SUBSTITUTED BENZOYLAMINO-INDAN-2-CARBOXYLIC ACIDS AND RELATED COMPOUNDS

FIELD OF THE INVENTION

The present invention is directed to substituted benzoylamino-indan-2-carboxylic acids and related compounds and intermediates thereto, their preparation including stereoselective synthetic processes to intermediates, pharmaceutical compositions containing the compounds, and the use of the compounds or compositions thereof having the ability to block the CXCR5 receptor and inhibit B cell function associated with receptor activation. The compounds having CXCR5 inhibitory activity are particularly useful in treating or preventing various inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor.

BACKGROUND OF THE INVENTION

CXCR5 is a non-promiscuous chemokine receptor belonging to the family of G-Coupled Protein receptors (GPCRs). Specifically, the CXCR5 receptor interacts with its CXCL13 ligand - which is constitutively expressed on stromal cells, such as follicular dendritic cells, and in lymphoid tissues. The CXCL13 ligand specifically attracts B cells and a small subset of T cells called B helper follicular T cells (T_{FH}). When the CXCR5/CXCL13 interaction is blocked by an antagonist, patients with Rheumatoid Arthritis (RA) and other autoimmune or inflammatory diseases in which the up-regulation of CXCR5 and/or its ligand CXCL13 are responsible for the pathogenesis or exacerbation of the disease, can be treated. While B cell depletion therapy with anti-CD20 monoclonal antibody (Rituximab) has shown as efficacious in the treatment of RA, blocking of B cells, such as CXCR5-expressing cells, is known to be of therapeutic benefit in experimental murine models of arthritis.

Furthermore, CXCR5 and/or CXCL13 is known to be up-regulated in patients with Rheumatoid Arthritis [*Arthritis Res Ther*. 2005;7(2):R217-29. Epub 2004 Dec 16.], Sjogren's syndrome [*Arthritis Rheum*. 2001 Nov;44(11):2633-41.], myasthenia gravis [*J Neuroimmunol*. 2005 Dec 30;170(1-2):172-8. Epub 2005 Oct 7] and multiple sclerosis [*Brain*. 2006

Jan;129(Pt 1):200-11. Epub 2005 Nov 9]. A linkage between CXCR5 and pancreatic carcinoma [*Cancer Res.* 2006 Oct 1;66(19):9576-82.] is also known. By blocking the receptor/ligand interaction with a CXCR5 antagonist, therapeutic benefits can be realized in the diseases mentioned above, and in other diseases in which B cell infiltration (or other lymphocyte subsets expressing the CXCR5 receptor) is responsible for the pathogenesis of the disease [*Front Biosci.* 2007 Jan 1;12:2194-2006, *J Rheumatol Suppl.* 2006 May;77:3-11].

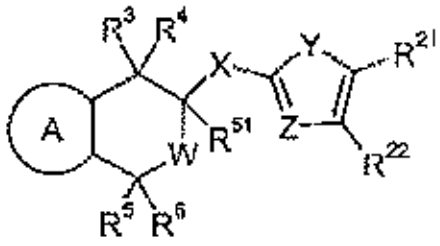
Infiltration of lymphocytes into tertiary ectopic germinal centers (GCs) is known to correlate well with increased disease severity and tolerance breakdown. By using *in vivo* murine models, such as $CXCR5^{-/-}$ and $CXCL13^{-/-}$ mice, for example, the absence of either the receptor or the ligand, results in an altered GC fine architecture caused by changed T and B cell localization. These mice are known to be protected against developing severe collagen-induced arthritis (CIA). Thus, since CXCR5 is selectively expressed on mature B cells, which are linked to the pathogenesis of RA, an antagonist that capable of blocking this receptor can modulate the arthritogenic response in affected individuals. Presently, Rheumatoid arthritis treatment with anti-CD20 antibodies has shown to be clinically effective; such as with patients on B cell directed therapy, who have shown long-lasting improvements in clinical signs and symptoms. The selective targeting of CXCR5, which is only expressed on mature B cells and B helper T cells is, therefore, not expected to affect B cell development or immuno-compromise the patient

Thus, an unmet need exists for CXCR5 antagonists for treatment of Rheumatoid Arthritis and other inflammatory, autoimmune diseases and cancers caused by the interaction of B cells expressing CXCR5 in response to CXCL13 expression.

SUMMARY OF THE INVENTION

The present invention is directed to antagonist compounds of the formula I, which have been found to block B cell migration in response to a ligand gradient, without peripheral B cell depletion. These compounds, therefore, provide a safety profile for the long-term treatment of inflammatory diseases.

The present invention relates to novel compounds of the formula I:



(I)

wherein:

ring A is a benzene ring or a monocyclic 5-membered or 6-membered aromatic heterocyclic ring comprising 1 or 2 identical or different hetero ring members chosen from the group consisting of N, N(R^1), O and S, which rings can all be substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S(O)$_m$-, cyano and nitro;

W is chosen from the group consisting of a bond or CH2;

X is chosen from the group consisting of N(R^7)C=O, N(R^7)S(O)$_m$, N(R^7)CR^8(R^9), C=ON(R^7), S(O)$_m$N(R^7), CR^8(R^9)N(R^7), CR^8(R^9)N(R^7)C=O, CR^8(R^9)N(R^7) S(O)$_m$;

Y is chosen from the group consisting of N(R^{11}), S, O, C(R^{12})=C(R^{13}), N=C(R^{14}) and C(R^{15})=N;

C(R^{12})=C(R^{13}) can be a 5-7 membered carbocycle or heterocycle with any substitution;

Z is chosen from the group consisting of N and C(R^{16});

R^2 is chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^3 and R^4 are independently of each other chosen from the group consisting of hydrogen, (C_1-C_4)-alkyl;

R^5 and R^6 are independently of each other chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^7 is chosen from the group consisting of hydrogen, $(C_1$-$C_4)$-alkyl and $(C_1$-$C_6)$-cycloalkyl;

R^8 and R^9 are independently of each other chosen from the group consisting of hydrogen and $(C_1$-$C_4)$-alkyl or together as $(C_1$-$C_6)$-cycloalkyl;

R^{11} is chosen from the group consisting of hydrogen, $(C_1$-$C_{10})$-alkyl, hydroxy-$(C_1$-$C_{10})$-alkyl-, $(C_1$-$C_{10})$-alkyloxy, $(C_1$-$C_{10})$-alkyl-$S(O)_m$-, $(C_1$-$C_{10})$-alkylcarbonyl-, amino, $(C_1$-$C_{10})$-alkylamino, di$((C_1$-$C_{10})$-alkyl)amino;

R^{12}, R^{15} and R^{16} are independently of each other chosen from the group consisting of hydrogen, halogen, $(C_1$-$C_{10})$-alkyl, hydroxy-$(C_1$-$C_{10})$-alkyl-, $(C_1$-$C_{10})$-alkyloxy, $(C_1$-$C_{10})$-alkyl-$S(O)_m$-, cyano, $(C_1$-$C_{10})$-alkylcarbonyl-, amino, $(C_1$-$C_{10})$-alkylamino, di$((C_1$-$C_{10})$-alkyl)amino and nitro;

R^{13}, R^{14}, R^{21} and R^{22} are independently of each other chosen from the group consisting of hydrogen, halogen, $(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_3)$-alkyl-, $(C_1$-$C_3)$-alkyloxy, $(C_1$-$C_3)$-alkyl-$S(O)_m$-, cyano, $(C_1$-$C_2)$-alkylcarbonyl-, amino, $(C_1$-$C_3)$-alkylamino, di$((C_1$-$C_3)$-alkyl)amino and nitro;

provided that the total number of C, N, O and S atoms which is present in any one of the groups R^{13}, R^{14}, R^{21} and R^{22}, does not exceed 4;

R^{51} is chosen from the group consisting of $COOR^{52}$, $CONR^{53}(R^{54})$, and 5-6 membered heterocycles containing 3 or more heteroatoms;

R^{52} is chosen from the group consisting of hydrogen and $(C_1$-$C_4)$-alkyl;

R^{53} is chosen from the group consisting of hydrogen, hydroxyl, $(C_1$-$C_4)$-alkyloxy, $(C_1$-$C_4)$-alkyl, cyano and R^{55}-SO_2-;

R^{54} is chosen from the group consisting of hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_2)$-alkylcarbonyl-, $(C_1$-$C_3)$-alkyl-$S(O)_m$-;

R^{33} is chosen from the group consisting of $(C_1$-$C_4)$-alkyl and phenyl;

R^{61} is chosen from the group consisting of hydrogen and $(C_1$-$C_4)$-alkyl;

R^{62} is chosen from the group consisting of hydrogen and $(C_1$-$C_4)$-alkyl;

heteroaryl is a monocyclic 5-membered or 6-membered aromatic heterocyclic ring which comprises 1, 2 or 3 identical or different hetero ring members chosen from the group consisting of N, $N(R^{61})$, O and S;

heterocyclyl is a monocyclic 4-membered to 7-membered heterocyclic ring which comprises 1 or 2 identical or different hetero ring members chosen from the group consisting of N, $N(R^{62})$, O, S, SO and SO_2 but two hetero ring members from the series consisting of $N(R^{62})$, O and S cannot be present in adjacent ring positions, which ring is saturated or partially unsaturated and can be substituted by one or more identical or different substituents chosen from the group consisting of $(C_1$-$C_4)$-alkyl;

m is an integer chosen from the group consisting of 0, 1 and 2, where all numbers m are independent of each other and can be identical or different;

all phenyl and heteroaryl groups in the compound of the formula Ia can independently of each other be substituted by one or more identical or different substituents chosen from the group consisting of halogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkyloxy, $(C_1$-$C_4)$-alkylsulfonyl and cyano;

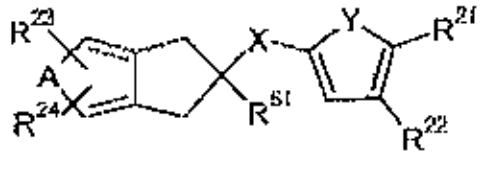
all alkyl groups in the compound of the formula Ia can independently of each other be substituted by one or more fluorine atoms;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The contents of each of the patent documents and other references cited herein are herein incorporated by reference in their entirety.

In a particular embodiment, the present invention includes the compound of formula Ia wherein:



(Ia)

wherein:

A is CH=CH or S;

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro when A is S;

X is N(H)C=O, $N(H)S(O)_2$, C=ON(H), or $S(O)_2N(H)$;

Y is $N(R^{11})$, S, O, $C(R^{12})=C(R^{13})$, $N=C(R^{13})$, or $C(R^{13})=N$, or fused optionally substituted 5-7 membered carbocyclyl;

R^{11} is hydrogen, (C_1-C_{10})-alkyl, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_1-C_{10})-alkyl-$S(O)_m$-, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, (C_1-C_{10})-alkylamino, or di((C1-C10)-alkyl)amino;

R^{12} is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_6)-cycloalkyloxy, (C_3-C_{10})-cycloalkenyloxy, (C_3-C_6)-cycloalkyl, (C_3-C_{10})-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], (C_3-C_6)-cycloalkyl(C_1-C_4)-alkyloxy, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_2-C_{10})-alkenyloxy, (C_1-C_{10})-alkyl-S-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, or nitro;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

R^{14} is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di$((C_1-C_3)$-alkyl)amino or nitro, provided that the total number of C, N, O and S atoms which is present in R^{14} does not exceed 4;

$R^{15}$is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})- alkenyl, (C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], hydroxy-(C_1-C_{10})-alkyl-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]((C_1-C_{10})-alkyl)amino or nitro;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, and is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di$((C_1-C_3)$-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{21} does not exceed 4;

R^{22} is hydrogen, halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, or is hydrogen, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di$((C_1-C_3)$-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{22} does not exceed 4;

R^{51} is COOH or $CONH(R^{53})$;

R^{53} is R^{55}-SO_2- or tetrazolyl;

R^{55} is (C_1-C_4)-alkyl or phenyl optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-sulfonyl and cyano; and

m is 0, 1, or 2;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, or (C_1-C_4)-alkyloxy;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, or (C_1-C_4)-alkyl when A is S;

X is N(H)C=O, N(H)S(O)$_2$, or C=ON(H);

Y is C(R^{12})=C(R^{13}), or C(R^{13})=N, or fused optionally substituted 5-6 membered carbocyclyl;

R^{12} is (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_4-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkenyl, (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], (C_2)-cycloalkyl(C_1)-alkyloxy, (C_3-C_4)-alkyloxy, (C_3)-alkenyloxy, (C_1-C_3)-alkyl-S-, or (C_3)-alkylcarbonyl-, phenyl;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

$R^{15}$is (C_1-C_6)-alkyl, (C_2-C_6)- alkenyl, or [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1)-alkyl)amino;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{51} is COOH;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

A is CH=CH.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{23} is hydrogen or halogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{24} is hydrogen or halogen when A is CH=CH;

Another particular embodiment according to the invention is the compound according to formula Ia wherein

X is N(H)C=O.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is $C(R^{12})=C(R^{13})$.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is $C(R^{13})=N$.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is fused optionally substituted 5-6 membered carbocyclyl.

Another particular embodiment according to the invention is the compound according to formula Ie wherein

R^{12} is (C_4-C_6)-alkyl, or more particularly isobutyl or propyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_{3-5})-alkenyl, or more particularly penten-1-yl, isobutene-1-yl or propen-1-yl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_4)-cycloalkyloxy (cyclobutyloxy).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_5-C_6)-cycloalkyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_5-C_6)-cycloalkenyl, or more particularlycyclopenten-1-yl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], or more particularly cyclopropylethyl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-cycloalkyl(C_1)-alkyloxy (cyclopropylmethyl).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3-C_4)-alkyloxy.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-alkenyloxy.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is phenyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is halogen, or (C_1)-alkyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl wherein the alkyl is optionally substituted by 1-3 fluorine atoms, or more particularly trifluoromethylyl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl (methyl).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl that is substituted by 2-3 fluorine atoms.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is halogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

$R^{15}$is [$(C_2$-$C_3)$-alkyl or (C_3)-alkenyl]($(C_1$-$C_{10})$-alkyl)amino.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{15} is $(C_2$-$C_3)$-alkyl(C_1)-alkyl)amino, or more particularly isopropylmethylamino..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{21} is hydrogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})$=$C(R^{13})$.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{51} is COOH.

Specific embodiments of the present invention are selected from the group consisting of

2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid
2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid,
2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid
5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid,
5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid,
5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid,
2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,
2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid,

2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,

2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,

5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,

2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid,

2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid,

2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid,

2-(3-Cyano-2-methyl-benzoylamino)-inden-2-carboxylic acid,

2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid,

2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid,

2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid,

2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid,

2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid,

2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,

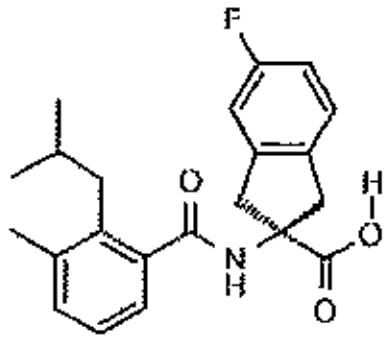
2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,

2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,

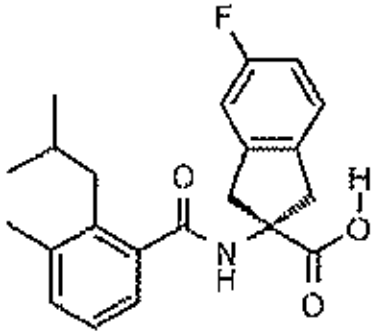
2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid,
4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5-Chloro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid,
2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide,
2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide, and
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid, or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound of the following structure



Another particular embodiment according to the invention is the compound of the following structure



Another particular embodiment according to the invention is a compound selected from Example 232, 150, 231, 149, 136, 158, 152, 159, 144, 397, 135, 161, 155, 132, 139, 125, 329, 262, 154, 143, 160, 163, 21, 87, 212, 103, 352, 395, 392, or 388.

Another particular embodiment according to the invention is a pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to formula Ia wherein and at least one of a pharmaceutically acceptable excipient and pharmaceutically acceptable carrier.

Another particular embodiment according to the invention is a method for the treatment of a patient suffering from, or subject to, a physiological condition that can be ameliorated by the administration of a pharmaceutically effective amount of an inhibitor of a CXCR5 receptor to the patient comprising administering the compound according to formula Ia to said patient.

Another particular embodiment according to the invention is the method of treatment wherein the physiological condition is an inflammatory disease.

Another particular embodiment according to the invention is the method of treatment the physiological condition is rheumatoid arthritis.

Another particular embodiment according to the invention is the method of treatment the physiological condition is asthma.

Another particular embodiment according to the invention is the method of treatment with the administering of the compound of claim 1 and another therapeutic agent is administered at the same time or sequentially.

Another particular embodiment according to the invention is a process for producing a compound according to formula Ia as described herein.

The present invention is also directed to a pharmaceutical composition comprising a compound of formula I, and method for using the compound of formula I or formula Ia for preventing and or treating inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor in a patient.

The invention is also directed to a process for preparing a compound that is an intermediate useful in preparing a compound of formula I or formula Ia.

Another aspect of the invention are methods of treating or preventing a physiological condition or a disease state a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of one or more compounds of formula I or formula Ia.

The amount of the compounds of formula I or formula Ia or other compounds capable of physiological condition or a disease state in any of the foregoing applications can be a pharmaceutically effective amount, a subclinical effective amount, or combinations thereof, so long as the final combination physiological condition or a disease state comprises a pharmaceutically effective amount of compounds that is effective in preventing and or treating inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor. in a patient.

List of Abbreviations

As used throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
AIBN	2,2'-azobisisobutyronitrile
BOC or Boc	*tert*-butyl carbamate
BOP	benzotriazol-1-yl-oxytris (dimethylamino) phosphonium
n-Bu$_3$SnH	tri-n-butyltin hydride
t-Bu	tert-butyl
Cbz	benzyl carbamate
$CsCO_3$	cesium carbonate
DAST	(diethylamino) sulfur trifluoride (Et_2NSF_3)
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane (CH_2Cl_2) or methylenechloride
DIC	1,3-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMP reagent	Dess-Martin Periodinane reagent
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
FMOC	9-fluorenylmethoxycarbonyl
HATU	O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF_6
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazole
HOSu	N-hydroxysuccinamide
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate

HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
$MgSO_4$	magnesium sulfate
Me	methyl
MeI	methyliodide
MeOH	methanol
MeOC(O)	methyl chloroformate
MOMCl	methoxymethylchloride
MOM	methoxymethyl
MS	mass spectroscopy
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
$Na_2C_4H_4O_6$	sodium tartrate
NMR	nuclear magnetic resonance
PTC	phase transfer catalyst
iPrOH	iso-propanol
P	Polymer bond
$KMnO_4$	potassium permanganate
K_2SO_4	potassium carbonate
PyBOP	benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium hexafluorophosphate
Na_2SO_4	Sodium sulfate
TBD	1,5,7-triazabicyclo[4.4.0]-dec-5-ene
RP-HPLC	reverse phase-high pressure liquid chromatography
RT	room temperature
TBSCl	*tert*-butyldimethylsilyl chloride
TCA	trichloroacetic acid
TFA	trifluoroacetic acid
Tf_2O	triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography

Definitions

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, "Bioisosterism In Drug Design" 21, 283 (1986); Yun, Hwahak Sekye, "Application of Bioisosterism To New Drug Design" 33, 576-579, (1933); Zhao, Huaxue Tongbao, "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design" 34-38, (1995); Graham, Theochem, "Theoretical Studies Applied To Drug Design ab initio Electronic Distributions In Bioisosteres" 343, 105-109, (1995)). Exemplary acid bioisosteres include -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydoxy-1-methylpyrazolyl and the like.

"Acidic functional group" means a moiety bearing an acidic hydrogen. Exemplary acid functional groups include carboxyl (-C(O)OH), -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl or 3-hydroxy-3cyclobutene-1,2-dione, imidazolyl mercapto, and the like, and an appropriate hydroxy such as an aromatic hydroxy, e.g., hydroxyphenyl, hydroxyheteroaryl such as 3,5-dioxo-1,2,4-oxadiazolidinyl 3-hydroxisoxazolyl or 3-hydoxy-1methylpyrazolyl.

"Acid protecting group" means an easily removable group that is known in the art to protect an acidic hydrogen of a carboxyl group against undesirable reaction during synthetic procedures, e.g., to block or protect the acid functionality while the reactions involving other functional sites of the compound are carried out, and to be selectively removable. Such acid protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups, as described in U.S. Pat. No. 3,840,556 and 3,719,66, the disclosures of which are hereby incorporated herein by reference. For suitable acid protecting

groups, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and sons, 1991. Acid protecting group also includes hydrogenation labile acid protecting group as defined herein. Exemplary acid protecting groups include esters such as substituted and unsubstituted C_{1-8} lower alkyl, e.g., methyl, ethyl, *t*-butyl, methoxymethyl, methylthiomethyl, 2,2,2-trichloroethyl and the like, tetrahydropyranyl, substituted and unsubstituted phenylalkyl such as benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like, cinnamyl, dialkylaminoalkyl, e.g., dimethylaminoethyl and the like, trimethylsilyl, substituted and unsubstituted amides and hydrazides, e.g., amides and hydrazides on N,N-dimethylamine, 7-nitroindole, hydrazine, N-phenylhydrazine and the like, acyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like, aroyloxyalkyl such as benzoyloxyethyl and the like, alkoxycarbonylalkyl such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like, alkoxycarbonyloxyalkyl such as *t*-butyloxycarbonyloxymethyl and the like, alkoxycarbonylaminoalkyl such as *t*-butyloxycarbonylaminomethyl and the like, alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like, acylaminoalkyl such as acetylaminomethyl and the like, heterocyclylcarbonyloxyalkyl such as 4-methylpiperazinyl-carbonyloxymethyl and the like, dialkylaminocarbonylalkyl such as dimethylaminocarbonyl-methyl and the like, (5-(lower alkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-*t*-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like, and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

"Acid labile amine protecting group" means an amine-protecting group as defined herein that is readily removed by treatment with acid while remaining relatively stable to other reagents. A preferred acid labile amine-protecting group is BOC.

"Aliphatic" means alkyl, alkenyl or alkynyl as defined herein.

"Aliphatic group substituent(s)" means substituents attached to an aliphatic group as defined herein inclusive or aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH,-C(O)-CH_2OH,-C(O)-CH_2SH,-C(O)-NH-CN-sulfo, phosphono, alkysulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, tetrazolyl,

arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxadiazolidinyl or 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H_2C=), oxo (O=), thioxo (S=), Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$-, $Y^1Y^2NSO_2$-, or $Y^3SO_2NY^1$- wherein R^2 is as defined herein, Y^1 and Y^2 are independently hydrogen, alkyl, aryl or heteroaryl, and Y^3 is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y^1Y^2N-, then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. Acidic/amide aliphatic group substituents are carboxy (acid), -C(O)-NHOH, $-C(O)CH_2OH$, $-C(O)-CH_2SH$, -C(O)-NH-CN, sulfo?), phosphono?), alkysulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxadiazolidinyl or 3-hydroxy-1-methylpyrazolyl and Y^1Y^2NCO-. Non-acidic polar aliphatic group substituents are hydroxy, oxo (O=), thioxo (S=), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-. Exemplary aliphatic groups bearing an aliphatic group substituent include methoxymethoxy, methoxyethoxy, ethoxyethoxy, (methoxy-, benzyloxy-, phenoxy-, or ethoxy-) carbonyl(methyl or ethyl), benzyloxycarbonyl, pyridylmethyloxy-carbonylmethyl, methoxyethyl, ethoxymethyl, *n*-butoxymethyl, cyclopentylmethyloxyethyl, phenoxypropyl, phenoxyallyl, trifluoromethyl, cyclopropyl-methyl, cyclopentylmethyl, carboxy(methyl or ethyl), 2-phenethenyl, benzyloxy, 1- or 2-

naphthyl- methoxy, 4-pyridyl-methyloxy, benzyloxyethyl, 3-benzyloxyallyl, 4-pyridylmethyl-oxyethyl, 4- pyridylmethyloxyallyl, benzyl, 2-phenethyl, naphthylmethyl, styryl, 4-phenyl-1,3-pentadienyl, phenyl-propynyl, 3-phenylbut-2-ynyl, pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl, 4- pyridyl-ethynyl, 4-pyridylvinyl, thienylethenyl, pyridylethenyl, imidazolyl-ethenyl, pyrazinylethenyl, pyridylpentenyl, pyridylhexenyl and pyridylheptenyl, thienyl-methyl, pyridylmethyl, imidazolylmethyl, pyrazinylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl- methoxymethyl, and the like.

"Acyl" means an H-CO- or (aliphatic or cyclyl)-CO- group wherein the aliphatic group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butenoyl, palmitoyl, acryloyl, propynoyl, cyclohexylcarbonyl, and the like.

"Alkenoyl" means an alkenyl-CO- group wherein alkenyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, cyclohexylbutenyl, decenyl, and the like. "Substituted alkenyl" means an alkenyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary alkenyl aliphatic group substituents include halo or cycloalkyl groups.

"Alkenyloxy" means an alkenyl-O- group wherein the alkenyl group is as herein described. Exemplary alkenyloxy groups include allyloxy, 3-butenyloxy, and the like.

"Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, heptoxy, and the like.

"Alkoxycarbonyl" means an alkyl-O-CO- group, wherein the alkyl group is as herein defined. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, *t*-butyloxycarbonyl, and the like.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain, more preferred is lower alkyl as defined herein. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain that may be straight or branched. "Substituted alkyl" means an alkyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO_2- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl groups is lower alkyl.

"Alkylsulfonylcarbamoyl" means an alkyl-SO_2-NH-C(=O)- group wherein the alkyl group is as herein described. Preferred alkysulfonylcarbamoyl groups are those wherein the alkyl group is lower alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as herein described. Exemplary alkylthio groups include methylthio ethylthio *i*-propylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about r carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. The alkynyl group may be substituted by one or more halo. Exemplary alkynyl groups include

ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl, decynyl, and the like. "Substituted alkynyl" means alkynyl as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Amine protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amine group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.W. Greene and P.G.M. Wuts, Protective groups in Organic synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Amine protecting group also includes "acid labile amine protecting group" and "hydrogenation labile amine protecting group". Exemplary amine protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxy-acetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

"Amide protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amide group against undesirable reaction during synthetic procedures and to be selectively removable after its conversion to the amide. The use of amide protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known for example, T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Amide protecting group also includes "acid labile amide protecting group" and "hydrogenation labile amide protecting group". Exemplary amide protecting groups are o-nitrocinnamoyl, picolinoyl, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycaronyl, 2-trimethylsilyethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-

nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

"Amino acid" as defined herein is selected from the group consisting of natural and unnatural amino acids. Amino acid is also meant to include amino acids having L or D stereochemistry at the α-carbon. Preferred amino acids are those possessing an α-amino group. The amino acids may be neutral, positive or negative depending on the substituents in the side chain. "Neutral amino acid" means an amino acid containing uncharged side chain substituents. Exemplary neutral amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine and cysteine. "Positive amino acid" means an amino acid in which the side chain substituents are positively charged at physiological pH. Exemplary positive amino acids include lysine, arginine, and histidine "Negative amino acid" means an amino acid in which the side chain substituents bear a net negative charge at physiological pH. Exemplary negative amino acids include aspartic acid and glutamic acid. Exemplary natural amino acids are isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine histidine, aspartic acid and glutamic acid. "Unnatural amino acid" means an amino acid for which there is no nucleic acid codon. Exemplary unnatural amino acids include, for example, the D-isomers of the natural α-amino acids as indicated above; Aib (aminobutyric acid), βAib (3-amino-isobutyric acid) Nva (norvaline), β-Ala, Aad (2-aminoadiphic acid), βAad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ-aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminopropionic acid), α-aminopimelic acid, TMSA (trimethylsilyl-Ala), allc (alloisoleucine), Nle (norleucine), *tert*-Leu, Cit (citrulline), Orn, Dpm (2,2'-diaminopimelic acid), α -or β- Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), and the like; cyclic amino acids; N^{α}-alkylated amino acids such as MeGly. (Na-methylglycine), EtGly (N^{α}-ethylglycine) and EtAsn (Na-ethylasparagine); and amino acids in which the α-carbon bears two side-chain substituents. The names of natural and unnatural amino acids and residues thereof used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in "Nomenclature of α-Amino Acids (Recommendations, 1974)" Biochemistry, 14(2), (1975). To the extent that the names and abbreviations of amino acids and residues thereof employed in this specification and appended claims differ from those noted, differing names and abbreviations will be made clear.

"Amino acid protecting group" mean a group that protects an acid or amine moiety of the amino acid or other reactive moiety on the side chain of an amino acid, e.g., hydroxy or thiol. For examples of "corresponding protected derivatives" of amino acid side chains, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Protecting groups for an acid group in an amino acid are described herein, for example in the sections "acidic functional group" and "hydrogenation labile acid protecting group". Protecting groups for an amine group in an amino acid are described herein, for example in the sections "amine protecting group", "acid labile amine protecting group" and "hydrogenation labile amine protecting group".

"Amino acid residue" means the individual amino acid units incorporated into the compound of the invention.

"Amino acid side chain" means the substituent found on the carbon between the amino and carboxy groups in α-amino acids. Exemplary amino acid side chains include isopropyl, methyl, and carboxymethyl for valine, alanine, and aspartic acid, respectively.

"Amino acid equivalent" means an amino acid that may be substituted for another amino acid in the peptides according to the invention without any appreciable loss of function. In making such changes, substitutions of like amino acids are made on the basis of relative similarity of side chain substituents, for example regarding size, charge, hydrophilicity, hydropathicity and hydrophobicity as described herein.

"Aromatic group" means aryl or heteroaryl as defined herein. Exemplary aromatic groups include phenyl, halo substituted phenyl, azaheteroaryl, and the like.

"Aroyl" means an aryl-CO-group wherein the aryl group is as herein described. Exemplary aroyl groups include benzoyl, 1-and 2-naphthoyl, and the like.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to 10 carbon atoms. Encompassed by aryl are fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclenylaryl and fused heterocyclylaryl as

defined herein when bonded through the aryl moiety thereof. The aryl is optionally substituted with one or more "ring group substituents" (preferably 1 to 3 substituents which may be the same or different, and are as defined herein. A "Substituted aryl" means an aryl group which is substituted as defined above. Exemplary aryl groups include phenyl or naphthyl, or substituted phenyl or substituted naphthyl.

"Aryldiazo" means an aryl-diazo-group wherein the aryl and diazo groups are as defined herein.

"Arylene" means an optionally substituted 1,2-, 1,3-, 1,4-, bivalent aryl group, wherein the aryl group is as defined herein. "Substituted arylene" means an arylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary arylene groups include optionally substituted phenylene, naphthylene and indanylene. A particular arylene is optionally substituted phenylene.

"Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein. Exemplary aryloxy groups include phenoxy and 2-naphtyloxy.

"Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined herein. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfonyl" means an aryl-SO_2- group wherein the aryl group is defined herein.

"Arylsulfonylcarbamoyl" means an aryl-SO_2-NH-C(=O)-group wherein the aryl group is herein described. An exemplary arylsulfonylcarbamoyl group is phenylsulfonylcarbamoyl.

"Arylsulfinyl" means an aryl-SO –group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as herein described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Basic nitrogen atom" means a sp^2 or sp^3 hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Exemplary basic nitrogen atoms include optionally substituted imino, optionally substituted amino and optionally substituted amidino groups.

"Carboxy" means an HO(O)C- (carboxylic acid) group.

"Coupling agent" means a compound that reacts with the hydroxyl moiety of a carboxy moiety thereby rendering it susceptible to nucleophilic attack. Exemplary coupling agents include DIC, EDCI, DCC, and the like.

"Cycloalkenyl" means an optionally substituted non aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond and which can be optionally fused by an aromatic group as defined herein. "Fused (aromatic) "cycloalkenyl" means fused arylcycloalkenyl and fused heteroarylcycloalkenyl as defined herein bonded through the cycloalkenyl moiety thereof. Preferred sizes of the rings of the ring system are about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". "Substituted cycloalkenyl" means an cycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are defined herein. Exemplary monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. An exemplary multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which can be optionally fused by an aromatic group as defined herein. Preferred sizes of the rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". "Fused (aromatic) cycloalkyl" means fused arylcycloalkyl and fused heteroarylcycloalkyl as defined herein bonded through the cycloalkyl moiety thereof. "Substituted cycloalkyl" means a cycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably1 to 3) which may be the same or different and are as defined herein. Exemplary monocyclic cycloalkyl include cyclopentyl, cyclohexyl,

cycloheptyl, and the like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, and the like.

"Cycloalkylene" means a bivalent cycloalkyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the cycloalkylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary monocyclic cycloalkylene groups include (1,1-, 1,2-, or 1,3-)cyclohexylene and (1,1- or 1,2-)cyclopentylene. "Substituted cycloalkylene" means an cycloalkylene group as defined above which is substituted with one or more "ring group substitutes" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Cyclic" or "Cyclyl" means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl as defined herein. The term "lower" as used in connection with the term cyclic is the same as noted herein regarding the cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

"Cyclyloxy" means a cyclyl-O- group wherein the cyclyl group is as herein described. Exemplary cycloalkoxy groups include cyclopentyloxy, cyclohexyloxy, quinuclidyloxy, pentamethylenesulfidoxy, tetrahydropyranyloxy, tetrahydrothiophenyloxy, pyrrolidinyloxy, tetrahydrofuranyloxy, or 7-oxabicyclo[2.2.1]heptanyloxy, hydroxytetrahydropyranyloxy, hydroxy-7-oxabicyclo[2.2.1]heptanyloxy, and the like.

"Cyclylsulfinyl" means a cyclyl-S(O)- group wherein the cyclyl group is as herein described.

"Cyclylsulfonyl" means a cyclyl-$S(O)_2$- group wherein the cyclyl group is as herein described.

"Cyclylthio" means a cyclyl-S- group wherein the cyclyl group is as herein described.

"Diazo" means a bivalent -N=N- radical.

"Displaceable moiety" means a group that where associated with L as defined herein is subject to being displaced by nucleophilic attack by a mono- or di-substituted amine moiety with or

without the presence of an agent that facilitates said attack, e.g., coupling agent. Exemplary displaceable moieties include hydroxy, aliphatic oxy, halo, N-oxysuccinimide, acyloxy, and the like.

"Effective amount" is means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

"Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl as defined herein. Preferred fused arylcycloalkenyls are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. "Substituted fused arylcycloalkenyl" means a fused arylcycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like.

"Fused arylcycloalkyl" means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. "Substituted fused arylcycloalkyl" means a fused arylcycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkyl includes 1,2,3,4-tetrahydro-naphthylene, and the like.

"Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl as defined herein. Preferred fused arylheterocyclenyls are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclenyl portion of the fused arylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused arylheterocyclenyl" means a fused arylheterocyclenyl group as defined above which is substituted with one or more "ring group

substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl portion of the fused arylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclenyl include 3H-indolinyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, and the like.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclyl portion of the fused arylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused arylheterocyclyl" means a fused arylheterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl portion of the fused arylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4- tetrahydroquinoline, 1H -2,3-dihydroisoindol- 2-yl, 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4- tetrahydrobenz[g]-isoquinolin-2-yl, and the like.

"Fused heteroarylcycloalkenyl" means a fused heteroaryl and cycloalkenyl as defined herein. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused heteroaryl-cycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcycloalkenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylcycloalkenyl" means a fused heteroarylcycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 30 which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcycloalkenyl may be a basic nitrogen atom.

The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkenyls include 5,6- dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5- dihydro-1H -benzimidazolyl, 4,5-di -hydrobenzoxazolyl, and the like.

"Fused heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl as defined herein. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused heteroarylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcycloalkyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylcycloalkyl" means a fused heteroarylcycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkyl include 5,6,7,8- tetrahydroquinolinyl, 5,6,7,8-tetra-hydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8- tetrahydroquinazolyl, 4,5,6,7 -tetrahydro-1H -benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5- diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, and the like.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom "Substituted fused heteroarylheterocyclenyl" means a fused heteroarylheterocyclenyl group as defined above which is substituted with one *or* more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused

heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulfur atom of the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S- oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclenyl include 7,8-dihydro[1, 7]naphthyridinyl, 1 ,2-dihydro[2,7]-naphthyridinyl, 6,7 -dihydro- 3H -imidazo [4,5- c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1 ,2-dihydro-1 ,6-naphthyridinyl, 1 ,2-dihydro-1, 7 -naphthyridinyl, 1 ,2-dihydro-1 ,8-naphthyridinyl. 1,2-dihydro-2,6-naphthyridinyl, and the like.

"Halo or halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Heteroaroyl" means an heteroaryl-CO- group wherein the heteroaryl group is as herein described. Exemplary heteroaroyl groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, 1- and 2-naphthoyl, pyridinoyl, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferably the ring system includes 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. Encompassed by heteroaryl are fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl and fused heteroarylheterocyclyl as defined herein when bonded through the heteroaryl moiety thereof. "Substituted heteroaryl" means a heteroaryl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. Exemplary heteroaryl and substituted heteroaryl groups include pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, , benzofurazanyl, azaindolyl, benzimidazolyl,

benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindolyl, 1,2,4-triazinyl, benzthiazolyl, furanyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, triazolyl, and the like. A preferred heteroaryl group is pyrazinyl.

"Heteroaryldiyl" means a bivalent radical derived from a heteroaryl, wherein the heteroaryl is as described herein. An exemplary heteroaryldiyl radical is optionally substituted pyridinediyl.

"Heteroarylsulfonylcarbamoyl" means a heteroaryl-SO_2-NH-C(=O)- group wherein the heteroaryl group is as herein described.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferably, the ring includes 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclenyl are fused arylheterocyclenyl and fused heteroarylheterocyclenyl as defined herein when bonded through the heterocyclenyl moiety thereof. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted heterocyclenyl" means a heterocyclenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetra-hydropyridine, 1,4,5,6-tetrahydro-pyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, and fluorodihydro-furanyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

Exemplary monocyclic thiaheterocyclenyl rings include dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferably, the ring system contains from 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclyl are fused arylheterocyclyl and fused heteroarylheterocyclyl as defined herein when bonded through the heterocyclyl moiety thereof. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. "Substituted heterocyclyl" means a heterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl may also be optionally oxidized to 20 the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclylene" means a bivalent heterocyclyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the heterocyclylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary heterocyclylene groups include (1,1-, 1,2- or 1,3-)piperidinylene and (1,1- or 1,2-)tetrahydrofuranylene. "Substituted heterocyclylene" means a heterocyclylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Hydrate" means a solvate wherein the solvent molecule(s) is/are H_2O.

"N -oxide" means a moiety of the following structure.

"Patient" includes both human and other mammals.

"Pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Exemplary esters include formates, acetates, propionates, butyrates, acrylates, ethylsuccinates, and the like.

"Pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups that may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propanoyl, butanoyl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds of this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion is provided in Design of Prodrugs, H. Bundgaard, ed., Elsevier (1985); Methods in Enzymology; K. Widder et al, Ed., Academic Press, 42, 309-396 (1985); A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bandaged, ed., Chapter 5; "Design and Applications of Prodrugs" 113-191 (1991);

Advanced Drug Delivery Reviews, H. Bundgard, 8, 1-38, (1992); J. Pharm. Sci., 77,285 (1988); Chem. Pharm. Bull., N. Nakeya et al, 32, 692 (1984); Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, 14 A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, E.B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulfamates, malonates, salicylates, propionates, methylene-bis-ß-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and laurylsulfonate salts, and the like. See, for example S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977) which is incorporated herein by reference. Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'- dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine,

dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.

"Ring group substituents" mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo anslogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH -C(O)-$CH_2$0H, -C(O)-CH_2SH -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl. heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl,3-hydoxy-1-methylpyrazoly, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl. cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, wherein Y^1, Y^2 and Y^3 are independently hydrogen, alkyl, aryl or heteroaryl. or for where the substituent is Y^1Y^2N-, then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. When a ring system is saturated or partially saturated, the "ring group substituents" further include, methylene (H2C=), oxo (O=) and thioxo (S=). Acidic/amide ring group substituents are carboxy (acid). -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3- cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydoxy-1-methylpyrazoly and Y^1Y^2NCO-. Non-acidic polar ring group substituents are hydroxy, oxo (O=), thioxo (S=), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or

its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heterearylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heterearylsulfinyl, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethenolates, methanolates, and the like.

Pharmacology

Experimental Methods and or Assays Used for Determining Activity:

<u>FLIPR Assay – human CXCR5:</u>

Changes in the intracellular Ca^{2+} are measured in RBL cell line stably transfected with human CXCR5 DNA. 9,000 cells/well are plated and incubated at 37°C, 5% CO_2 20h prior to the assay. On the following day, cells are washed once with assay buffer containing Hank's (Invitrogen, 14025-092) plus 20mM HEPES, pH 7.4 and loaded with dye by incubating for 30min at 37°C with 2 μM fluo-4/AM (Molecular Probes, F14202) in assay buffer plus 2.5mM probenecid. Cells are washed 3 times with assay buffer, then compounds in assay buffer plus 0.1% BSA are added into cells. Cells are washed 3 additional times with assay buffer, then stimulated with 10nM human CXCL13 (R&D, 801-CX/CF). Changes of intracellular Ca^{2+} are recorded using the 384-B FLIPR (Molecular Devices).

<u>FLIPR Assay – murine CXCR5</u>

Changes in the intracellular Ca^{2+} are measured in RBL cell line stably transfected with murine CXCR5 DNA. 9,000 cells/well are plated and incubated at 37°C, 5% CO_2 20h prior to

the assay. On the following day, cells are washed once with assay buffer containing Hank's (Invitrogen, 14025-092) plus 20mM HEPES, pH 7.4 and loaded with dye by incubating for 30min at 37°C with 2 µM fluo-4/AM (Molecular Probes, F14202) in assay buffer plus 2.5mM probenecid. Cellsare washed 3 times with assay buffer, then compounds in assay buffer plus 0.1% BSA are added into cells. Cells are washed 3 additional times with assay buffer, then stimulated with 6nM murine CXCL13 (R&D, 470-BC). Changes of intracellular Ca^{2+} are recorded using the 384-B FLIPR (Molecular Devices).

GTPγS Assay:

The [^{35}S]-GTPγS binding assay for CXCR5 is performed using membranes prepared from RBL cell line stably transfected with human CXCR5 DNA. 2.5 µM GDP, test compound at the desired concentration (or DMSO in the controls), 10µM un-labeled GTPγS (or buffer in controls) and 7.5µg cell membrane/well are mixed together (plate shaker) for 15min at RT. 750nM human CXCL13 and 400pM [^{35}S]-GTPγS are added and the plate shaken for 5min at RT. 1.134mg/well spa beads are then added and the plate shaken for 45min at RT. The reaction is stopped by centrifugation at 230g for 10 minutes and radioactivity measured on a Wallac Microbeta Trilux beta counter.

Chemotaxis Assay:

Wells in the assay plate are pre-coated with 150 µl RPMI (no phenol red) containing 1% BSA for 2h at room temperature. Pre-coating buffer is discarded and wells washed twice with CTX assay buffer (see below). CXCR5$^+$ HS Sultan cells (ATCC cat# CRL 1484) are added to the upper chamber of the transwell plate (Millipore Cat#MAMI C5S 10) at 0.6×10^5 cells / well and incubated with test compound for 15min at RT. CXCL13 ligand at 100nM (R&D, cat# 801-cx/cf) or CTX-buffer (RPMI no phenol red supplemented with 0.02% BSA, 1mM Na pyruvate) is added to the lower chamber. The two chambers are assembled and incubated at 37°C for 2h. The upper chamber is subsequently removed and cells in lower chamber are counted after adding colorimetric reagent (Promega Cat# G3581) and reading OD_{490}. CXCR5 specific migration = total migrated cell -spontaneous migrated cells (wells containing CTX buffer without ligand).

Experimental data below is a representation of inhibitory activity as indicated by IC_{50} values for the Examples herein. The particular embodiments below are exemplary and do not limit the equivalents pertaining thereto.

Table I

EXAMPLE	IC50
5	2.4
	0.493
18	3.05
7	0.844
	0.425
	0.105
38	0.675
9	0.47
11	2.93
13	1.06
24	ND
26	ND
44	~13
42	5.45
52	>30
46	18.6
119	>30
36	>30
56	>30
58	>30
48	>30
121	ND
29	~24
75	2.85
79	ND
87	0.268
81	~9.5
54	>30
77	ND
93	18.2
91	~27
89	17.35
97	0.537
103	0.98
99	~7.0
85	6.1
95	14.75
112	>30
111	~20.5
108	>30
109	>30
107	~30
116	>30
115	~10.15
113	>30

117	>30
123	18.3
125	0.099
127	2.3
128	15.26
132	0.056
21	0.266
135	0.093
130	3.87
133	0.535
32	~16
34	~19
138	8.2
143	0.232
146	0.446
144	0.023
141	1.05
139	0.087
60	>30
149	0.011
62	~30
152	0.013
64	>30
154	0.2
152	0.013
397	0.026
136	0.014
232	0.007
161	0.045
165	0.047
132	0.056
150	0.015
281	0.030
158	0.015
395	0.009
388	0.005
392	0.038
159	0.017

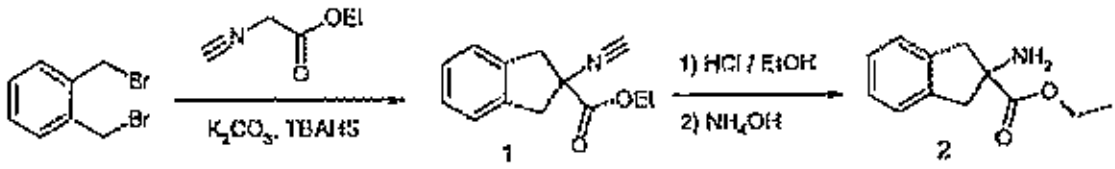
Preparation of Compounds of the Invention

The starting materials and intermediates of compounds of the invention may be prepared by the application or adaptation of known methods described below, their obvious chemical equivalents, or, for example, as described in literature by R.C. Larock in Comprehensive Organic Transformations, VCH publishers (1989).

Purification by HPLC refers to preparative high performance liquid chromatography using the following conditions: [C18 column, 10 micron particle size, gradient elution: 20-100% CH_3CN (0.1% TFA) in H_2O (0.1% TFA)].

EXAMPLES

EXAMPLE 1



Isocyano-indan-2-carboxylic acid ethyl ester (1) :

To a solution of ethyl isocyanoacetate (4.29g, 37.9mmol) in anhydrous ACN (400mL) is added anhydrous K_2CO_3 (K_2SO_4, 31.4g, 227mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.57g, 7.58mmol), and 1,2-bis-bromomethyl-benzene (10.0g, 37.9mmol). The resulting heterogeneous mixture is stirred at 75°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filter cake is washed with ACN (20mL) and the filtrate is concentrated *in vacuo*. The residue is dissolved in ethyl ether (150mL) and washed with water (1 x 10mL) and brine (3 x 10mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel; gradient elution: 20-100% EtOAc in heptane) to give a pure product as white solid (8.0g, 49%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.25 (s, 4H)

LC/MS (ES+) m/z = 449.25

EXAMPLE 2

2-Amino-indan-2-carboxylic acid ethyl ester (2):

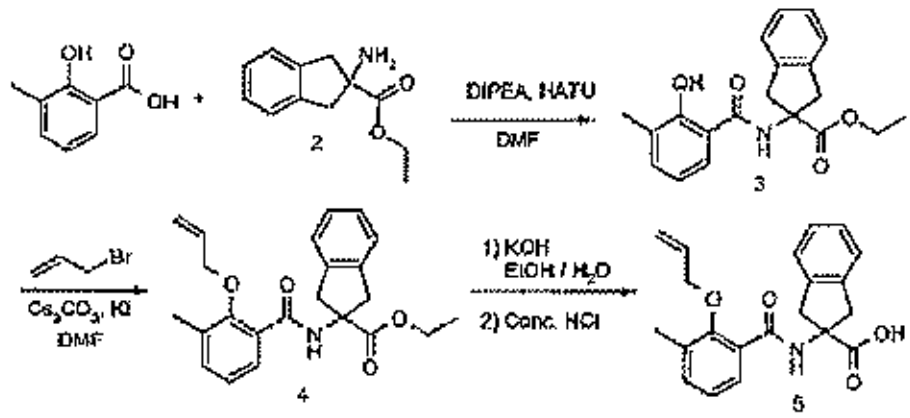
To a solution of 2-isocyano-indan-2-carboxylic acid ethyl ester (1) (8.0g, 37.2mmol) in absolute EtOH (200mL) is added concentrated HCl (5mL) dropwise. The resulting solution is stirred at RT for 5h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt

is dissolved in water (100mL) and extracted with of ethyl ether (3 x 5mL) to remove unwanted organic impurities. The aqueous layer is brought to pH=10 by addition of NH_4OH solution and then extracted with EtOAc (3 x 50mL). The combined EtOAc layer is washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (4.7g, 62%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.16-7.23 (m, 4H)

LC/MS (EZ+) m/z = 206.08

EXAMPLE 3



<u>2-(2-Hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3):</u>

To a solution of 2-hydroxy-3-methyl-benzoic acid (3.65g, 24mmol), 2-amino-indan-2-carboxylic acid ethyl ester (5.00g, 24mmol), HATU [O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium PF_6] (11.0g, 29mmol) in anhydrous DMF (30mL) is added DIPEA (8.30mL, 50mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel, gradient elution: 10-80% EtOAc in heptane) to give a pure product (3) as white solid (5.5g, 67%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 2.23(s, 3H), 3.40(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 6.70(t, 1H), 6.84(s, 1H), 7.15-7.25(m, 6H), 12.21(s, 1H)

LC/MS (ES+) m/z = 340.15

EXAMPLE 4

2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (4):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (300mg, 0.88mmol), anhydrous Cs_2CO_3 (573mg, 1.76mmol), and KI (30mg, 0.18mmol) in DMF (8mL) is added 3-bromo-propene (90µL, 1.06mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-30% EtOAc in heptane) to give a pure product (4) as white solid (303mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 2.26(s, 3H), 3.33(d, 2H), 3.75(d, 2H), 4.25(q, 2H), 5.21(d, 1H), 5.33(d, 1H), 5.86(m, 1H), 7.09(t, 1H), 7.19(br s 4H), 7.27(d, 1H), 7.88(d, 1H), 8.43(s, 1H)

LC/MS (ES+) m/z = 380.20

EXAMPLE 5

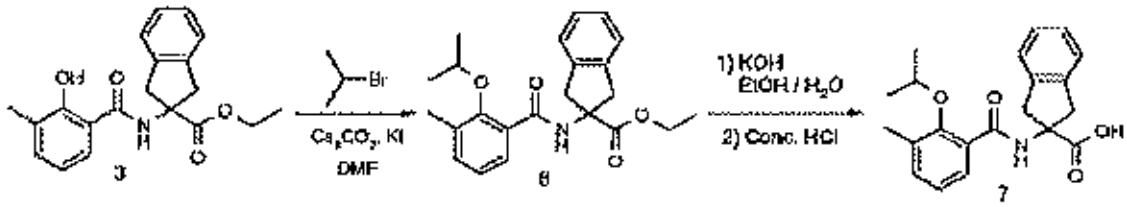
2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (5):

The mixture of 2-(2-allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (4) (168mg, 0.44mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (5) as white solid (150mg, 97%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 2.26(s, 3H), 3.34(d, 2H), 3.77(d, 2H), 4.23(d, 2H), 5.20(d, 1H), 5.32(d, 1H), 5.84(m, 1H), 7.10(t, 1H), 7.16-7.23(m, 4H), 7.29(d, 1H), 7.83(dd, 1H), 8.57(s, 1H)

LC/MS (ES+) m/z = 352.15

EXAMPLE 6



2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (300mg, 0.88mmol), anhydrous Cs_2CO_3 (573mg, 1.76mmol), and KI (30mg, 0.18mmol) in DMF (10mL) is added 2-bromo-propane (330µL, 3.52mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (6) as white solid (174mg, 52%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.03(d, 6H), 1.24(t, 3H), 2.25(s, 3H), 3.34(d, 2H), 3.77(d, 2H), 4.21(m, 1H), 4.25(q, 2H), 7.07(t, 1H), 7.17-7.26(m, 5H), 7.85(dd, 1H), 8.31(s, 1H)
LC/MS (ES+) m/z = 382.18

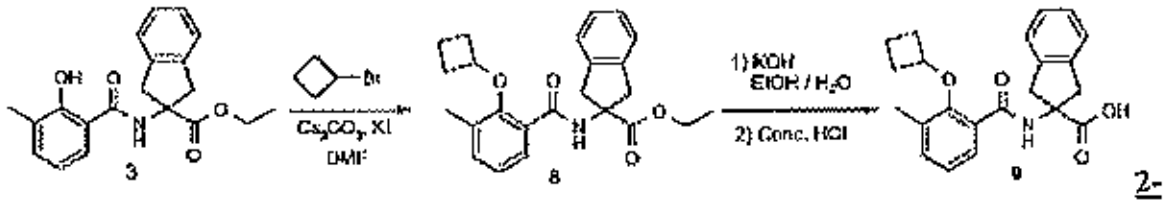
EXAMPLE 7

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (7):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6) (265mg, 0.69mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and the solution acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (7) as white solid (244mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.98(d, 6H), 2.24(s, 3H), 3.41(d, 2H), 3.85(d, 2H), 4.14(m, 1H), 7.08(t, 1H), 7.18-7.30(m, 5H), 7.88(d, 1H), 8.52(s, 1H)
LC/MS (ES+) m/z = 354.16

EXAMPLE 8



2-

(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (8):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (769mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added bromo-cyclobutane (130µL, 1.42mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (8) as white solid (320mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.18-1.34(m, 1H), 1.41-1.52(m, 1H), 1.87-2.07(m, 4H), 2.26(s, 3H), 3.36(d, 2H), 3.78(d, 2H), 4.22 - 4.29(m, 1H), 4.24(q, 2H), 7.07(t, 1H), 7.17-7.27(m, 5H), 7.86(dd, 1H), 8.33(s, 1H)

LC/MS (ES+) m/z = 394.19

EXAMPLE 9

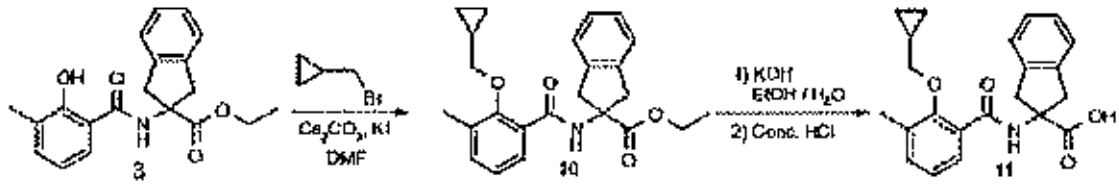
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (9):

The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (8) (250mg, 0.64mmol) and KOH (680mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and the solution acidified with conc. HCl until pH~3 to yield a precipitate. The precipitate is filtered to give a pure product (9) as white solid (190mg, 81%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.24(m, 1H), 1.45(m, 1H), 1.87-2.01(m, 4H), 2.26(s, 3H), 3.40(d, 2H), 3.81(d, 2H), 4.26(m, 1H), 7.08(t, 1H), 7.18-7.29(m, 5H), 7.82(dd, 1H), 8.48(s, 1H)

LC/MS (ES+) m/z = 366.16

EXAMPLE 10



<u>2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (10):</u>

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (769mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added bromomethylcyclopropane (229μL, 2.36mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (10) as white solid (330mg, 71%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.17(m, 2H), 0.50(m, 2H), 0.91(m, 1H), 1.24(t, 3H), 2.26(s, 3H), 3.36(d, 2H), 3.54(d, 2H), 3.79(d, 2H), 4.24(q, 2H), 7.08(t, 1H), 7.15-7.27(m, 5H), 7.86(dd, 1H), 8.44(s, 1H)
LC/MS (ES+) m/z = 394.18

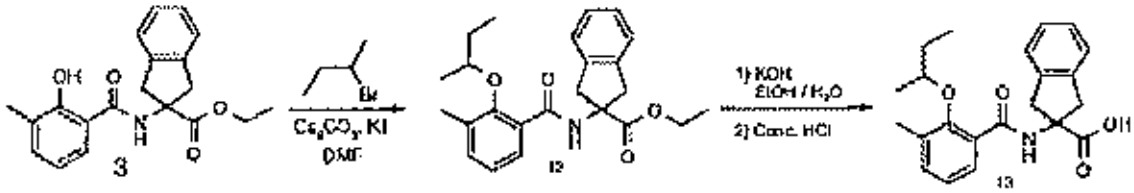
EXAMPLE 11

<u>2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (11):</u>
The mixture of 2-(2-cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (10) (240mg, 0.61mmol) and KOH (500mg, 8.93mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (11) as white solid (223mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.11(m, 2H), 0.51(m, 2H), 0.84(m, 1H), 2.26(s, 3H), 3.46(dd, 4H), 3.88(d, 2H), 7.11(t, 1H), 7.17-7.32(m, 5H), 7.89(d, 1H), 8.74(s, 1H)

LC/MS (ES+) m/z = 366.17

EXAMPLE 12



2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (12):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (574mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added 2-bromobutane (508µL, 4.72mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (12) as white solid (395mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.80(t, 3H), 0.93(d, 3H), 1.22-1.30(m, 4H), 1.48(m, 1H), 2.25(s, 3H), 3.33(dd, 2H), 3.76(dd, 2H), 3.97(m, 1H), 4.25(q, 2H), 7.01(t, 1H), 7.17-7.26(m, 5H), 7.87(dd, 1H), 8.35(s, 1H)

LC/MS (ES+) m/z = 396.19

EXAMPLE 13

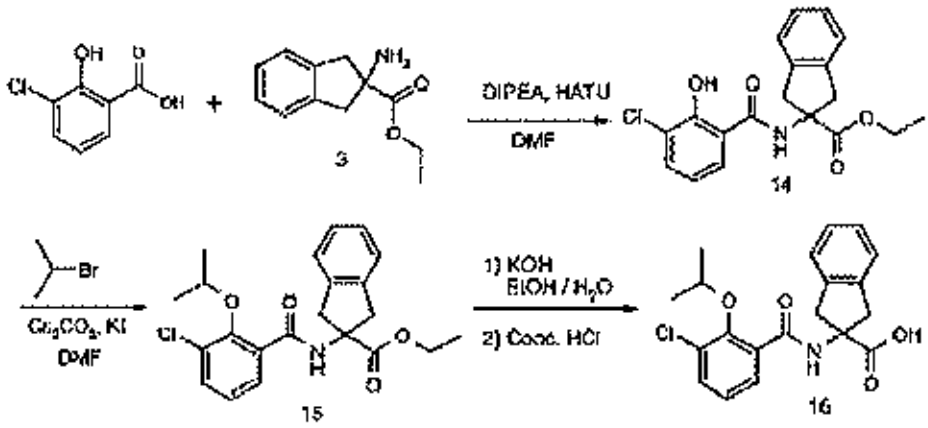
2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (13):

The mixture of 2-(2-sec-butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (12) (176mg, 0.44mmol) and KOH (500mg, 8.93mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (13) as white solid (162mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.79(t, 3H), 0.86(d, 3H), 1.18(m, 1H), 1.49(m, 1H), 2.25(s, 3H), 3.42(t, 2H), 3.86(dd, 2H), 3.91(m, 1H), 7.09(t, 1H), 7.19-7.31(m, 5H), 7.90(d, 1H), 8.59(s, 1H)

LC/MS (ES+) m/z = 368.17

EXAMPLE 14



2-(3-Chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14):

To a solution of 3-chloro-2-hydroxy-benzoic acid (413mg, 2.4mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (500mg, 2.4mmol), HATU (1.1g, 2.9mmol) in anhydrous DMF (10mL) is added DIPEA (0.88ml, 5.3mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (14) as white solid (420mg, 49%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.42(d, 2H), 3.73(d, 2H), 4.25(q, 2H), 6.76(t, 1H), 6.97(s, 1H), 7.23-7.29(m, 5H), 7.47(dd, 1H), 12.5(s, 1H)

LC/MS (ES+) m/z = 360.07, 362.08

EXAMPLE 15

2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (15):

To a suspension of 2-(3-chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14) (150mg, 0.42mmol), anhydrous Cs_2CO_3 (274mg, 0.84mmol), and KI (13mg, 0.08mmol) in DMF (7mL) is added 3-bromo-propene (237μL, 2.52mmol). The resulting reaction

suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (15) as white solid (137mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.05(d, 6H), 1.24(t, 3H), 3.33(d, 2H), 3.76(d, 2H), 4.25(q, 2H), 4.56(m, 1H), 7.11(t, 1H), 7.19-7.26(m, 4H), 7.46(dd, 1H), 7.95(dd, 1H), 8.28(s, 1H)
LC/MS (ES+) m/z = 402.13, 404.14

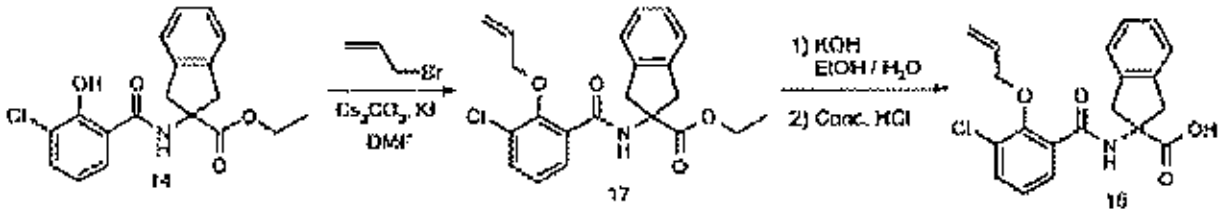
EXAMPLE 16

2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid (16):

The mixture of 2-(3-chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (15) (122mg, 0.30mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (16) as white solid (119mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.01(d, 6H), 3.40(d, 2H), 3.84(d, 2H), 4.55(m, 1H), 7.13(t, 1H), 7.19-7.26(m, 4H), 7.48(dd, 1H), 7.98(dd, 1H), 8.43(s, 1H)
LC/MS (ES+) m/z = 374.11, 376.13

EXAMPLE 17



2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid ethyl ester (17):

To a suspension of 2-(3-chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14) (250mg, 0.69mmol), anhydrous Cs_2CO_3 (453mg, 1.39mmol), and KI (23mg, 0.14mmol) in DMF (10mL) is added 3-bromo-propene (70μL, 0.83mmol). The resulting reaction

suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (17) as white solid (160mg, 58%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 3.32(d, 2H), 3.75(d, 2H), 4.25(q, 2H), 4.41(d, 2H), 5.20-5.34(m, 2H), 5.88(m, 1H), 7.13-7.26(m, 5H), 7.49(dd, 1H), 7.97(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 402.13, 404.14

EXAMPLE 18

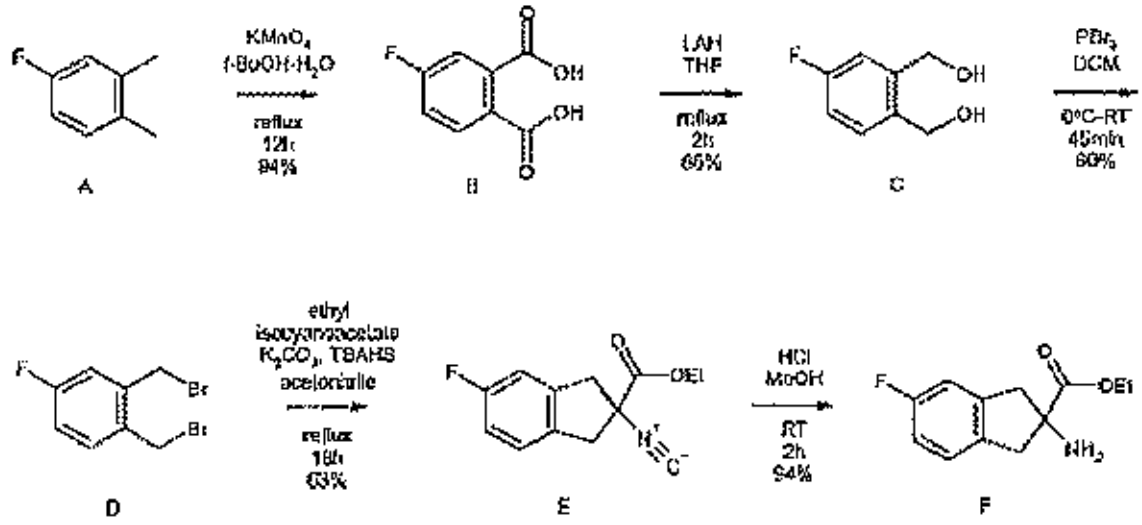
2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid (18):

The mixture of 2-(2-allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid ethyl ester (17) (140mg, 0.35mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. After filtration, the solid is purified by HPLC to give a pure product (18) as white solid (88mg, 68%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.35(d, 2H), 3.78(d, 2H), 4.41(d, 2H), 5.21-5.34(m, 2H), 5.87(m, 1H), 7.13-7.30(m, 5H), 7.50 (dd, 1H), 7.93(dd, 1H), 8.49(s, 1H)
LC/MS (ES+) m/z = 372.09, 374.10

EXAMPLE 19

2-Amino-5-fluoroindane-2-carboxylic acid ethyl ester



Preparation of B: 4-Fluoro-1,2-dimethyl benzene A (50.0g, 402.7mmol) and a large excess of $KMnO_4$ (400g, 2.54mol) are dissolved in 1500mL of a water/t-butanol (70/30%, v/v) mixture. The reaction mixture is refluxed overnight. EtOH (900mL) is added to destroy unreacted $KMnO_4$ and the alcohols are distilled off. The resulting brown suspension is filtered through a celite pad. The colorless solution is concentrated and acidified with conc. HCl to pH 1. The product is filtered and the aqueous phase is extracted with EtOAc and dried over Na_2SO_4. 70.0g (94%) of white solid B is obtained after evaporation under reduced pressure.

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.39 (m, 1H), 7.63 (br s, 1H), 7.99 (br s, 1H).

Preparation of C: LAH (37.5g, 989 mmol) is added to THF (850mL). The mixture is cooled in an ice bath and 4-fluorophthalic acid B (70.0g, 380 mmol) in THF (420mL) is added dropwise. After addition, the reaction mixture is refluxed for 2h. The mixture is cooled in an ice bath and water (35mL), aqueous 15% NaOH (35mL) and water (70mL) are added dropwise. The solid material is removed by filtration and washed with DCM, and the combined organic solutions are dried over Na_2SO_4 and evaporated under reduced pressure to give 51.2g (86%) of C.

^{1}H-NMR (400 MHz, $CDCl_3$) : 4.71 (t, J=4.5 Hz, 4H), 6.98 (m, 1H), 7.08 (m, 1H), 7.29 (m, 1H).

Preparation of D: To a solution of 2-hydroxy-methyl-5-fluoro-phenyl-methanol C (51.2g, 327.8 mmol) in 520mL of DCM is added phosphorous tribromide (37.3mL, 393.5 mmol) in DCM (520mL) dropwise at 0°C under a N_2 atmosphere and stirred for 45 min. The reaction mixture is quenched with water (70mL) added slowly and extracted with EtOAc, washed with water, satd. Na_2SO_4 solution and brine. The organic layer is evaporated under reduced pressure to give crude product, which is purified by silica gel 100-200 mesh column eluting with hexane to give 55.8g (60 %) of D.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.61 (m, 4H), 6.99 (m, 1H), 7.07 (m, 1H), 7.33 (m, 1H).

Preparation of E: A solution of 5-fluoro-1,2-bisbromomethylbenzeng (20.4g, 72.3 mmol), ethyl isocyanoacetate (5.7mL, 51mmol), tetrabutylammonium hydrogen sulfate (6.7g, 19.7mmol) and dry K_2SO_4 (41.8g, 303mmol) in ACN (1500mL) is refluxed for 18h. After completion of reaction, the mixture is cooled and filtered. The filtrate is concentrated under reduced pressure and dissolved with EtOAc. The organic layer is washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass obtained is purified by silica gel 100-200 mesh column eluting with 5% EtOAc-hexane to give 10.8g (63%) of E.

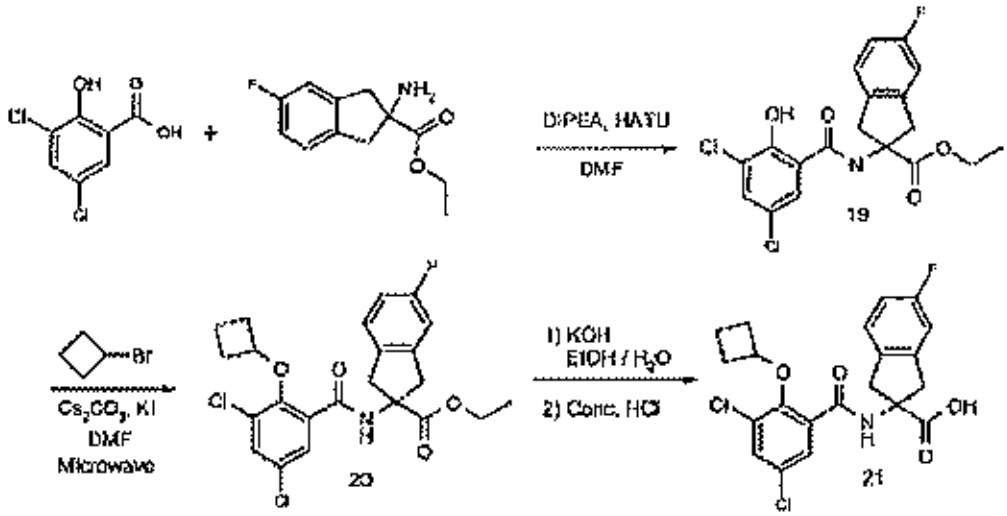
^{1}H-NMR (400 MHz, $CDCl_3$): 1.32 (m, 3 H), 3.43 (m, 2H), 3.66 (m, 2H), 4.32 (m, 2H), 6.94 (m, 2H), 7.17 (m, 1H).

Preparation of F: A methanolic solution of conc. HCl (35 %) (9.3mL in 110mL of MeOH) is added dropwise to a methanolic solution of 5-fluoro-2-isocyano-indan-2-carboxilic acid ethyl ester E (17.6g, 75.4 mmol) at RT and the mixture is stirred for 2h. The mixture is then neutralized by saturated $NaHCO_3$ solution and extracted with DCM (500mL). The organic layer is washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure to obtain 16.0g (94%) of F as yellowish semi solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (q, 3H), 1.62 (br s, 2H), 2.84 (m, 2H), 3.50 (q, 2H), 4.20 (m, 2H), 6.88 (m, 2H), 7.12 (t, J=7.6 Hz, 1H). ^{1}H-NMR (400 MHz, D_2O exchange, $CDCl_3$) : 1.26 (q, 3H), 2.83 (m, 2H), 3.49 (q, 2H), 4.20 (m, 2H), 6.88 (m, 2H), 7.12 (t, J=7 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) : 13.98, 45.14, 45.83, 61.21, 65.28, 111.82, 113.59, 125.54,

135.70, 142.44, 163.35, 176.05. IR (Neat): 1728 cm^{-1}. FIA-MS: 234 $[M+H]^+$. Qualitative GC-FID showed purity of 19 is 96.32 % (% by area normalization).

EXAMPLE 20



2-(3,5-Dichloro-2-hydroxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (19):

To a solution of 3,5-dichloro-2-hydroxy-benzoic acid (500mg, 2.42mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester F (1.08g, 4.84mmol), HATU (1.10g, 2.89mmol) in anhydrous DMF (15mL) is added DIPEA (599µl, 3.63mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (A) as white solid (779mg, 78%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.24(t, 3H), 3.39(dd, 2H), 3.68(dd, 2H), 4.24(q, 2H), 6.91-6.94(m, 2H), 7.14-7.18(m, 1H), 7.46(d, 1H), 7.52(d, 1H), 7.92(s, 1H), LC/MS (ES+) m/z = 412.06, 414.06

EXAMPLE 20

2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (20):

To a suspension 2-(3,5-dichloro-2-hydroxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (19) (624mg, 1.51mmol), anhydrous Cs_2CO_3 (984mg, 3.02mmol), and KI (50mg, 0.30mmol) in DMF (20mL) is added bromocyclobutane (711µL, 7.55mmol). The resulting reaction suspension is covered with argon and ran in a microwave reaction: 110°C, 2h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-50% EtOAc in heptane) to give a pure product (20) as white solid (365mg, 52%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.23-1.38(m, 4H), 1.51-1.55(m, 1H), 1.94-2.07(m, 4H), 3.32(t, 2H), 3.73(dd, 2H), 4.26(q, 2H), 4.58(m, 1H), 6.88-6.96(m, 2H), 7.18(br s, 1H), 7.47(s, 1H), 7.93(s, 1H), 8.27(s, 1H),
LC/MS (ES+) m/z = 466.12, 468.12

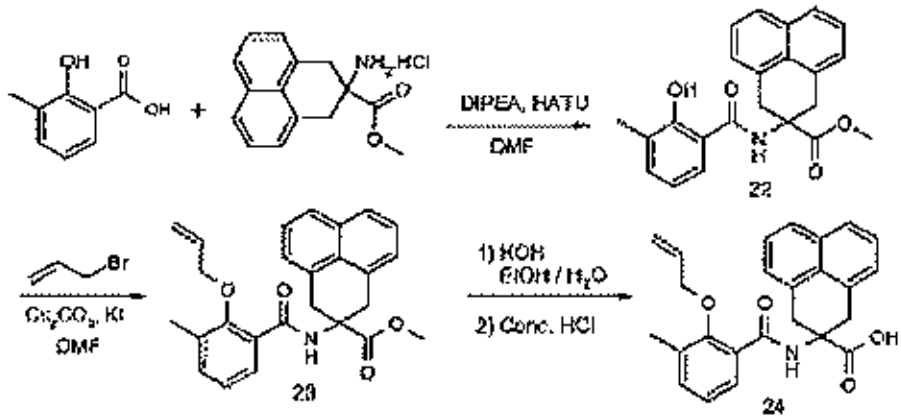
EXAMPLE 21

<u>2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid (21):</u>

The mixture of 2-(3,5-dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (20) (300mg, 0.64mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 6h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (21) as white solid (200mg, 71%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.32(m, 1H), 1.50(m, 1H), 1.92-2.09(m, 4H), 3.36(t, 2H), 3.75(dd, 2H), 4.56(m, 1H), 6.91-6.96(m, 2H), 7.16-7.20(m, 1H), 7.48(dd, 1H), 7.90(dd, 1H), 8.37(s, 1H),
LC/MS (ES+) m/z = 438.09, 440.08

EXAMPLE 22



2-(2-Hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22):

To a solution of 2-hydroxy-3-methyl-benzoic acid (1.12g, 7.4mmol), 2-amino-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (2.05g, 7.4mmol), HATU (3.38g, 8.9mmol) in anhydrous DMF (28mL) is added DIPEA (4.89mL, 29.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (300g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give the pure product (22) as white solid (353mg, 13%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.18(s, 1H), 3.70(s, 4H), 3.85(s, 3H), 6.30(s, 1H), 6.48(t, 1H), 6.58(d, 1H), 7.13(d, 1H), 7.33(d, 2H), 7.44(t, 2H), 7.75(d, 2H), 12.08(s, 1H)

LC/MS (ES+) m/z = 376.14

EXAMPLE 23

2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid ethyl ester (23):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22) (175mg, 0.47mmol), anhydrous Cs_2CO_3 (306mg, 0.94mmol), and KI (15.6mg, 0.09mmol) in DMF (8mL) is added 3-bromo-propene (199μL, 2.35mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The

residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (23) as white solid (107mg, 55%).

