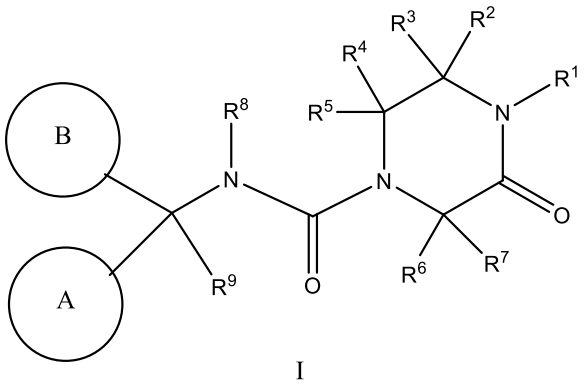
Compounds useful to treat $Na_v1.8$ sodium ion channel related conditions are disclosed in: ACS Med. Chem. Lett. 2015, 6, 650; BJP 2015, 172, 2654; PNAS 2007, 104, 8520; J. Med. Chem. 2008, 51, 407; JPET 2008, 324, 1204; and Neuropharmacology 2010, 59, 201.

$Na_v1.8$ compounds are also disclosed in: WO 2009/049180, WO 2009/049181, WO 2009/049183, WO 2014/120808; WO 2014/120815; WO 2014/120820; WO 2015/010065; and WO 2015/089361; WO 2017/209322; US 8,519,137; US 9,051,270; US 9,108,903; US 9,163,042; US 9,783,501; WO 2020/092667; WO2019/014352; WO2018/213426; US 8,629,149; and WO2011/026240.

SUMMARY

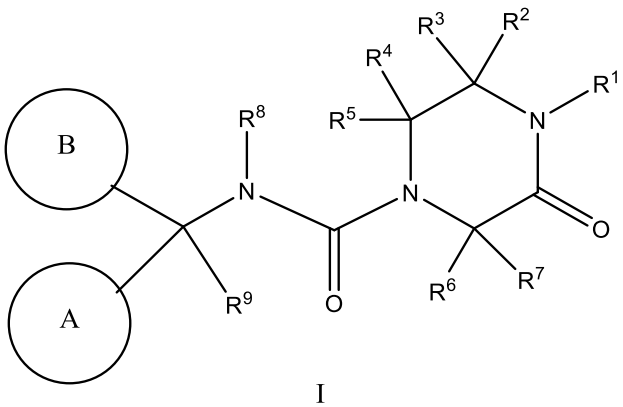
The present disclosure relates to novel compounds of structural formula I:



I

and pharmaceutically acceptable salts, hydrates and solvates thereof.

In one aspect, there is provided a compound of structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

one of A and B is independently selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^a, and

the other of A and B is independently selected from the group consisting of:

(1) C_{3-12}cycloalkyl,

(2) C_{2-11}cycloheteroalkyl,

(3) -C_{1-6}alkyl-C_{3-12}cycloalkyl,

(4) -C_{1-6}alkyl-C_{2-11}cycloheteroalkyl,

(5) -C_{1-6}alkyl-O-C_{3-12}cycloalkyl, and

(6) -C_{1-6}alkyl-O-C_{2-11}cycloheteroalkyl,

wherein alkyl, cycloalkyl and cycloheteroalkyl are unsubstituted or substituted with one to six substituents selected from R^b;

R^1 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) $-(CH_2)_tC(O)R^j$,

(9) $-(CH_2)_tC(O)NR^eR^j$,

(10) $-(CH_2)_nNR^eC(O)R^j$,

(11) $-(CH_2)_nNR^eC(O)OR^j$,

(12) $-(CH_2)_nNR^eC(O)N(R^e)_2$,

(13) $-(CH_2)_nNR^eC(O)NR^eR^j$,

(14) $-(CH_2)_nNR^eS(O)_mR^j$,

(15) $-(CH_2)_nNR^eS(O)mN(R^e)_2$,

(16) $-(CH_2)_nNR^eS(O)mNR^eR^j$, and

(17) $-(CH_2)_nNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^c;

