# Novel 5-Hydroxytryptamine (5-$HT_3$) Receptor Antagonists. II.[1] Synthesis and Structure–Activity Relationships of 4,5,6,7-Tetrahydro-1*H*-benzimidazole Derivatives

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**A novel series of 4,5,6,7-tetrahydro-1*H*-benzimidazole derivatives 4, 5, 6 and 7 was prepared and evaluated for activities as 5-hydroxytryptamine (5-$HT_3$) receptor antagonists which may be useful for the treatment of irritable bowel syndrome (IBS) as well as nausea and vomiting associated with cancer chemotherapy. These compounds were designed by modifying the aromatic-carbonyl part of *N*-(2-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-5-benzimidazolylcarboxamide 3, leaving the imidazole moiety unchanged as the amine part. The indole derivatives 7d, g, h and indolizine derivatives 7k, l were found to be highly potent on the von Bezold–Jarisch (B.J.) reflex test with $ID_{50}$ values of below 0.1 μg/kg, and the indoline derivative 6c, indole derivatives 7a, d, g, benzofurane derivative 7j and indolizine derivative 7k were observed to be very potent on the colonic contraction with $IC_{50}$ values of below 0.1 μM. In particular, 7l was the most potent on the B.J. reflex ($ID_{50}$ = 0.018 μg/kg), approximately 200 and 50 times more potent than ondansetron 1 and granisetron 2, and 7k was the most potent on the colonic contraction ($IC_{50}$ = 0.011 μM), approximately 70 and 6 times more potent than 1 and 2, respectively.**

**Key words** tetrahydrobenzimidazole; 5-$HT_3$ receptor antagonist; irritable bowel syndrome; vomiting; structure–activity relationship

In a preceding paper[1] we reported a novel series of fused imidazole derivatives as 5-hydroxytryptamine (5-$HT_3$) receptor antagonists, which may be useful for the treatment of irritable bowel syndrome (IBS) as well as for nausea and vomiting associated with cancer chemotherapy. *N*-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide **3** was found to exhibit potent 5-$HT_3$ receptor antagonistic activities on the von Bezold–Jarisch reflex (B.J. reflex)[2] in rats ($ID_{50}$ = 0.32 μg/kg, i.v.) and the colonic contraction in guinea pig[3] ($IC_{50}$ = 0.43 μM). The effects of **3** were more potent than those of ondansetron **1**[4] and the potency was almost the same as that of granisetron **2**[5] (Chart 1). The 4,5,6,7-tetrahydro-1*H*-benzimidazole part of **3** was assumed to be essential for the binding to the 5-$HT_3$ receptor because of the suitable position and direction of the N–C–N centroid in the conformationally restricted imidazole ring against the planar (2-methoxyphenyl)aminocarbonyl part.

These findings have prompted us to seek a more potent antagonist than **3**, leaving the 4,5,6,7-tetrahydro-1*H*-benzimidazole moiety unchanged as the amine part. Novel compounds **4**, **5**, **6** and **7** were designed by modifications of the (2-methoxyphenyl)anilide moiety of **3**, replacing the –NHCO– group (**4**), the 2-methoxy group (**5**) and the entire (2-methoxyphenyl)amino group (**6** and **7**), respectively. In the course of this study, some derivatives in **6** and **7** were found to be more potent than **1**, **2** and **3**. The synthesis and structure–activity relationships (SAR) of these compounds are described.

## Chemistry

The syntheses of compounds **3**, **4a—c**, **5a—l**, **6a—d** and **7a—l** (Tables 1—5) are shown in Chart 2 (method A—I). The reaction of a variety of substituted anilines **10** or cyclic amines **11** with the acyl chloride **9**, which was obtained from 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid **8**,[1,6] afforded 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamides **3**, **4a** and **5a—h**, **j—l** or **6a—c**, respectively (method A). The thiocarboxamide **4b** was prepared

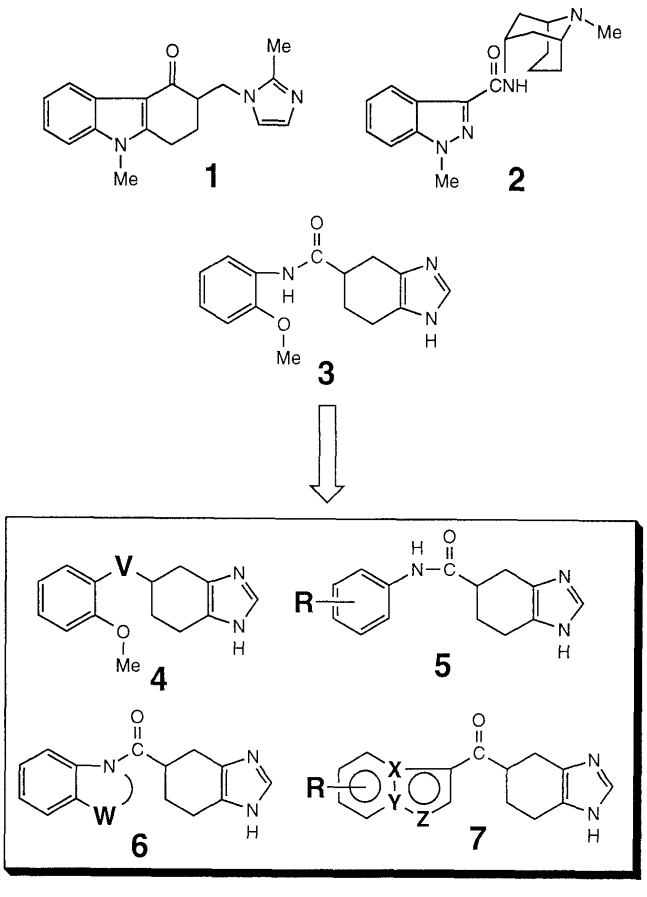


Chart 1

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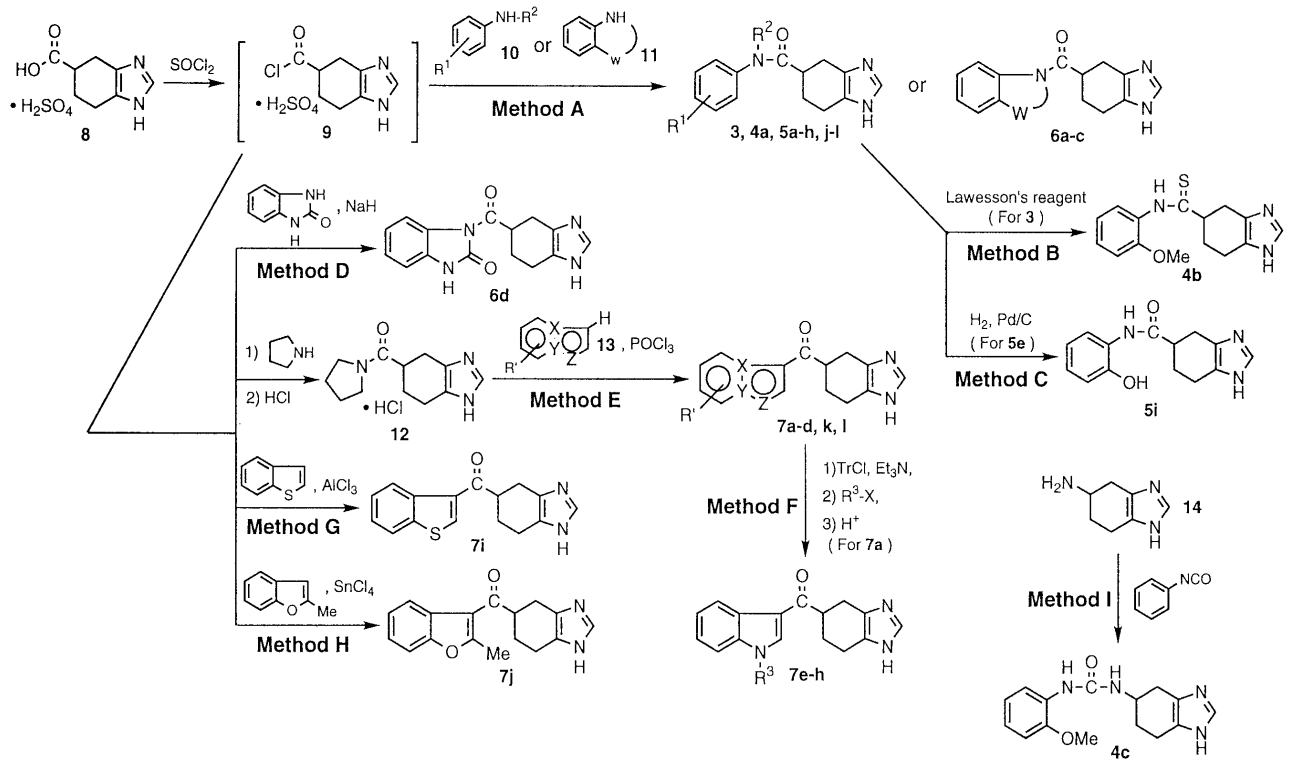
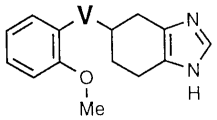



