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DESIGN AND SYNTHESIS OF NOVEL LIGANDS FOR THE 5-HT$_3$ AND THE 5-HT$_4$ RECEPTOR

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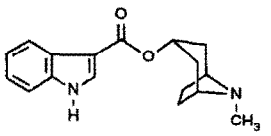
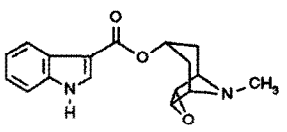
Abstract: A novel highly potent 5-HT$_3$ antagonist and Tropisetron analogue (1) is described with an increased efficacy to inhibit cisplatin induced emesis in ferrets. Four novel structural classes of gastroprokinetic benzamide bioisosteres (8-11) are presented. 5-HT derivatives 12-14 are described as ligands of the recently discovered 5-HT$_4$ receptor.

5-HT receptors have been recently subdivided into three major categories designated "5-HT$_1$-like", 5-HT$_2$ and 5-HT$_3$ [1], but there is also evidence for another type, the 5-HT$_4$ receptor [2-5]. It is perhaps in the 5-HT$_3$ receptor area, where the most spectacular developments have occured; a number of potent antagonists are currently being evaluated in clinical trials as antiemetics, antipsychotics and anxiolytic agents. Most 5-HT$_3$ receptor antagonists can be regarded as falling into three classes, differing in their pharmacological profile. In the first are selective 5-HT$_3$ antagonists such as MDL 72222 [6], Ondansetron [7] and Granisetron [8]. In the second are most gastrointestinal prokinetic benzamides, e.g. Cisapride, Renzapride, Metoclopramide and Zacopride [3]. These compounds are 5-HT$_3$ antagonists, but in addition are agonists at the 5-HT$_4$ receptor, resulting in a potent stimulation of the gastrointestinal motility [4]. The third class of 5-HT$_3$ antagonists is represented by Tropisetron (Navoban^R, ICS 205-930)[17], which has non-competitive 5-HT$_4$ antagonistic effects at high doses [2].

Our design of novel, selective 5-HT$_3$ antagonists is based on the structure of Tropisetron, where replacement of the tropine residue by scopine led to 1 (SDZ 214-322;[9]), a highly potent 5-HT$_3$ antagonist (Table I) with a competitive and weak 5-HT$_4$ antagonistic profile (Table II). Perhaps due to the reduced basicity of its nitrogen atom (1: pK_a=6.64; Tropisetron: pK_a=8.40 in aqueous solution), 1 was 100 times more potent than Tropisetron in inhibiting cisplatin-induced emesis in ferrets: 0.01 mg/kg i.V. completely protected all animals. 1 inhibited the Bezold-Jarisch reflex in rats with an ED50 (i.v.) of 0.72µg/kg. (Tropisetron: 3µg/kg).



Tropisetron



1 (SDZ 214-322)

Our design of 5-HT$_4$ agonists with favorably reduced degree of 5-HT$_3$ antagonism was first based on the class of prokinetic benzamides. The latter contain the 4-amino-5-chloro-2-methoxy benzamide moiety common to drugs such as Metoclopramide (2), Zacopride (3), Cisapride (4) and Renzapride (5). A particular characteristic of these structures is the possible intramolecular hydrogen bond between amide and methoxy group, which holds the carbonyl group in plane, forming a "virtual ring":

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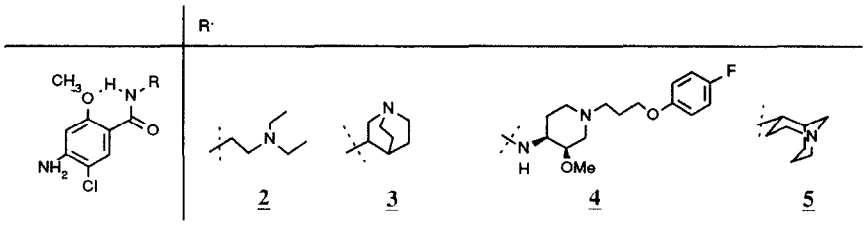
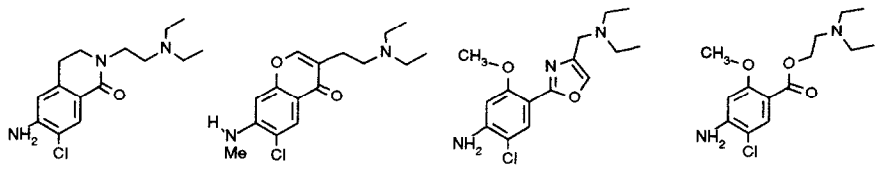
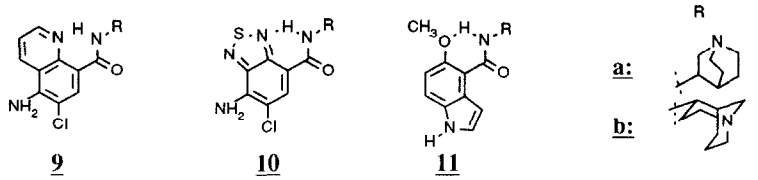


