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Synthesis, Structure and Quantitative Structure–Activity Relationships of σ Receptor Ligands, 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazines

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Abstract—A set of the title compounds having different substituents (R_1, R_2) on their phenyl groups was synthesized to find σ receptor binding affinity. Among the compounds, **2b** (R_1=R_2=Cl) has the most potent σ_1-binding activity, while **2a** (R_1=R_2=H, SA4503) was most selective to σ_1 over σ_2 receptor. The crystal structures of **2a** and **2b** were shown, by X-ray crystallography, to be similar except for the one torsional angle of their propylene parts. Quantitative structure–activity relationship study suggested the affinity of the compounds to the σ_1 receptor was dependent on the electronic feature, Swain–Lupton's R or S_π that was derived by molecular orbital method, of R_1 and R_2. © 1997 Elsevier Science Ltd.

Introduction

Recently, the σ receptor has been recognized as a unique receptor of being distinguishable from μ-opioid, κ-opioid or phencyclidine receptor, and categorized into two subtypes (σ_1, σ_2) possessing high or low affinity for (+)-benzomorphans such as (+)-pentazocine, respectively. Studies of elucidating the physiological position of the σ receptor revealed that it distributes over the gastrointestinal tract[1] and immune systems[2] as well as the central nervous system.[3] At the same time, possible roles of the receptor in several disorders of such systems are indicated. Particularly, decrease of σ receptor in hippocampus among Alzheimer's patients strongly suggested the involvement of σ receptor in dementia.[4] On the other hand, some antipsychotic compounds having the ability to bind to the σ receptor[5] were considered to be useful for schizophrenia.

We have been engaged in obtaining an orally available analgesic compound by the structural modification of **1** (lefetamine) that has limited analgesic and local anesthetic actions. In the study, σ-binding activity was found for one derivative, 1-[2-(3,4-dimethoxyphenyl)-ethyl]-4-(3-phenylpropyl)piperazines. Of those, SA4503 (**2a**·2HCl) (Scheme 1, R_1=R_2=H) potently and selectively bound to the σ_1 receptor subtype; its binding affinities to μ-, κ- and δ-receptors being very weak.[6] It induced the increase of extracellular acetylcholine in the rat frontal cortex and hippocampus which are known important for learning, but is not accompanied by striatal cholinomimetic adverse effects.[7] In this report, we present the synthesis and conformational analysis of crystals, and the quantitative structure–activity relationship (QSAR) studies of those title compounds.

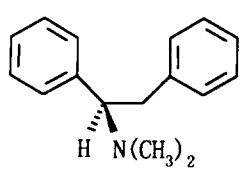

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Chart 1.

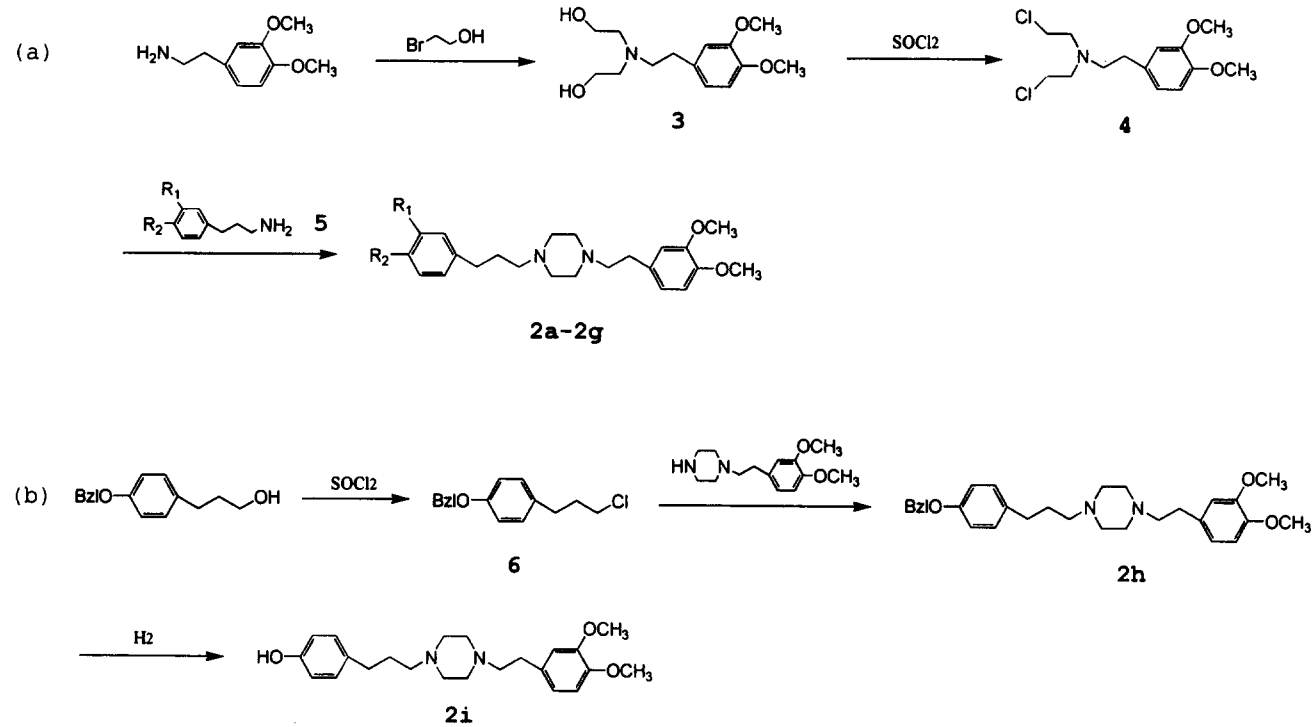
Results and Discussion

Synthesis

The title compounds were synthesized by the two different type-coupling reactions as shown in Scheme 1. *N,N*-bis(2-chloroethyl)-2-(3,4-dimethoxy)phenylethylamine (**4**) was treated with an adequate phenylpropylamine (**5**) for **2a–2g**, while benzyloxyphenylpropylchloride (**6**) was combined with *N*-[2-(3,4-dimethoxyphenyl)ethyl]piperazine[8] to afford **2h**, followed by hydrogenation to give **2i**. All the compounds (**2a–2i**) thus obtained were transformed into HCl salt and their chemistries are summarized in the Experimental section. Their spectroscopic features and elementary analyses support those structures.

