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Structure-activity relationships for apomorphine congeners. Conformational energies vs. biological activities

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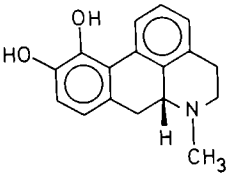
SUMMARY

A series of apomorphine congeners has been studied with respect to their ability to mimic the structural requirements of the dopamine pharmacophore in the potent and stereoselective dopamine receptor agonist (*R*)-apomorphine. Conformational energies of the mimicking structures calculated by molecular mechanics (MMP2) correlate well with the observed biological activities.

INTRODUCTION

Apomorphine (**1**) is one of the most important and most extensively studied dopamine (**2**) analogues. It is a very potent dopamine receptor agonist showing a high degree of stereospecificity. It has been shown that its agonist activity is exclusively confined to the 6a*R*-enantiomer [1]. The rigid structure of **1** [2], along with its high potency and stereoselectivity, has led to the conclusion that an apomorphine-like spatial relationship between the catechol ring, the nitrogen atom and the nitrogen lone pair (or hydrogen if the protonated form is considered) is required for dopamine agonist activity [3].



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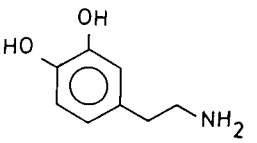

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Several structurally simplified apomorphine congeners have been prepared and tested for dopamine agonist activity in order to gain information about the structural requirements for the stimulation of dopamine receptors. Most of these congeners have been found to be of low activity or to be inactive as dopamine receptor agonists. However, in some cases moderate or even high dopaminergic activity has been observed. The apomorphine congeners discussed in the present work are shown in Fig. 1.

These congeners are in most cases ring-cleavage derivatives of **1**, and are generally much more flexible than compound **1** itself. The preferred conformations of these compounds are thus not necessarily apomorphine-like with respect to the dopamine pharmacophore (the catechol ring, the nitrogen atom and the nitrogen lone pair (or NH bond)). However, such a similarity of the lowest energy conformers of the free (non-receptor bound) molecule is not a requirement for apomorphine-like activity, provided that the molecule can adopt a conformation which has sufficiently low energy (high probability) and which has the 'correct' spatial relationships among the elements of the pharmacophore. On the other hand, if a high energy is required for a compound to attain 'correct' spatial relationships, as defined by the apomorphine structure, this should lead to a low activity.

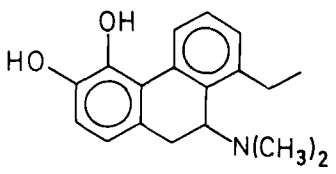
Our hypothesis is that the conformational energies required for compounds **3–14** to structurally mimic the dopamine part of apomorphine (**1**) are related to their activity as dopamine receptor agonists.

To investigate this hypothesis we performed extensive conformational analyses of these compounds employing molecular mechanics calculations (MMP2). Structures of compounds **3–14** that mimic the dopamine part of **1** have been constructed using high-performance interactive molecular graphics and least-squares molecular superimpositions.

COMPUTATIONAL METHODS

The energy-minimized structures and conformational energies were calculated using the molecular mechanics program MMP2 developed by Allinger and co-workers [4]. Input structures for MMP2 were constructed using the molecular modeling program MIMIC [5,6]. Extensive conformational analysis employing a large number of trial input structures was carried out for each compound in the search for the global energy minimum.

