (ESI) *m/z* = 369.0 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.60-7.70 (m, 2H), 7.30-7.35 (d, 1H, *J* = 8.0 Hz), 7.10-7.20 (m, 2H), 7.00-7.10 (m, 3H), 2.80-2.90 (s, 2H), 2.50-2.60 (d, 2H, *J* = 7.2 Hz), 1.75-1.85 (m, 2H), 1.65-1.75 (m, 1H), 1.55-1.65 (m, 2H), 1.35-1.45 (m, 2H).

Procedure for preparation of compound 4

A flask was charged with **compound 3** (0.30 g, 0.81 mmol), anhydrous dichloromethane (6 mL) and $TiCl_4$ (3.2 mL, 3.2 mmol, 1 M in CH_2Cl_2). The tube was stirred at ambient temperature for 1 h. N, N'-methanediylidene bis-(1,1,1-trimethylsilianamine) (0.45 g, 2.4 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The mixture was quenched with ice-water (10 mL) carefully with stirring. Brine (10 mL) was added, and the mixture was extracted with dichloromethane (10 mL × 3). The combined organic layers were washed with saturated brine (10 mL × 2). The separated organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **4** (0.31 g, 97% crude yield) as a pale yellow solid, which was used in the next step without further purification.

Procedure for preparation of compound 5

A steel clave was charged with a mixture of compound **4** (0.31 g, 0.79 mmol), KCN (0.20 g, 3.16 mmol), $(NH_4)_2CO_3$ (0.80 g, 8.32 mmol), Ethanol (3 mL) and H_2O (3 mL) carefully. The mixture was heated at 80 °C overnight. The reaction mixture was cooled, and poured into ice-water (40 mL). The mixture was extracted with ethyl

acetate (contained 10% iso-propanol) (50 mL × 3), and the combined organic layers were washed with brine (50 mL × 3). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound **5** (0.36 g, 102% crude yield) as a white solid, which was used in next step without further purification. **LC-MS:** t_R = 1.85 min in 3 min chromatography, MS (ESI) *m/z* = 439.0 $[M+H]^-$.

Procedure for preparation of compound 6

A flask was charged with a mixture of compound **5** (0.25 g, 0.57 mmol, crude), K_2CO_3 (0.30 g, 0.22 mmol) and DMF (5 mL). The mixture was stirred at ambient temperature for 1 h, and then iodomethane (90 mg, 0.63 mmol) in DMF (0.5 mL) was added dropwise via a syringe with stirring. The mixture was stirred at ambient temperature overnight. The reaction mixture was poured into brine (100 mL). The mixture was extracted with ethyl acetate (contained with 10% methanol) (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give crude product, which was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 1: 1 to give compound **6** (0.14 g, 54%) as a white solid. **LC-MS**: t_R = 2.29 min in 3 min chromatography, MS (ESI) *m/z* = 453.3 $[M+H]^+$.

Procedure for preparation of compound 7

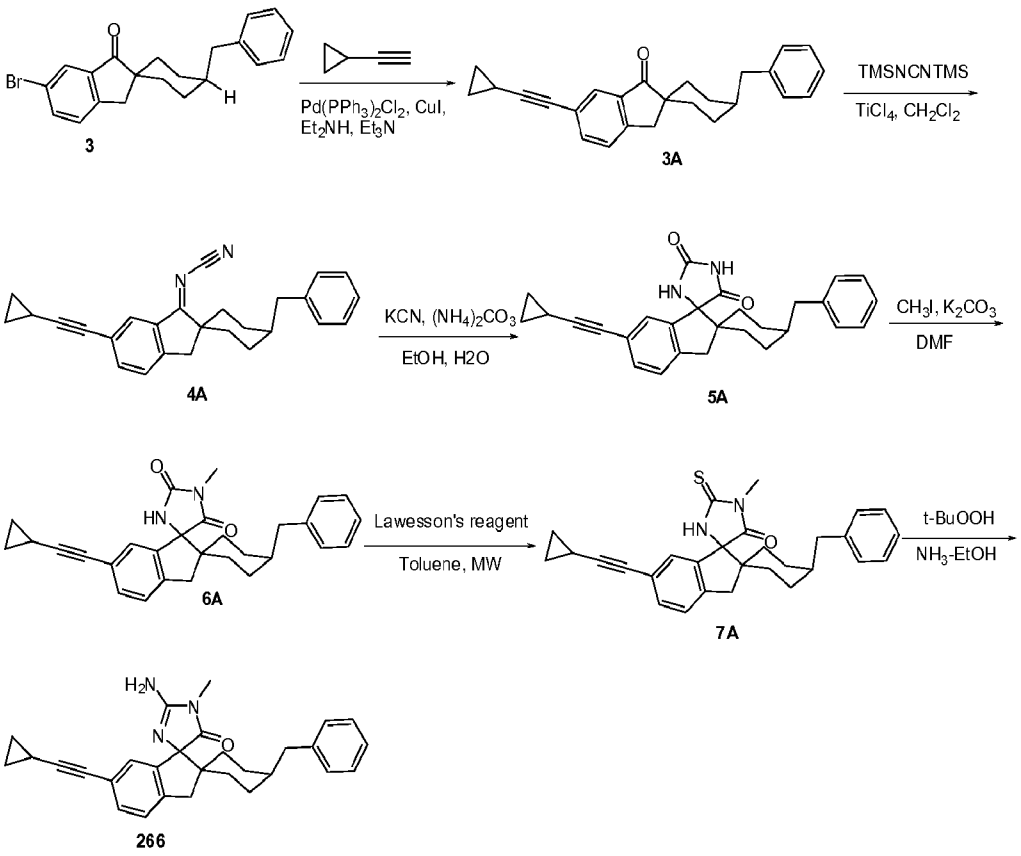
A sealed tube was charged with a mixture of compound **6** (0.13 g, 0.29 mmol), Lawesson's reagent (0.14 g, 0.35 mmol) in anhydrous toluene (3 mL) under nitrogen. The mixture was heated at 130 °C in a CEM microwave reactor for 1 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 2:1 to give compound **7** (60 mg, 44 %) as a white solid.

Procedure for preparation of compound 265

To a solution of compound **7** (60 mg, 0.13 mmol) in EtOH (4 mL) was added NH_3-H_2O (1 mL) and *tert*-butyl hydroperoxide (0.20 g, 2.2 mol). After addition, the mixture was stirred at ambient temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 265** (30

mg, 51%) as a white solid. **LC-MS**: t_R=1.88 min in 3 min chromatography, MS (ESI) *m/z* = 452.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 300 MHz): δ 7.35-7.45 (m, 1H), 7.20-7.30 (m, 3H), 7.10-7.20 (m, 4H), 3.05-3.15 (d, *J* = 16.8 Hz, 1H), 3.00-3.10 (s, 3H), 2.85-2.95 (d, *J* = 20.4 Hz, 1H), 2.55-2.65 (m, 2H), 1.80-2.00 (m, 2H), 1.45-1.80 (m ,5H), 1.25-1.35 (m, 1H), 1.05-1.15 (m, 1H).

Example 219. Synthesis of Compound 266



4.

Procedure for preparation of compound 3A

A flask was charged with **compound 3** described in Example 218 (0.30 g, 0.81 mmol), Et_3N (10 mL), Et_2N (2 mL), $Pd(PPh_3)_2Cl_2$ (0.034 g, 0.48 mmol), CuI (0.009 g, 0.047 mmol) and ethynyl cyclopropane (3 mL) under nitrogen at ambient temperature in turn. The reaction mixture was stirred at 60 °C for 48 h. After cooling down, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in ethyl acetate (100 mL), and the resulting organic mixture was washed with 1 N HCl aqueous

solution (30 mL), H_2O (30 mL) and brine (30 mL × 2) sucessively. The separated organic layer was dried over Na_2SO_4, filtered off the solid and concentrated *in vacuo* to give the crude product as red oil, which was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 100:1 to 5: 1 to give compound **3A** (0.28 g, 97%) as a yellow oil. **LC-MS**: t_R = 2.51 min in 3 min chromatography, MS (ESI) *m/z* = 355.1 $[M+H]^+$.

Procedure for preparation of compound 4A

A flask was charged with compound **3A** (0.15 g, 0.42 mmol), dried dichloromethane (3 mL) and $TiCl_4$ (1.7 mL, 1.7 mmol, 1 M in CH_2Cl_2). The tube was stirred at ambient temperature for 1 h. After cooling down, N, N'-methanediylidene bis-(1,1,1-trimethylsilianamine) (0.24 g, 1.3 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The mixture was quenched with ice-water (10 mL) carefully with stirring. Saturated brine (10 mL) was added, and the mixture was extracted with dichloromethane (10 mL×3). The combined organic layers were washed with saturated brine (10 mL × 2). The separated organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **4A** (0.16 g, 100% crude yield) as a pale yellow solid, which was used directly in next step.

Procedure for preparation of compound 5A

A steel clave was charged with a mixture of compound **4A** (0.31 g, 0.79 mmol), KCN (0.20 g, 3.16 mmol), $(NH_4)_2CO_3$ (0.80 g, 8.32 mmol), ethanol (3 mL) and H_2O (3 mL) carefully. The mixture was heated at 80 °C overnight, and the reaction mixture was cooled, and poured into ice-water (40 mL). The mixture was extracted with ethyl acetate (contained 10% iso-propanol) (50 mL × 3), and the combined organic layers were washed with saturated brine (50 mL × 3). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 50:1 to 2: 1 to give compound **5A** (0.40 g, 22%) as a pale yellow solid. **LC-MS**: t_R=2.50 min in 3 min chromatography, MS (ESI) *m/z* = 425.2 $[M+H]^+$.

Procedure for preparation of compound 6A

A flask was charged with a mixture of compound **5A** (40 mg, 0.094 mmol), K_2CO_3 (50 mg, 0.36 mmol) and DMF (3 mL). The mixture was stirred at ambient temperature for 1 h, and then a solution of iodomethane (14 mg, 0.099 mmol) in DMF (0.5 mL) was added dropwise via a syringe with stirring. The mixture was stirred at ambient temperature overnight. The reaction mixture was poured into saturated brine (50 mL). The mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with saturated brine (20 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **6A** (40 mg, 97% crude yield) as a white solid, which was used directly in next step. **LC-MS**: t_R = 2.50 min in 3 min chromatography, MS (ESI) *m/z* = 425.2 $[M+H]^+$.

Procedure for preparation of compound 7A

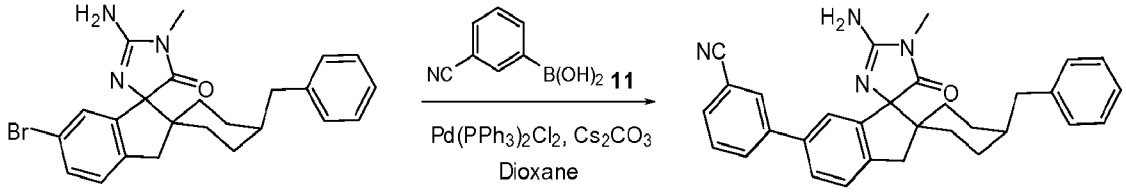
A sealed tube was charged with a mixture of compound **6A** (40 mg, 0.091 mmol), Lawesson's reagent (40 mg, 0.099 mmol) in anhydrous toluene (1 mL) under nitrogen. The mixture was heated at 130 °C in a CEM microwave reactor for 40 min. After cooling down, the solvent was removed by evaporation *in vacuo* and the residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 2:1 to give compound **7A** (10 mg, 24%) as a white solid. **LC-MS**: t_R = 2.65 min in 3 min chromatography, MS (ESI) *m/z* = 455.2 $[M+H]^+$.

Procedure for preparation of compound 266

To a solution of compound **7A** (10 mg, 0.022 mmol) in EtOH (1 mL) was added NH_3-H_2O (0.5 mL) and *tert*-butyl hydroperoxide (50 mg, 0.56 mol). After addition, the mixture was stirred at ambient temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 266** (9.1 mg, 94%) as a white solid. **LC-MS**: t_R = 1.97 min in 3 min chromatography, MS (ESI) *m/z* = 438.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.15-7.25 (m, 1H), 7.10-7.15 (m, 3H), 7.00-7.10 (m, 4H), 3.05-3.15 (s, 3H), 2.97-3.05 (d, *J* = 16.0 Hz, 1H), 2.90-2.97 (d, *J* = 15.6 Hz, 1H), 2.50-2.60 (d, *J* = 7.6 Hz, 2H), 1.75-1.85 (m, 1H), 1.40-1.75 (m,

4H), 1.30-1.40 (m ,2H), 1.20-1.30 (m, 2H), 1.05-1.15 (m, 1H), 0.70-0.80 (m, 2H), 0.50-0.60 (m, 2H).

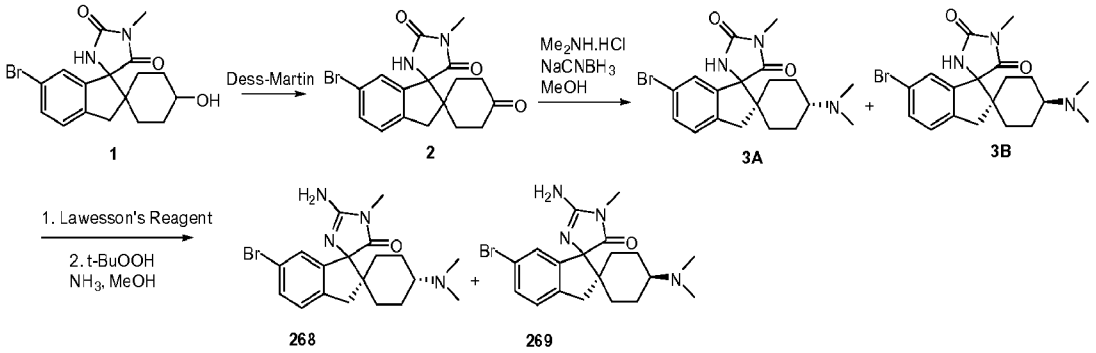
Example 220. Synthesis of Compound 267



265 **267**

A mixture of **compound 265** (10 mg, 0.022 mmol), 3-cyanophenylboronic acid (5 mg, 0.034 mmol), Cs_2CO_3 (0.2 mL, 0.40 mmol, 2M in water) and $Pd(PPh_3)_2Cl_2$ (1 mg, 0.0014 mmol) in 1,4-dioxane (0.5 mL) under nitrogen was stirred at 120 °C in a CEM microwave reactor for 20 min. After cooling down, saturated brine (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*, the resulting crude product was purified by preparative HPLC to give **compound 267** (7.7 mg, 74%) with 98% purity based on LC-MS as a pale yellow solid. **LC-MS**: t_R = 1.93 min in 3 min chromatography, MS (ESI) *m/z* = 475.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.95-8.00 (s, 1H), 7.85-7.95 (m, 1H), 7.60-7.70 (m, 2H), 7.55-7.60 (m, 1H), 7.45-7.55 (s, 1H), 7.40-7.45 (m, 1H), 7.20-7.30 (m, 2H), 7.05-7.15 (m, 3H), 3.17-3.25 (s, 3H), 3.05-3.17 (m, 2H), 2.55-2.65 (m, 2H), 1.85-1.95 (m, 1H), 1.55-1.85 (m, 5H), 1.20-1.45 (m, 3H).

Example 221. Synthesis of Compouds 268 and 269



Procedure for preparation of compound 2

To a solution of compound **1** (0.2 g, 0.53 mmol) in 1,2-dichloroethane (1.5 mL) in a 10 mL CEM microwave tube, there was added Dess-Martin periodinane (247 mg, 0.58 mmol). The resulting mixture was heated with a CEM microwave reactor at 70 °C for 5 min, washed with 1N NaOH aqueous solution, brine, and dried over Na_2SO_4. The solvent was removed to give compound **2** (156.0 mg, 77%), which was used for the next step without purification.

Procedure for preparation of compound 3A and 3B

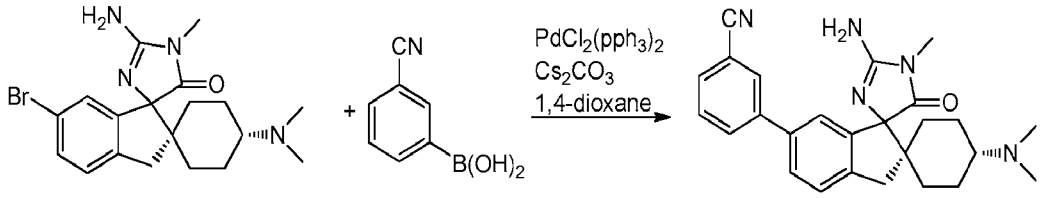
To a solution of compound **2** (156.0 mg, 0.41 mmol) in MeOH (3 mL), there was added dimethylamine hydrochloride (6.1 mg, 0.82 mmol), KOH (23 mg, 0.41mmol) followed by $NaCNBH_3$ (52 mg, 0.82 mmol). The resulting solution was stirred at room temperature overweekend, and purified by HPLC to give compound **3A** (82.8 mg, 39%), **LC-MS** t_R = 3.65 min in 16 min chromatography, MS (ESI) *m/z* 406 $[M+H]^+$. And compound **3B** (60.5mg, 32%), **LC-MS** t_R = 3.47 min in 16 min chromatography, MS (ESI) *m/z* 406 $[M+H]^+$.

Procedure for preparation of compounds 268 and 269

According to the similiar synthesis of **compound 291**, compound **3A** (50 mg, 0.12 mmol) afforded **compound 268** (3.2 mg, 5%) as a TFA salt. **LC-MS** t_R = 0.93 min in 3 min chromatography, MS (ESI) *m/z* 405 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 3.22 (m, 1H), 3.20 (s, 3H), 3.18 (m, 2H), 2.84 (s, 6H), 2.10-1.94 (m, 3H), 1.84-1.46 (m, 5H). And compound 3B (30 mg, 0.07 mmol) afforded **compound 269** (1.90 mg, 5%) as a TFA salt. **LC-MS**

t_R = 1.09 min in 3 min chromatography, MS (ESI) *m/z* 405 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (d, J = 7.6 Hz, 1H), 7.46 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 3.22 (m, 1H), 3.20 (s, 3H), 3.12 (m, 2H), 2.86 (s, 3H), 2.68 (s, 3H), 2.10-1.80 (m, 4H), 1.76 (m, 2H).

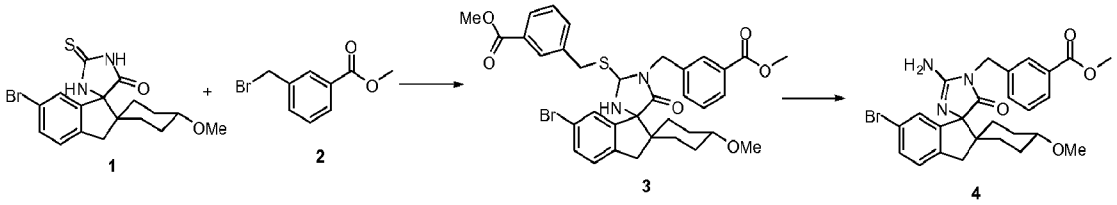
Example 222. Synthesis of Compound 270



1 VTP-000034615

According to a similar synthesis of **compound 251**, compound **1** (10.0 mg, 0.02 mmol) was reacted with 3-cyanophenylboronic acid to gave final product **compound 270** (0.91 mg, 8%) as a TFA salt. **LC-MS** t_R = 1.08 min in 3 min chromatography, MS (ESI) *m/z* 428$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.00 (s, 1H), 7.94 (m, 1H), 7.68 (m, 2H), 7.62 (m, 2H), 7.52 (m, 1H), 3.24 (m, 3H), 3.22 (s, 3H), 2.86 (s, 6H), 2.16-2.00 (m, 3H), 1.88-1.52 (m, 5H).

Example 223. Synthesis of Compound 271



Step 1.

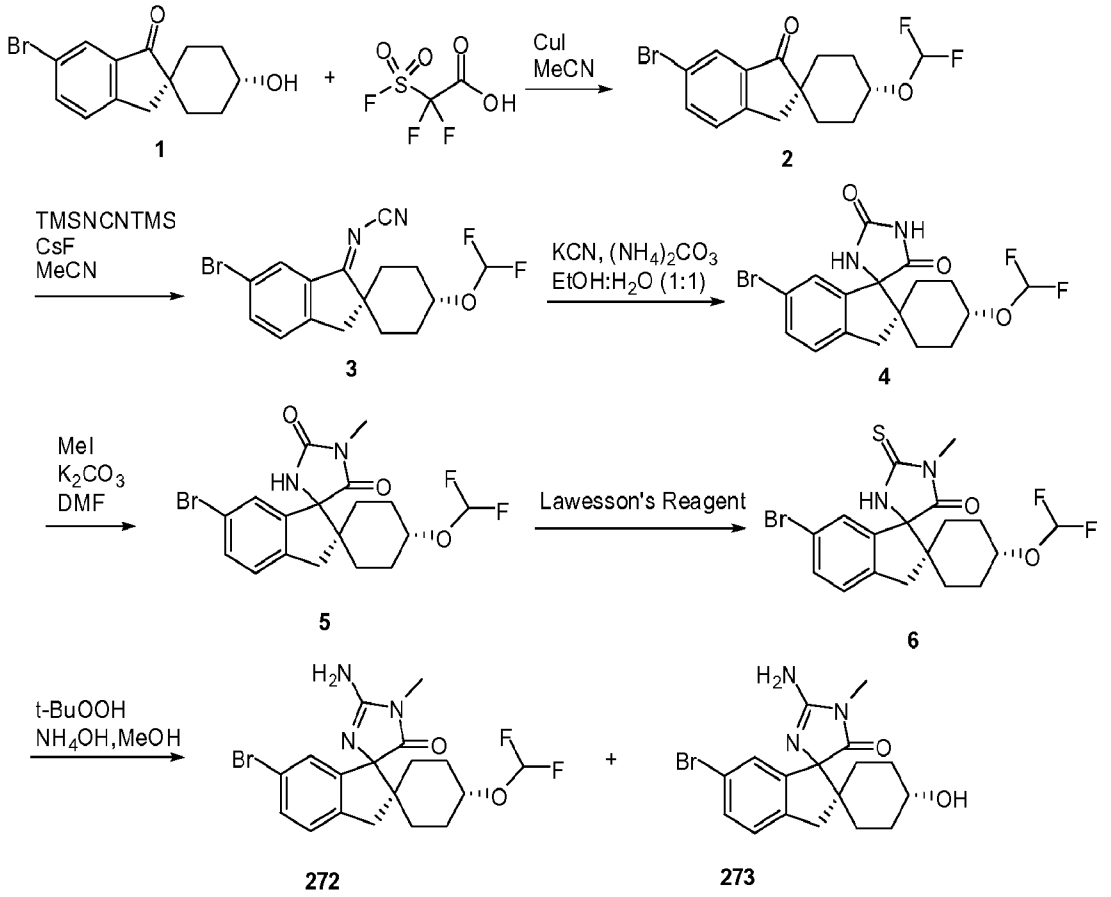
A flask containing **1** (67 mg, 0.17 mmol), cesium carbonate (130 mg, 0.4 mmol), and methyl 3-(bromomethyl)benzoate (86 mg, 0.37 mmol) in DMF (2 mL) was stirred overnight at room temperature. The reaction was diluted with water and the aqueous layer was extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent evaporated to afford a crude

mixture of **3**. The product was used as is in the next step. LC/MS ret = 2.3 min ES+ = 691 (M+1).

Step 2.

A mixture of **3** (~.17 mmol), ammonia (7M in MeOH, 1 mL), ammonium iodide (123 mg, 0.85 mmol) in MeOH (6 mL) was heated using microwave at 100 °C for 40 min. The solvent was evaporated and the crude mixture purified via Gilson to afford **compound 271** (7 mg). **LC/MS** tR = 1.64 min, ES+ = 526 (M+1). **^{1}HNMR** (MeOD) δ 8.01 (ap d, 1H, J = 7.6 Hz), 7.93 (s, 1H), 7.61 (d, 1H, J = 7.9 Hz), 7.54 (t, 2H, J = 8.2 Hz), 7.43 (d, 1H, J = 1.8 Hz), 7.31 (d, 1H, J = 7.9 Hz), 5.04 (d, 1H, J = 16.7 Hz), 4.92 (d, 1H, J = 16.4 Hz), 3.92 (s, 3H), 3.34 (s, 3H), 3.17 (m, 1H), 3.16 (d, 1H, J = 16 Hz), 3.07 (d, 1H, J = 16 Hz), 1.99 (m, 2H), 1.79 (ap d, 1H, J =13.5 Hz), 1.48-1.22 (m, 5H).

Example 224. Synthesis of Compound 272



Procedure for preparation of compound 2

A solution of (1r,4r)-6'-bromo-4-hydroxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**1**) (0.87 g, 2.95 mmol) and CuI (57.1 mg, 0.30 mmol) in anhydrous MeCN (9 mL) was heated at 60 °C under N_2 for 10 minutes to give a clear solution. 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.55 g, 0.32 mL, 3.10 mmol) was added to the solution dropwise, and the resulting solution was stirred at the same temperature for 5 min, cooled down to room temperature, quenched with water (15 mL), extracted with DCM (10 mL x 4). Combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuum. The residue was purified by flash chromatography (0 to 40% EtOAc/Hexane) to afford (1r,4r)-6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**2**) (0.55 g, 54%). **LC-MS** t_R = 2.06 min in 3 min chromatography, MS (ESI) *m/z* 345 $[M+H]^+$.

Procedure for preparation of compound 3

To a solution of (1r,4r)-6'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**2**) (364 mg, 1.05 mmol) and CsF (0.64 g, 4.2 mmol) in anhydrous MeCN (10 mL) there was added N,N'-methanediylidenebis(1,1,1-trimethylsilanamine) (0.95 mL, 4.2 mmol). The resulting solution was stirred at room temperature overnight. The reaction was added water (10 mL), extracted with DCM (10 mLx4), combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was removed in vacuum to give (E)-N-((1r,4r)-5'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)cyanamide (**3**) (0.39 g, 100%), which was used for next step without purification. **LC-MS** t_R = 2.04 min in 3 min chromatography, MS (ESI) *m/z* 369 $[M+H]^-$.

Procedure for preparation of compound 4

To a 50 mL sealed tube there was charged (E)-N-((1r,4r)-5'-bromo-4-(difluoromethoxy)spiro[cyclohexane-1,2'-indene]-3'(1'H)-ylidene)cyanamide (**3**) (0.39 g, 1.05 mmol), KCN (141 mg, 2.1 mmol), $(NH_4)_2CO_3$ (0.71 g, 7.3 mmol), and EtOH (3 mL) and water (3 mL). The tube was sealed, and heated at 75 °C overnight. The solution was cooled to room temperature, diluted with water (10 mL), extracted with EtOAc (5 mLx4). Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was removed in vacuum to give hydantoin **4** (423.3 mg), which was used for the next step without purification. **LC-MS** t_R = 1.62 min in 3 min chromatography, MS (ESI) *m/z* 415 $[M+H]^+$.

Procedure for preparation of compound 5

To a solution of above crude hydantoin 4 (158.9 mg, 0.38 mmol) in DMF (1 mL) there was added K_2CO_3 (0.42 g, 3.04 mmol) followed by MeI (59.7 mg, 0.42 mmol), the resulting mixture was stirred at room temperature for 45 min, reaction completion was confirmed by LC-MS. The mixture was then diluted with water (5 mL), extracted with DCM (5 mL x 4). Combined organics were washed with brine (5 mL), dried over Na_2SO_4, and the solvent was removed in vacuum to give compound **5** (170.1 mg), which was used for the next step without purification. **LC-MS** t_R = 1.76 min in 3 min chromatography, MS (ESI) *m/z* 429 $[M+H]^-$.

Procedure for preparation of compound 6

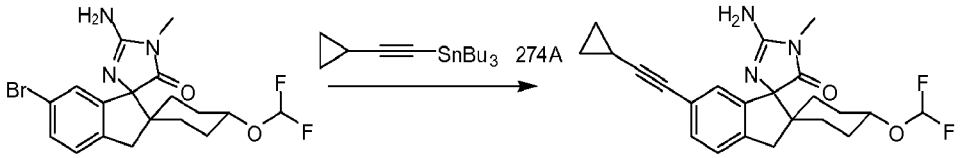
The above crude **5** (0.38 mmol) was dissolved in 1,4-dioxane (3 mL) and transfered to a 10 mL CEM tube. Lawesson's reagent (154 mg, 0.38 mmol) was added to the tube, and the resulting mixture was heated in a CEM microwave reactor at 120 °C for 130 min. Solvent was removed and the residue was purified with flash chromatography (0 to 60% EtOAc/Hexane) to give thio-hydantoin **6** (113.7 mg, 67%). **LC-MS** t_R = 1.94 min in 3 min chromatography, MS (ESI) *m/z* 445 $[M+H]^+$.

Procedure for preparation of compounds 272 and 273

To a solution of thio-hydantoin 6 (113.7 mg, 0.26 mmol) in MeOH (10 mL) there was added ammonium hydroxide (7 mL) followed by t-butyl hydroperoxide (~5.5 m in nonane, 0.8 mL). the resulting mixture was stirred at room temperature over weekend. Upon removal of solvent, the residue was purified by HPLC to give **compound 273** (1.10 mg, 1%). **LC-MS** t_R = 1.52 min in 3 min chromatography, MS (ESI) *m/z* 428 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (dd, J = 1.2, 7.8 Hz, 1H), 7.44 (d, J = 1.2 Hz,1H), 7.32 (d, J = 7.8 Hz, 1H), 6.38 (t, J = 76 Hz, 1H), 4.04 (m, 1H), 3.20 (s, 3H), 3.18 (m, 1H), 3.08 (m, 1H), 1.98 (m, 2H), 1.84 (m, 1H), 1.74-1.40 (m, 5H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.3 (d, J = 76 Hz). and **compound 272** (1.54 mg, 1.6%), **LC-MS** t_R = 1.05 min in 3 min chromatography, MS (ESI) *m/z* 378 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (dd, J = 1.2, 7.8 Hz, 1H), 7.44 (d, J = 1.2 Hz,1H), 7.28 (d, J = 7.8 Hz, 1H), 6.38 (t, J = 76 Hz, 1H), 3.46 (m, 1H), 3.18 (s, 3H), 3.20-3.04 (m, 2H), 1.94-78 (m, 3H), 1.54-1.26 (m, 5H).

Example 225. Synthesis of Compound 274

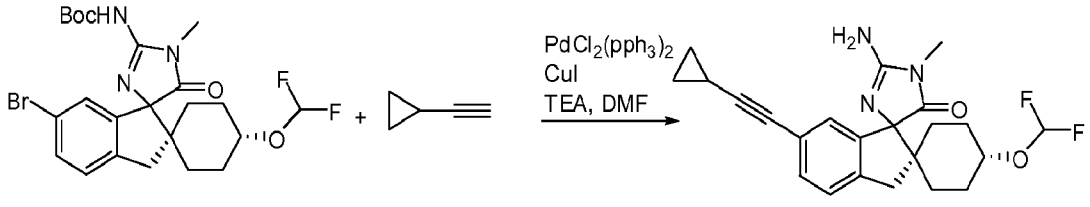
Method 1.



274a 274

A mixture containing compound **274a** (0.2 g, 0.468 mmol), compound **274A** (0.5 g, 1.41 mmol) in dry toluene (15 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then $PdCl_2(dppf)$ (20 mg, 0.023 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 45 min. After being cooled to room temperature, the mixture was diluted with EtOAc (10 mL), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by acidic preparative HPLC to give **compound 274** (30 mg, 15%) as a white solid. **LC-MS** t_R = 3.282 min in 7 min chromatography, MS (ESI) *m/z* 414.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.34 (m, 2H), 7.23 (s, 1H), 6.22-6.60 (m, 1H), 4.06 (m, 1H), 3.11-3.21 (m, 5H), 2.01 (m, 2H), 1.87 (d, J = 12.4 Hz, 1H), 1.68-1.77 (m, 1H), 1.40-1.60 (m, 5H), 0.8 (m, 2H), 0.71 (m, 2H). **^{19}F NMR** (CD_3OD 376 MHz) : δ -81.91

Method 2:

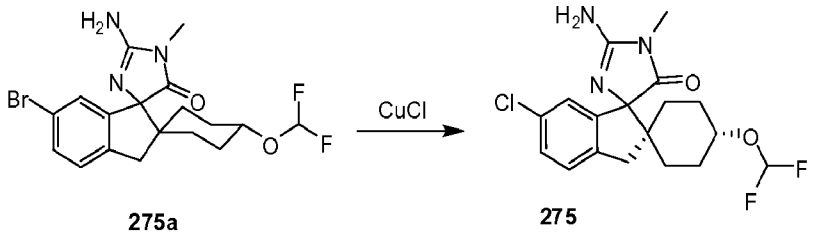


274b 274

A 10 mL CEM microwave tube was charged with compound 274b (48.2 mg, 0.11 mmol), PdCl2(pph3)2 (cat. amount), CuI (cat. amount), triethylamine (0.3 mL) and DMF (0.3 mL). The mixture was degassed then protected with N_2. In a separated tube, ethynylcyclopropane in Toluene was degassed at -78°C, then warmed to room temperature. After degassing, excess ethynylcyclopropane in Toluene was added to the

microwave tube with other reagents, and the resulting mixture was heated in a CEM microwave reactor at 120 °C for 60 min. The mixture was filtered, and purified by HPLC to give **compound 274** (5 mg, 11%) as a TFA salt. **LC-MS** t_R = 1.64 min in 3 min chromatography, MS (ESI) *m/z* 414 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.34 (m, 2H), 7.20 (s, 1H), 6.40 (t, J = 76 Hz, 1H), 4.04 (m, 1H), 3.20 (s, 3H), 3.16 (m, 2H), 1.98 (m, 2H), 1.84 (m, 1H), 1.76-1.40 (m, 6H), 0.86 (m, 2H), 0.66 (m, 2H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.1, -82.3 (d, J = 76 Hz).

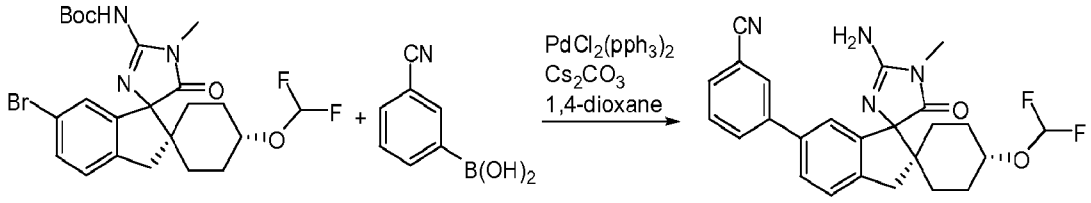
Example 226. Synthesis of Compound 275



275a **275**

In an 8 mL vial was charged with compound **275a** (20 mg, 0.047 mmol) and CuCl (23 mg, 0.234 mmol). DMF (3 mL) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 170 °C for 1 h. After cooling down, the solid was filtered and the filtrate was removed by evaporation *in vacuo* and the resulting residue was purified by acidic preparative HPLC to give **compound 275** (2.5 mg, 37%) as a whit solid, **LC-MS** t_R = 1.454 min in 3 min chromatography, MS (ESI) *m/z* 384.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.39 (d, J = 1.2 Hz, 2H), 7.34 (s, 1H), 6.23-6.61 (m, 1H), 4.06 (m, 1H), 3.11-3.24 (m, 5H), 1.96-2.07 (m, 2H), 1.84-1.97 (m, 1H), 1.67-1.75 (m, 1H), 1.54-1.62 (m, 5H), 1.45-1.54 (m, 1H). **^{19}F NMR** (CD_3OD 376 MHz) : δ -81.95.

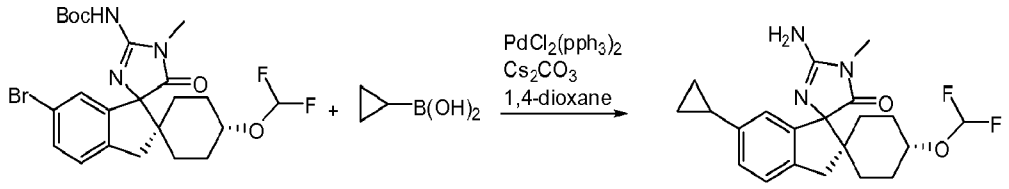
Example 227. Synthesis of Compound 276



1 276

According to a similar synthesis of **compound 251**, compound **1** (16.0 mg, 0.03 mmol) was reacted with 3-cyanophenylboronic acid to gave final product **compound 276** (10.1 mg, 74%) as a TFA salt. **LC-MS** t_R = 1.52 min in 3 min chromatography, MS (ESI) *m/z* 428 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.02 (s, 1H), 7.94 (m, 1H), 7.68 (m, 2H), 7.60 (m, 2H), 7.52 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.06 (m, 1H), 3.20 (sm, 5H), 2.02 (m, 2H), 1.88 (m, 1H), 1.80-1.44 (m, 5H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.2 (d, J = 76 Hz).

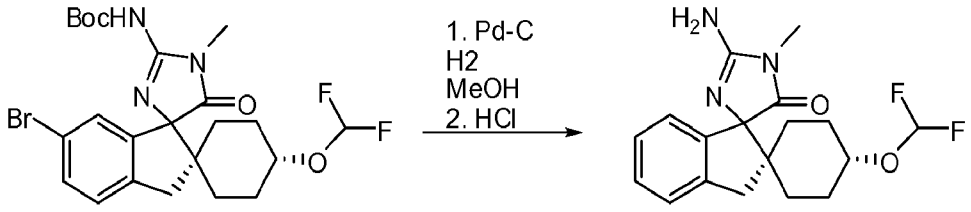
Example 228. Synthesis of Compound 277



1 277

According to a similar synthesis of **compound 251**, compound **1** (19.3 mg, 0.036 mmol) was reacted with cyclopropylboronic acid to gave final product **compound 277** (2.9 mg, 20%) as a TFA salt. **LC-MS** t_R = 1.51 min in 3 min chromatography, MS (ESI) *m/z* 390 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.24 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.38 (t, J = 76 Hz, 1H), 4.02 (m, 1H), 3.20 (s, 3H), 3.14 (m, 2H), 2.02-1.82 (m, 4H), 1.76-1.40 (m, 5H), 0.94 (m, 2H), 0.84 (m, 2H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.2 (d, J = 76 Hz).

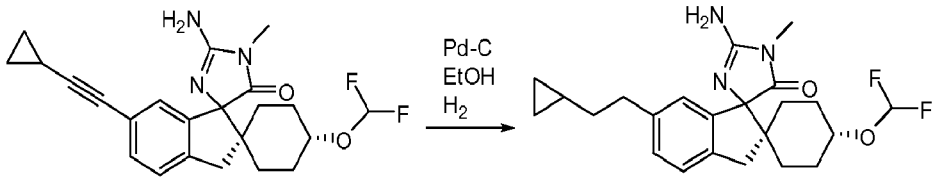
Example 229. Synthesis of Compound 278



1 278

A solution of compound **1** (10 mg, 0.019 mmol) and Pd-C (cat. amount) in MeOH (1 mL) was degassed and charged H_2 with a balloon, and stirred at room temperature for 1 hour. Upon filtration, the filtrate was concentrated and retreated with 4N HCl in 1,4-dioxane (2 mL) for overnight. Solvent was removed in vacuum and the residue was purified with HPLC to give **compound 278** (1.09 mg, 12%) as a TFA salt. **LC-MS** t_R = 1.36 min in 3 min chromatography, MS (ESI) *m/z* 350 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.38 (m, 2H), 7.26 (m, 1H), 7.18 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.04 (m, 1H), 3.18 (s, 3H), 3.16 (m, 2H), 2.04-1.40 (m, 8H); **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.5, -82.3 (d, J = 76 Hz).

Example 230. Synthesis of Compound 279

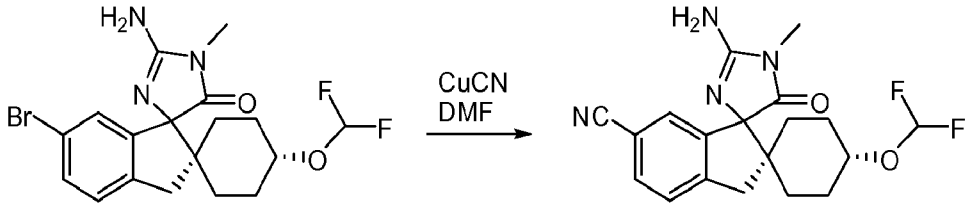


274 279

A solution of **compound 274** (3 mg, 0.007 mmol) and Pd-C (cat. amount) in EtOH (1 mL) was degassed and charged with a H_2 balloon, and stirred at room temperature for 3 hours. Upon filtration, the filtrate was purified with HPLC to give **compound 279** (1.54 mg, 41%) as a TFA salt. **LC-MS** t_R = 1.70 min in 3 min chromatography, MS (ESI) *m/z* 418 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.26 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.02 (s, 1H), 6.38 (t, J = 76 Hz, 1H), 4.04 (m, 1H), 3.20 (s, 3H), 3.16 (m, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.04-1.40 (m, 10H), 0.66 (m,

1H), 0.40 (m, 2H), 0.02 (m, 2H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.3 (d, J = 76 Hz).

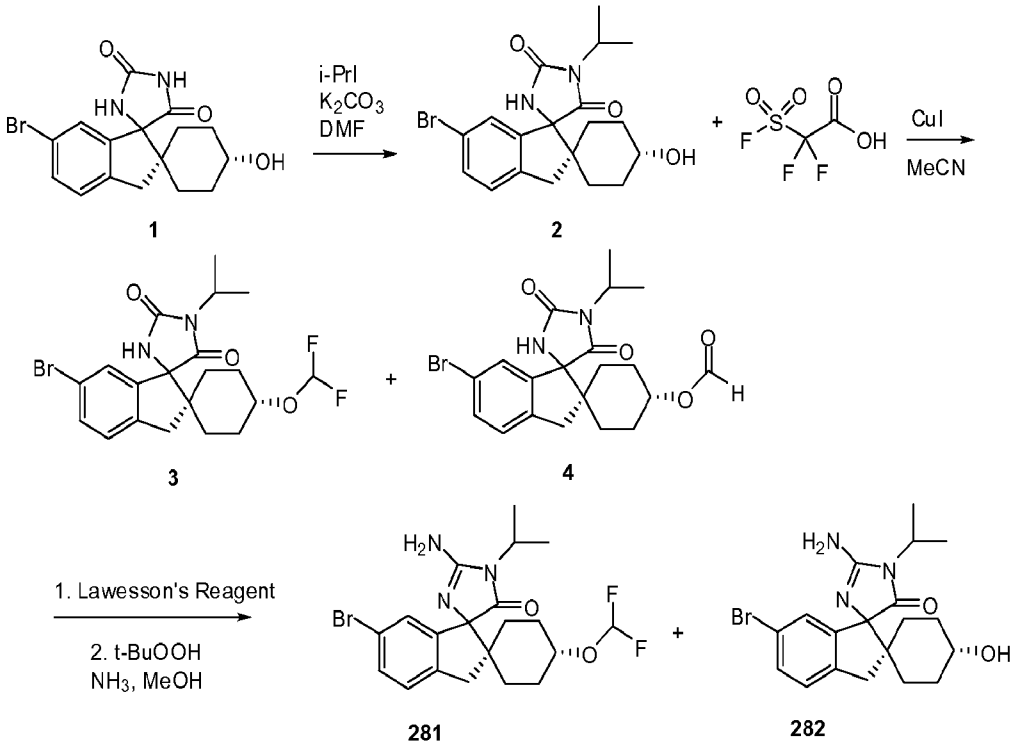
Example 231. Synthesis of Compound 280



1 **280**

In a 10 mL CEM microwave tube there was added compound **1** (5 mg, 0.012 mmol), CuCN (excess) followed by DMF (0.2 mL). The mixture was heated with a CEM microwave reactor at 150 °C for 90 min. The resulting mixture was carefully added 1 N HCl (0.3 mL) in a hood, filtered and purified with HPLC to give **compound 280** (3.0 mg, 51%) as a TFA salt. **LC-MS** t_R = 1.29 min in 3 min chromatography, MS (ESI) *m/z* 375 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.76 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 6.40 (t, J = 76 Hz, 1H), 4.04 (m, 1H), 3.26 (m, 2H), 3.20 (s, 3H), 2.02 (m, 2H), 1.86 (m, 1H), 1.78-1.40 (m, 5H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.3 (d, J = 76 Hz).

Example 232. Synthesis of Compounds 281 and 282



Procedure for preparation of compound 2

To a solution of compound **1** (0.29 g, 0.80 mmol) in DMF (1 mL) there was added K_2CO_3 (0.33 g, 2.4 mmol), followed by 2-iodopropane (52.6 mg, 0.88 mmol). The resulting mixture was stirred at room temperature over weekend, diluted with water (5 mL), extracted with DCM (5 mLx4). Combined organic layers were washed with brine (5 mL), the solvent was removed in vacuum, and the residue was purified by a flash chromatography (0-70% EtOAx/Hexane) to afford compound 2 (219.5 mg, 67%). **LC-MS** t_R = 1.49 min in 3 min chromatography, MS (ESI) *m/z* 407 $[M+H]^+$.

Procedure for preparation of compound 3& 4

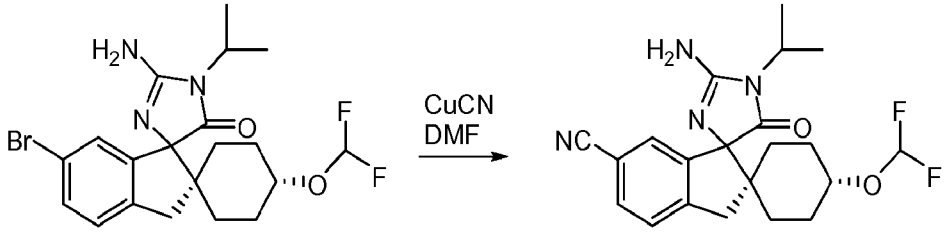
A solution of compound **1** (217.0 mg, 0.53 mmol) and CuI (10.0 mg, 0.05 mmol) in anhydrous MeCN (5 mL) was heated at 60 °C under N_2 for 10 minutes to give a clear solution. 2,2-difluoro-2-(fluorosulfonyl)acetic acid (99.1 mg, 0.56 mmol) was added to the solution dropwise, and the resulting solution was stirred at the same temperature for 5 min, cooled down to room temperature, quenched with water (10

mL), extracted with DCM (10 mL x 4). Combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuum to afford compound **3 and 4** as a 2:1 mixture (223.2 mg), which was used for the next step without purification. Compound **3**: **LC-MS** t_R = 1.96 min in 3 min chromatography, MS (ESI) *m/z* 457 $[M+H]^+$; Compound **4**: **LC-MS** t_R = 1.83 min in 3 min chromatography, MS (ESI) *m/z* 435 $[M+H]^+$.

Procedure for preparation of compounds 281 and 282

According to a similiar synthesis of **compound 291**, mixture of **3** and **4** (221.7 mg, 0.48 mmol) afforded **compound 281** (60.0 mg, 22%) as a TFA salt. **LC-MS** t_R = 1.56 min in 3 min chromatography, MS (ESI) *m/z* 456$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (dd, J = 0.8, 7.6 Hz, 1H), 7.44 (d, J =0.8 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.38 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.04 (m, 1H), 3.12 (m, 2H), 2.06-1.88 (m, 3H), 1.78-1.40 (m, 11H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.24 (d, J = 76 Hz). **Compound 282** (6.95 mg) as a TFA salt. **LC-MS** t_R = 1.42 min in 3 min chromatography, MS (ESI) *m/z* 456$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (m, 1H), 7.40 (s, 1H), 7.28 (m, 1H), 4.28 (m, 1H), 3.48 (m, 1H), 3.10 (m, 2H), 1.90 (m, 3H), 1.70-1.28 (m, 11H).

Example 233. Synthesis of Compound 283

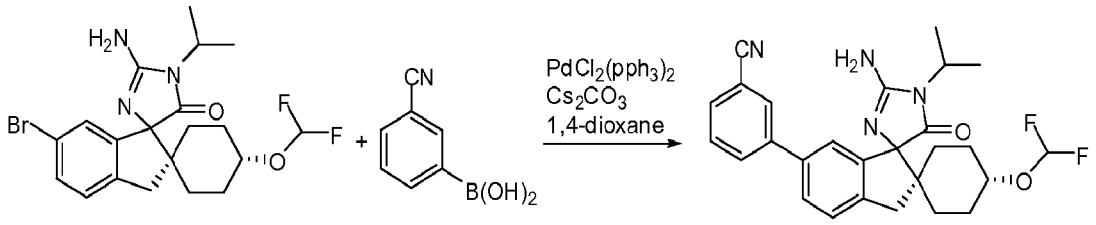


1 **283**

According to a similar synthesis of **compound 280**, compound **1** (5 mg, 0.01 mmol) was heat in a CEM microwave reactor at 150 °C for 130 min to afford **compound 283** (1.75 mg, 34%) as a TFA salt. **LC-MS** t_R = 1.43 min in 3 min chromatography, MS (ESI) *m/z* 403$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.76 (m, 2H), 7.58 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.04 (m, 1H), 3.20 (m, 2H),

2.06-1.94 (m, 3H), 1.78-1.30 (m, 11H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -75.8, -82.34 (d, J = 76 Hz).

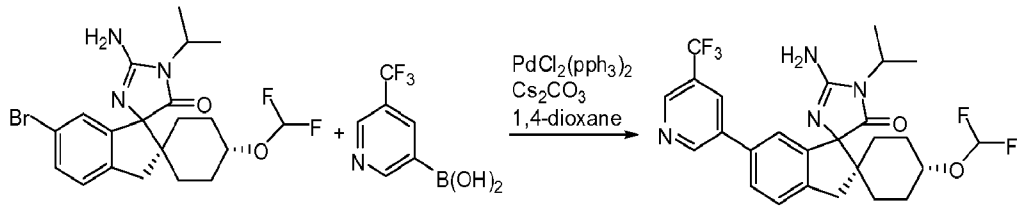
Example 234. Synthesis of Compound 284



1 **284**

According to a similar synthesis of **compound 251**, compound **1** (5.0 mg, 0.01 mmol) was reacted with 3-cyanophenylboronic acid to gave final product **compound 284** (1.42 mg, 24%) as a TFA salt. **LC-MS** t_R = 1.70 min in 3 min chromatography, MS (ESI) *m/z* 479$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.00 (s, 1H), 7.94 (m, 1H), 7.68 (m, 2H), 7.62 (m, 1H), 7.56 (s, 1H), 7.52 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.20 (m, 2H), 2.06-1.94 (m, 3H), 1.80-1.40 (m, 11H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.6, -82.28 (d, J = 76 Hz).

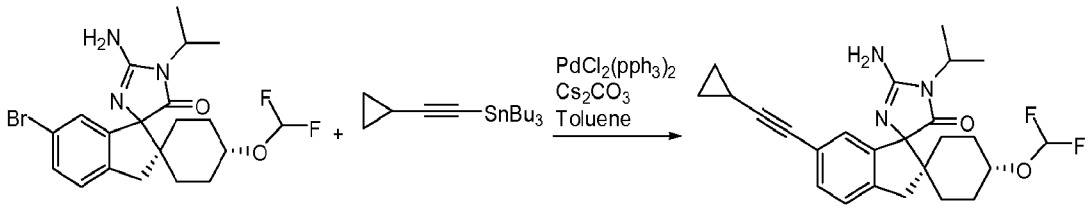
Example 235. Synthesis of Compound 285



1 **285**

According to a similar synthesis of **compound 251**, compound **1** (13.6 mg, 0.03 mmol) was reacted with (5-(trifluoromethyl)pyridin-3-yl)boronic acid to gave final product **compound 285** (1.80 mg, 9%) as a TFA salt. **LC-MS** t_R = 1.68 min in 3 min chromatography, MS (ESI) *m/z* 523$[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 9.04 (s, 1H), 8.84 (s, 1H), 8.38 (s, 1H), 7.78 (m, 1H), 7.66 (s, 1H), 7.56 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.22 (m, 2H), 2.08-1.90 (m, 3H), 1.80-1.42 (m, 11H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -64.34, -77.6, -82.28 (d, J = 76 Hz).

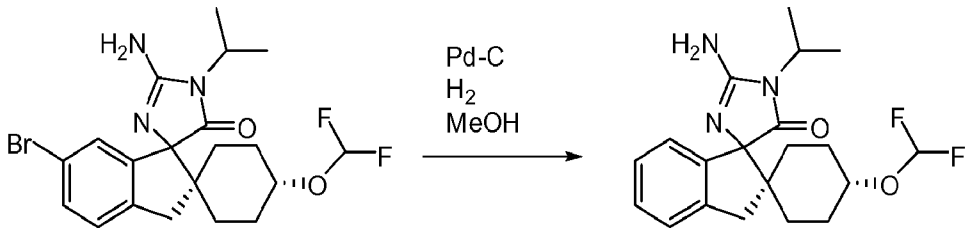
Example 236. Synthesis of Compound 286



1 286

A 10 mL CEM microwave tube was charged with compound **1** (13.0 mg, 0.028 mmol), PdCl2(pph3)2, Cs2CO3 and Toluene (0.5 mL), and degassed for 2-3 minutes, then flushed with N2. Tributyl(cyclopropylethynyl)stannane (0.1 mL, excess) was added, and the resulting mixture was heated with a CEM microwave reactor at 120 °C for 30 min. Upon filtration, the solvent was removed, and the residue was purified by HPLC to afford **compound 286** (4.29 mg, 28%) as a TFA salt. **LC-MS** t_R = 1.80 min in 3 min chromatography, MS (ESI) *m/z* 442 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.34 (m, 2H), 7.18 (s, 1H), 6.40 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.04 (m, 1H), 3.16 (m, 2H), 2.04-1.84 (m, 3H), 1.76-1.40 (m, 12H), 0.86 (m, 2H), 0.68 (m, 2H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.1, -82.3 (d, J = 76 Hz).

Example 237. Synthesis of Compound 287

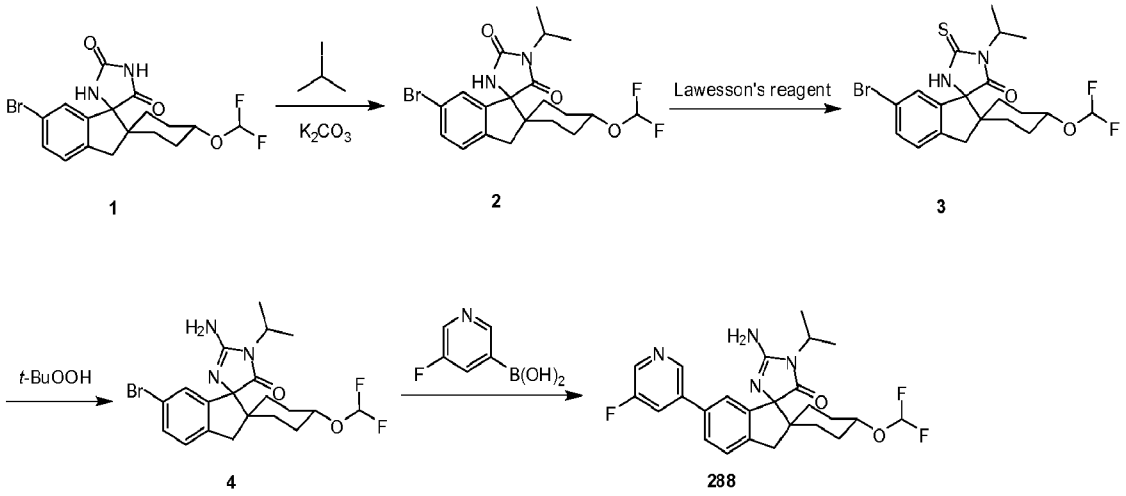


1 287

A solution of compound **1** (15 mg, 0.03 mmol) and Pd-C (cat. amount) in MeOH (2 mL) was degassed and charged H_2 with a balloon. The resulting mixture was stirred at room temperature for 45 min. Upon filtration, the filtrate was concentrated and purified with HPLC to give **compound 287** (5.26 mg, 36%) as a TFA salt. **LC-MS** t_R = 1.43 min in 3 min chromatography, MS (ESI) *m/z* 378 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400

MHz): δ 7.38 (m, 2H), 7.26 (m, 1H), 7.16 (m, 1H), 6.40 (t, J = 76 Hz, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.18 (m, 2H), 2.04-1.92 (m, 3H), 1.78-1.40 (m, 11H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -82.20 (d, J = 76 Hz).

Example 238. Synthesis of Compound 288



1. Procedure for preparation of compound 2

To a solution of compound **1** (0.23 g, 0.558 mmol) in DMF (3 mL) was added K_2CO_3 (0.15 g, 1.116 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then iodomethane (95 mg, 0.558 mmol) in DMF (1 mL) was added dropwise via a syringe with stirring. The mixture was stirred at room temperature overnight. The reaction mixture was partitioned between H_2O (25 mL) and ethyl acetate (25 mL). The separated organic phase was washed with saturated brine (3 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude. The crude was purified by preparative TLC (hexane/EtOAc = 3/1) to give compound **2** (0.18 g, 71%) as a white solid.

2. Procedure for preparation of compound 3

A 35 mL vial was charged with compound **2** (0.18 g, 0.395 mmol), Lawessons reagent (0.19 g, 0.474 mmol). Toluene (5 mL) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 1 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by preparative TLC (hexane/EtOAc = 3/1) to give compound **6** (56 mg, 30%) as a white solid.

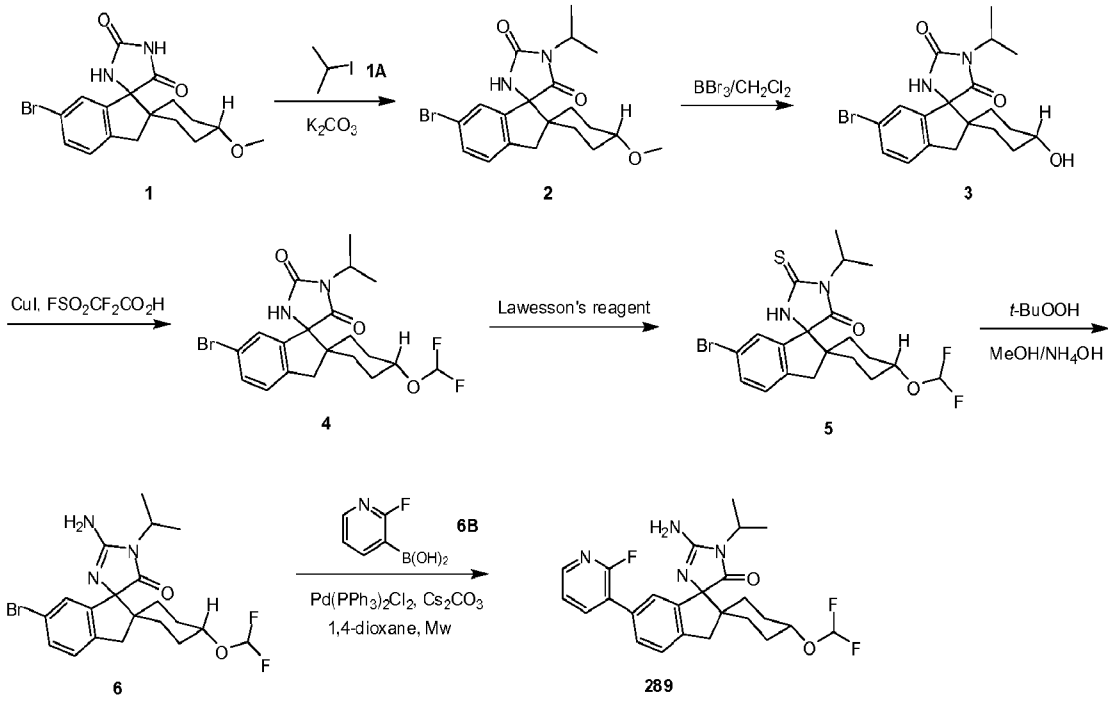
3. Procedure for preparation of compound 4

To a solution of compound **3** (56 mg, 0.118 mmol) in MeOH (4 mL) was added NH_3-H_2O (0.8 mL) and *tert*-butyl hydroperoxide (0.37 g, 2.36 mmol). After addition, the mixture was stirred at room temperature overnight. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (5 mL) and H_2O (2 mL). The organic layer was separated and washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to give compound **4** (15 mg, 28%) as a white solid.

4. Procedure for preparation of compound 288

A solution containing compound 4 (15 mg, 0.033 mmol), compound 4A (7 mg, 0.049 mmol) in dioxane (2 mL) and aqueous Cs_2CO_3 (2 M, 0.6 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2$(dppf) (1.5 mg, 0.002 mmol) was added. The reaction was heated to reflux overnight. The organic layer was separated and washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum to give the crude. The crude was purified by acidic preparative HPLC to give **compound 288** (6.6 mg, 42%) as a white solid.**LC-MS** t_R = 3.016 min in 7 min chromatography, MS (ESI) *m/z* 473.4 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 9.59 (s, 1H), 9.36 (d, J = 2.4 Hz, 1H), 8.84 (m, 1H), 8.64 (dd, J = 7.6, 1.6 Hz, 1H), 8.51 (s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 7.1-7.5 (m, 1H), 5.20 (m, 1H), 4.97 (m, 1H), 4.15 (m, 2H), 2.83-3.00 (m, 3H), 2.58-2.70 (m, 1H), 2.32-2.57 (m, 10H). **^{19}F NMR** (CD_3OD 376 MHz) : δ -81.88, -128.26.

Example 239. Synthesis of Compound 289



Procedure for preparation of compound 2

To a solution of compound **1** (500 mg, 2.32 mmol) in DMF (15 mL) was added K_2CO_3 (355 mg, 2.55 mmol) and compound **1A** (0.26 mL, 2.55 mmol). The reaction mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted with EtOAc (15 mL × 4). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc= 3: 1) to afford compound **2** (366 mg, 66%) as a white solid.

Procedure for preparation of compound 3

To a solution of compound **2** (80 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (0.4 mL, 1 M in CH_2Cl_2, 0.4 mmol) under N_2 at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. TLC showed compound **2** was completely consumed. The reaction was cooled to 0 °C and quenched with 1 N HCl, extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to afford compound **3** (30 mg, 39%) as a white solid.

^{1}H NMR ($CDCl_3$ 400 MHz): δ 7.48 (m, 1H), 7.25 (m, 2H), 5.43 (s, 1H), 4.22 (m, 1H), 3.51 (s, mH), 3.09-2.91 (m, 2H), 1.88 (m ,3H), 1.46 (m, 1H), 1.43 (m, 8H), 1.24 (m, 2H).

Procedure for preparation of compound 4

A solution of compound **3** (30 mg, 0.074 mmol) and CuI (3 mg, 0.015 mmol) in CH_3CN (1.5 mL) was stirred at 70 °C for 30 min. $FSO_2CFCOOH$ (14 mg, 0.078 mmol) in CH_3CN (0.2 mL) was added dropwise. The reaction mixture was continued stirring at 70 °C for 15 min and the solvent was removed. H_2O (10 mL) was added and the mixture extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to afford compound **4** (10 mg, 29%) as a white solid.

Procedure for preparation of compound 5

To a solution of compound **4** (25 mg, 0.055 mmol) in dry toluene (2 mL) was added Lawesson's reagent (33 mg, 0.082 mmol) under N_2. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 1 h. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **5** (12 mg, 46%) as a white solid.

Procedure for preparation of compound 6

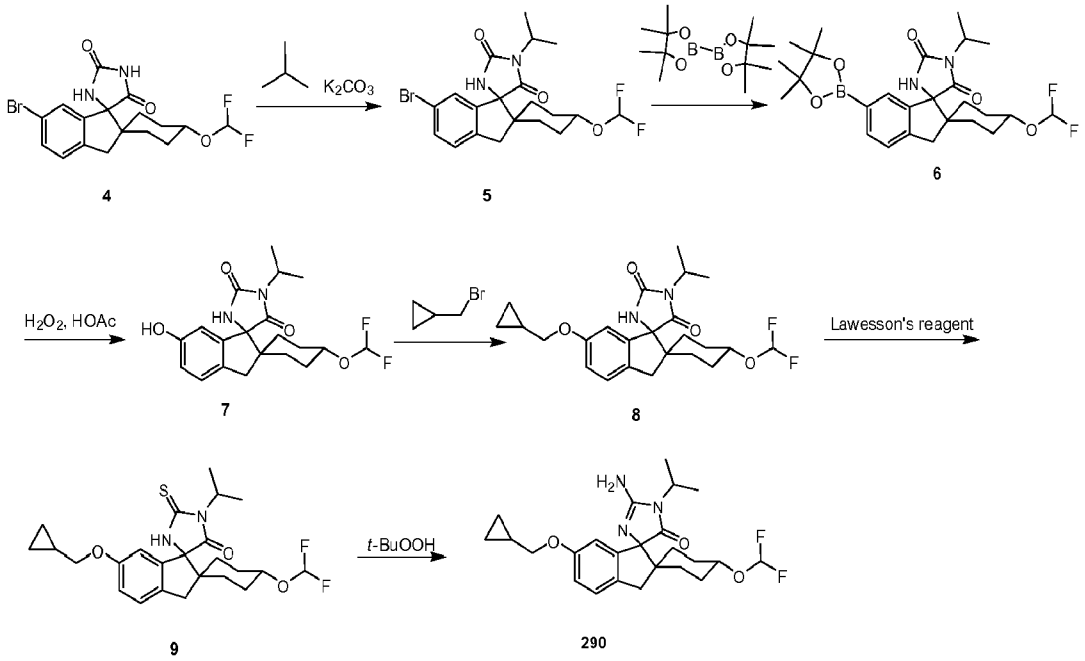
To a solution of compound **5** (12 mg, 0.021 mmol) in MeOH (3 mL) and $NH_3.H_2O$ (0.6 mL) was added *t*-BuOOH (65 mg, 0.424 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was removed and the residue was purified by preparative HPLC to give compound **6** (8 mg, 60%) as a white solid.

Procedure for preparation of compound 289

To a solution of compound **6** (8 mg, 0.0175 mmol) in 1, 4-dioxane (1 mL) was added compound **6B** (5 mg, 0.035 mmol), $PdCl_2(PPh_3)_2$ (5 mg) and Cs_2CO_3 solution (0.05 mL, 2M in H_2O, 0.1 mmol). The reaction mixture was heated in a CEM microwave reactor at 120 °C for 15 min. The solvent was removed under reduced pressure, and the residue was purified by preparative HPLC to give **compound 289** (2 mg, 24%) as a white solid.**LC-MS** t_R = 1.089 min in 2 min chromatography, MS (ESI) *m/z* 473 $[M+H]^+$, **^{1}H NMR** (CD_3OD 400 MHz): δ 8.11 (m, 1H), 7.94 (t, J = 15.6, 8.0

Hz, 1H), 7.51 (dd, J = 10.0, 8.0 Hz, 34.4, 2H), 7.43 (m, 2H), 6.50-6.13 (t, J = 151.6, 67.6 Hz, 1H), 4.19 (m, 0.3H), 3.98. (m ,0.5H), 3.38 (m, 1H), 3.08 (m, 2H), 2.01 (m, 1H), 1.48 (m, 2H), 1.65 (m, 0.4 H), 1.53 (m, 5H), 1.43 (m, 3H). **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -74.081, -81.921

Example 240. Synthesis of Compound 290



1. Procedure for preparation of compound 5

To a solution of compound **4** (0.28 g, 0.676 mmol) in DMF (10 mL) was added K_2CO_3 (280 mg, 2.029 mmol) and 2-iodo-propane (0.172, 1.014 mmol). The mixture was stirred for 3 h at room temperature. Then brine (15 mL) was added and extracted with of EtOAc (2 × 10 mL). The combined organic layers were separated, dried over Na_2SO_4, and evaporated to give crude compound **5** (280 mg, crude) as a white solid.

2. Procedure for preparation of compound 6

To a solution of compound **5** (280 mg, 0.614 mmol) in dry 1, 4-dioxane (5 mL) was added compound **5A** (172 mg, 0.675 mmol), KOAc (174 mg, 1.781 mmol) and $PdCl_2$(dppf) (21 mg, 0.0307 mmol) in a N_2 atmosphere. The mixture was heated to reflux overnight. Brine (5 mL) was added to quench the reaction and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4,

evaporated to give crude compound **6** (300 mg, crude) as a white solid, which was used for the next step without further purification.

3. Procedure for preparation of compound 7

To a solution of compound **6** (300 mg, 0.595 mmol) in THF (20 mL) was added HOAc (30 mL) and H_2O_2 (10 mL). The solution was stirred at room temperature overnight. Sat. $NaHSO_3$ (20 mL) was added to quench the reaction. Then the reaction mixture was neutralized with sat. Na_2CO_3 and the solution was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by acidic preparative HPLC to give compound **7** (100 mg, 43%) as a white solid.

4. Procedure for preparation of compound 8

To a solution of compound **7** (50 mg, 0.127 mmol) in DMF (3 mL) was added bromomethyl-cyclopropane (22 mg, 0.165 mmol) and K_2CO_3 (53 mg, 0.381 mmol). The reaction mixture was stirred at room temperature overnight. Sat. NH_4Cl (5 mL) solution was added to quench the reaction, and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, evaporated under vacuum. The residue was purified by acidic preparative HPLC to give compound **8** (10 mg, 18%) as a white solid.

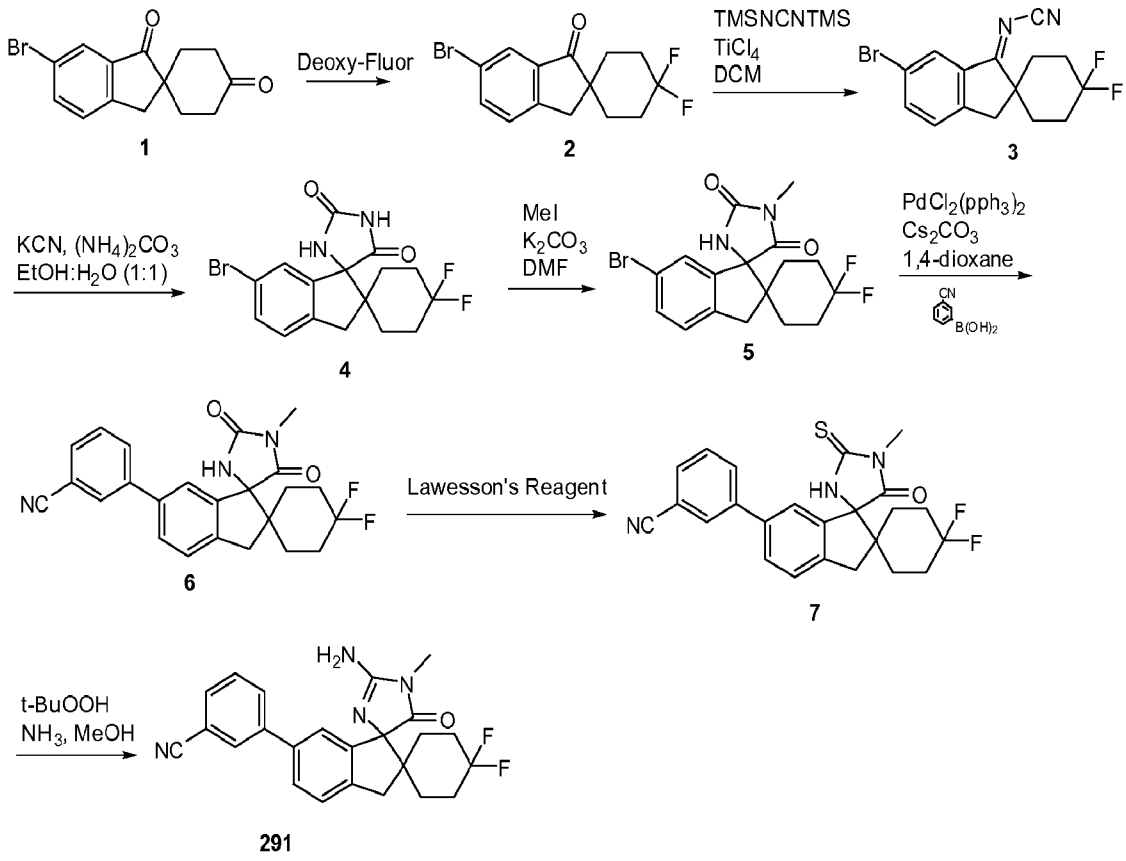
5. Procedure for preparation of compound 9

An 8 mL vial was charged with compound **8** (20 mg, 0.0446 mmol), Lawesson's reagent (22 mg, 0.0536 mmol). Toluene (2 mL) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 1 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography on silica gel (petroleum ether: EtOAc, 50: 1 to 10: 1) to give compound **9** (20 mg, 95%) as a white solid.

6. Procedure for preparation of compound 290

To a solution of compound **9** (20 mg, 0.0431 mmol) in MeOH (3 mL) was added NH_3-H_2O (0.6 mL) and *t*-butyl hydroperoxide (135 mg, 0.862 mmol). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (50 mL) and H_2O (20 mL). The organic layer was separated and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give **compound 290** (9.0 mg, 50%) as a white solid. **LC-MS** t_R = 1.161 min in 2 min chromatography, MS (ESI) *m/z* 448 $[M+H]^+$.^{1}**H NMR** (CD_3OD 300 MHz): δ 7.02 (d, J = 8.1 Hz, 1H), 6.68 (dd, J = 2.4, 7.4 Hz, 1H), 6.47 (d, J = 2.1 Hz, 1H), 5.90-6.40 (m, 1H), 4.05 (m, 1H), 3.80 (m, 1H), 3.54 (d, J = 6.9 Hz, 2H), 2.83 (m, 2H), 1.54-1.84 (m, 3H), 1.32-1.51 (m, 2H), 1.23 (m, 9H), 1.47 (m, 1H), 0.35 (m, 2H), 0.08 (m, 2H). ^{19}**F NMR** (CD_3OD 376 MHz): δ -74.61

Example 241. Synthesis of Compound 291



Procedure for preparation of compound 2

To a mixture of 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (1) (1.04 g, 3.55 mmol) and silica gel (500 mg) in a 50 mL plastic tube there was added Deoxy-Fluor (20 mL, 50% in Toluene) slowly. Heat was generated at the beginning, and the addition of Deoxy-Fluor was stopped for 5 min before the rest of the reagent was added. The tube was capped, and the mixture was stirred at room temperature for 4 hours. Water was added slowly, the solution was cooled to room temperature. Upon removal of Toluene, the residue was purified by flash chromatography to give 6'-bromo-4,4-difluorospiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**2**) (120.0 mg, 11%). **LC-MS** t_R = 2.00 min in 3 min chromatography, MS (ESI) *m/z* 315 $[M+H]^+$.

Procedure for preparation of compound 5

According to similar synthesis for **compound 250**, 6'-bromo-4,4-difluorospiro [cyclohexane-1,2'-inden]-1'(3'H)-one (**2**) (120.0 mg,0.38 mmol) was converted to

compound **5** (88.0 mg, 58% 3 steps). Compound **3**: **LC-MS** t_R = 1.96 min in 3 min chromatography, MS (ESI) *m/z* 339 $[M+H]^+$; Compound **4**: **LC-MS** t_R = 1.49 min in 3 min chromatography, MS (ESI) *m/z* 385 $[M+H]^+$; Compound **5**: **LC-MS** t_R = 1.78 min in 3 min chromatography, MS (ESI) *m/z* 399 $[M+H]^+$.

Procedure for preparation of compound 6

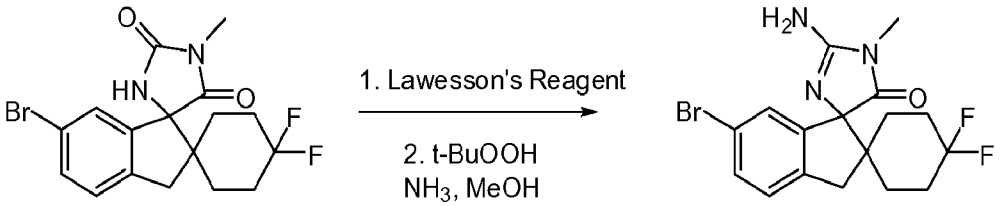
To a 10 mL CEM tube there was charged compound **5** (35.8 mg, 0.09 mmol), $PdCl_2(pph_3)_2$ (3.0 mg), Cs_2CO_3 (87 mg. 0.27 mmol), 1,4-dioxane (1 mL) and water (0.2 mL). The tube was heated in a CEM microwave reactor at 120 °C for 60 min. The solution was filtered, solvent was removed in vacuum, and the residue was purified with HPLC to give compound **6** (30.7 mg, 81%). **LC-MS** t_R = 1.76 min in 3 min chromatography, MS (ESI) *m/z* 422 $[M+H]^+$.

Procedure for preparation of compound 291

The above compound **6** (30.7 mg, 0.07 mmol) was dissolved in 1,4-dioxane (1 mL) and transfered to a 10 mL CEM tube. Lawesson's reagent (29.5 mg, 0.07 mmol) was added to the tube, and the resulting mixture was heated in a CEM microwave reactor at 120 °C for 90 min, then 130 °C for 60 min. Solvent was removed and the residue was purified with flash chromatography (0 to 60% EtOAc/Hexane) to give thio-hydantoin **7** (24.0 mg, 78%). **LC-MS** t_R = 1.92 min in 3 min chromatography, MS (ESI) *m/z* 438 $[M+H]^+$.

To a solution of thio-hydantoin **7** (24.0 mg, 0.05 mmol) in NH_3-MeOH (7 N in MeOH, 3 mL) there was added t-butyl hydroperoxide (~5.5 N in nonane, 0.5 mL). The resulting mixture was stirred at room temperature overnight. Upon removal of solvent, the residue was purified by HPLC to give **compound 291** (5.7 mg, 21%). **LC-MS** t_R = 1.43 min in 3 min chromatography, MS (ESI) *m/z* 421 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.02(s, 1H), 7.96 (m, 1H), 7.72 (m, 2H), 7.62 (m,2H), 7.52 (m, 1H), 3.24 (m, 2H), 3.20 (s, 3H), 2.20-1.84 (m, 5H), 1.72 (m, 2H), 1.54 (m, 1H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -93.78 (d, J = 237 Hz), -105.68 (d, J = 237 Hz).

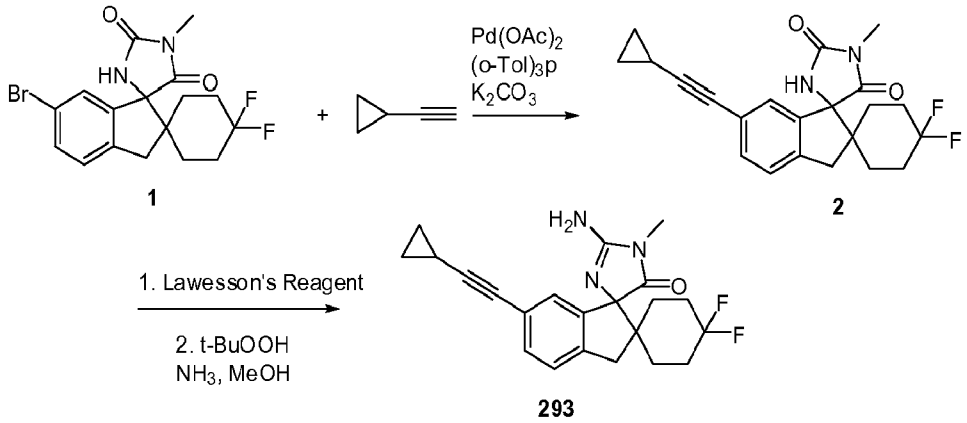
Example 242. Synthesis of Compound 292



1 292

According to the similiar synthesis of **compound 291**, compound **1** (14 mg, 0.035 mmol) afforded **compound 292** (3.8 mg, 21%) as a TFA salt. **LC-MS** t_R = 1.33 min in 3 min chromatography, MS (ESI) *m/z* 398 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.54 (dd, J = 0.8, 7.6 Hz, 1H), 7.48 (d, J = 0.8 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 3.22 (m, 2H), 3.20 (s, 3H), 2.20-1.80 (m, 5H), 1.64 (m, 2H), 1.48 (m, 1H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -94.35 (d, J = 237 Hz), -105.68 (d, J = 237 Hz).

Example 243. Synthesis of Compound 293



1 2 293

Procedure for preparation of compound 2

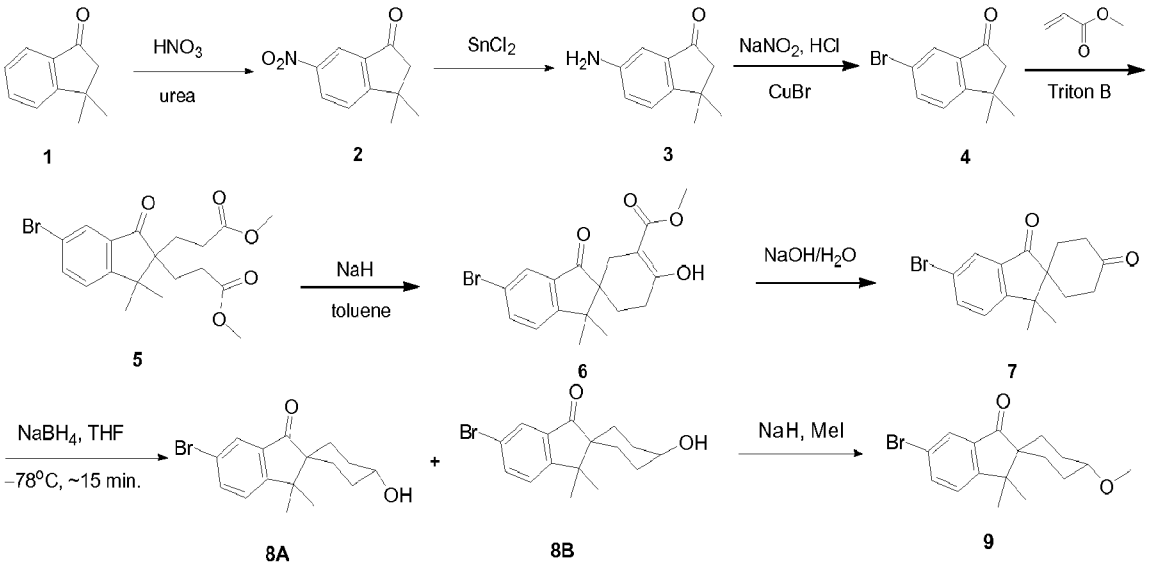
A 10 mL CEM microwave tube was charged with compound **1** (107 mg, 0.27 mmol), $Pd(OAc)_2$ (6.1 mg, 10 mol%), $(o\text{-}Tol)_3p$(16.4 mg, 20mol%) and K_2CO_3 (75 mg, 0.54 mmol). The mixture was degassed then protected with N_2. In a separated tube, ethynylcyclopropane in Toluene was degassed at -78°C, then warmed to room temperature. After degassing, excess ethynylcyclopropane in Toluene was added to the microwave tube with other reagents, and the resulting mixture was heated in a CEM microwave reactor at 120 °C for 180 min. The mixture was filtered, and purified by

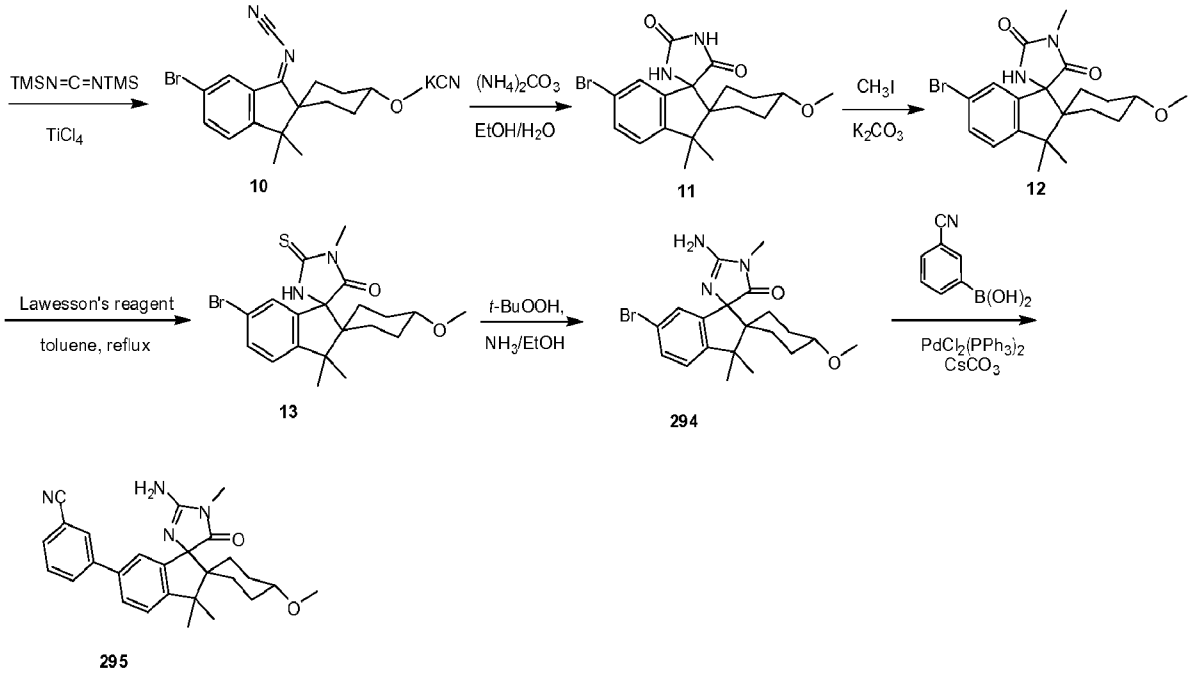
flash chromatography (0to 60% EtOAx/Hexane) to give compound **2** (28.9 mg, 11%). **LC-MS** t_R = 1.82 min in 3 min chromatography, MS (ESI) *m/z* 385 $[M+H]^+$.

Procedure for preparation of compound 293

According to the similiar synthesis of **compound 291**, compound **2** (28.9 mg, 0.075 mmol) afforded **compound 293** (9.0 mg, 75%) as a TFA salt. **LC-MS** t_R = 1.49 min in 3 min chromatography, MS (ESI) *m/z* 384 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.34 (m, 2H), 7.22 (s, 1H), 3.20 (m, 2H), 3.20 (s, 3H), 2.16-1.80 (m, 5H), 1.64 (m, 2H), 1.42 (m, 2H), 0.84 (m, 2H), 0.64 (m, 2H). **^{19}F NMR** (CD_3OD, 376 MHz): δ -77.4, -94.29 (d, J = 237 Hz), -105.69 (d, J = 237 Hz).

Example 244. Synthesis of Compounds 294 and 295





Procedure for preparation of compound 2

To a well-stirred solution of fuming nitric acid (40 mL) was added urea (0.2 g, 3.3 mmol) at room temperature. The solution was cooled to -15 °C and was stirred for 30 min. Compound **1** (10.0 g, 62.5 mmol) was added to the above solution slowly. The resulting mixture was stirred at -15 °C for 30 min. The reaction mixture was poured into ice (50.0 g) and filtered to collect the solid and dried *in vacuo* to give compound **2** (10.2 g, 80%) as a white solid. **^{1}H-NMR** ($CDCl_3$ 400 MHz): δ 8.51 (d, J = 2.0 Hz, 1H), 8.47 (dd, J = 2.4, 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 2.71 (s, 2H), 1.48 (s, 6H).

Procedure for preparation of compound 3

To a solution of $SnCl_2$ (44.9 g, 199 mmol) in concentrated HCl (30 mL) was added a solution of compound **2** (10.2 g, 49.8 mmol) in 95% ethanol (10 mL). The resulting mixture was stirred at room temperature overnight. The mixture was treated with 50% aqueous NaOH (100 mL) to form yellow solid. The resulting mixture was filtered, and the filter cake was dissolved in CH_2Cl_2 (200 mL) and then was filtered, and the filtrate was dried over Na_2SO_4 and concentrated to give compound **3** (8.0 g, 92%) as a white solid.

Procedure for preparation of compound 4

A mixture of compound **3** (4.5 g, 25.7 mmol) in ethanol (20 mL) and 40% HBr (10 mL) was cooled to -5 °C ~ 0 °C. Then to the above mixture was added a solution of $NaNO_2$ (2.13 g, 30.9 mmol) in H_2O (10 mL) slowly while keeping temperature between -5 °C ~ 0 °C. After addition, the mixture was stirred at -5 °C ~ 0 °C for1 h. Then the resulting diazonium salt solution was added at 0°C via a pipette to a mixture of CuBr (4.38 g, 30.9 mmol) in 40% aqueous HBr solution (20 mL) at 95 °C and the mixture was heated to reflux and was stirred for 15 min. After cooling down, the resulting mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude compound **4**, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 100: 1) to give compound **4** (3.3 g, 54%) as a white solid.

Procedure for preparation of compound 5

Compound **4** (3.0 g, 12.6 mol) was dissolved in dry toluene (400 mL) and was heated at 100 °C under N_2. Benzyltrimethylammoniumhydroxide (3 mL, 0.92 g/mL) was added dropwise to the reaction mixture at 100 °C and was stirred at 100 °C for 30 min. Methylacrylate (40 mL, 0.954 g/mL) was added dropwise to the reaction mixture. The reaction mixture was refluxed at 100 °C overnight. TLC (petroleum ether: ethyl acetate = 5: 1) showed compound **4** was consumed. The reaction mixture was poured into water (600 mL) and extracted with CH_2Cl_2 (200 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound **5** (4.0 g), which was purified by column chromatography (petroleum ether: ethyl acetate = 10: 1) to give pure compound **5** (1.7 g, 33%) as a red oil.

Procedure for preparation of compound 6

A mixture of compound **5** (1.7 g, 4.24 mmol) in dry toluene (100 mL) was added NaH (0.7 g, 16.97 mmol) slowly under N_2. The resulting mixture was heated at reflux overnight. The reaction mixture was added dropwise to water (200 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was dried over

Na_2SO_4 and concentrated *in vacuo* to give the crude compound **6** (1.1 g, crude), which was used in next step directly.

Procedure for preparation of compound 7

Compound **6** (1.1 g, 2.94 mmol) was dissolved in CH_3OH (20 mL) and $NaOH/H_2O$ (26 mL, 0.77 mol/L). The resulting mixture was heated at reflux for 4 h. TLC (petroleum ether: ethyl acetate = 5: 1) showed compound **6** was consumed. CH_2Cl_2 (50 mL) was added. The separated organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **7** (970 mg, 92%).**^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.78 (s, 1H), 7.65 (dd, J = 1.2 Hz, 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 2.92 (m, 2H), 2.26 (m, 2H), 1.87 (m, 4H), 1.18 (s, 6H).

Procedure for preparation of compound 8

Compound **7** (700 mg, 2.18 mmol) was dissolved in anhydrous THF (70 mL) and was cooled to -78 °C. $NaBH_4$ (24.8 mg, 0.66 mmol) was added dropwise to the reaction mixture at -78 °C. No more than 5 min, TLC (petroleum ether: ethyl acetate = 1: 1) showed compound **7** was consumed. CH_3OH (10 mL) and EtOAc (20 mL) was added and allowed to warm to room temperature. Water (50 mL) was added and concentrated *in vacuo* to remove THF and CH_3OH. EtOAc (30 mL × 3) was added again to dissolve the residue. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound **8** (650 mg, 90% crude yield), which was used in next step without purification.

Procedure for preparation of compound 9

Compound **8** (650 mg, 1.89 mmol) was dissolved in anhydrous THF (30 mL) and was cooled to 0 °C. NaH (379 mg, 9.47 mmol) was added to the reaction mixture at 0 °C slowly. After being stirred for 15 min, MeI (7.27 g, 37.89 mmol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and stirred at room temperature overnight. TLC (petroleum ether: ethyl acetate = 5: 1) showed compound **8** was consumed. Ethyl acetate (150 mL) and water (100 mL) was added. The separated organic layer was dried over Na_2SO_4 and concentrated *in vacuo*,

which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 5: 1) to give pure compound **9** (300 mg, 44% for the two steps) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.72 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.4 Hz 1H), 3.29 (s, 3H), 3.08 (m, 1H), 1.83 (m, 4H), 1.62 (m, 2H), 1.42 (m, 2H), 1.13 (s, 6H).

Procedure for preparation of compound 10

To a solution of compound **9** (100 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.6 mL, 0.6 mmol, 1M in CH_2Cl_2). The mixture was stirred at room temperature for 1 h. To the resulting mixture was added bis-trimethylsilylcarbodiimide (122 mg, 0.65 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water, extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* to give compound **10** (140 mg, 80%).

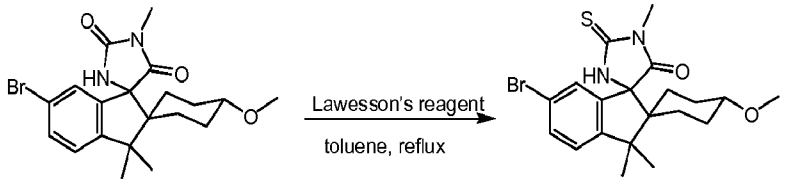
Procedure for preparation of compound 11

In a 30 mL steel autoclave was added compound **10** (140 mg, 0.39 mmol), KCN (100 mg, 1.56 mmol) and $(NH_4)_2CO_3$ (373 mg, 3.93 mmol). To this solid mixture was added EtOH (5 mL) and H_2O (5 mL). The steel autoclave was heated and stirred at 70 ^oC overnight. The reaction mixture was poured into ice-water, filtered to collect the solid and dried *in vacuo* to give compound **11** (44 mg, 29%) as a white solid.

Procedure for preparation of compound 12

To a solution of compound **11** (44 mg, 0.073 mmol) in DMF (3 mL) was added K_2CO_3 (20 mg, 0.146 mmol) and MeI (9 mg, 0.066 mmol). The mixture was stirred at room temperature for 3 h. The solution was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 3: 1) to give compound **12** (17 mg, 40%) as a white solid.

Procedure for preparation of compound 13



12 13

A mixture of compound **12** (17 mg, 0.04 mmol) and Lawesson'reagent (16 mg, 0.04 mmol) in toluene (2 mL) was heated at 130 °C for 30 min in a CEM microwave reactor. The mixture was cooled, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 3: 1) to give the compound **13** (8 mg, 45%).

Procedure for preparation of compound 294

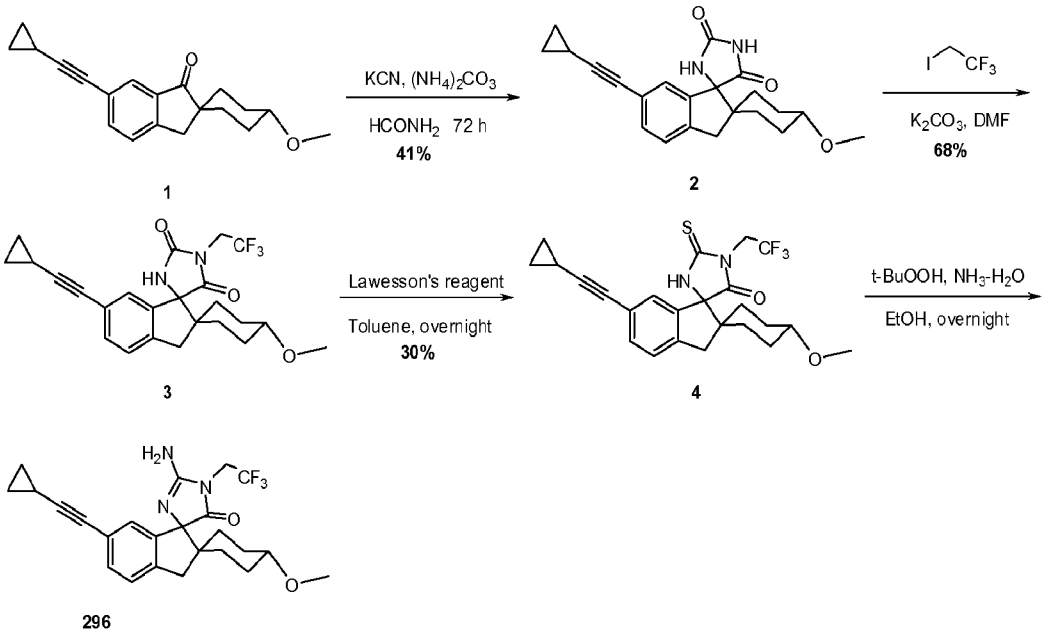
To a solution of compound **13** (8 mg, 0.02 mmol) in a mixture of MeOH (2 mL) and NH_4OH (4 mL) was added *t*-BuOOH (0.3 mL, 0.37 mmol, 65% in water). The mixture was stirred at room temperature overnight, and concentrated. Water (15 mL) and was added and the mixture was extracted with EtOAc (10 mL × 3), and the combined organic layer was dried over Na_2SO_4 and concentrated to give the residue which was purified by HPLC to give the **compound 294** (1.8 mg, 23%) as a white solid.**LC-MS**: t_R = 0.977 min in 2 min chromatography, MS (ESI) *m/z* = 419 $[M+H]^+$.^{1}**H NMR** (CD_3OD 400 MHz): δ 7.58 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.47 (d, *J* = 1.6 Hz,1H), 7.30 (d, *J* = 8.0 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 3.29 (m, 1H), 2.05 (m, 2H), 1.76 (m, 2H), 1.45 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 0.91 (m, 1H).

Procedure for preparation of compound 295

$Pd(PPh_3)_2Cl_2$ (8 mg) in a 10 mL of flask under N_2 was treated sequentially with compound **compound 294** (40 mg, 0.06 mmol), in 1,4-dioxane (3 mL), and compound **1A** (20 mg, 0.12 mmol), Cs_2CO_3 (2 N, 0.84 mL). The mixture was stirred at 120 °C 15 min under N_2 in CEM microwave reactor. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (CH_2Cl_2: MeOH = 10: 1) and by HPLC (0.1% TFA as additive) to give **compound 295** (8 mg, 24%) as a white solid.**LC-MS**: t_R = 1.076 min in 2 min chromatography, MS (ESI) *m/z*

= 442, 443 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.02(d, 1H), 7.92 (dd, 1H), 7.72 (m, 1H), 7.68 (m, 1H), 7.60 (t, 1H), 7.55 (d, 1H), 7.45 (d, 1H), 3.33 (s, 3H), 3.28 (m, 2H), 3.25 (m, 1H), 2.02 (m, 3H), 1.78 (m, 2H), 1.58 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 0.96 (m, 1H).

Example 245. Synthesis of Compound 296



Procedure for preparation of compound 2

A steel autoclave was charged with a mixture of compound **1** (1.5 g, 5.1 mmol), KCN (0.7 g, 10.7 mmol), and $(NH_4)_2CO_3$ (4.0 g, 41.7 mmol). Formamide (60 mL) was added to the tube. The mixture was heated at 120 °C for 72 h, and the reaction mixture was cooled, and poured into ice-water (200 ml). After acidification with concentrated aqueous HCl solution (10 mL), the mixture was extracted with ethyl acetate (4 × 100 mL), and the combined organic layers were washed with brine (2 × 100 mL). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (petroleum ether: EtOAc = 5: 1 to 1: 1) to give compound **2** (0.78 g, 41%) as pale yellow solid. **LC-MS**: t_R=1.83 min in 3 min chromatography, MS (ESI) *m/z* 365.1 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.27 (s, 1H), 7.20-7.25 (dd, J = 1.2, 5.2 Hz, 1H), 7.15-7.20 (d, 1H, J = 1.2 Hz), 7.05-

7.15 (d, 1H, J = 5.2 Hz), 6.05 (s, 1H), 3.35-3.40 (s, 3H), 3.00-3.10 (m, 2H), 2.90-3.00 (m, 1H), 1.95-2.05 (m, 2H), 1.15-1.45 (m, 6H), 0.75-0.85 (m, 2H), 0.65-0.75 (m, 2H).

Procedure for preparation of compound 3

A steel autoclave was charged with a mixture of compound **2** (0.15 g, 0.41 mmol), 1,1,1-trifluoro-2-iodo-ethane (0.30 g, 1.4 mmol) and K_2CO_3 (0.30 g, 5.2 mmol) in DMF (2 mL). The mixture was heated at 80 °C for 2 h in a CEM microwave reactor. The reaction mixture was then cooled and poured into brine (40 ml). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*, the resulting residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 50:1 to 2:1) to give compound **3** (0.12 g, 68%) as a white solid. **LC-MS**: t_R=2.11 min in 3 min chromatography, MS (ESI) *m/z* 447.1 $[M+H]^+$.

Procedure for preparation of compound 4

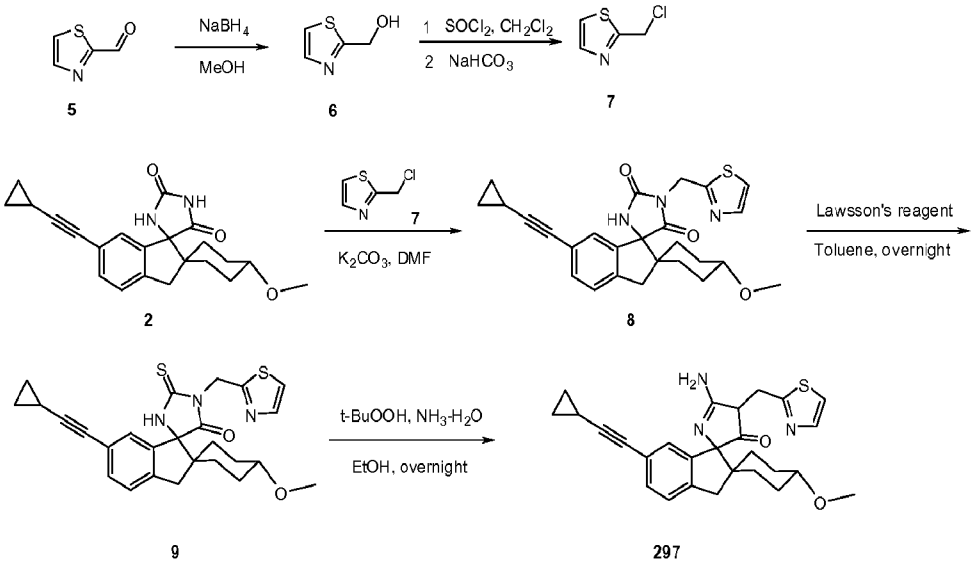
A flask equipped with a condenser and a nitrogen balloon was charged with a mixture of compound **3** (0.12 g, 0.22 mmol), Lawesson's reagent (0.48 g, 1.2 mmol) in toluene (30 mL). The reaction mixture was heated to 130 °C for 4 h. After cooling down, the precipitate was filtered off and washed with ethyl acetate (2 × 40 mL). The filtrate and the washing were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether: EtOAc, 50:1 to 2:1) to give compound **4** with 80% purity (30 mg, 30%) as a white solid.

Procedure for preparation of compound 296

To a solution of compound **4** (15 mg, 0.032 mmol) in EtOH (2 mL) was added NH_3-H_2O (0.5 ml) and *tert*-butyl hydroperoxide (0.10 g, 1.1 mol). After addition, the mixture was stirred at ambient temperature for 3 h. The mixture was concentrated *in vacuo* and the residue was purified by preparative RP-HPLC to give **compound 296** (6.4 mg, 31%) as a white solid. **LC-MS**: t_R =1.75 min in 3 min chromatography, MS (ESI) *m/z* 446.2 $[M+H]^-$. **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.35-7.40 (d, J = 8.0 Hz,

1H), 7.30-7.35 (d, J = 7.6 Hz, 1H), 7.18-7.22 (s, 1H), 4.58-4.70 (m, 1H), 4.45-4.55 (m, 1H), 3.35-3.40 (s, 3H), 3.15-3.25 (m, 2H), 3.05-3.15 (m, 1H), 1.95-2.15 (m, 2H), 1.80-1.90 (m ,1H), 1.40-1.50 (m, 4H), 1.25-1.40 (m, 2H), 0.85-0.95 (m, 2H), 0.65-0.75 (m, 2H).

Example 246. Synthesis of Compound 297



Procedure for preparation of compound 2

To a mixture of 2-formylthiazole (0.30 g, 2.65 mmol) and methanol (30 mL) was added sodium borohydride (0.20 g, 5.30 mmol) at 0 °C, the resulting mixture was stirred at ambient temperature for 1 h. Water (1 mL) was added to this reaction mixture to quench the reaction. The solvent was removed by evaporation *in vacuo*. H_2O (30 mL) was added and the mixture was adjusted to pH = 7-8 by addition of 1 N HCl. The mixture was extracted with ethyl acetate (contained 10% ethanol) (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give compound **6** (0.30 g, 100% crude yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.65-7.70 (d, J = 3.2 Hz, 1H), 7.20-7.30 (d, J = 3.2 Hz, 1H), 4.89-4.96 (s, 2H).

Procedure for preparation of compound 7

To a solution of compound **6** in CH_2Cl_2 (30 mL) was added $SOCl_2$ (0.34 g, 2.86 mmol) via a syringe at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to ambient temperature overnight. Saturated $NaHCO_3$ (15 mL) was added and the mixture was stirred at ambient temperature for another 10 min. After stirring, the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **7** (0.26 g, 74% crude yield) as a red oil, which was used for the next step without purification. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.75-7.85 (d, J = 3.2 Hz, 1H), 7.40-7.45 (d, J = 3.2 Hz, 1H), 4.90-4.95 (s, 2H).

Procedure for preparation of compound 297

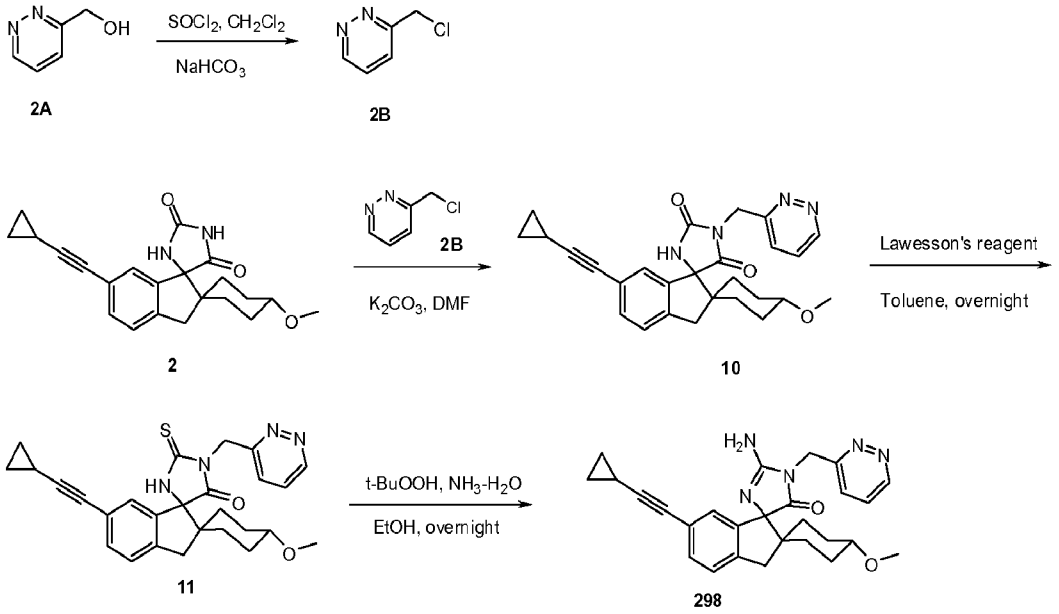
According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (0.10 g, 0.23 mmol) was alkylated with compound **7** (50 mg, 0.37 mmol) in the presence of K_2CO_3 (0.10 g, 0.72 mmol) in DMF (2 mL) to give compound **8** (0.12 g, 95%) as a yellow solid. **LC-MS**: t_R= 1.99 min in 3 min chromatography, MS (ESI) *m/z* 462.1 $[M+H]^+$. **^{1}H NMR**: ($CDCl_3$, 400 MHz): δ 7.55-7.85 (d, J = 3.2 Hz, 1H), 7.32-7.40 (m, 2H,), 7.20-7.30 (m, 2H), 5.70-5.75 (s, 1H), 5.00-5.10 (s, 2H), 3.35-3.45 (s, 3H), 3.18-3.22 (m, 1H), 3.10-3.18 (m, 1H), 3.05-3.10 (m, 1H). 2.05-2.15 (m. 1H), 1.95-2.05 (m, 2H), 1.35-1.50 (m, 6H), 0.85-0.95 (m, 2H), 0.75-0.85 (m, 2H).

Compound **8** (0.12 g, 0.26 mmol) was then reacted with Lawesson's reagent (0.25 g, 0.62 mmol) to give compound **9** with 74% purity (30 mg, 25%) as a yellow solid, which was used for the next step directly without purification. **LC-MS**: t_R=1.23 min in 3 min chromatography, MS (ESI) *m/z* 478 $[M+H]^+$.

Finally, compound **9** (30 mg, 0.063 mmol) was converted to **compound 297** (12 mg, 34%) as a white solid. **LC-MS**: t_R= 1.70 min in 3 min chromatography, MS (ESI) *m/z* 461.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.78-7.82 (d, J = 3.2 Hz, 1H), 7.60-7.70 (d, J = 3.2 Hz, 1H), 7.35-7.40 (d, J = 7.6 Hz, 1H), 7.28-7.35 (d, J = 7.6 Hz, 1H), 7.20-7.25 (s. 1H), 5.27-5.35 (d, J = 17.2 Hz, 1H), 5.20-5.27 (d, J = 17.6 Hz, 1H),

3.35-3.40 (s, 3H), 3.15-3.25 (m, 2H), 3.05-3.15 (m, 1H), 3.05-3.10 (m, 1H). 2.00-2.10 (m. 2H), 1.75-1.85 (m, 1H), 1.40-1.55 (m, 5H), 1.25-1.35 (m, 1H), 0.85-0.95 (m, 2H), 0.65-0.75 (m, 2H).

Example 247. Synthesis of Compound 298



Procedure for preparation of Compound 2B

To a solution of **2A** (200 mg, 1.8 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $SOCl_2$ (428 mg, 3.6 mmol) at 0 °C, the mixture was stirred at 0 °C for 10 min, then was allowed to warm to room temperature overnight. The reaction was quenched by addition of aq. sat. $NaHCO_3$ (10 mL), then was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **2B** (100 mg, 43%) as a yellow solid, which was used in the next step without further purification. **^{1}H NMR**: (DMSO-d_6 400 MHz): δ 9.21 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.73 (m, 1H), 5.05 (s, 2H).

***Procedure for preparation of* compound 298**

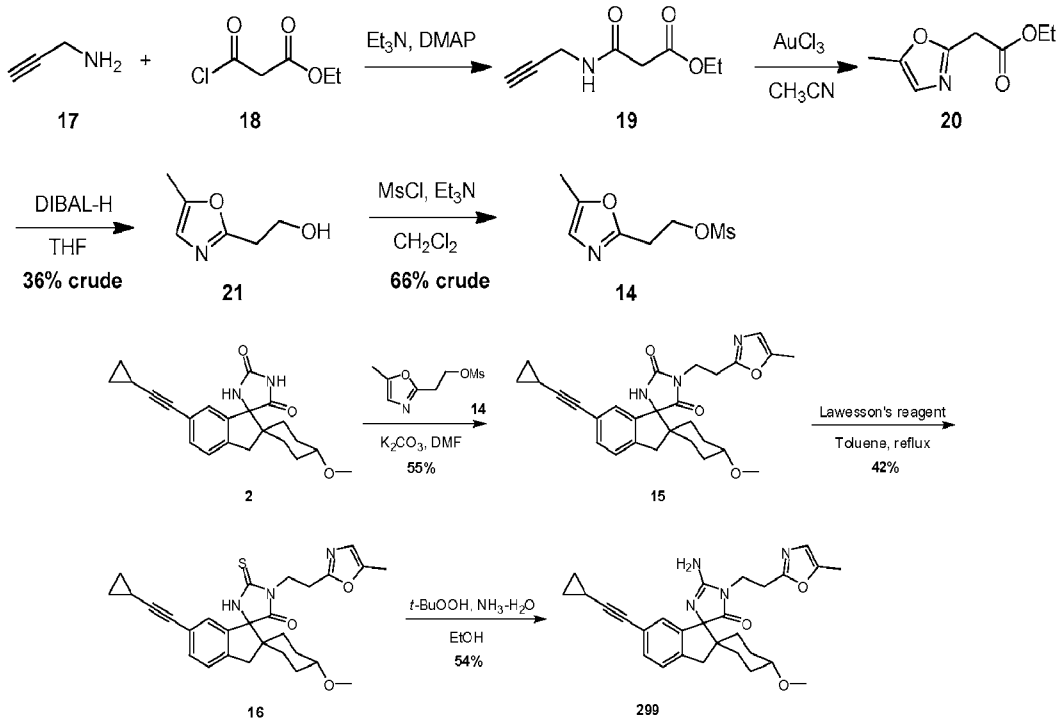
According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (200 mg, 0.54 mmol) was alkylated with compound **2B** (77.3 mg, 0.60 mmol) to give compound **10** (100 mg, 40%) as a yellow solid. which was used in the

next step without further purification ; **LCMS**: t_R = 1.239 min in 2 min chromatography, MS (ESI) *m/z* 457.2 $[M+H]^+$.

Compound **10** (15 mg, 0.032 mmol) was reacted wtih Lawesson's reagent (13.2 mg, 0.032 mmol) under a nitrogen atmosphere to afford compound **11** (10 mg, 64%) as a white solid. **LCMS**: t_R = 1.313 min in 2 min chromatography, MS (ESI) *m/z* 473.1 $[M+H]^+$.

Finally, compound **11** (10 mg, 0.02 mmol) in EtOH (1 mL) was converted to **compound 298** (1 mg, 10%) as a white solid. **LCMS**: t_R = 1.750 min in 2 min chromatography, MS (ESI) *m/z* 456.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.16 (d, J = 4.8 Hz, 1H), 7.77 (d, J = 4.8 Hz, 2H), 7.29 (d, J = 6.8 Hz, 2H), 7.24 (s, 1H), 5.18 (d, J = 16.8 Hz, 2H), 3.36 (s, 3H), 3.15-3.21 (m, 1H), 3.09 (s, 2H), 2.05-1.98 (m, 2H), 1.79-1.76 (m, 1H), 1.76-1.64 (m, 1H), 1.64-1.49 (m, 4H), 1.36-1.28 (m, 1H), 0.91(m, 2H), 0.7(m, 2H).

Example 248. Synthesis of Compound 299



Procedure for preparation of compound 19

To a stirred 0 °C solution of compound **17** (2.00 g, 36.30 mmol), Et_3N (3.70 g, 36.30 mmol) and DMAP (85 mg, 7.80 mmol) in CH_2Cl_2 (2 mL) under Argon was added dropwise slowly a solu tion of compound **18** (5.50 g, 36.30 mmol) in CH_2Cl_2 (12 mL). The raction was stirred at 0 °C for 1 h. The temperature was allowed to rise to room temperature. The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* to give crude product, which was purified by silica gel with hexane: ethyl acetate (4:1) to give compound **19** (4.10 g, 67%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.02 (s,1H), 4.27 (s,1H), 4.48 (s, 1H), 4.06 (s, 2H), 3.56-3.51 (m, 1H), 3.40-3.25 (m, 3H), 3.07-3.00 (m, 1H).

Procedure for preparation of compound 20

To a stirred solution of compound **19** (2.40 g, 14.2 mmol) in CH_3CN (40 mL) under Argon was added $AuCl_3$ (432 mg, 1.42 mmol) at room temperature. The reaction was heated to reflux overnight. The solvent was removed *in vacuo* to give crude product, which was purified by silica gel with hexane/ethyl acetate (10:1 to 5:1) to give compound **20** (1.00 g, 42%) as a ye llow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.65 (s, 1H), 4.20-4.15 (m, 2H), 3.76 (s, 3H), 1.25-1.20 (t , J = 7.2 Hz, 3H).

Procedure for preparation of compound 21

To a solution of compound **20** (0.60 g, 3.72 mmol) in anhydrous THF (30 mL) was added DIBAL-H (4.5 mL, 4.5 mmol, 1 M in toluene) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 4 h, and then was warmed to ambient temperature overnight. The mixture was cooled to 0 °C again, and then was quenched by adding H_2O (0.18 mL), 15% NaOH aq. (0.18 mL) and H_2O (0.45 mL). The mixture was warmed to ambient temperature, then $MgSO_4$ (5 g) and EtOAc (30 mL) were added with stirring. After stirring at ambient temperature for 15 min, the precipitate was filtered off and was washed with EtOAc (20 mL). The combined organic fractions were concentrated *in vacuo* to give crude compound **21** (0.17 g, 36% crude yield) as a yellow oil, which was used directly in next step without purification.

Procedure for preparation of compound 14

To a solution of compound **21** (0.16 g, 1.26 mmol, crude) and Et_3N (0.30 g, 2.96 mmol) in anhydrous THF (10 mL) was added MsCl (0.22 g, 1.89 mmol) at 0 °C under nitrogen with stirring. The mixture was stirred at 0 °C for 1 h, and then was warmed to ambient temperature overnight. The mixture was cooled to 0 °C again, and then H_2O (20 mL) and EtOAc (20 mL) were added with stirring. The mixture was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **14** (0.17 g, 66% crude yield) as a yellow oil, which was used directly in next step without purification.

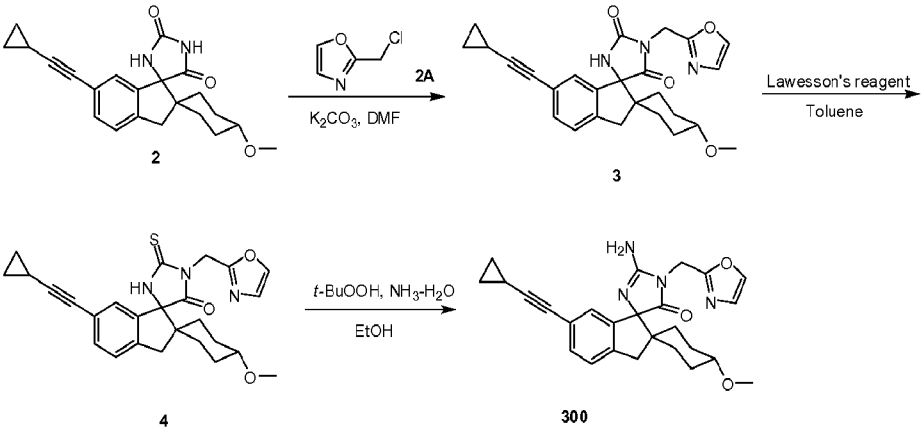
Procedure for preparation of compound 299

According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (100 mg, 0.27 mmol) was alylated with compound **14** to give compound **15** (70 mg, 55%) as a white solid. **LC-MS**: t_R = 1.897 min in 3 min chromatography, MS (ESI) *m/z* = 474 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.24 (d, J = 6.4 Hz, 1H), 7.12 (d, J = 7.6, 1H), 6.52 (s, 1H), 5.23 (m, 1H), 3.80 (t, J = 6.8 Hz, 1H), 3.28 (s, 3H), 2.98-3.05 (m, 5H), 2.14 (s, 3H), 1.85-2.03 (m, 2H), 1.78 (m, 1H), 1.15-1.35 (m, 6H), 0.80 (m, 2H), 0.71 (m, 2H).

Compound **15** (70 mg, 0.15 mmol) was then reacted with Lawesson's reagent to give compound **16** (22 mg, 30%, 42% purity) as a white solid. **LC-MS**: t_R = 1.434 min in 2 min chromatography, MS (ESI) *m/z* = 490 $[M+H]^+$.

Finally, compound **16** (22 mg, 0.018 mmol, 42% purity) was converted to **compound 299** (4.6 mg, 54%) as a white solid. **LC-MS**: t_R = 1.563 min in 3 min chromatography, MS (ESI) *m/z* = 473 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.13 (dd, J = 1.6, 8.0 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.83 (s, 1H), 6.53 (d, J = 1.2 Hz, 1H), 3.81 (t, J = 6.4 Hz, 2H), 3.29 (s, 3H), 3.01 (m, 3H), 2.98 (s, 2H), 2.09 (s, 3H), 1.89 (m, 2H), 1.59 (m, 1H), 1.05-1.50 (m, 6H), 0.75 (m, 2H), 0.60 (m, 2H).

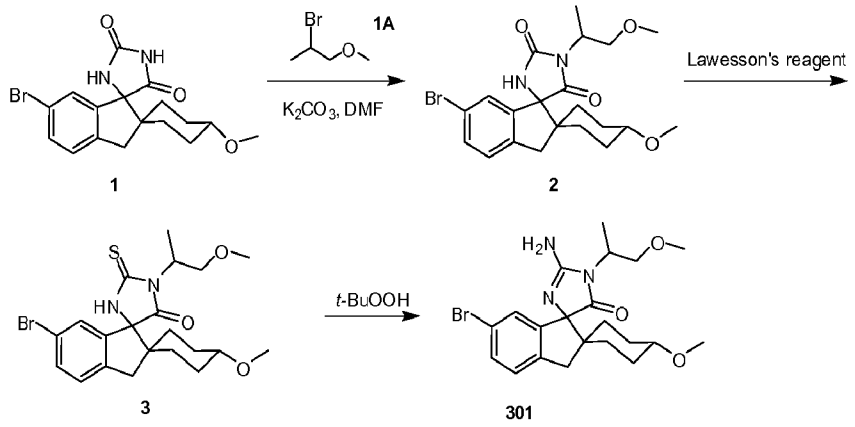
Example 249. Synthesis of Compound 300



According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (0.10 g, 0.27 mmol) was alkylated with 2-chloromethyl-oxazole **(2A)** (0.032 g, 0.27 mmol) to give compound **3** (0.056 g, 69%) as a pale yellow solid. **LC-MS**t_R = 1.770 min in 3 min chromatography, MS (ESI) *m/z* 446 $[M+H]^+$.**^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.51 (s, 1H), 7.24 (dt, J = 7.6, 1.2 Hz, 1H), 7.16 (m, 2H), 6.97 (s, 1H), 6.37 (s, 1H), 4.73 (s, 2H), 3.28 (s, 3H), 3.10 (m, 2H), 2.97 (d, J = 15.6, 1H), 2.01 (m, 1H), 1.88 (m, 2H), 1.15-1.60 (m, 6H), 0.80 (m, 2H), 0.68 (m, 2H).

Compound **3** (65 mg, 0.15 mmol) was then reacted with Lawesson's reagent (70 mg, 0.17 mmol) to give compound **4** (30 mg, 43%) as a pale yellow solid, which was converted **compound 300** (9.9 mg, 34%) as a white solid. **LC-MS**: t_R = 1.509 min in 3 min chromatography, MS (ESI) *m/z* 445 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.89 (s, 1H), 7.26 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 4.89 (s, 2H), 3.35 (s, 3H), 3.15 (m, 1H), 3.11 (d, J = 16.8 Hz, 1H), 3.06 (d, J = 15.6 Hz, 1H), 2.03 (m, 2H), 1.84 (m, 1H), 1.65 (m, 1H), 1.20-1.50 (m, 5H), 0.89 (m, 2H), 0.71 (m, 2H).

Example 250. Synthesis of Compound 301



Procedure for preparation of compound 2

To a solution of compound **1** (350 mg, 0.923 mmol) in DMF (15 mL) was added K_2CO_3 (382 mg, 2.77 mmol). After being stirred for 5 min, compound **1A** (169 mg, 1.1 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h, LCMS showed that the reaction was completed. The reaction mixture was poured into water (20 mL), extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and purified by preparative TLC (petroleum/ethyl acetate = 1:1) to give compound **2** (233 mg, 56%) as a white solid.

Procedure for preparation of compound 3

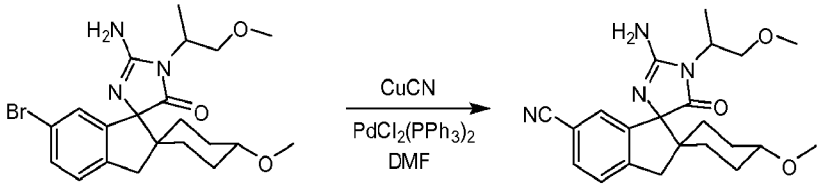
A solution of compound **2** (200 mg, 0.44 mmol) and Lawesson's Reagent (197 mg, 0.487 mmol) in dry toluene (20 mL) was heated to reflux for 5 h under N_2 atmosphere. LCMS showed that the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (petroleum/ethyl acetate = 2:1) to give compound **3** (180 mg, 87%) as a white solid.

Preparation of compound 301

A mixture of compound **3** (180 mg, 0.385 mmol) and *t*-butyl hydroperoxide (1.07 g of a 65% solution in water, 7.7 mmol) in NH_4OH/MeOH (4/20 mL) was stirred overnight at room temperature, LCMS showed that the reaction was completed. The solvent was concentrated under reduced pressure to dryness. Purification of this residue

by preparative TLC (petroleum/ethyl acetate = 1:1) afforded compound **compound 301** (130 mg, 75%) and one part was further purified by preparative HPLC to give compound **compound 301** (5.5 mg delivered) as a white solid. **LC-MS** t_R = 1.002 min in 2 min chromatography, MS (ESI) *m/z* 450.1 & 452.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.40-7.43 (d, J = 8.0 Hz, 1H), 7.23-7.25 (d, J = 8.0 Hz, 1H), 7.11-7.15 (d, J = 15.2 Hz, 1H), 4.27-4.32 (m, 1H), 3.77-3.90 (tt, 1H), 3.46-3.53 (m, 1H), 3.38-3.40 (d, J = 8.4 Hz, 6H), 3.12-3.18 (m, 1H), 3.05 (s, 2H), 1.96-2.06 (m, 2H), 1.86-1.92 (m, 1H), 1.59-1.65 (m, 1H), 1.24-1.44 (m, 7H).

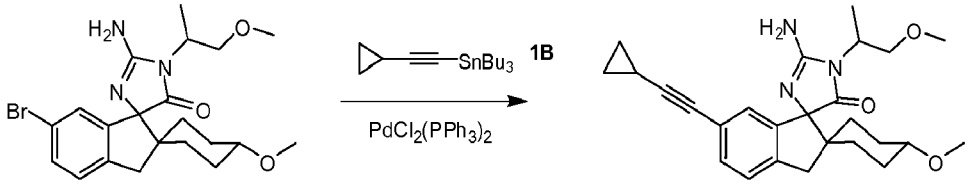
Example 251. Synthesis of Compound 302



301 302

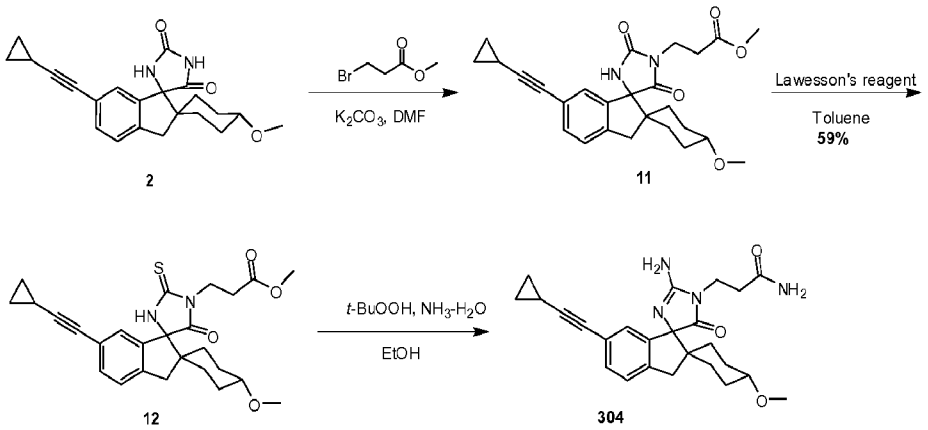
To a solution of **compound 301** (30 mg, 0.067 mmol) in DMF (5 mL) was added $PdCl_2(PPh_3)_2$ (3 mg) and CuCN (60 mg, 0.67 mmol) under N_2 atmosphere, the resulting mixture was degassed and purged with N_2 for three times. The reaction was heated to 180 °C for 30 min in microwave. LCMS showed that the reaction was completed, and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 15:1) and preparative HPLC to give **compound 302** (3.0 mg, 11%) as a white solid. **LC-MS** t_R = 0.932 min in 2 min chromatography, MS (ESI) *m/z* 397.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD, 400 MHz): δ 7.64-7.66 (d, J = 8.0 Hz, 1H), 7.49-7.51 (d, J = 8.0 Hz, 1H), 7.30-7.35 (d, J = 20.4 Hz, 1H), 4.27-4.32 (m, 1H), 3.78-3.90 (tt, 1H), 3.46-3.53 (m, 1H), 3.36-3.38 (d, J = 8.4 Hz, 6H), 3.13-3.17 (m, 3H), 1.96-2.06 (m, 2H), 1.87-1.92 (m, 1H), 1.62-1.66 (m, 1H), 1.28-1.40 (m, 7H).

Example 252. Synthesis of Compound 303



A solution containing **compound 301** (30 mg, 0.067 mmol) and compound **1B** (47 mg, 0.133 mmol) in toluene (4 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (3 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 30 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (petroleum/ethyl acetate = 1:1) and preparative HPLC to give **compound 303** (1.7 mg, 5.8%) as a white solid. **LC-MS** t_R = 0.947 min in 2 min chromatography, MS (ESI) *m/z* 436.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.19-7.27 (q, 2H), 6.94 (s, 1H), 4.27-4.34 (m, 1H), 3.78-3.91 (tt, 1H), 3.46-3.53 (m, 1H), 3.36-3.38 (d, J = 7.2 Hz, 6H), 3.13-3.19 (m, 3H), 1.83-2.09 (m, 3H), 1.54-1.65 (m, 1H), 1.22-1.49 (m, 8H) , 0.84-0.93 (m, 2H) , 0.65-0.78 (m, 2H).

Example 253. Synthesis of Compound 304

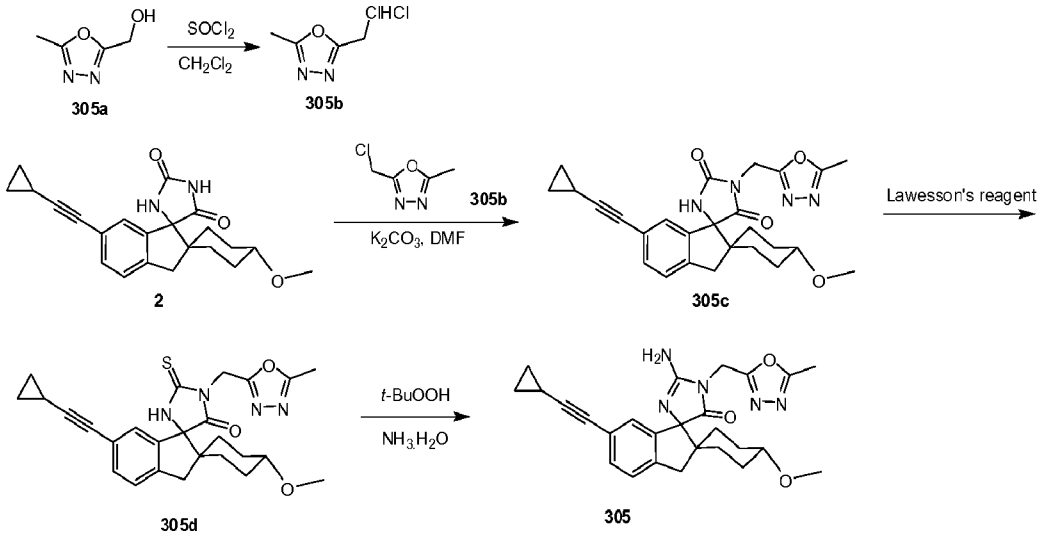


According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (65 mg, 0.18 mmol) was alkylated with 3-Bromo-propionic acid methyl ester (36 mg, 0.22 mmol) to give compound **11** (56 mg, 69%) as a white solid. **LC-MS**: t_R = 1.809 min in 3 min chromatography, MS (ESI) *m/z* = 451 $[M+H]^+$.**^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.27 (m, 2H), 7.13 (d, *J* = 10.4 Hz, 1H), 7.04 (s, 1H), 6.31 (s, 1H), 3.71 (t, *J* = 9.6 Hz, 2H), 3.56 (s, 3H), 3.28 (s, 3H), 3.10 (m, 2H), 2.97 (d, *J* = 21.2 Hz, 1H), 2.58 (t, *J* = 9.2 Hz, 2H), 1.70-2.10 (m, 3H), 1.15-1.40 (m, 6H), 0.80 (m, 2H), 0.70 (m, 2H).

