Structure–Activity Relationships of Dopamine- and Norepinephrine-Uptake Inhibitors

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Quantitative structure–activity relationship (QSAR) analysis of 3-phenyl-1-indanamines, 1-amino-4-aryltetralins, and 6-phenylpyrrolo[2,1-*a*] isoquinolines has been performed for catecholamine-uptake inhibition activities. Similar equations were obtained for these series of congeners indicating a common tendency that the increase in hydrophobicity of the substituents on the primary phenyl ring (ring C) enhances the activity, and the important aromatic ring which interacts with the receptor is this ring C. It was also indicated that the effect of the introduction of the second *N*-methyl group differs depending on the series of congeners. These results were used to characterize a binding model for a pharmacophore, which comprised a phenyl ring and a basic nitrogen. This model defined the necessary three-dimensional features leading to the uptake inhibition, and degree of fitness with this model predicted the strength of the activity. Furthermore, it appeared likely that a substituent existing in a specific region of the inhibitor molecule causes a steric hindrance with the receptor site and reduces the activity.

Keywords catecholamine; uptake inhibitor; antidepressant; regression analysis; physicochemical property; molecular mechanics calculation; receptor model; dummy atom; fitness; superimposing

Depression(manic-depressive psychosis) and schizophrenia are the two major intrinsic psychosis. Encephalic monoamines which are classified into catecholamines like dopamine (DA) and norepinephrine (NE) and indoleamines like serotonin (5-HT), have been considered to play an important role in the pathogeny of the depression. Therefore, it has long been accepted that an uptake inhibitor of the encephalic amines operates as an effective antidepressant.

Recently, the correlation of the monoamine-uptake inhibition with the antidepression was questioned because the physiological activity was not observed for a week,[1] whereas the uptake inhibition was observed immediately after the administration of the antidepressant.[2]

However, it is still strongly believed that the monoamine-uptake inhibition participates in the depression, since many clinically used antidepressants are potent uptake inhibitors.[3] Therefore, effective monoamine-uptake inhibitors without undesirable pharmacological properties such as anticholinergic and cardiotoxic effect are desired.[4] A selective DA-uptake inhibitor is also expected to be an antiparkinsonism.[5] Furthermore, the development of a potent catecholamine-uptake inhibitor would be of potential interest in elucidating the etiology of these psychoneurosis.

In this paper we will describe the quantitative structure–activity relationship (QSAR) of DA- and NE-uptake inhibitors to clarify the effect of physicochemical properties of substituents, and attempt to superimpose molecular structures of the inhibitors to define the three-dimensional features of the binding site of the receptor.

Methods

Biological Data The molecular structures of the compounds discussed here are shown in Fig. 1. The DA- and NE-uptake inhibitions by these compounds *in vitro* were taken from the literature.[6-10]

In the QSAR analysis, the IC_{50} values used were reported on the same standard within each series of congeners, so they could be compared directly. In the superimposing study, on the other hand, the IC_{50} values from different sources were compared by their ratio to nomifensine (**13**), since this was the most popular compound found in the various literature. The relative activity was expressed by the logarithm of the ratio of IC_{50} of a compound to the corresponding value of **13**.

Calculation The multiple regression analysis was carried out using the program package for multivariate analysis developed by Tanaka *et al.*,[11] and physicochemical parameters of the substituents were taken from ref. 12.

The molecular mechanics calculations were performed using Allinger's MM2 program,[13] and the superimposing calculations werre carried out by MOLFIT program developed in our laboratory following Froimowitz's

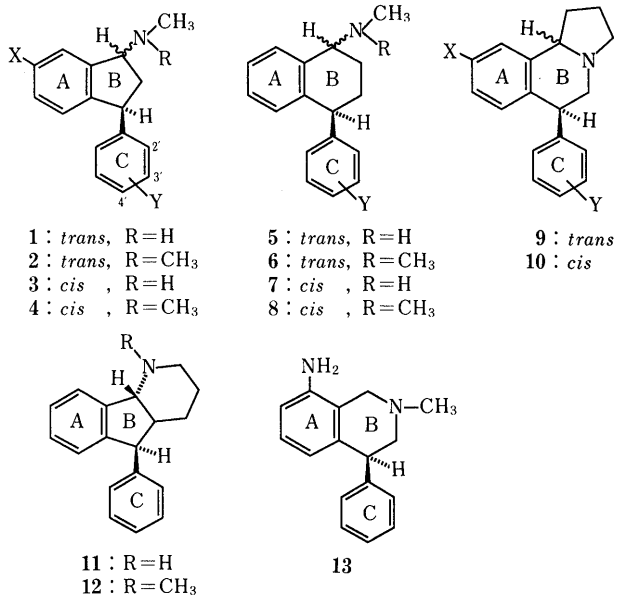

Fig. 1. Molecular Structure of the Catecholamine-Uptake Inhibitors

TABLE I. Physical Parameters Used in the QSAR Studies[a]

	H	CH_3	F	Cl	Br	CF_3	CH_3O	HO	C_4H_9	CN	CH_3S
Hydrophobicity π	0.0	0.56	0.14	0.71	0.86	0.88	−0.02	−0.76	2.13	−0.57	0.61
Taft's steric E_S	0.0	−1.24	−0.46	−0.97	−1.16	−2.40	−0.55	−0.55	−1.63	−0.51	−1.07

a) Taken from reference 12.

procedure.[14]

As the compounds shown in Fig. 1 are flexible, two conformations of a fused cyclopentene or cyclohexene ring with a pseudoaxial or pseudoequatorial phenyl ring, and three staggered conformations around the C–N bond were considered. But the dihedral angle of the C–C single bond connecting ring B and ring C were not specified, since it was assumed to rotate freely.

