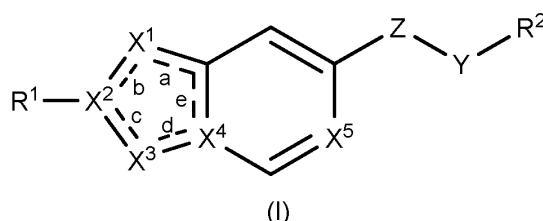


CLAIMS

1. A compound of general formula (I) including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



5

wherein

== represents a single or a double bond;

X¹ is N, X³ is NH, X² and X⁴ are C, a, c and d are single bonds and b and e are double bonds; or

10

X¹ is NH, X³ is N, X² and X⁴ are C, a, b and d are single bonds and c and e are double bonds; or

X¹ is N, X² is N, X³ is CR³ or C-N(R^{3a})(R^{3b}), X⁴ is C; b, c and e are single bonds and a and d are double bonds;

15

each R³, R^{3a} and R^{3b} is independently H or methyl; or

X¹ is N, X³ is O, X² and X⁴ are C, a, c and d are single bonds and b and e are double bonds;

X¹ and X⁴ are N, X² is C and X³ is CH; a and c are double bonds and b, d and e are single bonds;

20

X¹ is O, X³ is N, X² and X⁴ are C, a, b and d are single bonds and c and e are double bonds;

X⁵ is CH or N;

R¹ is

i. -O-R⁵, provided that X² is not N;

25

wherein R⁵ is a 5- or 6-membered carbocyclyl or heterocyclyl group optionally substituted with OH; or

ii. CH(R⁷)-N(R⁸)-C(O)OR⁹

R⁷ is H, phenyl or C₁₋₃ alkyl optionally substituted with one or more substituents selected from OH and O(C₁₋₄ alkyl);

30

R⁸ is H, methyl or C₂₋₃ alkyl optionally substituted with one or more substituents selected from OH and methoxy;

R⁹ is C₁₋₄ alkyl, optionally substituted with one or more substituents selected from halo, OH and methoxy; or

R⁷ and R⁸ together with the atoms to which they are attached combine to form a 5- or 6-membered heterocyclic ring optionally containing a further heteroatom selected from N, O and S and optionally substituted with C₁₋₃ alkyl; or

5 iii. CH(R⁷)-N(R⁸)-C(O)N(R⁹)(R¹⁰);

R⁷, R⁸ and R⁹ are as defined above and R¹⁰ is H or methyl; or

iv. CH(R¹¹)(R¹²);

R¹¹ is H, methyl, CH₂OR¹³, OR¹³ or N(R¹³)(R¹⁴);

each R¹³ and R¹⁴ is independently H or methyl;

10 R¹² is selected from:

a 5- or 6-membered carbocyclyl or an oxygen-containing heterocyclyl ring, wherein said carbocyclyl or heterocyclyl ring is optionally substituted with OH; and

15 a 6-membered aryl or 6-membered heteroaryl ring, wherein said aryl or heteroaryl ring is optionally substituted with one or more substituents selected from OH; methoxy; chloro; fluoro; C₁₋₆ alkyl optionally substituted with one or more substituents selected from halo, OH and CN; 3- to 6-membered cycloalkyl or heterocyclyl group, wherein said cycloalkyl or heterocyclyl group is optionally substituted with one or more substituents selected from halo, OH, CN and C₁₋₆ alkyl optionally substituted with one or more substituents selected from halo, OH and CN; and a 5-membered heteroaryl group optionally substituted with one or more substituents selected from C₁₋₄ alkyl and halo; or

20 when R¹² is a 6-membered aryl or heteroaryl ring, a substituent on R¹² may combine with R¹¹ and, together with the atom to which they are attached, form a 5- or 6-membered ring fused to the 6-membered aryl or heteroaryl ring R¹², wherein the 5- or 6-membered ring is optionally substituted with C₁₋₃ alkyl; or

25 v. C₂₋₆ alkyl optionally substituted with one or more substituents selected from phenyl, OR¹⁵ and N(R¹⁵)(R¹⁶);

each R¹⁵ and R¹⁶ is independently selected from H or C₁₋₃ alkyl; or

30 vi. a 3- to 8-membered cycloalkyl ring optionally substituted with one or more substituents selected from OH, CN, halo and C₁₋₄ alkyl optionally substituted with one or more substituents selected from halo, OH and CN;

35

Z is a linker selected from -NH-C(O)- and -C(O)-NH-;

Y is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$;

R^2 is 6- to 10-membered aryl, 5- to 10-membered heteroaryl or 3- to 10-membered carbocyclic ring system, wherein the aryl, heteroaryl or carbocyclic ring system is optionally substituted with one or more substituents selected from fluoro; chloro; CN; nitro; OH; C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, OH and CN; $\text{O}(\text{C}_{1-6}$ alkyl) optionally substituted with one or more substituents selected from halo, OH and CN, and $\text{NH}-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl optionally substituted with one or more substituents selected from halo and OH; or