Compound **11** (56 mg, 0.11 mmol) was then reacted with Lawesson's reagent (60 mg, 0.15 mmol) in anhydrous toluene (1 mL) under nitrogen to give compound **12** (25 mg, 59%) as a white solid. **LC-MS**: t_R = 1.931 min in 3 min chromatography, MS (ESI) *m/z* = 467 $[M+H]^+$.

Finally, compound **12** (25 mg, 0.054 mmol) was converted to **compound 304** (10.4 mg, 44%) as a white solid. **LC-MS**: t_R = 1.421 min in 3 min chromatography, MS (ESI) *m/z* = 435 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.24 (s, 2H), 6.90 (s, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 3.33 (s, 3H), 3.15 (m, 2H), 2.97 (d, *J* = 15.6 Hz, 1H), 2.54 (t, *J* = 8.4 Hz, 2H), 1.90-2.10 (m, 2H), 1.84 (m, 1H), 1.65 (m, 1H), 1.25-1.50 (m, 5H), 0.88 (m, 2H), 0.68 (m, 2H).

Example 254. Synthesis of Compound 305



Procedure for preparation of compound 305b

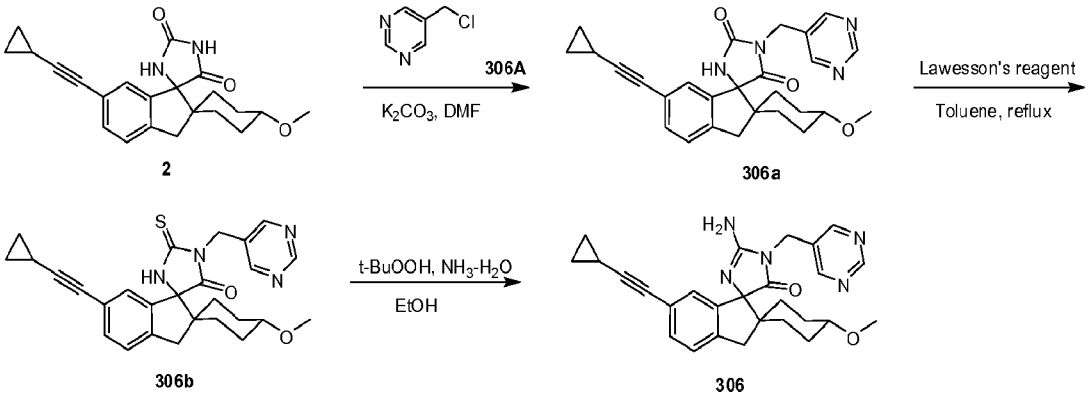
To a solution of compound **305a** (100 mg, 0.88 mol) in anhydrous CH_2Cl_2 (50 mL) was added $SOCl_2$ (130 mg, 1.2 mol). The resulting suspension was stirred at 15 °C for 12 h. The mixture was concentrated to afford the crude compound **305b** (95 mg, 80%) as a yellow oil, which was used in next step without purification.

Procedure for preparation of compound 305

According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (70 mg, 0.19 mmol) was alkylated with compound **38** (28 mg, 0.2 mmol) to give compound **39** (70 mg, 80%) as a white solid.

Compound **39** (40 mg, 0.9 mmol) was reacted with Lawesson's Reagent (40 mg, 1.0 mmol) to give compound **39A** (18 mg, 45%) as a white solid, which was converted to **compound 305** (2.20 mg, yield 15%) as a white solid. **LCMS**: t_R = 1.005 min in 2 min chromatography, MS (ESI) *m/z* = 460.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.20-7.30 (m, 2H), 7.00-7.10 (s, 1H), 5.00-5.05 (s, 2H), 3.30-3.40 (s, 3H), 3.25-3.30 (m, 1H), 3.05-3.10 (m, 2H), 2.55-2.60 (s, 3H), 1.95-2.10 (m, 1H), 1.85-1.90 (m, 1H), 1.55-1.75 (m, 1H), 1.20-1.50 (m, 5H), 0.85-0.95 (m, 2H), 0.65-0.75 (m, 2H).

Example 255. Synthesis of Compound 306

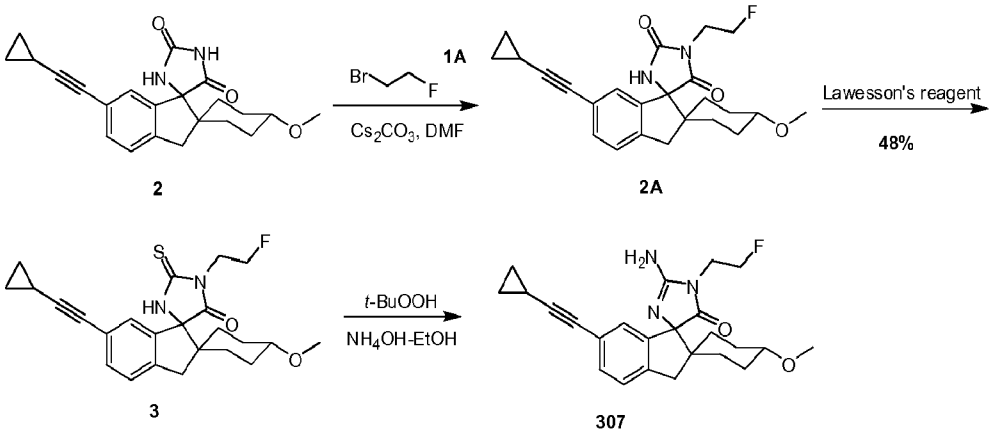


According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (100 mg, 0.27 mmol) was alkylated with 5-Chloromethyl pyrimidine

(**306A**) (38 mg, 0.30 mmol) to give compound **306a** (95 mg, 77%) as a white solid. **LC-MS**: t_R = 2.130 min in 3 min chromatography, MS (ESI) *m/z* 457 $[M+H]^+$.

Compound **306a** (90 mg, 0.20 mmol) was then reacted with Lawesson's reagent (120 mg, 0.30 mmol) to give compound **306b** (24 mg, 25%) as a white solid, which was converted to **compound 306** (6.0 mg, 26%) as a white solid. **LC-MS**: t_R = 1.639 min in 3 min chromatography, MS (ESI) *m/z* 456 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 300 MHz): δ 9.09 (s, 1H), 8.74 (s, 2H), 7.21 (m, 2H), 6.90 (s, 1H), 4.78 (s, 2H), 3.31 (s, 3H), 3.14 (m, 3H), 1.85-2.10 (m, 2H), 1.75 (m, 1H), 1.25-1.60 (m, 6H), 0.85 (m, 2H), 0.70 (m, 2H).

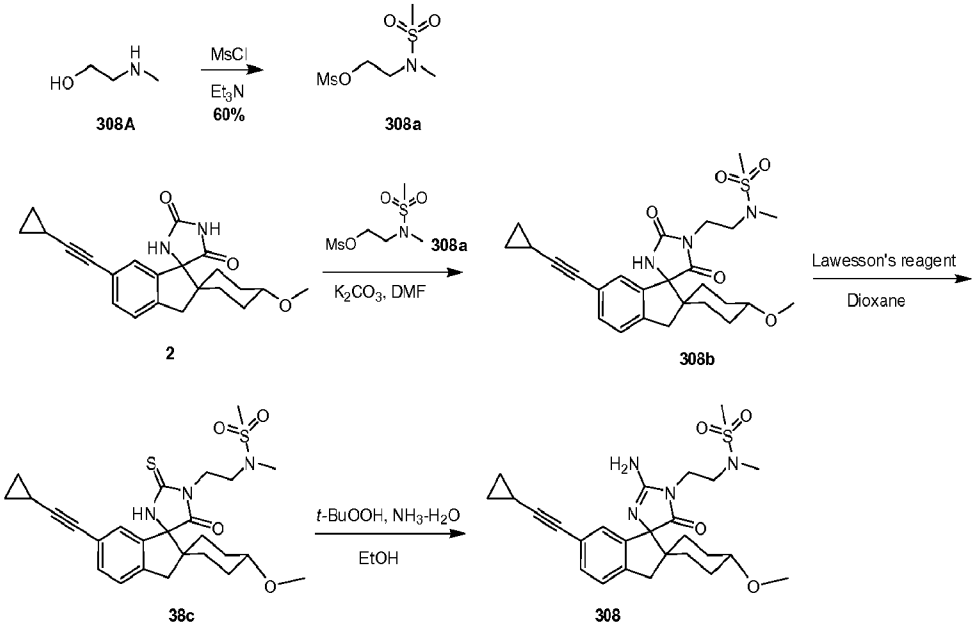
Example 256. Synthesis of Compound 307



According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (120 mg, 0.33 mmol) was alkylated with compound **1A** (50 mg, 0.40 mmol) to give compound **2A** (70 mg, 51%) as a white solid.

Compound **2A** (30 mg, 0.073 mmol) was then reacted with Lawesson's Reagent (33 mg, 0.080 mmol) to give compound **3** (15 mg, 48%), which was converted to **compound 307** (7.9 mg, 38%) as a white solid.**LC-MS** t_R = 1.014 min in 2 min chromatography, MS (ESI) *m/z* 410.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.37 (m, 2H), 7.19 (s, 1H), 4.67 (m, 1H), 4.55 (m, 1H), 4.07 (m, 2H), 3.37 (s, 3H), 3.19 (m, 3H), 2.07 (m, 2H), 1.90 (d, J = 12.0 Hz, 1H), 1.40 (m, 6H), 0.91 (m, 2H), 0.73 (m, 2H). **^{19}F NMR** (CD_3OD, 400 MHz): δ -76.97.

Example 267. Synthesis of Compound 308



Procedure for preparation of Compound 308a

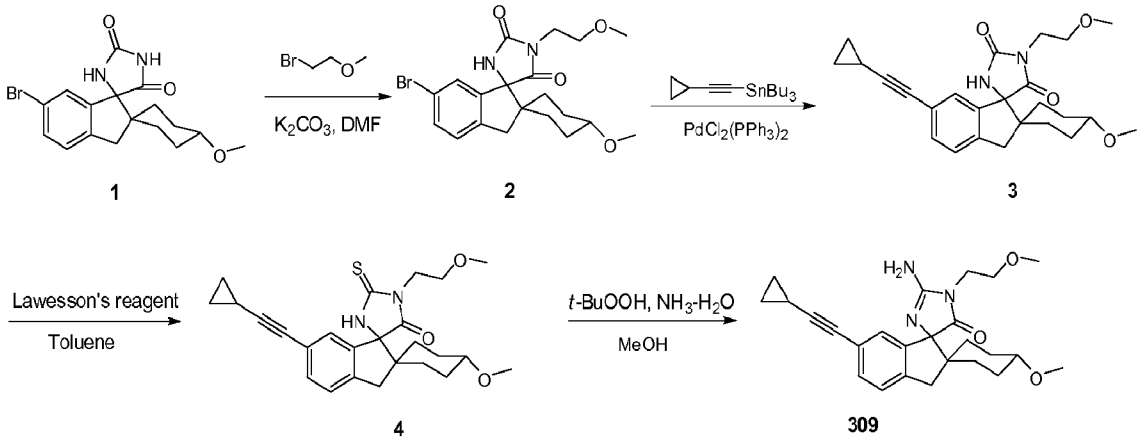
To a solution of compound **308A** (1.0 g, 13.3 mmol) and Et_3N (4.0 g, 40 mmol) in CH_2Cl_2 (30 mL) was added MsCl (3.2 g, 28 mmol) slowly. The reaction mixture was stirred at 25 °C for 10 h. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were concentrated *in vacuo* to give the crude compound **308a** (2.0 g, 60%) as a yellow oil, which was used directly in next step.

Procedure for preparation of compound 308

According to a similar synthesis of ***compound 296***, compound **2** described in Example 245 (70 mg, 0.19 mmol) was alkylated with compound **308a** (46 mg, 0.19 mmol) to give compound **308b** (93 mg, 80%) as a colorless oil.

Compound **308b** (90 mg, 0.17 mmol) was reacted with Lawesson's Reagent (75 mg, 0.18 mmol) in dry toluene (4 mL) to give compound **19** (31 mg, 30%) as a colorless oil, which was converted **compound 308** (15 mg, 50%) as a white solid. **LCMS**: t_R = 1.00 in 2 min chromatography, MS (ESI) *m/z* = 499.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.15-7.30 (m, 2H), 7.00-7.05 (s, 1H), 3.80-3.90 (m, 1H), 3.65-3.75 (m, 1H), 3.45-3.55 (m, 1H), 3.35-3.40 (s, 3H), 3.00-3.30 (m, 4H), 2.80-2.90 (s, 6H), 2.00-2.10 (m, 1H), 1.90-2.00 (m, 1H), 1.80-1.90 (m, 1H), 1.20-1.55 (m, 6H), 0.80-0.90 (m, 2H), 0.65-0.75 (m, 2H).

Example 258. Synthesis of Compound 309



Procedure for preparation of Compound 2

To a solution of compound **1** (500 mg, 1.3 mmol) in DMF (10 mL) was added K_2CO_3 (550 mg, 4 mmol). After stirring for 5 min, 1-bromo-2-methoxy-ethane (185 mg, 1.3 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The precipitate was filtered off, the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give compound **2** (400 mg, 80%) as a white solid.

Procedure for preparation of Compound 3

A suspension of compound **2** (100 mg, 0.23 mmol), tributyl-cyclopropylethynyl-stannane (420 mg, 1.2 mmol) and $PdCl_2(PPh_3)_2$ (16 mg, 0.03 mmol) in dry toluene (2.5 mL) was heated at 130 °C for 30 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 1: 1) to give compound **3** (50 mg, 50%) as a yellow oil.

Procedure for preparation of Compound 4

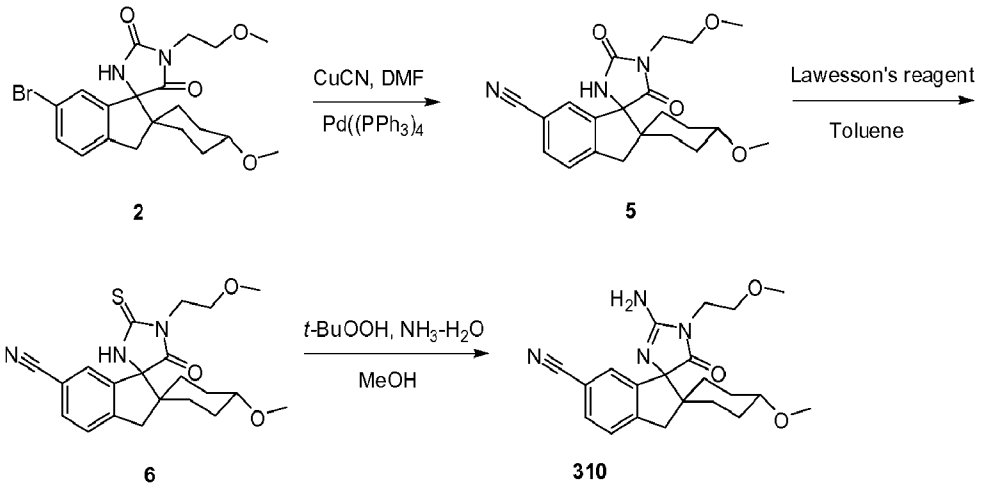
A suspension of compound **3** (50 mg, 0.12 mmol) and Lawesson's Reagent (50 mg, 0.13 mmol) in dry toluene (2 mL) was heated at 130 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was

purified by preparative TLC on silica gel (eluent: petroleum ether / ethyl acetate = 1/1) to give compound **4** (20 mg, 40%) as a colorless oil.

Procedure for preparation of compound 309

A solution of compound **4** (20 mg, 0.045 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in MeOH (2 mL) was stirred at 20 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 309** (16 mg, 80%) as a white solid. **LC-MS** t_R =1.020 min in 2 min chromatography, MS (ESI) *m/z* = 422.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.15-7.30 (m, 2H), 6.95-7.00 (s, 1H), 3.70-3.80 (m, 2H), 3.45-3.55 (m, 2H), 3.35-3.40 (s, 3H), 3.00-3.30 (m, 3H), 2.00-2.10 (m, 2H), 1.80-1.90 (m, 1H), 1.55-1.70 (m, 1H), 1.20-1.55 (m, 5H), 0.80-0.90 (m, 2H), 0.65-0.75 (m, 2H).

Example 259. Synthesis of Compound 310



Procedure for preparation of Compound 5

A suspension of compound **2** (100 mg, 0.23 mmol), CuCN (41 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.03 mmol) in dry DMF (2 mL) was heated under 180 °C for 45 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 1: 1) to give compound **5** (56 mg, 60%) as a white solid.

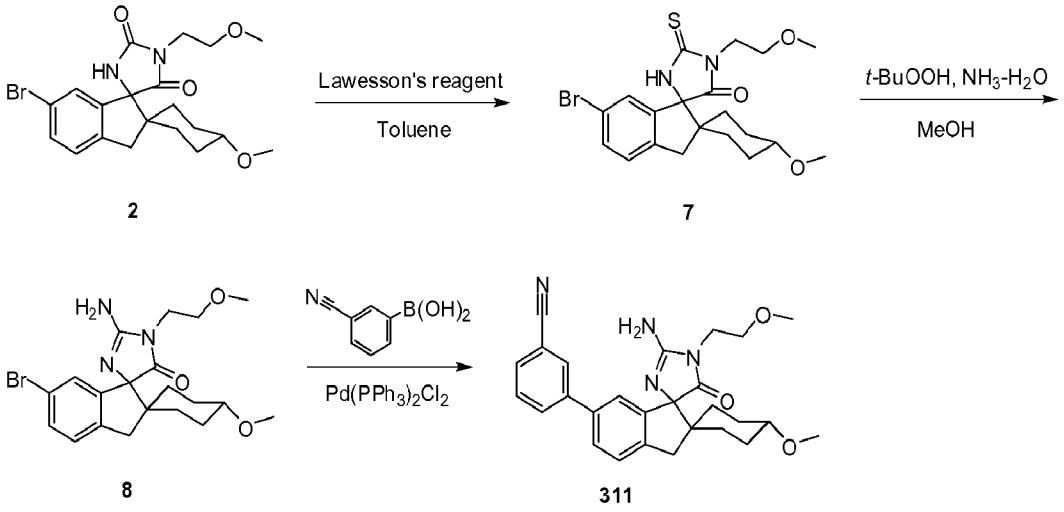
Procedure for preparation of Compound 6

A suspension of compound **5** (55 mg, 0.14 mmol) and Lawesson's Reagent (60 mg, 0.15 mmol) in dry toluene (2 mL) was heated under 130 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column (eluent: petroleum ether / ethyl acetate = 2/1) to give compound **6** (33 mg, 60%) as a colorless oil.

Procedure for preparation of compound 310

A solution of compound **6** (33 mg, 0.08 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (2 mL) was stirred at 20 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 310** as a white solid (24 mg, 60%). **LC-MS** t_R =1.450 min in 2 min chromatography, MS (ESI) *m/z* = 383.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 300 MHz): δ 7.60-7.65 (d, *J* = 7.8 Hz, 1H), 7.45-7.50 (d, *J* = 7.8 Hz, 1H), 7.25-7.30 (s, 1H), 3.70-3.80 (m, 2H), 3.50-3.60 (m, 2H), 3.35-3.40 (s, 3H), 3.10-3.30 (m, 3H), 2.00-2.10 (m, 2H), 1.80-1.90 (m, 1H), 1.55-1.70 (m, 1H), 1.20-1.45 (m, 4H).

Example 260. Synthesis of Compound 311



Procedure for preparation of Compound 7

A suspension of compound **2** (60 mg, 0.14 mmol) and Lawesson's Reagent (60 mg, 0.15 mmol) in dry toluene (2 mL) was heated under 130 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was

purified by preparative TLC on silica gel (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **7** (24 mg, 40%) as a colorless oil.

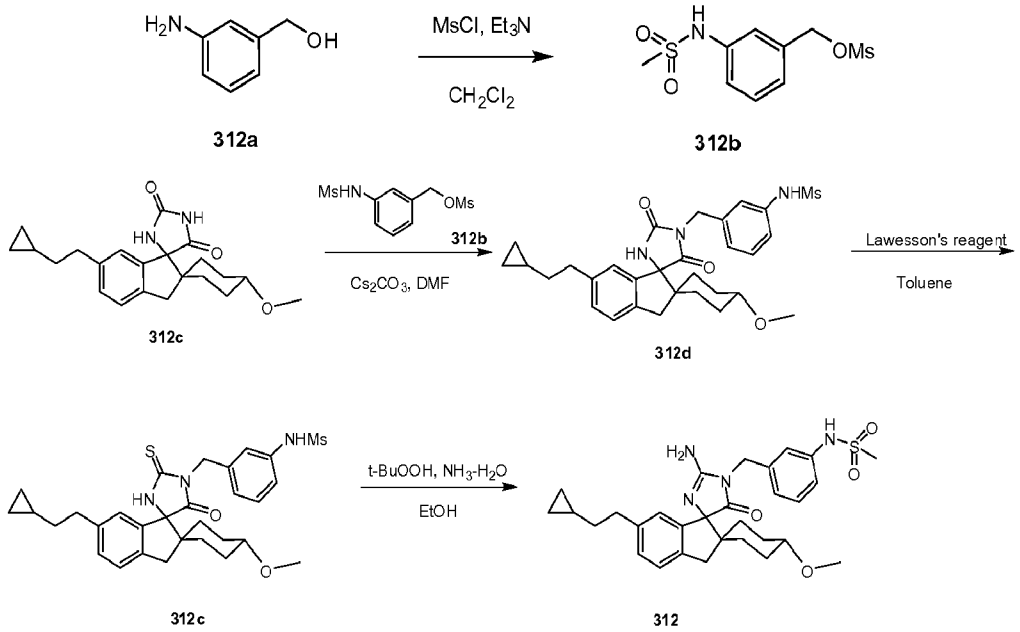
Procedure for preparation of Compound 8

A solution of compound **7** (24 mg, 0.05 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (2 mL) was stirred at 20 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give compound **8** (17 mg, 55%) as white a solid.

Procedure for preparation of Compound 311

A suspension of compound **8** (17 mg, 0.04 mmol), 3-cyanophenylboronic acid (4 mg, 0.05 mmol), $PdCl_2(PPh_3)$ (3 mg, 0.004 mmol) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (1 mL) was heated under 120 °C for 15 min in CEM microwave reactor. The mixture was concentrated in *vacuo* and the residue was purified by preparative HPLC to give **compound 311** (15 mg, 80%) as a white solid. **LC-MS** t_R =1.010 min in 2 min chromatography, MS (ESI) *m/z* = 459.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.90-8.05 (m, 2H), 7.55-7.70 (m, 3H), 7.45-7.55 (m, 2H), 3.85-4.05 (m, 2H), 3.50-3.60 (m, 2H), 3.35-3.40 (m, 6H), 3.10-3.30 (m, 3H), 2.00-2.15 (m, 2H), 1.90-2.00 (m, 1H), 1.55-1.70 (m, 1H), 1.20-1.45 (m, 4H).

Example 261. Synthesis of Compound 312



Procedure for preparation of compound 312b

To a solution of (3-amino-phenyl)-methanol (0.20 g, 1.414 mmol) and Et_3N (0.50 g, 4.94 mmol) in CH_2Cl_2 (20 mL) was added Methane sulfonyl chloride (0.50 g, 4.36 mmol) via a syringe slowly with stirring. After addition, the reaction mixture was stirred at ambient temperature overnight. The reaction was quenched by addtion 20 mL saturated $NaHCO_3$ with stirring. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude compound **312b** (0.40 g, 100%) as a brown oil, which was used directly in next step.

Procedure for preparation of compound 312

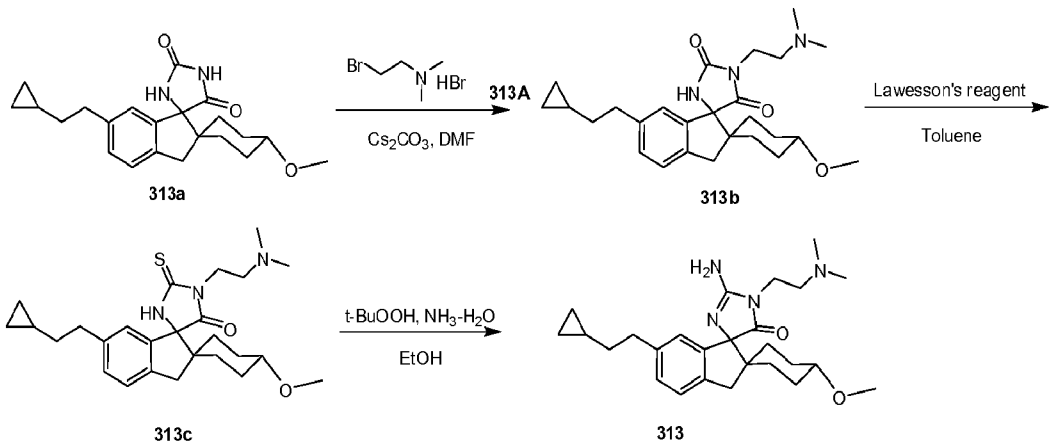
According to a similar synthesis of ***compound 296***, compound **312c** (50 mg, 0.14 mmol) was alkylated with methanesulfonic acid 3-methanesulfonylamino-benzyl ester (58 mg, 0.21 mmol) at the presence of Cs_2CO_3 (0.10 g, 0.31 mmol) to give compound **312d** (40 mg, 52%) as a white solid. **LC-MS:** t_R = 1.894 min in 3 min chromatography, MS (ESI) *m/z* 520 $[M-31]^+$, 552 $[M+H]^+$, 574 $[M+23]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.77 (s, 1H), 7.40, (d, J = 8.0 Hz, 1H), 7.33 (d, J = 5.2 Hz, 1H),

7.30 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.83 (s, 1H), 6.65 (s, 1H), 4.66 (s, 2H), 3.36 (s, 3H), 3.16 (d, J = 15.2 Hz, 1H), 3.09 (m, 5H), 2.66 (t, J = 7.6 Hz, 2H), 1.85-2.10 (m, 3H), 1.20-1.50 (m, 7H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Compound **312d** (40 mg, 0.073 mmol) was then reacted with Lawesson's reagent (40 mg, 0.099 mmol) in anhydrous Toluene (1 mL) to give compound **312e** (19 mg, 42%) as a white solid. **LC-MS**: t_R = 1.230 min in 2 min chromatography, MS (ESI) m/z 568 $[M+H]^+$.

Finally, compound **312e** (19 mg, 0.030 mmol) was reacted with NH_3-EtOH (1 mL) and *tert*-butyl hydroperoxide (100 mg, 1.11 mmol) to give **compound 312** (16.7 mg, 92%) as a white solid. **LC-MS**: t_R = 1.424 min in 3 min chromatography, MS (ESI) m/z 551 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.33, (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 7.15 (m, 3H), 6.87 (s, 1H), 4.78 (s, 2H), 3.32 (s, 3H), 3.15 (m, 1H), 3.10 (d, J = 15.6 Hz, 1H), 3.04 (d, J = 15.2 Hz, 1H), 2.93 (s, 3H), 2.69 (t, J = 7.6 Hz, 2H), 1.90-2.10 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H), 1.20-1.50 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.03 (m, 2H).

Example 262. Synthesis of Compound 313

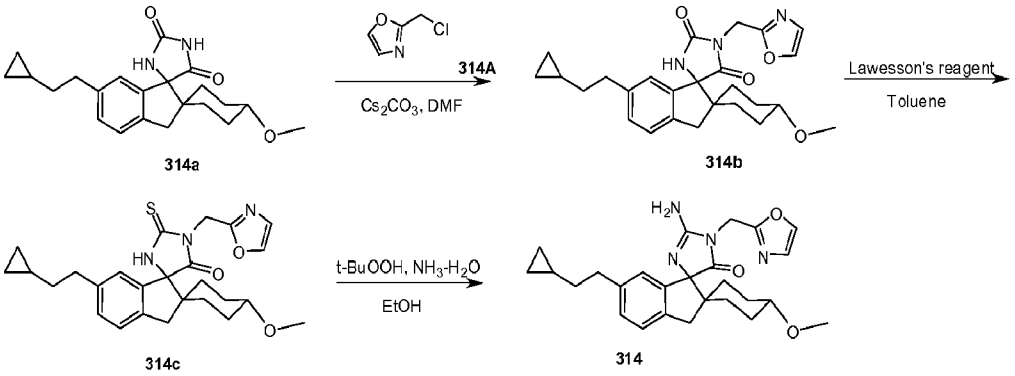


According to a similar synthesis of **compound 296**, compound **313a** (50 mg, 0.14 mmol) was alkylated with compound **1A** (35 mg, 0.15 mmol) to give compound

313b (28 mg, 47%), which was reacted wtih Lawesson's Reagent (30.9 mg, 0.077 mmol) in anhydrous toluene (2.5 mL) to give compound **313c** (21 mg, 70%).

Compound **313c** (21 mg, 0.046 mmol) was then reacted wtih *t*-BuOOH (127.9 mg, 0.92 mmol) in NH_4OH (1 mL) and EtOH (2.5 mL) to give **compound 313** (2.8 mg, 14%) as a white solid. **LC-MS**: t_R = 1.018min in 2 min chromatography, MS (ESI) *m/z* 439.4 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.259 (d, J = 11.6 Hz, 2H), 7.087 (s, 1H), 4.130 (d, J = 5.6 Hz, 2H), 3.352 (m, 5H), 3.173 (m, 3H), 2.940 (s, 6H), 2.711 (d, J = 14.8 Hz, 2H), 2.083 (m, 2H), 1.874 (d, J = 9.6 Hz, 1H), 1.447 (s, 6H), 1.32 (m, 1H), 0.68 (s, 1H), 0.42 (s, 2H), 0.02 (s, 2H).

Example 263. Synthesis of Compound 314



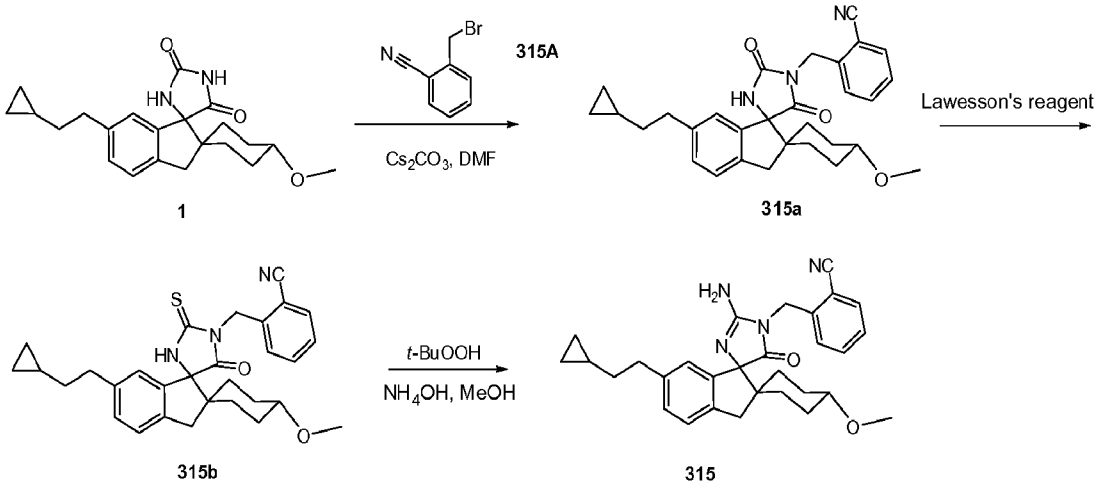
According to a similar synthesis of **compound 296**, compound **314a** (50 mg, 0.14 mmol) was alkylated with 2-chloromethyl oxazole (25 mg, 0.21 mmol) to give compound **314b** (40 mg, 63%) as a white solid.**LC-MS:** t_R = 2.038 min in 3 min chromatography, MS (ESI) *m/z* = 450 $[M+H]^+$.

Compound **314b** (50 mg, 0.11 mmol) was then reacted with Lawesson's reagent (60 mg, 0.15 mmol) to give compound **314c** (30 mg, 59%) as a white solid. **LC-MS**: t_R = 1.214 min in 2 min chromatography, MS (ESI) *m/z* = 466 $[M+H]^+$.

Compound **314c** (30 mg, 0.064 mmol) was then reacted with NH_3-EtOH (1 mL) and tert-butyl hydroperoxide (200 mg, 2.22 mmol) to give **compound 314** (20.6 mg, 72%) as a white solid. **LC-MS**: t_R = 1.383 min in 3 min chromatography, MS (ESI) *m/z* = 449 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.88 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H),

7.13 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 4.89 (m, 2H), 3.36 (s, 3H), 3.18 (m, 1H), 3.09 (d, J = 15.6 Hz, 1H), 3.05 (d, J = 15.6 Hz, 1H), 2.68 (t, J = 7.6 Hz, 2H), 1.90-2.10 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H), 1.20-1.50 (m, 5H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

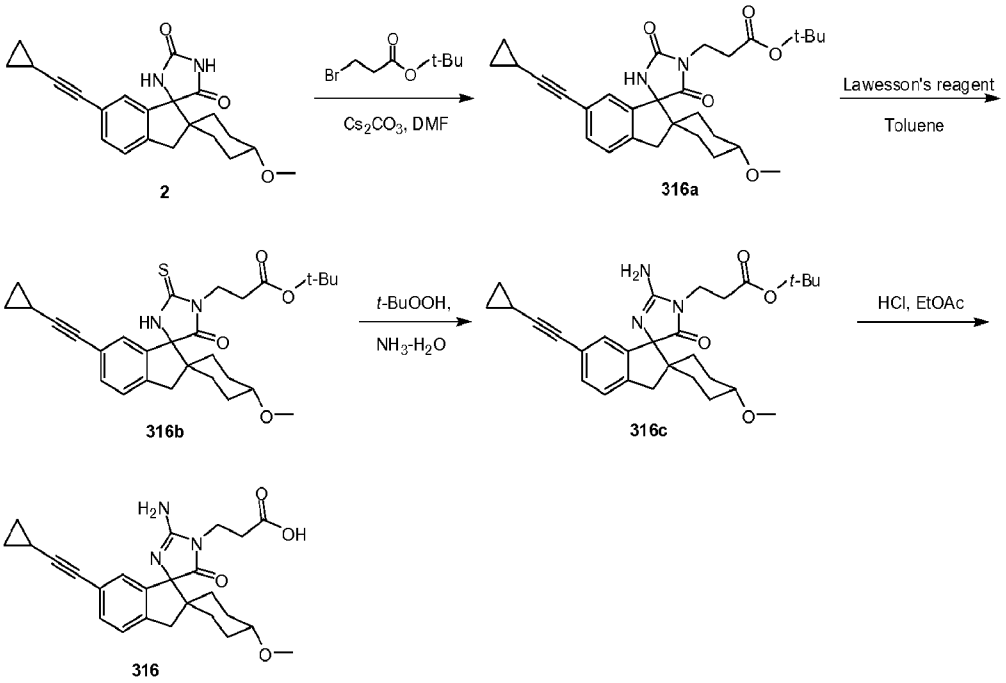
Example 264. Synthesis of Compound 315



According to a similar synthesis of **compound 296**, compound **1** (50 mg, 0.14 mmol) was alkylated with compound **315A** (26.5 mg, 0.14 mmol) to give compound **315a** (26 mg, 41%).

Compound **315a** (26 mg, 0.038 mmol) was then reacted with Lawesson'reagent (18.3 mg, 0.045 mmol) to give compound **315b** (20 mg, 75%), which was converted to **compound 315** (11.2 mg, 58%) as a white solid. **LC-MS** : t_R = 1.223 min in 2 min chromatography, MS (ESI) m/z = 483 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.80 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.23 (m, 2H), 7.14 (s, 1H), 5.13 (s, 2H), 3.35 (s, 3H), 3.20 (m, 1H), 3.06 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.01 (m, 2H), 1.75 (m, 1H), 1.50 (m, 6H), 1.33 (m, 1H), 0.69 (m, 1H), 0.39 (m, 2H), 0.01 (m, 2H).

Example 265. Synthesis of Compound 316



Procedure for preparation of compound 316a

According to a similar synthesis of ***compound 296***, compound **2** (0.20 g, 0.55 mmol) was alkylated with tert-butyl 3-bromopropanoate to give compound **316a** (0.20 g, 72%) as a white solid.^{1}**H NMR** ($CDCl_3$ 300 MHz): δ 7.29 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.08 (s, 1H), 5.45 (s, 1H), 3.73 (t, J = 7.2 Hz, 2H), 3.55 (s, 3H), 3.16 (d, J = 16.2 Hz, 1H), 3.07 (m, 1H), 3.01 (d, J = 15.3 Hz, 1H), 2.58 (t, J = 6.9 Hz, 2H), 1.70-2.10 (m, 3H), 1.40 (s, 9H), 1.20-1.35 (m, 6H), 0.85 (m, 2H), 0.75 (m, 2H).

Compound **316a** (0.19 g, 0.39 mmol) was then reacted with Lawesson;s Reagent to give compound **316b** (60 mg, 30%) as a white solid. **LC-MS**: t_R = 1.346 min in 2 min chromatography, MS (ESI) m/z = 453 $[M-56]^+$, 531 $[M+Na]^+$.

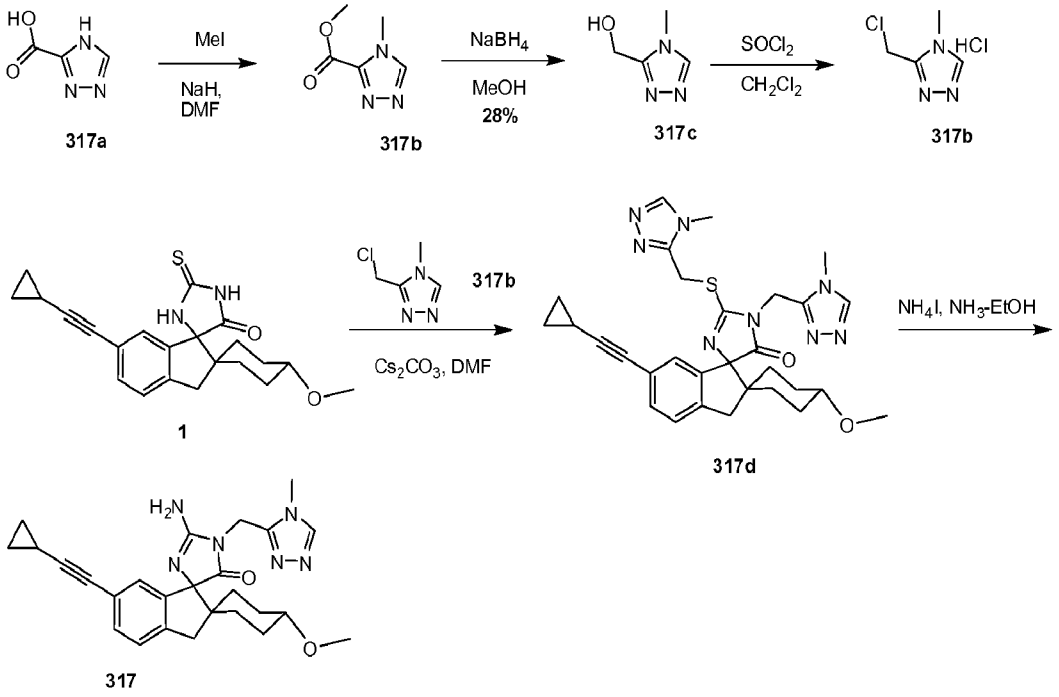
Compound **316b** (60 g, 0.12 mmol) was then converted to compound **316c** (20 mg, 34%) as a white solid.**LC-MS**: t_R = 1.716 min in 3 min chromatography, MS (ESI) m/z = 492 $[M+H]^+$.

Procedure for preparation of compound 316

A flask was charged with EtOAc (5 mL), the flask was immersed into ice-water for 5 min, and then dried HCl gas was bubbled into the flask at 0 °C for 5 min. After that, compound **316c** (18 mg, 0.037 mmol) was added and the resulting mixture was

stirred at ambient temperature overnight. The solvent was removed by evaporation *in vacuo* and the residue was purified by preparative HPLC (TFA as buffer) to give the product as a white solid with 90% purity, which was re-purified by preparative HPLC (TFA as buffer) to give pure **compound 316** (4.5 mg, 23%) as a white solid. **LC-MS**: t_R = 1.475 min in 3 min chromatography, MS (ESI) *m/z* = 436 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.33 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.25 (s, 1H), 3.94 (t, *J* = 5.7 Hz, 2H), 3.33 (s, 3H), 3.15 (m, 3H), 2.70 (m, 2H), 1.90-2.10 (m, 2H), 1.84 (m, 1H), 1.25-1.50 (m, 6H), 0.85 (m, 2H), 0.65 (m, 2H).

Example 266. Synthesis of Compound 317



Procedure for preparation of compound 317b

To a solution of compound **317a** (500 mg, 4.4 mmol) in anhydrous DMF (10 mL) was added NaH (318.5 mg, 13.2 mmol) and MeI (1.29 g, 8.8 mmol). The resulting suspension was stirred at 50 °C for 1 h in a CEM microwave reactor. Water (10 mL) was added and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **317b** (200 mg, 32%) as a yellow liquid which was used in the next step

without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.97 (s, 1H), 2.92 (s, 3H), 2.84 (s, 3H).

Procedure for preparation of compound 317c

To a solution of compound **317b** (200 mg, 1.41 mmol) in MeOH (5mL) was added $NaBH_4$ (214 mg, 5.67 mmol) under nitrogen, the reaction mixture was heated at reflux overnight. After cooling, water (2 mL) was added and the mixture was extracted with EtOAc (10 mL ×3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **317c** (50 mg, 28%) as a white solid which was used in the next step without further purification.**H NMR** (CD_3OD 400 MHz): δ 8.30 (s, 1H), 4.57 (s, 2H), 3.85 (s, 3H).

Procedure for preparation of compound 317d

To a solution of compound **317c** (50 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) was added $SOCl_2$ (58 mg, 0.48 mmol) at 0 °C. After addition, the mixture was warmed to ambient temperature and was stirred at room temperature overnight. The reaction was quenched with $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (5 mL × 3), washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **317d** (46 mg, 80%) as a yellow oil which was used in the next step without further purification.

Procedure for preparation of compound 317e

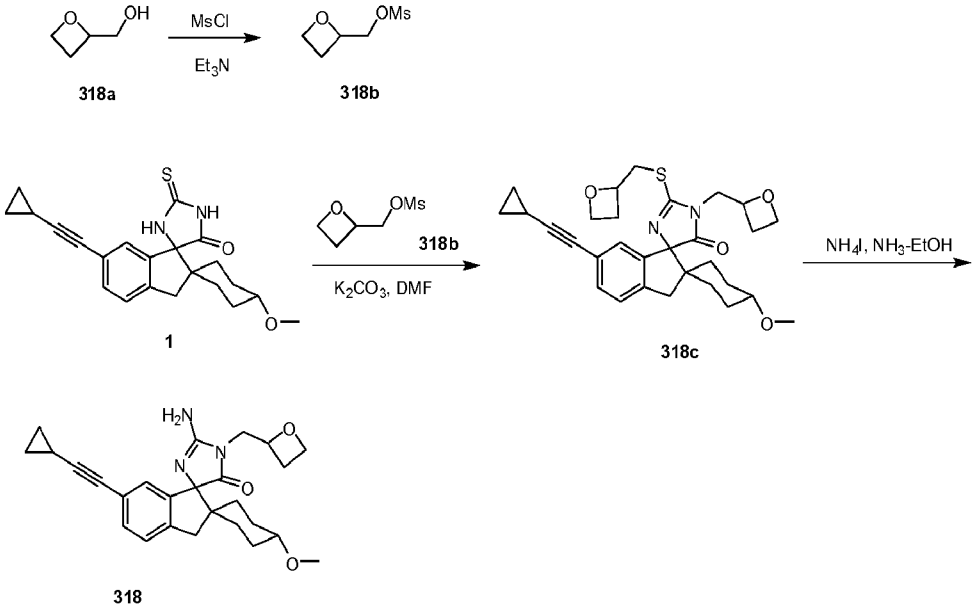
To a solution of compound **1** (20 mg, 0.052 mmol) in DMF (2 mL) was added Cs_2CO_3 (68 mg, 0.21 mmol) and compound **317d** (27.6 mg, 0.21 mmol), the reaction mixture was stirred at room temperature overnight. The mixture was filtered, and the filtrate was extracted with EA (10 mL × 3), washed with brine (30 mL), dried over Na_2SO_4, concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 1: 1 to give compound **317e** (10 mg, 33%) as a white solid. **LC-MS**: t_R = 1.153 min in 2 min chromatography, MS (ESI) *m/z* = 571.3 $[M+H]^+$.

Procedure for preparation of compound 317

A solution of compound **317e** (10 mg, 0.017 mmol), NH_4I (25 mg, 0.17 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated *in vacuo*, and the residue was purified

by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and by preparative HPLC to give **compound 317** (3.0 mg, 37%) as a white solid.**LC-MS**: t_R = 1.004 min in 2 min chromatography, MS (ESI) *m/z* = 459.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.32 (s, 1H), 7.31 (d, J = 8.0, Hz, 2H), 7.20 (s, 1H), 4.80 (s, 2H), 3.91-3.88 (s, 3H), 3.36 (s, 3H), 3.19-3.12 (m, 1H), 3.12 (s, 2H), 2.03-1.90 (m, 2H), 1.90-1.82 (m, 1H), 1.70-1.51 (m, 1H), 1.50-1.32 (m, 3H), 1.30-1.12 (m, 2H), 0.91-0.80 (m, 2H), 0.71-0.60 (m, 2H).

Example 267. Synthesis of Compound 318



Procedure for preparation of compound 318b

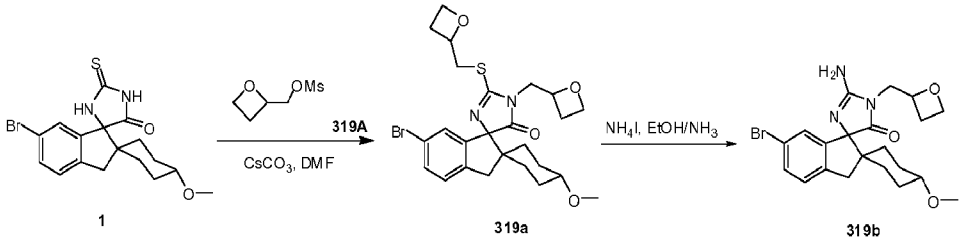
To a solution of compound **318a** (200 mg, 2.27 mmol) in CH_2Cl_2 (10 mL) was added MsCl (286 mg, 2.50 mmol) and Et_3N (689 mg, 6.81 mmol) at 0 °C, the mixture was stirred at 0 °C for 1 h. Then H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over Na_2SO_4 and concentrated to give compound **318b** as a yellow oil (160 mg, 42%), which was used for the next step without further purification.

Procedure for preparation of compound 318

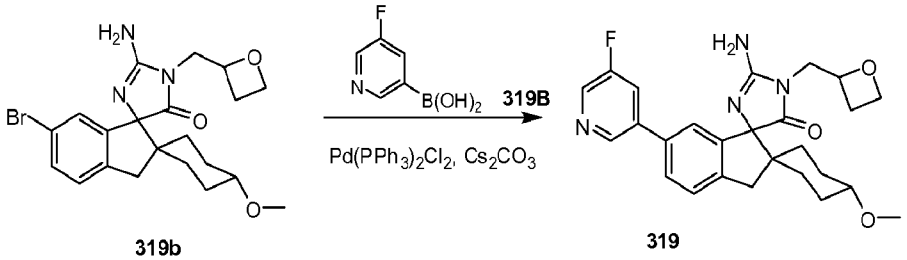
According to a similar synthesis of **compound 317**, compound **1** (200 mg, 0.53 mmol) was alkylated with compound **318b** (262 mg, 1.29 mmol) in the presence of Cs_2CO_3 (511 mg, 1.59 mmol) to give compound **318c** (200 mg, 73%) as a white solid.

Compound **318c** (200 mg, 0.38 mmol) was then converted to **compound 318** (50 mg, 30%) as a white solid. **LC-MS** t_R = 0.959 min in 2 min chromatography, MS (ESI) *m/z* 434 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.23 (m, 2H), 7.08 (m, 1H), 4.90 (m, 1H), 4.61 (m, 1H), 4.45 (m, 1H), 3.86 (m, 2H), 3.24 (s, 3H), 3.10 (m, 2H), 3.02 (m, 2H), 2.63 (m, 1H), 2.36 (m, 1H), 1.83 (m, 3H), 1.33 (m, 5H), 1.22 (m, 1H), 0.76 (m, 2H), 0.57 (m, 2H).

Example 268. Synthesis of Compound 319



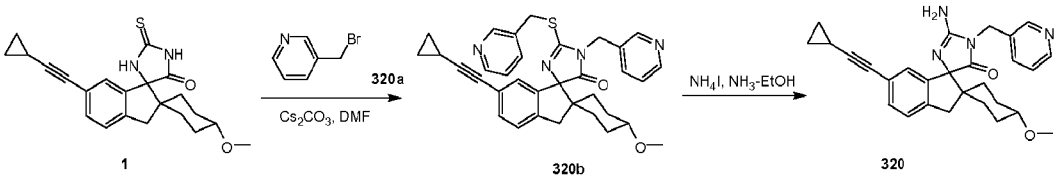
According to a similar synthesis of **compound 317**, compound **1** (150 mg, 0.38 mmol) was aklyated with compound **319A** (190 mg, 1.14 mmol) to give compound **319a** (151 mg, 74%) as a white solid. Compound **319a** (100 mg, 0.18 mmol) was reacted with NH_4I (217 mg, 1.49 mmol) in a solution of NH_3/EtOH (3 mL, 0.5 N) to give compound **319b** (50 mg, 59%) as a white solid.



Compound **319b** (20 mg, 0.04 mmol) in a 10 mL of flask under N_2 was treated sequentially with compound **319B** (12.6 mg, 0.08 mmol) in 1,4-dioxane (1 mL),

Cs_2CO_3 (2 N, 0.06 mL, 0.12 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mg). The mixture was heated at 120 °C at N_2 under microwave for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and HPLC (TFA buffer) to give **compound 319** (3.0 mg, 15%) as a white solid.**LC-MS** t_R = 0.930 min in 2 min chromatography, MS (ESI) *m/z* 465 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.57 (m, 1H), 8.35 (m, 1H), 7.84 (m, 1H), 7.65 (m, 1H), 7.50 (m, 1H), 7.45 (m, 1H), 4.92 (m, 1H), 4.60 (m, 1H), 4.46 (m, 1H), 3.92 (m, 2H), 3.26 (s, 3H), 3.15 (m, 1H), 3.12 (m, 2H), 2.55 (m, 1H), 2.39 (m, 1H), 1.98 (m, 3H), 1.39 (m, 4H), 1.23 (m, 1H).**^{19}F NMR** (CD_3OD 19F): δ -128.25.

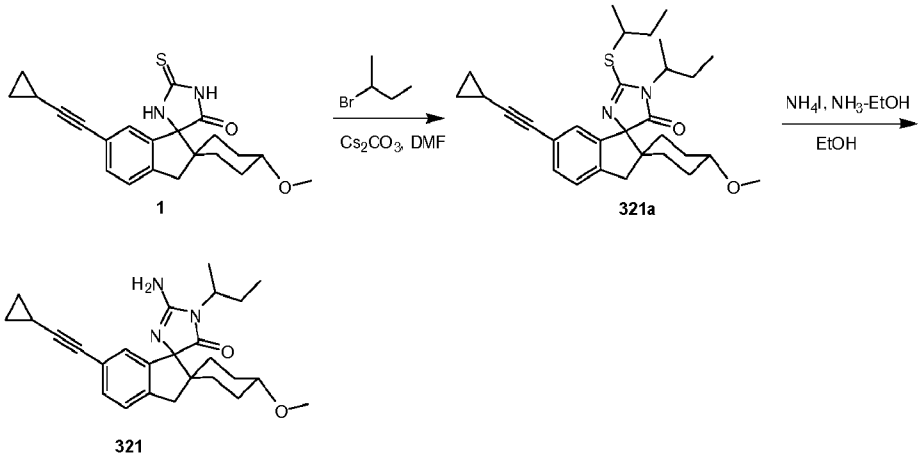
Example 269. Synthesis of Compound 320



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.076 mmol) was dialkylated with compound **320a** (79.8 mg, 0.315 mmol) to give compound **320b** (20 mg, 45%) as a yellow solid.**LC-MS** t_R = 1.003 min in 2 min chromatography, MS (ESI) *m/z* = 563.2 $[M+H]^-$.

Compound **320b** (20mg, 0.035 mmol) was then converted to **compound 320** (2.0 mg, 13%) as a white solid. **LC-MS** t_R = 0.918 min in 2 min chromatography, MS (ESI) *m/z* = 455.1 $[M+H]^+$.**^{1}H NMR** (CD_3OD, 400 MHz): δ 8.54 (s, 1H), 8.50-8.49 (d, *J* = 3.6 Hz, 1H), 7.85-7.75 (d, *J* = 7.2 Hz, 1H), 7.46-7.44 (m, 1H), 7.26-7.15 (m, 2H), 7.01-6.80 (s, 1H), 4.79 (s, 2H), 3.34 (s, 3H), 3.19-3.05 (m, 3H), 2.10-1.91 (m, 2H), 1.85-1.70 (m, 1H), 1.65-1.51 (m, 1H), 1.50-1.41 (m, 1H), 1.41-1.20 (m, 4H), 0.92-0.82 (m, 2H), 0.75-0.65 (m, 2H).

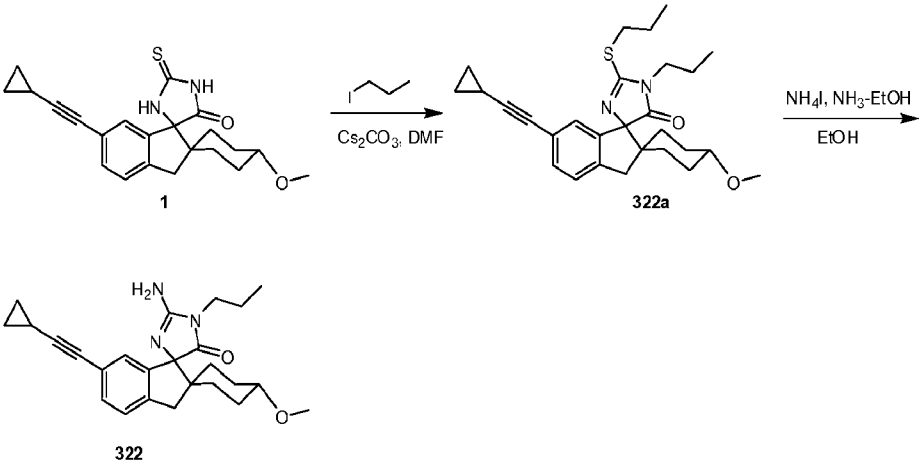
Example 270. Synthesis of Compound 321



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.079 mmol) was dialkylated with 2-bromo-butane (60 mg, 0.44 mmol) in DMF (2 mL) to give compound **321a** (38 mg, 97%) as a white solid, which was used directly in next step. **LC-MS**: t_R = 2.002 min in 3 min chromatography, MS (ESI) *m/z* = 493 $[M+H]^+$.

Compound **321a** (38 mg, 0.077 mmol) was then reacted with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (2 mL) to give **compound 321** (3.7 mg, 12%) as a white solid. **LC-MS**: t_R = 1.621 min in 3 min chromatography, MS (ESI) *m/z* = 420 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.13 (m, 2H), 6.79 (s, 1H), 3.85 (m, 1H), 3.23 (s, 3H), 3.03 (m, 1H), 2.99 (d, *J* = 16.0 Hz, 1H), 2.95 (d, *J* = 15.6 Hz, 1H), 1.93 (m, 2H), 1.88 (m, 2H), 1.67 (m, 2H), 1.15-1.45 (m, 8H), 0.82 (m, 5H), 0.61 (m, 2H).

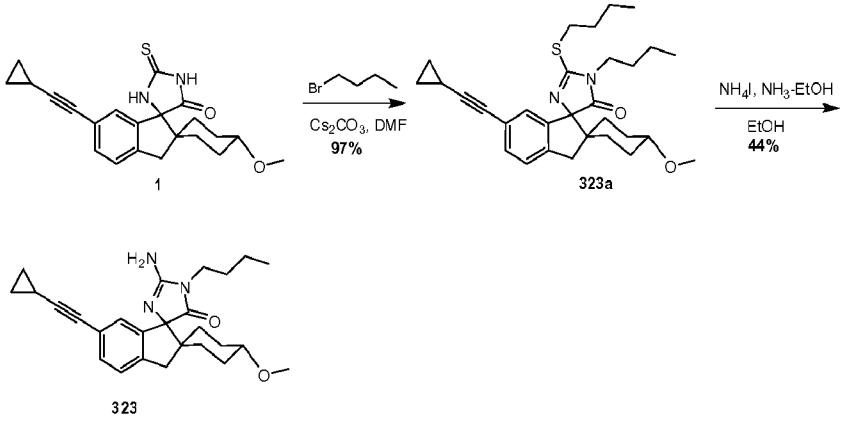
Example 271. Synthesis of Compound 322



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.079 mmol) was dialkylated to give compound **322a** (33 mg, 89%) as a pale yellow solid, which was used directly in next step. **LC-MS**: t_R = 1.862 min in 3 min chromatography, MS (ESI) *m/z* = 465 $[M+H]^+$.

Compound **322a** (33 mg, 0.071 mmol) was then converted to **compound 322** (14.3 mg, 50%) as a white solid. **LC-MS**: t_R = 1.561 min in 3 min chromatography, MS (ESI) *m/z* = 406 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.26 (m, 2H), 6.93 (s, 1H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 3.17 (m, 2H), 3.07 (d, *J* = 15.6 Hz, 1H), 2.03 (m, 2H), 1.87 (m, 1H), 1.67 (m, 3H), 1.25-1.50 (m, 5H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.87 (m, 2H), 0.73 (m, 2H).

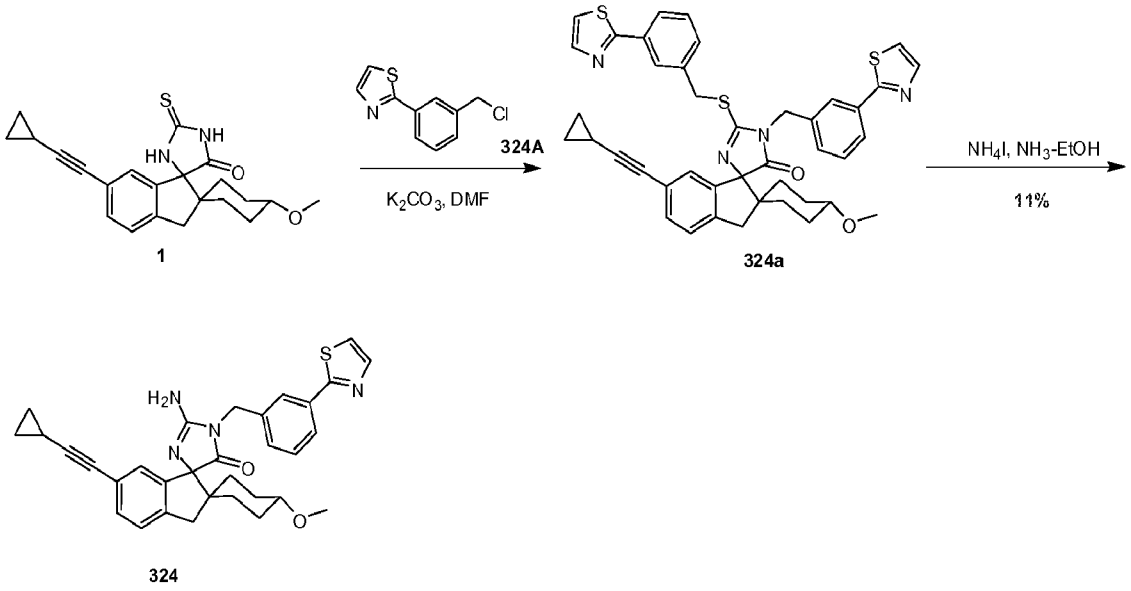
Example 272. Synthesis of Compound 323



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.079 mmol) was dialkylated to give compound **323a** (38 mg, 97%) as a white solid, which was used directly in next step. **LC-MS**: t_R = 2.010 min in 3 min chromatography, MS (ESI) *m/z* = 493 $[M+H]^+$.

Compound **323a** (38 mg, 0.077 mmol) was converted to **compound 323** (14.3 mg, 44%) as a white solid. **LC-MS**: t_R = 1.620 min in 3 min chromatography, MS (ESI) *m/z* = 420 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.16 (m, 2H), 6.82 (s, 1H), 3.45 (t, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 3.08 (m, 2H), 2.97 (d, *J* = 15.6 Hz, 1H), 1.93 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.55 (m, 3H), 1.25-1.40 (m, 7H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.79 (m, 2H), 0.63 (m, 2H).

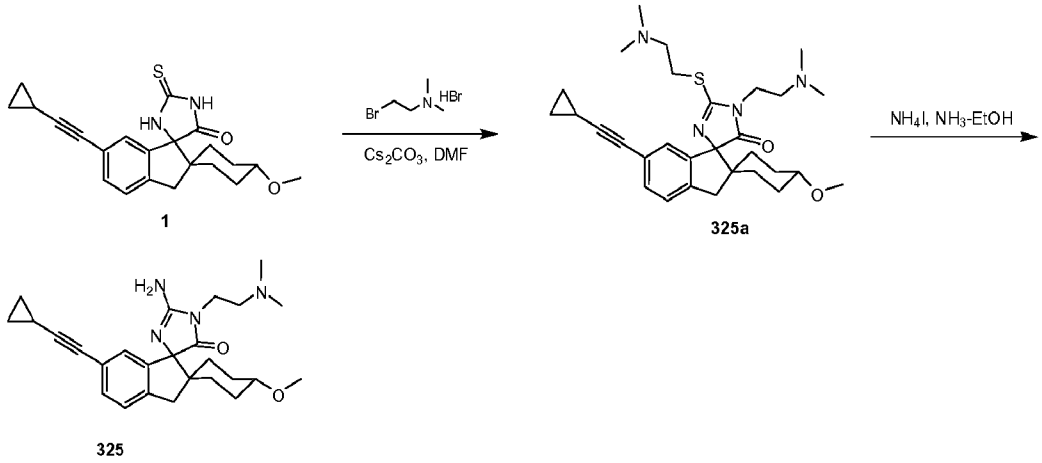
Example 273. Synthesis of Compound 324



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.080 mmol) was dialkylated with compound **324A** (35 mg, 0.17 mmol) in the presence of K_2CO_3 (54 mg, 0.40 mmol), to give compound **324a** (42 mg, 74%) as a white solid.

Compound **324a** (42 mg, 0.058 mmol) was then reacted with NH_4I (84 mg, 0.58 mmol) in NH_3-EtOH (2.5 mL) to give **compound 324** (3.3 mg, 11%) as a white solid. **LC-MS:** t_R = 1.127 min in 2 min chromatography, MS (ESI) *m/z* 537.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.94 (m, 2H), 7.88 (s, 1H), 7.67 (m, 1H), 7.55 (m, 2H), 7.35 (m, 2H), 7.24 (s, 1H), 4.90 (m, 2H), 3.32 (m, 3H), 3.16 (m, 3H), 2.02 (m, 2H), 1.82 (m, 1H), 1.47 (m, 5H), 1.32 (m, 1H), 0.90 (m, 2H), 0.072 (m, 2H).

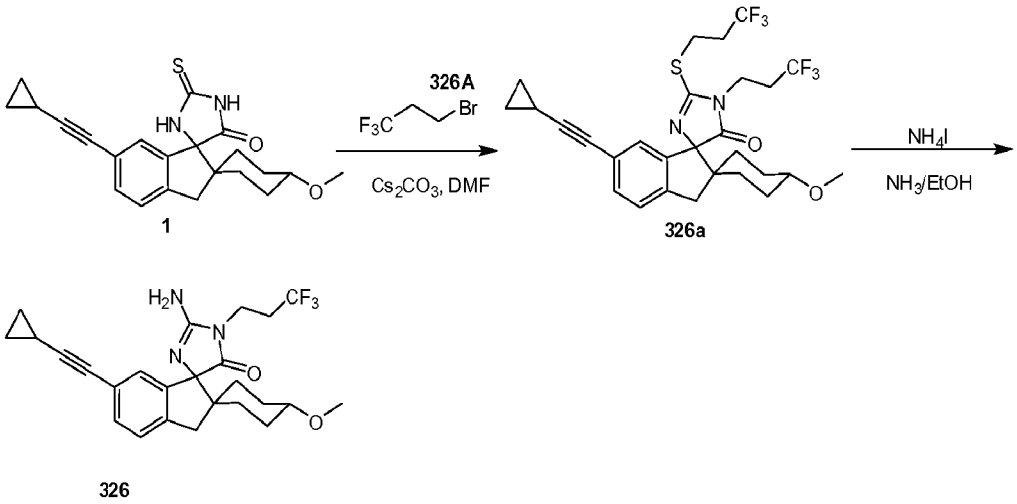
Example 274. Synthesis of Compound 325



According to a similar synthesis of **compound 317**, compound **1** (0.030 g, 0.079 mmol) was dialkylated with (2-Bromo-ethyl)-dimethyl-amine hydrobromide salt (0.25 g, 1.07 mmol) to give compound **325a** (15 mg, 10%) as a yellow oil.

Compound **325a** (15 mg, 0.029 mmol) was then reacted with NH_4I (50 mg, 0.35 mmol) and NH_3-EtOH (1 mL) to give **compound 325** (5.0 mg, 40%) as a white solid. **LC-MS**: t_R = 1.275 min in 3 min chromatography, MS (ESI) MS (ESI) *m/z* = 435 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.18 (dd, J = 1.2, 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.92 (s, 1H), 3.64 (t, J = 6.0 Hz, 2H), 3.26 (s, 3H), 3.08 (m, 1H), 2.95 (m, 2H), 2.55 (t, J = 6.0 Hz, 2H), 2.28 (s, 6H), 1.95 (m, 2H), 1.87 (m, 1H), 1.52 (m, 1H), 1.15-1.40 (m, 5H), 0.80 (m, 2H), 0.63 (m, 2H).

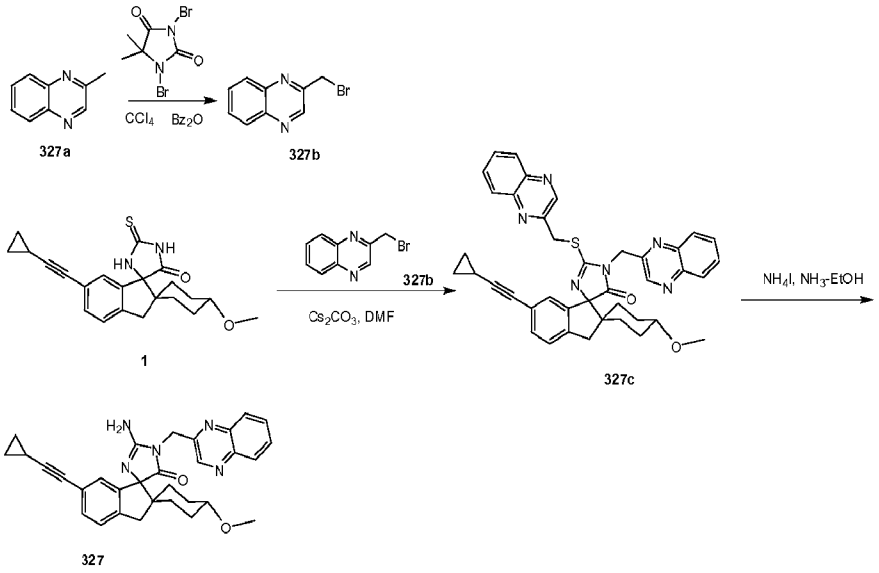
Example 275. Synthesis of Compound 326



According to a similar synthesis of **compound 317**, compound **1** (50 mg, 0.13 mmol) was dialkylated compound **326A** (70 mg, 0.13 mmol) to give compound **326a** (34 mg, 45%) as a white solid.

Compound **326a** (54 mg, 0.09 mmol) was then reacted with NH_4I (137 mg, 0.94 mmol) in NH_3/EtOH (2.5 mL) to give **compound 326** (3.3 mg, 8%) as a white solid.**LC-MS** t_R = 1.061 min in 2 min chromatography, MS (ESI) *m/z* 460.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.37 (m, 2H), 7.19 (s, 1H), 4.01 (m, 2H), 3.37 (s, 3H), 3.17 (m, 3H), 2.68 (m, 2H), 2.02 (m, 3H), 1.42 (m, 6H), 0.89 (m, 2H),0.71 (m, 2H). **^{19}F NMR** (CD_3OD 400 MHz): δ -77.05, -66.31.

Example 276. Synthesis of Compound 327



Procedure for preparation of compound 9

To a solution of compound **327a** (500 mg, 3.47 mmol) in anhydrous CCl_4 (10 mL) was added 1, 3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (694 mg, 2.42 mmol) and Bz_2O (92 mg, 0.38 mmol). The resulting suspension was heated at reflux for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to give compound **327b** (50 mg, 6%) as a yellow liquid.**^{1}H NMR** ($CDCl_3$ 300 MHz): δ 8.93 (s, 1H), 8.07-8.01 (m, 2H), 7.74-7.71 (m, 2H), 4.72 (s, 2H).

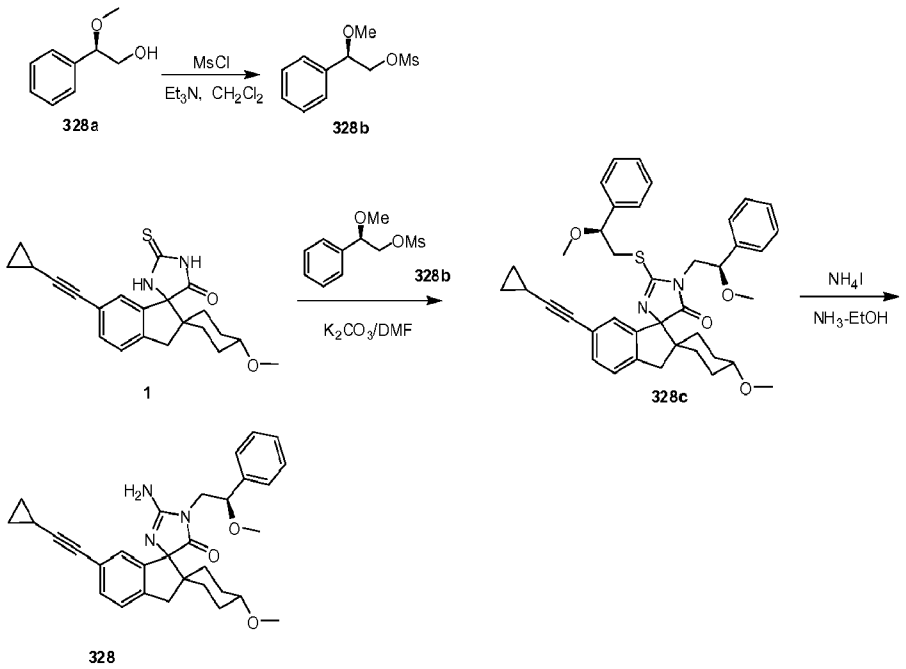
Procedure for preparation of compound 327

According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.076 mmol) was dialkylated with 2-(bromomethyl)quinoxaline (**327b**) to give compound **327c** (20 mg, 38%) as a yellow solid. **LC-MS**: t_R = 1.418 min in 2 min chromatography, MS (ESI) *m/z* 665.2 $[M+H]^+$.

Compound **327c** (20 mg, 0.03 mmol) was then converted to **compound 327** (2.20 mg, 14%) as a white solid. **LC-MS**: t_R = 0.935min in 2 min chromatography, MS (ESI) *m/z* 506.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.85-8.80 (s, 1H), 8.10-8.01 (m, 2H), 7.90-7.70 (m, 2H), 7.45-7.41 (s, 1H), 7.29-7.25 (dd, J = 1.6, 8.0 Hz, 1H), 7.25-

7.20 (d, J = 8.0 Hz, 1H), 5.40-5.30 (d, J = 19.6 Hz, 1H), 5.40-5.30 (d, J = 19.6 Hz, 1H), 3.28 (s, 3H), 3.20-3.10 (m, 2H), 3.05-2.95 (d, J = 19.6 Hz, 1H), 2.10-1.90 (m, 2H), 1.90-1.80 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1.30 (m, 4H), 1.30-1.10 (m, 1H), 0.91-0.81 (m, 2H), 0.72-0.61 (m, 2H).

Example 277. Synthesis of Compound 328



Procedure for preparation of compound 328b

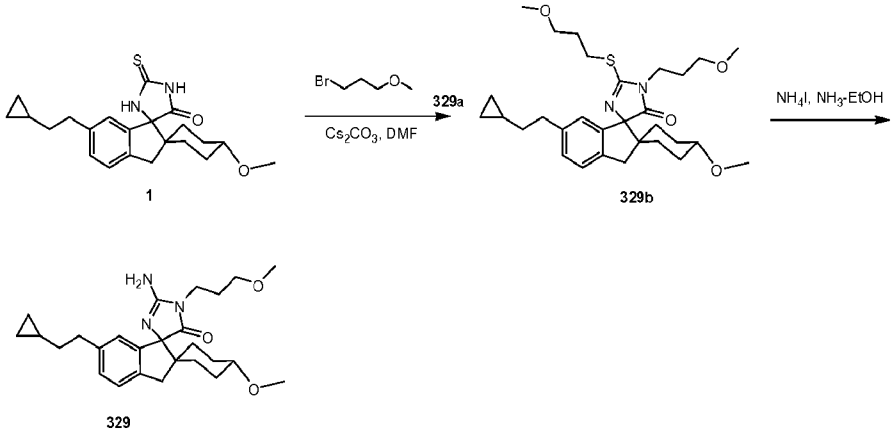
To a solution of compound **328a** (200 mg, 1.32 mmol) in CH_2Cl_2 (10 mL) was added MsCl (226 mg, 1.97 mmol) and Et_3N (266 mg, 2.63 mmol) at 0 °C, the mixture was stirred at 0 °C for 1 h. Then H_2O (20 mL) was added and extracted with EtOAc (3 × 20 mL), the organic layer was dried over Na_2SO_4 and concentrated to give compound **328b** (350 mg, crude) as a yellow oil, which was used for the next step without further purification.

Procedure for preparation of compound 328

According to a similar synthesis of **compound 317**, compound **1** (60 mg, 0.16 mmol) was diaklylated with compound **328b** (181 mg, 0.79 mmol), to give compound **328c** (100 mg, 98%).

Compound **328c** (125 mg, 0.19 mmol) was then reacted with NH_4I (280 mg, 1.93 mmol) in NH_3-EtOH (3 mL) to give **compound 328** (15.0 mg, 16%) as a white solid.**LC-MS**: t_R = 1.128 min in 2 min chromatography, MS (ESI) *m/z* = 498.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.40 (m, 6H), 7.31 (m, 1H), 7.08 (s, 1H), 4.53 (m, 1H), 3.99 (m, 1H), 3.87 (m,1H), 3.33 (s, 3H), 3.27 (d, *J* = 8.4 Hz, 3H), 3.18 (m, 2H), 3.09 (m, 1H), 2.03 (s, 2H), 1.68 (m, 1H),1.34 (m, 6H), 0.90 (m, 2H), 0.72 (m, 2H).

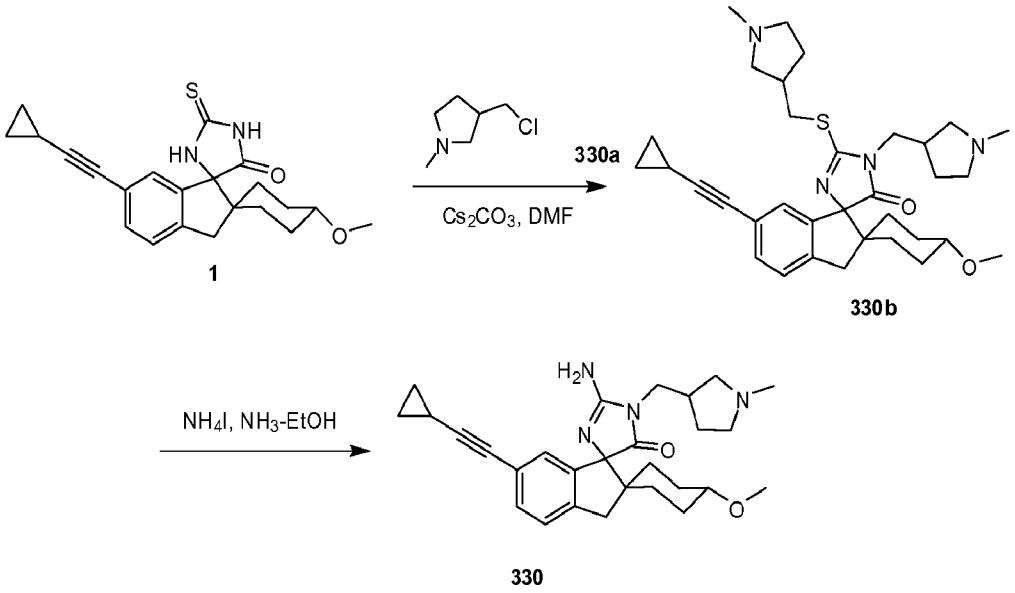
Example 278. Synthesis of Compound 329



According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.078 mmol) was diaklyated with 1-bromo-3-methoxy-propane (**329a**) (35 mg, 0.23 mmol) to give compound **329b** (25 mg, 61%) as a white solid.

Compound **329b** (25 mg, 0.048 mmol) was then reacted with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (2 mL) to give **compound 329** (18.3 mg, 87%) as a white solid. **LC-MS**: t_R = 1.604 min in 3 min chromatography, MS (ESI) *m/z* = 440 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): *δ* 7.18 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.78 (s, 1H), 3.59 (t, *J* = 6.8 Hz, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 3.33 (s, 3H), 3.15 (m, 1H), 3.09 (d, *J* = 15.6 Hz, 1H), 3.01 (d, *J* = 15.2 Hz, 1H), 2.91 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.80-2.10 (m, 5H), 1.61 (m, 1H), 1.25-1.50 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

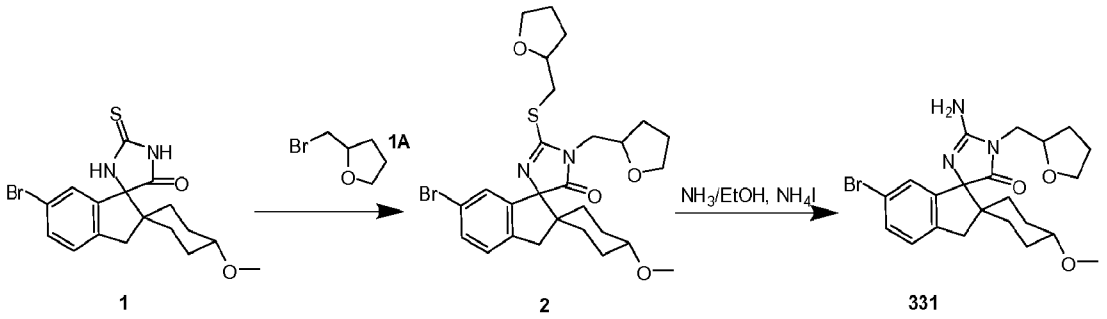
Example 279. Synthesis of Compound 330



According to a similar synthesis of **compound 317**, compound **1** (50 mg, 0.13 mmol) was dialkylated with 3-chloromethyl-1-methyl-pyrrolidine (**330a**) (52 mg, 0.39 mmol) to give compound **330b** (40 mg, 53%) as a pale yellow sticky oil.**LC-MS**: t_R = 1.166 min in 3 min chromatography, MS (ESI) *m/z* 575 $[M+H]^+$.

Compound **330b** (40 mg, 0.070 mmol) was then converted to **compound 330** (10.0 mg, 31%) as a white solid. **LC-MS**:, t_R = 1.298 min in 3 min chromatography, MS (ESI) *m/z* 461 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.21 (m, 2H), 6.88 (s, 1H), 3.52 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 3.16 (m, 2H), 3.07 (d, J = 12.8 Hz, 1H), 2.68 (m, 4H), 2.35 (m, 4H), 1.75-2.10 (m, 4H), 1.50-1.70 (m, 2H), 1.25-1.50 (m, 5H), 0.85-1.05 (m, 6H), 0.87 (m, 2H), 0.69 (m, 2H).

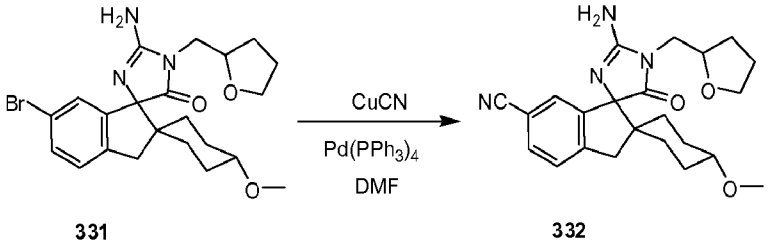
Example 280. Synthesis of Compound 331



According to a similar synthesis of **compound 317**, compound **1** (100 mg, 0.25 mmol) was dialkylated with compound **1A** (166 mg, 1.02 mmol) to give compound **2** (100 mg, 70%).

Compound **2** (100 mg, 0.18mmol) was then reacted with NH_4I (257.5 mg, 1.78 mmol) in NH_3/EtOH (5.0 N, 2mL) to give **compound 331** (25.1 mg, 31%) as a white solid.**LC-MS**: t_R = 0.953 min in 2 min chromatography, MS (ESI) *m/z* 462 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.54 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 1.6, 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 4.12 (m, 1H), 3.70-3.90 (m, 4H), 3.36 (s, 3H), 3.15 (m, 3H), 2.11-1.86 (m, 6H), 1.62 (m, 1H), 1.45 (m, 4H), 1.32 (m, 1H).

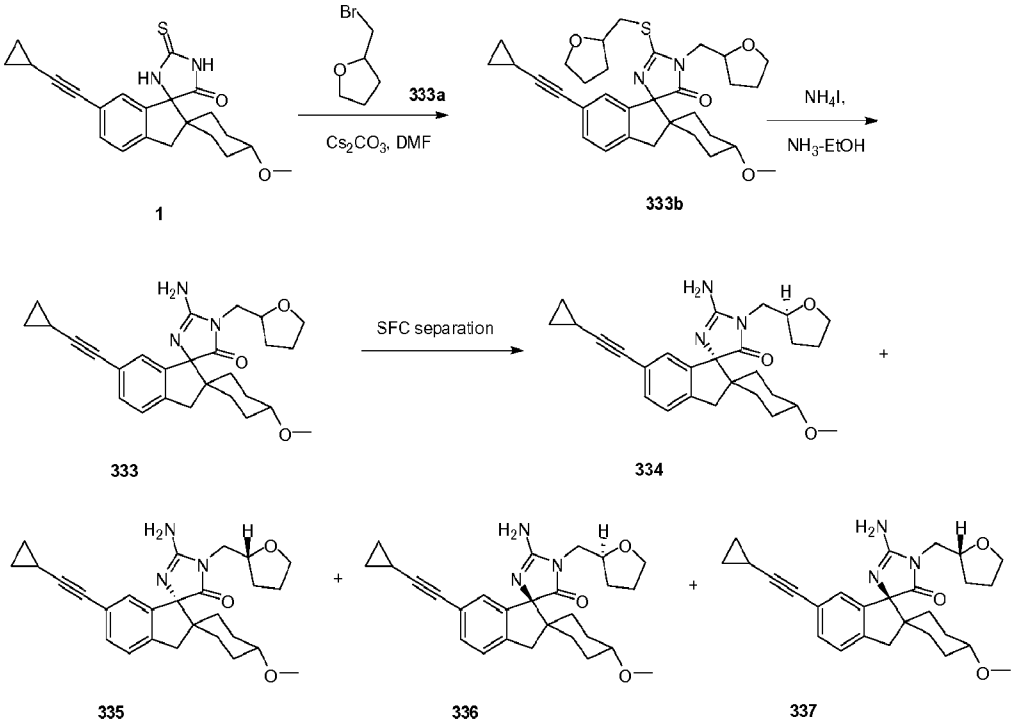
Example 281. Synthesis of Compound 332



To a solution of **compound 331** (25 mg, 0.054 mmol) in DMF (2 mL) was added CuCN (10 mg, 0.108 mmol) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) under N_2. The reaction mixture was heated at 180 °C for 40 min in a CEM microwave reactor. The reaction mixture was added water (20 mL) and extracted with EtOAc (30 mL), the combined organic layers were concentrated under reduced pressure and purified by HPLC (0.1% TFA as buffer) to give **compound 332** (5.7 mg, 41%) as a white solid. **LC-MS**: t_R = 0.892 min in 2 min chromatography, MS (ESI) *m/z* = 409 $[M+H]^+$.**^{1}H**

NMR (CD_3OD 400 MHz): δ 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 10.4 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 4.12 (m, 1H), 3.70-3.90 (m, 4H), 3.36 (s, 3H), 3.15 (m, 3H), 2.11-1.86 (m, 6H), 1.62 (m, 1H), 1.45 (m, 4H), 1.32 (m, 1H).

Example 282. Synthesis of Compounds 333, 334, 335, 336 and 337



According to a similar synthesis of **compound 317**, compound **1** (130 mg, 0.34 mmol) was alkylated with compound **333a** (225.7 mg, 1.36 mmol) to give compound **333b** (77 mg, 41%) as a white solid. **LC-MS** t_R = 1.408 min in 2 min chromatography, MS (ESI) m/z = 549.3 $[M+H]^-$.

Compound **333b** (20 mg, 0.036 mmol) was reacted with NH_4I (52.3 mg, 0.36 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 333** (2.00 mg, 12%) as a white solid. **LC-MS** t_R =1.162 min in 2 min chromatography, MS (ESI) m/z 448.4 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.36 (d, J = 7.6 Hz, 2H), 7.20 (s, 1H), 4.21-4.10 (m, 1H), 4.01-3.91 (m, 2H), 3.81-3.62 (m, 2H), 3.36 (s, 3H), 3.18-3.12 (m, 1H), 3.09-2.97 (d, J = 6.4 Hz, 2H), 2.20-2.01 (m, 2H), 2.00-1.80 (m, 3H), 1.70-1.51 (m, 1H), 1.50-1.30 (m, 5H), 1.30-1.20 (m, 2H), 0.95-0.82 (m, 2H), 0.82-0.62 (m, 2H).

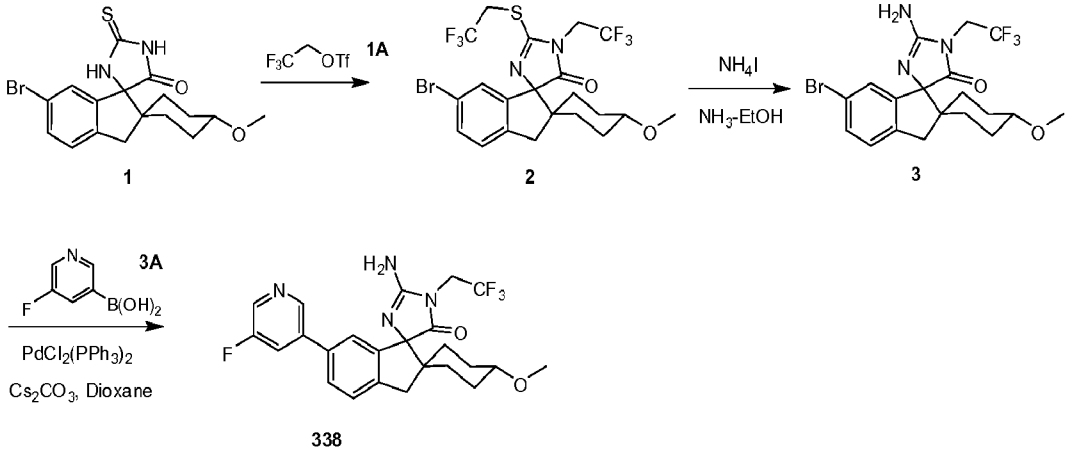
Another portion of compound **333b** (70 mg, 0.127 mmol) was reacted with NH_4I (183.3 mg, 1.27 mmol) in NH_3/EtOH and purified by preparative SFC to give compound **334** (3.20 mg, 6%) **LC-MS** t_R = 1.060 min in 2 min chromatography, MS (ESI) *m/z* = 448.2 $[M+H]^+$. **SFC**: t_R = 6.22 min in 15 min chromatography, ee = 86%. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.18 (s, 1H), 4.21-4.11 (m, 1H), 4.11-3.92 (m, 1H), 3.81-3.71 (m, 3H), 3.36 (s, 3H), 3.16-3.10 (m, 1H), 3.09-3.01 (d, *J* = 6.4 Hz, 2H), 2.20-1.85 (m, 6H), 1.72-1.51 (m, 1H), 1.50-1.30 (m, 5H), 1.31-1.21 (m, 1H), 0.93-0.82 (m, 2H), 0.82-0.61 (m, 2H).

& compound 335 (3.50 mg, 6%) **LC-MS** t_R = 1.022 min in 2 min chromatography, MS (ESI) *m/z* = 448.1 $[M+H]^+$; **SFC**: t_R = 6.49 min in 15 min chromatography, ee = 98%.**^{1}H NMR** (CD_3OD, 400 MHz): δ 7.30 (d, *J* = 7.6 Hz, 2H), 6.90 (s, 1H), 4.10-3.90 (m, 1H), 3.91-3.71 (m, 1H), 3.71-3.62 (m, 1H), 3.61-3.40 (m, 2H), 3.34 (s, 3H), 3.14-3.10 (m, 1H), 3.00-2.80 (d, *J* = 6.8 Hz, 2H), 2.01-1.70 (m, 6H), 1.60-1.40 (m, 2H), 1.40-1.10 (m, 5H), 0.80-0.71 (m, 2H), 0.70-0.51 (m, 2H).

& compound 336 (2.50 mg, 4%) **LC-MS** t_R = 1.053 min in 2 min chromatography, MS (ESI) *m/z* = 448.2 $[M+H]^+$. **SFC**: t_R = 6.95 min in 15 min chromatography, ee = 100%.**^{1}H NMR** (CD_3OD, 400 MHz): δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 4.10-3.90 (m, 1H), 3.90-3.71 (m, 2H), 3.71-3.62 (m, 1H), 3.62-3.50 (m, 1H), 3.34 (s, 3H), 3.16-3.14 (m, 1H), 3.08-2.96 (d, *J* = 8.4 Hz, 2H), 2.02-1.71 (m, 6H), 1.60-1.40 (m, 1H), 1.40-1.31 (m, 5H), 1.30-1.10 (m, 1H), 0.82-0.72 (m, 2H), 0.71-0.52 (m, 2H).

& compound 337 (2.80 mg, 5%) as white solid.**LC-MS** t_R =1.054 min in 2 min chromatography, MS (ESI) *m/z* = 448.2 $[M+H]^+$. **SFC**: t_R = 7.44 min in 15 min chromatography, ee = 92%.**^{1}H NMR** (CD_3OD, 400 MHz): δ 7.32 (d, *J* = 7.6 Hz, 2H), 7.15 (s, 1H), 4.10-3.91(m, 1H), 3.90-3.81 (m, 1H), 3.80-3.60 (m, 3H), 3.35 (s, 3H), 3.18-3.10 (m, 1H), 3.08-2.98 (d, *J* = 7.6 Hz, 2H), 2.10-1.71 (m, 6H), 1.60-1.40 (m, 1H), 1.40-1.21 (m, 5H), 1.20-1.10 (m, 1H), 0.82-0.72 (m, 2H), 0.72-0.62 (m, 2H).

Example 283. Synthesis of Compound 338



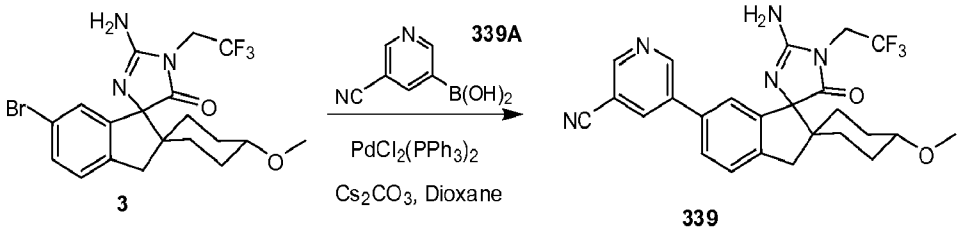
According to a similar synthesis of **compound 317**, compound **1** (40 mg, 0.10 mmol) was dialkylated with compound **1A** (47 mg, 0.2 mmol) to give compound **2** (43 mg, 76%) as a white solid.

Compound **2** (43 mg, 0.08 mmol) was reacted with NH_4I (112 mg, 0.77 mmol) in NH_3/EtOH (2.5 mL) to give compound **3** (13 mg, 37%) as a white solid.

Procedure for preparation of 338

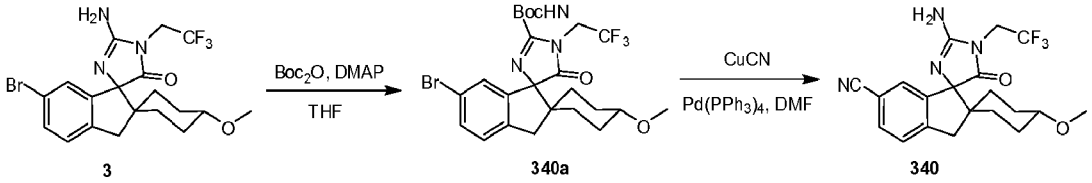
A suspension of compound **3** (13 mg, 0.03 mmol), compound **3A** (6 mg, 0.04 mmol), $PdCl_2(PPh_3)_2$ (2 mg) and Cs_2CO_3 (0.2 mL, 2 N in water) in 1,4-dioxane (0.72 mL) was heated under 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by acid preparative preparative HPLC to give **compound 338** (3.0 mg, 22%) as a white solid.**LC-MS** t_R = 0.841 min in 2 min chromatography, MS (ESI) *m/z* 477.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.71 (s, 1H), 8.49 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.75 (m, 1H), 7.64(m, 1H), 7.56(d, J = 6.8 Hz, 1H), 4.31 (m, 2H), 3.39 (s, 3H), 3.25 (m, 3H), 2.14 (m, 3H),1.47 (m, 5H).**^{19}F NMR** (CD_3OD 400 MHz): δ -73.34, -77.21, -128.26.

Example 284. Synthesis of Compound



A suspension of compound **3** described in Example 283 (30 mg, 0.07 mmol), compound **339A** (15 mg, 0.10 mmol), $PdCl_2(PPh_3)_2$ (5 mg) and Cs_2CO_3 (0.5 mL, 2 N in water) in 1,4-dioxane (1.7 mL) was heated under 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by acid preparative preparative HPLC to give **compound 339** (7.4 mg, 23%) as a white solid. **LC-MS** t_R = 2.686 min in 2 min chromatography, MS (ESI) *m/z* 484.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.09 (s, 1H), 8.91 (s, 1H), 8.47 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.65(s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 4.68 (m, 1H), 4.54 (m, 1H), 3.38(m, 3H), 3.33(m, 3H), 2.07 (m, 3H), 1.48 (m, 5H). **^{19}F NMR** (CD_3OD 400 MHz): δ -77.14, -71.99.

Example 285. Synthesis of Compound 340



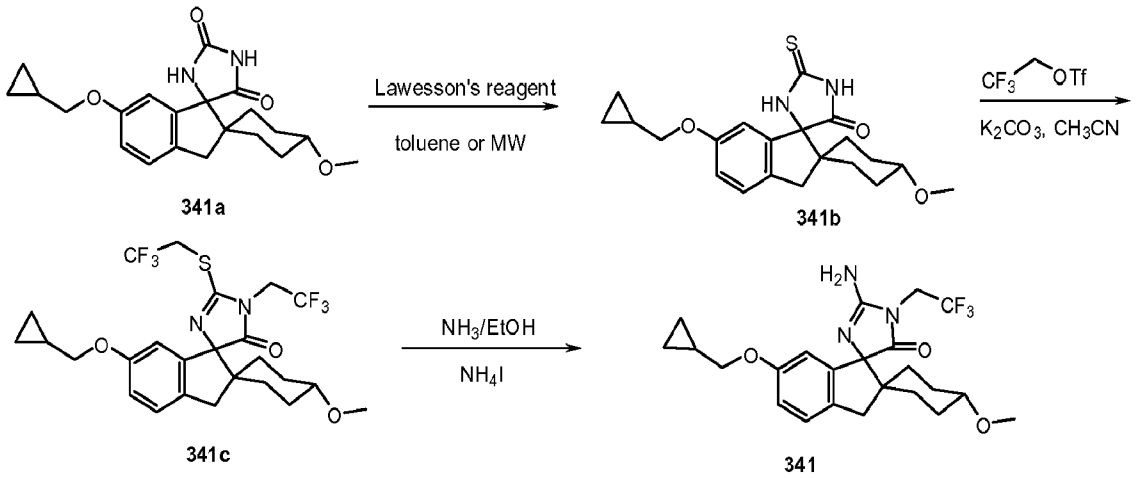
Procedure for preparation of compound 340a

A mixture of compound **3** described in Example 283 (15 mg, 0.033 mmol, crude), Boc_2O (14 mg, 0.066 mmol) and DMAP (0.008 g, 0.066 mmol) in THF (3 mL) was stirred at ambient temperature overnight. The solvent was removed by evaporation to yield the crude product which was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 3: 1 to afford compound **340a** (17 mg, 71%) as a white solid.**LC-MS:** t_R = 1.609 min in 2 min chromatography, MS (ESI) *m/z* 504, 506 $[M-56]^+$

Procedure for preparation of compound 340

A sealed tube was charged with compound **340a** (17 mg, 0.03 mmol), CuCN (30 mg, 0.33 mmol), $Pd(PPh_3)_4$ (2 mg, 0.0017 mmol) and DMF (1 mL) in turn under nitrogen. The tube was heated at 180 °C in a CEM microwave reactor for 1.5 h. Ethyl acetate (10 mL) and methanol (1 mL) were added with stirring, and the resulting precipitate was filtered off and washed with ethyl acetate (10 mL). The filtrate and washings were combined and washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give pure **compound 340** (6.2 mg, 51%) as a white solid. **LC-MS:** t_R = 1.527 min in 3 min chromatography, MS (ESI) *m/z* 407, $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.66 (d, *J*=8.0 Hz, 1H), 7.52 (d, *J* = 7.6, Hz, 2H), 7.32 (s, 1H), 4.37 (d, *J* = 8.8 Hz, 1H), 4.32 (d, *J* = 8.8 Hz, 1H), 3.38 (s, 3H), 3.22 (m, 3H), 1.99 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H), 1.45 (m, 1H), 1.35 (m, 3H). **^{19}F NMR** (CD_3OD, 400 MHz) δ -71.96

Example 286. Synthesis of Compound 341



Procedure for preparation of Compound 341b

To a solution of compound **341a** (80 mg, 0.21 mmol) in anhydrous toluene (2 mL) was added Lawesson's Reagent (84.8 mg, 0.21 mmol) under N_2, the mixture was stirred at 110 °C for 3h. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1

to afford compound **341b** (50 mg, 60%) as a white solid.**LCMS**: t_R = 1.258 min in 2 min chromatography, MS (ESI) *m/z* = 387.2$(M+H)^+$.

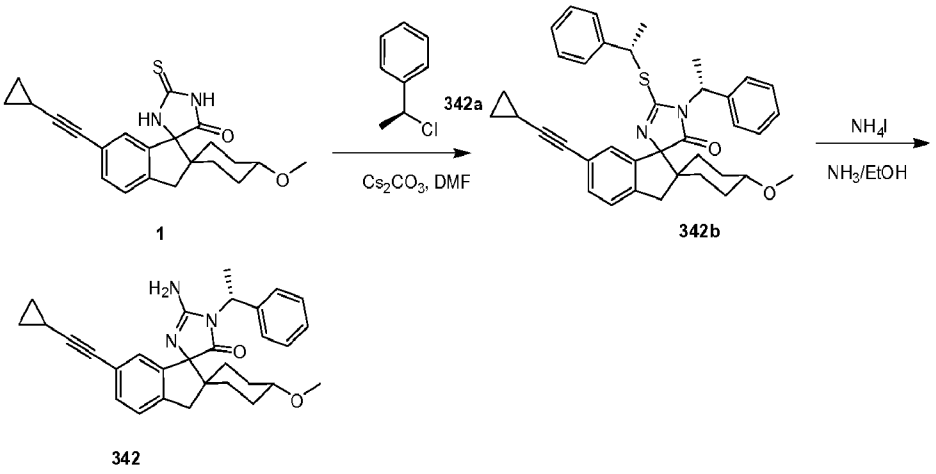
Procedure for preparation of Compound 341c

To a solution of compound **341b** (20 mg, 0.05 mmol) in CH_3CN (2 mL) was added K_2CO_3 (27.6 mg, 0.20 mmol). After stirring for 5 min, compound **341b** (48 mg, 0.20 mmol) was added. The reaction mixture was heated at 60 °C for 4 h. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to give compound **341c** (20 mg, 70%) as a white solid.***LCMS***: t_R = 1.622 min in 2 min chromatography, MS (ESI) *m/z* = 551.2 $(M+H)^+$.

Procedure for preparation of compound 341

A solution of compound **341c** (20 mg, 0.036 mmol), NH_4I (50 mg, 0.36 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and preparative HPLC to give **compound 341** (2.0 mg, 20%) as a white solid. **LCMS**: t_R = 1.968 min in 3 min chromatography, MS (ESI) *m/z* = 452.2 $(M+H)^+$. **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.20 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 1H), 4.36 (m, 2H), 3.77 (d, *J* = 8.0 Hz, 2H), 3.36 (s, 3H), 3.27-3.17 (m, 1H), 3.05-2.97 (s, 2H), 2.10-1.98 (m, 2H), 1.97-1.86 (m, 1H), 1.60-1.57 (m, 1H), 1.57-1.44 (m, 2H), 1.34-1.20 (m, 3H), 0.7-0.50 (m, 2H), 0.40-0.20 (m, 2H).**^{19}F NMR** (CD_3OD): δ: -66.52

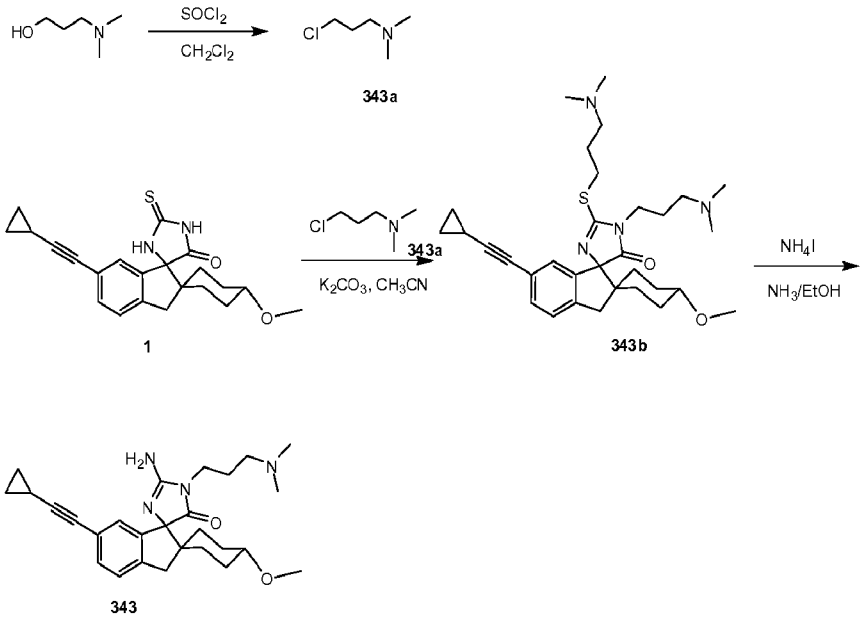
Example 287. Synthesis of Compound 342



According to a similar synthesis of **compound 317**, compound **1** (40 mg, 0.10 mmol) was dialkylated with (S)-(1-chloroethyl)benzene (**342a**) to give compound **342b** (15 mg, 24%) as a white solid.**LC-MS**: t_R = 1.812 min in 2 min chromatography, MS (ESI) *m/z* = 589.3 $[M+H]^+$.

Compound **342b** (15 mg, 0.025 mmol) was then converted to **compound 342** (2.00 mg, 16%) as a white solid.**LC-MS**: t_R = 0.988 min in 2 min chromatography, MS (ESI) *m/z* = 468.1 $[M+H]^+$.^{1}**H NMR** (CD_3OD 400 MHz): δ 7.48-6.95 (m, 8H), 5.38-5.32 (m, 1H), 3.31 (s, 3H), 3.09-3.01 (m, 1H), 3.00-2.93 (m, 2H), 2.10-1.89 (m, 1H), 1.88-1.70 (m, 3H), 1.60-1.20 (m, 5H), 1.20-0.9 (m, 3H), 0.90-0.80 (m, 2H), 0.7-0.6 (m, 2H).

Example 288. Synthesis of Compound 343



Procedure for preparation of compound 20

To a solution of 3-dimethylamino-propan-1-ol (1.0 g, 9.7 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $SOCl_2$ (1.26 g, 10.6 mmol) at 0 °C under N_2. After addition, the mixture was warmed to room temperature and was stirred at room temperature overnight. The solvent was removed *in vacuo* to give compound **343a** (0.94 g, 80%) as a white solid, which was used for the next step without further purification.**^{1}H NMR** ($CDCl_3$ 300 MHz): δ 3.84-3.5 (t, J = 6.3 Hz, 2H), 3.40-3.10 (m, 2H), 3.0-2.60 (d, J = 5.1 Hz, 6H), 2.50-2.20 (m, 2H).

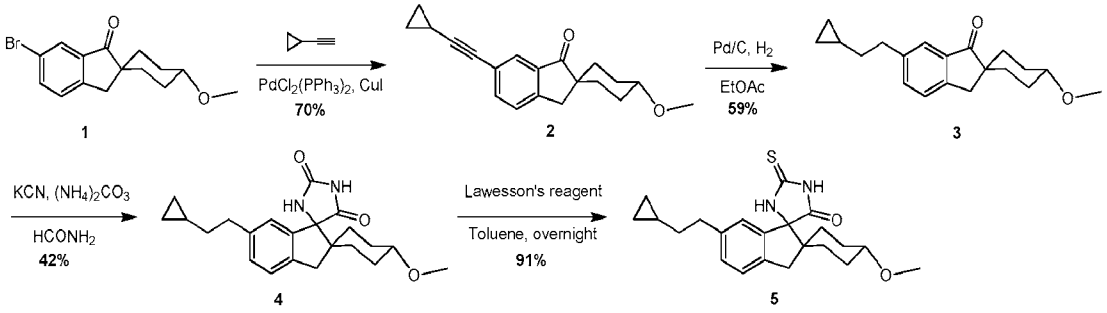
Procedure for preparation of compound 343

According to a similar synthesis of **compound 317**, compound **1** (30 mg, 0.078 mmol) was dialkylated with compound **343a** (38 mg, 0.32 mmol) to give compound **343b** (0.021 g, 50%) as a white solid. **LC-MS:** t_R = 0.782 min in 2 min chromatography, MS (ESI) m/z = 551.4 $[M+H]^+$.

Compound **343b** (20 mg, 0.036 mmol) was then reacted with NH_4I (52.1 mg, 0.36 mmol) and NH_3-EtOH (2 mL) to give **compound 343** (2.50 mg, 15%) as a white solid. **LC-MS**: t_R = 1.863 min in 3 min chromatography, MS (ESI) m/z = 449.3

$[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.27 (s, 2H), 6.90-6.80 (s, 1H), 3.50-3.41 (m, 2H), 3.36 (s, 3H), 3.16 (m, 2H), 3.09-2.91 (d, 15.6 Hz, 1H), 2.60-2.40 (m, 2H), 2.40-2.30 (s, 3H), 2.30-2.20 (s, 3H), 2.00-1.85 (m, 3H), 1.85-1.75 (m, 2H), 1.40-1.30 (m, 4H), 1.30-1.20 (m, 2H), 0.85-0.75 (m, 2H), 0.65-0.55 (m, 2H).

Example I-6 Synthesis of thiohydantoin intermediate



Procedure for preparation of compound 2

A flask equipped with a condenser and a nitrogen balloon was charged with compound **1** (7.5 g, 24.3 mmol), Et_2NH (20 mL), Et_3N (100 mL), $Pd(PPh_3)_2Cl_2$ (1.0 g, 1.5 mmol), CuI (0.29 g, 1.5 mmol) and Ethynyl cyclopropane (15 mL) in turn under nitrogen. The reaction mixture was stirred at 60 °C overnight. After cooling down, the solvent was removed by evaporation *in vacuo*. The residue was added ethyl acetate (150 mL), and then the mixture was filtered through a pad of silica gel and washed with ethyl acetate (50 mL × 2). The combined organic filtrates were washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate (100: 1 to 10: 1) to give compound **2** (5.0 g, 70%) as a red-brown solid. **^{1}H NMR**: ($CDCl_3$ 300 MHz): δ 7.75 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 3.42 (s, 3H), 3.25 (m, 1H), 3.00 (s, 2H), 2.15 (m, 2H), 1. 85 (m, 2H), 1.35-1.55 (m, 5H), 0.75-0.95 (m, 4H).

Procedure for preparation of compound 3

A mixture of compound **2** (4.0 g, 13.6 mmol), Pd/C (1.0 g), ethyl acetate (200 mL) and MeOH (20 mL) was stirred at temperature under 1 atm hydrogen atmosphere for 24 h. The precipitate was filtered off and washed with ethyl acetate (100 mL × 2).

The filtrate was concentrated by evaporation *in vacuo*. The residue was purified by preparative HPLC to give compound **3** (2.4 g, 59%) as a pale yellow oil. **LC-MS**: t_R = 2.371 min in 3 min chromatography, MS (ESI) *m/z* = 299 $[M+H]^+$. **^{1}H NMR**: ($CDCl_3$ 300 MHz): δ 7.65 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 3.36 (s, 3H), 3.27 (m, 1H), 2.95 (s, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.15 (m, 2H), 1. 75 (m, 2H), 1.25-1.55 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

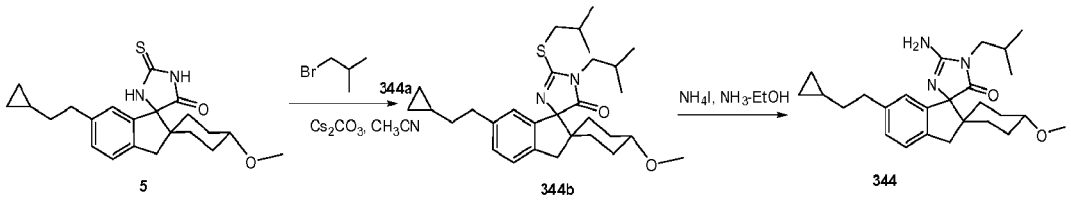
Procedure for preparation of compound 4

A steel autoclave was charged with a mixture of compound **3** (2.1 g, 7.0 mmol), $(NH_4)_2CO_3$ (4.0 g, 41.7 mmol), formamide (60 mL) and KCN (1.2 g, 18.5 mmol), carefully. The mixture was heated at 120-130 °C for 72 h. After cooling down, the reaction mixture was poured into ice-water (300 mL). The mixture was extracted with ethyl acetate (contained 20% iso-propanol) (200 mL × 3), and the combined organic layers were washed with brine (200 mL × 3). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound as a yellow oil, which was purified by preparative HPLC to give pure compound **4** (1.1 g, 42%) as a pale yellow oil. **LC-MS**: t_R = 1.747 min in 3 min chromatography, MS (ESI) *m/z* = 369 $[M+H]^+$. **^{1}H NMR:** ($CDCl_3$ 400 MHz): δ 8.45, (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.95 (s, 1H), 6.10 (s, 1H), 3.35 (s, 3H), 3.10 (m, 2H), 2.90 (d, J = 15.2, 1H), 2.60 (t, J = 7.6 Hz, 2H), 1.90-2.10 (m, 3H), 1.40-1.50 (m, 4H), 1.30-1.40 (m, 3H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Procedure for preparation of compound 5

A flask equipped with a condenser and a nitrogen balloon was charged with a mixture of compound **4** (1.1 g, 2.98 mmol), Lawesson's reagent (1.3 g, 3.21 mmol) in anhydrous toluene (15 mL) under nitrogen. The mixture was heated at 130 °C for 2 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate (50:1 to 5:1) to give compound **5** (1.0 g, 91%) as a white solid. **LC-MS**: t_R = 2.037 min in 3 min chromatography, MS (ESI) *m/z* = 385 $[M+H]^+$.

Example 289. Synthesis of Compound 344



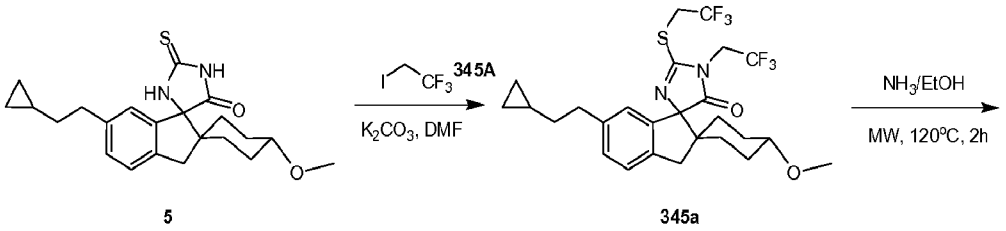
Procedure for preparation of compound 344a

A sealed tube was charged with a mixture of compound **5** described in Example I-6 (30 mg, 0.078 mmol), DMF (2 mL), Cs_2CO_3 (0.10 g, 0.31 mmol) and 1-bromo-2-methyl-propane (50 mg, 0.36 mmol). The mixture was heated at 80 °C for 2.5 h. After cooling down, H_2O (30 mL) was added and the mixture was extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate (4: 1) to give compound **344b** (28 mg, 72%) as a pale yellow solid. **LC-MS**: t_R = 2.695 min in 3 min chromatography, MS (ESI) *m/z* = 497 $[M+H]^+$.

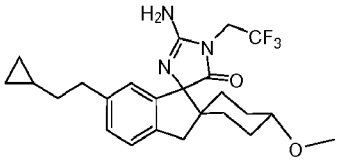
Procedure for preparation of compound 344

A sealed tube was charged with a mixture of compound **344b** (28 mg, 0.056 mmol), NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (1 mL). The mixture was heated at 120 °C in a CEM microwave reactor for 2 h. After cooling down, Ethyl acetate (30 mL) was added and the mixture was washed brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 344** (10.2 mg, 42%) as a white solid; **LC-MS**: t_R = 4.207 min in 7 min chromatography, MS (ESI) *m/z* = 424 $[M+H]^+$.**^{1}H NMR**: (CD_3OD, 300 MHz): δ 7.19 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 3.34 (s, 3H), 3.10 (m, 2H), 3.02 (d, J = 15.2 Hz, 1H), 2.67 (t, J = 7.6 Hz, 2H), 1.75-2.20 (m, 5H), 1.50-1.70 (m, 2H), 1.25-1.50 (m, 6H), 0.85-1.05 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Example 290. Synthesis of Compound 345



5 345a

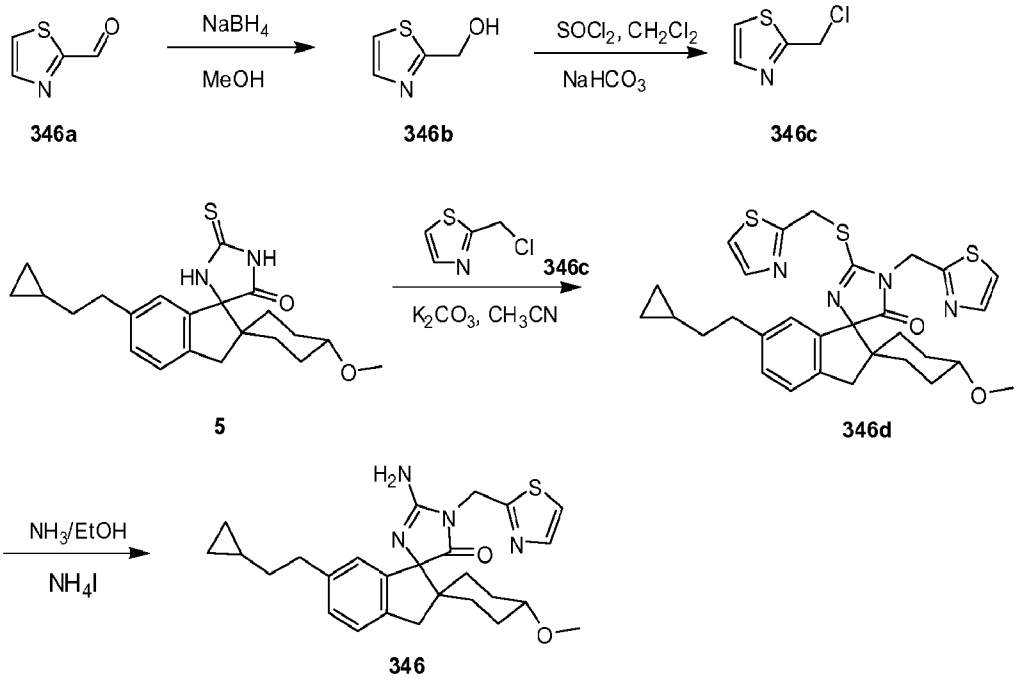


345

According to a similar synthesis of **compound 344**, compound **5** describe in Example I-6 (50 mg, 0.13 mmol) was dialkylated with compound **345A** (109 mg, 0.52 mmol) to give compound **345a** (29 mg, 41%) as a white solid.

Compound **345a** (29mg, 0.053mmol) was then reacted with NH_4I (77mg, 0.53mmol) in saturated NH_3/EtOH (2 mL) to give **compound 345** (3.20 mg, 13%) as a white solid. **LC-MS** t_R = 1.095 min in 2 min chromatography, MS (ESI) *m/z* 450.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.18-7.20 (d, J = 7.6 Hz, 1H), 7.09-7.11 (d, J = 7.6 Hz, 1H), 6.82 (s, 1H), 4.28-4.35 (m, 2H), 3.36 (s, 3H), 3.09-3.15 (m, 1H), 3.04-3.05 (d, J = 5.2 Hz, 2H), 2.64-2.68 (t, J = 7.6 Hz, 2H), 1.95-2.02 (m, 2H), 1.84-1.86 (m, 1H), 1.56-1.59 (t, J = 14.0 Hz,1H), 1.35-1.47 (m, 4H), 1.28-1.31 (d, 2H), 0.64-0.68 (m, 1H), 0.38-0.41 (m, 2H), 0.02 (m, 2H). **^{19}F NMR** (CD_3OD 19F): δ -71.87.

Example 291. Synthesis of Compound 346



Procedure for preparation of Compound 346b

To a solution of compound **346a** (300 mg, 2.65 mmol) in MeOH (30 mL) was added $NaBH_4$ (0.2 g, 5.26 mmol) at 0 °C. After addition, the mixture was warmed to room temperature and was stirred at room temperature for 1 h. The reaction was quenched with H_2O (10 mL) and the solvent was removed *in vacuo*. The residue was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **346b** (200 mg, 66%) as a yellow solid which was used in the next step without further purification. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 7.81 (d, J = 3.3 Hz, 1H), 7.71 (d, J = 3.0 Hz, 1H), 4.82-4.80 (d, J = 6.0 Hz, 2H).

Procedure for preparation of Compound 346c

To a solution of compound **346b** (70 mg, 0.60 mmol) in CH_2Cl_2 (2 mL) was added $SOCl_2$ (79.6 mg, 0.66 mmol) at 0 °C, After addition, the mixture was warmed to room temperature and was stirred at room temperature temperature overnight. The reaction was quenched with aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (5 mL

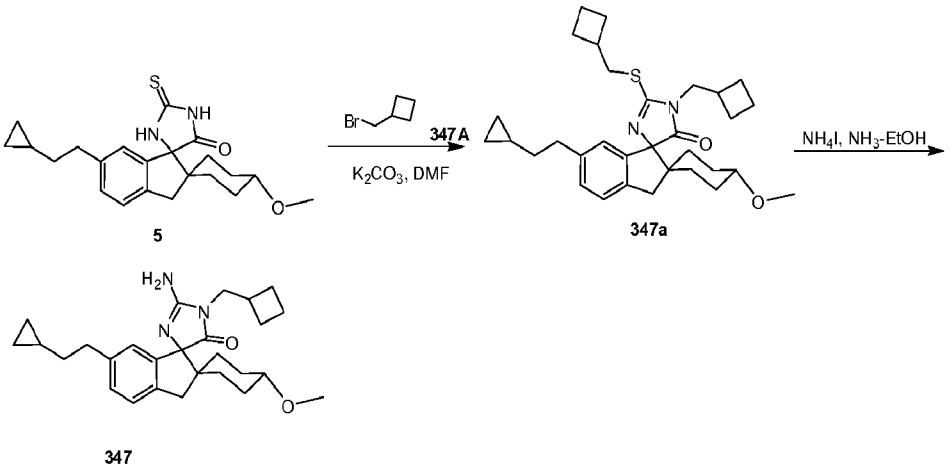
× 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to give compound **346c** (56.9 mg, 70%) as a yellow oil which was used in the next step without further purification.

Procedure for preparation of compound 346

According to a similar synthesis of **compound 344**, compound **5** (20 mg, 0.05 mmol) was alkylated with compound **346c** (27.6 mg, 0.20 mmol) to give compound **346d** (20 mg, 66%) as a white solid.**LCMS** : t_R = 1.555 min in 2 min chromatography, MS (ESI) *m/z* = 579.2 $[M+H]^+$.

Compound **346d** (20 mg, 0.034 mmol) was then reacted with NH_4I (49.6 mg, 0.34 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 346** (3.00 mg, 19%) as a white solid. **LCMS**: t_R = 1.204 min in 2 min chromatography, MS (ESI) *m/z* = 465.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.77 (d, *J* = 6.4 Hz, 1H), 7.76 (d, *J* = 3.2 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H),7.21 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 5.27 (s, 2H), 3.34 (s, 3H), 3.24-3.20 (m, 1H), 3.11-3.04 (d, *J* = 10.4 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.10-2.01 (m, 2H), 1.81- 1.78 (m, 1H), 1.54-1.41 (m, 5H), 1.45-1.27 (m, 2H), 0.69-0.64 (m, 1H), 0.40-0.37 (m, 2H), 0.11-0.05 (m, 2H).

Example 292. Synthesis of Compound 347

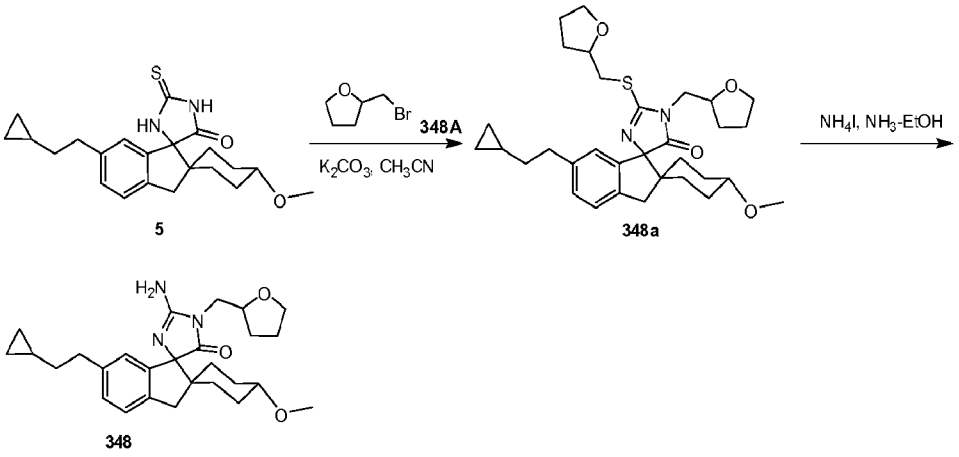


According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was alkylated with compound **347A** (77 mg, 0.52 mmol) to afford the crude

product **347a** (40 mg, 80%), which was used directly for the next step without further purification.

Compound **347a** (40 mg, 0.076 mmol) was then reacted with NH_4I (111 mg, 0.76 mmol) in a solution of NH_3/EtOH (5 mL, 5 N) to give **compound 347** (21 mg, 38%) as a white solid. **LC-MS** t_R = 1.146 min in 2 min chromatography, MS (ESI) *m/z* 436.2 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 11.4 (m, 1H), 10.89 (s, 1H), 8.52 (s, 1H), 7.21 (dd, *J* = 26, 18.4 Hz, 1H), 6.81 (s, 1H), 3.72 (m, 2H), 3.35 (s, 3H), 3.1 (m, 3H), 2.66 (m, 3H), 2.04 (m, 1H), 1.90 (m, 6H), 1.49 (m, 7H), 0.65 (m, 1H), 0.39 (m, 2H), 0.01 (m, 2H).

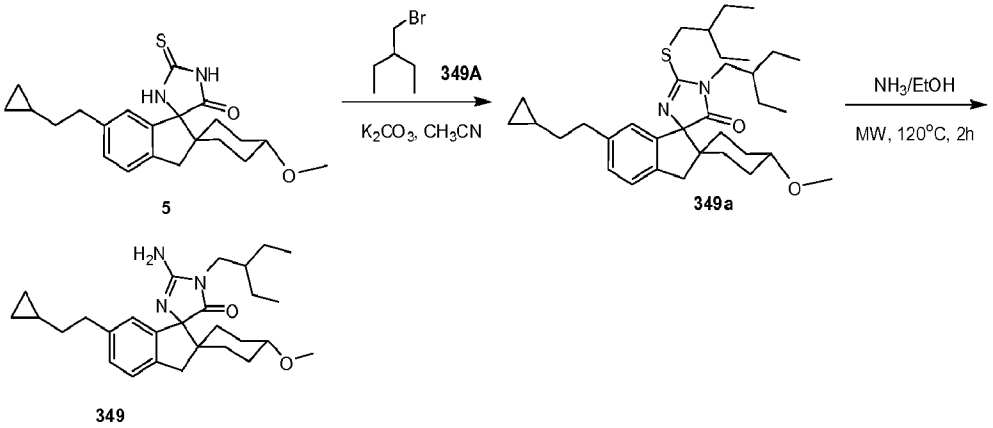
Example 293. Synthesis of Compound 348



According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was alkylated with compound **348A** (32 mg, 0.20 mmol) to give compound **348a** (22 mg, 51%).

Compound **348a** (22 mg, 0.040 mmol) was then reacted with NH_4I (58 mg, 0.40 mmol) in NH_3-EtOH (2.5 mL) to give **compound 348** (2.2 mg, 12%). **LC-MS**: t_R = 1.110 min in 2 min chromatography, MS (ESI) *m/z* = 452.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15 (m, 1H), 7.05 (m, 1H), 6.75 (m, 1H), 4.05 (m, 1H), 3.83 (m, 1H), 3.60 (m, 1H), 3.59 (m, 2H), 3.28 (m, 3H), 3.10 (m, 1H), 3.02 (m, 2H), 2.63 (m, 2H), 1.87 (m, 6H),1.41 (m, 8H), 0.60 (m,1H), 0.36 (m,2H), 0.049 (m,2H).

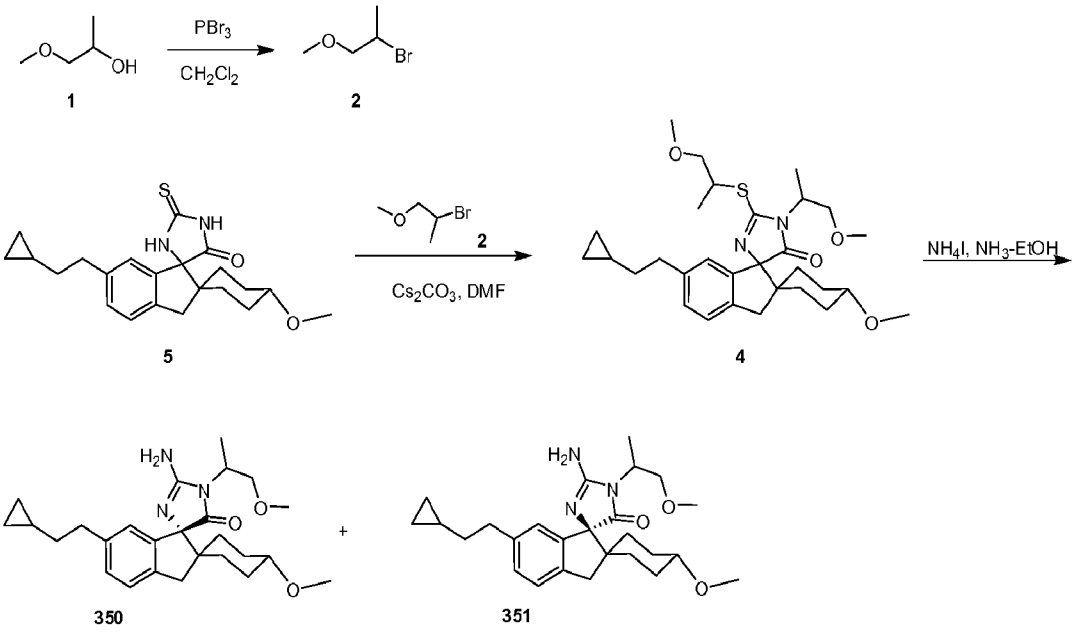
Example 294. Synthesis of Compound 349



According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was alkylated wtih compound **349A** (32 mg, 0.20 mmol) to give compound **349a** (44 mg, 44%) as a white solid.