Data processing was done on a personal computer NEC PC-9801 or a FACOM M-780/20 at Nagoya University Computational Center.

Results and Discussion

QSAR Analysis QSAR analysis of the following five series of compounds derived the structural factors influencing the DA- and NE-uptake inhibition. Multiple regression analyses were performed to attain the best correlation by stepwise procedure.

In the following equations, n is the number of compounds, r is the correlation coefficient, s is the standard deviation, F is the overall variance ratio, and the figures in parentheses are the 95% confidence intervals. $\pi_{3'}$ and $\pi_{4'}$ denote hydrophobic parameters of substituents at 3′ and 4′ positions, respectively, and $\sum E_s$ is the sum of the Taft's steric parameters for substituents on aromatic ring C. I_R and I_X are indicator variables that take the value of unity for substitution on the positions indicated as R and X in Fig. 1, respectively. The physicochemical parameters adopted in the regression equations are shown in Table I.

Equations 1—10 represent the best correlations for DA- and NE-uptake inhibitions, and the relations between observed IC_{50} and calculated IC_{50} are shown in Tables II—VI. The squared cross-correlation matrix of parameters used in each regression equation was examined, and no problematic collinearity was recognized.

TABLE II. Structural Features and Monoamine-Uptake Inhibitions of *trans*-*N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines (**1** and **2**)

No.	X	Y	R	$-\log IC_{50}$ of DA-uptake		$-\log IC_{50}$ of NE-uptake	
				Obsd.[a]	Calcd.[b]	Obsd.[a]	Calcd.[c]
1b	H	4′-F	H	7.54	7.53	8.54	8.75
1c	H	4′-Cl	H	8.25	8.48	9.29	9.21
1d	H	4′-Br	H	8.60	8.62	9.52	9.25
1e	H	4′-CF_3	H	6.80	6.30	7.17	7.58
1i	H	3′-Cl	H	7.85	8.16	9.92	9.43
1q	H	3′,4′-F	H	7.68	7.06	8.80	8.44
1r	H	3′,4′-Cl	H	9.00	8.69	9.58	9.54
1s	H	2′,4′-Cl	H	6.29	6.61	7.82	7.87
1v	H	3′-CF_3,4′-Cl	H	5.46	6.44	7.60	7.96
1A	F	3′,4′-Cl	H	9.92	9.13	9.15	9.21
1H	CH_3O	3′,4′-Cl	H	8.60	9.13	9.17	9.21
1I	HO	3′,4′-Cl	H	9.28	9.13	9.08	9.21
2a	H	H	CH_3	6.22	6.73	6.89	7.53
2b	H	4′-F	CH_3	6.49	6.32	7.00	7.18
2c	H	4′-Cl	CH_3	6.85	7.27	7.64	7.63
2d	H	4′-Br	CH_3	7.27	7.41	7.55	7.68
2i	H	3′-Cl	CH_3	7.15	6.95	7.82	7.86
2q	H	3′,4′-F	CH_3	6.60	5.85	7.21	6.87
2r	H	3′,4′-Cl	CH_3	7.55	7.48	7.62	7.96
2s	H	2′,4′-Cl	CH_3	5.70	5.40	7.05	6.29
2A	F	3′,4′-Cl	CH_3	7.92	7.92	7.68	7.63
2B	F	4′-F	CH_3	6.21	6.76	6.46	6.85
2F	CF_3	4′-F	CH_3	6.62	6.76	7.07	6.85
2H	CH_3O	3′,4′-Cl	CH_3	8.00	7.92	7.80	7.63
2I	HO	3′,4′-Cl	CH_3	8.10	7.92	7.80	7.63

a) Taken from reference 6. *b*) From Eq. 1. *c*) From Eq. 2.

***trans* *N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines (1 and 2)[6]**

$$\log(1/IC_{50})(DA) = 2.931\pi_{3'} + 3.379\pi_{4'} + 1.921\sum E_S - 1.209I_R + 0.435I_X + 7.940 \quad (1)$$
$$(\pm 0.740)\ (\pm 0.895)\ (\pm 0.464)\ (\pm 0.361)\ (\pm 0.411)\ (\pm 0.459)$$
$$n=25,\ r=0.926,\ s=0.480,\ F=22.849$$

$$\log(1/IC_{50})(NE) = 2.356\pi_{3'} + 2.040\pi_{4'} + 1.384\sum E_S - 1.573I_R - 0.331I_X + 9.101 \quad (2)$$
$$(\pm 0.537)\ (\pm 0.650)\ (\pm 0.337)\ (\pm 0.262)\ (\pm 0.299)\ (\pm 0.333)$$
$$n=25,\ r=0.949,\ s=0.346,\ F=34.469$$

These equations indicate that increase in hydrophobicity as well as decrease in steric volume of the substituents on ring C contributes to the enhancement of the inhibition activity. The negative sign of the I_R term in the above equations means that introduction of the second *N*-methyl group decreases the activity from the corresponding *N*-monomethylates. Moreover, despite the small number of examples, the plus and minus signs of the I_x coefficient in these equations also indicate the substituent at that position causes the opposite effect on the DA- and NE-uptake inhibitions.

