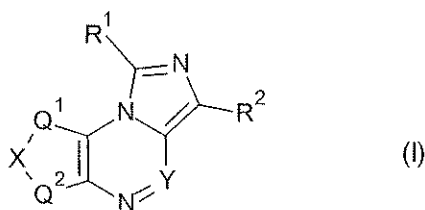


smaller IC₅₀ in this dofetilide assay means a greater probability of potent hERG blockade. In addition, the blockade of the hERG channel can be measured by electrophysiological experiments on cells which have been transfected with the hERG channel, by so-called whole-cell patch clamping (G. J. Diaz et al., Journal of Pharmacological and Toxicological Methods, 50 (2004), 187-199).

- vii. high free fraction in brain, i.e. the fraction of the compound bound to proteins should be low.
- viii. low lipophilicity.

Summary

In one aspect, there is provided a compound of formula I



where in formula I the variables X, Y, Q¹, Q², R¹ and R² have the following meanings:

X is C-R³ or N;

Q¹ is S or O and Q² is C-R⁴ or N and Q² is connected to X via a double bond while Q¹ is connected to X via a single bond; or

Q² is S or O and Q¹ is C-R⁴ or N and Q¹ is connected to X via a double bond while Q² is connected to X via a single bond;

Y is C-R⁵ or N;

R¹ is selected from the group consisting of hydrogen, halogen, cyano, nitro, R¹¹, OH, OR¹², S(O)_qR¹³, C(O)H, C(O)R¹⁴, C(O)OH, C(O)OR¹⁵, OC(O)R¹⁶, Y¹-NR¹⁷R¹⁸, Y¹-N(R¹⁹)-Y³-NR¹⁷R¹⁸, Y¹-N(R¹⁹)-Y²-R^{15a} and a moiety Z¹-Ar¹;

R² is selected from the group consisting of hydrogen, halogen, cyano, nitro, R²¹, OH, OR²², S(O)_qR²³, C(O)H, C(O)R²⁴, C(O)OH, C(O)OR²⁵, OC(O)R²⁶,

$Y^1-NR^{27}R^{28}$, $Y^1-N(R^{29})-Y^3-NR^{27}R^{28}$, $Y^1-N(R^{19})-Y^2-R^{25a}$ and a moiety Z^2-Ar^2 ;

provided that at least one of R^1 and R^2 is different from hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, cyano, nitro, R^{31} , OR^{32} , $S(O)_qR^{33}$, $C(O)H$, $C(O)R^{34}$, $C(O)OH$, $C(O)OR^{35}$, $OC(O)R^{36}$, $Y^1-NR^{37}R^{38}$, $Y^1-N(R^{39})-Y^3-NR^{37}R^{38}$, $Y^1-N(R^{39})-Y^2-R^{35a}$ and a moiety Z^3-Ar^3 ;

R^4 is selected from the group consisting of hydrogen, halogen, cyano, nitro, R^{41} , OR^{42} , $S(O)_qR^{43}$, $C(O)H$, $C(O)R^{44}$, $C(O)OH$, $C(O)OR^{45}$, $OC(O)R^{46}$, $Y^1-NR^{47}R^{48}$, $Y^1-N(R^{49})-Y^3-NR^{47}R^{48}$, $Y^1-N(R^{49})-Y^2-R^{45a}$ and a moiety Z^4-Ar^4 ;

R^5 is selected from the group consisting of hydrogen, halogen, cyano, nitro, R^{51} , OR^{52} , $S(O)_qR^{53}$, $C(O)H$, $C(O)R^{54}$, $C(O)OH$, $C(O)OR^{55}$, $OC(O)R^{56}$, $Y^1-NR^{57}R^{58}$, $Y^1-N(R^{59})-Y^3-NR^{57}R^{58}$, $Y^1-N(R^{59})-Y^2-R^{55a}$ and a moiety Z^5-Ar^5 ;

R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} and R^{56} , independently of each other, are selected from the group consisting of C_1 - C_8 -alkyl, C_2 - C_8 -alkenyl, C_2 - C_8 -alkynyl, C_3 - C_8 -cycloalkyl, C_5 - C_8 -cycloalkenyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, where the 6 aforementioned substituents may be unsubstituted, partially or completely halogenated or carry 1, 2 or 3 radicals R^y , and C-bound 5- to 8-membered heterocyclyl, which is saturated or partially unsaturated and has 1 or 2 heteroatom moieties as ring members, which are selected from the group consisting of O, N, S, $S(O)$, $S(O)_2$ or $N-R^x$, where heterocyclyl is unsubstituted or carries 1, 2, 3 or 4 radicals R^{yy} ;

