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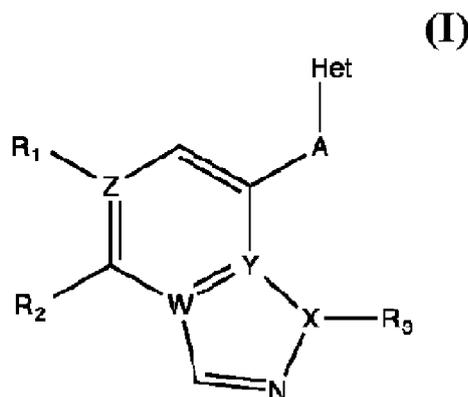
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(54) Title: ANTAGONISTS ACTING AT MULTIPLE PROSTAGLANDIN RECEPTORS FOR THE TREATMENT OF INFLAMMATION



(57) Abstract: Compounds (I), processes for their preparation, pharmaceutical compositions containing such compounds and their use in treating therapeutic conditions, in particular conditions mediated by the action of ligands on the FP, DP, EP₁, EP₄, IP, DP and TP prostaglandin (PG) receptors thereby providing a general anti-inflammatory response. (I)



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**ANTAGONISTS ACTING AT MULTIPLE PROSTAGLANDIN RECEPTORS
FOR THE TREATMENT OF INFLAMMATION**

By: Jose L. Martos, David F. Woodward, Jenny W. Wang, Steven Dabbs, and Jussi J. Kangasmetsa

5 **Cross-reference to related applications**

This application is a non-provisional application which claims the benefit of US provisional application 61/931,756, entitled "Antagonists Acting At Multiple Prostaglandin Receptors For The Treatment Of Inflammation" and filed on January 27, 2014 with docket number 19358PROV (AP), and which is incorporated by reference
10 herein in its entirety and serves a basis for a benefit and/or priority claim for the present application.

Field of the Invention

This invention relates to compounds, processes for their preparation, pharmaceutical compositions containing such compounds and to their use in treating
15 therapeutic conditions, in particular their use in the treatment of conditions mediated by the action of ligands for the FP, DP, EP₁, EP₂, EP₃, EP₄, IP, DP₁, FP and TP prostaglandin (PG) receptors. The present compounds, which in some embodiments can be antagonists, have the general structure as shown below and act at different prostaglandin receptors to thereby provide a general anti-inflammatory response.

20 **Background of the Invention:**

There are four G-protein-coupled receptors (GPCRs) which interact with the ligand prostaglandin E₂ which are designated subtypes EP₁, EP₂, EP₃ and EP₄. The EP₁ receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE₂. PGE₂ also has affinity for the other EP receptors (types EP₂, EP₃ and EP₄). The EP₁
25 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion.

Prostaglandin E₂ (PGE₂) exerts pain and pain related entities such as allodynia and hyperalgesia through the EP₁, EP₄ and EP₃ receptor subtypes (Woodward et al.

Pharmacol Rev. 63 : 471-538, 2011). Furthermore, it has been shown that in the EP₁ knockout mouse pain-sensitivity responses are reduced by approximately 50%. EP₁ receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury and inhibits mechanical hyperalgesia in a rodent model of post-operative pain. The efficacy of EP₁ receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity has been demonstrated. Thus, selective prostaglandin ligands depending on which prostaglandin EP receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced or absent potential for cardiovascular risk, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, as a result of sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDs and/or COX-2 inhibitors. (See Pub. No. US 2005/0065200, which is hereby incorporated by reference in its entirety, for other diseases that may be treated by EP₄ receptor antagonists).

The TP (also known as TxA₂) receptor is a prostanoid receptor subtype stimulated by the endogenous mediator thromboxane. Activation of this receptor results in various physiological actions primarily incurred by its platelet aggregatory and smooth muscle constricting effects, thus opposing those of prostacyclin receptor activation.

TP receptors have been identified in human kidneys in the glomerulus and extraglomerular vascular tissue. Activation of TP receptors constricts glomerular capillaries and suppresses glomerular filtration rates indicating that TP receptor antagonists could be useful for renal dysfunction in glomerulonephritis, diabetes mellitus and sepsis.

Activation of TP receptors induces bronchoconstriction, an increase in microvascular permeability, formation of mucosal edema and mucus secretion, which are typical characteristic features of bronchial asthma. TP antagonists have been investigated as potential asthma treatments resulting in, for example, orally active Seratrodast (AA-
5 2414). Ramatroban is another TP receptor antagonist currently undergoing phase III clinical trials as an anti-asthmatic compound.

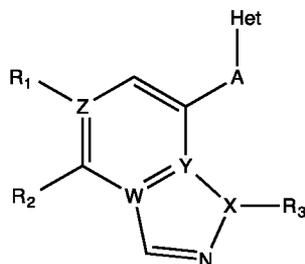
Since the DP₁ receptor may trigger an asthmatic response in certain individuals, compounds that have DP₁ antagonist properties may be useful as anti-asthmatic drugs. (See Pub. No. 2004/0162323, which is hereby incorporated by reference in its entirety,
10 for the disclosure of other diseases and conditions that may be treated with DP antagonists.)

Finally, the FP receptor modulates intraocular pressure and mediates smooth muscle contraction of the sphincter muscles in the gastrointestinal tract and the uterus and contractile smooth muscle of these and other organs. Thus, antagonists of the FP receptor
15 are useful for treating reproductive disorders. (See US Patent No. 6,511,999 which is hereby incorporated by reference in its entirety, for other diseases and conditions that may be treated with FP receptor antagonists.)

As further background for the present invention, see US Published Patent Application 2007/0060596, US patent No. 8,494,424 and US application 13/746,023, all
20 of which are hereby incorporated by reference in their entireties.

Summary of the Invention:

In one aspect, this present invention is directed to compounds of formula I:



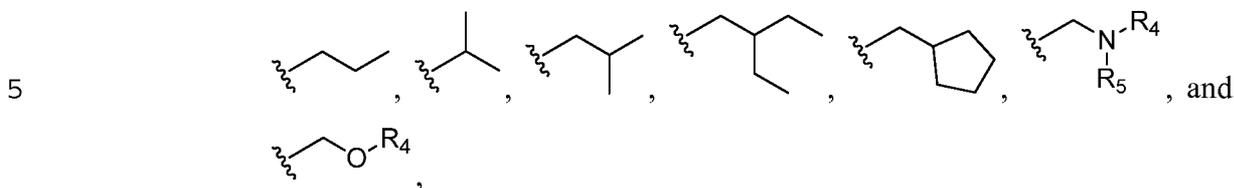
(I)

wherein:

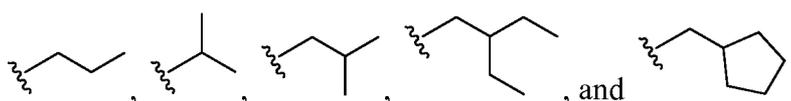
A is selected from the group consisting of C₁-C₃ alkylene and CO;

X is either CH or N, wherein:

when X is CH, R₃ is selected from the group consisting of:



and when X is N, R₃ is selected from the group consisting of:



W and Y are either C or N;

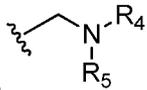
10 Z is either C or N, wherein:

when Z is C, R₁ is selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, CH₂OCH₃, F, Cl, Br, halogen, OCF₃, OCCl₃, OCB₃ and wherein C₁-C₃ alkyl may be optionally substituted by hydroxyl, halogen, amine and functional amines,

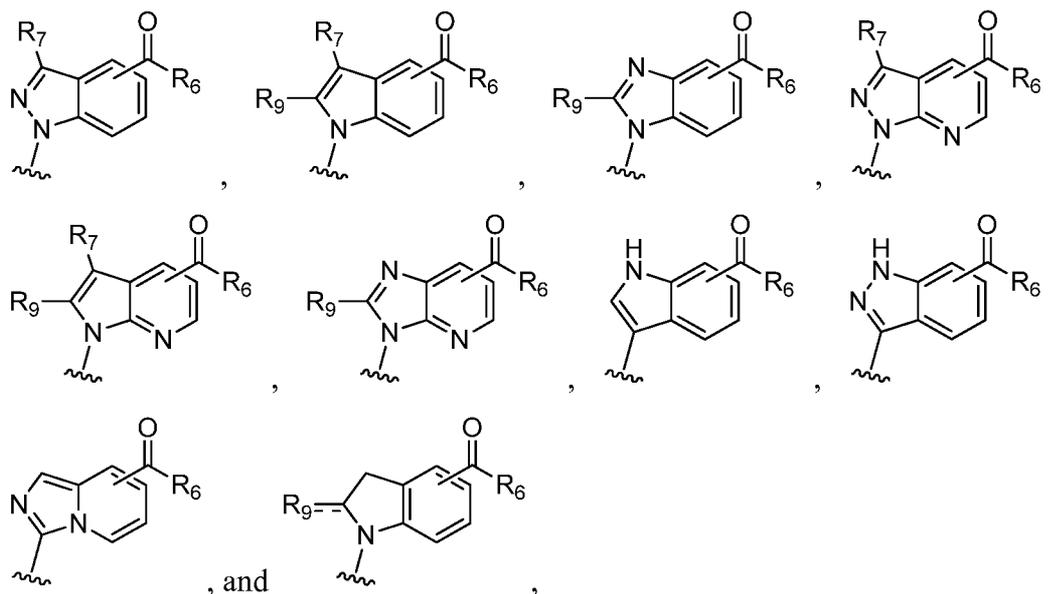
15 and when Z is N, there is no R₁ substituent;

R₂ is selected from the group consisting of H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, CH₂OCH₃, F, Cl, Br, halogen, and OCF₃;

R₄ and R₅ are independently selected from the group consisting of C₁ - C₃ alkyl and

20 substituted C₁ - C₃ alkyl, and when R₃ is , R₄ and R₅ can be joined to form a C₃-C₆ cycloalkyl;

Het is selected from the group consisting of:



5 wherein:

R₆ is selected from the group consisting of OH, OCH₃, OCH(CH₃)₂, and NHSO₂R₈;

R₇ is selected from the group consisting of H, CH₃, CH₂CH₃, OCH₃, CH₂OH, CH₂OCH₃, NH₂, C₁-C₃ alkylamino, and C₁-C₃ dialkylamino;

10 R₈ is selected from the group consisting of C₁-C₃ alkyl and substituted C₁ - C₃ alkyl; and,

R₉ is selected from the group consisting of O, OH, CH₃, halogen and OCH₃ the dashed bond represents the presence of a single or double bond;

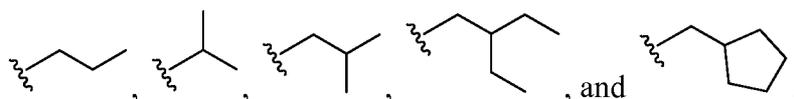
15 and wherein the compounds can be in the form of a tautomer, a racemate, an enantiomer, a diastereomer, or a pharmaceutically acceptable salt.

In some embodiments, A can be C₁-C₃ alkylene, CO or CH₂.

In some embodiments, Z can be C.

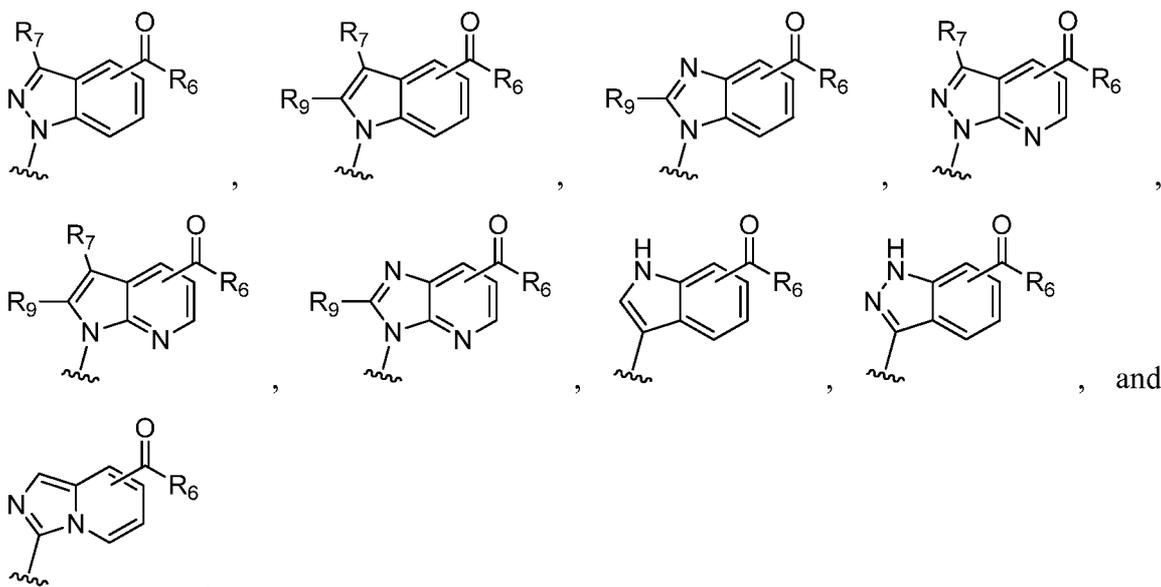
In some embodiments, X can be N.

In some embodiments, R₃ can be selected from group consisting of:

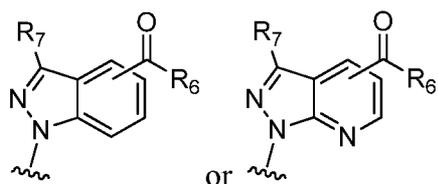


In some embodiments, R₁ can be halogen and R₂ can be H.

5 In some embodiments, Het can be selected from the group consisting of:



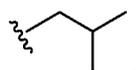
In some embodiments, Het can be:



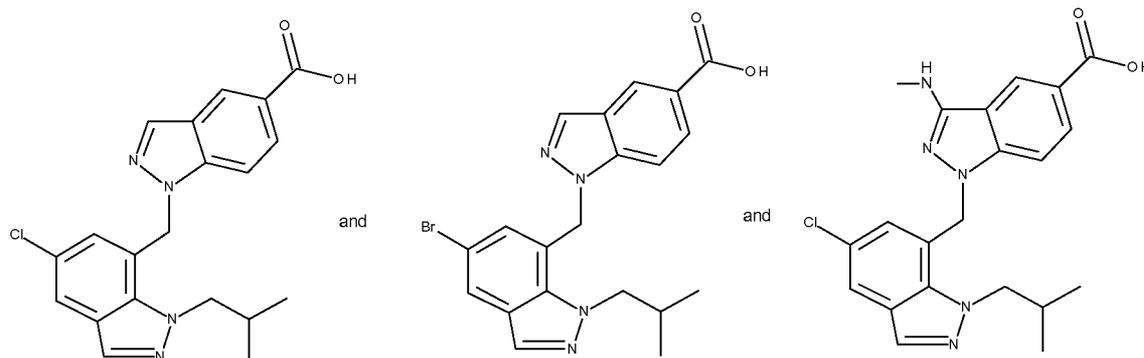
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In some embodiments, Z is C, R₁ is Cl or Br, and R₇ is H or NHCH₃.

In some embodiments, X is N, R₆ is OH and R₃ is:



In another aspect, the invention is directed to a compound selected from the group consisting of:



5 or a pharmaceutically acceptable salt thereof.

In another aspect, the invention is directed to a compound of general formula I as described herein, for use as an antagonist for a prostanoid receptor, or for use in the treatment of a condition mediated by prostanoid receptors.

10 In another aspect, the invention is directed to a compound of general formula I as described herein, for use in the treatment of a condition mediated by an EP₁ receptor.

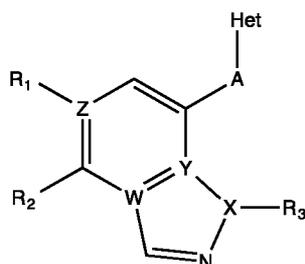
In another aspect, the invention is directed to a compound of general formula I as described herein, for use in the treatment of a condition mediated by an EP₄ receptor.

15 In another aspect, the invention is directed to a method of treating a human suffering from a therapeutic condition mediated by prostanoid receptors, the method comprising administering an effective amount of a compound according to general formula I as described herein.

20 A method of treating a patient suffering from a condition selected from the group consisting of inflammatory pain, neuropathic pain, visceral pain, fibrosis and a condition of the central nervous system mediated by prostanoid receptors, the method comprises administering to said patient an effective amount of a compound of general formula 1.

Some embodiments of the present invention are included in the following paragraphs:

1. A compound of formula (I):



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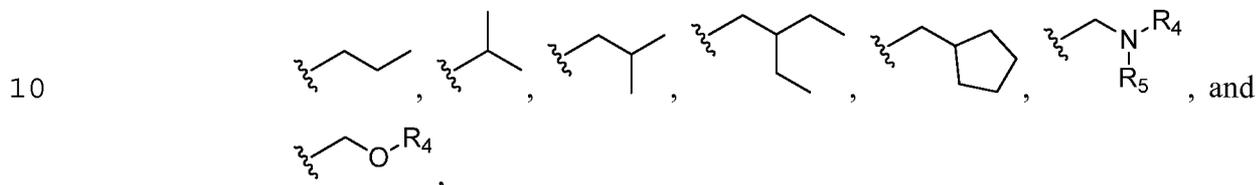
(I)

wherein:

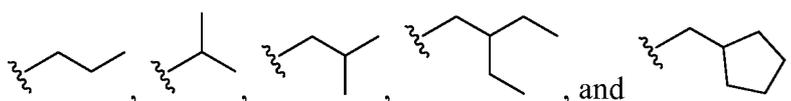
A is selected from the group consisting of C₁-C₃ alkylene and CO;

X is either CH or N, wherein:

when X is CH, R₃ is selected from the group consisting of:



and when X is N, R₃ is selected from the group consisting of:



W and Y are either C or N;

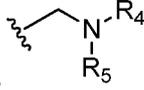
15 Z is either C or N, wherein:

when Z is C, R₁ is selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, CH₂OCH₃, F, Cl, Br, halogen, OCF₃, OCCl₃, OCB₃ and wherein C₁-C₃

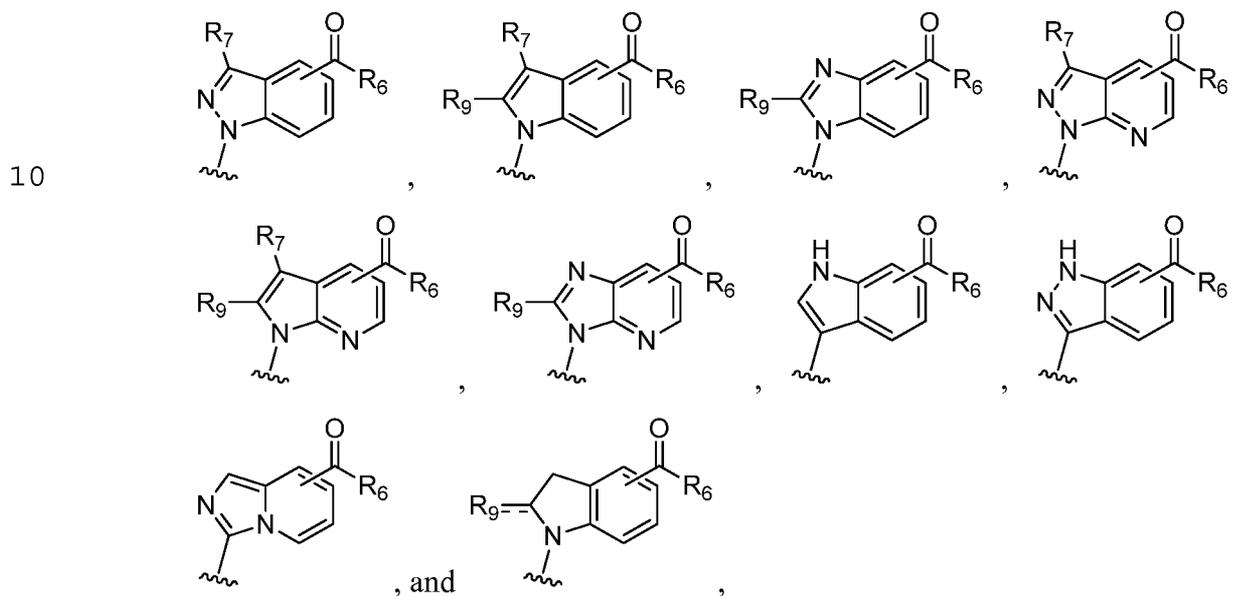
alkyl may be optionally substituted by hydroxyl, halogen, amine and functional amines,

and when Z is N, there is no R₁ substituent;

R₂ is selected from the group consisting of H, C₁–C₃ alkyl, C₁–C₃ haloalkyl,
5 CH₂OCH₃, F, Cl, Br, halogen, and OCF₃;

R₄ and R₅ are independently selected from the group consisting of C₁ – C₃ alkyl and
substituted C₁ – C₃ alkyl, and when R₃ is , R₄ and R₅ can be joined to
form a C₃–C₆ cycloalkyl;

Het is selected from the group consisting of:



wherein:

R₆ is selected from the group consisting of OH, OCH₃, OCH(CH₃)₂, and
15 NHSO₂R₈;

R₇ is selected from the group consisting of H, CH₃, CH₂CH₃, OCH₃, CH₂OH,
CH₂OCH₃, NH₂, C₁–C₃ alkylamino, and C₁–C₃ dialkylamino;

R_8 is selected from the group consisting of C_1 - C_3 alkyl and substituted C_1 - C_3 alkyl; and,

R_9 is selected from the group consisting of O, OH, CH_3 , halogen and OCH_3 the dashed bond represents the presence of a single or double bond;

5 and wherein the compounds may be in the form of a tautomer, a racemate, an enantiomer, a diastereomer, or a pharmaceutically acceptable salt.