***cis* *N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines (3 and 4)[6]**

$$\log(1/IC_{50})(DA) = 1.186\pi_{3'} + 1.001\pi_{4'} + 6.274 \quad (3)$$
$$(\pm 0.323)\ (\pm 0.332)\ (\pm 0.181)$$
$$n=21,\ r=0.918,\ s=0.283,\ F=48.543$$

$$\log(1/IC_{50})(NE) = 1.386\pi_{3'} + 1.054\pi_{4'} + 0.585I_R - 0.707I_X + 6.840 \quad (4)$$
$$(\pm 0.401)\ (\pm 0.390)\ (\pm 0.249)\ (\pm 0.286)\ (\pm 0.261)$$
$$n=21,\ r=0.912,\ s=0.316,\ F=19.868$$

For the DA-uptake inhibition, only the hydrophobicity

TABLE III. Structural Features and Monoamine-Uptake Inhibitions of *cis*-*N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines (**3** and **4**)

No.	X	Y	R	$-\log IC_{50}$ of DA-uptake		$-\log IC_{50}$ of NE-uptake	
				Obsd.[a]	Calcd.[b]	Obsd.[a]	Calcd.[c]
3a	H	H	H	5.85	6.27	6.49	6.84
3b	H	4′-F	H	6.48	6.41	6.92	6.99
3c	H	4′-Cl	H	6.92	6.98	7.62	7.59
3d	H	4′-Br	H	7.17	7.13	8.06	7.75
3i	H	3′-Cl	H	6.66	7.12	7.72	7.82
3q	H	3′,4′-F	H	6.82	6.58	7.48	7.18
3r	H	3′,4′-Cl	H	7.70	7.83	8.28	8.57
3A	F	3′,4′-Cl	H	8.30	7.83	7.85	7.87
3H	CH_3O	3′,4′-Cl	H	7.72	7.83	7.72	7.87
3I	HO	3′,4′-Cl	H	8.39	7.83	8.20	7.87
4a	H	H	CH_3	6.47	6.27	7.39	7.43
4b	H	4′-F	CH_3	6.60	6.41	7.62	7.57
4c	H	4′-Cl	CH_3	6.72	6.98	8.36	8.17
4d	H	4′-Br	CH_3	7.08	7.13	8.37	8.33
4i	H	3′-Cl	CH_3	7.27	7.12	9.11	8.41
4q	H	3′,4′-F	CH_3	6.74	6.58	7.54	7.77
4r	H	3′,4′-Cl	CH_3	7.57	7.83	8.62	9.16
4A	F	3′,4′-Cl	CH_3	7.51	7.83	8.43	8.45
4B	F	4′-F	CH_3	6.36	6.41	7.05	6.87
4F	CF_3	4′-F	CH_3	6.47	6.41	6.46	6.87
4H	CH_3O	3′,4′-Cl	CH_3	7.82	7.83	8.52	8.45

a) Taken from reference 6. *b*) From Eq. 3. *c*) From Eq. 4.

of 3′- and 4′-substituents on ring C were prominent, but the inhibition of NE-uptake was susceptible to the effect of substituents on the R and X positions. In any event, these equations demonstrate similar contributions of the physical properties of substituents as in compounds **1** and **2**.

***trans* *N*-Methyl- and *N,N*-Dimethyl-1-amino-4-phenyltetralins (5 and 6)**[7]

$$\log(1/IC_{50})(DA) = 2.196\pi_{3'} + 1.991\pi_{4'} + 1.366\sum E_S - 0.414I_R + 6.805$$
$$(\pm 0.663)\ (\pm 0.555)\ (\pm 0.299)\ (\pm 0.328)(\pm 0.276)$$
$$n=18,\ r=0.917,\ s=0.346,\ F=17.279 \quad (5)$$

$$\log(1/IC_{50})(NE) = 2.182\pi_{3'} + 1.638\pi_{4'} + 1.282\sum E_S - 0.564I_R + 7.557$$
$$(\pm 0.498)\ (\pm 0.417)\ (\pm 0.225)\ (\pm 0.248)(\pm 0.208)$$
$$n=18,\ r=0.946,\ s=0.265,\ F=27.947 \quad (6)$$

Equations 5 and 6 are essentially the same as Eqs. 1 and 2, and the negative coefficient of the I_R term explains the unfavorable effect of the second *N*-methyl group.

***cis* *N*-Methyl- and *N,N*-Dimethyl-1-amino-4-phenyltetralins (7 and 8)**[7]

$$\log(1/IC_{50})(DA) = 1.161\pi_{3'} + 0.949\pi_{4'} + 0.363\sum E_s - 0.468I_R + 5.426$$
$$(\pm 0.360)\ (\pm 0.302)\ (\pm 0.160)\ (\pm 0.174)(\pm 0.149)$$
$$n=17,\ r=0.914,\ s=0.173,\ F=15.294 \quad (7)$$

$$\log(1/IC_{50})(NE) = 1.504\pi_{3'} + 0.574\pi_{4'} + 0.705\sum E_S + 0.254I_R + 6.041$$
$$(\pm 0.387)\ (\pm 0.315)\ (\pm 0.172)\ (\pm 0.185)(\pm 0.162)$$
$$n=16,\ r=0.932,\ s=0.200,\ F=18.255 \quad (8)$$

These equations are also similar in their tendency to Eqs. 1 and 2. In this series, the effect of the introduction of the second *N*-methyl group is opposite in DA and NE.

***trans* 1,2,3,5,6,10b-Hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinolines (9)**[8] In this case, the predictor variable was a negative logarithm of the dissociation constant K_i. The regression analysis for this series of compounds using all available activity data did not give a good correlation either for DA or NE. Examination of these equations revealed that the compounds with a hydroxy group tended to exhibit quite different inclination in their activity. Thus, after removing the five compounds with a hydroxyl group, Eqs. 9 and 10 were obtained. Again, these equations were similar to Eqs. 1 and 2.

$$\log(1/K_i)(DA) = 2.071\pi_{3'} + 1.495\pi_{4'} + 1.124\sum E_S + 8.322 \quad (9)$$
$$(\pm 0.720)\ (\pm 0.550)\ (\pm 0.319)\ (\pm 0.271)$$
$$n=23,\ r=0.833,\ s=0.436,\ F=14.358$$

TABLE IV. Structural Features and Monoamine-Uptake Inhibitions of *trans*-*N*-Methyl- and *N,N*-Dimethyl-1-amino-4-phenyltetralins (**5** and **6**)

No.	Y	R	−log IC50 of DA-uptake		−log IC50 of NE-uptake	
			Obsd.[a]	Calcd.[b]	Obsd.[a]	Calcd.[c]
5a	H	H	6.68	6.80	7.40	7.56
5b	4′-F	H	6.66	6.46	7.52	7.20
5c	4′-Cl	H	7.00	6.89	7.52	7.48
5d	4′-Br	H	7.10	6.93	7.52	7.48
5e	4′-CF_3	H	5.36	5.28	6.16	5.92
5f	4′-CH_3O	H	6.40	6.01	6.82	6.82
5j	3′-CF_3	H	5.59	5.46	6.59	6.40
5k	3′-CH_3O	H	6.28	6.01	7.22	6.81
5n	2′-CH_3O	H	5.24	6.05	6.32	6.85
5r	3′,4′-Cl	H	7.22	7.13	7.70	7.78
5s	2′,4′-Cl	H	5.21	5.57	6.01	6.23
5u	3′-CH_3O, 4′-F	H	5.92	5.66	6.47	6.45
5v	3′-CF_3, 4′-Cl	H	5.14	5.55	6.05	6.32
6a	H	CH_3	6.08	6.39	6.85	6.99
6c	4′-Cl	CH_3	6.42	6.48	6.89	6.91
6e	4′-CF_3	CH_3	5.01	4.86	5.33	5.36
6j	3′-CF_3	CH_3	5.21	5.04	5.85	5.84
6r	3′,4′-Cl	CH_3	6.77	6.71	7.40	7.22

a) Taken from reference 7. *b*) From Eq. 5. *c*) From Eq. 6.

TABLE V. Structural Features and Monoamine-Uptake Inhibitions of *cis*-*N*-Methyl- and *N,N*-Dimethyl-1-amino-4-phenyltetralins (**7** and **8**)

No.	Y	R	−log IC50 of DA-uptake		−log IC50 of NE-uptake	
			Obsd.[a]	Calcd.[b]	Obsd.[a]	Calcd.[c]
7a	H	H	5.29	5.43	5.73	6.04
7b	4′-F	H	5.33	5.39	5.64	5.80
7c	4′-Cl	H	5.86	5.75	5.85	5.76
7d	4′-Br	H	5.80	5.82	5.85	5.72
7e	4′-CF_3	H	5.11	5.39	5.01	4.85
7f	4′-CH_3O	H	5.38	5.21	5.52	5.64
7j	3′-CF_3	H	5.60	5.58	5.59	5.67
7k	3′-CH_3O	H	5.30	5.20	5.85	5.62
7n	2′-CH_3O	H	4.95	5.23	—	—
7r	3′,4′-Cl	H	6.28	6.22	6.14	6.15
7s	2′,4′-Cl	H	5.77	5.39	—	—
7u	3′-CH_3O, 4′-F	H	—	—	5.48	5.38
7v	3′-CF_3, 4′-Cl	H	5.82	5.90	5.37	5.40
8a	H	CH_3	5.00	4.96	6.51	6.29
8c	4′-Cl	CH_3	5.25	5.28	5.94	6.02
8e	4′-CF_3	CH_3	4.91	4.92	4.85	5.11
8j	3′-CF_3	CH_3	5.15	5.11	6.05	5.93
8r	3′,4′-Cl	CH_3	5.70	5.75	6.40	6.40

a) Taken from reference 7. *b*) From Eq. 7. *c*) From Eq. 8.

TABLE VI. Structural Features and Monoamine-Uptake Inhibitions of *trans*-Hexahydro-6-arylpyrrolo[2,1-*a*]isoquinolines (**9**)

No.	X	Y	−log IC50 of DA-uptake		−log IC50 of NE-uptake	
			Obsd.[a]	Calcd.[b]	Obsd.[a]	Calcd.[c]
9a	H	H	7.95	8.32	9.22	9.07
9b	H	4′-F	8.08	8.01	8.85	8.87
9c	H	4′-Cl	8.77	8.29	9.80	8.89
9e	H	4′-CF_3	6.89	6.94	7.97	8.11
9f	H	4′-CH_3O	8.28	7.67	9.10	8.72
9g	H	4′-CH_3S	7.39	8.03	8.52	8.77
9h	H	4′-CN	7.08	6.90	7.86	8.42
9i	H	3′-Cl	8.60	8.32	9.35	8.46
9j	H	3′-CF_3	7.27	7.45	9.02	8.82
9k	H	3′-CH_3O	7.80	7.66	9.19	8.71
9l	H	2′-Cl	7.44	7.23	8.72	8.47
9m	H	2′-Br	7.58	7.02	8.82	8.35
9n	H	2′-CH_3O	6.56	7.70	8.48	8.73
9o	H	2′-CH_3S	6.73	7.12	8.35	8.41
9p	H	2′-CH_3	6.93	6.93	8.25	8.31
9r	H	3′,4′-Cl	9.00	8.67	9.17	9.28
9s	H	2′,4′-Cl	6.95	7.20	7.77	8.29
9t	H	3′,4′-CH_3O	7.14	7.01	8.47	8.36
9B	9-F	4′-F	8.11	8.01	9.26	8.87
9C	9-Cl	H	8.60	8.32	9.21	9.07
9D	9-Cl	4′-Cl	8.49	8.29	8.49	8.89
9E	9-CF_3	H	7.95	8.32	8.51	9.07
9G	9-CH_3O	H	8.55	8.32	8.66	9.07

a) Taken from reference 8. *b*) From Eq. 9. *c*) From Eq. 10.