Compound **349a** (44 mg, 0.080 mmol) was then reacted with NH_4I (116 mg, 0.80 mmol) in NH_3-EtOH (2.5 mL) to give **compound 349** (11.8 mg, 33%). **LC-MS:** t_R = 1.195 min in 2 min chromatography, MS (ESI) *m/z* = 452.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.28 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 3.59 (m, 2H), 3.31 (m, 3H),3.12 (m, 3H), 2.69 (m, 2H), 2.02 (m, 2H), 1.98 (m, 1H), 1.74 (m, 1H), 1.41 (m, 11H), 0.93 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 295. Synthesis of Compounds 350 and 351



Procedure for preparation of compound 2

To a solution of compound **1** (3.68 g, 0.04 mol) in CH_2Cl_2 (40 mL) was added phosphorus tribromide (5.4 g, 1.9 mL, 0.02 mol). The mixture was heated to reflux for 18 h. The mixture was quenched with 5% aqueous $NaHCO_3$, and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (2 × 40 mL), dried over Na_2SO_4, concentrated under reduced pressure to give compound **2** (3.1 g ,51%) as a yellow oil, which was used for the next step without purification.

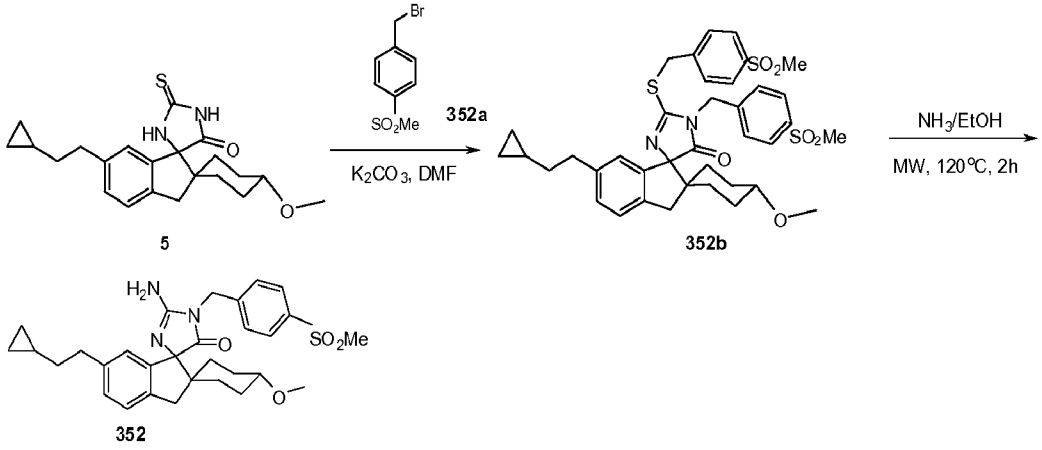
Procedure for preparation of compounds 350 and 351

According to a similar synthesis of **compound 344**, compound **5** (100 mg, 0.26 mmol) was alkylated with compound **2** (159 mg, 1.04 mmol) in the presence of Cs_2CO_3 (339 mg, 1.04 mmol) to give compound **4** (73 mg, 53%).

Compound **4** (79 mg, 0.15 mmol) was then reacted with NH_4I (217 mg, 1.5 mmol) in a solution of NH_3/EtOH (2 mL) to give **compound 350** (2.8 mg, 5%) **LC-MS** t_R = 1.052 min in 2 min chromatography, MS (ESI) *m/z* 440.2 $[M+H]^+$, **^{1}H NMR** (CD_3OD 400 MHz): δ 7.18-7.25 (m, 2H), 6.98-7.02 (d, J = 7.6, Hz, 1H), 4.15 (s, 1H), 3.61 (s, 1H), 3.49-3.58 (m, 1H), 3.30-3.43 (m, 6H), 3.01-3.12 (m, 4H), 2.68-2.72 (t, J = 7.8 Hz, 2H), 2.00-2.08 (m, 3H), 1.32-1.48 (m, 10H), 0.67 (m, 1H), 0.38-0.40 (d, J = 7.2 Hz, 2H), 0.01 (s, 2H).

and **compound 351** (7.8 mg, 15%) as a white solid. **LC-MS** t_R = 1.096 min in 2 min chromatography, MS (ESI) *m/z* 440.3 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.20-7.28 (dd, J = 7.6 Hz, 2H), 6.91-7.00 (d, J = 38.4 Hz, 1H), 4.52 (m, 1H), 3.73-3.87 (m, 1H), 3.52-3.56 (m, 1H), 3.30-3.31 (m, 6H), 3.01-3.18 (m, 3H), 2.69-2.72 (t, J = 7.6 Hz, 2H), 2.00-2.09 (m, 3H), 1.36-1.51 (m, 10H), 0.65-0.70 (m, 1H), 0.38-0.42 (m, 2H), 0.00 (m, 2H).

Example 296. Synthesis of Compound 352

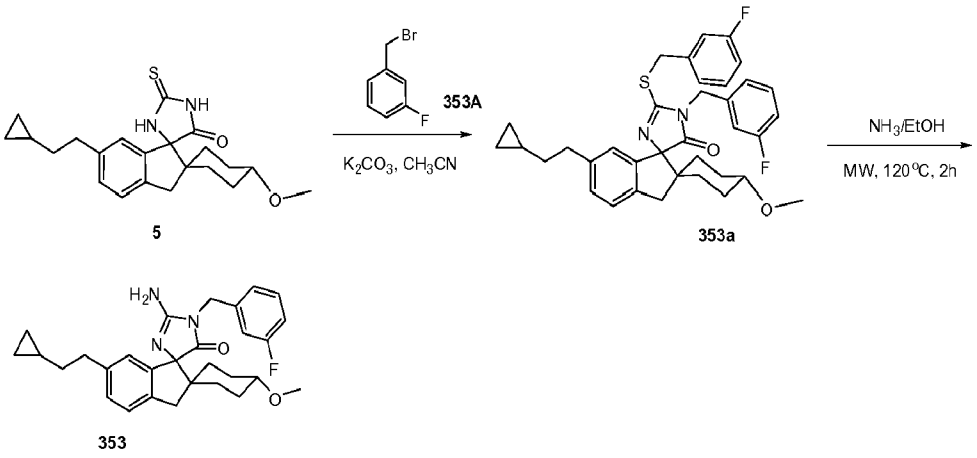


According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was alkylated with compound **352a** (38.9 mg, 0.156 mmol) to give compound

352b (30 mg, 53%) as a white solid. **LCMS** : t_R = 1.165 min in 2 min chromatography, MS (ESI) *m/z* = 415.1$[M+H]^+$.

Compound **352b** (30 mg, 0.041 mmol) was then heated with NH_4I (59 mg, 0.41 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 352** (11.0 mg, 57%) as a white solid. **LCMS**t_R = 1.196 min in 2 min chromatography, MS (ESI) *m/z* = 536.2$(M+H)^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.99-7.97 (d, *J* = 8.4 Hz, 2H), 7.56-7.54 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (d, *J* = 7.6 Hz, 1H), 7.25-7.20 (d, *J* = 7.6 Hz, 1H), 7.02 (m, 1H), 5.03 (s, 2H), 3.34 (s, 3H), 3.20-3.00 (m, 6H), 2.71-2.69 (t, J = 7.6 Hz, 2H), 2.10-1.90 (m, 2H), 1.85-1.75 (m, 1H), 1.50-1.20 (m, 7H), 0.71-0.60 (m, 1H), 0.40-0.30 (m, 2H), 0.10-0.01 (m, 2H).

Example 297. Synthesis of Compound 353

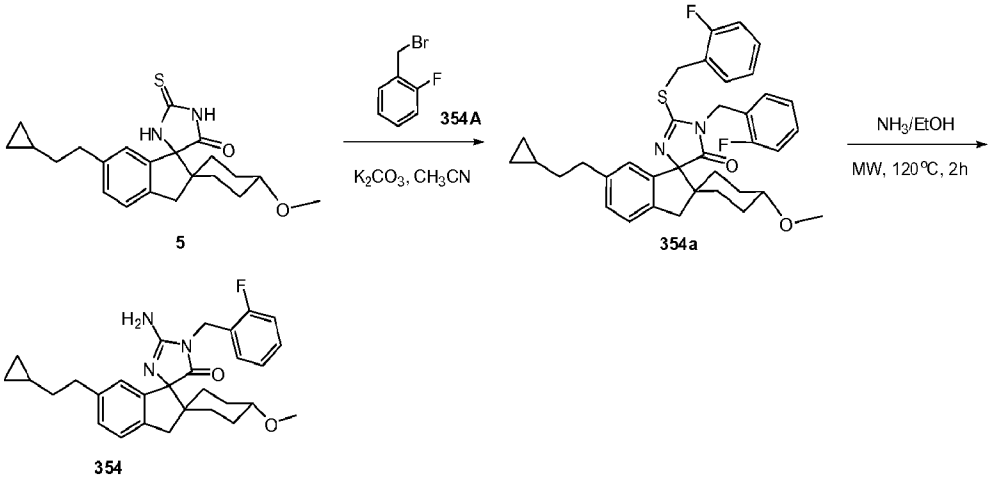


According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **353A** (98 mg, 0.52 mmol) to give compound **353a** (45 mg, 56%) as a white solid.

Compound **353a** (45 mg, 0.075 mmol) was then heated with NH_4I (109 mg, 0.75 mmol) in a solution of NH_3/EtOH (2 mL, 5 N) to give **compound 353** (9.2 mg, 26%) as a white solid. **LC-MS** t_R = 1.152 min in 2 min chromatography, MS (ESI) *m/z* 476.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.39-7.44 (dd, *J* = 8.0 Hz, 1H), 7.26-7.28 (d, *J* = 7.6 Hz, 1H), 7.20-7.22 (d, *J* = 8.0 Hz, 1H), 7.04-7.14 (m, 3H), 6.97 (s, 1H), 5.00 (s, 2H), 3.35 (s, 3H), 3.11-3.14 (m, 3H), 2.68-2.72 (t, *J* = 8.0 Hz, 2H), 2.01 (s, 2H), 1.81-

1.83 (d, J = 10.4 Hz, 1H), 1.41-1.49 (m, 5H), 1.27-1.35 (m, 2H), 0.60-0.68 (m, 1H), 0.37-0.40 (m, 2H), 0.03 (m, 2H).**^{19}F NMR** (CD_3OD 19F 400 MHz): δ -113.92

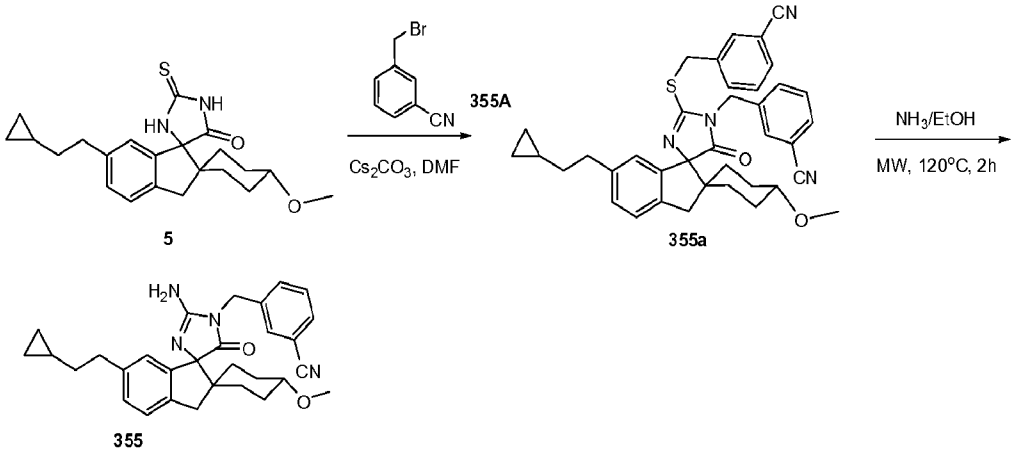
Example 298. Synthesis of Compound 354



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **354A** (98 mg, 0.52 mmol) to give compound **354a** (45 mg, 58%) as a white solid.

Compound **354a** (45 mg, 0.075 mmol) was then heated with NH_4I (109 mg, 0.75 mmol) in NH_3/EtOH (2 mL, saturated) to give **compound 354** (5.00 mg, 14%) as a white solid.**LC-MS** t_R = 1.127 min in 2 min chromatography, MS (ESI) *m/z* 476.3 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.40-7.43 (m, 1H), 7.32-7.38 (t, J = 7.2 Hz, 1H), 7.15-7.26 (m, 4H), 7.00 (s, 1H), 5.04 (s, 2H), 3.35 (s, 3H), 3.00-3.17 (m, 3H), 2.69-2.73 (t, J = 7.6 Hz, 2H), 1.94-2.01 (m, 2H), 1.65-1.68 (m, 1H), 1.42-1.53 (m, 5H), 1.23-1.35 (m, 2H), 0.63-0.69 (m, 1H), 0.36-0.43 (m, 2H), 0.02 (m, 2H).**^{19}F NMR** (CD_3OD 400 MHz): δ -118.84

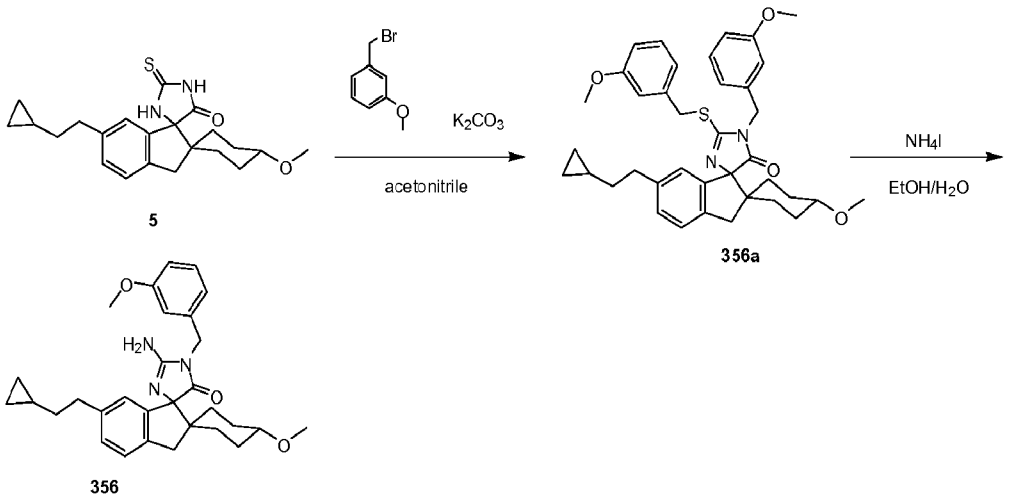
Example 299. Synthesis of Compound 355



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **355A** (95 mg, 0.52 mmol) to give compound **355a** (45 mg, 56%) as a white solid.

Compound **355a** (45 mg, 0.07 mmol) was then heated with NH_4I (107 mg, 0.7 mmol) in a solution of NH_3/EtOH (2 mL, 5 N) to give **compound 355** (2.7 mg, 8%) as a white solid. **LC-MS** t_R = 1.120 min in 2 min chromatography, MS (ESI) *m/z* 483.2 $[M+H]^+$;**^{1}H NMR** (CD_3OD 400 MHz): δ 7.73-7.75 (d, J = 7.2 Hz, 1H), 7.57-7.73 (m, 3H), 7.26-7.28 (d, J = 7.6 Hz, 1H), 7.21-7.23 (d, J = 8.0 Hz, 1H), 7.28-6.99 (s, 1H), 4.99 (s, 2H), 3.24 (s, 3H), 3.05-3.19 (m, 3H), 2.69-2.72 (t, J = 7.6 Hz, 2H), 1.99 (s, 2H), 1.77-1.80 (m, 1H), 1.41-1.48 (m, 4H), 1.28-1.35 (m, 3H), 0.62-0.67 (m, 1H), 0.36-0.39 (m, 2H), -0.01-0.00 (m, 2H).

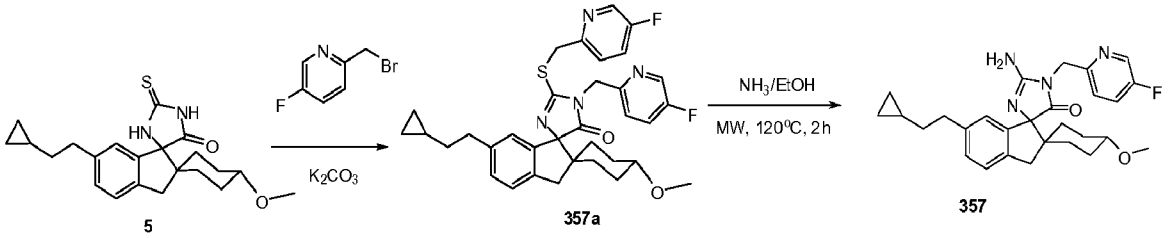
Example 300. Synthesis of Compound 356



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with 1-bromomethyl-3-methoxy-benzene (65 mg, 0.326 mmol) to give compound **356a** (30 mg, 38%) as a white solid.

Compound **356a** (30 mg, 0.049 mmol) was then heated with NH_4I (77 mg, 0.492 mmol) and NH_3-EtOH (2 mL, 5 N) to give compound **356** (8.0 mg, 33%) as a white solid. **LC-MS** t_R = 1.257 min in 2 min chromatography, MS (ESI) *m/z* 488 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.21 (m, 2H), 7.10 (d, J = 7.6 Hz, 1H), 6.84 (m, 4H), 4.60-4.70 (m, 2H), 3.73 (s, 3H), 3.31 (m, 3H), 3.00-3.15 (m, 3H), 1.81-2.02 (m, 3H), 1.58 (m, 1H), 1.22-1.48 (m, 6H), 0.65 (m, 1H), 0.38 (d, J = 8.4 Hz, 2H), 0.01 (d, J = 5.2 Hz, 2H).

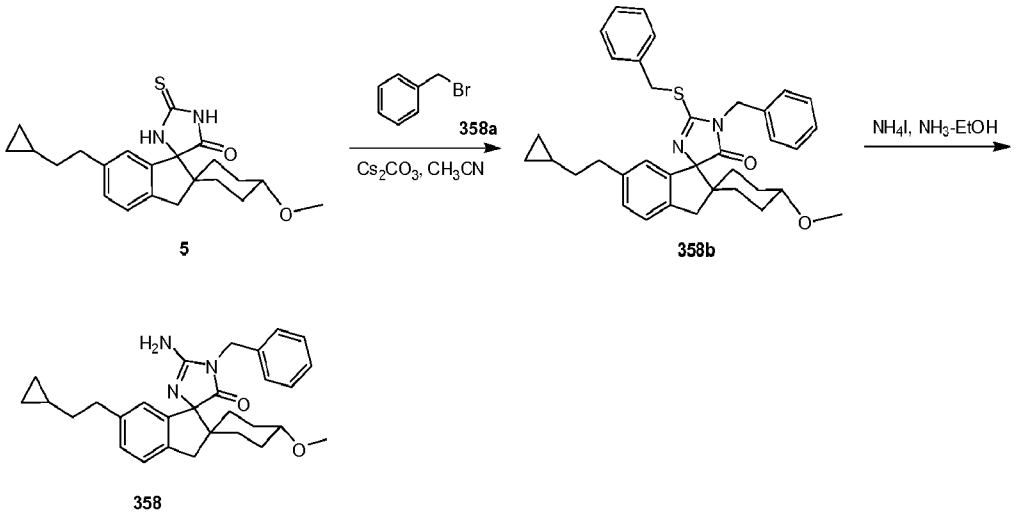
Example 301. Synthesis of Compound 357



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with 2-(bromomethyl)-5-fluoropyridine to give compound **357a**

(20 mg, 0.033 mmol), which was heated with NH_4I (47.6 mg, 0.33 mmol) in NH_3/EtOH (2 mL, 5 N) to give **compound 357** (9.10 mg, 57%) as a white solid. **LCMS** : t_R = 2.128 min in 3 min chromatography, MS (ESI) *m/z* = 477.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.41-8.40 (d, *J* = 2.8 Hz, , 1H), 7.60-7.55 (td, *J* = 2.8, 8.8 Hz, 1H), 7.38-7.30 (dd, J = 4.4, 8.8 Hz, 1H), 7.18-7.10 (d, *J* = 7.6 Hz, 1H), 7.10-7.01(d, *J* = 7.6 Hz, 1H), 6.90-6.80 (m, 1H), 4.70 (s, 2H), 3.35 (s, 3H), 3.2-3.10 (m, 1H), 3.09-3.05 (d, *J* = 15.8 Hz, 1H), 3.05-2.95 (d, *J* = 15.8 Hz, 1H), 2.69-2.60 (m, 2H), 2.10-1.90 (m, 2H), 1.90-1.80 (m, 1H), 1.70-1.51 (m, 1H), 1.51-1.21 (m,6H), 0.70-0.60 (m, 1H), 0.50-0.30 (m, 2H), 0.10-0.01 (m, 2H).

Example 302. Synthesis of Compound 358

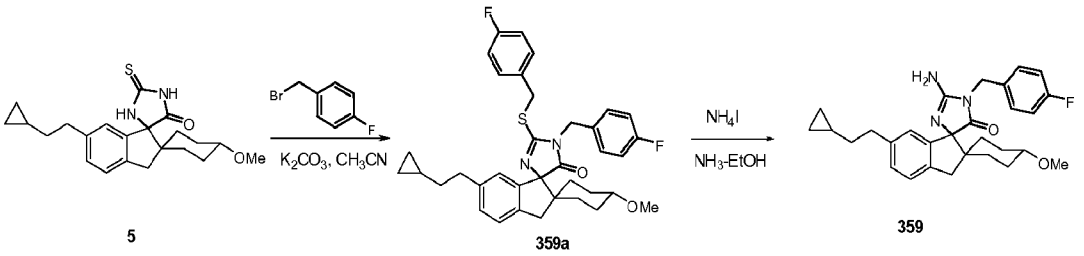


According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with bromomethylbenzene (50 mg, 0.29 mmol) to give compound **358b** (34 mg, 77%) as a pale yellow solid. **LC-MS**: t_R = 2.500 min in 3 min chromatography, MS (ESI) *m/z* 565 $[M+H]^+$.

Compound **358b** (34 mg, 0.060 mmol) was heated with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (1 mL) to give **compound 358** (14.4 mg, 59%) as a white solid. **LC-MS**: t_R = 4.202 min in 7 min chromatography, MS (ESI) *m/z* 458 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.29 (m, 5H), 7.18 (d, *J* = 7.6 Hz, 3H), 7.10 (d, *J* = 7.6

Hz, 3H), 6.78 (s, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 3.33 (s, 3H), 3.13 (m, 2H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.67 (t, *J* = 8.0 Hz, 1H), 1.96 (m, 2H), 1.83 (m, 1H), 1.64 (m, 1H), 1.30-1.50 (m, 4H), 1.38 (m, 2H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

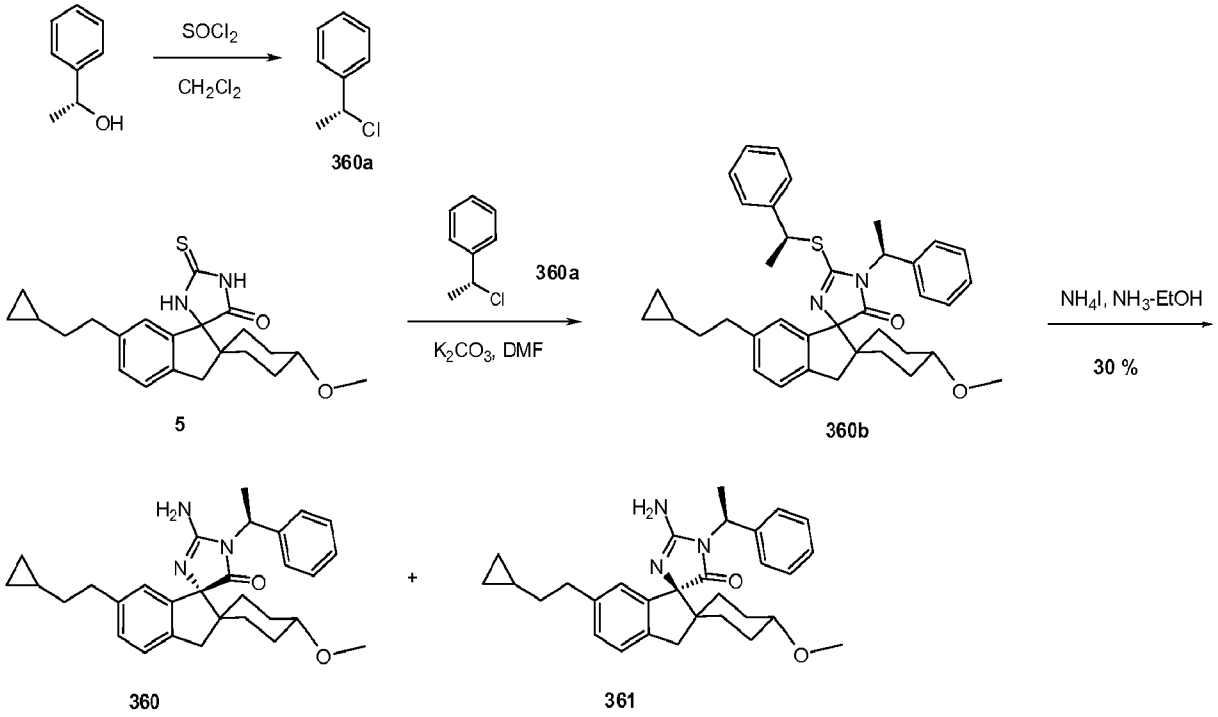
Example 303. Synthesis of Compound 359



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was alkylated with 1-bromomethyl-4-fluoro-benzene (55 mg, 0.3 mmol) to give compound **359a** (54 mg, 80%) as a white solid.

Compound **359a** (50 mg, 0.08 mmol) was heated with NH_4I (60 mg, 0.4 mmol) in a solution of NH_3-EtOH (3 mL, 5 N) to give **compound 359** (17 mg, 45%) as a white solid. **LC-MS**: t_R = 1.92 min in 3 min chromatography, MS (ESI) *m/z* 476.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.30-7.40 (m, 2H), 7.20-7.25 (d, 1H, *J* = 8.4 Hz), 7.15-7.20 (d, 1H, *J* = 8.4 Hz), 7.00-7.10 (m, 2H), 6.80-6.85 (s, 1H), 3.35-3.40 (s, 3H), 3.00-3.20 (m, 3H), 2.60-2.70 (m, 2H), 1.90-2.10 (m, 2H), 1.70-1.80 (m, 1H), 1.30-1.50 (m, 5H), 1.20-1.30 (m, 2H), 0.60-0.70 (m, 1H), 0.35-0.45 (m, 2H), 0.05-0.10 (m, 2H). **^{19}F NMR**: (CD_3OD 400 MHz): δ -115.20.

Example 304. Synthesis of Compounds 360 and 361



Procedure for preparation of compound 360a

To a solution of 1-phenyl-ethanol (100 mg, 0.81 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $SOCl_2$ (107 mg, 0.90 mmol) at 0 °C under N_2, the mixture was stirred at room temperature onnight. The solvent was removed *in vacuo* to give compound **360a** (90 mg, 80%) as a yellow oil which was used in the next step without further purification.**^{1}H NMR** (DMSO-d_6 400 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.29 (m, 3H), 5.28-5.26 (m, 1H), 1.72-1.71 (d, J = 6.8 Hz, 3H)

Procedure for preparation of compounds 360 and 361

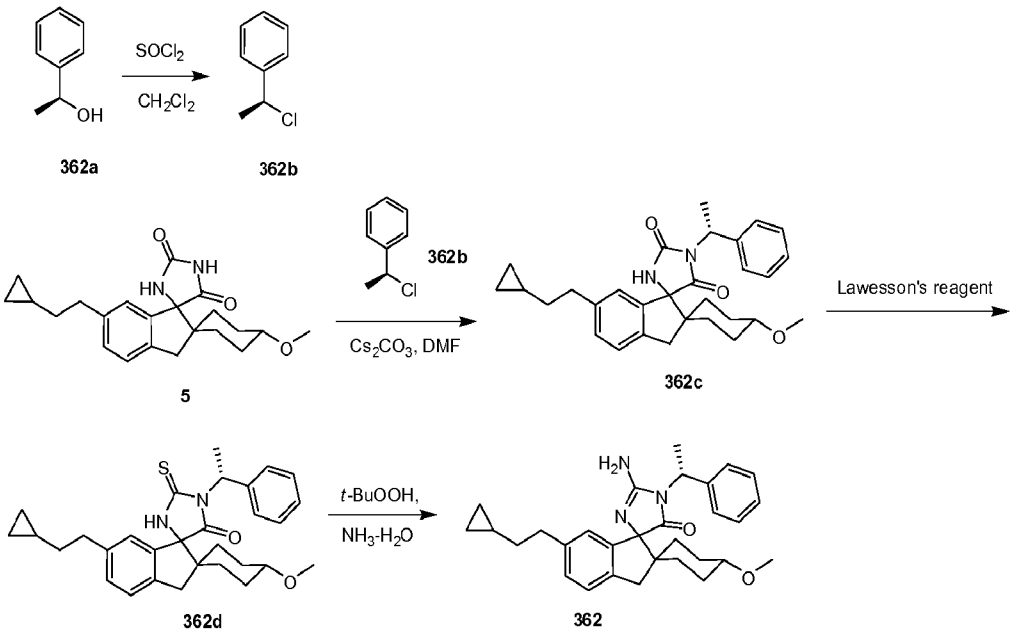
According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.077 mmol) was dialkylated with compound **360a** (21.9 mg, 0.15 mmol) to give compound **360b** (20 mg, 43%) as a white solid.**LC-MS**: t_R = 1.678 min in 2 min chromatography, MS (ESI) m/z = 593.3 $[M+H]^+$.

Compound **360b** (20 mg, 0.033 mmol) was then heated with NH_4I (48.4 mg, 0.33 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated under vacuum and the

residue was purified by preparative TLC (dichloromethane: methanol = 10: 1) and preparative HPLC to give **compound 360** (3.00 mg, 19%), **LC-MS**: t_R = 2.091 min in 3 min chromatography, MS (ESI) *m/z* = 472.3 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.47-7.45 (m, 3H), 7.44-7.28 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.28-7.19 (d, *J* = 7.8 Hz, 1H), 7.19-7.7.10 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.79 (s, 1H), 5.59-5.57 (q, *J* = 7.2 Hz, 1H), 3.32 (s, 3H), 3.31-3.14 (m, 1H), 3.08-3.03 (m,.2H), 2.67-2.62 (m, 2H), 2.10-1.99 (m, 2H), 1.90-1.80 (m, 1H), 1.75-1.67 (d, *J* = 6.8 Hz, 3H), 1.56-1.10 (m, 7H), 0.70-0.60 (m, 1H), 0.40-0.30 (m, 2H), 0.10-0.05 (m, 2H).

& **compound 361** (1.80 mg, 11%) as white solid. **LC-MS**: t_R = 2.330 min in 3 min chromatography, MS (ESI) *m/z* = 472.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.38-7.33 (m, 5H), 7.30-7.20 (d, *J* = 7.6 Hz, 1H), 7.20-7.10 (dd, *J* = 1.2 , 7.6 Hz, 1H), 6.84 (s, 1H), 5.50-5.40 (q, *J* = 7.2 Hz, 1H), 3.39 (s, 3H), 3.31-3.20 (m, 1H), 3.18-3.10 (d, *J* = 17.2 Hz, .2H), 3.10-3.00 (d, *J* = 17.2 Hz, .2H), 2.71-2.67 (t, *J* = 7.6 Hz, 2H), 2.20-2.10 (m, 1H), 2.10-1.95 (m, 2H), 1.95-1.90 (d, J = 7.2 Hz, 3H), 1.58-1.30 (m, 7H), 0.71-0.61 (m, 1H), 0.50-0.30 (m, 2H), 0.10-0.03 (m, 2H).

Example 305. Synthesis of Compound 362



Procedure for preparation of compound 362b

Synthesized by a route analogously to **compound 360a** described in Example 304, reaction of compound **362a** (100 mg, 0.81 mmol) with $SOCl_2$ gave compound **362b** (90 mg, 80%) as a yellow oil which was used in the next step without further purification. **^{1}H NMR** (DMSO-d_6 400 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.23 (m, 3H), 5.34-5.20 (m, 1H), 1.72-1.71 (d, J = 6.8 Hz, 3H).

Procedure for preparation of compound 362c

Synthesized by a route analogously to **compound 360b** described in Example 304, reaction compound **5** (50 mg, 0.14 mmol) and compound 362b gave compound **362c** (35 mg, 54%) as a white solid after purification by preparative TLC on silica gel eluted with hexane: EtOAc = 3: 1 to give. **LC-MS**: t_R = 1.515 min in 2 min chromatography, MS (ESI) m/z = 473.2 $[M+H]^+$.

Procedure for preparation of compound 362d

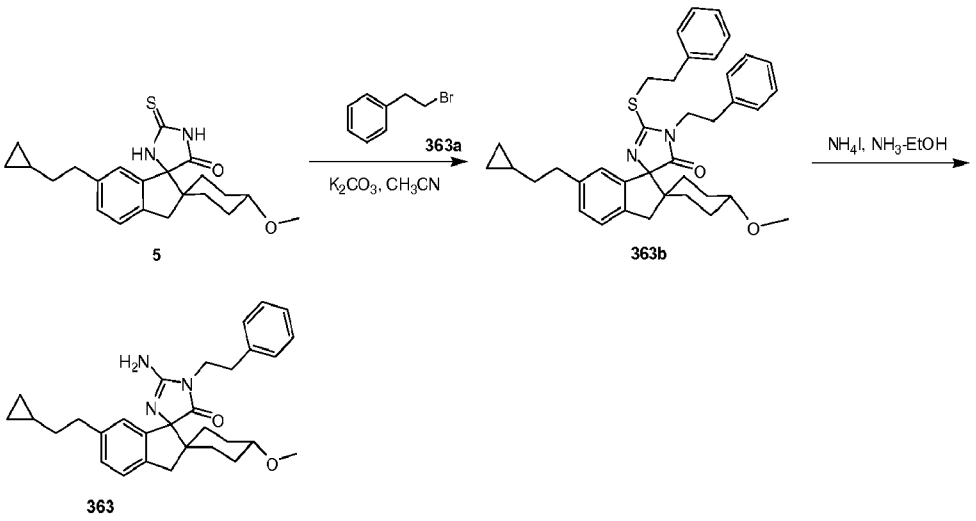
To a solution of compound **362c** (35 mg, 0.077 mmol) in anhydrous toluene (2 mL) was added Lawesson's Reagent (32.9 mg, 0.081 mmol) under N_2, the mixture was stirred at 130 °C in a CEM microwave reactor for 40 min. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc =3: 1 to give compound **362d** (15 mg, 41%) as a white solid.**LC-MS**: t_R = 1.628 min in 2 min chromatography, MS (ESI) m/z = 489.2 $[M+H]^+$.

Procedure for preparation of compound 362

To a solution of compound **362d** (15 mg, 0.03 mmol) in EtOH (10 mL) was added *t*-BuOOH (1.0 mL) and $NH_3.H_2O$ (3.0 mL), the mixture was stirred at room temperature overnight, LCMS analysis showed the complete consumption of compound **362d**, the mixture was concentrated in vacuum, and the residue was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and by prep-HPLC to give **compound 362** (1.80 mg, 12.5%) as a white solid. **LC-MS**: t_R = 1.017 min in 2 min chromatography, MS (ESI) m/z = 472.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.48-7.24 (m, 5H), 7.25-7.11(d, J = 7.6 Hz, 1H), 7.11-7.06 (d, J = 7.6 Hz, 1H), 6.84-6.62 (s, 1H), 5.46-5.34 (m, 1H), 3.36 (s, 3H), 3.21-3.14 (m, 1H), 3.10-2.98 (m,.2H), 2.66-2.62 (t, J = 7.6 Hz, 2H), 2.08-2.05 (m, 1H), 1.99-1.81 (m, 2H), 1.80-1.76

(d, J = 7.2 Hz, 3H), 1.56-1.20 (m, 7H), 0.68-0.61 (m, 1H), 0.41-0.30 (m, 2H), 0.10-0.03 (m, 2H).

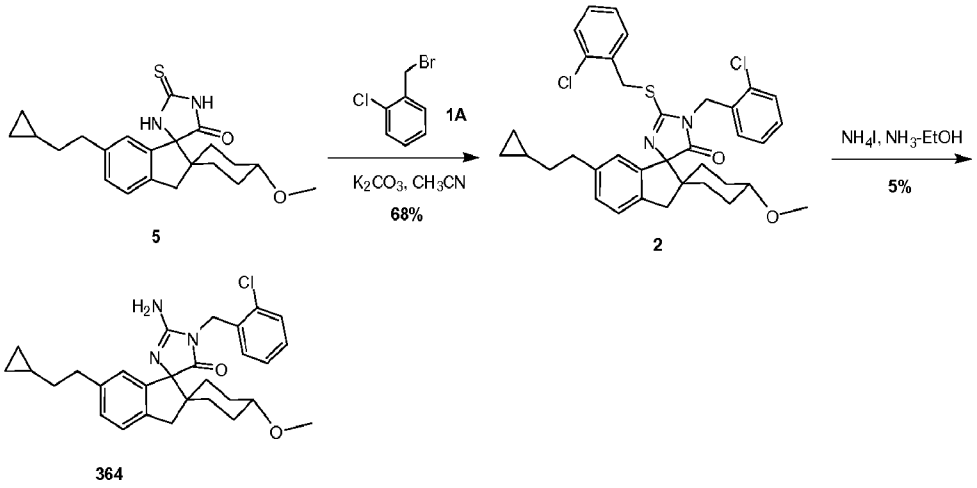
Example 306. Synthesis of Compound 363



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with 2-bromoethyl-benzene (**363a**) (0.10 g, 0.54 mmol) to give compound **363b** (56 mg, 72%) as a pale yellow solid. **LC-MS**: t_R = 2.649 min in 3 min chromatography, MS (ESI) m/z = 593 $[M+H]^+$.

Compound **363b** (56 mg, 0.084 mmol) was then heated with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (1 mL) to give **compound 363** (15.2 mg, 38%) as a white solid. **LC-MS**: t_R = 1.887 min in 3 min chromatography, MS (ESI) m/z = 472, $[M+H]^+$.**^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.25 (m, 4H), 7.20 (m, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.72 (s, 1H), 3.70-3.85 (m, 2H), 3.32 (s, 3H), 3.03 (m, 1H), 2.95 (m, 4H), 2.66 (t, J = 8.0 Hz, 2H), 1.90 (m, 2H), 1.58 (m, 2H), 1.45 (m, 2H), 1.30 (m, 2H), 1.20 (m, 1H), 1.05 (m, 1H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

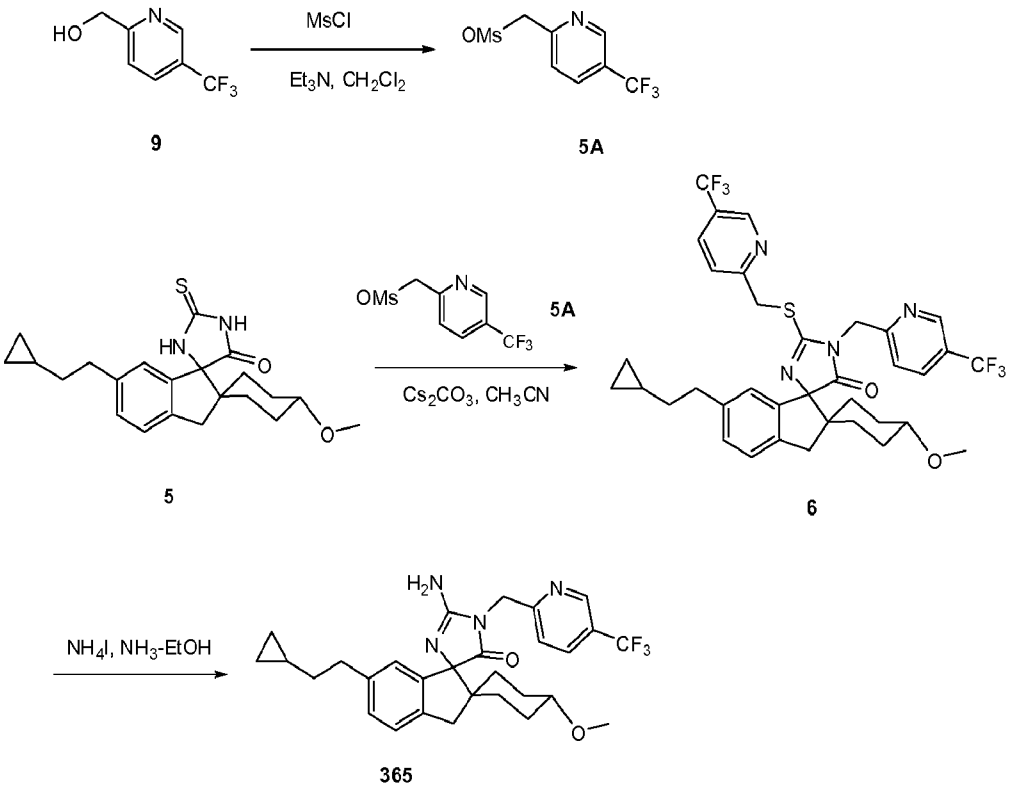
Example 307. Synthesis of Compound 364



According to a similar synthesis of **comound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **1A** (66 mg, 0.33 mmol) to give the crude compound **2** (56 mg, 68%), which was used for the next step directly.

Compound **2** (56 mg, 0.089 mmol) was then heated with NH_4I (128.5 mg, 0.89 mmol) in NH_3-EtOH (2.5 mL) to give **compound 364** (2 mg, 5%). **LC-MS**: t_R = 1.295 min in 2 min chromatography, MS (ESI) *m/z* = 492.4 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.49 (m, 1H), 7.36 (m, 2H), 7.33 (m, 1H), 7.26 (m, 2H), 7.09 (s, 1H), 5.00 (s, 2H), 3.31 (m, 3H), 3.30 (m, 1H), 3.05 (m, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.01 (m, 2H), 1.75 (m, 1H), 1.51 (m, 1H), 1.48 (m, 4H), 1.35 (m, 1H), 0.66 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Example 308. Synthesis of Compound 365



Procedure for preparation of Compound 5A

To a solution of compound **9** (100 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (114 mg, 1.12 mmol) and MsCl (71 mg, 0.61 mmol) under nitrogen, the mixture was stirred at room temperature for 4h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (5mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **5A** (86 mg, 60%) as yellow oil, which was used in the next step without further purification.^{1}**H NMR** ($CDCl_3$ 400 MHz): δ 8.90 (s, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 5.26 (s, 2H), 3.10 (s, 3H).

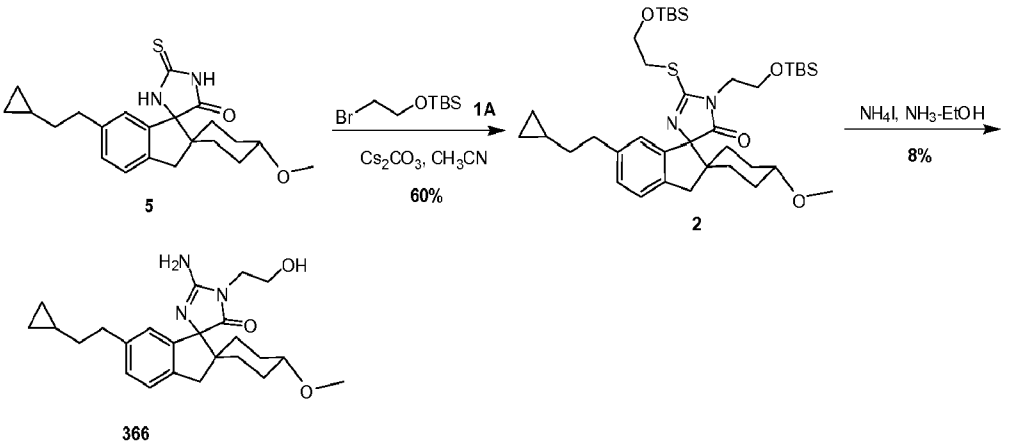
Procedure for preparation of compound 365

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **5A** (39.8 mg, 0.156 mmol) to afford compound

6 (30 mg, 55%) as a white solid.**LCMS**: t_R = 1.561 min in 2 min chromatography, MS (ESI) *m/z* = 703.2 $[M+H]^+$.

Compound **6** (30 mg, 0.042 mmol) was then heated with NH_4I (61.3 mg, 0.42mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 365** (4.90 mg, 26%) as a white solid. **LCMS**: t_R = 1.149 min in 2 min chromatography, MS (ESI) *m/z* = 527.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.80 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.01 (s, 1H), 4.91 (s, 2H), 3.37 (s, 3H), 3.21-3.15 (m, 1H), 3.15-2.91 (d, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.17-1.94 (m, 2H), 1.94-1.85 (m, 1H), 1.70-1.62 (m, 1H), 1.51-1.30 (m, 5H), 1.30-1.27 (m, 1H), 0.71-0.69(m, 1H), 0.43-0.35 (m, 2H), 0.1-0.05 (m, 2H).**^{19}F NMR** (CD_3OD 19F 400 MHz): δ -63.844.

Example 309. Synthesis of Compound 366

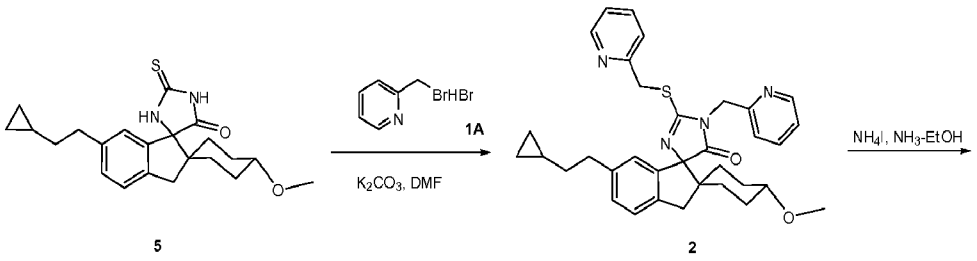


According to a similar synthesis of **compound 344**, compound **5** (45 mg, 0.12 mmol) was dialkylated with compound **1A** (84 mg, 0.35 mmol) in the presence of Cs_2CO_3 (191 mg, 0.59 mmol) to give compound **2** (41 mg, 60%).

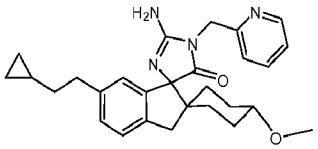
Compound **2** (41 mg, 0.070 mmol) was then heated NH_4I (101 mg, 0.70 mmol) in NH_3-EtOH (2.5 mL) to give **compound 366** (2.4 mg, 8%) as a white solid. **LC-MS**: t_R = 1. 137 min in 2 min chromatography, MS (ESI) *m/z* = 412.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.29 (m, 1H), 7.20 (m, 1H), 7.00 (s, 1H), 3.82 (m, 2H), 3.70 (m,

2H), 3.30 (m, 3H), 3.10 (m, 3H), 2.60 (m, 2H), 2.05 (m, 2H), 1.89 (m, 1H), 1.45 (m, 5H),1.32 (m, 1H), 0.69 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Example 310. Synthesis of Compound 367



5 2

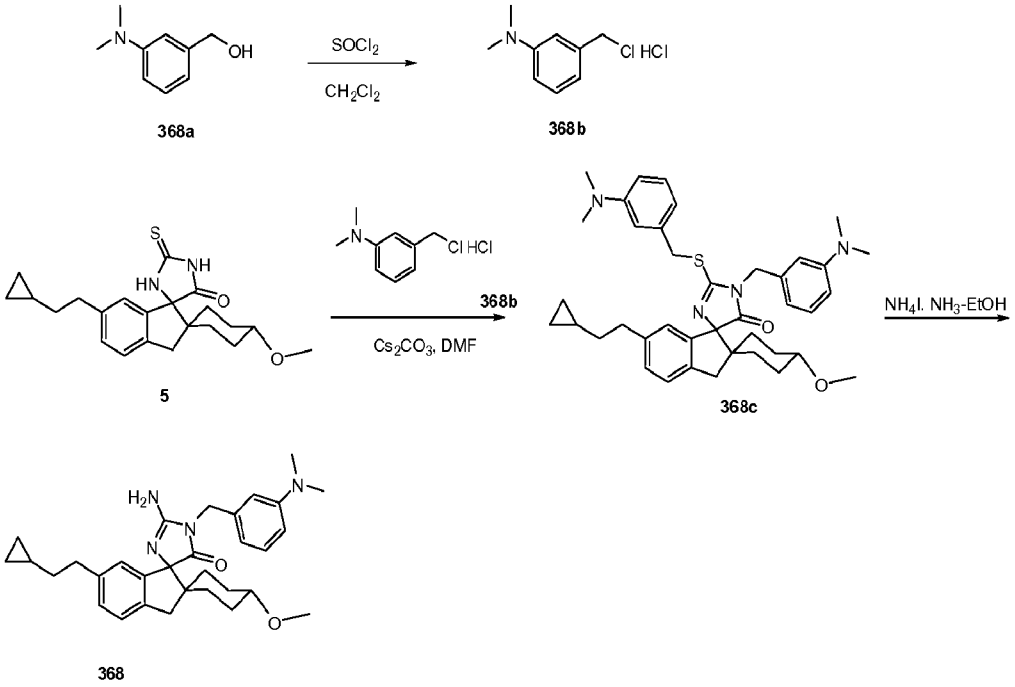


367

According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **1A** (134 mg, 0.52 mmol) at the presence of Cs_2CO_3 (170 mg, 0.52 mmol) to give compound **2** (45 mg, 56%) as a white solid.

Compound **2** (49 mg, 0.086 mmol) was heated with NH_4I (125 mg, 0.86 mmol) in a solution of NH_3/EtOH (2 mL, 5 N) to give **compound 367** (3.4 mg, 12%) as a white solid. **LC-MS** t_R = 1.085 min in 2 min chromatography, MS (ESI) *m/z* 459.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.51-8.52 (d, J = 4.4 Hz, 1H), 7.79-7.83 (t, J = 7.6 Hz, 1H), 7.11-7.42 (m, 5H), 4.97-5.06 (m, 2H), 3.24 -325 (m, 3H), 3.03-3.24 (m, 3H), 2.70-2.74 (t, J = 7.6 Hz, 2H), 2.02-2.03 (m, 2H), 1.79-1.82 (m, 1H), 1.28-1.52 (m,7H), 0.65-0.69 (m, 1H), 0.37-0.39 (m, 2H), 0.00 (m, 2H).

Example 311. Synthesis of Compound 368



Procedure for preparation of compound 368b

To a solution of (3-dimethylamino-phenyl)-methanol (0.20 g, 1.32 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.3 mL) via a syringe slowly with stirring. After addition, the reaction mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo* to give the crude compound **368b** (0.31 g, 100% crude) as a red solid, which was used directly in next step.

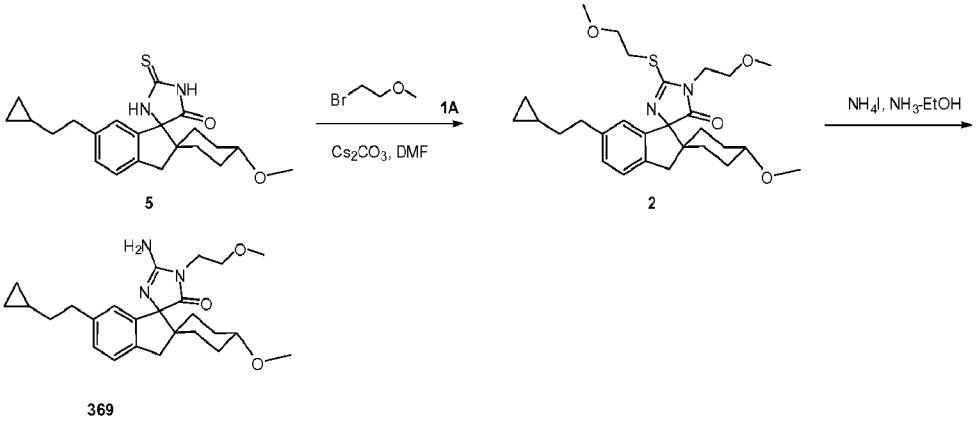
Procedure for preparation of compound 368

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **368b** (60 mg, 0.29 mmol) to give compound **368c** (13 mg, 26%) as a yellow oil. **LC-MS**: t_R = 2.323 min in 3 min chromatography, MS (ESI) *m/z* 651 $[M+H]^+$.

Compound **386c** (13 mg, 0.060 mmol) was then heated with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (2 mL) to give **compound 386** (5.4 mg, 54%) as a white solid. **LC-MS**: t_R = 1.622 min in 3 min chromatography, MS (ESI) *m/z* 501 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.21 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.71 (d, J = 11.2 Hz, 2H), 6.64 (d, J = 7.6 Hz, 1H), 4.68 (d, J

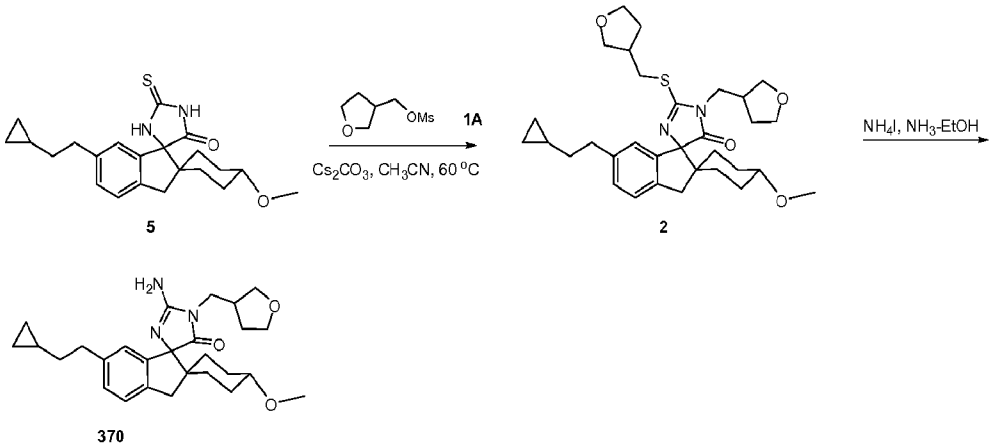
= 6.8 Hz, 2H), 3.35 (s, 3H), 3.13 (m, 2H), 3.04 (d, *J* = 15.2 Hz, 1H), 2.91 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.85-2.05 (m, 3H), 1.61 (m, 1H), 1.35-1.50 (m, 4H), 1.25-1.35 (m, 2H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Example 312. Synthesis of Compound 369



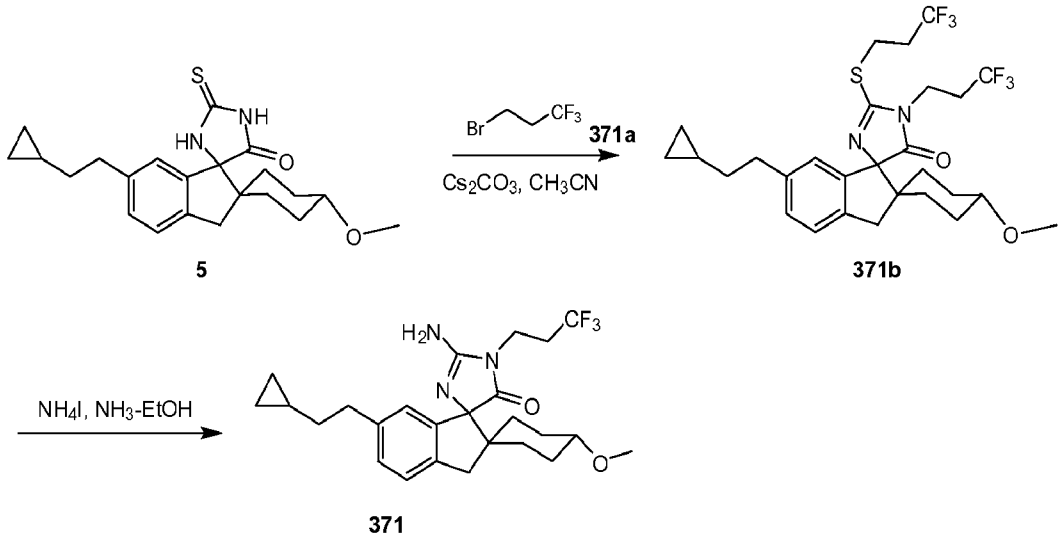
According to a similar synthesis of **compound 344**, compound **5** (45 mg, 0.12 mmol) was dialkylated with compound **1A** (40mg, 0.29 mmol) to give compound **2** (28 mg, 47%), which was heated with NH_4I (80.8 mg, 0.56 mmol) in NH_3-EtOH (5.0 N, 3mL) to give **compound 369** (10 mg, 42%) as a white solid. **LC-MS**: t_R = 1.053 min in 2 min chromatography, MS (ESI) *m/z* = 426 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 3.91 (m, 2H), 3.55 (m, 2H), 3.34 (s, 6H), 3.15 (m, 1H), 3.10 (m, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.01 (m, 2H), 1.87 (m, 1H), 1.46 (m, 7H), 0.66 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 313. Synthesis of Compound 370



According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **1A** (17.0 mg, 0.166 mmol) to give compound **2** (31 mg, 72%), which was heated with NH_4I (81.4 mg, 0.56 mmol) in NH_3-EtOH (5.0 N, 3mL) to give **compound 370** (5.7 mg, 30%) as a white solid. **LC-MS** t_R = 1.077 min in 2 min chromatography, MS (ESI) *m/z* = 452 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 3.89 (m, 2H), 3.72 (m, 4H), 3.45 (m, 1H), 3.34 (s, 3H), 3.12 (m, 3H), 2.01 (m, 3H), 1.89 (m, 1H), 1.64 (m, 1H), 1.45 (m, 6H), 1.30 (m, 1H), 0.65 (m, 1H),0.38 (m, 2H), 0.01 (m, 2H).

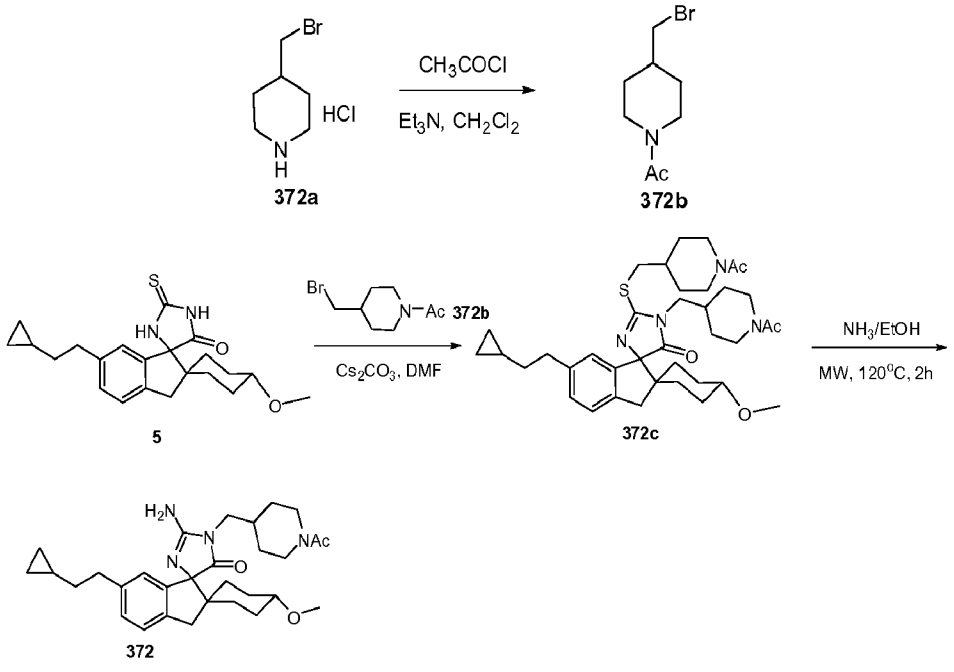
Example 314. Synthesis of Compound 371



According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with 3-bromo-1,1,1-trifluoro-propane (50 mg, 0.28 mmol) to give compound **371b** (36 mg, 80%) as a white solid. **LC-MS**: t_R = 2.581 min in 3 min chromatography, MS (ESI) *m/z* = 424 $[M+H]^+$.

Compound **371b** (36 mg, 0.062 mmol) was then heated with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (2 mL) to give **compound 371** (7.7 mg, 27%) as a white solid. **LC-MS**: t_R = 1.658 min in 3 min chromatography, MS (ESI) *m/z* = 464 $[M+H]^+$. **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.19 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 3.83 (m, 2H), 3.34 (s, 3H), 3.14 (m, 1H), 3.05 (d, J = 15.2 Hz, 1H), 3.02 (d, J = 15.2 Hz, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.56 (m, 2H), 1.75-2.10 (m, 3H), 1.50-1.60 (m, 1H), 1.25-1.50 (m, 6H), 0.85-1.05 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H). **^{19}F NMR**: (CD_3OD 400 MHz): δ -66.676

Example 315. Synthesis of Compound 372



Procedure for preparation of compound 372b

To a solution of 4-bromomethyl-piperidine hydrochloride salt (0.10 g, 0.47 mmol) anhydrous dichloromethane (10 mL) were added acetyl chloride (75 mg, 0.94

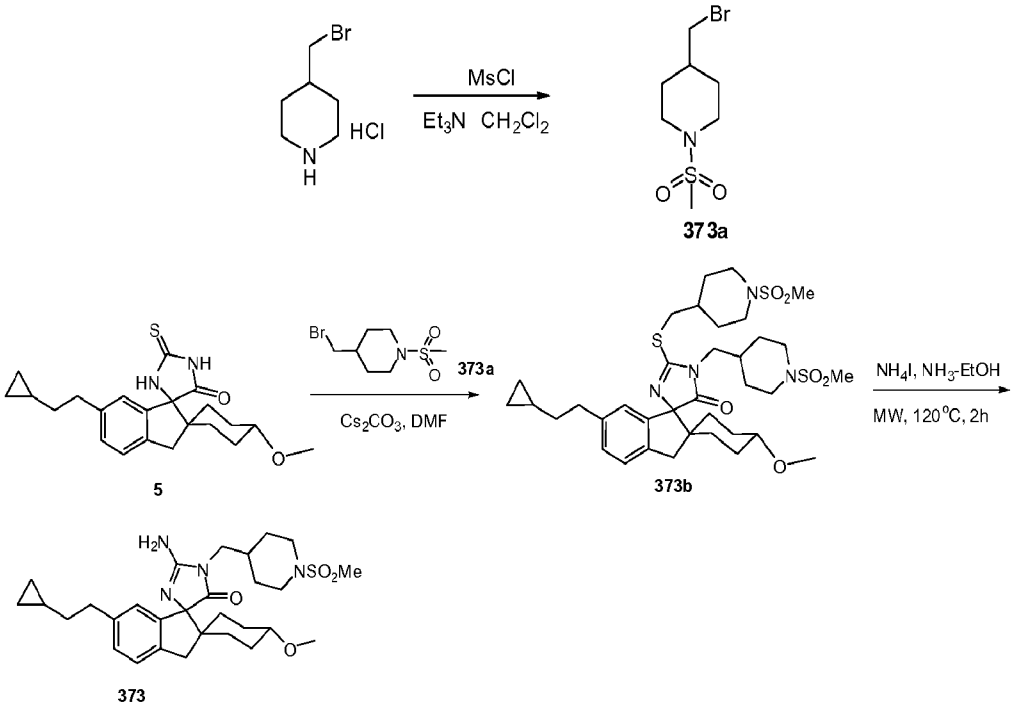
mmol) and triethyl-amine (0.10 g, 0.99 mmol) in turn. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched by adding brine (10 mL) with stirring. The mixture was separated and the aqueous layer was extracted with dichloromethane (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **372b** (0.12 g, crude) as a red oil, which was used directly in next step without purification.**^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.68 (m, 1H), 3.78 (m, 1H), 3.24 (d, J = 5.2 Hz, 2H), 2.96 (m, 1H), 2.62 (m, 1H), 2.04 (s, 3H), 1.87 (m, 2H), 1.16 (m, 2H).

Procedure for preparation of compound 372

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **372b** (60 mg, 0.078 mmol) to give compound **372c** (44 mg, 85%) as a yellow oil.**LC-MS**: t_R = 1.944 min in 3 min chromatography, MS (ESI) m/z = 663 $[M+H]^+$.

Compound **372c** (40 mg, 0.060 mmol) was then heated with NH_4I (100 mg, 0.69 mmol) and NH_3-EtOH (2 mL) to give **compound 372** (9.0 mg, 30%) as a white solid. **LC-MS**: t_R = 1.557 min in 3 min chromatography, MS (ESI) m/z = 507 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.18 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 4.46 (m, 1H), 3.83 (m, 1H), 3.42 (d, J = 7.2 Hz, 2H), 3.33 (s, 3H), 3.13 (m, 1H), 3.09 (m, 2H), 3.01 (d, J = 15.2 Hz, 1H), 3.02 (d, J = 15.2 Hz, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.56 (m, 1H), 2.05 (d, J = 7.2 Hz, 3H), 1.85-2.05 (m, 3H), 1.50-1.80 (m, 3H), 1.25-1.50 (m, 6H), 1.00-1.25 (m, 2H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

Example 316. Synthesis of Compound 373



Procedure for preparation of compound 373a

Synthesized by a route analogously to **compound 372b**, reaction of 4-bromomethyl-piperidine hydrochloride salt with MsCl gave crude compound **373a** (0.11 g, crude) as a pale yellow oil, which was used directly in next step without purification. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.80 (d, J = 12.0 Hz, 2H), 3.26 (d, J = 6.4 Hz, 2H), 2.72 (s, 3H), 2.63 (m, 2H), 1.92 (d, J = 12.8 Hz, 2H), 1.74 (m, 1H), 1.16 (dt, J = 4.0, 12.4 Hz, 2H).

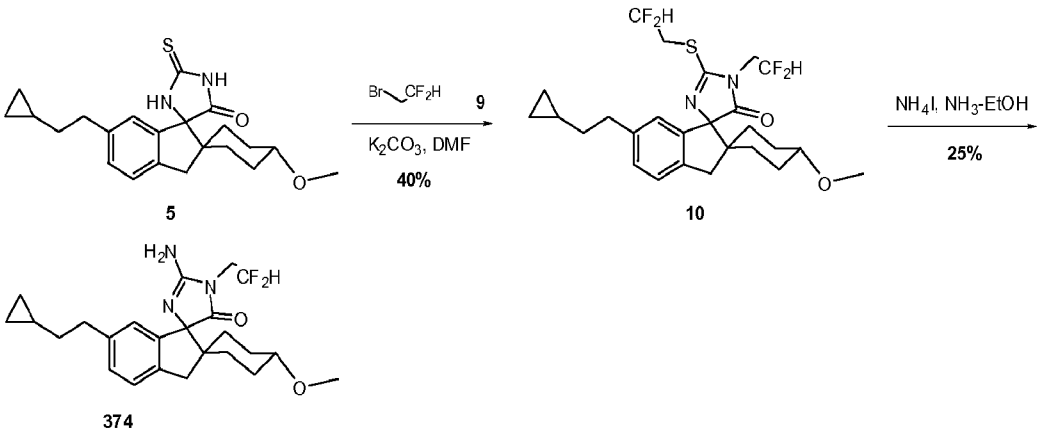
Procedure for preparation of compound 373

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was alkylated with compound **compound 373a** to give compound **373b** (47 mg, 82%) as a white solid.**LC-MS**: t_R = 2.082 min in 3 min chromatography, MS (ESI) m/z = 735 $[M+H]^+$.

Compound **373b** (40 mg, 0.054 mmol) was then converted to **compound 373** (10.7 mg, 36%) as a white solid. **LC-MS**: t_R = 1.610 min in 3 min chromatography, MS (ESI) m/z = 543 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.18 (d, J = 7.6 Hz, 1H),

7.09 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 3.71 (m, 2H), 3.44 (d, J = 6.8 Hz, 2H), 3.31 (s, 3H), 3.13 (m, 1H), 3.09 (d, J = 15.6 Hz, 1H), 3.02 (d, J = 15.2 Hz, 1H), 3.02 (d, J = 15.2 Hz, 1H), 2.81 (s, 3H), 2.73 (m, 1H), 2.67 (t, J = 7.6 Hz, 2H), 1.85-2.05 (m, 4H), 1.50-1.80 (m, 3H), 1.20-1.50 (m, 8H), 0.65 (m, 1H), 0.40 (m, 2H), 0.00 (m, 2H).

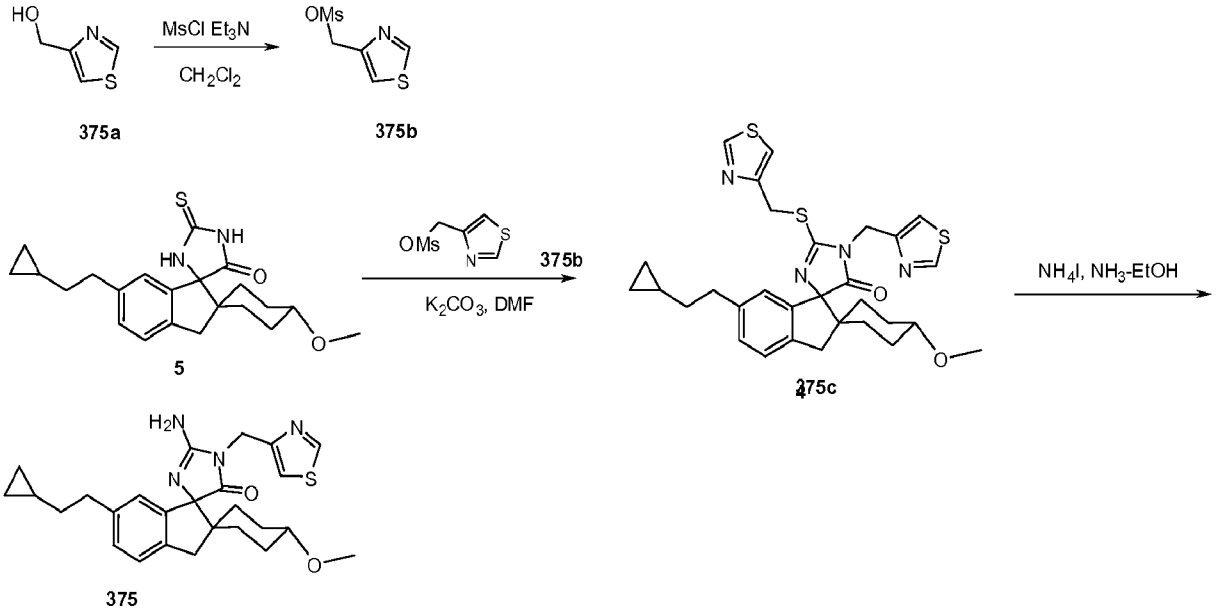
Example 317. Synthesis of Compound 374



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with 2-bromo-1,1-difluoro-ethane (**9**) (33 mg, 0.3 mmol) to give compound **10** (24 mg, yield 40%) as a white solid.

Compound **10** (20 mg, 0.04 mmol) was then heated with NH_4I (60 mg, 0.4 mmol) in a solution of NH_3-EtOH (3 mL, 5 N) to give **compound 374** (5 mg, 25%) as a white solid. **LCMS**: t_R = 1.58 min in 3 min chromatography, MS (ESI) m/z = 432.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.00-7.20 (m, 2H), 6.75-6.85 (s, 1H), 5.80-6.30 (m, 1H), 3.85-4.00 (m, 2H), 3.35-3.40 (s, 3H), 3.00-3.20 (m, 3H), 2.60-2.70 (m, 2H), 1.90-2.10 (m, 3H), 1.30-1.70 (m, 7H), 0.60-0.70 (m, 1H), 0.35-0.45 (m, 2H), 0.05-0.10 (m, 2H). **^{19}F NMR**: (CD_3OD 400 MHz): δ-124.396

Example 318. Synthesis of Compound 375



Procedure for preparation of Compound 27

To a solution of compound **375a** (100 mg, 0.86 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (175.4 mg, 1.73 mmol) and MsCl (109.3 mg, 0.95 mmol) under nitrogen, the mixture was stirred at room temperature for 4 h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give compound **375b** (72.8 mg, 75%) as a yellow oil which was used in the next step without further purification. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.79-8.78 (d, J = 2.0 Hz, 1H), 7.35-7.34 (d, J = 2.0 Hz, 1H), 4.73 (s, 2H), 3.65 (s, 3H).

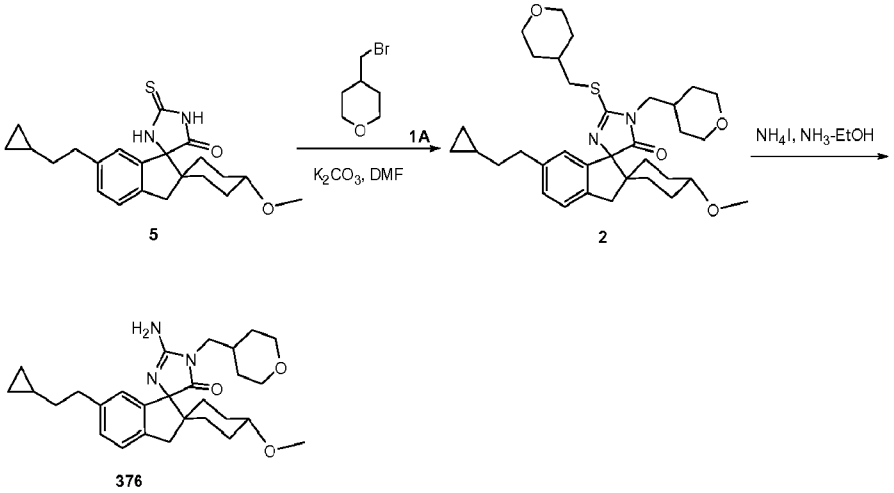
Procedure for preparation of compound 375

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.077 mmol) was dialkylated with compound **27** (28.9 mg, 0.156 mmol) to afford compound **375c** (30 mg, 55%) as a white solid. **LCMS**: t_R=1.626 min in 2 min chromatography, MS (ESI) m/z = 579.3 $[M+H]^+$.

Compound **375c** (20 mg, 0.034 mmol) was then heated with NH_4I (49.6 mg, 0.34 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 375** (8.10 mg, 51%) as a

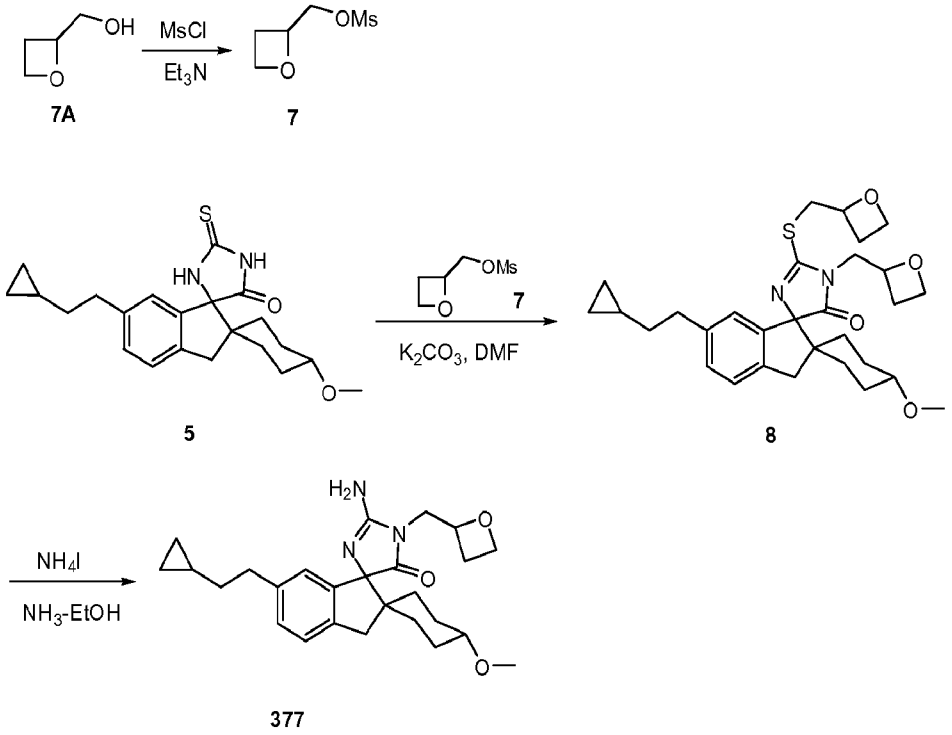
white solid. **LCMS**: t_R = 1.075 min in 2 min chromatography, MS (ESI) *m/z* = 465.2 $(M+H)^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.98-8.97 (d, *J* = 2.0 Hz, 1H), 7.54-7.52 (d, J = 7.6 Hz, 1H),7.25-7.19 (d, J = 7.6 Hz, 1H), 7.19-7.15 (d, J = 7.6 Hz, 1H), 7.10-7.04 (s, 1H), 5.10-5.01 (s, 2H) 3.33 (s, 3H), 3.20-3.10 (m, 2H), 3.10-3.05 (d, *J* = 15.2 Hz, 2H), 2.70-2.66 (t, *J* = 15.2 Hz, 2H), 2.10-1.98 (m,2H), 1.80-1.70 (m, 1H), 1.60-1.35 (m, 5H), 1.35-1.20 (m, 2H), 0.67-0.64 (m, 1H), 0.41-0.38 (m, 2H), 0.10-0.07 (m, 2H).

Example 319. Synthesis of Compound 376



According to a similar synthesis of **compound 344**, compound **5** (50 mg, 0.13 mmol) was dialkylated with compound **1A** (77 mg, 0.52 mmol) to afford the crude product **2** (45 mg, 80%), which was heated NH_4I (98 mg, 0.68 mmol) in a solution of NH_3/EtOH (5 mL, 5 N) to give **compound 376** (15 mg, 42%) as a white solid. **LC-MS** t_R = 1.057 min in 2 min chromatography, MS (ESI) *m/z* 466.2 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.13 (dd, *J* = 32.8, 7.6 Hz, 2H), 6.83 (s, 1H), 3.95 (t, *J* = 11.2 Hz, 2H), 3.4 (d, *J* = 7.2 Hz, 2H), 3.44 (s, 1H), 3.35 (m, 3H), 3.15 (d, *J* = 15.2 Hz, 1H), 3.0 (d, *J* = 15.2 Hz, 1H), 2.6 (t, *J* = 15.6 Hz, 2H), 2.0 (m, 5H), 1.6(m, 2H), 1.4 (m, 8H), 0.6 (m, 1H), 0.39 (d, *J* = 7.6 Hz, 2H), 0.68 (d, *J* = 12.4 Hz, 2H).

Example 320. Synthesis of Compound 377



Procedure for preparation of Compound 7

To a solution of compound **7A** (200 mg, 2.27 mmol) in CH_2Cl_2 (10 mL) was added MsCl (286 mg, 2.50 mmol) and Et_3N (689 mg, 6.81 mmol) at 0 °C, the mixture was stirred at 0 °C for 1 h. Then H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over Na_2SO_4 and concentrated to give compound **7** (160 mg, 42%) as a yellow oil, which was used for the next step without further purification.

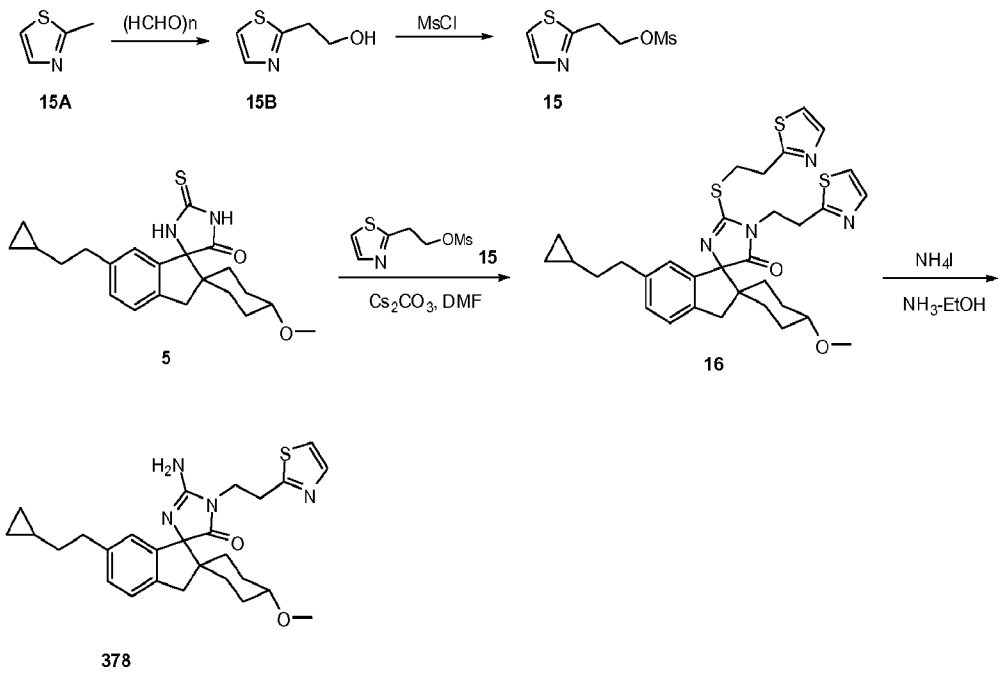
Procedure for preparation of Compound 377

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **7** (38.9 mg, 0.234 mmol) to give compound **8** (16 mg, 39%) as a white solid.

Compound **8** (20 mg, 0.038 mmol) was then heated with NH_4I (44.2 mg, 0.305 mmol) in a solution of NH_3/EtOH (2 mL, 0.5 N) to give **compound 377** (4.3 mg, 26%) as a white solid. **LC-MS** t_R = 0.920 min in 2 min chromatography, MS (ESI) *m/z* 438 $[M+H]^+$.**^{1}H NMR** (CD_3OD varian 400 MHz): δ 7.21 (d, J = 7.6 Hz, 2H), 7.11 (d, J =

7.6 Hz, 2H), 6.84 (d, J = 14.8 Hz, 1H), 5.01 (s, 1H), 4.67 (m, 1H), 4.54 (m, 1H), 3.76 (m, 2H), 3.36 (s, 3H), 3.12 (m, 3H), 2.69 (m, 3H), 2.52 (m, 1H), 2.00 (m, 3H), 1.85 (m, 1H), 1.40 (m, 6H), 0.71 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 321. Synthesis of Compound 378



Procedure for preparation of Compound 15B

Compound **15A** (6 g, 60.5 mmol) and $(HCHO)_n$ (2.76 g, 30.25 mmol) were heated together in a sealed tube at 165 °C for 3 h. After cooling, the reaction mixture was removed carefully and purified by column chromatography (CH_2Cl_2: EtOAc=1: 1) to give compound **15B** (1.6 g, 20%) as a yellow oil.

Procedure for preparation of Compound 15

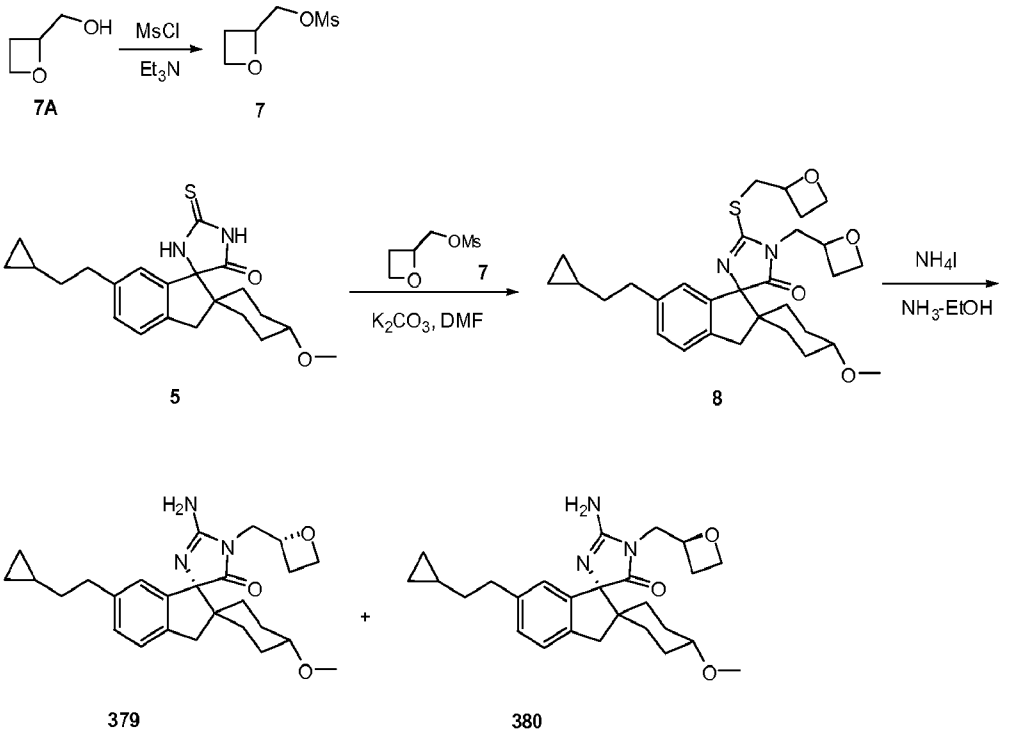
To a solution of compound **15B** (200 mg, 1.55 mmol) in CH_2Cl_2 (5 mL) was added MsCl (195 mg, 1.70 mmol) and Et_3N (470 mg, 4.65 mmol) at 0 °C, the mixture was stirred at 0 °C for 1 h. Then H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over Na_2SO_4 and concentrated to give compound **15** (150 mg, 47%) as a yellow oil, which was used for the next step without further purification.

Procedure for preparation of Compound 378

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **15** (48.5 mg, 0.234 mmol) to give compound **16** (40 mg, 85%) as a white solid.

Compound **16** (45 mg, 0.074 mmol) was then heated with NH_4I (86 mg, 0.593 mmol) in a solution of NH_3/EtOH (2 mL, 5 N) to give **compound 378** (2.5 mg, 7%) as a white solid. **LC-MS** t_R = 1.081 min in 2 min chromatography, MS (ESI) *m/z* 479 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.68 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 3.2 Hz, 1H), 7.20 (m, 2H), 7.01 (s, 1H), 4.15 (m, 2H), 3.42 (m, 2H), 3.22 (s, 3H), 3.00 (m, 1H), 2.97 (m, 2H), 2.69 (m, 2H), 1.97 (m, 2H), 1.63 (m, 1H), 1.47 (m, 5H), 1.31 (m, 2H), 0.69 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 323. Synthesis of Compounds 379 and 380



Procedure for preparation of Compound 7

To a solution of compound **7A** (200 mg, 2.27 mmol) in CH_2Cl_2 (10 mL) was added MsCl (286 mg, 2.50 mmol) and Et_3N (689 mg, 6.81 mmol) at 0 °C, the mixture

was stirred at 0 °C for 1 h. Then H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 × 20 mL), the organic layer was dried over Na_2SO_4 and concentrated to give compound **7** as a yellow oil (160 mg, 42%), which was used for the next step without further purification.

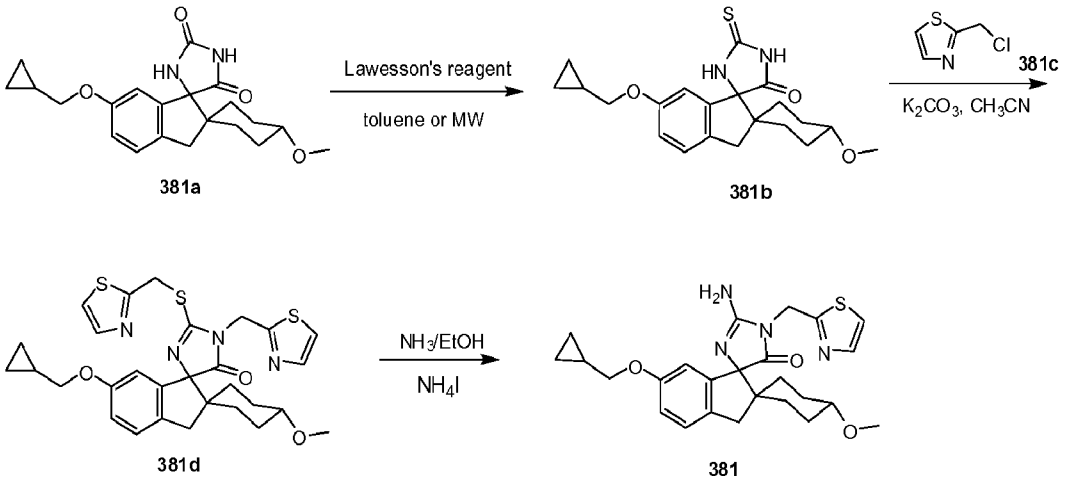
Procedure for preparation of Compounds 379 and 380

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was dialkylated with compound **7** (38.9 mg, 0.234 mmol) to give compound **8** (16 mg, 39%) as a white solid.

Compound **8** (20 mg, 0.038 mmol) was then heated with NH_4I (44.2 mg, 0.305 mmol) in a solution of NH_3/EtOH (2 mL, 0.5 N) and purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and HPLC and SFC to give **compound 379** (3.0 mg, 37%), **SFC:** t_R = 6.15 min in 16 min chromatography, ee = 98%, **LC-MS** t_R = 1.025 min in 2 min chromatography, MS (ESI) *m/z* 438 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.22 (m, 2H), 7.06 (m, 1H), 4.30 (m, 1H), 4.11 (m, 1H), 3.90 (m, 2H), 3.63 (m, 1H), 3.33 (s, 3H), 3.13 (m, 1H), 3.11 (m, 2H), 2.70 (m, 2H), 2.42 (m, 1H), 2.00 (m, 3H), 1.85 (m, 1H), 1.40 (m, 6H), 1.38 (m, 1H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

and **compound 380** (3.2 mg, 38%) as a white solid.**SFC:** t_R = 6.84 min in 16 min chromatography, ee = 98%, **LC-MS** t_R = 1.030 min in 2 min chromatography, MS (ESI) *m/z* 438 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.21 (d, J = 3.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 14.4 Hz, 1H), 5.01 (m, 1H), 4.67 (m, 1H), 4.54 (m, 1H), 3.86 (m, 2H), 3.33 (s, 3H), 3.15 (m, 1H), 3.09 (m, 2H), 2.71 (m, 3H), 2.65 (m, 1H), 2.00 (m, 3H), 1.66 (m, 1H), 1.40 (m, 6H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 323. Synthesis of Compound 381



Procedure for preparation of Compound 381b

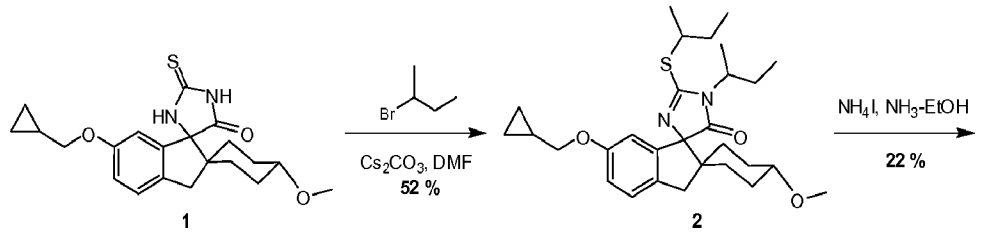
To a solution of compound **381a** (80 mg, 0.21mmol) in anhydrous toluene (2 mL) was added Lawesson's Reagent (84.8 mg, 0.21 mmol) under N_2, the mixture was stirred at 110 °C for 3 h. The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to afford compound **381b** (50 mg, 60%) as a white solid.**LCMS**: t_R=1.258 min in 2 min chromatography, MS (ESI) *m/z* = 387.2 $[M+H]^+$.

Procedure for preparation of compound 381

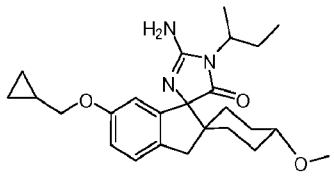
According to a similar synthesis of **compound 344**, compound **381b** (20 mg, 0.05 mmol) was dialkylated compound **381c** (26.7 mg, 0.20 mmol) to give compound **381d** (20 mg, 66%) as a white solid.**LCMS**: t_R=1.427 min in 2 min chromatography, MS (ESI) *m/z* = 387.2 $[M+H]^+$.

Compound **381d** (20 mg, 0.034 mmol) was then heated with NH_4I (49.4 mg, 0.34 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 381** (1.20 mg, 8%) as a white solid. **LCMS**: t_R = 1.827 min in 3 min chromatography, MS (ESI) *m/z* = 467.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.80 (s, 1H), 7.60 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 5.20 (s, 2H), 3.77 (d, *J* = 6.8 Hz, 2H), 3.35-3.33 (s, 3H), 3.20-3.15 (m, 1H), 3.14-2.93 (m, 2H), 2.10-1.90 (m, 2H), 1.90-1.80 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1.10 (m, 5H), 0.63-0.59 (m, 2H), 0.38-0.32 (m, 2H).

Example 324. Synthesis of Compound 382



1 2

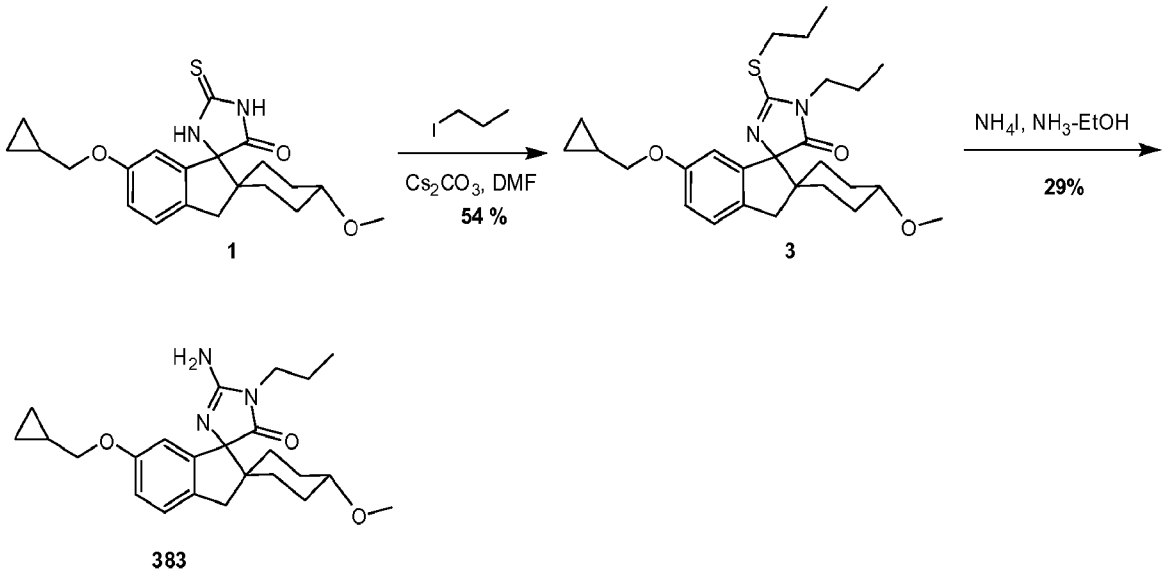


382

According to a similar synthesis of **compound 344**, compound **1** (30 mg, 0.077 mmol) was dialkylated with 2-bromo-butane (42.4 mg, 0.31 mmol) to give compound **2** (20 mg, 52%) as a white solid.**LC-MS** t_R = 1.488 min in 2 min chromatography, MS (ESI) *m/z* = 499.3 $[M+H]^+$.

Compound **2** (20 mg, 0.045 mmol) was then heated with NH_4I (57 mg, 0.40 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 382** (3.80 mg, 22%) as a white solid.**LC-MS** t_R = 1.05min in 2 min chromatography, MS (ESI) MS (ESI) *m/z* = 426.3 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.07-7.05 (d, *J* = 8.0 Hz, 1H), 6.80-6.69 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 4.01-3.82 (m, 1H), 3.73-3.64 (d, *J* = 6.8 Hz, 2H), 3.34 (s, 3H), 3.10-3.01 (m, 1H), 2.95-2.89 (d, *J* = 14.8 Hz, 1H), 2.87-2.82 (d, *J* = 15.2 Hz, 1H), 2.01-1.70 (m, 4H), 1.60-1.40 (m, 2H), 1.40-1.26 (m, 2H), 1.31-1.22 (m, 3H), 1.22-1.05 (m, 3H), 0.90-0.71 (m, 3H), 0.60-0.40 (m, 2H), 0.31-0.21 (m, 2H).

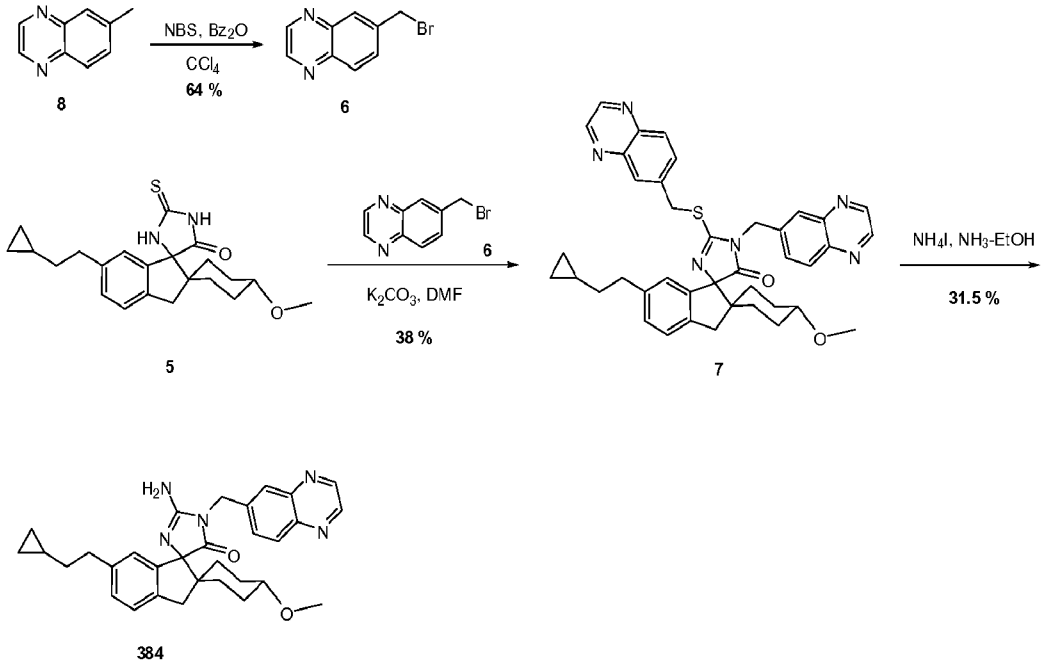
Example 325. Synthesis of Compound 383



According to a similar synthesis of **compound 344**, compound **1** (30 mg, 0.077 mmol) was dialkylated with 1-Iodo-propane (52.6 mg, 0.31 mmol) to give compound **3** (20 mg, 54%) as a white solid.**LC-MS** t_R = 1.37 min in 2 min chromatography, MS (ESI) MS (ESI) *m/z* = 471.2 $[M+H]^+$.

Compound **3** (20 mg, 0.042 mmol) was then heated with NH_4I (61 mg, 0.42 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 383** (5.10 mg, 29%) as a white solid. **LC-MS** t_R = 1.02 in 2 min chromatography, MS (ESI) MS (ESI) *m/z* = 412.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.08-7.06 (d, *J* = 8.0 Hz, 1H), 6.80-6.65 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.79-3.71 (m, 2H), 3.41-3.35 (t, *J* = 7.2 Hz, 2H), 3.38 (s, 3H), 3.10-3.01 (m, 1H), 2.95-2.90 (d, *J* =14.8 Hz, 1H), 2.95-2.85 (d, *J* = 14.4 Hz, 1H), 2.01-1.80 (m, 2H), 1.80-1.70 (m, 1H), 1.64-1.40 (m, 3H), 1.41-1.22 (m, 2H), 1.22-1.05 (m, 3H), 0.85-0.71 (t, *J* = 7.6 Hz, 3H), 0.60-0.40 (m, 2H), 0.31-0.12 (m, 2H).

Example 326. Synthesis of Compound 384



Procedure for preparation of compound 6

To a solution of compound **8** (100 mg, 0.69 mmol) in anhydrous CCl_4 (2 mL) was added NBS (135.9 mg, 0.76 mmol) and Bz_2O (3.80 mg, 0.015 mmol). The resulting suspension was heated at reflux for 12 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to give compound **6** (100 mg, 64%) as a yellow liquid.**^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.4-8.25 (m, 2H), 8.12-8.05 (m, 2H), 7.82-7.74 (dd, J = 2.0, 8.8 Hz, 1H), 4.62 (s, 2H),

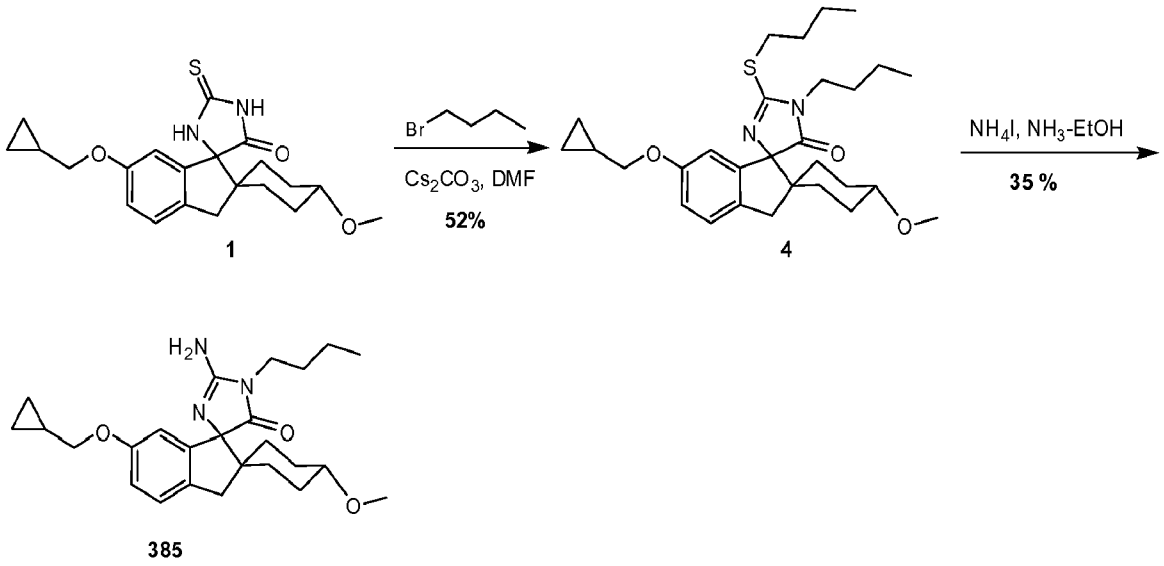
Procedure for preparation of compound 384

According to a similar synthesis of **compound 344**, compound **5** (30 mg, 0.078 mmol) was heated with compound **6** (69.1 mg, 0.31 mmol) to give compound **7** (20 mg, 38%) as a white solid,**LC-MS**: t_R = 1.436 min in 2 min chromatography, MS (ESI) *m/z* 669.3 $[M+H]^+$.

Compound **7** (20 mg, 0.029 mmol) was then heated with NH_4I (42.9 mg, 0.29 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 384** (4.80 mg 31%) as a white

solid.**LC-MS:** t_R = 0.940 min in 2 min chromatography, MS (ESI) *m/z* 510.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 9.03-8.97 (s, 2H), 8.25-8.17 (d, *J* = 8.7 Hz, 1H), 8.05-7.95 (s, 1H), 7.90-7.80 (dd, *J* = 1.8, 6.0 Hz, 1H), 7.35-7.30 (d, *J* = 7.8 Hz, 1 H), 7.30-7.20 (dd, *J* = 1.2, 7.5 Hz, 1 H), 7.09-7.01 (s, 1H), 5.23 (s, 2H) 3.38 (s, 3H), 3.25-3.10 (m, 3H), 2.80-2.68 (t, *J* = 7.5 Hz, 2H), 2.20-2.02 (m, 2H), 2.03-1.81 (m, 1H), 1.70-1.20 (m, 7H), 0.75-0.60 (m, 1H), 0.50-0.30 (m, 2H), 0.30-0.01 (m, 2H).

Example 327. Synthesis of Compound 385

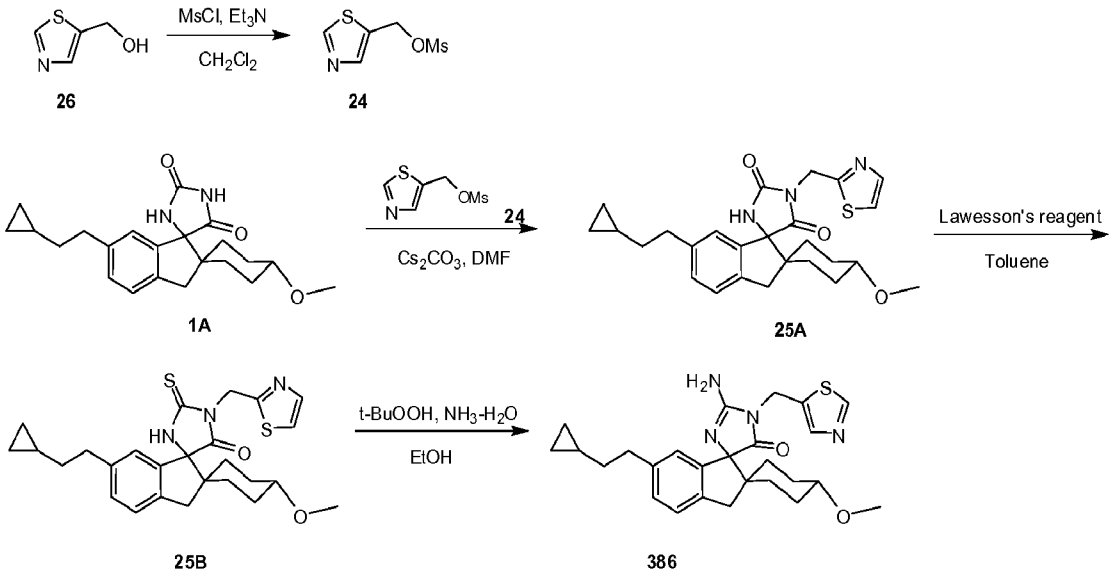


According to a similar synthesis of **compound 344**, compound **1** (30 mg, 0.077 mmol) was dialkylated 2-Bromo-butane (42.4 mg, 0.31 mmol) to give compound **4** (20 mg, 52%) as a white solid. **LC-MS** t_R = 1.47 min in 2 min chromatography, MS (ESI) MS (ESI) *m/z* = 499.3 $[M+H]^+$.

Compound **4** (20 mg, 0.045 mmol) was then heated with NH_4I (57 mg, 0.40 mmol) in NH_3-EtOH (2 mL, 5 N) to give **compound 385** (9.20 mg, 35%) as a white solid.**LC-MS** t_R = 1.056 min in 2 min chromatography, MS (ESI) *m/z* = 426.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.20-7.01 (d, *J* = 8.4 Hz, 1H), 6.80-6.60 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.75-3.60 (m, 2H), 3.45-3.35 (t, *J* = 7.2 Hz, 2H), 3.38 (s, 3H), 3.10-3.01 (m, 1H), 2.95-2.90 (d, *J* = 14.8 Hz, 1H), 2.90-2.81 (d, *J* =

14.8 Hz, 2H), 2.01-1.80 (m, 2H), 1.81-1.70 (m, 1H), 1.64-1.46 (m, 3H), 1.41-1.05 (m, 7H), 0.90-0.80 (t, J = 7.2 Hz, 3H), 0.60-0.40 (m, 2H), 0.31-0.12 (m, 2H).

Example 328. Synthesis of Compound 386



Procedure for preparation of compound 24

To a solution of thiazol-5-yl-methanol (0.20 g, 1.74 mmol) and Et_3N (0.40 g, 3.95 mmol) in CH_2Cl_2 (10 mL) was added methane sulfonyl chloride (0.40 g, 3.49 mmol) via a syringe slowly with stirring. After addition, the reaction mixture was stirred at ambient temperature for 7 h. The reaction was quenched by addtion 10 mL brine with stirring. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude compound **24** (0.40 g, crude) as a brown oil, which was used directly in next step.

Procedure for preparation of compound 386

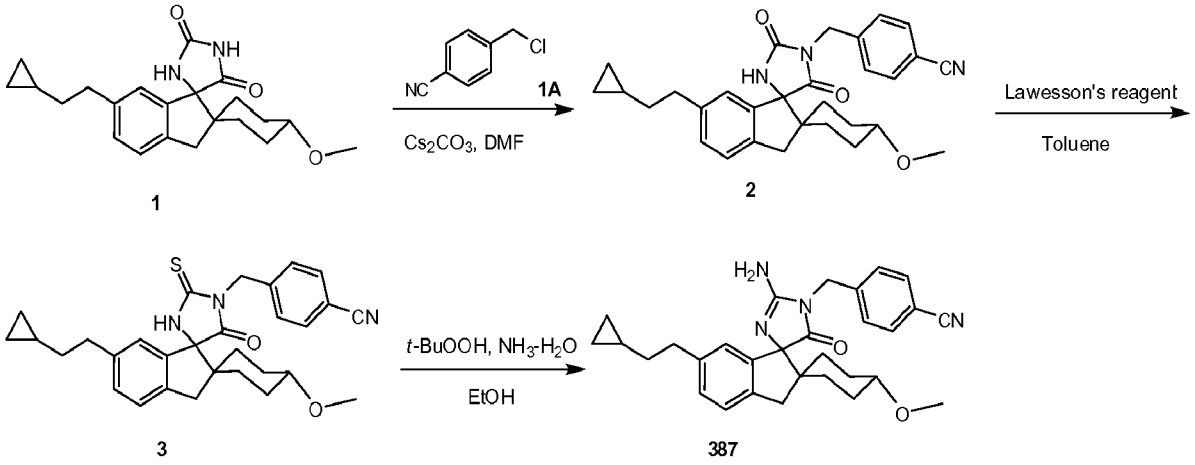
According to a similar synthesis of **compound 296**, compound **1A** (50 mg, 0.14 mmol) was alkylated with compound **24** to give compound **25A** (31 mg, 48%) as a white solid.^{1}**H NMR** ($CDCl_3$ varian 400 MHz): δ 8.73 (s, 1H), 7.86, (s, 1H), 7.21 (d, J

= 7.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.18 (m, 1H), 4.87 (s, 2H), 3.36 (s, 3H), 3.15 (d, *J* = 14.4 Hz, 1H), 3.09 (m, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 1.85-2.10 (m, 3H), 1.15-1.50 (m, 7H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Compound **25A** (31 mg, 0.069 mmol) was then reacted with Lawesson's reagent to give compound **25B** (13 mg, 41%) as a white solid.**LC-MS**: t_R = 1.214 min in 2 min chromatography, MS (ESI) *m/z* = 482 $[M+H]^+$.

Finaly, compound **25B** (13 mg, 0.027 mmol) was converted to **compound 386** (9.7 mg, 78%) as a white solid. **LC-MS**: t_R = 1.382 min in 3 min chromatography, MS (ESI) *m/z* = 465 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 8.95 (s, 1H), 7.90, (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 4.98 (s, 2H), 3.33 (s, 3H), 3.11 (m, 2H), 3.03 (d, *J* = 15.2 Hz, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 1.80-2.00 (m, 3H), 1.15-1.50 (m, 7H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Example 329. Synthesis of Compound 387

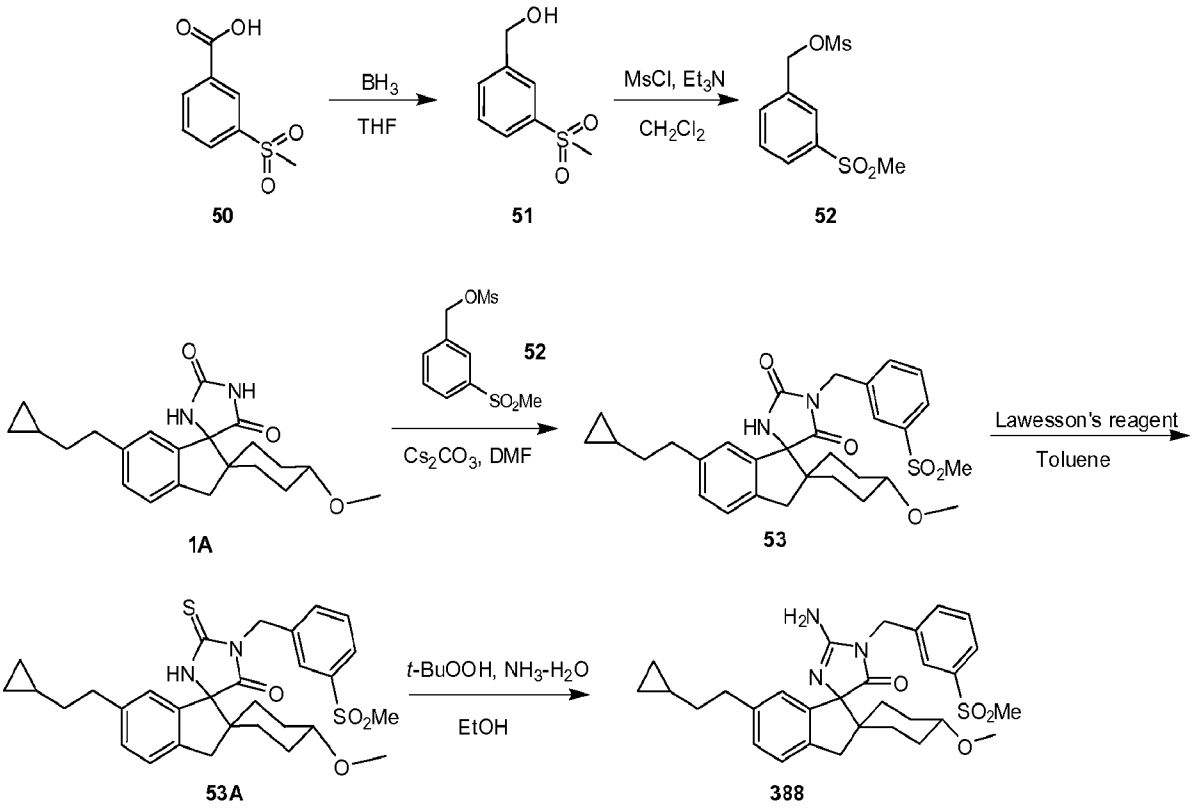


According to a similar synthesis of **compound 296**, compound **1** (50 mg, 0.14 mmol) was alkylated with compound **1A** (23 mg, 0.149mmol) to give compound **2** (20 mg, 31%) as a white solid.

Compound **2** (20 mg, 0.041 mmol) was then reacted with Lawesson's Reagent (18 mg, 0.046 mmol) in anhydrous toluene (2.5 mL) to give the crude product **3** (25 mg), which was converted to **compound 387** (2.5 mg, 10%) as a white solid.**LC-MS**: t_R =1.008 min in 2 min chromatography, MS (ESI) *m/z* 483.2$[M+H]^+$.**^{1}H NMR** (CD_3OD

400 MHz): δ 7.77 (d, J = 6.4 Hz, 2H), 7.49 (d, J = 6.4 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 4.92 (m, 2H), 3.34 (s, 3H), 3.16 (m, 3H), 2.72 (t, J = 7.6 Hz, 2H), 2.00 (m, 2H), 1.74 (m, 1H), 1.48 (m, 7H), 0.62 (m, 1H), 0.39 (m, 2H), 0.00 (m, 2H).

Example 330. Synthesis of Compound 388



Procedure for preparation of compound 51

A flask equipped with a nitrogen balloon was charged with 3-methanesulfonyl-benzoic acid (0.50 g, 2.5 mmol) and anhydrous THF (10 mL). The mixture was cooled down to 0 °C with an ice water bath. A complex of BH_3-THF (3.0 mL, 3.0 mmol, 1 M in THF) was added with stirring at 0 °C slowly and the mixture was warmed to ambient temperature, then stirred at ambient temperature overnight. The nixture was quenched by additing methanol (10 mL) carefully. The solvent was removed by evaporation in vacuo, the resiude was dissolved in ethyl acetate (100 mL). The mixture was washed

with 1N NaOH aqueous solution (30 mL), brine (30 mL × 2) in turn. The separated organic layer was dired over Na_2SO_4, filtered and concentrated to give crude compound **51** (0.25g, 50% crude yield) as a colorless oil, which was used directly in next step without purification.

Procedure for preparation of compound 52

To a solution of crude compound **51** (25 mg, 1.30 mmol) and Et_3N (0.40 g, 3.95 mmol) in CH_2Cl_2 (10 mL) was added Methane sulfonyl chloride (400 mg, 3.49 mmol) via a syringe slowly with stirring. After addition, the reaction mixture was stirred at ambient temperature overnight. The reaction was quenched by addtion 30 mL brine with stirring. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 2: 1 to give compound **52** (100 mg, 29%) as a pale yellow oil.

Procedure for preparation of compound 388

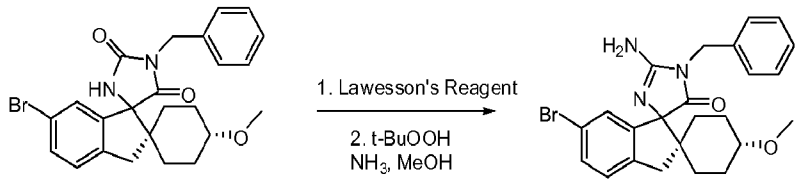
According to a similar synthesis of **compound 296**, compound **1A** (50 mg, 0.14 mmol) was alkylated with compound **52** give compound **53** (34 mg, 45%) as a white solid.**^{1}H NMR** ($CDCl_3$ varian 400): δ 7.89 (s, 1H), 7.87 (dd, J = 1.2, 7.6 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.14 (dd, J = 1.6, 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.89 (s, 1H), 6.06 (m, 1H), 4.73 (s, 2H), 3.36 (s, 3H), 3.14 (m, 2H), 3.03 (m, 4H), 2.65 (td, J = 2.8, 7.4 Hz, 2H), 1.80-2.10 (m, 3H), 1.20-1.50 (m, 7H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

Compound **53** (31 mg, 0.069 mmol) was then reacted with Lawesson's reagent to give compound **53A** (27 mg, 77 %) as a white solid. **LC-MS**: t_R = 1.245 min in 2 min chromatography, MS (ESI) *m/z* = 521 (M-31), 575 (M+23).

Finally, compound **53A** (27 mg, 0.027 mmol) was converted to **compound 388** (14.9 mg, 57%) as a white solid. **LC-MS**: t_R = 1.382 min in 3 min chromatography, MS (ESI) *m/z* = 465 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.91 (d, J = 8.0 Hz, 1H), 7.87, (s, 1H), 7.60-7.70 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.90 (s,

1H), 4.89 (m, 2H), 3.37 (s, 3H), 3.20-3.30 (m, 4H), 3.071 (m, 2H), 2.74 (m, 2H), 1.95-2.10 (m, 2H), 1.70-1.80 (m, 1H), 1.20-1.60 (m, 7H), 0.65 (m, 1H), 0.40 (m, 2H), 0.01 (m, 2H).

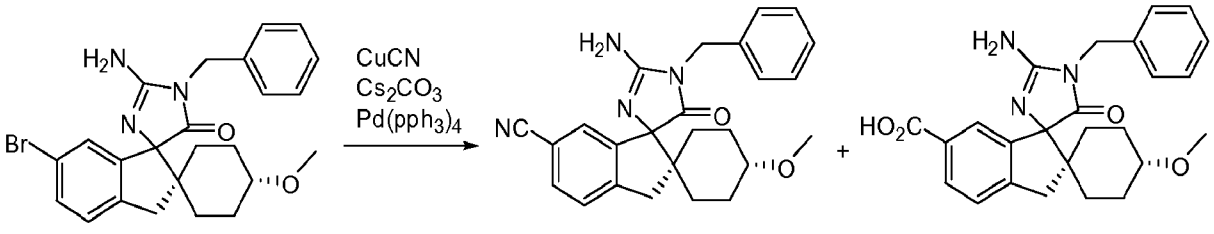
Example 331. Synthesis of Compound 389



1 389

According to a similiar synthesis of **compound 291**, compound **1** afforded **compound 389** (25 mg) as a TFA salt. **LC-MS** t_R = 1.45 min in 3 min chromatography, MS (ESI) *m/z* 468 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.76 (m, 1H), 7.74-7.28 (m, 7H), 4.90 (m, 2H), 3.28 (s, 3H), 3.20-3.04 (m, 3H), 2.04-1.92 (m, 2H), 1.76 (m, 1H), 1.42 (m, 3H), 1.24 (m, 2H).

Example 332. Synthesis of Compounds 390 and 391

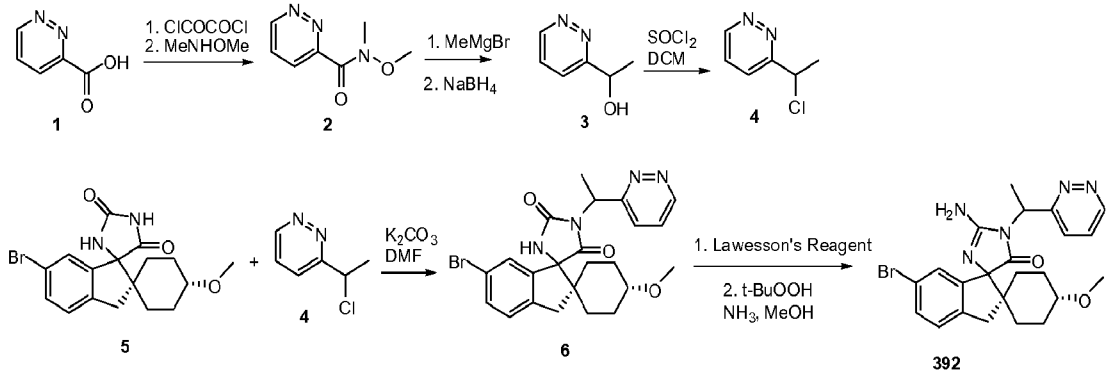


1 390 391

To a solution of compound **1** (10 mg, 0.021 mmol) in DMF (0.5 mL) in a 10 mL CEM microwave tube, there was add CuCN (excess), Cs_2CO_3 (2 eq), and $Pd(pph_3)_4$ (cat. amount). The resulting mixture was heated in a CEM microwave reactor at 160 oC for 180 min. The mixture was filtered, and the filtration was loaded directly to a HPLC to afford **compound 390** (5.9 mg, 52%) as a TFA salt. **LC-MS** t_R = 1.35 min in 3 min chromatography, MS (ESI) *m/z* 415 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.76 (m, 1H), 7.66 (m,1H), 7.56 (m, 1H), 7.42-7.32 (m, 5H), 4.90 (m, 2H), 3.28 (s, 3H), 3.24-

3.06 (m, 3H), 1.98 (m, 2H), 1.76 (m, 1H), 1.46-1.20 (m, 5H); and **compound 391** (2.9 mg, 25%) as a by-product, also a TFA salt. **LC-MS** t_R = 1.19 min in 3 min chromatography, MS (ESI) *m/z* 433 $[M]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.90 (m, 1H), 7.72 (m,1H), 7.48 (m, 1H), 7.42-7.30 (m, 5H), 4.90 (m, 2H), 3.32 (s, 3H), 3.20 (m, 3H), 1.98 (m, 2H), 1.78 (m, 1H), 1.42-1.24 (m, 5H).

Example 333. Synthesis of Compound 392



Step 1. Synthesis of N-methoxy-N-methylpyridazine-3-carboxamide (2)

To a solution of pyridazine-3-carboxylic acid (**1**) (0.44 g, 3.47 mmol) in DCM (10 mL), there was added oxalyl chloride (0.67 g, 5.2 mmol) followed by 2 drops of DMF. The reaction was stirred at room temperature for 1 hr, and the solvent was removed in vacuum to give acid chloride, which was used for the next step without purification.

To the above product there was added K_2CO_3 (1.44 g, 10.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.69 g, 5.2 mmol), followed by MeCN (10 mL). The resulting mixture was stirred at room temperature overnight, filtered through a cotton ball, and the filtration was concentrated to give N-methoxy-N-methylpyridazine-3-carboxamide **(2)** (0.41 g, 71% for two steps).

Step 2. Synthesis of 1-(pyridazin-3-yl)ethanol (3)

To a solution of N-methoxy-N-methylpyridazine-3-carboxamide **(2)** (0.41 g, 2.45 mmol) in anhydrous THF (8 mL) at -78°C, there was added methyl Grignard reagent (1.4 N in Toluene/THF (75:25), 3.5 mL). After finishing addition, the reaction

was stirred at the same temperature for another 1 hr, quenched with MeOH, and warmed up to 0 °C.

To the above solution there was added NaBH4 (excess), and resulting mixture was stirred at 0 oC for 30 min, warmed to room temperature, quenched with acetone. After adding silica gel (5 g), the solvent was removed, and the residue was solid loaded to column for purification. The column was eluented with 0 to 10% MeOH in DCM to give 1-(pyridazin-3-yl)ethanol **(3)** (0.19 g, 63% for 2 steps).

Step 3. Synthesis of 3-(1-chloroethyl)pyridazine (4)

To a solution of 1-(pyridazin-3-yl)ethanol **(3)** (50 mg, 0.40 mmol) in DCM (1 mL), there was added sulfurous dichloride (0.2 mL). The resulting solution was stirred at room temperature for 3 hrs. Solvent was removed to give 3-(1-chloroethyl)pyridazine **(4)**, which was used for the next step without purification.

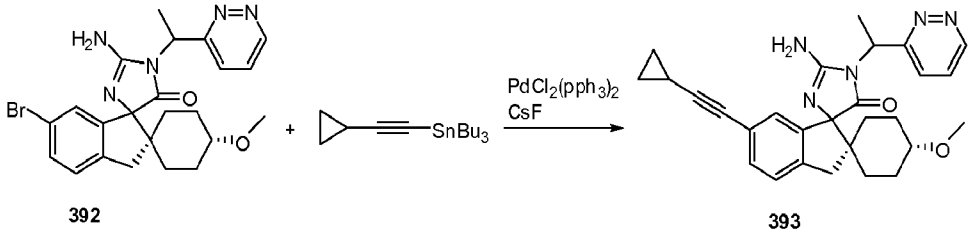
Step 4. Synthesis of compound 6

To a solution of hydantoin **5** (53.0 mg, 0.14 mmol) in DMF (0.2 mL0, there was added K2CO3 (excess) followed by 3-(1-chloroethyl)pyridazine **(4)** (0.2 mmol) in DMF (0.25 mL), the resulting mixture was heated at 70 oC for 4 hrs, cooled to room temperature, added water (5 mL), and extracted with DCM (5 mLx4). The combined organic layers were washed with brine, dried over Na2SO4, and the solvent was removed to give comound **6** (60.7 mg, 89%), **LC-MS** t_R = 1.45 min in 3 min chromatography, MS (ESI) *m/z* 4875 $[M]^+$.

Step 5. Synthesis of compound 392

According to a similiar synthesis of **compound 291**, comound 6 (30.4 mg, 0.06 mmol) afforded **compound 392** (11.0 mg,36 %) as a TFA salt. **LC-MS** t_R = 1.21 min in 3 min chromatography, MS (ESI) *m/z* 484 $[M]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 9.18 (m, 1H), 7.90 (m, H), 7.78 (m, 1H), 7.46 (m, 2H), 7.24 (m, 1H), 5.78 (m, 1H), 3.34 (s, 3H), 3.24-2.86 (m, 3H), 2.10-1.80 (m, 5H), 1.60 (m, 1H), 1.42-1.24 (m, 5H).

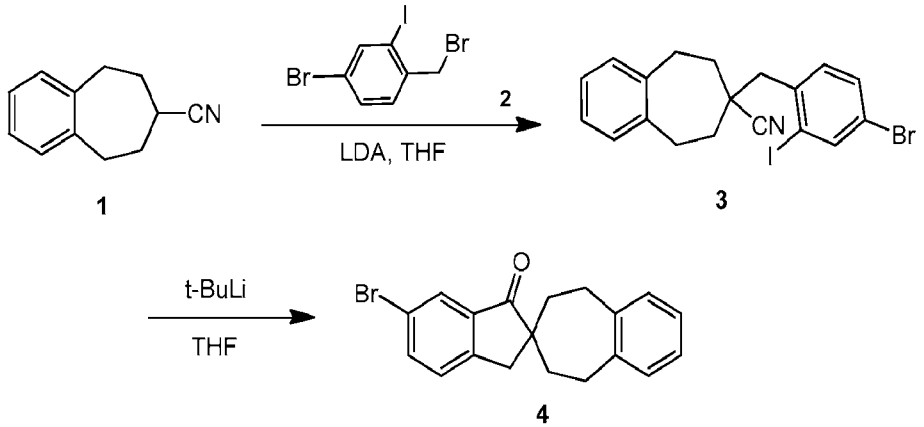
Example 334. Synthesis of Compound 393



392 393

To a 10 mL CEM microwave there was added **compound 392** (7 mg, 0.01 mmol), PdCl2(pph3)2 (cat.) and CsF (3 eq), there solid was degassed followed by blowing N_2 through the tube.Toluene (0.5 mL) was added, and the system was degassed again before tributyl(cyclopropylethynyl)stannane (exaee) was added. The resulting mixture was heated in a CEM microwave reactor at 120 °C for 30 min, filtered, solvent was removed, and the residuea was purified on HPLC to afford **compound 393** (3.4 mg, 52%) as a TFA salt. **LC-MS** t_R = 1.39 min in 3 min chromatography, MS (ESI) *m/z* 470 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 9.16 (m, 1H), 7.90 (m, H), 7.78 (m, 1H), 7.32-7.20 (m, 3H), 5.78 (m, 1H), 3.36 (s, 3H), 3.22-2.94 (m, 3H), 2.08-1.80 (m, 6H), 1.60-1.20 (m, 6H), 0.86 (d, 2H), 0.72 (m, 2H).

Example I-7. **Synthesis of 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'H)-one (4)**



1 3 4

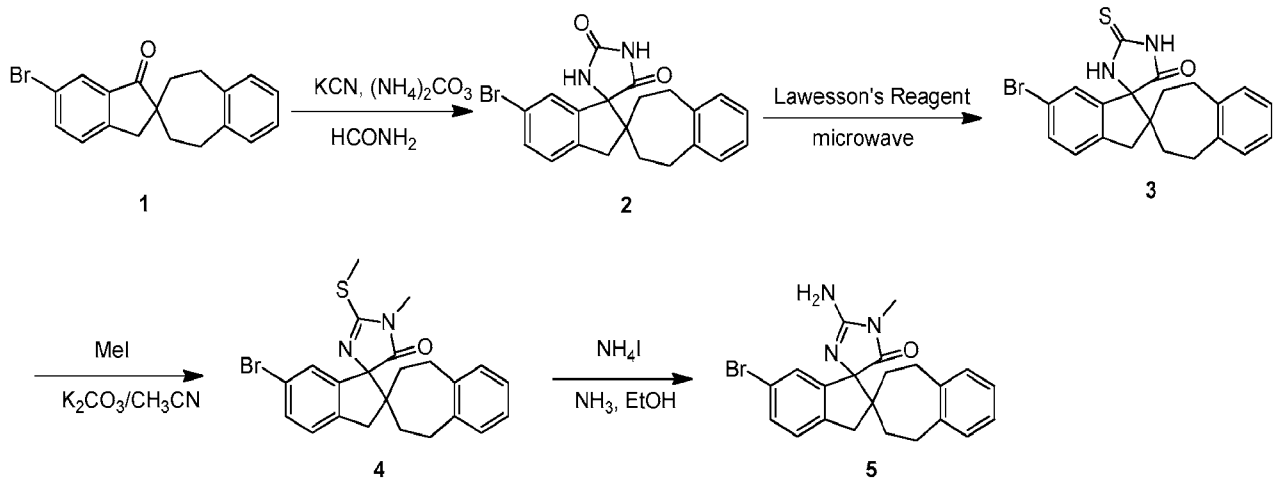
Procedure for preparation of compound 3

To a solution of LDA (23.4 mL, 42.1mmol, 1.8 M in THF) in THF (150 mL) was added slowly a solution of compound **1** (3.6 g, 21.05 mmol) in THF (77 mL) at -60 °C under a N_2 atmosphere. After being stirred at -60 °C for 1 h, a solution of compound **2** (7.05 g, 18.9 mmol)) in THF (23mL) was added slowly to the above solution. The resulting mixture was stirred at -60 °C for 2 h. The reaction mixture was quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel (petroleum: ethyl acetate, 10:1) to give compound **3** (2.5 g, yield 26%) as a yellow solid.