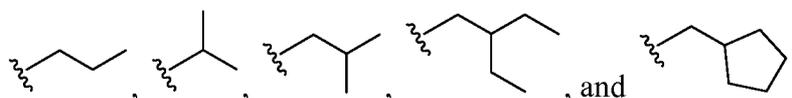
2. The compound of paragraph 1, wherein A is C_1 - C_3 alkyl.

3. The compound of paragraph 1, wherein A is CO.

4. The compound of paragraphs 1 or 2, wherein A is selected from the group
10 consisting of CH_2 , CH_2CH_2 or $CH_2CH_2CH_2$.

5. The compound of paragraphs 1 - 4, wherein Z is C and X is N.

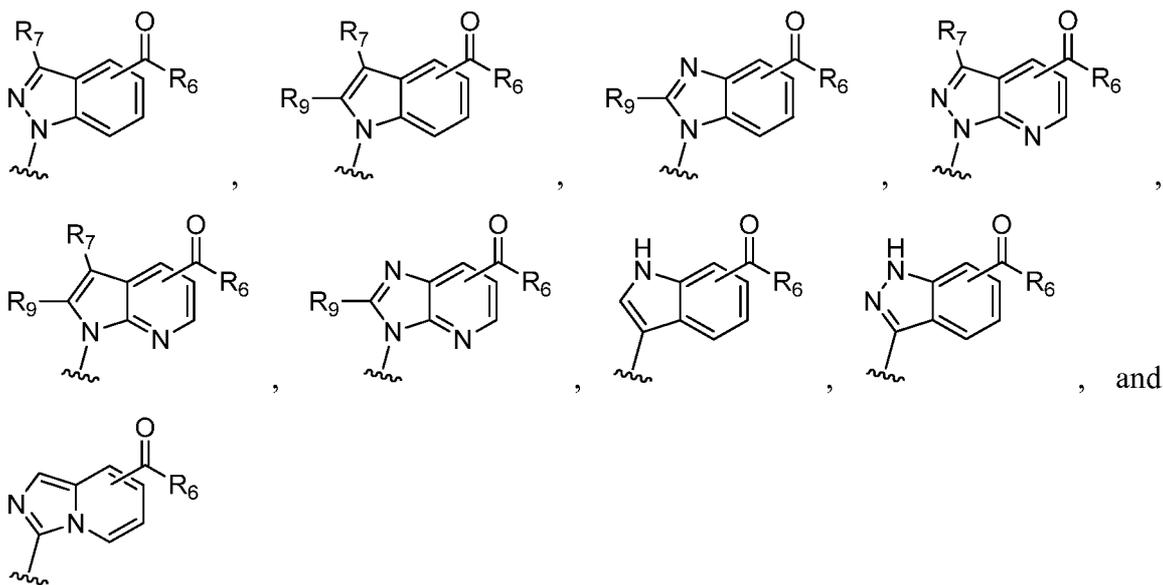
6. The compound of paragraph 5, wherein R_3 is selected from group consisting
of:



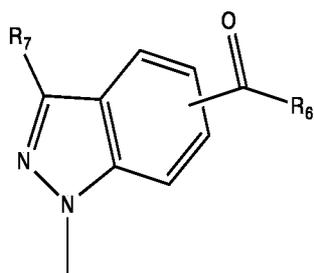
7. The compound of paragraphs 1 to 6, where R_1 is halogen.

8. The compound of paragraphs 1 to 6, wherein R_2 is H.

9. The compound of paragraphs 1 to 8, wherein Het is selected from the group
consisting of:

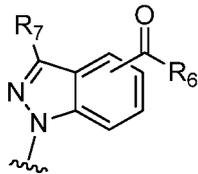


10. The compound of paragraph 9, wherein Het is



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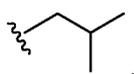
11. The compound of paragraph 9 wherein Het is selected from the group consisting of



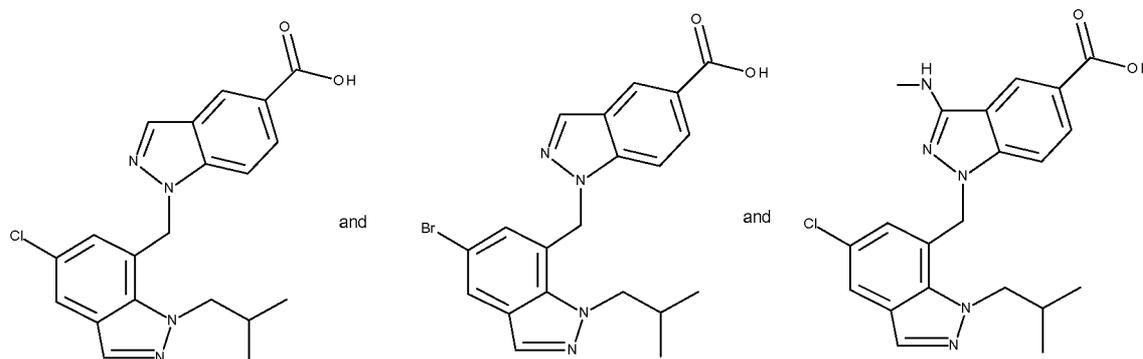
10

12. The compound of paragraph 1 wherein Z is C, R_1 is Cl or Br and R_7 is H or NCH_3 .

13. The compound of paragraph 12 wherein X is N, R_6 is OH and R_3 is



14. The compound of paragraph 13 selected from the group consisting of



5 or a pharmaceutical acceptable salt thereof.

15. The compound of paragraph 1 selected from the group consisting of:

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

1-(5-Fluoro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

10 1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

1-(5-Bromo-1-isopropyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;

15 1-[5-Bromo-1-(2-ethyl-butyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid;

1-[5-Chloro-1-(2-propyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid;

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid;

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;

5 3-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid;

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid;

10 1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-indazole-5-carboxylic acid;

1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic HCl salt;

1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;

15 1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;

3-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]imidazo[1,5-a]pyridine-7-carboxylic acid;

20 1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid;

3-Amino-1-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]indazole-5-carboxylic acid;

1-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]-3-(methylamino)indazole-5-carboxylic acid

or a pharmaceutically acceptable salt thereof.

15. The compound of paragraph 1, for use as an antagonist for a prostanoid receptor.

16. The compound of paragraph 1, for use in the treatment of a condition mediated by prostanoid receptors.

5 17. The compound of paragraph 14, for use in the treatment of a condition mediated by an EP₁ receptor.

18. The compound of paragraph 14, for use in the treatment of a condition mediated by an EP₄ receptor.

10 19. A method of treating a human suffering from a therapeutic condition mediated by prostanoid receptors, the method comprising administering an effective amount of a compound according to paragraph 1.

15 20. A method of treating a patient suffering from a condition selected from the group consisting of inflammatory pain, neuropathic pain, visceral pain, fibrosis and a condition of the central nervous system mediated by prostanoid receptors, the method comprises administering to said patient an effective amount of a compound of paragraph 1.

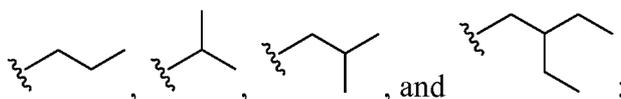
21. The compound of paragraph 1 wherein:

A is CH₂;

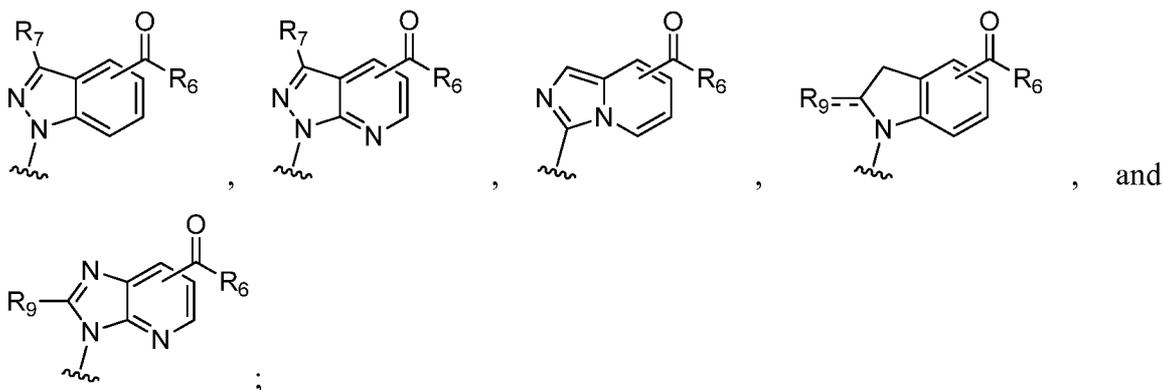
R₁ is selected from the group consisting of F, CF₃, Cl, Br, halogen, and OCF₃;

20 R₂ is selected from H, Cl, Br and OCF₃;

R₃ is selected from the group consisting of:



Het is selected from the group consisting of:



wherein R_6 is selected from the group consisting of OH and OCH_3 ,

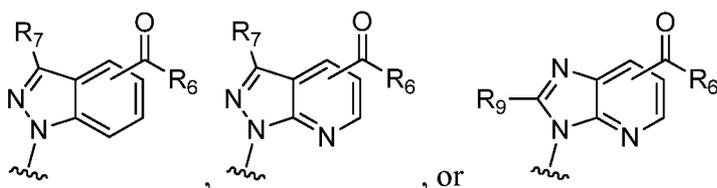
wherein R_7 is selected from the group consisting of H, CH_3 , NH_2 and $NHCH_3$,

5 wherein R_9 is O, OH, CH_3 , halogen and OCH_3 the dashed bond represents the presence of a single or double bond,

and, the compound can be in the form of a tautomer, a racemate, an enantiomer, a diastereomer, or a pharmaceutically acceptable salt.

22. The compound of paragraph 21 wherein W and Y are C, R_1 is selected from
10 Cl, Br, F, CF_3 , and OCF_3 .

23. The compound of paragraphs 21 and 22 wherein Het is:



wherein R_6 is OH,

wherein R_7 is selected from the group consisting of H, CH_3 , NH_2 and $NHCH_3$,

15 wherein R_9 is O, OH, CH_3 , halogen and OCH_3 the dashed bond represents the presence of a single or double bond,

and, the compounds can be in the form of a tautomer, a racemate, an enantiomer, a diastereomer, or a pharmaceutically acceptable salt.

Detailed Description of the Invention

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

Where substituents are specified as a range, the range encompasses each individual integer value of substituent including the beginning and ending value of the range. For example, the description of a substituent as " C_1 to C_6 alkyl" (or " $\text{C}_1\text{--C}_6$ alkyl") encompasses C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. Similarly, the description of a value of " n " (e.g. " $(\text{CH}_2)_n$ ") as being "0 to 3" (or "0–3") encompasses values of " n " of 0, 1, 2, and 3. A skilled person will realize upon a reading of the present disclosure that similar considerations apply to other substituents that can be described in terms of a range (e.g. "5 to 10 ring atoms" and "1 to 3 rings").

The term "acyl" means $-\text{C}(\text{O})\text{R}$ where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) or branched chain, or combination thereof, which may be fully saturated (referred to herein as a "saturated alkyl"), mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e. $\text{C}_1\text{--C}_{10}$ means one to ten carbons). Typical alkyl groups

include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. In some embodiments, all alkyls set forth as a substituent of the compounds provided herein are saturated alkyls. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, 5 isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. An "alkoxy" is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An "alkylthio" is an alkyl attached to the remainder of the molecule via a sulfur linker (-S-). A "haloalkoxy" is an alkoxy substituted with a halogen. When 10 the halogen is a fluoro, it may be referred to herein as a "fluoroalkoxy." The term "alkyl" includes saturated alkyl, alkenyl and alkynyl. A saturated alkyl may have from 1 to 10 or 1 to 6 carbon atoms. The term "alkenyl" by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) or branched hydrocarbon chain (e.g., two to ten, or two to six carbon atoms) having one or more double bonds. Examples of 15 unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), and the like. The term "alkynyl" by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) or branched hydrocarbon chain (e.g., two to ten or two to six carbon atoms) having one or more triple bonds. Examples of alkynyl groups include, but 20 are not limited to, ethynyl, 1- and 3-propynyl, 3-butynyl, and the like.

The term "alkylene", "alkenylene, and "alkynylene" by itself or as part of another substituent means a divalent radical derived from an alkyl, alkenyl, or alkynyl as exemplified, but not limited, by methylene, ethylene, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, vinylene and the like.

25 "Alkylene" refers to a divalent alkyl linking group.

The term "amino" as used herein means a $-\text{NH}_2$. The term "carboxy" as used herein means $-\text{COOH}$ (including pharmaceutically acceptable salts thereof).

The term "aryl" means, unless otherwise stated, an aromatic substituent of 3 to 14 atoms (e.g. 6 to 10) which can be a single ring or multiple rings (e.g., from 1 to 3 rings)

which may be fused together (i.e. a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring (e.g., phenyl, 1-naphthyl, 2-naphthyl, or 4-biphenyl). The term "heteroaryl" refers to aryl groups (or rings) that contain one or more (e.g., 4) heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized, the remaining ring atoms being carbon. The heteroaryl may be a monovalent monocyclic, bicyclic, or tricyclic (e.g., monocyclic or bicyclic) aromatic radical of 5 to 14 (e.g., 5 to 10) ring atoms where one or more, (e.g., one, two, or three or four) ring atoms are heteroatom selected from N, O, or S. Examples include, but are not limited to, thienyl, isoindolyl, benzoxazolyl, pyridazinyl, triazolyl, tetrazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-benzothiazolyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e. multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroaryl refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroaryl refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroaryl refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. An "arylene" and a "heteroarylene," alone or as part of another substituent means a divalent radical derived from an aryl and heteroaryl, respectively.

The terms "arylalkyl" and "heteroarylalkyl" is meant to include those radicals in which an aryl group or a heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon

atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

The term "Ethylenyl" refers to a $-\text{CH}_2\text{CH}_2-$ linking group.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si or S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2$, $-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom

The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, represent, unless otherwise stated, non-aromatic cyclic versions of "alkyl" and "heteroalkyl", respectively (*e.g.*, having 4 to 8 ring atoms). Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Heterocycloalkyls may include one or two ring heteroatoms selected from N, O, or $\text{S}(\text{O})_{n'}$, where n' is an integer from 0 to 2, the remaining ring atoms being carbon. The heterocycloalkyl or cycloalkyl ring is optionally

fused to one or more aryl or heteroaryl rings as defined herein (e.g., where the aryl and heteroaryl rings are monocyclic). The heterocycloalkyl or cycloalkyl ring fused to monocyclic aryl or heteroaryl ring may be referred to in this Application as “bicyclic heterocycloalkyl” ring or a “bicyclic cycloalkyl” ring. Additionally, one or two ring carbon atoms in the heterocycloalkyl ring can optionally be replaced by a –CO– group. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydropyranyl, thiomorpholino, dihydroindolyl, and the like. When the heterocycloalkyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic. When the heterocycloalkyl group contains at least one nitrogen atom, it may also be referred to herein as heterocycloamino and is a subset of the heterocycloalkyl group. When the heterocycloalkyl group is a saturated ring and is not fused to aryl or heteroaryl ring as stated above, it may be referred to herein as a saturated monocyclic heterocycloalkyl. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively; C1 – C3 alkyl includes methyl, ethyl and propyl.

The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” is meant to include, but not be limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term “methylene” refers to a –CH₂– linking group.

The term “oxo” as used herein means an oxygen that is double bonded to a carbon atom. The term “carbonyl” as used herein refers to a $-C(O)-$ group.

The symbol “ \sim ” indicates, as is customary in the art, the point of attachment of a substituent.

5 The terms "optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycloalkyl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the
10 heterocycloalkyl group is substituted with an alkyl group and situations where the heterocycloalkyl group is not substituted with alkyl.

Each of the above terms (*e.g.*, “alkyl,” “heteroalkyl,” “aryl” and “heteroaryl”) are meant to include both substituted and unsubstituted forms of the indicated radical unless stated otherwise.

15 Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: $-OR'$, $=O$, $=NR'$, $=N-OR'$, $-NR'R''$, $-SR'$, -halogen, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, -
20 $NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-N R''C(O)_2R'$, $-NR'-C(NR'R''R''')=NR''''$, $-NR-C(NR'R''R''')=NR''''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-CN$ and $-NO_2$ in a number ranging from zero to $(2m'+1)$, where m' is the total number of carbon atoms in such radical. R' , R'' , R''' and R'''' each independently refer to hydrogen, substituted or
25 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (*e.g.*, aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R' , R'' , R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached

to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including
 5 carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and may be selected from, for example: halogen, -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO₂R', -CONR'
 10 R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR'R", -NR"C(O)₂ R', -NR-C(NR'R"R''')=NR''', -NR'-C(NR'R")=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NR'SO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"' and R'''' are preferably independently selected from
 15 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R'''' groups when more than
 20 one of these groups is present.

Unless otherwise stated, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A "substituent group," as used herein, means, but is not limited to, a group selected from the following moieties:

25 (A) -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, 5 unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, 10 unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxo, -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

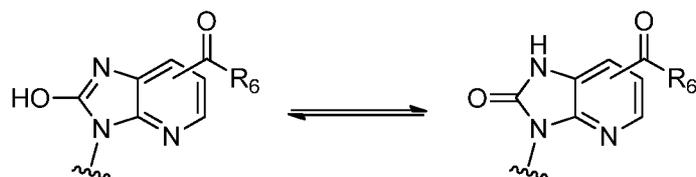
15 A “lower substituent” or “lower substituent group,” as used herein means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or 20 unsubstituted C₅-C₇ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; e.g., the R and S configurations for each asymmetric center as well as cis and trans configurations. Therefore, single 25 stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

The compounds of the present invention may have asymmetric centers and/or geometric isomers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, racemic forms are within the scope of this invention, unless the specific stereochemistry or isomeric form is specifically indicated. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this invention. Additionally, as used herein the term alkyl includes all the possible isomeric forms of the alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl, heteroaryl, heterocycloalkyl are substituted, they include all the positional isomers albeit only a few examples are set forth. Furthermore, all polymorphic forms, including amorphous form, and hydrates of a compound disclosed herein are within the scope of this invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, tautomers, geometric isomers and individual isomers are encompassed within the scope of the present invention, as are enantiomers. The compounds of the present invention do not include those which are known in the art to be too unstable to synthesize and/or isolate.

Certain compounds of the present invention can exist as tautomers which can interconvert between themselves. The structural depiction herein of a particular tautomer should not be construed as limiting the compound to the particular tautomer depicted. By way of example, 2-hydroxybenzimidazoles can exist as, and interconvert between, a hydroxy or keto tautomer:



A skilled person will realize upon reading the present disclosure that the structural depiction of a compound of the present invention comprising a 2-hydroxybenzimidazole

moiety as the hydroxy tautomer should not be construed as being limited to only the hydroxy tautomer and should be construed as including the keto tautomer even if the depicted hydroxy tautomer is the minor component in the tautomer interconversion equilibrium under a particular set of conditions. A skilled person will realize that similar considerations apply to other moieties (e.g. heterocycles) of the present invention that are capable of existing as different tautomers.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl.

Unless indicated otherwise, the term "derivative" in the context of a compound disclosed herein refers to a compound afforded by chemical modification, e.g., by the bonding of one or more substituent groups as described herein.

Where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. For example, where a moiety herein is $\text{R}^{1\text{A}}$ -substituted or unsubstituted alkyl, a plurality of $\text{R}^{1\text{A}}$ substituents may be attached to the alkyl moiety wherein each $\text{R}^{1\text{A}}$ substituent is optionally different. Where an R-substituted moiety is substituted with a plurality R substituents, each of the R-substituents may be differentiated herein using a prime symbol (') such as R' , R'' , etc. For example, where a moiety is $\text{R}^{1\text{A}}$ -substituted or unsubstituted alkyl, and the moiety is substituted with a plurality of $\text{R}^{1\text{A}}$ substituents, the plurality of $\text{R}^{1\text{A}}$ substituents may be differentiated as $\text{R}^{1\text{A}'}$, $\text{R}^{1\text{A}''}$, $\text{R}^{1\text{A}'''}$, etc. In some embodiments, the plurality of R substituents is 3. In some embodiments, the plurality of R substituents is 2.

Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. See e.g., Berge *et al.*, “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Additional information on suitable

pharmaceutically acceptable salts can be found in REMINGTON'S PHARMACEUTICAL SCIENCES, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base
5 or acid addition salts.

Thus, the compounds disclosed herein may exist as salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures), succinates, benzoates and salts with amino acids such as
10 glutamic acid. These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

15 The term "prodrug" is used according to its plain ordinary meaning and is intended to mean compounds that require a chemical or enzymatic transformation in order to release the active parent drug *in vivo* prior to producing a pharmacological effect.

A "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise
20 undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

The terms "treat" "treating" or "treatment" refers to any indicia of success in the
25 treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating;

improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer, in inhibiting its growth and or causing remission of cancer.

An "effective amount" of a compound is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. Where recited in reference to a disease treatment, an "effective amount" may also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of a disease, disorder or condition, or reducing the likelihood of the onset (or reoccurrence) of a disease, disorder or condition or symptoms thereof. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations.

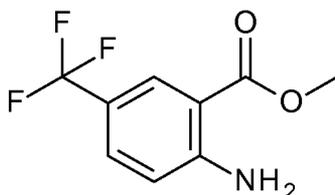
The term "topical" in the context of methods described herein relates in the customary sense to the administration of a compound or pharmaceutical composition which is incorporated into a suitable pharmaceutical carrier and administered at a topical treatment site of a subject. Accordingly, the term "topical pharmaceutical composition" includes those pharmaceutical forms in which the compound is administered externally by direct contact with a topical treatment site, e.g., the eye or the skin. The term "topical ocular pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directly to the eye. The term "topical epidermal pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directed to the epidermal layer of the skin, e.g., the palpebra, the supercilium, the scalp, or the body. The term "topical administering" refers to administering externally by direct contact with a topical treatment site. The term "topical epidermal administering" refers

to administering externally by direct contact with the epidermis. The term “topical ocular administering” refers to administering externally by direct contact with the eye.

