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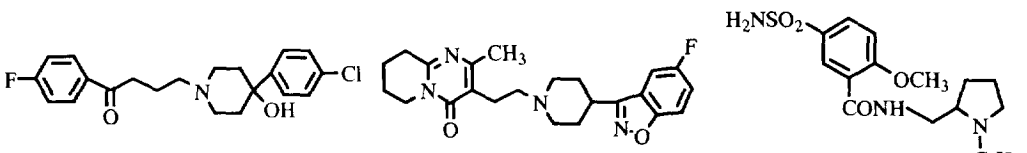
N-(2-PYRROLIDINYLMETHYL)BENZOXAZINE-8-CARBOXAMIDES EXHIBITING HIGH AFFINITIES for ALL of D_2, 5-HT_{1A}, and 5-HT_2 RECEPTORS

Takanobu Kuroita,* Tsuguo Ikebe, Shu Murakami, Shuzo Takehara, and Takeshi Kawakita

Research Laboratories, Yoshitomi Pharmaceutical Industries Ltd., 955 Koiwai Yoshitomi-cho, Chikujo-gun, Fukuoka 871, Japan.

Abstract: (*R*)-*N*-(1-Benzyl-2-pyrrolidinylmethyl)-6-methylthio-3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide exhibited high affinities for all of D_2, 5-HT_{1A}, and 5-HT_2 receptors (K_i=0.0042 μM, K_i=0.017 μM, and K_i=0.027 μM, respectively).

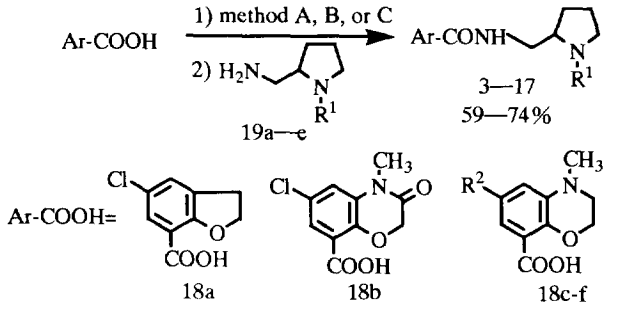
Antipsychotic agents have been well established since the introduction of chlorpromazine about 40 yeas ago. Although the positive symptoms (hallucination and delusion) can be treated with classical neuroleptic agents, such as haloperidol, negative symptoms (blunted affect, social withdrawal, and apathy) are poorly treated. These agents are also associated with involuntary movement disorders or extrapyramidal side effect (EPS). In order to dissolve these problems, some atypical antipsychotics have been investigated and developed. Risperidone, possesses potent 5-HT_2 and D_2 receptor antagonist properties, has been reported to ameliorate negative symptoms of schizophrenia.[1a,b] Another approach is an addition of serotonin 5-HT_{1A} receptor agonist to dopamine D_2 antagonist. A few of 5-HT_{1A} receptor agonists 8-OH-DPAT, buspirone, and ipsapirone have been found to reverse haloperidol-induced catalepsy.[2a,b] The arylpiperazine derivative, RWJ-37796, has been reported to bind with high affinity to D_2, D_3, 5-HT_{1A}, and α_1-adrenergic receptors.[3] Recently, it has also been reported that (1,2-benzisothiazole-3-yl)piperazine derivatives and benzisothiazole- and benzisoxazole-3-carboxamide derivatives exhibited an affinities for D_2, 5-HT_{1A}, and 5-HT_2 receptors, and were demonstrated antipsychotic activity in animal models.[4a-c] Thus, atypical antipsychotics would expect to produce their psychotherapeutic effects with a lower neurological side effects by interacting with 5-HT_{1A} and 5-HT_2 receptors.



