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6,7-Dihydro-5*H*-pyrrolo[1,2-*a*] imidazoles as potent and selective α_{1A} adrenoceptor partial agonists

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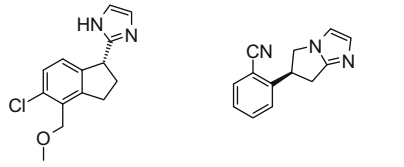
ABSTRACT

Novel pyrroloimidazoles 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 subtypes. Pyrimidine **19** possessed attractive CNS drug-like properties with good membrane permeability and no evidence for P-gp mediated efflux.

Recent reports described α_{1A} selective partial agonists having potential clinical utility in the treatment of stress urinary incontinence (SUI).[1] As part of a multi-series approach, we sought to discover templates which could deliver potent and selective α_{1A} partial agonist activity.[2–4] Biology studies indicated α_{1A} partial agonists impart their in vivo efficacy in models of SUI via a centrally mediated pathway, and partial agonism of the α_{1A} receptor may also drive SUI efficacy over undesired cardiovascular effects.[5] We therefore required preferred compounds which were partial agonists ($E_{max} < 60\%$) coupled with physicochemical properties which would allow good blood brain barrier (BBB) penetration (low TPSA, low molecular weight, few hydrogen bonding groups), and ideally improved metabolic stability when compared to compounds described in earlier publications, exemplified by **1**. Permeability and efflux in the MDCK mdr-1 cell line was used as a predictor of likely P-gp mediated efflux, and also as an in vitro predictor of BBB penetration.[6] Design of an alternative series led to the discovery of **2** (Fig. 1) which was more stable to metabolic activation than **1** but had sub-optimal pharmacology with respect to potency and intrinsic efficacy (E_{max}).[4] We now wish to report the results of follow-on work in this Letter to address these two issues.

Our medicinal chemistry strategy concentrated on the placement of substituents on the phenyl ring to increase potency and lower E_{max}, whilst retaining metabolic stability. A range of pyrroloimidazoles were synthesized to assess the effects of functional group changes. The core pyrroloimidazoles were efficiently synthesized according to the general scheme outlined in Scheme 1. The commercially available bromobenzaldehyde underwent a Wittig reaction to give the cinnamic acid **3**. Conjugate addition of nitromethane and reduction of the nitro group to the amine with tin chloride followed by cyclisation gave the lactam **4**.[7] The lactam was converted to the imidate ester using Meervein's reagent (trimethyltetrafluoroborate) which in turn was displaced with aminoethyldiethylacetal and cyclised under acidic conditions to give the pyrroloimidazole **5** in good yield. The aryl bromides were easily separated at this point on a chiral preparative HPLC column. Each enantiomer was reacted with a series of boronic acids, stannanes and N-linked heterocycles to give the final products **7–27** except compound **17** which was synthesized via a Heck reaction followed by hydrogenation.[8] Test compounds were assessed in vitro for their functional activity against human α_{1A} as well as other alpha sub-



1
α_{1A} EC_{50} 27nM (58%)
Selective over α_{1B}, α_{1D}, α_{2A}
HLM Cl_{int} 30µl/min/kg
MDCK mdr-1 AB/BA 40/36
Good BBB penetration

2
α_{1A} EC_{50} 51nM (74%)
Selective over α_{1B}, α_{1D}, α_{2A}
HLM Cl_{int} <7 µl/min/kg
MDCK mdr-1 AB/BA 35/41

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

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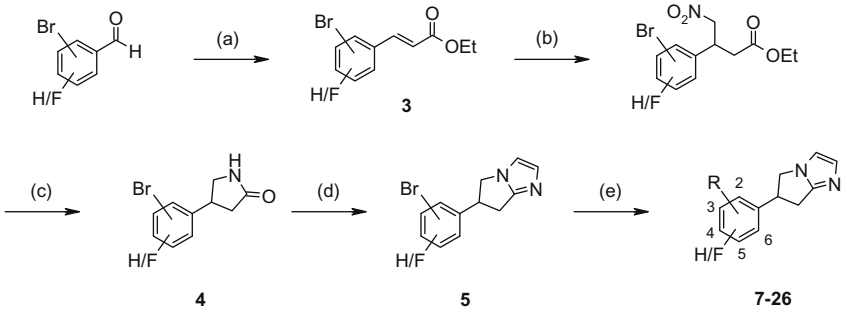