Comparisons of molecular structures and searches for an optimal fit between apomorphine (**1**) and possible mimicking conformations of congeners **3–14** were done using the program system SYBYL [7] on a VAX 11/750 computer and an Evans & Sutherland PS330 display system. The following atoms or points were used in the molecular least-squares fitting: (i) the center of the catechol ring; (ii) the catechol oxygens; and (iii) a point at a distance of 2.8 Å from the nitrogen atom in the direction of the nitrogen lone pair. This point is assumed to simulate a receptor site hydrogen bonding with the nitrogen atom [8,9]. The energy-minimized structure of (*R*)-apomorphine and the fitting points used in this study are shown in Fig. 2. The structures of **3–14** mimicking the structure of **1** with respect to the reference atoms or points described above were constructed by least-squares fitting of the reference points in **3–14** to the corresponding atoms or points in **1**. The energy of the resulting conformation was then calculated in each case by MMP2 minimization employing restrictions of movement on appropriate atoms in order to retain the fit between reference atoms or points. In cases where the fitting procedure resulted in more than one mimicking



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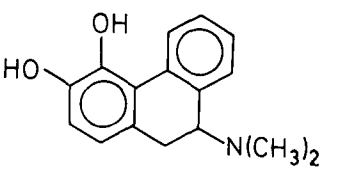

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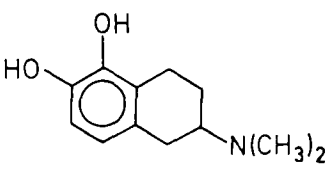

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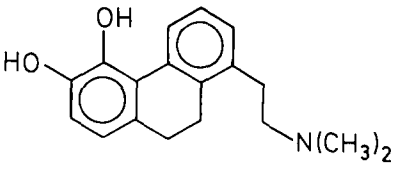

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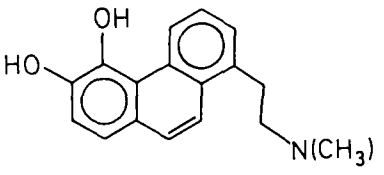

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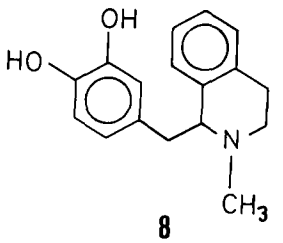

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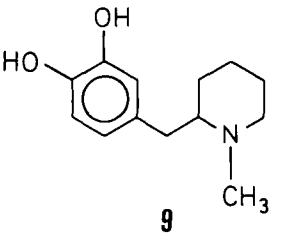

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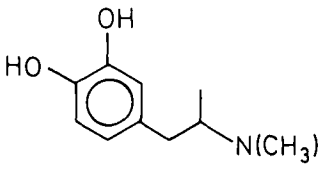

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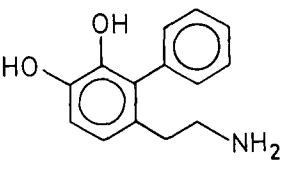

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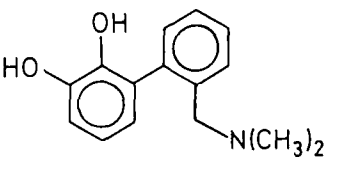

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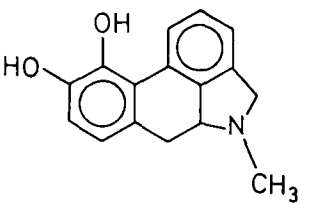

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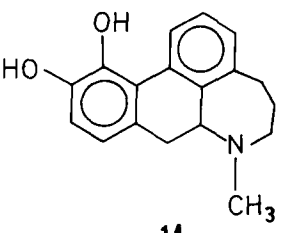

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Fig. 1. Apomorphine congeners studied.

structure the lowest energy one was used in the further analysis. A problem with this procedure is to decide the maximum allowed value for the rms-deviation in the least-squares fit. In some cases a high rms-deviation may be decreased if a structure with higher conformational energy is chosen. In the majority of cases in the present work the rms value was below 0.25 Å. The few exceptions are discussed below. All energy calculations were done on the unprotonated amines.

RESULTS AND DISCUSSION

A summary of calculated conformational energies for compounds **3-14** and the rms values for their fits to our model are given in Table 1. These energies are conformational energies (relative to the global energy minimum for each compound) calculated to be required for mimicking the dopamine pharmacophore of compound **1**. If differences in entropy are neglected, these energies may be interpreted in terms of probabilities of a compound fitting the dopamine pharmacophore. According to our hypothesis, this probability is then related to the dopaminergic activity.