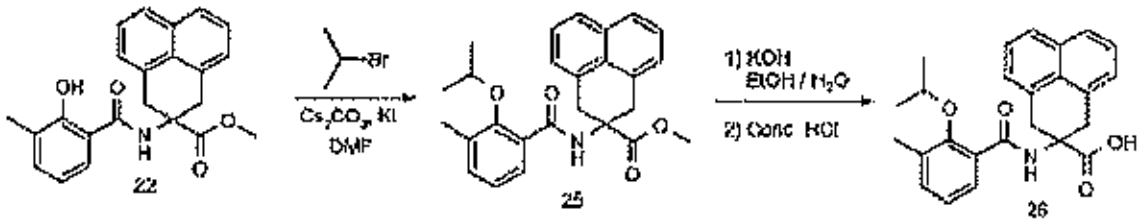
^{1}H NMR ($CDCl_3$, 300MHz): δ 2.08(s, 3H), 3.68-3.73(m, 6H), 3.84(s, 3H), 5.02-5.11(m, 2H), 5.28-5.40(m, 1H), 6.70(t, 1H), 7.16(dd, 1H), 7.28(dd, 1H), 7.39(t, 2H), 7.69(d, 2H), 7.79(dd, 1H), 8.10(s, 1H)
LC/MS (ES+) m/z = 416.23

EXAMPLE 24

2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid (24):
The mixture of 2-(2-allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid ethyl ester (23) (107mg, 0.26mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out from the water. The precipitate is filtered to give a pure product (24) as white solid (98mg, 94%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 2.09(s, 3H), 3.71-3.74(m, 6H), 5.06-5.11(m, 2H), 5.28-5.41(m, 1H), 7.01(t, 1H), 7.18(dd, 1H), 7.30(dd, 1H), 7.41(t, 2H), 7.70(d, 2H), 7.75(dd, 1H), 8.20(s, 1H)
LC/MS (ES+) m/z = 402.16

EXAMPLE 25



2-(2-Isopropoxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (25):
To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22) (175mg, 0.47mmol), anhydrous Cs_2CO_3 (306mg, 0.94mmol), and KI (16mg, 0.09mmol) in DMF (8mL) is added 2-bromo-propane (220μL, 2.35mmol). The

resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give the pure product (25) as white solid (143mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.51(d, 6H), 2.10(s, 3H), 3.71(s, 4H), 3.81(s, 3H), 3.81-3.89(m, 1H), 6.98(t, 1H), 7.16(dd, 1H), 7.31(d, 2H), 7.41(t, 2H), 7.71(d, 2H), 7.82(dd, 1H), 8.04(s, 1H)

LC/MS (ES+) m/z = 418.23

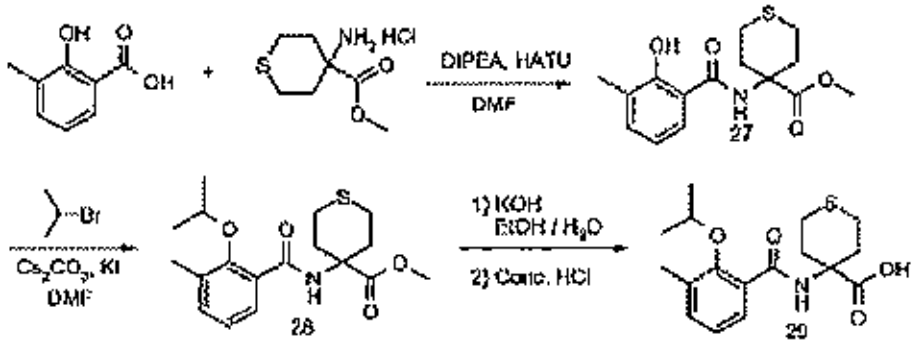
EXAMPLE 26

2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid (26): The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (25) (143mg, 0.34mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (26) as white solid (127mg, 93%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.49(d, 6H), 2.10(s, 3H), 3.71(s, 4H), 3.81(m, 1H), 6.99(t, 1H), 7.16(d, 1H), 7.33(d, 2H), 7.42(t, 2H), 7.72(d, 2H), 7.79(dd, 1H), 8.12(s, 1H)

LC/MS (ES+) m/z = 404.17

EXAMPLE 27



4-(2-hydroxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (27):

To a solution of HCl salt of 4-amino-tetrahydro-thiopyran-4-carboxylic acid methyl ester (529mg, 2.5mmol), 2-hydroxy-3-methyl-benzoic acid (380mg, 2.5mmol), HATU (1.14g, 3.0mmol) in anhydrous DMF (20mL) is added DIPEA (1.66mL, 10mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 10-80% EtOAc in heptane) to give a pure product (27) as white solid (102mg, 13%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.41(m, 4H), 2.72-2.80(m, 4H), 3.74(s, 3H), 6.36(s, 1H), 6.78(t, 1H), 7.25-7.30(m, 2H), 12.00(s, 1H)
LC/MS (ES+) m/z = 310.17

EXAMPLE 28

4-(2-Isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (28):

To a suspension of 4-(2-hydroxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (27) (98mg, 0.32mmol), anhydrous Cs_2CO_3 (208mg, 0.64mmol), and KI (11mg, 0.06mmol) in DMF (5mL) is added 2-bromopropane (150μL, 1.6mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (28) as white solid (92mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35(d, 6H), 2.33(s, 3H), 2.33-2.40(m, 4H), 2.63-2.69(m, 2H), 2.76-2.81(m, 2H), 3.76(s, 3H), 4.39(m, 1H), 7.10(t, 1H), 7.31(d, 1H), 7.84(dd, 1H), 8.28(s, 1H)
LC/MS (ES+) m/z = 352.13

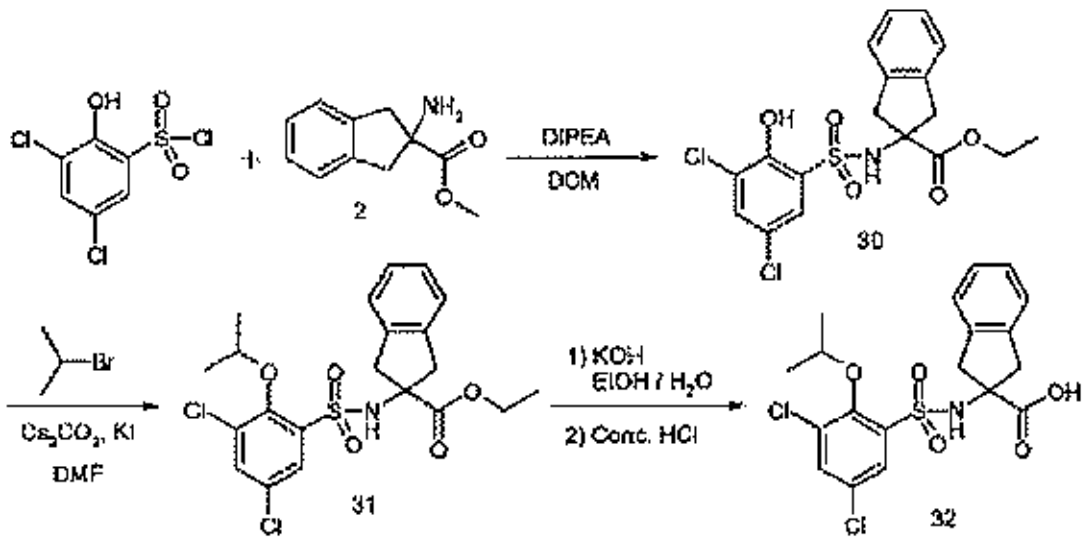
EXAMPLE 29

4-(2-Isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid (29):

The mixture of 4-(2-isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (28) (75mg, 0.21mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (29) as a pale yellow solid (68mg, 94%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.32(d, 6H), 2.33(s, 3H), 2.41-2.43(m, 4H), 2.64-2.74(m, 4H), 4.37(m, 1H), 7.11(t, 1H), 7.33(d, 1H), 7.86(dd, 1H), 8.42(s, 1H), 9.07(br s, 1H)
LC/MS (ES+) m/z = 338.11

EXAMPLE 30



2-(3,5-Dichloro-2-hydroxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (30):

To a solution of 2-amino-indan-2-carboxylic acid ethyl ester (3.14g, 15.3mmol) and 3,5-dichloro-2-hydroxy-benzenesulfonyl chloride (1g, 3.82mmol) in anhydrous DCM (dichloromethane, 20mL) is added DIPEA (631µL, 3.82mmol). The resulting solution is stirred at RT for 1 hour. The reaction solution is diluted in DCM (50mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (30) as white solid (450mg, 27%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.25(d, 2H), 3.57(d, 2H), 4.18(q, 2H), 5.60(s, 1H), 7.04-7.07(m, 2H), 7.14-7.17(m, 2H), 7.43(d, 1H), 7.49(d, 1H), 8.30(br s, 1H)
LC/MS (ES+) m/z = 447.04, 449.04, 430.01

EXAMPLE 31

2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (31):

To a suspension of 2-(3,5-dichloro-2-hydroxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (30) (226mg, 0.53mmol), anhydrous Cs_2CO_3 (300mg, 0.92mmol), and KI (15mg, 0.09mmol) in DMF (15mL) is added 2-bromopropane (432μL, 4.60mmol). The resulting reaction suspension is filled with argon and run in a microwave reaction: 110°C, 2.5h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-60% EtOAc in heptane) to give a pure product (31) as a white semi-solid (248mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.23(t, 3H), 1.27(d, 6H), 3.19(d, 2H), 3.50(d, 2H), 4.10(q, 2H), 5.12(m, 1H), 5.75(s, 1H), 6.98-7.01(m, 2H), 7.12-7.15(m, 2H), 7.47(dd, 1H), 7.58(dd, 1H),
LC/MS (ES+) m/z = 494.0

EXAMPLE 32

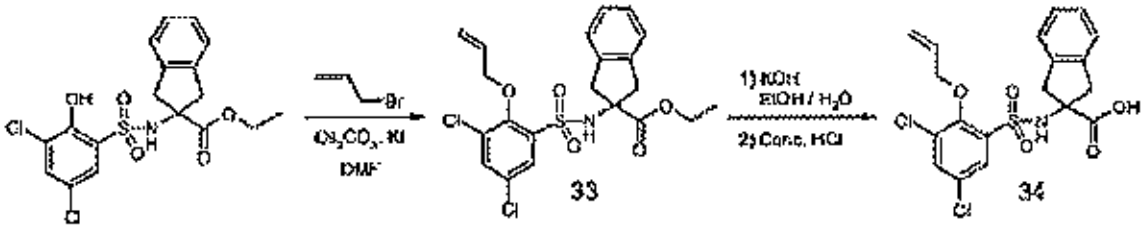
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid (32):

The mixture of 2-(3,5-dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (31) (248mg, 0.52mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (32) as white solid (230mg, 100%).

^{1}H NMR (CDOD, 300MHz): δ 1.27(d, 6H), 3.23(d, 2H), 3.48(d, 2H), 5.05(m, 1H), 6.98-7.01(m, 2H), 7.08-7.12(m, 2H), 7.44(d, 1H), 7.60(d, 1H)

LC/MS (ES-) m/z = 442.08, 444.08

EXAMPLE 33



<u>2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (33):</u>

To a suspension of 2-(3,5-dichloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (10) (200mg, 0.46mmol), anhydrous Cs_2CO_3 (300mg, 0.92mmol), and KI (15mg, 0.09mmol) in DMF (15mL) is added 3-bromo-propene (390µL, 4.6mmol). The resulting reaction suspension is filled in argon and run in a microwave reaction: 110°C, 2h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-60% EtOAc in heptane) to give a pure product (33) as white solid (162mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22(t, 3H), 3.21(d, 2H), 3.52(d, 2H), 4.09(q, 2H), 4.55(d, 2H), 5.36(dd, 2H), 5.68(s, 1H), 6.05(m, 1H), 6.99-7.02(m, 2H), 7.12-7.14(m, 2H), 7.52(d, 1H), 7.58(d, 1H)

LC/MS (ES-) m/z = 468.10, 470.10

EXAMPLE 34

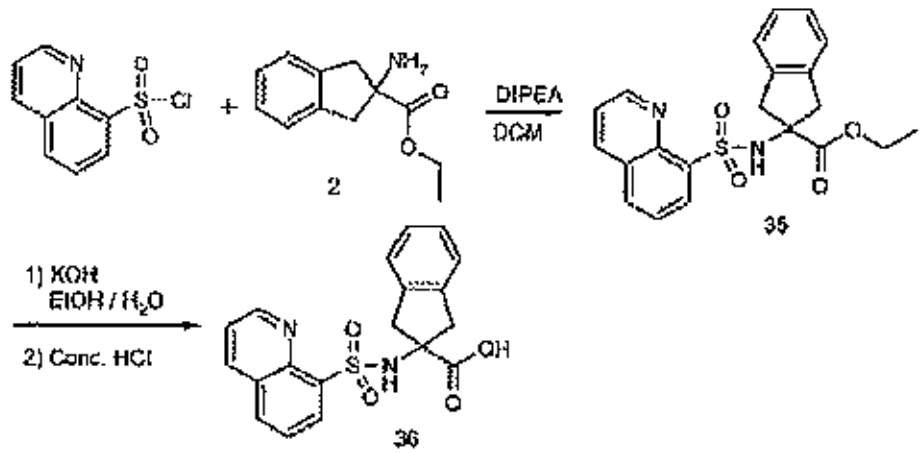
<u>2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid (34):</u>

The mixture of 2-(2-allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (33) (143mg, 0.30mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3.

After filtration, the solid is purified by HPLC to give a pure product (34) as white solid (91mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.24(d, 2H), 3.58(d, 2H), 4.53(d, 2H), 5.36(dd, 2H), 5.72(s, 1H), 6.03(m, 1H), 7.02-7.04(m, 2H), 7.13-7.17(m, 2H), 7.34(d, 1H), 7.60(d, 1H)
LC/MS (ES+) m/z = 459.03, 461.02, 442.00

EXAMPLE 35



2-(Quinoline-8-sulfonylamino)-indan-2-carboxylic acid ethyl ester (35):

To a solution of quinoline-8-sulfonyl chloride (400mg, 1.76mmol), 2-amino-indan-2-carboxylic acid ethyl ester (361mg, 1.76mmol) in anhydrous DCM (8mL) is added DIPEA (291µL, 1.76mmol). The resulting solution is stirred at RT overnight. The reaction solution is diluted with DCM (40mL), washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (35) as white solid (245mg, 35%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.08(t, 3H), 3.20(d, 2H), 3.46(d, 2H), 3.94(q, 2H), 6.74-6.78(m, 2H), 6.86-6.90(m, 2H), 7.32(s, 1H), 7.39(dd, 1H), 7.64(t, 1H), 8.01(dd, 1H), 8.18(dd, 1H), 8.34(dd, 1H), 8.67(dd, 1H),
LC/MS (ES+) m/z = 397.11

EXAMPLE 36

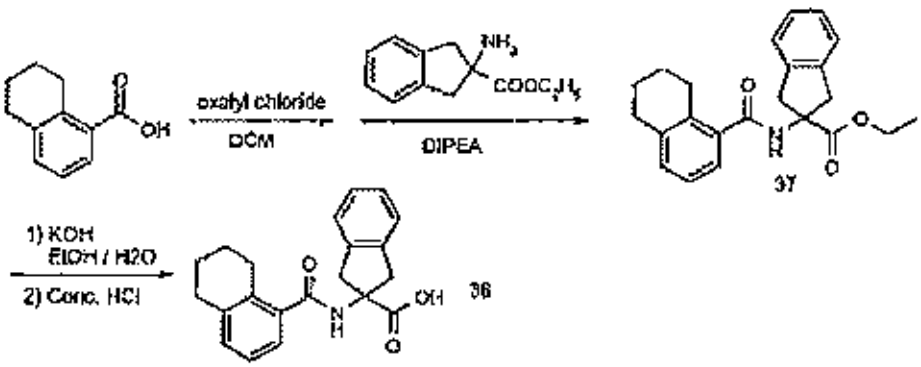
2-(Quinoline-8-sulfonylamino)-indan-2-carboxylic acid (36):

The mixture of 2-(quinoline-8-sulfonylamino)-indan-2-carboxylic acid ethyl ester (35) (210mg, 0.53mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (36) as white solid (195mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.18(d, 2H), 3.46(d, 2H), 6.66-6.69(m, 2H), 6.81-6.84(m, 2H), 7.40(dd, 1H), 7.65(t, 1H), 8.02(d, 1H), 8.18(dd, 1H), 8.34(dd, 1H), 8.64(dd, 1H)

LC/MS (ES+) m/z = 369.10

EXAMPLE 37



2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (500mg, 2.84mmol) in DCM (10mL) is added oxalyl chloride (0.50mL, 5.68mmol) dropwise. The resulting solution is stirred at RT for 2h. After the removal of DCM and excess oxalyl chloride, the residue, 2-amino-indan-2-carboxylic acid ethyl ester (583mg, 2.84mmol) and DIPEA (1.88mL, 11.3mmol) are dissolved in DCM (20mL). The resulting solution is stirred overnight. The reaction solution is diluted with DCM (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give the pure product (37) as white solid (610mg, 59%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(m, 4H), 2.76(m, 2H), 2.84(m, 2H), 3.34(d, 2H), 3.75d, 2H), 4.72(q, 2H), 6.20(s, 1H), 7.02-7.12(m, 3H), 7.18-7.25(m, 4H)
LC/MS (ES+) m/z = 364.18

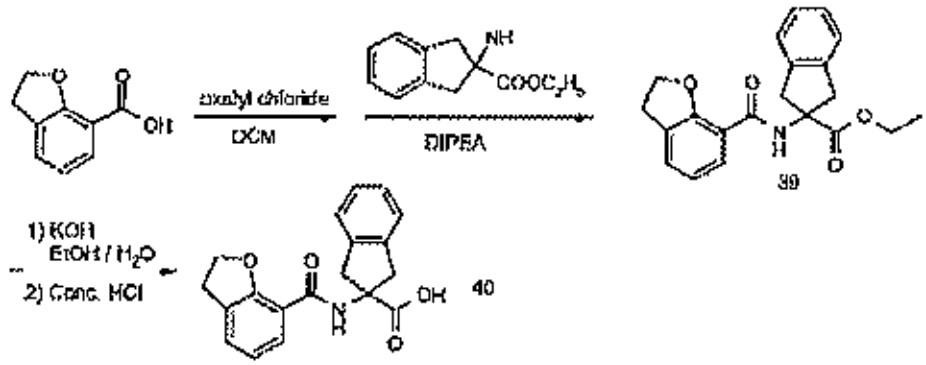
EXAMPLE 38

2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (38):

The mixture of 2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37) (400mg, 1.1mmol) and KOH (1g, 17.8mmol) is dissolved in EtOH (10mL) and water (2mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (38) as white solid (300mg, 82%).

^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.76(m, 2H), 3.38(d, 2H), 3.68(d, 2H), 4.85(s, 1H), 7.02-7.08(m, 3H), 7.14-7.23(m, 4H)
LC/MS (ES+) m/z = 336.15

EXAMPLE 39



2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (39):

To a solution of 2,3-dihydro-benzofuran-7-carboxylic acid (394mg, 2.4mmol) in DCM (10mL) is added oxalyl chloride (0.85mL, 9.6mmol). The resulting solution is stirred at RT for 2h. After the removal of DCM and excess oxalyl chloride, the residue, 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.4mmol) and DIPEA (3.17mL, 19.2mmol) are dissolved in DCM (20mL). The resulting solution is stirred at RT overnight. The reaction solution is diluted with DCM (40mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The

organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (39) as white solid (635mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.23(t, 3H), 3.22(t, 2H), 3.40(d, 2H), 3.77(d, 2H), 4.26(q, 2H), 4.67(t, 2H), 6.93(t, 1H), 7.17-7.30(m, 6H), 7.87(d, 1H), 8.18(s, H)
LC/MS (ES+) m/z = 352.12

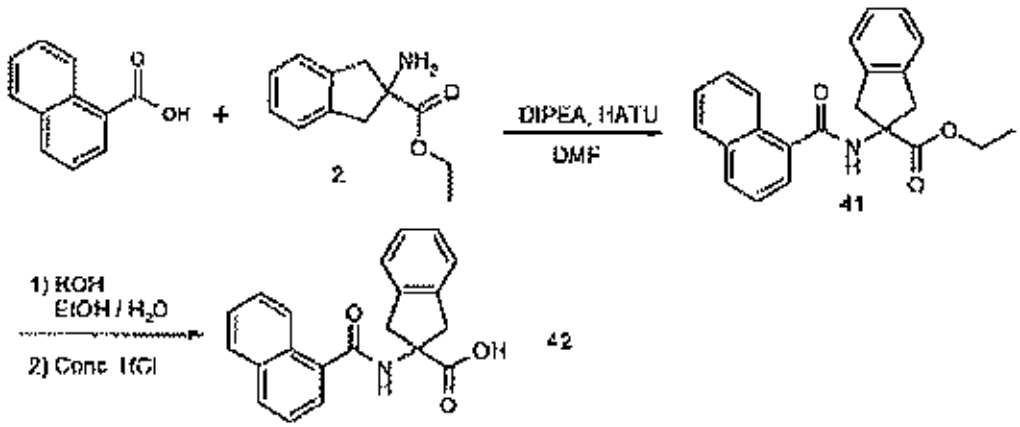
EXAMPLE 40

2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (40):

The mixture of 2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (39) (250mg, 0.71mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (40) as white solid (200mg, 87%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.22(t, 2H), 3.40(d, 2H), 3.82(d, 2H), 4.68(t, 2H), 6.94(t, 1H), 7.17-7.25(m, 4H), 7.30(d, 1H), 7.83(d, 1H), 8.28(s, 1H)
LC/MS (ES+) m/z = 324.11

EXAMPLE 41



2-[(Naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (41):

To a solution of naphthalene-1-carboxylic acid (300mg, 1.74mmol), 2-amino-indan-2-carboxylic acid ethyl ester (357mg, 1.74mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (8mL) is added DIPEA (431µL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (41) as white solid (383mg, 61%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.30(t, 3H), 3.40(d, 2H), 3.77(d, 2H), 4.29(q, 2H), 6.59(s, 1H), 7.20-7.24(m, 4H), 7.34(t, 1H), 7.46-7.52(m, 3H), 7.79-7.85(m, 2H), 8.28-8.31(m, 1H)
LC/MS (ES+) m/z = 360.19

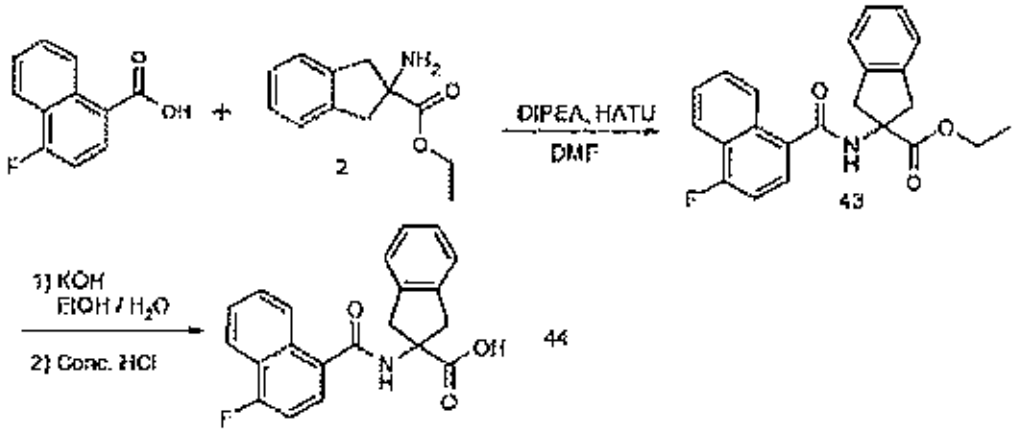
EXAMPLE 42

2-[(Naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (42):

The mixture of 2-[(naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (41) (220mg, 0.61mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (42) as white solid (196mg, 97%).

^{1}H NMR ($CDCl_3$ +drops of CD_3OD, 300MHz): δ 3.47(d, 2H), 3.82(d, 2H), 6.93(m, 1H), 7.19-7.28(m, 4H), 7.37-7.50(m, 4H), 7.81-7.89(m, 2H), 8.23-8.27(m, 1H)
LC/MS (ES+) m/z = 332.11

EXAMPLE 43



2-[(4-Fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (43):

To a solution of 4-fluoro-naphthalene-1-carboxylic acid (232mg, 1.22mmol), 2-amino-indan-2-carboxylic acid ethyl ester (250mg, 1.22mmol), HATU (696mg, 1.83mmol) in anhydrous DMF (8mL) is added DIPEA (302µL, 1.83mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (43) as white solid (340mg, 74%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.31(t, 3H), 3.42(d, 2H), 3.80(d, 2H), 4.31(q, 2H), 6.53(s, 1H), 7.03(dd, 1H), 7.19-7.26(m, 4H), 7.47-7.82(m, 3H), 8.07-8.10(m, 1H), 8.31-8.35(m, 1H)
LC/MS (ES+) m/z = 378.12

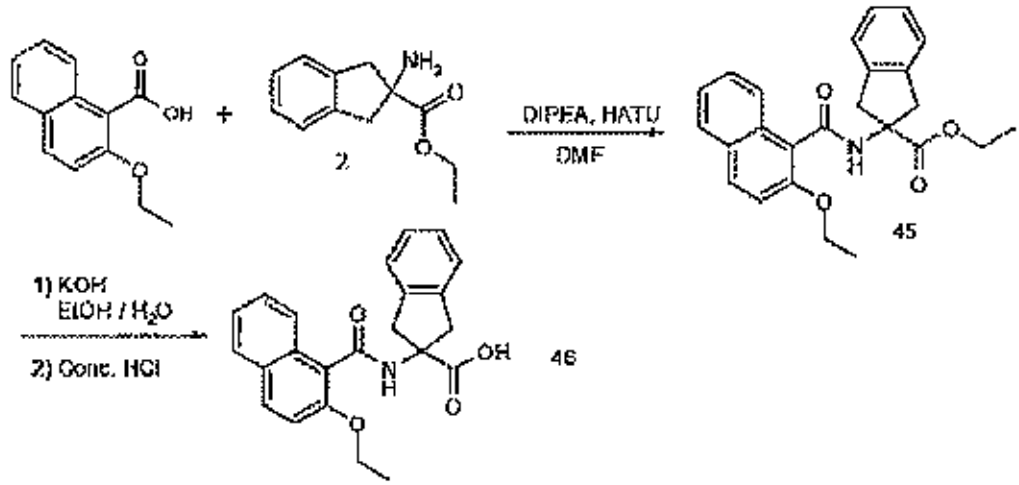
EXAMPLE 44

2-[(4-Fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (44):

The mixture of 2-[(4-fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (43) (180mg, 0.48mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 6h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (44) as white solid (174mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.46(d, 2H), 3.81(d, 2H), 6.99-7.06(m, 2H), 7.19-7.26(m, 4H), 7.48-7.54(m, 3H), 8.06-8.09(m, 1H), 8.24-8.28(m, 1H)
LC/MS (ES+) m/z = 350.09

EXAMPLE 45



<u>2-[(2-Ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (45):</u>
To a solution of 2-ethoxy-naphthalene-1-carboxylic acid (335mg, 1.55mmol), 2-amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385µL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (45) as white solid (420mg, 67%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.12(t, 3H), 1.35(t, 3H), 3.40(d, 2H), 3.76(d, 2H), 3.98(q, 2H), 4.32(q, 2H), 6.73(s, 1H), 7.19 (d, 1H), 7.16-7.23(m, 4H), 7.29-7.34(m, 1H), 7.42-7.48(m, 1H), 7.73(dd, 2H), 8.16(d, 1H)
LC/MS (ES+) m/z = 404.18

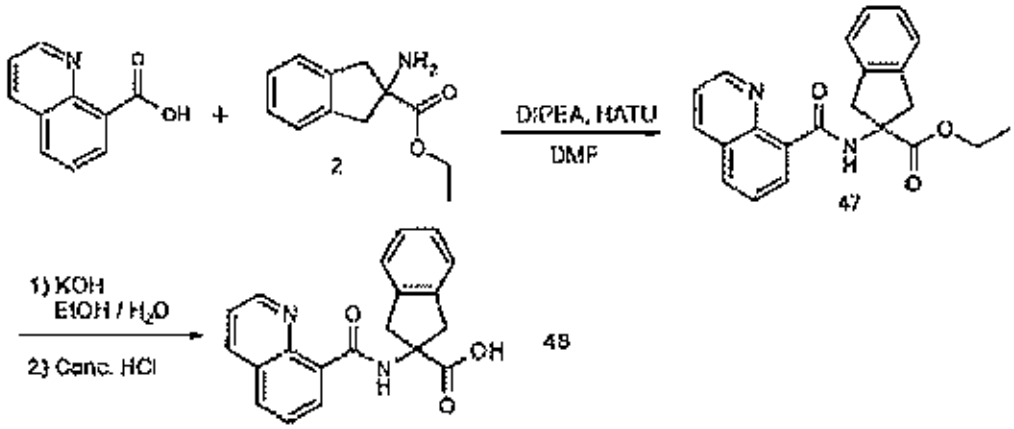
EXAMPLE 46

<u>2-[(2-Ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (46):</u>
The mixture of 2-[(2-ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (45) (270mg, 0.67mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL)

and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH ~ 4. The precipitate is filtered to give a pure product (46) as white solid (170mg, 68%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.18(t, 3H), 3.47(d, 2H), 3.82(d, 2H), 4.04(q, 2H), 7.09(s, 1H), 7.15-7.37 (m, 7H), 7.47(t, 1H), 7.78(dd, 2H), 8.07(d, 1H)
LC/MS (ES+) m/z = 376.19

EXAMPLE 47



<u>2-[(Quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (47):</u>

To a solution of quinoline-8-carboxylic acid (421mg, 2.43mmol), 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.43mmol), HATU (1.39g, 3.65mmol) in anhydrous DMF (15mL) is added DIPEA (603μL, 3.65mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (47) as white solid (281mg, 32%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.54(d, 2H), 3.86(d, 2H), 4.27(q, 2H), 7.17-7.27(m, 4H), 7.44(dd, 1H), 7.65(t, 1H), 7.94(dd, 1H), 8.24(dd, 1H), 8.80-8.84(m, 2H), 12.00(s, 1H)
LC/MS (ES+) m/z = 361.13

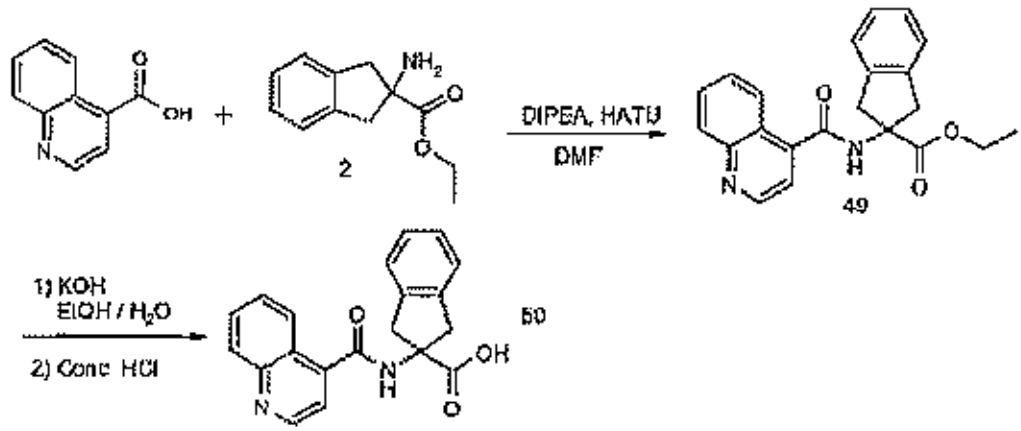
EXAMPLE 48

2-[(Quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (48):

The mixture of 2-[(quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (47) (190mg, 0.53mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give the pure product (48) as white solid (152mg, 86%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.50(d, 2H), 3.83(d, 2H), 7.17-7.24(m, 4H), 7.44-7.49(m, 1H), 7.64(t, 1H), 7.98(d, 1H), 8.28(dd, 1H), 8.69(d, 1H), 8.83(s, 1H)
LC/MS (ES+) m/z = 333.08

EXAMPLE 49



2-[(Quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (49):

To a solution of quinoline-4-carboxylic acid (301mg, 1.74mmol), 2-amino-indan-2-carboxylic acid ethyl ester (357mg, 1.74mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (8mL) is added DIPEA (431μL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-70% EtOAc in heptane) to give a pure product (49) as a pale yellow solid (370mg, 59%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34(t, 3H), 3.48(d, 2H), 3.82(d, 2H), 4.34(q, 2H), 6.86(s, 1H), 7.21-7.29(m, 5H), 7.51-7.56(m, 1H), 7.65-7.71(m, 1H), 7.98(d, 1H), 8.18(d, 1H), 8.73(d, 1H)

LC/MS (ES+) m/z = 361.14

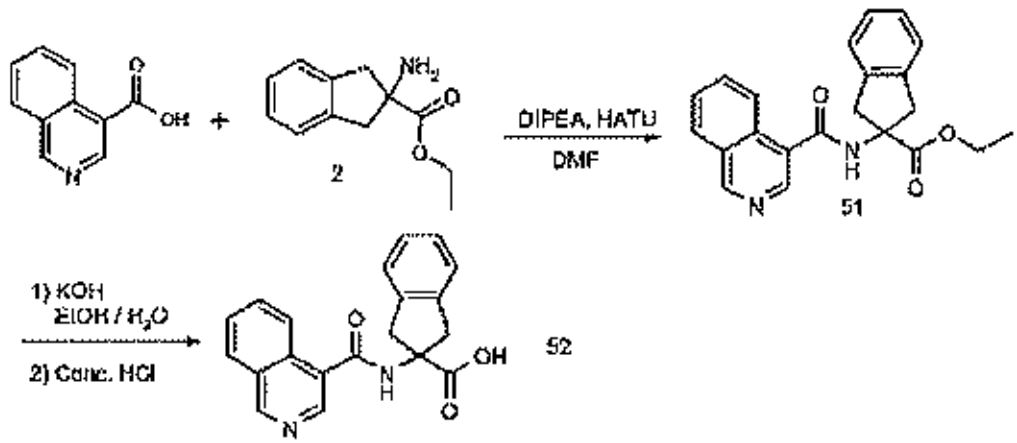
EXAMPLE 50

2-[(Quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid (50):

The mixture of 2-[(quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (49) (220mg, 0.61mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (50) as a pale yellow solid (98mg, 48%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.49(d, 2H), 3.83(d, 2H), 7.20-7.28(m, 4H), 7.50(d, 1H), 7.61(t, 1H), 7.79(t, 1H), 8.13(d, 1H), 8.24(d, 1H), 8.86(d, 1H)
LC/MS (ES+) m/z = 333.13

EXAMPLE 51



2-[(Isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (51):

To a solution of isoquinoline-4-carboxylic acid (211mg, 1.22mmol), 2-amino-indan-2-carboxylic acid ethyl ester (250mg, 1.22mmol), HATU (696mg, 1.83mmol) in anhydrous DMF (8mL) is added DIPEA (302µL, 1.83mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (51) as white solid (359mg, 82%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.49 (d, 2H), 3.79(d, 2H), 4.28(q, 2H), 6.96(s, 1H), 7.20-7.27(m, 4H), 7.57-7.62(m, 1H), 7.76-7.82(m, 1H), 7.86(d, 1H), 8.12(d, 1H), 8.54(d, 1H), 9.22(d, 1H)

LC/MS (ES+) m/z = 361.15

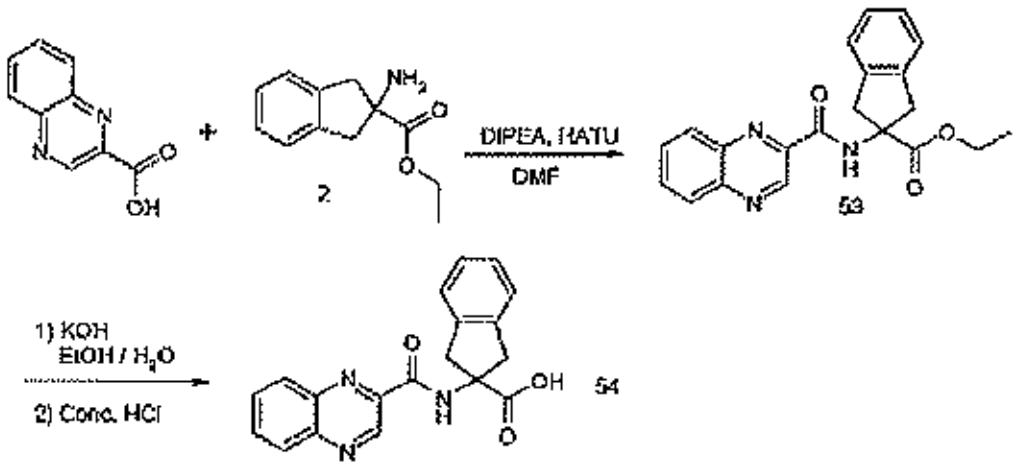
EXAMPLE 52

2-[(Isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid (52):

The mixture of 2-[(isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (51) (200mg, 0.55mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (52) as white solid (170mg, 93%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.38(d, 2H), 3.53(d, 2H), 7.19-7.27(m, 4H), 7.64(t, 1H), 7.83(t, 1H), 7.94(d, 1H), 8.09(d, 1H), 8.40(s, 1H), 8.71(d, 1H), 9.22(d, 1H)
LC/MS (ES+) m/z = 333.06

EXAMPLE 53



2-[(Quinoxaline-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (53):

To a solution of quinoxaline-5-carboxylic acid (400mg, 2.3mmol), 2-amino-indan-2-carboxylic acid ethyl ester (471mg, 2.3mmol), HATU (1.3g, 3.45mmol) in anhydrous DMF (15mL) is added DIPEA (570μL, 3.45mmol). The resulting solution is stirred at RT overnight.

After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (56) as an orange solid (605mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.55(d, 2H), 3.84(d, 2H), 4.28(q, 2H), 7.21-7.29(m, 4H), 7.79-7.89(m, 2H), 8.08-8.18(m, 2H), 8.46(s, 1H), 9.64(s, 1H)
LC/MS (ES+) m/z = 361.12

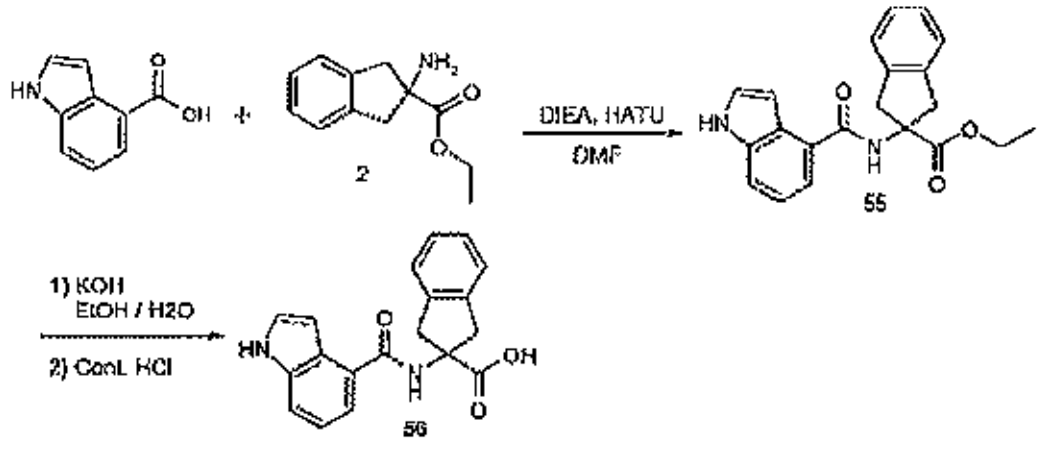
EXAMPLE 54

2-[(Quinoxaline-2-carbonyl)-amino]-indan-2-carboxylic acid (54):

The mixture of 2-[(quinoxaline-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (56) (480mg, 1.33mmol) and KOH (1g, 18mmol) is dissolved in EtOH (13mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (40mL) and acidified with conc. HCl dropwise until no more precipitate formed. The precipitate is filtered to give a pure product (54) as a brown solid (444mg, 100%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.58(d, 2H), 3.86(d, 2H), 7.21-7.30(m, 4H), 7.81-7.90(m, 2H), 8.10-8.18(m, 2H), 8.58(s, 1H), 9.61(s, 1H)
LC/MS (ES+) m/z = 361.12

EXAMPLE 55



2-[(1H-Indole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (55):

To a solution of 1H-indole-4-carboxylic acid (250mg, 1.55mmol), 2-amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385µL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a pure product (55) as white solid (278mg, 52%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.46(d, 2H), 3.78(d, 2H), 4.26(q, 2H), 6.78(m, 1H), 7.14-7.25(m, 6H), 7.46-7.49(m, 2H), 8.65(s, 1H)
LC/MS (ES+) m/z = 349.14

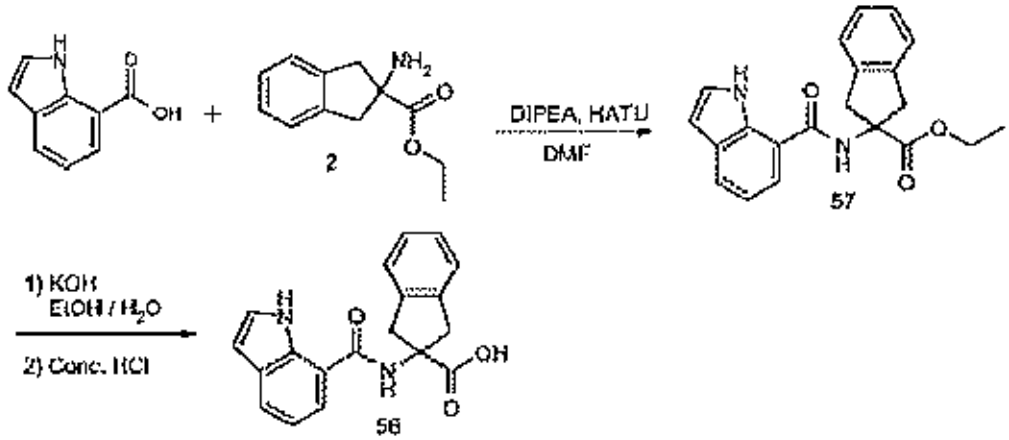
EXAMPLE 56

2-[(1H-Indole-4-carbonyl)-amino]-indan-2-carboxylic acid (56):

The mixture of 2-[(1H-indole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (55) (200mg, 0.57mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (56) as white solid (162mg, 89%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.50(d, 2H), 3.80(d, 2H), 6.68(m, 1H), 7.15-7.29(m, 6H), 7.46 (d, 1H), 7.53(dd, 1H), 9.79(s, 1H)
LC/MS (ES+) m/z = 321.15

EXAMPLE 57



2-[(1H-Indole-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (57):

To a solution of 1H-indole-7-carboxylic acid (250mg, 1.55mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385µL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a pure product (57) as white solid (378mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22(t, 3H), 3.44(d, 2H), 3.78(d, 2H), 4.25(q, 2H), 6.53(t, 1H), 6.93(s, 1H), 7.03(t, 1H), 7.18-7.27(m, 5H), 7.32(d, 1H), 7.77(d, 1H), 10.25(s, 1H)
LC/MS (ES+) m/z = 349.21

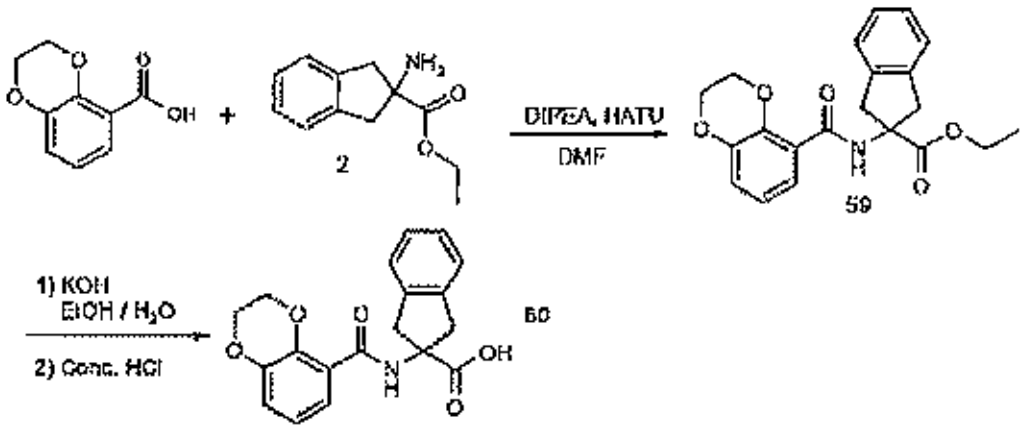
EXAMPLE 58

2-[(1H-Indole-7-carbonyl)-amino]-indan-2-carboxylic acid (58):

The mixture of 2-[(1H-indole-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (57) (220mg, 0.63mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (58) as an off white solid (186mg, 92%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.50(d, 2H), 3.79(d, 2H), 6.54(m, 2H), 7.06(t, 1H), 7.19-7.31(m, 5H), 7.42(d, 1H), 7.78(d, 1H), 10.25(s, 1H)
LC/MS (ES+) m/z = 325.15

EXAMPLE 59



2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (59):

To a solution of 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid (351mg, 1.95mmol), 2-amino-indan-2-carboxylic acid ethyl ester (400mg, 1.95mmol), HATU (1.11g, 2.93mmol) in anhydrous DMF (8mL) is added DIPEA (484µL, 2.93mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (59) as white solid (650mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.39(d, 2H), 3.74(d, 2H), 4.21- 4.33(m, 6H), 6.90(t, 1H), 6.98(dd, 1H), 7.17-7.24(m, 4H), 7.69(dd, 1H), 8.25(s, 1H)
LC/MS (ES+) m/z = 368.15

EXAMPLE 60

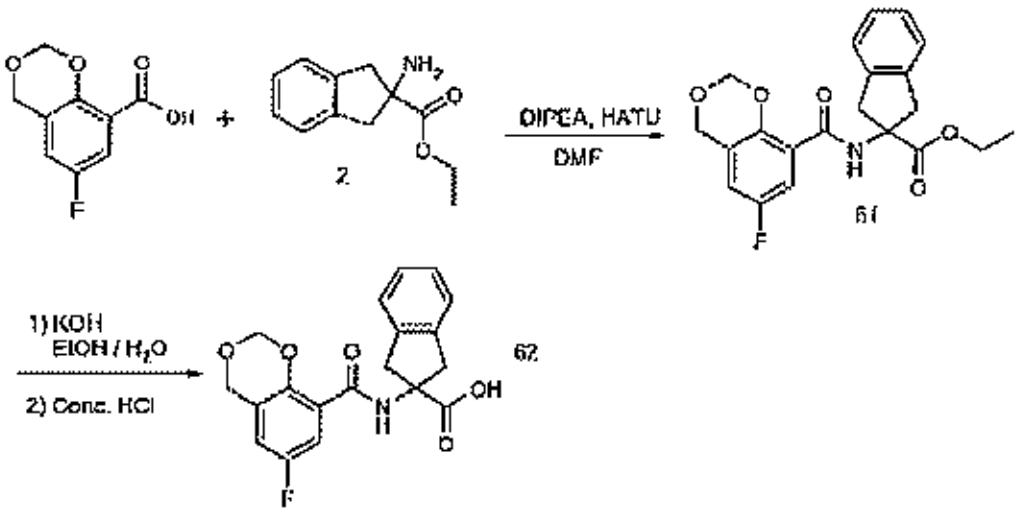
2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid (60):

The mixture of 2-[(2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (59) (495mg, 1.35mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After

concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (60) as white solid (440mg, 96%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.40(d, 2H), 3.78(d, 2H), 4.26- 4.33(m, 4H), 6.91(t, 1H), 7.49(dd, 1H), 7.18-7.25(m, 4H), 7.65(dd, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 340.11

EXAMPLE 61



2-[(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (61):

To a solution of 6-fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (386mg, 1.95mmol), 2-amino-indan-2-carboxylic acid ethyl ester (400mg, 1.95mmol), HATU (1.11g, 2.93mmol) in anhydrous DMF (8mL) is added DIPEA (484μL, 2.93mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (61) as white solid (720mg, 6%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.38(d, 2H), 3.74(d, 2H), 4.24(q, 2H), 4.90(s, 2H), 5.27(s, 2H), 6.79(dd, 1H), 7.17-7.24(m, 4H), 7.74(dd, 1H), 8.25(s, 1H)
LC/MS (ES+) m/z = 386.11

EXAMPLE 62

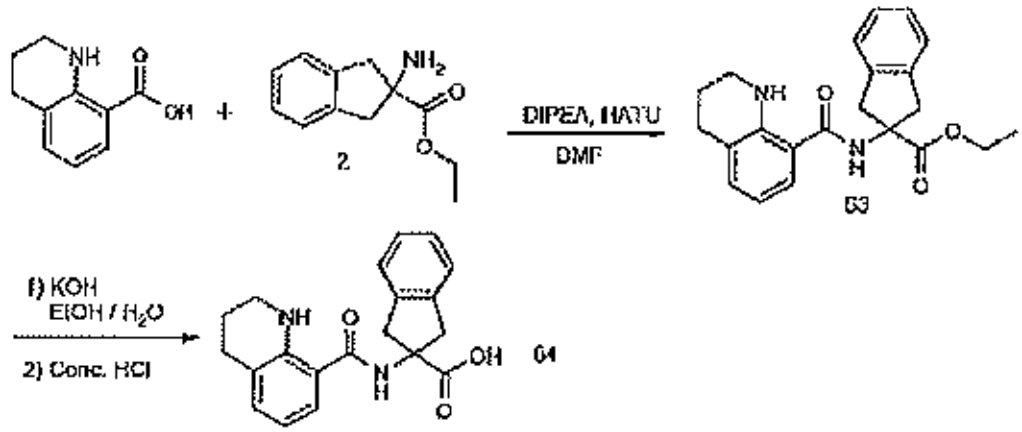
2-[(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid (62):

The mixture of 2-[(6-fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (61) (560mg, 1.45mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (62) as white solid (520mg, 100%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.39(d, 2H), 3.75(d, 2H), 4.92(s, 2H), 5.30(s, 2H), 6.85(dd, 1H), 7.18-7.25(m, 4H), 7.64(dd, 1H), 8.49(s, 1H)

LC/MS (ES-) m/z = 356.10

EXAMPLE 63



2-[(1,2,3,4-Tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (63):

To a solution of 1,2,3,4-tetrahydro-quinoline-8-carboxylic acid (173mg, 0.97mmol), 2-amino-indan-2-carboxylic acid ethyl ester (200mg, 0.97mmol), HATU (553mg, 1.46mmol) in anhydrous DMF (20mL) is added DIPEA (241µL, 1.46mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (63) as white solid (300mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.87(m, 2H), 2.74(t, 2H), 3.31-3.36(m, 4H), 3.73(d, 2H), 4.24(q, 2H), 6.38(t, 2H), 6.50(s, 1H), 6.95(d, 1H), 7.09(d, 1H), 7.17-7.24(m, 4H), 7.67(br s, 1H)

LC/MS (ES+) m/z = 365.18

EXAMPLE 64

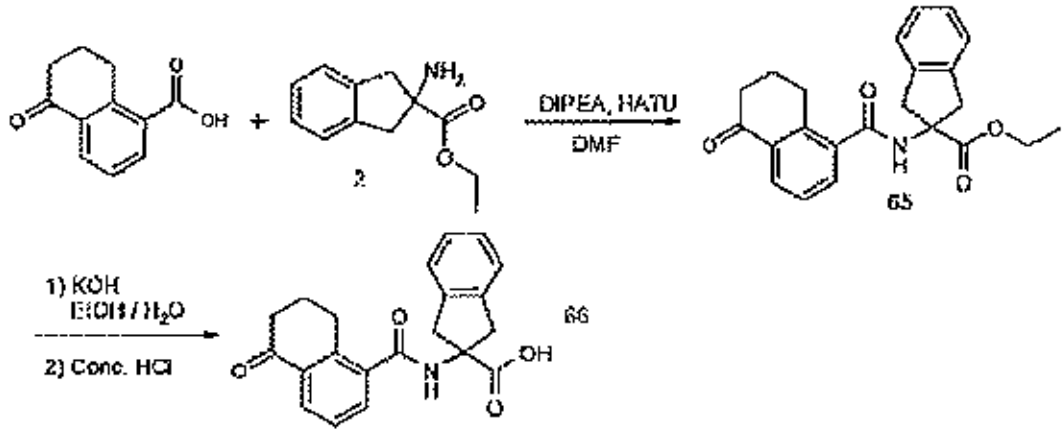
2-[(1,2,3,4-Tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (64):

The mixture of 2-[(1,2,3,4-tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (63) (259mg, 0.71mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (15mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl dropwise until precipitate falls out of the water. After the filtration, the solid is washed by water and collected. The filtrate is acidified with conc. HCl carefully again to see if more precipitate comes out or not. The combined solid is dried *in vacuo* to give a pure product (64) as a yellow solid (205mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.87(m, 2H), 2.74(t, 2H), 3.40-3.45(m, 4H), 3.81(d, 2H), 6.36(t, 1H), 6.48(s, 1H), 6.98(t, 2H), 7.18-7.26(m, 4H)

LC/MS (ES+) m/z = 337.17

EXAMPLE 65



2-[(5-Oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (65):

To a solution of 5-oxo-5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (430mg, 2.26mmol), 2-amino-indan-2-carboxylic acid ethyl ester (464mg, 2.26mmol), HATU (1g, 2.70mmol) in anhydrous DMF (20mL) is added DIPEA (446µL, 2.70mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (65) as white solid (828mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.30(t, 3H), 2.09(m, 2H), 2.63(t, 2H), 3.07(t, 2H), 3.38(d, 2H), 3.77(d, 2H), 4.29(q, 2H), 6.31(t, 2H), 7.20-7.26(m, 4H), 7.30(d, 1H), 7.50(dd, 1H), 8.05(dd, 1H)
LC/MS (ES+) m/z = 378.13

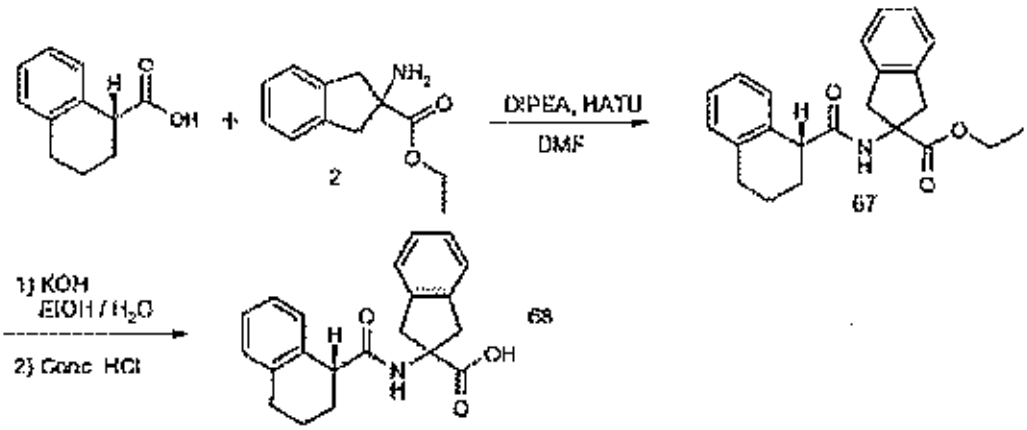
EXAMPLE 66

2-[(5-Oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (66):

The mixture of 2-[(5-oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (65) (250mg, 0.66mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the solid is purified by HPLC to give a pure product (66) as white solid (150mg, 65%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 1.98(m, 2H), 2.60(t, 2H), 2.97(t, 2H), 3.34(d, 2H), 3.58(d, 2H), 7.15-7.25(m, 4H), 7.38(d, 1H), 7.48(t, 1H), 7.94 (dd, 1H), 9.02(s, 1H)
LC/MS (ES+) m/z = 350.16

EXAMPLE 67



2-[((R)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (67):

To a solution of (R)-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (300mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (349mg, 1.7mmol), HATU (760mg, 2.0mmol) in anhydrous DMF (10mL) is added DIPEA (330µL, 2mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (67) as white solid (615mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.57-2.00(m, 3H), 2.17-2.26(m, 1H), 2.76(m, 2H), 3.10(dd, 2H), 3.57-3.68(m, 3H), 4.19(q, 2H), 5.87(s, 1H), 7.03-7.18 (m, 8H)

LC/MS (ES+) m/z = 364.16

EXAMPLE 68

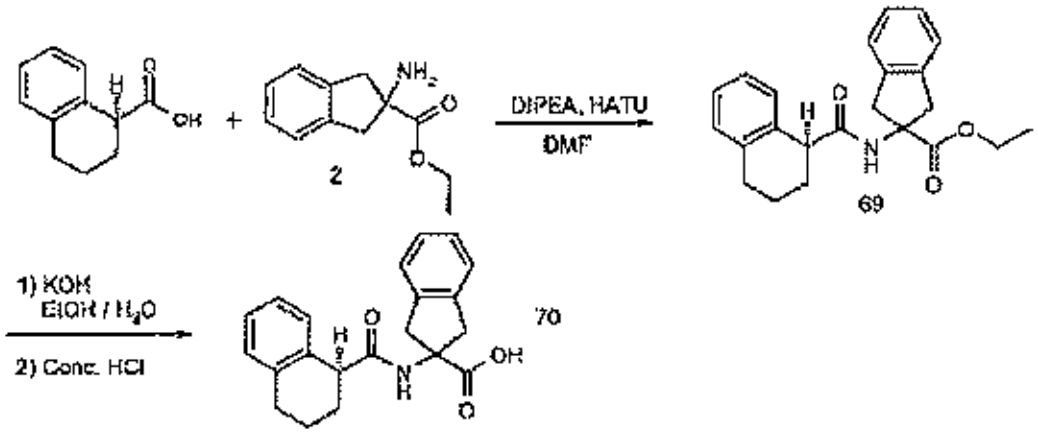
2-[((R)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (68):

The mixture of 2-[((R)-1,2,3,4-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (67) (440mg, 1.21mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (68) as white solid (391mg, 96%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.65-1.73(m, 2H), 1.93-1.96(m, 1H), 2.17-2.27(m, 1H), 2.69(t, 2H), 3.12(t, 2H), 3.63-3.70(m, 3H), 5.84(s, 1H), 6.86(d, 1H), 7.00(t, 1H), 7.07(d, 1H), 7.13-7.20(m, 5H)

LC/MS (ES-) m/z = 334.14

EXAMPLE 69



2-[((S)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (69):

To a solution of (S)-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (300mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (349mg, 1.7mmol), HATU (760mg, 2mmol) in anhydrous DMF (8mL) is added DIPEA (330µL, 2mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (69) as white solid (615mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.58-2.00(m, 3H), 2.17-2.26(m, 1H), 2.76(m, 2H), 3.10(dd, 2H), 3.57-3.68(m, 3H), 4.19(q, 2H), 5.87(s, 1H), 7.05-7.26(m, 8H)
LC/MS (ES+) m/z = 364.19

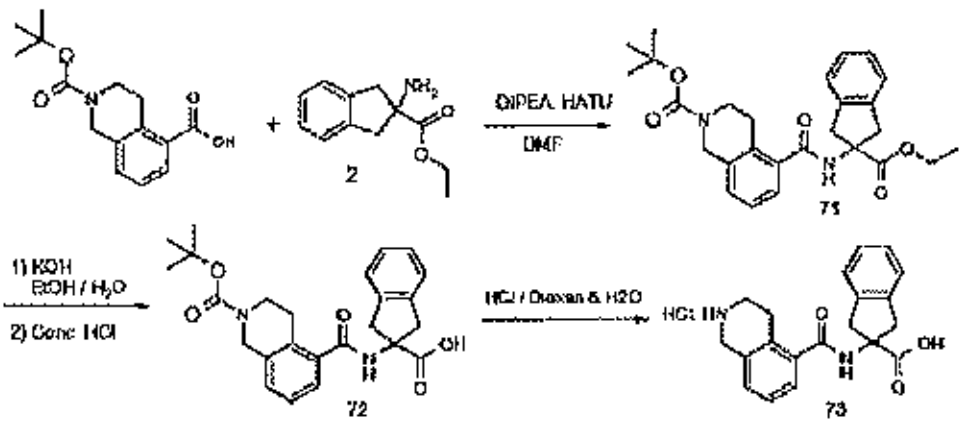
EXAMPLE 70

2-[((S)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (70):

The mixture of 2-[((S)-1,2,3,4-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (69) (440mg, 1.21mmol) and KOH (800mg, 14.2mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (70) as white solid (405mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.66-1.73(m, 2H), 1.93-1.96(m, 1H), 2.20-2.22(m, 1H), 2.69(t, 2H), 3.12(t, 2H), 3.17-3.71(m, 3H), 5.82(s, 1H), 6.87(d, 1H), 7.01(t, 1H), 7.07(d, 1H), 7.13-7.21(m, 5H)
LC/MS (ES+) m/z = 336.13

EXAMPLE 71



<u>5-(2-Ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (71):</u>

To a solution of 3,4-dihydro-1H-isoquinoline-2,5-dicarboxylic acid 2-tert-butyl ester (2g, 7.2mmol), 2-amino-indan-2-carboxylic acid ethyl ester (1.5g, 7.2mmol), HATU (3.27g, 8.6mmol) in anhydrous DMF (20mL) is added DIPEA (1.42mL, 8.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 20mL) and brine (2 x 20mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (71) as white solid (1.02g, 30%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.48(s, 9H), 2.95(t, 2H), 3.35(d, 2H), 3.57(t, 2H), 3.75(d, 2H), 4.27(q, 2H), 4.55(s, 2H), 6.26(s, 1H), 7.14-7.26(m, 7H)
LC/MS (ES+) m/z = 465.26

EXAMPLE 72

5-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (72):

The mixture of 5-(2-ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (71) (882mg, 1.78mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (15mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (72) as white solid (680mg, 88%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.46(s, 9H), 2.84(t, 2H), 3.36(d, 2H), 3.48(t, 2H), 3.74(d, 2H), 4.49(s, 2H), 6.57(br *s*, 1H), 7.10-7.19(m, 7H)
LC/MS (ES+) m/z = 381.17, 437.23

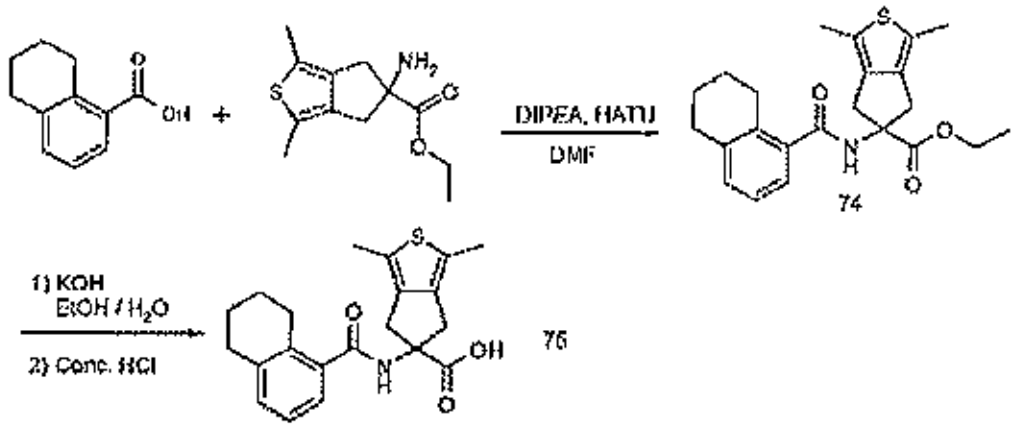
EXAMPLE 73

2-[(1,2,3,4-Tetrahydro-isoquinoline-5-carbonyl)-amino]-indan-2-carboxylic acid hydrochloride salt (73):

5-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (72) (650mg, 1.49mmol) is dissolved in 30% solution of TFA in DCM (10mL) and the resulting solution is stirred at RT for 2h. The solution is concentrated to give a TFA salt of 2-[(1,2,3,4-tetrahydro-isoquinoline-5-carbonyl)-amino]-indan-2-carboxylic acid (670mg, 100%). This TFA salt (250mg, 0.56mmol) is dissolved in 6N aqueous solution of HCl (20mL). The resulting suspension is stirred overnight and turned into a clear solution. The solution is concentrated to give a pure product (73) as white solid (130mg, 62%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.05(t, 2H), 3.32-3.37(m, 4H), 3.57(d, 2H), 4.27(s, 2H), 7.15-7.29(m, 7H), 8.98(s, 1H), 9.42(s, 2H), 12.51(br s, 1H)
LC/MS (ES+) m/z = 337.17

EXAMPLE 74



<u>1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (74):</u>

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (500mg, 2.84mmol), 5-amino-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (816mg, 3.41mmol), HATU (1.62g, 4.26mmol) in anhydrous DMF (15mL) is added DIPEA (704µL, 4.26mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (74) as white solid (1.10g, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.76(m, 4H), 2.25(s, 6H), 2.80(m, 4H), 2.97(d, 2H), 3.31(d, 2H), 4.26(q, 2H), 6.22(s, 1H), 7.15-7.15(m, 3H)
LC/MS (ES+) m/z = 398.16

EXAMPLE 75

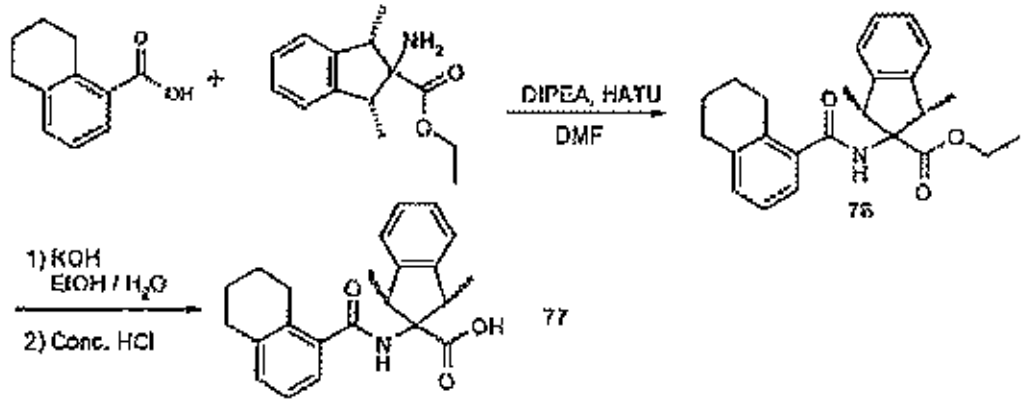
<u>1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid (75):</u>

The mixture of 1,3-dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (74) (942mg, 2.37mmol) and KOH (3g, 23mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water

(20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (75) as a pale brown solid (832mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.75(m, 4H), 2.25(s, 6H), 2.75(m, 4H), 3.03(d, 2H), 3.36(d, 2H), 6.26(s, 1H), 7.08-7.16(m, 3H)
LC/MS (ES+) m/z = 370.12

EXAMPLE 76



(cis)-1,3-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (76):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), (cis)-2-Amino-1,3-dimethyl-indan-2-carboxylic acid ethyl ester (636mg, 2.72mmol), HATU (1.3g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563µL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 50-50% EtOAc in heptane) to give a pure product (76) as white solid (79mg, 9%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.32(t, 3H), 1.50(d, 6H), 1.75(m, 4H), 2.75(br s, 2H), 2.88(br s, 2H), 3.80(q, 2H), 4.31(q, 2H), 5.73(s, 1H), 7.00-7.25(m, 7H)
LC/MS (ES+) m/z = 392.22

EXAMPLE 77

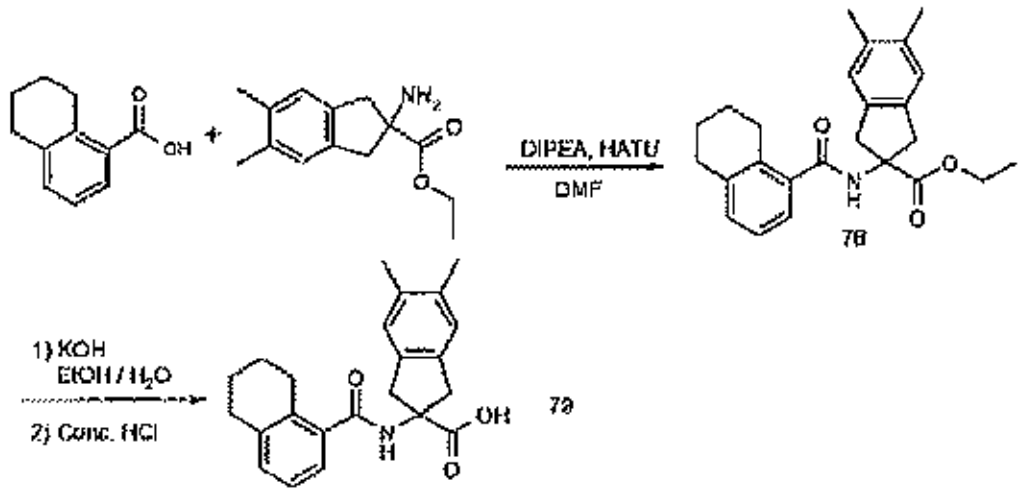
(cis)-1,3-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (77):

The mixture of (cis)-1,3-dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (76) (62mg, 1.2mmol) and KOH (300mg, 5.4mmol) is dissolved in EtOH (3mL) and water (0.3mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~ 4. The precipitate is filtered to give a pure product (77) as white solid (44mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.51(d, 6H), 1.74(m, 4H), 2.75(br s, 2H), 2.86(br s, 2H), 3.88(q, 2H), 5.81(s, 1H), 7.01-7.26(m, 7H)

LC/MS (ES+) m/z = 364.23

EXAMPLE 78



5,6-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (78):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (636mg, 2.72mmol), HATU (1.30g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563μL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is

purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (78) as white solid (817mg, 92%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(m, 4H), 2.23(s, 6H), 2.75(br s, 2H), 2.84(br s, 2H), 3.25(d, 2H), 3.69(d, 2H), 4.26(q, 2H), 6.20(s, 1H), 6.99-7.11(m, 5H)
LC/MS (ES+) m/z = 392.20

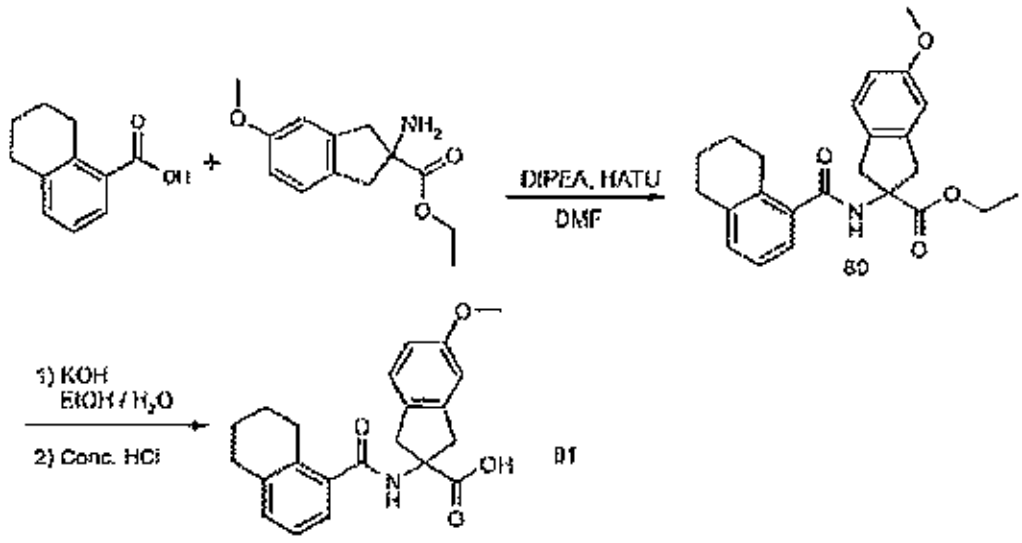
EXAMPLE 79

5,6-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (79):

The mixture of 5,6-dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (78) (438mg, 1.11mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (79) as a pale brown solid (390mg, 97%).

^{1}H NMR ($CDCl_3$ + drops CD_3OD, 300MHz): δ 1.73(m, 4H), 2.23(s, 6H), 2.74-2.80(m, 4H), 3.29(d, 2H), 3.69(d, 2H), 6.60(s, 1H), 6.99-7.08(m, 5H)
LC/MS (ES+) m/z = 364.23

EXAMPLE 80



5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (80):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5-methoxy-indan-2-carboxylic acid ethyl ester (639mg, 2.72mmol), HATU (1.3g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563µL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (52) as white solid (622mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.74(m, 4H), 2.75(br s, 2H), 2.84(br s, 2H), 3.27(dd, 2H), 3.69(dd, 2H), 3.78(s, 3H), 4.25(q, 2H), 6.26(s, 1H), 6.72-6.76(m, 2H), 7.01-7.11(m, 4H),

LC/MS (ES+) m/z = 394.21

EXAMPLE 81

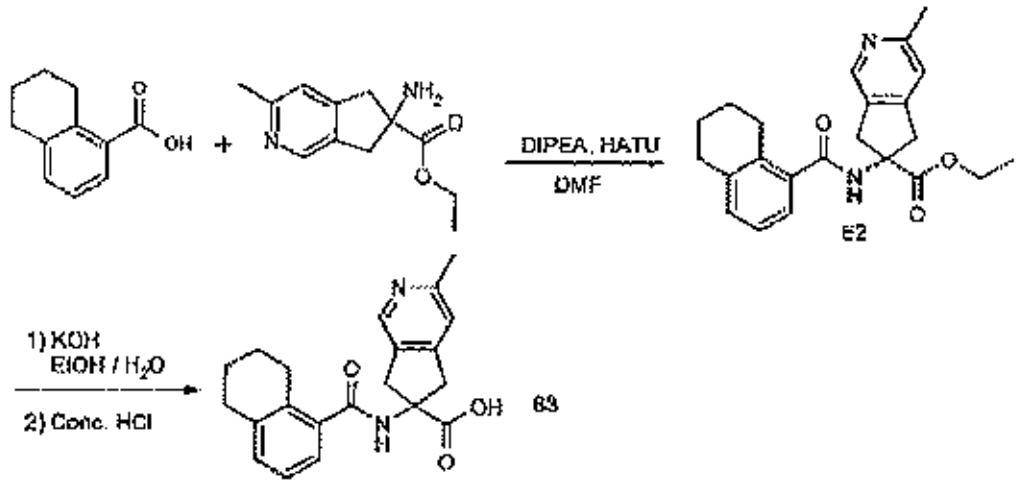
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (81):

The mixture of 5-methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (80) (458mg, 1.2mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (81) as a pale brown solid (448mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.72(m, 4H), 2.75-2.78(m, 4H), 3.32(dd, 2H), 3.78(dd, 2H), 3.78(s, 3H), 6.45(s, 1H), 6.73-6.77(m, 2H), 7.03-7.11(m, 4H).