Several types of substituted benzamides, as represented by sulpiride, have been shown to be selective and potent D_2 receptor antagonist.[5a,b] In contrast with substituted benzamides, we previously reported that a series of N-(2-pyrrolidinylmethyl)-2-methoxy-5-sulfamoylbenzamide derivative bearing a long alkyl (normal-nonyl) side chain at the 1-position of the pyrrolidine ring were found to possess high affinity for 5-HT_{1A} receptors.[6]

However these compounds **1-(*S*),(*R*)—2-(*S*),(*R*)** had low affinity for 5-HT2 receptors ($Ki > 1\ \mu M$). In quest of a novel atypical antipsychotics with high D2, 5-HT1A, and 5-HT2 affinities, we prepared three series of *N*-(2-pyrrolidinyl methyl)benzamide derivatives. In this communication, 2-methoxy-5-sulfamoylbenzamide moiety is replaced by benzofuran-7-carboxamide, 3-oxo-1,4-benzoxazine-8-carboxamide, and 1,4-benzoxazine-8-carboxamide moiety. We describe that some 1,4-benzoxazine-8-carboxamide derivatives bind with high affinity to 5-HT1A, 5-HT2, and D2 receptors.

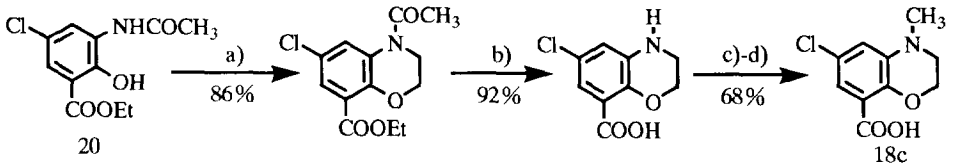
Compounds **3-(*S*),(*R*)—11-(*S*),(*R*)** were synthesized by coupling of corresponding carboxylic acids **18a—c** with enantiomers of (1-alkylpyrrolidin-2-yl)methylamine **19a—c**[7a,b] *via* mixed anhydrides or acid chlorides, as shown in Scheme 1. The carboxylic acids **18a,b** were prepared by literary procedures.[8a,b] The 1,4-Benzoxazine-8-carboxylic acid **18c** was prepared in 5 steps from ethyl 3-acetamido-5-chlorosalicylate **20** as described in Scheme 2. Receptor binding data at D2, 5-HT1A, and 5-HT2 receptors for compounds **3-(*S*),(*R*)—11-(*S*),(*R*)** were illustrated in Table I, along with that for **1-(*S*),(*R*)—2-(*S*),(*R*)**. Affinities for the dopamine receptors were measured by the ability of the compounds to displace [^{3}H]spiperone from the D2 receptors isolated from the striata of male Wistar rats. Serotonergic 5-HT1A and 5-HT2 receptor binding affinities were determined by displacement of [^{3}H]8-OH-DPAT and [^{3}H]ketanserin, respectively.



	R^1		R^2
19a	Et	18c	Cl
19b	n-Butyl	18d	H
19c	n-Nonyl	18e	SO_2NH_2
19d	Benzyl	18f	SCH_3
19e	Phenethyl		

method A: iso-BuOCOCl, N-methylmorpholine; method B: $SOCl_2$; method C: pivaloyl chloride, Et_3N

Scheme 1



a) 1,2-dibromoethane, K_2CO_3, DMF; b) NaOH, 70°C; c) $(CH_3)_2SO_4$, NaOH, 0°C; d) NaOH, 40°C

Scheme 2

Among the series of benzofuran-7-carboxamide derivatives, n-butyl substituted (*S*)-enantiomer **4-(*S*)** possessed the highest affinities for D2 and 5-HT1A receptors (Ki=0.038 μM and 0.018 μM, respectively),

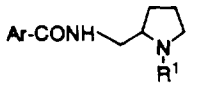
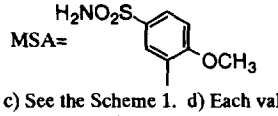
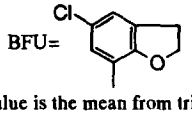


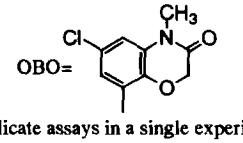
TABLE I. Affinities of Benzamides to D_2, 5-HT_{1A}, and 5-HT_2 receptors