R^2 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_sC(O)R^j$,

(10) -$(CH_2)_sC(O)NR^eR^j$,

(11) -$(CH_2)_sNR^eC(O)R^j$,

(12) -$(CH_2)_sNR^eC(O)OR^j$,

(13) -$(CH_2)_sNR^eC(O)N(R^e)_2$,

(14) -$(CH_2)_sNR^eC(O)NR^eR^j$,

(15) -$(CH_2)_sNR^eS(O)_mR^j$,

(16) -$(CH_2)_sNR^eS(O)mN(R^e)_2$,

(17) -$(CH_2)_sNR^eS(O)mNR^eR^j$, and

(18) -$(CH_2)_sNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^d,

wherein R^2 and R^3 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring, and wherein R^2 and R^4 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^3 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_sC(O)R^j$,

(10) -$(CH_2)_sC(O)NR^eR^j$,

(11) -$(CH_2)_sNR^eC(O)R^j$,

(12) -$(CH_2)_sNR^eC(O)OR^j$,

(13) -$(CH_2)_sNR^eC(O)N(R^e)_2$,

(14) -$(CH_2)_sNR^eC(O)NR^eR^j$,

(15) -$(CH_2)_sNR^eS(O)_mR^j$,

(16) -$(CH_2)_sNR^eS(O)mN(R^e)_2$,

(17) -$(CH_2)_sNR^eS(O)mNR^eR^j$, and

(18) -$(CH_2)_sNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^d;

R^4 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_sC(O)R^j$,

(10) -$(CH_2)_sC(O)NR^eR^j$,

(11) -$(CH_2)_sNR^eC(O)R^j$,

(12) -$(CH_2)_s$$NR^eC(O)OR^j$,

(13) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(14) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(15) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(16) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(17) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(18) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^f, and

wherein R^4 and R^5 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^5 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_s$$C(O)R^j$,

(10) -$(CH_2)_s$$C(O)NR^eR^j$,

(11) -$(CH_2)_s$$NR^eC(O)R^j$,

(12) -$(CH_2)_s$$NR^eC(O)OR^j$,

(13) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(14) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(15) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(16) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(17) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(18) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^f, and

wherein R^5 and R^7 and the carbon atoms they are attached to may form a 4-, 5- or 6- membered saturated ring;

R^6 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_sC(O)R^j$,

(10) -$(CH_2)_sC(O)NR^eR^j$,

(11) -$(CH_2)_sNR^eC(O)R^j$,

(12) -$(CH_2)_sNR^eC(O)OR^j$,

(13) -$(CH_2)_sNR^eC(O)N(R^e)_2$,

(14) -$(CH_2)_sNR^eC(O)NR^eR^j$,

(15) -$(CH_2)_sNR^eS(O)_mR^j$,

(16) -$(CH_2)_sNR^eS(O)mN(R^e)_2$,

(17) -$(CH_2)_sNR^eS(O)mNR^eR^j$, and

(18) -$(CH_2)_sNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^g, and

wherein R^6 and R^7 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^7 is selected from the group consisting of:

(1) hydrogen,

(2) deuterium,

(3) -C_{1-6}alkyl,

(4) -C_{2-6}alkenyl,

(5) -C_{2-6}alkynyl,

(6) -C_{3-6}cycloalkyl,

(7) -C_{2-6}cycloheteroalkyl,

(8) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(9) -$(CH_2)_s$C(O)R^j,

(10) -$(CH_2)_s$C(O)N$R^e R^j$,

(11) -$(CH_2)_s$NR^eC(O)R^j,

(12) -$(CH_2)_s$NR^eC(O)OR^j,

(13) -$(CH_2)_s$NR^eC(O)N$(R^e)_2$,

(14) -$(CH_2)_s$NR^eC(O)N$R^e R^j$,

(15) -$(CH_2)_s$NR^eS(O)$_m R^j$,

(16) -$(CH_2)_s$NR^eS(O)mN$(R^e)_2$,

(17) -$(CH_2)_s$NR^eS(O)mN$R^e R^j$, and

(18) -$(CH_2)_s$N$R^e R^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^g;