LC/MS (ES+) m/z = 366.20

EXAMPLE 82



3-Methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyridine-6-carboxylic acid ethyl ester (82):

To a solution of 1,2,3,4-tetrahydro-quinoline-8-carboxylic acid (240mg, 1.36mmol), 6-amino-3-methyl-6,7-dihydro-5H-[2]pyridine-6-carboxylic acid ethyl ester (not pure, 300mg, 1.36mmol), HATU (608mg, 1.60mmol) in anhydrous DMF (10mL) is added DIPEA (264µL, 1.60mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a product (82) as a colorless oil (100mg, 19%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.75(br s, 4H), 2.76(br s, 2H), 3.68(s, 2H), 3.86(q, 2H), 4.26(q, 2H), 7.02-7.12(m, 3H), 7.32(s, 1H), 7.52(s, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 379.22

EXAMPLE 83

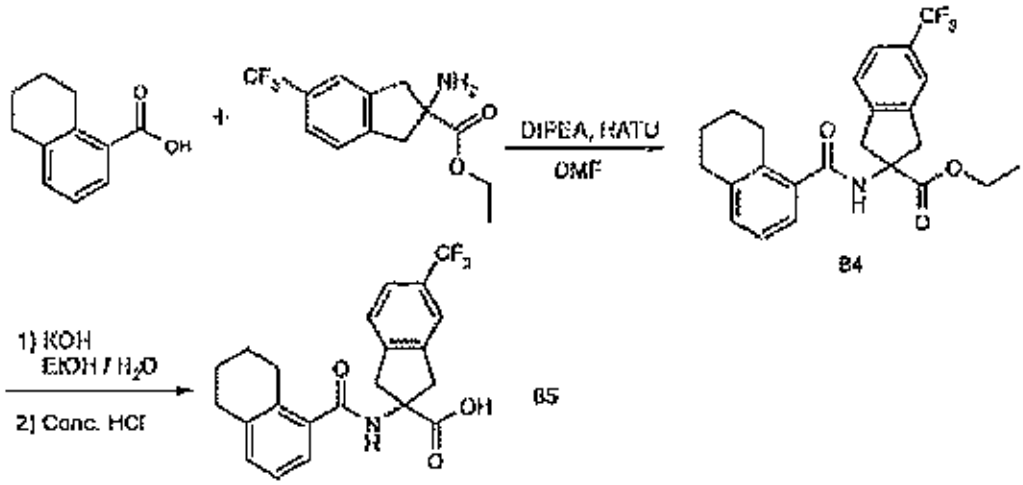
3-Methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyridine-6-carboxylic acid (83):

The mixture of 3-methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyridine-6-carboxylic acid ethyl ester (82) and KOH (1g, 17.9mmol) in EtOH (5mL) and water (0.3mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl dropwise until no more precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (83) as colorless oil (20mg, 22%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.77(br s, 4H), 2.79(br s, 2H), 3.69(m, 2H), 3.88(q, 2H), 7.06-7.15(m, 3H), 7.53(s, 1H), 8.56(s, 1H)

LC/MS (ES+) m/z = 351.11

EXAMPLE 84



2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (84):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (306mg, 1.74mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (583mg, 2.13mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (15mL) is added DIPEA (431µL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (80mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (84) as white solid (589mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.75(m, 4H), 2.76(br s, 2H), 2.83(br s, 2H), 3.44(dd, 2H), 3.74(dd, 2H), 4.26(q, 2H), 6.35(s, 1H), 7.02-7.12(m, 3H), 7.32(d, 1H), 7.46(br s, 2H) LC/MS (ES+) m/z = 432.17

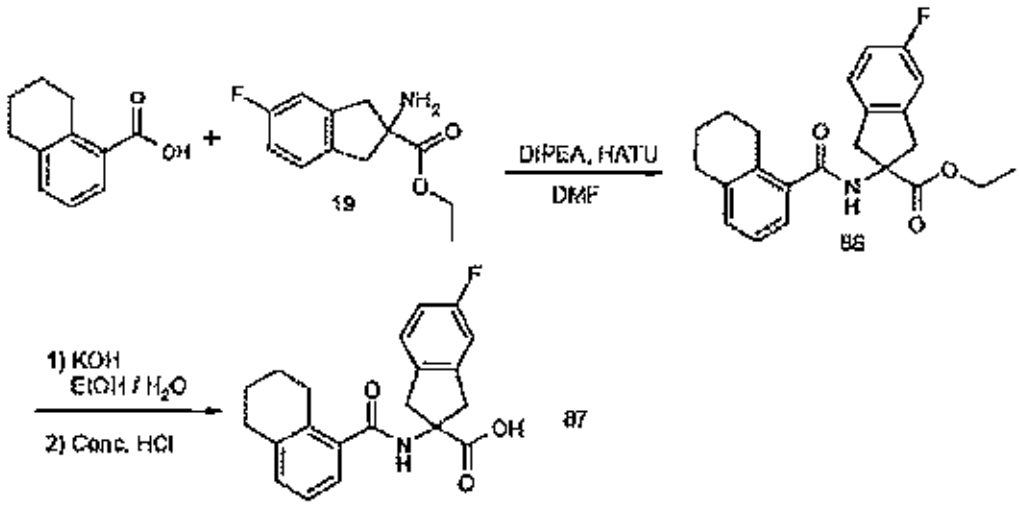
EXAMPLE 85

2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid (85):

The mixture of 2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (84) (437mg, 1.0mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (85) as white solid (408mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.74(m, 4H), 2.78(m, 4H), 3.49(dd, 2H), 3.76(dd, 2H), 6.69(s, 1H), 7.03-7.13(m, 3H), 7.32(d, 1H), 7.47(dd, 2H)
LC/MS (ES+) m/z = 404.15

EXAMPLE 86



<u>**5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (86):**</u>

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (610mg, 2.72mmol), HATU (1.30g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563µL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (86) as white solid (345mg, 40%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.75(m, 4H), 2.76(br s, 2H), 2.83(br s, 2H), 3.33(dd, 2H), 3.69(dd, 2H), 4.25(q, 2H), 6.29(s, 1H), 6.85-6.93(m, 2H), 7.02-7.16(m, 4H)
LC/MS (ES+) m/z = 382.16

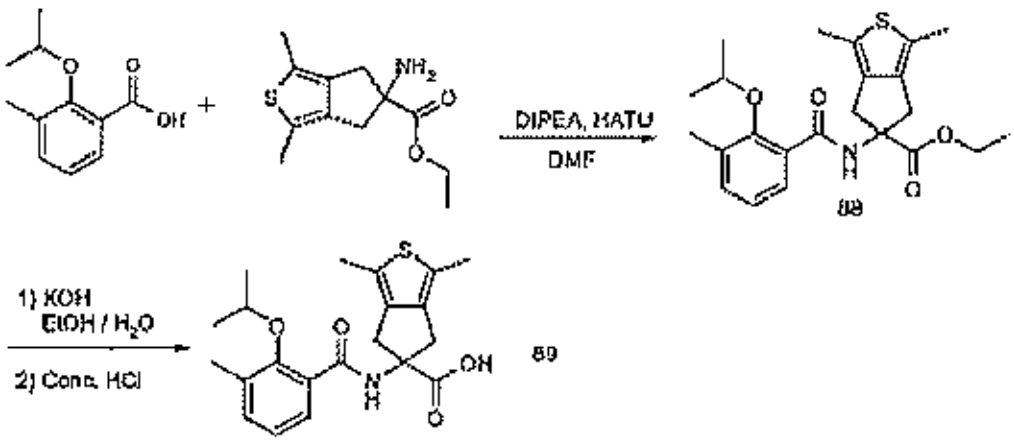
EXAMPLE 87

5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (87):

The mixture of 5-fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (86) (190mg, 0.50mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (87) as a pale brown solid (178mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.75(m, 4H), 2.76-2.81(m, 4H), 3.40(dd, 2H), 3.72(dd, 2H), 6.65(s, 1H), 6.86-6.94(m, 2H), 7.03-7.18(m, 4H)
LC/MS (ES+) m/z = 382.16

EXAMPLE 88



5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (88):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 5-amino-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (443mg, 1.85mmol), HATU (878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382μL,

2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (88) as a pale yellow solid (599mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.09(d, 6H), 1.23(t, 3H), 2.25(s, 6H), 2.28(s, 3H), 2.98(d, 2H), 3.33(d, 2H), 4.20-4.24(m, 3H), 7.08(t, 1H), 7.28(d, 1H), 7.87(d, 1H), 8.37(s, 1H)
LC/MS (ES+) m/z = 416.17

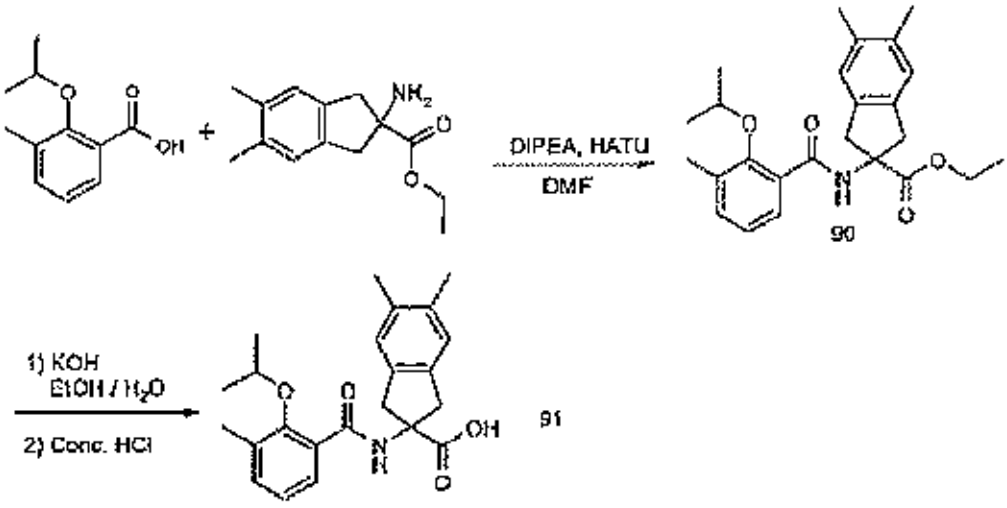
EXAMPLE 89

5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid (89):

The mixture of 5-(2-isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (88) (448mg, 1.08mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (89) as a brown solid (360mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 2.26(s, 6H), 2.28(s, 3H), 3.09(d, 2H), 3.43(d, 2H), 4.17(m, 1H), 7.12(t, 1H), 7.32(d, 1H), 7.91(d, 1H), 8.61(s, 1H)
LC/MS (ES+) m/z = 388.14

EXAMPLE 90



2-(2-Isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (90):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 2-amino-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (432mg, 1.85mmol), HATU 878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382μL, 2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (90) as white solid (591mg, 94%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.08(d, 6H), 1.24(t, 3H), 2.22(s, 6H), 2.24(s, 3H), 3.25(d, 2H), 3.70(d, 2H), 4.20-4.28(m, 3H), 7.00-7.08(m, 3H), 7.24(d, 1H), 7.83(d, 1H), 8.27(s, 1H)

LC/MS (ES+) m/z = 410.21

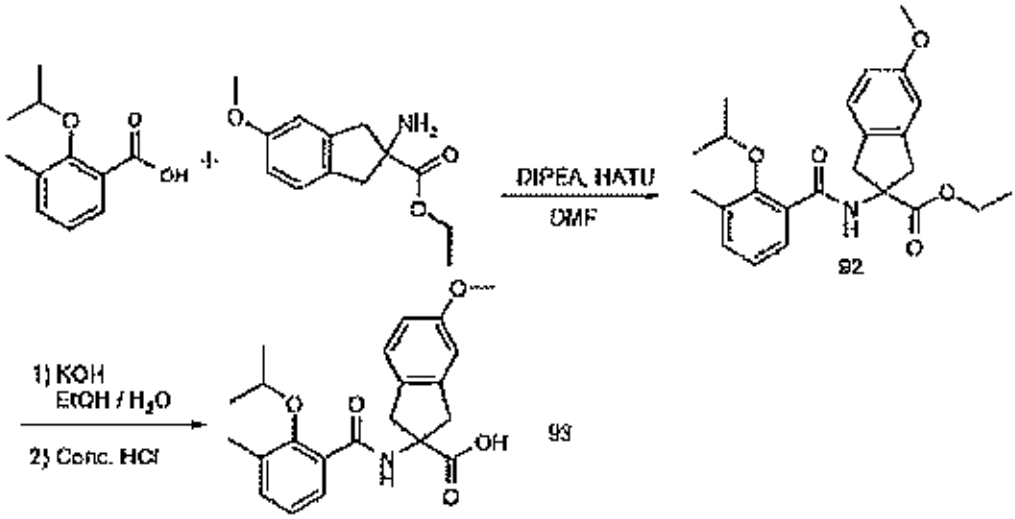
EXAMPLE 91

2-(2-Isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid (91):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (90) (440mg, 1.07mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give the pure product (91) as a pale brown solid (374mg, 92%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(d, 6H), 2.22(s, 6H), 2.25(s, 3H), 3.34(d, 2H), 3.80(d, 2H), 4.14(m, 1H), 7.01(s, 2H), 7.09(t, 1H), 7.29(d, 1H), 7.87(dd, 1H), 8.52(s, 1H)
LC/MS (ES+) m/z = 382.19

EXAMPLE 92



2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid ethyl ester (92):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 2-amino-5-methoxy-indan-2-carboxylic acid ethyl ester (435mg, 1.85mmol), HATU (878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382µL, 2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (92) as a pale yellow oil (569mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.07(d, 6H), 1.24(t, 3H), 2.25(s, 3H), 3.28(d, 2H), 3.72(dd, 2H), 3.78(s, 3H), 4.21-4.25(m, 3H), 6.73-6.78(m, 2H), 7.04-7.13(m, 2H), 7.26(d, 1H), 7.85(d, 1H), 8.32(s, 1H)
LC/MS (ES+) m/z = 412.18

EXAMPLE 93

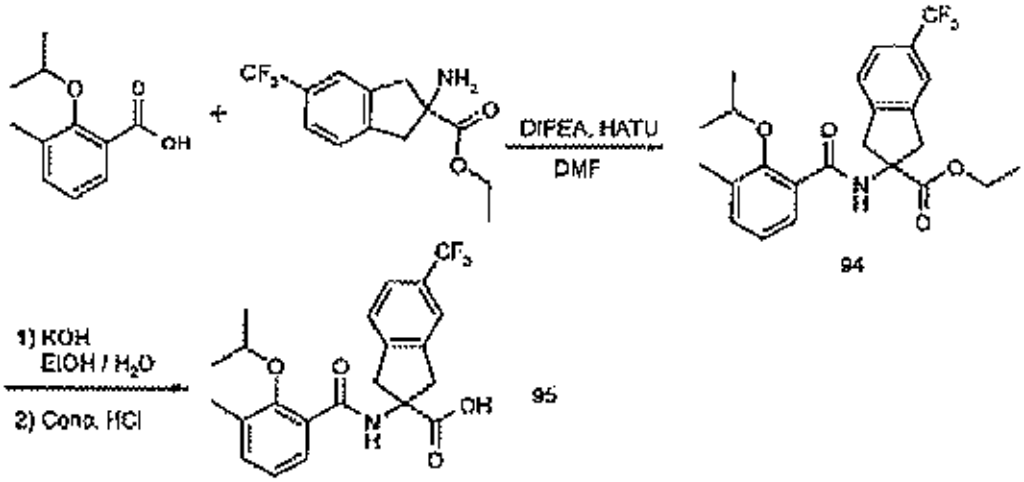
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid (93):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid ethyl ester (92) (410mg, 1mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (93) as white solid (400mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(m, 6H), 2.25(s, 3H), 3.34(d, 2H), 3.78(s, 3H), 3.80(dd, 2H), 4.16(m, 1H), 6.73-6.78(m, 2H), 7.05-7.14(m, 2H), 7.27-7.30(m, 1H), 7.88(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.17

EXAMPLE 94



2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (94):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (377mg, 1.94mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (650mg, 2.38mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column

chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (94) as white solid (842mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 1.24(t, 3H), 2.26(s, 3H), 3.43(d, 2H), 3.78(dd, 2H), 4.16-4.29(m, 1H), 4.25(q, 2H), 7.08(t, 1H), 7.26-7.35(m, 2H), 7.47(d, 2H), 7.85(dd, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 450.18

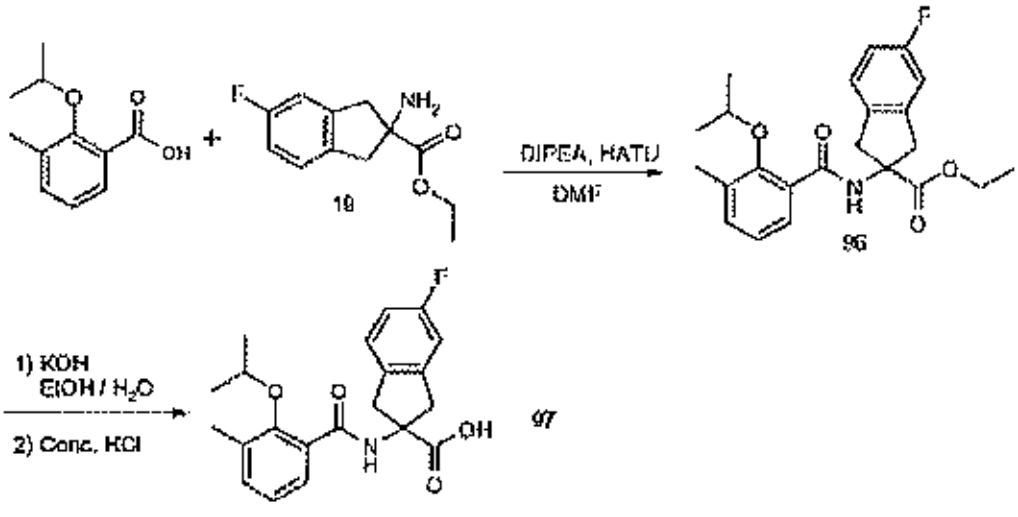
EXAMPLE 95

2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid (95):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (94) (690mg, 1.5mmol) and KOH (1.5g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (95) as a pale brown solid (495mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.99(d, 6H), 2.25(s, 3H), 3.48(d, 2H), 3.89(d, 2H), 4.15 (m, 1H), 7.10(t, 1H), 7.29-7.37(m, 2H), 7.49(d, 2H), 7.88(dd, 1H), 8.57(s, 1H)
LC/MS (ES+) m/z = 422.15

EXAMPLE 96



5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (96):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (400mg, 2.06mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (554mg, 2.47mmol), HATU 1.17g, 3.09mmol) in anhydrous DMF (10mL) is added DIPEA (511µL, 3.09mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (96) as white solid (709mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.07(m, 6H), 1.24(t, 3H), 2.26(s, 3H), 3.32(t, 2H), 3.72(dd, 2H), 4.23(m, 3H), 6.85-6.94(m, 2H), 7.05-7.28((m, 3H), 7.85(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 400.18

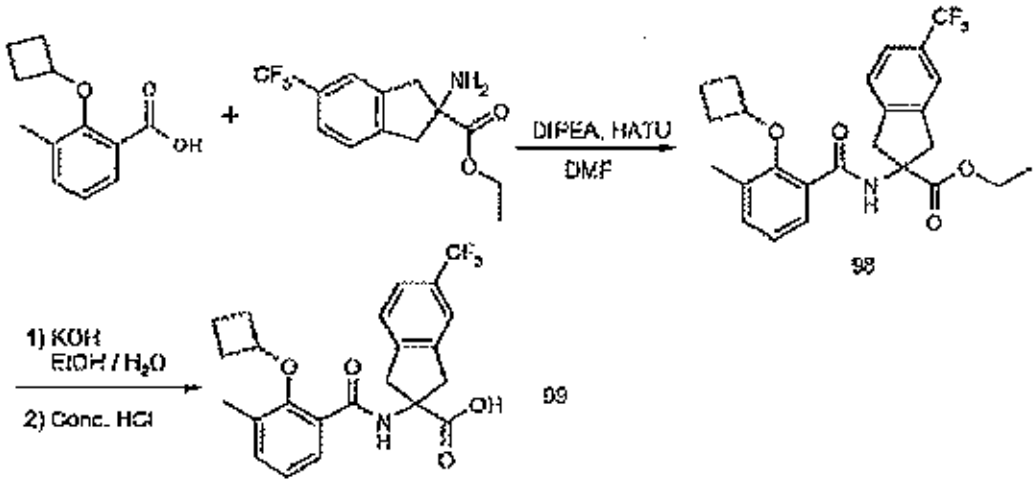
EXAMPLE 97

5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (97):

The mixture of 5-fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (96) (544mg, 1.36mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (97) as white solid (460mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(m, 6H), 2.26(s, 3H), 3.38(dd, 2H), 3.82(dd, 2H), 4.16(m, 1H), 6.87-6.95(m, 2H), 7.07-7.31((m, 3H), 7.88(dd, 1H), 8.56(s, 1H)
LC/MS (ES+) m/z = 372.16

EXAMPLE 98



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid ethyl ester (98):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (650mg, 2.38mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480µL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-60% EtOAc in heptane) to give a pure product (98) as white solid (800mg, 89%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.26-1.38(m, 1H), 1.45-1.55(m, 1H), 1.89-2.17(S, 3H), 2.27(s, 3H), 3.44(dd, 2H), 3.80(dd, 2H), 4.22-4.35(m, 3H), 7.08(t, 1H), 7.27(d, 1H), 7.34(d, 1H), 7.47(d, 2H), 7.85(d, 1H), 8.41(s, 1H)
LC/MS (ES+) m/z = 462.18

EXAMPLE 99

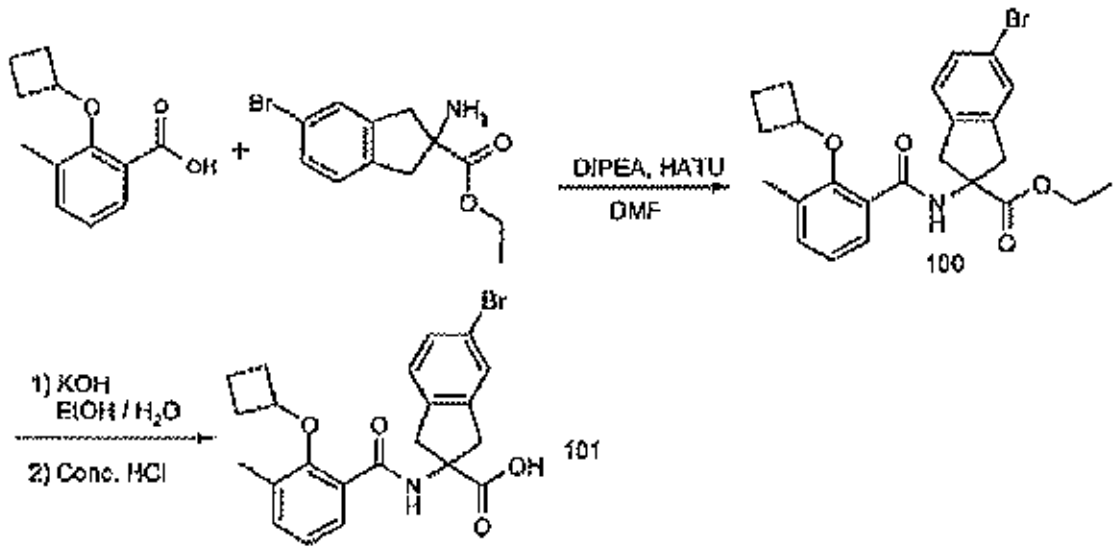
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid (99):

The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid ethyl ester (98) (648mg, 1.4mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more

precipitate formed. The precipitate is filtered to give a pure product (99) as a pale brown solid (595mg, 98%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.32(m, 1H), 1.41-1.51(m, 1H), 1.85-2.08(S, 3H), 2.25(s, 3H), 3.48(dd, 2H), 3.89(dd, 2H), 4.26(m, 1H), 7.09(t, 1H), 7.26-7.36(m, 2H), 7.49(d, 2H), 7.87(dd, 1H), 8.55(s, 1H)
LC/MS (ES+) m/z = 434.16

EXAMPLE 100



5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (100):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (250mg, 1.21mmol), 2-amino-5-bromo-indan-2-carboxylic acid ethyl ester (344mg, 1.21mmol), HATU (551mg, 1.45mmol) in anhydrous DMF (10mL) is added DIPEA (240µL, 1.45mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (100) as a colorless oil (520mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22-1.40(m, 4H), 1.48-1.63(m, 1H), 1.90-2.12(m, 4H), 2.27(s, 3H), 3.44(dd, 2H), 3.72(dd, 2H), 4.21-4.35(m, 3H), 7.05-7.12(m, 2H), 7.26-7.27(m, 3H), 7.85(dd, 1H), 8.38(s, 1H)

LC/MS (ES+) m/z = 472.14, 474.13

EXAMPLE 101

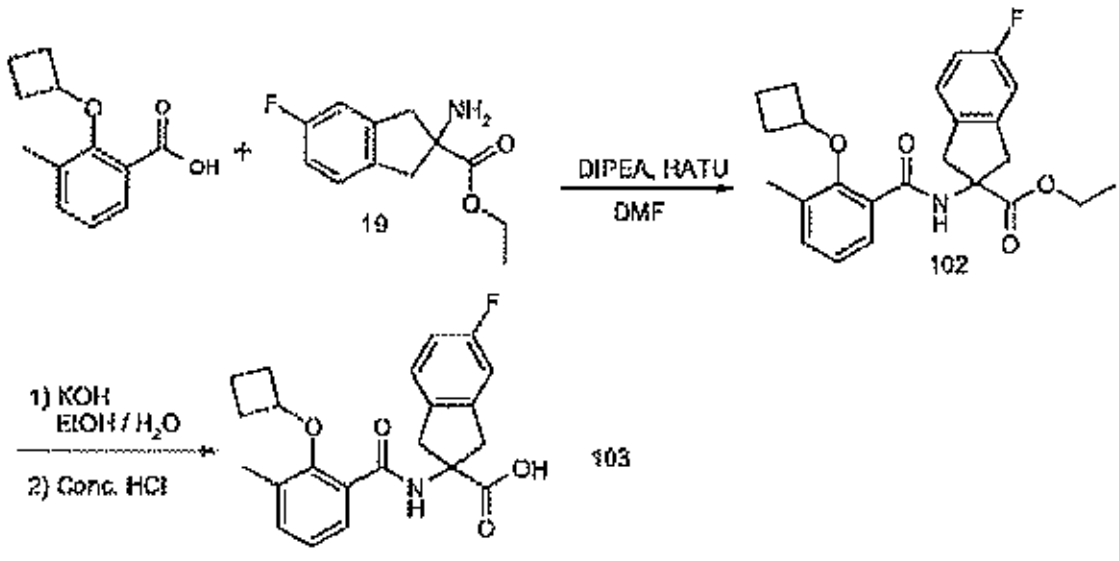
5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (101):

The mixture 5-bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (100) (442mg, 0.94mmol) and KOH (700mg, 12mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (101) as white solid (390mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(m, 1H), 1.49(m, 1H), 1.83-2.00(m, 4H), 2.22(s, 3H), 3.31-3.61(m, 4H), 4.33(m, 1H), 7.04 (t, 1H), 7.21(d, 1H), 7.28-7.37(m, 3H), 7.46(s, 1H), 8.67(s, 1H), 12.65(s, 1H)

LC/MS (ES+) m/z = 444.07, 446.06

EXAMPLE 102



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (102):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (523mg, 2.33mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (18mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred

at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (102) as white solid (681mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21-4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 412.19

EXAMPLE 103

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (103):

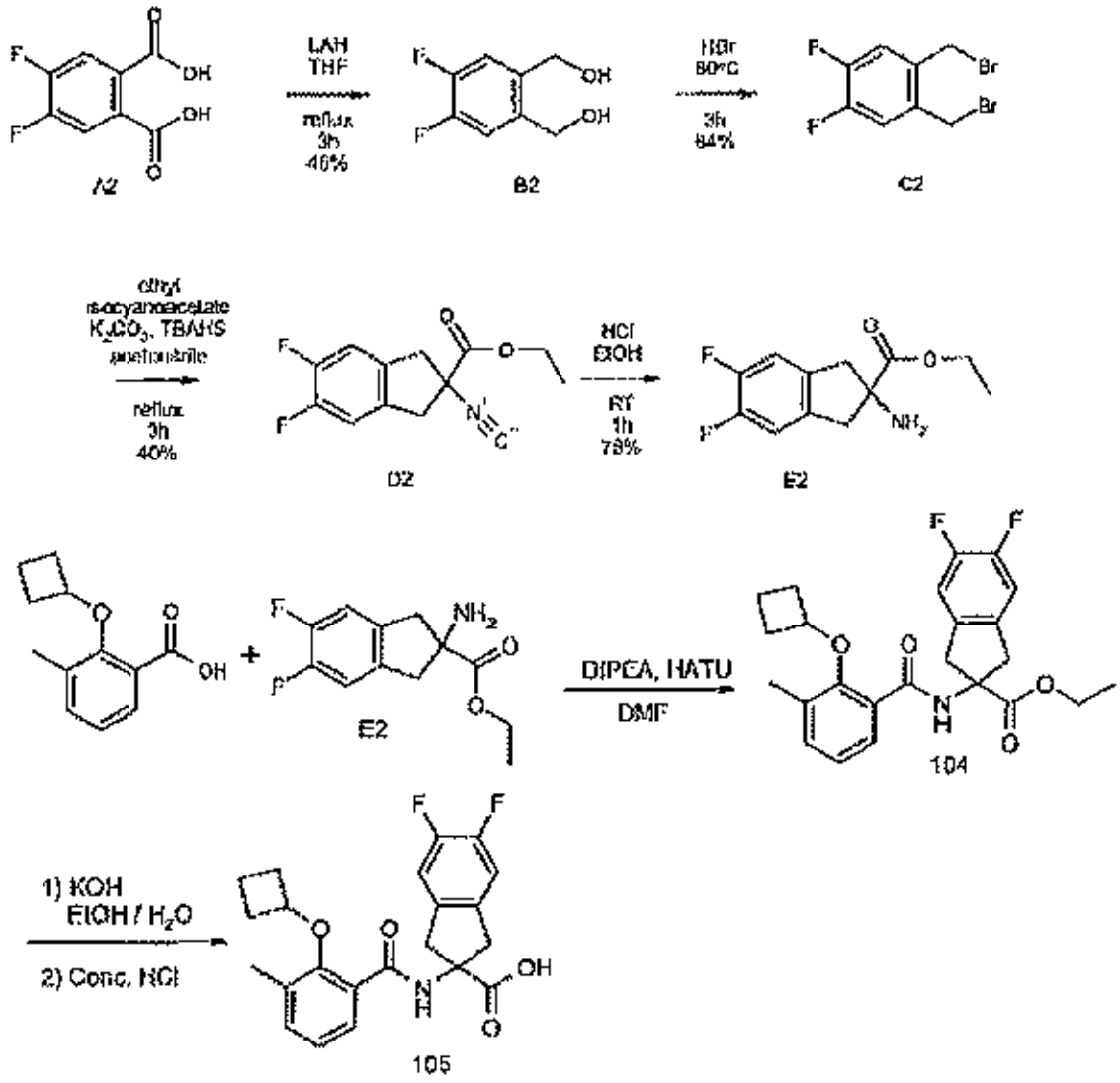
The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (102) (510mg, 1.24mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (103) as white solid (469mg, 99%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.15

Example 104

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid ethyl ester (104):



Preparation of B2: To a suspension of LAH (375mg, 9.9 mmol) in THF (5mL) is added a solution of 4,5-difluorophthalic acid A2 (1g, 4.95 mmol) in THF (15mL), dropwise at 0°C. The resulting mixture is refluxed for 3 hr following which it is cooled to 0°C and quenched by slow addition of EtOAc. The reaction mass is filtered through a pad of celite and the filter bed is washed with methanol. The combined filtrate is concentrated to yield crude product that is purified over silica eluting with 5% MeOH in DCM to yield B2 (400mg, 46%).

^{1}H-NMR (400 MHz, $CDCl_3$): 4.69 (s, 4H), 7.19 (t, J = 9.2 and 2 Hz, 2H); FIA-MS: m/z 173 (M + H).

Preparation of C2: A stirred suspension of B2 (1g, 5.74 mmol) in aq. HBr (47%, 10mL) is stirred at 80°C for 3h. The progress of the reaction is monitored by tlc. After complete

consumption of starting material, the reaction mixture is cooled to RT and extracted with DCM. The combined organics is washed with brine, dried and concentrated to give C2 (1.4g, 84%). The dibromide is rather unstable and is immediately utilized for the next step.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.59 (s, 4H), 7.19 (t, J = 9 and 2 Hz, 2H); FIA-MS: m/z 201 (M + H).

Preparation of D2: A mixture of dibromide C2 (5.5g, 18.33 mmol), ethylcyanoacetate (2.07g, 18.33 mmol), K_2CO_3 (14g, 106.3 mmol) and tetrabutylammonium hydrogensulfate (1.8g, 5.33 mmol) in CH_3CN (150mL) is refluxed for 3h. The reaction mixture is cooled to RT, filtered and concentrated. The residue is dissolved in ether, washed with water, brine, dried, concentrated to get a sticky mass that is purified over silica eluting with 10% EtOAc in hexanes to yield D2 (1.8g, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): 1.32 (t, J = 7.2 and 3 Hz, 3H), 3.40 (d, J = 16.3 Hz, 2H), 3.60 (d, J = 16.3 Hz, 2H), 4.30 (q, J = 7.2 and 2 Hz, 2H), 7.04 (t, J = 8.6 and 2 Hz, 2H).

Preparation of E2: To a stirred solution of D2 (2g, 7.96 mmol) in EtOH (50mL) is added conc HCl (1mL) and reaction mixture is stirred at RT for 1h. The reaction mixture is concentrated, diluted with water and extracted with ether. The organic layer is discarded and the aqueous layer is brought to pH 9-10 by using aq. ammonia solution maintaining internal temperature below 10°C. The resulting solution is extracted with EtOAc (3 x 50mL). The combined organics is washed with water, brine, dried, and concentrated to get a sticky mass that is purified over silica eluting with 10% EtOAc in hexanes to yield E2 (1.5g, 78%) as off-white solid of mp 69-71°C.

^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (t, J = 7.1and 3 Hz, 3H), 2.80 (d, J = 15.9 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 6.99 (t, J = 8.8 and 2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.7, 150.7, 150.5, 148.2, 148.1, 136.3, 136.26, 136.22, 113.24, 113.17, 113.11, 113.05, 65.2, 61.2, 45.2, 13.8; FIA-MS: m/z 242 (M + H); HPLC purity: 94.28% (qualitative).

Preparation of 104:

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (250mg, 1.21mmol), 2-amino-5,6-difluoro-indan-2-carboxylic acid ethyl ester E2 (292mg, 1.21mmol), HATU (551mg, 1.45mmol) in anhydrous DMF (10mL) is added DIPEA (240µL, 1.45mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-70% EtOAc in heptane) to give a pure product (104A) as white solid (420mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.30-1.41(m, 1H), 1.52-1.62(m, 1H), 1.96-2.16(m, 4H), 2.28(s, 3H), 3.34(d, 2H), 3.70(d, 2H), 4.23- 4.39(m, 3H), 6.99-7.11(m, 3H), 7.28(d, 1H), 7.85(dd, 1H), 8.43(s, 1H)
LC/MS (ES+) m/z = 430.22

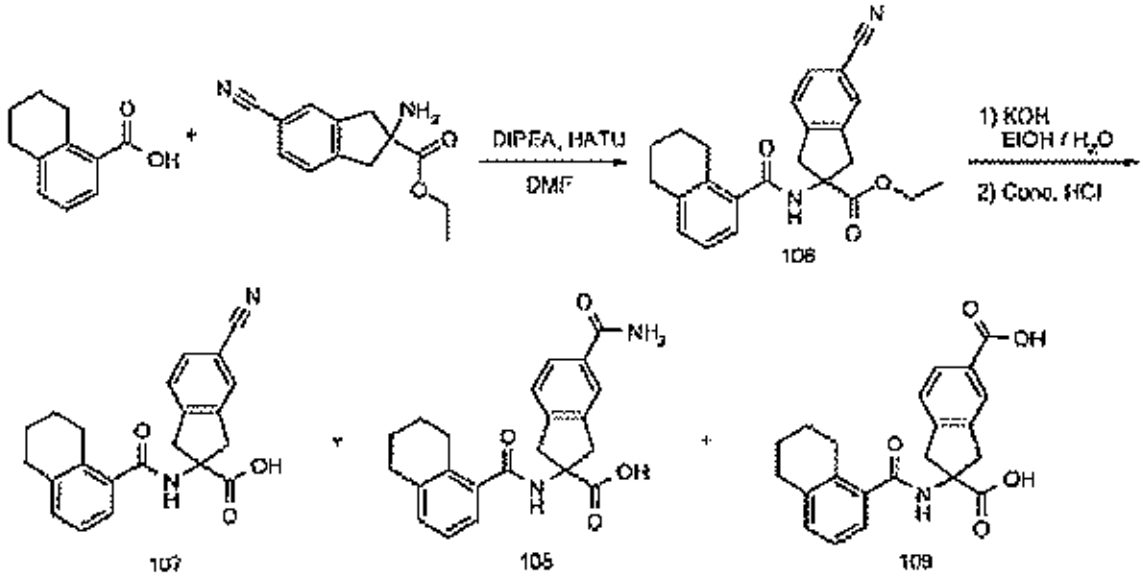
EXAMPLE 105

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid (105):

The mixture 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid ethyl ester (104) (367mg, 0.85mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the solid is purified by HPLC to give a pure product (105) as white solid (300mg, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.28(m, 1H), 1.48(m, 1H), 1.85-2.00(m, 4H), 2.21(s, 3H), 3.34(d, 2H), 3.51(d, 2H), 4.33(m, 1H), 7.02(t, 1H), 7.28-7.34(m, 4H), 8.69(s, 1H)
LC/MS (ES+) m/z = 430.22

EXAMPLE 106



5-Cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (106):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (306mg, 1.74mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (601mg, 2.61mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (15mL) is added DIPEA (431µL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-80% EtOAc in heptane) to give a pure product (106) as white solid (473mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.74(m, 4H), 2.76(br s, 2H), 2.82(br s, 2H), 3.47(dd, 2H), 3.72(t, 2H), 4.25(q, 2H), 6.47(s, 1H), 7.03-7.12(m, 3H), 7.31(d, 1H), 7.49(d, 2H)

LC/MS (ES+) m/z = 389.18

EXAMPLES 107, 108, 109

5-Cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (107):

5-Carbamoyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (108):

and 2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2,5-dicarboxylic acid (109):

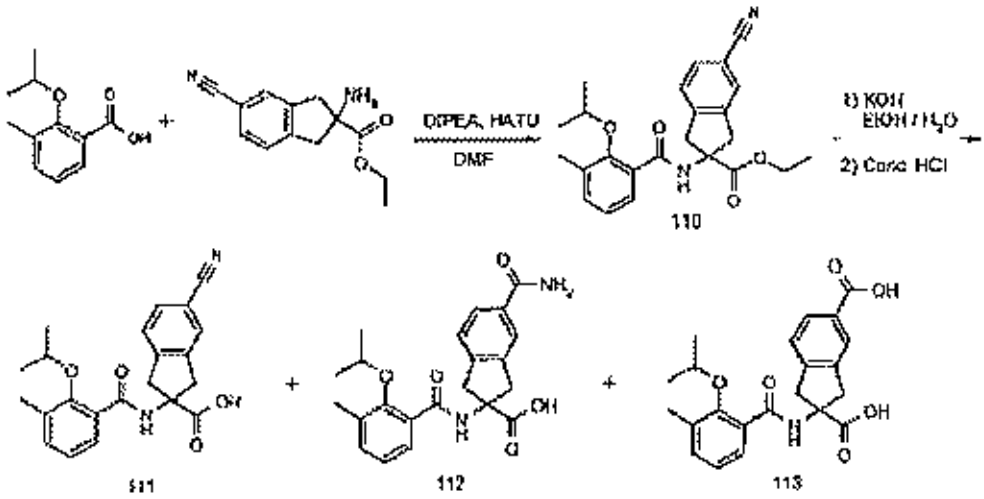
The mixture of 5-cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (106) (320mg, 0.82mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the solid is purified by HPLC to give 3 pure products: (107) as white solid (44mg, 15%), (108) as white solid (154mg, 50%) and (109) as white solid (28mg, 9%).

(107): ^{1}H NMR (CD_3OD, 300MHz): δ 1.75(m, 4H), 2.77(br s, 4H), 3.49(dd, 2H), 3.75(t, 2H), 7.04-7.12(m, 3H), 7.41(d, 1H), 7.54-7.59(m, 2H), 8.87(s, 1/3H)
LC/MS (ES+) m/z = 361.15

(108): ^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.76(m, 4H), 3.44(d, 2H), 3.73(dd, 2H), 7.04-7.11 (m, 3H), 7.32(d, 1H), 7.72(d, 2H), 8.87(s, 1/2H)
LC/MS (ES+) m/z = 379.17

(109): ^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.77(m, 4H), 3.45(dd, 2H), 3.74(t, 2H), 7.04-7.09(m, 3H), 7.33(d, 1H), 7.88(d, 2H), 8.88(s, 1/2H)
LC/MS (ES+) m/z = 380.16

EXAMPLE 110



5-Cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (110):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (377mg, 1.94mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (670mg, 2.91mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480µL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (3 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (110) as a white semisolid (680mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.12(m, 6H), 1.23(t, 3H), 2.27(s, 3H), 3.47(dd, 2H), 3.77(t, 2H), 4.21- 4.26(m, 3H), 7.08(t, 1H), 7.28-7.35(m, 2H), 7.51(d, 2H), 7.84(d, 1H), 8.47(s, 1H)
LC/MS (ES+) m/z = 407.19

EXAMPLE 111, 112, 113

5-Cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (111):

5-Carbamoyl-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (112):

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2,5-dicarboxylic acid (113):

The mixture of 5-cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (110) (527mg, 1.3mmol) and KOH (1.3g, 23mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely

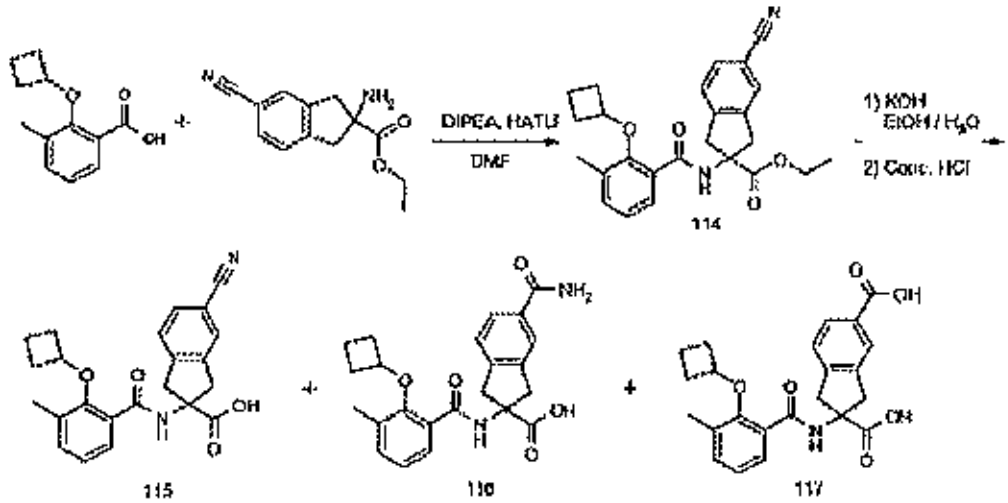
dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the solid is purified by HPLC to give 3 pure products: (111) as white solid (37mg, 8%), (112) as white solid (295mg, 57%) and (113) as white solid (62mg, 12%).

(111): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(m, 6H), 2.27(s, 3H), 3.49(dd, 2H), 3.90(dd, 2H), 4.19(m, 1H), 7.11(t, 1H), 7.34(t, 2H), 7.53(d, 2H), 7.88(dd, 1H), 8.65(s, 1H)
LC/MS (ES+) m/z = 379.16

(112): ^{1}H NMR ($CDCl_3$ + drops of D3OD, 300MHz): δ 1.08(dd, 6H), 2.26(s, 3H), 3.43(dd, 2H), 3.80(dd, 2H), 4.20(m, 1H), 7.08(t, 1H), 7.28-7.32(m, 2H), 7.67-7.77(m, 2H), 7.79(dd, 1H), 8.58(s, 1/4H)
LC/MS (ES+) m/z = 397.18

(113): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.04(m, 6H), 2.26(s, 3H), 3.45(dd, 2H), 3.81(t, 2H), 4.18(m, 1H), 7.08(t, 1H), 7.27-7.32(m, 2H), 7.80(d, 1H), 7.92(dd, 2H), 8.53(s, 1H)
LC/MS (ES+) m/z = 398.16

EXAMPLE 114



<u>5-Cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (114):</u>

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (670mg, 2.91mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480µL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-60% EtOAc in heptane) to give a pure product (114) as a white semisolid (682mg, 84%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.30-1.43(m, 1H), 1.51-1.65(m, 1H), 1.98-2.12(m, 4H), 2.28(s, 3H), 3.47(dd, 2H), 3.78(t, 2H), 4.22- 4.33(m, 3H), 7.08(t, 1H), 7.27-7.35(m, 2H), 7.51(d, 2H), 7.85(d, 1H), 8.47(s, 1H)
LC/MS (ES+) m/z = 419.19

EXAMPLES 115, 116, 117

<u>5-Cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (115):</u>

<u>5-Carbamoyl-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (116):</u>

<u>2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2,5-dicarboxylic acid (117):</u>

The mixture of 5-cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (114) (530mg, 1.3mmol) and KOH (1.3g, 23mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the obtained solid is purified by HPLC to give three pure products: (115) as white solid (167mg, 33%), (116) as white solid (239mg, 45%) and (117) as white solid (21mg, 4%).

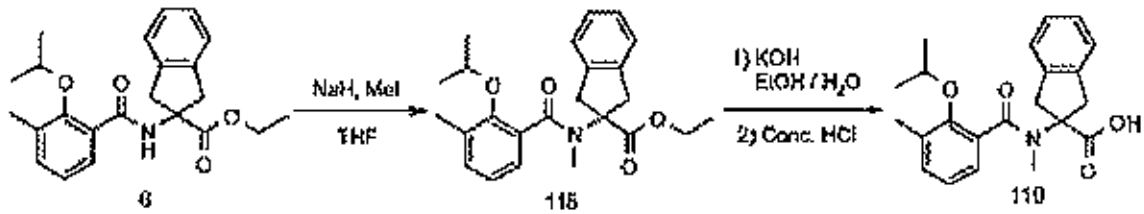
(115): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24-1.39(m, 1H), 1.46-1.56(m, 1H), 1.89-2.13(m, 4H), 2.10(s, 3H), 3.47(dd, 2H), 3.89(dd, 2H), 4.29(m, 1H), 7.09(t, 1H), 7.26-7.36(m, 2H), 7.52(d, 2H), 7.85(d, 2H), 8.60(s, 1H)

LC/MS (ES+) m/z = 391.13

(116): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.22-1.38(m, 1H), 1.46-1.56(m, 1H), 1.92-2.09(m, 4H), 2.26(s, 3H), 3.47(dd, 2H), 3.82(dd, 2H), 4.30(m, 1H), 7.08(t, 1H), 7.27-7.32(m, 2H), 7.66-7.72(m, 2H), 7.81(d, 1H), 8.57(s, 1H)
LC/MS (ES+) m/z = 409.14

(117): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.22-1.35(m, 1H), 1.42-1.52(m, 1H), 1.87-2.06(m, 4H), 2.26(s, 3H), 3.47(dd, 2H), 3.83(dd, 2H), 4.28(m, 1H), 7.08(t, 1H), 7.27-7.33(m, 2H), 7.82(d, 1H), 7.93(d, 2H), 8.53(s, 1H)
LC/MS (ES+) m/z = 410.17

EXAMPLE 118



6 115 110

2-[(2-Isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid ethyl ester (118):

To a solution of NaH (sodium hydride, 60% dispersion, 86.0mg, 2.15mmol)) in anhydrous THF (20mL) is added dropwise the solution of 2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6) (410mg, 1.07mmol) in THF (5mL) at 0°C. After stirring for 20min, methyl iodide (452µL, 7.26mmol) is added dropwise and the resulting suspension is warmed up to RT and continued stirring overnight. After being quenched by saturated aqueous solution of ammonium chloride (5mL), the reaction mixture is diluted in EtOAc (50mL). The organic layer is separated, washed with water (1 x 5mL) and brine (2 x 5mL), dried over anhydrous Na_2SO_4 and concentrated in *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-30% EtOAc in heptane) to give the pure product (118) as a colorless oil (240mg, 57%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.18(br d, 6H), 1.28(t, 3H), 2.24(s, 3H), 2.85(s, 3H), 3.44(d, 2H), 3.62(br d, 1H), 4.02(br d, 1H), 4.18-4.36(m, 3H), 7.00(t, 1H), 7.09(d, 1H), 7.18-7.20(m, 5H)

LC/MS (ES+) m/z = 396.21

EXAMPLE 119

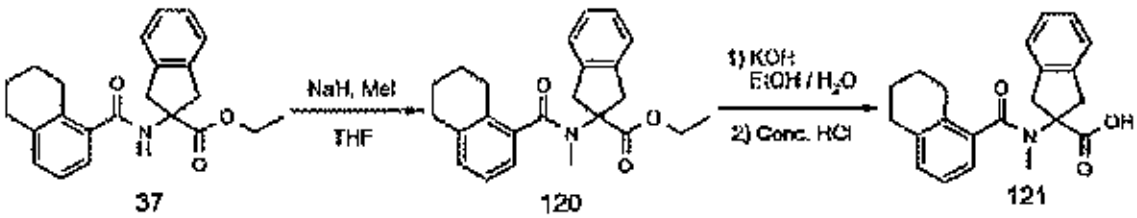
2-[(2-Isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid (119):

The mixture of 2-[(2-isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid ethyl ester (118') (200mg, 0.51mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (119) as a pale orange solid (170mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.15(br d, 6H), 2.24(s, 3H), 2.86(s, 3H), 3.46(d, 2H), 3.74(br d, 1H), 4.02(br d, 1H), 4.26(m, 1H), 6.99(t, 1H), 7.15-7.26(m, 6H), 8.79(br s, 1H)

LC/MS (ES+) m/z = 368.20

EXAMPLE 120



37 120 121

2-[Methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (120):

To a solution of NaH (sodium hydride, 60% dispersion, 124mg, 3.08mmol) in anhydrous THF (20mL) is added dropwise the solution of 2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37) (280mg, 0.77mmol) in THF (5mL) at 0°C. After stirring for 20min, methyl iodide (377µL, 6.05mmol) is added dropwise and the resulting suspension is warmed up to RT and continued stirring overnight. After being quenched by saturated ammonium chloride aqueous solution (5mL), the reaction mixture is diluted in EtOAc (50mL). The organic layer is separated, washed with water (1 x 5mL) and brine (2 x 5mL), dried over anhydrous Na_2SO_4 and concentrated in *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-30% EtOAc in heptane) to give a pure product (120) as a colorless semisolid (250mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.76(br s, 4H), 2.47(br s, 1H), 2.76(br s, 2H), 2.82(s, 3H), 2.82(br s, 1H), 3.45(d, 2H), 3.83(d, 2H), 4.24(m, 2H), 6.92(d, 1H), 7.05-7.08(m, 2H), 7.17-7.23(m, 4H)

LC/MS (ES+) m/z = 378.22

EXAMPLE 121

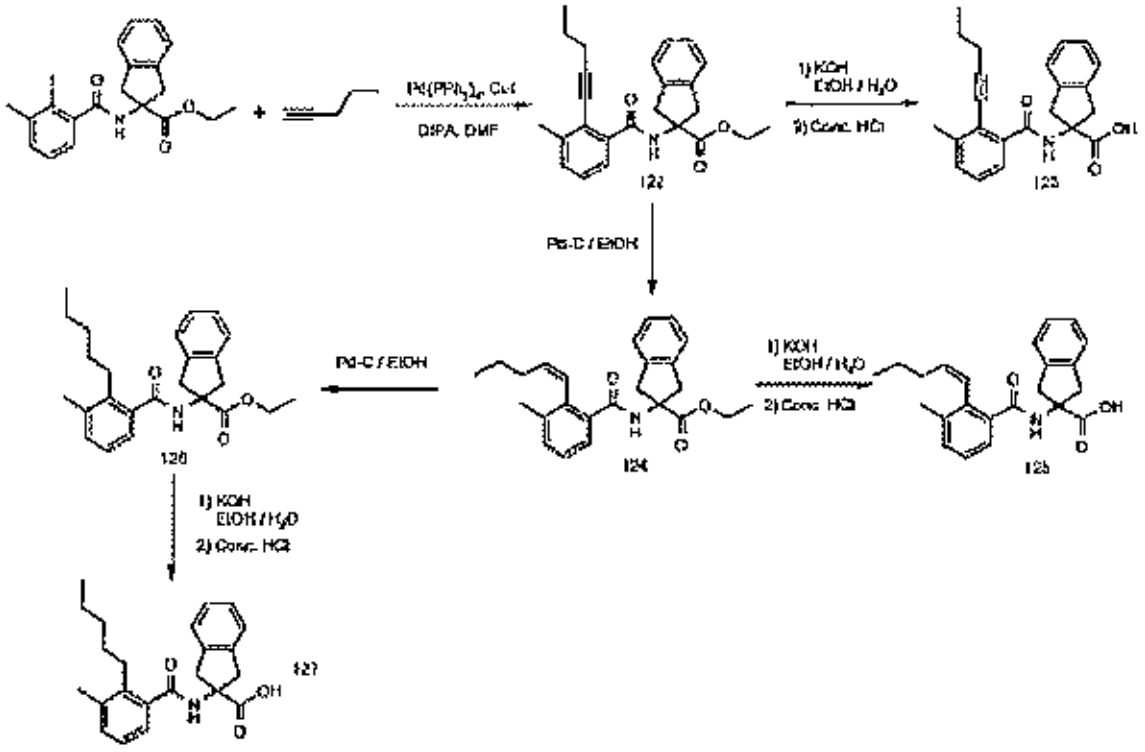
2-[Methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (121):

The mixture of 2-[methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (120) (226mg, 0.60mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~ 3. The precipitate is filtered to give a pure product (121) as a pale orange solid (150mg, 72%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.74(br s, 4H), 2.45(br s, 1H), 2.76-2.84(m, 3H), 2.85(s, 3H), 3.48(d, 2H), 3.90(d, 2H), 4.24(m, 2H), 6.96-7.26(m, 7H)

LC/MS (ES+) m/z = 350.16

EXAMPLE 122



2-(3-Methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (693mg, 1.54mmol) in anhydrous DMF (5mL) and DIPA (diisopropylamine, 10mL) is added $Pd(PPh_3)_4$ (89mg, 7.7%mmol), CuI (29mg, 0.154mmol) and pent-1-yne (1.5mL, 15.4mmol). The resulting solution is covered in argon and run in a microwave reaction: 110°C, 35minutes. After the removal of DMF and DIPA *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-40% EtOAc in heptane) to give a pure product (122) as a pale yellow solid (144mg, 24%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.99(t, 3H), 1.25(t, 3H), 1.51(m, 2H), 2.14(t, 1H), 2.39(s, 3H), 3.35(d, 2H), 3.77(d, 2H), 4.25(q, 2H), 7.17-7.30(m, 6H), 7.84(d, 1H), 8.21(s, 1H)

LC/MS (ES+) m/z = 390.18

EXAMPLE 123

2-(3-Methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid (123):

The mixture of 2-(3-methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122) (180mg, 0.46mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water

(1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. After filtration, the solid is purified by HPLC to give a pure product (123) as white solid (114mg, 69%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.99(t, 3H), 1.53(m, 2H), 2.14(t, 1H), 2.40(s, 3H), 3.39(d, 2H), 3.82(d, 2H), 7.18-7.32(m, 6H), 7.83(d, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 362.17

EXAMPLE 124

2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (124):

To a solution of 2-(3-methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122) (300mg, 0.77mmol) in absolute EtOH (18mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 30mg, 1.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product as white solid (168mg, 56%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.72(t, 3H), 1.13-1.30(m, 5H), 1.64(m, 2H), 2.16(s, 3H), 3.29(d, 2H), 3.69(d, 2H), 4.25(q, 2H), 5.56(dt, 1H), 6.29(d, 1H), 6.78(s, 1H), 7.17-7.26(m, 6H), 7.57(d, 1H)
LC/MS (ES+) m/z = 392.12

EXAMPLE 125

2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid (125):

The mixture of 2-[3-methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (124) (69mg, 0.18mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 5h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (125) as white solid (42mg, 64%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.73(t, 3H), 1.11-1.25(m, 2H), 1.62(q, 2H), 2.16(s, 3H), 3.33(d, 2H), 3.72(d, 2H), 5.54(dt, 1H), 6.25(d, 1H), 7.01(s, 1H), 7.18-7.28(m, 6H), 7.57(d, 1H)

LC/MS (ES+) m/z = 364.18

EXAMPLE 126

2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (126):

To a solution of 2-[3-methyl-2-((Z)-pent-1)-enyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (124) (92mg, 0.23mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 30mg, 1.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (126) as white solid (80mg, 89%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.88(t, 3H), 1.26-1.33(m, 7H), 1.42-1.47(m, 2H), 2.29(s, 3H), 2.64-2.69(m, 2H), 3.34(d, 2H), 3.74(d, 2H), 4.28(q, 2H), 6.18(s, 1H), 7.02-7.26(m, 7H)

LC/MS (ES+) m/z = 394.23

EXAMPLE 127

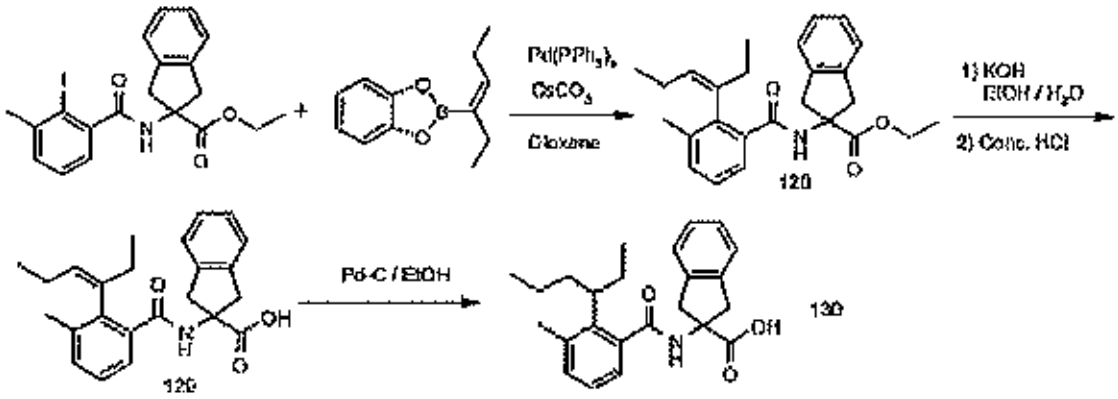
2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid (127):

The mixture of 2-(3-methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (126) (68mg, 0.17mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (127) as a pale brown solid (63mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.88(t, 3H), 1.26-1.30(m, 4H), 1.41-1.43(m, 2H), 2.30(s, 3H), 2.62-2.67(m, 2H), 3.40(d, 2H), 3.83(d, 2H), 6.22(s, 1H), 7.01-7.07(m, 2H), 7.17-7.26(m, 5H)

LC/MS (ES+) m/z = 366.20

EXAMPLE 128



2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (128):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 2-(1-Ethyl-but-1-enyl)-benzo[1,3,2]dioxaborole (709µL, 3.56mmol) in dioxane (15mL) is added $Pd(PPh_3)_4$ (103mg, 8.9%mmol) and 2M aqueous solution of $CsCO_3$ (1.34mL, 2.67mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (128) as a brown semi-solid (530mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.71(t, 3H), 0.99(t, 3H), 1.27(t, 3H), 1.75-2.05(m, 3H), 2.11-2.25(m, 1H), 2.21(s, 3H), 3.11(d, 1H), 3.33(d, 1H), 3.37(dd, 2H), 4.25(q, 2H), 5.54(t, 1H), 7.16-7.27(m, 6H), 7.66(d, 1H)

LC/MS (ES+) m/z = 406.25

EXAMPLE 129

2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (129):

The mixture of 2-[2-(-1-ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (128) (503mg, 1.24mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (40mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (129) as a brown solid (452mg, 97%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.68(t, 3H), 0.99(t, 3H), 1.83(m, 2H), 1.95-2.18(m, 2H), 2.20 (s, 3H), 3.11(d, 1H), 3.39(d, 1H), 3.72(dd, 2H), 5.54(t, 1H), 7.16-7.35(m, 6H), 7.63(d, 1H)

LC/MS (ES+) m/z = 378.21

EXAMPLE 130

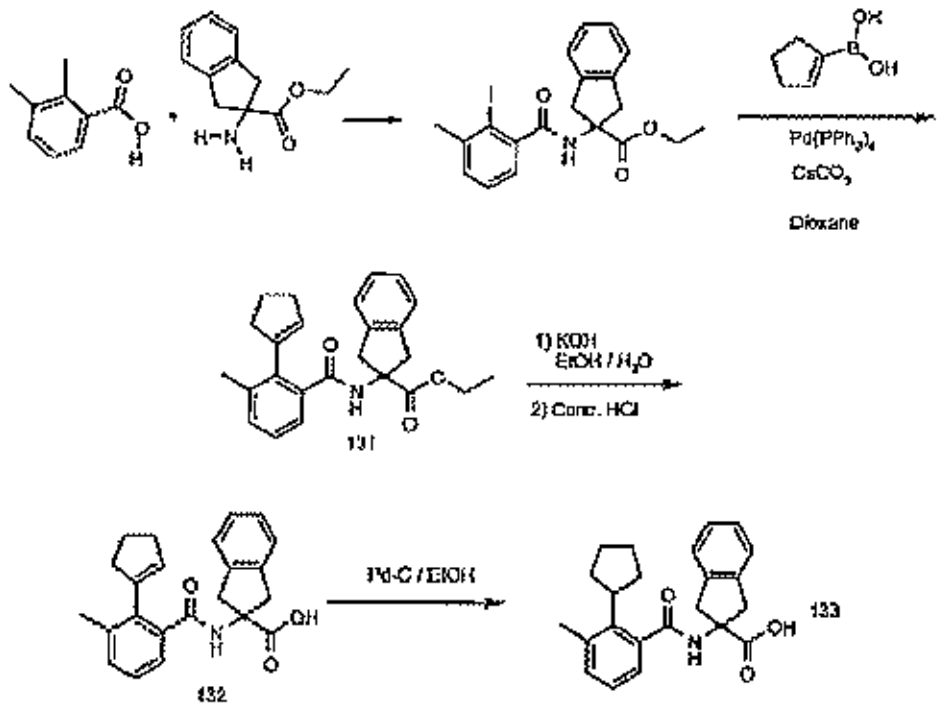
2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (130):

To a solution of 2-[2-(1-ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (129) (270mg, 0.72mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 46mg, 2.2%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 70°C, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (130) as white solid (75mg, 28%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.66-0.75(m, 6H), 0.83-1.26 (m, 2H), 1.56-1.69(m, 4H), 2.34(s, 3H), 2.87(m, 1H), 3.34-3.43(m, 2H), 3.72(d, 2H), 6.15(s, 1H), 7.00-7.25(m, 7H), 8.83(br s, 1H)

LC/MS (ES+) m/z = 380.22

EXAMPLE 131



2-(2-Iodo-3-methyl-benzoylamino)-indan-2-carboxylic Acid Ethyl Ester

A 100mL round bottom flask is charged with 2-Iodo-3-methylbenzoic Acid (1.92g, 7.31mmol) and dry DCM (25mL). A stirring bar is added and stirring initiated. After 5min, HTBU (2.37g, 7.31mmol) is added. After 5min, the 2-amino-indane-2-carboxylic Acid Ethyl Ester (1.50g, 7.31mmoles) is added followed by DIPEA (3.2mL, 18.37mmol). The reaction is allowed to stir for 118 hours. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/Dichloromethane) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70 mL). This is washed with dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 x 30mL) and brine (30 mL), dried over MgSO4, filtered and evaporated *in vacuo* to provide 2.04g of white solid. This material is dissolved in DCM (15mL). This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active elutant were collected. Fractions 10 through 15 are combined and evaporated *in vacuo* to constant weight to give 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester 1.04g of white solid.

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (131):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (800mg, 1.78mmol) and cyclopenten-1-ylboronic acid (796mg, 7.11mmol) in dioxane (20mL) is added $Pd(PPh_3)_4$ (412mg, 0.36mmol) and 2M aqueous solution of $CsCO_3$ (5.34mL, 10.7mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2.7h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5–40% EtOAc in heptane) to give a pure product (131) as a brown solid (589mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.72(m, 2H), 2.19(s, 3H), 2.33-2.43(m, 4H), 3.23(d, 2H), 3.70(dd, 2H), 4.25(q, 2H), 5.57(m, 1H), 6.99(s, 1H), 7.16-7.26(m, 6H), 7.58(d, 1H)
LC/MS (ES+) m/z = 390.22

EXAMPLE 132

<u>2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (132):</u>
The mixture of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (131) (560mg, 1.43mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (132) as a pale yellow solid (518mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.73(m, 2H), 2.19(s, 3H), 2.36-2.39(m, 4H), 3.27(d, 2H), 3.73(dd, 2H), 5.57(m, 1H), 7.16-7.29(m, 6H), 7.53(d, 1H)
LC/MS (ES+) m/z = 362.17

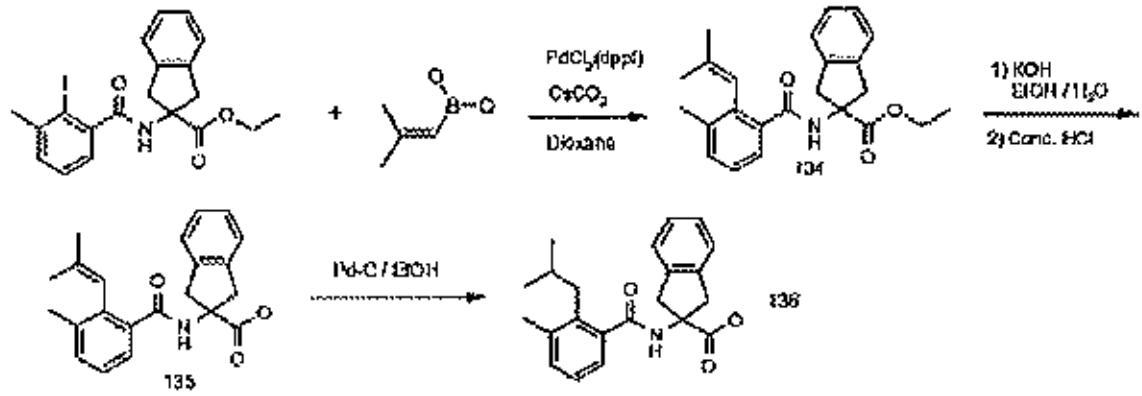
EXAMPLE 133

2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (133):
To a solution of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (132) (365mg, 1.01mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 192mg, 9%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 50°C, overnight. The catalyst is removed by

the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (133) as white solid (184mg, 50%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.55-1.77(m, 8H), 2.33(s, 3H), 3.22(m, 1H), 3.27(d, 2H), 3.77(dd, 2H), 6.22(m, 1H), 7.101-7.26(m, 7H)
LC/MS (ES+) m/z = 364.22

EXAMPLE 134



<u>2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (134):</u>

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 2,2-dimethylethyleneboronic acid (133mg, 1.34mmol) in dioxane (15mL) is added $PdCl_2$(dppf) ([1,1'-bis(diphenylphosphine)ferrocene]-dichloropalladium(II), 73mg, 8.9%mmol) and 2M aqueous solution of Cs_2CO_3 (1.34mL, 2.67mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (134) as a pale yellow solid (523mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.30(s, 3H), 1.65(s, 3H), 2.14(s, 3H), 3.24(br d, 2H), 3.70(br d, 2H), 4.25(q, 2H), 6.10(s, 1H), 7.02(s, 1H), 7.17-7.26(m, 6H), 7.69(d, 1H)
LC/MS (ES+) m/z = 378.22

EXAMPLE 135

<u>2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (135):</u>

The mixture 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (134) (283mg, 0.75mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (135) as white solid (250mg, 95%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.28(t, 3H), 1.68(s, 3H), 2.14(s, 3H), 3.28(d, 2H), 3.74(d, 2H), 6.09(s, 1H), 7.17-7.29(m, 6H), 7.66(d, 1H)
LC/MS (ES+) m/z = 350.19

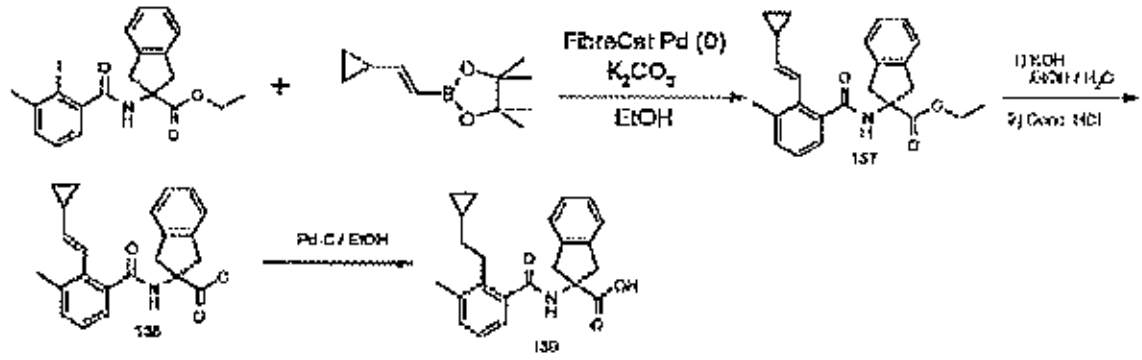
EXAMPLE 136

2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (136):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (135) (120mg, 0.34mmol) in acetic acid (15mL) is added the catalyst, Pd-C (5wt.%Pd, 72mg, 3.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 95°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed by EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (136) as white solid (65mg, 54%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.80(d, 6H), 1.75-1.78(m, 1H), 2.30(s, 3H), 2.68(d, 2H), 3.38(d, 2H), 3.76(d, 2H), 6.53(s, 1H), 7.03-7.25(m, 7H)
LC/MS (ES+) m/z = 352.15

EXAMPLE 137



2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (137):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (600mg, 1.34mmol) and 2-(2-cyclopropyl-vinyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1.11mL, 5.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 285mg, 0.13mmol) and 2M aqueous solution of K_2SO_4 (2.68mL, 5.36mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (137) as white solid (250mg, 49%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.47-0.50(m, 2H), 0.76-0.82(m, 2H), 1.29(t, 3H), 1.45(m, 1H), 2.27(s, 3H), 3.32(d, 2H), 3.72(d, 2H), 4.27(q, 2H), 5.30(dd, 1H), 6.45(dd, 1H), 6.52(s, 1H), 7.09-7.23(m, 6H), 7.39(d, 1H)

LC/MS (ES+) m/z = 390.20

EXAMPLE 138

2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (138):

The mixture 2-[2-(-2-cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (137) (220mg, 0.56mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (138) as white solid (209mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.47-0.50(m, 2H), 0.78-0.84(m, 2H), 1.43(m, 1H), 2.26(s, 3H), 3.38(d, 2H), 3.83(d, 2H), 5.24(dd, 1H), 6.34(d, 1H), 6.68(s, 1H), 7.11-7.26(m, 6H), 7.41(d, 1H)

LC/MS (ES+) m/z = 362.17

EXAMPLE 139

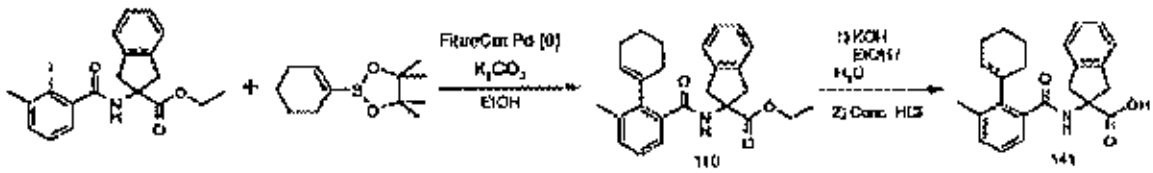
2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (139):

To a solution of 2-[2-((E)-2-cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (138) (120mg, 0.33mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (5wt.%Pd, 28mg, 1.3%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (139) as white solid (30mg, 25%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.00(m, 2H), 0.35-0.41(m, 2H), 0.66(m, 1H), 1.32-1.39(m, 2H), 2.30(s, 3H), 2.76-2.82(m, 2H), 3.40(d, 2H), 3.82(d, 2H), 6.23(s, 1H), 7.03-7.04(m, 2H), 7.16-7.26(m, 4H)

LC/MS (ES+) m/z = 364.13

EXAMPLE 140



2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (140):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (491mg, 1.09mmol) and 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (937μL, 4.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 240mg, 0.11mmol) and 2M aqueous solution of K_2SO_4 (2.18mL, 4.36mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (140) as white solid (95mg, 22%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.55(br t, 4H), 2.01-2.34(m, 4H), 2.21(s, 3H), 3.27(br t, 2H), 3.74(br d, 2H), 4.22-4.27(m, 2H), 5.56(s, 1H), 7.16-7.29(m, 7H), 7.63(d, 1H)
LC/MS (ES+) m/z = 404.22

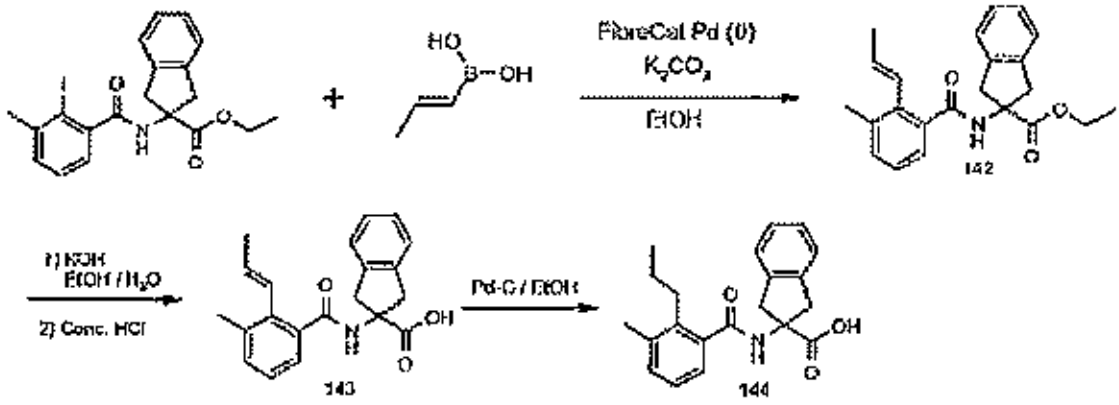
EXAMPLE 141

2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (141):

The mixture 2-(2-cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (141) (80mg, 0.20mmol) and KOH (300mg, 5.36mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (141) as white solid (71mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.41-1.56(m, 4H), 2.03-2.24(m, 4H), 2.21(s, 3H), 3.32(m, 2H), 3.83(d, 2H), 5.56(s, 1H), 7.16-7.34(m, 6H), 7.61(d, 1H)
LC/MS (ES+) m/z = 376.22

EXAMPLE 142



2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (142):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (600mg, 1.34mmol) and trans-1-propen-1-ylboronic acid (460mg, 5.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCat Pd(0), (4.84%Pd, 285mg, 0.13mmol) and 2M aqueous solution of K_2SO_4 (2.68mL, 5.36mmol). The resulting reaction mixture is covered with argon and run in a microwave

reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC and gave the pure product (142) as white solid (300mg, 63%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(dd, 3H), 2.25(s, 3H), 3.28(d, 2H), 3.71(d, 2H), 4.27(q, 2H), 5.75(dq, 1H), 6.37(d, 1H), 7.10-7.26(m, 6H), 7.36(d, 1H)
LC/MS (ES+) m/z = 364.18

EXAMPLE 143

2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid (143):

The mixture 2-[3-methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (142) (340mg, 0.94mmol) and KOH (700mg, 12.5mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (143) as white solid (315mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.75(dd, 3H), 2.25(s, 3H), 3.32(d, 2H), 3.73(d, 2H), 5.75(dq, 1H), 6.36(dd, 1H), 6.76(s, 1H), 7.10-7.24(m, 6H), 7.31(d, 1H)
LC/MS (ES+) m/z = 336.16

EXAMPLE 144

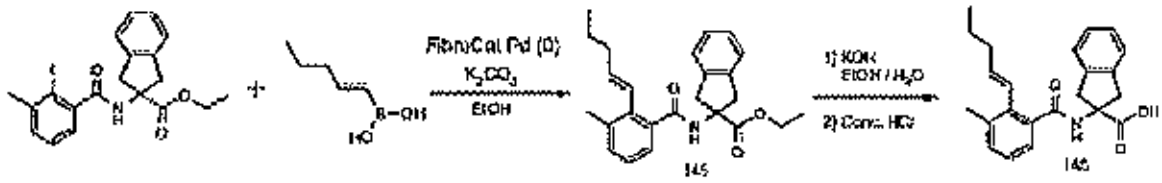
2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid (144):

To a solution of 2-[3-methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid (143) (220mg, 0.65mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (5wt.%Pd, 55mg, 2.6%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed with EtOH. The combined solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (144) as white solid (128mg, 58%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.91(t, 3H), 1.45(m, 2H), 2.45(s, 3H), 2.61-2.66(d, 2H), 3.40 (d, 2H), 3.82(d, 2H), 6.22(s, 1H), 7.04(d, 2H), 7.17-7.26(m, 5H)

LC/MS (ES+) m/z = 338.17

EXAMPLES 145-146



<u>2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (145):</u>

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (200mg, 0.45mmol) and *trans*-1-penten-1-ylboronic acid (205mg, 1.80mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 96mg, 0.045mmol) and 2M aqueous solution of K_2SO_4 (0.90mL, 1.80mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (145) as white solid (107mg, 60%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.93(t, 3H), 1.28(t, 3H), 1.42(m, 2H), 2.03(q, 3H), 2.26(s, 3H), 3.29(d, 2H), 3.70(d, 2H), 4.25(q, 2H), 5.75(dt, 1H), 6.37(d, 1H), 6.43(s, 1H), 7.09-7.25(m, 6H), 7.37(d, 1H)

LC/MS (ES+) m/z = 392.0

EXAMPLE 146

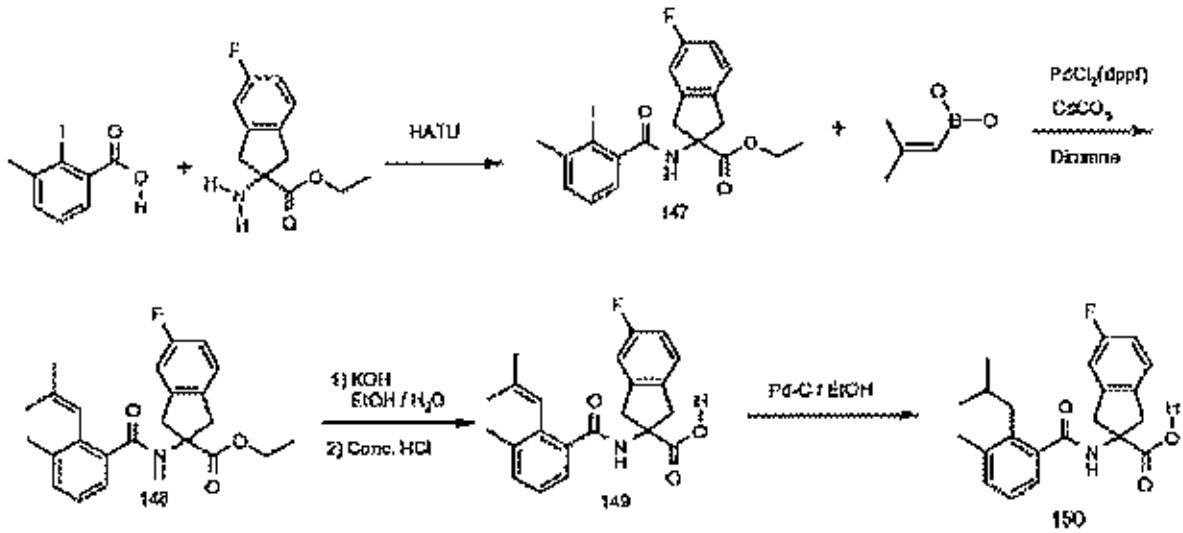
<u>2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid (146):</u>