Conformations of 2a and 2b in crystal state

Hydrochloride salt of compounds **2a** and **2b** were crystallized as colorless orthorhombic and monoclinic



Scheme 1. Synthesis of 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazines.

crystals with space groups $Pna2_1$ and Cc, respectively. Each of them had either the most selective or potent σ_1-binding activity as shown in the following section. The overall conformations of **2a** and **2b** in crystals were found to similar to each other (Fig. 1, Tables 1 and 2). Both compounds have the chair-formed piperazines and stretched phenylalkyl chains in which respective phenyl groups are apart. One torsional angle of the propylene part of phenylpropyl groups, however, was found to be different. Three torsional angles of **2b** were

Table 1. Positional parameters and U (eq) with the standard deviation in parentheses for the nonhydrogen atoms of **2a**·2HCl

Atom	x	y	z	U (eq)
C(1)	0.5303 (4)	1.618 (2)	0.124 (2)	0.072 (9)
C(2)	0.5213 (3)	1.472 (2)	0.216 (2)	0.070 (8)
C(3)	0.5487 (3)	1.368 (1)	0.286 (2)	0.057 (6)
C(4)	0.5858 (3)	1.4140 (1)	0.267 (1)	0.040 (4)
C(5)	0.5949 (3)	1.564 (1)	0.175 (2)	0.048 (6)
C(6)	0.5669 (4)	1.662 (2)	0.102 (2)	0.062 (7)
C(7)	0.6157 (3)	1.308 (1)	0.348 (1)	0.042 (5)
C(8)	0.6292 (3)	1.140 (1)	0.259 (2)	0.043 (5)
C(9)	0.6613 (3)	1.048 (1)	0.336 (1)	0.041 (5)
N(10)	0.6983 (2)	1.1378 (9)	0.298 (9)	0.027 (4)
C(11)	0.7120 (3)	1.072 (1)	0.147 (1)	0.031 (5)
C(12)	0.7481 (2)	1.166 (1)	0.107 (1)	0.027 (4)
N(13)	0.7774 (2)	1.1367 (9)	0.2259 (9)	0.025 (3)
C(14)	0.7631 (3)	1.191 (1)	0.377 (1)	0.032 (4)
C(15)	0.7272 (3)	1.097 (1)	0.412 (1)	0.035 (4)
C(16)	0.8125 (3)	1.238 (1)	0.181 (1)	0.036 (5)
C(17)	0.8441 (3)	1.208 (1)	0.287 (1)	0.045 (5)
C(18)	0.8791 (2)	1.287 (1)	0.219 (1)	0.040 (5)
C(19)	0.8993 (3)	1.195 (1)	0.112 (2)	0.053 (6)
C(20)	0.9310 (3)	1.267 (2)	0.048 (2)	0.051 (6)
C(21)	0.9431 (2)	1.440 (1)	0.090 (1)	0.036 (5)
C(22)	0.9220 (2)	1.536 (1)	0.195 (1)	0.033 (4)
C(23)	0.8905 (2)	1.464 (1)	0.259 (1)	0.034 (4)
O(24)	0.9742 (2)	1.523 (1)	0.036 (1)	0.049 (4)
C(25)	0.9959 (4)	1.430 (2)	−0.069 (2)	0.068 (8)
O(26)	0.9353 (2)	1.7097 (9)	0.227 (1)	0.046 (4)
C(27)	0.9180 (4)	1.804 (2)	0.347 (2)	0.060 (7)
CL(28)	0.80431 (6)	1.7488 (3)	0.274	0.039 (1)
CL(29)	0.70021 (6)	1.5607 (2)	0.2567 (5)	0.037 (1)

Table 2. Positional parameters and U (eq) with standard deviation in parentheses for the nonhydrogen atoms of **2b**·2HCl

Atom	x	y	z	U (eq)
C(1)	0.3958 (3)	0.474 (2)	0.452 (2)	0.048 (7)
C(2)	0.3999 (4)	0.626 (2)	0.455 (2)	0.056 (8)
C(3)	0.3712 (4)	0.719 (2)	0.445 (2)	0.055 (8)
C(4)	0.3390 (3)	0.658 (2)	0.426 (2)	0.049 (7)
C(5)	0.3357 (3)	0.505 (2)	0.425 (2)	0.052 (7)
C(6)	0.3648 (3)	0.411 (2)	0.438 (2)	0.045 (6)
C(7)	0.3080 (4)	0.757 (2)	0.398 (3)	0.06 (1)
C(8)	0.2790 (3)	0.712 (2)	0.511 (2)	0.053 (8)
C(9)	0.2495 (3)	0.824 (2)	0.479 (2)	0.046 (7)
N(10)	0.2197 (2)	0.780 (1)	0.575 (1)	0.028 (4)
C(11)	0.1931 (3)	0.904 (1)	0.558 (2)	0.039 (6)
C(12)	0.1617 (3)	0.862 (1)	0.657 (2)	0.038 (6)
N(13)	0.1468 (3)	0.722 (1)	0.582 (2)	0.034 (5)
C(14)	0.1725 (3)	0.601 (1)	0.606 (2)	0.035 (6)
C(15)	0.2041 (3)	0.635 (1)	0.507 (2)	0.039 (6)
C(16)	0.1138 (3)	0.681 (1)	0.668 (2)	0.038 (6)
C(17)	0.0874 (4)	0.797 (2)	0.628 (2)	0.051 (8)
C(18)	0.0517 (4)	0.745 (1)	0.678 (2)	0.049 (7)
C(19)	0.0328 (4)	0.652 (2)	0.558 (2)	0.053 (8)
C(20)	0.0009 (3)	0.608 (2)	0.601 (2)	0.047 (7)
C(21)	−0.0131 (3)	0.657 (1)	0.762 (2)	0.033 (5)
C(22)	0.0070 (4)	0.748 (1)	0.885 (2)	0.044 (7)
C(23)	0.0392 (4)	0.788 (1)	0.845 (2)	0.046 (7)
O(24)	−0.0445 (2)	0.621 (1)	0.818 (1)	0.045 (5)
C(25)	−0.0632 (3)	0.516 (2)	0.708 (2)	0.049 (7)
O(26)	−0.0087 (3)	0.789 (1)	1.041 (1)	0.059 (6)
C(27)	0.0075 (5)	0.896 (2)	1.156 (2)	0.07 (1)
CL(28)	0.4320	0.3625 (5)	0.4670	0.076 (3)
CL(29)	0.3583 (1)	0.2175 (4)	0.4351 (7)	0.065 (2)
CL(30)	0.1330	0.7612 (3)	0.1700	0.051 (2)
CL(31)	0.2361 (1)	0.7362 (4)	0.9814 (5)	0.052 (2)

all *anti* (C(8)–C(9)–N(10)–C(11) = 173.0°, C(7)–C(8)–C(9)–N(10)=175.9°, C(4)–C(7)–C(8)–C(9)=177.4°), while the corresponding torsions of **2a** were *anti* (C(8)–C(9)–N(10)–C(15)=158.7°), *gauche* (C(7)–C(8)–C(9)–N(10)=−83.51°), *anti* (C(4)–C(7)–C(8)–C(9)=174.7), respectively.

