

Phenyl or pyridinyl substituted indazoles derivatives

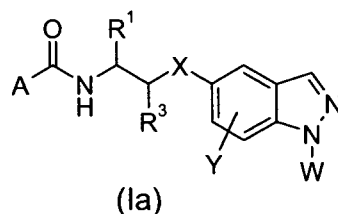
The present invention relates to novel indazolyl derivatives, to pharmaceutical compositions comprising such derivatives, to processes for preparing such novel derivatives and to the use of such derivatives as medicaments (for example in the treatment of an inflammatory disease state).

Sulphonamide derivatives are disclosed as anti-inflammatories in WO 2004/019935 and WO 2004/050631. Pharmaceutically active sulphonamides are also disclosed in Arch. Pharm. (1980) 313 166-173, J. Med. Chem. (2003) 46 64-73, J. Med. Chem (1997) 40 996-1004, EP 0031954, EP 1190710 (WO 200124786), US 5861401, US 4948809, US3992441 and WO 99/33786.

It is known that certain non-steroidal compounds interact with the glucocorticoid receptor (GR) and, as a result of this interaction, produce a suppression of inflammation (see, for example, US6323199). Such compounds can show a clear dissociation between anti-inflammatory and metabolic actions making them superior to earlier reported steroidal and non-steroidal glucocorticoids. The present invention provides further non-steroidal compounds as modulators (for example agonists, antagonists, partial agonists or partial antagonists) of the glucocorticoid receptor. {Modulators of the glucocorticoid receptor are disclosed in WO 2007/122165, WO 2008/076048 and WO 2008/043788.} These new compounds are contemplated to have improved properties such as selectivity or efficacy over the known compounds.

These new compounds are also contemplated to have an improved low LogD and thus an improved distribution volume *in vivo*. The systemic exposure of the compounds is also expected to be improved. Further the compounds are contemplated to have a lower melting point and improved crystallinity compared to the known compounds.

The present invention provides a compound of formula Ia:



wherein:

A is C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₇cycloalkyl, C₁₋₆haloalkyl, C₁₋₆alkylthio, C₁₋₆alkylC(O)-, C₁₋₆alkyloxyC(O)-, NR⁵R⁶, NR⁵R⁶C(O)- or C₅₋₁₀heteroaryl, all optionally substituted by one or more substituents independently selected from halo, cyano, hydroxyl, C₁₋₄alkyl, C₁₋₄alkoxy and C₁₋₄haloalkyl;

R⁵ and R⁶ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(O)- and C₃₋₇cycloalkylC(O)-, or R⁵ and R⁶ might form a ring with the nitrogen to which they are attached;

R¹ is hydrogen, C₁₋₄alkyl, C₁₋₄hydroxyalkyl-, C₁₋₄alkylOC₁₋₄alkyl-, C₁₋₄alkylthioC₁₋₄alkyl- or C₁₋₄haloalkyl;

R³ is C₅₋₁₀aryl, C₅₋₁₀arylC₁₋₄alkyl-, C₅₋₁₀arylO-, C₅₋₁₀arylC₁₋₄alkoxy-, C₅₋₁₀aryloxyC₁₋₄alkyl-, C₅₋₁₀heteroaryl-, C₅₋₁₀heteroarylC₁₋₄alkyl-, C₅₋₁₀heteroarylC₁₋₄alkoxy- or C₅₋₁₀heteroaryoxyC₁₋₄alkyl-, all of which are unsubstituted or optionally substituted by one or more substituents independently selected from B;

B is hydroxyl, halo, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₃hydroxyalkyl-, C₁₋₄alkoxyC₁₋₄alkyl-, C₃₋₆cycloalkyloxyC₁₋₄alkyl-, C₃₋₆cycloalkylO-, C₃₋₆cycloalkylthioC₁₋₄alkyl-, C₃₋₆cycloalkylthio-, C₁₋₃alkylS(O)_kC₁₋₄alkyl-, C₁₋₃alkylS(O)_k-, C₁₋₄haloalkyl or C₁₋₄haloalkoxy-, or B is one of the following groups which are linked to adjacent carbons on an aryl or heteroaryl ring (CH₂)_tOC₁₋₄alkylenylO(CH₂)_v- or (CH₂)_tO(CH₂)_v-;

k is 0, 1;

t and v are, independently, 0, 1, 2 or 3, and t and v are not both 0;

X is O or NH;

W is phenyl substituted by one or more substituents independently selected from - (CH₂)_nC(O)NR⁷R⁸, -(CH₂)_nNR⁹C(O)R⁸ or -(CH₂)_nC(O)NR⁹(CR¹⁴R¹⁵)C(O)NR⁷R⁸; and W is optionally further substituted by halogen or C₁₋₄alkyl;

R⁷ is hydrogen or C₁₋₄alkyl;

R⁸ and R⁹ are, independently, hydrogen, C₁₋₄alkyl (optionally substituted by one or two groups selected from hydroxyl, C₁₋₄alkoxy, NH₂, oxo, -C(O)NR¹⁰R¹¹, -NR¹⁰C₁₋₄alkyl, -C(O)NR¹⁰C₁₋₄alkyl, -NR¹⁰C(O)C₁₋₄alkyl, C₁₋₄alkylthio, C₅₋₁₀heterocyclyl, C₅₋₁₀aryl or C₅₋₁₀heteroaryl), C₃₋₇cycloalkyl (optionally substituted by -C(O)NH₂), C₅₋₁₀heterocyclyl, C₅₋₁₀aryl, C₅₋₁₀heteroaryl or -C(O)NR¹⁰R¹¹;

whereby C_{5-10} aryl or C_{5-10} heteroaryl are optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 , $-OCF_3$, hydroxy or cyano; and

whereby any heterocyclyl is optionally substituted by C_{1-4} alkyl, $-C_{1-4}$ alkoxy(C_{1-4} alkyl), oxo or hydroxyl;

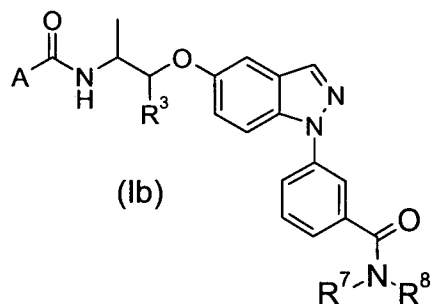
- 5 or R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom, the ring being optionally substituted by one or two groups selected from oxo, hydroxyl, C_{1-4} hydroxyalkyl-, C_{1-4} alkyl, $-C_{1-4}$ alkoxy(C_{1-4} alkyl) or $-(CH_2)_pC(O)NR^{12}R^{13}$; R^{10} , R^{11} , R^{12} and R^{13} are, independently, hydrogen or C_{1-4} alkyl;

- 10 n and p are, independently, 0, 1, 2, 3 or 4; and

Y is hydrogen, halo, C_{1-4} alkyl or C_{1-4} haloalkyl;

or a pharmaceutically acceptable salt thereof.

One embodiment relates to compounds of formula Ib



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and A, R^3 , R^7 and R^8 are defined as in compounds of formula Ia, or a pharmaceutically acceptable salt thereof.

One embodiment relates to compounds of formula Ia or Ib, wherein:

- 20 A is C_{3-7} cycloalkyl, C_{1-6} haloalkyl optionally substituted by cyano;

R^1 is C_{1-4} alkyl or C_{1-4} hydroxyalkyl;

R^3 is C_{5-10} aryl or C_{5-10} heteroaryl optionally substituted by C_{1-4} alkoxy;

X is O;

W is phenyl substituted by $-C(O)NR^7R^8$;

- 25 R^7 is hydrogen;

R^8 is C_{1-4} alkyl (optionally substituted by one or two groups selected from hydroxyl, $-C(O)NH_2$, $-NHC(O)C_{1-4}$ alkyl, C_{5-10} heterocyclyl, C_{5-10} aryl or C_{5-10} heteroaryl),

C₃₋₇ cycloalkyl, C₅₋₁₀ heterocyclyl or C₅₋₁₀ heteroaryl,

whereby any heterocyclyl is optionally substituted by C₁₋₄ alkyl or oxo;

or R⁷ and R⁸, together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom, the ring being

optionally substituted by one or two groups selected from oxo, hydroxyl, C₁₋₄ hydroxyalkyl or -C(O)NH₂; and

Y is hydrogen;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention provides a compound of formula Ia or Ib wherein A is C₁₋₆ haloalkyl. In a further embodiment A is C₁₋₄ haloalkyl. In a further embodiment the present invention provides a compound of formula Ia or Ib wherein A is fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, difluoropropyl or trifluoropropyl. In one embodiment A is difluoroethyl. In a further embodiment A is C₃₋₅ cycloalkyl substituted with cyano, hydroxyl or methoxy. In yet a further embodiment A is cyclopropyl, cyclobutyl or cyclopentyl, optionally substituted with cyano. In another embodiment A is cyclopropyl substituted with cyano.

One embodiment of the present invention provides a compound of formula Ia wherein R¹ is hydrogen, C₁₋₃ alkyl or C₁₋₃ hydroxyalkyl;

In another embodiment R¹ is methyl, ethyl or n-propyl, iso-propyl, n-butyl or iso-butyl. In a further embodiment R¹ is methyl.

In another embodiment R¹ is hydroxymethyl, hydroxyethyl or hydroxypropyl or hydroxybutyl. In a further embodiment R¹ is hydroxymethyl.

One embodiment of the present invention provides a compound of formula Ia or Ib wherein R³ is phenyl optionally substituted as recited above (for example optionally substituted by halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, CF₃, OCF₃, hydroxyl or cyano).

In one embodiment R³ is phenyl.

One embodiment of the present invention provides a compound of formula Ia or Ib wherein R³ is pyridyl optionally substituted as recited above (for example optionally substituted by halogen, C₁₋₃alkyl, C₁₋₃alkoxy, CF₃, OCF₃, hydroxyl or cyano).

In a further embodiment R³ is pyridyl. In yet a further embodiment R³ is pyridyl substituted with methoxy. In another embodiment R³ is methoxypyridin-3-yl.

One embodiment of the present invention provides a compound of formula Ia wherein X is O.

One embodiment of the present invention provides a compound of formula Ia or Ib wherein R⁷ is hydrogen, methyl or ethyl. In another embodiment R⁷ is hydrogen. In a further embodiment R⁷ is methyl.

One embodiment of the present invention provides a compound of formula Ia or Ib wherein W is phenyl substituted by -C(O)NR⁷R⁸; R⁷ is hydrogen; and R⁸ is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, aminooxomethyl, aminooxoethyl, aminooxopropyl, aminomethyloxomethyl, aminomethyloxoethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, acetylaminomethyl, acetylaminoethyl, oxoimidazolidinylmethyl, oxoimidazolidinylethyl, oxopyrrolidinylmethyl, oxopyrrolidinylethyl, oxidotetrahydrothiophenyl, dioxidotetrahydrothiophenyl, oxotertahydrofuranyl, tertahydrofuranyl, methyldioxooxazolidinylmethyl, dimethyldioxooxazolidinylmethyl, methyldioxooxazolidinylethyl, dimethyldioxooxazolidinylethyl, indazolylmethyl, indazolylethyl, aminooxophenylmethyl, aminooxophenylethyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridinylmethyl, pyridinylethyl, indazolylmethyl or indazolylethyl.

In another embodiment R⁸ is hydroxyethyl, hydroxybutyl, aminooxoethyl, aminomethyloxoethyl, aminooxopropyl, cyclopentyl, acetylaminoethyl, oxoimidazolidinylethyl, tetrahydrothiophenyl, oxopyrrolidinylethyl, dioxidotetrahydrothiophenyl, oxotertahydrofuranyl, tertahydrofuranyl, dimethyldioxooxazolidinylethyl, indazolylmethyl, aminooxophenylethyl, pyridinyl or pyridinylmethyl.

One embodiment of the present invention provides a compound of formula Ia or Ib wherein A is difluoroethyl or cyclopropyl substituted with cyano; R¹ is methyl or hydroxymethyl; R³ is phenyl or pyridyl substituted with methoxy; X is O; Y is hydrogen; W is phenyl substituted by -C(O)NR⁷R⁸;
 5 R⁷ is hydrogen; and
 R⁸ is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, aminooxomethyl, aminooxoethyl, aminooxopropyl, aminomethyloxomethyl, aminomethyloxoethyl, acetylaminomethyl, acetylaminoethyl, oxoimidazolidinylmethyl, oxoimidazolidinylethyl,
 10 oxopyrrolidinylmethyl, oxopyrrolidinylethyl, methyldioxooxazolidinylmethyl, dimethyldioxooxazolidinylmethyl, methyldioxooxazolidinylethyl, dimethyldioxooxazolidinylethyl, indazolylmethyl, indazolylethyl, aminooxophenylmethyl, aminooxophenylethyl, pyridinylmethyl, pyridinylethyl, indazolylmethyl or indazolylethyl.
 In another embodiment R⁸ is hydroxyethyl, hydroxybutyl, aminooxoethyl,
 15 aminomethyloxoethyl, aminooxopropyl, acetylaminoethyl, oxoimidazolidinylethyl, oxopyrrolidinylethyl, dimethyldioxooxazolidinylethyl, indazolylmethyl, aminooxophenylethyl or pyridinylmethyl.

A further embodiment of the present invention provides a compound of formula Ia or Ib
 20 wherein A is difluoroethyl or cyclopropyl substituted with cyano; R¹ is methyl or hydroxymethyl; R³ is phenyl or pyridyl substituted with methoxy; X is O; Y is hydrogen; W is phenyl substituted by -C(O)NR⁷R⁸;
 R⁷ is hydrogen; and R⁸ is C₅₋₆cycloalkyl. In one embodiment R⁸ is cyclopentyl.

A further embodiment of the present invention provides a compound of formula Ia or Ib
 25 wherein A is difluoroethyl or cyclopropyl substituted with cyano; R¹ is methyl or hydroxymethyl; R³ is phenyl or pyridyl substituted with methoxy; X is O; Y is hydrogen; W is phenyl substituted by -C(O)NR⁷R⁸;
 R⁷ is hydrogen; and R⁸ is C₅₋₆heterocyclyl, optionally substituted by methyl, ethyl or oxo.
 30 In one embodiment R⁸ is oxidotetrahydrothiophenyl, dioxidotetrahydrothiophenyl, tetrahydrothiophenyl, oxotertahydrofuranyl or tertahydrofuranyl.

In another embodiment R^8 is dioxidotetrahydrothiophenyl, oxotertahydrofuranyl or tertahydrofuranyl.

A further embodiment of the present invention provides a compound of formula Ia or Ib
5 wherein A is difluoroethyl or cyclopropyl substituted with cyano; R^1 is methyl or hydroxymethyl; R^3 is phenyl or pyridyl substituted with methoxy; X is O; Y is hydrogen; W is phenyl substituted by $-C(O)NR^7R^8$; R^7 is hydrogen; and R^8 is C_{5-6} heteroaryl. In one embodiment R^8 is pyridyl.

10 When R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring which optionally comprises a second ring-nitrogen atom, said ring is, for example, pyrrolidinyl, piperidinyl or piperazinyl.

One embodiment of the present invention provides a compound of formula Ia or Ib
15 wherein W is phenyl substituted by $-C(O)NR^7R^8$; and R^7 and R^8 , together form pyrrolidinyl, oxopyrrolidinyl, carbamoylpyrrolidinyl, hydroxymethylpyrrolidinyl, hydroxypyrrolidinyl, prolinamide, hydroxyprolinamide, piperidinyl, hydroxypiperidinyl, oxopiperidinyl, imidazolidinyl, oxoimidazolidinyl, hydroxyimidazolidinyl, piperazinyl, hydroxypiperazinyl or oxopiperazinyl.
20 In one embodiment R^7 and R^8 , together form carbamoylpyrrolidinyl, hydroxymethylpyrrolidinyl, hydroxypyrrolidinyl, prolinamide, hydroxyprolinamide or oxopiperazinyl.

Another embodiment of the present invention provides a compound of formula Ia or Ib
25 wherein A is difluoroethyl, amide or cyclopropyl substituted with cyano; R^1 is methyl or hydroxymethyl; R^3 is phenyl or pyridyl substituted with methoxy; X is O; Y is hydrogen; W is phenyl substituted by $-C(O)NR^7R^8$; R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom (for example the ring is
30 pyrrolidinyl, piperidinyl or piperazinyl), the ring being optionally substituted by one or two groups selected from oxo, hydroxyl, C_{1-4} hydroxyalkyl or $-C(O)NH_2$.

In one embodiment R^7 and R^8 , together form pyrrolidinyl, oxopyrrolidinyl, carbamoylpyrrolidinyl, hydroxymethylpyrrolidinyl, hydroxypyrrolidinyl, prolinamide, hydroxyprolinamide, piperidinyl, hydroxypiperidinyl, oxopiperidinyl, imidazolidinyl, piperazinyl, hydroxypiperazinyl, oxopiperazinyl, tetrahydrothiophenyl, oxidotetrahydrothiophenyl, dioxidotetrahydrothiophenyl, oxotertahydrofuranyl or tertahydrofuranyl.

In one embodiment R^7 and R^8 , together form carbamoylpyrrolidinyl, hydroxymethylpyrrolidinyl, hydroxypyrrolidinyl, prolinamide, hydroxyprolinamide or oxopiperazinyl.

One embodiment of the present invention provides a compound of formula Ia wherein Y is hydrogen.

