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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.

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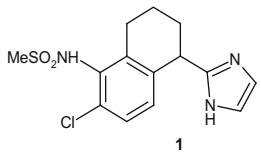
α_1-Adrenoceptors are members of the 7TM super family of G-protein-coupled receptors, and three subtypes of α_1-adrenoceptors have been cloned (α_{1A}, α_{1B}, α_{1D}), expressed and characterized.[1] Recent disclosures have suggested that selective partial agonists of the α_{1A} receptor may have clinical 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).

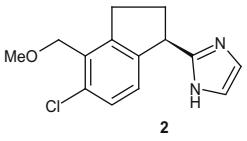
The α_{1A} pharmacology of these new templates was then compared to the original indanyl framework **3** (Table 1), and a key criteria for progression for new templates was a significant increase in activity over **3**.

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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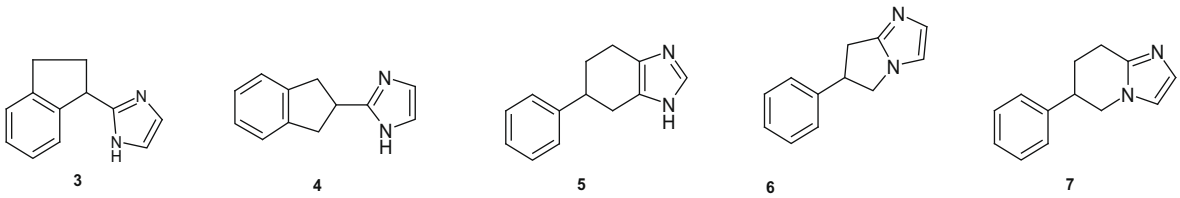
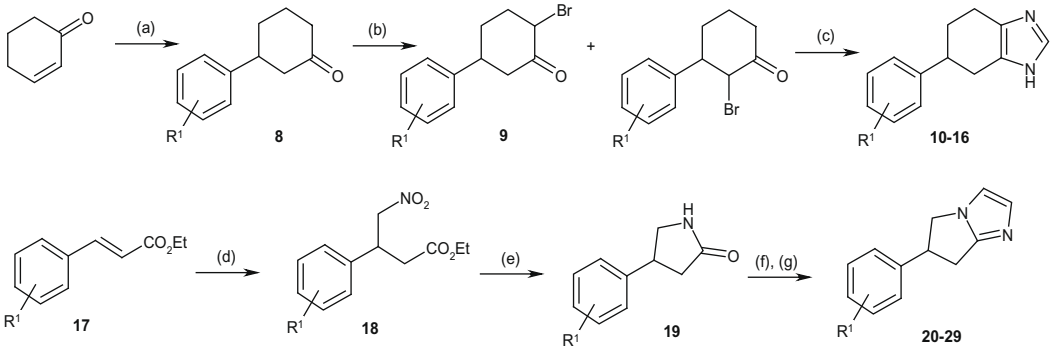


Figure 2. Structures of proposed new imidazole templates **4**–**7**.

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

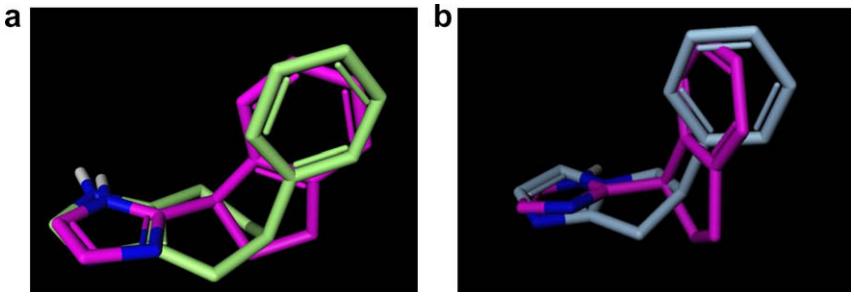
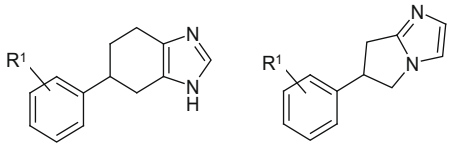


Figure 3. In silico overlap of (a) axial conformations of **5** (green) with **3** (purple) and (b) low energy conformation of **6** (blue) with **3** (purple).