Binding activities

The most potent σ_1-binding activity was found for **2b** (R_1=R_2=Cl) at phenyl ring A(Phe(A)), whilst **2h** that has R_2=OCH_2Ph was the least potent (Table 3). The effects of R_1 and R_2 on the activities among all the compounds, however, appear to be less remarkable. Similar behavior of substituents on the binding affinity was also observed for other σ ligands, benzomorphans,[9] bis(phenylalkyl)amines,[10] and phenylalkyldiamines.[11,12] Particularly, the phenylalkyldiamines having a comparable skeleton to **2** showed a similar activity sequence in terms of the substituents on the phenyl ring:[12] 3,4-Cl_2 > 4-Cl > 4-Br > 4-F for both lines of the compounds. Accordingly, we considered the activity deviation of **2** by those substituents to be significant, even though the effects are not large. Meanwhile, affinities to the σ_2 receptor seem a little more restricted than those of σ_1, as shown in Table 3. This behavior also resembles that of the phenylalkyldiamines.[12] Among those in Table 3, **2a** was the most specific to the σ_1 receptor due to its low σ_2 affinity.

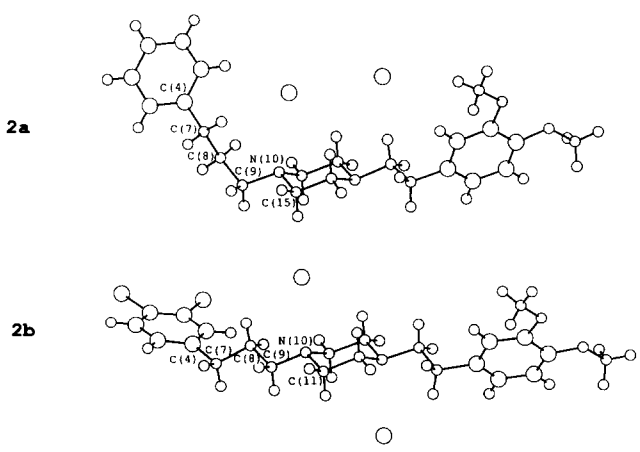
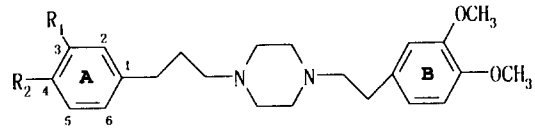


Figure 1. Structures of **2a** and **2b** found in their crystals.

QSAR

It has been suggested, for some σ ligands,[9–11] that electronic features contribute to the activity of substituents on an aryl ring. For those ligands, however, any explicit QSAR is not formulated. QSAR analysis of **2** will therefore be useful to further the study of σ ligands as well as σ receptors.

Table 3. σ-Receptor binding affinities of **2** and their physicochemical properties



2	R_1	R_2	R^a	$S_{\pi(3)}{}^b$	$pIC_{50}{}^c$ σ_1	$pIC_{50}{}^c$ σ_2	$\sigma_1/\sigma_2{}^d$
2b	Cl	Cl	−0.15	−1.619	8.16	6.81	22
2c	H	CF_3	0.19	−3.765	7.99	6.55	28
2a	H	H	0.00	−6.560	7.76	5.75	103
2i	H	OH	−0.64	−9.381	7.69	6.18	32
2d	H	Cl	−0.15	−8.164	7.66	—	—
2e	CF_3	H	0.00	−9.357	7.58	—	—
2f	H	Br	−0.17	−6.819	7.52	6.34	15
2g	H	F	−0.34	−8.241	7.48	—	—
2h	H	OCH_2Ph	—	−12.370	6.97	—	—

[a]Swain–Lupton's R value of R_2.
[b]Values multiplied by 1000, and used for Hansch-Fujita analysis.
[c]Negative logarithm of IC_{50}; IC_{50} was obtained as the average of 1–5 determinations; each concentration of the compound consists of triplicate points.
[d]IC_{50} (σ_1)/IC_{50} (σ_2)

The QSAR of compounds **2a–2i** were analyzed by the Hansch–Fujita method with several reported physicochemical descriptors that represent lipophilic, electronic, and steric effects of substituents on phenyl rings. For those compounds (**2a**, **2c**, **2d**, **2f**, **2g**) having only a *para*-substituent, Swain–Lupton's R,[13] which denotes the resonance nature of a substituent, was suggested to correlate with the activities (eq. 1). In the regression equation, n, r, and s represent the number of data, correlation coefficient, and the standard deviation, respectively. The figures in parentheses are the 95% confidence limits of the corresponding coefficients.

The inclusion of compound **2i** having 4-OH gave a poor result (r = 0.589). This irregularity may be caused by the hydrogen-bonding nature of hydroxyl group. Incidentally, since the R value for the benzyloxy group of **2h** is not yet reported, the R value of **2h** was estimated from eq. 1 to be −0.81. The reported R values of similar functional groups are −0.51 (MeO–), −0.44 (EtO–), −0.45 (PrO–), and −0.72 (*i*-PrO–).[13b,13c] Consequently, **2h** would be treated in the same equation.[14] Other descriptors (R^+,[16] R^-,[16] R^0,[16] σ_R^0,[17] σ_R^+[17]) representing resonance features also suggested similar trends. The R dependence of the affinity suggested in eq. 1 also appears to be true for the phenylalkyldiamines.[11,12] They show increased binding affinities with increased R values, indicating a similar binding manner to the σ_1 receptor.

$$pIC_{50} = 0.994\ (\pm 0.490) \cdot R + 7.775(\pm 0.099)$$
$$(n = 5,\ r = 0.966,\ s = 0.061,\ F_{1,3} = 41.67) \qquad (1)$$