In compounds **3**, **4**, **6** and **7** the piperidine ring of compound **1** has been opened to give a substituted phenanthrene (compound **7**), and three differently substituted dihydrophenanthrenes (compounds **3**, **4** and **6**) [10, 11]. This ring-cleavage drastically increases the flexibility of the remaining ring system.

The calculated lowest energy conformer of **3** and **4** has an axial dimethylamino group (Fig. 3b, compound **3**). The lowest energy conformer with an equatorial substituent (Fig. 3a, compound **3**) was calculated to be 3.7 kcal/mol higher in energy. This conformational energy difference in **3** is due to strong repulsive non-bonded interactions between the dimethylamino group and the ethyl group on the neighbouring phenyl ring. This energy difference is reduced to 1.1 kcal/mol in **4**. Only a conformation with an equatorial dimethylamino group can mimic the dopamine part of **1**. An axial substituent in **3** and **4** gives the 'ethylamino chain' a C-C-C-N gauche arrangement instead of the required anti. In order to obtain the optimal mimicking structures of **3** and **4**, the dimethylamino group must be rotated by ca. 120°. The energies of these structures are calculated to be high, 10.3 and 5.4 kcal/mol, respectively. Accordingly, in a series of different pharmacological tests, Cannon et al. have shown that compounds **3** and **4** do not have any appreciable apomorphine-like biological effects [10,11].

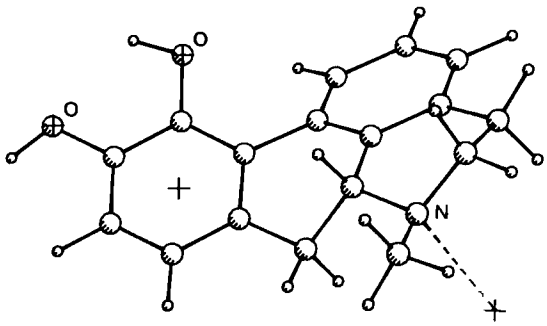

Fig. 2. Energy-minimized lowest energy structure of (*R*)-apomorphine. Crosses denote fitting points used in the superimposition studies.

TABLE I
CONFORMATIONAL ENERGIES AND ROOT-MEAN-SQUARE DEVIATIONS FOR THE FIT TO THE FOUR-POINT MODEL (SEE FIGURE 2). THE CONFORMATIONAL ENERGIES ARE THE ENERGY DIFFERENCES BETWEEN THE BEST-FIT APOMORPHINE-LIKE CONFORMATION AND THE GLOBAL ENERGY-MINIMUM FOR EACH MOLECULE

Compound	Conformational energy (kcal/mol)	Rms value (Å)
3	10.3	0.23
4	5.4	0.15
5	0.0	0.23
6	1.9	0.20
7	2.6	0.42
8	14.0	0.25
9	8.6	0.05
10	9.5	0.07
11	0.4	0.11
12	7.1	0.49
13	0.0	0.18
14	2.5	0.31

In compound **5**, the obstacle that made the energy of an equatorial dimethylamino group prohibitively high is removed, producing a 5,6-dihydroxy tetraline derivative [12]. In contrast to compounds **3** and **4**, the equatorial position of the dimethylamino group in **5** is calculated to be the preferred one (by 3.3 kcal/mol). All three staggered conformers with respect to the C-N bond have low conformational energies 0.0, 0.0 and 0.4 kcal/mol for H-C-N-lone pair dihedral angles of 180°, −58° and 66°, respectively. The conformer with a dihedral angle of 180° is an excellent mimic of **1** with respect to the pharmacophore used in this study.

As may be predicted from these calculations, compound **5** is a very potent dopamine receptor agonist [12].