One embodiment of the present invention provides a compound of formula Ia

wherein:

A is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkylthio, C_{1-6} alkylC(O), C_{1-6} alkyloxyC(O), NR^5R^6 , $NR^5R^6C(O)$ or C_{5-10} heteroaryl, all optionally substituted by one or more substituents independently selected from halo, cyano, hydroxyl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-4} haloalkyl;

R^5 and R^6 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(O) and C_{3-7} cycloalkylC(O), or R^5 and R^6 might form a ring with the nitrogen to which they are attached;

R^1 is hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkylOC C_{1-4} alkyl, C_{1-4} alkylthio C_{1-4} alkyl or C_{1-4} haloalkyl;

R^3 is C_{5-10} aryl, C_{5-10} aryl C_{1-4} alkyl, C_{5-10} arylO, C_{5-10} aryl C_{1-4} alkoxy, C_{5-10} aryloxy C_{1-4} alkyl, C_{5-10} heteroaryl, C_{5-10} heteroaryl C_{1-4} alkyl, C_{5-10} heteroaryl C_{1-4} alkoxy or C_{5-10} heteroaryoxy C_{1-4} alkyl, all of which are unsubstituted or optionally substituted by one or more substituents independently selected from B;

B is hydroxyl, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-3} hydroxyalkyl, C_{1-4} alkoxy C_{1-4} alkyl,

C_{3-6} cycloalkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyloxy, C_{3-6} cycloalkylthio C_{1-4} alkyl, C_{3-6} cycloalkylthio, C_{1-3} alkylS(O) $_k$ C_{1-4} alkyl, C_{1-3} alkylS(O) $_k$, C_{1-4} haloalkyl or C_{1-4} haloalkoxy,

or B is one of the following groups which are linked to adjacent carbons on an aryl or heteroaryl ring $(\text{CH}_2)_t\text{OC}_{1-4}\text{alkylenylO}(\text{CH}_2)_v$ or $(\text{CH}_2)_t\text{O}(\text{CH}_2)_v$;

k is 0, 1;

t and v are, independently, 0, 1, 2 or 3, and t and v are not both 0;

5 X is O or NH;

W is phenyl substituted by one or more substituents independently selected from $(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7\text{R}^8$, $(\text{CH}_2)_n\text{NR}^9\text{C}(\text{O})\text{R}^8$ or $(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^9(\text{CR}^{14}\text{R}^{15})\text{C}(\text{O})\text{NR}^7\text{R}^8$; and W is optionally further substituted by halogen or $\text{C}_{1-4}\text{alkyl}$;

R^7 is hydrogen or $\text{C}_{1-4}\text{alkyl}$;

10 R^8 and R^9 are, independently, hydrogen, $\text{C}_{1-4}\text{alkyl}$ (optionally substituted by one or two groups selected from hydroxyl, $\text{C}_{1-4}\text{alkoxy}$, NH_2 , oxo, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{C}_{1-4}\text{alkyl}$, $\text{C}(\text{O})\text{NR}^{10}\text{C}_{1-4}\text{alkyl}$, $\text{NR}^{10}\text{C}(\text{O})\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkylthio}$, $\text{C}_{5-10}\text{heterocyclyl}$, $\text{C}_{5-10}\text{aryl}$ or $\text{C}_{5-10}\text{heteroaryl}$), $\text{C}_{3-7}\text{cycloalkyl}$ (optionally substituted by $\text{C}(\text{O})\text{NH}_2$), $\text{C}_{5-10}\text{heterocyclyl}$, $\text{C}_{5-10}\text{aryl}$, $\text{C}_{5-10}\text{heteroaryl}$ or $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$; $\text{C}_{5-10}\text{aryl}$ or $\text{C}_{5-10}\text{heteroaryl}$ are optionally

15 substituted by halogen, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, CF_3 , OCF_3 , hydroxy or cyano; heterocyclyl is optionally substituted by $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}(\text{C}_{1-4}\text{alkyl})$, oxo or hydroxyl;

or R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom, the ring being optionally substituted by oxo, hydroxyl, $\text{C}_{1-4}\text{hydroxyalkyl}$, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}(\text{C}_{1-4}$

20 $\text{alkyl})$ or $(\text{CH}_2)_p\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$;

R^{14} and R^{15} are, independently, hydrogen, $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{1-4}\text{hydroxyalkyl}$; or R^{14} and R^{15} join to form a $\text{C}_{3-6}\text{cycloalkyl}$ ring;

R^{10} , R^{11} , R^{12} and R^{13} are, independently, hydrogen or $\text{C}_{1-4}\text{alkyl}$;

n and p are, independently, 0, 1, 2, 3 or 4;

25 Y is hydrogen, halo, $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{1-4}\text{haloalkyl}$;
or a pharmaceutically acceptable salt thereof.

For the avoidance of doubt, the present invention relates to any compound falling within the scope of compounds of formula Ia or Ib and any one specific compound mentioned
30 below.

In another aspect the present invention provides compounds selected from:

- 1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-D-prolinamide,
N-[(1S,2R)-2-{{1-(3-[(2R)-2-carbamoylpyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl}oxy}-1-methyl-2-phenylethyl]ethanedi-
5 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-(2-hydroxyethyl)benzamide,
N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
N-[(1S)-2-amino-1-methyl-2-oxoethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-
10 1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
N-[2-(acetylamino)ethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-[2-(2-oxoimidazolidin-1-yl)ethyl]benzamide,
15 2,2-difluoro-N-[(1S,2R)-2-{{1-(3-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl}oxy}-1-methyl-2-phenylethyl]propanamide,
2,2-difluoro-N-[(1S,2R)-2-{{1-(3-[(3R)-3-hydroxypyrrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl}oxy}-1-methyl-2-phenylethyl]propanamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
20 N-[(3R)-2-oxotetrahydrofuran-3-yl]benzamide,
1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-L-prolinamide,
2,2-difluoro-N-[(1S,2R)-1-methyl-2-[(1-{3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}-1H-indazol-5-yl)oxy]-2-phenylethyl]propanamide,
25 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-[2-(2-oxopyrrolidin-1-yl)ethyl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-[2-(5,5-dimethyl-2,4-dioxo-1,3-oxazolidin-3-yl)ethyl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
30 N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-(1H-indazol-3-ylmethyl)benzamide,

N-[(1R)-2-amino-2-oxo-1-phenylethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
 N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-methylbenzamide,
 5 N-(3-amino-3-oxopropyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
 (4R)-1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-4-hydroxy-L-prolinamide,
 1-({3-[5-({(1R,2S)-2-[(1-cyanocyclopropyl)carbonyl]amino}-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-D-prolinamide,
 10 or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides compounds selected from:

N-cyclopentyl-3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)benzamide,
 15 3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-pyridin-3-ylbenzamide,
 3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide,
 20 3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(tetrahydrofuran-3-yl)benzamide,
 3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(2-hydroxybutyl)benzamide,
 N-cyclopentyl-3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-3-hydroxy-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)benzamide, and
 25 3-(5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide,
 or a pharmaceutically acceptable salt thereof.

30 For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group

encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C₁₋₆' means a
5 carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl or i-hexyl.
10 The term C₁₋₄ alkyl having 1 to 4 carbon atoms and may be but are not limited to methyl, ethyl, n-propyl, i-propyl or t-butyl. The term "C₀" in C₀₋₄ alkyl refers to a situation where no carbon atom is present.

The term alkylene refers to a straight or branched chain alkyl group linking two other
15 atoms. It is, for example, CH₂ or CH₂CH₂.

The term "alkoxy", unless stated otherwise, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. The term "alkoxy" may include, but is not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, iso-butoxy,
20 cyclopropylmethoxy, allyloxy or propargyloxy.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, partially or completely saturated monocyclic, bicyclic or bridged hydrocarbon ring system. The term "C₁₋₆cycloalkyl" may be, but is not limited to cyclopropyl, cyclobutyl,
25 cyclopentyl or cyclohexyl.

In this specification, unless stated otherwise, the term "heterocycloalkyl" or "heterocyclyl" refers to an optionally substituted, partially or completely saturated monocyclic, bicyclic or bridged hydrocarbon ring system having one or more heteroatoms independently selected
30 from O, N or S. The term "C₁₋₆heterocycloalkyl" may be, but is not limited to pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, tetrahydrothiophenyl, oxotetrahydrothiophenyl, dioxotetrahydrothiophenyl, oxotetrahydrofuranlyl or tetrahydrofuranlyl.

In this specification, unless stated otherwise, the term “a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom” refers to heterocycloalkyl as defined above and may be, but is not limited to pyrrolidinyl, prolinamide or piperazinyl.

5

In this specification, unless stated otherwise, the terms “halo” and “halogen” may be fluorine (fluoro), iodine (iodo), chlorine (chloro) or bromine (bromo).

In this specification, unless stated otherwise, the term “haloalkyl” means an alkyl group as defined above, which is substituted with halo as defined above. The term “C₁₋₆haloalkyl” may include, but is not limited to fluoromethyl, difluoromethyl, difluoroethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl or fluorochloromethyl.

The term “C₁₋₃haloalkylO” or “C₁₋₃haloalkoxy” may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

15

In this specification, unless stated otherwise, the term “thioalkyl” means an alkyl group as defined above, which is substituted with sulphur atom. The term “C₁₋₆thioalkyl” may include, but is not limited to methylsulfanyl, ethylsulfanyl or propylsulfanyl.

20

The term “cycloalkylthio” means a sulphur atom substituted with a cycloalkyl as defined above such as for instance cyclopropylsulfanyl.

The term “C₁₋₄alkylthioalkyl” means a alkyl group with a sulphur atom between the carbon atoms. The term “C₁₋₄alkylthioC₁₋₄alkyl” may include, but is not limited to ethylsulfanylmethyl.

25

In this specification, unless stated otherwise, the term “C₅₋₁₀aryl” or aryl refers to an aromatic or partial aromatic group having 5 to 10 carbon atoms such as for example, phenyl or naphthyl. The term “C₅₋₁₀aryloxy” or “C₅₋₁₀arylO” refers to for example phenoxy.

30

In this specification, unless stated otherwise, the term “C₅₋₁₀heteroaryl” or heteroaryl refers to a mono- or bicyclic aromatic or partially aromatic ring with 5 to 10 atoms and containing one or more heteroatoms independently selected from nitrogen, oxygen or sulphur. Heteroaryl is, for example, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, furyl, thienyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, pyridinyl, pyrimidinyl, indolyl, indazolyl, benzofuryl, benzothienyl, dioxabicyclodecatrienyl, quinolinyl or isoquinolinyl.

When aryl (for example phenyl) or heteroaryl is substituted by (CH₂)_tOC₁₋₄alkylenylO(CH₂)_v or (CH₂)_tO(CH₂)_v; wherein t and v are, independently, 0, 1, 2 or 3, but t and v are not both 0; these substituents can be, for example, CH₂OCH₂O, OCH₂O, OCH₂CH₂O or OCH₂CH₂ linking adjacent carbons on the aryl or heteroaryl ring.

For the avoidance of doubt a group R³ defined as C₅₋₁₀aryl e.g. phenyl, substituted with a group C₁₋₂alkylS(O)_k includes a phenyl substituted with methylsulphonyl group.

It will be appreciated that throughout the specification, the number and nature of substituents on rings in the compounds of the invention will be selected so as to avoid sterically undesirable combinations.

Compounds of the present invention have been named with the aid of computer software (ACDLabs 10.06/Name(IUPAC)).

Compounds of the invention may include an asymmetric centre and be chiral in nature. Where the compound is chiral, it may be in the form of a single stereoisomer, such as a enantiomer, or it may be in the form of mixtures of these stereoisomers in any proportions, including racemic mixtures. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC. Alternatively the optical isomers may be obtained by asymmetric synthesis, or by synthesis from optically active starting materials.

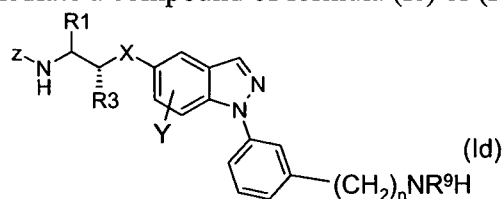
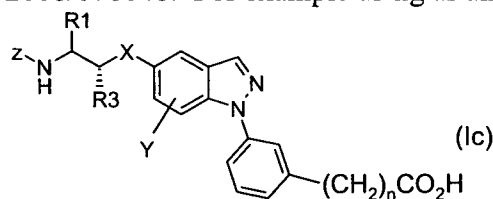
Compounds of the invention may be converted to a pharmaceutically acceptable salt thereof, such as an acid addition salt such as a hydrochloride, hydrobromide, phosphate, sulphate, acetate, ascorbate, benzoate, fumarate, hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate, *p*-toluenesulphonate, benzenesulphonate, ethanesulphonate, 2-naphthalenesulfonate, mesytilenesulfonate, nitric acid, 1,5-naphthalene-disulphonate, *p*-xylenesulphonate, aspartate or glutamate. They may also include basic addition salts such as an alkali metal salt for example sodium or potassium salts, an alkaline earth metal salt for example calcium or magnesium salts, a transition metal salt such as a zinc salt, an organic amine salt for example a salt of triethylamine, diethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, piperazine, procaine, dibenzylamine, *N,N*-dibenzylethylamine, choline or 2-aminoethanol or amino acids for example lysine or arginine.

The compounds of the invention, or a pharmaceutically acceptable salt thereof, may exist in solvated, for example hydrated, as well as unsolvated forms, or as cocrystals and the present invention encompasses all such forms.

Process

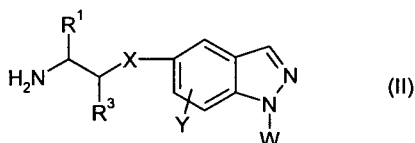
The compounds of the invention can be prepared using or adapting methods disclosed in the art, or by using or adapting the method disclosed in the Example below. Starting materials for the preparative methods are either commercially available or can be prepared by using or adapting literature methods.

A process for the synthesis of a compound of formula Ia or Ib can comprise using an acid/amine coupling reaction disclosed in WO 2007/122165, WO 2008/043788 or WO 2008/076048. For example using as an intermediate a compound of formula (Ic) or (Id):

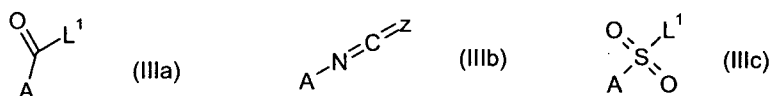


wherein R^1 , R^3 , X and Y are defined as above, and Z is A-C(O) or A-S(O)₂. A compound of the invention can be prepared if an acid of formula (Ic) is reacted with an amine of formula HNR^7R^8 or $HNR^9(CR^{14}R^{15})C(O)NR^7R^8$. Alternatively, a compound of the invention can be prepared by reaction of an amine of formula (Id) with an acid as defined by $HOC(O)R^8$. The compounds of formula (Ic) and (Id) can be synthesised from protected precursors such as alkylesters for the synthesis of (Ic), or from an N-protected precursor of NR^9H such as NR^9BOC or N_3 for the preparation of (Id).

One embodiment relates to a process for the preparation of compounds of formula Ia or Ib by coupling a compound of formula (II):



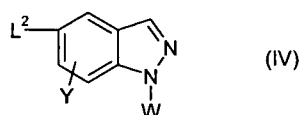
with acylation reagents of formula (IIIa), (IIIb) or (IIIc)



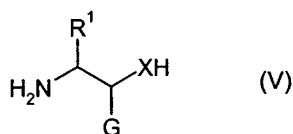
wherein R^1 , R^3 , A, X and Y are defined above, W is as defined above or can be a group that can be converted into W as defined above, and L^1 is a leaving group {such as halogen (for example chloro) or, when $L^1 = OH$, a leaving group generated by reaction of a coupling reagent (such as HATU with a carboxylic acid)}. The reaction may be performed in a suitable solvent (such as pyridine, THF or DMF), in the presence of a suitable base (such as a tri(C₁₋₆ alkyl)amine, for example diisopropylethylamine, or pyridine) and at a suitable temperature (such as -10° to 50°C).

A compound of formula (II) can be prepared according to step a, b or c.

a) A compound of formula (II) can be prepared by coupling a compound of formula (IV)



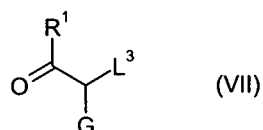
wherein W and Y are as defined above and L^2 is a leaving group (such as halogen or triflate) with a compound of formula (V)



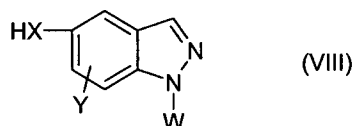
wherein R^1 and X are defined above and G corresponds to R^3 or a protected precursor to R^3 . The reaction can be performed in a suitable solvent (such as an aromatic solvent, for example toluene) or a polar, aprotic solvent, such as DMF or butyronitril, in the presence of a suitable base (such as an alkali metal alkoxide (for example sodium *tert*-butoxide) or, cesium carbonate, such as mediated by a suitable metal catalyst such as Copper(I) iodide at a suitable temperature (for example in the range 80° to 120°C).

Or,

- b) A compound of formula (II) can be prepared by reacting a compound of formula (VII)



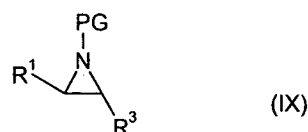
with a compound of formula (VIII)



wherein R^1 , X, W and Y are defined above, G corresponds to R^3 or a protected precursor to R^3 , and L^3 is a leaving group (such as halogen, mesylate or tosylate). The reaction can be performed in a suitable solvent (such as DCM, DMF or acetonitrile), in the presence of a suitable base (such as an alkali metal carbonate, for example cesium carbonate or potassium carbonate) at a suitable temperature (for example in the range -10 to 50°C), followed by a subsequent reductive amination step using or adopting literature methods.

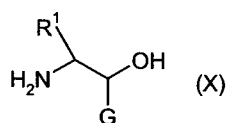
Or,

- c) a compound of formula (II) may be prepared by reacting a compound of formula (VIII) with a compound of formula (IX)



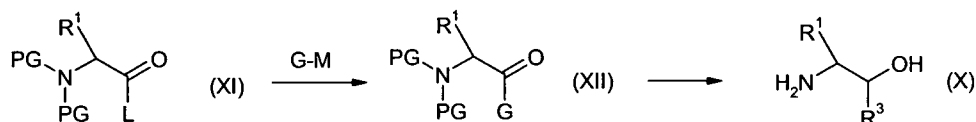
wherein R^1 and R^3 are as defined above, and PG is a suitable protecting group such as BOC, mesyl or tosyl or related carbonyl- or sulfonyl residues. The reaction can be performed in a suitable solvent such as DCM or toluene in the presence of a suitable base such as NaH or KOtBu, followed by a deprotection step using or adopting literature methods.

As a specific case of a compound of formula (V), a compound of formula (X) might be used to prepare a compound of formula (II)



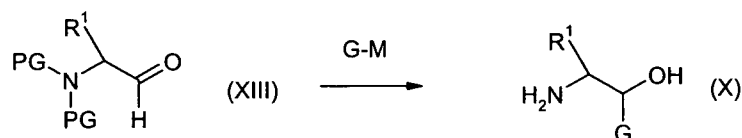
wherein R^1 and G are defined as in compounds of formula (V).

Compounds of formula (X) may be prepared by reacting a nucleophile G-M with a carbonyl compound of formula (XI) followed reduction and subsequent deprotection of the intermediate of formula (XII)



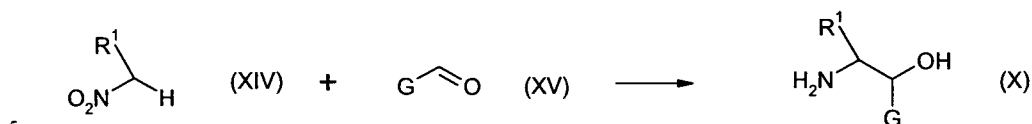
wherein R^1 , R^3 , G and PG are as defined above, and L is a leaving group (such as alkoxy, methoxy(methyl)amino), M is a metal such as Li or Mg-halide. The addition of the nucleophile may be performed in a suitable aprotic solvent such as THF at moderate temperature between -10 and 50°C . The following reduction and deprotection steps might be carried out by using or adopting literature methods.

