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N-[1-(2-Phenylethyl)pyrrolidin-3-yl]-1-adamantanecarboxamides as Novel 5-HT_2 Receptor Antagonists

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Abstract—A series of 1-adamantanecarboxamides was synthesized and examined for their potency as a selective 5-HT_2 receptor antagonist. We found (*S*)-*N*-{1-[2-(4-fluorophenyl)ethyl]pyrrolidin-3-yl}-1-adamantanecarboxamide hydrochloride hydrate (**10-(*S*)**, **Y-39241**) to have a high affinity and selectivity for 5-HT_2 receptors, and this potent anti-platelet effect of **Y-39241** was confirmed both in vitro and in vivo.

Serotonin (5-HT) not only induces potent vasoconstriction and platelet aggregation, but also synergistically amplifies the effects of such vasoactive and/or platelet aggregative substances such as TXA_2, norepinephrine, angiotensin II, ADP, and collagen.[1–4] Since these activities have been demonstrated to be mediated through 5-HT_2 receptors in platelets and vascular tissue,[5–7] peripheral 5-HT_2 receptor antagonists are thus expected to be useful in the treatment of cardiovascular diseases. Ketanserin, which has high affinity both for 5-HT_2 and α_1 receptors, inhibits collagen-induced platelet aggregation.[1,7] Sarpogrelate shows a more selective affinity for 5-HT_2 receptors than ketanserin, and is now clinically available for the treatment of peripheral arterial occlusive disease.[8,9] However, its anti-platelet activity is still not completely satisfactory, because its affinity for 5-HT_2 receptor is low. Therefore, a more potent and efficacious 5-HT_2 receptor antagonist is thus desired (Fig. 1).

We previously reported that (*S*)-*N*-{[1-(2-phenylethyl)pyrrolidin-2-yl]methyl}cyclohexanecarboxamide (**1**-(*S*)) had a high affinity and selectivity for 5-HT_{1A} receptors.[10] In the course of a further structure–activity relationship study of cyclohexanecarboxamide derivatives, we found that the replacement of the (*S*)-(pyrrolidin-2-yl)methyl moiety of **1-(*S*)** to the (*S*)-pyrrolidin-3-yl moiety provides 5-HT_2 receptor selective **2**-(***S***), despite

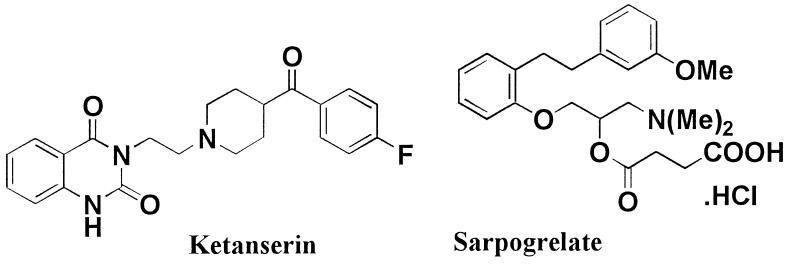

Figure 1. Known 5-HT_2 receptor antagonists.

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the moderate 5-HT_2 receptor affinity (Fig. 2). This result has prompted us to further investigate the structure–activity relationship study of a series of these derivatives. In this communication, we describe the influence of the bulky acyl substituent of carboxamides and the substituent on benzene ring at the 1-position of the pyrrolidine ring to the affinity for 5-HT_2 receptors, and the discovery of (*S*)-*N*-{1-[2-(4-fluorophenyl)ethyl]pyrrolidin-3-yl}-1-adamantanecarboxamide hydrochloride hydrate (**10-(*S*)**, **Y-39241**) as a novel and potent 5-HT_2 receptor antagonist.

Chemistry

Compounds (**2-(*S*)**, **(*R*)–4-(*S*)**, **(*R*)**) were prepared by the coupling of enantiomers of 3-amino-1-(2-phenylethyl) pyrrolidine **15**[11] with the acid chlorides of corresponding carboxylic acids **16a–c**, as shown in Scheme 1. The compounds (**6–14**) were prepared from commercially available (*S*)- and (*R*)-3-amino-1-benzylpyrrolidine **17** by three steps, as shown in Scheme 2. Compound **17** was treated with 1-adamantanecarbonyl chloride **16c** to give the amide **5**. *N*-Benzyl of amide **5** was removed by hydrogenolysis with 10% Pd–C and hydrazine monohydrate to give the amine **18**. Subsequent *N*-alkylation of **18** with variety of tosylates **19a–i** in the presence of K_2CO_3 afforded target compounds **6–14**.

Biological Assays

The affinities for the serotonergic 5-HT_2 and 5-HT_{1A} receptors were measured by the ability of the compounds to displace [^{3}H]ketanserin and [^{3}H]8-OH-DPAT from the 5-HT_2 and 5-HT_{1A} receptors isolated from the striata of male Wistar rats, respectively. The affinity for adrenargic α_1 and dopamine D_2 receptor binding was determined by a displacement of [^{3}H]prazosin and [^{3}H]spiperone, respectively.[12] The anti-platelet activity was determind by the inhibition of 5-HT plus collagen-induced platelet aggregation of rabbit platelet-rich plasma in vitro. The affinity of compounds **2-(*S*)**, **(*R*)–4-(*S*)**, **(*R*)**, along with **1-(*S*)**, **(*R*)**,[10] and compounds

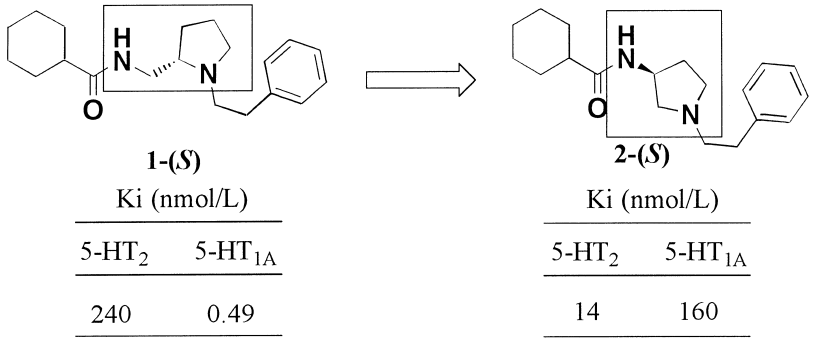
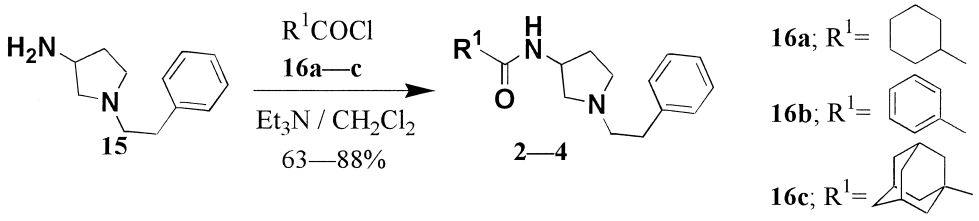
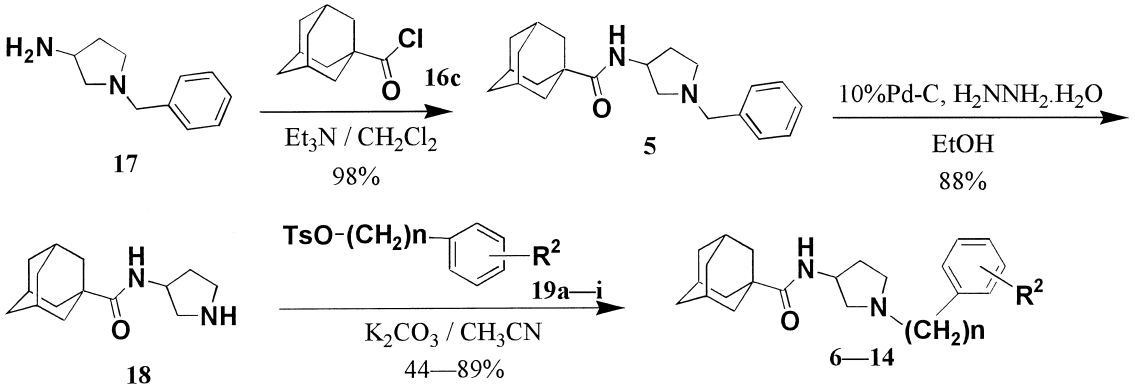