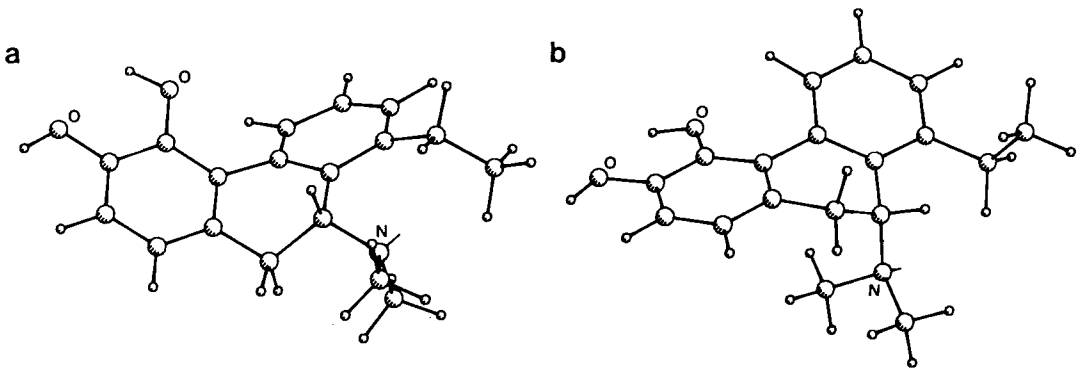

Fig. 3. (a) Calculated lowest energy conformation of compound **3** with an equatorial dimethylamino group; and (b) Global energy minimum conformer of compound **3**.

In compounds **6** and **7** the piperidine ring has been opened between the central ring and the nitrogen atom, yielding a 'free' ethylamino chain. In the calculated lowest energy conformer of both **6** and **7**, the ethylamino chain is in C-C-C-N anti conformation and is perpendicular to the phenyl ring to which it is attached. An optimal fit was found by rotation about the bonds in the ethylamino chain while monitoring the rms deviations between fitting points and the corresponding conformational energy. Least-squares superimpositions of compounds **1**, **4**, **5** and **6** are shown in Fig. 4. The energies required for the necessary conformational rearrangements of compounds **6** and **7** were calculated to be 1.9 and 2.6 kcal/mol, respectively. The rms value for compound **7** is higher than the average in this study (Table 1). However, we consider the fit to be satisfactory. The main reason for the quite high rms value is a less good fit between the oxygen atoms corresponding to the para-hydroxyl group in dopamine. It has been shown that this hydroxyl group is not crucial for the dopaminergic activity of dopamine analogues. If this oxygen is excluded in the least-squares fit the rms value for the fit between **1** and **7** becomes 0.08 Å.

The dopaminergic activities of **6** and **7** compared to that of **1** have been described as 'modest' in several pharmacological tests [10].

In compounds **8** and **9** the phenyl-phenyl bond has been cleaved. This decouples the catechol and the tetrahydroisoquinoline parts of **1**. In **9** the latter part is reduced to a piperidine ring. The calculated lowest energy conformers are shown in Fig. 5. In both cases strong non-bonded repulsion between hydrogen atoms prevent the two separated ring systems from attaining an apomorphine-like geometrical relationship between the catechol and the piperidine rings. The energy needed to mimic the apomorphine structure is high in both cases, 14.0 and 8.6 kcal/mol for **8** and **9**, respectively. Both compounds have accordingly been reported to be inactive as dopamine receptor agonists [13].

Compound **10**, N,N-dimethyl alpha-methyl dopamine, is the structurally simplest of the apomorphine congeners studied. It is closely related to dopamine itself. Cannon et al. [14] have shown that this compound is inert as a dopaminergic agonist in a variety of animal assays. They suggest that the absence of any postsynaptic dopamine agonist effects of **10** is due to the inability of this

