Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 619–624

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A NOVEL SERIES OF *N*-(HEXAHYDRO-1,4-DIAZEPIN-6-YL) AND *N*-(HEXAHYDROAZEPIN-3-YL)BENZAMIDES WITH HIGH AFFINITY FOR 5-HT_3 AND DOPAMINE D_2 RECEPTORS

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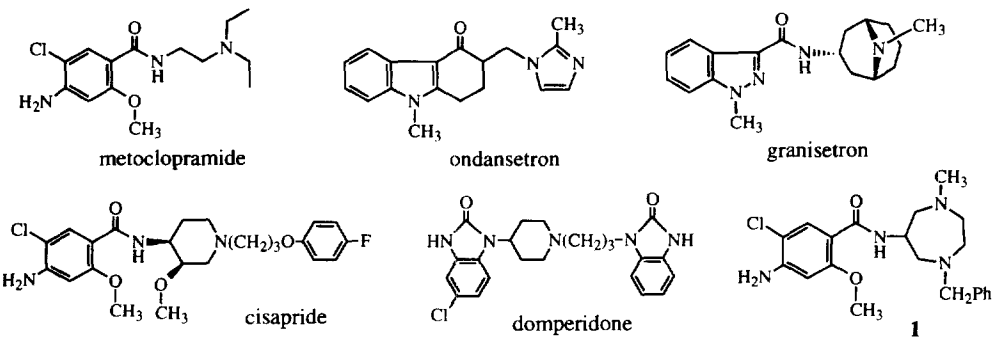
Received 27 January 1998; accepted 2 February 1998

Abstract: A novel series of benzamides with a hexahydro-1,4-diazepine or hexahydroazepine ring in the amine moiety were prepared, and their binding affinities for 5-HT_3 and dopamine D_2 receptors were evaluated. The *R* isomer of the 1-ethyl-4-methylhexahydro-1,4-diazepinylbenzamide (*R*)-**22** had potent affinity for both receptors. The *R*-enantiomer of the corresponding 1-ethylhexahydroazepinylbenzamide **28** showed potent affinity for dopamine D_2 receptors with reduced affinity for 5-HT_3 receptors, while the *S* isomer was found to be a potent and selective 5-HT_3 receptor antagonist.

Metoclopramide is a substituted benzamide that is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic.[1] Its effects are believed to be due to a combination of dopamine D_2 and serotonin-3 (5-HT_3) receptor antagonisms and a serotonin-4 (5-HT_4) receptor agonistic effect. However, metoclopramide often causes side effects such as extrapyramidal symptoms which further restrict its usefulness.[2] The potent and selective 5-HT_3 receptor antagonists such as ondansetron and granisetron have been shown clinically to be highly effective for the blockade of chemotherapy-induced nausea and emesis,[3] and the potent 5-HT_4 receptor agonist cisapride is clinically effective in the treatment of gastrointestinal motility disorders such as non-ulcer dyspepsia, gastro-oesophageal reflux, and constipation.[4] The traditional antiemetic domperidone, a peripheral dopamine D_2 receptor antagonist, has been shown to be effective for treatment of some symptoms of chronic upper gastrointestinal distress and for prevention of nausea and vomiting resulting from a variety of causes.[5] However, domperidone is only minimally effective against chemotherapy- or radiation-induced nausea and vomiting.[6] Recently, we reported the structurally novel and selective 5-HT_3 receptor antagonist 4-amino-*N*-(1-benzyl-4-methylhexahydro-1,4-diazepin-6-yl)-5-chloro-2-methoxybenzamide (**1**).[7] In the course of our studies on the structure-activity relationships (SARs) of **1**, the benzamides with a 1-ethyl-4-methylhexahydro-1,4-diazepine or 1-ethylhexahydroazepine ring in the amine moiety were found to be potent 5-HT_3 and dopamine D_2 receptor antagonists and to exhibit weak central nervous system depression and extrapyramidal syndrome. Thus, we expected that these benzamides would be broad antiemetic agents similarly to metoclopramide. Here, we describe the synthesis of a novel series of hexahydro-1,4-diazepinyl and hexahydroazepinylbenzamides and SARs concerning their affinities for 5-HT_3 and dopamine D_2 receptors.