Chart 2. Synthetic Methods A—I

Table 1. 5-$HT_3$ Receptor Antagonistic Activities



| No. | –V– | Synth. method[a] | $ID_{50}$ (μg/kg) of B.J. reflex[b] [95% confidence limits] | $IC_{50}$ (μM) of colonic contraction[c] [95% confidence limits] | $ID_{50}$ (μg/kg)/ $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| **3** | –NHCO– | A | 0.32 [0.19—0.54] | 0.43 [0.27—0.69] | 0.74 |
| **4a** | –N(Me)CO– | A | (18%)[d] | 3.7 [2.0—7.0] | >8 |
| **4b** | –NHCS– | B | (30%)[d] | 3.6 [1.9—6.8] | >8 |
| **4c** | –NHCONH– | I | 7.4 [4.3—13] | 7.6 [4.4—12] | 1.0 |
| **1** | | | 3.8 [1.5—7.9] | 0.78 [0.43—1.4] | 13 |
| **2** | | | 0.88 [0.71—0.96] | 0.069 [0.062—0.078] | 4.9 |

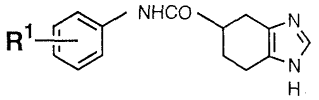
*a*) See Chart 2. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 μg/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT ($5 \times 10^{-5}$ M). *d*) % inhibition at 30 μg/kg.

by the treatment of **3** with Lawesson's reagent (method B). Debenzylation of the benzyl ether **5e** by catalytic hydrogenation gave the *N*-(2-hydroxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide **5i** (method C). The acyl chloride **9** was treated with the sodium salt of 2(3*H*)-benzimidazolone to give *N*-acylated compound **6d** (method D). The Vilsmeyer-type reaction on indoles and indolizines **13** with pyrrolidine amide **12**, which was prepared by the reaction of pyrrolidine with acyl chloride **9**, gave the ketone derivatives **7a—d, k, l** in the presence of phosphorous oxychloride (method E). 1-Substituted indole derivatives **7e—h** were prepared from 1*H*-indole derivative **7a**. A nitrogen atom in an imidazole of **7a** was protected by the triphenylmethyl group, which was a mixture of 1- and 3-substituted isomers. The mixture was alkylated at the 1-position of indole with $R^3$-X in the presence of sodium hydride, and deprotected under acidic condition to give **7e—h** (method F). The 3-benzothiophenyl ketone derivative **7i** or the 3-benzofuranyl ketone derivative **7j** was prepared by the reaction of benzothiophene or 2-methylbenzofurane in the presence of aluminum(III) chloride (method G) or tin(IV) chloride (method H) in low yield, respectively; although the Vilsmeier-type reaction with the pyrrolidine amide **12** has not been successful. The addition of 5-amino-4,5,6,7-tetrahydro-1*H*-benzimidazole to 2-methoxyphenylisocyanate afforded the urea derivative **4c** (method I).

## Pharmacological Results and Discussion

We evaluated the 5-$HT_3$ receptor antagonistic activities of the compounds **4a—c**, **5a—l**, **6a—d** and **7a—l** (Tables 1—5). We studied the 5-HT induced vagally mediated B.J. reflex (rats) and the contractile responses to 5-HT in the isolated distal colon (guinea pig).[3] These effects are

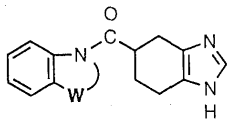
Table 2. 5-$HT_3$ Receptor Antagonistic Activities

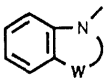
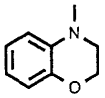
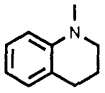
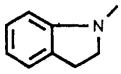
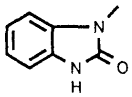


| No. | $-R^1$ | Synth. method[a] | $ID_{50}$ ($\mu$g/kg) of B.J. reflex[b] [95% confidence limits] | $IC_{50}$ ($\mu$M) of colonic contraction[c] [95% confidence limits] | $ID_{50}$ ($\mu$g/kg)/ $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|
| **5a** | -H | A | 2.3 [1.5—3.4] | 0.45 [0.31—0.64] | 5.1 |
| **5b** | 3-OMe | A | 6.0 [4.9—7.3] | 2.0 [0.30—14] | 3.0 |
| **5c** | 4-OMe | A | (32%)[d] | >10 | — |
| **5d** | 2-O*n*Bu | A | 0.70 [0.54—0.91] | 1.0 [0.70—1.4] | 0.70 |
| **5e** | $2\text{-}OCH_2PH$ | A | 3.1 [2.4—3.8] | 0.14 [0.090—0.21] | 22 |
| **5f** | 2-OPh | A | 1.0 [0.83—1.2] | 0.30 [0.18—0.52] | 3.3 |
| **5g** | $2\text{-}OCH_2CH{=}CH_2$ | A | 1.6 [1.4—2.0] | 0.39 [0.32—0.48] | 4.1 |
| **5h** | $2\text{-}OCH_2C{\equiv}CH$ | A | 1.6 [1.3—2.1] | 0.29 [0.22—0.38] | 5.5 |
| **5i** | 2-OH | C | 0.96 [0.86—1.1] | 0.42 [0.33—0.55] | 2.3 |
| **5j** | $2\text{-}COCH_3$ | A | 0.28 [0.24—0.33] | 1.2 [0.30—5.3] | 0.23 |
| **5k** | $2\text{-}COOCH_3$ | A | 0.65 [0.39—1.1] | 0.31 [0.18—0.51] | 2.1 |
| **5l** | $2\text{-}NO_2$ | A | 6.3 [5.0—7.9] | 4.5 [3.8—5.2] | 1.4 |

*a*) See Chart 2. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 $\mu$g/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT ($5\times10^{-5}$ M). *d*) % inhibition at 30 $\mu$g/kg.

Table 3. 5-$HT_3$ Receptor Antagonistic Activities



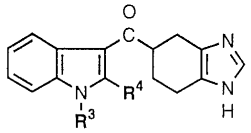
| No. |  | Synth. method[a] | $ID_{50}$ ($\mu$g/kg) of B.J. reflex[b] [95% confidence limits] | $IC_{50}$ ($\mu$M) of colonic contraction[c] [95% confidence limits] | $ID_{50}$ ($\mu$g/kg)/ $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|
| **6a** |  | A | 5.7 [4.8—6.8] | 0.67 [0.30—1.5] | 8.5 |
| **6b** |  | A | 5.8 [3.2—11] | 1.7 [1.1—2.8] | 3.4 |
| **6c** |  | A | 0.29 [0.23—0.37] | 0.049 [0.017—0.14] | 5.9 |
| **6d** |  | D | 0.80 [0.35—1.9] | 0.21 [0.040—1.1] | 3.8 |

*a*) See Chart 2. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 $\mu$g/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT ($5\times10^{-5}$ M).

known to be mediated by the activation of the neuronal 5-$HT_3$ receptor. Data are presented as the percent inhibition at the intravenous administration of the compounds (30 $\mu$g/kg) or $ID_{50}$ values ($\mu$g/kg) against the B.J. reflex induced by 5-HT (10 $\mu$g/kg, i.v.) in anesthetized rats and $IC_{50}$ values ($\mu$M) against the contraction of the isolated guinea pig colon by 5-HT (50 $\mu$M), respectively.

