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New Potent Neuroleptic Drugs of Benzamide Derivatives. I. Crystal and Molecular Structure of *N*-[(2*RS*, 3*RS*)-1-Benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide

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The crystal and molecular structure of the title compound has been determined by the X-ray diffraction method. The crystal is monoclinic, space group $P2_1/c$, $a=11.694(1)$ Å, $b=12.117(1)$ Å, $c=14.482(1)$ Å, $\beta=100.01(1)°$, and $Z=4$. The structure was solved by the direct method and refined by a block-diagonal least-squares procedure to a final R value of 0.082. An intramolecular hydrogen bond between the amide nitrogen and the methoxyl oxygen atoms forms a new six-membered ring fused with the benzene ring. Structural features are discussed in relation to neuroleptic activity.

Typical neuroleptic drugs are classified into five major types by their parent molecules, benzamide, butyrophenone, phenothiazine, benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline and pyrido[4,3-*b*]indole. These are antagonists to dopamine receptors located on synaptic membranes.[1] The molecular mechanisms for dopamine antagonists have not been completely established yet, though many studies on the structure-activity relationships and conformational requirements for neuroleptic drugs have been reported.[2–11]

The title compound, *N*-[(2*RS*,3*RS*)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide (YM-09151-2), is a potent dopamine antagonist** (Fig. 1), and in the present paper we described its three-dimensional crystal structure and discuss on its structural features in relation to neuroleptic activity.

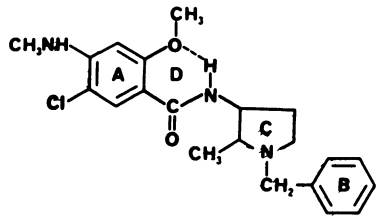


Fig. 1. Schematic structure of *N*-[(2*RS*, 3*RS*)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide and the notation of each ring.

Experimental and Structure Determination

The title compound was prepared by the reaction of 5-chloro-2-methoxy-4-methylaminobenzoic acid with (2*RS*,3*RS*)-3-amino-1-benzyl-2-methylpyrrolidine as described in the previous paper.[13] It was recrystallized from acetone solution to give colorless plate crystals.

Preliminary Weissenberg photographs indicated a monoclinic space group $P2_1/c$. A crystal, $0.6\times0.3\times0.4$ mm in size, was used for data collection on a Rigaku automated four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation ($\lambda=0.71073$ Å). Accurate unit-cell constants were determined using 40 high angle reflections of the angular range of $20°<2\theta<30°$. Density was measured by flotation in a mixture of benzene and carbon tetrachloride. The crystal data were summarized in Table 1.

Table 1. Crystal data

N-[(2*RS*,3*RS*)-1-Benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide	
$C_{21}H_{26}ClN_3O_2$	
M.W.=387.91	
Crystal system : Monoclinic	
Spase group : $P2_1/c$	
a/Å=11.694(1)	U/Å^3=2020.8(4)
b/Å=12.117(1)	Z=4
c/Å=14.482(1)	D_x/g cm^{-3}=1.275
β/°=100.01(1)	D_m/g cm^{-3}=1.27

A complete set of independent reflections was collected within the angular range of $2°\leqq2\theta\leqq50°$ in the θ-2θ scan mode at scanning rate of 4° (2θ) min^{-1}. Stationary background counts were accumulated for 10 s before and after each scan. Five reference reflections showed no significant intensity deterioration throughout the data collection. A total of 3548 independent reflections were measured, of which 796 weak reflections below background were considered zero-reflections; the observational threshold value, $F_{\rm lim}$, was 2.12. The intensities were corrected for Lorentz and polarization factors, but not for absorption and secondary extinction. The standard deviations were estimated by the equation of $\sigma^2(F_o)=\sigma_P{}^2\times(F_o)+qF_o{}^2$, where $\sigma_P(F_o)$ was evaluated by counting statisitcs and $q(3.64\times10^{-5})$ was derived from the variations of monitored reflections.[14]

The structure was solved by the direct method. The refinement of the structure was carried out by block-diagonal least-squares calculations. All the hydrogen atoms found on a difference map were included. The quantity minimized was

** The affinity for the present molecule, as determined by [^3H]spiperone binding to the synaptic membrane obtained from canine caudate nucleus, exceeds apparently that for haloperidol by a factor of about 3 and that for chloropromazine by a factor of about 30.[12]

TABLE 2. FRACTIONAL COORDINATES AND ISOTROPIC TEMPERATURE FACTORS

The B values accompanied with $\langle\ \rangle$ are the equivalent isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B=8\pi^2(U_1+U_2+U_3)/3$, where U_1, U_2, and U_3 are principal components of the mean square displacement matrix $\boldsymbol{U}$. Values in $\langle\ \rangle$ are anisotropicity defined by $(\sum(B-8\pi^2U_i)^2/3)^{1/2}$. The e.s.d.'s in ( ) refer to last decimal places.