Procedure for preparation of compound 4

A flame dried 100 mL RBF was charged with compound **3** (2.11 g, 4.5 mmol) and anhydrous THF (80 mL) under N_2 atmosphere. The resulting solution was stirred and chilled to -70°C, and *t*-BuLi (1.3 M, in hexane 6.95 mL, 9 mmol, 2 eq.) was added dropwise. Deep red was observed during the addition. The reaction was stirred another 1 h after the addition. The reaction was quenched with MeOH (0.4 mL), and followed by *aq*. HCl solution (2 M, 8 mL). The resulting solution was concentrated to remove organic solvent. The residue was stirred in 0.5 M aq. HCl solution (40 mL). The suspension was heated to reflux (oil bath 105 °C). The reaction was cooled down to room temperature and filter. The cake was washed with H_2O. The light yellow solid was collected and co-evaporated with MeOH two times to remove water to give crude product, which was purified by chromatography to give 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'H)-one (**4**) (450 mg, yield 35%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.80-8.01 (m, 1H), 7.63-7.66 (m, 1H), 7.30-7.32 (m, 1H), 7.00-7.18 (m, 4H), 3.10 (s, 2H), 2.91-2.97 (m, 2H), 2.81 (brs, 2H), 1.78-1.85 (m, 2H), 1.57-1.62 (m, 2H).

Example I-8. Synthesis of hydantoin 5-Method 1



1 2 3 4 5

Procedure for preparation of compound 2

A steel autoclave was charged with a mixture of compound **1** (1 g, 2.94 mmol), KCN (573 mg, 8.82 mmol) and $(NH4)_2CO_3$ (2.82 g, 29.4 mmol) in formamide (30 mL). The mixture was stirred at 110 °C for 72 h, cooled to room temperature, and poured into ice (20 g). After acidification with *conc.* HCl solution (10 mL), the resulting mixture was filtered, and the filter cake was dissolved in ethyl acetate (100 mL) and washed with water (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give compound **2** (80 mg, yield 8%) as a yellow solid.

Procedure for preparation of compound 3

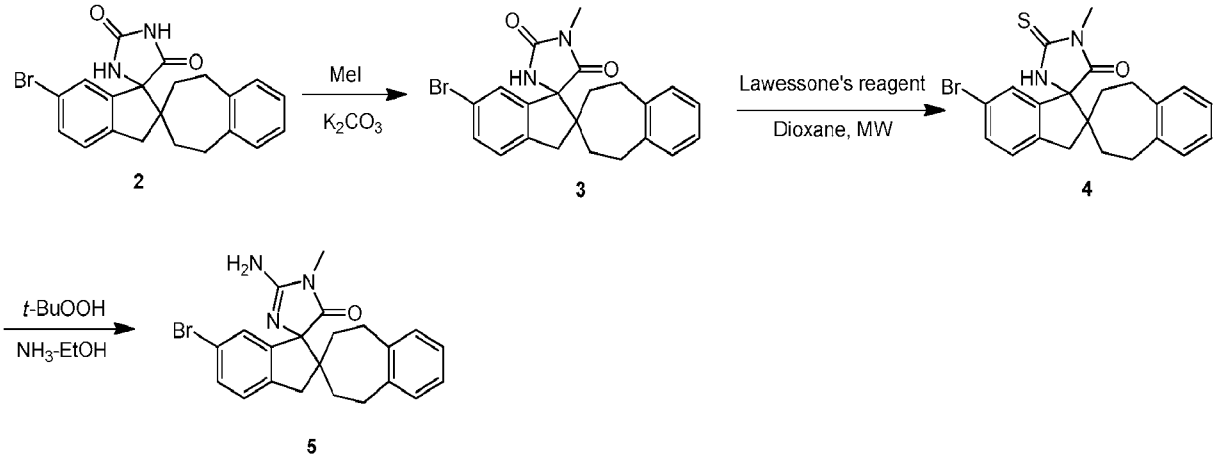
A suspension of compound **2** (20 mg, 0.049 mmol) and Lawesson's Reagent (20 mg, 0.049 mmol) in anhydrous dioxane (1 mL) was stirred at 150 °C for 35 min in a CEM microware reactor. The mixture was concentrated *in vacuo*, and the residue was purified by prep-TLC to give compound **3** (20 mg, 96%) as a yellow solid.

To a solution of compound **3** (20 mg, 0.047 mmol) in CH_3CN (2 mL) was added MeI (13.3 mg, 0.094 mmol) and K_2CO_3 (26 mg, 0.188mmol). After being stirred at 60°C for 10 min in microware, additional MeI (13.3 mg, 0.094 mmol) was added. The reaction mixture was stirred at 80°C for 10 min in microware, concentrated *in vacuo* to give compound **4** (25 mg, 100%) as a yellow solid.

Procedure for preparation of Compound 5

A solution of compound **4** (40 mg, 0.088 mmol) and NH_4I (127 mg, 0.088 mmol) in NH_3/EtOH (5.0 N, 2 mL) was stirred at 120°C in a microwave reactor for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was added CH_2Cl_2 (15 mL), and stirred for 30 min. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give compound **5** (35 mg, yield 92%) as a yellow solid.

Example I-9. Synthesis of hydantoin 5-Method 2



Procedure for preparation of compound 3

To a solution of compound **2** (500 mg, 0.86 mmol) in DMF (10 mL) was added K_2CO_3 (510 mg, 3.72 mmol) and MeI (350 mg, 0.86 mmol). The mixture was stirred at room temperature for 2 h. The mixture was added water (50 mL), the precipitate was collected by filtration to collected the solid, which was dried *in vacuo* a crude compound **3** (300 mg, 58%) as a white solid, which was used directly in next step without purification.

Procedure for preparation of compound 4

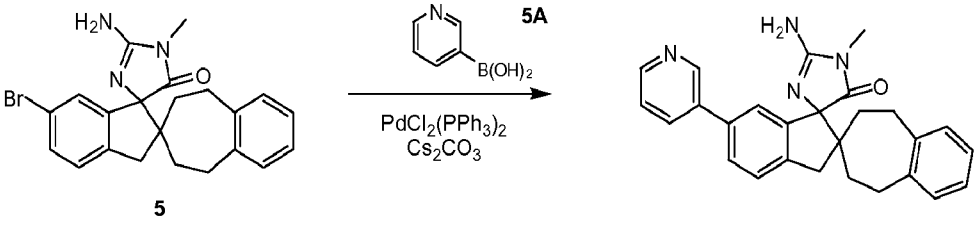
A mixture of compound **3** (300 mg, 0.42 mmol) and Lawesson'reagent (186 mg, 0.46 mmol) in dioxane (10 mL) was heated at 150 °C for 30 min in a CEM microwave reactor. The mixture was cooled, and concentrated *in vacuo*. The residue was purified

by preparative TLC (petroleum ether: ethyl acetate = 3: 1) to give compound **4** (180 mg, 58%).

Procedure for preparation of compound 5

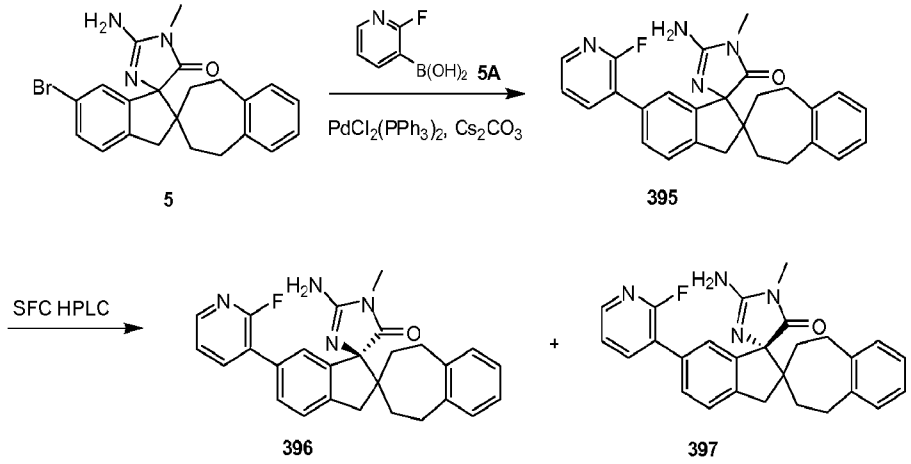
To a solution of compound **4** (500 mg, 1.14 mmol) in a mixture of MeOH (30 mL) and NH_3-EtOH (6 mL) was added *t*-BuOOH (2 mL, 22.8 mmol, 65% in water). The mixture was stirred at room temperature overnight, and concentrated. Water (25 mL) was added, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the residue which was purified by RP-HPLC to give compound **5** (250 mg, 52%) as a white solid.

Example 335. Synthesis of Compound 394



A solution containing hydantoin **5** (25 mg, 0.057 mmol) and compound **5A** (11 mg, 0.089 mmol) in dioxane (1.5 mL), and aqueous Cs_2CO_3 (2 M, 0.4 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (4 mg) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 15 min. After being cooled to room temperature, the mixture was diluted with EtOAc and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by preparative TLC (CH_2Cl_2: MeOH, 10:1) and HPLC to give **compound 394** (2.8 mg, yield 11%) as a white solid. **LC-MS** t_R = 0.863 min in 2 min chromatography, MS (ESI) *m/z* 423 $[M+H]^+$; **^{1}H NMR** (CD3OD 400 MHz): δ 8.77 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.60-7.63 (m, 1H), 7.50-7.52(m, 2H), 7.50 (s, 1H), 7.07-7.08 (m, 4H), 3.23-3.33 (m, 2H), 3.07-3.11 (m, 1H), 3.05(s, 3H), 3.95-3.04 (m, 1H), 2.69-2.73 (m, 1H), 2.55-2.67 (m, 1H), 2.14-2.19 (m, 1H) ; 1.68 (s, 2H), 1.29-1.35(m, 1H).

Example 336. Synthesis of Compounds 395, 396 and 397



Procedure for preparation of compound 395

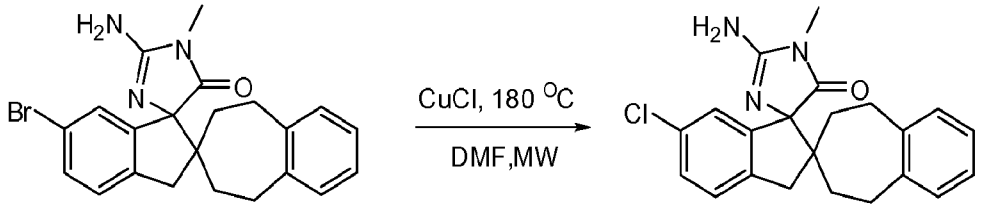
According to a similar synthesis of ***compound 394,*** hydantoin **5** (350 mg, 0.62 mmol), 1,4-dioxane (12 mL) was reacted with compound **5A** (175 mg, 1.24 mmol) to give **compound 395** (80 mg, 31%) as a white solid. **LC-MS** t_R = 0.921 min in 2 min chromatography, MS (ESI) *m/z* 441 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.22 (d, J = 4.8 Hz, 1H), 8.06 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.41 (m, 1H), 7.11 (m, 4H), 3.60 (m, 1H), 3.40 (m, 1H), 3.19 (s, 3H), 3.14 (m, 1H), 2.77 (m, 1H), 2.76 (m, 1H), 2.64 (m, 1H), 2.22 (m, 1H), 1.78 (m, 1H), 1.47 (m, 2H).

Procedure for preparation of compounds 396 and 397

Compound 395 (43 mg) was purified by preparative SFC to give two enantiomers of **compound 396** (16 mg, 38%), **LC-MS** t_R = 1.033 min in 2 min chromatography, MS (ESI) *m/z* 441 $[M+H]^+$. **SFC**: t_R = 2.630 min in 4 min chromatography, **ee** = 100%. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.20 (d, J = 4.8 Hz, 1H), 8.07 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.41 (m, 1H), 7.11 (m, 4H), 3.60 (m, 1H), 3.40 (m, 1H), 3.19 (s, 3H), 3.14 (m, 1H), 2.77 (m, 1H), 2.76 (m, 1H), 2.64 (m, 1H), 2.22 (m, 1H), 1.78 (m, 1H), 1.48 (m, 2H); and **compound 397** (19 mg, 44%) as a white solid. **LC-MS** t_R = 1.028 min in 2 min

chromatography, MS (ESI) *m/z* 441 $[M+H]^+$. **SFC**: t_R = 3.1580 min in 4 min chromatography, **ee** = 98.7%. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.20 (d, J = 4.4 Hz, 1H), 8.07 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.41 (m, 1H), 7.11 (m, 4H), 3.60 (m, 1H), 3.40 (m, 1H), 3.19 (s, 3H), 3.14 (m, 1H), 2.77 (m, 1H), 2.76 (m, 1H), 2.64 (m, 1H), 2.22 (m, 1H), 1.78 (m, 1H), 1.48 (m, 2H).

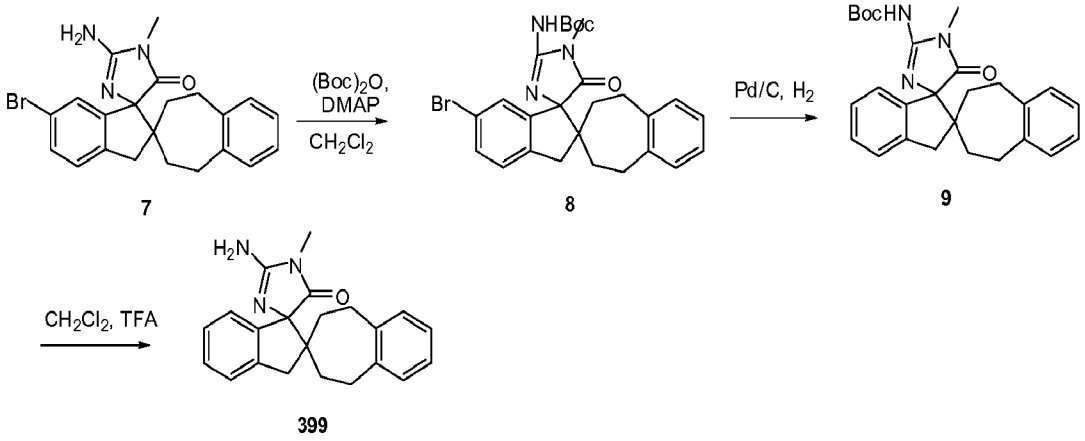
Example 337. Synthesis of Compound 398



5 **398**

To a solution of compound **5** (20 mg, 0.047 mmol) in DMF (4 mL) was added CuCl (64 mg, 0.85 mmol), the resulting mixture was heated at 180 °C in a CEM tube under microwave reactor for 0.5 h. After cooling, the mixture was concentrated under vacuum to give the residue, which was purified by preparative-basic HPLC to give **compound 398** (8.4 mg, 31%) as a white solid. **LC-MS** t_R = 1.062 min in 2 min chromatography, MS (ESI) *m/z* 380.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.28-7.33 (m, 2H), 7.19 (s, 1H), 6.98-6.70 (m, 4H), 3.38-3.42 (d, J = 15.6 Hz, 1H), 3.14-3.21 (m, 1H), 2.98-3.07 (m, 3H), 2.81-2.88 (t, J = 14.0 Hz, 1H), 2.61-2.65 (m, 1H), 2.56 (s, 1H), 2.47-2.52 (m, 1H), 2.02-2.08 (m, 1H), 1.58-1.63 (m, 1H), 1.19-1.37 (m, 2H).

Example 338. Synthesis of Compound 399



Procedure for preparation of compound 8

To a solution of compound **7** (45 mg, 0.1 mmol) and DMAP (25 mg, 0.2 mmol) in CH_2Cl_2 (8 mL) was added $(Boc)_2O$ (45 mg, 0.2 mmol). The reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 4: 1) to give compound **8** (50 mg, 95%) as a white solid.

Procedure for preparation of compound 9

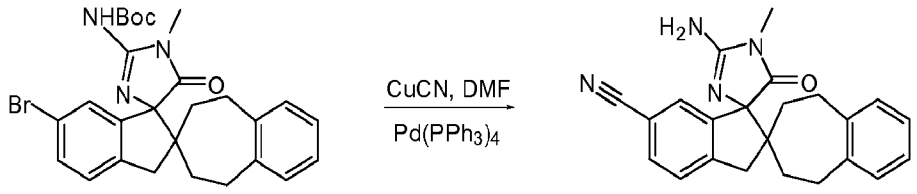
A solution of compound **8** (20 mg, 0.038 mmol) and Pd/C (4 mg) in MeOH (5 mL) was stirred under H_2 atmosphere (10 Psi) at 25 °C for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give crude compound **9** (18 mg, crude yield 100%), which was used directly to next step.

Procedure for preparation of compound 399

To a solution of compound **9** (18 mg, 0.046 mmol) in CH_2Cl_2 (8 mL) was added TFA (1 mL) dropwise. The reaction mixture was stirred at 25 °C for 2 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative RP-HPLC to give **compound 399** (8.8 mg, 50%) as a white solid. **LCMS**: t_R = 1.69 min in 3 min chromatography, MS (ESI) *m/z* 346.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.34-7.46 (m, 2H), 7.28-7.32 (m, 1H), 7.18-7.21 (d, J = 7.2 Hz, 1H), 7.04 (m, 4H), 3.50-

3.55 (d, J = 15.6 Hz, 1H), 3.29-3.31 (m, 1H), 3.18 (s, 3H), 3.11-3.14 (m, 1H), 2.95-3.02 (m, 1H), 2.71-2.77 (m, 1H), 2.57-2.63 (m, 1H), 2.18-2.22 (m, 1H), 1.71-1.76 (m, 1H), 1.38-1.48 (m, 2H).

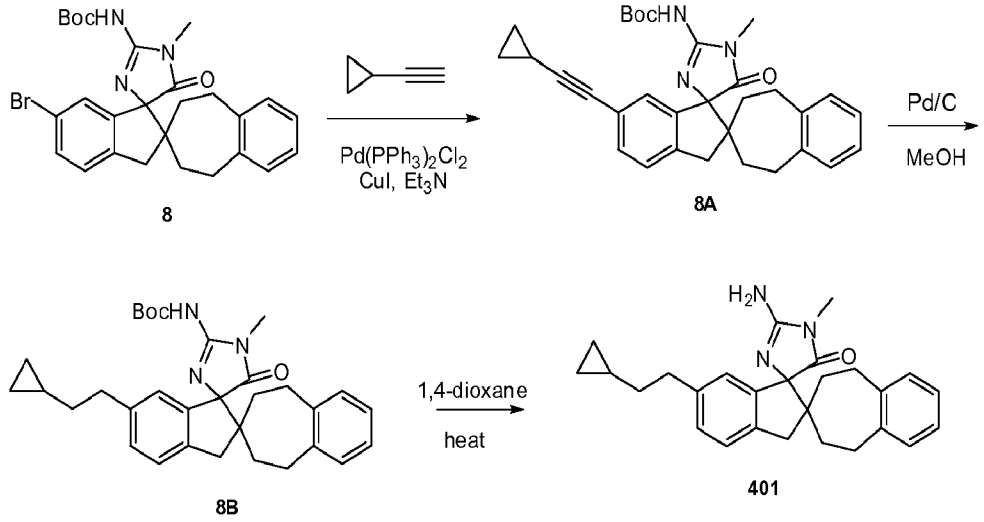
Example 339. Synthesis of Compound 400



8 **400**

A steel autoclave was charged with a mixture of compound **8** (30 mg, 0.057 mmol), CuCN (14 mg, 0.16 mmol), $Pd(PPh_3)_4$ (6 mg, 0.0052 mmol) and DMF (3 mL). The mixture was heated at 120 °C for 10 h. The mixture was filtered, the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative RP-HPLC to afford **compound 400** (5.8 mg, 15%) as a white solid; **LCMS**: t_R = 1.65 min in 3 min chromatography, MS (ESI) *m/z* 371.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.79-7.81 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.64-7.66 (d, J = 8.0 Hz, 1H), 7.11 (s, 4H), 3.61-3.65 (d, J = 12.4, Hz, 1H), 3.40 (m, 1H), 3.19 (s, 3H), 3.09-3.16 (m, 1H), 2.94-3.01 (m, 1H), 2.73-2.78 (m, 1H), 2.58-2.64 (m, 1H), 1.64-1.69 (m, 1H), 1.40-1.50 (m, 1H).

Example 340. Synthesis of Compound 401



Procedure for preparation of Compound 8A

An oven dried three-necked round bottom flask equipped with condenser was charged with compound **8** (66 mg, 0.126 mmol), Et_3N (4 mL) and Et_2NH (0.8 mL) under N_2 atmosphere. To this solution was added CuI (1.2 mg, 0.0063 mmol) and $PdCl_2(PPh_3)_2$ (4.4 mg, 0.0063 mmol). The system was degassed once again, then cyclopropyl acetylene (0.8 mL, excess) was added and the mixture was stirred at 60 °C (oil bath) overnight. The solvent was evaporated *in vacuo* and the residue was partitioned with ethyl acetate (20 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL), the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to dryness. The crude product was purified by preparative TLC (petroleum: ethyl acetate = 3: 1) to give compound **8A** (50 mg, 78%) as a yellow solid.

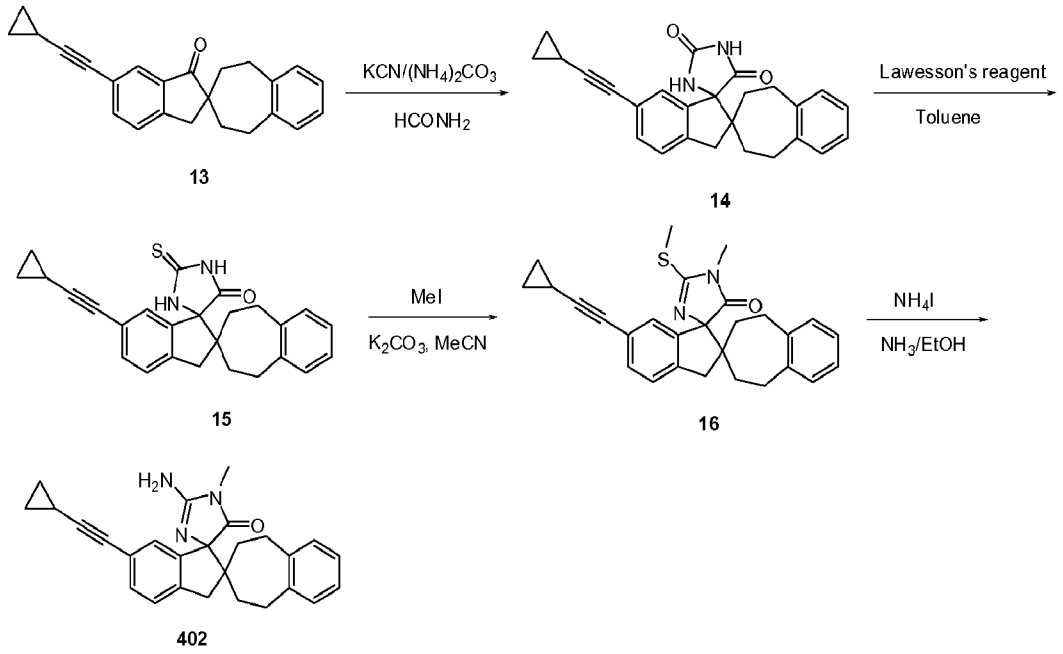
Procedure for preparation of Compound 8B

To a solution of compound **8A** (25mg, 0.049 mmol) in MeOH (3 mL) was added Pd/C (5 mg), the mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 2 h The reaction mixture was filtered through a Celite pad, the filtrate was concentrated in *vacuo* to give the residue, which was purified by preparative TLC (petroleum: ethyl acetate = 3: 1) to give compound **8A** (8 mg, 32%) as a white solid.

Procedure for preparation of compound 401

A solution of compound **4** (8 mg, 0.002 mmol) in 1,4-dioxane (1 mL) was heated at 120 °C in a microwave reactor for 15 min. The solvent was removed by evaporation i*n vacuo* to yield the crude compound, which was purified by HPLC to give compound **401** (4.5 mg, 52%) as a white solid. **LC-MS** t_R = 1.193 min in 2 min chromatography, MS (ESI) *m/z* 414 $[M+H]^+$; **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.30 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.06 (s, 4H), 6.99 (s, 1H), 3.45-3.50 (m, 1H), 3.23-3.32 (m, 1H), 3.33 (s, 3H), 2.86-3.10 (m, 2H), 2.67-2.71 (m, 3H), 2.54-2.59 (m, 1H), 2.11-2.16 (m, 1H), 1.68-1.71 (m, 1H), 1.27-1.48 (m, 4H) ; 0.67-0.68 (m, 1H), 0.38-0.40 (m, 2H), 0.01-0.03 (m, 2H).

Example 341. Synthesis of Compound 402



Procedure for preparation of compound 14

A steel autoclave was charged with a mixture of compound **13** (0.40 g, 1.2 mmol), KCN (0.15 g, 2.4 mmol) and $(NH_4)_2CO_3$ (1.0 g, 11.0 mmol) in Formamide (20 mL). The mixture was heated at 120 °C for 72 h. The reaction mixture was then cooled and poured into ice-water (200 mL). The mixture was extracted with ethyl acetate (3 ×

100 mL), and the combined organic layers were washed with brine (2 × 100 mL). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC eluting with petroleum ether: ethyl acetate = 2: 1 to give compound **14** (70 mg, 18%) as a yellow solid. **LC-MS**: t_R = 1.40 min in 2 min chromatography, MS (ESI) *m/z* 397.1 $[M+H]^+$.

Procedure for preparation of compound 15

A sealed tube was charged with a mixture of compound **14** (55 mg, 14 mmol), Lawessons reagent (0.15 g, 0.37 mmol) in toluene (30 mL) was heated at 120 °C for 6 h. After cooling down, the precipitate was filtered off and washed with ethyl acetate (2 × 40 mL). The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative TLC eluting with petroleum ether: ethyl acetate (2: 1) to give compound **15** (25 mg, 43%) as a yellow solid.

LC-MS: t_R = 2.21 min in 3 min chromatography, MS (ESI) *m/z* 413.1 $[M+H]^+$.

Procedure for preparation of compound 16

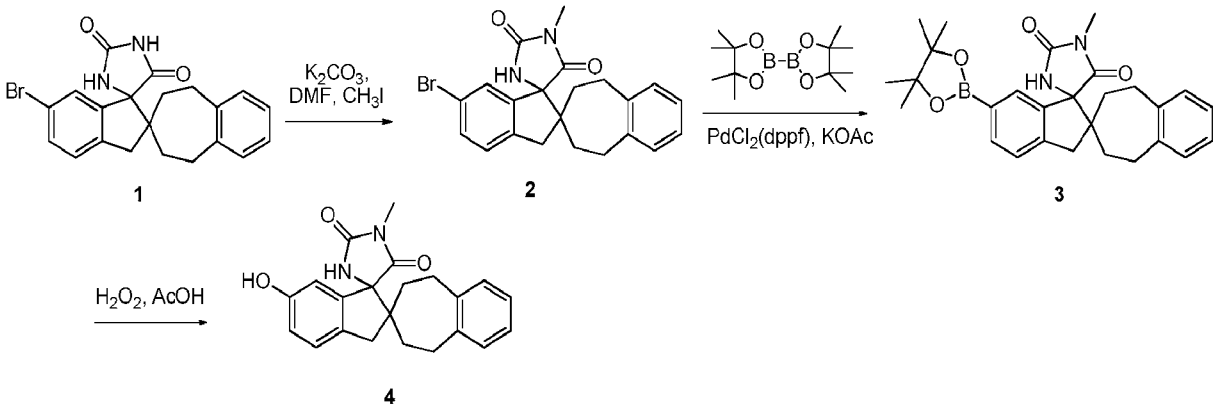
A mixture of compound 15 (25 mg, 0.061 mmol), iodomethane (20 mg, 0.14 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in DMF (2 mL) was stirred at ambient temperature overnight. The reaction mixture was poured into brine (30 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*, the resulting residue was purified by preparative TLC eluting with petroleum ether: ethyl acetate (10: 1) to give compound **16** (15 mg, 55%) as a yellow solid. **LC-MS**: t_R = 2.25 min in 3 min chromatography, MS (ESI) *m/z* 441.1 $[M+H]^+$.

Procedure for preparation of compound 402

A sealed tube was charged with a mixture of compound **16** (15 mg, 0.034 mmol), NH_4I (30 mg, 0.21 mmol) and a solution of NH_3 in ethanol (2 mL). The mixture was heated at 120 °C in a CEM microwave reactor for 3 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the residue was purified by preparative RP-HPLC to give **compound 402** (3.0 mg, 21%) with 99% purity as a white

solid. **LC-MS**: t_R = 1.89 min in 3 min chromatography, MS (ESI) *m/z* 410.2 $[M+H]^+$. **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.30-7.40 (s, 2H), 7.10-7.15 (s, 1H), 7.00-7.10 (s, 4H), 3.05-3.15 (s, 3H), 3.00-3.05 (m, 1H), 2.85-2.95 (m, 2H), 2.60-2.70 (m, 1H), 2.50-2.60 (m, 1H), 2.05-2.15 (m, 1H), 1.60-1.70 (m, 1H), 1.30-1.45 (m, 2H), 1.20-1.30 (m, 2H), 0.75-0.85 (m, 2H), 0.60-0.70 (m, 2H).

Example I-10. Synthesis of intermediate hydantoin 4



Procedure for preparation of compound 2

To a solution of compound **1** (200 mg, 0.49 mmol) in DMF (5 mL) was added K_2CO_3 (200 mg, 1.46 mmol) and CH_3I (76 mg, 0.51 mmol). The reaction mixture was stirred at 30 °C for 10 h. The mixture was filtered and filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **2** (175 mg, 85%) as a white solid.

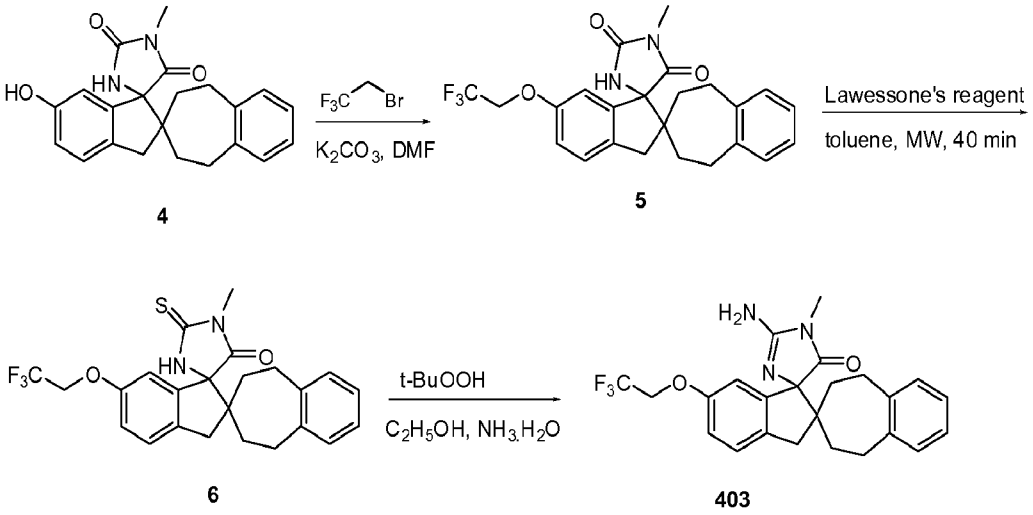
Procedure for preparation of compound 3

A suspension of compound **2** (170 mg, 0.4 mmol), compound **2A** (112 mg, 0.44 mmol), $PdCl_2(dppf)_2$ (50 mg, 0.08 mmol) and KOAc (118 mg, 1.2 mmol) in anhydrous 1,4-dioxane (6 mL) was heated at 100 °C for 60 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **3** (140 mg, 70%, 67% purity) as a yellow solid.

Procedure for preparation of compound 4

To a solution of compound **3** (140 mg, 0.39 mmol) in THF (8 mL) was added AcOH (1 mL) and H_2O_2 (3 mL). The reaction mixture was stirred at 30 °C for 10 h. The mixture was quenched by addition of saturated $NaHCO_3$ (6 mL) and then partitioned between EtOAc (2 × 20 mL) and water (10 mL). The organic layers were collected and concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 1: 1) to give hydantoin **4** (89 mg, 70%) as a colorless oil.

Example 342. Synthesis of Compound 403



Procedure for preparation of compound 5

To a solution of compound **4** (45 mg, 0.12 mmol) in DMF (4 mL) was added K_2CO_3 (35 mg, 0.25 mmol). After stirring for 5 min, 2-bromo-1,1,1-trifluoro-ethane (30 mg, 0.18 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered, the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **5** (31 mg, 78%) as a white solid.

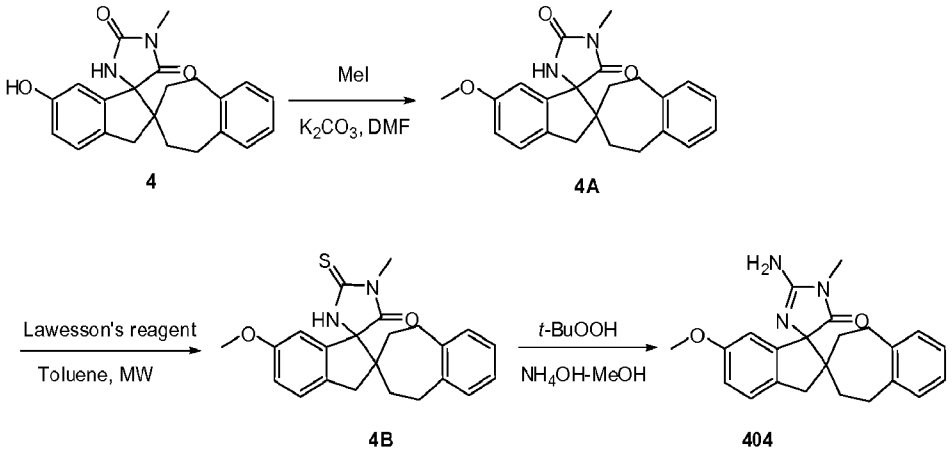
Procedure for preparation of compound 6

A suspension of compound **5** (27 mg, 0.06 mmol) and Lawesson's Reagent (24 mg, 0.06 mmol) in anhydrous toluene (1 mL) was heated at 130 °C for 40 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by prep. TLC (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **6** (21 mg, 65%, 73% purity) as a white solid.

Procedure for preparation of compound 403

A solution of compound **6** (21 mg, 0.046 mmol), *t*-BuOOH (90 mg, 0.9 mmol), $NH_3.H_2O$ (1 mL) in EtOH (3 mL) was stirred at 30 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative RP-HPLC to give **compound 403** (5.0 mg, 25%) as a white solid.**LCMS:** t_R = 1.79 min in 3 min chromatography, MS (ESI) *m/z* 444.2 $[M+H]^+$.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.40-7.47 (d, 1H), 7.05-7.38 (m, 5H), 6.92 (s, 1H), 4.49-4.59 (m, 2H), 3.50-3.55 (m, 2H), 3.17 (s, 3H), 3.08-3.13 (m, 1H), 2.92-3.01 (m, 1H), 2.60-2.80 (m, 2H), 2.13-2.20 (m, 1H), 1.70-1.77 (m, 1H), 1.35-1.50 (m, 2H).

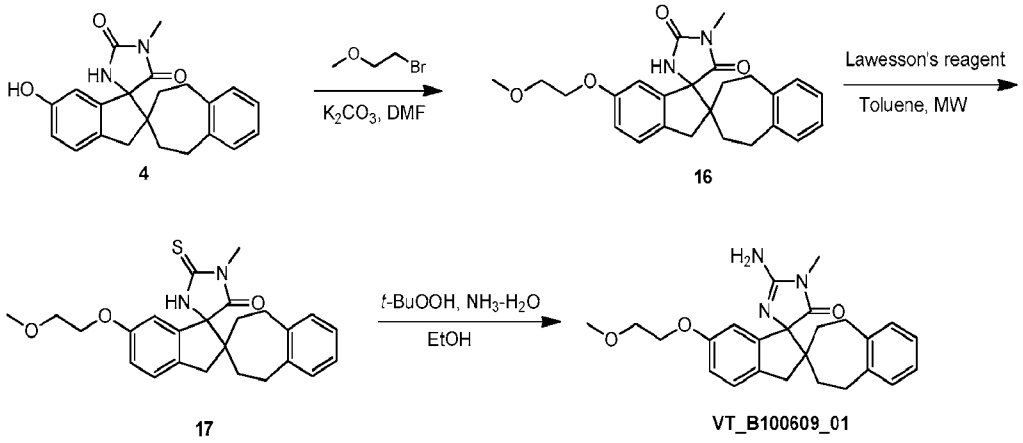
Example 343. Synthesis of Compound 404



According to a similar synthesis of **compound 403,** hydantoin **4** (30 mg, 0.08 mmol) was methylated with CH_3I (13 mg, 0.09 mmol) to give compound **4A** (15 mg, 50%) as a white solid. Compound **4A** (15 mg, 0.04 mmol) was then reacted with Lawesson's Reagent (18 mg, 0.04 mmol) to give compound **4B** (11 mg, 70%) as a

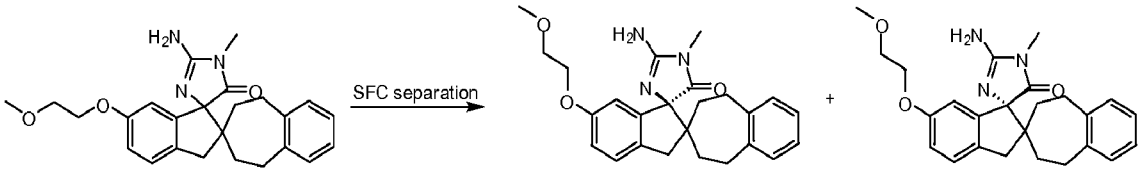
white solid. Finally, compound **4B** (11 mg, 0.03 mmol) was converted to **compound 404** (4.60 mg, 40%) as a white solid. **LC-MS**: t_R = 1.73 min in 3 min chromatography, MS (ESI) *m/z* 376.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15-7.20 (d, J = 8.0 Hz, 1H), 6.90-7.00 (m, 4H), 6.70-6.75 (dd, J = 2.4, 8.4 Hz, 1H), 6.45-6.55 (d, J = 1.6 Hz, 1H), 3.60-3.65 (s, 3H), 3.10-3.20 (m, 2H,), 2.90-3.00 (m, 4H), 2.75-2.90 (m 1H), 2.55-2.65 (m, 1H), 2.50-2.60 (m, 1H), 1.95-2.05 (m, 1H), 1.50-1.60 (s, 2H), 1.10-1.20 (m, 1H).

Example 344. Synthesis of Compound 405, 406 and 407



According to a similar synthesis of ***compound 403***, hydantoin **4** (800 mg, 2.2 mmol) was alkylated with 1-bromo-2-methoxy-ethane (350 mg, 2.4 mmol) to give compound **16** (430 mg, 50%) as a white solid. Compound **16** (420 mg, 1 mmol) was converted to thiohydantoin **17** (300 mg, 50%) as a white solid by a Lawesson's Reagent (420 mg, 1.05 mmol); Finally, compound **17** (300 mg, 0.69 mmol) afforded **compound 405** (170 mg, 55%) as a white solid. **LCMS:** t_R = 1.553 min in 3 min chromatography, MS ESI *m/z* 420.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.25-7.35 (d, J = 8.4 Hz, 1H,), 7.05-7.10 (m, 4H), 6.90-7.00 (d, J = 8.1 Hz, 1H,), 6.75-6.80 (s, 1H), 4.00-4.10 (s, 2H), 3.55-3.65 (m, 2H), 3.35-3.45 (m, 4H), 3.10-3.25 (m, 4H), 3.05-3.10 (m, 1H), 2.85-3.00 (m, 1H), 2.50-2.75 (m, 2H), 2.05-2.15 (m, 1H), 1.65-1.80 (m, 1H), 1.35-1.40 (m, 2H).

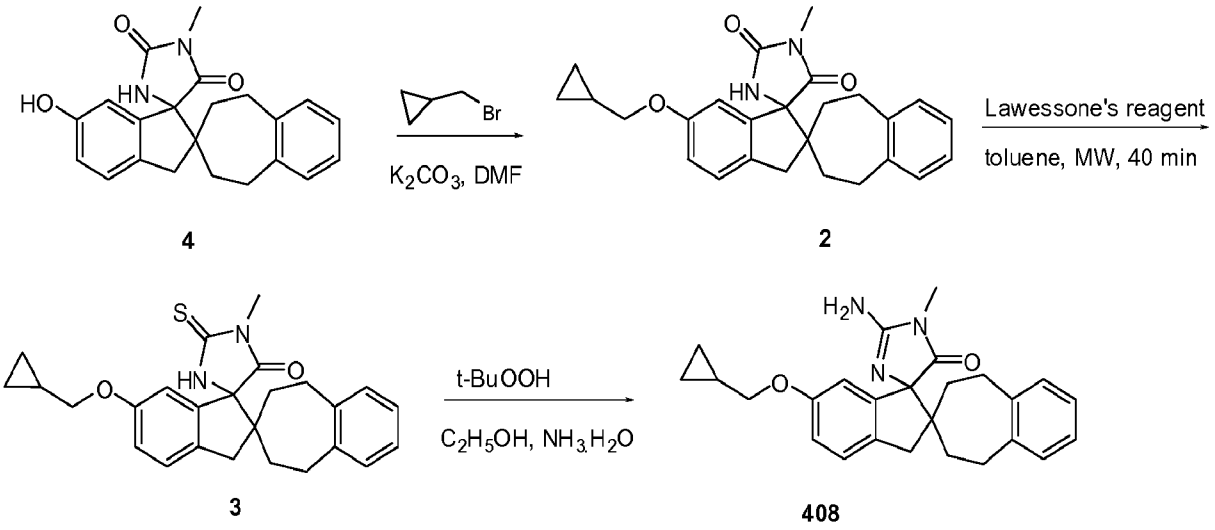
Procedure for preparation of compounds 406 and 407



405 406 407

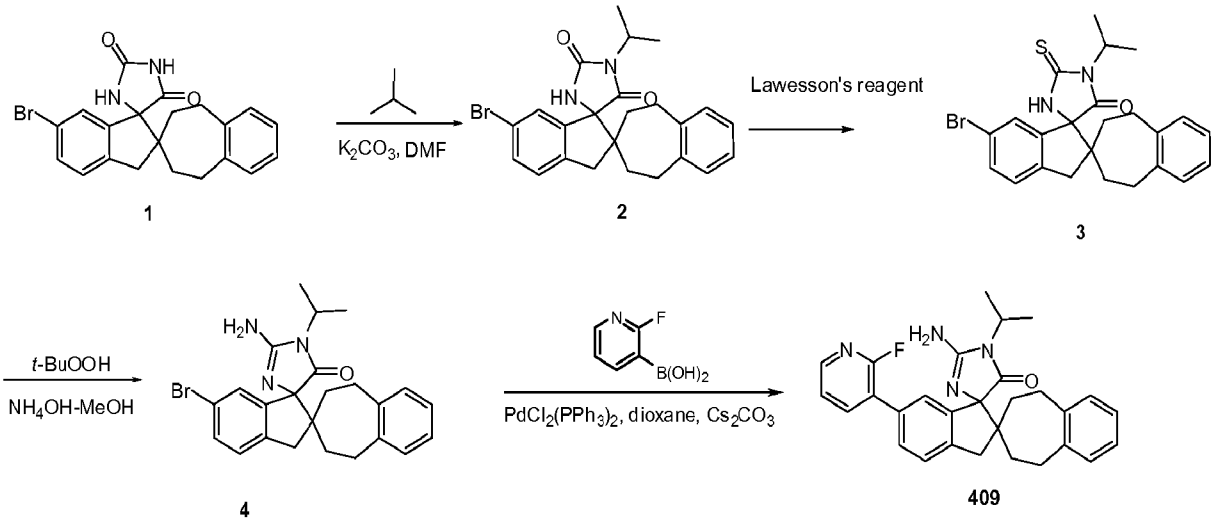
Compound 405 (50 mg, 0.12 mmol) was re-purified by preparative SFC to give **compound 406** (13.40 mg, 30%) as a white solid, **LCMS**: t_R = 1.565 min in 3 min chromatography, MS ESI *m/z* 420.1 $[M+H]^+$. **SFC**: t_R = 1.434 min in 8 min chromatography, ee = 100%.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.25-7.35 (d, J = 8.4 Hz, 1H,), 7.05-7.10 (s, 4H), 6.90-7.00 (d, J = 8.1 Hz, 1H,), 6.75-6.80 (s, 1H), 4.00-4.10 (s, 2H), 3.55-3.65 (m, 2H), 3.35-3.45 (m, 4H), 3.10-3.25 (m, 4H), 3.05-3.10 (m, 1H), 2.85-3.00 (m, 1H), 2.50-2.75 (m, 2H), 2.05-2.15 (m, 1H), 1.65-1.80 (m, 1H), 1.35-1.40 (m, 2H); and **compound 407** (18.10 mg, 32%) as the white solid, **LCMS**: t_R = 1.561 min in 3 min chromatography, MS (ESI) *m/z* 420.1 $[M+H]^+$. **SFC**: t_R = 3.338 min in 8 min chromatography, ee = 100%. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25-7.35 (d, J = 8.4 Hz, 1H,), 7.05-7.10 (s, 4H), 6.90-7.00 (d, J = 8.1 Hz, 1H,), 6.75-6.80 (s, 1H), 4.00-4.10 (s, 2H), 3.55-3.65 (m, 2H), 3.35-3.45 (m, 4H), 3.10-3.25 (m, 4H), 3.05-3.10 (m, 1H), 2.85-3.00 (m, 1H), 2.50-2.75 (m, 2H), 2.05-2.15 (m, 1H), 1.65-1.80 (m, 1H), 1.35-1.40 (m, 2H).

Example 345. Synthesis of Compound 408



According to a similar synthesis of ***compound 403***, hydantoin **4** (44 mg, 0.12 mmol) reacted with bromomethylcyclopropane (24 mg, 0.18 mmol) to give compound **2** (29 mg, 61%) as a white solid. Compound **2** (22 mg, 0.05 mmol) was then converted to thio-hydantoin **3** (19 mg, 85%, 90% purity) with a Lawesson's Reagent (23 mg, 0.06 mmol) in anhydrous toluene (2 mL). And compound **3** was further reacted with ammonia under oxidation conditions to give **compound 408** as a white solid (7.20 mg, 40%). **LCMS**: t_R = 1.81 min in 3 min chromatography, MS (ESI) *m/z* 416.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD, 400 MHz): δ 7.31-7.33 (d, J = 7.2 Hz, 1H), 7.09-7.12 (m, 4H), 6.94-6.97 (dd, J = 2.4, 8.4 Hz, 1H), 6.76 (s, 1H), 3.81 (s, 2H), 3.41-3.45 (d, J = 19.2 Hz, 1H), 3.20-3.24 (d, J = 19.2 Hz, 1H), 3.16 (s, 3H), 3.09-3.13 (m, 1H), 2.93-3.00 (m, 1H), 2.63-2.68 (m, 1H), 2.58-2.61 (m,1H), 2.14-2.17 (m, 1H), 1.73-1.77 (m, 1H), 1.31-1.44 (m, 2H), 1.19-1.27 (m, 1H), 0.56-0.64 (m, 2H), 0.28-0.39 (m, 2H).

Example 406. Synthesis of Compound 409



Procedure for preparation of compound 2

To a solution of compound **1** (700 mg, 1.7 mmol) in DMF (15 mL) was added K_2CO_3 (700 mg, 5.2 mmol). After stirring for 5 min, 2-iodo-propane (300 mg, 1.8 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The precipitate was filtered off and washed with ethyl acetate (2 × 40 mL), the filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: petroleum ether: ethyl acetate = 2: 1) to give compound **2** (410 mg, 52%) as a white solid.

Procedure for preparation of compound 3

A suspension of compound **2** (180 mg, 0.4 mmol) and Lawesson's Reagent (180 mg, 0.44 mmol) in dry toluene (4 mL) was heated under 130 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column (eluent: petroleum ether: ethyl acetate = 5: 1) to give compound **3** as a white solid (96 mg, 50%) as a white solid.

Procedure for preparation of compound 4

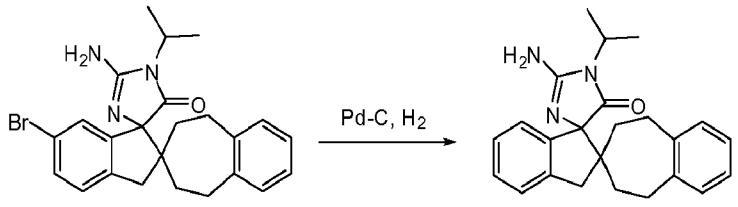
A solution of compound **3** (95 mg, 0.2 mmol), *t*-BuOOH (1.5 mL), $NH_3.H_2O$ (1.5 mL) in MeOH (8 mL) was stirred at 25 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (eluent: dichloromethane: MeOH = 12: 1) to give **compound 4** (47 mg, 50%) as a white

solid. **LC-MS**: t_R = 1.26 min, in 3 min chromatography; MS (ESI) *m/z* 452.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.30-7.35 (d, J = 11.2 Hz, 1H), 7.15-7.20 (d, J = 8.0 Hz, 1H), 6.90-7.00 (m, 5H), 4.05-4.15 (m, 1H), 3.20-3.25 (m, 1H), 3.05-3.15 (d, J = 15.2 Hz, 1H), 2.95-3.05 (m, 1H), 2.75-2.85 (m, 1H), 2.55-2.65 (m, 1H), 2.40-2.50 (m, 1H), 2.05-2.10 (m, 1H), 1.40-1.50 (m, 2H), 1.25-1.35 (m, 6H), 1.15-1.20 (m, 1H).

Procedure for preparation of compound 409

A suspension of compound **4** (14 mg, 0.03 mmol), 2-fluro-3-pyridine boronic acid (5.5 mg, 0.03 mmol), $PdCl_2(PPh_3)_2$ (2 mg, 2.8×10^{-3} mmol) and Cs_2CO_3 (0.1 mL, 2 N in water) in 1,4-dioxane (3 mL) was heated at 120 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by prep. HPLC to give **compound 409** (3.1 mg, 28%) as a white solid. **LCMS**: t_R = 1.85 min in 3 min chromatography, MS (ESI) *m/z* = 469.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.16-8.17 (d, J = 4.8 Hz, 1H), 8.03-8.05 (m, 1H), 7.61-7.63 (d, J = 8.0 Hz, 1H), 7.54-7.56 (d, J = 8.0 Hz, 1H), 7.38-7.40 (m, 2H), 7.07-7.10 (m, 4H), 4.21-4.26 (m, 1H), 3.53-3.57 (d, J = 16.0 Hz, 1H), 3.28-3.34 (d, J = 15.2 Hz, 1H), 3.09-3.16 (m, 1H), 2.93-3.00 (m, 1H), 2.72-2.77 (m, 1H), 2.57-2.62 (m, 1H), 2.21-2.26 (m, 1H), 1.70-1.75 (m, 1H), 1.40-1.50 (m, 8H).

Example 347. Synthesis of Compound 410

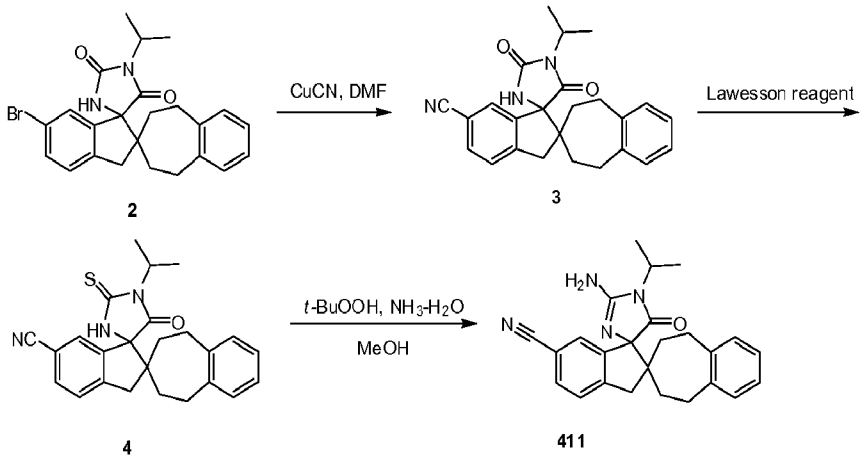


4 410

A solution of **compound 4** described in Example 346 (10 mg, 0.022 mmol) and Pd/C (2 mg) in MeOH (4 mL) was stirred at 25 °C under H_2 (10 psi) for 2 h. The mixture was filtered and filtrate was concentrated *in vacuo* to give the residue which was purified by preparative TLC on silica gel (Dichloromethane: MeOH = 12: 1) to give **compound 410** (4.3 mg, 55%) as a white solid. **LC-MS**: t_R = 1.82 min in 2 min

chromatography, MS (ESI) *m/z* 374.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.20-7.35 (m, 2H), 7.10-7.20 (m, 1H), 6.90-7.05 (m, 5H), 4.05-4.15 (m, 1H), 3.20-3.25 (m, 1H), 3.05-3.15 (d, J = 15.2 Hz, 1H), 2.95-3.05 (m, 1H), 2.75-2.85 (m, 1H), 2.55-2.65 (m, 1H), 2.40-2.50 (m, 1H), 2.05-2.10 (m, 1H), 1.40-1.50 (m, 2H), 1.25-1.35 (m, 6H), 1.15-1.20 (m, 1H).

Example 348. Synthesis of Compound 411



Procedure for preparation of compound 3

To a solution of compound **2** (100 mg, 0.22 mmol) in DMF (10 mL) was added CuCN (40 mg, 0.44 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) under N_2 at room temperature. The resulting mixture was stirred 30 min at 180 °C in a microwave reactor. Water (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to give the residue which was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 5: 1) to give compound **3** (46 mg, 52%) as a white solid.

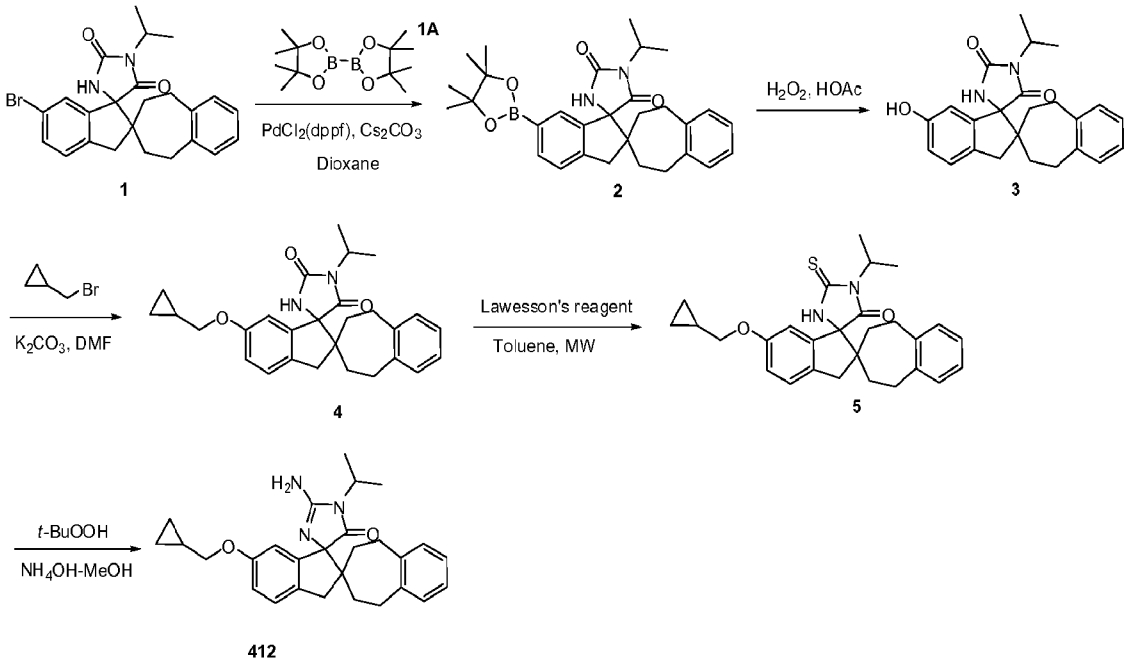
Procedure for preparation of compound 4

A mixture of compound **3** (46 mg, 0.115 mmol) and Lawesson'reagent (70 mg, 0.175 mmol) in toluene (2 mL) was heated at 130 °C for 30 min in a microwave reactor under N_2. The mixture was cooled, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 3: 1) to give compound **4** (19 mg, 40%) as a white solid.

Procedure for preparation of compound 411

To a solution of compound **4** (19 mg, 0.045 mmol) in a mixture of MeOH (10 mL) and NH_4OH (2 mL) was added *t*-BuOOH (0.5 mL, 65% in water). The mixture was stirred at room temperature overnight, and concentrated. Water (15 mL) and EtOAc (3 × 10 mL) were added, and the organic layer was dried over Na_2SO_4 and concentrated to give the residue which was purified by preparative HPLC to give the **compound 411** (8.1 mg, 44%) as a white solid. **LC-MS** : t_R = 0.931 min in 2 min chromatography, MS (ESI) *m/z* 399 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.78 (dd, J = 1.6, 8.0 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.10 (m, 4H), 4.24 (m, 1H), 3.60 (d, J = 16.4 Hz, 1H), 3.38 (m, 1H), 3.28 (m, 1H), 3.11 (m, 1H), 2.96 (m, 1H), 2.74 (m, 1H), 2.57 (m, 1H), 2.20(m, 1H), 1.61 (m, 1H), 1.48 (d, J = 6.8 Hz, 3H), 1.46 (d, J = 5.2 Hz, 3H), 1.39 (m, 1H).

Example 349. Synthesis of Compound 412



Procedure for preparation of Compound 2

A suspension of compound **1** (220 mg, 0.48 mmol), compound **1A** (185 mg, 0.73 mmol), $PdCl_2$(dppf) (70 mg, 0.1 mmol) and KOAc (150 mg, 1.5 mmol) in dry 1,4-

dioxane (5 mL) was heated under 100 °C for 60 min in CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column on silica gel (petroleum ether: ethyl acetate = 3: 1) to give compound **2** (300 mg, crude yield 100%) as a yellow solid.

Procedure for preparation of Compound 3

To a solution of compound **2** (300 mg, 0.6 mmol) in THF (15 mL) was added AcOH (1 mL) and H_2O_2 (3 mL). The reaction mixture was stirred at 30 °C for 10 h. The mixture was quenched with saturated $NaHCO_3$ (6 mL) and then balanced between EtOAc (2 × 20 mL) and water (10 mL). The organic layers were collected and concentrated *in vacuo* to give the residue, which was purified by preparative TLC (petroleum ether: ethyl acetate = 1: 1) to give compound **3** (70 mg, 35%) as a colorless oil.

Procedure for preparation of Compound 4

To a solution of compound **3** (35 mg, 0.09 mmol) in DMF (4 mL) was added K_2CO_3 (40 mg, 0.30 mmol). After stirring for 5 min, bromomethyl-cyclopropane (13 mg, 0.10 mmol) was added and the reaction mixture was stirred at 25 °C for 10 h. The mixture was filtered and filtrate was concentrated *in vacuo* to give the residue, which was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate = 2: 1) to give compound **4** (12 mg, 25%) as a white solid.

Procedure for preparation of Compound 5

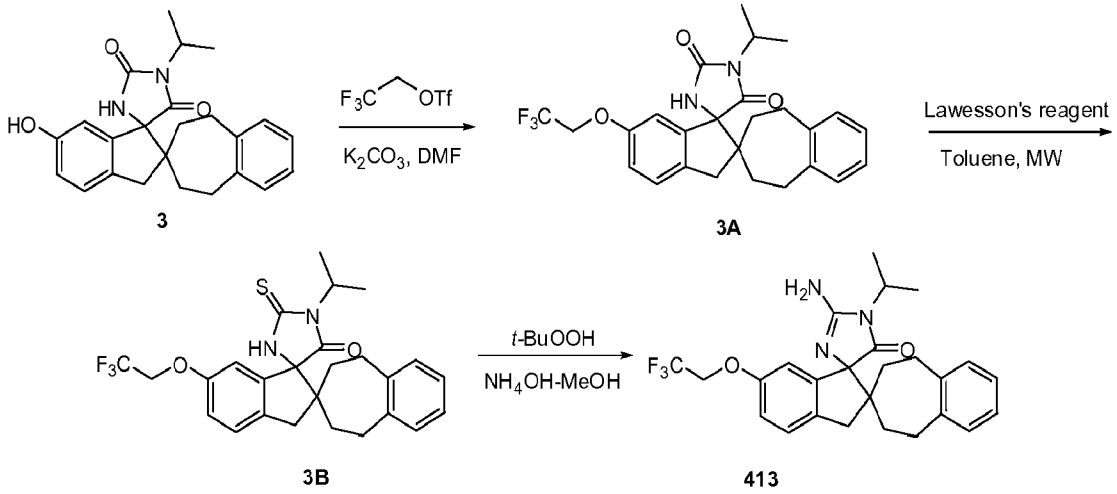
A suspension of compound **4** (13 mg, 0.03 mmol) and Lawesson's Reagent (13 mg, 0.03 mmol) in dry toluene (1 mL) was heated under 130 °C for 40 min in CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column (eluent: petroleum ether: ethyl acetate = 5: 1) to give compound **5** (6 mg, 50%) as a white solid.

Procedure for preparation of Compound 412

A solution of compound **5** (6 mg, 0.046 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in MeOH (2 mL) was stirred at 25 °C for 10 h. Then, the mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 412** (0.8 mg, 15%) as a white solid. **LC-MS**: t_R = 1.94 min in 3 min

chromatography, MS (ESI) *m/z* 443.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35-7.45 (d, J = 8.0 Hz, 1H), 7.00-7.15 (m, 4H), 6.85-6.90 (d, J = 1.6, 8.0 Hz, 1H), 6.50-6.55 (s, 1H), 4.15-4.35 (m, 1H), 3.75-3.80 (d, J = 8.4 Hz, 1H), 3.20-3.30 (s, 1H,), 3.15-3.20 (m, 1H), 3.05-3.15 (m 1H), 2.90-3.05 (m, 1H), 2.65-2.75 (m, 1H), 2.50-2.60 (m, 1H), 2.10-2.25 (m, 1H), 1.50-1.70 (m, 5H), 1.30-1.50 (m, 6H), 1.20-1.30 (m, 2H), 0.45-0.55 (m, 2H), 0.30-0.40 (m, 2H).

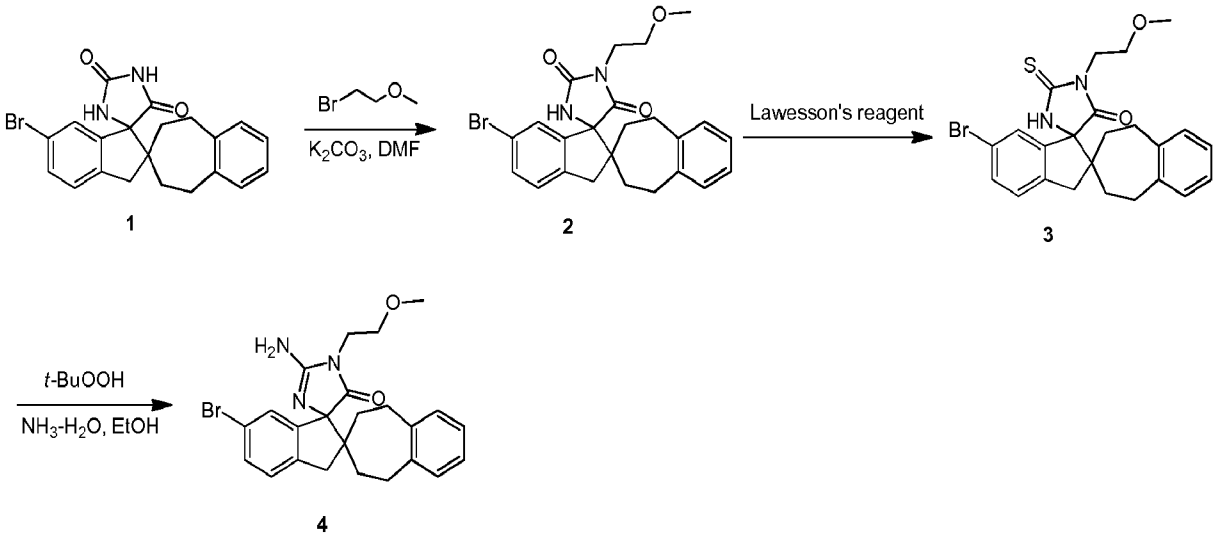
Example 350. Synthesis of Compound 413



According to a similar synthesis of ***compound 412,*** compound **3** (35 mg, 0.09 mmol) was alkylated with trifluoro-methanesulfonic acid 2, 2, 2-trifluoro-ethyl ester (23 mg, 0.10 mmol) to give compound **3a** (18 mg, 45%) as a white solid. A suspension of compound **3a** (18 mg, 0.04 mmol) was then reacted with Lawesson's Reagent (17 mg, 0.04 mmol) to give compound **3B** (8 mg, 45%) as a white solid. Finally, compound **3B** (8 mg, 0.016 mmol) was converted to **compound 413** (1.90 mg, 25%) as a white solid. **LC-MS**: t_R = 1.93 min in 3 min chromatography, MS (ESI) *m/z* 472.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15-7.20 (m, 1H,), 6.90-7.00 (m, 4H), 6.85-6.90 (dd, J = 2.4, 8.0 Hz, 1H), 6.50-6.55 (s, 1H), 4.30-4.40 (m, 2H), 4.15-4.35 (m, 1H), 3.75-3.80 (d, J = 8.4 Hz, 1H), 3.20-3.30 (s, 1H,), 3.15-3.20 (m, 1H), 3.05-3.15 (m 1H), 2.90-3.05 (m,

1H), 2.65-2.75 (m, 1H), 2.50-2.60 (m, 1H), 2.10-2.25 (m, 1H), 1.50-1.60 (s, 2H), 1.30-1.50 (m, 6H), 1.20-1.30 (m, 1H).

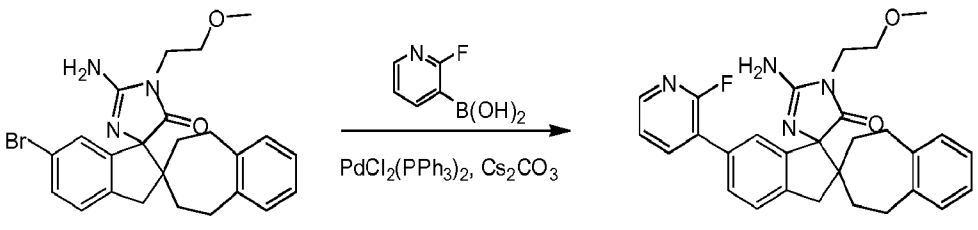
Example I-11. Synthesis of Hydantoin 4



1 2 3 4

According to a similar synthesis of ***compound 4*** described in Example 346, compound **1** (500 mg, 1.17 mmol) was alkylated with 1-Bromo-2-methoxy-ethane (180 mg, 1.3 mmol) to give compound **2** (360 mg, 65%) as a white solid. Compound **2** (200 mg, 0.43 mmol) was reacted with Lawesson's Reagent (190 mg, 0.47 mmol) to give compound **3** (84 mg, 50%) as a white solid. And compound **3** (80 mg, 0.17 mmol) was converted to hydantoin **4** (55 mg, 70%) as a white solid.

Example 351. Synthesis of Compound 414

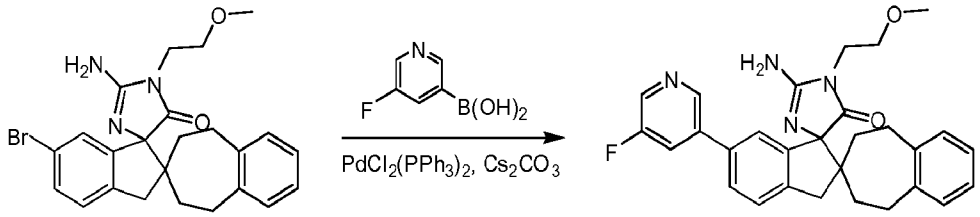


4 414

A suspension of compound **4** (25 mg, 0.05 mmol), 2-fluoro-3-pyridine boronic acid (10 mg, 0.06 mmol), $PdCl_2(PPh_3)_2$ (4 mg, 0.005 mmol) and Cs_2CO_3 (0.2 mL, 2 N

in water) in 1,4-dioxane (1 mL) was heated at 120 °C for 15 min in CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative HPLC to give **compound 414** (5.0 mg, 20%) as a white solid. **LCMS**: t_R = 1.086 min in 2 min chromatography, MS (ESI) *m/z* = 485.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.20-8.25 (d, *J* = 3.6 Hz, 1H), 8.05-8.10 (m, 1H), 7.65-7.70 (d, *J* = 4.8 Hz, 1H), 7.55-7.60 (d, *J* = 7.6 Hz, 1H), 7.40-7.45 (m, 2H), 7.05-7.15 (m, 4H), 3.80-4.00 (m, 2H), 3.55-3.60 (m, 3H), 3.35-3.40 (m, 1H), 3.30-3.35 (s, 3H), 3.10-3.20 (m, 1H), 2.95-3.05 (m, 1H), 2.75-2.80 (m, 1H), 2.60-2.70 (m, 1H), 2.20-2.30 (m, 1H), 1.75-1.85 (m, 1H), 1.40-1.55 (m, 2H).

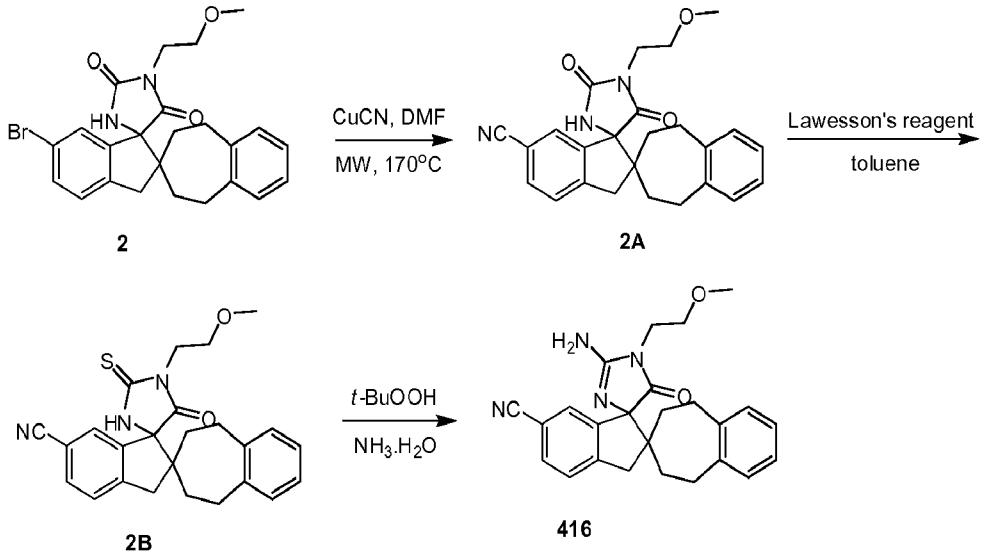
Example 352. Synthesis of Compound 415



4 **415**

Following a similar synthesis of ***compound 414,*** compound 4 (25 mg, 0.05 mmol) was reacted with 5-fluoro-3-pyridine boronic acid (10 mg, 0.06 mmol) to give **compound 415** (3.7 mg, 20%) as a white solid. LCMS: t_R = 1.088 min in 2 min chromatography, MS (ESI) *m/z* = 485.2 $[M+H]^+$. ^{19}F NMR: (CD_3OD 19f): δ -128.50. ^{1}H NMR (CD_3OD 400 MHz): δ 8.20-8.25 (s, 1H), 8.50-8.55 (s, 1H), 8.30-8.35 (m, 1H), 7.75-7.80 (d, *J* = 8.4 Hz, 1H), 7.50-7.55 (d, *J* = 8.0 Hz, 1H), 7.45-7.55 (d, *J* = 8.4 Hz, 1H), 7.10-7.15 (s, 1H), 6.90-7.00 (m, 4H), 3.55-3.65 (m, 2H), 3.40-3.45 (m, 2H), 3.25-3.35 (m, 1H), 3.20-3.25 (m, 4H), 2.90-3.00 (m, 1H), 2.80-2.90 (m, 1H), 2.55-2.60 (m, 1H), 2.40-2.50 (m, 1H), 2.00-2.10 (m, 1H), 1.50-1.60 (m, 2H), 1.15-1.25 (m, 1H).

Example 353. Synthesis of Compound 416



Procedure for preparation of compound 2A

A suspension of compound **2** (70 mg, 0.15 mmol), CuCN (27 mg, 0.30 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.02 mmol) in anhydrous DMF (2 mL) was heated at 180 °C for 45 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by preparative TLC on silica gel (petroleum ether: ethyl acetate =1: 1) to give compound **2A** (34 mg, 55%) as a white solid.

Procedure for preparation of compound 2B

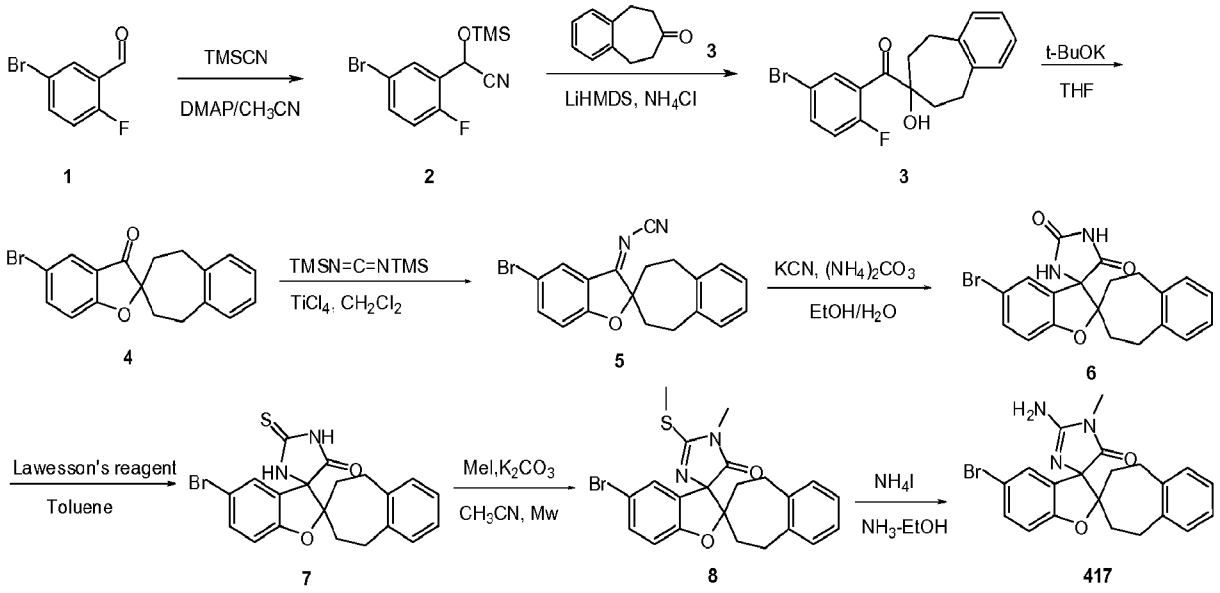
A suspension of compound **2A** (34 mg, 0.08 mmol) and Lawesson's Reagent (35 mg, 0.09 mmol) in anhydrous toluene (2 mL) was heated under 130 °C for 35 min in a CEM microwave reactor. The mixture was concentrated *in vacuo* and the residue was purified by column on silica gel (eluent: petroleum ether: ethyl acetate = 3: 1) to give compound **2B** (16 mg, 40%) as a white solid.

Procedure for preparation of compound 416

A solution of compound **2B** (16 mg, 0.04 mmol), *t*-BuOOH (0.5 mL), $NH_3.H_2O$ (0.5 mL) in EtOH (2 mL) was stirred at 20 °C for 10 h. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to give **compound 416** (1.70 mg, 10%) as a white solid. **LCMS**: t_R = 1.028 min in 2 min chromatography, MS (ESI) *m/z* = 415.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.50-7.55 (d, *J* = 7.6 Hz, 1H), 7.40-7.45 (d, *J* = 8.0 Hz, 1H,), 7.10-7.15 (s, 1H), 6.90-7.00 (m,

4H), 3.55-3.65 (m, 2H), 3.40-3.45 (m, 2H), 3.25-3.35 (m, 4H), 2.90-3.00 (m, 1H), 2.80-2.90 (m, 1H), 2.55-2.60 (m, 1H), 2.40-2.50 (m, 1H), 2.00-2.10 (m, 1H), 1.50-1.60 (m, 2H), 1.15-1.25 (m, 2H).

Example 354. Synthesis of Compound 417



Procedure for preparation of compound 2

To a solution of compound **1** (4.27 g, 21 mmol) and DMAP (0.029 g, 0.24 mmol) in anhydrous CH_3CN (40 mL) was added TMSCN (2.82 g, 28.4 mmol) via a syringe under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 4h at room temperature, and the solvent was removed under reduced pressure to give crude compound **2** (6.35 g, 100 %) which was used directly in the next step without further purification.

Procedure for preparation of compound 3

To a solution of compound **2** (6.35 g, 21 mmol) in THF (20 mL) was added LiHMDS (1 M in THF, 22 mL, 22 mmol) via a syringe at -78 °C under a nitrogen atmosphere. After 1 h a solution of compound **2A** (3.31 g, 20.66 mmol) in THF (32 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 1.5 h then

quenched by addition of a solution of sat. NH_4Cl (50 mL), the resulting mixture was stirred overnight at room temperature, extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over sodium sulfate, concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether: THF = 40: 1) to give compound **3** (3.21 g, 42 %) as a light yellow solid.

Procedure for preparation of compound 4

To a solution of compound **3** (3.21 g, 8.8 mmol) in THF (50 mL) was added *t*-BuOK (1.19 g, 10.6 mmol). The reaction mixture was heated to reflux for 50 min, cooled to room temperature, diluted with water (30 mL), extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over sodium sulfate, concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 40: 1) to give compound **4** (1.57 g, 51%) as a yellow solid.

Procedure for preparation of compound 5

To a solution of compound **4** (800 mg, 2.34 mmol) in CH_2Cl_2 (16 mL) was added $TiCl_4$ (4.10 mL, 1.0 M in dichloromethane, 4.10 mmol) dropwise. After stirring for 1 h at room temperature, bis-trimethylsilylcarbodiimide (1.20 g, 6.45 mmol) was added, and the final mixture was stirred at room temperature overnight. The reaction was quenched by addition of ice-water (30 mL) and stirred for 15 min, extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give compound **5** (840 mg, crude) which was used for the next step.

Procedure for preparation of compound 6

To a solution of compound **5** (840 mg, 2.30 mmol) in EtOH (8 mL) and H_2O (8 mL) was added KCN (596 mg, 9.18 mmol) and $(NH_4)_2CO_3$ (2.23 g, 23 mmol). The reaction was heated at 75 °C overnight. The reaction was cooled to room temperature, and was dissolved in EtOAc (200 mL), washed with watrer, brine, dried over Na_2SO_4

and concentrated to give compound **6** (800 mg, 80% crude) as a white solid. **^{1}H NMR** (DMSO-d_6 300 MHz): δ 11.02 (s, 1H), 8.71 (s, 1H), 7.46 (m, 2H), 7.14 (m, 4H), 6.95 (d, J = 8.4 Hz, 1H), 3.13 (m, 2H), 2.66 (m, 3H), 2.05 (m, 1H), 1.53 (m, 2H).

Procedure for preparation of compound 7

To a solution of compound **6** (600 mg, 1.46 mmol) in toluene (24 mL) was added Lawesson's reagent (647 mg, 1.60 mmol) under a nitrogen atmosphere. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 40 min. The solvent was removed and the residue was purified by chromatography (petroleum ether: EtOAc = 20: 1) to afford compound **7** (570 mg, 90%) as a white solid.

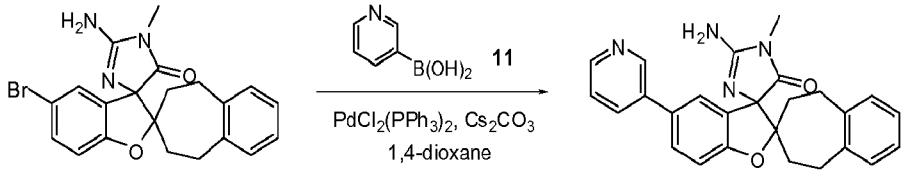
Procedure for preparation of compound 8

To a solution of compound **7** (570 mg, 1.33 mmol) in CH_3CN (45 mL) was added K_2CO_3 (554 mg, 3.99 mmol) followed by MeI (1.17 g, 7.97 mmol). The reaction mixture was heated at 60 °C for 10 min and then at 100 °C for 10 min in a CEM microwave reactor. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by chromatography (petroleum ether: EtOAc = 30: 1) to afford compound **8** (420 mg, 69%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.28 (d, J = 8.8 Hz, 1H), 7.06 (s, 4H), 6.82 (m, 2H), 3.24 (m, 2H), 2.94 (s, 3H), 2.62-2.39 (m, 7H), 1.67 (m, 1H), 1.36 (m, 1H).

Procedure for preparation of compound 417

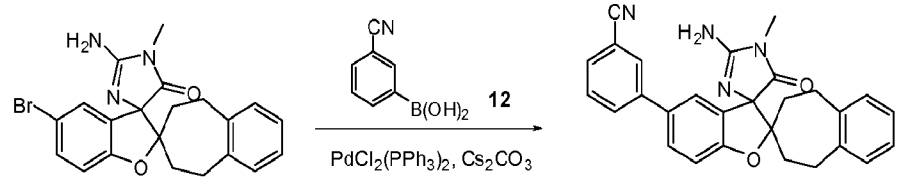
To a solution of compound **8** (20 mg, 0.044 mmol) in NH_3-EtOH (2 mL) was added NH_4I (52 mg, 0.35 mmol). The reaction mixture was heated at 120 °C in a CEM microwave reactor for 2 h. The solvent was removed and the residue was purified by preparative RP-HPLC to afford **compound 417** (4.2 mg, 22%) as a white solid. **LC-MS** t_R = 1.199 min in 2 min chromatography, m/z 428.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.58 (m, 2H), 7.19 (s, 4H), 6.98 (d, J = 8.1 Hz, 1H), 3.17 (s, 3H), 2.73-2.55 (m, 4H), 2.23 (m, 1H), 1.71-1.52 (m, 2H).

Example 355. Synthesis of Compound 418



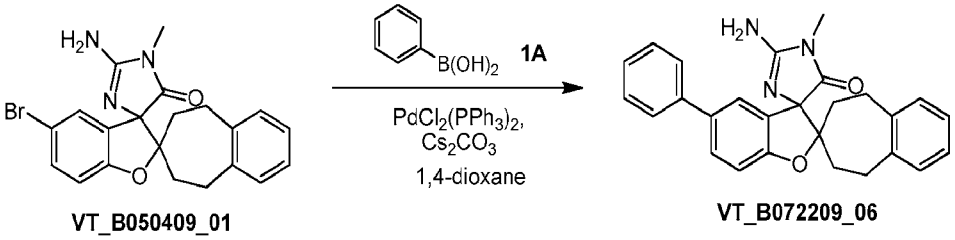
To a solution of compound **compound 417** (40 mg, 0.094 mmol) in 1,4-dioxane (1 mL) was added compound **11** (23 mg, 0.19 mmol), $PdCl_2(PPh_3)_2$ (10 mg) and aq. Cs_2CO_3 (0.1 mL, 2M in H_2O). The reaction mixture was heated at 120 °C in a CEM microwave reactor for 15 min under a nitrogen atmosphere. The solvent was removed under reduced pressure, and the residue was purified by preparative RP-HPLC to give **compound 418** (8 mg, 20%) as a white solid. **LC-MS** t_R = 1.016 min in 2 min chromatography, *m/z* 425.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 8.93 (m, 1H), 8.66 (m, 1H), 8.45 (m, 1H), 7.83 (m, 3H), 7.22-7.11 (m, 5H), 3.46 (m, 2H),3.23 (s, 3H), 2.74-2.61 (m, 3H), 2.35 (m, 1H), 1.78-1.57 (m, 2H).

Example 356. Synthesis of Compound 419



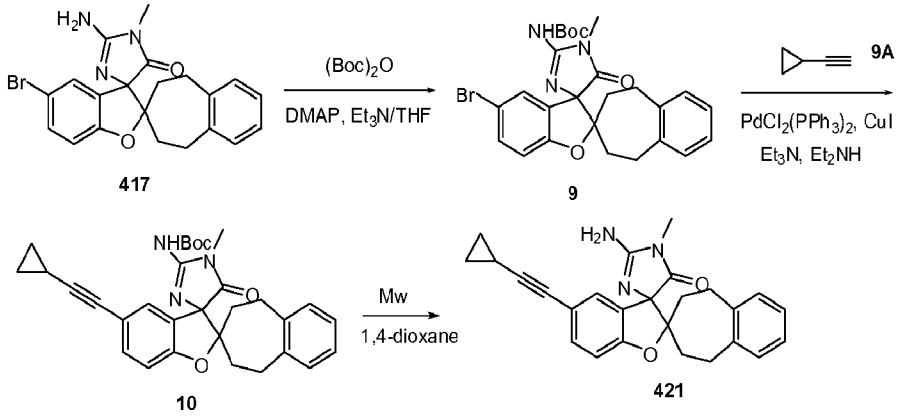
According to a similar synthesis of **compound 418**, compound **417** (20 mg, 0.047 mmol) was reacted with compound **12** (14 mg, 0.094 mmol) to give **compound 419** (7.5 mg, 36%) as a white solid. **LC-MS** t_R = 1.237 min in 2 min chromatography, MS (ESI) *m/z* 449.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.96 (m, 2H), 7.77-7.59 (m, 4H), 7.14 (m, 5H), 3.46 (m, 2H), 3.21 (s, 3H), 2.69 (m, 3H), 2.33 (m, 1H), 1.74-1.53 (m, 2).

Example 357. Synthesis of Compound 420



According to a similar synthesis of **compound 418**, compound **417** (20 mg, 0.047 mmol) was coupled with compound **1A** (12 mg, 0.094 mmol) to give **compound 420** (6.1 mg, 30%) as a white solid. **LC-MS** t_R = 1.265 min in 2 min chromatography, MS (ESI) *m/z* 424.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 7.38-7.43 (m, 3H), 7.23-7.29 (m, 2H), 7.12-7.17 (m, 1H), 7.06-7.07 (s, 1H), 6.97 (s, 4H), 6.87-6.89 (d, J = 8.1 Hz, 1H).

Example 358. Synthesis of Compound 421



Procedure for preparation of compound 9

To a solution of compound **417** (50 mg, 0.12 mmol) in THF (3 mL) was added $(Boc)_2O$ (32 mg, 0.14 mmol), Et_3N (14 mg, 0.14 mmol) and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 5: 1) to give compound **9** (60 mg, 99%) as a white solid.

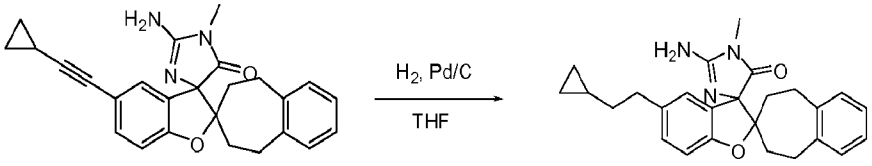
Procedure for preparation of compound 10

To a solution of compound **9** (60 mg, 0.11 mmol) in Et_3N (5 mL) and Et_2NH (1 mL) was added CuI (22 mg, 0.11 mmol) and $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol) under a nitrogen atmosphere. The reaction mixture was sealed and **9A** (75 mg, 0.11 mmol) was added and the reaction mixture was heated at 50 °C overnight. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 4: 1) to give compound **10** (38 mg, 65%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 8.72 (s, 1H), 7.63 (s, 1H), 7.28 (m, 3H), 7.07 (m, 4H), 7.03 (s, 1), 6.82 (d, J = 8.7 Hz, 1H), 3.79 (m ,2H), 3.02 (s, 3H), 2.58 (m, 3H), 2.14 (m, 1 H) 1.63 (m, 2H), 1.48 (s, 9H), 1.32 (m, 1H), 0.37 (m, 2H), 0.71 (m, 2H).

Procedure for preparation of compound 421

Compound **10** (38 mg, 0.074 mmol) was dissolved in 1, 4-dioxane (1 mL) and heated in a CEM microwave reactor at 120 °C for 15 min. The solvent was removed and the residue was purified by preparative RP-HPLC to afford **compound 421** (12 mg, 40%) as a white solid. **LC-MS** t_R = 1.257 min in 2 min chromatography, MS (ESI) *m/z* 412.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 300 MHz): δ 7.38 (d, J = 8.7 Hz, 2H), 7.13 (s, 4H), 6.96 (d, J = 8.4 Hz, 1H), 3.46 (m, 2H), 3.20 (s, 3H), 2.65 (m, 3H), 2.23 (m ,1H), 1.66 (m, 2H), 1.48 (m, 1H), 0.88 (m, 2H), 0.71 (m, 2H).

Example 329. Synthesis of Compound 422

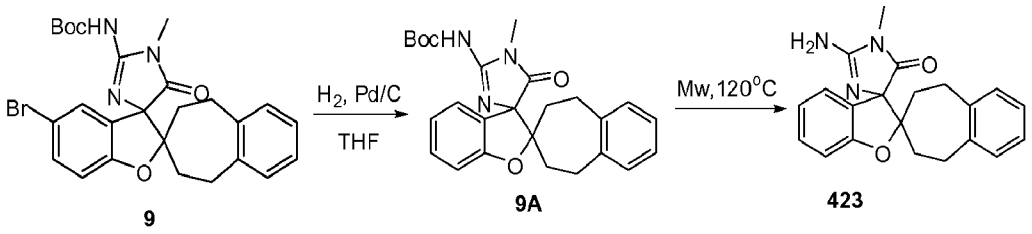


421 422

To a solution of compound **421** (10 mg, 0.0243 mmol) in THF (3 mL) was added Pd/C (10 mg). The reaction mixture was stirred under H_2 atmosphere at room temperature for 3 h. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by preparative HPLC to afford **compound 422** (3 mg,

30%) as a white solid. **LC-MS** t_R = 1.305 min in 2 min chromatography, MS (ESI) *m/z* 416.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.22 (d, J = 9.2 Hz, 1H), 7.13 (s, 5H), 6.91 (d, J = 8.4 Hz, 1H), 3.33 (m, 2H), 3.17 (s, 3H), 2.63 (m, 5H), 2.26 (m ,1H), 1.63-1.42 (m, 4H), 0.66 (m, 1H), 0.49 (m, 2H), 0.01 (m, 2H).

Example 330. Synthesis of Compound 423



9 9A 423

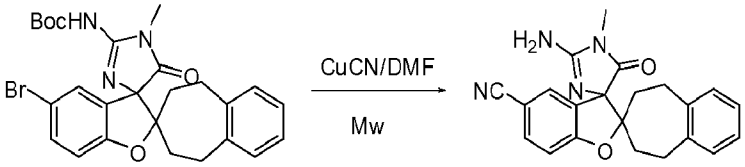
Procedure for preparation of compound 9A

To a solution of compound **9** (22 mg, 0.043 mmol) in MeOH (3 mL) was added Pd/C (10 mg). The reaction mixture was stirred under H_2 atmosphere at room temperature for 3 h. The solution was filtered and the filtrate was concentrated to give compound **9A** (11 mg, 60%).

Procedure for preparation of compound 423

Compound **9A** (11 mg, 0.024 mmol) was dissolved in 1,4-dioxane (1 mL) and heated in a CEM microwave reactor at 120 °C for 15 min. The solvent was removed and the residue was purified by preparative HPLC to afford **compound 423** (3 mg, 19%) as a white solid. **LC-MS** t_R = 1.145 min in 2 min chromatography, MS (ESI) *m/z* 348.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.31 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.07 (m, 4H), 6.92 (m, 2H), 3.22 (m, 2H), 3.09 (s, 3H), 2.56 (m ,3H), 2.18 (m, 1H), 1.53 (m, 2H).

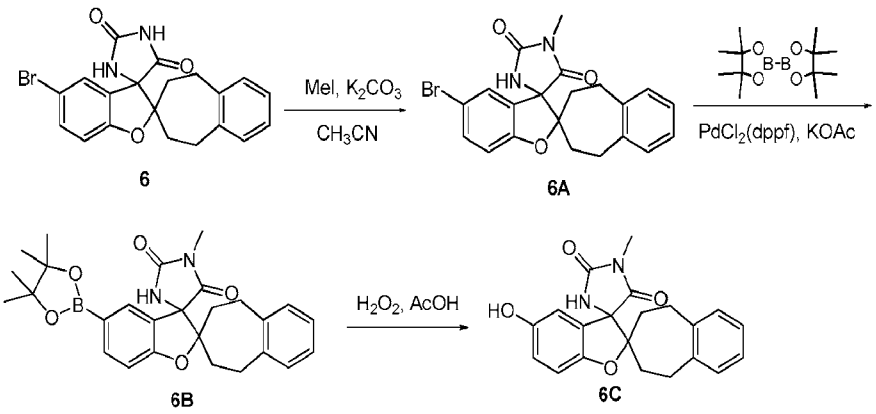
Example 361. Synthesis of Compound 424



9 424

To a solution of compound **9** (30 mg, 0.057 mmol) in DMF (2 mL) was added CuCN (25 mg, 0.29 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mg) under N_2. The reaction mixture was heated in a CEM microwave reactor at 150 °C for 1 h. Water (10 mL) was added and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to give **compound 424** (3 mg, 14%) as a white solid. **LC-MS** t_R = 1.148 min in 2 min chromatography, MS (ESI) *m/z* 373.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.83 (m, 2H), 7.16 (m, 5H), 3.43 (m, 2H), 3.28 (s, 3H), 2.74-2.58 (m, 3H), 2.29 (m, 1H), 1.27-1.56 (m ,2H).

Example I-12. Synthesis of hydantoin 6C



6 6A 6B 6C

Procedure for preparation of compound 6A

To a solution of compound **6** (820 mg, 1.99 mmol) in DMF (10 mL) and CH_3CN (10 mL) was added compound K_2CO_3 (332 mg, 2.39 mmol) and MeI (0.18 mL, 2.99 mmol). The reaction mixture was stirred at room temperature for 2 h. CH_3CN was removed and water (80 mL) was added, extracted with EtOAc (50 mL × 3). The organic

layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by chromatography (petroleum ether: EtOAc = 10: 1) to give compound **6A** (650 mg, 77%).

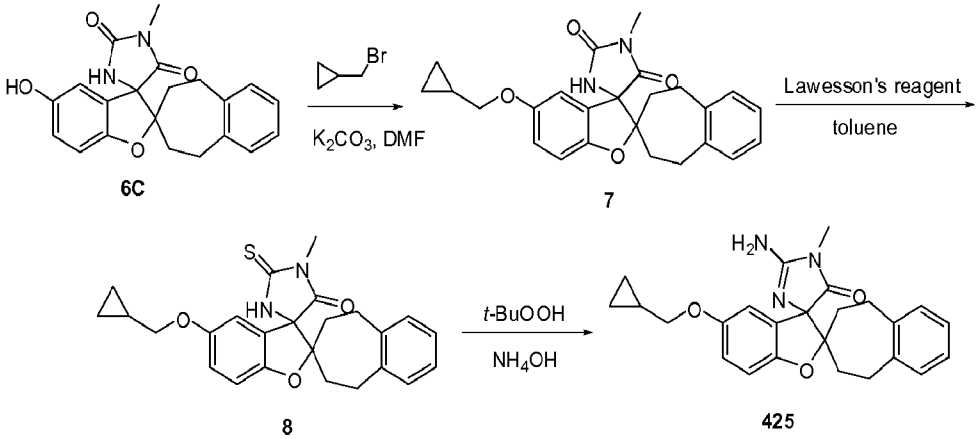
Procedure for preparation of compound 6B

To a solution of compound **6A** (560 mg, 1.526 mmol) in 1,4-dioxane (15 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (465 mg, 1.831 mmol), KOAc (449 mg, 4.578 mmol) and $PdCl_2$(dppf) under N_2. The reaction mixture was heated at 100 °C in a CEM microwave reactor for 1 h. The solution was filtered and the filtrate was concentrated to give compound **6B** (1 g, crude), which was used for the next step.

Procedure for preparation of compound 6C

To a solution of compound **6B** (1g, crude) in THF (80 mL) was added H_2O_2 (1.5 mL) and HOAc (5 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with $NaHSO_3$ solution (50 mL). After stirring for 30 min, the mixture was extracted with EtOAc (50 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the residue which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to afford compound **6C** (400 mg with 50% purity).

Example 362. Synthesis of Compound 425



6C 7 8 425

Procedure for preparation of compound 7

To a solution of compound **6C** (150 mg, 0.206 mmol) in DMF (5 mL) was added K_2CO_3 (34 mg, 0.24 mmol) followed by (bromomethyl)cyclopropane (42 mg, 0.309 mmol). The reaction mixture was stirred at room temperature for 2 days. Water was added and the mixture was extracted with EtOAc (20 mL × 2). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue which was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to afford compound 7 (40 mg, 47%) as a white solid. **^{1}H NMR** ($CDCl_3$ 300 MHz): δ 7.18 (s, 4H), 6.81 (s, 2H), 6.51 (s, 1H), 5.07 (s, 1H), 3.64 (d, J = 6.9 Hz, 2H), 3.40 (m, 2H), 2.96 (s, 3H), 2.57 (m, 3H), 2.08 (m, 1H), 1.53 (m, 1H), 1.48 (m, 1H), 1.15 (m, 1H), 0.53 (m, 2H), 0.25 (m, 2H).

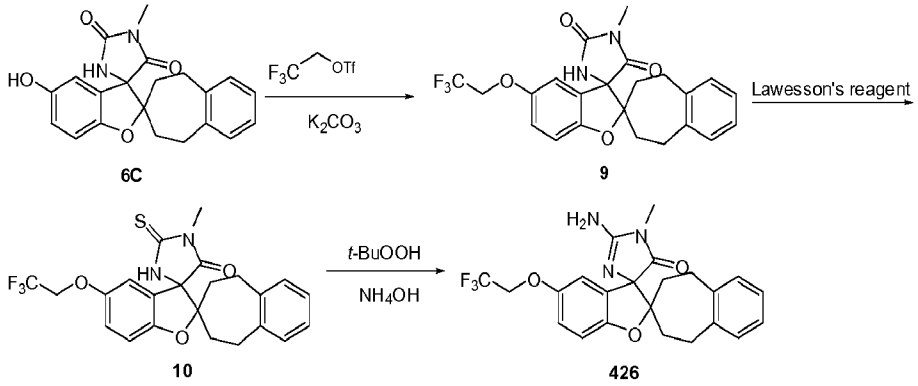
Procedure for preparation of compound 8

To a solution of compound **7** (40 mg, 0.0957 mmol) in dry toluene (1 mL) was added Lawesson's reagent (58 mg, 0.143 mmol) under N_2. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 60 min. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **8** (24 mg, 57%) as a white solid.

Procedure for preparation of compound 425

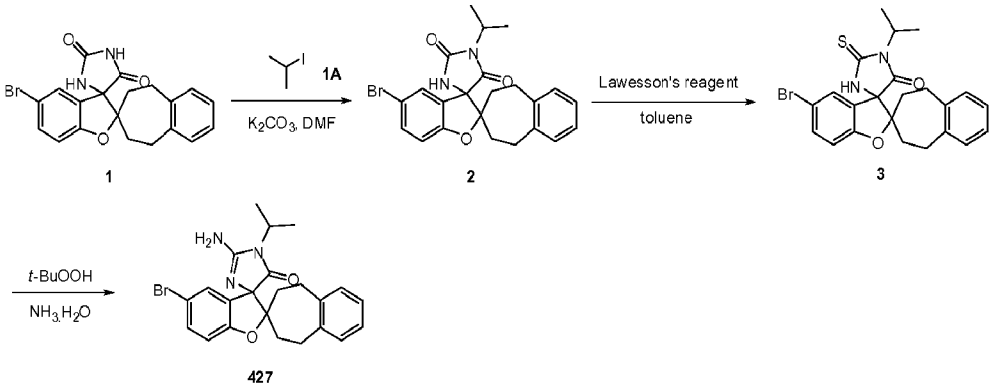
To a solution of compound **8** (24 mg, 0.055 mmol) in MeOH (3 mL) and $NH_3.H_2O$ (0.6 mL) was added *t*-BuOOH (162 mg, 1.11 mmol). The reaction mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The solvent was removed and the residue was purified by preparative HPLC to give **compound 425** (9.0 mg, 39%) as a white solid; **LC-MS** t_R = 1.231 min in 2 min chromatography, MS (ESI) *m/z* 418.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.13 (m, 4H), 6.98 (m, 3H), 3.79 (d, J = 6.8 Hz, 2H), 3.38 (m, 2H), 3.18 (s, 3H), 2.63 (m, 3H), 2.27 (m ,1H), 1.67-1.48 (m, 2H), 1.22 (m, 1H), 0.61 (m, 2H), 0.32 (m, 2H).

Example 363. Synthesis of Compound 426



According to a similar synthesis of **compound 425,** compound **6C** (100 mg, 0.137 mmol) was alkylated with 2,2,2-trifluoroethyl trifluoromethanesulfonate (96 mg, 0.412 mmol) to give compound **9** (35 mg, 81%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.19 (s, 4H), 6.87 (s, 2H), 6.61 (s, 1H), 4.21 (m, 1H), 3.27 (m, 1H), 2.96 (s, 3H), 2.64-2.47 (m, 3H), 2.06 (m, 1H), 1.61 (m, 1H), 1.42 (m, 1H). Compound **9** (35 mg, 0.0783 mmol) was then reacted with Lawesson's reagent (47 mg, 0.117 mmol) under N_2 to give compound **10** (29 mg, 81%) as a white solid. Finally, compound **10** (29 mg, 0.063 mmol) was converted to **compound 426** (8.0 mg, 29%) as a white solid. **LC-MS** t_R = 1.241 min in 2 min chromatography, MS (ESI) *m/z* 446.2 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.05 (m, 6H), 6.94 (m, 1H), 4.39 (m, 1H), 3.31 (m, 2H), 3.12 (s, 3H), 2.62-2.47 (m, 3H), 2.21 (m ,1H), 1.62-1.41 (m, 2H). **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -70.293, -71.342

Example 364. Synthesis of Compound 427



Procedure for preparation of compound 2

To a solution of compound **1** (100 mg, 0.243 mmol) in DMF (5 mL) was added K_2CO_3 (41 mg, 0.292 mmol) and 2-iodopropane **(1A)** (45 mg, 0.267 mmol). The reaction mixture was stirred at room temperture for 3 h. Water (15 mL) was added, and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **2** (68 mg, 62%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.35 (d, J = 8.8 Hz, 1H), 7.06 (m, 5H), 6.79 (d, J = 8.4 Hz, 1H), 4.23 (m, 1H), 3.25 (m, 2H), 2.66 (m, 2H), 2.48 (m ,1H), 2.06 (m, 1H), 1.59 (m, 1H), 1.43 (m, 1H), 1.32 (m, 6H).

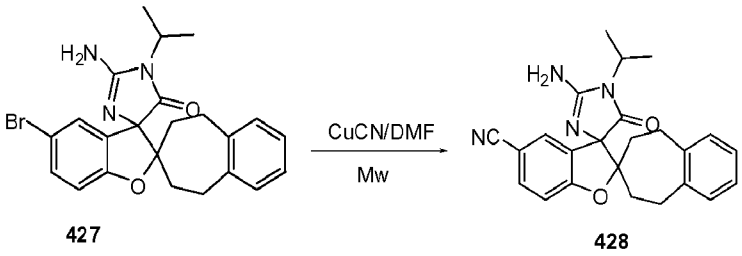
Procedure for preparation of compound 3

To a solution of compound **2** (68 mg, 0.149 mmol) in dry toluene (2 mL) was added Lawesson's reagent (91 mg, 0.224 mmol) under N_2. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 1 h. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **3** (46 mg, 66%) as a white solid.

Procedure for preparation of compound 427

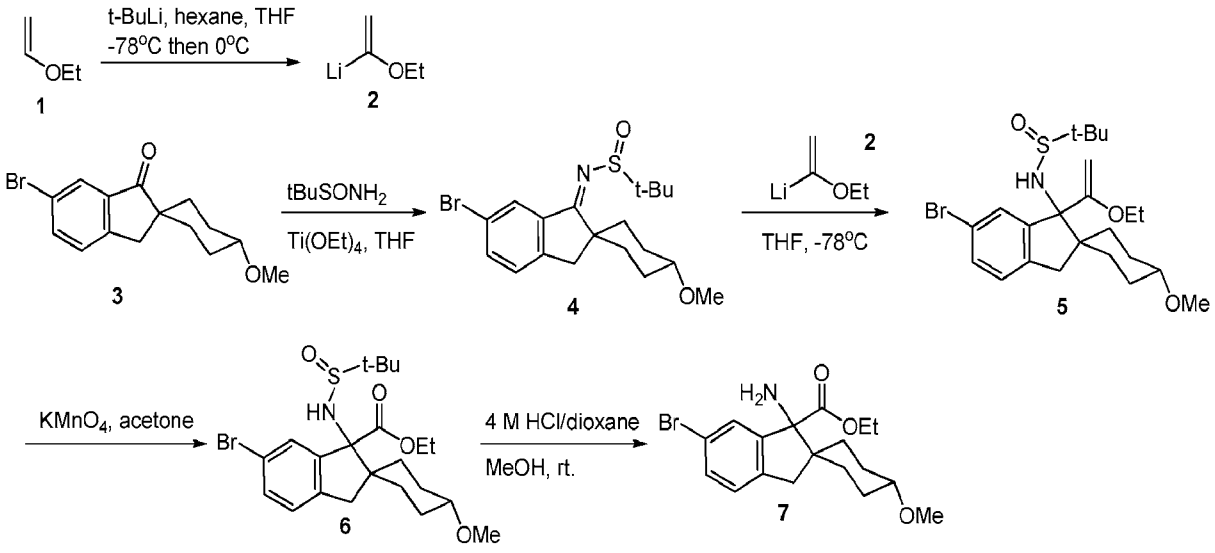
To a solution of compound **3** (46 mg, 0.0977 mmol) in MeOH (3 mL) and $NH_3.H_2O$ (0.6 mL) was added *t*-BuOOH (286 mg, 1.95 mmol). The reaction mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The solvent was removed and the residue was purified by preparative HPLC to give **compound 427** (13 mg, 30%) as a white solid. **LC-MS** t_R = 1.278 min in 2 min chromatography, MS (ESI) *m/z* 454.0 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 7.55 (m, 2H), 7.14 (m, 4H), 6.98 (d, J = 8.7 Hz, 1H), 4.26 (m, 1H), 3.39 (m, 1H), 3.28 (m, 1H), 2.77-2.53 (m ,3H), 2.24 (m, 1H), 1.63 (m, 2H), 1.49 (m, 6H).

Example 365. Synthesis of Compound 428



To a solution of compound **427** (30 mg, 0.066 mmol) in DMF (2 mL) was added CuCN (40 mg, excess) under N_2. The reaction mixture was heated in a CEM microwave reactor at 150 °C for 1 h. Water (10 mL) was added and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to give **compound 428** (2.1 mg, 8%). **LC-MS** t_R = 1.223 min in 2 min chromatography, MS (ESI) *m/z* 401.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 300 MHz): δ 7.81 (m, 2H), 7.18 (m, 5H), 4.26 (m, 1H), 3.45 (m, 2H), 2.78-2.57 (m, 3H), 2.26 (m, 1H), 1.74-1.53 (m ,2H), 1.49 (m, 6H).

Example I-13. Synthesis of (1s,4s)-ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (7)-Method 1



Step 1: Preparation of *N*-(5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)-ylidene)-2-methylpropane-2-sulfinamide (4)

To a solution of 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (**3**) (923 mg, 2.99 mmol) and 2-methylpropane-2-sulfinamide (1.450 g, 11.96 mmol, 4 eq.) in anhydrous THF (75 mL) was added $Ti(OEt)_4$ (5.46 g, 4.96 mL, 23.92 mmol, 8.0 eq). The resulting mixture was heated to reflux overnight. LC-MS showed ca. 45% conversion. After another 8 h, no further improvement. To the refluxing mixture was added 2-methylpropane-2-sulfinamide (0.725 g, 5.98 mmol, 2 eq.) and $Ti(OEt)_4$ (2.73 g, 2.5 mL, 11.96 mmol, 4.0 eq) and followed by another equal portions of 2-methylpropane-2-sulfinamide and $Ti(OEt)_4$ after 14 hours. The reaction mixture was refluxed for another 2 days, 93% conversion achieved at this point. The reaction was quenched with brine (3 mL) after cooled down to room temperature. The mixture was stirred for another 30 min before filtered through a short pad of Celite®. The filter cake was washed with EA, and the filtrate was concentrated to dryness. The residue was purified by silica gel chromatography. The fraction of desired product with 2-methylpropane-2-sulfinamide was dissolved in EA (100 mL) and washed with saturated aqueous $NaHCO_3$ (45 mL), 1 M NaOH (40 mL) and brine successively. Solvent was removed under reduced pressure after dried over Na_2SO_4 and filtered to afford 0.968 g of the desired product **4** as a light yellow solid. MS ESI +ve m/z 412 $(M+H)^+$.

Step 2: Preparation of *N*-(6'-bromo-1'-(1-ethoxyvinyl)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)-2-methylpropane-2-sulfinamide (5)

To solution of ethyl vinyl ether (**1**) (269 mg, 357 µL, 3.73 mmol, 5 eq.) in dry THF (10 mL) chilled to -78°C under N_2 was added 1.7 M *t*-BuLi in heptanes (1.75 mL, 2.98 mmol, 4 eq.) dropwise within 10 min. The temperature of the resulting yellow clear solution[1] was allowed to warm to 0°C slowly within 30 min. By removing dry ice and adding water to dry ice-acetone bath, finally the cooling bath was replaced with a ice water bath. The color changed from yellow to nearly colorless after being stirred ca 5 min at 0°C. Then the lithium regent solution (**2**) was cooled to -78°C again and cannulated to a solution of starting material **4** (307.5 mg, 0.746 mmol) in dry THF (5 mL) at -78°C with positive pressure. The resulting mixture was stirred at this

temperature for another 30 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether and EA, the combined organic phases were washed with water and brine, dried, and filtered. The solvent was removed under reduced pressure to generate off-white foam, which was purified by flash chromatography on silica gel 9:1eluted with EA in hexane (0-40%) to produce the desired product **5** and its diastereomers in a ratio (321 mg, yield 89%). MS ESI +ve m/z 484 $(M+H)^+$.

Step 3: Preparation of ethyl 6'-bromo-1'-(1,1-dimethylethylsulfinamido)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (6)

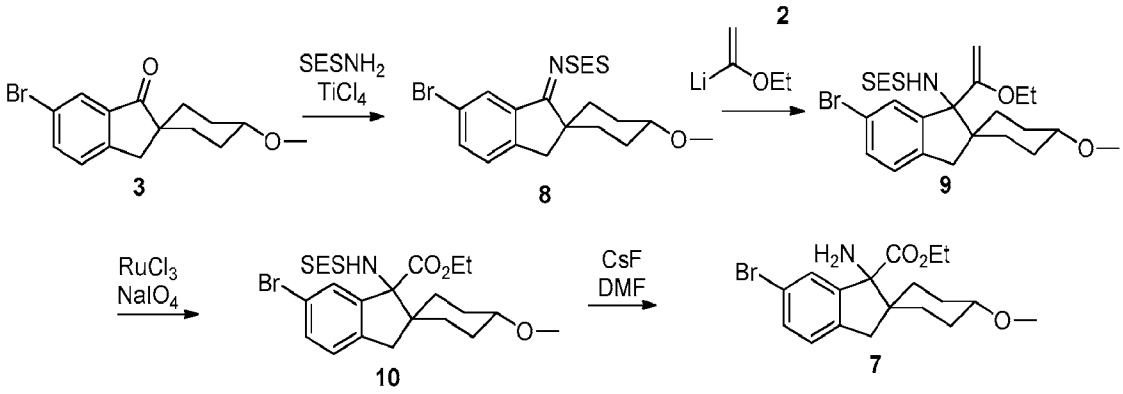
To a solution of *N*-(6'-bromo-1'-(1-ethoxyvinyl)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)-2-methylpropane-2-sulfinamide (**5**) (200 mg, 0.48 mmol) in acetone (15 mL) at room temperature (23°C) was added a $KMnO_4$ solution (5.8 mL, prepared by dissolving 9.5 g of $KMnO_4$ in 100 mL of H_2O). The mixture was stirred room temperature for 16 h. Another portion of $KMnO_4$ solution (2.2 mL) was added and stirred another 12 h. The reaction was quenched with 5% $NaHSO_3$, stirring until colorless clear solution achieved before combined. The combined organic phases were extracted with EA 2 times, washed with brine, dried over Na_2SO_4, evaporated after filtration. The residue was purified by flash chromatography on silica gel eluted with EA in hexane (0-60%) to afford the desired amino ester (**6**) (62.8 mg, 31%). MS ESI +ve m/z 486 $(M+H)^+$.

Step 4: Preparation of ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (7)

To a solution of ethyl 6'-bromo-1'-(1,1-dimethylethylsulfinamido)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (**6**) (62.8 mg, 0.129 mmol) in MeOH (5 mL) was added a 4 M HCl solution in dioxane (2 mL). The resulting mixture was stirred for 30 min. Solvent was removed under reduced pressure, and the residue **7** was used for next step without further purification. MS ESI +ve m/z 382 $(M+H)^+$.

EXAMPLE I-14

Synthesis of (1s,4s)-ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (7)-Method 2



Step 1. *N*-(5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)-ylidene)-2-(trimethylsilyl)ethanesulfonamide (8)

To a mixture of 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (**3**) (0.9822 g, 3.18 mmol, 1.0 equiv) and 2-(trimethylsilyl)ethanesulfonamide) (**$SESNH_2$**)(0.6338 g, 3.50 mmol, 1.1 equiv) in $ClCH_2CH_2Cl$ (10 mL), cooled to 0 °C, were successively added Et_3N (0.9 mL, 6.46 mmol, 2.0 equiv) and $TiCl_4$ (1.0 M in CH_2Cl_2, 3.4 mL, 3.4 mmol, 1.1 equiv). After 10 min, the ice bath was removed. The reaction mixture was stirred at room temperature for 3 h and then heated at 110 °C for 42 h. The reaction mixture was cooled to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 1.3685 g (91%) of *N*-(5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)-ylidene)-2-(trimethylsilyl)ethanesulfonamide (**8**) as a solid. LC-MS t_R = 2.31 min in 3 min chromatography, *m/z* 472, 474 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.67 (dd, J = 8.2, 1.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 3.39 (s, 3H), 3.29-3.21 (m, 3H), 2.98 (s, 2H), 2.16-2.12 (m, 2H), 1.80-1.76 (m, 2H), 1.62-1.57 (m, 2H), 1.42-1.33 (m, 2H), 1.21-1.17 (m, 2H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.97, 151.30,

137.91, 133.35, 127.50, 121.43, 78.10, 55.80, 51.79, 51.39, 39.55, 33.97, 28.60, 9.98, -1.93.

Step 2. *N*-(6'-bromo-1'-(1-ethoxyvinyl)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)-2-(trimethylsilyl)ethanesulfonamide (9)

To a solution of ethyl vinyl ether (7 mL, 73 mmol) in THF (10 mL) was added dropwise a solution of 1.7 M *t*-BuLi in pentane (26 mL, 44 mmol) at -78 °C under nitrogen. After 10 min, the reaction mixture was cooled in an ice bath and stirred for 45 min. To a solution of *N*-(5'-bromo-4-methoxyspiro[cyclohexane-1,2'-indene]-3'(1'*H*)-ylidene)-2-(trimethylsilyl) ethanesulfonamide (**2**) (1.3508 g, 2.86 mmol) in THF (20 mL) was added a solution of -ethoxyvinyllithium, obtained as described above, at -78 °C under nitrogen via a cannula. After 2 h, LC-MS indicated the disappearance of starting material. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and saturated brine (20 mL) and then vigorously stirred at room temperature for 1 h. The mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude product **9** (1.7654 g) was directly used in the next step without further purification. LC-MS t_R = 2.43 min in 3 min chromatography, *m/z* 544, 546 (MH^+), 480, 482.

Step 3. ethyl 6'-bromo-4-methoxy-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (10)

To a solution of $NaIO_4$ (5.9503 g, 27.82 mmol) in water (40 mL) was added $RuCl_3$ hydrate (0.0526 g, 0.25 mmol) followed by a solution of crude *N*-(6'-bromo-1'-(1-ethoxyvinyl)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-yl)-2-(trimethylsilyl)ethanesulfonamide (**9**) (1.0894 g), obtained as described above, in EtOAc (60 mL). The resulting mixture was vigorously stirred at room temperature for 30 min and LC-MS indicated the disappearance of starting material. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers was dried over Na_2SO_4, filtered and evaporated. The residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford ethyl 6'-bromo-4-methoxy-1'-(2-(trimethylsilyl)ethylsulfonamido) -1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (**10**) (0.5329 g, 50% in two

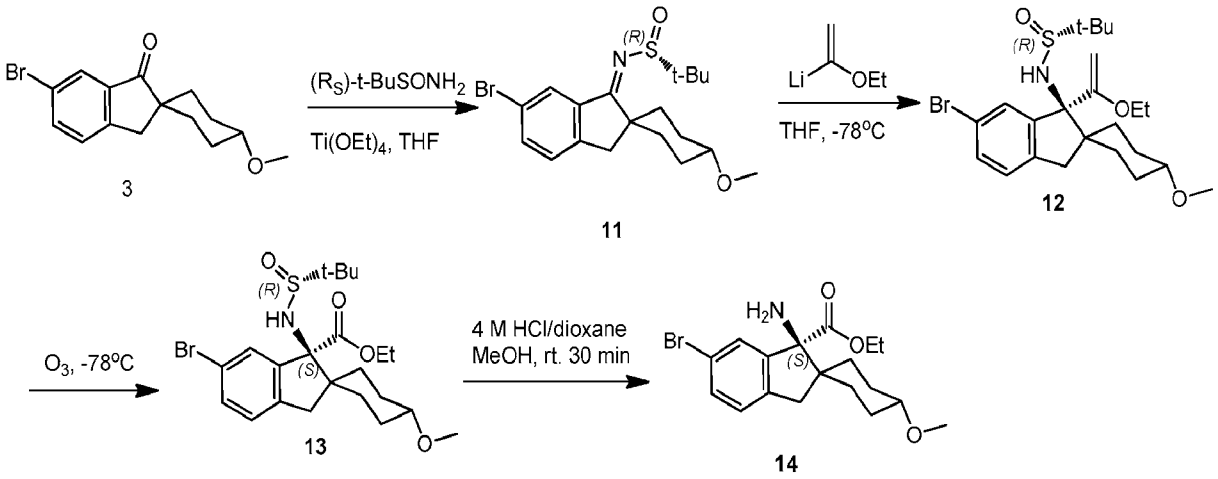
steps). LC-MS t_R = 2.27 min in 3 min chromatography, *m/z* 568, 570 (MNa^+), 333, 335; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 4.41-4.25 (m, 2H), 3.32 (s, 3H), 3.08-3.02 (m, 2H), 2.80 (d, J = 15.8 Hz, 1H), 2.16-2.04 (m, 3H), 1.91-1.87 (m, 2H), 1.80-1.72 (m, 1H), 1.40-1.22 (m, 7H), 0.95-0.88 (m, 1H), 0.80-0.72 (m, 1H), 0.65-0.57 (m, 1H), -0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13, 142.21, 140.91, 132.97, 132.25, 126.52, 119.45, 78.49, 75.10, 61.87, 55.79, 53.06, 50.92, 38.15, 28.64, 28.38, 28.33, 27.82, 14.18, 9.98, -2.28.

Step 4. ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (7)

A mixture of ethyl 6'-bromo-4-methoxy-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (**10**) (0.2229 g, 0.41 mmol) and CsF (0.7893 g, 5.20 mmol) in DMF (2 mL) was heated at 110 °C for 24 h. The mixture was diluted with MeOH, and concentrated in vacuo. The residue was extracted with Et_2O, filtered through Celite® 545, and evaporated. The crude product was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (6) (165.8 mg, 82%) as a TFA salt; LC-MS t_R = 1.17 min in 3 min chromatography, *m/z* 382, 384 (MH^+), 365, 367, 333, 335; ^1H NMR (400 MHz, CD_3OD) δ 7.47-7.45 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.27 (s, 3H), 3.14-3.07 (m, 2H), 2.96 (d, J = 16.4 Hz, 1H), 2.00-1.97 (m, 2H), 1.55-1.52 (m, 2H), 1.46-1.21 (m, 4H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.72, 143.43, 140.85, 134.40, 128.80, 128.11, 121.64, 79.44, 75.09, 64.34, 56.10, 52.49, 40.03, 31.05, 29.50, 29.44, 28.87, 14.24.

EXAMPLE I-15

Chiral Synthesis of (1r,1'S,4S)-ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (14)



Procedure for preparation of compound 11

The titled compound was synthesized according to the method described in Example I-13 step 1, compound 11 in similar yield starting from compound 3 and (R_S)-tert-butylsulfinamide.

Procedure for preparation of compound 12

To a solution of compound ethoxy-ethene (7.25 g, 0.101 mol) in anhydrous THF (100 mL) at -78 °C under a N_2 atmosphere was added dropwise of *t*-BuLi (63 mL, 0.10 mol, 1.6 M in hexane) and stirred for 20 min. The resulting mixture was then stirred at 0 °C for another 45 min. To the solution obtained formerly at -78 °C was added dropwise of compound **11** (8.24 g, 0.02 mol) in anhydrous THF (300 mL) and stirred for 2.5 h. The reaction was quenched with sat. NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was concentrated to give the residue which was purified by column on silica gel (petroleum/ethyl acetate = 10/1) and further purified by preparative HPLC (basic) to give compound **12** (5.2 g, 65%) as a white solid. **LC-MS** t_R = 1.351 min in 2 min chromatography, MS (ESI) *m/z* 484.1, 486.1 $[M+H]^+$. **SFC**: t_R = 3.76 min in 15 min chromatography, ee = 100%. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.82 (s, 1H), 7.37-7.39 (d, J = 8.0 Hz, 1H), 7.07-7.09 (d, J = 8.0 Hz, 1H), 4.33 (s, 1H), 4.31-

4.32 (d, J = 2.8 Hz, 1H), 4.22-4.23 (d, J = 2.8 Hz, 1H), 3.80-3.87 (m, 2H), 3.35 (s, 3H), 3.04-3.09 (m, 1H), 2.96-2.99 (d, J = 15.6 Hz, 1H), 2.56-2.60 (d, J = 15.6 Hz, 1H), 2.04 (s, 1H), 1.86-1.94 (m, 2H), 1.73-1.81 (m, 2H), 1.34-1.37 (t, J = 7.0 Hz, 3H), 1.27-1.16 (m, 3H), 1.00 (s, 9H).

Procedure for preparation of compound 13

Compound **12** (5.0 g, 10.33 mmol) was dissolved in CH_2Cl_2:MeOH = 5:1 (100 mL) and pyridine (20 mL) was added, the mixture was chilled to -78°C and ozone was bubbled through the mixture for 20 min, the mixture changed from colorless to blue, TLC showed that the reaction was completed. The mixture was purged with N_2 and treated with Me_2S at -78°C, then allowed to warm to room temperature and stirred for 3 h. The solvent was removed *in vacuo*, the residue was purified by preparative TLC (petroleum/ethyl acetate = 3/1) to give compound **13** (4.5 g, 90%) as a white solid and one portion of the crude product was further purified by preparative HPLC (basic) to give compound **3** (43.30 mg) as a white solid. **LC-MS** t_R = 1.316 min in 2 min chromatography, MS (ESI) *m/z* 486.1, 488.1 $[M+H]^+$.**SFC**: t_R = 4.37 min in 15 min chromatography, ee = 100%. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.77-7.78 (d, J =1.6 Hz, 1H), 7.48-7.51 (dd, J = 2.0, 8.0 Hz, 1H), 7.23-7.25 (d, J = 8.0 Hz, 1H), 4.24-4.39 (m, 1H), 3.36 (s, 3H), 3.07-3.14 (d, J = 27.2 Hz, 2H), 2.72-2.76 (d, J = 15.6 Hz, 1H), 2.11-2.14 (m, 1H), 1.94-2.00 (m, 2H), 1.78-1.86 (m, 1H), 1.25-1.44 (m, 6H), 1.17 (s, 9H), 0.98-1.09 (m, 1H).

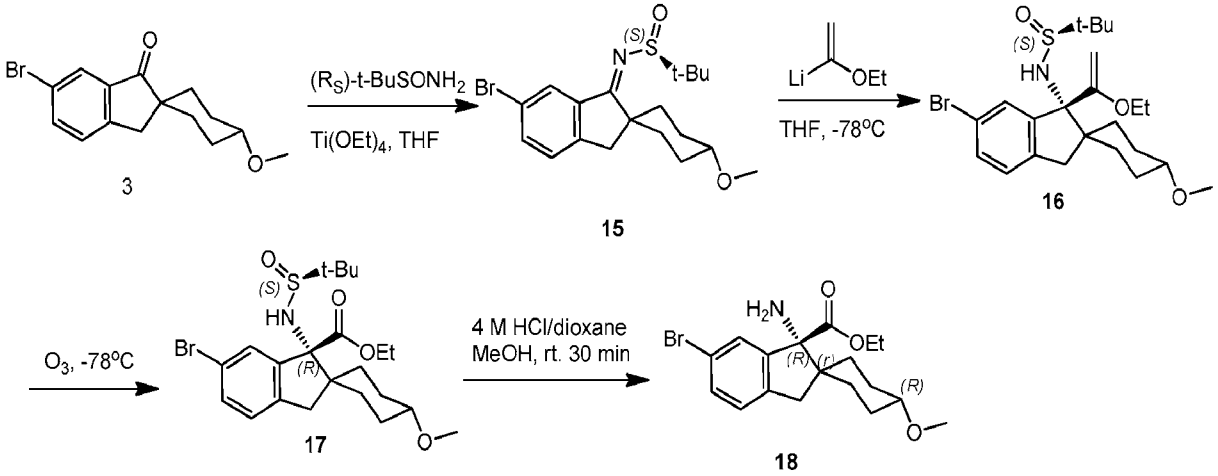
Procedure for preparation of compound 14

To a solution of compound **13** (4.5 g, 9.26 mmol) in MeOH (25 mL) was added a 4 M HCl solution in dioxane (10 mL). The resulting mixture was stirred for 30 min. LC-MS shown no starting material left and product was about 70% purity. Solvent was removed under reduced pressure to give crude product **14** (3.0 g, 85%) as a colorless oil; the residue was used for next step without further purification and one portion of the crude product was further purified by preparative HPLC (basic) to give **14** (39.70 mg) as a colorless oil. **LC-MS** t_R = 0.894 min in 2 min chromatography, MS (ESI) *m/z* 404.1, 406.1 $[M+Na]^+$. **SFC**: t_R = 6.25 min in 15 min chromatography, ee = 100%.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.48 (d, J = 2.0 Hz, 1H), 7.37-7.40 (dd, J = 2.0, 8.0 Hz,

1H), 7.16-7.18 (d, J = 8.0 Hz, 1H), 4.12-4.19 (m, 1H), 3.37 (s, 3H), 3.14-3.22 (m, 1H), 2.92-3.03 (q, J = 15.6 Hz, 14.0 Hz, 2H), 2.02-2.06 (m, 2H), 1.58-1.66 (m, 1H), 1.30-1.51 (m, 5H), 1.20-1.23 (t, J = 7.2 Hz, 3H).

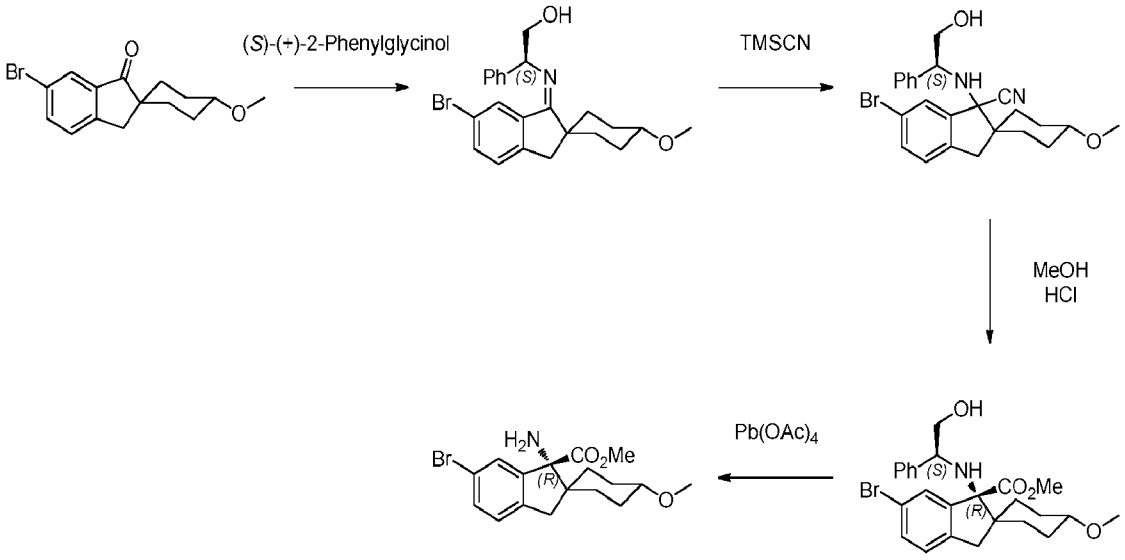
EXAMPLE I-16

Chiral Synthesis of (1r,1'R,4R)-ethyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (18)



The titled compound was synthesized as described in Example **I-15**. **LC-MS** t_R = 0.894 min in 2 min chromatography, MS (ESI) *m/z* 404.1, 406.1 $[M+Na]^+$. **SFC**: t_R = 6.25 min in 15 min chromatography, ee = 100%. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.48 (d, J = 2.0 Hz, 1H), 7.37-7.40 (dd, J = 2.0, 8.0 Hz, 1H), 7.16-7.18 (d, J = 8.0 Hz, 1H), 4.12-4.19 (m, 1H), 3.37 (s, 3H), 3.14-3.22 (m, 1H), 2.92-3.03 (q, J = 15.6 Hz, 14.0 Hz, 2H), 2.02-2.06 (m, 2H), 1.58-1.66 (m, 1H), 1.30-1.51 (m, 5H), 1.20-1.23 (t, J = 7.2 Hz, 3H).