Examples

The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

Example 1:
Methyl 2-amino-5-(trifluoromethyl)benzoate, Compound 1



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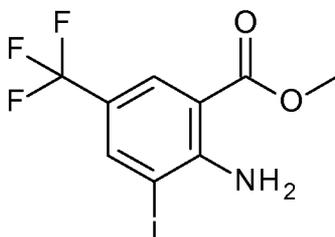
A solution of 2-amino-5-(trifluoromethyl)benzoic acid (1.07g, 5.2 mmoles) in methanol (20ml) was treated with concentrated sulphuric acid (0.5ml) and heated under microwave conditions at 125°C for 2h. The mixture was evaporated to dryness and treated with water (100ml) then basified to saturation with potassium carbonate and extracted with ethyl acetate (2 x 40ml). The combined extracts were dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with an ethyl acetate/ isohexane gradient. This gave the title compound 1 as a colorless oil (0.59g, 51%).

15

¹H-NMR(CDCl₃, 300 MHz) δ 8.15 (s, 1H, ArH), 7.47 (dd, J = 2 and 9Hz, 1H, ArH), 6.72 (d, J = 9Hz, 1H, ArH), 5.62 – 5.95 (brs, 2H, NH₂), 3.92 (s, 3H, CH₃).

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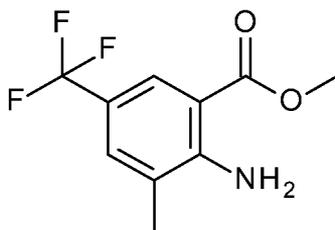
Example 2
Methyl 2-amino-3-iodo-5-(trifluoromethyl)benzoate, Compound 2



A solution of methyl 2-amino-5-(trifluoromethyl)benzoate (0.59g, 2.7 mmoles) in trifluoroacetic acid (5ml) was treated with N-iodosuccinimide (0.68g, 3.0 mmoles) and stirred at ambient temperature for 18h. The mixture was evaporated to dryness and the residue treated with water (25ml) and basified with potassium carbonate then extracted with dichloromethane (25ml). The organic phase was then washed with 10% sodium metabisulphite solution (25ml), separated and dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with an ethyl acetate/ isohexane gradient. This gave the title compound **2** as a white solid (0.633g, 68%).

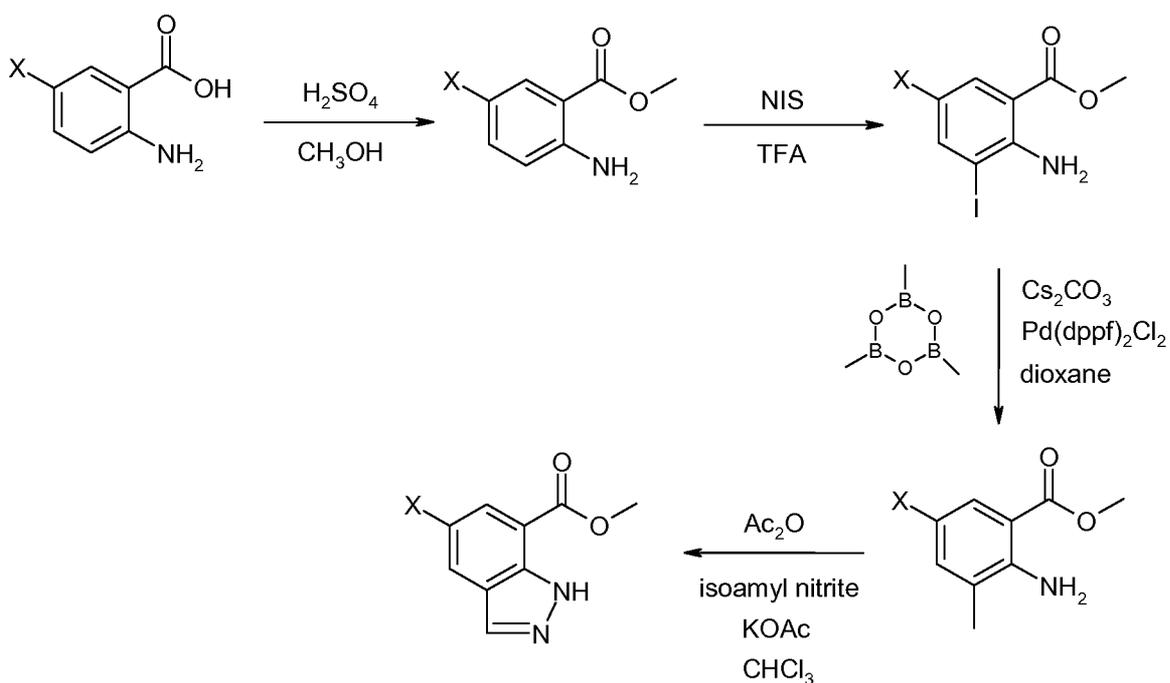
$^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 8.18 (d, $J = 3\text{Hz}$, 1H, ArH), 8.01 (d, $J = 3\text{Hz}$, 1H, ArH), 6.55 – 7.05 (brs, 2H, NH_2), 3.92 (s, 3H, CH_3).

Example 3
Methyl 2-amino-3-methyl-5-(trifluoromethyl)benzoate, Compound 3



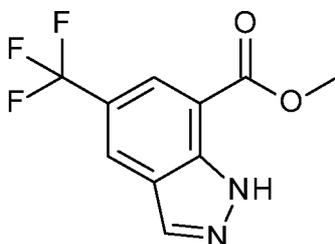
A mixture of methyl 2-amino-3-iodo-5-(trifluoromethyl)benzoate (0.633g, 1.83 mmoles), trimethylboroxine (0.56ml, 3.66 mmoles), cesium carbonate (1.2g, 3.66 mmoles) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.075g, 0.09 mmoles) in 1,4-dioxane (15 mL) was heated in a microwave reactor at 130°C for 1.5h. The mixture was partitioned between water (30ml) and ethyl acetate (2 x 30ml). The combined organics were dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with an ethyl acetate/ isohexane gradient. This gave the title compound **3** as an orange solid (0.41g, 96%).

$^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 8.07 (s, 1H, ArH), 7.38 (s, 1H, ArH), 6.05 – 7.35 (brs, 2H, NH_2), 3.92 (s, 3H, CH_3).



Scheme 1. Synthesis of Compounds 4 and 8

Example 4
Methyl 5-(trifluoromethyl)-1H-indazole-7-carboxylate, Compound 4



5

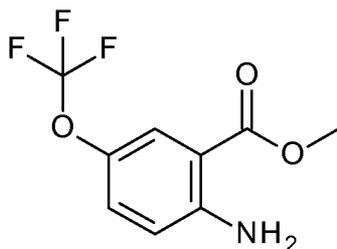
To a solution of compound 3, at 0°C and under nitrogen atmosphere, in chloroform (0.3M) was added acetic anhydride (2.3 equiv.) drop wise and the resulting mixture was stirred for 1h at r.t. Then potassium acetate (0.2 equiv.) was added followed by addition of isoamyl nitrite (2.2 equiv.) and the resulting mixture was heated at reflux for 16h. After, the reaction was cooled down to r.t. While cooling, a solid precipitation was observed. The solid was filtrated and dried *under vacuum* to give the title compound 4. (0.324g, 75%).

10

¹H-NMR(CDCl₃, 300 MHz) δ 11.40 – 11.60 (brs, 1H, ArH), 8.31 (s, 2H, 2 x ArH), 8.28 (d, J = 2Hz. 1H, ArH), 4.07 (s, 3H, CH₃).

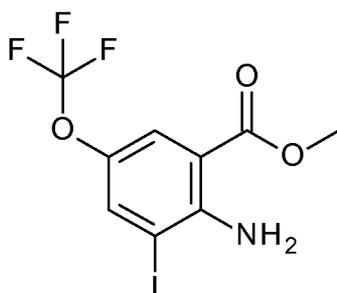
15

Example 5

Methyl 2-amino-5-(trifluoromethoxy)benzoate, Compound 5

The title compound was prepared as in the method of compound 1 from 2-amino-5-(trifluoromethoxy)benzoic acid to give a pale yellow oil (0.538g, 46%).

5 $^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 7.73 (d, $J = 3\text{Hz}$, 1H, ArH), 7.18 (dd, $J = 3$ and 9Hz, 1H, ArH), 6.66 (d, $J = 9\text{Hz}$, 1H, ArH), 5.67 – 5.91 (brs, 2H, NH_2), 3.89 (s, 3H, CH_3).

Example 6**Methyl 2-amino-3-iodo-5-(trifluoromethoxy)benzoate, Compound 6**

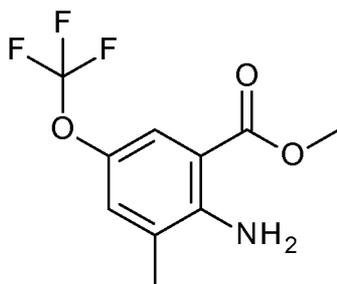
10

The title compound was prepared as in the method of compound 2 from methyl 2-amino-5-(trifluoromethoxy)benzoate to give a white solid (0.67g, 82%).

$^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 7.81 (d, $J = 3\text{Hz}$, 1H, ArH), 7.71 (d, $J = 3\text{Hz}$, 1H, ArH), 5.35 – 5.55 (brs, 2H, NH_2), 3.92 (s, 3H, CH_3).

15

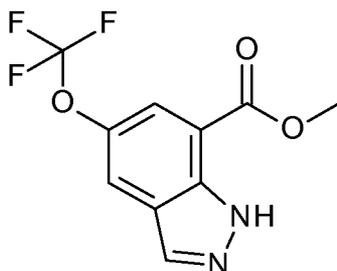
Example 7**Methyl 2-amino-3-methyl-5-(trifluoromethoxy)benzoate, Compound 7**



The title compound was prepared as in the method of compound **3** from methyl 2-amino-3-iodo-5-(trifluoromethoxy)benzoate to give an orange oil (0.413g, 89%).

¹H-NMR(CDCl₃, 300 MHz) δ 7.65 (d, J = 3Hz, 1H, ArH), 7.11 (d, J = 3Hz, 1H, ArH), 5.74 – 6.02 (brs, 2H, NH₂), 3.89 (s, 3H, CH₃), 2.19 (s, 3H, CH₃).

Example 8
Methyl 5-(trifluoromethoxy)-1H-indazole-7-carboxylate, Compound 8



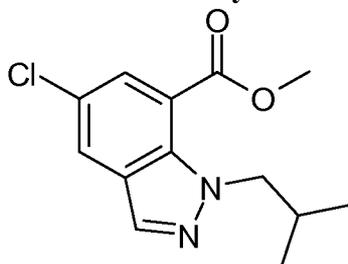
The title compound was prepared as in the method of compound **4** from methyl 2-amino-3-methyl-5-(trifluoromethoxy) benzoate to give an off-white solid (0.355g, 83%).

¹H-NMR(CDCl₃, 300 MHz) δ 11.39 (s, 1H, NH), 8.19 (s, 1H, ArH), 7.97 (s, 1H, ArH), 7.86 (s, 1H, ArH), 4.06 (s, 3H, CH₃).

General Method 1: Alkylation

To a solution of 5-substituted-indazole-7-carboxylic acid methyl ester, at room temperature and under nitrogen atmosphere, in N,N-dimethylformamide (0.18M) were added Cesium carbonate (1.2 equiv.) and the corresponding alkylating agent (1.1 equiv.). The resulting mixture was stirred for 18 h. Then, the reaction mixture was concentrated to dryness under vacuum and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated.

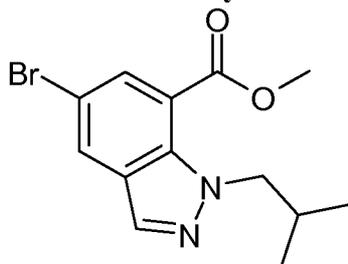
The mixture of regioisomers was separated by column chromatography in a SPE Silica cartridge using as eluent a gradient from iso-hexane/ethyl acetate 9:1 to 1:3 to isolate both regioisomers as colorless oils.

Example 9**5-Chloro-1-isobutyl-1H-indazole-7-carboxylic acid methyl ester, Compound 9**

Compound **9** was prepared following general method 1, using 5-chloro-1H-indazole-7-carboxylic acid methyl ester (see WO2011008572 which is incorporated by reference in its entirety) as starting material and 1-iodo-2-methylpropane as alkylating agent. Yield: 48%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.01 (s, 1H, ArH), 7.86 (s, 2H, ArH), 4.55 (d, 2H, J = 7.3 Hz, NCH₂), 3.99 (s, 3H, OCH₃), 2.02 (m, 1H, -CH(CH₃)₂), 0.80 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 267 M + H⁺

Example 10**5-Bromo-1-isobutyl-1H-indazole-7-carboxylic acid methyl ester, Compound 10**

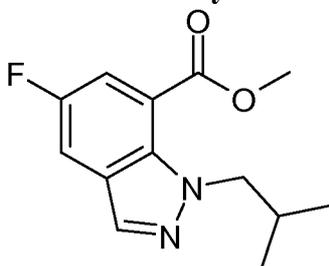
Compound **10** was prepared following general method 1, using 5-bromo-1H-indazole-7-carboxylic acid methyl ester as starting material and 1-iodo-2-methylpropane as alkylating agent. Yield: 70%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.05 (s, 1H, ArH), 8.00 (s, 1H, ArH), 7.95 (s, 1H, ArH), 4.55 (d, 2H, $J = 7.3$ Hz, NCH_2), 3.99 (s, 3H, OCH_3), 2.02 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 0.80 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$).

LC-MS: m/z 312 $\text{M} + \text{H}^+$

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Example 11
5-Fluoro-1-isobutyl-1H-indazole-7-carboxylic acid methyl ester, Compound 11

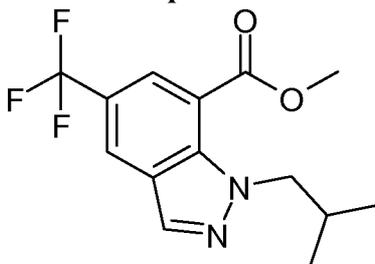


Compound 11 was prepared following general method 1, using 5-fluoro-1H-indazole-7-carboxylic acid methyl ester (see WO2011008572, incorporated by reference in its entirety) as starting material and 1-iodo-2-methylpropane as alkylating agent. Yield: 41%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.04 (s, 1H, ArH), 7.70 (dd, $J = 3$ and 10Hz, 1H, ArH), 7.57 (dd, $J = 3$ and 10Hz, 1H, ArH), 4.58 (d, $J = 7$ Hz, 2H, CH_2), 4.01 (s, 3H, CH_3), 1.97 – 2.09 (m, 1H, CH), 0.79 (d, $J = 8$ Hz, 6H, 2 x CH_3).

15

Example 12
1-Isobutyl-5-trifluoromethyl-1H-indazole-7-carboxylic acid methyl ester, Compound 12



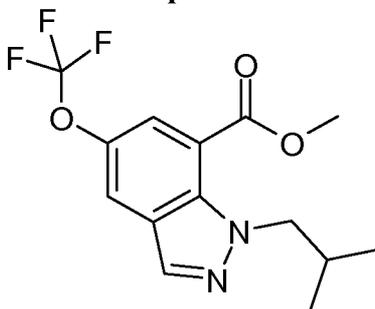
Compound 12 was prepared following general method 1, using compound 4 as starting material and 1-iodo-2-methylpropane as alkylating agent. Yield: 39%.

20

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.22 (s, 1H, ArH), 8.19 (s, 1H, ArH), 8.15 (s, 1H, ArH), 4.62 (d, $J = 5\text{Hz}$, 2H, CH_2), 4.03 (s, 3H, CH_3), 1.99 – 2.14 (m, 1H, CH), 0.82 (d, $J = 8\text{Hz}$, 6H, 2 x CH_3).

Example 13

5 1-Isobutyl-5-trifluoromethoxy-1H-indazole-7-carboxylic acid methyl ester, Compound 13

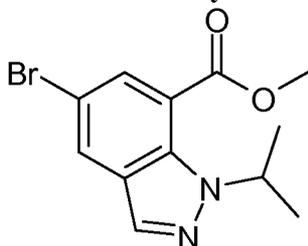


Compound **13** was prepared following general method 1, using compound **8** as starting material and 1-iodo-2-methylpropane as alkylating agent. Yield: 56%.

10 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 11.39 (s, 1H, NH), 8.19 (s, 1H, ArH), 7.97 (s, 1H, ArH), 7.86 (s, 1H, ArH), 4.06 (s, 3H, CH_3).

Example 14

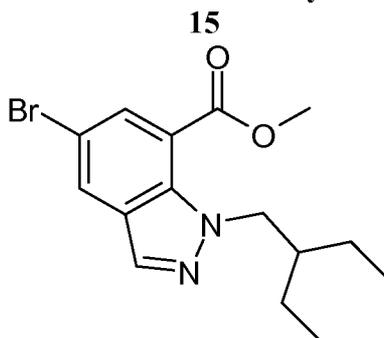
5-bromo-1-isopropyl-1H-indazole-7-carboxylic acid methyl ester, Compound 14



15 Compound **14** was prepared following general method 1, using 5-bromo-1H-indazole-7-carboxylic acid methyl ester as a starting material and 2-iodopropane as alkylating agent. Yield: 65%.

20 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.05 (s, 1H, ArH), 8.00 (d, 1H, $J = 2\text{ Hz}$, ArH), 7.93 (d, 1H, $J = 2\text{ Hz}$, ArH), 5.30 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 4.00 (s, 3H, OCH_3), 1.55 (d, 6H, $J = 6.7\text{ Hz}$, $\text{CH}(\text{CH}_3)_2$).

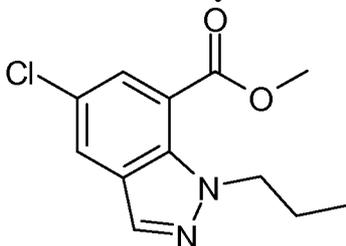
LC-MS: m/z 298 $\text{M} + \text{H}^+$

Example 15**5-Bromo-1-(2-ethyl-butyl)-1H-indazole-7-carboxylic acid methyl ester, Compound**

5 Compound **15** was prepared following general method 1, using 5-bromo-1H-indazole-7-carboxylic acid methyl ester as a starting material and 3-chloromethyl-pentane as alkylating agent. Yield: 22%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.10 (s, 1H, ArH), 8.03 (s, 1H, ArH), 7.93 (s, 1H, ArH), 4.38 (d, 2H, J = 7.3 Hz, NCH₂), 3.99 (s, 3H, OCH₃), 2.10 (m, 1H, -CH(CH₂CH₃)₂),
10 1.30 (m, 4H, -CH(CH₂CH₃)₂), 0.90 (m, 6H, -CH(CH₂CH₃)₂).

LC-MS: m/z 340 M + H⁺

Example 16**5-Chloro-1-Propyl-1H-indazole-7-carboxylic acid methyl ester, Compound 16**

15 Compound **16** was prepared following general method 1, using 5-chloro-1H-indazole-7-carboxylic acid methyl ester (WO2011008572) as a starting material and 1-iodopropane as alkylating agent. Yield: 39%.

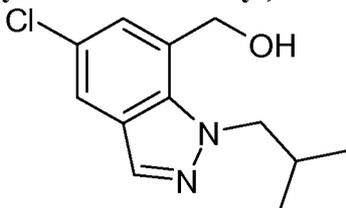
¹H-NMR (CDCl₃, 300 MHz) δ 8.02 (s, 1H, ArH), 7.87 (dd, 2H, J = 2, 6.2 Hz, ArH), 4.66 (t, 2H, J = 7.3 Hz, NCH₂), 4.00 (s, 3H, OCH₃), 1.78 (m, 2H, -CH₂CH₂CH₃),
20 0.86 (m, 3H, -CH₂CH₂CH₃).

LC-MS: m/z 253 M + H⁺

General method 2: Ester Reduction

To a solution of ester derivative (**9** to **16**), at room temperature and under nitrogen atmosphere, in dry toluene (5M) were added a 2M solution of DIBAH in toluene (5 equiv.). The resulting mixture was stirred for 18 h. Then, the reaction mixture was quenched with 10% Rochelle's salt solution and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with brine, dried (MgSO₄), filtered and the solvent evaporated to give the desired product as a colorless solid.

Example 17
(5-Chloro-1-isobutyl-1H-indazole-7-yl)-methanol, Compound 17



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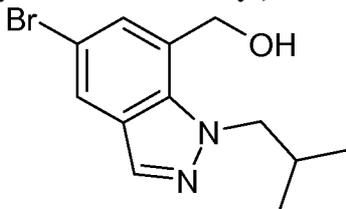
Compound **17** was prepared following general method 2, using compound **9** as a starting material. Yield: 91%.

¹H-NMR (CDCl₃, 500 MHz) δ 7.95 (s, 1H, ArH), 7.66 (s, 1H, ArH), 7.29 (s, 1H, ArH), 4.98 (s, 2H, -CH₂OH), 4.41 (d, 2H, J = 7.3 Hz, NCH₂), 2.23 (m, 1H, -CH(CH₃)₂), 2.01 (s, 1H, OH), 0.90 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

15

LC-MS: m/z 239 M + H⁺

Example 18
(5-Bromo-1-isobutyl-1H-indazole-7-yl)-methanol, Compound 18



20

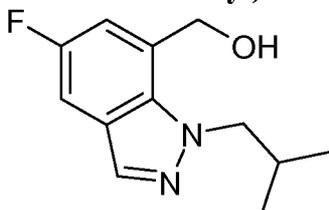
Compound **18** was prepared following general method 2, using compound **10** as a starting material. Yield: 90%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.95 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.40 (s, 1H, ArH), 5.00 (s, 2H, $-\text{CH}_2\text{OH}$), 4.42 (d, 2H, $J = 7.3$ Hz, NCH_2), 2.28 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 0.95 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$).

