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# 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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**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.

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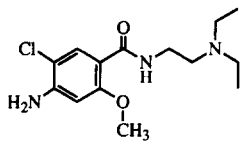
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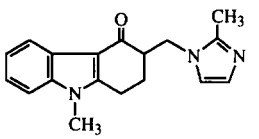
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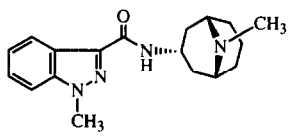
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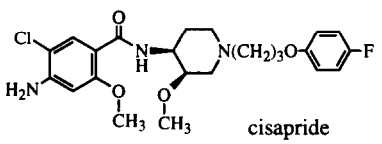
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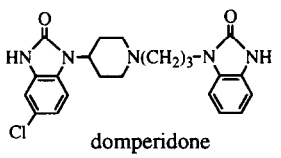
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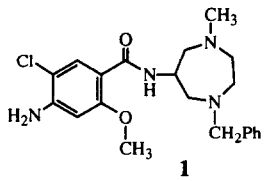
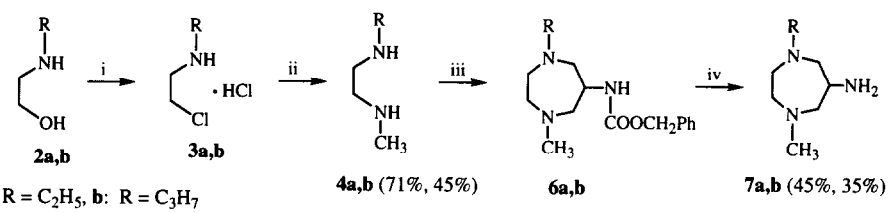

**1**

## 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**

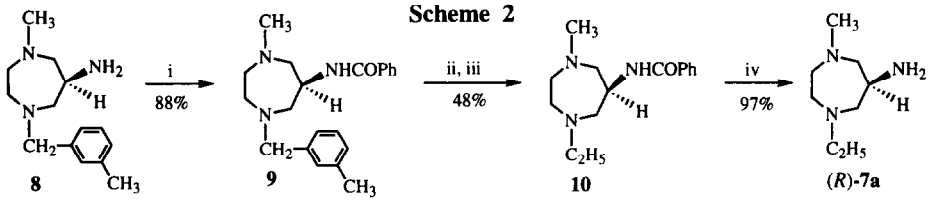



Reagents: (i) $SOCl_2$, $CHCl_3$; (ii) aq. $CH_3NH_2$, EtOH; (iii) 2-benzyloxycarbonylaminopropenal (**5**), MeOH then $NaBH_4$; (iv) HBr

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

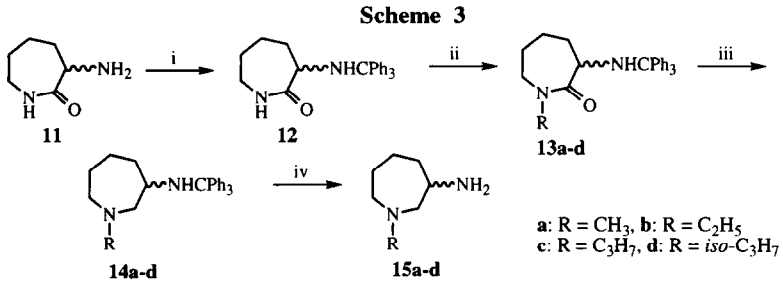
**Scheme 2**




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.

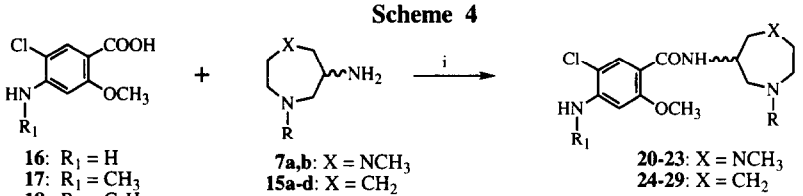
**Scheme 3**




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, $CH_2Cl_2$.

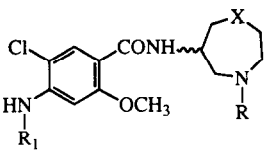
## Results and discussion

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.

## References and Notes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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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