Since QSAR between the electronic parameters and activities was suggested, inclusion of the other compounds into QSAR analysis was examined with a descriptor calculated by a molecular orbital (MO) method. To this end, all the compounds (**2a–2i**) were subjected to semiempirical PM3 calculations. The initial structures for the calculations were taken from the most potent **2b** structure obtained by X-ray crystallography. This is because we neither have data about the active conformation of **2a–2i** in σ receptors nor did conformational analysis seem to be successful in limiting the number of possible starting conformations in a practical sense. In fact, rigid rotator approximation (stepwise rotation by 30°) for the phenylpropyl unit by CHARMm force field[18] ($\varepsilon = r$) suggested there were about 650 conformations within 5 kcal/mol of the global minimum structure, and 100 conformations for the phenethyl part. Among those low-energy conformations were found some structures resembling those shown in the crystal states. The structure of **2b** in the crystal state partly satisfied the proposed geometric requirement of some pharmacophores for σ receptor binding.[19] Namely, the distance between the respective basic nitrogen and the aromatic ring of **2b** ranged from 5 to 9 Å, and that of the two aromatic cycles was 14 Å. Since X-ray structures of some small molecules have been used in drug research when their receptor-bound forms were not known,[20] and for the reasons mentioned above, we considered using the X-ray structure of **2b** as a possible binding structure.

Among the calculated properties such as the highest occupied molecular orbital (HOMO) energy, the lowest unoccupied molecular orbital (LUMO) energy, the frontier electron densities, charges, and superdelocalizabilities, etc. in those structures, the electron density of the highest occupied π orbital (HOPO) seemed to correlate with the activities. This would be consistent with the use of R in eq. 1. Although HOPO was found in four MOs (HOMO-1 to HOMO-4), no specific location for each molecule was identified: electron density was therefore added over the four highest occupied MOs for every atom. After the summation, the

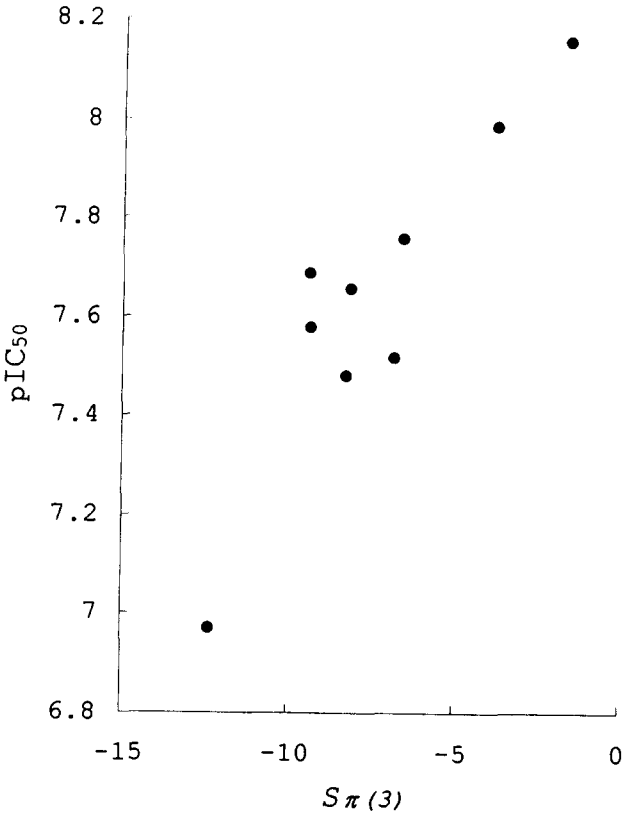


Figure 2. Correlation between $S_{\pi(3)}$ and σ_1-binding affinities (pIC_{50}). $S_{\pi(3)}$ of **2i** was calculated for **2i** with a water molecule hydrogen-bonding to its 4-OH group.

densities were divided by the corresponding MO energies over a series of molecules to give S_π. Consequently, S_π would be equivalent to superdelocalizability that is principally limited to the nature of HOPO, particularly for the atoms without large HOMO. $S_{\pi(3)}$ (S_π at C(3), see Table 3) showed a satisfactory correlation with the activities (eq. 2) (Fig. 2), with compound **2i** still found to be an outlier. The correlation between $S_{\pi(3)}$ (**2a**, **2c**, **2d**, **2f**, **2g**, and **2i**) and the R values of their *para*-substituents was r = 0.908, and for those compounds except **2i**, r = 0.910, suggesting $S_{\pi(3)}$ would be a good reflection of R. Then, $S_{\pi(3)}$ will be applicable to those compounds having more than two functional groups on the phenyl ring.

$$pIC_{50} = 0.103\ (\pm 0.035) \cdot S_{\pi(3)} + 8.369(\pm 0.269)$$
$$(n = 8,\ r = 0.947,\ s = 0.124,\ F_{1,6} = 52.18) \quad (2)$$

Hammett's electronic parameter, σ, is considered to consist of two independent electronic natures, field and resonance effects, and the σ has been divided into different parameters, such as Swain–Lupton's F and R,[13] respectively. On the other hand, Hammett's σ is reported to be equivalent to the linear combination of the atomic charges calculated by the MO method.[21] These results suggest that F and R or their comparable descriptors could be estimated separately by MO calculations. The descriptor, S_π, used in the present study would be just the case for the R. The remainder MOs will also be useful in determining the other Swain–Lupton's parameter, F.

The effect of the Phe(A) group rotation (180°) that controls the location of R_1(3-Cl) of **2b** was taken into account to examine the correlation. The correlation of the derived value with the original orientation of the Phe(A) group found in the crystal state gave a better result (eq. 2) than that of the rotated one. As for the substituent R_1(3-CF_3) of **2e**, the orientation of the Phe(A) whose R_1 of **2e** occupies the same location to that of **2b** was preferable for obtaining the correlation. $S_{\pi(3)}$ calculated for the structure found in the **2a** crystal gave a similar but less satisfactory (r = 0.906) result. This may suggest the conformation found in the **2b** crystal is closer to the intrinsic active conformation than **2a**.

