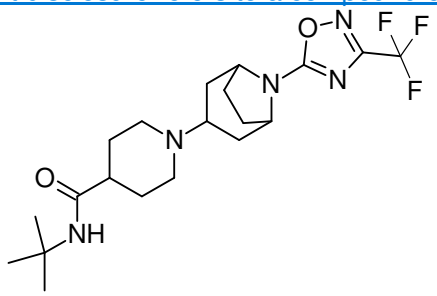
common in cancer both as a result of the disease or a side effect of chemotherapy. Activation of muscarinic receptors has been shown to be analgesic across a number of pain states through the activation of receptors in the spinal cord and higher pain centres in the brain. Increasing endogenous levels of acetylcholine through acetylcholinesterase inhibitors, direct activation of muscarinic receptors with agonists or allosteric modulators has been shown to have analgesic activity. In contrast blockade of muscarinic receptors with antagonists or using knockout mice increases pain sensitivity. Evidence for the role of the M_1 receptor in pain is reviewed by D. F. Fiorino and M. Garcia-Guzman, 2012.

More recently, a small number of compounds have been identified which display improved selectivity for the M_1 mAChR subtype over the peripherally expressed mAChR subtypes (Bridges et al., 2008 Bioorg Med Chem Lett; Johnson et al., 2010 Bioorg Med Chem Lett; Budzik et al., 2010 ACS Med Chem Lett). Despite increased levels of selectivity versus the M_3 mAChR subtype, some of these compounds retain significant agonist activity at both this subtype and the M_2 mAChR subtype. Herein we describe a series of compounds which unexpectedly display high levels of selectivity for the M_1 and/or M_4 mAChR over the M_2 and M_3 receptor subtypes.

Summary

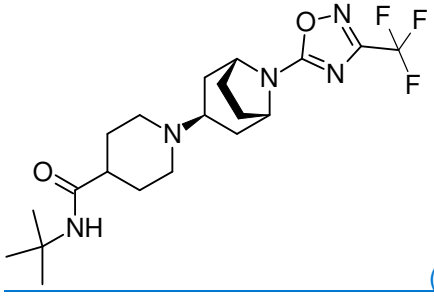
In a first aspect, the present disclosure refers to a compound of formula (1):



(1);

or a salt thereof.

In a second aspect, the present disclosure refers to a compound of formula (2):



(2).

In one aspect, the present disclosure refers to a salt of the compound as disclosed herein.

In another aspect, the present disclosure refers to a pharmaceutically acceptable salt of the compound as disclosed herein.

In another aspect, the present disclosure refers to an acid addition salt of the compound as disclosed herein.

In another aspect, the present disclosure refers to a hydrochloride salt of the compound as disclosed herein.

In another aspect, the present disclosure refers to a monohydrochloride salt of the compound as disclosed herein.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound of the first aspect, or a salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound of the second aspect, and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure refers to use of the compound of the first aspect, or a salt thereof, in the manufacture of a medicament for treating a disorder selected from a cognitive disorder and a psychotic disorder in a subject.

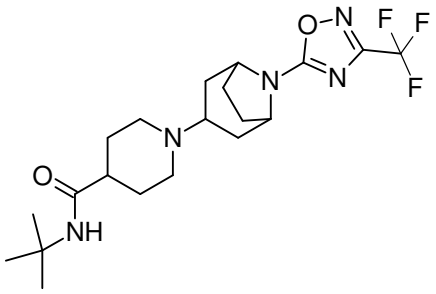
In another aspect, the present disclosure refers to use of the compound according to the second aspect in the manufacture of a medicament for treating a disorder selected from a cognitive disorder and a psychotic disorder in a subject.

In yet another aspect, the present disclosure refers to use of the compound of the first aspect, or a salt thereof, in the manufacture of a medicament for treating or lessening the severity of acute pain, chronic pain, neuropathic pain, or inflammatory pain in a subject.

The Invention

The present invention provides compounds having activity as muscarinic M_1 and/or M_4 receptor agonists. More particularly, the invention provides compounds that exhibit selectivity for the M_1 and/or M_4 receptor relative to the M_2 and M_3 receptor subtypes.

Accordingly, the invention provides a compound of the formula (1):



(1);

or a salt thereof.

The invention further provides a compound of the formula (1a):