The mixture 2-[3-methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (145) (170mg, 0.43mmol) and KOH (60mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (146) as white solid (160mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.93(t, 3H), 1.42(m, 2H), 2.05(q, 3H), 2.26(s, 3H), 3.33(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 5.73(dt, 1H), 6.35(d, 1H), 6.68(s, 1H), 7.11-7.21(m, 6H), 7.34(d, 1H)

LC/MS (ES+) m/z = 364.18

EXAMPLES 147-150



EXAMPLE 147

5-Fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (147):

To a solution of 2-iodo-3-methyl-benzoic acid (3.85g, 14.7mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (3.00g, 13.4mmol), HATU (6.10g, 16.1mmol) in anhydrous DMF (6mL) is added DIPEA (3.30mL, 20.1mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is recrystallized from EtOAc to give a pure product (147) as white solid (3.90g, 62%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 2.44 (s, 3H), 3.45-3.67(m, 4H), 4.28 (q, 2H), 6.32 (s, 1H), 6.85-6.94(m, 2H), 7.12-7.26(m, 4H)

LC/MS (ES+) m/z = 468.03

EXAMPLE 148

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (148):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and 2,2-dimethyethylenelboronic acid (342mg, 3.42mmol) in EtOH

(10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (148) as a colorless oil (245mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.34(d, 3H), 1.71(dd, 3H), 2.15(s, 3H), 3.25(br dd, 2H), 3.65(br dd, 2H), 4.24(q, 2H), 6.12(s, 1H), 6.86-6.92(m, 2H), 7.19-7.26(m, 4H), 7.65(d, 1H)

LC/MS (ES+) m/z = 396.18

EXAMPLE 149

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (149):

The mixture 5-fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (148) (245mg, 0.62mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (149) as white solid (230mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.32(s, 3H), 1.73(s, 3H), 2.15(s, 3H), 3.27(t, 2H), 3.68(dd, 2H), 6.12(s, 1H), 6.86-6.93(m, 2H), 7.13-7.30(m, 4H), 7.61(d, 1H)

LC/MS (ES+) m/z = 368.10

EXAMPLE 150

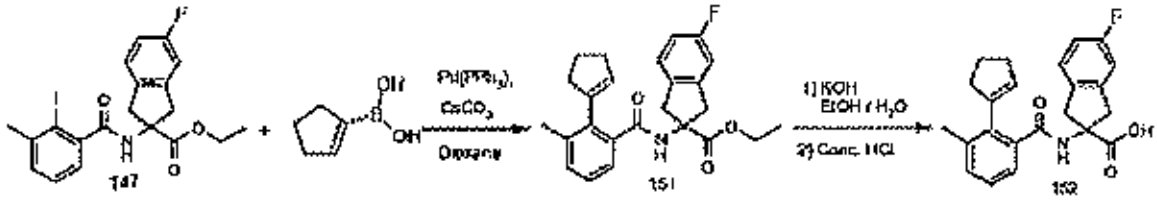
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (150):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (149) (230mg, 0.63mmol) in acetic acid (10mL) is added the catalyst, Pd-C (5wt.%Pd, 134mg, 6.3%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 95°C, overnight. The catalyst is removed by filtration through a pre-

column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (150) as white solid (200mg, 86%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.81(dd, 6H), 1.78(m, 1H), 2.30(s, 3H), 2.68(d, 2H), 3.37(t, 2H), 3.69(dd, 2H), 6.88-6.93(m, 3H), 7.13-7.30(m, 4H), 7.32(s, 1H)
LC/MS (ES+) m/z = 370.19

EXAMPLE 151-152



2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (151):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and cyclopenten-1-ylboronic acid (383mg, 3.42mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified HPLC to give a pure product (151) as white solid (240mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.76(m, 2H), 2.20(s, 3H), 2.38-2.41(m, 4H), 3.25(dd, 2H), 3.66(dd, 2H), 4.25(q, 2H), 5.62(t, 1H), 6.87-6.93(m, 2H), 7.12-7.30(m, 4H), 7.53(d, 1H), 8.39(br s, 1H)
LC/MS (ES+) m/z = 408.22

EXAMPLE 152

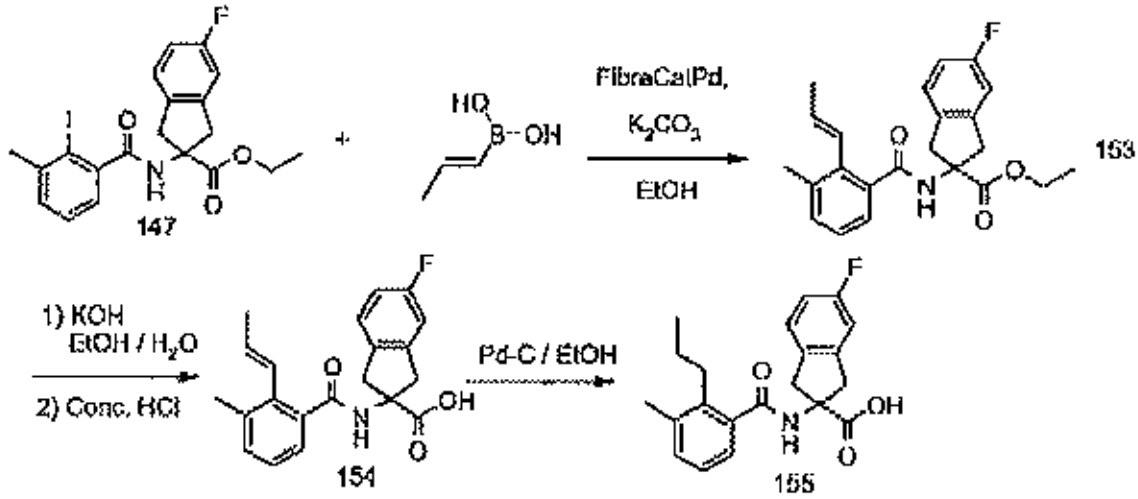
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (152):

The mixture of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (151) (190mg, 0.47mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is

completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (152) as white solid (182mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.72(m, 2H), 2.18(s, 3H), 2.34(t, 4H), 3.20(t, 2H), 3.66(dd, 2H), 5.55(s, 1H), 6.84-6.89(m, 2H), 7.07-7.26(m, 4H), 7.56(d, 1H)
LC/MS (ES+) m/z = 380.19

EXAMPLE 153



5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (153):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and trans-1-propen-1-ylboronic acid (294mg, 3.42mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (153) as white solid (165mg, 51%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.75(m, 3H), 2.26(s, 3H), 3.27(dd, 2H), 3.62(dd, 2H), 4.26(q, 2H), 5.76(dq, 1H), 6.38(d, 1H), 6.44(s, 1H), 6.85-6.91(m, 2H), 7.11-7.22(m, 3H), 7.35(d, 1H)
LC/MS (ES+) m/z = 382.21

EXAMPLE 154

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (154):

The mixture 5-fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (153) (260mg, 0.68mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.2mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 2.5h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The filtered compound is purified by HPLC to give a pure product (154) as white solid (267mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.76(m, 3H), 2.26(s, 3H), 3.31(t, 2H), 3.65(dd, 2H), 5.76(dq, 1H), 6.38(d, 1H), 6.80(s, 1H), 6.85-6.93(m, 2H), 7.10-7.22(m, 3H), 7.31(d, 1H)

LC/MS (ES+) m/z = 354.18

EXAMPLE 155

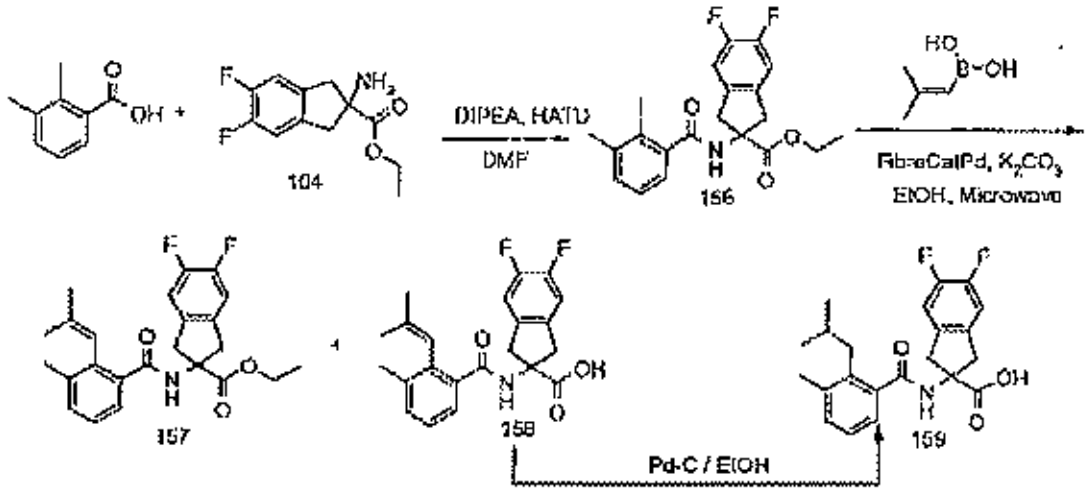
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (155):

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (154) (270mg, 0.76mmol) is dissolved in absolute EtOH (15mL) by heating. The resulting solution is cooled down to RT under argon and then is added the catalyst, Pd-C (5wt.%Pd, 125mg, 5.9%mmol). The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 50°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (155) as white solid (210mg, 78%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.92(t, 3H), 1.46(m, 2H), 2.30(s, 3H), 2.65-2.68(m, 2H), 3.36(t, 2H), 3.71(dd, 2H), 6.85-6.93(m, 2H), 7.03-7.18(m, 4H)

LC/MS (ES+) m/z = 356.14

EXAMPLE 156



5,6-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (156):

To a solution of 2-iodo-3-methyl-benzoic acid (1.50g, 5.75mmol), 2-amino-5,6-difluoro-indan-2-carboxylic acid ethyl ester (1.39g, 5.75mmol), HATU (2.63g, 6.90mmol) in anhydrous DMF (6mL) is added DIPEA (1.14mL, 6.90mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (200mL) and washed with water (1 x 20mL) and brine (2 x 20mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (156) as white solid (2.32g, 83%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 2.45(s, 3H), 3.48(d, 2H), 3.63(d, 2H), 4.27(q, 2H), 6.38 (s, 1H), 7.04(t, 2H), 7.10-7.13(m, 1H), 7.24-7.27(m, 2H)
LC/MS (ES+) m/z = 486.02

EXAMPLES 157 and 158

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (157) and 5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (158):

To a solution of 5,6-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.82mmol) and 2,2-dimethylethyleneboronic acid (328mg, 3.28mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 180mg, 8.2%mmol) and 2M aqueous solution of K_2SO_4 (1.64mL, 3.28mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 6h. After concentration *in vacuo*, the residue is purified by HPLC to give two

pure products: (157) as white solid (100mg, 29%) and (158) as white solid as well (120mg, 38%).

(157): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.38(d, 3H), 1.76(s, 3H), 2.15(s, 3H), 3.27(d, 2H), 3.59(d, 2H), 4.24(q, 2H), 6.14(s, 1H), 6.98-7.31(m, 5H), 7.61(d, 1H)
LC/MS (ES+) m/z = 414.20

(158): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34(d, 3H), 1.79(s, 3H), 2.15(s, 3H), 3.26(d, 2H), 3.75(d, 2H), 6.09(s, 1H), 7.02(t, 2H), 7.21-7.34(m, 3H), 7.77(d, 1H)
LC/MS (ES+) m/z = 386.19

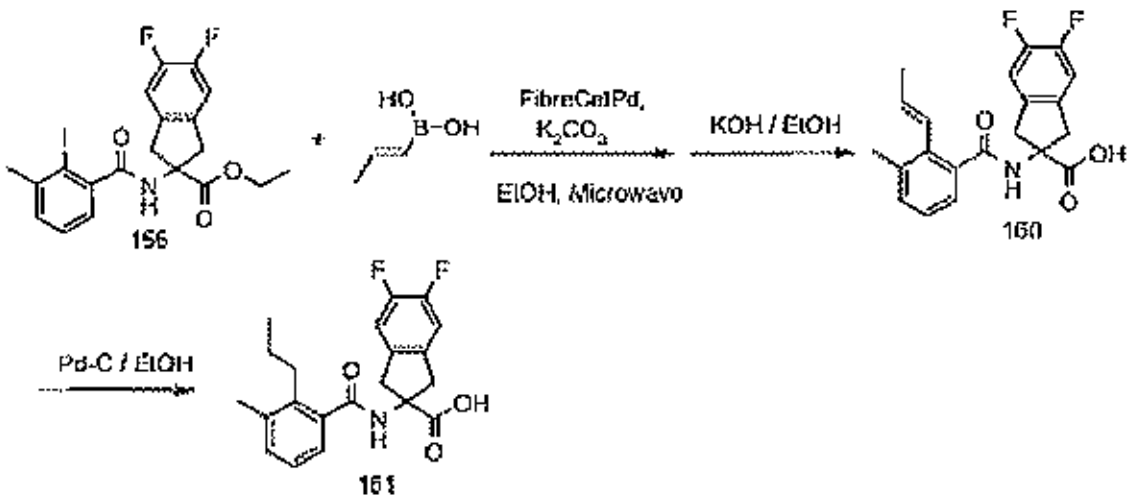
EXAMPLE 159

5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (159):

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (158) (200mg, 0.63mmol) is dissolved in acetic acid (15mL) by heating. The resulting solution is cooled down to RT and then the catalyst, Pd-C (5wt.%Pd, 134mg, 6.3%mmol) is added under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 95°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (159) as white solid (170mg, 84%).

(159): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.83(d, 6H), 1.80(m, 1H), 2.32(s, 3H), 2.68(d, 2H), 3.39(d, 2H), 7.00-7.20(m, 5H), 7.44(s, 1H)
LC/MS (ES+) m/z = 388.17

EXAMPLES 160-161



<u>5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid (160):</u>

To a solution of 5,6-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.82mmol) and trans-1-propen-1-ylboronic acid (282mg, 3.28mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 180mg, 8.2%mmol) and 2M aqueous solution of K_2SO_4 (1.64mL, 3.28mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 5h. After concentration *in vacuo*, the residue is purified by HPLC to give a white solid (160mg), which is dissolved in EtOH (5mL) and water (0.2mL) together with KOH (600mg, 10.7mmol) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration is purified by HPLC to give a pure product (160) as white solid (127mg, 42% overall yield).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.80(dd, 3H), 2.27(s, 3H), 3.36(d, 2H), 3.63(d, 2H), 5.77(dq, 1H), 6.40(d, 1H), 7.01(t, 2H), 7.10-7.29(m, 4H)
LC/MS (ES+) m/z = 372.15

EXAMPLE 161

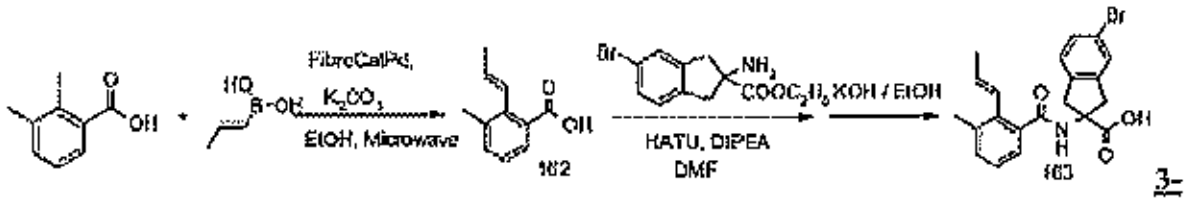
<u>5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid (161):</u>

5,6-Difluoro-2-[3-methyl-2-(-propenyl)-benzoylamino]-indan-2-carboxylic acid (160) (110mg, 0.30mmol) is dissolved in absolute EtOH (15mL) by heating. The resulting solution is cooled to RT and catalyst, Pd-C (5wt.%Pd, 64mg, 3.0%mmol) is added under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 50°C, overnight.

The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (161) as white solid (80mg, 71%).

^{1}H NMR (DMSO-d6, 300MHz): δ 0.86(q, 3H), 1.40(m, 2H), 2.27(s, 3H), 2.58(m, 2H), 3.29(d, 2H), 3.52(d, 2H), 7.00(d, 1H), 7.08(t, 1H), 7.18(d, 1H), 7.29(t, 2H), 8.87(s, 1H), 12.58(s, 1H)
LC/MS (ES+) m/z = 374.14

EXAMPLE 162



3-

Methyl-2-((E)-propenyl)-benzoic acid (162):

To a solution of 2-iodo-3-methyl-benzoic acid (708mg, 2.70mmol) and trans-1-propen-1-ylboronic acid (526mg, 6.12mmol) in EtOH (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 235mg, 0.15mmol) and 2M aqueous solution of K_2SO_4 (3.06mL, 6.12mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (162) as a pale yellow solid (500mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.90(dd, 3H), 2.34(s, 3H), 5.68(dq, 1H), 6.67(d, 1H), 7.20(t, 1H), 7.35(d, 1H), 7.70(d, 1H)
LC/MS (ES+) m/z = 177.10, 218.13

EXAMPLE 163

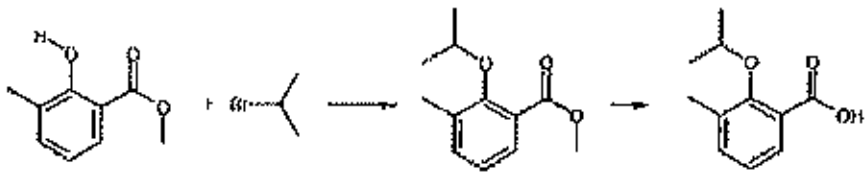
5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (163):

To a solution of 3-methyl-2-((E)-propenyl)-benzoic acid (162) (470mg, 2.67mmol), 2-amino-5-bromo-indan-2-carboxylic acid ethyl ester (835mg, 2.94mmol) and HATU (1.22mg, 3.20mmol) in anhydrous DMF (12mL) is added DIPEA (529μL, 3.20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is

purified by flash column chromatography (300g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a white solid (1.12g), which is dissolved in EtOH (15mL) and water (1mL) together with KOH (1.20g, 21mmol) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (100mL) and acidified with conc. HCl until no more precipitate came out of the water. The filtered compound is purified by HPLC to give a pure product (163) as white solid (1.03g, 93% overall yield).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.74(dd, 3H), 2.25(s, 3H), 3.30(dd, 2H), 3.74(dd, 2H), 5.73(dq, 1H), 6.32(d, 1H), 6.51(s, 1H), 7.08-7.38(m, 6H)
LC/MS (ES+) *m/z* = 414.09, 416.09

EXAMPLE 164



164

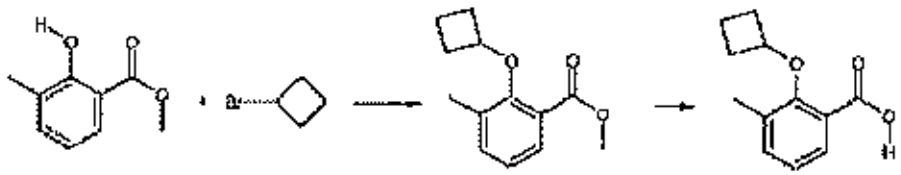
<u>2-Isopropoxy-3-methyl-benzoic acid (164):</u>

A 250mL round bottom flask is charged with methyl 2-hydroxy-3-methylbenzoate (10g, 60.18mmol) and dry N,N-dimethylformamide (DMF, 120mL). A stirring bar is added and stirring is initiated. After 2 minutes 2-Bromopropane (8.1mL, 86.65mmol) is added via syringe. KI (20mg, cat.) and $CsCO_3$ (44.42g, 136.32mmol) are added in order. The reaction is capped. The reaction flask is fitted with a heating mantle that is warmed to 43°C. After 4 days, tlc analysis (silica, 1:3 EtOAc:heptanes) indicates that the starting phenol is consumed and converted to a single spot as visualized by UV analysis. The heating source is removed from the reaction flask. After stirring for an additional 2h at ambient temperature, the contents of the reaction flask are filtered through a pad of Celite. The Celite pad is washed with EtOAc:heptanes (1:1, 200mL). The filtrate is transferred to a separatory funnel and washed with brine (100mL), water (100mL), saturated aqueous $NaHCO_3$ (100mL). This washing sequence is repeated (1 time) followed by a final washing with brine (50mL). The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo*. Pumping to constant weight provided 11.88g of pale yellow oil. The 250mL flask containing the above material is charged with 1,4-dioxane (50mL) and MeOH (100mL). A stirring bar is added and stirring is initiated.

After dissolution, water (50mL) is added followed by the LiOH hydrate (5.7g, 135.8mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, 55mL). The contents of the flask are transferred to a separatory funnel containing EtOAc (100mL). The layers are separated. The aqueous layer is extracted with EtOAc (50mL). The combined organic extracts are washed with water (50mL) and brine (50mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Pumping to constant weight gives 10.19g (52.46mmol, 87.18 %) of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.18 (d, 6 H), 2.22, (s, 3H), 4.19 (m, 1H), 7.03 (dd, 1H), 7.38, (dd, 1H), 7.48 (dd, 1H).
LC/MS m/z=195.

EXAMPLE 165



166

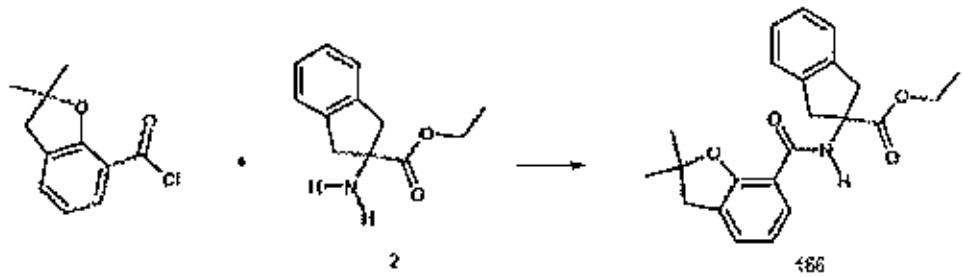
<u>2-Cyclobutoxy-3-methyl-benzoic acid (165):</u>

A 100mL round bottom flask is charged with methyl 2-hydroxy-3-methylbenzoate (5g, 30.09mmol) and dry N,N-dimethylformamide (DMF, 60mL). A stirring bar is added and stirring is initiated. After 2min bromocyclobutane (5g, 37.04mmoles) is added via syringe. Potassium iodide (10mg, cat.) and $CsCO_3$ (22.21g, 68.16mmol) are added in order. The reaction is capped. The reaction flask is fitted with a heating mantle that is warmed to 43°C. After 4 days, tlc analysis (silica, 1:3 EtOAc:heptanes) indicates that the starting phenol had been consumed and converted to a single spot as visualized by UV analysis. The heating source is removed from the reaction flask. After stirring for an additional 16h at ambient temperature, the contents of the reaction flask are filtered through a pad of Celite. The Celite pad is washed with EtOAc:heptanes (1:1, 200mL). The filtrate is transferred to a separatory funnel and washed with brine (50mL), water (50mL), saturated aqueous $NaHCO_3$ (50mL). This washing sequence is repeated (1x) followed by a final washing with brine (50mL). The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo*. Pumping to constant weight gives 5.94g of pale yellow oil. The 100mL flask containing the above material is

charged with 1,4-dioxane (30mL) and MeOH (30mL). A stirring bar is added and stirring is initiated. After dissolution, water (10mL) is added followed by the LiOH hydrate (2.80g, 66.78mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, 30mL). The contents of the flask are transferred to a seperatory funnel that contains EtOAc (80mL). The layers are separated. The aqueous layer is extracted with EtOAc (40mL). The combined organic extracts are washed with water (50mL) and brine (50mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Pumping to constant weight gives 5.3g (25.70mmol, 85.40 %) of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.37 (m, 1 H), 1.42 (m, 1 H), 2.02 – 2.26, (m, 4 H), 2.22 (s, 3 H) 4.35 (m, 1H), 7.03 (dd, 1H), 7.36, (dd, 1H), 7.47 (dd, 1H).
LC/MS m/z = 207.

EXAMPLE 166



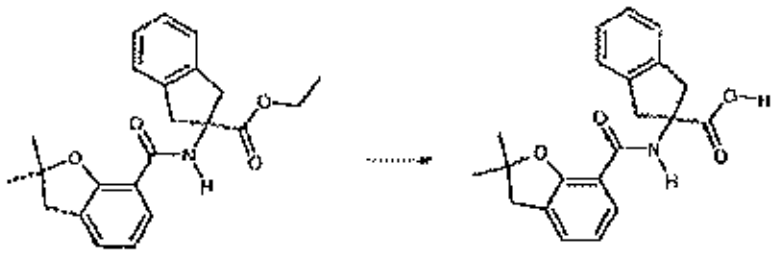
2-[(2,2-Dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (166):

A test tube (25 x 150 mm) containing a stirring bar and 2-amino-indane-2-carboxylic acid ethyl ester (0.5g, 2.436mmol) is charged with dry DCM (3mL). Stirring is initiated. After dissolution, the DIPEA (1.50mL, 8.6mmol) and 4-dimethylaminopyridine (2mg, 17μmol) are added. A solution of 2,2-dimethy-2,3-dihydro-1-benzofuran-7-carbonyl chloride (0.73g, 3.47mmol) in dry DCM (4mL) is added to the reaction tube. After stirring for 18h, tlc analysis (silica, 10 % CH_3OH in DCM) indicates complete consumption of the starting amine. The reaction mixture is diluted with DCM (10mL) and washed with 5% aqueous HCl (2 x 5mL) and brine (5mL), dried over $MgSO_4$ filtered and evaporated by pumping to constant weight gives 0.72g of a light brown gum. This material is purified by chromatography (silica, 0% to 20 % EtOAc in DCM) on the ISCO Companion using a 40g cartridge (silica). Fractions 17 -

22 are combined, evaporated and pumped to a constant weight to provide 0.62g (67 %) of a glassy solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.14 (t, 3 H), 1.37 (s, 6 H) 3.03, (s, 2 H), 3.43 (dd, 4H), 4.12 (q, 2H), 6.91 (dd, 1H), 7.16 - 7.27 (m, 4H), 7.35 (dd, 1H), 7.56 (d, 1H), 8.32 (s, 1H).
LC/MS m/z = 380.

EXAMPLE 167



167

2-[(2,2-Dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (167):

A 50mL round bottom flask containing the 2-[(2,2-dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.45g, 1.179mmol) is charged with MeOH (25mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (8mL) and the LiOH (108mg, 2.58mmol) are added. After 56h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 3 by slowly adding dilute aqueous HCl (3%, ~20mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (30mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 460mg of material. The sample is purified by column chromatography (silica, 2 % to 15 % CH_3OH in DCM) using an ISCO Companion and a 12g cartridge. Fraction 3 is collected and evaporated. After pumping to constant weight, 375mg (90 %) of a dry white powder is obtained.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.36 (s, 6 H) 2.99, (s, 2 H), 3.40 (dd, 4H), 6.88 (dd, 1H), 7.11 - 7.20 (m, 4H), 7.30 (dd, 1H), 7.57 (d, 1H), 8.34 (s, 1H).
LC/MS m/z = 352.

EXAMPLE 168

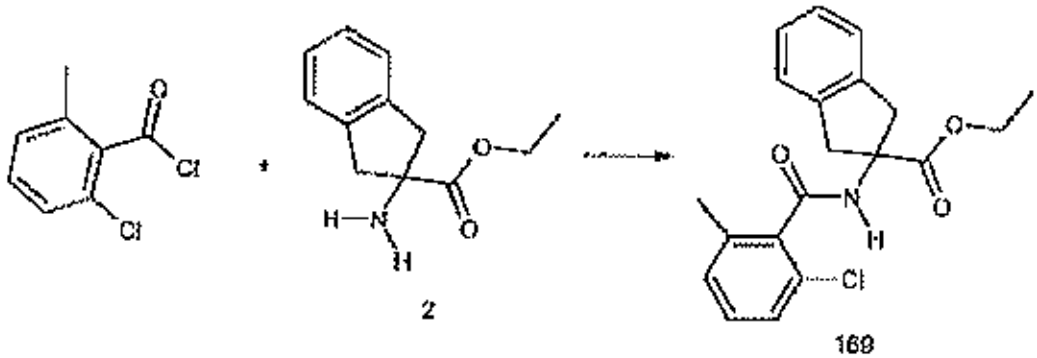


168

2-Chloro-6-methylbenzoyl chloride(168):

A round bottom flask containing the 2-chloro-6-methy-benzoic acid (1.5g, 8.79mmol) and a stirring bar is charged with dry DCM (10mL). Stirring is initiated. After several min, a solution of thionyl chloride (in DCM (2M), 6.6mL, 13.2mmol) is added via syringe. 2 drops of DMF are then added. The reaction immediately began to bubble gently. After 2h bubbling ceases. After 3h, the solvent is removed from the reaction mixture *in vacuo*. The oily residue is redissolved in DCM (6mL) and the solvent once again removed *in vacuo*. The residue is dissolved in dry DCM (6mL) and used without further purification in the next reaction sequence.

EXAMPLE 169



169

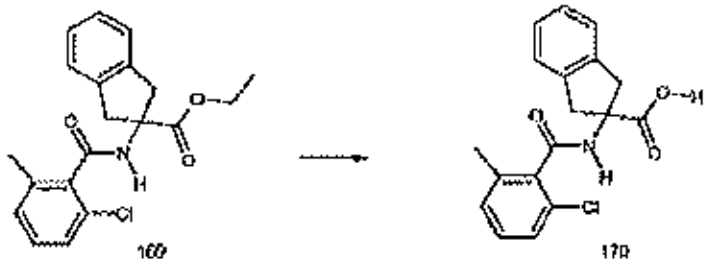
2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid ethyl ester (169):

A test tube (25 x 150 mm) containing a stirring bar and 2-amino-indan-2-carboxylic acid ethyl ester (0.53g, 2.58mmol) is charged with dry DCM (3mL). Stirring is initiated. After dissolution, the DIPEA (1.50mL, 8.6mmol) and 4-dimethylaminopyridine (2mg, 17μmol) are added. A solution of 2-chloro-6-methylbenzoyl chloride (5.8mmol) in dry DCM (4mL), as prepared above, is added to the reaction tube. After stirring for 18h, tlc analysis (silica, 10 % CH_3OH in DCM) indicates complete consumption of the amine. The reaction mixture is diluted with DCM (10mL) and washed with 5% aqueous HCl (2 x 5mL) and brine (5mL), dried over MgSO4 filtered and evaporated by pumping to constant weight gives 1.07g of light brown solid. This material is purified by chromatography (silica, 2 % to 20 % EtOAc in

DCM) on the ISCO Companion using a 40g cartridge. Fractions 6 - 10 are combined, evaporated and pumped to yield a constant weight 550mg of white amorphous solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.19 (t, 3 H) 3.33, (s, 3 H), 3.45 (dd, 4H), 4.13 (q, 2H), 6.88 (dd, 1H), 7.12 - 7.47 (m, 7H), 9.11 (s, 1H).
LC/MS m/z = 358.

EXAMPLE 170

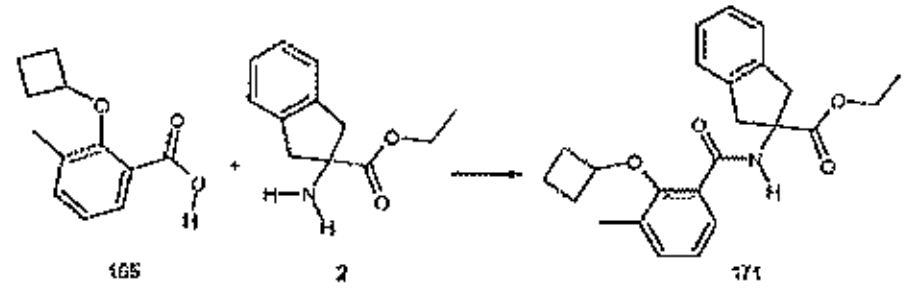


<u>2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid (170):</u>

A 100mL round bottom flask containing the 2-(2-chloro-6-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (0.255g, 0.712mmol) is charged with MeOH (15mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (5mL) is added and starting material begins to precipitate out. Tetrahydrofuran is added to re-solublize the starting material. LiOH (90mg, 2.14mmol) is added. After 16h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 3 by slowly adding dilute aqueous HCl (3%, ~20mL). The contents of the flask are poured into an addition funnel containing DCM (30mL). The layers are separated. The aqueous layer is extracted with DCM (20mL). The combined organic extracts are washed with water (30mL) and brine (20mL), dried over MgSO4, filtered and concentrated to yield 280mg of material. The material is purified by column chromatography (silica, 2% to 15 % CH_3OH in DCM) using an ISCO Companion and a 12g cartridge. Fraction 2 is collected and evaporated. After pumping to constant weight, 130mg of dry white powder is obtained.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.27, (s, 3 H), 3.45 (dd, 4H), 7.14 - 7.39 (m, 7H), 8.96 (s, 1H). LC/MS m/z = 330.

EXAMPLE 171

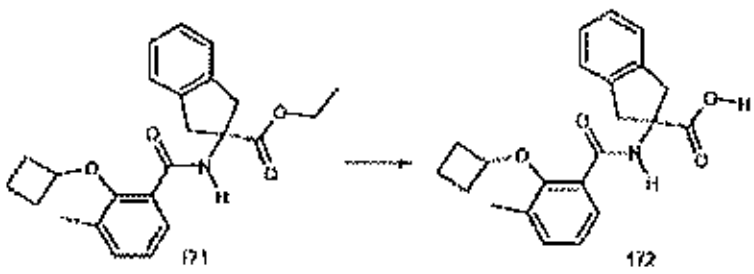


165 2 171

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (171):

A 25mL vial containing a stirring bar is charged with 2-cyclobutoxy-3-methyl-benzoic acid (1.01g, 4.87mmol) and dry DCM (14mL). Stirring is initiated. HBTU (1.84g, 4.86mmol) is added. After 5min, the 2-aminoindane-2-carboxylic acid ethyl ester (1g, 4.87mmol) is added followed by the DIPEA (1.9mL, 10.92mmol). The reaction is allowed to stir for 12 days. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (70mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (3%, 35mL), saturated aqueous $NaHCO_3$ (35mL) and brine (35mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 2.56g of an off-white solid. This material is dissolved in 15mL of DCM. This is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10% EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 100 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 7 through 22 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 1.73g.

EXAMPLE 172



171 172

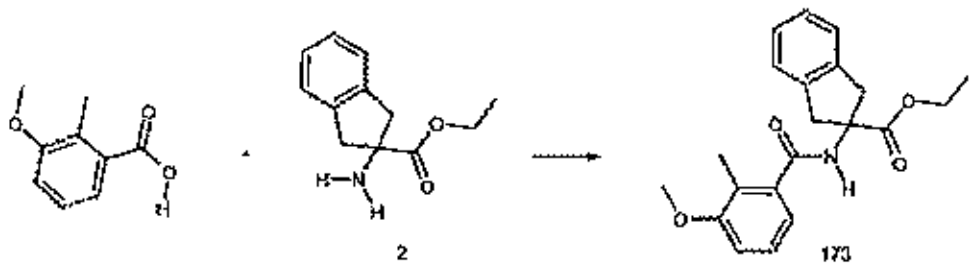
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (172):

A 50mL flask containing the 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid ethyl ester (1.72g, 4.37mmol) is charged with 1,4-dioxane (16mL) and MeOH (16mL). A stirring bar is added and stirring is initiated. After dissolution, water (8mL) is added followed

by the LiOH (458mg, 10.91mmol). After 20h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~25mL). The contents of the flask are poured into a separatory funnel containing EtOAc (60mL). The layers are separated. The aqueous layer is extracted with EtOAc (30mL). The combined organic extracts are washed with water (35mL) and brine (35mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 1.58g of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.16 – 1.27 (m, 1H), 1.38 – 1.53 (m, 1H), 1.78 – 2.03 (m, 4H), 2.23, (s, 3 H), 3.44 (dd, 4H), 4.34 (m, 1H), 7.03 (dd, 1H), 7.17 - 7.37 (m, 6H), 8.64 (s, 1H), 12.59 (bs, 1H).
LC/MS m/z = 364.

EXAMPLE 173



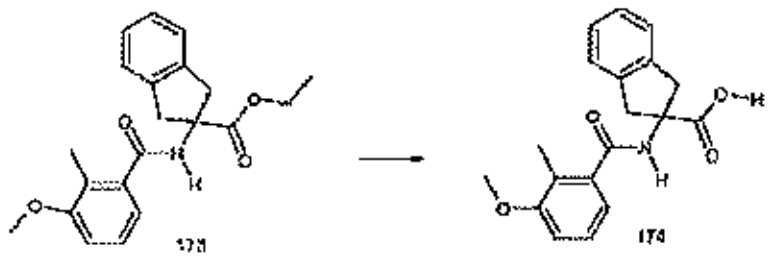
2-(3-Methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (173):

A 100mL round bottom flask is charged with 2-amino-indane-2-carboxylic acid ethyl ester (750mg, 3.65mmol) and dry DCM (10mL). A stirring bar is added and stirring is initiated. The HBTU (1.38g, 3.65mmol) is added. After 2min, the 2-methyl-3-methoxy-benzoic acid (0.61g, 3.65mmol) and DIPEA (1.5mL, 8.6mmol) are added. The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.1g of thick brownish gum. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes over 2 column volumes followed by a step gradient to 30% EtOAc then 50% and then 70% EtOAc for 3 column volumes each with ramp of 1 column volume. 35mL fractions are collected.

Fractions 15 through 21 are combined and evaporated in vacuo. Pumping to a constant weight gives a white solid (1.15 g).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.19 (t, 3 H), 2.12 (s, 3 H), 3.54 (dd, 4H), 3.78 (s, 3 H), 4.12 (q, 2H), 6.79 (d, 1H), 6.99 (d, 1H), 7.14 - 7.24 (m, 6H), 8.97 (s, 1H).
LC/MS m/z = 354.

EXAMPLE 174

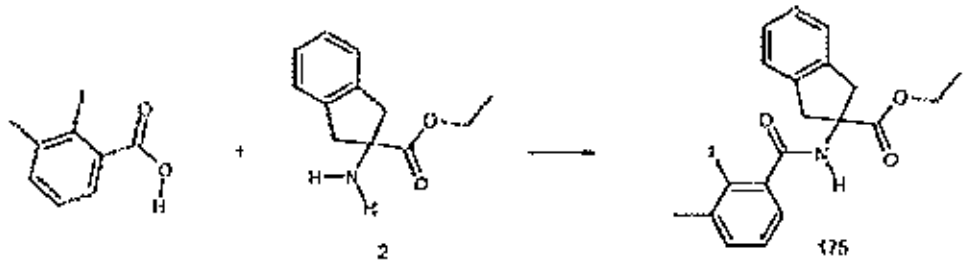


<u>2-(3-Methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid (174):</u>

A 40mL vial containing the 2-(3-methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (0.65g, 1.84mmol) is charged with THF (10mL) MeOH (10mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH (267mg, 6.36mmol). After 36h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into an addition funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated to yield 620mg of amorphous white solid. The sample is purified by column chromatography (silica, 2% to 15 % CH_3OH in DCM) using an ISCO Companion and a 40g cartridge. Fractions 14-16 are collected and evaporated by pumping to constant weight gives 380mg of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.11, (s, 3 H), 3.44 (dd, 4H), 3.77, (s, 3 H), 6.79 (d, 1H), 6.97 (d, 1H), 7.13-7.23 (m, 5H), 8.82 (s, 1H), 12.49 (s, 1H).
LC/MS m/z = 326.

EXAMPLE 175



2 175

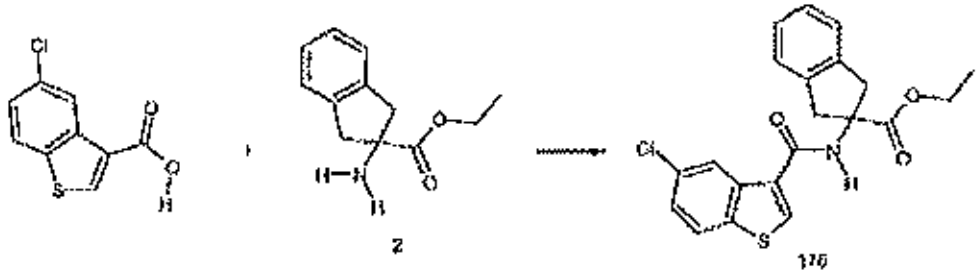
2-(2-Iodo-3-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (175):

A 100mL round bottom flask is charged with 2-iodo-3-methylbenzoic acid (1.92g, 7.31mmol) and dry DCM (25mL). A stirring bar is added and stirring is initiated. After 5min, the HBTU (2.37g, 7.31mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester (1.5g, 7.31mmol) is added followed by N,N-diisopropylethyl-amine (3.2mL, 18.37mmol). The reaction is allowed to stir for 118h. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70mL). This is washed,dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 X 30mL) and brine (30mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 2.04g of a white solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active eluent are collected. Fractions 10 through 15 are combined and evaporated *in vacuo*. Pumping to constant weight gives 1.04g a white solid material.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.20 (t, 3 H), 2.39 (s, 3 H), 3.52 (dd, 4H), 4.15 (q, 2H), 6.79 (d, 1H), 6.97 (d, 1H), 7.16 - 7.24 (m, 4H), 7.28 - 7.38 (m, 2H), 9.15 (s, 1H).

LC/MS m/z = 450.

EXAMPLE 176

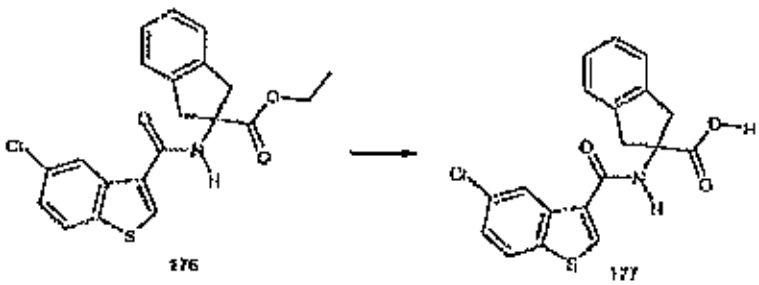


2 176

2-[(5-Chloro-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (176):

To a 40mL vial containing a stirring bar, 5-chloro-benzo[b]thiophene-3-carboxylic acid (518g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8.0mmol) are added. Then 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 20h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.64g of off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 7 through 31 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.94g.

EXAMPLE 177



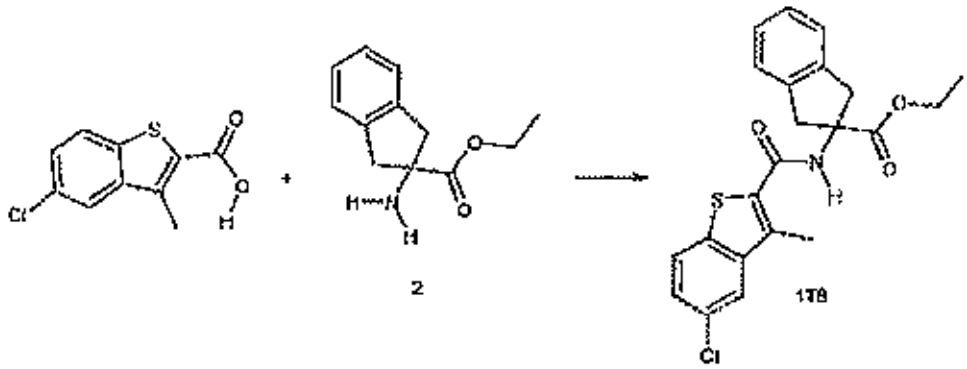
176 177

2-[(5-Chloro-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid (177):

A 50mL flask containing the 2-[(5-chloro-3-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (0.66g, 1.65mmol) is charged with 1,4-dioxane (10mL) and MeOH 10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH (173mg, 4.13mmol). After 15h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated. Pumping to constant weight gives 590mg of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.52 (dd, 4H), 7.15 – 7.27 (m, 4H), 7.46 (dd, 1H), 8.09 (d, 1H), 8.44 (d, 1H), 8.52 (s, 1H), 8.99 (s, 1H), 12.55 (bs, 1H).
LC/MS m/z = 372.

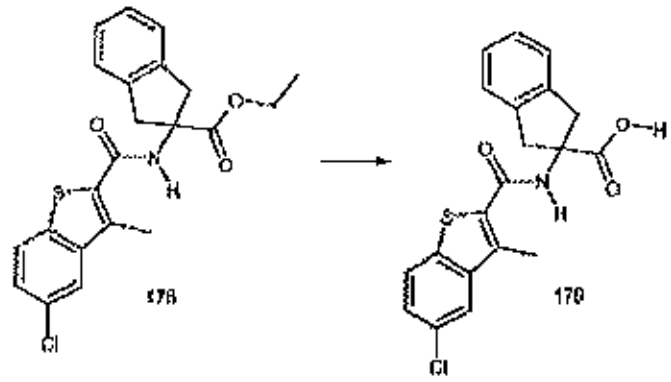
EXAMPLE 178



2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester(178):

To a 40mL vial containing a stirring bar, 5-chloro3-methyl-benzo[b]thiophene-2-carboxylic acid ([50451-84-8], 0.81g, 3.53mmol) is charged with dry DCM (10mL). Stirring is initiated. HBTU (1.34g, 3.54mmol) and the DIPEA (1.4mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (0.725g, 3.53mmol) is added. The reaction is allowed to stir for 240h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (80mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.26g of a off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a step gradient to 30% and then 50% and then 70 % EtOAc for 2 column volumes each with a ramp of 1 column volume. 25mL fractions are collected. Fractions 22 through 60 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.78g.

EXAMPLE 179



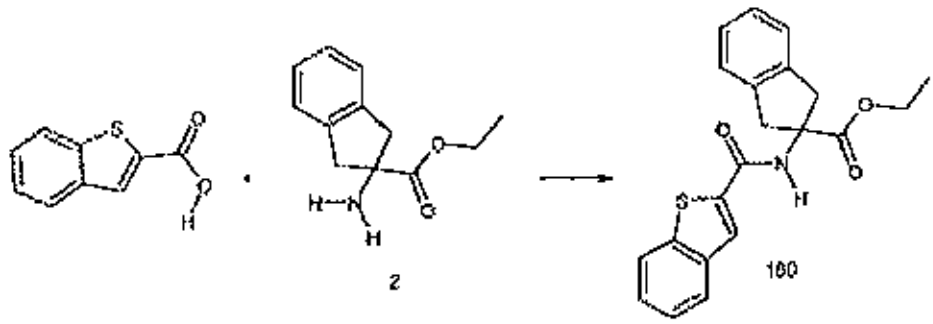
178 179

2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid (179):

40mL vial containing the 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (0.53g, 1.28mmol) is charged with MeOH (7.5mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (3.8mL) is added followed by the LiOH (134mg, 3.20mmol). After 36h, tlc analysis (silica, 5% i-PrOH/ DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated to yield 360mg of amorphous white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.45 (s, 3H) 3.49 (dd, 4H), 7.35 – 7.29 (m, 4H), 7.48 (dd, 1H), 7.92 (d, 1H), 8.02 (d, 1H), 8.96 (s, 1H).
LC/MS m/z = 386.

EXAMPLE 180

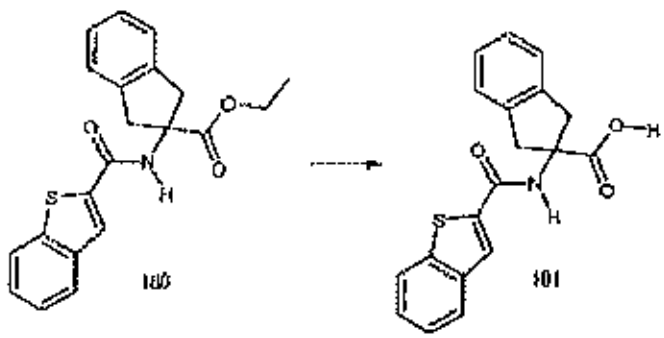


2 180

2-[(Benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (180):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-2-carboxylic acid (518g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and the DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 110h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/ DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated *in vacuo* to provide 1.54g of an off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 13 through 27 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.62g.

EXAMPLE 181

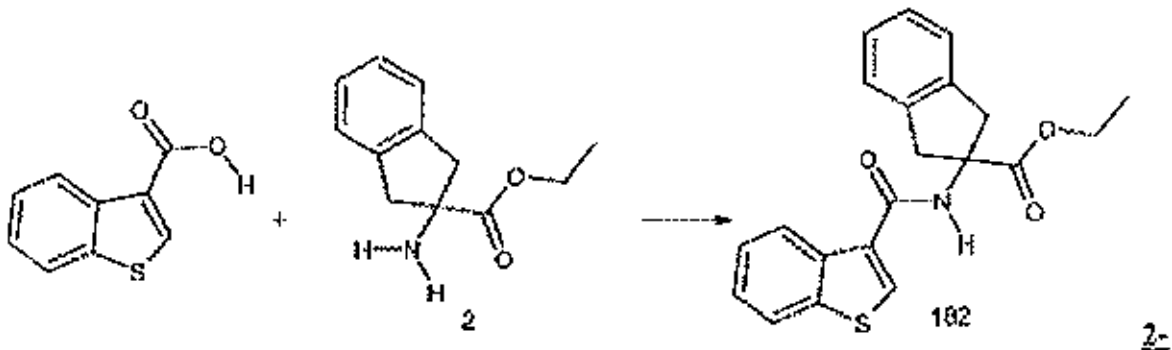


2-[(Benzo[b]thiophene-2-carbonyl)-amino]-Indane-2-carboxylic acid (181):

A 50mL flask containing the 2-[(Benzo[b]thiophene-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.37g, 1.01mmol) is charged with 1,4-dioxane (6mL) and MeOH 6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3.0mL) is added followed by the LiOH (106mg, 2.53mmol). After 18h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 290mg (89 %) of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.57 (dd, 4H), 7.15 – 7.32 (m, 4H), 7.45 – 7.48 (m, 2H) 7.91 (dd, 1H), 8.01 (dd, 1H), 8.18 (s, 1H), 9.11 (s, 1H), 12.58 (bs, 1H).
LC/MS m/z = 338.

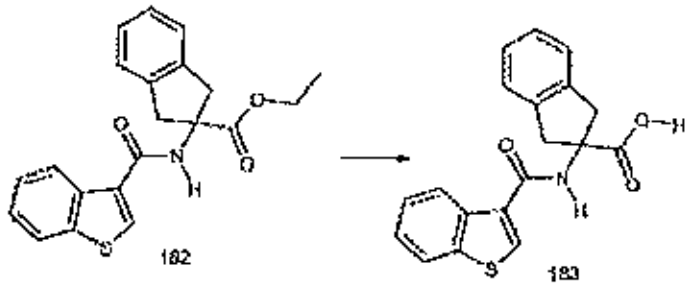
EXAMPLE 182



2-[(Benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (182):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-3-carboxylic acid ([5381-25-9], 434g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 20h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.64g of off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 4 through 16 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.69g.

EXAMPLE 183



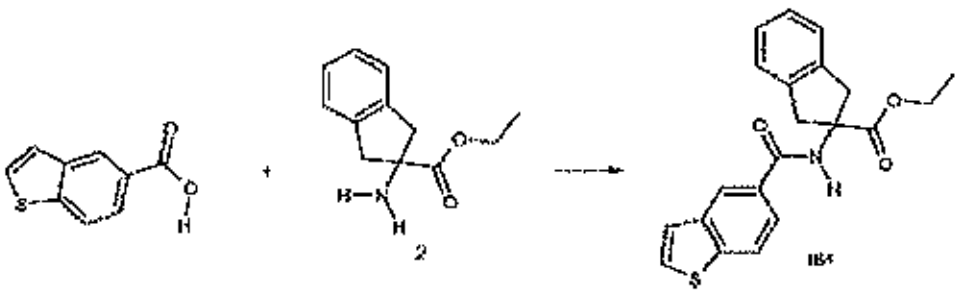
182 183

2-[(Benzo[b]thiophene-3-carbonyl)-amino]-Indane-2-carboxylic acid (183):

A 50mL flask containing the 2-[(benzo[b]thiophene-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (182, 0.40g, 1.10mmol) is charged with 1,4-dioxane (10mL) and MeOH 10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5.0mL) is added followed by the LiOH (115mg, 2.74mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Dilute aqueous HCl (3%, ~15mL) and EtOAc (25mL) are added to the reaction flask. After stirring for 10min, the contents of the flask are poured into a separatory funnel. The layers are separated. The aqueous layer is extracted with EtOAc (30mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 450mg of a dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.52 (dd, 4H), 7.18 – 7.28 (m, 4H), 7.38 – 7.43 (m, 2H) 8.03X (dd, 1H), 8.37 - 8.41 (m, 2H), 8.92 (s, 1H), 13.53 (bs, 1H).
LC/MS m/z = 338.

EXAMPLE 184



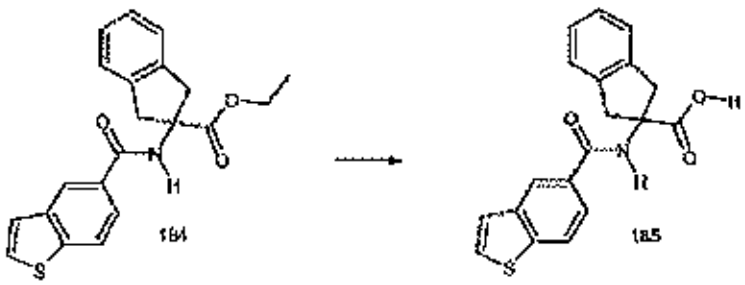
2 184

2-[(Benzo[b]thiophene-5-carbonyl)-amino]-Indane-2-carboxylic acid ethyl ester(184):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-5-carboxylic acid (434g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 64h. Analysis by tlc of the

reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated in vacuo to provide 1.4g of an off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 4 through 16 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.79g.

EXAMPLE 185

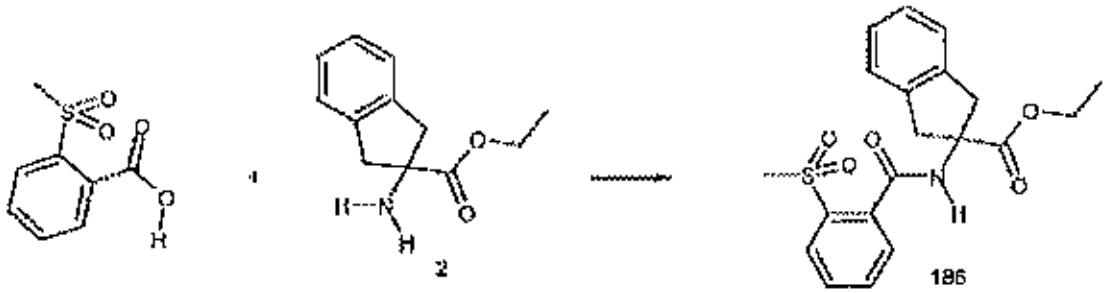


2-[(Benzo[b]thiophene-5-carbonyl)-amino]-indane-2-carboxylic acid (185):

A 50mL flask containing the 2-[(benzo[b]thiophene-5-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (184, 0.45g, 1.25mmol) is charged with 1,4-dioxane (8mL) and MeOH (8mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.0mL) is added followed by the LiOH (131mg, 3.11mmol). After 114h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.42g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.57 (dd, 4H), 7.18 - 7.28 (m, 5H), 7.59 (d, 1H), 7.78 - 7.93 (m, 2H), 8.08 (d, 1H), 8.41 (s, 1H), 8.91 (s, 1H).
LC/MS m/z = 338.

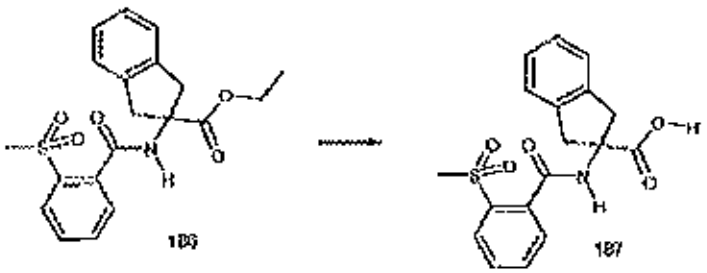
EXAMPLE 186



2-[(2-methylsulfonylbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (186):

To a 40mL vial containing a stirring bar, 2-(methylsulfonyl)benzoic acid (0.4g, 2.88mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol). The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by the DIPEA (0.95mL, 8mmol). The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated in vacuo to provide 1.32g of white solid. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 5 through 8 are combined and evaporated in vacuo. Pumping to a constant weight gives amorphous white solid 0.71g.

EXAMPLE 187



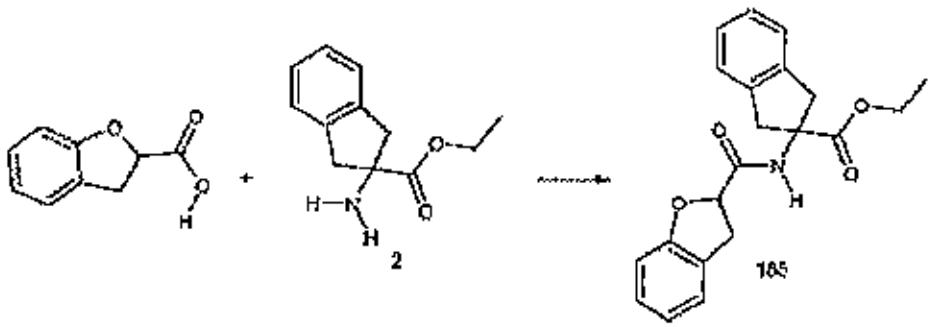
2-[(2-methylsulfonylbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid (187):

A 50mL flask containing 2-[(2-methylsulfonylbenzene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (186, 0.50g, 1.27mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL)

is added followed by the LiOH (133mg, 3.17mmol). After 69h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.46g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.37 – 3.61 (m, 7 H), 7.16 – 7.23 (m, 4 H), 7.54 (d, 1H), 7.69 (dd, 1H), 7.79 (dd, 1H), 7.93 (d, 1H), 9.25 (s, 1H), 12.55 (s, 1H).
LC/MS m/z = 360.

EXAMPLE 188

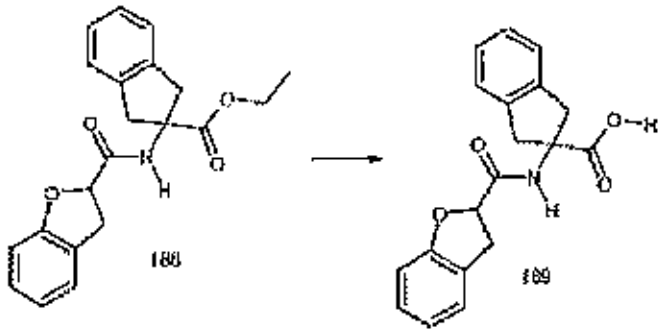


<u>2-[(2,3-Dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid acid ethyl ester(188):</u>

To a 40mL vial containing a stirring bar, 2,3-dihydro-1-benzofuran-2-carboxylic acid (0.4g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and the DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 16h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.47g of viscous yellow oil. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are

collected. Fractions 3 through 6 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.68g.

EXAMPLE 189



188 189

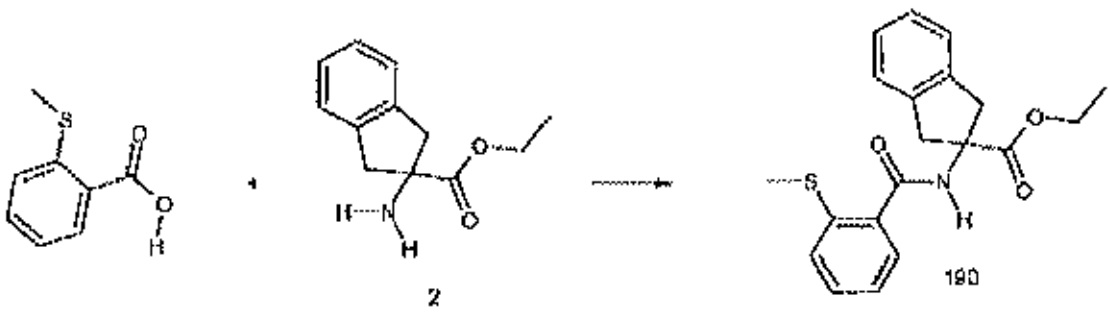
<u>2-[(2,3-Dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid (189):</u>

A 50mL flask containing the 2-[(2,3-dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.447g, 1.39mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH hydrate (133mg, 3.17mmol). After 19h, tlc analysis (silica, 5% *i*-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.43g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.17 (dd, 1H), 3.21 – 3.58 (m, 5H), 5.13 (dd, 1H), 6.79 (dd, 1H), 6.84 (dd, 1H), 7.03 – 7.28 (m, 6H) 8.64 (s, 1H), 12.55 (bs, 1H).

LC/MS m/z = 324.

EXAMPLE 190

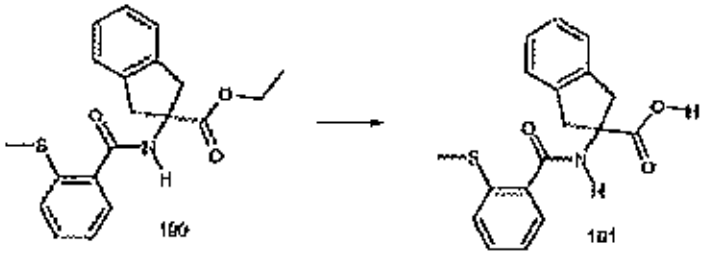


2 190

<u>2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (190):</u>

To a 40mL vial containing a stirring bar, 2-(methythiol)benzoic acid ([3724-10-5], 0.410g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) is added. After 2min, the 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by DIPEA (0.95mL, 8.0mmol). The reaction is allowed to stir for 38h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.49g of viscous yellow oil. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 8 through 15 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.69g.

EXAMPLE 191



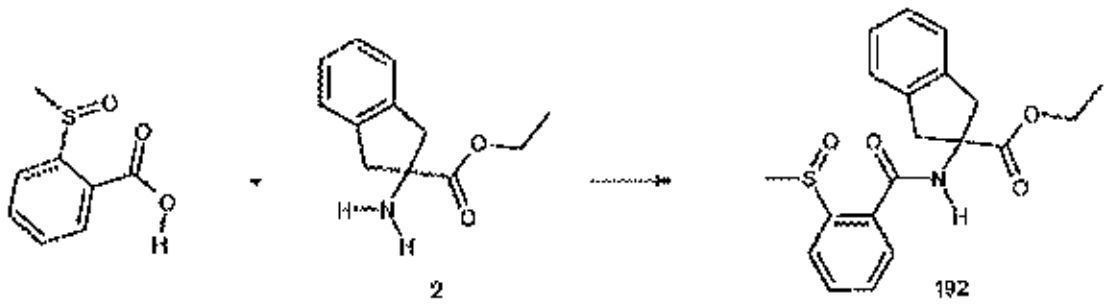
190 191

2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid (191):

A 50mL flask containing the 2-[(2-methylthiobenzene-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.510g, 1.44mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH hydrate (150mg, 3.58mmol). After 96h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated. Pumping to constant weight gives 0.34g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.37 (s, 3 H), 3.47 (dd, 4 H), 7.14– 7.21 (m, 5 H), 7.22–7.44 (m, 3 H), 8.88 (s, 1H), 12.46 (s, 1H).
LC/MS m/z = 328.

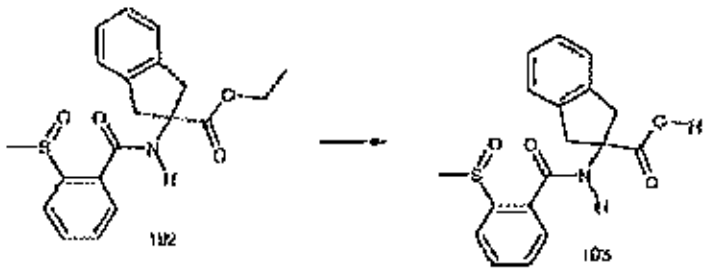
EXAMPLE 192



2-[(2-methylsulfinylbenzoyl)-amino]-indan-2-carboxylic acid ethyl ester (192):

To a 40mL vial containing a stirring bar, 2-(methylsulfinyl)benzoic acid (0.449g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) is added. The 2-aminoindane-2-carboxylic acid ethyl ester ([500mg, 2.44mmol) is added followed by DIPEA (0.95mL, 8.0mmol). The reaction is allowed to stir for 94h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.2g of yellow foam. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 100% EtOAc over 8 column volumes and then hold for 5 column volumes. 25mL fractions are collected. Fractions 9 through 18 are combined and evaporated *in vacuo* to a constant weight to give 0.75g of amorphous off-white solid.

EXAMPLE 193

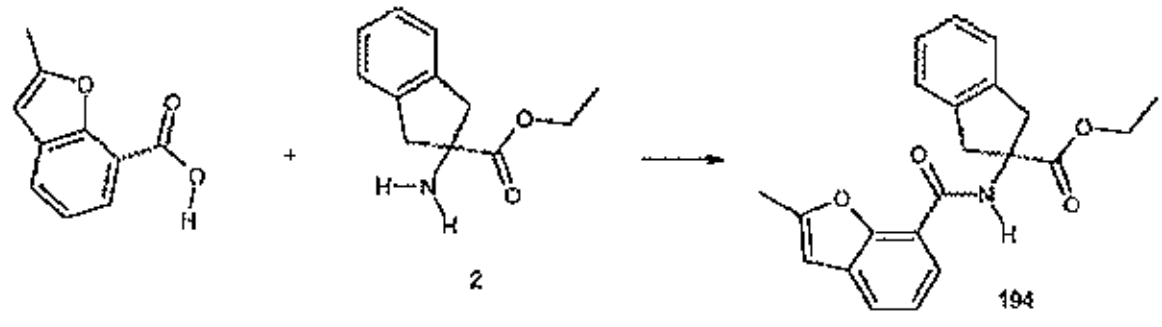


2-[(2-methylsulfinylbenzoyl)-amino]-indan-2-carboxylic acid (193):

A 50mL flask containing the 2-(2-methylsulfinylbenzoyl-amino)-indan-2-carboxylic acid ethyl ester (0.50g, 1.34mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH (141mg, 3.36mmol). After 39h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by vacuum to constant weight of 0.39g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.35 (s, 3 H), 3.48 (dd, 4 H), 7.16 – 7.27 (m, 4 H), 7.60 (dd, 1H), 7.67 – 7.84, (m, 2 H), 8.07 (d, 1H), 9.22 (s, 1H), 12.63 (bs, 1H).
LC/MS m/z = 344.

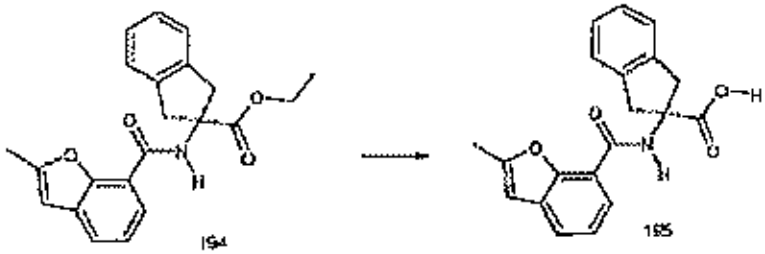
EXAMPLE 194



2-[(2-Methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (194):
To a 25mL vial containing a stirring bar, 2-methylbenzofuran-7-carboxylic acid (0.343g, 1.95mmol) is charged with dry DCM (6mL). Stirring is initiated. HBTU (738mg, 1.95mmol) is added. The 2-aminoindane-2-carboxylic acid ethyl ester (400mg, 1.95mmol) is added followed by DIPEA (0.75mL, 4.31mmol). The reaction is allowed to stir for 16h. Analysis by tlc of the reaction mixture (silica, 10% EtOH/dichloromethane) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.97g of yellow oil. This material is dissolved in 10mL of DCM. This is purified utilizing an ISCO Companion with a 40g

cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 90% over 15 column volumes and then 100 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 2 through 7 are combined and evaporated *in vacuo* to a constant weight to give 0.63g of amorphous white solid.

EXAMPLE 195



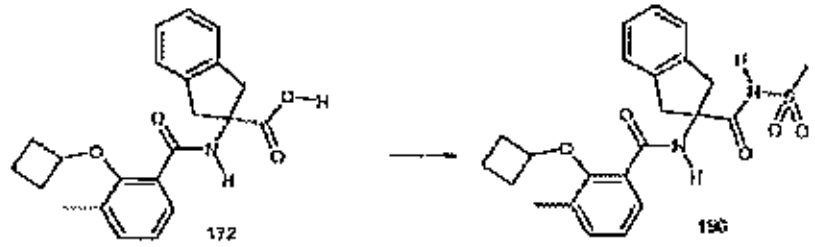
194 195

2-[(2-Methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (195):

A 50mL flask containing the 2-[(2-methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.40g, 1.10mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (115mg, 2.75mmol). After 18h, tlc analysis (silica, 5% *i*-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by vacuum to constant weight to give 0.37g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.42, (s, 3 H), 3.47 (dd, 4H), 6.68, (s, 1 H), 7.17-7.27 (m, 5 H) 7.57 (dd, 1H), 7.67 (dd, 1H), 8.68 (s, 1H), 12.63 (s, 1H).
LC/MS m/z = 336.

EXAMPLE 196

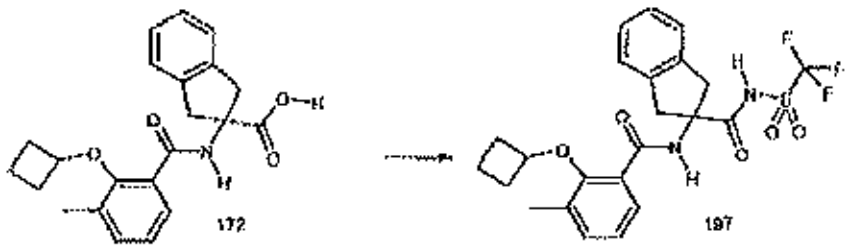


2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide (196):

A 30mL vial is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (245mg, 0.67mmol) and dry DCM (5.0mL). A stirring bar is added and stirring is initiated. The methanesulfonamide (89mg, 0.936mmol) is added. To the resultant suspension, (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (120mg, 0.624mmol) and 4-dimethylaminopyridine (76mg, 0.62mmol) are added. After 6 days, tlc analysis (silica, 10% MeOH in DCM) indicates that the starting acid is consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory funnel and washed with dilute aqueous HCl (3 N, 3 x 20mL) and brine, dried over $MgSO_4$, filtered and evaporated by pumping to constant weight gives 0.26g of amorphous white foam. This material is dissolved in DCM (5mL) and applied to a 12g column (silica) on an ISCO Companion. The column is eluted with 1% iPrOH in DCM for 3 column volumes followed by a linear gradient to 30% iPrOH in DCM over 15 column volumes. 12mL fractions of UV active eluent are collected. Fractions 4 through 9 are combined and evaporated to a constant weight to give 0.2g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.01 – 1.31 (m, 2H), 1.45 – 1.68 (m, 2H), 1.72 – 1.83 (m, 2H), 2.21 (s, 3 H), 3.18 (s, 3 H), 3.42 (m, 4H), 4.18 (m, 1 H), 7.16 (t, 1 H), 7.19 – 7.22 (m, 2H), 7.27 – 7.36 (m, 2H), 7.38 (d, 1H), 7.62 (d, 1H), 8.43 (s, 1H), 11.59 (s, 1H).
LC/MS m-/z = 441.

EXAMPLE 197

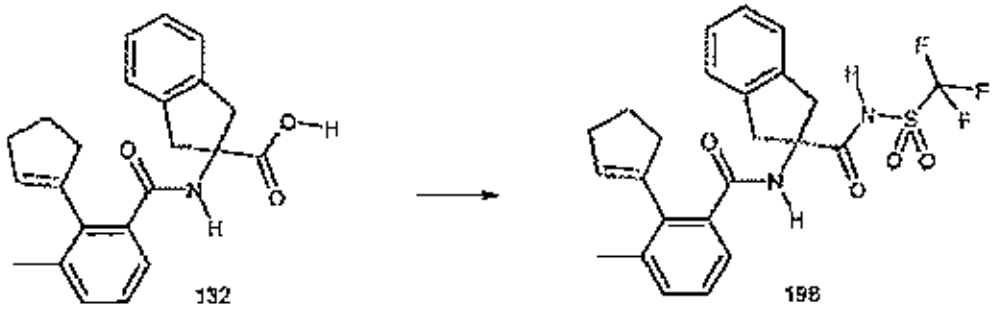


2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide (197):

A 30mL vial is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7.0mL). A stirring bar is added and stirring is initiated, and then trifluoromethanesulfonamide (198mg, 1.33mmol) is added. To the resultant suspension, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (170mg, 0.88mmol) and 4-dimethylaminopyridine (108mg, 0.88mmol) are added. After 8 days, tlc analysis (silica, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory funnel and washed with dilute aqueous HCl (3 N, 2 x 20mL) and brine, dried over $MgSO_4$, filtered and evaporated to constant weight to give 0.51g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.21 – 1.38 (m, 1H), 1.41 – 1.56 (m, 1H), 1.91 – 2.04 (m, 4H), 2.23 (s, 3 H), 3.42 (m, 4H), 4.37 (m, 1 H), 7.04 (t, 1 H), 7.14 – 7.21 (m, 4H), 7.31 (d, 1H), 7.51 (d, 1H), 8.66 (s, 1H), 8.95 (s, 1H).
LC/MS m/z = 497.

EXAMPLE 198



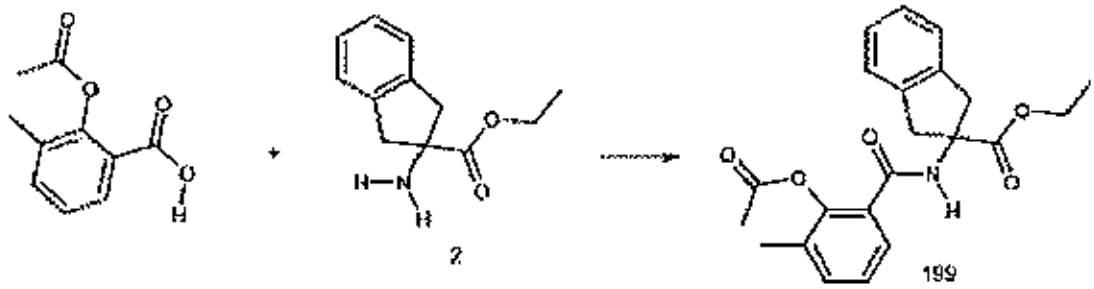
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide (198):

A 50mL flask is charged with 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7.0mL). A stirring bar is added and stirring is initiated. Trifluoromethanesulfonamide (198mg, 1.33mmol) is added. To the resultant suspension, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride 170mg, 0.88mmol) and 4-dimethylaminopyridine ([MFCD00006418], 108mg, 0.88mmol) are added. After 80h, tlc analysis (silica, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory

funnel and washed with dilute aqueous HCl (3 N, 2 X 20mL) and brine, dried over $MgSO_4$, filtered and evaporated to constant weight to give 0.50g of white solid.

