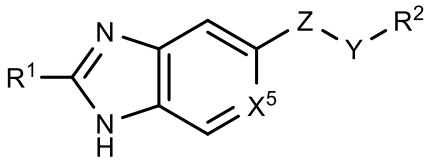
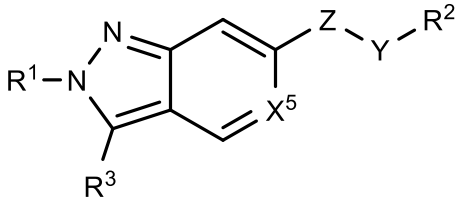
CLAIMS

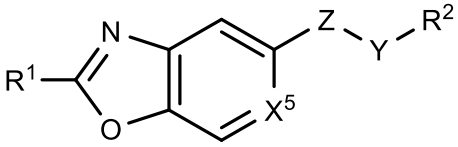
1. A compound of formula (IA), (IB), (IC), (ID) or (IE), including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



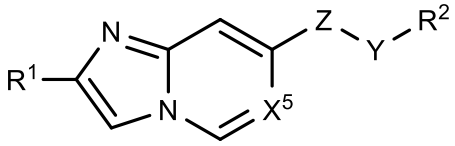
(IA)



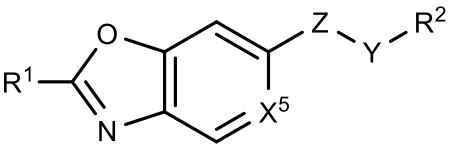
(IB)



(IC)



(ID)



(IE)

wherein

X^5 is CH;

R^1 is

$CH(R^{11})(R^{12})$;

R^{11} is H;

R^{12} is selected from:

(i) a 3- to 8-membered cycloalkyl ring optionally substituted with one or more substituents selected from OH, CN, halo and C_{1-4} alkyl optionally substituted with one or more substituents selected from halo, OH and CN;

(ii) a 5- or 6-membered carbocyclic or oxygen-containing heterocyclic ring optionally substituted with OH;

(iii) phenyl substituted with a first substituent selected from OH and methoxy; and a second substituent selected from fluoro and chloro;

(iv) phenyl with a first substituent selected from OH and methoxy; a second substituent selected from fluoro and chloro; and a third substituent selected from C_{1-4} alkyl

optionally substituted with OH or CN;

(v) phenyl substituted with a first substituent selected from OH and methoxy; and a second substituent selected from:

C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, OH and CN; and

3- to 6-membered cycloalkyl or heterocyclyl, wherein said cycloalkyl or heteorcyclyl group is 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;

(vi) phenyl substituted with a 5-membered heteroaryl ring optionally substituted with one or more C_{1-4} alkyl groups;

(vii) 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 $CH(R^{11})$; and

(viii) a 6-membered aryl or heteroaryl ring and a substituent on R^{12} combines with R^{11} to form an indoline, indane or dihydrobenzofuran ring system;

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

Y is $-CH_2-$ or $-CH(CH_3)-$;

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; $O(C_{1-6}$ alkyl) optionally substituted with one or more substituents selected from halo, OH and CN, and $NH\text{-}C(O)O\text{-}C_{1-6}$ alkyl optionally substituted with one or more substituents selected from halo and OH; or

Y and R^2 together form a group $–CH_2\text{-}C(R^{17})(R^{18})\text{-}CH_2\text{-}N(R^{19})\text{-}C(O)OR^{20}$;

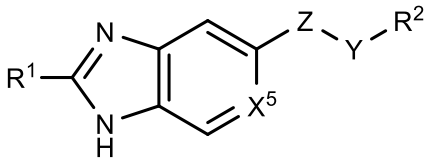
wherein each of R^{17}, R^{18} and R^{19} is independently H or C_{1-4} alkyl or R^{18} and R^{19} combine and together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring optionally substituted with C_{1-3} alkyl; and

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.

2. The compound according to claim 1 which is a compound of general formula (IA):



(IA)

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3. A compound according to claim 1 or 2, wherein:
R^{12} is phenyl substituted with OH at the 2-position and with a second substituent selected from fluoro and chloro; or
R^{12} 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 C_{3-4} alkyl having a single OH substituent; or an enantiomer isotopic variant, salt and/or solvate thereof.

4. A compound according to any one of claims 1 to 3 wherein Y is CH_2, or an enantiomer isotopic variant, salt and/or solvate thereof.

5. A compound according to any one of claims 1 to 4 wherein R^2 is selected from

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;

unsubstituted cyclopentyl, cyclohexyl or cycloheptyl;

cyclopropyl or cyclobutyl substituted with one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} haloalkyl; and

phenyl or a 5- or 6-membered heteroaryl ring optionally substituted with one or more substituents selected from fluoro, chloro, OH, C_{1-6} alkyl optionally substituted with one or more substituents selected from OH and halo, O(C_{1-6} alkyl) and O(C_{1-6} haloalkyl), or an enantiomer isotopic variant, salt and/or solvate thereof.

6. A compound according to any one of claims 1 to 3 or 5 wherein Y and R^2 together form:
a C_{3-4} 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, C_{1-4} alkyl and C_{1-4} haloalkyl; or

a group $–CH_2-C(R^{17})(R^{18})-CH_2-N(R^{19})-C(O)OR^{20}$, wherein each of R^{17}, R^{18}, R^{19} and R^{20} is independently H or methyl, or R^{18} and R^{19} combine with the atoms to which they are attached to form a 6-membered heterocyclic ring; and R^{20} is C_{1-6} alkyl.

7. A compound 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);

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);

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);

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-dimethyl-propyl]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-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-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);
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 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);
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-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);
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);
and salts and solvates of the above.

8. The compound of claim 7, which is 2-(2-Adamantyl)-N-[2-[(2-hydroxyphenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 5); or a salt thereof.

9. The compound of claim 7, which is 2-(2-Adamantyl)-N-[2-[(5-chloro-2-hydroxy-phenyl)methyl]-1H-benzimidazol-5-yl]acetamide (Compound 5.2); or a salt thereof.

10. The compound of claim 7, which is 2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)-N-[2-

[1-(trifluoromethyl)cyclopropyl]-1H-benzimidazol-5-yl]acetamide (Compound 23); or a salt thereof.

11. The compound of claim 7, which is N-(Cycloheptylmethyl)-2-[(2-hydroxyphenyl)methyl]indazole-6-carboxamide (Compound 13); or a salt thereof.

12. The compound of claim 7, which is 2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]-N-[2-[1-(trifluoromethyl) cyclopropyl]-1H-benzimidazol-5-yl]acetamide (Compound 22); or a salt thereof.

13. A compound according to any one of claims 1 to 12 for use in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

14. The use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable excipient.