

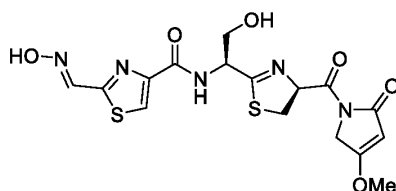
ANTICANCER COMPOUNDS

The present invention relates to new anticancer compounds, their use as anticancer agents, their pharmaceutical compositions and methods for their synthesis.

5 BACKGROUND OF THE INVENTION

In 1957 Yamaguchi *et al.* reported the isolation of althiomycin from a *Streptomyces* assigned to *Streptomyces althioticus*, *n. sp* (Yamaguchi, H *et al.* J. of Antibiotics A, 1957, 10, 195-200). This paper also disclosed its antibiotic activity against both gram positive and gram negative bacteria.

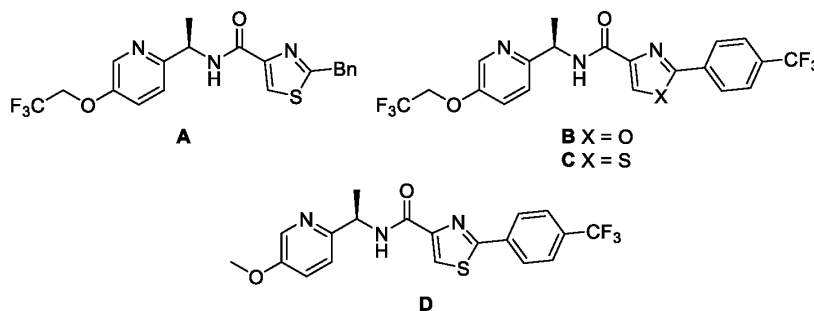
10 Its structure was elucidated in 1974 by Umezawa *et al.* (J. of Antibiotics 1974, 27, 897-899).



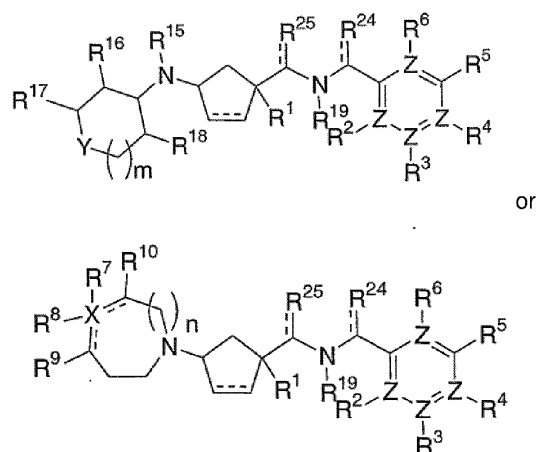
althiomycin

The cytotoxic activity of althiomycin against several gastric and liver cancer cell lines was described in international patent application publication **WO2002066046**. In particular
 15 althiomycin had IC₅₀ values in the micro molar range against gastric cancer cell lines SNU-638, SNU-216 and AGS (0.77 μM, 0.77 μM and 0.85 μM, respectively) and against liver cancer cell lines HepG2, Hep3B and SK-HEP-1 (1.43 μM, 0.88 μM and 0.81 μM, respectively).

International patent application publication **WO2010137351** discloses compounds A-D, which have blocking activities of T-type calcium channels or voltage sodium channels as the
 20 tetrodotoxin-sensitive (TTX-S) blockers such as Nav_{1.3} and Nav_{1.7} with IC₅₀ values in the micro molar range. This patent application also discloses the use of these compounds in the treatment of several diseases, including cancer.



International patent application publication **WO2005014537** discloses compounds of general formula:



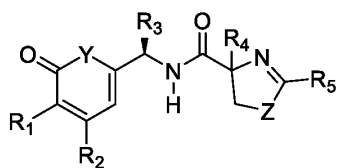
5 wherein R^1 - R^{10} , R^{15} - R^{19} , R^{24} - R^{25} , X, Y, Z, m and n take several meanings;

which are modulators of chemokine receptor activity and their use in the prevention or treatment of inflammatory and immunoregulatory disorders and diseases.

Since cancer is a leading cause of death in animals and humans, efforts have been and continue to be undertaken in order to obtain further anticancer therapies which are both active and safe to be administered to patients suffering from cancer.

SUMMARY OF THE INVENTION

In a first aspect, the present invention is directed to a compound of formula I or a pharmaceutically acceptable salt or ester thereof



I

15 wherein:

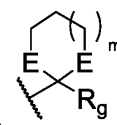
R_1 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

R_2 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, $-OR_a$, $-OSO_2R_b$, $-NR_cR_d$, $-NR_c(C=O)R_f$, and $-NR_cSO_2R_b$, wherein the optional substituents are one or more substituents R_x ;

- 5 R_3 is selected from halogen-substituted or unsubstituted C_1 - C_{12} alkyl, halogen-substituted or unsubstituted C_2 - C_{12} alkenyl, halogen-substituted or unsubstituted C_2 - C_{12} alkynyl and substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I;

- 10 R_4 is selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

- R_5 is selected from $-C(OR_e)_2R_g$, $-C(SR_e)_2R_g$, $-CH(OR_a)R_g$, $-CH(O-(C=O)R_f)R_g$, $-CH(NR_cR_d)R_g$, $-CH(NR_c-(C=O)R_f)R_g$, $-CH(NR_c-OR_h)R_g$, $-(C=O)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-O-$
 15 $(C=O)R_f)R_g$, $-(C=N-O-(C=O)OR_a)R_g$, $-(C=N-O-[(P=O)(OR_a)_2])R_g$, $-(C=N-NR_cR_d)R_g$, $-(C=O)OR_a$, $-(C=O)NR_c-OR_h$, $-(C=O)NR_cR_d$, $-(C=CH_2)R_g$, and $-(C=CH_2)OR_a$; or R_5 is a



where m is 0, 1 or 2 and each E group is independently selected from O and S;

Y and Z are independently selected from $-O-$, $-S-$, $-(NH)-$, and $-(NProt^{NH})-$, where $Prot^{NH}$ is a protecting group for amino;

- 20 each group R_a is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, and $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the
 25 optional substituents are one or more substituents R_x ;

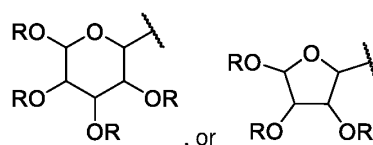
each group R_b is independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x ;

- 30 each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more

substituents R_x ; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

each group R_e is substituted or unsubstituted C_1 - C_{12} alkyl group, wherein the optional substituents are one or more substituents R_x ;

- 5 each group R_f is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x , and a group of formula:



- 10 where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(\text{C}=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$, and substituted or unsubstituted $-(\text{C}=\text{O})\text{NH}(\text{C}_1\text{-C}_6)\text{alkyl}$, wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-,
15 benzylidene-, and *p*-methoxybenzylidene- acetals;

each group R_g is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

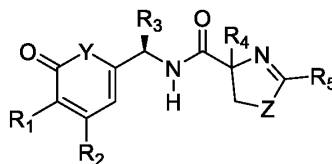
- each group R_h is independently selected from hydrogen, a protecting group for OH, substituted
20 or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted heterocyclo- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the
25 optional substituents are one or more substituents R_x ;

- substituents R_x are selected from the group consisting of C_1 - C_{12} alkyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkenyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkynyl groups which may be optionally substituted with at least one group R_y , halogen atoms, oxo groups, thio groups, cyano groups,
30 nitro groups, OR_y , OCOR_y , OCOOR_y , COR_y , COOR_y , OCONR_yR_z , CONR_yR_z , SR_y , $\text{S}(=\text{O})\text{R}_y$, SO_2R_y , OSO_2OR_y , SSR_y , $\text{P}(=\text{O})(\text{R}_y)\text{OR}_z$, $\text{OP}(=\text{O})(\text{OR}_y)_2$, NR_yR_z , $\text{NR}_y\text{C}(=\text{O})\text{R}_z$, $\text{NR}_y\text{C}(=\text{O})\text{OR}_z$,

$\text{NR}_y\text{C}(=\text{O})\text{NR}_y\text{R}_z$, $\text{NR}_y\text{C}(=\text{NR}_y)\text{NR}_y\text{R}_z$, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y , OR_y , OCOR_y , OCOOR_y , NR_yR_z , NR_yCOR_z , and $\text{NR}_y\text{C}(=\text{NR}_y)\text{NR}_y\text{R}_z$, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y , and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

each R_y and R_z is independently selected from the group consisting of hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl groups, $\text{C}_1\text{-C}_{12}$ alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a $\text{C}_1\text{-C}_{12}$ alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings, and heterocycloalkyl group comprising a $\text{C}_1\text{-C}_{12}$ alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s).

In a further aspect, the present invention is directed to a compound of formula I or a pharmaceutically acceptable salt or ester thereof



I

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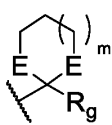
wherein:

- R_1 is selected from hydrogen, halogen, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, and substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl, wherein the optional substituents are one or more substituents R_x ;
- R_2 is selected from hydrogen, halogen, substituted or unsubstituted $\text{C}_1\text{-C}_{24}$ alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_{24}$ alkenyl, substituted or unsubstituted $\text{C}_2\text{-C}_{24}$ alkynyl, $-\text{OR}_a$, $-\text{OSO}_2\text{R}_b$, $-\text{NR}_c\text{R}_d$, $-\text{NR}_c(\text{C}=\text{O})\text{R}_f$, and $-\text{NR}_c\text{SO}_2\text{R}_b$, wherein the optional substituents are one or more substituents R_x ;
- R_3 is selected from halogen-substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ alkyl, halogen-substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkenyl, halogen-substituted or unsubstituted $\text{C}_2\text{-C}_{12}$ alkynyl and

substituted or unsubstituted C₃-C₆ cycloalkyl-C₁-C₁₂ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I;

- 5 R₄ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

R₅ is selected from -C(OR_e)₂R_g, -C(SR_e)₂R_g, -CH(OR_a)R_g, -CH(O-(C=O)R_f)R_g, -CH(NR_cR_d)R_g, -CH(NR_c-(C=O)R_f)R_g, -CH(NR_c-OR_h)R_g, -(C=O)R_g, -(C=NR_e)R_g, -(C=N-OR_h)R_g, -(C=N-O-(C=O)R_f)R_g, -(C=N-NR_cR_d)R_g, -(C=O)OR_a, -(C=O)NR_c-OR_h, and -(C=O)NR_cR_d; or R₅ is a

- 10  group where m is 0, 1 or 2 and each E group is independently selected from O and S;

Y and Z are independently selected from -O-, -S-, -(NH)-, and -(NProt^{NH})-, where Prot^{NH} is a protecting group for amino;

- 15 each group R_a is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, substituted or unsubstituted C₂-C₂₄ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, and -(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x;

- 20 each group R_b is independently selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x;

- 25 each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

- 30 each group R_e is substituted or unsubstituted C₁-C₁₂ alkyl group, wherein the optional substituents are one or more substituents R_x;

each group R_f is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂

alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, -CH₂O(CH₂CH₂O)_pCH₂CH₃ and -CH₂O(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x;

- 5 each group R_g is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

- 10 each group R_h is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, -(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the optional substituents are one or more substituents R_x;

- 15 substituents R_x are selected from the group consisting of C₁-C₁₂ alkyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkenyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkynyl groups which may be optionally substituted with at least one group R_y, halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y, OCOR_y, OCOOR_y, COR_y, COOR_y, OCONR_yR_z, CONR_yR_z, SR_y, S(=O)R_y, SO₂R_y, SSR_y, P(=O)(R_y)OR_z, NR_yR_z, NR_yCOR_z, NR_yC(=O)NR_yR_z, NR_yC(=NR_y)NR_yR_z, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y, OR_y, OCOR_y, OCOOR_y, NR_yR_z, NR_yCOR_z, and NR_yC(=NR_y)NR_yR_z, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y, and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and
- 20
- 25
- 30

- each R_y and R_z is independently selected from the group consisting of hydrogen, C₁-C₁₂ alkyl groups, C₁-C₁₂ alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C₁-C₁₂ alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings, and heterocycloalkyl group comprising a C₁-C₁₂ alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s).
- 35

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound according to the present invention, or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier.

5 In a yet further aspect of the present invention, there is provided a dosage form comprising a pharmaceutical composition according to the present invention.

In a yet further aspect of the present invention, there is provided a compound, pharmaceutical composition or dosage form according to the present invention for use as a medicament.

10 In a yet further aspect of the present invention, there is provided a compound, pharmaceutical composition or dosage form according to the present invention for use in the treatment of cancer.

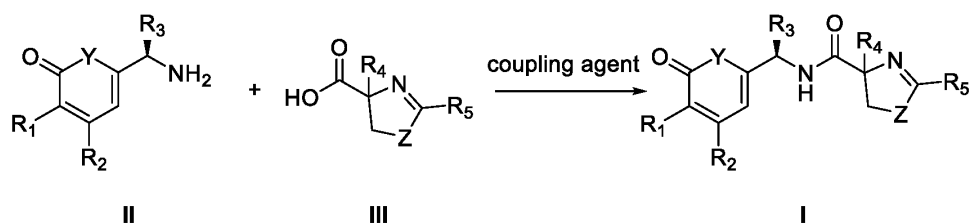
In a yet further aspect of the present invention, there is provided the use of a compound, pharmaceutical composition or dosage form according to the present invention for the manufacture of a medicament, preferably for the treatment of cancer.

15 In a yet further aspect of the present invention, there is provided a method for the prevention or treatment of cancer, comprising administering an effective amount of a compound according to the present invention, administering an effective amount of a pharmaceutical composition according to the present invention, or administering an effective amount of a dosage form according to the present invention to a patient in need thereof, notably a human.

20 In a yet further aspect of the present invention, there is provided the use of a compound according to the present invention for the treatment of cancer.

In a yet further aspect of the present invention, there is provided a kit comprising a therapeutically effective amount of a compound according to the present invention and a pharmaceutically acceptable carrier. The kit is preferably for use in the treatment of cancer.

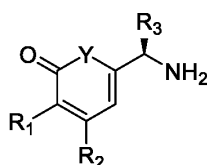
25 In a yet further aspect of the present invention, there is provided a process for obtaining compounds of formula I or a pharmaceutically acceptable salt or ester thereof, comprising the coupling of a compound of formula II with a compound of formula III in accordance to Scheme I:



Scheme I

wherein R_1 , R_2 , R_3 , R_4 , R_5 , Y , and Z are as defined in the compound of formula I or an appropriately protected group as needed.

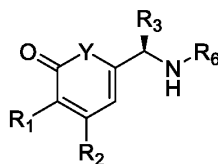
- In a yet further aspect of the present invention, there is provided the use of intermediate compounds of formula II or a salt thereof:



II

wherein R_1 , R_2 , R_3 , and Y are as defined for compounds of formula I, or an appropriately protected group as needed, in the manufacture of compounds of formula I as defined herein or a pharmaceutically acceptable salt or ester thereof.

- In a yet further aspect of the present invention, there are provided intermediate compounds of formula IIa:



IIa

wherein:

- R_1 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

- R_2 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, $-OR_a$, $-OSO_2R_b$, $-NR_cR_d$, $-NR_c(C=O)R_f$, and $-NR_cSO_2R_b$, wherein the optional substituents are one or more substituents R_x ;

R_3 is selected from halogen-substituted or unsubstituted C_1 - C_{12} alkyl, halogen-substituted or unsubstituted C_2 - C_{12} alkenyl, halogen-substituted or unsubstituted C_2 - C_{12} alkynyl, and

substituted or unsubstituted C₃-C₆ cycloalkyl-C₁-C₁₂ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I;

R₆ is selected from hydrogen and a carbamate protecting group for amino;

- 5 Y is selected from -O-, -S-, -(NH)-, and -(NProt^{NH})-, where Prot^{NH} is a protecting group for amino, with the proviso that when R₂ is hydrogen, then Y is selected from -O- and -S-;

- R_a is selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, substituted or unsubstituted C₂-C₂₄ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, and -(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x;
- 10

- each group R_b is independently selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x;
- 15

- each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;
- 20

R_i is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, -CH₂O(CH₂CH₂O)_pCH₂CH₃, and -CH₂O(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25, wherein the optional substituents are one or more substituents R_x;

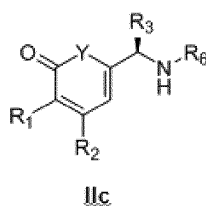
- 25 substituents R_x are selected from the group consisting of C₁-C₁₂ alkyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkenyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkynyl groups which may be optionally substituted with at least one group R_y, halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y, OCOR_y, OCOOR_y, COR_y, COOR_y, OCONR_yR_z, CONR_yR_z, SR_y, S(=O)R_y, SO₂R_y, OSO₂OR_y, SSR_y, P(=O)(R_y)OR_z, OP(=O)(OR_y)₂, NR_yR_z, NR_yC(=O)R_z, NR_yC(=O)OR_z, NR_yC(=O)NR_yR_z, NR_yC(=NR_y)NR_yR_z, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y, OR_y, OCOR_y, OCOOR_y, NR_yR_z, NR_yCOR_z, and NR_yC(=NR_y)NR_yR_z, aralkyl groups comprising an alkyl groups having from 1 to
- 30

- 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y , and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

- each R_y and R_z is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl groups, C_1 - C_{12} alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C_1 - C_{12} alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings and heterocycloalkyl group comprising a C_1 - C_{12} alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s);

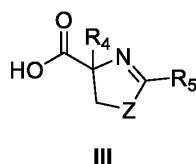
or a salt thereof.

- 15 In a yet further aspect of the present invention, there is provided the use of intermediate compounds of formula **IIc** or a salt thereof:



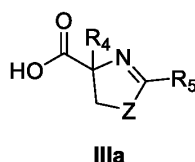
- wherein R_1 , R_2 , R_3 , and Y are as defined for compounds of formula **I**, or an appropriately protected group as needed, and R_6 is selected from hydrogen and a carbamate protecting group for amino, in the manufacture of compounds of formula **I** as defined herein or a pharmaceutically acceptable salt or ester thereof.

In a yet further aspect of the present invention, there is provided the use of intermediate compounds of formula **III** or a salt thereof:



wherein R_4 , R_5 , and Z are as defined for the compounds of formula I, or an appropriately protected group as needed, in the manufacture of compounds of formula I as defined herein or a pharmaceutically acceptable salt or ester thereof.

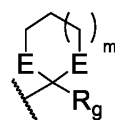
- In a yet further aspect of the present invention, there are provided intermediate
5 compounds of formula IIIa:



wherein R_4 is selected from unsubstituted C_1 - C_{12} alkyl, unsubstituted C_2 - C_{12} alkenyl and unsubstituted C_2 - C_{12} alkynyl;

- R_5 is selected from $-C(OR_e)_2R_g$, $-C(SR_e)_2R_g$, $-CH(OR_a)R_g$, $-CH(O-(C=O)R_f)R_g$, $-CH(NR_c-$
10 $(C=O)R_f)R_g$, $-CH(NR_c-OR_h)R_g$, $-(C=O)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-O-(C=O)R_f)R_g$, $-(C=N-O-(C=O)OR_a)R_g$, $-(C=N-O-[(P=O)(OR_a)_2])R_g$, $-(C=N-NR_cR_d)R_g$, $-(C=O)OR_a$, $-(C=O)NR_c-$

OR_h , $-(C=O)NR_cR_d$, $-(C=CH_2)R_g$, and $-(C=CH_2)OR_a$; or R_5 is a
or 2 and each E group is independently selected from O and S;



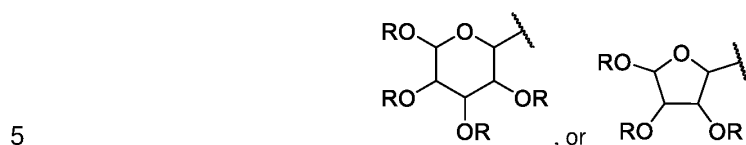
Z is selected from $-O-$, $-S-$, $-(NH)-$, and $-(NProt^{NH})-$, where $Prot^{NH}$ is a protecting group for amino;

- each group R_a is independently selected from hydrogen, a protecting group for OH, substituted
15 or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, and $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the
20 optional substituents are one or more substituents R_x ;

- each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ; or R_c and R_d together with the nitrogen atom to which they are attached form a
25 heterocyclic group;

each group R_e is substituted or unsubstituted C_1 - C_{12} alkyl group, wherein the optional substituents are one or more substituents R_x ;

each group R_f is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x , and a group of formula:



where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(\text{C}=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$, and substituted or unsubstituted $-(\text{C}=\text{O})\text{NH}(\text{C}_1\text{-C}_6)\text{alkyl}$, wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

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each group R_g is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

15 each group R_h is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted heterocyclo- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$,
 20 wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the optional substituents are one or more substituents R_x ;

substituents R_x are selected from the group consisting of C_1 - C_{12} alkyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkenyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkynyl groups which may be optionally substituted with at least one group R_y , halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y , OCOR_y , OCOOR_y , COR_y , COOR_y , OCONR_yR_z , CONR_yR_z , SR_y , $\text{S}(=\text{O})\text{R}_y$, SO_2R_y , OSO_2OR_y , SSR_y , $\text{P}(=\text{O})(\text{R}_y)\text{OR}_z$, $\text{OP}(=\text{O})(\text{OR}_y)_2$, NR_yR_z , $\text{NR}_y\text{C}(=\text{O})\text{R}_z$, $\text{NR}_y\text{C}(=\text{O})\text{OR}_z$, $\text{NR}_y\text{C}(=\text{O})\text{NR}_y\text{R}_z$, $\text{NR}_y\text{C}(=\text{NR}_y)\text{NR}_y\text{R}_z$, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y , OR_y , OCOR_y , OCOOR_y , NR_yR_z , NR_yCOR_z , and $\text{NR}_y\text{C}(=\text{NR}_y)\text{NR}_y\text{R}_z$, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above,

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aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y , and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

each R_y and R_z is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl groups, C_1 - C_{12} alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C_1 - C_{12} alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings and heterocycloalkyl group comprising a C_1 - C_{12} alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s); or a salt thereof.

In a yet further aspect of the present invention, it is provided the isolation of compound **1** from a sponge of the order Lithistida, family Theonellidae, genus Discodermia (du Bocage 1869), and the formation of derivatives from the isolated compound.

In a yet further aspect of the present invention, there is provided purified compound **1**.

In a yet further aspect of the present invention, there is provided isolated compound **1**.

In a yet further aspect of the present invention, there is provided compound **1** at a purity of above about 80%, above about 90%, above about 95%, above about 98%, above about 99%, above about 99.5% or above about 99.9%.

In a yet further aspect of the present invention, there is provided compound **1** in amorphous form.

In a yet further aspect of the present invention, there is provided compound **1** in crystalline form.

In a further aspect, there is provided a composition comprising compound **1** in crystalline form. In a yet further embodiment, the composition may comprise compound **1** in at least 30% crystalline form, in at least 50% crystalline form, in at least 75% crystalline form, in at least 90% crystalline form, in at least 95% crystalline form, in at least 99% crystalline form, or in about 100% crystalline form.

In a yet further aspect of the present invention, there is provided a pharmaceutically acceptable salt or ester of compound **1**.

In a yet further aspect of the present invention, there is provided a solvate of compound **1**, for example a hydrate.

In a yet further aspect of the present invention, there is provided a stable composition of compound **1**.

5 In a yet further aspect of the present invention, there is provided a solid pharmaceutical composition (including a tablet, pill, capsule, or granule) or a liquid composition (including a solution, suspension or emulsion) of compound **1** or a pharmaceutically acceptable salt or ester thereof.

10 In a yet further aspect of the present invention there is provided a pharmaceutical composition adapted for oral, topical or parenteral administration of compound **1** or a pharmaceutically acceptable salt or ester thereof.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following embodiments apply to all aspects of the present invention.

15 In the compounds defined by a Markush formula in this specification, the groups can be selected in accordance with the following guidance:

20 Alkyl groups may be branched or unbranched, and preferably have from 1 to about 24 carbon atoms. One preferred class of alkyl groups has from 1 to about 12 carbon atoms. One more preferred class of alkyl groups has from 1 to about 8 carbon atoms or from 1 to about 6 carbon atoms. Even more preferred are alkyl groups having 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl, *sec*-butyl and isobutyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise stated, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

25 Cycloalkylalkyl groups are non-cyclic alkyl groups substituted with a cycloalkyl group. A preferred class of cycloalkylalkyl group has a cycloalkyl moiety with from 3 to about 6 carbon ring atoms and an alkyl moiety with from 1 to about 12 carbon atoms. One more preferred class of cycloalkylalkyl groups has a cycloalkyl moiety with from 3 to about 4 carbon ring atoms and an alkyl moiety with from 1 to about 6 carbon atoms. Cyclopropylmethyl is a particularly preferred cycloalkyl group in the compounds of the present invention.

30 Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more unsaturated linkages and from 2 to about 12 carbon atoms. One more preferred class of alkenyl and alkynyl groups has from 2 to about 8 carbon atoms or from 2 to about 6 carbon atoms. Even more preferred are alkenyl and alkynyl groups

having 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Suitable aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated and/or fused rings and from 6 to about 18 carbon ring atoms. Preferably aryl groups contain from 6 to about 14 carbon ring atoms. Specially preferred aryl groups include substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted phenanthryl and substituted or unsubstituted anthryl. The most preferred aryl group is substituted or unsubstituted phenyl.

Suitable heterocyclic groups may be saturated or unsaturated and include heteroaromatic and heteroalicyclic groups, the latter of which may be partially unsaturated, both the aromatic and the alicyclic heterocyclic groups containing from 1 to 3 separated and/or fused rings and from 5 to about 18 ring atoms. Preferably heteroaromatic and heteroalicyclic groups contain from 5 to about 10 ring atoms, more preferably 5, 6 or 7 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinolizyl.

Heterocycloalkyl groups are non-cyclic alkyl groups substituted with a heterocyclic group. A preferred class of heterocycloalkyl group has a heterocyclic moiety with from 5 to about 10 ring atoms and 1 or 2 heteroatoms independently selected from O, N and S, and an alkyl moiety with from 1 to about 6 carbon atoms. One more preferred class of cycloalkylalkyl groups has a heterocyclic moiety with from 5 to 6 ring atoms and 1 or 2 heteroatoms independently selected from O and N and an alkyl moiety with from 1 to about 6 carbon atoms. Even more preferred are substituted or unsubstituted morpholino-C₃-C₅ alkyl and substituted or

unsubstituted piperazinyl-C₃-C₅alkyl. [4 λ ²-morpholine]-(CH₂)₄- and [1-methyl-4 λ ²-piperazine]-(CH₂)₃ are most preferred heterocycloalkyl groups in the compounds of the present invention.

Suitable monosaccharides include aldoses, a saccharide bearing an aldehyde functional group at the terminal position, and more particularly an aldohexose, a saccharide with 6 carbon atoms, or an aldopentose, a saccharide with 5 carbon atoms, preferably an aldohexose. It will thus be in particular allose, altrose, glucose, mannose, gulose, idose, galactose, talose, ribose, arabinose, xylose or lyxose, in D or L form. The monosaccharide will be preferably in a cyclized form, in particular in a pyranose form, a 6-member ring, or in a furanose form, a 5 member ring. In these cases, the aldehyde functional group borne by the saccharide is in a hemiacetal form, also called a pseudoaldehyde functional group. It is particular preferred the piranose form.

By "monosaccharide residue" is meant, in the context of the present invention, the part of the monosaccharide, as defined above, that is connected to the rest of the molecule via its carbon atom 1 following a condensation reaction between the aldehyde, or pseudoaldehyde, functional group of the monosaccharide and a hydroxy (OH) functional group.

Suitable halogen groups or substituents in the compounds of the present invention include F, Cl, Br and I. Fluorine is the most preferred halogen group in the compounds of the present invention.

The term halogen-substituted group refer to a group substituted with one or more halogen atoms at one or more suitable positions, wherein the halogen atoms at each halogen-substituted group may be the same or different.

The terms "pharmaceutically acceptable salt" and "ester" refers to any pharmaceutically acceptable salt or ester which, upon administration to the patient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of both. Generally, nonaqueous media like ether, ethyl acetate, ethanol, 2-propanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, and organic acid addition salts such as,

for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and *p*-toluenesulfonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, *N,N*-dialkylmethanolamine, triethanolamine and basic aminoacids salts.

The compounds of the invention may be in amorphous form or in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that all forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Stereoisomerism about the asymmetric carbons with unspecified stereochemistry is possible, therefore in such cases the asymmetric carbon can have (*R*) or (*S*) configuration. All diastereomers generated by a specific configuration of such asymmetric carbons in conjunction with the other asymmetric carbons present in the molecule, and mixtures thereof, are considered within the scope of the present invention. Stereoisomerism about the double bond (geometric isomerism) is also possible, therefore in some cases the molecule could exist as (*E*)-isomer or (*Z*)-isomer. If the molecule contains several double bonds, each double bond will have its own stereoisomerism, that could be the same or different than the stereoisomerism of the other double bonds of the molecule. Furthermore, compounds referred to herein may exist as atropoisomers. The single stereoisomers including diastereoisomers, geometric isomers and atropoisomers of the compounds referred to herein, and mixtures thereof fall within the scope of the present invention.

In addition, compounds referred to herein may exist in isotopically-labelled forms. All pharmaceutically acceptable salts, esters and isotopically labelled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.

Protected forms of the compounds disclosed herein are considered within the scope of the present invention. Suitable protecting groups are well known for the skilled person in the art. A general review of protecting groups in organic chemistry is provided by Wuts, P.G.M. and Greene T.W. in *Protecting Groups in Organic Synthesis*, 4th Ed. Wiley-Interscience, and by Kocienski P.J. in *Protecting Groups*, 3rd Ed. Georg Thieme Verlag. These references provide sections on protecting groups for OH and amino groups. All these references are incorporated by reference in their entirety.

Within the scope of the present invention a protecting group for OH is defined to be the O-bonded moiety resulting from the protection of the OH group through the formation of a suitable protected OH group. Examples of such protected OH groups include ethers, silyl ethers, esters, sulfonates, sulfenates and sulfinates, carbonates, and carbamates. In the case of ethers

the protecting group for the OH can be selected from methyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, [(3,4-dimethoxybenzyl)oxy]methyl, *p*-nitrobenzyloxymethyl, *o*-nitrobenzyloxymethyl, [(*R*)-1-(2-nitrophenyl)ethoxy]methyl, (4-methoxy-phenoxy)methyl, guaiacolmethyl, [(*p*-phenylphenyl)oxy]methyl, *t*-butoxy-methyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *O*-bis(2-acetoxyethoxy)methyl, tetrahydropyranyl, fluorous tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxy-tetrahydrothiopyranyl *S,S*-dioxide, 1-[(2-chloro-4-methyl)-phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1-(4-chlorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-hydroxyethyl, 2-bromoethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1,1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 1-(2-cyanoethoxy)ethyl, 2-trimethylsilyl ethyl, 2-(benzylthio)ethyl, 2-phenylselenyl ethyl, *t*-butyl, cyclohexyl, 1-methyl-1'-cyclopropylmethyl, allyl, prenyl, cinnamyl, 2-phenallyl, propargyl, *p*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, pentadienyl nitrobenzyl, pentadienyl-nitropiperonyl, halobenzyl, 2,6-dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluorous benzyl, 4-fluorousalkoxybenzyl, trimethylsilylxylyl, *p*-phenylbenzyl, 2-phenyl-2-propyl, *p*-acylaminobenzyl, *p*-azidobenzyl, 4-azido-3-chlorobenzyl, 2-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, *p*-(methylsulfinyl)benzyl, *p*-siletanylbenzyl, 4-acetoxybenzyl, 4-(2-trimethylsilyl)ethoxymethoxybenzyl, 2-naphthylmethyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxide, 2-quinolinylmethyl, 6-methoxy-2-(4-methylphenyl)-4-quinolinemethyl, 1-pyrenylmethyl, diphenylmethyl, 4-methoxydiphenylmethyl, 4-phenyldiphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, tris(4-*t*-butylphenyl)methyl, α -naphthyl diphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 4,4'-dimethoxy-3''-[*N*-(imidazolylmethyl)]trityl, 4,4'-dimethoxy-3''-[*N*-(imidazolethyl)carbamoyl]trityl, bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenz[*a,c,g,i*]fluorenylmethyl)-4,4''-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-phenylthioxanthyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and 4,5-bis(ethoxycarbonyl)-[1,3]-dioxolan-2-yl, benzisothiazolyl *S,S*-dioxide. In the case of silyl ethers the protecting group for the OH can be selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl,

diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluororous silyl. In the case of esters the protecting group for the OH together with the oxygen

5 atom of the unprotected OH group to which it is attached form an ester that can be selected from formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trichloroacetamide, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, phenylacetate, diphenylacetate, 3-phenylpropionate, bisfluorous chain type propanoyl, 4-pentenoate, 4-oxopentanoate,

10 4,4-(ethylenedithio)pentanoate, 5-[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]levulinate, pivaloate, 1-adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate, 4-bromobenzoate, 2,5-difluorobenzoate, *p*-nitrobenzoate, picolinate, nicotinate, 2-(azidomethyl)benzoate, 4-azidobutyrate, (2-azidomethyl)phenylacetate, 2-[[[(tritylthio)oxy]methyl]benzoate, 2-[[[(4-methoxytritylthio)oxy]methyl]benzoate, 2-[[methyl(trityl-

15 thio)amino]methyl]benzoate, 2-[[[(4-methoxytrityl)thio]methylamino]-methyl]benzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxymethyl)benzoate, 6-(levulinylloxymethyl)-3-methoxy-2-nitrobenzoate, 6-(levulinylloxymethyl)-3-methoxy-4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsilyloxybutyrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate,

20 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2-(chloroacetoxymethyl)benzoate, 2-[(2-chloroacetoxymethyl)ethyl]benzoate, 2-[2-(benzyloxy)ethyl]benzoate, 2-[2-(4-methoxybenzyloxy)ethyl]benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenolate, *o*-(methoxycarbonyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N,N*-tetramethyl-

25 phosphorodiamidate, and 2-chlorobenzoate. In the case of sulfonates, sulfenates and sulfonates the protecting group for the OH together with the oxygen atom of the unprotected OH group to which it is attached form a group that can be selected from sulfate, allylsulfonate, methanesulfonate, benzylsulfonate, tosylate, 2-[(4-nitrophenyl)ethyl]sulfonate,

30 2-trifluoromethylbenzenesulfonate, 4-monomethoxytritylsulfonate, alkyl 2,4-dinitrophenylsulfonate, and 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate. In the case of carbonates the protecting group for the OH together with the oxygen atom of the unprotected OH group to which it is attached form a carbonate group that can be selected from methyl carbonate, methoxymethyl carbonate, 9-fluorenylmethyl carbonate, ethyl carbonate, bromoethyl carbonate,

35 2-(methylthiomethoxy)ethyl carbonate, 2,2,2-trichloroethyl carbonate, 1,1-dimethyl-2,2,2-trichloroethyl carbonate, 2-(trimethylsilyl)ethyl carbonate, 2-[dimethyl(2-naphthylmethyl)silyl]ethyl carbonate, 2-(phenylsulfonyl)ethyl carbonate, 2-(triphenylphosphonio)ethyl carbonate, *cis*-[4-[[[(methoxytrityl)sulfonyl]oxy]-tetrahydrofuran-3-yl]oxy carbonate, isobutyl carbonate, *t*-butyl carbonate, vinyl carbonate, allyl carbonate,

cinnamyl carbonate, propargyl carbonate, *p*-chlorophenyl carbonate, *p*-nitrophenyl carbonate, 4-ethoxy-1-naphthyl carbonate, 6-bromo-7-hydroxycoumarin-4-ylmethyl carbonate, benzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, anthraquinon-2-ylmethyl carbonate, 2-dansylethyl carbonate, 2-(4-nitrophenyl)ethyl carbonate, 2-(2,4-dinitrophenyl)ethyl carbonate, 2-(2-nitrophenyl)propyl carbonate, alkyl 2-(3,4-methylenedioxy-6-nitrophenyl)propyl carbonate, 2-cyano-1-phenylethyl carbonate, 2-(2-pyridyl)amino-1-phenylethyl carbonate, 2-[*N*-methyl-*N*-(2-pyridyl)]amino-1-phenylethyl carbonate, phenacyl carbonate, 3',5'-dimethoxybenzoin carbonate, methyl dithiocarbonate, and *S*-benzyl thiocarbonate. And in the case of carbamates the protecting group for the OH together with the oxygen atom of the unprotected OH group to which it is attached form a carbamate that can be selected from dimethylthiocarbamate, *N*-phenylcarbamate, *N*-methyl-*N*-(*o*-nitrophenyl)carbamate.

Within the scope of the present invention an amino protecting group is defined to be the *N*-bonded moiety resulting from the protection of the amino group through the formation of a suitable protected amino group. Examples of such protected amino groups include carbamates, ureas, amides, heterocyclic systems, *N*-alkyl amines, *N*-alkenyl amines, *N*-alkynyl amines, *N*-aryl amines, imines, enamines, *N*-metal derivatives, *N*-N derivatives, *N*-P derivatives, *N*-Si derivatives, and *N*-S derivatives. In the case of carbamates the protecting group for the amino group together with the nitrogen atom of the unprotected amino group to which it is attached form a carbamate that can be selected from methylcarbamate, ethylcarbamate, 9-fluorenylmethylcarbamate, 2,6-di-*t*-butyl-9-fluorenylmethylcarbamate, 2,7-bis(trimethylsilyl)fluorenylmethylcarbamate, 9-(2-sulfo)fluorenylmethylcarbamate, 9-(2,7-dibromo)fluorenylmethylcarbamate, 17-tetrabenz[*a,c,g,i*]fluorenylmethylcarbamate, 2-chloro-3-indenylmethylcarbamate, benz[*f*]inden-3-ylmethylcarbamate, 1,1-dioxobenzo[*b*]-thiophene-2-ylmethylcarbamate, 2-methylsulfonyl-3-phenyl-1-prop-2-enylcarbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methylcarbamate, 2,2,2-trichloroethylcarbamate, 2-trimethylsilylethylcarbamate, (2-phenyl-2-trimethylsilyl)ethylcarbamate, 2-phenylethylcarbamate, 2-chloroethylcarbamate, 1,1-dimethyl-2-haloethylcarbamate, 1,1-dimethyl-2,2-dibromoethylcarbamate, 1,1-dimethyl-2,2,2-trichloroethylcarbamate, 2-(2'-pyridyl)ethylcarbamate, 2-(4'-pyridyl)ethylcarbamate, 2,2-bis(4'-nitrophenyl)ethylcarbamate, 2-[(2-nitrophenyl)dithio]-1-phenylethylcarbamate, 2-(*N,N*-dicyclohexylcarboxamido)ethylcarbamate, *t*-butylcarbamate, C₈F₁₉CH₂CH₂C(CH₃)₂-carbamate, 1-adamantylcarbamate, 2-adamantylcarbamate, 1-(1-adamantyl)-1-methylethylcarbamate, 1-methyl-1-(4-byphenyl)ethylcarbamate, 1-(3,5-di-*t*-butylphenyl)-1-methylethylcarbamate, triisopropylsilylcarbamate, vinylcarbamate, allylcarbamate, prenylcarbamate, 1-isopropylallylcarbamate, cinnamylcarbamate, 4-nitrocinnamylcarbamate, 3-(3'-pyridyl)prop-2-enylcarbamate, hexadienylcarbamate, propargylcarbamate, but-2-ynylbiscarbamate, 8-quinolylcarbamate, *N*-hydroxypiperidinyllcarbamate, alkylidithiocarbamate, benzylcarbamate, 3,5-di-*t*-

- butylbenzylcarbamate, *p*-methoxybenzylcarbamate, *p*-nitrobenzylcarbamate, *p*-bromobenzylcarbamate, *p*-chlorobenzylcarbamate, 2,4-dichlorobenzylcarbamate, 4-methylsulfinylbenzylcarbamate, 4-trifluoromethylbenzylcarbamate, C₈F₁₇CH₂CH₂-C₆H₄-CH₂-carbamate, (C₈F₁₇CH₂CH₂)₃Si-C₆H₄-CH₂-carbamate, 2-naphthylmethylcarbamate, 9-anthrylmethylcarbamate, diphenylmethylcarbamate, 4-phenylacetoxymethylcarbamate, 4-azidobenzylcarbamate, 4-azido-methoxybenzylcarbamate, *m*-chloro-*p*-acyloxybenzylcarbamate, *p*-(dihydroxyboryl)benzylcarbamate, 5-benzisoxazolymethylcarbamate, 2-(trifluoromethyl)-6-chromonylmethylcarbamate, 2-methylthioethylcarbamate, 2-methylsulfonyl ethylcarbamate, 2-(*p*-toluenesulfonyl)ethylcarbamate, 2-(4-nitrophenylsulfonyl)ethylcarbamate, 2-(2,4-dinitrophenylsulfonyl)ethylcarbamate, 2-(4-trifluoromethylphenylsulfonyl)ethylcarbamate, [2-(1,3-dithianyl)]methylcarbamate, 2-phosphonioethylcarbamate, 2-[phenyl(methyl)sulfonyl]ethylcarbamate, 1-methyl-2-(triphenylphosphonio)ethylcarbamate, 1,1-dimethyl-2-cyanoethylcarbamate, 2-dansylethylcarbamate, 2-(4-nitrophenyl)ethylcarbamate, 4-methylthiophenylcarbamate, 2,4-dimethylthiophenylcarbamate, *m*-nitrophenylcarbamate, 3,5-dimethoxybenzylcarbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethylcarbamate, α -methylnitropiperonylcarbamate, *o*-nitrobenzylcarbamate, 3,4-dimethoxy-6-nitrobenzylcarbamate, phenyl(*o*-nitrophenyl)methylcarbamate, 2-nitrophenylethylcarbamate, 6-nitroveratrylcarbamate, 4-methoxyphenacylcarbamate, 3',5'-dimethoxybenzoincarbamate, 9-xanthenylmethylcarbamate, *t*-amylcarbamate, 1-methylcyclobutylcarbamate, 1-methylcyclohexylcarbamate, 1-methyl-1-cyclopropylmethylcarbamate, cyclobutylcarbamate, cyclopentylcarbamate, cyclohexylcarbamate, isobutylcarbamate, isobornylcarbamate, cyclopropylmethylcarbamate, *p*-decyloxybenzylcarbamate, diisopropylmethylcarbamate, 2,2-dimethoxycarbonylvinylcarbamate, *o*-(*N,N*-dimethylcarboxamido)benzylcarbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propylcarbamate, butynylcarbamate, 1,1-dimethylpropynylcarbamate, 2-iodoethylcarbamate, 1-methyl-1-(4'-pyridyl)ethylcarbamate, 1-methyl-1-(*p*-phenylazophenyl)ethylcarbamate, *p*-(*p*'-methoxyphenylazo)benzylcarbamate, *p*-(phenylazo)benzylcarbamate, 2,4,6-trimethylbenzylcarbamate, isonicotinylcarbamate, 4-(trimethylammonium)benzylcarbamate, *p*-cyanobenzylcarbamate, di(2-pyridyl)methylcarbamate, 2-furanylmethylcarbamate, phenylcarbamate, 2,4,6-tri-*t*-butylphenylcarbamate, 1-methyl-1-phenylethylcarbamate, and *S*-benzyl thiocarbamate. In the case of ureas the protecting groups for the amino group can be selected from phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl, 4-hydroxyphenylaminocarbonyl, 3-hydroxytryptaminocarbonyl, and *N'*-phenyl-aminothiocarbonyl. In the case of amides the protecting group for the amino group together with the nitrogen atom of the unprotected amino group to which it is attached form an amide group that can be selected from formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, pent-4-enamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, 2,2-dimethyl-2-(*o*-nitrophenyl)acetamide, *o*-nitrophenoxyacetamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)-

propanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *o*-nitrobenzamide, 3-(4-*t*-butyl-2,6-dinitrophenyl)-2,2-dimethylpropanamide, *o*-benzoyloxymethylbenzamide, 2-(acetoxymethyl)benzamide, 2-[(*t*-butyldiphenylsiloxy)methyl]benzamide, 3-(3',6'-dioxo-2',4',5'-trimethylcyclohexa-1',4'-diene)-3,3-dimethylpropionamide, *o*-hydroxy-*trans*-cinnamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, acetoacetamide, 3-(*p*-hydroxyphenyl)propanamide, (*N*-dithiobenzoyloxycarbonylamino)acetamide, and *N*-acetylmethionine amide. In the case of heterocyclic systems the protecting group for the amino group together with the nitrogen group of the unprotected amino group to which it is attached form a heterocyclic system that can be selected from 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dichlorophthalimide, *N*-tetrachlorophthalimide, *N*-4-nitrophthalimide, *N*-thiodiglycolyl, *N*-dithiasuccinimide, *N*-2,3-diphenylmaleimide, *N*-2,3-dimethylmaleimide, *N*-2,5-dimethylpyrrole, *N*-2,5-bis(triisopropylsiloxy)pyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, *N*-1,1,3,3-tetramethyl-1,3-disilaisoindoline, *N*-diphenylsilyldiethylene, *N*-5-substituted-1,3-dimethyl-1,3,5-triazacyclohexan-2-one, *N*-5-substituted-1,3-benzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, and 1,3,5-dioxazine. In the case of *N*-alkyl, *N*-alkenyl, *N*-alkynyl or *N*-aryl amines the protecting group for the amino group can be selected from *N*-methyl, *N*-*t*-butyl, *N*-allyl, *N*-prenyl, *N*-cinnamyl, *N*-phenylallyl, *N*-propargyl, *N*-methoxymethyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypentyl, *N*-cyanomethyl, *N*-2-azanorbornenes, *N*-2,4-dinitrophenyl, *o*-methoxyphenyl, *p*-methoxyphenyl, *N*-benzyl, *N*-4-methoxybenzyl, *N*-2,4-dimethoxybenzyl, *N*-2-hydroxybenzyl, *N*-9-phenylfluorenyl, *N*-fluorenyl, *N*-ferrocenylmethyl, *N*-2-picolyamine *N*-Oxide, *N*-7-methoxycoumar-4-ylmethyl, *N*-diphenylmethyl, *N*-bis(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methylphenyl)diphenylmethyl, and *N*-(4-methoxyphenyl)diphenylmethyl. In the case of imines the protecting group for the amino group can be selected from *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[2-pyridyl]mesityl)methylene, *N*-(*N*,*N*-dimethylaminomethylene), *N*-(*N*,*N*-dibenzylaminomethylene), *N*-(*N*-*t*-butylaminomethylene), *N*,*N*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene, and *N*-*t*-butylidene. In the case of enamines the protecting group for the amino group can be selected from *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl), *N*-2,7-dichloro-9-fluorenylmethylene, *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl, *N*-(1,3-dimethyl-2,4,6-(1*H*,3*H*,5*H*)-trioxypyrimidine-5-ylidene)methyl, *N*-4,4,4-trifluoro-3-oxo-1-butenyl, and *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl). In the case of *N*-metal derivatives the protecting group for the amino group together with the nitrogen atom of the unprotected amino group form a derivative that can be selected from *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-diethylborinic acid derivative, *N*-9-borabicyclononane derivative, *N*-difluoroborinic acid derivative, and 3,5-bis(trifluoromethyl)phenylboronic acid derivative; and also including *N*-[phenyl(pentacarbonylchromium)]carbenyl, *N*-[phenyl(pentacarbonyltungsten)]carbenyl, *N*-[methyl(pentacarbonylchromium)]carbenyl, *N*-[methyl(pentacarbonyltungsten)]carbenyl, *N*-

copper chelate, *N*-zinc chelate, and a 18-crown-6-derivative. In the case of N-N derivatives the protecting group for the amino group together with the nitrogen atom of the unprotected amino group to which it is attached form a derivative that can be selected from *N*-nitro derivative, *N*-nitroso derivative, *N*-oxide derivative, azide derivative, triazene derivative, and *N*-trimethylsilylmethyl-*N*-benzylhydrazine derivative. In the case of *N*-P derivatives the protecting group for the amino group together with the nitrogen group of the unprotected amino group to which it is attached form a N-P derivative that can be selected from *N*-diphenylphosphinamide, dimethylthiophosphinamide, diphenylthiophosphinamide, dialkyl phosphoramidate, dibenzyl phosphoramidate, diphenyl phosphoramidate, and iminotriphenylphosphorane. In the case of N-Si derivatives the protecting group for the amino group can be selected from *t*-butyldiphenylsilyl and triphenylsilyl. In the case of N-S derivatives the protecting group for the amino group together with the nitrogen atom of the unprotected amino group to which it is attached from a N-S derivative that can be selected from *N*-sulfenyl or *N*-sulfonyl derivatives. The *N*-sulfenyl derivatives can be selected from benzenesulfenamide, 2-nitrobenzenesulfenamide, 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, 1-(2,2,2-trifluoro-1,1-diphenyl)ethylsulfenamide, and *N*-3-nitro-2-pyridinesulfenamide. The *N*-sulfonyl derivatives can be selected from methanesulfonamide, trifluoromethanesulfonamide, *t*-butylsulfonamide, benzylsulfonamide, 2-(trimethylsilyl)ethanesulfonamide, *p*-toluenesulfonamide, benzenesulfonamide, *o*-anisylsulfonamide, 2-nitrobenzenesulfonamide, 4-nitrobenzenesulfonamide, 2,4-dinitrobenzenesulfonamide, 2-naphthalenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide, 2-(4-methylphenyl)-6-methoxy-4-methylsulfonamide, 9-anthracenesulfonamide, pyridine-2-sulfonamide, benzothiazole-2-sulfonamide, phenacylsulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide, 2,4,6-trimethoxybenzenesulfonamide, 2,6-dimethyl-4-methoxybenzenesulfonamide, pentamethylbenzenesulfonamide, 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide, 4-methoxybenzenesulfonamide, 2,4,6-trimethylbenzenesulfonamide, 2,6-dimethoxy-4-methylbenzenesulfonamide, 3-methoxy-4-*t*-butylbenzenesulfonamide, and 2,2,5,7,8-pentamethylchroman-6-sulfonamide.

The mention of these groups should not be interpreted as a limitation of the scope of the invention, since they have been mentioned as a mere illustration of protecting groups for OH and amino, but further groups having said function may be known by the skill person in the art, and they are to be understood to be also encompassed by the present invention.

Suitable coupling agents are well known for the skilled person in the art. Examples of coupling agents are *N,N'*-dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC) and its salts, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC methiodide), *N,N'*-diisopropylcarbodiimide, 1-*t*-butyl-3-ethyl carbodiimide, *N*-cyclohexyl-*N'*-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMC), *N,N'*-di-*t*-

butylcarbodiimide, 1,3-Di-p-tolylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), 1,1'-carbonyl-di-(1,2,4-triazole) (CDT), oxalic acid diimidazolide, 2-chloro-1,3-dimethylimidazolidinium chloride (DMC), 2-chloro-1,3-dimethylimidazolidinium tetrafluoroborate (CIB), 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP), 2-fluoro-1,3-dimethylimidazolidinium

5 hexafluorophosphate (DFIH), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP), bromotris(dimethylamino)-phosphonium hexafluorophosphate (BROP), chlorotripyrrolidinophosphonium hexafluorophosphate (PyCIOP),

10 bromotripyrrolidinophosphonium hexafluorophosphate, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(benzotriazol-1-yl)-N,N,N',N'-bis(tetramethylene)uronium

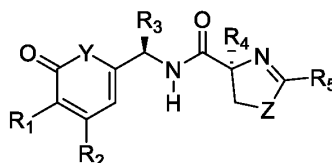
15 hexafluorophosphate (HBPYU), O-benzotriazol-1-yl-N,N,N',N'-bis(pentamethylene)uronium hexafluorophosphate (HBPipU), (benzotriazol-1-yloxy)dipiperidinocarbenium tetrafluoroborate (TBPipU), O-(6-chlorobenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HCTU), O-(6-chloro-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium (TCTU), O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TDBTU), O-(2-oxo-

20 1(2H)pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU), O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium hexafluorophosphate (HOTU), O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), N,N,N',N'-tetramethyl-O-(N-succinimidyl)uronium hexafluorophosphate (HSTU), N,N,N',N'-tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate (TSTU), dipyrrolidino(N-succinimidyloxy)carbenium (HSPYU), and S-(1-oxido-2-pyridyl)-N,N,N',N'-tetramethylthiuronium tetrafluoroborate (TOTT).

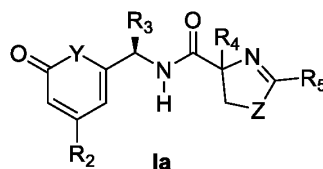
To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and

30 it also meant to refer to the approximation of such given value that would reasonable be inferred based on the ordinary skill in the art, including equivalents and approximations due to experimental and/or measurement conditions for such given value.

Particularly preferred stereochemistry of said compounds of formula I is the following

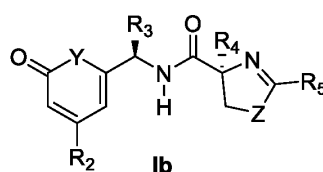


In another embodiment, particularly preferred compounds of formula **I** are those also having formula **la** or a pharmaceutically acceptable salt or ester thereof

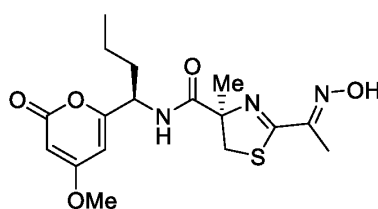


wherein R₂, R₃, R₄, R₅, Y, and Z have the same meanings given above.

- 5 Particularly preferred stereochemistry of said compounds of formula **Ia** is the following



In another embodiment, the compound of formula **I**, **Ia**, or **Ib** is not a natural product, more preferably the compound of formula **I**, **Ia**, or **Ib** is not compound **1** of formula



- 10 In compounds of formula **I**, particularly preferred R₁ is selected from hydrogen, halogen and substituted or unsubstituted C₂-C₆ alkynyl, being more preferred R₁ hydrogen and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group.

- 15 In compounds of formula **I**, **Ia** and **Ib**, particularly preferred R₂ is hydrogen, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, -OR_a, and -NR_cR_d, wherein the optional substituents are one or more substituents R_x; wherein R_a, R_c and R_d are defined herein. Further particularly preferred R₂ is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, wherein the optional substituents are one or more substituents R_x; -OR_a, and -NR_cR_d; where R_a is selected from hydrogen, a silylether protecting group for OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₆alkyl, -(CH₂CH₂O)_pCH₂CH₃ where p is from 1 to about 15, and the optional substituents are one or more substituents R_x; and R_c and R_d are independently selected from substituted or unsubstituted C₁-C₆ alkyl wherein the optional substituents are one or more
- 20

substituents R_x . Particularly preferred R_a is hydrogen, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 10 and the optional substituents are one or more substituents R_x , and a silylether protecting group for OH selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorosilyl. Particularly preferred R_c and R_d are independently selected from substituted or unsubstituted C_1 - C_4 alkyl wherein the optional substituents are one or more substituents R_x . More preferred R_2 is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted vinyl, substituted or unsubstituted allyl, wherein the optional substituents are one or more substituents R_x , $-OR_a$, and $-NR_cR_d$ where R_a is selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted *n*-heptyl, substituted or unsubstituted allyl, substituted or unsubstituted 1-methyl-2-propenyl, substituted or unsubstituted 2-methyl-2-propenyl, substituted or unsubstituted 2-butenyl, substituted or unsubstituted 3-butenyl, substituted or unsubstituted propargyl, substituted or unsubstituted 1-methyl-2-propynyl, substituted or unsubstituted 2-butylnyl, substituted or unsubstituted 3-butylnyl, substituted or unsubstituted cyclopropylmethyl, substituted or unsubstituted 2-cyclopropylethyl, and $-(CH_2CH_2O)_pCH_2CH_3$ wherein p is from 1 to about 5 and the optional substituents are one or more substituents R_x ; and R_c and R_d are selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Most preferred R_2 is hydrogen, methyl, vinyl, allyl, NEt_2 , and OR_a where R_a is selected from hydrogen, methyl, ethyl, *n*-butyl, *n*-heptyl, allyl, propargyl, cyclopropylmethyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, and $-(CH_2CH_2O)_3CH_2CH_3$.

In another embodiment, in compounds of formula **I**, **1a** and **1b**, particularly preferred R_2 is hydrogen, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, $-OR_a$, and $-NR_cR_d$, wherein the optional substituents are one or more substituents R_x ; wherein

R_a , R_c and R_d are defined herein, other than when R_2 is $-OR_a$, R_a is not unsubstituted methyl. Further particularly preferred R_2 is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, wherein the optional substituents are one or more substituents R_x , $-OR_a$, and $-NR_cR_d$; where R_a is selected from hydrogen, a silylether protecting group for OH, substituted C_1 - C_{12} alkyl, unsubstituted C_2 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_6 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x ; and R_c and R_d are independently selected from substituted or unsubstituted C_1 - C_6 alkyl wherein the optional substituents are one or more substituents R_x . Particularly preferred R_a is hydrogen, substituted or unsubstituted C_2 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ wherein p is from 1 to about 10 and the optional substituents are one or more substituents R_x , and a silylether protecting group for OH selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorous silyl. Particularly preferred R_c and R_d are independently selected from substituted or unsubstituted C_1 - C_4 alkyl wherein the optional substituents are one or more substituents R_x . More preferred R_2 is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted vinyl, substituted or unsubstituted allyl, wherein the optional substituents are one or more substituents R_x , $-OR_a$, and $-NR_cR_d$ where R_a is selected from hydrogen, substituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted *n*-heptyl, substituted or unsubstituted allyl, substituted or unsubstituted 1-methyl-2-propenyl, substituted or unsubstituted 2-methyl-2-propenyl, substituted or unsubstituted 2-butenyl, substituted or unsubstituted 3-butenyl, substituted or unsubstituted propargyl, substituted or unsubstituted 1-methyl-2-propynyl, substituted or unsubstituted 2-butylnyl, substituted or unsubstituted 3-butylnyl, substituted or unsubstituted cyclopropylmethyl, substituted or unsubstituted 2-cyclopropylethyl, and $-(CH_2CH_2O)_pCH_2CH_3$ wherein p is from 1 to about 5 and the optional substituents are one or more substituents R_x ; and R_c and R_d are selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl,

substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Most preferred R_2 is hydrogen, methyl, vinyl, allyl, NEt_2 , and OR_a where R_a is selected from hydrogen, ethyl, *n*-butyl, *n*-heptyl, allyl, propargyl, cyclopropylmethyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, and $-(CH_2CH_2O)_3CH_2CH_3$.

- 5 In compounds of formula **I**, **1a** and **1b**, particularly preferred R_3 is selected from halogen-substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I. More preferred R_3 is halogen-substituted or unsubstituted methyl, halogen-substituted or unsubstituted ethyl, halogen-substituted or unsubstituted *n*-propyl, halogen-substituted or unsubstituted isopropyl, halogen-substituted or unsubstituted *n*-butyl, halogen-substituted or unsubstituted *t*-butyl, halogen-substituted or unsubstituted isobutyl and halogen-substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I. Most preferred R_3 is *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl.

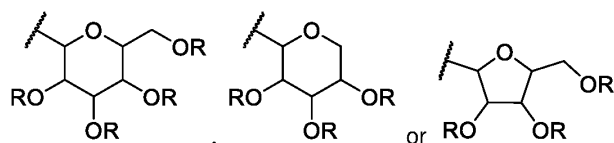
- In compounds of formula **I**, **1a** and **1b**, particularly preferred R_4 is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl wherein the optional substituents are one or more substituents R_x . More preferred R_4 is hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Most preferred R_4 is hydrogen and methyl.

- In compounds of formula **I**, **1a** and **1b**, particularly preferred R_5 is selected from $-C(OR_e)_2R_g$, $-CH(NR_cR_d)R_g$, $-(C=O)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-O-(C=O)R_f)R_g$, $-(C=N-O-(C=O)OR_a)R_g$, $-(C=N-O-[(P=O)(OR_a)_2])R_g$, $-(C=N-NR_cR_d)R_g$, $-(C=CH_2)R_g$, and $-(C=CH_2)OR_a$; or R_5 is selected from $-CH(OR_a)R_g$, $-CH(NR_cR_d)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-NR_cR_d)R_g$; or R_5 is selected from $-CH(OR_a)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$;

wherein:

- R_h is selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted heterocyclo- C_1 - C_6 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 15 and a substituted or unsubstituted monosaccharide residue of formula:

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where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C₁-C₆ alkyl group, substituted or unsubstituted -(C=O)-(C₁-C₆)alkyl, and substituted or unsubstituted -(C=O)NH(C₁-C₆)alkyl, wherein the optional substituents are one or more substituents R_x; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

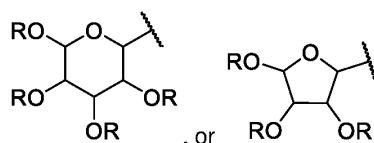
R_g is substituted or unsubstituted C₁-C₆ alkyl, wherein the optional substituents are one or more substituents R_x;

R_c and R_d are independently selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl, wherein the optional substituents are one or more substituents R_x;

R_a is substituted or unsubstituted C₁-C₆ alkyl, wherein the optional substituents are one or more substituents R_x;

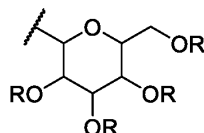
R_e is substituted or unsubstituted C₁-C₆ alkyl, wherein the optional substituents are one or more substituents R_x; and

R_f is selected from substituted or unsubstituted C₁-C₆ alkyl, -CH₂O(CH₂CH₂O)_pCH₃ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x, and a group of formula:



where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C₁-C₆ alkyl group, substituted or unsubstituted -(C=O)-(C₁-C₆)alkyl, and substituted or unsubstituted -(C=O)NH(C₁-C₆)alkyl, wherein the optional substituents are one or more substituents R_x; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals.

More preferred R_h is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted heterocyclo- C_1 - C_6 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 10, and a substituted or unsubstituted monosaccharide residue of formula



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wherein each R group is, at each occurrence, independently selected from hydrogen and substituted or unsubstituted $-(C=O)-(C_1-C_6)alkyl$; wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

10

More preferred R_g is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x .

15

More preferred R_a is selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x .

20

More preferred R_c and R_d are independently selected from hydrogen and substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x .

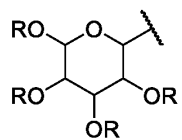
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More preferred R_e is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x .

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More preferred R_f is substituted or unsubstituted methyl, substituted or unsubstituted

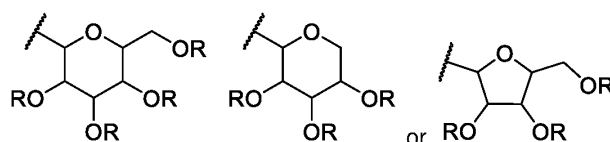
ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ where *p* is from 1 to about 10 and the optional substituents are one or more substituents R_x , and a group of formula:



where each R group is, at each occurrence, independently selected from hydrogen, and substituted or unsubstituted C_1 - C_6 alkyl group; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals.

More preferred R_5 is selected from $-\text{CH}(\text{NR}_c\text{R}_d)\text{R}_g$, $-(\text{C}=\text{O})\text{R}_g$, $-(\text{C}=\text{NR}_c)\text{R}_g$, $-(\text{C}=\text{N}-\text{OR}_h)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{R}_f)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{OR}_a)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-[(\text{P}=\text{O})(\text{OR}_a)_2])\text{R}_g$, $-(\text{C}=\text{N}-\text{NR}_c\text{R}_d)\text{R}_g$, $-(\text{C}=\text{CH}_2)\text{R}_g$, and $-(\text{C}=\text{CH}_2)\text{OR}_a$ wherein:

R_h is selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted heterocyclo- C_1 - C_6 alkyl, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$ where *p* is from 1 to about 15, and a substituted or unsubstituted monosaccharide residue of formula:



where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(\text{C}=\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$, and substituted or unsubstituted $-(\text{C}=\text{O})\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}$; wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene-acetals;

R_g is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ;

R_a is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are

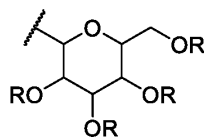
one or more substituents R_x ;

R_c and R_d are independently selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ; and

5 R_f is selected from substituted or unsubstituted C_1 - C_6 alkyl and $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x .

Even more preferred R_5 is $-\text{CH}(\text{NR}_c\text{R}_d)\text{R}_g$, $-(\text{C}=\text{O})\text{R}_g$, $-(\text{C}=\text{NR}_c)\text{R}_g$, $-(\text{C}=\text{N}-\text{OR}_h)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{R}_f)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{OR}_a)\text{R}_g$, $-(\text{C}=\text{N}-\text{O}-[(\text{P}=\text{O})(\text{OR}_a)_2])\text{R}_g$, $-(\text{C}=\text{N}-\text{NR}_c\text{R}_d)\text{R}_g$, $-(\text{C}=\text{CH}_2)\text{R}_g$, and $-(\text{C}=\text{CH}_2)\text{OR}_a$ wherein:

10 R_h is selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n -propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted n -butyl, substituted or unsubstituted t -butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted sec -butyl, substituted or unsubstituted allyl, substituted or unsubstituted propargyl, substituted or
15 unsubstituted morpholino- n -butyl, substituted or unsubstituted piperazinyl- n -propyl, $-(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_2\text{CH}_3$ where p is from 1 to about 5, and a substituted or unsubstituted monosaccharide residue of formula:



20 wherein each R group is, at each occurrence, independently selected from hydrogen and substituted or unsubstituted $-(\text{C}=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$; wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups may form an isopropylidene ketal;

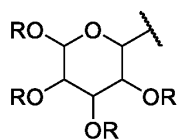
25 each R_g group is independently selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n -propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted n -butyl, substituted or unsubstituted t -butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted sec -butyl, wherein the optional substituents are one or more substituents R_x ;

30 R_a is selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n -propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted n -butyl, substituted or unsubstituted t -butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted sec -butyl, wherein the optional

substituents are one or more substituents R_x ;

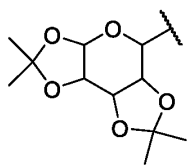
R_c and R_d are independently selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x ; and

R_f is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ where p is from 1 to about 5 and the optional substituents are one or more substituents R_x and a group of formula:

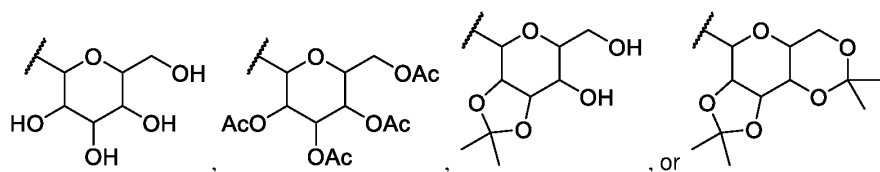


where each R group is, at each occurrence, hydrogen or two adjacent OR groups form an isopropylidene ketal.

Most preferred R_5 is $-\text{CH}(\text{NH}_2)\text{Me}$, $-(\text{C}=\text{O})\text{Me}$, $-(\text{C}=\text{NR}_c)\text{Me}$, $-(\text{C}=\text{N}-\text{OR}_h)\text{Me}$, $-(\text{C}=\text{N}-\text{O}(\text{C}=\text{O})\text{R}_f)\text{Me}$, $-(\text{C}=\text{N}-\text{NH}_2)\text{Me}$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{OR}_a)\text{Me}$, $-(\text{C}=\text{N}-\text{O}-[(\text{P}=\text{O})(\text{OR}_a)_2])\text{Me}$, $-(\text{C}=\text{CH}_2)\text{Me}$, or $-(\text{C}=\text{CH}_2)\text{OR}_a$ where R_a is ethyl or benzyl, R_c is $-(\text{CH}_2)_3\text{NHBoc}$, R_f is $-(\text{CH}_2)_5\text{NHBoc}$, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{Me}$ or a group of formula:



and R_h is selected from hydrogen, methyl, allyl, propargyl, $-(\text{CH}_2)_3\text{NHBoc}$, $-(\text{CH}_2)_3\text{NH}_2$, $-(\text{CH}_2)_3\text{SH}$, $-(\text{CH}_2)_4\text{OH}$, $-(\text{CH}_2)_4\text{OP}(=\text{O})(\text{OH})_2$, $-(\text{CH}_2)_4\text{OP}(=\text{O})(\text{O}^t\text{Bu})_2$, $-(\text{CH}_2)_4-4\lambda^2\text{-morpholine}$, $-(\text{CH}_2)_3-1\text{-methyl-4}\lambda^2\text{-piperazine}$, $-(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_3$, and a monosaccharide residue of formula:

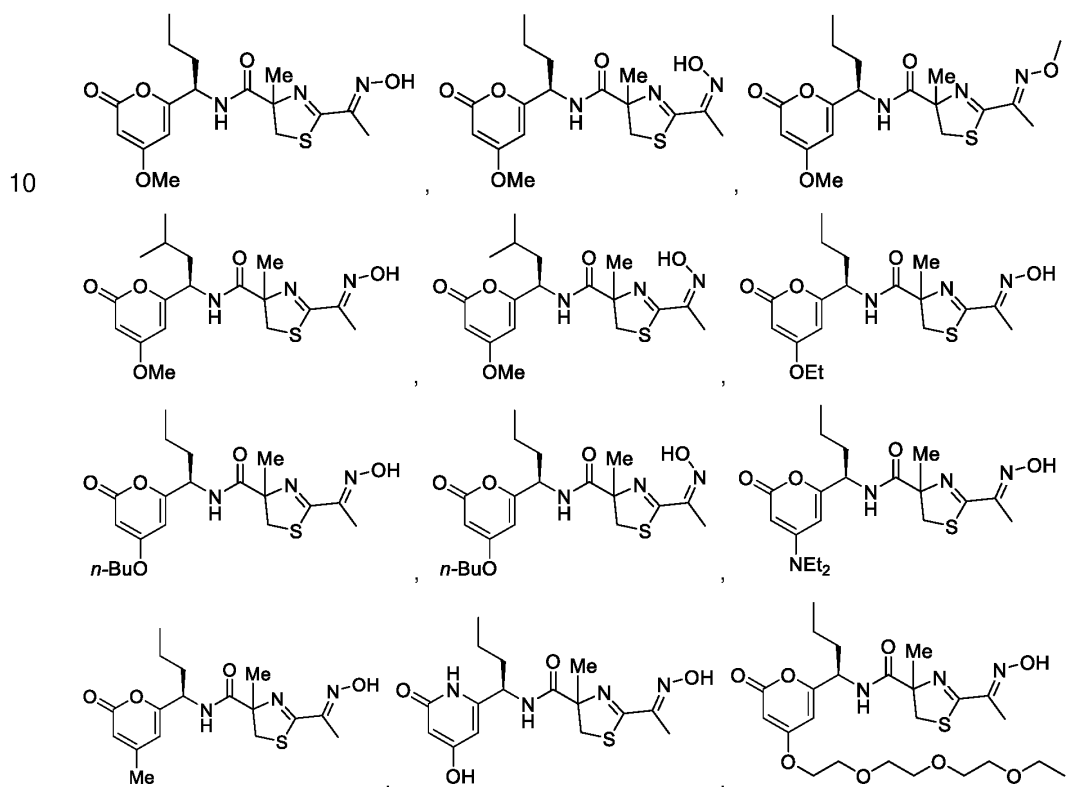


In compounds of formula **I**, **la**, and **lb** particularly preferred Y is -O- or -NH-. Most preferred Y is -O-.

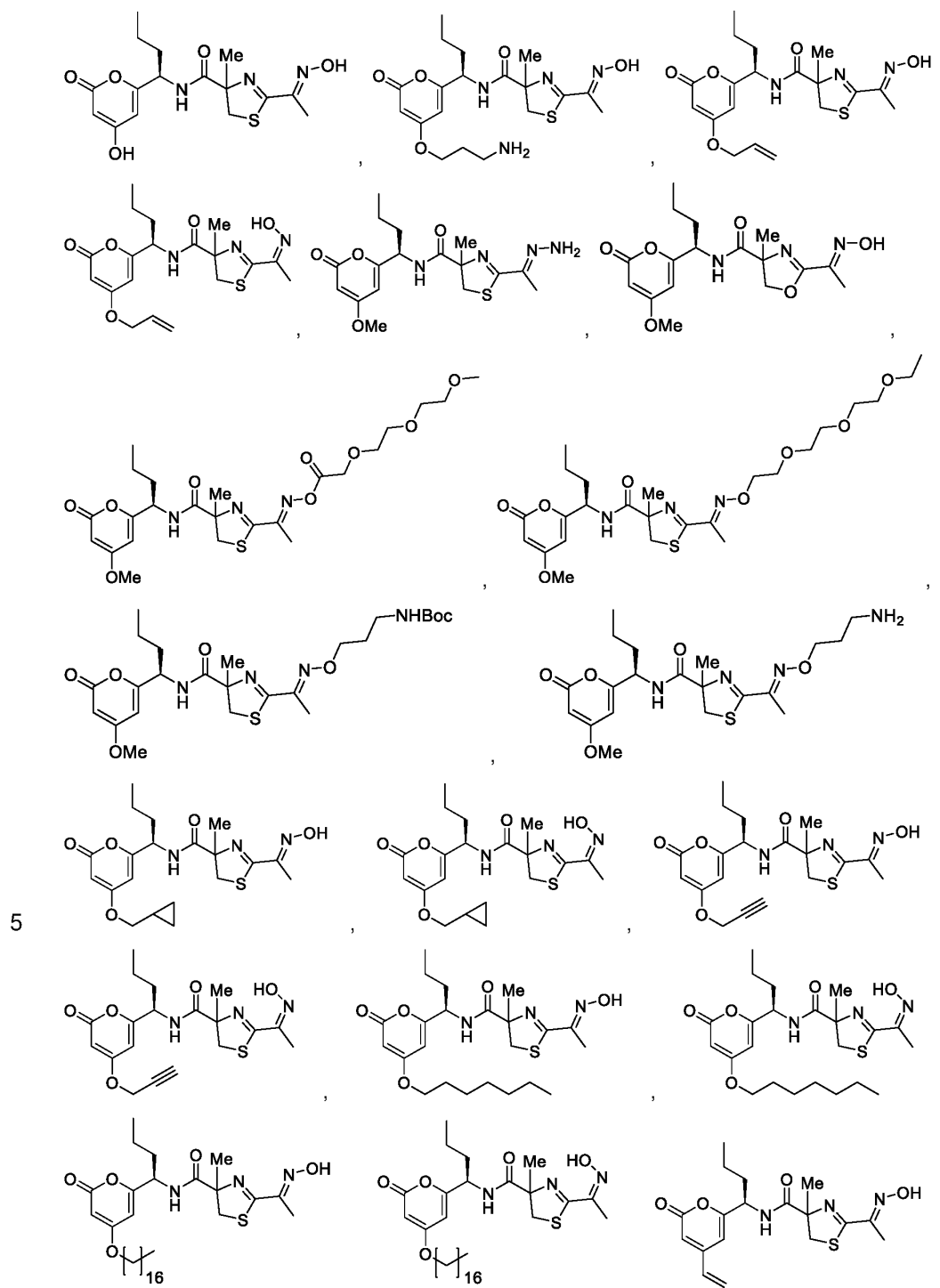
In compounds of formula **I**, **la**, and **lb** particularly preferred Z is -S- or -O-. Most preferred Z is -S-.

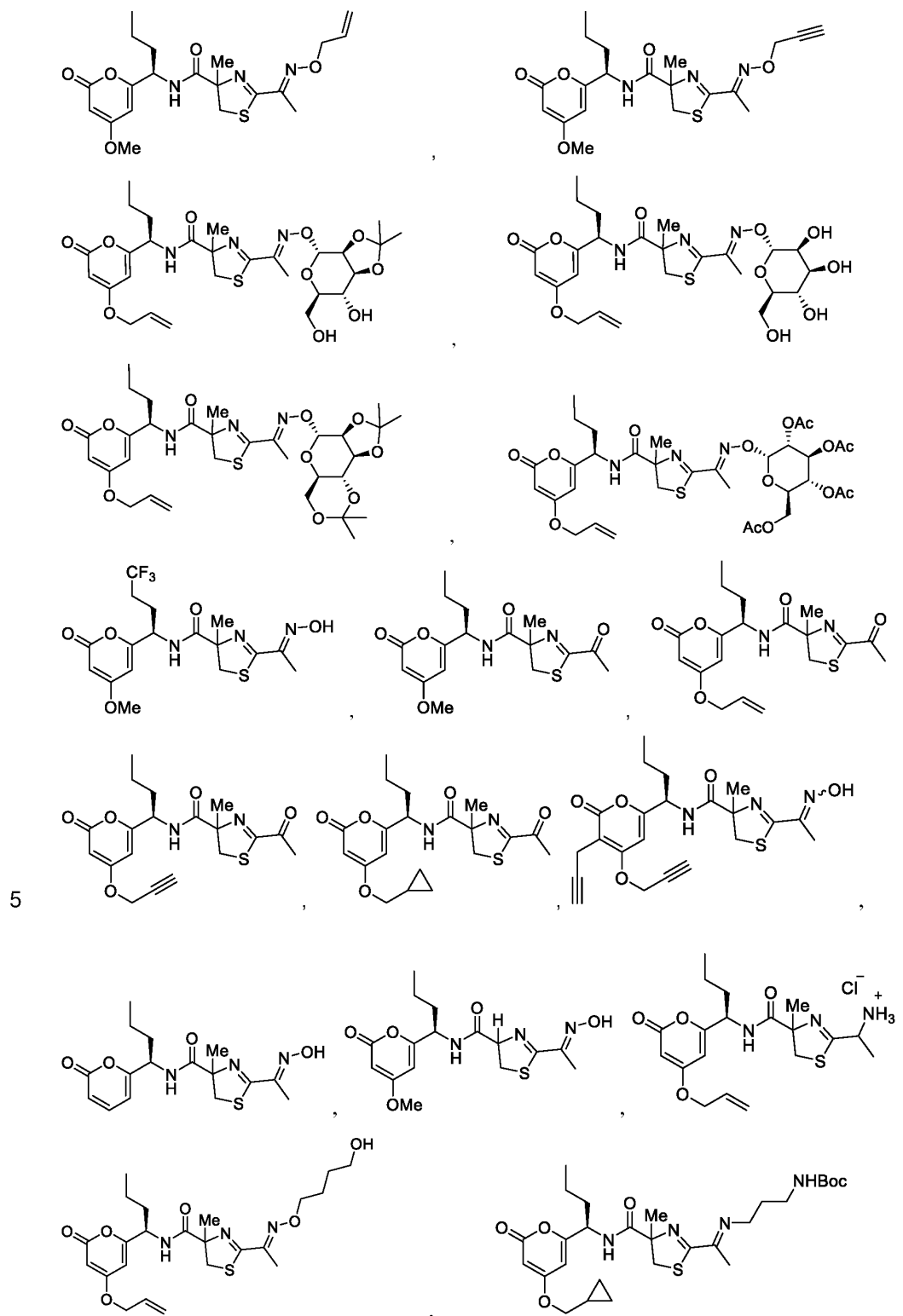
In additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations of preferred substitutions in the formula **I**, **la** or **lb** above.