Alternatively, compounds of formula (X) may be prepared by a reaction of a nucleophile G-M with an aldehyde of formula (XIII) and a subsequent deprotection.



wherein R^1 , R^3 , G and PG are as defined above, and M is a metal such as an alkali metal (e.g. Li) or Mg-halide. The reaction may be performed by following disclosed protocols for addition of carbanions to aldehydes.

Another way to prepare a compound of formula (X) is the reaction of a nitroalkyle of formula (XIV) with an aldehyde of formula (XV), followed by reduction of the nitro function



wherein R^1 , R^3 and G are as defined above. Both steps may be carried out by following or adopting literature methods.

Medical use

Because of their ability to bind to the glucocorticoid receptor the compounds of the invention are useful as anti-inflammatory agents, and can also display antiallergic, immunosuppressive and anti-proliferative actions. Thus, a compound of formula Ia, or a pharmaceutically acceptable salt thereof can be used as a medicament for the treatment or prophylaxis of one or more of the following pathologic conditions (disease states) in a mammal (such as a human):

(i) Lung diseases, which coincide with inflammatory, allergic and/or proliferative processes:

chronically obstructive lung diseases of any origin, mainly bronchial asthma, chronic obstructive pulmonary disease

bronchitis of different origins

Adult respiratory distress syndrome (ARDS), acute respiratory distress syndrome

Bronchiectases

all forms of restructive lung diseases, mainly allergic alveolitis

all forms of pulmonary edema, mainly toxic pulmonary edema

sarcoidoses and granulomatoses, such as Boeck's disease

(ii) Rheumatic diseases/auto-immune diseases/degenerative joint diseases, which coincide with inflammatory, allergic and/or proliferative processes:

all forms of rheumatic diseases, for example rheumatoid arthritis, acute rheumatic fever, polymyalgia rheumatica, collagenoses, Behçet's disease

reactive arthritis

inflammatory soft-tissue diseases of other origins

arthritic symptoms in degenerative joint diseases (arthroses)

traumatic arthritides

collagen diseases of other origins, for example systemic lupus erythematosus, discoid

5 lupus erythematosus, scleroderma, polymyositis, dermatomyositis, polyarteritis nodosa, temporal arteritis

Sjögren's syndrome, Still syndrome, Felty's syndrome

Vitiligo

Soft-tissue rheumatism

10 (iii) Allergies, which coincide with inflammatory, allergic and/or proliferative processes:

All forms of allergic reactions, for example Quincke's edema, insect bites, allergic

reactions to pharmaceutical agents, blood derivatives, contrast media, etc., anaphylactic shock, urticaria, contact dermatitis (e.g. allergic and irritative), allergic vascular diseases

Allergic vasculitis

15 inflammatory vasculitis

(iv) Vascular inflammations (vasculitides)

Panarteritis nodosa, temporal arteritis, erythema nodosum

Polyarteritis nodosa

Wegner's granulomatosis

20 Giant-cell arteritis

(v) Dermatological diseases, which coincide with inflammatory, allergic and/or proliferative processes:

atopic dermatitis (mainly in children)

exfoliative dermatitis,

25 psoriasis

erythematous diseases, triggered by different noxae, for example radiation, chemicals, burns, etc.

acid burns

bullous dermatoses, such as, for example, autoimmune pemphigus vulgaris, bullous

30 pemphigoid

diseases of the lichenoid group

itching (for example of allergic origins)

- all forms of eczema, such as, for example, atopic eczema or seborrheal eczema
rosacea
pemphigus vulgaris
erythema exudativum multiforme
5 erythema nodosum
balanitis
Pruritis, such as, for example, allergic origin)
Manifestation of vascular diseases
vulvitis
10 inflammatory hair loss, such as alopecia areata
cutaneous T-cell lymphoma
Rashes of any origin or dermatoses
Psoriasis and parapsoriasis groups
Pityriasis rubra pilaris
15 (vi) Nephropathies, which coincide with inflammatory, allergic and/or proliferative
processes:
nephrotic syndrome
all nephritides, such as, for example, glomerulonephritis
(vii) Liver diseases, which coincide with inflammatory, allergic and/or proliferative
20 processes:
acute liver cell decomposition
acute hepatitis of different origins, for example virally-, toxically- or pharmaceutical agent-
induced
chronically aggressive and/or chronically intermittent hepatitis
25 (viii) Gastrointestinal diseases, which coincide with inflammatory, allergic and/or
proliferative processes:
regional enteritis (Crohn's disease)
Gastritis
Reflux esophagitis
30 ulcerative colitis
gastroenteritis of other origins, for example native sprue

(ix) Proctological diseases, which coincide with inflammatory, allergic and/or proliferative processes:

anal eczema

fissures

5 haemorrhoids

idiopathic proctitis

(x) Eye diseases, which coincide with inflammatory, allergic and/or proliferative processes:

allergic keratitis, uveitis iritis

10 conjunctivitis

blepharitis

optic neuritis

chorioiditis

sympathetic ophthalmia

15 (xi) Diseases of the ear-nose-throat area, which coincide with inflammatory, allergic and/or proliferative processes:

allergic rhinitis, hay fever

otitis externa, for example caused by contact dermatitis, infection, etc.

otitis media

20 (xii) Neurological diseases, which coincide with inflammatory, allergic and/or proliferative processes:

cerebral edema, mainly tumor-induced cerebral edema

multiple sclerosis

acute encephalomyelitis

25 different forms of convulsions, for example infantile nodding spasms

Meningitis

spinal cord injury

Stroke

30 (xiii) Blood diseases, which coincide with inflammatory, allergic and/or proliferative processes:

acquired haemolytic anemia

thrombocytopenia such as for example idiopathic thrombocytopenia

M. Hodgkins or Non-Hodgkins lymphomas,

thrombocythemias,

erythrocytoses

(xiv) Tumor diseases, which coincide with inflammatory, allergic and/or proliferative
5 processes:

acute lymphatic leukaemia

malignant lymphoma

lymphogranulomatoses

lymphosarcoma

10 extensive metastases, mainly in breast and prostate cancers

(xv) Endocrine diseases, which coincide with inflammatory, allergic and/or
proliferative processes:

endocrine orbitopathy

thyrotoxic crisis

15 de Quervain's thyroiditis

Hashimoto's thyroiditis

Hyperthyroidism

Basedow's disease

Granulomatous thyroiditis

20 Lymphadenoid goiter

(xvi) Transplants, which coincide with inflammatory, allergic and/or proliferative
processes;

(xvii) Severe shock conditions, which coincide with inflammatory, allergic and/or
proliferative processes, for example anaphylactic shock

25 (xviii) Substitution therapy, which coincides with inflammatory, allergic and/or
proliferative processes, with:

innate primary suprarenal insufficiency, for example congenital adrenogenital syndrome

acquired primary suprarenal insufficiency, for example Addison's disease, autoimmune
adrenitis, meta-infective, tumors, metastases, etc.

30 innate secondary suprarenal insufficiency, for example congenital hypopituitarism

acquired secondary suprarenal insufficiency, for example meta-infective, tumors, etc.

(xix) Emesis, which coincides with inflammatory, allergic and/or proliferative processes:

for example in combination with a 5-HT₃-antagonist in cytostatic-agent-induced vomiting.

(xx) Pains of inflammatory origins, e.g., lumbago

5

Without prejudice to the foregoing, the compounds of the invention can also be used to treat disorders such as: diabetes type I (insulin-dependent diabetes), Guillain-Barré syndrome, restenoses after percutaneous transluminal angioplasty, Alzheimer's disease, acute and chronic pain, arteriosclerosis, reperfusion injury, thermal injury, multiple organ injury
10 secondary to trauma, acute purulent meningitis, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, granulocyte transfusion, Conies Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis,
15 myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, oesophageal varices, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, glucose intolerance, hyperglycemia, diabetes
20 mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, rheumatic fever, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, hypercalcemia, acute
25 adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, Little's syndrome, systemic inflammation, inflammatory bowel disease, Wegener's granulomatosis, giant cell arthritis, osteoarthritis, angioneurotic edema, tendonitis, bursitis, autoimmune chronic active hepatitis, hepatitis, cinhosis, panniculitis, inflamed cysts, pyoderma gangrenosum, eosinophilic fasciitis,
30 relapsing polychondritis, sarcoidosis Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, erythema nodosum acne, hirsutism, toxic epidermal necrolysis, erythema multiform, psychoses, cognitive disorders (such as memory

disturbances) mood disorders (such as depression and bipolar disorder), anxiety disorders and personality disorders.

As used herein the term "congestive heart failure" (CHF) or 'congestive heart disease' refers to a disease state of the cardiovascular system whereby the heart is unable to efficiently pump an adequate volume of blood to meet the requirements of the body's tissues and organ systems. Typically, CHF is characterized by left ventricular failure (systolic dysfunction) and fluid accumulation in the lungs, with the underlying cause being attributed to one or more heart or cardiovascular disease states including coronary artery disease, myocardial infarction, hypertension, diabetes, valvular heart disease, and cardiomyopathy. The term "diastolic congestive heart failure" refers to a state of CHF characterized by impairment in the ability of the heart to properly relax and fill with blood. Conversely, the term "systolic congestive heart failure" refers to a state of CHF characterized by impairment in the ability of the heart to properly contract and eject blood.

As will be appreciated by one of skill in the art, physiological disorders may present as a "chronic" condition, or an "acute" episode. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of physiological disorders contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear.

In another aspect the present invention provides a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, for use in therapy (such as a therapy described above).

In yet another aspect the present invention provides the use of a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a glucocorticoid receptor mediated disease state (such as a disease state described above).

In a further aspect the invention provides the use of a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an inflammatory condition (such as an arthritic).

In one aspect the invention provides the use of a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a respiratory disorder.

In a still further aspect the invention provides the use of a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma.

In another aspect the invention provides the use of a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of COPD.

In another aspect the present invention provides a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, for use in treating an inflammatory condition, respiratory disorder, asthma and/or COPD.

The present invention further provides a method of treating a glucocorticoid receptor mediated disease state (such as a disease state described above), an inflammatory condition, asthma and/or COPD, in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

In the context of the present specification, the term "therapy" and "treatment" also includes prophylaxis and prevention unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the terms "inhibitor" and "antagonist" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the agonist. An agonist may be a full or partial agonist.

The term "disorder", unless stated otherwise, means any condition and disease associated with glucocorticoid receptor activity.

Pharmaceutical composition

In order to use a compound of formula Ia, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a mammal, said active ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore another aspect the present invention provides a pharmaceutical composition comprising a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, (active ingredient) and a pharmaceutically acceptable adjuvant, diluent or carrier. One embodiment relates to the use of a pharmaceutical composition comprising a compound of formula Ia, or a pharmaceutically acceptable salt thereof, for treating a glucocorticoid receptor mediated disease state (such as a disease state described above), an inflammatory condition, respiratory disorder, asthma and/or COPD.

A further aspect the present invention provides a process for the preparation of said composition comprising mixing the active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition can comprise from 0.05 to 99 %w (per cent by weight), for example from 0.05 to 80 %w, such as from 0.10 to 70 %w (for example from 0.10 to 50 %w), of active ingredient, all percentages by weight being based on total composition.

A pharmaceutical composition of the present invention can be administered in a standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. Thus, a compound of formula Ia, or a pharmaceutically acceptable salt thereof, may be formulated into the form of, for example, an aerosol, a powder (for example dry or dispersible), a tablet, a capsule, a syrup, a granule, an aqueous or oily solution or suspension, an (lipid) emulsion, a suppository, an ointment, a cream, drops, or a sterile injectable aqueous or oily solution or suspension.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule containing between 0.1 mg and 10 g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous, intraarticular or intramuscular injection.

In one embodiment a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, is administered orally.

In another embodiment a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, is administered by inhalation.

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β -cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. Tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention further relates to a combination therapy or composition wherein a compound of formula Ia, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, is administered concurrently (possibly in the same composition) or sequentially with one or more agents for the treatment of any of the above disease states.

For example, for the treatment of rheumatoid arthritis, osteoarthritis, COPD, asthma or allergic rhinitis a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, can be combined with one or more agents for the treatment of such a condition. Where such a combination is to be administered by inhalation, then the one or more agents is selected from the list comprising:

- a PDE4 inhibitor including an inhibitor of the isoform PDE4D;
- a selective β .sub2. adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol or indacaterol;
- a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine;
- a modulator of chemokine receptor function (such as a CCR1 receptor antagonist);
- an inhibitor of p38 kinase function;
- an inhibitor of matrix metalloproteases, such as targeting MMP-2, -9 or MMP-12;
- or,
- an inhibitor of neutrophil serine proteases, such as neutrophil elastase or proteinase 3.

In another embodiment of the invention where such a combination is for the treatment of COPD, asthma or allergic rhinitis, a compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, can be administered by inhalation or by the oral route and the other agent, e.g. xanthine (such as aminophylline or theophylline) can be administered by inhalation or by the oral route. A compound of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, and the other agent, e.g. xanthine may be administered together. They may be administered sequentially. Or they may be administered separately.

The following Examples illustrate the invention. The following abbreviations are used in the Examples:

The following Examples illustrate the invention:

TFA Trifluoroacetic acid;

THF Tetrahydrofuran

DCM Dichloromethane

HPLC High Performance Liquid Chromatography;

LC/MS Liquid Column Chromatography / Mass Spectroscopy;

GC Gas Chromatography

DMSO Dimethylsulfoxide;

APCI-MS Atmospheric Pressure Chemical Ionisation Mass Spectroscopy;

NMP 1-methyl-2-pyrrolidinone

DIEA N,N-diisopropylethylamine

HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate

HBTU 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium

hexafluorophosphate(V)

r.t. Room temperature, which is a temperature in the range from of 16°C to 25°C

General Methods

NMR spectra were recorded on a Varian Mercury-VX 300 MHz instrument or a Varian Inova 400MHz instrument. The central peaks of chloroform-d (H 7.27 ppm), acetone (H 2.05 ppm), dichloromethane-d₂ (H 5.32 ppm) or DMSO-*d*₆ (H 2.50 ppm) were used as internal references. Alternatively, NMR spectra were recorded on a Varian Inova Unity

500MHz instrument. Proton-NMR experiments were acquired using dual suppression of residual solvent peak and H₂O.

The following methods was used for chiral SFC analysis:

Using an Analytical Method Development System from Thar Technologies, Inc. Using
5 CO₂ as mobile phase with MeOH as modifier and pressure at 150 bar. Columns used was kept at +37°C by using an column oven. Detection was carried out on 254nm.

Chiral SFC (method A) Chiralpak® AS, 0.46x25cm column, 30% MeOH, 3 mL/min.

Chiral SFC (method B) Chiralpak® IB, 0.46x25cm column , 35% MeOH, 2 mL/min.

The following method was used for LC/MS analysis:

10 Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 mL/min; Wavelength 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Gradient 15-95%/B 2.7 min, 95% B 0.3 min.

The following method was used for GC-MS analysis:

Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-
15 Packard GC. MS system equipped with EI ionisation chamber, 70eV.

The following method was used for HPLC analysis:

LC Method A: HPLC method A was performed with Agilent 1100 series machines on Kromassil © C18 5µm 3.0x100mm colum. Aqueous phase was water/TFA (99.8/0.1) and organic phase was acetonitrile/TFA (99.92/0.08). Flow was 1 ml/min and gradient was set
20 from 10 to 100% of organic phase during 20 minutes. Detection was carried out on 220, 254 and 280 nm.

LC Method B: HPLC method B was performed with Agilent 1100 series machines on XTerra® RP₈ 5µm 3.0x100mm colum. Aqueous phase was 15 nM NH₃ in water and organic phase was acetonitrile. Flow was 1 ml/min or 0.6 ml/min when indicated and
25 gradient was set from 10 to 100% of organic phase during 20 minutes. Detection was carried out on 220, 254 and 280 nm.

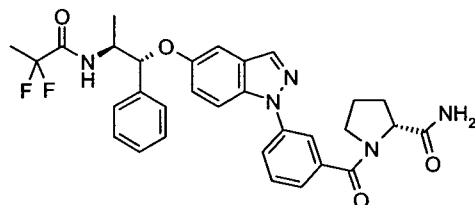
Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

Preparative HPLC system A:

30 Column: XBridge C18, dimention (150 X 30mm, 5µm packing), 20ml/min solvent speed and gradient 20% to 90 % MeCN (0.1 TFA) in Water (0.1% TFA) over 20 min)

Example 1

1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-D-prolinamide



- 5 In a 10 mL round-bottomed flask, 2,2-difluoropropanoic acid (25.04 mg, 0.23 mmol), and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (90 mg, 0.24 mmol) were dissolved in DMF (1.5 mL). At room temperature N-ethyl-N-isopropylpropan-2-amine (0.051 mL, 0.31 mmol) was slowly added via a syringe. After 10 min continued stirring (R)-1-(3-(5-((1R,2S)-2-amino-1-phenylpropoxy)-1H-indazol-1-yl)benzoyl)pyrrolidine-2-carboxamide (**1a**, 100 mg, 0.21 mmol) in THF (0.5 mL) was added and stirring was continued over night. The mixture was diluted with ethyl acetate and washed with sat. aq. sodium bicarbonate and brine. After drying over sodium sulfate and removal of the volatiles the crude was dissolved in acetonitril / water (1:1) and subjected to HPLC-purification [Kromasil 100 C18, acetonitril/water 35:65 to 65:35]. After freeze drying 34 mg (29%) of a colourless powder were obtained.

