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Novel 2-imidazoles as potent, selective and CNS penetrant α_{1A} adrenoceptor partial agonists

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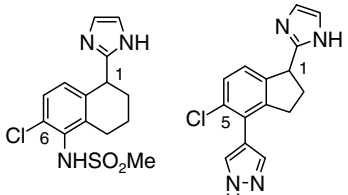
ABSTRACT

A novel series of central nervous system (CNS) penetrant indane 2-imidazoles have been identified as potent, partial agonists of the α_{1A} adrenergic receptor, having good selectivity over the α_{1B}, α_{1D} and α_2 sub-types. A key structural motif to impart selectivity is a methylene spacer between the indane and a pendant substituent, which includes heterocycles, sulphones and ethers. Introduction of an *ortho*-halogen to this group led to a lowering of intrinsic efficacy (E_{max}).

In the preceding letter,[1] we reported the rationale behind and the discovery of a series of substituted 2-imidazole α_{1A} partial agonists for potential utility in treating stress urinary incontinence (SUI), exemplified by compounds **1** and **2** with selectivity over other α_1 and α_2 subtypes.[2]



1 **2**

The imidazole and the pendent functional groups were key for driving potency, and intrinsic efficacy was modulated by small groups at the 5 position in the indane or 6 position in the tetrahydronaphthalene.

We believed that CNS penetration as well as partial agonism (E_{max} < 60%) could be key for driving the desired efficacy in SUI vs. undesired cardiovascular (CV) effects and a rationale will be reported in a separate letter.[3] The limited central exposure of compound **1** (rat free plasma/CSF 1:0.08), could be rationalised from in vitro MDCK-mdr1 screening,[4] whereby **1** had an AB/BA ratio of 7/29. This indicated that P-gp mediated efflux could be having a negative impact on the potential of **1** to cross the blood–brain barrier (BBB). The basic imidazole was crucial for agonist activity, and therefore our medicinal chemistry strategy focused on less polar bioisosteric replacements for the sulfonamide to reduce the potential for P-gp recognition and improve BBB penetration (**1** has a total polar surface area (TPSA) of 83 Å^2).

The 2-imidazoles were synthesised according to the general scheme outlined in Scheme 1. Reduction of the indanone[5] to the alcohol, conversion to the benzylic chloride and reaction with sodium cyanide gave the nitrile **3**. Selective hydrolysis of the ester followed by mild reduction of the activated acid furnished the benzyl alcohol. This was converted into a key intermediate, chloromethylcyano indane **4** and enabled attachment of a variety of functional groups to the 4-position via nucleophilic displacement. Transformation of the nitrile to the imidazole was carried out via Pinner reaction to the imidate ester, displacement with aminoethyl-diethylacetal and finally cyclisation under acidic conditions. Compounds **8** and **17** were synthesised from the corresponding methyl dihydroindeneacetate.[6] The starting material for **19** was made in five steps from methyl 2-fluoro-6-iodobenzoate. Compounds **11–14** were made via a cyclocarbonylation reaction of the trimethylsilyl-acetylenes as the key step (Scheme 2) in 40–65% yields[7] and the resultant indanones converted to the imidazoles in a similar way to that described in Scheme 1. We had previously shown that screening racemic mixtures was possible in this series,[1] however, interesting compounds were separated by chiral