Particularly preferred compounds of formula **I**, **la** or **lb** are compounds:

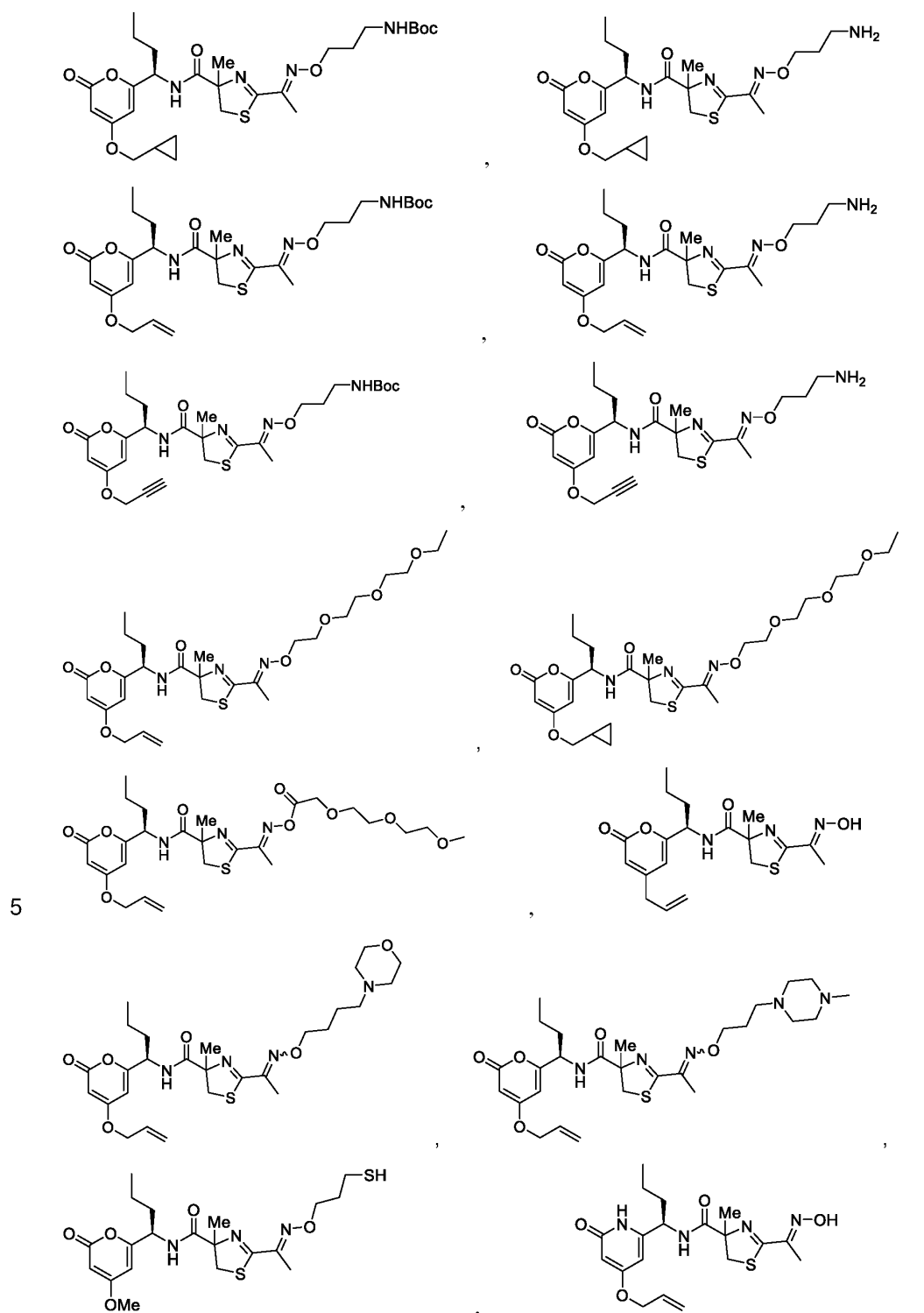


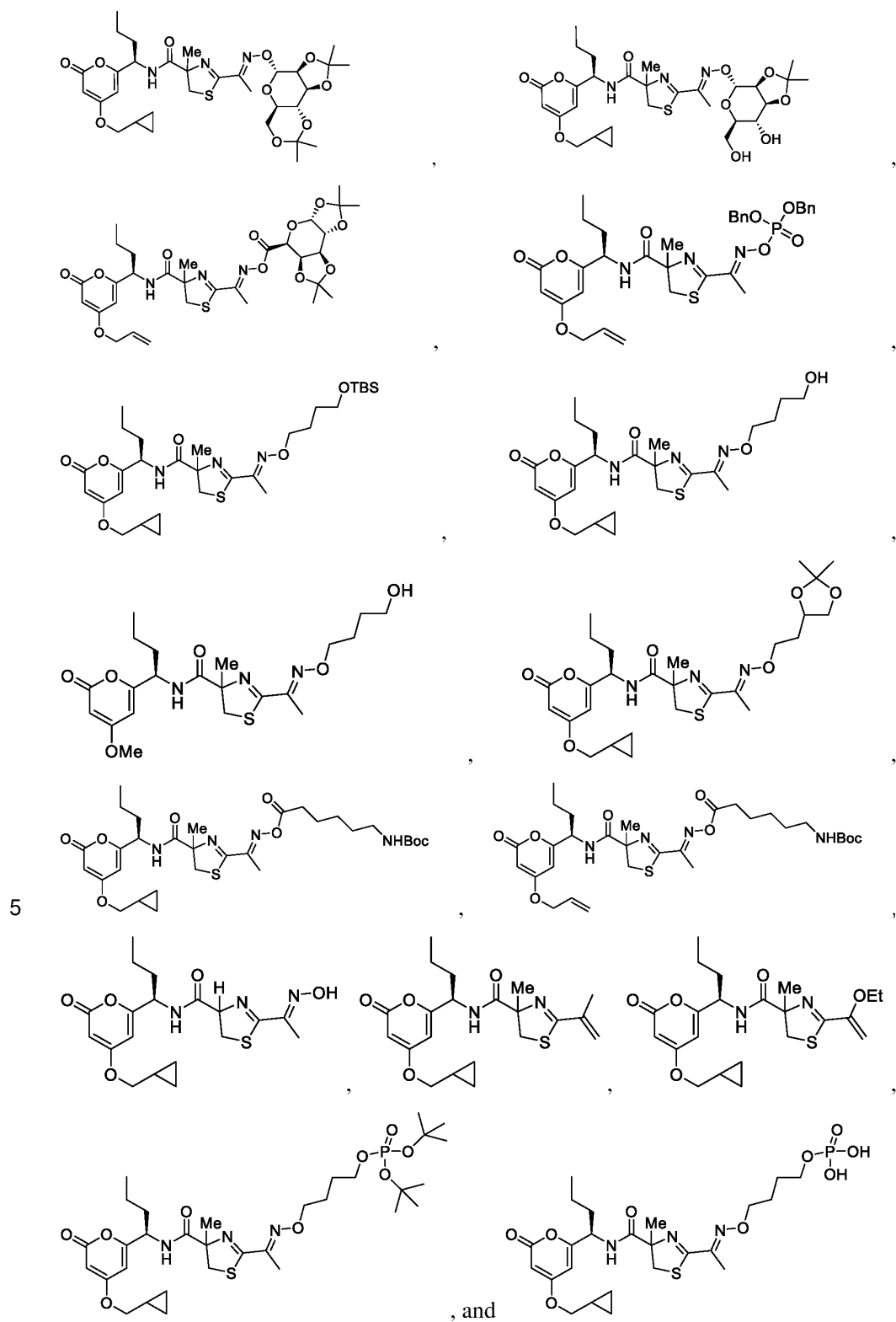
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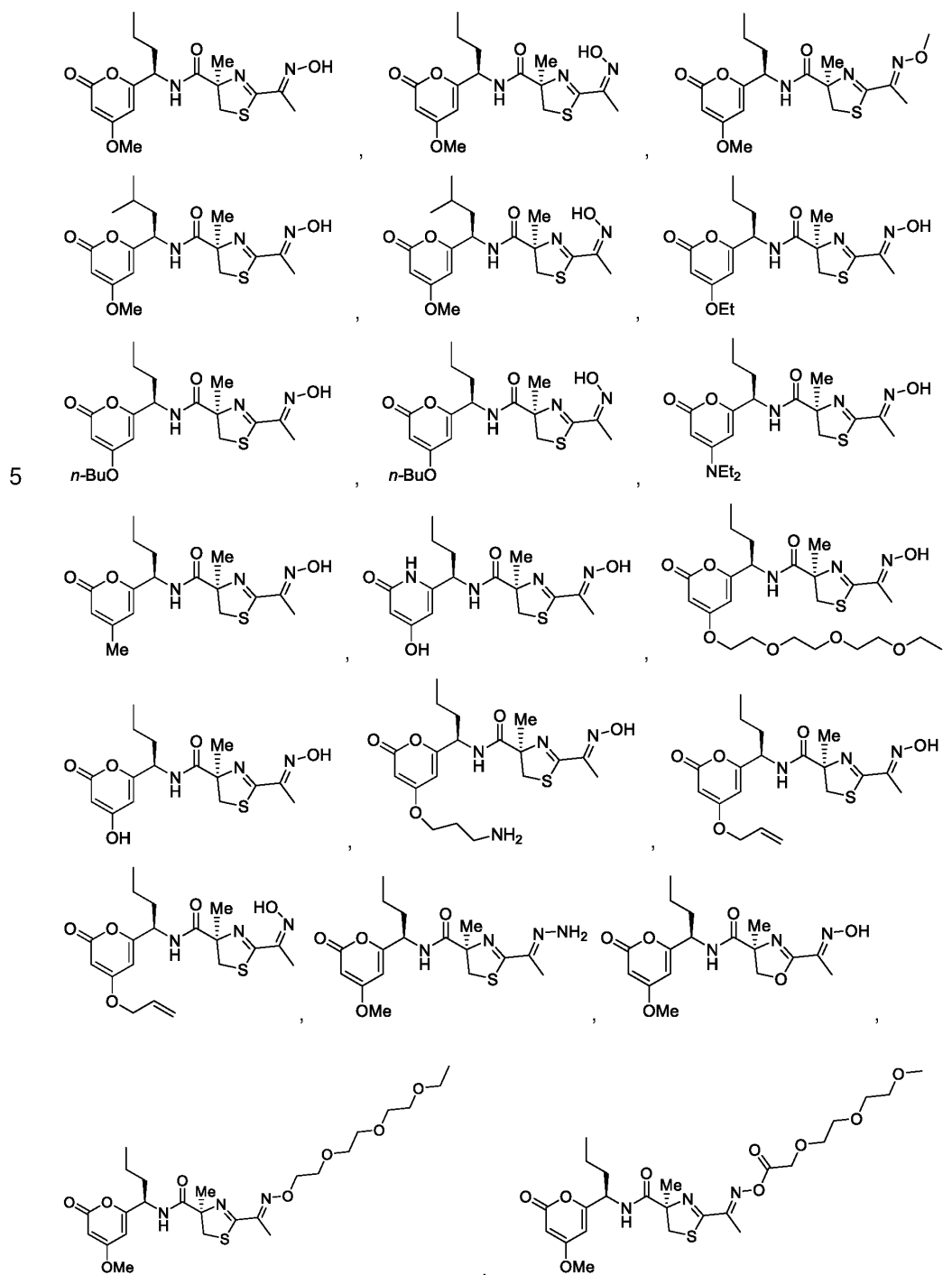
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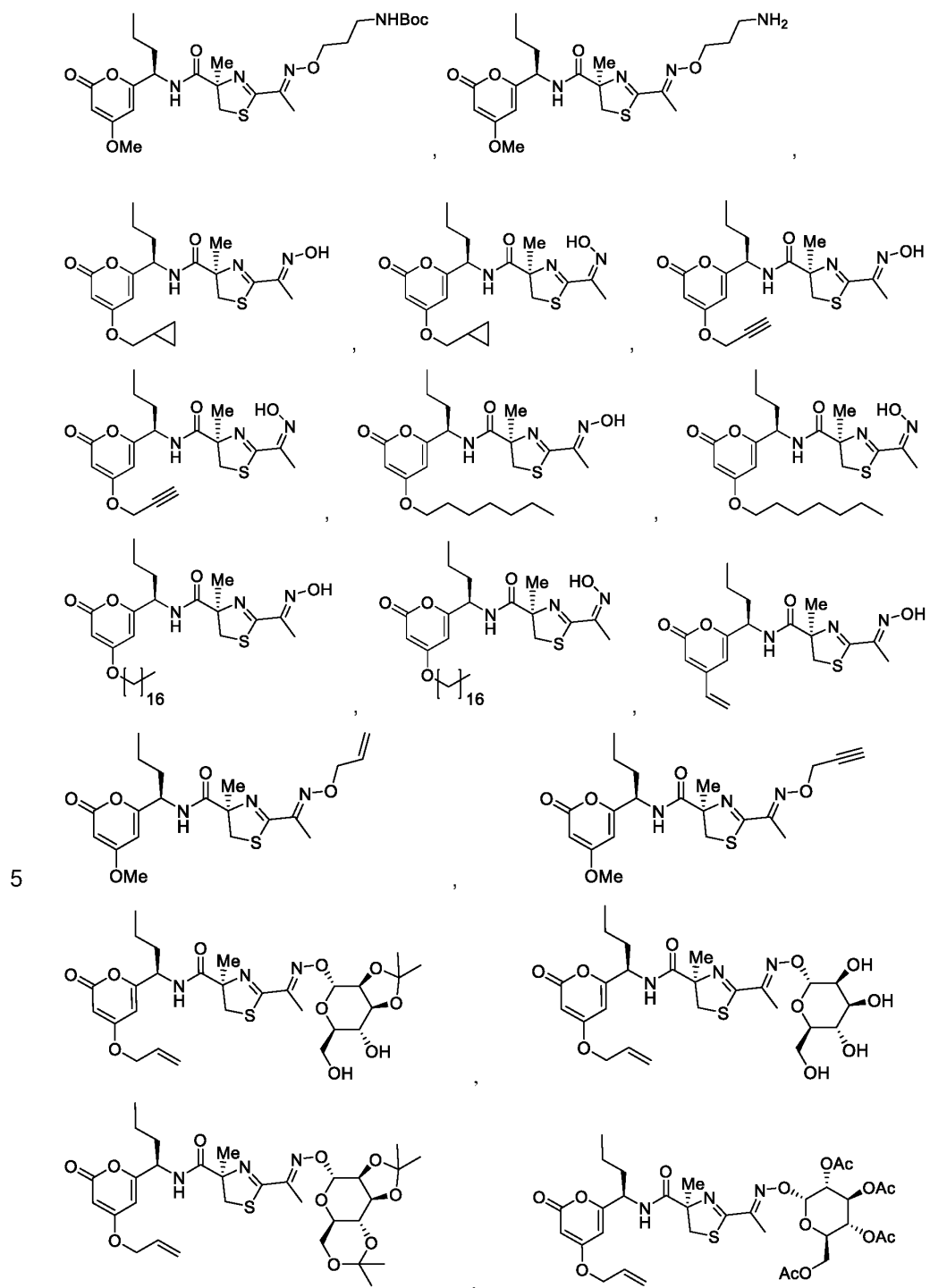


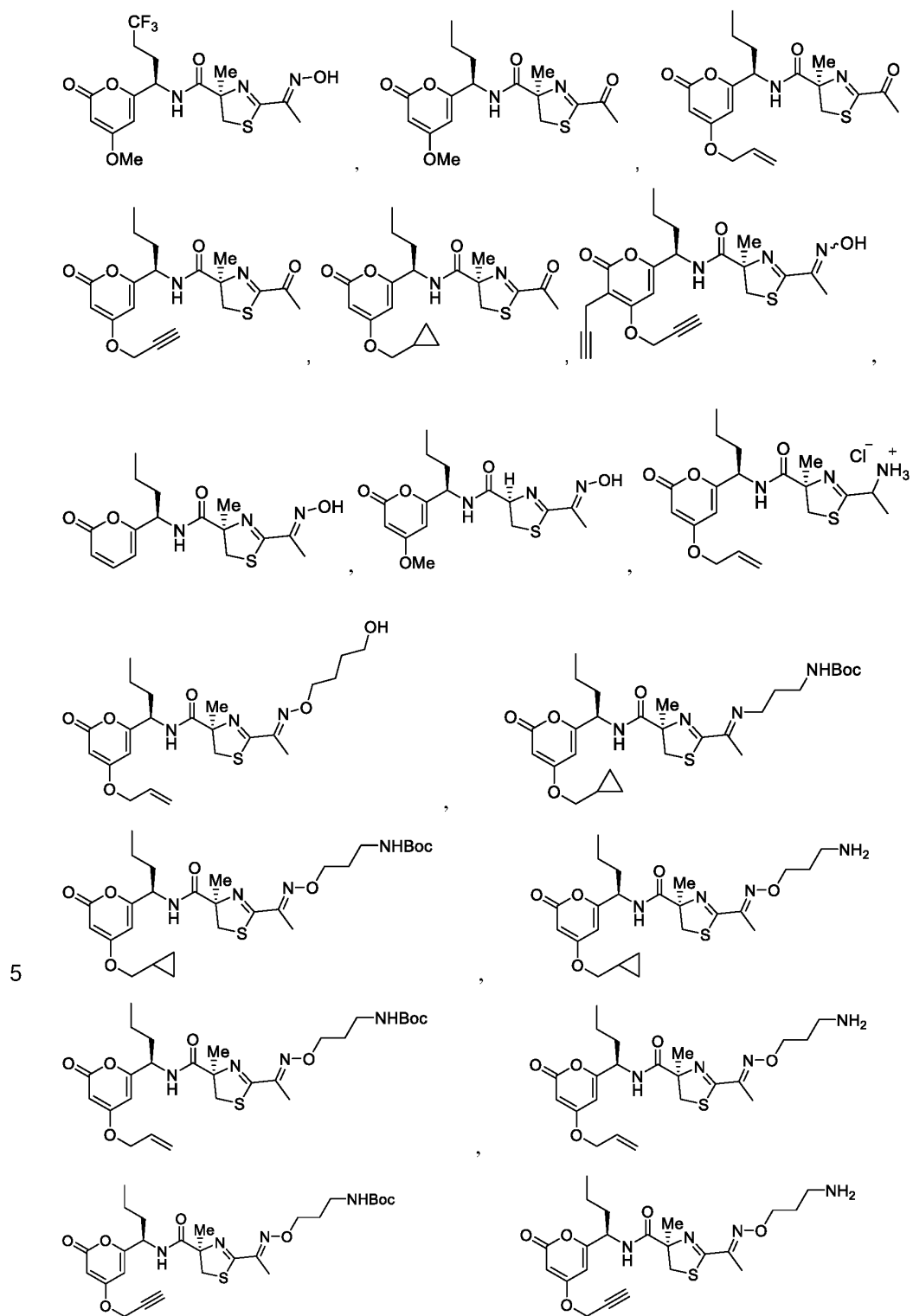
or pharmaceutically acceptable salts or esters thereof.

More preferred compounds of the invention are compounds

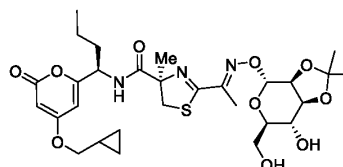
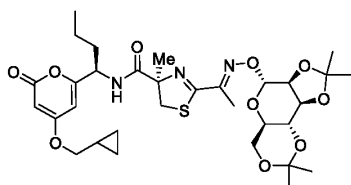
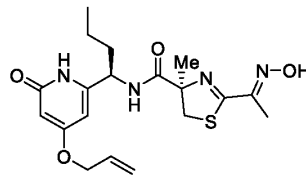
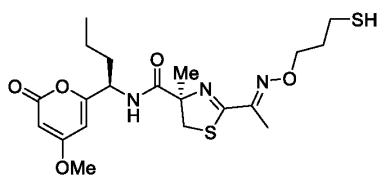
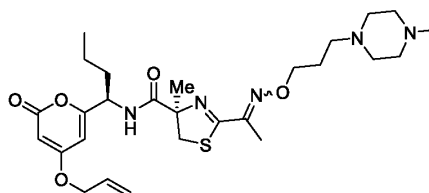
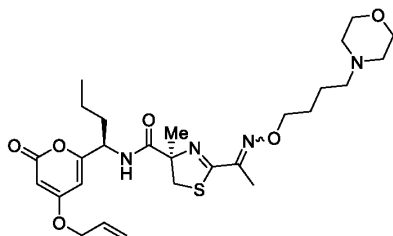
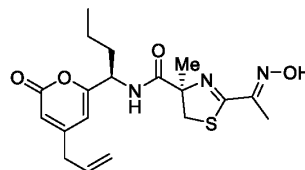
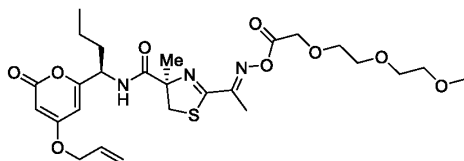
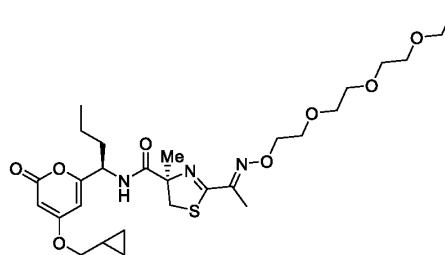
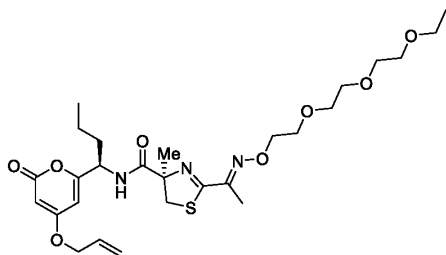


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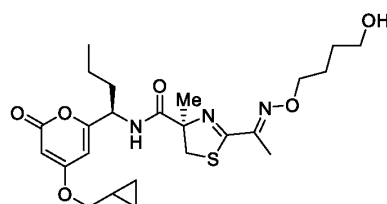
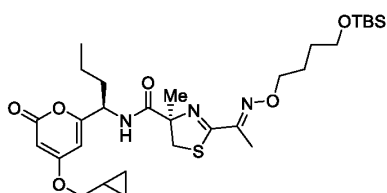
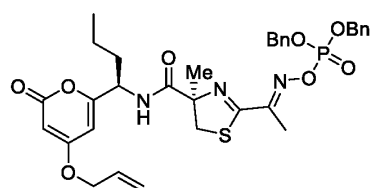
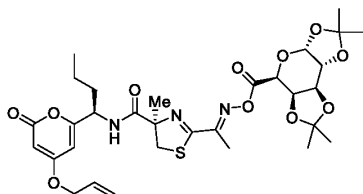


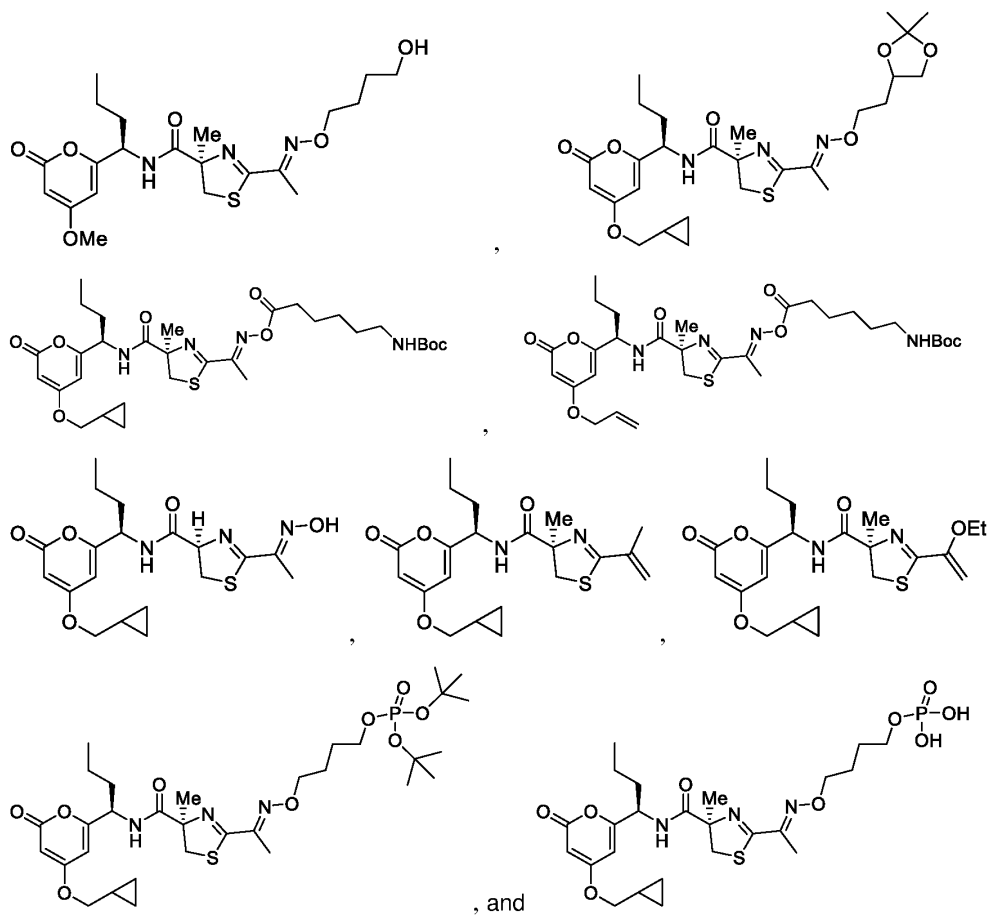


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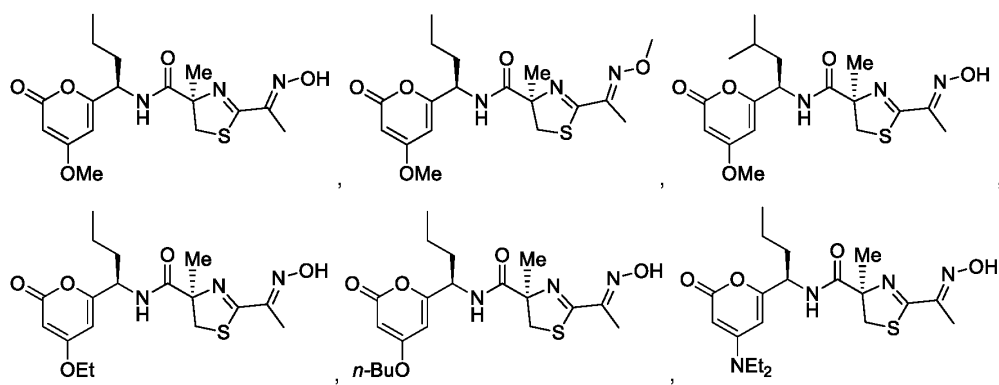
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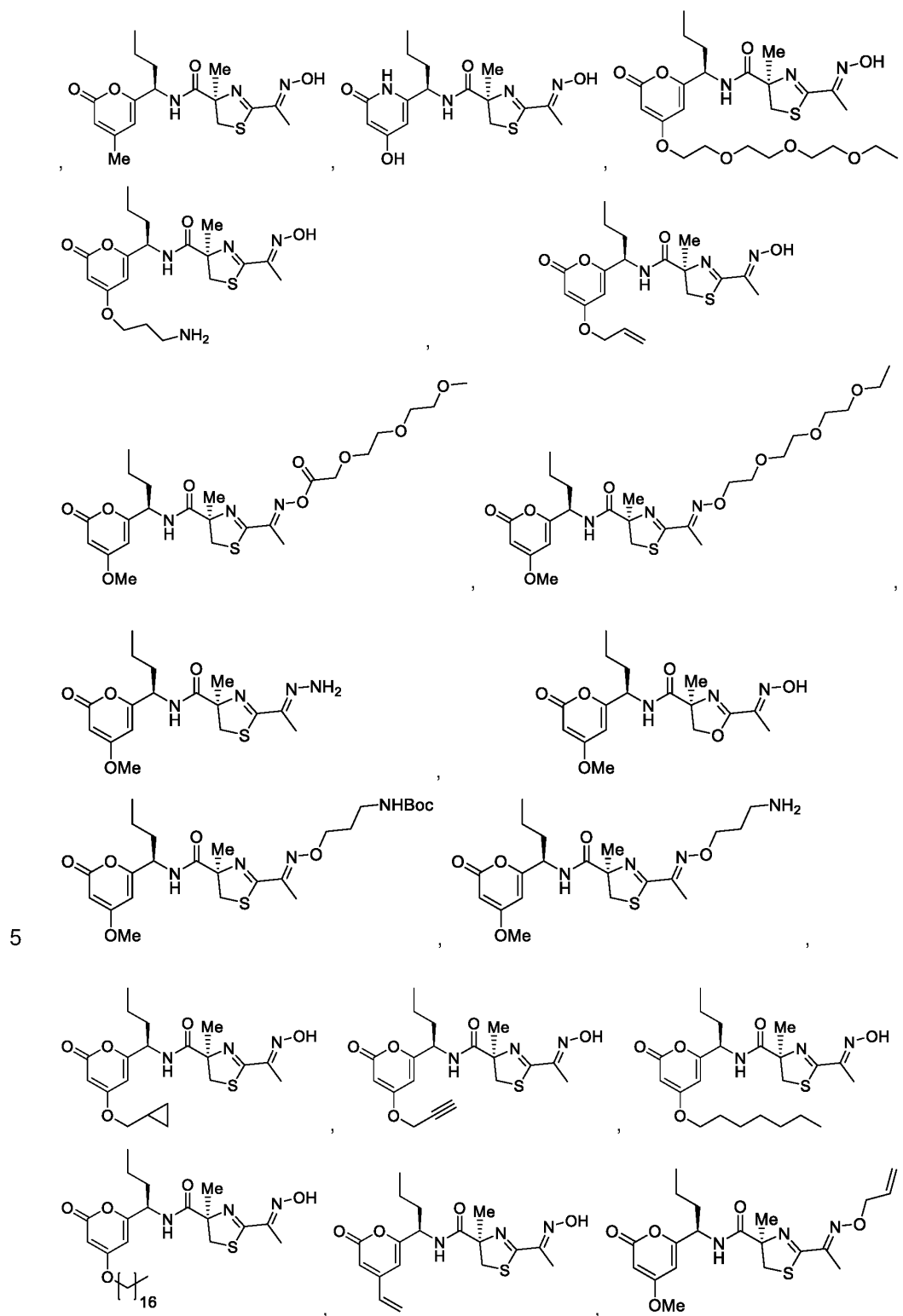


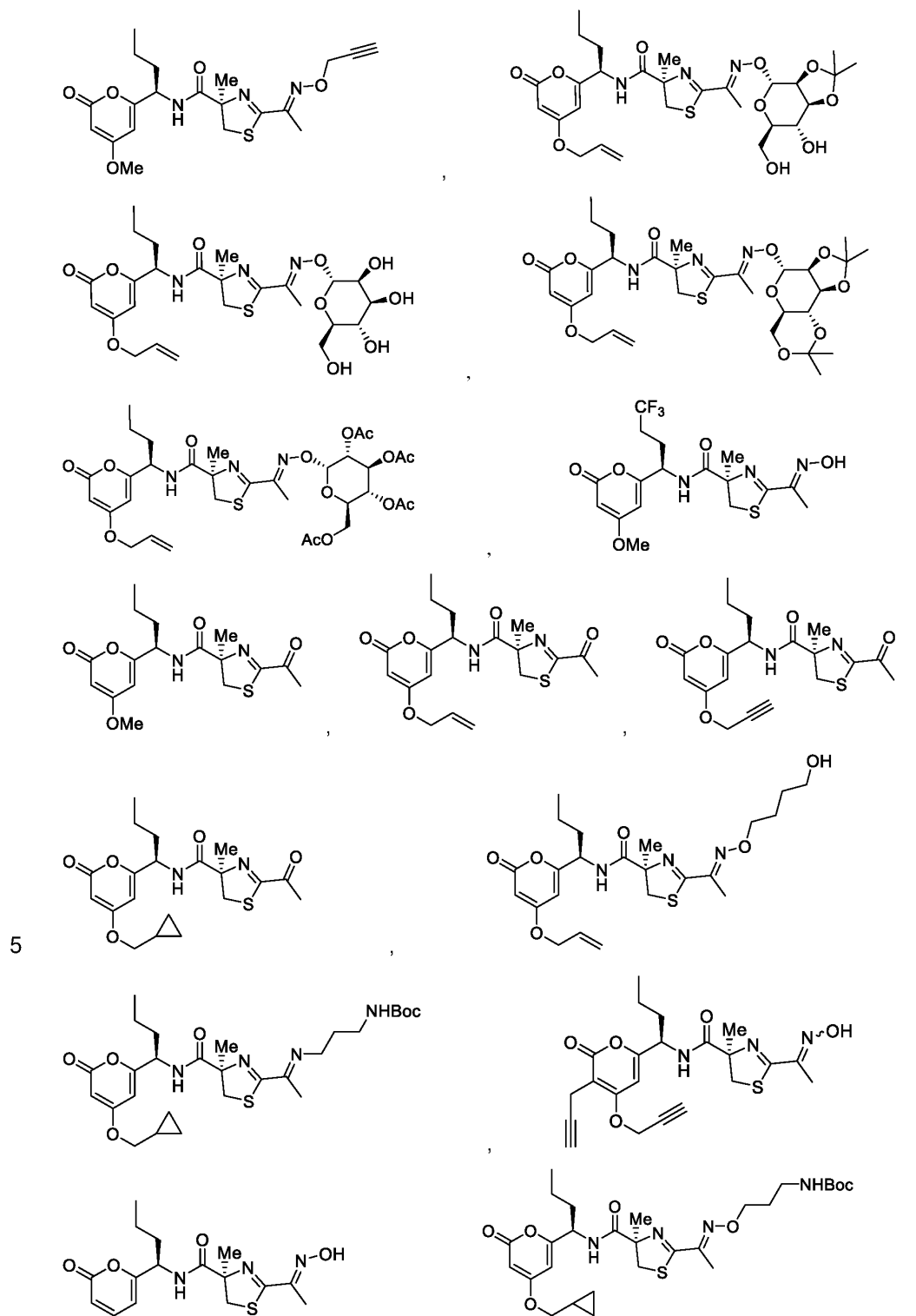


5 or pharmaceutically acceptable salts or esters thereof.

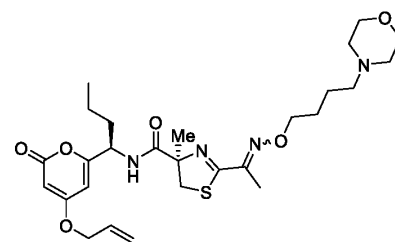
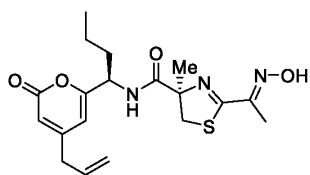
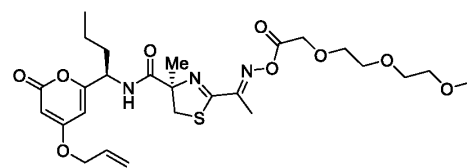
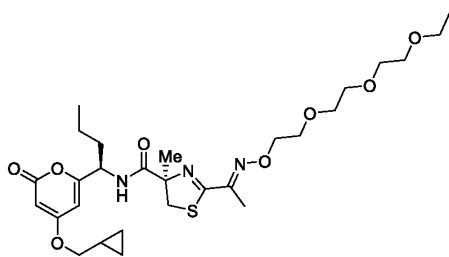
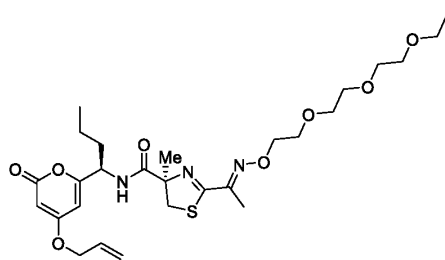
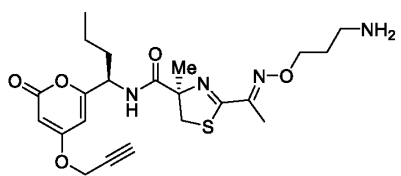
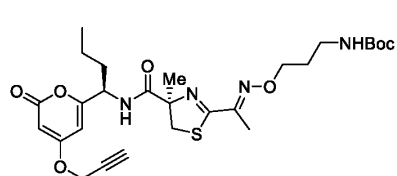
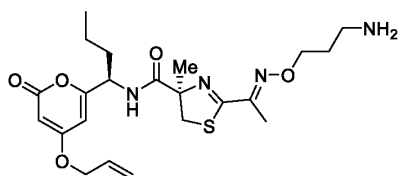
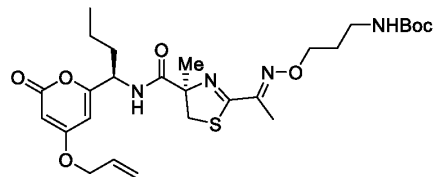
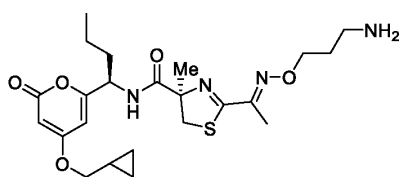
Even more preferred compounds of the invention are selected from



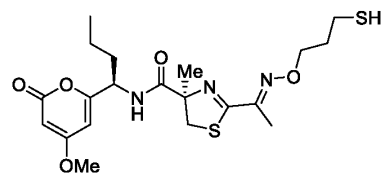
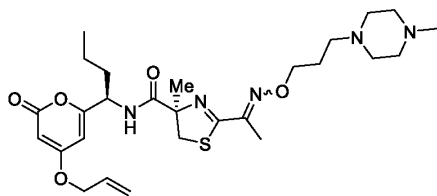


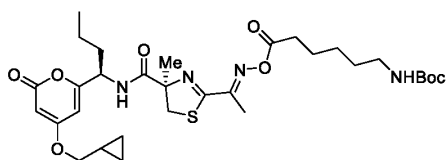
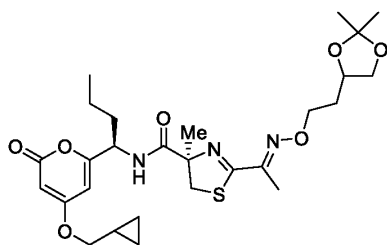
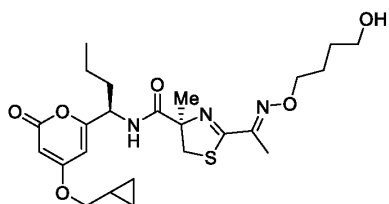
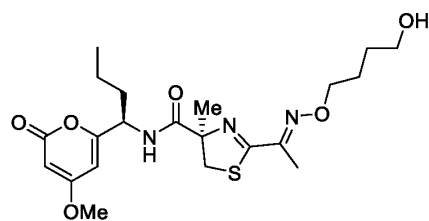
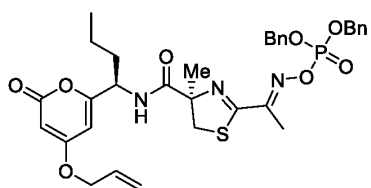
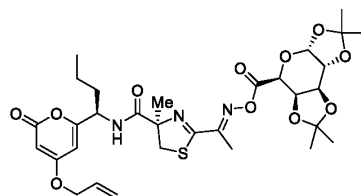
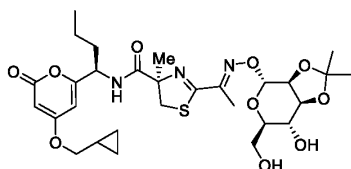
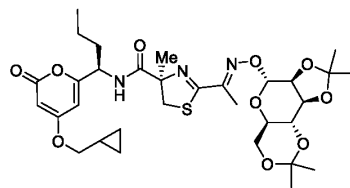
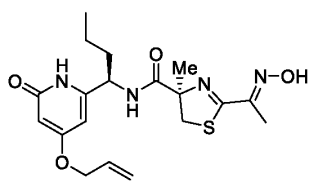


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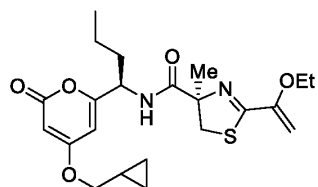
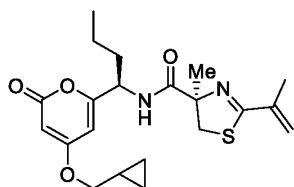
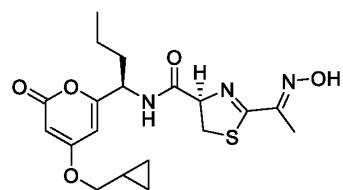
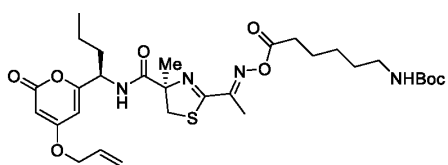


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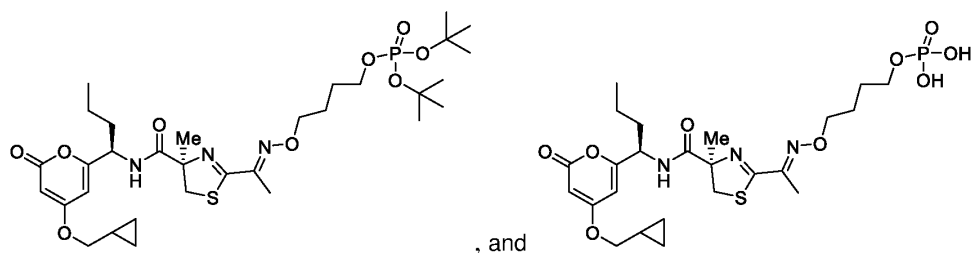




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49



or pharmaceutically acceptable salts or esters thereof.

Particularly preferred compounds include compounds 1, 2, 64, 70, 71, 71a, 72, 72a, 73a, 74, 74a, 75, 75a, 76, 76a, 78, 93, 94, 95, 98, 107, 110, 111, 113, 115, 116, 128, 136, 137, 141, 144, 145, 147, 148, 149, 152, 153, 154, 155, 156, 157, 158, 159, 161, 163, 164, 165, 166, 170, 172, 175, 178, 179, 182, 183, 185, 191, and 192 or pharmaceutically acceptable salts or esters thereof. Further preferred compounds include compounds 71, 74, 74a, 75, 75a, 76, 76a, 113, 115, 149, 153, 154, 156, 158, 161, 163, 170, 179 and 192, or pharmaceutically acceptable salts or esters thereof.

Preferred compounds of formula I further include compounds wherein:

R₁ is selected from hydrogen and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group;

R₃ is selected from halogen-substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₄ cycloalkyl-C₁-C₄ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

and R₂, R₄, R₅, Y and Z are defined herein.

Further preferred compounds of formula I include compounds wherein:

R₁ is selected from hydrogen, and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group;

R₃ is selected from halogen-substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₄ cycloalkyl-C₁-C₄ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

R₄ is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl; being most preferred hydrogen and methyl.

and R₂, R₅, Y and Z are defined herein.

Further preferred compounds of formula I include compounds wherein:

5 R₁ is selected from hydrogen, and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group;

R₃ is selected from halogen-substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₄ cycloalkyl-C₁-C₄ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

10 R₄ is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl; being most preferred hydrogen and methyl;

Y is O;

and R₂, R₅, and Z are defined herein.

Further preferred compounds of formula I include compounds wherein:

15 R₁ is selected from hydrogen, and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group;

20 R₃ is selected from halogen-substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₄ cycloalkyl-C₁-C₄ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

R₄ is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl; being most preferred hydrogen and methyl;

Y is O;

25 Z is S;

and R₂ and R₅ are defined herein.

Further preferred compounds of formula I include compounds wherein:

30 R₁ is selected from hydrogen, and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; being hydrogen the most preferred R₁ group;

R₃ is selected from halogen-substituted or unsubstituted C₁-C₆ alkyl and substituted or unsubstituted C₃-C₄ cycloalkyl-C₁-C₄ alkyl, wherein the optional substituents are one or more

substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

R_4 is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; being most preferred hydrogen and methyl;

5 Y is O;

Z is S;

R_2 is selected from hydrogen, methyl, vinyl, allyl, NEt_2 , and OR_a where R_a is selected from hydrogen, methyl, ethyl, *n*-butyl, *n*-heptyl, allyl, propargyl, cyclopropylmethyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, and $-(CH_2CH_2O)_3CH_2CH_3$;

10 and R_5 is defined herein.

Further preferred compounds of formula I include compounds wherein:

R_1 is selected from hydrogen, and substituted or unsubstituted C_2 - C_6 alkynyl, wherein the optional substituents are one or more substituents R_x ; being hydrogen the most preferred R_1 group;

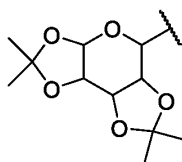
15 R_3 is selected from halogen-substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; being most preferred *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl;

20 R_4 is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; being most preferred hydrogen and methyl;

Y is O;

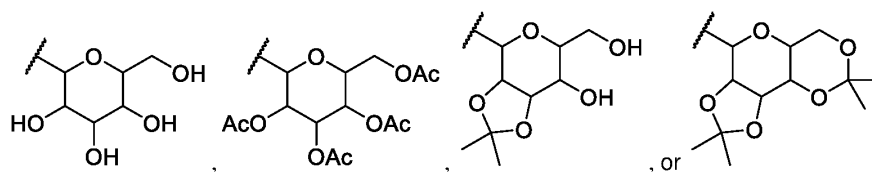
Z is S;

25 R_5 is selected from $-CH(NH_2)Me$, $-(C=O)Me$, $-(C=NR_c)Me$, $-(C=N-OR_h)Me$, $-(C=N-O(C=O)R_f)Me$, $-(C=N-NH_2)Me$, $-(C=N-O-(C=O)OR_a)Me$, $-(C=N-O-[(P=O)(OR_a)_2])Me$, $-(C=CH_2)Me$, or $-(C=CH_2)OR_a$ where R_a is ethyl or benzyl, R_c is $-(CH_2)_3NHBoc$, R_f is $-(CH_2)_5NHBoc$, $-CH_2O(CH_2CH_2O)_2Me$ or a group of formula:



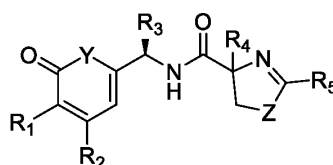
30 and R_h is selected from hydrogen, methyl, allyl, propargyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, $-(CH_2)_3SH$, $-(CH_2)_4OH$, $-(CH_2)_4OP(=O)(OH)_2$, $-(CH_2)_4OP(=O)(O^tBu)_2$, $-(CH_2)_4-[4\lambda^2\text{-morpholine}]$, $-(CH_2)_3-[1\text{-methyl-}4\lambda^2\text{-piperazine}]$, $-(CH_2CH_2O)_3CH_2CH_3$, and a monosaccharide residue of formula:

52



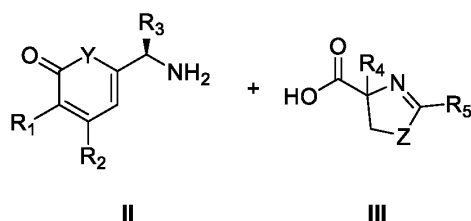
and R_2 is defined herein.

Compounds of formula I



I

- 5 wherein R_1 , R_2 , R_3 , R_4 , R_5 , Y , and Z are as defined above, can be obtained synthetically by coupling an amine of formula II with a carboxylic acid of formula III

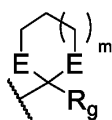


II

III

wherein R_1 , R_2 , R_3 , R_4 , R_5 , Y , and Z in the compounds of formula II and III are as defined above in the compounds of formula I or an appropriately protected group as needed.

- 10 In the process for the manufacture of a compound of formula I, particularly preferred R_1 , R_2 , R_3 , and Y in the intermediates of formula II and particularly preferred R_4 , R_5 , and Z in the intermediates of formula III are as defined above in preferred embodiments of compounds of formula I or an appropriately protected group as needed; and particularly preferred R_5 is selected from $-C(OR_e)_2R_g$ and a



- 15 group where m is 0, 1 or 2 and each E group is independently selected from O and S, R_e is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x , and R_g is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl wherein the optional substituents are one or more substituents R_x . More preferred R_5 is a $-C(OR_e)_2R_g$ group where R_g and R_e are independently substituted or unsubstituted C_1 - C_6 alkyl
- 20 wherein the optional substituents are one or more substituents R_x . More preferred R_g and R_e are

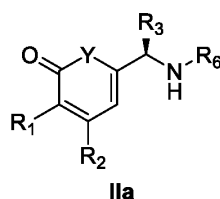
- independently substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x. Most preferred R₅ is -C(OEt)₂Me.

Moreover, when the compound of formula **I** has a R₅ group of formula -C(OR_e)₂R_g this process can further comprise a deprotection step to give a compound of formula **I** where R₅ is - (C=O)R_g.

- Moreover, when the compound of formula **I** has a R₅ group of formula -(C=O)R_g, the process can further comprise a reaction with hydroxylamine, with an hydrazine, with a primary amine, with a methylenation reagent or with an orthoester to give a compound of formula -(C=N-OH)R_g or -(C=N-NR_dR_d)R_g, -(C=NR_e)R_g, -(C=CH₂)Me, or -(C=CH₂)OR_a, respectively.

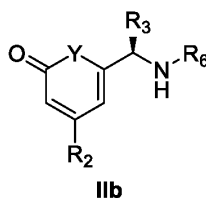
- Moreover, when the compound of formula **I** has a R₅ group of formula -(C=N-OH)R_g, the process can further comprise alkylation, acylation, or phosphorylation of the OH group of the oxime to give the corresponding ether, ester or phosphate.

In addition, with this invention there are provided novel intermediates of formula **IIa**:



wherein R₁, R₂, R₃, R₆ and Y are as defined above in the previous disclosure of intermediates of formula **IIa**.

- In another embodiment, particularly preferred intermediates of formula **IIa** are those also having formula **IIb** or a salt thereof



In intermediates of formula **IIa**, particularly preferred R_1 is selected from hydrogen, halogen and substituted or unsubstituted C_2 - C_6 alkynyl, wherein the optional substituents are one or more substituents R_x ; being hydrogen the most preferred R_1 group.

In intermediates of formula **IIa**, **IIb** or **IIc**, particularly preferred R_2 is selected from
 5 hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, wherein the optional substituents are one or more substituents R_x , $-OR_a$, $-OSO_2R_b$, and $-NR_cR_d$; where R_a is selected from hydrogen, a silylether protecting group for OH, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_6 alkyl,
 10 and $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x ; R_b is selected from substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted aryl, wherein the optional substituents are one or more substituents R_x ; and R_c and R_d are independently selected from substituted or unsubstituted C_1 - C_6 alkyl wherein the optional substituents are one or more substituents R_x . Particularly preferred R_a is
 15 selected from hydrogen, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where p is from 1 to about 10 and the optional substituents are one or more substituents R_x , and a silyl ether protecting group for OH selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl,
 20 dimethylhexylsilyl, 2-norbornyldimethylsilyl, *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl, and fluorosilyl. Particularly
 25 preferred R_b is selected from substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted phenyl, wherein the optional substituents are one or more substituents R_x . Particularly preferred R_c and R_d are independently selected from substituted or unsubstituted C_1 - C_4 alkyl wherein the optional substituents are one or more substituents R_x . More preferred R_2 is selected from hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted
 30 ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted vinyl, substituted or unsubstituted allyl, wherein the optional substituents are one or more substituents R_x , $-OR_a$, $-OSO_2R_b$, and $-NR_cR_d$; where R_a is selected from hydrogen, substituted or unsubstituted methyl,
 35 substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted *n*-heptyl, substituted or unsubstituted allyl, substituted or unsubstituted 1-methyl-

2-propenyl, substituted or unsubstituted 2-methyl-2-propenyl, substituted or unsubstituted 2-butenyl, substituted or unsubstituted 3-butenyl, substituted or unsubstituted propargyl, substituted or unsubstituted 1-methyl-2-propynyl, substituted or unsubstituted 2-butyryl, substituted or unsubstituted 3-butyryl, substituted or unsubstituted cyclopropylmethyl, substituted or unsubstituted 2-cyclopropylethyl, and $-(CH_2CH_2O)_pCH_2CH_3$ wherein p is from 1 to about 5 and the optional substituents are one or more substituents R_x ; R_b is selected from substituted or unsubstituted methyl and substituted or unsubstituted phenyl wherein the optional substituents are one or more substituents R_x ; and R_c and R_d are independently selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Most preferred R_2 is selected from hydrogen, methyl, vinyl, allyl, OTosyl, ONs, OTf, NEt_2 , and OR_a where R_a is hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-heptyl, allyl, propargyl, cyclopropylmethyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, and $-(CH_2CH_2O)_3CH_2CH_3$.

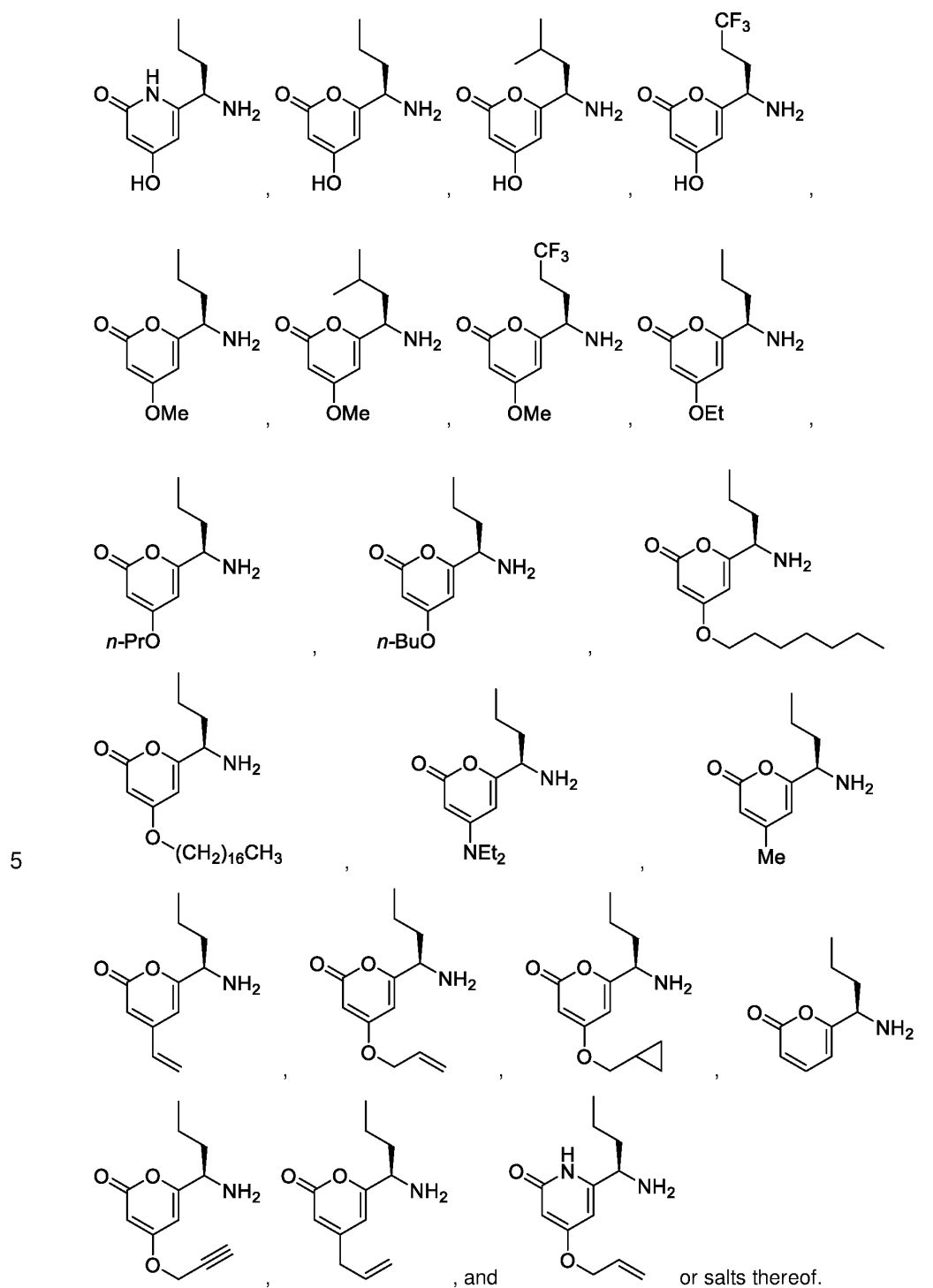
In intermediates of formula **IIa**, **IIb** or **IIc**, particularly preferred R_3 is selected from halogen-substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I. Particularly preferred R_3 is an halogen substituted or unsubstituted C_1 - C_6 alkyl, wherein the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I. More preferred R_3 is selected from halogen-substituted or unsubstituted methyl, halogen-substituted or unsubstituted ethyl, halogen-substituted or unsubstituted *n*-propyl, halogen-substituted or unsubstituted isopropyl, halogen-substituted or unsubstituted *n*-butyl, halogen-substituted or unsubstituted *t*-butyl, halogen-substituted or unsubstituted isobutyl and halogen-substituted or unsubstituted *sec*-butyl, wherein the halogen substituents are one or more substituents independently selected from F, Cl, Br and I. Most preferred R_3 is *n*-propyl, 3,3,3-trifluoropropyl and isobutyl.

In intermediates of formula **IIa**, **IIb** or **IIc** particularly preferred R_6 is hydrogen or *t*-butoxycarbonyl.

In intermediates of formula **IIa**, **IIb** or **IIc** particularly preferred -Y- is -O- or -NH- with the proviso that when R_2 is hydrogen then Y is -O-. Most preferred Y is -O-.

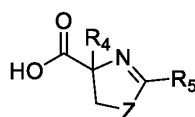
In additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations of preferred substitutions in the formula **IIa**, **IIb** or **IIc** above.

Particularly preferred intermediates of formula **Ila**, **Ilb** or **Ilc** are selected from:



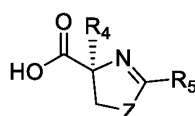
In addition, with this invention we provide novel intermediates of formula **IIla**

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**IIIa**

wherein R_4 , R_5 and Z are as defined above in the previous disclosure of intermediates of formula **IIIa**.

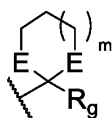
Particularly preferred stereochemistry of said intermediates of formula **IIIa** is the following

**IIIb**

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In intermediates of formula **IIIa** or **IIIb**, particularly preferred R_4 is unsubstituted C_1 - C_6 alkyl. More preferred R_4 is selected from unsubstituted methyl, unsubstituted ethyl, unsubstituted *n*-propyl, unsubstituted isopropyl, unsubstituted *n*-butyl, unsubstituted *t*-butyl, unsubstituted isobutyl, and unsubstituted *sec*-butyl. Most preferred R_4 is methyl.

10 In intermediates of formula **IIIa** or **IIIb**, particularly preferred R_5 is selected from - $C(OR_e)_2R_g$ and a



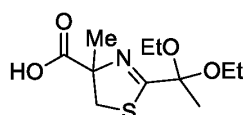
group where m is 0, 1 or 2, and each E group is independently selected from -O- and -S-; where each R_g and R_e groups are, independently, a substituted or unsubstituted C_1 - C_6 alkyl group, wherein the optional substituents are one or more substituents R_x . Particularly preferred R_g and R_e are substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Particularly preferred m is 0 or 1 and particularly preferred E is -O-. More preferred R_5 is - $C(OR_e)_2R_g$, wherein R_e and R_g are independently selected from substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *t*-butyl, substituted or unsubstituted isobutyl, and substituted or unsubstituted *sec*-butyl, wherein the optional substituents are one or more substituents R_x . Most preferred R_5 is - $C(OEt)_2Me$.

25 In intermediates of formula **IIIa** or **IIIb** particularly preferred Z group is -O- or -S-. Most preferred Z group is -S-.

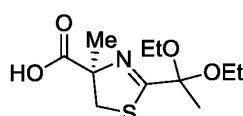
In additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations or preferred substitutions in the formula **IIIa** and **IIIb** above.

A particularly preferred intermediate of formula **IIIa** is

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Even more preferred intermediate of formula **IIIb** is



In the present description and definitions, when there are several groups R, R_a, R_c, R_d, R_e, R_f, R, R_x, R_y or R_z present in the compounds of the invention, and unless it is stated explicitly so, it should be understood that they can be each independently different within the given definition, i.e. R_a does not represent necessarily the same group simultaneously in a given compound of the invention.

Compound **1** was originally isolated from a sponge of the order Lithistida, family Theonellidae, genus Discodermia (du Bocage 1869). This sponge was collected by hand using Rebreather diving system in Halmahera, Indonesia (2° 16.307' N / 127° 44.466' E) at depths ranging between 6 and 73 m. A sample of the specimen was deposited at the Centre for Advanced Studies of Blanes in Girona, Spain, with the reference code HALM-706.

Description: massive irregular sponge, with many fouling organisms, red in color, approximately of 5 cm thick in average, 12 x 6 cm in diameter. Widely separated and irregularly distributed oscula, which are oval and measure 0.5-0.8 mm across. With smaller round pores, 0.20-0.25 mm in diameter, widely separated and irregularly distributed over the whole surface.

Megascleres:

- Discotriaenes 250-350 µm in diameter with short conical rhabd measuring 87-108 µm long.
- Desmas tetracles are about 300-450 µm in size and 100-110 µm thick.

Microscleres:

- Acanthorhabds smaller ones are fusiform, massive, 15-22 µm long and 2-4.5 µm thick.

Skeletal arrangement:

Surfaces are smooth and covered with a dense crust of ectosomal round to oval discotriaenes.

Desmas form a relatively dense skeleton with meshes about 500-600 μm wide.

Additionally, compounds of the invention can be obtained by total synthesis, or by modifying compound **1** already obtained from the natural source or by further modifying those already modified by using a variety of chemical reactions. Thus, hydroxyl groups can be acylated by standard coupling or acylation procedures, for instance by using acetic acid, acetyl chloride or acetic anhydride in pyridine or the like. Formate groups can be obtained by heating hydroxyl precursors with isocyanates. Hydroxyl groups can be converted into halogen groups through intermediate sulfonates for iodide, bromide or chloride, or directly using a sulfur trifluoride for fluorides; or they can be reduced to hydrogen by reduction of intermediate sulfonates. Hydroxyl groups can also be converted into alkoxy groups by alkylation using an alkyl bromide, iodide or sulfonate, or into amino lower alkoxy groups by using, for instance, a protected 2-bromoethylamine. Amido groups can be alkylated or acylated by standard alkylation or acylation procedures, for instance by using, respectively, KH and methyl iodide or acetyl chloride in pyridine or the like. Ester groups can be hydrolyzed to carboxylic acids or reduced to aldehyde or to alcohol. Carboxylic acids can be coupled with amines to provide amides by standard coupling or acylation procedures. When necessary, appropriate protecting groups can be used on the substituents to ensure that reactive groups are not affected. The procedures and reagent needed to prepare these derivatives are known to the skilled person and can be found in general textbooks such as March's Advanced Organic Chemistry 6th Edition 2007, Wiley Interscience.

An important feature of the above described compounds of formula **I**, **la** or **lb** is their bioactivity and in particular their cytotoxic activity against tumor cells. Thus, with this invention we provide pharmaceutical compositions of compounds of formula **I**, **la** or **lb**, or a pharmaceutically acceptable salt or ester thereof that possess cytotoxic activities and their use as anticancer agents. The present invention further provides pharmaceutical compositions comprising a compound of formula **I**, **la** or **lb**, or a pharmaceutically acceptable salt or ester thereof, with a pharmaceutically acceptable carrier or diluent.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) composition for oral, topical or parenteral administration.

Administration of the compounds of formula **I**, **la**, or **lb** or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, and intraperitoneal and intravenous administration.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account.

- 5 Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compound of the invention have anticancer activity against several cancer types which include, but are not limited to, solid tumours, lung cancer, colon cancer, breast cancer and pancreas cancer.

- 10 Thus, in alternative embodiments of the invention, the pharmaceutical composition comprising the compounds of formula I and the kits as defined above is for the treatment of solid tumours, lung cancer, colon cancer, breast cancer and pancreas cancer.

In the present application, by "cancer" it is meant to include tumors, neoplasias and any other malignant disease having as cause malignant tissue or cells.

- 15 The term "treating", as used herein, unless otherwise indicated, means reversing, attenuating, alleviating or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

- 20 The compounds and compositions according to the present invention can be administered to an animal that has also undergone surgery as treatment for the cancer. In one embodiment of the present invention, the additional method of treatment is radiation therapy.

- 25 In a specific embodiment of the present invention, the compound or composition according to the present invention is administered concurrently with radiation therapy. In another specific embodiment, the radiation therapy is administered prior or subsequent to administration of the compound or composition of the present invention, preferably at least an hour, three hours, five hours, 12 hours, a day, a week, a month, more preferably several months (e.g. up to three months) prior or subsequent to administration of a compound or composition of the present invention.

- 30 Any radiation therapy protocol can be used depending upon the type of cancer to be treated. For example, but not by way of limitation x-ray radiation can be administered; in particular, high-energy megavoltage (radiation of greater than 1 MeV energy) can be used for deep tumors, and electron beam and orthovoltage x-ray radiation can be used for skin cancers.

Gamma-ray emitting radioisotopes, such as radioactive isotopes of radium, cobalt and other elements can also be administered.

EXAMPLES

EXAMPLE 1: DESCRIPTION OF THE MARINE ORGANISM AND COLLECTION SITE

- 5 A sponge of the genus *Discodermia* du Bocage, 1869 was collected by hand using Rebreather diving system in Halmahera, Indonesia (2° 16.307' N / 127° 44.466' E) at depths ranging between 6 and 73 m. The animal material was identified by Dr. María Jesús Uriz (Centre for Advanced Studies of Blanes). A sample of the specimen was deposited at the Centre for Advanced Studies of Blanes in Girona, Spain, with the reference code HALM-706.

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Megascleres:

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- 20 Skeletal arrangement:

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Desmas form a relatively dense skeleton with meshes about 500-600 µm wide.

EXAMPLE 2: ISOLATION OF COMPOUND 1

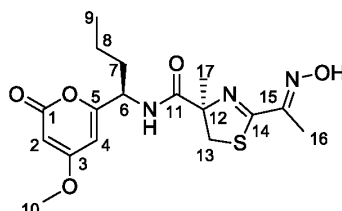
- 25 The frozen specimen of Example 1 was diced and extracted at room temperature under magnetic stirring, firstly with a mixture of 1:1 CH₂Cl₂/CH₃OH (3 x 500 mL) and later with H₂O (1 x 300 mL). Organic and aqueous extracts were evaporated to provide a dry residue of 5.3 g and 213 mg, respectively.

- 30 The organic extract was subjected to step gradient VLC on Lichroprep RP-18 from H₂O to CH₃OH and subsequently from CH₃OH to CH₂Cl₂. The fraction eluted with H₂O/CH₃OH 1:3 (80.4 mg) was subjected to semipreparative reversed phase HPLC (XBridge C18, 5 µm, 10 x 150mm, isocratic H₂O + 0.04% TFA/CH₃CN + 0.04% TFA (65:35) for 3 minutes, gradient from

35 to 60% CH₃CN + 0.04% TFA in 19 minutes and from 65 to 100% CH₃CN + 0.04% TFA in 3 minutes, UV detection, flow 3 mL/min).

- Fraction H5, with a retention time of 14.2 min, was subsequently purified with semi-preparative reversed phase HPLC (SymmetryPrep C18, 7 μ m, 7.8 x 150 mm, isocratic H₂O + 0.04% TFA/CH₃CN + 0.04% TFA (75:25) for 3 minutes, gradient from 25 to 80% CH₃CN + 0.04% TFA in 18 min, UV detection, flow 2.8 mL/min) to afford compound **1** (14.1 mg, retention time 11.3 min).

- Compound **1**: White powder. (+)ESIMS m/z 382.3 [M+H]⁺, 404.1 [M+Na]⁺, 785.2 [2M+Na]⁺, 157.2 [C₆H₉N₂OS]⁺, 181.2 [C₁₀H₁₃O₃]⁺; (+)HRESIMS m/z 382.1430 [M+H]⁺ (calcd for C₁₇H₂₄N₃O₅S 382.1431, Δ = 0.36 ppm); ¹H (500 MHz) and ¹³C NMR (125 MHz) see Table 1.

Compound **1**Table 1. ¹H and ¹³C NMR data of Compound **1** in CD₃OD and CD₃CN.

N ^o	CD ₃ OD		CD ₃ CN	
	δ ¹³ C	δ ¹ H, m, J (Hz)	δ ¹³ C	δ ¹ H, m, J (Hz)
1	166.7	—	164.5	—
2	88.9	5.54, d (2.2)	88.7	5.41, d (2.3)
3	173.4	—	172.1	—
4	100.8	6.04, d (2.1)	99.7	5.89, dd (2.3, 0.5)
5	165.2	—	165.1	—
6	52.2	4.75, m	51.6	4.66, m
7	35.3	1.85, m	35.0	1.78, m
8	20.2	1.47, m 1.39, m	19.8	1.42, m 1.34, m
9	13.8	0.99, t (7.4)	13.8	0.94, t (7.4)
10	57.0	3.84, s	57.1	3.78, s
11	176.6	—	174.8	—
12	85.6	—	85.3	—
13	40.6	3.54, d (11.5) 3.18, d (11.5)	40.7	3.54, d (11.6) 3.17, d (11.6)
14	170.3	—	168.6	—

N ^o	CD ₃ OD		CD ₃ CN	
	$\delta^{13}\text{C}$	$\delta^1\text{H}$, m, J (Hz)	$\delta^{13}\text{C}$	$\delta^1\text{H}$, m, J (Hz)
15	152.8	–	153.7	–
16	11.0	2.18, s	11.3	2.17, s
17	25.0	1.53, s	25.1	1.48, s
NH	–	7.84, d (8.7)	–	7.07, d (85)
OH	–	11.82, s*	–	9.73, s
* Assigned from spectrum acquired in CD ₃ OH.				

Absolute configuration of the aminoacid residues in compound **1** was determined by Marfey's analysis (Marfey, P. Carlsberg Res. Commun. 1984, 49, 591-596).

0.3 mg of compound **1** were dissolved in 0.5 mL of 6N HCl in a sealed vial and heated at 110 °C for 16 h. The solvent was evaporated under a N₂ stream, the residue was dissolved in 50 µL of water, and 0.7 mg of fluorodinitrophenyl-5-L-alaninamide (L-FDAA, Marfey's reagent) in 100 µL of acetone and 40 µL of 1N aqueous NaHCO₃ were added. The resulting mixture was heated at 40 °C for 1 h and, after cooling at room temperature, neutralised with 100 µL of 2N HCl. Finally, the mixture was diluted with 700 µL of water and filtrated (45 µm filter) prior to HPLC-MS analysis.

Standards of all stereoisomers of the aminoacid residues present in compound **1** were derivatized in the same manner as the compound hydrolysed. Racemic methyl 4-methyl-2-(pyridin-3-yl)-4,5-dihydrothiazole-4-carboxylate was prepared following the procedure described by Singh *et al.* in J. Org. Chem. 2004, 69, 4551-4554.

Relative retention times to unreacted L-FDAA of both, the derivative hydrolysed and the derivative aminoacid standards, were determined by reversed phase HPLC-MS: Symmetry C18, 5 µm, 4.6×150 mm, gradient H₂O + 0.04% TFA/CH₃CN + 0.04% TFA from 20% to 50% CH₃CN + 0.04% TFA in 30 min, UV (215 and 350 nm) and (+)ESIMS detection, flow 0.8 mL/min.

Comparison of these retention times unambiguously confirmed the presence in compound **1** of 2-methyl-L-cysteine.

Norvaline residue could not be obtained by simple hydrolysis of compound **1**, and therefore the compound was first subjected to an oxidative ozonolysis protocol. To do that, a stream of ozone in O₂ was bubbled through a solution of compound **1** (0.3 mg) in CH₂Cl₂ (3 mL) for 5 min. The solvent was evaporated under a N₂ stream and the residue was dissolved in 2 mL of hydrogen peroxide (35%) : formic acid (1:9) at 0 °C and kept for 2h. Then, the solvent was removed under a stream of N₂; the resultant residue was hydrolyzed in acidic conditions and immediately

subjected to Marfey's derivatization as described above. Finally, it was analyzed by HPLC-MS in same conditions previously depicted for non-oxidized sample.

Comparison of relative retention times of authentic standards of L- and D-norvaline derivatized following the same procedure with the amino acid residue of natural sample confirmed the presence of D-norvaline in compound **1**.

These results have been confirmed by the total synthesis of compound **1** described in Example 7.

EXAMPLE 3: SCALE-UP OF ISOLATION OF COMPOUND 1

A second group of samples of the specimen of Example 1 (926 g) was diced and extracted at room temperature under magnetic stirring, firstly with a mixture of 1:1 CH₂Cl₂/CH₃OH (6 x 500 mL) and later with H₂O (2 x 300 mL). Organic extract was evaporated to provide three dry residues A (19.5 g), B (16.8 g) and C (10.7 g), while the aqueous extract gave a residue of 2.4 g.

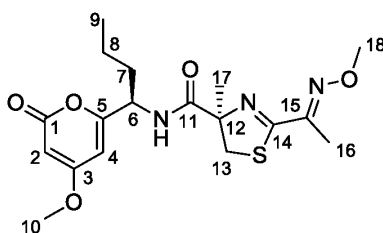
Residues A, B and C were subjected to step gradient VLC on Lichroprep RP-18 from H₂O to CH₃OH and subsequently from CH₃OH to CH₂Cl₂. For residue A, fractions eluted with H₂O/CH₃OH 1:3 (172.0 mg), CH₃OH (800.0 mg) and CH₃OH/CH₂Cl₂ 1:1 (619.8 mg) contained compound **1**. For residues B and C, fractions eluted with CH₃OH/H₂O 1:1 (445.6 mg B, 225.1 mg C), CH₃OH/H₂O 3:1 (286.3 mg B, 149.5 mg C), CH₃OH (2.1 g B, 962.5 mg C) and CH₃OH/CH₂Cl₂ 1:1 (3.26 g B, 618.8 mg C) were the ones containing compound **1**. All these fractions were subjected to flash chromatography normal phase (12 g Silica column, isocratic *n*-Hex/EtOAc 70:30 for 8-9 minutes, from 30 to 70% EtOAc in 27-29 minutes, isocratic 70% EtOAc for 6-8 minutes and from 70 to 100% EtOAc in 4-7 minutes, wavelength 254 and 280 nm, flow 30 mL/min) to afford Compound **1** (196 mg, retention time 8-13 min).

EXAMPLE 4: METHYLATION OF COMPOUND 1

To a solution of Compound **1** (1.4 mg) in anhydrous DMF (1.5 mL) was added Cs₂CO₃ (5 mg) and methyl iodide (40 µL). The reaction mixture was stirred at room temperature overnight. Then, the solution was subjected to analytical HPLC (Symmetry C18, 5 µm, 4.6 x 150mm, isocratic H₂O + 0.04% TFA/CH₃CN + 0.04% TFA (75:25) for 3 minutes, gradient from 25 to 80% CH₃CN + 0.04% TFA in 18 min, UV detection, flow 1 mL/min) to give Compound **2** (0.5 mg).

Compound **2**: White powder. (+)ESIMS *m/z* 396.2 [M+H]⁺, 418.1 [M+Na]⁺; (+)HRESIMS *m/z* 396.1582 [M+H]⁺ (calcd for C₁₈H₂₆N₃O₅S 396.1588, Δ= 1.5 ppm); ¹H (500 MHz) see Table 2.