APCI-MS: m/z 576.2 [MH^+]

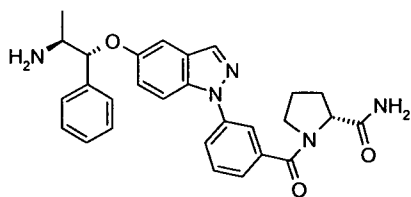
- 1H NMR (400 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.21 (0.7H, s), 8.19 (0.3H, s), 7.89 (0.6H, s), 7.82 (0.6H, m), 7.78 - 7.72 (1.3H, m), 7.63 (1H, t), 7.56 (1H, t), 7.45 - 7.39 (2.7H, m), 7.38 - 7.20 (5.3H, m), 7.13 (1H, m), 6.96 (0.7H, s), 6.91 (0.3H, s), 5.28 (1H, d), 4.37 (0.7H, m), 4.23 (1.3H, m), 3.65 - 3.56 (1.3H, m), 3.51 - 3.34 (0.7H, m; partially covered by water signal), 2.19 (1H, m), 1.93 - 1.73 (3H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) rt = 9.40 min

LC (method B) rt = 8.43 min

25

1-{{3-[5-{{(1R,2S)-2-amino-1-phenylpropyl}oxy}}-1H-indazol-1-yl]phenyl}carbonyl}-D-prolinamide (**1a**)

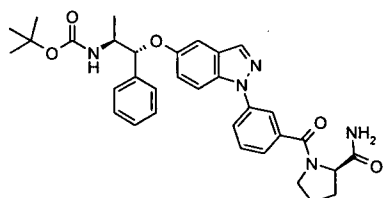


In a 100 mL round-bottomed flask, tert-butyl (1R,2S)-1-(1-(3-((R)-2-carbamoylpyrrolidine-1-carbonyl)phenyl)-1H-indazol-5-yloxy)-1-phenylpropan-2-ylcarbamate (**1b**, 472 mg, 0.81 mmol) was dissolved in ethyl acetate (12 mL). At room temperature hydrogen chloride (3 mL, 6N in iso-propanol) was added and stirring was continued for 20 h. Thereafter temperature was raised to 50°C and stirring was continued for an additional hour. The mixture was transferred to a separation funnel and extracted with water and 0.5M aq. hydrogen chloride. The aqueous phases were combined and basified with sodium carbonate. Ethyl acetate was added to the mixture and the phases were separated. The organic phase was extracted once more with ethyl acetate and the combined organic phases were washed with brine and dried over sodium sulfate. After removal of the volatiles the residue was taken up in dioxane / water (1:2) and freeze dried to obtain a yield 284 mg of colourless powder (73 %).

APCI-MS: m/z 484.1 [MH^+]

1H NMR (400 MHz, DMSO- d_6) δ 8.19 (1H, s), 8.17 (1H, s), 7.89 (1H, s), 7.82 (1H, d), 7.78 - 7.70 (2H, m), 7.62 (1H, t), 7.55 (1H, t), 7.42 (2H, m), 7.38 - 7.21 (6H, m), 7.15 (1H, m), 6.98 - 6.89 (1H, m), 5.11 (1H, d), 4.37 (1H, dd), 4.21 (0H, m), 3.61 (2H, m), 3.47 (1H, m), 3.18 (1H, quintet), 2.18 (1H, m), 1.93 - 1.74 (3H, m), 1.07 (3H, d).

Tert-butyl [(1S,2R)-2-{[1-(3-{[(2R)-2-carbamoylpyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]carbamate (**1b**)



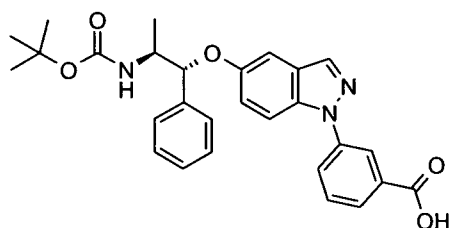
To a solution of 3-(5-((1R,2S)-2-(tert-butoxycarbonylamino)-1-phenylpropoxy)-1H-indazol-1-yl)benzoic acid (**1c**, 461 mg, 0.95 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (378 mg, 0.99 mmol) in DMF (3 mL) N-ethyl-N-isopropylpropan-2-amine (0.313 mL, 1.89 mmol) was

added dropwise at room temperature and a slight exothermic reaction was observed. After stirring at room temperature for 1 hour the mixture was diluted with ethyl acetate and washed with brine, 0.5M hydrochloric acid, brine, aqu. sat. sodium bicarbonate and again brine. Drying over sodium sulfate and evaporation of the solvent the residue was dissolved
5 in a dioxane-water mixture (1:2) and freeze-dried to give 477 mg (86%) of a colourless solid.

APCI-MS: m/z 528.1 [$MH^+ - C_4H_9$], 584.1 [MH^+]

1H NMR (400MHz, DMSO- d_6) δ 8.20 (0.7H, s), 8.18 (0.3H, s), 7.90 (0.7H, s), 7.82 (0.7H, d), 7.78 - 7.72 (1.4H, m), 7.63 (1H, t), 7.56 (1H, t), 7.46 - 7.28 (5.3H, m), 7.28 - 7.19 (2H, m), 7.09 (1H, m), 7.00 (1H, d), 6.98 - 6.90 (1H, m), 5.25 (1H, d), 4.37 (0.7H, dd), 4.21
10 (0.3H, dm), 3.84 (1H, dd), 3.60 (1.3H, m), 3.47 (0.7H, m), 2.19 (1H, m), 1.94 - 1.74 (3H, m), 1.28 (9H, s), 1.17 (3H, d).

3-[5-({(1R,2S)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzoic acid (1c)
15

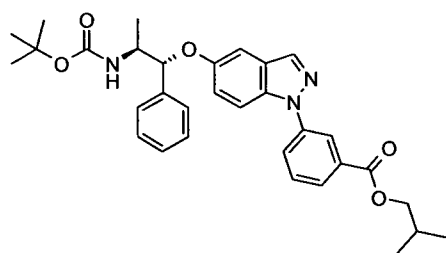


In a 50 mL round-bottomed flask was dissolved isobutyl 3-(5-((1R,2S)-2-(tert-butoxycarbonylamino)-1-phenylpropoxy)-1H-indazol-1-yl)benzoate (**1d**, 1.23 g, 2.26 mmol) in 1,4-dioxane (10 mL) and water (2 mL) to give a colorless solution. Aqueous
20 sodium hydroxide (2M, 3.3 mL) was added and the solution was heated to 80°C for 1 h. The mixture was concentrated in vacuo, diluted with water to approx. 100 mL and washed with MTBE. The organic phase was extracted with 0.5M aq. sodium hydroxide. The aqueous phases were combined, acidified with 2M hydrochloric acid and extracted with ethyl acetate. After evaporation of the organic phase the product was obtained as a yellow
25 oil. Dissolving in acetonitril / water (1:1) and freeze-drying yielded 980 mg (89%) of a colourless solid.

APCI-MS: m/z 488.2 [MH^+]

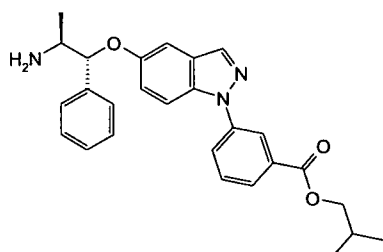
^1H NMR (400 MHz, CDCl_3) δ 8.43 (1H, t), 8.06 (2H, d), 8.02 (2H, s), 7.97 (2H, d), 7.70 - 7.59 (2H, m), 7.47 - 7.33 (7H, m), 7.33 - 7.21 (7H, m), 6.98 (1H, m), 5.51 - 5.37 (1H, m), 4.09 (1H, m), 1.46 (9H, s), 1.18 (3H, d).

5 2-Methylpropyl 3-[5-((1R,2S)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzoate (1d)



In a 25 mL round-bottomed flask was isobutyl 3-(5-((1R,2S)-2-amino-1-phenylpropoxy)-1H-indazol-1-yl)benzoate (**1e**, 1.10 g, 2.48 mmol) and di-tert-butyl dicarbonate (0.627 mL, 2.73 mmol) dissolved in THF (5 mL). At 0°C triethylamine (0.516 mL, 3.72 mmol) was added dropwise. The ice bath was removed and stirring was continued over night. The mixture was diluted with ethyl acetate (80 mL) and washed with sat. aq. ammonium acetate and with brine. After drying over sodium sulfate and removal of the solvents the crude was obtained as a pale yellow oil and subjected to flash chromatography on silica gel (heptane/MTBE=5:4). 1.23 g (91%) of the product were obtained as a colourless foam. APCI-MS: m/z 544.3 [MH^+]

Isobutyl 3-(5-((1R,2S)-2-amino-1-phenylpropoxy)-1H-indazol-1-yl)benzoate (1e)



A 15 mL vial was charged with cesium carbonate (1.043 g, 3.20 mmol), (1R,2S)-2-amino-1-phenylpropan-1-ol (0.181 g, 1.20 mmol), 2-(dimethylamino)acetic acid (0.052 g, 0.50 mmol), copper(I) iodide (0.048 g, 0.25 mmol) and butyronitrile (3.8 mL) and heated at 85°C for 30 min.

A 3 mL vial was charged with isobutyl 3-(5-iodo-1H-indazol-1-yl)benzoate (**1f**, 0.420 g, 1 mmol) and butyronitrile (0.8 mL) and heated to 60 °C for 10 min.

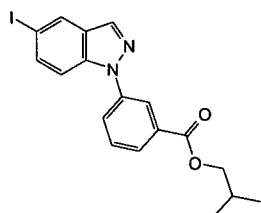
The Iodoindazole solution was transferred to the catalyst mixture in one portion. The vessel was rinsed with butyronitrile (0.4 mL) and this solution was transferred to the catalyst mixture as well. The reaction mixture was then stirred at 85 °C overnight, cooled and filtered through a plug of silica using ethyl acetate/methanol (9/1) as eluent. The solvents were evaporated at reduced pressure and the crude product was purified by flash chromatography on silica, using a gradient of ethyl acetate in heptane (both solvents containing 2% TEA) as eluent to give the title compound (70 mg, 16 %).

APCI-MS: $m/z = 444.2$ [MH⁺]

¹H NMR (400 MHz, CD₃OD) δ 8.31 (1H, t), 8.06 (1H, s), 8.01 (1H, d), 7.96 (1H, d), 7.68 (2H, dd), 7.43 (2H, d), 7.37 (2H, t), 7.29 (2H, m), 7.11 (1H, d), 5.18 (1H, d), 4.16 (2H, d), *(1H in solvent peak), 2.11 (1H, m), 1.2 (3H, d), 1.05 (6H, d).

LC (method A) $rt = 10.9$ min

Isobutyl 3-(5-iodo-1H-indazol-1-yl)benzoate (**1f**)



A 50 mL.s flask was charged with sodium carbonate (0.700 g, 6.60 mmol), 3-(5-iodo-1H-indazol-1-yl)benzoic acid (2.185 g, 6 mmol) and NMP (15 mL) at 40 °C with magnetic stirring. After a couple of minutes 1-bromo-2-methylpropane (0.971 mL, 9.00 mmol) was added in one portion. After one hour at 40°C, the temperature was raised to 55 °C and another portion of 1-bromo-2-methylpropane (0.971 mL, 9.00 mmol) was added. The stirring was continued overnight.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed twice with water, dried over Na₂SO₄, filtered and evaporated to dryness to afford the title compound as a syrup (2.5 g, 99 %). The product solidified to a beige material upon standing.

APCI-MS: $m/z = 421$ [MH⁺]

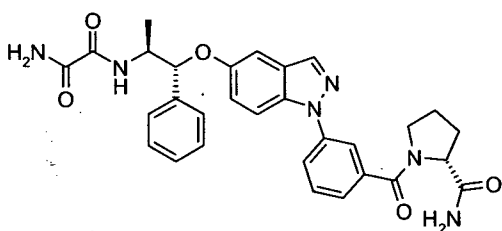
^1H NMR (400 MHz, CDCl_3) δ 8.38 (1H, t), 8.19 (1H, d), 8.16 (1H, d), 8.07 (1H, dt), 7.92 (1H, ddd), 7.70 (1H, dd), 7.64 (1H, t), 7.56 (1H, d), 4.17 (2H, d), 2.12 (1H, m), 1.05 (6H, d).

LC (method A) r_t = 17.6 min

5

Example 2

N-[(1S,2R)-2-{[1-(3-{[(2R)-2-carbamoylpyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]ethanediamide



- 10 The title compound was prepared according to the protocol described for example 2, starting from 2-amino-2-oxoacetic acid (17.62 mg, 0.20 mmol) and (R)-1-(3-(5-((1R,2S)-2-amino-1-phenylpropoxy)-1H-indazol-1-yl)benzoyl)pyrrolidine-2-carboxamide (87 mg, 0.18 mmol). Yield after freeze drying: 14 mg (14%) of a colourless powder.

APCI-MS: m/z 555.1 [MH^+]

- 15 ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.57 (1H, d), 8.22 (0.7H, s), 8.20 (0.3H, s), 7.93 (1H, s), 7.87 (0.7H, s), 7.82 (0.7H, d), 7.77 - 7.72 (2.3H, m), 7.63 (1H, m), 7.55 (1H, m), 7.44 - 7.39 (2.7H, m), 7.38 - 7.28 (2.7H, m), 7.27 - 7.20 (2H, m), 7.12 (1H, m), 6.96 (0.7H, m), 6.92 (0.3H, m), 5.40 (1H, d), 4.36 (0.7H, m), 4.21 (1.3H, m), 3.60 (1.3H, m), 3.46 (0.7H, m), 2.19 (1H, m), 1.92 - 1.74 (3H, m), 1.28 (3H, d).

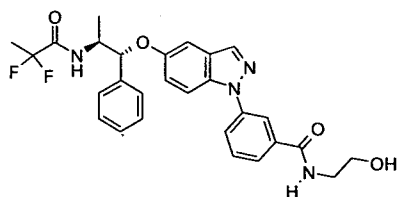
- 20 LC (method A) r_t = 7.58 min

LC (method B) r_t = 7.08 min

Example 3

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(2-hydroxyethyl)benzamide

25



A solution of 3-[5-((1R,2S)-2-((2,2-difluoropropanoyl)amino)-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzoic acid (**3a**) in DCM 3 mL and NMP 0.1 mL was added to a mixture of HBTU (127 mg, 0.33 mmol) and 2-aminoethanol (30 mg, 0.50 mmol). TEA (0.140 mL, 1.00 mmol) was added to the mixtures and the solution was stirred over weekend. The mixture was diluted with 15% NaHSO₄ (2 ml), the organic layer was separated (phase separator) and the water layer was back extracted with DCM 3 mL, the combined organic layers were evaporated. The crude product was dissolved in MeCN 3 mL and purified by mass directed autopreparation using Preparativ HPLC system A, the pure fractions were combined and freeze dried to obtain the title compound (40 mg, 46%).

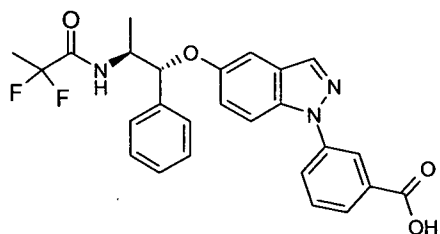
APCI-MS: $m/z = 523$ [MH^+]

¹H NMR (300 MHz, DMSO-d₆) δ 8.72 (1H, d), 8.61 (1H, t), 8.22 (1H, d), 8.16 (1H, t), 7.89 – 7.82 (2H, m), 7.78 (1H, d), 7.64 (1H, t), 7.44 – 7.39 (2H, m), 7.37 – 7.31 (2H, m), 7.29 – 7.20 (2H, m), 7.13 (1H, d), 5.28 (1H, d), 4.74 (1H, t), 4.27 – 4.18 (1H, m), 3.52 (2H, q), 3.43 – 3.38 (2H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.5$ min

LC (method B) $rt = 8.9$ min

3-[5-((1R,2S)-2-((2,2-difluoropropanoyl)amino)-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzoic acid (**3a**)



Isobutyl 3-[5-((1R,2S)-2-((2,2-difluoropropanoyl)amino)-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzoate (**1e**) (1.97 g, 3.68 mmol) was dissolved in MeOH (10 mL) and THF (10.00 mL), lithium hydroxide (0.264 g, 11.03 mmol) dissolved in water (10.00 mL) was added to the solution and stirred over night at room temperature. The mixture was diluted with

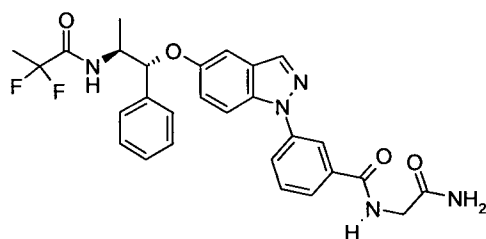
water and washed with TBME, acidified (2M HCl) and extracted with EtOAc x 2, the organic phases were combined and dried with Na₂SO₄, filtered, evaporated to obtain the title compound (1.760 g, 100 %) as dry film.

APCI-MS: $m/z = 480$ [MH⁺]

- 5 ¹H NMR (400 MHz, DMSO-d₆) δ 13.22 (1H, s), 8.71 (1H, d), 8.25 - 8.20 (2H, m), 8.02 - 7.97 (1H, m), 7.92 (1H, d), 7.77 (1H, d), 7.69 (1H, t), 7.42 (2H, d), 7.34 (2H, t), 7.28 - 7.21 (2H, m), 7.14 (1H, d), 5.29 (1H, d), 4.27 - 4.18 (1H, m), 1.49 (3H, t), 1.32 (3H, d).

Example 4

- 10 N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide

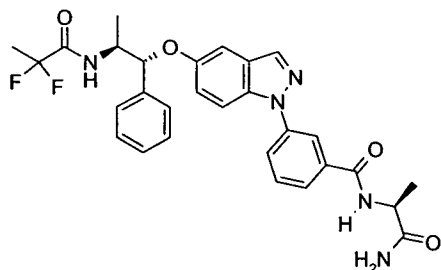


Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (3a) and glycine hydrochloride.

- 15 APCI-MS: $m/z = 536$ [MH⁺]
¹H NMR (300 MHz, DMSO-d₆) δ 8.87 (1H, t), 8.72 (1H, d), 8.22 (1H, d), 8.19 (1H, t), 7.91 - 7.84 (2H, m), 7.81 (1H, d), 7.66 (1H, t), 7.44 - 7.38 (2H, m), 7.37 - 7.31 (2H, m), 7.29 - 7.20 (3H, m), 7.14 (1H, d), 7.05 (1H, s), 5.28 (1H, d), 4.29 - 4.17 (1H, m), 3.83 (2H, d), 1.49 (3H, t), 1.32 (3H, d).
 20 LC (method A) $r_t = 9.1$ min
 LC (method B) $r_t = 8.6$ min

Example 5

- 25 N-[(1S)-2-amino-1-methyl-2-oxoethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and L-alaninamide hydrochloride.

APCI-MS: $m/z = 550$ [MH^+]

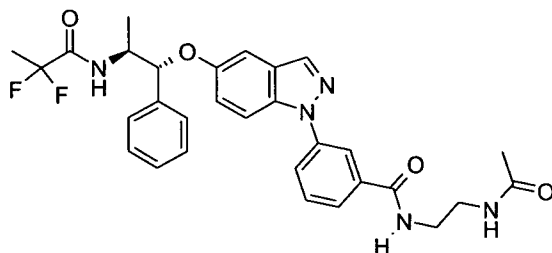
¹H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.63 (1H, d), 8.22 (1H, d), 8.21 (1H, t), 7.91 - 7.85 (2H, m), 7.79 (1H, d), 7.64 (1H, t), 7.44 - 7.39 (2H, m), 7.37 - 7.31 (2H, m), 7.28 - 7.20 (3H, m), 7.13 (1H, d), 6.99 (1H, s), 5.28 (1H, d), 4.48 - 4.38 (1H, m), 4.28 - 4.17 (1H, m), 1.49 (3H, t), 1.36 - 1.30 (6H, m).