Example I-17. Synthesis of Methyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate



Step 1. Preparation of (*S*)-2-((5'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-3'(1'*H*)-ylidene)amino)-2-phenylethanol

A mixture of *cis*-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one (2.0105 g, 6.50 mmol), (*S*)-(+)-2-phenylglycinol (0.9290 g, 6.77 mmol), and *p*-TsOH monohydrate (0.0640 g, 0.34 mmol) in toluene was refluxed with a Dean-Stark trap for 2 d and LC-MS indicated about 70% conversion of starting material. After removal of the solvent at reduced pressure, the crude product was directly used in the next step without further purification. LC-MS t_R = 1.27 min in 3 min chromatography, *m*/z 428, 430 (MH^+).

Step 2. Preparation of 6'-bromo-1'-(((*S*)-2-hydroxy-1-phenylethyl)amino)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carbonitrile

A solution of (*S*)-2-((5'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-3'(1'*H*)-ylidene)amino)-2-phenylethanol, obtained as described above, in dry CH_2Cl_2 (8 mL) was cooled with ice-water, and then TMSCN (1.8 mL, 13.5 mmol) and dry MeOH (3.6 mL) were added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 24 h. After removal of the solvent at reduced pressure, the crude

product was directly used in the next step without further purification. LC-MS t_R = 2.02 min in 3 min chromatography, *m/z* 455, 457 (MH^+).

Step 3. Preparation of methyl 6'-bromo-1'-(((*S*)-2-hydroxy-1-phenylethyl)amino)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate

The 6'-bromo-1'-(((*S*)-2-hydroxy-1-phenylethyl)amino)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carbonitrile, obtained as described above, was dissolved in 40 mL of saturated methanolic HCl. The resulting mixture was heated at 100 °C for 18 h. The methanol was evaporated and the residue was diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, water, and brine, respectively, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.2166 g (7%) of amino esters as a mixture of diastereomers, and recovered 1.5226 g (75%) of *cis*-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'*H*)-one.

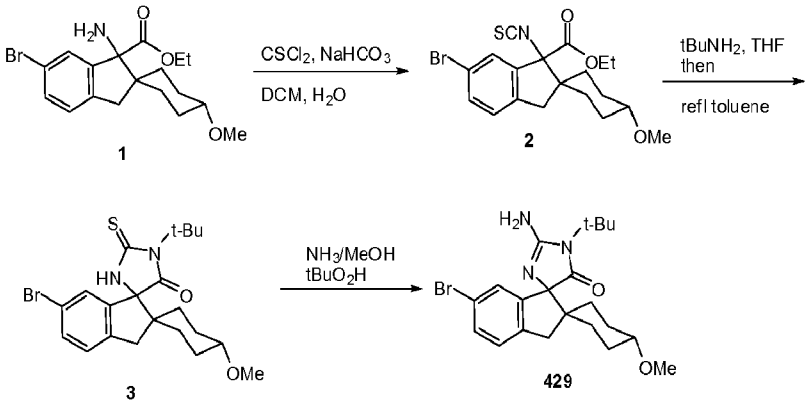
The amino esters was further purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford methyl 6'-bromo-1'-(((*S*)-2-hydroxy-1-phenylethyl)amino)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate as a TFA salt. LC-MS t_R = 1.96 min in 3 min chromatography, t_R = 9.49 (major), 9.99 (minor) min in 16 min chromatography as a ratio of (93:7), *m/z* 488, 490 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.21-6.95 (m, 8H), 4.17 (dd, *J* = 10, 4 Hz, 1H), 3.94 (s, 3H), 3.65 (dd, *J* = 11, 4 Hz, 1H), 3.45 (t, *J* = 10 Hz, 1H), 3.34 (s, 3H), 3.18-3.01 (m, 3H), 2.29-2.15 (m, 2H), 1.93-1.85 (m, 2H), 1.39-1.27 (m, 3H), 0.99-0.93 (m, 1H).

Step 4. methyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate

To a solution of methyl 6'-bromo-1'-(((*S*)-2-hydroxy-1-phenylethyl)amino)-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (0.0180 g, 0.03 mmol) in CH_2Cl_2 (3 mL) and MeOH (1.5 mL) was added $Pb(OAc)_4$ (0.0500 g, 0.11 mmol) at 0 °C. The mixture was stirred for 2 h. After the solvents were evaporated

under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0136 g (94%) of methyl 1'-amino-6'-bromo-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate as a TFA salt. LC-MS t_R = 1.11 min in 3 min chromatography, *m/z* 368, 370 (MH^+), 351, 353, 319, 321; ^1H NMR (400 MHz, CD_3OD) δ 7.57-7.54 (m, 2H), 7.31 (d, *J* = 8 Hz, 1H), 3.79 (s, 3H), 3.35 (s, 3H), 3.25-3.15 (m, 2H), 3.04 (d, *J* = 16 Hz, 1H), 2.09-2.06 (m, 2H), 1.61-1.29 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.36, 143.46, 140.64, 134.50, 128.89, 128.09, 121.70, 79.44, 75.22, 56.11, 54.06, 52.58, 39.97, 31.11, 29.52, 29.44, 28.88.

Example 366. Synthesis of Compound 429



Step 1: Preparation of isothiocyanide 2

Crude compound **1** (0.13 mmol) was added to a solution of $NaHCO_3$ (714 mg, 8.5 mmol) in H_2O (10 mL) and DCM (1 mL) which was chilled at 0 °C, to this stirred mixture was added thiophosgene (12 μL, 18.4 mg, 0.16 mmol) and stirred for 30 h at °C, then another portion of thiophosgene (8 μL, 0.11 mmol). The reaction was diluted with DCM and the separated organic phase was washed with saturated brine and dried over anhydrous Na_2SO_4, and filtered, and concentrated to produce the desired product (1s,4s)-ethyl 6'-bromo-1'-isothiocyanato-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (**2**) as an oil.

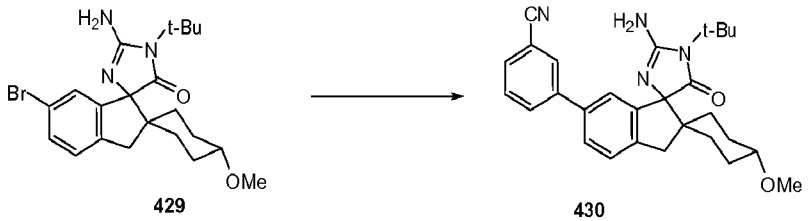
Step 2: Preparation of thiohydantoin 3

To a solution of (1s,4s)-ethyl 6'-bromo-1'-isothiocyanato-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (2) obtained in previous step in THF (3 mL) was added tert-butylamine (0.2 mL), and stirred for 12 h. The reaction was diluted with EA washed with 1 M HCl, brine, and dried over anhydrous Na_2SO_4, and filtered, and concentrated. The residue was dissolved in toluene (3 mL) and refluxed 2.5 h. The reaction mixture was concentrated to dryness. The residue was used for next step without further purification. The solvent was removed under reduced pressure and the residue was dissolved in DCM (2 mL) and hexane (2 mL) and evaporated to afford 209 mg of 6-bromo-1'-methyl-2-phenyl-2'-thioxo-2',3'- dihydro-1'*H*-spiro[chroma*N*-4,4'-pyrimidin]-6'(5'H)-one (**3**) as a white foam. This product was used for next without further purification. MS ESI +ve m/z 451 $(M+H)^+$.

Step 3:Preparation of acylguanidine 4

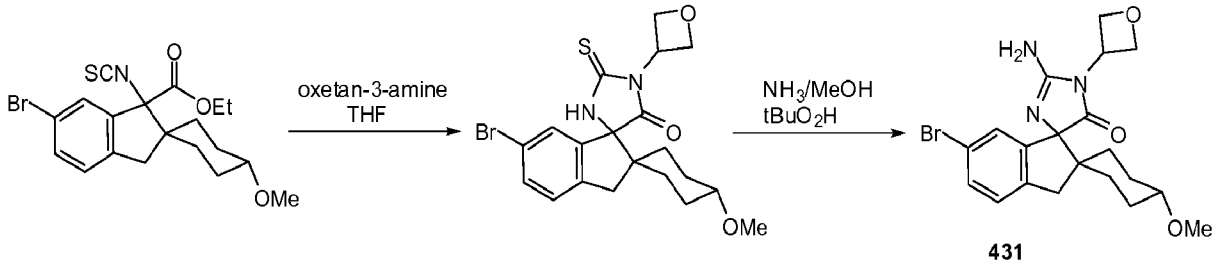
To the solution of above crude product in 7 M NH_3 solution in MeOH (8 mL) was added $tBuO_2H$ solution (5 M in nonane, 1 mL). The resulting mixture was stirred overnight before diluted with EA, then washed with 5% $NaHSO_3$, and brine successively, and dried over Na_2SO_4. Solvent was removed under reduced pressure, the residue was purified by preparative HPLC to afford the desired product 2.51 mg as TFA salt. MS ESI +ve m/z 434 $(M+H)^+$. t_R: 1.60 min. ^1H NMR (400 MHz, CD_3OD) δ: 7.51 (dd, *J* = 8.4, 2.0, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 3.35 (s, 3H), 3.18 (m, 1H), 3.12 (d, *J* = 15.6 Hz, 1H), 3.05 (d, *J* = 15.6 Hz, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.68 (s, 9H), 1.48-1.27 (m, 5H).

Example 367 Synthesis of Compound 430



The title compound was made by the method described in example **27**. MS ESI +ve m/z 457 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 8.00 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.71-7.68 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 3.36 (s, 3H), 3.21 (d, *J* = 15.6 Hz, 1H), 3.19 (m, 1H), 3.13 (d, *J* = 15.6 Hz, 1H), 2.11 (m, 1H), 2.01 (m, 1H), 1.92 (m, 1H), 1.69 (s, 9H), 1.48-1.42 (m, 3H), 1.37-1.29 (m, 2H).

Example 368. Synthesis of Compound 431



431

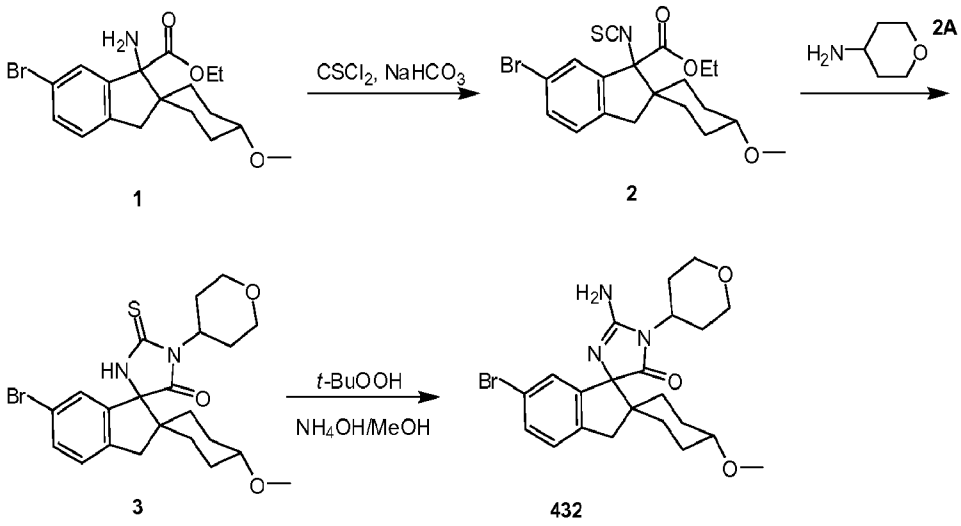
Step 1:

A mixture of (1s,4s)-ethyl 6'-bromo-1'-isothiocyanato-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-1'-carboxylate (110 mg, 0.26 mmol) and oxeta*N*-3-amine (80 mg, 1.09 mmol) was stirred at room temperature for 2 h and concentrated to dry give the desired product. MS ESI +ve m/z 451 $(M+H)^+$.

Step 2:

To the solution of above crude product (35 mg, 0.078 mmol) in 7 M NH_3 solution in MeOH (3 mL) was added $tBuO_2H$ solution (5 M in nonane, 0.6 mL). The resulting mixture was stirred overnight before diluted with EA, then washed with 5% $NaHSO_3$, and brine successively, and dried over Na_2SO_4. Solvent was removed under reduced pressure, the residue was purified by preparative HPLC to afford the desired product 6.3 mg as TFA salt. MS ESI +ve m/z 434 $(M+H)^+$. t_R: 1.24 min. ^1H NMR (400 MHz, CD_3OD) δ: 7.53 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 5.26 (m, 1H), 5.14 (m, 2H), 4.86 (m, 2H), 3.34 (s, 3H), 3.17 (d, *J* = 16.0 Hz, 1H), 3.16 (m, 1H), 3.08 (d, *J* = 16.0 Hz, 1H), 2.08 (m, 1H), 2.01 (m, 1H), 1.92 (m, 1H), 1.69 (s, 9H), 1.52 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.47-1.41 (m, 2H), 1.36-1.28 (m, 2H).

Example 369. Synthesis of Compound 432



General procedure for preparation of compound 2

To compound **1** (200 mg, 0.523 mmol) was added CH_2Cl_2 (10 mL), H_2O (10 mL) and $NaHCO_3$ (439 mg, 5.23 mmol). To this stirred mixture was added thiophosgene (144 mg, 1.26 mmol.) was added. The mixture was stirred for 50 min, LC-MS shown no starting material left. After extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (2 × 10 mL), dried and solvent was removed under reduced pressure to give crude compound **2** (200 mg, 90%) as a yellow oil, which was used for next step without further purification.

General procedure for preparation of compound 3

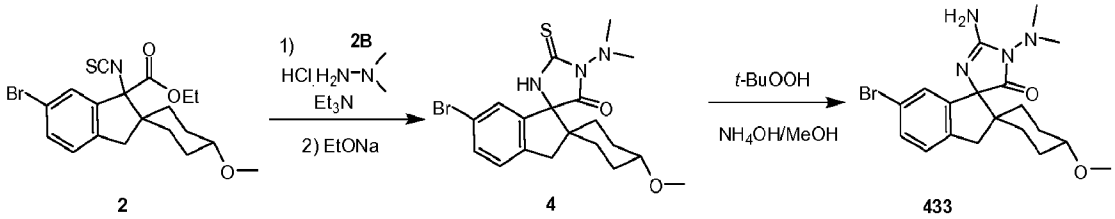
To a solution of compound **2** (50 mg, 0.118 mmol) in THF (5 mL) was added compound **2A** (24 mg, 0.236 mmol). The mixture was stirred overnight at r.t., LC-MS showed the reaction was completed. The reaction was diluted with EtOAc (20 mL) and washed with 1 M HCl (2 × 5 mL) to remove excess amine, followed by saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL) washing. Solvent was removed after dried over Na_2SO_4 to give crude compound **3** (50 mg, 88%) as a yellow oil. The residue was used for next step without further purification.

Procedure for preparation of compound 432

To a solution of compound **3** (50 mg, 0.104 mmol) in MeOH (5 ml) and NH_4OH (1 ml) was added a solution of *t*-BuO_2H (289 mg, 2.09 mmol, 65% in water). The

mixture was stirred overnight and evaporated to remove solvent. The residue was purified by preparative HPLC (basic) to give **compound 432** (7.0 mg, 15%) as a white solid. **LC-MS** t_R = 0.962 min in 2 min chromatography, MS (ESI) MS (ESI) *m/z* 462.1, 464.1 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.41-7.43 (dd, J=1.6, 8.0 Hz, 1H), 7.23-7.25 (d, J= 8.0 Hz, 1H), 7.13 (s, 1H), 3.99-4.08 (m, 3H), 3.43-3.49 (t, J= 7.6 Hz, 2H), 3.36 (s, 3H), 3.14-3.17 (m, 1H), 3.00-3.08 (m, 2H), 2.38-2.58 (m, 2H), 1.89-2.05 (m, 3H), 1.56-1.63 (m, 3H), 1.29-1.43 (m, 4H).

Example 370. Synthesis of Compound 433



1. Procedure for preparation of compound 4

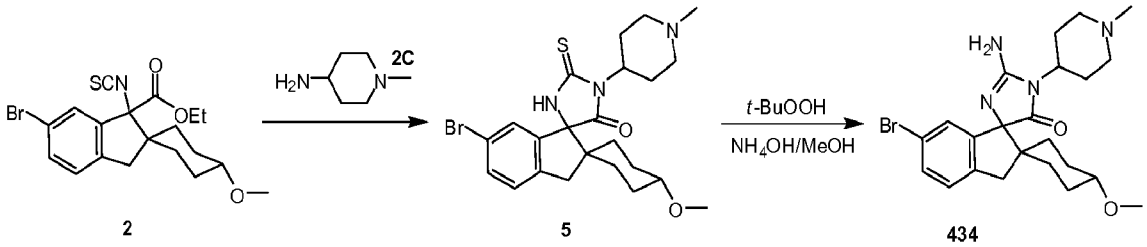
To a solution of compound **2** (50 mg, 0.118 mmol) in THF (5 mL) was added compound **2B** (31 mg, 0.236 mmol) and Et_3N (24 mg, 0.236 mmol). The mixture was stirred overnight at r.t., LC-MS showed only have intermediate, EtONa (16 mg, 0.236 mmol) was added, the mixture was stirred overnight at r.t., LC-MS showed the reaction completed, the reaction was diluted with EtOAc (20 mL) and washed with 1 M HCl (2 × 5 mL) to remove excess amine, followed by saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL) washing. Solvent was removed after dried over Na_2SO_4 to give crude compound **4** (50 mg, 97%) as a yellow oil. The residue was used for next step without further purification.

2. Procedure for preparation of compound 433

To a solution of compound **4** (50 mg, 0.114 mmol) in MeOH (5 ml) and NH_4OH (1 ml) was added a solution of t-BuO_2H (317 mg, 2.28 mmol, 65% in water). The mixture was stirred overnight and evaporated to remove solvent. The residue was purified by preparative HPLC (basic) to give **compound 433** (10.0 mg, 22%) as a white solid. **LC-MS** t_R = 0.971 min in 2 min chromatography, MS (ESI) *m/z* 421.1, 423.1

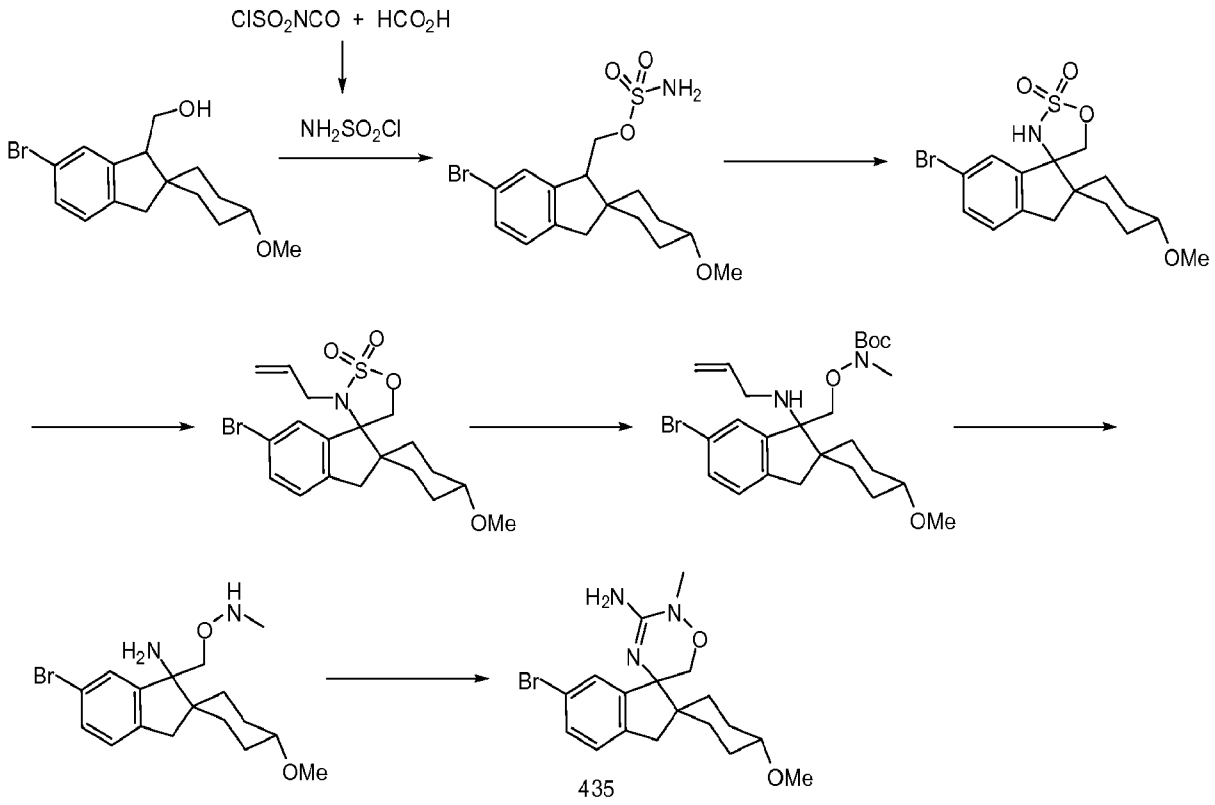
$[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.40-7.42 (dd, J = 1.6, 8.0 Hz, 1H), 7.23-7.25 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 3.35 (s, 3H), 3.11-3.20 (m, 1H), 2.98-3.09 (m, 2H), 2.87-2.91 (d, J = 16.0 Hz, 6H), 1.92-2.06 (m, 3H), 1.64-1.71 (m, 1H), 1.28-1.42 (m, 4H).

Example 371. Synthesis of Compound 434



The titled compound as a white solid was synthesized as described in Example 369, starting from compound 2 and 1-methylpiperidin-4-amine. **LC-MS** t_R = 0.717 min in 2 min chromatography, MS (ESI) *m/z* 475.2, 477.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.40-7.42 (dd, J = 2.0, 8.0 Hz, 1H), 7.22-7.24 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 3.87 (m, 1H), 3.35 (s, 3H), 3.14 (m, 1H), 3.02-3.04 (d, J = 8.0 Hz, 2H), 2.96-2.98 (m, 2H), 2.43-2.61 (m, 2H), 2.29 (s, 3H), 1.89-2.16 (m, 6H), 1.56-1.70 (m, 3H), 1.26-1.42 (m, 3H).

Example 372. Synthesis of Compound 435



Step 1:

To chlorosulfonyl isocyanate (1.6 mL, 2.60 g, 18.38 mmol) in toluene (8 mL) was added formic acid (0.69 mL, 846 mg, 18.38 mmol) dropwise. The mixture was stirred for 10 min at room temperature and concentrated to dry to afford sulfamoyl chloride, which was used without purification.

To a solution of alcohol (226 mg, 0.69 mmol) in N,*N*-dimethylacetamide (3 mL) at 0°C under N_2 atmosphere was added sulfamoyl chloride (241 mg, 2.08 mmol, 3 eq.) . The resulting mixture was stirred at room temperature overnight. The reaction was diluted with EA and washed with H_2O, and brine successively, and dried over Na_2SO_4, and filtered, and evaporated under reduced pressure to afford the crude product, which was used for next step without future purification.

Step 2:

To a solution of above crude product in dry DCM (10 mL) under N_2 atmosphere was added MgO (64 mg, 1.59 mmol, 2.3 eq.), $Rh_2(OAc)_4$ (11 mg, 3.6 mmol%) and

$PhI(OAc)_2$ (244 mg, 0.76 mmol, 1.1 eq.). The resulting mixture was stirred for 3 h at room temperature, then filtered through a short pad of $MgSO_4$ and washed with DCM. The filtrate was evaporated and residue was purified by silica gel column and eluted with EA/hexane (0-60%) to afford the desired product 168 mg as white solid.

Step 3:

To a solution of above product (138 mg, 0.34 mmol) in DCM (8 mL) at room temperature was added allyl iodide (0.4 mL), Bu_4NCl (16 mg, 0.058 mmol) and 40% NaOH (3 mL). The reaction mixture was extracted with DCM after stirred overnight. The organic phase was washed with H_2O, brine successively, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to dryness to produce the desired product.

Step 4:

To a solution of *tert*-butyl hydroxy(methyl)carbamate (600 mg, 4.08 mmol, prepared according the procedure described in *Org. Lett* **2007**, *9*, 4009) in anhydrous DMF (2.5 mL) at room temperature under N_2 atmosphere was added NaH (60%, 163 mg, 4.08 mmol). The mixture was stirred for 15 min, then a solution of above crude product in anhydrous DMF (1.5 mL) was added. The resulting mixture was stirred 16 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EA, the separated organic phase was washed with H_2O, brine successively, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to dryness. The residue was used for next step without further purification. MS ESI +ve m/z 509 $(M+H)^+$.

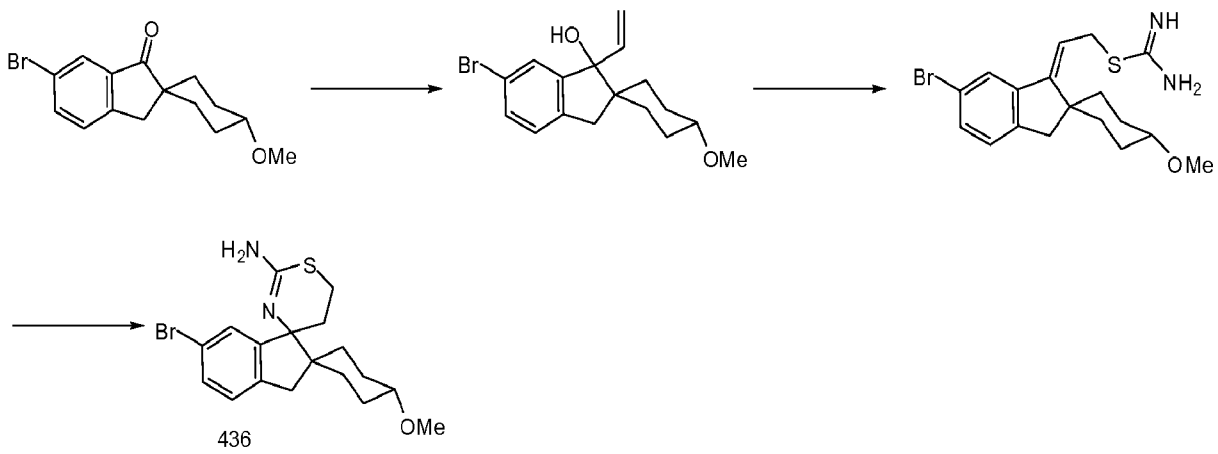
Step 5:

A solution of above product and $RhCl_3$ nH_2O in EtOH (5 mL) was refluxed for 3 h and concentrated. The residue was dissolved in 20% TFA in DCM and stirred for 30 min. The reaction was concentrated and purified by preparative HPLC to afford the desire product as TFA salt. It was dissolved in DCM and washed with aqueous $NaHCO_3$ and bring, and dried over anhydrous Na_2SO_4, and filtered, and concentrated to dryness to afford 4.5 mg of the desire product as free amine. MS ESI +ve m/z 369 $(M+H)^+$.

Step 6:

To a solution of above product (4.5 mg, 0.012 mmol) in EtOH (3 mL) was added a solution of cyanogen bromide (0.2 M in THF, 0.2 mL, 0.04 mmol). The resulting mixture was stirred overnight. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC to afford the desire product as TFA salt. MS ESI +ve m/z 394 $(M+H)^+$. t_R: 1.31 min. ^1H NMR (400 MHz, CD_3OD) δ: 7.52 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 7.6, *J* = 1.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.09 (d, *J* = 12.4 Hz, 1H), 3.43 (s, 3H), 3.35 (s, 3H), 3.17 (m, 1H), 3.06 (d, *J* = 16.4 Hz, 1H), 2.85 (d, *J* = 16.4 Hz, 1H), 2.04 (m, 2H), 1.70 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.61 (td, *J* = 13.6, 4.0 Hz, 1H), 1.51-1.29 (m, 4H).

Example 373. Synthesis of Compound 436



436

Step 1:

To a solution of (1s,4s)-6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (353 mg, 1.14 mmol) in anhydrous THF (8 mL) at -78°C was added a solution of vinylmagnesiun bromide in THF (1 M, 5.7 mL, 5.7 mmol) dropwise. The reaction temperature was allowed to warm to room temperature and stirred for another 1 h. The reaction was chilled to 0°C and quenched with sat. aq. NH_4Cl and extracted with ethyl ether (2 × 20 mL). The combined organic phases were washed with H_2O, brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified through flash chromatography on silica gel to afford 320 mg of (1r,4r)-6'-

bromo-4-methoxy-1'-vinyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-1'-ol. MS ESI +ve m/z 319 $(M+H-H_2O)^+$.

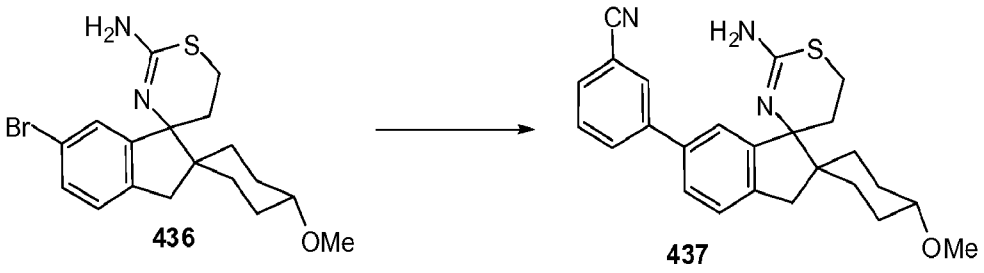
Step 2:

The mixture of (1r,4r)-6'-bromo-4-methoxy-1'-vinyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-1'-ol (162 mg, 0.48 mmol) and thiourea (55 mg, 0.72 mmol) in HOAc (3 mL) and 1 M HCl (1.2 mL) was stirred at room temperature for 20 min then 40°C for 12 h. The solvents was removed under reduced pressure to give 252 mg of a mixture of 2-((1r,4r)-5'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-3'(1'H)-ylidene)ethyl carbamimidothioate HCl salt and thiourea. It was used for next step without purification. MS ESI +ve m/z 395 $(M+H)^+$.

Step 3:

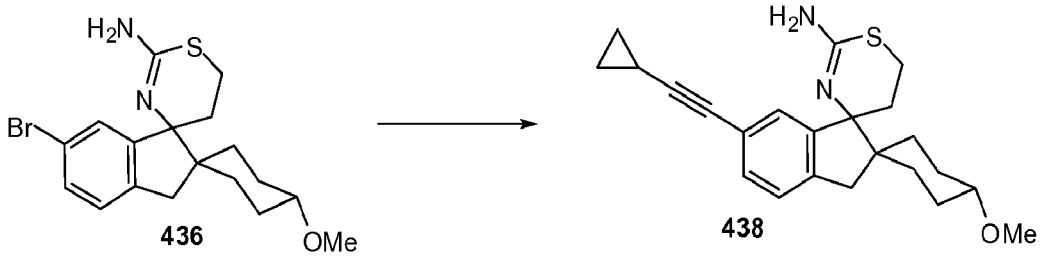
Above mixture of 2-((1r,4r)-5'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-3'(1'H)-ylidene)ethyl carbamimidothioate HCl salt and thiourea (98 mg, ca. 0.187 mmol) was dissolved in TFA (1.5 mL) contain $MeSO_3H$ (0.15 mL) and stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with sat $NaHCO_3$. The separated aqueous phase was extracted with ethyl acetate once and the combined organic phases were washed with brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC to afford 69 mg of the desired product as TFA salt. MS ESI +ve m/z 395 $(M+H)^+$. t_R: 1.25 min. ^1H NMR (400MHz, CD_3OD): 7.50-7.46 (m, 2H), 7.25 (d, J = 7.2 Hz, 1H), 3.39-3.18 (m, 3H), 3.36 (s, 3H), 3.03 (d, J = 16.4 Hz, 1H), 2.96 (d, J = 16.4 Hz, 1H), 2.48 (m, 1H), 2.34 (m, 1H), 2.07 (m, 2H), 1.65-1.51 (m, 4H), 1.43-1.32 (m, 2H).

Example 374. Synthesis of Compound 437



A mixture of compound 436 (15.9 mg, 0.03 mmol), 3-cyanophenylboronic acid (20 mg, 0.14 mmol), Cs_2CO_3 (60 mg, 0.18 mmol) and a catalytic amount of $PdCl_2(PPh_3)_2$ in 1,4-dioxane (3 mL) and H_2O (0.2 mL) was heated at 110°C in microwave oven for 15 min and 130°C in microwave oven for another 10 min. 10 mL of water was added and extracted with EA, the separated organic phase was washed with brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified through preparative HPLC to give the desired product. MS ESI +ve m/z 418 $(M+H)^+$. t_R: 1.37 min. ^1H NMR (400MHz, CD_3OD): 8.00 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.67-7.58 (m, 2H), 7.57 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 3.36 (m, 1H), 3.23 (m, 2H), 2.5-2.44 (m, 2H), 2.10 (m, 2H), 2.07 (m, 2H), 1.66-1.56 (m, 4H), 1.45-1.39 (m, 2H).

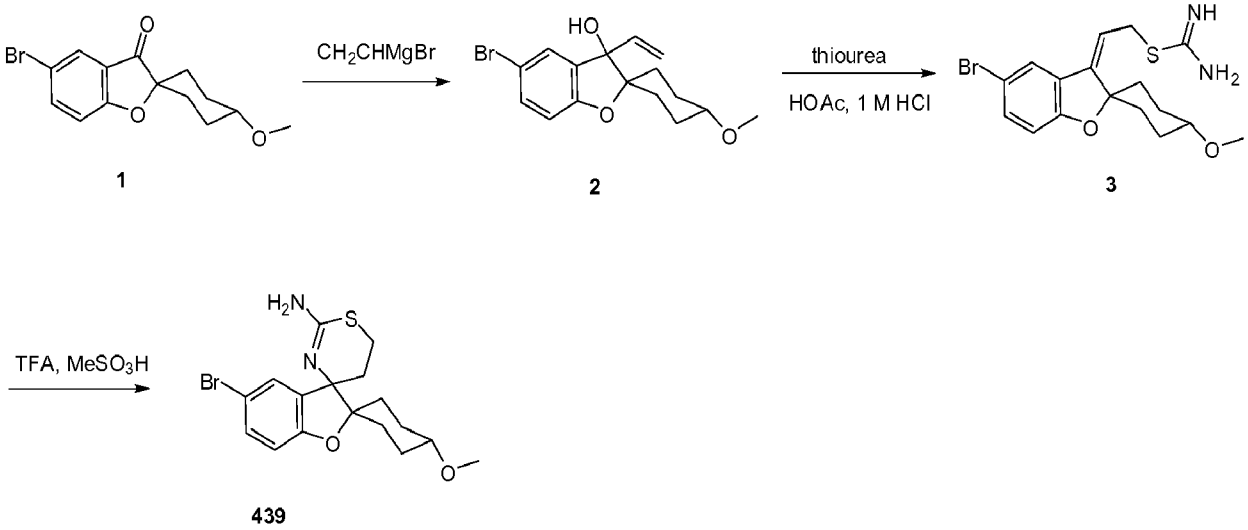
Example 375. Synthesis of Compound 438



A mixture of compound 436 (41 mg, 0.08 mmol), Cs_2CO_3 (72 mg, 0.22 mmol) and a catalytic amount of $PdCl_2(PPh_3)_2$ in toluene (3 mL) was de-gased and purged with N_2 3 times, then, followed by adding tributyl(cyclopropylethynyl)stannane (43 mg, 0.12 mmol). The resulting mixture was heated at 130°C in microwave oven for 10 min. The reaction was diluted with EA, washed with aqueous CsF solution, and brine

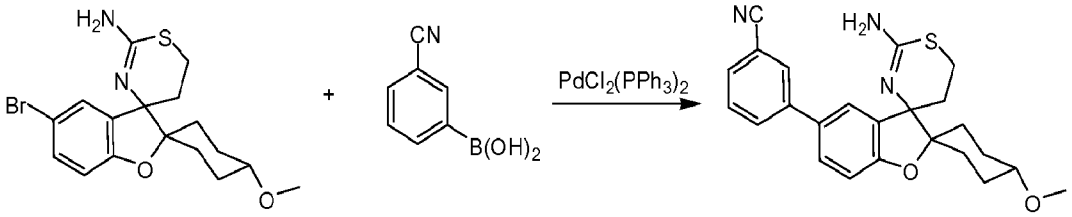
successively, and dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified through preparative HPLC to give the desired product. MS ESI +ve m/z 381 $(M+H)^+$. t_R: 1.47 min. ^1H NMR (400MHz, CD_3OD): 7.32 (d, J = 8.4 Hz, 1H), 7.30-7.24 (m, 2H), 3.36 (s, 3H), 3.35-3.18 (m, 3H), 3.05 (d, J = 16.4 Hz, 1H), 2.98 (d, J = 16.4 Hz, 1H), 2.46 (m, 1H), 2.33 (m, 1H), 2.07 (m, 2H), 1.65-1.34 (m, 7H), 0.88 (m, 2H), 0.71 (m, 2H).

Example 376. Synthesis of Compound 439



The titled compound was synthesized as described in **Example 373** starting from compound **1**. **LC-MS** t_R = 0.772 min in 2 min chromatography, MS (ESI) *m/z* 397, 399 $[M+H]^+$. **^1H NMR** (CD_3OD 400 MHz): δ 7.53 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 2.0, 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.27-3.37 (m, 6H), 2.49-2.60 (m, 2H), 2.00-2.10 (m, 2H), 1.40-1.47 (m, 1H), 1.52-1.69 (m, 5H).

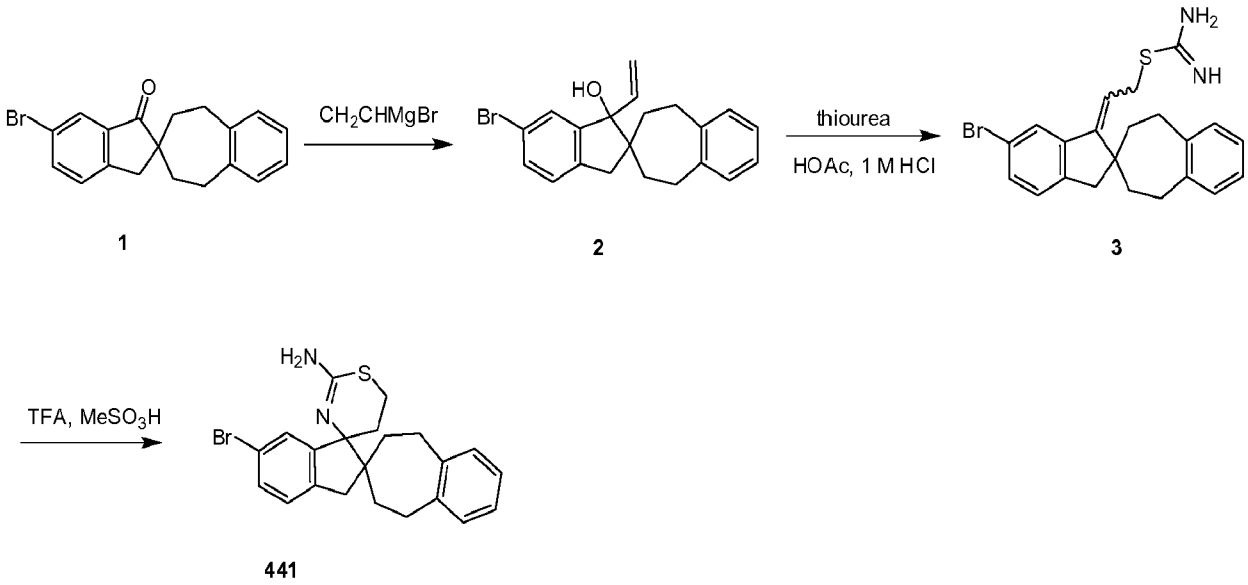
Example 377. Synthesis of Compound 440



1 1A 440

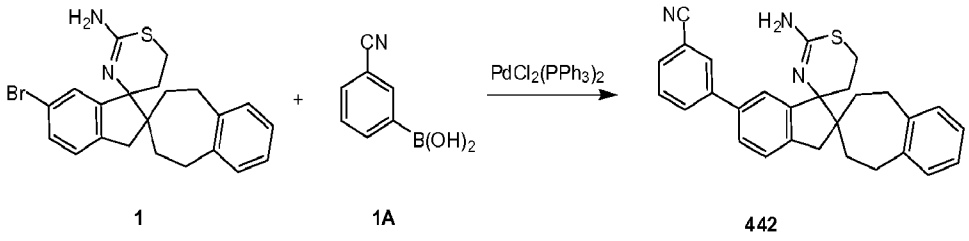
A solution containing compound **1A** (19 mg, 0.126 mmol) and compound **1** (50 mg, 0.126 mmol) in 1, 4-dioxane (3.2 mL), and aqueous Cs_2CO_3 (2 M, 1.5 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (5 mg, 0.006 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 35 min. TLC showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (hexane: EtOAc = 5:1) and preparative HPLC to give product **compound 440** (1.0 mg, 2%) as a white solid. **LC-MS** t_R = 0.965 min in 2 min chromatography, MS (ESI) *m/z* 420 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.69 (m, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.45 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.32 (s, 3H), 3.10-3.20 (m, 2H), 2.98-3.10 (m, 1H), 1.94-2.03 (m, 4H), 1.59-1.77 (m, 5H), 1.18 (m, 1H).

Example 378. Synthesis of Compound 441



The titled compound was synthesized as described in **Example 373** starting from compound **1**. **LC-MS** t_R = 0.923 min in 2 min chromatography, MS (ESI) *m/z* 427, 429 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.46 (dd, J = 1.6 , 8.0 Hz, 1H), 7.41 (d, J = 1.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.03 (m, 4H), 3.18 (m, 2H), 3.11 (m, 2H), 2.92-3.02 (m, 2H), 2.63 (m, 2H), 2.42 (m, 1H), 2.27 (m, 1H), 1.77 (m, 2H), 1.40-1.50 (m, 2H).

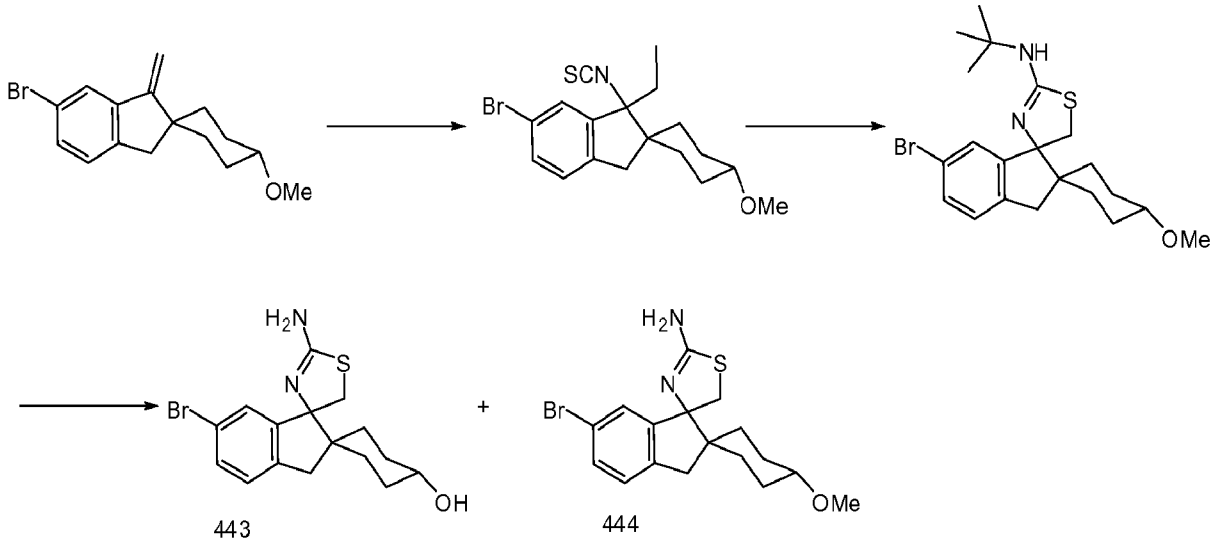
Example 379. Synthesis of Compound 442



The titled compound was synthesized as described in **Example 377,** in 26% yield starting from compound **1 and 1A. LC-MS** t_R = 1.121 min in 2 min chromatography, MS (ESI) *m/z* 450 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.04 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.62 (s,

1H), 7.55 (d, J = 8.0 Hz, 1H), 7.15 (m, 4H), 3.41 (m, 2H), 3.27 (m, 2H), 3.06-3.16 (m, 2H), 3.74 (m, 2H), 3.48-3.61 (m, 2H), 1.94 (m, 2H), 1.55-1.66 (m, 2H).

Example 380. Synthesis of Compounds 443 and 444



Step 1:

To a solution of (1s,4s)-6'-bromo-4-methoxy-1'-methylene-1',3'-dihydrospiro[cyclohexane-1,2'-indene] (10.3 mg, 0.034 mmol), I_2 (20 mg, 0.104 mmol) in DCM (2 mL) was added KSCN (16.5 mg, 0.17 mmol), catalytic amount of tetrabutylammonium chloride and H_2O (0.1 mL). The mixture was stirred at room temperature overnight and quenched with 10% $NaHSO_3$ and extracted with DCM once. The separated organic phase was washed with brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated to generate the crude product (1r,4r)-6'-bromo-1'-(iodomethyl)-1'-isothiocyanato-4-methoxy-1',3'-dihydrospiro[cyclohexane-1,2'-indene], which was used for next step without further purification.

Step 2:

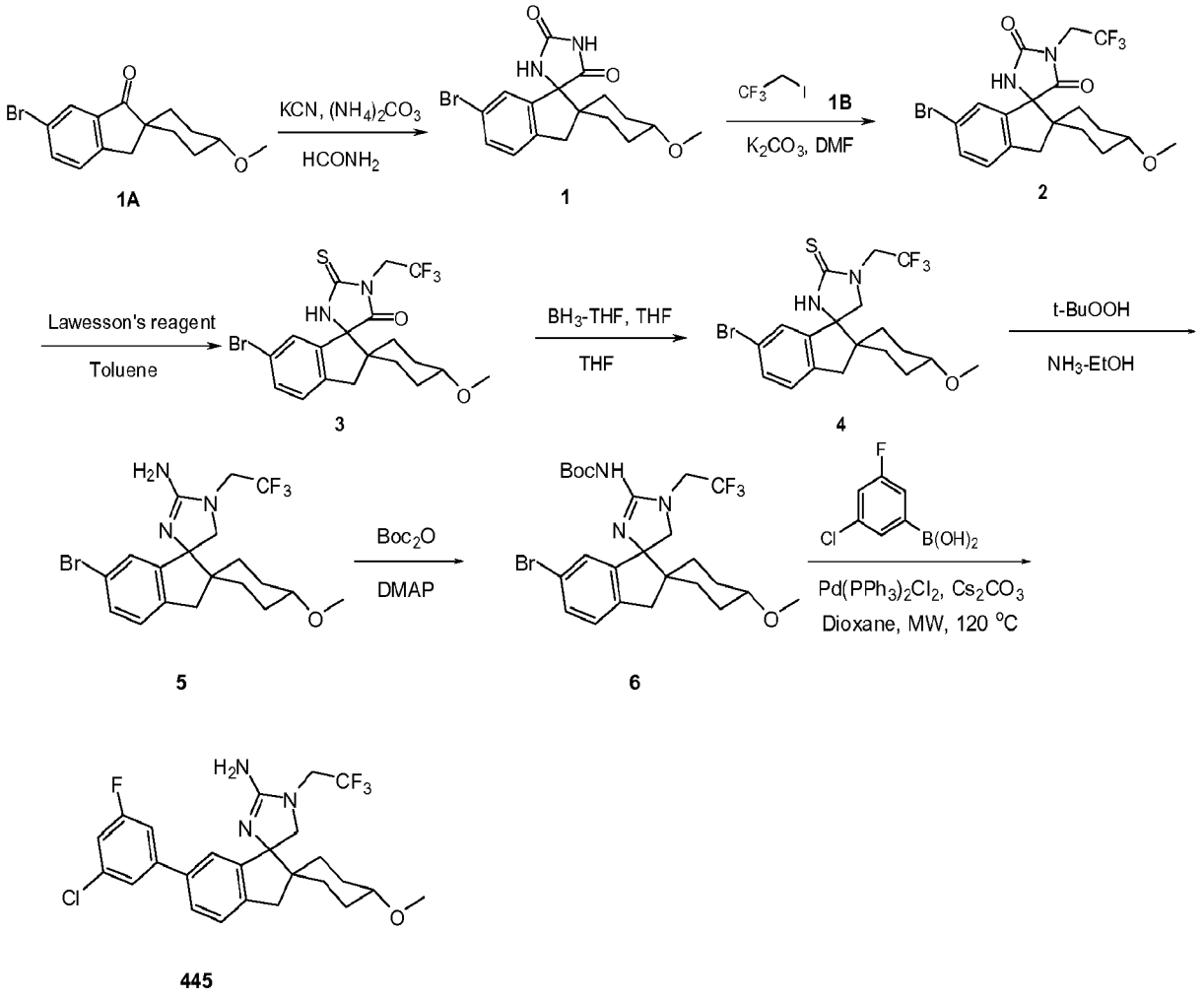
To a solution of above crude product in THF (3 mL) was added tert-butylamine (5 mg, 7 μL, 0.068 mmol). The mixture was stirred overnight at room temperature and concentrated. The residue was purified by preparative HPLC to give 8 mg of the desired product. MS ESI +ve m/z 437 $(M+H)^+$.

Step 3:

Above product in concentrated HCl (2 mL) was refluxed for 60-90 min. The reaction was cool to room temperature and diluted with EA, neutralized with K_2CO_3, washed with brine, and dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC to give 1.7 mg of **compound 443** and 3 mg of **compound 444**. **Compound 443:** MS ESI +ve m/z 367 $(M+H)^+$. t_R: 1.07 min. ^1H NMR (400MHz, CD_3OD): 7.70 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.64 (d, *J* = 12.4 Hz, 1H), 3.54 (m, 1H), 3.03 (d, *J* = 16.4 Hz, 1H), 2.97 (d, *J* = 16.4 Hz, 1H), 1.92 (m, 2H), 1.64 (m, 2H), 1.54-1.42 (m, 4H).

Compound 444: MS ESI +ve m/z 381 $(M+H)^+$. t_R: 1.27 min. ^1H NMR (400MHz, CD_3OD): 7.70 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 4.05 (d, *J* = 12.4 Hz, 1H), 3.65 (d, *J* = 12.4 Hz, 1H), 3.36 (s, 3H), 3.20 (m, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.97 (d, *J* = 16.4 Hz, 1H), 2.06 (m, 2H), 1.67-1.62 (m, 2H), 1.54-1.52 (m, 2H), 1.40-1.33 (m, 2H).

Example 381. Synthesis of Compound 445



Procedure for preparation of compound 1

A steel autoclave was charged with a mixture of compound **1A** (3.0 g, 9.7 mmol), KCN (1.4 g, 21.5 mmol) and $(NH_4)_2CO_3$ (9.5 g, 98.9 mmol) in formamide (60 mL). The mixture was heated at 120 °C for 72 h. The reaction mixture was then cooled and poured onto ice, then was extracted with ethyl acetate: isopropanol = 3:1 (200 mL × 3). The combined organic fractions were washed with brine (200 mL × 2). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was washed with a mixed solvent of petroleum ether: ethyl acetate = 10: 1 (50 mL × 2) to give compound **1** (2.4 g, 68%) as a yellow solid with 70% purity on LC-MS, which

was used for the next step without purification. **LC-MS**: t_R = 1.69 min in 3 min chromatography, MS (ESI) *m/z*=379.25 $[M+H]^+$.

Procedure for preparation of compound 2

A steel autoclave was charged with a mixture of compound **1** (0.8 g, 1.41 mmol), 1,1,1-trifluoro-2-iodo-ethane (1.5 g, 7.14 mmol) and K_2CO_3 (1.0 g, 7.24 mmol) in DMF (30 mL). The mixture was heated at 80 °C in a CEM microwave reactor for 2 h. The reaction mixture was then cooled and poured into brine (100 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3). The separated organic phase was dried over Na_2SO_4 and concentrated *in vacuo*, the resulting residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 20:1 to 3:1 to give compound **2** (0.60 g, 92%) as a pale yellow solid.

LC-MS: t_R = 2.02 min in 3 min chromatography, MS (ESI) *m/z*=461.5 $[M+H]^+$.

Procedure for preparation of compound 3

A sealed tube was charged with a mixture of compound **2** (0.20 g, 0.43 mmol), Lawessons's reagent (0.20 g, 0.48 mmol) in dioxane (2 mL) was heated to 150 °C in a CEM microwave reactor for 1h. After cooling down, the precipitate was filtered off and washed with Ethyl acetate (20 mL × 2). The filtrate and the washing were concentrated *in vacuo* and the residue was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 2:1 to give compound **3** (0.15 g, 73%) as a white solid.

Procedure for preparation of compound 4

To a solution of compound **3** (0.15 g, 0.31 mmol) in anhydrous THF (2 mL) was added BH_3.THF (1 M in THF, 20 mL, 20 mmol) at room temperature. After addition, the mixture was stirred at reflux for 72 h. After cooling down, the mixture was quenched with methanol (20 mL) carefully, then was concentrated under vacuum and the residue was dissolved in CH_2Cl_2 (50 mL). The mixture was washed with 1 N NaOH (10 mL) and brine (20 mL × 2) in turn. The separated organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 5: 1 to give compound **4** (60 mg, 42%) as a white solid with 59% purity on LC-MS, which was used directly in next step

directly. **LC-MS**: t_R = 2.15 min in 3 min chromatography, MS (ESI) *m/z* = 463.4 $[M+H]^+$.

Procedure for preparation of compound 5

To a solution of compound **4** (60 mg, 0.13 mmol) in EtOH (4 mL) was added NH_3-H_2O (1 mL) and *tert*-butyl hydroperoxide (0.20 g, 2.22 mol). After addition, the mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo*. H_2O (20 mL) was added to the residue, and the resulting mixture was extracted with ethyl acetate (contained 10% methanol) (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over Na_2SO_4, filtered off the solid and concentrated *in vacuo* to give the crude product, which was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 1: 1 to give compound **5** with 76% purity (50 mg, 86%) as a white solid, which was used directly in next step. **LC-MS**: t_R = 1.62 min min in 3 min chromatography, MS (ESI) *m/z* = 446.0 $[M+H]^+$.

Procedure for preparation of compound 6

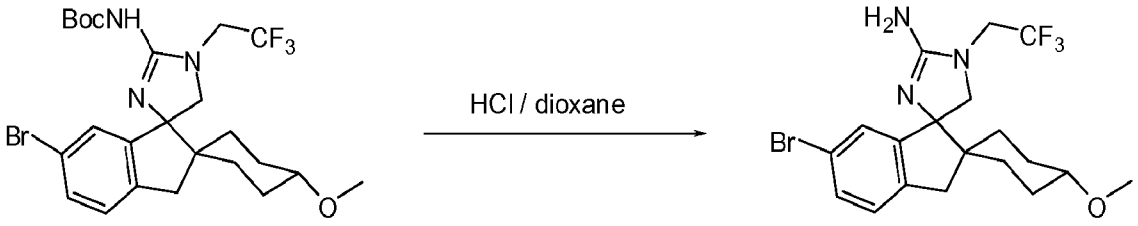
A mixture of compound **5** (50 mg, 0.11 mmol, 76% purity), *tert*-Butyl dicarbonate (48 mg, 0.22 mmol) and DMAP (27 mg, 0.22 mmol) in THF (5 mL) was stirred at ambient temperature overnight. The solvent was removed by evaporation *in vacuo*, the residue was purified by preparative TLC on silica gel eluting with petroleum ether: ethyl acetate = 2: 1 to give compound **6** (30 mg, 50%) as a white solid. **LC-MS**: 699-091-1B, t_R = 2.06 min in 3 min chromatography, MS (ESI) *m/z* = 546.2 $[M+H]^+$.

***Procedure for preparation of* compound 445**

A mixture of compound **6** (10 mg, 0.018 mmol), 3-chloro-5-fluoro benzeneboronic acid (6 mg, 0.034 mmol), Cs_2CO_3 (2 M, 0.2 mL) and $Pd(PPh_3)_2Cl_2$ (1 mg) in 1,4-dioxane (0.5 mL) under nitrogen was stirred at 120 °C in a CEM microwave reactor for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified preparative TLC and then preparative HPLC to give **compound 445** with 98% purity (3.4 mg, 38%). **^{1}H NMR**: (CD_3OD, 400 MHz): δ 7.55-7.65 (dd, J = 2.0, 6.0 Hz, 1H), 7.50-7.55 (s, 1H), 7.40-7.45 (s, 1H), 7.35-7.40 (d, J = 7.6 Hz, 1H), 7.25-7.30 (m, 1H), 7.10-7.20 (m, 1H), 4.25-4.30 (d, J = 8.8 Hz, 1H), 4.20-4.25 (d, J = 9.2 Hz, 1H)

4.10-4.20 (d, J = 10.4 Hz, 1H), 3.80-3.90 (d, J = 10.0 Hz, 1H), 3.20-3.25 (s, 3H), 3.10-3.15 (m, 1H), 2.95-3.05 (s, 2H), 1.95-2.10 (m, 2H), 1.45-1.60 (m, 3H), 1.20-1.40 (m, 3H). **LC-MS** t_R = 1.85 min in 3 min chromatography, MS (ESI) m/z =496.1 $[M+H]^+$. **HRMS**: MS (ESI) m/z =496.1764 $[M+H]^+$.

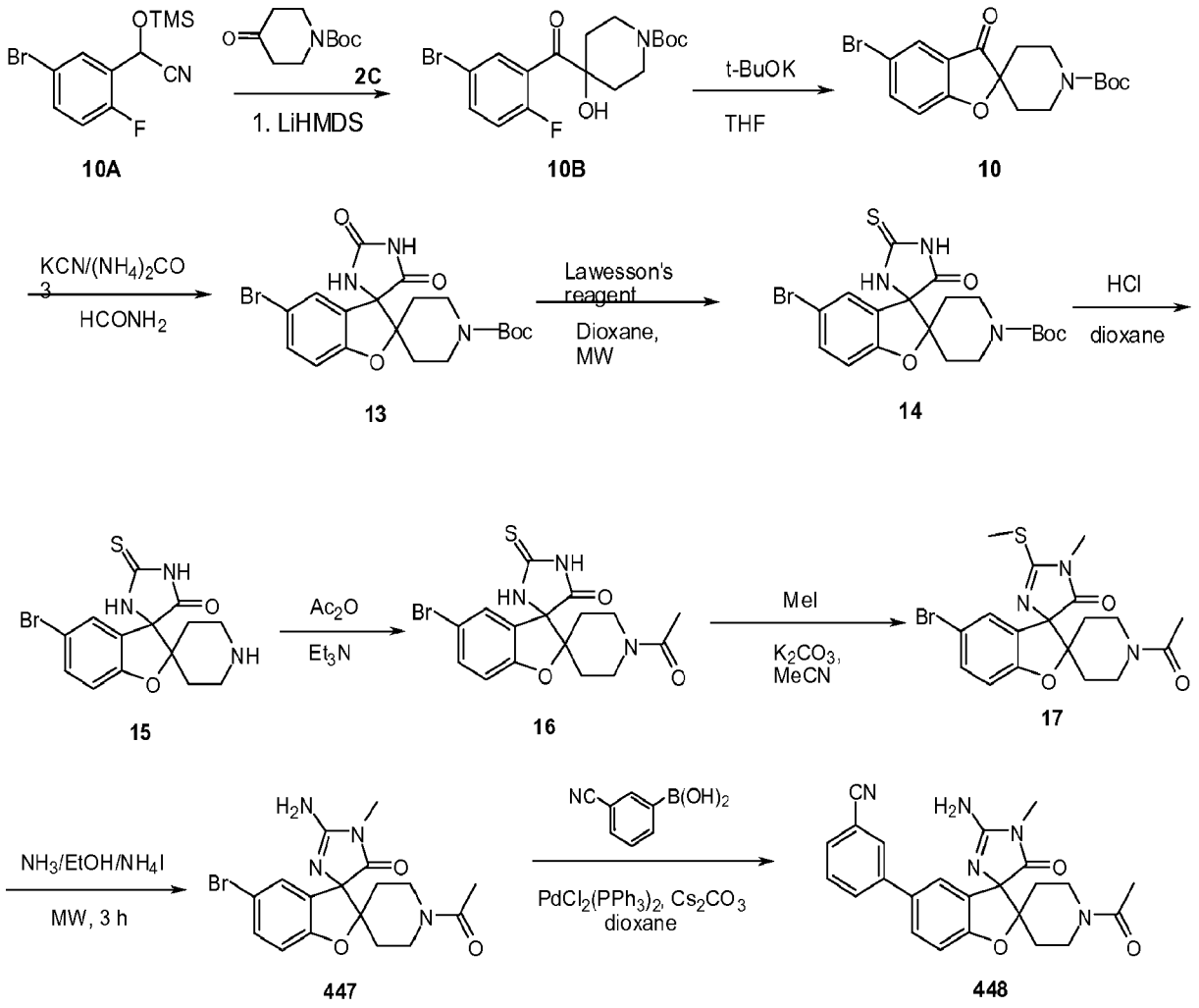
Example 382. Synthesis of Compound 446



6 **446**

A mixture of compound **6** (10 mg, 0.018 mmol) in HCl/dioxane (2 mL, 4 M in dioxane) was stirred at ambient temperature for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified preparative HPLC to give **compound 446** with 93% purity (1.1 mg, 14%). **^{1}H NMR**: (300 MHz): δ 7.45-7.55 (m, 2H), 7.20-7.30 (m, 1H), 4.25-4.30 (d, J = 11.6 Hz, 1H), 4.20-4.25 (d, J = 12.0 Hz, 1H) 4.10-4.20 (d, J = 13.6 Hz, 1H), 3.75-3.85 (d, J = 14.0 Hz, 1H), 3.35-3.40 (s, 3H), 3.10-3.25 (m, 1H), 2.85-3.00 (s, 2H), 1.95-2.10 (m, 2H), 1.45-1.60 (m, 3H), 1.25-1.45 (m, 3H). **LC-MS**: t_R = 1.65 min in 3 min chromatography, MS (ESI) m/z =466.1 $[M+H]^+$.

Example 383. Synthesis of Compounds 447 and 448



Procedure for preparation of Compound 10B

To a solution of 2-(5-bromo-2-fluorophenyl)-2-(trimethylsilyloxy) acetonitril (25.0 g, 82.7 mmol) in anhydrous THF (150 mL) was added LiHMDS (1.0 M in THF, 91.0 mL, 91.0 mmol) dropwise via an addition funnel at -78 °C under nitrogen. After 1.5 h, a solution of 4-oxopiperidine-1-carboxylic acid *tert*-butyl ester (18.1 g, 91.0 mmol) in anhydrous THF was added dropwise via an addition funnel at -78 °C under nitrogen. After addition, the reaction mixture was stirred at -78 °C for 3 h. 1 N HCl (200 mL) was added via an addition funnel at -78 °C carefully. After that, the reaction mixture was allowed to warm to ambient temperature and kept at this temperature overnight. The mixture was separated and the aqueous layer was extracted with EtOAc

(3 × 150 mL). The combined organic layers were washed with brine (2 × 200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: petroleum ether: EtOAc = 50: 1 to 10: 1) to give pure compound **10B** (32.0 g, 77% yield) as a white solid.

Procedure for preparation of Compound 10

10 Sealed tubes were charged with compound **10B** (3.2 g, 6.59 mmol), THF (10 mL) and t-BuOK (0.81 g, 7.25 mmol) in each of them. These tubes were heated at 70 °C for 30 min in a CEM microwave reactor parallelly. After cooling down, all the reactions were quenched by addition of 10 mL H_2O in each of them and combined and separated, the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 100: 1 to 10: 1 to geive compound **10** (15.0 g, 60%) as a white solid.

Procedure for preparation of Compound 13

A steel autoclave was charged with a mixture of compound **10** (3 g, 7.8 mmol), KCN (1.02 g, 15 mmol), $(NH_4)_2CO_3$ (5.65 g, 58 mmol) and formamide (30 mL) and the mixture was heated at 100 °C for 72 h. The reaction mixture was cooled and poured into ice, then was filtrated to collect the solid, which was dissolved in ethyl acetate (100 mL) and was washed with water (2 × 50 mL), dried over Na_2SO_4 and concentrated to give the crude product which was was purified by column chromatography on silica gel eluting with hexane: EtOAc (10:1 to 3:1) to give compound **13** (0.7 g, 20%) as a yellow solid. **^{1}H NMR** (CDCl3 300 MHz): δ 8.20 (s, 1H), 7.31 (d, J = 7.6 Hz, 2H), 1.40-1.97 (m, 8H), 1.24-1.29 (s, 9H).

Procedure for preparation of Compound 14

To a solution of compound **13** (400 mg, 0.88 mmol) in anhydrous 1, 4-dioxane (10 mL) was added Lawesson's Reagent (393.2 mg, 0.97 mmol) under a nitrogen atmosphere, the mixture was stirred at 120 °C for 30min in a CEM microwave reactor.

The solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to afford compound **14** (100 mg, 24%) as a white solid. **LCMS**: t_R =1.335 min in 2 min chromatography, MS (ESI) *m/z* 490 $[M+Na]^+$.

Procedure for preparation of Compound 15

To a solution of compound **14** (50 mg, 0.11 mmol) was added HCl/dioxane (4.0 M, 2 mL) under a nitrogen atmosphere, the mixture was stirred at room temperature for 2 h, the solvent was removed *in vacuo* to give compound **15** (30 mg, 76%), which was used in the next step without further purification. **LCMS**: t_R = 0.872 min in 2 min chromatography, MS (ESI) *m/z* 368 $[M+H]^+$.

Procedure for preparation of Compound 16

To a solution of compound **15** (30 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added Ac_2O (8.3 mg, 0.08 mmol), Et_3N (16.4 mg, 0.16 mmol) and DMAP (0.09 mg, 0.008 mmol) under nitrogen at 0 °C. After stirring at 0 °C for 2 h, water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give compound **16** (25 mg, 75%), which was used in the next step without further purification. **LCMS**: t_R = 1.097 min in 2 min chromatography, MS (ESI) *m/z* 410 $[M+H]^+$.

Procedure for preparation of Compound 17

To a solution of compound **16** (25 mg, 0.06 mmol) in CH_3CN (2 mL) was added K_2CO_3 (16.5 mg, 0.12 mmol), and MeI (17.6 mg, 0.12 mmol) under nitrogen, the mixture was heated at 60 °C for 10 min and at 100°C for another 10 min in a CEM microwave reactor. The mixture was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel eluting with hexane: EtOAc = 3: 1 to give compound **17** (20 mg, 76%) as a white solid. **LCMS**: t_R = 1.097 min in 2 min chromatography, MS (ESI) *m/z* 410 $[M+H]^+$.

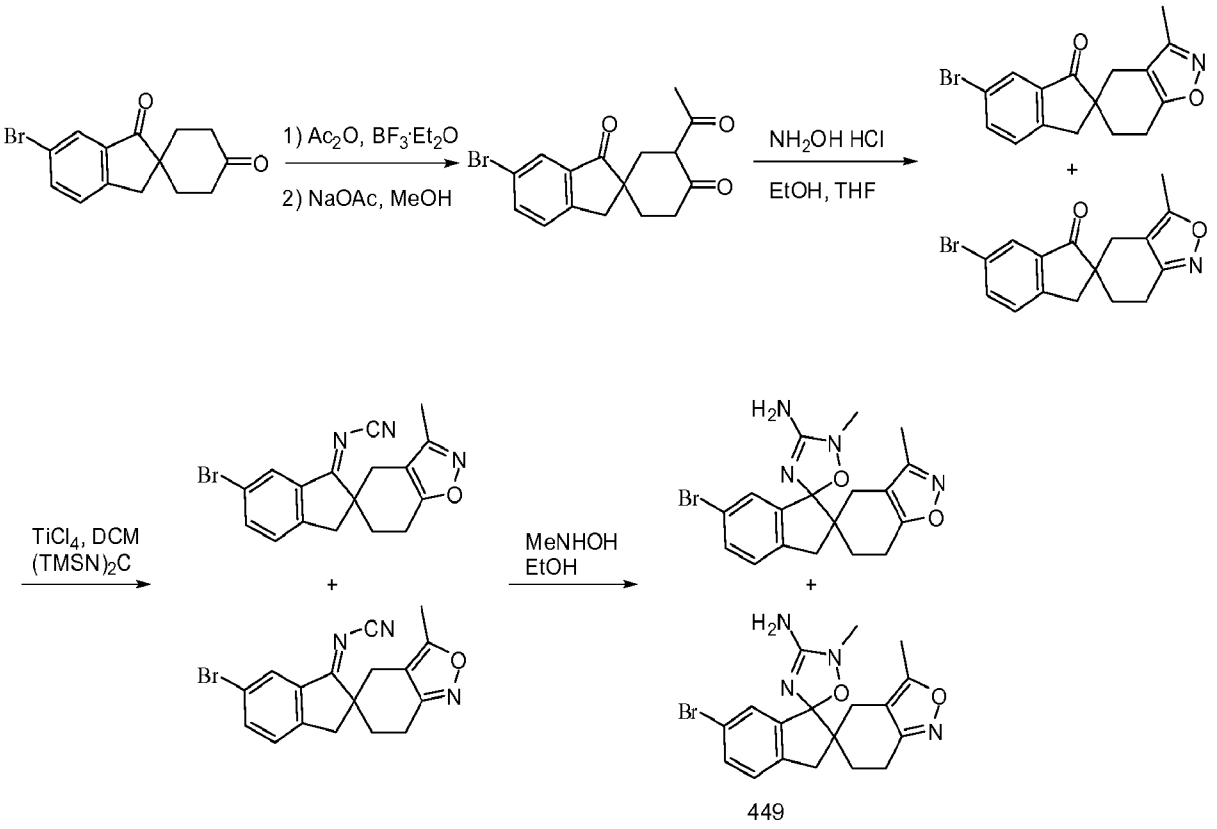
Procedure for preparation of compound 447

A solution of compound **17** (20 mg, 0.046 mmol), NH_4I (68 mg, 0.46 mmol) in NH_3-EtOH (2 mL, 5 N) was heated at 120 °C in a CEM microwave reactor for 3 h. After being cooled, the mixture was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 and preparative HPLC to give **compound 447** (8 mg, 43%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.41 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.88 (m, 2H), 3.54 (m, 2H), 3.10 (s, 3H), 2.17 (s, 3H), 1.89-1.92 (m, 2H), 1.62-1.79 (m, 2H). **LCMS**: t_R = 1.410 min in 2 min chromatography, MS (ESI) *m/z* 407 $[M+H]^+$.

Procedure for preparation of compound 448

To a solution of **compound 447** (7 mg, 0.017 mmol) in 1,4-dioxane (2 mL) were added 3-cyanophenylboronic acid (3.78mg, 0.025mmol), Cs_2CO_3 (2 N, 0.2 mL) and $Pd(PPh_3)_2Cl_2$ (0.1 mg, 0.00017 mmol) under nitrogen, the mixture was heated at 120 °C in a CEM microwave reactor for 15 min, LCMS analysis showed the complete consumption of compound **compound 447**. **W**ater (2 mL) was added and the mixture was filtered through a pad of celite, then was washed with EtOAc (3 × 10mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give the crude product which was purified by preparative TLC on silica gel eluting with dichloromethane: methanol = 10: 1 followed by preparative HPLC to afford **compound 448** (1.2 mg, 16%) as a white solid.**^{1}H NMR** (CD_3OD 400 MHz): δ 7.81 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 3H), 7.23 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.75-3.80 (m, 2H), 3.38-3.47 (m, 2H), 3.01 (s, 3H), 2.0 (s, 3H), 1.72-1.85 (m, 2H), 1.42-1.56 (m, 2H). **LCMS**:t_R = 1.558 min in 2 min chromatography, MS (ESI) *m/z* 430.2 $[M+H]^+$.

Example 384. Synthesis of Compound 449



Step 1: Preparation of 3-acetyl-6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione

To a suspension of 6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (545.6 mg, 1.86 mmol) and Ac_2O (3 mL) which was stirred at room temperature was added $BF_3{\cdot}Et_2O$ (1 mL) was added dropwise. The mixture color turned dark brown within several minutes. The reaction mixture was quenched with ice-water after being stirred overnight, and stirred another 1 h before diluted with EA. It was washed with saturated aqueous $NaHCO_3$ and brine successively, and dried over anhydrous Na_2SO_4, and filtered, and evaporated to produce 580 mg of brown foam. The brown foam was dissolved in MeOH (6 mL). To this solution was added a solution of NaOAc (610 mg, 7.44 mmol) in H_2O (1 mL). The mixture was heated to reflux for 3 h. Organic solvent was removed under reduced pressure before re-dissolved in EA (60 mL). The resulting solution was washed with H_2O and brine successively, and dried over anhydrous

Na_2SO_4, and filtered, and evaporated to produce dark oil, which was purified by flash chromatography on silica gel to afford 294.5 mg of the desired product as light yellow solid. MS ESI +ve m/z 335 $(M+H)^+$. t_R: 1.86 min.

Step 2: Preparation of 6'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[d]isoxazole-5,2'-inden]-1'(3'H)-one and 6'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[c]isoxazole-5,2'-inden]-1'(3'H)-one

A mixture of 3-acetyl-6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (41.5 mg, 0.124 mmol) and $NH_2OH{\cdot}HCl$ (26 mg, 0.374 mmol) and EtOH/THF (2/0.5 mL) charged in a 10-mL CEM microwave test tube was heated in a CEM microwave reactor at 100°C for 10 min. To this mixture was added 3-acetyl-6'-bromospiro[cyclohexane-1,2'-indene]-1',4(3'H)-dione (41.5 mg, 0.124 mmol) solution in THF (0.5 mL) and $NH_2OH{\cdot}HCl$ (45 mg, 0.647 mmol). The mixture was heated to 110°C for another 10 min in the CEM microwave reactor. $NaHCO_3$ (158 mg, 1.88 mmol) was added and stirred for 5 min before filtered and evaporated. The residue was purified by flash chromatography on silica gel to afford 70 mg of the desired product as a mixture with the ratio close 1:1. MS ESI +ve m/z 332 $(M+H)^+$. t_R: 1.80 min.

Step 3: Preparation of N-(5'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[c]isoxazole-5,2'-indene]-3'(1'H)-ylidene)cyanamide and N-(5'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[d]isoxazole-5,2'-indene]-3'(1'H)-ylidene)cyanamide

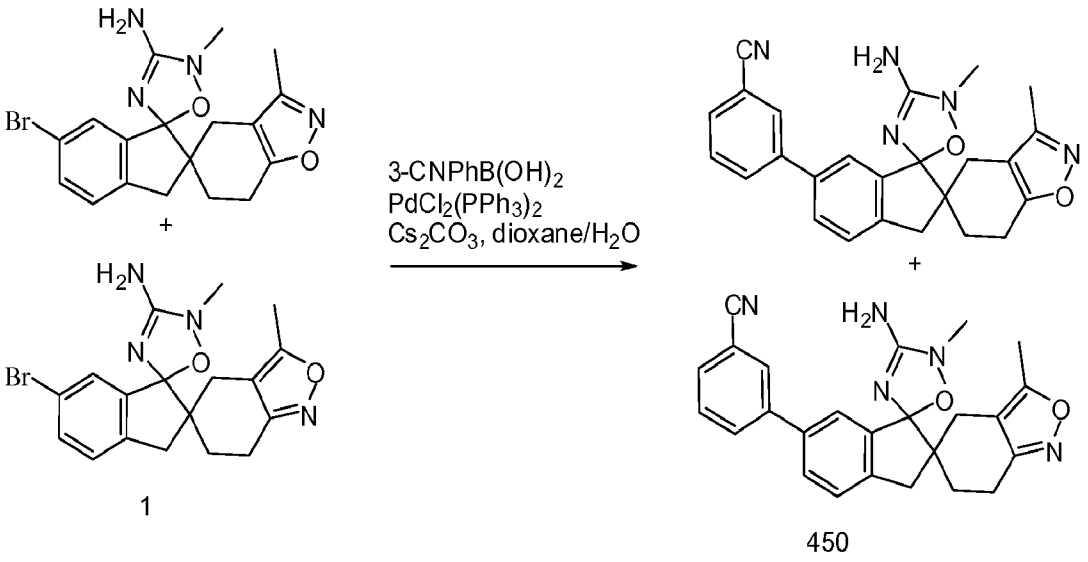
To a solution of of 6'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[d]isoxazole-5,2'-inden]-1'(3'H)-one and 6'-bromo-3-methyl-6,7-dihydro-4*H*-spiro[benzo[c]isoxazole-5,2'-inden]-1'(3'H)-one (ca 1:1 ration) (70 mg, .021 mmol) in anhydrous DCM (5 mL) under N2 atmosphere at room temperature was added $TiCl_4$ (1.0 M solution in DCM, 0.42 mL, 0.42 mmol) dropwise. The resulting yellow suspension was stirred for 1 h before bis-trimethylsilylcarbodiimide (86 mg, 105 μL, 0.46 mmol) was added. The resulting mixture was stirred overnight. $TiCl_4$ (1.0 M solution in DCM, 0.42 mL, 0.42 mmol) was added followed by bis-trimethylsilylcarbodiimide (86 mg, 105 μL, 0.46 mmol). The mixture was stirred for

another 16 h before quenched by ice-water. The mixture was stirred another 30 min and extracted with DCM 3 times, the combined organic layers were dried over anhydrous Na_2SO_4, and filtered, and evaporated to produce 76 mg of crude product, which was used for next step without further purification. MS ESI +ve m/z 356 $(M+H)^+$. t_R: 1.80 min.

Step 4: Preparation of compound 449

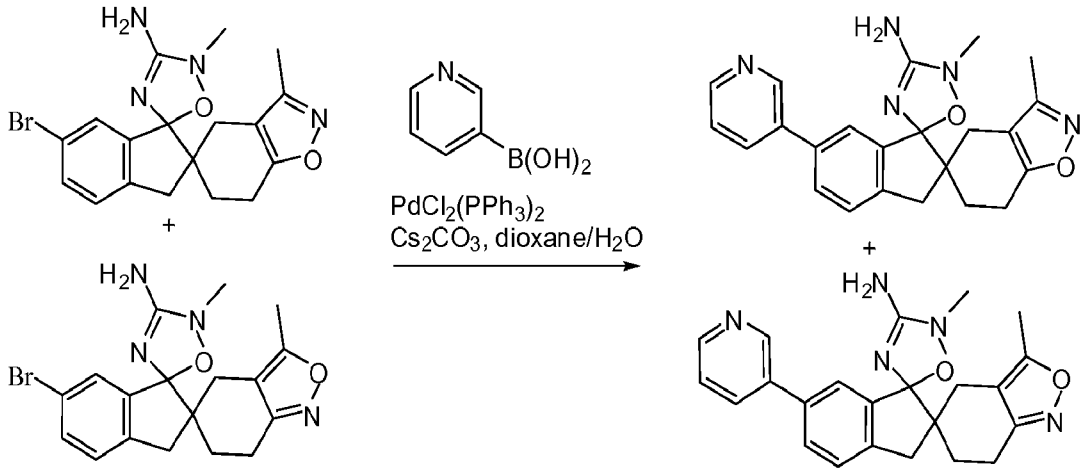
To a suspension of above crude product in EtOH (3 mL) was added a solution of N-methylhydroxylamine (1.5 mL, prepared by adding 25wt% NaOMe in MeOH (72 μL, 1.26 mmol) to a solution of MeNHOH·HCl (117 mg, 1.4 mmol) in EtOH (10 mL) being stirred for 5 min). After being stirred overnight, another portion of *N*-methylhydroxylamine (1.5 mL) was added followed by another same portion of *N*-methylhydroxylamine after 10 min. The mixture was stirred overnight and evaporated to dryness and purified by preparative HPLC to afford 80 mg of the desired product as TFA salt. MS ESI +ve m/z 403 $(M+H)^+$. t_R: 1.27 min. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.72 (m, 1H), 7.60 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.37, 3.36, 3.35, 3.34 (four s, total 3H), 3.01-2.39 (m, 6H), 2.29, 2.25, 2.17, 2.13 (four s, total 3H), 2.30-1.87 (m, 2H).

Example 385. Synthesis of Compound 450



To a solution of compound 1 TFA salt (10 mg, 0.019 mmol), 3-cyanophenylboronic acid (6 mg, 0.041mmol) and Cs_2CO_3 (40 mg, 0.12 mmol) in 1,4-dioxane (2 mL) and H_2O (0.1 mL) charged in a 10 mL CEM microwave test tube was added $PdCl_2(PPh_3)_2$ (2 mg, 0.0028mmol), then the system was degassed by sweeping N_2. The tube was sealed and heated to 110°C for 10 min in a CEM microwave reactor. Due to low conversion $PdCl_2(PPh_3)_2$ (2 mg, 0.0028mmol), and 3-cyanophenylboronic acid (6 mg, 0.041mmol) was added and heated at 110°C for another 10 min in microwave reactor. Solvent was removed in vacuum and the residue was purified by preparative HPLC to yield 5.7 mg of the desired product as a TFA salt. MS ESI +ve m/z 426 $(M+H)^+$. t_R: 1.45 min. ^1H NMR (400 MHz, CD_3OD) δ: 8.04 and 8.01 (tow s, toatal 1H), 7.98 and 7.93 (two d, J = 8.0 Hz, total 1H), 7.85 and 7.84 (two s, total 1H), 7.81-7.63 (m, 3H), 7.44 (d, J = 7.6 Hz, 1H), 3.39, 3.38, 3.36 and 3.35 (four s, 3H), 3.10-2.45 (m, 6H), 2.31, 2.26, 2.19 and 2.14 (four s, 3H), 2.32-1.91 (m, 2H).

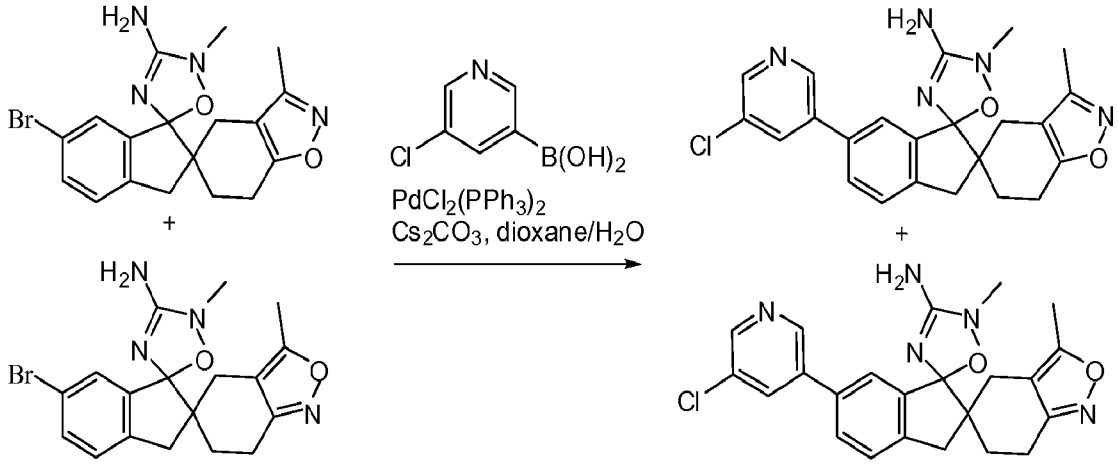
Example 386. Synthesis of Compound 451



451

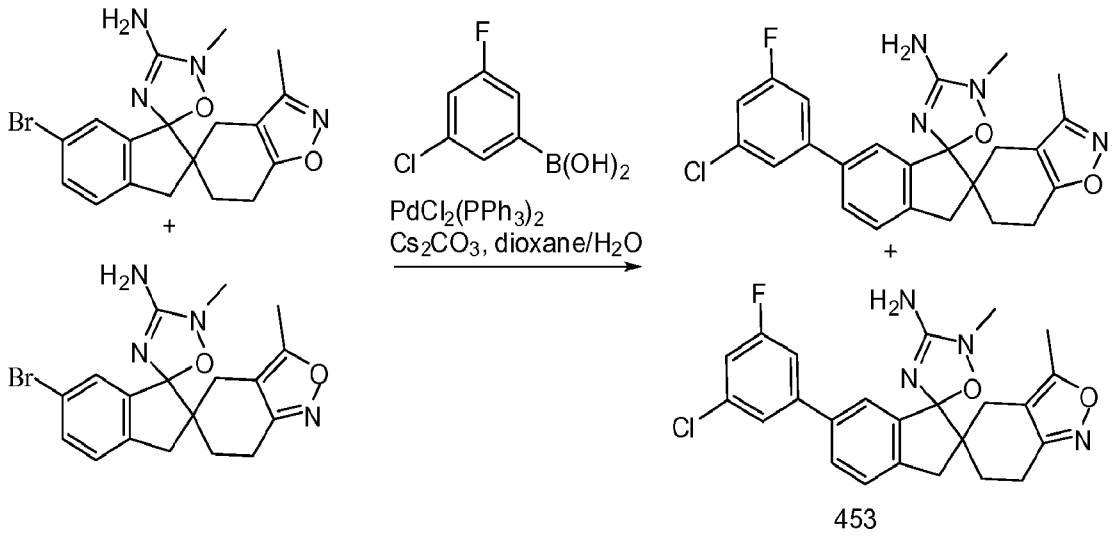
The title compound was made by the method described in example 385. MS ESI +ve m/z 402 $(M+H)^+$. t_R: 1.07 min. ^1H NMR (400 MHz, CD_3OD) δ: 9.20 (s, 1H), 8.88-8.83 (m, 2H), 8.12 (m, 1H), 8.03 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 3.39, 3.38, 3.37 and 3.36 (four s, 3H), 3.13-2.44 (m, 6H), 2.30, 2.26, 2.19 and 2.14 (four s, 3H), 2.34-1.93 (m, 2H).

Example 387. Synthesis of Compound 452



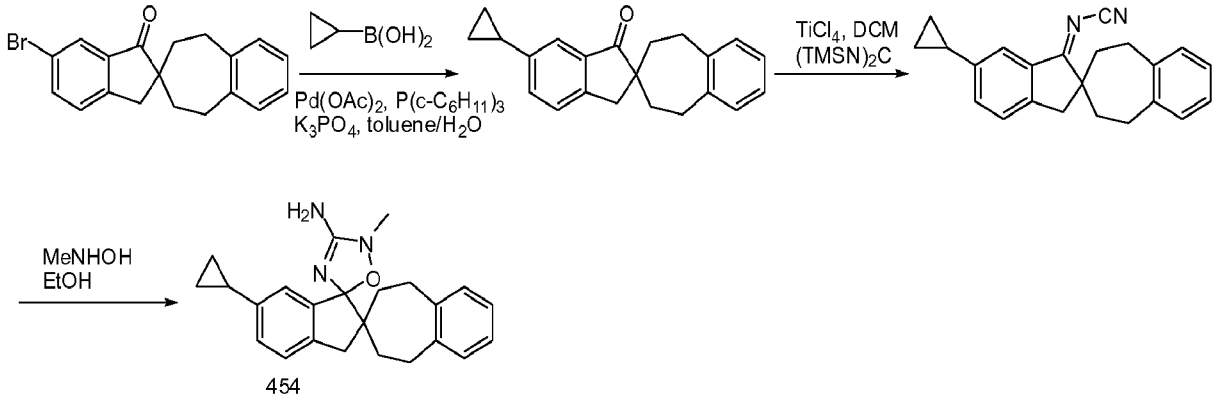
The title compound was made by the method described in example 385. MS ESI +ve m/z 436 $(M+H)^+$. t_R: 1.37 min. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.80 (s, 1H), 8.60 (s, 1H), 8.23 (s, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 3.39, 3.38, 3.36 and 3.35 (four s, 3H), 3.11-2.45 (m, 6H), 2.31, 2.26, 2.19 and 2.14 (four s, 3H), 2.32-1.91 (m, 2H).

Example 388. Synthesis of Compound 453



The title compound was made by the method described in example 385. MS ESI +ve m/z 453 $(M+H)^+$. t_R: 1.74 min. ^1H NMR (400 MHz, CD_3OD) δ: 7.82 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.44-7.38 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 3.39, 3.38, 3.36 and 3.35 (four s, 3H), 3.09-2.45 (m, 6H), 2.30, 2.26, 2.19 and 2.14 (four s, 3H), 2.32-1.90 (m, 2H); ^{19}F NMR (376 MHz, CD_3OD) δ: -112.29, -112.83, -112.85, -112.88.

Example 389. Synthesis of Compound 454



454

Step 1:

A mixture of 6'-bromo-5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-inden]-1'(3'H)-one (50 mg, 0.147 mmol), K_3PO_4 (125 mg, 0.588 mmol), cyclopropylboronic acid (19 mg, 0.220 mmol), tricyclohexylphosphine (4.2 mg, 0.015 mmol, 10mol%), toluene (3 mL), H_2O (0.15 mL) and $Pd(OAc)_2$ (3.4 mmol, 0.0147mmol) charged in a 10-mL CEM microwave reactor was charged N_2. The mixture was heated at 110°C for 70 min. The reaction mixture was diluted with EA and washed with H_2O and brine, and dried over anhydrous Na_2SO_4, and filtered, and evaporated to produce the crude product, which was used for next step without further purification; MS ESI +ve m/z 303 $(M+H)^+$. t_R: 2.30 min.

Step 2:

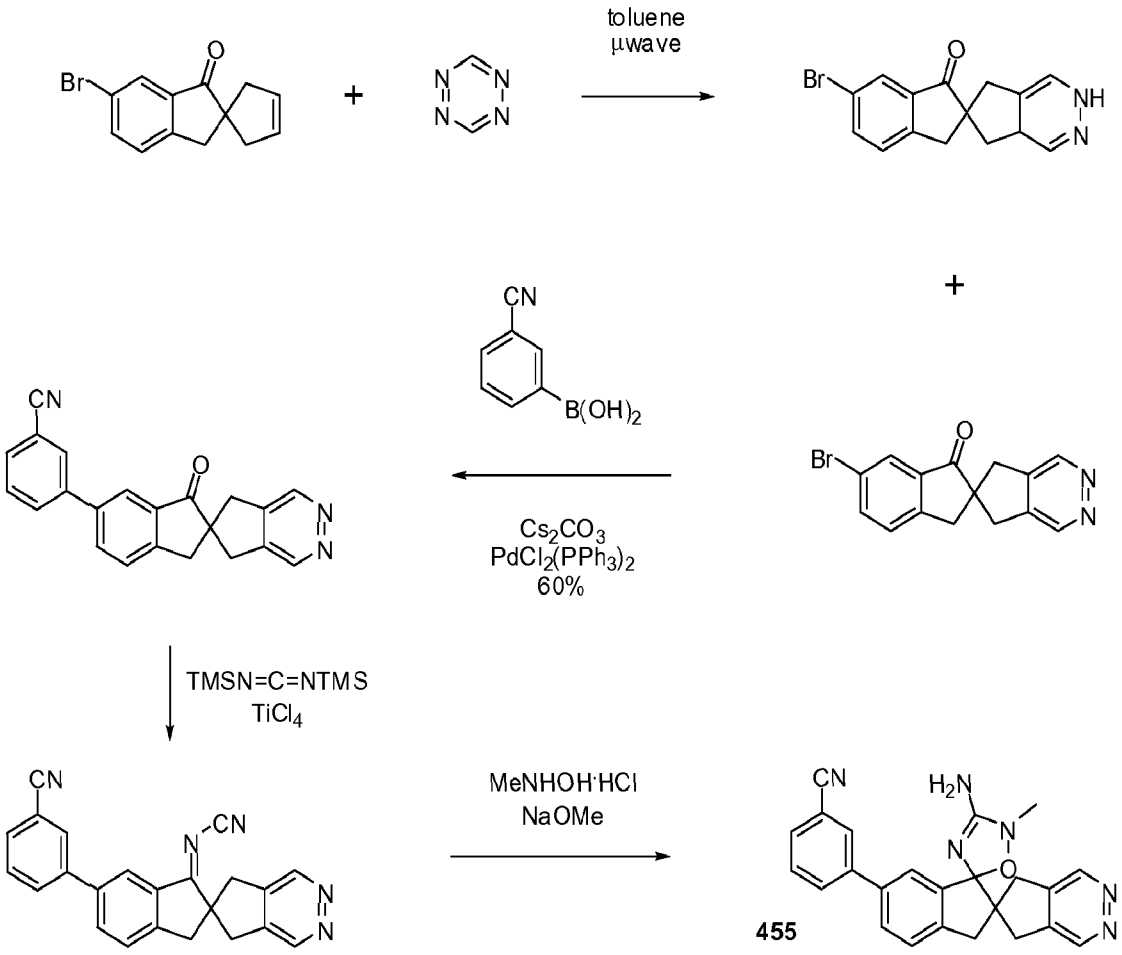
To a solution of of above crude product in anhydrous DCM (5 mL) under N_2 atmosphere at room temperature was added $TiCl_4$ (1.0 M solution in DCM, 0.42 mL, 0.42 mmol) dropwise. The resulting yellow suspension was stirred for 1 h before bis-

trimethylsilylcarbodiimide (86 mg, 105 μL, 0.46 mmol) was added. The resulting mixture was stirred overnight. $TiCl_4$ (1.0 M solution in DCM, 0.65 mL, 0.65 mmol) was added followed by bis-trimethylsilylcarbodiimide (137 mg, 167 μL, 0.735 mmol). The mixture was stirred for another 16 h before quenched by ice-water. The mixture was stirred another 30 min and extracted with DCM 3 times, the combined organic layers were dried over anhydrous Na_2SO_4, and filtered, and evaporated to produce the desired crude product, which was used for next step without further purification. MS ESI +ve m/z 327 $(M+H)^+$. t_R: 2.29 min.

Step 3:

To a suspension of above crude product in EtOH (3 mL) was added a solution of *N*-methylhydroxylamine (4.15 mL, prepared by adding 25wt% NaOMe in MeOH (72 μL, 1.26 mmol) to a solution of MeNHOH·HCl (117 mg, 1.4 mmol) in EtOH (10 mL) being stirred for 5 min). After being stirred overnight, the reaction mixture was evaporated to dryness and purified by preparative HPLC to afford 54 mg of the desired product as TFA salt. MS ESI +ve m/z 374 $(M+H)^+$. t_R: 1.78 min. ^1H NMR (400 MHz, CD_3OD) δ: 7.52 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.18-7.07 (m, 4H), 3.22 (s, 3H), 3.34-2.94 (m, 4H), 2.81-2.64 (m, 2H), 2.06-1.49 (m, 5H), 1.05-0.95 (m, 2H), 0.68 (m, 2H).

Example 390. Synthesis of Compound 455



Step 1. 6'-bromo-5,7-dihydrospiro[cyclopenta[*d*]pyridazine-6,2'-inden]-1'(3'*H*)-one and 6'-bromo-2,4a,5,7-tetrahydrospiro[cyclopenta[*d*]pyridazine-6,2'-inden]-1'(3'*H*)-one

A 10 mL microwave tube was charged with 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'*H*)-one (0.3045 g, 1.16 mmol), 1,2,4,5-tetrazine (0.1120 g, 1.36 mmol), and toluene (5 mL). The tube was heated in a CEM microwave reactor at 150 °C for 1 h. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0657 g (18%) of 6'-bromo-5,7-dihydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one, 0.0083 g (2%) of 6'-

bromo-2,4a,5,7-tetrahydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one, and recover 0.0550 g (18%) of 6'-bromospiro[cyclopent[3]ene-1,2'-inden]-1'(3'*H*)-one.

For 6'-bromo-5,7-dihydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one, LC-MS t_R = 1.35 min in 3 min chromatography, *m/z* 315, 317 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 9.17 (s, 2H), 7.59-7.55 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 3.36 (d, *J* = 17.9 Hz, 2H), 3.13 (d, *J* = 17.9 Hz, 2H), 3.08 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 207.41, 152.76, 152.37, 148.80, 139.59, 137.86, 129.84, 128.04, 122.99, 57.87, 43.33, 42.33.

For 6'-bromo-2,4a,5,7-tetrahydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one, LC-MS t_R = 1.41 min in 3 min chromatography, *m/z* 317, 319 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 9.22 (m, 1H), 9.14 (m, 1H), 7.86-7.85 (m, 1H), 7.74-7.71 (m, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 3.37-3.30 (m, 1H), 2.95-2.71 (m, 4H), 2.22-2.16 (m, 1H), 1.90-1.84 (m, 1H).

Step 2. 3-(1'-oxo-1',3',5,7-tetrahydrospiro[cyclopenta[*d*]pyridazine-6,2'-inden]-6'-yl)benzonitrile

A 10 mL microwave tube was charged with 6'-bromo-5,7-dihydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one (0.0600 g, 0.19 mmol), 3-cyanophenylboronic acid (0.1221 g, 0.83 mmol), Cs_2CO_3 (0.2822 g, 0.87 mmol), 1,4-dioxane (4 mL), water (1 mL), and $PdCl_2(PPh_3)_2$ (0.0360 g, 0.05 mmol). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0386 g (60%) of 3-(1'-oxo-1',3',5,7-tetrahydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-6'-yl)benzonitrile. LC-MS t_R = 1.43 min in 3 min chromatography, *m/z* 338 (MH^+).

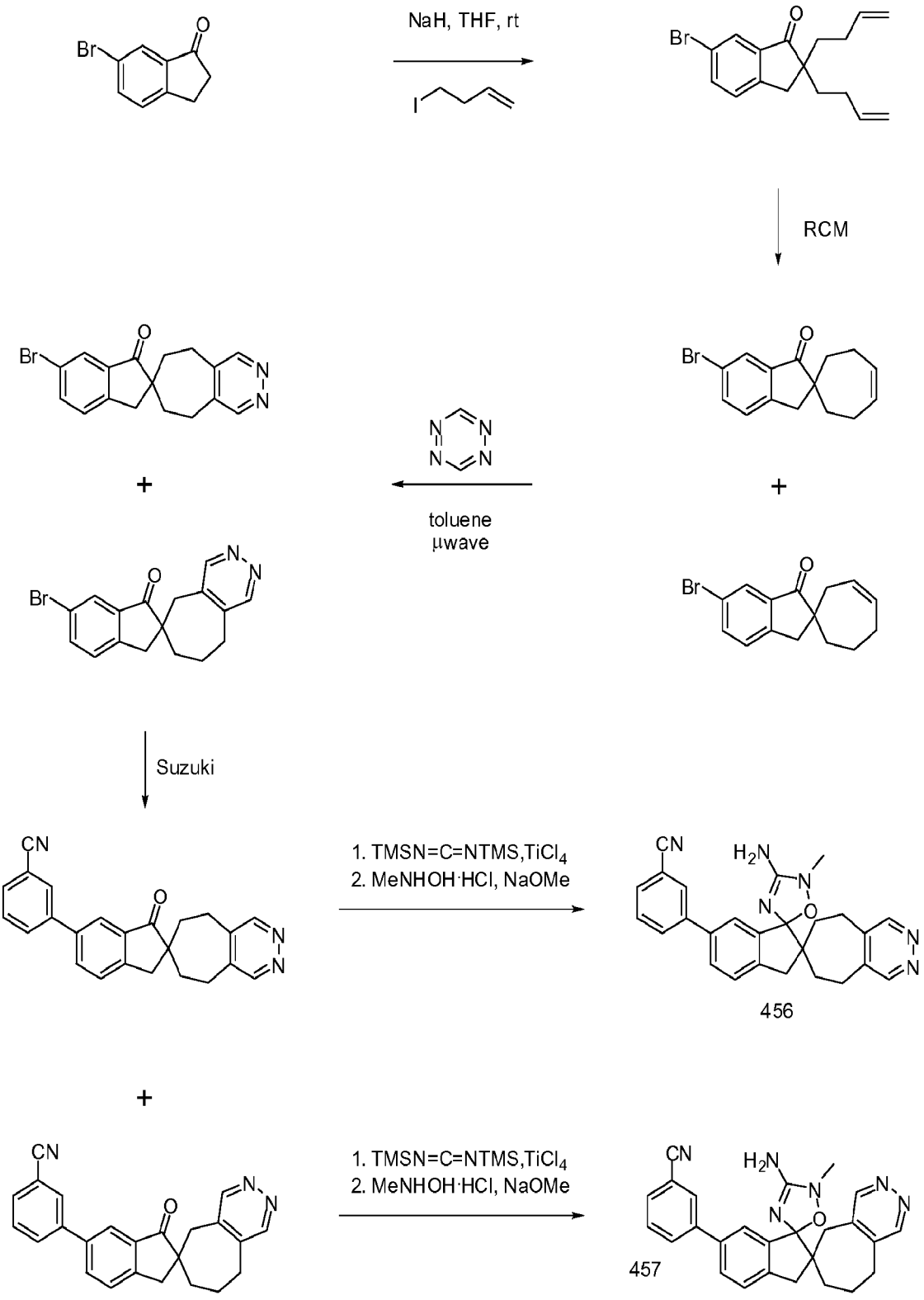
Step 3. *N*-(5'-(3-cyanophenyl)-5,7-dihydrospiro[cyclopenta[*d*]pyridazine-6,2'-inden]-3'(1'*H*)-ylidene)cyanamide

To a solution of 3-(1'-oxo-1',3',5,7-tetrahydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-6'-yl)benzonitrile (0.0386 g, 0.11 mmol) in CH_2Cl_2 (5 mL) was added 0.5 mL of 1.0 *M* $TiCl_4$ in CH_2Cl_2 at room temperature. After 1.5 h, 0.4 mL of bis(trimethylsilyl)carbodiimide was added to the yellow solution. The resulting mixture was then stirred at room temperature for 20 h. The mixture was quenched with ice, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was directly used in the next step without further purification. LC-MS t_R = 1.43 min in 3 min chromatography, *m/z* 362 (MH^+).

Step 4. compound 455

A 50 mL flask was charged with 32 mL of EtOH, 0.8452 g of sodium methoxide (25 wt. % solution in MeOH), and 0.3707 g of *N*-methylhydroxylamine hydrochloride. The suspension was filtered through HPLC filter and 10 mL of the filtrate was added to *N*-(5'-(3-cyanophenyl)-5,7-dihydrospiro[cyclopenta[d]pyridazine-6,2'-inden]-3'(1'*H*)-ylidene)cyanamide, obtained as described above. The resulting mixture was stirred at room temperature overnight. The mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford **compound 455** as a TFA salt. LC-MS t_R = 1.23 min in 3 min chromatography, *m/z* 409 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 9.36 (m, 2H), 8.03-7.48 (m, 7H), 3.78 (d, *J* = 16 Hz, 1H), 3.48 (d, *J* = 16 Hz, 1H), 3.35-3.17 (m, 7H).

Example 391. Synthesis of Compounds 456 and 457



Step 1. 6-bromo-2,2-di(but-3-en-1-yl)-2,3-dihydro-1*H*-inden-1-one

To a stirred solution of 6-bromo-1-indanone (0.5330 g, 2.52 mmol) in dry THF (10 mL) was added NaH (0.3380 g, 60% in a mineral oil, 8.45 mmol) at 0 °C under nitrogen. After being stirred for 10 min, 4-iodobut-1-ene (1.3450 g, 7.39 mmol) was added and then the mixture was stirred at ambient temperature for 20 h. The reaction mixture was cooled to 0 °C, quenched with 1 N HCl, extracted with ethyl acetate, and dried over Na_2SO_4. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.1304 g of 6-bromo-2,2-di(but-3-en-1-yl)-2,3-dihydro-1*H*-inden-1-one. LC-MS t_R = 2.33 min in 3 min chromatography, *m/*z 319, 321 (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 5.76-5.66 (m, 2H), 4.94-4.87 (m, 4H), 2.98 (s, 2H), 1.98-1.63 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.23, 151.43, 138.85, 137.85, 137.54, 127.94, 126.75, 121.55, 114.81, 52.87, 37.28, 36.58, 28.54.

Step 2. 6'-bromospiro[cyclohept[4]ene-1,2'-inden]-1'(3'*H*)-one and 6'-bromospiro[cyclohept[3]ene-1,2'-inden]-1'(3'*H*)-one

To a solution of 6-bromo-2,2-di(but-3-en-1-yl)-2,3-dihydro-1*H*-inden-1-one (0.1300 g, 0.41 mmol) in toluene (40 mL) was added Hoveyda-Grubbs catalyst 2nd generation [301224-40-8] (0.0308 g, 0.049 mmol). The resulting mixture was heated at 120 °C under nitrogen for 20 h. After the solvent was evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.1204 g (100%) of a mixture of 6'-bromospiro[cyclohept[4]ene-1,2'-inden]-1'(3'*H*)-one and 6'-bromospiro[cyclohept[3]ene-1,2'-inden]-1'(3'*H*)-one as observed by ^{1}H NMR. LC-MS t_R = 2.25 min in 3 min chromatography, *m/*z 291, 293 (MH^+).

Step 3. 6'-bromo-5,6,8,9-tetrahydrospiro[cyclohepta[*d*]pyridazine-7,2'-inden]-1'(3'*H*)-one and 6'-bromo-5,7,8,9-tetrahydrospiro[cyclohepta[*d*]pyridazine-6,2'-inden]-1'(3'*H*)-one

A 10 mL microwave tube was charged with a mixture of 6'-bromospiro[cyclohept[4]ene-1,2'-inden]-1'(3'*H*)-one and 6'-bromospiro[cyclohept[3]ene-1,2'-inden]-1'(3'*H*)-one (0.1204 g), obtained as described

above, 1,2,4,5-tetrazine (0.0767 g, 0.93 mmol), and toluene (5 mL). The tube was heated in a CEM microwave reactor at 150 °C for 1 h. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.1646 g of a mixture of 6'-bromo-5,6,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-1'(3'*H*)-one and 6'-bromo-5,7,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one. LC-MS t_R = 6.21, 6.35 min in 16 min chromatography, t_R = 1.49 min in 3 min chromatography, *m/z* 343, 345 (MH^+).

Step 4. 3-(1'-oxo-1',3',5,6,8,9-hexahydrospiro[cyclohepta[*d*]pyridazine-7,2'-inden]-6'-yl)benzonitrile and 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[cyclohepta[*d*]pyridazine-6,2'-inden]-6'-yl)benzonitrile

A 10 mL microwave tube was charged with a mixture of 6'-bromo-5,6,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-1'(3'*H*)-one and 6'-bromo-5,7,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-1'(3'*H*)-one (0.1646 g), obtained as described above, 3-cyanophenylboronic acid (0.2530 g, 1.7 mmol), Cs_2CO_3 (0.6177 g, 1.9 mmol), 1,4-dioxane (4 mL), water (1 mL), and $PdCl_2(PPh_3)_2$ (0.0360 g, 0.05 mmol). The tube was heated in a CEM microwave reactor at 110 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0281 g of 3-(1'-oxo-1',3',5,6,8,9-hexahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-6'-yl)benzonitrile and 0.0925 g of 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-6'-yl)benzonitrile.

For 3-(1'-oxo-1',3',5,6,8,9-hexahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-6'-yl)benzonitrile, LC-MS t_R = 1.51 min in 3 min chromatography, *m/z* 366 (MH^-); ^1H

NMR (400 MHz, CD_3OD) δ 9.35 (m, 2H), 8.03-7.97 (m, 4H), 7.75-7.63 (m, 3H), 3.40-3.23 (m, 6H), 2.01-1.85 (m, 4H).

For 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-6'-yl)benzonitrile, LC-MS t_R = 1.54 min in 3 min chromatography, *m/z* 366 (MH^-); ^1H NMR (400 MHz, CD_3OD) δ 9.36 (m, 2H), 7.99-7.89 (m, 3H), 7.74-7.56 (m, 4H), 3.45-2.89 (m, 6H), 2.15-1.72 (m, 4H).

Step 5. Preparation of compound 456

To a solution of 3-(1'-oxo-1',3',5,6,8,9-hexahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-6'-yl)benzonitrile (0.0281 g) in CH_2Cl_2 (5 mL) was added 0.5 mL of 1.0 *M* $TiCl_4$ in CH_2Cl_2 at room temperature. After 1.5 h, 0.4 mL of bis(trimethylsilyl)carbodiimide was added to the yellow solution. The resulting mixture was then stirred at room temperature for 18 h. The mixture was quenched with ice, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product (0.0830g) was directly used in the next step without further purification. LC-MS t_R = 1.51 min in 3 min chromatography, *m/z* 390 (MH^+).

A 50 mL flask was charged with 33 mL of EtOH, 1.5833 g of sodium methoxide (25 wt. % solution in MeOH), and 0.6517 g of *N*-methylhydroxylamine hydrochloride. The suspension was filtered through HPLC filter and 12 mL of the filtrate was added to *N*-(5'-(3-cyanophenyl)-5,6,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-7,2'-inden]-3'(1'*H*)-ylidene)cyanamide, obtained as described above. The resulting mixture was stirred at room temperature for 16 h. The mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford **compound 456** as a TFA salt. LC-MS t_R = 1.09, 1.23 min in 3 min chromatography, *m/z* 437 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 9.25 (m, 2H), 8.04-7.50 (m, 7H), 3.51-3.03 (m, 9H), 2.25-1.75 (m, 4H).

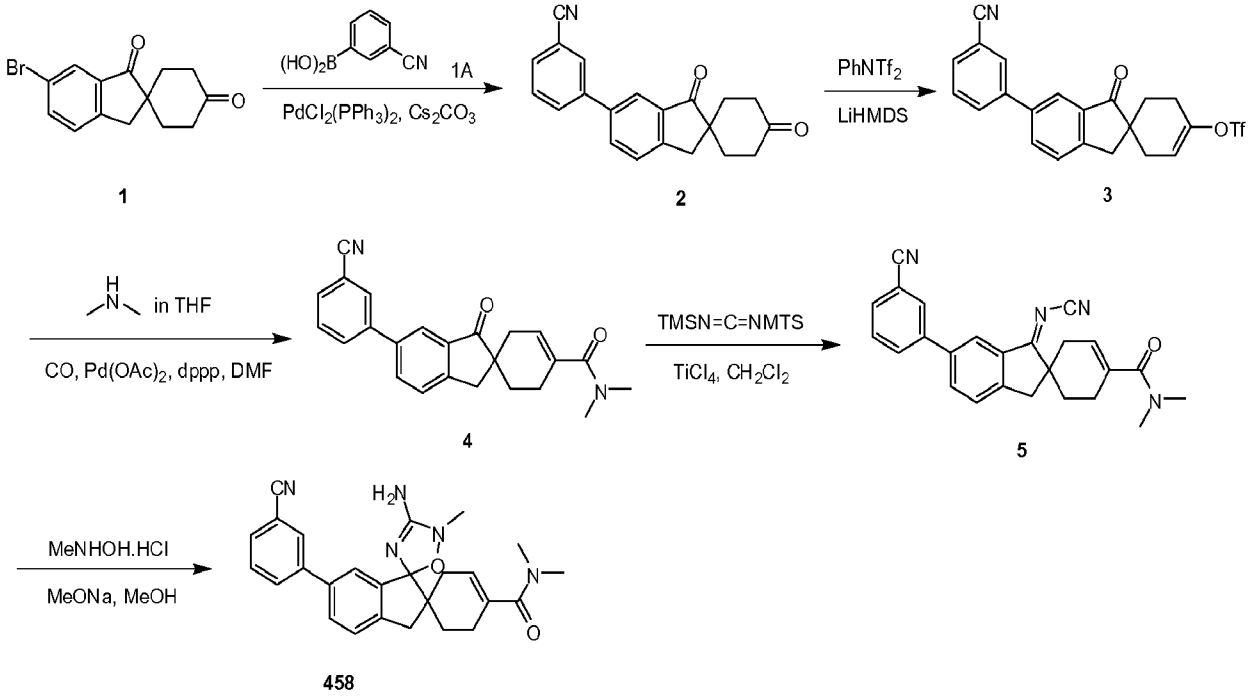
Step 6. Preparation of compound 457

To a solution of 3-(1'-oxo-1',3',5,7,8,9-hexahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-6'-yl)benzonitrile (0.0925 g) in CH_2Cl_2 (10 mL) was added 1.0 mL of 1.0 *M*

$TiCl_4$ in CH_2Cl_2 at room temperature. After 1.5 h, 0.8 mL of bis(trimethylsilyl)carbodiimide was added to the yellow solution. The resulting mixture was then stirred at room temperature for 18 h. The mixture was quenched with ice, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the crude product (0.1630 g) was directly used in the next step without further purification. LC-MS t_R = 1.58 min in 3 min chromatography, *m/z* 390 (MH^+).

A 50 mL flask was charged with 33 mL of EtOH, 1.5833 g of sodium methoxide (25 wt. % solution in MeOH), and 0.6517 g of *N*-methylhydroxylamine hydrochloride. The suspension was filtered through HPLC filter and 23 mL of the filtrate was added to *N*-(5'-(3-cyanophenyl)-5,7,8,9-tetrahydrospiro[cyclohepta[d]pyridazine-6,2'-inden]-3'(1'*H*)-ylidene)cyanamide, obtained as described above. The resulting mixture was stirred at room temperature for 16 h. The mixture was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford **compound 457** as a TFA salt. LC-MS t_R = 1.19, 1.25 min in 3 min chromatography, *m/z* 437 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 9.25 (m, 2H), 8.16-7.35 (m, 7H), 3.63-1.62 (m, 13H).

Example 392. Synthesis of Compound 458



Step 1: Preparation of compound 2

A mixture of compound **1** (1.5 g, 5.1 mmol), 3-cyanophenylboronic acid (1.2 g, 7.7 mmol), aq. Cs_2CO_3 (2 M, 20 mL) and $Pd(PPh_3)_2Cl_2$ (0.15 g, 0.21 mmol) in 1,4-dioxane (20 mL) under a nitrogen atmosphere was stirred at 80 °C for 1 h. After cooling down, H_2O (50 mL) was added with stirring. The mixture was separated and the aqueous layer was extracted with ethyl acetate (100 mL × 2). The combined organic fractions were washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel eluting with petroleumn ether: ethyl acetate = 50: 1 to 20: 1 to give compound **2** (1.4 g, 87.5% yield) as a pale yellow solid. **^{1}H NMR**: ($CDCl_3$ 400 MHz): δ 7.95-8.05 (d, 1H, J = 5.2 Hz), 7.88-7.95 (s, 1H), 7.80-7.88 (m, 2H), 7.68-7.73 (d, 1H, J = 7.6 Hz), 7.55-7.68 (m, 2H), 3.30-3.35 (s, 2H), 2.70-2.80 (m, 2H), 2.45-2.55 (m, 2H), 2.25-2.35 (m, 2H), 1.90-2.00 (m, 2H). **LC-MS**: t_R = 1.96 min in 3 min chromatography, MS (ESI) m/z 316.1 $[M+H]^+$.

Step 2: Preparation of compound 3

To a solution of compound **2** in THF (60 mmL) was added LiHMDS (10 mL, 10 mmol, 1.0 M in THF) dropwise at -78 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 h and a solution of $PhNTf_2$ (3.2 g, 8.88 mmol) in THF (20 mL) was added. The reaction mixture was stirred at -78 °C for another 2 h and then allowed to warm to ambient temperature for 4 h. The reaction mixture was quenched with brine (50 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate = 50: 1 to 20: 1 to give compound **3** (1.5 g, 78.9% yield) as a pale yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.85-7.95 (d, 1H, J = 5.2 Hz), 7.80-7.85 (s, 1H), 7.75-7.80 (m, 2H), 7.60-7.65 (m, 1H), 7.45-7.55 (m, 2H), 7.20-7.35 (m, 1H), 5.80-5.85 (m, 1H), 3.05-3.15 (d, 1H, J = 14.0 Hz), 2.90-3.00 (d, 1H, J = 14.0 Hz), 2.60-2.70 (m, 1H), 2.45-2.55 (m, 2H), 1.95-2.10 (m, 2H), 1.60-1.70 (m, 1H). **LC-MS**: t_R = 2.30 min in 3 min chromatography, MS (ESI) *m/z* 448.1 $[M+H]^+$.

Step 3: Preparation *of compound 4*

A mixture of compound **3** (0.70 g, 1.6 mmol), dimethylamine in THF (40 mL, 80 mmol, 1 M in THF), $Pd(OAc)_2$ (0.011 g, 0.048 mmol) and dppp (20 mg, 0.048 mmol) was stirred at 70 °C under CO (10 PSI) atmosphere for 24 h. The precipitate was filtered off and the filtrate was concentrated *in vacuo* and then the residue was purified by column chromatography on silica gel eluting with dichloromethane: methanol = 100: 1 to 50: 1 to give compound **4** (0.43 g, yield: 72.9%) as a brown solid. **^{1}H NMR** (DMSO-d_6 400 MHz): δ 8.20-8.25 (s, 1H), 8.05-8.15 (m, 2H), 7.95-8.00 (s, 1H), 7.70-8.00 (d, 1H, J = 7.6 Hz), 7.55-7.65 (m, 2H), 5.75-5.85 (m, 1H), 3.82 (m, 1H), 3.10-3.20 (d, 1H, J = 17.6 Hz), 2.90-3.00 (d, 1H, J = 17.6 Hz), 2.70-2.80 (m, 6H), 2.25-2.40 (m, 2H), 1.95-2.05 (m, 1H), 1.65-1.75 (m, 1H), 1.50-1.60 (m, 1H).

LC-MS: t_R = 1.90 min in 3 min chromatography, MS (ESI) *m/z* 371.1 $[M+H]^+$.

Step 4: Preparation of compound 5

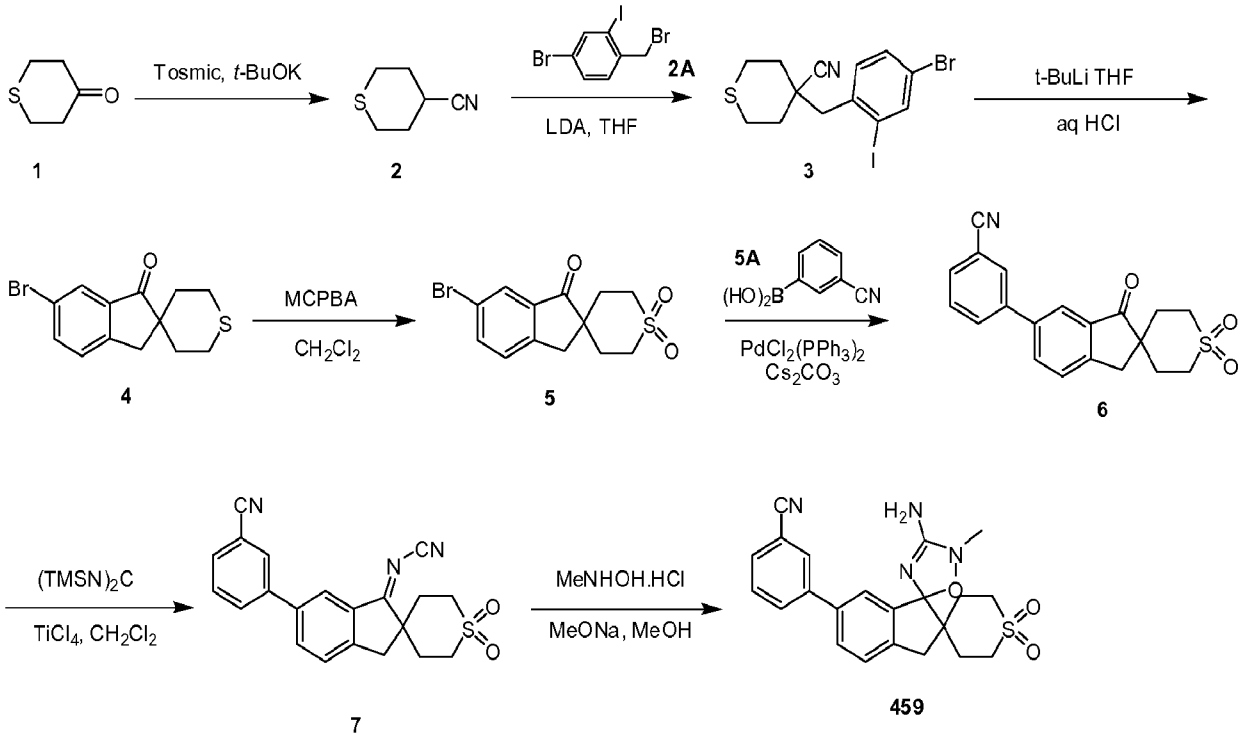
To a solution of compound **4** (50 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (3 mL) was added $TiCl_4$ (0.26 mL, 0.26 mmol, 1 M in CH_2Cl_2) under a nitrogen atmosphere, the mixture was stirred in microwave at 50 °C for 15 min, then bis(trimethylsilyl)carbodiimide (50 mg, 0.26 mmol) was added. The mixture was stirred at 60 °C in microwave for 15 min. The mixture was poured into ice-water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give crude compound **5** (60 mg, crude) as a pale yellow solid which was used directly for the next step without purification.

Step 5: Preparation of compound 458

To a solution of N-methylhydroxylamine hydrochloride (13 mg, 0.15mmol) in MeOH (5 mL) was added MeONa (75 mg, 0.15mmol, 25% (Wt.) in MeOH), followed by compound **5** (60mg, 0.15mmol). After stirred at ambient temperature overnight, the reaction was completed detecting by LC-Ms, and the solvent was removed *in vacuo* to give the crude product which was purified by preparative HPLC to afford **compound 458** (15 mg, 22.7% yield for 2 steps) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.95-8.00 (s, 1H), 7.90-7.95 (d, 1H, J = 8.0 Hz), 7.70-7.75 (d, 1H, J = 7.6 Hz), 7.60-7.70 (m, 2H), 7.55-7.60 (dd, 1H, J = 4.0, 8.0 Hz), 5.80-5.90 (m,1H), 3.10-3.20 (m, 3H), 3.05-3.10 (m, 3H), 2.95-3.05 (m, 3H), 2.75-2.85 (d, 1H, J = 15.6 Hz), 2.45-2.55 (m, 1H), 2.30-2.40 (m, 2H), 1.95-2.10 (m, 1H), 1.65-1.80 (m, 2H).

LC-Ms: t_R = 1.55 min in 3 min chromatography, MS (ESI) m/z 442.2 $[M+H]^+$.

Example 393. Synthesis of Compound 459



Step 1: Preparation of compound 2

To a stirred solution of t-BuOK (9.66 g, 86 mmol) in THF (500 mL) was added Tosmic (16.8 g, 86 mmol) and compound **1** (10 g, 86 mmol) at -10 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was evaporated and the residue was extracted with ether, the extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was dissolved in MeOH (125 mL). To this solution was added a solution of sodium (3.9 g, 172 mmol) in MeOH (250 mL), and then the mixture was refluxed for 1 h. The reaction mixture was evaporated and the residue was purified by column chromatography on a silica gel (hexanes: EtOAc = 20: 1) to afford compound **2** (2 g, yield 23%). **^{1}H NMR** ($CDCl_3$ 400MH): δ 2.73-2.82 (m, 3H), 2.48-2.52 (m, 2H), 1.97-2.10 (m, 4H).

Step 2: Preparation of compound 3

To a solution of LDA (6 mL, 10.8 mmol, 1.8 M in THF) in THF (15 mL) was added the solution of compound **2** (690 mg, 5.4 mmol) in THF (5 mL) slowly at -60 °C, and the reaction mixture was stirred at -60 °C for 1 h. To the resulting mixture was

added the solution of compound **2A** (1.83 g, 4.9 mmol)) in THF (5 mL). The resulting mixture was stirred at -60 °C for 2 h, and then quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by chromatography on silica gel to give compound **3** (372 mg, yield 24%) as a yellow solid.

Step 3: Preparation of compound 4

A flame dried 50 mL RBF was charged with compound **3** (372 mg, 0.88 mmol) and anhydrous THF (15 mL) under N_2 atmosphere. The resulting solution was stirred and cooled to -70 °C, and 1.3 M t-BuLi solution in hexane (1.36 mL, 1.76 mmol, 2 eq.) was added dropwise. Deep red color was observed during the addition. The reaction was stirred another 1 h after the addition. The reaction was quenched with MeOH (0.1 mL), and followed by 2 M aq. HCl solution (2 mL). The resulting solution was concentrated to remove organic solvent. The residue was stirred in 0.5 M aq. HCl solution (10 mL). The suspension was heated to reflux (oil bath 105 °C). The reaction was cooled down to room temperature and filter. The cake was washed with H_2O. The light yellow solid was collected and co-evaporated with MeOH two times to remove water to give crude product, which was purified by chromatography on silica gel to give compound **4** (150 mg, yield 56%) as a white solid.

Step 4: Preparation of compound 5

To a solution of compound **4** (80 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) and was dropwise *m*-CPBA (186 mg, 1.08 mmol) kept below 20 °C. The solution was stirred at room temperature for 2 h. The solid was filtered off, and the filtrate washed with $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **5** (80 mg, 95%). **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.92 (m, 1H), 7.66 (m, 1H), 7.36 (m, 1H), 3.65-3.70 (m, 1H), 3.35 (m, 1H), 3.11 (m, 2H), 2.97-3.01 (m, 2H), 2.30 (m, 4H).

Step 5: Preparation of compound 6

A mixture of compound **5** (100mg, 0.3 mmol), compound **5A** (89 mg, 0.6 mmol), Cs_2CO_3 (2 M, 0.45 mL) and $Pd(PPh_3)_2Cl_2$ (10 mg) in 1,4-dioxane (5 mL) under a nitrogen atmosphere was stirred in microwave at 120 °C for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified pre-TLC to give compound **6** (40 mg, yield 30%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.05 (m, 1H), 7.87 (m, 3H), 7.72 (m, 3H), 7.60 (m, 1H), 3.69-3.75 (m, 2H), 3.17 (m, 2H), 3.01 (m, 2H), 2.30 (m, 4H).

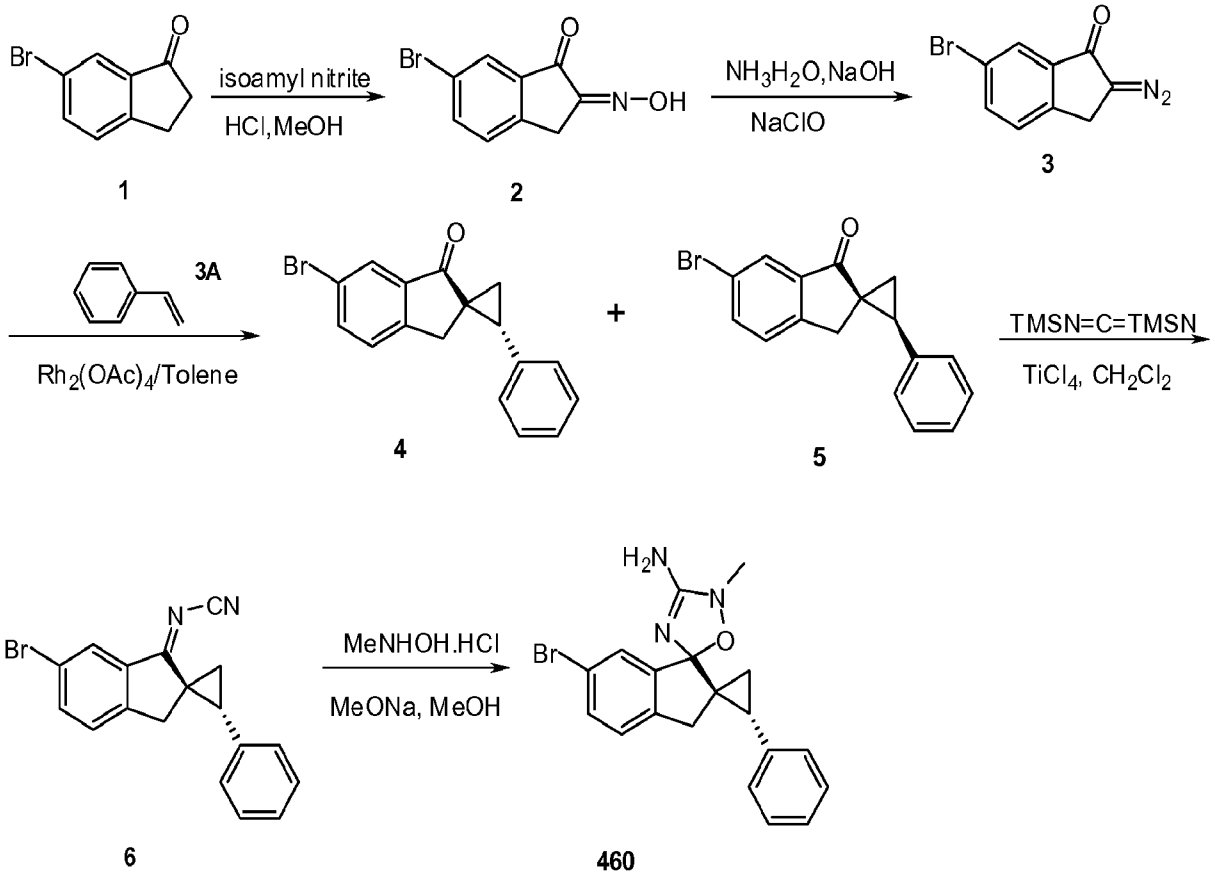
Step 6: Preparation of compound 7

To a solution of compound **6** (40 mg, 0.11 mmol) in DCM (3 mL) was added $TiCl_4$ (0.22 mL, 0.22 mmol) and the mixture was stirred in microwave at 50 °C for 10 min. After the reaction, *bis*-trimehtlysilylcarbodiimide (62 mg, 0.33 mmol) was added and the mixture was stirred in microwave at 60 °C for 10 min. The reaction was quenched with ice water and extracted with CH_2Cl_2, the organic layer was washed with water, brine, dried and concentrated to give the product **7** (20 mg, 57%).