LC-MS: m/z 284 $\text{M} + \text{H}^+$

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Example 19
(5-Fluoro-1-isobutyl-1H-indazole-7-yl)-methanol, Compound 19

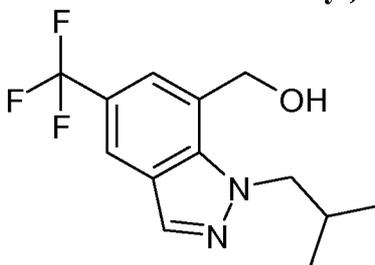


Compound **19** was prepared following general method 2, using compound **11** as a starting material. Yield: 93%.

10

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.94 (s, 1H, ArH), 7.29 (dd, $J = 3$ and 10Hz, 1H, ArH), 7.17 (dd, $J = 3$ and 10Hz, 1H, ArH), 4.98 (s, 2H, CH_2), 4.38 (d, $J = 7$ Hz, 2H, CH_2), 2.38 – 2.53 (brs, 1H, OH), 2.14 – 2.28 (m, 1H, CH), 0.92 (d, $J = 8$ Hz, 6H, 2 x CH_3).

Example 20
(1-Isobutyl-5-trifluoromethane-1H-indazole-7-yl)-methanol, Compound 20



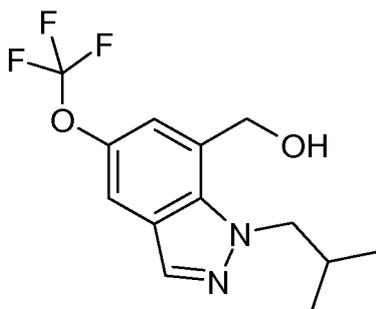
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Compound **20** was prepared following general method 2, using compound **12** as a starting material. Yield: 93%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.08 (s, 1H, ArH), 8.01 (s, 1H, ArH), 7.55 (s, 1H, ArH), 5.07 (s, 2H, CH_2), 4.47 (d, $J = 5$ Hz, 2H, CH_2), 2.19 – 2.34 (m, 1H, CH), 0.97 (d, $J = 8$ Hz, 6H, 2 x CH_3).

20

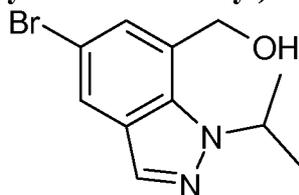
Example 21
(1-Isobutyl-5-trifluoromethoxy-1H-indazole-7-yl)-methanol, Compound 21



Compound **21** was prepared following general method 2, using compound **13** as a starting material. Yield: 100%.

¹H-NMR(CDCl₃, 300 MHz) δ 8.01 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.24 (s, 1H, ArH), 5.01 (d, J = 6Hz, 2H, CH₂), 4.44 (d, J = 7.5Hz, 2H, CH₂), 2.18 – 2.32 (m, 1H, CH), 2.09 (t, J = 6Hz, 1H, OH), 0.95 (d, J = 8Hz, 6H, 2 x CH₃).

Example 22
(5-Bromo-1-isopropyl-1H-indazol-7-yl)-methanol, Example 22

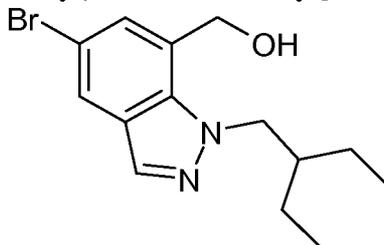


Compound **22** was prepared following general method 2, using compound **14** as a starting material. Yield: 92%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.02 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.40 (s, 1H, ArH), 5.25 (m, 1H, -NCH(CH₃)₂), 5.00 (s, 2H, -CH₂OH), 1.60 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 270 M + H⁺

Example 23
[5-Bromo-1-(2-ethyl-butyl)-1H-indazol-7-yl]-methanol, Compound 23

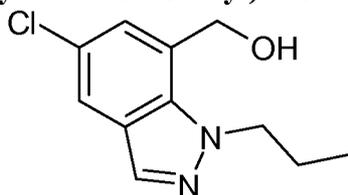


Compound **23** was prepared following general method 2, using compound **15** as a starting material. Yield: 90%.

¹H-NMR (CDCl₃, 300 MHz) δ 7.83 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.30 (s, 1H, ArH), 5.05 (s, 2H, CH₂OH), 4.25 (d, 2H, J = 7.3 Hz, NCH₂), 2.00 (m, 1H, -CH(CH₂CH₃)₂), 1.25 (m, 4H, -CH(CH₂CH₃)₂), 0.90 (m, 6H, -CH(CH₂CH₃)₂).

LC-MS: m/z 312 M + H⁺

Example 24
(5-Chloro-1-propyl-1H-indazol-7-yl)-methanol, Compound 24



Compound **24** was prepared following general method 2, using compound **16** as a starting material. Yield: 89%.

¹H-NMR (CDCl₃, 300 MHz) δ 7.90 (s, 1H, ArH), 7.62 (m, 2H, ArH), 7.26 (m, 1H, ArH), 4.95 (s, 2H, CH₂OH), 4.55 (t, 2H, J = 7.3 Hz, NCH₂), 1.88 (m, 2H, -CH₂CH₂CH₃), 0.94 (m, 3H, -CH₂CH₂CH₃).

LC-MS: m/z 225 M + H⁺

General method 3A: Preparation of methylsulfonate derivative and reaction with corresponding heterocycles

To a solution of benzyl alcohol derivative, at room temperature and under nitrogen atmosphere, in dry dichloromethane (6M) were added DIPEA (1.1 equivalents) methane sulfonic anhydride. (1.1 equivalents) The resulting mixture was stirred for 2 h. Then, the reaction mixture was quenched with water and the mixture was extracted with more dichloromethane. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated to give the desired product as yellow oil.

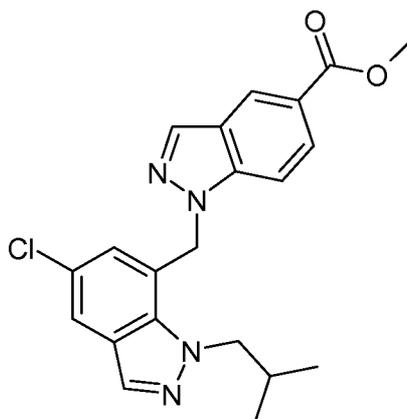
To a solution of heterocycle, at room temperature and under nitrogen atmosphere, in dry DMF (4M) was added a solution of the methylsulfonate (1.1 equiv) prepared above in dry DMF followed by caesium carbonate (1.2 equivalents). The resulting mixture was stirred for 16h at room temperature. Then, the reaction mixture was diluted with ethyl acetate and 2M solution of HCl. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated. The residue was purified in a 20G SPE cartridge using a eluent gradient from isohexane/ethyl acetate 9:1 to 1:1 as appropriate to isolate the desired product.

General method 3B. Preparation of methylsulfonate derivative and reaction with corresponding heterocycles

To a solution of benzyl alcohol derivative, at room temperature and under nitrogen atmosphere, in dry dichloromethane (6M) were added DIPEA (1.1 equivalents) methane sulfonic anhydride. (1.1 equivalents) The resulting mixture was stirred for 2 h. Then, the reaction mixture was quenched with water and the mixture was extracted with more dichloromethane. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated to give the desired product as yellow oil.

To a solution of heterocycle, at room temperature and under nitrogen atmosphere, in dry DMF (4M) was added sodium hydride 60% (1.3 equivalents) and the resulting mixture was stirred for 30min. A solution of the methylsulfonate (1.1 equiv) prepared above in dry DMF was then added and the resulting mixture was stirred for 16h at room temperature. Then, the reaction mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated. The residue was purified in a 20G SPE cartridge using a eluent gradient from isohexane/ethyl acetate 9:1 to 1:1 as appropriate to isolate the desired product.

Example 25 **1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 25**



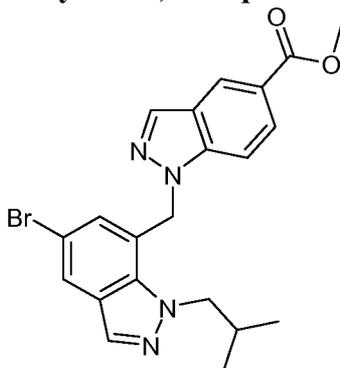
Compound **25** was prepared following general method 3A, using compound **17** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle.

5 Yield: 40%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.60 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.05 (d, 1H, $J = 8.9$ Hz, ArH), 8.00 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.30 (d, 1H, $J = 8.9$ Hz, ArH), 6.75 (s, 1H, ArH), 6.00 (s, 2H, ArCH₂N), 4.42 (d, 2H, $J = 7.3$ Hz, NCH₂), 3.95 (s, 3H, -CO₂CH₃), 2.25 (m, 1H, -CH(CH₃)₂), 0.90 (d, 6H, $J = 6.7$ Hz, CH(CH₃)₂).

10 LC-MS: m/z 397 M + H⁺

Example 26
1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 26



15

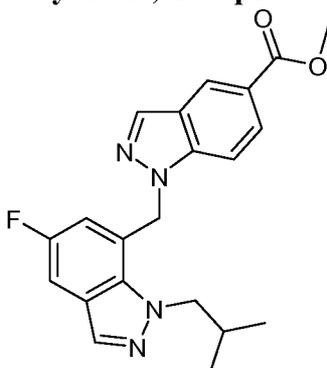
Compound **26** was prepared following general method 3A, using compound **18** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 65%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.55 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.10 (d, 1H, J = 8.9 Hz, ArH), 7.85 (s, 1H, ArH), 7.30 (d, 1H, J = 8.9 Hz, ArH), 7.27 (s, 1H, ArH), 6.90 (s, 1H, ArH), 6.00 (s, 2H, ArCH₂N), 4.40 (d, 2H, J = 7.3 Hz, NCH₂), 3.95 (s, 3H, -CO₂CH₃), 2.30 (m, 1H, -CH(CH₃)₂), 0.85 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 442 M + H⁺

Example 27

10 **1-(5-Fluoro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 27**



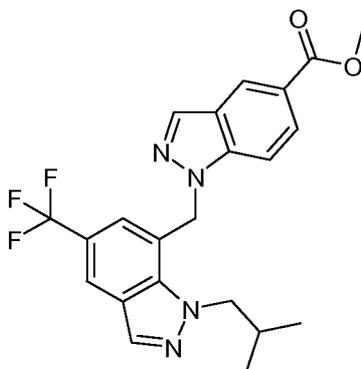
Compound **27** was prepared following general method 3A, using compound **19** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 53%.

¹H-NMR(CDCl₃, 300 MHz) δ 8.58 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.07 (dd, J = 2 and 7.5Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.27 – 7.33 (m, 2H, 2 x ArH), 6.46 (dd, J = 4 and 10.5Hz, 1H, ArH), 6.05 (s, 2H, CH₂), 4.38 (d, J = 5Hz, 2H, CH₂), 3.95 (s, 3H, CH₃), 2.25 – 2.38 (m, 1H, CH), 0.95 (d, J = 8Hz, 6H, 2 x CH₃).

20

Example 28

1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 28

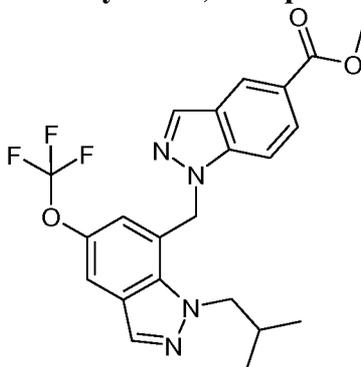


Compound **28** was prepared following general method 3A, using compound **20** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 41%.

- 5 $^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 8.58 (s, 1H, ArH), 8.21 (s, 1H, ArH), 8.17 (s, 1H, ArH), 8.01 – 8.09 (m, 2H, 2 x ArH), 7.29 (s, 1H, ArH), 7.09 (s, 1H, ArH), 6.05 (s, 2H, CH₂), 4.41 (d, J = 5Hz, 2H, CH₂), 3.98 (s, 3H, CH₃), 2.23 – 2.38 (m, 1H, CH), 0.93 (d, J = 8Hz, 6H, 2 x CH₃).

Example 29

- 10 **1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 29**



- 15 Compound **29** was prepared following general method 3A, using compound **21** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 46%.

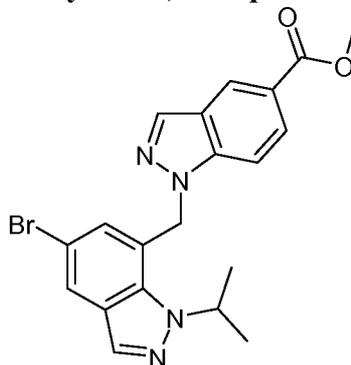
$^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 8.58 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.02 – 8.08 (m, 2H, 2 x ArH), 7.54 (s, 1H, ArH), 7.29 (d, J = 5Hz, 1H, ArH), 6.61 (s, 1H, ArH), 6.01

(s, 2H, CH₂), 4.41 (d, J = 7.5Hz, 2H, CH₂), 3.95 (s, 3H, CH₃), 2.25 – 2.39 (m, 1H, CH), 0.95 (d, J = 8Hz, 6H, 2 x CH₃).

Example 30

1-(5-Bromo-1-isopropyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid methyl ester, Compound 30

5



Compound 30 was prepared following general method 3A, using compound 22 as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 30%.

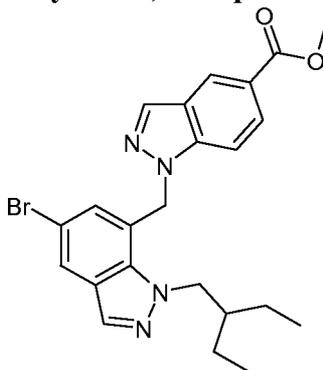
10 ¹H-NMR (CDCl₃, 300 MHz) δ 8.53 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.03 (d, 1H, J = 8.9 Hz, ArH), 7.95 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.25 (d, 1H, J = 8.9 Hz, ArH), 7.03 (s, 1H, ArH), 5.95 (s, 2H, ArCH₂N), 5.60 (m, 1H, NCH(CH₃)₂), 3.95 (s, 3H, -CO₂CH₃), 1.45 (d, 6H, J = 6.7 Hz, NCH(CH₃)₂).

LC-MS: m/z 428 M + H⁺

15

Example 31

1-[5-Bromo-1-(2-ethyl-butyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid methyl ester, Compound 31



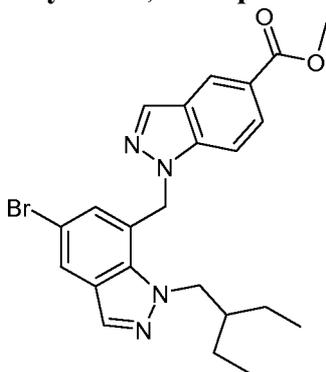
Compound **31** was prepared following general method 3A, using compound **23** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 47%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.51 (s, 1H, ArH), 8.17 (s, 1H, ArH), 8.05 (d, 1H, J = 8.9 Hz, ArH), 7.82 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.65 (d, 1H, J = 8.9 Hz, ArH), 6.95 (s, 1H, ArH), 6.00 (s, 2H, ArCH₂N), 4.30 (d, 2H, J = 7.3 Hz, NCH₂), 3.95 (s, 3H, -CO₂CH₃), 2.03 (m, 1H, -CH(CH₂CH₃)₂), 1.30 (m, 4H, CH(CH₂CH₃)₂), 0.90 (m, 6H, CH(CH₂CH₃)₂).

LC-MS: m/z 470 M + H⁺

10

Example 32
1-[5-Chloro-1-(2-propyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid methyl ester, Compound 32



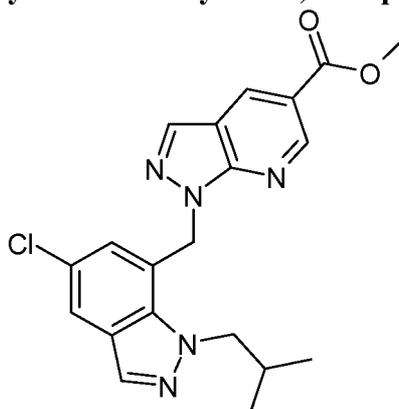
Compound **32** was prepared following general method 3A, using compound **24** as a starting material and 1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 47%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.57 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.05 (d, 1H, J = 8.9 Hz, ArH), 7.94 (s, 1H, ArH), 7.64 (s, 1H, ArH), 7.30 (d, 1H, J = 8.9 Hz, ArH), 6.80 (s, 1H, ArH), 6.00 (s, 2H, ArCH₂N), 4.55 (t, 2H, J = 7.3 Hz, NCH₂CH₂CH₃), 3.96 (s, 3H, -CO₂CH₃), 1.89 (m, 2H, NCH₂CH₂CH₃), 0.97 (t, 3H, J = 7.3 Hz, NCH₂CH₂CH₃).

LC-MS: m/z 383 M + H⁺

Example 33

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methyl ester, Compound 33



5 Compound **33** was prepared following general method 3A, using compound **17** as a starting material and 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methyl ester as the heterocycle. Yield: 53%.

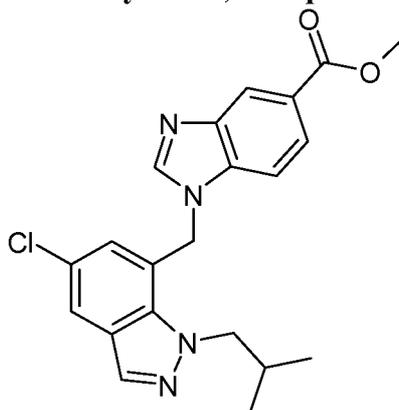
¹H-NMR (CDCl₃, 300 MHz) δ 9.25 (s, 1H, ArH), 8.80 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.00 (s, 1H, ArH), 7.67 (s, 1H, ArH), 7.10 (s, 1H, ArH), 6.10 (s, 2H, ArCH₂N),
10 4.55 (d, 2H, J = 7.3 Hz, NCH₂), 3.97 (s, 3H, -CO₂CH₃), 2.37 (m, 1H, -CH(CH₃)₂), 0.95 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 398 M + H⁺

Example 34

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-benzimidazole-5-carboxylic acid methyl ester, Compound 34

15



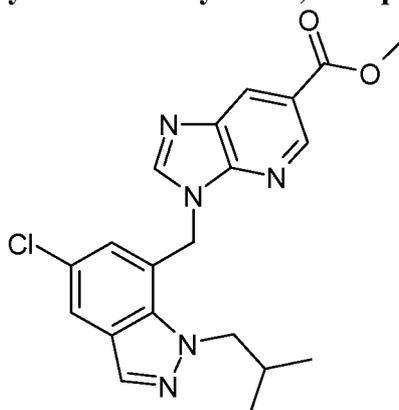
Compound **34** was prepared following general method 3A, using compound **17** as a starting material and 1H-benzoimidazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 40%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.62 (s, 1H, ArH), 8.09 (d 1H, J = 8.5Hz, ArH),
 5 8.03 (s, 1H, ArH), 7.75 (s, 1H, ArH), 7.40 (d, 1H, J = 8.5Hz, ArH), 7.29 (s, 1H, ArH),
 6.92 (s, 1H, ArH), 5.73 (s, 2H, ArCH₂N), 4.09 (d, 2H, J = 7.3 Hz, NCH₂), 3.98 (s, 3H, -
 CO₂CH₃), 2.12 (m, 1H, -CH(CH₃)₂), 0.82 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 397 M + H⁺

Example 35

10 **3-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid methyl ester, Compound 35**



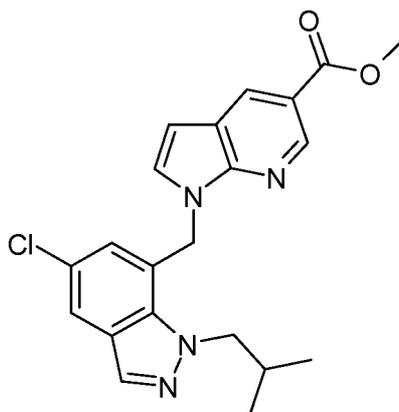
Compound **35** was prepared following general method 3A, using compound **17** as a starting material and 3H-Imidazo[4,5-b]pyridine-6-carboxylic acid methyl ester as the
 15 heterocycle. Yield: 30%.

¹H-NMR (CDCl₃, 300 MHz) δ 9.17 (s, 1H, ArH), 8.76 (s 1H, ArH), 8.00 (s, 1H, ArH), 7.92 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.16 (s, 1H, ArH), 5.85 (s, 2H, ArCH₂N), 4.08 (d, 2H, J = 7.3 Hz, NCH₂), 4.01 (s, 3H, -CO₂CH₃), 2.20 (m, 1H, -CH(CH₃)₂), 0.87 (d, 3H, J = 6.7 Hz, CH(CH₃)₂), 0.78 (d, 3H, J = 6.7 Hz, CH(CH₃)₂)

20 LC-MS: m/z 398 M + H⁺

Example 36

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester, Compound 36

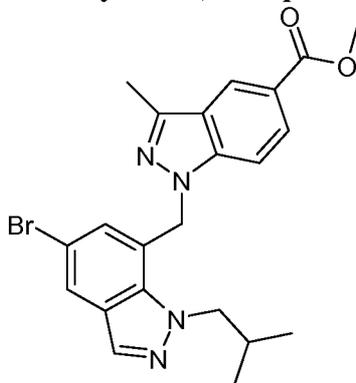


Compound **36** was prepared following general method 3A, using compound **17** as a starting material and 1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid methyl ester as the heterocycle. Yield: 73%.