LC (method A) $rt = 9.5$ min

LC (method B) $rt = 8.9$ min

Example 6

N-[2-(acetylamino)ethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and N-(2-aminoethyl)acetamide.

APCI-MS: $m/z = 564$ [MH^+]

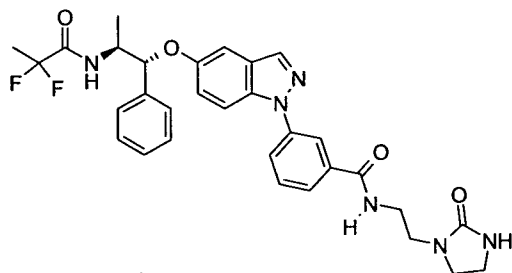
¹H NMR (400 MHz, DMSO- d_6) δ 8.73 - 8.64 (2H, m), 8.22 (1H, s), 8.15 (1H, s), 7.97 (1H, t), 7.88 - 7.79 (3H, m), 7.64 (1H, t), 7.42 (2H, d), 7.34 (2H, t), 7.28 - 7.20 (2H, m), 7.14 (1H, d), 5.28 (1H, d), 4.23 (1H, q), 3.34 - 3.28 (2H, m), 3.21 (2H, q), 1.80 (3H, s), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.4$ min

LC (method B) $rt = 8.9$ min

Example 7

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-
N-[2-(2-oxoimidazolidin-1-yl)ethyl]benzamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and 1-(2-aminoethyl)imidazolidin-2-one.

APCI-MS: $m/z = 591$ [MH^+]

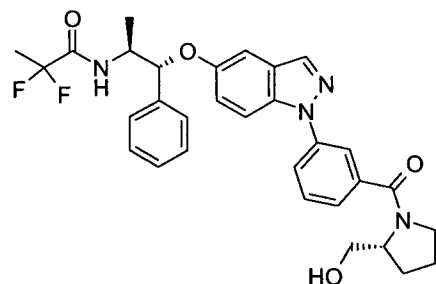
1H NMR (300 MHz, DMSO- d_6) δ 8.75 - 8.66 (2H, m), 8.22 (1H, d), 8.13 (1H, t), 7.89 - 7.84 (1H, m), 7.83 - 7.76 (2H, m), 7.64 (1H, t), 7.44 - 7.39 (2H, m), 7.34 (2H, t), 7.29 - 7.20 (2H, m), 7.13 (1H, d), 6.26 (1H, s), 5.28 (1H, d), 4.29 - 4.18 (1H, m), 3.45 - 3.34 (2H, m), 3.27 - 3.15 (6H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.4$ min

LC (method B) $rt = 8.9$ min

Example 8

2,2-Difluoro-N-[1-(1S,2R)-2-{[1-(3-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]propanamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and (2R)-pyrrolidin-2-ylmethanol.

APCI-MS: $m/z = 563$ $[MH^+]$

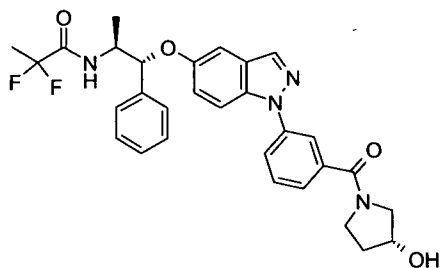
1H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.20 (1H, d), 7.82 - 7.72 (3H, m), 7.61 (1H, t), 7.50 - 7.38 (3H, m), 7.37 - 7.30 (2H, m), 7.28 - 7.19 (2H, m), 7.13 (1H, d), 5.28 (1H, d), 4.30 - 4.08 (2H, m), 3.61 - 3.57 (1H, m), 3.50 - 3.35 (4H, m), 2.01 - 1.80 (3H, m),
 1.77 - 1.62 (1H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 10.5$ min

LC (method B) $rt = 9.6$ min

Example 9

2,2-Difluoro-N-[(1S,2R)-2-{[1-(3-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]propanamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (3a) and (3R)-pyrrolidin-3-ol.

APCI-MS: $m/z = 549$ $[MH^+]$

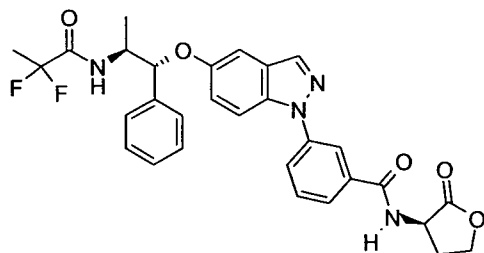
1H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.21 (1H, d), 7.84 - 7.73 (3H, m), 7.62 (1H, t), 7.51 - 7.46 (1H, m), 7.44 - 7.39 (2H, m), 7.37 - 7.30 (2H, m), 7.28 - 7.20 (2H, m), 7.13 (1H, d), 5.28 (1H, d), 4.37 - 4.30 (1H, m), 4.28 - 4.16 (2H, m), 3.64 - 3.51 (2H, m), 3.46 - 3.43 (1H, m), 3.30 - 3.26 (1H, m), 2.01 - 1.74 (2H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.4$ min

LC (method B) $rt = 8.8$ min

Example 10

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[(3R)-2-oxotetrahydrofuran-3-yl]benzamide



Prepared similarly to Example 3 from 3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzamide (**3a**) and (3R)-3-aminodihydrofuran-2(3H)-one hydrochloride.

5 APCI-MS: $m/z = 563$ [MH^+]

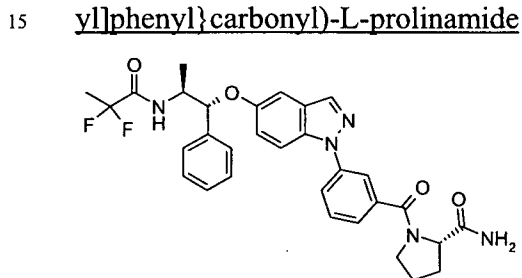
1H NMR (400 MHz, DMSO- d_6) δ 9.16 (1H, d), 8.71 (1H, d), 8.23 (1H, s), 8.18 (1H, s), 7.95 - 7.91 (1H, m), 7.85 (1H, d), 7.79 (1H, d), 7.69 (1H, t), 7.42 (2H, d), 7.34 (2H, t), 7.28 - 7.21 (2H, m), 7.14 (1H, d), 5.29 (1H, d), 4.85 - 4.77 (1H, m), 4.45 - 4.40 (1H, m), 4.32 - 4.20 (2H, m), 2.50 - 2.44 (1H, m), 2.40 - 2.30 (1H, m), 1.49 (3H, t), 1.32 (3H, d).

10 LC (method A) $rt = 10.7$ min

LC (method B) $rt = 10.0$ min

Example 11

1-({3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl)oxy]-1H-indazol-1-yl}phenyl)carbonyl)-L-prolinamide



Prepared similarly to Example 3 from 3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl)oxy]-1H-indazol-1-yl]benzamide (**3a**) and L-prolinamide.

APCI-MS: $m/z = 576$ [MH^+]

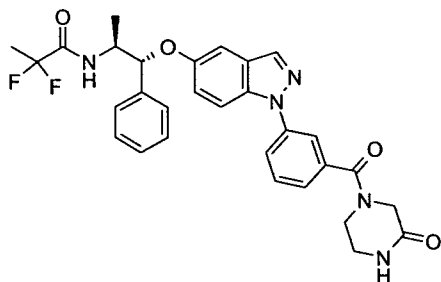
20 1H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.21 (1H, s), 7.90 - 7.79 (1H, m), 7.75 (1H, d), 7.66 - 7.52 (2H, m), 7.46 - 7.39 (2H, m), 7.37 - 7.30 (3H, m), 7.29 - 7.20 (3H, m), 7.13 (1H, d), 6.98 - 6.90 (1H, m), 5.28 (1H, d), 4.40 - 4.33 (1H, m), 4.28 - 4.17 (1H, m), 3.66 - 3.41 (2H, m), 2.24 - 2.11 (1H, m), 1.94 - 1.71 (3H, m), 1.49 (3H, t), 1.37 - 1.27 (3H, m).

LC (method A) $rt = 9.4$ min

LC (method B) $rt = 8.7$ min

Example 12

2,2-Difluoro-N-{(1S,2R)-1-methyl-2-[(1-{3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}-1H-indazol-5-yl)oxy]-2-phenylethyl}propanamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (3a) and piperazin-2-one.

APCI-MS: $m/z = 562$ [MH^+]

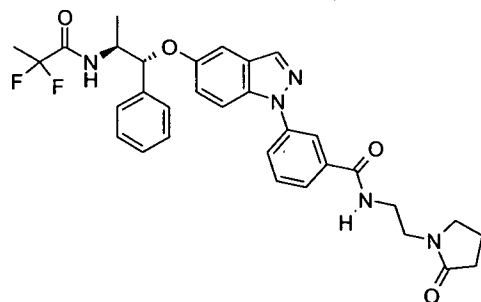
1H NMR (400 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.21 (1H, d), 8.13 (1H, s), 7.86 - 7.82 (1H, m), 7.80 - 7.74 (2H, m), 7.64 (1H, t), 7.44 - 7.39 (3H, m), 7.34 (2H, t), 7.28 - 7.19 (2H, m), 7.13 (1H, d), 5.28 (1H, d), 4.27 - 4.18 (1H, m), 4.15 - 3.92 (2H, m), 3.39 - 3.34 (2H, m), 3.29 - 3.19 (2H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.1$ min

LC (method B) $rt = 8.6$ min

Example 13

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[2-(2-oxopyrrolidin-1-yl)ethyl]benzamide



Prepared similarly to Exampel 3 from 3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and 1-(2-aminoethyl)pyrrolidin-2-one hydrochloride.

APCI-MS: $m/z = 590$ [MH^+]

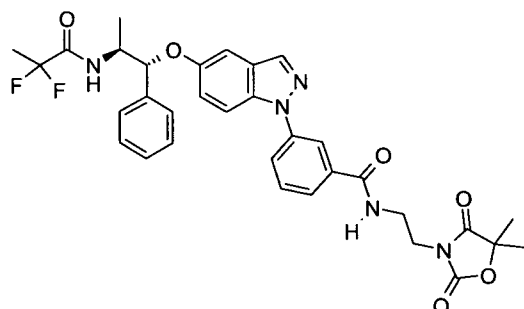
¹H NMR (300 MHz, DMSO- d_6) δ 8.74 - 8.66 (2H, m), 8.22 (1H, d), 8.10 (1H, t), 7.89 - 7.75 (2H, m), 7.64 (1H, t), 7.44 - 7.39 (2H, m), 7.37 - 7.30 (2H, m), 7.29 - 7.19 (3H, m), 7.14 (1H, d), 5.28 (1H, d), 4.28 - 4.18 (1H, m), 3.44 - 3.27 (6H, m), 2.16 (2H, t), 1.95 - 1.84 (2H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.9$ min

LC (method B) $rt = 9.2$ min

Example 14

3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[2-(5,5-dimethyl-2,4-dioxo-1,3-oxazolidin-3-yl)ethyl]benzamide



Prepared similarly to Exampel 3 from 3-[5-((1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and 3-(2-aminoethyl)-5,5-dimethyl-1,3-oxazolidine-2,4-dione hydrochloride.

APCI-MS: $m/z = 634$ [MH^+]

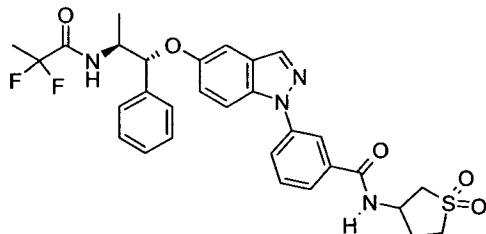
¹H NMR (300 MHz, DMSO- d_6) δ 8.83 (1H, t), 8.72 (1H, d), 8.22 (1H, d), 8.04 (1H, t), 7.89 - 7.84 (1H, m), 7.80 - 7.71 (2H, m), 7.64 (1H, t), 7.44 - 7.40 (2H, m), 7.37 - 7.31 (2H, m), 7.29 - 7.19 (2H, m), 7.14 (1H, d), 5.28 (1H, d), 4.28 - 4.18 (1H, m), 3.64 - 3.58 (2H, m), 3.55 - 3.48 (2H, m), 1.49 (3H, t), 1.45 (6H, s), 1.32 (3H, d).

LC (method A) $rt = 11.7$ min

LC (method B) $rt = 10.8$ min

Example 15

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide



Prepared similarly to Exampel 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and tetrahydrothiophen-3-amine 1,1-dioxide.

APCI-MS: $m/z = 597$ [MH^+]

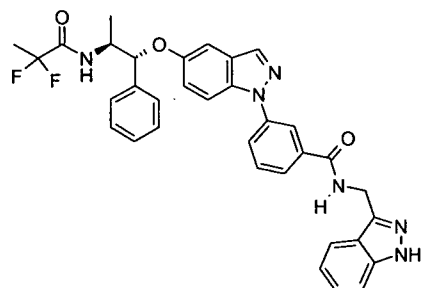
1H NMR (400 MHz, DMSO- d_6) δ 8.90 (1H, d), 8.71 (1H, d), 8.23 (1H, s), 8.19 - 8.16 (1H, m), 7.92 - 7.89 (1H, m), 7.85 (1H, d), 7.77 (1H, d), 7.67 (1H, t), 7.44 - 7.40 (2H, m), 7.36 - 7.31 (2H, m), 7.28 - 7.21 (2H, m), 7.14 (1H, d), 5.28 (1H, d), 4.78 - 4.66 (1H, m), 4.29 - 4.17 (1H, m), 3.52 (1H, dd), 3.39 - 3.33 (1H, m), 3.25 - 3.15 (1H, m), 3.10 (1H, dd), 2.49 - 2.40 (1H, m), 2.29 - 2.16 (1H, m), 1.49 (3H, t), 1.32 (3H, d)

LC (method A) $rt = 10.6$ min

LC (method B) $rt = 10.0$ min

Example 16

3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(1H-indazol-3-ylmethyl)benzamide



Prepared similarly to Exampel 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and 1-(1H-indazol-3-yl)methanamine.

APCI-MS: $m/z = 609$ [MH^+]

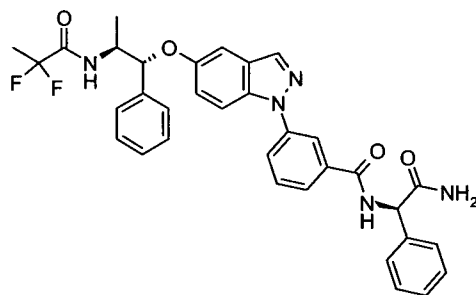
^1H NMR (300 MHz, DMSO- d_6) δ 9.27 (1H, t), 8.71 (1H, d), 8.21 - 8.18 (2H, m), 7.90 - 7.80 (2H, m), 7.77 (2H, d), 7.64 (1H, t), 7.51 - 7.46 (1H, m), 7.44 - 7.39 (2H, m), 7.37 - 7.29 (3H, m), 7.28 - 7.18 (2H, m), 7.13 (1H, d), 7.10 - 7.03 (2H, m), 5.27 (1H, d), 4.85 (2H, d), 4.28 - 4.17 (1H, m), 1.49 (3H, t), 1.31 (3H, d).

5 LC (method A) r_t = 11.6 min

LC (method B) r_t = 11.2 min

Example 17

10 N-[(1R)-2-amino-2-oxo-1-phenylethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and (2R)-2-amino-2-phenylethanamide hydrochloride.

15 APCI-MS: m/z = 612 [MH^+]

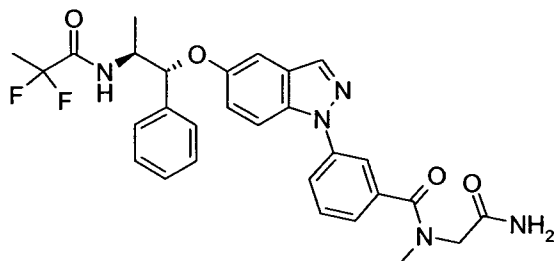
^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (1H, d), 8.72 (1H, d), 8.22 (2H, d), 7.94 - 7.86 (2H, m), 7.78 (1H, d), 7.72 (1H, s), 7.64 (1H, t), 7.53 (2H, d), 7.42 (2H, d), 7.38 - 7.20 (8H, m), 7.14 (1H, d), 5.65 (1H, d), 5.29 (1H, d), 4.24 (1H, dd), 1.50 (3H, t), 1.32 (3H, d).

LC (method A) r_t = 11.1 min

20 LC (method B) r_t = 10.5 min

Example 18

N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-methylbenzamide



Prepared similarly to Exampel 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and N-methylglycinamide hydrochloride.

5 APCI-MS: $m/z = 550$ [MH^+]

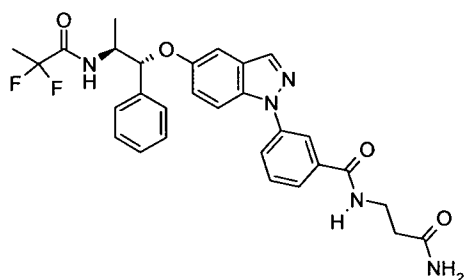
1H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.20 (1H, s), 7.84 - 7.56 (4H, m), 7.51 - 7.29 (6H, m), 7.28 - 7.20 (2H, m), 7.19 - 7.10 (2H, m), 5.28 (1H, d), 4.27 - 4.17 (1H, m), 4.04 (1H, s), 3.83 (1H, s), 2.96 (3H, s), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.0$ min

10 LC (method B) $rt = 8.4$ min

Example 19

N-(3-amino-3-oxopropyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide



15

Prepared similarly to Exampel 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and beta-alaninamide hydrochloride.