Step 7: Preparation of Compound 459

To a solution of N-methylhydroxylamine hydrochloride (4.4 mg, 0.05 mmol) in MeOH (1 mL) was added NaOMe (10% in MeOH, 24.3 mg, 0.045 mmol) and the mixture was stirred for 5 min. Then a solution of compound **7** (20 mg, 0.05 mmol) in MeOH (2 mL) was added to above solution. Then reaction mixture was stirred at room temperature for 5 min. Then the solution was concentrated *in vacuo* and the residue was purified pre-TLC and HPLC to give compound **459** (2 mg, yield 10%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.93 (m, 2H), 7.70 (m, 4H), 7.39 (d, J = 7.6 Hz, 1H), 3.38 (m, 1H), 3.20 (s, 3H), 3.18 (m, 5H), 2.56 (m, 1H), 2.30 (m, 2H), 1.72-1.77 (m, 1H). **LC-MS** t_R = 0.989 min in 2 min chromatography, MS (ESI) *m/z* 423 $[M+H]^+$

Example 394. Synthesis of Compound 460



Procedure for preparation of compound 2

A solution of compound **1** (6.3 g, 0.03 mmol) in methanol (60 mL) was warmed to 40 °C, then 3 mL of concentrated HCl was added dropwise, followed by isoamyl nitrite (4.38 mL, 0.033 mmol). The reaction mixture was stirred at 40 °C for 1 h. The formed precipitate was collected by filtration, washed with methanol (2 × 25 mL), dried in the vacuo to dryness to give compound **2** (4.0 g, 56%) as a yellow solid. **^{1}H NMR** (DMSO-d_6 400 MHz): δ 12.75 (s, 1H), 7.87-7.89 (dd, J = 2.0, 8.0 Hz, 1H), 7.83-7.85 (m, 1H), 7.57-7.59 (d, J = 8.8 Hz, 1H), 3.71 (s, 2H).

Procedure for preparation of compound 3

A solution of compound **2** (2.5 g, 10.4 mmol) in 1.2 N aq. NaOH solution (10 mL) and water (250 mL) was cooled to 4 °C, then ammonia (3 mL) was added,

followed by 5% aq. NaClO solution (40 mL). After addition, the mixture was warmed to ambient temperature and stirred for 3 h, then was extracted with CH_2Cl_2 (3 × 125 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give compound **3** (1.1 g, 46%) as a yellow solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.87 (s, 1H), 7.61-7.63 (d, J = 8.0 Hz, 1H), 7.25-7.27 (d, J = 8.0 Hz, 1H), 3.96 (s, 2H).

Procedure for preparation of compounds 4 and 5

To a suspension of $Rh_2(OAc)_4$ (26 mg, 0.059 mmol) in anhydrous toluene (10 mL) was added compound **3A** (4.41g,42.3mmol) at 20~25 °C, then a solution of compound **3** (1.0 g,4.23 mmol) in toluene (10 mL) was added dropwise to the mixture over 30 min and stirred for one more hour. The mixture was filtered, and the filtrate was concentrated *in vacuo*, the residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 50: 1 to 30: 1) to give two isomers: **compound 4** (250 mg, 30%) and **compound 5** (600 mg, 64%). **^{1}H NMR compound 4** ($CDCl_3$ 400 MHz): δ 7.78 (d, J = 1.6 Hz, 1H), 7.68-7.71 (dd, J = 2.0, 8.4 Hz, 1H), 7.39-7.42 (d, J = 8.4 Hz, 1H), 7.21-7.31 (m, 5H), 3.35-3.36 (d, J = 2.8 Hz, 2H), 2.93-2.98 (t, J = 8.0 Hz, 1H), 2.19-2.22 (m, 1H), 1.76-1.80 (m, 1H). **LC-MS:** t_R = 1.43 min in 2 min chromatography, MS (ESI) *m/z* 312.9 $[M+H]^+$. **^{1}H NMR compound 5** ($CDCl_3$ 400 MHz) δ 7.94 (d, J = 1.2 Hz, 1H), 7.65-7.67 (dd, J = 2.0, 8.0 Hz, 1H), 7.33-7.37 (t, J = 7.2, 14.8 Hz, 2H), 7.26-7.29 (m, 2H), 7.14-7.16 (d, J = 7.2 Hz, 2H), 2.94-3.00 (m, 2H), 2.73-2.77 (d, J = 18.0 Hz, 1H), 2.02-2.07 (m, 1H), 1.74-1.77 (m, 1H).

LC-MS: t_R = 1.36 min in 2 min chromatography, MS (ESI) *m/z* 312.9 $[M+H]^+$.

Procedure for preparation of compound 6

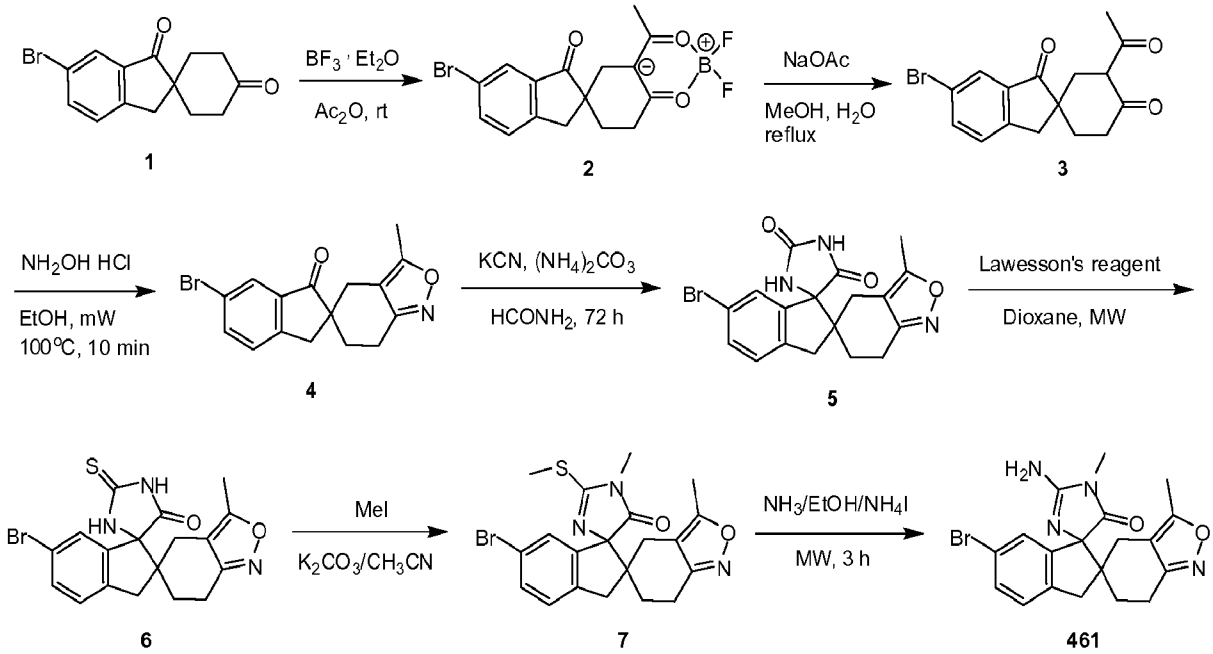
To a solution of **compound 4** (60 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a solution of $TiCl_4$ (0.387 mL, 0.38 mmol in CH_2Cl_2) at ambient temperature. After stirring for 1 h, bis(trimethylsilyl)carbodiimid (70 mg, 0.38 mmol) was added, then the final mixture was stirred at ambient temperature for 20 h. The reaction mixture was quenched by addition of ice (5 g), extracted with CH_2Cl_2 (10 mL).

The separated organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo* to give compound **6** (70 mg, 42%) with 39% purity, which was used in next step directly without purification. **LC-MS**: t_R = 1.505 min in 2 min chromatography, MS (ESI) *m/z* 336.9 $[M+H]^+$.

Procedure for preparation of compound 460

To a solution of MeNHOH.HCl (17.4 mg, 0.208 mmol) in methanol (1 mL) was added MeONa (10.3 mg, 0.187 mmol). The mixture was stirred at ambient temperature for 10 min, then a solution of compound **6** (60 mg, 0.19 mmol) in methanol (3 mL) was added dropwise at ambient temperature and stirred for 10 min. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative RP-HPLC to give **compound 460** (2.7 mg, 34%) as a white solid. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35-7.44 (m, 2H), 7.21-7.31 (m, 2H), 7.12-7.19 (m, 2H), 7.05-7.07 (m, 1H), 7.00-7.02 (m, 1H), 2.99-3.33 (m, 3H),2.38-2.78 (m, 3H), 1.45-1.51 (m, 1H), 1.21-1.30 (m, 1H). **LC-MS**: t_R = 1.15 min in 2 min chromatography, MS (ESI) *m/z* 384.0 $[M+H]^+$.

Example 395. Synthesis of Compound 461



***Procedure for preparation of* compound 2**

To a suspension of compound **1** (545.6 mg, 1.86 mmol) in Ac_2O (3 mL) was added BF_3 Et_2O (1 mL) dropwise at room temperature. The mixture was stirred overnight and quenched with ice water. The mixture was stirred another 1 h and extracted with ethyl acetate (25 mL) washed with H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) successively, then was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude compound **2** (600 mg, 84%) as a light brown foam, which was used in next step without further purification.

Procedure for preparation of compound 3

To a solution of crude compound **2** (300 mg, 0.78 mmol) in MeOH (3 mL) was added a solution of NaOAc (305 mg, 3.72 mmol) in H_2O (0.5 mL). The mixture was heated at reflux for 3 h. MeOH was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL) successively, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The oil was purified by column chromatography on silica gel (hexanes: EtOAc = 20: 1) to give compound **3** (153 mg, 69%); **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.85 (s, 1H), 7.65 (s, 1H), 7.27-7.29 (d, J = 8.0 Hz, 1H), 2.87 (m, 2H), 2.65 (m, 1H), 2.48 (m, 2H), 2.12 (m, 2H), 2.10 (s, 3H), 1.51 (m, 2H).

Procedure for preparation of compound 4

To a solution of compound **3** (153 mg, 0.46 mmol) in a mixture of EtOH (10 mL) and THF (2.5 mL) was added NH_2OH HCl (95 mg, 1.37 mmol). The mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes: EtOAc = 10: 1) to give compound **4** (100 mg, 66%) as a light yellow solid.

***Procedure for preparation of* compound 5**

A steel autoclave was charged with a mixture of compound **4** (1.8 g, 5.4 mmol), KCN (706 mg, 10.8 mmol) and $(NH_4)_2CO_3$ (3.9 g, 40.5 mmol) in formamide (50 mL). The mixture was stirred at 80 °C for 72 h, cooled to room temperature and poured into

ice (50 g). After acidification with *conc.* HCl solution (20 mL), the resulting mixture was filtered and the filter cake was dissolved in ethyl acetate (100 mL) and washed with water (5 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to give compound **5** (1 g, 47%). as a brown solid, which was used in next step without purification.

***Procedure for preparation of* compound 6**

A suspension of compound **5** (400 mg, 0.99 mmol) and Lawesson's Reagent (402 mg, 0.99 mmol) in anhydrous 1,4-dioxane (15 mL) was stirred at 150 °C for 30 min in a CEM microware reactor. The mixture was concentrated *in vacuo*, and the residue was purified by prep-TLC to give compound **6** (140 mg, 34%) as a white solid.

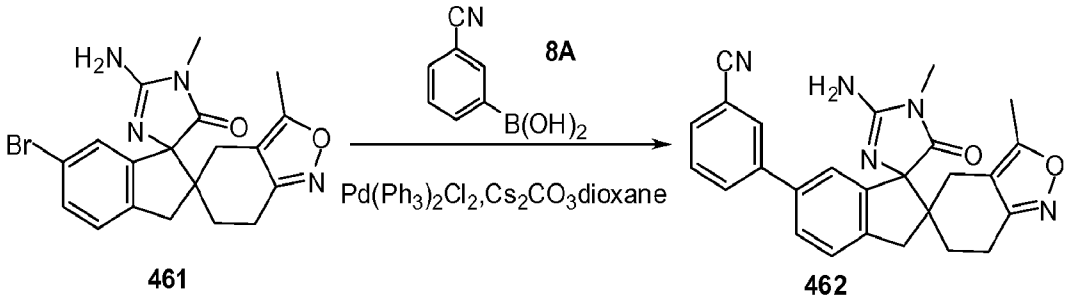
***Procedure for preparation of* compound 7**

To a solution of compound **6** (230 mg, 0.55 mmol) in CH_3CN (15 mL) was added K_2CO_3 (304 mg, 2.2 mmol). After being stirred for 5 min, MeI (155 mg, 1.1 mmol) was added. The reaction mixture was stirred at 60 °C for 15 min in a CEM microwave reactor. The mixture was concentrated *in vacuo*, the residue was purified by prep-TLC to give compound **7** (120 mg, 50%) as a white solid.

Procedure for preparation of compound 461

A solution of compound **7** (140 mg, 0.31 mmol) and NH_4I (362 mg, 2.5 mmol) in NH_3/EtOH (5.0 N, 5mL) was stirred at 120 °C in a microwave reactor for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was added CH_2Cl_2 (15 mL) and stirred for 30 min. The mixture was filtered, concentrated and purified by prep-HPLC (basic) to give **compound 461** (80 mg, 57%) as a white solid. **LC-MS** t_R = 0.882 min in 2 min chromatography, MS (ESI) *m/z* 414, 417 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.52-7.53 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 1H), 3.38 (m, 1H), 3.29 (s, 3H), 2.81 (m, 3H), 2.53 (m, 1H), 2.34 (m, 1H), 2.22 (m, 2H), 2.17 (m, 2H), 1.78 (m,1H).

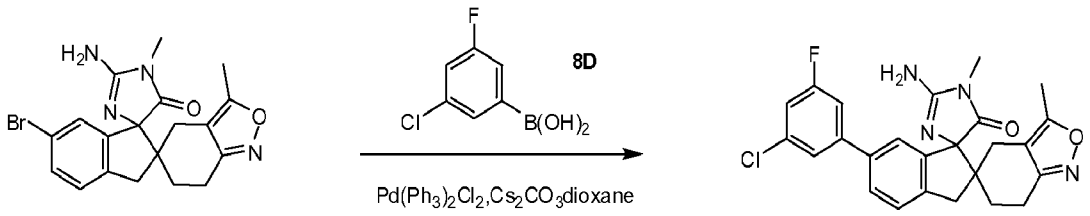
Example 396. Synthesis of Compound 462



461 462

To a solution of compound **461** (20 mg, 0.047 mmol) in 1,4-dioxane (1 mL) was added compound **8A** (15 mg, 0.10 mmol) and aq.Cs_2CO_3 (2M, 0.072 mL, 0.14 mmol), and deoxygenated by bubbling a stream of nitrogen. Then $PdCl_2(PPh_3)_2$ (50 mg, 0.071 mmol) was added The reaction mixture was heated at 120 °C in a CEM microwave reactor for 30 min. The solvents were removed under reduced pressure, and the residue was purified by preparative HPLC to give **compound 462** (4.1 mg, 19%). **LC-MS**: t_R = 1.08 min in 2 min chromatography, MS (ESI) *m/z* 438.2 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.934 (s, 1H), 7.85-7.87 (d, J = 8.0 Hz, 1H), 7.61-7.63 (d, J = 8.0 Hz, 2H), 7.51-7.54 (t, J = 8.0, Hz, 2H), 7.35-7.40 (t, J = 8.0, 10.6 Hz, 1H), 3.21-3.29 (m, 1H), 3.12-3.15 (s, 3H), 2.67-2.80 (m, 3H), 2.46-2.50 (d, J = 13.2, 1H), 2.23-2.31 (t, J = 18.4, 15.6 Hz, 1H), 2.10-2.18 (t, J = 15.6, 18.8 Hz, 2H), 1.91-2.07 (m, 2H), 1.73-1.91 (m, 1H).

Example 397. Synthesis of Compound 463

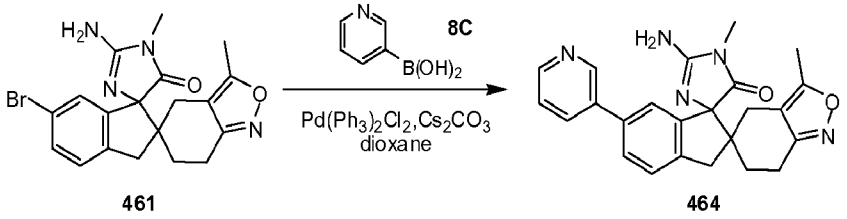


461 463

According to a similar synthesis of **compound 462**, **compound 461** (20 mg, 0.05 mmol) was coupled with compound **8D** (16.8 mg, 0.097 mmol) to give **compound 463** (2.5 mg, 11%) as a white solid. **LC-MS** t_R = 1.036 min in 2 min chromatography,

MS (ESI) *m/z* 464 [MH+]. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.61-7.64 (m, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 10.0 Hz, 1H), 7.11-7.15 (m, 1H), 3.30 (m, 1H), 3.12-3.15 (s, 3H), 2.71-2.76 (m, 3H), 2.45-2.50 (m, 1H), 2.30 (m, 1H), 2.15 (m, 2H), 2.05 (m, 2H), 1.85 (m, 1H).

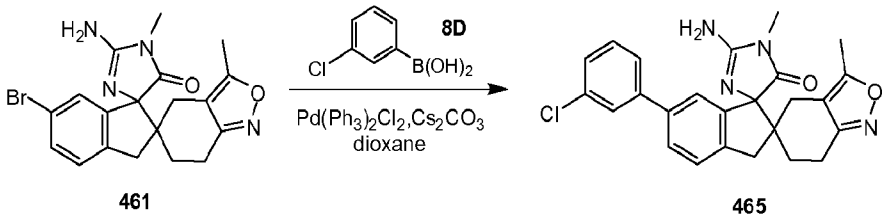
Example 398. Synthesis of Compound 464



461 464

According to a similar synthesis of **compound 462**, **compound 461** (20 mg, 0.048 mmol) was coupled with compound **8C** (12 mg, 0.096 mmol) to give **compound 464** (2.8 mg, 14%) as a white solid. **LC-MS** t_R = 0.757 min in 2 min chromatography, MS (ESI) *m/z* 414 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.66 (d, J = 1.2 Hz, 1H), 8.40 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.47 (m, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 7.19 (m, 1H), 3.29 (m, 1H), 2.99 (s, 3H), 2.66 (m, 4H), 2.18 (m, 3H), 1.98 (m, 2H), 1.67 (m, 1H).

Example 399. Synthesis of Compound 465

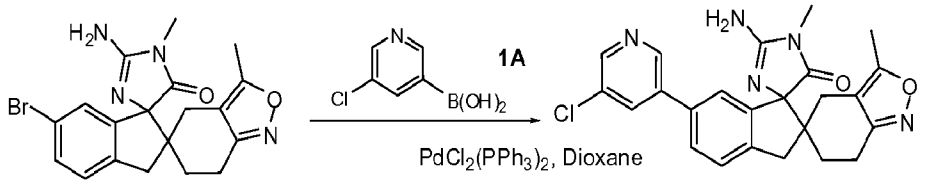


461 465

According to a similar synthesis of **compound 462**, **compound 461** (20 mg, 0.048 mmol) was coupled with compound **8D** (11.3 mg, 0.072 mmol) to give **compound 465** (11 mg, 50%.); **LC-MS** t_R = 1.021 min in 2 min chromatography, MS (ESI) *m/z* 447 $[M+H]^+$. **^{1}HNMR** (CD_3OD, 400 MHz): δ 7.65-7.63 (m, 2H), 7.57-7.54 (m, 2H), 7.45-7.38 (m, 2H), 7.34 (d, J = 8.0 Hz, 1 H), 3.36-3.32 (m, 1H), 3.23 (s, 3H),

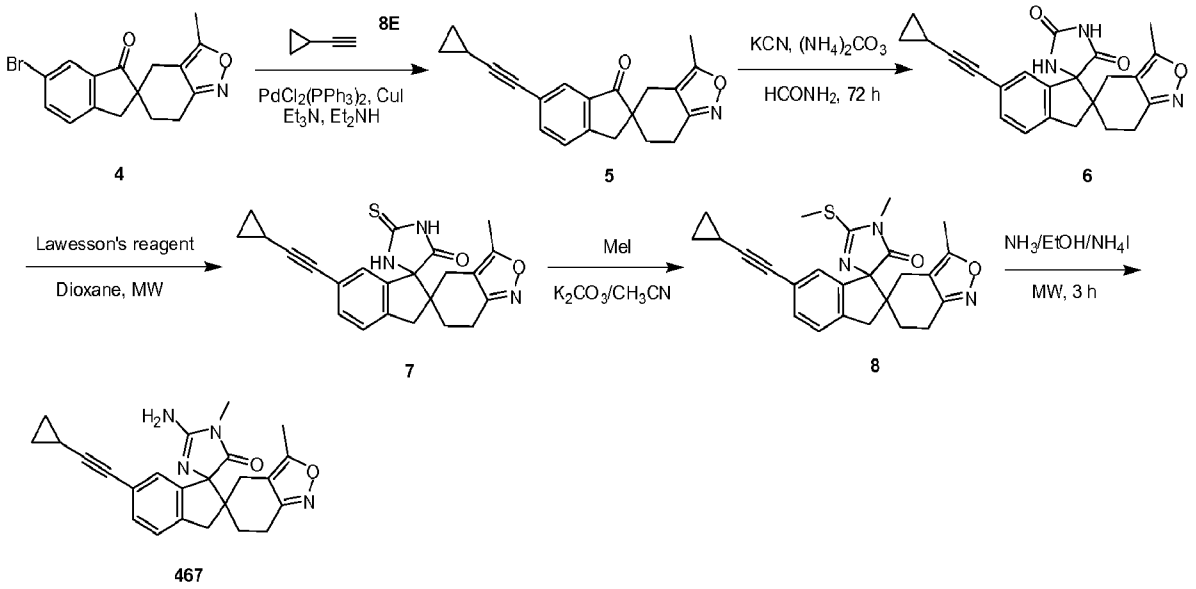
2.88-2.75 (m, 3H), 2.54 (m, 1H), 2.41 (m, 1H), 2.23 (m, 2H), 2.14-2.09 (m, 2H), 1.98-1.83 (m, 1H).

Example 400. Synthesis of Compound 466



According to a similar synthesis of **compound 462**, compound **461** (30 mg, 0.072 mmol) was coupled with compound **1A** (23 mg, 0.144 mmol) to give **compound 466** (1.5 mg, 6%) as white solid. **LC-MS** t_R = 0.921 min in 2 min chromatography, MS (ESI) *m/z* 448.0 $[M+H]^-$. **^{1}H NMR** (CD_3OD 400 MHz): δ 8.50 (s, 1H), 8.33 (s, 1H), 7.92 (s, 1H), 7.43 (s, 1H), 7.25 (m, 1H), 7.12 (m, 1H), 2.89 (m, 3H), 2.58 (m, 1H), 2.15-2.38 (m, 1H), 1.88-2.03 (m, 4H), 1.59 (m, 1H).

Example 401. Synthesis of Compound 467



***Procedure for preparation of* compound 5**

Compound **4** (500 mg, 1.5 mmol) was dissolved in Et_3N (10 mL) and Et_2NH (2 mL) was added $Pd(PPh_3)_2Cl_2$ (150 mg) and CuI (142.5 mg) under a nitrogen atmosphere. Compound **8E** (1 mL) was added by syringe. The system was degassed purged N_2 one more time, the reaction was heated at 50 °C for 12 h, LCMS indicated that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified preparative TLC (hexanes: EtOAc = 2: 1) to give compound **5** (262 mg, 55%) as a yellow solid.

***Procedure for preparation of* compound 6**

A steel autoclave was charged with a mixture of compound **5** (262 mg, 0.83 mmol), KCN (107 mg, 1.65 mmol), $(NH_4)_2CO_3$ (594 mg, 6.19 mmol) and formamide (20 mL). The mixture was heated at 80 °C for 72 h, then was cooled and poured into ice. After acidification with concentrated HCl solution to pH = 1, the mixture was filtered, and the solid was dissolved in CH_2Cl_2 (500 mL). The organic layer was washed with water (2 × 200 mL), dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2: MeOH = 50: 1) to give compound **5** (178 mg, 55%) as an orange solid.

***Procedure for preparation of* compound 7**

To solution of compound **5** (100 mg, 0.26 mmol) and Lawesson'reagent (104 mg, 0.26 mmol) in dioxane (3 mL) was heated at 150 °C for 30 min in a microwave reactor. The mixture was cooled, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexanes: EtOAc = 20: 1) to give compound **7** (30 mg, 38%) as a light orange solid.

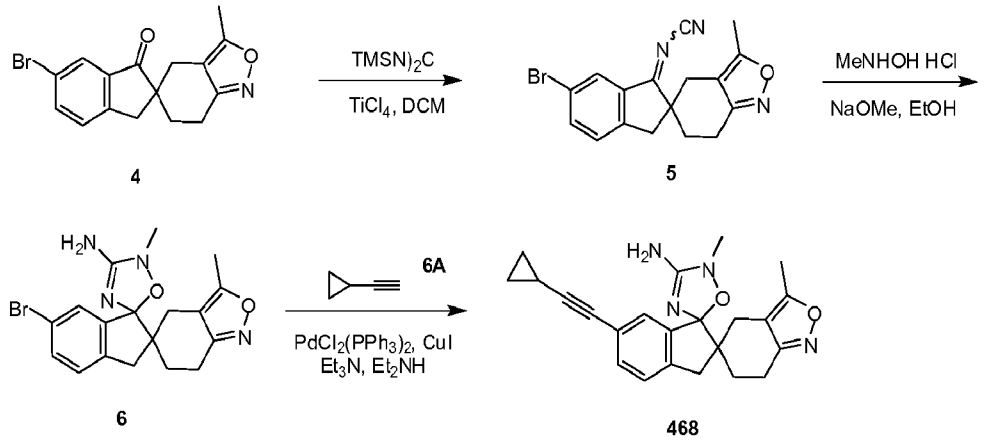
***Procedure for preparation of* compound 8**

To a solution of compound **7** (70 mg, 0.17 mmol) in CH_3CN (2 mL) was added K_2CO_3 (96 mg, 0.69 mmol) and MeI (48 mg, 0.34 mmol). The mixture was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (hexanes: EtOAc = 3: 1) to give compound **8** (38 mg, 51%) as a white solid.

Procedure for preparation of compound 467

A solution of compound **7** (38 mg, 0.088 mmol) and NH_4I (102 mg, 0.70 mmol) in a solution of NH_3/EtOH (2 mL, 0.5 N) was heateded at 120 °C in a CEM microwave reactor for 3 h. The mixture was concentrated *in vacuo* and the residue was added CH_2Cl_2 (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) and preparative HPLC to give **compound 467** (3.1 mg, 8.8%) as a white solid. **LC-MS** t_R = 0.979 min in 2 min chromatography, MS (ESI) *m/z* 401 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.24 (m, 3H), 3.20 (m, 3H), 2.94 (m, 1H), 2.74 (m, 3H), 2.63 (m, 1H), 2.44 (m, 1H), 2.25 (m, 2H), 2.00 (m, 1H), 1.70 (m, 1H), 1.40 (m, 1H), 1.18 (m, 1H), 0.74 (m, 2H), 0.63 (m, 2H).

Example 402. Synthesis of Compound 468



***Procedure for preparation of* compound 5**

To a solution of compound **4** (100 mg, 0.3 mmol) in dichloromethane (5 mL) was added $TiCl_4$ (0.6 mL, 1.0 M in CH_2Cl_2, 0.6 mmol) and the mixture was reacted in microwave at 50 °C for 10 min. After the reaction, *bis*-trimehtlysilylcarbodiimide (168 mg, 0.9 mmol) was added and the mixture was reacted in microwave at 60 °C for 10 min. The reaction was quenched by addition of ice water and extracted with CH_2Cl_2, the organic layer was washed with water, brine, dried and concentrated to give the product **5** (104 mg, 97%) as a yellow oil, which was used in next step without purification.

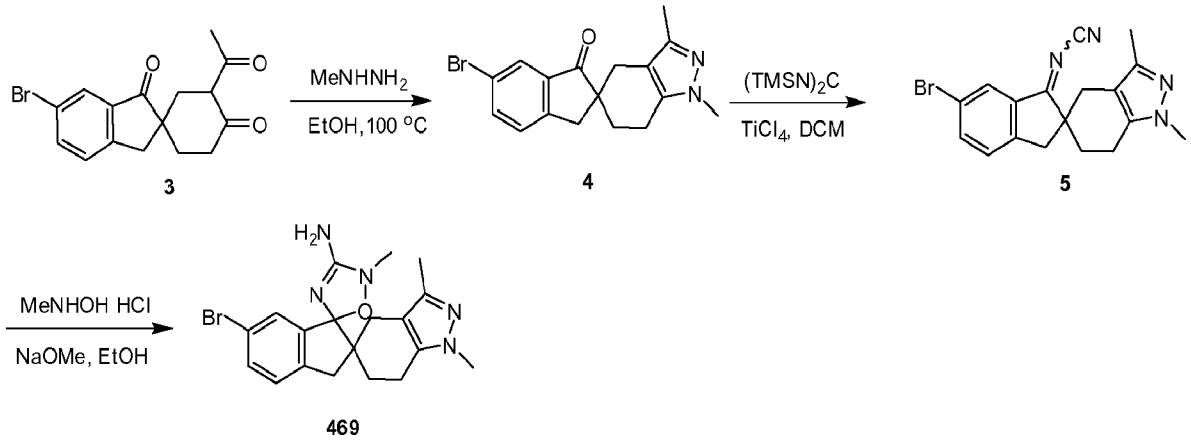
***Procedure for preparation of* compound 6**

To a solution of MeNHOH.HCl (24.4 mg, 0.29 mmol) in MeOH (5 mL) was added NaOMe (10 wt% in MeOH, 141 mg, 0.26 mmol) and the mixture was stirred for 5 min. Then to a solution of compound **5** (104 mg, 0.29 mmol) in MeOH (8 mL) was added to above solution. Then final reaction mixture was stirred at room temperature for 45 min. Then the solution was concentrated and the residue was purified, which was purified preparative TLC to give compound **6** (80 mg, 68%) as a white solid.

Procedure for preparation of compound 468

The compound **6** (40 mg, 0.1 mmol) was dissolved in Et_3N (3 mL) and Et_2NH (1 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (5 mg) and CuI (5 mg). Compound **6A** (0.5 mL) was added by syringe. The system was degassed purged N_2 one more time, the reaction was heated 50 °C for 12 h, LCMS indicated that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified preparative TLC and preparative HPLC to give **compound 468** (1.9 mg, 5%) as a white solid. **LC-MS** t_R = 0.994 min in 2 min chromatography, MS (ESI) *m/z* 389 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 7.15-7.17 (d, J = 5.6 Hz, 2H), 7.00-7.02 (d, J = 8.0 Hz, 1H), 2.92 (s, 3H), 2.73 (m, 2H), 2.55 (m, 3H), 2.20 (m, 5H), 1.74 (m, 1H), 1.37 (m, 1H), 0.82 (m, 2H), 0.64 (m,2H).

Example 403. Synthesis of Compound 469



Procedure for preparation of compound 4

To a solution of compound **3** (140 mg, 0.42 mmol) in anhydrous EtOH (5 mL) was added CH_3NHNH_2 (95 mg, 2.09 mmol). The reaction mixture was heated at reflux overnight. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give compound **4** (42 mg, 29%) as a white solid.

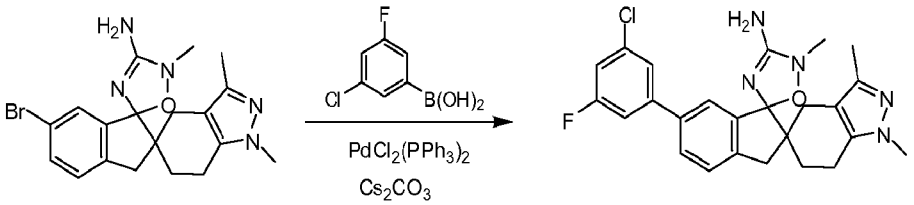
Procedure for preparation of compound 5

To a solution of compound **4** (42 mg, 0.12 mmol) in anhydrous dichloromethane (2 mL) was added $TiCl_4$ (115 mg, 0.61 mmol). The mixture was heated at 50 °C for 10 min in a microwave reactor, then N, N'-methanediylidene bis (1,1,1-trimethylsilianamine) (168 mg, 0.36 mmol) was added. The reaction mixture was hrated at 60 °C for 40 min in a microwave reactor. The reaction mixture was poured into ice (20 g) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by preparative TLC (EtOAc) to give compound **5** (10 mg, 24%) as a white solid.

Procedure for preparation of compound 469

To a solution of compound **5** (10 mg, 0.027 mmol) in MeOH (2 mL) was added MeNHOHHCl (2.3 mg, 0.027 mmol) and MeONa solution (10 wt % in MeOH, 13.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 469** (10 mg, 88%) as a white solid. **LC-MS** t_R = 0.851 min in 2 min chromatography, MS (ESI) *m/z* 418 $[M+H]^+$. **^{1}HNMR** (CD_3OD, 400 MHz): δ 7.60-7.48 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 3.73 (m, 3H), 2.20-3.15 (m, 3H), 2.88-2.63 (m, 3H), 2.60-2.56 (m, 3H), 2.18-1.94 (m, 4H), 1.81-1.80 (m, 1H).

Example 404. Synthesis of Compound 470

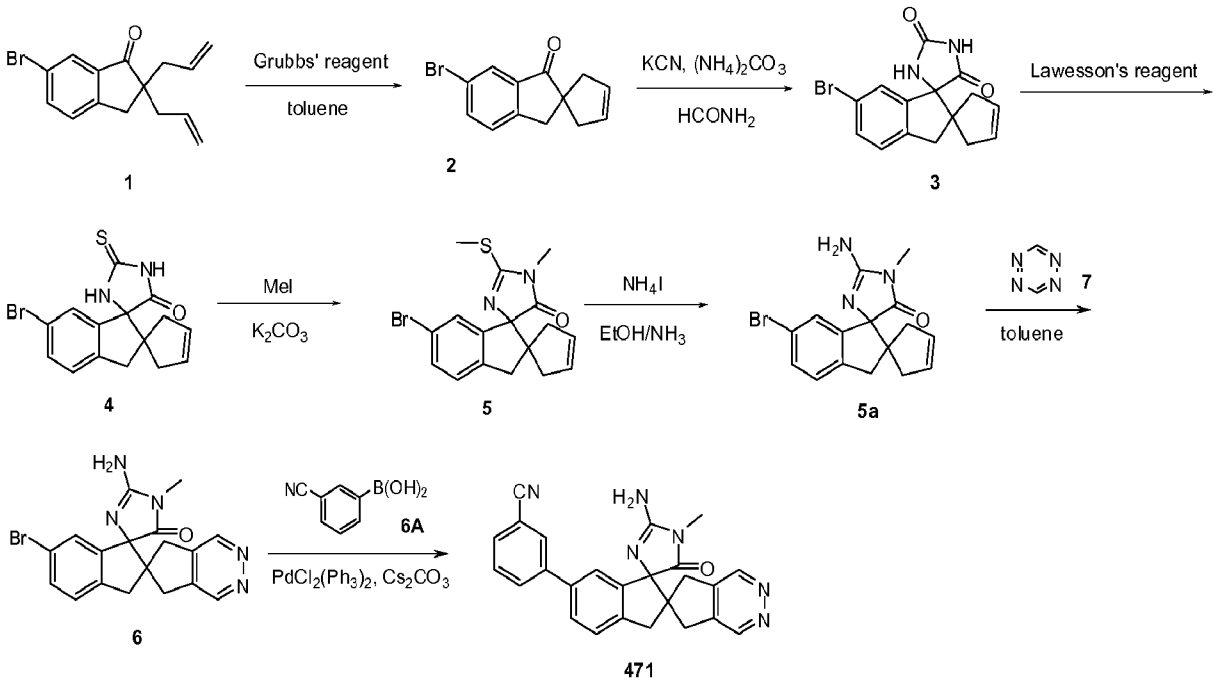


469 470

To a solution of **compound 469** (20 mg, 0.048 mmol) and 3-chloro-5-fluoro-phenyl bronic acid (12.6 mg, 0.072 mmol) in dioxane (3 mL) was added $PdCl_2(PPh_3)_2$ (6.7 mg, 0.009 mmol) and Cs_2CO_3 (2N, 0.048 mL, 0.096 mmol). The reaction mixture

was heated at 110 °C for 15 min in a microwave reactor under nitrogen, then diluted with ethyl acetate (80 mL), washed with brine (2 × 50 mL), dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by preparative HPLC to give **compound 470** (11 mg, 50%) as a white solid. **LC-MS** t_R = 0.983 min in 2 min chromatography, MS (ESI) *m/z* 466 $[M+H]^+$. **^{1}HNMR** (CD_3OD, 400 MHz): δ 7.61-7.58 (m, 2H), 7.47 (s, 1H), 7.35-7.29 (m, 2H), 7.19 (d, J = 7.2 Hz, 1H), 3.74-3.66 (m, 3H), 3.14-3.06 (m, 3H), 2.92-2.73 (m, 2H), 2.69-2.59 (m, 3H), 2.16-2.03 (m, 4H), 1.84-1.81 (m, 1H), 1.27-1.25 (m, 1H).

Example 405. Synthesis of Compound 471



Procedure for preparation of compound 2

To a solution of compound **1** (7.0 g, 24.1 mmol) in toluene (600 mL) was added Grubbs Catalyst 1st generation (2.98 g, 3.62 mmol), and the reaction mixture was refluxed overnight. The mixture was concentrated *in vacuo* to give the residue, which was purified by chromatography (petroleum ether: EtOAc=100:1) to give **compound 2** (5.21 g, 82%) as a white solid. **LC-MS** t_R = 1.464 min in 2 min chromatography, MS

(ESI) *m/z* 263.0 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.83 (s, 1H), 7.62 (m, 1H), 7.28 (m, 1H), 5.66 (s, 2H), 3.06 (s, 2H), 2.84 (d, J = 14.8 Hz, 2H), 2.29 (d, J = 14.8 Hz, 2H).

Procedure for preparation of compound 3

A steel autoclave was charged with a mixture of compound **2** (2 g, 7.6 mmol), KCN (988 mg, 15.2 mmol), and $(NH_4)_2CO_3$ (5.8 g, 60.8 mmol), formamide (60 mL) was added. The mixture was heated at 80 °C for 72 h. The reaction mixture was then cooled and poured into ice. After acidification with concentrated HCl (50 mL), the mixture was filtrated to give the solid, which was dissolved in ethyl acetate (600 mL) and washed with water (2 × 150 mL). The combined organic phase was dried and concentrated to give compound **3** (2.2 g, 87%) as a white solid, which was used in the next step without purification.

Procedure for preparation of compound 4

To a solution of compound **3** (600 mg, 1.8 mmol) in 1,4-dioxane (45 mL) was added Lawesson's reagent (800 mg, 2.97mmol) under a nitrogen atmosphere. The reaction mixture was heated in a CEM microwave reactor at 120 °C for 60 min. The solvent was removed under reduced pressure, and the residue was purified by chromatography (petroleum ether: EtOAc = 5: 1) to give compound **4** (410 mg, 65%) as a white solid.

Procedure for preparation of compound 5

To a solution of compound **4** (300 mg, 0.86 mmol) in CH_3CN (15 mL) was added compound K_2CO_3 (478 mg, 3.44 mmol) and MeI (488 mg, 3.44 mmol). The reaction mixture was heated at 60 °C for 10 min and then at 100 °C for 10 min in a CEM microwave reactor. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 15: 1) to afford compound **5** (240 mg, 71%).

Procedure for preparation of compound 5a

To a solution of compound **5** (420 mg, 1.11 mmol) in NH_3/EtOH (10 mL) was added NH_4I (1.13 g, 7.80 mmol). The reaction mixture was heated at 120 °C in a CEM microwave reactor for 3 h. The solution was concentrated to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH = 10: 1) to afford **compound 5a** (399 mg, 90%) as a white solid. **LC-MS** t_R = 1.054 min in 2 min chromatography, MS (ESI) *m/z* 346.0 $[M+H]^+$. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.43 (m, 1H), 7.12 (s, 1H), 7.08 (m, 1H), 5.09 (m, 2H), 3.31 (d, J = 15.2 Hz, 1H), 3.07 (s, 3H), 2.82 (d, J = 12.0 Hz, 1H), 2.53-2.36 (m, 2H), 2.27 (m, 1H), 1.91 (m, 1H).

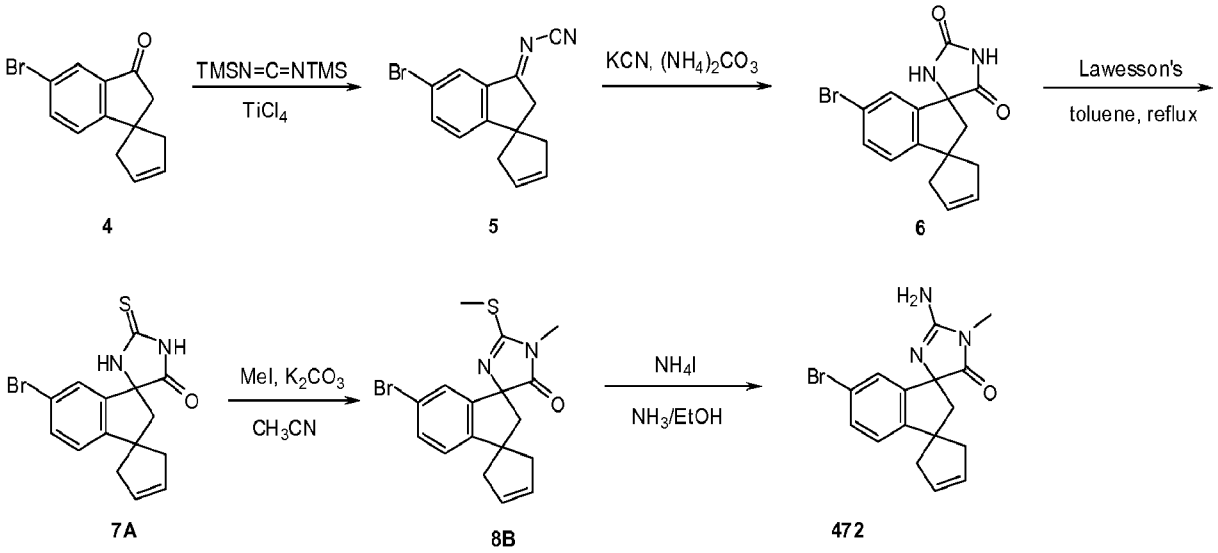
Procedure for preparation of compound 6

To a solution of compound **5a** (100 mg, 0.29 mmol) in anhydrous toluene (3 mL) was added compound **7** (52 mg, 0.636 mmol) under a nitrogen atmosphere. The reaction mixture was heated at 150 °C in a CEM microwave reactor for 1 h. The solution was concentrated to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH = 8: 1) to afford compound **6** (30 mg, 26%) as a red solid.

Procedure for preparation of compound 471

$Pd(PPh_3)_2Cl_2$ (10 mg, 0.14 mmol) in a 10 mL of flask under a nitrogen atmosphere was treated sequentially with compound **6** (30 mg, 0.075 mmol), 1,4-dioxane (1 mL), Cs_2CO_3 (2 N, 0.1 mL) and compound **6A** (22 mg, 0.15 mmol). The mixture was heated at 120 °C under a nitrogen atmosphere in a microwave reactor for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by preparative HPLC to afford **compound 471** (3.1 mg, 10%). **LC-MS** t_R = 0.978 min in 2 min chromatography, MS (ESI) *m/z* 421.0 $[M+H]^+$. **^{1}H NMR** (CD_3OD 400 MHz): δ 9.10 (d, J = 15.6 Hz, 2H), 7.98 (s, 1H), 7.88 (m, 1H), 7.67 (m, 2H), 7.56 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 3.43 (m, 1H), 3.26 (m, 2H), 3.16 (s, 3H), 3.02 (m, 1H), 2.92 (m, 1H), 2.58 (m, 1H).

Example 406. Synthesis of Compound 472



Procedure for preparation of compound 5

To a solution of compound **4** (477 mg, 1.8 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 3.6 mL, 3.6 mmol) at room temperature. After the mixture was stirred in microwave at 50 °C for 15 min., bis-trimethylsilylcarbodiimide (1.17 mL, 5.4 mmol) was added, and the mixture was stirred in microwave at 60 °C for 25 min. TLC showed the reaction was completed, and the mixture was poured into ice-water (10 mL), and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, concentrated to give compound **5** (400 mg, 90%) as a yellow solid, which was used for the next step without purification.

Procedure for preparation of 6

A steel clabe was charged with a mixture of compound **5** (400 mg, 1.39 mmol), KCN (362 mg, 5.57 mmol) in EtOH (4 mL) and H_2O (4 mL). The mixture was heated at 80 °C for 24 h. The reaction mixture was cooled to room temperature and poured into ice (10 g) and filtered. The filter cake was washed with water (10 mL × 2) and CH_2Cl_2 (10 mL × 2), dried under reduced pressure to give **compound 6** (440 mg, 78%) as a white solid. **LC-MS** t_R = 1.219 min in 2 min chromatography, MS (ESI) *m/z* 333,

335 $[M+H]^-$; **^{1}H NMR** (DMSO 400 MHz): δ 10.82 (m, 1H), 8.52 (d, J = 27.2 Hz, 1H), 7.53 (m, 1H), 7.34 (m, 2H), 5.78 (d, J = 6.4 Hz, 2H), 2.61 (m, 4H), 2.23 (m, 2H).

Procedure for preparation of compound 7A

A suspension of compound **6** (100 mg, 0.3 mmol) and Lawesson's reagent (121 mg, 0.3 mmol) in anhydrous toluene (4 mL) was heated at 130 °C for 35 min in a CEM microwave reactor. The reaction mixture was concentrated under reduced pressure, and the residue was purified by prep-TLC (petroleum ether: EtOAc = 3: 1) to give compound **7A** (70 mg, 67%) as a white solid.

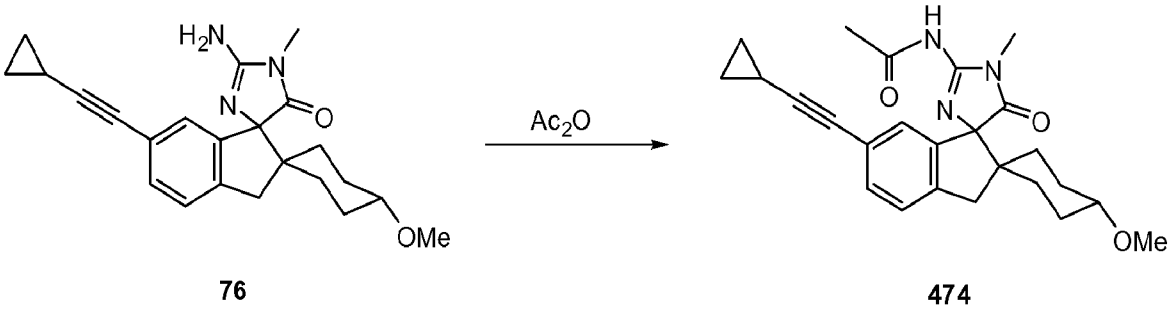
Procedure for preparation of compound 8B

To a solution of compound **7A** (70 mg, 0.2 mmol) in CH_3CN (2 mL) was added K_2CO_3 (110 mg, 0.8 mmol). After being stirred for 5 min., MeI (56.5 mg, 0.4 mmol) was added, and the reaction mixture was heated at 60 °C for 15 min in a CEM microwave reactor. The reaction mixture was concentrated under reduced pressure, and ther residue was purified by prep-TLC (petroleum ether: EtOAc = 5: 1) to give compound **8B** (60 mg, 79%).

Procedure for preparation of compound 472

A solution of compound **8B** (30 mg, 0.08 mmol) and NH_4I (92 mg, 0.64 mmol) in NH_3/EtOH (5.0 N, 2 mL) was heated at 120 °C in a microwave reactor for 3 h. The reaction mixture was concentrated, and the residue was purified by prep-HPLC (acidic) to give **compound 472** (1.8 mg, 7%) as a white solid. **LC-MS** t_R = 1.077 min in 2 min chromatography, MS (ESI) *m/z* 348, 350 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.51 (dd, J = 1.6 Hz, 4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 5.81 (s, 2H), 2.91 (m, 2H), 2.87 (s, 3H), 2.61 (m, 2H), 2.44 (m, 1H), 2.40 (m, 1H).

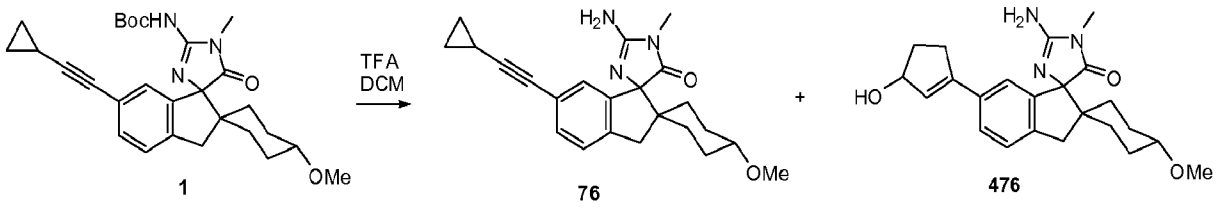
Example 407. Synthesis of Compound 473



76 **474**

To a solution of **compound 76** (7.38 mg, 0.02 mmol) in pyridine was added acetic anhydride (5drops). The resulting solution was stirred at room temperature for 30 min, quenched with MeOH, and purified with a revised phase HPLC to give **compound 474** (8.3 mg, 80 %) as a TFA salt. **LC-MS:** tR = 1.84 min, 3 min method, MS (ESI) *m/z* 420 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.28 (m, 2H), 7.10 (s, 1H), 3.32 (s, 3H), 3.20-3.08 (m, 6H), 2.28 (s, 3H), 2.04-1.98 (m, 2H), 1.84 (m, 1H), 1.56-1.20 (m, 6H), 0.84 (m, 2H), 0.64 (m, 2H).

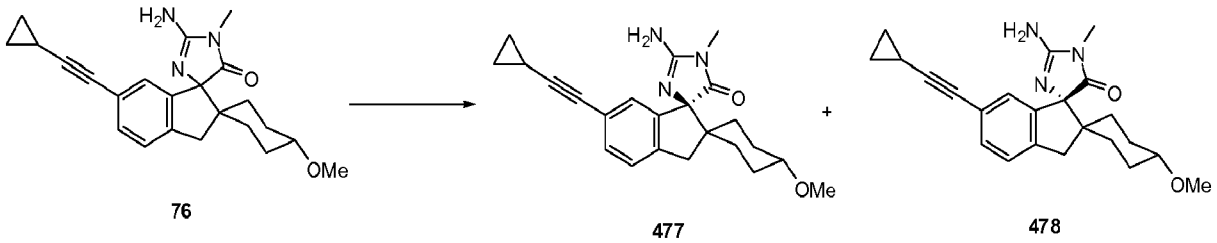
Example 408. Synthesis of Compound 476



1 **76** **476**

Compound 1 was dissolved in DCM (1 mL) and treated wtih TFA (1 mL) at room temperature for 30 min, and purified by a HPLC to give compound 76 (5.7 mg) as TFA salt, along with compound 476 (5.0 mg, TFA salt) as a by-product. **LC-MS:** tR = 1.17 min, 3 min method, MS (ESI) *m/z* 396 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.28 (m, 2H), 7.04 (s, 1H), 6.38 (s, 1H), 4.78 (m, 1H), 3.32 (s, 3H), 3.20-3.04 (m, 6H), 2.76-2.38 (m, 2H), 2.10-1.80 (m, 4H), 1.48-1.24 (m, 6H).

Example 409. Synthesis of Compounds 477 and 478



Compound 76 (5 mg, was purified on a chiral HPLC followed by a revised phase HPLC to give **compound 478** (1.53 mg) as a TFA salt, t_R = 37.86 min (ADH column, eluented with 80%Hexane/EtOH with 0.1%diethylamine, flow rate 4 mL/min); **LC-MS:** MS (ESI) *m/z* 378 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.32 (m, 2H), 7.18 (s, 1H), 3.34 (s, 3H), 3.20-3.12 (m, 6H), 2.06-1.96 (m, 2H), 1.82 (m, 1H), 1.44-1.24 (m, 6H), 0.84 (m, 2H), 0.68 (m, 2H); and **compound 477** (1.64 mg) as a TFA salt, t_R = 42.76 min (ADH column, eluented with 80%Hexane/EtOH with 0.1%diethylamine, flow rate 4 mL/min); **LC-MS:** MS (ESI) *m/z* 378 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.34 (m, 2H), 7.18 (s, 1H), 3.34 (s, 3H), 3.20-3.10 (m, 6H), 2.06-1.96 (m, 2H), 1.82 (m, 1H), 1.44-1.24 (m, 6H), 0.84 (m, 2H), 0.66 (m, 2H).

Example 410. Synthesis of Compounds 488-518 and 592-604

Microsorb 1s: Column: Varian Microsorb 100 C18, 30 x 4.6 mm

UV-Detection: 210 - 380 nm

Eluent A: Water (0.15 % TFA), Eluent B: Acetonitrile

Gradient:	Time (min)	% Eluent B	Flow mL/min
	0.00	5	3.5
	0.18	5	3.5
	2.00	98	3.5
	2.20	98	3.5
	2.30	5	3.5
	2.50	5	3.5

Microsorb 4s MeOH: Column: Varian Microsorb 100 C18, 30 x 4.6 mm

UV-Detection: 210 - 380 nm

Eluent A: Water (0.13 % TFA), Eluent B: Methanol

Gradient:	Time (min)	% Eluent B	Flow mL/min
	0.00	5	2.4
	0.35	5	2.4
	3.95	100	2.4
	4.45	100	2.4
	4.55	5	2.4
	4.90	5	2.4

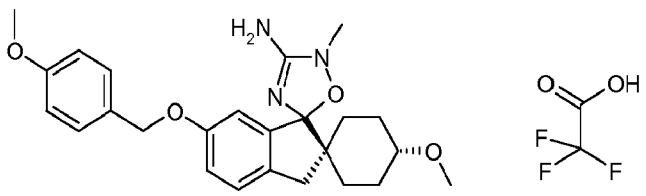
Microsorb 7s MeOH: Column: Varian Microsorb C18, 20 x 4.6 mm

UV-Detection: 210 - 380 nm

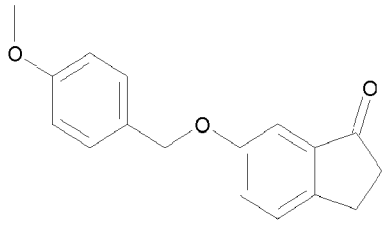
Eluent A: Water (0.13 % TFA), Eluent B: Methanol

Gradient:	Time (min)	% Eluent B	Flow mL/min
	0.00	5	5.2
	0.25	5	5.2
	1.90	100	5.2
	2.05	100	5.2
	2.15	5	5.2
	2.25	5	5.2

A. Compound 504



Step 1. 6-(4-Methoxy-benzyloxy)-indan-1-one

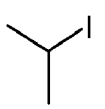
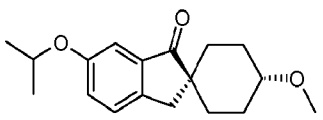
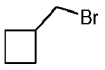
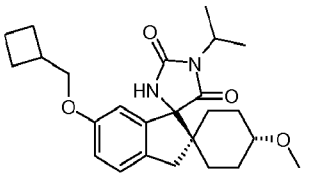
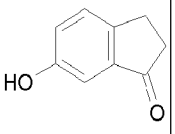
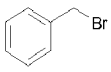
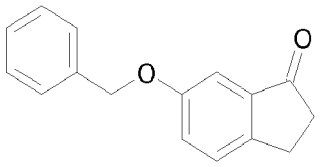


4-methoxybenzylchloride (9.19 mL, 67.5 mmol) was added to a mixture of 6-hydroxy-1-indanone (10 g, 67.5 mmol) and potassium carbonate (14 g, 101 mmol) in 15 mL DMF. The mixture was reacted at RT for 14 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was separated and the solvents were removed by evaporation. The residue was dissolved in DCM and filtered through a plug of activated basic alumina. 6-(4-Methoxy-benzyloxy)-indan-1-one (18 g, 99%) was obtained after evaporation of the filtrate. The material was taken to the next step without further purification.

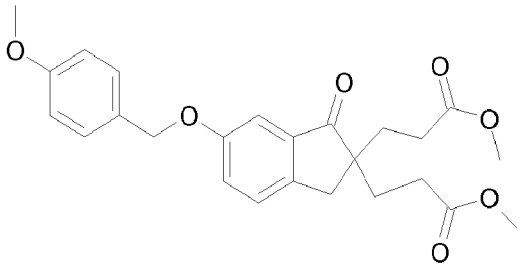
HPLC (Method: Microsorb 1s) ,

Rt: 1.46 min; Mass: $(M+H)^+ = 269$

By using the same synthetic strategy as for **compound 504 step1** the following compound was obtained:

No.	Starting material 1	Starting material 2	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.1.1	compound 505 Step1			**289**	**Microsorb 1s**	**1.55**
1.1.2	**compound 4.1.1**			**427**	**Microsorb 1s**	**1.75**
1.1.3				**239**	**Microsorb 1s**	**1.52**

Compound 504 Step2

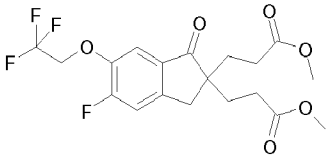


6-(4-Methoxy-benzyloxy)-indan-1-one (13.5 g 95%, 47.8 mmol) was mixed with methyl acrylate (17.33 mL, 191 mmol) and heated to 60°C. Potassium fluoride (60% on alumina, Aldrich, 22.2 g, 382 mmol) was added in portions. The mixture was cooled to RT and Celite was added. The mixture was washed with DCM (200 mL). Evaporation yielded the crude product Compound 504 Step2 (14.8 g, 70%). The material was taken to the next step without further purification.

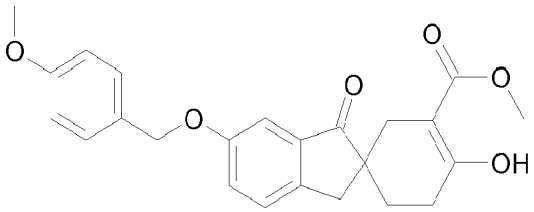
HPLC (Method: Microsorb 1s)

Rt: 1.55 min; Mass: $(M+H)^+$ = 441

By using the same synthetic strategy as for **compound 504 step2** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.2.1	compound 518 Step1		**421**	**Microsorb 1s**	**1.46**

Compound 504 Step3

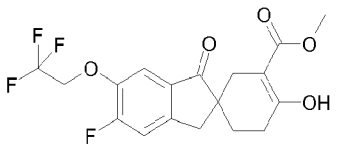


Potassium-3,7-dimethyl-octan-3-olate (14.4 g, 36.7 mmol, 50% in heptane, BASF) in toluene (50 mL) was heated to reflux under nitrogen. Compound 504 Step2 (14.7 g, 33.4 mmol) was added in toluene (50 mL). The mixture was refluxed for 12 h. The solvents were evaporated and the crude product Compound 504 Step3 was taken to the next step without further purification.

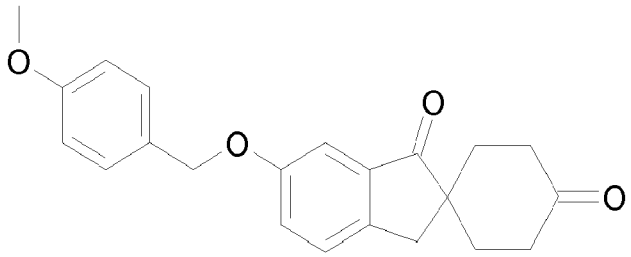
HPLC (Method: Microsorb 1s)

Rt: 1.69 min; Mass: $(M+H)^+$ = 409

By using the same synthetic strategy as for **compound 504 step3** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.3.1	1.2.1		389	Microsorb 1s	1.58

Compound 504 Step4

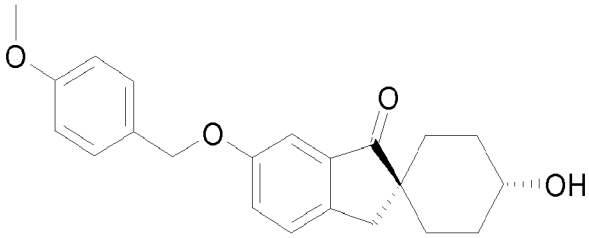


To Compound 504 Step3 (2.78 g) in MeOH (20 mL) was added 4 M aqueous NaOH (7.0 mL, 28.0 mmol). The mixture was stirred for 2 h at 70°C. The mixture was cooled to RT. The precipitate was filtered, washed with water and dried to give Compound 504 Step4 (1.2 g, 50%).

HPLC (Method: Microsorb 1s)

Rt: 1.49 min; Mass: $(M+H)^+ = 351$

Compound 504 Step5

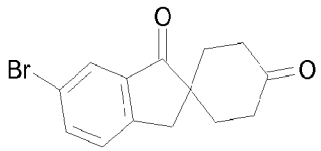
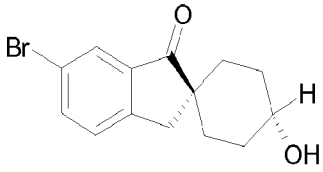
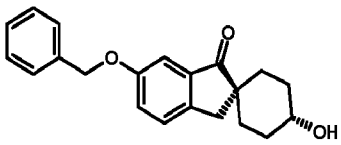
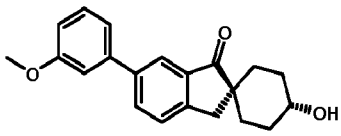


Sodium borohydride (1.1 g , 29.2 mmol) was added portionwise over a peroiod of 1 h to Compound 504 Step4 (10.2 g) in THF (70 mL) at -78°C. After 1 h the mixture was heated to 4°C and stirred for 12 h. Acetone (13.7 mL) was added. After 15 min the mixture was diluted with water and extracted with EA. The organic layer was separated and the solvents were evaporated to yield Compound 504 Step5 (8.0 g) that was taken to the next step without further purification. The material contained the diasteromeric alcohol as minor impurity.

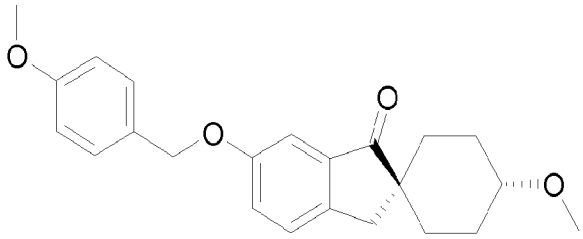
HPLC (Method: Microsorb 1s)

Rt: 1.50 min; Mass: $(M+H)^+ = 353$

By using the same synthetic strategy as for **Compound 504 step5** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.5.1			295/297 (Br)	Microsorb 1s	1.31
1.5.2	2.3.1		323	Microsorb 4s MeOH	3.22
1.5.3	23.1.1		323	Microsorb 4s MeOH	3.21

Compound 504 Step6

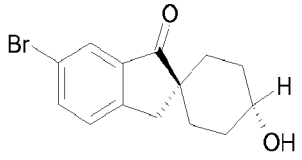
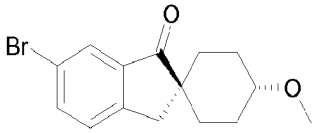
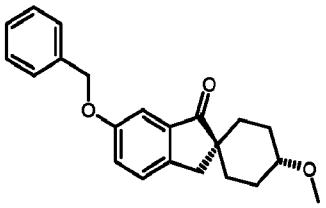


Methyliodide (5.71 mL, 90.8 mmol) was added to Compound 504 Step5 (8 g, 22.7 mmol) in DMF (70 mL) followed by portionwise addition of sodium hydride (60 % in mineral oil, 4.54 g, 114 mmol). The mixture was stirred for 2 h at RT and 2 h at 40°C. Methanol was added (1 mL). The reaction was diluted with water and extracted with DCM. The organic layer was separated and the solvents were evaporated. The crude product was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to give Compound 504 Step6 (4.5 g) as a white solid.

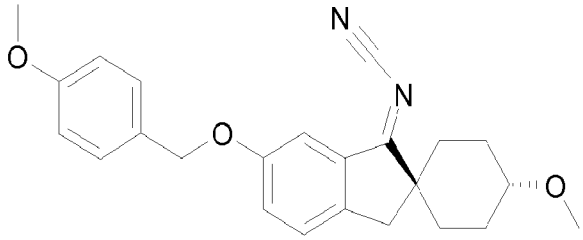
HPLC (Method: Microsorb 1s)

Rt: 1.77 min; Mass: $(M+H)^+ = 367$

By using the same synthetic strategy as for **Compound 504 step6** the following compound was obtained:

No.	Starting materials	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.6.1			309/311 (Br)	Microsorb 1s	1.55
1.6.2	1.5.2		337	Microsorb 4s MeOH	3.45

Compound 504 Step7

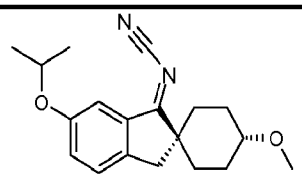
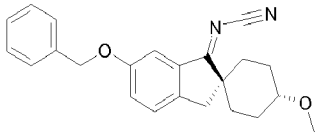


Compound 504 Step6 (96 mg, 0.26 mmol) was dissolved in anhydrous acetonitrile (2 mL) and evaporated to dryness. The residue was dissolved in acetonitrile (6 mL) and cesium fluoride (160 mg, 1.05 mmol) and 1,3-bis(trimethylsilyl)carbodimide (0.24 mL, 1.05 mmol) were added. The mixture was stirred at 50°C for 13 h. The reaction mixture was quenched with water and extracted with EA. The organic layer was separated. Evaporation yielded Compound 504 Step7. Toluene was added (2 mL) and evaporated to dryness to remove traces of water. The residual material was taken to the next step without further purification.

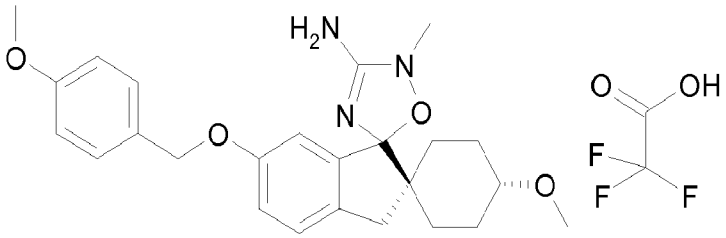
HPLC (Method: Microsorb 1s)

Rt: 1.70 min; Mass: $(M+H)^+ = 391$

By using the same synthetic strategy as for **Compound 504 step7** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
1.7.1	**1.1.1**		**313**	**Microsorb 1s**	**1.59**
1.7.2	**1.1.3**		**361**	**Microsorb 4s MeOH**	**3.51**

Compound 504 Step8

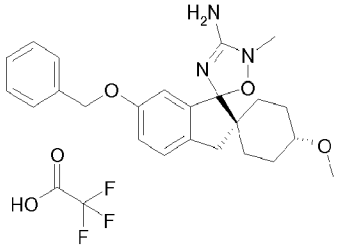
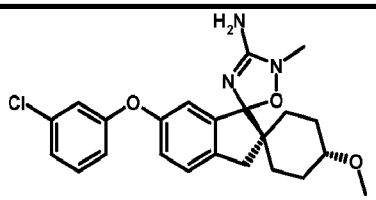
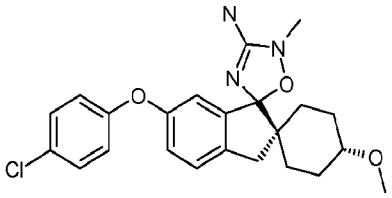
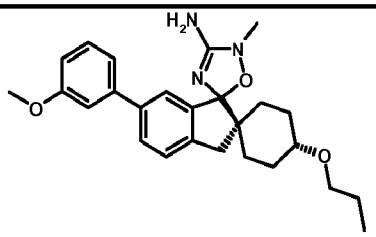
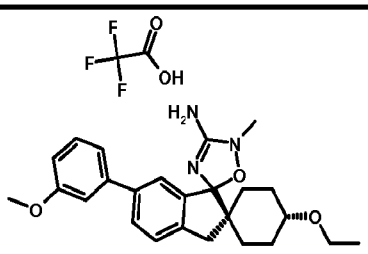


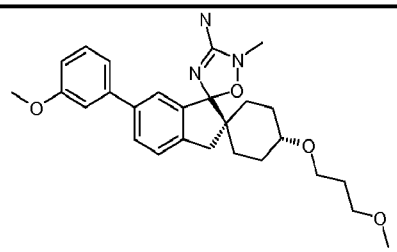
A mixture of N-methylhydroxylamine hydrochloride (43 mg, 0.51 mmol) in anhydrous EtOH (2 mL) was treated with sodium hydride (60 % in mineral oil, 18 mg, 0.46 mmol) and added to a mixture of Compound 504 Step7 (100 mg, 0.26 mmol) in anhydrous EtOH (2 mL). The mixture was stirred for 45 min at RT. Water was added and the mixture was extracted with EA. The solvents were evaporated and the residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to give the desired product Compound 504 (21 mg, 12%).

HPLC (Method: Microsorb 1s):

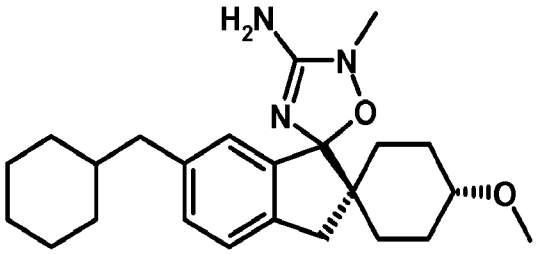
Rt: 1.33/1.39 min; Mass: $(M+H)^+ = 438$

By using the same synthetic strategy as for Compound 504 **step8** the following compounds were obtained:

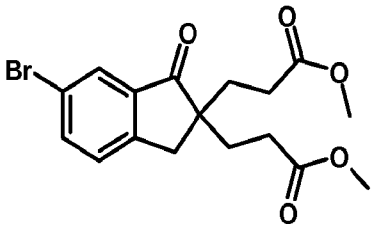
No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 516	**1.7.2**		**408**	**Microsorb 4s MeOH**	**2.82/ 3.08**
Compound 594	**32.3.2**		**428**	**Microsorb 4s MeOH**	**3.20**
Compound 595	32.3.3		428	Microsorb 4s MeOH	2.88/ 3.19
Compound 596	32.3.4		436	Microsorb 4s MeOH	3.05/ 3.29
Compound 597	**32.3.5**		**422**	**Microsorb 1s MeOH**	**1.42/ 1.50**

Compound 601	32.3.6		466	Microsorb 4s MeOH	2.94/ 3.19

B. Compound 488



Compound 488 Step1. 3-[6-Bromo-2-(2-methoxycarbonyl-ethyl)-1-oxo-indan-2-yl]-propionic acid methyl ester

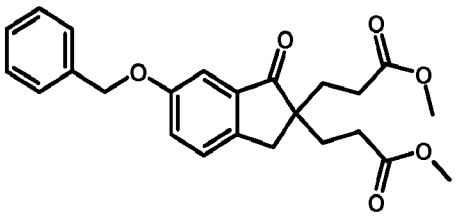


To 6-bromo-1-indanone (25 g, 0.12 mol) in dioxane (150 mL) was added Triton B (2.48 mL, 6.3 mmol) and hydroquinone (5 mg, 0.05 mmol). After stirring the mixture for 10 min at 50°C methylacrylate (21.5 mL, 0.24 mol) in 50 mLdioxane was added. The mixture was stirred for 4 h at 50°C and 14 h at RT. Then 2 mLmethylacrylate was added and the reaction was stirred for 1 h at 50°C. The reaction mixture was poured onto water, extracted with EA and the solvents were evaporated. The residue was purified by MPLC (340 g silicagel, gradient: CH/EA 100:0 to 50:50) to give 3-[6-Bromo-2-(2-methoxycarbonyl-ethyl)-1-oxo-indan-2-yl]-propionic acid methyl ester (38 g, 84%).

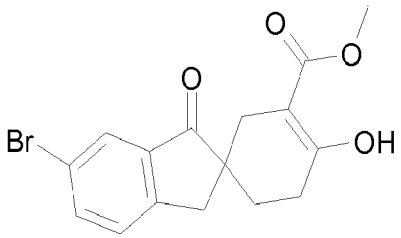
HPLC (Method: Microsorb 4s MeOH) ,

Rt: 3.18 min; Mass: $(M+H)^+$ = 383/385 (Br)

By using the same synthetic strategy as for compound 488 **step 1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
2.1.1	1.1.3		411	Microsorb 4s MeOH	3.36

Compound 488 Step2

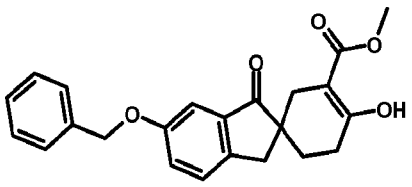


200 mL toluene which contained 2.5 g (108 mmol) of sodium were heated to reflux. Under an atmosphere of nitrogen 3-[6-Bromo-2-(2-methoxycarbonyl-ethyl)-1-oxo-indan-2-yl]-propionic acid methyl ester (compound 504 Step1) (38 g, 99.3 mmol) in 200 mLToluol were added. The reaction was RF for 14 h and 0.5g sodium was added. After 2.5h under reflux the mixture was cooled to RT and 0.5 M aqueous HCl (400 mL) was added. The aqueous layer was extracted with EA and the organic layer was evaporated. The residue was purified by MPLC (340 g silicagel, gradien CH/EA 100:0 to 70:30) to give Compound 488 Step2 (17 g, 49%).

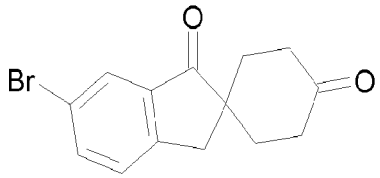
HPLC (Method: Microsorb 4s MeOH) ,

Rt: 3.54 min; Mass: $(M+H)^+$ = 351/353 (Br)

By using the same synthetic strategy as for Compound 488 **step 2** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
2.2.1	**2.1.1**		**379**	**Microsorb 4s MeOH**	**3.66**

Compound 488 Step3

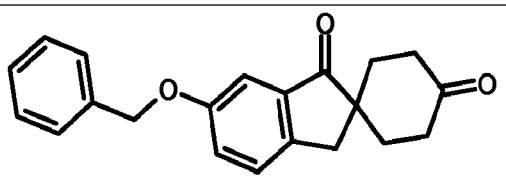


To Compound 488 Step2 (17.1 g, 48.7 mmol) in MeOH (170 mL) was added 1 M aqueous NaOH (200 mL, 200mmol). The mixture was stirred for 2 h at 120 °C. The reaction was cooled and the precipitate was filtered off, washed with water and MeOH and dried to give Compound 488 Step3 (12.6 g, 81%).

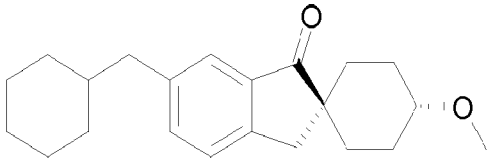
HPLC (Method: Microsorb 4s MeOH) ,

Rt: 2.98 min; Mass: $(M+H)^+$ = 293/395 (Br)

By using the same synthetic strategy as for compound 488 **step 3** the following compounds were obtained:

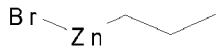
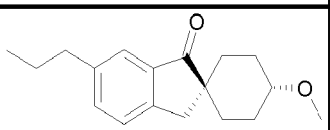
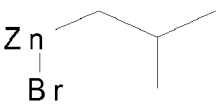
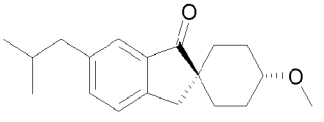
No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
2.3.1	**2.2.1**		**321**	**Microsorb 4s MeOH**	**3.23**

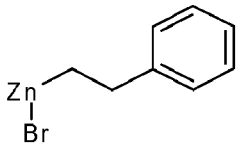
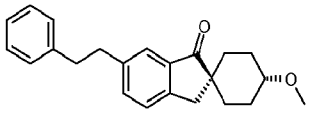
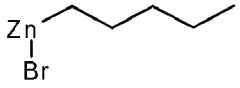
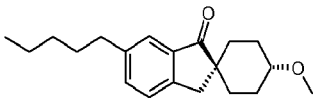
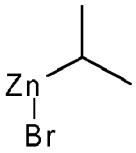
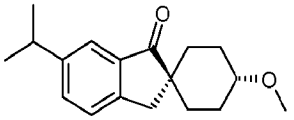
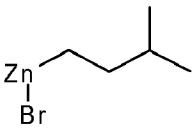
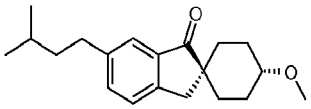
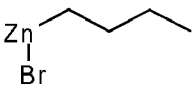
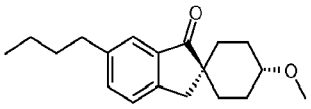
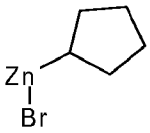
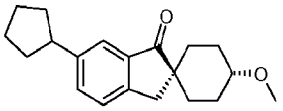
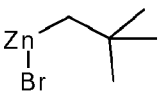
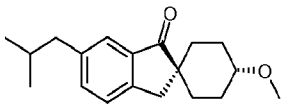
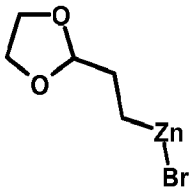
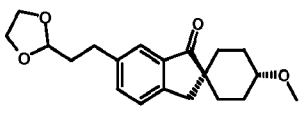
Compound 488 Step4



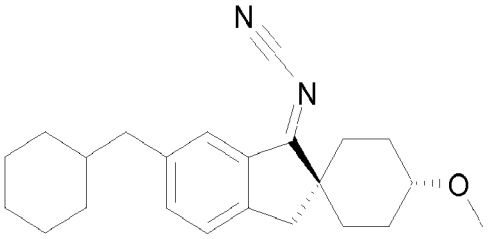
To compound **1.6.1** (300 mg, 0.97 mmol) in dioxane (12 mL) was added $PdCl_2$dppf (72 mg, 0.1 mmol) and (cyclohexyl)methyl zinc-bromide (9.6 mL, 4.8 mmol) under argon atmosphere. The mixture was stirred for 1.5 h at 50°C. Then the reaction was diluted with DCM and water was added. The layers was separated and the organic layer was washed with brine and aqueous ammoniumchloride solution. The organic layer was evaporated. The residue was purified by MPLC (50 g silicagel, gradient petrol PE/EA 100:0 to 70:30) to give Compound 488 Step4 (213 mg, 67%).
HPLC (Method: Microsorb 1s) ,
Rt: 1.99 min; Mass: $(M+H)^+$ = 327

By using the same synthetic strategy as for **Compound 488 step4** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt mint
2.4.1			272	Microsorb 1s	1.65
2.4.2			287	Microsorb 1s	1.74

2.4.3			**335**	**Microsorb 1s**	**1.75**
2.4.4			**301**	**Microsorb 1s**	**1.88**
2.4.5			**273**	**Microsorb 1s**	**1.78/ 1.81**
2.4.6			**301**	**Microsorb 1s**	**1.84**
2.4.7			**287**	**Microsorb 1s**	**1.91**
2.4.8			**299**	**Microsorb 1s**	**1.93**
2.4.9			**325**	**Microsorb 1s**	**1.97**
2.4.10			**331**	**Microsorb 7s**	**1.38**

Compound 488 Step5

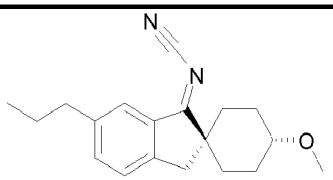
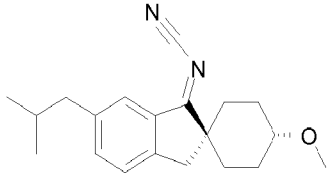


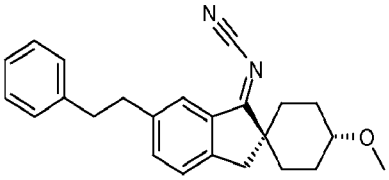
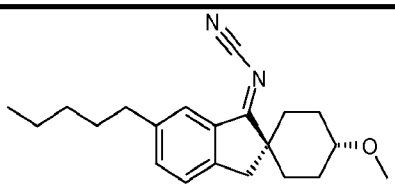
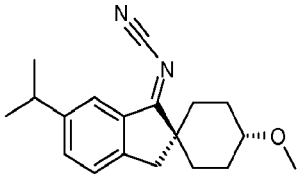
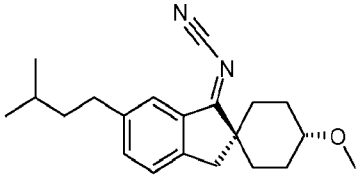
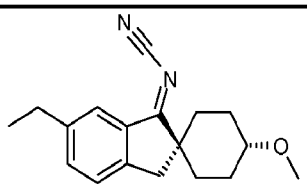
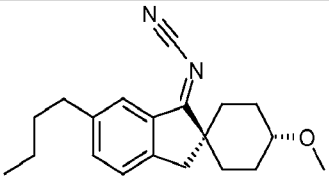
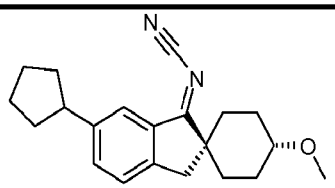
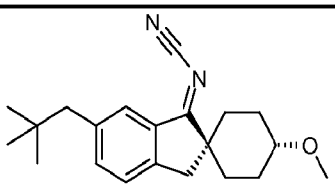
A mixture of Compound 488 Step4 (210 mg, 0.64 mmol) and titanium-(IV)chloride (1N in DCM) (1.29 mL, 1.29 mmol) was stirred for 1 h at RT. Then 1,3-bis(trimethylsiyl)carbodiimide (0.48 mL, 2.07 mmol) was added. The reaction was stirred for 2 h at RT. The reaction was quenched with water and extracted with DCM. The organic layer was evaporated and the crude product Compound 488 Step5 was taken to the next step.

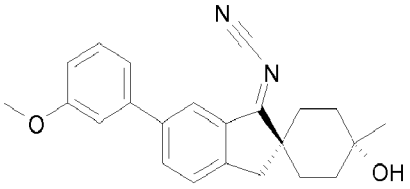
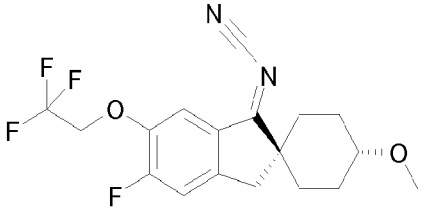
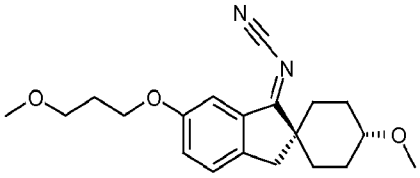
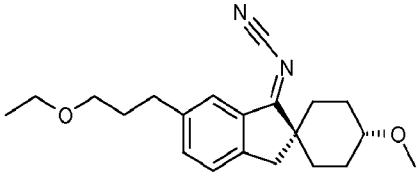
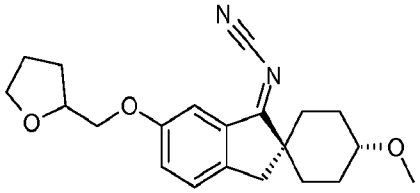
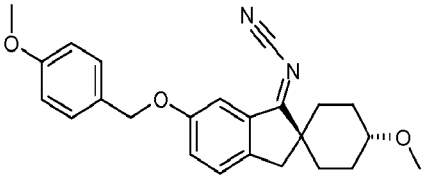
HPLC (Method: Microsorb 1s)

Rt: 1.99 min; Mass: $(M+H)^+ = 351$

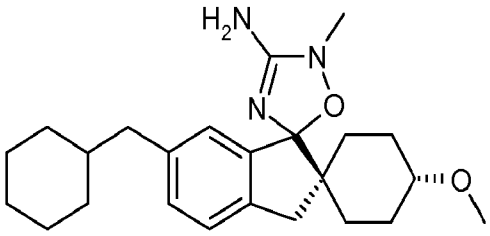
By using the same synthetic strategy as for **Compound 488 step5** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
2.5.1	2.4.1		297	Microsorb 1s	1.70
2.5.2	2.4.2		311	Microsorb 1s	1.77

2.5.3	2.4.3		359	Microsorb 1s	1.78
2.5.4	2.4.4		325	Microsorb 1s	1.89
2.5.5	2.4.5		297	Microsorb 1s	1.81/1.83
2.5.6	2.4.6		325	Microsorb 1s	1.87
2.5.7	Compound 502 step1		283	Microsorb 1s	1.72
2.5.8	2.4.7		311	Microsorb 1s	1.92
2.5.9	2.4.8		323	Microsorb 1s	1.97
2.5.10	2.4.9		325	Microsorb 1s	1.97

2.5.11	Compound 517 Step2		361	Microsorb 1s	1.54
2.5.12	Compound 518 Step3		371	Microsorb 1s	1.66
2.5.13	Compound 602 Step1		343	Microsorb 1s	1.60
2.5.14	Compound 603 Step2		341	Microsorb 1s	1.68
2.5.15	Compound 602 Step2		355	Microsorb 1s	1.55
2.5.16	Compound 504 Step6		391	Microsorb 1s	1.67

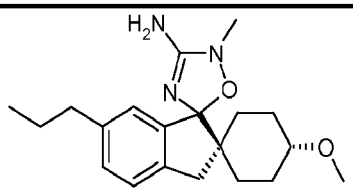
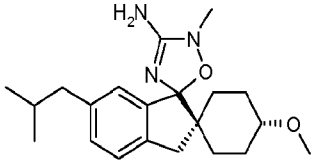
Compound 488 step6



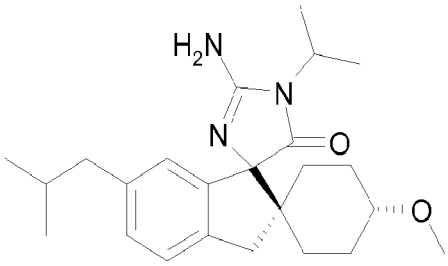
A mixture of N-methylhydroxylamine (35 mg, 0.42mmol) in EtOH (2 mL) was treated with sodium hydride (60 % in Mineral Oil) (16.8 mg, 0.42 mmol) and added to a mixture of Compound 488 Step5 (73 mg, 0.21 mmol) in EtOH (2 mL). The reaction was stirred for 1 h at RT.Water was added and the mixture was extracted with EA. The solvents were evaporated and the residue was purified by MPLC (10 g Silicagel, CH/EE 100:0 to 50:50) to give the desired product compound 488 (43 mg, 52%). (Method: Microsorb 7s MeOH)

Rt: 1.52/1.65 min; Mass: $(M+H)^+ = 398$

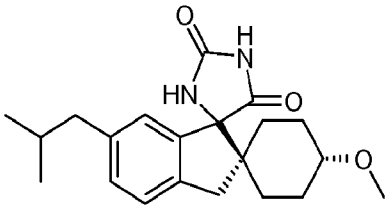
By using the same synthetic strategy as for compound 488 step6 the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 489	2.5.1		297	Microsorb 1s	1.27/ 1.36
Compound 490	2.5.2		297	Microsorb 1s	1.34/ 1.44

C. Compound 491



Compound 491 Step1

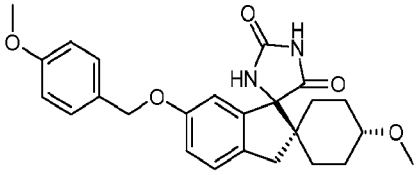
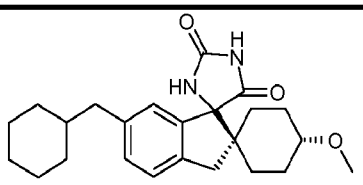
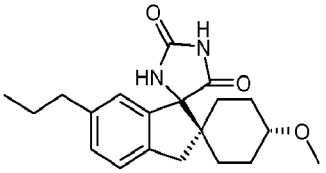


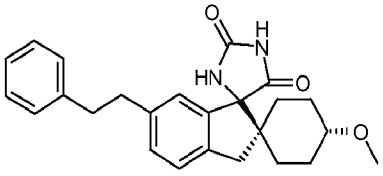
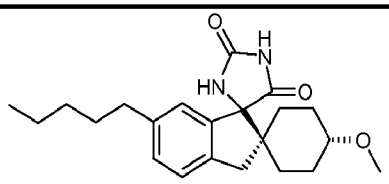
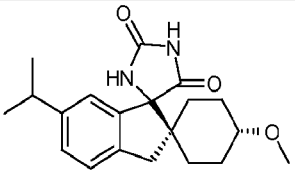
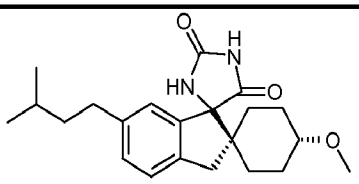
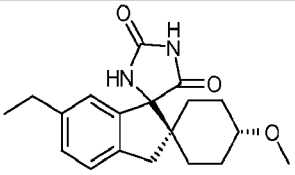
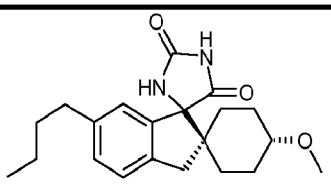
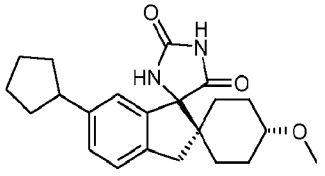
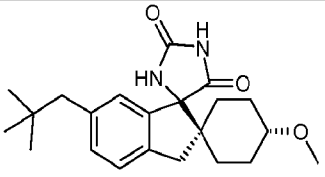
Compound **2.5.2** (155 mg, 0.5 mmol), potassium cyanide (65 mg, 1 mmol) and ammonium carbonate (336 mg, 3.5 mmol) in EtOH (1.5 mL) and water (1.5 mL) were stirred for 14 h at 75°C in a sealed tube. The mixture was cooled, diluted with water and extracted with EA. The organic layer was washed with brine and evaporated. The crude product Compound 491 Step1 was taken to the next step.

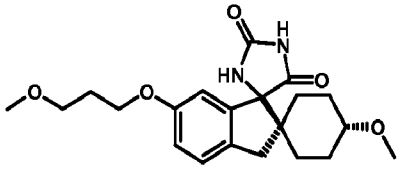
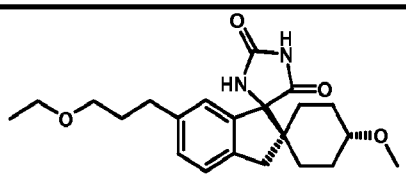
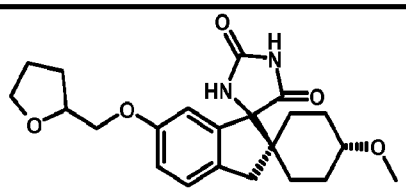
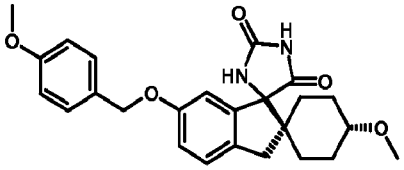
HPLC (Method: Microsorb 1s) ,

Rt: 1.38 min; Mass: $(M+H)^+ = 357$

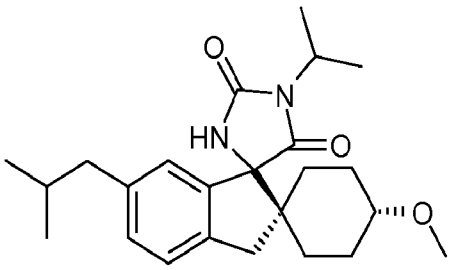
By using the same synthetic strategy as for **Compound 491 step1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
3.1.1	Compound 504 Step7		**437**	**Microsorb 1s**	**1.33**
3.1.2	Compound 488 Step5		**397**	**Microsorb 1s**	**1.66**
3.1.3	**2.5.1**		**343**	**Microsorb 1s**	**1.30**

3.1.4	2.5.3		405	Microsorb 1s	1.44
3.1.5	2.5.4		371	Microsorb 1s	1.58
3.1.6	2.5.5		343	Microsorb 1s	1.34/ 1.37
3.1.7	2.5.6		371	Microsorb 1s	1.55
3.1.8	2.5.7		329	Microsorb 1s	1.27
3.1.9	2.5.8		357	Microsorb 1s	1.47
3.1.10	2.5.9		410	Microsorb 1s	1.47
3.1.11	2.5.10		371	Microsorb 1s	1.51

3.1.12	**2.5.13**		**389**	**Microsorb 1s**	**1.19**
3.1.13	**2.5.14**		**387**	**Microsorb 1s**	**1.28**
3.1.14	**2.5.15**		**401**	**Microsorb 1s**	**1.15**
3.1.15	**2.5.16**		**437**	**Microsorb 1s**	**1.42**

Compound 491 Step2

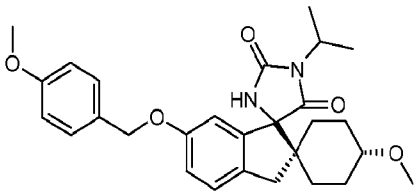
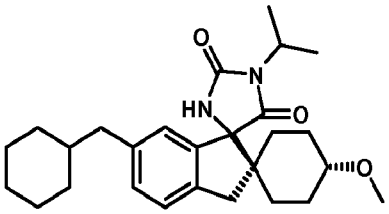
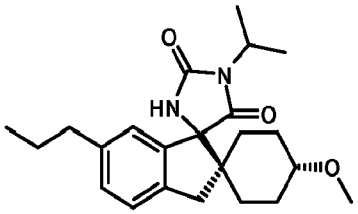
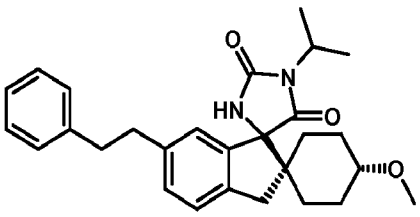
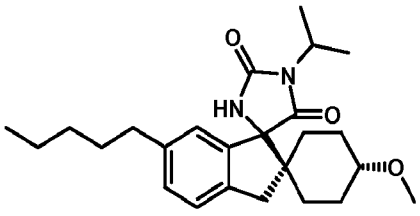


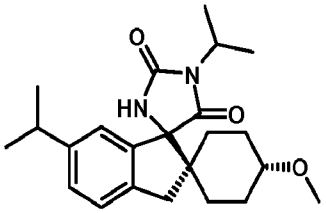
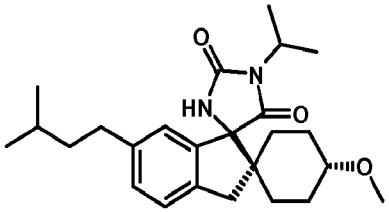
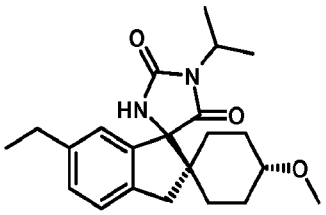
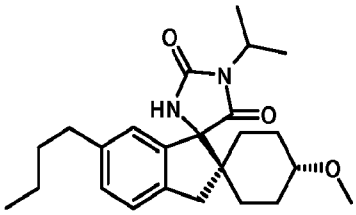
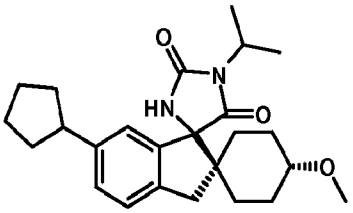
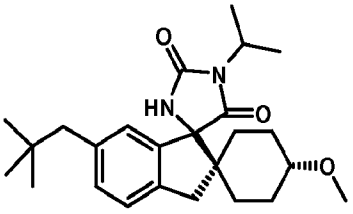
Compound 491 Step1 (155 mg, 0.3 mmol, purity: 72%), 2-iodopropane (35 µl, 0.35 mmol) and K_2CO_3 (49 mg, 0.35 mmol) in DMF (3 mL) were stirred for 14 h at RT. Then 0.02 mL2-iodopropane was added and the mixture was stirred for 3 h. The reaction was diluted with DCM and extracted with water. The organic layer was evaporated. The residue was purified by MPLC (10 g silicagel, gradient CH/EA 100:0 to 70:30) to give Compound 491 Step2 (89 mg, 71%).

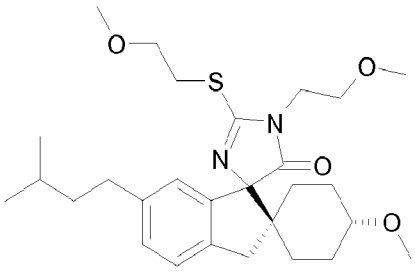
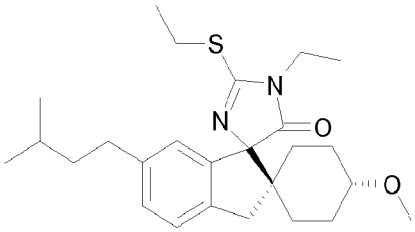
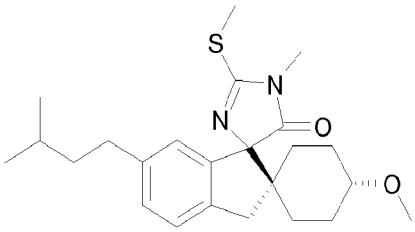
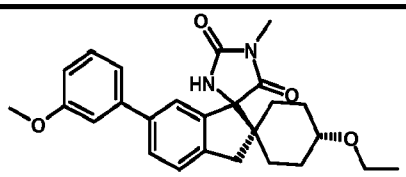
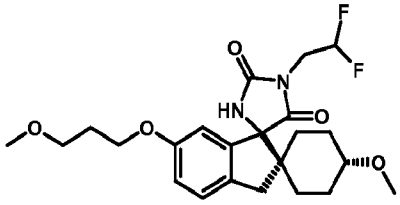
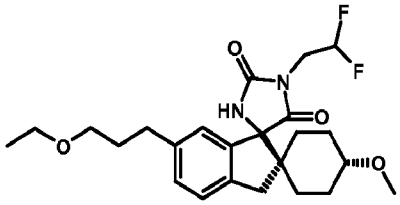
HPLC (Method: Microsorb 1s) ,

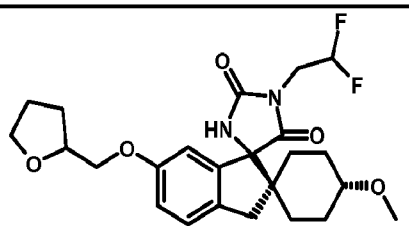
Rt: 1.64 min; Mass: $(M+H)^+$ = 399

By using the same synthetic strategy as for **Compound 491 step2** the following compounds were obtained:

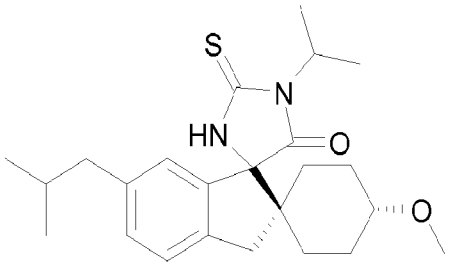
No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
3.2.1	3.1.1		479	Microsorb 1s	1.54
3.2.2	3.1.2		439	Microsorb 1s	1.99
3.2.3	3.1.3		385	Microsorb 1s	1.57
3.2.4	3.1.4		447	Microsorb 1s	1.80
3.2.5	3.1.5		413	Microsorb 1s	1.88

3.2.6	3.1.6		385	Microsorb 1s	1.66/ 1.68
3.2.7	3.1.7		429	Microsorb 1s	2.03
3.2.8	3.1.8		371	Microsorb 1s	1.59
3.2.9	3.1.9		399	Microsorb 1s	1.77
3.2.10	3.1.10		411	Microsorb 1s	1.77
3.2.11	3.1.11		413	Microsorb 1s	1.79

3.2.12	**3.3.15**			**503**	**Microsorb 1s**	**1.93**
3.2.13	**3.3.15**			**443**	**Microsorb 1s**	**2.08**
3.2.14	**3.3.15**			**443**	**Microsorb 1s**	**1.72/ 1.83**
3.2.15	**32.4.1**			**435**	**Microsorb 1s**	**1.56**
3.2.16	3.1.12			**453**	**Microsorb 7s**	**1.30**
3.2.17	**3.1.13**			**451**	**Microsorb 1s**	**1.50**

3.2.18	3.1.14			465	Microsorb 7s	1.28

Compound 491 Step3



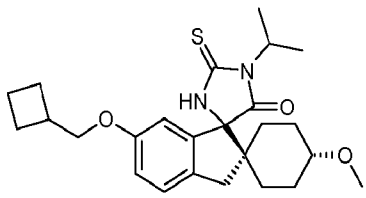
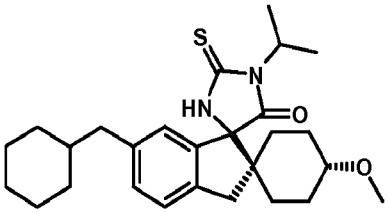
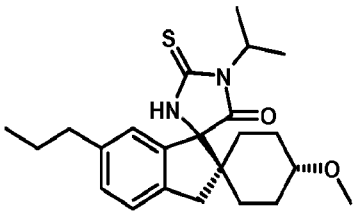
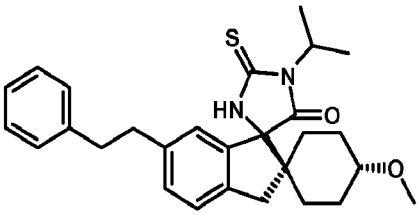
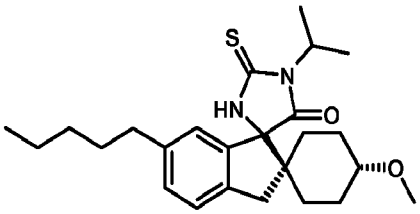
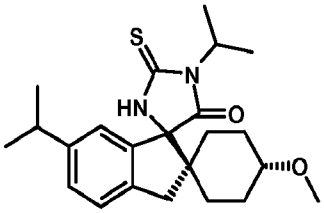
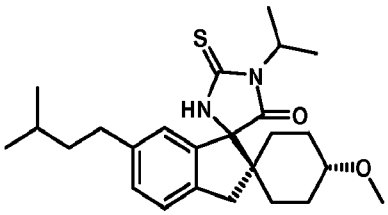
Compound 491 Step2 (88 mg, 0.22 mmol) and 2,4-bis-(4-methoxy-phenyl)-[1,3,2,4]dithiadiphosphetane 2,4-disulfide (178.6 mg, 0.44 mmol) in dioxane (4 mL) were stirred for 1 h at 130°C in the microwave. Then additional (178.6 mg, 0.44 mmol) 2,4-bis-(4-methoxy-phenyl)-[1,3,2,4]dithiadiphosphetane 2,4-disulfide was added and the mixture was stirred for 1 h under the same conditions. The solvent was evaporated. The residue purified by MPLC (25 g silicagel, gradient: CH/EA 100:0 to 60:40 to give Compound 491 Step 3 (66 mg, 72%).

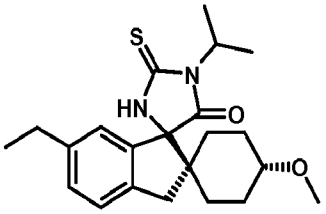
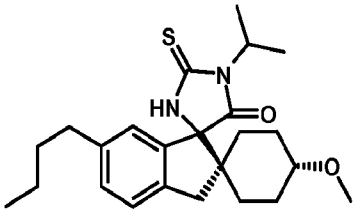
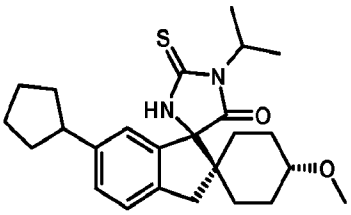
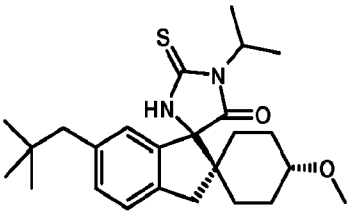
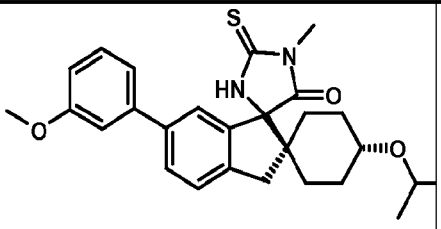
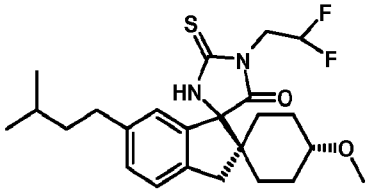
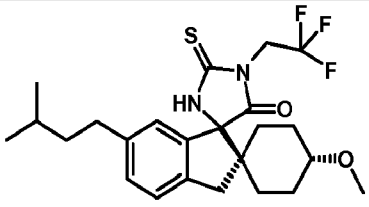
HPLC (Method: Microsorb 1s) ,

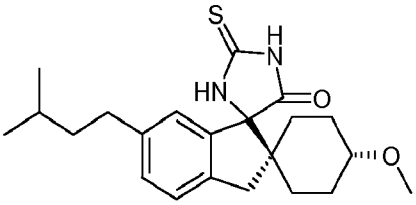
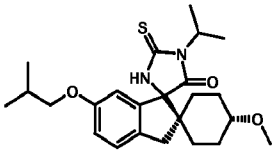
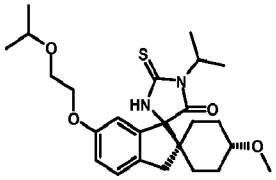
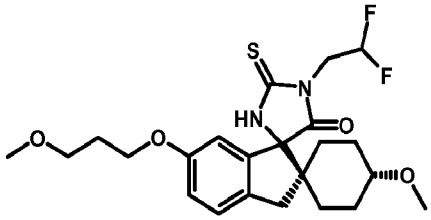
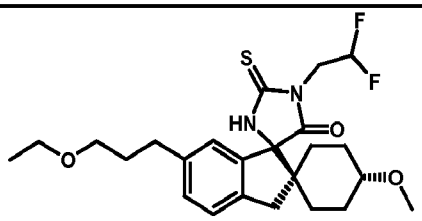
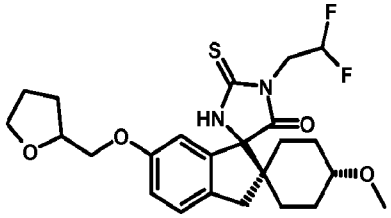
Rt: 1.81 min; Mass: $(M+H)^+ = 415$

By using the same synthetic strategy as for **compound 491 step3** the following compounds were obtained:

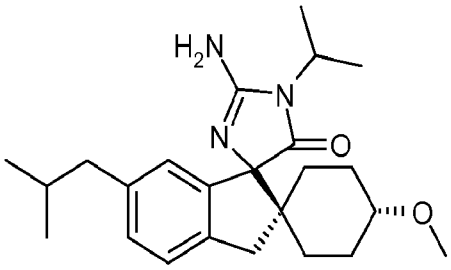
No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min

3.3.1	1.1.2		443	Microsorb 1s	1.94
3.3.2	3.2.2		445	Microsorb 1s	2.13
3.3.3	3.2.3		401	Microsorb 1s	1.74
3.3.4	3.2.4		463	Microsorb 1s	1.96
3.3.5	3.2.5		429	Microsorb 1s	2.05
3.3.6	3.2.6		401	Microsorb 1s	1.85/ 1.88
3.3.7	3.2.7		412	Microsorb 1s	1.59

3.3.8	3.2.8		387	Microsorb 1s	1.78
3.3.9	3.2.9		415	Microsorb 1s	1.92
3.3.10	3.2.10		427	Microsorb 1s	1.93
3.3.11	3.2.11		429	Microsorb 1s	1.97
3.3.12	Compound 510 Step5		465	Microsorb 1s	1.80
3.3.13	Compound 511 Step1		451	Microsorb 1s	1.87
3.3.14	Compound 512 Step1		469	Microsorb 1s	1.91

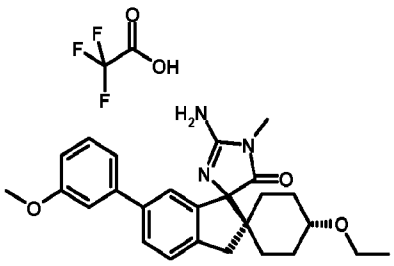
3.3.15	3.1.7		387	Microsorb 7s MeOH	1.51
Compound 599	Compound 599 Step2		431	Microsorb 1s	1.88
Compound 600	39.2.1		461	Microsorb 1s	1.76
Compound 602	3.2.16		469	Microsorb 1s	1.56
Compound 603	3.2.17		467	Microsorb 1s	1.64
Compound 604	3.2.18		481	Microsorb 1s	1.55

Compound 491 Step4

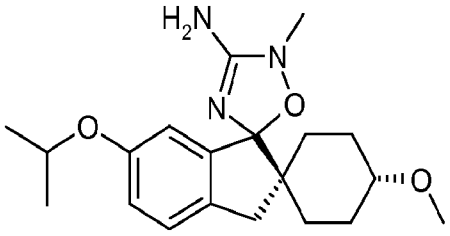


Compound 491 Step3 (65 mg, 0.16 mmol) and tert-butyl hydroperoxide (6 M in decane, 0.55 mL, 3.30 mmol) and 5 mL ammonia in methanol (7 M) were stirred for 3 d. The solvent was evaporated and the residue purified by MPLC (10 g silicagel, gradient: DCM/MeOH 100:0 to 90:10) to give Compound 491 Step4 (22 mg, 35%).
HPLC (Method: Microsorb 7s MeOH)
Rt: 1.55 min; Mass: $(M+H)^+$ = 398

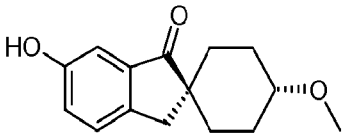
By using the same synthetic strategy as for **Compound 491 step 4** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 598	**32.5.2**		**434**	**Microsorb 1s**	**1.41**

D. Compound 505



Compound 505 Step1

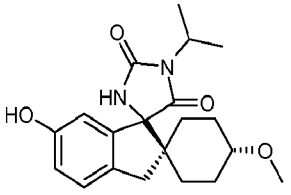


Compound 504 Step 6 (900 mg, 2.46 mmol) was added to a mixture of DCM (5 mL), TFA (5 mL), water (0.050 mL), and triisopropylsilane (1 mL). The mixture was stirred at RT for 5 min. The solvents were evaporated and the residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the desired product Compound 505 Step1 (300 mg, 50%) as an oil.

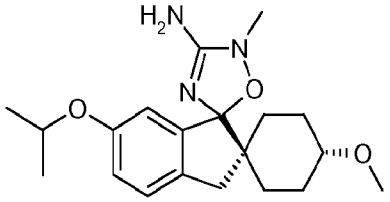
HPLC (Method: Microsorb 1s):

Rt: 1.12 min; Mass: $(M+H)^+ = 247$

By using the same synthetic strategy as for **compound 505 step1** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
4.1.1	**3.2.1**		**359**	**Microsorb 1s**	**1.25**

Compound 505 Step 2

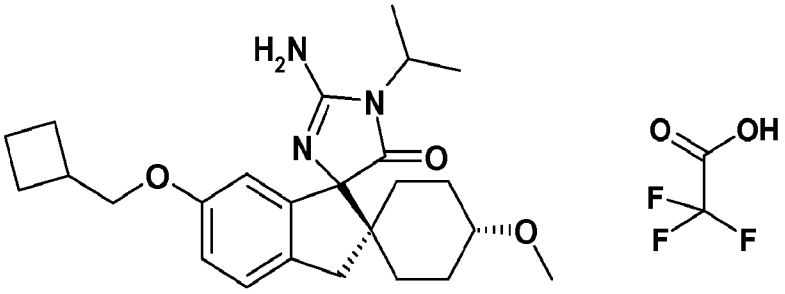


A mixture of N-methylhydroxylamin hydrochloride (77 mg, 0.92 mmol) in anhydrous EtOH (3 mL) was treated with sodium hydride (60 % in mineral oil, 34 mg, 0.86 mmol) and added to a mixture of compound **1.7.1** (120 mg) in anhydrous EtOH (3 mL). The mixture was stirred for 3 h min at RT. Water was added and the mixture was extracted with EA. The solvents were evaporated and the residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol). The base was liberated by dissolution in DCM and extraction with aqueous potassium carbonate solution. Separation of the organic layer and evaporation of the solvents yields the desired product Compound 505 (5 mg, 5%) as a white solid.

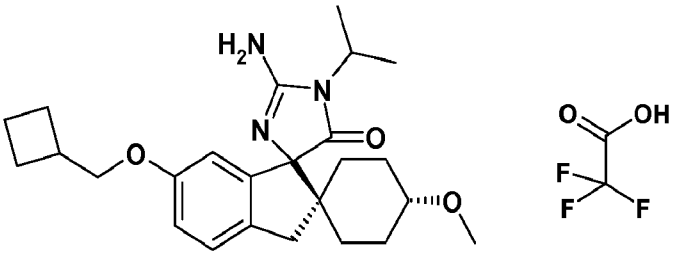
HPLC (Method: Microsorb 1s):

Rt: 1.27/1.34 min; Mass: $(M+H)^+ = 360$

E. Compound 506



Compound 506 Step1

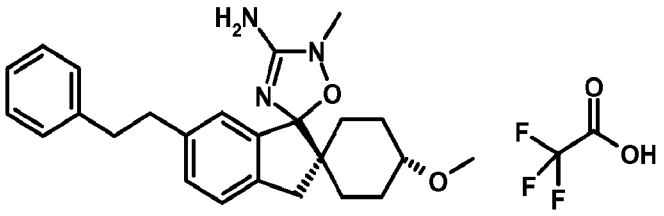


Compound **3.3.1** (260 mg) was mixed with ammonia (7 M in MeOH, 2 mL) and tert.-butylhydroperoxide (5.5 M in nonane, 0.49 mL, 2.70 mmol) and stirred for 48 h at RT. DCM and $Na_2S_2O_3$ (10% in water) were added. The organic layer was separated and the solvents were evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the desired product Compound 506 (25 mg) as a white solid.

HPLC (Method: Microsorb 1s)

Rt: 1.56 min; Mass: $(M+H)^+ = 426$

F. Compound 492



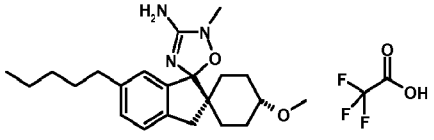
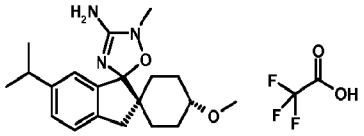
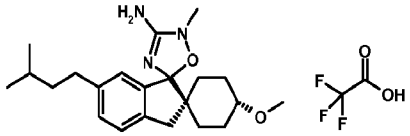
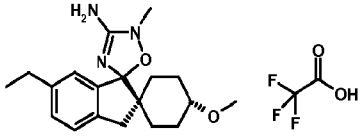
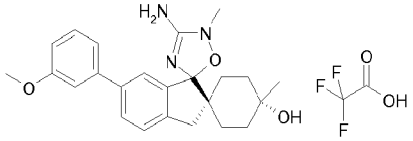
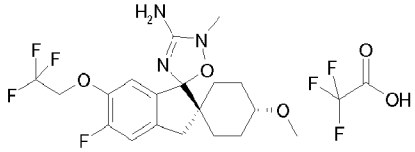
Compound 492 Step1

The product was obtained in analogy to compound 505 step 2 from compound **2.5.3**. The crude product was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the product as TFA salt compound 492 as a white solid (101 mg, 80 %).

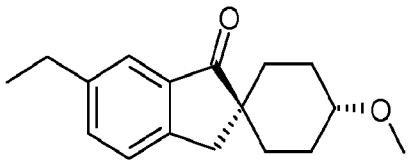
HPLC (Method: Microsorb 1s)

Rt: 1.38 / 1.47 min, Mass: $(M+H)^+ = 406$

By using the same synthetic strategy as for **compound 492 step1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 493	**2.5.4**		**372**	**Microsorb 1s**	**1.43/ 1.54**
Compound 497	**2.5.5**		**344**	**Microsorb 1s**	**1.31/ 1.39**
Compound 501	**2.5.6**		**372**	**Microsorb 1s**	**1.40/ 1.51**
Compound 502	**2.5.7**		**330**	**Microsorb 1s**	**1.23/ 1.32**
Compound 517	**2.5.11**		**408**	**Microsorb 1s**	**1.18/ 1.26**
Compound 518	**2.5.12**		**418**	**Microsorb 1s**	**1.28**

Compound 502 step1

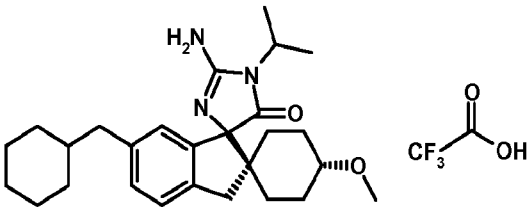


To compound **1.6.1** (300 mg, 0.97 mmol) and $PdCl_2dppf$ (70 mg, 0.096 mmol) in dioxane (10 mL) at 0°C diethyl-zinc in hexane (1 M, 2.00 mL, 2.00 mmol) was added under argon atmosphere. The mixture was allowed to warm to RT and stirred for 14 h. The mixture was purified by MPLC (25 g silicagel, gradient CH/EA 100:0 to 60:40) to give Compound 502 Step1 (197 mg, 79%).

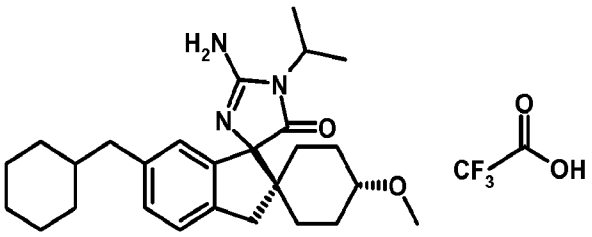
HPLC (Method: Microsorb 1s) ,

Rt: 1.69 min; Mass: $(M+H)^+ = 259$

G. Compound 495



Compound 495 Step1

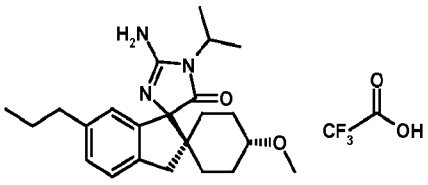
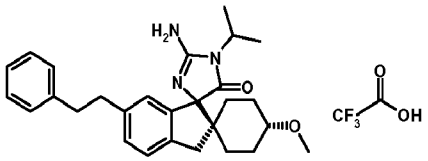
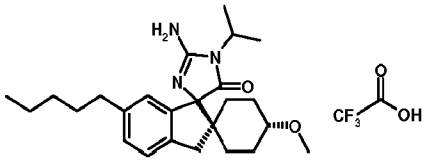
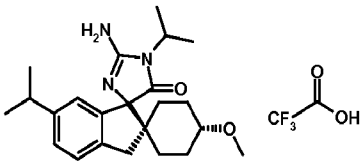
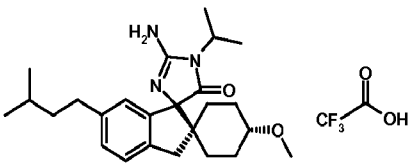
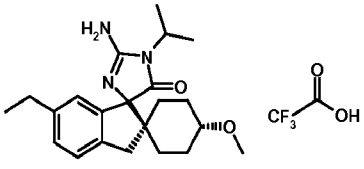
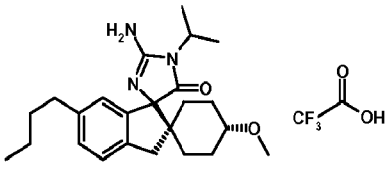


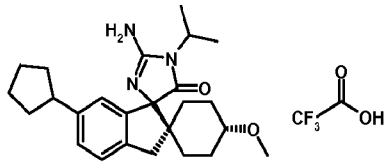
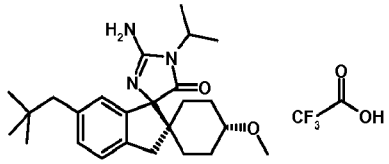
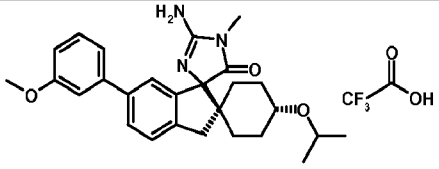
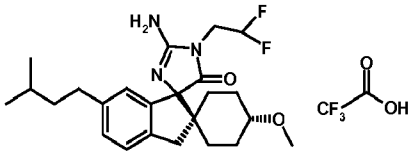
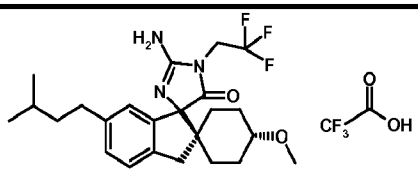
Compound **3.3.2** (50 mg, 0.11 mmol) was mixed with ammonia (7 M in MeOH, 3 mL) and tert.-butylhydroperoxide (6 M in decane, 0.38 mL, 2.28 mmol). The mixture was stirred for 3 d at RT. The solvents were evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the desired product **compound 495** (30 mg, 50 %) as a white solid.

HPLC (Method: Microsorb 1s)

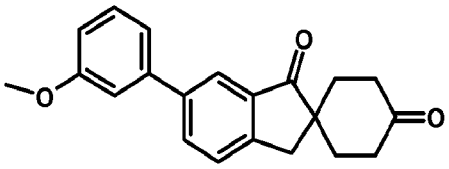
Rt: 1.71 min; Mass: $(M+H)^+ = 438$

By using the same synthetic strategy as for **compound 495 step1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 494	3.3.3		384	Microsorb 1s	1.43
Compound 496	3.3.4		446	Microsorb 1s	1.58
Compound 503	3.3.5		412	Microsorb 1s	1.62
Compound 499	3.3.6		384	Microsorb 7s	1.47
Compound 498	3.3.7		412	Microsorb 1s	1.59
Compound 500	3.3.8		370	Microsorb 1s	1.37
Compound 508	3.3.9		398	Microsorb 7s	1.52

Compound 507	**3.3.10**		**410**	**Microsorb 1s**	**1.54**
Compound 509	**3.3.11**		**412**	**Microsorb 7s**	**1.53**
Compound 510	**3.3.12**		**448**	**Microsorb 1s**	**1.43**
Compound 511	**3.3.13**		**434**	**Microsorb 7s**	**1.48**
Compound 512	**3.3.14**		**452**	**Microsorb 7s**	**1.53**

Compound 510 Step1



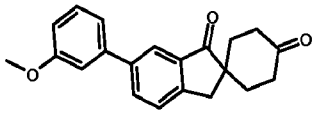
The reaction was split between 7 microwave vials (20 mL). To Compound 488 Step3 (4.99 g, 16.7 mmol) in 61 mL dioxane was added 3-methoxyphenyl boronic acid (3.05 g, 20.0 mmol), Na2CO3 solution (2 M in water, 25 mL, 51.8 mmol) and 1,1'-bis(diphenylphosphino)-ferrocene-dichloropalladium-(II). Argon was bubbled through the mixture for 1 min and the vials with the mixture were heated in the microwave to 140°C for 30 min. The content of the vials was pooled and the mixture concentrated. The residue was mixed with DCM, filtered over silica and the filtrate washed with aqueous saturated ammonium chloride solution and brine. The organic phase was dried

and evaporated. The crude product was purified by MPLC (340 g silicagel, gradient: CH/EA 1:0 to 1:1, 90 min). The product was dissolved in DCM and washed with aqueous NaOH solution. The organic layer was evaporated to yield the product Compound 510 Step1 (3.25 g, 61%)

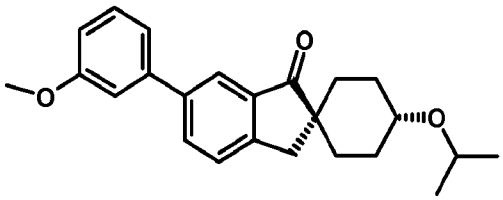
HPLC (Method: Microsorb 1s) ,

Rt: 1.51 min; Mass: $(M+H)^+$ = 321

By using the same synthetic strategy as for **Compound 510 step1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^-$	HPLC Method	Rt min
23.1.1	**Compound 488 step 3**		**321**	**Microsorb 4s MeOH**	**3.21**

Compound 510 Step2

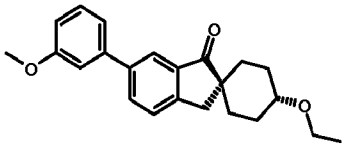


To a mixture of anhydrous iron-(III) chloride 15.2 mg (0.094 mmol) and Compound 510 Step1 (600 mg, 1.87 mmol) in ACN (20 mL) isopropoxy-trimethylsilane (1.66 mL, 9.36 mmol) and triethylsilane (1.05 mL, 6.56 mmol) were added successively at RT under an argon atmosphere. The mixture was stirred 14 h. 50 mg of iron-(III) chloride were added and the mixture was stirred for 24 h at RT. The mixture was diluted with phosphate buffer (pH 7) and extracted with DCM. The mixture was evaporated and the crude product purified by HPLC (C18, eluent A: water + 0.13 % TFA, eluent B: ACN). The first eluting diastereomer was collected. Freeze drying gave the product **Compound 510 Step2** as a white powder.

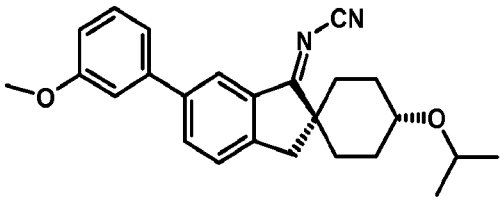
HPLC (Method: Microsorb 1s) ,

Rt: 1.95 min; Mass: $(M+H)^+$ = 365

By using the same synthetic strategy as for **Compound 510 step2** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* [M+H]+	HPLC Method	Rt min
23.2.1	**23.1.1**		**351**	**Microsorb 1s MeOH**	**1.88**

Compound 510 Step3

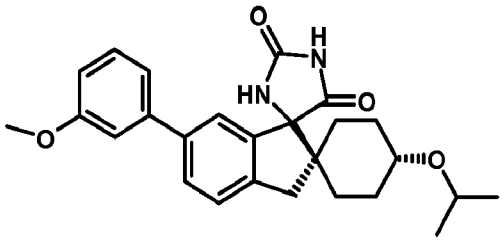


To **Compound 510 Step2** (300 mg, 0.82 mmol) in dry DCM (3 mL) titanium-(IV) chloride (1 N in DCM, 1.73 mL, 1.73 mmol) was added. The mixture was stirred for 45 min at RT. 1,3-bis(trimethylsilyl)carbodimid (0.67 mL, 2.88 mmol) was added and the mixture stirred for 2 h at RT. The mixture was diluted with water and extracted with DCM. The organic layer was evaporated to yield the product **Compound 510 Step3** as white solid (310 mg, 97 %.)

HPLC (Method: Microsorb 1s) ,

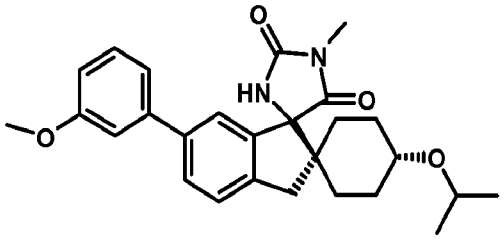
Rt: 1.96 min; Mass: $(M+H)^+$ = 389

Compound 510 Step4



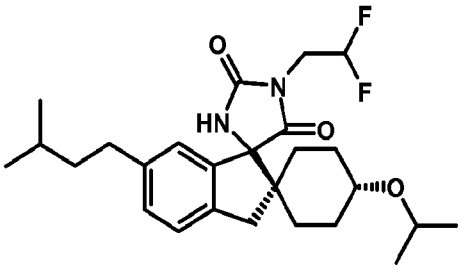
Compound 510 Step3 (247 mg, 0.64 mmol), potassium cyanide (82.7 mg, 1.27 mmol) and ammonium carbonate (428 mg, 4.45 mmol) in EtOH (1.0 mL) and water (1.0 mL) were stirred for 14 h at 75°C in a sealed tube. The mixture was cooled, diluted with water and extracted with EA. The organic layer was evaporated. The crude product was evaporated and purified by MPLC (25 g silicagel, gradient: DCM/MeOH 100:0 to 93:3). The product **Compound 510 Step4** was obtained as white solid (150 mg, 54%).
HPLC (Method: Microsorb 1s) ,
Rt: 1.51 min; Mass: $(M+H)^+$ = 335

Compound 510 Step5



Compound 510 Step4 (150 mg, 0.35 mmol), methyliodide (24 µl, 0.38 mmol) and K_2CO_3 (105 mg, 0.76 mmol) in ACN (5 mL) were mixed and stirred in the microwave for 20 min at 100°C. The reaction was diluted with DCM and water and the mixture extracted with DCM. The organic layer was evaporated. The was residue purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the desired product **Compound 510 Step5** (150 mg, 97%).
HPLC (Method: Microsorb 1s) ,
Rt: 1.63 min; Mass: $(M+H)^+$ = 449

Compound 511 Step1

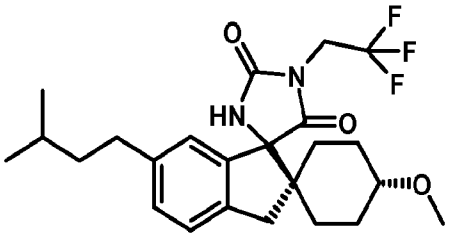


Compound 511 Step1 was prepared from **3.1.7** (87 %, 167 mg, 0.40 mmol) in analogy to **Compound 510 Step2**. Instead of 2-iodopropane 2-bromo-1,1-difluoroethane (63 mg, 0.44 mmol) was used to obtain 173 mg (95%) **Compound 511 Step1** as a colorless resin.

HPLC (Method: Microsorb 7s) ,

Rt: 1.57 min; Mass: $(M+H)^+$ = 435

Compound 512 Step1

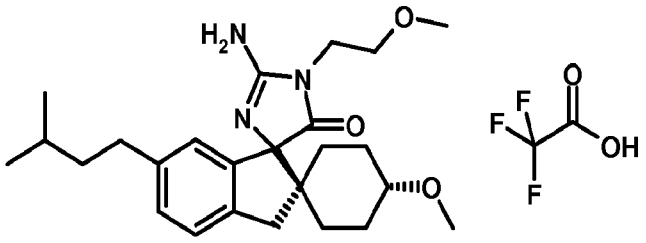


Compound 512 Step1 was prepared from **3.1.7** (87% 167 mg, 0.40 mmol) in analogy to **Compound 491 Step2**. Instead of 2-iodopropane 2,2,2-trifluoroethyltrifluoromethylsulfonate (63 µl, 0.44 mmol) was used to obtain 165 mg (93%) **Compound 512 Step1** as a colorless resin.

HPLC (Method: Microsorb 7s) ,

Rt: 1.61 min; Mass: $(M+H)^+$ = 453.

H. Compound 513



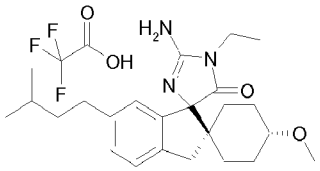
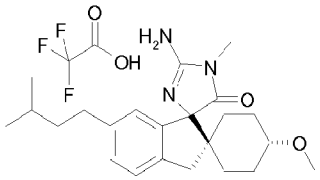
Compound 513 Step1

Product **3.2.12** (152 mg, 0.3 mmol) and ammonium iodide (350 mg, 2.41 mmol) in ammonia (2 M in EtOH, 6.0 mL, 17.3 mmol) were stirred for 2 h at 120°C in the microwave. The solvents were evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the product as TFA salt compound 513 as a white solid (98.8 mg, 60 %).

