M4 ACTIVATORS/MODULATORS AND USES THEREOF

FIELD

[0001] The present disclosure generally relates to novel pyridine azaspiro compounds which are agonists/activators/modulators of the muscarinic M4 receptor and are useful in the treatment of M4-mediated diseases and disorders, but not limited to schizophrenia, Alzheimer's disease, dementia related psychosis, dementia with Lewy Bodies, Parkinson's disease and related memory and executive dysfunction, bipolar disorder, agitation, and psychosis associated therewith.

BACKGROUND

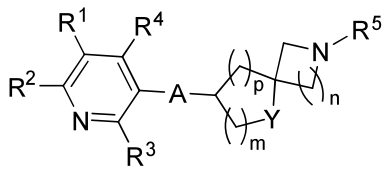
[0002] Patients with Schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, depression and various other neurological/neurodegenerative diseases frequently suffer from behavioral and cognitive impairments resulting in debilitating disruption to their daily lives. Over the years, many pharmacological treatments have been discovered that provide some improvement in behavior and cognitive function. However, the improvement is modest at best, and as is often the case, the underlying dose-limiting adverse effects associated with these treatments, including extrapyramidal and metabolic side-effects, lead to partial responsiveness, and non-compliance.

[0003] The muscarinic acetylcholine receptor (mAChR) is a viable mechanism for treating such diseases. There are five mAChR subtypes (M1-M5) that have been identified and are part of the G protein-coupled receptor (GPCR) superfamily. These subtypes are distributed widely throughout the periphery and the central nervous system (CNS), with the M1 and M4 subtypes being predominantly expressed in the CNS. The M4 agonist HTL0016878 being developed for the treatment of major symptoms of Alzheimer's Disease entered into a Phase 2 clinical study.

[0004] Thus, a need exists for agonists of the muscarinic M4 receptors f to treat M4-mediated diseases and disorders such as Parkinson's Disease, Schizophrenia, Alzheimer's Disease and others described herein.

SUMMARY

[0004a] Provided herein are compounds having a structure of Formula (I):



(I),

or a pharmaceutically acceptable salt of the compound,

wherein:

A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and optionally substituted with 1 to 3 substituents independently selected from halogen, OH, and C_{1-3}alkyl;

Y is a bond, O, S, CH_2, CHF, CF_2, or C(OH)H;

m is 1 or 2;

n is 1 or 2;

p is 1 or 2;

R^1 is H, halogen, CN, OH, –N(R^6)(R^7), C_{1-6}alkyl, C_{2-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -$[O]_{0-1}$-C_{3-6}cycloalkyl, -$[O]_{0-1}$-C_{6-10}aryl, -$[O]_{0-1}$-4-8 membered heterocycle or -$[O]_{0-1}$-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -$[O]_{0-1}$-C_{3-6}cycloalkyl, -$[O]_{0-1}$-C_{6-10}aryl, -$[O]_{0-1}$-4-8 membered heterocycle,-$[O]_{0-1}$-5-10 membered heteroaryl, -NH-C_{3-6}cycloalkyl, -NH-C_{6-10}aryl, -NH-4-8 membered heterocycle, -NH-5-10 membered heteroaryl, -N(C_{1-6}alkyl)-C_{3-6}cycloalkyl, -N(C_{1-6}alkyl)-C_{6-10}aryl, -N(C_{1-6}alkyl)-4-8 membered heterocycle, or -N(C_{1-6}alkyl)-5-10 membered heteroaryl, R^1 is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, CN, OH, =O, SO_2, and C_{1-3}alkyl,

R^2 is H, halogen, CN, OH, –N(R^6)(R^7), C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{2-6}heteroalkyl, C_{3-6}cycloalkyl, or 4-8 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S;

R^3 is halogen, CN, OH, –N(R^6)(R^7), C_{1-6}alkyl, C_{2-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -$[O]_{0-1}$-C_{3-6}cycloalkyl, -$[O]_{0-1}$-C_{6-10}aryl, -$[O]_{0-1}$-4-8 membered heterocycle, or -$[O]_{0-1}$-5-10 membered heteroaryl, -NH-C_{3-6}cycloalkyl, -NH-C_{6-10}aryl, -NH-4-8 membered heterocycle, -NH-5-10 membered heteroaryl, -N(C_{1-6}alkyl)-C_{3-6}cycloalkyl, -N(C_{1-6}alkyl)-C_{6-10}aryl, -N(C_{1-6}alkyl)-4-8 membered heterocycle, or -N(C_{1-6}alkyl)-5-10 membered heteroaryl, wherein the heterocycle and heteroaryl each comprises 1, 2, or 3 ring heteroatoms selected from N, O, and S, and the C_{3-6}cycloalkyl, -C_{6-10}aryl, 4-8 membered heterocycle, or 5-10 membered heteroaryl is substituted with 0, 1, 2, or 3 R^{3a} substituents;