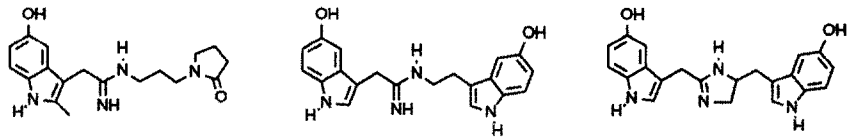
In search of bioisosters for prokinetic benzamides, the "virtual ring" was replaced by a six-membered lactam and a pyrone, leading to the potential Metoclopramide-substitutes 6 and 7 [10].



5-HT_4 agonism (Table II) of 6 was demonstrated in the electrical field stimulated guinea pig ileum (FSGPI) [11], where it proved to be weaker than Metoclopramide. Compound 7 fulfilled the conformational, but probably not the electrostatic requirements of a Metoclopramide-mimetic and was devoid of 5-HT_4 agonistic activity. Oxazole 8 was slightly more potent than Metoclopramide in its FSGPI-effects and proved to be a 5-HT_4 antagonist, similar to the structurally related 5-HT_4 antagonist SDZ 205-557 [15].
Amides 9, 10, and 11 - all capable of forming an intramolecular hydrogen bond - were identified as potent benzamide-mimetics and 5-HT_4 agonists. None of the compounds was selective for the 5-HT_4 receptor; all retained 5-HT_3 antagonism.

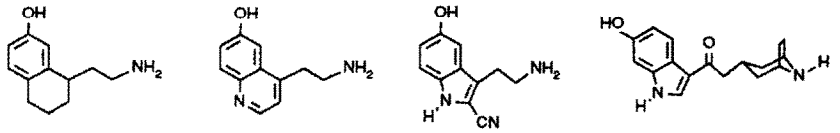


Due to the difficulty to separate 5-HT_3 antagonistic properties from 5-HT_4 agonism within the class of benzamides and related bioisosteres, we focused our design of selective 5-HT_4 agonists on 5-HT itself. Some simple analogs of 5-HT were prepared and tested for 5-HT_4 agonism in the FSGPI. Amidine derivatives 12 and 13 were identified as potent 5-HT_4 agonists lacking 5-HT_3 antagonism. Although in vitro equipotent with Zacopride, 13 showed only very modest oral activity as a gastrointestinal prokinetic drug. Incorporation of the metabolically labile amidine functionality into a five-membered ring in 14 erased 5-HT_4 agonism.



12 13 14

The tetralin-, quinoline- and 2-cyano-analogs of 5-HT - 15, 16 and 17 - were devoid of 5-HT_4 agonistic effects up to 10^{-4}M, but instead were agonists at 5-HT_3 receptors, comparable to 2-Me-5-HT, phenylbiguanide and 5-Methoxytryptamine, the few representatives of this class.