65



Compound 2

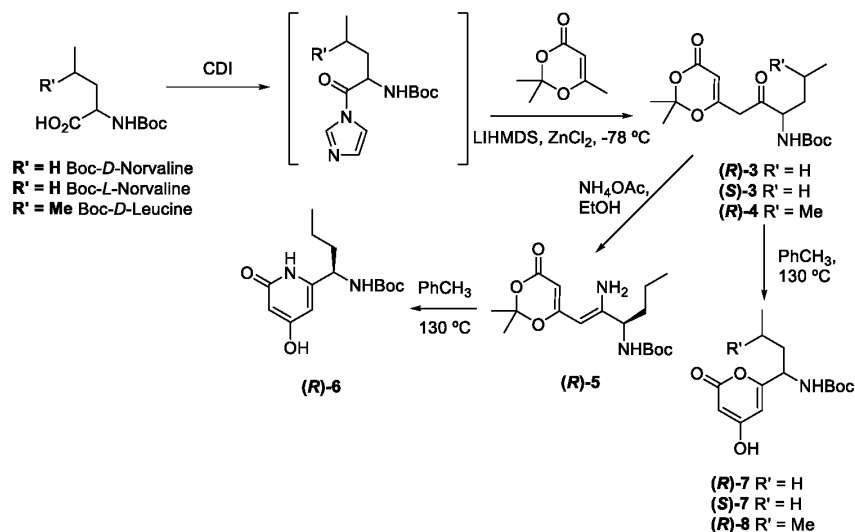
Table 2. ^1H NMR data of compound 2 in CD_3OH and CDCl_3 .

N°	CD_3OH δ ^1H , m, J (Hz)	CDCl_3 δ ^1H , m, J (Hz)
1	-	-
2	5.54, d (2.2)	5.43, d (2.2)
3	-	-
4	6.03, dd (2.2, 0.7)	5.89, d (2.2)
5	-	-
6	*	4.73, q (7.94)
7	1.84, m	1.88, m
8	1.47, m 1.38 m	1.37, m
9	0.98, t (7.4)	0.96, t (7.3)
10	3.84, s	3.79, s
11	-	-
12	-	-
13	3.56, d (11.7) 3.19, d (11.7)	3.53, d (11.6) 3.21, d (11.6)
14	-	-
15	-	-
16	2.18, s	2.18, s
17	1.52, s	1.52, s
18	3.99, s	4.03, s
NH	7.84, d (8.8)	7.11, d (8.8)
* Overlapped with H_2O signal in CH_3OH		

5 EXAMPLE 5: SYNTHESIS OF INTERMEDIATES OF FORMULA II

Scheme 2 provides some examples of the synthesis of intermediates of formula II and of some (S)-analogs used to confirm the stereochemistry of compound 1.

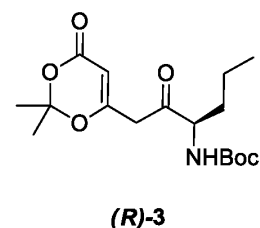
66



Scheme 2

Synthesis of intermediate **(R)-3**

- To a solution of Boc-*D*-norvaline (20 g, 92.0 mmol, commercial chemical from Chem-impex) in 2-Me-THF (368 mL, 4 mL/mmol) under nitrogen atmosphere at 23 °C was added 1,1'-carbonyldiimidazole (CDI) (15.7 g, 96.6 mmol, 1.05 equiv). The reaction mixture was for 2 hours at 23 °C. A solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (30.55 mL, 230 mmol, 2.5 equiv) in 2-Me-THF (368 mL, 4 mL/mmol) was slowly added to a precooled at -78 °C dilution of LiHMDS (368 mL, 1.0 M in THF, 368 mmol, 4.0 equiv) in 2-Me-THF (368 mL, 4 mL/mmol). The reaction mixture was stirred at -78 °C for 1 hour. ZnCl₂ (31.3 g, 230 mmol, 2.5 equiv) was added in one portion and the reaction mixture was stirred at -78 °C for 30 minutes. Finally, the solution of the intermediate previously prepared was added, by cannula, at -78 °C. The reaction mixture was stirred at -78 °C for 4 hours. An aqueous saturated solution of NH₄Cl was added and the aqueous layers were extracted with EtOAc. The combined organic layers were dried over anhydrous NaSO₄, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (CH₂Cl₂:EtOAc, 9:1) to give pure **(R)-3** (12.9 g, 41% yield).

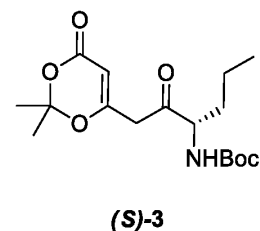


- ¹H NMR (300 MHz, CDCl₃): δ 5.35 (s, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.27 (td, *J* = 7.9, 4.7 Hz, 1H), 3.43 (s, 2H), 1.77 (m, 2H), 1.68 (s, 6H), 1.58-1.28 (m, 2H), 1.43 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H).
¹³C NMR (75 MHz, CDCl₃): δ 203.2, 164.5, 160.8, 155.7, 107.4, 97.1, 80.4, 59.8, 43.9, 33.0, 28.5, 25.2, 18.8, 13.9.

MS (ES): *m/z* 364.3 [M+Na]⁺.R_f: 0.13 (Hex:EtOAc 4:1).

- Synthesis of analog **(S)-3**

In a first flask, CDI (3.9 g, 24.15 mmol) was added in portions to a solution of Boc-L-norvaline (5.0 g, 23 mmol, commercial chemical from Chem-impex) in 2-Me-THF (92 mL), with gas evolution. This mixture was stirred for 2 h. In another flask, at -78 °C, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (7.6 mL, 57 mmol) in 2-Me-THF (92 mL) was added slowly to a solution of LiHMDS (57.5 mL, 1.0 M in THF, 57.5 mmol) in 2-Me-THF (92 mL). After stirring at the same temperature for 1 h, the first mixture was added via canula. The reaction was stirring at -78 °C for 4 h and then quenched with saturated aqueous solution of NH₄Cl. Extraction with EtOAc, and dryness of the organic layers over Na₂SO₄ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 9/1 to 7/3) to afford **(S)-3** (2.0 g, 64% yield).

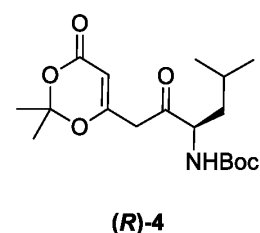


¹H NMR (300 MHz, CDCl₃): δ 5.35 (s, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.27 (td, *J* = 7.9, 4.7 Hz, 1H), 3.43 (s, 2H), 1.77 (m, 2H), 1.69 (s, 6H), 1.58-1.28 (m, 2H), 1.43 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H).
¹³C NMR (75 MHz, CDCl₃): δ 203.2, 164.5, 160.8, 155.7, 107.4, 97.1, 80.4, 59.8, 43.9, 33.0, 28.5, 25.2, 18.8, 13.9.
 MS (ES): *m/z* 364.3 [M+Na]⁺, 705.2 [2M+Na]⁺.
 R_f: 0.5 (Hex:EtOAc 6:4).

Synthesis of intermediate **(R)-4**

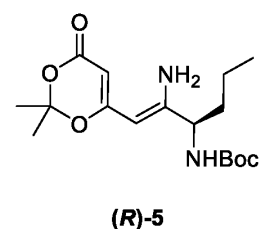
In a first flask, CDI (1.66 g, 10.29 mmol) was added in portions to a solution of Boc-D-leucine (2.27 g, 9.8 mmol) in Et₂O (40 mL), with gas evolution. This mixture was stirred for 2 h. In another flask, at -78 °C, a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (4.2 mL, 29.4 mmol) in Et₂O (30 mL) was added slowly to a solution of LiHMDS (29.4 mL, 1.0 M in THF, 29.4 mmol) in Et₂O (29.4 mL). After stirring at the same temperature for 1 h, ZnCl₂ (2.67 g, 29.4 mmol) was added in one portion. After 30 min, the first mixture was added via canula. The reaction was stirring at -78 °C for 4 h and then quenched with saturated aqueous solution of NH₄Cl. Extraction with EtOAc, and dryness of the organic layers over Na₂SO₄ gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/EtOAc 9/1) to afford pure **(R)-4** (0.42 g, 12% yield).

¹H NMR (300 MHz, CDCl₃): δ 5.35 (s, 1H), 4.87 (d, *J* = 8.0 Hz, 1H), 4.38-4.21 (m, 1H), 3.44 (d, *J* = 3.5 Hz, 2H), 1.70 (s, 6H), 1.55 (m, 2H), 1.44 (s, 9H), 1.37 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 6H).



Synthesis of intermediate **(R)-5**

A solution of **(R)-3** (330 mg, 0.97 mmol), NH₄OAc (373 mg, 4.85 mmol) in ethanol (4 mL) was stirred at 23 °C for 24 h. After evaporating the solvent, the crude was triturated with EtOAc to remove the solids by filtration. The solvent was evaporated to obtain



(R)-5 (329 mg, 100% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.53 (s, 1H), 4.92 (s, 1H), 4.75 (s, 1H), 4.53 (s, 1H), 3.91 (s, 1H), 1.74 (s, 6H), 1.73-1.53 (m, 1H), 1.44 (s, 2H), 1.43 (s, 9H), 1.49-1.31 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H).

5 ¹³C NMR (101 MHz, CDCl₃): δ 168.0, 162.9, 157.5, 155.9, 105.7, 86.6, 28.4, 25.7, 25.5, 19.5, 13.8.

MS (ES): *m/z* 341.3 [M+H]⁺.

Synthesis of intermediate **(R)-6**

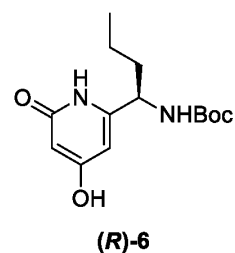
10 A solution of **(R)-5** (329 mg, 0.96 mmol) in toluene (100 mL) was stirred in a bath at 130 °C for 2 h. Evaporation of the solvent under vacuo gave a crude which purified by flash chromatography over silica gel (CH₂Cl₂/CH₃OH 98/2) to give **(R)-6** (93 mg, 34% yield).

¹H NMR (500 MHz, CD₃OD): δ 5.95 (d, *J* = 2.21 Hz, 1H), 5.66 (d, *J* = 2.2 Hz, 1H), 4.36 (s, 1H), 1.71-1.55 (m, 4H), 1.43 (s, 12H), 0.95 (t, *J* = 7.4 Hz, 3H).

15 ¹³C NMR (125 MHz, CD₃OD): δ 171.1, 168.0, 157.8, 153.4, 99.2, 80.7, 53.5, 37.7, 32.8, 28.7, 23.7, 20.5, 14.4, 13.9.

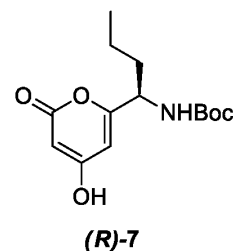
MS (ES): *m/z* 283.3 [M+H]⁺.

R_f: 0.26 (CH₂Cl₂:MeOH 9:1).



Synthesis of intermediate **(R)-7**

(R)-3 (10.74 g, 31.5 mmol) was dissolved in toluene (315 mL, 10 mL/mmol) and heated in a bath at 130 °C for 30 minutes. Evaporation of the solvent under vacuum afforded **(R)-7** crude (8.91 g) that was used

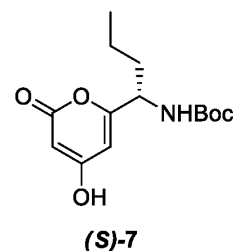


¹H NMR (400 MHz, CDCl₃): δ 10.50 (s, 1H), 6.09 (d, *J* = 1.8 Hz, 1H), 5.56 (s, 1H), 5.23 (d, *J* = 8.5 Hz, 1H), 4.36 (q, *J* = 7.8 Hz, 1H), 1.78 (s, 1H), 1.67 (s, 1H), 1.43 (s, 9H), 0.92 (t, *J* = 7.3 Hz, 3H).
¹³C NMR (75 MHz, CDCl₃): δ 171.6, 166.9, 165.2, 155.8, 129.2, 128.4, 125.5, 100.9, 90.9, 80.9, 53.0, 35.3, 28.5, 19.3, 13.8.
 MS (ES): *m/z* 306.1 [M+Na]⁺.
 R_f: 0.35 (CH₂Cl₂:MeOH 9:1).
 Optical rotation: [α]_D +101.6 (c 0.018, MeOH).

Synthesis of analog **(S)-7**

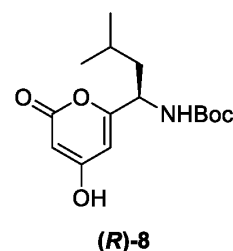
A solution of **(S)-3** (700 mg, 2.05 mmol) in toluene (12 mL) was stirred in a bath at 130 °C for 30 min. Evaporation of the solvent under vacuum gave a crude of **(S)-7** which was used in the next step without purification.

¹H NMR (300 MHz, CDCl₃): δ 6.08 (d, *J* = 2.1 Hz, 1H), 5.56 (d, *J* = 2.0 Hz, 1H), 5.16 (d, *J* = 8.5 Hz, 1H), 4.50-4.27 (m, 1H), 1.90-1.57 (m, 2H), 1.50-1.38 (m, 10H), 1.00-0.81 (m, 3H).

Synthesis of intermediate **(R)-8**

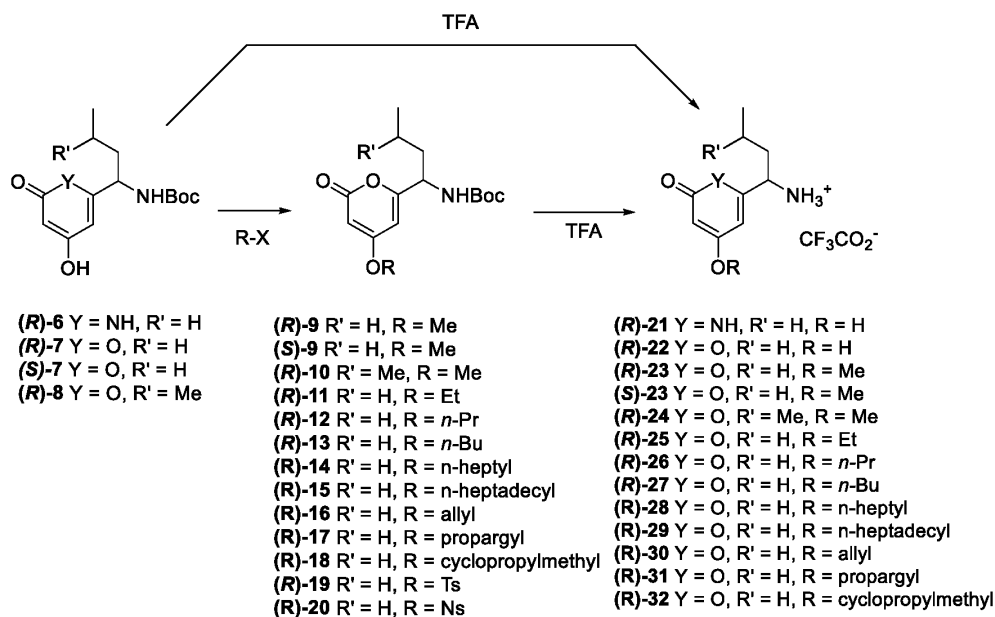
A solution of **(R)-4** (400 mg, 1.12 mmol) in toluene (120 mL) was stirred in a bath at 130 °C for 30 min. Evaporation of the solvent under vacuum gave of **(R)-8** crude which was used in the next step without purification.

¹H NMR (300 MHz, CDCl₃): δ 6.09 (s, 1H), 5.55 (s, 1H), 5.27 (d, *J* = 10.6 Hz, 2H), 4.41 (m, 1H), 1.59 (m, 3H), 1.41 (s, 9H), 0.91 (m, 6H).
 MS (ES): *m/z* 320.3 [M+Na]⁺.



Scheme 3 provides more examples of the synthesis of intermediates of formula II and of some (S)-analogs used to confirm the stereochemistry of compound 1.

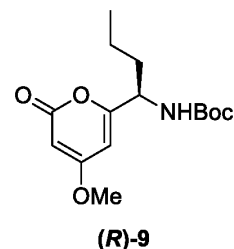
70



Scheme 3

Synthesis of intermediate (*R*)-**9**

To a solution of (*R*)-**7** (8.92 g, 31.46 mmol) in acetone (314.6 mL, 10 mL/mmol) under nitrogen atmosphere at 23 °C was added K₂CO₃ (21.74 g, 157.3 mmol, 5.0 equiv) and dimethyl sulfate (14.9 mL, 157.3 mmol, 5.0 equiv). The reaction mixture was stirred for 2 hours at 23 °C, filtered over Celite®, washed with CH₂Cl₂, and the solvent was removed under vacuum. The crude obtained was purified by column chromatography (Hexane:EtOAc, from 9:1 to 7:3) to give (*R*)-**9** pure (5.39 g, 60% yield for two steps).



¹H NMR (400 MHz, CDCl₃): δ 5.93 (d, *J* = 2.2 Hz, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 5.30 (s, 1H), 4.88 (d, *J* = 8.8 Hz, 1H), 4.38 (q, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 1.79 (ddt, *J* = 13.3, 9.3, 6.5 Hz, 1H), 1.70-1.61 (m, 1H), 1.43 (s, 9H), 1.42-1.21 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

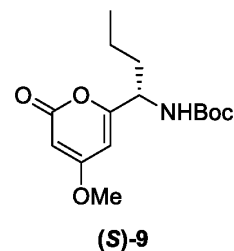
¹³C NMR (75 MHz, CDCl₃): δ 171.3, 164.6, 163.7, 155.1, 103.3, 100.0, 88.5, 56.2, 53.6, 52.7, 35.4, 29.9, 28.5, 19.3, 13.8.

MS (ES): *m/z* 320.0 [M+Na]⁺.

Rf: 0.3 (Hex:EtOAc 6:4).

Synthesis of analog (*S*)-**9**

A mixture of (*S*)-**7** (560 mg, 1.98 mmol), acetone (20 mL), K₂CO₃ (1.37 g, 9.88 mmol) and dimethyl sulfate (0.94 mL, 9.88 mmol) was stirred at 23 °C for 2 h. Filtration over Celite® and washing with CH₂Cl₂ gave a crude which was purified by flash chromatography on silica gel

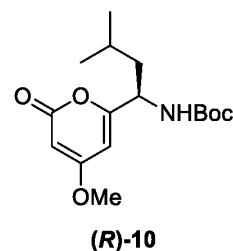


(hexane/EtOAc 8/2 to 6/4) to yield **(S)-9** (268 mg, 48% yield for 2 steps).

¹H NMR (300 MHz, CDCl₃): δ 5.91 (d, *J* = 2.2 Hz, 1H), 5.40 (dd, *J* = 2.2, 0.6 Hz, 1H), 4.94 (d, *J* = 8.8 Hz, 1H), 4.43-4.24 (m, 1H), 3.77 (d, *J* = 0.6 Hz, 3H), 1.75 (ddd, *J* = 13.4, 9.4, 6.8 Hz, 1H), 1.66-1.56 (m, 1H), 1.39 (d, *J* = 0.6 Hz, 10H), 1.31 (ddd, *J* = 8.7, 4.9, 1.5 Hz, 1H), 0.89 (dd, *J* = 7.7, 7.0 Hz, 3H).

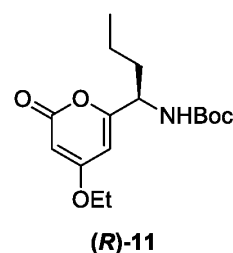
Synthesis of intermediate **(R)-10**

A mixture of **(R)-8** (79 mg, 0.26 mmol), acetone (2.6 mL), K₂CO₃ (183 g, 1.33 mmol) and dimethyl sulfate (0.13 mL, 1.33 mmol) was stirred at 23 °C for 2 h. Filtration over Celite® and washing with CH₂Cl₂ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 8/2 to 6/4) to yield **(R)-10** (74 mg, 89% yield for 2 steps). ¹H NMR (300 MHz, CDCl₃): δ 5.94 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.87 (d, *J* = 8.9 Hz, 1H), 4.43 (q, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 1.61 (m, 3H), 1.41 (s, 9H), 0.97-0.85 (m, 6H).



Synthesis of intermediate **(R)-11**

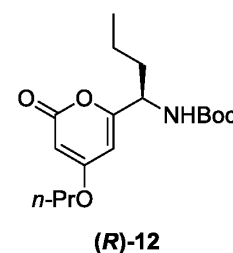
A mixture of **(R)-7** (80 mg, 0.28 mmol), CH₂Cl₂ (5.6 mL), Ag₂O (130 mg, 0.56 mmol) and iodoethane (0.67 mL, 8.4 mmol) was stirred at 23 °C for 24 h. Filtration over Celite® and washing with CH₂Cl₂ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 8/2 to 6/4) to yield **(R)-11** (37 mg, 42% yield for 2 steps). ¹H NMR (300 MHz, CDCl₃): δ 5.91 (d, *J* = 2.2 Hz, 1H), 5.37 (d, *J* = 2.2 Hz, 1H), 4.92 (d, *J* = 8.9 Hz, 1H), 4.35 (q, *J* = 7.8 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 1.76 (dq, *J* = 9.2, 6.8 Hz, 1H), 1.62 (td, *J* = 8.3, 7.4, 3.4 Hz, 1H), 1.40 (s, 9H), 1.45-1.17 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H).



Synthesis of intermediate **(R)-12**

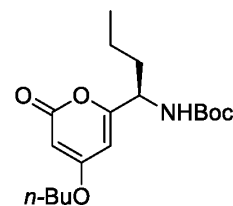
A mixture of **(R)-7** (50 mg, 0.176 mmol), acetone (1.8 mL), K₂CO₃ (121 mg, 0.88 mmol) and iodopropane (0.2 mL, 1.76 mmol) was stirred at 23 °C for 5 h. Filtration over Celite® and washing with CH₂Cl₂ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 8/2 to 6/4) to yield **(R)-12** (35 mg, 100% yield for 2 steps).

¹H NMR (300 MHz, CDCl₃): δ 5.93 (d, *J* = 2.2 Hz, 1H), 5.39 (dd, *J* = 2.3, 0.8 Hz, 1H), 4.98-4.81 (m, 1H), 4.37 (q, *J* = 7.9 Hz, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 1.79 (m, 4H), 1.42 (s, 9H), 1.40-1.19 (m, 2H), 1.01 (td, *J* = 7.5, 0.8 Hz, 3H), 0.92 (td, *J* = 7.3, 0.8 Hz, 3H).



Synthesis of intermediate **(R)-13**

A mixture of **(R)-7** (50 mg, 0.176 mmol), acetone (1.8 mL), K₂CO₃ (121 mg, 0.88 mmol) and iodobutane (0.16 mL, 1.76 mmol) was stirred at 23 °C for 5 h. Filtration over Celite® and washing with CH₂Cl₂ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 8/2 to 6/4) to yield **(R)-13** (34 mg, 100% yield for 2 steps).

**(R)-13**

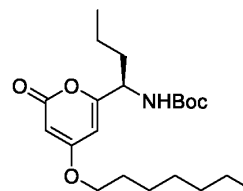
¹H NMR (400 MHz, CDCl₃): δ 5.92 (d, *J* = 2.2 Hz, 1H), 5.39 (d, *J* = 2.2 Hz, 1H), 4.88 (d, *J* = 8.9 Hz, 1H), 4.37 (q, *J* = 7.9 Hz, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 1.86-1.66 (m, 3H), 1.62 (s, 1H), 1.54-1.27 (m, 11H), 0.94 (dt, *J* = 13.8, 7.4 Hz, 6H).

MS (ES): *m/z* 362.3 [M+Na]⁺, 701.5 [2M+Na]⁺.

R_f: 0.37 (Hex:EtOAc 7:3).

Synthesis of intermediate **(R)-14**

(R)-7 (69 mg) was dissolved in acetone (2.4 mL) and then Cs₂CO₃ (119 mg) and 1-bromoheptane (57 μL) were added. This suspension was refluxed for 2 h. Then the reaction mixture was allowed to cool to 23 °C, filtered through a plug of Celite® and washed with EtOAc (3 x 10 mL) and evaporated to dryness. Purification by flash chromatography over silica gel (CH₂Cl₂/EtOAc 100:0 to 95:5) yielded **(R)-14** (78 mg, 84% yield for 2 steps).

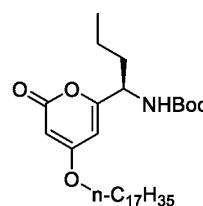
**(R)-14**

¹H NMR (400 MHz, CDCl₃): δ 5.92 (d, *J* = 2.2 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 4.90 (d, *J* = 8.9 Hz, 1H), 4.36 (q, *J* = 7.8 Hz, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 1.85-1.68 (m, 3H), 1.71-1.55 (m, 1H), 1.42 (s, 9H), 1.41-1.21 (m, 10H), 0.98-0.83 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 170.4, 164.6, 163.3, 154.9, 100.0, 88.6, 80.0, 69.0, 52.5, 35.2, 31.6, 28.8, 28.4, 28.3, 25.7, 22.5, 19.0, 14.0, 13.5.

Synthesis of intermediate **(R)-15**

To a solution of **(R)-7** (63 mg, 0.222 mmol) in acetone (2.2 mL) was added Cs₂CO₃ (109 mg, 0.334 mmol) and 1-bromoheptadecane (106 mg, 0.334 mmol) at 23 °C. The reaction mixture was refluxed for 4 h. The reaction mixture was cooled to 23 °C, filtrated over Celite® and washed with EtOAc. The crude obtained was purified by flash chromatography on silica gel (CH₂Cl₂:EtOAc from 100:0 to 95:5) to field **(R)-15** (93 mg, 80% yield).

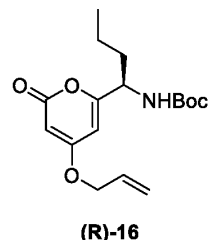
**(R)-15**

¹H NMR (400 MHz, CDCl₃): δ 5.92 (d, *J* = 2.2 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 4.90 (d, *J* = 8.9 Hz, 1H), 4.36 (q, *J* = 7.9 Hz, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 1.83-1.72 (m, 3H), 1.76-1.55 (m, 1H), 1.42 (s, 9H), 1.47-1.22 (m, 30H), 0.96-0.80 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.4, 164.5, 163.3, 154.9, 100.0, 88.6, 80.0, 69.1, 52.5, 35.2, 31.9, 29.7, 29.6 (x2), 29.5 (x2), 29.3, 29.2 (x2), 28.4, 28.3, 25.8, 22.7, 19.0, 14.1, 13.6.

Synthesis of intermediate (**R**)-16

- 5 To a solution of (**R**)-7 (7.05 g, 24.88 mmol) in acetone (250 mL) was added Cs_2CO_3 (12.16 g, 37.32 mmol) and allyl bromide (3.23 mL, 37.32 mmol) at 23 °C. The reaction mixture was refluxed for 1 h. Filtration over Celite® and washing with EtOAc gave a crude which was purified in an automatic system for flash chromatography on (SiO_2 , Hex:EtOAc 70:30) to yield (**R**)-16 (5.0 g, 62% yield).



- 10 ^1H NMR (400 MHz, CDCl_3): δ 6.03-5.91 (m, 2H), 5.46-5.27 (m, 3H), 4.87 (d, J = 9.0 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 4.37 (m, 1H), 1.79 (ddt, J = 13.4, 9.5, 6.6 Hz, 2H), 1.43 (d, J = 0.5 Hz, 9H), 1.33 (td, J = 15.1, 7.4 Hz, 2H), 1.00-0.81 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 169.8, 164.3, 163.7, 154.9, 130.6, 119.4, 99.8, 89.1, 80.0, 69.5, 52.5, 35.1, 28.3, 19.0, 13.5.

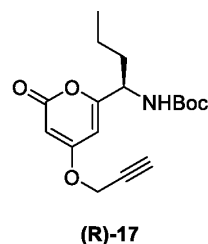
- 15 MS (ES⁺): m/z 346.3 [$\text{M}+\text{Na}$]⁺.

Optical rotation: $[\alpha]_D$ +82.1 (c 0.045, MeOH).

R_f: 0.31 (Hex:EtOAc 7:3).

Synthesis of intermediate (**R**)-17

- 20 To a solution of (**R**)-7 (2.88 g, 10.16 mmol) in acetone (102 mL) was added Cs_2CO_3 (4.97 g, 15.25 mmol) and propargyl bromide (1.7 mL, 15.25 mmol) at 23 °C. The reaction mixture was refluxed for 2 h. The reaction mixture was cooled to 23 °C, filtered over Celite® and washed with EtOAc. The crude obtained was purified in an automatic system for flash chromatography on (SiO_2 , CH_2Cl_2 :EtOAc from 99:1 to 95:5) to yield (**R**)-17 (2.31 g, 71% yield).



- 25 ^1H NMR (400 MHz, CDCl_3): δ 5.96 (d, J = 2.2 Hz, 1H), 5.55 (dd, J = 2.4, 0.7 Hz, 1H), 4.95 (d, J = 8.8 Hz, 1H), 4.66 (d, J = 2.5 Hz, 2H), 4.42 (q, J = 7.8 Hz, 1H), 2.62 (td, J = 2.6, 0.9 Hz, 1H), 1.87-1.71 (m, 1H), 1.74-1.60 (m, 1H), 1.42 (s, 9H), 1.40-1.21 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

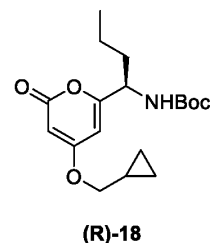
- 30 ^{13}C NMR (100 MHz, CDCl_3): δ 168.9, 164.0, 154.9, 99.5, 89.8, 80.1, 77.6, 75.7, 56.4, 52.5, 35.1, 28.3, 19.0, 13.5.

MS (ES⁺): m/z 344.2 [$\text{M}+\text{Na}$]⁺.

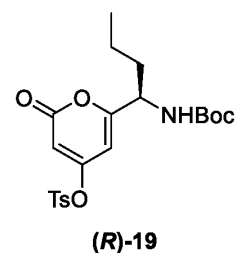
R_f: 0.37 (Hex:EtOAc 7:3).

Synthesis of intermediate **(R)-18**

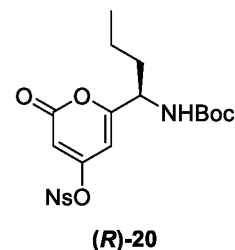
- To a solution of **(R)-7** (9.9 g, 34.94 mmol) in DMF (800 mL) was added K_2CO_3 (9.66 g, 69.89 mmol) at 23 °C. The reaction mixture was stirred for 30 min at 23 °C and cyclopropylmethyl bromide (3.7 mL, 38.44 mmol) was added at 23 °C. The reaction mixture was stirred overnight at 60 °C. The reaction mixture was concentrated under vacuum, diluted with EtOAc, filtrated over Celite® and washed with EtOAc. The crude obtained was purified in an automatic system for flash chromatography (SiO₂, Hex:EtOAc 70:30) to field **(R)-18** (10.13 g, 86% yield).
- ¹H NMR (400 MHz, CDCl₃): δ 5.95 (d, J = 2.2 Hz, 1H), 5.34 (d, J = 2.2 Hz, 1H), 4.91 (d, J = 8.9 Hz, 1H), 4.37 (q, J = 7.6 Hz, 1H), 3.75 (dd, J = 7.1, 1.3 Hz, 2H), 1.77 (ddt, J = 13.3, 9.5, 6.5 Hz, 1H), 1.69-1.53 (m, 1H), 1.41 (s, 9H), 1.46-1.13 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.72-0.59 (m, 2H), 0.39-0.26 (m, 2H).
- ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 164.5, 163.5, 154.9, 99.9, 88.5, 80.0, 73.7, 52.5, 35.1, 28.3, 19.0, 13.5, 9.4, 3.3 (x2).
- MS (ES⁺): m/z 360.2 [M+Na]⁺.
- Optical rotation: $[\alpha_D]$ +82.1 (c 0.046, MeOH).
- R_f: 0.32 (Hex:EtOAc 7:3).

Synthesis of intermediate **(R)-19**

- A solution of **(R)-7** (37 mg, 0.124 mmol), *p*-toluenesulfonyl chloride (24 mg, 0.124 mmol) and triethylamine (0.017 mL, 0.124 mmol) in CH₂Cl₂ (2 mL) was stirred at 23 °C for 2 h. The reaction mixture was quenched with water and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄ and filtered off to afford **(R)-19** (54 mg, 100% yield).
- ¹H NMR (400 MHz, CDCl₃): δ 7.85-7.77 (m, 2H), 7.42-7.34 (m, 2H), 6.09 (d, J = 2.2 Hz, 1H), 5.90 (d, J = 2.2 Hz, 1H), 4.85 (d, J = 8.6 Hz, 1H), 4.37 (q, J = 7.8 Hz, 1H), 2.46 (s, 3H), 1.75 (ddt, J = 13.7, 9.6, 6.3 Hz, 1H), 1.67-1.53 (m, 1H), 1.42 (s, 9H), 1.36-1.18 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).
- ¹³C NMR (100 MHz, CDCl₃): δ 166.0, 162.3, 161.7, 154.8, 146.7, 131.5, 130.3, 128.4, 101.3, 99.5, 80.3, 52.6, 35.0, 28.2, 21.8, 18.9, 13.5.

Synthesis of intermediate **(R)-20**

- To a solution of **(R)-7** (600 mg, 2.12 mmol) in CH₂Cl₂ (6 mL) was added *N,N*-diisopropylethylamine (0.44 mL, 2.54 mmol) at 23 °C. The reaction mixture was stirred for 10 min at 23 °C and 4-nitrobenzenesulfonyl chloride (469 mg, 2.12 mmol) was added at 23 °C. The reaction mixture was stirred for 24 h at 23 °C and diluted with HCl 1N. The layers were separated and the organic layer was dried over anhydrous Na₂SO₄,



filtered and concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO₂) to yield **(R)-20** (791 mg, 80% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.60-8.38 (m, 2H), 8.31-8.06 (m, 2H), 6.10 (dd, *J* = 2.0, 1.3 Hz, 1H), 5.96 (d, *J* = 2.3 Hz, 1H), 4.80 (d, *J* = 8.0 Hz, 1H), 4.36 (d, *J* = 8.0 Hz, 1H), 1.63 (d, *J* = 5.9 Hz, 2H), 1.47-1.38 (m, 9H), 1.25 (s, 2H), 0.98-0.89 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 161.3, 151.7, 140.3, 130.0, 125.0, 102.0, 99.3, 80.7, 77.4, 52.9, 35.0, 29.9, 28.4, 19.2, 13.7, 1.2.

MS (ES⁺): *m/z* 491.1 [M+Na]⁺.

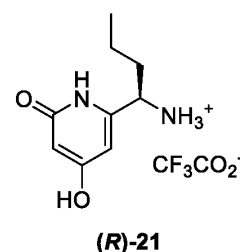
R_f: 0.55 (Hex:EtOAc 7:3).

10 Synthesis of intermediate **(R)-21**

A solution of **(R)-6** (31 mg, 0.11 mmol), CH₂Cl₂ (1.2 mL) and trifluoroacetic acid (0.34 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained **(R)-21** (100% yield) was used in the next step without further purification.

¹H NMR (300 MHz, CD₃OD): δ 6.38 (t, *J* = 1.8 Hz, 1H), 5.99 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.21 (td, *J* = 7.5, 1.3 Hz, 1H), 2.06-1.80 (m, 2H), 1.49-1.24 (m, 3H), 0.98 (td, *J* = 7.4, 1.3 Hz, 3H).

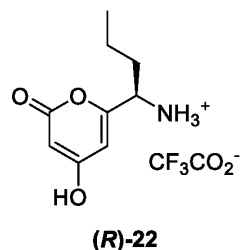
MS (ES): *m/z* 387.2 [2M+Na]⁺.



20 Synthesis of intermediate **(R)-22**

A solution of **(R)-7** (19 mg, 0.067 mmol), CH₂Cl₂ (0.7 mL) and trifluoroacetic acid (0.2 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid to obtain **(R)-22** crude (13 mg, 100% yield) which was used in the next step without further purification.

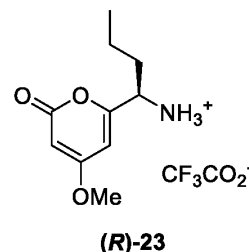
¹H NMR (300 MHz, CD₃OD): δ 6.33 (d, *J* = 1.0 Hz, 1H), 4.92 (s, 1H), 4.36-3.98 (m, 1H), 2.02-1.74 (m, 2H), 1.54-1.18 (m, 2H), 0.99 (td, *J* = 7.3, 1.9 Hz, 3H).



Synthesis of intermediate **(R)-23**

30 To a solution of **(R)-9** (5.39 g, 18.1 mmol) in CH₂Cl₂ (202 mL, 37.5 mL/g) at 23 °C was added trifluoroacetic acid (59.3 mL, 11 mL/g). The reaction mixture was stirred for 1.5 hours at 23 °C. Evaporation of the solvent under vacuum gave **(R)-23** crude that was used in the next step without further purification.

35 ¹H NMR (300 MHz, CDCl₃): δ 6.16 (s, 1H), 5.54 (s, 1H), 4.13 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 1.92 (q, *J* = 7.7 Hz, 2H), 1.29 (m, 2H), 0.93

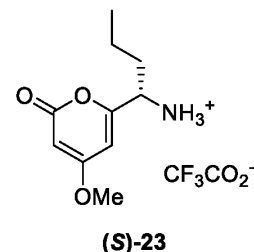


(t, $J = 7.3$ Hz, 3H), 0.87 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3): δ 171.5, 165.4, 157.5, 141.6, 117.7, 104.0, 103.3, 89.8, 56.7, 53.1, 33.2, 29.9, 18.8, 13.3.

Synthesis of analog (**S**)-23

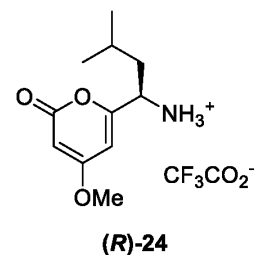
- 5 A solution of (**S**)-9 (253 mg, 0.85 mmol), CH_2Cl_2 (9.5 mL) and trifluoroacetic acid (2.8 mL) was stirred at 23 °C for 1 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained (**S**)-23 (100% yield) was used in the next step without further purification.



- 10 ^1H NMR (300 MHz, CD_3OD): δ 6.35 (dd, $J = 2.3, 0.8$ Hz, 1H), 5.69 (dd, $J = 2.3, 0.8$ Hz, 1H), 4.26-4.10 (m, 1H), 3.89 (d, $J = 0.8$ Hz, 3H), 2.04-1.76 (m, 2H), 1.47-1.23 (m, 2H), 1.03-0.89 (m, 3H).

Synthesis of intermediate (**R**)-24

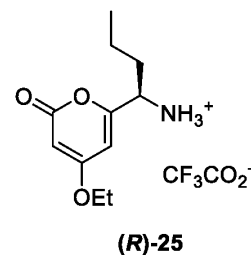
- 15 A solution of (**R**)-10 (74 mg, 0.24 mmol), CH_2Cl_2 (9 mL) and trifluoroacetic acid (2.6 mL) was stirred at 23 °C for 1 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained (**R**)-24 (100% yield) was used in the next step without further purification.



- 20 ^1H NMR (400 MHz, CDCl_3): δ 6.15 (d, $J = 2.1$ Hz, 1H), 5.49 (d, $J = 2.0$ Hz, 1H), 4.07 (dd, $J = 9.7, 5.8$ Hz, 1H), 3.81 (s, 3H), 1.82 (dd, $J = 9.3, 5.2$ Hz, 1H), 1.74-1.60 (m, 1H), 1.56-1.42 (m, 1H), 0.91 (d, $J = 6.5$ Hz, 6H).

Synthesis of intermediate (**R**)-25

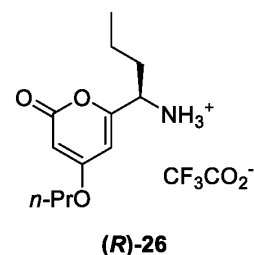
- 25 A solution of (**R**)-11 (37 mg, 0.112 mmol), CH_2Cl_2 (4 mL) and trifluoroacetic acid (1.23 mL) was stirred at 23 °C for 1h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained (**R**)-25 (100% yield) was used in the next step without further purification.



- 30 ^1H NMR (300 MHz, CD_3OD) δ 6.33 (dd, $J = 2.3, 1.2$ Hz, 1H), 5.65 (d, $J = 1.9$ Hz, 1H), 4.14 (dd, $J = 7.2, 1.2$ Hz, 3H), 2.04-1.76 (m, 2H), 1.46-1.24 (m, 4H), 0.98 (td, $J = 7.3, 1.3$ Hz, 3H).

Synthesis of intermediate **(R)-26**

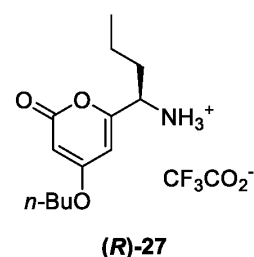
- A solution of **(R)-12** (35g, 0.1 mmol), CH₂Cl₂ (1.3 mL) and trifluoroacetic acid (0.37 mL) was stirred at 23 °C for 1 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained **(R)-26** (100%) was used in the next step without further purification.



¹H NMR (300 MHz, CD₃OD) δ 6.06 (dd, *J* = 2.3, 0.7 Hz, 1H), 5.52 (d, *J* = 2.2 Hz, 1H), 4.31 (dd, *J* = 9.2, 5.5 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 1.90-1.55 (m, 4H), 1.44 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

10 Synthesis of intermediate **(R)-27**

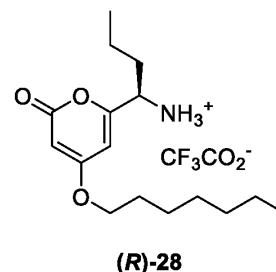
- A solution of **(R)-13** (34 mg, 0.14 mmol), CH₂Cl₂ (1.3 mL) and trifluoroacetic acid (0.37 mL) was stirred at 23 °C for 1 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained **(R)-27** (100%) was used in the next step without further purification.



¹H NMR (300 MHz, CD₃OD) δ 6.35 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.67 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.16 (ddd, *J* = 9.1, 6.3, 1.0 Hz, 1H), 4.07 (td, *J* = 6.4, 0.9 Hz, 2H), 2.04-1.67 (m, 4H), 1.59-1.22 (m, 4H), 0.98 (tdd, *J* = 7.4, 2.2, 0.8 Hz, 6H).

Synthesis of intermediate **(R)-28**

- 20 To a solution of **(R)-14** (76 mg) in CH₂Cl₂ (2.85 mL) was added trifluoroacetic acid (0.84 mL). After being stirred for 2 hours, the mixture was evaporated to dryness and then evaporated with toluene to remove trifluoroacetic acid to obtain **(R)-28**

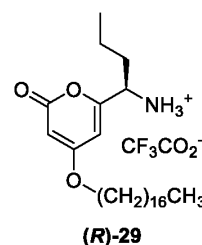


- ¹H NMR (400 MHz, CDCl₃): δ 6.14 (d, *J* = 2.1 Hz, 1H), 5.50 (d, *J* = 2.1 Hz, 1H), 4.13 (t, *J* = 7.5 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 1.91 (q, *J* = 7.7 Hz, 2H), 1.83-1.71 (m, 2H), 1.46-1.19 (m, 10H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.7, 165.4, 157.2, 104.0, 89.8, 69.9, 52.9, 32.9, 31.6, 28.8, 28.2, 25.6, 22.5, 18.5, 14.0, 13.1.

30 Synthesis of intermediate **(R)-29**

- A solution of **(R)-15** (91 mg, 0.174 mmol) in CH₂Cl₂ (3.5 mL) and trifluoroacetic acid (1.0 mL) was stirred at 23 °C for 1 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude containing **(R)-29** (116 mg, >100%) was used in the next step without further purification.

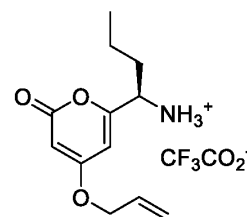


^1H NMR (400 MHz, CDCl_3): δ 6.16 (d, $J = 2.1$ Hz, 1H), 5.52 (d, $J = 2.1$ Hz, 1H), 4.14 (t, $J = 7.5$ Hz, 1H), 3.95 (t, $J = 6.5$ Hz, 2H), 1.92 (q, $J = 7.5$ Hz, 2H), 1.77 (dd, $J = 8.3, 6.2$ Hz, 2H), 1.44-1.21 (m, 32H), 0.93 (t, $J = 7.3$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.9, 165.7, 157.1, 104.2, 89.8, 70.0, 53.0, 32.9, 31.9, 29.7 (x2), 29.6, 29.5, 29.4, 29.2, 28.3, 25.6, 22.7, 18.6, 14.1, 13.1.

Synthesis of intermediate (**R**)-30

A solution of (**R**)-16 (5.0 g, 15.46 mmol) in CH_2Cl_2 (180 mL) and trifluoroacetic acid (55 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude containing (**R**)-30 (5.21 g, 100%) was used in the next step without further purification.



(**R**)-30

^1H NMR (400 MHz, CDCl_3): δ 6.38 (d, $J = 2.2$ Hz, 1H), 5.97-6.07 (m, 1H), 5.68 (d, $J = 2.2$ Hz, 1H), 5.32-5.46 (m, 2H), 4.63 (td, $J = 5.5, 1.5$ Hz, 2H), 4.18 (dd, $J = 8.9, 6.1$ Hz, 1H), 1.99-1.82 (m, 2H), 1.45-1.28 (m, 2H), 0.98 (t, $J = 7.3$ Hz, 3H).

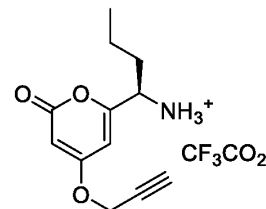
^{13}C NMR (100 MHz, CDCl_3): δ 169.8, 163.9, 157.7, 130.9, 118.2, 103.2, 89.9, 69.8, 52.0, 32.7, 18.2, 12.3.

MS (ES+): m/z 224.1 $[\text{M}+\text{H}]^+$.

Optical rotation: $[\alpha]_D -14.3$ (c 0.015, MeOH).

Synthesis of intermediate (**R**)-31

A solution of (**R**)-17 (2.31 g, 7.18 mmol) in CH_2Cl_2 (87 mL) and trifluoroacetic acid (25.4 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude containing (**R**)-31 was used in the next step without further purification.



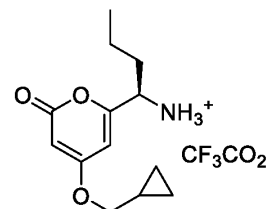
(**R**)-31

^1H NMR (400 MHz, CDCl_3): δ 8.48 (br s, 2H), 6.19 (d, $J = 2.0$ Hz, 1H), 5.67 (d, $J = 2.1$ Hz, 1H), 4.70 (t, $J = 2.0$ Hz, 2H), 4.14 (t, $J = 7.1$ Hz, 1H), 2.66 (t, $J = 2.3$ Hz, 1H), 1.92 (q, $J = 7.9$ Hz, 2H), 1.39-1.26 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 169.0, 164.6, 157.7, 103.6, 91.2, 78.2, 75.1, 57.0, 52.8, 32.9, 18.5, 13.1.

Synthesis of intermediate (**R**)-32

A solution of (**R**)-18 (8.9 g, 26.44 mmol) in CH_2Cl_2 (334 mL) and trifluoroacetic acid (98 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude containing (**R**)-32 (13.9 g, >100%) was used in the next step without further



(**R**)-32

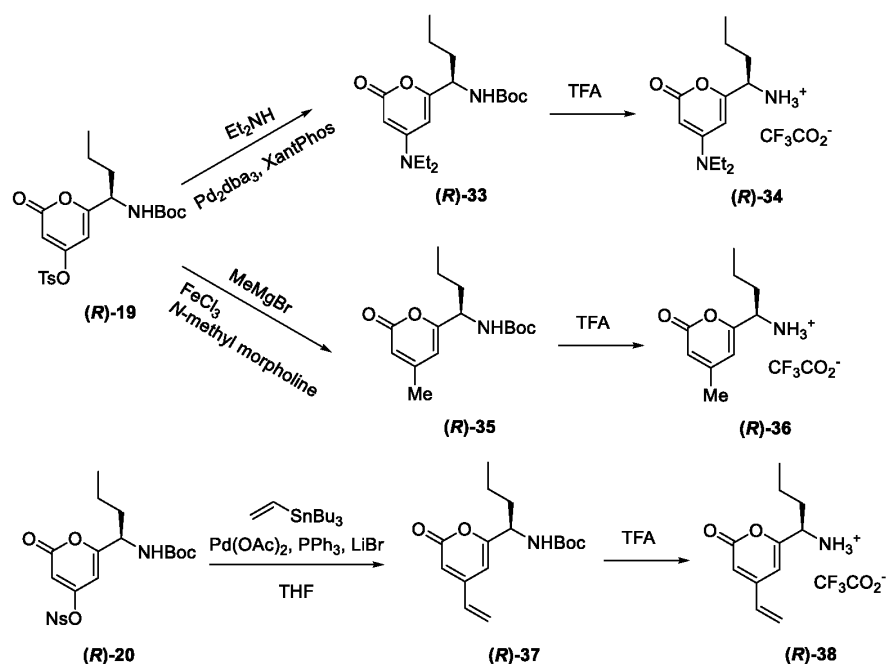
purification.

^1H NMR (400 MHz, CDCl_3): δ 8.51 (s, 2H), 6.18 (d, J = 1.8 Hz, 1H), 5.48 (s, 1H), 4.13 (t, J = 7.3 Hz, 1H), 3.80 (d, J = 7.2 Hz, 2H), 1.91 (q, J = 7.6 Hz, 2H), 1.38-1.18 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H), 0.72-0.62 (m, 2H), 0.39-0.30 (m, 2H).

5 ^{13}C NMR (100 MHz, CDCl_3): δ 170.6, 157.2, 104.2, 89.8, 74.7, 52.9, 32.8, 18.5, 13.1, 9.2, 3.4, 3.3.

Optical rotation: $[\alpha]_D$ -89 (c 0.037, MeOH).

Scheme 4 provides more examples of the synthesis of intermediates of formula II.

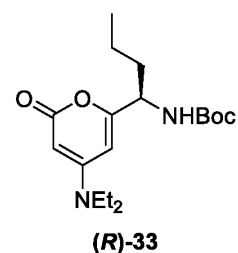


Scheme 4

Synthesis of intermediate (R)-33

To a mixture of $\text{Pd}_2(\text{dba})_3$ (10 mg, 0.115 mmol), XantPhos (13 mg, 0.023 mmol) and NaOtBu (33 mg, 0.34 mmol) was added (R)-19 (100 mg, 0.23 mmol) in 1,4-dioxane (2 mL) and diethylamine (0.034 mL, 0.69 mmol). The reaction was warmed to 105 $^\circ\text{C}$ for 4 h and then cooled to 23 $^\circ\text{C}$ and quenched with water. Extraction with CH_2Cl_2 gave a crude which was purified by flash chromatography over silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2) to afford (R)-33 (36 mg, 47% yield).

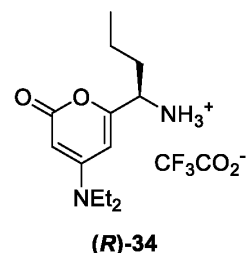
^1H NMR (300 MHz, CDCl_3) δ 5.88 (d, J = 2.4 Hz, 1H), 4.99 (d, J = 2.4 Hz, 1H), 4.34 (d, J = 8.4 Hz, 1H), 3.32 (dt, J = 12.0, 7.2 Hz, 4H), 1.89-1.55 (m, 6H), 1.42 (s, 9H), 1.19 (m, 3H), 0.92 (t, J = 7.3 Hz, 3H).



Synthesis of intermediate **(R)-34**

A solution of **(R)-33** (44 mg, 0.13 mmol), CH₂Cl₂ (1.65 mL) and trifluoroacetic acid (0.5 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained **(R)-34** (100% yield) was used in the next step without further purification.

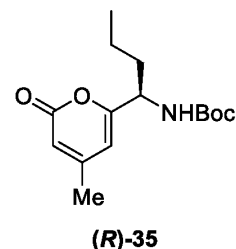
¹H NMR (300 MHz, CD₃OD) δ 6.55 (s, 1H), 4.89 (s, 1H), 4.17 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.46 (q, *J* = 7.1 Hz, 4H), 3.02 (m, 1H), 2.06-1.74 (m, 2H), 1.49-1.25 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.99 (t, *J* = 7.3 Hz, 3H).

10 Synthesis of intermediate **(R)-35**

To a solution of **(R)-19** (20 mg, 0.046 mmol), THF (0.2 mL), and FeCl₃ (0.4 mg, 0.0023 mmol), at -15 °C, was added *N*-methyl-morpholine (0.04 mL, 0.41 mmol), and 1.4 M methylmagnesium bromide in THF/tol. The reaction was allowed to reach 23 °C in 3 h and then quenched with a saturated aqueous solution of ammonium chloride. The extraction with EtOAc gave a crude which was purified by flash chromatography on silica gel (Hexane/EtOAc 8/2) to afford **(R)-35** (13 mg, 100% yield).

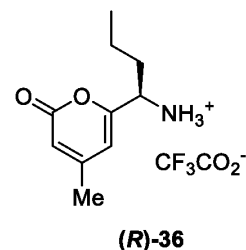
¹H NMR (300 MHz, CDCl₃) δ 5.99 (d, *J* = 1.5 Hz, 2H), 4.91 (d, *J* = 8.9 Hz, 1H), 4.37 (q, *J* = 7.9 Hz, 1H), 2.13 (d, *J* = 1.1 Hz, 3H), 1.84-1.54 (m, 4H), 1.42 (s, 9H), 0.92 (td, *J* = 7.5, 2.0 Hz, 3H).

20 MS (ES): *m/z* 304.1 [M+Na]⁺.

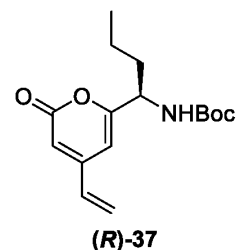
Synthesis of intermediate **(R)-36**

A solution of **(R)-35** (15 mg, 0.053 mmol), CH₂Cl₂ (1.8 mL) and trifluoroacetic acid (0.36 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude contained **(R)-36** (100% yield) was used in the next step without further purification.

¹H NMR (300 MHz, CDCl₃) δ 6.19 (d, *J* = 1.4 Hz, 1H), 6.07 (s, 1H), 4.19-3.99 (m, 1H), 2.16 (d, *J* = 1.4 Hz, 3H), 1.89 (t, *J* = 7.8 Hz, 2H), 1.46-1.07 (m, 2H), 1.00-0.74 (m, 3H).

30 Synthesis of intermediate **(R)-37**

To a solution of **(R)-20** (491 mg, 1.05 mmol) in THF (18 mL) was added palladium(II) acetate (12 mg, 0.05 mmol), triphenylphosphine (28 mg, 0.10 mmol) and lithium bromide (273 mg, 3.15 mmol) at 23 °C. The reaction mixture was turned to a yellow-to-orange, stirred for 10 min at 23 °C and tri-*n*-butyl(vinyl)tin (0.52 mL, 3.15 mmol) was added at 23 °C. The reaction mixture was refluxed for 1 h and concentrated under



vacuum. An aqueous solution of KF 2M was added to the crude and the mixture was stirred for 30 min at 23 °C. Filtration over Celite® and washing with Et₂O gave a crude which was purified in an automatic system for flash chromatography (SiO₂) to yield **(R)-37** (158 mg, 51% yield).

¹H NMR (400 MHz, CDCl₃): δ 6.53-6.41 (m, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 6.05 (d, *J* = 1.5 Hz, 1H), 5.92 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.63 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 4.43 (q, *J* = 8.1 Hz, 1H), 1.88-1.72 (m, 2H), 1.43 (s, 9H), 1.34 (dt, *J* = 15.8, 8.1 Hz, 2H), 0.94 (td, *J* = 7.3, 2.5 Hz, 3H).

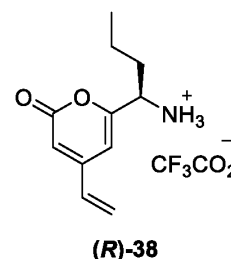
¹³C NMR (100 MHz, CDCl₃): δ 163.1, 162.9, 155.1, 151.6, 133.5, 130.5, 128.7, 128.6, 122.9, 111.3, 110.1, 99.9, 80.3, 77.5, 77.4, 77.2, 76.8, 67.6, 52.9, 35.5, 29.8, 29.6, 28.5, 27.0, 24.0, 22.3, 19.3, 13.7, 1.2.

MS (ES⁺): *m/z* 316.3 [M+Na]⁺.

R_f: 0.25 (Hex:EtOAc 4:1).

Synthesis of intermediate **(R)-38**

A solution of **(R)-37** (1.01 g, 3.44 mmol) in CH₂Cl₂ (37 mL) and trifluoroacetic acid (11 mL) was stirred at 23 °C for 2 h and then evaporated to dryness. The crude was evaporated three times with toluene to remove trifluoroacetic acid. The crude containing **(R)-38** (1.06 g, 100% yield) was used in the next step without further purification.



¹H NMR (400 MHz, CDCl₃): δ 6.79 (s, 3H), 6.62-6.44 (m, 2H), 6.18 (s, 1H), 6.01 (d, *J* = 17.5 Hz, 1H), 5.74 (d, *J* = 10.8 Hz, 1H), 4.26 (t, *J* = 7.5 Hz, 1H), 1.98 (q, *J* = 7.8 Hz, 2H), 1.46-1.28 (m, 2H), 0.98-0.81 (m, 3H).

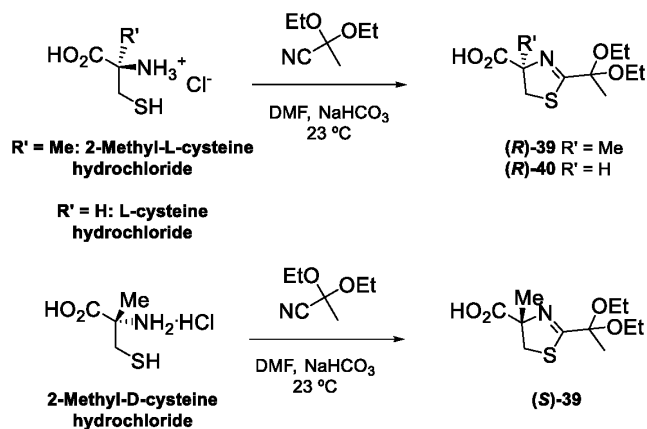
¹³C NMR (100 MHz, CDCl₃): δ 163.9, 160.9, 160.5, 160.1, 159.7, 156.4, 152.6, 132.5, 125.0, 116.6, 113.7, 112.3, 104.1, 53.6, 33.2, 29.9, 18.8, 17.7, 13.3.

MS (ES⁺): *m/z* 194.3 [M+H]⁺.

EXAMPLE 6 SYNTHESIS OF INTERMEDIATES OF FORMULA III

Scheme 5 provides some examples of the synthesis of an intermediate of formula III.

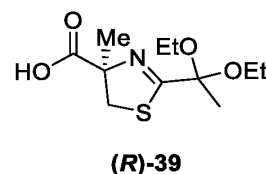
82



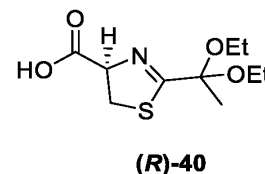
Scheme 5

Synthesis of intermediate **(R)-39**

- 2-Methyl-L-cysteine hydrochloride (Obtained following the procedure described in Recent Res. Devel. Organic Chem. 2004, 8, 323-339) (13 g, 75.74 mmol) was dissolved in the minimum quantity of H_2O , cooled at 0°C and basified with an aqueous saturated solution of NaHCO_3 until pH 8. Evaporation of the solvent under vacuum afforded the corresponding sodium salt which was dissolved in an aqueous saturated solution of NaHCO_3 (151 mL, 2 mL/mmol). The aqueous solution was cooled to 0°C and was added DMF (151 mL, 2 mL/mmol) and 2,2-diethoxypropanenitrile (20 mL, 128 mmol, 1.7 equiv). The reaction mixture was stirred overnight at 23°C . After cooling at 0°C , HCl 0.5 M was added until pH 2. The aqueous layer was extracted with a mixture 50:50 of Hex:EtOAc (x3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to afford crude **(R)-39** (11.39 g, 57% yield) which was used in the next step without further purification.
- ^1H NMR (300 MHz, CDCl_3): δ 3.72 (d, $J = 11.6$ Hz, 1H), 3.60-3.47 (m, 4H), 3.16 (d, $J = 11.6$ Hz, 1H), 1.59 (d, $J = 1.9$ Hz, 6H), 1.20 (t, $J = 7.1$, 6H).
- ^{13}C NMR (100 MHz, CDCl_3): δ 175.6, 163.3, 100.5, 84.5, 57.9, 57.9, 40.7, 24.2, 23.9, 15.4.
- Optical rotation: $[\alpha]_D -4.4$ (c 0.098, MeOH).

20 Synthesis of intermediate **(R)-40**

- To a solution of L-cysteine (250 mg, 2.06 mmol) in water (27 mL) and NaHCO_3 (2 g) at 0°C , were added DMF (27 mL) and 2,2-diethoxypropionitrile (0.42 mL, 2.7 mmol). The reaction was stirred for 24 h at 23°C and after cooling to 0°C 1M HCl was added to pH=2.
- The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give **(R)-40** (191 mg, 37% yield).

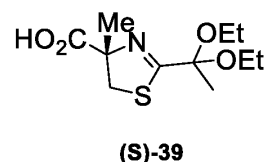


^1H NMR (300 MHz, CDCl_3): δ 5.31 (dd, $J = 10.1, 7.5$ Hz, 1H), 3.74-3.40 (m, 5H), 2.94 (d, $J = 26.1$ Hz, 1H), 1.59 (s, 3H), 1.20 (q, $J = 7.0$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 182.2, 175.2, 165.8, 103.0, 80.1, 60.3, 60.0, 39.3, 37.1, 34.2, 26.2, 17.7.

5 Synthesis of intermediate **(S)-39**

2-Methyl-D-cysteine hydrochloride (3.1 g, 17.9 mmol) was dissolved in the minimum quantity of H_2O , cooled at 0°C and basified with an aqueous saturated solution of NaHCO_3 until pH 8. Evaporation of the solvent under vacuum afforded the corresponding sodium salt



10 which was dissolved in a saturated aqueous solution of NaHCO_3 (35.8 mL, 2 mL/mmol). The aqueous solution was cooled to 0°C and was added DMF (35.8 mL, 2 mL/mmol) and 2,2-diethoxypropanenitrile (4.7 mL, 30.4 mmol, 1.7 equiv). The reaction mixture was stirred overnight at 23°C . After cooling at 0°C , HCl 0.5 M was added until pH 2. The aqueous layer was extracted with a mixture 50:50 of Hex:EtOAc (x3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to afford crude **(S)-39** (3.34 g, 71% yield) which was used in the next step without further purification.

^1H NMR (400 MHz, CDCl_3): δ 3.69 (dd, $J = 11.5, 0.7$ Hz, 1H), 3.54 (m, 4H), 3.12 (dd, $J = 11.6, 0.7$ Hz, 1H), 1.57 (d, $J = 0.7$ Hz, 3H), 1.56 (d, $J = 0.7$ Hz, 3H), 1.19 (tt, $J = 7.1, 0.8$ Hz, 6H).

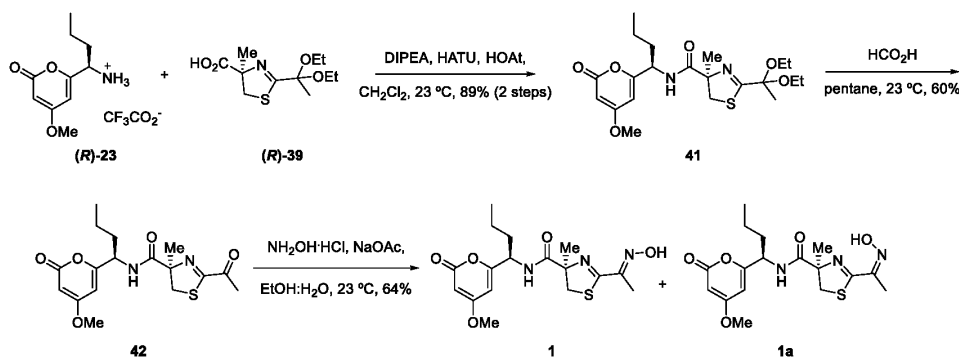
^{13}C NMR (100 MHz, CDCl_3): δ 176.3, 164.0, 101.5, 85.7, 58.9, 58.8, 37.8, 32.7, 24.9, 16.5, 16.4.

20 MS (ES+): m/z 262.3 $[\text{M}+\text{H}]^+$.

Optical rotation: $[\alpha_D] +4.6$ (c 0.096, MeOH).

EXAMPLE 7. SYNTHESIS OF COMPOUNDS **1** AND **1a**

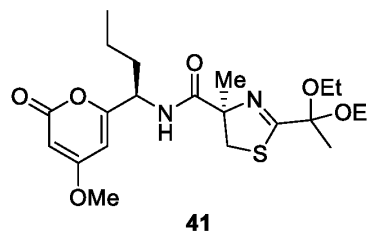
Scheme 6 provides an example of the synthesis of compounds **1** and **1a**



Scheme 6

Synthesis of intermediate **41**

To a solution of (*R*)-**23** (6.76 g, 21.7 mmol) and (*R*)-**39** (5.68 g, 21.7 mmol) in CH₂Cl₂ (152 mL) was sequentially added at 23 °C *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (17.02 g, 44.7 mmol, 2.06 equiv), 1-hydroxy-7-azabenzotriazole (HOAt) (6.2 g, 45.1 mmol, 2.08 equiv), and *N,N*-diisopropylethylamine (16.24 mL, 93 mmol, 4.29 equiv). The reaction mixture was stirred for 15 hours at 23 °C, diluted with CH₂Cl₂ and washed with an aqueous saturated solution of NaHCO₃, HCl 0.5 M, and an aqueous saturated solution of NaCl. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified by column chromatography (Hex:EtOAc, from 8:2 to 6:4) to give pure **41** (8.5 g, 89% for two steps).



¹H NMR (400 MHz, CDCl₃): δ 7.02 (d, *J* = 9.0 Hz, 1H), 5.96-5.70 (m, 1H), 5.45-5.33 (m, 1H), 4.72 (td, *J* = 8.5, 6.2 Hz, 1H), 3.77 (s, 3H), 3.67-3.43 (m, 5H), 3.15 (d, *J* = 11.7 Hz, 1H), 1.87 (ddt, *J* = 13.1, 9.7, 6.4 Hz, 1H), 1.71 (ddd, *J* = 9.6, 8.3, 5.5 Hz, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.44-1.28 (m, 2H), 1.22 (q, *J* = 7.2 Hz, 6H), 0.94 (t, *J* = 7.3 Hz, 3H).

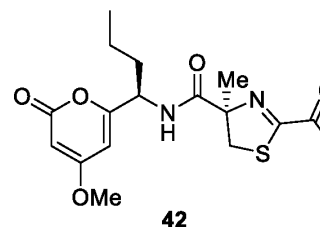
¹³C NMR (75 MHz, CDCl₃): δ 177.1, 174.7, 171.0, 164.1, 163.2, 100.5, 99.8, 88.6, 85.4, 58.0, 56.1, 51.0, 40.6, 34.9, 25.5, 24.0, 19.3, 15.4, 13.8.

MS (ES⁺): *m/z* 463.3 [M+Na]⁺.

R_f: 0.29 (Hex:EtOAc 1:1).

Synthesis of intermediate **42**

Over **41** (4.25 g, 9.6 mmol) was added at 23 °C pentane (255 mL, 60 mL/g) and formic acid (170 mL, 40 mL/g). The reaction mixture was stirred vigorously for 2 hours at 23 °C. The solvent was removed under vacuum. The obtained crude was purified by column chromatography (CH₂Cl₂:EtOAc, from 9:1 to 8:2) to obtain pure **42** (4.25 g, 60% yield).

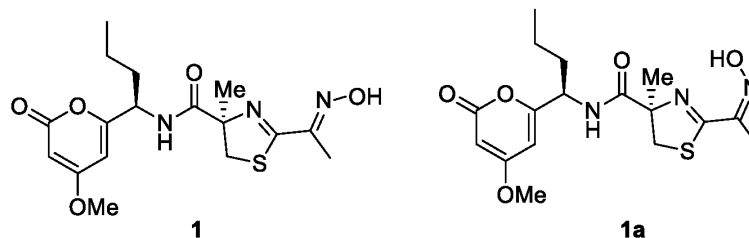


¹H NMR (400 MHz, CDCl₃): δ 7.01 (d, *J* = 8.9 Hz, 1H), 5.91 (dd, *J* = 2.2, 0.4 Hz, 1H), 5.42 (t, *J* = 2.1 Hz, 1H), 4.74 (q, *J* = 7.8 Hz, 1H), 3.82-3.75 (m, 3H), 3.63 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.28 (dd, *J* = 11.9, 0.9 Hz, 1H), 2.56 (d, *J* = 0.9 Hz, 3H), 1.95-1.73 (m, 1H), 1.54 (d, *J* = 2.0 Hz, 3H), 1.46-1.29 (m, 1H), 0.96 (td, *J* = 7.3, 1.7 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 193.1, 173.2, 170.8, 170.4, 164.0, 162.0, 100.3, 88.6, 86.1, 56.0, 51.1, 40.1, 34.8, 26.3, 24.5, 19.0, 13.5.

MS (ES⁺): *m/z* 367.1 [M+H]⁺, 389.1 [M+Na]⁺.

Synthesis of compounds **1** and **1a**



To a solution of **42** (4.25 g, 11.6 mmol) in ethanol (127.6 mL, 11 mL/mmol) and H₂O (127.6 mL, 11 mL/mmol) was added at 23 °C hydroxylamine hydrochloride (5.96 g, 84.7 mmol, 7.4 equiv) and sodium acetate (4.28 g, 52.2 mmol, 4.5 equiv). The reaction mixture was stirred for 24 hours at 23 °C. The solvent was removed under vacuum, the residue obtained was dissolved in H₂O and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified by semipreparative HPLC (X-Bridge Prep C18, 5 μm, 19 x 150 mm, isocratic H₂O:CH₃CN (62:38) flow: 15 mL/min, UV detection) to yield **1a** (320 mg, 7% yield, retention time: 6.0 min) and **1** (2.72 g, 64% yield, retention time: 9.3 min). Synthetic **1** exhibited physical, spectroscopic (¹H, ¹³C NMR and MS) and biological characteristics equivalent to those reported in Example 2.

Compound **1**

¹H NMR (500 MHz, CD₃OD): δ 6.08 (dd, *J* = 2.2, 0.7 Hz, 1H), 5.55 (d, *J* = 2.2 Hz, 1H), 4.72 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.84 (s, 3H), 3.59 (d, *J* = 11.7 Hz, 1H), 3.22 (d, *J* = 11.6 Hz, 1H), 2.17 (s, 3H), 1.87 (dddd, *J* = 13.7, 9.6, 6.6, 5.4 Hz, 1H), 1.82-1.69 (m, 1H), 1.55 (s, 3H), 1.53-1.32 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 176.5, 173.4, 170.3, 166.7, 165.2, 152.9, 100.8, 88.9, 85.6, 57.0, 52.1, 40.6, 35.2, 25.0, 20.2, 13.8, 11.0.

MS (ES⁺): *m/z* 382.3 [M+H]⁺, 404.1 [M+Na]⁺.

R_f: 0.36 (Hex:EtOAc 1:1).

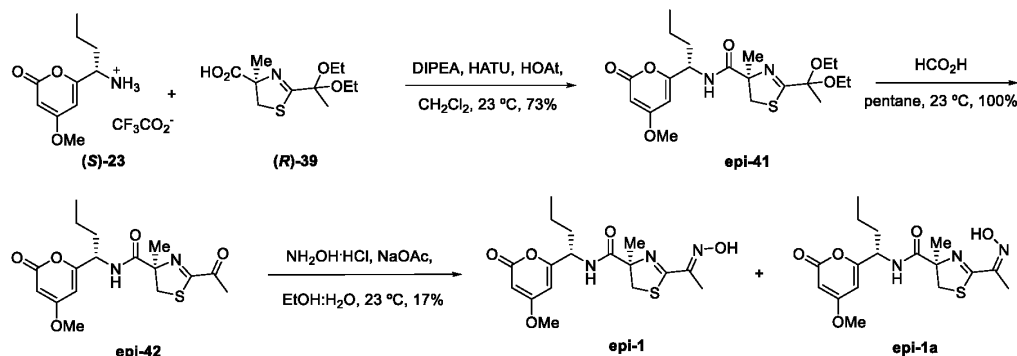
Compound **1a**

¹H NMR (500 MHz, CD₃OD): δ 6.08 (dd, *J* = 2.2, 0.7 Hz, 1H), 5.55 (d, *J* = 2.2 Hz, 1H), 4.72 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.84 (s, 3H), 3.59 (d, *J* = 11.7 Hz, 1H), 3.22 (d, *J* = 11.6 Hz, 1H), 2.17 (s, 3H), 1.87 (dddd, *J* = 13.7, 9.6, 6.6, 5.4 Hz, 1H), 1.82-1.69 (m, 1H), 1.55 (s, 3H), 1.53-1.32 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 173.5, 171.0, 164.6, 164.5, 162.4, 147.2, 100.1, 88.5, 83.6, 56.0, 51.0, 40.9, 35.0, 24.8, 19.2, 19.0, 13.5.

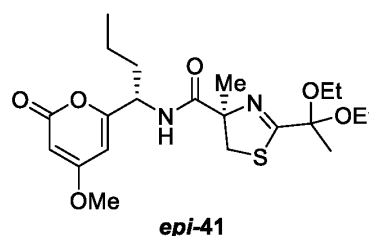
EXAMPLE 8. SYNTHESIS OF COMPOUNDS **epi-1** AND **epi-1a**

Scheme 7 provides a comparative example of the synthesis of compounds **epi-1** and **epi-1a**



Synthesis of analog **epi-41**

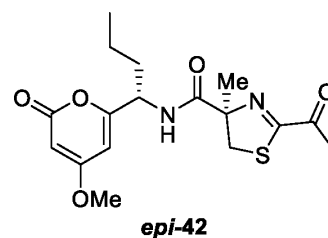
- 5 To a suspension of **(S)-23** (24 mg, 0.076 mmol) and **(R)-39** (19 mg, 0.076 mmol) in CH_2Cl_2 (0.5 mL) were added HATU (60 mg, 0.16 mmol), HOAt (22 mg, 0.16 mmol) and DIPEA (0.057 mL, 0.33 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH_2Cl_2 , washing of the organic layer with 0.5M HCl, with brine and then dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc from 9/1 to 7/3) to afford **epi-41** (33 mg, 73% yield).



- 15 ^1H NMR (500 MHz, CD_3OD): δ 6.15 (d, $J = 2.1$ Hz, 1H), 5.58 (d, $J = 2.2$ Hz, 1H), 4.67 (dd, $J = 9.3, 5.5$ Hz, 1H), 3.87 (s, 3H), 3.62 (d, $J = 11.7$ Hz, 1H), 3.66-3.47 (m, 4H), 3.24 (d, $J = 11.7$ Hz, 1H), 1.92-1.79 (m, 1H), 1.79-1.70 (m, 1H), 1.58 (s, 3H), 1.47 (s, 3H), 1.42-1.26 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 6H), 0.95 (t, $J = 7.4$ Hz, 3H).
- ^{13}C NMR (125 MHz, CD_3OD): δ 178.0, 176.6, 173.4, 166.6, 165.3, 111.4, 101.6, 100.8, 88.9, 86.2, 58.8, 58.8, 57.0, 52.3, 41.2, 35.3, 25.1, 24.2, 20.2, 15.5 (x2), 13.8.

20 Synthesis of analog **epi-42**

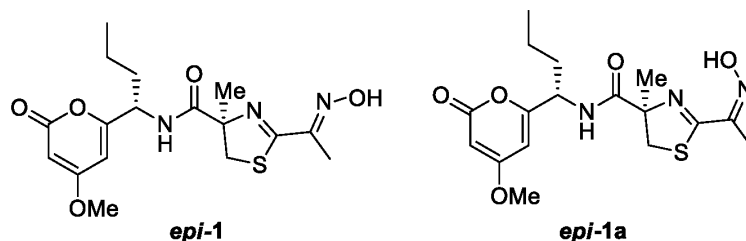
- To a mixture of **epi-41** (10 mg, 0.023 mmol) and pentane (0.6 mL) was added formic acid (0.4 mL). The reaction was stirred vigorously at 23 °C or 2 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving **epi-42** (100%).



- 25 ^1H NMR (500 MHz, CD_3OD): δ 6.15 (dd, $J = 2.2, 0.7$ Hz, 1H), 5.59 (d, $J = 2.2$ Hz, 1H), 4.71 (dd, $J = 9.3, 5.8$ Hz, 1H), 3.87 (s, 3H), 3.71 (d, $J = 11.8$ Hz, 1H), 3.32 (d, $J = 11.9$ Hz, 1H), 1.96-1.67 (m, 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.47-1.27 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ 194.9, 175.6, 173.5, 171.7, 166.8, 165.3, 100.9, 88.9, 87.4, 57.1, 52.4, 41.3, 35.0, 24.5, 20.3, 20.2, 13.8.

Synthesis of analogs **epi-1** and **epi-1a**



- 5 To a solution of **epi-44** (8 mg, 0.023 mmol) in ethanol (0.5 mL) and water (0.5 mL), were added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (11 mg, 0.16 mmol) and NaOAc (8 mg, 0.10 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and after evaporation of the solvent; the obtained crude was purified by HPLC method, using an XBridge C18 5 μm
- 10 $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to give **epi-1a** (0.6 mg) and **epi-1** (1.5 mg, 17% yield).

