



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

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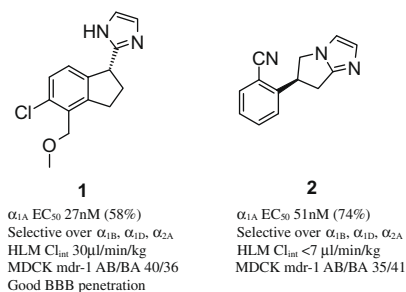
### ABSTRACT

Novel pyrroloimidazoles have been identified as potent partial agonists of the  $\alpha_{1A}$  adrenergic receptor, with good selectivity over the  $\alpha_{1B}$ ,  $\alpha_{1D}$  and  $\alpha_{2A}$  receptor subtypes. Pyrimidine **19** possessed attractive CNS drug-like properties with good membrane permeability and no evidence for P-gp mediated efflux.

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Recent reports described  $\alpha_{1A}$  selective partial agonists having potential clinical utility in the treatment of stress urinary incontinence (SUI).<sup>1</sup> As part of a multi-series approach, we sought to discover templates which could deliver potent and selective  $\alpha_{1A}$  partial agonist activity.<sup>2–4</sup> Biology studies indicated  $\alpha_{1A}$  partial agonists impart their in vivo efficacy in models of SUI via a centrally mediated pathway, and partial agonism of the  $\alpha_{1A}$  receptor may also drive SUI efficacy over undesired cardiovascular effects.<sup>5</sup> 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.<sup>6</sup> 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 ( $E_{\max}$ ).<sup>4</sup> 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 synthe-

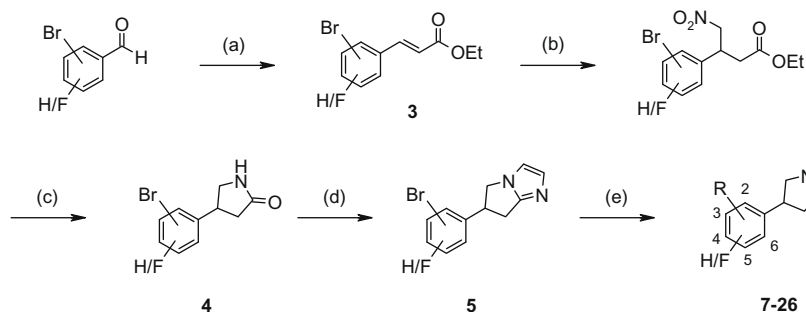


**Figure 1.** Structures, pharmacology and ADME properties of imidazole  $\alpha_{1A}$  partial agonists **1** and **2**.

sized 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**.<sup>7</sup> The lactam was converted to the imidate ester using Meervein's reagent (trimethyltetrafluoroborate) which in turn was displaced with aminoethyl diethylacetal 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.<sup>8</sup> Test compounds were assessed in vitro for their functional activity against human  $\alpha_{1A}$  as well as other alpha sub-

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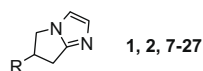
E-mail address: lee.roberts@pfizer.com (L.R. Roberts).



**Scheme 1.** Reagents and conditions: (a)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ , toluene, reflux 2 h; (b)  $\text{MeNO}_2$ , DBU, 0 °C to rt; (c) (i)  $\text{SnCl}_2$ ,  $\text{EtOAc}$ , rt; (ii)  $\text{EtOH}$ , reflux overnight; (d) (i)  $\text{Me}_3\text{OBF}_4$ ,  $\text{CH}_2\text{Cl}_2$ , rt; (ii)  $\text{H}_2\text{NCH}_2\text{CH}(\text{OEt})_2$ ,  $\text{HCl}$ ,  $\text{EtOH}$ , rt; (iii)  $\text{HCl}$ /dioxane,  $\text{H}_2\text{O}$ , 100 °C; (e) either (i)  $\text{R}_3\text{SnBu}_3$ ,  $\text{PdCl}_2(\text{Ph}_3\text{P})_2$  or (ii)  $\text{RB}(\text{OH})_2$ ,  $\text{Pd}$  or (iii) Pyrazole,  $\text{CuI}$  (20 mol %), Phenanthroline (20 mol %),  $\text{Cs}_2\text{CO}_3$ ,  $\text{MeCN}$ , microwave or (iv)  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(o\text{-tol})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{MeCN}$ , 160 °C, microwave followed by  $\text{H}_2$  (60psi), 10%  $\text{Pd/C}$ ,  $\text{EtOH}$ , 60 °C.

