Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 5, pp. 695-698, 1994

0960-894X/94 $6.00+0.00

0960-894X(94)E0049-K

PYRAZOLO[1,5-a]PYRIDINES AND PYRAZOLO[1,5-b]PYRIDAZINES AS $5HT_3$-ANTAGONISTS

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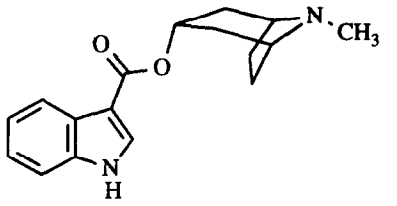
Abstract: The synthesis of 3-carboxamide and 3-carboxylates of pyrazolo[1,5-a]pyridines and pyrazolo[1,5-b]pyridazines is described. These compounds are characterized as potent and selective $5HT_3$-antagonists in vitro and in vivo.

Antagonists of the serotonin $5HT_3$ receptor are now used clinically for the treatment of emesis evoked by cancer chemotherapy and have proven active in animal models of anxiety, schizophrenia, memory disorders and drug dependency[1].

Among the series of $5HT_3$-antagonists, which have been described in recent years, are the indolyl derivatives like tropisetron **1**[1], the structure of which has been the starting point for the synthesis of the indazolyl derivative granisetron **2**, ureas like **3** which due to intramolecular hydrogen binding can be regarded as indole isosteres[2], and fused heteroaromatics such as 3-carboxamido-indolizines- and imidazopyridines[3]



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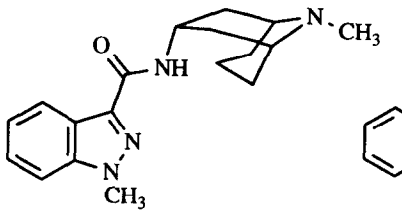

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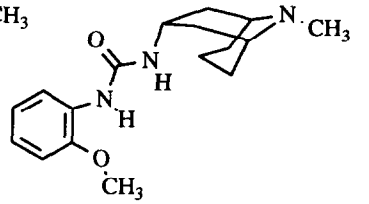

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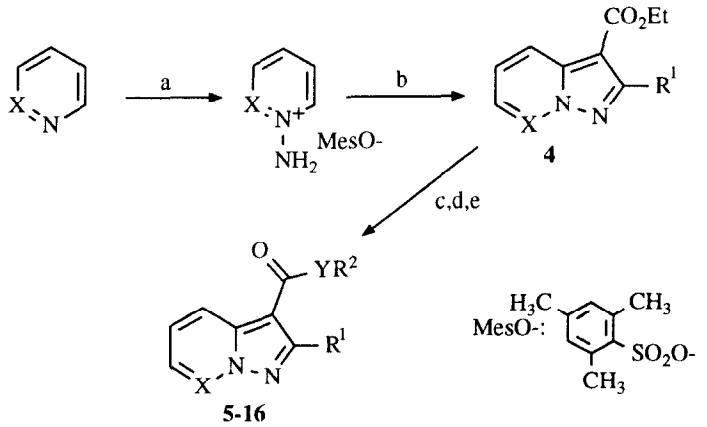
Since the indole ring system is an important entity of many biologically important molecules, the identification of new indole isosteres can be important in the search for new pharmaceuticals.

Therefore, we now wish to present the use of pyrazolo[1,5-a]pyridines and pyrazolo[1,5-b]pyridazines as indole isosteres in a series of potent and selective $5HT_3$-antagonists.

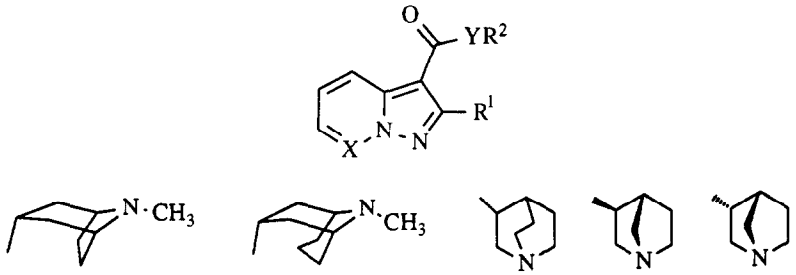


a. H_2N Mes, CH_2Cl_2, 90–95%; b. $R^1C{\equiv}CCO_2Et$, THF, K_2CO_3, 20–40%; c. NaOH, H_2O, EtOH, reflux, 90%; d. $SOCl_2$, THF, reflux, 90%; e. R^2–Y–H, THF, Et_3N, 40–85%.