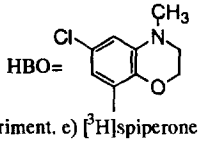
Compd.[a] No.	Ar[b]	R^1	isomer	Condition[c]	$[\alpha]_D$ (c=1, MeOH)	Ki[d] (μM) D_2[e]	5-HT_{1A}[f]	5-HT_2[g]
1-(*S*)[h]	MSA	n-Bu	S	—	—	0.051	1.2	> 1
1-(*R*)[h]	MSA	n-Bu	R	—	—	0.23	4.5	> 1
2-(*S*)[h]	MSA	n-Nonyl	S	—	—	0.18	0.081	2.3
2-(*R*)[h]	MSA	n-Nonyl	R	—	—	0.092	0.016	3.7
3-(*S*)	BFU	Et	S	A	-37.7	0.0065	> 1	> 1
3-(*R*)	BFU	Et	R	A	+40.3	> 1	> 1	> 1
4-(*S*)	BFU	n-Bu	S	A	-67.2	0.0038	0.018	3.3
4-(*R*)	BFU	n-Bu	R	A	+63.0	0.019	0.33	0.4
5-(*S*)	BFU	n-Nonyl	S	A	-54.6	> 1	0.57	> 1
5-(*R*)	BFU	n-Nonyl	R	A	+50.8	0.084	0.33	> 1
6-(*S*)	OBO	Et	S	B	-37.8	>1	> 1	> 1
6-(*R*)	OBO	Et	R	B	+40.4	> 1	> 1	> 1
7-(*S*)	OBO	n-Bu	S	B	-59.5	>1	> 1	> 1
7-(*R*)	OBO	n-Bu	R	B	+58.1	> 1	> 1	> 1
8-(*S*)	OBO	n-Nonyl	S	B	-53.8	>1	> 1	> 1
8-(*R*)	OBO	n-Nonyl	R	B	+56.8	> 1	> 1	> 1
9-(*S*)	HBO	Et	S	C	-43.7	0.016	> 1	> 1
9-(*R*)	HBO	Et	R	C	+40.7	> 1	> 1	> 1
10-(*S*)	HBO	n-Bu	S	C	-63.7	0.012	0.034	0.30
10-(*R*)	HBO	n-Bu	R	C	+62.7	0.63	0.43	0.086
11-(*S*)	HBO	n-Nonyl	S	C	-57.1	0.75	0.28	> 1
11-(*R*)	HBO	n-Nonyl	R	C	+58.3	0.69	> 1	> 1

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)The abbreviations used were as follows:

MSA= 

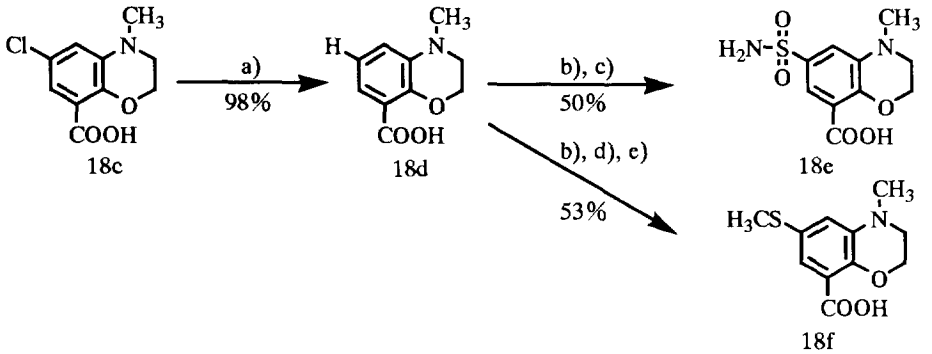
BFU= 

OBO= 

HBO= 

c) See the Scheme 1. d) Each value is the mean from triplicate assays in a single experiment. e) [^{3}H]spiperone binding. f) [^{3}H]8-OH-DPAT binding. g) [^{3}H]ketanserin binding. h) D_2 and 5-HT_2 receptor affinities of compounds 1a,b-2a,b have previously been reported.[5]