Since several trials to include **2i** in eq. 2 failed, the possibility that some functional groups of the receptor around the 4-OH group of **2i** may affect the activity was considered. Descriptor $S_{\pi(3)}$ was calculated for **2i** with a number of water molecules placed around the 4-OH group. This is to allow the 4-OH to participate in hydrogen bonding, where water molecules were used as the H-bonding functional group of the σ receptor. Equation 3 includes the $S_{\pi(3)}$ of **2i** having one water molecule H-bonding to the oxygen of the 4-OH. This implies that an H-bonding functional group can locate close to the *para*-substituent of the Phe(A).

$$pIC_{50} = 0.096\ (\pm 0.040) \cdot S_{\pi(3)} + 8.349(\pm 0.315)$$
$$(n = 9,\ r = 0.907,\ s = 0.151,\ F_{1,7} = 32.53) \quad (3)$$

Conclusion

σ Receptor-binding activity was found in newly synthesized 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazines having *meta*- and/or *para*-substituent(s) on the phenyl ring. The activity was suggested to be quantitatively dependent on Swain–Lupton's electronic parameter, R of the *para*-substituent, and this relationship was successfully extended to include those having a *meta*-substituent with the use of a descriptor derived by MO calculations. The descriptor, S_π, bears resonance nature, and will be useful for other QSAR analysis.

Experimental

Chemistry

Melting points were determined in open glass capillaries with a Büchi 535 melting-point apparatus and were uncorrected. Elemental analyses were performed by an varioEL elemental analyzer. NMR spectra were measured on a JEOL GSX400 spectrometer using tetramethylsilane as an internal standard.

***N,N*-bis(2-hydroxyethyl)-2-[(3,4-dimethoxy)phenyl]ethylamine (3).** Anhydrous K_2CO_3 was added to an EtOH (250 mL) solution of homoveratrylamine (20.0 g, 110.4 mmol) and 2-bromoethanol (73.4 g, 587.3 mmol), and

the solution refluxed for 24 h with stirring. The solution was cooled, filtrated, and then concentrated in vacuo to give a residue. The $CHCl_3$ (300 mL) solution of the residue was washed with 10% $NaHCO_3$, satd NaCl aqueous solutions, and dried over anhyd Na_2SO_4. The residue remained after the solvent removal under reduced pressure was purified by silica gel column chromatography affording 13.49 g (46%) of oil (**3**). ^1H NMR($CDCl_3$) δ: 2.69–2.74 (8H, m), 2.78–2.82 (2H, m), 3.57–3.60 (4H, m), 3.85 (3H, s), 3.87 (3H, s), 6.72–6.75 (2H, m), 6.79–6.82 (1H, m).

***N,N*-bis(2-chloroethyl)-2-(3,4-dimethoxyphenyl)ethylamine(4)·HCl**. A 14.38-g quantity of $SOCl_2$ (120.9 mmol) was added dropwise to a stirred solution of **3** (10.86 g, 40.3 mmol) and $CHCl_3$ (50mL) in an ice-bath, and the mixture refluxed for 45 min. The mixture was cooled and the solvent removed under reduced pressure. The addition of *i*-PrOH gave a solid product of **4**·HCl (10.23 g, 74%) (mp 147–149°C). ^1H NMR ($CDCl_3$) δ: 3.18–3.22 (2H, m), 3.43–3.47 (2H, m), 3.59 (4H, t, J = 6.3 Hz), 3.87 (3H, s), 3.89 (3H, s), 4.10 (4H, t, J = 6.3 Hz), 6.77–6.84 (3H, m), 13.6 (1H, br).

General procedure for the preparation of phenylpropylamines (5)

A 5.38-g quantity of $SOCl_2$ (45.2 mmol) was added dropwise to a slurry of properly substituted cinnamic acid (28.0 mmol) in $CHCl_3$ (30 mL) below 10°C, then heated to reflux (3.5 h) after the one-drop addition of DMF. Removal of the solvent of the cooled mixture under reduced pressure gave cinnamoyl chloride.

A solution (10 mL) of the cinnamoyl chloride (30.1 mmol) in ether was added to a vigorously stirred aq ammonia solution (90 mL, ca. 7.4 N), and stirring was continued for 18.5 h. Cinnamoyl amide was obtained as a precipitant by filtration.

THF (60 mL) suspension of $LiAlH_4$ (1.52 g, 40.0 mmol) was stirred for 5 h in a Soxhlet's extractor having a thimble filter with the cinnamoyl amide (20.0 mmol) in it. After the careful addition of water (2.88 g) and AcOEt (4 mL) to the suspension in an ice bath, anhyd Na_2SO_4 was added, and then filtrated. The organic layer was concentrated in vacuo to obtain phenylpropylamine (**5**), and was used for the following reaction without further purification.

^1H NMR δ: **5b** ($CDCl_3$); 1.71–1.97 (2H, m), 2.60–2.64 (2H, m), 2.70–2.74 (2H, m), 7.15 (1H, dd, J = 2.0, 8.3), 7.27 (1H, d, J = 2.0), 7.33 (1H, d, J = 8.3), **5c** ($CDCl_3$); 1.73–1.80 (2H, m), 2.31 (2H, s), 2.60–2.63 (2H, m), 2.69–2.75 (2H, m), 7.30 (2H, d, J = 8.3), 7.53 (2H, d, J = 8.3), **5d** (DMSO-d_6); 1.59–1.64 (2H, m), 2.50–2.54 (2H, m), 2.57–2.60 (2H, m), 7.22 (2H, d, J = 8.8), 7.31 (2H, d, J = 8.8), **5e** ($CDCl_3$); 1.76–1.82 (2H, m), 2.70–2.76 (4H, m), 7.37–7.46 (4H, m), **5f** ($CDCl_3$); 1.71–1.78(2H,m), 2.60–2.67 (2H, m), 2.70–2.75 (2H, m), 7.06 (2H, d, J = 8.3), 7.39 (2H, d, J = 8.3), **5g** ($CDCl_3$); 1.71–1.78 (2H, m), 2.63 (2H, t, J = 7.81), 2.72 (2H, t, J = 7.08), 6.96 (2H, ddd, J = 8.79, 1.96, 6.59), 7.13 (2H, dd, J = 8.79, 5.62).

General procedure for the preparation of 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazines (2a–2g)·HCl

A mixture of **4**·HCl (1.54 g, 4.5 mmol), phenylpropylamine (**5**) (9.0 mmol), NaI (1.35 g, 9.0 mmol), and anhyd K_2CO_3 (1.87 g, 13.5 mmol) in DMF (45 mL) was stirred for 13 h at 60°C. Water (50 mL) and AcOEt (100 mL) were added to the mixture in an ice bath. The organic layer was treated with water and saline, dried over anhyd Mg_2SO_4, and evaporated in vacuo to give a residue. The residue was then subjected to silica gel column chromatography ($CHCl_3$–EtOH) to give 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazine (**2a–2g**) free base. The product was transformed into HCl salt by adding 6 N HCl to the EtOH soln of the free base. HCl salt obtained was then subjected to recrystallization in EtOH. Yield (free base): **2a**; 77% (as HCl salt), **2b**; 84%, **2c**; 92%, **2d**; quant, **2e**; quant, **2f**; 89%, **2g**; 35%.