Table 2
In vitro functional α_{1A}, α_{1B} and α_{1D} agonist activity, in vitro ADME data and log*D* values for compounds **5, 6, 10–16** and **20–29**



Compds	R^1	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]	Log*D*	HLM Clint (μl/min/mg)	PAMPA Papp (10^{-6} cm/s)
5a	H	123	75	>10,000	>10,000	2.6	7	47
6a	H	73	74	>10,000	7360 (30%)	1.9	15	51
10	2-Cl	276	60	>10,000	>10,000	3.1	10	34
11	3-Cl	514	71	>10,000	>10,000	3.3	21	39
12	4-Cl	>10,000	—	>10,000	>10,000	3.3	16	NT
13	2-OMe	144	95	>10,000	3500 (25%)	2.8	NT	NT
14	3-OMe	1050	60	>10,000	>10,000	2.6	NT	NT
15	4-OMe	>10,000	—	>10,000	>10,000	2.6	16	NT
16	2-CH_2OMe	76	87	>10,000	>10,000	2.2	<7	41
16a	2-CH_2OMe	48	83	>10,000	>10,000	2.2	<7	30
16b	2-CH_2OMe	70	85	>10,000	>10,000	2.2	<7	27
20	2-Cl	19	56	1100 (20%)	364 (50%)	2.6	18	51
21	4-Cl	3460	45	>10,000	>10,000	2.6	32	34
22	2-OMe	22	82	NT	NT	1.9	37	57
23	3-OMe	578	56	>10,000	>10,000	2.0	23	47
24	4-OMe	939	27	NT	NT	2.0	30	57
25	2-F	42	63	1770 (36%)	301 (58%)	2.0	NT	NT
26	2-$OCHF_2$	11	75	NT	NT	2.3	22	35
27	2-$C(O)NH_2$	371	87	NT	NT	NT	NT	NT
28	2-CN	51	74	>10,000	>10,000	1.3	<7	23
29	2-CH_2OMe	82	77	>10,000	>10,000	1.8	<7	25

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

10 and **13**) when compared to 3 and 4-substittution (examples **11**, **12**, **14** and **15**). The preferred methoxymethyl group was then introduced and this led to an increase in α_{1A} activity in example **16**. Enantiomer separation again showed both enantiomers were active, with **16a** the slightly more potent enantiomer. This series did combine good α_{1A} potency, selectivity and attractive ADME properties (good HLM stability and passive membrane permeability). However, this series generally had high E_{max} values, indicative of full agonism and more complex analogues proved too challenging to make via the synthetic route outlined, and so this series was halted.

Attention was then turned to the pyrrolo-imidazole template. For clarity only the analogues (**20–29**) from the more potent enantiomeric series are reported, although the absolute stereochemistry was not determined at this time. Chloro and methoxy analogues **20–24** suggested that 2-substitution increased potency over **6a,** however the 2-Cl analogue **20** had poor selectivity over α_{1B} and α_{1D}. Further 2-substituents were then introduced to expand the SAR. Small lipophilic groups were well tolerated, such as fluoro (**25**) and $OCHF_2$ (**26**) whereas the amide **27** lost potency. However, **25** still had poor selectivity over α_{1B} and α_{1D}. The nitrile **28** had acceptable potency, good selectivity, excellent metabolic stability and passive membrane permeability. Interestingly the methoxymethyl group (**29**), which was preferred in the indanyl 2-imidazole lead **2**, did not increase potency in this case.

The nitrile **28** had the best balance of pharmacology and in vitro ADME properties, and was assessed further. Compound **28** had no activity against the hERG channel (up to 22 μM), and no $K_i < 1$ μM were found when the compound was screened against a panel of 150 receptors, ion channels and enzymes at Cerep. The aqueous solubility of highly crystalline **28** free base was also measured at >0.5 mg/ml across a pH range of 1–9. Additionally, **28** had excellent flux when assessed in MDCK MDR-1 cells (A-B flux = 34×10^{-6} cm/s, B-A flux = 41×10^{-6} cm/s) which was indicative of excellent passive permeability combined with no evidence of P-pg mediated efflux. This solubility and flux data should be predictive of both good oral

absorption and good BBB penetration.[9] Compound **28** was also progressed to rat i.v. pharmacokinetics, and showed moderate clearance (Cl 34 ml/min/kg) and low volume of distribution (Vd 1.5 L/kg) after bolus solution dosing (0.3 mg/kg).

The remaining concern with the pyrrolo-imidazoles was α_{1A} E_{max}, which was viewed to be too high at 70–80%.[10] The Letter immediately following this one[11] will detail how α_{1A} E_{max} was reduced and EC_{50} activity was increased, whilst retaining the desired ADME and CNS drug-like properties of **28**.

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7. CAUTION should be exercised in the handling of nitro compounds. DSC analysis was determined on all alkyl nitro analogues **18**. If an exotherm was observed at >200 °C then the RaNi conditions at 100 °C were deemed to be safe. For analogues with DSC exotherms at <200 °C the more ambient $SnCl_2$ conditions were employed.
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