Figure 2. Conversion of (pyrrolidin-2-yl)methyl moiety to pyrrolidin-3-yl moiety.



Scheme 1.



Scheme 2. **19a**: $n=3$, R^2 = H; **19b**: $n=4$, R^2 = H; **19c**: $n=2$, R^2=2-F; **19d**: $n=2$, R^2=3-F; **19e**: $n=2$, R^2=4-F; **19f**: $n=2$, R^2=4-Cl; **19g**: $n=2$, R^2 =4-OCH_3; **19h**: $n=2$, R^2=4-CF_3; **19i**: $n=2$, R^2=4-CN.

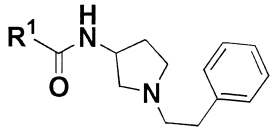
6–**14** for 5-HT_2, 5-HT_{1A} and adrenergic α_1 receptors, and inhibitory activities on platelet aggregation in vitro are shown in Tables 1 and 2.

Results and Discussion

A replacement of the (*S*)-(pyrrolidin-2-yl)methyl moiety of **1-(*S*)** to the (*S*)-pyrrolidin-3-yl moiety inverts the selectivity for 5-HT_2 over 5-HT_{1A}. A replacement of the cyclohexyl ring of compound **2-(*S*)** to the benzene ring (**3-(*S*)**) reduced the affinity for 5-HT_2 receptors, however, the compound **4-(*S*)** bearing a more bulky adamantan-1-yl group significantly increased the 5-HT_2 affinity and the anti-platelet activity without 5-HT_{1A} binding markedly increased. Opposite enantiomers (**1-(*R*)**–**4-(*R*)**) were similarly examined, thus resulting in an inverse selectivity (5-HT_{1A} > 5-HT_2). As a result, the bulky acyl substituent appears to be necessary in order to increase the affinity for 5-HT_2 receptors.

We next investigated the effects of various arylalkyl groups, while focusing on the chain length of the alkyl chain and substituents on the benzene ring. The length of the alkyl chain between the pyrrolidine ring and benzene ring had a substantial effect on the 5-HT_2 affinity. Compared with **4-(*S*)**, the one carbon chain analogue **5** and the four carbon chain analogue **7** both have a considerably reduced 5-HT_2 binding affinity (K_i = 240 nmol/L and 12 nmol/L, respectively). The three carbon chain analogue **6** preserved 5-HT_2 affinity (K_i = 0.32 nmol/L), despite a complete loss of selectivity versus 5-HT_{1A} receptor binding (K_i = 0.19 nmol/L). The position of the substituents on the benzene ring has some effect on 5-HT_2 affinity. The compound bearing a fluorine atom on the 4-position of the benzene ring (**10-(*S*)**[13]) has a higher affinity for 5-HT_2 receptors than 2-substituted analogue **8** and 3-substituted analogue **9**. Compounds **4-(*S*)**, **8** and **10-(*S*)**, which have a potent 5-HT_2 binding affinity (K_i = 0.24 nmol/L, 0.14 nmol/L, and 0.09 nmol/L respectively) also possess a potent anti-platelet activity (IC_{50} = 3.0 nmol/L, 3.8 nmol/L and 1.9 nmol/L, respectively). 4-Chloro-analogue **11** has a slightly reduced 5-HT_2 affinity (K_i = 0.44 nmol/L). Not only compound **12**, which has an electron donating methoxy group on the 4-position of the benzene ring, decreased the 5-HT_2 affinity, but also compounds **13** and **14**, which have an electron withdrawing trifluoromethyl group and cyano group on the 4-position of the benzene ring, respectively, decreased the 5-HT_2