R^{17} and R^{18} , independently of each other, are selected from the group consisting of hydrogen, tri- C_1 - C_4 -alkylsilyl, C_1 - C_8 -alkyl, C_2 - C_8 -alkenyl, C_2 - C_8 -alkynyl, C_3 - C_8 -cycloalkyl, C_5 - C_8 -cycloalkenyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, where the 6 aforementioned substituents may be unsubstituted, partially or completely halogenated or carry 1, 2 or 3 radicals R^v , C_1 - C_8 -alkylcarbonyl, C_1 - C_4 -haloalkylcarbonyl, C_1 - C_8 -alkylsulfonyl, C_1 - C_4 -haloalkylsulfonyl, and C-bound 5- to 8-membered heterocyclyl, which is saturated or partially unsaturated and has 1 or 2 heteroatom moieties as ring members, which are selected from the group

consisting of O, N, S, S(O), S(O)₂ or N-R^x, where heterocyclyl is unsubstituted or carries 1, 2, 3 or 4 radicals R^{yy} or R¹⁷ and R¹⁸, together with the nitrogen atom, to which they are attached, form an N-bound 5- to 8-membered heterocyclyl, which is saturated, partially unsaturated or aromatic and in addition to the nitrogen atom may have 1 or 2 further heteroatom moieties as ring members, which are selected from the group consisting of O, N, S, S(O), S(O)₂ or N-R^x, where heterocyclyl is unsubstituted or carries 1, 2, 3 or 4 radicals R^{yy}.

R¹⁹, R²⁹, R³⁹, R⁴⁹ and R⁵⁹, independently of each other, are hydrogen or have one of the meanings given for R¹¹;

R²⁷ and R²⁸ are as defined for R¹⁷ and R¹⁸;

R³⁷ and R³⁸ are as defined for R¹⁷ and R¹⁸;

R⁴⁷ and R⁴⁸ are as defined for R¹⁷ and R¹⁸;

R⁵⁷ and R⁵⁸ are as defined for R¹⁷ and R¹⁸;

R^{15a}, R^{25a}, R^{35a}, R^{45a} and R^{55a}, independently of each other, have one of the meanings given for R¹¹;

q is 0, 1 or 2

Ar¹, Ar², Ar³, Ar⁴ and Ar⁵, independently of each other, are selected from the group consisting of aryl, monocyclic 5- or 6-membered hetaryl and bicyclic 9 or 10 membered hetaryl, where hetaryl has 1, 2 or 3 heteroatoms as ring members which are selected from O, S and N, where aryl and hetaryl are unsubstituted or may carry 1, 2, 3 or 4 identical or different substituents R^{Ar};

Y¹ is a single bond, C₁-C₄-alkylene, Y⁵-O-Y⁶, Y⁵-S(O)_q-Y⁶, Y⁵-C(O)-Y⁶, Y⁵-C(S)-Y⁶, Y⁵-C(O)O-Y⁶, Y⁵-OC(O)-Y⁶, or Y⁵-N(R⁷)-Y⁴;

Y² is a single bond, C₁-C₄-alkylene, Y⁵-O-Y⁶, Y⁵-S(O)_q-Y⁶, Y⁵-C(O)-Y⁶, Y⁵-C(S)-Y⁶, Y⁵-C(O)O-Y⁶, Y⁵-OC(O)-Y⁶, or Y⁵-N(R⁷)-Y⁴;

Y³ is a single bond, C₁-C₄-alkylene, Y⁵-S(O)_q-Y⁶, Y⁵-C(O)-Y⁶, Y⁵-C(S)-Y⁶, Y⁵-C(O)O-Y⁶, or Y⁵-OC(O)-Y⁶;

Y⁴ is a C₁-C₄-alkylene, Y⁵-S(O)_q-Y⁶, Y⁵-C(O)-Y⁶, Y⁵-C(S)-Y⁶, Y⁵-C(O)O-Y⁶, or Y⁵-OC(O)-Y⁶;

Y⁵ is a single bond or C₁-C₄-alkylene;

Y⁶ is a single bond or C₁-C₄-alkylene;

Z^1, Z^2, Z^3, Z^4 and Z^5 are independently of each other selected from a single bond, C₁-C₄-alkylene, Y^5-O-Y^6 , $Y^5-S(O)_q-Y^6$, $Y^5-C(O)-Y^6$, $Y^5-C(S)-Y^6$, $Y^5-C(O)O-Y^6$, $Y^5-OC(O)-Y^6$ and $Y^5-N(R^7)-Y^4$;