5 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 9.07 (d, $J = 2\text{Hz}$, 1H, ArH), 8.65 (d, $J = 2\text{Hz}$, 1H, ArH), 7.98 (s, 1H, ArH), 7.71 (d, $J = 2\text{Hz}$, 1H, ArH), 7.05 – 7.08 (m, 2H, 2 x ArH), 6.58 (d, $J = 3\text{Hz}$, 1H, ArH), 5.85 (s, 2H, CH_2), 4.07 (d, $J = 7.5\text{Hz}$, 2H, CH_2), 3.98 (s, 3H, CH_3), 2.12 – 2.28 (m, 1H, CH), 0.75 (d, $J = 8\text{Hz}$, 6H, 2 x CH_3).

Example 37

10 **1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-indazole-5-carboxylic acid methyl ester, Compound 37**



15 Compound **37** was prepared following general method 3A, using compound **18** as a starting material and 3-methyl-1H-indazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 76%.

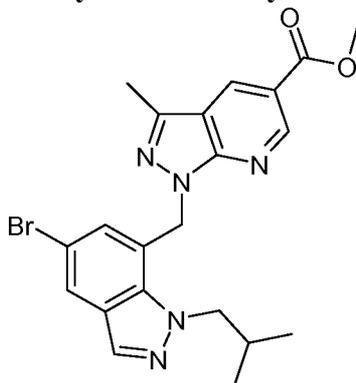
$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.50 (s, 1H, ArH), 8.03 (d, 1H, $J = 8.9\text{ Hz}$, ArH), 7.95 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.15 (d, 1H, $J = 8.9\text{ Hz}$, ArH), 6.85 (s, 1H, ArH),

5.92 (s, 2H, ArCH₂N), 4.35 (d, 2H, J = 7.3 Hz, NCH₂), 3.93 (s, 3H, -CO₂CH₃), 2.65 (s, 3H, CH₃), 2.25 (m, 1H, -CH(CH₃)₂), 0.85 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 457 M + H⁺

Example 38

5 **1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methyl ester, Compound 38**



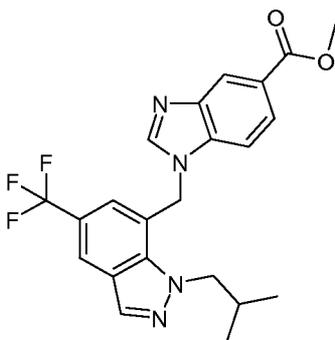
Compound **38** was prepared following general method 3A, using compound **18** as a starting material and 3-Methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methyl ester as the heterocycle. Yield: 50%.

¹H-NMR (CDCl₃, 300 MHz) δ 9.20 (s, 1H, ArH), 8.70 (s, 1H, ArH), 7.95 (s, 1H, ArH), 7.78 (s, 1H, ArH), 7.15 (s, 1H, ArH), 6.05 (s, 2H, ArCH₂N), 4.53 (d, 2H, J = 7.3 Hz, NCH₂), 4.00 (s, 3H, -CO₂CH₃), 2.62 (s, 3H, CH₃), 2.32 (m, 1H, -CH(CH₃)₂), 0.95 (d, 3H, J = 6.7 Hz, CH(CH₃)₂), 0.85 (d, 3H, J = 6.7 Hz, CH(CH₃)₂).

15 LC-MS: m/z 458 M + H⁺

Example 39

1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-benzimidazole-5-carboxylic acid methyl ester, Compound 39



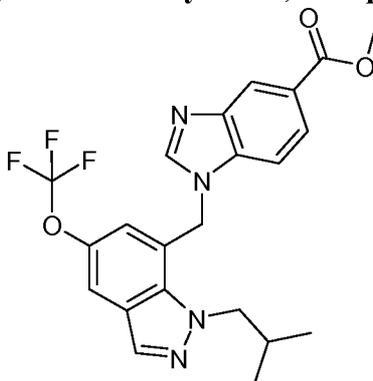
Compound **39** was prepared following general method 3A, using compound **20** as a starting material and 1H-benzimidazole-5-carboxylic acid methyl ester as the heterocycle.

5 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.74 (s, 1H, ArH), 8.13 - 8.23 (m, 3H, 3 x ArH), 7.83 (s, 1H, ArH), 7.47 (d, $J = 9\text{Hz}$, 1H, ArH), 7.27 (s, 1H, ArH), 5.80 (s, 2H, CH_2), 4.08 (d, $J = 5\text{Hz}$, 2H, CH_2), 2.15 - 2.31 (m, 1H, CH), 0.81 (d, $J = 8\text{Hz}$, 6H, 2 x CH_3).

LC-MS: m/z 417 ($\text{M} + \text{H}^+$).

Example 40

10 **1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-benzimidazole-5-carboxylic acid methyl ester, Compound 40**



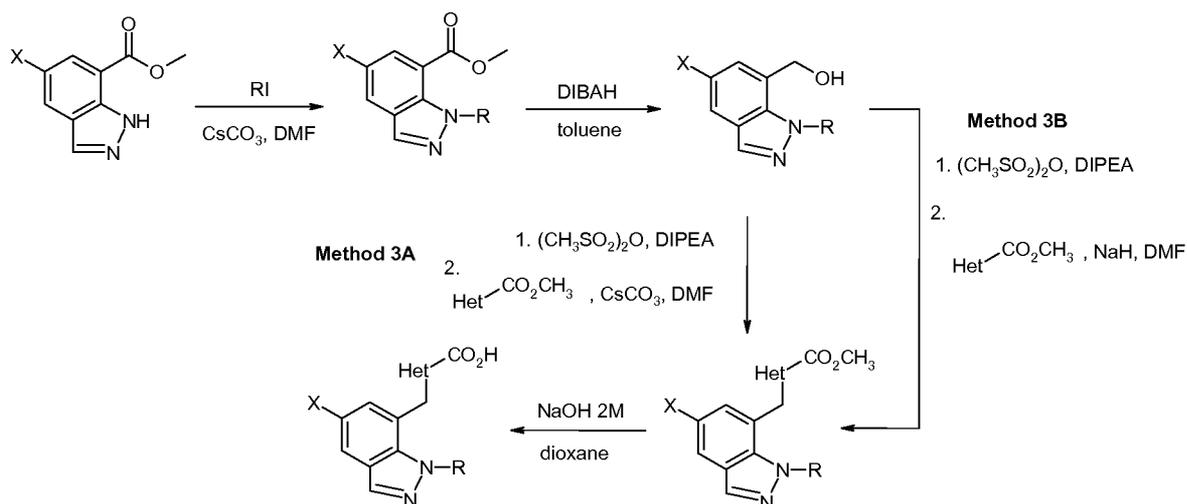
15 Compound **40** was prepared following general method 3A, using compound **21** as a starting material and 1H-benzimidazole-5-carboxylic acid methyl ester as the heterocycle. Yield: 65%.

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.63 (s, 1H, ArH), 8.11 (s, 1H, ArH), 8.09 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.65 (s, 1H, ArH), 7.38 (d, $J = 9\text{Hz}$, 1H, ArH), 6.80 (s, 1H,

ArH), 5.77 (s, 2H, CH₂), 4.14 (d, J = 7.5Hz, 2H, CH₂), 3.97 (s, 3H, CH₃), 2.18 – 2.32 (m, 1H, CH), 0.88 (d, J = 8Hz, 6H, 2 x CH₃).

General method 4: Ester hydrolysis

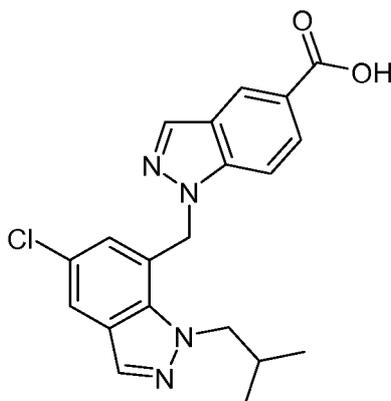
To a solution of methyl ester derivative (**25** to **40**) in dioxane (6M) was added a
 5 2M aqueous solution of sodium hydroxide. (4 equivalents) The resulting mixture was
 heated at 60°C for 16 h. Then, the reaction mixture was allowed to cool, neutralised to pH
 7 with 2M solution of HCl and diluted with ethyl acetate. The organic layer was
 separated, washed with Brine, dried (MgSO₄), filtered and the solvent evaporated to give
 the desired product as yellow oil. The residue was purified in a 20G SPE cartridge using
 10 an eluent gradient from isohexane/ethyl acetate 9:1 to 1:1 as appropriate to isolate the
 desired product.



Scheme 2. Synthesis of compounds **41-56**

15

Example 41 1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 41



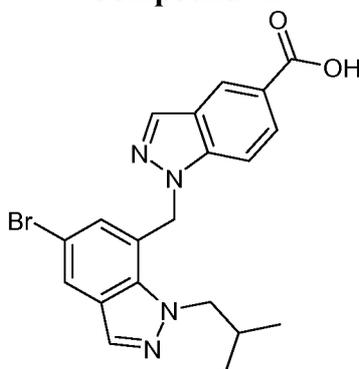
Compound **41** was prepared from compound **25** following general method 4.
Yield: 80%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.65 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.10 (d, 1H, J = 8.9 Hz, ArH), 8.00 (s, 1H, ArH), 7.65 (s, 1H, ArH), 7.33 (d, 1H, J = 8.9 Hz, ArH), 6.75 (s, 1H, ArH), 6.03 (s, 2H, ArCH₂N), 4.35 (d, 2H, J = 7.3 Hz, NCH₂), 1.55 (m, 1H, -CH(CH₃)₂), 0.85 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 383 M + H⁺

Example 42

10 **1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 42**



Compound **42** was prepared from compound **26** following general method 4.
Yield: 80%.

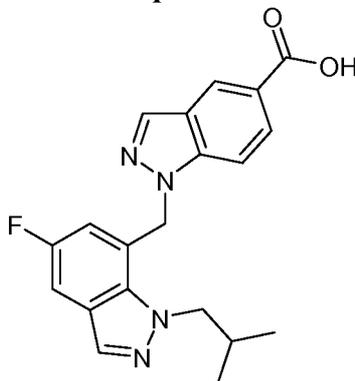
15 ¹H-NMR (CDCl₃, 300 MHz) δ 8.67 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.10 (d, 1H, J = 8.9 Hz, ArH), 8.00 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.35 (d, 1H, J = 8.9 Hz, ArH),

6.97 (s, 1H, ArH), 6.03 (s, 2H, ArCH₂N), 4.37 (d, 2H, J = 7.3 Hz, NCH₂), 2.25 (m, 1H, -CH(CH₃)₂), 0.95 (d, 3H, J = 6.7 Hz, CH(CH₃)₂), 0.85 (d, 3H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 429 M + H⁺

Example 43

5 1-(5-Fluoro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 43



Compound **43** was prepared from compound **27** following general method 4. Yield: 54%.

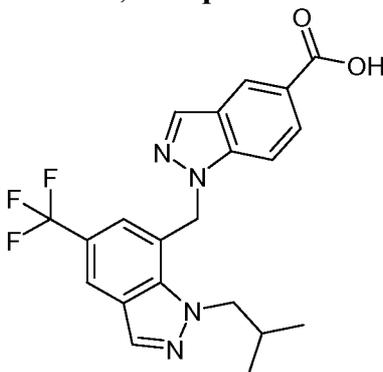
10 ¹H-NMR(CDCl₃, 300 MHz) δ 8.69 (s, 1H, ArH), 8.28 (s, 1H, ArH), 8.13 (dd, J = 2 and 7.5Hz, 1H, ArH), 8.01 (s, 1H, ArH), 7.27 – 7.38 (m, 2H, 2 x ArH), 6.48 (dd, J = 4 and 10.5Hz, 1H, ArH), 6.05 (s, 2H, CH₂), 4.43 (d, J = 5Hz, 2H, CH₂), 2.25 – 2.38 (m, 1H, CH), 0.95 (d, J = 8Hz, 6H, 2 x CH₃).

LC-MS: m/z 367 (M + H⁺).

15

Example 44

1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 44



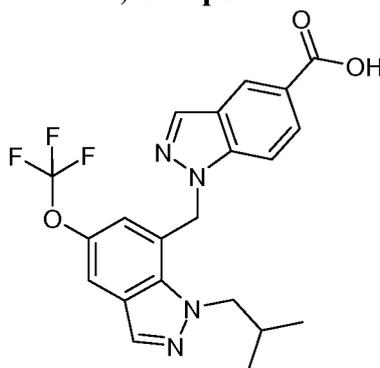
Compound **44** was prepared from compound **28** following general method 4.
Yield: 54%.

¹H-NMR(CDCl₃, 300 MHz) δ 8.68 (s, 1H, ArH), 8.27 (s, 1H, ArH), 8.17 (s, 1H, ArH), 8.11 (dd, J = 2 and 9Hz, 1H, ArH), 8.05 (s, 1H, ArH), 7.33 (d, J = 9Hz, 1H, ArH),
5 7.13 (s, 1H, ArH), 6.05 (s, 2H, CH₂), 4.41 (d, J = 5Hz, 2H, CH₂), 2.23 – 2.38 (m, 1H, CH), 0.93 (d, J = 8Hz, 6H, 2 x CH₃).

LC-MS: m/z 417 (M + H⁺).

Example 45
1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 45

10



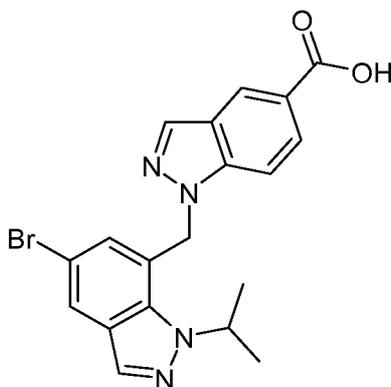
Compound **45** was prepared from compound **29** following general method 4.
Yield: 62%.

¹H-NMR(CDCl₃, 300 MHz) δ 8.69 (s, 1H, ArH), 8.27 (s, 1H, ArH), 8.04 – 8.14
15 (m, 2H, 2 x ArH), 7.54 (s, 1H, ArH), 7.32 (d, J = 5Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.03 (s, 2H, CH₂), 4.42 (d, J = 7.5Hz, 2H, CH₂), 2.24 – 2.40 (m, 1H, CH), 0.95 (d, J = 8Hz, 6H, 2 x CH₃).

LC-MS: m/z 433 (M + H⁺).

Example 46
1-(5-Bromo-1-isopropyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid, Compound 46

20



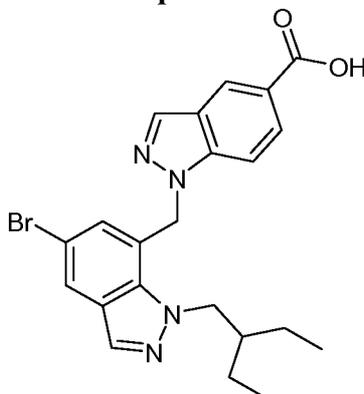
Compound **46** was prepared from compound **30** following general method 4.
Yield: 85%.

¹H-NMR (CDCl₃, 300 MHz) δ 8.55 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.00 (d, 1H, J = 8.9 Hz, ArH), 7.97 (s, 1H, ArH), 7.80 (s, 1H, ArH), 7.23 (d, 1H, J = 8.9 Hz, ArH), 6.97 (s, 1H, ArH), 5.95 (s, 2H, ArCH₂N), 5.05 (m, 1H, NCH(CH₃)₂), 1.40 (d, 6H, J = 6.7 Hz, NCH(CH₃)₂).

LC-MS: m/z 415 M + H⁺

Example 47

10 **1-[5-Bromo-1-(2-ethyl-butyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid, Compound 47**



Compound **47** was prepared from compound **31** following general method 4.
Yield: 90%.

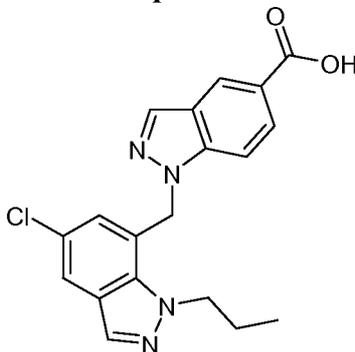
15 ¹H-NMR (CDCl₃, 300 MHz) δ 8.63 (s, 1H, ArH), 8.20 (s, 1H, ArH), 8.05 (d, 1H, J = 8.9 Hz, ArH), 7.80 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.65 (d, 1H, J = 8.9 Hz, ArH),

7.00 (s, 1H, ArH), 6.00 (s, 2H, ArCH₂N), 4.30 (d, 2H, J = 7.3 Hz, NCH₂), 2.00 (m, 1H, -CH(CH₂CH₃)₂), 1.30 (m, 4H, CH(CH₂CH₃)₂), 0.90 (m, 6H, CH(CH₂CH₃)₂).

LC-MS: m/z 457 M + H⁺

Example 48

5 **1-[5-Chloro-1-(2-propyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid, Compound 48**



Compound **48** was prepared from compound **32** following general method 4. Yield: 65%.

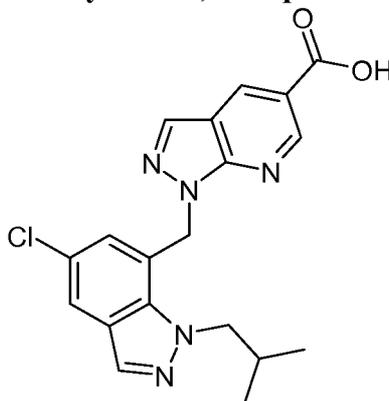
10 ¹H-NMR (CDCl₃, 300 MHz) δ 8.67 (s, 1H, ArH), 8.25 (s, 1H, ArH), 8.11 (d, 1H, J = 8.9 Hz, ArH), 7.99 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.35 (d, 1H, J = 8.9 Hz, ArH), 6.81 (s, 1H, ArH), 6.02 (s, 2H, ArCH₂N), 4.55 (t, 2H, J = 7.3 Hz, NCH₂CH₂CH₃), 1.86 (m, 2H, NCH₂CH₂CH₃), 0.88 (t, 3H, J = 7.3 Hz, NCH₂CH₂CH₃).

LC-MS: m/z 369 M + H⁺

15

Example 49

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, Compound 49

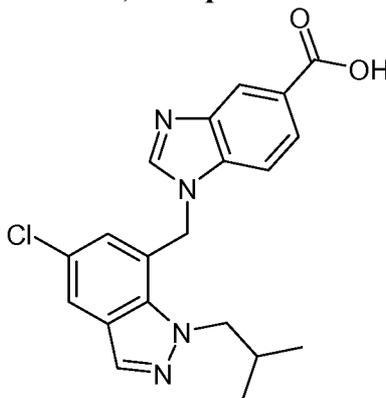


Compound **49** was prepared from compound **33** following general method 4.
Yield: 60%.

¹H-NMR (CDCl₃, 300 MHz) δ 9.23 (s, 1H, ArH), 8.76 (s, 1H, ArH), 8.06 (s, 1H, ArH), 7.93 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.01 (s, 1H, ArH), 6.02 (s, 2H, ArCH₂N),
5 4.47 (d, 2H, J = 7.3 Hz, NCH₂), 2.26 (m, 1H, -CH(CH₃)₂), 0.88 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 384M + H⁺

Example 50
10 **1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid, Compound 50**

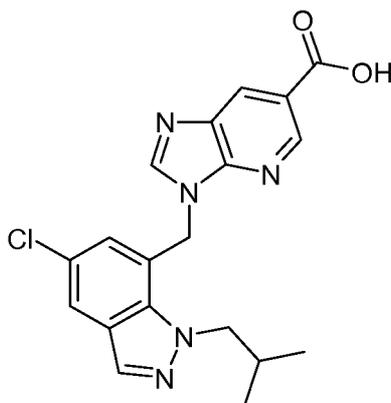


Compound **50** was prepared from compound **34** following general method 4.
Yield: 70%.

¹H-NMR (CH₃OD, 300 MHz) δ 8.52 (s, 1H, ArH), 8.33 (bs 1H, ArH), 8.12 (s,
15 1H, ArH), 8.09 (s, 1H, ArH), 7.81 (s, 1H, ArH), 7.60 (d, 1H, J = 8.5Hz, ArH), 6.85 (s,
1H, ArH), 6.02 (s, 2H, ArCH₂N), 4.21 (d, 2H, J = 7.3 Hz, NCH₂), 2.23 (m, 1H, -
CH(CH₃)₂), 0.80 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 383 M + H⁺

Example 51
20 **3-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid, Compound 51**



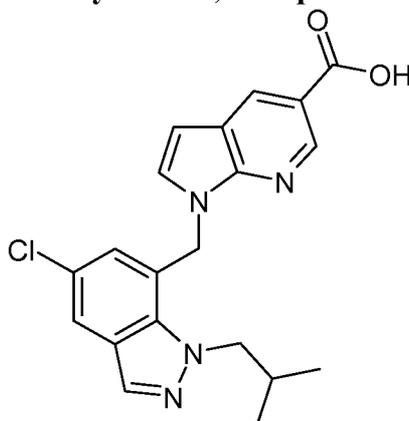
Compound **51** was prepared from compound **35** following general method 4.
Yield: 70%.

¹H-NMR (CDCl₃, 300 MHz) δ 9.31 (s, 1H, ArH), 8.90 (s 1H, ArH), 8.14 (s, 1H, ArH), 8.11 (s, 1H, ArH), 7.91 (s, 1H, ArH), 7.47 (s, 1H, ArH), 6.01 (s, 2H, ArCH₂N), 4.25 (d, 2H, J = 7.3 Hz, NCH₂), 2.33 (m, 1H, -CH(CH₃)₂), 0.91 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 384 M + H⁺

Example 52

10 **1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid, Compound 52**



Compound **52** was prepared from compound **36** following general method 4.
Yield: 66%.