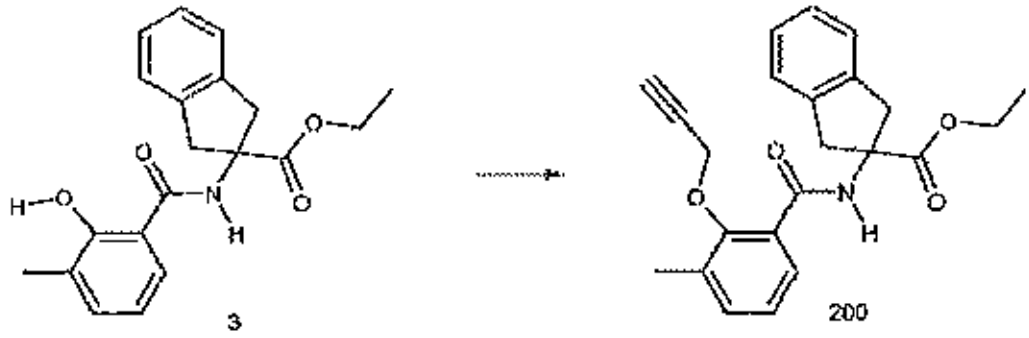
^{1}H NMR (300 MHz, DMSO-d6): δ 1.76 (m, 2H), 2.17 (s, 3 H), 2.22 – 2.42 (m, 4H), 3.38 (dd, 4H), 5.39, (s, 1 H), 7.04 – 7.29 (m, 7H), 8.02 (s, 1H), 8.94 (s, 1H).
LC/MS m/z = 493.

EXAMPLE 199



<u>2-(2-Acetoxy-3-methyl-benzoyl-amino)-indane-2-carboxylic acid ethyl ester (199):</u>
A 40mL vial containing a stirring bar is charged with 2-acetoxyl-3-methyl-benzoic acid (1g, 4.87mmol) and dry DCM (14mL), and stirring is initiated. After dissolution is complete, HBTU (1.85g, 4.87mmoles) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (1g, 4.87mmol) is added followed by DIPEA (2.1mL, 12.18mmol). The reaction is allowed to stir for 110h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (100mL). This is washed consecutively with dilute aqueous HCl (3%, 40mL), saturated aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3g of a light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with an 80g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc over 12 column volumes. Fractions 19 through 27 are combined and evaporated *in vacuo* to give 1.38g of white solid.

EXAMPLE 200

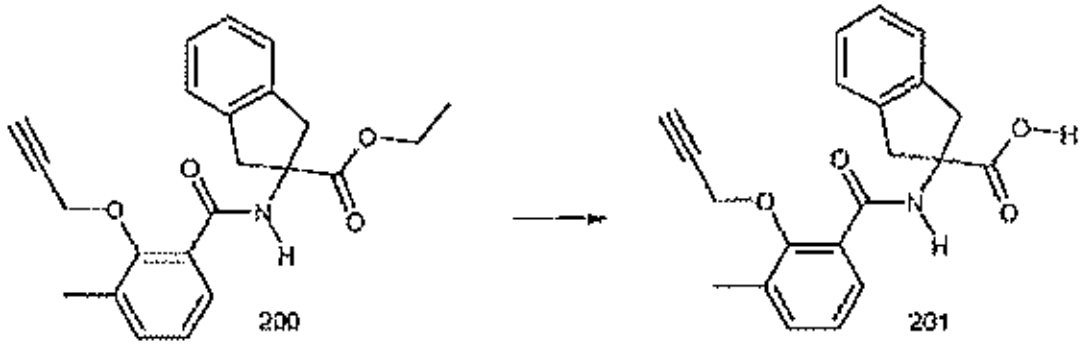


3 200

2-(3-Methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (200):

A 100mL round bottom flask containing the 2-(hydroxy-3-methyl-benzoyl)-indan-2-carboxylic acid ethyl ester (3) (0.29g 0.855mmol) is charged with DMF (4mL) and a stirring bar is added. After dissolution of the starting material, K_2SO_4 (0.3g, 2.17mmol) is added followed by a solution of propargyl bromide in toluene (11.59 M, 240µL, 2.78mmol). After stirring for 62h tlc analysis (silica, 1:1 EtOAc/heptanes) indicates that the starting material had been consumed. The material is cleanly converted to a UV positive spot with a slightly lower Rf. The reaction is diluted with EtOAc (80mL) and filtered through a pad of Celite. The filtrate is transferred to a separatory funnel. This is washed repeatedly with a saturated aqueous solution of $NaHCO_3$ (2 x 50mL) and brine (50mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield 2.09g of a light brown oil. This is purified (silica, 40g ISCO column 10% EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes for 10 column volumes). 17mL fractions of UV positive eluent are collected. Fractions 4 through 10 are combined, evaporated *in vacuo* and pumped to constant weight to give 0.21g of white solid.

EXAMPLE 201



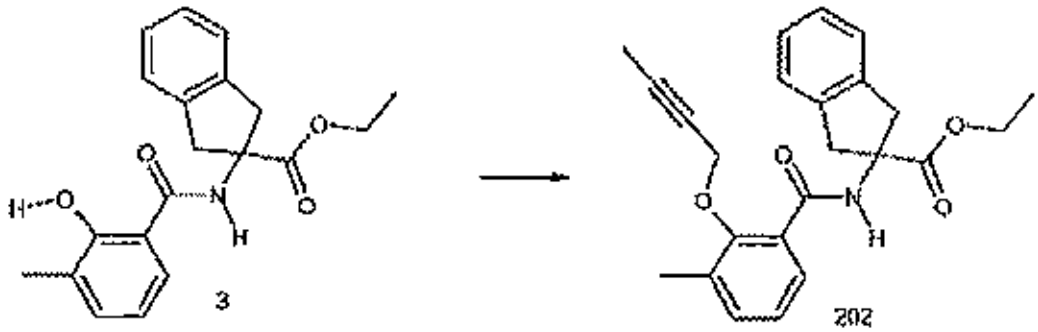
200 201

2-(3-Methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (201):

A 50mL flask containing the 2-(3-methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.20g, 0.53mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (56mg, 1.35mmol). After 108h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated to constant weight to give 0.2g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.26 (s, 3 H), 3.43 (dd, 4H), 4.52 (s, 2 H), 7.08 (dd, 1H), 7.12 – 7.38 (m, 6H), 8.79 (s, 1H), 12.53 (bs, 1H).
LC/MS m/z = 350.

EXAMPLE 202

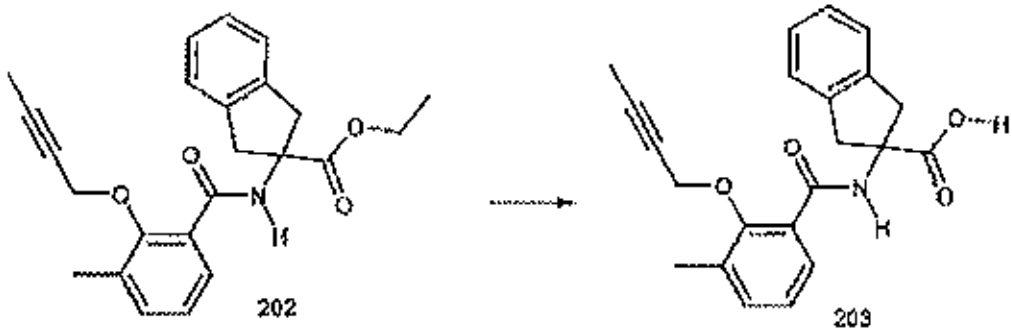


<u>2-(3-Methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (202):</u>

A 100mL round bottom flask containing the 2-(hydroxy-3-methyl-benzoyl)-indan-2-carboxylic acid ethyl ester (0.62g, 1.87mmol) is charged with DMF (3mL) and a stirring bar is added. After dissolution of the starting material, the K_2SO_4 (0.791g, 5.95mmol) is added followed by a solution of 1-bromo-2-butyne (537µL, 5.95mmol). After stirring for 110h tlc analysis (silica, 1:1 EtOAc/heptanes) indicates that the starting material is consumed. The material is cleanly converted to a UV positive spot with a slightly lower Rf. The reaction is diluted with EtOAc (80mL) and filtered through a pad of Celite. The filtrate is transferred to a separatory funnel. This is washed repeatedly with a saturated aqueous solution of $NaHCO_3$ (2 x 50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield 0.75g of a light brown oil. This is purified (silica, 40g ISCO column 10% EtOAc in heptanes for 3

column volumes followed by a linear gradient to 50% EtOAc in heptanes for 10 column volumes), 17mL fractions of UV positive eluent are collected. Fractions 2 through 8 are combined, evaporated *in vacuo* and pumped dry to yield 0.79g of a white solid.

EXAMPLE 203

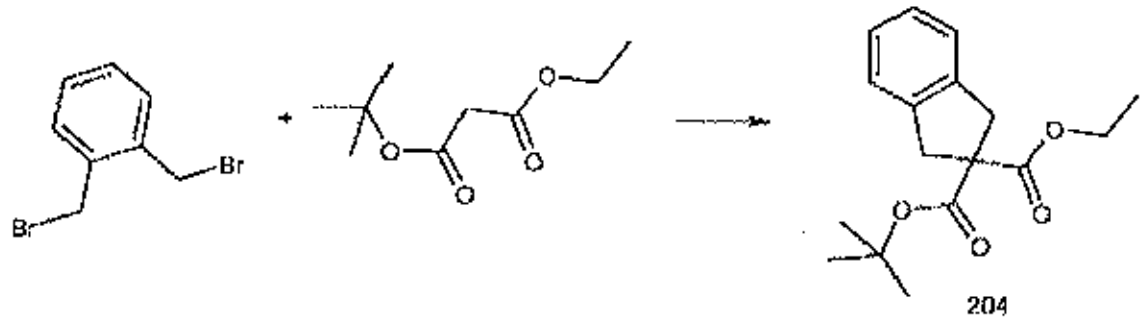


2-(3-Methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (203):

A 100mL flask containing 2-(3-methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (0.30g, 0.77mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (81mg, 1.93mmol). After 14h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.25g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.77 (s, 3 H), 2.24 (s, 3 H), 3.44 (dd, 4H), 4.42 (s, 2 H), 7.08 (dd, 1H), 7.14 – 7.23 (m, 4H), 7.31 (d, 2 H), 8.75 (s, 1H), 12.52 (bs, 1H).
LC/MS m/z = 364.

EXAMPLE 204

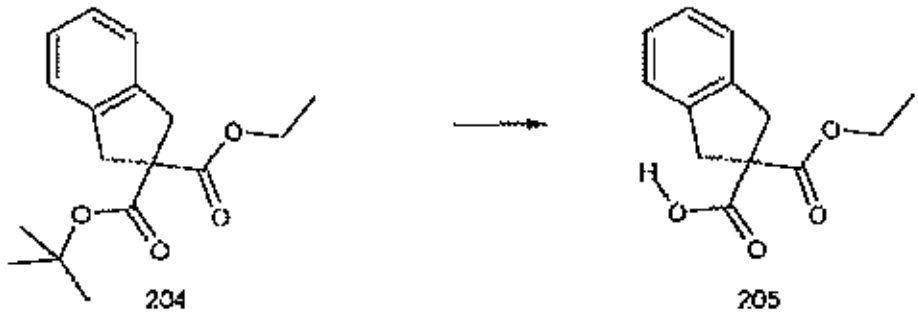


204

Indan-2,2-dicarboxylic acid *tert*-butyl ester ethyl ester (204):

A 3-neck flask containing a stirring bar is fitted with an addition funnel and flushed with nitrogen. The flask is charged with NaH (60% dispersion in oil, 3.38g, 84.48mmol) and dry THF (50mL), and then stirring is initiated. *t*-Butyl ethyl malonate (8mL, 42.24mmol) is added dropwise via syringe over a period of 5 minutes. After 1/2 hour the addition funnel is charged with a solution of o-xylenedibromide (11.15g, 42.24mmol) in dry tetrahydrofuran (THF, 50mL). The solution is added to the reaction mixture over a period of 30 minutes. At the end of this time the addition funnel is washed with dry THF (10mL). This is also added to the reaction mixture. The reaction mixture is allowed to stir for 6 days. The reaction mixture is then transferred to a round-bottom flask and the solvent removed under reduced pressure. The resultant white semi-solid is dissolved in a mixture of EtOAc (200mL) and water (150mL.) this is transferred to a separatory funnel. The layers are separated. The aqueous phase is extracted with EtOAc (150mL). The organic extracts are combined, washed with brine (150mL), dried over $MgSO_4$, filtered and evaporated to constant weight to give 12.44g of viscous oil. This material is diluted with heptanes (30mL) and applied to a silica gel column (300g). The material is eluted with EtOAc/heptanes (5 % over 5 column volumes) with a gradient to 75 % EtOAc in heptanes over 7 column volumes. 43mL fractions of UV positive eluent are collected. Fractions 11 - 20 are combined and evaporated by pumping to a constant weight to give 9.82g of clear viscous oil.

EXAMPLE 205

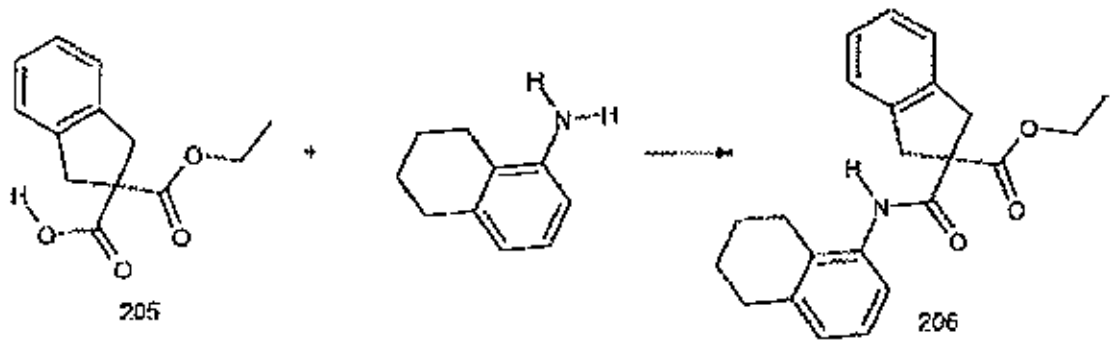


204 205

Indan-2,2-dicarboxylic acid ethyl ester (205):

A 200mL round bottom flask is charged with indan-2,2-dicarboxylic acid *tert*-butyl ester ethyl ester (8.69g, 29.93mmol). DCM (40mL) and a stirring bar are added. Stirring is initiated. Trifluoroacetic acid (20.0mL, 269mmol) is added. After 20h, tlc analysis (silica, 1:1 ethyl acetate:heptanes), indicates complete consumption of starting material. The reaction mixture is diluted with DCM (50mL) and evaporated under reduced pressure. The resultant oil is diluted with DCM (55mL) and evaporated under reduced pressure. The resultant oil is diluted with toluene (50mL) and evaporated under reduced pressure by pumping to constant weight to give 6.78g of white solid material.

EXAMPLE 206



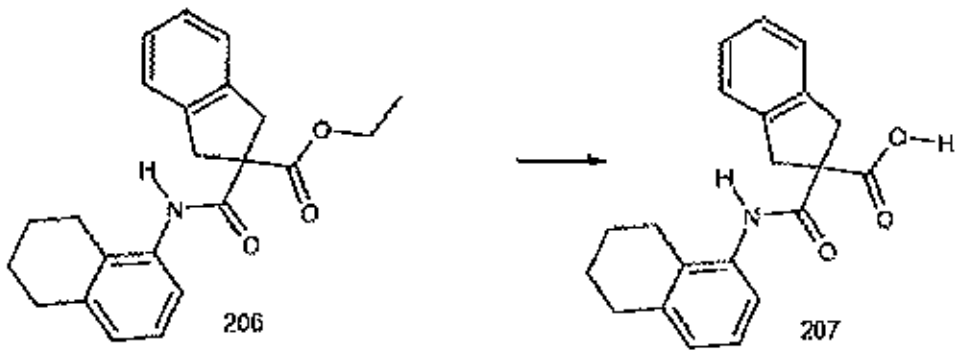
205 206

2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (206):

A 25mL reaction vial containing a stirring bar is charged with indane-2-carboxylic acid ethyl ester (0.48g, 1.79mmol) and dry DCM (7mL). Stirring is initiated. After dissolution is complete, HBTU (0.68g, 1.79mmol) is added. After 5min, the 5,6,7,8-tetrahydro1-naphthylamine (0.26mL, 1.79mmol is added followed by DIPEA (0.72mL, 4.12mmol). The reaction is allowed to stir for 68h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting acid. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (40mL). This is

washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.50g of a light purple solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 12 column volumes. 17mL fractions of eluent are collected. Fractions 11 through 16 are combined and evaporated *in vacuo* by pumping to constant weight to give 0.41 of white solid material.

EXAMPLE 207



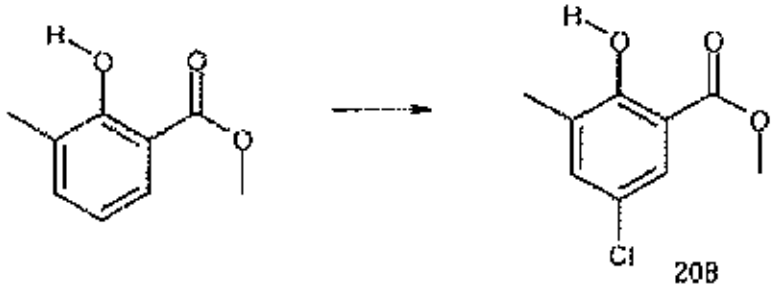
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid (207):

A 100mL flask containing 2-(5,6,7,8-tetrahydro-naphthalene-1-yl-carbamoyl)-indan-2-carboxylic acid ethyl ester (0.23g, 0.63mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (67mg, 1.58mmol). After 14h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.18g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.58 - 1.78 (m, 4 H), 2.43 - 2.58 (m, 2 H), 2.63 - 2.78 (m, 2 H), 3.57 (dd, 4H), 6.96 (dd, 1H), 6.98 - 7.08 (m, 2H), 7.09 - 7.19 (m, 2H), 7.20 - 7.28 (m, 2 H), 9.15 (s, 1H), 12.82 (bs, 1H).

LC/MS *m/z* = 336.

EXAMPLE 208



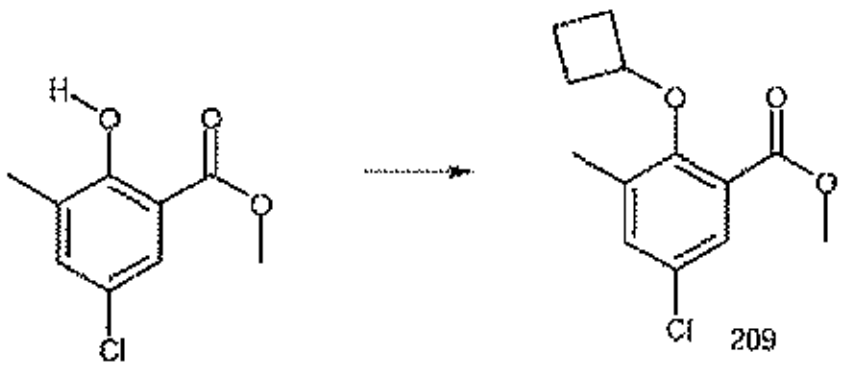
208

2-Hydroxy-3-methyl-5-chlorobenzoic acid methyl ester (208):

A 250mL 3-neck round bottom flask is charged with 2-hydroxy-3-methyl-5-benzoic acid methyl ester (5g, 30.1mmol) and dry DCM (50mL). A stirring bar is added and the flask is immersed in an ice/water bath. After 10 minutes, sulfuryl chloride (2.9mL, 36.1mmol) is added via syringe over a period of 5 minutes. After 0.5h, the ice-water bath is removed. After 2 additional h, tlc Analysis (silica, 40% EtOAc-heptanes) indicates no reaction.

After 27 days, tlc analysis (silica, 40% EtOAc-heptanes) still indicated no reaction. MeOH (50mL) is added to the reaction mixture. A white crystalline solid began to precipitate. The precipitate is collected by suction filtration to give 2.1g of white solid. A 2nd crop of 1.25g of additional white solid is collected from the filtrate.

EXAMPLE 209



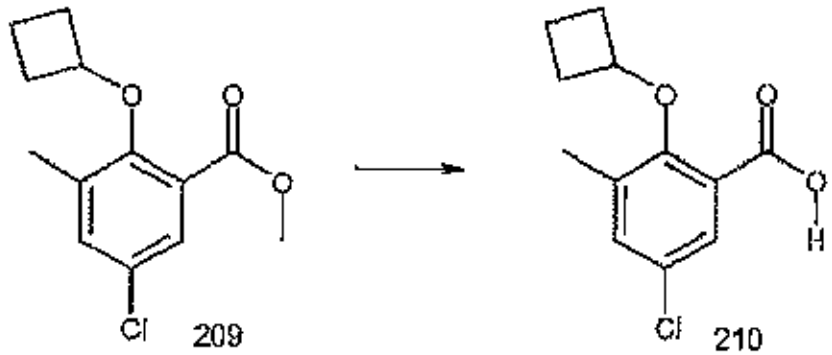
209

5-Chloro-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (209):

A 100mL round bottom flask is charged with 5-chloro-2-hydroxy-3-methyl-benzoic acid methyl ester (0.92g, 4.59mmol). Dry N,N-dimethylformamide (DMF, 15mL) and a stirring bar are added. Stirring is initiated. After dissolution, K_2SO_4 (1.90g, 13.76mmol) and bromocyclobutane (0.65mL, 6.88mmol) are added. After 12 days, tlc analysis (silica, 25 %

EtOAc/heptanes) indicated a slight consumption of starting material and the appearance of a UV positive spot with a slightly higher R_f value. The reaction is fitted with a heating mantle and warmed to 37°C. After 3 more days, tlc analysis (silica, 25% EtOAc/heptanes) indicates a slight consumption of starting material and complete conversion to a UV positive spot with a slightly higher R_f value. The reaction mixture is filtered through a pad of Celite. The filtrate is diluted with EtOAc and (100mL) and transferred to a separatory funnel. The EtOAc solution is washed with saturated $NaHCO_3$ (2 x 25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight togive 0.79g of semi-solid material.

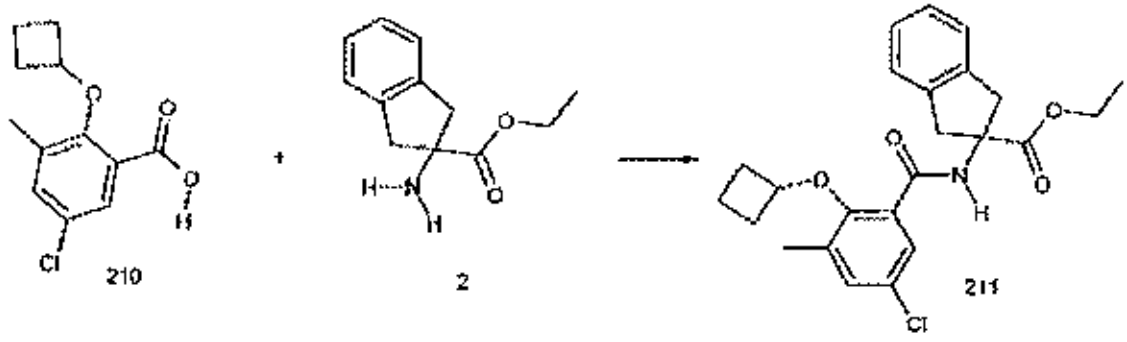
EXAMPLE 210



5-Chloro-2-cyclobutoxy-3-methyl-benzoic acid (210):

A 100mL flask containing 5-chloro-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (0.57g, 2.23mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (237mg, 5.65mmol). After 39h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.53g of white solid.

EXAMPLE 211

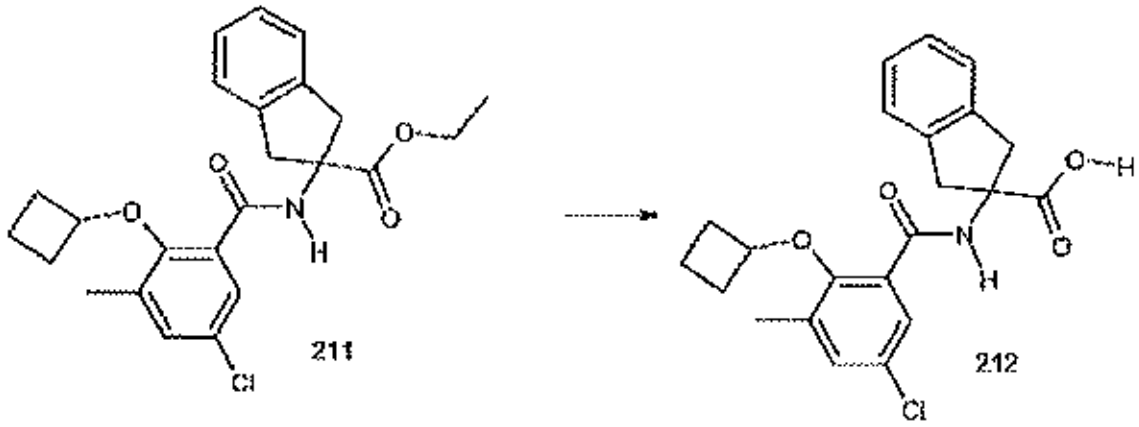


2-

(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (211):

A 100mL round bottom flask containing a stirring bar is charged with 2-cyclobutoxyl-3-methyl-5-chloro-benzoic acid (0.36g, 1.5mmol) and dry DCM (7mL). Stirring is initiated. After dissolution is complete, HBTU (567mg, 1.5mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester (307mg, 1.50mmol) is added followed by DIPEA (0.74mL, 3.74mmol). The reaction is allowed to stir for 39h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (100mL). This is washed consecutively with dilute aqueous HCl (3%, 40mL), saturated aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.8g of a light orange solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 70% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 8 through 11 are combined and evaporated *in vacuo* by pumping to a constant weight to give 0.48g white solid.

EXAMPLE 212



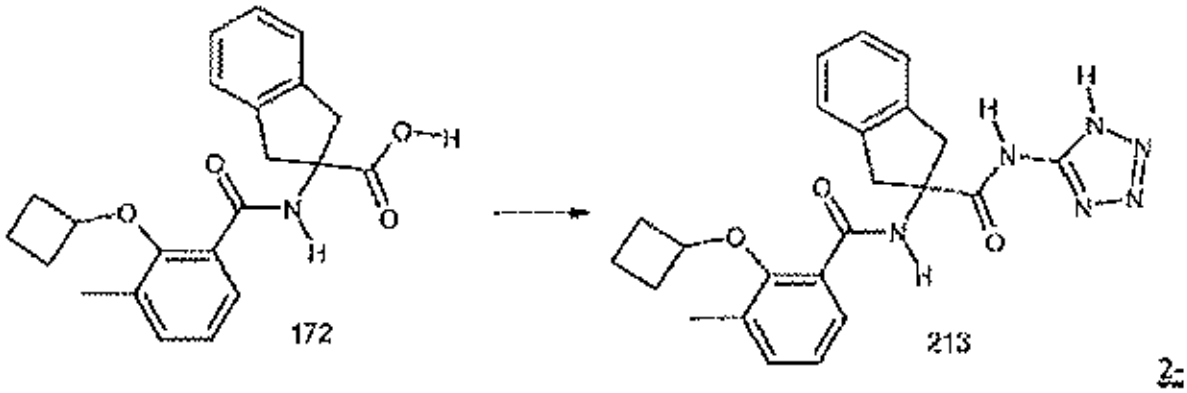
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (212):

A 100mL flask containing 2-(5-chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.3g, 0.7mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (74mg, 1.77mmol). After 20h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.21g of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.17 – 1.28 (m, 1 H), 1.49 (m, 1 H), 1.78 – 1.95 (m, 2 H), 1.96 – 2.04 (m, 2 H), 3.46 (dd, 4H), 4.28 (m, 1H), 7.15 – 7.26 (m, 5H), 7.39 (d, 1H), 8.78 (s, 1H), 12.62 (bs, 1H).

LC/MS m/z = 400.

EXAMPLE 213



172 213

2-

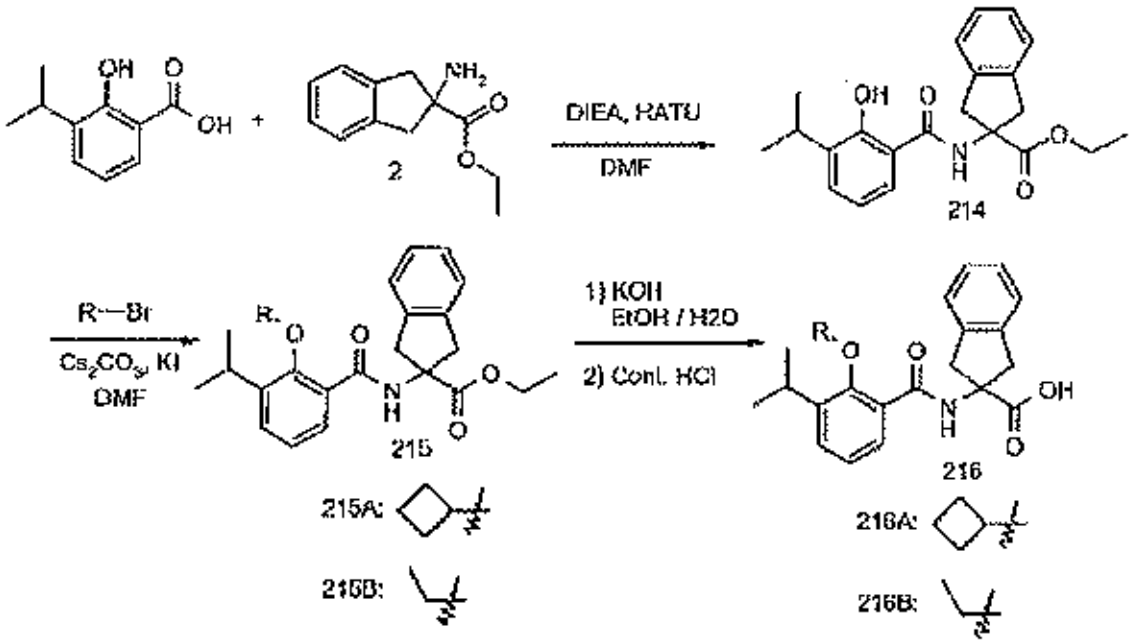
(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (1H-tetrazol-5-yl)-amide (213):

A 40mL tube is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7mL). A stirring bar is added and stirring is initiated. 5-Amino-1H-tetrazole (113mg, 1.33mmol) is added. To the resultant suspension, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (170mg, 0.88mmol) and 4-dimethylaminopyridine (108mg, 0.88mmol) is added. After 11 1/2 days, tlc analysis (silica, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to an Erlenmeyer flask containing saturated aqueous ammonium chloride (50mL). This mixture is allowed to stir. After 16h of stirring, this mixture contained a white solid that is collected by suction filtration and washed with water (2 x 25mL). Air drying gives 0.26g of white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.01 – 1.31 (m, 2 H), 1.62 (m, 2 H), 1.73 – 1.93 (m, 2 H), 2.22 (s, 3 H), 3.39 (dd, 4H), 4.19 (m, 1H), 7.08 (t, 1H), 7.19 – 7.51 (m, 5H), 7.57 (dd, 1H), 8.61 (s, 1H), 12.01 (bs, 1H).

LC/MS m/z = 433.

EXAMPLE 214



2-(2-Hydroxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (214):

To a solution of 2-hydroxy-3-isopropyl-benzoic acid (539mg, 2.99mmol), 2-amino-indan-2-carboxylic acid ethyl ester (737mg, 3.59mmol), HATU (1.36g, 3.59mmol) in anhydrous DMF (30mL) is added DIPEA (0.59mL, 3.59mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (222) as white solid (920mg, 84%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.21(d, 6H), 1.24(t, 3H), 3.32-3.44(m, 1H), 3.41(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 6.74-6.81(m, 2H), 7.16(d, 1H), 7.18-7.25(m, 3H), 7.32(d, 1H), 12.26(s, 1H)
LC/MS (ES+) m/z = 368.17

EXAMPLES 215A and 215B

2-(2-Cyclobutoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (215A) and 2-(2-Ethoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (215B):

To a suspension of 2-(2-hydroxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (214) (1eq., 0.82mmol), anhydrous Cs_2CO_3 (2eq., 1.64mmol), and KI (0.2eq., 0.16mmol) in DMF (15mL) is added RBr (4eq., 3.28mmol). The resulting reaction suspension is heated in a microwave vessel (215A: 130°C, 2hr; 215B: 50°C, 30min). After the removal of DMF *in*

vacuo, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-50% EtOAc in heptane) to give a pure product (215) as white solid (215A: 340mg, 98%; 215B: 300mg, 93%).

215A: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.19(d, 6H), 1.26(t, 3H), 1.16-1.57(m, 2H), 1.87-2.07(m, 4H), 3.24-3.38(m, 1H), 3.36(d, 2H), 3.78(d, 2H), 4.26(q, 2H), 4.15-4.30(m, 1H), 7.12-7.26(m, 5H), 7.35(dd, 1H), 7.83(dd, 1H), 8.20(s, 1H).
LC/MS (ES+) m/z = 422.24

215B: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.13(t, 3H), 1.20(d, 6H), 1.26(t, 3H), 3.24(m, 1H), 3.35(d, 2H), 3.72(q, 2H), 3.78(d, 2H), 4.26(q, 2H), 7.14-7.26(m, 5H), 7.36(dd, 1H), 7.82(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 396.22

EXAMPLES 216A and 216B

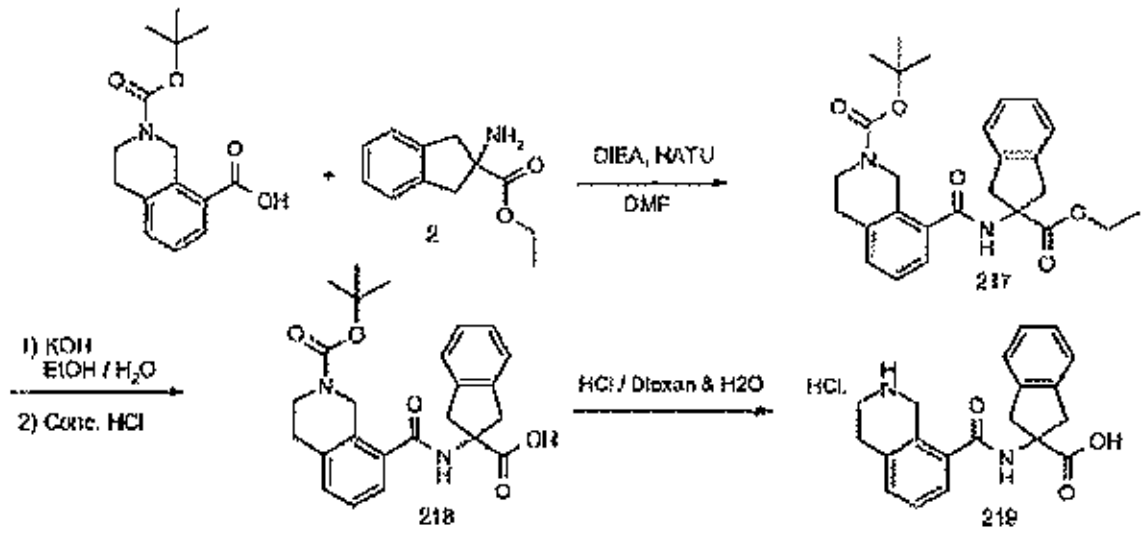
2-(2-Cyclobutoxy-3-isopropyl-benzoylamino)-Indan-2-carboxylic acid (216A) and 2-(2-Ethoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid (216B):

The mixture of (215) (1eq., 0.69mmol) and KOH (13eq., 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (216) as white solid (216A: 190mg, 70%; 216B: 220mg, 91%).

216A: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.17(d, 6H), 1.13-1.30(m, 1H), 1.41(m, 1H), 1.78-2.02(m, 4H), 3.27(m, 1H), 3.38(d, 2H), 3.81(d, 2H), 4.13(m, 1H), 7.09(t, 1H), 7.13-7.23(m, 4H), 7.34(dd, 1H), 7.81(dd,1H), 8.37(s, 1H).
LC/MS (ES+) m/z = 394.19

216B: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.08(t, 3H), 1.39(d, 6H), 3.20(m, 1H), 3.46(d, 2H), 3.55(q, 2H), 3.88(d, 2H), 7.18-7.27(m, 5H), 7.42(dd, 1H), 7.89(dd, 1H), 8.63(s, 1H)
LC/MS (ES+) m/z = 368.19

Example 217



8-(2-Ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (217):

To a solution of 3,4-dihydro-1H-isoquinoline-2,8-dicarboxylic acid 2-tert-butyl ester (2.0g, 7.2mmol), 2-amino-indan-2-carboxylic acid ethyl ester (1.5g, 7.2mmol), HATU (3.3g, 8.6mmol) in anhydrous DMF (70mL) is added DIPEA (1.4mL, 8.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (217) as white solid (3.3g, 99%).

Example 218

8-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (218):

The product (217) (2.46g, 5.3mmol) and KOH (2.5g, 45mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when the KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (218) as white solid (1.4g, 61%).

^{1}HNMR (DMSO-d6, 300MHz): δ 1.40(s, 9H), 2.79(t, 2H), 3.34(d, 2H), 3.52(t, 2H), 3.57(d, 2H), 4.59(s, 2H), 7.10-7.31(m, 7H), 8.88(s,1H), 11.56-12.92(br s, 1H)
LC/MS (ES+) m/z = 437.26

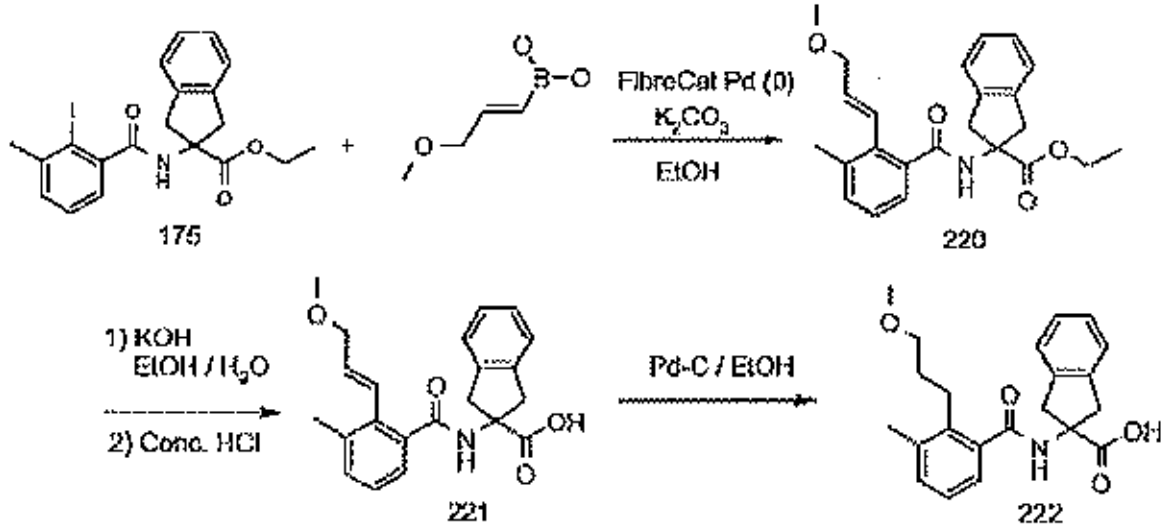
Example 219

2-[(1,2,3,4-Tetrahydro-isoquinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (219):

To a solution of 8-(2-carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (226) (128mg, 0.29mmol) in 6ml dioxane is added dropwise 4N solution of HCl in dioxane/water (0.72mL) and the resulting solution is stirred at RT for 4h. The concentration gave an HCl salt of (219) as white solid (246mg, 100%).

^{1}HNMR (DMSO-d6, 300MHz): δ 3.04(t, 3H), 3.28-3.41(m, 4H), 3.58(d, 2H), 4.31(s, 2H), 7.13-7.27(m, 4H), 7.32(s, 3H), 9.05(s, 1H), 9.30-9.57(br s, 1H), 12.46-12.77(br s, 1H)
LC/MS (ES+) m/z = 337.18

Example 220



2-[2-(3-Methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (220):

To a solution of 2-(2-Iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 3-methoxy-1-propenylboronic acid (206mg, 1.78mmol) in 10mL EtOH/10mL dioxane is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 195mg, 0.089mmol) and 2M aqueous solution of K_2SO_4 (1.78mL, 3.56mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 4h. After concentration *in vacuo*, the residue is purified by HPLC to give the product (220) as pale yellow oil.

Example 221

2-[2-(3-Methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (221):

The product (220) and KOH (1.0g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the obtained brown solid is purified by HPLC to give pure product (221) as white solid (200mg, 62%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 2.28(s, 3H), 3.31(s, 1H), 3.37(s, 4H), 3.78(d, 2H), 3.93(dd, 2H), 5.83(dt, 1H), 6.44(s, 1H), 6.64(d, 1H), 7.10-7.35(m, 7H)
LC/MS (ES+) m/z = 366.15

Example 222

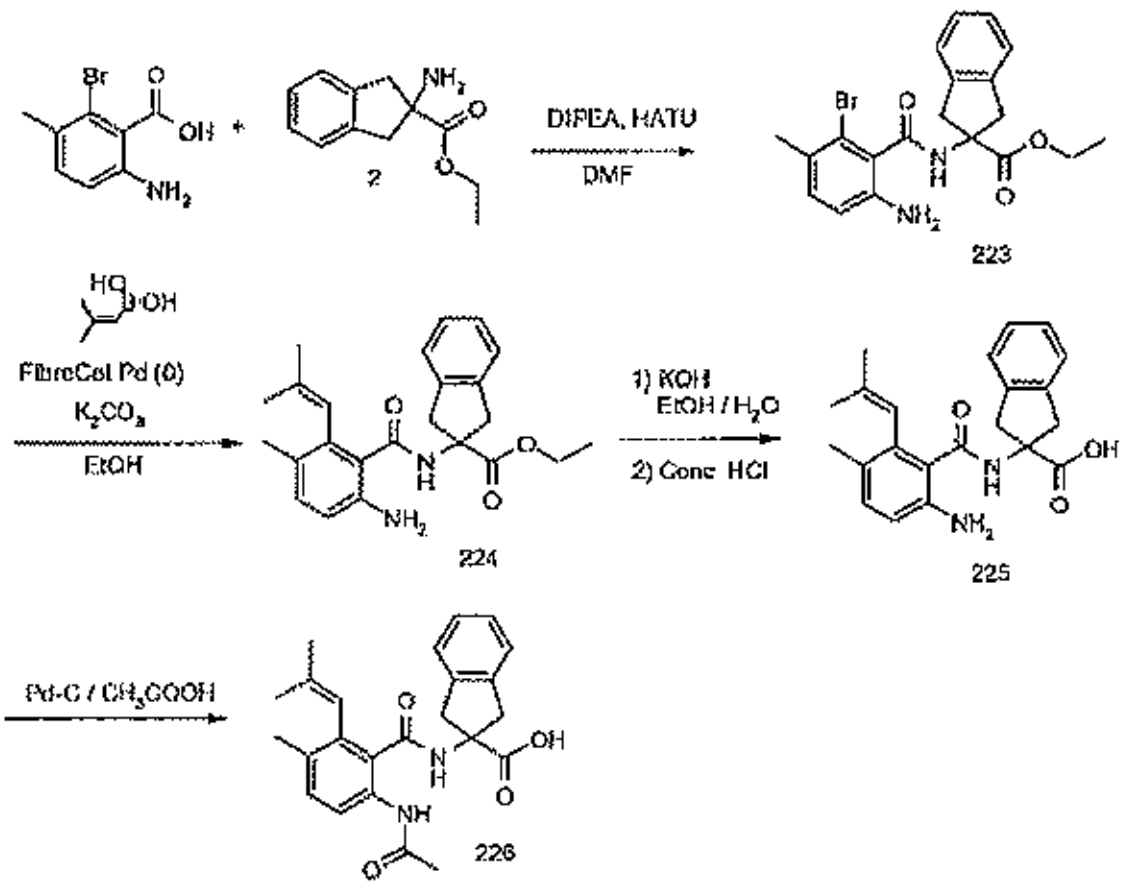
2-[2-(3-Methoxy-propyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (222):

To a solution of 2-[2-(3-methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (229) (120mg, 0.34mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (5wt.%Pd, 93mg, 4.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 50°C, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (222) as white solid (80mg, 49%).

^{1}HNMR (DMSO-d6, 300MHz): δ 1.64(m, 2H), 2.27(s, 3H), 2.59-2.69(m, 2H), 3.16-3.40(m, 7H), 3.56(d, 2H), 6.97-7.24(m, 7H), 8.84(s, 1H), 12.48(s, 1H)

LC/MS (ES+) m/z = 368.18

Example 223



2-[6-Acetylamino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (223):

To a solution of 6-amino-2-bromo-3-methyl-benzoic acid (688mg, 2.99mmol), 2-amino-indan-2-carboxylic acid ethyl ester (737mg, 3.59mmol), HATU (1.36g, 3.59mmol) in anhydrous DMF (30mL) is added DIPEA (0.59mL, 3.59mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give 278mg brown oil (223).

EXAMPLE 224

2-[6-Amino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (224)

To a solution of (223) (278mg, 0.67mmol) and 2,2-dimethylethyleneboronic acid (134mg, 1.34mmol) in 10ml EtOH is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 195mg, 0.089mmol) and 2M aqueous solution of K_2SO_4 (1.78mL, 3.56mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 5h. After concentration *in vacuo*, the residue is purified by HPLC to give 380mg brown semi-solid (224).

EXAMPLE 225

2-[6-Amino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (225)

The mixture (224) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the crude solid is purified by HPLC to give 48mg brown solid (225).

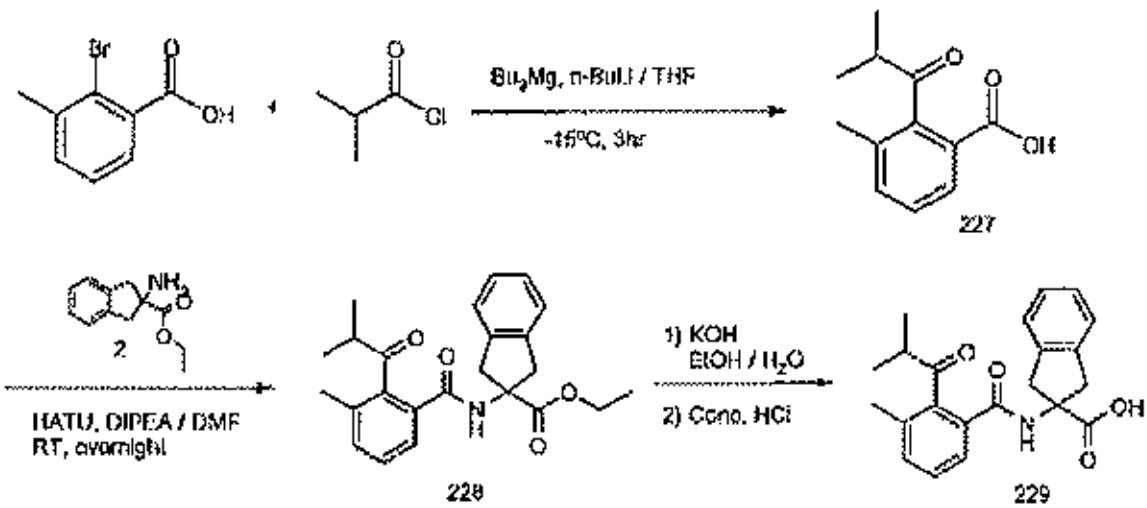
EXAMPLE 226

2-[6-Acetylamino-3-methyl-2-(2-methyl-propenyl)-benzoylaminol-indan-2-carboxylic acid (226)

To a solution of (225) (48mg, 0.1mmol) in acetic acid (10mL) is added the catalyst, Pd-C (5wt.%Pd, 21mg, 1%mmol) under argon. The resulting reaction mixture is moved to the Parr apparatus to run hydrogenation: 55psi, 90°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (226) as white solid (35mg, 86%).

^{1}HNMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.17(s, 3H), 1.70(s, 3H), 2.08(d, 3H), 2.16(d, 3H), 3.26(d, 2H), 3.72(d, 2H), 5.89(s, 1H), 7.12~7.25(m, 5H), 7.48(s, 1H), 7.74(d, 1H)
LC/MS (ES+) m/z = 407.18

Example 227



2-Isobutyryl-3-methyl-benzoic acid (227):

The solution of 2-bromo-3-methyl-benzoic acid (1.5g, 6.98mmol) in 10mL THF is treated with 1M Bu_2Mg/heptane at -15°C under argon. After stirring for 30min, 1.6M n-BuLi/hexane is added dropwise at -15°C and the mixture is left for 1hr. Then isobutyryl chloride (2.95ml, 27.9mmol) is added dropwise. After another 30min stirring, the reaction is quenched with 2N HCl aqueous solution (2ml). After concentration, the residue is purified by HPLC to give a pure product (227) as white solid (840mg, 58%).

^{1}HNMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.62(d, 3H), 1.31(d, 3H), 2.51(s, 3H), 2.61(s, 1H), 7.42-7.50(m, 2H), 7.68(m, 1H)
LC/MS (ES-) m/z = 205.06

Example 228

2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (228):
To a solution of 2-isobutyryl-3-methyl-benzoic acid (227) (200mg, 0.97mmol), 2-amino-indan-2-carboxylic acid ethyl ester (220mg, 1.07mmol), HATU (441mg, 1.16mmol) in anhydrous DMF (10mL) is added DIPEA (192μL, 1.16mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in DCM (50mL) and washed with water (1 x 5mL) and brine (1 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (228) as a pale yellow solid (340mg, 89%).

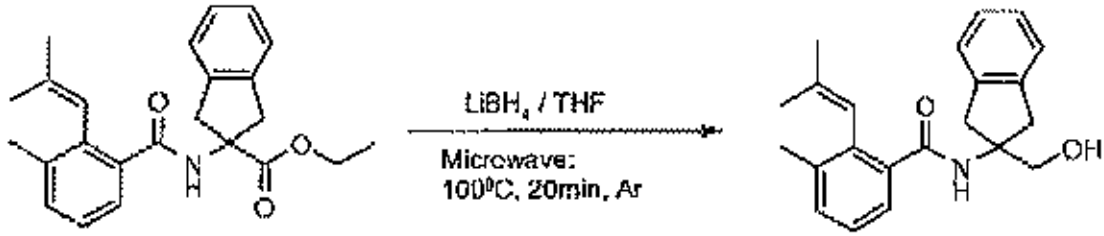
^{1}HNMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 1.25(t, 3H), 2.24(s, 3H), 2.86(m, 1H), 3.36(d, 2H), 3.72(d, 2H), 4.23(q, 2H), 6.47(s, 1H), 7.14-7.43(m, 7H)
LC/MS (ES+) m/z = 394.23

Example 229

2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid (229):
The mixture of 2-(2-isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (228) (170mg, 0.43mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (229) as white solid (140mg, 89%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.07(d, 6H), 2.25(s, 3H), 2.87(m, 1H), 3.35(d, 2H), 3.74(d, 2H), 7.16-7.42(m, 7H)
LC/MS (ES+) m/z = 366.16

Example 230



134 230

N-(2-Hydroxymethyl-indan-2-yl)-3-methyl-2-(2-methyl-propenyl)-benzamide (230):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (80mg, 0.21mmol) in anhydrous THF (1mL) is added dropwise 2M $LiBH_4$/THF (0.84mL, 1.68mmol) at RT under argon. The resulting solution is heated for 20min at 100°C on microwave. After cooling to room temperature, the reaction solution is poured into ice-water and aq. NH_4Cl saturated solution to reach pH 7. The solution is extracted with EtOAc (50mL x 3). The combined EtOAc phase is washed with brine (10ml x 2), dried over Na_2SO_4 and concentrated. The residue is purified by HPLC to give a pure product (230) as white solid (58mg, 82%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.38(s, 3H), 1.80(s, 1H), 2.16(s, 1H), 3.11(d, 2H), 3.33(d, 2H), 3.88(s, 2H), 6.11(s, 1H), 6.71(br s, 1H), 7.13-7.33(m, 6H), 7.60(d, 1H)
LC/MS (ES+) m/z = 336.21

EXAMPLES 231 AND 232

Chiral Separation of Example 150 into Examples 231 and 232

1. Experimental conditions:

	Instrument: Americhrom Global Technologies VERSAPrep 100 (Detector module, Fraction Collection and Recycle and Injection Valves Module, Pump Module, Sample Injection Pump Module)
Software:	Chiralpak AD, 20 mmID x 250mm, 10micron
Eluent:	EtOH / Heptane (20/80) with 0.1 TFA (Pre-mixed)
Flow rate:	15mL/min

Detection:	UV214nm
Column temperature:	RT
Injection volume:	1mL
Concentration:	~ 10mg/mL

2. Results:

Sample	Enantiomer 1	Enantiomer 2
	RT (min)	RT (min)
	iMax Time 6.78	iMax Time 10.02
	47.7mg, white solid	45.1mg, white solid

Fraction 1(-) (231):

^{1}HNMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.24-3.38(m, 2H), 3.43-3.62(m, 2H), 6.90-7.28(m, 6H), 8.83(s, 1H), 12.51(s, 1H)

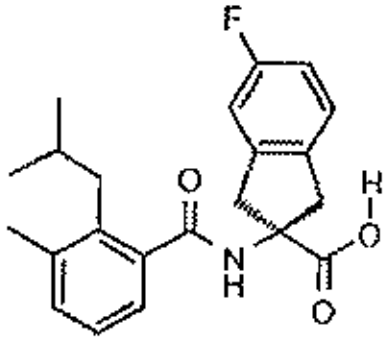
LC/MS (ES+) m/z = 370.18

Fraction 2(+) (232):

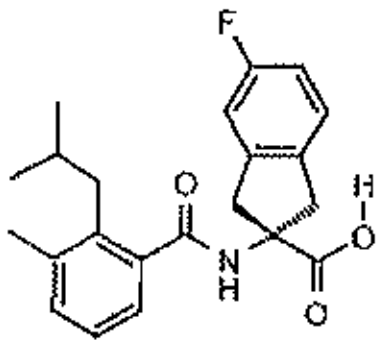
^{1}HNMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.24-3.38(m, 2H), 3.43-3.62(m, 2H), 6.90-7.28(m, 6H), 8.83(s, 1H), 12.51(s, 1H)

LC/MS (ES+) m/z = 370.18

The structures for the enantiomers are as follows:

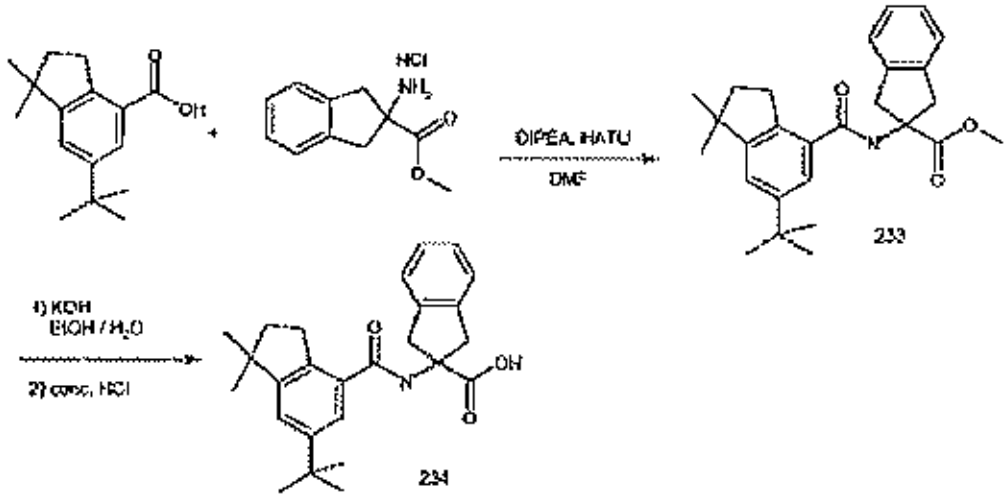


and



. However, the structures are not assigned to either of the particular eluting fraction.

EXAMPLE 233



2-[(6-tert-Butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (233):

To a solution of 6-*tert*-butyl-1,1-dimethyl-indan-4-carboxylic acid (1g, 4.1mmol), HCl salt of 2-amino-indan-2-carboxylic acid methyl ester (924mg, 4.1mmol), HATU (1.85g, 4.9mmol) in anhydrous DMF (13mL) is added DIPEA (2.5mL, 14.4mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 100mL), 1N HCl (1 x 100mL) and brine (1 x 100mL). The organic layer is dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash column chromatography (60g silica gel, gradient elution: 10-60% EtOAc in heptane) to give pure product as white solid (660mg, 39%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.20(s, 6H), 1.27(s, 9H), 1.80(t, 2H), 2.87(t, 2H), 3.37(s, 2H), 3.57(s, 2H), 3.63(s, 1H), 3.64(s, 3H), 7.15-7.29(m, 6H), 8.78(s, 1H)
LC/MS (ES+) m/z = 420.24

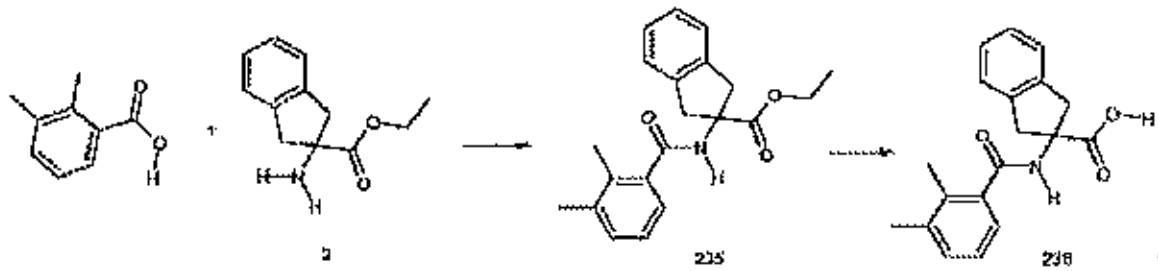
EXAMPLE 234

2-[(6-tert-Butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid (234):
A mixture of 2-[(6-tert-butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (600mg, 1.4mmol) and KOH (1.8g, 30.8mmol) is dissolved in EtOH (25mL) and water (2mL) under water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is neutralized with 1N HCl and extracted with EtOAc (3 x 150mL), the

organic washes are combined and concentrated *in vacuo*. The residue is purified by preparative HPLC (C18 column 10 micron, gradient elution: 20-100% ACN 0.1% TFA in H_2O 0.1% TFA). Product crystallizes out of the collected fractions on standing. Filtration and drying gave pure product as white solid (454mg, 78%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.20(s, 6H), 1.27(s, 9H), 1.79(t, 2H), 2.87(t, 2H), 3.37(s, 2H), 3.55(s, 2H), 3.61(s, 1H), 7.12-7.29(m, 6H), 8.62(s, 1H)
LC/MS (ESI+) m/z = 406.22

Example 235



2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (235) :

2-Amino-indane-2-carboxylic acid ethyl ester (250mg, 1.2 mmol), 2,3-dimethyl-benzoic acid (183mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After a few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (350mg, 87%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.3 (t, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 3.55 (dd, 4H), 4.28 (q, 2H), 6.19 (s, 1H), 7.04 - 7.22 (m, 7H).
LC/MS m/z = 338.17.

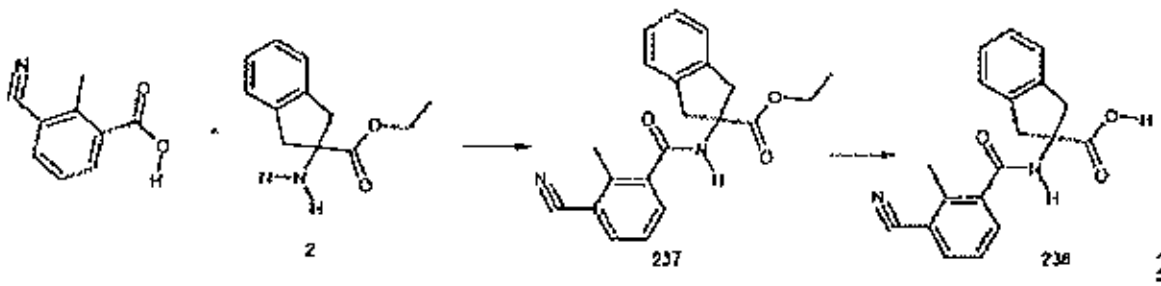
EXAMPLE 236

2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid (236) :

The mixture of 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (235) (290mg, 0.86 mmol), KOH (50% aqueous solution, 1.92g, 17.2mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration gives 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid (236) as white solid (240mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.22 (s, 3H), 2.25 (s, 3H), 3.61 (dd, 4H), 6.24 (s, 1H), 7.06 (m, 2H), 7.18 - 7.23 (m, 5H).
LC/MS m/z = 310.13.

EXAMPLE 237



(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (237) :

2-Amino-indane-2-carboxylic acid ethyl ester (250mg, 1.2 mmol), 3-cyano-2-methyl-benzoic acid (196mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After a few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (373mg, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.3 (t, 3 H), 2. 6 (s, 3 H), 3.57 (dd, 4H), 4.29 (q, 2H), 6.23 (s, 1H), 7.23 - 7.30 (m, 5H), 7.51 (d, 1 H), 7.64 (d, 1 H).
LC/MS m/z = 349.16.

EXAMPLE 238

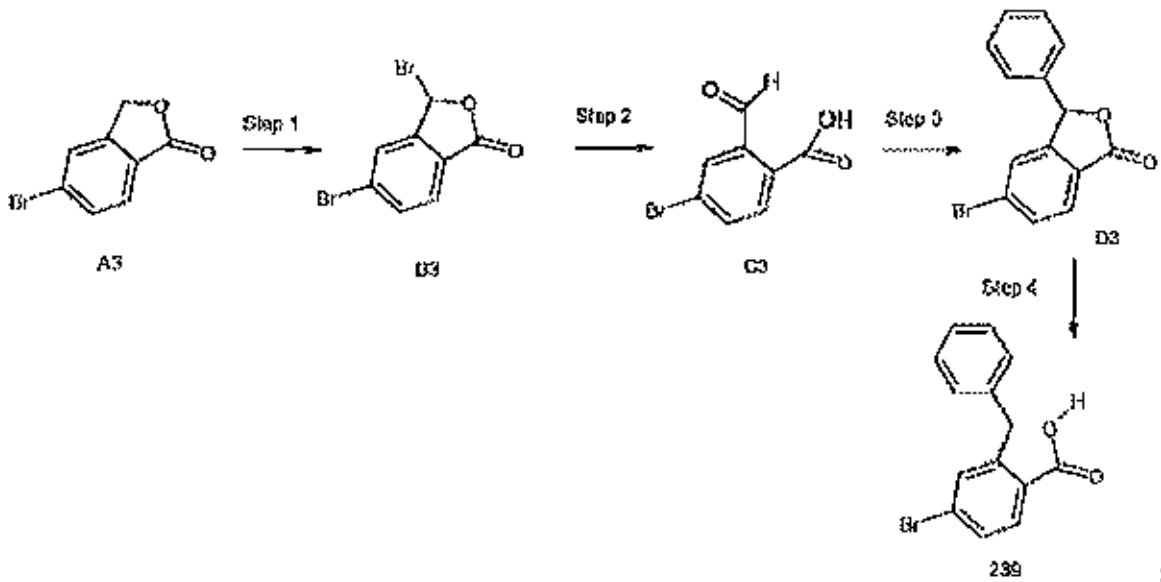
2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid (238) :

The mixture of 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (310mg, 0.89 mmol), KOH (50% aqueous solution, 2g, 17.8 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid (238) as white solid (270mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.56 (s, 3H), 3.62 (dd, 4H), 6.30 (s, 1H), 7.22 - 7.31 (m, 5H), 7.51 (d, 1 H), 7.65 (d, 1 H).
LC/MS m/z = 321.12.

EXAMPLE 239

2-Benzyl-4-bromo-benzoic acid (239):



Ste

p 1

3,5-Dibromo-3H-isobenzofuran-1-one (B3): The mixture of 5-bromo-3H-isobenzofuran-1-one (A3) (51.5g, 242 mmol) in bromobenzene (100mL) is heated to 158°C. Bromine (18.8mL, 363 mmol) is added dropwise to the mixture over 2h. The mixture is stirred for another 30 min. at 158°C. The bromobenzene is removed by distillation under vacuum. The residue is vacuum dried 1 hour at 120°C to yield a black crystalline residue. Recrystallization: The residue is

dissolved in hot isopropyl ether (300mL). Activated charcoal (1 g) is added, stirred and filtered while hot. The filtrate is cooled in ice-water bath (0°C) over night. The solid is filtered and is rinsed with cold isopropyl ether (2 x 10mL) and vacuum dry over KOH (KOH) to yield 3,5-dibromo-3H-isobenzofuran-1-one (B3) (38g, 54%, mp: 100°C).

Step 2

4-Bromo-2-formyl-benzoic acid (C3): The mixture of 3,5-dibromo-3H-isobenzofuran-1-one (B3) (38g, 130 mmol) in a solution of 10N NaOH (28.6mL, 286 mmol) and water (240mL) is heated for 2h at 80°C. Activated charcoal (2g) is added and the mixture is refluxed for another 1 hour. Mixture is hot filtered and acidified with 2N methanesulfonic acid (100mL). The resulting mixture is cooled in an ice-water bath for 1h. The solid is filtered and washed with water (4 x 25mL) and vacuum dried under KOH to yield 4-bromo-2-formyl-benzoic acid (C3) (26.5g, 89%, mp: 202°C). Recrystallization: Dissolved 4-bromo-2-formyl-benzoic acid (C3) in hot EtOH (220mL) and cooled the mixture in an ice-water bath for 4h. The solid is filtered and rinsed with cold EtOH (3 x 20mL). The solid is then vacuum dried over KOH to yield 4-bromo-2-formyl-benzoic acid (16.8g, 63%, mp: 204-205°C).

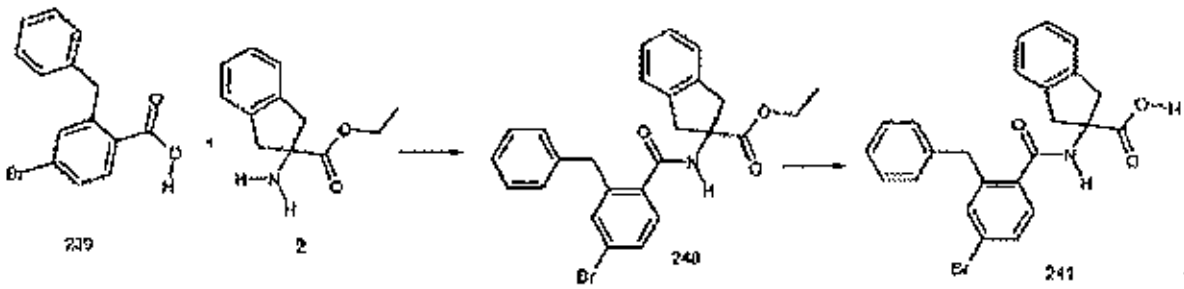
Step 3

5-Bromo-3-phenyl-3H-isobenzofuran-1-one (D3): A mixture of 1L with a condenser and an addition funnel is purged with N_2 and magnesium turnings (5g, 206 mmol) in tetrahydrofuran (80mL) are added. Bromobenzene (32g, 206 mmol) in tetrahydrofuran (80mL) is added dropwise over 1¼ hour by maintaining the mixture temperature at 30°C. The resulting mixture is stirred for 45 min. at 30°C. 4-Bromo-2-formyl-benzoic acid (C3) (18.9g, 83 mmol) in anhydrous tetrahydrofuran (200mL) is added dropwise over 45 min. The mixture is stirred for 2h at 30°C. The mixture is cooled in an ice-water bath and water (120mL) and 5N HCl solution (80mL) are added. The mixture is stirred overnight. THF is removed *in vacuo* and extracted with DCM (3 x 100mL). The combined organics are washed with water (2 x 100mL), dried over Na_2SO_4, filtered and the solvent is removed *in vacuo* to yield 5-bromo-3-phenyl-3H-isobenzofuran-1-one (22.5g, 94%). Recrystallization: 5-bromo-3-phenyl-3H-isobenzofuran-1-one is dissolved in hot acetone (250mL) and the mixture cooled in an ice-water bath over night. The resultant solid is filtered, rinsed with cold ACN (2 x 15mL), and then vacuum dried over KOH to yield 5-bromo-3-phenyl-3H-isobenzofuran-1-one (D3) (14.4g, 61%, mp: 189°C).

Step 4

2-Benzyl-4-bromo-benzoic acid (239): The mixture of 5-bromo-3-phenyl-3H-isobenzofuran-1-one (D3) (14.4g, 50 mmol), iodine (9g, 70 mmol), amorphous red phosphorous (7.8g, 250 mmol), acetic acid (125mL) and distilled water (15mL) are taken in this order in a 3-neck flask with a mechanical stirrer and condenser. After stirring overnight at 50°C (90% product and 10% starting material), the reaction is quenched by adding into water (500mL), added ether (200mL) and filtered off phosphorous. The aqueous layer is extracted with ether (3 x 100mL) and the combined organic layers are washed with sodium bisulfite solution (100mL) and water (2 x 100mL). The organic phase is extracted using 1N NaOH aqueous solution (4 X 100mL), washed again with water (4 x 100mL), dried over Na_2SO_4 and evaporated to get the neutral fraction (2g, mp 180°C). The basic phase is acidified with 5N HCl (150mL) and extracted with DCM (4 x 100mL). The combined extracts are washed with water (3 x 100mL), dried over Na_2SO_4 and evaporated to get product (12g, mp 137°C). This is further recrystallized from boiling ACN (50mL) to afford 2-benzyl-4-bromo-benzoic acid (239) (10g, 83%, mp 145°C).

EXAMPLE 240



2-(2-Benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (240) : 2-Amino-indene-2-carboxylic acid ethyl ester (2) (250mg, 1.2 mmol), 2-benzyl-4-bromo-benzoic acid (239) (354mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/ heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (495mg, 86%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.26 (t, 3 H), 3.35 (dd, 4H), 4.14 (s, 3 H), 4.24 (q, 2H), 6.12 (s, 1H), 7.05 - 7.39 (m, 12H).
LC/MS m/z = 478.13.

EXAMPLE 241

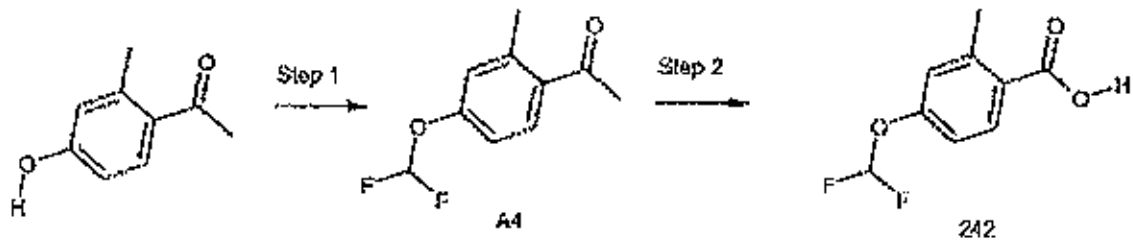
2-(2-Benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid (241) :

The mixture of 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (240) (339mg, 0.71 mmol), KOH (50% aqueous solution, 1.58g, 14.14 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid (241) as white solid (310mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.37 (dd, 4H), 4.10 (s, 2H), 6.23 (s, 1H), 7.01 - 7.38 (m, 12H).
LC/MS m/z = 450.06.

EXAMPLE 242

4-Difluoromethoxy-2-methyl-benzoicacid (242):



Step 1

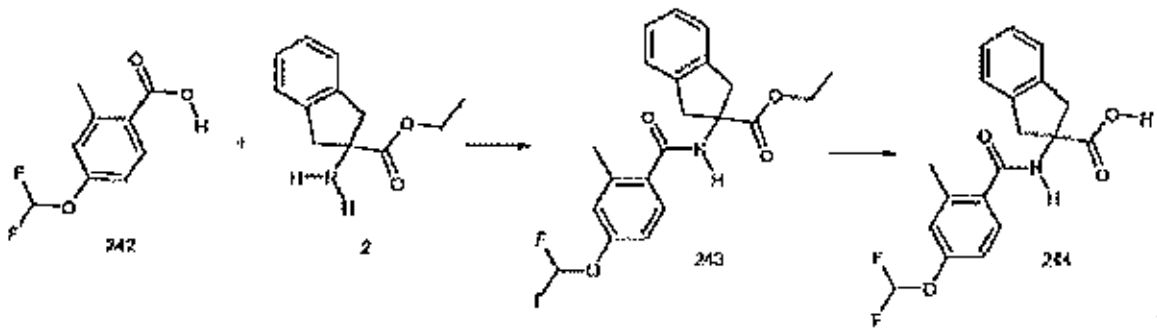
1-(4-Difluoromethoxy-2-methyl-phenyl)-ethanone (A4): To a stirred suspension of 1-(4-hydroxy-2-methyl-phenyl)-ethanone (15g, 100 mmol) in dioxane (30mL) is added water (25mL) followed by the addition of NaOH (20g, 500 mmol). Reaction is heated to 65°C and passed gaseous chlorodifluoromethane (30g, 150 mmol) using a glass tube dipped below the solution level for 75 minutes. Stirred for 30min longer and left at RT over the weekend. Water (100mL) and ether (40mL) are added after transferring to a separatory funnel. A semi-

gelatinous material settled at the bottom of the aqueous layer after some time. The bottom aqueous layer is drained off and extracted with ether (2 x 40mL). The combined ether layers are washed with water (5 x 25mL), dried over solid K_2SO_4, evaporated and distilled (0.04 mm Hg, 61-64°C) to afford 1-(4-difluoromethoxy-2-methyl-phenyl)-ethanone (A4) (16.2g, 81%). Rf in the 0.60 with ether.

Step 2

4-Difluoromethoxy-2-methyl-benzoic acid (242): A stirred solution of sodium hypochlorite (5.25% Aqueous, 204mL, 143 mmol) and 2N aqueous KOH (22mL, 44 mmol) are heated to 50°C and 1-(4-difluoromethoxy-2-methyl-phenyl)-ethanone (A4) (5.8g, 29 mmol) is added. After maintaining the temperature at 50-70°C for 3h and keeping at RT overnight, the reaction is reheated to 50°C and sodium metabisulfite (4.5g) is added in 3 portions. The reaction is then acidified with 12N HCl and stirred well. The precipitated white solid is filtered off, rinsed with a little water and air dried to afford 4-difluoromethoxy-2-methyl-benzoic acid (242) (5.4g, 92%). The product is recrystallized from 1:1 mixture of ACN and water; mp: 117-119°C. Elemental Analysis: Actual C (53.23),H (3.88), F (18.66) Theoretical C (53.47),H (3.99), F (18.80).

EXAMPLE 243



2-(4-Difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (243) : 2-Amino-indane-2-carboxylic acid ethyl ester (2) (250mg, 1.2 mmol), 4-difluoromethoxy-2-methyl-benzoic acid (242) (246mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel

column using 20-50% EtOAc in heptane as a gradient to afford 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (415mg, 89%).

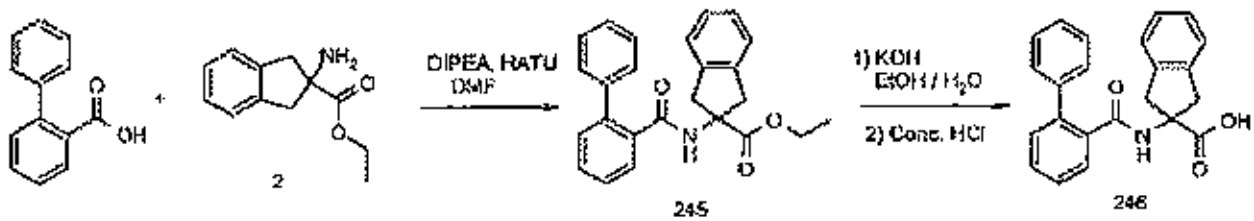
^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.29 (t, 3 H), 2.42 (s, 3 H), 3.56 (dd, 4H), 4.27 (q, 2H), 6.21 (s, 1H), 6.91 (m, 2H), 7.22 (m, 4H), 7.33 (d, 1H).
LC/MS m/z = 390.16.

EXAMPLE 244

<u>2-(4-Difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid (244) :</u>
The mixture of 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (243) (301mg, 0.77 mmol), KOH (50% aqueous solution, 1.73g, 15.5 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (10mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid (244) as white solid (245mg, 88%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.37 (s, 3H), 3.62 (dd, 4H), 6.23 (s, 1H), 6.92 (m, 2H), 7.24 (m, 5H).
LC/MS m/z = 362.10.

EXAMPLE 245



<u>2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (245):</u>
To a solution of biphenyl-2-carboxylic acid (289mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381µL, 2.19mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers are concentrated *in vacuo* and the residue purified by flash column chromatography (12g silica

gel, gradient elution: 0-30% EtOAc in heptane) to give product (245) as off-white solid (525mg, 93%).