^1H NMR ($CDCl_3$) δ: **2a**; 2.19–2.27 (2H, m), 2.75 (2H, t, J = 7.3), 3.04 (2H, m), 3.16–3.20 (2H, m), 3.30 (2H, m), 3.51 (4H, d, J = 11.0), 3.86 (3H, s), 3.89 (3H, s), 4.04 (4H, m), 6.76–6.84 (3H, m), 7.15–7.17 (2H, m), 7.23–7.33 (3H, m), 13.65 (1H, br), 13.85 (1H, br). **2b**; 2.18–2.24 (2H, m), 2.71–2.75 (2H, m), 3.05–3.15 (2H, m), 3.18–3.20 (2H, m), 3.25–3.30 (2H, m), 3.52–3.54 (4H, m), 3.87 (3H, s), 3.89 (3H, s), 4.01–4.10 (4H, m), 6.76–6.84 (3H, m), 7.04 (1H, dd, J = 2.2, 8.1), 7.27 (1H, s). **2c**; 2.15–2.26 (2H, m), 2.68–2.83 (2H, m), 3.02–3.06 (2H, m), 3.16–3.20 (2H, m), 3.27–3.31 (2H, m), 3.48–3.54 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 4.00–4.08 (4H, m), 6.75–6.83 (3H, m), 7.04 (1H, d, J = 8.1), 7.12 (1H, d, J = 8.1), 7.31 (1H, d, J = 8.1), 7.58 (1H, d, J = 8.1). **2d**; 2.21 (2H, m), 2.73 (2H, m), 3.04 (2H, m), 3.18 (2H, m), 3.30 (2H, m), 3.51 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 4.04 (4H, m), 6.76 (1H, d, J = 5.8), 6.82 (2H, d, J = 8.8), 7.11 (2H, d, J = 8.8), 7.28 (2H, m). **2e**; 2.22–2.30 (2H, m), 2.80–2.84 (2H, m), 3.10–3.31 (6H, m), 3.55–3.57 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 4.07 (4H, m), 6.76–6.83 (3H, m), 7.38–7.53 (4H, m). **2f**; 2.21–2.23 (2H, m), 3.00–3.10 (2H, m), 3.28–3.31 (2H, m), 3.52–3.54 (4H, m), 4.00–4.15 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 6.76–6.83 (3H, m), 7.06 (2H, d, J = 8.3), 7.44 (2H, d, J = 8.3), 13.7 (2H, br). **2g**; 2.19–2.25 (2H, m), 2.73 (2H, t, J = 7.3), 3.05 (2H, br), 3.16–3.20 (2H, m), 3.31 (2H, br), 3.53–3.55 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 4.04 (4H, br), 6.76–6.78 (2H, m), 6.82 (1H, d, J = 8.8), 7.00 (2H, dd, J = 8.8, 8.8), 7.14 (2H, dd, J = 8.8, 5.1), 13.62 (1H, br), 13.78 (1H, br).

2a; mp (°C): 258–260 (dec). Anal. calcd for $C_{23}H_{32}N_2O_2 \cdot 2HCl$: C, 62.58; H, 7.76; N, 6.35. Found: C, 62.30; H, 8.00; N, 6.10. **2b**; mp (°C): 267 (dec). Anal. calcd for $C_{23}H_{30}Cl_2N_2O_2 \cdot 2HCl$: C, 54.13; H, 6.32; N, 5.49. Found: C, 54.00; H, 6.70; N, 5.20. **2c**; mp (°C):

261–265 (dec). Anal. calcd for $C_{24}H_{31}F_3N_2O_2 \cdot 1.25HCl \cdot 0.5EtOH$: C, 59.45; H, 7.03; N, 5.55. Found: C, 59.40; H, 7.30; N, 5.50. High-resolution FAB-MS *m/z* calcd, 437.2416; found, 437.2398. **2d**; mp (°C): 269 (dec). Anal. calcd for $C_{23}H_{31}ClN_2O_2 \cdot 2HCl$: C, 58.05; H, 6.99; N, 5.89. Found: C, 58.30; H, 7.10; N, 5.60. **2e**; mp (°C): 270 (dec). Anal. calcd for $C_{24}H_{31}F_3N_2O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 55.60; H, 6.61; N, 5.40. Found: C, 55.90; H, 6.50; N, 5.20. **2f**; mp (°C): 259–265 (dec). Anal. calcd for $C_{23}H_{31}BrN_2O_2 \cdot 1.75HCl$: C, 54.04; H, 6.46; N, 5.48. Found: C, 53.80; H, 6.70; N, 5.20, High-resolution FAB-MS *m/z* calcd, 447.1647; found 447.1636. **2g**; mp (°C): 263–268(dec). Anal. calcd for $C_{23}H_{31}FN_2O_2 \cdot 2HCl$: C, 60.13; H, 7.24; N, 6.10. Found: C, 59.90; H, 7.20; N, 5.80.

3-(4-benzyloxyphenyl)propylchloride (6). After the dropwise addition of $SOCl_2$ (2.6 g, 20.6 mmol) to a refluxing $CHCl_3$ (16 mL) solution of 3-(4-benzyloxyphenyl)propylalcohol[22] (2.0 g, 8.3 mmol), the mixture was kept refluxing for 2 h. The cooled mixture was quenched with some water and extracted with ether. The ether layer was washed with saline, and dried over anhyd $MgSO_4$. Concentration of the organic layer gave **6** (2.6 g, quant), and was used for the succeeding reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 1.92–1.99 (2H, m), 2.63–2.68 (2H, m), 3.89–3.95 (2H, m), 5.02 (2H, s), 6.90 (2H, d, *J* = 8.3 Hz), 7.09 (2H, d, *J* = 8.3 Hz), 7.31–7.44 (5H, m).