$$\log(1/K_i)(\mathrm{NE}) = 1.394\pi_{3'} + 0.584\pi_{4'} + 0.615\sum E_S + 9.071 \quad (10)$$
$$(\pm 0.676)\ (\pm 0.516)\ (\pm 0.300)\ (\pm 0.254)$$
$$n=23,\ r=0.680,\ s=0.412,\ F=5.443$$

To date only these five series of compounds have been studied extensively for their catecholamine-uptake inhibition. From the preceding equations describing the effect of the physical properties of the substituents on the biological activity, we drew the following conclusions.

In all cases, hydrophobic but, at the same time, smaller substituents at the 3′- and 4′-positions of ring C increase the uptake inhibition. Moreover, although there were not so many compounds with a ring A substituent, no significant effect of the substituent on ring A was exhibited. Therefore, the important aromatic ring which interacts with the receptor site must be ring C rather than ring A.

While phenolic OH groups of the catecholamines seem to be the important pharmacophore, there are many highly active inhibitors without a phenolic OH group. Moreover, no equations were obtained which displayed a substantial effect of ionic properties of the substituents, so their affinity for the receptor must originate from the stacking effect of aromatic rings rather than an ionic interaction or a phenolic hydrogen bonding.

The nitrogen atom must operate as an acceptor instead of a donor of a hydrogen bonding, since a number of tertiary amines have the activity. Judging from the minus or plus sign of the I_R term, the effect of introduction of the second *N*-methyl group depended on the series of congeners.[15]

Superimposition of the Inhibitor Molecules The facts above led us to wonder whether a common characteristic three-dimensional arrangement of functional groups in a molecule interprets the observed activity pattern.

All the inhibitors in Fig. 1 have at least one phenyl ring and a basic nitrogen atom held by the molecular framework in a position that mimics the binding conformation of DA and NE. As is evident from the simple structures of DA and NE, the catechol moiety and the nitrogen atom must be the essential functional groups interacting with their receptor. To deduce the required spatial relation between these groups, we compared the structures of the eight fundamental compounds (**2a**—**9a**),[16] adding four other inhibitors, namely, *cis* 1,2,3,5,6,10b-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinoline (**10**),[8] 5-phenyl-1,2,3,4,4a,9b-hexahydro-5*H*-indeno[1,2-*b*]pyridines (**11** and **12**),[9] and nomifensine (**13**).[10] Hereafter, we will deal with the unsubstituted compounds in Fig. 1, and the relative activities calculated for these 12 compounds are summarized in Table VII. As is evident from the table, the inhibition activity upon the DA- and NE-uptake showed a similar tendency, so we will discuss them together.[17]

In the search for the intramolecular geometric factors, distances from the nitrogen atom to the center of ring C or to the plane of this ring were calculated based on the MM2 minimized conformations. But, none of such steric parameters relating either to ring C or to ring A were significantly correlated with the activity.

Then, another possibility was explored: the concept that three-dimensional complementarity of an inhibitor to the receptor site is more important than the intramolecular arrangement of the functional groups.

To simulate the interaction between the inhibitors and the receptor site, dummy atoms were built onto selected key features of the inhibitor molecules. The dummy atoms or receptor points of the potent inhibitors should match if the chosen binding features are relevant to the activity.

As shown in Fig. 2, perpendicular points at a distance of 3.5 Å above and below the center of ring C (RP1 and RP2) were used for phenyl ring receptor points, and a receptor point at a distance of 2.8 Å from the nitrogen atom in the direction of the lone pair (RP3) was used for the interaction between the nitrogen and a hydrogen donor atom in the receptor.[18] A fitting point was also assumed on the carbon atom to which phenyl ring C is adjacent (FP1) in order to hold this phenyl ring in the proper direction, because the QSAR analysis revealed that the 3′- and 4′-substituents enhanced the activity, possibly due to interaction with the same receptor site with which the 3,4-dihydroxy groups of DA and NE interact.

To illustrate the positional relation of the four fitting points, we set the origin of a coordinate at the center of ring C, and FP1 was arranged on the *x*-axis. A right triangle was drawn with the *x*-axis and RP3 as shown in Fig. 2, and the lengths of the three sides were designated *a*, *b*, and *c*, respectively.

When an inhibitor molecule shown in Fig. 1 binds to a receptor, the binding conformation is not necessarily the one with minimum energy, because even if the binding

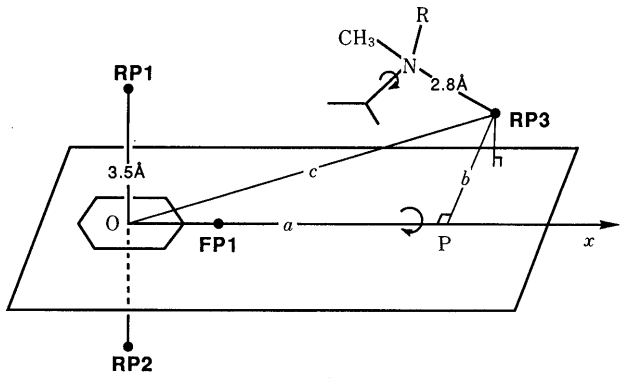

Fig. 2. Pharmacophore Model for Catecholamine-Uptake Inhibitors

The phenyl ring receptor points (RP1 and RP2) are assumed at 3.5 Å perpendicularly above and below the center of the phenyl ring. A fitting point (FP1) is set on the carbon atom to which the phenyl ring is adjacent. A hydrogen bonding receptor point (RP3) is also assumed at 2.8 Å from the nitrogen atom in the direction of the lone pair. Let the origin O be at the center of the phenyl ring, and the point P be at the foot of the perpendicular from RP3 to the O—FP1 vector. The distances O—P, RP3—P, and RP3—O are referred to as *a*, *b*, and *c*, respectively.

