by mucus congestion including chronic bronchitis and severe asthma.

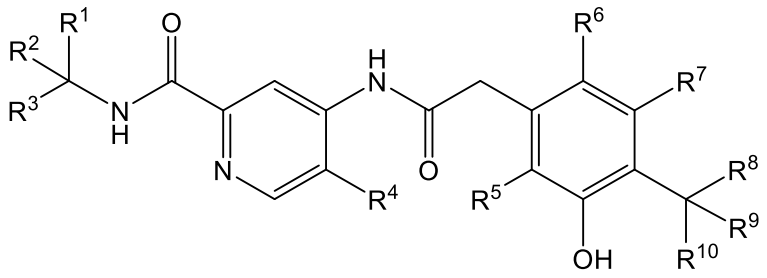
TMEM16A modulation has been implicated as a therapy for dry mouth (xerostomia), resultant from salivary gland dysfunction in Sjorgen's syndrome and radiation therapy, dry eye, cholestasis and gastrointestinal motility disorders.

Our application, WO2019/145726 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. Many of the compounds of the present invention have advantages over related compounds exemplified in WO2019/145726. These advantages include reduced lipophilicity (as represented by reduced log D values) and lower metabolic clearance, properties which lead to improved pharmacokinetics (PK) when the compounds are administered systemically, including orally. In particular, reduced lipophilicity leads to increased solubility in water. Several of the compounds of the present invention have either or both improved solubility and lower metabolic clearance than the compounds exemplified in WO2019/145726. This leads to advantages such as lower efficacious dose, longer half-life following administration or, in the case of oral administration, higher bioavailability.

Summary

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



(I)

wherein:

R^8 and R^9 together with the carbon atom to which they are attached form either a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in addition to the R^{10} group, with one or more substituents selected from OH, F and CH_2OH; or an ethenyl group optionally substituted with one or two halogen substituents;

R^{10} is selected from H, CN, OH, cycloalkyl optionally substituted with OH, and C_{1-4} alkyl optionally substituted with one or more substituents selected from halo, OH and a 3- to 6-membered cycloalkyl or heterocyclic group, either of which is optionally substituted with OH; or

R^8, R^9 and R^{10} together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system optionally substituted with one or more substituents selected from OH, F and CH_2OH;

provided that:

i. when R^5 and R^7 are H and R^6 is H or F, R^1, R^2, R^3, R^8, R^9 and R^{10} are not all methyl; and

ii. when R^2, R^3, R^8, R^9 and R^{10} are all methyl, R^5, R^6 and R^7 are not all H; and

iii. when R^1 is CN and R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 10-membered oxygen-containing heterocyclic ring, R^8, R^9 and R^{10} are not all methyl; and

iv. R^9 and R^{10} are not both OH.

Suitably there is provided a compound of general formula (I). There is also provided salts, such as pharmaceutically acceptable salts, of a compound of formula (I). There is also provided solvates, such as hydrates, or a compound of formula (I).

Since the compounds of general formula (I) are positive modulators of TMEM16A, they are useful for treating diseases and conditions in which modulation of TMEM16A plays a role, especially respiratory diseases and conditions.

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.

Detailed Description of the Invention

In the present specification, except where the context requires otherwise due to express language or necessary implication, the word “comprises”, or variations such as “comprises” or “comprising” is used in an inclusive sense i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in