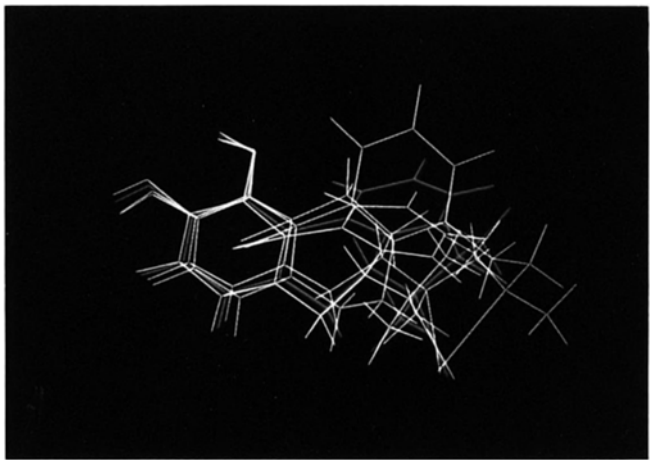

Fig. 4. Least-squares superimposition of compounds **1** (red); **4** (green); **5** (yellow); and **6** (cyan).

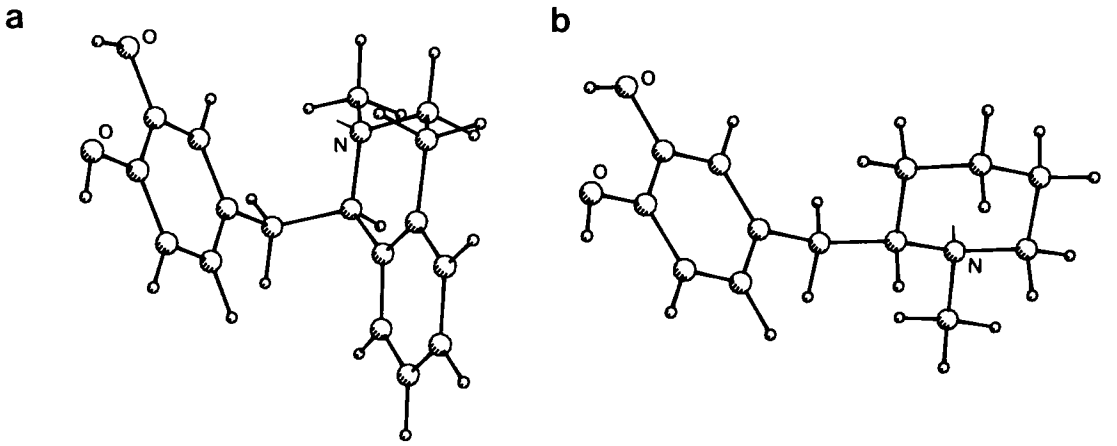

Fig. 5. Calculated lowest energy conformers of (a) Compound **8**; and (b) Compound **9**.

compound to conformationally mimic dopamine in its biologically active structure, as defined by the conformation of the dopamine part in **1**. Our calculations support this hypothesis. The lowest energy conformation of **10** is calculated to have the alkyl chain almost perpendicular to the aromatic ring (dihedral angle 78°) and the C-C-C-N part in a gauche arrangement. Strong repulsive interactions between the alpha-methyl group and the aromatic ortho-hydrogens result in a high conformational energy, 9.5 kcal/mol, for a structure that mimics apomorphine.

Compounds **11** and **12** are both formally derived by ring-cleavage of the non-aromatic rings in **1**. The calculated lowest energy conformers for **11** and **12** are shown in Fig. 6. The energies required for **11** and **12** to mimic the dopamine pharmacophore of **1** are calculated to be drastically different for the two compounds. For **11** only a minor adjustment of the conformation is necessary for an excellent fit to our model (Table 1). The corresponding energy requirement is calculated to be only 0.4 kcal/mol. In contrast, compound **12** has to rearrange considerably in order to fit the model. For instance, the interplanar angle between the two aromatic rings has to decrease from ca. 90° to 29° with concomitant strong steric repulsions between groups in the ortho positions of the biphenyl system. This conformational rearrangement is calculated to require 7.1 kcal/mol. Least-squares superimpositions of compounds **1**, **9**, **11** and **12** are shown in Fig. 7. The resulting rms value for the fit between the apomorphine-like conformation of **12** and compound **1** is quite high (Table 1). However, all attempts to lower this rms value resulted in an even higher conformational energy. The observed biological activities parallel the calculated conformational energies very satisfactorily. Compound **11** has been reported to be very potent in inhibiting the specific binding of ^{3}H-apomorphine to calf caudate homogenate [15], while compound **12** does not show any appreciable apomorphine-like activity [16].