The inhibitory effect of the compounds on the B.J. reflex was examined (Table 1). Changing –V– from –NHCO– group in compound **3** to $-N(CH_3)CO-$ group (**4a**) or –NHCS–group (**4b**) rendered these compounds inactive; however, urea derivative **4c** (–NHCONH– group as –V–) displayed a weak activity. The 2-methoxyanilide moiety has been reported to adopt a planar conformation by intramolecular hydrogen bonding.[1,7,8] In the $^1$H-NMR spectrum, the $\delta$ value of the hydrogen atom at the 6-position of the benzene ring in **3** has been observed to be shifted downfield ($\delta=7.86$),[1] because of the influence of the carbonyl group; however, this shift was not observed in the *N*-methylated derivative **4a** ($\delta=ca.$ 7.1). These data suggest that the anilide moiety of **4a** may not adopt the flat conformation as shown in Chart 3. Consequently, the planar conformation of the anilide moiety may be favorable for binding to the 5-$HT_3$ receptor. The hydrogen-bonding ability of the oxygen atom on the amide moiety in **3** is seen as essential, because the thioamide

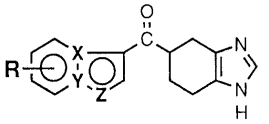
Table 4. 5-$HT_3$ Receptor Antagonistic Activities

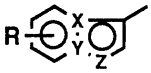
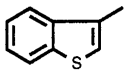
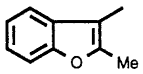
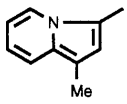
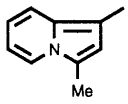


| No. | $-R^3$ | $-R^4$ | Synth. method[a] | $ID_{50}$ ($\mu$g/kg) of B.J. reflex[b] [95% confidence limits] | $IC_{50}$ ($\mu$M) of colonic contraction[c] [95% confidence limits] | $ID_{50}$ ($\mu$g/kg)/ $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|
| **7a** | –H | –H | E | 0.16 [0.12—0.21] | 0.039 [0.021—0.073] | 4.1 |
| **7b** | –H | –Me | E | 0.16 [0.12—0.20] | 3.3 [0.90—12] | 0.048 |
| **7c** | –H | $-CH_2Ph$ | E | 1.4 [0.94—2.0] | 0.19 [0.040—0.81] | 7.4 |
| **7d** | –Me | –H | E | 0.044 [0.031—0.062] | 0.10 [0.040—0.28] | 0.44 |
| **7e** | –*n*Bu | –H | F | 0.24 [0.13—0.46] | 0.21 [0.050—0.85] | 1.1 |
| **7f** | $-CH_2Ph$ | –H | F | 0.38 [0.33—0.45] | 0.60 [0.34—1.0] | 0.63 |
| **7g** | $-CH_2CH=CH_2$ | –H | F | 0.10 [0.053—0.19] | 0.026 [0.018—0.039] | 3.8 |
| **7h** | $-CH_2C\equiv CH$ | –H | F | 0.063 [0.055—0.073] | 0.11 [0.020—0.75] | 0.57 |

*a*) See Chart 2. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 $\mu$g/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT ($5\times10^{-5}$ M).

Table 5. 5-$HT_3$ Receptor Antagonistic Activities



| No. |  | Synth. method[a] | $ID_{50}$ ($\mu$g/kg) of B.J. reflex[b] [95% confidence limits] | $IC_{50}$ ($\mu$M) of colonic contraction[c] [95% confidence limits] | $ID_{50}$ ($\mu$g/kg)/ $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|
| **7i** |  | G | 0.66 [0.59—0.74] | 0.13 [0.040—0.45] | 5.1 |
| **7j** |  | H | 2.8 [2.4—3.3] | 0.091 [0.032—0.26] | 31 |
| **7k** |  | E | 0.093 [0.072—0.12] | 0.011 [0.0060—0.020] | 8.5 |
| **7l** |  | E | 0.018 [0.012—0.028] | 0.14 [0.030—0.59] | 0.13 |

*a*) See Chart 2. *b*) i.v., vagally mediated bradycardia induced by 5-HT (10 $\mu$g/kg, i.v.) in rats. *c*) Contraction of isolated guinea pig colon induced by 5-HT ($5\times10^{-5}$ M).

derivative **4b** was inactive. The reduced activity of **4c** may be due to the change in the distance and direction of the imidazole part in the 4,5,6,7-tetrahydro-1*H*-benzimidazole ring from the carbonyl oxygen atom.

All of the *N*-(substituted phenyl)-4,5,6,7-tetrahydro-1*H*-5-benzimidazolyl)carboxamides **5a**—**l** were found to be active, and $ID_{50}$ values of **5d**, **f**, and **i**—**k** were below 1 $\mu$g/kg (Table 2). In particular, the 2-acetyl derivative **5j** exhibited strong 5-$HT_3$ receptor antagonistic activity ($ID_{50}=0.28$ $\mu$g/kg) nearly equal to **3**. The substituents on the benzene ring must adopt a planar conformation in which there are no adverse steric interactions to possess the activity.[8] Thus, the 2-acetyl derivative **5j** may adopt a flat conformation by hydrogen bonding. Indeed, the $\delta$ value of the hydrogen atom at the 6-position of benzene ring of **5j** was also shifted downfield (8.01) (Chart 3).

As described above, **3** and **5j** are supposed to possess a flat part including both the carbonyl group and either a pseudo 6–5 (in the former)- or 6–6 (in the latter)-membered ring system. Therefore, we prepared compounds **6a**—**d** possessing either a 6–6 or 6–5 fused bicyclic system (Table 3). The benzoxadine derivative **6a** and the 1,2,3,4-tetrahydro-1-quinoline derivative **6b** were shown to be about 18 times weaker than **3**. On the contrary, the 1-indoline derivative **6c** and the 2-benzimidazolone derivative **6d** were found to have almost the same potency as **3**. In the $^1$H-NMR spectrum, the $\delta$ value of the hydrogen atom at the $\alpha$-position of the anilide nitrogen atom in **6c** was shifted downfield (8.08), while that in **6a** was not ($\delta=ca.$ 7.6) (Chart 3). These results suggest that the

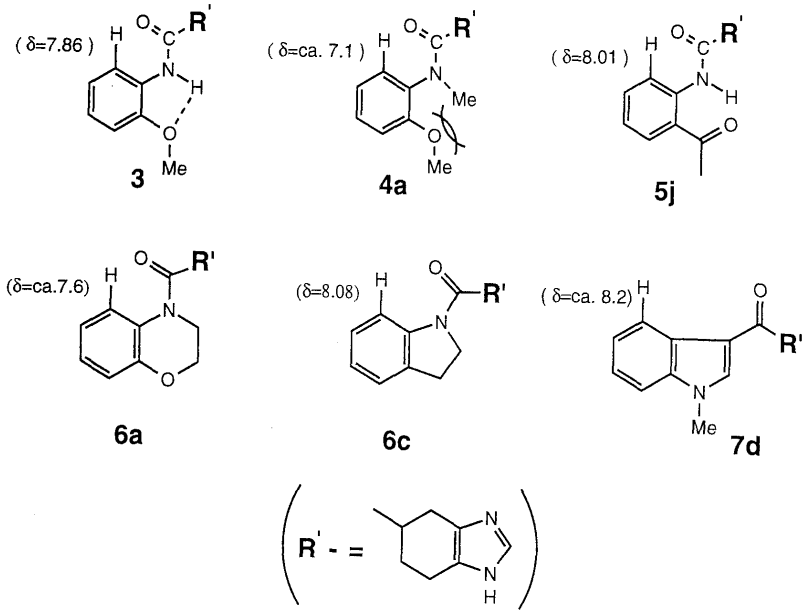



Chart 3

orientation of the carbonyl oxygen atom of **6c** differs from that of **6a**, which has an extra $sp^3$ carbon atom in the 6–6 fused bicyclic system. Accordingly, the planar conformation of the anilide moiety produced by the $sp^2$ hybridization of the nitrogen atom may result in easier binding to the 5-$HT_3$ receptor.[9]

We therefore turned our attention to a preparation of indole derivatives **7a**—**h**, possessing 6–5 fused aromatic ring (Table 4). Non-substituted compound **7a** had double the potency of **3**. Although the 2-methyl derivative **7b** retained the same potency as **7a**, the introduction of the larger 2-benzyl group (**7c**) reduced the potency. As shown in Chart 4, the steric repulsion between $R^4$ and the 4,5,6,7-tetrahydro-1*H*-benzimidazole ring in **A** may be much greater for **7c** than that in **7a** or **7b**. These results suggest that the methyl group is allowable as the substituent at the 2-position, whereas Fludzinski *et al.* reported that 1-methylindazole derivative **B** was active but 2-methyl isomer **C** was inactive (Chart 4).[10] The 1-methyl derivative **7d** was a strong 5-$HT_3$ receptor antagonist ($ID_{50}=0.044\,\mu g/kg$), approximately 7 times more potent than **3**. In the $^1$H-NMR spectrum, $\delta$ value of H at 4-position of compounds **7d** was shifted downfield ($\delta = ca.$ 8.2), suggesting the planarity of the indole-carbonyl moiety (Chart 3). Although the other 1-substituted derivatives **7e**—**h** showed potent activity, the tendency was observed to reduce activity for the more hindered substituents.

The indole moiety was converted to the other 6–5 fused aromatic rings such as in the compounds **7i**—**l** (Table 5). Both 3-benzothiophene derivative **7i** and 2-methyl-3-benzofurane derivative **7j** were shown to be markedly weaker than corresponding **7a** and **7b**. 1-Methyl-3-indolizine derivative **7k** was potent, and 3-methyl-1-indolizine derivative **7l** showed the strongest 5-$HT_3$ receptor antagonistic activity ($ID_{50}=0.018\,\mu g/kg$), approximately 200, 50 and 20 times more potent than **1**, **2** and **3**, respectively.

Overall, on the B.J. reflex test the indole and indolizine derivatives such as **7d** and **7l** were seen as more potent

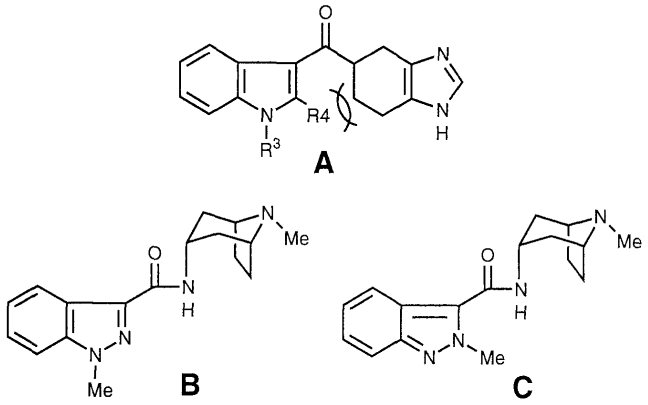



Chart 4

than the benzanilide or indoline derivatives **3** and **5j** or **6c**. These results are interpreted to indicate that the full aromaticity in the 6–5-fused aromatic part may be beneficial in the binding to the receptor. Similar results were observed in the azabicycloamine derivatives.[5,8,9]

The inhibitory effect of the compounds on the colonic contraction induced by 5-HT was evaluated (Tables 1—5). The $ID_{50}$ value ($\mu g/kg$)/$IC_{50}$ value ($\mu M$) ratios exhibit relative values between the activities on the B.J. reflex and colonic contraction. The values were almost equal if similar SARs were observed in the two experiments. Most of the *N*-(2-substituted-phenyl)carboxamide derivatives exhibited activity closely similar to **3** (Table 2). Especially, compound **5e** was more potent than **3**, whereas it was 10 times less potent than **3** on the B.J. reflex test, resulting in the $ID_{50}/IC_{50}$ ratio of 22 for **5e**. In contrast, the ratio for **5j** was 0.23. In Table 3, compound **6c** was found to be highly potent with an $IC_{50}$ value of 0.049 $\mu M$, which was slightly greater than **2** and about 9 times higher than **3**. In Table 4 compounds **7a**, **d**, **g** and **h** were also found to be potent with $IC_{50}$ values of below 0.1 $\mu M$; **7a** and **7g** were much more potent than **6c** ($ID_{50}$ values of 0.039 and 0.026 $\mu M$, respectively). However, the potency of compound **7b** was lower with the $ID_{50}/IC_{50}$ ratio of 0.048.

In Table 5 all compounds exhibited strong activity with compound **7k** showing the most potent ($IC_{50}=0.011\ \mu M$); a large difference was observed in the $ID_{50}/IC_{50}$ ratio: 31 for **7j** and 0.13 for **7l**.

In the isolated colonic contraction test, the indoline derivative **6c** was found to be a highly potent antagonist as were indole derivatives **7a** and **7g** and indolizine derivative **7k**, although **6c** does not possess a fully aromatized fused ring system. The $ID_{50}/IC_{50}$ ratios were observed over a wide range of 0.048 to 31.

At present it is difficult to completely idendify the cause of the discrepancy in the SARs in the above two experiments, although we postulated the following: (1) species difference or different methods of *in vivo* or *in vitro* test may be responsible; (2) different subtypes of 5-$HT_3$ receptors may exist in the heart and the colon; (3) the combination of the aromatic-carbonyl part and the 4,5,6,7-tetrahydro-1*H*-benzimidazole moiety as the amine part might have been mismatched. The first and the second possibilities have also been suggested by other reports.[11] With respect to the third possibility, it is felt that sufficient optimization has been accomplished in this series by the modification of the aromatic-carbonyl part of **3** to **4**, **5**, **6** and **7**, leaving the 4,5,6,7-tetrahydro-1*H*-benzimidazole moiety unchanged as the amine part. In particular, the 3-methyl-1-indolizinyl derivative **7l** showed the most potent activity on the B.J. reflex ($ID_{50}=0.018\ \mu g/kg$), approximately 200 and 50 times greater than **1** and **2**, respectively; and the 1-methyl-3-indolizinyl derivative **7k** exhibited the most potent activity on the colonic contraction ($IC_{50}=0.011\ \mu M$), approximately 70 and 6 times more potent than **1** and **2**, respectively.

However, all of these compounds are racemates possessing an asymmetric carbon atom at 5-position in 4,5,6,7-tetrahydro-1*H*-benzimidazole ring. We will report the preparation of several optical active isomers and the evaluation their pharmacological activities in detail as well as studying the 5-$HT_3$ receptor pharmacophore using three dimensional molecular modeling.

## Conclusion

Optimization of compound **3** was accomplished in this series by modification of the aromatic-carbonyl part of **3** to **4**, **5**, **6** and **7**, leaving the 4,5,6,7-tetrahydro-1*H*-benzimidazole moiety unchanged as the amine part. Compounds **7d, g, h, k** and **l** were found to be highly potent by the B.J. reflex test with $ID_{50}$ values of below 0.1 $\mu g/kg$, and compounds **6c, 7a, d, g, j** and **k** were very potent on the colonic contraction with $IC_{50}$ values of below 0.1 $\mu M$. In particular, 3-methyl-1-indolizinyl derivative **7l** was the most potent on the B.J. reflex ($ID_{50}=0.018\ \mu g/kg$), approximately 200 and 50 times more potent than **1** and **2**, and 1-methyl-3-indolizinyl derivative **7k** was the most potent on the colonic contraction ($IC_{50}=0.011\ \mu M$), approximately 70 and 6 times more potent than **1** and **2**, respectively.

### Experimental

All melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. $^1$H-NMR spectra were measured with a JEOL FX90Q, a FX100, a FX270 or FX400 spectrometer; chemical shifts are recorded in $\delta$ units using tetramethylsilane as an internal standard and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=double doublet and dt=double triplet. Mass spectra were recorded with a Hitachi M-80 electron impact (EI) or a JEOL JMS-DX300 (FAB) spectrometer. Elemental analyses were performed with a Yanaco MT-5. All organic solvent extracts were dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator under reduced pressure.

***N*-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Hydrochloride[1] (3) [Method A]** Thionyl chloride (3 ml, 41.4 mmol) was added to a solution of 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid hydrogensulfate **8**[1,6] (5.42 g, 20.5 mmol) in 1,2-dichloroethane (50 ml). The mixture was heated at 55—60 °C for 1 h, then concentrated to afford a crude acyl chloride **9**. 1,2-Dichloroethane (50 ml) was added to the residue, and 2-anisidine (6.25 g, 50.7 mmol) at less than 30 °C was added dropwise to the mixture. After the addition was completed, the mixture was stirred for 2 h at room temperature, then poured into a solution of $H_2O$ (60 ml) and MeOH (30 ml), and the pH of the aqueous layer was adjusted to 4.8 by the addition of 10% aqueous NaOH. After separation, MeOH (15 ml) was added to the aqueous layer. Ten percent aqueous NaOH was then added slowly at 5 °C until the pH of the aqueous layer became 11.0. The resulting precipitate was collected and washed with a mixture of $H_2O$–MeOH (3 : 1) to give 5.62 g (100% yield) of a solid. The solid (5.07 g, 18.7 mmol) was treated with one equivalent of dry hydrogen chloride in EtOH to give 5.66 g (98% yield) of **3**, mp >250 °C. $^1$H-NMR dimethyl sulfoxide (DMSO-$d_6$) $\delta$: 1.78—2.28 (2H, m), 2.56—2.88 (4H, m), 2.90—3.14 (1H, m), 3.80 (3H, s), 6.78—7.16 (3H, m), 7.86 (1H, br d, $J$=8 Hz), 8.86 (1H, s), 9.28 (1H, br s). EI-MS *m/z*: 271 ($M^+$, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2\cdot HCl$: C, 58.54; H, 5.89; Cl, 11.52; N, 13.65. Found: C, 58.24; H, 5.98; Cl, 11.68; N, 13.48.

