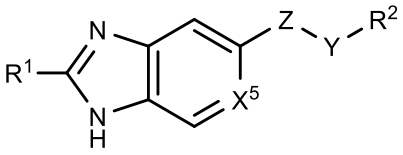
by mucus congestion including chronic bronchitis and severe asthma.

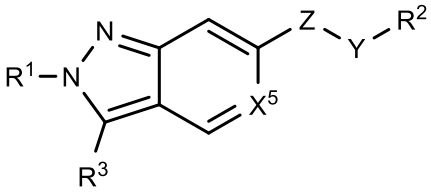
TMEM16A modulation has been implicated as a therapy for dry mouth (xerostomia), resultant from salivary gland dysfunction in Sjorgen's syndrome and radiation therapy, dry eye, cholestasis and gastrointestinal motility disorders.

Our application, PCT/GB2019/050209 relates to compounds which are positive modulators of TMEM16A and which are therefore of use in the treatment of diseases and conditions in which modulation of TMEM16A plays a role, particularly respiratory diseases and conditions. The present inventors have developed further compounds which are positive modulators of TMEM16A.

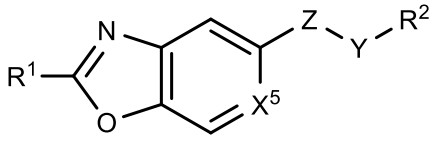
In an aspect, there is provided a compound of formula (IA), (IB), (IC), (ID) or (IE), including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



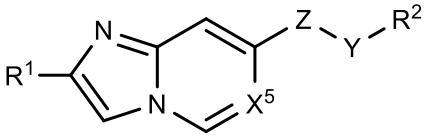
(IA)



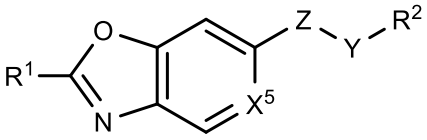
(IB)



(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-C(O)O-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 $–CH_2$-$C(R^{17})(R^{18})$-CH_2-$N(R^{19})$-$C(O)OR^{20}$;

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

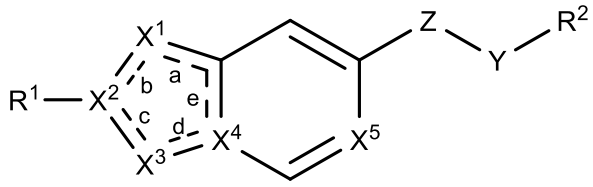
Y and R^2 together form a 3- to 8-membered carbocyclic ring optionally substituted with one or more substituents selected from halo, OH, CN and C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, OH and CN.

In another aspect, there is provided a compound as defined above for use in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable excipient.

In a first example of the present disclosure there is provided a compound of general formula (I) including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



(I)

wherein

⚌ represents a single or a double bond;

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; or

X^1 is NH, X^3 is N, X^2 and X^4 are C, a, b and d are single bonds and c and e are double bonds; or

X^1 is N, X^2 is N, X^3 is CR^3 or $C\text{-}N(R^{3a})(R^{3b})$, 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; or

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;

X^1 and X^4 are N, X^2 is C and X^3 is CH; a and c are double bonds and b, d and e are single bonds;

X^1 is O, X^3 is N, X^2 and X^4 are C, a, b and d are single bonds and c and e are double bonds;

X^5 is CH or N;