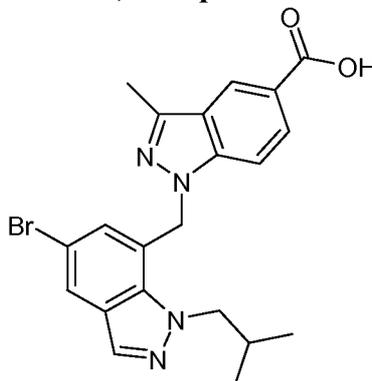
15 ¹H-NMR(CDCl₃, 300 MHz) δ 9.02 (d, J = 2Hz, 1H, ArH), 8.62 (d, J = 2Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.70 (d, J = 2Hz, 1H, ArH), 7.03 (d, J = 3Hz, 1H, ArH), 6.99 (d,

J = 2Hz, 1H, ArH), 6.57 (d, J = 3Hz, 1H, ArH), 5.85 (s, 2H, CH₂), 4.05 (d, J = 7.5Hz, 2H, CH₂), 2.07 – 2.23 (m, 1H, CH), 0.71 (d, J = 8Hz, 6H, 2 x CH₃).

LC-MS: m/z 383 and 385 (M + H⁺).

Example 53

5 1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-indazole-5-carboxylic acid, Compound 53



Compound **53** was prepared from compound **37** following general method 4. Yield: 50%.

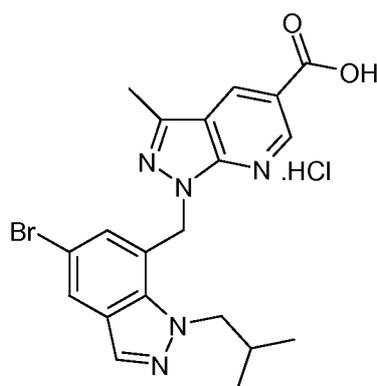
10 ¹H-NMR (CDCl₃, 300 MHz) δ 8.60 (s, 1H, ArH), 8.10 (d, 1H, J = 8.9 Hz, ArH), 7.97 (s, 1H, ArH), 7.80 (s, 1H, ArH), 7.20 (d, 1H, J = 8.9 Hz, ArH), 6.90 (s, 1H, ArH), 5.92 (s, 2H, ArCH₂N), 4.40 (d, 2H, J = 7.3 Hz, NCH₂), 2.70 (s, 3H, CH₃), 2.20 (m, 1H, -CH(CH₃)₂), 0.85 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 443 M + H⁺

15

Example 54

1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic HCl salt, Compound 54



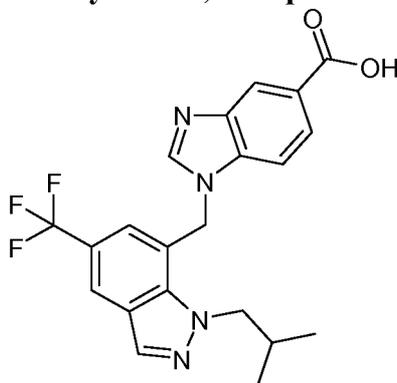
Compound **54** was prepared from compound **38** following general method 4.
Yield: 60%.

¹H-NMR (CH₃OD, 300 MHz) δ 9.20 (s, 1H, ArH), 8.85 (s, 1H, ArH), 8.05 (s, 1H, ArH), 7.90 (s, 1H, ArH), 7.20 (s, 1H, ArH), 6.10 (s, 2H, ArCH₂N), 4.55 (d, 2H, J = 7.3 Hz, NCH₂), 2.65 (s, 3H, CH₃), 2.32 (m, 1H, -CH(CH₃)₂), 0.90 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 444 M + H⁺

Example 55

10 **1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-benzimidazole-5-carboxylic acid, Compound 55**

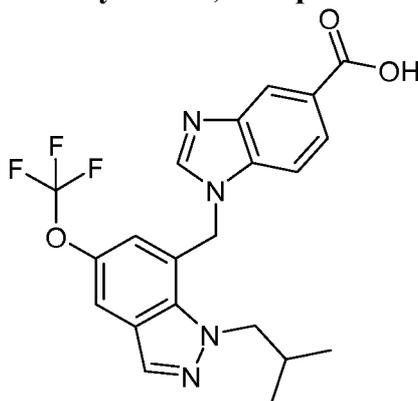


Compound **55** was prepared from compound **39** following general method 4.
Yield: 13%.

15 ¹H-NMR(CDCl₃, 300 MHz) δ 8.74 (s, 1H, ArH), 8.13 - 8.23 (m, 3H, 3 x ArH), 7.83 (s, 1H, ArH), 7.47 (d, J = 9Hz, 1H, ArH), 7.27 (s, 1H, ArH), 5.80 (s, 2H, CH₂), 4.08 (d, J = 5Hz, 2H, CH₂), 2.15 - 2.31 (m, 1H, CH), 0.81 (d, J = 8Hz, 6H, 2 x CH₃).

LC-MS: m/z 417 ($M + H^+$).

Example 56
1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-benzimidazole-5-carboxylic acid, Compound 56



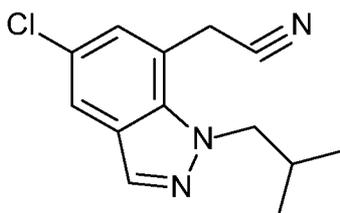
5

Compound **56** was prepared from compound **40** following general method 4. Yield: 65%.

$^1\text{H-NMR}$ (CD_3OD , 300 MHz) δ 8.55 (s, 1H, ArH), 8.02 – 8.11 (m, 2H, 2 x ArH), 7.95 (s, 1H, ArH), 7.32 – 7.41 (m, 2H, 2 x ArH), 6.71 (s, 1H, ArH), 5.82 (s, 2H, CH_2),
 10 4.11 (d, $J = 7.5\text{Hz}$, 2H, CH_2), 2.11 – 2.29 (m, 1H, CH), 0.82 (d, $J = 8\text{Hz}$, 6H, 2 x CH_3).

LC-MS: m/z 433 ($M + H^+$).

Example 57
2-(5-Chloro-1-isobutyl-indazol-7-yl)acetonitrile, Compound 57



15

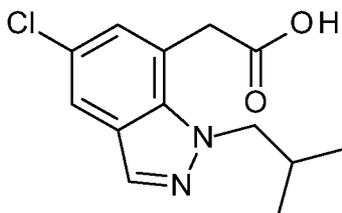
To a solution of compound **17** (1g, 4.2 mmol), at room temperature and under nitrogen atmosphere, in dry dichloromethane (10 mL) were added DIPEA (0.8 mL, 4.62 mmol) and methane sulfonic anhydride. (0.8 g, 4.62 mmol) The resulting mixture was stirred for 2 h. Then, the reaction mixture was quenched with water and the mixture was extracted with more dichloromethane. The organic layer was separated, washed with

Brine, dried (MgSO₄), filtered and the solvent evaporated to give the desired product as yellow oil.

The residue (4.2 mmol) was dissolved in DMF (20ml), treated with sodium cyanide (0.4g, 8.2 mmol) and stirred at 80°C under a nitrogen atmosphere for 1h. The mixture was evaporated to dryness and the residue partitioned between water (50ml) and ethyl acetate (2 x 50ml). The combined organics were washed with saturated brine (50ml) then dried over sodium sulphate, filtered and evaporated to dryness. This gave the title compound as a brown oil (0.994g, 82%).

¹H-NMR(CDCl₃, 300 MHz) δ 7.97 (s, 1H, ArH), 7.71 (s, 1H, ArH), 7.41 (s, 1H, ArH), 4.32 (d, J = 7.5Hz, 2H, CH₂), 4.12 (s, 2H, CH₂), 2.15 – 2.30 (m, 1H, CH), 0.96 (d, J = 8Hz, 6H, 2 x CH₃).

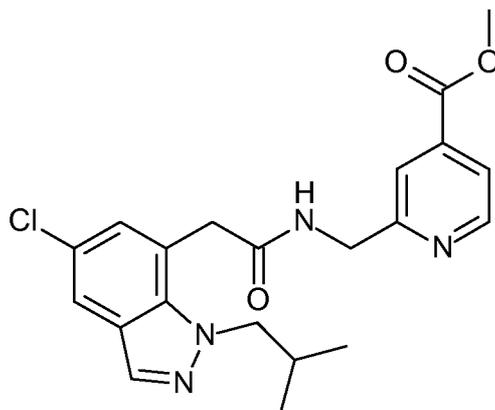
Example 58
2-(5-Chloro-1-isobutyl-indazol-7-yl)acetic acid, Compound 58



A solution of compound **57** (0.16g, 0.65 mmoles) in conc hydrochloric acid (1ml) was heated at 50°C for 1h. Water (1ml) was added and the mixture heated at 80°C for 18h. The mixture was cooled and water (10ml) added then extracted with ethyl acetate (2 x 15ml). The combined organics were dried over sodium sulphate, filtered and evaporated to dryness to give the title compound as an off-white solid (0.155g, 90%).

¹H-NMR(CDCl₃, 300 MHz) δ 9.20 – 10.20 (brs, 1H, OH), 7.97 (s, 1H, ArH), 7.66 (d, J = 2Hz, 1H, ArH), 7.22 (d, J = 2Hz, 1H, ArH), 4.31 (d, J = 7.5Hz, 2H, CH₂), 3.99 (s, 2H, CH₂), 2.09 – 2.23 (m, 1H, CH), 0.91 (d, J = 8Hz, 6H, 2 x CH₃).

Example 59
Methyl 2-[[[2-(5-chloro-1-isobutyl-indazol-7-yl)acetyl]amino]methyl]pyridine-4-carboxylate, Compound 59



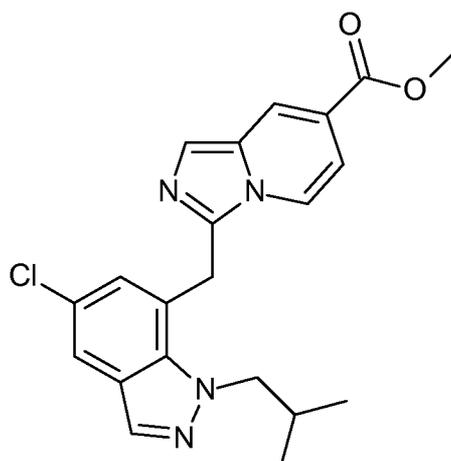
A mixture of compound **58** (0.155g, 0.58 mmoles) and methyl 2-(aminomethyl)pyridine-4-carboxylate dihydrochloride (0.139g, 0.58 mmoles) (see WO2003070732, example 6, step 2 for preparation, which is incorporated by reference in its entirety) in dichloromethane (20ml) was treated with N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate (0.264g, 0.69 mmoles) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.133g, 0.69 mmoles) and N-methylmorpholine (0.255ml, 2.32 mmoles) then stirred at ambient temperature under a nitrogen atmosphere for 18h. The mixture was washed with water (2 x 20ml) and saturated brine (20ml) then separated and dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with an ethyl acetate/ isohexane gradient. This gave the title compound as a colorless oil (0.184g 76%).

¹H-NMR(CDCl₃, 300 MHz) δ 8.55 (d, J = 6Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.68 – 7.74 (m, 2H, 2 x ArH), 7.66 (d, J = 3Hz, 1H, ArH), 7.22 (d, J = 3Hz, 1H, ArH), 6.69 – 6.79 (brs, 1H, NH), 4.57 (d, J = 6Hz, 2H, CH₂), 4.29 (d, J = 7.5Hz, 2H, CH₂), 3.98 (s, 2H, CH₂), 3.93 (s, 3H, CH₃), 2.09 – 2.24 (m, 1H, CH), 0.89 (d, J = 8Hz, 6H, 2 x CH₃).

Example 60

Methyl 3-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]imidazo[1,5-a]pyridine-7-carboxylate, Compound 60

20

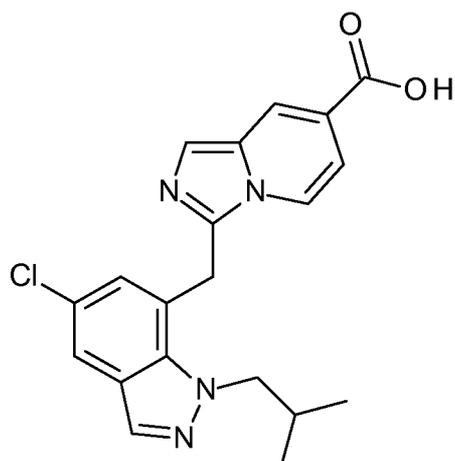


A solution/ suspension of compound **59** (0.184 g, 0.44 mmol) in toluene was treated with phosphorus oxychloride (1 ml) and stirred at 90°C under a nitrogen atmosphere for 22.5h. The mixture was cooled and treated with water (20 ml) then
5 neutralised by addition of solid sodium hydrogen carbonate. The mixture was then extracted with ethyl acetate (2 x 25ml) and the organics separated and dried over sodium sulphate, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with an ethyl acetate/ isohexane gradient to give the title compound as a yellow oil (0.092g, 52%).

10 $^1\text{H-NMR}(\text{CDCl}_3, 300 \text{ MHz}) \delta$ 8.35 (s, 1H, ArH), 7.98 (s, 1H, ArH), 7.75 (s, 1H, ArH), 7.59 – 7.65 (m, 2H, 2 x ArH), 7.15 (dd, $J = 2$ and 7.5Hz, 1H, ArH), 6.72 (d, $J = 2$ Hz, 1H, ArH), 4.79 (s, 2H, CH_2), 4.32 (d, $J = 7.5$ Hz, 2H, CH_2), 3.95 (s, 3H, CH_3), 2.15 – 2.31 (m, 1H, CH), 0.89 (d, $J = 8$ Hz, 6H, 2 x CH_3).

Example 61

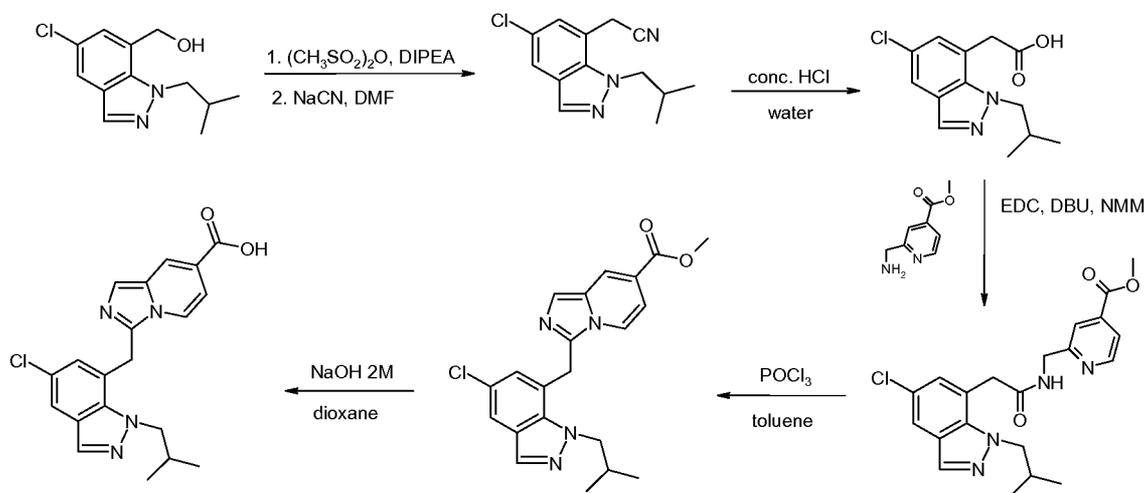
15 **3-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]imidazo[1,5-a]pyridine-7-carboxylic acid, Compound 61**



Compound **61** was prepared from compound **60** following general method 4.
Yield: 67%.

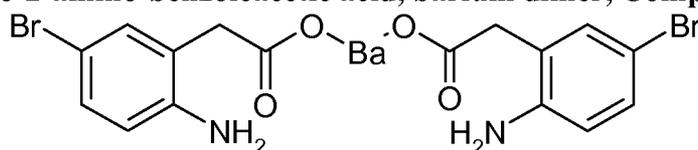
$^1\text{H-NMR}$ (CD_3OD , 300 MHz) δ 8.31 (s, 1H, ArH), 7.95 (d, $J = 7.5\text{Hz}$, 1H, ArH),
5 7.70 (s, 1H, ArH), 7.66 (d, $J = 2\text{Hz}$, 1H, ArH), 7.62 (s, 1H, ArH), 7.23 (dd, $J = 2$ and
7.5Hz, 1H, ArH), 6.77 (d, $J = 2\text{Hz}$, 1H, ArH), 4.85 (s, 2H, CH_2), 4.21 (d, $J = 7.5\text{Hz}$, 2H,
 CH_2), 2.06 – 2.24 (m, 1H, CH), 0.83 (d, $J = 8\text{Hz}$, 6H, 2 x CH_3).

LC-MS: m/z 383 and 385 ($\text{M} + \text{H}^+$).



10 Scheme 3. Synthesis of compound **61**

Example 62
5-bromo-2-amino-benzoicacetic acid, barium dimer, Compound 62

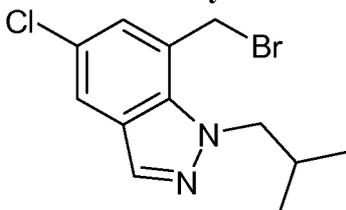


To a suspension of 5-bromo-2-oxyindole in water was added barium hydroxide
 5 and the resulting mixture was heated at reflux for 16h. Then, the reaction was cool down
 to 0°C and conc. HCl was added to reach pH 8. The mixture was heated at reflux for 30',
 and then heated at 70°C for 2h followed by heating at 50°C for 16h.

The reaction was stopped, cooled down to 0°C resulting in the precipitation of a
 solid that was collected by filtration and dried in a *vacuum* oven for 16h.

10

Example 63
7-Bromomethyl-5-chloro-1-isobutyl-1H-indazole, Compound 63

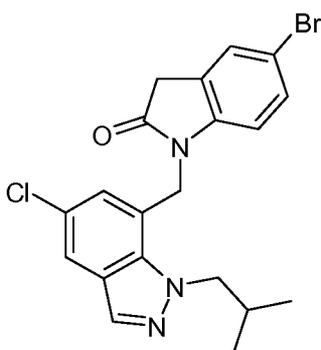


15

To a solution of compound 17 (0.25g, 1.05 mmol) in dichloromethane (10
 mL) was added a 1M solution of PB₃ in dichloromethane (1.15 mL, 1.15 mmol) and the
 resulting mixture was stirred at r.t. for 16h. Then, the reaction was quenched by adding
 water and diluted with more dichloromethane. The organic layer was separated, washed
 with Brine, dried (MgSO₄), filtered and the solvent was evaporated to give the title
 compound as a yellow oil. (0.263 g, 83%)

¹H-NMR (CDCl₃, 300 MHz) δ 7.99 (s, 1H, ArH), 7.69 (s, 1H, ArH), 7.32 (s, 1H,
 20 ArH), 4.79 (s, 2H, -CH₂Br), 4.48 (d, 2H, J = 7.3 Hz, NCH₂), 2.29 (m, 1H, -CH(CH₃)₂),
 0.98 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

Example 64
**5-Bromo-1-(5-chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1,3-dihydro-indol-2-one,
 Compound 64**

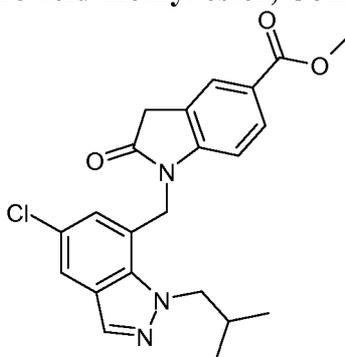


A mixture of compound **62** (0.78g, 1.31 mmol) and compound **63** (0.263g, 0.872 mmol) in tetrahydrofuran (9 mL) was heated at 110°C under microwave conditions for 1h. Then, the reaction mixture was filtered over Celite and the filtrate was concentrated to dryness *under vacuum*. Then, the residue was purified by chromatography column on a
 5 20g SPE cartridge to give the title compound as a colorless solid. (0.185 g, 49%)

¹H-NMR (CDCl₃, 300 MHz) δ 7.99 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.34 (d, 1H, J = 8.9 Hz, ArH), 6.81 (s, 1H, ArH), 6.46 (d, 1H, J = 8.9 Hz, ArH), 5.35 (s, 2H, ArCH₂N), 4.41 (d, 2H, J = 7.3 Hz, NCH₂), 3.77 (s, 2H, NCOCH₂-), 2.32 (m, 10 1H, -CH(CH₃)₂), 0.98 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 433 M + H⁺

Example 65
1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester, Compound 65



15

A mixture of compound **64** (0.1g, 0.231 mmol), molybdenumhexacarbonyl (0.03g, 0.115 mmol), Hermann's catalyst (0.022g, 0.023 mmol), Xantphos (0.027g, 0.0426 mmol), triethylamine (0.643 mL, 0.462 mmol) in a mixture of tetrahydrofuran (3 mL) and methanol (0.9 mL) was heated at 150°C under microwave conditions for 10

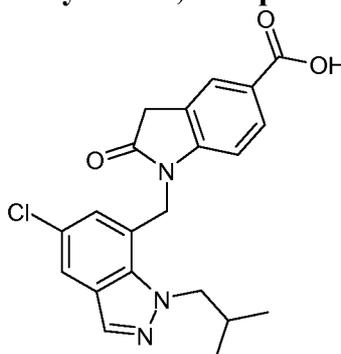
minutes. Then, the reaction was quenched by adding water and diluted with ethyl acetate. The organic layer was separated, washed with Brine, dried (MgSO_4), filtered and the solvent was evaporated. Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title compound as a colorless solid. (0.043 g, 45%)

5 $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.04 (s, 1H, ArH), 7.99 (s, 1H, ArH), 7.95 (d, 1H, $J = 8.9$ Hz, ArH), 7.61 (s, 1H, ArH), 6.80 (s, 1H, ArH), 6.63 (d, 1H, $J = 8.9$ Hz, ArH), 5.40 (s, 2H, ArCH_2N), 4.42 (d, 2H, $J = 7.3$ Hz, NCH_2), 3.92 (s, 3H, $-\text{CO}_2\text{CH}_3$), 3.80 (s, 2H, NCOCH_2-), 2.34 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 0.98 (d, 6H, $J = 6.7$ Hz, $\text{CH}(\text{CH}_3)_2$).