R^8 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{3-6}cycloalkyl, and

(4) -C_{2-6}cycloheteroalkyl,

wherein each alkyl, cycloalkyl and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from halogen;

R^9 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl, and

(4) -C_{2-6}alkynyl,

wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with one to five substituents selected from halogen;

each R^a is independently selected from the group consisting of:

(1) CN,

(2) oxo,

(3) halogen,

(4) $–S(O)_2C_{1-6}$alkyl,

(5) $-C_{1-6}$alkyl,

(6) $-C_{2-6}$alkenyl,

(7) $-C_{2-6}$alkynyl,

(8) $-C_{3-6}$cycloalkyl,

(9) $-C_{2-6}$cycloheteroalkyl,

(10) aryl,

(11) heteroaryl,

(12) $–C_{1-6}$alkyl-aryl,

(13) $–C_{1-6}$alkyl-heteroaryl,

(14) $–C_{1-6}$alkyl-C_{3-6}cycloalkyl,

(15) $–C_{1-6}$alkyl-C_{2-6}cycloheteroalkyl,

(16) $-C_{2-6}$alkenyl-C_{3-6}cycloalkyl,

(17) $-C_{2-6}$alkenyl-C_{2-6}cycloheteroalkyl,

(18) $–C_{2-6}$alkenyl-aryl,

(19) $-C_{2-6}$alkenyl-heteroaryl,

(20) $-C_{2-6}$alkynyl-C_{3-6}cycloalkyl,

(21) $-C_{2-6}$alkynylC_{2-6}cycloheteroalkyl,

(22) $-C_{2-6}$alkynyl-aryl,

(23) $-C_{2-6}$alkynyl–heteroaryl,

(24) -OH,

(25) $-(CH_2)_p$-O-C_{1-6}alkyl,

(26) $-(CH_2)_p$ -O-C_{2-6}alkenyl,

(27) $-(CH_2)_p$ -O-C_{2-6}alkynyl,

(28) $–(CH_2)_p$ -O-C_{3-6}cycloalkyl,

(29) –$(CH_2)_p$ -O-C_{2-6}cycloheteroalkyl,

(30) –$(CH_2)_p$ -O-aryl,

(31) –$(CH_2)_p$ -O-heteroaryl,

(32) -OC_{1-6}alkyl-C_{3-6}cycloalkyl,

(33) -OC_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(34) -OC_{1-6}alkyl-aryl,

(35) -OC_{1-6}alkyl-heteroaryl,

(36) -S(O)$_r$R^h,

(37) -C_{1-6}alkyl-S(O)$_r$R^h,

(38) -N(R^k)$_2$,

(39) -C(O)R^L, and

(40) –NR^{k}R^L,

wherein each R^a is unsubstituted or substituted with one to six substituents selected from halogen, CF_3, OH, C_{1-6}alkyl, and -OC_{1-6}alkyl;

each R^b is independently selected from the group consisting of:

(1) CN,

(2) oxo,

(3) halogen,

(4) –S(O)$_2C_{1-6}$alkyl,

(5) -C_{1-6}alkyl,

(6) -C_{1-6}alkenyl,

(7) -C_{2-6}alkynyl,

(8) -C_{3-6}cycloalkyl,

(9) -C_{2-6}cycloheteroalkyl,

(10) aryl,

(11) heteroaryl,

(12) –C_{1-6}alkyl-aryl,

(13) –C_{1-6}alkyl-heteroaryl,

(14) –C_{1-6}alkyl-C_{3-6}cycloalkyl,

(15) –C_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(16) -C_{2-6}alkenyl-C_{3-6}cycloalkyl,