Scheme 1. Reagents and conditions: (a) $Ph_3P=CHCO_2Et$, toluene, reflux 2 h; (b) $MeNO_2$, DBU, 0 °C to rt; (c) (i) $SnCl_2$, EtOAc, rt; (ii) EtOH, reflux overnight; (d) (i) Me_3OBF_4, CH_2Cl_2, rt; (ii) $H_2NCH_2CH(OEt)_2$, HCl, EtOH, rt; (iii) HCl/dioxane, H_2O, 100 °C; (e) either (i) $RSnBu_3$, $PdCl_2(Ph_3P)_2$ or (ii) $RB(OH)_2$, Pd or (iii) Pyrazole, CuI (20 mol %), Phenanthroline (20 mol %), Cs_2CO_3, MeCN, microwave or (iv) $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, MeCN, 160 °C, microwave followed by H_2 (60psi), 10% Pd/C, EtOH, 60 °C.

Table 1
In vitro functional α_{1A} agonist activity, in vitro ADME data and physicohemical properties for compounds **1**, **2**, **7–27**


1, 2, 7-27

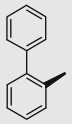
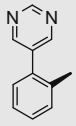
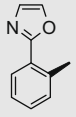
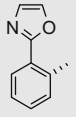
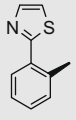
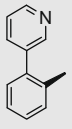
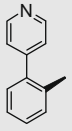
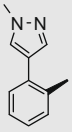
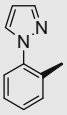
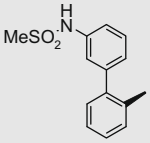
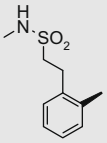
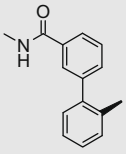
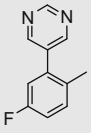
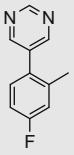
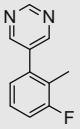
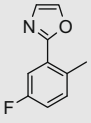
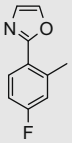
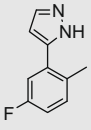
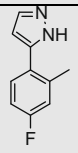
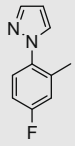
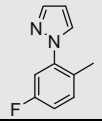
Compd	R	α_{1A} EC_{50} (nM)[a,b]	α_{1A} E_{max} (%)	α_{1B} EC_{50} (E_{max}) (nM)	α_{1D} EC_{50} (E_{max}) (nM)	α_{2A} Ki (nM)	HLM Clint µl/min/mg	MDCK/mdr-1 P-gp (AB/BA $P_{app} \times 10^{-6}$ cms^{-1})	TPSA Å^2	Log $D_{7.4}$
1	–	31	60	>10,000	>7000	>1700	30	40/36	38	2.6
2		51	74	>10,000	>10,000	>4500	<7	35/41	42	1.3
7		12	83	>10,000	729 (51%)	213	NT	NT	18	1.7
8		0.4	98	>6500	391 (75%)	>3800	<8	NT	44	1.2
9		2	91	>1400	146 (49%)	805	12	NT	43	2.2
10		92	62	>10,000	>3570	1020	NT	NT	43	2.2
11		3	83	NT	NT	1750	18	NT	58	2.3
12		1	90	760 (54%)	119 (71%)	991	8	44/47	31	2.1
13		81	68	>10,000	656 (48%)	112	17	NT	31	2.1

Table 1 (*continued*)