Analog **epi-1a**

- ^1H NMR (500 MHz, CD_3OD): δ 6.16 (dq, $J = 2.3, 0.8$ Hz, 1H), 5.61-5.56 (m, 1H), 4.69 (dd, $J = 9.2, 5.8$ Hz, 1H), 3.87 (t, $J = 0.8$ Hz, 3H), 3.57 (dt, $J = 11.5, 0.8$ Hz, 1H), 3.19 (dt, $J = 11.5, 0.8$ Hz, 1H), 2.19 (t, $J = 0.8$ Hz, 3H), 1.93-1.68 (m, 2H), 1.51 (t, $J = 0.9$ Hz, 3H), 1.35 (m, 1H), 0.98-0.90 (m, 3H).
- 15

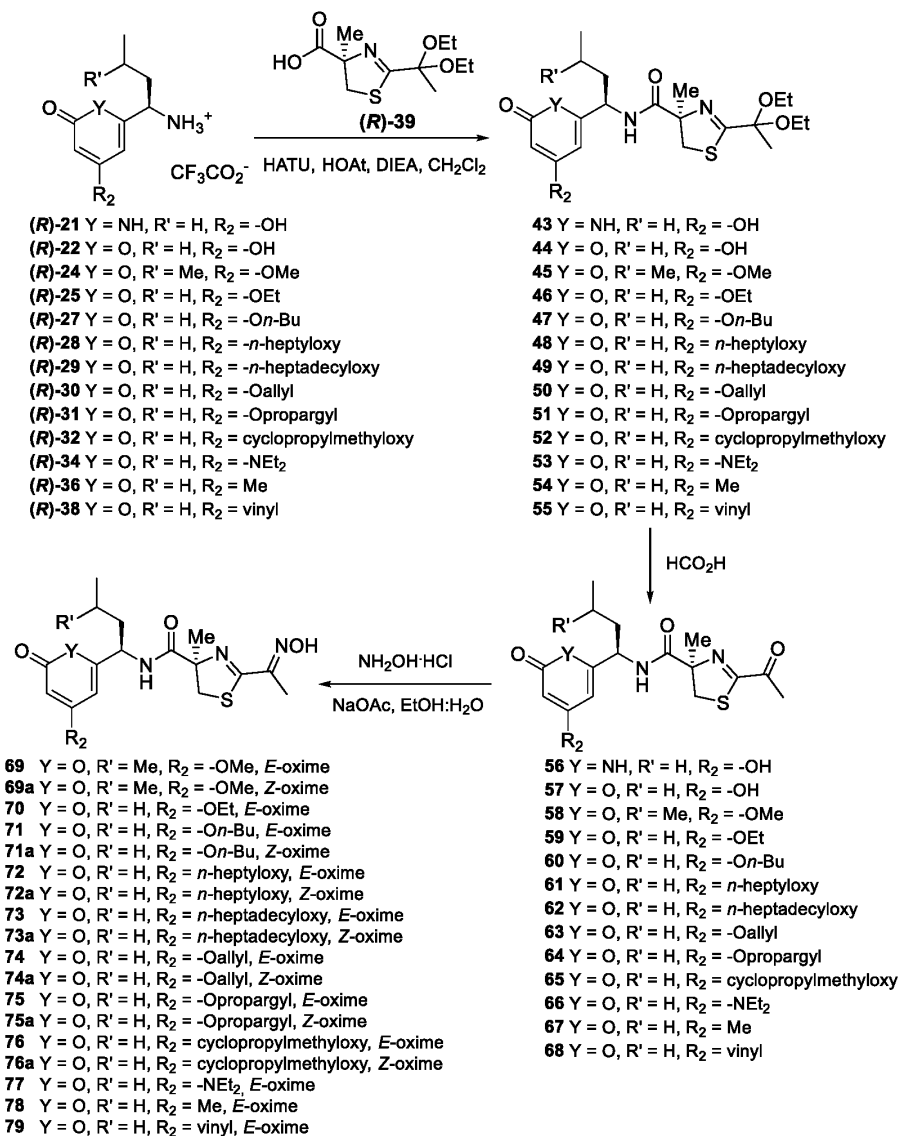
^{13}C NMR (125 MHz, CD_3OD): δ 176.5, 173.4, 170.1, 166.6, 165.2, 152.8, 100.7, 88.7, 85.4, 56.9, 52.2, 40.5, 35.0, 24.8, 20.1, 13.7, 10.8.

Analog **epi-1**

- ^1H NMR (500 MHz, CD_3OD) δ 6.13 (d, $J = 2.2$ Hz, 1H), 5.57 (d, $J = 2.2$ Hz, 1H), 4.68 (td, $J = 8.9, 5.6$ Hz, 1H), 3.86 (s, 3H), 3.60 (d, $J = 11.7$ Hz, 1H), 3.21 (d, $J = 11.6$ Hz, 1H), 2.16 (s, 3H), 1.82 (dd, $J = 9.3, 6.0$ Hz, 1H), 1.73 (dd, $J = 9.2, 4.8$ Hz, 1H), 1.52 (s, 4H), 1.46-1.26 (m, 1H), 0.93 (t, $J = 7.4$ Hz, 3H).
- 20

EXAMPLE 9. SYNTHESIS OF MORE COMPOUNDS OF FORMULA I

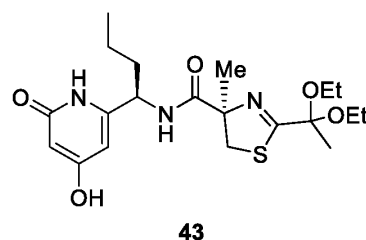
Scheme 8 provides another example of the synthesis of more compounds of formula I.



Scheme 8

5 Compound 43

To a suspension of **(R)-21** (20 mg, 0.11 mmol) and **(R)-39** (27 mg, 0.11 mmol) in CH₂Cl₂ (1.3 mL) were added HATU (43 mg, 0.11 mmol), HOAt (16 mg, 0.11 mmol) and DIPEA (0.082 mL, 0.47 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic



layer with 0.5M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/CH₃OH 98/2) to afford **43** (46 mg, 100% yield).

- ¹H NMR (300 MHz, CD₃OD): δ 5.90 (m, 1H), 5.66 (m, 1H), 4.76 (q, *J* = 7.7 Hz, 1H), 3.71-3.45 (m, 5H), 3.26-3.17 (m, 1H), 1.79 (q, *J* = 7.7 Hz, 2H), 1.59 (d, *J* = 1.9 Hz, 3H), 1.50 (d, *J* = 0.7 Hz, 3H), 1.37 (m, 2H), 1.28-1.14 (m, 6H), 1.06-0.89 (m, 3H).
MS (ES): *m/z* 448.3 [M+Na]⁺, 851.4 [2M+H]⁺.

Compound **44**

- To a suspension of (*R*)-**22** (12 mg, 0.067 mmol) and (*R*)-**39** (16 mg, 0.067 mmol) in CH₂Cl₂ (0.8 mL) were added HATU (26 mg, 0.067 mmol), HOAt (10 mg, 0.067 mmol) and DIPEA (0.05 mL, 0.29 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/CH₃OH 98/2) to afford **44** (31 mg, 100% yield).

- ¹H NMR (400 MHz, CDCl₃): δ 7.21 (d, *J* = 8.9 Hz, 1H), 6.04-5.98 (m, 1H), 5.51 (dd, *J* = 2.2, 0.5 Hz, 1H), 4.71 (td, *J* = 8.5, 6.7 Hz, 1H), 3.65-3.43 (m, 5H), 3.23-3.12 (m, 1H), 2.81 (s, 3H), 1.80 (dddd, *J* = 51.2, 17.5, 9.1, 5.1 Hz, 1H), 1.52 (s, 3H), 1.51-1.25 (m, 3H), 1.22 (dtd, *J* = 7.8, 7.1, 0.6 Hz, 4H), 0.94 (t, *J* = 7.3 Hz, 3H).

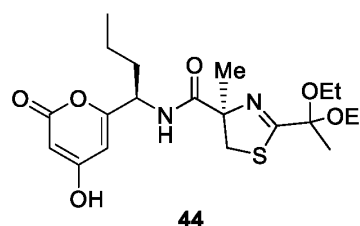
- ¹³C NMR (100 MHz, CDCl₃): δ 177.6, 175.2, 170.7, 170.6, 165.9, 165.4, 163.3, 100.8, 100.4, 91.0, 85.1, 57.9 (x2), 55.7, 51.4, 43.7, 40.5, 38.8, 34.7, 25.2, 23.9, 19.2, 18.8, 17.4, 15.4, 13.7, 12.7.

MS (ES): *m/z* 449.1 [M+Na]⁺.

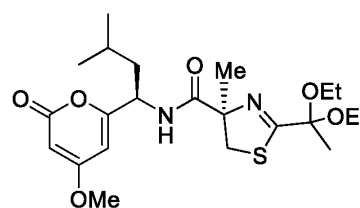
Compound **45**

- To a suspension of (*R*)-**39** (63 mg, 0.24 mmol) and (*R*)-**24** (74 mg, 0.24 mmol) in CH₂Cl₂ (2.2 mL) were added HATU (188 mg, 0.49 mmol), HOAt (69 mg, 0.49 mmol) and DIPEA (0.18 mL, 1.03 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5 M HCl and brine and, finally, dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 9/1 to 7/3) to obtain **45** (50 mg, 47% yield).

- ¹H NMR (300 MHz, CDCl₃): δ 7.03 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 2.3 Hz, 1H), 5.37 (d, *J* = 2.2 Hz, 1H), 4.78 (td, *J* = 8.9, 6.0 Hz, 1H), 3.76 (s, 3H), 3.67-3.41 (m, 5H), 3.14 (d, *J* = 11.7 Hz, 1H), 1.74-1.62 (m, 1H), 1.60 (s, 2H), 1.59 (s, 3H), 1.51 (s, 3H), 1.29-1.14 (m, 6H), 0.93 (dd, *J* = 6.2, 3.5 Hz, 6H).



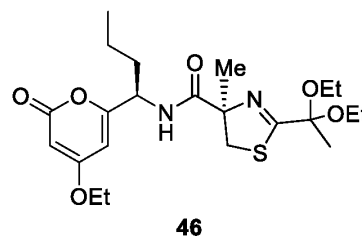
44



45

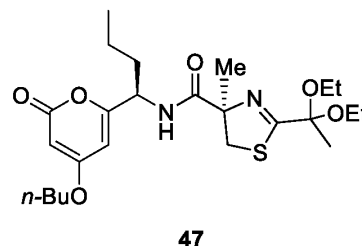
Compound 46

- To a suspension of (*R*)-**25** (24 mg, 0.112 mmol) and (*R*)-**39** (29 mg, 0.112 mmol) in CH₂Cl₂ (1 mL) were added HATU (88 mg, 0.23 mmol), HOAt (32 mg, 0.23 mmol) and DIPEA (0.083 mL, 0.48 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc from 9/1 to 7/3) to afford **46** (38 mg, 73% yield).
- ¹H NMR (300 MHz, CDCl₃) δ 7.00 (d, *J* = 8.9 Hz, 1H), 5.81 (d, *J* = 2.0 Hz, 1H), 5.34 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.70 (td, *J* = 8.5, 6.2 Hz, 1H), 4.03-3.90 (m, 2H), 3.64-3.42 (m, 5H), 3.13 (dd, *J* = 11.7, 0.9 Hz, 1H), 1.84 (m, 1H), 1.68 (m, 1H), 1.59 (d, *J* = 0.9 Hz, 3H), 1.54-1.48 (m, 3H), 1.37 (td, *J* = 7.0, 0.9 Hz, 3H), 1.24-1.14 (m, 6H), 0.97-0.88 (m, 3H).
- MS (ES): *m/z* 477.2 [M+Na]⁺.



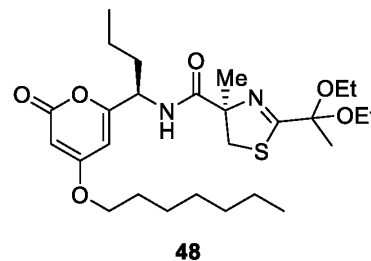
Compound 47

- To a suspension of (*R*)-**27** (24 mg, 0.1 mmol) and (*R*)-**39** (26 mg, 0.11 mmol) in CH₂Cl₂ (1 mL) were added HATU (39 mg, 0.103 mmol), HOAt (14 mg, 0.104 mmol) and DIPEA (0.075 mL, 0.43 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5 M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/EtOAc 9/1) to afford **47** (48 mg, 100% yield).
- ¹H NMR (300 MHz, CDCl₃) δ 7.02 (d, *J* = 8.9 Hz, 1H), 5.82 (dt, *J* = 2.2, 0.6 Hz, 1H), 5.35 (d, *J* = 2.2 Hz, 1H), 4.72 (td, *J* = 8.7, 6.2 Hz, 1H), 3.90 (t, *J* = 6.4 Hz, 2H), 3.67-3.45 (m, 5H), 3.15 (dd, *J* = 11.7, 0.6 Hz, 1H), 1.97-1.62 (m, 4H), 1.60 (d, *J* = 0.6 Hz, 3H), 1.53 (s, 3H), 1.51-1.30 (m, 4H), 1.26-1.13 (m, 6H), 1.00-0.85 (m, 6H).
- MS (ES): *m/z* 505.3 [M+Na]⁺.
- R_f: 0.62 (Hex:EtOAc 1:1).



Compound 48

- A mixture of (*R*)-**28** (0.199 mmol) and (*R*)-**39** (55 mg) was coevaporated with toluene and then HATU (82 mg) and HOAt (30 mg) were added. Reaction flask was evacuated and filled with N₂. CH₂Cl₂ (2 mL) and DIPEA (156 μL) were introduced via syringe. The mixture was stirred at 23 °C for 16 h. Then, it was diluted with CH₂Cl₂ before washing twice



with HCl 0.5 N and once with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. Crude residue was purified on a system for flash chromatography with a SiO₂ column eluting with mixtures of hexane/EtOAc from 100:0 to 50:50 in 15 min to afford **48** (71 mg, 68% yield).

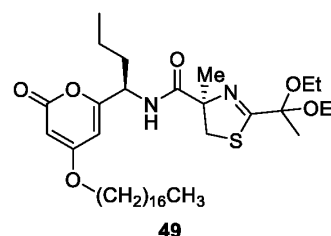
5 ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.9 Hz, 1H), 5.82 (dd, *J* = 2.2, 0.6 Hz, 1H), 5.34 (d, *J* = 2.2 Hz, 1H), 4.71 (td, *J* = 8.5, 6.2 Hz, 1H), 3.88 (td, *J* = 6.5, 1.1 Hz, 2H), 3.60 (d, *J* = 11.7 Hz, 1H), 3.60-3.44 (m, 4H), 3.14 (d, *J* = 11.7 Hz, 1H), 1.85 (ddt, *J* = 13.6, 9.6, 6.3 Hz, 1H), 1.78-1.61 (m, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.44-1.24 (m, 10H), 1.24-1.17 (m, 6H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H).

10 ¹³C NMR (100 MHz, CDCl₃): δ 176.7, 174.4, 170.1, 164.0, 162.8, 100.2, 99.8, 88.6, 85.2, 69.0, 57.7, 57.6, 50.7, 40.3, 34.7, 31.6, 28.8, 28.3, 25.7, 25.3, 23.7, 22.5, 19.0, 15.2, 14.0, 13.5.

Compound **49**

To a solution of (*R*)-**29** (93 mg, 0.174 mmol) and (*R*)-**39** (48 mg, 0.183 mmol) in CH₂Cl₂ (1.2 mL) was sequentially added

15 *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (72 mg, 0.188 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (26 mg, 0.190 mmol), and *N,N*-diisopropylethylamine (137 μL, 0.785 mmol) at 23 °C. The



20 reaction mixture was stirred overnight at 23 °C, diluted with CH₂Cl₂ and washed HCl 0.5 M. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO₂, Hex:EtOAc) to obtain **49** (91 mg, 78% yield for 2 steps).

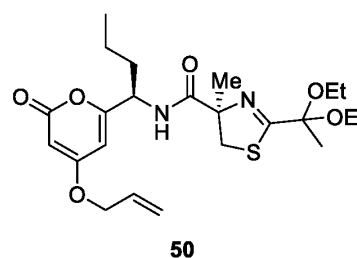
25 ¹H NMR (400 MHz, CDCl₃): δ 7.03 (d, *J* = 8.9 Hz, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.35 (d, *J* = 2.2 Hz, 1H), 4.72 (td, *J* = 8.6, 6.2 Hz, 1H), 3.89 (td, *J* = 6.6, 1.1 Hz, 2H), 3.61 (d, *J* = 11.7 Hz, 1H), 3.61-3.45 (m, 4H), 3.15 (d, *J* = 11.7 Hz, 1H), 1.93-1.79 (m, 1H), 1.79-1.62 (m, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.44-1.23 (m, 32H), 1.24-1.18 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H).

30 ¹³C NMR (100 MHz, CDCl₃): δ 176.8, 174.4, 170.1, 164.0, 162.8, 100.2, 99.9, 88.6, 85.2, 69.0, 57.7, 57.6, 50.8, 40.3, 34.7, 31.9, 29.7, 29.6, 29.5 (x2), 29.3, 29.2, 28.4, 25.8, 25.3, 23.7, 22.7, 19.0, 15.2, 14.1, 13.5.

Compound **50**

To a solution of (*R*)-**30** (5.20 g, 15.42 mmol) and (*R*)-**39** (4.03 g, 15.42 mmol) in CH₂Cl₂ (110 mL) was sequentially

35 added *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (7.20 g, 18.50 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (2.60 g, 19.00 mmol), and *N,N*-diisopropylethylamine (1.37 mL, 10.90 mmol) at 23 °C. The



tetramethyluronium hexafluorophosphate (HATU) (5.86 g, 15.42 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (2.11 g, 15.42 mmol), and *N,N*-diisopropylethylamine (10.74 mL, 61.66 mmol) at 23 °C. The reaction mixture was stirred overnight at 23 °C, diluted with CH₂Cl₂ and washed HCl 0.5 M. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified by in an automatic system for flash chromatography (SiO₂, Hex:EtOAc 50:50) to obtain **50** (6.08 g, 85% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.02 (d, *J* = 8.9 Hz, 1H), 6.01-5.88 (m, 1H), 5.86 (dd, *J* = 2.2, 0.6 Hz, 1H), 5.46-5.24 (m, 3H), 4.72 (td, *J* = 8.5, 6.3 Hz, 1H), 4.46 (dt, *J* = 5.5, 1.5 Hz, 1H), 3.70-3.39 (m, 5H), 3.16 (d, *J* = 11.6 Hz, 1H), 1.92-1.83 (m, 1H), 1.75-1.66 (m, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.40-1.28 (m, 2H), 1.25-1.17 (m, 6H), 0.93 (td, *J* = 7.4, 2.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 176.8, 174.5, 169.6, 163.8, 163.1, 130.6, 119.5, 100.2, 99.7, 89.2, 85.2, 69.5, 57.8, 57.7, 50.8, 40.4, 34.7, 25.3, 23.7, 19.0, 15.2, 13.5.

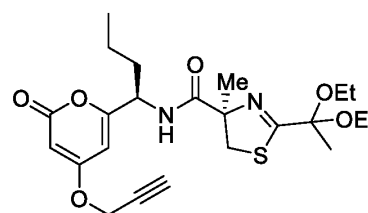
MS (ES⁺): 489.2 [M+Na]⁺.

Optical rotation: [α]_D +51.5 (c 0.037, MeOH).

R_f: 0.25 (Hex:EtOAc 7:3).

Compound 51

To a solution of (*R*)-**31** (2.41 g, 7.18 mmol) and (*R*)-**39** (1.98 g, 7.56 mmol) in CH₂Cl₂ (53 mL) was sequentially added *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*,*N'*-



51

tetramethyluronium hexafluorophosphate (HATU) (2.96 g, 7.79 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (1.08 g, 7.87 mmol), and *N,N*-diisopropylethylamine (5.6 mL, 32.46 mmol) at 23 °C. The reaction mixture was stirred overnight at 23 °C, diluted with CH₂Cl₂ and washed HCl 0.5 M. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO₂, Hex:EtOAc from 10:0 to 50:50) to obtain **51** (3.37 g, 100% yield for 2 steps).

¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.9 Hz, 1H), 5.86 (dd, *J* = 2.3, 0.6 Hz, 1H), 5.52 (d, *J* = 2.3 Hz, 1H), 4.72 (td, *J* = 8.6, 6.2 Hz, 1H), 4.63 (d, *J* = 2.5 Hz, 2H), 3.60 (d, *J* = 11.8 Hz, 1H), 3.63-3.43 (m, 4H), 3.15 (d, *J* = 11.8 Hz, 1H), 2.62 (t, *J* = 2.4 Hz, 1H), 1.86 (ddt, *J* = 13.6, 9.6, 6.3 Hz, 1H), 1.76-1.62 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.45-1.28 (m, 2H), 1.27-1.16 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 176.9, 174.5, 168.6, 163.4 (2x), 100.2, 99.3, 89.9, 85.1, 77.7, 75.6, 57.7, 57.6, 56.4, 50.8, 40.3, 34.6, 25.3, 23.7, 19.0, 15.2, 13.5.

MS (ES⁺): 487.3 [M+Na]⁺.

R_f: 0.35 (Hex:EtOAc 50:50).

Compound 52

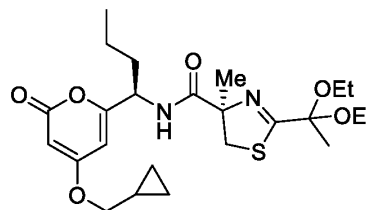
To a solution of (*R*)-**32** (9.28 g, 26.41 mmol) and (*R*)-**39** (6.90 g, 26.41 mmol) in CH₂Cl₂ (180 mL) was sequentially added *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (10.04 g, 26.41 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (3.62 g, 26.41 mmol), and *N,N*-diisopropylethylamine (18.4 mL, 105.66 mmol) at 23 °C. The reaction mixture was stirred overnight at 23 °C, diluted with CH₂Cl₂ and washed HCl 0.5 M. The aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The obtained crude was purified by in an automatic system for flash chromatography (SiO₂, Hex:EtOAc 50:50) to obtain **52** (12.1 g, 95% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.03 (d, *J* = 8.9 Hz, 1H), 5.85 (dd, *J* = 2.2, 0.5 Hz, 1H), 5.31 (d, *J* = 2.2 Hz, 1H), 4.71 (td, *J* = 8.5, 6.2 Hz, 1H), 3.80-3.67 (m, 2H), 3.61 (d, *J* = 11.8 Hz, 1H), 3.61-3.42 (m, 4H), 3.14 (d, *J* = 11.7 Hz, 1H), 1.86 (ddt, *J* = 13.7, 9.5, 6.3 Hz, 1H), 1.75-1.62 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.45-1.15 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.74-0.58 (m, 2H), 0.38-0.27 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 176.8, 174.4, 170.0, 163.9, 162.9, 100.2, 99.8, 88.6, 85.2, 73.7, 57.7, 57.6, 50.8, 40.3, 34.7, 25.3, 23.7, 19.0, 15.2, 13.5, 9.4, 3.3 (x2).

MS (ES⁺): 503.3 [M+Na]⁺.

R_f: 0.49 (Hex:EtOAc 1:1).

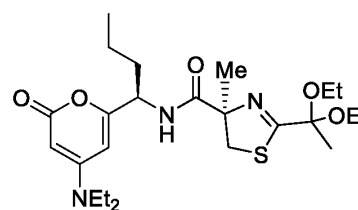


52

Compound **53**

To a suspension of (*R*)-**34** (31 mg, 0.13 mmol) and (*R*)-**39** (34 mg, 0.13 mmol) in CH₂Cl₂ (1.5 mL) were added HATU (51 mg, 0.13 mmol), HOAt (19 mg, 0.13 mmol) and DIPEA (0.1 mL, 0.56 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5 M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/CH₃OH 98/2) to afford **53** (38 mg, 60% yield).

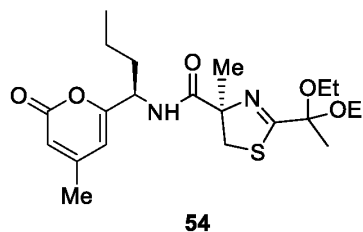
¹H NMR (300 MHz, CDCl₃) δ 7.04 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 2.3 Hz, 1H), 4.96 (d, *J* = 2.3 Hz, 1H), 4.67 (td, *J* = 8.4, 6.8 Hz, 1H), 3.68-3.42 (m, 5H), 3.29 (qd, *J* = 7.3, 3.5 Hz, 4H), 3.14 (d, *J* = 11.7 Hz, 1H), 1.95-1.64 (m, 2H), 1.60 (s, 3H), 1.53 (s, 3H), 1.34 (dd, *J* = 9.8, 6.8 Hz, 2H), 1.28-1.08 (m, 12H), 0.93 (t, *J* = 7.3 Hz, 3H).



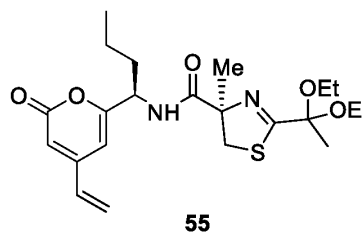
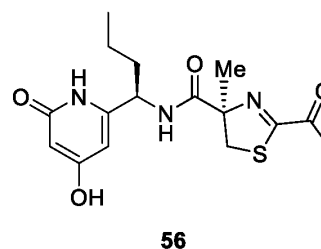
53

Compound **54**

- To a suspension of (*R*)-**36** (10 mg, 0.053 mmol) and (*R*)-**39** (14 mg, 0.053 mmol) in CH₂Cl₂ (0.4 mL) were added
- 5 HATU (42 mg, 0.10 mmol), HOAt (15 mg, 0.10 mmol) and DIPEA (0.040 mL, 0.22 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5 M HCl, with brine and then dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂/EtOAc 6/4) to afford **54** (7 mg, 100% yield).
- ¹H NMR (300 MHz, CDCl₃) δ 7.08 (d, *J* = 8.9 Hz, 1H), 5.96 (t, *J* = 1.3 Hz, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 4.72 (td, *J* = 8.5, 6.6 Hz, 1H), 3.75-3.45 (m, 5H), 3.36 (d, *J* = 11.8 Hz, 1H), 2.10 (d, *J* = 1.2 Hz, 3H), 1.89-1.68 (m, 2H), 1.66 (s, 3H), 1.46-1.27 (m, 8H), 0.93 (t, *J* = 7.3 Hz, 3H).
- MS (ES): *m/z* 447.2 [M+Na]⁺.
- 15 R_f: 0.33 (Hex:EtOAc 1:1).

Compound **55**

- To a suspension of (*R*)-**38** (1.06 g, 3.45 mmol) and (*R*)-**39** (1.1 g, 3.45 mmol) in CH₂Cl₂ (24 mL) was sequentially added *O*-(7-azabenzotriazol-1-yl)-*N,N,N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (1.3 g, 3.45 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (473 mg, 3.45 mmol), and *N,N*-diisopropylethylamine (2.4 mL, 13.79 mmol) at 23 °C. The reaction mixture was stirred overnight at 23 °C, filtered through Celite® and the filtrate was concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO₂, Hex:EtOAc) to obtain **55** (1.35 g, 90% yield).
- 20 ¹H NMR (400 MHz, CDCl₃): δ 6.45 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.33 (d, *J* = 1.5 Hz, 1H), 6.04-5.99 (m, 1H), 5.94 (d, *J* = 17.5 Hz, 1H), 5.61 (d, *J* = 10.8 Hz, 1H), 4.79 (td, *J* = 8.5, 6.3 Hz, 1H), 3.81 (d, *J* = 11.8 Hz, 1H), 3.64-3.45 (m, 4H), 3.19 (d, *J* = 11.8 Hz, 1H), 1.94-1.83 (m, 1H), 1.82-1.70 (m, 1H), 1.64 (s, 6H), 1.45-1.29 (m, 2H), 1.23 (td, *J* = 7.1, 2.6 Hz, 6H), 0.95 (t, *J* = 7.4 Hz, 3H).
- 30 ¹³C NMR (75 MHz, CDCl₃): δ 162.6, 151.4, 133.5, 123.1, 111.4, 100.4, 99.7, 58.2, 58.1, 51.6, 40.5, 35.1, 25.5, 24.0, 19.3, 15.3, 13.7.
- MS (ES+): *m/z* 459.2 [M+Na]⁺.
- R_f: 0.43 (Hex:EtOAc 1:1).

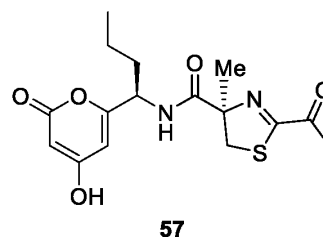
35 Compound **56**

To a mixture of **43** (46 mg, 0.11 mmol) and pentane (3.4 mL) was added formic acid (2.3 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **56** (100%) which was used in the next step without further purification.

- 5 MS (ES): m/z 352.2 $[M+H]^+$, 703.2 $[2M+H]^+$.

Compound 57

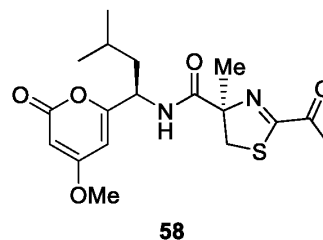
- 10 To a mixture of **44** (16 mg, 0.034 mmol) and pentane (0.96 mL) was added formic acid (0.64 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **57** (13 mg, 100% yield) which was used in the next step without further purification.



- ¹H NMR (500 MHz, CDCl₃) δ 7.16 (d, J = 8.4 Hz, 1H), 6.09 (d, J = 2.0 Hz, 1H), 5.58 (d, J = 2.1 Hz, 1H), 4.75 (td, J = 8.5, 7.0 Hz, 1H), 3.60 (d, J = 11.9 Hz, 1H), 3.30 (d, J = 11.9 Hz, 1H), 2.57 (s, 3H), 1.98-1.76 (m, 2H), 1.56 (s, 3H), 1.51-1.31 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).
 15 MS (ES): m/z 375.1 $[M+Na]^+$, 727.1 $[2M+Na]^+$.

Compound 58

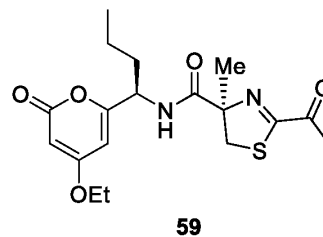
- 20 To a mixture of **45** (57 mg, 0.13 mmol) and pentane (3.4 mL) was added formic acid (2.3 mL). The reaction was stirred vigorously at 23 °C for 2 h and then evaporated to dryness with toluene to remove efficiently the formic acid. The crude was chromatographed on silica gel (CH₂Cl₂/EtOAc from 9/1 to 8/2) to give **58** (47 mg, 100% yield).



- ¹H NMR (300 MHz, CDCl₃) δ 6.98 (d, J = 8.9 Hz, 1H), 5.93 (d, J = 2.2 Hz, 1H), 5.43 (d, J = 2.2 Hz, 1H), 4.81 (td, J = 8.5, 6.9 Hz, 1H), 3.85-3.70 (m, 3H), 3.62 (d, J = 11.9 Hz, 1H), 3.27 (d, J = 11.9 Hz, 1H), 2.56 (s, 3H), 1.82-1.56 (m, 3H), 1.53 (s, 3H), 0.97 (t, J = 6.4 Hz, 6H).

Compound 59

- 30 To a mixture of **46** (35 mg, 0.077 mmol) and pentane (2.1 mL) was added formic acid (1.4 mL). The reaction was stirred vigorously at 23 °C for 2 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **59** (30 mg, 100% yield) which was used in the next step without further purification.



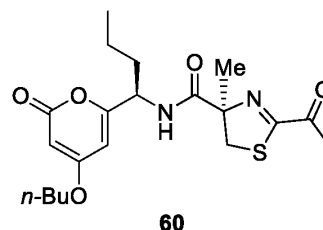
^1H NMR (300 MHz, CDCl_3) δ 6.08 (d, $J = 2.0$ Hz, 1H), 5.55 (d, $J = 2.1$ Hz, 1H), 5.18 (d, $J = 8.4$ Hz, 1H), 4.36 (d, $J = 7.9$ Hz, 1H), 2.17 (d, $J = 1.1$ Hz, 1H), 2.06 (s, 0H), 1.93-1.59 (m, 12H), 1.53 (d, $J = 1.1$ Hz, 1H), 1.49-1.29 (m, 16H), 0.92 (t, $J = 7.3$ Hz, 5H).

MS (ES): m/z 381.2 $[\text{M}+\text{H}]^+$, 403.3 $[\text{M}+\text{Na}]^+$.

5 Rf: 0.2 (Hex:EtOAc 6:4).

Compound 60

To a mixture of **47** (48 mg, 0.1 mmol) and pentane (3.2 mL) was added formic acid (2.2 mL). The reaction was stirred vigorously at 23 °C for 2 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **60** (100% yield) which was used in the next step without further purification.



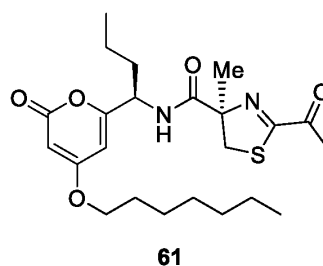
^1H NMR (300 MHz, CDCl_3) δ 7.04 (d, $J = 8.9$ Hz, 1H), 5.92 (d, $J = 2.2$ Hz, 1H), 5.41 (d, $J = 2.2$ Hz, 1H), 4.74 (q, $J = 7.8$ Hz, 1H), 4.01-3.89 (m, 2H), 3.63 (d, $J = 11.9$ Hz, 1H), 3.28 (d, $J = 11.9$ Hz, 1H), 2.56 (d, $J = 1.4$ Hz, 3H), 1.95-1.65 (m, 4H), 1.64-1.17 (m, 7H), 1.05-0.87 (m, 6H).

MS (ES): m/z 409.3 $[\text{M}+\text{H}]^+$, 431.1 $[\text{M}+\text{Na}]^+$.

Rf: 0.27 (Hex:EtOAc 6:4).

Compound 61

A mixture of **48** (69 mg) and pentane (3.6 mL) and formic acid (2.4 mL) was vigorously stirred for 2 h and the volatiles were evaporated to dryness. The crude was coevaporated few times with a mixture of CH_2Cl_2 /toluene to eliminate the acid and give crude **61** (59 mg, 100% yield) which was used in the next step without further purification.

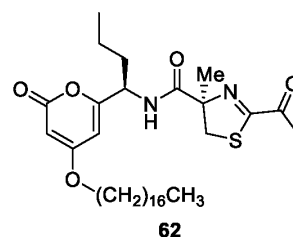


^1H NMR (400 MHz, CDCl_3): δ 7.04 (d, $J = 8.9$ Hz, 1H), 5.91 (d, $J = 2.2$ Hz, 1H), 5.40 (d, $J = 2.2$ Hz, 1H), 4.73 (dt, $J = 8.8, 7.5$ Hz, 1H), 3.91 (td, $J = 6.5, 1.7$ Hz, 2H), 3.61 (d, $J = 12.0$ Hz, 1H), 3.26 (d, $J = 11.9$ Hz, 1H), 2.55 (s, 3H), 1.93-1.67 (m, 4H), 1.53 (s, 3H), 1.47-1.18 (m, 10H), 0.95 (t, $J = 7.3$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.2, 173.2, 170.4, 170.3, 164.3, 161.7, 100.8, 88.9, 86.0, 69.2, 51.0, 40.1, 34.8, 31.6, 29.6, 28.8, 28.3, 26.3, 25.7, 24.5, 22.5, 19.0, 14.0, 13.5.

Compound 62

Over **49** (89 mg, 0.134 mmol) was added at 23 °C pentane (4.6 mL) and formic acid (3.1 mL). The reaction mixture was stirred vigorously for 2 hours at 23 °C and the volatiles were evaporated under vacuum. The obtained crude was evaporated few times



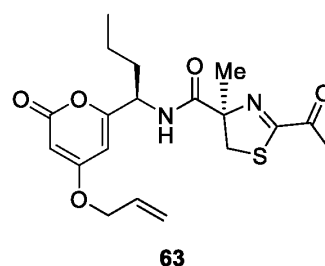
with a mixture of CH₂Cl₂:toluene to eliminate formic acid to give crude **62** which was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.03 (d, *J* = 9.0 Hz, 1H), 5.90 (d, *J* = 2.1 Hz, 1H), 5.39 (d, *J* = 2.2 Hz, 1H), 4.73 (dt, *J* = 8.8, 7.6 Hz, 1H), 3.90 (td, *J* = 6.5, 1.7 Hz, 2H), 3.61 (d, *J* = 11.9 Hz, 1H),
5 3.26 (d, *J* = 11.9 Hz, 1H), 2.55 (s, 3H), 1.93-1.66 (m, 4H), 1.53 (s, 3H), 1.46-1.18 (m, 32H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CD₃OD): δ 193.1, 173.2, 170.4, 170.2, 164.2, 161.7, 100.8, 88.9, 86.0, 69.2, 51.0, 40.1, 34.9, 31.9, 29.6 (x3), 29.5, 29.4, 29.3, 29.1, 28.3, 26.3, 25.7, 24.5, 22.6, 19.0, 14.1, 13.5.

10 Compound **63**

Over **50** (6.0 g, 12.92 mmol) was added at 23 °C pentane (314 mL) and formic acid (212 mL). The reaction mixture was stirred vigorously for 2 hours at 23 °C and the volatiles were evaporated under vacuum. The obtained crude was
15 evaporated few times with a mixture of CH₂Cl₂:toluene to eliminate formic acid to give crude **63** (6.0 g, >100% yield) which was used in the next step without further purification.



¹H NMR (400 MHz, CDCl₃): δ 7.11 (d, *J* = 8.9 Hz, 1H), 5.97 (d, *J* = 2.2 Hz, 1H), 5.99-5.89 (m, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 5.44-5.28 (m, 2H), 4.75 (q, *J* = 7.9 Hz, 1H), 4.49 (td, *J* = 5.5, 1.5 Hz, 2H), 3.60 (d, *J* = 11.9 Hz, 1H), 3.27 (d, *J* = 11.9 Hz, 1H), 2.55 (s, 3H), 2.03-1.67 (m, 2H),
20 1.53 (s, 3H), 1.45-1.26 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 193.3, 173.3, 170.6, 169.8, 164.1, 162.2, 130.7, 119.9, 100.8, 89.6, 86.3, 69.8, 51.2, 40.3, 35.1, 26.5, 24.8, 24.7, 19.3 (x2), 13.7.

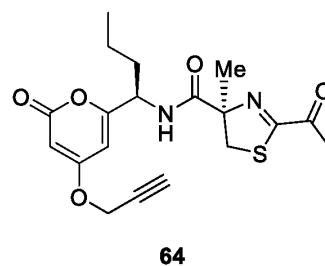
MS (ES⁺): 393.2 [M+H]⁺, 415.2 [M+Na]⁺.

25 Optical rotation: [α]_D +51.0 (c 0.014, MeOH).

R_f: 0.39 (Hex:EtOAc 1:1).

Compound **64**

Over **51** (3.57 g, 7.68 mmol) was added at 23 °C pentane (186 mL) and formic acid (125 mL). The reaction mixture was stirred vigorously for 2 hours at 23 °C and the volatiles were evaporated under vacuum. The obtained crude was
30 evaporated few times with a mixture of CH₂Cl₂:toluene to eliminate formic acid to give crude **64** which was used in the next step without further purification.



¹H NMR (400 MHz, CDCl₃): δ 7.05 (d, *J* = 8.9 Hz, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.58 (d, *J* = 2.3 Hz, 1H), 4.75 (q, *J* = 8.1 Hz, 1H), 4.66 (d, *J* = 2.5 Hz, 2H), 3.61 (d, *J* = 11.9 Hz, 1H), 3.27 (d, *J* =

11.9 Hz, 1H), 2.63 (t, $J = 2.4$ Hz, 1H), 2.55 (s, 3H), 1.95-1.72 (m, 2H), 1.54 (s, 3H), 1.47-1.28 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H).

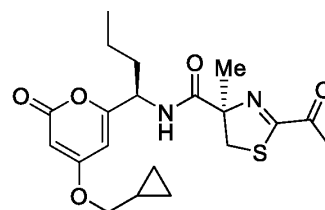
^{13}C NMR (100 MHz, CDCl_3): δ 193.2, 173.3, 168.7, 163.8, 163.1, 162.3, 100.3, 90.1, 86.0, 77.8, 75.5, 56.5, 51.0, 40.1, 34.8, 26.3, 24.5, 19.0, 13.5.

5 MS (ES⁺): 391.2 [M+H]⁺, 413.1 [M+Na]⁺.

R_f: 0.26 (Hex:EtOAc 60:40).

Compound 65

Over **52** (9.0 g, 18.73 mmol) was added at 23 °C pentane (460 mL) and formic acid (315 mL). The reaction mixture was stirred vigorously for 2 hours at 23 °C and the volatiles were evaporated under vacuum. The obtained crude was evaporated few times with a mixture of CH_2Cl_2 :toluene to eliminate formic acid to give crude **65** (7.61 g, 100% yield) which was used in the next step without further purification.



65

15 ^1H NMR (400 MHz, CDCl_3): δ 7.05 (d, $J = 8.9$ Hz, 1H), 5.94 (d, $J = 2.2$ Hz, 1H), 5.37 (d, $J = 2.3$ Hz, 1H), 4.73 (q, $J = 7.9$ Hz, 1H), 3.76 (dd, $J = 7.1, 1.9$ Hz, 2H), 3.61 (d, $J = 11.9$ Hz, 1H), 3.27 (d, $J = 12.0$ Hz, 1H), 2.55 (s, 3H), 1.94-1.73 (m, 1H), 1.66-1.53 (m, 1H), 1.53 (s, 3H), 1.52-1.16 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H), 0.70-0.61 (m, 2H), 0.33 (t, $J = 5.2$ Hz, 2H).

20 ^{13}C NMR (100 MHz, CDCl_3): δ 193.2, 173.2, 170.4, 164.3, 163.0, 161.8, 100.8, 88.9, 86.0, 73.9, 51.0, 40.1, 34.8, 26.3, 24.5, 19.0, 13.5, 9.3, 3.4, 3.3.

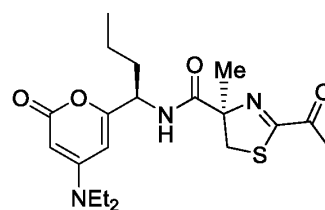
MS (ES⁺): 407.1 [M+H]⁺, 429.2 [M+Na]⁺.

Optical rotation: $[\alpha]_D +56.2$ (c 0.019, MeOH).

R_f: 0.47 (Hex:EtOAc 1:1).

Compound 66

25 To a mixture of **53** (30 mg, 0.062 mmol) and pentane (1.8 mL) was added formic acid (1.2 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **66** (100% yield) which was used in the next step without further purification.

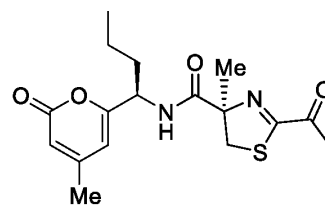


66

30 ^1H NMR (300 MHz, CDCl_3): δ 7.16 (d, $J = 8.8$ Hz, 1H), 5.94 (d, $J = 2.4$ Hz, 1H), 5.04 (dd, $J = 5.5, 2.3$ Hz, 1H), 4.80-4.60 (m, 1H), 3.63 (d, $J = 11.9$ Hz, 1H), 3.38-3.18 (m, 5H), 2.56 (s, 3H), 1.95-1.63 (m, 2H), 1.55 (s, 3H), 1.37-1.05 (m, 8H), 0.96 (t, $J = 7.3$ Hz, 3H).

MS (ES): m/z 408.2 [M+H]⁺.

Compound 67



67

To a mixture of **54** (16 mg, 0.037 mmol) and pentane (0.96 mL) was added formic acid (0.64 mL). The reaction was stirred vigorously at 23 °C for 2 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **67** (100% yield) which was used in the next step without further purification.

- 5 ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 9.0 Hz, 1H), 6.04-5.93 (m, 2H), 4.75 (q, *J* = 8.0 Hz, 1H), 3.68-3.60 (d, *J* = 11.9 Hz, 1H), 3.28 (d, *J* = 11.9 Hz, 1H), 2.57 (s, 3H), 2.14 (s, 3H), 1.94-1.74 (m, 2H), 1.55 (s, 3H), 1.46-1.27 (m, 2H), 1.04-0.90 (m, 3H).

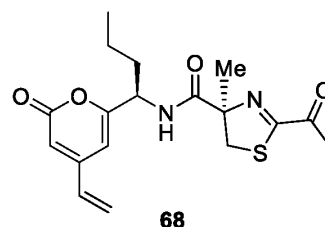
MS (ES): *m/z* 351.2 [M+H]⁺, 373.1 [M+Na]⁺.

R_f: 0.42 (Hex:EtOAc 1:1).

10 Compound **68**

Over **55** (1.35 g, 3.1 mmol) was added at 23 °C pentane (70 mL) and formic acid (47 mL). The reaction mixture was stirred vigorously for 2 hours at 23 °C and the volatiles were evaporated under vacuum. The obtained crude was

- 15 evaporated few times with a mixture of CH₂Cl₂:toluene to eliminate formic acid, The obtained crude was purified in an automatic system for flash chromatography (SiO₂) to yield **68** (454 mg, 40% yield).

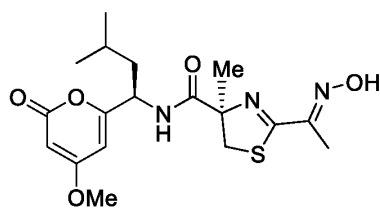


- 20 ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 9.0 Hz, 1H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.26 (d, *J* = 1.3 Hz, 1H), 6.04 (dd, *J* = 1.5, 0.8 Hz, 1H), 5.89 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.61 (dd, *J* = 10.8, 0.8 Hz, 1H), 4.84-4.68 (m, 1H), 3.62 (dd, *J* = 11.9, 0.9 Hz, 1H), 3.25 (dd, *J* = 11.9, 0.9 Hz, 1H), 2.54 (d, *J* = 0.9 Hz, 3H), 1.94-1.72 (m, 2H), 1.54 (s, 1H), 1.53-1.20 (m, 2H), 0.99-0.80 (m, 3H).

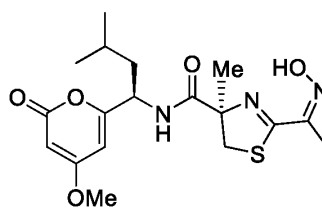
MS (ES⁺): *m/z* 363.2 [M+H]⁺, 385.1 [M+Na]⁺.

R_f: 0.50 (Hex:EtOAc 1:1).

25 Compounds **69** and **69a**



69



69a

To a solution of **58** (47 mg, 0.13 mmol) in ethanol (1.32 mL) and water (1.32 mL), were added NH₂OH·HCl (61 mg, 0.95 mmol) and NaOAc (44 mg, 0.58 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc.

- 30 The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent the

obtained crude was purified by HPLC method, using an XBridge C18 5 μ m H₂O/CH₃CN to obtain **69a** (1.6 mg) and **69** (16.7 mg, 35% yield).

Compound **69a**

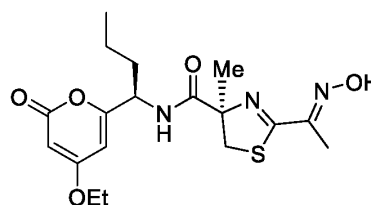
¹H NMR (500 MHz, CDCl₃) δ 6.96 (d, J = 8.9 Hz, 1H), 5.94 (dd, J = 2.2, 0.6 Hz, 1H), 5.43 (d, J = 2.2 Hz, 1H), 4.81 (td, J = 8.7, 6.5 Hz, 1H), 3.80 (d, J = 0.7 Hz, 3H), 3.69 (dd, J = 11.7, 0.7 Hz, 1H), 3.22 (dd, J = 11.7, 0.7 Hz, 1H), 2.20 (d, J = 0.7 Hz, 3H), 1.82-1.51 (m, 3H), 1.63 (s, 3H), 0.96 (dd, J = 8.4, 6.4 Hz, 6H).

Compound **69**

¹H NMR (500 MHz, CDCl₃) δ 8.70 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 5.93 (d, J = 2.2 Hz, 1H), 5.43 (d, J = 2.2 Hz, 1H), 4.81 (td, J = 8.7, 6.6 Hz, 1H), 3.79 (s, 3H), 3.54 (d, J = 11.6 Hz, 1H), 3.24 (d, J = 11.6 Hz, 1H), 2.23 (s, 3H), 1.84-1.56 (m, 3H), 1.52 (s, 3H), 0.97 (dd, J = 9.5, 6.5 Hz, 6H).

Compound **70**

To a solution of **59** (35 mg, 0.077 mmol) in ethanol (0.85 mL) and water (0.85 mL), were added NH₂OH·HCl (40 mg, 0.57 mmol) and NaOAc (28 mg, 0.35 mmol). After stirring for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc. The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent the obtained crude

**70**

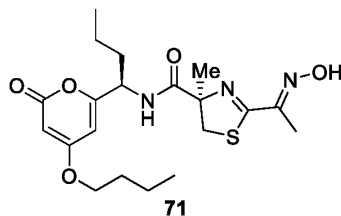
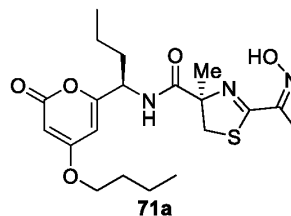
was purified by HPLC method, using an XBridge C18 5 μ m H₂O/CH₃CN to give **70** (8 mg, 22% yield).

¹H NMR (400 MHz, CD₃OD): δ 6.02 (dd, J = 2.2, 0.7 Hz, 1H), 5.51 (d, J = 2.2 Hz, 1H), 4.74 (dd, J = 9.1, 5.8 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.55 (d, J = 11.5 Hz, 1H), 3.17 (d, J = 11.5 Hz, 1H), 2.18 (s, 3H), 1.52 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H).

MS (ES⁺): m/z 396.2 [M+H]⁺, 418.2 [M+Na]⁺.

R_f: 0.17 (Hex:EtOAc 6:4).

Compounds **71** and **71a**

**71****71a**

To a solution of **60** (45 mg, 0.11 mmol) in ethanol (1.2 mL) and water (1.2 mL), were added NH₂OH·HCl (56 mg, 0.81 mmol) and NaOAc (41 mg, 0.5 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc.

The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent the obtained crude was purified by HPLC method, using an XBridge C18 5 μ m H₂O/CH₃CN to give **71a** (2.5 mg) and **71** (15.9 mg, 34% yield).

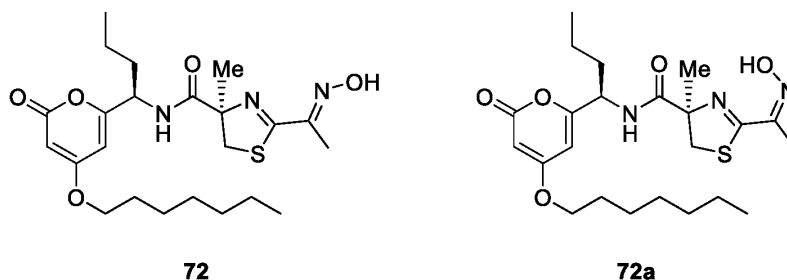
Compound **71**

- 5 ¹H NMR (400 MHz, CD₃OD): δ 6.03 (d, J = 2.2 Hz, 1H), 5.52 (d, J = 2.2 Hz, 1H), 4.74 (dd, J = 9.2, 5.7 Hz, 1H), 4.02 (t, J = 6.4 Hz, 2H), 3.56 (d, J = 11.5 Hz, 1H), 3.17 (d, J = 11.4 Hz, 1H), 2.18 (d, J = 0.7 Hz, 3H), 1.92-1.70 (m, 4H), 1.53 (s, 3H), 1.49-1.35 (m, 3H), 0.98 (q, J = 7.5 Hz, 6H).
MS (ES⁺): m/z 424.3 [M+H]⁺, 446.1 [M+Na]⁺.
10 R_f: 0.53 (Hex:EtOAc 6:4).

Compound **71a**

- ¹H NMR (500 MHz, CDCl₃) δ 7.00 (d, J = 8.9 Hz, 1H), 5.91 (d, J = 2.2 Hz, 1H), 5.41 (d, J = 2.2 Hz, 1H), 4.80-4.59 (m, 1H), 3.94 (td, J = 6.5, 1.1 Hz, 2H), 3.70 (d, J = 11.7 Hz, 1H), 3.23 (d, J = 11.6 Hz, 1H), 2.20 (s, 3H), 1.88-1.67 (m, 4H), 1.64 (s, 3H), 1.56-1.29 (m, 4H), 0.96 (dt, J = 8.1, 7.4 Hz, 6H).
15

Compounds **72** and **72a**



- Compound **61** (0.131 mmol) was dissolved in ethanol (1.4 mL) prior to addition of water (1.4 mL), NH₂OH HCl (67 mg, 0.963 mmol) and NaOAc (48 mg, 0.591 mmol). This mixture was stirred for 16 h and then ethanol was evaporated. Aqueous residue was diluted with brine and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness and the crude was chromatographed on a system for flash chromatography with a SiO₂ column eluting with mixtures of hexane/ EtOAc from 100:0 to 60:40 in 40 min. This purification allowed to separate both stereoisomers.
20

Compound **72**

- ¹H NMR (400 MHz, CDCl₃): δ 9.31 (s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 2.2 Hz, 1H), 5.41 (d, J = 2.1 Hz, 1H), 4.73 (q, J = 7.9 Hz, 1H), 3.91 (t, J = 6.5 Hz, 2H), 3.51 (d, J = 11.6 Hz, 1H), 3.24 (dd, J = 11.6, 0.5 Hz, 1H), 2.22 (s, 3H), 1.95-1.66 (m, 4H), 1.51 (s, 3H), 1.45-1.17 (m, 10H), 0.95 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H).
25

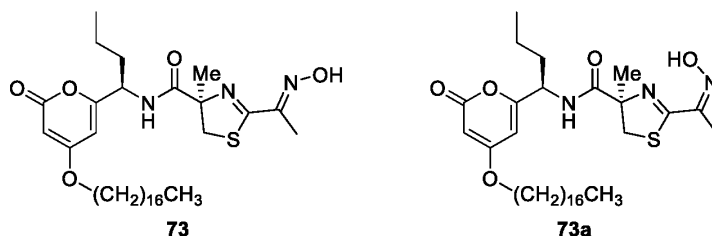
^{13}C NMR (100 MHz, CDCl_3): δ 174.2, 170.4, 167.9, 164.5, 162.1, 153.0, 100.7, 88.9, 84.3, 69.2, 51.0, 39.9, 34.7, 31.6, 28.8, 28.4, 25.7, 24.6, 22.5, 19.0, 14.0, 13.6, 11.2.

Compound **72a**

^1H NMR (400 MHz, CDCl_3): δ 7.05 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 2.2 Hz, 1H), 5.40 (d, J = 2.3 Hz, 1H), 4.73 (q, J = 7.9 Hz, 1H), 3.91 (t, J = 5.8 Hz, 2H), 3.68 (d, J = 11.7 Hz, 1H), 3.22 (d, J = 11.6 Hz, 1H), 2.19 (s, 3H), 1.89-1.66 (m, 4H), 1.63 (s, 3H), 1.43-1.17 (m, 10H), 0.94 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 173.3, 172.4, 170.5, 164.7, 163.7, 162.1, 100.5, 88.9, 83.9, 69.2, 51.1, 40.9, 35.1, 31.6, 28.8, 28.4, 25.7, 24.9, 22.5, 19.1, 14.0, 13.6, 11.8.

10 Compounds **73** and **73a**



To a solution of crude **62** (79 mg, 0.134 mmol) in EtOH (1.5 mL) and H_2O (1.5 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (69 mg, 0.992 mmol) and NaOAc (49 mg, 0.603 mmol) at 23 °C. The reaction mixture was stirred overnight at 23 °C and concentrated under vacuum. The residue obtained was diluted with an aqueous saturated solution of NaCl and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO_2 , Hex:EtOAc) to afford **73** (33 mg, 41% yield for 2 steps) and **73a** (7 mg, 8% yield for 2 steps).

20 Compound **73**

^1H NMR (400 MHz, CDCl_3): δ 9.32 (s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 2.1 Hz, 1H), 5.40 (d, J = 2.2 Hz, 1H), 4.73 (q, J = 7.7 Hz, 1H), 3.91 (t, J = 6.5 Hz, 2H), 3.51 (d, J = 11.6 Hz, 1H), 3.24 (d, J = 11.6 Hz, 1H), 2.22 (s, 3H), 1.95-1.66 (m, 4H), 1.51 (s, 3H), 1.46-1.15 (m, 30H), 0.95 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.2, 170.3, 167.9, 164.5, 162.0, 153.0, 100.7, 88.9, 84.3, 69.2, 51.0, 39.9, 34.8, 31.9, 29.7, 29.6, 29.5 (x2), 29.3, 29.2, 28.4, 25.8, 24.6, 22.7, 19.1, 14.1, 13.6, 11.2.

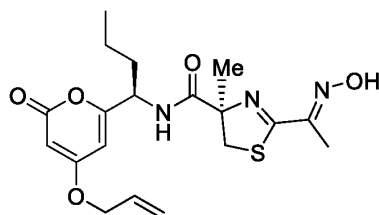
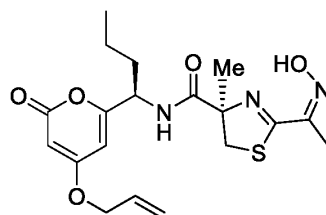
Compound **73a**

^1H NMR (500 MHz, CDCl_3): δ 8.29 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 5.39 (d, J = 2.2 Hz, 1H), 4.73 (q, J = 7.9 Hz, 1H), 3.91 (td, J = 6.6, 1.9 Hz, 2H), 3.55 (d, J = 11.6 Hz, 1H), 3.23 (d, J =

11.6 Hz, 1H), 2.24 (s, 3H), 1.94-1.68 (m, 4H), 1.52 (s, 3H), 1.45-1.18 (m, 32H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 173.9, 170.3, 167.9, 164.4, 162.2, 153.4, 100.6, 88.9, 84.3, 69.2, 51.0, 39.9, 34.8, 31.9, 29.7, 29.6, 29.5 (x2), 29.3, 29.2, 28.4, 25.8, 24.7, 22.7, 19.1, 14.1, 13.6, 11.3.

Compounds **74** and **74a**

**74****74a**

To a solution of crude **63** (700 mg, 1.78 mmol) in EtOH (20 mL) and H_2O (20 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (920 mg, 13.23 mmol) and NaOAc (660 mg, 8.04 mmol) at 23°C . The reaction mixture was stirred for 24 h at 23°C and concentrated under vacuum. The residue obtained was diluted with an aqueous saturated solution of NaCl and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The obtained crude was purified by flash chromatography on silica gel (CH_2Cl_2 :EtOAc, from 90:10 to 70:30) to afford **74** (387 mg, 53% yield) and **74a** (45 mg, 6% yield).

Compound **74**

^1H NMR (400 MHz, CD_3OD): δ 6.06 (d, $J = 2.2$ Hz, 1H), 6.04-5.94 (m, 1H), 5.53 (d, $J = 2.2$ Hz, 1H), 5.43-5.29 (m, 2H), 4.74 (dd, $J = 9.1, 5.8$ Hz, 1H), 4.58 (td, $J = 5.5, 1.5$ Hz, 2H), 3.55 (d, $J = 11.5$ Hz, 1H), 3.17 (d, $J = 11.5$ Hz, 1H), 2.17 (s, 3H), 1.92-1.77 (m, 2H), 1.52 (s, 3H), 1.50-1.34 (m, 2H), 0.98 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.4, 169.8, 168.2, 164.4, 162.3, 152.9, 130.6, 119.5, 100.5, 89.5, 84.3, 69.6, 51.0, 39.9, 34.7, 24.6, 19.0, 13.6, 11.2.

MS (ES $^+$): m/z 408.2 $[\text{M}+\text{H}]^+$, 430.1 $[\text{M}+\text{Na}]^+$.

Optical rotation: $[\alpha]_D^{25} +53.7$ (c 0.071, MeOH).

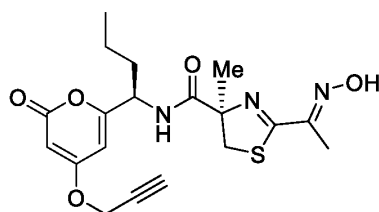
R_f: 0.29 (Hex:EtOAc 6:4).

Compound **74a**

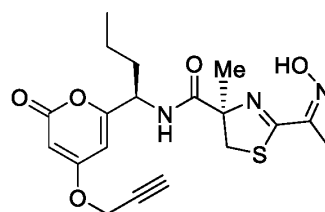
^1H NMR (400 MHz, CDCl_3): δ 10.44 (br s, 1H), 7.07 (d, $J = 8.9$ Hz, 1H), 6.01-5.88 (m, 1H), 5.42 (dd, $J = 3.3, 1.7$ Hz, 1H), 5.39-5.31 (m, 2H), 4.73 (td, $J = 8.3, 6.7$ Hz, 1H), 4.48 (dt, $J = 5.5, 1.5$ Hz, 2H), 3.65 (d, $J = 11.7$ Hz, 1H), 3.21 (d, $J = 11.7$ Hz, 1H), 2.19 (s, 3H), 1.89-1.65 (m, 2H), 1.60 (s, 3H), 1.41-1.28 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 173.5, 169.9, 164.6, 164.5, 162.5, 147.2, 130.5, 119.6, 100.3, 89.4, 83.6, 69.6, 51.0, 40.8, 35.0, 24.7, 19.2, 19.0, 13.5.

Compounds **75** and **75a**



75



75a

- 5 To a solution of crude **64** (3.0 g, 7.68 mmol) in EtOH (85 mL) and H_2O (85 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (3.95 g, 56.86 mmol) and NaOAc (2.84 g, 34.58 mmol) at 23°C . The reaction mixture was stirred overnight at 23°C and concentrated under vacuum. The residue obtained was diluted with an aqueous saturated solution of NaCl and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum.
- 10 The obtained crude was purified by flash chromatography on silica gel (Hex:EtOAc, from 100:0 to 40:60) to afford **75** (1.44 mg, 46% yield for 2 steps) and **75a** (392 mg, 12% yield for 2 steps).

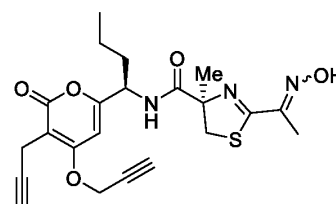
Compound **75**

- ^1H NMR (400 MHz, CD_3OD): δ 6.07 (d, $J = 2.2$ Hz, 1H), 5.64 (d, $J = 2.3$ Hz, 1H), 4.81 (d, $J = 2.4$ Hz, 2H), 4.78-4.69 (m, 1H), 3.54 (d, $J = 11.5$ Hz, 1H), 3.18 (d, $J = 11.5$ Hz, 1H), 3.15-3.13 (m, 1H), 2.18 (s, 3H), 1.92-1.76 (m, 2H), 1.52 (s, 3H), 1.49-1.35 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H).
- 15 ^{13}C NMR (125 MHz, CDCl_3): δ 174.3, 168.7, 168.0, 163.8, 162.7, 153.1, 100.1, 90.1, 84.3, 77.8, 75.6, 56.5, 51.0, 39.9, 34.8, 24.7, 19.0, 13.6, 11.3.
- MS (ES $^+$): m/z 406.1 $[\text{M}+\text{H}]^+$.
- 20 R_f: 0.29 (Hex:EtOAc 6:4).

Compound **75a**

- ^1H NMR (400 MHz, CDCl_3): δ 7.02 (d, $J = 8.7$ Hz, 1H), 5.94 (d, $J = 2.2$ Hz, 1H), 5.56 (dd, $J = 2.3$, 0.8 Hz, 1H), 4.74 (q, $J = 8.1$ Hz, 1H), 4.66 (dt, $J = 2.4$, 1.2 Hz, 2H), 3.69 (dd, $J = 11.7$, 0.8 Hz, 1H), 3.22 (dd, $J = 11.7$, 0.9 Hz, 1H), 2.63 (t, $J = 2.4$ Hz, 1H), 2.20 (s, 3H), 1.91-1.64 (m, 2H), 1.63 (s, 3H), 1.46-1.32 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H).
- 25 ^{13}C NMR (100 MHz, CDCl_3): δ 173.9, 168.7, 167.5, 163.7, 162.8, 153.3, 100.0, 90.1, 84.2, 77.7, 75.6, 56.5, 51.0, 39.9, 34.8, 24.7, 19.1, 13.6, 11.3.

Compound **141**



141

During the purification of one scale-up batch of compound **75** (1.44 g, HPLC: 78.8%) by preparative reversed phase HPLC (Sunfire C18, CH₃CN:H₂O from 40% to 60% CH₃CN in 30 minutes, UV detection, flow: 15 mL/min) it was obtained **141** (*t_R* 16.8 min, 201 mg) and **75** (*t_R* 14.6 min, 718 mg).

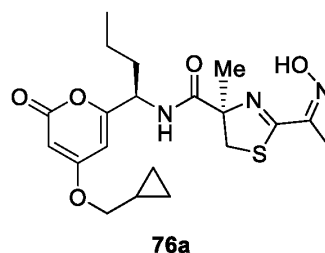
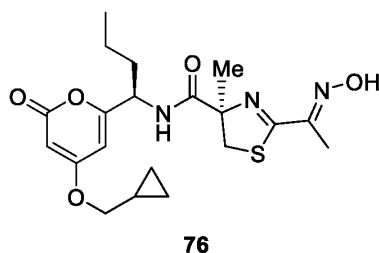
- 5 ¹H NMR (400 MHz, CDCl₃): δ 8.71 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.28 (s, 1H), 4.85-4.71 (m, 2H), 3.57 (d, *J* = 11.6 Hz, 1H), 3.33 (d, *J* = 2.7 Hz, 2H), 3.24 (d, *J* = 11.6 Hz, 1H), 2.62 (t, *J* = 2.4 Hz, 1H), 2.23 (s, 3H), 1.99-1.72 (m, 2H), 1.54 (s, 3H), 1.48-1.25 (m, 1H), 1.29-1.23 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.92- 0.80 (m, 1H).

- 10 ¹³C NMR (125 MHz, CDCl₃): δ 174.3, 168.6, 164.5, 162.5, 153.2, 102.9, 95.7, 84.4, 80.8, 77.9, 76.8, 67.6, 57.1, 51.6, 40.1, 34.9, 25.0, 19.2, 13.7, 13.3, 11.5.

MS (ES⁺): *m/z* 444.1 [M+H]⁺.

R_f: 0.29 (Hex:EtOAc 6:4).

Compounds **76** and **76a**



- 15 To a solution of crude **65** (33 mg, 0.08 mmol) in EtOH (0.9 mL) and H₂O (0.9 mL) was added NH₂OH·HCl (42 mg, 0.6 mmol) and NaOAc (30 mg, 0.36 mmol) at 23 °C. The reaction mixture was stirred for 24 h at 23 °C and concentrated under vacuum. The residue obtained was diluted with an aqueous saturated solution of NaCl and extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum.
- 20 The obtained crude was purified by flash chromatography on silica gel (Hex:EtOAc, from 100:0 to 40:60) to afford **76** (15 mg, 44% yield) and **76a** (3 mg, 9% yield).

Compound **76**

- 25 ¹H NMR (400 MHz, CD₃OD): δ 7.85 (d, *J* = 8.6 Hz, 1H), 6.05 (s, 1H), 5.48 (s, 1H), 4.74 (q, *J* = 6.8, 5.0 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.56 (d, *J* = 11.5 Hz, 1H), 3.17 (d, *J* = 11.5 Hz, 1H), 2.19 (s, 3H), 1.96-1.72 (m, 2H), 1.52 (s, 3H), 1.43 (ddd, *J* = 29.8, 14.7, 7.4 Hz, 4H), 1.31-1.16 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.63 (d, *J* = 7.6 Hz, 2H), 0.35 (d, *J* = 5.0 Hz, 2H).

¹³C NMR (100 MHz, CD₃OD): δ 175.1, 171.2, 168.8, 165.3, 163.8, 151.5, 126.4, 99.7, 87.9, 84.2, 74.0, 50.7, 39.1, 33.9, 23.6, 18.8, 12.5, 9.6, 9.0, 2.3.

MS (ES⁺): *m/z* 422.1 [M+H]⁺, 444.2 [M+Na]⁺.

- 30 Optical rotation: [α]_D +55 (c 0.022, MeOH).

R_f: 0.42 (hexanes:EtOAc 1:1).

Compound **76a**

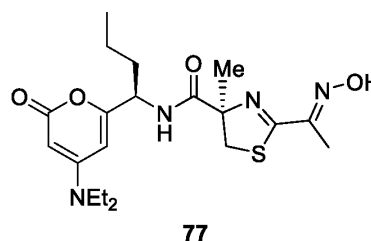
¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 5.94 (t, *J* = 2.1 Hz, 1H), 5.41-5.33 (m, 1H), 4.73 (q, *J* = 7.9 Hz, 1H), 3.76 (dd, *J* = 7.2, 2.1 Hz, 3H), 3.57 (d, *J* = 11.6 Hz, 1H), 3.23 (dd, *J* = 11.7, 1.9 Hz, 1H), 2.24 (s, 3H), 2.20 (s, 1H), 1.95-1.65 (m, 2H), 1.64 (s, 1H), 1.54 (s, 2H), 1.45-1.31 (m, 2H), 1.23 (d, *J* = 18.1 Hz, 2H), 0.95 (q, *J* = 7.4 Hz, 3H), 0.83 (s, 1H), 0.67 (dd, *J* = 7.9, 1.3 Hz, 3H), 0.38-0.29 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 173.8, 170.1, 168.4, 164.3, 162.3, 153.3, 100.5, 88.9, 84.2, 73.8, 51.1, 39.9, 34.8, 24.7, 19.1, 13.6, 11.3, 9.4, 3.4 (x2).

MS (ES⁺): *m/z* 422.1 [M+H]⁺.

10 Compound **77**

To a solution of **66** (25 mg, 0.062 mmol) in ethanol (0.7 mL) and water (0.7 mL), were added NH₂OH·HCl (31 mg, 0.45 mmol) and NaOAc (23 mg, 0.28 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc. The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent



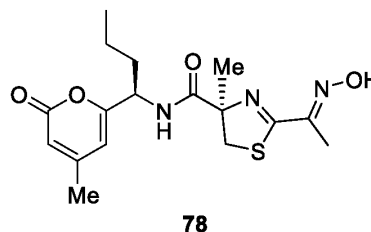
the obtained crude was purified by HPLC method, using an XBridge C18 5 μm H₂O/CH₃CN to give **77** (2.9 mg, 12% yield).

¹H NMR (500 MHz, CD₃OD) δ 6.10 (dd, *J* = 2.4, 0.7 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 4.75 (dt, *J* = 9.3, 5.8 Hz, 1H), 3.60 (d, *J* = 11.5 Hz, 1H), 3.43-3.34 (m, 4H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.20 (s, 3H), 1.97-1.76 (m, 2H), 1.56 (s, 3H), 1.54-1.34 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H).

MS (ES): *m/z* 423.2 [M+H]⁺, 445.2 [M+Na]⁺.

25 Compound **78**

To a solution of **67** (16 mg, 0.045 mmol) in ethanol (0.4 mL) and water (0.4 mL), were added NH₂OH·HCl (19 mg, 0.33 mmol) and NaOAc (14 mg, 0.18 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc.



The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent the obtained crude was purified by HPLC method, using an XBridge C18 5 μm H₂O/CH₃CN to give **78** (2.9 mg, 18% yield).

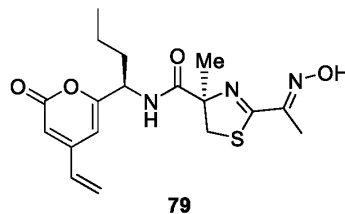
¹H NMR (400 MHz, CD₃OD): δ 7.81 (d, *J* = 8.7 Hz, 1H), 6.14 (d, *J* = 1.5 Hz, 1H), 6.02 (s, 1H), 4.75 (ddd, *J* = 8.9, 5.9, 3.0 Hz, 1H), 3.54 (d, *J* = 11.5 Hz, 1H), 3.17 (d, *J* = 11.5 Hz, 1H), 2.18 (s, 3H), 2.15 (d, *J* = 1.2 Hz, 3H), 1.90-1.78 (m, 2H), 1.53 (s, 3H), 1.49-1.36 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

MS (ES): m/z 366.2 [M+H]⁺, 388.1 [M+Na]⁺.

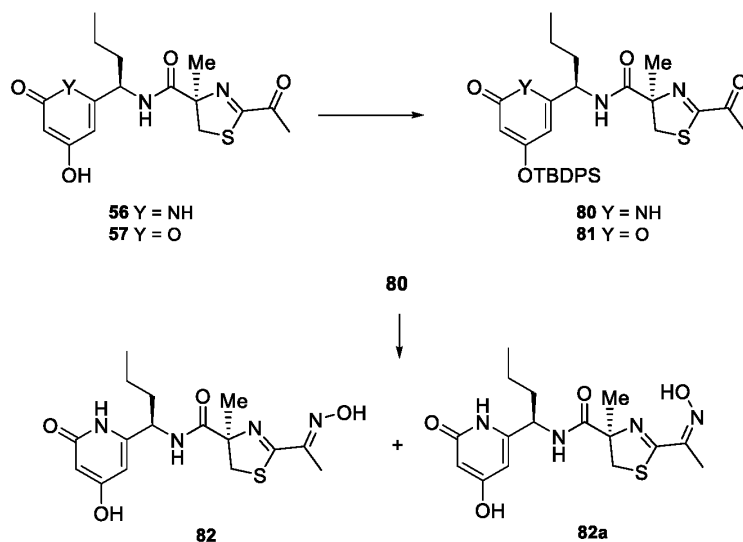
R_f: 0.35 (hexanes:EtOAc 6:4).

Compound 79

- To a solution of crude **68** (453 mg, 1.25 mmol) in ethanol (5 mL) was added NH₂OH·HCl (131 mg, 1.88 mmol) at 23 °C. The reaction mixture was stirred at 70 °C for 3 h and diluted with H₂O. The resulting precipitate was concentrated under vacuum. The obtained crude was purified in an automatic system for flash chromatography (SiO₂) to obtain **79** (217 mg, 46%).
- ¹H NMR (400 MHz, CD₃OD): δ 6.58 (dd, J = 17.5, 10.8 Hz, 1H), 6.47 (d, J = 1.5 Hz, 1H), 6.11 (d, J = 1.4 Hz, 1H), 6.02 (d, J = 17.5 Hz, 1H), 5.66 (d, J = 10.8 Hz, 1H), 4.85-4.72 (m, 1H), 3.62-3.46 (m, 1H), 3.37-3.22 (m, 1H), 3.18 (dd, J = 11.5, 0.9 Hz, 1H), 2.19 (s, 3H), 1.90-1.69 (m, 2H), 1.56 (s, 3H), 1.57-1.33 (m, 2H), 0.99 (td, J = 7.4, 2.9 Hz, 3H).
- ¹³C NMR (100 MHz, CD₃OD): δ 176.6, 170.3, 164.9, 164.5, 153.9, 152.9, 134.5, 124.0, 111.5, 100.5, 85.6, 52.3, 40.8, 35.4, 25.2, 20.2, 13.8, 11.0.
- MS (ES⁺): m/z 378.2 [M+H]⁺, 400.1 [M+Na]⁺.
- R_f: 0.39 (hexanes:EtOAc 1:1).



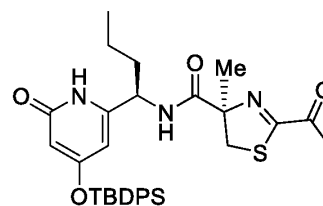
Scheme 9 provides further examples of the synthesis of more compounds of formula I.



Scheme 9

Compound **80**

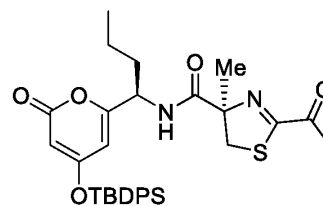
A solution of **56** (38 mg, 0.11 mmol), imidazole (16 mg, 2.2 mmol), CITBDPS (0.066 mL, 2.2 mmol) in acetonitrile (1.0 mL) was stirred at 23 °C for 2 h. The reaction mixture was diluted with CH₂Cl₂ and washed with a saturated aqueous solution of NH₄Cl. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude obtained was purified by flash chromatography over silica gel (CH₂Cl₂/ EtOAc 1/1) to afford **80** (36 mg, 56% yield).

**80**

¹H NMR (300 MHz, CDCl₃): δ 7.66 (m, 4H), 7.52-7.29 (m, 6H), 5.86 (d, *J* = 2.2 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H), 4.79-4.62 (m, 1H), 3.58 (d, *J* = 11.8 Hz, 1H), 3.14 (d, *J* = 11.7 Hz, 1H), 2.04 (d, *J* = 0.6 Hz, 3H), 1.65 (m, 2H), 1.44 (s, 3H), 1.34-1.07 (m, 2H), 1.07 (s, 9H), 0.93-0.74 (m, 3H). MS (ES): *m/z* 590.5 [M+H]⁺.