(17) -C_{2-6}alkenyl-C_{2-6}cycloheteroalkyl,

(18) –C_{2-6}alkenyl-aryl,

(19) -C_{2-6}alkenyl-heteroaryl,

(20) -C_{2-6}alkynyl-C_{3-6}cycloalkyl,

(21) -C_{2-6}alkynyl-C_{2-6}cycloheteroalkyl,

(22) -C_{2-6}alkynyl-aryl,

(23) -C_{2-6}alkynyl–heteroaryl,

(24) -OH,

(25) -$(CH_2)_q$-O-C_{1-6}alkyl,

(26) -$(CH_2)_q$-O-C_{2-6}alkenyl,

(27) -$(CH_2)_q$ -O-C_{2-6}alkynyl,

(28) –$(CH_2)_q$ -O-C_{3-6}cycloalkyl,

(29) –$(CH_2)_q$ -O-C_{2-6}cycloheteroalkyl,

(30) –$(CH_2)_q$ -O-aryl,

(31) –$(CH_2)_q$ -O-heteroaryl,

(32) -OC_{1-6}alkyl-C_{3-6}cycloalkyl,

(33) -OC_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(34) -OC_{1-6}alkyl-aryl,

(35) -OC_{1-6}alkyl-heteroaryl,

(36) -S$(O)_rR^i$,

(37) -C_{1-6}alkyl-S$(O)_rR^i$,

(38) -$N(R^k)_2$,

(39) -C$(O)R^L$, and

(40) –NR^kR^L,

wherein each R^b is unsubstituted or substituted with one to six substituents selected from halogen, CF_3, OCF_3, CN, CH_2CF_3, CF_2CH_3, -C_{1-6}alkyl, and -OC_{1-6}alkyl;

R^c is selected from:

(1) -C_{1-6}alkyl,

(2) OH,

(3) halogen, and

(4) -OC$_{1-6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^d is selected from:

(1) -C$_{1-6}$alkyl,

(2) OH,

(3) halogen, and

(4) -OC$_{1-6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^e is selected from:

(1) hydrogen, and

(2) C$_{1-6}$alkyl;

R^f is selected from:

(1) -C$_{1-6}$alkyl,

(2) OH,

(3) halogen, and

(4) -OC$_{1-6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^g is selected from:

(1) -C$_{1-6}$alkyl,

(2) OH,

(3) halogen, and

(4) -OC$_{1-6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^h is selected from:

(1) hydrogen,

(2) C$_{1-6}$alkyl,

(3) C$_{3-6}$cycloalkyl,

(4) aryl, and

(5) heteroaryl;

R^i is selected from:

(1) hydrogen,

(2) $C_{1\text{-}6}$alkyl,

(3) $C_{3\text{-}6}$cycloalkyl,

(4) aryl, and

(5) heteroaryl;

R^j is selected from:

(1) hydrogen,

(2) $C_{1\text{-}6}$alkyl,

(3) $C_{3\text{-}6}$alkenyl,

(4) $C_{3\text{-}6}$alkynyl,

(5) $C_{3\text{-}6}$cycloalkyl,

(6) $C_{2\text{-}5}$cycloheteroalkyl,

(7) aryl, and

(8) heteroaryl;

R^k is selected from:

(1) hydrogen, and

(2) $C_{1\text{-}6}$alkyl;

R^L is selected from:

(1) hydrogen,

(2) $C_{1\text{-}6}$alkyl,

(3) $C_{3\text{-}6}$cycloalkyl,

(4) aryl, and

(5) heteroaryl;

m is independently selected from 0, 1 and 2;

n is independently selected from 2, 3, 4, 5 and 6;

p is independently selected from 0, 1, 2 and 3;

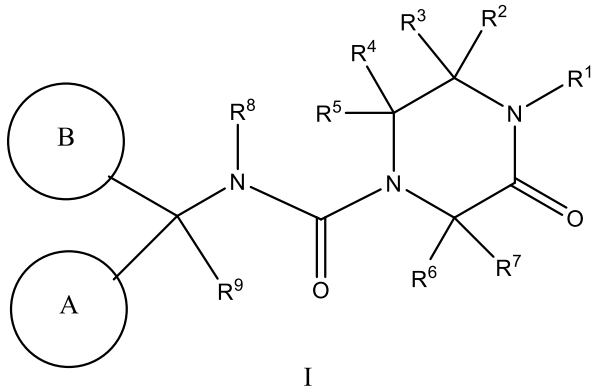
q is independently selected from 0, 1, 2 and 3;

r is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2, 3, 4, 5, and 6; and

t is independently selected from 0, 1, 2, 3, 4, 5, and 6.