Compd	R	α_{1A} EC_{50} (nM)[a,b]	α_{1A} E_{max} (%)	α_{1B} EC_{50} (E_{max}) (nM)	α_{1D} EC_{50} (E_{max}) (nM)	α_{2A} Ki (nM)	HLM Clint μl/min/mg	MDCK/mdr-1 P-gp (AB/BA $P_{app} \times 10^{-6}$ cms^{-1})	TPSA Å^2	Log $D_{7.4}$
14		9	85	NT	NT	380	<7	NT	36	2.0
15		5	80	>10,000	>10,000	1100	18	NT	36	1.4
16		4	59	>10,000	>10,000	114	22	11/46	64	2.5
17		12	64	>10,000	>10,000	280	<8	NT	72	1.2
18		19	57	>10,000	>10,000	202	10	16/42	47	2.5
19		19	77	>10,000	>3400	>2370	<8	NT	44	1.3
20		1	65	>10,000	>2600	>2780	<8	34/39	44	1.3
21		62	59	>10,000	>10,000	>3310	<8	NT	44	1.3
22		33	43	>10,000	>10,000	>2160	13	NT	44	2.4
23		3	70	990 (41%)	276 (49%)	469	16	NT	44	2.3
24		15	54	>10,000	276 (51%)	1470	<8	NT	47	2.2

(*continued on next page*)

Table 1 (*continued*)

Compd	R	α_{1A} EC_{50} (nM)[a,b]	α_{1A} E_{max} (%)	α_{1B} EC_{50} (E_{max}) (nM)	α_{1D} EC_{50} (E_{max}) (nM)	α_{2A} Ki (nM)	HLM Clint µl/min/mg	MDCK/mdr-1 P-gp (AB/BA $P_{app} \times 10^{-6}$ cms^{-1})	TPSA Å^2	Log $D_{7.4}$
25		3	70	>10,000	NT	NT	10	NT	47	2.1
26		5	80	>10,000	>10,000	NT	9	NT	36	1.7
27		27	56	>10,000	>4100	>3230	12	NT	36	1.8

NT denotes not tested.

[a] Values are geometric means of at least two experiments.

[b] See Ref. 8 for description of assay conditions.

types, in human liver microsomes (HLM), MDCK mdr-1 and Log $D_{7.4}$ assays (Table 1).[9]

Absolute stereochemistry was determined on one of the enantiomers of the simple bromopyrroloimidazole (**6**) which showed it to have *R* stereochemistry (Fig. 2).[10] Where this intermediate has been used, the absolute stereochemistry of the final compounds derived from this and its opposite enantiomer are shown. Examples **19**–**27**, although single enantiomers, are of unknown absolute stereochemistry. Unlike the previous indane imidazole series, all of the pyrroloimidazoles were separated into their constitutive enantiomers before screening as each enantiomer was active against α_{1A} and had a different selectivity profile as illustrated by compounds **9** and **10**, whereby **10** is significantly weaker against α_{1A} but has similar α_{2A} Ki's.

In the preceding paper, we showed that substitution on the 2-position of the phenyl ring was optimal to retain potency. Replacement of the nitrile in compound **2** with a range of simple heterocycles **8**–**15** was then investigated, with the aim of maintaining the Log $D_{7.4}$ in a similar range to **2** (1.0–2.0) with the simple phenyl **7** shown in comparison. The heterocycles were all potent and very full agonists (except compound **10**), showing varying degrees of agonism against α_{1B}, α_{1D} and antagonism against α_{2A}. The most potent compound was the pyrimidine **8**, which was very potent against α_{1A} had some α_{1D} activity but weak against α_{2A}. This should be contrasted to the 4-pyridine **13** which had moderate potency against α_{1A} and as an antagonist against α_{2A}. The N-linked pyrazole **15** was very potent and full α_{1A} agonist and was selective across the range of α subtypes.

