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

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Abstract—Novel 2-imidazoles 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. Sulfonamide **23** possessed attractive drug-like properties with respect to physicochemical and ADME properties and wide ligand selectivity.

α_1-Adrenoceptors are members of the 7TM super family of G-protein-coupled receptors, and three sub-types of α_1-adrenoceptors have been cloned (α_{1A}, α_{1B}, α_{1D}), expressed and characterized.[1] Sub-type selective agonists of the α_{1A} receptor have been shown to be efficacious in in vivo models of stress urinary incontinence (SUI).[2] However, full α_{1A} agonists possess a narrow therapeutic index over α_{1A} mediated cardiovascular effects.[3] Recently, workers at Roche disclosed in vitro, in vivo and PhIIa clinical data on the α_{1A} partial agonist Ro-115-1240 (Dabuzalgron) **1**, that demonstrated its potential as a treatment for SUI with minimal effects on cardiovascular parameters.[4] The selectivity of **1** for its urological endpoint over cardiovascular and other side effects was postulated, in part, to be due to partial α_{1A} agonism.[5] We now wish to report our own work in the area of α_{1A} partial agonists for the treatment of SUI.

Compounds **1**, A-61603 **2**[6] and ABT-866 **3**[7] are reported to be potent and selective α_{1A} agonists (Fig. 1). However, imidazolines have known hydrolytic stability issues,[8] and 4-linked imidazoles can suffer from potent P450 inhibition.[9] To circumvent these issues we decided to introduce a 2-linked imidazole such aas **4**,[10] reasoning that (i) imidazoles are hydrolytically stable fragments and (ii) flanking imidazole nitrogen atoms with a 2-substituent is a precedented strategy for reducing P450 inhibition.[11] Some evidence of 2-linked imidazoles with adrenergic receptor agonist activity had also been reported, with simple naphthalenes **5** showing weak α_1 agonist activity.[12] Encouraged by this finding, our strategy focused on inserting the 2-imidazole fragment into a conformationally constrained template **4** which would incorporate functional groups, such as sulfonamides, that were known to confer α_{1A} agonist activity.

The target compounds were synthesized according to the general route outlined in Scheme 1. Reduction of the cyclic ketone **6** to benzylic alcohol **7** was followed by chlorination and cyanide displacement to give the benzylic nitrile **9**. The nitrile was then converted to the imino-ether **10** by reaction with ethanol saturated with HCl gas. Displacement of **10** with a glycine aldehyde equivalent followed by cyclization under acidic conditions afforded the required imidazoles.[13]

When heterocyclic substituents were introduced in the 4-position, the 4-Br indanyl nitriles **24** were employed as key intermediates. Palladium mediated cross-coupling with the required heterocyclic coupling partner (boronic ester/acid, stannane or cuprate) afforded the desired intermediates **25**. Transformation to final compounds then followed the same procedure as in previous examples. Test compounds were assessed in vitro for their