In another aspect, there is provided a compound of structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

one of A and B is independently selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^a, and

the other of A and B is independently selected from the group consisting of:

(1) -C_{3-12}cycloalkyl,

(2) -C_{2-11}cycloheteroalkyl,

(3) -C_{1-6}alkyl-C_{3-12}cycloalkyl,

(4) -C_{1-6}alkyl-C_{2-11}cycloheteroalkyl,

(5) -C_{1-6}alkyl-O-C_{3-12}cycloalkyl, and

(6) -C_{1-6}alkyl-O-C_{2-11}cycloheteroalkyl,

wherein alkyl, cycloalkyl and cycloheteroalkyl are unsubstituted or substituted with one to six substituents selected from R^b;

R^1 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) $-(CH_2)_tC(O)R^j$,

(9) $-(CH_2)_tC(O)NR^eR^j$,

(10) $-(CH_2)_nNR^eC(O)R^j$,

(11) $-(CH_2)_nNR^eC(O)OR^j$,

(12) $-(CH_2)_nNR^eC(O)N(R^e)_2$,

(13) $-(CH_2)_nNR^eC(O)NR^eR^j$,

(14) $-(CH_2)_nNR^eS(O)_mR^j$,

(15) $-(CH_2)_nNR^eS(O)mN(R^e)_2$,

(16) $-(CH_2)_nNR^eS(O)mNR^eR^j$, and

(17) $-(CH_2)_nNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^c;

R^2 is selected from the group consisting of:

(1) hydrogen,

(2) $-C_{1-6}$alkyl,

(3) $-C_{2-6}$alkenyl,

(4) $-C_{2-6}$alkynyl,

(5) $-C_{3-6}$cycloalkyl,

(6) $-C_{2-6}$cycloheteroalkyl,

(7) $-C_{1-6}$alkyl-O-C_{1-6}alkyl-,

(8) $-(CH_2)_sC(O)R^j$,

(9) $-(CH_2)_sC(O)NR^eR^j$,

(10) $-(CH_2)_sNR^eC(O)R^j$,

(11) $-(CH_2)_sNR^eC(O)OR^j$,

(12) $-(CH_2)_sNR^eC(O)N(R^e)_2$,

(13) $-(CH_2)_sNR^eC(O)NR^eR^j$,

(14) $-(CH_2)_sNR^eS(O)_mR^j$,

(15) $-(CH_2)_sNR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^d,

wherein R^2 and R^3 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring, and wherein R^2 and R^4 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^3 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) -$(CH_2)_s$$C(O)R^j$,

(9) -$(CH_2)_s$$C(O)NR^eR^j$,

(10) -$(CH_2)_s$$NR^eC(O)R^j$,

(11) -$(CH_2)_s$$NR^eC(O)OR^j$,

(12) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(13) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(14) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(15) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^d;

R^4 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) -$(CH_2)_sC(O)R^j$,

(9) -$(CH_2)_sC(O)NR^eR^j$,

(10) -$(CH_2)_sNR^eC(O)R^j$,

(11) -$(CH_2)_sNR^eC(O)OR^j$,

(12) -$(CH_2)_sNR^eC(O)N(R^e)_2$,

(13) -$(CH_2)_sNR^eC(O)NR^eR^j$,

(14) -$(CH_2)_sNR^eS(O)_mR^j$,

(15) -$(CH_2)_sNR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_sNR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_sNR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^f, and

wherein R^4 and R^5 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^5 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) -$(CH_2)_sC(O)R^j$,

(9) -$(CH_2)_sC(O)NR^eR^j$,

(10) -$(CH_2)_s$$NR^eC(O)R^j$,

(11) -$(CH_2)_s$$NR^eC(O)OR^j$,

(12) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(13) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(14) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(15) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^f, and

wherein R^5 and R^7 and the carbon atoms they are attached to may form a 4-, 5- or 6- membered saturated ring;