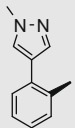
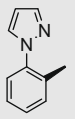
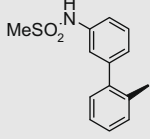
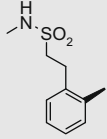
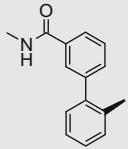
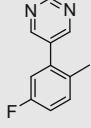
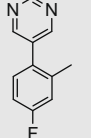
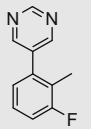
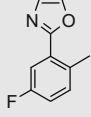
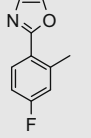
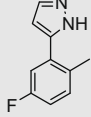
**Table 1**

In vitro functional  $\alpha_{1A}$  agonist activity, in vitro ADME data and physicochemical properties for compounds **1**, **2**, **7–27**



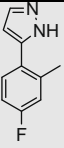
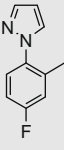
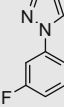
| Compd     | R | $\alpha_{1A}$ $\text{EC}_{50}$<br>(nM) <sup>a,b</sup> | $\alpha_{1A}$ $E_{\text{max}}$<br>(%) | $\alpha_{1B}$ $\text{EC}_{50}$ ( $E_{\text{max}}$ )<br>(nM) | $\alpha_{1D}$ $\text{EC}_{50}$ ( $E_{\text{max}}$ )<br>(nM) | $\alpha_{2A}$ $\text{Ki}$<br>(nM) | HLM Clint $\mu\text{l}/\text{min}/\text{mg}$ | MDCK/mdr-1 P-gp (AB/BA)<br>$P_{\text{app}} \times 10^{-6} \text{ cm s}^{-1}$ | TPSA<br>$\text{\AA}^2$ | Log $D_{7,4}$ |
|-----------|---|-------------------------------------------------------|---------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------|----------------------------------------------|------------------------------------------------------------------------------|------------------------|---------------|
| <b>1</b>  | — | 31                                                    | 60                                    | >10,000                                                     | >7000                                                       | >1700                             | 30                                           | 40/36                                                                        | 38                     | 2.6           |
| <b>2</b>  |   | 51                                                    | 74                                    | >10,000                                                     | >10,000                                                     | >4500                             | <7                                           | 35/41                                                                        | 42                     | 1.3           |
| <b>7</b>  |   | 12                                                    | 83                                    | >10,000                                                     | 729 (51%)                                                   | 213                               | NT                                           | NT                                                                           | 18                     | 1.7           |
| <b>8</b>  |   | 0.4                                                   | 98                                    | >6500                                                       | 391 (75%)                                                   | >3800                             | <8                                           | NT                                                                           | 44                     | 1.2           |
| <b>9</b>  |   | 2                                                     | 91                                    | >1400                                                       | 146 (49%)                                                   | 805                               | 12                                           | NT                                                                           | 43                     | 2.2           |
| <b>10</b> |   | 92                                                    | 62                                    | >10,000                                                     | >3570                                                       | 1020                              | NT                                           | NT                                                                           | 43                     | 2.2           |
| <b>11</b> |   | 3                                                     | 83                                    | NT                                                          | NT                                                          | 1750                              | 18                                           | NT                                                                           | 58                     | 2.3           |
| <b>12</b> |   | 1                                                     | 90                                    | 760 (54%)                                                   | 119 (71%)                                                   | 991                               | 8                                            | 44/47                                                                        | 31                     | 2.1           |
| <b>13</b> |   | 81                                                    | 68                                    | >10,000                                                     | 656 (48%)                                                   | 112                               | 17                                           | NT                                                                           | 31                     | 2.1           |

Table 1 (continued)

| Compd | R                                                                                   | $\alpha_{1A}$ EC <sub>50</sub><br>(nM) <sup>a,b</sup> | $\alpha_{1A}$ E <sub>max</sub><br>(%) | $\alpha_{1B}$ EC <sub>50</sub> (E <sub>max</sub> )<br>(nM) | $\alpha_{1D}$ EC <sub>50</sub> (E <sub>max</sub> )<br>(nM) | $\alpha_{2A}$ Ki<br>(nM) | HLM Clint $\mu$ l/<br>min/mg | MDCK/mdr-1 P-gp (AB/BA)<br>$P_{app} \times 10^{-6}$ cm s <sup>-1</sup> | TPSA<br>Å <sup>2</sup> | Log D <sub>7.4</sub> |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------|------------------------------------------------------------|------------------------------------------------------------|--------------------------|------------------------------|------------------------------------------------------------------------|------------------------|----------------------|
| 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                                                                                 | $\alpha_{1A}$ EC <sub>50</sub><br>(nM) <sup>a,b</sup> | $\alpha_{1A}$ E <sub>max</sub><br>(%) | $\alpha_{1B}$ EC <sub>50</sub> (E <sub>max</sub> )<br>(nM) | $\alpha_{1D}$ EC <sub>50</sub> (E <sub>max</sub> )<br>(nM) | $\alpha_{2A}$ Ki<br>(nM) | HLM Clint $\mu$ l/<br>min/mg | MDCK/mdr-1 P-gp (AB/BA)<br>$P_{app} \times 10^{-6}$ cm s <sup>-1</sup> | TPSA<br>Å <sup>2</sup> | Log D <sub>7.4</sub> |
|-------|-----------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------|------------------------------------------------------------|------------------------------------------------------------|--------------------------|------------------------------|------------------------------------------------------------------------|------------------------|----------------------|
| 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.