TABLE VII. Relative Activities of DA- and NE-Uptake Inhibitors Used in the Superimposition Study[a]

Compd.	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10**	**11**	**12**	**13**
DA	1.10	1.46	0.85	−0.29	0.31	1.09	1.39	−0.84	0.31	−0.85	−0.15	0.00
NE	1.29	1.69	0.79	0.30	0.85	1.97	1.19	−0.80	1.23	−0.25	0.57	0.00

a) The pharmacological data were taken from references 5—10 and converted into relative values as described in the text.

TABLE VIII. Conformational Energy, Steric Parameters (*a*, *b*, and *c*), and *rms* Distance Calculated from the MM2 Results

		C–N dihedral angle[a] 60					180					300				
		ΔE[b]	*a*[c]	*b*[c]	*c*[c]	*rms*[d]	ΔE[b]	*a*[c]	*b*[c]	*c*[c]	*rms*[d]	ΔE[b]	*a*[c]	*b*[c]	*c*[c]	*rms*[d]
2a	ax[e]	0.25	5.46	5.29	7.61	1.76	1.97	4.20	5.27	6.47	1.22	3.32	7.14	1.76	7.36	1.10
	eq[e]	0.00	8.19	1.90	8.41	1.92	0.22	6.61	3.94	7.70	1.24	0.55	5.83	2.02	6.17	0.03[f]
3a	ax[e]	1.30	0.30	1.82	1.85	3.44	0.82	2.43	5.25	5.79	1.82	2.51	3.01	5.47	6.24	1.76
	eq[e]	1.42	3.20	4.57	5.58	1.49	1.70	5.67	4.64	7.33	1.26	0.00	7.61	3.55	8.40	1.97
4a	ax[e]	0.71	0.28	1.55	1.57	2.94	2.14	1.73	4.91	5.20	1.64	1.54	2.48	5.51	6.04	1.75
	eq[e]	3.43	3.21	4.58	5.59	1.53	1.77	5.40	4.69	7.15	1.32	0.00	7.64	3.54	8.42	2.00
5a	ax[e]	1.65	7.72	3.38	8.43	1.97	12.31	6.35	4.59	7.83	1.75	1.28	6.02	2.03	6.35	0.14[f]
	eq[e]	0.00	7.14	4.31	8.34	2.03	0.30	7.79	3.92	8.72	2.19	1.50	7.84	0.62	7.87	1.49
6a	ax[e]	2.46	6.78	4.33	8.04	1.95	4.38	5.53	5.81	8.02	1.74	2.81	5.67	2.17	6.07	0.10[f]
	eq[e]	0.00	6.99	4.39	8.26	1.96	3.57	7.49	4.32	8.64	2.18	—[g]	—	—	—	—
7a	ax[e]	0.00	1.24	4.43	4.60	2.62	2.20	4.81	5.98	7.68	1.75	0.59	5.49	5.47	7.75	1.61
	eq[e]	1.61	1.76	2.98	3.46	2.59	1.08	5.59	5.00	7.50	1.66	0.27	4.99	5.43	7.38	1.69
8a	ax[e]	—[g]	—	—	—	—	3.70	4.99	5.94	7.75	1.97	0.00	5.47	5.46	7.73	1.88
	eq[e]	1.13	1.54	2.78	3.18	2.80	4.81	5.23	5.21	7.38	1.64	1.77	4.42	5.46	7.02	1.70
9a	ax[e]											0.00	0.87	2.52	2.66	3.29
	eq[e]	0.80	5.79	2.12	6.16	0.00[f]										
10	ax[e]											0.57	0.62	2.71	2.78	3.32
	eq[e]	0.00	5.93	1.43	6.10	0.32[f]										
11	ax[e]	1.55	5.13	5.37	7.43	1.72	1.44	3.51	5.44	6.47	1.66	2.94	7.32	1.43	7.64	1.14
	eq[e]	0.35	8.46	1.52	8.60	2.11	3.38	6.67	4.08	7.82	1.57	0.00	5.54	2.04	5.90	0.25[f]
12	ax[e]	2.72	5.01	5.43	7.39	1.73	3.84	3.35	5.35	6.31	1.68	4.55	7.23	2.54	7.66	1.27
	eq[e]	3.92	8.47	1.86	8.67	2.15	4.15	6.58	4.13	7.77	1.54	0.00	5.39	2.11	5.78	0.34[f]
13	ax[e]											0.00	0.67	2.57	2.66	3.34
	eq[e]	0.11	5.80	1.82	6.08	0.15[f]										

a) The three staggered angles (degree) of $C_{aromatic}$-C–N-lone pair. *b*) Excess energy (kcal mol^{-1}) from the respective global minimum is shown. *c*) The lengths of the three sides (Å) of the right triangle shown in Fig. 2. *d*) The *rms* distance (Å) calculated between the four fitting points of one molecule and the corresponding points of the active conformation of **9a**. *e*) The conformer having a cyclopentene or cyclohexene ring with a pseudoaxial or pseudoequatorial phenyl ring is referred to as ax or eq, respectively. *f*) Data of the characteristic conformation with small *rms* distances and low steric energy are underlined. *g*) This conformation converged to a different one in the course of the energy minimization.

conformation is unstable, intermolecular stabilization by hydrogen bonding or π–π stacking can compensate for the intramolecular instability caused by the unfavorable conformational change.[19] In this report we assumed that all conformations within 5 kcal mol^{-1} of the global minimum were accessible.[20] Thus, the inhibitor molecule can adopt any conformation by rotating the C–N and the C–C bonds (see Fig. 2), when it binds most effectively in the receptor biding site.