***N*-(2-Methoxyphenyl)-*N*-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (4a) 4a** was prepared by method A using *N*-methyl-2-anisidine[12] instead of 2-anisidine in 78% yield. mp 124—127 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.52—2.86 (7H, m), 3.10 (3H, s), 3.84, 3.87 (each 1.5H, s), 6.64 (2H, s), 6.88—7.46 (4H, m), 7.52—7.70 (1H, m). EI-MS *m/z*: 285 ($M^+$, as a free base). *Anal.* Calcd for $C_{16}H_{19}N_3O_2\cdot C_4H_4O_4\cdot 0.7H_2O$: C, 58.02; H, 5.94; N, 10.15. Found: C, 57.89; H, 5.66; N, 9.87.

***N*-Phenyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 0.75 Fumarate (5a) 5a** was prepared by method A using aniline instead of 2-anisidine in 22% yield, mp 186—188 °C (MeOH–AcOEt). FAB-MS (Pos.) *m/z*: 242 ($M^+ +1$, as a free base). *Anal.* Calcd for $C_{14}H_{15}N_3O\cdot 0.75C_4H_4O_4\cdot 0.7H_2O$: C, 59.88; H, 5.73; N, 12.32. Found: C, 59.89; H, 5.58; N, 12.26. Free base, $^1$H-NMR ($CDCl_3$–$CD_3OD$) $\delta$: 1.75—2.44 (2H, m), 2.46—3.00 (5H, m), 6.88—7.77 (6H, m).

***N*-(3-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 0.5 Fumarate (5b) 5b** was prepared by method A using 3-anisidine instead 2-anisidine in 53% yield, mp 195—196 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.60—2.21 (2H, m), 2.41—2.93 (5H, m), 3.73 (3H, s), 6.63 (1H, s), 6.54—6.68 (1H, m), 7.16 (1H, s), 7.09—7.44 (2H, m), 7.56 (1H, s), 9.96 (1H, s). EI-MS *m/z*: 271 ($M^+$, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2\cdot 0.5C_4H_4O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.87; H, 5.85; N, 1246.

***N*-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 0.5 Fumarate (5c) 5c** was prepared by method A using 4-anisidine instead of 2-anisidine in 25% yield, mp 217—218 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.60—2.24 (2H, m), 2.40—2.95 (5H, m), 3.72 (3H, s), 6.58 (1H, s), 6.87 (2H, d, $J$=9 Hz), 7.53 (2H, d, $J$=9 Hz), 7.55 (1H, s), 9.81 (1H, s). EI-MS *m/z*: 271 ($M^+$, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3O_2\cdot 0.5C_4H_4O_4\cdot H_2O$: C, 61.33; H, 5.87; N, 12.62. Found: C, 61.28; H, 5.84; N, 12.61.

***N*-((2-*n*-Butyloxy)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5d) 5d** was prepared by method A using 2-(*n*-butyloxy)aniline[13] instead of 2-anisidine in 74% yield, mp 157—160 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.93 (3H, t, $J$=8 Hz), 1.22—2.27 (6H, m), 2.34—3.10 (5H, m), 4.00 (2H, t, $J$=8 Hz), 6.55 (2H, s), 6.75—7.20 (3H, m), 7.70 (1H, s), 7.83 (1H, d, $J$=7 Hz), 8.94 (1H, s). EI-MS *m/z*: 313 ($M^+$, as a free base). *Anal.* Calcd for $C_{18}H_{23}N_3O_2\cdot C_4H_4O_4\cdot 0.4H_2O$: C, 60.51; H, 6.42; N, 9.62. Found: C, 60.21; H, 6.10; N, 9.71.

***N*-((2-Benzyloxy)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 0.5 Fumarate (5e) 5e** was prepared by method A using 2-(benzyloxy)aniline[14] instead of 2-anisidine in 72% yield, mp 199—201 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.61—2.23 (2H,

m), 2.40—3.09 (5H, m), 5.20 (2H, s), 6.60 (1H, s), 6.79—7.16 (3H, m), 7.26—7.59 (5H, m), 7.66 (1H, s), 7.84 (1H, d, $J=8$ Hz), 9.18 (1H, s). EI-MS $m/z$: 347 ($M^+$, as a free base). *Anal.* Calcd for $C_{21}H_{21}N_3O_2 \cdot 0.5C_4H_4O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.18; H, 5.83; N, 10.36.

***N*-((2-Phenoxy)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5f)** **5f** was prepared by method A using 2-(phenoxy)aniline[15] instead of 2-anisidine in 76% yield, mp 182—183 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.48—2.08 (2H, m), 2.35—2.94 (5H, m), 6.59 (2H, s), 6.80—7.52 (8H, m), 7.65 (1H, s), 7.84—8.07 (1H, m), 9.47 (1H, s). EI-MS $m/z$: 333 ($M^+$, as a free base). *Anal.* Calcd for $C_{20}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.2H_2O$: C, 63.63; H, 5.21; N, 9.27. Found: C, 63.70; H, 5.24; N, 9.23.

***N*-((2-Allyloxy)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5g)** **5g** was prepared by method A using 2-(allyloxy)aniline[16] instead of 2-anisidine in 28% yield, mp 145—147 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.64—2.12 (2H, m), 2.60—3.04 (5H, m), 4.52—4.64 (2H, m), 5.16—5.50 (2H, m), 5.84—6.26 (1H, m), 6.56 (2H, s), 6.76—7.08 (3H, m), 7.68 (1H, m), 7.84 (1H, br d, $J=8$ Hz), 9.08 (1H, s). EI-MS $m/z$: 297 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 59.71; H, 5.73; N, 9.95. Found: C, 59.88; H, 5.59; N, 10.09.

***N*-((2-Propargyloxy)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5h)** **5h** was prepared by method A using 2-(propargyloxy)aniline[17] instead of 2-anisidine in 33% yield, mp 123—125 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.68—2.12 (2H, m), 2.60—3.10 (5H, m), 3.56 (1H, t, $J=3$ Hz), 6.54 (2H, s), 6.80—7.20 (3H, m), 7.64 (1H, s), 7.80—7.92 (1H, m), 9.14 (1H, s). EI-MS $m/z$: 295 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5MeOH \cdot 0.5H_2O$: C, 59.17; H, 5.54; N, 9.63. Found: C, 59.21; H, 5.56; N, 9.46.

***N*-((2-Acetyl)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5j)** **5j** was prepared by method A using 2-acetylaniline instead of 2-anisidine in 75% yield, mp 94—98 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.60—2.32 (2H, m), 2.36—2.98 (5H, m), 2.64 (3H, s), 6.62 (2H, s), 7.21 (1H, dt, $J=2$, 8 Hz), 7.60 (1H, $J=2$, 8 Hz), 7.71 (1H, s), 8.01 (1H, dd, $J=2$, 8 Hz), 8.38 (1H, dd, $J=2$, 8 Hz), 11.50 (1H, s). EI-MS $m/z$: 283 ($M^+$, as a free base). *Anal.* Calcd for $C_{16}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5CH_3CN \cdot 0.5H_2O$: C, 58.80; H, 5.52; N, 11.43. Found: C, 58.81; H, 5.38; N, 11.43.

***N*-((2-Methoxycarbonyl)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5k)** **5k** was prepared by method A using methyl anthranilate instead of 2-anisidine in 53% yield, mp 95—97 °C (MeOH–AcOEt). FAB-MS (Pos.) $m/z$: 300 ($M^+ + 1$, as a free base). *Anal.* Calcd for $C_{16}H_{17}N_3O_3 \cdot C_4H_4O_4$: C, 57.59; H, 5.63; N, 11.19. Found: C, 57.30; H, 5.23; N, 11.00. Free base. $^1$H-NMR ($CDCl_3$) $\delta$: 1.75—2.44 (2H, m), 2.50—3.21 (5H, m), 3.90 (3H, s), 6.90—7.73 (2H, m), 7.52 (1H, s), 8.02 (1H, dd, $J=2$, 8 Hz), 8.72 (1H, d, $J=8$ Hz), 11.24 (1H, s).