Y and R^2 together form a group $-\text{CH}_2-\text{C}(\text{R}^{17})(\text{R}^{18})-\text{CH}_2-\text{N}(\text{R}^{19})-\text{C}(\text{O})\text{OR}^{20}$;

- 10 wherein each of R^{17} , R^{18} and R^{19} is independently H or C_{1-4} alkyl or R^{18} and R^{19} combine and together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring optionally substituted with C_{1-3} alkyl; and

R^{20} is C_{1-6} alkyl optionally substituted with one or more halo substituents; or

- Y and R^2 together form a C_{3-10} alkyl group substituted with one or more substituents selected from halo, OH and CN; or

Y and R^2 together form a 3- to 8-membered carbocyclic ring optionally substituted with one or more substituents selected from halo, OH, CN and C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, OH and CN;

provided that:

- 20 I. when X^1 is N, X^3 is NH, X^2 and X^4 are C, a, c and d are single bonds and b and e are double bonds:

A. when R^1 is $\text{CH}(\text{R}^{11})(\text{R}^{12})$; where R^{11} is H or methyl and R^{12} is phenyl which is unsubstituted or substituted with 1 or 2 substituents, wherein the substituents are selected from halo and methoxy:

- 25 i. R^2 is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with 1 or 2 substituents selected from halo, C_{1-4} alkyl, C_{1-4} alkoxy and a 5-membered heteroaryl ring; and
- ii. Y and R^2 do not combine to form a 3- to 8-membered cycloalkyl ring optionally substituted with methyl; or a C_{3-10} alkyl group optionally substituted with CN

- 30 B. when R^1 is $\text{CH}(\text{R}^{11})(\text{R}^{12})$; where R^{12} is phenyl and R^{11} together with a substituent on R^{12} and the atoms to which they are attached combine to form a 5- or 6-membered ring fused to the phenyl ring R^{12} , wherein the 5- or 6-membered ring is optionally substituted with C_{1-3} alkyl:

- i. R^2 is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with 1, 2 or 3 substituents, wherein the substituents are selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy; and
 - ii. Y and R^2 do not combine to form C_{3-10} alkyl substituted with CN;
 - 5 C. when R^1 is $CH(R^{11})(R^{12})$; where R^{11} is H and R^{12} is cyclohexyl:
 R^2 is not phenyl optionally substituted with 1, 2 or 3 substituents, wherein the substituents are selected from halo, methyl, methoxy; unsubstituted 5- to 8 membered heteroaryl;
 - 10 D. when R^1 is C_{2-6} alkyl optionally substituted with a single substituent selected from OH and phenyl:
 R^2 is not phenyl or 5- to 10 membered heteroaryl, either of which is optionally substituted with one or two substituents, wherein the substituents are selected from halo, methyl, trifluoromethyl, $O(C_{1-4}$ alkyl) or a 5-membered heteroaryl ring;
 - 15 E. when R^1 is an unsubstituted 3- to 8-membered cycloalkyl ring:
 R^2 is not phenyl optionally substituted with one substituent selected from halo, OH, methyl, trifluoromethyl, $O(C_{1-4}$ alkyl) or a 5-membered heteroaryl ring;
- 20 II. when X^1 is N, X^2 is N, X^3 is CR^3 or $C-N(R^{3a})(R^{3b})$, X^4 is C; b, c and e are single bonds and a and d are double bonds; each R^3 , R^{3a} and R^{3b} is independently H or methyl:
 - A. when R^1 is $CH(R^{11})(R^{12})$; and R^{11} is H and R^{12} is phenyl which is unsubstituted or substituted with 1 or 2 substituents selected from halo and methoxy:
 R^2 is not phenyl optionally substituted with one halo substituent;
 - 25 B. when R^1 is C_{2-6} alkyl optionally substituted with phenyl:
 R^2 is not phenyl or naphthyl optionally substituted with one or two substituents selected from halo, methoxy and a 5-membered heteroaryl group;
- 30 III. when X^1 is N, X^3 is O, X^2 and X^4 are C, a, c and d are single bonds and b and e are double bonds:
 - A. when R^1 is $CH(R^{11})(R^{12})$; and R^{11} is H and R^{12} is phenyl which is unsubstituted or substituted with 1 or 2 substituents selected from halo and methoxy:
 - 35 i. R^2 is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with one or two substituents selected from halo, C_{1-4} alkyl, C_{1-4} alkoxy and a 5-membered heteroaryl group; and

ii. Y and R² do not combine to form a C₃₋₁₀ alkyl group substituted with one or more substituents selected from halo and OH

B. when R¹ is CH(R¹¹)(R¹²); and R¹² is phenyl and a substituent on R¹² combines with R¹¹ and the atoms to which they are attached to form a 5- or 6-membered ring fused to the 6-membered aryl or heteroaryl ring R¹², wherein the 5- or 6-membered ring is optionally substituted with C₁₋₃ alkyl:

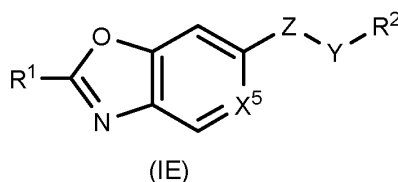
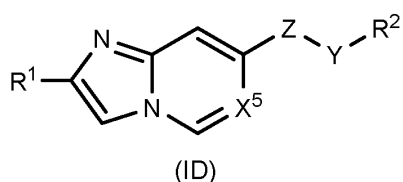
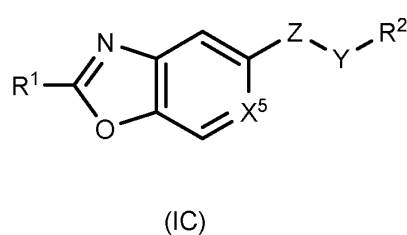
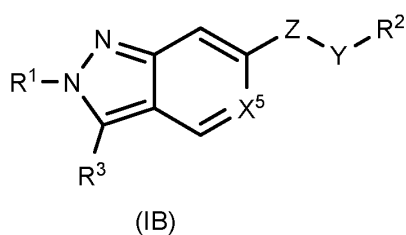
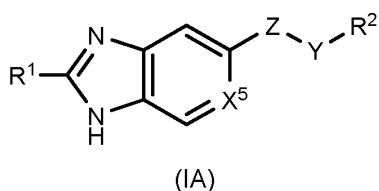
Y and R² do not combine to form C₃₋₁₀ alkyl substituted with one or more halo substituents;

IV. when X¹ is O, X³ is N, X² and X⁴ are C, a, b and d are single bonds and c and e are double bonds; R¹ is CH(R¹¹)(R¹²); and R¹¹ is H and R¹² is phenyl which is unsubstituted or substituted with 1 or 2 substituents selected from halo and methoxy:

i. R² is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with one, two or three substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy and a 5-membered heteroaryl group; and

ii. Y and R² do not combine to form an unsubstituted 3- to 8-membered cycloalkyl ring; or a C₃₋₁₀ alkyl group substituted with one or more substituents selected from halo and OH.

2. A compound according to claim 1 which is a compound of general formula (IA), (IB), (IC), (ID) or (IE):



wherein R¹, X⁵, Z, Y and R² are as defined in claim 1.

3. A compound according to claim 2, which is a compound of general formula (IA) provided that:

5 A. when R^1 is $CH(R^{11})(R^{12})$; where R^{11} is H or methyl and R^{12} is phenyl which is unsubstituted or substituted with 1 or 2 substituents, wherein the substituents are selected from halo and methoxy:

i. R^2 is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with 1 or 2 substituents selected from halo, C_{1-4} alkyl, C_{1-4} alkoxy and a 5-membered heteroaryl ring; and
10 ii. Y and R^2 do not combine to form a 3- to 8-membered cycloalkyl ring optionally substituted with methyl; or a C_{3-10} alkyl group substituted with CN

15 B. when R^1 is $CH(R^{11})(R^{12})$; where R^{11} is H and R^{12} is phenyl and a substituent on R^{12} combines with R^{11} and the atoms to which they are attached to form a 5- or 6-membered ring fused to the 6-membered aryl or heteroaryl ring R^{12} , wherein the 5- or 6-membered ring is optionally substituted with C_{1-3} alkyl:

i. R^2 is not phenyl or heteroaryl, wherein said phenyl or heteroaryl is optionally substituted with 1, 2 or 3 substituents, wherein the substituents are selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy; and
20 ii. Y and R^2 do not combine to form C_{3-10} alkyl substituted with CN;

25 C. when R^1 is $CH(R^{11})(R^{12})$; where R^{11} is H and R^{12} is cyclohexyl: R^2 is not phenyl optionally substituted with 1, 2 or 3 substituents, wherein the substituents are selected from halo, methyl, methoxy; unsubstituted 5- to 8 membered heteroaryl;

30 D. when R^1 is C_{2-6} alkyl optionally substituted with a single substituent selected from OH and phenyl:

R^2 is not phenyl or 5- to 10 membered heteroaryl, either of which is optionally substituted with one or two substituents, wherein the substituents are selected from halo, methyl, trifluoromethyl, $O(C_{1-4}$ alkyl) or a 5-membered heteroaryl ring;

35 E. when R^1 is an unsubstituted 3- to 8-membered cycloalkyl ring: R^2 is not phenyl optionally substituted with one substituent selected from halo, OH, methyl, trifluoromethyl, $O(C_{1-4}$ alkyl) or a 5-membered heteroaryl ring.