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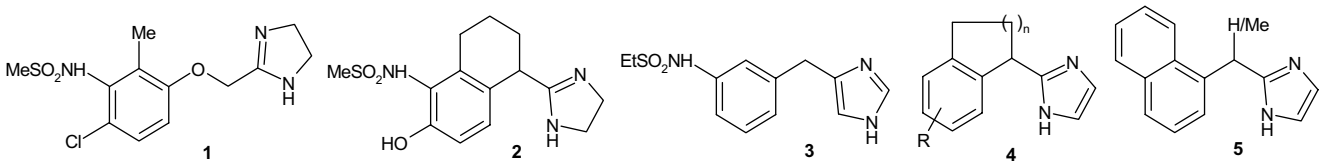
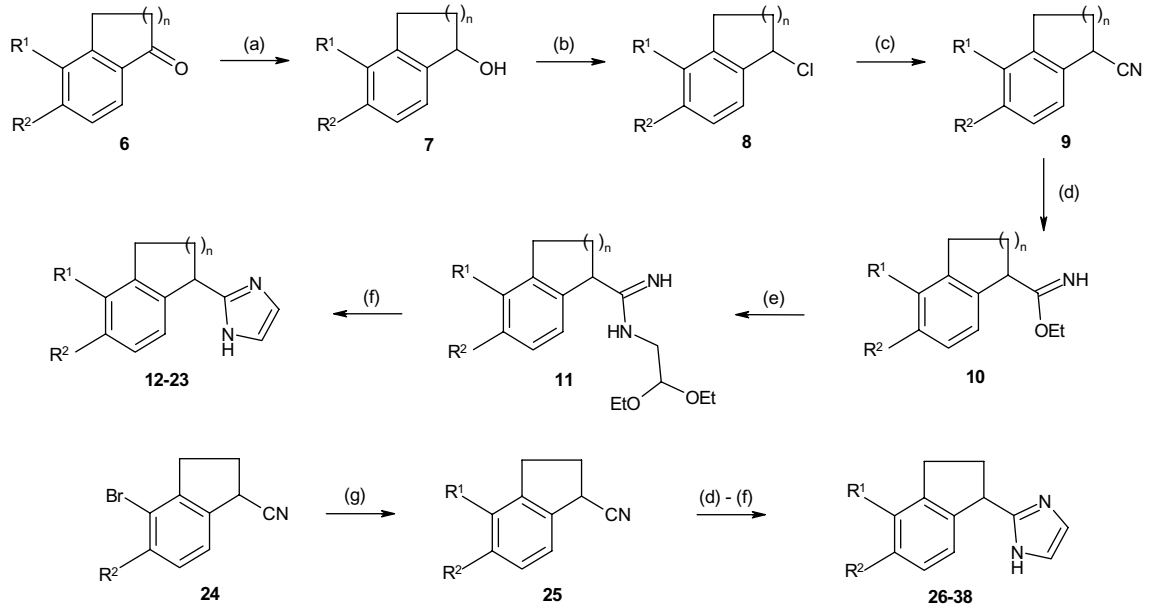
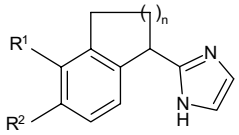


Figure 1.



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt; (b) $SOCl_2$, CH_2Cl_2, 0 °C; (c) NaCN, DMSO, rt to 50 °C; (d) saturated HCl/EtOH, 0 °C; (e) $H_2NCH_2CH(OEt)_2$, EtOH, rt; (f) aq 2 M HCl, 100 °C; (g) $HetB(OH)_2$, $Pd(PPh_3)_4$, PhMe, reflux; or $HetZnCl$, $Pd(PPh_3)_4$, dioxane, reflux; or $HetSnR_3$ (R = Me or *n*-Bu), $Pd(PPh_3)_4$, CuI, LiCl, dioxane, reflux.

Table 1. In vitro functional α_{1A}, α_{1B}, α_{1D} and α_{2A} agonist activity for compounds **1**, **3**, **12**–**23**



Compound	*n*	R^1	R^2	$\alpha_{1A}EC_{50}$[a,b] (nM)	α_{1A} E_{max} (%)	α_{1B} EC_{50} (E_{max})[a,b] (nM)	α_{1D} EC_{50} (E_{max})[a,b] (nM)	α_{2A} EC_{50} (E_{max})[b,c] (nM)
1	—	—	H	25[d]	60	>10,000	>10,000	>10,000
3	—	—	H	9	96	>10,000	>10,000	>10,000
12	1	H	H	473	54	>10,000	>10,000	NT
13	2	H	H	385	71	791 (58%)	364 (74%)	722 (105%)
14	1	$MeSO_2NH$	H	70	87	>10,000	>10,000	>10,000
15	1	$EtSO_2NH$	H	32	86	>10,000	>10,000	>10,000
16	1	*n*-$PrSO_2NH$	H	1340	54	>10,000	>10,000	NT
17	2	$MeSO_2NH$	H	234	79	>10,000	>10,000	>10,000
17a	2	$MeSO_2NH$	H	142	79	>10,000	>10,000	>10,000
17b	2	$MeSO_2NH$	H	2150	47	>10,000	>10,000	>10,000
18	1	MeNHC(O)	H	2200	59	>10,000	>10,000	4340 (44%)
19	1	MeO	H	32	65	>10,000	>10,000	27 (100%)
20	1	MeO	Me	167	40	>10,000	>10,000	327 (89%)
21	1	MeO	Cl	451	24	>10,000	>10,000	NT
22	1	$MeSO_2NH$	Me	33	83	>10,000	>10,000	NT
23	2	$MeSO_2NH$	Cl	43	61	>10,000	>10,000	>10,000

NT denotes not tested.

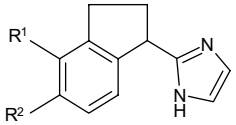
[a] See Ref. 14 for description of assay conditions.

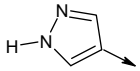
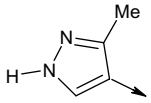
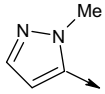
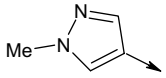
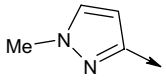
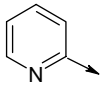
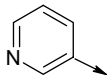
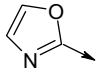
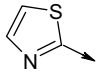
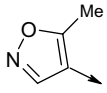
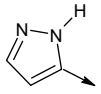
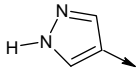
[b] Values are geometric means of at least three experiments.

[c] See Ref. 15 for description of assay conditions.

[d] Data on Ro-115-1240 **1** are in good agreement with published data (Ref. 5).

Table 2. In vitro functional α_{1A}, α_{1B}, α_{1D} and α_{2A} agonist activity for compounds **26**–**38**



Compound	R^1	R^2	$\alpha_{1A}EC_{50}$[a,b] (nM)	α_{1A} E_{max} (%)	$\alpha_{1B}EC_{50}$ (E_{max})[a,b] (nM)	$\alpha_{1D}EC_{50}$ (E_{max})[a,b] (nM)	$\alpha_{2A}EC_{50}$ (E_{max})[b,c] (nM)
26		H	52	83	600 (32%)	336 (57%)	>10,000
27		H	14	84	>10,000	319 (52%)	>10,000
28		H	3	91	902 (14%)	634 (66%)	>10,000
29		H	278	58	>10,000	>10,000	>10,000
30		H	>2900	12	>10,000	>10,000	>10,000
31		H	>1300	19	>10,000	>10,000	>10,000
32		H	1150	53	>10,000	>10,000	>10,000
33		H	2060	36	>10,000	>10,000	4580 (25%)
34		H	170	63	>10,000	1390 (38%)	>10,000
35		H	426	64	>10,000	3190 (27%)	>10,000
36		H	111	63	>10,000	>10,000	>10,000
37		Cl	322	40	>10,000	>10,000	>10,000
38		Cl	78	52	>10,000	>10,000	>10,000

NT denotes not tested.

[a] See Ref. 14 for description of assay conditions.

[b] Values are geometric means of at least three experiments.

[c] See Ref. 15 for description of assay conditions.

functional agonist activity at human α_{1A}, α_{1B}, α_{1D} and α_{2A} receptors (see Tables 1 and 2).[14,15]

Indane **12** and tetrahydronaphthalene **13** demonstrated weak α_{1A} functional agonism in vitro, however, **12** was more selective over α_{1B} and α_{1D}. Introduction of the methanesulfonamide in compound **14** led to an increase in α_{1A} potency. Extension of the sulfonamide to the ethyl analogue **15** improved potency slightly, but *n*-propyl example **16** reduced potency significantly. Ring size also affected potency, with the tetrahydronaphthalene sulfonamide **17** showing threefold weaker α_{1A} activity than **14**. To determine whether the α_{1A} activity resided in a single enantiomer, analogue **17** was separated into enantiomers **17a** and **17b**.[16] It was found that enantiomer **17a** retained the potency, E_{max} and selectivity of the racemic mixture whereas **17b** had far weaker activity. Following this result all further analogues were screened as racemic mixtures.

Replacement of the sulfonamide was then investigated. Secondary amide **18** was poorly tolerated, indicating the positioning of H-bond donor and acceptor groups was important for activity. In contrast, the methoxy substitution in **19** gave equivalent α_{1A} potency, and began to confer partial agonism by reducing E_{max}. However, this change also conferred poor selectivity over α_{2A}.

Introduction of a 5-substituent in examples **20**–**23** gave interesting and quite different results. In the case of methoxy examples **20** and **21** there was a decrease in α_{1A} potency but E_{max} also dropped to a level below that for Ro-115-1240 **1**. Unfortunately, the additional methyl substituent did not improve α_{2A} selectivity. In the case of sulfonamides **22** and **23** the 5-substituent had the opposite effect, and increased α_{1A} potency. E_{max} remained high for compound **22** at 83%, however, the tetrahydronaphthalene **23** had an attractive pharmacological profile, combining excellent potency, low E_{max} and good selectivity.