R^6 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) -$(CH_2)_s$$C(O)R^j$,

(9) -$(CH_2)_s$$C(O)NR^eR^j$,

(10) -$(CH_2)_s$$NR^eC(O)R^j$,

(11) -$(CH_2)_s$$NR^eC(O)OR^j$,

(12) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(13) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(14) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(15) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^g, and

wherein R^6 and R^7 and the carbon atoms they are connected to can from a -C_{3-5}cycloalkyl ring;

R^7 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl,

(4) -C_{2-6}alkynyl,

(5) -C_{3-6}cycloalkyl,

(6) -C_{2-6}cycloheteroalkyl,

(7) -C_{1-6}alkyl-O-C_{1-6}alkyl-,

(8) -$(CH_2)_s$$C(O)R^j$,

(9) -$(CH_2)_s$$C(O)NR^eR^j$,

(10) -$(CH_2)_s$$NR^eC(O)R^j$,

(11) -$(CH_2)_s$$NR^eC(O)OR^j$,

(12) -$(CH_2)_s$$NR^eC(O)N(R^e)_2$,

(13) -$(CH_2)_s$$NR^eC(O)NR^eR^j$,

(14) -$(CH_2)_s$$NR^eS(O)_mR^j$,

(15) -$(CH_2)_s$$NR^eS(O)mN(R^e)_2$,

(16) -$(CH_2)_s$$NR^eS(O)mNR^eR^j$, and

(17) -$(CH_2)_s$$NR^eR^j$,

wherein each CH_2, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from R^g;

R^8 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{3-6}cycloalkyl, and

(4) -C_{2-6}cycloheteroalkyl,

wherein each alkyl, cycloalkyl and cycloheteroalkyl is unsubstituted or substituted with one to five substituents selected from halogen;

R^9 is selected from the group consisting of:

(1) hydrogen,

(2) -C_{1-6}alkyl,

(3) -C_{2-6}alkenyl, and

(4) -C_{2-6}alkynyl,

wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with one to five substituents selected from halogen;

each R^a is independently selected from the group consisting of:

(1) CN,

(2) oxo,

(3) halogen,

(4) –$S(O)_2C_{1-6}$alkyl,

(5) -C_{1-6}alkyl,

(6) -C_{2-6}alkenyl,

(7) -C_{2-6}alkynyl,

(8) -C_{3-6}cycloalkyl,

(9) -C_{2-6}cycloheteroalkyl,

(10) aryl,

(11) heteroaryl,

(12) –C_{1-6}alkyl-aryl,

(13) –C_{1-6}alkyl-heteroaryl,

(14) –C_{1-6}alkyl-C_{3-6}cycloalkyl,

(15) –C_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(16) -C_{2-6}alkenyl-C_{3-6}cycloalkyl,

(17) -C_{2-6}alkenyl-C_{2-6}cycloheteroalkyl,

(18) –C_{2-6}alkenyl-aryl,

(19) -C_{2-6}alkenyl-heteroaryl,

(20) -C_{2-6}alkynyl-C_{3-6}cycloalkyl,

(21) -C_{2-6}alkynylC_{2-6}cycloheteroalkyl,

(22) -C_{2-6}alkynyl-aryl,

(23) -C_{2-6}alkynyl–heteroaryl,

(24) -OH,

(25) -$(CH_2)_p$-O-C_{1-6}alkyl,

(26) -$(CH_2)_p$ -O-C_{2-6}alkenyl,

(27) -$(CH_2)_p$ -O-C_{2-6}alkynyl,

(28) –$(CH_2)_p$ -O-C_{3-6}cycloalkyl,

(29) –$(CH_2)_p$ -O-C_{2-6}cycloheteroalkyl,

(30) –$(CH_2)_p$ -O-aryl,

(31) –$(CH_2)_p$ -O-heteroaryl,

(32) -OC_{1-6}alkyl-C_{3-6}cycloalkyl,

(33) -OC_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(34) -OC_{1-6}alkyl-aryl,

