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N-(QUINUCLIDIN-3-YL)-2-(1-METHYL-1*H*-INDOL-3-YL)-2-OXO-ACETAMIDE: A HIGH AFFINITY 5-HT$_3$ RECEPTOR PARTIAL AGONIST

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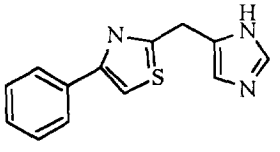
Abstract: The enantiomers of the indolyl-2-oxoacetamide **5** were found to have 5-HT$_3$ receptor partial agonist activity with (*R*)-**5** having higher potency than (*S*)-**5**.

In contrast to the plethora of 5-HT$_3$ receptor antagonists that have been reported,[1,2] relatively few 5-HT$_3$ receptor agonists have been described. In addition to the natural agonist 5-HT, agonists that have been used as pharmacological tools for investigating 5-HT$_3$ receptor activity include 2-methyl-5-hydroxytryptamine (2-Me-5HT)[3] and 1-(m-chlorophenyl)biguanide.[4] More recently, 5-HT$_3$ receptor agonist activity has been reported for the imidazole **1**,[5] the *N*-(*R*)-3-quinuclidinyl benzoylurea **2**,[6] and a series of phenylureas derived from histamine as exemplified by **3**.[7] While investigating structure-activity relationships among high affinity 5-HT$_3$ receptor antagonists related to the 3-quinuclidinyl indole-3-carboxamide **4**,[2] we prepared the racemic indolyl-2-oxoacetamide **5** and determined that this compound had 5-HT$_3$ receptor affinity comparable to **4**.[8,9] However, further evaluation revealed two interesting facets relative to the progenitor **4**: 1) a reversal in the enantioselectivity of the isomers of **5** for binding to the 5-HT$_3$ receptor , and 2) both isomers of **5** were found to be 5-HT$_3$ receptor partial agonists. Details of these findings are reported herein.



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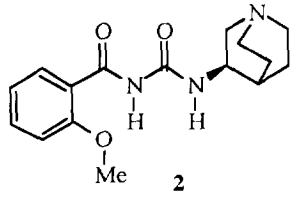

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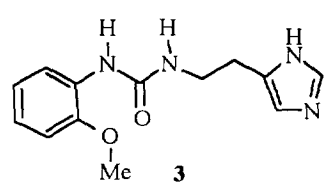

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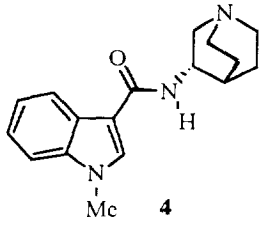

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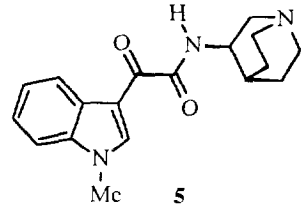

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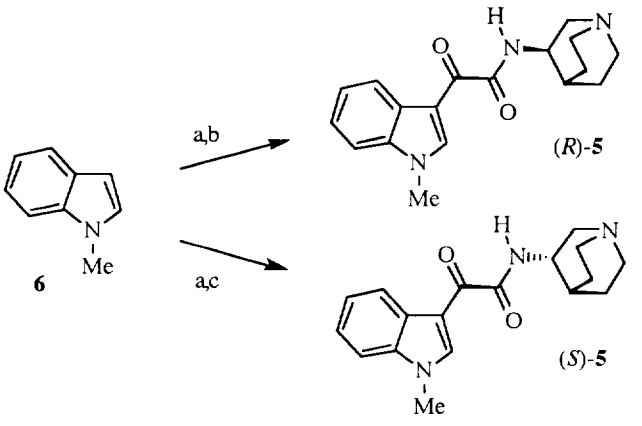
The enantiomers of **5** were prepared by treatment of 1-methylindole (**6**) with oxalyl chloride followed by reaction of the resultant glyoxalyl chloride with (*R*)- or (*S*)-3-aminoquinuclidine. Conversion to the hydrochloride salt was effected with ethanolic HCl, (*S*)-**5**: mp 303-304 °C, $[\alpha]^{25}_D$ -16.3° (c 1.1, H_2O); (*R*)-**5**: mp 301-303 °C, $[\alpha]^{25}_D$ +15.8° (c 0.9, H_2O).