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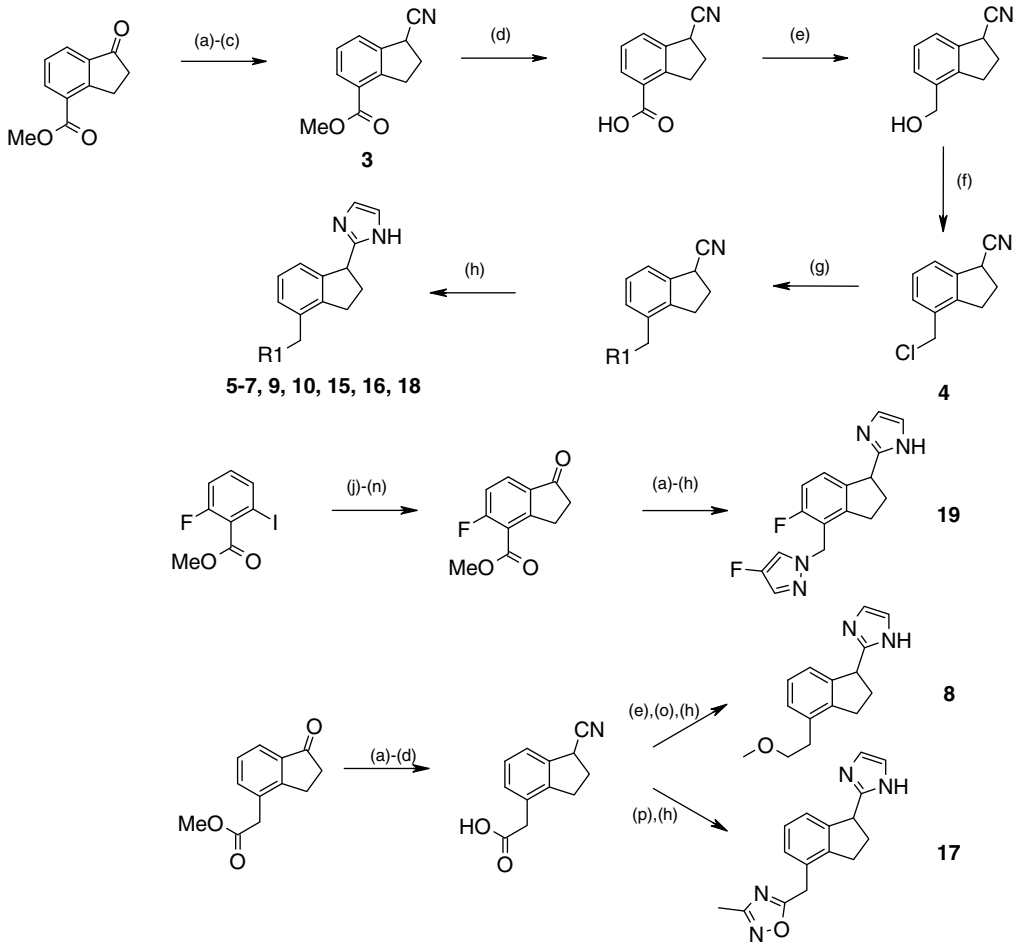
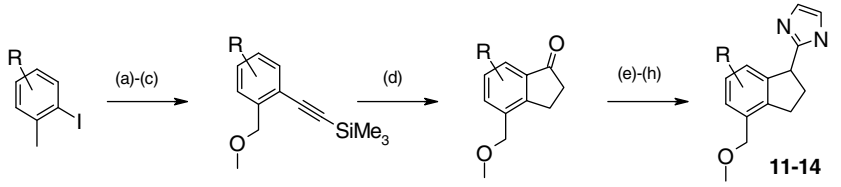


Scheme 1. Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C–rt; (b) $SOCl_2$, CH_2Cl_2, 0 °C; (c) NaCN, DMSO, rt; (d) LiOH, THF/H_2O, rt; (e) i—CDI, THF; ii—$NaBH_4$, THF/H_2O; (f) $SOCl_2$; (g) NuH, K_2CO_3, 60 °C or NuH, NaH, THF, 0 °C to reflux or i—NaSMe, DMF; ii—Oxone™, THF, H_2O, 0 °C; (h) i—satd HCl/EtOH; ii—$H_2NCH_2CH(OEt)_2$, EtOH, rt; iii—2 M HCl, 100 °C; (j) *t*-butyl acrylate, MeCN, Et_3N, $Pd(OAc)_2$, *o*-Tol_3P, 45 °C; (k) H_2, Pd/C, EtOH, 50 psi, rt; (l) TFA, DCM; (m) LiOH, THF/H_2O, rt, overnight; (n) i—$(COCl)_2$, DCM 0 °C; ii—$AlCl_3$, DCM, 40 °C then MeOH; (o) MeI, AgO, reflux; (p) i—NMM, acetamide oxime, HBTU, DCM; ii—MeCN, reflux.



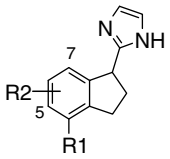
Scheme 2. Reagents and conditions: (a) CCl_4, NBS, $(PhCO_2)_2$, reflux; (b) NaOMe, MeOH, reflux; (c) TMS-acetylene, CuI, $PdCl_2(PPh_3)_2$, DMF, Et_3N, rt; (d) $[Rh(COD)Cl]_2$, PPh_3, EtN_3, THF, H_2O, CO (>1000 psi), 160 °C; (e) i—$NaBH_4$, EtOH, 0 °C–rt; (f) $SOCl_2$, CH_2Cl_2, 0 °C; (g) NaCN, DMSO, RT; (h) i—satd HCl/EtOH; ii—$H_2NCH_2CH(OEt)_2$, EtOH, rt; iii—2 M HCl, 100 °C.