APCI-MS: $m/z = 550$ [MH^+]

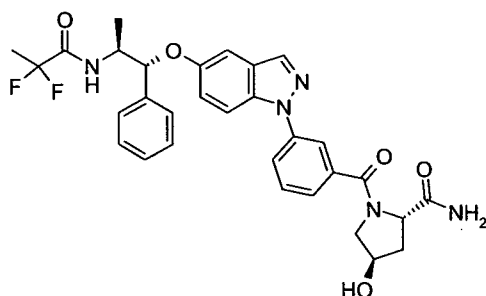
20 1H NMR (300 MHz, DMSO- d_6) δ 8.74 - 8.66 (2H, m), 8.22 (1H, d), 8.14 (1H, t), 7.89 - 7.74 (3H, m), 7.64 (1H, t), 7.45 - 7.30 (5H, m), 7.29 - 7.20 (2H, m), 7.13 (1H, d), 6.83 (1H, s), 5.28 (1H, d), 4.27 - 4.18 (1H, m), 3.46 (2H, dd), 2.37 (2H, t), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 9.1$ min

LC (method B) $rt = 8.6$ min

Example 20

(4R)-1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-4-hydroxy-L-prolinamide



Prepared similarly to Example 3 from 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide (**3a**) and (4R)-4-hydroxy-L-prolinamide.

APCI-MS: $m/z = 592$ [MH^+]

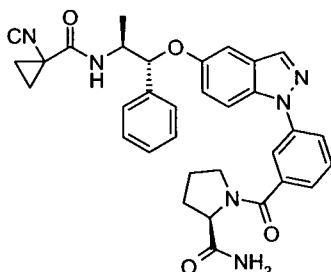
1H NMR (300 MHz, DMSO- d_6) δ 8.71 (1H, d), 8.22 (1H, d), 7.91 - 7.89 (1H, m), 7.86 - 7.81 (1H, m), 7.74 (1H, d), 7.64 (1H, t), 7.58 - 7.53 (1H, m), 7.50 - 7.47 (1H, m), 7.44 - 7.39 (2H, m), 7.37 - 7.30 (2H, m), 7.28 - 7.20 (2H, m), 7.14 (1H, d), 6.96 (1H, s), 5.28 (1H, d), 4.46 (1H, t), 4.27 - 4.18 (2H, m), 3.81 - 3.73 (1H, m), 3.36 - 3.33 (2H, m), 2.21 - 2.10 (1H, m), 1.95 - 1.84 (1H, m), 1.49 (3H, t), 1.32 (3H, d).

LC (method A) $rt = 8.3$ min

LC (method B) $rt = 7.8$ min

Example 21

1-{{3-[5-{{(1R,2S)-2-{{(1-cyanocyclopropyl)carbonyl}amino}-1-phenylpropyl}oxy}-1H-indazol-1-yl]phenyl}carbonyl}-D-prolinamide



The title compound was prepared according to the protocol described for Example 1, starting from 1-cyanocyclopropanecarboxylic acid (23.76 mg, 0.21 mmol) and (R)-1-(3-(5-

((1*R*,2*S*)-2-amino-1-phenylpropoxy)-1*H*-indazol-1-yl)benzoyl)pyrrolidine-2-carboxamide (94 mg, 0.19 mmol). Yield after freeze drying: 53 mg (47%) of a colourless powder.

APCI-MS: m/z 577.1 [MH^+]

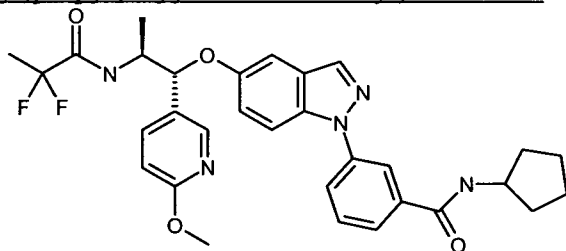
1H NMR (400 MHz, DMSO- d_6) δ 8.22 (0.7H, s), 8.20 (0.3H, s), 8.04 (1.3H, d), 7.90 (0.7H, s), 7.82 (0.7H, d), 7.75 (1.3H, d), 7.63 (1.3H, t), 7.55 (1H, t), 7.42 (3H, d), 7.36 - 7.29 (3.3H, m), 7.24 (3H, m), 7.13 (1.3H, m), 6.98 (0.7H, s), 6.93 (0.3H, s), 5.34 (1H, d), 4.37 (0.7H, m), 4.22 (1.3H, m), 3.65 - 3.57 (1.3H, m), 3.47 (0.7H, m), 2.19 (1H, m), 1.93 - 1.73 (3H, m), 1.45 (2H, m), 1.29 (3H, d), 1.20 (1H, m).

LC (method A) rt = 9.36 min

LC (method B) rt = 8.31 min

Example 22

N-cyclopentyl-3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)benzamide



To N-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (20 mg, 37 μ mol), cyclopentylamine (4.4 mg, 51 μ mol), Tri-*t*-butylphosphoniumtetrafluoroborat (2.1 mg, 7 μ mol) and trans-bis(acetato)bis[o-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (5.6 mg, 7 μ mol) in 1 ml THF was added molybdenum hexacarbonyl (4.6 mg, 18 μ mol). The microwave vessel was closed and radiated in microwave reactor (CEM discover) at 150 W and 125°C for 6 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified by preparative thin layer chromatography on silica gel (ethyl acetate 100%) to yield 6.7 mg (32 %) of N-cyclopentyl-3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)benzamide

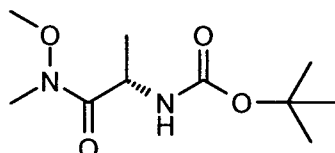
ES+MS: m/z 578 [MH^+]

1H -NMR (300 MHz, $CDCl_3$); δ = 8.20 (d, 1H), 8.05 (dd, 1H), 8.01 (s, 1H), 7.81 (m, 1H), 7.72 (d, 1H), 7.66 (d, 1H), 7.60 (dd, 1H), 7.57 (t, 1H), 7.15 (dd, 1H), 6.98 (d, 1H), 6.75

(d, 1H), 6.67 (br, 1H), 6.15 (br, 1H), 5.36 (d, 1H), 4.41 (m, 1H), 4.38 (m, 1H), 3.92 (s, 3H), 2.10 (m, 2H), 1.77 (t, 3H), 1.64-1.74 (m, 4H), 1.52 (m, 2H), 1.29 (d, 3H).

[(1S)-2-(methoxymethylamino)-1-methyl-2-oxoethyl]-carbamic acid t-butyl ester

5

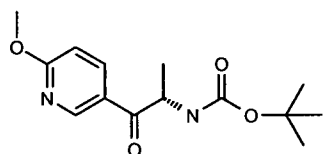


Boc-Ala-OH (200g, 1057 mmol) in 3400 ml dichloromethane were cooled to 0°C. 1,1'-Carbonyldiimidazol (205,7g, 1268 mmol) was added in multiple portions over 30 min and stirring was continued for 30 minutes at 0°C. Triethylamine (175,8 ml, 1268 mmol) was added
 10 over 20 min at 2°C followed by N,O-dimethyl hydroxylamine mono hydrochloride (123,7 g, 1268 mmol) in multiple portions and stirring was continued for 30 minutes at 0°C. After stirring for 14 hours at room temperature the mixture was diluted with 4 L t-butyl methyl ether and washed with 1M HCl solution (2 times 800 ml, 15 min stirring, then phase separation), saturated NaHCO₃ solution (1,3 L) and brine (1,3L). After drying over Na₂SO₄ the solvent
 15 was removed i.vac., and the white crystalline product purified by recrystallization in 500 ml t-butyl methyl ether to yield 217,8 g (89%) of [(1S)-2-(methoxymethylamino)-1-methyl-2-oxoethyl]-carbamic acid t-butyl ester.

¹H-NMR (300 MHz, CDCl₃); δ = 5.25 (br, 1H), 4.67 (dq, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 1.43 (s, 9H), 1.30 (d, 3H).

20

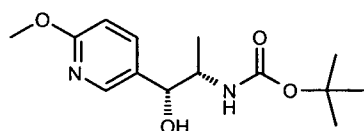
[(1S)-2-(6-methoxy-3-pyridinyl)-1-methyl-2-oxoethyl]-carbamic acid t-butyl ester



To 248ml Isopropylmagnesium chloride (2M in THF, 496 mmol) were added 20,97g (495 mmol) lithium chloride and the resulting suspension was stirred for 60min at room
 25 temperature. At 0° to 10°C 93g (495 mmol) 5-Brom-2-methoxypyridin were added over 30 min and stirred for 60min at room temperature. In parallel 91,91g (396 mmol) [(1S)-2-(methoxymethylamino)-1-methyl-2-oxoethyl] carbamic acid t-butyl ester were suspended

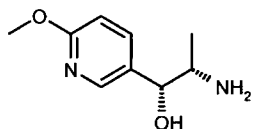
in 425 ml THF and over 40 min at 20° bis 25°C 198 ml isopropylmagnesium chlorid (2M in THF, 396 mmol) were added and stirred for additional 15 minutes at room temperature. The clear LiCl/5-Brom-2-methoxypyridin/iPrMgBr solution was slowly added to the Weinreb amid suspension at 20° to 25°C and stirred over night. The reaction mixture was cooled to 2°C and added slowly to a mixture of 70 ml conc. HCl and 210 ml water at 2°C. While the addition an external cooling bath at -15°C was used to keep the internal temperature in the range of 0° to 5°C. The pH was adjusted to 5 and 210 ml tert.-butyl methyl ether were added and the mixture stirred for 15min at room temperature, phases were separated and the organic phase was washed with water (210 ml) and brine (210 ml). The solvent was evaporated and the residue resolved in 130 ml THF. 1050 ml n-heptane were added and the mixture was heated to 60°C to form a single phase. The volume was reduced to 675 ml and the mixture cooled to room temperature over 1 h and cooled to 2°C over 30 min. After 60 min at 2°C the product is filtered off and dried in vacuum to yield 87,45 g [(1S)-2-(6-methoxy-3-pyridinyl)-1-methyl-2-oxoethyl]-carbamic acid t-butyl ester. ¹H-NMR (300 MHz, CDCl₃); δ = 8.81 (d, 1H), 8.14(dd, 1H), 6.81 (d, 1H), 5.52 (br, 1H), 5.18 (dq, 1H), 4.01 (s, 3H), 1.44 (s, 9H), 1.40 (d, 3H).

[(1S,2R)-2-Hydroxy-2-(6-methoxy-3-pyridinyl)-1-methylethyl]-carbamic acid t-butyl ester



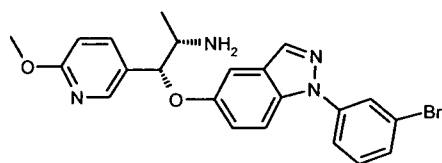
To [(1S)-2-(6-methoxy-3-pyridinyl)-1-methyl-2-oxoethyl]-carbamic acid t-butyl ester. (102 g, 364 mmol) in 2-propanol (310 mL) and toluene (475 mL) was added aluminum tri iso-propylate (44,6 g, 218 mmol). The reaction mixture was stirred at 50°C for 72 hours and water (220 ml) ethyl acetate (550 ml) were added. The mixtures pH is adjusted to 4 (10 ml 6M HCl) and extracted with ethyl acetate (first phase sep. was decanted). The organic phase is washed with brine (220 ml), dried over MgSO₄, the solvent is removed i.vac., and the product purified by chromatography on silica gel (3000g, ethyl acetate in hexane 0% to 50%). Yield 100,7 g (98 %) [(1S,2R)-2-Hydroxy-2-(6-methoxy-3-pyridinyl)-1-methylethyl]-carbamic acid t-butyl ester.

¹H-NMR (300 MHz, CDCl₃); δ = 8.07 (d, 1H), 7.56 (dd, 1H), 6.72 (d, 1H), 4.75 (m, 1H), 4.57 (d, 1H), 3.98 (m, 1H) 3.92 (s, 3H), 3.81 (br, 1H), 1.44 (s, 9H), 1.00 (d, 3H).

(1R,2S)-2-Amino-1-[6-methoxypyridin-3-yl]propan-1-ol

To [(1S,2R)-2-Hydroxy-2-(6-methoxy-3-pyridinyl)-1-methylethyl]-carbamic acid t-butyl ester
 5 (33 g, 117mmol) in 290 mL 1,4-dioxane was added 292 ml HCl in 1,4-dioxane (4 M, 1168
 mmol) and the mixture was stirred for two hours at room temperature. The solvent is removed
 i.vac., and the residual HCl salt three times coevaporated with 100 mL toluene. The residue
 (32,53 g) was suspended in 325 mL acetonitrile and 176,2 g K₂CO₃ was added and the mixture
 was stirred over night at 60°C. After cooling to room temperature the suspension was filtered
 10 through a path of cellites and the solid residues were washed with additional 500 ml
 acetonitrile. Acetonitrile filtrates were combined and the solvent was removed i.vac to yield
 8,35 g (39,2 %) (1R,2S)-2-Amino-1-[6-methoxypyridin-3-yl]propan-1-ol as free base. The
 cellites with the residue were suspended in additional 750 mL acetonitrile and additional 100 g
 K₂CO₃ were added. Stirring at 60°C was repeated over night. After cooling to room
 15 temperature the suspension was filtered through an additional path of cellites and the solid
 residues were washed with additional 500 ml acetonitrile. Combination of filtrates yields 8,45
 g (39,6 %) (1R,2S)-2-amino-1-[6-methoxypyridin-3-yl]propan-1-ol as free base, 16.8 g
 overall.

¹H-NMR (300 MHz, CDCl₃); δ = 8.05 (d, 1H), 7.57 (dd, 1H), 6.71 (d, 1H), 4.47 (d, 1H),
 20 3.91 (s, 3H), 3.13 (dq, 1H), 0.94 (d, 3H).

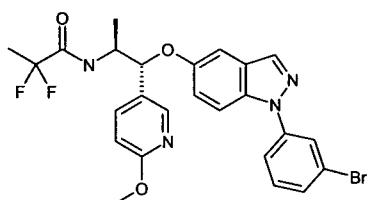
(1R,2S)-1-{[1-(3-Bromophenyl)-1H-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-amine

(1R,2S)-2-Amino-1-[6-methoxypyridin-3-yl]propan-1-ol (200 mg, 0.79 mmol),
 25 copper(I)iodide (30 mg, 0.16 mmol), N,N-dimethylglycin (32 mg, 0.31 mmol) and caesium
 carbonate (512 mg, 1.57 mmole) were suspended in butyronitrile (1.6 mL). The reaction
 vessel was capped and the mixture was stirred at 110 °C for 2 hours. Then 1-(3-

bromophenyl)-5-iodoindazole (266 mg, 0.79 mmole) was added and heating to 130°C was continued for 20 hours. The solvent was removed i.vac., and the product purified by chromatography on silica gel. (ethyl acetate in hexane 0 to 100%, then methanol in ethyl acetate 10%) to yield 307 mg (86%) (*1R,2S*)-1-{[1-(3-Bromophenyl)-1H-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-amine.

¹H-NMR (300 MHz, CDCl₃); δ = 8.21 (d, 1H), 7.98 (d, 1H), 7.83 (t, 1H), 7.60 (m, 3H), 7.44 (ddd, 1H), 7.35 (t, 1H), 7.19 (dd, 1H), 7.02 (d, 1H), 6.72 (d, 1H), 5.23 (d, 1H), 3.89 (s, 3H), 3.54 (dq, 1H), 1.27 (d, 3H)

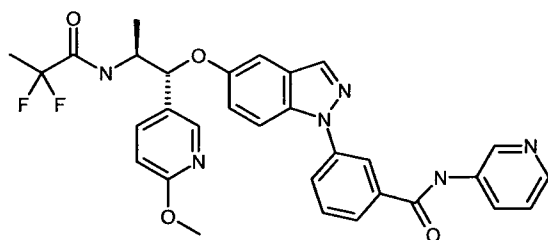
10 N-[(*1R,2S*)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide



1,1'-Carbonyldiimidazol (217 mg, 1.34 mmol) was added to 2,2-difluoropropionic acid (111 mg, 1.0 mmol) in 4 mL THF and stirred for 7 hours. (*1R,2S*)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-amine (304 mg, 0.67 mmol) in THF (2 mL) was added and stirring was continued for 64 hours at room temperature. The solvent was removed i.vac., and the product purified by chromatography on silica gel. (ethyl acetate in hexane 0 to 40%) to yield 205 mg (56%) N-[(*1R,2S*)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide.

¹H-NMR (300 MHz, CDCl₃); δ = 8.19 (d, 1H), 8.00 (d, 1H), 7.86 (t, 1H), 7.64 (d, 1H), 7.63 (m, 1H), 7.60 (dd, 1H), 7.46 (ddd, 1H), 7.37 (t, 1H), 7.16 (dd, 1H), 6.97 (d, 1H), 6.76 (d, 1H), 6.67 (br, 1H), 5.36 (d, 1H), 4.39 (dq, 1H), 3.92 (s, 3H), 1.77 (t, 3H), 1.28 (d, 3H).

25 **Example 23** 3-(5-{[(*1R,2S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1H-indazol-1-yl)-N-(pyridin-3-yl)benzamide



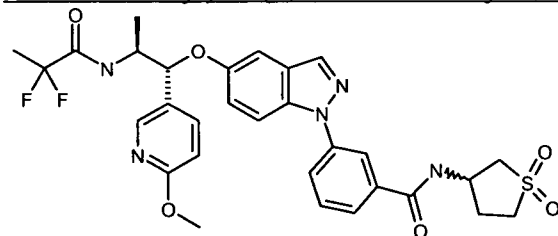
To N-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (37 mg, 68 μ mol), 3-aminopyridine (19.2 mg, 204 μ mol), tri-*t*-butylphosphoniumtetrafluoroborat (8.9 mg, 31 μ mol) and trans-
 5 bis(acetato)bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (10.3 mg, 14 μ mol) in 1.9 ml THF was added molybdenum hexacarbonyl (12.5 mg, μ mol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 150 W and 125°C for 6 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified by preparative thin layer chromatography on silica gel (ethyl acetate 100%) to
 10 yield 22 mg (55%) 3-(5-([(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy)-1*H*-indazol-1-yl)-*N*-(pyridin-3-yl)benzamide.

ES+MS: m/z 587 [MH^+]

1H -NMR (300 MHz, $CDCl_3$); δ = 8.74 (d, 1H), 8.41 (d, 1H), 8.31 (m, 2H), 8.20 (m, 2H), 7.89 (d, 1H), 7.86 (d, 1H), 7.68 (d, 1H), 7.64 (t, 1H), 7.61 (dd, 1H), 7.33 (dd, 1H), 7.17
 15 (dd, 1H), 6.99 (d, 1H), 6.75 (d, 1H), 6.68 (d, 1H), 5.37 (d, 1H), 4.40 (dq, 1H), 3.92 (s, 3H), 1.77 (t., 3H), 1.25 (d, 3H).