a: oxalyl chloride, ether, rt; b: (*R*)-3-aminoquinuclidine, CH_2Cl_2;
c: (*S*)-3-aminoquinuclidine, CH_2Cl_2.

A receptor binding profile indicated that both isomers of **5** were selective 5-HT_3 receptor ligands with high affinity for the 5-HT_3 receptor in rat brain cortical membranes labeled with [^{3}H]RS 42358-197.[10] Significantly, the enantioselectivity of 5-HT_3 receptor binding was reversed relative to prototypical 3-quinuclidinyl amides such as **4**[2] and related high affinity ligands in which the (*S*)-enantiomers have higher affinity than the (*R*)-enantiomers.[1,2] A similar reversal of enantioselectivity has been noted for the benzoylurea **2**[6] and for *N*-(quinuclidin-3-yl)-1,8-naphthalimides.[11,12]

TABLE 1. Receptor Binding Profile of (*S*)-**5** and (*R*)-**5**

receptor[a]	Binding pK_i[b] (*S*)-**5**	(*R*)-**5**	receptor[a]	Binding pK_i[b] (*S*)-**5**	(*R*)-**5**
5-HT_{1A}	<4	<4	Adrenergic α_{2B}	4.6 ± 0.2	5.5 ± 0.3
5-HT_{1D}	<4	4.4 ± 0.4	Adrenergic β_1	<4	<5
5-HT_{2A}	4.6 ± 0.1	4.9 ± 0.1	Adrenergic β_2	<4	<5
5-HT_{2C}	4.9 ± 0.3	4.8 ± 0.1	Dopamine D_1	<4	<4
5-HT_3	7.9 ± 0.1	9.6 ± 0.2	Dopamine D_2	<4	<4
5-HT_4	6.4 ± 0.1	6.6 ± 0.1	Muscarinic M_1	4.6 ± 0.2	5.0 ± 0.1
Adrenergic α_{1A}	4.6 ± 0.1	<5	Muscarinic M_2	4.3 ± 0.1	4.3 ± 0.1
Adrenergic α_{1B}	4.8 ± 0.1	<5	Muscarinic M_3	4.5 ± 0.1	4.3 ± 0.1
Adrenergic α_{2A}	4.5 ± 0.1	5.1 ± 0.1	Muscarinic M_4	—	4.6 ± 0.1

[a]Radioligand binding assays were performed as described in reference 13. [b]mean pK_i±SEM (n = 3)

Inhibition of 2-Me-5-HT induced bradycardia (von Bezold-Jarish (B-J) reflex) in the anesthetized rat is a standard assay for in vivo 5-HT_3 receptor antagonist activity.[3] When tested in this protocol, it was found that both enantiomers of **5** induced bradycardia in the absence of 2-Me-5-HT, i.e., these compounds appeared have 5-HT_3 agonist activity (Table 2). The relative potencies of (*S*)-**5** and (*R*)-**5** were in accord with the affinities from the binding studies (Table 1) and both enantiomers were partial agonists, eliciting 57% and 41% of the maximal 2-Me-5-HT response, respectively. The bradycardia induced by (*S*)-**5** and (*R*)-**5** was blocked by the 5-HT_3 antagonist granisitron, indicating that the observed activity was indeed mediated by the 5-HT_3 receptor.