although compound **4**-(*S*) was virtually devoid of 5-HT2 receptor affinity (*K*i>1 μM). The replacement of n-butyl substituent with short (ethyl) or long (n-nonyl) side chain resulted in reduced activities (**3**-(*S*),(*R*) and **5**-(*S*),(*R*)), as depicted in Table I. Unfortunately, 3,4-dihydro-3-oxo-2H-1,4-benzoxazine-8-carboxamide derivatives **6**-(*S*),(*R*)—**8**-(*S*),(*R*) were found to be virtually inactive for all three receptors. Similar to that observed for **4**-(*S*), normal-butyl substituted (*S*)-enantiomer **10**-(*S*) possessed the highest affinities for D2 and 5-HT1A receptors (*K*i=0.012 μM and 0.034 μM, respectively) among the 3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide derivatives. However, compound **10**-(*S*) showed moderate affinity to the 5-HT2 receptor (*K*i=0.30 μM). The (*R*)-enantiomer **10**-(*R*) showed higher affinity for the 5-HT2 receptors (*K*i=0.086 μM) than its counterpart **10**-(*S*), although compound **10**-(*R*) had weaker D2 and 5-HT1A receptor affinities. Thus, there was some differences in affinities for three receptors between the enantiomers, and the influence of the length of alkyl side chain at the 1-position of the pyrrolidine ring was different among the benzamides. 3,4-Dihydro-2*H*-1,4-benzoxazine-8-carboxamide derivatives **10**-(*S*),(*R*) showed slightly higher affinity for the 5-HT2 receptors than benzofuran-7-carboxamide derivatives **4**-(*S*),(*R*).



a) Pd/C, H_2, 1N NaOH; b) $ClSO_3H$, 100℃; c) NH_4OH; d) Zn, H_2SO_4; e) CH_3I, NaOH

Scheme 3

Furthermore, we prepared a series of *N*-(2-pyrrolidinylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide derivatives **12**—**17**-(*S*),(*R*). Compounds **12**—**17**-(*S*),(*R*) were synthesized by coupling of corresponding carboxylic acids **18c**—**g** with enantiomers of (1-substituted pyrrolidin-2-yl)methylamine **19b**, **d**, and **e** as shown in Scheme 1. The coupling conditions were performed by a mixed anhydride method (method C), as illustrated in Scheme 1. The 6-unsubstituted or 6-substituted 3,4-dihydro-2*H*-1,4-Benzoxazine-8-carboxylic acids **18d**—**18g** were prepared from 6-chloro-3,4-dihydro-2*H*-1,4-Benzoxazine-8-carboxylic acid **18c**, as described in Scheme 3. Receptor binding data at D2, 5-HT1A, and 5-HT2 receptors for compounds **12**—**17**-(*S*),(*R*) are displayed in Table I, along with that for haloperidol and risperidone. A decrease in affinities at all three receptors was observed when the Cl atom at position 6 was removed (compound **12**). Replacement of the Cl atom at position 6 with H_2NSO_2 (compound **13**) resulted in decrease in affinities at all three receptors. However, methylthio analogues **14**-(*S*),(*R*) showed slightly higher affinities for all three receptors than **10**-

(*S*), (*R*) respectively. Thus, when the side chain was n-butyl group, the (*S*)-enantiomers possessed higher affinities for D2 and 5-HT1A receptors than its counterpart, contrary to affinities for 5-HT2 receptors. In contrast, the opposite result was observed when the butyl group at position 1 of pyrrolidine was replaced with phenethyl group (**15**-(*S*) vs. **15**-(*R*)). Interestingly, the favorite results were observed when the butyl group at the position 1 of pyrrolidine were replaced with benzyl group (**16**-(*S*), **17**-(*S*) vs. **16**-(*R*), **17**-(*R*), respectively). The benzyl substituted (*R*)-enantiomers **16**-(*R*), **17**-(*R*) possessed higher affinities for all three receptors than their counterparts **16**-(*S*), **17**-(*S*), respectively. Especially, (*R*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-6-methylthio-3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide **17**-(*R*)[9] bound with high affinity to D2, 5-HT1A, and 5-HT2 receptors (*Ki*=0.0042 μM, *Ki*=0.017 μM, and *Ki*=0.027 μM, respectively). These results indicated that the structural change at position 1 of pyrrolidine are more sensitive to the stereoselectivity for binding to each three receptors as compared to aromatic part of benzamides. The modifications of benzamide structure are also effective to the affinities for all three receptors.