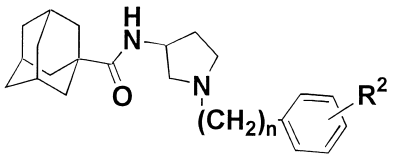
Table 1. Affinities of substituted carboxamides for 5-HT_2, 5-HT_{1A} and α_1 receptors



Compound no.[a]	R^1	Configuration	Binding affinity K_i (nmol/L) 5-HT_2[b]	5-HT_{1A}[c]	α_1[d]	Anti-platelet aggregation[h] IC_{50} (nmol/L)
1-(*S*)[e]		*S*	240	0.49	NT[g]	NT[g]
1-(*R*)[e]		*R*	>1000[f]	190	NT[g]	NT[g]
2-(*S*)		*S*	14	160	140	NT[g]
2-(*R*)		*R*	300	1.1	>1000[f]	NT[g]
3-(*S*)		*S*	59	370	>1000[f]	NT[g]
3-(*R*)		*R*	200	14	93	NT[g]
4-(*S*)		*S*	0.24	26	6.4	3.0
4-(*R*)		*R*	7.2	0.17	6.7	180
Sarpogrelate			7.9	>1000[f]	>1000[f]	260
Ketanserin			0.66	>1000[f]	3.5	26

[a]All compounds gave satisfactory IR, ^{1}H NMR, MS and elemental analysis. The enantiomeric purities of the enantiomers were confirmed to be >98% ee by HPLC (column: Chiralpac OD (DAICEL Chemical Industries, Ltd)).
[b][^{3}H]Ketanserin binding.
[c][^{3}H]8-OH-DPAT binding.
[d][^{3}H]Prazosin binding.
[e]5-HT_2, 5-HT_{1A} and α_1 receptor affinities of compounds **1-(*S*)**, **(*R*)** have previously been reported.[10]
[f]IC_{50} value.
[g]Not tested.
[h]Inhibitory activities of the compounds on platelet aggregation in vitro. Values represent the concentration required for a 50% inhibition of platelet aggregation.

Table 2. Affinities of adamantanecarboxamides for 5-HT_2, 5-HT_{1A} and α_1 receptors



Compound no.[a]	R^2	n	Configuration	Binding affinity K_i (nmol/L) 5-HT_2[b]	5-HT_{1A}[c]	α_1[d]	Anti-platelet aggregation[g] IC_{50} (nmol/L)
5	H	1	*S*	240	91	>1000[e]	2200
4-(*S*)	H	2	*S*	0.24	26	6.4	3.0
6	H	3	*S*	0.32	0.19	29	41
7	H	4	*S*	12	1.1	21	NT[f]
8	2-F	2	*S*	0.14	20	7.6	3.8
9	3-F	2	*S*	0.55	14	97	99
10-(*S*)	4-F	2	*S*	0.09	79	3.0	1.9
10-(*R*)	4-F	2	*R*	26	0.53	17	NT[f]
11	4-Cl	2	*S*	0.44	77	12	54
12	4-OCH_3	2	*S*	11	>1000[e]	110	NT[f]
13	4-CF_3	2	*S*	11	92	62	NT[f]
14	4-CN	2	*S*	5.5	>1000[e]	110	NT[f]

[a]All compounds gave satisfactory IR, ^{1}H NMR, MS and elemental analysis. The enantiomeric purities of the enantiomers were confirmed to be >98% ee by HPLC (column: Chiralpac OD (DAICEL Chemical Industries, Ltd)).
[b][^{3}H]Ketanserin binding.
[c][^{3}H]8-OH-DPAT binding.
[d][^{3}H]Prazosin binding.
[e]IC_{50} value.
[f]Not tested.
[g]Inhibitory activities of the compounds on platelet aggregation in vitro. Values represent the concentration required for a 50% inhibition of platelet aggregation.

affinity. These facts suggest that the bulk of the substituents is therefore more important than the electronic features.