R^x is selected from the group consisting of hydrogen, C₁-C₈-alkyl, C₂-C₈-alkenyl, C₂-C₈-alkynyl, C₃-C₈-cycloalkyl, C₅-C₈-cycloalkenyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, where the 6 aforementioned substituents may be unsubstituted, partially or completely halogenated or carry 1, 2 or 3 radicals R^y , phenyl and phenyl-C₁-C₄-alkyl, where phenyl and phenyl-C₁-C₄-alkyl are unsubstituted or may carry 1, 2, 3 or 4 radicals R^{yy} ;

R^y is selected from the group consisting of cyano, OH, OR^{y2} , $S(O)_qR^{y3}$, $C(O)H$, $C(O)R^{y4}$, $C(O)OH$, $C(O)OR^{y5}$, $OC(O)R^{y6}$, $Y^1-NR^{y7}R^{y8}$, $Y^1-N(R^{y9})-Y^3-NR^{y7}R^{y8}$ and $Y^1-N(R^{y9})-Y^2-R^{y0}$;

R^{yy} is selected from the group consisting of cyano, halogen, R^{y1} , OH, OR^{y2} , $S(O)_qR^{y3}$, $C(O)H$, $C(O)R^{y4}$, $C(O)OH$, $C(O)OR^{y5}$, $OC(O)R^{y6}$, $Y^1-NR^{y7}R^{y8}$, $Y^1-N(R^{y9})-Y^3-NR^{y7}R^{y8}$ and $Y^1-N(R^{y9})-Y^2-R^{y0}$;

$R^{y0}, R^{y2}, R^{y3}, R^{y4}, R^{y5}$ and R^{y6} , independently of each other, are selected from the group consisting of C₁-C₈-alkyl, C₂-C₈-alkenyl, C₂-C₈-alkynyl, C₃-C₈-cycloalkyl, C₅-C₈-cycloalkenyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, and C-bound 5- to 8-membered heterocyclyl, which is saturated or partially unsaturated and has 1 or 2 heteroatom moieties as ring members, which are selected from the group consisting of O, N, S, S(O), S(O)₂, NH or or N-(C₁-C₄-alkyl);

R^{y7} and R^{y8} are as defined for R^{y0} or, together with the nitrogen atom, to which they are attached, form an N-bound 5- to 8-membered heterocyclyl, which is saturated or partially unsaturated and in addition to the nitrogen atom may have 1 or 2 further heteroatom moieties as ring members, which are selected from the group consisting of O, N, S, S(O), S(O)₂, NH or or N-(C₁-C₄-alkyl), where heterocyclyl is unsubstituted or carries 1, 2, 3 or 4 radicals selected from C₁-C₄-alkyl;

R^{y9} is hydrogen or has one of the meanings given for R^{y0} ;

R^{Ar} is selected from the group consisting of halogen, cyano, nitro, OH, $C(O)NH_2$, R^{Ar1} , OR^{Ar2} , $S(O)_qR^{Ar3}$, $C(O)H$, $C(O)R^{Ar4}$, $C(O)OH$, $C(O)OR^{Ar5}$, $OC(O)R^{Ar6}$, $Y^1-NR^{Ar7}R^{Ar8}$, $Y^1-N(R^{Ar9})-Y^3-NR^{Ar7}R^{Ar8}$, $Y^1-N(R^{Ar9})-Y^2-R^{Ar0}$, where R^{Ar0}, R^{Ar1} ,

R^{Ar2} , R^{Ar3} , R^{Ar4} , R^{Ar5} and R^{Ar6} have one of the meanings given for R^{11} , R^{Ar7} and R^{Ar8} are as defined for R^{17} and R^{18} , and R^{Ar9} has one of the meanings given for R^{19} ;

R^Z has one of the meanings given for R^x ;

5 the N-oxides, tautomers, the prodrugs and the pharmaceutically acceptable salts thereof.

In one aspect, there is provided the compound as described herein for the use in the treatment of a medical disorder, selected from neurological and psychiatric disorders which can be treated by modulation of phosphodiesterase type 10 in a mammalian.

10 In one aspect, there is provided the compound as described herein for the use in the treatment of drug abuse in a mammalian.

In one aspect, there is provided a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound as described herein.

15 In one aspect, there is provided the use of at least one compound as described herein in the manufacture of a medicament for treating a medical disorder, selected from neurological and psychiatric disorders which can be treated by modulation of phosphodiesterase type 10.

In one aspect, there is provided the compound as described herein for use in treating, controlling, ameliorating or reducing the risk of depression in a mammalian.