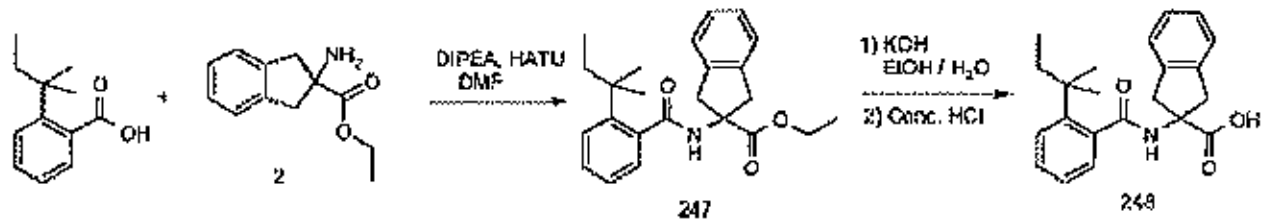
EXAMPLE 246

2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid (246):

2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (525mg, 1.36mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (246) as white solid (453mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.92(d, 2H), 3.63(d, 2H), 5.84(s, 1H), 7.08-7.12(m, 2H), 7.15-7.19(m, 2H), 7.24(s, 4H), 7.30(dd, 2H), 7.40-7.54 (m, 2H), 7.85 (dd, 1H)
LC/MS (ES+) m/z = 358.14

EXAMPLE 247



2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (247):

To a solution of 2-(1,1-dimethyl-propyl)-benzoic acid (140mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190μL, 1.1mmol). The resulting solution is stirred at RT overnight. Water (10mL) is then poured into the reaction mixture, and then the reaction mixture is extracted with EtOAc (3 x 5mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (247) as yellow oil (220mg, 89%).

EXAMPLE 248

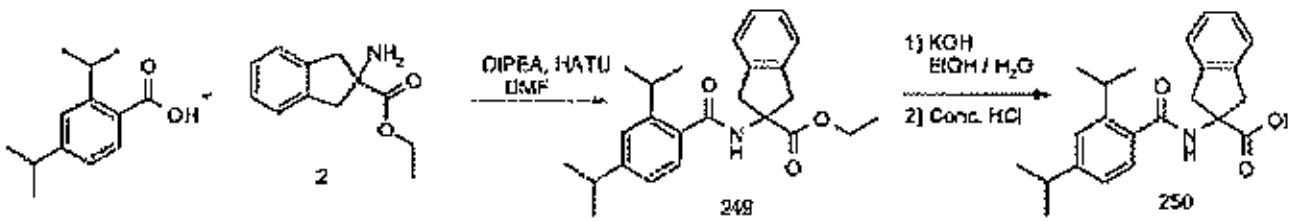
2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid (248):

2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (220mg, 0.58mmol) is dissolved in EtOH (8mL), and solid KOH (600mg, 10mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (248) as white solid (158mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.53(t, 3H), 1.29(s, 6H), 1.66-1.73(q, 2H), 3.44(d, 2H), 3.80(d, 2H), 6.14(s, 1H), 7.13-7.14(m, 1H), 7.15(d, 1H), 7.22(d, 4H), 7.32(d, 1H), 7.34 (t, 1H), 7.37 (dd, 1H)

LC/MS (ES+) m/z = 352.17

EXAMPLE 249



2-(2,4-Diisopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (249):

To a solution of 2,4-diisopropyl-benzoic acid (150mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190µL, 1.10mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (249) as off-white solid (211mg, 73%).

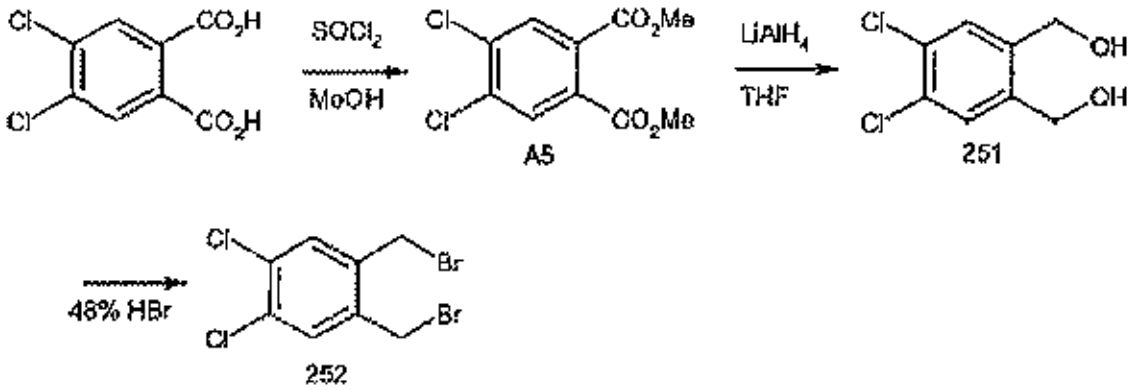
EXAMPLE 250

2-(2,4-Diisopropyl-benzoylamino)-indan-2-carboxylic acid (250):

2-(2,4-diisopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (211mg, 0.54mmol) is dissolved in EtOH (8mL), and solid KOH (823mg, 14mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (250) as white solid (188mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.12(d, 6H), 1.21(d, 6H), 2.83-2.92(m, 1H), 3.10-3.19(m, 1H), 3.41(d, 2H), 3.82(d, 2H), 6.18(s, 1H), 7.00-7.10(m, 2H), 7.16(s, 1H), 7.22-7.31(m, 4H)
LC/MS (ES+) m/z = 366.20

EXAMPLE 251



Dimethyl 4,5-Dichlorophthalate (A5):

Thionyl chloride (150mL, 2.05 mol) is added dropwise over 2h to a magnetically stirred solution of 4,5-dichlorophthalic acid (130.43g, 469.8 mmol) in MeOH (1L) at RT. After stirring overnight, the MeOH is removed *in vacuo* on a rotary evaporator. The residue is dissolved in EtOAc (750mL) and extracted with water (1 x 500mL) and saturated aqueous $NaHCO_3$ (1 x 500mL). The organic layer is separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford A5 (122.8g) as a pale yellow liquid. [A. Rosowsky, C. M. Vaidya,h. Bader, J. E. Wright, B. A. Teicher, *J. Med. Chem.* 40, 286-299 (1997); E. J. Hennessy, S. L. Buchwald, *J. Org. Chem.*, 70, 7371-7375 (2005)]

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.92 (s, 3H), 7.82 (s, 1H)

4,5-Dichloro-1,2-bis(hydroxymethyl)benzene (251):

A solution of dimethyl 4,5-dichlorophthalate A5 (98.86g, 375.78 mmol) in tetrahydrofuran (150mL) is added dropwise over 1h to a mechanically stirred suspension of LAH (20.8g,

548.1 mmol) in tetrahydrofuran (1.5L). During the addition, the reaction is cooled in an ice-water bath. When the addition is completed, the reaction is stirred overnight at RT. The excess LAH is decomposed by cautious addition of water (20mL), 10% aqueous NaOH (40mL) and water (20mL). The solids are removed by filtration through a celite pad and washed with tetrahydrofuran. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to afford crude 251 as white solid that is purified by crystallization from acetone (150mL)-heptane (150mL). The crystals are collected by filtration, washed with heptane and dried to give 4,5-dichloro-1,2-bis(hydroxymethyl)benzene (37.2g). The combined filtrate and wash afforded a second crop of 251 (18.8g, 24.1%). [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983); O. Farooq, *Synthesis*, 1035-1036 (1994)]

^{1}H NMR (DMSO-d6, 300MHz): δ 4.49 (d, 2H), 5.32 (t, 1H), 7.57 (s, 1H)
EI-MS m/z 209,207
Anal. Calcd. for $C_8H_8Cl_2O_2$: C, 46.41;H, 3.89. Found: C, 46.50;H, 3.83

EXAMPLE 252

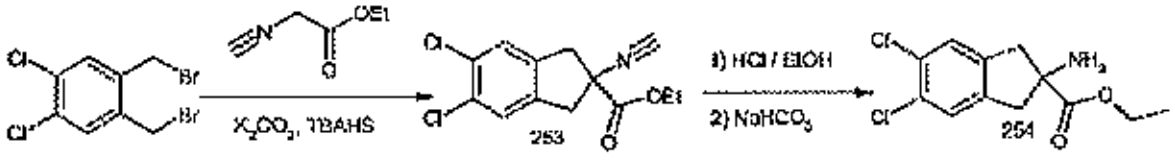
1,2-Bis-(bromomethyl)-4,5-dichlorobenzene (252):

A mixture of 4,5-dichloro-1,2-bis(hydroxymethyl)benzene (251, 32.87g, 158.75 mmol) and 48% aqueous hydrobromic acid (160mL) is heated at reflux temperature for 6h. The reaction is cooled and extracted with diethyl ether (1 x 450mL + 2 x 200mL). The combined organic extracts are backwashed with water (1 x 200mL) and with brine (1 x 200mL). The organic layer is separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford a light yellow solid that is dissolved in heptane-0.5% EtOAc by heating and placed atop a column of silica gel (7.2cm x 23cm) prepared in heptane-0.5% EtOAc and flash chromatographed taking 500mL fractions and eluting with heptane-0.5% EtOAc (1.6L), and heptane-1% EtOAc (4L). The product containing fractions (5-14) are combined and concentrated *in vacuo* on a rotary evaporator to give 1,2-bis-(bromomethyl)-4,5-dichlorobenzene (252, 50.01g) as a colorless liquid. [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983)]

^{1}H NMR ($CDCl_3$, 300MHz): δ 4.55 (s, 2H), 7.46 (s, 1H)
EI-MS m/z 330,332,334,336

Anal. Calcd. for $C_8H_6Br_2Cl_2$: C, 28.87;H, 1.82. Found: C, 28.84;H, 1.68

EXAMPLE 253



4.

5-Dichloro-isocyano-indan-2-carboxylic acid ethyl ester (253) :

To a solution of ethyl isocyanoacetate (3.85mL, 35mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (29g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7mmol), and 1,2-bis-(bromomethyl)-4,5-dichlorobenzene (11.6g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as white powder (6.63g, 66%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.46 (s, 2H)

LC/MS (ES+) m/z = 286.14

EXAMPLE 254

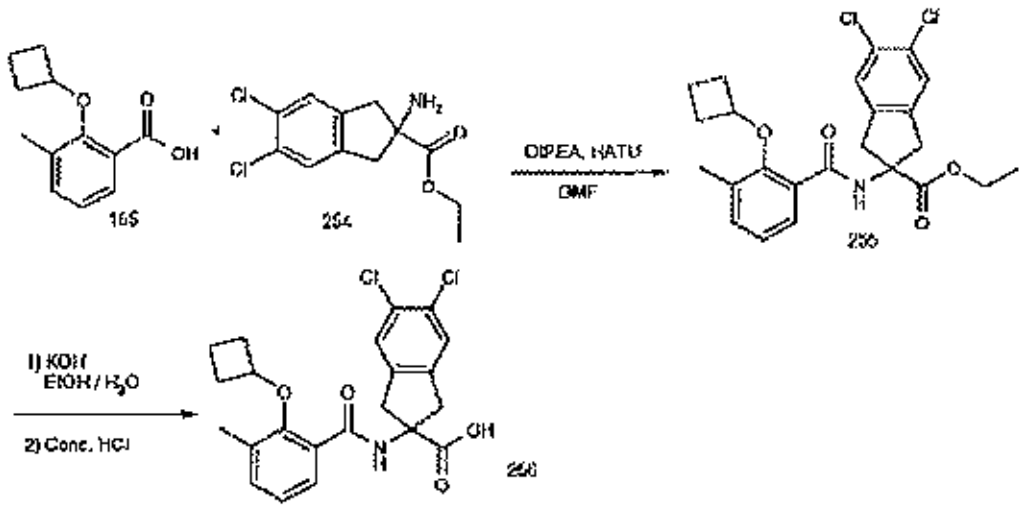
2-Amino-4,5-dichloro-indan-2-carboxylic acid ethyl ester (254):

To a solution of 4,5-dichloro-isocyano-indan-2-carboxylic acid ethyl ester (253) (6.63g, 23.2mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt is dissolved in water (100mL) and extracted with ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc (3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (5.2g, 82%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.46 (s, 2H)

LC/MS (ESI+) m/z = 275.18

EXAMPLE 255



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid ethyl ester (255):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (225mg, 1.1mmol), 2-amino-4,5-dichloro-indan-2-carboxylic acid ethyl ester (254) (360mg, 1.31mmol), HATU 622mg, 1.64mmol) in anhydrous DMF (10mL) is added DIPEA (360µL, 2.20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (255) as white powder (460mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21- 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ESI+) m/z = 428.93

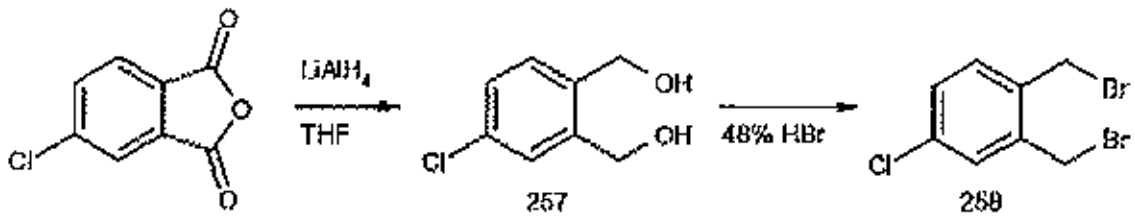
EXAMPLE 256

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid (256):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid ethyl ester (255) (460mg, 0.99mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with concentrated HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (256) is obtained as white solid (405mg, 94%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 434.32

EXAMPLE 257



4-Chloro-1,2-bis(hydroxymethyl)benzene (257):

A solution of 4-chlorophthalic anhydride (24.83g, 136.01 mmol) in tetrahydrofuran (100mL) is added dropwise to a mechanically stirred suspension of LAH (8.72g, 229.78 mmol) in tetrahydrofuran (500mL). After stirring overnight at room temperature, the excess LAH is decomposed by cautious addition of water (8.5mL), 10% aqueous NaOH (17mL) and water (8.5mL). The reaction is diluted with tetrahydrofuran (300mL) and the solids are removed by filtration through a celite pad and washed with tetrahydrofuran. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to afford diol 257 as a colorless liquid (22.16g) that crystallized on standing. Crystallization is effected in benzene. [O. Farooq, *Synthesis*, 1035-1036 (1994); R. F. Bird, E. E. Turner, *J. Chem. Soc.* 5050-5051 (1952); J. Tirouflet, *Compt. rend.*, 238, 2246-2247 (1954)]

^{1}H NMR (DMSO-d6, 300MHz): δ 4.48 (t, 2H), 4.52 (t, 2H), 5.15 (t, 1H), 5.24 (t, 1H), 7.27 (dd, 1H), 7.38 (s, 1H), 7.41 (t, 1H)

EXAMPLE 258

1,2-Bis(bromomethyl)-4-chlorobenzene (258):

A mixture of 4-chloro-1,2-bis(hydroxymethyl)benzene (257, 20.57g, 119.17 mmol) and 48% aqueous hydrobromic acid (140mL) is heated at 137°C for 4.5h. The reaction is cooled to RT then diluted with cold water (250mL) and extracted with diethyl ether (1 x 400mL + 2 x 200mL). The combined organic extracts are washed with water (1 x 200mL), with brine (1 x 200mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford crude dibromide 258 as a yellow liquid. This material is dissolved in heptane-0.5% EtOAc, placed atop a column of silica gel (7.2cm x 22cm) and flash chromatographed taking 400mL fractions eluting with heptane-0.5% EtOAc (1.6L) and heptane-1% EtOAc (3L). Product containing fractions (5-9) are combined and concentrated *in vacuo* on a rotary evaporator to afford dibromide 258 as a colorless liquid (34.46g). [D. R. Lyon, F.G. Mann, G. H.. Cookson, *J. Chem. Soc.*, 662-670 (1947)]

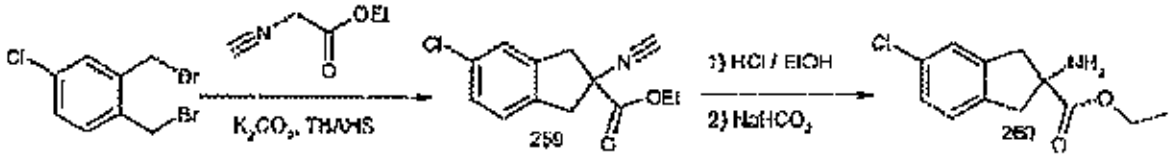
^{1}H NMR ($CDCl_3$, 300MHz): δ 4.58 + 4.61 (s + s, 4H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)
EI-MS 298,300
Anal. Calcd. For $C_8H_7Br_2Cl$: C, 32.20;H, 2.36. Found: C, 32.30;H, 2.22

Alternate Route:

A magnetically stirred mixture of 4-chloro-*ortho*-xylene (5g, 35.56 mmol), *N*-bromosuccinimide (12.65g, 71.07 mmol), AIBN (0.55g) and CCl_4 (150mL) is heated at reflux temperature for 3.5h, and then cooled to RT. The solids are removed by filtration and washed with CCl_4. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to give crude dibromide 10 as a colorless liquid that is dissolved in heptane-1% EtOAc, placed atop a column of silica gel (7.2cm x 18cm) prepared in heptane-1% EtOAc and flash chromatographed taking 200mL fractions eluting with heptane-1% EtOAc. Product containing fractions (7-11) are combined and concentrated *in vacuo* on a rotary evaporator to afford impure 258 as colorless liquid.

^{1}H NMR ($CDCl_3$, 300MHz): δ 4.46 (s, 0.3H), 4.51 (s, 0.6H), 4.58 + 4.61 (pr s, 4H), 7.26-7.29 (m, 2.5H), 7.36 (d, 1.2H).

EXAMPLE 259



4-Chloro-isocyano-indan-2-carboxylic acid ethyl ester (259) :

To a solution of ethyl isocyanoacetate (3.85mL, 35.0mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (29g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7mmol), and 1,2-bis(bromomethyl)-4-chlorobenzene (10.4g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as a colorless oil (5.06g, 58%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)
LC/MS (ES+) m/z = 250.56

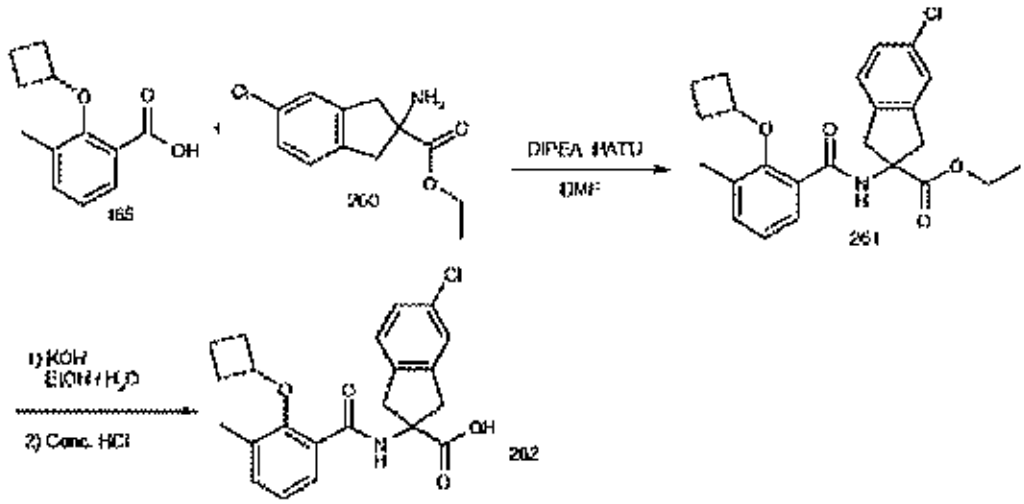
EXAMPLE 260

2-Amino-4-chloro-indan-2-carboxylic acid ethyl ester (260):

To a solution of 4-chloro-isocyano-indan-2-carboxylic acid ethyl ester (259) (5.06g, 20.2mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt is dissolved in water (100mL) and extracted with of ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc (3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (4.2g, 87%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)
LC/MS (EZ+) m/z = 239.58

EXAMPLE 261



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid ethyl ester (261):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (213mg, 1.04mmol), 2-amino-4-chloro-indan-2-carboxylic acid ethyl ester (260) (298mg, 1.24mmol), HATU (591mg, 1.55mmol) in anhydrous DMF (10mL) is added DIPEA (345µL, 2.07mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (261) as white powder (370mg, 83%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21-4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)
LC/MS (ES+) m/z = 428.93

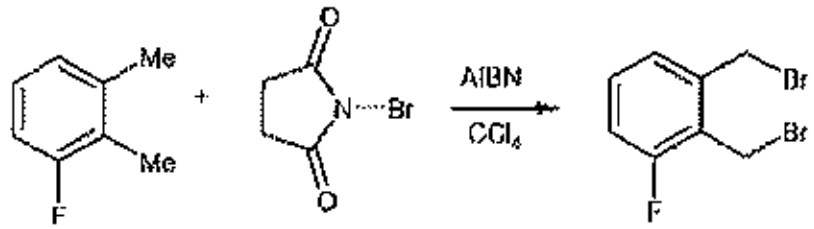
EXAMPLE 262

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid (262):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid ethyl ester (261) (370mg, 0.86mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (262) is obtained as white solid (320mg, 93%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 399.93

EXAMPLE 263



263

1,2-Bis(bromomethyl)- 3-fluorobenzene (263):

A magnetically stirred mixture of 3-fluoro-*ortho*-xylene (5.05g, 40.67 mmol), *N*-bromosuccinimide (15.23g, 85.56 mmol), AIBN (78mg) and CCl_4 (75mL) is heated at reflux temperature for 1.75h, then cooled to RT. The solids are removed by filtration and washed with CCl_4. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to give crude dibromide 263 as a yellow liquid that is dissolved in heptane-0.5% EtOAc, placed atop a column of silica gel (7.2cm x 18cm) prepared in heptane-0.5% EtOAc and flash chromatographed taking 200mL fractions eluting with heptane-0.5% EtOAc. Product containing fractions are combined and concentrated *in vacuo* on a rotary evaporator to afford a colorless liquid. On standing crystals form in the liquid. The liquid is separated using a pipette. The process is repeated once more. The resulting liquid is pure 1,2 bis(bromomethyl)-3-fluorobenzene. [J. E. Rice, A. Czech, N. Hussain, E. J. La Voie, *J. Org. Chem.*, 53, 1775-1779 (1988) ; R. A. Aitken, P. K.g. Hodgson, M. J. Morrison, A. O. Oyewale, *J. Chem. Soc. (Perkin 1)*, 402-415 (2002)]

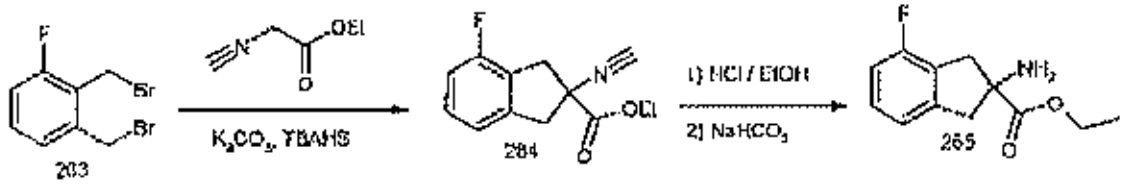
^{1}H NMR ($CDCl_3$, 300MHz): δ 4.63 (s, 3H), 4.70 (s, 3H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)

F NMR ($CDCl_3$, 300MHz): δ 115.26 (d)

LC-MS 3.23 (no parent ion)

Anal. Calcd. for $C_8H_7Br_2F$: C, 34.08;H, 2.50; F, 6.74. Found: C, 34.11;H, 2.28; F, 6.88

EXAMPLE 264



3-Fluoro-isocyano-indan-2-carboxylic acid ethyl ester (264) :

To a solution of ethyl isocyanoacetate (3.85mL, 35.0mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (K_2SO_4, 29.0g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7.0mmol), and 1,2-bis(bromomethyl)-3-fluorobenzene (9.87g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as colorless oil (4.5g, 55%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)

LC/MS (ES+) m/z = 234.26

EXAMPLE 265

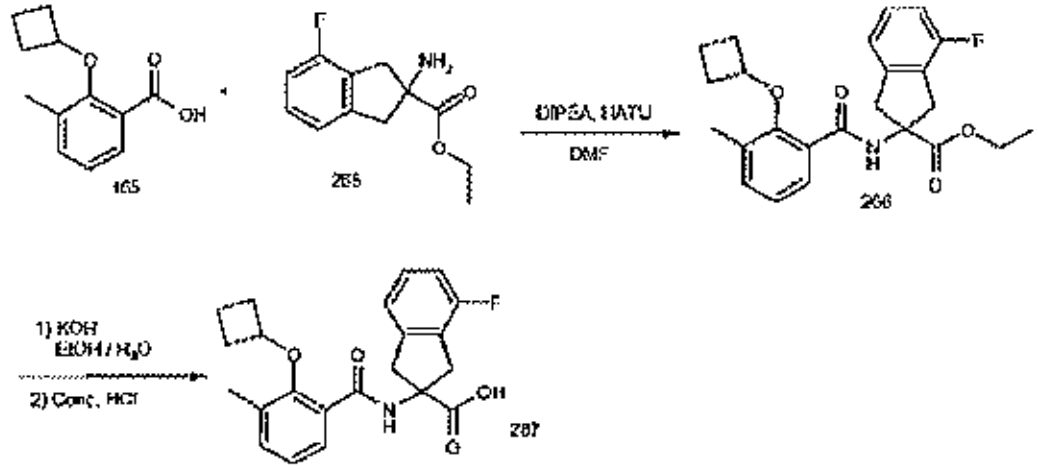
2-Amino-3-fluoro-indan-2-carboxylic acid ethyl ester (265):

To a solution of 2-isocyano-indan-2-carboxylic acid ethyl ester (264) (4.5g, 19.3mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride

salt is dissolved in water (100mL) and extracted with of ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc 3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (2.3g, 53%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)
LC/MS (EZ+) m/z = 223.08

EXAMPLE 266



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid ethyl ester (266):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (127mg, 0.61mmol), 2-Amino-3-fluoro-indan-2-carboxylic acid ethyl ester (265) (165mg, 0.74mmol), HATU 352mg, 0.93mmol) in anhydrous DMF (10mL) is added DIPEA (204µL, 1.23mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (266) as a colorless oil (210mg, 84%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21 - 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.39(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 412.19

EXAMPLE 267

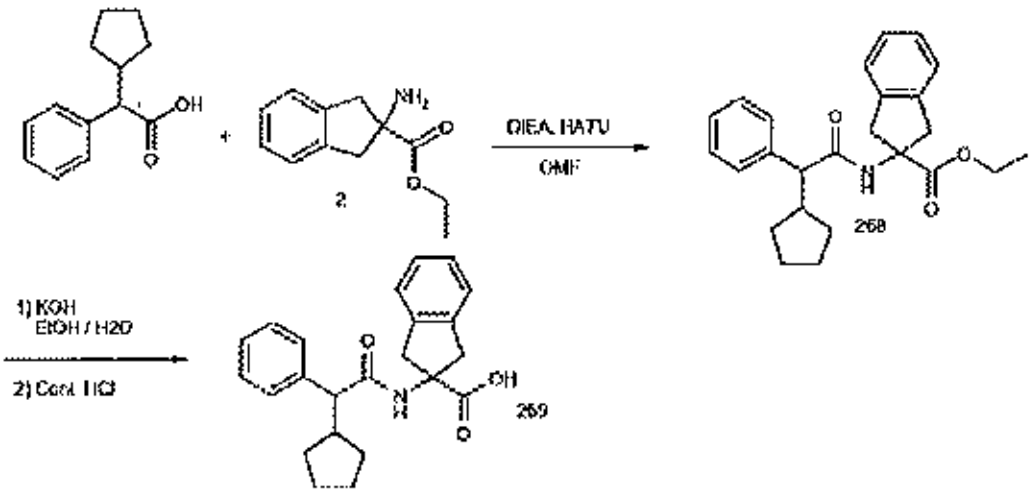
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid (267):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid ethyl ester (7) (210mg, 0.51mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with concentrated HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (267) is obtained as white solid (168mg, 86%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.15

EXAMPLE 268



2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid ethyl ester (268):

To a solution of α-phenylcyclopenteacetic acid (2.04g, 10mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (2.05g, 10mmol), HATU (7.60g, 20mmol) in anhydrous DMF (50mL) is

added DIPEA (3.30mL, 20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with saturated $NaHCO_3$ (1 x 100mL), water (1 x 100mL) and brine (1 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (268) as a solid (3.16g, 82%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 0.91(m, 1H), 1.23(m, 2H), 1.29 (t, 3H), 1.35-1.64(m, 4H), 1.65-1.81(m, 1H), 2.34-2.49(m, 1H), 2.78(d, 2H), 2.89-3.03(d, 1H), 3.13-3.23(m, 2H), 3.42-3.52(m, 2H), 7.1-7.35(m, 9H)
LC/MS (ES+) m/z = 392.19

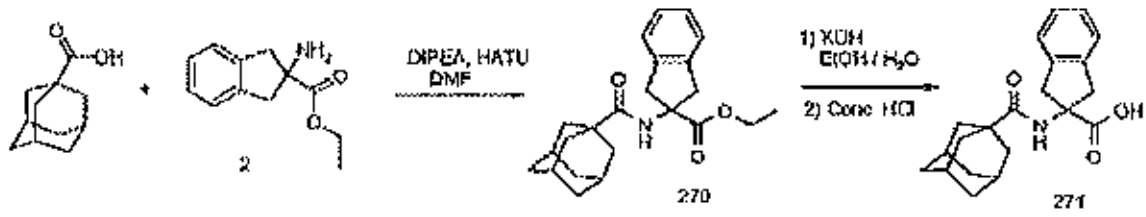
EXAMPLE 269

2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid (269):

2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid ethyl ester (268) (1g, 2.56mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and washed with EtOAc (20ml). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The solid precipitate is collected via filtration and dried under vacuum. The desired product (269) is obtained as white solid (710mg, 71%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 0.91(m, 1H), 1.23(m, 2H), 1.35-1.64(m, 4H), 1.65-1.81(m, 1H), 2.34-2.49(m, 1H), 2.89-3.03(d, 1H), 3.13-3.23(m, 2H), 3.42-3.52(m, 2H), 7.1-7.35(m, 9H), 8.57(s, 1H)
LC/MS (ES+) m/z = 364.46

EXAMPLE 270



2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid ether ester (270):

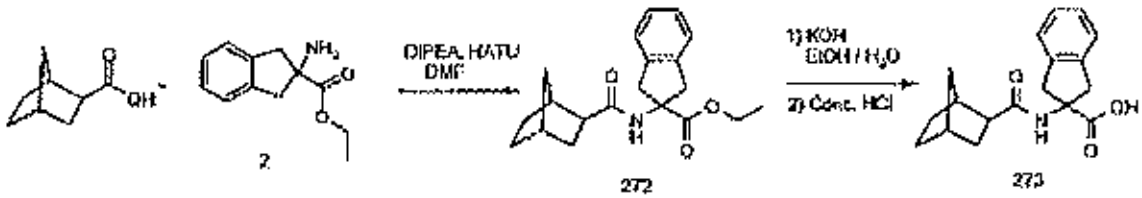
To a solution of adamantane-1-carboxylic acid (131mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190µL, 1.1mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (270) as white solid (261mg, 97%).

2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid (271):

2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid ether ester (261mg, 0.71mmol) is dissolved in EtOH (8mL), and solid KOH (823mg, 14mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (271) as white solid (159mg, 66%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.62-1.76 (q, 6H), 1.76 (d, 6H), 2.02 (s, 3H), 3.25(d, 2H), 3.79(d, 2H), 6.04(s, 1H), 7.15(d, 1H), 7.21 (s, 4H)
LC/MS (ES+) m/z = 340.18

EXAMPLE 272



2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (272):

To a solution of bicyclo[2.2.1]heptane-2-carboxylic acid (102mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190µL, 1.10mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture and then extracted with EtOAc (3x 5mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (272) as yellow oil (148mg, 62%).

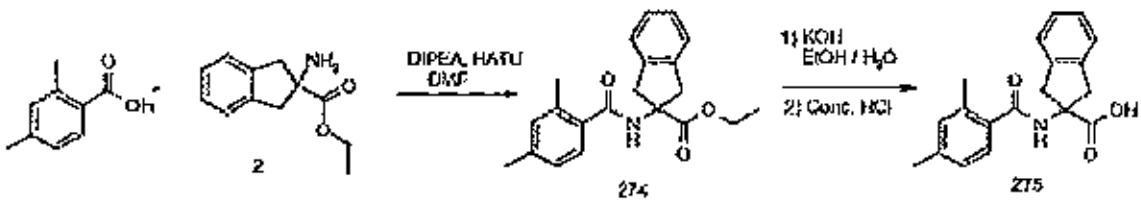
EXAMPLE 273

2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid (273):

2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (148mg, 0.45mmol) is dissolved in EtOH (8mL), and solid KOH (600mg, 10mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (273) as white solid (105mg, 77%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.14 (d, 1H), 1.26-1.40 (m, 4H), 1.44-1.54(q, 2H), 1.57-1.67 (m, 1H), 2.27(d, 2H), 2.58-2.64(m, 1H) 3.27(t, 2H), 3.75(d, 2H), 5.97(s, 1H), 7.20 (s, 4H)
LC/MS (ES+) m/z = 300.13

EXAMPLE 274



2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (274):

To a solution of 2,4-dimethyl-benzoic acid (219mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381µL, 2.19mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture, and then extracted with EtOAc (3x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (274) as white solid (414mg, 84%).

EXAMPLE 275

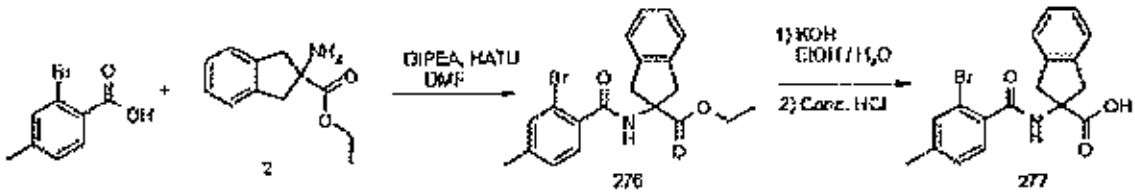
2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid (275):

2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (414mg, 1.23mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (275) as white solid (350mg, 92%).

^{1}H NMR (CDCl$_3$, 300MHz): 2.30(s, 6H), 3.41(d, 2H), 3.84(d, 2H), 6.20(s, 1H), 6.96(d, 1H), 7.00(s, 1H), 7.13(d, 1H), 7.24(d, 4H)

LC/MS (ES+) m/z = 310.14

EXAMPLE 276



2-(2-Bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (276):

To a solution of 2-bromo-4-methyl-benzoic acid (314mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381µL, 2.19mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (276) as off-white solid (445mg, 76%).

EXAMPLE 277

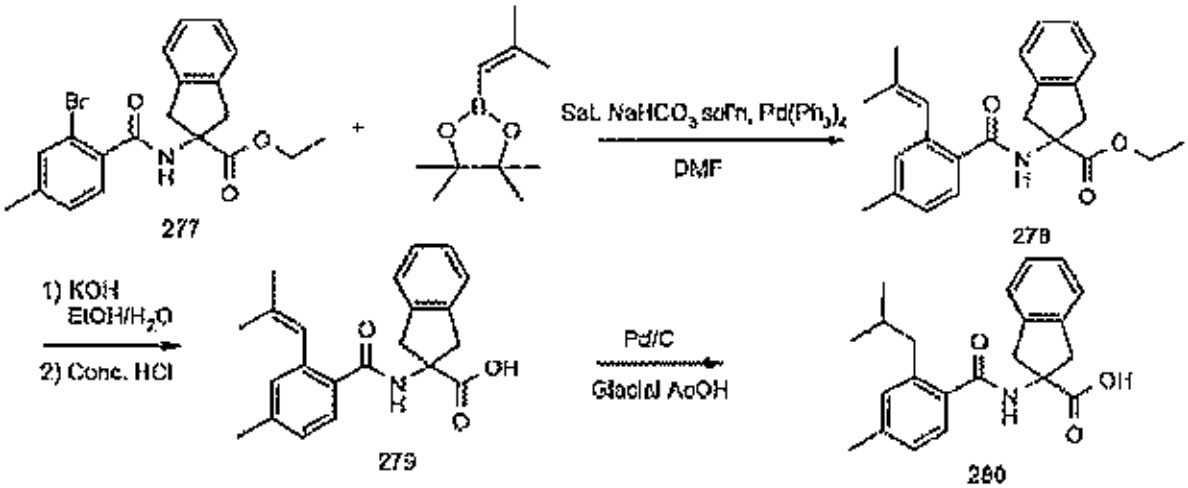
2-(2-Bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid (277):

2-(2-bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (445mg, 1.11mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with conc. HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (277) as white solid (415mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): 2.33 (s, 3H), 3.45(d, 2H), 3.83(d, 2H), 6.70(s, 1H), 7.15(d, 1H), 7.19-7.25 (m, 4H), 7.35(s, 1H), 7.51 (d, 1H)

LC/MS (ESI+) m/z = 374.04, 376.04

EXAMPLE 278



2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (278):

A mixture of 2-(2-bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (880mg, 2.2mmol), 4,4,5,5-tetramethyl-2-(2-methyl-propenyl)-[1,3,2]dioxaborolane (903µL, 4.4mmol) and saturated $NaHCO_3$ solution (4.4mL) in anhydrous DMF (20mL) is degassed with N_2. While under N_2 atmosphere, tetrakis(triphenylphosphine)palladium (196mg, 10mol%) is added and the reaction is heated in a 110°C oil bath for 2h. The reaction is cooled to room temperature, poured into water (40mL) and extracted with EtOAc (2 x 30mL). The combined organic layers are washed with water (15mL) and brine (20mL) then concentrated *in vacuo*. The residue is purified by flash column chromatography (24g silica gel, gradient elution: 0-50% EtOAc in heptane) to give product (278) as a reddish-brown viscous oil (764mg, 92%).

EXAMPLE 279

2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (279):

2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (764mg, 2.02mmol) is dissolved in EtOH (25mL), and solid KOH (2.32g, 40mmol) and water (2.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in a mixture of water (40mL) and EtOAc (20mL) and the organic layer is

separated. The aqueous layer is adjusted to approximately pH 7 with conc. HCl then extracted with EtOAc (2 x 15mL). The combined organic layers are concentrated *in vacuo* to yield product (279) as off-white solid (544mg, 78%).

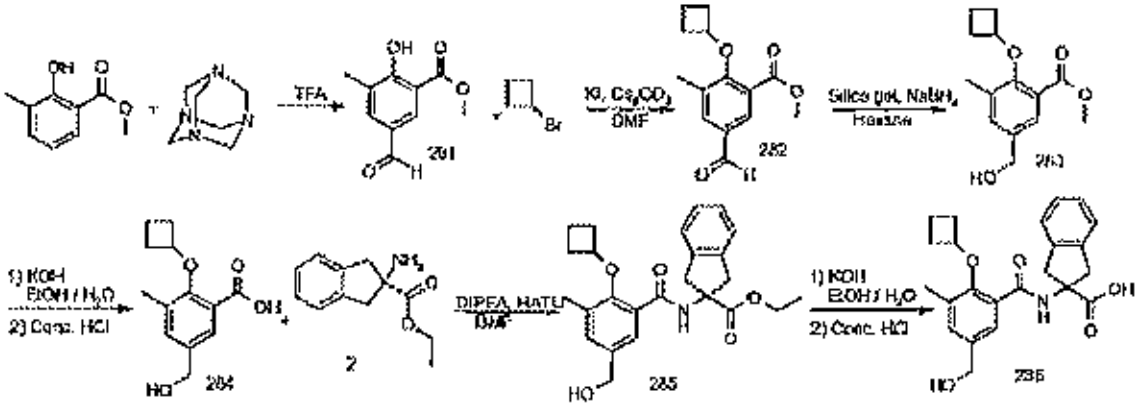
^{1}H NMR ($CDCl_3$, 300MHz): 1.49 (s, 3H), 1.70 (s, 3H), 2.34 (s, 3H), 3.34(d, 2H), 3.82(d, 2H), 6.01 (s, 1H), 6.87 (s, 1H), 7.14(d, 1H), 7.22 (s, 4H), 7.31(d, 1H), 7.91 (d, 1H)
LC/MS (ES+) m/z = 350.17

2-(2-Isobutyl-4-methyl-benzoylamino)-indan-2-carboxylic acid (280):

To a solution of 2-[4-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (510mg, 1.45mmol) in glacial acetic acid (65mL) under N_2 is added Pd/C (10% Pd, 138mg, 10mol%). The reaction is hydrogenated at 60psi H_2 and 90°C overnight. The reaction is cooled to RT and filtered through Celite, washing the filter cake with water (2 x 15mL) and MeOH (2 x 15mL); the filtrate is concentrated *in vacuo*. The residue is dissolved in water (75mL) and extracted with EtOAc (2 x 30mL). The combined organic layers are washed with a 5% $NaHCO_3$ solution (3 x 20mL), water (20mL) and brine (20mL) then dried over anhydrous Na_2SO_4. The organic layer is concentrated *in vacuo* to give product (280) as white solid (350mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): 0.78 (d, 6H), 1.72-1.81 (m, 1H), 2.30(s, 3H), 2.55 (d, 2H), 3.38 (d, 2H), 3.77(d, 2H), 6.30 (s, 1H), 6.94 (d, 1H), 6.95 (s, 1H), 7.16(d, 1H), 7.20 (s, 4H)
LC/MS (ES+) m/z = 352.22

EXAMPLE 281



5-Formyl-2-hydroxy-3-methyl-benzoic acid methyl ester (281):

To a solution of HMTA (1,3,5,7-Tetraaza-tricyclo[3.3.1.1^{3,7}]decane, 8.43g, 60.2mmol) in TFA (100mL) is added 2-hydroxy-3-methyl-benzoic acid methyl ester (5g, 30.1mmol) and the reaction is refluxed (78°C) overnight. The reaction is cooled to 50°C and water (400mL) is added with stirring. The mixture is stirred at 50°C for 2h then cooled to RT and extracted with EtOAc (2 x 200mL). The combined organic layers are washed with brine (75mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash column chromatography (120 silica gel, gradient elution: 0-50% EtOAc in heptane) to give product (281) as off-white solid (5.05g, 86%).

EXAMPLE 282

2-Cyclobutoxy-5-formyl-3-methyl-benzoic acid methyl ester (282):

To a mixture of bromocyclobutane (1.39g, 10.3mmol), potassium iodide (43mg, 5mol%), and $CsCO_3$ (3.84g, 11.84mmol) in DMF (18mL) is added 5-formyl-2-hydroxy-3-methyl-benzoic acid methyl ester (1.0g, 5.15mmol). The reaction is placed in the microwave reactor and heated at 110°C for 6h. Water (50mL) is added to the reaction and the solution is extracted with EtOAc (3x 40mL). The combined organic layers are dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give product (282) as orange-yellow oil (1.20g, 94%).

EXAMPLE 283

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid methyl ester (283):

A mixture of 2-cyclobutoxy-5-formyl-3-methyl-benzoic acid methyl ester (676mg, 2.7mmol), silica gel (5.15g) and $NaBH_4$ (103mg, 2.7mmol) in hexane (30mL) is heated at 40°C overnight. The mixture is cooled to RT and filtered, washing the solids with EtOAc (15mL) and diethyl ether (15mL). The filtrate is concentrated *in vacuo* to give product (283) as viscous yellow oil (566mg, 84%).

EXAMPLE 284

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid (284):

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid methyl ester (410mg, 1.64mmol) is dissolved in EtOH (15mL), and solid KOH (1.90g, 32.8mmol) and water (1.5mL) are added. The mixture is stirred at RT for 1h then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with conc. HCl then extracted with EtOAc (3 x 10mL). The combined organic layers are dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give product (284) as viscous yellow oil (387mg, 100%).

EXAMPLE 285

2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (285):

To a solution of 2-cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid (410mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (425mg, 1.7mmol), HATU (760mg, 2mmol) in anhydrous DMF (5mL) is added DIPEA (435µL, 2.5mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture, and then extracted with EtOAc (3 x 7mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by reverse phase chromatography (gradient elution: 20-100% ACN in water) to give product (285) as colorless oil (70mg, 10%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.14-1.24 (m, 1H), 1.34-1.44 (q, 1H), 1.80-1.86 (m, 2H), 1.90-1.99 (m, 2H), 2.20(s, 3H), 3.37 (d, 2H), 3.81(d, 2H), 4.13-4.24 (m, 1H), 4.55 (s, 2H) 7.17-7.24 (m, 4H), 7.26 (d, 1H), 7.78 (d, 1H), 8.45 (s, 1H)
LC/MS (ES+) m/z = 396.16

EXAMPLE 286

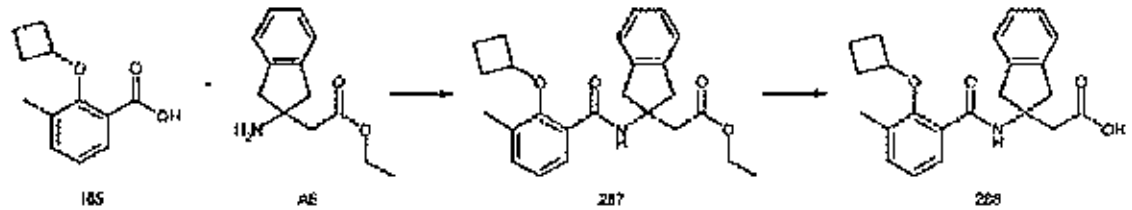
2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (286):

2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (70mg, 0.16mmol) is dissolved in ethanol (1.5mL), and solid KOH (191mg, 3.3mmol) and water (150µL) are added. The mixture is stirred at room temperature for 30min then concentrated *in vacuo*. The residue is dissolved in water (1.5mL) and acidified with conc. HCl until no more white solid precipitated. The mixture is extracted with ethyl acetate (2 x

8mL) and the combined organic layers are concentrated *in vacuo* to give product (286) as white solid (60mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.14-1.24 (m, 1H), 1.34-1.44 (q, 1H), 1.80-1.86 (m, 2H), 1.90-1.99 (m, 2H), 2.20(s, 3H), 3.37 (d, 2H), 3.81(d, 2H), 4.13-4.24 (m, 1H), 4.55 (s, 2H) 7.17-7.24 (m, 4H), 7.26 (d, 1H), 7.78 (d, 1H), 8.45 (s, 1H)
LC/MS (ES+) m/z = 396.16

EXAMPLE 287



185 A6 287 288

2-aminoindan-2-acetic acid ethyl ester (A6)

This compound is prepared according to the US Patent WDF2006/134111.

2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid ethyl ester (287)

To a solution of 2-cyclobutyloxy-3-methylbenzoic acid (210mg-1.02mmol), 2-aminoindan-2-acetic acid ethyl ester (A6)(260mg-1.02mmol) and HATU (470mg-1.224mmol-1.2eq) in dry DMF (10mL) is added diisopropylethylamine (0.36mL-2.24mmol-2.2eq) and the resulting solution is stirred at RT overnight. After the removal of the DMF in vacuo, the residue is dissolved in EtOAc (60mL) and washed with water (2 x 20mL) and brine (2 x 20mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (120g silica gel, 15% EtOAc in heptane) to give the pure product as colorless oil (400mg, 96%).

LC/MS(ES+) m/z 408

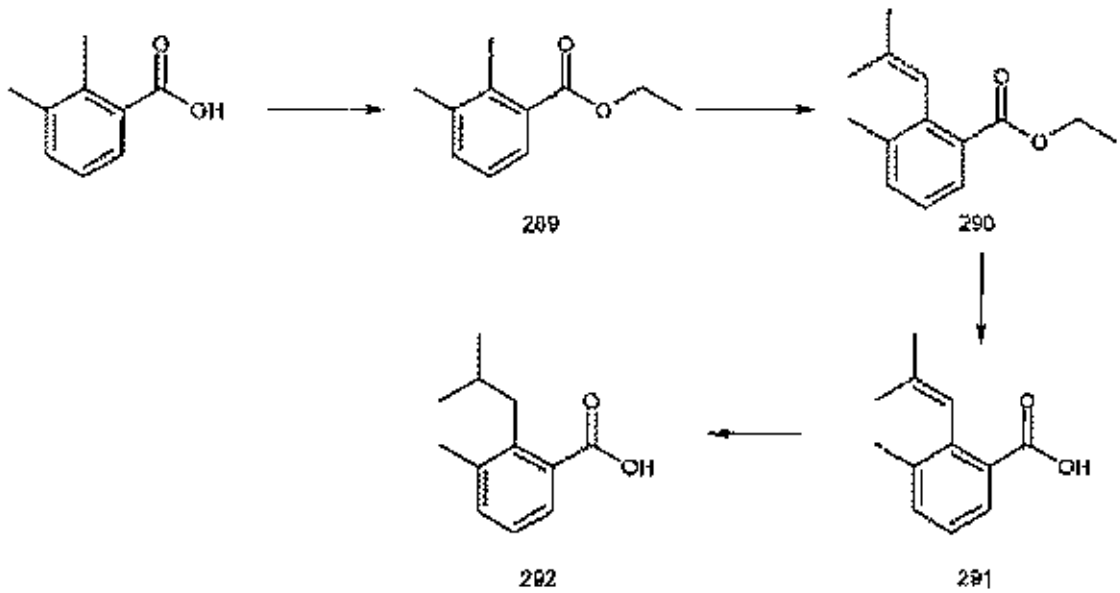
EXAMPLE 288

2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid (288)

A solution of the 2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid ethyl ester (288) (400mg-1mmol) in EtOH(15mL)/ water (1mL) is treated with NaOH pellets (800mg-20mmol) and stirred at RT for 24h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with HCl to pH 2-3. The product is extracted into EtOAc (3 x 20mL) and the combined extracts washed with water (2 x 10mL) and brine (2 x 15mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is triturated with heptane and the pure product isolated by filtration to give white solid (350mg, 92%).

LC/MS(ES+) m/z 380

Example 289



2-iodo-3-methylbenzoic acid ethyl ester (289)

A solution of the 2-iodo-3-methylbenzoic acid (6g-0.023mol) in EtOH (150mL) is treated with concentrated HCl (20mL) and refluxed for 48h. After removal of the EtOH *in vacuo*, the residue is diluted with water (125mL) and cooled to 0°C in an ice bath. The pH is adjusted to 10 with solid NaOH pellets and extracted with EtOAc (3 x 75mL). The organic extracts are washed with water (2 x 50mL) and brine (2 x 50mL) and dried over $MgSO_4$. Concentrated *in vacuo* to give the product as a pale yellow oil. (6g, 90%).

LC/MS(ES+) m/z 291

Example 290

3-methyl-2-(2-methyl-1-propenyl)benzoic acid ethyl ester (290)

A suspension of the 2-iodo-3-methylbenzoic acid ethyl ester (289) (2.9g-0.01mol) and 2-methyl-1-propenylboronic acid pinacol ester (3.64g-0.02mol-2eq) in dry DMF(50mL) and saturated $NaHCO_3$ (10mL) is degassed for 10 minutes and then treated with tetrakis(triphenylphosphine)palladium(0) (400mg). The mixture is stirred at 110°C overnight. The reaction is cooled and the DMF removed *in vacuo* and the residue diluted with water (120mL). The aqueous is filtered through hyflo and extracted with EtOAc (3 x 75mL). The organic extracts are washed with water (2 x 50mL) and brine (2 x 50mL), and dried over $MgSO_4$. The organic extracts are concentrated *in vacuo* and purified by flash chromatography (400g silica gel, 5% EtOAc in heptane) to give the product as pale yellow oil (1.85g, 85%).

LC/MS (ES+) m/z 218

Example 291

3-methyl-2-(2-methy-1-propenyl)benzoic acid (291)

A solution of the 3-methyl-2-(2-methy-1-propenyl)benzoic acid ethyl ester (290)(3g-0.014mol) in MeOH (50mL) is treated with 2N NaOH(10mL) and refluxed for 6h. The solvent is removed *in vacuo* and the residue diluted with water (75mL). The aqueous phase is extracted with EtOAc (30mL) and then separated and acidified to pH 2-3 with concentrated HCl. The solid precipitated is extracted into EtOAc (3 x 50mL). The extracts are washed with water (2 x 30mL) and brine (2 x 30mL), and dried over $MgSO_4$ and concentrated *in vacuo* to give the product as white solid (2.0g, 75%).

^1H NMR ($CDCl_3$, 300MHz): 1.43 (s, 3H), 1.91 (s, 3H), 2.24 (s, 3H), 6.35 (s, 1H), 7.2-7.27 (t, 1H), 7.37-7.44 (m, 1H), 7.79-7.81 (d, 1H).
LC/MS (ES+) m/z 191

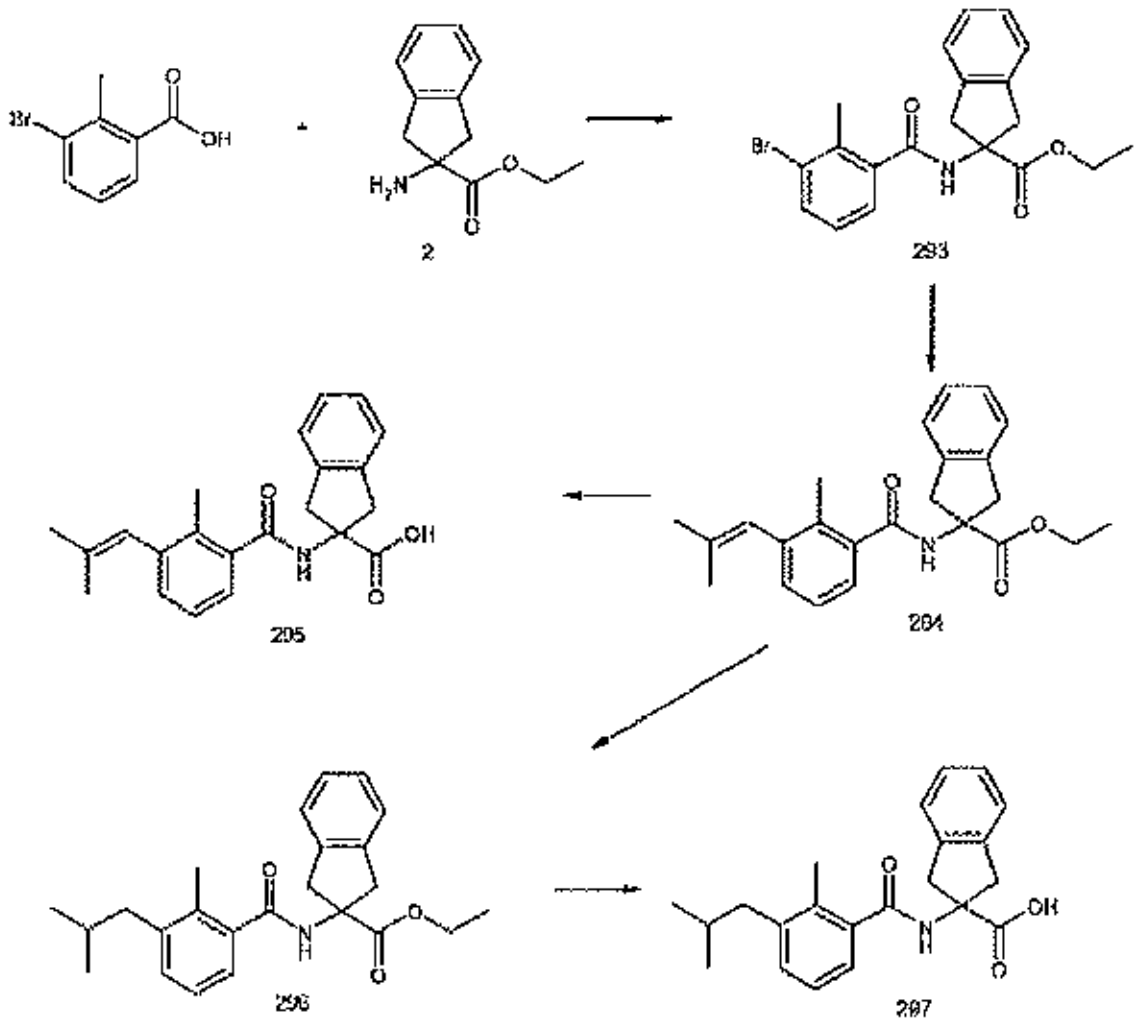
Example 292

2-isobutyl-3-methylbenzoic acid (292)

A solution of the 3-methyl-2-(2-methy-1-propenyl)benzoic acid (291)(2g, 10.5mmol) in MeOH (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar/30°C using the Thales nanotechnology H-cube for 48h. The MeOH is concentrated *in vacuo* to give the product as colorless oil (1.85g, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): 0.92 (d, 6H), 1.78-1.90 (m, 1H), 2.38 (s, 3H), 7.1-7.2 (t, 1H), 7.35-7.38 (d, 1H), 7.75-7.80 (d, 1H).
LC/MS (E/S+) m/z 193

Example 293



2-(3-bromo-2-methylbenzoylamino)Indan-2-carboxylic acid ethyl ester (293)

This compound is prepared in a similar manner to example 287. The crude product obtained is purified by flash chromatography (120g silica gel, 20% EtOAc in heptane) to give the pure product as white solid (1.9g, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.20-1.25 (t, 3H), 3.30-3.40 (d, 2H), 3.40 (s, 3H), 3.70-3.80 (d,2H), 4.25-4.40 (m, 2H), 6.30-6.40 (s, 1H), 6.95-7.05 (t,1H), 7.20-7.30 (m,2H), 7.55-7.60 (d, 1H).
LC/MS(ES+) m/z 403

Example 294

2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid ethyl ester (294)

A suspension of 2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid ethyl ester (293) (402mg-1mmol) and 2-methyl-1-propenylboronic acid (200mg, 2mmol, 2eq) in dry DMF (20mL) and saturated $NaHCO_3$ (5mL) is degassed for 10min and then treated with tetrakis(triphenylphosphine)palladium(0) (400mg). The mixture is stirred at 110°C for 5h. The reaction is cooled and the DMF removed *in vacuo* and the residue diluted with water (80mL). The aqueous is filtered through celite and extracted with EtOAc (3 x 50mL). The organic extracts are washed with water (2 x 30mL) and brine (2 x 30mL), and dried over $MgSO_4$. The organic phase is then concentrated *in vacuo* and purified by flash chromatography (120g silica gel, 30% EtOAc in heptane) to give pale yellow oil (350mg, 92%).

LC/MS (E/S+) m/z 378

Example 295

2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid (295)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (120g silica gel, 20% EtOAc in heptane) gives white solid. (20mg, 6%)

LC/MS (E/S+) m/z 350

Example 296

2-(2-methyl-3-isobutylylbenzoylamino)indan-2-carboxylic acid ethyl ester (296)

A solution of 2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid ethyl ester (294) (700mg, 1.86mmol) in glacial AcOH (125mL) is treated with the catalyst, Pd-C (10wt.%Pd, 360mg) under nitrogen. The resulting reaction mixture is then hydrogenated in a Paar apparatus at 55psi 75°C overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is dissolved in EtOAc (75mL) and washed with water (30mL) and brine (30mL), and dried over $MgSO_4$ and concentrated *in vacuo* to leave the product as white solid (660mg, 94%).

LC/MS (E/S+) m/z 380

Example 297

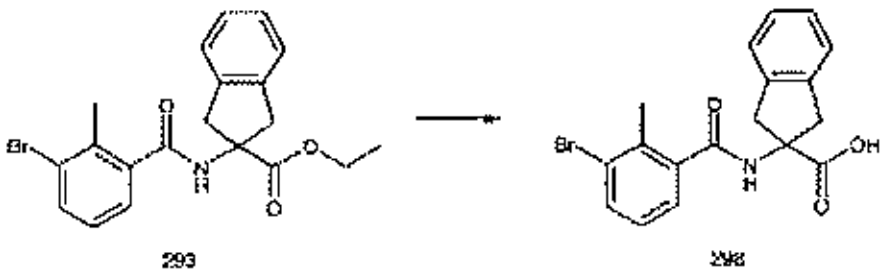
2-(2-methyl-3-isobutylylbenzoylamino)indan-2-carboxylic acid (297)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (120g silica gel, 50% EtOAc in heptane) gives the product as white solid. (130mg, 21%)

^{1}H NMR (DMSO-d6, 300MHz): 0.87-0.89 (d, 6H), 1.73-1.82 (m, 1H), 2.21 (s, 3H), 2.40-2.45 (m, 2H), 3.32-3.36 (d, 2H), 3.53-3.59 (d, 2H), 7.00-7.23 (m, 7H), 8.83 (s, 1H), 11.0 (s, 1H).

LC/MS (E/S+) m/z 353

Example 298

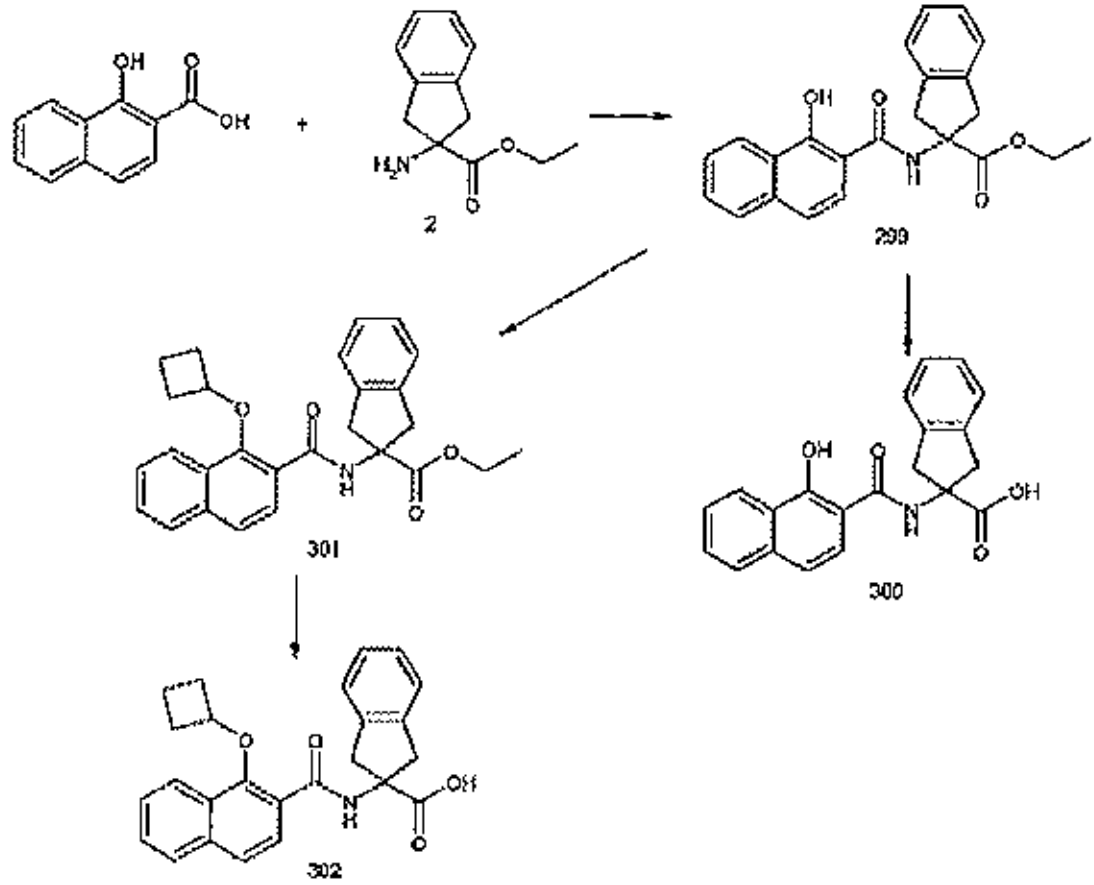


293 298

2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid (298)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give the product as white solid (270mg, 96%)

^{1}H NMR (DMSO-d6, 300MHz): 2.33 (s, 3H), 2.29-3.35 (d, 2H), 3.54-3.60 (d, 2H), 7.13-7.24 (m, 6H), 7.63-7.66 (d, 1H), 8.99 (s, 1H), 12.55-12.60 (s, 1H).
LC/MS (E/S+) m/z 376



Example 299

2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (299)

This compound is prepared in a similar manner to example 287. Purification by flash chromatography (400g silica gel, 30% EtOAc in heptane) gives orange oil. (1.75g, 93%)

LC/MS (E/S+) m/z 376

Example 300

2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (300)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give white solid. (280mg, 99%)

^{1}H NMR (DMSO-d6, 300MHz): 3.48-3.53 (d, 2H), 3.63-3.69 (d, 2H), 7.17-7.28 (m, 5H), 7.34-7.37 (d, 1H), 7.53-7.66 (m, 2H), 7.85-7.88 (d, 1H), 7.96-7.99 (d, 1h), 8.26-8.28 (d, 1H), 9.22 (s, 1H).

LC/MS (E/S+) m/z 376

Example 301

2-[(1-cyclobutyloxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (301)

A solution of 2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (289) (560mg, 1.5mmol) in dry DMF is treated with NaH oil dispersion (60%, 100mg, 2.25mmol, 1.5eq) and stirred for 10 min. The cyclobutyl bromide (405mg, 3mmol, 2eq) is added and the reaction heated and stirred in the microwave at 150°C for 3hours. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (75mL) and washed with water (2x30mL) and brine (30mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (200g silica gel, 10% EtOAc in heptane) to give white solid. (290mg, 45%)

LC/MS (E/S+) m/z 430

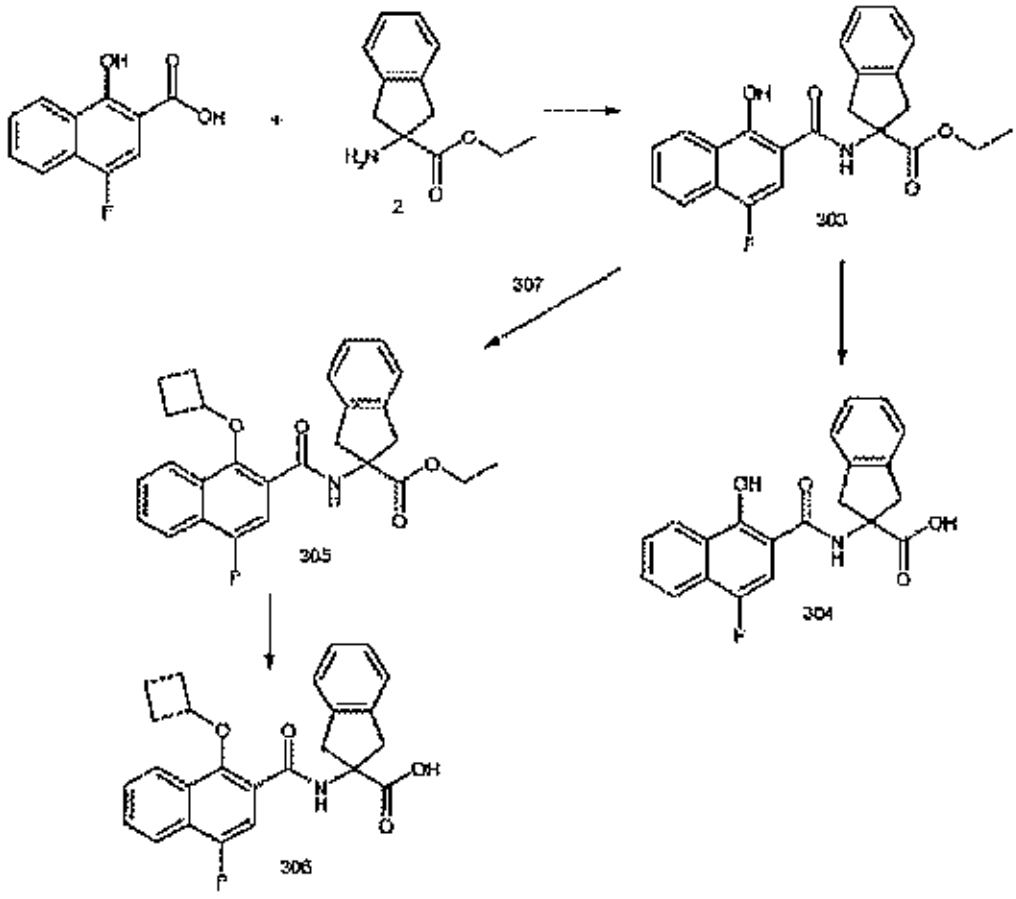
Example 302

2-[(1-cyclobutyloxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (302)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (400g silica gel, gradient elution: 25-60% EtOAc in heptane) gives the product as white solid. (20mg, 9%)

LC/MS (E/S+) m/z 402

Example 303



2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (303)

This compound is prepared in a similar manner to example 287. Purification by flash chromatography (400g silica gel, 30% EtOAc in heptane) gives orange oil. (1.67g, 85%)

^{1}H NMR (DMSO-d6, 300MHz): 1.13-1.16 (t,3H), 3.46-3.52 (d,2H), 3.64-3.69 (d, 2H), 4.11-4.18 (q, 2H), 7.19-7.29 (m, 4H), 7.69-7.72 (t, 1H), 7.76-7.81 (t, 1H), 7.93-8.01 (m,2H), 8.31-8.34 (d, 1H), 9.26 (s,1H), 13.90 (s, 1H).

LC/MS (E/S+) m/z 394

Example 304

2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (304) This compound is prepared in a similar manner to example 288. The organic extract is evaporated *in vacuo* to give the product as white solid. (270mg, 97%)

^{1}H NMR (DMSO-d6, 300MHz): 3.47-3.58 (d, 2H), 3.64-3.75 (d, 2H), 7.18-7.29 (m, 5H), 7.66-7.75 (m,1H), 7.77-7.85 (m, 1H), 7.95-8.8.01 (m, 1H), 8.31-8.34 (d,1H), 9.16 (s, 1H),12.75 (s, 1H).
LC/MS (E/S-) m/z 364

Example 305

2-[(1-cyclobutyloxy-4-fluoronaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (305)

A solution of 2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (303) (197mg, 0.5mmol) and 3,3-dimethyl-1,2,5-thiadiazolidine-5 triphenylphosphine-1,1-dioxide (example 307, 245mg, 0.6mmol, 1.2eq) in DCM (6mL) is treated with cyclobutanol (44mg, 0.6mmol, 1.2eq) and stirred at RT for 6 days. The crude reaction mixture is purified by flash chromatography (100g silica gel, 100% DCM) to give coloriess oil. (120mg, 54%)

LC/MS (E/S+) m/z 448

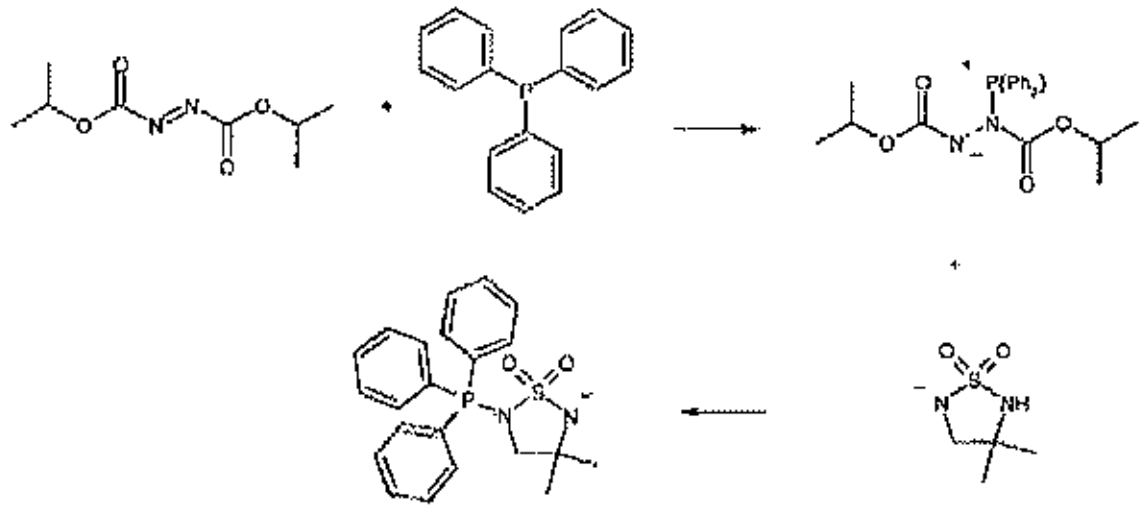
Example 306

2-[(1-cyclobutyloxy-4-fluoronaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (306)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give white solid. (95mg, 84%)

^{1}H NMR (DMSO-d6, 300MHz): 1.20-1.33 (m, 1H), 1.44-1.54 (m, 1H), 3.42-3.47 (d, 2H), 3.58-3.63 (d, 2H), 4.49-4.57 (m, 1H), 7.17-7.36 (m, 6H), 7.69-7.75 (m, 2H), 8.03-8.06 (m, 1H), 8.17-8.19 (m, 1H), 8.88 (s, 1H), 12.70 (s,1H).
LC/MS (E/S+) m/z 420

Example 307

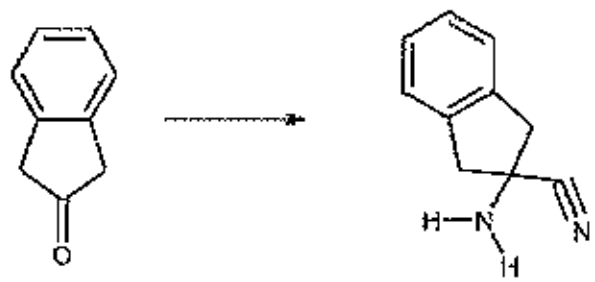


307

3,3-dimethyl-1,2,5-thiadiazolidine-5 triphenylphosphine-1,1-dioxide (307)

A solution of triphenylphosphine (4.4g, 0.016mol) and 3,3-dimethyl-1,2,5-thiadiazoli-dine-1,1-dioxide (2.5g, 0.016mol) in dry THF (50mL) is treated dropwise with diisopropyldiazodicarboxylate (3.3g, 0.016mol). The white solid precipitated is stirred at RT for a further 4h. The product is then collected by filtration and washed with diethyl ether (5.7g, 86%).

Example 308



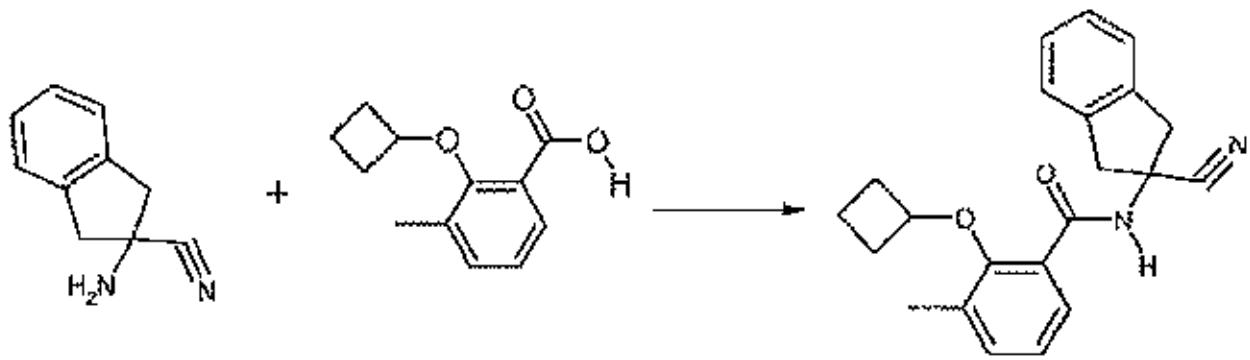
(308)

2-Amino-indan-2-carbonitrile (308)

A 250mL round bottom flask is charged with 2-indanone (2.64g, 19.98mmol) and iPrOH (40mL). A stirring bar is added and stirring is initiated. After dissolution, an aqueous solution of ammonium hydroxide (29 %, 8.3 M 16mL, 132.3mmol) is added. Ammonium chloride

(2.14g, 39.96mmol) and NaCN (1.96g, 39.96mmol) are added. After 11 days, tlc analysis (silica, 2:1, heptanes:EtOAc) indicates that the starting indone is consumed. The organic solvent is removed *in vacuo*. The resultant material is transferred to a separatory funnel and partitioned between DCM (200mL) and water (100mL). The phases are separated. The aqueous phase is extracted with DCM (100mL). The organic extracts are combined and washed with brine (100mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 2.6g of dark brown solid. This material is dissolved in DCM (15mL). This solution is applied to a column (Silica, 40 g) which is fitted to an ISCO Companion. The gradient is 1% iPrOH in DCM for 4 column volumes followed by a linear gradient to 20 % iPrOH in DCM over 10 column volumes. The eluent is collected in 17mL fractions. Fractions 15 to 32 are combined and evaporated by pumping to constant weight to give light beige solid (0.82g, 26 %).