We finally selected compound **10-(*S*)** to examine the inhibitory effect on mouse pulmonary thromboembolic death induced by both collagen and 5-HT. Compound **10-(*S*)** significantly decreased the mortality rate at 0.1 mg/kg, po or higher in a dose-dependent manner (Fig. 3A).[14] Sarpogrelate also significantly inhibited mouse thromboembolic death at 10 mg/kg, po (Fig. 3B). However, the ED_{50} value for compound **10-(*S*)** (0.04 mg/kg) was lower than that for sarpogrelate (2.2 mg/kg).

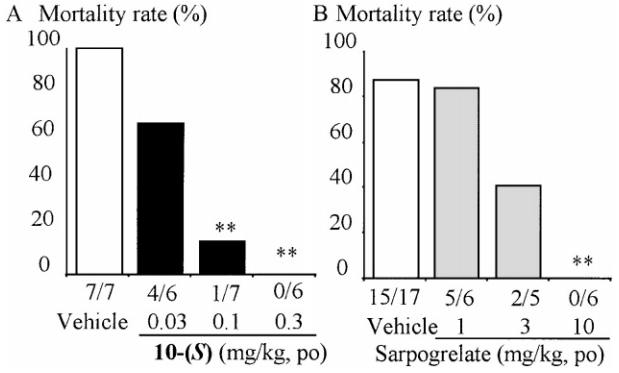


Figure 3. Effect of compound **10-(*S*)** and sarpogrelate on the 5-HT plus collagen-induced pulmonary thromboembolic death in mice $^{**}P < 0.01$ versus vehicle.

In conclusion, we found (*S*)-*N*-{1-[2-(4-fluorophenyl) ethyl]pyrrolidin-3-yl}-1-adamantanecarboxamide hydrochloride hydrate (**10-(*S*)**, **Y-39241**) to have a potent affinity for 5-HT_2 receptor. **Y-39241** was also effective in preventing 5-HT plus collagen-induced platelet aggregation both in vitro and in vivo. In the future we intend to perform further biochemical and pharmacological studies on compound **Y-39241**.[15]

Acknowledgements

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12. Compound **2-(*S*)**, **(*R*)**–**14** had no affinity for dopamine D_2 receptors (data not shown).
13. Data of **10-(*S*)**: colourless crystals, mp 201–204 °C. ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 1.58–2.05 (16H, m), 2.05–2.45 (1H, m), 2.90–3.82 (8H, m), 4.27–4.60 (1H, m), 7.10–7.23 (2H, m), 7.28–7.40 (2H, m), 7.71–7.91 (1H, m), 10.99–11.18 (0.4H, m), 11.18–11.41 (0.6H, m). Anal. calcd for $C_{23}H_{31}FN_2O{\cdot}HCl{\cdot}H_2O$: C, 65.00; H, 8.06; N, 6.59. Found: C, 64.95; H, 7.87; N, 6.81. Optical rotations were measured in methanol at 25 °C for compound **10-(*S*)** (+1.2°, $c = 1.0$) and **10-(*R*)** (−1.4°, $c = 1.0$).
14. The test drugs were administered orally to male ddY mice after fasting overnight. One hour after administration, the mixture of collagen (10 μg/10 g BW) and 5-HT (100 μg/10 g BW) was injected intravenously, and the mortality of mice within 10 min was determined. The results were expressed as the mortality rate based on the number of animals and their percentages, and the statistical analysis between the vehicle control group and the treated group was performed by Fischer's exact test. The dose (ED_{50}) producing a 50% reduction in mortality was calculated using a probit analysis.
15. Other adamantanecarboxamide derivatives, 4-[4-(1-adamantanecarboxamido)butyl]-1-(2-methoxyphenyl)piperazine[16] and LY-353433[17] are known as 5-HT_{1A} and 5-HT_4 antagonists, respectively.
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