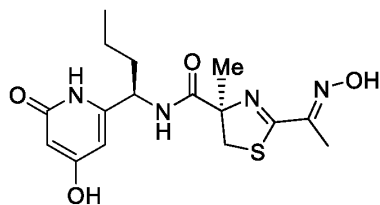
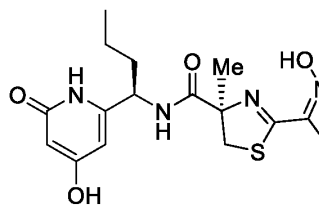
Compound **81**

A solution of **57** (42 mg, 0.12 mmol), imidazole (10 mg, 0.14 mmol) and CITBDPS (0.034 mL, 0.13 mmol) in acetonitrile (1.0 mL) was stirred at 23 °C for 2 h. The reaction mixture was diluted with CH₂Cl₂ and washed with a saturated aqueous solution of NH₄Cl. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude obtained was purified by flash chromatography over silica gel (CH₂Cl₂/EtOAc 1/1) to yield **81** (32 mg, 46% yield).

**81**

¹H NMR (300 MHz, CDCl₃): δ 7.74-7.57 (m, 4H), 7.56-7.29 (m, 6H), 6.96 (d, *J* = 9.0 Hz, 1H), 5.87 (d, *J* = 2.2 Hz, 1H), 5.23 (d, *J* = 2.2 Hz, 1H), 4.67 (q, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 12.0 Hz, 1H), 3.26 (d, *J* = 11.9 Hz, 1H), 2.53 (d, *J* = 0.5 Hz, 3H), 1.91-1.64 (m, 2H), 1.52 (s, 3H), 1.07 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H).

MS (ES): *m/z* 591.3 [M+H]⁺, 613.2 [M+Na]⁺.

Compounds **82** and **82a****82****82a**

To a solution of **80** (35 mg, 0.059 mmol) in ethanol (0.7 mL) and water (0.7 mL), were added NH₂OH·HCl (30 mg, 0.45 mmol) and NaOAc (22 mg, 0.28 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc.

The organic layers were dried over anhydrous Na_2SO_4 and after evaporation of the solvent the obtained crude was purified by HPLC method, using an XBridge C18 5 μm $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to give **82a** (1.5 mg) and **82** (5.6 mg, 26% yield).

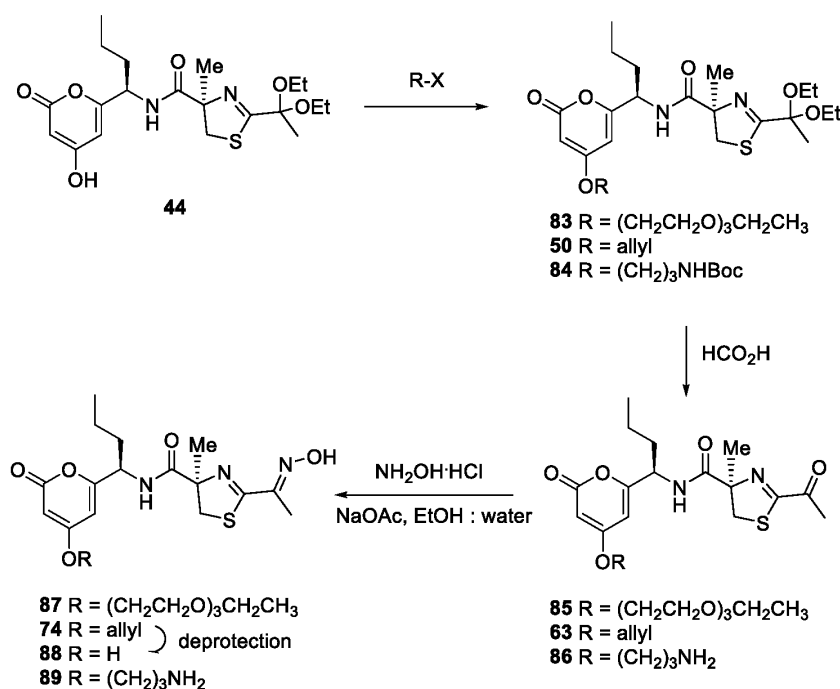
Compound **82**

- 5 ^1H NMR (500 MHz, CDCl_3): δ 5.87 (s, 1H), 5.28 (d, $J = 0.7$ Hz, 1H), 4.69 (t, $J = 7.6$ Hz, 1H), 3.55-3.44 (m, 1H), 3.14 (d, $J = 11.6$ Hz, 1H), 2.12 (s, 3H), 1.77 (t, $J = 7.7$ Hz, 2H), 1.50 (d, $J = 1.5$ Hz, 3H), 1.35 (ddd, $J = 41.7, 14.0, 7.0$ Hz, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

Compound **82a**

- 10 ^1H NMR (500 MHz, CD_3OD): δ 6.01 (d, $J = 2.1$ Hz, 1H), 5.67 (d, $J = 2.2$ Hz, 1H), 4.69 (dd, $J = 8.6, 6.8$ Hz, 1H), 3.58 (d, $J = 11.5$ Hz, 1H), 3.18 (d, $J = 11.5$ Hz, 1H), 2.21 (s, 3H), 1.85-1.69 (m, 2H), 1.50 (s, 3H), 1.45-1.22 (m, 3H), 0.94 (t, $J = 7.4$ Hz, 3H).

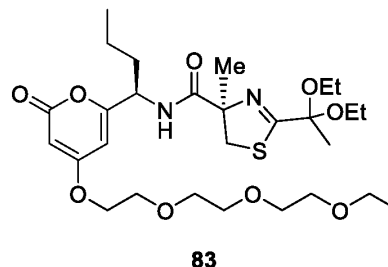
Scheme 10 provides further examples of the synthesis of more compounds of formula I.



Scheme 10

Compound **83**

A mixture of **44** (31 mg, 0.085 mmol), K₂CO₃ (59 mg, 0.42 mmol), and 1-ethoxy-2-(2-(2-iodoethoxy)ethoxy)ethane (122 mg, 0.42 mmol) in acetone (0.85 mL) was stirred at 23 °C for 24 h and then filtered over Celite®. Evaporation of the solvent gave a crude which was chromatographed on silica gel (CH₂Cl₂/EtOAc 7/3) to afford **83** (11 mg, 83% yield).

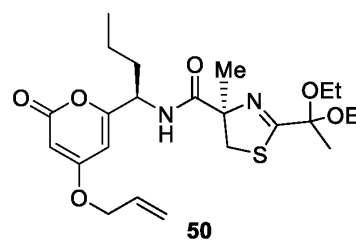


¹H NMR (300 MHz, CDCl₃): δ 7.03 (d, *J* = 8.8 Hz, 1H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.37 (d, *J* = 2.2 Hz, 1H), 4.84-4.75 (m, 1H), 4.76-4.63 (m, 1H), 4.10-4.01 (m, 2H), 4.01-3.91 (m, 1H), 3.86-3.76 (m, 2H), 3.74-3.41 (m, 11H), 3.15 (d, *J* = 11.7 Hz, 1H), 1.93-1.61 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.46-1.16 (m, 9H), 0.90 (dt, *J* = 17.4, 7.2 Hz, 3H).

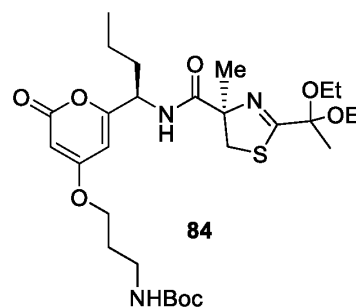
MS (ES): *m/z* 609.3 [M+Na]⁺.

Compound **50**

A mixture of **44** (30 mg, 0.07 mmol), K₂CO₃ (29 mg, 0.21 mmol), and allylbromide (0.18 mL, 2.1 mmol) in DMF (0.6 mL) was stirred at 23 °C for 5 h and then filtered over Celite®. Evaporation of the solvent gave a crude which was chromatographed on silica gel (CH₂Cl₂/EtOAc 8/1) to afford **50** (18 mg, 55% yield).

Compound **84**

A mixture of **44** (50 mg, 0.12 mmol), K₂CO₃ (83 mg, 0.6 mmol), and *t*-butyl-(3-iodopropyl)carbamate (171 mg, 0.6 mmol) in acetone (1 mL) was stirred at 23 °C for 24 h and then filtered over Celite®. Evaporation of the solvent gave a crude which was chromatographed on silica gel (CH₂Cl₂/EtOAc) to afford **84** (40 mg, 57% yield).



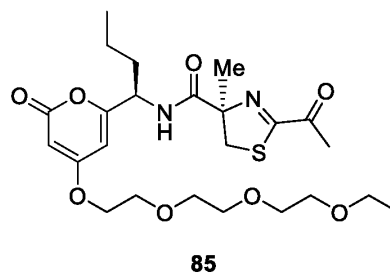
¹H NMR (300 MHz, CDCl₃): δ 7.70 (s, 1H), 7.56-7.45 (m, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.84 (d, *J* = 2.1 Hz, 1H), 5.36 (d, *J* = 2.1 Hz, 1H), 4.68 (dd, *J* = 15.6, 7.8 Hz, 2H), 4.40-4.22 (m, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.68-3.36 (m, 5H), 3.24 (d, *J* = 6.5 Hz, 2H), 3.15 (d, *J* = 11.8 Hz, 1H), 2.79 (d, *J* = 1.6 Hz, 1H), 1.98-1.67 (m, 4H), 1.60 (s, 3H), 1.52 (s, 3H), 1.42 (s, 9H), 1.26-1.15 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 3H).

MS (ES): *m/z* 539.2 [M+H]⁺, 606.2 [M+Na]⁺.

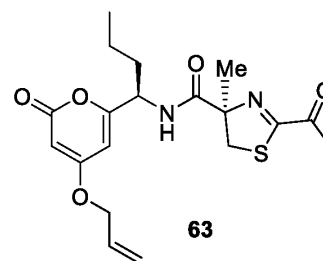
Compound **85**

To a mixture of **83** (30 mg, 0.05 mmol) and pentane (1.8 mL) was added formic acid (1.2 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving **85** (100%).

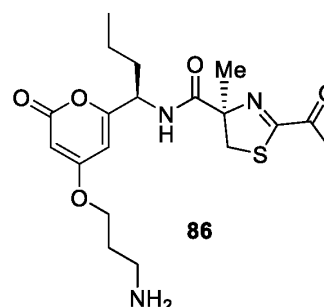
¹H NMR (300 MHz, CDCl₃): δ 7.03 (d, *J* = 8.9 Hz, 1H), 5.96 (d, *J* = 2.2 Hz, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 4.72 (m, 1H), 4.08 (m, 2H), 3.82 (m, 2H), 3.74-3.48 (m, 11H), 3.28 (d, *J* = 12.0 Hz, 1H), 2.56 (s, 3H), 1.90-1.61 (m, 2H), 1.54 (s, 3H), 1.34 (m, 2H), 1.30-1.13 (m, 6H), 0.99 (t, 3H).

Compound **63**

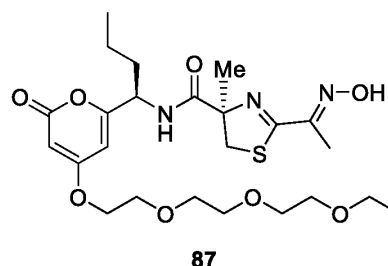
To a mixture of **50** (58 mg, 0.1 mmol) and pentane (2.9 mL) was added formic acid (2 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving **63** crude (100%) which was used immediately in the next step.

Compound **86**

To a mixture of **84** (40 mg, 0.068 mmol) and pentane (2 mL) was added formic acid (1.4 mL). The reaction was stirred vigorously at 23 °C for 1.5 h and then evaporated to dryness with toluene to remove efficiently the formic acid giving crude **86** (100%) which was used in the next step without further purification.

Compound **87**

To a solution of **85** (26 mg, 0.051 mmol) in ethanol (0.6 mL) and water (0.6 mL), were added NH₂OH·HCl (26 mg, 0.45 mmol) and NaOAc (19 mg, 0.28 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc. The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent



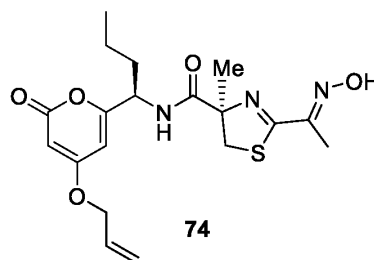
the obtained crude was purified by HPLC method, using an XBridge C18 5 μm H₂O/CH₃CN to give **87** (12.2 mg, 46% yield).

¹H NMR (300 MHz, CDCl₃): δ 9.45 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.81 (dd, *J* = 2.3, 0.7 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 4.70 (m, 1H), 4.05 (m, 2H), 3.82 (m, 2H), 3.72-3.47 (m, 7H), 3.15 (d, *J* = 11.5 Hz, 1H), 2.22 (d, *J* = 0.4 Hz, 3H), 1.99-1.65 (m, 2H), 1.58 (s, 3H), 1.47-1.27 (m, 2H), 1.21 (td, *J* = 7.0, 0.5 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

5 MS (ES): *m/z* 528.3 [M+H]⁺, 550.3 [M+Na]⁺.

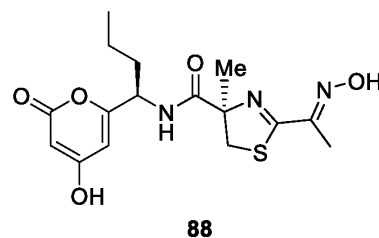
Compound 74

To a solution of **63** crude in ethanol (1.1 mL) and water (1.1 mL), were added NH₂OH·HCl (51 mg, 0.45 mmol) and NaOAc (19 mg, 0.45 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc. The organic layers were dried over anhydrous Na₂SO₄ and after evaporation of the solvent the obtained crude was purified by chromatography on silica gel (CH₂Cl₂/EtOAc 1/1) to afford **74** (17 mg, 34% yield).



Compound 88

To a solution of **74** (15 mg, 0.04 mmol) in CH₂Cl₂ (1 mL) was added PhSiH₃ (0.09 mL, 0.74 mmol) followed by addition of Pd(PPh₃)₄ in one portion. The mixture was stirred at 23 °C for 20 min until disappeared of starting material (reaction followed by TLC). After removing of volatiles, the residue was purified by chromatography on silica gel (CH₂Cl₂:EtOAc 1/1) to afford **88** (4.2 mg, 34% yield).



¹H NMR (400 MHz, CDCl₃): δ 10.74 (s, 1H), 10.17 (s, 1H), 7.30 (d, *J* = 10.4 Hz, 1H), 6.17 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 4.80 (dt, *J* = 10.2, 7.8 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.24 (d, *J* = 11.9 Hz, 1H), 2.22 (s, 3H), 1.83 (tt, *J* = 15.1, 6.1 Hz, 2H), 1.51 (s, 3H), 1.45-1.23 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

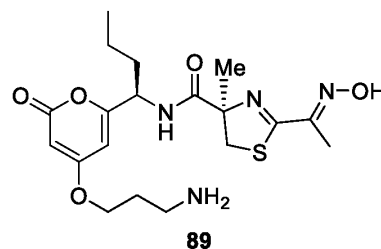
¹³C NMR (100 MHz, CD₃OD): δ 175.9, 172.3, 169.5, 167.4, 162.1, 152.1, 103.2, 92.5, 84.1, 50.6, 40.3, 34.0, 24.6, 19.1, 13.5, 11.2.

MS (ES): *m/z* 368.1 [M+H]⁺, 390.0 [M+Na]⁺.

30 R_f: 0.12 (CH₂Cl₂:CH₃OH 9:1).

Compound 89

To a mixture of **86** (28 mg, 0.068 mmol) in ethanol (0.75 mL) and water (0.75 mL), were added NH₂OH·HCl (34 mg, 0.50 mmol) and NaOAc (25 mg, 0.31 mmol). After stirring at 23 °C for 24 h the ethanol was evaporated under vacuum and the aqueous layer was extracted with EtOAc.

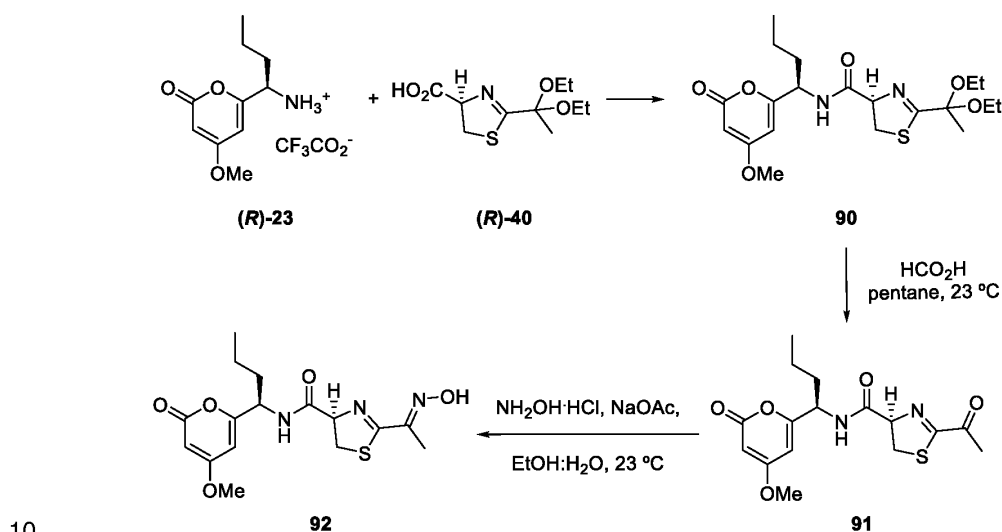


The organic layers were dried over anhydrous Na_2SO_4 and after evaporation of the solvent the obtained crude was purified by HPLC method, using an Sunfire C18 5 μm , 10 x 150 mm; $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 28% isocratic to give **89** (0.7 mg).

^1H NMR (500 MHz, CD_3OD): δ 6.06 (d, $J = 2.0$ Hz, 1H), 5.56 (d, $J = 2.0$ Hz, 1H), 4.74 (m, 1H), 4.14 (t, $J = 6.0$ Hz, 2H), 3.54 (d, $J = 11.5$ Hz, 1H), 3.18 (d, $J = 11.5$ Hz, 1H), 3.01 (t, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 2.09 (m, 2H), 1.86 (m, 2H), 1.54 (s, 3H), 1.51-1.36 (m, 2H), 0.99 (t, $J = 7.0$ Hz, 3H).

MS (ES): m/z 425.1 $[\text{M}+\text{H}]^+$, 447.2 $[\text{M}+\text{Na}]^+$.

Scheme 11 provides further examples of the synthesis of more compounds of formula I.



Scheme 11

Compound **90**

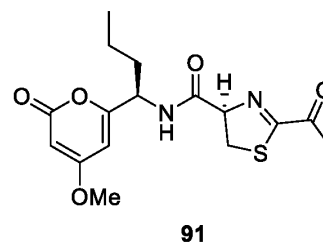
To a suspension of (**R**)-**40** (30 mg, 0.19 mmol) and (**R**)-**23** (37 mg, 0.19 mmol) in CH_2Cl_2 (1.3 mL) were added HATU (149 mg, 0.39 mmol), HOAt (54 mg, 0.39 mmol) and DIPEA (0.14 mL, 0.81 mmol) and the mixture was stirred at 23 $^\circ\text{C}$ overnight. Dilution with CH_2Cl_2 , washing of the organic layer with 0.5M HCl and brine and, finally, dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 6/4) to afford **90** (26 mg, 33% yield).

^1H NMR (400 MHz, CDCl_3): δ 6.96 (d, $J = 8.7$ Hz, 1H), 5.84 (t, $J = 1.9$ Hz, 1H), 5.37 (d, $J = 2.1$ Hz, 1H), 5.18-5.07 (m, 1H), 4.72 (td, $J = 8.4, 6.5$ Hz, 1H), 3.75 (d, $J = 1.6$ Hz, 3H), 3.66-3.38 (m, 6H), 1.90-1.69 (m, 2H), 1.59 (d, $J = 1.7$ Hz, 3H), 1.39-1.29 (m, 2H), 1.27-1.12 (m, 6H).

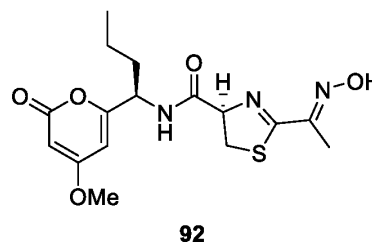
^{13}C NMR (75 MHz, CDCl_3): δ 180.6, 172.1, 172.0, 165.2, 164.0, 101.6, 101.0, 89.6, 80.2, 59.1, 57.2, 52.2, 39.8, 35.8, 35.5, 25.0, 20.3, 16.4, 16.4, 14.8.

Compound **91**

- Over **90** (82 mg, 0.19 mmol) was added at 23 °C pentane (4.3 mL) and formic acid (2.9 mL). The reaction mixture was stirred vigorously for 1.5 hours at 23 °C. The solvent was removed under vacuum to obtain crude **91** (75 mg) which was used in the next step without further purification.
- MS (ES⁺): *m/z* 353.1 [M+H]⁺.

Compound **92**

- A mixture of **91** (75 mg), ethanol (2.3 mL), water (2.3 mL), hydroxylamine hydrochloride (108 mg, 1.55 mmol) and NaOAc (77 mg, 0.94 mmol) was stirred overnight at 23 °C. Then ethanol was evaporated, brine was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The resulting crude was chromatographed over silica gel (Hex: EtOAc, from 100:0 to 50:50) to give **92** (4.5 mg).



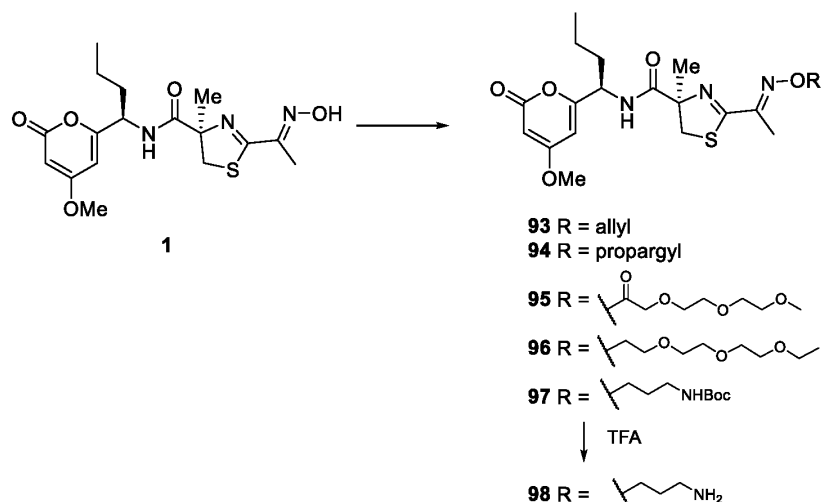
- ¹H NMR (500 MHz, (CD₃)₂CO): δ 11.25 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 6.03 (dd, *J* = 2.2, 0.7 Hz, 1H), 5.43 (d, *J* = 2.2 Hz, 1H), 5.24 (t, *J* = 9.2 Hz, 1H), 4.75 (td, *J* = 8.9, 5.5 Hz, 1H), 3.84 (s, 3H), 3.50 (d, *J* = 9.2 Hz, 2H), 2.15 (d, *J* = 0.6 Hz, 3H), 1.86 (ddt, *J* = 13.6, 9.8, 6.2 Hz, 1H), 1.76 (dtd, *J* = 14.0, 9.4, 5.2 Hz, 1H), 1.49 (dddd, *J* = 15.5, 7.9, 6.2, 4.0 Hz, 1H), 1.40 (ddt, *J* = 13.7, 9.8, 6.9 Hz, 1H), 0.95 (t, *J* = 7.3 Hz, 3H).

- ¹³C NMR (100 MHz, (CD₃)₂CO): δ 171.8, 170.8, 170.2, 165.2, 163.7, 152.9, 99.7, 99.5, 88.5, 79.9, 56.6, 51.7, 35.2, 33.9, 19.9, 13.9, 11.1.

MS (ES⁺): *m/z* 368.1 [M+H]⁺.

- Scheme 12 provides a further example of the synthesis of some compounds of formula I.

115



Scheme 12

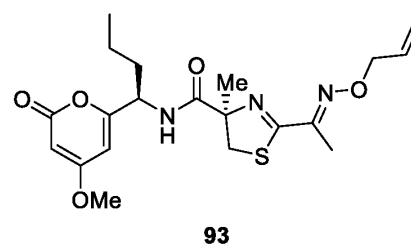
Compound **93**

To a solution of **1** (11 mg, 0.029 mmol) in acetone (2 mL) was added Cs₂CO₃ (14 mg, 0.043 mmol) and allyl bromide (4 μL, 0.043 mmol) at 23 °C. The reaction mixture was stirred for 2.5 h at 23 °C, filtrated over Celite® and washed with EtOAc. The crude obtained was purified in an automatic system for flash

chromatography (SiO₂, Hex:EtOAc from 95:5 to 50:50) to give **93** (7 mg, 58% yield).

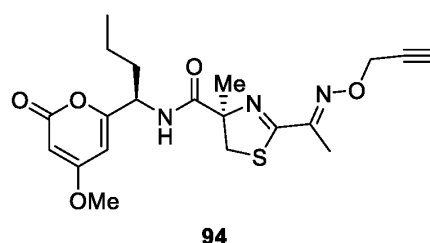
¹H NMR (400 MHz, CDCl₃): δ 7.08 (d, *J* = 8.8 Hz, 1H), 6.01 (dddd, *J* = 17.3, 10.5, 6.1, 5.7 Hz, 1H), 5.88 (dd, *J* = 2.3, 0.5 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.38-5.22 (m, 2H), 4.78-4.67 (m, 3H), 3.78 (s, 3H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.19 (dd, *J* = 11.6, 0.4 Hz, 1H), 2.20 (s, 3H), 1.89 (ddt, *J* = 13.4, 9.5, 6.5 Hz, 1H), 1.76 (dddd, *J* = 13.6, 9.7, 8.0, 5.6 Hz, 1H), 1.51 (s, 3H), 1.47-1.22 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 174.1, 170.8, 167.8, 164.1, 162.4, 151.9, 133.3, 118.4, 100.1, 88.5, 84.3, 76.3, 55.9, 50.9, 39.8, 34.7, 24.7, 19.0, 13.6, 12.0.

Compound **94**

To a solution of **1** (11.6 mg, 0.03 mmol) in acetone (2.2 mL) was added Cs₂CO₃ (15 mg, 0.046 mmol) and propargyl bromide (5 μL, 0.046 mmol) at 23 °C. The reaction mixture was stirred for 2.5 h at 23 °C, filtrated over Celite® and washed with EtOAc. The crude obtained was purified in an automatic system

for flash chromatography (SiO₂, Hex:EtOAc from 98:2 to 50:50) to yield **94** (11.7 mg, 91% yield).



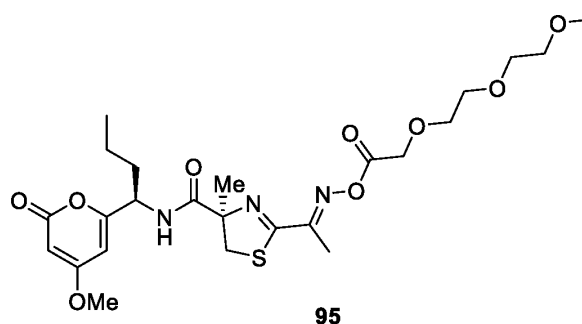
116

¹H NMR (400 MHz, CDCl₃): δ 7.06 (d, *J* = 8.8 Hz, 1H), 5.88 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 2.5 Hz, 1H), 4.81 (d, *J* = 2.4 Hz, 2H), 4.72 (q, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 3.52 (d, *J* = 11.7 Hz, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.52 (t, *J* = 2.5 Hz, 1H), 2.21 (s, 3H), 1.95-1.82 (m, 1H), 1.81-1.68 (m, 1H), 1.50 (s, 3H), 1.46-1.28 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H).

5 ¹³C NMR (100 MHz, CD₃OD): δ 174.0, 170.8, 167.4, 164.0, 162.4, 153.0, 100.1, 88.5, 84.3, 78.7, 75.2, 62.8, 55.9, 50.9, 39.9, 34.7, 24.7, 19.0, 13.6, 12.1.

Compound 95

To a solution of **1** (12 mg, 0.031 mmol), CH₂Cl₂ (0.5 mL), EDC-HCl (12 mg, 0.062 mmol) and DIPEA (11 μL, 0.062 mmol) were added 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (9 μL, 0.062 mmol) and catalytic DMAP. The reaction mixture was stirred for 24 h, diluted with CH₂Cl₂,



and the organic layer was washed with 0.5 M HCl and an aqueous saturated solution of HNaCO₃ and then dried over anhydrous Na₂SO₄ to give a crude which was purified by HPLC method, using an XBridge C18 5 μm H₂O/CH₃CN to give **95** (9 mg, 53% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.02 (d, *J* = 8.9 Hz, 1H), 5.90 (m, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 4.81-4.68 (m, 1H), 4.44 (s, 2H), 3.83-3.77 (m, 5H), 3.75-3.70 (m, 2H), 3.68-3.65 (m, 2H), 3.63 (d, *J* = 11.7 Hz, 1H), 3.58-3.54 (m, 2H), 3.38 (s, 2H), 3.27 (d, *J* = 11.7 Hz, 1H), 2.36 (s, 3H), 1.93-1.71 (m, 2H), 1.53 (s, 3H), 1.46-1.28 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

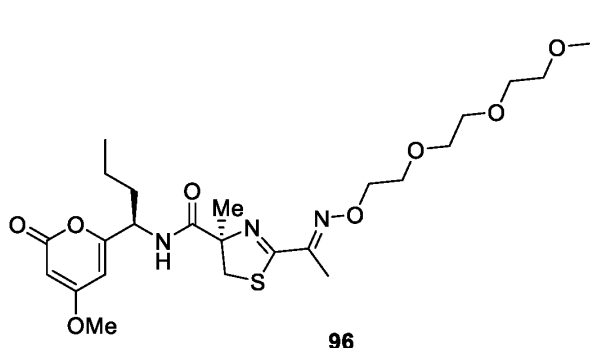
¹³C NMR (100 MHz, CD₃OD): δ 176.6, 173.5, 170.3, 166.7, 165.2, 152.9, 100.8, 88.9, 85.6, 72.9, 71.8, 71.6, 71.3, 69.1, 59.1, 57.0, 54.8, 52.1, 49.7, 40.6, 35.2, 34.8, 26.8, 26.1, 25.0, 20.2, 13.8, 11.0.

MS (ES): *m/z* 542.3 [M+H]⁺, 564.2 [M+Na]⁺.

R_f: 0.25 (hexanes:EtOAc 1:1).

Compound 96

A mixture of **1** (9.3 mg, 0.024 mmol), K₂CO₃ (16 mg, 0.12 mmol), and 1-ethoxy-2-(2-(2-iodoethoxy)ethoxy)ethane (34 mg, 0.12 mmol) in acetone (0.24 mL) was stirred at 23 °C for 24 h and then filtered over Celite®. Evaporation of the solvent gave a crude which was chromatographed

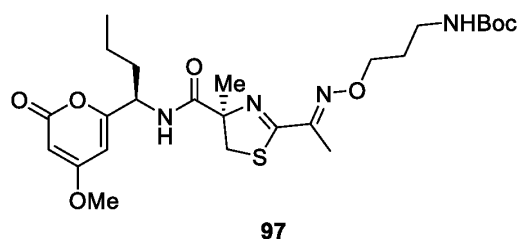


on silica gel (CH₂Cl₂/EtOAc 1/1) to yield **96** (11 mg, 83% yield).

- ¹H NMR (500 MHz, CDCl₃): δ 7.07 (d, *J* = 8.7 Hz, 1H), 5.88 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.73 (td, *J* = 8.4, 6.8 Hz, 1H), 4.43-4.32 (m, 2H), 3.79 (s, 5H), 3.69-3.63 (m, 6H), 3.62-3.57 (m, 2H), 3.56-3.47 (m, 3H), 3.20 (d, *J* = 11.6 Hz, 1H), 2.19 (s, 3H), 1.95-1.73 (m, 2H), 1.51 (s, 3H), 1.44-1.28 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).
 MS (ES): *m/z* 542.3 [M+H]⁺, 564.3 [M+Na]⁺.

Compound **97**

- A mixture of **1** (16 mg, 0.042 mmol), potassium carbonate (29 mg, 0.21 mmol), and *t*-butyl-(3-iodopropyl)-carbamate (60 mg, 0.21 mmol) in acetone (0.4 mL) was stirred at 23 °C for 18 h and then filtered over Celite®. Evaporation of the solvent

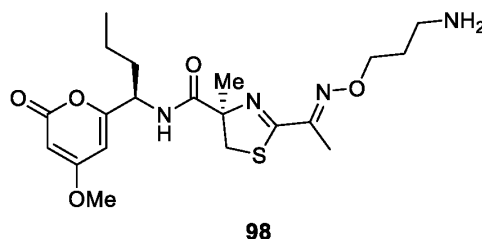


- on silica gel (CH₂Cl₂/EtOAc 9/1) to afford **97** (22 mg, 100% yield).

- ¹H NMR (500 MHz, CDCl₃): δ 7.06 (d, *J* = 8.8 Hz, 1H), 5.88 (dd, *J* = 2.3, 0.5 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.83-4.58 (m, 1H), 4.28 (t, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.30-3.11 (m, 3H), 2.17 (s, 3H), 1.98-1.61 (m, 4H), 1.50 (s, 3H), 1.43 (s, 9H), 1.41-1.15 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).
 MS (ES): *m/z* 539.3 [M+H]⁺, 561.2 [M+Na]⁺.

Compound **98**

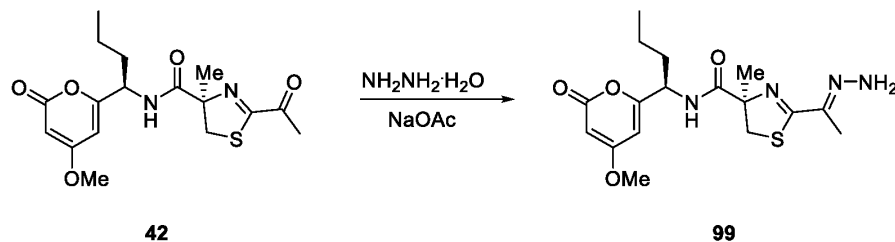
- To a solution of **97** (30 mg, 0.055 mmol) in CH₂Cl₂ (0.6 mL) was added TFA (0.26 mL) dropwise. The mixture was stirred 2 h at 23 °C and then all volatiles were evaporated (co-evaporation with toluene 3 times). The crude oil was purified by chromatography on silica gel (CH₂Cl₂/CH₃OH 15/1) to afford **98** (12.5 mg, 55% yield).



- ¹H NMR (500 MHz, CDCl₃): δ 7.02 (d, *J* = 8.8 Hz, 1H), 5.96 (d, *J* = 2.2 Hz, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 4.69 (q, *J* = 7.9 Hz, 1H), 4.35 (dt, *J* = 7.5, 4.9 Hz, 2H), 3.80 (s, 3H), 3.69 (d, *J* = 11.6 Hz, 1H), 3.24-3.01 (m, 3H), 2.21 (s, 3H), 2.18-2.08 (m, 2H), 1.88-1.75 (m, 2H), 1.54 (s, 3H), 1.47-1.29 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).
 MS (ES): *m/z* 439.2 [M+H]⁺, 461.1 [M+Na]⁺.

- Scheme 13 provides further examples of the synthesis of more compounds of formula I.

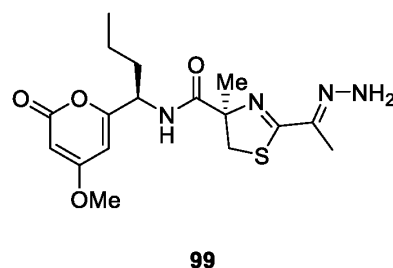
118



Scheme 13

Compound **99**

To a solution of **42** (11.6 mg, 0.032 mmol) in ethanol (0.3 mL) and water (0.3 mL), were added 50% hydrazine hydrate (0.015 mL) and NaOAc (12 mg, 0.14 mmol). After stirring at 23 °C for 24 h the solvents were evaporated under vacuum to dryness. The obtained crude was purified by chromatography on silica gel (CH₂Cl₂/EtOAc 1/1) to afford **99** (10 mg, 83% yield).

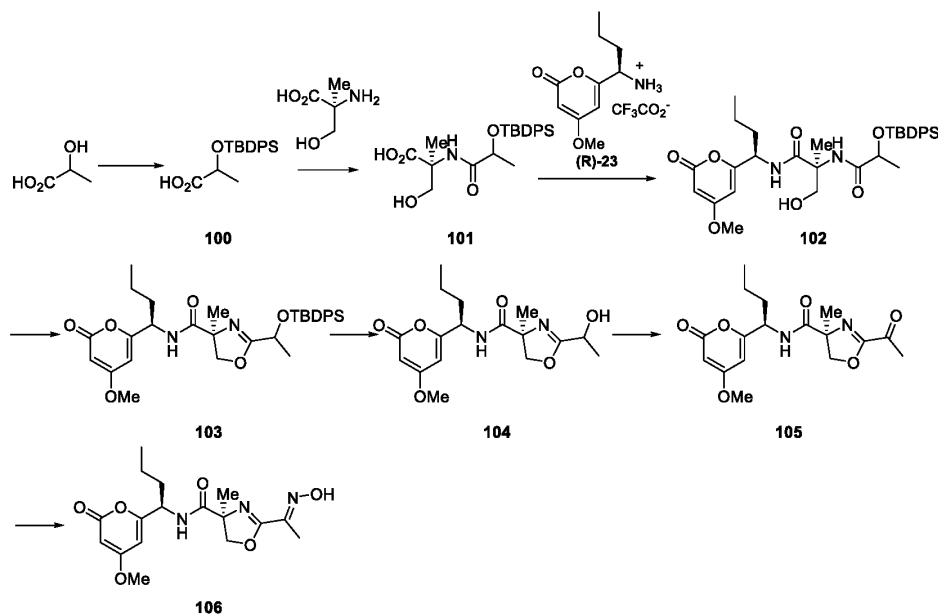


¹H NMR (500 MHz, CDCl₃): δ 7.14 (d, *J* = 8.9 Hz, 1H), 5.90 (m, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.82-4.62 (m, 1H), 3.79 (s, 3H), 3.50 (d, *J* = 11.6 Hz, 1H), 3.17 (d, *J* = 11.6 Hz, 1H), 2.11 (s, 3H), 1.88 (m, 1H), 1.76 (m, 1H), 1.52 (s, 3H), 1.48-1.21 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

MS (ES): *m/z* 381.2 [M+H]⁺, 403.1 [M+Na]⁺.

15 EXAMPLE 10 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 14 provides an example of the synthesis of additional compounds of formula I.



Scheme 14

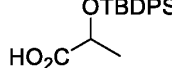
Compound 100

To a stirred solution of lactic acid (1.0 g, 11.1 mmol) with imidazole (1.13 g, 16.6 mmol) in anhydrous DMF (33 mL) was added in portions *tert*-butyldimethylsilyl chloride (2.8 mL; 11.1 mmol). After 48 h at 23 °C the solution was diluted with hexane and washed once with water, once with saturated NaHCO₃ and once with brine. The organic layer was dried over Na₂SO₄ and the solvent was removed under reduced pressure to yield **100** (3.1 g, 85% yield) as a colourless oil.

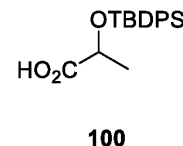
¹H NMR (500 MHz, CDCl₃): δ 7.65 (m, 4H), 7.40 (m, 6H), 4.32 (q, *J* = 7.0 Hz, 1H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.11 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 207.1, 135.7, 130.2, 130.1, 127.9, 127.8, 69.1, 30.9, 30.8, 26.8, 26.7, 21.0, 19.1.

MS (ES): *m/z* 351.2 [M+Na]⁺.



100



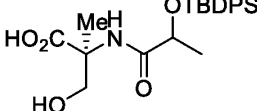
Compound 101

15 To a stirred solution of **100** (140 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (3 mL), was added at 0 °C *N*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC-HCl) (89 mg, 0.47mmol) and 1-Hydroxybenzotriazole hydrate (HOBt) (63 mg, 0.47 mmol). After 10 min at 0 °C, (L)- α -methylserine (Across Organics) (50 mg, 0.43

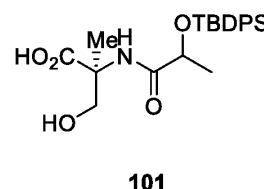
20 mmol) and Et_3N (0.06 mL) were added. The crude mixture was stirred 18 h at 23 °C, diluted with CH_2Cl_2 and acidified with aqueous HCl (0.5 M) to pH~2 and extracted with CH_2Cl_2 . The combined organic phase was dried over Na_2SO_4 , filtrated and concentrated in vacuo to yield **101** (170 mg; 92% yield) that was used without further purification as a mixture of two diastereomers.

25 ^1H NMR (300 MHz, CDCl_3) δ 7.96 (s, 1H), 7.86 (s, 1H), 7.66 (m, 8H), 7.61 (m, 1 H), 4.27 (m, 2H), 3.98 (dd, J = 11.4, 2.7 Hz, 2H), 3.78 (d, J = 11.4, 1.7 Hz, 2H), 1.27 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H), 1.20 (s, 18 H).

MS (ES): m/z 452.3 $[\text{M}+\text{Na}]^+$.



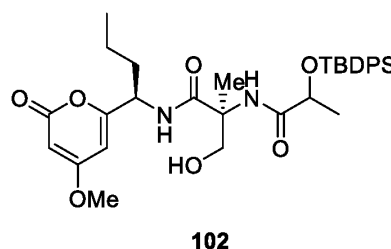
101



Compound 102

To a stirred solution of **101** (170 mg, 0.40 mmol) and (*R*)-**23** (84 mg, 0.40 mmol) in anhydrous CH₂Cl₂ (3 mL) were added 1-[Bis(dimethylamino) methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxid hexafluorophosphate (HATU) (212 mg, 0.56 mmol), 1-Hydroxy-7-azabenzotriazole (HOAt) (76 mg, 0.56 mmol) and Diisopropylethylamine (DIPEA) (0.29 mL, 1.68 mmol) and the mixture was stirred at 23 °C overnight. After dilution with CH₂Cl₂, the

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organic layer was washed with 0.5 M HCl, brine and, finally, dried over Na₂SO₄. Filtration and evaporation of the solvent gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc) to afford **102** (102 mg, 46% yield) as a mixture of two diastereomers.

¹H NMR (300 MHz, CDCl₃): δ 8.06 (d, *J* = 8.3 Hz, 2H), 7.82 (s, 2H), 7.66 (m, 8H), 7.40 (m, 12 H), 5.88 (d, *J* = 2.3 Hz, 1H), 5.85 (d, *J* = 2.3 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 4.69 (m, 2H), 4.28 (m, 6H), 4.0 (t, *J* = 10.5 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 1.89-1.62 (m, 4H), 1.50 (s, 3H), 1.43 (s, 3H), 1.35 (m, 4H), 1.30 (d, *J* = 7.5 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H), 1.12 (s, 9H), 1.09 (s, 9H), 0.92 (t, *J* = 7.3 Hz, 6H).

MS (ES): *m/z* 609.2 [M+H]⁺.

10 Compound **103**

To a stirred solution of **102** (100 mg, 0.16 mmol) in anhydrous CH₂Cl₂ (1.5 mL) was added dropwise diethylaminosulfur trifluoride (DAST) (0.02 mL, 0.18 mmol) at -78 °C. After 1.5 h, the reaction mixture was

quenched by addition of K₂CO₃ (34 mg, 0.25 mmol) in one portion at -78 °C. After warming to 23 °C, the mixture was further diluted with saturated aqueous

sodium bicarbonate and extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated to yield **103** (96 mg; 100% yield) that was used without

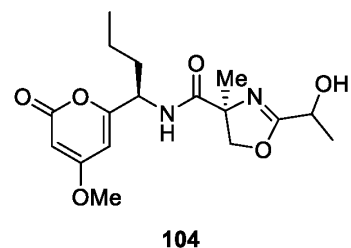
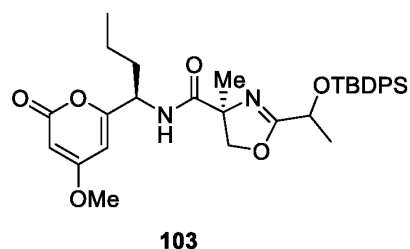
further purification as a mixture of two diastereomers. ¹H NMR (300 MHz, CDCl₃): δ 7.66 (m, 8H), 7.38 (m, 12 H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 5.78 (d, *J* = 2.3 Hz, 1H), 5.40 (d, *J* = 2.2 Hz, 1H), 5.37 (d, *J* = 2.2 Hz, 1H), 4.66 (m, 2H), 4.50-4.25 (m, 4H), 3.97 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 1.90-1.57 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.28 (m, 10H), 1.06 (s, 18H), 0.92 (t, *J* = 7.3 Hz, 6H).

MS (ES): *m/z* 591.2 [M+H]⁺.

Compound **104**

To a stirred solution of **103** (96 mg, 0.16 mmol) in anhydrous THF (1.5 mL) was added tetrabutylammonium fluoride (TBAF) (0.25 mL, 0.25 mmol) dropwise. After 1 h at 23° C the reaction mixture was quenched with a saturated aqueous ammonium chloride and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated to obtain crude **104** (55 mg; 99% yield)

that was used without further purification as a mixture of two diastereomers.



¹H NMR (300 MHz, CDCl₃): δ 7.05 (t, *J* = 9.6 Hz, 2H), 5.89 (d, *J* = 2.3 Hz, 1H), 5.87 (d, *J* = 2.3 Hz, 1H), 5.40 (d, *J* = 2.2 Hz, 2H), 4.67 (m, 2H), 4.58-4.22 (m, 4H), 4.10 (m, 2H), 3.76 (s, 6H), 1.86-1.60 (m, 4H), 1.5 (s, 6H), 1.46-1.30 (m, 10H), 0.92 (t, *J* = 7.3 Hz, 6H).

MS (ES): *m/z* 353.1 [M+H]⁺.

5 Compound **105**

To a solution of **104** (57 mg, 0.16 mmol) in anhydrous CH₂Cl₂ (1.6 mL) at 23 °C was successively added NaHCO₃ (41 mg, 0.49 mmol) and Dess-Martin periodinane (DMP) (139 mg, 0.33 mmol) in portions. After 1 h at 23 °C (reaction followed

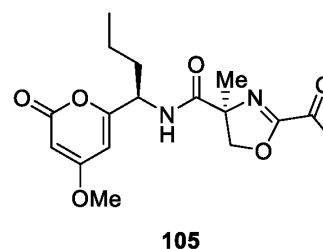
10 by TLC (Hex:EtOAc 1:1), the reaction mixture was quenched

with a 1:1 mixture of aqueous saturated solution of NaHCO₃

and 10% solution of Na₂S₂O₃. The mixture was stirred for 1 h at 23 °C and extracted with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to give an oil that was purified by flash chromatography on silica gel (hexane/EtOAc) to

15 afford **105** (9 mg, 18% yield) as a white solid.

¹H NMR (300 MHz, CDCl₃): δ 6.84 (d, *J* = 9.3 Hz, 1H), 5.87 (d, *J* = 2.3 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 4.70 (m, 1H), 4.63 (d, *J* = 9.3 Hz, 1H), 4.23 (d, *J* = 9.3 Hz, 1H), 3.78 (s, 3H), 2.55 (s, 3H), 1.92-1.71 (m, 2H), 1.56 (s, 3H), 1.44-1.30 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).



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Compound **106**

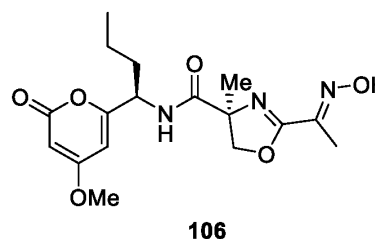
20 To a solution of **105** (7 mg, 0.02 mmol) in ethanol (0.22 mL) and water (0.22 mL), were added NH₂OH·HCl (10 mg, 0.146 mmol) and NaOAc (7 mg, 0.09 mmol). After stirring at 23 °C for 24 h, solvent was

25 extracted with EtOAc. The combined organic layer was

dried over Na₂SO₄, filtered, and concentrated to give a crude that was purified by chromatography on silica gel (CH₂Cl₂/EtOAc 1/1) to afford **106** (1.6 mg, 23% yield).

¹H NMR (300 MHz, CDCl₃): δ 6.85 (d, *J* = 9.3 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 5.35 (d, *J* = 2.3 Hz, 1H), 4.63 (m, 1H), 4.14 (d, *J* = 9.3 Hz, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.72 (s, 3H), 2.14 (s, 3H), 1.82-1.67 (m, 2H), 1.48 (s, 3H), 1.30 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

30 MS (ES): *m/z* 366.2 [M+H]⁺.

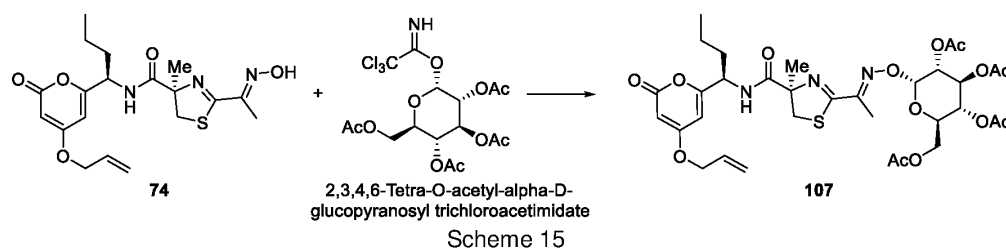


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EXAMPLE 11 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 15 provides an example of the synthesis of additional compounds of formula I.

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A mixture of **74** (37 mg; 0.091 mmol), 2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl trichloroacetimidate (30 mg, 0.061 mmol) and freshly activated 4Å MS (244 mg) were dissolved/suspended in CH_2Cl_2 (1.0 mL) and stirred for 1 h at 23 °C. Then, the temperature was decreased to -20 °C and TMSOTf (12 μL ; 0.064 mmol) was slowly added. The reaction was allowed to get into 23 °C. and then stirred overnight. Subsequently, Et_3N was added to quench the reacting mixture and the resulting suspension filtered through a bylayer pad of Celite® (on top) and Na_2SO_4 (below). The solids were thoroughly washed with CH_2Cl_2 and the whole filtrate concentrated in vacuum, giving rise to a yellow-orange gel that was purified by flash chromatography on silica gel (Hex:EtOAc from 70:30 to 0:100) to afford pure **107** (23 mg, 51% yield).

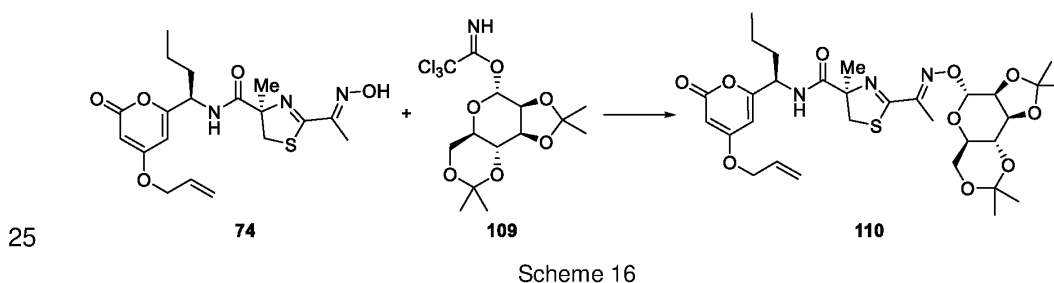
^1H NMR (400 MHz, CDCl_3): δ 7.08 (d, J = 8.9 Hz, 1H), 6.00 (d, J = 5.6 Hz, 1H), 5.98-5.92 (m, 1H), 5.41-5.36 (m, 3H), 5.15 (dd, J = 2.8, 2.8 Hz, 1H), 4.92 (dd, J = 9.3, 2.8 Hz, 1H), 4.73 (q, J = 7.8, 1H), 4.65 (dd, J = 5.6, 2.8 Hz, 1H), 4.49 (dt, J = 5.6, 1.2 Hz, 2H), 4.23 (dd, J = 4.0, 2.7, 2H), 3.93 (ddd, J = 8.8, 5.0, 3.4, 1H), 3.53 (d, J = 11.6, 1H), 3.21 (d, J = 11.6, 1H), 2.17 (s, 3H), 2.10 (bs, 9H), 1.92-1.70 (m, 2H), 1.86 (s, 3H), 1.50 (s, 3H), 1.49-1.28 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 173.9, 170.8, 169.8, 169.8, 169.3, 167.5, 164.1, 162.4, 153.4, 130.7, 123.4, 119.8, 100.6, 98.7, 89.6, 84.88, 74.9, 70.2, 69.8, 67.9, 67.4, 63.3, 51.1, 40.0, 35.0, 24.9, 21.4, 21.0, 20.9, 20.9, 19.2, 13.7, 12.2.

MS (ES⁺): m/z 738 $[\text{M}+\text{H}]^+$, 760 $[\text{M}+\text{Na}]^+$.

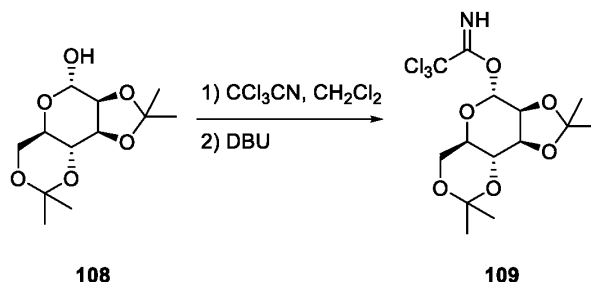
R_f: 0.21 (Hex:EtOAc 50:50).

Scheme 16 provides an example of the synthesis of an additional compound of formula I.



a) Synthesis of **109**

123



To a solution of **108** (570 mg, 2.190 mmol) [obtained as described in *Bioorg. Med. Chem.* **2013**, 21, 4839-4845] in anhydrous CH_2Cl_2 (11 mL), CCl_3CN (2.20 mL, 21.90 mmol) and DBU (66 μL , 0.44 mmol) were added dropwise in this order at 23 $^\circ\text{C}$. The reaction was stirred for 1 h and then, concentrated in vacuum. The resulting dark red crude was subjected to a chromatographic column (SiO_2 , Hexane + 1% Et_3N : EtOAc + 1% Et_3N from 80:20 to 50:50) giving rise to **109** (827 mg; 93% yield) as a white solid.

^1H NMR (400 MHz): δ 8.59 (s, 1H), 6.26 (s, 1H), 4.92 (dd, J = 5.9, 3.4 Hz, 1H), 4.86 (d, J = 5.8 Hz, 1H), 4.43 (ddd, J = 8.3, 6.2, 4.2 Hz, 1H), 4.14-4.09 (m, 2H), 4.03 (dd, J = 8.9, 4.2 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz): δ 160.8, 113.6, 109.6, 104.9, 84.9, 83.0, 79.4, 72.8, 67.2, 27.1, 26.1, 25.3, 24.9.

MS (ES): m/z 426-428 $[\text{M}+\text{Na}]^+$.

R_f: 0.64 (Hex:EtOAc 2:1).

15 b) Synthesis of **110**

A freshly-prepared stock solution (840 μL ; 5% mol) of $\text{Pd}(\text{PhCN})(\text{OTf})_2$ catalyst in CH_2Cl_2 , prepared by stirring $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ (10 mg; 0.026 mmol) and AgOTf (14 mg; 0.052 mmol) in CH_2Cl_2 (3.5 mL) at 23 $^\circ\text{C}$ for 5 min, was added to a solution of **109** (50 mg; 0.124 mmol) and **74** (61 mg; 0.161 mmol) in CH_2Cl_2 , (700 μL) at 23 $^\circ\text{C}$. The reaction mixture was stirred at 23 $^\circ\text{C}$ overnight, then, treated with benzene (1 mL) and directly poured on a chromatographic column (SiO_2 , CH_2Cl_2 to CH_2Cl_2 :MeOH 98.2:1.8). According to this procedure, compound **110** (27.5 mg, 34% yield) was afforded as a foamy white solid (predominantly as a α anomer).

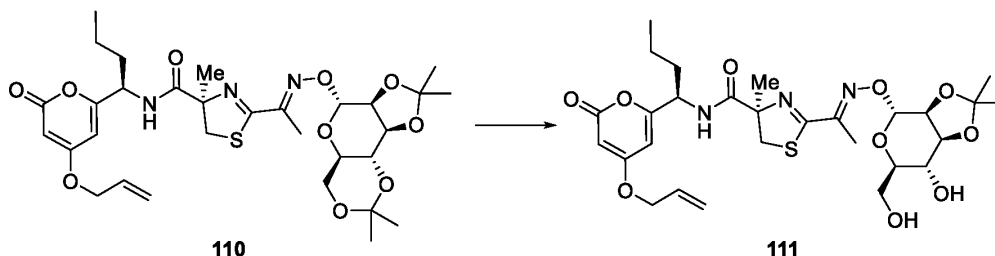
^1H NMR (400 MHz, CDCl_3): δ 9.25 (s, 1H), 7.10 (d, J = 8.9 Hz, 1H), 6.00-5.91 (m, 1H), 5.69 (bs, 1H), 5.42-5.30 (m, 3H), 4.93-4.91 (dd, J = 6.0, 3.6 Hz, 1H), 4.87 (d, J = 6.0 Hz, 1H), 4.73 (q, J = 7.9 Hz, 1H), 4.49 (bd, J = 6.6 Hz, 2H), 4.38 (m, 1H), 4.22 (dd, J = 7.7, 3.9 Hz, 1H), 4.08 (bd, J = 5.2 Hz, 2H), 3.52 (d, J = 11.6 Hz, 1H), 3.20 (d, J = 11.6 Hz, 1H), 2.19 (s, 3H), 1.93-1.72 (m, 2H), 1.51 (s, 3H), 1.50 (s, 3H), 1.49-1.28 (m, 11H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 169.8, 167.5, 164.1, 162.5, 153.8, 130.8, 119.8, 113.0, 109.3, 109.0, 100.6, 89.6, 84.8, 84.7, 83.3, 80.0, 73.5, 69.7, 66.8, 51.1, 40.0, 35.0, 27.1, 26.1, 25.3, 24.9, 24.6, 19.2, 13.7, 12.2.

MS (ES⁺): m/z 650 $[\text{M}+\text{H}]^+$, 672 $[\text{M}+\text{Na}]^+$.

Rf: 0.39 (CH₂Cl₂:MeOH 50:1).

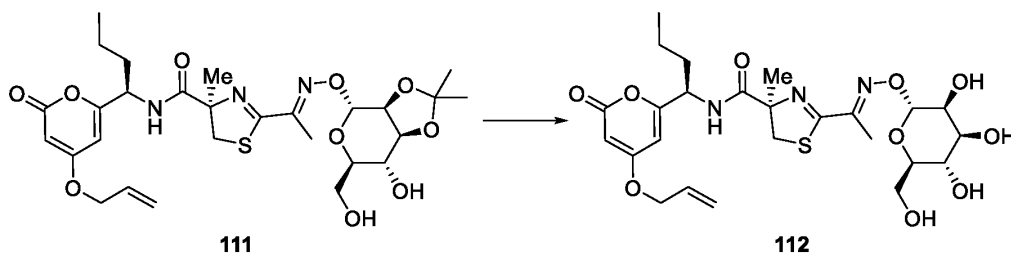
Scheme 17 provides an example of the synthesis of an additional compound of formula I.



Scheme 17

- 5 Compound **110** (31 mg, 0.048 mmol) was dissolved in aqueous AcOH (80%, 1.0 mL) and stirred at 65 °C for 4h. Then, the solution was diluted with toluene (1.5 mL) and the volatiles vacuum evaporated, affording an oily beige crude. Co-evaporation of aqueous AcOH with toluene was repeated twice more. The obtained crude was purified by column chromatography (SiO₂, CH₂Cl₂ to CH₂Cl₂:MeOH 10:1) to obtain compound **111** (18 mg, 62% yield) as a waxy white solid.
- 10 ¹H NMR (500 MHz, CDCl₃): δ 7.04 (d, *J* = 8.9 Hz, 1H), 5.99-5.92 (m, 1H), 5.72 (bs, 1H), 5.42-5.34 (m, 3H), 5.01 (dd, *J* = 6.0, 4.3 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.72 (q, *J* = 8.0 Hz, 1H), 4.49 (bd, *J* = 5.5 Hz, 2H), 4.25 (dd, *J* = 8.0, 4.3 Hz, 1H), 3.97 (bd, *J* = 8.3, 5.8, 3.4 Hz, 1H), 3.86 (d, *J* = 11.5, 3.4 Hz, 1H), 3.74 (d, *J* = 11.5, 5.8 Hz, 1H), 3.54 (d, *J* = 11.6 Hz, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.19 (s, 3H), 1.90-1.72 (m, 2H), 1.52 (s, 6H), 1.37 (s, 3H), 1.42-1.31 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).
- 15 ¹³C NMR (125 MHz, CDCl₃): δ 174.0, 169.9, 167.6, 164.2, 162.4, 153.9, 130.7, 119.8, 113.0, 108.7, 100.7, 89.6, 84.7, 84.6, 82.7, 80.7, 71.0, 69.8, 64.5, 51.2, 40.1, 35.0, 26.1, 25.0, 24.7, 19.2, 13.7, 12.2.
- MS (ES⁺): *m/z* 610 [M+H]⁺, 632 [M+Na]⁺.
- 20 Rf: 0.12 (CH₂Cl₂:MeOH 50:1).

Scheme 18 provides an example of the synthesis of an additional compound of formula I.



Scheme 18

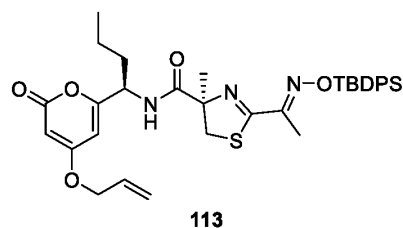
- A solution of **111** (180 mg, 0.29 mmol) in aqueous AcOH (80%, 10 mL) was heated at 100 °C for 4h. Then, the solution was diluted with toluene (10 mL) and the volatiles vacuum evaporated,
- 25

affording an oily beige crude. Co-evaporation of aqueous AcOH with toluene was repeated (x5) to afford a beige crude that was purified by flash chromatography (SiO₂, CH₂Cl₂ to CH₂Cl₂:MeOH 90:10). Final purification was carried out by HPLC on a C18 Symmetry preparative column, flow rate 15 mL/min, H₂O:CH₃CN mixtures to obtain compound 112 (60 mg, 36% yield).

- 5 ¹H NMR (500 MHz, CDCl₃): δ 7.07 (d, *J* = 8.8 Hz, 1H), 6.00-5.92 (m, 1H), 5.72 (d, *J* = 2.5, 1H), 5.44-5.34 (m, 3H), 4.72 (q, *J* = 8.0 Hz, 1H), 4.61 (t, *J* = 4.9 Hz, 1H), 4.50 (bd, *J* = 5.6, 2H), 4.41 (dd, *J* = 5.3, 2.5 Hz, 1H), 4.20 (dd, *J* = 6.8, 4.5 Hz, 1H), 4.09 (td, *J* = 6.4, 3.5 Hz, 1H), 3.87 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.77 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.55 (d, *J* = 11.6 Hz, 1H), 3.20 (d, *J* = 11.6 Hz, 1H), 2.20 (s, 3H), 1.92-1.73 (m, 2H), 1.52 (s, 3H), 1.42-1.28 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).
- 10 ¹³C NMR (100 MHz, CDCl₃): δ 174.2, 170.1, 167.9, 164.6, 162.5, 154.0, 130.7, 119.8, 110.5, 100.8, 89.6, 84.6, 80.8, 75.6, 71.9, 71.6, 69.9, 63.7, 51.2, 40.3, 34.9, 25.0, 19.2, 13.7, 12.5.
- MS (ES⁺): *m/z* 570 [M+H]⁺, 592 [M+Na]⁺.

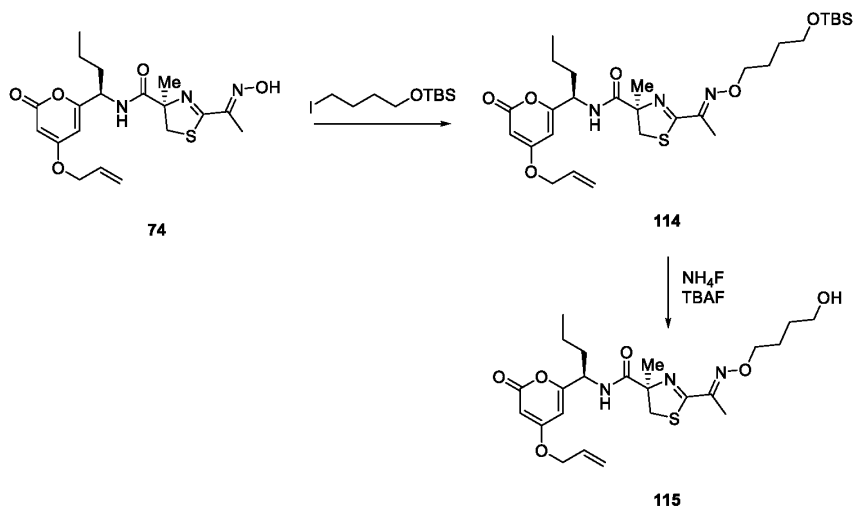
Compound 113

- 15 To a solution of **74** (121 mg) in dry DMF (3 mL) was added imidazole (47 mg), DMAP (1 mg) and TBDPSCI (85 μL) and reaction mixture was stirred overnight at 23 °C. To quench the reaction, aqueous saturated solution of NH₄Cl (10 mL) was added and mixture was
- 20 extracted with EtOAc (3 x 10 mL). Combined organic phases were washed with water (3 x 10 mL) and brine (10 mL) and then dried over anhydrous Na₂SO₄, filtered and evaporated. Crude residue was purified on CombiFlash with a SiO₂ column and eluting with hexane/EtOAc from 100:0 to 0:100 in 30 min. to yield Compound **113** (108 mg, 56% yield).
- 25 ¹H NMR (400 MHz, CDCl₃): δ 7.75-7.66 (m, 2H), 7.48-7.33 (m, 8H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.03-5.87 (m, 1H), 5.94 (d, *J* = 2.2 Hz, 1H), 5.42 (d, *J* = 2.3 Hz, 1H), 5.43-5.36 (m, 1H), 5.34 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.73 (q, *J* = 8.0 Hz, 1H), 4.48 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.46 (d, *J* = 11.6 Hz, 1H), 3.15 (d, *J* = 11.6 Hz, 1H), 2.35 (s, 3H), 1.89 (dq, *J* = 9.5, 6.8 Hz, 1H), 1.78 (dddd, *J* = 13.6, 9.6, 7.9, 5.7 Hz, 1H), 1.50 (s, 3H), 1.49-1.20 (m, 2H), 1.15 (s, 9H), 0.97 (t, *J* = 7.3 Hz, 3H).
- 30 ¹³C NMR (100 MHz, CDCl₃): δ 174.2, 169.7, 168.5, 164.1, 162.4, 157.2, 135.5, 132.8, 130.6, 129.9, 127.6, 119.6, 100.4, 89.4, 84.3, 69.6, 51.0, 39.7, 34.7, 27.1, 24.8, 19.6, 19.1, 13.6, 11.8.



Scheme 19 provides an example of the synthesis of additional compounds of formula I.

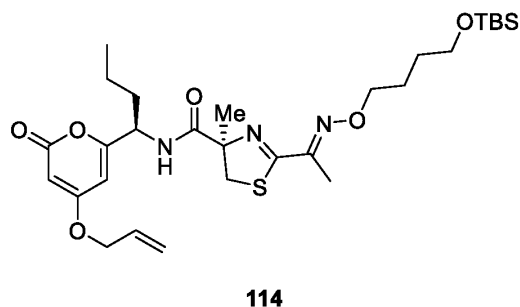
126



Scheme 19

Compound 114

To a solution of **74** (77 mg, 0.190 mmol) in acetone (2 mL) Cs₂CO₃ (310 mg, 0.952 mmol) and *tert*-Butyl(4-iodobutoxy)dimethylsilane (0.25 mL, 0.952 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C overnight, filtered, washed with EtOAc, and concentrated under reduced pressure. The resulting residue was purified by combiflash in SiO₂ (CH₂Cl₂:EtOAc from 100:0 to 90:10) to yield **114** (80 mg, 71% yield).



¹H NMR (400 MHz, CD₃OD): δ 7.85 (d, *J* = 8.6 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 6.05-5.92 (m, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 5.46-5.27 (m, 2H), 4.75 (ddd, *J* = 8.8, 7.3, 4.3 Hz, 1H), 4.58 (dt, *J* = 5.6, 1.5 Hz, 2H), 4.22 (t, *J* = 6.5 Hz, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 3.58 (dd, *J* = 11.5, 5.8 Hz, 1H), 3.19 (d, *J* = 11.6 Hz, 1H), 2.19 (d, *J* = 2.2 Hz, 3H), 1.97-1.70 (m, 4H), 1.60 (dd, *J* = 8.7, 6.1 Hz, 2H), 1.52 (d, *J* = 1.9 Hz, 3H), 1.49-1.34 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

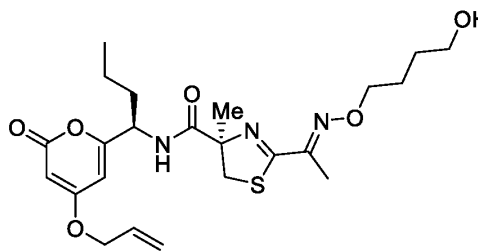
¹³C NMR (100 MHz, CD₃OD): δ 175.0, 170.7, 168.0, 165.1, 163.9, 151.4, 131.1, 118.0, 99.5, 88.4, 84.2, 74.9, 69.6, 62.5, 50.8, 39.3, 33.9, 28.8, 25.4, 25.0, 23.5, 18.8, 17.7, 12.5, 10.4, -6.5.

MS (ES⁺): *m/z* 594 [M+H]⁺, 616 [M+Na]⁺.

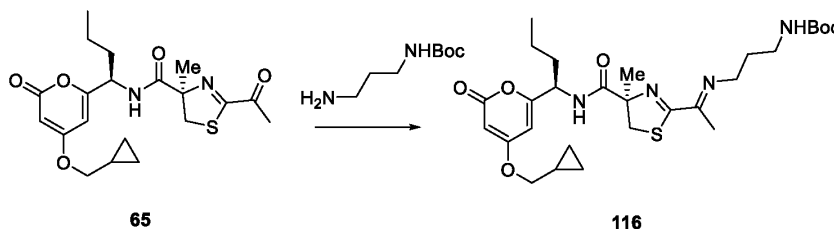
127

Compound **115**

- To a solution of **114** (70 mg, 0.118 mmol) in anhydrous THF (1 mL) ammonium fluoride (22 mg, 0.589 mmol) and TBAF (0.60 mL, 1.0 M in THF, 0.589 mmol) were added at 23 °C. The reaction mixture was stirred for 4 h at 23 °C, quenched with a saturated aqueous solution of NaCl, extracted with CH₂Cl₂ (2x10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash in SiO₂ (CH₂Cl₂ to CH₂Cl₂:EtOAc 1:1) to yield **115** (40 mg, 71% yield).
- ¹H NMR (400 MHz, CD₃OD): δ 6.06 (d, *J* = 2.2 Hz, 1H), 6.05-5.91 (m, 1H), 5.54 (d, *J* = 2.2 Hz, 1H), 5.46-5.29 (m, 2H), 4.74 (dd, *J* = 9.1, 5.8 Hz, 1H), 4.59 (dt, *J* = 5.5, 1.6 Hz, 2H), 4.23 (t, *J* = 6.5 Hz, 2H), 3.63-3.50 (m, 3H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.19 (s, 3H), 1.89-1.73 (m, 3H), 1.62 (dd, *J* = 8.9, 6.2 Hz, 2H), 1.52 (s, 3H), 1.45-1.32 (m, 1H), 0.99 (q, *J* = 8.1, 7.4 Hz, 3H).
- ¹³C NMR (100 MHz, CD₃OD): δ 174.9, 170.7, 168.0, 165.1, 163.9, 151.5, 131.1, 118.0, 99.5, 88.4, 84.2, 74.9, 69.6, 61.2, 50.7, 39.3, 33.8, 28.6, 25.3, 23.5, 18.8, 12.4, 10.3.
- MS (ES⁻): *m/z* 478 [M-H].

**115**

Scheme 20 provides an example of the synthesis of an additional compound of formula I.



Scheme 20

Compound **116**

- To a solution of **65** (42 mg, 0.103 mmol) in anhydrous toluene (1 mL), N-Boc-1,3-propanediamine (19 mg, 0.107 mmol), *p*TsOH (1 mg, 0.005 mmol) and molecular sieve were added and was refluxed for 2 h. Then, reaction mixture was filtered through Celite® and the filtrate was evaporated. The resulting residue was purified by combi flash in SiO₂ (from Hexane + 1% Et₃N to Hex:EtOAc:Et₃N 1:1:0.01) to yield **116** (29 mg, 50% yield).
- ¹H NMR (500 MHz, CDCl₃): δ 7.10 (d, *J* = 8.9 Hz, 1H), 5.92 (d, *J* = 2.2 Hz, 1H), 5.34 (d, *J* = 2.2 Hz, 1H), 5.22 (br s, 1H), 4.75-4.70 (m 1H), 3.76 (dd, *J* = 7.1, 2.8 Hz, 2H), 3.53 (t, *J* = 6.6 Hz, 2H), 3.50 (d, *J* = 11.7 Hz, 1H), 3.30-3.26 (m, 2H), 3.16 (d, *J* = 11.7 HZ, 1H), 2.20 (s, 3H), 1.914-

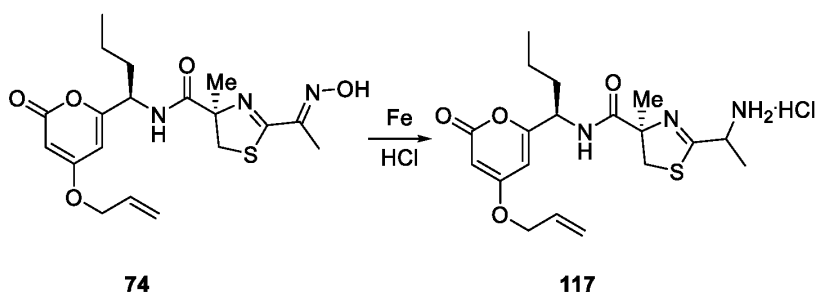
1.84 (m, 3H), 1.80-1.73 (m, 1H), 1.52 (s, 3H), 1.42 (s, 9H), 1.45-1.33 (m, 1H), 1.24-1.19 (m, 1H), 0.98-0.94 (m, 4H), 0.68-0.64 (m, 2H), 0.34-0.31 (m, 2H).

^{13}C NMR (125 MHz, CDCl_3): δ 174.1, 173.7, 170.1, 170.0, 164.1, 162.3, 156.0, 100.5, 88.9, 88.8, 85.6, 73.8, 50.9, 30.6, 34.9, 30.1, 28.4, 28.3, 24.9, 19.0, 14.78, 13.6, 9.4, 3.4, 3.3.

5 MS (ES⁺): m/z 563 [M+H]⁺.

R_f: 0.55 (Hex:EtOAc:Et₃N 9:1:0.01).

Scheme 21 provides an example of the synthesis of an additional compound of formula I.



Scheme 21

10 Compound **117**

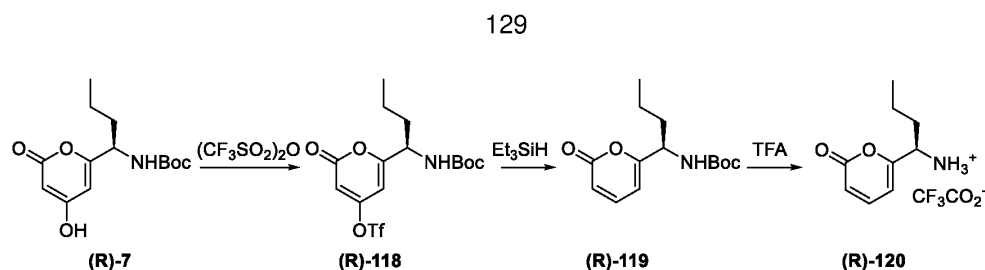
To a solution of **74** (50 mg, 0.123 mmol) in MeOH (1 mL) were added iron powder (14 mg, 0.24 mmol) and conc. HCl and the reaction mixture was stirred at 23 °C for 3 h. Then the reaction mixture was quenched with a saturated aqueous solution of Na_2CO_3 and was extracted with 10% MeOH in CH_2Cl_2 . The organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2 :MeOH) to afford **117** (23 mg, 48% yield).

15

^1H NMR (400 MHz, CD_3OD): δ 6.32-5.91 (m, 1H), 5.64-5.50 (m, 1H), 5.49-5.25 (m, 1H), 4.73 (dt, J = 9.0, 6.3 Hz, 1H), 3.90-3.36 (m, 2H), 1.89-1.76 (m, 2H), 1.59-1.33 (m, 5H), 0.96 (ddd, J = 8.6, 5.7, 1.8 Hz, 3H).