4. A compound according to any one of claims 1 to 3 wherein X^5 is CH.

5. A compound according to any one of claims 1 to 4 wherein:

R¹ is CH(R⁷)-N(R⁸)-C(O)OR⁹ or wherein:

R⁷ is H, phenyl and C₁₋₃ alkyl substituted with methoxy;

R⁸ is H, methyl or ethyl optionally substituted with OH or OCH₃; or

5 R⁷ and R⁸ together with the atoms to which they are attached combine to form a 5- or 6-membered heterocyclic ring selected from a heterocyclic ring containing only the nitrogen atom attached to R⁸ and a heterocyclic ring containing the nitrogen atom attached to R⁸ and one further heteroatom selected from a nitrogen and oxygen atom; wherein the heterocyclic ring is unsubstituted or substituted with methyl or ethyl;

10 R⁹ is C₂₋₄ alkyl optionally substituted with one or more halo substituents; and

R¹⁰ is H or methyl; or

R¹ is C₂₋₃ alkyl which is unsubstituted or is substituted with a single substituent selected from phenyl and OR¹⁵, wherein R¹⁵ is H or methyl; or

R¹ is a 3- to 4-membered ring optionally substituted with one or more substituents selected from C₁₋₄ alkyl and C₁₋₄ haloalkyl.

20 6. A compound according to any one of claims 1 to 4, wherein R¹ is CH(R¹¹)(R¹²).

7. A compound according to claim 6 wherein R¹¹ is H and R¹² is a 5- or 6-membered carbocyclic or oxygen-containing heterocyclic ring optionally substituted with OH.

25 8. A compound according to claim 6 wherein R¹¹ is H, methyl or methoxy and R¹² is a 6-membered aryl or heteroaryl ring wherein said aryl or heteroaryl ring is optionally substituted with one or more substituents selected from OH, methoxy, chloro, fluoro, C₁₋₆ alkyl optionally substituted with halo or OH and a 5-membered heteroaryl group optionally substituted with one or more substituents selected from C₁₋₄ alkyl and halo.

30

9. A compound according to claim 8 wherein R¹¹ is H and either:

R¹² is phenyl substituted with a first substituent selected from OH and methoxy; and a second substituent selected from fluoro and chloro; or

35

R¹² is phenyl with a first substituent selected from OH and methoxy; a second substituent

selected from fluoro and chloro; and a third substituent selected from C₁₋₄ alkyl optionally substituted with OH or CN; or

5 R¹² is phenyl substituted with a first substituent selected from OH and methoxy; and a second substituent selected from:

C₁₋₆ alkyl optionally substituted with one or more substituents selected from halo, OH and CN; and

10 3- to 6-membered cycloalkyl or heterocyclyl, wherein said cycloalkyl or heterocyclyl group is optionally substituted with one or more substituents selected from halo, OH, CN and C₁₋₆ alkyl optionally substituted with one or more substituents selected from halo, OH and CN; or

15 R¹² is phenyl substituted with a 5-membered heteroaryl ring optionally substituted with one or more C₁₋₄ alkyl groups; or

R¹² is unsubstituted pyridyl or pyridyl having a single substituent selected from OH, methoxy, fluoro and chloro at the ring position adjacent to the atom attached to CH(R¹¹); or

20 R¹² is a 6-membered aryl or heteroaryl ring and a substituent on R¹² combines with R¹¹ to form an indoline, indane or dihydrobenzofuran ring system.

10. A compound according to claim 9 wherein:

25 R¹² is phenyl substituted with OH at the 2-position and with a second substituent selected from fluoro and chloro; or

R¹² is phenyl substituted with a first substituent which is OH and a second substituent selected from fluoro and chloro and a third substituent selected from C₃₋₄ alkyl having a single OH substituent.

30 11. A compound according to any one of claims 1 to 10 wherein Y is CH₂.

12. A compound according to any one of claims 1 to 11 wherein R² is selected from

35 an unsubstituted bridged carbocyclic ring system selected from bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo-[2.2.1]heptanyl, bicyclo-[2.2.2]octanyl or adamantyl, especially bicyclo-[2.2.1]heptanyl and adamantyl; and

unsubstituted cyclopentyl, cyclohexyl or cycloheptyl; and

cyclopropyl or cyclobutyl substituted with one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ haloalkyl; and

phenyl or a 5- or 6-membered heteroaryl ring optionally substituted with one or more substituents selected from fluoro, chloro, OH, C₁₋₆ alkyl optionally substituted with one or more substituents selected from OH and halo, O(C₁₋₆ alkyl) and O(C₁₋₆ haloalkyl).

10

13. A compound according to any one of claims 1 to 10 wherein Y and R² together form:

a C₃₋₄ alkyl group substituted with one or more halo substituents; or

a cyclopropyl or cyclobutyl ring optionally substituted with one or more substituents selected from halo, C₁₋₄ alkyl and C₁₋₄ haloalkyl; or

a group -CH₂-C(R¹⁷)(R¹⁸)-CH₂-N(R¹⁹)-C(O)OR²⁰, wherein each of R¹⁷, R¹⁸, R¹⁹ and R²⁰ is independently H or methyl, or R¹⁸ and R¹⁹ combine with the atoms to which they are attached to form a 6-membered heterocyclic ring; and R²⁰ is C₁₋₆ alkyl.