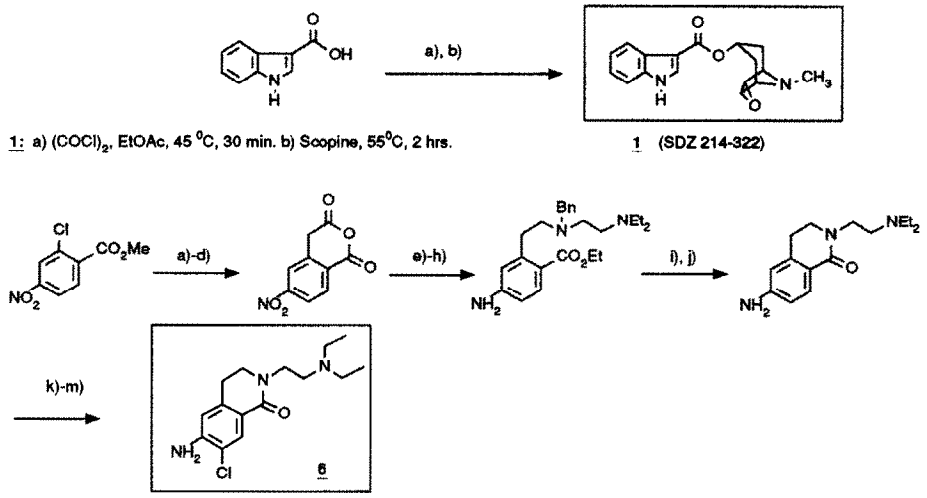


15 16 17 18

5-HT_3 agonistic activity was discovered for 18, which is structurally related to Tropisetron and Ondansetron, considering the distance of its basic nitrogen from the aromatic nucleus.

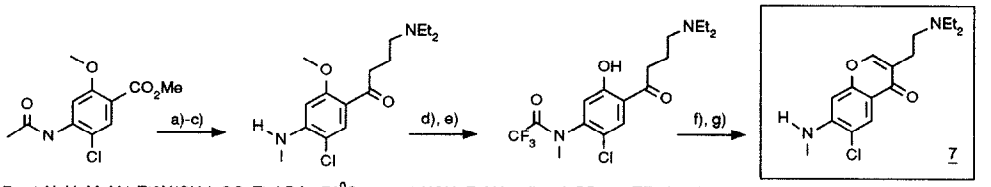
In summary, our search for selective 5-HT_3 antagonists and 5-HT_4 agonists has led to the discovery of one highly potent 5-HT_3 antagonist and analogue of Tropisetron with an increased potency to inhibit cisplatin-induced emesis in ferrets (1). A series of potential gastrointestinal prokinetic benzamide bioisosteres are described (8-11) together with novel 5-HT_3 agonists (15-18). Amidines 12-14 display affinity to the new 5-HT_4 receptor and contribute to the elucidation of its structure-activity relationships [16].

Scheme I

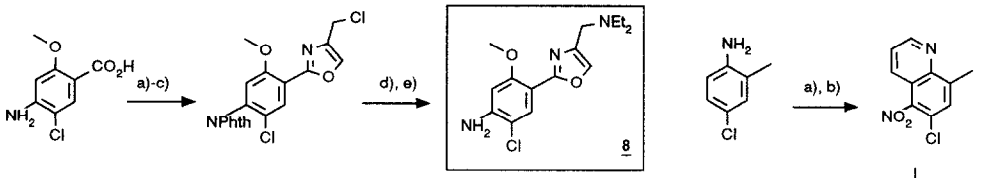


1: a) $(COCl)_2$, EtOAc, 45 °C, 30 min. b) Scopine, 55°C, 2 hrs. 1 (SDZ 214-322)

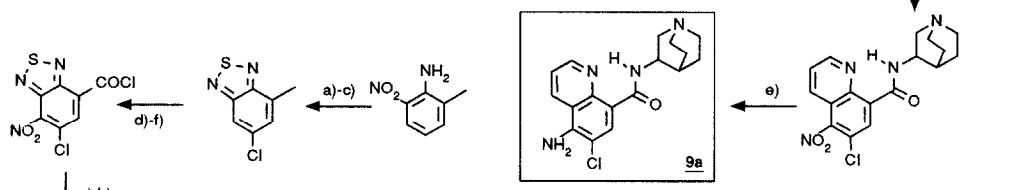
6: a) 2N NaOH, EtOH b) CuBr, NaOH, Ethyl acetoacetate c) 2N NaOH, EtOH d) Ac_2O e) $BnNH(CH_2)_2NEt_2$ f) EtOH, HCl g) Pd, C, H_2 h) B_2H_6 i) Pd, C, H_2, HOAc j) To, reflux k) NBS l) NCS m) Pd, C, H_2, EtOH



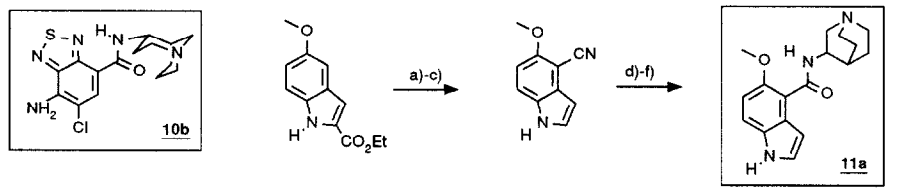
7: a) NaH, MeI b) Et2N(CH$_2$)$_3$CO$_2$Et, LDA, -78°C to r t. c) KOH, EtOH, reflux d) BBr_3 e) TFAA f) Dimethylformamide dimethyl acetal, toluene reflux g) 2N HCl reflux



8: a) Phthalic anhydride b) Im_2CO, NH_3 c) 1,3-dichloro acetone d) $HNEt_2$ e) H_2NNH_2

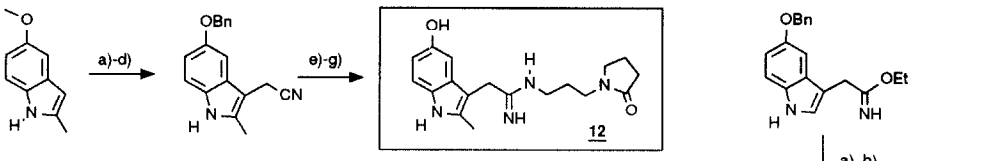


9a: a) Acrolein, toluene, pTsOH b) HNO_3, H_2SO_4 c) $K_2Cr_2O_7$ d) Im_2CO, 3-Aminoquinuclidine (rac) e) Fe, HOAc

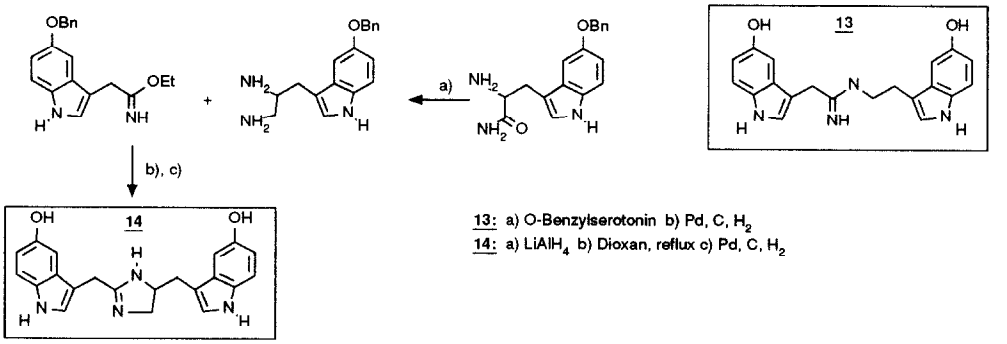


10b: a) NCS b) H_2, Pd/C c) $SOCl_2$ d) HNO_3 (65%) e) $K_2Cr_2O_7$ f) $SOCl_2$ g) R-NH_2 (rac.) h) Fe, 2N HOAc

11a: a) Br_2, AcOH b) NaOH c) CuCN, N-Methylpyrrolidon d) KOH, HO(CH$_2$)$_2$OH e) DCC, N-Hydroxysuccinimide f) 3-Aminoquinuclidine (rac)

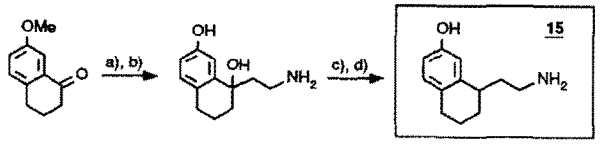


12: a) CH_2O, $HNEt_2$ b) MeI, NaCN c) BBr_3 d) BnBr e) Et_2O/HCl f) R-NH_2 g) Pd, C, H_2

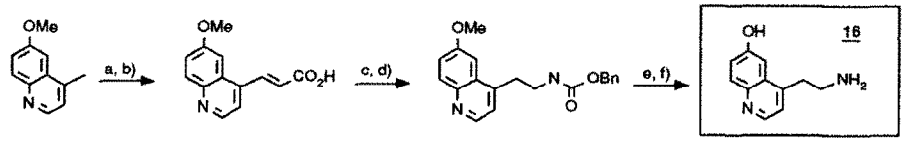


13: a) O-Benzylserotonin b) Pd, C, H_2

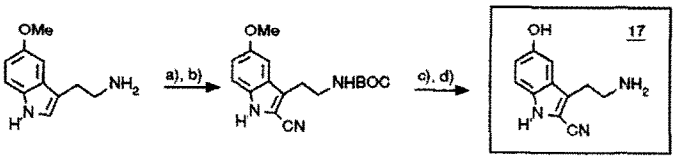
14: a) $LiAlH_4$ b) Dioxan, reflux c) Pd, C, H_2



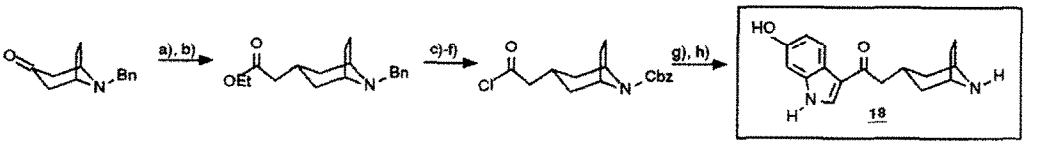
15: a) LDA, MeCN b) $LiAlH_4$ c) Pd, C, H_2 d) BBr_3



16: a) Chloralhydrate b) KOH c) Pd, C, H_2 d) $(PhO)_2P(O)N_3$, BnOH e) Pd, C, H_2 f) BBr_3



17: a) BOC_2O b) $ClSO_2CNO$, DMF c) TFA d) BBr_3



18: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH b) Na, NH_3 c) Pd, C, H_2 d) Benzyl chloroformate e) NaOH f) $SOCl_2$ g) 5-Methoxyindole MeMgI h) BBr_3

References and Notes

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Table I

	Effects at 5-HT$_3$ receptors						
	Antagonism[1]			Agonism[1]			Binding[2]
	RVN pA_2	RH pA_2	GPI pA_2	RVN pD_2	RH pD_2	GPI pD_2	N1E cells pK_D
Tropisetron	10.2	10.6	7.9				9.1
Ondansetron	9.2	10.1	7.1				7.7
Granisetron	9.9	10.1	7.8				8.9
1	10.6	11.0	8.8				9.2
2	7.3	7.1	5.2				
3	10.1		8.5				
4	6.5	7.1	7.2				
5	8.5	8.6	7.6				8.5
9a	9.0		7.9				
9b			6.7				
10a	8.9		7.7				
10b	7.7		6.8				
11a			7.2				
15				6.0	5.7	5.2	
16				5.8		4.5	
17				7.2	4.0	5.4	
18			6.0	7.0	6.0		
2-Me-5-HT				5.6	5.5	5.1	

1) Effects are measured in the isolated rabbit vagus nerve (RVN) [12], isolated perfused rabbit heart (RH) [13] and in the isolated guinea pig ileum (GPI) [14] longitudinal muscle preparation
2) Membranes from N1E-115 cells were used and the experiments were carried out with [^{3}H]-Tropisetron (ICS 205-930) as the radioligand [17]

Table II

	Effects at 5-HT$_4$ receptors		
	Antagonism	Agonism	
	NSGPI[2] pA_2	FSGPI[1] pD_2	NSGPI[2] pD_2
Tropisetron	5.7 [3]		
Ondansetron		5.1	
1	6.3	0	
2		5.5	
3		6.2	5.9
4		6.0	
5		7.1	5.7
6		5.2	5.1
7		0	
8	6.1	6.0	
9a		7.2	6.0
9b		7.5	7.1
10a		5.8	5.5
10b		7.2	6.0
11a		6.6	7.1
12		5.8	
13		6.3	
14		0	
215-557	7.0		
5-HT		7.0	7.9

1) FSGPI (low frequency field stimulation of guinea-pig ileum) is a suitable model for the pharmacological analysis of 5-HT receptor [11]
2) NSGPI (non-electrically stimulated guinea-pig ileum) is less sensitive for 5-HT$_4$ agonists than FSGPI
3) Tropisetron behaves as a non-competitive 5-HT$_4$ antagonist; pD2'=5.7