<sup>a</sup> Values are geometric means of at least two experiments.<sup>b</sup> See Ref. 8 for description of assay conditions.

types, in human liver microsomes (HLM), MDCK mdr-1 and Log D<sub>7.4</sub> assays (Table 1).<sup>9</sup>

Absolute stereochemistry was determined on one of the enantiomers of the simple bromopyrroloimidazole (**6**) which showed it to have *R* stereochemistry (Fig. 2).<sup>10</sup> 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  $\alpha_{1A}$  and had a different selectivity profile as illustrated by compounds **9** and **10**, whereby **10** is significantly weaker against  $\alpha_{1A}$  but has similar  $\alpha_{2A}$  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<sub>7.4</sub> 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  $\alpha_{1B}$ ,  $\alpha_{1D}$  and antagonism against  $\alpha_{2A}$ . The most potent compound was the pyrimidine **8**, which was very potent against  $\alpha_{1A}$  had some  $\alpha_{1D}$  activity but weak against  $\alpha_{2A}$ . This should be contrasted to the 4-pyridine **13** which had moderate potency against  $\alpha_{1A}$  and as an antagonist against  $\alpha_{2A}$ . The N-linked pyrazole **15** was very potent and full  $\alpha_{1A}$  agonist and was selective across the range of  $\alpha$  subtypes.

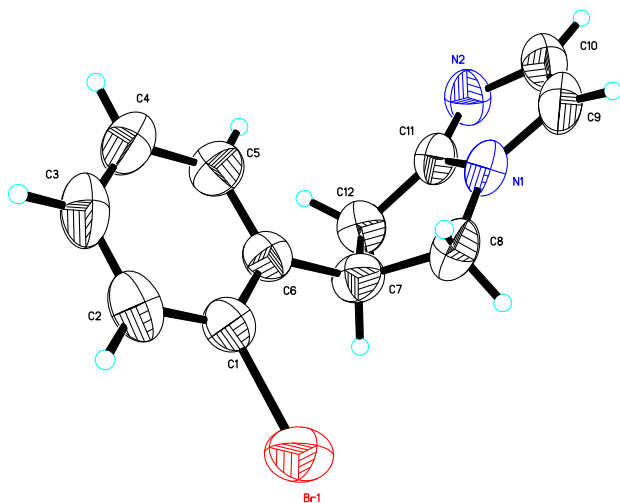
In an effort to lower the E<sub>max</sub> from substitution at the 2-position alone, compounds such as sulfonamides **16** and **17** as well as the amide **18** were synthesized. They retained potency, had a more desirable E<sub>max</sub> of 59%, 64% and 57%, respectively and were selective over the other  $\alpha_1$  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  $\alpha_{2A}$  antagonist activity ( $\alpha_{2A}$  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  $\alpha_{1A}$  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<sub>max</sub> 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<sub>max</sub> to some degree with different drop-offs in  $\alpha_{1A}$  potency and on the whole the selectivity against the other  $\alpha$  subtypes was improved. On balance **20** was the compound of most interest being selective over other  $\alpha_1$  and  $\alpha_2$  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<sub>max</sub> 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<sub>max</sub> of 43%, whilst being very selective against all other  $\alpha$  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  $\mu$ M), and

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

no  $K_i$ 's  $< 3 \mu\text{M}$  were found when the compound was screened against a panel of 150 receptors, ion channels and enzymes at Cer-ep. It showed very weak CYP inhibition,  $<10\%$  at  $3 \mu\text{M}$  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-gp 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  $\alpha_{1A}$  agonists with potentially good CNS penetration in an inherently more ADME favourable template over the original indane imidazoles.

## Acknowledgements

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- Madin-Darby canine kidney (MDCK) cell line expressing the P-glycoprotein transporter (P-gp). Flux across cells was measured at  $10 \mu\text{M}$  substrate concentrations. Figures quoted correspond to the flux rates ( $P_{app} \times 10^{-6} \text{ cm s}^{-1}$ ) 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.
- Caution should be exercised in the handling of nitro compounds. DSC analysis was determined on all alkyl nitro analogues.
- Typical experimental procedure (compound 8)*: To a solution of aryl bromide **5** (50 mg, 0.19 mmol) in MeCN (2 ml) was added  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (6.7 mg, 0.0095 mmol) followed by 5-pyrimidineboronic acid (47 mg, 0.38 mmol) and finally aq 2 M  $\text{Na}_2\text{CO}_3$  (285  $\mu\text{l}$ ). The mixture was heated at  $160^\circ\text{C}$  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 ( $\text{MgSO}_4$ ). The crude product was chromatographed on silica gel using DCM/MeOH (0–5%) as eluant to give 38 mg (76%) of **8**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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). ESI-MS:  $m/z$ :  $[\text{M}+\text{H}]^+$  263 (100%).
- Assay conditions: The Roche clinical agent Ro 115–1240 had an  $E_{\text{max}}$  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  $\alpha_{1A}$  (clone 54),  $\alpha_{1B}$  (SNB0000700, clone 11) and  $\alpha_{1D}$  (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  $E_{\text{max}}$  calculated as a per relative to  $10 \mu\text{M}$  phenylephrine response.
- 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](http://www.ccdc.cam.ac.uk/data_request/cif).