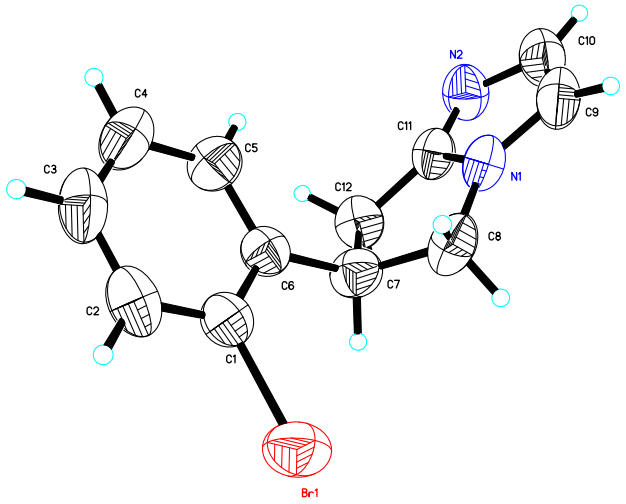


Figure 2. X-ray of the *R* enantiomer of bromophenylpyrroloimidazole **6**.

In an effort to lower the E_{max} from substitution at the 2-position alone, compounds such as sulfonamides **16** and **17** as well as the amide **18** were synthesized. They retained potency, had a more desirable E_{max} of 59%, 64% and 57%, respectively and were selective over the other α_1 subtypes. Unfortunately, **16** and **18** had asymmetry in the MDCK mdr-1 P-gp assay and likely BBB impairment. Compounds **16** and **17** had fairly high TPSA values, but the amide **18** had a surprisingly high AB/BA ratio for a TPSA of 47. These three compounds also had quite pronounced α_{2A} antagonist activity (α_{2A} Ki 114 nM for **16**, 280 nM for **17** and 202 nM for **18**).

The results above indicated that balancing the desired pharmacological and ADME characteristics through modification of just the 2-position was unlikely to be successful. Moving the heterocycle to the 3- or 4-positions of the phenyl ring was highly detrimental to α_{1A} potency (data not shown).

The strategy then focused on retaining the 2-heterocycle and introducing small groups around the ring in an effort to reduce E_{max} and gain more selectivity. Using the pyrimidine **8** as a starting place, a fluoro group (chosen to minimise increases in Log *D*) was moved around the phenyl ring. Compounds **19, 20** and **21** all modulated E_{max} to some degree with different drop-offs in α_{1A} potency and on the whole the selectivity against the other α subtypes was improved. On balance **20** was the compound of most interest being selective over other α_1 and α_2 subtypes, it also had excellent HLM stability and good flux in the MDCK assay.

Placement of a fluoro group at the 4-position consistently lowered the E_{max} when compared across a range of heterocycles in the 2-position and brought in selectivity, exemplified by **22**, **24** and **27**. Compound **22** was very interesting as it retained a good level of potency but was very partial, having an E_{max} of 43%, whilst being very selective against all other α subtypes tested. **27** had reasonable HLM stability and with a low TPSA was expected to have good CNS penetration.

The pyrimidine **20** had a good balance of pharmacology and in vitro ADME properties, and was assessed further. Compound **20** had no activity against the hERG channel (up to 22 µM), and

no Ki's < 3 μM were found when the compound was screened against a panel of 150 receptors, ion channels and enzymes at Cerep. It showed very weak CYP inhibition, <10% at 3 μM against CYP1A2, 2C9, 2D6 and 3A4. Additionally, **20** had excellent flux when assessed in MDCK mdr-1 cells (A–B 34, B–A 39) which was indicative of excellent permeability combined with no evidence of P-pg mediated efflux which should be predictive of good BBB penetration.

In summary, this novel series of pyrroloimidazoles has been identified as potent and selective partial α_{1A} agonists with potentially good CNS penetration in an inherently more ADME favourable template over the original indane imidazoles.

Acknowledgements

We would like to thank Lucy Rogers and Linda Kitching for screening data; Simon Wheeler, Alan Jessiman, Adam Stennett, Michael Ralph, Helen Mason, Katherine England, Debbie Lovering and Edward Pegden for compound synthesis and Cheryl Doherty for X-ray analysis. We also thank Satish Dayal for ADME assessment of compounds **7**–**27**.