each R^{3a} is independently selected from halogen, CN, OH, =O, =N(C_{1-3}alkly), SO_2, C_{1-6}alkyl, C_{2-10}alkene, C_{1-6}hydroxyalkyl , C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylene-O-C_{1-6}alkyl, C_{0-6}alkylene-NH_2, C_{0-6}alkylene-NH(C_{1-6}alkyl), C_{0-6}alkylene-N(C_{1-6}alkyl)$_2$, -S-C_{1-6}alkyl, C_{0-6}alkylene-SO_2C_{1-6}alkyl, C_{0-6}alkylene-C(O)NH_2, C_{0-6}alkylene-C(O)NH(C_{1-6}alkyl), C_{0-6}alkylene-C(O)N(C_{1-6}alkyl)$_2$, C_{0-6}alkylene-NHC(O)C_{1-6}alkyl, C_{0-6}alkylene-COOH, C_{0-6}alkylene-C_{3-6}cycloalkyl, C_{1-6}alkylene-O-C_{1-6}alklyeneSi(C_{1-3}alkyl)$_3$, and C_{0-6}alkylene-3-6 membered heterocycle comprising 1, 2, or 3 heteroatoms selected from N, O, and S;

R^4 is H, halogen, CN, or OH;

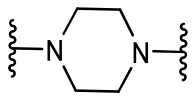
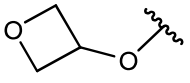
R^5 is -CO_2-Z, or a bioisostere thereof;

each R^6 and R^7 is independently H, C_{1-6}alkyl, C(O)-C_{1-6}alkyl, spiro or bicyclic C_{8-14}cycloalkyl, 8-14 membered heterocycle comprising 1, 2, or 3 ring heteroatoms selected from N, O, and S, and when R^6 or R^7 is other than H, it can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, CN, =O, SO_2, OH, C_{0-6}alkylene-NH_2, C_{0-6}alkylene-NH(C_{1-6}alkyl), C_{0-6}alkylene-N(C_{1-6}alkyl)$_2$, C_{0-6}alkylene-SO_2C_{1-6}alkyl, C_{1-6}alkyl and C_{1-6}alkoxy, or

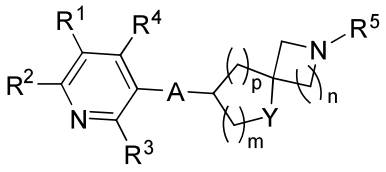
R^6 and R^7, together with the nitrogen to which they are attached, form a 4-10 membered heterocycle comprising 0-2 additional ring heteroatoms independently selected from N, O, and S; and

Z is C_{1-7}alkyl, C_{1-7}haloalkyl, C_{3-6}cycloalkyl, or C_{2-6}alkyne, and Z is optionally substituted with C_{1-6}alkoxy

or C_{3-6}cycloalkyl;

with the proviso that when R^1, R^2, and R^4 are each H, Y is CH_2, m, n, and p are each 1, A is , and R^3 is trifluoroethoxy, trifluoromethoxy, difluoromethoxy, methoxy, or , then R^5 is not $CO_2CH_2CH_3$

[0005] Provided herein are compounds having a structure of Formula (I), or an *N*-oxide thereof, or a pharmaceutically acceptable salt of the compound or the *N*-oxide thereof:


(I),

wherein A is a 6-8 membered heterocycle comprising 1 or 2 ring nitrogen atoms and optionally substituted with 1 to 3 C_{1-3}alkyl groups; Y is a bond, S, CH_2, CHF, CF_2, or C(OH)H; m is 1 or 2; n is 1 or 2; p is 1 or 2; R^1 is H, halogen, CN, OH, –N(R^6)(R^7), C_{1-6}alkyl, C_{2-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -[O]$_{0-1}$-C_{3-6}cycloalkyl, -[O]$_{0-1}$-C_{6-10}aryl, -[O]$_{0-1}$-4-8 membered heterocycle, -[O]$_{0-1}$-5-10 membered heteroaryl, -NH-C_{3-6}cycloalkyl, -NH-C_{6-}