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Identification of *N*-substituted 8-azatetrahydroquinolone derivatives as selective and orally active M_1 and M_4 muscarinic acetylcholine receptors agonists

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ABSTRACT

We designed and synthesized *N*-substituted 8-azatetrahydroquinolone derivatives as selective M_1 and M_4 muscarinic acetylcholine receptors agonists. Optimization of selected derivatives led to the discovery of compound **7** as a highly potent M_1 and M_4 agonist with weak hERG inhibition. Oral administration of compound **7** improved psychosis-like behavior in rats.

Schizophrenia is a complex psychiatric disorder characterized by three major types of symptoms: (i) positive symptoms (e.g., hallucination, delusion, and excitement), (ii) negative symptoms (e.g., flattened affect, apathy, and social withdrawal), and (iii) cognitive impairment symptoms (e.g., deficit in working memory, executive function, attentional processing, and memory).[1] Although dopamine D_2 antagonists are currently used to treat schizophrenia, particularly its positive symptoms, there is an ongoing need for alternative treatments, because of the extrapyramidal side effects (EPS)[2] of D_2 antagonists and the high number of non-responders.[3]

Many of the important central actions of acetylcholine (ACh) are mediated by the muscarinic ACh receptors (mAChRs).[4] To date, five mAChR subtypes (M_1–M_5) have been identified and are considered to play important roles in the peripheral and central nervous systems (CNS).[5] M_1 and M_4 mAChR subtypes are the most heavily expressed in CNS and represent attractive therapeutic targets for cognitive impairment, Alzheimer's disease and schizophrenia.[6] In fact, clinical trials with xanomeline (Fig. 1), an M_1 and M_4 mAChR preferring orthosteric agonist, have demonstrated the efficacy of this agent as both an antipsychotic and a cognition-enhancing agent.[7] Data from mAChR-knockout mice have also suggested that selective M_1 mAChR agonists would be beneficial for psychosis and cognitive dysfunction,[8] whereas M_4 mAChR agonists would be useful for the treatment of schizophrenia.[9] This proposal is further supported by recent studies showing that M_4 mAChR modulates the dynamics of cholinergic and dopaminergic neurotransmission and that loss of M_4 mAChR function results in dopamine hyperfunction.[10] In addition, M_1 mAChR agonistic activity of *N*-desmethylclozapine, a major metabolite of clozapine, suggests that M_1 mAChR may also play an important role in the antipsychotic effect of clozapine.[11] Put together, these findings suggest that selective activators of M_1 and M_4 mAChRs may provide a novel treatment for schizophrenia.

Despite the promising results shown by xanomeline in clinical trials for Alzheimer's disease and schizophrenia, there are concerns over its peripheral side effects, especially gastrointestinal (GI) distress, which may ultimately limit the therapeutic use of this agent. The adverse effect of xanomeline on GI is thought to be primarily due to activation of the peripheral M_3 mAChR. Indeed, identification of highly selective M_1 and M_4 mAChRs agonists is challenging, because of the high sequence homology and conservation of the orthosteric ACh binding site among mAChR subtypes. However, the recent discovery of AC-42 as an allosteric M_1 mAChR agonist led to the identification of several other selective allosteric ligands for the M_1 mAChR.[12] Using the M_4 mAChR positive allosteric modulator (PAM) LY2033298, Christopoulos and co-workers showed that M_4 mAChR possesses an allosteric binding site.[13] This led to

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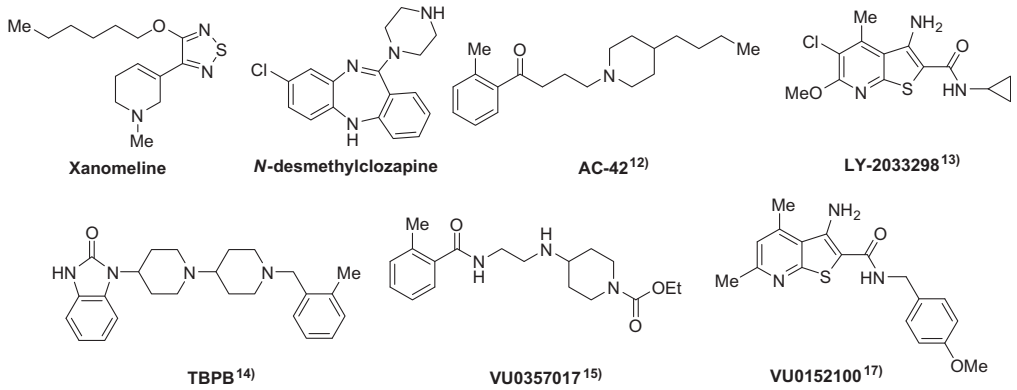


Figure 1. Structures of various mAChR agonists and modulators.