1-[3-(4-benzyloxyphenyl)propyl]-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine (2h)·HCl. The mixture of 1-(3,4-dimethoxyphenethyl)piperazine[23] (1.3 g, 5.2 mmol), **6** (2.0 g, 7.7 mmol), NaI (1.4 g, 9.2 mmol) and K_2CO_3 (1.4 g, 10.2 mmol) in DMF (15 mL) was stirred for 30 min at 100°C. The mixture was cooled, water was added, and then the mixture extracted with ether. The organic layer was worked up with saline, dried over anhyd Mg_2SO_4 and evaporated to give residue. The residue was applied on a silica gel column ($CHCl_3$–MeOH) and afforded 1.13 g (47%) of **2h**. The product was converted into HCl salt by adding HCl (3 N)–MeOH to a solution of **2h** and EtOH, and recrystallized in EtOH. ^{1}H NMR ($CDCl_3$) δ: 2.10–2.20 (2H, m), 2.68–2.71 (2H, m), 2.95–3.05 (2H, m), 3.15–3.20 (2H, m), 3.21–3.30 (2H, m), 3.50–3.60 (4H, m), 4.00–4.18 (4H, m), 3.86 (3H, s), 3.89 (3H, s), 5.05 (2H, s), 6.77–6.84 (3H, m), 6.92 (2H, d, *J* = 8.8 Hz), 7.07 (2H, d, *J* = 8.8 Hz), 7.32–7.45 (5H, m), mp (°C) 245–251 (dec). Anal. calcd for $C_{30}H_{38}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 64.74; H, 7.43; N, 5.03. Found: C, 64.60; H, 7.50; N, 4.70.

1-[2-(3,4-dimethoxyphenyl)ethyl]-4-[3-(4-hydroxyphenyl)-propyl]piperazine (2i)·HCl. The suspension of **2h**·HCl (150 mg, 0.27 mmol) and 5% Pd/C (150 mg) in a mixed solution of MeOH (1 mL), AcOH (1 mL), and water (1 mL) was stirred with H_2 gas bubbling in it for 20 h. The mixture was then made ca. pH 13 by the careful addition of satd $NaHCO_3$ aq soln, and filtrated through super-hyflo-cel. Concentration of the filtrate under reduced pressure gave 93.2 mg (89%) (**2i**) of amorphous solid. The solid (80 mg) was converted into HCl salt in MeOH, and then recrystallized in EtOH to give 61 mg (77%) of **2i**·2HCl. ^{1}H NMR ($CDCl_3$) δ: 1.90–2.00 (2H, m), 2.95–3.00 (2H, m), 3.05–3.15 (2H, m), 3.25–3.70 (12H, m), 3.72 (3H, s), 3.75 (3H, s), 6.69 (2H, d, *J* = 8.1 Hz), 6.78 (1H, d, *J* = 8.1 Hz), 6.89 (1H, d, *J* = 8.1 Hz), 6.90 (1H, s), 7.02 (2H, d, *J* = 8.1 Hz), 9.21 (1H, br), 11.7 (1H, br), 11.9 (1H, br), mp (°C) 215–222. Anal. calcd for $C_{23}H_{32}N_2O_3 \cdot 2HCl \cdot H_2O$: C, 58.10; H, 7.63; N, 5.89. Found: C, 58.00; H, 7.70; N, 5.50.

X-ray analysis

Colorless crystals of **2a** and **2b** as HCl salt both obtained from aq MeCN soln under MeCN milieu were used for X-ray measurements at 293 K (Rigaku AFC diffractometer equipped with a graphite monochrometer). Reflection data were collected by an ω-2θ scan technique. Corrections were applied for Lorentz and polarization effects. The structures were solved by direct methods with use of the program SAYTAN.[24] Non-H atoms were refined by using the full-matrix least-square method with anisotropic temperature factors,[26] and hydrogen atoms were ideally calculated and included only in the calculations of structure factors. Crystal data: **2a**, $C_{23}H_{32}N_2O_2 \cdot 2HCl$, F.W. = 441.44, orthorhombic, space group *Pna2*$_1$, *a* = 36.067 (2) Å, *b* = 7.317 (2) Å, *c* = 8.794 (2) Å, α = β = γ = 90°, *V* = 2320.8 (7) Å^3, *Z* = 4, D_{calcd} = 1.263 g/cm^3; **2b**, $C_{23}H_{30}N_2O_2Cl_2 \cdot 2HCl$, F.W. = 510.33, monoclinic, space group *Cc*, *a* = 39.508 (3) Å, *b* = 8.915 (2) Å, *c* = 7.278 (3) Å, α = γ = 90.00°, β = 93.13 (2)°, *V* = 2559.9 (9) Å^3, *Z* = 4, D_{calcd} = 1.324 g/cm^3. Summaries of data collection, data reduction, and refinement are shown in Table 4.

Binding activity

Binding activities to σ_1 and σ_2 receptors were measured as reported elsewhere[7a] with the use of (+)-[^{3}H]-pentazocine and 1,3-[^{3}H]-ditolylguanidine in the presence of (+)-[^{3}H]-pentazocine, respectively.

Molecular orbital calculations

Initial coordinates were obtained from the molecules found in crystals. As a possible starting structure, the Phe(A) group rotation (180°) that controls the position of R_1, or the orientation of R_2, was also taken into account for **2b**, **2e**, **2i**, and **2h**. The phenyl part of the benzyl group in **2h** was placed in the plane of the Phe(A). Semiempirical PM3[26] calculations were done on the free bases with MOPAC (ver. 6) through QUANTA[18] interface on IRIS Indigo/Elan. All the coordinates were optimized within PM3. The structures obtained after the optimization did not show remarkable changes from those of any of the starting molecules.

Table 4. Crystallographic details

	2a·2HCl	**2b·2HCl**
Formula	$C_{23}H_{32}N_2O_2 \cdot 2HCl$	$C_{23}H_{30}N_2O_2Cl_2 \cdot 2HCl$
M_r	441.44	510.33
Crystal system	Orthorhombic	Monoclinic
Space group	$Pna2_1$	Cc
Cell constant		
a (Å)	36.067(2)	39.508(3)
b (Å)	7.317(2)	8.915(2)
c (Å)	8.794(2)	7.278(3)
α (°)	90.00	90.00
β (°)	90.00	93.13(2)
γ (°)	90.00	90.00
Volume (Å^3)	2320.8(7)	2559.9(9)
Z	4	4
Dx (g/cm^3)	1.263	1.324
μ (Cu-Kα) (/cm)	27.12	44.68
F (000)	944	1072
Crystal size (mm^3)	1.0 × 0.3 × 1.2	0.3 × 0.1 × 1.0
Temperature of data collection (°C)	20	20
Data collection method	ω-2θ scan	ω-2θ scan
Scan speed in 2θ (deg/min)	12	12
Scan range in ω (deg)	1.575 + 0.15 tan θ	1.52 + 0.15 tan θ
Data range measured (deg)	3≤2θ≤130	2≤2θ≤130
Data collected	h, k, −l	±h, k, −l
No. of unique data measured	1962	2020
No. of data with $F_0>3\sigma$ (F_0)	1892	1829
No. of variables	293	306
Goodness of fit	1.906	1.748
R_F	0.078	0.065
R_{wF}	0.120	0.088