20 EXAMPLE 12. SYNTHESIS OF FURTHER INTERMEDIATES OF FORMULA II

Scheme 22 provides further examples of the synthesis of intermediates of formula II



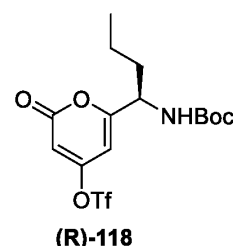
Scheme 22

Compound (*R*)-118

5 A solution of triflic anhydride (2.88 mL, 2.88 mmol) in CH₂Cl₂ (14 mL) was slowly added at -20 °C to a stirred solution (**R**)-**7** (681 mg, 2.4 mmol) and triethylamine (0.4 mL, 2.88 mmol). Once the addition was complete, the cooling bath was removed and stirring continued for 2.5 h at 23 °C. For work up, the mixture was washed with HCl (1 M) and the aqueous layer extracted with CH₂Cl₂ (x3). The combined organic phases were dried over anhydrous MgSO₄, filtered, concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc) to give (**R**)-**118** (730 mg, 73% yield) as a pale yellow oil.

10

(R)-118



¹H NMR (400 MHz, CDCl₃): δ 6.19 (d, *J* = 2.2 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 4.83 (d, *J* = 8.3 Hz, 1H), 4.46 (d, *J* = 7.4 Hz, 1H), 1.83 (ddt, *J* = 12.8, 9.6, 6.2 Hz, 1H), 1.73-1.61 (m, 1H), 1.44 (s, 9H), 1.42-1.24 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

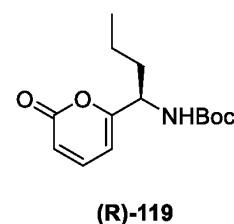
¹³C NMR (100 MHz, CDCl₃): δ 167.7, 161.3, 161.0, 154.9, 118.5 (q, *k* = 321.1 Hz), 103.4, 98.6, 80.9, 53.0, 35.1, 31.1, 28.4, 19.2, 13.7.

MS (ES⁺): *m/z* 438.0 [M+Na]⁺.

R_f: 0.27 (Hex:EtOAc 9:1).

20 Compound (*R*)-119

To a solution of (**R**)-**118** (660 mg, 1.59 mmol) in degassed DMF (10.5 mL), was added successively Pd(PPh₃)₄ (0.367 mL, 0.32 mmol) and triethylsilane (0.5 mL, 3.18 mmol) and the resulting mixture was heated to 60 °C for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organics were washed with water, dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified using flash column chromatography (hexane:EtOAc) to give (**R**)-**119** (90 mg, 23% yield) as a colorless solid.



¹H NMR (400 MHz, CDCl₃): δ 7.32-7.26 (m, 1H), 6.20 (dd, *J* = 9.4, 1.0 Hz, 1H), 6.13 (d, *J* = 6.5 Hz, 1H), 4.90 (d, *J* = 8.8 Hz, 1H), 4.41 (q, *J* = 7.9 Hz, 1H), 1.79 (ddt, *J* = 13.3, 9.5, 6.5 Hz, 1H), 1.66 (dq, *J* = 13.9, 7.7 Hz, 1H), 1.42 (s, 9H), 1.38-1.24 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H).

130

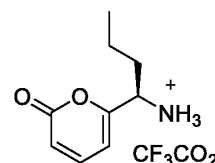
^{13}C NMR (100 MHz, CDCl_3): δ 164.3, 162.3, 155.1, 143.7, 132.2, 129.7, 128.8, 128.6, 127.2, 123.5, 114.6, 102.7, 80.3, 52.8, 35.4, 29.8, 28.4, 19.2, 13.7.

MS (ES⁺): m/z 290.3 $[\text{M}+\text{Na}]^+$.

R_f: 0.13 (Hex:EtOAc 4:1).

5 Compound **(R)-120**

To a solution of **(R)-119** (84 mg, 0.31 mmol) in CH_2Cl_2 (11.3 mL) was added TFA (3.46 mL) at 23 °C. After being stirred for 2 hours, the mixture was concentrated to dryness to obtain crude **(R)-120** which was used in the next without further purification.

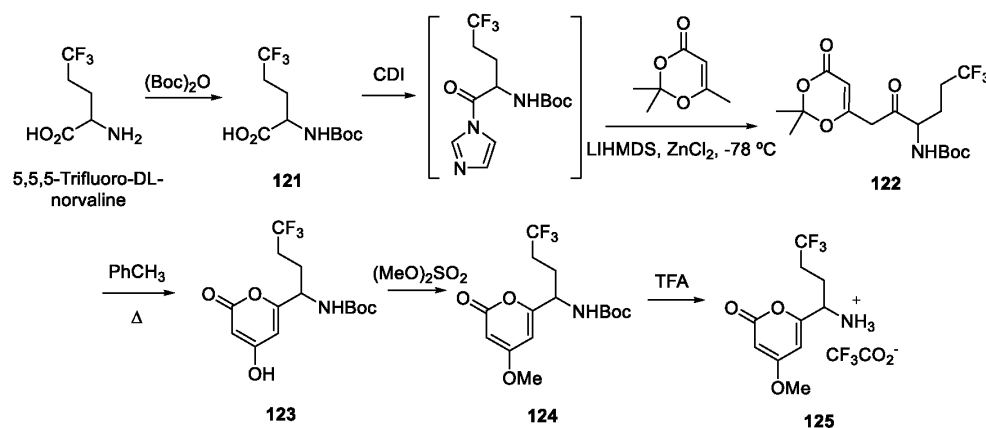


- 10 ^1H NMR (400 MHz, CD_3OD): δ 7.51 (ddd, J = 9.6, 6.5, 1.0 Hz, 1H), **(R)-120**
7.27-6.99 (m, 1H), 6.49 (dd, J = 6.6, 1.0 Hz, 1H), 6.35 (dt, J = 9.4, 1.0 Hz, 1H), 4.18 (dd, J = 9.0, 6.1 Hz, 1H), 2.08-1.72 (m, 2H), 1.49-1.17 (m, 3H), 1.02-0.88 (m, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 162.6, 159.2, 145.1, 129.9, 129.2, 126.3, 117.2, 107.1, 53.5, 34.3, 19.6, 13.7.

15 **EXAMPLE 13. SYNTHESIS OF INTERMEDIATE 125**

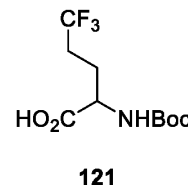
Scheme 23 provides an example of the synthesis of intermediate **125**



Scheme 23

Compound **121**

- 20 To a solution of 5,5,5-Trifluoro-DL-norvaline (206 mg, 1.2 mmol) and Na_2CO_3 (383 mg, 3.6 mmol) in H_2O (2.4 mL) was dropwise added Boc anhydride (276 mg, 1.2 mmol) dissolved in 1,4-dioxane (2.4 mL) at 0 °C. The reaction mixture was stirred at 23 °C for 5 hours and then, was diluted with EtOAc and washed with HCl 0.5 N (x2) and once with a saturated

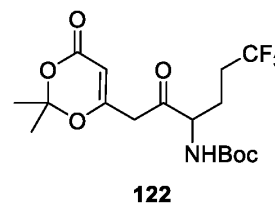


aqueous solution of NaCl (x1). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure to obtain crude **121** (326 mg, 100% yield) which was used in the next step without further purification.

- ¹H NMR (400 MHz, CD₃OD): δ 4.17 (dd, *J* = 9.0, 4.9 Hz, 1H), 2.36-2.14 (m, 2H), 2.08 (ddt, *J* = 16.2, 10.8, 5.4 Hz, 1H), 1.95-1.81 (m, 1H), 1.45 (s, 9H).
- ¹³C NMR (100 MHz, CD₃OD): δ 174.9, 158.0, 129.8 (q, *J*_{C-F} = 275 Hz, CF₃), 80.7, 53.7, 31.2 (q, *J*_{C-F} = 29 Hz, CH₂CF₃), 28.7, 25.4.

Compound **122**

- In a first flask, CDI (203 mg, 1.25 mmol) was added in portions to a solution of **121** (324 mg, 1.2 mmol) in 2-Me-THF (94.8 mL), with gas evolution. This mixture was stirred for 2 h at 23 °C. In another flask, at -78 °C, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.53 mL, 3.6 mmol) in 2-Me-THF (3.6 mL) was added slowly to a solution of LiHMDS (3.6 mL, 1.0 M in THF, 3.6 mmol) in 2-Me-THF (4.8 mL).



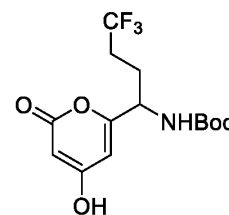
- After stirring at the same temperature for 1h, ZnCl₂ (488 mg, 3.6 mmol) was added at -78 °C and the reaction mixture was stirred 30 minutes at -78 °C. The first mixture was added via cannula. The reaction was stirring at -78 °C for 4 h and then quenched with saturated aqueous solution of NH₄Cl. Extraction with EtOAc, and dryness of the organic layers over Na₂SO₄ gave a crude which was purified by flash chromatography on silica gel (hexane/EtOAc 9/1 to 7/3) to afford **122** (256 mg, 54% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.41 (d, *J* = 8.2 Hz, 1H), 5.32 (s, 1H), 4.28 (t, *J* = 7.2 Hz, 1H), 3.45 (d, *J* = 3.3 Hz, 2H), 2.29-2.01 (m, 4H), 1.65 (s, 6H), 1.41 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 201.7, 164.05, 160.6, 155.4, 126.6 (q, *J*_{C-F} = 276 Hz, CF₃), 107.3, 96.9, 80.7, 58.3, 43.6, 29.9 (q, *J*_{C-F} = 29 Hz, CH₂CF₃), 28.1, 24.9, 24.7, 23.1.

Compound **123**

- A solution of **122** (253 mg, 0.640 mmol) in toluene (6.4 mL) was refluxed for 30 min. After cooling to 23 °C, it was evaporated to dryness and crude residue was purified in CombiFlash with hexane/EtOAc 60:40 to 40:60 in 20 min. It was obtained **123** (121 mg, 56% yield) as a clear oil.

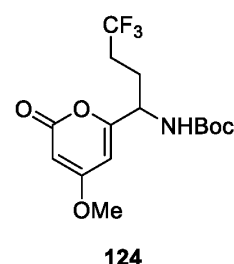


¹H NMR (400 MHz, CDCl₃): δ 6.05 (s, 1H), 5.51 (s, 1H), 5.30 (s, 1H), 5.22 (s, 1H), 2.30-1.75 (m, 4H), 1.36 (s, 9H).

Compound **124**

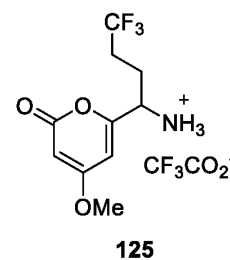
A mixture of **123** (119 mg, 0.353 mmol), acetone (3.5 mL), K₂CO₃ (244 mg, 1.76 mmol) and dimethyl sulfate (0.17 mL, 0.475 mmol) was stirred at 23 °C for 2h. Filtration over Celite® and washing with EtOAc gave a crude which was purified In CombiFlash over silica gel with mixtures
 5 hexane/EtOAc 100:0 to 0:100 in 20 min to yield **124** (111 mg, 90% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.96 (d, *J* = 2.2 Hz, 1H), 5.44 (d, *J* = 2.2 Hz, 1H), 5.12 (d, *J* = 9.4 Hz, 1H), 4.45 (q, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 2.24-1.79 (m, 4H), 1.41 (s, 9H).
 10 ¹³C NMR (100 MHz, CDCl₃): δ 170.8, 163.8, 161.7, 154.8, 126.5 (q, *J*_{C-F} = 276 Hz, CCF₃), 100.3, 88.7, 80.6, 56.0, 51.5, 30.5 (q, *J*_{C-F} = 29 Hz, CH₂CF₃), 28.2, 25.8.

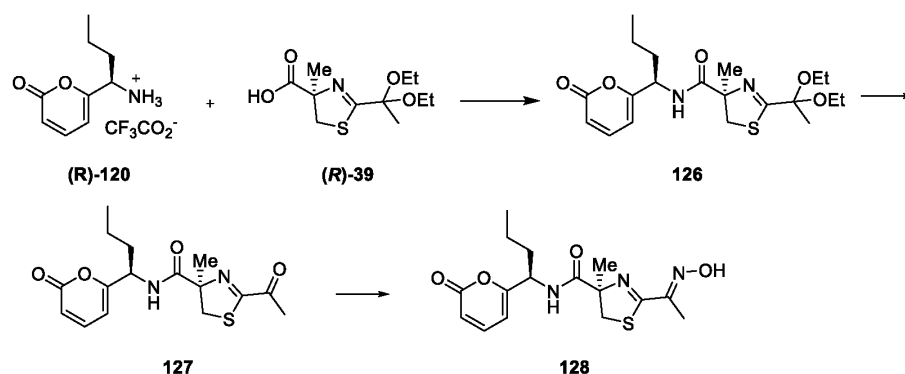
Compound **125**

To a solution of **124** (109 mg, 0.310 mmol) in CH₂Cl₂ (4 mL) was added TFA (1.2 mL). After being stirred for 1 h at 23 °C, the mixture was evaporated to dryness and then evaporated with toluene to eliminate TFA to obtain crude **125** (113 mg) which was used in the next step without further purification.

¹H NMR (400 MHz, CD₃OD): d 6.40 (d, *J* = 2.2 Hz, 1H), 5.71 (d, *J* = 2.2 Hz, 1H), 4.96 (s, 2H), 4.34-4.26 (m, 1H), 3.89 (s, 3H), 2.44-2.11 (m, 4H).
 20 ¹³C NMR (100 MHz, CD₃OD): d 172.2, 165.1, 157.8, 127.9 (q, *J*_{C-F} = 275 Hz, CCF₃), 105.3, 90.8, 57.3, 52.4, 30.5 (q, *J*_{C-F} = 30 Hz, CH₂CF₃), 24.8 (q, *J*_{C-F} = 3.1 Hz, CH₂CH₂CF₃).

EXAMPLE 14. SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

25 Scheme 24 provides a further example of the synthesis of additional compounds of formula I.

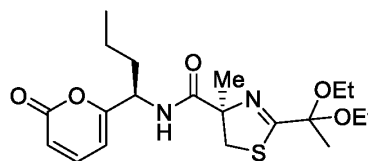


Scheme 24

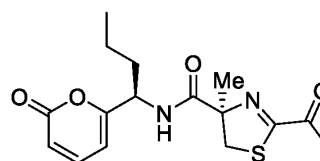
Compound **126**

133

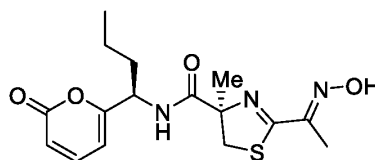
- To a suspension of (**R**)-**120** (90 mg, 0.032 mmol) and (**R**)-**39** (84 mg, 0.32 mmol) were coevaporated 3 times with toluene to remove water, then the mixture was dissolved in CH₂Cl₂ (2.2 mL) were added HATU (122 mg, 0.032 mmol), HOAt (44 mg, 0.32 mmol) and DIPEA (0.22 mL, 0.128 mmol) and the mixture was stirred at 23 °C overnight. Dilution with CH₂Cl₂, washing of the organic layer with 0.5M HCl and a saturated aqueous solution of NaCl and, finally, dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The crude obtained was purified by flash chromatography on silica gel (hexane/EtOAc 6/4) to afford **126** (100 mg, 77% yield).
- ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.20 (m, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.16 (dd, *J* = 9.4, 1.0 Hz, 1H), 6.06 (dd, *J* = 6.5, 1.1 Hz, 1H), 4.75 (q, *J* = 7.9 Hz, 1H), 3.65-3.37 (m, 4H), 3.15 (dd, *J* = 11.7, 1.0 Hz, 1H), 1.92-1.79 (m, 1H), 1.81-1.67 (m, 1H), 1.60 (d, *J* = 0.9 Hz, 3H), 1.54 (d, *J* = 0.9 Hz, 3H), 1.44-1.28 (m, 2H), 1.21 (qd, *J* = 7.2, 1.0 Hz, 6H), 0.93 (td, *J* = 7.3, 0.9 Hz, 3H).
- ¹³C NMR (100 MHz, CDCl₃): δ 177.2, 174.4, 163.5, 161.5, 143.2, 114.7, 102.4, 100.2, 85.1, 57.8, 57.7, 51.0, 40.4, 34.8, 25.3, 23.7, 19.1, 15.2 (x2), 13.5.
- MS (ES⁺): *m/z* 433.3 [M+Na]⁺.
- R_f: 0.33 (Hex:EtOAc 1:3).

**126**

- Compound **127**
- A mixture of **126** (100 mg, 0.24 mmol), pentane (7.3 mL) and formic acid (4.87 mL) was vigorously stirred for 2h at 23 °C. The volatiles were concentrated under vacuum with toluene to dryness to afford crude **127** (73 mg, 90% yield) which was used in the next step without purification.
- ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.17 (m, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 6.30-6.07 (m, 2H), 4.79 (q, *J* = 7.1, 6.0 Hz, 1H), 3.63 (dd, *J* = 12.1, 3.2 Hz, 1H), 3.28 (dd, *J* = 12.0, 3.1 Hz, 1H), 2.56 (d, *J* = 3.8 Hz, 2H), 1.97-1.77 (m, 1H), 1.55 (d, *J* = 3.6 Hz, 2H), 1.46-1.17 (m, 2H), 0.97 (q, *J* = 5.7, 4.2 Hz, 3H).
- ¹³C NMR (100 MHz, CDCl₃): δ 193.2, 173.2, 170.4, 162.7, 161.7, 143.4, 114.9, 103.0, 86.1, 51.1, 40.1, 35.0, 26.3, 24.6, 19.1, 13.6.

**127**

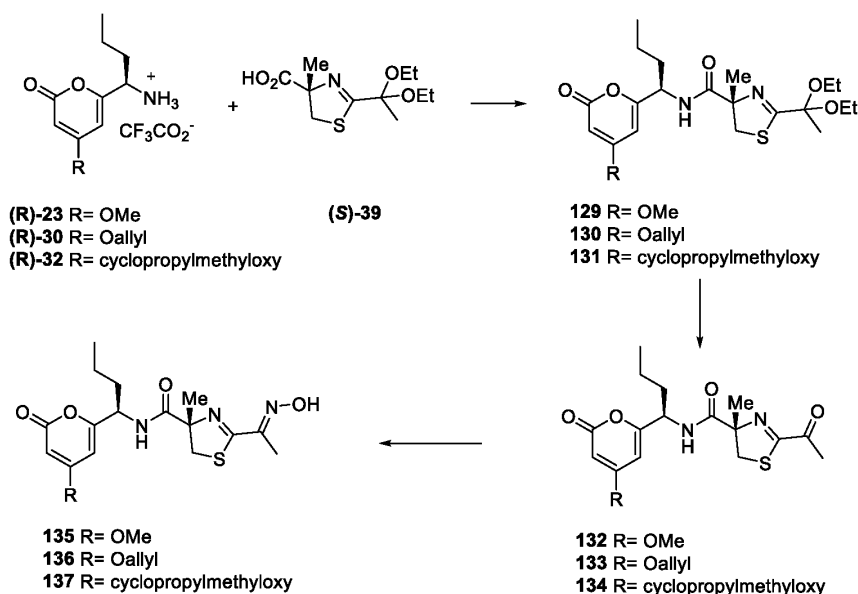
- Compound **128**
- A mixture of **127** (70 mg, 0.21 mmol), ethanol (2.3 mL), water (2.3 mL), hydroxylamine hydrochloride (38 mg, 7.3 mmol) and NaOAc (77 mg, 0.94 mmol) was stirred for 24h. Then ethanol was concentrated under vacuum, a saturated aqueous solution of NaCl was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over

**128**

anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure. The crude was chromatographed over silica gel ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ from 95/5 to 8/2) to afford **128** (29 mg, 40% yield).

- ^1H NMR (400 MHz, CD_3OD): δ 7.84 (d, $J = 8.6$ Hz, 1H), 7.46 (dd, $J = 9.4, 6.6$ Hz, 1H), 6.31-6.16 (m, 2H), 4.77 (ddd, $J = 8.8, 7.3, 4.3$ Hz, 1H), 3.52 (d, $J = 11.5$ Hz, 1H), 3.18 (d, $J = 11.5$ Hz, 1H), 2.18 (s, 3H), 1.94-1.75 (m, 2H), 1.52 (s, 3H), 1.49-1.34 (m, 1H), 0.99 (t, $J = 7.4$ Hz, 3H).
MS (ES⁺): m/z 352.3 $[\text{M}+\text{H}]^+$, 374.1 $[\text{M}+\text{Na}]^+$.

Scheme 25 provides further examples of the synthesis of compounds of formula I:

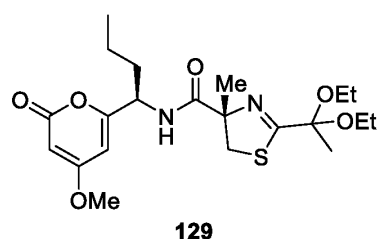


10

Scheme 25

Compound **129**

- A mixture of **(S)-39** (410 mg, 1.6 mmol) and **(R)-23** (488 mg, 1.6 mmol) is coevaporated with toluene and then HATU (597 mg, 1.6 mmol) and HOAt (215 mg, 1.6 mmol) were added. Reaction flask is evacuated and filled with N_2 and CH_2Cl_2 (11 mL) and DIPEA (1.1 mL, 6.4 mmol) were introduced via syringe. The reaction mixture is stirred 16 h at 23 °C. Then, it is diluted with CH_2Cl_2 before washing with HCl 0.5 N (x2) and with a saturated aqueous solution of NaCl. Combined organic layers were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. Crude residue is purified on a system for flash chromatography with a SiO_2 column eluting with mixtures of hexane/EtOAc from 100:0 to 50:50 in 15 min to obtain **129** (458 mg, 66% yield).



135

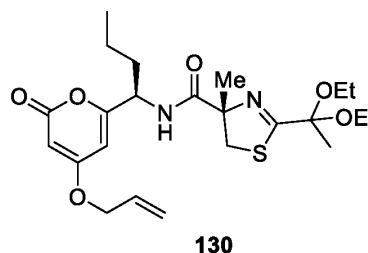
^1H NMR (400 MHz, CDCl_3): δ 7.02 (d, J = 8.5 Hz, 1H), 5.93 (m, 1H), 5.41 (d, J = 2.2 Hz, 1H), 4.65 (td, J = 8.4, 6.2 Hz, 1H), 3.78 (d, J = 0.7 Hz, 3H), 3.60 (m, 1H), 3.52 (m, 4H), 3.15 (dd, J = 11.7, 0.7 Hz, 1H), 1.84 (ddd, J = 13.4, 9.4, 6.7 Hz, 1H), 1.64 (dd, J = 8.9, 5.5 Hz, 1H), 1.59 (d, J = 0.7 Hz, 3H), 1.48 (s, 3H), 1.29 (m, 1H), 1.21 (m, 6H), 0.89 (t, J = 7.3 Hz, 3H).

5 ^{13}C NMR (100 MHz, CDCl_3): δ 177.7, 175.8, 172.2, 165.4, 164.2, 101.4, 101.0, 89.7, 86.4, 58.9, 58.8, 57.2, 52.1, 41.6, 35.8, 26.3, 24.9, 20.2, 16.5 (x2), 14.8.

MS (ES⁺): m/z 463.3 $[\text{M}+\text{Na}]^+$.

Compound 130

A mixture of (**S**)-**39** (269 mg, 1.0 mmol) and (**R**)-**30** (337 mg, 1.0 mmol) is coevaporated with toluene and then HATU (392 mg, 1.0 mmol) and HOAt (141 mg, 1.0 mmol) were added. Reaction flask is evacuated and filled with N_2 and CH_2Cl_2 (7.2 mL) and DIPEA (0.7 mL, 4.0 mmol) were introduced via syringe. The reaction mixture is stirred 16 h at 23 °C. Then, it is diluted with CH_2Cl_2 before washing with HCl 0.5 N (x2) and with a saturated aqueous solution of NaCl. Combined organic layers were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. Crude residue is purified on a system for flash chromatography with a SiO_2 column eluting with mixtures of hexane/EtOAc from 100:0 to 50:50 in 15 min to obtain **130** (240 mg, 50% yield).



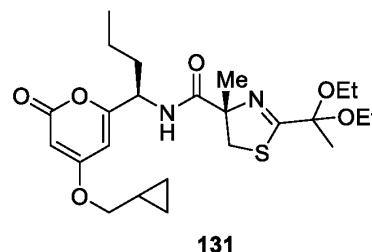
20 ^1H NMR (400 MHz, CDCl_3): δ 6.94 (dd, J = 8.6, 3.3 Hz, 1H), 5.80 (m, 2H), 5.22 (m, 3H), 4.51 (dq, J = 11.6, 5.4, 4.0 Hz, 1H), 4.34 (d, J = 4.4 Hz, 2H), 3.38 (m, 5H), 2.99 (dd, J = 11.7, 3.6 Hz, 1H), 1.68 (dtd, J = 11.2, 8.0, 7.4, 3.9 Hz, 1H), 1.50 (tq, J = 8.4, 4.6, 3.9 Hz, 1H), 1.42 (d, J = 3.4 Hz, 3H), 1.31 (d, J = 3.4 Hz, 3H), 1.04 (ddt, J = 11.0, 6.9, 3.0 Hz, 6H), 0.73 (td, J = 7.5, 3.3 Hz, 3H).

25 ^{13}C NMR (100 MHz, CDCl_3): δ 176.2, 174.3, 169.6, 163.8, 162.9, 130.6, 119.2, 100.0, 99.7, 89.1, 85.0, 69.4, 57.5, 57.4, 50.7, 40.2, 34.4, 24.9, 23.5, 18.8, 15.1, 13.4.

MS (ES⁺): m/z 489.2 $[\text{M}+\text{Na}]^+$.

Compound 131

30 A mixture of (**S**)-**39** (408 mg, 1.6 mmol) and (**R**)-**32** (548 mg, 1.6 mmol) is coevaporated with toluene and then HATU (593 mg, 1.6 mmol) and HOAt (214 mg, 1.6 mmol) were added. Reaction flask is evacuated and filled with N_2 and CH_2Cl_2 (11 mL) and DIPEA (1.1 mL, 6.4 mmol) were introduced via syringe. The reaction mixture is stirred 16 h at 23 °C. Then, it is diluted with CH_2Cl_2 before washing with HCl 0.5 N (x2) and with a saturated aqueous solution of NaCl. Combined organic layers were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. Crude residue is



purified on a system for flash chromatography with a SiO₂ column eluting with mixtures of hexane/EtOAc from 100:0 to 50:50 in 15 min to obtain **131** (343 mg, 46% yield).

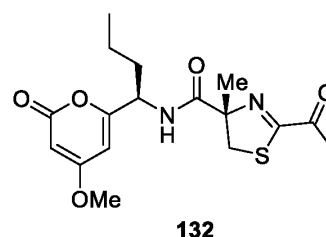
¹H NMR (400 MHz, CDCl₃): δ 6.92 (d, *J* = 8.5 Hz, 1H), 5.81 (dt, *J* = 2.2, 0.7 Hz, 1H), 5.21 (dd, *J* = 2.2, 0.6 Hz, 1H), 4.51 (td, *J* = 8.4, 6.1 Hz, 1H), 3.93 (qd, *J* = 7.2, 0.6 Hz, 1H), 3.62 (m, 2H), 3.38 (m, 5H), 3.00 (dd, *J* = 11.7, 0.7 Hz, 1H), 1.68 (m, 1H), 1.49 (m, 1H), 1.42 (d, *J* = 0.6 Hz, 3H), 1.32 (s, 3H), 1.14 (m, 2H), 1.05 (m, 7H), 0.74 (t, *J* = 7.3 Hz, 3H), 0.49 (m, 2H), 0.18 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 176.1, 174.3, 170.0, 163.9, 162.7, 100.0, 99.8, 88.5, 85.0, 73.6, 57.5, 57.3, 50.7, 40.2, 34.4, 24.9, 23.5, 18.8, 15.1, 13.4, 9.3, 3.2 (x2).

MS (ES⁺): *m/z* 503.3 [M+Na]⁺.

Compound **132**

A mixture of **129** (458 mg, 1.07 mmol), pentane (24 mL) and formic acid (16 mL) was vigorously stirred for 2h at 23 °C. The volatiles were concentrated under vacuum with toluene to dryness to afford crude **132** (398 mg, 100% yield) which was used in the next step without purification.



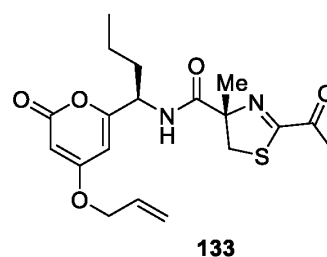
¹H NMR (400 MHz, CDCl₃): δ 6.93 (d, *J* = 8.5 Hz, 1H), 5.99 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.45 (dd, *J* = 2.3, 1.1 Hz, 1H), 4.68 (q, *J* = 7.8 Hz, 1H), 3.81 (d, *J* = 1.2 Hz, 3H), 3.67 (dd, *J* = 12.0, 1.3 Hz, 1H), 3.28 (dd, *J* = 11.9, 1.2 Hz, 1H), 2.56 (d, *J* = 1.2 Hz, 2H), 1.85 (m, 1H), 1.72 (m, 1H), 1.50 (d, *J* = 1.3 Hz, 3H), 1.30 (m, 2H), 0.92 (td, *J* = 7.3, 1.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.4, 174.5, 172.2, 171.5, 165.5, 163.3, 101.8, 89.9, 87.4, 57.3, 52.4, 41.5, 35.8, 27.6, 25.7, 20.3, 14.8.

MS (ES⁺): *m/z* 367.3 [M+H]⁺.

Compound **133**

A mixture of **130** (240 mg, 0.6 mmol), pentane (12.5 mL) and formic acid (8.4 mL) was vigorously stirred for 2h at 23 °C. The volatiles were concentrated under vacuum with toluene to dryness to obtain crude **133** (252 mg, 100% yield) which was used in the next step without purification.



¹H NMR (400 MHz, CDCl₃): δ 6.94 (d, *J* = 8.5 Hz, 1H), 5.99 (m, 3H), 5.41 (m, 4H), 4.69 (q, *J* = 7.8 Hz, 1H), 4.51 (dq, *J* = 5.8, 1.4 Hz, 2H), 3.67 (dd, *J* = 12.0, 1.1 Hz, 1H), 3.28 (dd, *J* = 11.9, 1.2 Hz, 1H), 2.56 (d, *J* = 1.2 Hz, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.50 (d, *J* = 1.2 Hz, 3H), 1.30 (tt, *J* = 14.3, 6.8 Hz, 3H), 0.92 (m, 3H).

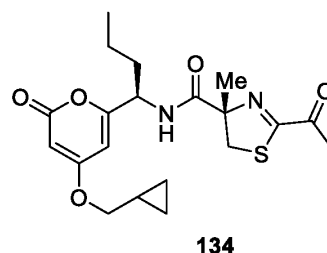
¹³C NMR (100 MHz, CDCl₃): δ 194.4, 174.5, 171.0, 166.2, 163.4, 159.6, 131.8, 120.9, 102.0, 90.7, 87.4, 70.9, 52.4, 41.5, 35.8, 27.6, 25.7, 20.3, 14.8.

MS (ES⁺): *m/z* 393.2 [M+H]⁺.

137

Compound **134**

A mixture of **131** (343 mg, 1.07 mmol), pentane (18 mL) and formic acid (12 mL) was vigorously stirred for 2 h at 23 °C. The volatiles were concentrated under vacuum with toluene to dryness to afford crude **134** (360 mg, 100% yield) which was used in the next step without purification.



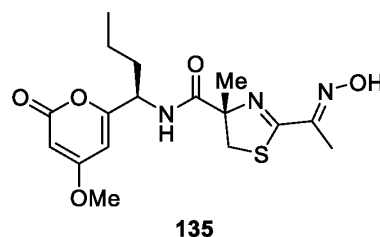
¹H NMR (400 MHz, CDCl₃): δ 6.93 (d, *J* = 8.6 Hz, 1H), 6.01 (d, *J* = 2.2 Hz, 1H), 5.39 (d, *J* = 2.3 Hz, 1H), 4.69 (q, *J* = 7.8 Hz, 1H), 3.79 (dd, *J* = 7.1, 2.7 Hz, 2H), 3.68 (d, *J* = 11.9 Hz, 1H), 3.28 (dd, *J* = 11.9, 0.6 Hz, 1H), 2.56 (d, *J* = 0.6 Hz, 3H), 1.86 (ddt, *J* = 14.0, 9.1, 7.1 Hz, 1H), 1.71 (m, 1H), 1.51 (s, 3H), 1.29 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 4H), 0.68 (m, 3H), 0.35 (dt, *J* = 6.2, 4.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.4, 174.5, 173.6, 171.4, 165.5, 163.2, 102.1, 90.1, 87.4, 75.1, 52.4, 41.5, 35.8, 27.6, 25.7, 20.3, 14.8, 10.6, 4.7, 4.6.

MS (ES⁺): *m/z* 407.1 [M+H]⁺.

Compound **135**

A mixture of **132** (392 mg, 1.07 mmol), ethanol (12 mL), water (12 mL), hydroxylamine hydrochloride (550 mg, 7.9 mmol) and NaOAc (395 mg, 4.8 mmol) was stirred overnight at 23 °C. Then ethanol was concentrated under vacuum, a saturated aqueous solution of NaCl was



added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The crude was chromatographed over silica gel (hexane/EtOAc from 100:0 to 50:50) to afford **135** (231 mg, 57% yield).

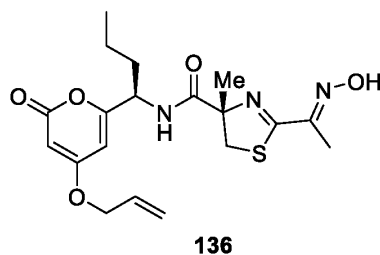
¹H NMR (400 MHz, CDCl₃): δ 11.10 (s, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 5.92 (t, *J* = 1.9 Hz, 1H), 5.40 (t, *J* = 2.0 Hz, 1H), 4.61 (qd, *J* = 7.4, 6.7, 1.5 Hz, 1H), 3.73 (d, *J* = 1.7 Hz, 3H), 3.45 (dd, *J* = 11.6, 1.8 Hz, 1H), 3.12 (dd, *J* = 11.6, 1.6 Hz, 1H), 2.10 (m, 3H), 1.76 (m, 1H), 1.62 (dddt, *J* = 13.6, 9.6, 5.7, 2.0 Hz, 1H), 1.40 (d, *J* = 1.6 Hz, 3H), 1.19 (m, 2H), 0.81 (td, *J* = 7.3, 1.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 174.4, 170.9, 168.4, 164.4, 162.3, 151.8, 100.0, 88.3, 84.0, 55.8, 50.7, 39.6, 34.2, 24.3, 18.7, 13.3, 10.8.

MS (ES⁺): *m/z* 382.3 [M+H]⁺.

Compound **136**

A mixture of **133** (239 mg, 0.61 mmol), ethanol (6.7 mL), water (6.7 mL), hydroxylamine hydrochloride (314 mg, 4.5 mmol) and NaOAc (225 mg, 2.7 mmol) was stirred overnight at 23 °C. Then ethanol was concentrated under



vacuum, a saturated aqueous solution of NaCl was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The crude was chromatographed over silica gel (hexane/EtOAc from 100:0 to 50:50) to afford **136** (131 mg, 53% yield).

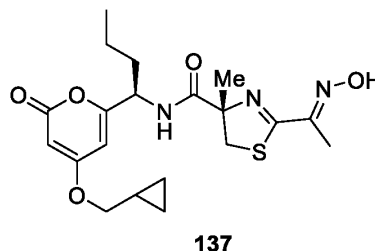
5 ¹H NMR (400 MHz, CDCl₃): δ 10.14 (s, 1H), 7.12 (m, 1H), 6.01 (t, *J* = 1.7 Hz, 1H), 5.94 (dddd, *J* = 16.0, 9.7, 6.3, 5.1 Hz, 1H), 5.46 (t, *J* = 1.7 Hz, 1H), 5.39 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.33 (dp, *J* = 10.5, 1.1 Hz, 1H), 4.69 (q, *J* = 7.7 Hz, 1H), 4.49 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.54 (dt, *J* = 11.6, 1.0 Hz, 1H), 3.24 (dd, *J* = 11.6, 1.3 Hz, 1H), 2.19 (m, 3H), 1.83 (dtd, *J* = 9.8, 7.7, 6.1 Hz, 1H), 1.70 (m, 1H), 1.47 (m, 3H), 1.25 (m, 3H), 0.88 (td, *J* = 7.4, 1.2 Hz, 3H).

10 ¹³C NMR (100 MHz, CDCl₃): δ 174.5, 169.9, 168.1, 164.6, 162.3, 152.6, 130.5, 119.6, 100.6, 89.4, 84.3, 69.6, 51.0, 40.0, 34.5, 24.4, 18.9, 13.5, 11.2.

MS (ES⁺): *m/z* 408.2 [M+H]⁺.

Compound **137**

A mixture of **134** (341 mg, 0.84 mmol), ethanol (9.2 mL), water (9.2 mL), hydroxylamine hydrochloride (432 mg, 6.2 mmol) and NaOAc (310 mg, 3.8 mmol) was stirred overnight at 23 °C. Then ethanol was concentrated under vacuum, a saturated aqueous solution of NaCl was added, and the aqueous phase was extracted with



20 EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The crude was chromatographed over silica gel (hexane/EtOAc from 100:0 to 50:50) to afford **137** (178 mg, 50% yield).

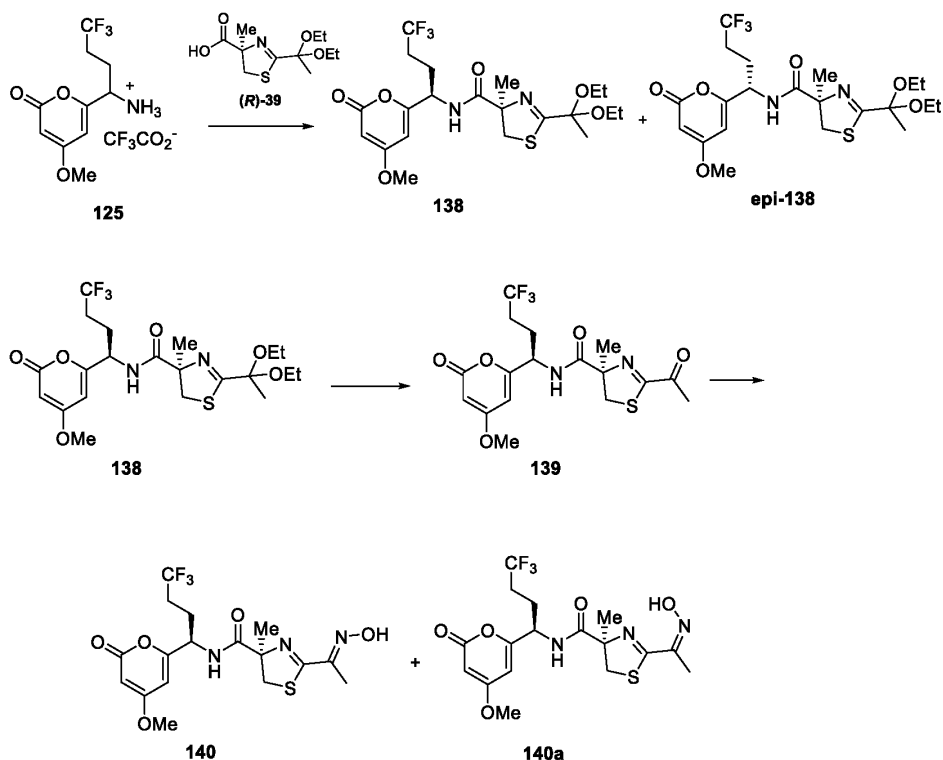
¹H NMR (400 MHz, CDCl₃): δ 10.45 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.00 (d, *J* = 2.1 Hz, 1H), 5.40 (dd, *J* = 2.2, 0.7 Hz, 1H), 4.67 (q, *J* = 7.7 Hz, 1H), 3.76 (m, 2H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.22 (dd, *J* = 11.5, 0.7 Hz, 1H), 2.17 (d, *J* = 0.7 Hz, 3H), 1.82 (ddt, *J* = 13.7, 9.2, 6.8 Hz, 1H), 1.68 (m, 1H), 1.45 (s, 3H), 1.25 (m, 2H), 0.86 (m, 3H), 0.62 (m, 2H), 0.30 (m, 2H).

25 ¹³C NMR (100 MHz, CDCl₃): δ 174.5, 170.3, 168.2, 164.8, 162.2, 152.4, 100.6, 88.8, 84.2, 73.8, 50.9, 39.9, 34.4, 24.3, 18.9, 13.4, 11.1, 9.3, 3.3 (x2).

MS (ES⁺): *m/z* 422.1 [M+H]⁺.

30 Scheme 26 provides further examples of the synthesis of compounds of formula I:

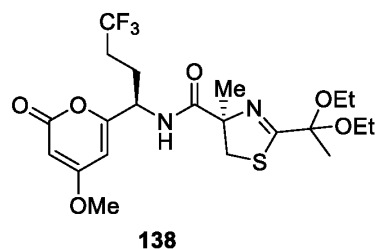
139



Scheme 26

Compound **138**

- 5 A mixture of **125** (113 mg, 0.310 mmol) and **(R)-39** (85 mg) is coevaporated with toluene and then HATU (128 mg) and HOAt (47 mg) were added. Reaction flask is evacuated and filled with N₂ and CH₂Cl₂ (2.2 mL) and DIPEA (0.24 mL) were introduced via syringe. The reaction mixture is stirred 16 h at 23 °C. Then, it is
- 10 diluted with CH₂Cl₂ before washing with HCl 0.5 N (x2) and with a saturated aqueous solution of NaCl. Combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. Crude residue is purified on a system for flash chromatography with a SiO₂ column eluting with mixtures of hexane/EtOAc from 80:20 to 50:50 in 30 min to obtain **138** (47 mg, 31% yield). Compound **epi-138** was also isolated with
- 15 a similar yield.

Compound **138**

¹H NMR (400 MHz, CDCl₃): δ 7.18 (d, *J* = 9.3 Hz, 1H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 4.82 (td, *J* = 9.0, 5.2 Hz, 1H), 3.79 (s, 3H), 3.65-3.42 (m, 5H), 3.17 (d, *J* = 11.7 Hz, 1H),

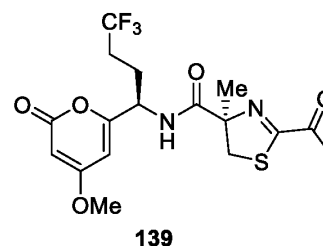
140

2.24- 2.07 (m, 3H), 2.09-1.95 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 177.2, 174.7, 170.5, 163.2, 161.0, 126.4 (q, $J_{\text{C-F}} = 276$ Hz, CF_3), 100.3, 100.2, 88.8, 85.1, 57.8, 57.6, 56.0, 49.8, 40.2, 30.5 (q, $J_{\text{C-F}} = 30$ Hz, CH_2CF_3), 25.5, 25.3, 23.7, 15.12.

Compound **139**

A mixture of **138** (47 mg, 0.095 mmol), pentane (2.4 mL) and formic acid (1.6 mL) was vigorously stirred for 2h at 23 °C. The volatiles were concentrated under vacuum with toluene to dryness to afford **139**. The crude was used in the next step without purification.

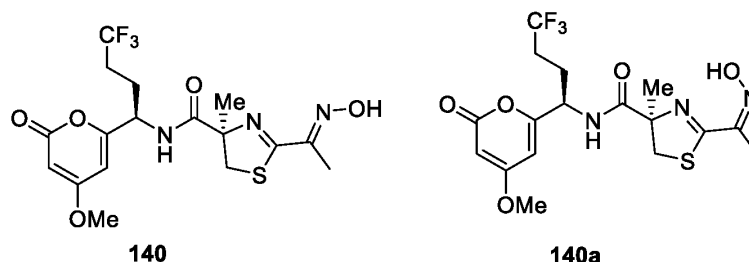


^1H NMR (400 MHz, CDCl_3): δ 7.17 (d, $J = 9.1$ Hz, 1H), 5.96

(d, $J = 2.2$ Hz, 1H), 5.47 (d, $J = 2.2$ Hz, 1H), 4.83 (q, $J = 7.4, 6.7$ Hz, 1H), 3.81 (s, 3H), 3.62 (d, $J = 12.0$ Hz, 1H), 3.28 (d, $J = 12.0$ Hz, 1H), 2.55 (s, 3H), 2.23-2.04 (m, 4H), 1.56 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 173.6, 170.6, 163.5, 162.6, 160.0, 126.4 (q, $J_{\text{C-F}} = 276$ Hz, CF_3), 101.2, 89.1, 86.0, 56.2, 50.0, 40.0, 30.5 (q, $J_{\text{C-F}} = 30$ Hz, CH_2CF_3), 26.3, 25.8, 24.6.

Compounds **140** and **140a**



A mixture of **139** (40 mg, 0.095 mmol), ethanol (1.0 mL), water (1.0 mL), hydroxylamine hydrochloride (49 mg, 0.7 mmol) and NaOAc (35 mg, 0.43 mmol) was stirred for 16h at 23 °C. Then ethanol was concentrated under vacuum, a saturated aqueous solution of NaCl was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure. The crude was chromatographed on a system for flash chromatography with a SiO_2 column eluting with mixtures of hexane/EtOAc from 100:0 to 50:50 in 50 min. This purification allowed to separate both stereoisomers, **140** (21.8 mg, 53% yield for 2 steps) and **140a** (4.8 mg, 12% yield).

140

^1H NMR (400 MHz, CDCl_3): δ 8.91 (s, 1H), 7.25 (d, $J = 9.3$ Hz, 1H), 5.95 (d, $J = 2.2$ Hz, 1H), 5.46 (d, $J = 2.3$ Hz, 1H), 4.82 (q, $J = 8.1$ Hz, 1H), 3.80 (s, 3H), 3.53 (d, $J = 11.7$ Hz, 1H), 3.23 (d, $J = 11.6$ Hz, 1H), 2.22 (s, 3H), 2.22-2.02 (m, 4H), 1.53 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.5, 170.6, 168.2, 163.7, 160.4, 153.2, 126.4 (q, $J_{\text{C-F}} = 276$ Hz, CF_3), 101.0, 89.1, 84.3, 56.1, 50.0, 39.8, 30.5 (q, $J_{\text{C-F}} = 30$ Hz, CH_2CF_3), 25.7, 24.8, 11.2.

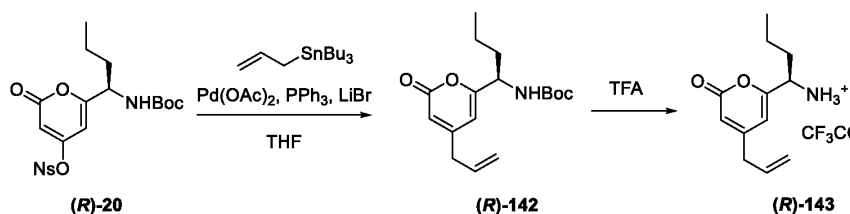
140a

^1H NMR (400 MHz, CDCl_3): δ 9.12 (s, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 6.03 (d, $J = 2.2$ Hz, 1H), 5.50 (d, $J = 2.2$ Hz, 1H), 4.80 (q, $J = 8.1$ Hz, 1H), 3.83 (s, 3H), 3.56 (d, $J = 11.6$ Hz, 1H), 3.25 (d, $J = 11.5$ Hz, 1H), 2.22 (s, 3H), 2.20-1.96 (m, 4H), 1.48 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.4, 170.7, 168.3, 163.9, 160.5, 153.1, 126.4 (q, $J_{\text{C-F}} = 277$ Hz, CF_3), 101.1, 93.3, 89.0, 84.3, 56.2, 50.1, 40.1, 30.5 (q, $J_{\text{C-F}} = 30$ Hz, CH_2CF_3), 25.4, 24.4, 11.2.

10 EXAMPLE 15. SYNTHESIS OF ADDITIONAL INTERMEDIATES OF FORMULA II

Scheme 27 provides further examples of the synthesis of intermediates of formula II



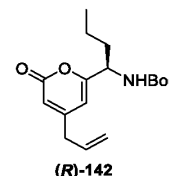
Scheme 27

Synthesis of (R)-142

15 To a solution of **(R)-20** (30 mg, 0.64 mmol) in THF (11 mL) was added palladium(II) acetate (7 mg, 0.032 mmol), triphenylphosphine (17 mg, 0.064 mmol) and lithium bromide (167 mg, 1.92 mmol) at 23 °C. The reaction mixture was turned to a yellow-to-orange, stirred for 10 min at 23 °C and allyltributylstannane (0.34 mL, 1.088 mmol) was added at 23 °C. The reaction mixture was refluxed for 2 h and concentrated under vacuum. An aqueous solution of KF 2M was added to the crude and the mixture was stirred for 30 min at 23 °C. Filtration over Celite® and washing with Et₂O gave a crude which was purified in an automatic system for flash chromatography (SiO₂) to yield **(R)-142** (46.8 mg, 24% yield).

25 ^1H NMR (400 MHz, CDCl_3): δ 6.48 (dq, $J = 15.7, 6.7$ Hz, 1H), 6.24 (s, 1H), 6.18 (dd, $J = 16.3, 1.8$ Hz, 1H), 5.94 (d, $J = 1.5$ Hz, 1H), 4.92 (m, 1H), 4.46-4.31 (m, 1H), 1.93 (dd, $J = 6.8, 1.6$ Hz, 2H), 1.86-1.63 (m, 2H), 1.39-1.23 (m, 2H), 0.98-0.86 (m, 3H).

MS (ES⁺): m/z 330.3 $[\text{M}+\text{Na}]^+$.



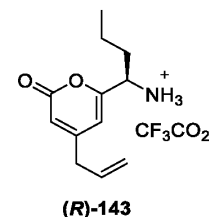
Synthesis of (*R*)-**143**

To a solution of (*R*)-**142** (46.8 mg, 0.15 mmol) in CH₂Cl₂ (1.7 mL) was added TFA (0.5 mL). After being stirred for 2 h, the reaction mixture was evaporated to dryness to obtain crude (*R*)-**143** (48.9 mg, 100% yield)

5 which was used in the next step without further purification.

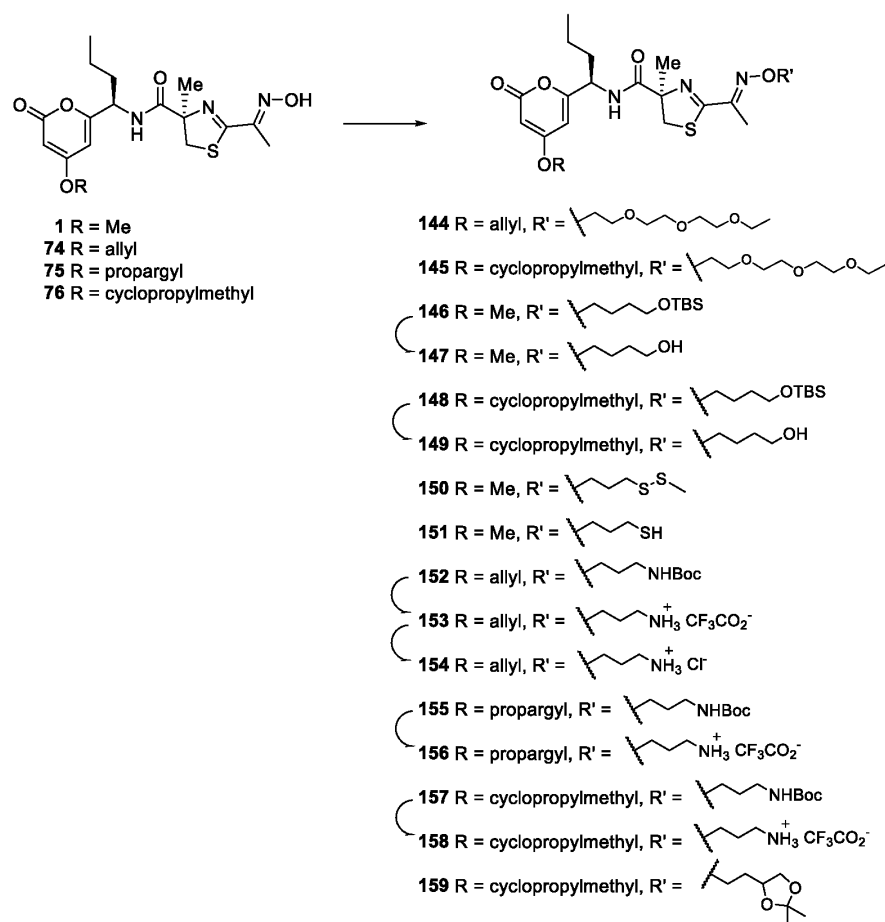
¹H NMR (400 MHz, CDCl₃): δ 8.24 (dd, *J* = 12.9, 8.5 Hz, 2H), 5.81 (td, *J* = 17.3, 7.3 Hz, 1H), 5.38 (d, *J* = 10.1 Hz, 1H), 5.16 (d, *J* = 17.1 Hz, 1H), 3.88 (d, *J* = 7.3 Hz, 2H), 2.07-1.83 (m, 2H), 1.42-1.22 (m, 2H), 1.04-0.78 (m, 3H).

MS (ES⁺): *m/z* 230.3 [M+Na]⁺, 208.3 [M+H]⁺.



10 EXAMPLE 16. SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 28 provides further examples of the synthesis of compounds of formula I

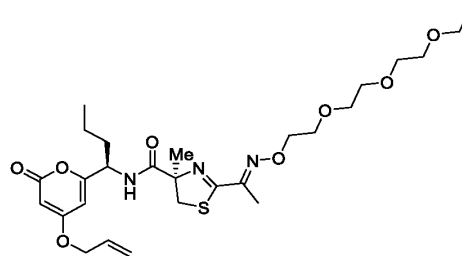


Scheme 28

143

Synthesis of **144**

To a solution of **74** (75 mg, 0.184 mmol) in acetone (2 mL), K₂CO₃ (127 mg, 0.920 mmol) and 2-[2-(2-ethoxyethoxy)ethoxy]ethyl iodide (233 mg, 0.920 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C overnight. The reaction mixture was filtered, washing with EtOAc and evaporated. The resulting residue was purified by combi flash in

**144**

SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 4:4) to yield **144** (60 mg, 58% yield).

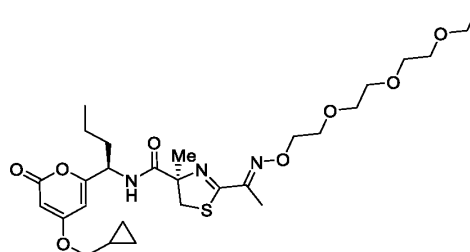
¹H NMR (400 MHz, CD₃OD): δ 7.86 (d, *J* = 8.5 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 1H), 6.04-5.95 (m, 1H), 5.54 (d, *J* = 2.2 Hz, 1H), 5.48-5.23 (m, 2H), 4.75 (dt, *J* = 9.2, 5.8 Hz, 1H), 4.59 (d, *J* = 5.4 Hz, 2H), 4.33 (t, *J* = 4.7 Hz, 2H), 3.77 (t, *J* = 4.7 Hz, 2H), 3.67-3.58 (m, 7H), 3.59-3.50 (m, 4H), 3.20 (d, *J* = 11.5 Hz, 1H), 2.21 (s, 3H), 1.93-1.76 (m, 2H), 1.53 (s, 3H), 1.50-1.31 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CD₃OD): δ 174.9, 170.7, 167.8, 165.1, 164.0, 152.1, 131.2, 118.0, 99.5, 88.4, 84.3, 74.3, 70.3, 70.2, 70.1, 69.6, 69.5, 69.0, 66.1, 50.8, 39.3, 33.8, 23.5, 18.8, 14.1, 12.5, 10.5.

MS (ES⁺): *m/z* 568.2 [M+H]⁺, 590.2 [M+Na]⁺.

Synthesis of **145**

To a solution of **76** (74 mg, 0.176 mmol) in acetone (2 mL), K₂CO₃ (121 mg, 0.879 mmol) and 2-[2-(2-ethoxyethoxy)ethoxy]ethyl iodide (223 mg, 0.879 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C overnight. The reaction mixture was filtered, washing with EtOAc and evaporated. The resulting residue was purified by combi flash in SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 6:4) to yield **145** (79 mg, 79% yield).

**145**

¹H NMR (400 MHz, CD₃OD): δ 7.86 (d, *J* = 8.6 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 4.75 (td, *J* = 8.8, 5.8 Hz, 1H), 4.33 (t, *J* = 4.7 Hz, 2H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.77 (t, *J* = 4.7 Hz, 2H), 3.66-3.59 (m, 7H), 3.59-3.44 (m, 4H), 3.20 (d, *J* = 11.6 Hz, 1H), 2.22 (s, 3H), 1.90-0.76 (m, 2H), 1.52 (s, 3H), 1.49-1.34 (m, 3H), 1.25-1.21 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.67-0.57 (m, 2H), 0.37-0.33 (m, 2H).

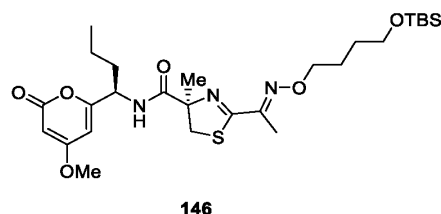
¹³C NMR (100 MHz, CD₃OD): δ 176.3, 176.2, 172.5, 169.1, 166.6, 165.2 (x2), 153.5, 101.0, 89.3, 85.7 (x2), 75.7, 75.3, 71.6 (x2), 71.5, 70.9, 70.4, 67.5, 52.2, 52.1, 40.7, 35.3, 35.2, 24.9, 20.2, 15.5, 13.9, 11.9, 10.4, 3.7.

MS (ES⁺): *m/z* 582.2 [M+H]⁺, 604.2 [M+Na]⁺.

Rf: 0.43 (CH₂Cl₂:EtOAc 6:4).

Synthesis of **146**

To a solution of **1** (85 mg, 0.22 mmol) in acetone (2 mL) was added Cs₂CO₃ (363 mg, 1.1 mmol) and *tert*-butyl(4-iodobutoxy)dimethylsilane (0.3 mL, 1.1 mmol) and the reaction was stirred at 23 °C overnight. Evaporation to dryness of the reaction mixture following by purification by flash

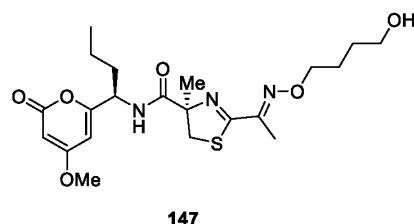


chromatography on silica gel (CH₂Cl₂:EtOAc) gave **146** (100 mg, 30% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.07 (d, *J* = 8.5 Hz, 1H), 5.86 (t, *J* = 2.5 Hz, 1H), 5.39 (d, *J* = 2.5 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 2H), 3.76 (s, 3H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.48 (dd, *J* = 11.8, 3.1 Hz, 1H), 3.18 (dd, *J* = 14.5, 9.4 Hz, 2H), 2.15 (d, *J* = 2.5 Hz, 3H), 1.96-1.50 (m, 6H), 1.48 (s, 3H), 1.42-1.26 (m, 2H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 6H), 0.02 (s, 3H).
¹³C NMR (100 MHz, CDCl₃): δ 174.2, 170.8, 167.9, 164.0, 162.5, 162.4, 151.4, 100.1, 100.0, 88.5, 84.3, 75.4, 74.1, 62.7, 55.9, 50.9, 39.8, 34.7, 30.0 (x2), 29.1, 25.9, 25.6, 24.7, 19.0, 18.3, 13.6, 11.8, 6.3, -5.3.

Synthesis of **147**

To a mixture of **146** (100 mg, 0.18 mmol) and NH₄F (34 mg, 0.9 mmol) in THF (16 mL) was added TBAF (0.9 mL, 1.0 M in THF, 0.9 mmol) at 23 °C. After being stirred for 4 h, 0.3 mL of TBAF was added to complete the reaction. After 2 h, the reaction was quenched with an aqueous saturated solution of NaCl and



extracted with CH₂Cl₂. The organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporation of the volatiles gave a crude which was purified by flash chromatography on silica gel (CH₂Cl₂:EtOAc) to afford **147** (54 mg, 37% yield).

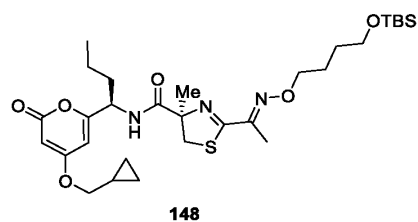
¹H NMR (400 MHz, CDCl₃): δ 7.06 (d, *J* = 8.8 Hz, 1H), 5.87 (dd, *J* = 2.2, 0.5 Hz, 1H), 5.40 (d, *J* = 2.3 Hz, 1H), 4.71 (td, *J* = 8.3, 6.8 Hz, 1H), 4.25 (td, *J* = 6.4, 1.0 Hz, 2H), 3.77 (s, 3H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.41-3.27 (m, 3H), 3.18 (d, *J* = 11.6 Hz, 1H), 2.17 (s, 3H), 1.92-1.62 (m, 6H), 1.50 (s, 3H), 1.48-1.29 (m, 2H), 1.29-1.17 (m, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 174.1, 170.9, 167.9, 164.1, 162.4, 151.6, 100.1, 88.5, 84.3, 75.2, 62.5, 59.3, 55.9, 50.9, 39.9, 34.8, 29.7, 29.1, 25.6, 24.8, 24.3, 19.8, 19.0, 13.7, 13.6, 11.9.

145

Synthesis of **148**

To a solution of **76** (458 mg, 1.08 mmol) in acetone (11 mL), Cs₂CO₃ (1.77 g, 5.43 mmol) and *tert*-butyl(4-iodobutoxy)dimethylsilane (1.41 mL, 5.43 mmol) were added and was stirred at 23 °C overnight. The reaction mixture was filtered washing with EtOAc.



and evaporated. The resulting residue was purified by combi flash in SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 9:1) to yield **148** (587 mg, 89% yield).

¹H NMR (400 MHz, CD₃OD): δ 7.85 (d, *J* = 8.6 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 5.48 (s, 1H), 4.74 (td, *J* = 8.8, 5.7 Hz, 1H), 4.23 (t, *J* = 6.4 Hz, 2H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.58 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.20 (s, 3H), 1.94-1.71 (m, 4H), 1.64-1.57 (m, 2H), 1.52 (s, 3H), 1.51-1.32 (m, 2H), 1.28-1.20 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.72-0.57 (m, 2H), 0.37-0.33 (m, 2H), 0.05 (s, 6H).

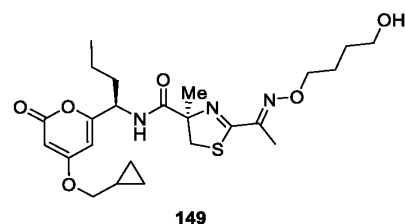
¹³C NMR (100 MHz, CD₃OD): δ 175.0, 171.2, 168.0, 165.3, 163.8, 151.5, 99.7, 87.9, 84.3, 74.9, 73.9, 62.5, 50.8, 39.2, 33.9, 28.8, 25.4, 25.0, 23.5, 18.8, 12.5, 10.4, 9.0, 2.3, -6.6.

MS (ES⁺): *m/z* 608.2 [M+H]⁺, 630.2 [M+Na]⁺.

R_f: 0.53 (CH₂Cl₂:EtOAc 9:1).

Synthesis of **149**

To a solution of **148** (95 mg, 0.156 mmol) in anhydrous MeOH (1 mL), PPTS (14 mg, 0.054 mmol) was added and was stirred at 23 °C for 3h. Then, the solvent was removed under pressure and the resulting oil was dissolved in EtOAc and washed with an aqueous saturated solution of NaHCO₃ and H₂O. The



combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated. The resulting residue was purified by combi flash in SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 1:1) to obtain **149** (0.59 g, 77% yield).

¹H NMR (400 MHz, CD₃OD): δ 7.87 (d, *J* = 8.6 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 4.74 (td, *J* = 8.9, 5.7 Hz, 1H), 4.23 (t, *J* = 6.5 Hz, 2H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.70-3.49 (m, 3H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.20 (s, 3H), 1.88-1.74 (m, 4H), 1.68-1.57 (m, 2H), 1.52 (s, 3H), 1.50-1.32 (m, 2H), 1.25-1.20 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.70-0.54 (m, 2H), 0.37-0.33 (m, 2H).

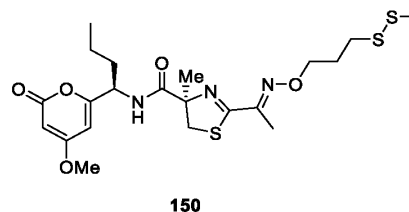
¹³C NMR (100 MHz, CD₃OD): δ 176.4, 172.6, 169.3, 166.7, 165.2, 152.9, 101.1, 89.2, 85.7, 76.3, 75.3, 62.6, 52.2, 40.7, 35.2, 30.0, 26.8, 24.9, 20.3, 13.9, 11.8, 10.4, 3.7.

MS (ES⁺): *m/z* 494.2 [M+H]⁺, 516.2 [M+Na]⁺.

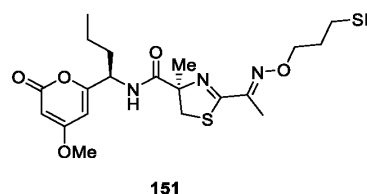
R_f: 0.46 (CH₂Cl₂:EtOAc 1:1).

Synthesis of **150**

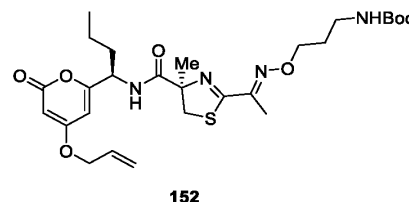
- To a solution of **1** (60 mg, 0.16 mmol) in acetone (1.6 mL) was added K₂CO₃ (110 mg, 0.8 mmol) and 1-(3-iodopropyl)-2-methyldisulfane (200 mg, 0.8 mmol) at 23 °C. After being stirred overnight, the reaction mixture was diluted with CH₂Cl₂ and H₂O was added. Extraction with CH₂Cl₂, dryness over anhydrous Na₂SO₄, filtered, and evaporation of the organic layers gave a crude which was purified by flash chromatography on silica gel to afford **150** (15 mg, 19% yield).
- ¹H NMR (400 MHz, CDCl₃): δ 7.08 (d, *J* = 8.8 Hz, 1H), 5.93-5.86 (m, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 4.73 (q, *J* = 7.9 Hz, 1H), 4.33 (t, *J* = 6.1 Hz, 2H), 3.79 (s, 3H), 3.52 (d, *J* = 11.6 Hz, 1H), 3.29 (t, *J* = 6.7 Hz, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.79 (td, *J* = 7.0, 2.2 Hz, 3H), 2.19 (d, *J* = 0.6 Hz, 3H), 2.13 (p, *J* = 6.7 Hz, 2H), 1.95-1.70 (m, 2H), 1.52 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H).
- ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 170.9, 167.7, 164.1, 162.4, 152.0, 100.2, 88.6, 84.4, 73.4, 56.0, 50.9, 39.9, 38.7, 35.1, 34.8, 32.3, 29.7, 28.8, 24.8, 19.1, 13.6, 12.0, 4.6.

Synthesis of **151**

- To a solution of **150** (15 mg, 0.03 mmol) in EtOAc (1.8 mL) and MeOH (2.7 mL) was added a mixture of DL-Dithiothreitol (DTT) (0.075 mL, 1.0 M in H₂O, 0.075 mmol) in 0.05 M NaH₂PO₄ in EDTA (1.8 mL) at 23 °C. The reaction mixture was stirred for 7 h and the reaction was quenched with H₂O. Extraction with CH₂Cl₂, dryness over anhydrous Na₂SO₄, filtered, and evaporation of the organic layers gave a crude which was purified by flash chromatography on silica gel to afford **151** (7 mg, 26% yield).
- ¹H NMR (400 MHz, CDCl₃): δ 7.07 (d, *J* = 8.8 Hz, 1H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.79-4.63 (m, 1H), 4.32 (dt, *J* = 10.3, 6.1 Hz, 2H), 3.79 (s, 3H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.19 (d, *J* = 11.6 Hz, 1H), 2.83-2.57 (m, 5H), 2.18 (s, 3H), 2.08-1.66 (m, 4H), 1.56-1.48 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

Synthesis of **152**

- To a solution of **74** (1.03 g, 2.53 mmol) in acetone (25 mL) was added Cs₂CO₃ (1.24 g, 3.79 mmol) and *tert*-butyl (3-iodopropyl)carbamate (1.08 g, 3.79 mmol). The reaction mixture was refluxed for 30 min and, after allowed to cool to 23 °C, filtrated through a Celite® plug that was washed with EtOAc. Organic filtrate was evaporated and crude residue was purified in a flash chromatography system over silica gel eluting with mixtures hexane:EtOAc from 80:20 to 60:40 in 20 min to yield pure **152** (1.47 g, 100% yield).



147

^1H NMR (400 MHz, CDCl_3): δ 7.06 (d, J = 8.7 Hz, 1H), 6.01-5.88 (m, 1H), 5.90 (d, J = 2.1 Hz, 1H), 5.42-5.30 (m, 3H), 4.78-4.65 (m, 2H), 4.47 (dt, J = 5.6, 1.5 Hz, 2H), 4.27 (t, J = 6.0 Hz, 2H), 3.50 (d, J = 11.6 Hz, 1H), 3.22 (q, J = 7.9, 6.9 Hz, 2H), 3.18 (d, J = 11.6 Hz, 1H), 2.16 (s, 3H), 1.94-1.68 (m, 4H), 1.49 (s, 3H), 1.42 (s, 9H), 1.39-1.29 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

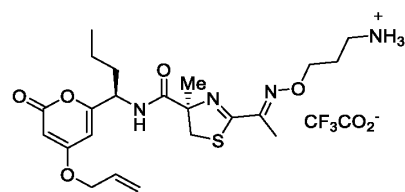
5 ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 169.6, 167.7, 164.0, 162.4, 155.9, 151.8, 130.6, 119.5, 100.3, 89.3, 84.3, 79.1, 73.0, 69.5, 50.9, 39.8, 37.6, 34.7, 29.4, 28.3, 24.7, 19.0, 13.5, 11.8.

MS (ES⁺): m/z 587.3 $[\text{M}+\text{Na}]^+$, 565.3 $[\text{M}+\text{H}]^+$.

R_f: 0.16 (hexanes:EtOAc 7:3).

Synthesis of **153**

10 To a solution of **152** (1.47 g, 2.6 mmol) in CH_2Cl_2 (55 mL) was added TFA (16 mL). After being stirred for 2.5 hours, the reaction mixture was evaporated to dryness. Crude residue was purified in CombiFlash with CH_2Cl_2 :MeOH mixtures from 100:0 to 90:10 in 20

**153**

15 min to give pure **153** (1.4 g, 100% yield).

^1H NMR (400 MHz, CDCl_3): δ 8.07 (s, 2H), 7.01 (d, J = 8.8 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 6.01-5.86 (m, 1H), 5.43 (d, J = 2.2 Hz, 1H), 5.41-5.28 (m, 2H), 4.69 (q, J = 7.9 Hz, 1H), 4.47 (dd, J = 5.6, 1.6 Hz, 2H), 4.28 (td, J = 8.1, 7.3, 4.0 Hz, 2H), 3.55 (d, J = 11.5 Hz, 1H), 3.14 (d, J = 11.6 Hz, 1H), 3.09 (s, 2H), 2.16 (s, 3H), 2.14-2.05 (m, 2H), 1.78 (m, 2H), 1.52 (s, 3H), 1.48-1.21 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H).

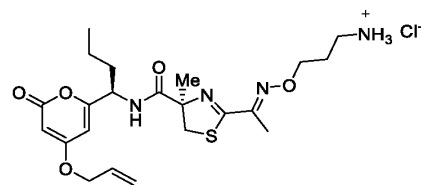
20 ^{13}C NMR (100 MHz, CDCl_3): δ 174.0, 170.1, 167.7, 164.7, 162.4, 152.7, 130.5, 119.5, 100.7, 89.3, 84.3, 71.7, 69.7, 50.9, 40.1, 37.4, 34.6, 27.2, 24.7, 19.0, 13.5, 11.8.

MS (ES⁺): m/z 465.2 $[\text{M}+\text{H}]^+$.

R_f: 0.8 (CH_2Cl_2 :MeOH 9:1).

25 Synthesis of **154**

153 (424 mg) was treated with 2M NaOH and extracted with CH_2Cl_2 (x2). The organic layers were dried over anhydrous Na_2SO_4 , filtered, and the volatiles were evaporated. 5-6 N of HCl in 2-propanol was added to the crude and then evaporated to dryness to give **154** (135 mg, 37% yield) as a foamed solid.

**154**

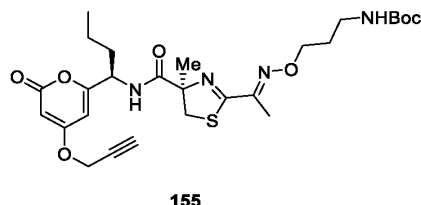
30 ^1H NMR (400 MHz, CD_3OD): δ 6.10 (s, 1H), 6.01 (m, 1H), 5.43 (s, 1H), 5.34 (m, 1H), 4.75 (m, 1H), 4.61 (m, 2H), 4.33 (m, 2H), 3.61 (d, J = 11.6 Hz, 1H), 3.23 (d, J = 11.6 Hz, 1H), 3.08 (m, 2H), 2.24 (s, 3H), 2.09 (m, 1H), 1.85 (m, 2H), 1.55 (m, 3H), 1.53-1.31 (m, 2H), 0.99 (m, 3H).

35 ^{13}C NMR (100 MHz, CD_3OD): δ 174.6, 170.8, 168.1, 165.2, 163.7, 152.5, 131.1, 118.0, 99.8, 88.5, 88.4, 84.1, 71.6, 69.6, 50.8, 39.3, 36.8, 33.8, 27.1, 23.4, 18.8, 12.4, 10.4.

MS (ES⁺): m/z 465.2 [M+H]⁺.

Synthesis of **155**

To a solution of **75** (53 mg, 0.131 mmol) in acetone (5 mL) was added Cs₂CO₃ (64 mg, 0.196 mmol) and *tert*-butyl (3-iodopropyl)carbamate (56 mg, 0.196 mmol). The reaction mixture was refluxed for 30 min and, after allowed to cool to 23 °C, filtrated through a Celite® plug that was washed with EtOAc. Organic filtrate was evaporated and crude residue was purified in a flash chromatography system over silica gel eluting with mixtures hexane:EtOAc from 80:20 to 60:40 in 20 min to yield pure **155** (67 mg, 91% yield).

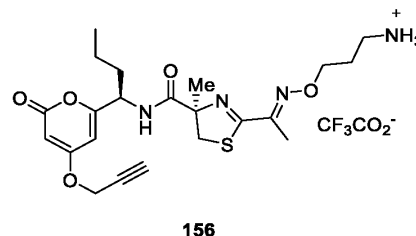


¹H NMR (400 MHz, CDCl₃): δ 7.05 (d, J = 8.7 Hz, 1H), 5.89 (d, J = 2.2 Hz, 1H), 5.53 (d, J = 2.2 Hz, 1H), 4.76 (tt, J = 3.8, 2.0 Hz, 1H), 4.71 (td, J = 8.4, 6.8 Hz, 1H), 4.64 (d, J = 2.4 Hz, 2H), 4.26 (t, J = 6.1 Hz, 2H), 3.49 (d, J = 11.6 Hz, 1H), 3.21 (q, J = 9.6, 8.0 Hz, 2H), 3.18 (d, J = 11.6 Hz, 1H), 2.62 (t, J = 2.4 Hz, 1H), 2.16 (s, 3H), 1.95-1.78 (m, 3H), 1.81-1.66 (m, 1H), 1.49 (s, 3H), 1.41 (s, 9H), 1.46-1.25 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 174.0, 168.6, 167.7, 163.6, 162.8, 155.9, 151.8, 99.9, 90.0, 84.3, 79.1, 77.7, 75.6, 73.0, 56.4, 50.9, 39.8, 37.6, 34.7, 29.4, 28.3, 24.7, 19.0, 13.5, 11.8.

Synthesis of **156**

To a solution of **155** (67 mg, 0.119 mmol) in CH₂Cl₂ (2.5 mL) was added TFA (0.7 mL). After being stirred for 30 min, the reaction mixture was evaporated to dryness. Crude residue was purified in CombiFlash with CH₂Cl₂:MeOH mixtures from 100:0 to 90:1 to obtain pure **156** (55 mg, 80% yield).

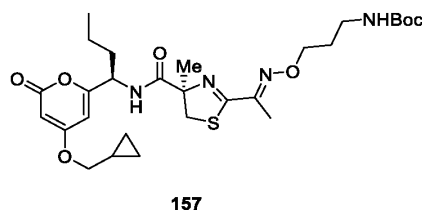


¹H NMR (400 MHz, CDCl₃): δ 7.02 (d, J = 8.8 Hz, 1H), 5.97 (d, J = 2.2 Hz, 1H), 5.58 (d, J = 2.2 Hz, 1H), 4.72 (q, J = 7.9 Hz, 1H), 4.66 (d, J = 2.5 Hz, 2H), 4.37-4.23 (m, 2H), 3.56 (d, J = 11.6 Hz, 1H), 3.16 (d, J = 11.6 Hz, 1H), 3.11 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 2.4 Hz, 1H), 2.16 (s, 3H), 2.13-2.05 (m, 2H), 1.90-1.67 (m, 2H), 1.53 (s, 3H), 1.49-1.26 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 174.2, 169.2, 167.8, 164.5, 162.8, 152.8, 100.5, 90.1, 84.3, 77.8, 75.6, 71.8, 56.6, 50.9, 40.1, 37.6, 34.6, 27.2, 24.7, 19.0, 13.5, 11.8.

