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N-(QUINUCLIDIN-3-YL)-1,8-NAPHTHALIMIDES WITH 5-HT$_3$ RECEPTOR ANTAGONIST AND 5-HT$_4$ RECEPTOR AGONIST PROPERTIES

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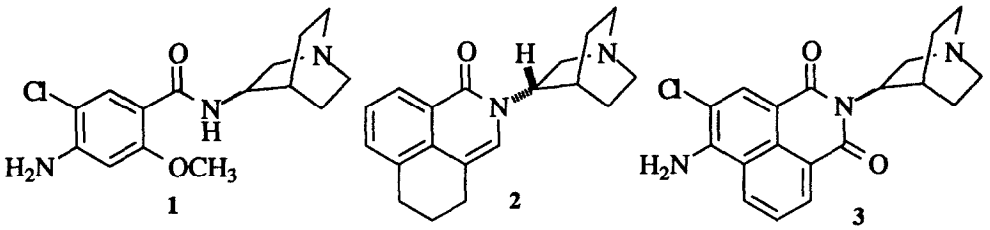
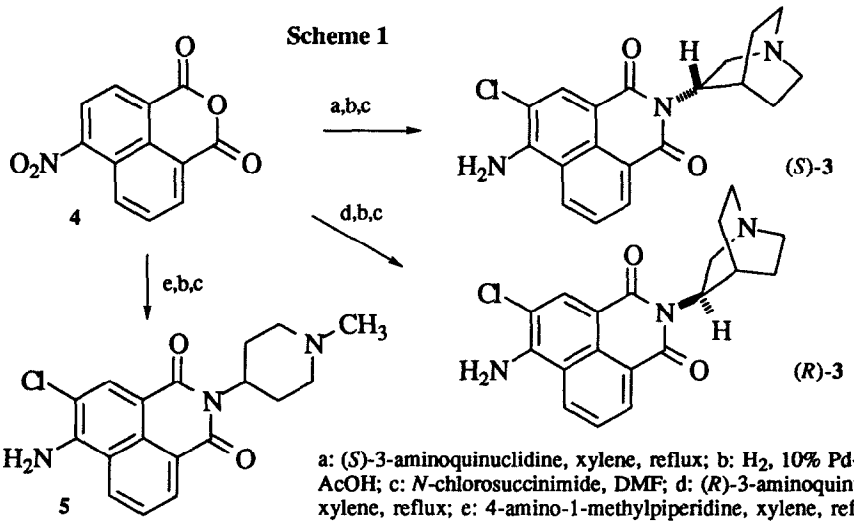
Abstract: The enantiomers of *N*-(quinuclidin-3-yl)-4-amino-3-chloro-1,8-naphthalimide (**3**) were examined for interactions at 5-HT$_3$ and 5-HT$_4$ receptors. (**R**)-3 was found to be a potent 5-HT$_3$ receptor antagonist while (**S**)-3 was found to be a 5-HT$_4$ receptor agonist with reduced 5-HT$_3$ receptor affinity.

The 5-HT$_4$ receptor represents the fourth distinct class of serotonin receptor to be characterized[1] and has been identified in central nervous system[2], gastrointestinal[3], and cardiac[4] tissues. In the search for agonists and antagonists of this receptor it was noted that several high-affinity 5-HT$_3$ receptor antagonists displayed weak interaction with the 5-HT$_4$ receptor. For example, tropisetron (ICS 204-930) was found to be a weak 5-HT$_4$ receptor antagonist[1] and zacopride (**1**) was shown to be a weak 5-HT$_4$ receptor agonist.[5] Recently, a number of more selective and potent 5-HT$_4$ receptor agonists[6-8] and antagonists[9-15] have been reported. While exploring the structure-activity relationships among hybrid structures of zacopride (**1**) and the high affinity 5-HT$_3$ receptor antagonist **2**[16,17], we prepared the enantiomers of the *N*-(quinuclidin-3-yl)-1,8-naphthalimide **3**.[18,19] In this communication, we report that both (*S*)-**3** and (*R*)-**3** have 5-HT$_3$ receptor antagonist and 5-HT$_4$ receptor agonist properties, and that there is a reversal of the enantioselectivity of the isomers in the interactions with these receptors.