References

1. (a) Roman, F.; Pascaud, X.; Vauché, D.; Junien, J. L. *Life Sciences*, **1988**, *42*, 2217. (b) Roman, F.; Pascaud, X.; Chomette, G.; Bueno, L.; Junien, J. L. *Gastroenterology*, **1989**, *97*, 76. (c) Roman, F. J.; Pascaud, X.; Salmon, R.; Chomette, G.; Junien, J. L. *Gastroenterology*, **1991**, *100*, A662.

2. (a) Wolfe, S. A. Jr.; De Souza, E. B. In *Sigma Receptors*; Itzhak, Y., Ed.; Academic: London, 1994; pp 287. (b) Carr, D. J. J.; Costa, B. R. D.; Radesca, L.; Blalock, J. E. *J. Neuroimmunol.* **1991**, *35*, 153.

3. Jansen, K. L. R.; Faull, R. L. M.; Dragunow, M.; Leslie, R. A. *Brain Res.* **1991**, *559*, 172.

4. Jansen, K. L. R.; Faull, R. L. M.; Storey, P.; Leslie, R. A. *Brain Res.* **1993**, *623*, 299.

5. (a) Largent, B. L.; Winkström, H.; Snowman, A. M.; Snyder, S. H. *Eur. J. Pharmacol.* **1987**, *155*, 345. (b) Snyder, S. H.; Largent, B. L. *J. Neuropsychiatry* **1989**, *1*, 7.

6. Matsuno, K.; Nakazawa, M.; Okamoto, K.; Kawashima, Y.; Mita, S. *Eur. J. Pharmacol.* **1996**, *306*, 271.

7. Kobayashi, T.; Matsuno, K.; Nakata, K.; Mita, S. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 106.

8. Shiozawa, A.; Ichikawa, Y.; Komuro, C.; Idzu, G.; Ishikawa, M.; Kurashige, S.; Miyazaki, H.; Yamanaka, H.; Sakamoto, T. *Chem. Pharm. Bull.* **1984**, *32*, 553.

9. Danso-Danquah, R.; Bai, X.; Zhang, X.; Mascarella, S. W.; Williams, W.; Sine, B.; Bowen, W. D.; Caroll, F. I. *J. Med. Chem.* **1995**, *38*, 2978.

10. Glennon, R. A.; Ismaiel, A. M.; Smith, J. D.; Yousif, M.; El-Ashmawy, M. B.; Herndon, J. L.; Fisher, J. B.; Howie, K. B.; Server, A. C. *J. Med. Chem.* **1991**, *34*, 1855.

11. Zhang, Y; Williams, W.; Bowen, W. D.; Rice, C. *J. Med. Chem.* **1996**, *39*, 3564.

12. He, X.-s.; Bowen, W. D.; Lee, K. S.; Williams, W.; Weinberger, D. R.; de Costa, B. R. *J. Med. Chem.* **1993**, *36*, 566.

13. (a) Swain, C. G.; Lupton, E. C. Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. (c) Hansch, C.; Rockwell, S. D.; Jow, P. Y. C.; Leo, A.; Steller, E. E. *J. Med. Chem.* **1977**, *20*, 304.

14. The magnitude of the estimated R value (−0. 81) may be a little larger than that expected from another report.[15] However, even with the R value of −0.6, a good correlation (r = 0. 977) was obtained and thus supports this trend.

15. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.*, **1991**, *91*, 165.

16. Hansch, C.; Leo, A. In *Exploring QSAR (Fundamentals and Applications in Chemistry and Biology)*; Heller, S. R., Ed.; American Chemical Society: Washington D.C., 1995; p 14.

17. (a) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Japan* **1966**, *39*, 2274. (b) Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Japan* **1972**, *45*, 1198. (c) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Japan* **1959**, *32*, 965. (d) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Japan* **1959**, *32*, 971.

18. Molecular Simulations, 9685 Scranton Road, San Diego, CA 92121-3752, U.S.A.

19. (a) Gilligan, P. J.; Cain, G. A.; Christos, T. E.; Cook, L.; Drummond, S.; Johnson, A. L.; Kergaye, A. A.; McElroy, J. F.; Rohrbach, K. W.; Schmidt, W. K.; Tam, S. W. *J. Med. Chem.* **1992**, *35*, 4344. (b) Glennon, R. A.; Ablordeppy, S. Y.;

Ismaiel, A. M.; El-Ashmawy, M. B.; Fisher, J. B.; Howie, K. B. *J. Med. Chem.* **1994**, *37*, 1214.

20. Abraham, D. J.; In *Computer-Aided Drug Design, Methods and Applications*; Perun, T. J; Propst, C. L., Eds; Marcel Dekker: New York, 1989; p 104.

21. (a) Sotomatsu, T.; Murata, Y.; Fujita, T. *J. Comput. Chem.* **1989**, *10*, 94. (b) Kim, K. H.; Martin, Y. C. *J. Org. Chem.* **1991**, *56*, 2723.

22. (a) Herbert, R. B.; Kattah, A. E. *Tetrahedron* **1990**, *20*, 7105. (b) Ronald, R. C.; Wheeler, C. J. *J. Org. Chem.* **1984**, *49*, 1685.

23. Shiozawa, A.; Ichikawa, Y.; Komuro, C.; Idzu, G.; Ishikawa, M.; Kurashige, S.; Miyazaki, H.; Yamanaka, H.; Sakamoto, T. *Chem. Pharm. Bull.* **1984**, *32*, 553.

24. Debaerdemaeker, T.; Germain, G.; Main, P.; Tate, C.; Wollfson, M. M. A System of Computer Programs for the Atomic Solution of Crystal Structure from X-Ray Diffraction Data; University of York, U.K., Louvain, Belgium, 1987.

25. The Universal Crystallographic Computing System—Osaka; The Computation Center, Osaka University, Japan, 1979.

26. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.

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