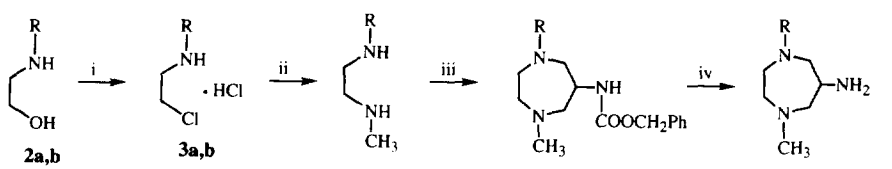
0960-894X/98/$19.00
PII: S0960-894X(98)00078-X



Chemistry

We previously reported efficient formation of 6-protected amino-1,4-disubstituted hexahydro-1,4-diazepine ring including the 1-benzyl-4-methyl and 1,4-dimethyldiazepines.[8] This method was used for preparation of the 1-ethyl-4-methyl and 1-methyl-4-propyldiazepines (**7a,b**) from *N, N'*-dialkylated ethylenediamines and 2-benzyloxycarbonylaminopropenal (**5**) (Scheme 1). The available 2-ethylamino and 2-propylaminoethanols (**2a,b**) were treated with thionyl chloride in refluxing $CHCl_3$, followed by reaction of the resulting chloroethylamine hydrochlorides **3a,b** with aqueous methylamine in EtOH at *ca.* 50 °C to give the *N*-ethyl- and *N*-propyl-*N'*-methylethylenediamines (**4a,b**) in 71% and 45% yields from **2a** and **2b**, respectively. Brief reaction of **4a,b** with **5** at 5 °C in MeOH followed by $NaBH_4$ reduction afforded the hexahydro-1,4-diazepines **6a,b**. Deprotection of **6a,b** gave the desired 6-aminohexahydro-1,4-diazepines **7a** and **7b** in 45% and 35% yields from **4a** and **4b**, respectively.

Scheme 1



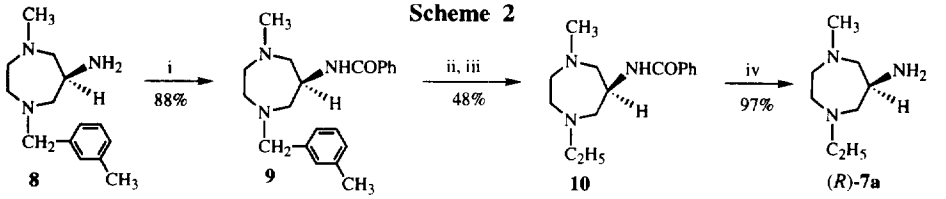
a: R = C_2H_5, **b**: R = C_3H_7

Reagents: (i) $SOCl_2$, $CHCl_3$; (ii) aq. CH_3NH_2, EtOH; (iii) 2-benzyloxycarbonylaminopropenal (**5**), MeOH then $NaBH_4$; (iv) HBr

The optically active amine of **7a** was prepared as shown in Scheme 2, where the synthesis of the *R*-enantiomer (*R*)-**7a** is depicted. The known (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine[9] (**8**) was treated with benzoyl chloride in the presence of Et_3N to give the benzamide **9** in 88% yield. After hydrogenation of **9** with Pd/C, reaction of the debenzylated product with acetaldehyde in MeOH followed by $NaBH_4$ reduction produced the 1-ethyl-4-methyldiazepine **10** in 48% yield. Finally, acid hydrolysis of **10** afforded the amine (*R*)-**7a** in 97% yield with high enantiomeric purity.