20 14. A compound according to claim 1 selected from:

2-(1-Adamantyl)-N-[2-(cyclohexylmethyl)-1H-benzimidazol-5-yl]acetamide (Compound 1);

2-(1-Adamantyl)-N-[2-(tetrahydropyran-2-ylmethyl)-1H-benzimidazol-5-yl] acetamide (Compound 1.1);

2-(2-Adamantyl)-N-(2-benzyl-1H-benzimidazol-5-yl) (Compound 2);

25 2-(2-Adamantyl)-N-[2-(2-phenylethyl)-1H-benzimidazol-5-yl]acetamide (Compound 2.1);

2-(2-Adamantyl)-N-[2-[methoxy(phenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 2.2);

2-(2-Adamantyl)-N-[2-[(2-methoxyphenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 2.3);

30 2-(2-Adamantyl)-N-[2-[(R)-methylamino(phenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 3);

2-(1-Adamantyl)-N-[2-[(2-chloro-3-pyridyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 4);

2-(2-Adamantyl)-N-[2-[(2-hydroxyphenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 5);

35

2-(2-Adamantyl)-N-[2-[(4-hydroxyphenyl)methyl]-1H-benzimidazol-5-yl]acetamide

- (Compound 5.1);
2-(2-Adamantyl)-N-[2-[(5-chloro-2-hydroxy-phenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 5.2);
2,2,2-Trifluoroethyl N-[[5-[[2-(1-adamantyl)acetyl]amino]-1H-benzimidazol-2-yl]methyl]carbamate (Compound 6);
2-(1-Adamantyl)-N-[2-[[3-(3,5-dimethylisoxazol-4-yl)phenyl]methyl]-3H-benzimidazol-5-yl]acetamide (Compound 7);
tert-Butyl N-[[5-[[2-(2-adamantyl)acetyl]amino]-1H-benzimidazol-2-yl]methyl] carbamate (Compound 8);
2-(2-Adamantyl)-N-(2-tetrahydrofuran-3-yloxy-1H-benzimidazol-5-yl)acetamide (Compound 9);
N-(Cycloheptylmethyl)-2-[(2-hydroxyphenyl)methyl]-1,3-benzoxazole-5-carboxamide (Compound 10);
2-(1-Adamantyl)-N-[3-amino-2-[(2-hydroxyphenyl)methyl]indazol-6-yl]acetamide (Compound 11);
2-Cyclohexyl-N-(2-isopropyl-1,3-benzoxazol-5-yl)acetamide (Compound 12);
N-(Cycloheptylmethyl)-2-[(2-hydroxyphenyl)methyl]indazole-6-carboxamide (Compound 13);
2-(1-Adamantyl)-N-(2-benzyl-3H-imidazo[4,5-c]pyridin-6-yl)acetamide (Compound 14);
2-Benzyl-N-(cycloheptylmethyl)imidazo[1,2-a]pyridine-7-carboxamide (Compound 15);
2-(1-Adamantyl)-N-(2-benzylindazol-6-yl)acetamide (Compound 16);
2-(1-Adamantyl)-N-(2-benzyl-3-methyl-indazol-6-yl)acetamide (Compound 17);
N-(2-*tert*-Butyl-1H-benzimidazol-5-yl)-2-(5-chloro-2-hydroxy-phenyl)acetamide (Compound 18);
tert-Butyl N-[3-[(2-benzyl-1H-benzimidazole-5-carbonyl)amino]-2,2-dimethylpropyl]carbamate (Compound 19);
2-*tert*-Butyl-N-(cycloheptylmethyl)-3H-benzimidazole-5-carboxamide (Compound 20);
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-[1-(trifluoromethyl) cyclopropyl]-1H-benzimidazole-5-carboxamide (Compound 21);
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-[[1-(trifluoromethyl) cyclopropyl]methyl]-1H-benzimidazole-5-carboxamide (Compound 21.1);
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-(3,3,3-trifluoropropyl)-1H-benzimidazole-5-carboxamide (Compound 21.2);
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-[1-(trifluoromethyl) cyclopropyl]-1,3-benzoxazole-5-carboxamide (Compound 21.3);
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-[[1-(trifluoromethyl)