Compound **11** has no methyl group on nitrogen, and thus does not mimic apomorphine in this respect. However, our calculated results for the dimethylamino derivative of **11** are very similar to those for **11**. The calculated mimicking conformational energy is 0.6 kcal/mol and the rms value is 0.25. Thus, the dimethylamino derivative should be equipotent to compound **11**.

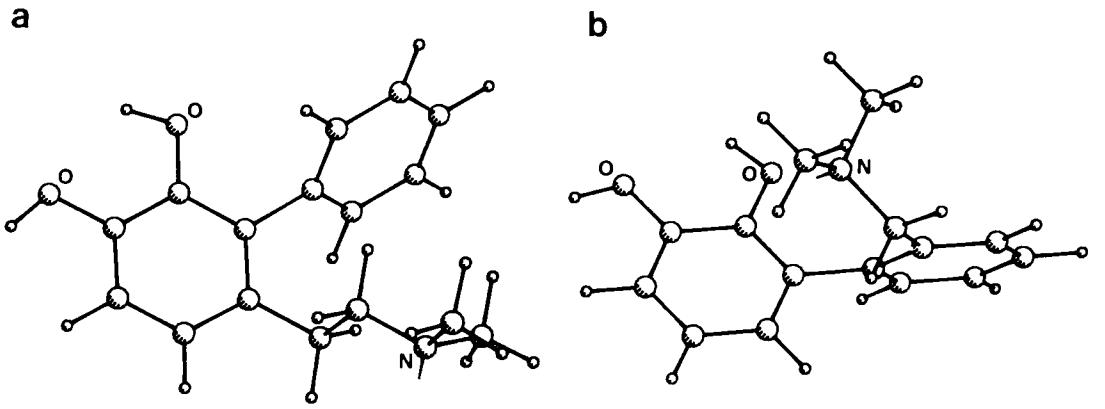

Fig. 6. Calculated lowest energy conformers of (a) Compound **11**; and (b) Compound **12**.

In compounds **13** and **14**, the six-membered nitrogen-containing ring in **1** is replaced by five- and seven-membered rings, respectively. Compound **13** is very rigid, and in its global energy minimum shows a very close structural fit to **1** (Table 1). Accordingly, this should be a highly active compound. Although no detailed biological data are available, a patent reports this compound to possess pharmacological activity as a central dopaminergic stimulant agent [17].

Compound **14** is considerably more flexible than its homologues **1** and **13**. The seven-membered ring is calculated to prefer a chair conformation with the N-methyl group in an axial position. This is in complete agreement with the structure of **14** as observed in the crystalline state [18]. The nitrogen lone pair is thus in a 'wrong' direction with respect to our model. Furthermore, the catechol ring-C-C-N conformation is gauche. Thus, compound **14**, in contrast to compound **13**, has

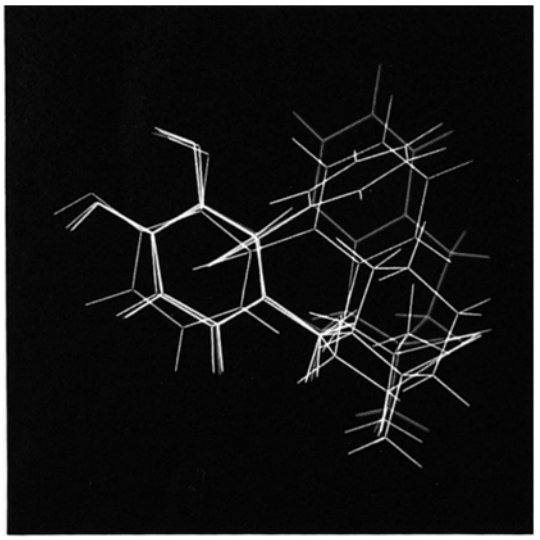

Fig. 7. Least-squares superimposition of compounds **1** (red); **9** (green); **11** (yellow); and **12** (cyan).