Atom	x	y	z	B/Å^2
Cl	−0.11376(7)	0.16625(8)	0.27342(6)	6.21⟨302⟩
O(1)	0.2810(2)	0.3404(2)	0.1185(1)	4.32⟨171⟩
O(2)	0.2259(2)	0.4314(2)	0.3858(1)	4.8⟨16⟩
N(1)	−0.0712(2)	0.1259(2)	0.0813(1)	5.2⟨24⟩
N(2)	0.3390(2)	0.4577(2)	0.2766(2)	5.2⟨28⟩
N(3)	0.5796(2)	0.4913(2)	0.2690(1)	3.9⟨3⟩
C(1)	0.0097(2)	0.1916(2)	0.1331(2)	3.8⟨7⟩
C(2)	0.0016(2)	0.2190(2)	0.2256(2)	4.0⟨9⟩
C(3)	0.0803(2)	0.2870(2)	0.2774(2)	3.9⟨11⟩
C(4)	0.1745(2)	0.3325(2)	0.2436(2)	3.3⟨4⟩
C(5)	0.1856(2)	0.3021(2)	0.1520(2)	3.4⟨4⟩
C(6)	0.1048(2)	0.2349(2)	0.0986(2)	3.7⟨9⟩
C(7)	−0.0836(3)	0.1143(3)	−0.0192(2)	6.1⟨23⟩
C(8)	0.2990(3)	0.3060(3)	0.0271(2)	5.1⟨19⟩
C(9)	0.2492(2)	0.4095(2)	0.3077(2)	4.0⟨6⟩
C(10)	0.4190(3)	0.5374(3)	0.3301(2)	5.5⟨20⟩
C(11)	0.5370(3)	0.4871(3)	0.3574(2)	5.1⟨19⟩
C)12)	0.5395(3)	0.3720(3)	0.3998(2)	5.6⟨15⟩
C(13)	0.5559(3)	0.6042(3)	0.2343(2)	6.1⟨10⟩
C(14)	0.4399(3)	0.6365(3)	0.2686(2)	5.7⟨17⟩
C(15)	0,7018(3)	0.4599(3)	0.2734(2)	5.7⟨19⟩
C(16)	0.7337(2)	0.4512(3)	0.1765(2)	5.0⟨9⟩
C(17)	0.6555(3)	0.4143(3)	0.1011(2)	6.3⟨20⟩
C(18)	0.6909(4)	0.3965(3)	0.0164(2)	8.1⟨34⟩
C(19)	0,8040(4)	0.4155(3)	0.0078(3)	9.5⟨54⟩
C(20)	0.8805(3)	0.4539(4)	0.0827(3)	8.6⟨39⟩
C(21)	0.8457(3)	0.4734(3)	0.1669(2)	6.3⟨14⟩
H(1)	0.075(2)	0.308(2)	0.338(1)	0.9(5)
H(2)	0.116(2)	0.215(2)	0.040(1)	1.0(5)
H(3)	−0.125(2)	0.096(2)	0.109(2)	2.5(7)
H(4)	−0.106(2)	0.189(3)	−0.051(2)	4.3(9)
H(5)	−0.147(3)	0.064(3)	−0.041(2)	4.3(10)
H(6)	−0.016(3)	0.090(3)	−0.041(2)	3.6(9)
H(7)	0.377(2)	0.338(3)	0.024(2)	3.7(9)
H(8)	0.238(2)	0.334(2)	−0.022(2)	2.8(7)
H(9)	0.302(2)	0.223(2)	0.026(1)	2.7(6)
H(10)	0.359(2)	0.429(3)	0.225(2)	3.8(9)
H(11)	0.379(2)	0.556(3)	0.388(2)	3.9(9)
H(12)	0,583(2)	0.543(3)	0.407(2)	1.7(9)
H(13)	0.617(2)	0.355(3)	0.425(2)	7.4(9)
H(14)	0.499(3)	0.324(3)	0.355(2)	3.4(10)
H(15)	0.491(2)	0.378(2)	0.447(2)	6.7(8)
H(16)	0.558(2)	0.606(2)	0.161(2)	6.4(6)
H(17)	0.636(2)	0.650(2)	0.257(2)	6.4(7)
H(18)	0.451(2)	0.704(2)	0.308(2)	6.2(7)
H(19)	0.373(2)	0.643(2)	0.214(2)	6.7(6)
H(20)	0.751(2)	0.521(2)	0.314(2)	4.2(6)
H(21)	0.682(2)	0.388(2)	0.325(2)	7.4(7)
H(22)	0.576(2)	0.402(2)	0.110(2)	3.1(7)
H(23)	0.633(2)	0.368(2)	−0.033(2)	6.9(7)
H(24)	0.829(2)	0.412(3)	−0.053(2)	8.3(10)
H(25)	0.962(2)	0.473(2)	0.079(2)	6.9(7)
H(26)	0.903(2)	0.495(3)	0.220(2)	5.8(9)