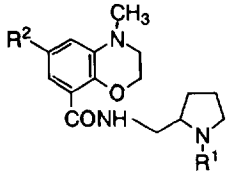


TABLE II. Affinities of Benzamides to D_2, 5-HT_{1A}, and 5-HT_2 receptors

Compd.[a] No.	R^1	R^2	isomer	Method[b]	$[\alpha]_D$ (c=1, MeOH)	*Ki*[c] (μM)		
						D_2[d]	5-HT_{1A}[e]	5-HT_2[f]
12	n-Bu	H	recemate	C	—	0.27	0.17	2.2
13	n-Bu	SO_2NH_2	recemate	C	—	0.67	0.45	3.0
14-(*S*)	n-Bu	SCH_3	S	C	-59.6	0.0036	0.019	2.1
14-(*R*)	n-Bu	SCH_3	R	C	+61.5	0.017	0.12	0.022
15-(*S*)	CH_2CH_2Ph	Cl	S	C	-94.9	0.80	0.01	0.28
15-(*R*)	CH_2CH_2Ph	Cl	R	C	+96.8	0.057	0.035	1.7
16-(*S*)	Benzyl	Cl	S	C	-88.9	0.31	0.22	0.42
16-(*R*)	Benzyl	Cl	R	C	+90.9	0.21	0.021	0.099
17-(*S*)[g]	Benzyl	SCH_3	S	C	-23.6	0.27	0.88	0.55
17-(*R*)[g]	Benzyl	SCH_3	R	C	+24.1	0.0042	0.017	0.027
haloperidol						0.0015	1.8	0.043
risperidone						0.0018	0.13	0.00014

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) See the Scheme 1. c) Each value is the mean from triplicate assays in a single experiment.
d) [^{3}H]spiperone binding. e) [^{3}H]8-OH-DPAT binding. f) [^{3}H]ketanserin binding. g) Fumarate

In conclusion, we found that a novel (*R*)-*N*-(1-benzyl-2-pyrrolidinylmethyl)-6-methylthio-3,4-dihydro-2*H*-1,4-benzoxazine-8-carboxamide **17**-(*R*) showed high affinities for D2, 5-HT1A, and 5-HT2 receptors. Such compound would be atypical antipsychotics which elicit its psychotherapeutic effects with a lower neurological side effects by interacting with 5-HT1A and 5-HT2 receptors. Extensive biochemical and pharmacological studies are on going on the compound **17**-(*R*) with high affinities to D2, 5-HT1A, and 5-HT2 receptors.

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References and Notes

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9. Data of **17**-(*R*): colourless crystals, m.p. 120-122 ℃; IR (KBr) ν : 3350, 1710, 1640, 1580 cm^{-1}; ^{1}H-NMR (270 MHz, DMSO-d6): δ 8.41-8.31 (br, 1H), 7.42-7.21 (m, 5H), 7.01 (d, 1H, J = 2.6 Hz), 6.69 (d, 1H, J = 2.6 Hz), 6.61 (s, 2H, Fumarate), 4.26 (t, 2H, J = 4.6 Hz), 4.12 (d, 1H, J = 3.2 Hz), 3.65-3.50 (1H, m), 3.43 (d, 1H, J = 3.2 Hz), 3.30 (t, 2H, J = 4.6 Hz), 2.88 (s, 3H), 2.98-2.78 (m, 2H), 2.43 (s, 3H), 2.39-2.23 (m, 1H), 2.02-1.83 (m, 1H), 1.79-1.51 (m, 3H).

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