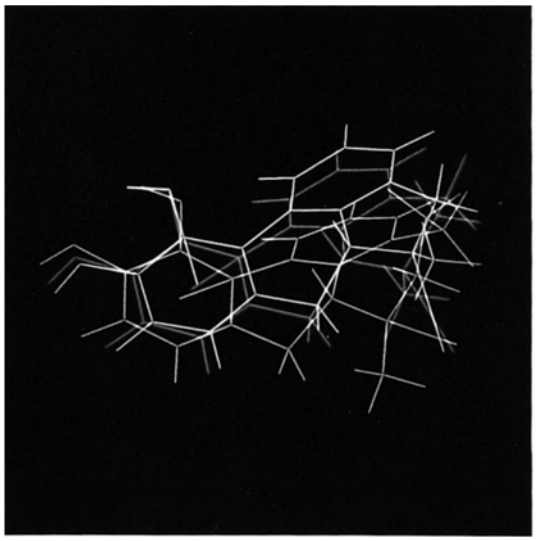

Fig. 8. Least-squares superimposition of compounds **1** (red); **13** (green); and **14** (cyan).

to undergo considerable conformational rearrangements to fit the apomorphine model. An optimal fit to our model was obtained by a conformation in which the seven-membered ring has a twist-boat conformation. The conformational energy for this conformer was calculated to be 2.5 kcal/mol.

Pharmacological testing of **14** showed no dopaminergic effects [18]. On the basis of conformational energies alone, compound **14** should be expected to show a higher activity than was observed. Least-squares superimpositions of compounds **1**, **13** and **14** are shown in Fig. 8.

A comparison between calculated energies and observed biological activities is shown in graphical form in Fig. 9. Since the biological data used refer to different types of tests and may involve different receptor subclasses, we have not attempted to make a quantitative comparison. The biological activities are thus described as high, moderate or low in relation to the corresponding activity of our reference molecule apomorphine (**1**). In this description we have followed the interpretation of the pharmacological data made by the original investigators.

CONCLUSIONS

Although the molecules studied in the present work belong to several different classes of compounds, Fig. 9 shows that there is a strong correlation between the calculated conformational en-