LC-MS: m/z 412 $\text{M} + \text{H}^+$

10

Example 66
1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid, Compound 66



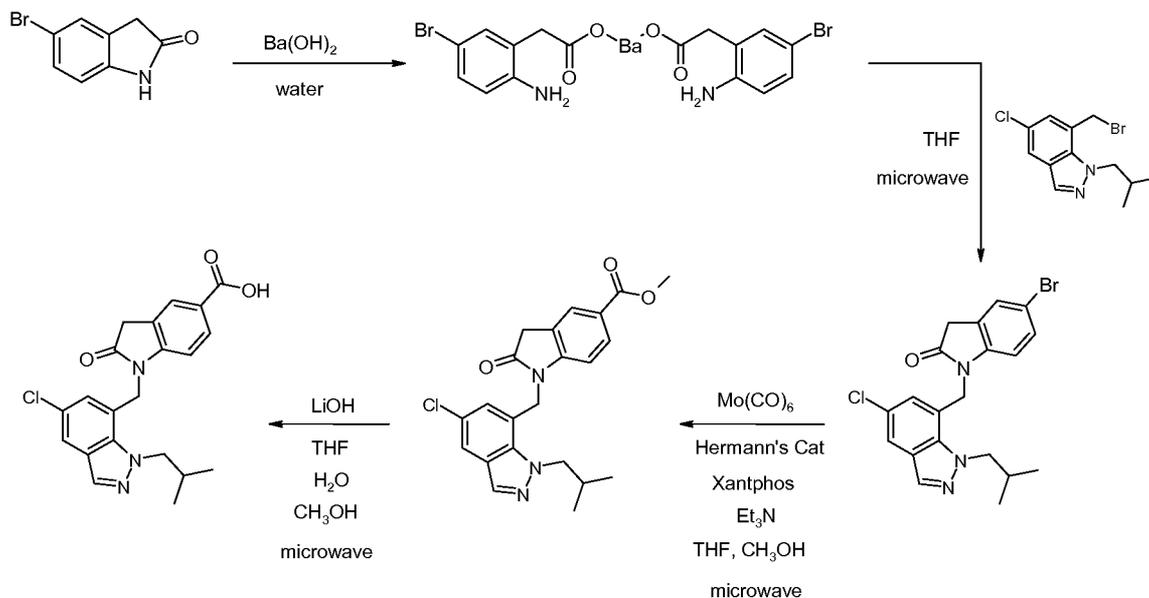
15 A mixture of compound **65** (0.021g, 0.05 mmol), lithium hydroxide (0.09g, 0.208 mmol) in a mixture of tetrahydrofuran (1.5 mL), water (0.5 mL) and methanol (0.5 mL) was heated at 100°C under microwave conditions for 10 minutes. Then, the reaction was quenched by adding water and diluted with ethyl acetate. The organic layer was separated, washed with Brine, dried (MgSO_4), filtered and the solvent was evaporated.

20 Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title compound as a colorless solid. (0.016 g, 80%)

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.09 (s, 1H, ArH), 8.02 (d, 1H, $J = 8.9$ Hz, ArH), 7.99 (s, 1H, ArH), 7.62 (s, 1H, ArH), 6.80 (s, 1H, ArH), 6.65 (d, 1H, $J = 8.9$ Hz, ArH),

5.40 (s, 2H, ArCH₂N), 4.43 (d, 2H, J = 7.3 Hz, NCH₂), 3.82 (s, 2H, NCOCH₂-), 2.34 (m, 1H, -CH(CH₃)₂), 0.87 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

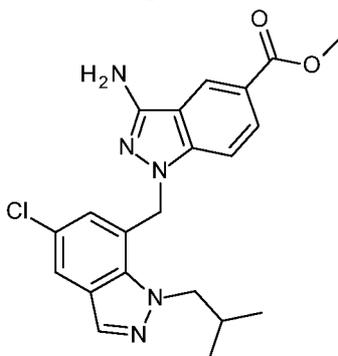
LC-MS: m/z 398 M + H⁺



5 Scheme 4. Synthesis of compound 66

Example 67

Methyl 3-amino-1-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]indazole-5-carboxylate, Compound 67



10 A mixture of compound 17 (0.112g, 0.47 mmol), methyl 3-amino-1H-indazole-5-carboxylate (0.075g, 0.39 mmol), di-tert-butyl azocarboxylate (0.135g, 0.59 mmol), triphenylphosphine (0.155g, 0.59 mmol), in tetrahydrofuran (4 mL) was heated at 140°C under microwave conditions for 20 minutes. Then, the reaction was quenched by adding water and diluted with ethyl acetate. The organic layer was separated, washed with Brine,

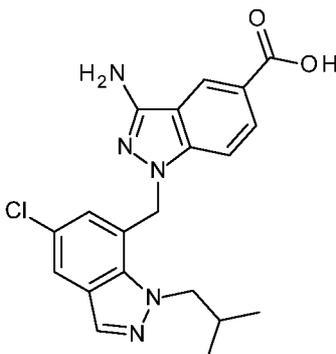
dried (MgSO₄), filtered and the solvent was evaporated. Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title compound as a colorless solid. (0.090 g, 56%)

¹H-NMR (CDCl₃, 300 MHz) δ 8.41 (s, 1H, ArH), 8.01 (dd, 1H, J= 1.8, 9 Hz, ArH), 7.97 (s, 1H, ArH), 7.64 (d, 1H, J= 1.8 Hz, ArH), 7.11 (d, 1H, J= 9 Hz, ArH), 6.81 (s, 1H, ArH), 5.75 (s, 2H, ArCH₂N), 4.38 (d, 2H, J = 7.3 Hz, NCH₂), 4.33 (bs, 2H, NH₂), 3.94 (s, 3H, -CO₂CH₃), 2.29 (m, 1H, -CH(CH₃)₂), 0.91 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 412 M + H⁺

Example 68

10 **3-Amino-1-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]indazole-5-carboxylic acid, Compound 68**



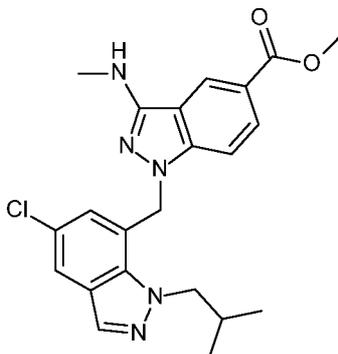
A mixture of compound **67** (0.045g, 0.11 mmol), lithium hydroxide (0.02g, 0.44 mmol) in a mixture of tetrahydrofuran (2 mL), water (1 mL) and methanol (1 mL) was heated at 100°C under microwave conditions for 10 minutes. Then, the reaction was quenched by adding water and diluted with ethyl acetate. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent was evaporated.

Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title compound as a colorless solid. (0.026 g, 60%)

20 ¹H-NMR (CH₃OD, 300 MHz) δ 8.55 (s, 1H, ArH), 8.01 (s, 2H, ArH), 7.69 (d, 1H, J= 1.8 Hz, ArH), 7.26 (d, 1H, J= 9 Hz, ArH), 6.78 (bs, 1H, ArH), 5.81 (s, 2H, ArCH₂N), 4.37 (d, 2H, J = 7.3 Hz, NCH₂), 2.25 (m, 1H, -CH(CH₃)₂), 0.87 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 398 M + H⁺

Example 69
Methyl 1-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]-3-(methylamino)indazole-5-carboxylate, Compound 69



5

A mixture of compound **67** (0.054g, 0.13 mmol), p-toluenesulphonic acid (0.003g, 0.013 mmol), in trimethylorthoformate (3 mL) was heated at 100°C in a closed vessel for 16h. Then, the reaction was concentrated to dryness *under vacuum*. The residue was dissolved in tetrahydrofuran (4 mL), sodium borohydride was added (0.015g, 10 0.395 mmol) and the resulting mixture was heated at 60°C for 5 h.

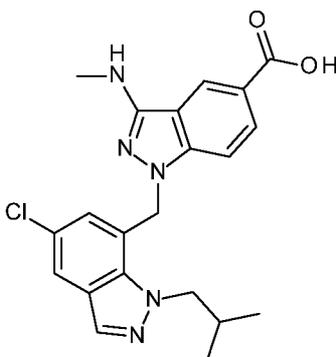
The reaction was stopped and let to cool down. Then it was quenched slowly by adding water followed by adding ethyl acetate. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent was evaporated. Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title 15 compound as a colorless solid. (0.022 g, 40%)

¹H-NMR (CDCl₃, 300 MHz) δ 8.36 (s, 1H, ArH), 7.97 (s, 1H, ArH), 7.96 (dd, 1H, J= 1.8, 9 Hz, ArH), 7.64 (d, 1H, J= 1.8 Hz, ArH), 7.01 (d, 1H, J= 9 Hz, ArH), 6.86 (s, 1H, ArH), 5.79 (s, 2H, ArCH₂N), 4.46 (d, 2H, J = 7.3 Hz, NCH₂), 3.94 (s, 3H, -CO₂CH₃), 3.11 (s, 3H, NCH₃), 2.33 (m, 1H, -CH(CH₃)₂), 0.94 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

20

LC-MS: m/z 426 M + H⁺

Example 70
1-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]-3-(methylamino)indazole-5-carboxylic acid, Compound 70



A mixture of compound **69** (0.021g, 0.05 mmol), lithium hydroxide (0.09g, 0.2 mmol) in a mixture of tetrahydrofuran (1 mL), water (0.5 mL) and methanol (0.5 mL) was heated at 100°C under microwave conditions for 10 minutes. Then, the reaction was quenched by adding water and diluted with ethyl acetate. The organic layer was separated, washed with Brine, dried (MgSO₄), filtered and the solvent was evaporated.

Then, the residue was purified by chromatography column on a 20g SPE cartridge to give the title compound as a colorless solid. (0.015 g, 70%)

¹H-NMR (CH₃OD, 300 MHz) δ 8.36 (s, 1H, ArH), 7.92 (m, 2H, ArH), 7.58 (d, 1H, J= 1.8 Hz, ArH), 6.91 (d, 1H, J= 9 Hz, ArH), 6.74 (bs, 1H, ArH), 5.72 (s, 2H, ArCH₂N), 4.39 (d, 2H, J = 7.3 Hz, NCH₂), 2.25 (m, 1H, -CH(CH₃)₂), 0.87 (d, 6H, J = 6.7 Hz, CH(CH₃)₂).

LC-MS: m/z 412 M + H⁺

The above compounds were tested for PG antagonist activity as follows using human recombinant prostanoid receptor (DP₁, EP₁₋₄, FP, IP and TP) stable cell lines:

In order to measure the response of G_s and G_i coupled prostanoid receptors as a Ca²⁺ signal, chimeric G protein cDNAs were used. Stable cell lines over-expressing human prostanoid DP₁, EP₁₋₄, FP, IP, and TP receptors were established as follows:

Briefly, human prostanoid DP₁, EP₂, and EP₄ receptor cDNAs were co-transfected with chimeric G_{qs} cDNA containing a haemagglutinin (HA) epitope; human prostanoid EP₃ receptors were co-transfected with chimeric G_{qi}-HA; human EP₁, FP, IP, and TP

receptor cDNAs were expressed with no exogenous G-proteins. G_{qs} and G_{qi} chimeric cDNAs (Molecular Devices, Sunnyvale, CA, U.S.A.), as well as cDNAs of prostanoid receptors, were cloned into a pCEP₄ vector with a hygromycin B selection marker. Transfection into HEK-293 EBNA (Epstein-Barr virus nuclear antigen) cells was achieved by the FuGENE 6 transfection Reagent (Roche Applied Science, Indianapolis, IN, USA). Stable transfectants were selected according to hygromycin resistance. Because G_{qs} and G_{qi} contained an HA epitope, G-protein expression was detected by Western blotting analysis using anti-mouse HA monoclonal antibody and horseradish peroxidase (HRP)-conjugated secondary antibody, while functional expression of prostanoid receptors was detected by FLIPR screening (Matias *et al.*, 2004). These stable cell lines were validated using previously published antagonists at 10 μ M against serial dilutions of standard agonists by FLIPR functional assays for Ca²⁺ Signaling (as described below).

Ca²⁺ signaling studies were performed using a FLIPR TETRA system (Molecular Devices, Sunnyvale, CA, USA) in the 384-format. This is a high-throughput instrument for cell-based assays to monitor Ca²⁺ signaling associated with GPCRs and ion channels. Cells were seeded at a density of 5 x 10⁴ cells/well in BioCoat poly-D-lysine coated, black wall, clear bottom 384-well plates (BD Biosciences, Franklin lakes, NJ, USA) and allowed to attach overnight in an incubator at 37°C. The cells were then washed twice with HBSS-HEPES buffer (Hanks' balanced salt solution without bicarbonate and phenol red, 20mM HEPES, pH 7.4) using an ELx405 Select CW Microplate Washer (BioTek, Winooski, VT, USA). After 60 min of dye-loading in the dark using the Ca²⁺-sensitive dye Fluo-4AM (Invitrogen, Carlsbad, CA, USA), at a final concentration of 2 x 10⁻⁶M, the plates were washed 4 times with HBSS-HEPES buffer to remove excess dye and leaving 50 μ l of buffer in each well. The plates were then placed in the FLIPR TETRA instrument and allowed to equilibrate at 37°C. AGN-211377 was added in a 25 μ l volume to each well to give final concentrations of 0.1 μ M, 0.3 μ M, 1 μ M, 3 μ M, 10 μ M, and 30 μ M; or 0.067 μ M, 0.1 μ M, 0.2 μ M, 0.3 μ M, 0.67 μ M, and 1 μ M for cells over-expressing TP receptors. After 4.5 minutes, a 7-point serial dilution of the standard agonist for the corresponding receptor, in a 25 μ l volume was injected at the final concentrations from 10⁻¹¹M to 10⁻⁵M in 10-fold serial dilution increments for cells expressing human

recombinant DP₁, EP₁, EP₂, EP₃, EP₄, FP, and IP receptors. The dose range for the standard agonist for human recombinant TP receptors was from 10⁻¹²M to 10⁻⁶M. HBSS-HEPES buffer was used as the negative control for the standard agonists. Cells were excited with LED (light emitting diode) excitation at 470–495nm and emission was measured through an emission filter at 515–575nm. Assay plates were read for 3.5 minutes using the FLIPR^{TETRA}. The peak increase in fluorescence intensity was recorded for each well. On each plate, negative controls, dose response of positive controls, and co-treatments of antagonist-agonist for each dose were in triplicates. Standard agonists were as follows: DP =BW 245C, EP₁-EP₄=PGE₂, FP =17-phenyl-PGF_{2α}, IP =Cicaprost, and TP =U-46619. The peak fluorescence change in each well containing drug was expressed relative to vehicle controls with the standard agonist at 10⁻⁶M (the positive control). To obtain concentration-response curves, compounds were tested in triplicate in each plate over the desired concentration range.

Ca²⁺ Signal Studies on Human Recombinant Prostanoid Receptor DP₂

FLIPR functional assays were conducted at Millipore to monitor the activity anti-asthmatic against human DP₂ receptors stably expressed in the Chem-5 proprietary host cell line generated by Millipore. Prior to standard agonist addition, the compounds were spotted at 10μM along with vehicle control (1% Ethanol in HBSS-HEPES buffer) across the assay wells. The assay plate was incubated at room temperature for 10 minutes in the dark. Then an 8-point serial dilution dose response from 10⁻¹²M to 10⁻⁵M of the standard agonist PGD₂ was performed. Assay plates were read for 90 seconds using the FLIPR^{TETRA}. The fluorescence measurements were collected to calculate IC₅₀ values. The assays were done at least 3 times to give n=3.

Data Processing

All plates were subjected to appropriate baseline corrections. Maximum fluorescence values were exported. The raw data of n=1 was first processed by Activity Base using nonlinear regression curve fit to calculate the percentage activity of each data point relative to the positive control (=10⁻⁶M of the standard agonist). Then n=3 of this data were exported to GraphPad Prism 4 to calculate the average EC₅₀ of the standard

agonist, and the IC_{50} (the concentration of the antagonist required to inhibit half the standard agonist activity) were calculated using nonlinear regression curve fit, with constraints of bottom constant equal to 0 and top constant equal to 100. Calculation of $K_b = [\text{Antagonist Concentration}] / (IC_{50}/EC_{50} - 1)$. When no antagonism was detected or when $K_b \geq 10,000nM$, the antagonist is defined as not active (NA).

FLIPR data

Compound Number	FP	DP1	EP1	EP2	EP3	EP4	IP	TP
41	70	460	730	9200	NA	24	NA	40
42	40	590	2300	NA	NA	22	NA	160
43	700	1700	NA	NA	NA	100	NA	450
44	150	1000	1500	PAg	NA	28	PAg	Ag
45	80	300	800	NA	NA	5	Ag	Ag
46	200	NA	3000	NA	NA	330	NA	1400
47	3000	1400	500	5000	NA	1700	1000	700
48	500	5500	NA	NA	NA	130	NA	740
49	1900	3500	9800	NA	NA	90	8900	170
50	NA	NA	NA	NA	NA	80	NA	5000
51	4900	NA	NA	NA	NA	280	8000	280
52	700	Ag	600	NA	3400	90	5500	20
53	70	640	5700	NA	NA	90	NA	1000
54	600	200	NA	NA	NA	380	9500	1600
55	3000	NA	4000	NA	NA	80	8900	Ag
56	NA	5200	9000	NA	NA	6	9000	30
61	600	4700	NA	NA	NA	200	NA	NA
68	35	3700	NA	NA	NA	60	9300	1300
70	17	1000	2300	7000	8100	1	900	300

PAg = partial agonist, Ag = agonist, NA = not active

As shown in TABLE 1, the preferred compounds of this invention are pan antagonists having activity at the FP, DP, EP₁, EP₄ and TP receptors, many are inactive at the EP₂ and EP₃ receptors. Thus, these compounds have a biological selectivity profile making them useful in treating diseases and conditions which are mediated by FP, DP, EP₁, EP₄ and TP receptors, without the side effects mediated by IP and EP₃ receptors. Moreover, open EP₂ and IP receptors may impart additional therapeutic benefit, with

particular respect to inflammatory diseases and diseases with an inflammatory component.

Thus, the compounds of this invention compound may be administered to treat DP₁, FP, EP₁, TP and/or EP₄ receptor mediated diseases or conditions.

5 For example, said condition or disease may be related to inflammation, or said DP₁, FP, EP₁, TP and/or EP₄ receptor mediated condition or disease may be selected from the group consisting of allergic conditions, asthma, allergic asthma, allergic rhinitis, uveitis and related disorders, atherosclerosis, blood coagulation disorders, bone disorders, cancer, cellular neoplastic transformations, chronic obstructive pulmonary diseases and
10 other forms of lung inflammation, congestive heart failure, diabetic retinopathy, diseases or conditions requiring a treatment of anti-coagulation, diseases requiring control of bone formation and resorption, fertility disorders, , gangrene, glaucoma, hyperpyrexia, immune and autoimmune diseases, inflammatory conditions, metastatic tumor growth, migraine, mucus secretion disorders, nasal congestion, nasal inflammation, occlusive vascular
15 diseases, ocular hypertension, ocular hypotension, osteoporosis, rheumatoid arthritis , pain, perennial rhinitis, pulmonary congestion, pulmonary hypotension, Raynaud's disease, rejection in organ transplant and by-pass surgery, respiratory conditions, hirsutism , rhinorrhea, shock, sleep disorders, and sleep-wake cycle disorders.

Said compound may be administered as a surgical adjunct in ophthalmology for
20 cataract removal and artificial lens insertion, ocular implant procedures, photorefractive radial keratotomy and other ophthalmological laser procedures or as a surgical adjunct in a procedure involving skin incisions, relief of pain and inflammation and scar formation/keloids post-surgery, for treating sports injuries and general aches and pains in muscles and joints.

25 Preferably, said DP₁, FP, EP₁, TP, and/or EP₄ receptor mediated condition or disease is an EP₁ and/or EP₄ receptor mediated condition or disease.

Preferably, said DP₁, FP, EP₁, TP and/or EP₄ receptor mediated condition or disease is an allergic condition, e.g. a dermatological allergy, or an ocular allergy, or a respiratory allergy, e.g. nasal congestion, rhinitis, and asthma.

Said condition or disease may be related to pain.

5 Said condition or disease characterized by fibrosis

Said condition or disease may be selected from the group consisting of arthritis, migraine, and headache.

10 Said condition or disease may be associated with the gastrointestinal tract, wherein said condition or disease may be peptic ulcer, heartburn, reflux esophagitis, erosive esophagitis, non-ulcer dyspepsia, infection by *Helicobacter pylori*, alrinitis, and irritable bowel syndrome.

15 Said condition or disease may be selected from the group consisting of hyperalgesia and allodynia, or said condition or disease may be related to mucus secretion, wherein said mucus secretion is gastrointestinal, or occurs in the nose, sinuses, throat, or lungs.

Said condition or disease is related to abdominal cramping, e.g. said condition or disease may be irritable bowel syndrome.

Said condition or disease may be a bleeding disorder, or a sleep disorder, or mastocytosis.

20 Said condition or disease may be associated with elevated body temperature, or ocular hypertension and glaucoma, or ocular hypotension.

Said condition may relate to surgical procedures to treat pain, inflammation and other unwanted sequelae wherein said surgical procedure includes incision, laser surgery or implantation.

The present invention also relates to a method of treating inflammation resulting from inflammatory diseases characterized by monocytic infiltration caused by the secretion of cytokines and/or chemokines by administration, to a patient in need of said treatment, of a pharmaceutical composition comprising a compound of the present invention

The current finding that the compounds of this invention are effective in attenuating the production of TNF family cytokines (TNF α), and the classical interleukin-1 (IL-1) family cytokines is especially important. These cytokines exert a broad spectrum of biological and pathological effects. They play key roles in inflammation and RA pathogenesis by stimulating the release of multiple proinflammatory cytokines, including themselves, through the NF κ B signaling pathway. Although alleviating the symptoms of RA in 50-65% of patients, a TNF α antibody is very expensive to use compared to chemically synthesized small molecules, inconvenient to administer usually requiring injections, and has been linked to tuberculosis, lymphoma, and other adverse effects. Unlike a TNF α antibody that totally eliminates all circulating TNF α in the system; the compounds of this invention only attenuate the production of TNF α by inhibiting proinflammatory PG receptors. Therefore the adverse effects associated with a TNF α antibody in elevating infectious and cancerous tendency is less likely.