CHEMISTRY. The ethyl pyrazolo[1,5-a]pyridine-3-carboxylates and ethyl pyrazolo[1,5-b] pyridazine-3-carboxylates **4** were prepared by a 1,3-dipolar cycloaddition reaction between pyridine or pyridazine-**N**-imide and ethyl propiolate or ethyl tetrolate by a procedure essentially as described by Tamura[4]. Hydrolysis of **4** followed by treatment with thionylchloride and subsequently with amines or alcohols by routine procedures gave in moderate to good yields **5–16**, which were purified and tested as oxalates or hydrochlorides[5].

$5HT_3$-ANTAGONISM. Compounds **1–16** potently displaced the binding of ^{3}H-GR 65630 to rat cortical membranes with IC_{50}'s between 23 nM and 818 nM[6].

The $5HT_3$-receptor antagonism was determined by measuring the ability of the compounds to antagonize the 5HT induced reflex bradycardia, the von Bezold-Jarisch reflex, in the rat[7] and by their ability to inhibit the 5HT-induced depolarization in rat vagus nerve[8].



R^2: I II III IV V

No.	R^1	R^2	X	Y	a: $5HT_3$ binding IC_{50} (nM)	Bezold-Jarisch ED_{50} (µg/kg)	Rat vagus nerve IC_{50} nM
1	-	-	-	-	3.1±0.63	0.5	1.4
5	H	I	CH	O	28±0.40	2	-
6	H	I	CH	NH	34±0.85	0.7	105
7	H	II	CH	NH	170±15	5	300
8	H	III	CH	NH	75±8	1	83
9	H	IV	CH	NH	72±9	8	419
10	H	V	CH	NH	52±4.3	2	124
11	H	I	N	NH	429±96	30	-
12	H	II	N	NH	818±87	>100	-
13	CH_3	I	N	NH	122±15	50	-
14	CH_3	II	N	NH	>300	>50	-
15	CH_3	I	CH	NH	26±3	1.2	42
16	CH_3	II	CH	NH	64±75	6	100

Table 1: $5HT_3$-antagonism. a: inhibition of binding of ^{3}H-GR 65630 to rat cortical membranes. The data represent the mean ± SEM.

Compared with tropisetron (**1**), the pyrazolo[1,5-a]pyridines and pyrazolo[1,5-b]pyridazines in the Bezold Jarisch test were slightly less potent $5HT_3$-antagonists. In the series of pyrazolo[1,5-a]pyridines, **5–10** and **15–16,** the tropane amides and esters were the more potent in vitro and approximately equipotent with the quinuclidine amide in vivo.

The pyrazolo[1,5-b]pyridazines **11–12** are considerably less potent than the corresponding pyrazolo[1,5-a]pyridines **6–7**. Introduction of a methyl-group in position 2, as in the $5HT_3$-agonist, 2-methyl-5-hydroxytryptamine, increased the receptor affinity of pyrazolo[1,5-b]pyridazines, **13** and **14**, while the 2-methylpyrazolo[1,5-a]pyridines were as potent as their unsubstituted counterparts **6** and **7**. In contrast to the relative high potency of the 2-methylpyrazolo[1,5-a]-pyridines, the corresponding 2-methylimidazole-derivative is reported to be inactive, possibly due to infavourable steric interaction between the methyl group and the amine-NH[9].

The compounds, examplified by **5–6**, are selective $5HT_3$-antagonists which have low affinities for $5HT_{1A}$-, $5HT_2$- or dopamine-D_2-receptors ($IC_{50} > 10\,\mu M$). We therefore conclude that the pyrazolo[1,5-a]pyridine can be a useful bioisoster for indolo groups.

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(*Received in Belgium* 28 *September* 1993; *accepted* 11 *January* 1994)