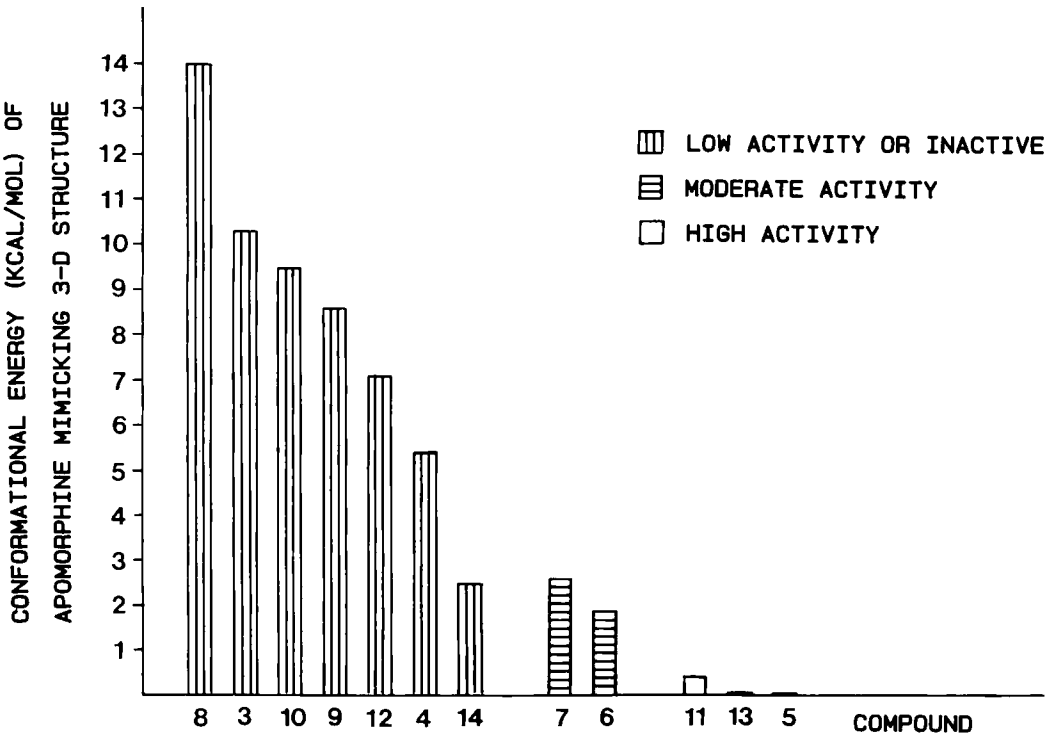

Fig. 9. Relationships between the calculated energies required for compounds **3**–**14** to mimic the apomorphine pharmacophore and their observed biological (apomorphine-like) activities.

ergies and the observed biological activities, which supports our hypothesis. Calculated conformational energies may thus be a valuable tool in the design of new compounds based on the structure of an existing biologically active molecule.

ACKNOWLEDGEMENTS

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REFERENCES

1 Saari, W.S., King, S.W. and Lotti, V.J., J. Med. Chem., 16 (1973) 171–172.
2 Giesecke, J., Acta Crystallogr., Sect. B, 29 (1973) 1785–1791.
3 Kaiser, C. and Jain, T., Med. Res. Q. 5 (1985) 145–229.
4 Burkert, U. and Allinger, N.L., Molecular Mechanics, American Chemical Society, Washington, D.C., 1982. (The MM2/MMP2 programs are available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405 and from Molecular Design Ltd., 2132 Farallon Drive, San Leandro, CA 94577.)
5 Liljefors, T., J. Mol. Graph., 1 (1983) 111–117.
6 Von der Lieth, C. W., Carter, R. E., Dolata, D.P. and Liljefors, T., J. Mol. Graph., 2 (1984) 117–123.
7 Molecular modeling system SYBYL, TRIPOS Associates, Inc., 6548 Clayton Road, St. Louis, MO 63117.
8 Andrews, P.R., Lloyd, E.J., Martin, J.L. and Munro, S.L.A., J. Mol. Graph., 4 (1986) 41–45.
9 Lloyd, J.E. and Andrews, P.R., J. Med. Chem., 29 (1986) 453–462.
10 Cannon, J.G., Borgmann, R.J, Aleem, M.A. and Long, J.P., J. Med. Chem., 16 (1973) 219 224.
11 Cannon, J.G., Smith, R.V., Aleem, M.A. and Long, J.P., J. Med. Chem., 18 (1975) 108–110.
12 Cannon, J.G., Kim, J.C., Aleem, M.A. and Long, J.P., J. Med. Chem., 15 (1972) 348–350.
13 Ginos, J.Z., Cotzias, G.C., Tolosa, E., Tang, L.C. and LoMonte, A., J. Med. Chem., 18 (1975) 1194–1200.
14 Cannon, J.G., Perez, Z., Long, J.P., Rusterholz, D.B., Flynn, J.R., Costall, B., Fortune, D.H. and Naylor, R.J., J. Med. Chem., 22 (1978), 901–907.
15 Seeman, P., Titeler, M., Tedesco, J., Weinreich, P. and Sinclair, D., Adv. Biochem. Psychopharmacol., 19 (1978) 167–176.
16 Misiorny, A., Ross, S.B. and Stjernstrom, N.E., Acta Pharm. Suecica, 14 (1977) 105–112.
17 Sandoz GmbH, Derwent No. 83-790018/42, DE Patent 3312–420–A, Oct. 13, 1983.
18 Berney, D., Petcher, T.J., Schultz, J., Weber, H.P. and White, T.G., Experentia, 31 (1975) 1327–1328.