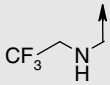
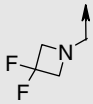
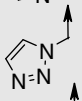
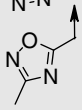
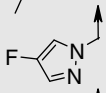
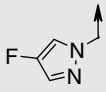
HPLC and retested individually and in all cases one of the enantiomers was much more potent (compounds **6**, **11**, **14**, **15**, **17** and **19**).[8] Test compounds were assessed in vitro for their functional agonist activity at human α_{1A} receptors, in human liver microsomes (HLM), MDCK mdr-1 P-gp and Log*D* assays (Table 1).[9]

We had shown previously that the indane ring system was more potent than the tetrahydronaphthalene and that compounds such as sulfonamide **1**, although selective and metabolically stable, had a high TPSA with an associated cost to CNS penetration by introducing P-gp mediated efflux. As an opening strategy, the sulfonamide NH was replaced with a CH_2 in an attempt to lower TPSA. The CH_2 group is weakly acidic and we wondered if it could act as a weak H-bond donor. The benzylic sulfone **5** did retain α_{1A} potency, partial agonism and selectivity, however, this compound still showed efflux in the MDCK assay, likely driven again by a fairly high TPSA (71 Å^2). The fact that there was such little drop-off in potency between the sulfonamide and sulfone suggests that a hydrogen-bond donor was probably not the main requisite for α_{1A} activity and this somewhat contrasts to our earlier conclusions.[1] The orientation and hydrogen bond acceptor ability of the pendant group could be more important.

The strategy then focused on replacing the sulfone in **5** with isosteres having some H-bond accepting capacity but without the high TPSA penalty. Hydrogen bond acceptor capacity has been described using a $\log K_B$ scale by Abraham. A sulfone and a sulfonamide have values of 1.2–1.6 and 1.2–1.4, respectively. Other functional groups in a similar range include dialkylethers with $\log K_B$ values of around 0.7–1.3 depending on the nature of the sub-

Table 1
In vitro functional α_{1A} agonist activity for compounds **1**, **2** and **5**–**19.**



Compound	R^1	R^2	α_{1A} EC_{50}[b,c]	α_{1A} E_{max}[b,c]	HLM Cl_{int} (μl/min/mg)	MDCK/mdr-1	TPSA Å^2	Log$D_{7.4}$
1	—	—	43 nM (30–63) *n* = 10	64% (60–69)	<7	7/29	83	1.5
2	—	—	78 nM (61–100) *n* = 4	52% (48–56)	24	30/44	57	2.6
5			84 nM (57–126) *n* = 4	70% (64–77)	<7	2/9	71	0.7
6[a]		H	37 nM (26–52) *n* = 15	69% (64–74)	12	40/36	38	1.8
7		H	62 nM (47–82) *n* = 8	64% (57–72)	115	N/T	38	2.1
8		H	168 nM (30–949) *n* = 3	50% (46–53)	38	39/39	38	2.0
9		H	195 nM (149–256) *n* = 8	60% (52–69)	26	N/T	41	2.0
10		H	879 nM (148–5220) *n* = 4	34% (30–38)	14	N/T	32	2.0
11[a]		5-F	62 nM (41–96) *n* = 8	59% (56–62)	11	39/37	38	2.0
12		6-F	59 nM (35–100) *n* = 4	87% (79–95)	20	N/T	38	2.3
13		7-F	658 nM (454–955) *n* = 7	49% (42–56)	17	N/T	38	1.8
14[a]		5-Cl	31 nM (20–49) *n* = 8	60% (54–67)	30	40/36	38	2.6
15[a]		H	32 nM (19–53) *n* = 8	69% (64–74)	18	33/44	47	1.8
16		H	90 nM (33–243) *n* = 4	62% (55–69)	N/T	9/24	59	N/A
17[a]		H	111 nM (51–240) *n* = 8	44% (33–55)	44	34/36	68	2.0
18		H	17 nM (10–29) *n* = 8	83% (75–90)	30	N/T	47	2.4
19[a]		5-F	9 nM (6–16) *n* = 12	60% (53–66)	24	38/44	47	2.6

NT, not tested.
[a] Separated by chiral HPLC and single enantiomer shown (See Ref.[8]).
[b] See Ref.[9] for description of assay conditions.
[c] Values are geometric means of at least three experiments and >95% confidence limits shown in parentheses.

stituents.[10] This prompted the design and synthesis of the methoxymethyl isostere **6**, which had a much lower TPSA (38 Å^2 for **6** vs 71 Å^2 for **5**). Importantly, it retained α_{1A} potency, partial agonism and selectivity over other α subtypes but with no evidence of P-gp-mediated efflux. The importance of conformation of compounds **5** and **6** (Fig. 1a and b) should be contrasted to the directly attached methoxy analogue (Fig. 1c) we had previously reported that was not selective over α_{2A} (α_{1A} 32 nM vs a_{2A} 27 nM).[1]

Table 2
Physicochemical, pharmacological and ADME properties of **14** and **19.**