On the assumption that ring C is fixed in the receptor under constraint of some undefined intermolecular interaction, then RP1, RP2, and FP1 should be held in a certain position. At the same time, RP3 must determine its most effective fitting position in the receptor site, changing the C–N bond rotational angle and the ring B conformation. Values *a*, *b*, and *c* shown in Table VIII indicate the positional relation between ring C and RP3 at individual local minimum concerning ring B conformation and the C–N bond rotation. There is one additional conformational freedom in these molecules: according to the rotation of the C–C single bond connecting ring B and ring C, RP3 revolves around the *x*-axis on the circumference of a circle with the radius b. Therefore, if two conformers of different compounds in Table VIII have comparable values of *a*, *b*, and *c*, then these two compounds can superimpose their fitting points (RP1, RP2, RP3, and FP1) on each other by rotation of this C–C bond.

With the aim of finding an active conformation adoptable by all potent inhibitors, we compared the semirigid compounds **9a** and **11**, respectively the strongest DA- and NE-uptake inhibitors in Table VII. As seen in Table VIII, **9a** and **11** have a characteristic conformation with $a \fallingdotseq 5.7$ Å, $b \fallingdotseq 2.1$ Å, and $c \fallingdotseq 6.0$ Å, indicating that the four fitting points of these molecules can be superimposed on each other.

A good fit is defined as one in which the root mean squares (*rms*) distance between the four fitting points of one molecule and the corresponding fitting points of a template molecule is less than 0.5 Å, and at the same time, the energy of that molecule is within 5 kcal mol^{-1} of the global minimum conformation.[20] As it was most potent, **9a** was selected as the template.

Subsequently, the conformer with comparable values of *a*, *b*, and *c* was sought among the compounds in Table VIII. The twelve compounds were classified into three groups, namely good fit and high activity, poor fit and low activity, and good fit but low activity.

All the highly active inhibitors, *e.g.* **5a**, **9a**, **11**, and **13** were included in the first group, and very good superimposition of the four fitting points of these four compounds can be seen in Fig. 3.

The rather weak inhibitors **3a**, **4a**, **7a**, and **8a** were included in the second group, and as seen in Table VIII, they did not adopt the conformer with comparable *a*, *b*, and *c* values. When the coincidence of the FP1 was neglected, the remaining three fitting points of this second group of compounds were also superimposed very well as shown in Fig. 4. This fact suggests that not only the π–π aromatic interaction, but the direction of ring C in the receptor site is important for the potent activity. In accordance with the QSAR results, the hydrophobic

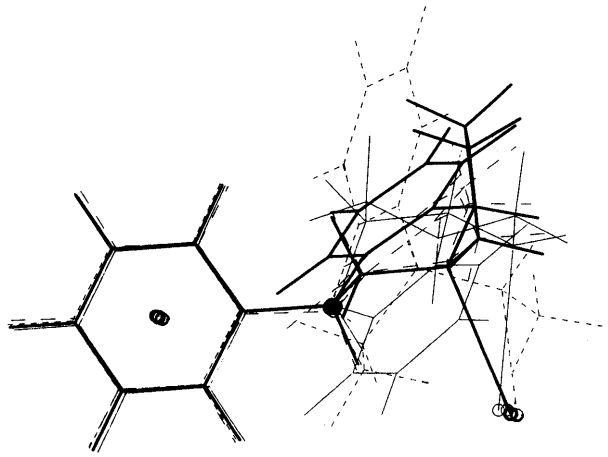

Fig. 3. Superimposition of the Four Potent Inhibitors

The first group of compounds displays good fit and high activity. The four fitting points (RP1, RP2, FP1, and RP3) are included in a least-squares fitting procedure. **5a**, – – –; **9a**, ——; **11**, ——; **13**, ------.

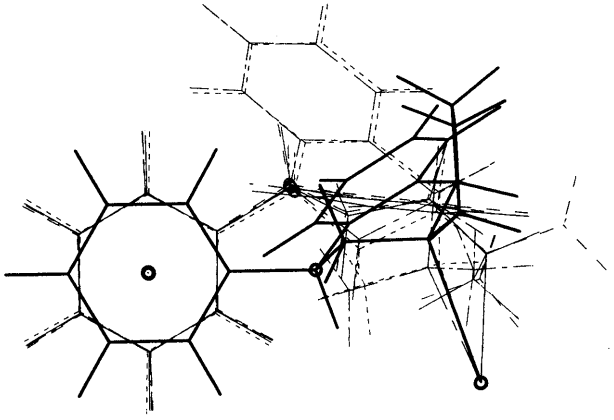

Fig. 4. Superimposition of the Four Weak Inhibitors

The three fitting points of compounds in the second group which display poor fit and low activity are superimposed onto the corresponding points of **9a** (FP1 is disregarded). **9a** (template), ——; **3a**, ——; **4a**, ------; **7a**, – – –; **8a**, –·–·–.

