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Potent and selective α_{1A} adrenoceptor partial agonists—Novel imidazole frameworks

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ABSTRACT

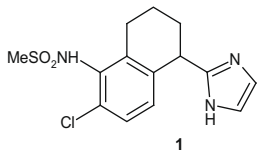
Novel imidazole frameworks have been identified as potent partial agonists of the α_{1A} adrenergic receptor, with good selectivity over the α_{1B}, α_{1D} and α_{2A} receptor sub-types. Nitrile **28** possessed attractive CNS drug-like properties with good membrane permeability and no P-pg mediated efflux. **28** also possessed excellent solubility, metabolic stability and wide ligand selectivity.

α_1-Adrenoceptors are members of the 7TM super family of G-protein-coupled receptors, and three subtypes of α_1-adrenoceptors have been cloned (α_{1A}, α_{1B}, α_{1D}), expressed and characterized.[1] Recent disclosures have suggested that selective partial agonists of the α_{1A} receptor may have clinical utility in the treatment of stress urinary incontinence (SUI).[2] In addition, α_{1A} partial agonists may have increased selectivity for SUI efficacy over undesired cardiovascular effects when compared to full α_{1A} agonists.[2] Recently, we described a novel series of 2-imidazole α_{1A} partial agonists with excellent selectivity over α_{1B}, α_{1D} and α_{2A} and attractive drug-like properties.[3] However, as part of our work on this mechanism, biology studies indicated that α_{1A} partial agonists impart their in vivo efficacy in models of SUI via a centrally mediated pathway,[4] rather than a direct effect on urethral smooth muscle. Compounds such as our initial lead compound **1** were shown to have poor BBB penetration, which was linked to high P-pg mediated efflux when assessed in MDCK MDR-1 cells. Further work was then undertaken to improve BBB penetration by reducing TPSA and compound **2** was identified (Fig. 1) which showed excellent BBB penetration.[4,5] As part of a multi-series approach to α_{1A} partial agonists, we then sought to discover further imidazole templates which could deliver potent and selective α_{1A} partial agonist activity with physicochemical properties aligned with good BBB penetration (low TPSA, low mwt, few hydrogen bonding groups), and ideally improved metabolic stability when compared to **2**. We now wish to report the results of that work in this Letter and the article following this one.

The initial medicinal chemistry strategy focused on simple templates linking an aryl ring to an imidazole in a variety of conformationally constrained systems **4–7** (Fig. 2).

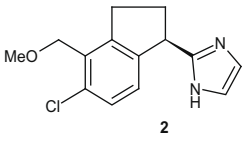
The α_{1A} pharmacology of these new templates was then compared to the original indanyl framework **3** (Table 1), and a key criteria for progression for new templates was a significant increase in activity over **3**.

The isomerised 2-indanyl 2-imidazole **4** showed weaker activity and was not taken further. In contrast, the tetrahydrobenzimidazole **5** showed encouraging α_{1A} activity with excellent selectivity when screened as a racemic mixture. Screening of single enantiomers **5a** and **5b** showed that both exhibited α_{1A} pharmacology but **5a** was slightly more potent. Absolute stereochemistry was not determined at this time. N-Alkylated imidazole structures **6** and **7** were particularly interesting as they lacked the N–H of most imidazole or imidazoline α-agonists.[6] The 5,5-system **6** showed good α_{1A} activity whereas the 6,5 template **7** had slightly reduced activity. The single enantiomers **6a** and **6b** showed a very different activity profile, with essentially all the α_{1A} pharmacology residing in enantiomer **6a**.



1

α_{1A} EC_{50} 43nM (61%)
Selective over α_{1B}, α_{1D}, α_{2A}
HLM Clint <7 μl/min/mg
MDCK MDR-1 7/29
Poor BBB penetration



2

α_{1A} EC_{50} 27nM (58%)
Selective over α_{1B}, α_{1D}, α_{2A}
HLM Clint 30 μl/min/mg
MDCK MDR-1 40/36
Good BBB penetration

Figure 1. Structures, pharmacology and ADME properties of imidazole α_{1A} partial agonists **1** and **2**.

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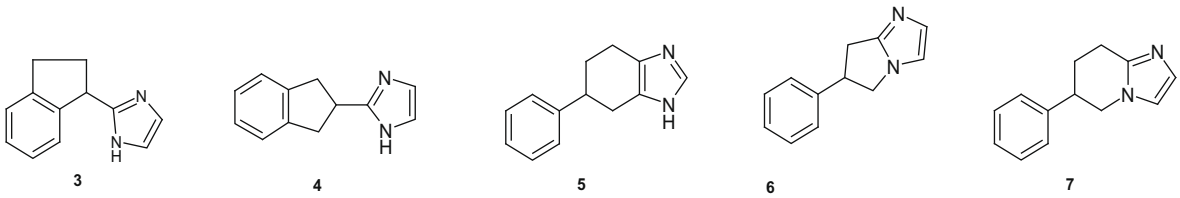
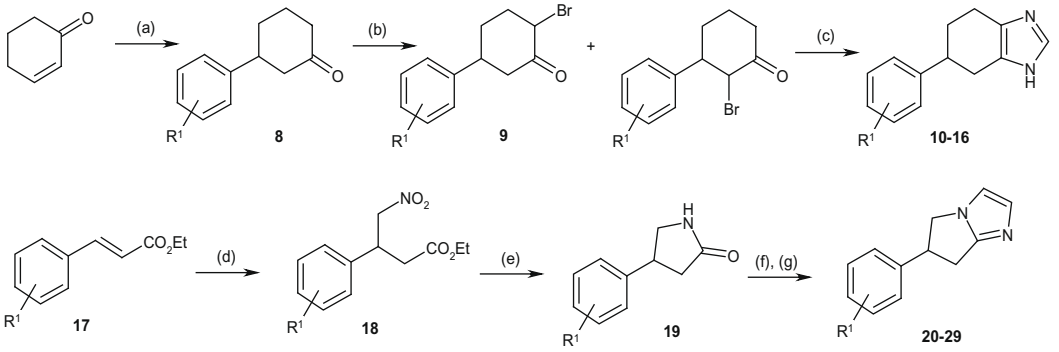