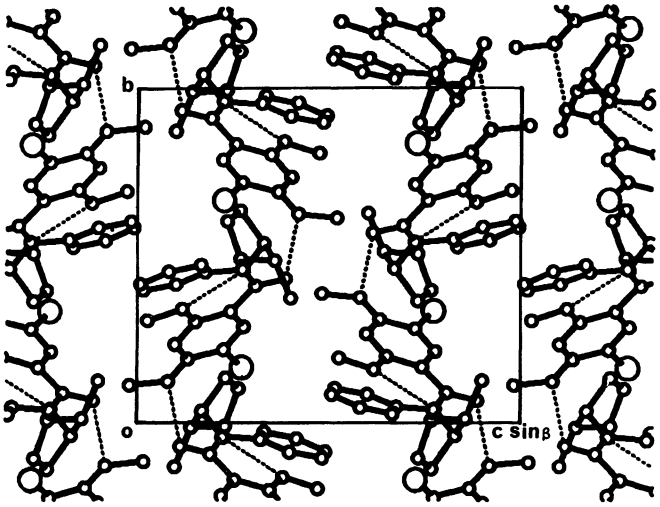


Fig. 2. Crystal structure of *N*-[(2*RS*, 3*RS*)-1-Benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide projected along the a axis, and drawn by TSD:XTAL.[24]

$\sum w(|F_o|-|F_c|)^2$, with $w=1/\sigma^2(F_o)$. In the refinemetn procedure, the zero-reflections were assumed to be $F_o=F_{lim}$, but those for which $|F_c|<F_{lim}$ were omitted. The final R was 0.082; the maximum shifts of parameters in the last cycle were 0.3 σ for C, 0.2 σ for N, 0.07 σ for O, 0.01 σ for Cl and 0.9 σ for H atoms. Atomic scattering factors used were taken from "International Tables for X-Ray Crystallography."[15] Atomic parameters are listed in Table 2.[16]

Results and Discussion

Crystal Structure. The crystal structure is shown in Fig. 2. An intermolecular hydrogen bond is observed between the amino nitrogen N(1) and the carbonyl oxygen O(2) in the molecule related by screw, the N(1)-O(2) distance being 3.059 Å. The other intermolecular contacts are all larger than the sum of the van der Waals radii. The molecules are arranged to form columns along the screw axis by mediating the intermolecular hydrogen bond system. Benzamide moieties are inner part of the column, whereas pyrrolidine rings and benzyl groups are protruded from it and dove-tailed with those of adjacent one. Thus the molecules have some mobility in the latter two parts, as indicated by rather large temperature factors.