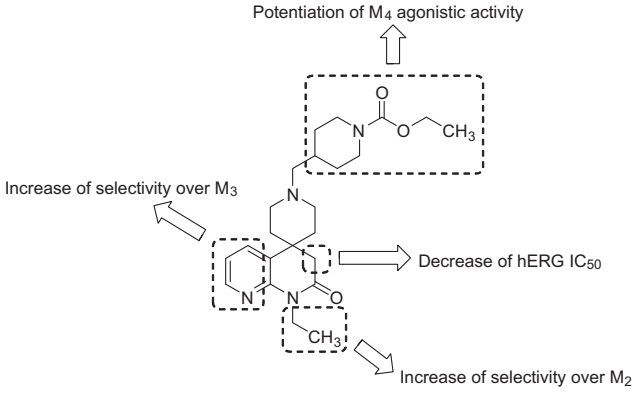


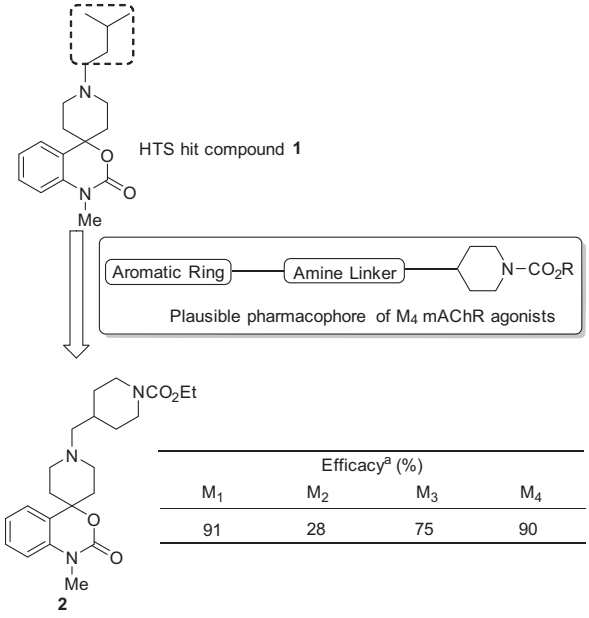
Figure 2. Summary of our SAR approach.

the identification of a number of M_1 and M_4 mAChRs allosteric agonists and/or modulators (Fig. 1).[12] Especially, reports on the centrally active modulators TBPB,[14] VU0357017[15] (M_1 mAChR agonist) VU0456940[16] (M_1 mAChR PAM) and VU0152100[17] (M_4 mAChR PAM) indicate that selective activation/modulation of central M_1 and M_4 mAChRs is an attractive strategy for identifying novel compounds for the treatment of CNS diseases. So far, only few compounds with selective activation of both M_1 and M_4 mAChRs have been reported.[18]

Here, we describe the design, synthesis and evaluation of *N*-substituted 8-azatetrahydroquinolone derivatives as selective M_1 and M_4 mAChRs agonists (Fig. 2).

In our search for compounds with M_4 mAChR agonistic activity, we found the 4-spirobenzoxadinone scaffold **1** as a promising lead compound. A search in the recent patent literature for M_4 mAChR agonists revealed that the *N*-carboxypiperidine unit is a common structure among M_4 mAChR agonists. To potentiate compound **1** agonistic activity for M_4 mAChR, we replaced its isobutyl unit with the *N*-carbethoxypiperidine unit. Although the obtained compound **2** showed potent M_1 and M_4 mAChRs agonistic activity, it also activated the M_3 mAChR (Fig. 3).[19]

In a further attempt to improve bioactivity of compound **2**, a series of related compounds were synthesized and their structure-activity relationships (SARs) were evaluated. The results of this evaluation are summarized in Table 1. Replacement of the benzene unit in **2** by a pyridine unit to avoid the formation of an aniline structure resulted in a significant decrease in M_3 mAChR agonistic activity (7% at 1 μM and 11% at 10 μM) (compound **3**). On the other hand, removal of the methyl group from the nitrogen atom at the 1-position increased M_1 and M_4 mAChRs agonistic activity, but deteriorated



	Efficacy[a] (%)			
M_1	M_2	M_3	M_4
91	28	75	90

Figure 3. Using the common pharmacophore of M_4 mAChR agonists in the 4-spirobenzoxadinone scaffold of compound **1** led to compound **2**. [a] Maximum efficacy of each mAChR subtypes was defined as 100%. Concentration of the test compound was 10 μM.

hERG inhibition[20] (compound **4**). Replacement of the carbamate unit by an amide unit led to a decrease in M_2 and M_3 mAChRs agonistic activity, although this modification improved hERG inhibition (IC_{50}: 2.8 μM) (compound **5**). Due to its weak hERG inhibition, the 8-azatetrahydroquinolone **5** was finally selected for further optimization. Using the result obtained from removal of the methyl group at the 1-position (compound **4**), we introduced a methyl (compound **6**), an ethyl (compound **7**), or an *n*-propyl (compound **8**) group to compound **5**. Among the resulting compounds, compound **7** showed potent activation of M_1 (93% at 10 μM) and M_4 (125% at 10 μM) mAChRs with weak to negligible activation of M_2 (27% at 10 μM), M_3, (3% at 10 μM) and M_5 (3% at 10 μM) mAChRs. Compound **7** also exhibited weak hERG inhibition (IC_{50}: 2.9 μM). On the other hand, the *n*-propyl substituted compound **8** displayed increased M_2 mAChR agonistic activity (54% at 10 μM) and strong hERG inhibition (IC_{50}: 0.67 μM).

Finally, we evaluated the antipsychotic and off-target effects of the synthesized compounds both *in vitro* and *in vivo*. Oral administration of compounds **3**–**7** significantly reversed methamphetamine(METH)-induced hyperlocomotion in rats (Table 1).[21] Based