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The discovery of VU0486846: steep SAR from a series of M_1 PAMs based on a novel benzomorpholine core

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ABSTRACT

This letter describes the chemical optimization of a new series of M_1 positive allosteric modulators (PAMs) based on a novel benzomorpholine core, developed via iterative parallel synthesis, and culminating in the highly utilized rodent *in vivo* tool compound, VU0486846 (**7**), devoid of adverse effect liability. This is the first report of the optimization campaign (SAR and DMPK profiling) that led to the discovery of VU0486846 and details all of the challenges faced in allosteric modulator programs (both steep and flat SAR, as well as subtle structural changes affecting CNS penetration and overall physiochemical and DMPK properties).

Introduction

M_1 (muscarinic acetylcholine receptor subtype 1) positive allosteric modulators (PAMs) represent an exciting therapeutic strategy to treat multiple domains of cognitive dysfunction in CNS disorders such as schizophrenia and Alzheimer's disease.[1–5] However, the great potential of this target has been hindered, originally by non-selective orthosteric ligands (**1**),[6] and then by potent ago-PAMs **2**–**5** (in cell lines (M_1 PAM EC_{50}s < 100 nM) and M_1 agomist potency <1 μM) and native tissues) that proved to be cognitive disrupting and proconvulsive due to over stimulation of the M_1 receptor (Fig. 1).[7–12] Recently, we disclosed the first M_1 PAM free from adverse events, VU6004256 (**6**),[13] and with robust efficacy in NMDA receptor 1 (NR1) knock-down mice.[14] With the goal of providing the community with an improved, and much needed, M_1 PAM *in vivo* tool compound, here we report on VU0486846 (**7**). PAM **7** (M_1 PAM EC_{50} ~250 nM for human and rat), based on a novel benzomorpholine core, is a significant structural departure within the M_1 PAM field that has proven to be a valuable rodent *in vivo* M_1 PAM tool compound, devoid of agonist activity in native systems, free from adverse effects and highly efficacious in multiple rodent cognition models.[15] Here, we describe for the first time the optimization campaign (SAR and DMPK profiles).

As briefly detailed in the initial disclosure of **7**,[15] we scaffold-hopped from the prototypical 6,6-fused ring system of **2** to a novel benzomorpholine core (as in **7**) wherein we simultaneously increased sp^3 character while bringing the Lewis basic oxygen of the quinolone into the 6,6-ring system. These modifications of the core also created a new stereogenic center, which, in the case of **7**, the (*R*)-enantiomer displayed enantiopreference.[15] Here, we will detail the synthesis, SAR, and DMPK profiles of a multi-dimensional optimization campaign within the benzomorpholine series that ultimately led to the discovery of **7**, an M_1 PAM with a balance of overall properties as a new *in vivo* tool compound, free from adverse effect liability.

The synthesis of diverse analogs **13** was straightforward and starting materials were readily available from commercial sources (see Scheme 1).[15] Ethyl 2,3-dibromopropanoate **8** was condensed with various substituted 2-aminophenols to provide the racemic heterocyclic cores **9** in 52–80% yields. Alkylation with substituted

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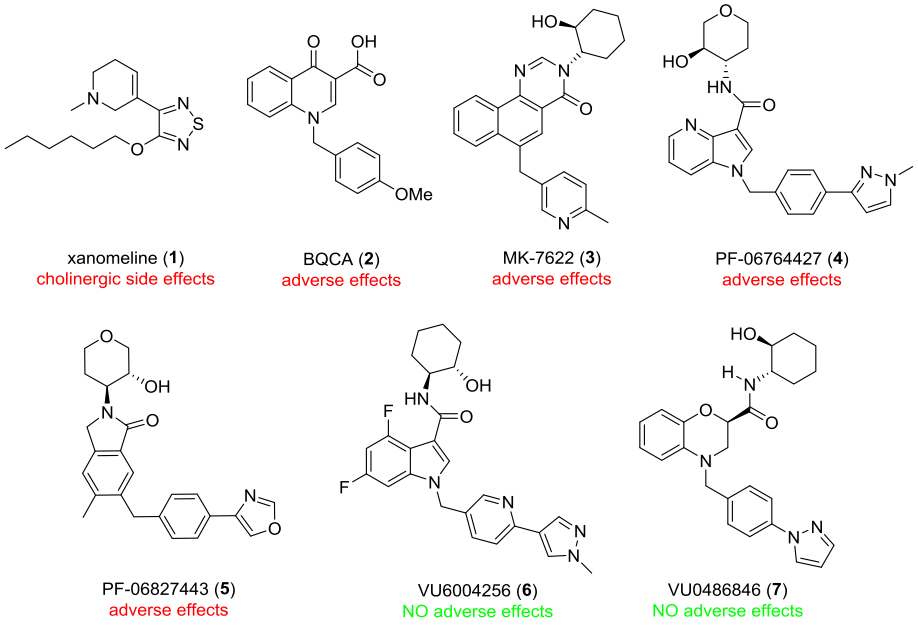
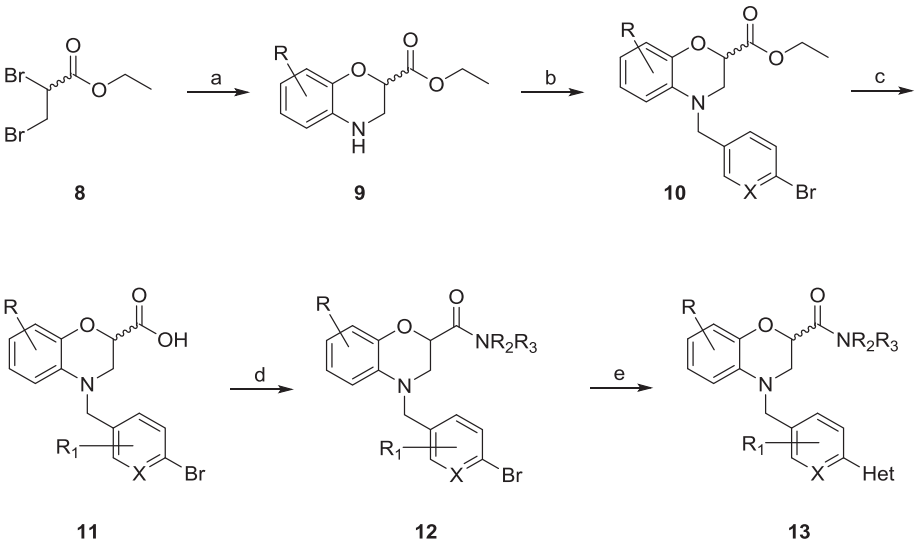