(35) -OC_{1-6}alkyl-heteroaryl,

(36) -$S(O)_rR^h$,

(37) -C_{1-6}alkyl-$S(O)_rR^h$,

(38) -$N(R^k)_2$,

(39) -$C(O)R^L$, and

(40) –NR^kR^L,

wherein each R^a is unsubstituted or substituted with one to six substituents selected from halogen, CF_3, OH, C_{1-6}alkyl, and -OC_{1-6}alkyl;

each R^b is independently selected from the group consisting of:

(1) CN,

(2) oxo,

(3) halogen,

(4) –$S(O)_2C_{1-6}$alkyl,

(5) -C_{1-6}alkyl,

(6) -C_{1-6}alkenyl,

(7) -C_{2-6}alkynyl,

(8) -C_{3-6}cycloalkyl,

(9) -C_{2-6}cycloheteroalkyl,

(10) aryl,

(11) heteroaryl,

(12) –C_{1-6}alkyl-aryl,

(13) –C_{1-6}alkyl-heteroaryl,

(14) –C_{1-6}alkyl-C_{3-6}cycloalkyl,

(15) –C_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(16) -C_{2-6}alkenyl-C_{3-6}cycloalkyl,

(17) -C_{2-6}alkenyl-C_{2-6}cycloheteroalkyl,

(18) –C_{2-6}alkenyl-aryl,

(19) -C_{2-6}alkenyl-heteroaryl,

(20) -C_{2-6}alkynyl-C_{3-6}cycloalkyl,

(21) -C_{2-6}alkynyl-C_{2-6}cycloheteroalkyl,

(22) -C_{2-6}alkynyl-aryl,

(23) -C_{2-6}alkynyl–heteroaryl,

(24) -OH,

(25) -$(CH_2)_q$-O-C_{1-6}alkyl,

(26) -$(CH_2)_q$-O-C_{2-6}alkenyl,

(27) -$(CH_2)_q$ -O-C_{2-6}alkynyl,

(28) –$(CH_2)_q$ -O-C_{3-6}cycloalkyl,

(29) –$(CH_2)_q$ -O-C_{2-6}cycloheteroalkyl,

(30) –$(CH_2)_q$ -O-aryl,

(31) –$(CH_2)_q$ -O-heteroaryl,

(32) -OC_{1-6}alkyl-C_{3-6}cycloalkyl,

(33) -OC_{1-6}alkyl-C_{2-6}cycloheteroalkyl,

(34) -OC_{1-6}alkyl-aryl,

(35) -OC_{1-6}alkyl-heteroaryl,

(36) -$S(O)_rR^i$,

(37) -C_{1-6}alkyl-$S(O)_rR^i$,

(38) -$N(R^k)_2$,

(39) -C(O)R^L, and

(40) –NR^kR^L,

wherein each R^b is unsubstituted or substituted with one to six substituents selected from halogen, CF_3, OCF_3, CN, CH_2CF_3, CF_2CH_3, -$C_{1\text{-}6}$alkyl, and -$OC_{1\text{-}6}$alkyl;

R^c is selected from:

(1) -$C_{1\text{-}6}$alkyl,

(2) OH,

(3) halogen, and

(4) -$OC_{1\text{-}6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^d is selected from:

(1) -$C_{1\text{-}6}$alkyl,

(2) OH,

(3) halogen, and

(4) -$OC_{1\text{-}6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^e is selected from:

(1) hydrogen, and

(2) $C_{1\text{-}6}$alkyl;

R^f is selected from:

(1) -$C_{1\text{-}6}$alkyl,

(2) OH,

(3) halogen, and

(4) -$OC_{1\text{-}6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^g is selected from:

(1) -$C_{1\text{-}6}$alkyl,

(2) OH,

(3) halogen, and

(4) -$OC_{1\text{-}6}$alkyl,

wherein alkyl is unsubstituted or substituted with one to three halogens;

R^h is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{3-6}cycloalkyl,

(4) aryl, and

(5) heteroaryl;

R^i is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{3-6}cycloalkyl,

(4) aryl, and

(5) heteroaryl;