The 1-alkylated 3-aminohexahydroazepines (**15a-d**) were prepared from the commercially available α-amino-ε-caprolactam (**11**) as shown in Scheme 3. Protection of the 3-amino group of **11** with a triphenylmethyl (trityl) group, followed by treatment of the resulting caprolactam **12** with various alkyl halides in the presence of sodium hydride, gave the 1-alkylated 3-tritylaminohexahydroazepin-2-ones **13a-d** in good

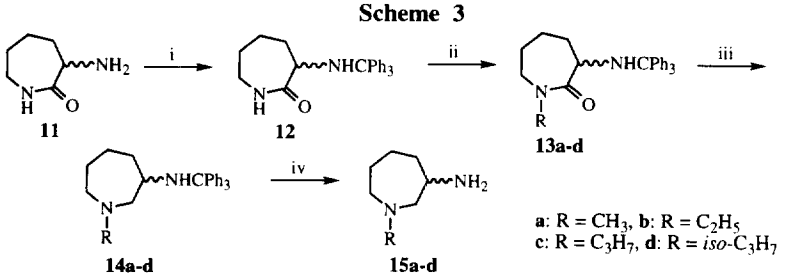
Scheme 2



Reagents: (i) PhCOCl, Et_3N, $CHCl_3$; (ii) Pd/C, H_2, EtOH; (iii) CH_3CHO, MeOH then $NaBH_4$; (iv) 35% aq. HCl.

yields. Reduction of the carbonyl group of **13a-d** with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) in toluene gave the hexahydroazepines **14a-d**. The desired amines **15a-d** were obtained by acid hydrolysis of **14a-d**. The enantiomers (*R*)-**15b** and (*S*)-**15b** were also prepared from (*R*)- and (*S*)-α-amino-ε-caprolactams[10] [(*R*)-**11** and (*S*)-**11**], respectively, according to the similar method described above.

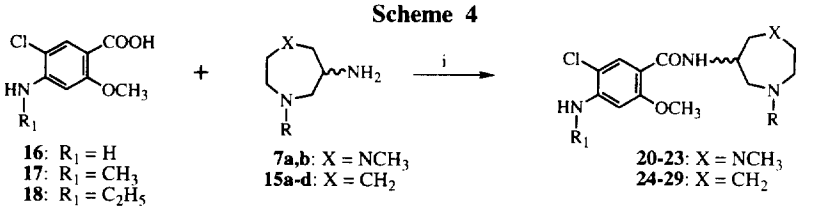
Scheme 3



Reagents: (i) Ph_3CCl, Et_3N, $CHCl_3$; (ii) NaH, R-I, THF; (iii) Vitride®, toluene; (iv) 10% aq. HCl.

Condensation of the amines **7a,b**, **15a-d**, (*R*)-**7a**, (*S*)-**7a**, (*R*)-**15b**, and (*S*)-**15b** thus prepared with 4-amino-5-chloro-2-methoxybenzoic acid (**16**) and its derivatives **17** and **18** using 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride gave the desired benzamides **20–29** in over 90% yield (Scheme 4).

Scheme 4



Reagent: (i) 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, CH_2Cl_2.

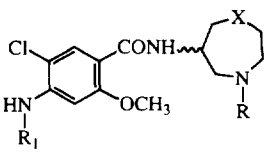
Results and discussion

The affinities of the benzamides prepared were determined using binding assays; for 5-HT_3 receptors, competition for [^{3}H]GR65630 binding site in rat cortical membranes[11] was used, while affinity for dopamine D_2 receptors was evaluated with [^{3}H]spiperone in the rat striatum[12] (Table 1). For comparison, data for metoclopramide, the selective 5-HT_3 receptor antagonist ondansetron, and the selective dopamine D_2 receptor antagonist domperidone were included in Table.

Metoclopramide exhibited weak affinity for both receptors. Most of the benzamides with a hexahydro-1,4-diazepine ring showed high affinity for 5-HT_3 receptors with IC_{50} values ranging between 1.5 nM and 24 nM and moderate to high affinity for dopamine D_2 receptors. In general, affinity for 5-HT_3 receptors was stronger than that for dopamine D_2 receptors. First the effect of the substituent in the hexahydro-1,4-diazepine ring was discussed, while keeping the 4-amino-5-chloro-2-methoxybenzoyl moiety constant. The benzamide **19** (R = CH_3) is a selective 5-HT_3 receptor antagonist like **1** (R = CH_2Ph).[7] Replacement of the methyl group of **19** by an ethyl (giving **20**) resulted in a slight increase of affinity for 5-HT_3 receptors. The propyl derivative **21** decreased affinity. Thus, the small substituent such as methyl and ethyl groups found to be essential for recognition of 5-HT_3 receptors. On the other, the binding affinities for dopamine D_2 receptors of **20** and **21** were much higher than that of the methyl counterpart **19**, although the reason for this is unclean. In particular, compound **20** with an ethyl group displayed potent affinity compared with metoclopramide (IC_{50}; 127 nM *vs.* 480 nM). For both receptor bindings, the optimum substituent in the hexahydro-1,4-diazepine ring was found to be an ethyl group. The influence of the substituent at the amino group of the 4-amino-5-chloro-2-methoxybenzoyl moiety of **20** was examined. Introduction of a methyl group (giving **22**) enhanced affinity for both receptors. The ethyl derivative **23** slightly decreased affinity for dopamine D_2 receptors compared with that of **20** (IC_{50}; 181 nM *vs.* 127 nM) and showed great potent affinity for 5-HT_3 receptors. The affinities for both receptors of the enantiomers of **20** and **22** were studied. The affinities for dopamine D_2 receptors of the (*R*)-enantiomers of **20** and **22** [(*R*)-**20** and (*R*)-**22**] were *ca.* 2-fold higher than those of the respective racemate, while their affinities for 5- HT_3 receptors were almost similar. In contrast, the (*S*)-enantiomers [(*S*)-**20** and (*S*)-**22**] exhibited weak affinity for dopamine D_2 receptors, but retained strong affinity for 5-HT_3 receptors. Thus, there were marked differences in affinity for dopamine D_2 receptors between the enantiomers. (*R*)-**22**[13] showed lower affinity for 5-HT_3 or dopamine D_2 receptors than ondansetron or domperidone, respectively. Its affinity for both receptors, however, was much higher than that of metoclopramide.

The influence of *N*-substituents of the hexahydroazepine ring on affinity for dopamine D_2 and 5-HT_3 receptors was next examined. Compounds **24**—**27** with methyl, ethyl, propyl, and isopropyl groups, respectively, displayed moderate affinity for 5-HT_3 receptors with the exception of the isopropyl derivative **27**. Their affinity for dopamine D_2 receptors were weak to moderate. The IC_{50} of the ethyl derivative **25** was approximately the same affinity for 5-HT_3 and dopamine D_2 receptors. Compound **25** showed much higher affinity for 5-HT_3 and dopamine D_2 receptors than metoclopramide. As the optimum substituent in the hexahydroazepine ring, an ethyl group was selected. Introduction of a methyl group into the 4-amino group on the benzoyl moiety of **25** (yielding **28**) enhanced in affinity for both receptors. There was observed a similar result concerning 1-ethyl-4-methylhexahydro-1,4-diazepine derivatives. Replacement of the methyl group of **28** with an ethyl group (giving **29**) resulted in decreases in affinity for both receptors. Finally, we examined the affinity for both receptors of the enantiomers of **25** and **28**. The affinities of (*S*)-**25** and (*S*)-**28** for 5-HT_3 receptors were *ca.* 2-fold higher than those of each racemate, whereas their affinities for dopamine D_2 receptors were considerably decreased as compared to the corresponding racemate. In contrast, the (*R*)-enantiomers of **25** and **28** exhibited potent affinity for dopamine D_2 receptors along with weak affinity for 5-HT_3 receptors. The affinity for dopamine D_2 receptors of (*R*)-**28** was much higher than that of the (*R*)-**22** in a hexahydro-1,4-diazepine ring (4.5 nM *vs.* 35 nM). Interestingly, (*R*)-1-ethyl-4-methylhexahydro-1,4-diazepinylbenzamides showed strong affinity for both dopamine D_2 and 5-HT_3 receptors compared with the corresponding (*S*)-enantiomer. On the other hand, in the case of the benzamides having a 1-ethylhexahydroazepine ring, (*S*)- or

Table. Affinity for 5-HT_3 and Dopamine D_2 Receptors of Hexahydro-1,4-diazepinyl and Hexahydroazepinylbenzamides



Compd.[a]	R_1	R	X	Binding Assay: IC_{50} (nM) 5-HT_3[b]	D_2[c]
19[d]	H	CH_3	NCH_3	9.6	>1000
20	H	C_2H_5	NCH_3	8.5	127
21	H	C_3H_7	NCH_3	24	218
22	CH_3	C_2H_5	NCH_3	4.8	61
23	C_2H_5	C_2H_5	NCH_3	1.9	181
(***R***)-**20**[e]	H	C_2H_5	NCH_3	12	87
(***S***)-**20**[e]	H	C_2H_5	NCH_3	7.0	517
(***R***)-**22**[e]	CH_3	C_2H_5	NCH_3	2.9	35
(***S***)-**22**[e]	CH_3	C_2H_5	NCH_3	1.5	320
24	H	CH_3	CH_2	36	230
25	H	C_2H_5	CH_2	33	39
26	H	C_3H_7	CH_2	37	57
27	H	*iso*-C_3H_7	CH_2	640	87
28	CH_3	C_2H_5	CH_2	6.6	11
29	C_2H_5	C_2H_5	CH_2	50	25
(***R***)-**25**[e]	H	C_2H_5	CH_2	134	19
(***S***)-**25**[e]	H	C_2H_5	CH_2	10	>1000
(***R***)-**28**[e]	CH_3	C_2H_5	CH_2	97	4.5
(***S***)-**28**[e]	CH_3	C_2H_5	CH_2	4.5	367
metoclopramide				880	480
ondansetron				1.4	>1000
domperidone				>100	2.5

a) All compounds gave satisfactory results on IR, ^{1}H-NMR, MS, and elemental analysis. *b)* Determined in rat cortical membranes using [^{3}H]GR65630. *c)* Determined in rat brain synaptic membranes using [^{3}H]spiperone. *d)* See ref. 7. *e)* The enantiomeric purities of the enantiomers were confirmed to be >98% ee by chiral HPLC [column; CHIRALPAK AS (DAICEL Chemical Industries Ltd, Japan) or CHIRAL-AGP (Shinwa Chemical Industries Ltd, Japan)].

(*R*)-enantiomer had strong affinity for 5-HT_3 or dopamine D_2 receptors, respectively.

In conclusion, replacement of the amine part of a potent and selective 5-HT_3 receptor antagonist **1** by a 1-ethyl-4-methylhexahydro-1,4-diazepine or 1-ethylhexahydroazepine ring resulted in a remarkable increase in affinity for dopamine D_2 receptors. In particular, the (*R*)-enantiomer of **22** showed potent affinity for 5-HT_3 and dopamine D_2 receptors. The affinity for each receptor of the 1-ethylhexahydroazepinylbenzamides was separated by the optical isomer; the (*S*)-enantiomer showed strong affinity for 5-HT_3 receptors, whereas the (*R*)-enantiomer had potent affinity for dopamine D_2 receptors.

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13. Data of (*R*)-**22**: dimaleate, mp 161—161.5 °C (MeOH—^{i}PrOH), IR (KBr) ν: 1587, 1518 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 7.5 Hz), 2.70 (s, 3H), 2.85 (d, 3H, *J* = 5 Hz), 2.89 (q, 2H, *J* = 7.5 Hz), 3.0—3.3 (m, 8H), 3.96 (s, 3H), 4.31 (m, 1H), 6.14 (s, 4H), 6.18 (br d, 1H, *J* = 5 Hz), 6.25 (s, 1H), 7.75 (s, 1H), 8.37 (d, 1H, *J* = 7.5 Hz), Chiral HPLC (CHIRALPAK AS): t_R = 24.4 min [(*S*)-**22**: t_R = 28.0 min]. To determine *in vivo* 5-HT_3 and dopamine D_2 receptor antagonistic activities of (*R*)-**22**, inhibition of apomorphine-induced emesis in dogs[14] (ID_{50}; 0.13 mg/kg, po) and of 2-methyl-5-HT-induced bradycardia (von Bezold-Jarisch reflex) in rats[15] (ED_{50}; 1.4 μg/kg, iv), respectively, were examined.
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