- cyclopropyl)methyl]-1,3-benzoxazole-5-carboxamide (Compound 21.4);
2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]-N-[2-[1-(trifluoromethyl)
cyclopropyl]-1H-benzimidazol-5-yl]acetamide (Compound 22);
2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)-N-[2-[1-(trifluoromethyl)cyclopropyl]-1H-
5 benzimidazol-5-yl]acetamide (Compound 23);
2-Benzyl-N-(3,3,3-trifluoropropyl)-1H-benzimidazole-5-carboxamide (Compound 24);
2-Benzyl-N-(cyclopentylmethyl)-1H-benzimidazole-5-carboxamide (Compound 24.1);
2-Benzyl-N-(cycloheptylmethyl)-1H-benzimidazole-5-carboxamide (Compound 24.2);
N-(Cycloheptylmethyl)-2-[(2-fluoro-6-hydroxy-phenyl)methyl]-1H-benzimidazole-5-
10 carboxamide (Compound 25);
N-(Cycloheptylmethyl)-2-[(5-fluoro-2-hydroxy-phenyl)methyl]-1H-benzimidazole-5-
carboxamide (Compound 25.1);
N-(Cycloheptylmethyl)-2-[(3-fluoro-2-hydroxy-phenyl)methyl]-1H-benzimidazole-5-
carboxamide (Compound 25.2);
15 N-(Cycloheptylmethyl)-2-[(2-hydroxy phenyl)methyl]-1H-benzimidazole-5-carboxamide
(Compound 25.3);
N-(Cycloheptylmethyl)-2-[(4-fluoro-2-hydroxy-phenyl)methyl]-1H-benzimidazole-5-
carboxamide (Compound 25.4);
N-(Cycloheptylmethyl)-2-[(3-hydroxyphenyl)methyl]-1H-benzimidazole-5-car
20 boxamide (Compound 25.5);
2-(5-Chloro-2-hydroxy-phenyl)-N-[2-(2,2-dimethylpropyl)-1H-benzimidazol-5-yl]acetamide
(Compound 26);
N-(2-*tert*-Butyl-1H-benzimidazol-5-yl)-2-(5-chloro-2-hydroxy-phenyl)acetamide
(Compound 27);
25 N-(Cycloheptylmethyl)-2-(1-methylcyclobutyl)-3H-benzimidazole-5-carboxamide
(Compound 28);
2-[[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]methyl]-N-[[1-
(trifluoromethyl)cyclopropyl]methyl]-1H-benzimidazole-5-carboxamide (Compound 29);
2-[[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]methyl]-N-(3,3,3-
30 trifluoropropyl)-1H-benzimidazole-5-carboxamide (Compound 29.1);
N-[[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]methyl]-2-[1-
(trifluoromethyl)cyclopropyl]-1H-benzimidazole-5-carboxamide (Compound 30);
2-[[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]methyl]-N-(3,3,3-
trifluoropropyl)-1H-benzimidazole-5-carboxamide (Compound 31);
35 2-[[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]methyl]-N-[1-
(trifluoromethyl)cyclopropyl]-1H-benzimidazole-5-carboxamide (Compound 31.1);

2-[[5-Fluoro-2-hydroxy-3-(2-hydroxy-1,1-dimethyl-ethyl)phenyl)methyl]-N-[[1-(trifluoromethyl)cyclopropyl)methyl]-1H-benzimidazole-5-carboxamide (Compound 32);

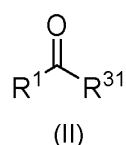
2-[(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)methyl]-N-[1-(trifluoromethyl)cyclopropyl]imidazo[1,2-a]pyridine-7-carboxamide (Compound 33);

5 and salts and solvates of the above.

15. A process for the preparation of a compound according to any one of claims 1 to 14 comprising:

A. for a compound of general formula (IA):

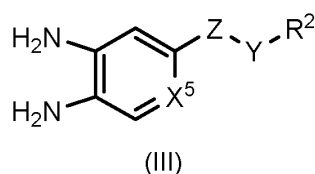
10 reacting a compound of general formula (II):



wherein R¹ is as defined in claim 1 and R³¹ is OH or halo;

with a compound of general formula (III):

15



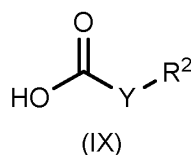
wherein X⁵, Z, Y and R² are as defined in claim 1;

in the presence of a coupling reagent under basic conditions; or

20

B. for a compound of formula (IA) in which Z is -NHC(O)- (i.e. the NH is attached to the benzimidazole):

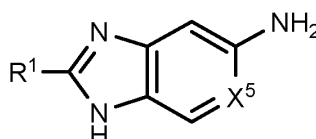
reacting a compound of general formula (IX):



25

wherein R² is as defined in claim 1

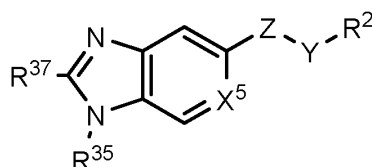
with a compound of general formula (XVII):



(XVII)

wherein R^1 and X^5 are as defined for general formula (I);
in the presence of an amine and a coupling reagent; or

- 5 C. for a compound of general formula (IA) in which R^1 is OR^5 :
reacting a compound of general formula (XXI):



(XXI)

wherein X^5 , Z, Y and R^2 are as defined in claim 1, R^{35} is a protecting group and R^{37} is halo;

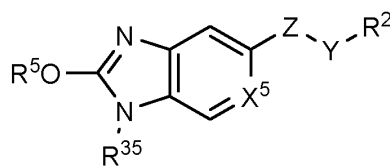
- 10 with a compound of general formula (XXII):



wherein R^1 is as defined in claim 1;

in the presence of a strong base, for example a metal hydride such as sodium hydride;