***N*-((2-Nitro)phenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide Fumarate (5l)** **5l** was prepared by method A using 2-nitroaniline instead of 2-anisidine in 31% yield, mp 144—146 °C (MeOH–MeCN). FAB-MS (Pos.) $m/z$: 287 ($M^+ + 1$, as a free base). *Anal.* Calcd for $C_{14}H_{14}N_4O_3 \cdot C_4H_4O_4$: C, 53.73; H, 4.50; N, 13.92. Found: C, 53.89; H, 4.30; N, 13.71. Free base. $^1$H-NMR ($CDCl_3$) $\delta$: 1.75—2.44 (2H, m), 2.50—3.10 (5H, m), 7.00—7.85 (2H, m), 7.50 (1H, s), 8.02—8.40 (1H, m), 8.75 (1H, br d, $J=8$ Hz).

**4-[(4,5,6,7-Tetrahydro-1*H*-5-benzimidazolyl)carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine Fumarate (6a)** **6a** was prepared by method A using 1,4-benzoxazine[18] instead of 2-anisidine in 72% yield, mp 176—178 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.58—2.20 (2H, m), 2.44—2.80 (4H, m), 3.12—3.48 (1H, m), 3.80—4.02 (2H, m), 4.16—4.38 (2H, m), 6.56 (2H, s), 6.72—7.12 (3H, m), 7.44—7.80 (1H, m), 7.72 (1H, s). EI-MS $m/z$: 283 ($M^+$, as a free base). *Anal.* Calcd for $C_{16}H_{17}N_3O_2 \cdot C_4H_4O_4$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.95; H, 5.28; N, 10.55.

**1-[(4,5,6,7-Tetrahydro-1*H*-5-benzimidazolyl)carbonyl]-1,2,3,4-tetrahydroquinoline Fumarate (6b)** **6b** was prepared by method A using 1,2,3,4-tetrahydroquinoline instead of 2-anisidine in 33% yield, mp 98—100 °C (MeOH–AcOEt). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.60—2.08 (4H, m), 2.30—2.88 (6H, m), 3.04—3.34 (1H, m), 3.58—3.82 (2H, m), 6.60 (2H, s), 6.94—7.44 (4H, m), 7.55 (1H, s). EI-MS $m/z$: 281 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{19}N_3O \cdot C_4H_4O_4 \cdot 2H_2O$: C, 58.19; H, 6.27; N, 9.69. Found: C, 58.43; H, 5.93; N, 9.53.

**5-[(1-Indolinyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Hydrochloride (6c)** **6c** was prepared by method A using indoline instead of 2-anisidine in 89% yield, mp >250 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.62—2.30 (2H, m), 2.60—3.50 (7H, m), 4.10 (2H, t, $J=8$ Hz), 6.86—7.30 (3H, m), 8.08 (1H, br d, $J=8$ Hz), 8.88 (1H, s). EI-MS $m/z$: 267 ($M^+$, as a free base). *Anal.* Calcd for $C_{16}H_{17}N_3O \cdot HCl$: C, 63.26; H, 5.97; N, 13.83; Cl, 11.67. Found: C, 63.15; H, 5.97; N, 13.80; Cl, 11.78.

***N*-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carbothioamide 0.5 Fumarate (4b) [Method B]** A mixture of **3** (0.24 g, 0.89 mmol) and Lawesson's reagent (0.36 g, 0.89 mmol) in toluene (10 ml) was heated under reflux for 6 h. The mixture was concentrated, $H_2O$ added, basified with 1 N NaOH and extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and recrystallized from MeOH–AcOEt by an addition of 0.5 eq of fumaric acid to give 0.20 g (80% yield) of **4b** as a solid, mp 218—219 °C. FAB-MS (Pos.) $m/z$: 288 ($M^+ + 1$, as a free base). *Anal.* Calcd for $C_{15}H_{17}N_3OS \cdot 0.5C_4H_4O_4$: C, 59.11; H, 5.54; N, 12.16; S, 9.28. Found: C, 58.91; H, 5.46; N, 12.01; S, 9.68. $^1$H-NMR ($CDCl_3$) $\delta$: 1.91—2.40 (2H, m), 2.40—3.35 (5H, m), 3.82 (3H, s), 6.77—7.32 (3H, m), 7.45 (1H, s), 8.76 (1H, br d, $J=8$ Hz), 9.50 (2H, br s).

***N*-(2-Hydroxyphenyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxamide 0.5 Fumarate (5i) [Method C]** **5e** (0.24 g, 0.7 mmol) was hydrogenated in EtOH (15 ml) over 10% palladium-on-carbon (30 mg) at room temperature for 3 h. After the catalyst was removed by filtration, the filtrate was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and recrystallized from MeOH–$CH_3CN$ to give 0.10 g (56% yield) of the product as a viscous liquid, which was treated with 0.5 eq of fumaric acid in MeOH–$CH_3CN$ to give **5i**, mp 203—205 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.51—2.26 (2H, m), 2.30—3.21 (5H, m), 6.56 (1H, s), 6.51—7.08 (3H, m), 7.70 (1H, s), 7.74 (1H, d, $J=9$ Hz), 9.31 (1H, s), 10.40 (2H, br s). EI-MS $m/z$: 259 ($M^+$, as a free base). *Anal.* Calcd for $C_{14}H_{15}N_3O_2 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$: C, 59.25; H, 5.59; N, 12.96. Found: C, 59.21; H, 5.32; N, 12.90.

**1-[(4,5,6,7-Tetrahydro-1*H*-5-benzimidazolyl)carbonyl]-2,3-dihydrobenzimidazol-2-one (6d) [Method D]** 2-Hydroxybenzimidazole (1.61 g, 12.0 mmol) was added portionwise to a suspension of 60 w/w% sodium hydride (0.50 g, 12.5 mmol) in dimethyl formamide (DMF) (30 ml) at 0 °C. At 0 °C, to the mixture was added dropwise a solution of acyl chloride hydrogensulfate **9**, obtained from 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid hydrogensulfate **8** (0.78 g, 3.0 mmol) as shown in general method A, in DMF (3 ml). The mixture was stirred for 1 h at room temperature and concentrated. 0.5 N HCl (30 ml) was added to the residue, then the resulting precipitates were removed by filtration. The filtrate was basified by the addition of $K_2CO_3$. The resulting precipitate was collected and washed with hot acetone to give 0.20 g (24% yield) of **6d**, mp 271—274 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.56—2.30 (2H, m), 2.40—2.84 (5H, m), 3.94—4.30 (1H, m), 6.84—7.26 (3H, m), 7.40 (1H, s), 7.90—8.08 (1H, m). EI-MS $m/z$: 282 ($M^+$, as a free base). *Anal.* Calcd for $C_{15}H_{14}N_4O_2 \cdot 0.4H_2O$: C, 62.23; H, 5.15; N, 19.35. Found: C, 62.41; H, 5.02; N, 19.60.

**5-[(1-Methyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole 0.5 Fumarate (7d) [Method E]** (i) A mixture of acyl chloride hydrogensulfate **9**, obtained from 5-(4,5,6,7-tetrahydro-1*H*-benzimidazole)-carboxylic acid hydrogensulfate **8** (5.3 g, 20 mmol) as shown in method A, in acetonitrile (50 ml) was added dropwise to a solution of pyrrolidine (14.2 g, 200 mmol) in acetonitrile (50 ml) at less than 2 °C, followed by stirring for 1 h at room temperature. After concentration, saline (30 ml) was added to the residue, the mixture was extracted with $CHCl_3$ (50 ml × 3), dried and concentrated. The residue was treated with 4 N hydrogen chloride in AcOEt (5.0 ml) in EtOH–AcOEt (20—25 ml) to give 4.25 g (83% yield) of *N*-[(4,5,6,7-tetrahydro-1*H*-benzimidazol-5-yl)carbonyl]pyrrolidine hydrochloride **12** as a solid, mp 234—236 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.50—2.15 (6H, m), 2.45—3.05 (5H, m), 3.10—3.60 (4H, m), 8.80 (1H, s). EI-MS $m/z$ 219 ($M^+$, as a free base). *Anal.* Calcd for $C_{12}H_{17}N_3O \cdot HCl \cdot 0.2H_2O$: C, 55.57; H, 7.15; Cl, 13.67; N, 16.20. Found: C, 55.64; H, 6.99; Cl, 13.79; N, 16.18.