Example 24

3-(5-([(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy)-1*H*-indazol-1-yl)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide



To N-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (40 mg, 73 μ mol), tetrahydrothiophen-3-amine 1,1-dioxide (13 mg, 135 μ mol), tri-*t*-butylphosphoniumtetrafluoroborat (2.6 mg, 9 μ mol)
 25 and trans-bis(acetato)bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (2.8 mg, 14 μ mol)

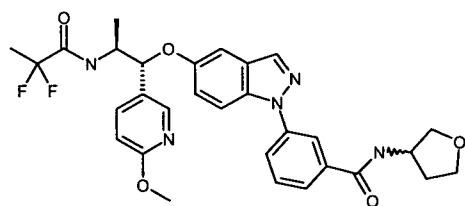
in 2 mL THF was added molybdenum hexacarbonyl (9.3 mg, 35 μ mol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 150 W and 125°C for 6 minutes (5 minutes ramp time). Additional tetrahydrothiophen-3-amine 1,1-dioxide (13 mg, 135 μ mol), tri-*t*-butylphosphoniumtetrafluoroborat (1.3 mg, 4 μ mol) and trans-bis(acetato)bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (1.4 mg, 2 μ mol) were added and microwave radiation was continued for 8 minutes. Then the solvent was removed i.vac., and the product purified by chromatography on silica gel (ethyl acetate in hexane 0% to 30% then additional 5 % methanol) to yield 6.5 mg (14%) 3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide.

ES+MS: m/z 628 [MH^+]

1H -NMR (300 MHz, $CDCl_3$); δ = 8.20 (d, 1H), 8.11 (d, 1H), 8.01 (s, 1H), 7.85 (m, 1H), 7.71 (d, 1H), 7.63 (t, 1H), 7.60 (dd, 1H), 7.16 (dd, 1H), 7.08 (m, 1H), 6.99 (d, 1H), 6.76 (d, 1H), 6.67 (d, 1H), 5.36 (d, 1H), 5.00 (m, 1H), 4.39 (dq, 1H), 3.92 (s, 3H), 3.47 (m, 1H), 3.29 (m, 1H), 3.16 (m, 2H), 2.63 (m, 1H), 2.44 (m, 1H), 1.77 (t, 3H), 1.29 (d, 3H).

Example 25

3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(tetrahydrofuran-3-yl)benzamide



To *N*-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (37 mg, 68 μ mol), 3-aminotetrahydrofuran (18 mg, 204 μ mol), tri-*t*-butylphosphoniumtetrafluoroborat (8.8 mg, 31 μ mol) and trans-bis(acetato)bis[o-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (10.3 mg, 14 μ mol) in 1.5 mL THF was added molybdaenhexacarbonyl (12.5 mg, 47 μ mol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 150 W and 125°C for 10 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified by preparative thin layer chromatography on silica gel (ethyl acetate 100%) to

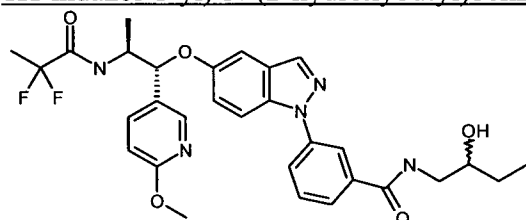
yield 11 mg (30%) 3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(tetrahydrofuran-3-yl)benzamide.

ES+MS: m/z 580 $[MH^+]$

1H -NMR (300 MHz, $CDCl_3$); δ = 8.20 (d, 1H), 8.08 (dd, 1H), 8.02 (s, 1H), 7.83 (m, 1H), 7.71 (m, 1H), 7.67 (d, 1H), 7.60 (dd, 1H), 7.58 (t, 1H), 7.16 (dd, 1H), 6.99 (d, 1H), 6.76 (d, 1H), 6.66 (br, 1H), 6.43 (br, 1H), 5.36 (d, 1H), 4.75 (m, 1H), 4.40 (dq, 1H), 4.01 (m, 1H), 3.92 (s, 3H), 3.91 (m, 1H), 3.83 (m, 2H), 2.38 (m, 1H), 1.95 (m, 1H), 1.77 (t, 3H), 1.29 (d, 3H).

Example 26

3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(2-hydroxybutyl)benzamide



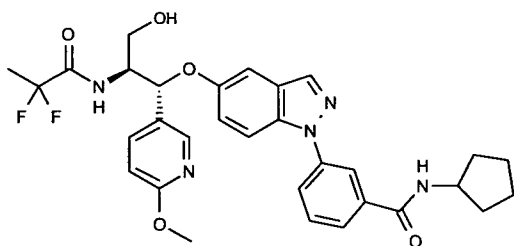
To *N*-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (50 mg, 92 μ mol), 1-amino-2-butanol (25 mg, 275 μ mol), tri-*t*-butylphosphoniumtetrafluoroborate (12 mg, 41 μ mol) and *trans*-bis(acetato)bis[o-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (mg, 7 μ mol) in 2 mL THF was added molybdenum hexacarbonyl (17 mg, 64 μ mol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 150 W and 125°C for 10 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified by chromatography on silica gel (ethyl acetate in hexane 0% to 100%) to yield 35 mg (66%) 3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(2-hydroxybutyl)benzamide.

ES+MS: m/z 582 $[MH^+]$

1H -NMR (300 MHz, $CDCl_3$); δ = 8.20 (d, 1H), 8.11 (s, 1H), 8.01 (s, 1H), 7.82 (m, 1H), 7.73 (d, 1H), 7.66 (d, 1H), 7.60 (dd, 1H), 7.57 (t, 1H), 7.16 (dd, 1H), 6.98 (d, 1H), 6.75 (d, 1H), 6.74 (br, 1H), 6.66 (br, 1H), 5.36 (d, 1H), 4.40 (dq, 1H), 3.92 (s, 3H), 3.76 (m, 1H), 3.74 (dddd, 1H), 3.34 (dddd, 1H), 1.77 (t, 3H), 1.57 (m, 2H), 1.29 (d, 3H), 1.00 (t, 3H).

Example 27

N-cyclopentyl-3-(5-{[(1*R*, 2*S*)-2-[(2,2-difluoropropanoyl)amino]-3-hydroxy-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)benzamide



5

To N-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-3-*tert*-butoxy-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (37 mg, 60 μmol), cyclopentylamine (7.1 mg, 84 μmol), Tri-*t*-butylphosphoniumtetrafluoroborat (3.5 mg, 12 μmol) and trans-bis(acetato)bis[o-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (9.1 mg, 12 μmol) in 1.6 ml THF was added molybdenum hexacarbonyl (7.6 mg, 29 μmol). The microwave vessel was closed and radiated in microwave reactor (CEM discover) at 150 W and 125°C for 6 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified by preparative thin layer chromatography on silica gel (ethyl acetate in hexane 50%) to yield 15 mg of 3-(5-{[(1*R*,2*S*)-3-*tert*-butoxy-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-N-cyclopentylbenzamide, which were treated with 178 μl trifluoroacetic acid in 0.6 ml dichloromethane over 18 hours at room temperature. Saturated sodium hydrogen carbonate solution was added, the mixture was stirred vigorously and extracted with ethyl acetate after 30 minutes. Then the solvent was removed i.vac., and the product purified by preparative thin layer chromatography on silica gel (ethyl acetate 100%) to yield 15 mg of N-cyclopentyl-3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-3-hydroxy-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)benzamide.

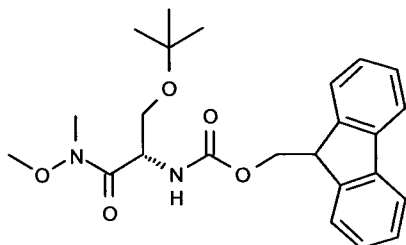
20

ES+MS: m/z 594 $[MH^+]$

1H -NMR (400 MHz, $CDCl_3$); δ = 8.17 (d, 1H), 8.02 (s, 1H), 7.97 (s, 1H), 7.77 (d, 1H), 7.69 (d, 1H), 7.66 (dd, 1H), 7.61 (d, 1H), 7.56 (t, 1H), 7.08 (dd, 1H), 6.98 (d, 1H), 6.74 (d, 1H), 6.24 (d, 1H), 5.42 (d, 1H), 4.42 (ddd, 1H), 4.35 (m, 1H), 4.20 (d, 1H), 3.90 (s, 3H), 3.78 (m, 1H), 2.76 (br, 1H), 2.11 (m, 2H), 1.66 (t, 3H), 1.64-1.74 (m., 4H), 1.52 (m, 2H).

25

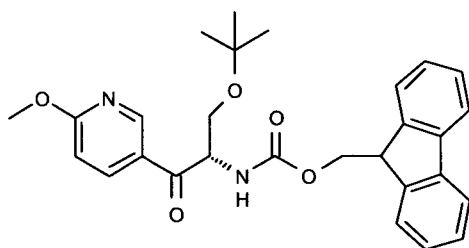
carbamic acid, [(1S)-1-[(1,1-dimethylethoxy)methyl]-2-(methoxymethylamino)-2-oxoethyl]-, 9H-fluoren-9-ylmethyl ester



- 5 FMOC-SER(TBU)-OH (50 g, 130 mmol) in 320 ml dichloromethane were cooled to 0°C. 1,1'-Carbonyldiimidazol (28.3 g, 175 mmol) were added in multiple portions and stirring was continued for 30 minutes at 0°C. Triethylamine (24,2 ml, 175 mmol) was added followed by N,O-dimethyl hydroxylamine mono hydrochloride (17 g, 175 mmol) in multiple portions and stirring was continued for 30 minutes at 0°C. After stirring for 14 hours at room temperature
- 10 the mixture was diluted with 400 ml t-butyl methylether and washed with 1M HCL solution (2 times 100 ml), saturated NaHCO₃ solution and brine. After drying over Na₂SO₄ the solvent was removed i.vac., and the product purified by chromatography on silica gel (ethyl acetate in hexane, 0% to 70%) to yield 39,2 g of *carbamic acid, [(1S)-1-[(1,1-dimethylethoxy)methyl]-2-(methoxymethylamino)-2-oxoethyl]-, 9H-fluoren-9-ylmethyl ester* (92%).
- 15 ¹H-NMR (300 MHz, CDCl₃); δ = 7.76 (d, 2H), 7.61 (m, 2H), 7.40 (dd, 2H), 7.31(dd, 2H), 5.68 (d, 1H), 4.87 (br, 1H), 4.36 (d, 2H), 4.24 (t, 1H), 3.78 (s, 3H), 3.62 (m, 2H), 3.25 (s, 3H), 1.16 (s, 9H).

9H-fluoren-9-ylmethyl [(2S)-3-tert-butoxy-1-(6-methoxypyridin-3-yl)-1-oxopropan-2-yl]carbamate

20



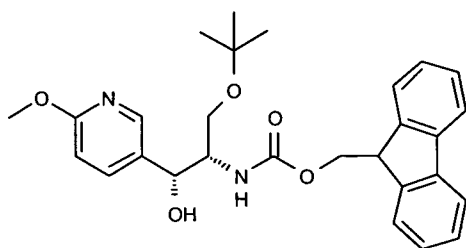
64 ml Isopropylmagnesium chloride (2M in THF, 128 mmol) were added to 5-Brom-2-methoxypyridin (10 g, 53 mmol) and carbamic acid, [(1S)-1-[(1,1-dimethylethoxy)methyl]-2-

(methoxymethylamino)-2-oxoethyl]-, 9H-fluoren-9-ylmethyl ester (18.1 g, 43 mmol) in 55 ml THF at -15°C and stirred over night while the mixture was warmed to room temperature. The reaction mixture was cooled to 2°C and added slowly to a 2M HCl-ice mixture and stirred vigorously. The pH was adjusted to 5 and the aqueous phase extracted with ethyl acetate.

5 After drying over Na₂SO₄ the solvent was removed i.vac., and the product purified by chromatography on silica gel (ethyl acetate in hexane, 0 to 100%) to yield 3.28 g (13%) 9H-fluoren-9-ylmethyl [(2S)-3-tert-butoxy-1-(6-methoxypyridin-3-yl)-1-oxopropan-2-yl]carbamate.

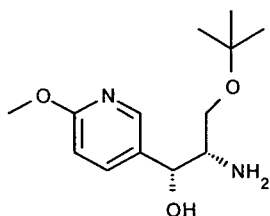
¹H-NMR (300 MHz, CDCl₃); δ = 8.82 (d, 1H), 8.16 (dd, 1H), 7.77 (d, 2H), 7.63 (m, 2H),
10 7.41 (dd, 2H), 7.32 (dd, 2H), 6.81 (d, 1H), 5.95 (d, 1H), 5.29 (m, 1H), 4.40 (d, 2H), 4.25 (t, 1H), 4.02 (s, 3H), 3.76 (dd, 1H), 3.66 (dd, 1H), 1.02 (s, 9H).

9H-fluoren-9-ylmethyl [(1R,2S)-3-tert-butoxy-1-hydroxy-1-(6-methoxypyridin-3-yl)propan-2-yl]carbamate



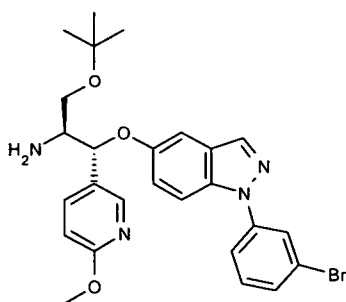
15 9H-fluoren-9-ylmethyl [(2S)-3-tert-butoxy-1-(6-methoxypyridin-3-yl)-1-oxopropan-2-yl]carbamate (2.26 g, 4.76 mmol) in 2-propanol (4.4 mL) and toluene (6 mL) was added aluminum tri iso-propylate (300 mg, 1.4 mmol). The reaction mixture was stirred at 65°C for 72 hours, additional aluminum tri iso-propylate (300 mg, 1.4 mmol) was added and
20 stirring was continued for 24 hours. Water was added, the mixture was stirring for 15 minutes and extracted with ethyl acetate. The organic phase was dried over Na₂SO₄, the solvent is removed i.vac., and the product purified by chromatography on silica gel (ethyl acetate in hexane 0% to 100%) to yield 1.46 g (65%) 9H-fluoren-9-ylmethyl [(1R,2S)-3-tert-butoxy-1-hydroxy-1-(6-methoxypyridin-3-yl)propan-2-yl]carbamate.

25 ¹H-NMR (300 MHz, CDCl₃); δ = 8.18 (s, 1H), 7.78 (d, 2H), 7.66 (m, 3H), 7.41 (dd, 2H), 7.32 (dd, 2H), 6.75 (d, 1H), 5.64 (d, 1H), 4.91 (m, 1H), 4.41 (m, 2H), 4.23 (m, 2H), 3.93 (s, 3H), 3.50 (dd, 2H), 1.18 (s, 9H).

(1R,2S)-2-amino-3-tert-butoxy-1-(6-methoxypyridin-3-yl)propan-1-ol

To 9H-fluoren-9-ylmethyl [(1R,2S)-3-tert-butoxy-1-hydroxy-1-(6-methoxypyridin-3-yl)propan-2-yl]carbamate (2.38 g, 5.0 mmol) in 19 mL N,N-dimethylformamid was added piperidine (4.9 mL, 50 mmol) at room temperature. The reaction mixture was stirred 20 hours at room temperature. The reaction mixture was added to ice-water and the precipitate removed by filtration through cellites followed by careful washing of the solids with water. The aqueous filtrate was extracted with 10% methanol in dichloromethane and the organic phase was dried over Na₂SO₄. The solvent was removed i.vac., and the product purified by chromatography on silica gel. (methanol in dichloromethane 0% to 10%) to yield 426 mg (34 %) (1R,2S)-2-amino-3-tert-butoxy-1-(6-methoxypyridin-3-yl)propan-1-ol.

¹H-NMR (400 MHz, CDCl₃); δ = 8.13 (d, 1H), 7.63 (dd, 1H), 6.76 (d, 1H), 4.62 (d, 1H), 3.94 (s, 3H), 3.47 (dd, 1H), 3.35 (dd, 1H), 3.09 (m, 1H), 1.20 (s, 9H).

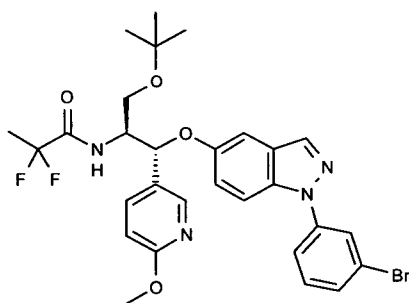
(1R,2S)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-3-tert-butoxy-1-(6-methoxypyridin-3-yl)propan-2-amine

(1R,2S)-2-Amino-3-tert-butoxy-1-(6-methoxypyridin-3-yl)propan-1-ol (350 mg, 1.38 mmol), copper(I)iodide (52 mg, 0.28 mmol), N,N-dimethylglycine (57 mg, 0.55 mmol) and caesium carbonate (896 mg, 2.75 mmole) were suspended in butyronitrile (2.9 mL). The reaction vessel was capped and the mixture was stirred at 110 °C for 2 hours. Then 1-(3-bromophenyl)-

5-iodoindazole (465 mg, 1.38 mmole) was added and heating to 130°C was continued for 20 hours. The mixture was filtered through cellites followed by careful washing of the solids with 10% triethylamine in methanol. The solvent was removed i.vac., and the product purified by chromatography on silica gel. (ethyl acetate in dichloromethane 0 to 100%, then methanol in ethyl acetate 10% + 1% triethylamine) to yield 122 mg (17%) (*1R,2S*)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-3-*tert*-butoxy-1-(6-methoxypyridin-3-yl)propan-2-amine.

¹H-NMR (300 MHz, CDCl₃); δ = 8.22 (d, 1H), 8.01 (d, 1H), 7.86 (t, 1H), 7.67 (dd, 1H), 7.62 (ddd, 1H), 7.60 (d, 1H), 7.45 (ddd, 1H), 7.36 (t, 1H), 7.13 (dd, 1H), 7.04 (d, 1H), 6.75 (d, 1H), 5.18 (d, 1H), 3.91 (s, 3H), 3.58 (dd, 1H), 3.50 (dd, 1H), 3.37 (m, 1H), 1.20 (s, 1H)

N-[*(1R,2S)*-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-3-*tert*-butoxy-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide

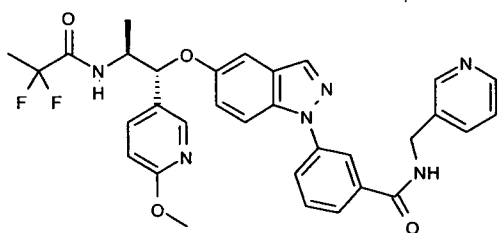


1,1'-Carbonyldiimidazol (74 mg, 0.46 mmol) was added to 2,2-difluoropropionic acid (50 mg, 0.46 mmol) in 1.2 mL THF and stirred for 3 hours. (*1R,2S*)-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-3-*tert*-butoxy-1-(6-methoxypyridin-3-yl)propan-2-amine (120 mg, 0.23 mmol) in THF (1.2 ml) was added and stirring was continued for 20 hours at room temperature. Water and ethyl acetate were added, the mixture was stirred vigorously, extracted with ethyl acetate after 30 minutes and washed with brine. The solvent was removed i.vac., and the product purified by chromatography on silica gel. (ethyl acetate in hexane 0 to 50%) to yield 52 mg (37%) *N*-[*(1R,2S)*-1-{[1-(3-bromophenyl)-1H-indazol-5-yl]oxy}-3-*tert*-butoxy-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide.