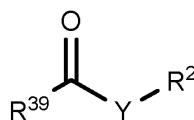
to give a compound of general formula (XX):



(XX)

wherein R^5 , X^5 , Z, Y and R^2 are as defined in claim 1 and R^{35} is as defined above; and
deprotecting the compound of general formula (XX); or

- 20 D. for a compound of general formula (IA) in which Z is -NHC(O)-:
reacting a compound of general formula (XVII) as defined above with a compound of
general formula (XXVI):

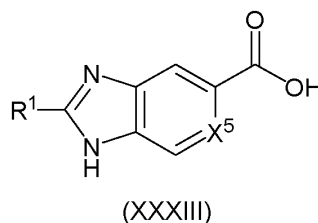


(XXVI)

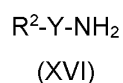
- 25 wherein R^2 is as defined in claim 1 and R^{39} is halo;
in the presence of an amine and a coupling reagent; or

E. for a compound of general formula (IA) in which Z is

-C(O)NH- (i.e. -C(O) is attached to the benzimidazole group):
 reacting a compound of general formula (XXXIII):



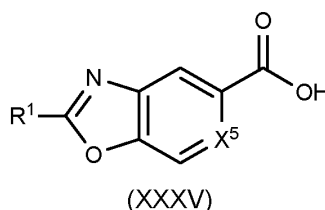
- 5 wherein R¹ and X⁵ are as defined in claim 1;
 with a compound of general formula (XVI):



wherein R² and Y are as defined in claim 1;

- 10 in the presence of an amine and a coupling reagent; or

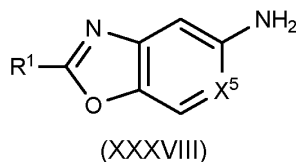
F. for a compound of general formula (IC) in which Z is -C(O)NH-:
 reacting a compound of general formula (XXXV):



15

wherein R¹ and X⁵ are as defined in claim 1;
 with a compound of general formula (XXVI) as defined above;
 in the presence of an amine and a coupling reagent; or

- 20 G. for a compound of general formula (IC) in which Z is -NHC(O)-:
 reacting a compound of general formula (XXXVIII):

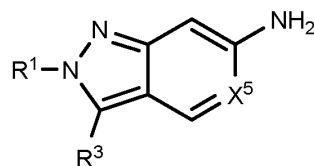


wherein R¹ and X⁵ are as defined in claim 1;

- 25 with a compound of general formula (XXVI) as defined above;
 in the presence of an amine and a coupling reagent; or

H. for a compound of general formula (IB) in which Z is -NHC(O)-:

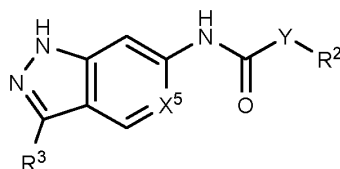
reacting a compound of general formula (IX) as defined above with a compound of general formula (XL):



(XL)

- 5 wherein R^1 , R^3 and X^5 are as defined in claim 1;
in the presence of an amine and a coupling reagent; or

I. for a compound of general formula (IB) in which Z is $-NHC(O)-$:
reacting a compound of general formula (XLV):



(XLV)

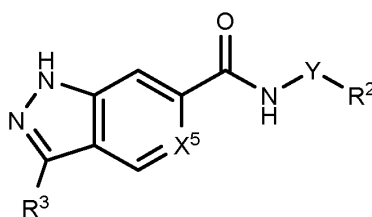
wherein R^2 , R^3 , X^5 and Y are as defined in claim 1;
with a compound of general formula (XLVIII):



(XLVIII)

wherein R^1 is as defined in claim 1 and R^{43} is halo;
under mildly basic conditions; or

J. for a compound of general formula (IB) in which Z is $-C(O)NH-$:
reacting a compound of general formula (XLVII):

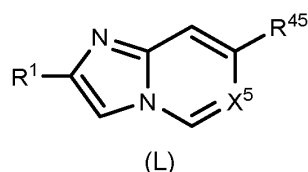


(XLVII)

wherein Y, R^2 , R^3 and X^5 are as defined in claim 1;
with a compound of general formula (XLVIII) as defined above; or

K. for a compound of general formula (ID):

reacting a compound of general formula (L):

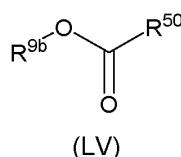


wherein R¹ and X⁵ are as defined in claim 1 and R⁴⁵ is halo;

- 5 with formic acid, methane sulfonyl chloride, triethylamine and a compound of general formula (XVI) as defined above in the presence of 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos); or

- L. converting a compound of general formula (I) in which R¹ and/or R² comprises a phenyl group substituted with alkoxy, to a compound of general formula (I) in which R¹ and/or R² comprises phenyl substituted with OH by treatment with boron tribromide; or