R^j is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{3-6}alkenyl,

(4) C_{3-6}alkynyl,

(5) C_{3-6}cycloalkyl,

(6) C_{2-5}cycloheteroalkyl,

(7) aryl, and

(8) heteroaryl;

R^k is selected from:

(1) hydrogen, and

(2) C_{1-6}alkyl;

R^L is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{3-6}cycloalkyl,

(4) aryl, and

(5) heteroaryl;

m is independently selected from 0, 1 and 2;

n is independently selected from 2, 3, 4, 5 and 6;

p is independently selected from 0, 1, 2 and 3;

q is independently selected from 0, 1, 2 and 3;

r is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2, 3, 4, 5, and 6; and

t is independently selected from 0, 1, 2, 3, 4, 5, and 6.

The compounds of structural formula I, and examples thereof, are inhibitors of $Na_v1.8$ sodium ion channel activity (or $Na_v1.8$ inhibitors) and may be useful in the treatment and prevention of diseases, disorders and conditions mediated by $Na_v1.8$ sodium ion channel activity, such as nociception, osteoarthritis, peripheral neuropathy, inherited erythromelalgia, multiple sclerosis, asthma, itch, atopy, allergic or contact dermatitis, renal failure, cholestasis, pruritus, acute itch, chronic itch, migraine, neurodegeneration following ischemia, epilepsy, pain, inflammatory pain, spontaneous pain, acute pain, acute pain due to fractures, musculoskeletal damage, pancreatitis and renal colic, peri-operative pain, post-operative pain, neuropathic pain, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, sciatica, pain caused by 2° or 3° burn injury, optic neuritis, pain resulting from cancer and chemotherapy, chronic pelvic pain, pain syndromes, and complex regional pain syndromes. In one example,

the condition, disease or disorder is a pain disorder, an acute pain disorder or chronic pain disorder. In another example, the condition, disease or disorder is an acute pain disorder.

Also disclosed are pharmaceutical compositions comprising the compounds of the present of structural formula I and a pharmaceutically acceptable carrier. In another aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Further disclosed are methods for the treatment, management, prevention, alleviation, amelioration, suppression or control of disorders, diseases, and conditions that may be responsive to inhibition of $Na_v1.8$ sodium ion channel activity in a subject in need thereof by administering the presently disclosed compounds and pharmaceutical compositions.

Further disclosed is the use of compounds of structural formula I for manufacture of a medicament useful in treating diseases, disorders and conditions that may be responsive to the inhibition of $Na_v1.8$ sodium ion channel activity. In another aspect, there is provided use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a disorder, condition, or disease that is responsive to the inhibition of $Na_v1.8$ channel activity in a mammal in need thereof.

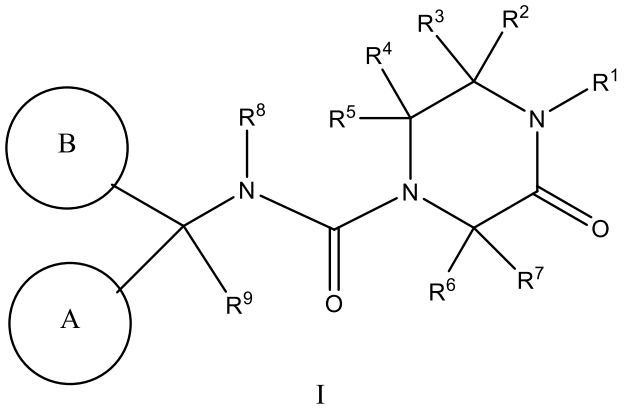
In another aspect, there is provided use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, prevention or control of a pain disorder, a cough disorder, an acute itch disorder or chronic itch disorder.

In another aspect, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

Also disclosed is the treatment or prevention of these diseases, disorders and conditions by administering the disclosed compounds in combination with a therapeutically effective amount of another agent that may be useful to treat the disease, disorder and condition. Further described are processes for preparing the compounds of this disclosure.

DETAILED DESCRIPTION OF THE INVENTION

Provided arenovel compounds of structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

one of A and B is independently selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^a, and

the other of A and B is independently selected from the group consisting of: