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Isatin replacements applied to the highly selective, muscarinic M_1 PAM ML137: Continued optimization of an MLPCN probe molecule

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ABSTRACT

This Letter describes the continued optimization of an MLPCN probe molecule (ML137) with a focused effort on the replacement/modification of the isatin moiety present in this highly selective M_1 PAM. A diverse range of structures were validated as viable replacements for the isatin, many of which engendered sizeable improvements in their ability to enhance the potency and efficacy of acetylcholine when compared to ML137. Muscarinic receptor subtype selectivity for the M_1 receptor was also maintained.

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Acetylcholine (ACh) is a critical neurotransmitter influencing a broad range of physiological processes both inside and outside of the central nervous system by binding to both nicotinic (nAChR) and muscarinic acetylcholine receptors (mAChR). The challenges associated with developing highly selective mAChR ligands interacting at the orthosteric binding site of ACh are most significantly impacted by the high level of receptor homology displayed across the five mAChR subtypes (M_1 through M_5).[1] Despite this seemingly insurmountable roadblock towards the production of truly selective muscarinic agonists, a great deal of information has been learned from M_{1-5} KO mice[2] and the testing of less-than-selective muscarinic agonists in preclinical and clinical experiments. The clinical promise for dual, or potentially individual, M_1/M_4 mAChR activators in treating aspects of both Alzheimer's disease and schizophrenia has been demonstrated with the orthosteric agonist xanomeline;[3,4] however, this clinical candidate's limited selectivity (particularly against M_3) ultimately caused its withdrawal from further clinical trials irrespective of the encouraging positive outcomes. A new and exciting chapter in the search for selective/specific mAChR activators commenced with the identification of novel positive allosteric modulators (PAMs) and allosteric agonists through the use of functional high throughput screening (HTS) assays.[5] These next-generation ligands have the novel benefit of interacting at sites removed from the orthosteric binding site, where the potential for selective interactions with just one of the five mAChR is greatly enhanced. This revitalized interest in selectively activating the mAChRs has been very successful, providing a number of M_1 PAMs (BQCA,[6] ML137,[7] and ML169[8]), M_4 PAMs (ML108,[9] ML173,[10] ML253,[11] and ML293[12]) and M_5 PAMs (ML129,[13] and ML172[14]). Here we describe the continued structural exploration around the M_1 PAM, MLPCN probe molecule ML137.

Figure 1 shows the development of two M_5 PAMs and one M_1 PAM from a common HTS lead, VU0119498, all of which share the isatin core in common. Although VU0119498 displayed PAM activity at the M_1, M_3, and M_5 mAChRs,[13] specific structural modifications resulted in highly preferring (ML129) or completely selective (ML172) M_5 PAMs and a highly selective M_1 PAM (ML137). The ability to dial in muscarinic receptor subtype selectivity was facilitated by the wide variety of commercially available

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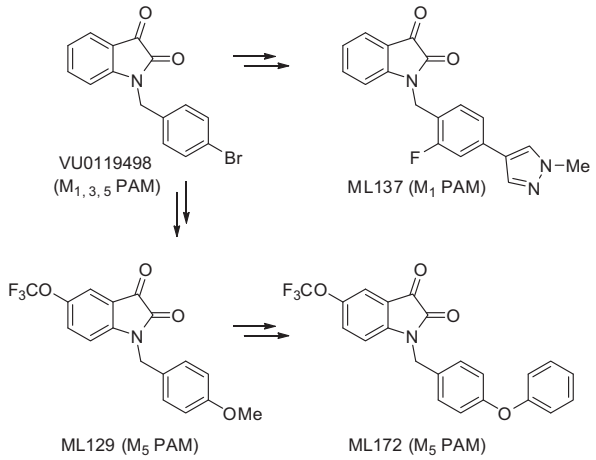


Figure 1. HTS lead VU0119498 parlayed into selective M_1 and M_5 PAMs.

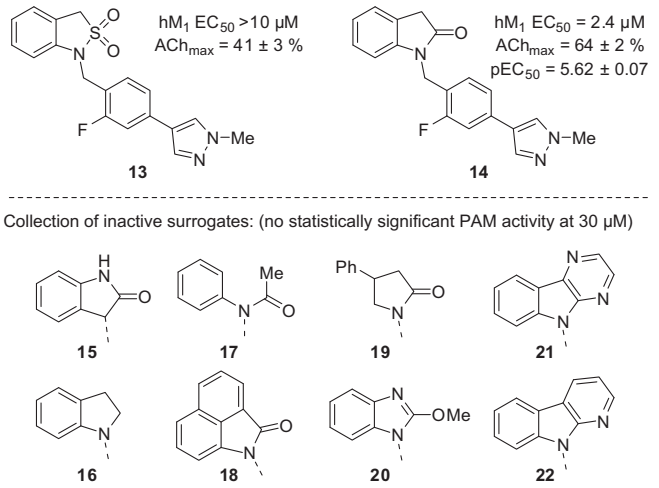


Figure 2. Rapid foray into isatin replacements while holding the benzyl pyrazole constant.

substituted isatins and the efficiency of analog preparation, clearly demonstrating that this scaffold can be very advantageous. However, it was also appreciated that the isatin motif has an established history of appearing in a wide range of medicinal chemistry targets across the full spectrum of potential clinical indications.[15] Additionally, HTS hits containing the isatin core are so frequent that the isatin scaffold has earned a position of notoriety in some measures of HTS promiscuity.[16] As such, it seemed reasonable to explore replacements, or modifications, to the isatin core in the context of ML129, ML137, and ML172.