- M. converting a compound of general formula (I) in which R¹ is CH(R⁷)-N(R⁸)-C(O)OR^{9a} into a compound of general formula (I) in which R¹ is CH(R⁷)-N(R⁸)-C(O)OR^{9b}; where R^{9a} and R^{9b} are different from one another but are both as defined above for R⁹ by a process comprising treating the compound of general formula (I) in which R¹ is CH(R⁷)-N(R⁸)-C(O)OR^{9a} with an acid to give a product similar to general formula (I) but in which the R¹ substituent is replaced by CH(R⁷)-NH(R⁸); and
- 20 treating the product with a compound of general formula (LV):



wherein R^{9b} is as defined above and R⁵⁰ is halo.

- 25 16. A compound according to any one of claims 1 to 14 for use in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

17. The use of a compound according to any one of claims 1 to 14 in the manufacture of a medicament for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.
- 30

18. A method for the treatment or prophylaxis of diseases and conditions affected by

modulation of TMEM16A, the method comprising administering to a patient in need of such treatment an effective amount of a compound according to any one of claims 1 to 14.

19. A compound for use according to claim 16, the use according to claim 17 or a
5 method according to claim 18 wherein the diseases and conditions affected by modulation of TMEM16A comprise respiratory diseases and conditions, dry mouth (xerostomia), intestinal hypermobility, cholestasis and ocular conditions.

20. A compound for use, a use or a method according to claim 19, wherein:
10 the respiratory disease or condition is selected from cystic fibrosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, including non-cystic fibrosis bronchiectasis, asthma and primary ciliary dyskinesia;
the dry mouth (xerostomia) results from Sjorgens syndrome, radiotherapy treatment or from xerogenic drugs;
15 the intestinal hypermobility is associated with a condition selected from gastric dyspepsia, gastroparesis, chronic constipation and irritable bowel syndrome; and
the ocular condition is dry eye disease.

21. A pharmaceutical composition comprising a compound according to any one of
20 claims 1 to 14 and a pharmaceutically acceptable excipient.

22. A pharmaceutical composition according to claim 21 further comprising one or more
additional active agents suitable for the treatment or prophylaxis of respiratory diseases
and conditions.

25

23. A product comprising a compound according to any one of claims 1 to 14 and an
additional agent useful in the treatment or prevention of respiratory conditions as a
combined preparation for simultaneous, sequential or separate use in the treatment of a
disease or condition affected by modulation of TMEM16A.

30

24. A pharmaceutical composition according to claim 22 or a product according to
claim 23, wherein the additional active agent is selected from:

β 2 adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol,
salbutamol, formoterol, salmeterol, indacaterol, terbutaline, orciprenaline, bitolterol
35 mesylate, pirbuterol, olodaterol, vilanterol and abediterol;

antihistamines, for example histamine H₁ receptor antagonists such as loratadine, cetirizine, desloratadine, levocetirizine, fexofenadine, astemizole, azelastine and chlorpheniramine or H₄ receptor antagonists;

dornase alpha;

- 5 corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate mometasone furoate and fluticasone furoate;

Leukotriene antagonists such as montelukast and zafirlukast;

- anticholinergic compounds, particularly muscarinic antagonists such as ipratropium, tiotropium, glycopyrrolate, acclidinium and umeclidinium;

- CFTR repair therapies (e.g. CFTR potentiators, correctors or amplifiers) such as Ivacaftor, QBW251, Bamacaftor (VX659), Elexacaftor (VX445), VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 and FDL-176 and CFTR correctors such as Lumacaftor and Tezacaftor or combinations thereof (for example
15 a combination of Ivacaftor, Tezacaftor and Elexacaftor);

Antibiotics;

Antivirals such as ribavirin and neuraminidase inhibitors such as zanamivir;

Antifungals such as PUR1900;

- Airway hydrating agents (osmolytes) such as hypertonic saline and mannitol
20 (Bronchitol®); and

Mucolytic agents such as N-acetyl cysteine.

ENaC inhibitors such as:

amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651, BI1265162, ETD001 and compounds having a cation selected from:

- 25 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido) ethyl]-6-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

- 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido) methyl]-6-[[2-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

- 30 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-5-[4-({bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino)methyl]piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

- 35 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*R*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-

- carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*S*)-3-
 {bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-
 carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
 5 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-
 6-[(1*r*,4*r*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-
 pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-benzodiazol-3-
 ium;
 10 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-
 6-[(1*s*,4*s*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-
 pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-benzodiazol-3-
 ium;
 and a suitable anion, for example halide, sulfate, nitrate, phosphate,
 formate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate,
 15 succinate, mandelate, methane sulfonate or p-toluene sulfonate;
 Antibiotics;
 Airway hydrating agents (osmolytes) such as hypertonic saline and mannitol
 (Bronchitol®); and
 Mucolytic agents e.g. N-acetyl cysteine.