Molecular Structure. The stereoscopic view of the molecule is shown in Fig. 3. The bond lengths and bond angles are shown in Fig. 4 together with numbering system. The lengths C(2)–C(3) and C(5)–C(6) are short in comparison with the other lengths in the ring, whereas angles C(2)–C(1)–C(6) and C(3)–C(4)–C(5) are somewhat small. Moreover, the lengths C(1)–N(1) and C(4)–C(9) are short. These results indicate that the molecule has the contribution of the quinonoidal form shown in Fig. 5. This should be related to the hydrogen bond between N(1) and O(2) as mentioned above. The benzene ring A is almost planar with maximum atomic deviation of 0.013 Å.[16] The *N*-methylamino, methoxyl, and carbamoyl groups attached to this ring also lie on the plane. Torsion angles in

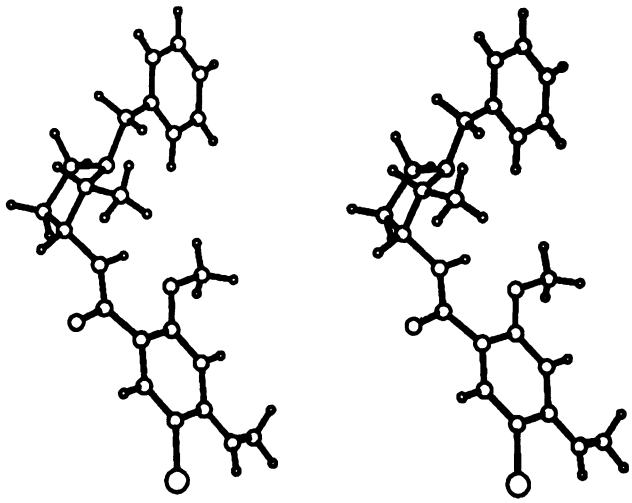


Fig. 3. Stereoscopic view of *N*-[(2*RS*, 3*RS*)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide, drawn by TSD: XTAL.[24]

benzamide moiety are listed in Table 3.

An intramolecular hydrogen bond between the amide N(2) and the methoxyl O(1) (Fig. 6) forms a new six-membered ring (hereafter called as ring D) fused with the benzene ring A. This type of hydrogen bond is also observed in the benzamide neuroleptics such as metoclopramide[17] and sulpiride.[18] The N(2)–O(1) distance, 2.680 Å, is almost the same as that of metoclopramide, 2.683 Å.[17] The rings A and D are almost coplanar (the dihedral angle between them being 3.8°), and constitute a rigid part of this molecule.

The bond lengths and angles of the pyrrolidine ring do not differ significantly from those reported for the other related compound.[19] This ring has an intermediate conformation between the envelope and half-chair forms (deviations from the mean plane are −0.224, 0.326, −0.159, 0.177, and 0.039 Å for C(10), C(11), N(3), C(13), and C(14) atoms, respectively); the value of pseudorotation phase angle P is −9.85° (for the

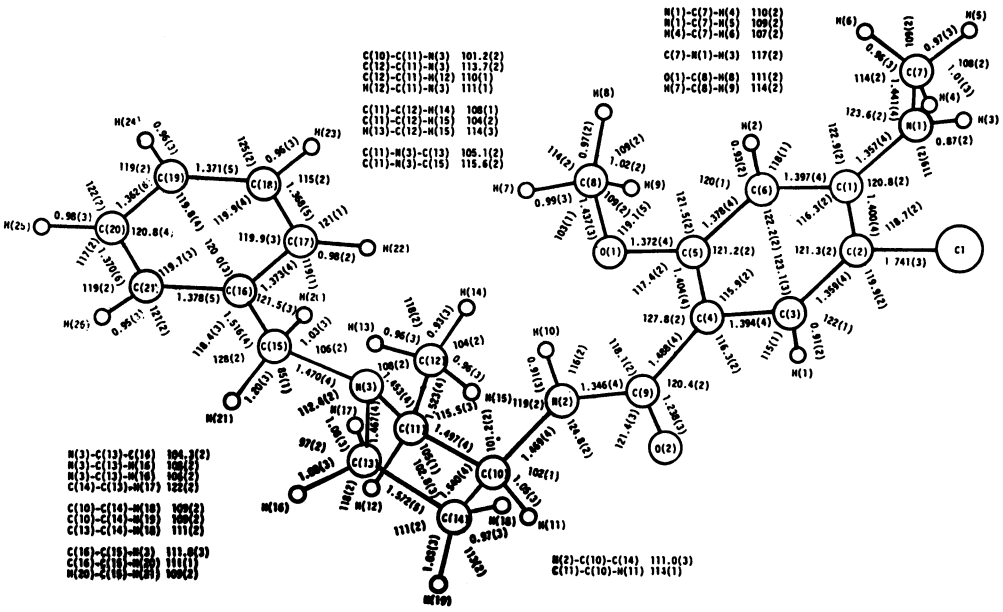


Fig. 4. Atomic numbering of *N*-[(2*RS*, 3*RS*)-1-benzyl-2-methyl-3pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide with bond lengths (l/Å) and angles (ϕ/°). Standard deviations are in parentheses.