	14	19
α_{1a} Ki	83 nM	5 nM
Log $D_{7.4}$	2.6	2.6
HLM, Cl_i (μl/min/mg)	30	24
DLM, Cl_i (μl/min/mg)	35	82[a]
hERG activity	>10 μM	>10 μM
Cerep/Bioprint™ panel (170 assays across receptor, enzyme and ion channel targets)	>50× selective against all targets	>50× selective against all targets
CYP2C9, 2C19, 2D6, 3A4 inhibition	2C9 and 3A4 < 35% at 10 μM 2C19 IC_{50} 5.7 μM 2D6 IC_{50} 6.6 μM	<50% inhibition at 10 μM
Dog PK (IV)	Cl 14 ml/min/kg Vd 0.9 L/kg $T_{1/2}$ 0.9 h	Cl 25 ml/min/kg Vd 3 L/kg $T_{1/2}$ 1.5 h
Rat free plasma/CSF	1:1	1:1

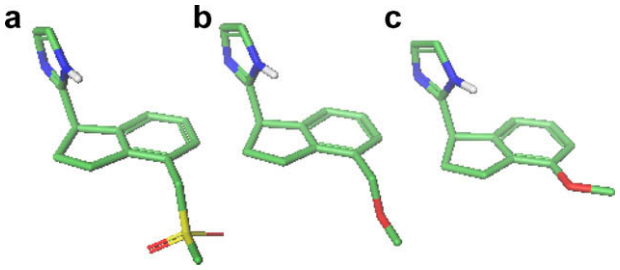


Figure 1. In-silico prediction of conformation of compounds **5** (a), **6** (b) and methoxy analogue (c).

The key difference is the preferred out-of-plane orientation of the pendent methylene sulfone in Figure 1a (**5**) and methoxymethyl substituent in Figure 1b (**6**) which seems to bring in selectivity compared to the planar methoxy in Figure 1c.

Variation in the size, type and position of the ether such as compounds **7** and **8**, tended to be detrimental to potency and/or HLM stability driven by higher Log*D*. The only amines showing any activity had low pK_as, courtesy of adjacent fluorines such as **9** and **10**.[11]

Placing small halogens on the aromatic ring, e.g., 5-F **11** and 5-Cl **14** analogs, showed good potency with lower E_{max} values. On balance, **14** had the better in vitro profile of the two. Fluorine in the other positions either had a big drop-off in potency or increased the E_{max} significantly (**12** and **13**).

Benzylic heterocycles were investigated as they also have the propensity to act as strong hydrogen bond acceptors. Initial success came with the benzylic N-linked pyrazole **15** which had good potency, selectivity and low E_{max}. Other N- or C-linked heterocycles had reduced potency. The triazole **16** with a slightly higher TPSA of 59 Å^2, had a resultant asymmetry in the MDCK assay. In this instance, other factors such as hydrogen bond basicity of the exposed nitrogen on the triazole may make it more susceptible to P-gp efflux. The oxadiazole **17** was interesting as it had a low E_{max} but showed compromised potency and was highly susceptible to microsomal oxidation. The addition of a fluoro group to the pyrazole **18** increased potency but raised the E_{max}. By adding a further fluorine to the 5-postion of the indane the E_{max} was lowered to 58% with a further increase in potency. Single enantiomer **19** had the best overall in vitro pharmacology profile.

Both **14** and **19** were selective over the other α subtypes, the hERG channel and a wide ligand panel of receptors, enzymes and ion channels although we did see some weak CYP inhibition (Table 2). Interestingly, compound **14** had a binding K_i of 83 nM whereas **19** was much more potent at 5 nM, but the pharmacological relevance for the difference in binding activity is not well understood. In rat experiments, the free plasma/cerebral spinal fluid (CSF) ratio after iv infusion to steady state was 1:1 for both compounds. This indicated that both compounds had excellent BBB penetration.[12] Compound **14** had moderate clearance in the dog to give a human PK predicted clearance in the range 4–11 ml/min/kg with a low volume of distribution (consistent with an essentially neutral compound) and bioavailability of around 65%.

In summary, 2-substituted imidazole α_{1A} partial agonists with methylene spaced groups at the 4-position of the indane gave excellent selectivity over α_{1B}, α_{1D} and α_{2A}. E_{max} can be modulated by placement of a halogen at the 5-position. Compounds **14** and **19** were identified as having the best balance of pharmacological properties. Keeping the polar surface area of the compounds low resulted in no P-gp efflux as predicted from the MDCK assay with good CNS penetration. This work also demonstrated the use of ethers and heterocycles as bioisosteric replacements of sulfonamides. The in vivo efficacy of **14** in models of SUI and selectivity over CV endpoints will be reported separately.[3]

Acknowledgements

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