Fig. 1. Structures representative of a classical 'M$_1$ agonist' (**1**), that engenders cholinergic side effects, M$_1$ ago-PAMs **2**–**5**, that are M$_1$ agonists in native systems and engender adverse effects, and M$_1$ PAMs **6** and **7**, which are devoid of adverse effects.



Scheme 1. Synthesis of M$_1$ PAM analogs **13**.[a] [a]Reagents and conditions: (a) substituted 2-aminophenols, CH_3CN, K_2CO_3, 60 °C, 52–80%; (b) 4-bromoAr(Het)bromide, K_2CO_3, CH_3CN, 80 °C, 66–74%; (c) KOH, THF/H_2O (2:1), rt, 95–98%; (d) HNR_2R_3, HATU, DIEA, DMF, rt, 66–80%; (e) Het-NH, (1*S*,2*S*)-N^1,N^2-dimethylcyclohexane-1,2-diamine, CuI, K_3PO_4, dioxane, rt, 35–50%, or Ar(Het)-$B(OH)_2$, 5 mol% $Pd(PPh_3)_4$, THF:H_2O, 45 °C, 54–86%.

4-bromo benzyl bromides or the analogous heterocyclic congeners proceeded smoothly delivering **10** inyields ranging from 66 to 74%. A quantitative hydrolysis of the ester gave **11,** which then underwent a HATU-mediated amide coupling with diverse primary and secondary amines to provide derivatives **12** as mixtures of diastereomers. Finally, either a copper-mediated coupling with heterocycles, or a Suzuki coupling protocol, produced the putative M$_1$ PAMs **13** in 35–86% yield. To facilitate more rapid SAR, we initially screened analogs **13** as racemates, and used the racemic version of **7**, **14** (VU0484043, M$_1$ EC_{50} = 0.92 μM, pEC_{50} = 6.10 ± 0.13, ACh Max 77 ± 7; M$_2$-M$_5$ EC_{50}s > 30 μM) as a reference compound.[15]

Initial SAR around **14** with analogs **15**–**20** showed overall 'flat' SAR in terms of M$_1$ PAM potency, but significant impact on physiochemical and DMPK properties. Of the structural changes in Fig. 2, introduction of a quaternary carbon at the chiral center, as in **16**, led to a diminution in potency (M$_1$ EC_{50} = 7.3 μM, 61% ACh Max); however, all other modifications were within 2- to 3-fold of **14**. A major finding was that the *des*-oxy tetrahydroisoquinoline analog **15** was essentially equipotent to **14**, suggesting that the key intramolecular hydrogen bond (IMHB) of PAMs **4**–**7**[7–14] may not be a key tenet in this new series (however, this will be disclosed in a subsequent publication).[16] Other changes, represented by **17**–**20**, while active as M$_1$ PAMs, negatively impacted plasma protein binding (f_u < 0.001) and/or decreased CNS penetration (brain/plasma K_ps < 0.05) relative to **14** (f_u = 0.11, rat K_p = 0.17, mouse K_p = 0.7).

Based on these data, we next explored the 'fluorine walk', a strategy that has been highly successful in allosteric modulator optimization, particularly for other M$_1$ PAM scaffolds.[17,18] This exercise led to intriguing SAR (Fig. 3) relative to **14**. While incorpo-