(ii) Phosphorous oxychloride (12.6 g, 82.2 mmol) was added to a suspension of 1-methylindole (5.4 g, 41 mmol) and **12** (7.0 g, 27 mmol) in 1,2-dichloroethane (70 ml), and the mixture was stirred for 7 h at 80—85 °C, followed by cooling to 0 °C. Cold $H_2O$ (70 ml) was added dropwise to the mixture at below 25 °C. After separation, the aqueous layer was basified with 20% NaOH, then extracted with $CHCl_3$ (40 ml × 2). Cold $H_2O$ (70 ml) was added to the combined $CHCl_3$ solu-

tion, followed by the addition of 6 N HCl to adjust pH to 2.4 to 2.8, then the organic layer was removed. The acidic aqueous solution was washed with $CHCl_3$ (40 ml), followed by the addition of MeOH (40 ml). This solution was slightly basified with 20% NaOH. The resulting precipitate was collected and washed with a mixture of $H_2O$–MeOH (1 : 1) to give 6.87 g (90% yield) of a solid. Free base of **7d**, $^1$H-NMR ($CDCl_3$–DMSO-$d_6$) $\delta$: 1.80—2.32 (2H, m), 2.56—3.04 (4H, m), 3.32—3.60 (1H, m), 3.90 (3H, s), 7.12—7.20 (3H, m), 7.40 (1H, s), 7.92 (1H, s), 8.20—8.40 (1H, m). EI-MS *m/z*: 279 ($M^+$). The solid (2.79 g, 10.0 mmol) was treated with fumaric acid (0.58 g, 5.0 mmol) in EtOH (20 ml) to give 3.24 g (96% yield) of **7d** as a solid, mp 224—225 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.56—2.24 (2H, m), 2.40—2.89 (4H, m), 3.40—3.77 (1H, m), 3.90 (3H, s), 6.61 (1H, s), 7.15—7.41 (2H, m), 7.48—7.73 (1H, m), 7.66 (1H, s), 8.16—8.37 (1H, m), 8.50 (1H, s). EI-MS *m/z*: 279 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{17}N_3O \cdot 0.5C_4H_4O_4$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.56; H, 5.66; N, 12.35.

**5-[(3-Indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7a)** **7a** was prepared by method E using indole instead of 1-methylindole in 54% yield, mp 153—154 °C (MeOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.62—2.12 (2H, m), 2.45—2.82 (4H, m), 3.40—3.68 (1H, m), 6.52 (2H, m), 6.82—7.50 (3H, m), 7.60 (1H, br s), 8.00—8.22 (1H, m), 8.34 (1H, br d, $J$=4 Hz)). FAB-MS (Pos.) *m/z*: 266 ($M^+$+1, as a free base). *Anal.* Calcd for $C_{16}H_{15}N_3O \cdot C_4H_4O_4 \cdot 0.65H_2O \cdot 0.15$MeCN: C, 61.07; H, 5.24; N, 11.05. Found: C, 61.11; H, 5.01; N, 11.04.

**5-[(2-Methyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole 0.5 Fumarate (7b)** **7b** was prepared by method E using 2-methylindole instead of 1-methylindole in 33% yield, mp 221—223 °C (MeOH–$Et_2O$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.55—3.02 (6H, m), 2.69 (3H, s), 3.35—3.75 (1H, m), 6.59 (1H, s), 7.09—7.24 (2H, m), 7.31—7.39 (1H, m), 7.70 (1H, s), 7.85—7.96 (1H, m), 8.10 (1H, br s), 11.97 (1H, s). EI-MS *m/z*: 279 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{17}N_3O \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$: C, 66.75; H, 5.75; N, 12.29. Found: C, 66.73; H, 5.75; N, 12.29.

**5-[(2-Benzyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7c)** **7c** was prepared by method E using 2-benzylindole[19] instead of 1-methylindole in 30% yield, mp 183—186 °C (EtOH–$Et_2O$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.70—2.20 (2H, m), 2.70—2.85 (4H, m), 3.58 (1H, m), 4.49 (2H, s), 6.60 (2H, s), 7.00—7.97 (5H, m), 7.25 (5H, br s), 7.67 (1H s), 12.00 (1H, s). EI-MS *m/z*: 355 ($M^+$, as a free base). *Anal.* Calcd for $C_{23}H_{21}N_3O \cdot C_4H_4O_4 \cdot 0.1H_2O$: C, 68.52; H, 5.37; N, 8.88. Found: C, 68.38; H, 5.50; N, 8.87.

**5-[(1-Methyl-3-indolizinyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Hydrochloride (7k)** **7k** was prepared by method E using 1-methylindolizine[20] instead of 1-methylindole in 88% yield, mp 255—258 °C (EtOH–AcOEt). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.82—2.00 (1H, m), 2.08—2.22 (1H, m), 2.34 (3H, s), 2.64—3.00 (4H, m), 3.68—3.84 (1H, m), 7.08 (1H, t, $J$=6 Hz), 7.30 (1H, t, $J$=6 Hz), 7.76 (1H, d, $J$=6 Hz), 7.78 (1H, s), 8.98 (1H, s), 9.76 (1H, d, $J$=6 Hz). EI-MS *m/z*: 279 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{17}N_3O \cdot$HCl: C, 64.66; H, 5.75; Cl, 11.23; N, 13.31. Found: C, 64.28; H, 5.91; Cl, 11.27; N, 13.09.

**5-[(3-Methyl-1-indolizinyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Hydrochloride (7l)** **7l** was prepared by method E using 3-methylindolizine[21] instead of 1-methylindole in 87% yield, mp 250—255 °C (EtOH). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.76—1.92 (1H, m), 2.12—2.20 (1H, m), 2.48 (3H, s), 2.62—2.90 (4H, m), 3.64—3.72 (1H, m), 7.02 (1H, t, $J$=6 Hz), 7.28 (1H, t, $J$=6 Hz), 7.38 (1H, s), 8.26 (1H, d, $J$=6 Hz), 8.34 (1H, d, $J$=6 Hz), 8.94 (1H, s). EI-MS *m/z*: 279 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{17}N_3O \cdot$HCl: C, 64.66; H, 5.75; Cl, 11.23; N, 13.31. Found: C, 64.43; H, 5.85; Cl, 11.14; N, 13.21.

**5-[[1-(2-Propenyl)indol-3-yl]carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7g) [Method F]** (i) Trityl chloride (1.92 g, 6.89 mmol) was added to a solution of 5-(3-indolylcarbonyl)-4,5,6,7-tetrahydrobenzimidazole (free base of **7a**) (1.82 g, 6.86 mmol) and triethylamine (0.96 ml, 6.9 mmol) in DMF (30 ml) and the mixture was stirred for 15 h at room temperature. After evaporation, the residue was dissolved in $CHCl_3$ (30 ml), washed with $H_2O$ (20 ml) and saturated aqueous $NaHCO_3$ (20 ml), dried and concentrated. The residue was purified by short silica gel column chromatography ($CHCl_3$–MeOH) to give 2.70 g (78% yield) of a mixture of 1- and 3-trityl-5-(3-indolylcarbonyl)-4,5,6,7-tetrahydrobenzimidazole.

(ii) The mixture of 1- and 3-isomers (0.19 g, 0.37 mmol) was added portionwise to a suspension of 60 w/w% sodium hydride (0.02 g, 0.5 mmol) in DMF (2 ml), followed by stirring for 30 min at room temperature. At 0 °C to the mixture was added dropwise of a solution of allyl bromide (0.05 g, 0.41 mmol) in DMF (0.5 ml), then stirred at room temperature for 10 h. $H_2O$ (4 ml) and $CHCl_3$ (6 ml) were added to the mixture, and the organic layer was separated, dried and concentrated. The residue was suspended in dioxane (5 ml) and 1 N HCl (2 ml), then the mixture was heated to 100 °C for 30 min; after cooling it was washed with $Et_2O$ (5 ml × 2). The aqueous layer was basified with 20% NaOH and extracted with $CHCl_3$, then dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and treated with one equivalent of fumaric acid in MeOH–AcOEt to give 0.11 g (66% yield) of **7g** as a solid, mp 144—145 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 160—2.20 (2H, m), 2.60—2.84 (4H, m), 3.36—3.66 (1H, m), 4.76—4.92 (2H, m), 4.92—5.24 (2H, m), 5.76—6.24 (1H, m), 6.50 (2H, m), 7.00—7.70 (4H, m), 8.06—8.24 (1H, m), 8.40 (1H, s). EI-MS *m/z*: 305 ($M^+$, as a free base). *Anal.* Calcd for $C_{19}H_{19}N_3O \cdot C_4H_4O_4 \cdot 0.3H_2O$: C, 64.72; H, 5.57; N, 9.84. Found: C, 64.68; H, 5.52; N, 9.79.