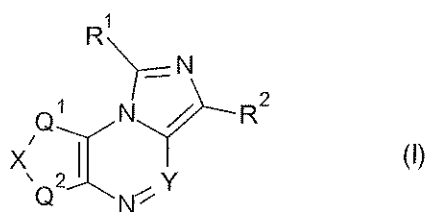
20

Brief Description of the Invention

The present invention is thus based on the object of providing compounds which inhibit PDE10A at low concentrations.

25 The compounds are further intended to display at least one of the properties i. to viii. mentioned above, in particular high selectivity with regard to inhibition of PDE10A, high selectivity vis-à-vis other phosphodiesterases such as , enhanced metabolic stability, in particular microsomal stability, cytosolic stability or hepatocyte stability, low affinity to the HERG receptor, low inhibition of cytochrome P450 (CYP)
30 enzymes, suitable solubility in water and suitable pharmacokinetics.

This object and further objects are achieved by the compounds of the general formula I described below, the N-oxides, the prodrugs, the hydrates and the tautomers thereof and the pharmaceutically suitable salts thereof:



where in formula I the variables X, Y, Q¹, Q², R¹ and R² have the following
 5 meanings:

X is C-R³ or N;

- 5,6-dimethyl-8-(2-methylpyridin-3-yl)-3-thia-1,4,7,8a-tetraaza-as-indacene
 5,6-dimethyl-8-propyl-3-thia-1,4,7,8a-tetraaza-as-indacene
 5,6-dimethyl-8-(3-methylpyridin-4-yl)-3-thia-1,4,7,8a-tetraaza-as-indacene
 5,6-dimethyl-8-(6-methylpyridin-3-yl)-3-thia-1,4,7,8a-tetraaza-as-indacene
 5 5,6-dimethyl-8-bromo-3-thia-1,4,7,8a-tetraaza-as-indacene
 5,6-dimethyl-3-thia-1,4,7,8a-tetraaza-as-indacene
 2,5,6-trimethyl-8-propyl-3-thia-1,4,7,8a-tetraaza-as-indacene
 2-methoxy-5,6-dimethyl-8-propyl-3-thia-1,4,7,8a-tetraaza-as-indacene
 5,6-Dimethyl-8-propyl-1-thia-3,4,7,8a-tetraaza-as-indacene
 10 3-(5,6-Dimethyl-3-thia-1,4,7,8a-tetraaza-as-indacen-8-yl)-benzamide
 5,6-Dimethyl-8-(2-methyl-pyridin-4-yl)-3-thia-1,4,7,8a-tetraaza-as-indacene
 and the N-oxides, the tautomers, the hydrates, the prodrugs and the
 pharmaceutically acceptable salts thereof.
- 15 30. The compound as claimed in any of claims 1 to 29 for the use in the treatment of a
 medical disorder, selected from neurological and psychiatric disorders which can
 be treated by modulation of phosphodiesterase type 10 in a mammalian.
31. The compound as claimed in any of claims 1 to 29 for the use in the treatment of
 20 drug abuse in a mammalian.
32. Pharmaceutical composition which comprises a pharmaceutically acceptable
 carrier and a compound as claimed in any one of claims 1 to 29.
- 25 33. Use of at least one compound as claimed in any of claims 1 to 29 in the
manufacture of a medicament A method for treating a medical disorder, selected
 from neurological and psychiatric disorders which can be treated by modulation
 of phosphodiesterase type 10, ~~said method comprising administering an effective~~
~~amount of at least one compound as claimed in any of claims 1 to 29 to a subject~~
 30 ~~in need thereof.~~
34. The ~~use~~method of claim 33 for treating, controlling, ameliorating or reducing the
 risk of CNS disorders in a mammalian.

35. The ~~method-use~~ of claim 33 for treating, controlling, ameliorating or reducing the risk of schizophrenia in a mammalian.
- 5 | 36. The ~~use~~~~method~~ of claim 33 for treating, controlling, ameliorating or reducing cognitive dysfunction associated with schizophrenia in a mammalian.
37. The ~~use~~~~method~~ of claim 33 for treating, controlling, ameliorating or reducing the risk of bipolar disorders in a mammalian.
- 10 | 38. The compound as claimed in any of claims 1 to 29 for use in treating, controlling, ameliorating or reducing the risk of depression in a mammalian.
- 15 | 39. The ~~method-use~~ of claim 33 for treating, controlling, ameliorating or reducing cognitive dysfunction associated with Alzheimer's disease in a mammalian.
40. The ~~method-use~~ of claim 33 for treating, controlling, ameliorating or reducing the risk of diet-induced obesity in a mammalian.