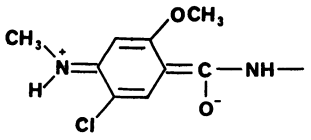
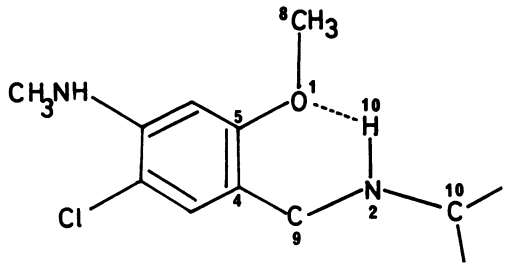


Fig. 5. Quinonoidal form of the benzamide moiety.

envelope conformation P is 18° or −18°, while for a half-chair P=0°).[20] Torsion angles of this ring are also given in Table 3. The methyl group and the acylamino group attached to this ring are in the same side about the least-squares plane of the ring, the internal rotation angle of these two groups around the C(10)–C(11) bond being 47.4° as shown in Fig. 7. On the other hand, the relative orientation of the methyl group and benzyl group is *trans*, to relax their steric repulsions. As a result, the molecule takes a rather folded conformation; the nitrogen lone pair lobe is buried by the methyl, methoxyl, and benzyl groups.



N(2)——H(10)	0.909(25)Å
N(2)------O(1)	2.680(3) Å
H(10)-----O(1)	1.945(25)Å
N(2)-H(10)-O(1)	137(2)°
C(9)-N(2)-H(10)	116(2)°
C(9)-N(2)-O(1)	87.7(2)°
C(10)-N(2)-H(10)	119(2)°
C(10)-N(2)-O(1)	147.5(2)°
C(5)-O(1)-N(2)	88.8(2)°
C(5)-O(1)-H(10)	101.7(8)°
C(8)-O(1)-N(2)	152.2(2)°
C(8)-O(1)-H(10)	139.2(8)°

Fig. 6. Intramolecular hydrogen bond.

TABLE 3. TORSION ANGLES ϕ/°

C(8)–O(1)–C(5)–C(4)	176.4(2)	C(10)–C(14)–C(13)–N(3)	6.0(3)
C(8)–O(1)–C(5)–C(6)	357.5(4)	N(2)–C(10)–C(11)–C(12)	312.5(3)
C(7)–N(1)–C(1)–C(2)	345.3(3)	C(14)–C(10)–C(11)–C(12)	193.8(3)
C(7)–N(1)–C(1)–C(6)	165.7(4)	C(13)–N(3)–C(11)–C(12)	172.7(3)
C(3)–C(4)–C(9)–N(2)	181.9(2)	C(11)–N(3)–C(13)–C(14)	326.5(3)
C(5)–C(4)–C(9)–N(2)	0.2(4)	C(13)–C(14)–C(10)–C(11)	22.3(3)
C(4)–C(9)–N(2)–C(10)	174.8(4)	C(14)–C(10)–C(11)–N(3)	317.0(3)
C(9)–N(2)–C(10)–C(11)	111.1(3)	C(14)–C(13)–N(3)–C(15)	200.0(2)
C(9)–N(2)–C(10)–C(14)	225.3(3)	C(15)–N(3)–C(11)–C(12)	297.1(3)
N(2)–C(10)–C(11)–N(3)	75.7(3)	C(11)–N(3)–C(15)–C(16)	172.0(2)
N(2)–C(10)–C(14)–C(13)	264.1(3)	C(13)–N(3)–C)15)–C(16)	292.7(3)
C(10)–C(11)–N(3)–C(13)	48.3(3)	N(3)–C(15)–C(16)–C(17)	325.6(4)
C(10)–C(11)–N(3)–C(15)	172.7(2)	N(3)–C(15)–C(16)–C(21)	150.3(3)

The torsion angle A–X–Y–B is the dihedral angle between planes AXY and XYB, measured clockwise when viewed down the bond X–Y.