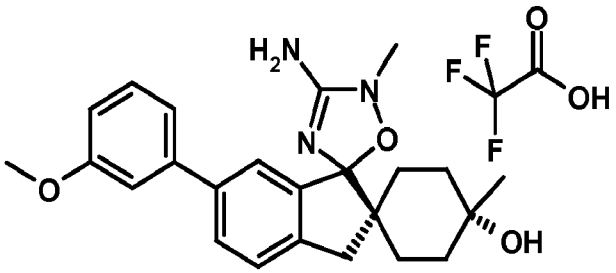
HPLC (Method: Microsorb 1s)

Rt: 1.52 min, Mass: $(M+H)^+ = 428$

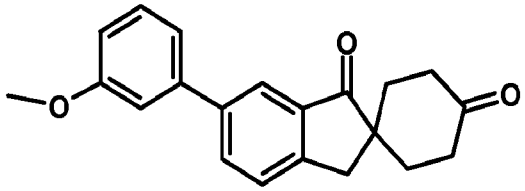
By using the same synthetic strategy as for compound 513 **step1** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 514	**3.2.13**		**398**	**Microsorb 7s MeOH**	**1.50**
Compound 515	**3.2.14**		**384**	**Microsorb 7s MeOH**	**1.48**

I. Compound 517



Compound 517 Step1

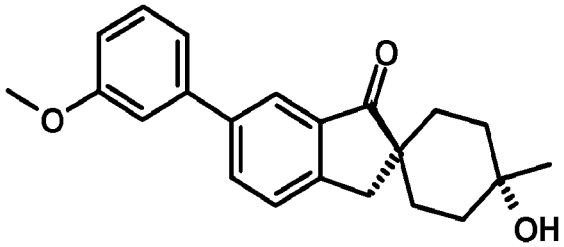


To Compound 488 Step3 (1.5 g, 5.12 mmol), 3-methoxyphenylboronic acid (930 mg, 6.12 mmol), $PdCl_2$dppf (200 mg, 0.27 mmol) and potassium carbonate (2M in water, 7.65 mL, 15.3 mmol) in dioxane (18 mL) and MeOH (6 mL) were stirred for 30 min at 140°C in the microwave. The solvents were evaporated. To the residue was added DCM. The organic layer was washed with ammoniumchloride solution and with brine. The DCM was evaporated. The crude product was purified by MPLC (100 g silicagel, gradient: CH/EA 100:0 to 50:50). The product **Compound 517 Step1** was obtained as a solid (1.39 g, 85%).

HPLC (Method: Microsorb 1s) ,

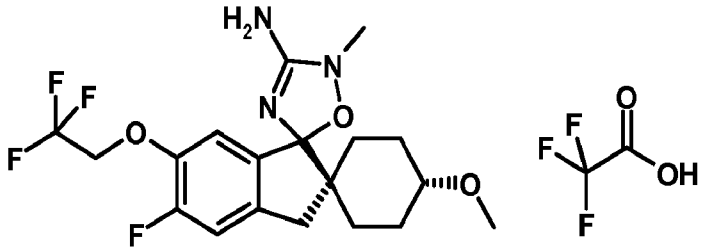
Rt: 1.53 min; Mass: $(M+H)^+$ = 321

Compound 517 Step2

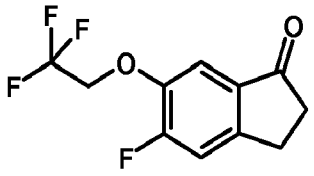


To Compound 517 Step1 (1.39 g, 4.34 mmol) in THF at -78°C was added methylmagnesium chloride (3 M, 1.6 mL, 4.8 mmol) in THF. After stirring for 1.5 h at -78°C the mixture was warmed to RT. The reaction was coolded down to 0°C and methylmagnesium chloride (1mL) was added. The reaction was quenched with ammoniumchloride solution and extracted with DCM. The organic layer was washed with brine and the solvent was evaporated. The crude product was purified by MPLC (120 g silicagel, gradient: DCM/MeOH 100:0 to 95:5) and then by MPLC (120 g silicagel, gradient: CH/EA 100:0 to 50:50). The first eluting stereoisomer was collected. The product **Compound 517 Step2** was obtained as a solid (1.39 g, 85%).
HPLC (Method: Microsorb 1s) ,
Rt: 1.48 min; Mass: $(M+H)^+$ = 337

J. Compound 518



Compound 518 Step1

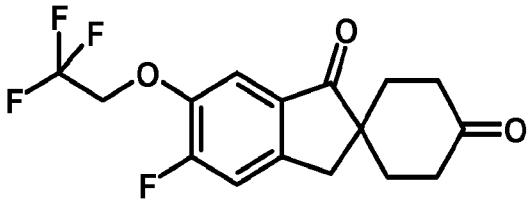


5-Fluoro-6-hydroxy-indan-1-one (7.50 g, 45.1 mmol) and K_2CO_3 (17.0 g, 123 mmol) in DMF (50 mL) were stirred for 10 min at 80°C. Then 2,2,2-trifluoroethyl-trifluoro-methanesulphonate (10.7 g, 46.1 mmol) was added and the mixture was stirred for 2 min at 80°C. Water was added and the mixture was extracted with EA. The organic layer separated and the solvents were evaporated to give Compound 518 Step1 (10.4 g, 93%).

HPLC (Method: Microsorb 1s) ,

Rt: 1.34 min; Mass: $(M+H)^+ = 249$

Compound 518 Step2

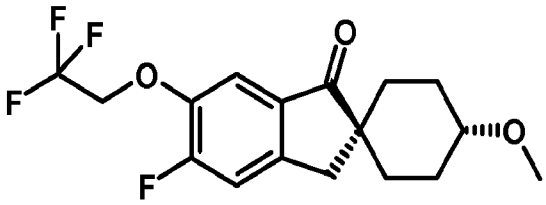


To compound **1.3.1** (28.5 g) in dioxane (80 mL) was added 4 M aqueous HCl (50 mL). The mixture was stirred for 14 h at 120°C. The solvents were evaporated. The was residue purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: methanol) to yield the desired product Compound 518 Step2 (4.8 g).

HPLC (Method: Microsorb 1s)

Rt: 1.49 min; Mass: $(M+H)^+ = 331$

Compound 518 Step3

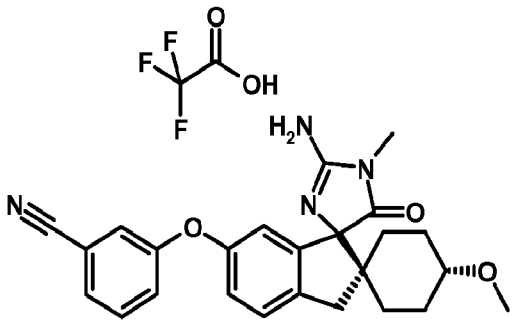


To compound 518 Step2 (1.30 g, 3.94 mmol) and ferric chloride (31.9 mg, 0.20 mmol) in anhydrous acetonitrile (50 mL) was added methoxytrimethylsilane (5.43 mL, 39.4 mmol) and triethylsilane (6.29 mL, 39.4 mmol). The mixture was stirred 10 min at RT. The solvents were evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield the desired product Compound 518 Step3 (610 mg, 45%) as the earlier eluting diastereomer.

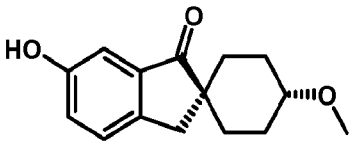
HPLC (Method: Microsorb 1s)

Rt: 1.64 min; Mass: $(M+H)^+ = 347$

K. Compound 592



Compound 592 Step1



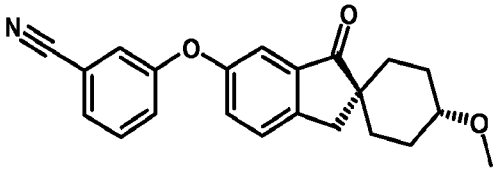
To 6'-bromo-4-methoxyspiro[cyclohexane-1,2'-inden]-1'(3'H)-one (1.00 g, 3.23 mmol) in dioxane/water (1:1, 10 mL) was added potasium hydroxid (1.05g, 18.7

mmol), tris(dibenzylideneacetone)dipalladium(0) (150 mg, 0.16 mmol) and di-tert-butyl-(2′,4′,6′-triisopropyl-3,4,5,6-tetramethyl-biphenyl-2-yl)-phosphane (280 mg, 0.58 mmol). The mixture was stirred in the microwave for 10 min at 140°C. The mixture was diluted with EA and 1 M HCl and extracted with EA. The organic layer was washed with brine, dried and evaporated. The residue was purified by MPLC (100 g siliciagel, gradient: CH/EA 100:0 to 40:60 over 70 min). The product **compound 592 Step 1** was obtained as a yellow resin (660 mg, 83%).

HPLC (Method: Microsorb 7s MeOH),

Rt: 1.16 min; Mass $(M+H)^+$ 247

Compound 592 Step2

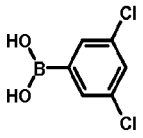
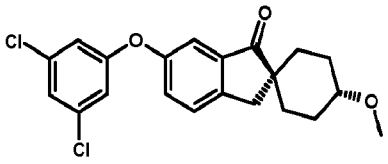
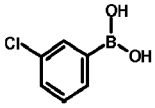
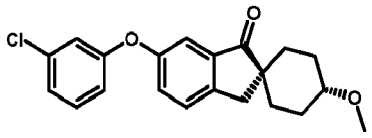
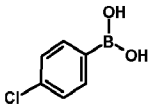
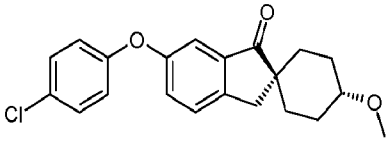


Compound 592 Step1 (275 mg, 1.12 mmol), 3-cyanophenylboronic acid (330 mg, 2.25 mmol, copper(II)-acetate (17.3 mg, 0.095 mmol) and molecular sieves (4 A, 1.0 g) in DCM (7 mL) were mixed, than pyridine (442 µl, 5.58 mmol) was added and argon was bubbled through the mixture. The mixture was stirred in a sealed tube for 14 h at RT. The tube was opened and 17 mg copper(II)-acetate was added. The vial was closed again and stirred 14 h at RT. Then it was opened again and stirred with a drying tube over night at RT. 270 mg 3-cyanophenyl boronic acid, 17 mg copper(II)-acetate and 440 µL pyridine were added and the mixture stirred at RT for 3 days. The precipitate was separated, the filtrate was diluted with DCM, saturated $NaHCO_3$-solution and brine. The organic layer was separated and the solvent was evaporated. The crude product was pyrified by MPLC (25 g siliciagel, gradient: CH/EA 100:0 to 50:50 over 50 min) to give **Compound 592 Step 2** (197 mg, 51%) as a white solid.

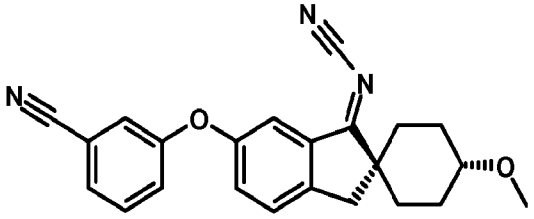
HPLC (Method: Microsorb 1s),

Rt: 1.65 min; Mass $(M+H)^+$ 348

By using the same synthetic strategy as for **Compound 592 step 2** the following compounds were obtained:

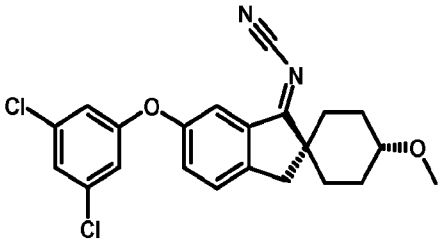
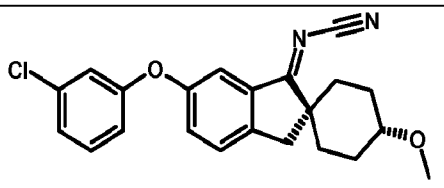
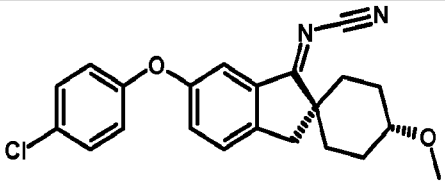
No.	Starting material 1	Starting material 2	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
32.2.1	Compound 592 Step 1			391	Microsorb 1s	2.04
32.2.2	Compound 594 Step 1			357	Microsorb 4s MeOH	3.56
32.2.3	Compound 595 Step 1			357	Microsorb 4s MeOH	3.53

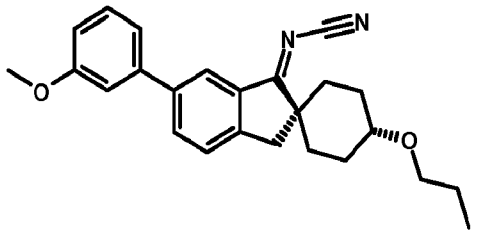
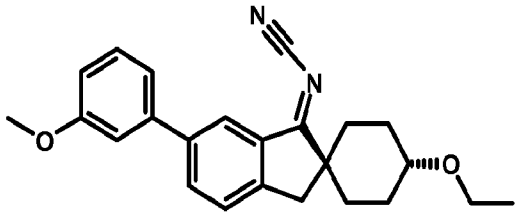
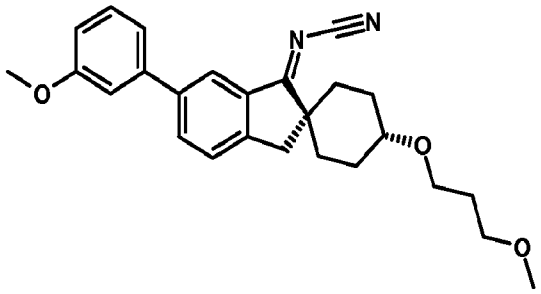
Compound 592 Step 3



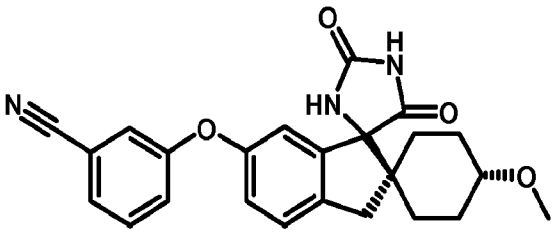
To **compound 592 Step 2** (195 mg, 0.561 mmol) in DCM (anhydrous, 12 mL) titanium(IV)-chloride (1 N in dioxane, 1.11 mL, 1.11 mmol) was added and the mixture stirred at RT for 1 h. Then 1,3-bis(trimethylsilyl)carbodiimde (418 µl, 1.80 mmol) was added and mixture stirred at RT for 3 h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was separated and the solvent was evaporated to give **compound 592 Step** 3 (239 mg, purity 85%, 97%) as a resin.
HPLC (Method: Microsorb 1s),
Rt: 1.67 min; Mass $(M+H)^+$ 372

By using the same synthetic strategy as for **compound 592 step 3** the following compounds were obtained:

No.	Starting material 1	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
32.3.1	32.2.1		415/417	Microsorb 1s	2.01
32.3.2	32.2.2		381	Microsorb 4s MeOH	3.56
32.3.3	32.2.3		381	Microsorb 4s MeOH	3.52/3.67

32.3.4	**Compound 597 step 1**		**389**	**Microsorb 4s MeOH**	**3.71**
32.3.5	**23.2.1**		**375**	**Microsorb 1s MeOH**	**1.88**
32.3.6	**36.1.1**		**419**	**Microsorb 1s MeOH**	**3.58**

Compound 592 Step 4

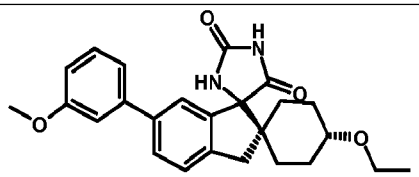


Compound 592 Step 3 (188 mg, 0.506 mmol), potassium cyanide (66 mg, 1.01 mmol) and ammonium carbonate (500 mg, 5.20 mmol) in EtOH (1.5 mL) and water (1.5 mL) were mixed and stirred for 14 h at 75°C. The mixture was cooled, diluted with water and EA. The mixture extracted with EA. The organic layer was washed with brine, dried and evaporated to give **compound 592 Step 4** as a withe solid of 90% purity (164 mg, 70%).

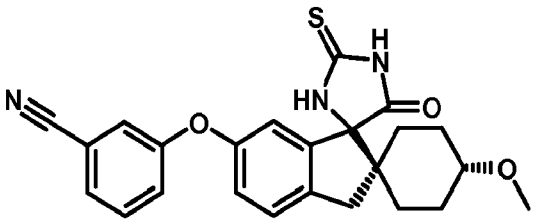
HPLC (Method: Microsorb 1s),

Rt: 1.34 min; Mass: $(M+H)^+ = 418$

By using the same synthetic strategy as for **compound 592 step 4** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
32.4.1	**32.3.5**		**421**	**Microsorb 1s**	**1.45**

Compound 592 Step 5

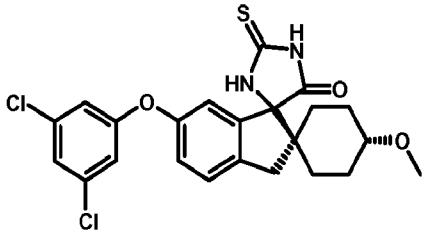
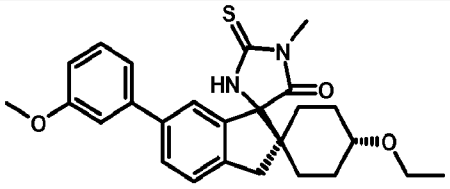


To **compound 592-Step 4** (164 mg, purity 90%, 0.35 mmol) in toluene (anhydrous, 10 mL) 2,4-bis-(4-methoxy-phenyl)-[1,3,2,4]dithiadiphosphetane 2,4-disulfide (145 mg,0.36 mmol) was added and nitrogen was bubbled trough the mixture. Then the reaction was stirred for 14 h at 125°C. The solvent was evaporated. The residue was purified by MPLC (25 g silicagel, gradient: CH/EA 100:0 to 50:50 over 50 min) to give **compound 592-Step 5** (107 mg, 71%) as a yellow resin.

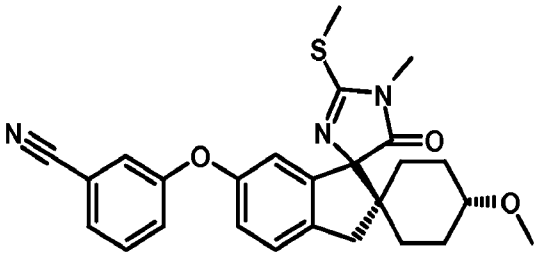
HPLC (Method: Microsorb 1s),

Rt: 1.45 min; Mass: $(M+H)^+ = 434$

By using the same synthetic strategy as for **compound 592 step 5** the following compounds were obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
32.5.1	Compound 593 Step 1		477/479	Microsorb 1s	1.70
32.5.2	3.2.15		451	Microsorb 1s	1.73

Compound 592 Step 6

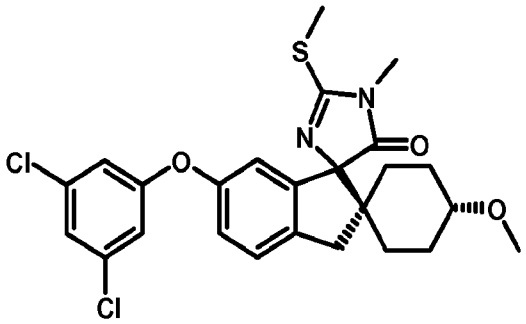


Compound 592 Step 5 (107 mg, 0.25 mmol), methyliodide (62 µl, 1.0 mmol) and K_2CO_3 (160 mg, 1.16 mmol) in ACN (anhydrous, 3 mL) were mixed and stirred in the microwave first for 20 min at 60°C then 20 min at 100°C. The reaction was diluted with DCM and water and the mixture extracted with DCM. The organic layer was evaporated to yield the desired product **compound 592 Step 6** (100 mg, purity 88%, 77%) as a colorless resin.

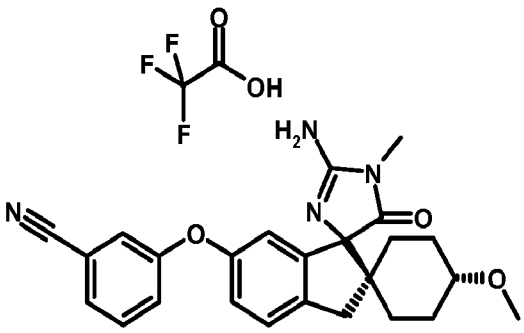
HPLC (Method: Microsorb 1s),

Rt: 1.61 min; Mass: $(M+H)^+ = 462$

By using the same synthetic strategy as for **compound 592 step 6** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
32.6.1	**32.5.1**		**505/507**	**Microsorb 1s**	**1.98**

Compound 592 Step 7

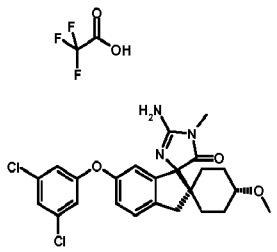


Compound 592 Step 6 (100 mg, 0.19 mmol) and ammonium iodide (221 mg, 1.53 mmol) in ammonia (2 M in EtOH, 4.0 mL, 8 mmol) were stirred for 3 h at 120°C in the microwave. The solvents were evaporated. The residue was purified by HPLC (eluent A: water + 0.13% TFA, eluent B: methanol) to yield the product as TFA salt **compound 592** as a white solid (69 mg, 67 %).

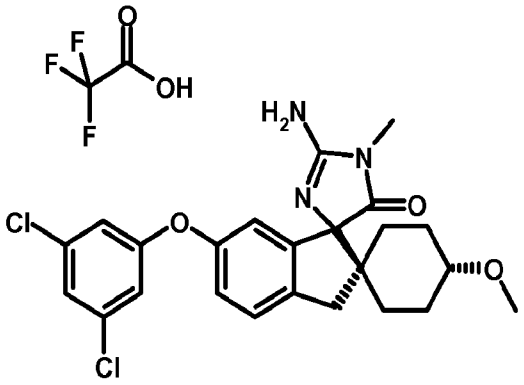
HPLC (Method: Microsorb 1s)

Rt: 1.30 min, Mass: $(M+H)^+ = 431$

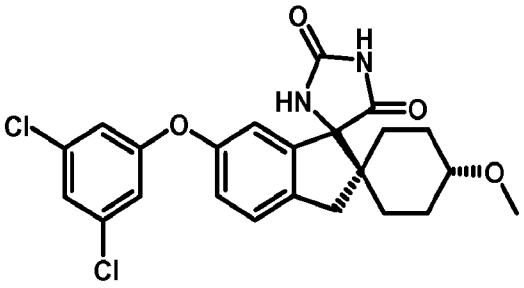
By using the same synthetic strategy as for **compound 592 step 7** the following compound was obtained:

No.	Starting material	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
Compound 593	32.6.1		474/476	Microsorb 1s MeOH	1.54

L. Compound 593



Compound 593 Step 1

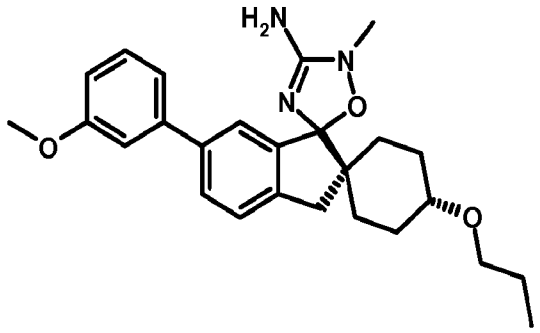


Product **32.3.1** (166 mg, 0.40 mmol), potassium cyanide (52 mg, 0.80 mmol) and ammoniumcarbonate (270 mg, 2.81 mmol) in EtOH (1.5 mL) and water (1.5 mL) were mixed and stirred for 14 h at 75°C. The mixture was cooled, diluted with water and EA. The mixture extracted with EA. The organic layer was washed with brine, dried and evaporated to give **compound 593 Step 1** as a withe solid of 80% purity (176 mg, 76%).

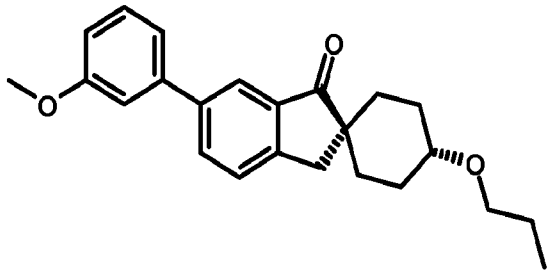
HPLC (Method: Microsorb 1s),

Rt: 1.60 min; Mass: $(M+H)^+$ = 461/46

M. Compound 596



Compound 596-Step 1



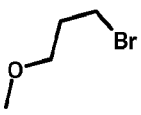
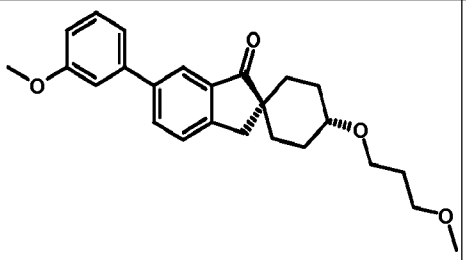
To product 1.5.3 (200 mg, 0.62 mmol) in THF was added NaH (112 mg, 2.79 mmol) and the mixture was stirred for 30 min at RT. Then 1-iodopropane (131.7 mg, 0.78 mmol) was added slowly at 0°C and the mixture was allowed to warm up and stirred for 14 h at RT. The mixture was quenched with water and the organic layer was

evaporated. The residue was extracted with DCM. The organic layer was washed with brine, dried and evaporated. The crude product was purified by HPLC (eluent A: water + 0.13% TFA, eluent B: methanol) to yield the product **compound 596** step 1 as a white solid (100 mg, 44 %).

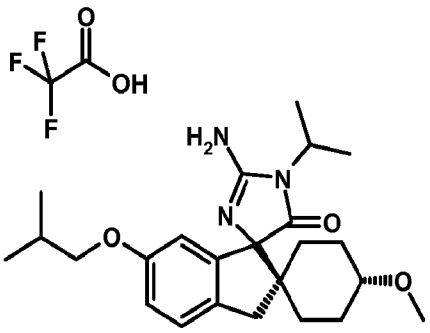
HPLC (Method: Microsorb 4s)

Rt: 3.66 min, Mass: $(M+H)^+ = 365$

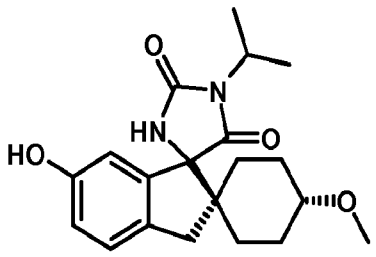
By using the same synthetic strategy as for **compound 596 step 1** the following compound was obtained:

No.	Starting material 1	Starting material 2	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
36.1.1	**1.5.3**			**395**	**Microsorb 4s**	**3.51**

N. Compound 599



Compound 599 Step1

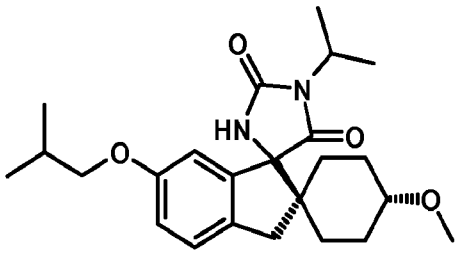


Product **3.2.1** (2.6 g, 5.43 mmol) and trifluoroacetic acid containing 5% water (5.0 mL) in DCM (5.0 mL) were mixed and stirred for 5 min at RT. The solvents were evaporated, the residue was stirred in MeOH, the precipitate was filtered off and the filtrate was evaporated to give **compound 599 Step1** as an orange oil (2.3 g, 80 % purity, 95 % yield).

HPLC (Method: Microsorb 1s)

Rt: 1.25 min, Mass: $(M+H)^+ = 359$

Compound 599 Step2

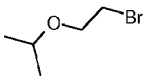
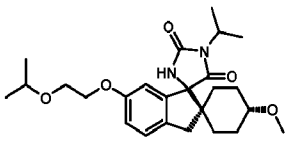


To **compound 599 Step1** (300 mg, 0.67 mmol) in DMF (anhydrous, 1.0 mL), 1-iodo-2-methylpropane (0.95 mL, 8.04 mmol) and sodiumhydride (320 mg, 60%, 8.035 mmol) were mixed together und stirred for 20 h at 35 °C. The mixture was diluted with 2 M HCl and extracted with DCM. The organic layer was separated and evaporated. The crude product was purified by MPLC (gradient DCM/MeOH 100:0 to 98:2 over 30 min) to give **compound 599 Step2** as an oil (300 mg, 85% purity, 92% yield).

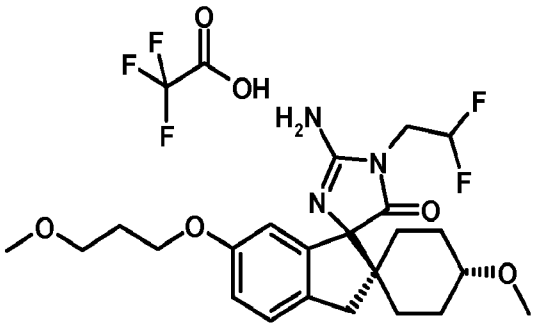
HPLC (Method: Microsorb 1s)

Rt: 1.69 min, Mass: $(M+H)^+ = 415$

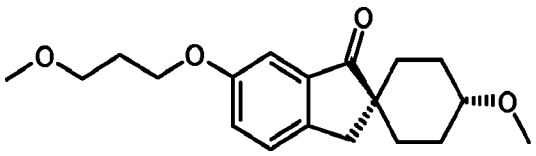
By using the same synthetic strategy as for **compound 599 step2** the following compound was obtained:

No.	Starting material 1	Starting material 2	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
39.2.1	Compound 599 Step1			445	Microsorb 1s	1.56

O. Compound 602



Compound 602 Step1



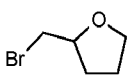
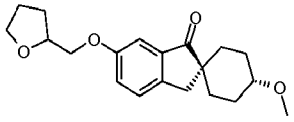
Product **compound 592 step1** (200 mg, 0.812 mmol), 1-bromo-3-methoxypropane (130 mg, 0.850 mmol) and potasium carbonate (340 mg, 2.46 mmol) in DMF (3 mL) were mixed and stirred for 14 h at 100°C. The mixture was diluted with

EA and extracted with water. The organic layer was separated and the solvent was evaporated to give **compound 602 Step1** as a yellow resin (234 mg, 91%).

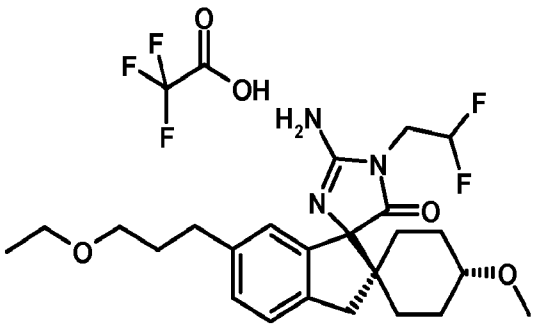
HPLC (Method: Microsorb 1s)

Rt: 1.52 min, Mass: $(M+H)^+ = 319$

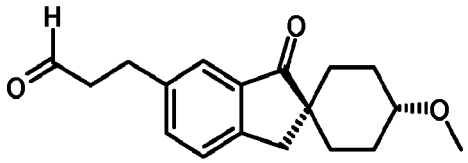
By using the same synthetic strategy as for **compound 602 step1** the following compound was obtained:

No.	Starting material 1	Starting material 2	Product	MS *m/z* $[M+H]^+$	HPLC Method	Rt min
42.1.1	Compound 592 step1			331	Microsorb 1s	1.49

P. Compound 603



Compound 603 Step1

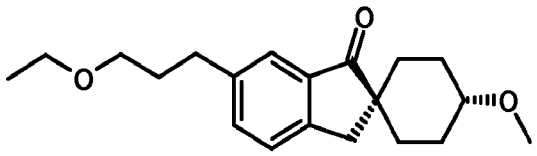


Product **2.4.10** (395 mg, 1.20 mmol), trifluoroacetic acid (4.0 mL) and water (50 µL, 2.78 mmol) in DCM (4.0 mL) were mixed and stirred for 14 h at RT. The mixture was diluted with DCM and quenched with saturated $NaHCO_3$ and NaOH (1 M). The organic layer was washed with water, dried and evaporated to give **compound 603 Step1** as a yellow solid (285 mg, 83%).

HPLC (Method: Microsorb 1s)

Rt: 1.31 min, Mass: $(M+H)^+ = 287$

Compound 603 Step2

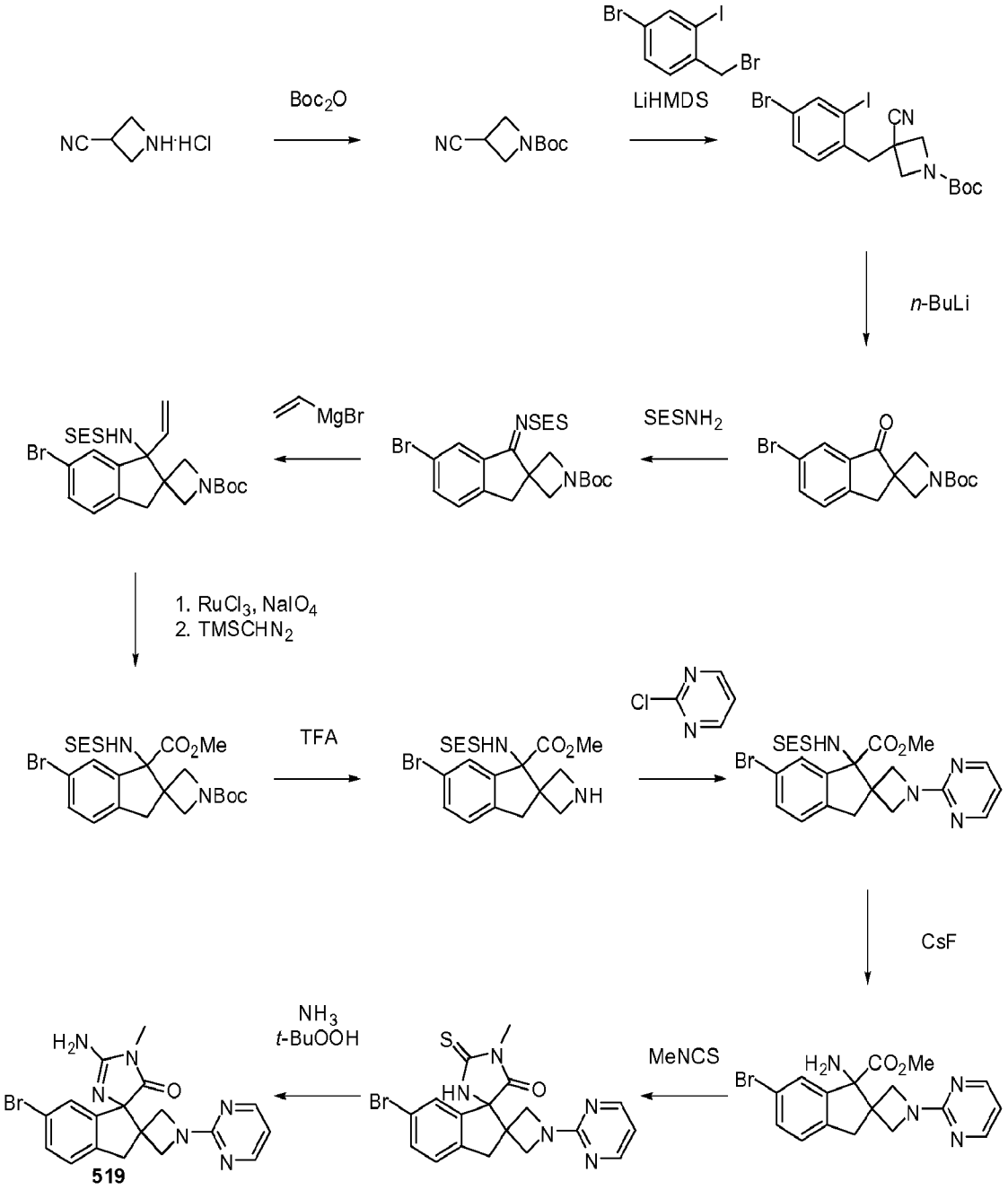


To **compound 603 Step1** (200 mg, 0.698 mmol) in ACN (anhydrous, 5 mL) ferric chloride (5.7 mg, 0.035 mmol) was added. Then trimethylethoxysilane (328 µL, 2.108 mmol) and triethylsilane (343 µL, 2.153 mmol) were added successively at RT under an argon atmosphere. The mixture was stirred for 14 h at RT. The mixture was diluted with phosphate buffer (pH7) and extracted with DCM. The organic layer was separated and evaporated. The crude product was purified by MPLC (25 g silicagel, gradient: CH/EA 100:0 to 70:30 over 45 min) to give **compound 603 Step2** as a resin (134 mg, 61 %).

HPLC (Method: Microsorb 1s)

Rt: 1.63 min, Mass: $(M+H)^+ = 317$

Example 411. Synthesis of Compound 519



Step 1. *tert*-butyl 3-cyanoazetidine-1-carboxylate

A mixture of azetidine-3-carbonitrile hydrochloride (5.03 g, 42 mmol), Boc_2O (10.75 g, 49 mmol), and $NaHCO_3$ (10.1 g, 120 mmol) in CH_2Cl_2 (50 mL) and H_2O (20 mL) was vigorously stirred at room temperature for 15 h. The organic phase was

separated and aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 7.3143 g (95%) of *tert*-butyl 3-cyanoazetidine-1-carboxylate as a solid. LC-MS t_R = 1.27 min in 3 min chromatography, *m/z* 183 (MH^+), 168 (MH^+-15), 127 (MH^+-56); ^1H NMR (400 MHz, $CDCl_3$) δ 4.23-4.15 (m, 4H), 3.43-3.35 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.40, 119.43, 80.68, 52.37, 28.21, 16.99.

Step 2. *tert*-butyl 3-(4-bromo-2-iodobenzyl)-3-cyanoazetidine-1-carboxylate

To a solution of *tert*-butyl 3-cyanoazetidine-1-carboxylate (2.1774 g, 11.95 mmol) and 4-bromo-1-(bromomethyl)-2-iodobenzene (5.0227 g, 13.36 mmol) in THF (30 mL) was added LiHMDS (1.0 *M* in THF, 15 mL, 15 mmol) at -78 °C. The mixture was allowed to slowly warm to room temperature over 20 h. The reaction mixture was then quenched with saturated NH_4Cl, extracted with EtOAc, and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 4.2959 g (75%) of *tert*-butyl 3-(4-bromo-2-iodobenzyl)-3-cyanoazetidine-1-carboxylate as foam. LC-MS t_R = 2.17 min in 3 min chromatography, *m/z* 477, 479 (MH^+), 462, 464 (MH^+-15), 421, 423 (MH^+-56).

Step 3. *tert*-butyl 6'-bromo-1'-oxo-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate

To a solution of *tert*-butyl 3-(4-bromo-2-iodobenzyl)-3-cyanoazetidine-1-carboxylate (4.2876 g, 8.99 mmol) in THF (120 mL) was added *n*-BuLi (2.5 *M* in hexane, 3.8 mL, 9.5 mmol) at -78 °C dropwise over 10 min under nitrogen. After 1 h, the reaction mixture was quenched with saturated NH_4Cl, diluted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 1.7020 g (54%) of *tert*-butyl 6'-bromo-1'-oxo-1',3'-dihydrospiro[azetidine-3,2'-

indene]-1-carboxylate as a solid. LC-MS t_R = 1.90 min in 3 min chromatography, *m/z* 352, 354 (MH^+), 337, 339 (MH^+-15), 296, 298 (MH^+-56); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.74-7.71 (m, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 4.23 (d, *J* = 8.2 Hz, 2H), 3.88 (d, *J* = 8.2 Hz, 2H), 3.40 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.38, 156.03, 150.44, 138.17, 137.24, 127.88, 127.29, 122.19, 80.05, 57.88, 44.70, 39.67, 28.35.

Step 4. *tert*-butyl 6'-bromo-1'-(((2-(trimethylsilyl)ethyl)sulfonyl)imino)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate

A mixture of *tert*-butyl 6'-bromo-1'-oxo-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate (0.2863 g, 0.8 mmol), 2-(trimethylsilyl)ethanesulfonamide (0.2000 g, 1.1 mmol), and $Ti(OEt)_4$ (0.6900 g, 3.0 mmol) in 1,2-dichloroethane (3 mL) was heated at 110 °C for 20 h. The reaction mixture was then quenched with ice, extracted with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.4031 g (96%) of *tert*-butyl 6'-bromo-1'-(((2-(trimethylsilyl)ethyl)sulfonyl)imino)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate. LC-MS t_R = 2.31 min in 3 min chromatography, *m/z* 515, 517 (MH^+), 459, 461 (MH^+-56).

Step 5. *tert*-butyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1'-vinyl-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate

To a solution of *tert*-butyl 6'-bromo-1'-(((2-(trimethylsilyl)ethyl)sulfonyl)imino)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate (0.4031 g, 0.78 mmol) in THF (3 mL) was added vinylmagnesium bromide (1.0 *M* in THF, 3 mL, 3.0 mmol) at 0 °C under nitrogen. The mixture was allowed to slowly warm to room temperature over 18 h. The reaction mixture was then quenched with saturated NH_4Cl, extracted with EtOAc, and dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the crude product was directly used in the next

step without further purification. LC-MS t_R = 2.31 min in 3 min chromatography, *m/z* 543, 545 (MH^+), 487, 489 (MH^+-56).

Step 6. 6'-bromo-1-(tert-butoxycarbonyl)-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylic acid

A mixture of *tert*-butyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1'-vinyl-1',3'-dihydrospiro[azetidine-3,2'-indene]-1-carboxylate, obtained as described above, and $NaIO_4$ (1.3800 g, 6.45 mmol), and $RuCl_3$ hydrate (0.0180 g, 0.0867 mmol) in CH_3CN (4 mL), CH_2Cl_2 (3 mL), and H_2O (3 mL) was vigorously stirred at room temperature for 18 h. The reaction mixture was then diluted with CH_2Cl_2, dried over Na_2SO_4. After the solvent was evaporated under reduced pressure, the crude product was directly used in the next step without further purification. LC-MS t_R = 1.98 min in 3 min chromatography, *m/z* 533, 535 (MH^+-28), 505, 507 (MH^+-56).

Step 7. 1-*tert*-butyl 1'-methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1,1'-dicarboxylate

A mixture of 6'-bromo-1-(tert-butoxycarbonyl)-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylic acid, obtained as described above, and $TMSCHN_2$ (2.0 *M* in hexane, 1 mL) in CH_2Cl_2 (6 mL) and MeOH (3 mL) was stirred at room temperature for 19 h. After the solvent was evaporated under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 0.3263 g (72% in three steps) of 1-*tert*-butyl 1'-methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1,1'-dicarboxylate as foam. LC-MS t_R = 2.20 min in 3 min chromatography, *m/z* 575, 577 (MH^+), 547, 549 (MH^+-28), 519, 521 (MH^+-56).

Step 8. methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate

A mixture of 1-*tert*-butyl 1'-methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1,1'-

dicarboxylate (0.3010 g, 0.52 mmol) and TFA (1 mL) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 h. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.2346 g (76%) of TFA salt of methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate. LC-MS t_R = 1.50 min in 3 min chromatography, *m/z* 475, 477 (MH^+).

Step 9. methyl 6'-bromo-1-(pyrimidin-2-yl)-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate

To a solution of methyl 6'-bromo-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate trifluoroacetate (0.2196 g, 0.37 mmol) and 2-chloropyrimidine (0.1080 g, 0.94 mmol) in MeOH (4 mL) was added Et_3N (0.5 mL) at room temperature. The mixture was stirred at 80 °C for 18 h and then concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0803 g (39%) of methyl 6'-bromo-1-(pyrimidin-2-yl)-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate. LC-MS t_R = 1.87 min in 3 min chromatography, *m/z* 553, 555 (MH^+).

Step 10. methyl 1'-amino-6'-bromo-1-(pyrimidin-2-yl)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate

A mixture of methyl 6'-bromo-1-(pyrimidin-2-yl)-1'-(2-(trimethylsilyl)ethylsulfonamido)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate (0.0803 g, 0.145 mmol) and CsF (0.6400 g, 4.2 mmol) in DMF (1.5 mL) was heated at 110 °C for 18 h. The mixture was diluted with MeOH, filtered through HPLC filter, and then purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™

5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.0249 g (34%) of TFA salt of methyl 1'-amino-6'-bromo-1-(pyrimidin-2-yl)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate. LC-MS t_R = 1.05 min in 3 min chromatography, *m/z* 389, 391 (MH^+).

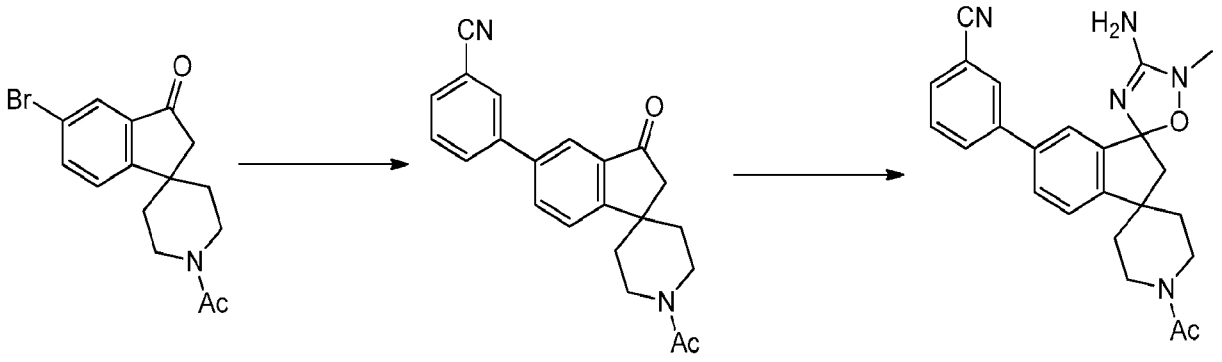
Step 11.

To a solution of methyl 1'-amino-6'-bromo-1-(pyrimidin-2-yl)-1',3'-dihydrospiro[azetidine-3,2'-indene]-1'-carboxylate trifluoroacetate (0.0249 g, 0.0494 mmol) in CH_2Cl_2 (1.5 mL) was added Et_3N (0.15 mL) followed by methylisothiocyanate (0.0615 g, 0.84 mmol). The reaction mixture was heated at 110 °C for 15 h and then concentrated under reduced pressure. The crude product was directly used in the next step without further purification. LC-MS t_R = 1.54 min in 3 min chromatography, *m/z* 430, 432 (MH^+).

Step 12. Compound 519

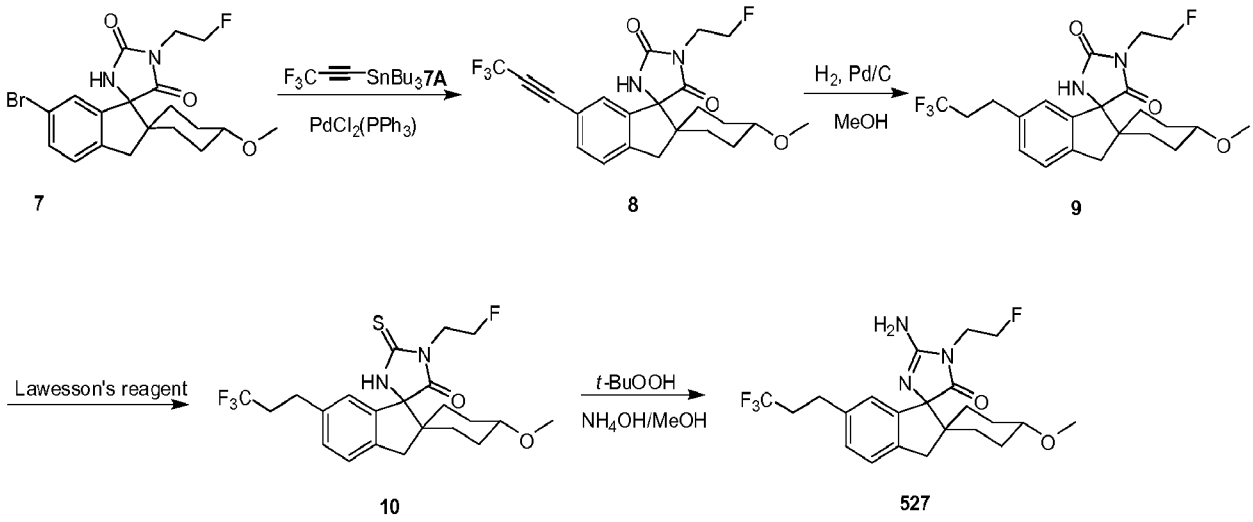
A mixture of 3-methyl-2-thioxo-imidazolidin-4-one, obtained as described above, ammonia (*ca.* 7 *N* solution in MeOH, 2 mL), and TBHP (~5.5 *M* solution in nonane, 0.5 mL) was stirred at room temperature for 19 h. After the solvent was evaporated under reduced pressure, the residue was purified by reversed-phase HPLC (SunFire™ Prep C_{18} OBD™ 5μm 19 × 50 mm column, 10% →90% MeOH/H_2O, 0.1% CF_3COOH over 8 min and then 90% MeOH/H_2O, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford compound 519 as a TFA salt. LC-MS t_R = 1.09 min in 3 min chromatography, *m/z* 413, 415 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.36 (d, *J* = 5.0 Hz, 2H), 7.58-7.54 (m, 2H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.74 (t, *J* = 5.0 Hz, 1H), 4.25 (d, *J* = 9.1 Hz, 1H), 4.17 (d, *J* = 9.8 Hz, 1H), 4.12 (d, *J* = 9.8 Hz, 1H), 3.92 (d, *J* = 9.1 Hz, 1H), 3.66 (d, *J* = 16.4 Hz, 1H), 3.42 (d, *J* = 16.1 Hz, 1H), 3.23 (s, 3H).

Example 412. Synthesis of Compound 591



The title compound was made by the method described in example 389. MS ESI +ve m/z 416 $(M+H)^+$. t_R: 1.15 min. ^1H NMR (400 MHz, CD_3OD) δ: 8.06-7.98 (m, 2H), 7.88 (m, 2H), 7.78 (m, 1H), 7.69 (m, 2H), 7.56 (d, *J* = 6.8 Hz, 1H), 3.43 (m, 7H), 3.14 (m, 1H), 2.84 (m, 1H), 2.39-1.68 (m, 4H).

Example 413. Synthesis of Compound 527



Procedure for preparation of compound 8

A solution containing **7A** (0.216 g, 0.56 mmol) and compound 7 (0.2 g, 0.47 mmol) in toluene (5 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (20 mg, 0.047 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at

130 °C for 40 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (5 mL) and aqueous CsF (4 M, 5 mL), and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC over silica gel eluted with petroleum ether: EtOAc = 3: 1 to give compound **8** (80 mg, 38%) as a yellow solid. **LC-MS:** t_R = 1.173 min in 2min chromatography MS (ESI) *m/z* 439.1 $[M+H]^+$.

Procedure for preparation of compound 9

A Parr flask was charged with compound **8** (80 mg, 0.182 mmol) and methanol (5 mL), 10% Pd/C (10 mg) was added. The suspension was degassed under vacuum and flushed several times with hydrogen and then pressurized with hydrogen (50 Psi) at 60 °C with vigorous stirring for 24 h. The precipitate was filtered off and washed with methanol (2 × 50 mL). The filtrate and washings were concentrated by evaporation *in vacuo*. The residue was purified by preparative TLC over silica gel eluting with petroleum ether: EtOAc = 3: 1 to give compound **9** (40 mg, 49%) as a yellow solid. **LC-MS:** t_R = 1.335 min in 2min chromatography, MS (ESI) *m/z* 443.2 $[M+H]^+$.

Procedure for preparation of compound 10

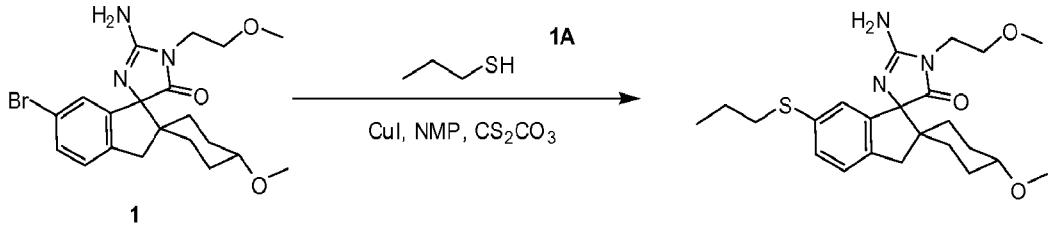
To a solution of compound **9** (40 mg, 0.090 mmol) in anhydrous toluene (5 mL) was added Lawesson's reagent (40 mg, 0.099 mmol) under a nitrogen atmosphere, the mixture was heated at reflux for 12 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 3: 1) to give compound **10** (30 mg, 73%) as a white solid. **LC-MS** t_R = 1.420 min in 2min chromatography, MS (ESI) *m/z* 459.1 $[M+H]^+$.

Procedure for preparation of compound 527

To a solution of compound **10** (30 mg, 0.065 mmol) in MeOH (10 mL) was added NH_4OH (3 mL) and *tert*-butyl hydroperoxide (1 mL). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (20 mL)

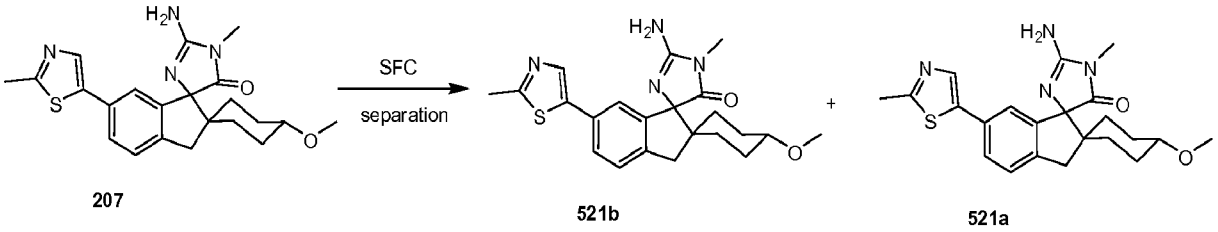
and H_2O (20 mL). The organic layer was separated and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give **VT_B011010_03** (5 mg, 17%) as a white solid. **LC-MS** t_R = 1.118 min in 2 min chromatography, MS (ESI) *m/z* 442.2 $[M+H]^+$. **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.26 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 6.89 (s, 1H), 4.61-4.70 (m, 1H), 4.40-4.49 (m, 1H), 3.70-3.94 (m, 2H), 3.36 (s, 3H), 3.12-3.22 (m, 1H), 3.02-3.12 (m, 2H), 2.71-2.89 (m, 2H), 2.36-2.53 (m, 2H), 1.95-2.08 (m, 2H), 1.83-1.95 (m, 1H), 1.58-1.66 (m, 1H), 1.35-1.51 (m, 2H), 1.20-1.33 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -76.92, -68.15.

Example 414. Synthesis of Compound 533



A mixture of compound **1** (50 mg, 0.115 mmol), compound **1A** (8.6 mg, 0.115 mmol), CuI (21.8 mg, 0.115 mmol) and Cs_2CO_3 (75 mg, 0.23 mmol) in NMP (1 mL) was placed into CEM microwave reactor and irradiated at 195 °C for 1 h. After being cooled to room temperature, the mixture was partitioned between H_2O (10 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to dryness. The residue was purified by RP-HPLC (acidic) to give compound **533** (5.3 mg, 12%) as a white solid. **LC-MS** t_R = 1.152 min in 2 min chromatography, MS (ESI) m/z 432.1 $[M+H]^+$; **^{1}H-NMR** (MeOD 400 MHz): δ 7.32-7.38 (m, 2H), 7.15 (s, 1H), 3.90-3.97 (m, 2H), 3.56-3.59 (m, 2H), 3.33 (s, 6H), 3.07 (m, 1H), 2.98-3.03 (m, 2H), 2.90-2.94 (m, 2H), 2.02-2.10 (m, 2H), 1.89 (m, 1H), 1.61-1.67 (m, 2H), 1.32-1.46 (m, 5H), 1.01-1.04 (m, 3H).

Example 415. Synthesis of Compounds 521a and 521b

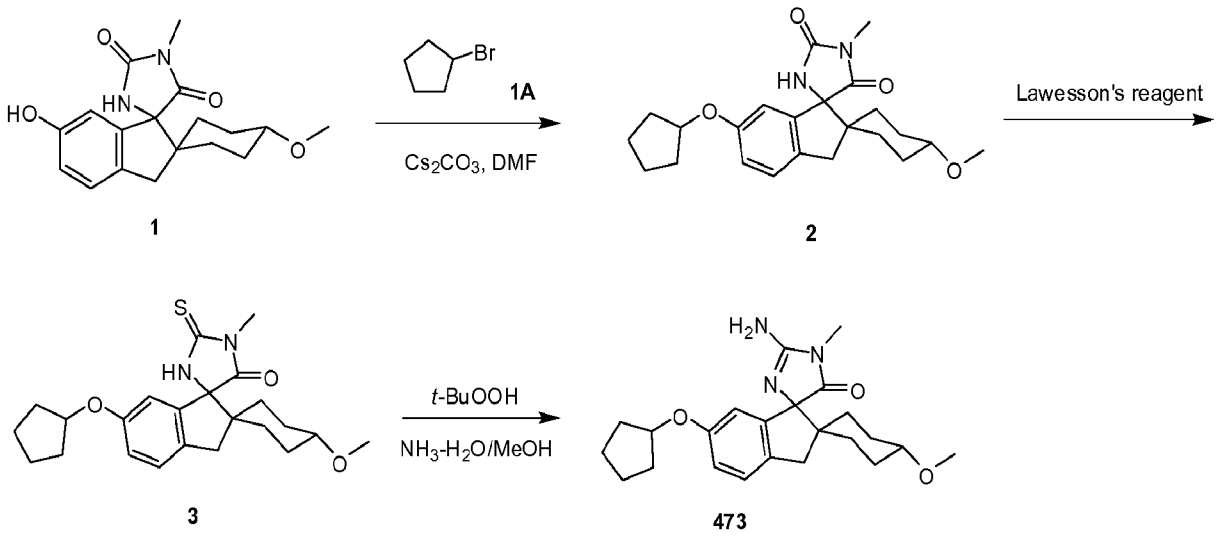


207 521b 521a

40 mg of **compound 207** was purified by preparative SFC HPLC to give **compound 521b** (11.3 mg, 28%), **LC-MS:** t_R = 1.009 min in 2min chromatography, MS (ESI) *m/z* = 411.1 $[M+H]^-$; **CHIRAL SFC-MS**: t_R = 4.362 min in 8 min chromatography (OD-H_S_4_5_40_3ML_8min), MS (ESI) *m/z* = 411.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.71 (s, 1H), 7.38-7.40 (d, *J* = 8.0 Hz, 1H), 7.23-7.25 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 3.24 (s, 3H), 2.98-3.05 (m, 3H), 2.94 (s, 3H), 2.59 (s, 3H), 1.83-1.91 (m, 2H), 1.72 (m, 1H), 1.52 (m, 1H), 1.26-1.28 (m, 2H), 1.16-1.18 (m, 2H).

and **compound 521a** (8.6 mg, 21%), **LC-MS:** t_R = 1.017 min in 2min chromatography, MS (ESI) *m/z* = 411.1 $[M+H]^+$; **CHIRAL SFC-MS**: t_R = 5.544 min in 8 min chromatography (OD-H_S_4_5_40_3ML_8min), MS (ESI) *m/z* = 411.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.71 (s, 1H), 7.38-7.40 (d, *J* = 8.0 Hz, 1H), 7.24-7.26 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 3.24 (s, 3H), 2.98-3.05 (m, 3H), 2.94 (s, 3H), 2.59 (s, 3H), 1.84-1.92 (m, 2H),1.72 (m, 1H), 1.48-1.55 (m, 1H), 1.16-1.28 (m, 4H).

Example 416. Synthesis of Compound 473



Procedure for preparation of compound 2

To a solution of compound **1** (50 mg, 0.15 mmol) in DMF (5 mL) was added compound **1A** (33.5 mg, 0.225 mmol) and Cs_2CO_3 (58 mg, 0.17 mmol). After addition, the mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo* to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc= 1: 1) to give compound **2** with 84% purity (60 mg, 94%) as a white solid. **LC-MS** t_R= 1.113 min in 2min chromatography, MS (ESI) *m/z* = 399.2 $[M+H]^+$

Procedure for preparation of compound 3

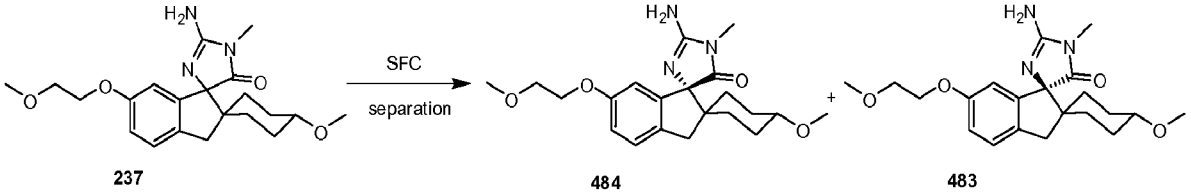
To a mixture of compound **2** (60 mg, 0.15 mmol) was added Lawesson's reagent (60 mg, 0.15 mmol) in toluene (4 mL). The reaction was heated at 130 °C in a CEM microwave reactor for 1 h. After cooling down, the precipitate was filtered off and washed with ethyl acetate (40 mL× 2). The filtrate and the washing were concentrated in *vacuo* and the residue was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to give compound **3** with 80% purity (38 mg, 62%) as a pale yellow solid. **LC-MS** t_R= 1.416 min in 2min chromatography, MS (ESI) *m/z* 415.1 $[M+H]^+$

Procedure for preparation of compound 473

To a solution of compound **3** (38 mg, 0.09 mmol) in MeOH (4 mL) was added NH_3-H_2O (1 mL) and *tert*-butyl hydroperoxide (263 mg, 1.8 mmol). After addition, the

mixture was stirred at ambient temperature overnight. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give **compound 473** (6.3 mg, 16%) as a white solid. **LC-MS** t_R= 1.000 min in 2min chromatography, MS (ESI) *m/z* 398.2 $[M+H]^+$; **^{1}H NMR**: (CD_3OD 400M Hz): δ 7.16 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.47 (s, 1H), 4.73 (m, 1H), 3.34 (s, 3H), 3.14 (m, 1H), 2.93-3.02 (m, 5H), 1.76-2.03 (m, 9H), 1.62 (m, 3H), 1.24-1.39 (m, 4H).

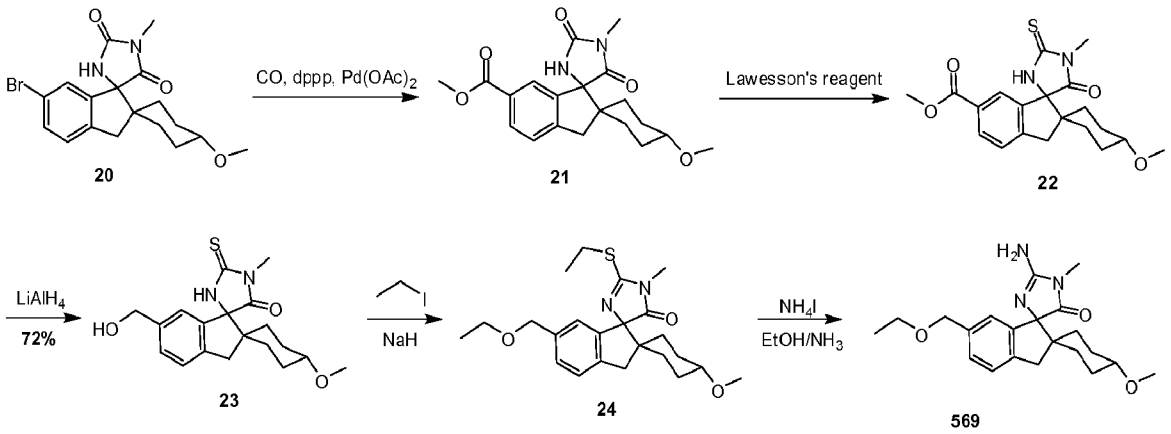
Example 417. Synthesis of Compounds 483 and 484



237 484 483

40 mg of **compound 237** was purified by preparative SFC HPLC to give **compound 484** (10.3 mg, 28%), **LC-MS:** t_R = 0.844 min in 2min chromatography, MS (ESI) *m/z* = 388.0 $[M+H]^+$.**CHIRAL SFC-MS**: t_R = 5.87 min in 15 min chromatography,Column: OJ-H, Method: 5-40_2.5mL, Co-solvent: MeOH (0.05% DEA); **^{1}H NMR** (MeOD 300MHz): δ 7.25 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.78 (s, 1H), 4.07 (d, J = 2.4 Hz, 2H), 3.69 (d, J = 2.1 Hz, 2H), 3.56 (s, 3H), 3.52 (s, 3H), 3.38 (s, 3H), 3.29 (m, 3H), 2.04 (m, 2H), 1.83 (m, 1H), 1.24-1.42 (m, 5H); and **compound 483** (8.0 mg, 20%), **LC-MS:** t_R = 0.852 min in 2min chromatography, MS (ESI) *m/z* = 388.1 $[M+H]^+$; **CHIRAL SFC-MS**: t_R = 7.92 min in 16 min chromatography, Column: OJ-H, Method: 5-40_2.5mL, Co-solvent: MeOH (0.05% DEA); **^{1}H NMR** (MeOD 300MHz): δ 7.25 (d, J = 5.4 Hz, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.78 (s, 1H), 4.07 (d, J = 2.4 Hz, 2H), 3.69 (d, J = 2.1 Hz, 2H), 3.56 (s, 3H), 3.52 (s, 3H), 3.38 (s, 3H), 3.29 (m, 3H), 2.04 (m, 2H), 1.83 (m, 1H), 1.25-1.42 (m, 5H).

Example 418. Synthesis of Compound 569



Procedure for preparation of compound 21

To a solution of compound **20** (600 mg, 1.53 mmol) in MeOH (10 mL) and DMSO (30 mL) was added dppp (314 mg, 0.76 mmol), $Pd(OAc)_2$ (171 mg, 0.76 mmol) and Et_3N (6 mL). The reaction was heated at 80 °C under CO atmosphere (40 psi) for 16 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the residue, which was purified by preparative TLC (CH_2Cl_2: MeOH, 10: 1) to afford compound **21** (270 mg, 47%) as a white solid.

Procedure for preparation of compound 22

To a solution of compound **21** (50 mg, 0.134 mmol) in dry toluene (2 mL) was added Lawesson's reagent (55 mg, 0.161 mmol) under nitrogen. The reaction mixture was heated at 120 °C for 2 h. After cooling down, the solvent was removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc, 1: 1) to give compound **22** (45 mg, 86%) as a white solid.

Procedure for preparation of compound 23

A solution of $LiAlH_4$ (13 mg, 0.348 mmol) in THF (2 mL) was stirred at 0 °C and a mixture of compound **22** (45 mg, 0.116 mmol) in THF (1 mL) was added dropwise. After addition, the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of 5 drops of water and 3 M of NaOH aqueous solution. After stirring for 10 min, the mixture was filtered and the filtrated was concentrated to

give crude compound **23** (30 mg, 72%), which was used for the next step without purification.

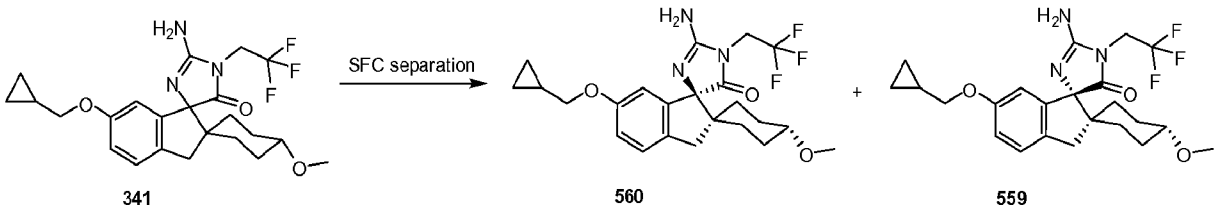
Procedure for preparation of compound 24

To a solution of compound **23** (30 mg, 0.083 mmol) in DMF (3 mL) was added NaH (33 mg, 0.83 mmol) at 0 °C. After stirring for 30 min, iodo-ethanethe (104 mg, 0.667 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of water (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc, 3: 1) to afford compound **24** (23 mg, 67%) as a white solid.

Procedure for preparation of compound 569

A sealed tube was charged with compound **24** (23 mg, 0.055 mmol), NH_4I (81 mg, 0.55 mmol). NH_3-EtOH (2 mL, 5 N) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 120 °C for 2 h. After cooling down, the solvent was removed and the residue was purified by preparative TLC (CH_2Cl_2: MeOH, 10: 1) and acidic RP-HPLC to give compound **569** (5.5 mg, 27%) as a white solid. **LC-MS** t_R = 0.893 min in 2min chromatography, MS (ESI) *m/z* 372.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.25 (s, 2H), 7.09 (s, 1H), 4.37 (s, 2H), 3.45 (m, 2H), 3.25 (s, 3H), 3.09 (s, 3H), 3.03-3.06 (m, 3H), 1.89-2.01 (m, 2H), 1.77 (m, 1H), 1.22-1.34 (m, 5H), 1.11 (t, J = 7.6 Hz, 3H).

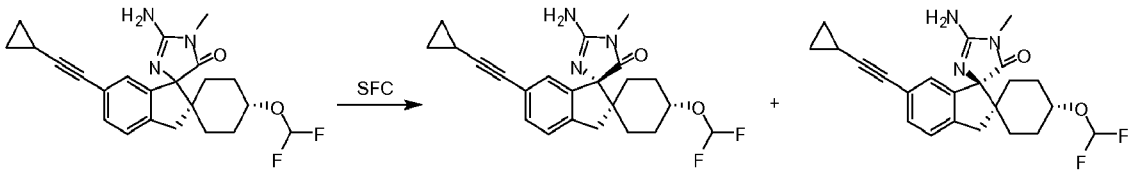
Example 419. Synthesis of Compound 559 and 560



Compound 341 (40 mg, 0.088 mmole) was purified by preparative SFC to give **compound 560** (12.60 mg, 31%), **LCMS**: t_R = 0.975 min in 2min chromatography, MS (ESI) *m/z* 452.0 $[M+H]^+$; **SFC**: t_R = 4.49 min in 15 min chromatography (OJ-H_5_5_40%_2, 35ML), ee = 100%; **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.07 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 6.8 Hz, 1H), 6.40 (s, 1H), 4.23 (m, 2H), 3.67 (d, J = 6.4 Hz, 2H), 3.23 (s, 3H), 2.93-3.06 (m, 1H), 2.84-2.93 (m, 2H), 1.83-1.98 (m, 2H), 1.72-1.83 (m, 1H), 1.39-1.72 (m, 1H), 1.31-1.39 (m, 2H), 1.22-1.28 (m, 2H), 1.05-1.10 (m, 1H), 0.40-0.50 (m, 2H), 0.20-0.30 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -72.07.

and **compound 559** (10.90 mg, 27%) as a white solid, **LCMS**: t_R = 0.958 min in 2min chromatography, MS (ESI) *m/z* 452.1 $[M+H]^-$; **SFC**: t_R = 6.76 min in 15 min chromatography (OJ-H_5_5_40%_2, 35ML), ee = 98%; **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.07 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.39 (s, 1H), 4.23 (m, 2H), 3.72 (d, J = 6.8 Hz, 2H), 3.24 (s, 3H), 2.93-3.03 (m, 1H), 2.85-2.93 (m, 2H), 1.83-1.98 (m, 2H), 1.73-1.83 (m, 1H), 1.45-1.68 (m, 1H), 1.22-1.32 (m, 2H), 1.10-1.18 (m, 2H), 1.01-1.10 (m, 1H), 0.39- 0.50 (m, 2H), 0.22-0.29 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -72.07.

Example 420. Synthesis of Compounds 522 and 523

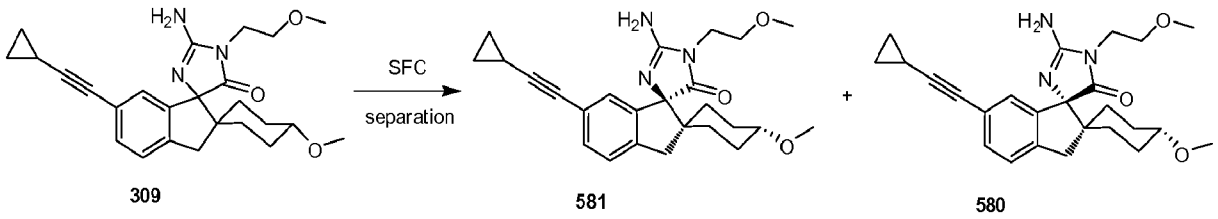


274 523 522

Compound 274 (50 mg, 0.121 mmol) was re-purified by preparative SFC to give **compound 523** (20 mg), **LC-MS** t_R = 3.070 min in 7min chromatography, MS (ESI) *m/z* 414.5 $[M+H]^+$; **SFC** t_R = 3.652 min in 8 min chromatography (OD-H_S_3_5_40_3ML_8MIN.M), ee = 100%; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.12 (s, 2H), 6.80 (s, 1H), 6.08-6.46 (t, J = 76.0 Hz, 1H), 3.86 (m, 1H), 2.95-3.05 (m, 2H), 2.92 (s, 3H), 1.70-1.90 (m, 3H), 1.40-1.54 (m, 3H), 1.17-1.34 (m, 3H), 0.75 (m, 2H), 0.58 (m, 2H). **^{19}F NMR** (CD_3OD 400 MHz 19F): δ –81.48.

And **compound 522** (24 mg) as a white solid, **LC-MS** t_R = 3.061 min in 7min chromatography, MS (ESI) *m/z* 414.5 $[M+H]^+$; **SFC** t_R = 4.179 min in 8 min chromatography (OD-H_S_3_5_40_3ML_8MIN.M), ee = 96%; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.11 (s, 2H), 6.81 (s, 1H), 6.08-6.46 (m, J = 76.0 Hz, 1H), 3.86 (m, 1H), 2.95-3.05 (m, 2H), 2.92 (s, 3H), 1.70-1.90 (m, 3H), 1.40-1.54 (m, 3H), 1.17-1.34 (m, 3H), 0.75 (m, 2H), 0.58 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz 19F) : δ –81.47.

Example 421. Synthesis of Compounds 580 and 581

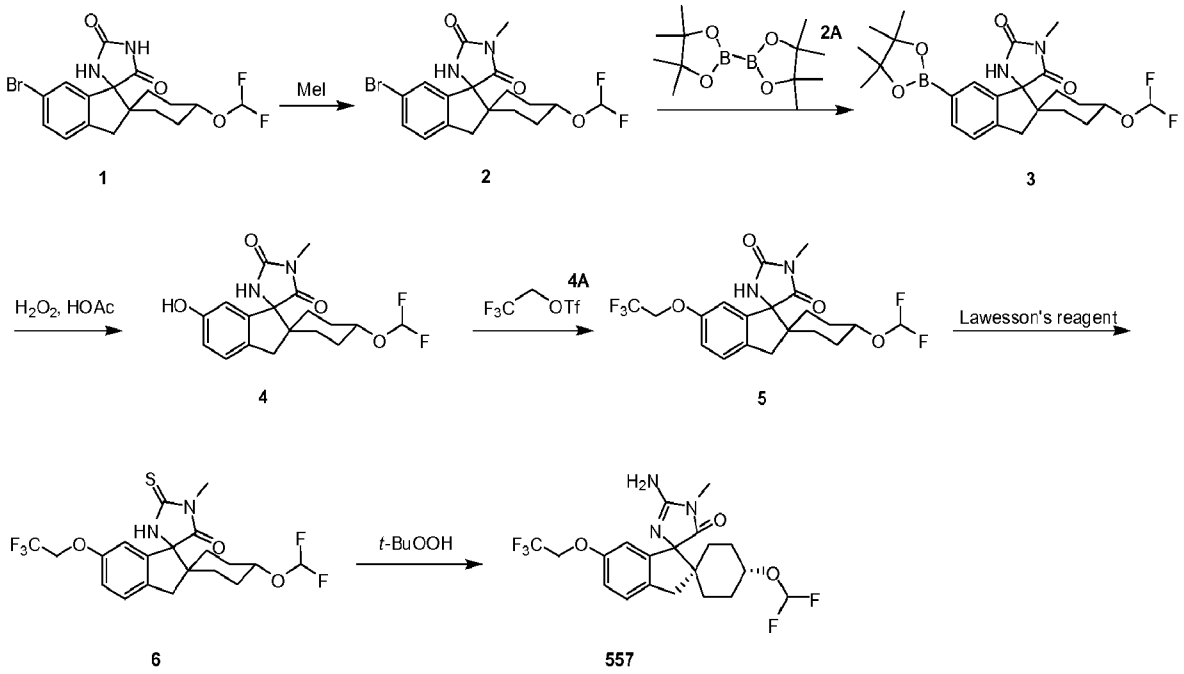


309 581 580

Compound 309 (40 mg) was purified by preparative SFC column to give **compound 581**, **LC-MS**: t_R = 0.969 min in 2 min chromatography, MS (ESI) m/z 422.1 $[M+H]^+$; **SFC:** t_R = 5.77 min in 15 min chromatography **ee** = 96%, Column: OJ-H, Method: 5-40_2.5mL, Co-solvent: IPA (0.05% DEA); **^{1}H NMR** (CD_3OD 400 MHz): δ 7.30-7.36 (m, 2H), 7.15 (s, 1H), 3.85-3.99 (m, 2H), 3.55-3.59 (m, 2H), 3.36 (m, 6H), 3.09-3.20 (m, 3H), 2.02-2.09 (m, 2H), 1.89 (m, 1H), 1.31-1.44 (m, 6H), 0.86-0.90 (m, 2H), 070-0.72 (m, 2H).

And **compound 580, LC-MS**: t_R = 0.967 min in 2 min chromatography, MS (ESI) m/z 422.1 $[M+H]^+$; **SFC:** t_R = 6.39 min in 15 min chromatography, **ee** = 96.5%, Column: OJ-H, Method: 5-40_2.5mL, Co-solvent: IPA (0.05% DEA); **^{1}H NMR** (CD_3OD 400 MHz): δ 7.35 (dd, J = 1.2, 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz 1H), 7.14 (s, 1H), 3.87-3.98 (m, 2H), 3.55-3.58 (m, 2H), 3.36 (m, 6H), 3.09-3.20 (m, 3H), 2.02-2.09 (m, 2H), 1.89 (m, 1H), 1.30-1.46 (m, 6H), 0.86-0.90 (m, 2H), 069-0.72 (m, 2H).

Example 422. Synthesis of Compound 557



Procedure for preparation of compound 2

To a solution of compound **1** (0.20 g, 0.483 mmol) in DMF (4 mL) was added K_2CO_3 (0.166 g, 0.208 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then iodomethane (74 mg, 0.531 mmol) in DMF (2 mL) was added dropwise via a syringe with stirring. The mixture was stirred at room temperature overnight. The reaction mixture was partitioned between H_2O (25 mL) and ethyl acetate (25 mL). The separated organic phase was washed with saturated brine (3 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by preparative TLC (hexane: EtOAc = 3: 1) to give compound **2** (0.15 g, 73%) as a white solid.

Procedure for preparation of compound 3

To a solution of compound **2** (0.2 g, 0.467 mmol) in dioxane (5 mL) was added compound 2A (0.131 g, 0.514 mmol), KOAc (0.132 g, 1.4 mmol). The mixture was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2$(dppf) (1.6 mg, 0.002 mmol) was added. The mixture was heated to reflux overnight in a N_2 atmosphere. The reaction mixture was cooled to room temperature

and the solide was filtered off. The filtrate was concentrated *in vacuo* to give the crude compound **3** (0.2 g, crude). It can be used for the next step without further purification.

Procedure for preparation of compound 4

To a solution of compound **3** (0.2 g, crude) in dioxane (10 mL) was added H_2O_2 (10 mL) and HOAc (30 mL). The final solution was stirred at room temperature overnight. Then the solvent was evaporated *in vacuo* and the residue was purified by preparative TLC (hexane; EtOAc = 1:1) to give the compound **4** (0.1 g, 65%) as a white solid.

Procedure for preparation of compound 5

To a solution of compound **4** (0.1 g, 0.273 mmol) in DMF (3 mL) was added K_2CO_3 (83 mg, 0.501 mmol) and compound **4A** (70 mg, 0.306 mmol). The mixture was stirred at room temperature and monitored by TLC. When the compound **4** was consumed, Sat.NH_4Cl (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 5 mL). The combined organic layers were separated, dried over Na_2SO_4, and evaporated *in vacuo* to give the crude. The crude was purified by preparative TLC (hexane: EtOAc = 3:1) to give the compound **5 (**20 mg, 16%) as a white solid.

Procedure for preparation of compound 6

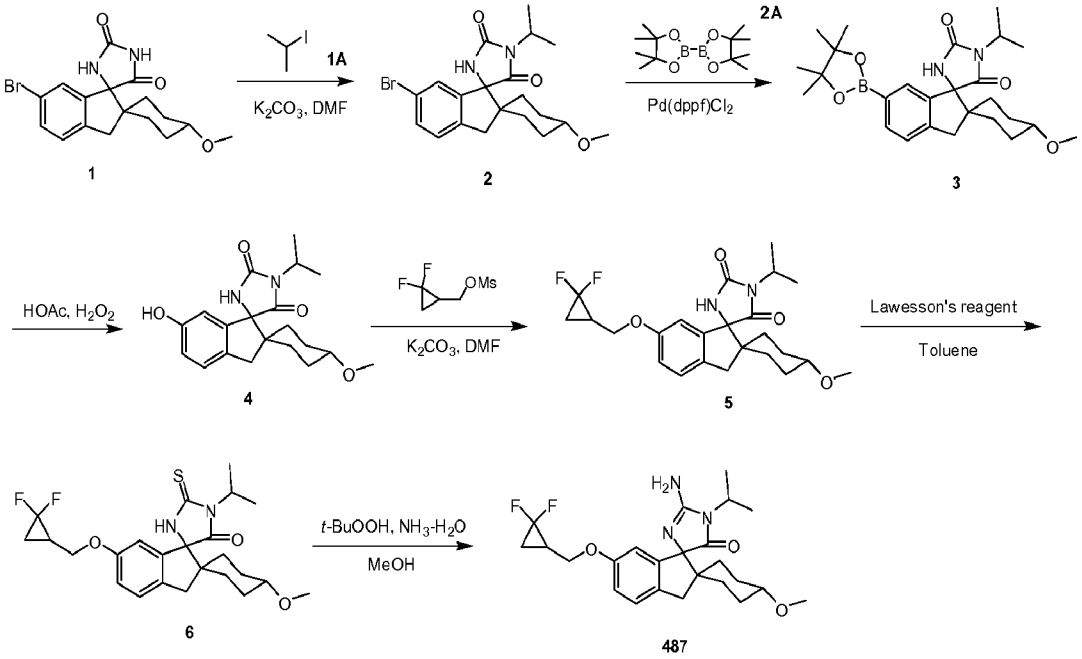
An 8 mLvial was charged with compound **5** (20 mg, 0.0446 mmol), Lawesson's reagent (19.9 mg, 0.0491 mmol). Toluene (3 mL) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 130 °C for 1 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by preparative TLC (hexane: EtOAc = 2:1) to give compound **6** (10 mg, 47%) as a white solid.

Procedure for preparation of compound 557

To a solution of compound **6** (10 mg, 0.022 mmol) in MeOH (2.5 mL) was added NH_3-H_2O (0.5 mL) and *tert*-butyl hydroperoxide (66 mg, 0.447 mmol). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (50 mL) and H_2O (20 mL). The organic layer was separated

and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give **compound 557** (2.8 mg, 28%) as a white solid; **LC-MS** t_R = 1.015 min in 2min chromatography, MS (ESI) *m/z* 448.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.44 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 6.32-6.69 (m, 1H), 4.61 (m, 1H), 4.15 (m, 1H), 3.16-3.34 (m, 5H), 2.13 (m, 2H), 1.94 (m, 1H), 1.77-1.87 (m, 1H), 1.52-1.72 (m, 4H); **^{19}F NMR** (CD_3OD 400 MHz 19F): δ -77.00, -81.94.

Example 423. Synthesis of Compound 487



Procedure for preparation of compound 2

To a solution of compound **1** (1.2 g, 3.17 mmol) in DMF (20 mL) was added K_2CO_3 (530 mg, 3.81 mmol) and compound **1A** (0.38 mL, 3.81 mmol). The reaction mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by chromatography (petroleum ether: EtOAc = 5: 1) to afford compound **2** (1.07 g, 80%) as a white solid.

Procedure for preparation of compound 3

To a solution of compound **2** (405 mg, 0.964 mmol) in 1, 4-dioxane (10 mL) was added compound **2A** (294 mg, 1.157 mmol), KOAc (280 mg, 2.892 mmol) and Pd(dppf)Cl_2 (120 mg) under N_2. The reaction mixture was refluxed overnight. The solution was filtered and the filtrate was concentrated to give the residue, which was purified by chromatography (petroleum ether: EtOAc = 8: 1) to afford compound **3** (450 mg, 98%) as a white solid.

Procedure for preparation of compound 4

To a solution of compound **3** (450 mg, 0.96 mmol) in THF (10 mL) was added HOAc (1.2 mL) and H_2O_2 (3.6 mL). The reaction was stirred at room temperature overnight. The reaction was quenched with $Na_2S_2O_3$ solution (15 mL), and stirred for 15 min. The mixture was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give compound **4** (315 mg, 90%) as awhite solid.

Procedure for preparation of compound 5

To a solution of compound **4** (80 mg, 0.223 mmol) in DMF (3 mL) was added K_2CO_3 (62 mg, 0.446 mmol) and compound **4A** (62 mg, 0.335 mmol). The reaction mixture was heated at 50 °C overnight. LCMS showed the reaction was completed. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to afford compound **5** (80 mg, 80%) as a white solid. **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.12 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 5.31 (s, 1H), 4.23 (m, 3H), 3.91 (m, 2H), 3.28 (s, 3H), 3.06-2.88 (m, 6H), 2.03 (m, 1H), 1.91 (m, 2H), 1.57 (m, 1H), 1.33 (m, 6H), 1.25 (m, 4H).

Procedure for preparation of compound 6

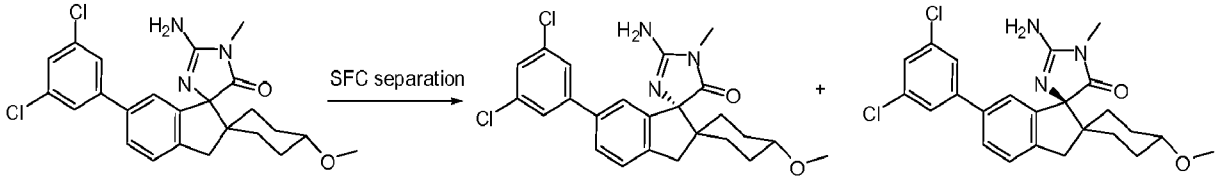
To a solution of compound **5** (77 mg, 0.172 mmol) in dry toluene (2.5 mL) was added Lawesson's reagent (104 mg, 0.258 mmol) under nitrogen. The reaction mixture was heated in a CEM microwave reactor at 130 °C for 60 min. The solvent was

removed under reduced pressure, and the residue was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **6** (67 mg, 84%) as a white solid.

Procedure for preparation of compound 487

To a solution of compound **6** (67 mg, 0.144 mmol) in MeOH (3 mL) and NH_3-H_2O (0.6 mL) was added *t*-BuOOH (422 mg, 2.89 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by preparative HPLC to give **compound 487** (19.5 mg, 30%) as a white solid, **LC-MS** t_R = 1.032 min in 2min chromatography, MS (ESI) *m/z* 488 $[M+H]^+$; **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 8.02 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 6.79 (m, 1H), 6.51 (s, 1H), 4.19 (m, 1H), 3.95 (m, 2H), 3.38. (s ,3H), 3.12-2.95 (m, 3H), 2.03 (m, 3H), 1.88 (m, 1H), 1.52 (m, 2H), 1.46 (m, 6 H), 1.32 (m, 2H), 1.21 (m, 3H); **^{19}F NMR** (CD_3OD 400 MHz): δ -130.560, -145.261

Example 424. Synthesis of Compounds 479 and 480



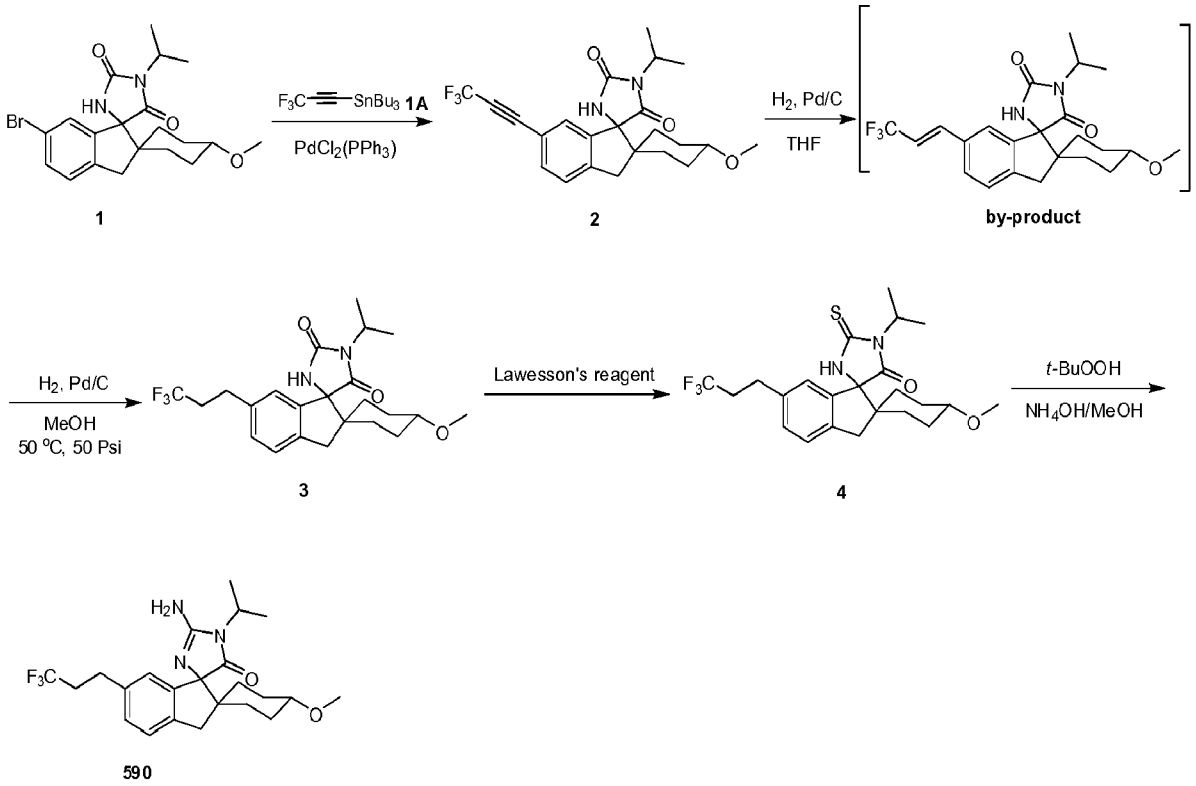
182 480 479

Compound 182 (53 mg) was purified by SFC to give compound **480** (15.2 mg), **LC-MS** t_R = 0.978 min in 2min chromatography, MS (ESI) *m/z* 458.2 $[M+H]^+$; **SFC**: t_R = 1.63 min in 10 min chromatography, ee = 100%, Column: OD-3, Method: 40_2.5ml, Co-Solvent: IPA (0.05%DEA); **^{1}H NMR** (CD_3OD 400 MHz): δ 7.63-7.68 (t, J = 7.6 Hz, 3H), 7.57 (s, 1H), 7.44-7.52 (t, J = 8.0 Hz, 2H), 3.38 (s, 3H), 3.16-3.27 (m, 6H), 2.05-2.12 (m, 2H), 1.88-1.91 (m, 1H), 1.33-1.49 (m, 5H).

And **compound 479** (20.6 mg) as a white solid, **LC-MS** t_R = 1.101 min in 2min chromatography, MS (ESI) *m/z* 458.1 $[M+H]^+$; **SFC**: t_R = 5.87 min in 10 min chromatography, ee = 100%, Column: OD-3; Method: 40_2.5ml, Co-Solvent: IPA (0.05%DEA); **^{1}H NMR** (DMSO-d_6 400 MHz): δ 7.54-7.70 (m, 4H), 7.36-7.38 (d, J =

7.6 Hz, 1H), 7.07 (s, 1H), 6.52-6.81 (brs, 1H), 3.22 (s, 3H), 2.95-3.09 (q, 3H), 2.90 (s, 3H), 1.64-1.97 (m, 3H), 1.09-1.36 (m, 5H).

Example 425. Synthesis of Compound 590



Procedure for preparation of compound 2

A solution containing the compound **1A** (164 mg, 0.427 mmol) and compound **1** (150 mg, 0.356 mmol) in toluene (8 mL) was deoxygenated by bubbling a stream of nitrogen through the reaction mixture for 5 min. Then, $PdCl_2(PPh_3)_2$ (13 mg, 0.018 mmol) was added. The reaction vial was sealed and placed into CEM microwave reactor and irradiated at 125 °C for 45 min. After being cooled to room temperature, the mixture was partitioned between EtOAc (10 mL) and aqueous CsF (4 M, 10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 ×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the residue, which was purified preparative TLC (petroleum/ethyl acetate = 3:1) to give compound **2** (100 mg, 65%) as a white solid.

Procedure for preparation of compound 3

To a solution of compound **2** (100 mg, 0.23 mmol) in THF (10 mL) was added Pd/C (10 mg, 10 wt %). The reaction mixture was stirred at room temperature for overnight under H_2 atmosphere, LCMS showed only by-product was formed, the reaction mixture was filtered and the filtrate was concentrated, the residue was dissolved in MeOH (10 mL) was added dry Pd/C (10 mg, 10 wt%). The reaction mixture was stirred at 50 ^{o}C for overnight under H_2 (50 Psi) atmosphere, LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated to give compound **3** (80 mg, crude, 80%) as a white solid, which was used directly for next step without further purification.

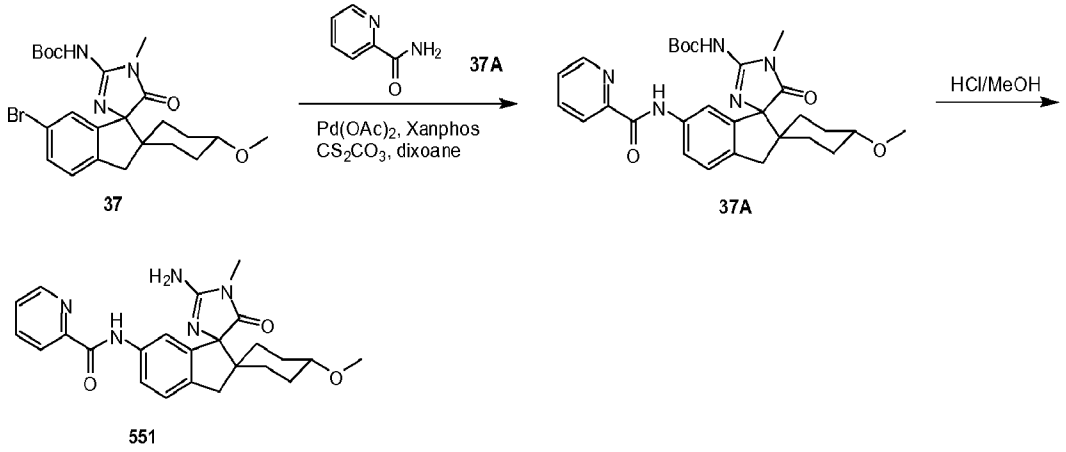
Procedure for preparation of compound 4

A solution of compound **3** (80 mg, 0.18 mmol) and Lawesson's Reagent (89 mg, 0.219 mmol) in dry toluene (10 mL) was heated at reflux for 5 h under a nitrogen atmosphere. LCMS showed that the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (CH_2Cl_2/MeOH = 15:1) to give compound **4** (50 mg, 61%) as a white solid.

Procedure for preparation of compound 590

A mixture of compound **4** (50 mg, 0.11 mmol) and *t*-butyl hydroperoxide (305 mg of a 65% solution in water, 2.2 mmol) in NH_4OH/MeOH (2 mL/10 mL) was stirred overnight at room temperature, LCMS showed that the reaction was completed, which was concentrated under reduced pressure to dryness. Purification of this residue by preparative TLC (CH_2Cl_2/MeOH = 10:1) and preparative HPLC to gave compound **590** (6.7 mg, 14%) as a white solid, **LC-MS** t_R = 1.055 min in 2min chromatography, MS (ESI) *m/z* 438.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.11-7.13 (d, J = 7.6 Hz, 1H), 7.03-7.05 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 4.07-4.14 (m, 1H), 3.26 (s, 3H), 2.97-3.05 (m, 1H), 2.87-2.93 (m, 2H), 2.70-2.77 (m, 2H), 2.24-2.36 (m, 2H), 1.91-1.97 (m, 1H), 1.75-1.85 (m, 2H), 1.42-1.48 (m, 1H), 1.25-1.35 (m, 7H), 1.15-1.21 (m, 3H); **^{19}F NMR** (CD_3OD 400 MHz 19F): δ -68.09

Example 426. Synthesis of Compound 551



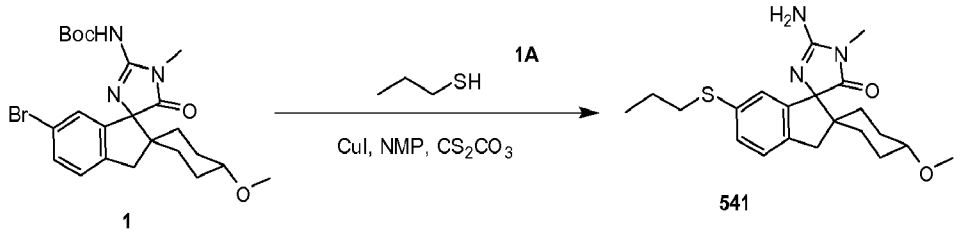
Procedure for preparation of compound 37A

To a solution of compound **37** (50 mg, 0.102 mmol) in *t*-BuOH (2 mL) was added compound **37A** (19 mg, 0.152 mmol), K_3PO_4 (32 mg, 0.152 mmol), $Pd_2(dba)_3$ (5 mg) and 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-i-propylbiphenyl (5 mg,). The reaction mixture was heated at 80~100 °C under a nitrogen atmosphere for 16 h. The mixture was filtered and the filtrate was concentrated by evaporation *in vacuo* to give the residue, which was purified by preparative TLC (petroleum: EtOAc, 1: 1) to afford compound **37A** (40 mg, 74%) as a white solid.

Procedure for preparation of compound 551

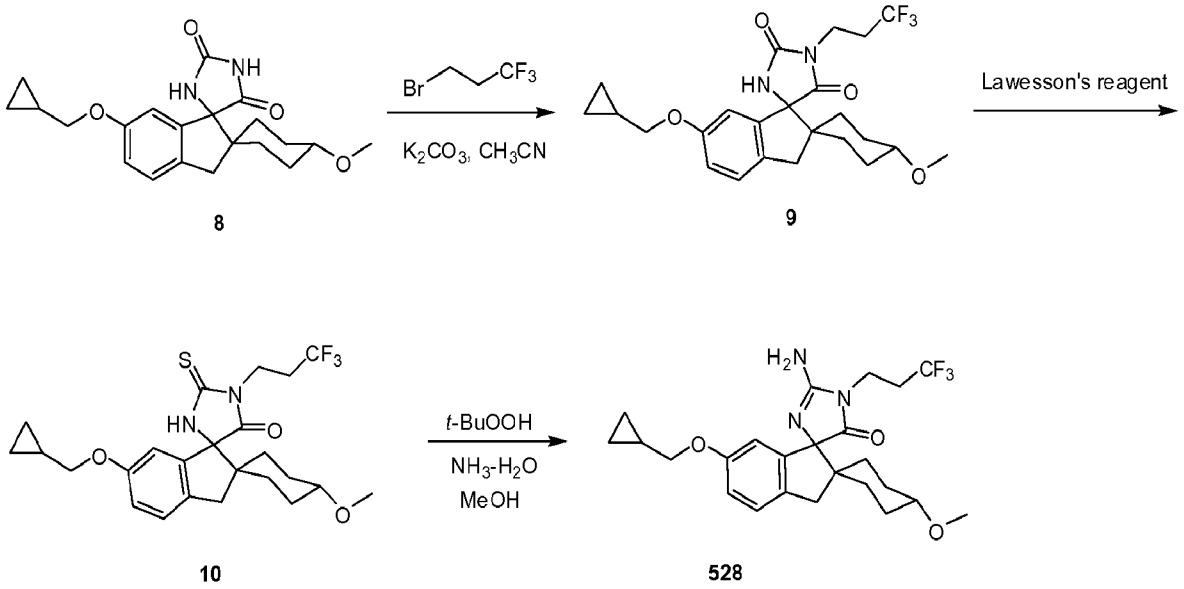
A solution of compound **37A** (50 mg, 0.093 mmol) in HCl/MeOH (10 mL, 5 M) was stirring at room temperature overnight. LCMS showed the reaction was completed and 3 N aqueous NaOH was added until pH = 9. MeOH was removed and the aqueous phase was extracted with EtOAc (3 × 20 mL). the organic layer was washed with brine, dried over Na2SO4 and concentrated to give the residue, which was purified by acidic RP-HPLC to give compound **VT_B111609_07** (10 mg, 25%) as a white solid, **LC-MS** t_R = 0.900 min in 2min chromatography, MS (ESI) *m/z* 434.1 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.72 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.64 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 3.16-3.23 (m, 6H), 2.04-2.11 (m, 2H), 1.91 (m, 1H), 1.49-1.53 (m, 4H), 1.35-1.47 (m, 1H).

Example 427. Synthesis of Compound 541



A mixture of compound **1** (50 mg, 0.1 mmol), compound **1A** (7.6 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol) and Cs_2CO_3 (66 mg, 0.2 mmol) in NMP (1 mL) was placed into CEM microwave reactor and irradiated at 195 °C for 1 h. After being cooled to room temperature, the mixture was partitioned between H_2O (10 mL) and EtOAc(20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to dryness. The residue was purified by RP-HPLC (acidic) to give the compound **541** (3.5 mg, 9%) as a white solid, **LC-MS** t_R = 0.971 min in 2 min chromatography, MS (ESI) m/z 388.1 $[M+H]^+$; **^{1}H-NMR** (CD_3OD 400 MHz): δ 7.31-7.38 (m, 2H), 7.22 (s, 1H), 3.33 (s, 3H), 3.13 (s, 3H), 3.07 (m, 1H), 2.98-3.03 (m, 2H), 2.88-2.94 (m, 2H), 2.02-2.09 (m, 2H), 1.84 (m, 1H), 1.61-1.67 (m, 2H), 1.30-1.45 (m, 5H), 1.01-1.04 (m, 3H)

Example 428. Synthesis of Compound 528



Procedure for preparation of compound 9

To a solution of compound **8** (100 mg, 0.27 mmol) in CH_3CN (5 mL) was added K_2CO_3 (74 mg, 0.54 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then 3-bromo-1, 1, 1-trifluoro-propane (47.8 mg, 0.27 mmol) in CH_3CN (5 mL) was added dropwise via a syringe with stirring. The mixture was stirred at 60 °C overnight, and then the mixture was filtered off, the filtrate was concentrated to give compound **9** (97 mg, 80%) as a white solid, which was used for the next step directly without purification. **LC-MS** t_R = 1.392 min in 2min chromatography, MS (ESI) *m/z* 467.2 $[M+H]^+$.

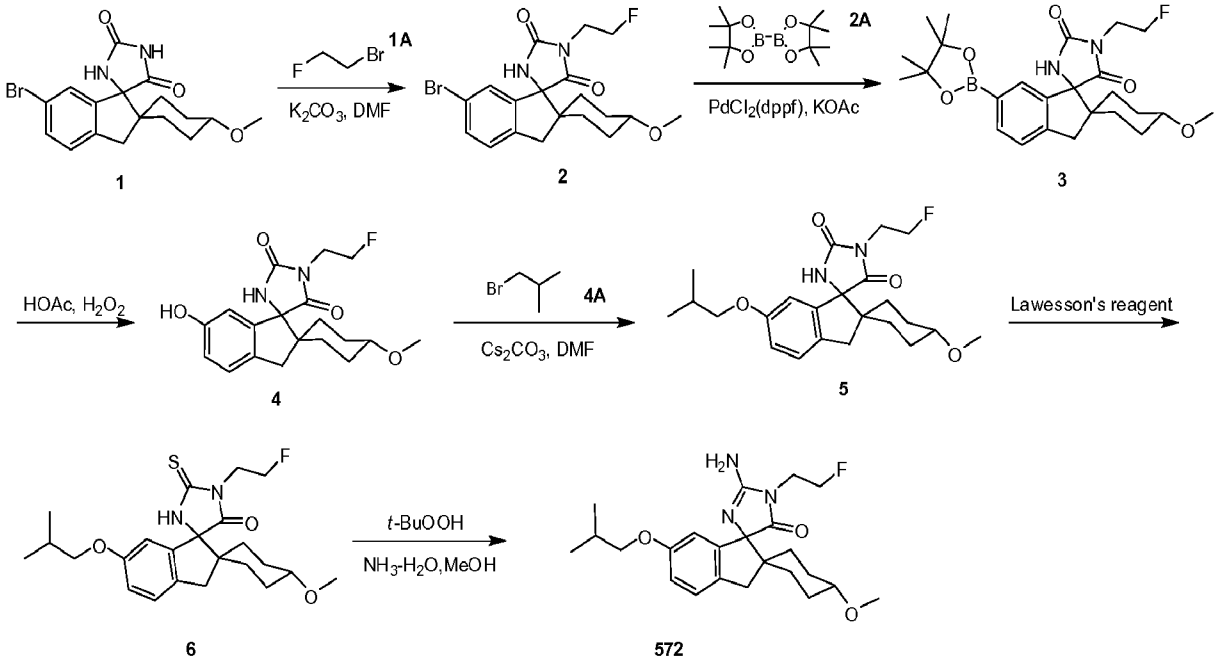
Procedure for preparation of compound 10

To a solution of compound **9** (90 mg, 0.19 mmol) in anhydrous toluene (10 mL) was added Lawesson's reagent (84 mg, 0.20 mmol) under a nitrogen atmosphere, the mixture was heated to reflux for 12 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography on silica gel eluting with petroleum ether: EtOAc (3: 1) to give compound **10** (65 mg, 70%) as a white solid. **LC-MS** t_R = 1.503 min in 2min chromatography, MS (ESI) *m/z* 483.1 $[M+H]^+$.

Procedure for preparation of compound 528

To a solution of compound **10** (65 mg, 0.135 mmol) in MeOH (10 mL) was added NH_3-H_2O (3 mL) and *tert*-butyl hydroperoxide (1 mL). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (50 mL) and H_2O (20 mL). The organic layer was separated and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by basic RP-HPLC to give **compound 528** (28.10 mg, 44%) as a white solid. **LC-MS**: t_R = 1.150 min in 2min chromatography, MS (ESI) *m/z* 466.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.19 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 3.80-3.86 (t, J = 9.6 Hz, 2H), 3.75-3.76 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 3.06-3.17 (m, 1H), 2.96-3.06 (m, 2H), 2.49-2.60 (m, 2H), 1.95-2.10 (m, 2H), 1.85-1.95 (m, 1H), 1.53-1.60 (m, 1H), 1.30-1.53 (m, 2H), 1.10-1.35 (m, 3H), 0.5-0.7 (m, 2H), 0.2-0.4 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -66.67.

Example 429. Synthesis of Compound 572



Procedure for preparation of compound 2

To a solution of compound **1** (300 mg, 0.79 mmol) in DMF (5 mL) was added K_2CO_3 (328 mg, 2.37 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then compound **1A** (96 mg, 0.79 mmol) in DMF (2 mL) was added dropwise via a syringe with stirring. The mixture was stirred at 40 °C for 1 h. The reaction mixture was partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The separated organic phase was washed with brine (3 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **2** (335 mg, 100%) as a white solid, which was used for the next step directly without purification. **LC-MS** t_R = 1.094 min in 2min chromatography, MS (ESI) *m/z* = 425.0 $[M+H]^+$.

Procedure for preparation of compound 3

To a solution of compound 2 (340 mg, 0.8 mmol) in 1, 4-dioxane (20 mL) was added compound **2A** (243 mg, 0.96 mmol), $PdCl_2$(dppf) (100 mg), and KOAc (235 mg, 2.4 mmol). The mixture was refluxed for 4 h under nitrogen. After cooling down, the mixture was filtered and the filtrate was concentrated to give compound **3** (370 mg, crude), which was used for the next step directly without purification.**LC-MS** t_R = 1.182 min in 2min chromatography, MS (ESI) *m/z* = 473.2 $[M+H]^+$.

Procedure for preparation of compound 4

To a solution of compound **3** (370 mg, 0.8 mmol) in THF (8 mL) was added HOAc (3 mL) and H_2O_2 (5 mL), the mixture was stirred at room temperature overnight. Then quenched with aqeous $NaHSO_3$ (10 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to give compound **4** (200 mg, 70%) as a white solid. **LC-MS** t_R = 0.924 min in 2min chromatography, MS (ESI) *m/z* = 363.1 $[M+H]^+$.

Procedure for preparation of compound 5

To a solution of compound **4** (95 mg, 0.26 mmol) in DMF (5 mL) was added compound **4A** (40 mg, 0.26 mmol) and Cs_2CO_3 (325 mg, 1.0 mmol), the mixture was stirred at 40 °C for 4 h. Then quenched with H_2O (10 mL), extracted with EtOAc (3 × 15 mL), the combined organic layer was dried over Na_2SO_4, filtered and concentrated to

give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 3: 1) to give compound **5** (100 mg, 91%) as a white solid. **LC-MS** t_R = 1.163 min in 2min chromatography, MS (ESI) *m/z* = 419.2 $[M+H]^+$.

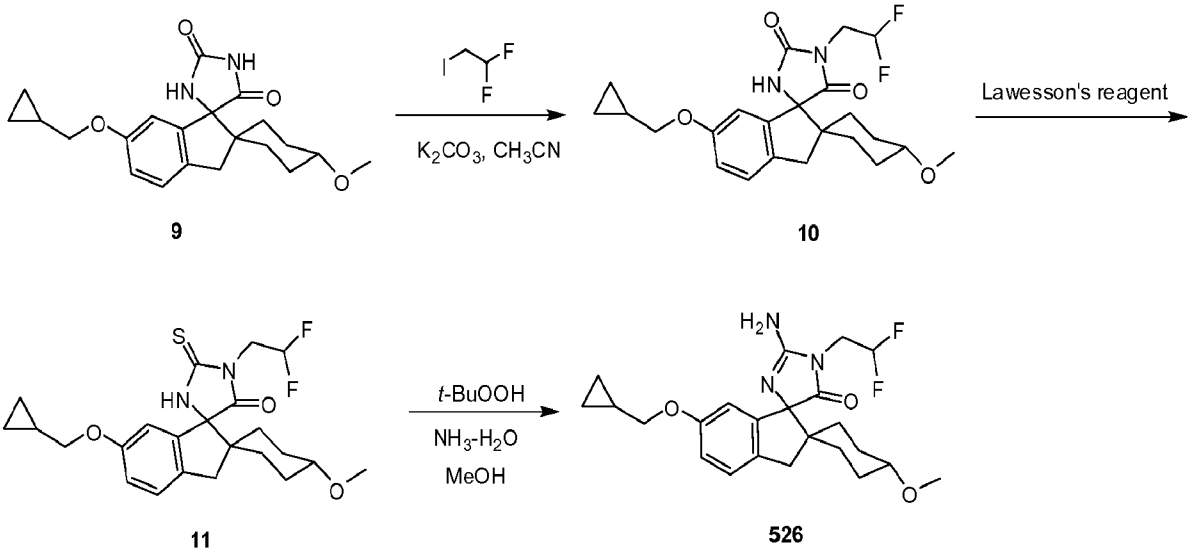
Procedure for preparation of compound 6

A 8 mL vial was charged with compound **5** (130 mg, 0.316 mmol) and Lawesson's reagent (138 mg, 0.342 mmol). Toluene (2 mL) was added, and the vial was sealed and placed into CEM microwave reactor and irradiated at 140 °C for 1 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography over silica gel (petroleum ether: EtOAc, 50: 1 to 10: 1) to give compound **6** (35 mg, 25%) as a whit solid. **LC-MS** t_R = 1.244 min in 2min chromatography, MS (ESI) *m/z* = 435.2 $[M+H]^+$.

Procedure for preparation of compound 572

To a solution of compound **6** (35 mg, 0.080 mmol) in MeOH (10 mL) was added NH_3-H_2O (3 mL) and *tert*-butyl hydroperoxide (117 mg, 0.8 mmol). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation. The residue was purified by preparative HPLC to give **compound 572** (4.8 mg, 14%) as a white solid. **LC-MS** t_R = 1.011 min in 2min chromatography, MS (ESI) *m/z* = 418.2 $[M+H]^+$; **^{1}H NMR**: (CD_3OD 400 MHz): δ 7.14-7.16 (d, *J* = 8.4 Hz, 1H), 6.81-6.84 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 4.43-4.57 (m, 2H), 3.89-4.03 (m, 2H), 3.59-3.61 (d, *J* = 6.4 Hz, 1H), 3.25 (s, 1H), 2.91-3.09 (m, 3H), 1.76-1.97 (m, 4H), 1.22-1.41 (m, 5H), 1.18-1.21 (m, 6H); **^{19}F NMR** (CD_3OD 19F 400 MHz): δ -75.932

Example 430. Synthesis of Compoud 526



9 10 11 526

Procedure for preparation of compound 10

To a solution of compound **9** (100 mg, 0.27 mmol) in CH_3CN (5 mL) was added K_2CO_3 (74 mg, 0.54 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then 1, 1-difluoro-2-iodo-ethane (51.8 mg, 0.27 mmol) in CH_3CN (5 mL) was added dropwise via a syringe with stirring. The mixture was stirred at 60 °C overnight. Then the mixture was filtered off, the filtrate was concentrated to give compound **10** (90 mg, 77%) as a white solid, which was used for the next step directly without purification. **LC-MS** t_R = 1.337 min in 2min chromatography, MS (ESI) *m/z* 435.2 $[M+H]^+$.

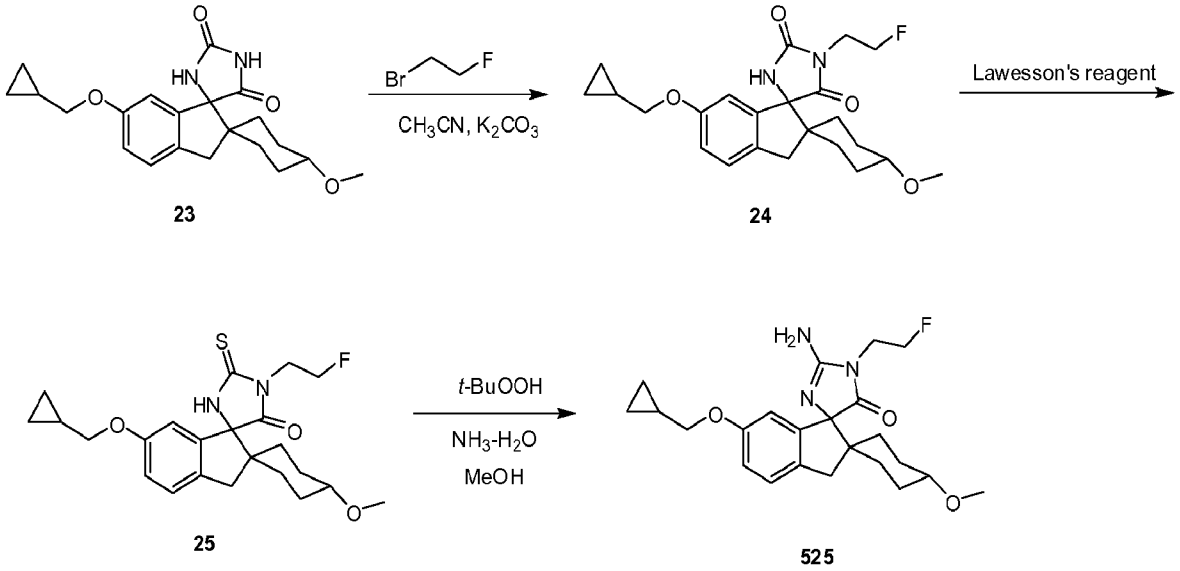
Procedure for preparation of compound 11

To a solution of compound **10** (90 mg, 0.20 mmol) in anhydrous toluene (10 mL) was added Lawesson's reagent (92 mg, 0.22 mmol) under a nitrogen atmosphere, the mixture was heated at reflux for 12 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography over silica gel petroleum ether: EtOAc = 3: 1 to give compound **11** (65 mg, 70%) as a white solid.**LC-MS** t_R = 1.439 min in 2min chromatography, MS (ESI) *m/z* 451.1 $[M+H]^+$.

Procedure for preparation of compound 526

To a solution of compound **11** (65 mg, 0.14 mmol) in MeOH (10 mL) was added NH_3-H_2O (3 mL) and *tert*-butyl hydroperoxide (1 mL). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (20 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by basic preparative HPLC to give **compound 526** (25.20 mg, 40%) as a white solid. **LC-MS**: t_R = 1.109 min in 2min chromatography, MS (ESI) *m/z* 434.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.19 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 5.92-6.22 (t, J = 55.6 Hz, 1H), 3.92-4.04 (d, J = 12.4 Hz, 2H), 3.75-3.77 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 3.05-3.17 (m, 1H), 2.96-3.01 (m, 2H), 1.95-2.10 (m, 2H), 1.81-1.95 (m, 1H), 1.56-1.63 (m, 1H), 1.30-1.56 (m, 2H), 1.17-1.30 (m, 3H), 0.5-0.7 (m, 2H), 0.2-0.4 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -124.36

Example 431. Synthesis of Compound 525



Procedure for preparation of compound 24

To a solution of compound **23** (100 mg, 0.27 mmol) in CH_3CN (5 mL) was added K_2CO_3 (74 mg, 0.54 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then 1-bromo-2-fluoro-ethane (41 mg, 0.27 mmol) in CH_3CN (5 mL) was added dropwise via a syringe with stirring. The mixture was stirred at 60 °C overnight. Then the mixture was filtered off, the filtrate was concentrated to give compound **24** (87 mg, 77%) as a white solid which was used for the next step directly without purification. **LC-MS** t_R = 1.303 min in 2min chromatography, MS (ESI) *m/z* 417.2 $[M+H]^+$.

Procedure for preparation of compound 25

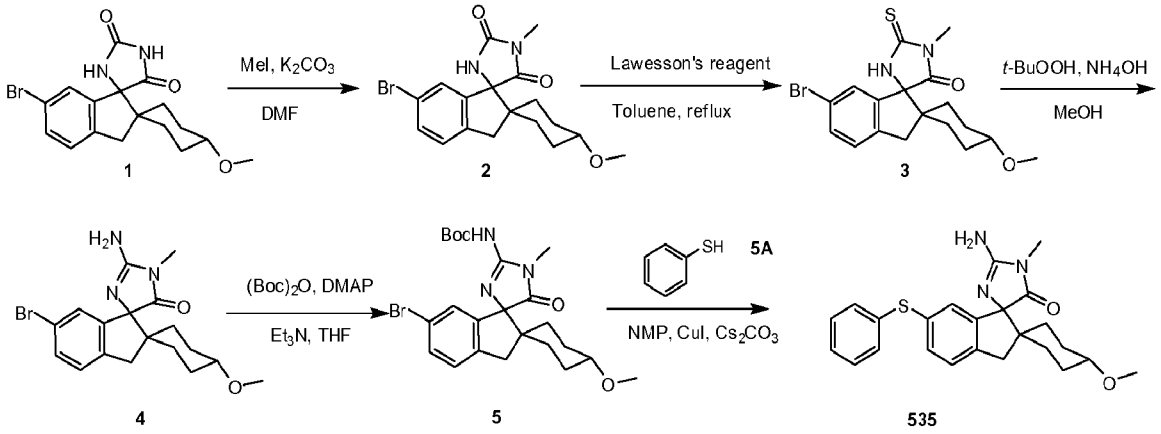
To a solution of compound **24** (87 mg, 0.209 mmol) in anhydrous toluene (10 mL) was added lawsson`s reagent (93 mg, 0.23 mmol) under a nitrogen atmosphere, the mixture was heated at reflux for 12 h. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography on silica gel eluting with petroleum ether: EtOAc (3: 1) to give compound **25** (63 mg, 70%) as a white solid. **LC-MS** t_R = 1.406 min in 2min chromatography, MS (ESI) *m/z* 433.2 $[M+H]^+$.

Procedure for preparation of compound 525

To a solution of compound **25** (63 mg, 0.145 mmol) in MeOH (10 mL) was added NH_3-H_2O (3 mL) and *tert*-butyl hydroperoxide (1 mL). After addition, the mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (20 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by basic RP-HPLC to give **compound 525** (39.60 mg, 65%) as a white solid. **LC-MS**: t_R = 1.083 min in 2min chromatography, MS (ESI) *m/z* 416.2 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.19 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.53 (s, 1H), 4.59-4.70 (m, 1H), 4.49-4.59 (m, 1H), 3.82-3.95 (m, 2H), 3.75 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 3.05-3.17 (m, 1H), 2.90-3.05 (m, 2H), 1.95-2.03 (m, 2H), 1.82-1.92

(m, 1H), 1.52-1.64 (m, 1H), 1.30-1.52 (m, 2H), 1.10-1.30 (m, 3H), 0.50-0.70 (m, 2H), 0.20-0.40 (m, 2H); **^{19}F NMR** (CD_3OD 400 MHz): δ -76.90.

Example 432. Synthesis of Compound 535



Procedure for preparation of compound 2

To a solution of compound **1** (6.0 g, 15.9 mmol, crude) in DMF (80 mL) was added K_2CO_3 (3.3 g, 23.8 mmol). After addition, the resulting mixture was stirred at room temperature for 10 min. Then iodomethane (2.1 g, 15.9 mmol) in DMF (2 mL) was added dropwise via a syringe with stirring. The mixture was stirred at room temperature overnight. The reaction mixture was partitioned between H_2O (200 mL) and ethyl acetate (600 mL). The separated organic phase was washed with saturated brine (3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude compound **5** (6.13 g, 90%) as a white solid, which was used for the next step directly without purification.

Procedure for preparation of compound 3

To a solution of compound **2** (4.0 g, 10.2 mmol) in toluene (100 mL) was added Lawesson's reagent (4.53 g, 11.2 mmol). The resulting mixture was heated at reflux overnight. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by column chromatography over silica gel (petroleum ether: EtOAc = 10: 1) to give compound **3** (4.7 g, 68%) as a whit solid.

Procedure for preparation of compound 4

To a solution of compound **3** (4.7 g, 11.5 mmol) in MeOH (450 mL) was added NH_3-H_2O (90 mL) and *tert*-butyl hydroperoxide (31.9 g, 230.4 mmol). After addition, the mixture was stirred at 40°C for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (600 mL) and H_2O (100 mL). The organic layer was separated and washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude compound **4** (3.8 g, 60% purity, 72%) as a white solid, which was used for the next step directly without purification.

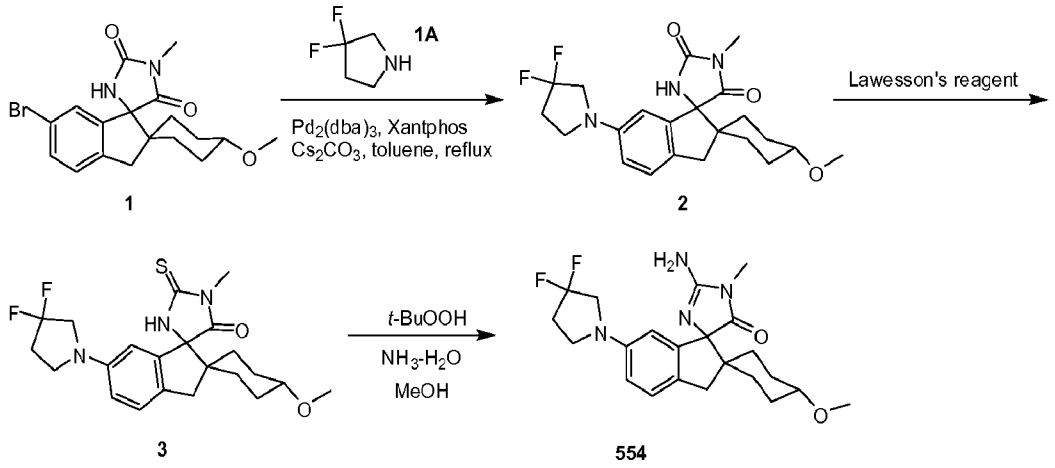
Procedure for preparation of compound 5

To a solution of compound **4** (3.8 g, 60% purity, 9.7 mmol) in THF (40 mL) was added Boc_2O (8.5 g, 38.9 mmol), DMAP (2.4 g, 19.4 mmol) and Et_3N (2 mL, 19.4 mmol). After addition, the mixture was stirred at 40 °C for 24 h. The solvent was removed by evaporation *in vacuo*. The resulting residue was purified by column chromatography over silica gel (petroleum ether: EtOAc = 10: 1) to give compound **5** (1.7 g, 61%) as a whit solid.

Procedure for preparation of compound 535

A mixture of compound **5** (50 mg, 0.1 mmol), compound **5A** (11.2 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Cs_2CO_3 (66 mg, 0.2 mmol) in NMP (1 mL) was placed into CEM microwave reactor and irradiated at 195°C for 1 h under nitrogen atmosphere. After being cooled to room temperature, the mixture was added brine (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to dryness. The residue was purified by RP-HPLC to give compound **compound 535** (15 mg, 36%) as a white solid. **LC-MS**: t_R = 0.987 min in in 2 min chromatography, MS (ESI) m/z 422.0 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.26-7.38 (m, 8H), 3.36 (s, 3H), 3.10-3.21 (m, 6H), 2.02-2.09 (m, 2H), 1.84-1.87 (m, 1H), 1.30-1.45 (m, 5H).

Example 433. Synthesis of Compound 554



Procedure for preparation of compound 2

To a solution of compound **1** (150 mg, 0.38 mmol) in toluene (5 mL) was added compound **1A** (82 mg, 0.57 mmol), Cs_2CO_3 (371 mg, 1.14 mmol), $Pd_2(dba)_3$ (7.5 mg), and Xantphos (30 mg) under a nitrogen atmosphere. The reaction mixture was refluxed overnight, then quenched with H_2O (10 mL), the reaction was extracted with EtOAc (3 × 20 mL), the combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to give the residue, which was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to afford compound **2** (108 mg, 68%) as a white solid.

Procedure for preparation of compound 3

An 8 mL vial was charged with compound **2** (116 mg, 0.27 mmol) and Lawesson's reagent (112 mg, 0.27 mmol). Toluene (5 mL) was added, and the vial was refluxed overnight. After cooling down, the solvent was removed by evaporation *in vacuo* and the resulting residue was purified by preparative TLC (petroleum ether: EtOAc = 1: 1) to give compound **3** (70 mg, 58%) as a whit solid.

Procedure for preparation of compound 554

To a solution of compound **3** (100 mg, 0.23 mmol) in MeOH (5 mL) was added NH_3-H_2O (1 mL) and *tert*-butyl hydroperoxide (219 mg, 4.6 mmol). After addition, the

mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation *in vacuo*. The residue was partitioned between EtOAc (contained 10% methanol) (10 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give **compound 554** (6.6 mg, 7%) as a white solid. **LC-MS** t_R = 0.915 min in 2min chromatography, MS (ESI) *m/z* = 419 $[M+H]^+$; **^{1}H NMR** (CD_3OD 400 MHz): δ 7.23 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.46 (s, 1H), 3.67 (m, 2H), 3.52 (m, 2H), 3.48 (m, 2H), 3.21 (s, 3H), 3.09 (m, 1H), 3.04 (m, 2H), 2.50 (m, 2H), 2.05 (m, 2H), 1.83 (m, 1H), 1.49-1.29 (m, 5H); **^{19}F NMR** (19F CD_3OD): δ -96.71.

Example 434. Biological Data

A. BACE Enzyme Assay

Inhibitory activity of compounds was assessed by a fluorescence quench assay of BACE activity using commercially available substrate HiLyte Fluor™488-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-Lys-(QXL™ 520)-OH (AnaSpec, San Jose, CA) and truncated human beta-secretase (residues 1-458, His_6-tagged at the C-terminus) expressed in insect cells *D. melanogaster* S2 using a baculovirus expression system (Mallender *et al.*, Characterization of recombinant, soluble beta-secretase from an insect cell expression system., Mol Pharmacol **59**:619-26, 2001). The assay was performed at room temperature in 96-well white opaque Optiplates aque Optiplates (PerkinElmer, Waltham, MA) in a total volume of 200 µl of the incubation mixture containing 50 mM sodium acetate buffer, pH 4.5, 0.4 µM FRET substrate, 2.4 nM enzyme, 5% DMSO, and 0.05% Brij-35. The tested compounds were serially diluted in DMSO and pre-incubated with the substrate. The reaction was started by addition of enzyme, and the progress of the reaction was followed by measuring fluorescence with an excitation wavelength of 480 nm and an emission wavelength of 520 nm. Ten measurements were taken every 5-10 min, and the intensity of fluorescence was regressed against time in order to derive velocities of reaction in all 96 wells. These velocities were used for

calculating percent inhibition using an uninhibited control containing 5% DMSO and a fully inhibited control incubations performed in the absence of enzyme. IC_{50} values were calculated by fitting percent inhibition *vs.* inhibitor concentration into a four-parametric logistic model using XLFit software (IDBS, Guildford, UK).

B. BACE cell asay

H4 neuroglioma cell line that stably expresses Amyloid Precursor Protein (APP) containing the KM-NL Swedish mutation (H4-APPsw) was generated. For the assay, cells are treated overnight in the presence of inhibitor and the culture media are subjected to ELISA analysis of soluble Amyloid Beta 1-40 (Aβ 1-40).