From this investigation we concluded that a sulfonamide N–H coupled with a small lipophilic group in the 5-position was crucial for tuning potency, E_{max} and selectivity. To test this hypothesis further, we then investigated additional replacements for the sulfonamide. We reasoned that polar heterocyclic substituents may act as effective sulfonamide bioisosteres.[17] A series of compounds was then synthesized, with a focus on the indane template for synthetic expedience.

Heterocycles which included a hydrogen-bond donor, exemplified by pyrazoles **26**, **27** and **28**, retained potent α_{1A} agonism, however, the 2-linked isomer **26** had poorer selectivity than **27** or **28**. Removal of the hydrogen-bond donor by *N*-methylation in examples **29**, **30** and **31** led to a significant loss of α_{1A} agonist activity. Further five and six-membered heterocycles **32**–**36**, which just contained hydrogen-bond acceptors, were also investigated but did not deliver the required α_{1A} potency and E_{max} levels. Again, this SAR suggested a hydrogen-bond donor was important for α_{1A} agonist potency. We then re-introduced a 5-substituent into the most promising heterocyclic compounds to determine if this would reduce α_{1A} E_{max}, as had been the case for sulfonamide **23**. We were pleased to find that a 5-chloro group in compounds **37** and **38** reduced α_{1A} E_{max} to below that for Ro-115-1240 **1**, but with a concomitant decrease in α_{1A} potency. The compound from this series that had the best combination of potent α_{1A} EC_{50}, low E_{max} and good selectivity was analogue **38**, however, this compound was not superior to sulfonamide **23** with respect to α_{1A} potency.

Table 3. Physicochemical, pharmacological and ADME properties of **23**

	23
*c*log *P*	2.3
Log $D_{7.4}$	1.5
HLM, Cl_i μL/min/mg	<7
Hheps, Cl_i μL/min/million cells	<5
CaCO-2 flux, AB/BA	18/19
hERG activity	0% activity @ 10 μM
Cerep/Bioprint™ panel (170 assays across receptor, enzyme and ion channel targets)	>50× selectivity against all targets
CYP2C9, 2C19, 2D6, 3A4 inhibition	<25% inhibition @ 10 μM

Compound **23** was then progressed to further screening to assess its overall drug-like properties, and these data are summarized in Table 3.

These data showed that **23** had attractive drug-like properties; combining low lipophilicity, excellent selectivity over the hERG channel and P450 enzymes and against a wide panel of receptors, enzymes and ion channels. In addition, **23** had excellent in vitro metabolic stability combined with good membrane permeability along with no evidence of P-gp mediated efflux in CaCO-2 cells.

In summary we have discovered a novel series of 2-substituted imidazole α_{1A} adrenoceptor partial agonists with excellent selectivity over α_{1B}, α_{1D} and α_{2A}. In particular, sulfonamide **23** and pyrazole **38** were identified as having the best balance of pharmacological properties. This work also demonstrated the use of heterocycles with hydrogen-bond donors as effective bioisosteric replacements of sulfonamides. Additional screening highlighted the attractive drug-like properties of sulfonamide **23**. Further advances in the SAR of this series along with in vivo efficacy and pharmacokinetic data will be reported in the near future.

Acknowledgments

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13. Imidazole final compounds were screened as racemic mixtures apart from example 17, which was separated into single enantiomers by chiral preparative HPLC.
14. Human α_{1A} (clone 54), α_{1B} (SNB0000700, clone 11) and α_{1D} (SNB0000706, clone 23) were expressed in Chinese Hamster Ovary cells. Receptor activation was determined via calcium mobilization through the Gq pathway using calcium-sensitive fluorescent dyes (Molecular Devices, part number R8033), measured by a Fluorescent Light Imaging Plate Reader (FLIPr). 11 Point concentration response curves were calculated, with E_{max} calculated as a percent relative to 10 μM phenylephrine response.
15. Human α_{2A} (clone SNB0000670) was expressed in Chinese Hamster Ovary K-1 cells. Receptor activation was determined via a beta-lactamase reporter gene assay. 11 Point concentration response curves were calculated, with E_{max} calculated as a percent relative to 1 μM dexmeditomidine response.
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