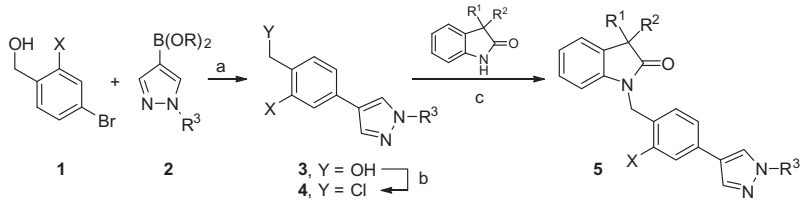
Our first efforts focused on a large and extensive library which thoroughly and rapidly explored small modifications to the isatin core employing commercially available benzyl, biphenyl and biaryl ethers similar to those found in ML129 and ML172. As is often the case with steep allosteric SAR,[5] this effort proved unfruitful (data and structures not shown). We then hypothesized that a more focused effort directed solely at replacing the isatin moiety, while retaining the exact biaryl from ML137, could be more productive. These analogs and the requisite phenylpyrazoles were prepared according to the general synthesis route appearing in Scheme 1.

Readily available 4-bromobenzyl alcohols **1** undergo Suzuki reactions with pyrazole boronic acids/esters **2** employing standard conditions and provided the biaryl benzyl alcohols **3**. Ghosez' reagent (1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine) in DCM smoothly converted the benzylic alcohol into the corresponding benzyl chloride **4**. With ample quantities of **4** in place, isatin or a variety of isatin replacements could be alkylated, employing a range of bases, to give analogs **5** and the majority of structures appearing in Figure 2 and Table 1. Alternative routes towards the preparation of these initial analogs can be seen in Schemes 2 and 3.

Scheme 2 depicts the alkylation of isatin with a 4-bromobenzyl bromide **6** using a carbonate base in acetonitrile to give N-benzylated isatins **7**. Next, a trifluoromethyl group was introduced at the ketone carbon employing the conditions of Shreeve, and co-workers,[17] to yield the aryl bromides **8**. A Suzuki reaction analogous to the first step in Scheme 1 could then provide analogs **9**, as well as a diverse range of alternative biaryls, simply by changing the boronate in the final step.

Scheme 3 shows the route used in the preparation of sultam **13** (See Fig. 2 for structure), which was necessary due to a lack of reactivity and selectivity (N vs C benzylation) associated with the desired parent sultam. Starting from commercially available benzylic amine **11** and sulfonyl chloride **10**, the linear sulfonamide **12** was prepared in 93% yield. The nitrogen-aryl bond was then formed using Cu(I) catalysis in degassed toluene to give the desired sultam **13**, in 59% yield.

Figure 2 shows the functional activity for two active analogs along with a host of unsuccessful isatin replacements (inactive at human M_1 (hM_1) up to a concentration of 30 μM). Although not as potent (EC_{50}) as their parent ML137 (hM_1 EC_{50} = 0.60 μM, ACh_{max} = 45 ± 3%, pEC_{50} = 6.22 ± 0.02),[18] both **13** and **14** produced comparable efficacy (% ACh_{max}) at the highest concentration tested of 30 μM and, more importantly, no longer contained the isatin core. Indolinone **14** appeared to be more promising than sultam **13** from activity and synthesis standpoints and so was explored further. While reduction of the isatin ketone was gratifyingly tolerated, attachment of the biaryl at the resultant methylene (as in **15**) or further reduction of the amide carbonyl to the indoline **16** was not tolerated. The overall planarity of the indolinone core appeared to be important for PAM activity since scission of the 5-membered lactam to give the *N*-acetyl amide **17** provided an inactive compound. However, annulation of a second aryl ring, as in **18**, proved detrimental to activity as well, despite maintaining a planar system. The remaining analogs in Figure 2 (**19–22**) attempted to mimic various heteroatom interactions potentially occurring with ML137 or **14**, but all retained no hM_1 PAM activity.



Scheme 1. Reagents and conditions: (a) $PdCl_2$(dppf)·DCM, Cs_2CO_3, THF/H_2O, 160 °C, 10 min; (b) Ghosez' reagent (1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine), DCM, rt, 15 h; (c) base (i.e. K_2CO_3, NaH, etc.), aprotic solvent (i.e. DCM, DMF, MeCN), 0 °C to rt.

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