Materials

H4 neuroglioma cell line: ATCC, Cat #HTB-148

Dulbecco's Minimal Essential Medium (DMEM): Invitrogen, Cat #11995

Fetal bovine serum (FBS): Hyclone, Cat #SH30070.03)

Penicillin/streptomycin: Invitrogen, Cat#15140-122

Zeocin: Invitrogen, Cat #R25001

0.5% Trypsin/EDTA: Invitrogen, Cat #25300

96-well plate for compound serial dilution in DMSO

96-well deep well plate

96-well Black Polymer BTM P-D-L plate: Nunc, Cat #152037

96-well White polystyrene ½ area optiplate: Corning, Cat #3642

DMSO: Sigma, Cat #494429

Aβ 1-40 ELISA kit: Covance, Cat #sig38940

CellTiter Glo Viability Assay: Promega, Cat #G7571

Aβ 1-40 AlphaLISA kit: PerkinElmer, Cat #AL202F

Microscope

Wallac Victor^2 Multilabel HTS counter

PerkinElmer Fusion-Alpha FP-HT Multiplate reader

SpectraMax 384 plus plate reader

Generation and maintenance of H4-APPsw cell line

H4 neuroglioma cell line was cultured in DMEM with 10% FBS and 1% penicillin/streptomycin (Culture Medium) at 37°C, 5% CO_2. The culture plate (150 mm) with 50% confluence of H4 cells was transfected with 15 ug plasmid pcDNA3.1/Neo(+) containing a 2310-bp insert of APPsw at Hind3/Xba1 sites. 24 hrs after transfection, the cells were replaced into three new plates (150 mm) in fresh Culture Medium with 250 ug/mL Zeocin. The stably transfected cell colonies were isolated in about 2-3 weeks. The levels of APPsw expression were analyzed by immunoblotting and the production of Aβ 1-40 was detected by ELISA of culture supernatants. The selected clones are maintained in Culture Medium with 250μg/mL Zeocin and routinely split in 3-4 days to maintain 20-80% confluence.

Assay Protocol

Final Assay Conditions (96-well plate)

H4-APPsw cells	$6x10^3$cells/well
DMEM	200μL
DMSO	0.2%

Day 1

Split cells. Split H4-APPsw cells in Culture Medium and culture overnight such that cells will be ~80% confluent next morning.

Day 2

Create Compound Dilution Plate. After determining the desired final concentration of compound to be tested, create a 500X dilution plate. Add DMSO, but not inhibitor, to each well of Column 1. Use Column 2 for Control Compound (BACE inhibitor IV, EMD Bioscience, Cat #565788) serial dilution starting at 5mM (final concentration of 2.5μM). Add compounds of interest at 500X desired final concentration to wells A3-

A10. Add DMSO, but not inhibitor, to each well of Columns 11 and 12. Dilute contents of Row A 1:3 in Row B, then continue through Rows C-H.

Create Media Plate. To create a 2X solution of compound in media, add 996µL Culture Medium to each well of a 96-well 2mL deep well plate (Media Plate) in biosafety hood. Add 4µL 5mM control compound to Media Plate wells A1-D1 for determination of full inhibition. Add 4µL from Compound Dilution Plate to corresponding wells of Medium Plate (do not add additional DMSO to wells A1-D1).

Add media to Cell Plate. With a multichannel pipettor, mix each well of Media Plate several times to insure homogeneity. Add 100µL of mixture to Black polymer bottom P-D-L plates. Next, place Medium Plate and Cell Plate in the incubator.

Add cells to Cell Plate. Trypsinize and count H4-APPsw cells. Dilute cells $6x10^5$ cells/mL in Culture Medium and remove Cell Plate from incubator. Vortex cells to homogeneity, then using a multichannel repeating pipettor, add 100µL cell suspension to Cell Plate, adding cells from Row H to Row A. Place Cell Plate in incubator.

Change media in Cell Plate. After 5h, check Cell Plate by microscope to insure cells are attached. In culture hood, remove media from Cell Plate using multichannel repeating pipettor. Add 100µl Culture Medium to each well. Remove Media Plate from incubator and mix with pipettor as previous. Add 100µl from each well of Media Plate to corresponding well in Cell Plate. Place Cell Plate in incubator overnight.

Day 3

Perform ELISA to determine levels of secreted Aβ 1-40. After 16h incubation, spin Cell Plate for 8 min at 1200 rpm. The primary reading of Aβ 1-40 levels is done using PerkinElmer AlphaLISA technology. Follow the manufacturer's protocol for performing AlphaLISA in a white ½ area Optiwell plate using Row 12 for peptide standard (1:2 dilutions, starting at 15ng/ml). Data are acquired using PerkinElmer Fusion-Alpha FP-HT, Alpha protocol (Count Time 0.6s, Count Time Ratio 30%:70%). To validate IC50 determinations, a second Aβ 1-40 ELISA was performed using a kit

from Covance that uses different antibodies to Aβ 1-40 and a different detection method (absorbance at 490nM) than the PerkinElmer kit.

Perform viability assay to determine compound toxicity. Remove remaining media from Cell Plate and add 100μL CellTiter Glo reagent to cells. Incubate 9 min at room temperature and read luminescence counts on Wallac Victor^2 Multilabel HTS counter.

Data Reduction

Export data from Fusion using Columnar Report format into a separate file for each plate. Upload data into Activity Base using RIA-DOSE-RESPONSE protocol (Version 1). Data from at least eight doses were fitted to a four parameter logistical model using XLfit software to determine potency.

Results

The *in vitro* cell activity studies were carried out for compounds of the invention and the data is shown below:

COMPOUND NO.	IC_{50}
1-4	*****
5-7	****
8	*****
9	****
10	**
11-12	*****
13	****
14	*****
15	**
16	*****
17	***
18	*****

19-20	****
21-23	**
25	*****
26	**
27	*
28-29	****
30-31	**
34-35	***
36	*
38	#
39	*
40-41	**
42	*****
43-45	**
46-47	*
49-50	***
52	**
53	#
54	**
56-57	**
58	*****
59	****

represents IC_{50} less than 50 μM; * represents IC_{50} less than 10 μM; ** represents IC_{50} less than 5 μM; *** represents IC_{50} less than 1 μM; **** represents IC_{50} less than 500 nM; ***** represents IC_{50} less than 100 nM.

Example 435. BACE Assay

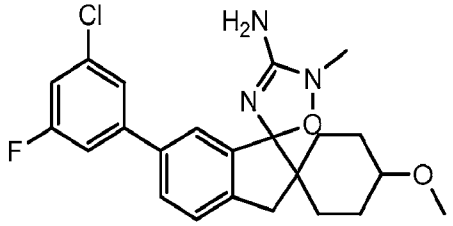
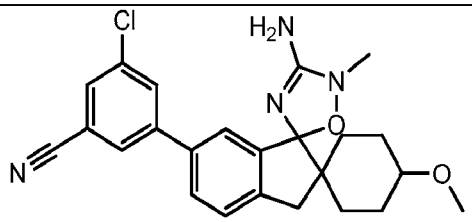
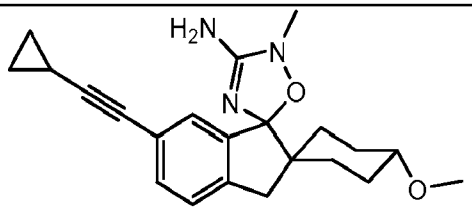
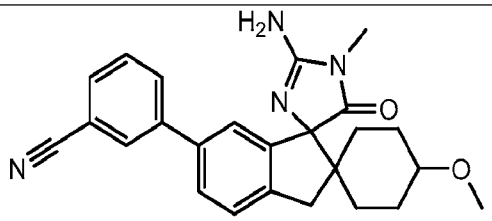
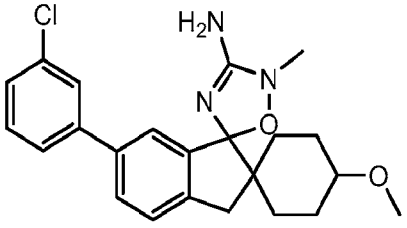
For each compound being tested, the BACE activity was monitored in a fluorescence quenching assay (FRET) using the ectodomain of BACE (aa 1-454) fused to a myc-his tag and secreted from HEK293/$BACE_{ect.}$ cells into OptiMEM™ (Invitrogen) as enzyme source and a substrate peptide derived from the APP-Swedish mutation which possesses a Cy3-fluorophore at the N-terminus and a Cy5Q-quencher at the C-terminus (Cy3-SEVNLDAEFK-Cy5Q-NH2; Amersham). The substrate was dissolved at 1 mg/mL in DMSO.

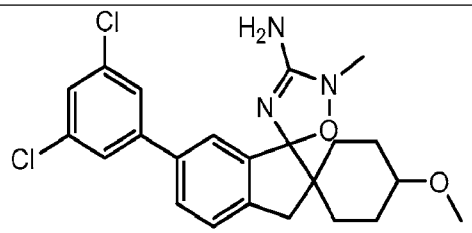
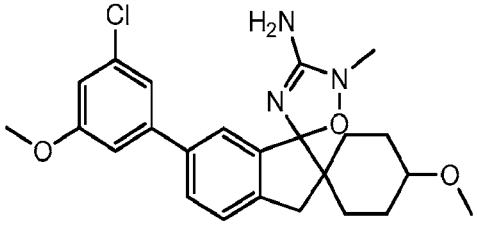
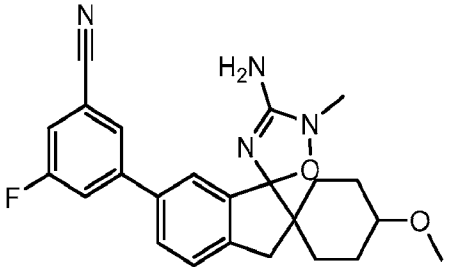
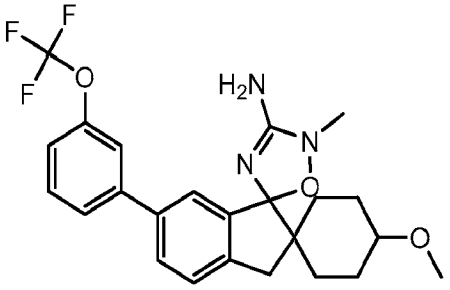
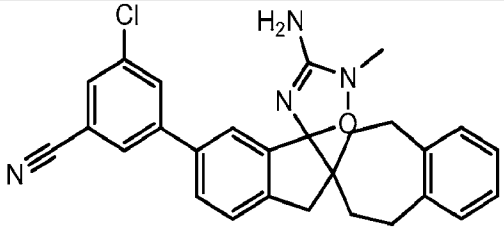
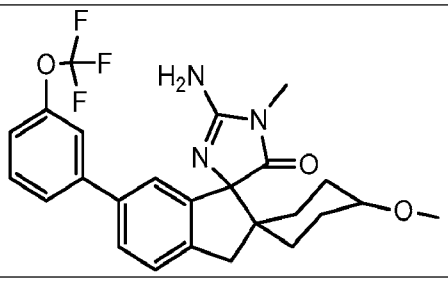
The assay was performed in the presence of 5 µl OptiMEM (supernatant collected over 24 hours and cleared from cellular debris by centrifugation) containing the ectodomain of BACE, 25 µl water containing the desired concentration of test compound and 1% DMSO, 1 µM substrate peptide, 20 mM NaOAc, pH 4.4 and 0.04% Triton-X100 in a total assay volume of 50 µl in a 384 well plate. In general, 25 µl of compound dilution were given to the plate followed by the addition of 10 µl of BACE containing OptiMEM™ diluted 1:2 in water with 0.2% Triton X-100. The reaction was started with the addition of 15 µl substrate in NaOAc buffer. The reaction was incubated at 30°C in a fluorimeter and the cleavage of the substrate was recorded as kinetic for 60 min. at ex: 530 nm, em: 590 nm. Blank wells containing either no inhibitor or no enzyme were included on each plate.

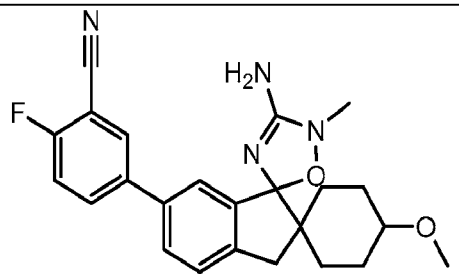
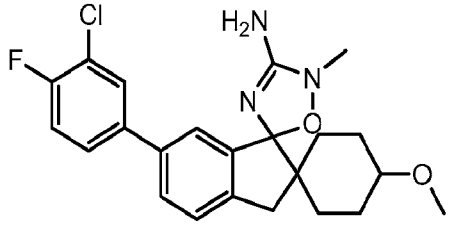
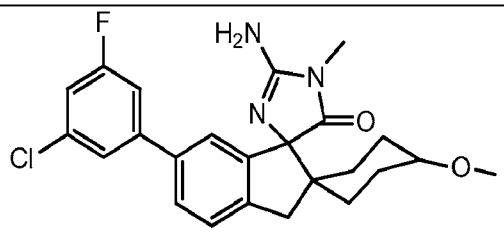
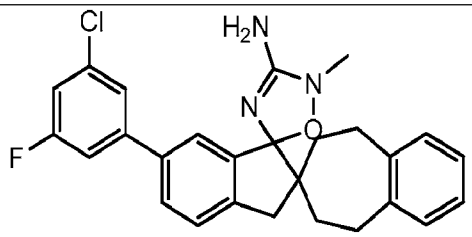
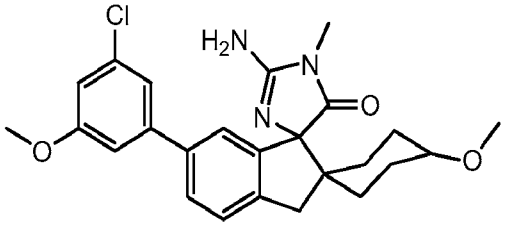
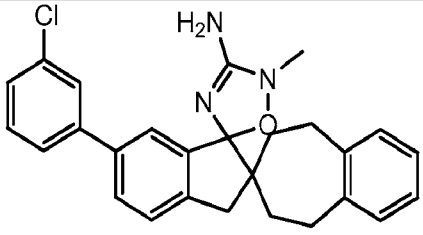
The intensity of fluorescence was regressed against time in order to derive velocities of reaction in all 384 wells. These velocities were used for calculating percent inhibition using an uninhibited control containing 1% DMSO and a fully inhibited control incubations performed in the absence of enzyme. IC_{50} values were calculated by fitting percent inhibition *vs.* inhibitor concentration using standard software like GraphPadPrism.

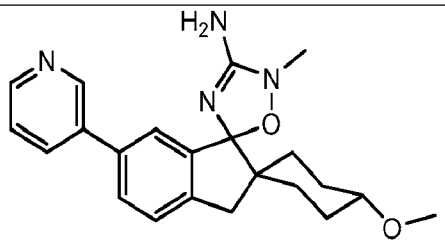
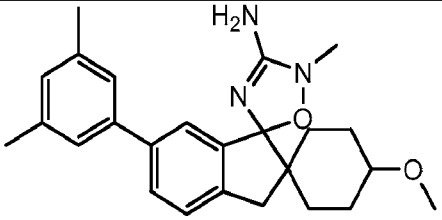
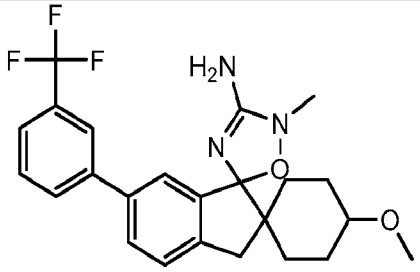
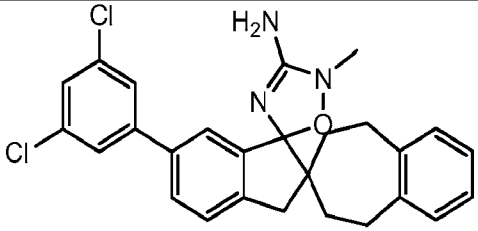
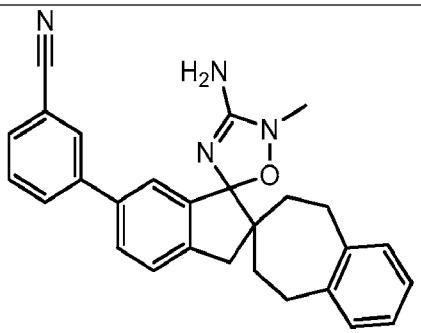
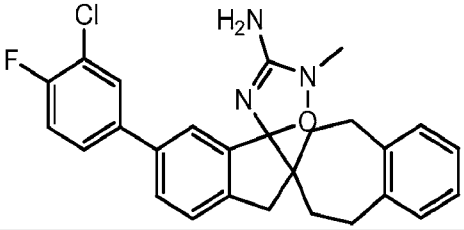
Using this assay protocol, compound dilutions were either done using a Tecan Freedom EV0(assay format A) or manually using multichannel pipettes (assay format B).

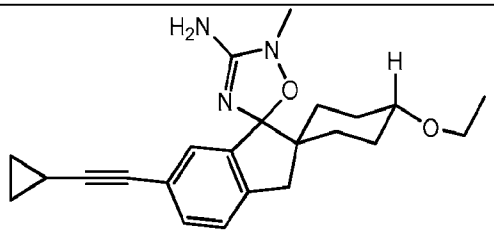
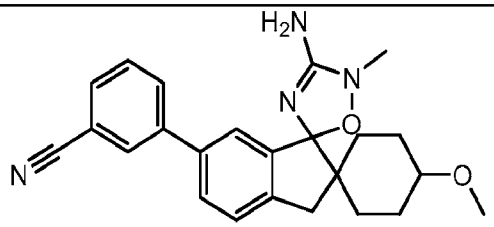
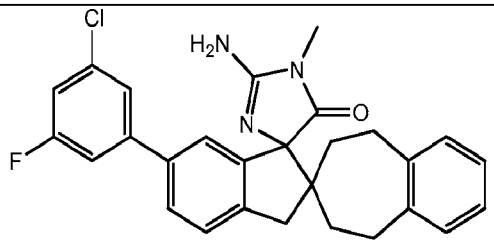
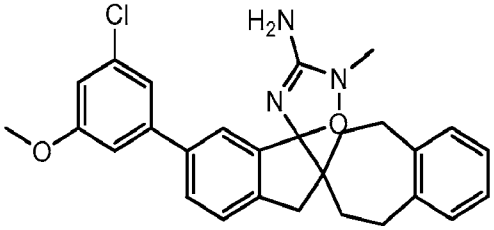
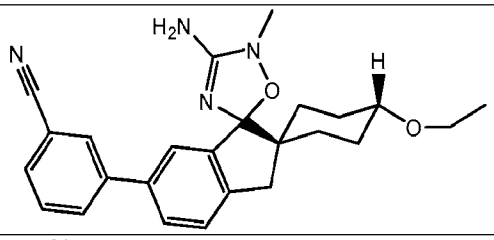
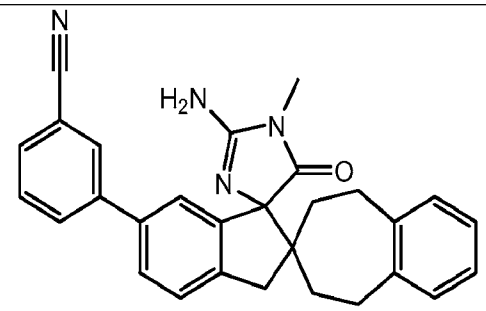
The BACE inhibitor activities of compounds of the invention were tested according to protocols described in Example 434A or Example 435, and are shown below:

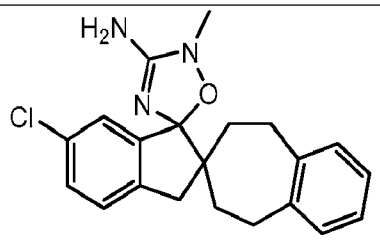
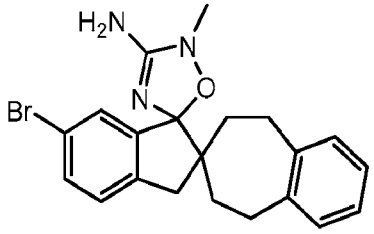
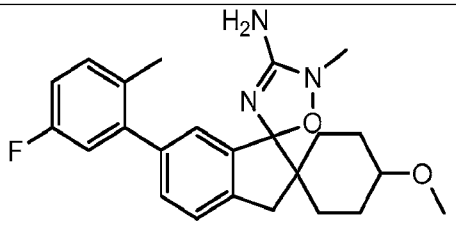
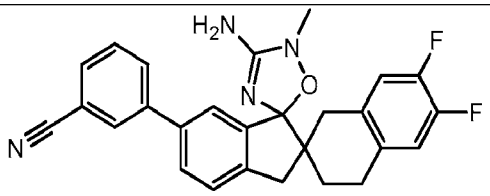
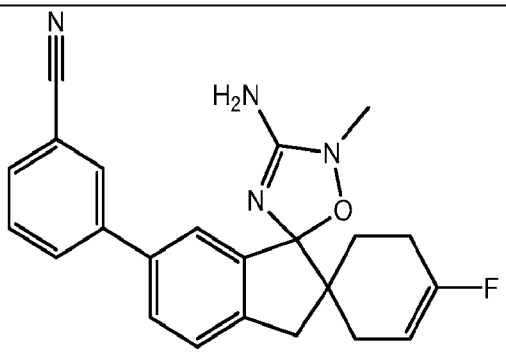
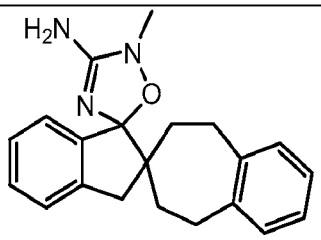
Compound No.	Structure/ Ex. No.	IC_{50} (nM)
1	 Ex. 49	2.6[a]
2	 Ex. 50	3.5[a]
3	 Ex. 54	4.5[a]
4	 Ex. 27	4.0[a]
5	 Ex. 33	4.5[a]

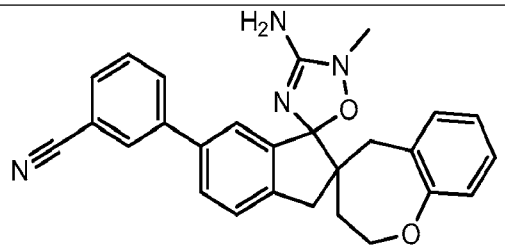
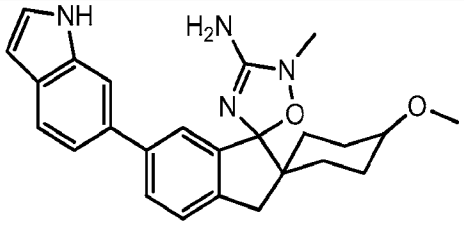
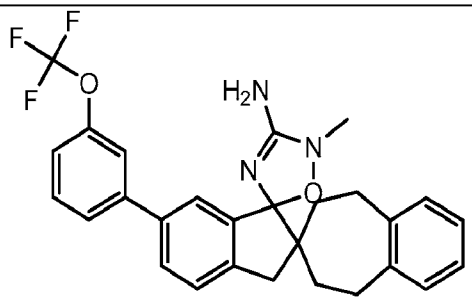
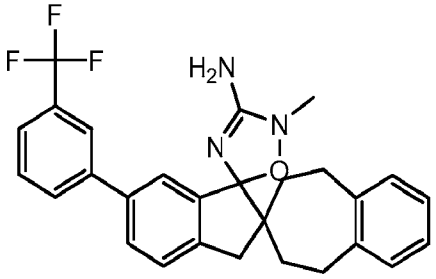
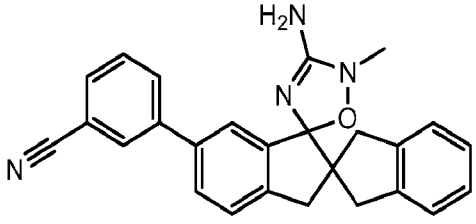
6	 Ex. 35	4.8[a]
7	 Ex. 51	5.9[a]
8	 Ex. 38	5.9[a]
9	 Ex. 37	7.0[a]
10	 Ex. 47	7.4[a]
11		7.8[a]

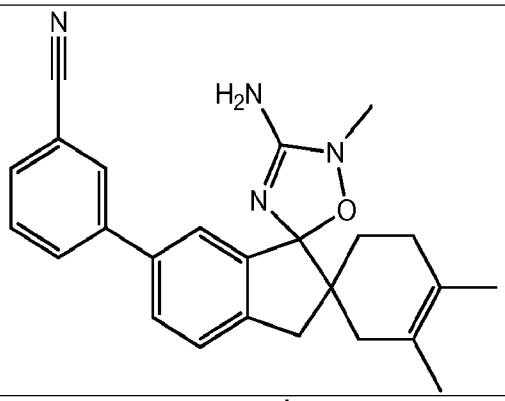
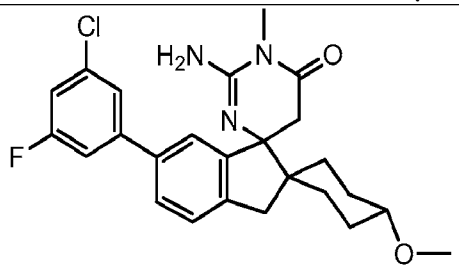
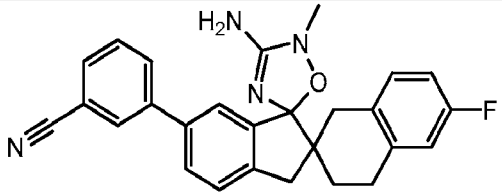
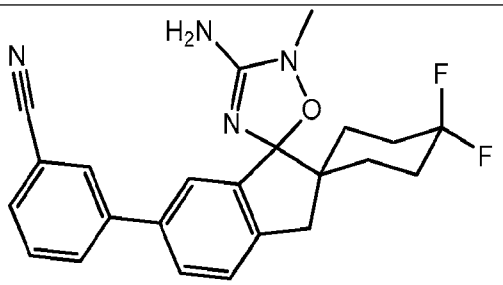
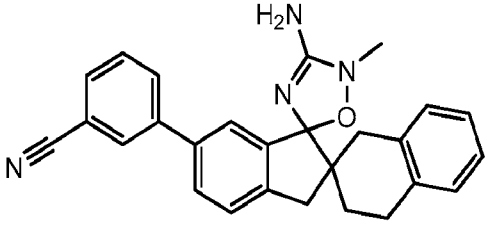
	Ex. 29	
12	 Ex. 39	7.9[a]
13	 Ex. 32	8.8[a]
14	 Ex. 30	11.1[a]
15	 Ex. 45	11.2[a]
16	 Ex. 55	11.5[a]
17	 Ex. 43	12.1[a]

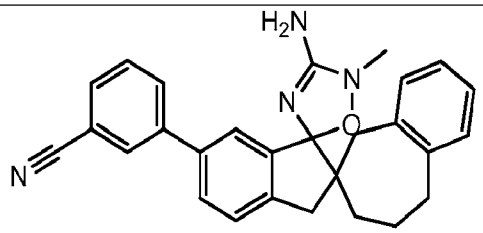
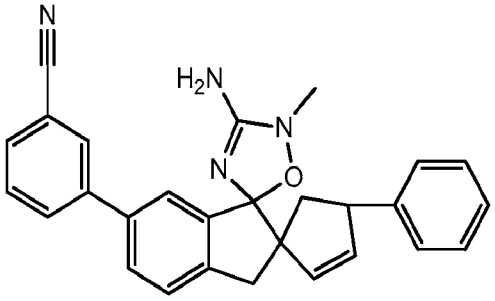
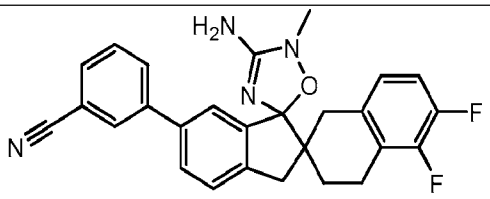
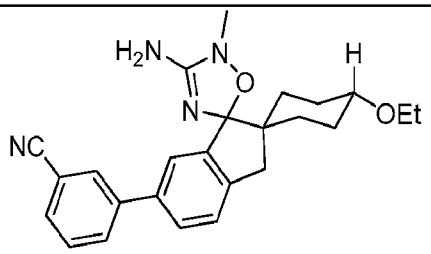
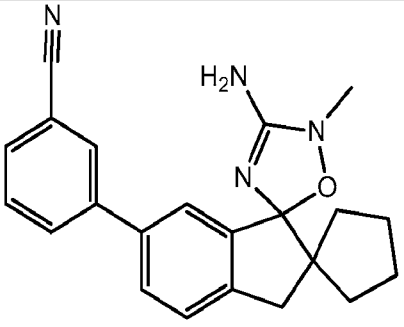
18	 Ex. 59	16.8[a]
19	 Ex. 34	14.6[a]
20	 Ex. 36	18.7[a]
21	 Ex. 46	18.9[a]
22	 Ex. 20	19.3[a]
23		20.7[a]

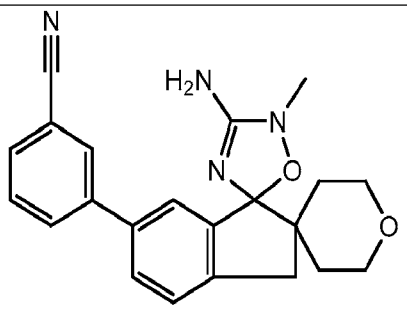
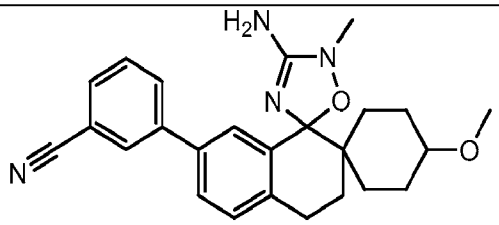
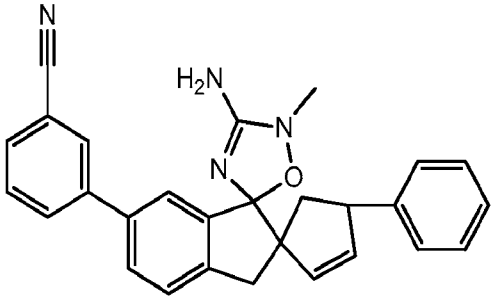
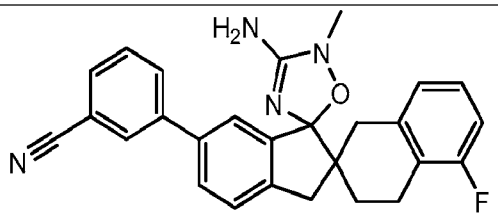
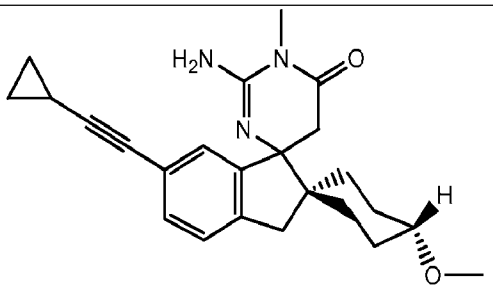
	Ex. 44	
24	 Ex. 14	21.0 [a]
25	 Ex. 17	26.2 [a]
26	 Ex. 15	
27	 Ex. 48	38.3 [a]
28		41.7 [a]
29	 Ex. 15	5.3 [b]

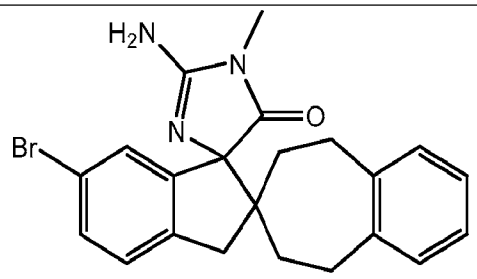
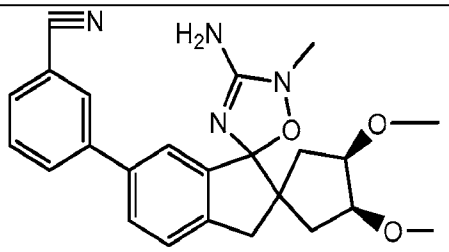
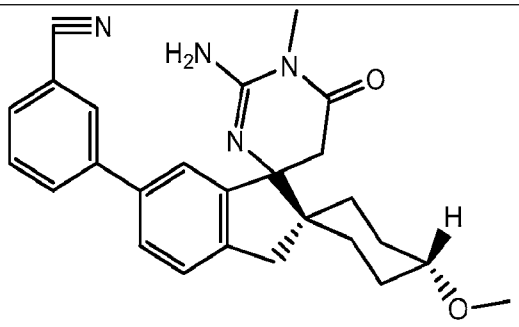
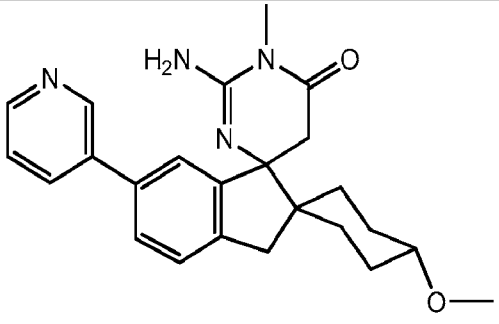
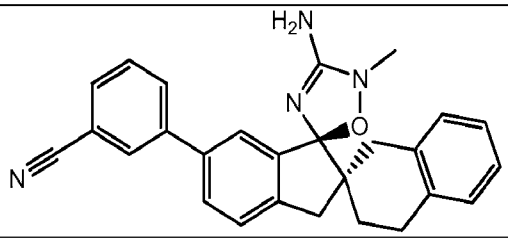
30	 Ex. 21	61.6 [a]
31	 Ex. 57	64.0 [a]
32	 Ex. 36a	74.1 [a]
33	 Ex. 26	89.0 [a]
34	 Ex. 14	93.3 [a]
35	 Ex. 58	104.6 [a]

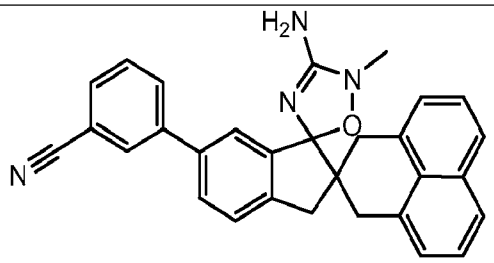
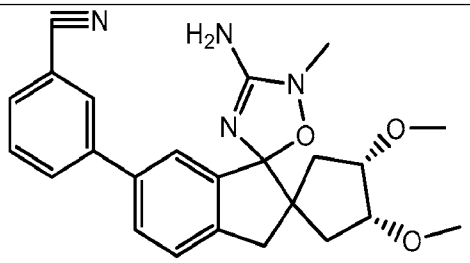
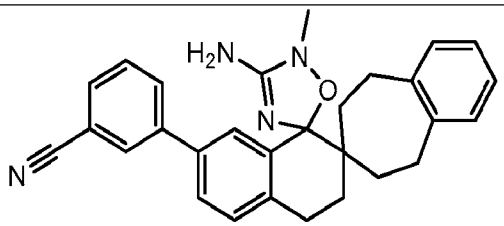
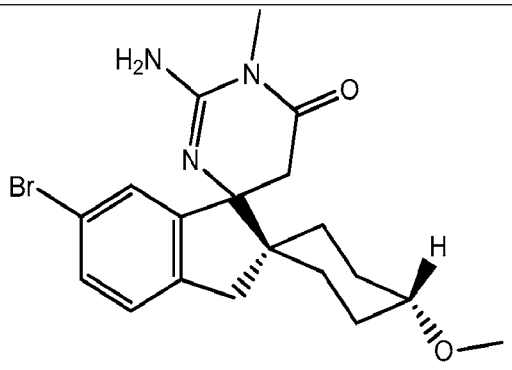
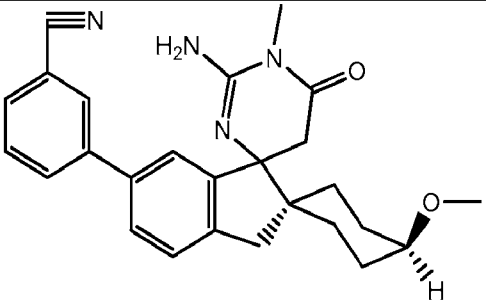
36	 Ex. 52	121.7[a]
37	 Ex. 60	125.6[a]
38	 Ex. 41	130.4[a]
39	 Ex. 42	157.6[a]
40	 Ex. 23	159.6[a]

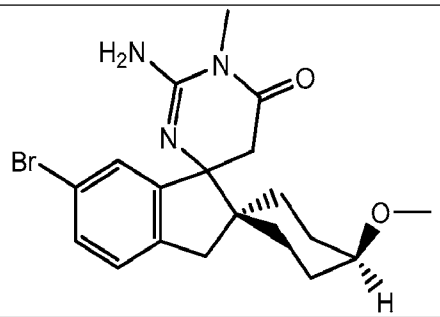
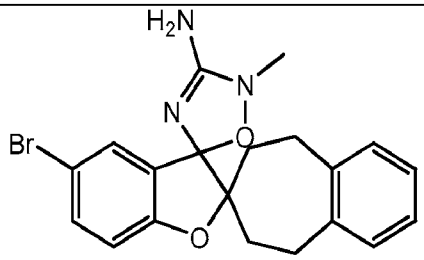
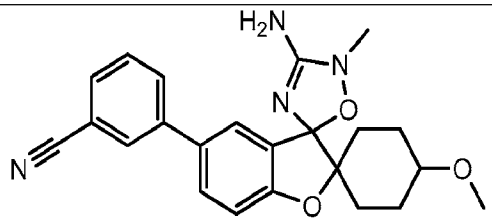
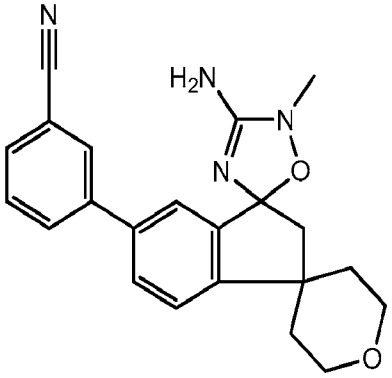
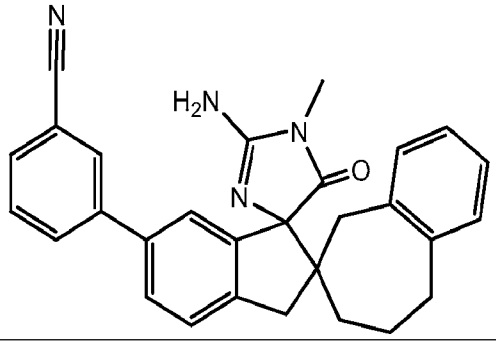
41		161.1[a]
42	 Ex. 7	172.7[a]
43	 Ex. 25	178.4[a]
44	 Ex. 14	189.1[a]
45	 Ex. 1	194.7[a]

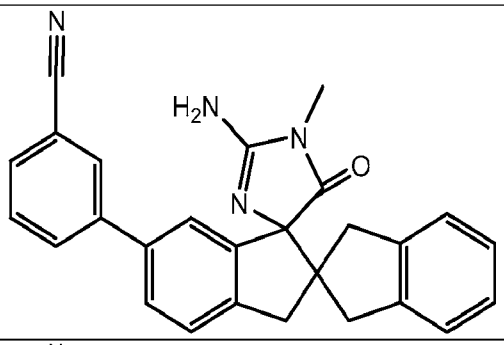
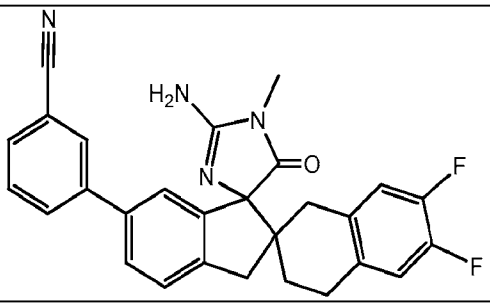
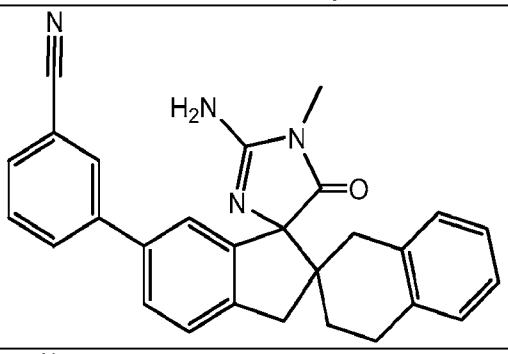
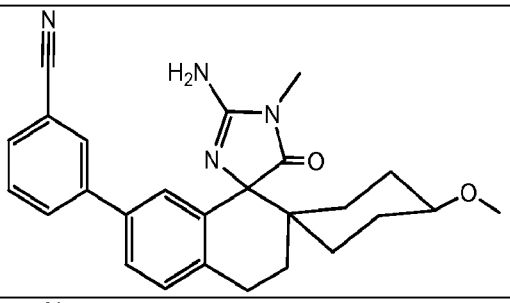
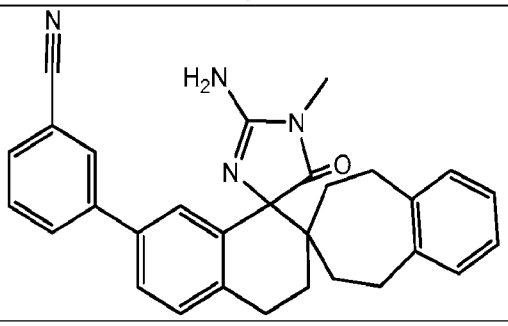
46	 Ex. 18	292.9[a]
47	 fraction A Ex. 12	295.2[a]
48	 Ex. 19	378.3[a]
49	 Ex. 11 and 28	41.7[a]
50	 Ex. 9	443.2[a]

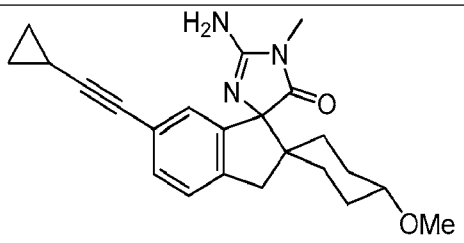
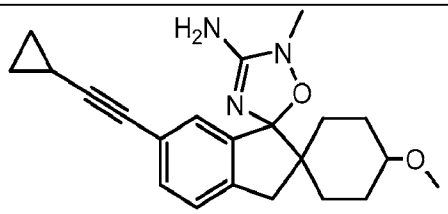
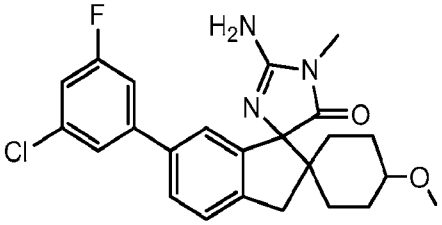
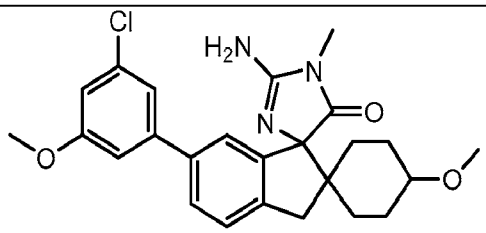
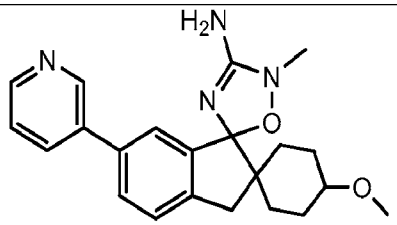
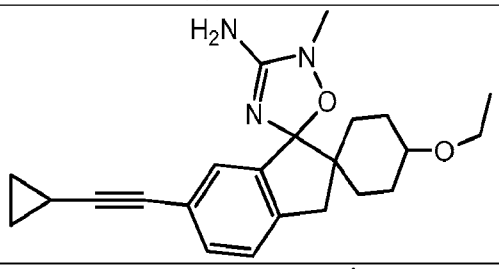
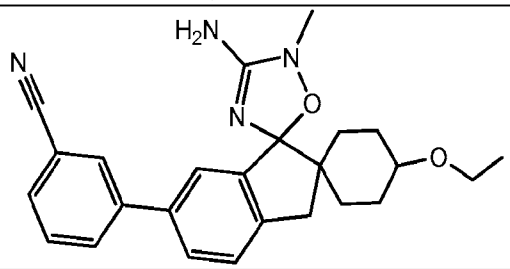
51	 Ex. 2	465.8[a]
52	 Ex. 31	505.8[a]
53	 FRACTION B Ex. 12	514.4[a]
54	 Ex. 24	617.9[a]
55	 Ex. 8	670.4[a]

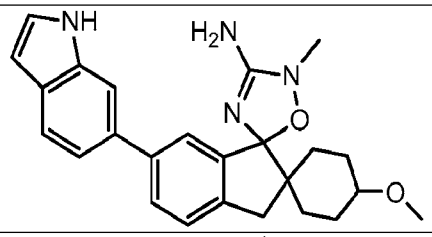
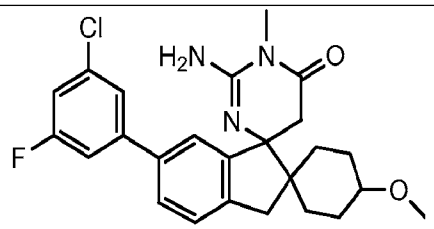
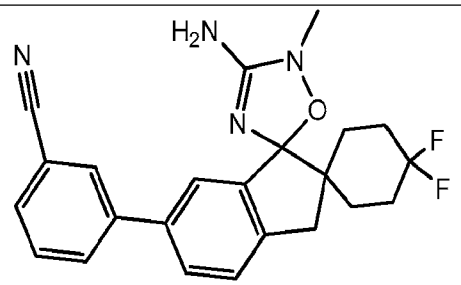
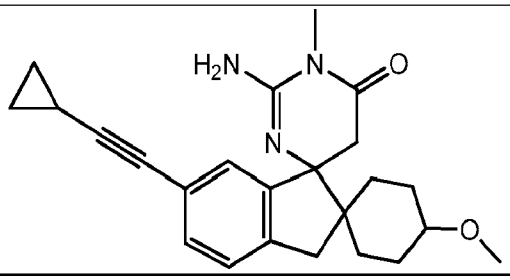
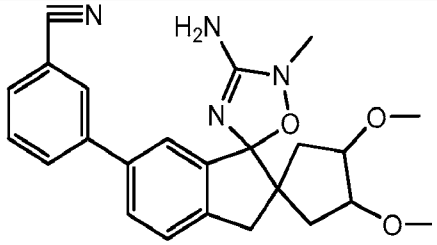
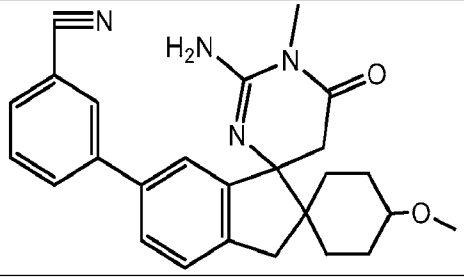
56	 Ex. 15	204.3[b]
57	 Ex. 10	935.52[a]
58	 Ex. 5	969.7[a]
59	 Ex. 6	1554.9[a]
60		1856.1[a]

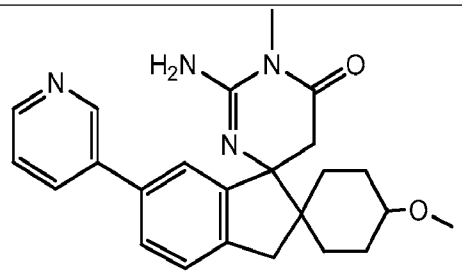
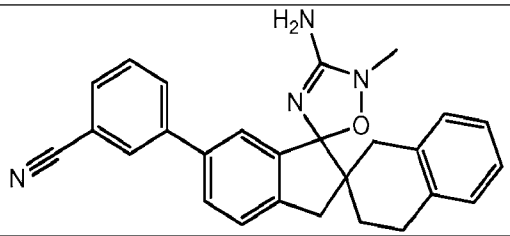
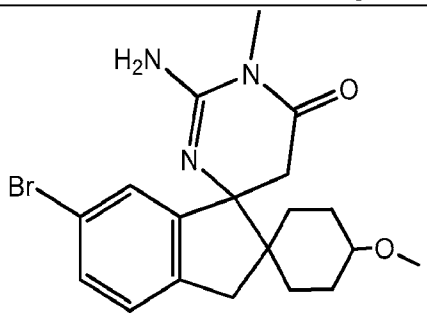
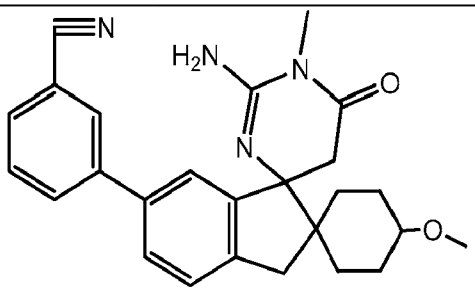
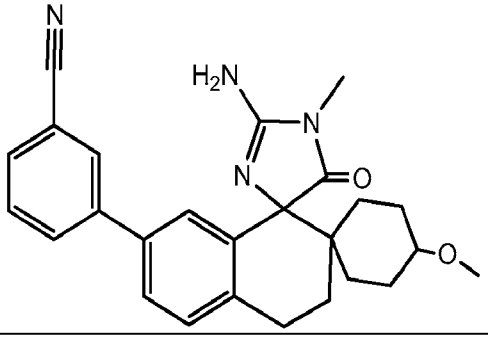
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66		200000[a]
67	 Ex. 16	138.5[a]
68	 Ex. 40	1778.6[a]
69	 Ex. 3	4702.2[a]
70		

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76	 Ex. 56	2.1[a]
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81		
82		432.3[a]

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94	Ex. 61	222.2[a]
95	Ex. 62	136.8[a]
96	Ex. 63	28.3[a]

97	Ex. 64	3881.1[a]
98	Ex. 64	3322.6[a]
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103	Ex. 69	46.0[a]
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157	Ex. 120	342.7[b]

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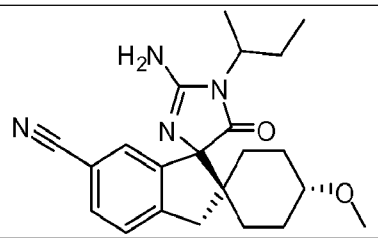
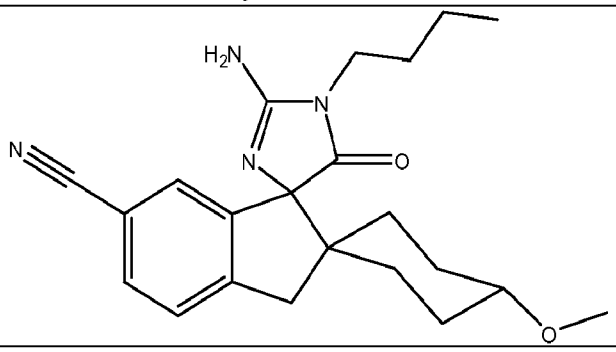
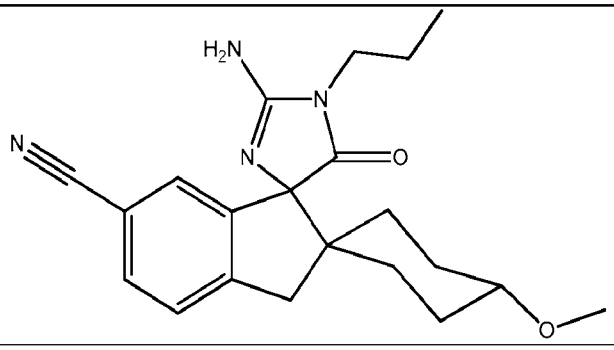
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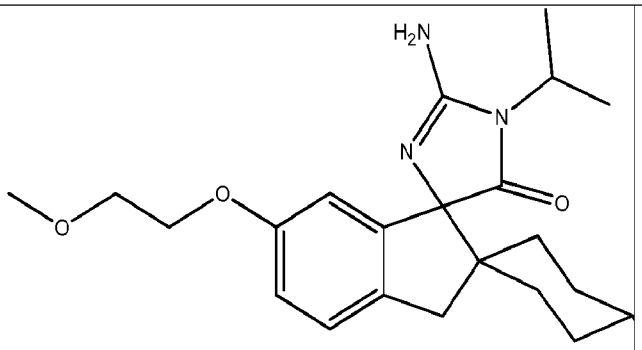
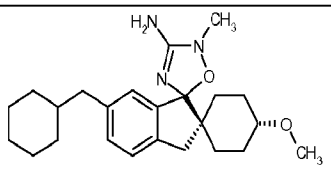
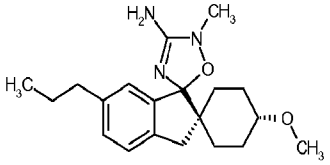
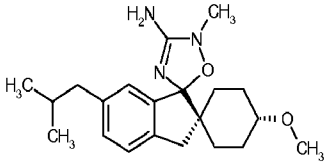
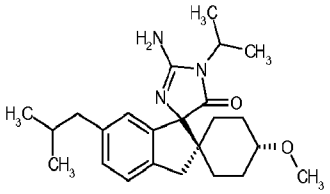
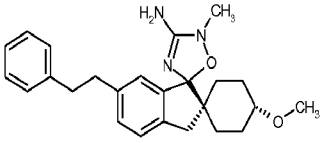
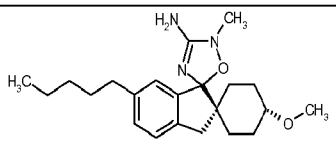
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395	Ex. 336	6.7[a]
396	Ex. 336	213.0[b]
397	Ex. 336	3.4[b]
398	Ex. 337	33.8[b]
399	Ex. 338	74.6[b]
400	Ex. 339	43.0[b]
401	Ex. 340	25.6[b]
402	Ex. 341	72.5[b]
403	Ex. 342	
404	Ex. 343	46.8[b]
405	Ex. 344	11.4[b]
406	Ex. 344	6.3[b]
407	Ex. 344	2134.5[b]
408	Ex. 345	9.7[b]
409	Ex. 346	19.1[b]
410	Ex. 347	566[b]
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412	Ex. 349	79.3[b]
413	Ex. 350	48.3[b]
414	Ex. 351	6.3[b]

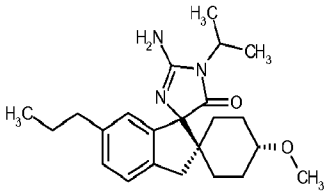
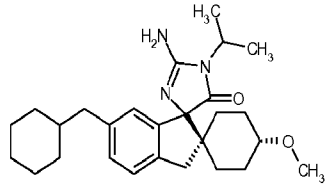
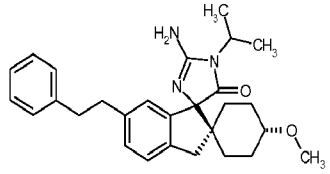
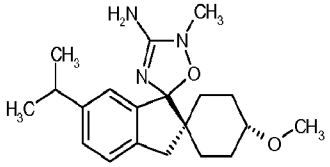
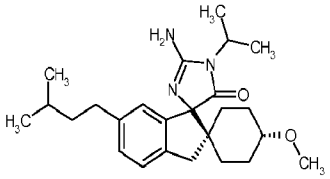
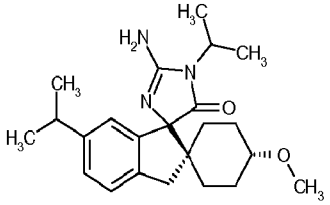
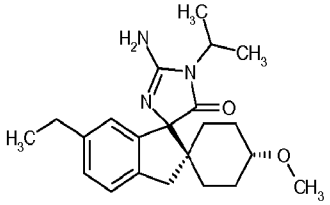
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417	Ex. 354	
418	Ex. 355	8.7[b]
419	Ex. 356	134.9[b]
420	Ex. 357	23.1[b]
421	Ex. 358	14.8[b]
422	Ex. 359	6.8[b]
423	Ex. 360	186.2[b]
424	Ex. 361	53.6[b]
425	Ex. 362	4.1[b]
426	Ex. 363	7.0[b]
427	Ex. 364	182.4[b]
428	Ex. 365	293.2[b]
429	Ex. 366	1673.5[b]
430	Ex. 367	
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433	Ex. 370	575.2[b]
434	Ex. 371	532.7[b]

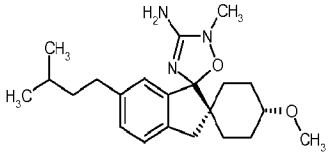
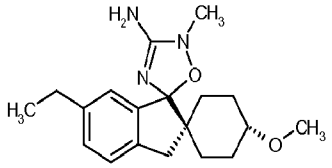
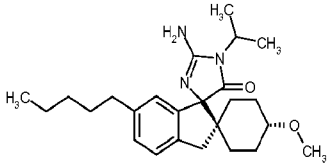
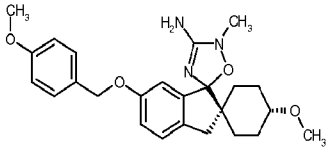
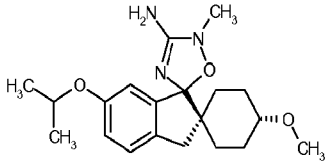
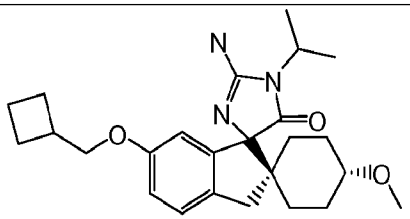
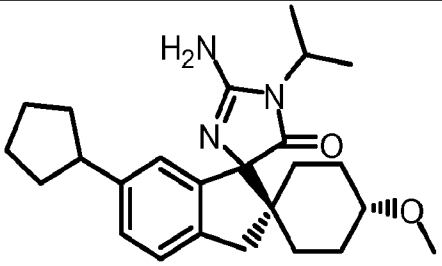
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437	Ex. 374	
438	Ex. 375	79.1[b]
439	Ex. 376	30000.0[b]
440	Ex. 377	730.2[b]
441	Ex. 378	19460.0[b]
442	Ex. 379	1166.5[b]
443	Ex. 380	6230.5[b]
444	Ex. 380	1446.0[b]
445	Ex. 381	339.7[b]
446	Ex. 382	4327.0
447	Ex. 383	13,500.0[b]
448	Ex. 383	1,949.0[b]
449	Ex. 384	206.8[a]
450	Ex. 385	8.4[a]
451	Ex. 386	58.6[a]
452	Ex. 387	7.0[a]
453	Ex. 388	6.2[a]
454	Ex. 389	128.3[a]
455	Ex. 390	2456.1[a]

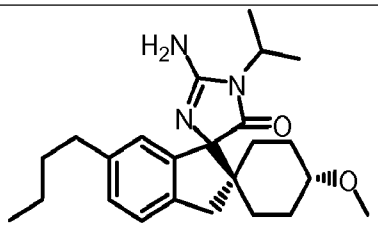
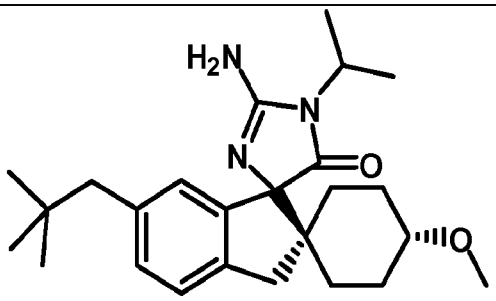
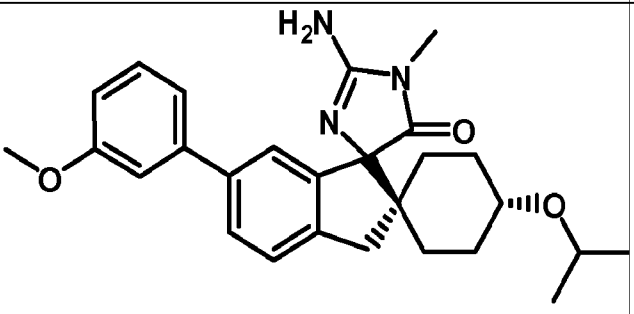
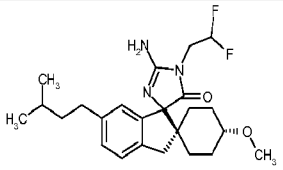
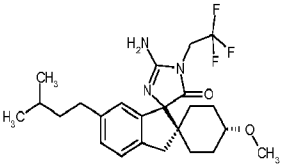
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458	Ex. 392	3702.8[a]
459	Ex. 393	693.3[a]
460	Ex. 394	9805.4[a]
461	Ex. 395	16.7[a]
462	Ex. 396	1.4[a]
463	Ex. 397	1.1[a]
464	Ex. 398	7.9[a]
465	Ex. 399	1.2[a]
466	Ex. 400	13.2[a]
467	Ex. 401	2.8[a]
468	Ex. 402	16.7[a]
469	Ex. 403	1519.7[a]
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471	Ex. 405	869.5[a]
472	Ex. 406	13,500.0[b]
473	Ex. 416	

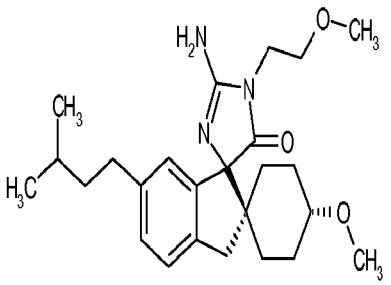
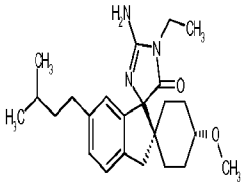
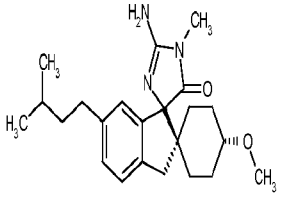
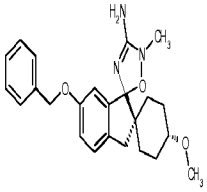
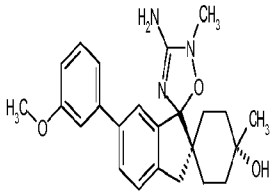
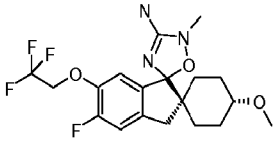
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475	Ex. 76	5158.0[a]
476	Ex. 408	33.1[a]
477	Ex. 409	693.5[a]
478	Ex. 409	2.2[a]
479	Ex. 424	604.1[b]
480	Ex. 424	4.2[b]
481		273.6[b]
482		42.8[b]
483	Ex. 417	960.5[b]
484	Ex, 417	7.2[b]
485		99.1[b]

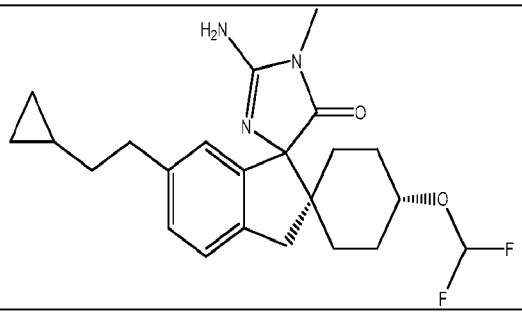
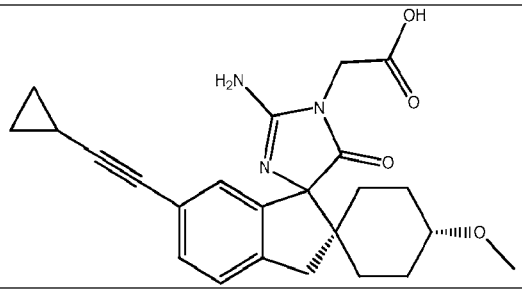
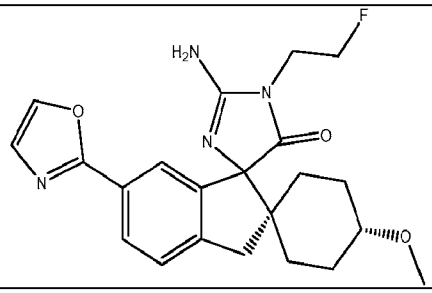
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487	Ex. 423	21.2[b]
488	 Ex. 410B	76.3[b]
489	 Ex. 410B	92.8[b]
490	 Ex. 410B	72.8[b]
491	 Ex. 410C	78.2[b]
492	 Ex. 410F	403[b]
493	 Ex. 410F	29.8[b]

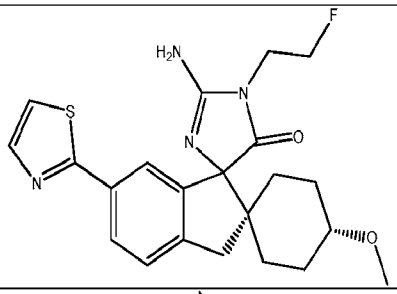
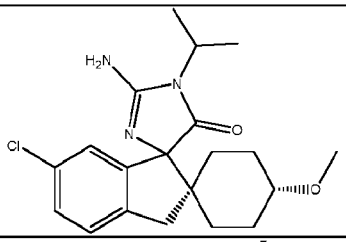
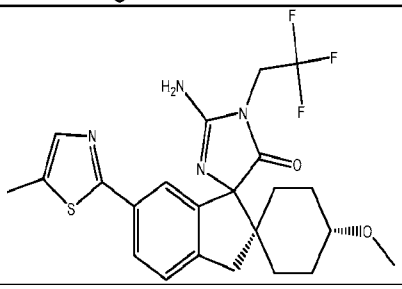
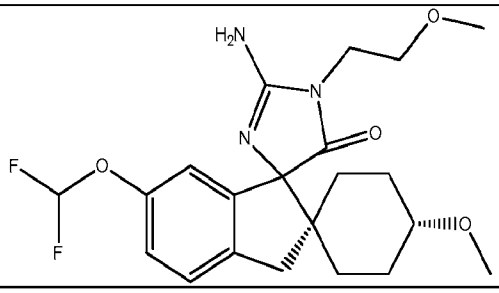
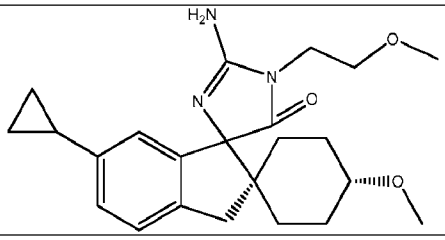
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496	 Ex. 410G	187.8[b]
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498	 Ex. 410G	27.1[b]
499	 Ex. 410G	148.9[b]
500	 Ex. 410G	199.3[b]

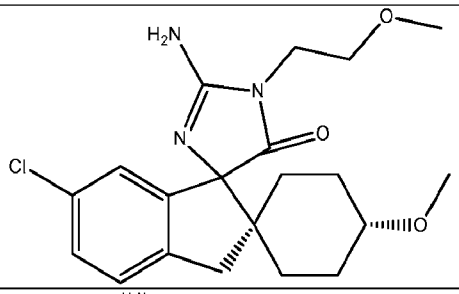
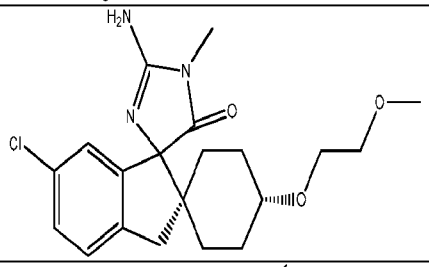
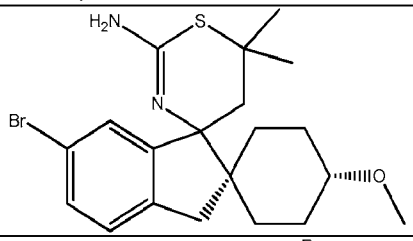
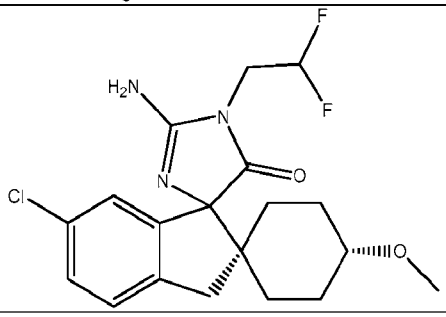
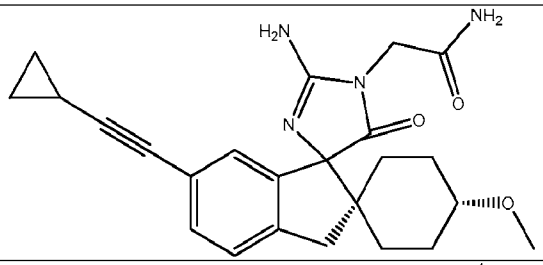
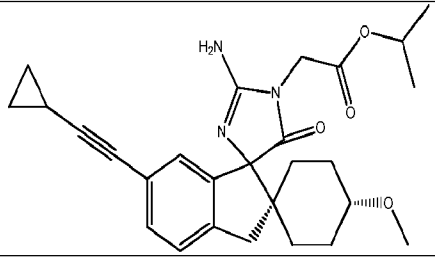
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502	 Ex.410F	521.1[b]
503	 Ex. 410G	39[b]
504	 Ex. 410A	807[b]
505	 Ex. 410D	170.6[b]
506	 Ex. 410E	34.3[b]
507	 Ex. 410G	128[b]

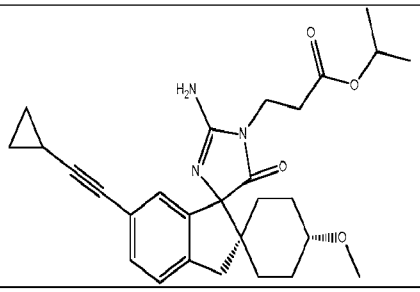
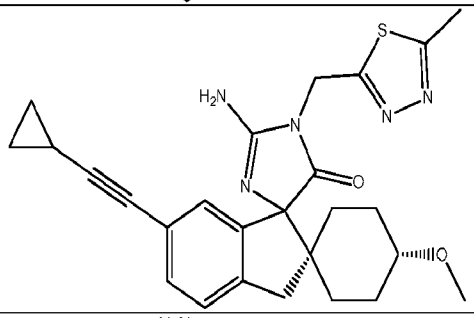
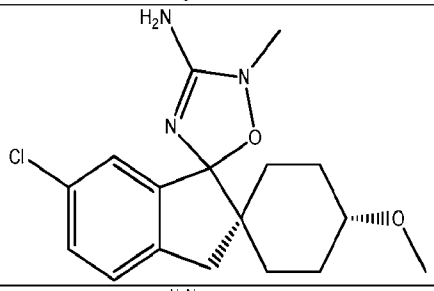
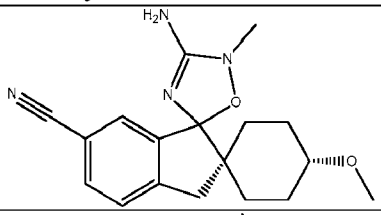
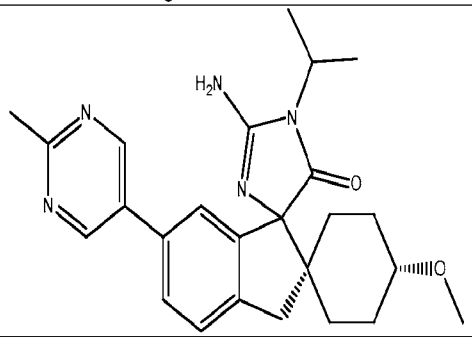
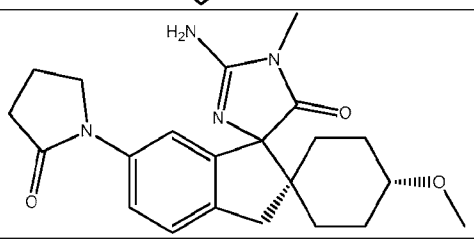
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511	 Ex. 410G	9[b]
512	 Ex. 410G	77[b]

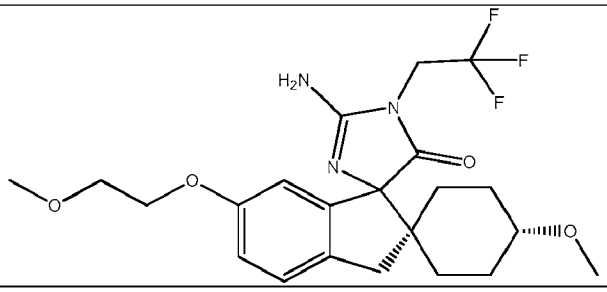
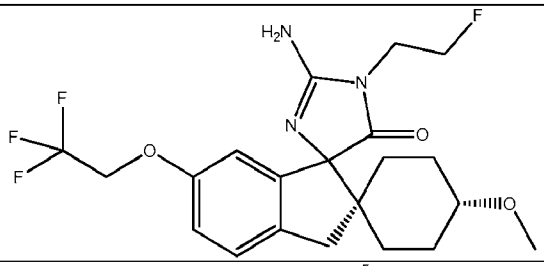
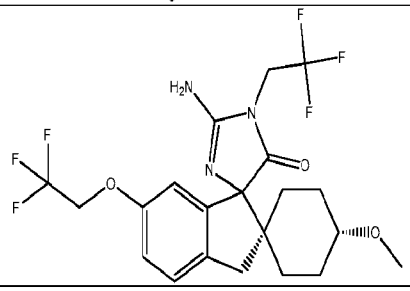
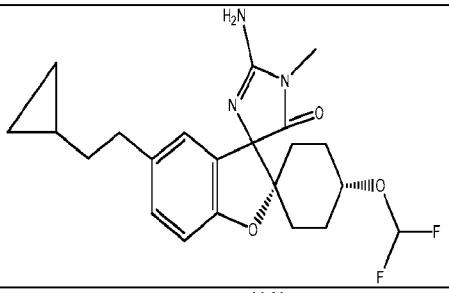
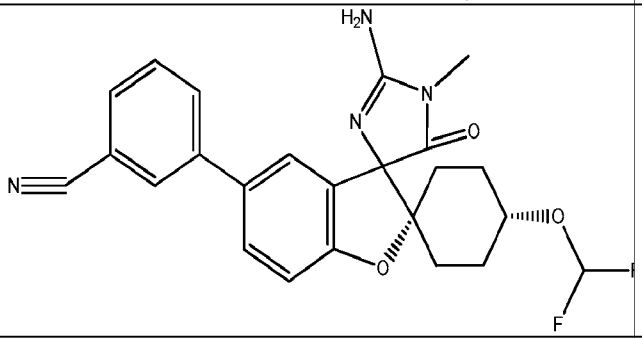
513	 Ex. 410H	9[b]
514	 Ex. 410H	8[b]
515	 Ex. 410H	10[b]
516	 Ex. 410A	890[b]
517	 Ex. 410F and 410I	877.1[b]
518	 Ex. 410F and 410J	53[b]

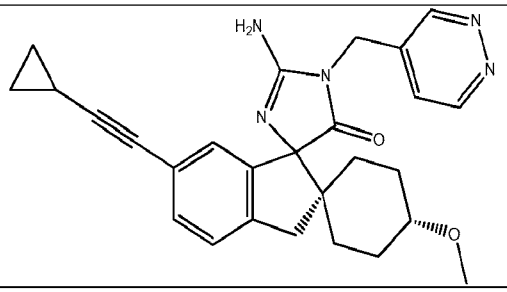
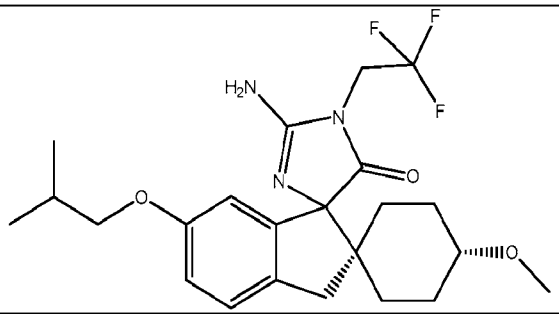
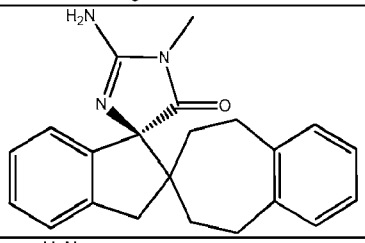
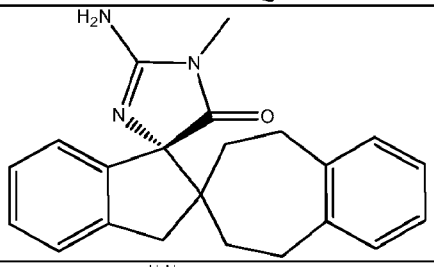
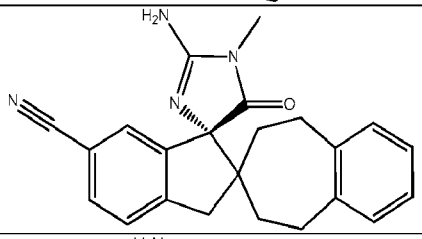
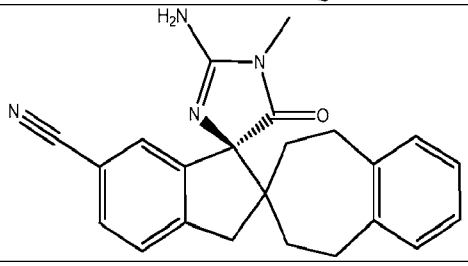
519	Ex. 411	
520		
521a	Ex. 415	14[b]
521b	Ex. 416	691[b]
522	Ex. 420	294[b]
523	Ex. 420	2.4[b]
524		5.0[b]
525	Ex. 431	6.8[b]
526	Ex. 430	9.0[b]
527	Ex. 413	16[b]
528	Ex. 428	10[b]
529		128[b]

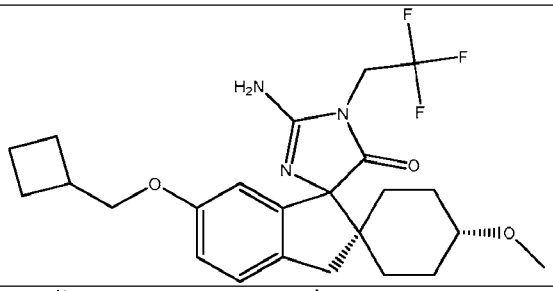
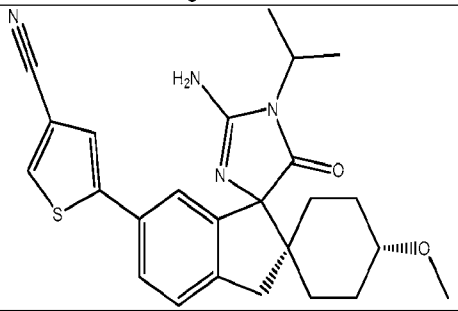
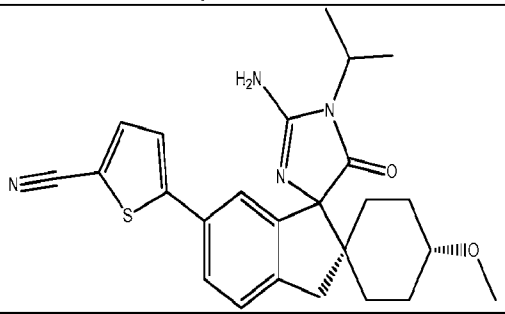
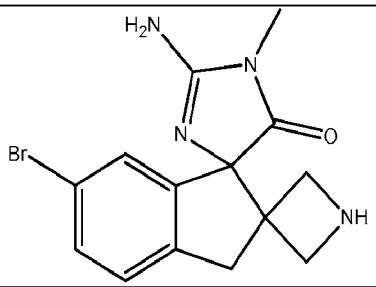
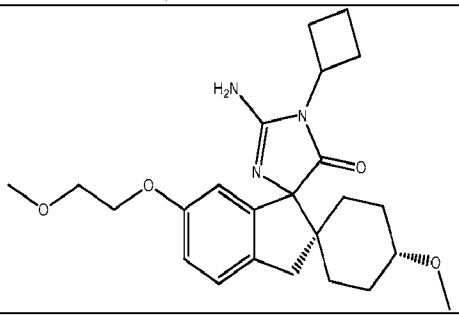
530		115[b]
531		169[b]
532		320[b]
533	Ex. 414	8.9[b]
534		128[b]
535	Ex. 432	40[b]
536		172[b]

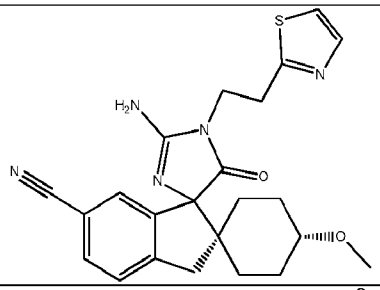
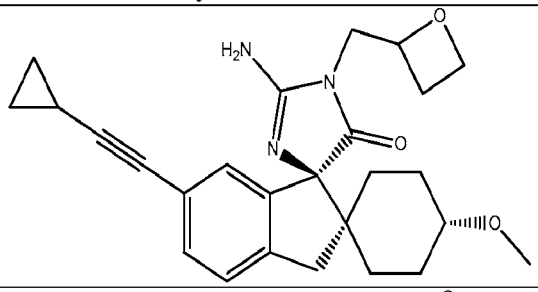
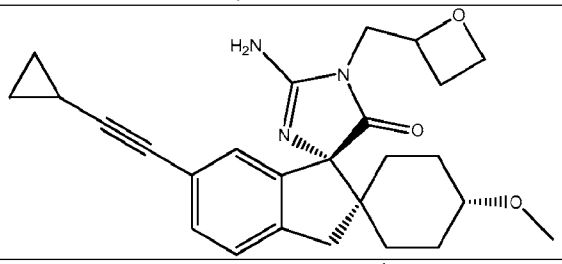
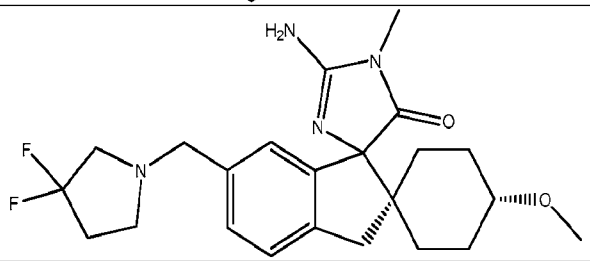
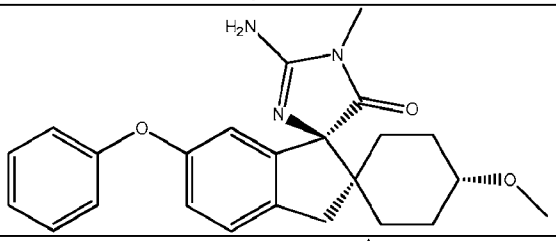
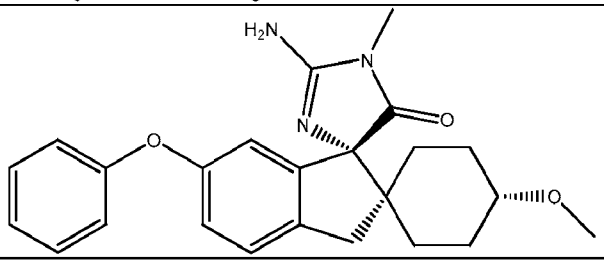
537		88[b]
538		614[b]
539		2440[b]
540		138[b]
541	Ex. 427	4.0[b]
542		11[b]
543		4.5[b]

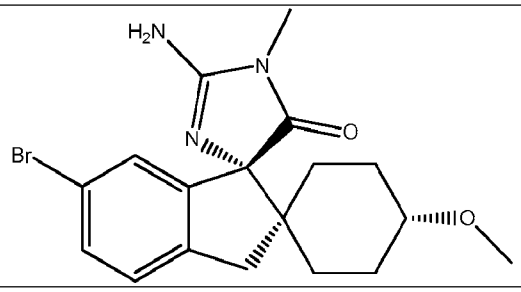
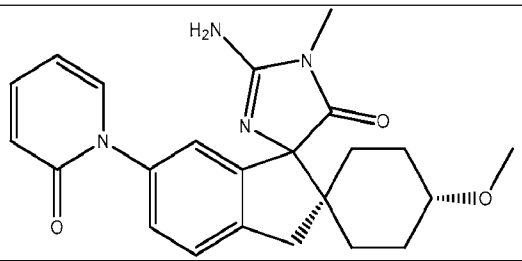
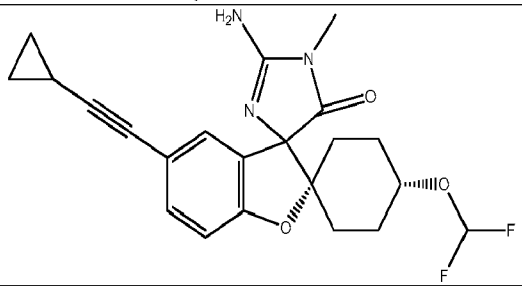
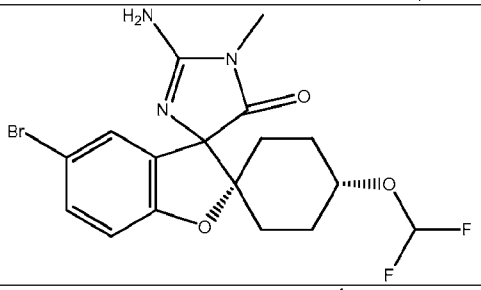
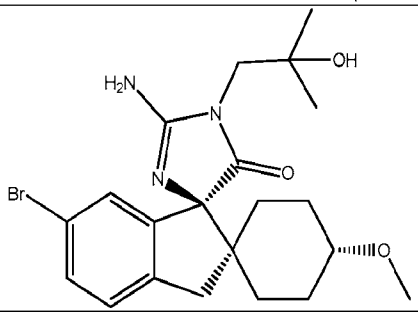
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545		9.4[b]
546		212[b]
547		157[b]
548		23[b]
549		110[b]

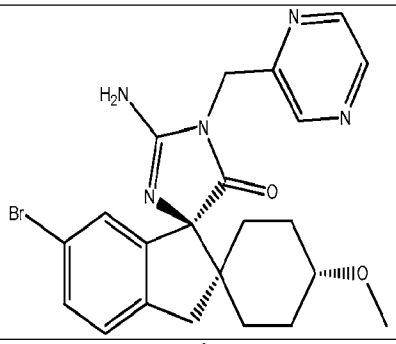
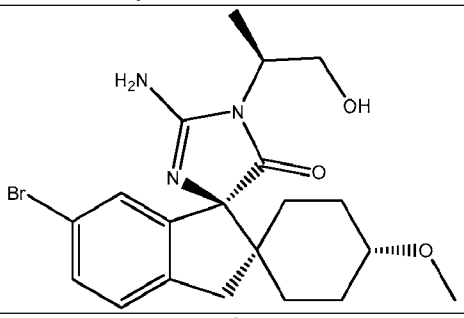
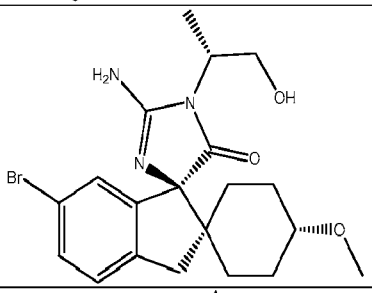
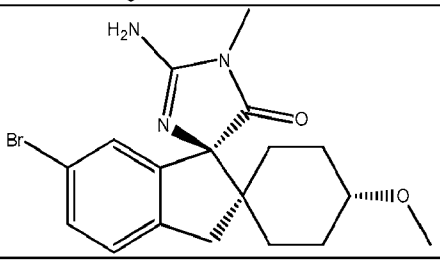
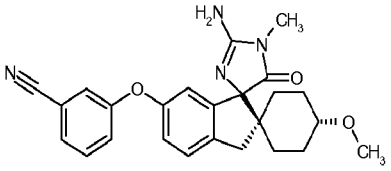
550		77[b]
551	Ex. 426	12[b]
552		25[b]
553		34[b]
554	Ex. 433	30[b]
555		149.0[b]
556		176.6[b]
557	Ex. 422	8[b]

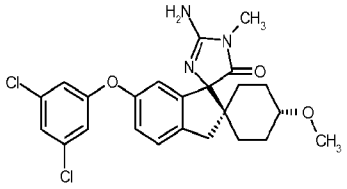
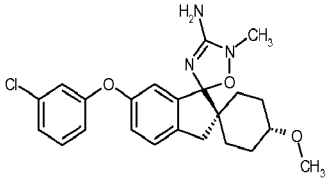
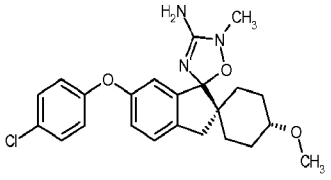
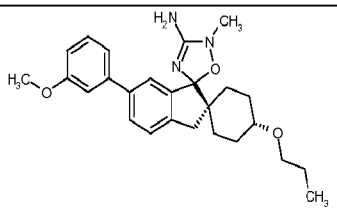
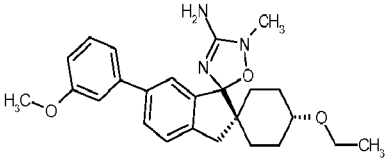
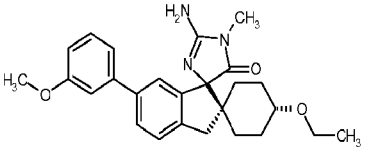
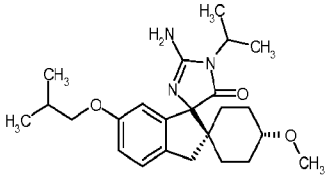
558		4,079.5[b]
559	Ex. 419	7[b]
560	Ex. 419	3,106.0[b]
561		11.7[b]
562		8,052.0[b]
563		168.7[b]
564		60.0[b]
565		1,452.5[b]

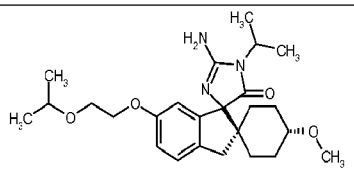
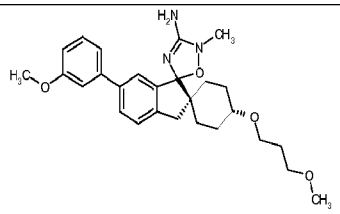
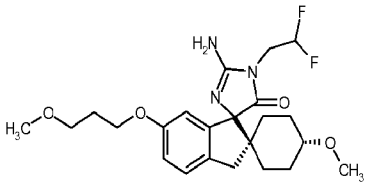
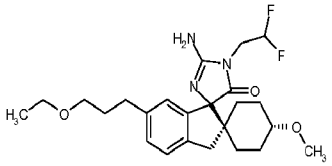
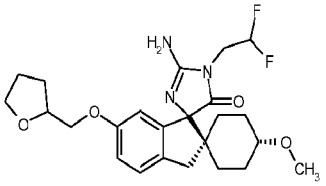
566		134.2[b]
567		250.5[b]
568		546.7[b]
569	Ex. 418	13.2[b]
570		13500[b]
571		111.7[b]
572	Ex. 429	7.0[b]

573		57.9[b]
574		78.6[b]
575		
576		108.3[b]
577		247.6[b]
578		3.9[b]

579		15.9[b]
580	Ex. 421	6[b]
581	Ex. 421	181[b]
582		457.9[b]
583		267.8[b]
584		423.8[b]
585		4,226.0[b]

586		2,119.0[b]
587		13,500.0[b]
588		19,370.0[b]
589		4,509.3[b]
590	Ex. 425	
591	Ex. 412	
592	 Ex. 410K	7[b]

593	 Ex. 410K	6[b]
594	 Ex. 410A	99[b]
595	 Ex. 410A	105[b]
596	 Ex. 410A	455[b]
597	 Ex. 410A	86[b]
598	 Ex. 410C	15[b]
599	 Ex. 410N	12[b]

600	 Ex. 410C	390[b]
601	 Ex. 410A	293[b]
602	 Ex. 410C and 410O	6.2[b]
603	 Ex. 410B and 410P	102[b]
604	 Ex. 410C	31[b]

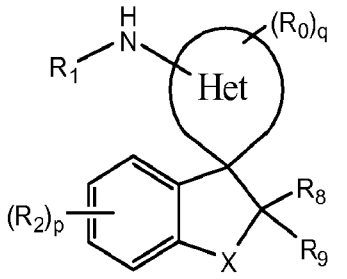
[a]IC_{50} values were determined according to protocols described in Example 434A.

[b]IC_{50} values were determined according to protocols described in Example 435.

CLAIMS

What is claimed is:

1. A compound represented by the following Structural Formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

ring Het is a 5 membered monocyclic heterocycle or a 6 membered monocyclic heterocycle;

X is -O-, $-C(R_aR_b)-C(R_3R_4)-$, $-C(R_3R_4)-C(R_aR_b)-$ or $-C(R_3R_4)-$;

R_a and R_b are each independently –H, -halogen, (C_1-C_4)alkyl, methoxy, fluoromethoxy, methoxy(C_1-C_4)alkyl and fluoro(C_1-C_4)alkyl;

each R_0 is independent selected from –H, =O, =S, $=NR_{15}$, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -CN, $-NO_2$, halogen, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-NR_{11}S(O)_iR_5$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, $-C(=O)R_5$, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, each of the (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_3)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl group represented by R_0 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen,

-CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl, heteroaryl, $-NR_6R_7$, $-NR_{11}S(O)_iR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-S(O)_iR_5$-, $-S(O)_iNR_{12}R_{13}$, $-OR_5$, $-C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-C(O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=O)OR_5$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$ and $-C(=S)R_5$, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_0 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl;

R_1 is -H, -OH, -$(C_1$-$C_4)$alkoxy, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, or heteroaryl$(C_1$-$C_6)$alkyl; wherein each alkyl, aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from halogen, -CN, -OH, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_3)$alkoxy and halo$(C_1$-$C_3)$alkoxy;

each R_2 is independently selected from a) -H, -halogen, -CN, $-NO_2$, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, and $-C(=O)R_5$,; and b) $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, $(C_4$-$C_8)$cycloalkenyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, and heteroaryl$(C_2$-$C_6)$alkynyl, wherein each of the $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, $(C_4$-$C_8)$cycloalkenyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl,

and heteroaryl(C_2-C_6)alkynyl groups represented by R_2 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, -NO_2, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)R_5$, -$C(=S)OR_5$, -$OC(=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$C(=O)R_5$, -$C(=S)R_5$, -$OC(=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=O)OR_5$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=O)R_5$, -$C(=S)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_2 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_3 and R_4 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkyl($C_1$-$C_6$)alkyl, ($C_3$-$C_8$)cycloalkyl($C_2$-$C_6$)alkynyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_3$-$C_9$)heterocycloalkyl($C_1$-$C_6$)alkyl, ($C_3$-$C_9$)heterocycloalkyl($C_2$-$C_6$)alkynyl, aryl, aryl($C_1$-$C_6$)alkyl, aryl($C_2$-$C_6$)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-

C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkynyl represented by R_3 and R_4 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_9)heterocycloalkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_3 and R_4 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

or R_3 and R_4, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A optionally contains 1 to 3 heteroatoms independently selected from O, N, and S and when the heteroatom is nitrogen, the nitrogens is substituted with -H, (C_1-C_3)alkyl or halo(C_1-C_3)alkyl, and when the heteroatom is sulfur, the sulfurs is optionally mono or di-oxygenated; and ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylamino($C_1$-$C_6$)alkyl, cyano($C_1$-$C_6$)alkyl, ($C_1$-

C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_2-C_6)alkynyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl(C_2-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_2-C_6)alkynyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, and heteroaryl(C_2-C_6)alkynyl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on ring A are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_5 is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl, each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl in the groups represented by R_5 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, =O, $-NR_6C(=NH)NR_6R_7$, $-C(=O)OR_c$, $-OR_c$, $-SR_c$, $-C(=O)NR_6R_7$, $-C(=O)R_c$, $-S(O)_iR_c$, $-NO_2$, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and $-NR_6R_7$;

R_c is –H, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl;

R_6 and R_7 are each independently -H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_9)heterocycloalkyl, (C_3-C_9)heterocycloalkyl(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl, or heteroaryl(C_1-C_6)alkyl , all of which groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_8 and R_9, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or

9-14 membered polycyclic ring , wherein ring A optionally contains 1 to 3 heteroatoms independently selected from O, N, and S and when the heteroatom is nitrogen, the nitrogen is substituted with -H, $(C_1$-$C_3)$alkyl or halo$(C_1$-$C_3)$alkyl, and when the heteroatom is sulfur, the sulfur is optionally mono or di-oxygenated; and ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of from halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, -$C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, and heteroaryl$(C_2$-$C_6)$alkynyl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on ring A are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl; or

when R_3 and R_4, together with the carbon to which they are attached, form a ring A, R_8 and R_9 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$NR_{11}S(O)_iR_5$, -$C(=O)OR_5$, -$OC(=O)OR_5$, -$C(=S)OR_5$, -$O(C=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$NR_{11}(C=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=S)R_5$, and -$C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl,

$(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkynyl, wherein each $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl$(C_2$-$C_6)$alkynyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_2$-$C_6)$alkynyl, aryl, aryl$(C_1$-$C_6)$alkyl, aryl$(C_2$-$C_6)$alkynyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkynyl group represented by R_8 and R_9 is optionally substituted with 1 to 5 substituents independently selected from the group consisting of -halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-NR_{11}S(O)_iR_5$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_{12}R_{13}$, $-NR_{11}(C=O)NR_{12}R_{13}$, $-NR_{11}(C=S)NR_{12}R_{13}$, $-C(=S)R_5$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the substituents on the groups represented by R_8 and R_9 are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl;

R_{11} is –H or $(C_1$-$C_6)$alkyl, wherein $(C_1$-$C_6)$alkyl is optionally substituted with 1 to 5 substituents independently selected from halogen, CN, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl and heteroaryl, wherein the $(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl and heteroaryl groups are each optionally substituted with 1 to 3 substitutes independently selected from the group consisting of halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl;

R_{12} and R_{13} are each independently -H, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_3)$alkylamino$(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl or heteroaryl$(C_1$-$C_6)$alkyl, wherein the $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_3$-$C_9)$heterocycloalkyl$(C_1$-$C_6)$alkyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl and heteroaryl$(C_1$-$C_6)$alkyl group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl;

or R_{12} and R_{13}, together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of halogen, -CN, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-S(O)_iNR_{12}R_{13}$, $-NR_{11}S(O)_iR_5$, $-C(=O)OR_5$, $-OC(=O)OR_5$, $-C(=S)OR_5$, $-O(C=S)R_5$, $-C(=O)NR_6R_7$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_6R_7$, $-NR_{11}C(=S)R_5$, $-NR_{11}(C=O)OR_5$, $-O(C=O)NR_6R_7$, $-NR_{11}(C=S)OR_5$, $-O(C=S)NR_6R_7$, $-NR_{11}(C=O)NR_6R_7$, $-NR_{11}(C=S)NR_6R_7$, $-C(=S)R_5$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, wherein the 3-8 membered ring optionally contains 1 to 3 additional heteroatoms, which are independently selected from O, N and S, wherein when the additional heteroatom is nitrogen, the nitrogen is substituted with -H, $(C_1$-$C_3)$alkyl or halo$(C_1$-$C_3)$alkyl, and when the additional heteroatom is sulfur, the sulfur is optionally mono or di-oxygenated;

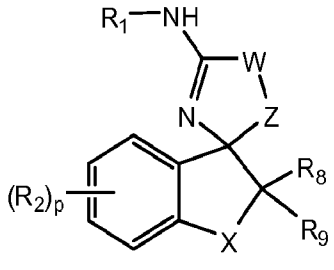
R_{15} is -H or $(C_1$-$C_6)$alkyl optionally substituted with 1 to 5 –F.

i is 0, 1 or 2;

p is 1, 2 3 or 4; and

q is 1, 2 or 3.

2. The compound of Claim 1, wherein the compound is represented by the following Structural Formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is -O-, -CH_2-$C(R_3R_4)$-, or -$C(R_3R_4)$-;

W is -$N(R_{14})$-, -S-, -O-;

Z is -C(=O)-, -C(=S)-, -$C(=NR_{15})$-, -O-, -$C(=O)C(R_{16}R_{17})$-, -$C(=S)C(R_{16}R_{17})$-, -$C(=NR_{15})C(R_{16}R_{17})$-, -$N(R_{18})$-, -$(CR_{16}R_{17})_m$- or -O-$(CR_{16}R_{17})$-, provided when W is –S- or –O-, Z is not –O-;

R_1 is -H, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, or heteroaryl$(C_1$-$C_6)$alkyl;

each R_2 is independently selected from a) -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -C(=O)OR_5, -$C(=O)NR_{12}R_{13}$, and -$C(=O)R_5$; and b) $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, heteroaryl, phenoxy, and benzyloxy, each optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -C(=O)OR_5, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy ,$(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl;

R_3 and R_4 are each idependently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -C(=O)OR_5, -$C(=O)NR_{12}R_{13}$, -$C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, or heteroaryl, wherein each $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, aryl, or heteroaryl is optionally substituted with 1 to 3 substituents independently

selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

or R_3 and R_4, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

R_5 is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, (C_3-C_7) cycloheteroalkyl, aryl, heteroaryl or benzyl, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_6 and R_7 are each independently -H, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8) cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

R_8 and R_9, together with the carbon to which they are attached, form ring A, which is a 3-14 membered monocyclic ring, 9-14 membered bicyclic ring or 9-14 membered polycyclic ring , wherein ring A is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl,

-Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl; or

when R_3 and R_4, together with the carbon to which they are attached, form a ring A, R_8 and R_9 are each independently -H, -halogen, -CN, -NO_2, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl, wherein each (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, aryl, or heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl;

R_{11} is -H, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

R_{12} and R_{13} are each independently -H, (C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_3)alkylamino(C_1-C_6)alkyl, or di(C_1-C_3)alkylamino(C_1-C_6)alkyl;

or R_{12} and R_{13}, together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_6)alkoxy(C_1-C_3)alkyl, wherein the 3-8 membered

ring optionally contains 1 to 3 additional heteroatoms, which are independently selected from O, N and S, wherein when the additional heteroatom is nitrogen, the nitrogens is substituted with -H, (C_1-C_3)alkyl or halo(C_1-C_3)alkyl, and when the additional heteroatom is sulfur, the sulfurs is optionally mono or di-oxygenated;

R_{14} is -H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, cycloheteroalkyl(C_1-C_3)alkyl, (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, each optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl and (C_1-C_3)alkoxy;

R_{15} is -H or (C_1-C_6)alkyl;

R_{16} and R_{17} are each independently -H or (C_1-C_3)alkyl;

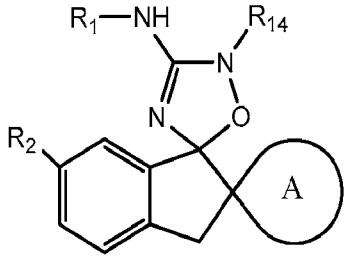
R_{18} is -H or (C_1-C_3)alkyl;

i is 0, 1 or 2;

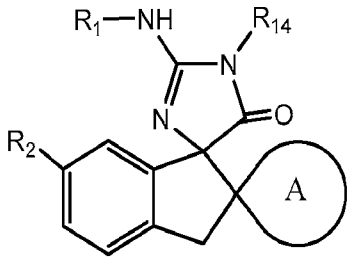
p is 1 or 2; and

m is 1 or 2.

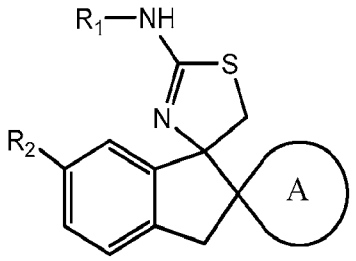
3. The compound of Claim 1 or Claim 2, wherein the compound is represented by any one of the following Structural Formulas:



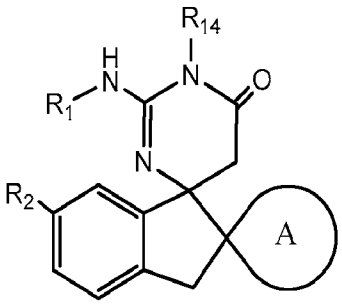
(Va),



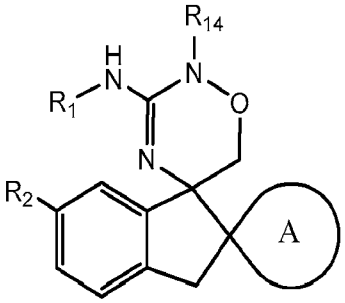
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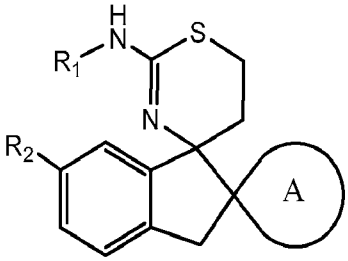
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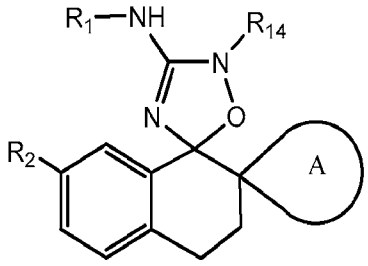
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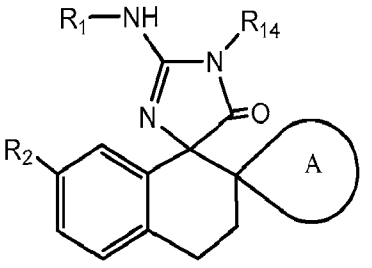
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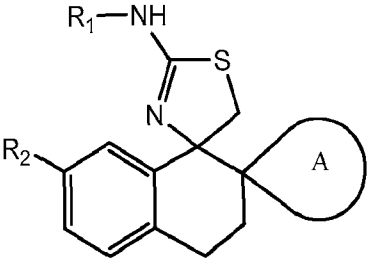
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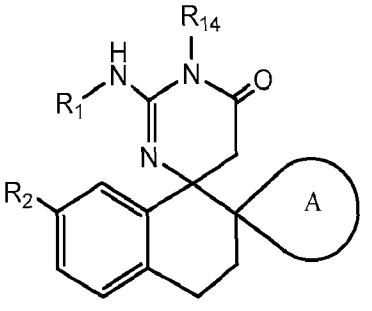
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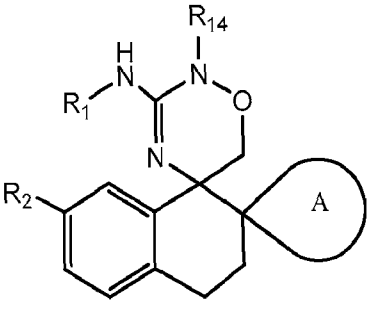
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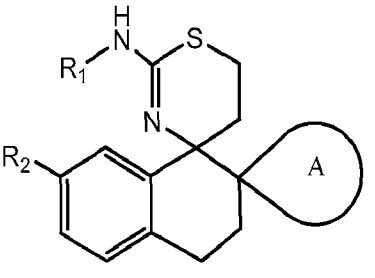
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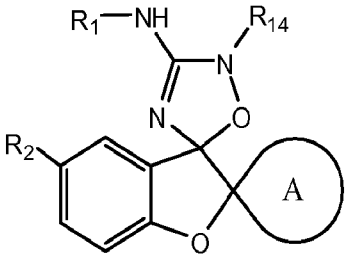
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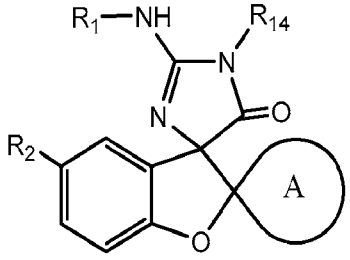
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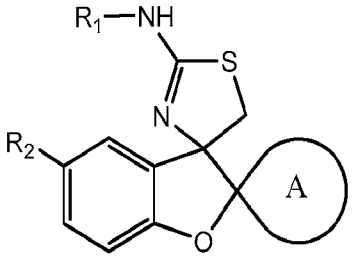
(XVIa),



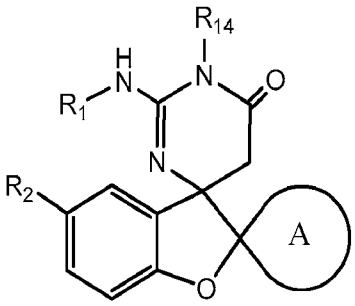
(XVIIa),



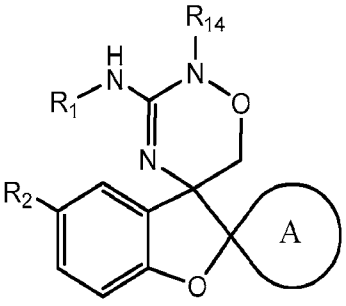
(XVIIIa)



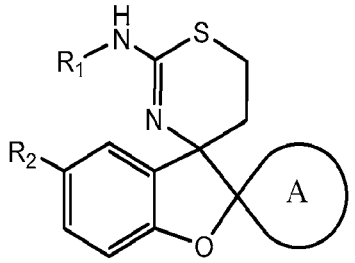
(XIXa),



(XXa),



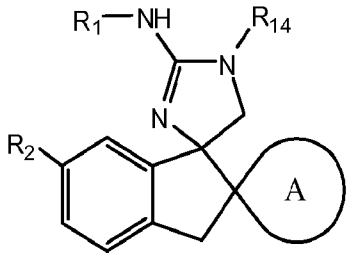
(XXIa), or



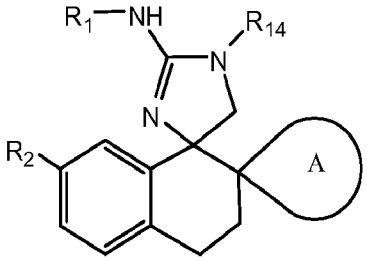
(XXIIa),

or a pharmaceutically acceptable salt thereof.

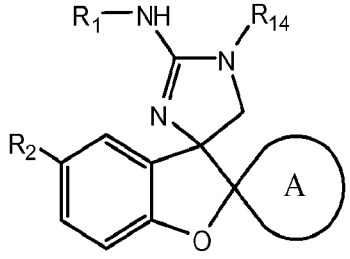
4. The compound of Claim 1 or Claim 2, wherein the compound is represented by any one of the following Structural Formulas:



(XXIIIa),



(XXIVa), or



(XXVa),

or a pharmaceutically acceptable salt thereof.

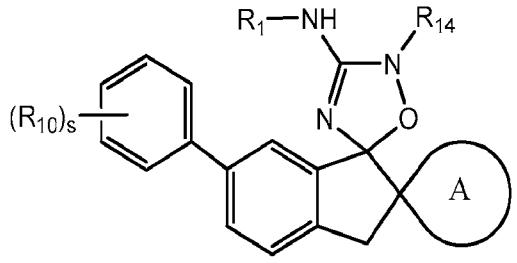
5. The compound of any one of Claims 1-4, wherein ring A is a 5-7 membered monocyclic ring or a 9-14 membered bicyclic or tricyclic fused ring optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$,

$-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylsulfonylaminoalkyl, hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl, wherein ring A contains 0 to 2 heteroatoms, which are independently selected from O, N and S.

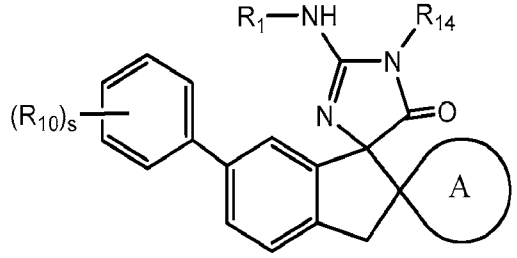
6. The compound of Claim 5, wherein ring A is selected from the group consisting of tetrahydrofuran, tetrahydropyran, cyclopentane, cyclohexane, cyclohexene, cycloheptane, oxepane, 1,3-dioxane, piperidine, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, tetrahydronaphthalene, decahydronaphthalene, 5,6,7,8-tetrahydroquinoline, 5,6,7,8-tetrahydroisoquinoline, 2,3,4,5-tetrahydrobenzo[b]oxepine, and 2,3-dihydro-1H-phenalene, each of which is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and phenyl, wherein the phenyl is optionally substituted with F, -Cl, -Br, -CN, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy.

7. The compound of any one of Claims 1-6, wherein R_2 is a pyridinyl, thiophenyl, pyrrolyl or pyrimidinyl, each optionally substituted with 1 to 3 substituents independently selected from the group consiting of halogen, -CN, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl.

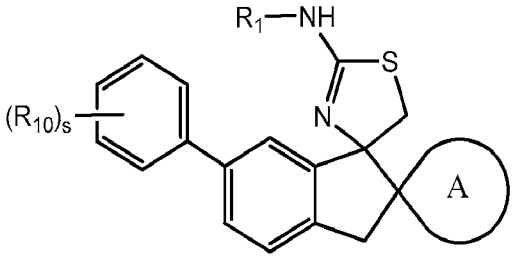
8. The compound of any one of Claims 1-6, wherein the compound is represented by the following Structural Formula:



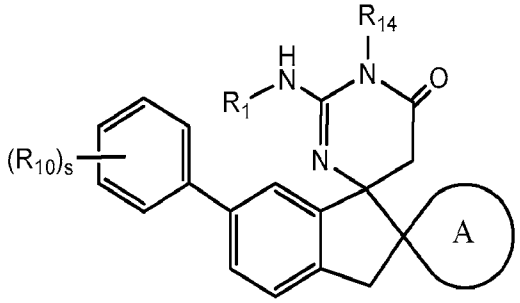
(Vb),



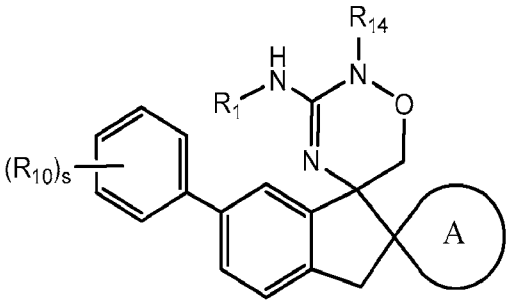
(VIb)



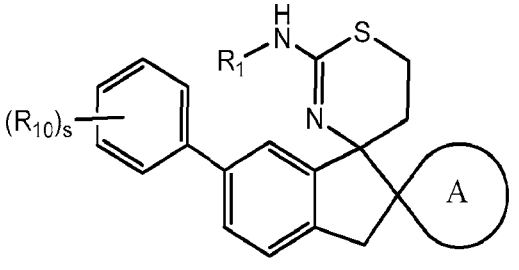
(VIIb),

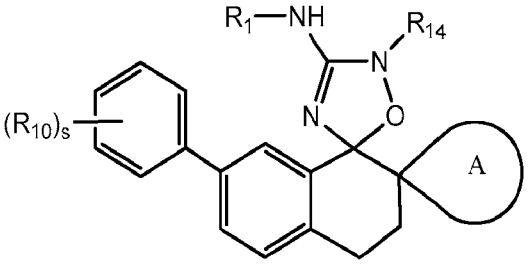


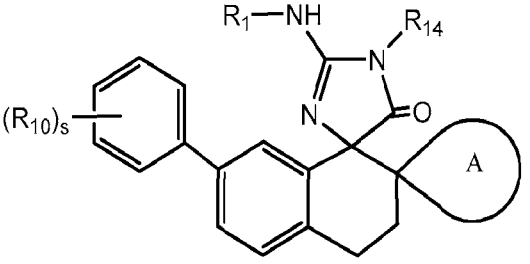
(VIIIb),

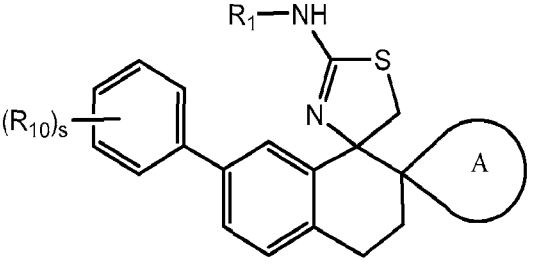


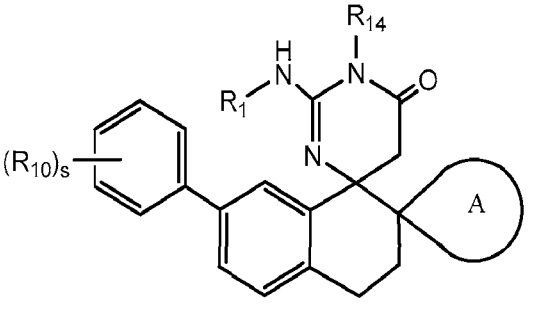
(IXb),

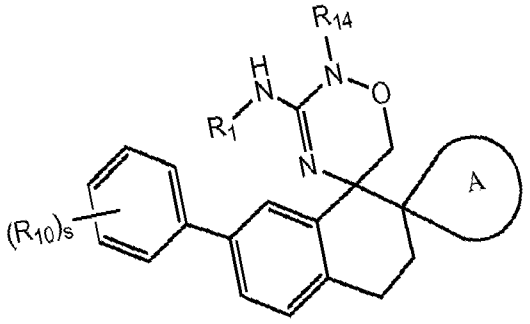

(Xb),

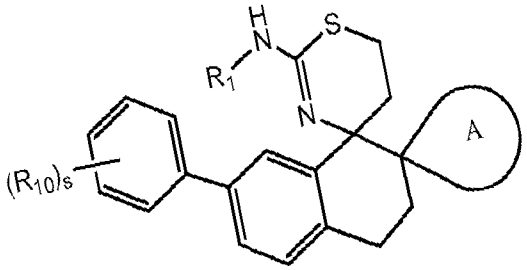

(XIb),

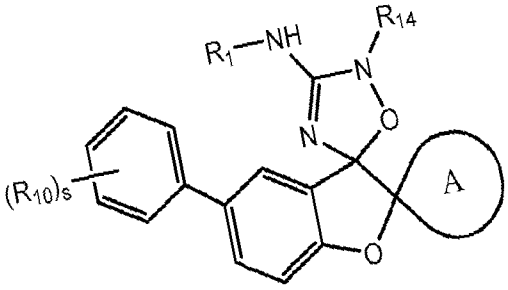

(XIIb),

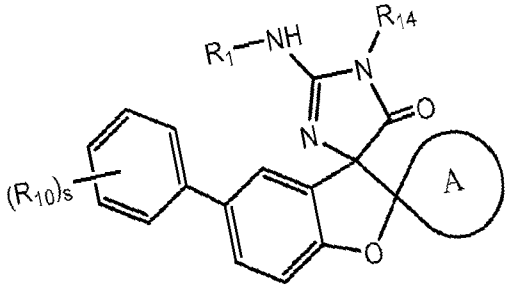

(XIIIb),

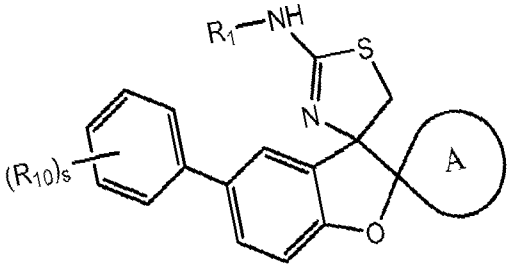

(XIVb),

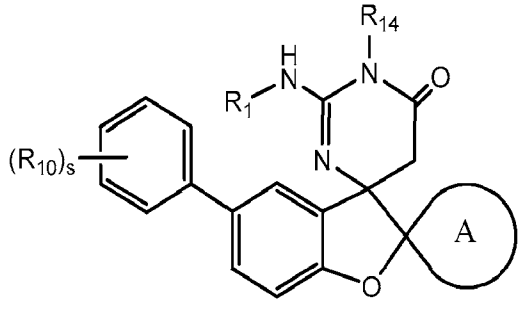

(XVb),

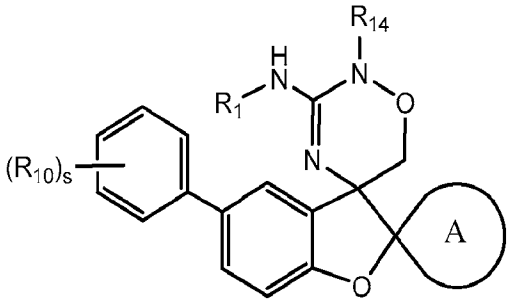

(XVIa),

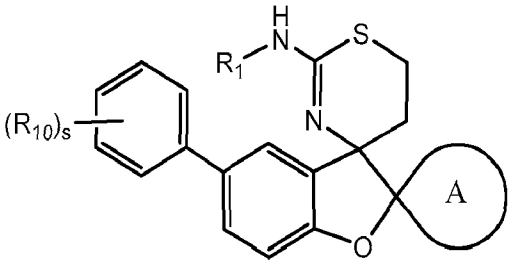

(XVIIb),


(XVIIIb)


(XIXb),


(XXb),


(XXIb), or

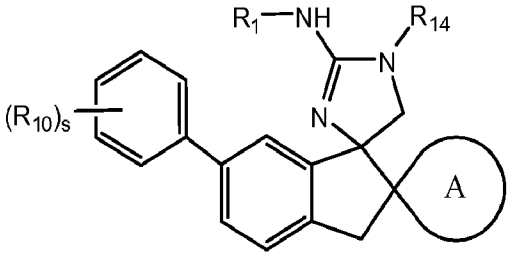

(XXIIb),

or a pharmaceutically acceptable salt thereof, wherein R_{10} is independently selected from the group consisting of -halogen, -CN, -NO_2, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)R_5$, -$C(=S)OR_5$, -$OC(=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$C(=O)R_5$, -$C(=S)R_5$, -$OC(=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=O)OR_5$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=O)R_5$, -$C(=S)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_2$-$C_6$)alkenyl, halo($C_1$-$C_6$)alkyl, ($C_1$-$C_3$)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the groups represented by R_{10} are each optionally substituted with 1 to 3 substituents independently selected from

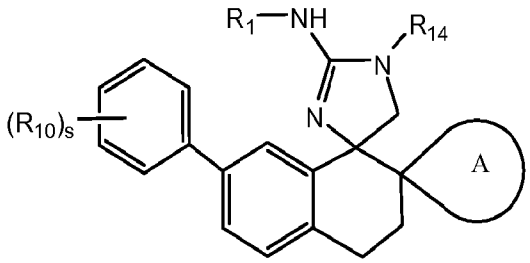
halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

and s is 0, 1, 2 or 3.

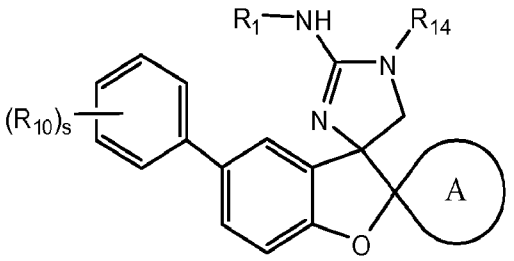
9. The compound of any one of Claims 1-6, wherein the compound is represented by the following Structural Formula:



(XXIIIb),



(XXIVb), or



(XXVb),

or a pharmaceutically acceptable salt thereof, wherein R_{10} is independently selected from the group consisting of --halogen, -CN, -NO_2, -OR_5, -SR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$S(O)_iNR_{12}R_{13}$, -$C(=O)OR_5$, -$OC(=O)R_5$, -$C(=S)OR_5$, -$OC(=S)R_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$NR_{11}C(=S)R_5$, -$C(=O)R_5$, -$C(=S)R_5$, -$OC(=O)OR_5$, -$O(C=O)NR_{12}R_{13}$, -$NR_{11}(C=O)OR_5$, -$NR_{11}(C=S)OR_5$, -$O(C=S)NR_{12}R_{13}$, -$NR_{11}(C=O)NR_{12}R_{13}$, -$NR_{11}(C=S)NR_{12}R_{13}$, -$C(=O)R_5$, -$C(=S)R_5$, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkynyl, ($C_3$-$C_8$)cycloalkyl, ($C_4$-$C_8$)cycloalkenyl, ($C_3$-$C_9$)heterocycloalkyl, ($C_2$-$C_6$)alkenyl,

halo(C_1-C_6)alkyl, (C_1-C_3)alkylsulfonylaminoalkyl, hydroxy(C_1-C_6)alkyl, cyano(C_1-C_6)alkyl, (C_1-C_3)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy ,(C_1-C_6)alkoxy(C_1-C_3)alkyl, aryl and heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups in the groups represented by R_{10} are each optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_3)alkoxy, halo(C_1-C_3)alkoxy and (C_1-C_3)alkoxy(C_1-C_6)alkyl;

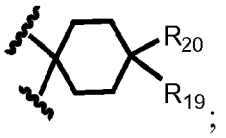
and s is 0, 1, 2 or 3.

10. The compound of any one of Claims 8 and 9, wherein R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl and halo(C_1-C_6)alkoxy.

11. The compound of Claim 10, wherein R_{10} is independently selected from the group consisting of -F, -Cl, -Br, -CN, -Me, -Et, -OMe, -CF_3, -OCF_3.

12. The compound of any one of the proceeding Claims, wherein R_1 is -H and R_{14}, when present, is -Me.

13. The compound of any one of Claims 1, 3, 4 and 7-12, wherein ring A is represented by the following structural formula:



wherein:

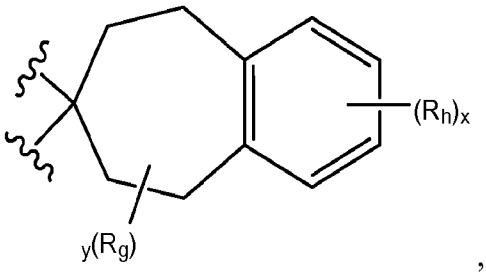
R_{19} and R_{20} are each independently selected from -H, halogen, -CN, -OR_5, -NR_6R_7, -$S(O)_iR_5$, -$NR_{11}S(=O)_iR_5$, -$C(=O)OR_5$, -$C(=O)NR_{12}R_{13}$, -$NR_{11}C(=O)R_5$, -$C(=S)NR_{12}R_{13}$, -$C(=O)R_5$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl, wherein each of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl and heteroaryl(C_1-C_6)alkyl groups represented by R_{19} and R_{20} is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, -CN,

-OH, -$NR_{11}SO_2(C_1$-$C_3)$alkyl, -$NR_{11}C(=O)$-$(C_1$-$C_3)$alkyl, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$alkoxy$(C_1$-$C_6)$alkyl.

14. The compound of Claim 13, wherein:

R_{20} is –H and R_{19} is –OH, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy or $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkoxy.

15. The compound of any one of Claims 1, 3, 4 and 7-12, wherein ring A is represented by the following structural formula:



,

wherein:

R_g and R_h, for each occurrence, are independently –H, -halogen, -CN, $-NO_2$, $-OR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl, heteroaryl, each $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, aryl and heteroaryl represented by R_b is optionally substituted with 1 to 3 substituents selected from the group consisting of -F, -Cl, -Br, -CN, $-OR_5$, $-SR_5$, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}S(=O)_iR_5$, $-C(=O)OR_5$, $-C(=O)NR_{12}R_{13}$, $-NR_{11}C(=O)R_5$, $-C(=S)NR_{12}R_{13}$, $-C(=O)R_5$, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_9)$heterocycloalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_1$-$C_6)$alkyl, , hydroxy$(C_1$-$C_6)$alkyl, cyano$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, halo$(C_1$-$C_3)$alkoxy,$(C_1$-$C_6)$alkoxy$(C_1$-$C_3)$alkyl, aryl and heteroaryl;

x is an integer from 1 to 4; and

y is an integer from 1 to 6.

16. The compound of Claim 15, wherein R_g is –H and R_h is –H.

17. The compound of any one of Claims 1-6 and 12-16, wherein:

R_1 is –H or –C(=O)(C_1-C_3)alkyl;

R_2 is –H, halogen, -CN, -OR_5, -C(=O)$NR_{12}R_{13}$, -C(=O)OR_5, -C(O)R_5, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl, (C_5-C_6)heterocycloalky(C_1-C_3)alkyl, wherein the heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl, triazole and thiophenyl, the heterocycloalkyl is selected from oxetanyl, tretrahydrafuran, tetrapyran, piperidine, pyrrolidinyl and pyrrolidinonyl, and each of (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_4-C_6)cycloalkenyl, phenyl, phenyl(C_1-C_3)alkyl, heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_5-C_6)heterocycloalkyl and (C_5-C_6)heterocycloalky(C_1-C_3)alkyl groups represented by R_2 is optionally substituted with 1 to 5 substituents independently selected from halogen, -CN, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, (C_2-C_6)alkynyl, -NR_6R_7, -S(O)$_i$$R_5$, -C(O)$R_5$, -OH, ($C_3$-$C_6$)cycloalkyl, ($C_1$-$C_3$)alkoxy and halo($C_1$-$C_3$)alkoxy; and

R_{14}, when present, is –H, -OR_5, -NR_6R_7, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl, wherein the heteroaryl is selected from pyridyl, pyridazinyl, pyridinonyl, pyridazinonyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyrimidyl, indolyl, quinolyl, quinoxalinyl and thiophenyl and triazolyl, the (C_3-C_5)heterocycloalkyl is selected from oxetanyl, tetrahydrofuran, tetrahydropyran, piperidinyl and pyrrolidinyl, and each of the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_3)alkyl, (C_3-C_5)heterocycloalkyl, (C_3-C_5)heterocycloalkyl(C_1-C_3)alkyl, heteroaryl, phenyl, phenyl(C_1-C_3)alkyl and heteroaryl(C_1-C_3)alkyl groups represented by R_{14} is optionally substituted with 1

to 3 substituents independently selected from halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkoxy, $-NR_6R_7$, $-S(O)_iR_5$, $-NR_{11}SO_2R_5$, -OH, $-COOR_5$, $-C(=O)R_5$, $-C(=O)NR_{12}R_{13}$ and thiazolyl.

18. The compound of any one of Claims 1-17, wherein:

R_5 is selected from the group consisting of –H, $(C_1$-$C_3)$alkyl, halo$(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_3)$alkyl, phenyl and phenyl$(C_1$-$C_3)$alkyl, wherein the phenyl group in the groups represented by R_5 is optionally substituted with 1 to 3 substituents independently selected from -F, -Cl, -Br, -CN, =O, $-NR_6R_7$, $(C_1$-$C_3)$alkyl, halo$(C_1$-$C_3)$alkyl and $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl;

R_6 is –H or $(C_1$-$C_3)$alkyl;

R_7 is –H, $(C_1$-$C_3)$alkyl, halo$(C_1$-$C_3)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl;

R_{11} is –H or $(C_1$-$C_3)$alkyl;

R_{12} is –H or $(C_1$-$C_3)$alkyl; and

R_{13} is –H, $(C_1$-$C_3)$alkyl, halo$(C_1$-$C_3)$alkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl, or R_{12} and R_{13} together with the nitrogen atom to which they are attached forms a pyrrolidine or piperidine ring.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt thereof.

20. A method of inhibiting BACE activity in a subject in need of such treatment comprising administering to the subject an effective amount of a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt thereof.

21. A method of treating a BACE mediated disorder in a subject comprising administering to the subject an effective amount of a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21, wherein the disorder is selected from the group consisting of Alzheimer's disease, cognitive impairment, Down's Syndrome, HCHWA-D, cognitive decline, senile dementia, cerebral amyloid angiopathy, degenerative dementia, other neurodegenerative disorders, and glaucoma.

23. The method of Claim 22, wherein the disorder is Alzheimer's disease.

24. The method of Claim 22, wherein the disorder is glaucoma.