Proinflammatory elements TNF, RANTES, and MCP-1 are involved in the cascade of events in the early and late stages of atherosclerosis. Plasma MCP-1 levels have been linked to cardiovascular disease risk factors in clinical studies. Platelet activation leads to the release of MIP-1 α , RANTES, and IL-8, which attract leukocytes and further activate other platelets. These evidences provide a direct linkage between homeostasis, infection, and inflammation and the development of atherosclerosis. The compounds of this invention are able to target multiple biomarkers of inflammation, thrombosis, and atherothrombosis simultaneously, which may confer pharmaceutical potential on the compounds of this invention in treating atherosclerosis and atherothrombosis. As a result, the compounds of this invention are unlikely to be associated with cardiovascular liability as in the case of the COXIBs, conversely it may even have a beneficial effect on cardiovascular function.

In summary, because of their ability to suppress the synthesis of some key proinflammatory cytokines/chemokines IL-8, MCP-1, MDC, RANTES, and TNF α , the compounds of the present invention are not only at least as effective as COXIBs and NSAIDs in RA treatment, but also are a safer therapy in RA treatment. They are also a potential therapy for cardiovascular diseases.

The compounds of this invention treat or prevent inflammation at least in part by the decreasing the amount of the secretion of certain cytokines and/ or chemokines that result from the exposure of the patient to a stimulant. In particular, the secretion of VEGF, MIP-1 β , IL-8, , MCP-1, MDC, and RANTES is reduced in those instances where said secretions are triggered by lipopolysaccharides (LPS) and or TNF α .

Interleukin-8 (IL-8): functions as a potent chemoattractants and activator of neutrophils, IL-8 is produced in response to stimulation with either IL-1 or TNF α . IL-8 not only accounts for a significant proportion of the chemotactic activity for neutrophils in rheumatoid arthritis (RA) synovial fluids, but also is a potent angiogenic factor in the RA synovium.

Monocyte chemoattractant protein-1 (MCP-1, or CCL-2): is not only believed to play a role in inflammatory diseases characterized by monocytic infiltration, such as RA rheumatoid arthritis, psoriasis, and atherosclerosis, but is also implicated in other diseases, such as atopic dermatitis, renal disease, pleurisy, allergy and asthma, colitis, endometriosis, polymyositis and dermatomyositis, uveitis, restenosis, brain inflammation and obesity. MCP-1 also controls leukocyte trafficking in vascular cells involved in diabetes and diabetes-induced atherosclerosis. MCP-1 antibodies are potential therapeutic agents for treating MCP-1/CCR2-mediated multiple inflammatory diseases.

Tumor necrosis factor α (TNF α): mainly secreted by macrophages and recognized for its importance in activating the cytokine cascade. TNF α stimulates the production of proinflammatory cytokines/chemokines, collagenases, metalloproteinases, and other inflammatory mediators; activates endothelial cells and neutrophils; promotes T- and B-cell growth, as well as stimulating bone resorption. The TNF α antibody infliximab not only decreases the production of local and systemic proinflammatory

cytokines/chemokines, but also reduces serum MMP-3 production, nitric oxide synthase activity, VEGF release, and angiogenesis in inflamed joints.

Macrophage-derived chemokine (MDC) induces chemotaxis for monocyte-derived dendritic cells, activated T cells and natural killer (NK) cells (Ho *et al.*, 2003).
5 Highly expressed by the three major cell types involved in allergic inflammation: eosinophils, basophils, and Th2 lymphocytes (Garcia *et al.*, 2005), as well as highly expressed in atopic dermatitis (Pivaresi *et al.*, 2005), MDC plays a role in inflammatory diseases such as allergic asthma and atopic dermatitis (Ho *et al.*, 2003). Significantly enhanced in keratinocytes of patients with atopic dermatitis, MDC could be a candidate
10 therapeutic target for inflammatory skin disease such as atopic dermatitis (Qi *et al.*, 2009). MDC is also implicated in disease activity of RA. After combination treatment with the disease-modifying anti-rheumatic drugs leflunomide and methotrexate in RA patients, plasma MCP-1 and MDC concentrations were significantly lower, and so was the recruitment of inflammatory cells into the sites of inflammation (Ho *et al.*, 2003).
15 Moreover, MDC also amplify platelet activation and has been associated with the pathogenesis of atherosclerotic disease including thrombosis (Gleissner *et al.*, 2008).

Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) is a chemoattractant for blood monocytes, memory T-helper cells and eosinophils, and plays an active role in recruiting leukocytes into inflammatory sites. It also stimulates the
20 release of histamine from basophils, activates eosinophils and causes hypodense eosinophils, which is associated with diseases such as asthma and allergic rhinitis. RANTES receptor CCR5 is also expressed on cells involved in atherosclerosis (e.g. monocytes/macrophages, T lymphocytes, or Th1-type cells), and is specialized in mediating RANTES-triggered atherosclerotic plaque formation (Zernecke *et al.*, 2008).
25 Like MCP-1, stimulation with RANTES enhances production of IL-6 and IL-8 in RA fibroblast-like synovial cells; elevated MMP-3 production by chondrocytes, and inhibited proteoglycan synthesis and enhanced proteoglycan release from the chondrocytes (Iwamoto *et al.*, 2008). Both MCP-1 and RANTES were found to play an important role in allergic lung inflammation, lung leukocyte infiltration, bronchial hyper-
30 responsiveness, and the recruitment of eosinophils in the pathogenesis of asthma (Conti

et al., 2001). Similar to MCP-1, RANTES also enhances the inflammatory response within the nervous system, which plays an apparent role in the pathogenesis of multiple sclerosis (Conti *et al.*, 2001). Inhibitors for RANTES may provide clinical benefits in treating inflammation, CNS disorders, parasitic disease, cancer, autoimmune and heart
5 diseases (Castellani *et al.*, 2007).

The compounds of the present invention wherein said product is packaged and labelled for the treatment or prevention of a disease or condition selected from the group consisting of uveitis, allergic conditions, asthma, allergic asthma, allergic rhinitis, atherosclerosis, blood coagulation disorders, bone disorders, cancer, cellular neoplastic
10 transformations, chronic obstructive pulmonary diseases and other forms of lung inflammation, congestive heart failure, diabetic retinopathy, diseases or conditions requiring a treatment of anti-coagulation, diseases requiring control of bone formation and resorption, fertility disorders, hyperpyrexia, gangrene, glaucoma, hypothermia, immune and autoimmune diseases, inflammatory conditions, metastatic tumor growth,
15 migraine, mucus secretion disorders, nasal congestion, nasal inflammation, occlusive vascular diseases, ocular hypertension, ocular hypotension, osteoporosis, pain, perennial rhinitis, pulmonary congestion, pulmonary hypotension, Raynaud's disease, rejection in organ transplant and by-pass surgery, respiratory conditions, rheumatoid arthritis, rhinorrhea, shock, sleep disorders, sleep-wake cycle disorders, sports injuries , muscle
20 aches and pains , and surgical adjunct for minimizing pain , inflammation and scar/keloid formation.

Those skilled in the art will readily understand that for administration the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which, per se, are well known in the art. Specifically, a drug to be administered
25 systemically, it may be formulated as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

For solid dosage forms, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium

saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycerol monostearate or glycerol distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874, which are hereby incorporated by reference in their entireties, to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the compounds of the present invention and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, subcutaneously, intramuscularly or intravenously. Injectable formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds of the present invention administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 ng/kg/day or about 1 ng/kg/day to about 100 mg/kg/day.

For ophthalmic application, solutions are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methylcellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmologically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmologically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

Similarly, an ophthalmologically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

5 Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of the present invention are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, 10 preservative system, and emollient.

The actual dose of the compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

15 A skilled person will also realize that the compounds of the present invention can be used in the manufacture of a medicament for the treatment of the disorders mentioned herein (e.g. the DP₁, FP, EP₁, TP and/or EP₄ receptor mediated diseases or conditions mentioned herein).

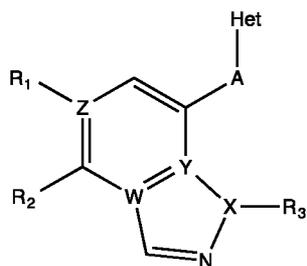
20 Patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are incorporated herein by reference to the same extent as if each individual application or publication was specifically and individually incorporated herein by reference.

25 The present invention is not to be limited in scope by the exemplified embodiments, which are only intended as illustrations of specific aspects of the invention. Various modifications of the invention, in addition to those disclosed herein, will be apparent to those skilled in the art by a careful reading of the specification, including the claims, as originally filed. It is intended that all such modifications will fall within the scope of the appended claims.

Claims

What is claimed is:

1. A compound of formula (I):



5

(I)

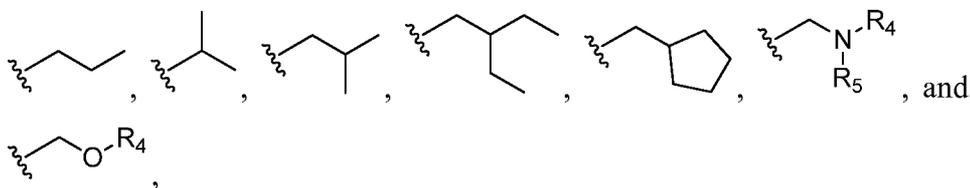
wherein:

A is selected from the group consisting of C₁-C₃ alkylene and CO;

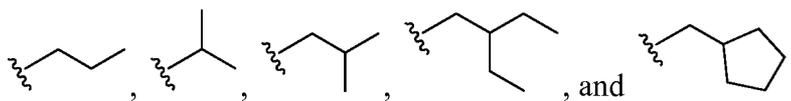
X is either CH or N, wherein:

when X is CH, R₃ is selected from the group consisting of:

10



and when X is N, R₃ is selected from the group consisting of:



W and Y are either C or N;

15

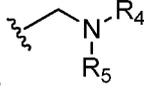
Z is either C or N, wherein:

when Z is C, R₁ is selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, CH₂OCH₃, F, Cl, Br, halogen, OCF₃, OCCl₃, OCB₃ and wherein C₁-C₃

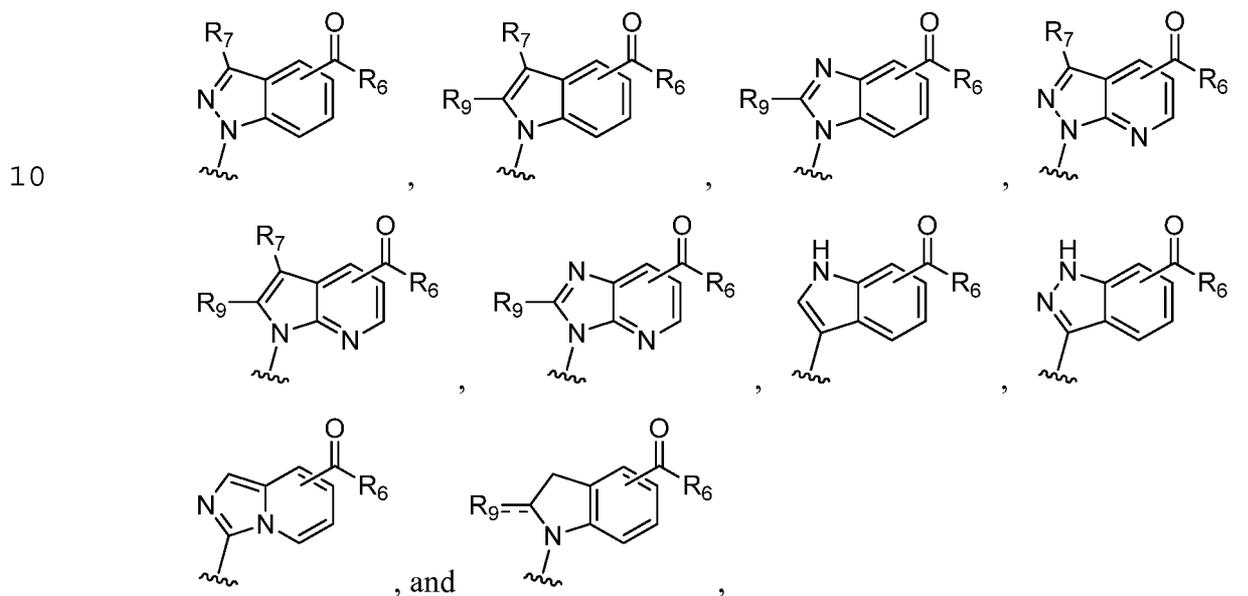
alkyl may be optionally substituted by hydroxyl, halogen, amine and functional amines,

and when Z is N, there is no R₁ substituent;

R₂ is selected from the group consisting of H, C₁–C₃ alkyl, C₁–C₃ haloalkyl,
5 CH₂OCH₃, F, Cl, Br, halogen, and OCF₃;

R₄ and R₅ are independently selected from the group consisting of C₁ – C₃ alkyl and
substituted C₁ – C₃ alkyl, and when R₃ is , R₄ and R₅ can be joined to
form a C₃–C₆ cycloalkyl;

Het is selected from the group consisting of:



wherein:

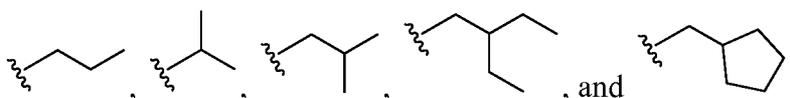
R₆ is selected from the group consisting of OH, OCH₃, OCH(CH₃)₂, and
15 NHSO₂R₈;

R₇ is selected from the group consisting of H, CH₃, CH₂CH₃, OCH₃, CH₂OH,
CH₂OCH₃, NH₂, C₁–C₃ alkylamino, and C₁–C₃ dialkylamino;

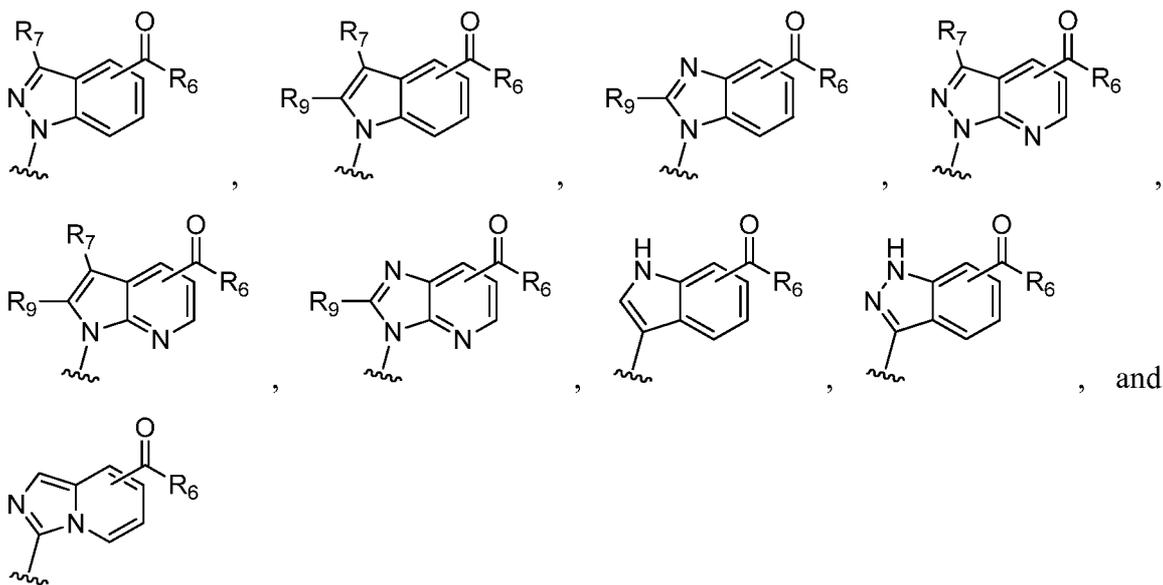
R_8 is selected from the group consisting of C_1 - C_3 alkyl and substituted C_1 - C_3 alkyl; and,

R_9 is selected from the group consisting of O, OH, CH_3 , halogen and OCH_3 the dashed bond represents the presence of a single or double bond;

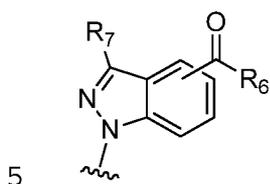
- 5 and wherein the compounds can be in the form of a tautomer, a racemate, an enantiomer, a diastereomer, or a pharmaceutically acceptable salt.
2. The compound of claim 1, wherein A is C_1 - C_3 alkyl.
3. The compound of claim 1, wherein A is CO.
4. The compound of claim 2, wherein A is CH_2 .
- 10 5. The compound of claim 1, wherein Z is C and X is N.
6. The compound of claim 5, wherein R_3 is selected from group consisting of:



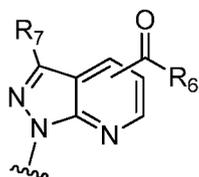
7. The compound of claim 6, where R_1 is halogen.
8. The compound of claim 6, wherein R_2 is H.
- 15 9. The compound of claim 1, wherein Het is selected from the group consisting of:



10. The compound of claim 9, wherein Het is:



11. The compound of claim 9 wherein Het is:

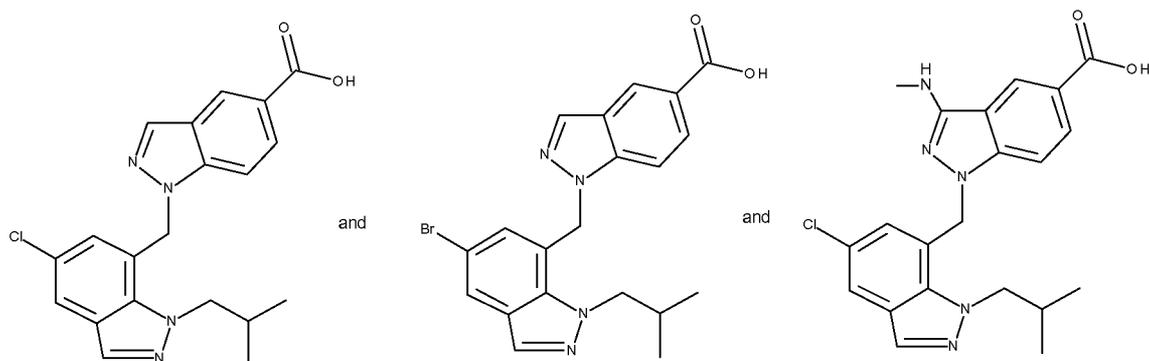


12. The compound of claim 1 wherein Z is C, R₁ is Cl or Br and R₇ is H or NCH₃.

13. The compound of claim 12 wherein X is N, R₆ is OH and R₃ is



14. The compound of claim 13 selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 selected from the group consisting of:

- 1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 5 1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 1-(5-Fluoro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 10 1-(5-Bromo-1-isopropyl-1H-indazol-7-ylmethyl)-1H-indazole-5-carboxylic acid;
- 1-[5-Bromo-1-(2-ethyl-butyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid;
- 1-[5-Chloro-1-(2-propyl)-1H-indazol-7-ylmethyl]-1H-indazole-5-carboxylic acid;
- 1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid;
- 15 1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;
- 3-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid;

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid;

1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-indazole-5-carboxylic acid;

1-(5-Bromo-1-isobutyl-1H-indazol-7-ylmethyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic HCl salt;

1-(1-Isobutyl-5-trifluoromethyl-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;

1-(1-Isobutyl-5-trifluoromethoxy-1H-indazol-7-ylmethyl)-1H-benzoimidazole-5-carboxylic acid;

3-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]imidazo[1,5-a]pyridine-7-carboxylic acid;

1-(5-Chloro-1-isobutyl-1H-indazol-7-ylmethyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid;

3-Amino-1-[(5-chloro-1-isobutyl-indazol-7-yl)methyl]indazole-5-carboxylic acid;

1-[(5-Chloro-1-isobutyl-indazol-7-yl)methyl]-3-(methylamino)indazole-5-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, for use as an antagonist for a prostanoid receptor.

17. The compound of claim 1, for use in the treatment of a condition mediated by prostanoid receptors.

18. The compound of claim 14, for use in the treatment of a condition mediated by an EP₁ receptor.

19. The compound of claim 14, for use in the treatment of a condition mediated by an EP₄ receptor.

20. A method of treating a human suffering from a therapeutic condition mediated by prostanoid receptors, the method comprising administering an effective amount of a compound according to claim 1.

5 21. A method of treating a patient suffering from a condition selected from the group consisting of inflammatory pain, neuropathic pain, visceral pain, fibrosis and a condition of the central nervous system mediated by prostanoid receptors, the method comprises administering to said patient an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2015/013119

A. CLASSIFICATION OF SUBJECT MATTER		
INV. C07D231/56	C07D401/12	C07D403/06
A61K31/4184	A61K31/437	A61P23/00
C07D471/04	A61K31/416	
A61P25/00		
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007/060596 A1 (GIBLIN GERARD M P [GB] ET AL) 15 March 2007 (2007-03-15) cited in the application claims 1,8 -----	1-21
A	US 2010/093819 A1 (MORITA KOHEI [JP] ET AL) 15 April 2010 (2010-04-15) claims 1,15 -----	1-21
A	WO 2013/096496 A2 (ALLERGAN INC [US]; CARLING WILLIAM R [GB]; MARTOS JOSE L [GB]; KANGASM) 27 June 2013 (2013-06-27) claims 1,19 -----	1-21
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search	Date of mailing of the international search report	
25 February 2015	05/03/2015	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gettins, Marc	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2015/013119

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