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Binding of an imidazopyridoindole at imidazoline I_2 receptors

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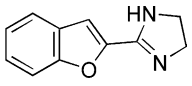
Abstract—3,5,6,11-Tetrahydro-2*H*-imidazo[1′,2′:1,2]pyrido[3,4-*b*]indole (**10**) might be viewed as a fusion structure of two classes of I_2 imidazoline receptor ligands: 2-(2-benzofuranyl)-2-imidazolines and β-carbolines. Its high affinity ($K_i = 7.3$ nM) provides insight to how the two classes of agents might bind relative to one another at I_2 receptors.

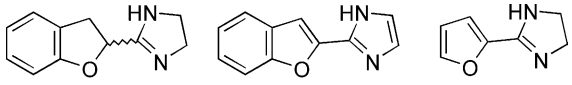
Imidazoline binding sites (IBS), which have been variously referred to in the literature as imidazoline/guanidinium receptive sites (IGRS) or simply as imidazoline receptors, were proposed to explain actions of guanidine-containing (more typically, imidazoline-containing) agents that could not be accounted for by their interaction with adrenergic receptors.[1–4] Two main types of imidazoline receptors have been proposed: I_1 and I_2 receptors, and there is some evidence for others.[1–4] Although the exact pharmacological significance of I_2 receptors has yet to be firmly established, there are indications that they might be involved in opioid-induced antinociception, neuroprotection, depression and other CNS disorders.[1,3,4]

Most I_2 ligands possess an imidazoline ring, and a general problem associated with these compounds is a lack of selectivity for I_2 receptors versus I_1 and/or α_2-adrenergic receptors. This is not to say that imidazoline receptor selectivity cannot be altered. For example, certain 2-arylimidazolines are fairly selective for I_2 versus I_1 receptors whereas others are selective for I_1 versus I_2 receptors.[5] One of the most widely used I_2 ligands is 2-(2-benzofuranyl)-2-imidazoline (2-BFI; **1**). This agent binds at I_2 receptors with high affinity ($K_i < 10$ nM), displays modest selectivity versus I_1 receptors (I_1 K_i ca. 70 nM) and low affinity for α_2-adrenergic receptors (K_i ca. 4000 nM).[1,2] A tritiated version has been introduced as a radioligand.[6,7]



1

Surprisingly little has been published on the structure-affinity relationships of 2-BFI (**1**). Nevertheless, it is known that reduction of the benzofuranyl ring to its 2,3-dihydro analogue RX801080 (**2**; $K_i \approx 50$ nM) reduces I_2 affinity by >10-fold,[8] and oxidation of the imidazoline ring to an imidazole reduces affinity by several hundred-fold (LSL 60101, **3**; $K_i \approx 350$–880 nM).[2,7,9] 2-BFI aryl ring substituents are tolerated depending upon the nature and location of the substituent,[8] but the presence of the benzenoid portion of 2-BFI is a requirement for binding as seen by the >1000-fold reduced affinity of **4** ($K_i = 2340$ nM) as compared with **1** ($K_i = 2$ nM).[5]



2 **3** **4**

An intact benzofuran ring is not necessary for I_2 binding. For example, compounds **5**–**7** bind with high affinity at I_2 receptors (K_i ca. 1–5 nM); **5** and **7** also display 794- and 1479-fold selectivity for I_2 over I_1 receptors.[10–12] Tracizoline (**6**; I_2 $K_i = 2$ nM, I_1 $K_i = 10$ nM) is an example of an agent that displays very low affinity for α_2-adrenergic receptors ($K_i = 7{,}413$ nM) but little selectivity versus I_1 receptors.[10]

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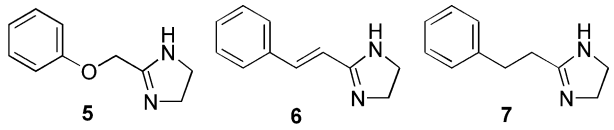
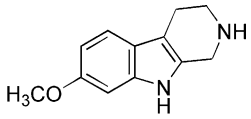


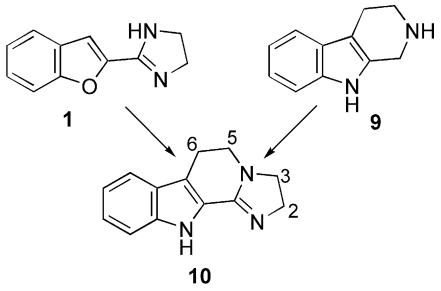
5 6 7

We have recently described structure–affinity relationships for the binding of a class of imidazoline-lacking I_2 ligands: β-carbolines. In particular 7-methoxy-1,2,3,4-tetrahydro-β-carboline (**8**) binds at I_2 receptors with high affinity ($K_i = 12$ nM) and displays reduced affinity for I_1 ($IC_{50} > 10{,}000$ nM) and α_2-adrenergic ($K_i = 8{,}840$ nM) receptors.[13] As such, β-carbolines offer entry to I_2 receptor ligands with enhanced selectivity.