Figure 2. Structures of proposed new imidazole templates **4**–**7**.

Table 1
In vitro functional α_{1A}, α_{1B}, α_{1D} and α_{2A} agonist activity for compounds **3**–**7**

Compds	α_{1A} EC_{50} (nM)[a,b]	α_{1A} E_{max} (%)	α_{1B} EC_{50} (nM) (E_{max})[a,b]	α_{1D} EC_{50} (nM) (E_{max})[a,b]	α_{2A} EC_{50} (nM) (E_{max})[a,b]
3	473	54	>10,000	>10,000	NT
4	1650	26	>10,000	>10,000	>10,000
5	234	78	>10,000	>10,000	>10,000
5a	123	75	>10,000	>10,000	>10,000
5b	315	76	>10,000	>10,000	>10,000
6	83	80	>10,000	>10,000	>10,000
6a	73	74	>10,000	7360 (30%)	>10,000
6b	>10,000	25	>10,000	>10,000	>10,000
7	721	68	>10,000	>10,000	>10,000

NT denotes not tested.
[a] See Ref. 3 for description of assay conditions.
[b] Values are geometric means of at least three experiments.



Scheme 1. Reagents and conditions: (a) either (i) ArBr, Mg, CuI, TMS-Cl or (ii) $ArB(OH)_2$, cat. $Pd(OAc)_2$, cat. $SbCl_3$, AcOH, 50 °C; (b) NBS, Amberlyst-15, EtOAc, rt; (c) Formamidine acetate, Hunigs base, DMSO, 80 °C; (d) $MeNO_2$, DBU, 0 °C to rt; (e) either (i) RaNi, 100 psi H_2, 100 °C or (ii) $SnCl_2$, EtOAc, rt; (f) Me_3OBF_4, CH_2Cl_2, rt; (g) (i) $H_2NCH_2CH(OEt)_2$, HCl, EtOH, rt; (ii) HCl/dioxane, H_2O, 100 °C.

With two new templates **5** and **6** in hand, synthetic routes were devised which would give access to aryl-substituted analogues (Scheme 1). The tetrahydrobenzimidazoles were accessed via a three step route from cyclohexenone. Conjugate addition of either an aryl cuprate or aryl boronic acid gave the 3-aryl cyclohexanones **8**. Bromination with NBS proceeded in a non-selective fashion to give regioisomeric α-bromoketones **9**. These could not be separated and so were reacted as a crude mixture with formamidine acetate to afford the desired compounds **10**–**16**. Reactions (b) and (c) were poor yielding, but were sufficiently robust to allow initial SAR investigations to be carried out. The pyrrolo-imidazole series was accessed using an efficient four step procedure. Conjugate addition of nitromethane to the unsaturated esters **17** proceeded in high yield (80–100%), and was followed by reduction of nitro compounds **18** to the primary amines which underwent spontaneous cyclisation to the lactam **19**.[7] Conversion of the lactam to the cyclic imino-ether was effected with Meerweins reagent. This was followed by displacement with a glycine aldehyde equivalent, and cyclisation afforded the desired target compounds, which were then separated into the individual enantiomers by preparative chiral HPLC.

In silico modeling was also carried out, to increase our understanding of how **5** and **6** overlapped with the 1-indanyl 2-imidazole **3**. It was hoped this modeling would then guide substitution off the aryl ring of **5** and **6**. The equatorial conformation of **5** overlapped poorly with the highly constrained 1-indanyl template **3**. We then speculated that **5** could adopt an axial conformation with only a small energy penalty (0.8 kcal/mol),[8] and this overlapped much better, with both imidazole and aryl rings in close alignment (Fig. 3). This suggested that substitution in the 2-position of the aryl ring of **5** should overlap with the key methoxymethyl group of compound **2**. Similar modeling was carried out for the pyrrolo-imidazole framework **6**. In this case the alignment of the aromatic rings appeared to be less optimal (Fig. 3), however the modeling again suggested the 2-position to have the best overlap. A small range of analogues were then prepared to test these hypotheses. To rapidly assess potency, selectivity and drug-like properties, pharmacology and in vitro ADME data (log *D*, human liver microsome stability (HLM) and Pampa membrane permeability) was generated in parallel.

In the tetrahydrobenzimidazoles **10**–**16** we were pleased to see that a 2-substituent did give better α_{1A} potency (Table 2, examples