**5-[((1-*n*-Butyl)-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7e)** **7e** was prepared by method F using *n*-butyl iodide instead of allyl bromide in 85% yield, mp 104—106 °C (EtOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.88 (3H, t, $J$=7 Hz), 1.00—1.42 (2H, m), 1.58—2.10 (4H, m), 2.58—2.82 (4H, m), 3.36—3.68 (1H, m), 4.18 (2H, d, $J$=7 Hz), 6.50 (2H, s), 7.04—7.30 (2H, m), 7.40—7.62 (1H, m), 7.58 (1H, s), 8.02—8.24 (1H, m), 8.42 (1H, s). EI-MS *m/z*: 321 ($M^+$, as a free base). *Anal.* Calcd for $C_{20}H_{23}N_3O \cdot C_4H_4O_4 \cdot 0.8H_2O$: C, 63.78; H, 6.38; N, 9.30. Found: C, 63.82; H, 6.14; N, 9.33.

**5-[(1-Benzyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7f)** **7f** was prepared by method F using benzyl bromide instead of allyl bromide in 82% yield, mp 117—118 °C (EtOH–AcOEt). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.60—2.22 (2H, m), 2.60—2.84 (4H, m), 3.36—3.76 (1H, m), 5.42 (2H, s), 6.52 (2H, m), 7.00—7.56 (8H, m), 7.58 (1H, s), 8.04—8.24 (1H, m), 8.60 (1H, s). EI-MS *m/z*: 355 ($M^+$, as a free base). *Anal.* Calcd for $C_{23}H_{21}N_3O \cdot C_4H_4O_4 \cdot 0.75H_2O$: C, 66.86; H, 5.51; N, 8.66. Found: C, 66.83; H, 5.48; N, 8.88.

**5-[(1-Propargyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7h)** **7h** was prepared by method F using propargyl bromide instead of allyl bromide in 77% yield, mp 130—131 °C (EtOH–MeCN). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.62—2.22 (2H, m), 2.60—2.85 (4H, m), 3.35—3.56 (1H, m), 5.19 (2H, d, $J$=3 Hz), 6.60 (2H, s), 7.24—7.44 (2H, m), 7.55—7.70 (1H, m), 7.67 (1H, m), 8.20—8.32 (1H, m), 8.55 (1H, s). EI-MS *m/z*: 303 ($M^+$, as a free base). *Anal.* Calcd for $C_{19}H_{17}N_3O \cdot C_4H_4O_4 \cdot 1.3H_2O$: C, 62.38; H, 5.37; N, 9.49. Found: C, 62.38; H, 5.19; N, 9.21.

**5-[(3-Benzothiophenyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7i) [Method G]** Aluminum(III) chloride (0.40 g, 3.0 mmol) was added to a mixture of benzothiophene (4.6 ml, 39 mmol) and acyl chloride hydrogensulfate **9**, obtained from 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid hydrogensulfate **8** (0.53 g, 2.0 mmol). After stirring for 3 h at 60 °C, the mixture was poured into cold aqueous $K_2CO_3$ (20 ml), extracted with $CHCl_3$ (30 ml), dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and treated with one equivalent of fumaric acid in EtOH–$CH_3CN$ to give 0.04 g (5% yield) of **7i** as a solid, mp 135—137 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.74—1.84 (2H, m), 2.10—2.20 (1H, m), 2.60—2.80 (4H, m), 3.88—3.90 (1H, m), 6.51 (2H, s), 7.45—7.65 (3H, m), 8.10 (1H, d, $J$=8 Hz), 8.65 (1H, d, $J$=8 Hz), 9.13 (1H, s). EI-MS *m/z*: 282 ($M^+$, as a free base). *Anal.* Calcd for $C_{16}H_{14}N_2OS \cdot C_4H_4O_4 \cdot 0.3$EtOH $\cdot 0.2H_2O$: C, 59.50; H, 4.90; N, 6.74; S, 7.71. Found: C, 59.41; H, 5.07; N, 6.53; S, 7.91.

**5-[(2-Methyl-3-benzofuranyl)carbonyl]-4,5,6,7-tetrahydro-1*H*-benzimidazole Fumarate (7j) [Method H]** Tin(IV) chloride (2.2 ml, 18.8 mmol) was added to a mixture of 2-methylbenzofurane (1.80 ml, 14.4 mmol), nitrobenzene (20 ml) and acyl chloride hydrogensulfate **9**, obtained from 4,5,6,7-tetrahydro-1*H*-benzimidazole-5-carboxylic acid hydrogensulfate **8** (5.50 g, 18.9 mmol), and the mixture was heated at 85 °C for 15 h. The mixture was cooled to room temperature and poured into 1 N HCl (10 ml) and $Et_2O$ (40 ml). The aqueous solution was basified to pH 10 by the addition of 10% NaOH and extracted with $CHCl_3$–MeOH (9 : 1), then dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH) and treated with one equivalent of fumaric acid in EtOH to give 0.22 g (4% yield) of **7j** as a solid, mp 178—180 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.71—2.18 (2H, m), 2.55—2.85 (4H, m), 2.77 (3H, s), 3.56—3.64 (1H, m), 6.61 (2H, s), 7.34—7.38 (2H, m), 7.60 (1H, s), 7.63 (1H, dd, $J$=2, 8 Hz), 7.93 (1H, dd, $J$=2, 8 Hz). EI-MS *m/z*: 280 ($M^+$, as a free base). *Anal.* Calcd for $C_{17}H_{16}N_2O_2 \cdot C_4H_4O_4$: C, 63.22; H, 5.02; N,7.10. Found: C, 63.53; H, 5.09; N, 7.07.

**1-(2-Methoxyphenyl)-3-(4,5,6,7-tetrahydro-1*H*-5-benzimidazolyl)urea (4c) [Method I]** A solution of 5-amino-4,5,6,7-tetrahydro-1*H*-benzimidazole **14**[22] (obtained from its dihydrochloride salt (0.70 g, 3.3 mmol) by neutralization) and 2-methoxyphenylisocyanate (0.60 g, 4.0 mmol) in DMF (3 ml) was stirred for 1 h at room temperature. The mixture was concentrated, dissolved in dilute HCl, washed with $CH_2Cl_2$, basified by $K_2CO_3$ and extracted with $CHCl_3$–MeOH (9 : 1). The organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–conc. $NH_4OH$) and crystallized from $CHCl_3$ to give 0.17 g (17% yield) of **4c** as a solid, mp 148—150 °C. $^1$H-NMR ($CD_3OD$) $\delta$: 1.75—2.25 (2H, m), 2.30—3.12 (5H, m), 3.85 (3H, s), 3.95—4.30 (1H, m), 6.82—7.00 (3H, m), 7.50 (1H, m), 7.85—8.10 (1H, m). EI-MS *m/z*: 286 ($M^+$, as a free base). *Anal.* Calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.58. Found: C, 62.69; H, 6.24; N, 19.38.

**Biological Methods** Doses are expressed in terms of free base. 5-HT was purchased from E. Merck (Darmstadt, FRG) as creatinine sulfate.

**Von Bezold–Jarisch Reflex Test**[2] Male Wistar rats weighing 200 to 250 g were anesthetized with urethane (1.25 mg/kg, i.p.), and then tracheas were cannulated. Arterial blood pressure and heart rate were recorded on a polygraph through a pressure transducer and cardiotachometer, respectively, connected to a catheter placed in the carotid artery. The femoral vein was also cannulated for drug injection. 5-$HT_3$ at a dose of 10 $\mu$g/kg was intravenously administered to rats at intervals of 15 min. After a stable response to 5-HT was obtained, drugs were intravenously administered to rats 10 min before 5-HT injection.

**Contraction of Isolated Guinea Pig Colon**[3] The distal portion of the colon was removed from Hartley guinea pigs (300 to 500 g), cleaned in fresh Krebs–bicarbonate buffer at room temperature and then divided into approximately 20 mm segments. Isomeric contraction under a loading tension of 1 g was recorded. Submaximal contraction was first elicited by repeated concentrations of $10^{-6}$ M 5-HT until constant response was obtained. Test compounds were added to the bath after a concentration–response curve for 5-HT had been obtained. The tissue was exposed to the test compound for 30 min before rechallange with 5-HT (control). Each test compound was examined at one or two different concentrations in the same preparation.

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