Synthesis of **157**

To a solution of **76** (9 mg, 0.021 mmol) in acetone (5 mL) was added Cs₂CO₃ (10 mg, 0.031 mmol) and *tert*-butyl (3-iodopropyl)carbamate (9 mg, 0.031 mmol). The reaction mixture was refluxed for 30 min

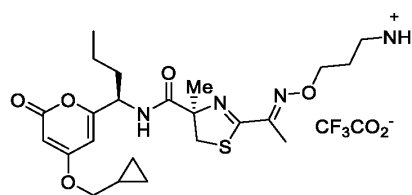


and, after allowed to cool to 23 °C, filtrated through a Celite® plug that was washed with EtOAc. Organic filtrate was evaporated to obtain crude **157** (10 mg, 81% yield) which was used in the next without further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.09 (t, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 2.2 Hz, 1H), 5.35 (t, *J* = 1.7 Hz, 1H), 4.79-4.68 (m, 1H), 4.64 (s, 1H), 4.28 (t, *J* = 6.0 Hz, 1H), 3.76 (dd, *J* = 7.1, 1.9 Hz, 2H), 3.52 (dd, *J* = 11.6, 8.6 Hz, 1H), 3.28-3.14 (m, 4H), 2.18 (s, 3H), 2.07-1.95 (m, 2H), 1.90 (dd, *J* = 8.0, 4.9 Hz, 1H), 1.69 (s, 2H), 1.51 (d, *J* = 2.9 Hz, 3H), 1.43 (s, 9H), 1.25 (d, *J* = 2.2 Hz, 3H), 0.96 (td, *J* = 7.3, 1.5 Hz, 3H), 0.66 (q, *J* = 6.1 Hz, 1H), 0.33 (dt, *J* = 6.1, 4.7 Hz, 1H).

Synthesis of **158**

To a solution of **157** (12 mg, 0.021 mmol) in CH₂Cl₂ (0.4 mL) was added TFA (0.1 mL). After being stirred for 30 min, the reaction mixture was evaporated to dryness. Crude residue was purified in CombiFlash with CH₂Cl₂:MeOH mixtures from 100:0 to 85:15 to afford pure **158** (4.9 mg, 49% yield).

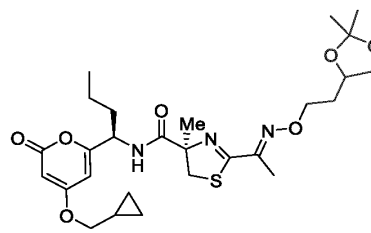
**158**

¹H NMR (400 MHz, CDCl₃): δ 7.85 (s, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.01 (d, *J* = 2.1 Hz, 1H), 5.44 (d, *J* = 2.2 Hz, 1H), 4.72 (q, *J* = 7.9 Hz, 1H), 4.30 (dt, *J* = 12.0, 5.9 Hz, 2H), 3.76 (dd, *J* = 7.2, 1.7 Hz, 2H), 3.58 (d, *J* = 11.6 Hz, 1H), 3.15 (d, *J* = 11.6 Hz, 1H), 2.36 (s, 1H), 2.17 (s, 3H), 2.10 (q, *J* = 5.3, 4.3 Hz, 2H), 1.79 (m, 2H), 1.55 (s, 3H), 1.36 (m, 2H), 1.27-1.15 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.70-0.60 (m, 2H), 0.38-0.25 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 174.2, 170.9, 167.9, 165.6, 162.2, 152.9, 101.4, 89.0, 84.3, 74.2, 72.0, 50.9, 40.2, 37.8, 34.5, 27.2, 24.7, 19.1, 13.5, 11.8, 9.3, 3.3 (x2).

Synthesis of **159**

To a solution of **76** (50 mg, 0.121 mmol) in acetone (1.5 mL), Cs₂CO₃ (196 mg, 0.604 mmol) and 4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (155 mg, 0.604 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C overnight. Then was filtered washing with EtOAc. and evaporated. The resulting residue was purified by combi flash in SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 8:2) to afford **159** (60 mg, 91% yield).

**159**

¹H NMR (400 MHz, CD₃OD): δ 7.85 (d, *J* = 8.6 Hz, 1H), 6.05 s, 1H), 5.48 (s, 1H), 4.75 (td, *J* = 8.6, 5.8 Hz, 1H), 4.30 (t, *J* = 6.3 Hz, 2H), 4.21 (p, *J* = 6.3 Hz, 1H), 4.08 (dt, *J* = 8.0, 4.8 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.70-3.48 (m, 2H), 3.20 (d, *J* = 11.5 Hz, 1H), 2.20 (s, 3H), 1.99-1.93 (m, 2H), 1.91-1.76 (m, 2H), 1.52 (s, 3H), 1.50-1.38 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28-1.14 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.71-0.50 (m, 2H), 0.36-0.33 (m, 2H).

150

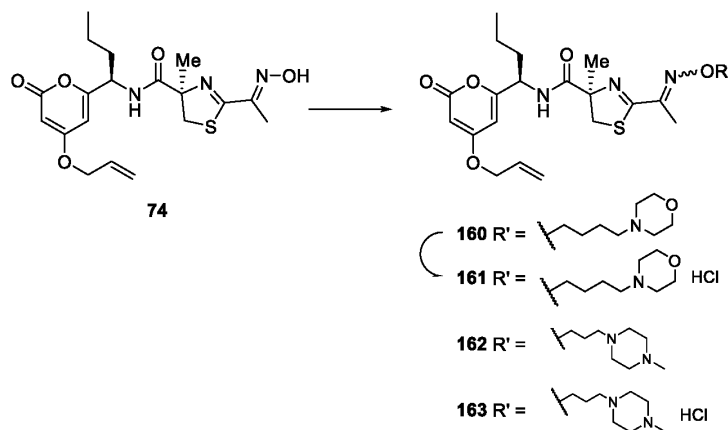
^{13}C NMR (100 MHz, CD_3OD): δ 174.9, 171.2, 167.8, 165.3, 163.8, 151.9, 108.5, 99.7, 87.9, 84.3, 73.9, 73.3, 71.9, 69.1, 50.8, 39.3, 33.9, 32.9, 25.9, 24.6, 23.5, 18.9, 12.5, 10.5, 8.98, 2.3.

MS (ES⁺): m/z 550.3 $[\text{M}+\text{H}]^+$, 572.3 $[\text{M}+\text{Na}]^+$.

R_f: 0.5 (CH_2Cl_2 :EtOAc 8:2).

5 Example 17 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

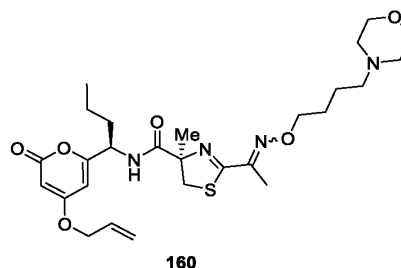
Scheme 29 provides further examples of the synthesis of compounds of formula I



Scheme 29

Synthesis of **160**

- 10 In a schlenk tube was poured anhydrous Cs_2CO_3 (88 mg, 0.269 mmol), **74** (43 mg, 0.105 mmol) and 4-(4-chlorobutyl)morpholine hydrochloride (23 mg, 0.108 mol). Then, the solids were suspended in acetone (1.4 mL) and the mixture refluxed overnight. When
- 15 cooled down, the suspension filtered through Celite®, washed with EtOAc and the filtrate was concentrated under vacuum. The resulting brown oily crude was subjected to a chromatographic purification (SiO_2 , Hex:EtOAc from 50:50 to 0:100 followed by EtOAc:MeOH 95:5) to yield **160** (28 mg, 48% yield) as a ca. (50:50) mixture of geometrical estereoisomers
- 20 and as pale orangish oil.



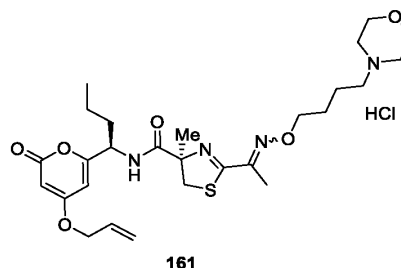
- ^1H NMR (500 MHz, CDCl_3): δ 7.08 (d, J = 8.8 Hz, 1H) 7.02 (d, J = 8.5 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H), 5.98-5.91 (m, 2H), 5.90 (d, J = 2.2 Hz, 1H), 5.43-5.38 (m, 6H), 4.71 (q, J = 7.8, 6.9 Hz, 1H), 4.67 (q, J = 7.8, 6.9 Hz, 1H), 4.49 (m, 4H), 4.23 (td, J = 6.4, 5.3 Hz, 4H), 3.71 (t, J = 4.9 Hz, 8H), 3.54 (d, J = 11.6 Hz, 1H), 3.49 (d, J = 11.6 Hz, 1H), 3.20 (d, J = 2.3 Hz, 1H), 3.17 (d, J = 2.3 Hz, 1H), 2.45 (bs, 8H), 2.39-2.36 (m, 4H), 2.15 (s, 6H), 1.92-1.80 (m, 2H), 1.79-1.64 (m, 6H), 1.59 (pd, J = 6.8, 6.1, 3.4 Hz, 4H), 1.49 (s, 3H), 1.46 (s, 3H), 1.43-1.25 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H).

MS (ES⁺): *m/z* 571.3 [M+Na]⁺, 549.2 [M+H]⁺.

R_f: 0.15 (EtOAc).

Synthesis of **161**

- 160** (160 mg, 0.292 mmol) was dissolved in a solution of HCl in 2-propanol (15 mL, 6 M) and stirred for 10 min. Then, the volatiles were vacuum-evaporated and the brown residue treated twice more under the same conditions. When the starting compound was totally transformed, the resulting brown and dense residue was dried in a vacuum-assisted oven overnight, resulting **161** (146 mg, 85% yield) as a pale brown solid and a ca. (50:50) mixture of geometrical estereoisomers.

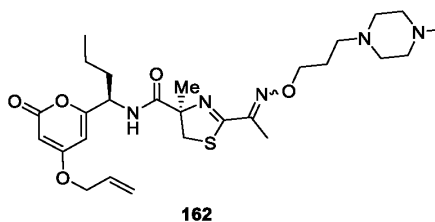


- ¹H NMR (400 MHz, CDCl₃): δ 8.67 (brs, 1H), 8.58 (brs, 1H), 6.10-5.87 (m, 4H), 5.48-5.30 (m, 6H), 4.75-4.59 (m, 2H), 4.49 (brt, *J* = 6.4 Hz, 4H), 4.44-3.40 (m, 16H), 2.38 (brs, 6H), 1.97-1.72 (m, 12H), 1.70-1.23 (m, 16H), 1.22 (s, 3H), 1.20 (s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

MS (ES⁺): *m/z* 549.3 [M+H]⁺.

Synthesis of **162**

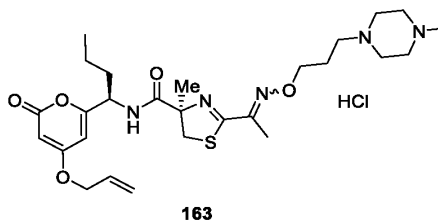
- In a schlenk tube was poured anhydrous K₂CO₃ (36 mg, 0.258 mmol), **74** (35 mg, 0.086 mmol) and 3-(4-methylpiperazin-1-yl)propyl methanesulfonate (26 mg, 0.086 mol). Then, the solids were suspended in acetone (1.4 mL) and the mixture refluxed overnight. When cooled down, the suspension was treated with a buffer solution Na₂CO₃:NaHCO₃ (pH = 9.51) (20 mL), stirred and extracted with CH₂Cl₂ (4x25 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The resulting brown oily crude was subjected to a chromatographic purification (SiO₂, EtOAc:MeOH from 90:0 to 0:100) to obtain **162** (42 mg, 97% yield) as a ca. (50:50) mixture of geometrical estereoisomers and as waxy solid.
- ¹H NMR (500 MHz, (CD₃)₂SO): δ 7.87 (m, 2H), 6.11 (d, *J* = 2.1 Hz, 1H), 6.01 (d, *J* = 2.2 Hz, 1H), 6.04-5.93 (m, 2H), 5.60 (d, *J* = 2.2 Hz, 1H), 5.57 (d, *J* = 2.2 Hz, 1H), 5.42 (ddd, *J* = 12.4, 1.6, 0.7 Hz, 1H), 5.38 (ddd, *J* = 12.3, 1.6, 0.7 Hz, 1H), 5.36-5.25 (m, 2H), 4.62 (d, *J* = 5.5 Hz, 2H), 4.60 (d, *J* = 5.6 Hz, 2H), 4.58-4.51 (m, 2H), 4.19 (td, *J* = 6.4, 2.3 Hz, 4H), 3.60-3.52 (ddd, *J* = 11.4, 7.9, 0.7 Hz, 2H), 3.19 (ddd, *J* = 11.4, 7.9, 0.7 Hz, 2H), 2.45-2.20 (m, 20H), 2.15 (s, 6H), 2.13 (s, 6H), 1.82-1.70 (m, 10H), 1.45 (s, 3H), 1.43 (s, 3H), 1.42-1.16 (m, 16H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H).



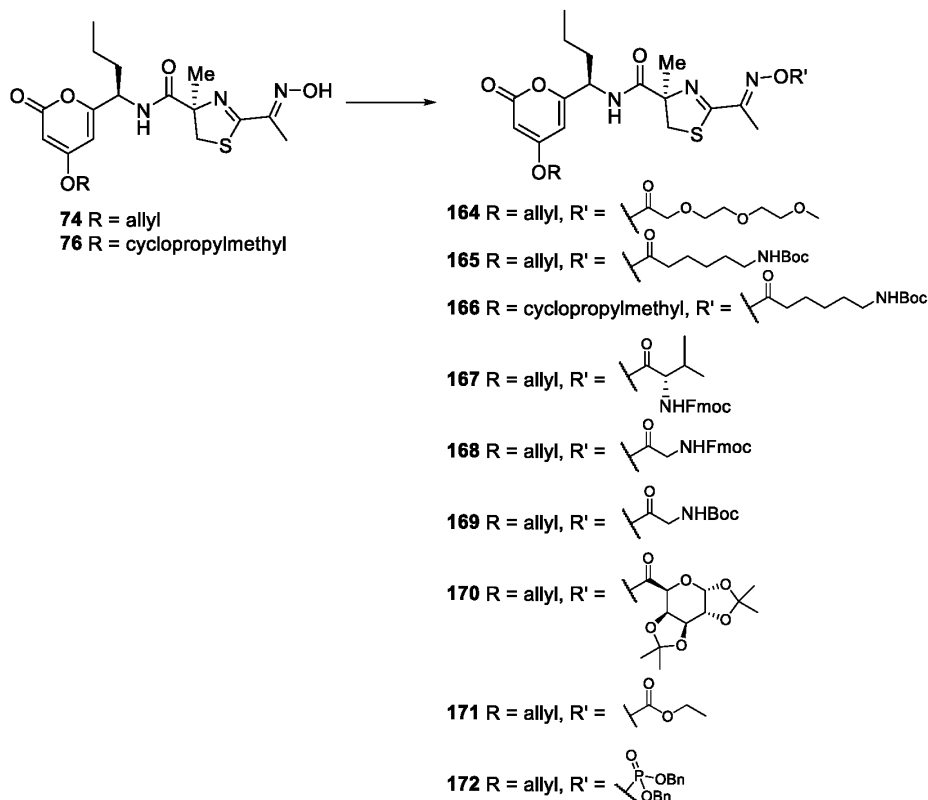
MS (ES⁺): *m/z* 570.3 [M+Na]⁺, 548.2 [M+H]⁺.

Synthesis of **163**

- 162** (77 mg, 0.14 mmol) was dissolved in a solution of HCl in 2-propanol (7 mL, 6 M) and stirred for 10 min. Then, the volatiles were vacuum-evaporated and the brown residue treated twice more under the same conditions. When the starting compound was totally transformed, the resulting brown and dense residue was dried in a vacuum-assited oven over overnight, resulting **163** (75 mg, 91% yield) as a pale brown solid and a ca. (50:50) mixture of geometrical estereoisomers.
- ¹H NMR (400 MHz, CDCl₃): δ 8.30-8.50 (m, 1H), 6.07-5.88 (m, 4H), 5.48-5.30 (m, 6H), 4.75-4.60 (m, 2H), 4.49 (brt, *J* = 6.4 Hz, 4H), 4.44-2.63 (m, 16H), 2.94 (brs, 6H), 2.51-2.15 (m, 3H), 2.33 (brs, 6H), 2.10-1.54 (m, 14H), 1.52-1.17 (m, 11H), 0.96 (t, *J* = 7.4Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).
- MS (ES⁺): *m/z* 548.2 [M+H]⁺.

EXAMPLE 18 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

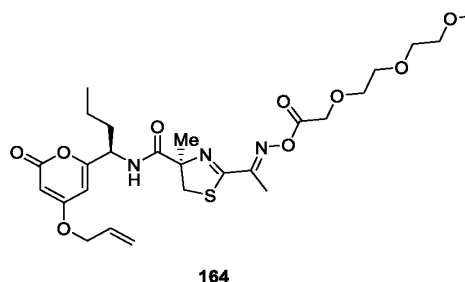
Scheme 30 provides further examples of the synthesis of compounds of formula I



Scheme 30

Synthesis of **164**

To a solution of **74** (51.1 mg, 0.125 mmol) CH₂Cl₂ (2 mL) was sequentially added EDC HCl (48 mg, 0.25 mmol), DIPEA (43.5 μL, 0.25 mmol), 2-(2-(2-methoxyethoxy)ethoxy)-acetic acid (38.37 μL, 0.25 mmol) and DMAP (cat) and the reaction mixture was stirred at 23 °C for 24 h. Once the reaction was finished, the solution was washed with HCl 0.5 N (previously cooled) and an aqueous saturated solution of NaHCO₃. Finally, the organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give an oil crude. The crude was purified with combiflash, using reverse phase column with this gradient: 5 min 10% CH₃CN; 20 min 50% CH₃CN and 15 min 50% CH₃CN to give **164** (22 mg, 31% yield).

**164**

¹H NMR (400 MHz, CD₃OD): δ 8.10-8.03 (m, 1H), 6.74-6.67 (m, 1H), 6.13-5.95 (m, 2H), 5.55 (d, *J* = 2.2 Hz, 1H), 5.49 (d, *J* = 0.9 Hz, 1H), 5.42 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.33 (dt, *J* = 10.5, 1.2 Hz, 1H), 5.05 (s, 2H), 4.75 (dd, *J* = 9.2, 5.7 Hz, 1H), 4.63-4.56 (m, 2H), 3.69-3.51 (m, 4H), 3.40-3.28 (m, 11H), 3.18 (dd, *J* = 11.5, 0.8 Hz, 1H), 3.08 (d, *J* = 0.8 Hz, 3H), 2.19 (d, *J* = 0.8 Hz, 3H), 1.94-1.75 (m, 1H), 1.53 (d, *J* = 0.8 Hz, 3H), 1.47-1.32 (m, 1H), 1.29 (s, 1H), 1.04-0.95 (m, 3H).

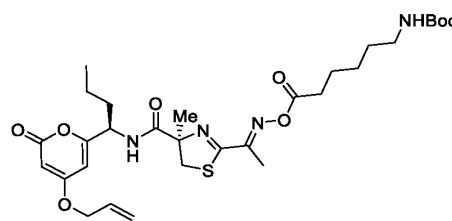
¹³C NMR (100 MHz, CD₃OD): δ 152.9, 132.6, 119.4, 107.9, 100.9, 89.8, 85.6, 71.0, 52.2, 49.5, 49.0, 48.9, 40.6, 39.3, 35.2, 25.0, 20.3, 13.8, 11.0.

MS (ES⁺): *m/z* 590.2 [M+Na]⁺, 568.3 [M+H]⁺.

R_f: 0.27 (CH₂Cl₂:EtOAc 6:4).

Synthesis of **165**

To a solution of **74** (20 mg, 0.048 mmol) in CH₂Cl₂ (1 mL), *N*-(*tert*-butoxycarbonyl)-6-aminohexanoic acid (12 mg, 0.053 mmol), DMAP (0.5 mg, 0.005 mmol) and a solution of DCC (11 mg, 0.053 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23 °C overnight. Then was filtered and evaporated to yield crude **165** (30 mg, 99% yield) which was used in the next step without further purification.

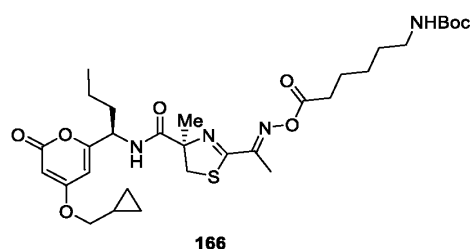
**165**

¹H NMR (400 MHz, (CD₃)₂CO): δ 8.12 (d, *J* = 5.7 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 6.56 (d, *J* = 5.8 Hz, 1H), 6.09-5.85 (m, 2H), 5.48-5.38 (m, 2H), 5.31 (d, *J* = 10.5 Hz, 1H), 4.89-4.68 (m, 1H), 4.61 (d, *J* = 5.5 Hz, 2H), 3.69 (d, *J* = 11.6 Hz, 1H), 3.30 (d, *J* = 11.6 Hz, 1H), 3.08 (q, *J* = 6.7 Hz, 2H), 2.99 (s, 3H), 2.79 (s, 4H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 1.90-1.62 (m, 4H), 1.55 (s, 4H), 1.39 (s, 9H), 1.12 (dd, *J* = 21.1, 11.4 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).

MS (ES⁺): *m/z* 621.2 [M+H]⁺, 643.2 [M+Na]⁺.

Synthesis of 166

To a solution of **76** (50 mg, 0.118 mmol) in CH₂Cl₂ (2 mL), *N*-(*tert*-butoxycarbonyl)-6-aminohexanoic acid (30 mg, 0.130 mmol), DMAP (1.4 mg, 0.012 mmol) and a solution of DCC (27 mg, 0.130 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23 °C overnight.



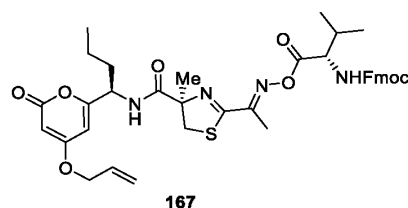
Then was filtered and evaporated to yield crude **166** (75 mg, 99% yield) which was used in the
10 next step without further purification.

¹H NMR (400 MHz, (CD₃)₂CO): δ 8.17-8.00 (m, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 6.62-6.51 (m, 1H), 6.01 (d, *J* = 2.3 Hz, 1H), 5.94 (s, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 4.83-4.68 (m, 1H), 3.88 (dd, *J* = 7.1, 2.3 Hz, 2H), 3.69 (d, *J* = 11.6 Hz, 1H), 3.31 (d, *J* = 11.6 Hz, 1H), 3.07 (q, *J* = 6.6 Hz, 2H), 2.99 (s, 3H), 2.81 (d, *J* = 12.4 Hz, 4H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.35 (s, 3H), 1.76 (m, 2H), 1.55 (s, 3H), 1.53-1.44 (m, 2H), 1.39 (s, 9H), 1.33-1.18 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.64-0.56 (m, 2H), 0.36 (dt, *J* = 6.1, 4.4 Hz, 2H).

MS (ES⁺): *m/z* 657.2 [M+Na]⁺.

Synthesis of 167

To a solution of **74** (43 mg, 0.106 mmol) in CH₂Cl₂ (1 mL) Fmoc-L-Val (40 mg, 0.117 mmol), DMAP (1 mg, 0.0106 mmol) and a solution of DCC (24 mg, 0.117 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23



25 °C overnight. Then was filtered and evaporated to yield crude **167** (76 mg, 99% yield) which was used in the next step without further purification.

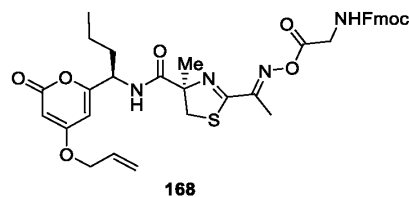
¹H NMR (400 MHz, CD₃OD): δ 8.03 (d, *J* = 6.3 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 6.69 (d, *J* = 6.3 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 5.97-5.87 (m, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 5.39-5.18 (m, 2H), 4.75 (dd, *J* = 9.1, 5.9 Hz, 1H), 4.50 (d, *J* = 5.5 Hz, 2H), 4.41-4.32 (m, 2H), 4.27 (d, *J* = 6.6 Hz, 1H), 4.20 (t, *J* = 6.9 Hz, 1H), 3.67 (d, *J* = 11.6 Hz, 1H), 3.27 (d, *J* = 11.5 Hz, 1H), 2.34 (s, 3H), 2.26-2.14 (m, 1H), 1.91-1.75 (m, 2H), 1.53 (s, 3H), 1.51-1.17 (m, 2H), 1.07-0.89 (m, 9H).

¹³C NMR (100 MHz, CD₃OD): δ 174.3, 170.7, 168.7, 165.1, 164.0, 163.4, 160.4, 157.4, 143.8, 141.2, 131.1, 127.2, 126.8, 124.8, 119.6, 118.0, 99.6, 88.6, 84.5, 69.6, 66.6, 59.1, 50.8, 39.9, 35.5, 33.8, 30.3, 23.4, 18.9, 18.2, 17.3, 12.5, 12.3.

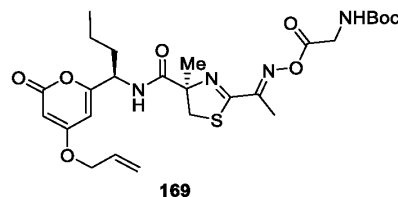
35 MS (ES⁺): *m/z* 729.2 [M+H]⁺, 751.2 [M+Na]⁺.

Synthesis of **168**

- To a solution of **74** (42 mg, 0.102 mmol) in CH₂Cl₂ (1 mL) Fmoc-Gly (33 mg, 0.112 mmol), DMAP (1 mg, 0.0102 mmol) and a solution of DCC (23 mg, 0.112 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23 °C overnight. Then was filtered and evaporated to yield crude **168** (69 mg, 99% yield) which was used in the next step without further purification.
- ¹H NMR (400 MHz, CD₃OD): δ 8.04-8.03 (m, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 6.8 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 5.98-5.91 (m, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 5.42-5.19 (m, 2H), 4.75 (dd, *J* = 9.2, 5.7 Hz, 1H), 4.53 (d, *J* = 5.8 Hz, 2H), 4.35 (d, *J* = 7.1 Hz, 2H), 4.21 (t, *J* = 7.2 Hz, 1H), 4.13 (s, 2H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.27 (d, *J* = 11.5 Hz, 1H), 2.34 (s, 3H), 1.87-1.79 (m, 2H), 1.54 (s, 3H), 1.50-1.27 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).
- ¹³C NMR (100 MHz, CD₃OD): δ 174.3, 170.7, 168.7, 165.1, 164.0, 163.4, 160.4, 157.3, 143.8, 141.2, 131.1, 127.4, 126.8 (x2), 124.8, 119.6, 118.0, 99.5, 88.5, 84.5, 69.6, 66.6, 59.1, 50.8, 39.9, 35.6, 33.8, 30.3, 23.4, 18.9, 18.2, 17.3, 12.5, 12.3.
- MS (ES⁺): *m/z* 687.2 [M+H]⁺, 709.3 [M+Na]⁺.

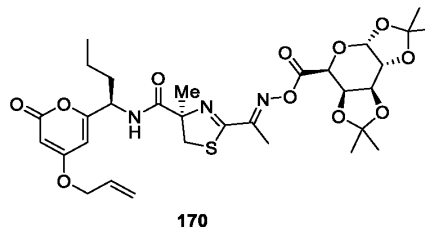
Synthesis of **169**

- To a solution of **74** (25 mg, 0.062 mmol) in CH₂Cl₂ (1 mL) Boc-Gly (12 mg, 0.068 mmol), DMAP (0.7 mg, 0.061 mmol) and a solution of DCC (14 mg, 0.068 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23 °C overnight. Then was filtered and evaporated to yield crude **169** (35 mg, 99% yield) which was used in the next step without further purification.
- ¹H NMR (400 MHz, (CD₃)₂CO): δ 8.24-8.09 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 6.71-6.51 (m, 2H), 6.13-5.93 (m, 2H), 5.42 (dd, *J* = 15.1, 2.0 Hz, 2H), 5.36-5.24 (m, 1H), 4.75 (dt, *J* = 8.9, 4.5 Hz, 1H), 4.67-4.55 (m, 2H), 4.10 (d, *J* = 6.0 Hz, 2H), 3.75-3.64 (m, 1H), 3.31 (d, *J* = 11.6 Hz, 1H), 3.06 (s, 3H), 2.35 (s, 3H), 1.96-1.69 (m, 2H), 1.56 (s, 3H), 1.53-1.44 (m, 1H), 1.44 (s, 9H), 1.33-1.23 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H).
- ¹³C NMR (100 MHz, (CD₃)₂CO): δ 172.9, 169.7, 167.5, 164.3, 162.7, 159.6, 147.2, 131.7, 118.3, 106.6, 98.8, 88.5, 84.7, 78.7, 69.4, 50.8, 41.3, 40.1, 38.4, 34.2, 27.7 (x2), 24.0, 19.0, 13.0, 12.4.
- MS (ES⁺): *m/z* 565.2 [M+H]⁺, 587.3 [M+Na]⁺.



Synthesis of **170**

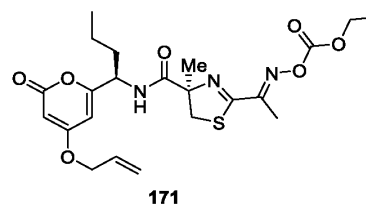
To a solution of **74** (32 mg, 0.079 mmol) in CH₂Cl₂ (1 mL), 1,2:3,4-di-*O*-isopropylidene- α -D-galacturonide (18 mg, 0.066 mmol), DMAP (1.6 mg, 0.0131 mmol) and a solution of DCC (27 mg, 0.131 mmol) in CH₂Cl₂ (0.5 mL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h and at 23 °C overnight. Then was filtered and evaporated. The resulting residue was purified in preparative HPLC to yield **170** (25 mg, 57% yield).



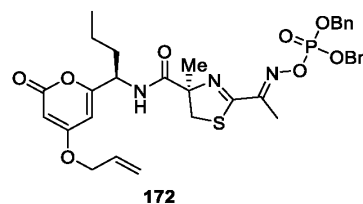
- ¹H NMR (500 MHz, (CD₃)₂CO): δ 7.51 (d, J = 8.7 Hz, 1H), 6.05-5.99 (m, 1H), 6.02 (s, 1H), 5.63 (d, J = 5.1 Hz, 1H), 5.52-5.36 (m, 2H), 5.31 (d, J = 10.5 Hz, 1H), 4.85-4.67 (m, 4H), 4.61 (d, J = 5.5 Hz, 2H), 4.50 (dd, J = 5.1, 2.6 Hz, 1H), 3.70 (d, J = 11.6 Hz, 1H), 3.33 (d, J = 11.6 Hz, 1H), 2.37 (s, 3H), 1.95-1.69 (m, 2H), 1.56-1.29 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.97 (t, J = 7.4 Hz, 3H).
- ¹³C NMR (125 MHz, (CD₃)₂CO): δ 173.8, 170.6, 167.1, 165.2, 163.6, 161.1, 132.7, 119.2, 109.7, 99.8, 97.4, 89.5, 85.7, 73.0, 71.9, 71.1, 70.3, 69.0, 51.8, 41.1, 35.2, 26.4, 26.2, 25.1, 25.0, 24.9, 20.0, 13.9, 13.5.
- MS (ES⁺): m/z 664.2 [M+H]⁺, 686.3 [M+Na]⁺.

Synthesis of **171**

- To a solution of **74** (50 mg, 0.124 mmol) in THF (1 mL) ethyl chloroformate (24 μ L, 0.248 mmol) and Et₃N (52 μ L, 0.373 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1h. Then was diluted with H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to yield crude **171** (58 mg, 99% yield) which was used in the next step without further purification.
- ¹H NMR (400 MHz, (CD₃)₂CO): δ 7.50 (d, J = 8.7 Hz, 1H), 6.08-5.98 (m, 1H), 6.02 (s, 1H), 5.52-5.37 (m, 2H), 5.31 (d, J = 10.6, 1H), 4.75 (td, J = 8.9, 5.7 Hz, 1H), 4.61 (dt, J = 5.5, 1.6 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 11.6 Hz, 1H), 3.31 (d, J = 11.6 Hz, 1H), 2.34 (s, 3H), 1.96-1.68 (m, 2H), 1.55 (s, 3H), 1.68-1.16 (m, 5H), 0.96 (t, J = 7.3 Hz, 3H).
- MS (ES⁺): m/z 480.3 [M+H]⁺, 502.2 [M+Na]⁺.

Synthesis of **172**

- To a solution of **74** (50 mg, 0.124 mmol) in THF (1.50 mL), dibenzyl diisopropylphosphoramidite (62 μ L, 0.185 mmol) and tetrazole (1.24 mL, 0.557 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C for 2h. The reaction mixture was cooled to -45 °C, followed by



dropwise addition of a solution of *m*CPBA (0.106 g, 0.618 mmol) in CH₂Cl₂ (1.5 mL). The reaction mixture was warmed to 23 °C and stirred for 1h. The reaction was diluted an aqueous saturated solution of Na₂S₂O₃, extracted with EtOAc, and washed an aqueous saturated solution of Na₂S₂O₃ and with an aqueous saturated solution of NaHCO₃. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated. The resulting residue was purified by combi flash in SiO₂ (hexane:EtOAc from 100:0 to 50:50) to afford **172** (26 mg, 32% yield).

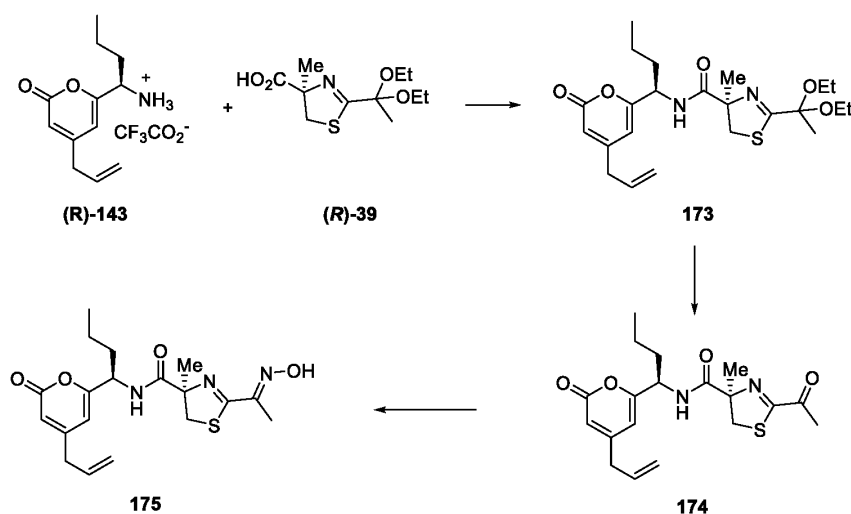
¹H NMR (400 MHz, CD₃OD): δ 7.92 (d, *J* = 8.6 Hz, 1H), 7.40-7.32 (m, 10H), 6.07 (d, *J* = 2.2 Hz, 1H), 6.05-5.89 (m, 1H), 5.51 (d, *J* = 2.2 Hz, 1H), 5.38 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.21 (s, 2H), 5.19 (s, 2H), 4.80-4.74 (m, 1H), 4.54 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.70 (d, *J* = 11.6 Hz, 1H), 3.36-3.17 (m, 1H), 2.22 (s, 3H), 1.97-1.71 (m, 2H), 1.55 (s, 3H), 1.55-1.21 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CD₃OD): δ 175.6, 172.1, 167.2, 166.0, 165.3, 162.9, 162.8, 136.8, 136.7, 132.5, 129.8, 129.7, 129.6 (x3), 129.7, 129.3 (x3), 129.2, 119.5, 101.0, 89.8, 85.9, 72.1 (x2), 72.0 (x2), 71.0, 52.2, 41.2, 35.2, 24.7, 20.3, 13.8, 12.7.

MS (ES⁺): *m/z* 668.3 [M+H]⁺, 690.2 [M+Na]⁺.

EXAMPLE 19 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 31 provides further examples of the synthesis of compounds of formula I



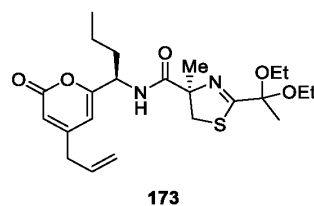
20

Scheme 31

Synthesis of **173**

A mixture of (R)-143 (48 mg, 0.15 mmol) and (R)-39 (47 mg, 0.15 mmol) was evaporated with toluene and then HATU (58 mg, 0.15 mmol) and HOAt (21 mg, 0.15 mmol) were added. Reaction flask was evacuated, filled with N₂ and CH₂Cl₂ (1.1 mL) and

25

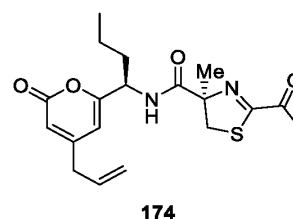


- DIPEA (0.1 mL, 0.6 mmol) were added via syringe at 23 °C. The reaction mixture was stirred 16 h at 23 °C. Then, it was diluted with CH₂Cl₂ before washing twice with HCl 0.5 N and once with an aqueous saturated solution of NaCl. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was purified on a system for flash chromatography on silica gel (Hex:EtOAc) to give **173** (20 mg, 68% yield).

- ¹H NMR (400 MHz, CDCl₃): δ 7.12-7.04 (m, 1H), 6.45 (dq, *J* = 15.8, 6.8 Hz, 1H), 6.19 (d, *J* = 1.5 Hz, 1H), 6.18-6.10 (m, 1H), 5.92-5.88 (m, 1H), 4.75 (td, *J* = 8.5, 6.5 Hz, 1H), 3.63 (d, *J* = 11.7 Hz, 1H), 3.60-3.44 (m, 4H), 3.15 (dd, *J* = 11.7, 0.8 Hz, 1H), 1.91 (dd, *J* = 6.7, 1.6 Hz, 2H), 1.89-1.67 (m, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.46-1.27 (m, 2H), 1.21 (m, 6H), 0.96-0.90 (m, 3H).
- ¹³C NMR (100 MHz, CDCl₃): δ 178.3, 174.1, 162.9, 161.8, 151.8, 136.2, 128.1, 109.5, 100.4, 100.3, 85.0, 58.0, 57.9, 51.3, 40.6, 35.0, 28.0, 27.0, 25.5, 23.9, 19.3, 19.0, 18.9, 17.7, 15.4, 15.3, 13.7 (x2).
- MS (ES⁺): *m/z* 473.1 [M+Na]⁺.

Synthesis of **174**

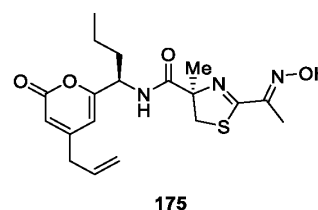
- A mixture of **173** (20 mg, 0.044 mmol), pentane (1 mL) and formic acid (0.7 mL) was vigorously stirred for 2 h and the volatiles were evaporated. The crude was evaporated few times with a mixture of CH₂Cl₂/toluene to eliminate the acid. The crude obtained was purified by flash chromatography on silica gel (hex:EtOAc) to give **174** (6 mg, 17% yield).



- ¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.9 Hz, 1H), 6.46 (dq, *J* = 15.8, 6.8 Hz, 1H), 6.31-6.08 (m, 3H), 5.94 (s, 1H), 4.85-4.70 (m, 1H), 3.64 (d, *J* = 11.9 Hz, 1H), 3.27 (d, *J* = 11.9 Hz, 1H), 2.56 (s, 3H), 1.93 (dd, *J* = 6.7, 1.6 Hz, 3H), 1.90-1.59 (m, 4H), 1.55 (s, 3H), 1.49-1.23 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).
- MS (ES⁺): *m/z* 399.2 [M+Na]⁺, 377.1 [M+H]⁺.

Synthesis of **175**

- A mixture of **174** (6 mg, 0.015 mmol), EtOH (0.2 mL), H₂O (0.2 mL), NH₂OH·HCl (7 mg, 0.11 mmol) and NaOAc (5 mg, 0.06 mmol) was stirred at 23 °C for 24 h. Then ethanol was evaporated, a aqueous saturated solution of NaCl was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The crude was chromatographed over silica gel (hex:EtOAc) to afford **175** (2 mg, 34% yield).



- ¹H NMR (400 MHz, CD₃OD): δ 6.66-6.52 (m, 1H), 6.41 (s, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 5.98 (s, 1H), 4.80 (m, 1H), 3.61 (dd, *J* = 11.5, 1.1 Hz, 1H), 3.17 (dd, *J* = 11.5, 1.1 Hz, 1H), 2.20 (d, *J* =

159

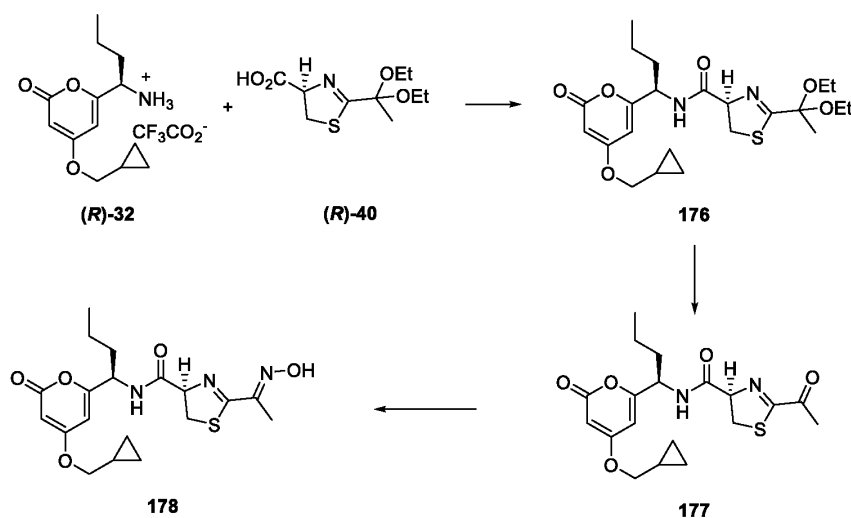
1.1 Hz, 3H), 1.92 (dt, $J = 6.8, 1.4$ Hz, 3H), 1.92-1.79 (m, 2H), 1.57 (s, 3H), 1.34-1.13 (m, 2H), 1.00 (t, $J = 7.4$, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 176.5, 170.4, 165.3, 164.1, 154.5, 152.9, 138.4, 128.9, 109.5, 101.0, 85.7, 40.7, 35.4, 30.4, 25.3, 20.3, 19.0, 13.9, 11.0.

5 MS (ES⁺): m/z 399.2 $[\text{M}+\text{Na}]^+$, 377.1 $[\text{M}+\text{H}]^+$.

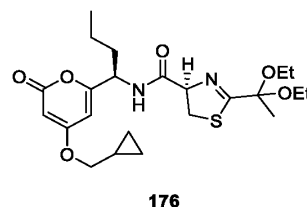
EXAMPLE 20 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 32 provides further examples of the synthesis of compounds of formula I



10 Synthesis of **176**

A mixture of **(R)-32** (600 mg, 1.71 mmol) and **(R)-40** (422 mg, 1.71 mmol) was evaporated with toluene and then HATU (649 mg, 1.71 mmol) and HOAt (234 mg, 1.71 mmol) were added. Reaction flask was evacuated, filled with N_2 and CH_2Cl_2 (12 mL)



15 and DIPEA (1.2 mL, 6.84 mmol) were added via syringe at 23

$^{\circ}\text{C}$. The reaction mixture was stirred 16 h at 23 $^{\circ}\text{C}$. Then, it was diluted with CH_2Cl_2 before washing twice with HCl 0.5 N and once with an aqueous saturated solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. The residue was purified on a system for flash chromatography on silica gel (CH_2Cl_2 :EtOAc) to give **176** (660 mg, 63% yield).

20 ^1H NMR (400 MHz, CDCl_3): δ 6.98 (d, $J = 8.8$ Hz, 1H), 5.90-5.73 (m, 1H), 5.28 (dd, $J = 2.2, 1.2$ Hz, 1H), 5.14 (ddd, $J = 10.1, 8.4, 1.3$ Hz, 1H), 4.71 (td, $J = 8.4, 6.5$ Hz, 1H), 3.71 (ddd, $J = 7.2, 3.2, 1.1$ Hz, 2H), 3.61-3.38 (m, 5H), 1.89-1.75 (m, 1H), 1.74-1.59 (m, 1H), 1.57 (d, $J = 1.5$ Hz, 3H), 1.42-1.25 (m, 2H), 1.24-1.11 (m, 6H), 0.89 (td, $J = 7.3, 1.3$ Hz, 3H), 0.61 (dt, $J = 8.0, 1.0$ Hz, 1H), 0.28 (dt, $J = 4.8, 1.2$ Hz, 2H).

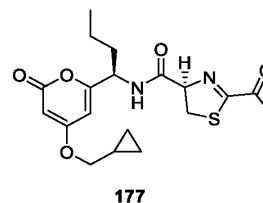
160

^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 170.0, 164.0, 162.7, 88.7, 78.8, 77.4, 77.1, 76.8, 73.7, 57.8, 50.9, 34.6, 34.2, 23.8, 19.0, 15.2, 15.1, 13.5, 9.4, 3.3 (x2).

MS (ES⁺): m/z 489.2 $[\text{M}+\text{Na}]^+$.

Synthesis of **177**

- 5 To **176** (75 mg, 0.16 mmol) was added pentane (8.4 mL) and formic acid (5.6 mL). The mixture was stirred for 1 h, and then toluene was added to quench the reaction. The volatiles were evaporated under vacuum and the crude was coevaporated with toluene twice. The crude was purified by flash chromatography on silica gel (CH_2Cl_2 :EtOAc) to yield **177** (23 mg, 40% yield).



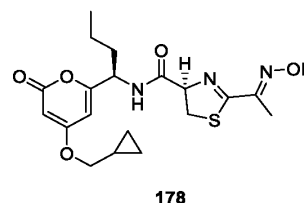
- 10 ^1H NMR (400 MHz, CDCl_3): δ 6.99 (d, J = 8.8 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 5.35 (d, J = 2.2 Hz, 1H), 5.24 (dd, J = 10.9, 10.2 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 3.77 (td, J = 6.9, 1.8 Hz, 2H), 3.68-3.48 (m, 2H), 2.55 (s, 3H), 1.95-1.69 (m, 2H), 1.48-1.17 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H), 0.66 (dd, J = 8.0, 1.2 Hz, 2H), 0.33 (td, J = 4.7, 2.2 Hz, 2H).

- 15 ^{13}C NMR (100 MHz, CDCl_3): δ 192.9, 172.8, 170.1, 169.4, 164.1, 161.8, 100.8, 88.9, 80.1, 73.9, 51.3, 34.8, 34.2, 26.3, 19.1, 13.6, 9.4, 3.4 (x2).

MS (ES⁺): m/z 393.2 $[\text{M}+\text{H}]^+$, 415.3 $[\text{M}+\text{Na}]^+$.

Synthesis of **178**

- 20 To a solution of **177** (22 mg, 0.056 mmol) in EtOH (0.6 mL) and H_2O (0.6 mL), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (10 mg, 0.14 mmol) and NaOAc (20 mg, 0.24 mmol) were added at 23 °C and was stirred at 23 °C overnight. Then ethanol was evaporated. The aqueous residue was diluted with brine and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and evaporated. The resulting residue was purified by combi flash on silica gel (CH_2Cl_2 :EtOAc) to afford **178** (14 mg, 61% yield).



- 25 ^1H NMR (400 MHz, CD_3OD): δ 6.17 (dd, J = 2.2, 0.8 Hz, 1H), 5.50 (d, J = 2.2 Hz, 1H), 5.17 (d, J = 9.4 Hz, 1H), 4.73 (dd, J = 9.3, 5.5 Hz, 1H), 3.88 (dd, J = 8.4, 7.2 Hz, 2H), 3.54-3.35 (m, 2H), 2.16 (d, J = 3.1 Hz, 3H), 1.96-1.70 (m, 2H), 1.59-1.34 (m, 2H), 0.98 (dt, J = 10.4, 7.3 Hz, 3H), 0.71-0.60 (m, 2H), 0.44-0.30 (m, 2H).

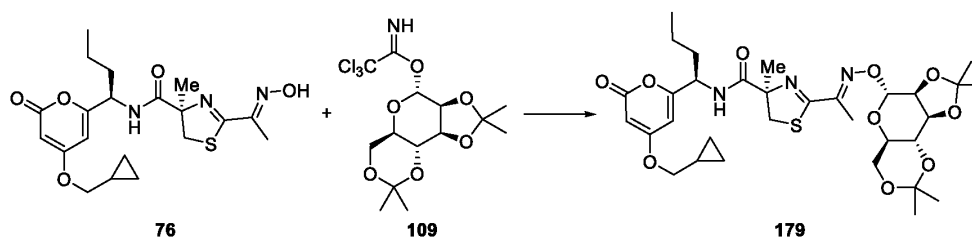
- 30 ^{13}C NMR (100 MHz, CD_3OD): δ 171.4, 171.3, 170.9, 165.5, 164.0, 151.5, 99.7, 87.7, 78.7, 74.0, 73.9, 50.9, 33.8, 32.7, 18.8, 12.4, 9.6, 9.0, 2.2.

MS (ES⁺): m/z 408.2 $[\text{M}+\text{H}]^+$, 430.1 $[\text{M}+\text{Na}]^+$.

EXAMPLE 21 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

- 35 Scheme 33 provides further examples of the synthesis of compounds of formula I

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Scheme 33

Synthesis of **179**

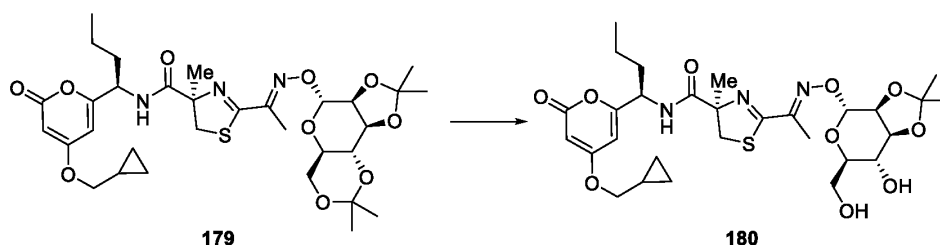
A freshly-prepared stock solution (700 μ L; 5% mol) of $\text{Pd}(\text{PhCN})(\text{OTf})_2$ catalyst in CH_2Cl_2 , prepared by stirring $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ (9 mg; 0.024 mmol) and AgOTf (12 mg; 0.047 mmol) in CH_2Cl_2 (3.5 mL) at 23 $^\circ\text{C}$ for 5 min, was added to a solution of **109** (37 mg; 0.0091 mmol) and **76** (50 mg; 0.139 mmol) in CH_2Cl_2 (500 μ L) at 23 $^\circ\text{C}$. The reaction mixture was stirred at 23 $^\circ\text{C}$ overnight, then, treated with benzene (1 mL) and directly poured on a chromatographic column (SiO_2 , CH_2Cl_2 :MeOH from 10:0 to 98.2:1.8). According to this procedure, **179** (31 mg, 51% yield) was afforded as a foamy white solid (predominantly as a α anomer).

^1H NMR (400 MHz, CDCl_3): δ 9.38 (s, 1H), 7.14 (dd, J = 8.8, 2.9 Hz, 1H), 5.93 (dd, J = 4.3, 2.1 Hz, 1H), 5.67 (s, 1H), 5.37 (t, J = 2.2 Hz, 1H), 4.91 (dd, J = 6.0, 3.9 Hz, 1H), 4.87 (d, J = 5.9 Hz, 1H), 4.73 (q, J = 8.5, 7.9 Hz, 1H), 4.38 (dt, J = 7.8, 5.2 Hz, 1H), 4.22 (dd, J = 7.7, 3.8 Hz, 1H), 4.08 (brs, 1H), 4.07 (s, 1H), 3.84-3.69 (m, 2H), 3.52 (d, J = 11.6 Hz, 1H), 3.22 (dd, J = 11.6, 2.3 Hz, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 1.93-1.71 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.45-1.30 (m, 1H), 1.30-1.12 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H), 0.66 (m, 2H), 0.33 (dt, J = 6.0, 4.7 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 174.3, 174.1, 170.3, 170.2, 168.2, 167.5, 164.5, 164.4, 162.4, 162.2, 153.8, 153.1, 112.9, 109.3, 109.0, 108.9, 100.9, 100.7 (x2), 100.6, 89.1 (x2), 89.0 (x2), 84.8, 84.6 (x2), 84.4, 83.3, 83.2, 80.1, 79.8, 74.1, 74.0, 73.8, 73.5, 66.8, 51.2, 51.1, 40.0, 39.9 (x2), 35.0, 34.9, 27.1, 27.0, 26.1, 26.0, 25.3, 25.2, 24.9, 24.8, 24.7, 24.6, 24.5, 19.2, 13.7 (x2), 12.2 (x2), 11.4, 11.3, 9.6, 9.5, 3.5 (x2).

MS (ES $^+$): m/z 664.2 $[\text{M}+\text{H}]^+$, 686.3 $[\text{M}+\text{Na}]^+$.

Scheme 34 provides an example of the synthesis of an additional compound of formula I.



Scheme 34

Synthesis of **180**

179 (30 mg; 0.045 mmol) was dissolved in a mixture of TFA:CHCl₃:H₂O (2.5:100:1, 1.1 mL) and stirred for 5 h at 23 °C. Then, the solution was diluted with toluene (1.5 mL) and the volatiles vacuum co-evaporated, affording oily beige crude. **180** (18 mg, 66% yield) was obtained by purification over flash chromatography on silica gel (CH₂Cl₂:MeOH from 100:0 to 90:10) as a waxy solid.

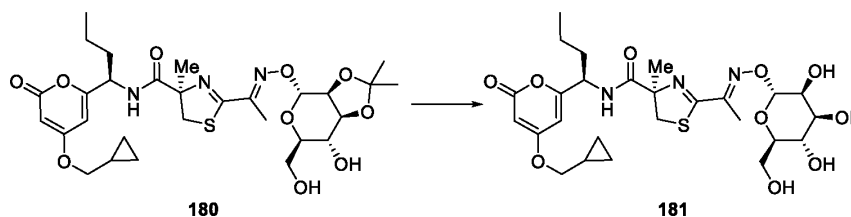
¹H NMR (500 MHz, CDCl₃): δ 7.07 (d, *J* = 8.7 Hz, 1H), 5.94 (d, *J* = 2.0 Hz, 1H), 5.72 (s, 1H), 5.36 (d, *J* = 2.1 Hz, 1H), 5.01 (dd, *J* = 5.9, 4.2 Hz, 1H), 4.89 (d, *J* = 5.9 Hz, 1H), 4.72 (m, 1H), 4.25 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.97 (m, 1H), 3.86 (d, *J* = 11.5, 3.4 Hz, 1H), 3.75 (m, 3H), 3.54 (d, *J* = 11.6 Hz, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.20 (s, 3H), 1.90-1.72 (m, 2H), 1.52 (s, 6H), 1.37 (s, 3H), 1.42-1.31 (m, 2H), 1.22 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.64 (m, 2H), 0.34 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 173.8, 170.1, 167.5, 164.3, 162.1, 153.8, 112.8, 108.6, 100.7, 88.9, 84.5, 84.4, 82.5, 80.5, 73.8, 70.7, 64.3, 51.0, 39.9, 34.8, 29.7, 25.9, 24.8, 24.5, 19.0, 13.6, 12.1, 9.4, 3.4 (x2).

MS (ES⁺): *m/z* 624.2 [M+H]⁺, 646.3 [M+Na]⁺.

R_f: 0.39 (CH₂Cl₂:MeOH 15:1).

Scheme 35 provides an example of the synthesis of an additional compound of formula I.



Scheme 35

20 Synthesis of **181**

A solution of **180** (17 mg; 0.027 mmol) in aqueous AcOH (80%, 1.0 mL) was heated for 4.5 h at 80 °C. Then, when cooled down, diluted with toluene (1.5mL) and the volatiles vacuum evaporated giving an oily beige crude. **181** (14.6 mg, 92% yield) was obtained by purification over flash chromatography on silica gel (CH₂Cl₂:MeOH from 100:0 to 90:10) as a pale yellow solid.

¹H NMR (500 MHz, (CD₃)₂SO): δ 7.90 (d, *J* = 8.5 Hz, 1H), 6.03 (d, *J* = 2.2 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H), 5.46 (d, *J* = 4.8 Hz, 1H), 5.26 (bd, *J* = 5.3 Hz, OH), 4.98 (bs, OH), 4.65 (bs, OH), 4.60 (q, *J* = 7.8 Hz, 1H), 4.41 (bs, OH), 4.16 (m, 1H), 4.07 (bs, 1H), 3.92 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.85 (m, 1H), 3.71 (bs, 1H), 3.57-3.49 (m, 2H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.19 (s, 3H), 1.75 (q, *J* = 7.6 Hz, 2H), 1.45 (s, 3H), 1.43-1.24 (m, 2H), 1.18 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.57 (dt, *J* = 9.7, 3.1 Hz, 2H), 0.30 (dt, *J* = 6.0, 4.2 Hz 2H).

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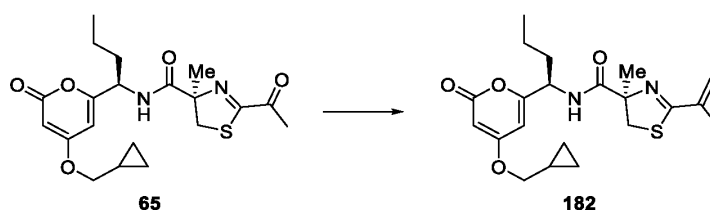
^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$): δ 172.6, 170.0, 165.9, 164.7, 163.1, 153.2, 111.0, 98.6, 88.0, 84.2, 81.0, 75.4, 73.5, 70.9, 69.1, 63.1, 50.3, 39.6, 33.5, 24.0, 18.8, 13.4, 12.3, 9.4, 3.1.

MS (ES⁺): m/z 584.2 [M+H]⁺, 606.3 [M+Na]⁺.

R_f: 0.16 (CH_2Cl_2 :MeOH 15:1).

5 EXAMPLE 22 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 36 provides further examples of the synthesis of compounds of formula I



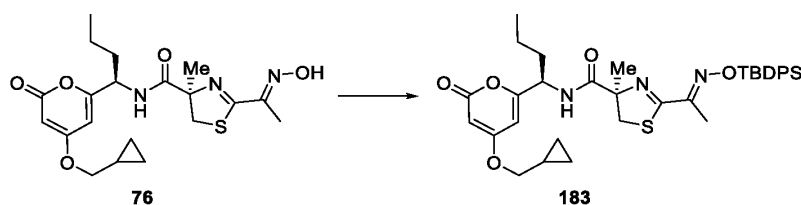
Scheme 36

- To a solution of Methyltriphenylphosphonium bromide (58 mg, 0.28 mmol) in THF (0.7 mL) was added *n*BuLi (0.175 mL, 1.6 M, 0.28 mmol) dropwise at 23 °C. The yellow suspension was stirred for 2.5 h and a solution of **65** (55 mg, 0.14 mmol) in THF (0.4 mL) was added. After 2h the reaction was refluxed for 3h and then overnight at 23 °C. The reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with CH_2Cl_2 . The crude was purified by flash chromatography on silica gel (CH_2Cl_2 :EtOAc) to give a fraction (7 mg) that contained **182**. This fraction was then purified by flash chromatography on silica gel (hexane:EtOAc) to give **182** (4 mg, 7% yield).

- ^1H NMR (400 MHz, CDCl_3): δ 7.12 (d, J = 8.6 Hz, 1H), 5.91 (dt, J = 2.2, 0.5 Hz, 1H), 5.65 (d, J = 1.4 Hz, 1H), 5.56 (d, J = 1.6 Hz, 1H), 5.34 (d, J = 2.2 Hz, 1H), 4.71 (q, J = 7.8 Hz, 1H), 3.83-3.68 (m, 2H), 3.64-3.53 (m, 1H), 3.24 (dd, J = 11.5, 0.6 Hz, 1H), 2.09 (dt, J = 1.5, 0.7 Hz, 3H), 1.95-1.66 (m, 2H), 1.51 (s, 3H), 1.44-1.18 (m, 3H), 1.00-0.90 (m, 3H), 0.73-0.57 (m, 2H), 0.33 (q, J = 5.2 Hz, 2H).

MS (ES⁺): m/z 405.2 [M+H]⁺, 427.3 [M+Na]⁺.

Scheme 37 provides a further example of the synthesis of compounds of formula I

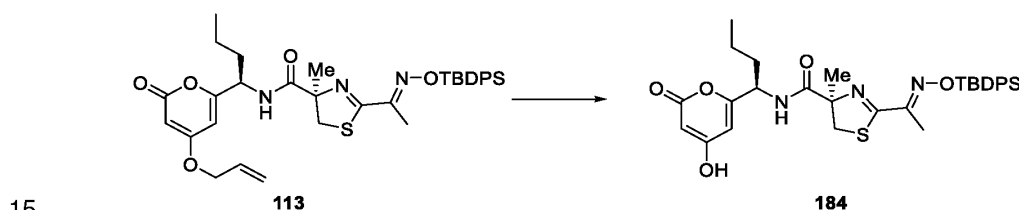


Scheme 37

To a solution of **76** (80 mg, 0.19 mmol) in DMF (0.2 mL) was added slowly CITBDPS (52 μ L, 0.199 mmol) and then a crystal of DMAP at 23 $^{\circ}$ C. The reaction mixture was stirred at 23 $^{\circ}$ C overnight. Then was quenched by dilution with CH_2Cl_2 , washed with 0.5M HCl and an aqueous saturated solution of NaCl. The organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The crude obtained was purified by flash chromatography on silica gel (CH_2Cl_2 :EtOAc) to afford **183** (119 mg, 91% yield).

^1H NMR (400 MHz, CD_3OD): δ 7.73-7.64 (m, 4H), 7.46-7.30 (m, 6H), 6.06 (dd, J = 2.2, 0.7 Hz, 1H), 5.46 (d, J = 2.2 Hz, 1H), 4.80-4.70 (m, 1H), 3.80 (dd, J = 7.2, 3.0 Hz, 2H), 3.57 (d, J = 11.6 Hz, 1H), 3.15 (d, J = 11.5 Hz, 1H), 2.40 (s, 3H), 1.90-1.75 (m, 2H), 1.53 (s, 3H), 1.51-1.16 (m, 2H), 1.12 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H), 0.72-0.39 (m, 2H), 0.30 (dt, J = 4.7, 1.3 Hz, 2H).
 ^{13}C NMR (100 MHz, CD_3OD): δ 176.2, 172.6, 166.7, 165.3, 159.1, 136.5, 134.1, 131.1, 128.8, 101.1, 89.3, 85.8, 75.3, 61.5, 52.3, 40.7, 35.3, 27.6, 25.0, 20.4, 20.3, 14.5, 13.9, 12.0, 10.4, 3.7.
 MS (ES $^{+}$): m/z 660.3 [$\text{M}+\text{H}$] $^{+}$, 682.3 [$\text{M}+\text{Na}$] $^{+}$.

Scheme 38 provides a further example of the synthesis of compounds of formula I



Scheme 38

To a solution of **113** (106 mg) in CH_2Cl_2 (4.1 mL) was added tetrakis(triphenylphosphine)palladium(0) (9 mg), acetic acid (47 μ L) and tributyltin hydride (265 μ L). The reaction mixture was stirred for 30 minutes and poured over a silica gel column to purify. Elution with hexane:EtOAc from 100:0 to 0:100 gave **184** (>100% yield).

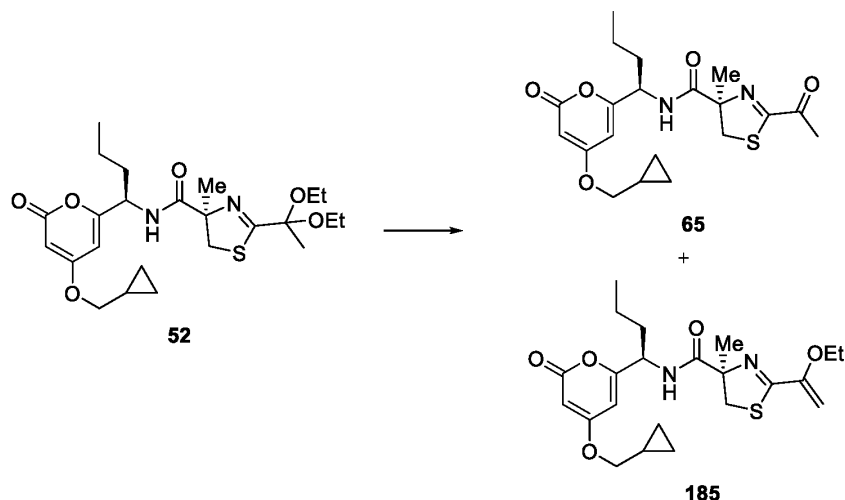
^1H NMR (400 MHz, CDCl_3): δ 7.76-7.67 (m, 4H), 7.45-7.32 (m, 6H), 6.13 (d, J = 2.1 Hz, 1H), 5.59 (d, J = 2.1 Hz, 1H), 4.70 (q, J = 7.9 Hz, 1H), 3.37 (d, J = 11.6 Hz, 1H), 3.15 (d, J = 11.6 Hz, 1H), 2.35 (s, 3H), 1.99-1.77 (m, 2H), 1.49 (s, 3H), 1.45-1.27 (m, 2H), 1.15 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 175.4, 170.5, 169.1, 165.7, 162.5, 157.1, 135.5, 132.8, 132.7, 129.9, 127.6 (x2), 101.4, 91.3, 83.9, 51.6, 39.5, 34.3, 27.1, 24.5, 19.5, 19.1, 13.6, 11.8.

EXAMPLE 23 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 39 provides further examples of the synthesis of compounds of formula I

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Scheme 39

Synthesis of **185**

A mixture of **52** (138 mg, 0.29 mmol) and HCl in 1,4-dioxane (4 mL, 4 M, 16 mmol) was stirred for 60 min at 23 °C and the volatiles were evaporated to dryness. The crude was coevaporated few times with toluene to eliminate the acid. The resulting residue was purified in preparative HPLC to yield **65** (30 mg, 25%) and **185** (15 mg, 12%), while 50 mg of starting material was recovered.

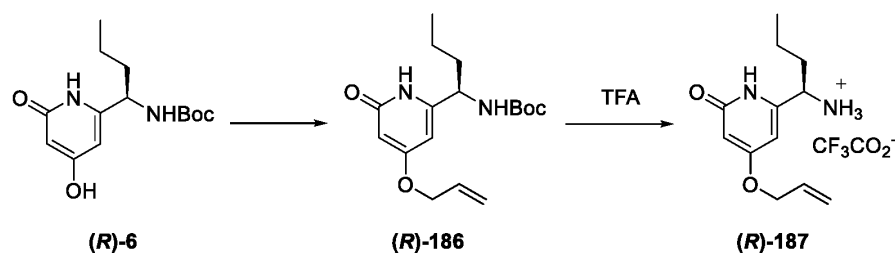
¹H NMR (500 MHz, CDCl₃): δ 7.07 (d, *J* = 8.7 Hz, 1H), 5.91 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 2.2 Hz, 1H), 5.10 (d, *J* = 2.9 Hz, 1H), 4.72 (td, *J* = 8.4, 6.6 Hz, 1H), 4.45 (d, *J* = 2.9 Hz, 1H), 3.90 (q, *J* = 7.0 Hz, 2H), 3.83-3.69 (m, 2H), 3.60 (d, *J* = 11.6 Hz, 1H), 3.22 (d, *J* = 11.6 Hz, 1H), 1.92-1.87 (m, 1H), 1.76-1.71 (m, 1H), 1.54 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.45-1.30 (m, 2H), 1.27-1.19 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.75-0.51 (m, 2H), 0.37-0.22 (m, 2H).

¹³C NMR (125 MHz, CDCl₃): δ 174.4 170.1, 167.2, 164.3, 162.8, 153.5, 100.2, 90.4, 88.8, 84.8, 73.7, 64.5, 51.0, 40.7, 34.6, 29.7, 24.6, 19.0, 14.7, 13.6, 9.4, 3.4.

MS (ES⁺): *m/z* 435.2 [M+H]⁺, 457.3 [M+Na]⁺.

EXAMPLE 24 SYNTHESIS OF ADDITIONAL INTERMEDIATES OF FORMULA II

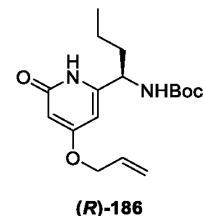
Scheme 40 provides a further example of the synthesis of intermediates of formula II



Scheme 40

Synthesis of (*R*)-186

- To a suspension of (*R*)-6 (50 mg, 0.2 mmol) in acetone (4 mL) and K₂CO₃ (37 mg, 0.3 mmol) was added 3-bromoprop-1-ene (15 μ L, 0.2 mmol) dropwise at 23 °C. The reaction mixture was stirred at 40 °C for 23 h, cooled to 23 °C and filtered. The filtrate was evaporated to dryness and the residue was dissolved in EtOAc, washed with H₂O (2x100 mL) and an aqueous saturated solution of NaCl. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a crude, which upon column chromatography (SiO₂, EtOAc) gave (*R*)-186 (16 mg, 29% yield).



- ¹H NMR (400 MHz, CD₃OD): δ 7.16 (d, J = 8.2 Hz, 1H), 6.10-5.95 (m, 2H), 5.78 (d, J = 2.4 Hz, 1H), 5.41 (dq, J = 17.3, 1.7 Hz, 1H), 5.30 (dq, J = 10.5, 1.4 Hz, 1H), 5.04-4.94 (m, 2H), 4.56 (dt, J = 5.5, 1.6 Hz, 1H), 4.39 (s, 1H), 1.62 (tt, J = 13.7, 6.2 Hz, 2H), 1.44 (s, 9H), 1.32-1.20 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).

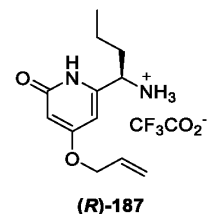
- ¹³C NMR (10 MHz, CD₃OD): δ 170.9, 167.9, 152.9, 136.6, 133.3, 118.6, 99.0, 96.6, 80.8, 70.2, 53.4, 37.7, 28.7, 20.5, 13.9.

MS (ES⁺): m/z 323.3 [M+H]⁺.

R_f: 0.18 (EtOAc).

Synthesis of (*R*)-187

- To a solution of (*R*)-146 (658 mg, 2.04 mmol) in CH₂Cl₂ (7.2 mL) was added TFA (24.5 mL). After being stirred for 2 h at 23 °C, the reaction mixture was evaporated to dryness to obtain crude (*R*)-187 (652 mg, 95% yield) which was used in the next step without further purification.

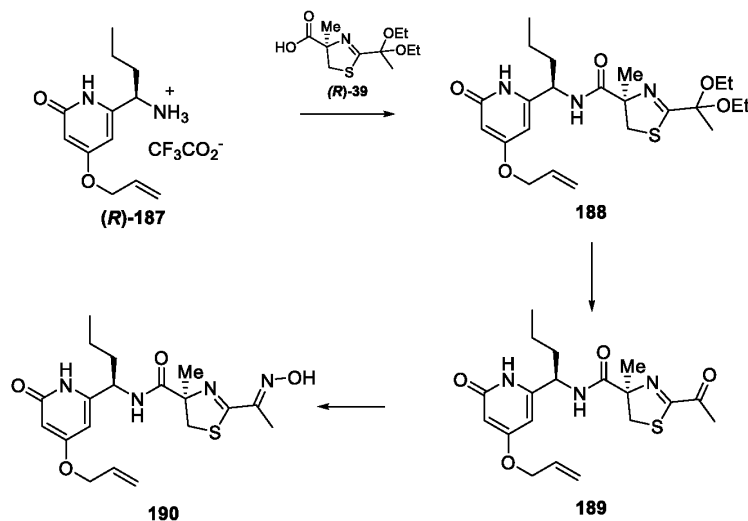


- ¹H NMR (400 MHz, CD₃OD): δ 6.53 (s, 1H), 6.27 (d, J = 1.9 Hz, 1H), 6.11-5.93 (m, 3H), 5.48-5.37 (m, 2H), 5.36-5.26 (m, 2H), 5.04-4.91 (m, 1H), 4.68 (d, J = 4.9 Hz, 1H), 4.64-4.56 (m, 3H), 4.16 (dt, J = 14.6, 7.3 Hz, 2H), 3.37-3.25 (m, 7H), 1.97-1.82 (m, 4H), 1.43 (dd, J = 13.9, 7.1 Hz, 1H), 1.41-1.28 (m, 1H), 1.29 (s, 1H), 1.25-1.13 (m, 0H), 1.05-0.84 (m, 7H).

EXAMPLE 25 SYNTHESIS OF ADDITIONAL COMPOUNDS OF FORMULA I

Scheme 41 provides a further example of the synthesis of compounds of formula I

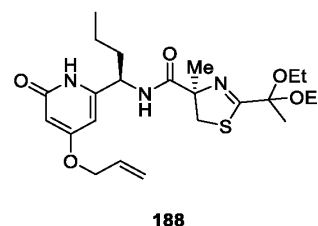
167



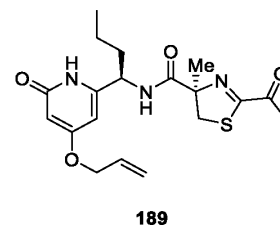
Scheme 41

Synthesis of **188**

- A mixture of **(R)-187** (552 mg, 1.7 mmol) and **(R)-39** (452 mg, 1.7 mmol) was evaporated with toluene and then HATU (657 mg, 1.7 mmol) and HOAt (237 mg, 1.7 mmol) were added. Reaction flask was evacuated, filled with N₂ and CH₂Cl₂ (12 mL) and DIPEA (1.2 mL, 6.9 mmol) were added via syringe. The mixture was stirred 16 h at 23 °C. Then, it was diluted with CH₂Cl₂ before washing twice with HCl 0.5 N and once with an aqueous saturated solution of NaCl. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was purified on a system for flash chromatography on silica gel (CH₂Cl₂:EtOAc) to afford **188** (517 mg, 64% yield).
- ¹H NMR (400 MHz, CD₃OD): δ 6.09 (dd, *J* = 2.4, 0.5 Hz, 1H), 6.08-5.96 (m, 1H), 5.79 (d, *J* = 2.3 Hz, 1H), 5.45-5.35 (m, 1H), 5.33-5.25 (m, 1H), 4.72-4.66 (m, 1H), 4.59-4.55 (m, 2H), 3.69-3.46 (m, 4H), 3.23 (d, *J* = 11.8, 1H), 1.84-1.67 (m, 2H), 1.60 (s, 3H), 1.44 (s, 3H), 1.48-1.32 (m, 2H), 1.20 (m, 6H), (0.94 (t, *J* = 7.4 Hz, 3H).

Synthesis of **189**

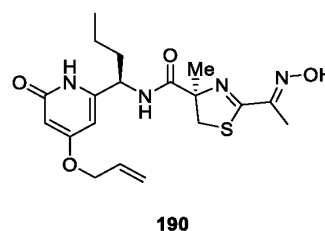
- A mixture of **188** (517 mg, 1.11 mmol), pentane (27 mL) and formic acid (18 mL) was vigorously stirred for 2 h and the volatiles were evaporated. The crude was evaporated few times with a mixture of CH₂Cl₂/toluene to eliminate formic acid. The crude mixture was purified by silica gel column chromatography (CH₂Cl₂:EtOAc) to give **189** (350 mg, 80% yield).



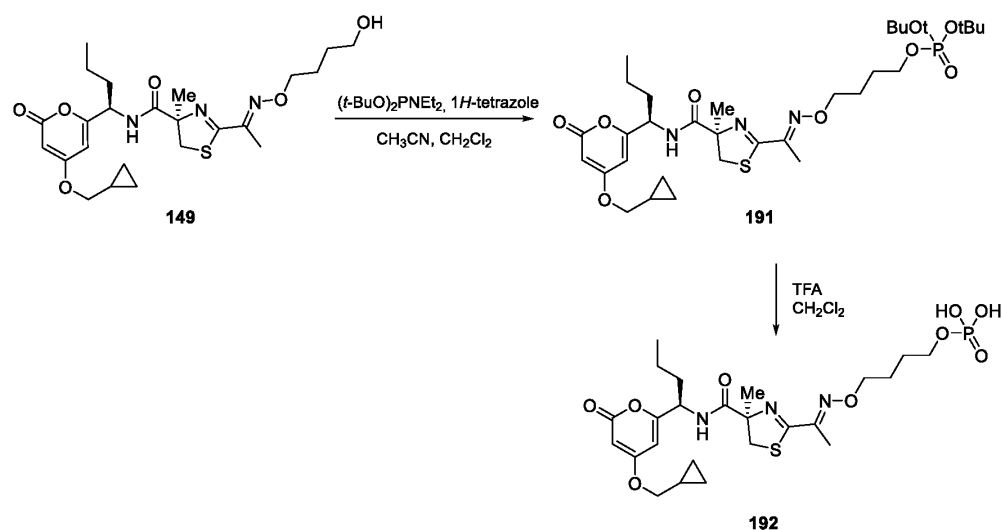
^1H NMR (400 MHz, CD_3OD): δ 6.08-5.93 (m, 2H), 5.77 (d, J = 2.4 Hz, 1H), 5.45-5.34 (m, 1H), 5.34-5.24 (m, 1H), 4.78 (m, 1H), 4.54 (dt, J = 5.5, 1.6 Hz, 2H), 3.66-3.60 (m, 1H), 3.31-3.27 (m, 1H), 2.56 (m, 2H), 1.56 (s, 3H), 1.49-1.25 (m, 2H), 1.01-0.96 (m, 3H).