¹H-NMR (300 MHz, CDCl₃); δ = 8.13 (d, 1H), 8.02 (d, 1H), 7.86 (t, 1H), 7.71 (dd, 1H), 7.63 (ddd, 1H), 7.61 (d, 1H), 7.45 (ddd, 1H), 7.37 (t, 1H), 7.13 (dd, 1H), 7.06 (d, 1H), 6.76 (br, 1H), 6.72 (d, 1H), 5.27 (d, 1H), 4.51 (m, 1H), 4.01 (dd, 1H), 3.89 (s, 3H), 3.49 (dd, 1H), 1.57 (t, 3H), 1.18 (s, 9H).

Example 28

3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(pyridin-3-ylmethyl)benzamide



5

To *N*-[(1*R*,2*S*)-1-{[1-(3-bromophenyl)-1*H*-indazol-5-yl]oxy}-1-(6-methoxypyridin-3-yl)propan-2-yl]-2,2-difluoropropanamide (50 mg, 92 μmol), 3-aminomethylpyridine (30 mg, 275 μmol), tri-*t*-butylphosphoniumtetrafluoroborate (12 mg, 41 μmol) and trans-bis(acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (13.9 mg, 18 μmol) in 2 ml
 10 THF was added molybdenum hexacarbonyl (17 mg, 64 μmol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 150 W and 125°C for 10 minutes (5 minutes ramp time). Then the solvent was removed i.vac., and the product purified chromatography on silica gel (hexane / ethyl acetate 0 to 100%) to yield 19 mg (35%) 3-(5-{[(1*R*,2*S*)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl]oxy}-1*H*-indazol-1-yl)-*N*-(pyridin-3-ylmethyl)benzamide.

15

ES+MS: m/z 601 [MH^+]

20

1H -NMR (300 MHz, $CDCl_3$); δ = 8.62 (br, 1H), 8.55 (br, 1H), 8.19 (d, 1H), 8.12 (m, 1H), 8.00 (s, 1H), 7.84 (d, 1H), 7.74 (m, 2H), 7.67 (d, 1H), 7.58 (m, 2H), 7.29 (dd, 1H), 7.15 (dd, 1H), 6.98 (d, 1H), 6.75 (d, 1H), 6.69 (m, 2H), 5.35 (d, 1H), 4.68 (d, 2H), 4.39 (dq, 1H), 3.92 (s, 3H), 1.76 (t, 3H), 1.28 (d, 3H).

AssayHuman Glucocorticoid Receptor (GR) Assay

The radioligand GR binding assay is based on a competition assay using 3H -labeled
 25 Dexamethasone. Dexamethasone is known to bind in the ligand binding domain of GR and compete for binding with endogenous ligands like e.g. cortisol (Necela, 2003).

In the GR radioligand binding assay, test compounds were serially diluted in semi-log steps (10 concentrations) with a final concentration of 10 μM. Test compounds (1 μL) and

controls (1 μ L) in 100% DMSO were added to 96 Greiner V-bottom polypropylene plates. 0% control was 6.7% DMSO (final concentration in assay) and 100% control was 6.7 μ M Dexamethasone.

The full length GR was diluted to a final concentration of 3.3% (0.495 mg/ml) in assay
5 buffer (20mM Tris-HCl, 1mM EDTA, 10% (w/v) Glycerol, 20mM Sodium molbydate, pH 7.4). 45 μ L of GR was added to each well and the plates were incubated for 15 min at room temperature.

³H-dexamethasone solution was diluted to a concentration of 70 nM in assay buffer (7nM
10 final assay concentration) and 5 μ L was added to each well. The samples were mixed for 5 min using a plate shaker at 700 rpm, before incubation for 2 h at room temperature.

50 μ L ice-cold charcoal solution (pH 7.4: 2% Charcoal, 0,2% Dextran T70 in 20mM Tris-HCl, 1mM EDTA and 20mM Sodium molbydate) was added to each well and the samples were mixed on plate shaker for 5 minutes.

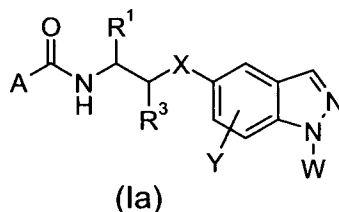
The plate was then centrifuged for 1.5 min at 1500 rpm, the samples (80 μ L) were
15 transfered from each well to a filter plate (Millipore, 0.45 μ m, MHVBN45) on a vacuum manifold and then collected into new plates (Greiner, 96 well white/transparent, 655095). The filter plate was washed once with 20 μ l of water and then 100 μ L of scintillation liquid was added to each well and mixed by incubation on plate shaker for 5 min. Radioactivity was measured in a 1450 Microbeta Trilux Reader (Wallac) counting cpm for 2 minutes per
20 well. The data obtained from each replicate experiment were analysed using the software ActivityBase, version 5.4.3 (ID Business Solutions Ltd) and IC₅₀ values were calculated.
Ref: Necela, BM, Cidlowski, JA, Trends Pharmacol Sci, 24: 58, 2003

Example	GR Binding IC ₅₀
Nr	[nM]
1	2.81
2	19.9
3	1.69
4	1.61
5	1.93
6	5.06

7	16.9
8	6.88
9	5.65
10	1.73
11	6.77
12	2.54
13	38.4
14	40.2
15	1.72
16	42.4
17	3.55
18	4.22
19	2.29
20	75.9
21	2.91
22	1.37
23	0.86
24	4.46
25	2.99
26	4.13
27	13.6
28	1.39

CLAIMS

1. A compound of formula Ia:



wherein:

- 5 A is C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₇cycloalkyl, C₁₋₆haloalkyl, C₁₋₆alkylthio, C₁₋₆alkylC(O)-, C₁₋₆alkyloxyC(O)-, NR⁵R⁶, NR⁵R⁶C(O)- or C₅₋₁₀heteroaryl, all optionally substituted by one or more substituents independently selected from halo, cyano, hydroxyl, C₁₋₄alkyl, C₁₋₄alkoxy and C₁₋₄haloalkyl;
- R⁵ and R⁶ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(O)- and C₃₋₇cycloalkylC(O)-, or R⁵ and R⁶ might form a ring with the nitrogen to which they are attached;
- R¹ is hydrogen, C₁₋₄alkyl, C₁₋₄hydroxyalkyl-, C₁₋₄alkylOC₁₋₄alkyl-, C₁₋₄alkylthioC₁₋₄alkyl- or C₁₋₄haloalkyl;
- R³ is C₅₋₁₀aryl, C₅₋₁₀arylC₁₋₄alkyl-, C₅₋₁₀arylO-, C₅₋₁₀arylC₁₋₄alkoxy-, C₅₋₁₀aryloxyC₁₋₄alkyl-, C₅₋₁₀heteroaryl-, C₅₋₁₀heteroarylC₁₋₄alkyl-, C₅₋₁₀heteroarylC₁₋₄alkoxy- or C₅₋₁₀heteroaryoxyC₁₋₄alkyl-, all of which are unsubstituted or optionally substituted by one or more substituents independently selected from B;
- 15 B is hydroxyl, halo, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₃hydroxyalkyl-, C₁₋₄alkoxyC₁₋₄alkyl-, C₃₋₆cycloalkyloxyC₁₋₄alkyl-, C₃₋₆cycloalkylO-, C₃₋₆cycloalkylthioC₁₋₄alkyl-, C₃₋₆cycloalkylthio-, C₁₋₃alkylS(O)_kC₁₋₄alkyl-, C₁₋₃alkylS(O)_k-, C₁₋₄haloalkyl or C₁₋₄haloalkoxy-, or B is one of the following groups which are linked to adjacent carbons on an aryl or heteroaryl ring (CH₂)_tOC₁₋₄alkylenylO(CH₂)_v- or (CH₂)_tO(CH₂)_v-;
- k is 0, 1;
- t and v are, independently, 0, 1, 2 or 3, and t and v are not both 0;
- 25 X is O or NH;
- W is phenyl substituted by one or more substituents independently selected from - (CH₂)_nC(O)NR⁷R⁸, -(CH₂)_nNR⁹C(O)R⁸ or -(CH₂)_nC(O)NR⁹(CR¹⁴R¹⁵)C(O)NR⁷R⁸; and W is optionally further substituted by halogen or C₁₋₄alkyl;
- R⁷ is hydrogen or C₁₋₄alkyl;

R^8 and R^9 are, independently, hydrogen, C_{1-4} alkyl (optionally substituted by one or two groups selected from hydroxyl, C_{1-4} alkoxy, NH_2 , oxo, $-C(O)NR^{10}R^{11}$, $-NR^{10}C_{1-4}$ alkyl, $-C(O)NR^{10}C_{1-4}$ alkyl, $-NR^{10}C(O)C_{1-4}$ alkyl, C_{1-4} alkylthio, C_{5-10} heterocyclyl, C_{5-10} aryl or C_{5-10} heteroaryl),

5 C_{3-7} cycloalkyl (optionally substituted by $-C(O)NH_2$), C_{5-10} heterocyclyl, C_{5-10} aryl, C_{5-10} heteroaryl or $-C(O)NR^{10}R^{11}$;

whereby C_{5-10} aryl or C_{5-10} heteroaryl are optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 , $-OCF_3$, hydroxy or cyano; and

whereby any heterocyclyl is optionally substituted by C_{1-4} alkyl, $-C_{1-4}$ alkoxy(C_{1-4} alkyl),

10 oxo or hydroxyl;

or R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom, the ring being optionally substituted by one or two groups selected from oxo, hydroxyl, C_{1-4} hydroxyalkyl-, C_{1-4} alkyl, $-C_{1-4}$ alkoxy(C_{1-4} alkyl) or $-(CH_2)_pC(O)NR^{12}R^{13}$;

15 R^{10} , R^{11} , R^{12} and R^{13} are, independently, hydrogen or C_{1-4} alkyl;

n and p are, independently, 0, 1, 2, 3 or 4; and

Y is hydrogen, halo, C_{1-4} alkyl or C_{1-4} haloalkyl;

or a pharmaceutically acceptable salt thereof.

20 2. The compound according to claim 1, wherein:

A is C_{3-7} cycloalkyl, C_{1-6} haloalkyl optionally substituted by cyano;

R^1 is C_{1-4} alkyl or C_{1-4} hydroxyalkyl;

R^3 is C_{5-10} aryl or C_{5-10} heteroaryl optionally substituted by C_{1-4} alkoxy;

X is O;

25 W is phenyl substituted by $-C(O)NR^7R^8$;

R^7 is hydrogen;

R^8 is C_{1-4} alkyl (optionally substituted by one or two groups selected from hydroxyl, $-C(O)NR^{10}R^{11}$, $-NR^{10}C(O)C_{1-4}$ alkyl, C_{5-10} heterocyclyl, C_{5-10} aryl or C_{5-10} heteroaryl), C_{3-7} cycloalkyl, C_{5-10} heterocyclyl or C_{5-10} heteroaryl,

30 whereby any heterocyclyl is optionally substituted by C_{1-4} alkyl or oxo;

or R^7 and R^8 , together with the nitrogen to which they are attached, form a 5- or 6-membered ring optionally comprising a second ring-nitrogen atom, the ring being

optionally substituted by one or two groups selected from oxo, hydroxyl, C₁₋₄hydroxyalkyl or -C(O)NR¹²R¹³;

R¹⁰, R¹¹, R¹² and R¹³ are hydrogen; and

Y is hydrogen;

5 or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein A is difluoroethyl or cyclopropyl substituted with cyano; R¹ is methyl or hydroxymethyl; R³ is phenyl or pyridyl substituted with methoxy.

10

4. The compound according to any one of claims 1 to 3, wherein W is phenyl substituted by -C(O)NR⁷R⁸; R⁷ is hydrogen; and

R⁸ is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, aminooxomethyl, aminooxoethyl, aminooxopropyl, aminomethyloxomethyl, aminomethyloxoethyl,

15 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, acetylaminomethyl, acetylaminoethyl, oxoimidazolidinylmethyl, oxoimidazolidinylethyl, oxopyrrolidinylmethyl,

oxopyrrolidinylethyl, oxidotetrahydrothiophenyl, dioxidotetrahydrothiophenyl,

oxotertahydrofuranyl, tertahydrofuranyl, methyldioxooxazolidinylmethyl,

dimethyldioxooxazolidinylmethyl, methyldioxooxazolidinylethyl,

20 dimethyldioxooxazolidinylethyl, indazolylmethyl, indazolylethyl, aminooxophenylmethyl,

aminooxophenylethyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridinylmethyl,

pyridinylethyl, indazolylmethyl or indazolylethyl.

5. The compound according to any one of claims 1 to 3, wherein W is phenyl substituted by -C(O)NR⁷R⁸; and

25

R⁷ and R⁸, together form pyrrolidinyl, oxopyrrolidinyl, carbamoylpyrrolidinyl,

hydroxymethylpyrrolidinyl, hydroxypyrrolidinyl, prolinamide, hydroxyprolinamide,

piperidinyl, hydroxypiperidinyl, oxopiperidinyl, imidazolidinyl, piperazinyl,

hydroxypiperazinyl, oxopiperazinyl, tetrahydrothiophenyl, oxidotetrahydrothiophenyl,

30 dioxidotetrahydrothiophenyl, oxotertahydrofuranyl or tertahydrofuranyl.

6. Compounds selected from

- 1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-D-prolinamide,
N-[(1S,2R)-2-{[1-(3-{[(2R)-2-carbamoylpyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]ethanediamide,
5 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(2-hydroxyethyl)benzamide,
N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
N-[(1S)-2-amino-1-methyl-2-oxoethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
10 N-[2-(acetylamino)ethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[2-(2-oxoimidazolidin-1-yl)ethyl]benzamide,
15 2,2-difluoro-N-[(1S,2R)-2-{[1-(3-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]propanamide,
2,2-difluoro-N-[(1S,2R)-2-{[1-(3-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}phenyl)-1H-indazol-5-yl]oxy}-1-methyl-2-phenylethyl]propanamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[(3R)-2-oxotetrahydrofuran-3-yl]benzamide,
20 1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-L-prolinamide,
2,2-difluoro-N-[(1S,2R)-1-methyl-2-[(1-{3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}-1H-indazol-5-yl)oxy]-2-phenylethyl]propanamide,
25 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[2-(2-oxopyrrolidin-1-yl)ethyl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-[2-(5,5-dimethyl-2,4-dioxo-1,3-oxazolidin-3-yl)ethyl]benzamide,
3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide,
30 3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-(1H-indazol-3-ylmethyl)benzamide,

- N-[(1R)-2-amino-2-oxo-1-phenylethyl]-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
- N-(2-amino-2-oxoethyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]-N-methylbenzamide,
- 5 N-(3-amino-3-oxopropyl)-3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]benzamide,
- (4R)-1-({3-[5-({(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-phenylpropyl}oxy)-1H-indazol-1-yl]phenyl}carbonyl)-4-hydroxy-L-prolinamide,
- 1-[[3-(5-{{(1R,2S)-2-{{(1-cyanocyclopropyl)carbonyl}amino}-1-phenylpropyl}oxy)-1H-indazol-1-yl)phenyl]carbonyl}-D-prolinamide,
- 10 N-cyclopentyl-3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)benzamide,
- 3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-pyridin-3-ylbenzamide,
- 15 3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide,
- 3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(tetrahydrofuran-3-yl)benzamide,
- 3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(2-hydroxybutyl)benzamide,
- 20 N-cyclopentyl-3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-3-hydroxy-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)benzamide, and
- 3-(5-{{(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(6-methoxypyridin-3-yl)propyl}oxy)-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide,
- 25 or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6, together with a pharmaceutically acceptable adjuvant, diluent or carrier.

- 30 8. A compound according to any one of claims 1 to 6 for use in therapy.

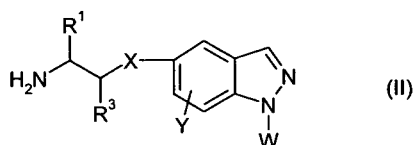
9. The use of a compound according to any one of claims 1 to 6, or a pharmaceutical composition according to claim 7, in the manufacture of a medicament for use in the treatment of a glucocorticoid receptor mediated disease state.
- 5 10. The use of a compound according to any one of claims 1 to 6, or a pharmaceutical composition according to claim 7, in the manufacture of a medicament for use in the treatment of inflammatory conditions or respiratory disorder.
11. The use of a compound according to any one of claims 1 to 6, or a pharmaceutical
10 composition according to claim 7, in the manufacture of a medicament for use in the treatment of asthma.
12. The use of a compound according to any one of claims 1 to 6, or a pharmaceutical composition according to claim 7, in the manufacture of a medicament for use in the
15 treatment of COPD.
13. A method of treating a glucocorticoid receptor mediated disease state, inflammatory condition, respiratory disorder, asthma and/or COPD in a mammal, which comprises administering to a mammal in need of such treatment an effective amount of a compound
20 according to any one of claims 1 to 6, or a pharmaceutical composition according to claim 7.
14. A combination of a compound according to any one of claims 1 to 6, and one or more agents selected from the list comprising:
- 25
- a PDE4 inhibitor;
 - a selective β .sub2. adrenoceptor agonist;
 - a muscarinic receptor antagonist;
 - a modulator of chemokine receptor function;
 - an inhibitor of p38 kinase function;

30

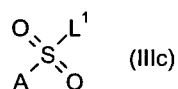
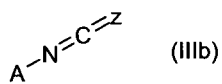
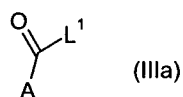
 - an inhibitor of matrix metalloproteases, for example targeting MMP-2, -9 or MMP-12; or

- an inhibitor of neutrophil serine proteases, for example neutrophil elastase or proteinase 3.

15. A process for the preparation of compounds of formula Ia according to claim 1, by
 5 coupling a compound of formula (II):



with acylation reagents of formula (IIIa), (IIIb) or (IIIc)



wherein R^1 , R^3 , A, X and Y are defined above, W is as defined above and L^1 is a leaving
 10 group or, when $L^1 = OH$, a leaving group generated by reaction of a coupling reagent.