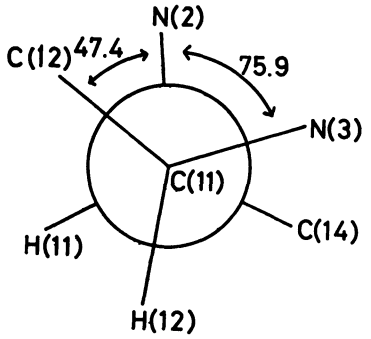


Fig. 7. Internal rotation angle along the C(10)–C(11) bond.

Bond angles in the benzene ring B are all close to 120°, but bond lengths are relatively shorter than 1.395 Å, probably due to the large thermal motions. This ring is almost planar with maximum atomic deviation of 0.014 Å.[16] The dihedral angle between this ring and the benzene ring A is 19.5°, so that these are nearly parallel. Relevant torsion angles are listed in Table 3.

Structure-activity Relationships. Every active neuroleptics ever known has at least a tertiary amino nitrogen atom and benzene or isosteric aromatic ring, and belong to one of the nine general structures classified by Janssen.[21] The present compound belongs to the class of the benzamide neuroleptic molecules with a common partial structure of the type A–C–N–C–C–N– (A= benzene or isosteric aromatic ring). Moreover, the present study reveals that this compound can also belong to another class with the type AA'–C–C–N– (AA'= indole or an isosteric aromatic fused ring structure), if the rings A and D are assumed to form an isosteric aromatic fused ring structure.

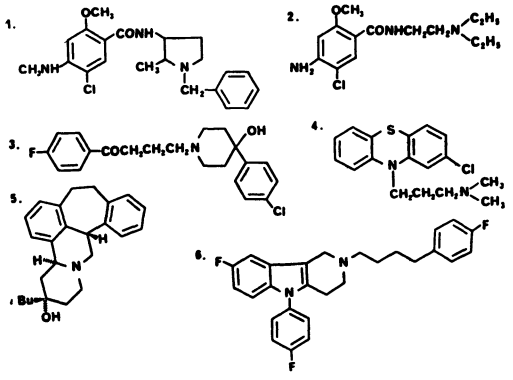
Geometrical parameters to express the relative arrangement of the benzene ring and the tertiary amino nitrogen atom have been used in the study of structure of neuroleptic drugs; the first is the distance, *l*, between the nitrogen atom and the center of the benzene ring, and the second is the deviation, *d*, of the nitrogen atom from the mean plane of the benzene ring.[8] Table 4 lists these parameters for the present molecule together with other typical neuroleptics. The distance, *l*, of the present molecule is almost the same as that of metoclopramide[17] and also compatible of those of the other classes of the neuroleptics. Moreover, the deviation, *d*, of the present molecule agrees with the values of the other neuroleptics except for chlorpromazine hydrochloride (for the active conformer of (+)-butaclamol,[8] see a foot-note of Table 4).

In addition to these two parameters, however, one more structural aspect should be taken into account. The tertiary amino nitrogen atom, common to all neuroleptic molecules should play an important role to be recognized by and interact with receptors. Since the nitrogen atom of the present molecule seemed to be buried, we calculated the accessible surface area of it.[23] The calculated area is zero. It suggests that the nitrogen lone pair lobe is unfavorable to interact with them and the present conformation may be different from that under the binding condition. A probable active conformer could be obtained by changing the pyrrolidine ring conformation so as to expose the nitrogen atom with retaining the two geometrical parameters.

Table 4. Geometrical parameters for typical dopamine antagonists

Compound	Type	Distance *l*/Å	Deviation *d*/Å	Reference
1. YM-09151-2	Benzamide	6.26	0.9	This work
2. Metoclopramide	Benzamide	6.3	1.6	Ref. 16
3. Haloperidol	Butyrophenone	7.3	1.4	Ref. 7
4. Chlorpromazine	Phenothiazine			
Base		5.12	1.5	Ref. 4
HCl		6.70	3.7	Ref. 4
5. (+)-Butaclamol	Benzo[6,7]cyclohepta[1,2,3-*de*]pyrido-[2,1-*a*]isoquinoline	5.1	0.19 (0.9)[a]	Ref. 8
6. Flutroline	Pyrido[4,3-*b*]indole	5.12	0.6	Ref. 22

a) By model building, the authors obtained an active conformer, in which the *d*-value was 0.9 Å.



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