Synthesis of **190**

- 5 A mixture of **189** (346 mg, 0.88 mmol), ethanol (9.7 mL), H_2O (9.7 mL), hydroxylamine hydrochloride (430 mg, 6.2 mmol) and NaOAc (290 mg, 3.5 mmol) was stirred at 23 °C for 24 h. Then ethanol was evaporated, an aqueous saturated solution of NaCl was added, and the aqueous phase was extracted
- 10 with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The crude was chromatographed over silica gel (CH_2Cl_2 :Methanol) to give **190** (242 mg, 67% yield).
- ^1H NMR (400 MHz, CD_3OD): δ 6.13-5.94 (m, 2H), 5.77 (dd, J = 2.4, 1.1 Hz, 1H), 5.39 (dp, J = 17.2, 1.5 Hz, 1H), 5.29 (dp, J = 10.6, 1.4 Hz, 1H), 4.76 (dd, J = 9.0, 6.3 Hz, 1H), 4.54 (dt, J = 5.3, 1.5 Hz, 2H), 3.48 (dd, J = 11.5, 1.1 Hz, 1H), 3.18 (dd, J = 11.5, 1.1 Hz, 1H), 2.20 (d, J = 1.2 Hz, 3H), 1.92-1.73 (m, 2H), 1.52 (d, J = 1.1 Hz, 3H), 1.52-1.36 (m, 1H), 1.40-1.27 (m, 2H), 0.99 (td, J = 7.4, 1.1 Hz, 3H).
- ^{13}C NMR (100 MHz, CDCl_3): δ 176.7, 170.7, 170.5, 167.9, 152.9, 151.1, 133.3, 118.6, 99.9, 97.0, 85.5, 70.2, 52.3, 40.7, 36.7, 24.8, 20.5, 13.8, 11.0.
- 20 MS (ES $^+$): m/z 407.1 $[\text{M}+\text{H}]^+$.
R_f: 0.33 (CH_2Cl_2 :MeOH 9:1).



Scheme 42 provides further examples of the synthesis of compounds of formula I.



Scheme 42

Synthesis of **191**

To a solution of **149** (54 mg, 0.110 mmol) in anhydrous CH₃CN (4.50 mL) and anhydrous CH₂Cl₂ (4.50 mL), 1*H*-tetrazole (3 mL, 1.317 mmol) and (tBuO)₂PNEt₂ (0.150 mL, 0.550 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C for 1h, then 70% tBuOOH solution (2.20 mL, 15.37 mmol) was added and the mixture was stirred at 23 °C overnight. An 10% aqueous solution of NaHSO₃ (5 mL) was added and the mixture was stirred for 15 min. The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and washed with H₂O (1 x 10 mL). The organic extract was dried over anhydrous Na₂SO₄, filtered and evaporated. The resulting residue was purified by combiflash in SiO₂ (from CH₂Cl₂ to CH₂Cl₂:EtOAc 1:1) to yield **191** (50 mg, 67% yield).

¹H NMR (400 MHz, CD₃OD): δ 6.06 (d, *J* = 2.2 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 4.74 (dd, *J* = 9.1, 5.9 Hz, 1H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.01 (q, *J* = 6.2 Hz, 2H), 3.86 (d, *J* = 7.1 Hz, 2H), 3.58 (d, *J* = 11.5 Hz, 1H), 3.20 (d, *J* = 11.6 Hz, 1H), 2.20 (s, 3H), 1.88-1.75 (m, 6H), 1.52 (s, 3H), 1.47 (s, 18H), 1.44-1.10 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.76-0.50 (m, 2H), 0.44-0.27 (m, 2H).

¹³C NMR (100 MHz, CD₃OD): δ 174.8, 171.2, 168.0, 165.3, 163.8, 151.6, 99.7, 87.9, 84.2, 82.8, 82.7, 74.5, 73.9, 66.7, 66.7, 50.7, 39.2, 33.9, 28.8 (x2), 26.5, 26.4, 25.3, 23.5, 18.9, 12.5, 10.4, 9.0, 2.3.

MS (ES⁺): *m/z* 686.2 [M+H]⁺.

Synthesis of **192**

To a solution of **191** (150 mg, 0.219 mmol) in CH₂Cl₂ (13 mL) TFA (0.385 mL, 5.03 mmol) was added. The reaction mixture was stirred at 23 °C for 1h. The mixture was evaporated to dryness, and coevaporated several times with toluene. The resulting residue was purified in preparative HPLC (SunFire from 5% to 100% CH₃CN + 0.04% TFA) to yield **192** (110 mg, 88% yield).

¹H NMR (500 MHz, CD₃OD): δ 7.87 (d, *J* = 8.6 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 4.78-4.68 (m, 1H), 4.26 (t, *J* = 6.2 Hz, 2H), 4.08-3.96 (m, 2H), 3.88 (d, *J* = 7.1 Hz, 2H), 3.59 (d, *J* = 11.5 Hz, 1H), 3.20 (d, *J* = 11.5 Hz, 1H), 2.22 (s, 3H), 1.94-1.71 (m, 6H), 1.54 (s, 3H), 1.52-1.46 (m, 1H), 1.43-1.37 (m, 1H), 1.28-1.21 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.70-0.60 (m, 2H), 0.41-0.32 (m, 2H).

¹³C NMR (125 MHz, CD₃OD): δ 174.9, 171.3, 168.0, 165.4, 163.8, 151.7, 99.7, 87.8, 84.3, 74.5, 73.9, 65.9 (x2), 50.7, 39.3, 33.8, 26.7, 26.6, 25.1, 23.5, 18.8, 12.4, 10.3, 8.9, 2.2.

MS (ES⁺): *m/z* 574.2 [M+H]⁺, 596.2 [M+Na]⁺.

EXAMPLE 26. BIOASSAYS FOR THE DETECTION OF ANTITUMOR ACTIVITY

The aim of this assay is to evaluate the *in vitro* cytostatic (ability to delay or arrest tumor cell growth) or cytotoxic (ability to kill tumor cells) activity of the samples being tested.

Cell Lines

Name	N° ATCC (when applicable)	Species	Tissue	Characteristics
A549	CCL-185	human	lung	lung carcinoma (NSCLC)
HT29	HTB-38	human	colon	colorectal adenocarcinoma
MDA-MB-231	HTB-26	human	breast	breast adenocarcinoma
PSN-1	Ref. 1	human	pancreas	pancreatic adenocarcinoma

Ref. 1 Yamada, T. *et al.* (1986) Establishment of a human pancreatic adenocarcinoma cell line (PSN-1) with amplifications of both c-myc and activated c-Ki-ras by a point mutation. Biochem. Biophys. Res. Commun. 140, 167-173.

5 EVALUATION OF CYTOTOXIC ACTIVITY USING THE SRB COLORIMETRIC ASSAY

A colorimetric assay, using sulforhodamine B (SRB) reaction has been adapted to provide a quantitative measurement of cell growth and viability (following the technique described by V. Vichai and K. Kirtikara (2006) Nature Protoc. 1, 1112-1116.)

10 This form of assay employs 96-well cell culture microplates. All the cell lines used in this study were obtained from the American Type Culture Collection (ATCC), unless otherwise indicated, and derive from different types of human cancer.

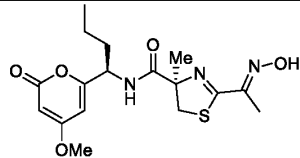
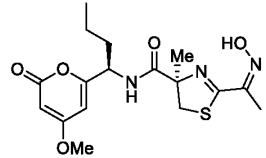
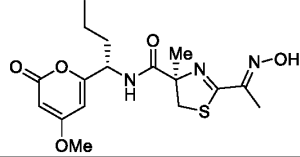
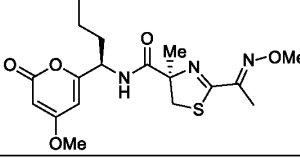
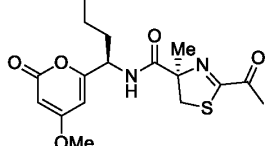
15 Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) (for A549, HT-29 and MDA-MB-231) or RPMI (for PSN-1) supplemented with 10% Fetal Bovine Serum (FBS), 2mM L-glutamine, 100 U/mL penicillin and 100 U/mL streptomycin at 37 °C, 5% CO₂ and 98% humidity. For the experiments, cells were harvested from subconfluent cultures using trypsinization and resuspended in fresh medium before counting and plating.

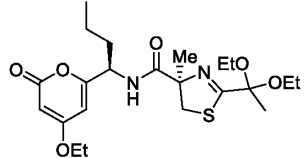
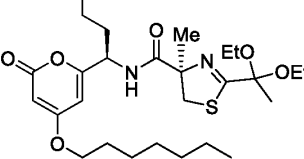
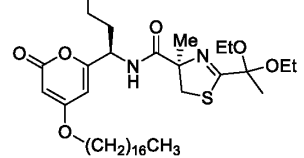
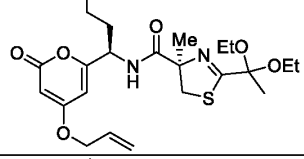
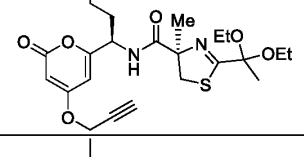
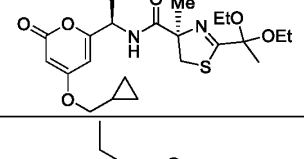
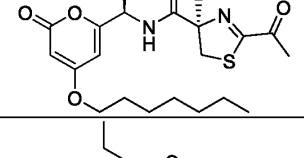
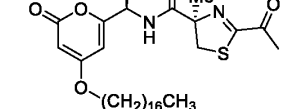
20 Cells were seeded in 96 well microtiter plates, at 5×10^3 cells per well in aliquots of 150 μ L, and allowed to attach to the plate surface for 18 hours (overnight) in drug free medium. After that, one control (untreated) plate of each cell line was fixed (as described below) and used for time zero reference value. Culture plates were then treated with test compounds (50 μ L aliquots of 4X concentrated compound stock solutions made in complete culture medium) using ten serial dilutions (concentrations ranging from 10 to 0.00262 μ g/mL) and triplicate cultures (final concentration of DMSO being 1%). After 72 hours treatment, the antitumor effect was measured by using the SRB methodology: Briefly, cells were washed twice with PBS, fixed for 15 min in
25 1% glutaraldehyde solution at room temperature, rinsed twice in PBS, and stained in 0.4% SRB solution for 30 min at room temperature. Cells were then rinsed several times with 1% acetic acid solution and air-dried at room temperature. SRB was then extracted in 10 mM trizma base

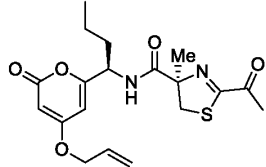
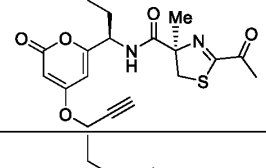
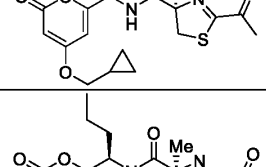
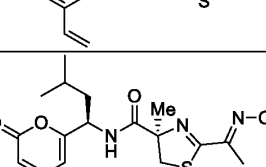
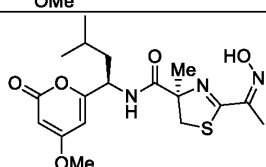
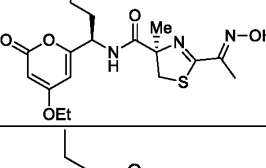
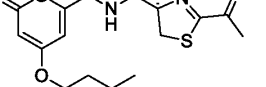
solution and the absorbance measured in an automated spectrophotometric plate reader at 490 nm. Effects on cell growth and survival were estimated by applying the NCI algorithm (Boyd MR and Paull KD. *Drug Dev. Res.* 1995, 34, 91-104).

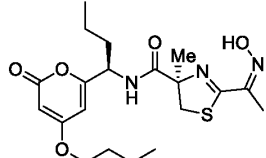
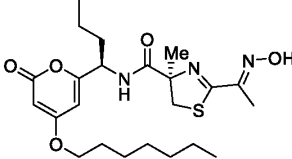
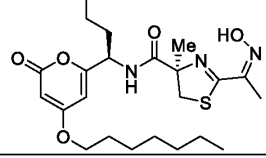
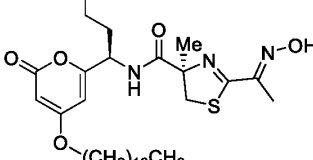
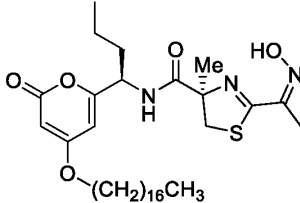
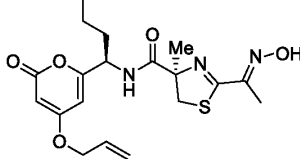
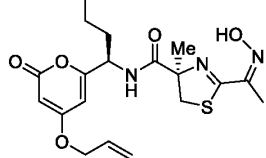
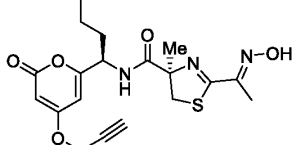
- Using the mean $\pm$ SD of triplicates, a dose-response curve was automatically generated using nonlinear regression analysis to a 4-parameter logistic curve. Three reference parameters were calculated (NCI algorithm) by automatic interpolation: GI₅₀ = compound concentration that produces 50% cell growth inhibition, as compared to control cultures; TGI = total cell growth inhibition (cytostatic effect), as compared to control cultures, and LC₅₀ = compound concentration that produces 50% net cell killing (cytotoxic effect).
- 10 Table 3 illustrates data on the biological activity (GI₅₀) of compounds of the present invention (GI₅₀ value).

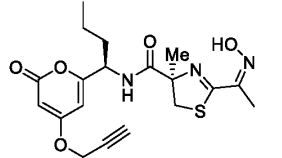
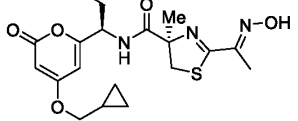
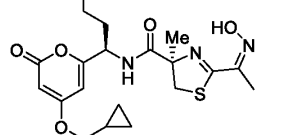
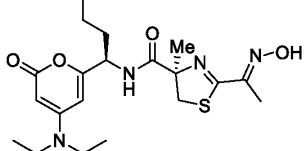
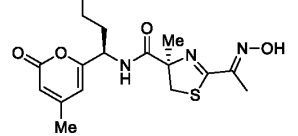
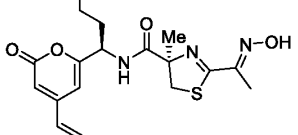
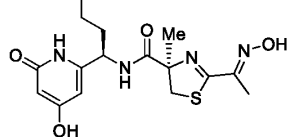
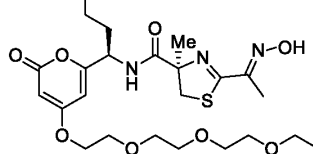
Table 3. Cytotoxicity assay-Activity Data (GI₅₀ Molar)

Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
1		1.15E-08	1.44E-08	3.41E-08	2.88E-08
1a		1.44E-07	1.52E-07	2.04E-07	3.41E-07
<i>epi</i> -1		2.88E-06	3.41E-06	3.93E-06	5.77E-06
2		2.53E-07	2.12E-07	4.30E-07	3.29E-07
42		2.46E-05	8.73E-06	4.64E-06	5.19E-06

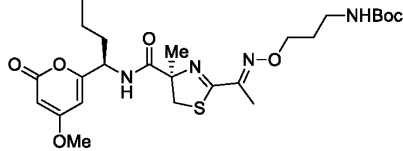
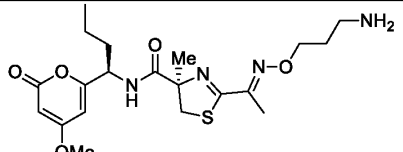
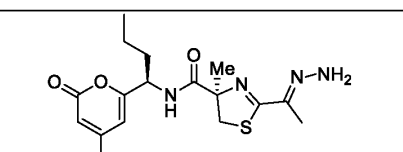
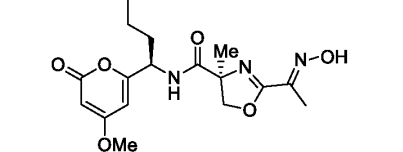
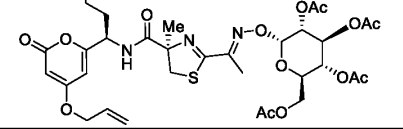
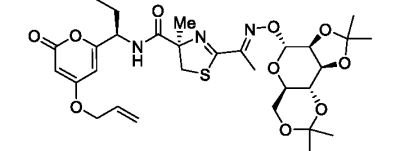
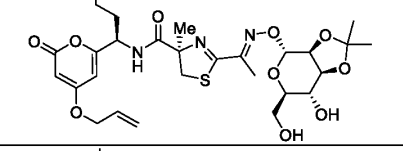
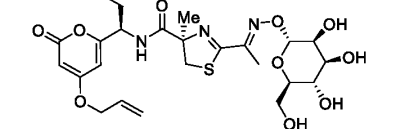
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
46		2.42E-06	2.18E-06	1.52E-06	4.62E-06
48		3.43E-06	2.29E-06	2.29E-06	2.10E-06
49		1.34E-06	9.32E-07	1.50E-06	1.46E-06
50		6.43E-07	5.14E-07	5.36E-07	8.14E-07
51		3.44E-07	2.15E-07	3.23E-07	3.66E-07
52		1.27E-06	1.21E-06	1.29E-06	1.77E-06
61		1.84E-06	1.40E-06	1.44E-06	1.73E-06
62		1.61E-06	1.10E-06	1.69E-06	1.64E-06

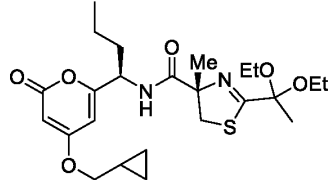
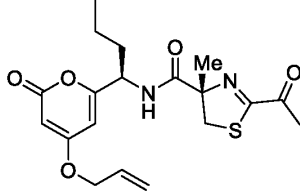
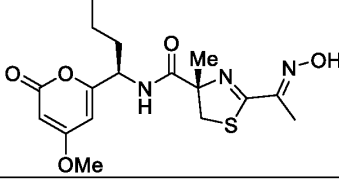
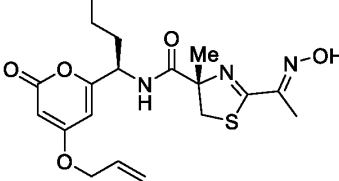
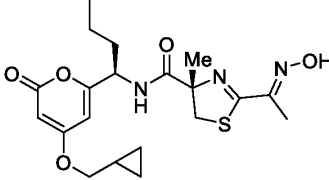
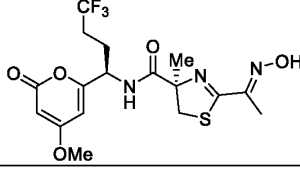
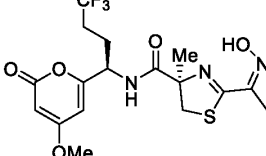
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
63		8.15 E-07	5.10 E-07	4.84 E-07	4.08 E-07
64		9.99E-08	6.15E-08	5.38E-08	7.17E-08
65		1.89E-06	1.08E-06	1.03E-06	1.25E-06
68		1.10E-05	9.10E-06	6.62E-06	4.69E-06
69		2.20E-06	1.59E-06	1.62E-06	1.52E-06
69a		5.06E-06	3.79E-06	4.55E-06	6.32E-06
70		1.44E-08	1.49E-08	2.38E-08	1.49E-08
71		7.08E-09	7.56E-09	1.44E-08	1.04E-08

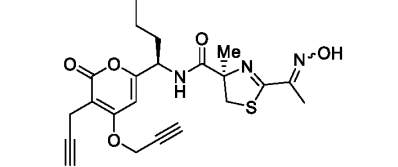
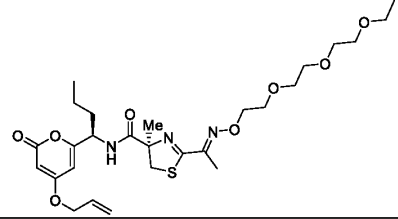
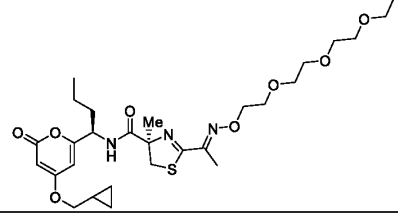
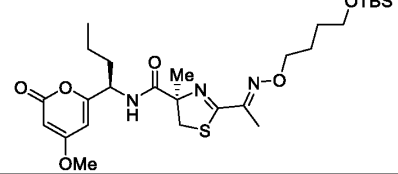
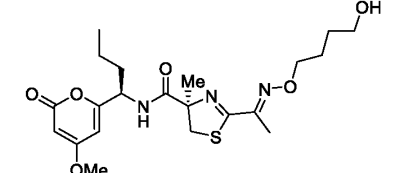
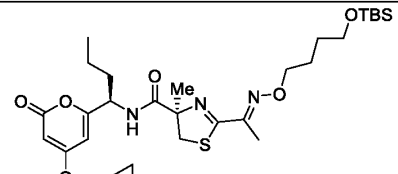
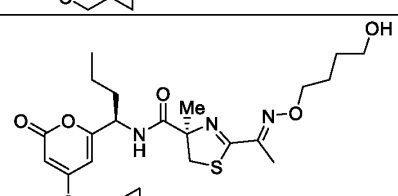
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
71a		1.65E-08	1.70E-08	3.54E-08	3.07E-08
72		2.58E-08	3.01E-08	3.01E-08	2.15E-08
72a		1.10E-07	1.83E-07	1.03E-07	1.25E-07
73		3.80E-07	3.96E-07	3.30E-07	3.47E-07
73a		6.44E-08	6.27E-08	6.60E-08	5.94E-08
74		4.17E-09	2.94E-09	4.91E-09	3.19E-09
74a		8.10E-09	7.61E-09	9.82E-09	1.25E-08
75		1.01E-09	9.62E-10	1.38E-09	1.18E-09

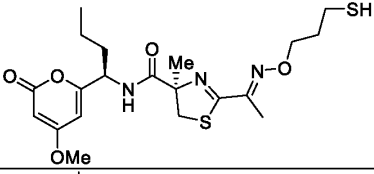
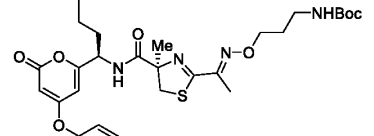
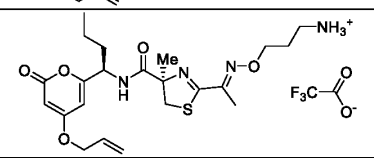
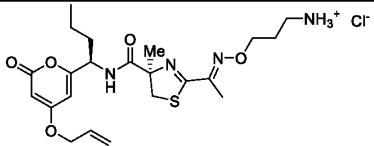
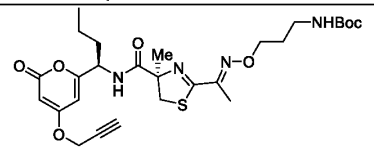
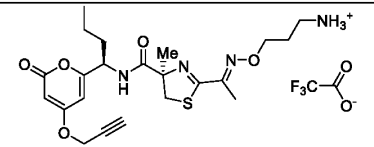
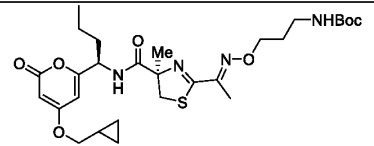
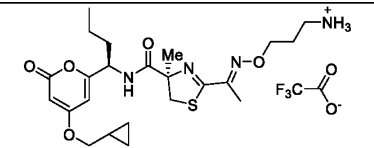
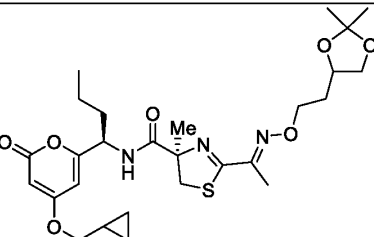
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
75a		2.12E-09	1.18E-09	2.71E-09	2.00E-09
76		3.56E-09	3.80E-09	3.80E-09	3.08E-09
76a		3.80E-09	4.27E-09	4.51E-09	4.51E-09
77		2.15E-06	1.18E-06	1.96E-06	2.37E-06
78		2.49E-08	4.38E-08	4.38E-08	3.28E-08
79		4.24E-07	3.97E-07	3.44E-07	4.77E-07
82		1.64E-06	4.91E-07	1.12E-06	3.55E-07
87		5.69E-06	5.50E-06	6.82E-06	7.01E-06

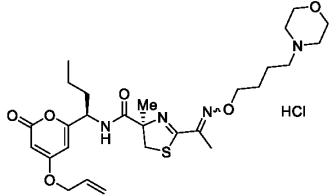
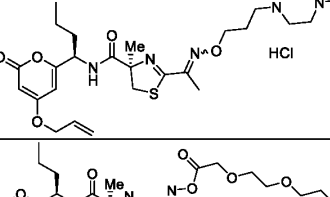
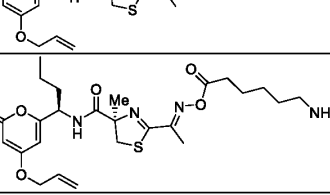
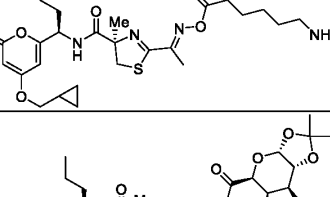
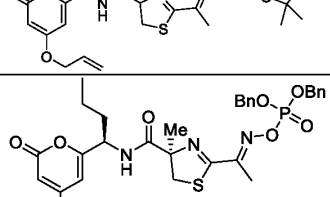
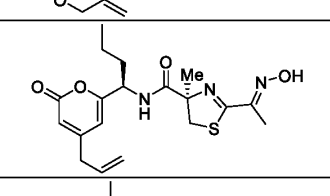
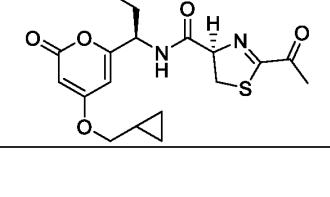
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
88		2.04E-05	1.14E-05	2.18E-05	1.88E-05
89		1.65E-05	8.95E-06	5.89E-06	6.36E-06
92		1.55E-06	1.28E-06	9.53E-07	9.53E-07
93		2.14E-08	2.35E-08	3.80E-08	2.85E-08
94		3.58E-08	2.26E-08	3.58E-08	3.58E-08
95		2.03E-08	4.06E-08	4.43E-08	3.32E-08
96		1.77E-06	1.51E-06	2.95E-06	2.22E-06

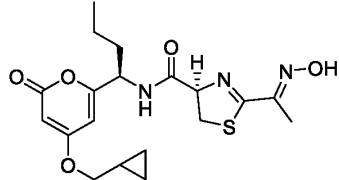
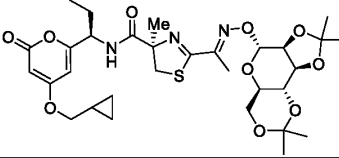
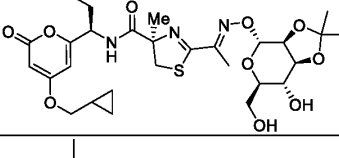
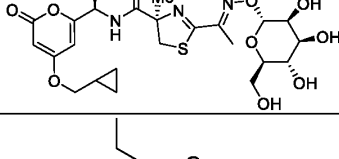
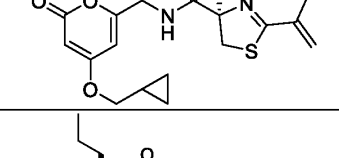
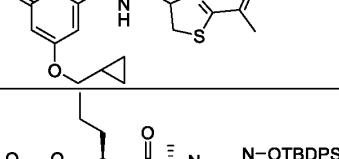
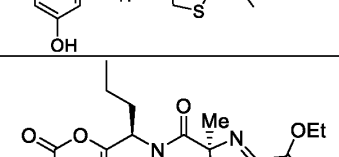
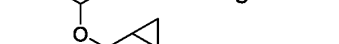
Compound	GI ₅₀ (M)			
	A549	HT29	MDA-MB-231	PSN-1
97 	6.31 E-07	5.94E-07	1.15E-06	8.35 E-07
98 	2.21E-08	2.51E-08	3.42E-08	2.74E-08
99 	5.78E-07	4.47E-07	6.57E-07	9.20E-07
106 	1.01E-06	7.12E-07	8.76E-07	1.56E-06
107 	5.29E-08	5.29E-08	7.86E-08	6.10E-08
110 	4.31E-08	3.69E-08	7.85E-08	5.69E-08
111 	2.62E-08	2.46E-08	2.95E-08	3.77E-08
112 	4.04E-06	1.11E-06	2.11E-06	1.23E-06

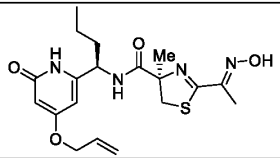
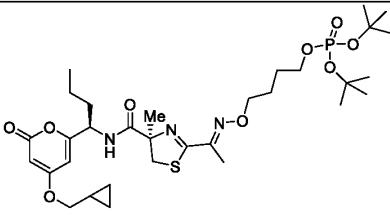
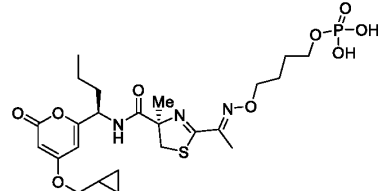
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
131		2.08E-07	1.96E-07	3.33E-07	3.12E-07
133		9.43E-06	4.59E-06	3.82E-06	5.61E-06
135		2.46E-06	1.26E-06	2.33E-06	1.26E-06
136		7.12E-08	8.59E-08	7.85E-08	8.10E-08
137		1.26E-07	1.09E-07	1.49E-07	1.45E-07
140		6.66E-07	3.44E-07	4.59E-07	6.43E-07
140a		2.53E-06	1.52E-06	2.27E-06	2.76E-06

Compound	GI ₅₀ (M)			
	A549	HT29	MDA-MB-231	PSN-1
141 	2.25E-07	1.78E-07	2.48E-07	3.38E-07
144 	7.22E-08	6.52E-08	1.62E-07	1.25E-07
145 	4.81E-08	6.19E-08	1.22E-07	1.12E-07
146 	1.94E-06	1.02E-06	2.82E-06	2.11E-06
147 	1.48E-07	1.37E-07	2.87E-07	2.43E-07
148 	2.63E-07	5.92E-08	2.47E-07	2.96E-07
149 	6.69E-09	6.28E-09	8.91E-09	1.36E-08

Compound	GI ₅₀ (M)			
	A549	HT29	MDA-MB-231	PSN-1
151 	8.56E-07	5.05E-07	1.34E-06	1.21E-06
152 	1.95E-08	1.95E-08	2.66E-08	2.13E-08
153 	3.98E-09	3.380E-09	4.32E-09	3.98E-09
154 	4.79E-09	5.59E-09	6.79E-09	7.78E-09
155 	3.74E-08	4.09E-08	7.48E-08	7.30E-08
156 	1.28E-09	2.43E-09	2.60E-09	2.43E-09
157 	5.37E-09	5.02E-09	5.37E-09	5.54E-09
158 	5.43E-09	6.06E-09	1.21E-08	6.27E-09
159 	4.91E-08	6.37E-08	6.73E-08	5.09E-08

Compound	GI ₅₀ (M)			
	A549	HT29	MDA-MB-231	PSN-1
161 	4.96E-09	5.47E-09	6.49E-09	5.13E-09
163 	1.61E-08	1.56E-08	1.66E-08	1.64E-08
164 	6.52E-09	4.58E-09	7.22E-09	6.52E-09
165 	5.48E-09	5.32E-09	7.41E-09	6.44E-09
166 	4.73E-09	4.57E-09	7.09E-09	6.30E-09
170 	3.01E-09	2.41E-09	5.57E-09	2.71E-09
172 	8.09E-08	5.69E-08	1.08E-07	1.00E-07
175 	5.36E-08	1.10E-07	2.55E-07	3.83E-07
177 	2.27E-06	1.55E-06	1.61E-06	> 2.55E-05

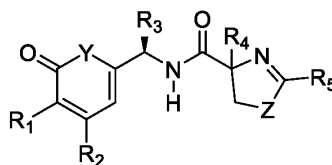
Compound		GI ₅₀ (M)			
		A549	HT29	MDA-MB-231	PSN-1
178		4.17E-08	7.61E-08	4.91E-08	3.68E-08
179		9.04E-09	6.48E-09	1.37E-08	1.43E-08
180		5.93E-07	3.69E-07	4.17E-07	5.29E-07
181		>1.71E-05	4.97E-06	6.34E-06	6.85E-06
182		6.18E-08	7.42E-08	9.15E-08	8.16E-08
183		5.76E-09	5.46E-09	5.00E-09	8.18E-09
184		4.79E-06	2.97E-06	4.46E-06	4.13E-06
185		1.61E-07	2.07E-07	2.28E-07	1.40E-07

Compound	GI ₅₀ (M)			
	A549	HT29	MDA-MB-231	PSN-1
190 	5.90E-07	2.44E-07	2.39E-07	3.44E-07
191 	4.96E-07	5.54E-07	6.12E-07	8.75E-07
192 	9.07E-09	7.15E-09	1.64E-08	2.79E-08

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CLAIMS

1. A compound of formula I or a pharmaceutically acceptable salt or ester thereof



I

wherein:

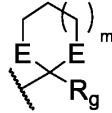
- 5 R₁ is selected from hydrogen, halogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

- R₂ is selected from hydrogen, halogen, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, substituted or unsubstituted C₂-C₂₄ alkynyl, -OR_a, -OSO₂R_b, -NR_cR_d, -NR_c(C=O)R_f, and -NR_cSO₂R_b, wherein the optional substituents are one or more substituents R_x;
- 10

- R₃ is selected from halogen-substituted or unsubstituted C₁-C₁₂ alkyl, halogen-substituted or unsubstituted C₂-C₁₂ alkenyl, halogen-substituted or unsubstituted C₂-C₁₂ alkynyl and substituted or unsubstituted C₃-C₆ cycloalkyl-C₁-C₁₂ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br and I;
- 15

- R₄ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

- 20 R₅ is selected from -C(OR_e)₂R_g, -C(SR_e)₂R_g, -CH(OR_a)R_g, -CH(O-(C=O)R_f)R_g, -CH(NR_cR_d)R_g, -CH(NR_c-(C=O)R_f)R_g, -CH(NR_c-OR_h)R_g, -(C=O)R_g, -(C=NR_c)R_g, -(C=N-OR_h)R_g, -(C=N-O-(C=O)R_f)R_g, -(C=N-O-(C=O)OR_a)R_g, -(C=N-O-[(P=O)(OR_a)₂])R_g, -(C=N-NR_cR_d)R_g, -(C=O)OR_a, -

(C=O)NR_c-OR_h, -(C=O)NR_cR_d, -(C=CH₂)R_g, and -(C=CH₂)OR_a; or R₅ is a  group where m is 0, 1 or 2 and each E group is independently selected from O and S;

- 25 Y and Z are independently selected from -O-, -S-, -(NH)-, and -(NProt^{NH})-, where Prot^{NH} is a protecting group for amino;

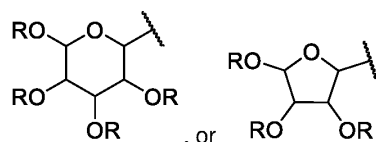
each group R_a is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, and $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x ;

each group R_b is independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x ;

each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

each group R_e is substituted or unsubstituted C_1 - C_{12} alkyl group, wherein the optional substituents are one or more substituents R_x ;

each group R_f is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, $-CH_2O(CH_2CH_2O)_pCH_2CH_3$, $-CH_2O(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x , and a group of formula:



where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(C=O)-(C_1-C_6)$ alkyl, and substituted or unsubstituted $-(C=O)NH(C_1-C_6)$ alkyl, wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

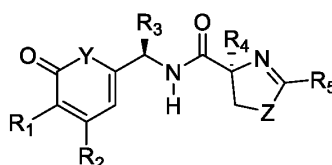
each group R_g is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

each group R_n is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted heterocyclo- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the optional substituents are one or more substituents R_x ;

substituents R_x are selected from the group consisting of C_1 - C_{12} alkyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkenyl groups which may be optionally substituted with at least one group R_y , C_2 - C_{12} alkynyl groups which may be optionally substituted with at least one group R_y , halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y , $OCOR_y$, $OCOOR_y$, COR_y , $COOR_y$, $OCONR_yR_z$, $CONR_yR_z$, SR_y , $S(=O)R_y$, SO_2R_y , OSO_2OR_y , SSR_y , $P(=O)(R_y)OR_z$, $OP(=O)(OR_y)_2$, NR_yR_z , $NR_yC(=O)R_z$, $NR_yC(=O)OR_z$, $NR_yC(=O)NR_yR_z$, $NR_yC(=NR_y)NR_yR_z$, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y , OR_y , $OCOR_y$, $OCOOR_y$, NR_yR_z , NR_yCOR_z , and $NR_yC(=NR_y)NR_yR_z$, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y , and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

each R_y and R_z is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl groups, C_1 - C_{12} alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C_1 - C_{12} alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings and heterocycloalkyl group comprising a C_1 - C_{12} alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s).

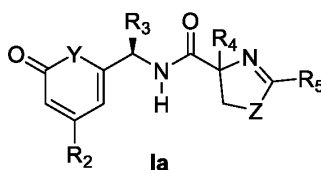
2. The compound according to claim 1 which also has formula



wherein R₁, R₂, R₃, R₄, R₅, Y, and Z are as defined in claim 1; or a pharmaceutically acceptable salt or ester thereof.

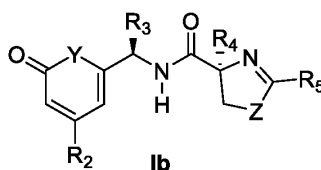
3. The compound according to claim 1 or 2 wherein R₁ is selected from hydrogen, halogen and substituted or unsubstituted C₂-C₆ alkynyl, wherein the optional substituents are one or more substituents R_x; or a pharmaceutically acceptable salt or ester thereof.

4. The compound according to claim 1 which also have formula **1a**:



wherein R₂, R₃, R₄, R₅, Y, and Z are as defined in claim 1; or a pharmaceutically acceptable salt or ester thereof.

5. The compound according to claim 4 which also has formula **1b**:



wherein R₂, R₃, R₄, R₅, Y and Z are as defined in claim 1; or a pharmaceutically acceptable salt or ester thereof.

6. The compound according to any preceding claim wherein R₂ is selected from hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, wherein the optional substituents are one or more substituents R_x, -OR_a, and -NR_cR_d, where R_a is selected from hydrogen, a silylether protecting group for OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₆alkyl, -(CH₂CH₂O)_pCH₂CH₃ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x; and R_c and R_d are independently selected from substituted or unsubstituted C₁-C₆ alkyl wherein the optional substituents are one or more substituents R_x; or a pharmaceutically acceptable salt or ester thereof.

7. The compound according to claim 6, wherein R₂ is selected from hydrogen, methyl, vinyl, allyl, NEt₂, and OR_a where R_a is selected from hydrogen, methyl, ethyl, *n*-butyl, *n*-heptyl, allyl,

propargyl, cyclopropylmethyl, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, and $-(CH_2CH_2O)_3CH_2CH_3$; or a pharmaceutically acceptable salt or ester thereof.

8. The compound according to any preceding claim, wherein R_3 is selected from halogen-substituted or unsubstituted C_1 - C_6 alkyl and substituted or unsubstituted C_3 - C_4 cycloalkyl- C_1 - C_4 alkyl wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I; or a pharmaceutically acceptable salt or ester thereof.

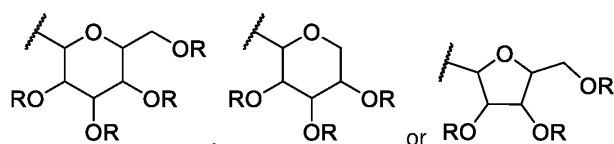
9. The compound according to claim 8, wherein R_3 is selected from *n*-propyl, 3,3,3-trifluoropropyl, and isobutyl; or pharmaceutically acceptable salt or ester thereof.

10. The compound according to any preceding claim, wherein R_4 is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ; or a pharmaceutically acceptable salt or ester thereof.

11. The compound according to claim 10, wherein R_4 is hydrogen or methyl; or a pharmaceutically acceptable salt or ester thereof.

12. The compound according to any preceding claim, wherein R_5 is selected from $-C(OR_e)_2R_g$, $-CH(NR_cR_d)R_g$, $-(C=O)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-O-(C=O)R_f)R_g$, $-(C=N-O-(C=O)OR_a)R_g$, $-(C=N-O-[(P=O)(OR_a)_2])R_g$, $-(C=N-NR_cR_d)R_g$, $-(C=CH_2)R_g$, and $-(C=CH_2)OR_a$ wherein:

R_h is selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted C_2 - C_6 alkenyl, substituted or unsubstituted C_2 - C_6 alkynyl, substituted or unsubstituted heterocyclo- C_1 - C_6 alkyl, $-(CH_2CH_2O)_pCH_2CH_3$ where *p* is from 1 to about 15 and a substituted or unsubstituted monosaccharide residue of formula:



- where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(C=O)-(C_1-C_6)alkyl$, and substituted or unsubstituted $-(C=O)NH(C_1-C_6)alkyl$; wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

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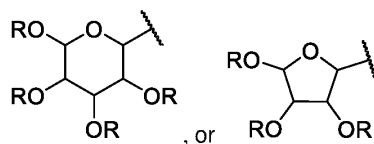
R_g is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ;

R_c and R_d are independently selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ;

5 R_a is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ;

R_e is substituted or unsubstituted C_1 - C_6 alkyl, wherein the optional substituents are one or more substituents R_x ; and

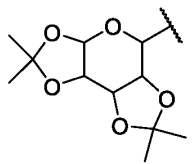
10 R_f is selected from substituted or unsubstituted C_1 - C_6 alkyl, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_p\text{CH}_3$ where p is from 1 to about 15 and the optional substituents are one or more substituents R_x , and a group of formula:



15 where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl group, substituted or unsubstituted $-(\text{C}=\text{O})-(C_1-C_6)\text{alkyl}$, and substituted or unsubstituted $-(\text{C}=\text{O})\text{NH}(C_1-C_6)\text{alkyl}$, wherein the optional substituents are one or more substituents R_x ; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

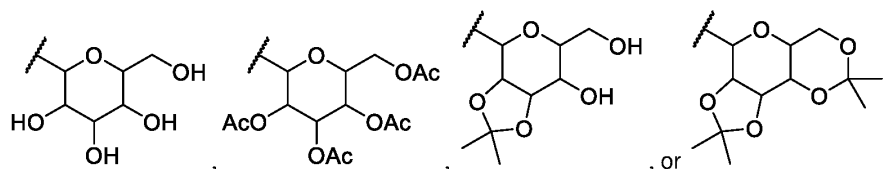
20 or a pharmaceutically acceptable salt or ester thereof.

13. The compound according to claim 12 wherein R_5 is selected from $-\text{CH}(\text{NH}_2)\text{Me}$, $-(\text{C}=\text{O})\text{Me}$, $-(\text{C}=\text{NR}_c)\text{Me}$, $-(\text{C}=\text{N}-\text{OR}_h)\text{Me}$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{R}_f)\text{Me}$, $-(\text{C}=\text{N}-\text{NH}_2)\text{Me}$, $-(\text{C}=\text{N}-\text{O}-(\text{C}=\text{O})\text{OR}_a)\text{Me}$, $-(\text{C}=\text{N}-\text{O}-[(\text{P}=\text{O})(\text{OR}_a)_2])\text{Me}$, $-(\text{C}=\text{CH}_2)\text{Me}$, or $-(\text{C}=\text{CH}_2)\text{OR}_a$ where R_a is ethyl or benzyl, R_c is $-(\text{CH}_2)_3\text{NHBoc}$, R_f is $-(\text{CH}_2)_5-\text{NHBoc}$, $-\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{Me}$ or a group of formula:



25 and R_h is selected from hydrogen, methyl, allyl, propargyl, $-(\text{CH}_2)_3\text{NHBoc}$, $-(\text{CH}_2)_3\text{NH}_2$, -

(CH₂)₃SH, -(CH₂)₄OH, -(CH₂)₄OP(=O)(OH)₂, -(CH₂)₄OP(=O)(O^tBu)₂, -(CH₂)₄-[4λ²-morpholine], -(CH₂)₃-[1-methyl-4λ²-piperazine], -(CH₂CH₂O)₃CH₂CH₃, and a monosaccharide residue of formula:



5 or a pharmaceutically acceptable salt or ester thereof.

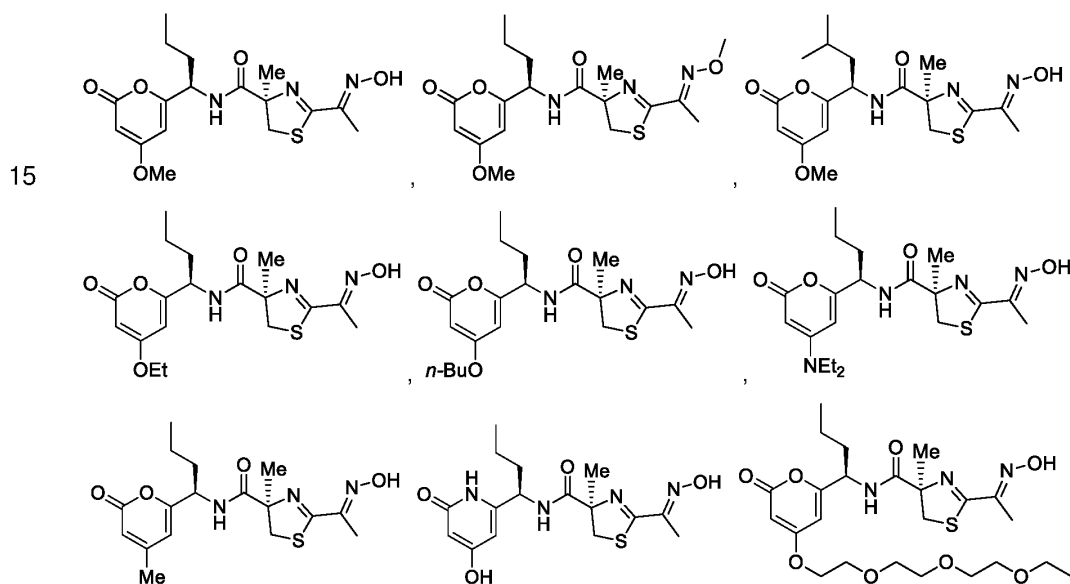
14. The compound according to any preceding claim, wherein Z is -S- or -O-; or pharmaceutically acceptable salt or ester thereof.

15. The compound according to claim 14, wherein Z is -S-; or a pharmaceutically acceptable salt or ester thereof.

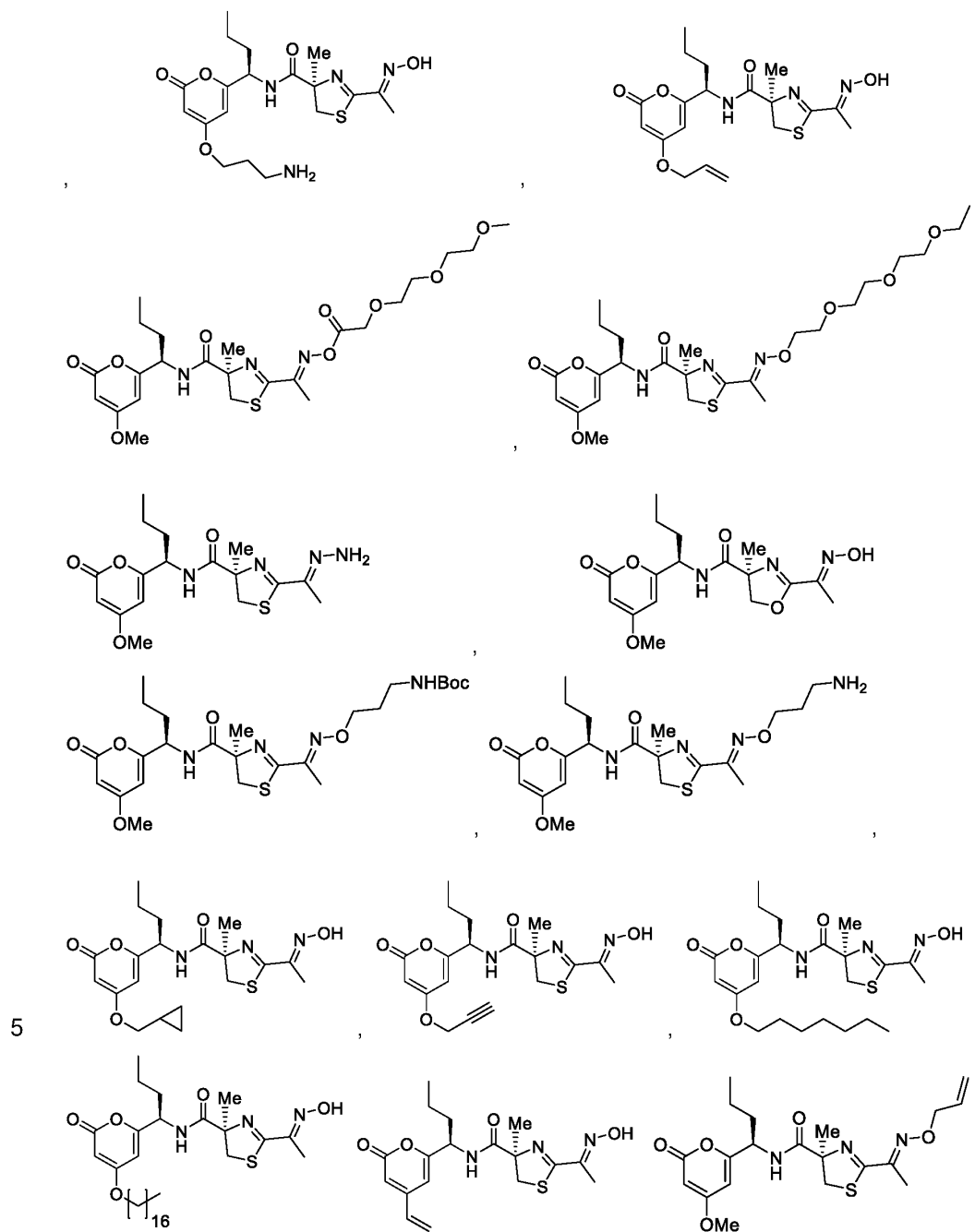
10 16. The compound according to any preceding claim, wherein Y is -O- or -NH-; or a pharmaceutically acceptable salt or ester thereof.

17. The compound according to claim 16, wherein Y is -O-; or a pharmaceutically acceptable salt or ester thereof.

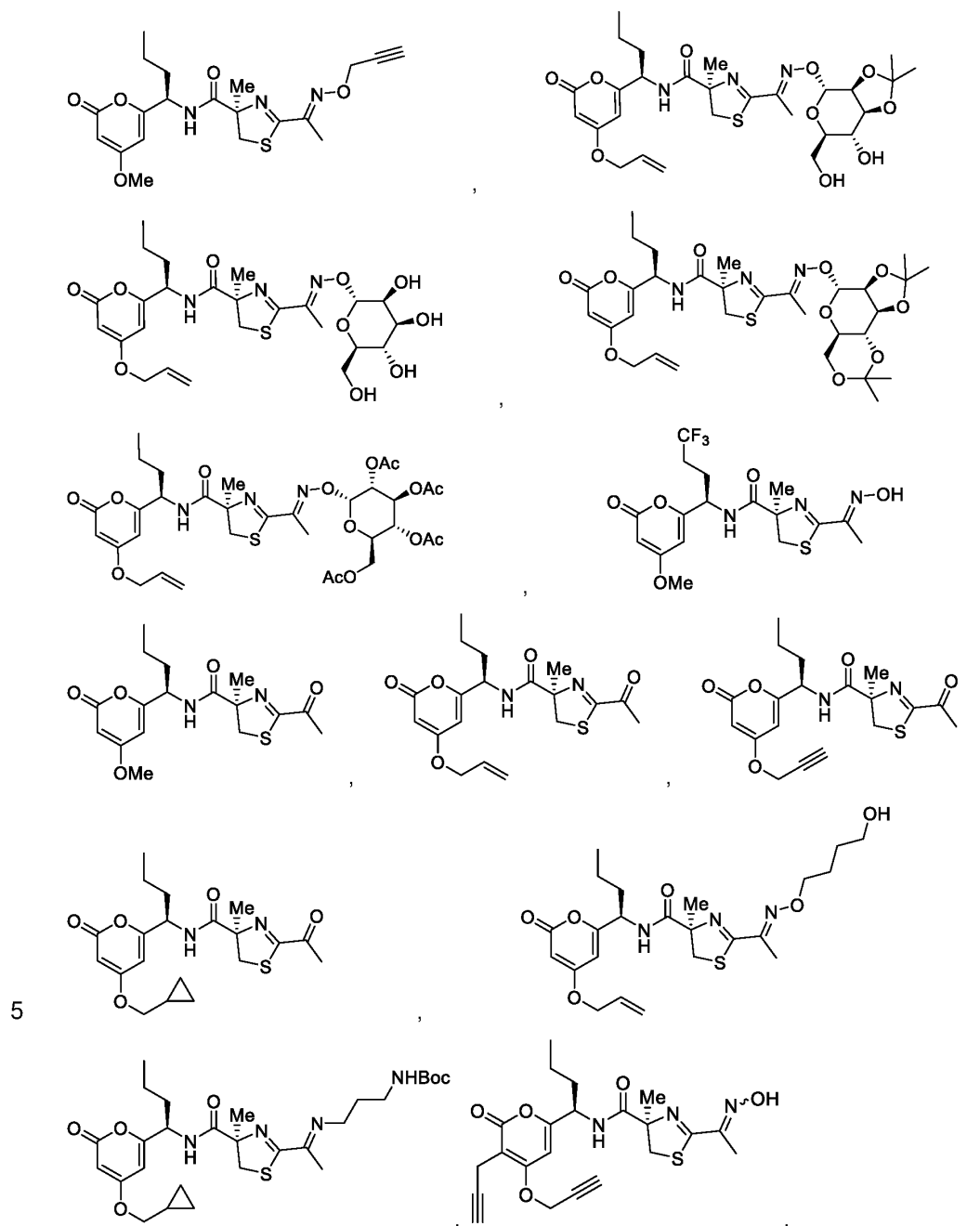
18. The compound according to claim 1 selected from



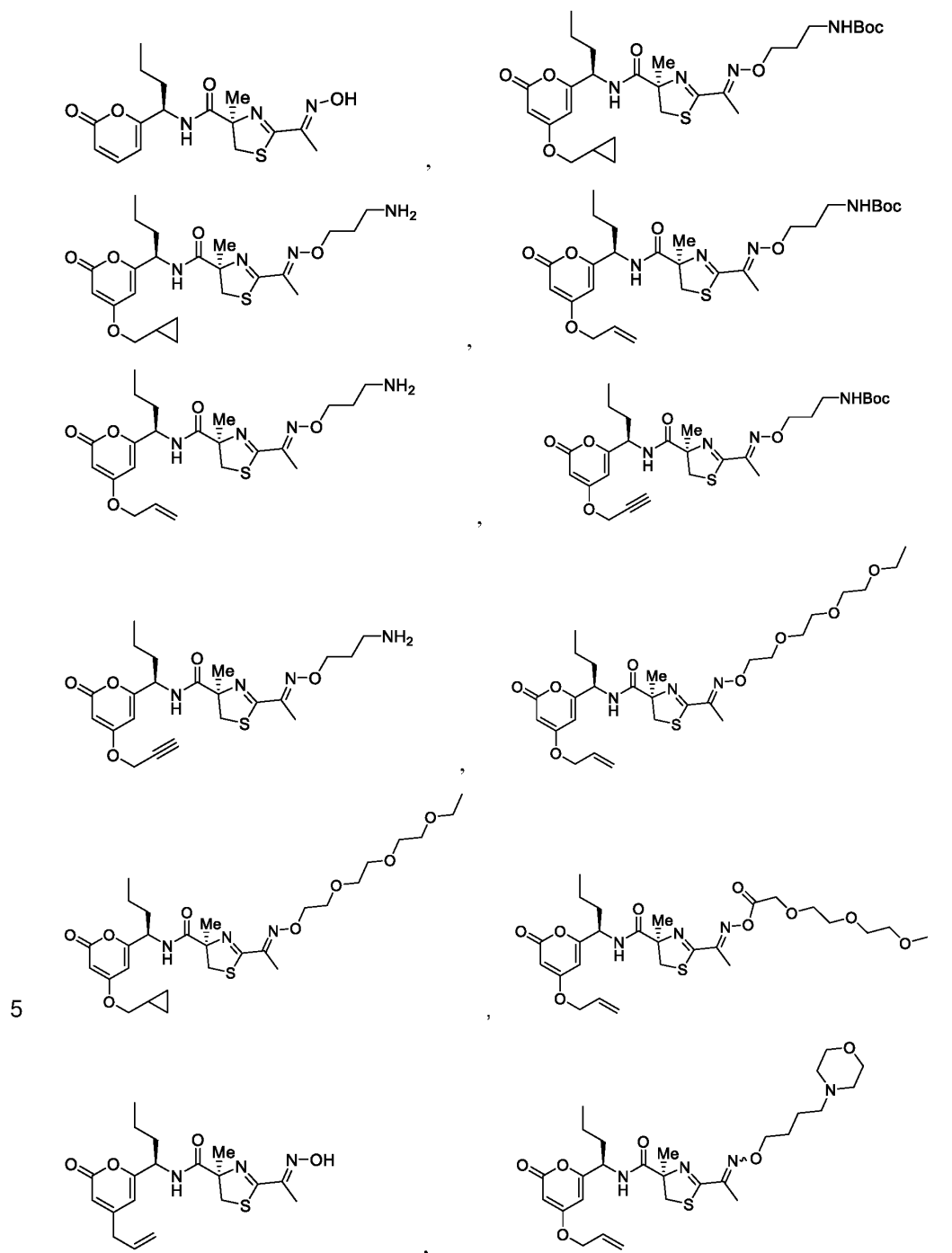
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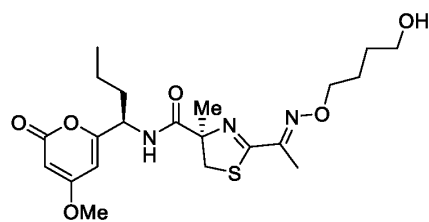
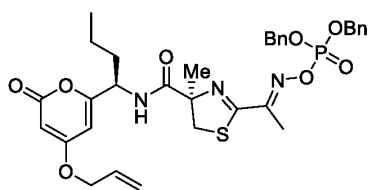
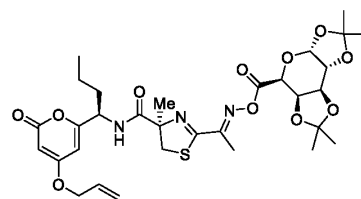
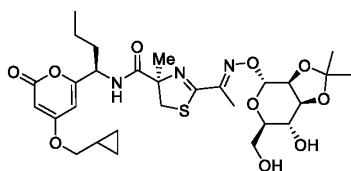
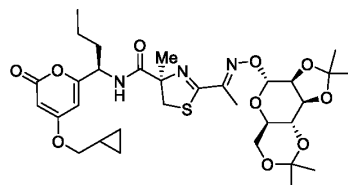
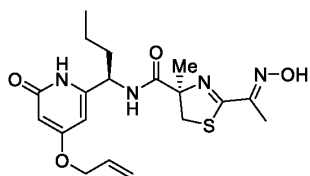
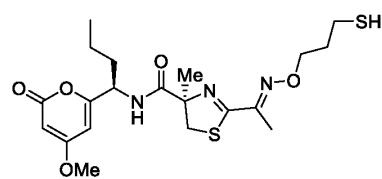
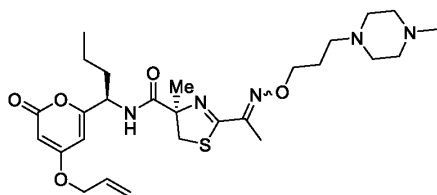
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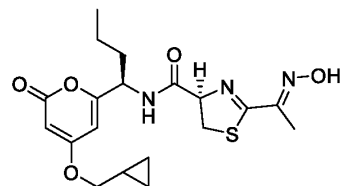
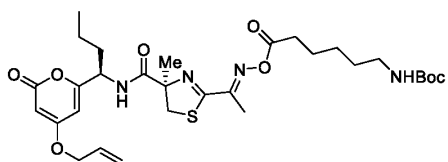
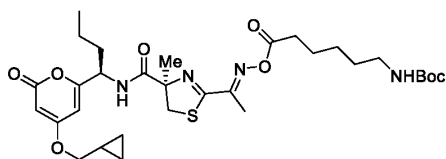
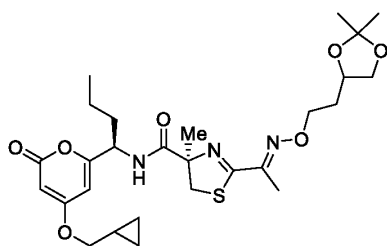
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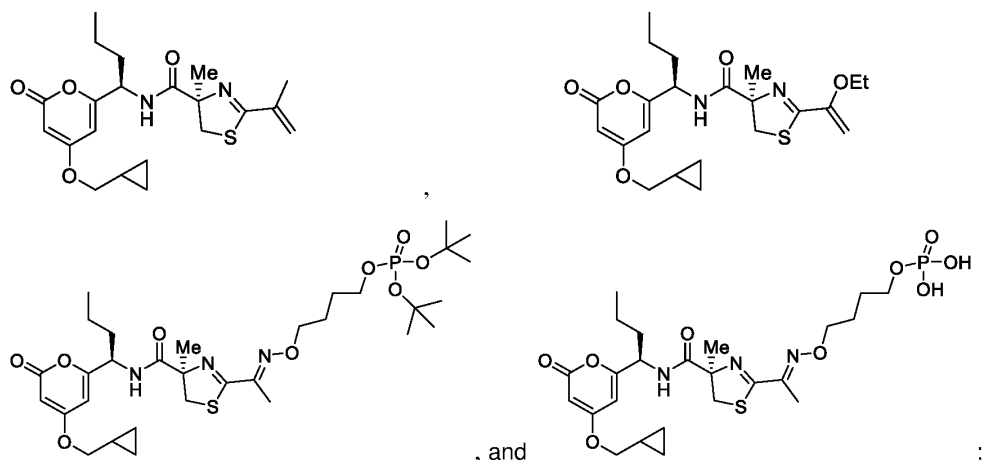
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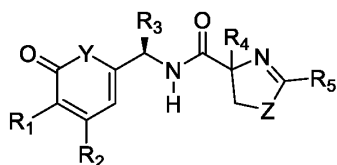


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or a pharmaceutically acceptable salt or ester thereof.

19. The compound according to claim 1, of formula I or a pharmaceutically acceptable salt or ester thereof



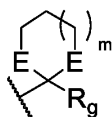
I

wherein:

- R₁ is selected from hydrogen, halogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;
- R₂ is selected from hydrogen, halogen, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, substituted or unsubstituted C₂-C₂₄ alkynyl, -OR_a, -OSO₂R_b, -NR_cR_d, -NR_c(C=O)R_f, and -NR_cSO₂R_b, wherein the optional substituents are one or more substituents R_x;
- R₃ is selected from halogen-substituted or unsubstituted C₁-C₁₂ alkyl, halogen-substituted or unsubstituted C₂-C₁₂ alkenyl, halogen-substituted or unsubstituted C₂-C₁₂ alkynyl and substituted or unsubstituted C₃-C₆ cycloalkyl-C₁-C₁₂ alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br and I;
- R₄ is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or

unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

- R₅ is selected from -C(OR_e)₂R_g, -C(SR_e)₂R_g, -CH(OR_a)R_g, -CH(O-(C=O)R_f)R_g, -CH(NR_cR_d)R_g, -CH(NR_c-(C=O)R_f)R_g, -CH(NR_c-OR_h)R_g, -(C=O)R_g, -(C=NR_c)R_g, -(C=N-OR_h)R_g, -(C=N-O-(C=O)R_f)R_g, -(C=N-NR_cR_d)R_g, -(C=O)OR_a, -(C=O)NR_c-OR_h, and -(C=O)NR_cR_d; or R₅ is a



group where m is 0, 1 or 2 and each E group is independently selected from O and S;

Y and Z are independently selected from -O-, -S-, -(NH)-, and -(NProt^{NH})-, where Prot^{NH} is a protecting group for amino;

- 10 each group R_a is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₂₄ alkyl, substituted or unsubstituted C₂-C₂₄ alkenyl, substituted or unsubstituted C₂-C₂₄ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, and -(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25 and the
- 15 optional substituents are one or more substituents R_x;

each group R_b is independently selected from substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x;

- 20 each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

- 25 each group R_e is substituted or unsubstituted C₁-C₁₂ alkyl group, wherein the optional substituents are one or more substituents R_x;

- each group R_f is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, -CH₂O(CH₂CH₂O)_pCH₂CH₃ and -CH₂O(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25
- 30 and the optional substituents are one or more substituents R_x;

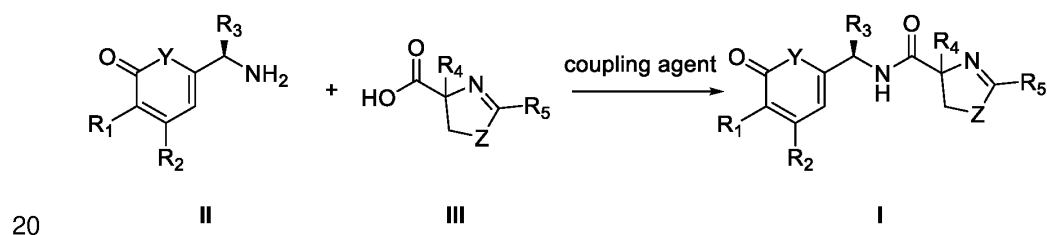
each group R_g is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂

alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x;

- each group R_n is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, -(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the optional substituents are one or more substituents R_x;
- 10 substituents R_x are selected from the group consisting of C₁-C₁₂ alkyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkenyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkynyl groups which may be optionally substituted with at least one group R_y, halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y, OCOR_y, OCOOR_y, COR_y, COOR_y, OCONR_yR_z, CONR_yR_z, SR_y, S(=O)R_y,
 15 SO₂R_y, SSR_y, P(=O)(R_y)OR_z, NR_yR_z, NR_yCOR_z, NR_yC(=O)NR_yR_z, NR_yC(=NR_y)NR_yR_z, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y, OR_y, OCOR_y, OCOOR_y, NR_yR_z, NR_yCOR_z, and NR_yC(=NR_y)NR_yR_z,
 20 aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y, and where
 25 there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

- each R_y and R_z is independently selected from the group consisting of hydrogen, C₁-C₁₂ alkyl groups, C₁-C₁₂ alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C₁-C₁₂ alkyl group that is substituted with an aryl group having from 6 to 18 carbon
 30 atoms in one or more rings and heterocycloalkyl group comprising a C₁-C₁₂ alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s).

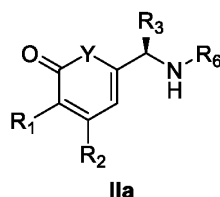
20. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 19, or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier.
21. A dosage form comprising a pharmaceutical composition as defined in claim 20.
- 5 22. A compound as defined in any of claims 1 to 19 or a pharmaceutical composition as defined in claim 20 or dosage form as defined in claim 21 for use as a medicament.
23. A compound as defined in any of claims 1 to 19, a pharmaceutical composition as defined in claim 20 or a dosage form as defined in claim 21 for use in the treatment of cancer.
24. The compound, composition or dosage form as claimed in claim 23, wherein the cancer is
10 selected from solid tumours, lung cancer, colon cancer, breast cancer and pancreas cancer.
25. A method of treating a patient in need thereof, comprising administering a therapeutically acceptable amount of a compound as defined in any of claims 1 to 19, a pharmaceutical composition as defined in claim 20 or a dosage form as defined in claim 21.
26. The method according to claim 25, wherein the method is a method of treating cancer in a
15 patient in need thereof.
27. The method according to claim 26, wherein the cancer is selected from solid tumours, lung cancer, colon cancer, breast cancer and pancreas cancer.
28. A process for obtaining a compound as defined in any of claims 1 to 19 comprising the coupling of a compound of formula II with a compound of formula III in accordance to Scheme 1



wherein R_1 is as defined for the compounds of formula I in claim 1 or 3 or an appropriately protected group as needed and R_2 , R_3 , R_4 , R_5 , Y , and Z are as defined for the compounds of formula I in any of claims 1 or 6 to 17 or an appropriately protected group as needed.

29. An intermediate compound of formula IIa

200



wherein:

5 R_1 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ;

R_2 is selected from hydrogen, halogen, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, $-OR_a$, OSO_2R_b , $-NR_cR_d$, $-NR_c(C=O)R_f$, and $-NR_cSO_2R_b$, wherein the optional substituents are one or more substituents R_x ;

10 R_3 is selected from halogen-substituted or unsubstituted C_1 - C_{12} alkyl, halogen-substituted or unsubstituted C_2 - C_{12} alkenyl, halogen-substituted or unsubstituted C_2 - C_{12} alkynyl and substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, wherein the optional substituents are one or more substituents R_x and the halogen substituents are one or more substituents independently selected from F, Cl, Br, and I;

15 R_6 is selected from hydrogen and a carbamate protecting group for amino;

Y is selected from $-O-$, $-S-$, $-(NH)-$, and $-(NProt^{NH})-$, where $Prot^{NH}$ is a protecting group for amino, with the proviso that when R_2 is hydrogen, then Y is selected from $-O-$ and $-S-$;

20 R_a is selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{24} alkyl, substituted or unsubstituted C_2 - C_{24} alkenyl, substituted or unsubstituted C_2 - C_{24} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, and $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x ;

25 each group R_b is independently selected from substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein the optional substituents are one or more substituents R_x ;

each group R_c and R_d are independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and

substituted or unsubstituted C₂-C₁₂ alkynyl, wherein the optional substituents are one or more substituents R_x; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

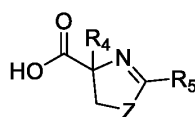
- 5 R_i is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, -CH₂O(CH₂CH₂O)_pCH₂CH₃, and -CH₂O(CH₂CH₂O)_pCH₃ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x;

- 10 substituents R_x are selected from the group consisting of C₁-C₁₂ alkyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkenyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkynyl groups which may be optionally substituted with at least one group R_y, halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y, OCOR_y, OCOOR_y, COR_y, COOR_y, OCONR_yR_z, CONR_yR_z, SR_y, S(=O)R_y, SO₂R_y, OSO₂OR_y, SSR_y, P(=O)(R_y)OR_z, OP(=O)(OR_y)₂, NR_yR_z, NR_yC(=O)R_z, NR_yC(=O)OR_z, NR_yC(=O)NR_yR_z, NR_yC(=NR_y)NR_yR_z, aryl groups having from 6 to 18 carbon atoms in one or more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y, OR_y, OCOR_y, OCOOR_y, NR_yR_z, NR_yCOR_z, and NR_yC(=NR_y)NR_yR_z, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y, and where there is more than one optional substituents on any given group the optional substituents R_y may be the same or different; and

- 25 each R_y and R_z is independently selected from the group consisting of hydrogen, C₁-C₁₂ alkyl groups, C₁-C₁₂ alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C₁-C₁₂ alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings and heterocycloalkyl group comprising a C₁-C₁₂ alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s);
- 30 or a salt thereof.

30. An intermediate compound of formula **IIIa**

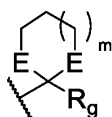
202



IIIa

wherein R_4 is selected from unsubstituted C_1 - C_{12} alkyl, unsubstituted C_2 - C_{12} alkenyl and unsubstituted C_2 - C_{12} alkynyl;

- R_5 is selected from $-C(OR_e)_2R_g$, $-C(SR_e)_2R_g$, $-CH(OR_a)R_g$, $-CH(O-(C=O)R_f)R_g$, $-CH(NR_c-(C=O)R_f)R_g$, $-CH(NR_c-OR_h)R_g$, $-(C=O)R_g$, $-(C=NR_c)R_g$, $-(C=N-OR_h)R_g$, $-(C=N-O-(C=O)R_f)R_g$, $-(C=N-O-(C=O)OR_a)R_g$, $-(C=N-O[(P=O)(OR_a)_2])R_g$, $-(C=N-NR_cR_d)R_g$, $-(C=O)OR_a$, $-(C=O)NR_c-OR_h$, $-(C=O)NR_cR_d$, $-(C=CH_2)R_g$, and $-(C=CH_2)OR_a$; or R_5 is a



group where m is 0, 1, or 2 and each E group is independently selected from O and S;

- 10 Z is selected from $-O-$, $-S-$, $-(NH)-$, and $-(NProt^{NH})-$, where $Prot^{NH}$ is a protecting group for amino;

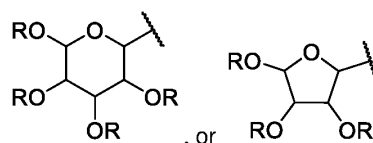
each group R_a is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted C_3 - C_6 cycloalkyl- C_1 - C_{12} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, $-(CH_2CH_2O)_pCH_2CH_3$, and $-(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x ;

- each group R_c and R_d is independently selected from hydrogen, a protecting group for amino, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, wherein the optional substituents are one or more substituents R_x ; or R_c and R_d together with the nitrogen atom to which they are attached form a heterocyclic group;

each group R_e is substituted or unsubstituted C_1 - C_{12} alkyl group, wherein the optional substituents are one or more substituents R_x ;

- each group R_f is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, $-CH_2O(CH_2CH_2O)_pCH_2CH_3$, $-CH_2O(CH_2CH_2O)_pCH_3$ wherein p is from 1 to about 25 and the optional substituents are one or more substituents R_x , and a group of formula:

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where each R group is, at each occurrence, independently selected from hydrogen, substituted or unsubstituted C₁-C₆ alkyl group, substituted or unsubstituted -(C=O)-(C₁-C₆)alkyl, and substituted or unsubstituted -(C=O)NH(C₁-C₆)alkyl, wherein the optional substituents are one or
 5 more substituents R_x; or two adjacent OR groups form an isopropylidene ketal or an acetal group selected from methylene-, methoxymethylene-, ethoxymethylene-, ethylidene-, benzylidene-, and *p*-methoxybenzylidene- acetals;

each group R_g is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl and substituted or unsubstituted C₂-C₁₂ alkynyl,
 10 wherein the optional substituents are one or more substituents R_x;

each group R_h is independently selected from hydrogen, a protecting group for OH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted C₃-C₆cycloalkyl-C₁-C₁₂alkyl, substituted or unsubstituted heterocyclo-C₁-C₁₂alkyl, substituted or unsubstituted aryl,
 15 substituted or unsubstituted heterocyclic group, -(CH₂CH₂O)_pCH₂CH₃, -(CH₂CH₂O)_pCH₃, wherein p is from 1 to about 25, and substituted or unsubstituted monosaccharide residue, wherein the optional substituents are one or more substituents R_x;

substituents R_x are selected from the group consisting of C₁-C₁₂ alkyl groups which may be optionally substituted with at least one group R_y, C₂-C₁₂ alkenyl groups which may be optionally
 20 substituted with at least one group R_y, C₂-C₁₂ alkynyl groups which may be optionally substituted with at least one group R_y, halogen atoms, oxo groups, thio groups, cyano groups, nitro groups, OR_y, OCOR_y, OCOOR_y, COR_y, COOR_y, OCONR_yR_z, CONR_yR_z, SR_y, S(=O)R_y, SO₂R_y, OSO₂OR_y, SSR_y, P(=O)(R_y)OR_z, OP(=O)(OR_y)₂, NR_yR_z, NR_yC(=O)R_z, NR_yC(=O)OR_z, NR_yC(=O)NR_yR_z, NR_yC(=NR_y)NR_yR_z, aryl groups having from 6 to 18 carbon atoms in one or
 25 more rings which may optionally be substituted with one or more substituents which may be the same or different selected from the group consisting of R_y, OR_y, OCOR_y, OCOOR_y, NR_yR_z, NR_yCOR_z, and NR_yC(=NR_y)NR_yR_z, aralkyl groups comprising an alkyl groups having from 1 to 12 carbon atoms substituted with an optionally substituted aryl group as defined above, aralkyloxy groups comprising an alkoxy group having from 1 to 12 carbon atoms substituted
 30 with an optionally substituted aryl group as defined above, and a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s), said heterocyclic group optionally being substituted with one or more substituents R_y, and where there is more than one optional substituents on any

given group the optional substituents R_y may be the same or different; and

- each R_y and R_z is independently selected from the group consisting of hydrogen, C_1 - C_{12} alkyl groups, C_1 - C_{12} alkyl groups that are substituted with at least one halogen atom, aralkyl groups comprising a C_1 - C_{12} alkyl group that is substituted with an aryl group having from 6 to 18 carbon atoms in one or more rings and heterocycloalkyl group comprising a C_1 - C_{12} alkyl group that is substituted with a 5- to 14- membered saturated or unsaturated heterocyclic group having one or more rings and comprising at least one oxygen, nitrogen or sulphur atom in said ring(s);

or a salt thereof.