References and notes

1. Musselman, D. M.; Ford, A. P. D. W.; Gennevois, D. J.; Harbison, M. L.; Laurent, A. L.; Mokatrin, A. S.; Stoltz, R. R.; Blue, D. R. *BJU Int.* **2004**, *93*, 78.
2. Whitlock, G. A.; Conlon, K.; McMurray, G.; Roberts, L. R.; Stobie, A.; Thurlow, R. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2930.
3. Roberts, L. R.; Bryans, J.; Conlon, K.; McMurray, G.; Stobie, A.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6437.
4. Whitlock, G. A.; Brennan, P. E.; Roberts, L. R.; Stobie, A. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 3118.
5. Conlon, K.; Christy, C.; Whitlock, G. A.; Roberts, L. R.; Stobie, A.; Thurlow, R. J.; McMurray, G. *JPET*, submitted for publication.
6. Madin-Darby canine kidney (MDCK) cell line expressing the P-glycoprotein transporter (P-gp). Flux across cells was measured at 10 μM substrate concentrations. Figures quoted correspond to the flux rates ($P_{app} \times 10^{-6}$ cm s^{-1}) for apical to basolateral (AB) and basolateral to apical (BA) directions. See reference: Mahar Doan, K. M.; Humphreys, J. E.; Webster, L. O.; Wring, S. A.; Shampine, L. J.; Serabjit-Singh, C. J.; Adkison, K. K.; Polli, J. W. *J. Pharm. Exp. Ther.* **2002**, *303*, 1029.
7. *Caution* should be exercised in the handling of nitro compounds. DSC analysis was determined on all alkyl nitro analogues.
8. *Typical experimental procedure (compound* **8***):* To a solution of aryl bromide **5** (50 mg, 0.19 mmol) in MeCN (2 ml) was added $Pd(PPh_3)_2Cl_2$ (6.7 mg, 0.0095 mmol) followed by 5-pyrimidineboronic acid (47 mg, 0.38 mmol) and finally aq 2 M Na_2CO_3 (285 μl). The mixture was heated at 160 °C in the microwave for 10 min. The reaction was partitioned between DCM (2 ml) and water (2 ml). The separated aqueous layer was washed with DCM (2 ml) and the combined organics dried ($MgSO_4$). The crude product was chromatographed on silica gel using DCM/MeOH (0–5%) as eluant to give 38 mg (76%) of **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.70 (s, 2H), 7.45 (ddd, *J* = 8, 8, 1.6 Hz, 1H), 7.40–7.35 (m, 2H), 7.23 (dd, *J* = 8, 2 Hz, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 4.20 (dd, *J* = 10.2, 7.8 Hz, 1H), 4.13–4.05 (m, 1H), 4.00 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.25 (dd, *J* = 16, 8.6 Hz, 1H) and 3.02 (dd, *J* = 16, 6.6 Hz, 1H). ESCI-MS: *m/z*: $[M+H]^+$ 263 (100%).
9. Assay conditions: The Roche clinical agent Ro 115–1240 had an E_{max} of 60% in our hands, which was in line with published data, see Blue, D. R.; Daniels, D. V.; Gever, J., R.; Jett, M. F.; O'Yang, C.; Tang, H. M.; Williams, T. J.; Ford, A. P. D. W. BJU Int. **2004**, *93*, 162. Ro 115-1240 was reported not to cause cardiovascular effects at the dose tested in the clinic, see Ref. 1 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 mobilisation through the Gq pathway using calcium-sensitive fluorescent dye (Molecular Devices, part number R8033), measured by a Fluorescent Light Imaging Plate Reader (FLIPr). Eleven point concentration response curves were calculated, with E_{max} calculated as a per relative to 10 μM phenylephrine response.
10. CCDC 724363 contains the supplementary crystallographic data for compound **6***:* This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.