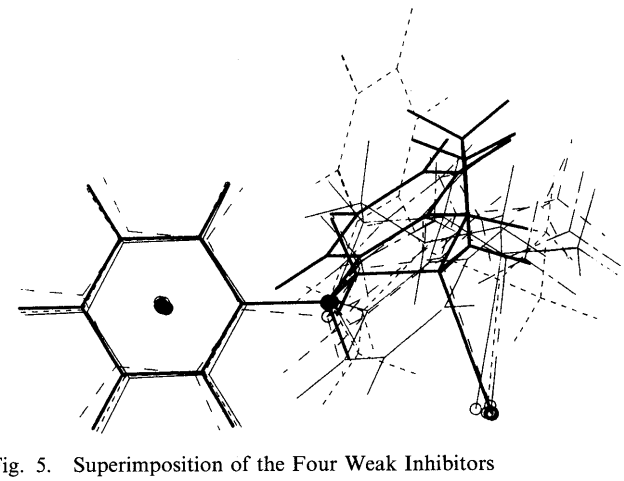

Fig. 5. Superimposition of the Four Weak Inhibitors

The four fitting points of compounds in the third group which display good fit but low activity are superimposed. It is seen that the substituents on the nitrogen atom of this group commonly extend into a specific region. **9a** (template): ——, **2a**, –·–·–; **6a**, ------; **10**, – – –; **12**, ——.

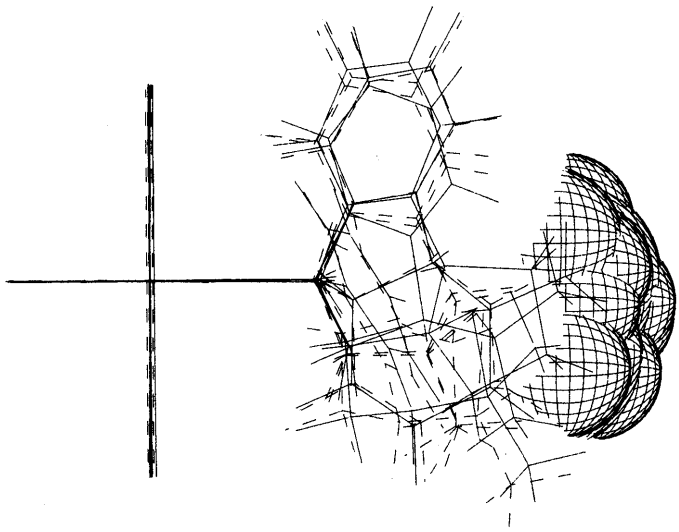

Fig. 6. Superimposition of the First and Third Groups of Compounds

These groups of compounds exhibit very good fit on all four points. The hatched spheres show the van der Waals surface of the specific region in which only the third group of compounds exists. First group, – – –; third group, ——.

interaction of 3′- or 4′-substituent with the receptor must be responsible for the activity.

Correlation between the best *rms* distance of each compound and the inhibition activity of DA- or NE-uptake was examined for the first and second groups of inhibitors.

$$\text{DA activity} = 1.451\,rms - 0.677 \quad (11)$$
$$(\pm 0.440) \quad (\pm 0.403)$$
$$n=8,\ r=0.934,\ s=0.374,\ F=40.964$$

$$\text{NE activity} = 1.367\,rms - 0.358 \quad (12)$$
$$(\pm 0.600) \quad (\pm 0.550)$$
$$n=8,\ r=0.875,\ s=0.510,\ F=19.574$$

Therefore, it is concluded that the degree of correspondence of the four fitting points is proportional to the activity of these inhibitors.

Despite the small *rms* value of the third group of compounds, *e.g.* **2a**, **6a**, **10**, and **12**, they actually displayed only weak inhibition activity. The excellent superimposition of their four fitting points is shown in Fig. 5. Different from the other two groups, these weak inhibitor invariably extended into a specific region. Figure 6 shows the superimposition of the first and the third groups. The hatched spheres are the van der Waals surface of this specific region into which only the third group of compounds extends. The steric interaction between the substituent extending into this region and the receptor may hinder the effective binding. This is consistent with the observation in the preceding regression analysis, that is, Eqs. 1, 2, 5, and 6 predicted the negative effect of introduction of the second *N*-methyl group which must extend into that specific region as seen in Fig. 6.

Further QSAR analyses of drugs for the central nervous system are in progress.

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15) The negative coefficient of the I_R term in Eqs. 1, 2, 5, 6, and 7 indicates an unfavorable effect of the introduction of the second *N*-methyl group. Contrarily, the positive sign of the I_R term in Eqs. 4 and 8 shows the favorable effect of the second *N*-methyl group to NE-uptake inhibition by *cis* 3-phenyl-1-indanamines and *cis* 1-amino-4-phenyltetralins. Although, it is not clear why *N,N*-dimethyl derivatives of these *cis* compounds are stronger inhibitors of NE-uptake, this fact suggests a possibility of selective NE-uptake inhibitors. This report, however, does not discuss about the selectivity.
16) We could not find the inhibition data of *trans* 3-phenyl-1-indanamine (**1a**).
17) The correlation between the inhibition activities of DA- and NE-uptake was as follows.

NE activity = 0.88795 DA activity + 0.41173
$n = 12$, $r = 0.889$

18) It is usually assumed that an aromatic group interacts via a planar hydrophobic (π–π) bond with an aromatic group of the receptor protein located approximately 3.5—4.5 Å away, and the nitrogen atom is assumed to form a linear hydrogen bond, 2.8 Å long, with an electronegative atom of the receptor, *e.g.*: P. R. Andrews, E. J. Lloyd , J. L. Martin, S. L. Munro, M. Sadek, and M. G. Wong, "Topics in Molecular Pharmacology," Vol. 3 (Mol. Graphics Drug Des.), ed. by A. S. V. Burgen, G. C. K. Roberts, and M. S. Tute, Elsevier Science Publishers B. V., New York, 1986, p. 215 and references cited therein.
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