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Pyrazino[1,2-*a*]indoles as novel high-affinity and selective imidazoline I_2 receptor ligands

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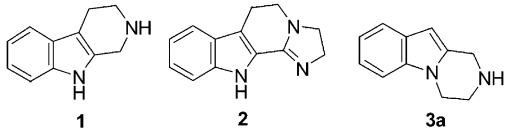
Abstract—1,2,3,4-Tetrahydropyrazino[1,2-*a*]indoles are described as a novel class of I_2 imidazoline receptor ligands. In particular, 8-methoxy-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (8-OMe THPI; **3c**) binds with high affinity at I_2 imidazoline receptors ($K_i = 6.2$ nM) and with exceptional (≥ 1000-fold) selectivity relative to its affinity for I_1 imidazoline receptors, $\alpha_2$adrenergic receptors, and 5-HT_{2A} and 5-HT_{2C} serotonin receptors.

Imidazoline receptors have been categorized as belonging to at least two different types: I_1 and I_2 receptors.[1–3] Agents binding at I_2 receptors usually possess an imidazoline moiety, and typically suffer from a lack of selectivity for I_2 receptors versus I_1 and/or α_2-adrenergic receptors. Only recently have I_2 ligands with appreciable selectivity become available.[1–5] One of the most widely used I_2 ligands is 2-(2-benzofuranyl)-2-imidazoline (2-BFI).[2] 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).[2] Its tritiated version has been introduced as a radioligand.[6,7]

Given the previous unavailability of selective agents, it has been difficult to identify potential physiological or therapeutic roles for I_2 receptors. Some have suggested that imidazoline receptors might represent regulatory binding sites on monoamine oxidase (MAO), but this issue is controversial.[2,3] Evidence also suggests that I_2 receptors might be involved in opioid-induced antinociception, neuroprotection, depression and other CNS disorders.[1–3]

β-Carbolines represent a new class of imidazoline receptor ligands and several have been demonstrated to bind with K_i values of <10 nM.[8,9] Fully unsaturated β-carbolines seem to bind both at I_1 and I_2 receptors whereas 3,4-dihydro and 1,2,3,4-tetrahydro-β-carbolines are more selective for I_2 receptors.[9] We have recently reported on the structure–affinity relationships for the binding of β-carboline analogues at imidazoline I_2 receptors. Compound **1**, for example, binds at I_2 receptors with high affinity ($K_i = 9.4$ nM) and displays reasonable selectivity over I_1 ($K_i = 9{,}910$ nM) and α_2-adrenergic ($K_i = 1600$ nM) receptors.[9] A problem with β-carbolines, not common to the imidazolines class of I_2 ligands, is that they typically bind at 5-HT_{2A} receptors;[10] but, **1** shows low affinity (5-HT_{2A} $K_i = 3{,}800$ nM) for these receptors.[11] Compound **2** also binds with high affinity at I_2 receptors ($K_i = 7.3$ nM)[12] but displays reduced selectivity that is likely due to the presence of the fused imidazoline ring. It was reasoned that an intact piperidine ring might not be necessary for I_2 binding and that **3a**, which represents an analogue of **2** lacking both the imidazoline ring and a portion of the piperidine ring, might retain high affinity but display enhanced selectivity. Hence, we prepared and evaluated compound **3a** with the expectation that it would bind at I_2 receptors.



1 **2** **3a**

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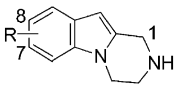
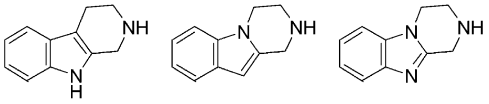
Table 1. Radioligand binding data for compounds **3** and **4**[a]



	R	I_2; K_i, nM (±SEM)	α_2-Adrenergic K_i, nM (±SEM)
3a	H	6.5 (±5.4)	516 (±210)
3b	7-OCH_3	250 (±27)	4510 (±1330)
3c	8-OCH_3	6.2 (±3.3)	9550 (±1070)
4	—	6790 (±3270)	13,400 (±1230)

[a] Values are means of at least three experiments using binding assays as previously reported.[9,14] Compounds were synthesized following literature procedures.[13]



1 **3a** **4**

Figure 1. Possible structural relationships between 1,2,3,4-tetrahydro-β-carboline (**1**), 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (**3a**), and a hydrid structure **4**.

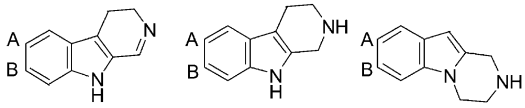
Tetrahydropyrazino[1,2-*a*]indole **3a**, prepared as previously described,[13] was found to bind at I_2 receptors with high affinity (I_2 $K_i = 6.5$ nM; Table 1). Compound **3a** also showed nearly 100-fold selectivity for I_2 versus α_2-adrenergic receptors ($K_i = 516$ nM).

It quickly became apparent, although **3a** binds with high affinity, that it might not bind as initially envisioned. That is, **3a** might also be viewed as a β-carboline analogue where the indolic nitrogen atom has been moved from the β-carboline 9-position to a ring-fusion position (Fig. 1).

One means to test this hypothesis was to re-incorporate the indolic nitrogen atom to afford **4**. However, **4** was found to bind with >1000-fold reduced affinity at I_2 receptors ($K_i = 6{,}790$ nM). The low affinity of **4** suggested that **3a** might not bind in the same manner as **1** (as shown in Fig. 1). Alternatively, I_2 receptors might not accommodate the hybridization state of the added nitrogen atom of **4**.

Another study to determine how **3a** might bind relative to **1** was to compare several methoxy-substituted derivatives. Introduction of a methoxy group at the 7-position (i.e., position B; Table 2) of 3,4-dihydro-β-carbolines and 1,2,3,4-tetrahydro-β-carbolines has little effect on I_2 affinity compared to the parent unsubstituted compounds. However, a methoxy group at the 6-position (i.e., position A; Table 2) is not as well tolerated. In the pyrazinoindole series, incorporation of a methoxy group at the 8-position (position A) had no effect on affinity whereas incorporation at the 7-position (position B) resulted in reduced affinity. On the basis of these comparisons, it is concluded that the pyrazinoindoles **3** (or at least compound **3c**) likely bind(s), relative to compound **1**, at I_2 receptors as shown in Figure 1. Apparently, the added nitrogen atom of **4** accounts for its reduced affinity.

Table 2. Comparative I_2 radioligand binding data for three series of compounds (from left to right: 3,4-dihydro-β-carbolines, 1,2,3,4-tetrahydro-β-carbolines, and 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles)[a]



	I_2; K_i, nM		
H	7.3	9.4	6.5
A-OCH_3	480	1640	6.2
B-OCH_3	18	12	250

[a] Binding data for the β-carboline derivatives were reported earlier and are included only for comparison. Data for the pyrazinoindoles are from Table 1.

Compound **3c** (8-OMe THPI; $K_i = 6.2$ nM) binds at I_2 receptors with high affinity and with >1000-selectivity over α_2-adrenergic receptors. It was also found that **3c** (I_1 $IC_{50} = 8280 \pm 340$ nM) binds with >1000-fold selectivity over I_1 receptors. Unlike many β-carbolines, **3c** displays low affinity for 5-HT_{2A} ($K_i = 5{,}830$ nM) and 5-HT_{2C} ($K_i = 9{,}930$ nM) serotonin receptors,[13] making it a rather selective I_2 ligand. Future studies are planned to further characterize the pharmacology of **3c**, and to utilize **3c** as a template for the development of novel I_2 ligands.

Acknowledgements

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