Example 309



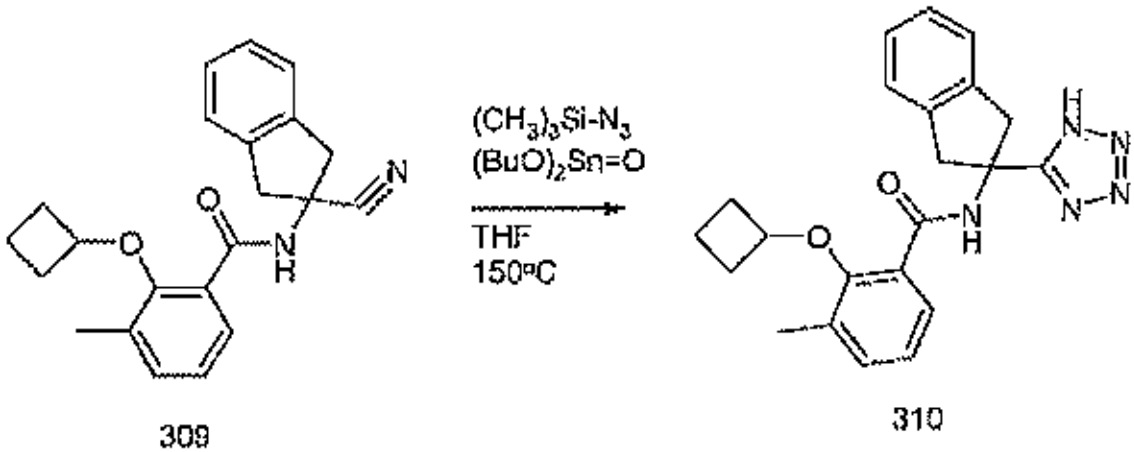
308 309

N-(2-Cyano-indan-2-yl)-2-cyclobutoxy-3-methyl-benzamide (309)

A 30mL vial is charged with 2-cyclobutoxy-3-methyl-benzoic acid (734mg, 3.56mmol) and dry DCM (10mL). A stirring bar is added and stirring is initiated. After 5min, HTBU (1.35g, 3.56mmol) is added. After 5min, 2-amino-indane-2-carbonitrile. (308, 563mg, 3.56mmol) is added followed by DIPEA (1.5mL, 8.95mmol). The reaction is allowed to stir for 38h. Analysis of the reaction mixture by tlc (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed saturated aqueous $NaHCO_3$ (2 X 20mL) and brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide

1.2g of thick black oil. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 8 column volumes and then 90% EtOAc in heptanes for 2 column volumes. 17mL fractions of UV active eluent are collected. Fractions 27 through 30 are combined and evaporated *in vacuo* to give white solid (0.51g, 41%).

Example 310



309 310

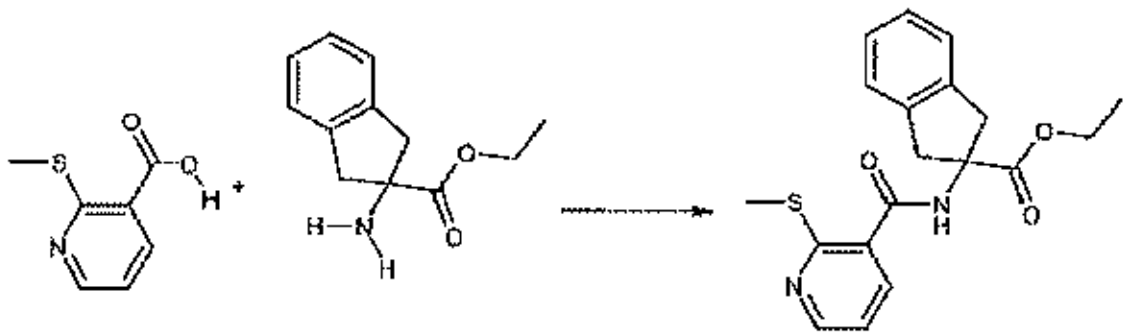
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide (310)

A 10mL microwave reaction vial is charged with N-2-(cyano-indan-2-yl)-2-cyclobutoxy-3-methyl-benzamide (309, 300mg, 0.87mmol) and dry tetrahydrofuran (THF, 4mL). A stirring bar is added and stirring is initiated. After 1 minute, trimethylsislyazide (228 µL, 1.73mmol) and di-n-butyltinoxide (22mg, 0.087mmol) are added to the reaction vial. The reaction vial is capped and inserted into an Emyrs Optimizer microwave apparatus. The reaction vial is prestirred for 10sec. The temperature is set to hold at 150°C for 10min. At the end of this process, additional aliquots of trimethylsislyazide (228 µL, 1.73mmol) and di-n-butyl tin oxide (22mg, 0.087mmol) are added to the reaction vial. The reaction vial is capped and inserted into a Emyrs Optimizer microwave apparatus. The reaction vial is pre-stirred for 10sec. The temperature is set to hold at 150°C for 10min. tlc analysis (silica, 10 % MeOH in DCM) indicates that the starting material is completely consumed. The contents of the reaction vial are reconstituted in DCM (8mL) and iPrOH (4mL). This solution is stirred for 10min and filtered through a pad of Celite. The filtrate is evaporated under reduced pressure

by pumping to constant weight to give 0.4g of light yellow foam. The foam is dissolved in DCM (10mL) and applied to an ISCO Companion (silica, 40 g) Column. The following gradient is applied: 1% iPrOH in DCM for 4 column volumes, followed by a linear gradient to 50 % iso-propanol in DCM over 10 Column Volumes. 14mL fractions of UV-active eluent are collected. Fractions 2 to 6 are combined and evaporated by pumping to constant weight to give white solid (0.31g, 92%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.08-1.25(m, 2H), 1.38-1.51(m, 1H), 1.71-1.96 (m, 4H), 2.22 (s, 3 H) 3.79-3.93 (m, 4H), 4.35 (m, 1H), 7.03 (dd, 1H), 7.1-7.37(m, 6H), 8.98(s, 1H). LC/MS (ES+) m/z = 390.16.

Example 311



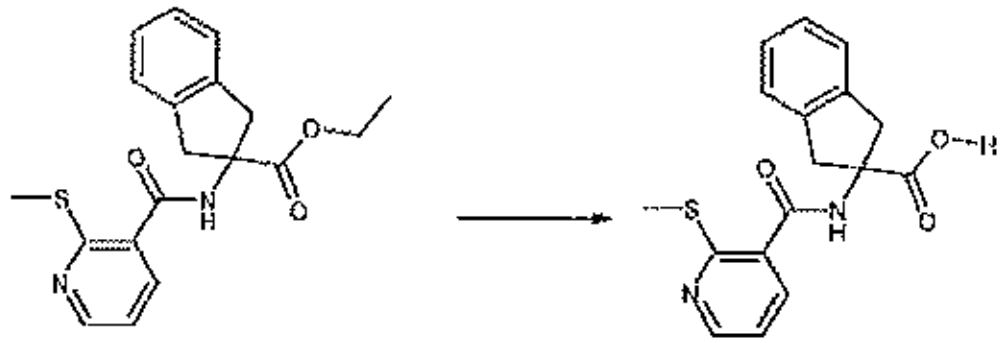
311

2-[(2-Methylsulfanyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (311)

40mL vial is charged with 2-(methylthio)-nicotnic acid (0.37g, 2.19mmol) and dry DCM (8mL). A stirring bar is added and stirring is initiated. After dissolution 5min, HTBU (831mg, 2.19mmol) is added. After 5min, the 2-amino)-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 14 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed with brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.23g of light yellow foam. The foam is dissolved in 10mL of DCM. This solution is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over

3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 8 through 12 are combined and evaporated *in vacuo* by pumping to constant weight under reduced pressure gives solid white (0.47g, 60%).

Example 312



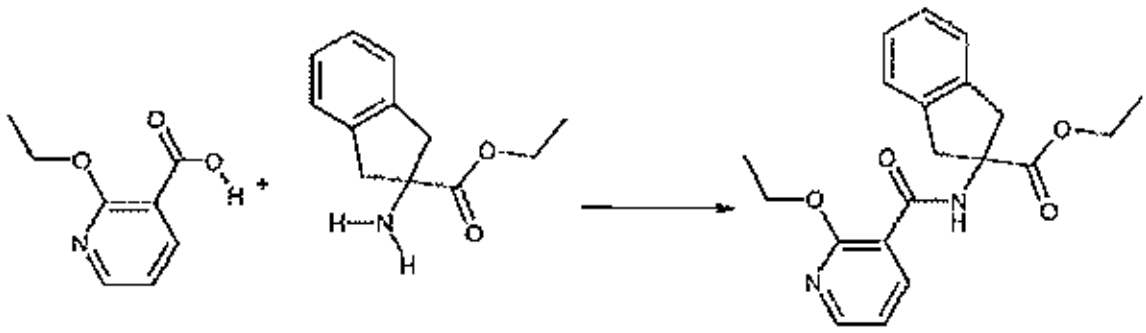
311 312

2-[(2-Methylsufamyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid (312)

To a 100mL flask containing 2-[(2-methylsufamyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (311, 490mg, 1.38mmol) is added 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH (146mg, 3.5mmol). After 40h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The contents of the flask are diluted with iPrOH (30mL). Dowex Highly Acidic Ion Exchange Resin (10 g) is added. The reaction flask is capped and allowed to stir at ambient temperature. After 7 days, additional iPrOH (35mL) is added to the reaction flask. The contents of the reaction flask are filtered through a pad of Celite and concentrated under reduced pressure by pumping to constant weight to give white solid (0.44g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.41 (s, 3 H), 3.26-3.48 (m, 4H), 7.16-7.25 (m, 5H), 7.71 (dd, 1H), 8.51 (dd, 1 H), 9.01(s, 1H).
LC/MS (ES+) m/z = 329.14.

Example 313

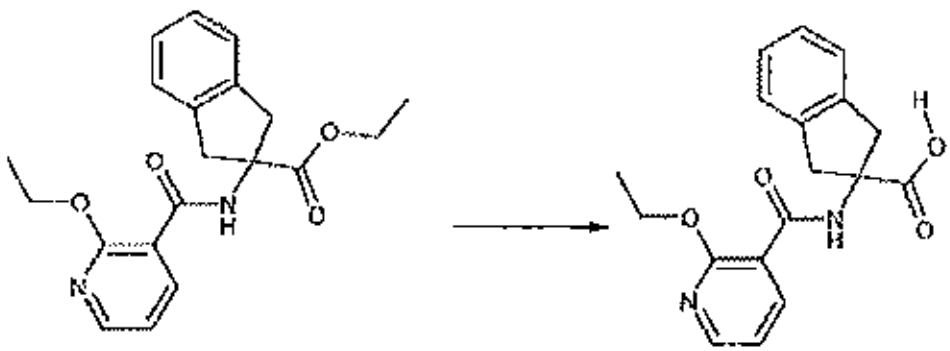


313

2-[(2-Ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (313)

A 40mL vial is charged with 2-ethoxynicotnic acid (366mg, 2.19mmol) and dry DCM (7mL). A stirring bar is added and stirring is initiated. After dissolution 5min, HTBU (831mg, 2.19mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 17 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed with brine (20mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 2.38g of light yellow syrup. The syrup is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 1 % iPrOH/DCM over 4 column volumes followed by a linear gradient to 30% iPrOH/DCM over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 5 through 10 are combined and evaporated *in vacuo* by pumping to constant weight to yield white solid (0.34g, 44%).

Example 314



313 314

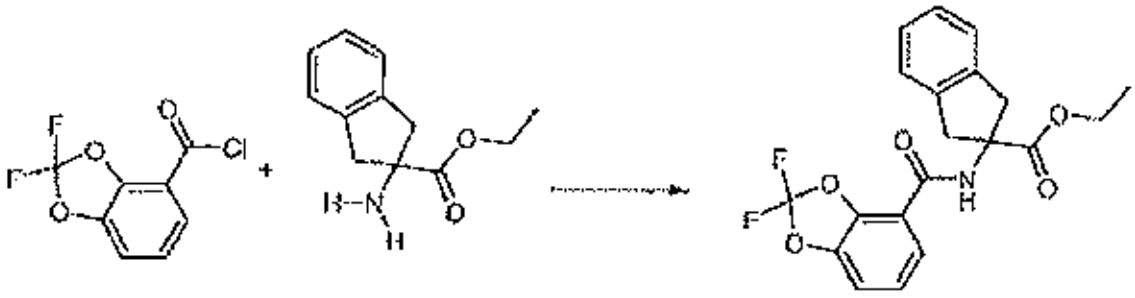
2-[(2-Ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid (314)

A 100mL flask containing 2-[(2-ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester ([313], 340mg, 0.96mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (102mg, 2.42mmol). After 13 days, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The contents of the flask are diluted with iPrOH (30mL). Dowex Highly Acidic Ion Exchange Resin (2g) is added. The reaction flask is capped and allowed to stir at ambient temperature. After 18h, additional iPrOH (35mL) is added to the reaction flask. The contents of the reaction flask are filtered through a pad of Celite and concentrated under reduced pressure by pumping to constant weight to yield 0.44g of white solid. This material is dissolved in a mixture of DCM (10mL) and iPrOH (3mL). Celite (15 g) is added to the flask. The solvent is removed under reduced pressure. The remaining material is transferred to a 40mL plastic syringe that is fitted with a fritted disk. The syringe is fitted onto an ISCO Companion which had a 40g column (silica). The following gradient is applied. 1 % IPrOH/DCM for 4 column volumes. Then a linear gradient to 50 % iPrOH/DCM over 10 column volumes. Hold at 50 % iPrOH/DCM for 2 Column Volumes. 14mL fractions are collected. Fractions 39 - 41 are combined and evaporated by pumping to constant weight to yield white solid (0.28g, 89%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.22 (t, 3H), 3.26-3.63 (m, 4H), 4.36 (q, 2H), 7.14-7.25 (m, 5H), 8.13 (dd, 1H), 8.28 (dd, 1 H), 8.76 (s, 1H).

LC/MS (ES+) m/z = 327.11.

Example 315

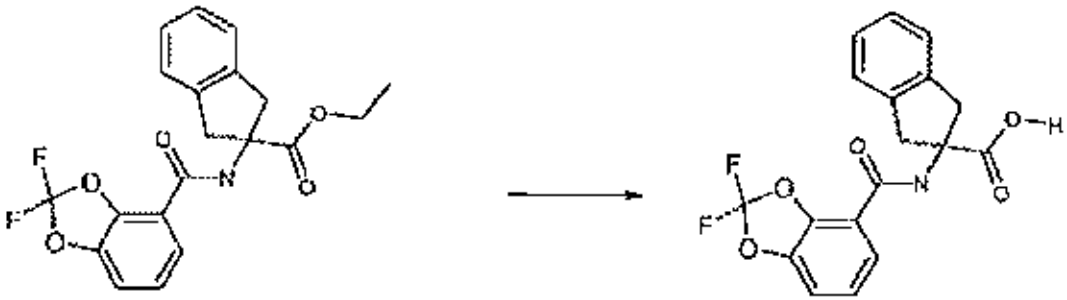


315

2-[(2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (315)

A 100mL round bottom flask is charged with 2-aminoindan-2-carboxylic acid (340mg, 1.66mmol) and dry DCM (6mL). A stirring bar is added and stirring is initiated. DIPEA (0.46mL, 2.65mmol) is added. 2-[(2,2-difluoro-benzo[1,3]dioxole-4-carbonyl chloride (438mg, 1.99mmol) is added. 4-Dimethylaminopyridine ([MFCD00006418], 2mg, cat.) is added. The reaction is capped. After 18 days, tlc analysis (silica, 5% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with dilute aqueous HCl (2x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to yield 0.73g of dark brown foam. This is diluted with DCM and applied to a silica column (40 g) on an ISCO Companion. The column is eluted with 3 column volumes of 10 % EtOAc-heptanes followed by a linear gradient to 50 % EtOAc/heptanes over 10 Column Volumes. And then 90 % EtOAc/heptanes for 2 Column Volumes. 17mL fractions of UV positive eluent are collected. Fraction 8-10 are combined and evaporated by pumping to constant weight to give light orange solid (0.57g, 88 %).

Example 316



315 316

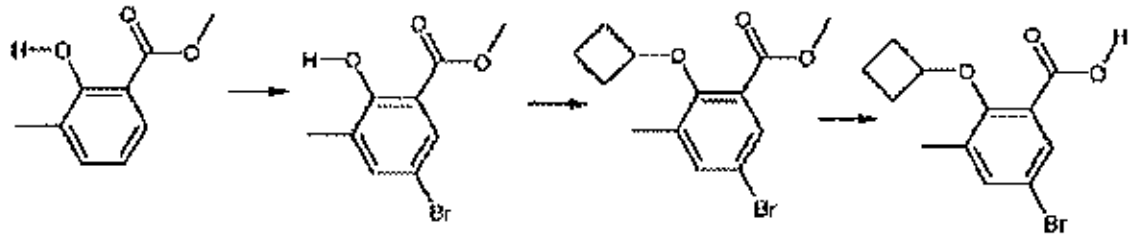
2-[(2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl)-amino]-indan-2-carboxylic acid (316)

A 100mL flask containing 2-[(2,2-difluoro-1,3-benzodioxole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.38g, 0.98mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (103mg, 2.46mmol). After 70h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%,

~6mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.33g, 94%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.26-3.63 (m, 4H), 7.13-7.32 (m, 5H), 7.48 (dd, 1H), 7.55 (dd, 1 H), 8.97 (s, 1H), 12.63 (bs, 1H).
LC/MS (ES+) m/z = 362.05.

Example 317



317

5-Bromo-2-cyclobutoxy-3-methyl-benzoic acid (317)

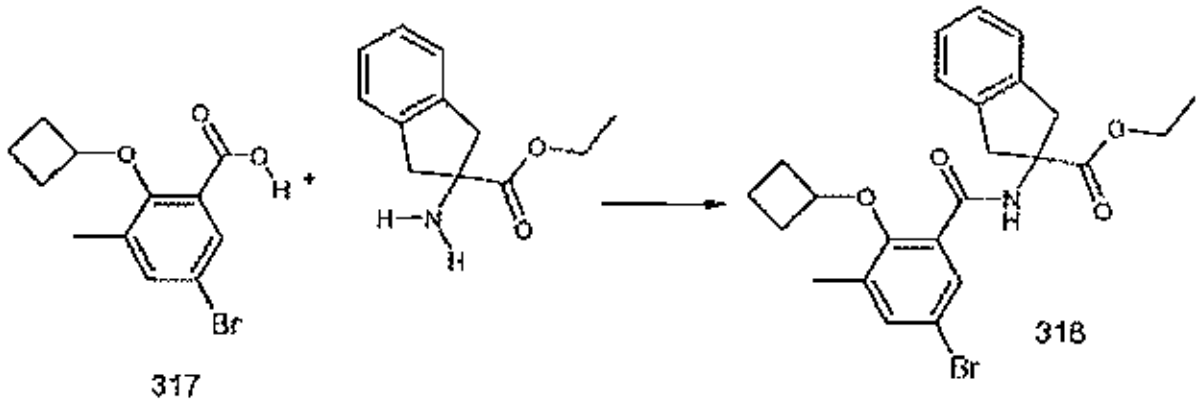
A 250mL 3-necked round bottom flask which is fitted with an addition funnel, a N_2 inlet and a stopper. The flask is charged with bromine (3.6mL, 70.11mmol) and DCM (40mL). A stirring bar is added and stirring is initiated. The reaction flask is immersed in an ice-water bath. After stirring for 15min, the addition funnel is charged with a solution of methyl 2-hydroxy-3-methylbenzoate (10g, 60.18mmol) in 1,4-dioxane (40mL). This solution is added to the stirred reaction mixture dropwise over 30min. The addition funnel is then washed with 1,4-dioxane (10mL). This too is added to the reaction mixture. The reaction mixture is then allowed to slowly warm to ambient temperature. After 18 days, the contents of the reaction flask are transferred to a round bottom flask. The solvent is removed under reduced pressure by pumping to constant weight to give 17.66g of light yellow solid. This solid is triturated with ice-cold MeOH (75mL). The resultant crystals are collected by suction filtration. Air-drying provides white solid (14.26g, 97%).

A 100mL round bottom flask is charged with 5-bromo-2-hydroxy-3-methyl-benzoic acid methyl ester 4.05g, 16.53mmol) as prepared above. Dry DMF (20mL) and a stirring bar are added. Stirring is initiated. After dissolution, K_2SO_4 (6.85g, 49.59mmol) and bromocyclobutane (2.35mL, 24.8mmol) are added. The reaction flask is fitted with a heating mantle. The temperature of the mantle is set to 35 degrees C. After 8 days, tlc analysis (silica, 25 % EtOAc/heptanes) indicates a slight consumption of starting material and the appearance of a UV positive spot with a slightly higher R_f value. The reaction is fitted with a heating mantle and warmed to 37°C. After 3 more days, tlc analysis (silica, 25 % EtOAc/heptanes) indicates consumption of starting material and complete conversion to a UV positive spot with a slightly higher R_f value. The reaction mixture is filtered through a pad of Celite. The filtrate is diluted with EtOAc and (100mL) and transferred to a separatory funnel. The EtOAc solution is washed with saturated $NaHCO_3$ (2 x 25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to give semi-solid material (2.09g, 42 %). This material is utilized in the subsequent step.

A 100mL flask containing 5-bromo-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (2.07g, 7.25mmol) as prepared above is charged with 1,4-dioxane (12mL) and MeOH (12mL). A stirring bar is added and stirring is initiated. After dissolution, water (6mL) is added followed by the LiOH (768mg, 18.31mmol). After18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~11mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (50mL). The layers are separated. The aqueous layer is extracted with EtOAc (40mL). The combined organic phases are washed with water (40mL) and brine (40mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give a while solid (1.82g, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.16-1.25 (m, 2H), 1.38-1.51 (m, 1H), 1.71-2.12 (m, 3H), 2.23 (s, 3H), 4.37 (m, 1H), 7.53-7.62 (m, 2H).
LC/MS (ES+) m/z = 390.16.

Example 318

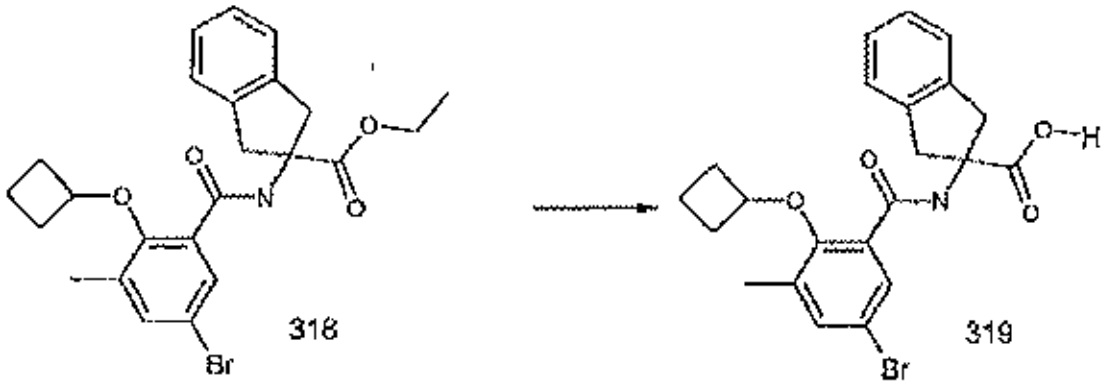


317 318

2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (318)

A 100mL round bottom flask which contains a stirring bar is charged with 2-cyclobutoxyl-3-methyl-5-bromo-benzoic acid 317 (695mg, 2.44mmol) and dry DCM (8mL). Stirring is initiated. After dissolution is complete, HTBU (924mg, 2.44mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by DIPEA (1.3mL, 6.1mmol). The reaction is allowed to stir for 15 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to give 1.42g of light orange solid. This solid is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 4 through 9 are combined and evaporated in vacuo. This yields white solid material (0.8g, 70%).

Example 319



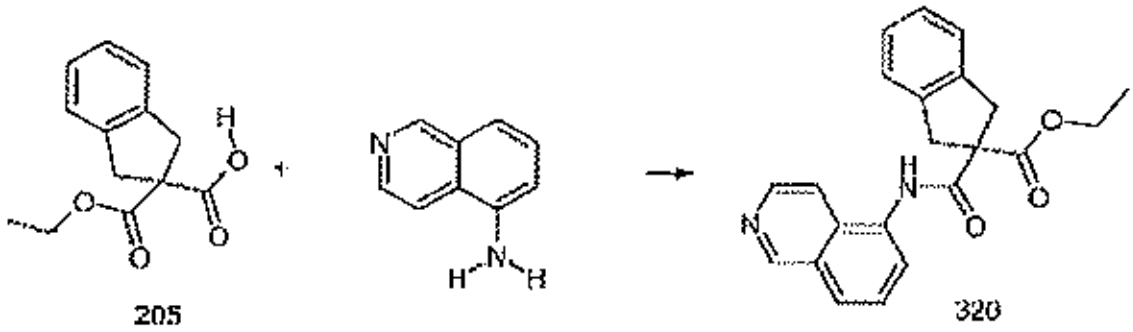
2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (319)

A 30mL reaction vial is charged with 2-(5-bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.29g, 0.61mmoles) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (65mg, 1.55mmol). After 38h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.26g, 95%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.11-1.27(m, 2H), 1.43-1.57(m, 1H), 1.79-1.99 (m, 4H), 2.21 (s, 3 H) 3.55-3.84 (m, 4H), 4.37 (m, 1H), 7.18-7.33 (m, 4H), 7.35 (d, 1H), 7.51 (d, 1H), 8.78 (s, 1H) 12.62 (s, 1H).

LC/MS (ES+) m/z = 446.11.

Example 320

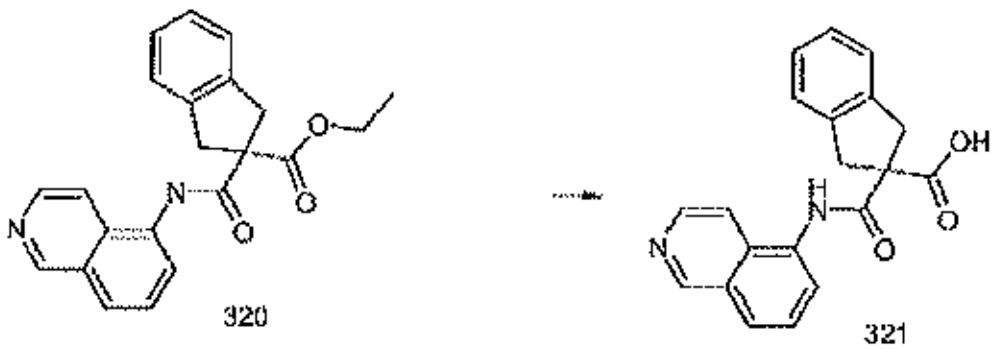


205 320

2-(Isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid Ethyl Ester (320)

A 25mL reaction vial which contains a stirring bar is charged with indane-2-carboxylic acid ethyl ester (205, 1.0g, 4.27mmol) and dry DCM (15mL). Stirring is initiated. After dissolution is complete, the HTBU (1.62g, 4.27mmol) is added. After 5min, the 5,-aminoisoquinoline. (616mg, 4.27mmol) is added followed by DIPEA (1.72mL, 9.8mmol). The reaction is allowed to stir for 63h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting acid. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (40mL). The organic phase is washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.13g of light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10% EtOAC in heptanes over 4 column volumes followed by a linear gradient to 90% EtOAc over 12 column volumes. 17mL fractions of eluent are collected. Fractions 17 through 31 are combined and evaporated *in vacuo*. This gives white solid (1.39g, 90%).

Example 321



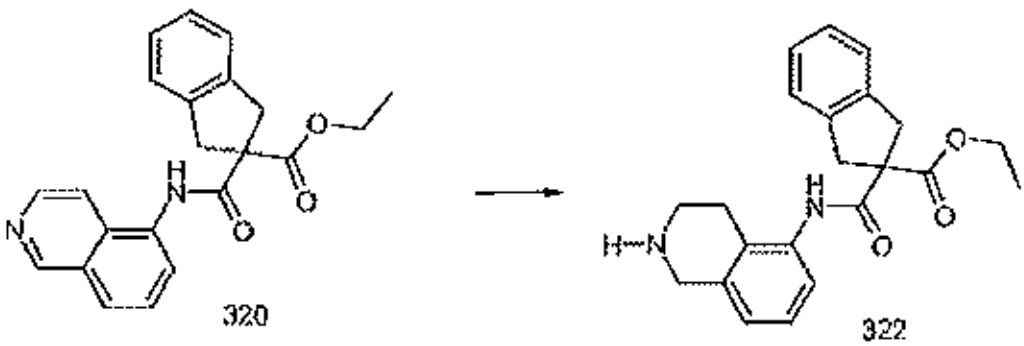
320 321

2-(Isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid (321)

A 30mL reaction viel is charged with 2-(isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (320, 354mg, 0.98mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (104mg, 252mmol). After 20h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 64h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate by pumping to constant weight to give 0.29g of off white solid. This material is triturated with DCM (15mL). The solids are collected by suction filtration and washed with DCM (20mL). Suction drying provides off white solid (280mg, 86%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.55-3.76 (m, 4H), 4.37 (m, 1H), 7.02-7.19 (m, 4H), 7.61 (dd, 1H), 7.78 (d, 1H), 8.06 (d, 1H), 8.46 (d, 1H), 8.57 (d, 1H), 9.30 (s, 1H) 13.77 (s, 1H). LC/MS (ES+) m/z = 333.11.

Example 322

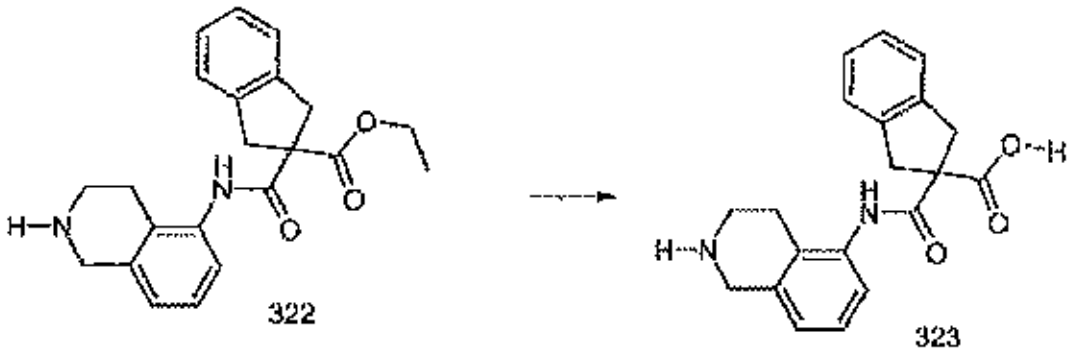


2-(1,2,3,4-Tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (322)

A 100mL Parr reaction vessel is charged with 2-(isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (320, 500mg, 1.39mmol) and EtOH (10mL). The reaction vessel is agitated by swirling until dissolution occurred. Acetic acid (10mL) and platinum (IV) oxide

(117mg, 0.52mmol) are added. The vessel is fitted on a Parr hydrogenation apparatus, flushed with N_2 and then evacuated. The vessel is charged with hydrogen to 50 psi. The apparatus is set to agitate. After 4h, agitation is ceased. The reaction vessel is evacuated and flushed with nitrogen. This process is repeated. The contents of the reaction vessel are diluted with iPrOH (50mL) and filtered through a pad of celite. Solvent is removed from the filtrate under reduced pressure. The resulting residue is reconstituted in iPrOH (15mL) and toluene (15mL). The solvent is removed under reduced pressure. This process is repeated. Pumping to constant weight yields light beige solid (0.5g, 99%).

Example 323



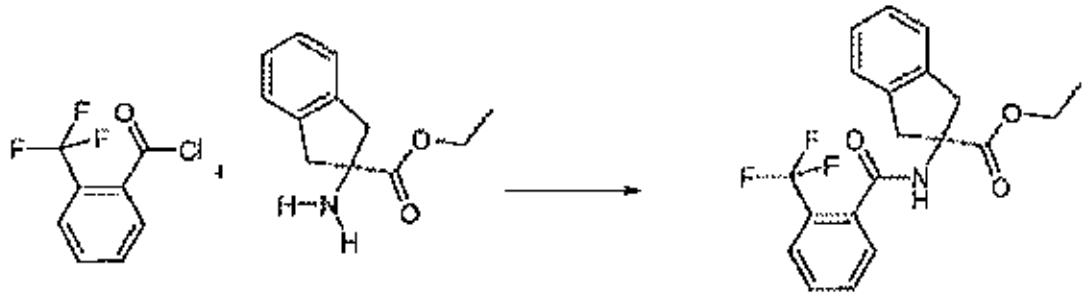
2-(1,2,3,4-Tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid (323)

A 250mL round bottom flask containing 2-(1,2,3,4-tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (322, 440mg, 1.21mmoles) is charged with 1,4-dioxane (7mL) and MeOH (7mL). A stirring bar is added and stirring is initiated. After dissolution, water (3.5mL) is added followed by the LiOH monohydrate (128mg, 3.05mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 24h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The resultant residue is reconstituted with iPrOH/ toluene (1:1, 25mL). The solvent is removed *in vacuo*. This process is repeated twice. Pumping to constant weight provides an off-white solid (400mg, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.58 (m, 1H), 2.99 (m, 1H), 3.43-3.71 (m, 4H), 3.81 (m, 1H), 6.72 (d, 1H), 7.01 (dd, 1H), 7.04-7.18 (m, 4H), 7.84 (d, 1H), 11.82 (s, 1H).

LC/MS (ES+) m/z = 337.15.

Example 324

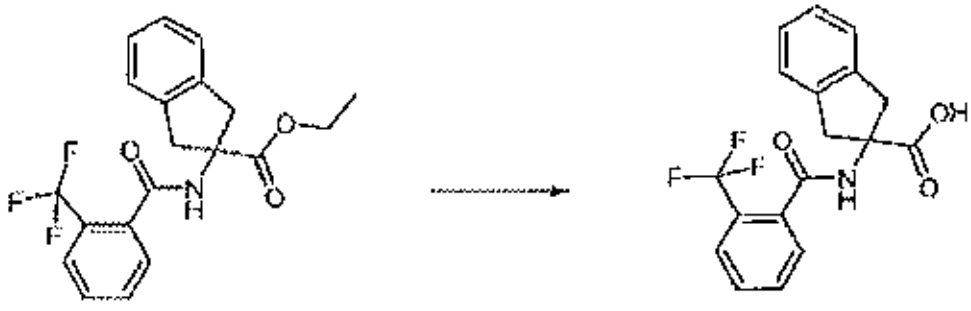


324

2-(2-Trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (324)

A 30mL viet is charged with 2-aminoindan-2-carboxylic acid (450mg, 2.19mmol) and dry DCM (5mL). A stirring bar is added and stirring is initiated. DIPEA (0.61mL, 3.51mmol) is added. 2-(trifluoromethyl)-benzoyl chloride (388 µL, 2.63mmol) and DMAP (3mg, cat.) are added. The reaction is capped. After 38 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). The organic phase is washed with dilute aqueous HCl (2x 25mL), saturated aqueous $NaHCO_3$ (2 x 25mL), and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 0.84g of light orange solid. This is diluted with DCM and applied to a silica column ((24 g) on an ISCO Companion. 14mL fractions of UV positive eluent are collected. Fraction 4 - 10 are combined and evaporated by pumping to constant weight to give light yellow solid (0.76g, 92%).

Example 325



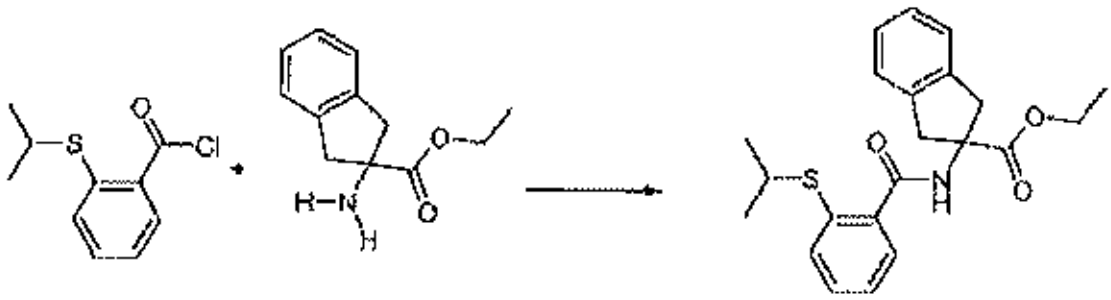
324 325

2-(2-Trifluoromethyl-benzoylamino)-indan-2-carboxylic acid (325)

A 100mL flask containing 2-(2-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (324, 0.57g, 1.51mmol) is charged with 1,4-dioxane (9mL) and MeOH (9mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.5mL) is added followed by the LiOH monohydrate (160mg, 3.81mmol). After 110h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~9mL). The contents of the flask are poured into a seperatory funnel which contains EtOAc (40mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over MgSO4, filtered and concentrated by pumping to constant weight yields off white solid (0.51g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.23-3.63 (m, 4H), 7.11-7.23 (m, 4H), 7.47 (d, 1H), 7.60-7.76 (m, 3H), 9.12 (s, 1H), 12.55 (s, 1H).
LC/MS (ES+) m/z = 350.11.

Example 326



326

2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (326)

A 30mL reaction vial is charged with 2-isopropylsulfanylbenzoic acid (430mg, 2.19mmol) and dry DCM (7mL). A stirring bar is added. Stirring is initiated. After dissolution is complete, the HTBU (831mg, 2.19mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 3 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM)

indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.87g of light yellow solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 32 through 40 are combined and evaporated *in vacuo*. This provides white solid material (0.69g, 82 %).

Example 327



326 327

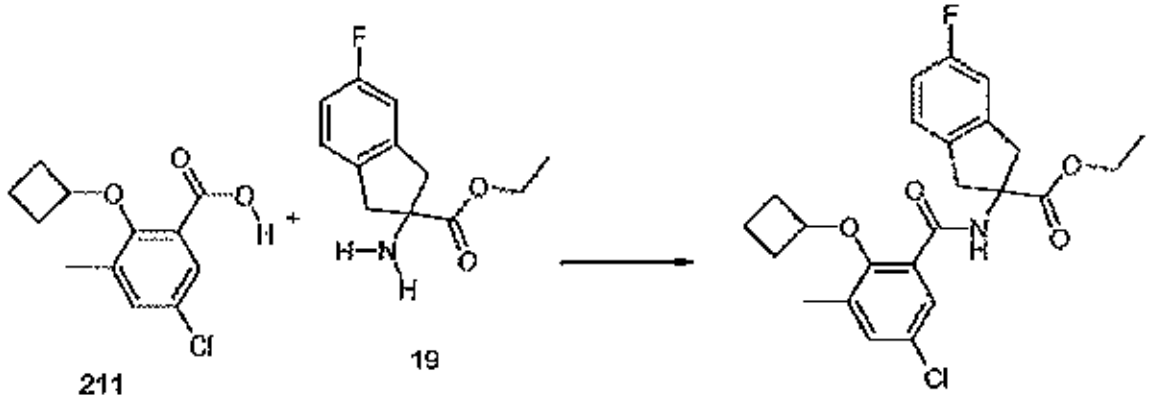
2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid (327)

A 100mL flask containing 2-(2-isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (326, 0.52g, 1.45mmol) is charged with 1,4-dioxane (8mL) and MeOH (8mL). A stirring bar is added and stirring is initiated. After dissolution, water (4mL) is added followed by the LiOH monohydrate (145mg, 3.46mmol). After 20 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~9mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (40mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.45g, 93%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.14 (d, 6H), 3.24-3.623 (m, 5H), 7.12-7.44 (m, 8H), 8.85 (s, 1H), 12.92 (s, 1H).

LC/MS (ES+) m/z = 356.15.

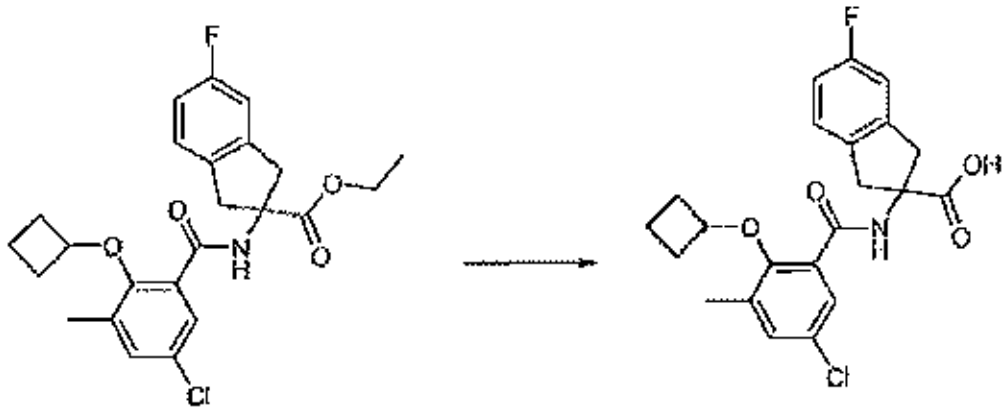
Example 328



2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (328)

A 40mL reaction vial is charged with 2-cyclobutoxyl-3-methyl-5-chloro-benzoic acid (221, 0.40g, 1.62mmol) and dry DCM (5mL). A stirring bar is added. Stirring is initiated. After dissolution is complete, the HBTU (630mg, 1.66mmol) is added. After 5min, the 2-amino-5-fluoro-indane-2-carboxylic acid ethyl ester. (19, 371mg, 1.66mmol is added followed by DIPEA (0.74mL, 4.16mmol). The reaction is allowed to stir for 5 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1g of light yellow oil. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 24g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 70% EtOAc in heptanes over 10 column volumes. 17mL fractions are collected. Fractions 22 through 28 are combined and evaporated *in vacuo* by pumping to a constant weight to give white solid (0.65g, 88%).

Example 329



328 329

2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (329)

A 100mL flask containing 2-(5-chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (328, 0.49g, 1.09mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (117mg, 2.78mmol). After 1 day, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~8mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (25mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give white solid (0.45g, 98%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.22-1.37(m, 1H), 1.43-1.57(m, 1H), 1.78-1.95 (m, 4H), 2.03 (s, 3 H) 3.285-3.63 (m, 5H), 4.37 (m, 1H), 6.98 (m, 1H), 7.06-7.11 (m, 1H), 7.20-7.27 (m, 2H), 7.385 (d, 1H), 8.82 (s, 1H) 12.67 (s, 1H).
LC/MS (ES+) m/z = 418.18

Example 330

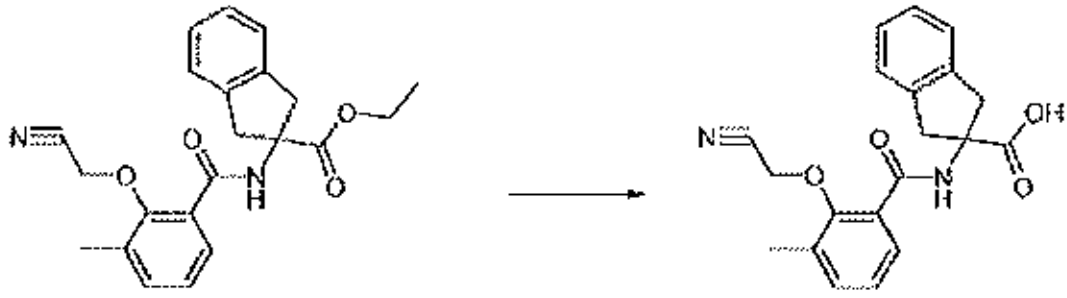


3 330

2-(2-Cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (330)

A 30mL reaction vial is charged with 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3, 400mg, 1.18mmol) and dry DMF (5mL). A stirring bar is added and stirring is initiated. After dissolution, K_2SO_4 (326mg, 2.36mmol) and bromoacetonitrile (164 µL, 2.36mmol) are added in turn. The reaction vial is capped and placed in a heating block which is set atop of an orbital shaker. The heating block is set at 55°C. After 16h, tlc analysis (silica, 1:1 EtOAc in heptanes) indicates that the starting material is completely consumed. Heating is terminated. After sitting at ambient temperature for 1 day, the contents of the flask are filtered through a pad of Celite. The filtrate is transferred to a separatory funnel which contains EtOAc (40mL). The layers are separated. The organic phase is washed with water (20mL), saturated aqueous $NaHCO_3$ and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give dark brown solid (0.42g). This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 25g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 4 through 6 are combined and evaporated *in vacuo*. This provides white solid (0.26g, 58 %).

Example 331



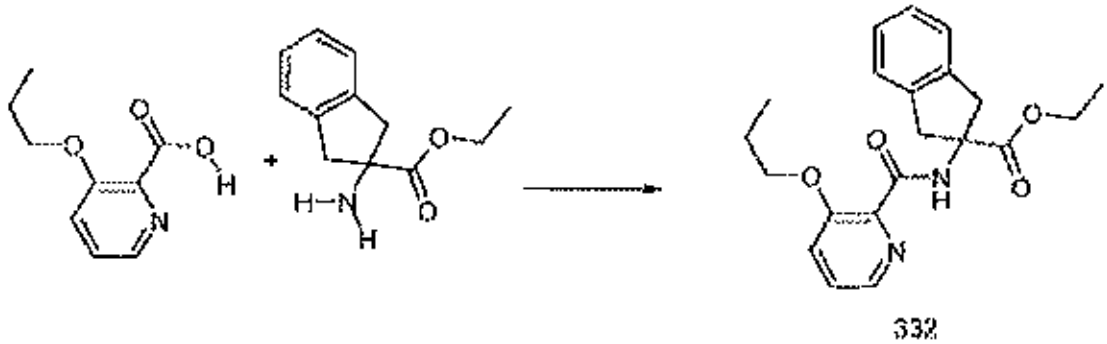
330 331

2-(2-Cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (331)

A 100mL flask containing 2-(2-cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (330, 0.25g, 0.66mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (71mg, 1.67mmol). After 18h, tlc analysis (silica, 5 % MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~8mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (25mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give white solid (0.23g, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.26-3.63 (m, 4H), 3.43 (s, 3H), 4.56 (s, 2H), 7.07 (dd, 1H), 7.14-7.23 (m, 5H), 7.29 (dd, 1H), 8.81 (s, 1H), 12.55 (bs, 1H).
LC/MS (ES+) m/z = 351.14.

Example 332

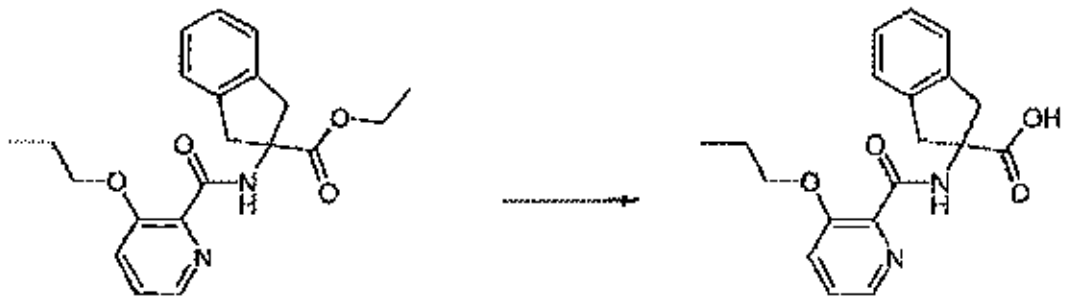


332

2-[(3-Propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester(332)

A 40mL reaction vial which contains a stirring bar is charged with 3-*n*-propoxypicolinic acid (397mg, 2.19mmol) and dry DCM (6mL). Stirring is initiated. After 2min, the HTBU (831mg, 2.195mmol) is added. After 5min, the 2-amino)-indane-2-carboxylic acid ethyl ester (450mg, 2.19mmol is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir at ambient temperature. After 20 days, analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.23g of light orange solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions eluent are collected. Fractions 57 through 67 are combined and evaporated *in vacuo* by pumping to constant weight to give white solid (0.8g, 99%).

Example 333



332 333

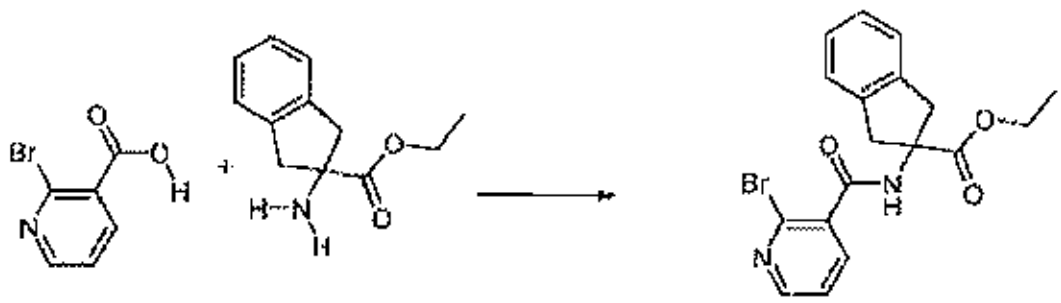
2-[(3-Propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid (333)

A 100mL round bottom flask which contains 2-[(3-propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (332, 620mg, 1.68mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (178mg, 4.25mmol). After 22h, tlc

analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 125h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 10mL) and the solvent is removed. This process is repeated 1 time. Pumping to constent weight provides 0.58g of white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.76 (t,3H), 1.71 (dt, 2H), 3.17-3.53 (m, 4H), 3.98 (t, 2H), 7.03-7.12 (m, 4H), 7.43 (dd, 1H), 7.55 (dd, 1H), 7.43 (dd, 1H), 8.12 (dd, 1H), 8.86 (s, 1H).
LC/MS (ES+) m/z = 341.14

Example 334



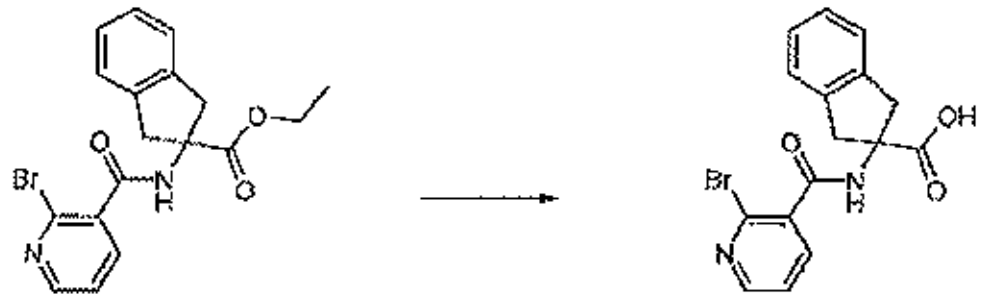
334

2-[(2-Bromo-pyridinyl-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester(334)

A 40mL reaction vial which contains a stirring bar is charged with 2-bromonicotinic acid (1.18g, 5.85mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.22g, 5.85mmol) is added. After 5min, 2-Amino-indan-2-carboxylic acid ethyl ester (1.2g, 5.25mmol is added followed by DIPEA (2.55mL, 14.62mmol). The reaction is allowed to stir for 32 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous $NaHCO_3$ (2 x 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.1g of light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes

followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 30 through 43 are combined and evaporated *in vacuo* to yield white solid, (1.62g, 72%).

Example 335



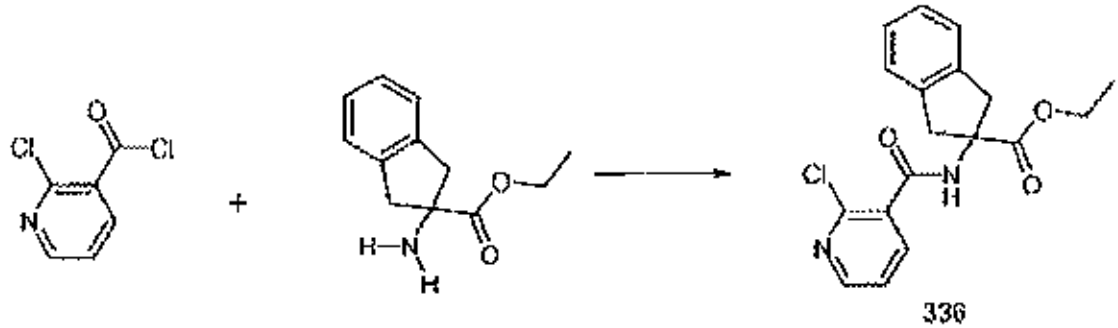
334 335

2-[(2-Bromo-pyridinyl-3-carbonyl)-amino]-indan-2-carboxylic acid (335)

A 50mL round bottom flask which contains 2-[(2-bromo-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (335, 356mg, 0.92mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (97mg, 2.31mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 6h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.32g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.23-3.53 (m, 4H), 7.03-7.18 (m, 4H), 7.49 (dd, 1H), 7.86 (dd, 1H), 8.40-8.51 (m, 2H).
LC/MS (ES+) m/z = 361.02.

Example 336



336

2-[(2-Chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (336)

A 100mL round bottom flask is charged with 2-amino-indan-2-carboxylic acid (1.5g, 7.31mmol) and dry DCM (15mL). A stirring bar is added and stirring is initiated. DIPEA (2mL, 11.69mmol) is added. 2-[chloronicotinoyl chloride (1.54g, 8.77mmol) and DMAP (8mg, cat.) are added. The reaction is capped. After 2 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with water (2 x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to give 2.15g of off-white solid. This is dissolved with DCM (20mL) and applied to a silica column ((80 g) on an ISCO Companion. The column is eluted with 10 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 75% EtOAc in heptanes over 12 column volumes. 17mL fractions of UV positive eluent are collected. Fractions 14 - 20 are combined and evaporated by pumping to constant weight to give light yellow solid (2g, 79%).

Example 337

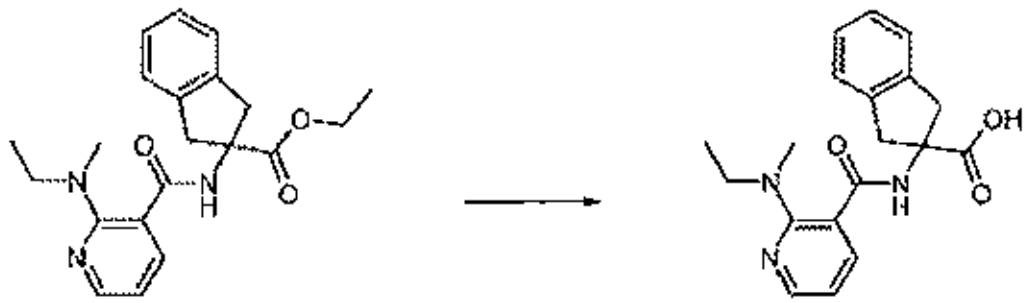


336 337

2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (337)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight to give 0.78g of viscous yellow oil. The material is dissolved in DCM (10mL) and applied to an ISCO chromatography column (silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight to give off-white solid (0.41g, 93%).

Example 338



337 338

2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (338)

A 100mL round bottom flask which contains 2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (337, 650mg, 1.77mmol) is charged with 1,4-dioxane (10mL) and MeOH (10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH monohydrate (187mg, 4.46mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 18h, the contents of the flask are filtered through a pad of celite. The solvent is removed from the

filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed under reduced pressure. This process is repeated 1 time. Pumping to constant weight gives beige solid (0.58g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.07 (t,3H), 3.18-3.48 (m,4H), 3.37 (q, 2H), 6.75 (dd, 1H), 7.03-7.13 (m, 4H), 7.63 (dd, 1H), 8.15 (dd, 1H), 8.77 (s, 1H).
LC/MS (ES+) m/z = 340.17.

Example 339

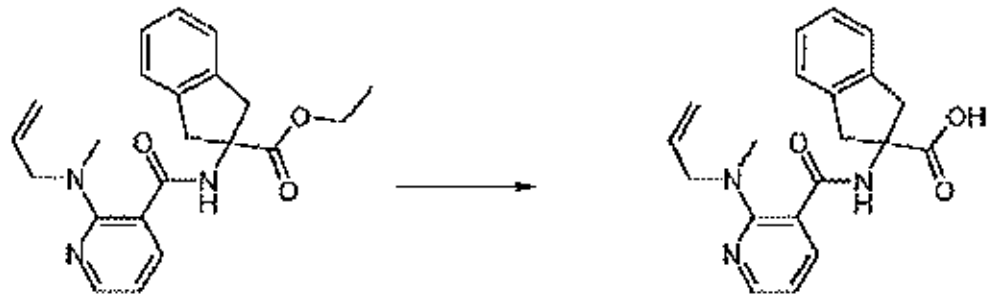


336 339

2-{[2-(Allylmethyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (339)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-allylmethylamine (1.1mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 21 days, tlc analysis silica, (2:1 EtOAc:heptanes) indicates that the starting material is consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight to give 0.85mg of dark brown material. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 25 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 2 to 8 are combined and evaporated by pumping to constant weight give off-white solid (0.43g, 98).

Example 340



339 340

2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (340)

A 100mL round bottom flask which contains 2-{[2-(allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (339, 280mg, 0.74mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (78mg, 1.86mmol). After 38h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 15 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.26g, 100%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.82 (s,3H) 3.18-3.48 (m,4H), 3.92 (dd,2H), 5.04-5.22 (m, 2H), 5.86-6.02 (m, 1H), 6.79 (dd, 1H), 7.04-7.11 (m, 4H), 7.67 (dd, 1H), 8.16 (dd, 1H), 8.77 (s, 1H).

LC/MS (ES+) m/z = 352.20.

Example 341

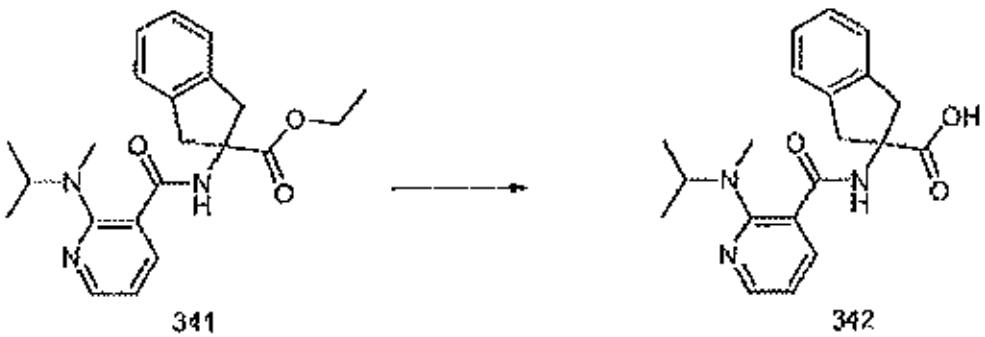


336 341

2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (341)

A 25mL microwave reaction vessel is charged with 2-{2-(chloro-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (341, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30sec DIPEA (2.1mL, 11.6mmol) and N-methylethylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in a oil bath which is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.78g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight yield 0.41g of off-white solid.

Example 342



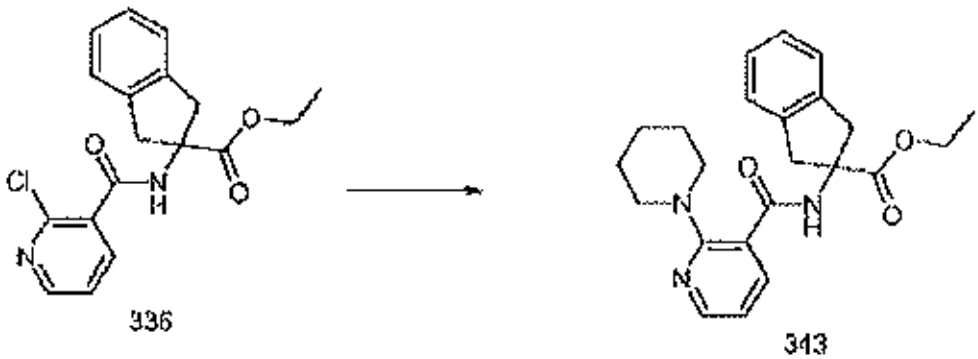
341 342

2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (342)

A 100mL round bottom flask which contains 2-{[2-(isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (341, 220mg, 0.58mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (61mg, 1.46mmol). After 16h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.2g, 98%).

^{1}H NMR (DMSO-d6, 300 MHz): δ 1.15 (d,6H), 2.48 (s,3H), 3.18-3.42 (m,4H), 4.18 (septet, 1H), 6.78 (dd, 1H), 7.05-7.12 (m, 4H), 7.67 (dd, 1H), 8.16 (dd, 1H), 8.81 (s, 1H).
LC/MS (ES+) m/z = 354.17

Example 343

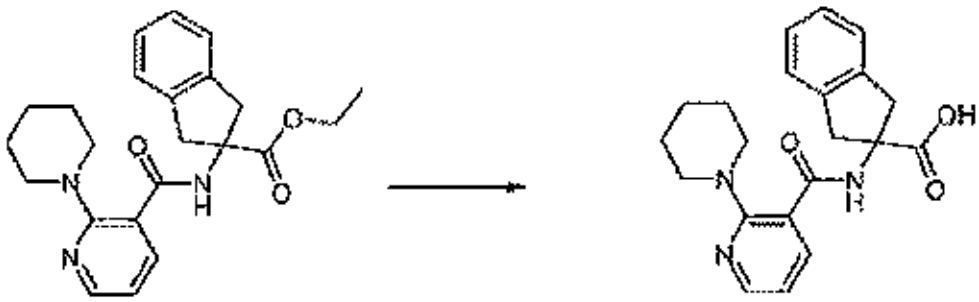


2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (343)

25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A

stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material is consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.78g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight give off-white solid (0.41g, 90%).

Example 344



343 344

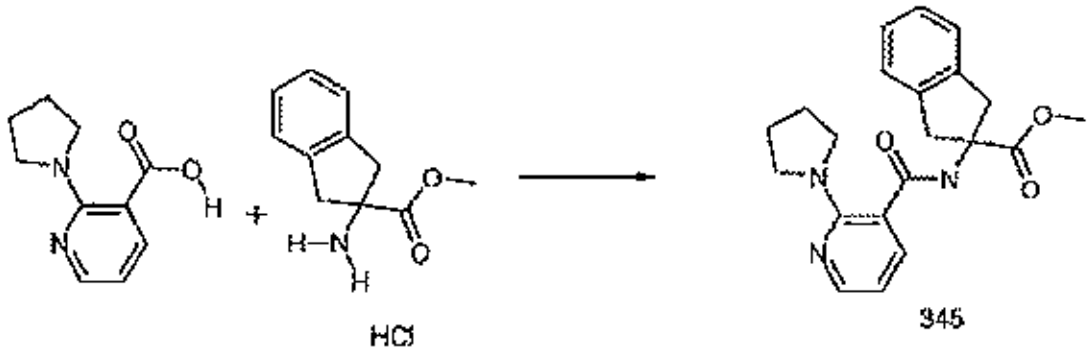
2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid (344)

A 100mL round bottom flask which contains 2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (343, 330mg, 0.84mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (89mg, 2.12mmol). After 62h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 38h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is

removed. This process is repeated 1 time. Pumping to constant weight provides 0.3g of a white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 1.52 (m,2H), 1.76 (m, 4H), 3.13 (m, 4H), 3.18-3.43 (m, 4H), 3.92 (dd, 2H), 6.94 (dd, 1H), 7.05-7.12 (m, 4H), 7.81 (dd, 1H), 8.24 (dd, 1H), 9.35 (s, 1H).
LC/MS (ES+) m/z = 366.17.

Example 345



2-[(2-Pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (345)

A 40mL reaction vial which contains a stirring bar is charged with 2-(1-pyrrolidinyl)-nicotinic acid (422mg, 2.2mmol) and dry DCM (6mL). Stirring is initiated. After 2min, the HTBU (833mg, 2.2mmol) is added. After 5min, 2-amino-indan-2-carboxylic acid methyl ester HCl salt. (0.5g, 2.2mmol) is added followed by DIPEA (1.17mL, 6.7mmol). The reaction vial is capped and allowed to stir at ambient temperature. After 18h, analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous $NaHCO_3$ (2 X 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.05g of light yellow solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 24g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV active eluant are collected. Fractions 6 through 12 are combined and evaporated *in vacuo* to give white solid (0.73g, 91%).

Example 346



345 346

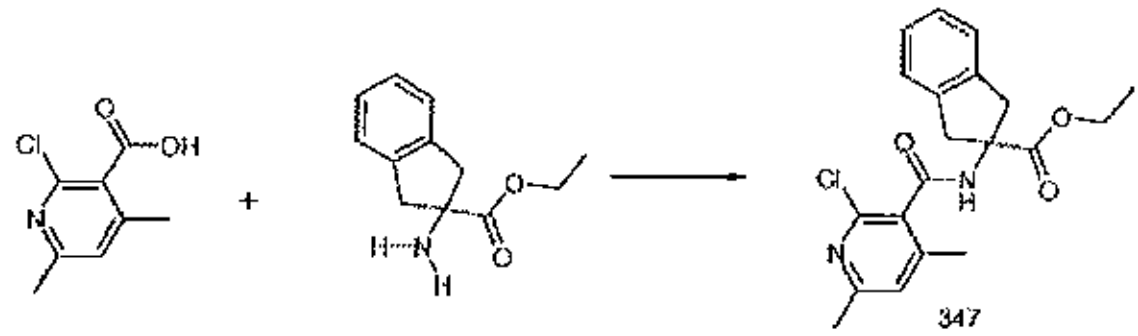
2-[(2-Pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid (346)

A 100mL round bottom flask which contains 2-[(2-pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (345, 440mg, 1.20mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (128mg, 3.05mmol). After 30h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 18h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides 0.38g of white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 1.82 (m, 4H), 3.21-3.48 (m, 8H), 3.92 (dd, 2H), 6.59 (dd, 1H), 7.04-7.11 (m, 4H), 7.46 (dd, 1H), 8.08 (dd, 1H), 8.22 (bs, 1H).

LC/MS (ES+) m/z = 352.14.

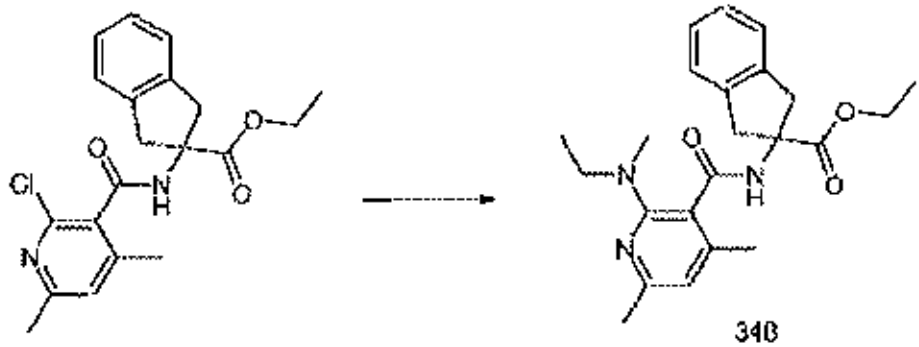
Example 347



2-[(2-Chloro-4,6-dimethyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (347)

A 40mL vial is charged with 2-chloro-4,6-dimethylnicotinic acid (497mg, 2.68mmol) and dry DCM (9mL). A stirring bar is added and stirring is initiated. After 2min, the HTBU (1.02g, 2.68mmol) is added. After 5min, 2-amino)-indane-2-carboxylic acid ethyl ester. (550mg, 2.68mmol) is added followed by DIPEA (1.2mL, 6.74mmol). The reaction is allowed to stir for 14 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70mL). This is washed dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 x 30mL) and brine (30mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to provide1.6g of yellow foam. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active elutant are collected. Fractions 32 through 40 are combined and evaporated in vacuo to give yellow semi-solid material. (0.67g, 67%).

Example 348

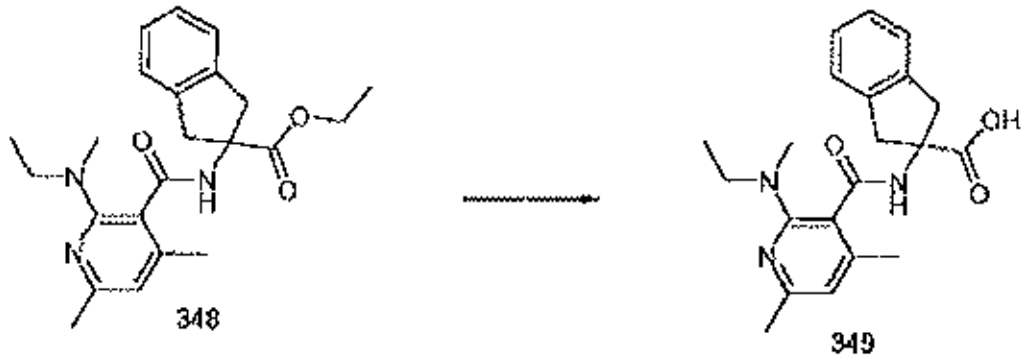


347 348

2-{[2-(Ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (348)

A 25mL microwave reaction vessel is charged with 2-{2-(chloro-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (347, 480mg, 1.29mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds, N-ethylmethylamine (2mL, 23.28 mmole) is added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in a Smith Optimizer microwave apparatus. The pre-stir is set at 20sec followed by heating to 100°C. Hold time is set to 18min. TLC analysis silica, 2:1 EtOAc:heptanes) indicates that a new Spot appears with a higher R_f value as visualized by UV. Starting material is still present. N-Ethylmethylamine (506 µL, 5.89, mmole) is added. The reaction vessel is sealed with a crimped cap. The reaction vial is immersed in an oil bath that is heated at 80°C. After 5 days, tlc analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been converted to a higher moving spot as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 1.3g of viscous yellow oil. The material is dissolved in DCM (10mL) and applied to an ISCO Chromatography Column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 Column Volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 9 are combined and evaporated by pumping to constant weight to give white solid (0.41g, 83%).

Example 349



348 349

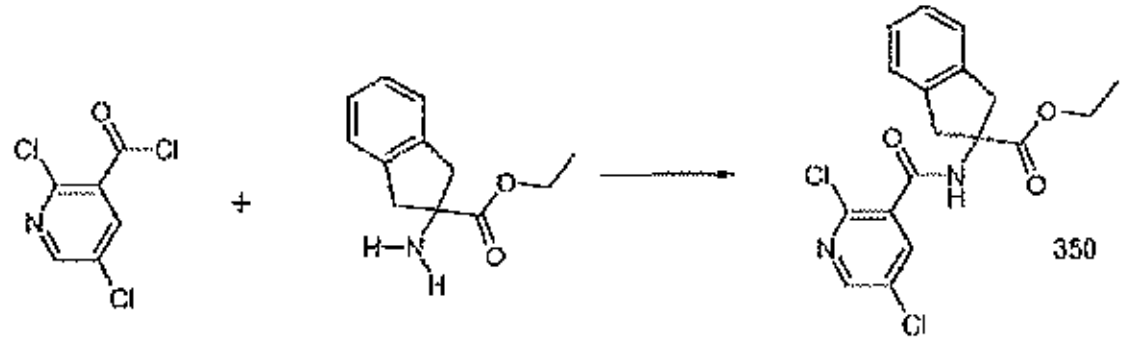
2-{[2-(Ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (349)

A 100mL round bottom flask which contains 2-{[2-(ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (348, 260mg, 0.66mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (70mg, 1.66mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 38h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.18g, 75%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.03 (t, 3H), 3.17-3.53 (m, 6H), 6.41 (s, 1H), 7.05-7.12 (m, 4H), 8.05 (s, 1H).

LC/MS (ES+) m/z = 368.25.

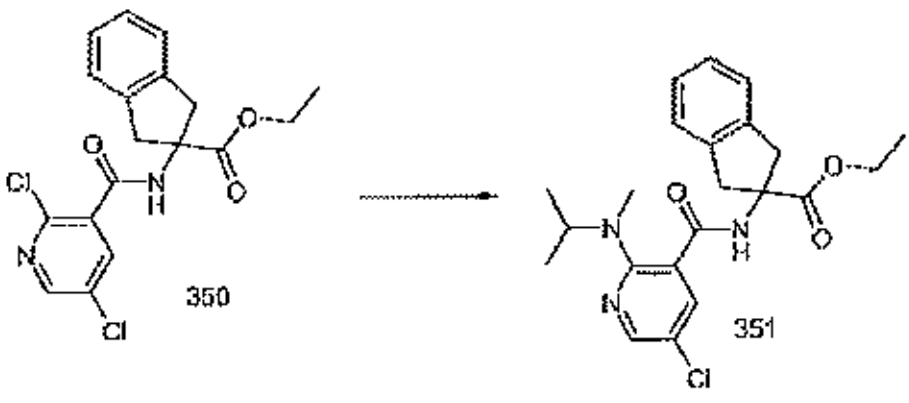
Example 350



2-[(2,5-Dichloro-pyridine-3-carbonyl)-amino]-Indan-2-carboxylic acid ethyl ester (350)

A 30mL reaction vial is charged with 2-aminoindan-2-carboxylic acid ethyl ester (1g, 4.87mmol) and dry DCM (5mL). A stirring bar is added and stirring is initiated. DIPEA (1.35mL, 7.8mmol) is added. 2,5-dichloro-pyridine3-carbonyl chloride (1.23g, 5.85mmol) and DMAP (8mg, cat.) are added. The reaction is capped. After 57 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting has been completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with water (2x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 1.99g of off-white solid. This is diluted with DCM (20mL) and applied to a silica column ((80 g) on an ISCO Companion. The column is eluted with 5 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 75% EtOAc in heptanes over 12 column volumes. 17mL fractions of UV positive eluent are collected. Fraction 12 - 16 are combined and evaporated by pumping to constant weight to give light yellow solid (1.39g, 75%).

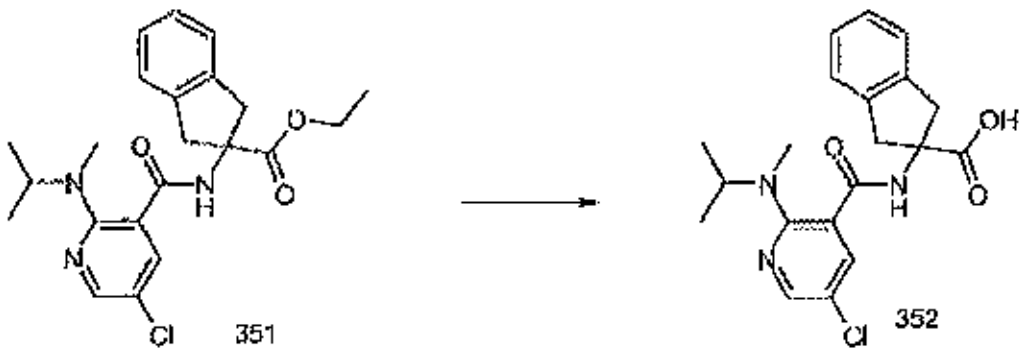
Example 351



2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (351)

A 40mL reaction vial is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester 350, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30sec DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vial is tightly sealed with Teflon coated cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 7 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.84g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 2 to 5 are combined and evaporated by pumping to constant weight to give a light yellow solid (0.42g, 85%).

Example 352



2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid (352)

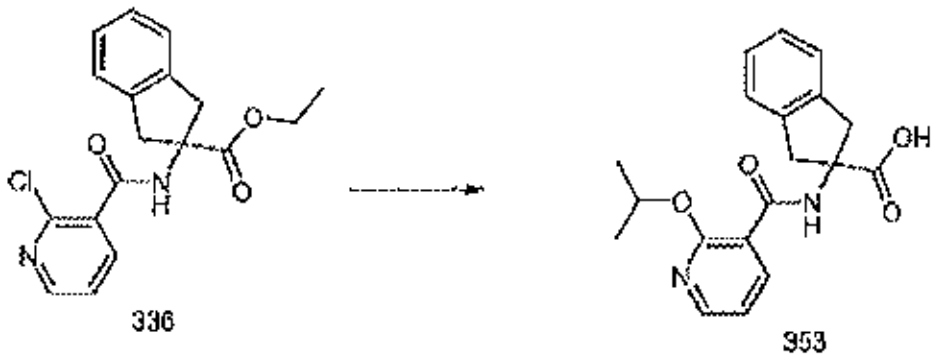
A 100mL round bottom flask which contains 2-{[5-chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (351, 270mg, 0.58mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (62mg, 1.48mmol).

After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 20h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.21g, 94%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.09 (t, 3H), 2.71 (s,3H), 3.22-3.48 (m, 4H), 4.18 (septet, 1H), 7.04-7.11 (m, 4H), 7.65 (s, 1H), 8.17 (s, 1H), 8.48 (s, 1H), 8.72 (bs, 1H).

LC/MS (ES+) m/z = 390.10.