The 5-HT_3 (partial) agonist activity of (*S*)-**5** and (*R*)-**5** was subsequently confirmed in the rat isolated vagus nerve[14] (Table 2). In this preparation, under the conditions used, 5-HT mediates depolarization of the vagus nerve through the 5-HT_3 receptor. Methiothepin (1 μM) was used to block 5-HT_1 and 5-HT_2 receptors, and GR 113808 (10 μM) was used to block 5-HT_4 receptors. The data in Table 2 indicate that (*R*)-**5** was significantly more potent than 5-HT, and was a partial agonist, in agreement with the data from the anesthetized rat.

TABLE 2. 5-HT_3 Agonist Activity of (*S*)-**5** and (*R*)-**5**

	Induction of B-J Reflex in the Anesthetized Rat		Depolarization of Isolated Rat Vagus Nerve	
	ED_{50} (μg/kg, iv)	% control[a]	pEC_{50} (95% C.I.)[b]	Maximum response (μV)
(*S*)-**5**	8.5	33	5.67 (5.06-6.28)	167 ± 9[c]
(*R*)-**5**	0.6	24	7.45 (7.15-7.75)	140 ± 11[d]
2-Me-5-HT	7.7	58	5.21 (5.09-5.34)[e]	363 ± 21[e]
5-HT	—	—	6.01 (5.92-6.11)	340 ± 21[c]

[a]% decrease in heart rate relative to pre-dose control. [b]n = 12 for 5-HT; n = 8 for (*S*)-**5** and (*R*)-**5**. [c]Measured at 10 μM agonist. [d]Measured at 1 μM agonist. [e]Reference 14.

An X-ray structure determination on the hydrochloride salt of (*R*)-**5** (Figure 1) indicated that in the solid state the molecule exists in an extended conformation with the carbonyls oriented in a trans-coplanar relationship, as expected on electrostatic grounds. In order to explore the possible structural relationships among agonists **1**-**3** and **5**, low energy conformations of these compounds were determined and superimpositions were performed using SYBYL.[15] The (*R*)-3-quinuclidinyl agonists **2** and (*R*)-**5** showed good overlap when **2** was placed in an extended (local minimum) conformation; i.e., the aromatic moieties and the distal carbonyls, nitrogens, and quinuclidinyl rings could occupy the same regions of space (Figure 2). However, reasonable overlap of low energy conformations of the imidazole containing agonists **1** and **3** with (*R*)-**5** could not be attained, indicating that on the basis of these limited examples a unifying pharmacophore for the 5-HT_3 receptor agonist binding site could not be proposed. Although a possible relationship of agonist **3** to 5-HT has been proposed,[7] a similar relationship of **2** and (*R*)-**5** to the natural agonist is not apparent.

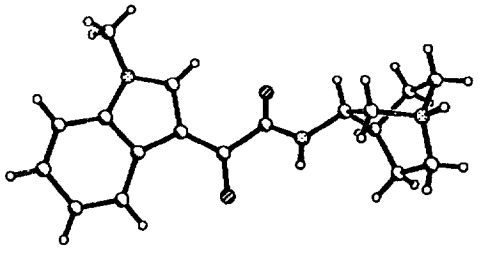


Figure 1. X-ray structure of (*R*)-**5**•HCl

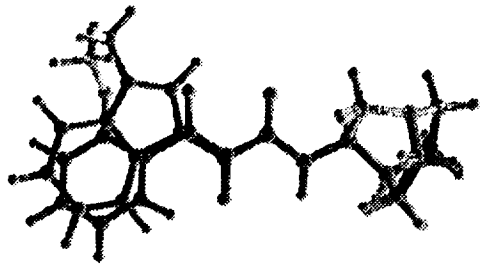


Figure 2. Overlap of **2** and (*R*)-**5**

In conclusion, both enantiomers of **5** were found to be selective 5-HT_3 receptor partial agonists with the (*R*)-isomer having greater affinity, but slightly less intrinsic activity, than the (*S*)-isomer. Both isomers have interesting behavioral effects in animal models and these effects will be described in a future publication.

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