8

Detailed QSAR studies conducted with various I_2 ligands have shown that I_2 receptors prefer a more planar structure than I_1 receptors, and that there exist receptor regions that favor or disfavor steric bulk and electronic character.[11,14–16] However, these studies were conducted primarily on imidazoline-containing ligands. It might be possible to extrapolate these findings to further enhance the affinity and selectivity of the β-carbolines if it can be shown how the β-carbolines bind relative to imidazolines. The purpose of the present investigation was to provide evidence for this. That is, the goal of the investigation was not necessarily to develop an agent with enhanced selectivity for I_2 versus I_1 or α_2-adrenergic receptors. Rather, it was to define how β-carbolines might bind relative to the imidazolines, and specifically, relative to 2-BFI (**1**). To this extent we fused an imidazoline moiety to 1,2,3,4-tetrahydro-β-carboline (**9**) to afford 3,5,6,11-tetrahydro-2*H*-imidazo[1′,2′:1,2]pyrido[3,4-*b*]indole (**10**).[17]



1 9 10

Compound **10** (I_2 $K_i = 7.3 \pm 3.8$ nM) was found to bind at I_2 receptors with an affinity comparable to that of 1,2,3,4-tetrahydro-β-carboline (**9**; I_2 $K_i = 9.4$ nM), and displayed moderate affinity for I_1 ($IC_{50} = 180 \pm 30$ nM) and α_2-adrenergic ($K_i = 710 \pm 30$ nM) receptors.[18] Whereas **9** binds at I_2 receptors and α_2-adrenergic receptors with >1000-fold and 170-fold selectivity, respectively,[13] the selectivity of **10** is somewhat lower, and must be directly attributable to the presence of the embedded imidazoline structure. Nevertheless, **10**, which incorporates relevant structural features of the imidazoline and β-carboline classes of I_2 ligands, provides important insight as to how these agents might bind at I_2 receptors relative to one another. It should now be possible to utilize or extrapolate the results of SARs and QSAR studies with imidazolines to enhance the affinity of β-carboline derivatives for I_2 imidazoline receptors, and to include β-carbolines in future QSAR studies.

Acknowledgements

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Abramovitch and Shapiro.[21] A stirred solution of 2-bromoethylamine hydrobromide (2.3 g, 113 mmol) and the carbolin-2-one (2.1 g, 113 mmol) in $POCl_3$ (100 mL) was heated at reflux for 3 h. Solvent was removed under reduced pressure to give an oil; a solution of NaOMe (4.9 g, 90 mmol) in MeOH (40 mL) was added to the oil and the reaction mixture was allowed to stir at room temperature for 24 h. Solvent was removed under reduced pressure and H_2O (150 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL); the organic portions were combined and solvent was removed under reduced pressure. The oily product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 19:1) to afford a yellow solid (0.5 g, 19%): mp 224–226 °C. The oxalate salt was prepared and recrystallized from 2-PrOH to afford **10** as a yellow solid: mp 247–248 °C. MALDI-TOF/MS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}N_{14}H_3$, 212.27; found 212.19. ^{1}H NMR (DMSO-d_6) δ 3.24 (t, 2H, J = 7.62 Hz, $-CH_2-$), 3.69 (t, 2H, J = 7.62 Hz, $-CH_2$), 3.84–4.02 (m, 4H, $(-CH_2-)_2$), 7.14–7.19 (m, 1H, ArH), 7.35–7.40 (m, 1H, ArH), 7.55 (d, 1H, J = 8.50 Hz, ArH), 7.72 (d, 1H, J = 8.21 Hz, ArH), 12.98 (bs, 1H, –NH–). Anal. calcd for ($C_{13}H_{13}N_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$), C, 58.91; H, 5.11; N, 13.74. Found: C, 59.21; H, 5.02; N, 13.71.

18. Radioligand binding studies using crude P2 membranes prepared from rat (male, Wistar ~250 g) whole brains and kidneys; I_1, I_2 and α_2-adrenoceptor competition binding was performed as previously described.[13] Each assay was analyzed individually using GraphPad Prism version 3.03 for Windows, (GraphPad Software; San Diego, CA, USA) and the IC_{50} value determined. In the case of the I_2 and α_2-adrenoceptor binding, this was then used to calculate the K_i using the method of Cheng and Prusoff.[22]
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