Example 353



336 353

2-[2-(Isopropoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid (353)

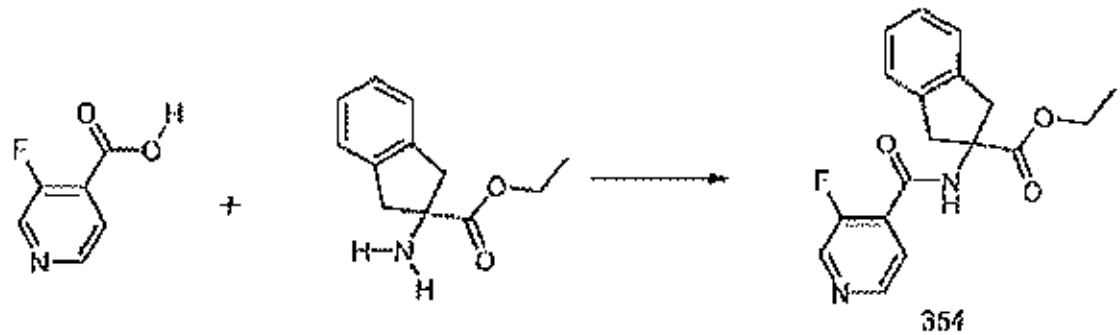
A 10mL microwave reaction vial is charged with iPrOH (4mL, 51.9mmol). A stirring bar is added and stirring is initiated. A suspension of NaH in oil (104mg, 2.61mmol) is added. After 2min, 2-[(2-Chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (336, 450mg, 1.31mmol) is added. The reaction flask is loosely capped and allowed to stir at ambient temperature. After 7 days, tlc analysis (silica, 2:1, EtOAc/heptanes) indicates that the starting material is consumed. Dowex Highly Acidic Ion Exchange Resin (0.5g) is added to the reaction flask. The flask is allowed to stir at ambient temperature. After 1 week, the reaction mixture is diluted with iPrOH (20mL) and filtered through a pad of Celite. The filtrate is transferred to a round bottom flask and evaporated under reduced pressure. The residue is reconstituted with iPrOH (10mL) and toluene (10mL). The solvent is removed under reduced pressure. The reconstitution and evaporation steps are repeated. Pumping to

constant weight yields amorphous white solid (0.40 g). This material is dissolved in DCM (5mL). This solution is applied to an ISCO Companion that is fitted with a 12g column (silica). The column is eluted with 5% ACN/DCM for 5 column volumes followed by a linear gradient to 90 % ACN/DCM over 10 Column Volumes. 14mL fractions of UV active eluent are collected. Fractions 6-9 are combined and evaporated by pumping to constant weight give white solid (0.1g, 12%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.21 (d, 6H), 3.23-3.58 (m, 4H), 5.33 (septet, 1H), 7.13 (dd, 1H), 7.20-7.26 (m, 4H), 8.17 (dd, 1H), 8.29 (dd, 1H), 8.77 (s, 1H) 13.77 (bs, 1H).

LC/MS (ES+) m/z = 341.10.

Example 354



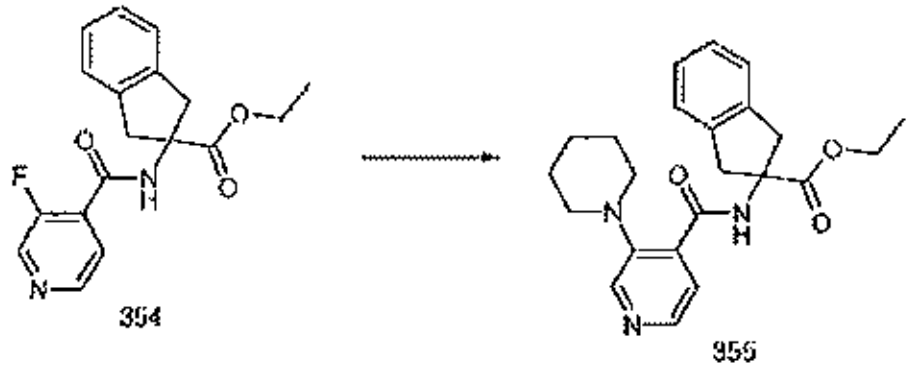
354

2-[(2-Fluoro-pyridine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354)

A 40mL reaction vial which contains a stirring bar is charged with 3-fluoroisinicotinic acid (825mg, 5.85mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.22g, 5.85mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (1.2g, 5.25mmol) is added followed by DIPEA (2.55mL, 14.62mmol). The reaction is allowed to stir for 7 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (75mL). This is washed consecutively with brine (25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.93g of light yellow solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 5 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 65% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV

active eluent are collected. Fractions 4 through 9 are combined and evaporated in vacuo. This yields white solid (1.5g, 94%).

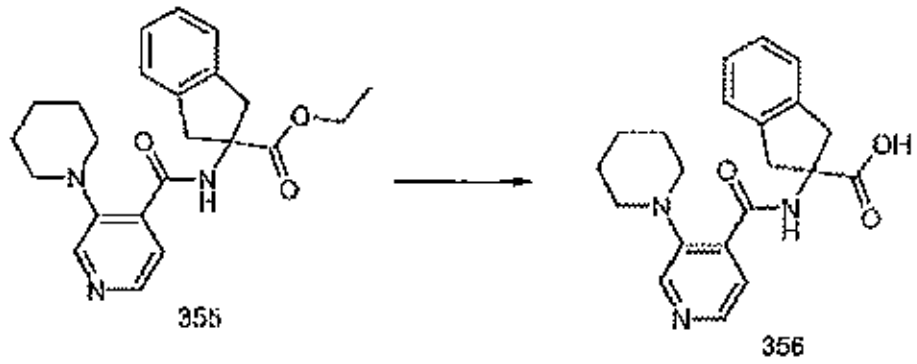
Example 355



2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (355)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354, 500mg, 1.52mmol), 1,4-dioxane (1.5mL) and piperidine (1.51mL, 15.23mmol). A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 1.2g of yellow semi-solid. The residue is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions are collected. Fractions 42-50 are combined and evaporated by pumping to constant weight to give white solid (0.56g, 93%).

Example 356



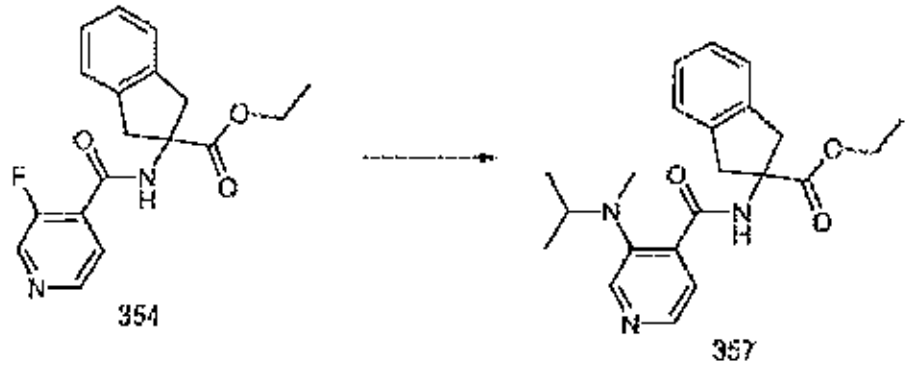
355 356

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid (356)

A 100mL round bottom flask which contains 2-[(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (355, 370mg, 0.94mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (100mg, 2.38mmol). After 68h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 20h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.35g, 96%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.43 (m, 2H), 1.78 (m, 4H) 2.96 (m, 4H), 3.22-3.46 (m, 4H), 7.05-7.12 (m, 4H), 7.46 (d, 1H), 8.28 (d, 1H), 8.40 (s, 1H), 9.83 (bs, 1H).
LC/MS (ES+) m/z = 366.16.

Example 357

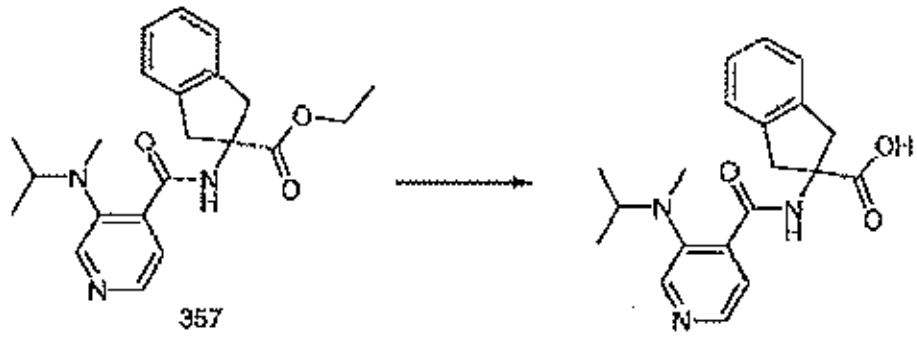


354 357

2-{[3-(Isopropyl-methyl-amino)- pyridine-4-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (357)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354, 500mg, 1.52mmol), 1,4-dioxane (2mL) and piperidine 2mL, 29.5mmol). A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. After this sequence is completed, the reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 0.71g of brown syrup. This is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 5-11 are combined and evaporated by pumping to constant weight to give 0.29g of an amorphous white solid (0.29g, 51%).

Example 358



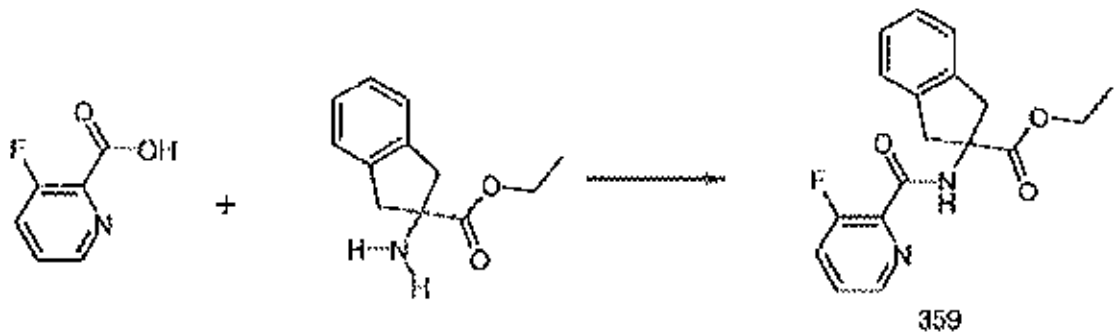
357 358

2-{[3-(Isopropyl-methyl-amino)- pyridine-4-carbonyl]-amino}-indan-2-carboxylic acid (358)

2- {[3-(Isopropyl-methyl-amino)-pyridine-4'-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester 357, 270mg, 0.71mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (75mg, 1.94mmol). After 4 days, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 3h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.22g, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.03 (d, 6H), 2.69 (s, 3H), 3.77 (septet, 1H), 7.05-7.12 (m, 4H), 7.43 (d, 1H), 8.21 (d, 1H), 8.39 (s, 1H).
LC/MS (ES+) m/z = 354.19.

Example 359

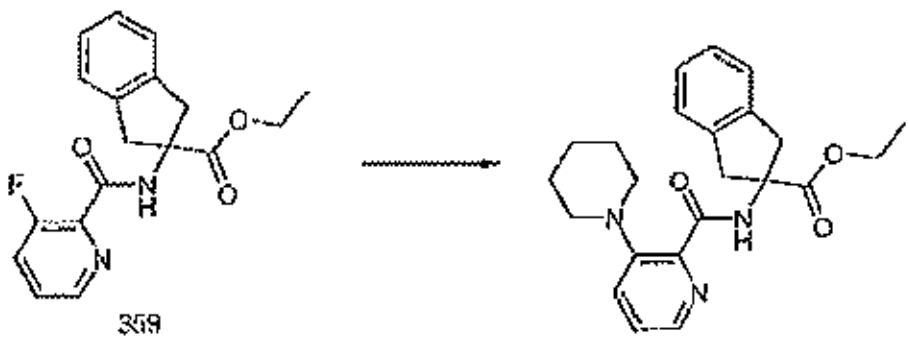


359

2-[(3-Fluoro-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (359)

A 40mL reaction vial which contains a stirring bar is charged with 3-Fluoropyridine-2-carboxylic acid (997mg, 7.07mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.7g, 7.07mmol) is added. After 5min, 2-Amino-indan-2-carboxylic acid ethyl ester (1.45g, 7.07mmol) is added followed by DIPEA (2.50mL, 14.5mmol). The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous NaHCO3 (2 X 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to provide 4.15g of light orange solid. This material is dissolved in 20mL of DCM. This material is purified utilizing an ISCO Companion with an 80g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV active elutant are collected. Fractions 6 through 14 are combined and evaporated *in vacuo*. This yields 2.04g white solid (2.04g, 88%).

Example 360



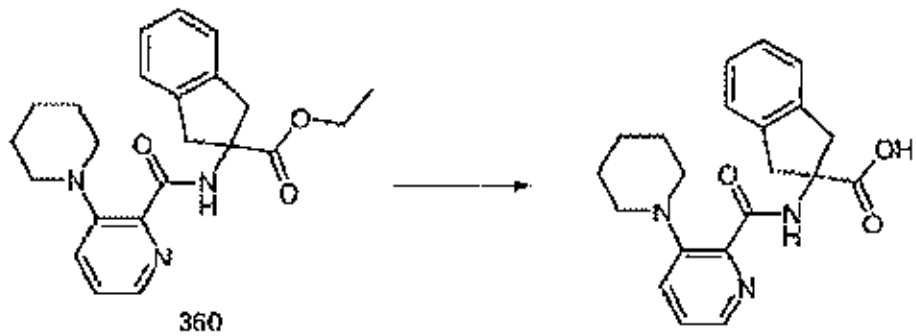
359 360

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (360)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (359, 488mg, 1.49mmol), 1,4-dioxane (1.5mL) and piperidine (1.51mL, 15.23mmol). A stirring bar is added. The reaction vial is crimped sealed.

The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 1.02g of off white solid. This is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV Active eluent are collected. Fractions 2-10 are combined and evaporated by pumping to constant weight to give white solid (0.5g, 86%).

Example 361



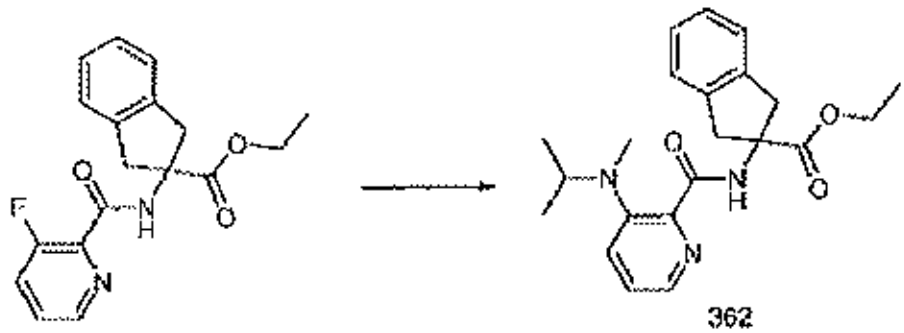
360 361

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid (361)

A 100mL round bottom flask which contains 2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (360, 370mg, 0.94mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by LiOH monohydrate (100mg, 2.38mmol). After 38h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material has been completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.29, 84%).

^{1}H NMR 300MHz): δ 1.43 (m, 2HH), 1.78 (m, 4H), 2.96 (m, 4H), 3.22-3.46 (m, 4H), 7.05-7.12 (m, 4H), 7.46 (d, 1H), 8.28 (d, 1H), 8.40 (s, 1H), 9.83 (bs, 1H).
LC/MS (ES+) m/z = 366.16.

Example 362

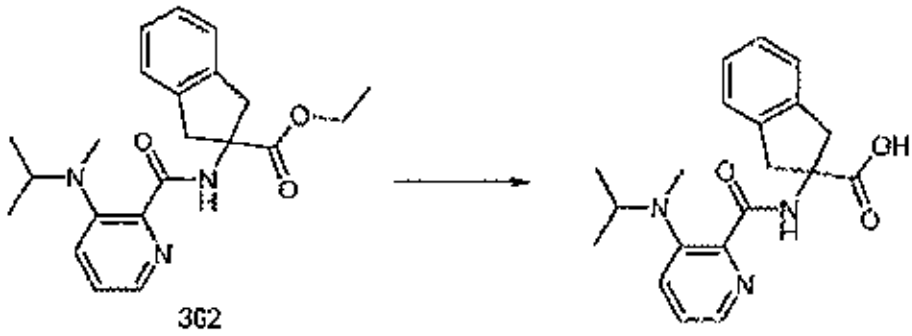


359 362

2-{[3-Isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (362)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridiine-2-carbonyl)-amino}-indan-2-carboxylic acid ethyl ester (359, 492mg, 1.5mmol), 1,4-dioxane (1.5mL) and N-methylisopopyl amine (2mL, 19.25mmol).and DIPEA (2mL, 11.48mmol) are added. A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 155°C with a fixed hold time of 90min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constat weight gives 0.75g of brown syrup. This is dissolved in DCM (10mL) and applied to an ISCO Companion which had been fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV Active eluent are collected. Fractions 7-15 are combined and evaporated by pumping to constant weight to give amorphous white solid (0.38g, 67%).

Example 363



362 363

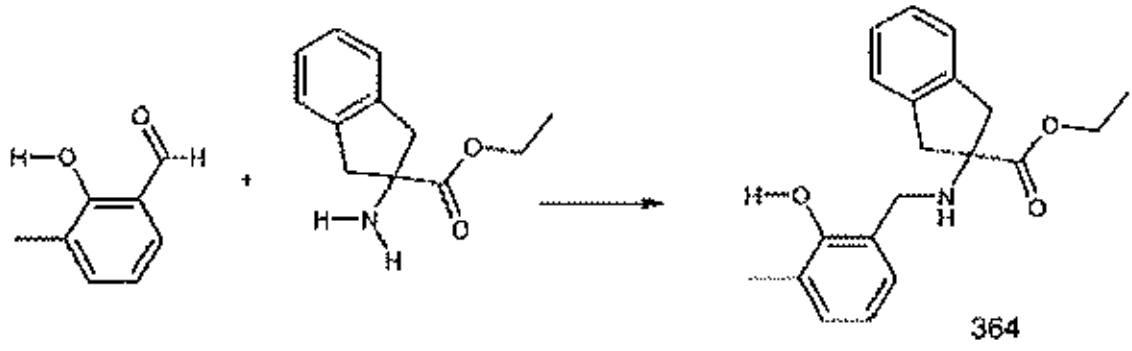
2-{[3-Isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-Indan-2-carboxylic acid (363)

A 100mL round bottom flask which contains 2-{[[3-isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (362, 370mg, 0.97mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by LiOH monohydrate (103mg, 2.46mmol). After 62h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material has been completely consumed. Amberlyst highly acidic exchange resin (0.7 g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides a white solid (0.33, 96%).

^{1}H NMR 300MHz): δ 1.04 (d, 6H), 2.39 (s, 3H), 3.18-3.53 (m, 4H), 3.64 (septet, 1H), 7.02-7.12 (m, 4H), 7.28 (dd, 1H), 7.36 (dd, 1H), 7.98 (dd, 1H), 8.84 (s, 1H).

LC/MS (ES+) m/z = 354.17.

Example 364

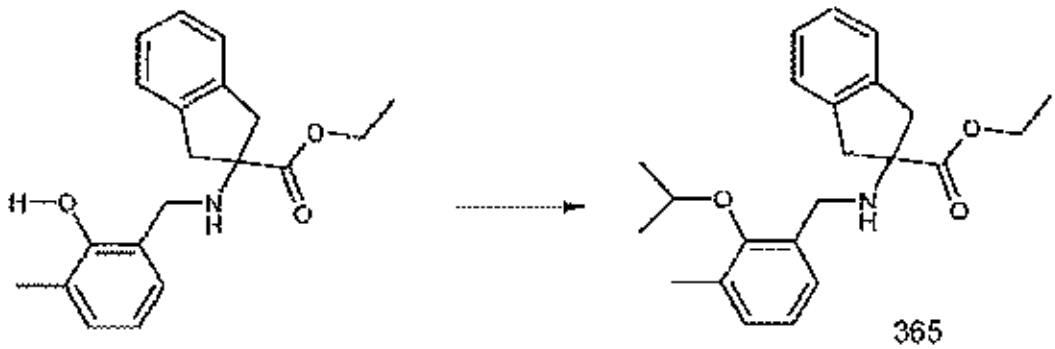


364

2-(2-Hydroxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (364)

A 10mL microwave reaction vessel is charged with 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.44mmol) and dry tetrahydrofuran (THF, 5mL). A stirring bar is added and stirring is initiated. After dissolution, 2-hydroxy-3-methyl-benzaldehyde (0.3mL, 2.43mmol) is added. Stirring is continued. Phenylsilane (0.61mL, 4.87mmol) and dibutyltin dichloride (53 µL, 244 µM) are added. The reaction vial is crimped sealed and placed in a Smith Microwave Apparatus. The pre-stir time is set to 10sec. Heating is set at 100°C for 10min. The contents of the reaction vial are transferred to a round bottom flask and evaporated by pumping to a constant weight yields 1.67g of light yellow solid. This material is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g Cartridge (silica). The column is eluted with 5 % EtOAc/heptanes for 3 column volumes followed by a linear gradient to 50 % EtOAc/heptanes over 10 column volumes and then 90 % EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 5 to 8 are combined and evaporated by pumping to constant weight to give 0.59g of white solid material (0.59g, 74%).

Example 365



364

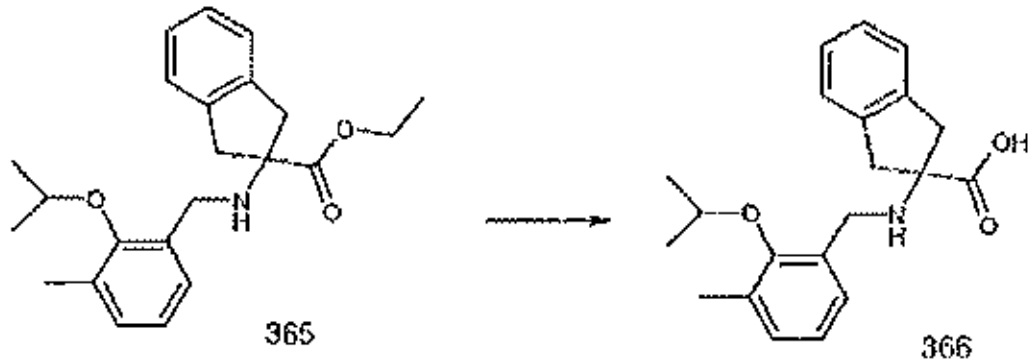
365

2-(2-Isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (365)

A 100mL round bottom flask containing the 2-(2-hydroxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (364, 1.01g, 3.10mmol) is charged with dry tetrahydrofuran (THF, 10mL). A stirring bar is added and stirring is initiated. After dissolution, iPrOH ([67-63-0], 0.47mL, 6.21mmol) and triphenylphosphine ([603-35-0], 1.63g, 6.21mmol) are added in turn. After dissolution of the triphenylphosphine, diisopropylazodicarboxylate (1.20mL, 6.21mmol) is added. The reaction flask is capped and allowed to stir at ambient temperature overnight. After 24h, tlc analysis (silica, 1:2 EtOAc/Heptanes) indicates that the starting material is completely consumed and converted to a higher moving spot as visualized by UV. The stirring bar is removed from the reaction flask and the solvent removed under reduced pressure. Pumping to constant weight gives 2.06g of viscous yellow oil. This is dissolved in DCM (10mL) and applied to an ISCO Companion which had been fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 60 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 17mL fractions of UV Active eluent are collected. Fractions 5-14 are combined and evaporated by pumping to constant weight to give viscous residue (0.42g, 37%).

^{1}H NMR 300MHz): δ 1.18 (d, 6H), 1.22 (t, 3H), 2.18 (s, 3H), 2.98-3.41 (m, 4H), 3.61 (d, 2H), 4.16 (q, 1H), 6.90 (dd, 1H), 7.04 (dd, 1H), 7.11-7.20 (m, 4H)
LC/MS (ES+) m/z = 368.24.

Example 366



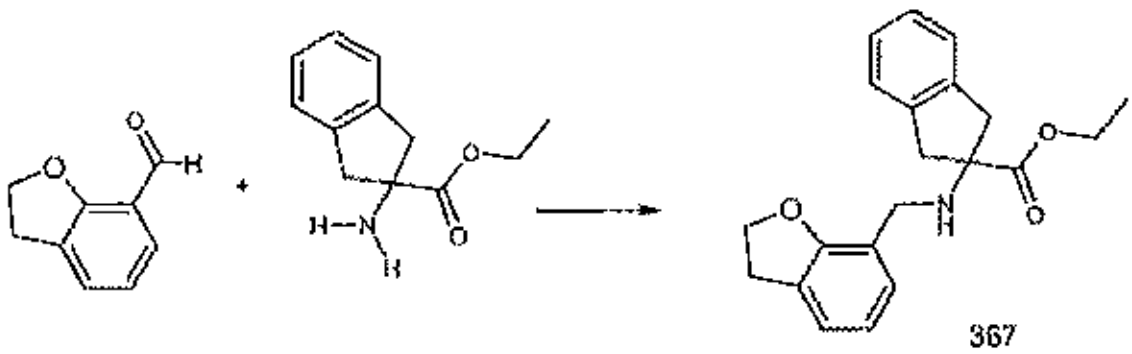
2-(2-Isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid (366)

A 100mL round bottom flask containing 2-(2-isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (365, 360mg, 0.98mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (104mg, 2.47mmol). After 39h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 15 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provided white solid (0.24g, 72%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.12 (d, 6H), 2.17 (s, 3H), 2.77-3.68 (m, 6H), 4.16 (septet, 1H), 6.84 (dd, 1H), 6.97-7.22 (m, 6H).

LC/MS (ES+) m/z = 340.20.

Example 367



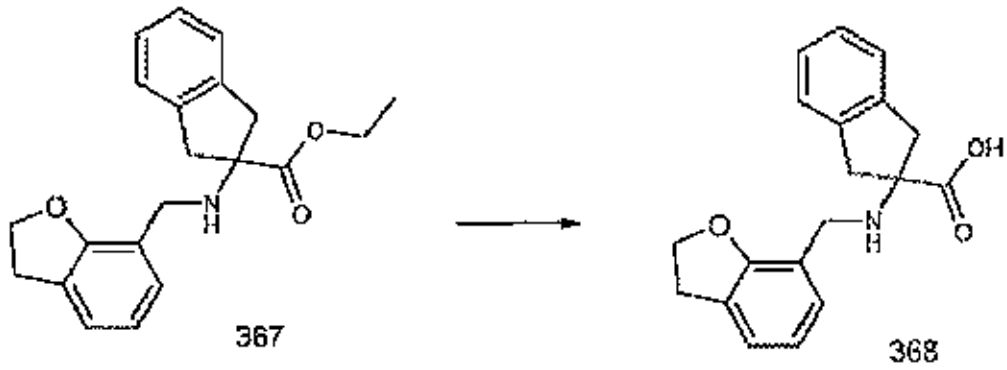
367

2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid ethyl ester (367)

A 10mL microwave reaction vessel is charged with 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.44mmol) and dry tetrahydrofuran (THF, 5mL). A stirring bar is added and stirring is initiated. After dissolution, 2,3-dihydro-1-benzofuran-7carbaldehyde (361mg, 2.43mmol) is added. Stirring is continued. Phenylsilane ([694-18-1], 0.61mL, 4.87mmol) and dibutyltin dichloride (53 µL, 244 µM) are added. The reaction vial is crimped sealed and placed in a Smith Microwave Apparatus. The pre-stir time is set to 10sec. Heating is set at

100°C for 10min. The contents of the reaction vial are transferred to a round bottom flask and evaporated by pumping to a constant weight yields 1.56g of light yellow oil. This material is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g Cartridge (silica). The column is eluted with 5 % EtOAc/heptanes for 3 column volumes followed by a linear gradient to 50 % EtOAc/heptanes over 10 column volumes and then 90 % EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 7 to 11 are combined and evaporated by pumping to constant weight yields 0.59g of white solid material (0.52g, 63%).

Example 368



2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid (368)

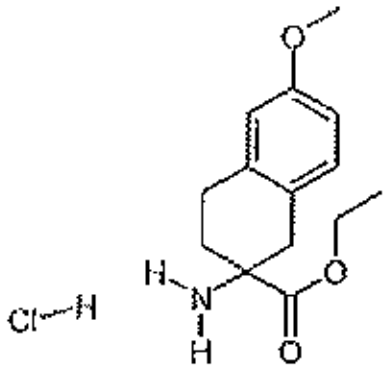
A 100mL round bottom flask containing 2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid ethyl ester (367, 350mg, 1.037mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (110mg, 2.52mmol). After 16h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 6h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provided white solid (0.31g, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ2.77-3.58 (m, 6H), 3.11 (t, 2H), 4.45 (t, 2H), 6.70 (dd, 1H), 7.02-7.11 (m, 6H).

LC/MS (ES+) m/z = 310.14.

2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl esters 369, 370, 371, 372 and 373 are synthesized according to the method of Michael Cox in Eur. Pat. Appl. EP 82-304382.

Example 369

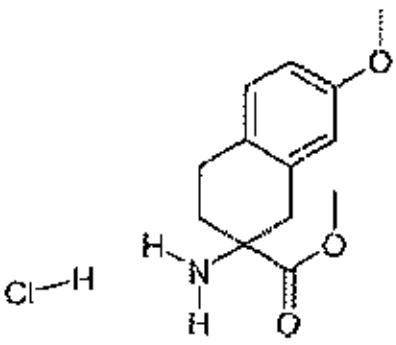


369

2-Amino-6-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester hydrochloride salt (369)

LC/MS (ES+) m/z = 250.18.

Example 370



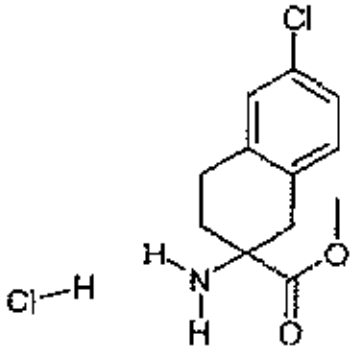
370

Example 370

2-Amino-7-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester; hydrochloride (370)

LC/MS (ES+) m/z = 336.16.

Example 371

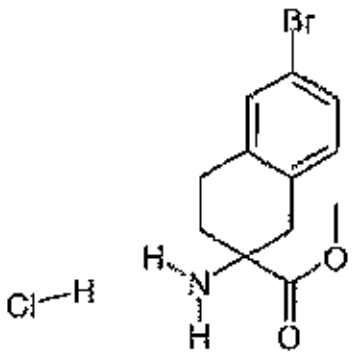


371

2-Amino-6-chloro-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester hydrochloride salt (371)

LC/MS (ES+) m/z = 340.11.

Example 372

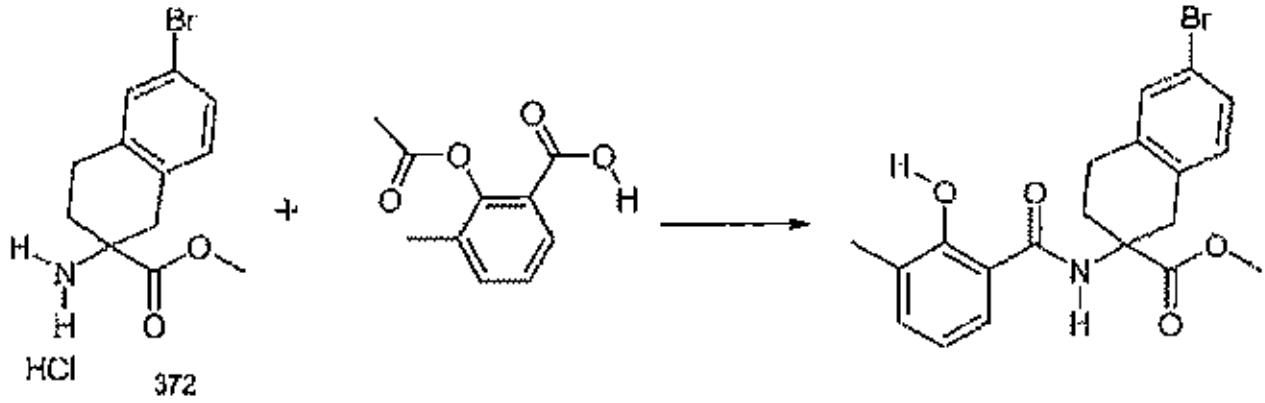


372

2-Amino-6-bromo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester hydrochloride salt (372)

LC/MS (ES+) m/z = 340.11.

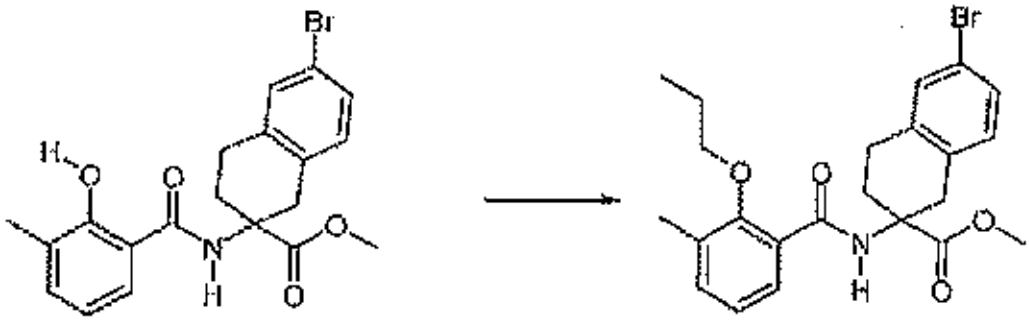
Example 373



2-(2-Hydroxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (373)

A 40mL vial which contains a stirring bar is charged with 2-acetoxyl-3-methyl-benzoic acid ([2386-93-4], 1.69g, 8.7mmol) and dry DCM (10mL). Stirring is initiated. After dissolution is complete, The HTBU (3.29g, 8.7mmol) is added. After 5min, the 2-amino-6-bromo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic Acid hydrochloride Salt (372, 1.25g, 3.9mmol is added followed by DIPEA (3.4mL, 19.5mmol). An additional alliquot of dry DCM (4mL) is added. The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (100mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to provide 5.2g of thick brownish gum. This material is purified utilizing an ISCO Companion with a 120g cartridge of silica. The gradient is 2 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 30% EtOAc over 10 column volumes then to 100% EtOAc over 12 column volumes. 170mL fractions of UV active eluent are collected. Fractions 13 through 23 are combined and evaporated *in vacuo*. This yields a foamy material (0.42g, 26%).

Example 374

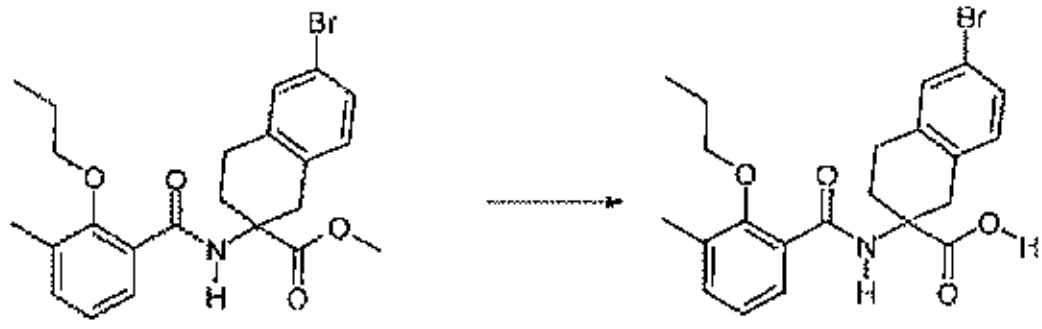


373 374

2-(2-Propoxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (374)

A 100mL round bottom flask which contains 6-bromo-(2-hydroxoxy-3-methyl-benzoylamino)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (373, 0.39g, 0.932mmol) and a stirring bar is charged with dry DMF (10mL). Stirring is initiated. K_2SO_4 (0.258g, 1.86mmol), KI (1mg, 6 μM), and 1-bromopropane (0.2mL, 2.24mmol) are added in turn. The reaction flask is immersed in an oil bath and fitted with a reflux condenser. The oil bath is heated to 79°C. The reaction is stirred for 2h at this temperature then the oil bath is turned off. After 16h at ambient temperature, heating is reinitiated at 53°C for an additional hour. Analysis by tlc (silica, 1:1 EtOAc:Heptanes), indicates consumption of starting material and appearance of a spot with a slightly lower R_f. The reaction is again allowed to cool to ambient temperature and filtered through a bed of Celite. The resulting solution is diluted with EtOAc (60mL) and washed repeatedly with brine (4 x 40mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to a constant weight yields light yellow oil (0.42g, 98%).

Example 375



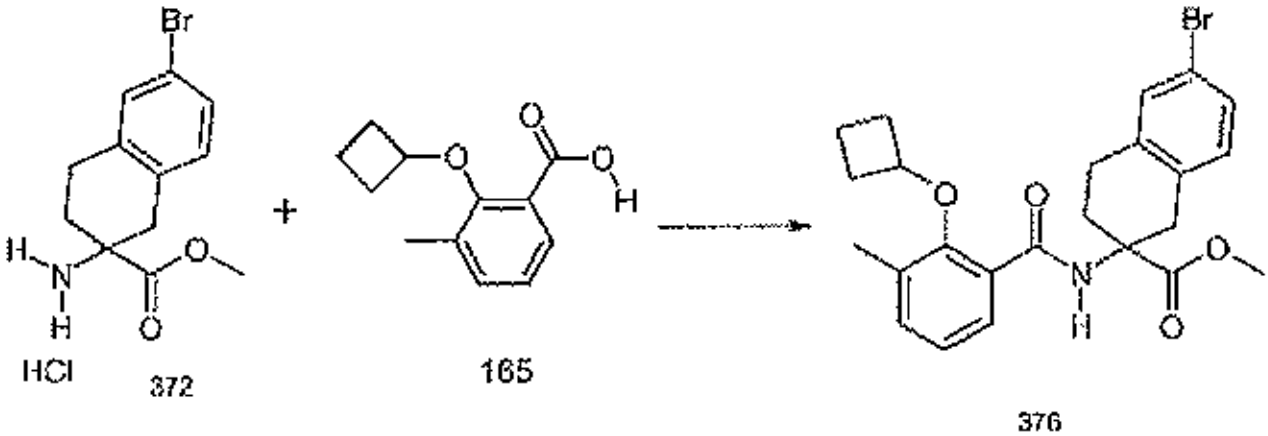
374 375

2-(2-Propoxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (375)

50mL flask containing the 6-bromo-2-(2-propoxy-3-methyl-benzoylamino)-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester (374, 0.34g, 0.74mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (77mg, 1.44mmol). After 16hours, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel that contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.30g, 91%).

^{1}H NMR (300 MHz, DMSO-d6): δ 0.82 (t, 3H), 1.43 (m, 1H), 1.96-2.08 (m, 1 H), 2.19 (s, 3 H), 2.38-2.91 (m, 1 H), 2.73-2.91 (m, 2 H), 3.02-3.38 (m, 5 H), 3.58-3.64 (m, 3 H), 7.03 – 7.09 (m, 2 H), 7.27 – 7.36 (m, 3 H), 8.36 (s, 1H), 12.56 (bs, 1H).
LC/MS m/z = 448.10.

Example 376

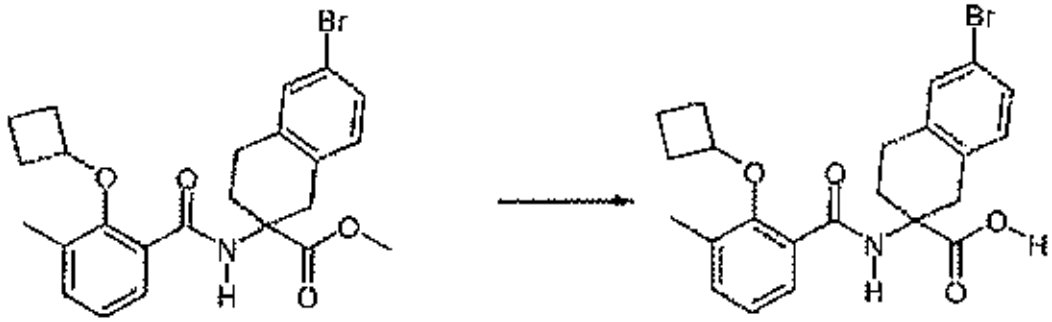


2-(2-cyclobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (376)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoiic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg,

2.17mmol) is added. 2-Amino-6-bromo-1,2,3,4-tertrahydonaphtahalene-2-carboxylic acid methyl ester; hydrochloride salt (372, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1N, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.18g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions are collected. Fractions 9 through 15 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.81g, 79%).

Example 377



376 377

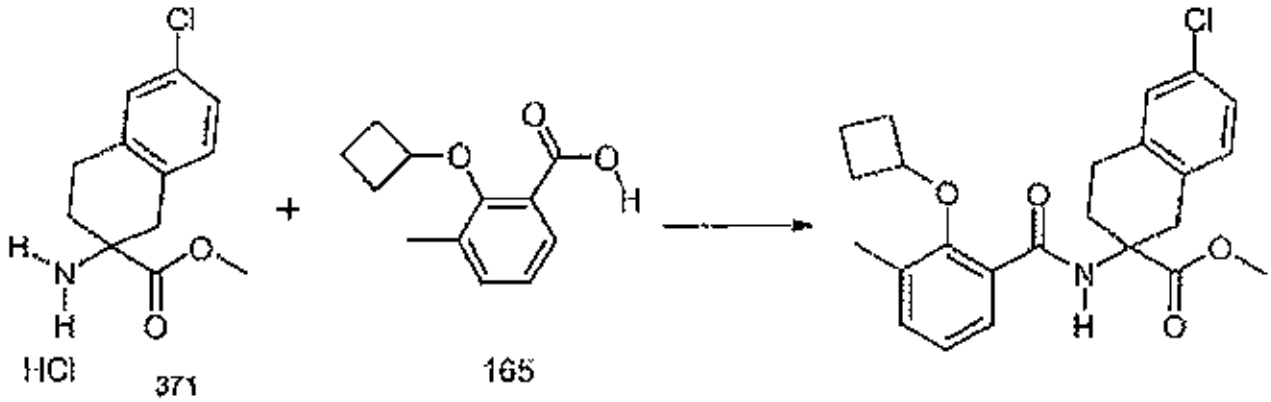
2-(2-cylobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (377)

A 50mL flask containing the 2-(2-cylobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (376, 0.44g, 0.93mmol) is charged with 1,4-dioxane (9mL) and MeOH (9mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.5mL) is added followed by the LiOH monohydrate (173mg, 4.12mmol). After 64h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The

aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.40g, 98 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.17-1.34 (m, 1H), 1.39-1.57 (m, 1H), 1.78-2.16 (m, 4 H), 2.21 (s, 3 H), 2.37-2.42- (m, 1 H), 2.74-2.98 (m, 2 H), 3.15-3.27 (m, 3 H), 4.34 (m, 1 H), 7.01 – 7.11 (m, 2 H), 7.25 – 7.35 (m, 3 H), 8.34 (s, 1H), 12.53 (bs, 1H).
LC/MS m/z = 460.05

Example 378

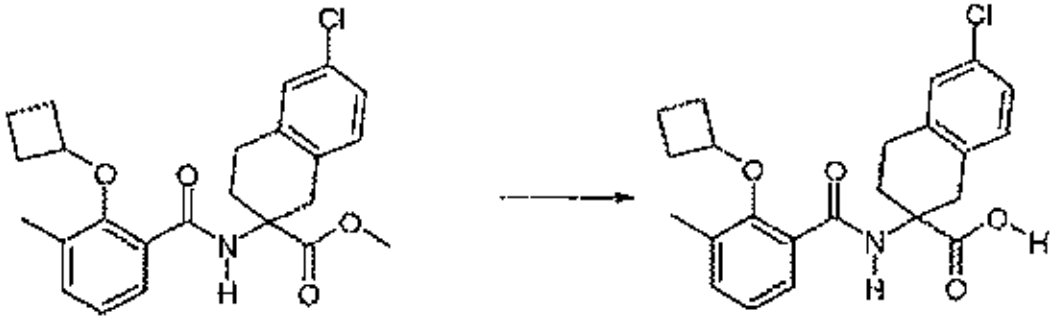


2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (375)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoiic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg, 2.17mmol) is added. 2-Amino-6-chloro-1,2,3,4-tertrahydonaphtahalene-2-carboxylic acid methyl ester, hydrochloride salt (371, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1 N, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.18g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient

to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions of UV active eluent are collected. Fractions 2 through 11 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.65g, 70%).

Example 379



378 379

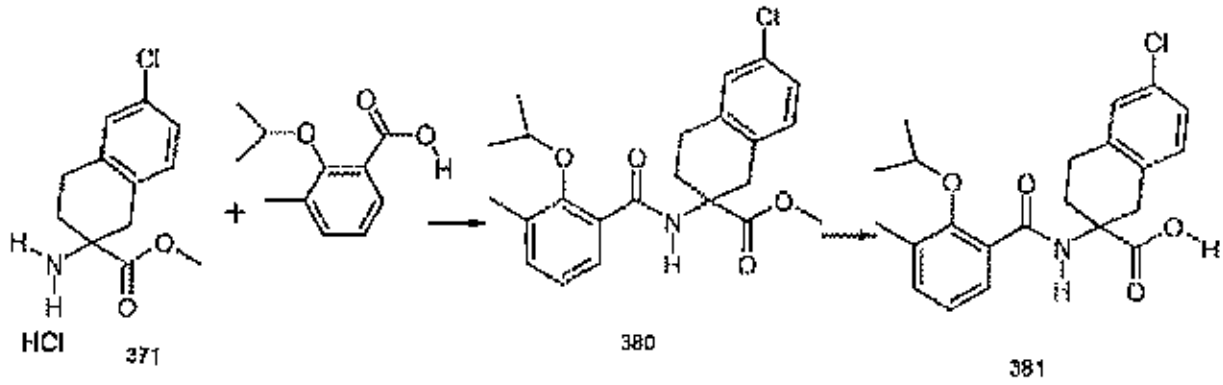
2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (379)

A 50mL flask containing the 2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (378, 0.42g, 0.98mmolg) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (103mg, 2.45mmol). After 260h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material has been completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.38g, 93 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.08-1.17 (m, 1H), 1.21-1.36 (m, 1H), 1.78-2.13 (m, 4 H), 2.21 (s, 3 H), 2.37-2.43- (m, 1 H), 2.77-2.98 (m, 2 H), 3.17-3.37 (m, 3 H), 4.34 (m, 1 H), 7.02 (dd, 1H), 7.10 – 7.35 (m, 5 H), 8.35 (s, 1H), 12.57 (bs, 1H).

LC/MS m/z = 414.15

Examples 380 and 381



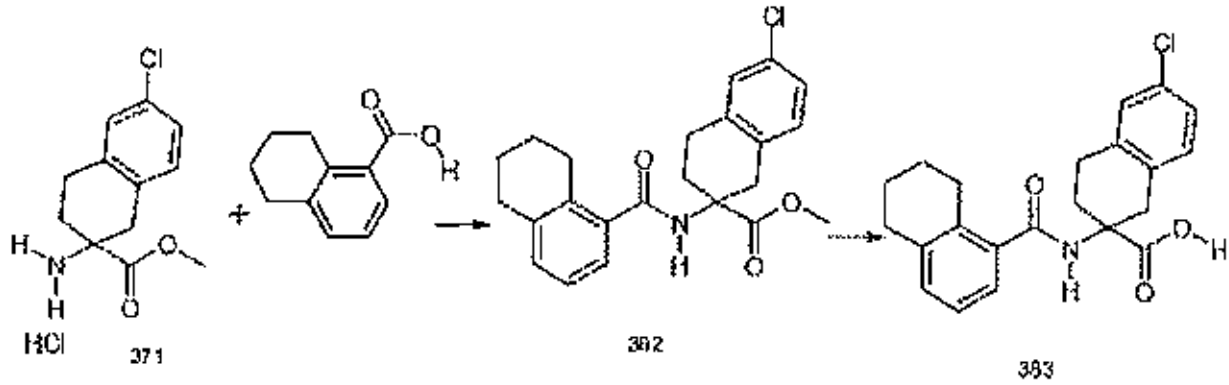
2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (380)

2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (381)

2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (381) is synthesized according to the procedure for product 379 above excepting that 2-isopropoxy-3-methylbenzoiic acid 2-cyclobutoxy-3-methylbenzoic acid is substituted for 2-cyclobutoxy-3-methylbenzoiic acid in the amide bond formation step. Yield = 94% for step one. Step 2 yields white solid material (0.43g, 81 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 0.98 (d, 3H), 1.03 (d, 3H), 1.97-2.07 (m, 1 H), 2.21 (s, 3 H), 2.38-2.42- (m, 1 H), 2.76-2.93 (m, 2 H), 3.08-3.41 (m, 3 H), 4.19 (m, 1 H), 7.03 (dd, 1H), 7.11 – 7.20 (m, 3 H), 7.27 – 7.35 (m, 2 H), 8.35 (s, 1H), 12.52 (bs, 1H).
LC/MS m/z = 414.15

Examples 382 and 383

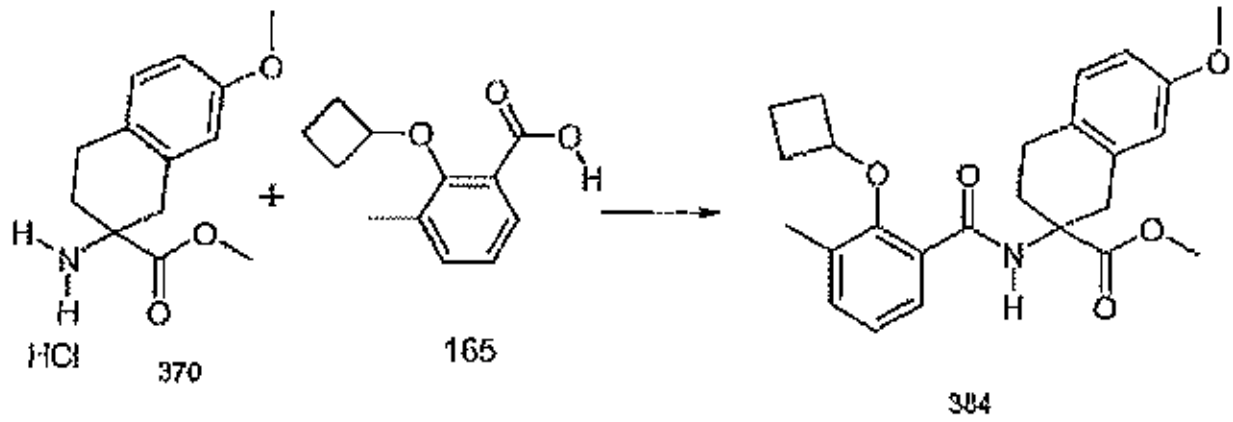


6-Chloro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydro-naphthalene-2-carboylic acid (383)

6-Chloro-2-[(5,6,7,8-tetrahydronaphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (383) is synthesized according to the procedure for product 379 above excepting that 5,6,7,8-tetrahydro-1-naphthalene carboxylic acid is substituted for 2-cyclobutoxy-3-methylbenzoic acid in the amide bond formation step. Yield = 83 % for step one. Step 2 yields a white solid material (0.42g, 99 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.56-1.78 (m, 4 H), 1.88-2.08 (m, 3 H), 2.33-2.41 (m, 1 H), 2.48-3.07 (m, 8 H), 6.92 (dd, 1H), 7.03 – 7.18 (m, 5 H), 8.72 (s, 1H), 12.49 (bs, 1H). LC/MS m/z = 384.11

Example 384

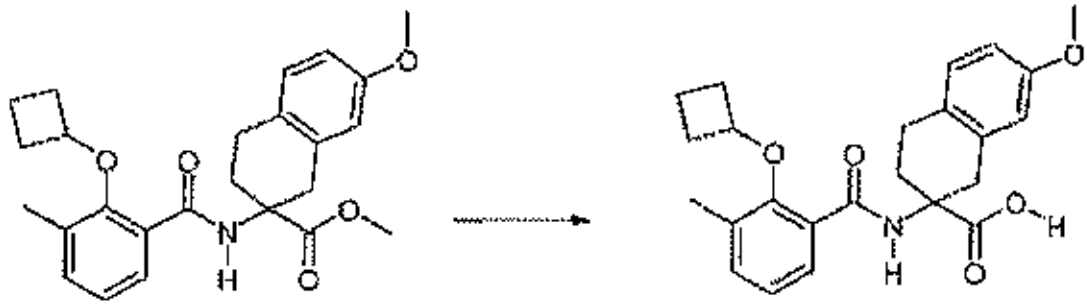


6-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester (384)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg, 2.17mmol) is added. 2-Amino-7-methoxy-1,2,3,4-tetrahydonaphthalene-2-carboxylic acid methyl ester hydrochloride salt (370, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1N, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to

provide 1.2g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions of UV active eluent are collected. Fractions 9 through 15 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.86g, 83%).

Example 385



384 385

2-(2-cyclobutoxy-3-methyl-benzoylamino)-6-methoxy-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (385)

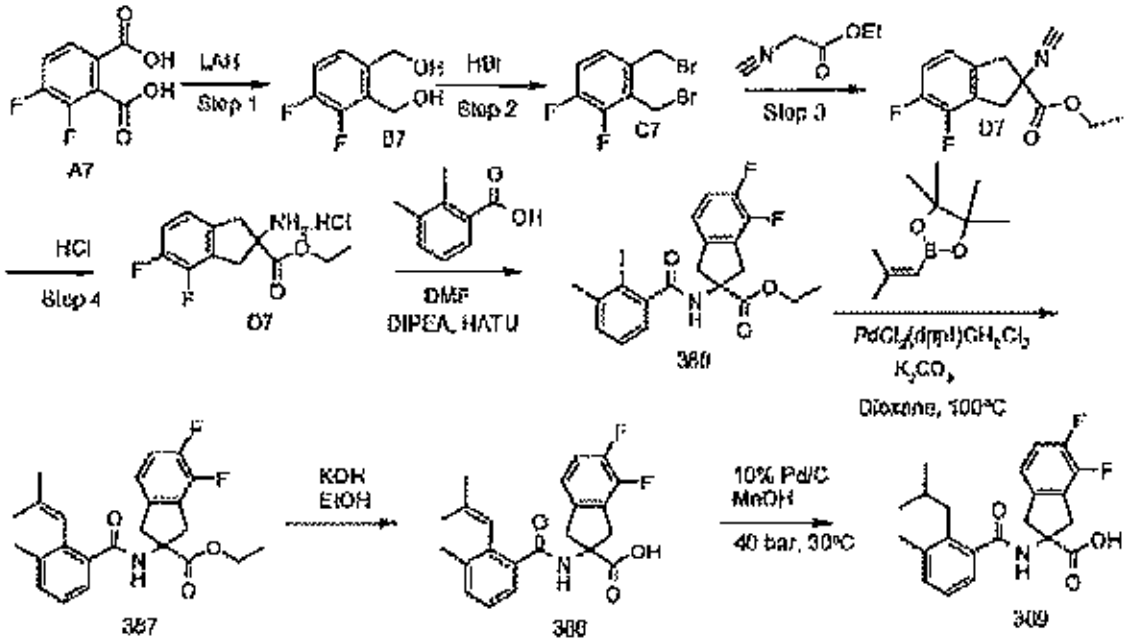
A 50mL flask containing the 2-(2-cyclobutoxy-3-methyl-benzoylamino)-6-methoxy-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (384, 0.45g, 1.06mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (111mg, 2.65mmol). After 37h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material has been completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.43g, 99 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.18-1.33 (m, 1H), 1.41-1.57 (m, 1H), 1.79-2.11 (m, 4 H), 2.21 (s, 3 H), 2.37-2.43~ (m, 1 H), 2.63-2.91 (m, 2 H), 3.07-3.37 (m, 3 H), 3.41 (s, 3H), 4.37

(m, 1 H), 6.69-6.72 (m, 2H), 7.00-7.05 (m, 2H), 7.26 – 7.35 (m, 2H), 8.31 (s, 1H), 12.49 (bs, 1H).

LC/MS m/z = 410.15

Examples 386 - 389



(2,3-Difluoro-6-hydroxymethyl-phenyl)-methanol (A7)

To a suspension of LAH (6.2g, 0.163mol) in dry THF (100 ml) is added a solution of compound 3,4-difluoro-phthalic acid (15g, 0.074mol) in THF (75mL), drop wise at 0°C. The resulting mixture is refluxed for 3h. After 3h the reaction mixture is cooled and quenched with saturated Na_2SO_4 solution. Then the reaction mass is filtered through a pad of celite and the bed is washed thoroughly with MeOH. The combined filtrate is concentrated to yield a crude product that is purified by column chromatography (silica, 5% MeOH in DCM). Combination of appropriate fractions followed by removal of the solvent yields white solid (7g, 54.2%).

1,2-Bis-bromomethyl-3,4-difluoro-benzene (B7)

A suspension of (2,3-difluoro-6-hydroxymethyl-phenyl)-methanol (8g, 0.046mol) in 80mL aq. HBr (47%) is stirred at 80°C for 3h. After complete consumption of starting material, the reaction mixture is cooled to RT and extracted with EtOAc. The combined organic layer is washed with brine, dried and concentrated to give brown solid (13g, 94.2%) that is used without further purification.

4,5-Difluoro-2-Isocyano-indan-2-carboxylic acid ethyl ester: (C7)

A mixture of compound 1,2-bis-bromomethyl-3,4-difluoro-benzene (8g, 0.027mol), ethyl isocyanoacetate (3.01g, 0.0266mol), K_2CO_3 (22.07g, 0.159mol) and tetrabutylammonium hydrogen sulphate (5.45g, 0.016mol) in ACN (200 ml) is refluxed for overnight. After complete consumption of starting material the reaction mixture is cooled to RT and ACN is removed under reduced pressure. Water (300 mL) is added to the crude mass and then extracted with EtOAc (3x250 mL). The combined organic extracts are washed with water, dried and concentrated to give a crude product. The crude product is purified by column chromatography (silica, 3% EtOAc in hexane) and the the solvent removed to give a viscous liquid (1.6 g, 23.7%).

4,5-Difluoro-2-amin-indan-2-carboxylic acid ethyl ester hydrochloride salt (D7)

A stirred solution of 4,5-difluoro-2-isocyano-indan-2-carboxylic acid ethyl ester (6g, 0.0237mol) in EtOH (100mL) is immersed in an ice water bath and allowed to cool. After cooling, concentrated HCl (5 ml) is added. The reaction mixture is removed from the ice-water bath, allowed to come to ambient temperature and stirred at for 3h. Then the reaction mixture is concentrated, diluted with water and extracted with ether (2x50 mL). The organic layer is discarded and the aqueous layer is cooled and pH is adjusted to 9-10 using aq. ammonia solution. The resulting solution is extracted with EtOAc (3x100 mL). The combined extracts are washed with water, dried and concentrated to give a viscous mass (4.5 g, 78%). This crude mass is immediately cooled to 5°C and acidified with methanolic HCl and concentrated to give 4,5-difluoro-2-amin-indan-2-carboxylic acid ethyl ester hydrochloride salt.

<u>4,5-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (386):</u>

To a solution of 2-iodo-3-methyl-benzoic acid (1.31g, 5mmol), 2-amino-4,5-difluoro-indan-2-carboxylic acid ethyl ester HCl salt (D7, 1.38g, 5mmol), HATU [O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 3.8g, 10mmol) in anhydrous DMF (20mL) is added DIPEA (N, N-diisopropylethylamine, 3.3mL, 15mmol). The resulting solution is stirred at room temperature for two days. After the removal of DMF *in vacuo*, the residue obtained is dissolved in ethyl acetate (200mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

The obtained residue is purified by flash column chromatography (24g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (386) as white solid (1.93g, 79%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 7.13-7.30(m, 3H), 7.52(m, 2H)
LC/MS (ES+) m/z = 486.1

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (387):

To a solution of 6-(4,5-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (386) (2.55g, 5.25mmol) and and 2-methyl-1-propenyl boronic acid pinacol ester (364mg, 10.5mmol) in dioxane (100mL) is added dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (350mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (7.87mL, 15.75mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously for 6h. Reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (387) as light brown solid (1.24g, 57%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 3H), 7.52(m, 2H)
LC/MS (ES+) m/z = 414.47

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (388):

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (387) (650mg, 1.57mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (4mL). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue obtained is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The solid precipitate is collected via filtration, dried under vacuum, and then purified on an HPLC. The desired product (388) is obtained as white solid (440.0mg, 73%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 5H)

LC/MS (ES+) m/z = 386.3

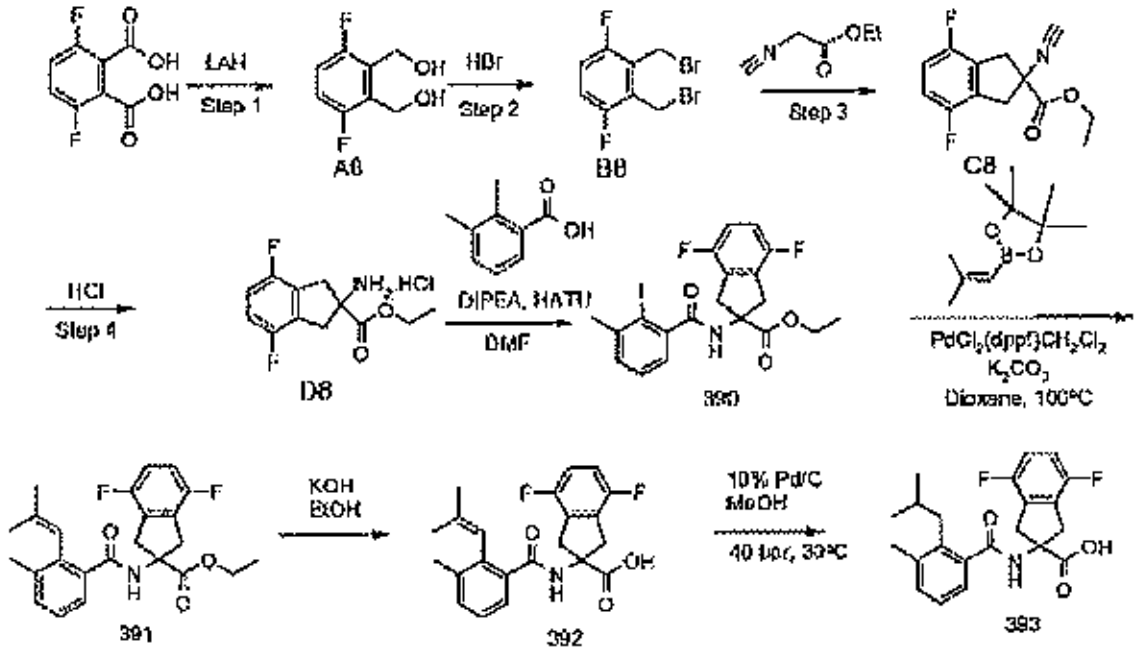
<u>4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (389)</u>

A solution of 4,5-difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (388) (220mg, 0.57mmol) in methanol (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar and 30°C using the Thales nanotechnology H-Cube for 24 hours. The methanol is concentrated to dryness *in vacuo* to give the product (389) as white solid powder.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.77(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.31(d, 2H), 3.48(d, 2H), 7.00-7.39(m, 5H)

LC/MS (ES+) m/z = 388.3

EXAMPLES 390-393



2-Amino-4,7-difluoro-indan-2-carboxylic acid ethyl ester HCl salt was prepared from

3,6-difluoro-phthalic acid as indicated by the scheme above regarding A7-D7 utilizing the same procedures as for the synthesis of 2-amino-4,5-difluoro-inden-2-carboxylic acid ethyl ester HCl salt.

4,7-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (390):

To a solution of 2-iodo-3-methyl-benzoic acid (1.31g, 5mmol), 2-amino-4,7-difluoro-indan-2-carboxylic acid ethyl ester HCl salt (1.38g, 5mmol), HATU [O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 3.80g, 10mmol) in anhydrous DMF (20mL) is added DIPEA (N, N-diisopropylethylamine, 3.3mL, 15mmol). The resulting solution is stirred at RT for two days. After the removal of DMF *in vacuo*, the residue obtained is dissolved in EtOAc (200mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue is purified by flash column chromatography (40g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (390) as white solid (1.83g, 75%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 7.13-7.30(m, 5H)
LC/MS (ES+) m/z = 486.1

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (391):

To a solution of 4,7-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (390) (451mg, 1mmol) and 2-methyl-1-propenyl boronic acid pinacol ester (364mg, 2mmol) in dioxane (20mL) was added dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct (65mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (1.5mL, 3mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously for 4h. The reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (391) as light brown oil (150mg, 36%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 5H)

LC/MS (ES+) m/z = 414.47

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (392):

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (391) (133mg, 0.32mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution was added 5M KOH (2ml). The reaction mixture was stirred at RT. After concentration *in vacuo*, the residue obtained is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 100mL EtOAc. The organic phases were collected, concentrated to dryness, and then the resulting residue is purified on an HPLC. The desired product (392) is obtained as white solid (38mg, 28%).

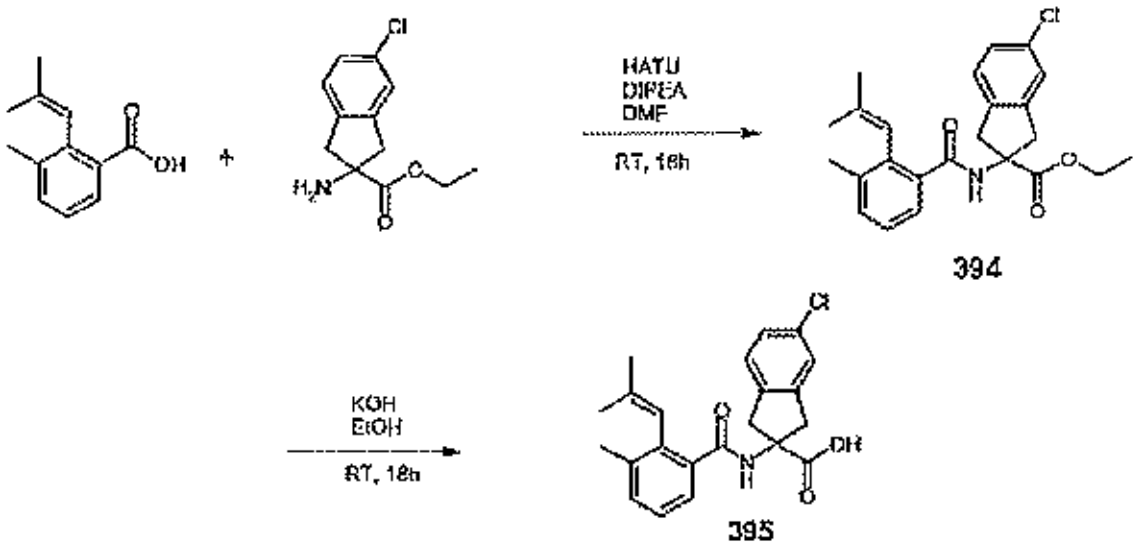
^{1}H NMR (DMSO-d6, 300MHz): δ 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 5H)
LC/MS (ES+) m/z = 386.3

4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (393)

A solution of 4,7-difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (392) (82mg, 0.21mmol) in MeOH (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar and 30°C using the Thales nanotechnology H-Cube for 5h. The MeOH is concentrated to dryness *in vacuo* to give the product (393) as white solid powder.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.72(m, 1H), 2.28(s, 3H), 2.61(d, 2H), 3.42(d, 2H), 3.51(d, 2H), 6.93-7.30(m, 5H)
LC/MS (ES+) m/z = 388.3

EXAMPLES 394-395



5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (394):

To a solution of 3-methyl-2-(2-methyl-propenyl)-benzoic acid (95mg, 0.50mmol), 5-chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (120mg, 0.5mmol), HATU [O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 380mg, 1mmol) in anhydrous DMF (10mL) is added DIPEA (N, N-diisopropylethylamine, 0.25mL, 1.5mmol). The resulting solution is stirred at RT for 18h. After the removal of DMF *in vacuo*, the resulting residue is dissolved in EtOAc (200mL) and washed with saturated$NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue is purified by flash column chromatography (40g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (394) as white solid (120mg, 58%).

^{1}H NMR (d-DMSO, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 6H)
LC/MS (ES+) m/z = 411.93

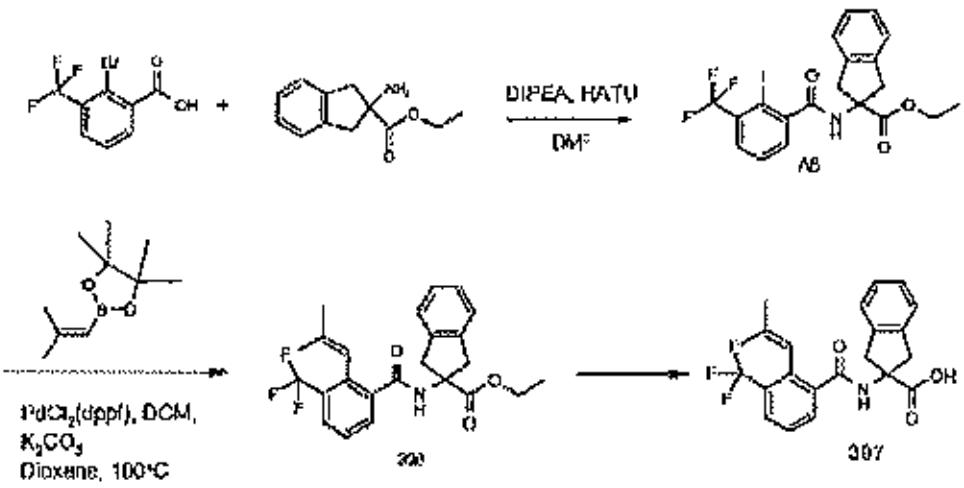
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (395):

5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (394) (120mg, 0.3mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution is added 5M KOH (2mL). The reaction mixture is stirred at RT overnight. After

concentration *in vacuo*, the resulting residue is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 100mL EtOAc. The organic phases are collected, concentrated to dryness, and then the resulting residue is purified on an HPLC. The desired product (395) is obtained as white solid (73mg, 63%).

^{1}H NMR (d-DMSO, 300MHz): δ 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 6H)
LC/MS (ES+) m/z = 383.88

EXAMPLES 394-395



2-(2-Iodo-3-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (A8):

To a solution of 2-bromo-3-(trifluoromethyl) benzoic acid (5g, 18.59mmol), 2-amino-indan-2-carboxylic acid ethyl ester (3.82g, 18.59mmol), HATU (14.14g, 37.19mmol) in anhydrous DMF (75mL) is added DIPEA (6.15mL, 37.19mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the resulting residue is dissolved in EtOAc (300mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-50% ethyl acetate in heptane) to give a pure product (A8) as a light brown solid (4.9g, 58%).

^{1}H NMR (d-DMSO, 300MHz): 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), .12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)

LC/MS (ES+) m/z = 455.1

2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (396)

To a solution of 42-(2-Iodo-3-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (A8) (500mg, 1.10mmol) and 2-methyl-1-propenyl boronic acid pinacol ester (400mg, 2.20mmol) in dioxane (20mL) is added dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium (II) DCM adduct (71.8mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (1.65mL, 3.30mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously overnight. Reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (396) as light brown oil (100mg, 21%).

^{1}H NMR (d-DMSO, 300MHz): 1.10 (t, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), .12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)
LC/MS (ES+) m/z = 431.27

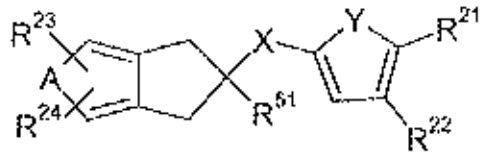
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid (397):

2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (2) (100mg, 0.32mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution is added 5M KOH (2mL). The reaction mixture is heated to reflux and stirred for 1h. After concentration *in vacuo*, the resulting residue is dissolved in water (10mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 50mL ether (3X). Organic phases are collected, concentrated to dryness, then the resulting residue is purified on an HPLC. The desired product (397) is obtained as white solid (40.0mg, 43%).

^{1}H NMR (d-DMSO, 300MHz): 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)
LC/MS (ES+) m/z = 403.13

What is claimed is:

1. A compound of the formula Ia



wherein:

A is CH=CH or S;

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro when A is S;

X is N(H)C=O, $N(H)S(O)_2$, C=ON(H), or $S(O)_2N(H)$;

Y is $N(R^{11})$, S, O, $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, or fused optionally substituted 5-7 membered carbocyclyl;

R^{11} is hydrogen, (C_1-C_{10})-alkyl, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_1-C_{10})-alkyl-$S(O)_m$-, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, (C_1-C_{10})-alkylamino, or di((C_1-C_{10})-alkyl)amino;

R^{12} is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_6)-cycloalkyloxy, (C_3-C_{10})-cycloalkenyloxy, (C_3-C_6)-cycloalkyl, (C_3-C_{10})-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], (C_3-C_6)-cycloalkyl(C_1-C_4)-alkyloxy, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_2-C_{10})-alkenyloxy, (C_1-C_{10})-alkyl-S-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, or nitro;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

R^{14} is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro, provided that the total number of C, N, O and S atoms which is present in R^{14} does not exceed 4;

$R^{15}$is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})- alkenyl, (C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], hydroxy-(C_1-C_{10})-alkyl-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]((C_1-C_{10})-alkyl)amino or nitro;

R^{21} is hydrogen when Y is $C(R^{12})$=$C(R^{13})$, N=$C(R^{14})$, or $C(R^{15})$=N, and is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{21} does not exceed 4;

R^{22} is hydrogen, halogen, (C_1)-alkyl when Y is $C(R^{12})$=$C(R^{13})$, N=$C(R^{14})$, or $C(R^{15})$=N, or is hydrogen, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{22} does not exceed 4;

R^{51} is COOH or CONH(R^{53});

R^{53} is R^{55}-SO_2- or tetrazolyl;

R^{55} is (C_1-C_4)-alkyl or phenyl optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-sulfonyl and cyano; and

m is 0, 1, or 2;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

2. The compound according to claim 1 wherein

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, or (C_1-C_4)-alkyloxy;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, or (C_1-C_4)-alkyl when A is S;

X is N(H)C=O, N(H)S$(O)_2$, or C=ON(H);

Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$, or fused optionally substituted 5-6 membered carbocyclyl;

R^{12} is (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_4-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkenyl, (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], (C_3)-cycloalkyl(C_1)-alkyloxy, (C_3-C_4)-alkyloxy, (C_3)-alkenyloxy, (C_1-C_3)-alkyl-S-, or (C_3)-alkylcarbonyl-, phenyl;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

$R^{15}$is (C_1-C_6)-alkyl, (C_2-C_6)- alkenyl, or [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1)-alkyl)amino;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{51} is COOH;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

3. The compound according to claim 1 wherein

A is CH=CH.

4. The compound according to claim 1 wherein

X is N(H)C=O.

5. The compound according to claim 1 wherein

Y is $C(R^{12})=C(R^{13})$.

6. The compound according to claim 1 wherein

Y is $C(R^{15})=N$.

7. The compound according to claim 1 wherein

Y is fused optionally substituted 5-6 membered carbocyclyl.

8. The compound according to claim 1 wherein

R^{21} is hydrogen.

9. The compound according to claim 1 wherein

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$.

10. The compound according to claim 1 wherein

R^{51} is COOH.

11. The compound according to claim 1 selected from:
2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid
2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid,
2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid;
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid
5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,

5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,

2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid,

2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid,

5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid,

5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid,

2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,

2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid,

2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,

2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid,

2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,

2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,

5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid,

5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,

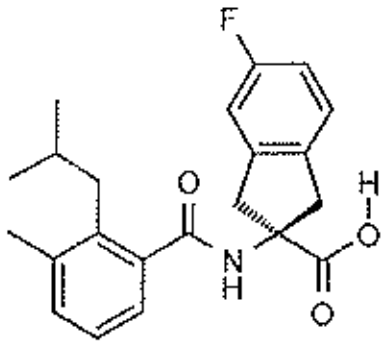
5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,

2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid,
2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid,
2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid,
2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid,
2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid,
2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid,
4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5-Chloro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid,
2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide,
2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,

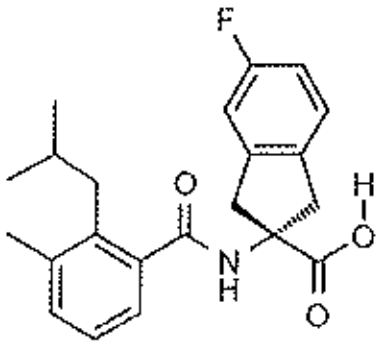
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide, and
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid, or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

12. The compound according to claim 1 of the following structure



13. The compound according to claim 1 of the following structure



14. A pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to claim 1 and at least one of a pharmaceutically acceptable excipient and pharmaceutically acceptable carrier.

15. Use of the compound according to claim 1 for the manufacture of a medicament for the treatment of a patient suffering from, or subject to, a physiological condition that can be ameliorated by the administration of a pharmaceutically effective amount of an inhibitor of a CXCR5 receptor to the patient.

16. The use according to claim 15 wherein the physiological condition is an inflammatory disease.

17. The use according to claim 15 wherein the physiological condition is rheumatoid arthritis.

18. The use according to claim 15 wherein the physiological condition is asthma.

19. The use of claim 15 wherein with the administering of the compound of claim 1 and another therapeutic agent is administered at the same time or sequentially.

20. A process for producing a compound according to claim 1 as described herein.