The enantiomers of **3** were prepared in three steps from 4-nitro-1,8-naphthalic anhydride (**4**) as described in Scheme 1. Affinity at the 5-HT_3 receptor was determined in rat cerebro cortical membranes by measurement of displacement of [^{3}H]quipazine.[20] In vivo 5-HT_3 receptor antagonist activity was determined by antagonism of the von Bezold-Jarisch (B-J) reflex in anesthetized rats.[21] 5-HT_4 receptor agonist (or antagonist) activity was determined in the rat esophageal muscularis mucosae preparation.[22] Results of the 5-HT_3 and 5-HT_4 receptor assays are presented in Table 1.

Scheme 1



a: (*S*)-3-aminoquinuclidine, xylene, reflux; b: H_2, 10% Pd-C, AcOH; c: *N*-chlorosuccinimide, DMF; d: (*R*)-3-aminoquinuclidine, xylene, reflux; e: 4-amino-1-methylpiperidine, xylene, reflux.

An initial interesting finding was that (*R*)-**3** had ca. 10-fold greater 5-HT_3 receptor affinity than (*S*)-**3**.[19] This was in contrast to the higher 5-HT_3 receptor affinity of the (S)-enantiomers of zacopride (**1**) (Table 1) and compound **2**.[17] The in vivo 5-HT_3 receptor antagonist activity of (*R*)-**3** was also significantly greater than that of (*S*)-**3** in the B-J assay. When tested for 5-HT_4 receptor activity, (*R*)-**3** was found to be a weak agonist in the esophageal preparation. However, (*S*)-**3** was found to be a potent agonist in this system. The same enantioselectivity of 5-HT_4 receptor agonist activity was observed for the zacopride enantiomers in the esophageal preparation where (*S*)-zacopride exhibited ca. 10-fold greater agonist activity than (*R*)-zacopride.

Table 1. Activity at 5-HT_3 and 5-HT_4 Receptors

	5-HT_3 Receptor		5-HT_4 Receptor	
	Binding[a]	Inhibition of	Agonist activity	
	pK_i + SEM	B-J Reflex[b]	esophagus[c]	
compound		ug/kg iv (95% CL)	pEC50 (95% CL)	i.a.[d]
(*S*)-**3**	8.0 ± 0.1	77 (47-128)	7.9 (7.7-8.4)	0.8
(*R*)-**3**	9.1 ± 0.1	4.5 (3.0-6.8)	<6	-
5	7.4 ± 0.1	288 (195-417)	7.5 (7.3-7.6)	0.9
(*S*)-zacopride	9.6 ± 0.1	nt[e]	7.2 (7.1-7.2)	0.9
(*R*)-zacopride	8.5 ± 0.1	nt	6.3 (6.1-6.5)	0.9
ondansetron	8.5 ± 0.2	2.6 (1.5-4.7)	nt	
5-HT	-	-	8.2 (8.1-8.3)	1.0

[a]Determined in rat cerebro cortical membranes using [^{3}H]quipazine. [b]In the anesthetized rat. [c]Relaxation of carbachol contracted rat esophageal muscularis mucosae. [d]Intrinsic activity relative to 5-HT. [e]not tested.

Additional SAR work around structure **3** produced the 4-piperidinyl analogue **5** which retained the 5-HT_4 agonist properties of (*S*)-**3** but had less affinity for the 5-HT_3 receptor. Unfortunately, further development of this series was precluded by adverse toxicological findings. However, results of animal behavioral studies with these agents offer information regarding serotonergic mechanisms in the CNS. In addition, SAR information gained has allowed preparation of more potent and selective 5-HT_4 agonists. Results of these studies will be presented in due course.

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