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Self-consistent molecular modelling approach for receptor identification and drug design: Basis and data base needs*

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Abstract

The central problem in drug design is the lack of understanding of the molecular structural features of receptors. In this work, a new self-consistent molecular modelling approach, based on drug-(model) receptor interaction studies, is developed to aid in the identification of receptor's active site structure and the design of drugs. For a given molecule, be it a drug, nutrient, model receptor, biomolecule or moiety likely to form part of an active site structure of a receptor model, the data base holds the following information: the cartesian coordinates and net charges on all the atoms including hydrogens, complete all-valence electron (CNDO) wavefunctions and energies in a coordinate system fixed at a convenient point on the molecule. The methodology can also be employed to understand, at the molecular level, drug-drug, drug-nutrient interactions and the molecular origin of adverse effects of drugs.

Key words: Data base, drug design, receptors, drug-receptor, drug-nutrient interactions, molecular modelling.

1. Introduction

Biological activity of a drug is the result of its interaction with receptor(s). All drugs taken in higher dosages or for longer duration have adverse effects. Something like the Newton's third law of motion, the beneficial effect of any drug is always accompanied by its side effects. It is the dream of every drug design group to develop ideal drugs–those with none or least side or adverse effects. The advent of modern computers, be it PCs or minis or work stations or supers, coupled with sophisticated 3D-graphic systems, has led to the era of molecular modelling. Here one pictures, on the video graphic terminal, the possible mode of binding of drugs at the receptor sites in cases where the receptor structures are known. Receptor models considered in these cases are usually enzymes or proteins whose crystal structures have already been solved. It is reported[1] that significant reductions in research and development costs are possible in the chemical and drug industry by the application of a molecular modelling approach. Almost all the leading chemical and pharmaceutical industries in the west have groups actively involved in using computers and molecular orbital methods. Many successes have been reported in obtaining newer candidate drugs, whose discovery would not have been possible without the aid of molecular modelling[2–6]. Although drug design is essentially an experimental

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science, molecular modelling procedures demand scientists with a theoretical background to interact with the experimentalists. Thus, the role of theoreticians is beginning to gain its due place in this vital sector. In fact, a molecular theorist has co-authored the patent of a recent pharmaceutical product in Europe[7]. However, in India there appears to be no active group either in the industry or in research institutions in this area. The little that is attempted in academic institutions is said to be often desultory in nature[8].

Our approach envisages a self-consistent molecular modelling, based on drug-(model)receptor interaction studies. Before going into an outline of our approach, it is appropriate to mention here the cost and time involved in bringing a new drug to market and some facts about drug action. It costs about US $ 40 to 90 million, according to 1986 estimates, together with an initial investment of US $ 50 to 150 million. The time consumed being around 7–10 years, after a lead is found. Only one out of nearly 10,000 newly synthesized compounds is likely to become a drug! Further satisfactory therapy is available to only about one-third of all ailments!. *i.e.* for 66% of ailments we have no drugs of choice. Some facts on drug action are that a majority of drugs bir d reversibly at the receptor sites, with weak binding energies, their molecular mechanism of action not being understood. Further, the molecular and structural features of a majority of receptors are unknown. As an analogy, we can compare the current understanding of receptors to, something similar to, the description of an elephant by a group of blind persons. Despite intense efforts[9–12], receptors are today where enzymes were 25 years ago! It is this lack of understanding of the molecular structural features of receptors that constitutes the central problem in drug design and the consequential high costs and delay in the arrival of safer drugs to the market.

2. The approach

We have initiated an entirely different approach, based on the following premises, to solve the dilemma.

2.1. All drug-receptor interactions can essentially be regarded as an exercise in quantum mechanical intermolecular perturbation theory.

As an analogy to drug-receptor interaction, we can look upon it as a clap by hands, the sound being related to the strength of interaction. No matter how well we look at one of the hands, which incidentally can assume any allowed shape, we cannot say anything about the sound or strength of the clap (fig. 1). We have to look at both the partners, if we have to arrive at any understanding of the drug action. Quantum mechanics is the only theory which has many successes in the understanding of the molecular structure and activities of atoms and molecules. It also provides an ideal tool, the perturbation method, to study the weak interactions between two systems. We apply this tool in the understanding of drug-receptor interactions as a majority of drug-receptor bindings are weak and the processes are reversible.

It is fairly easy to understand that as the molecule approaches its receptor site, there is some optimal distance at which a weak (reversible) complex is formed (fig. 2) where,

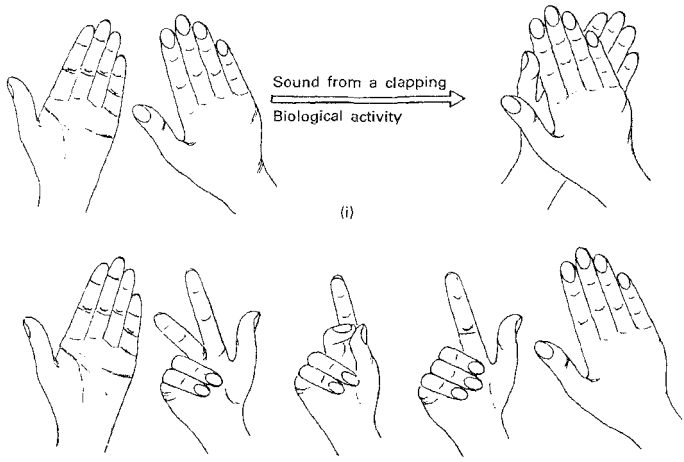


FIG. 1. An analogy to drug-receptor interactions, the sound being related to the strength of interaction *viz.* biological activity (i), and no matter how well we look at one of the partners (ii), we cannot say anything about the strength/sound of a clap. Hence, any correlation of activity to structure or property of either one of the partners is less effective towards understanding the mechanism of action.

there is a net balance between the repulsive and attractive forces, with the latter in a dominant role. Thus, the drug-receptor binding refers to the interactions in the medium-range, with a small intermolecular overlap and a mixed combination of energies of repulsive and attractive kinds.

According to the quantum mechanical theory of intermolecular forces in regions of small orbital overlap[13], the binding energy of a drug-receptor complex (fig. 3) can be split into the following components.

1. Electrostatic energy—the interaction energy between net charges on various atoms of the two molecules. In an MO picture, the situation refers to interaction between electrons in the occupied orbitals of the two molecules. The net effect could either be attractive or repulsive and the effect is operative at all intermolecular separations—*i.e.* at all ranges.
2. Exchange repulsion energy,
3. Polarisation energy,

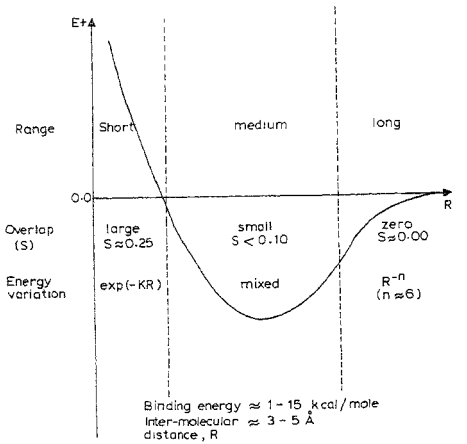


FIG. 2. A typical spherically averaged intermolecular potential energy curve, together with the common terminologies employed in discussion on intermolecular affairs. The drug-receptor binding process falls in the category of interactions in the medium range.

4. Dispersion energy, and
5. Charge transfer energy.

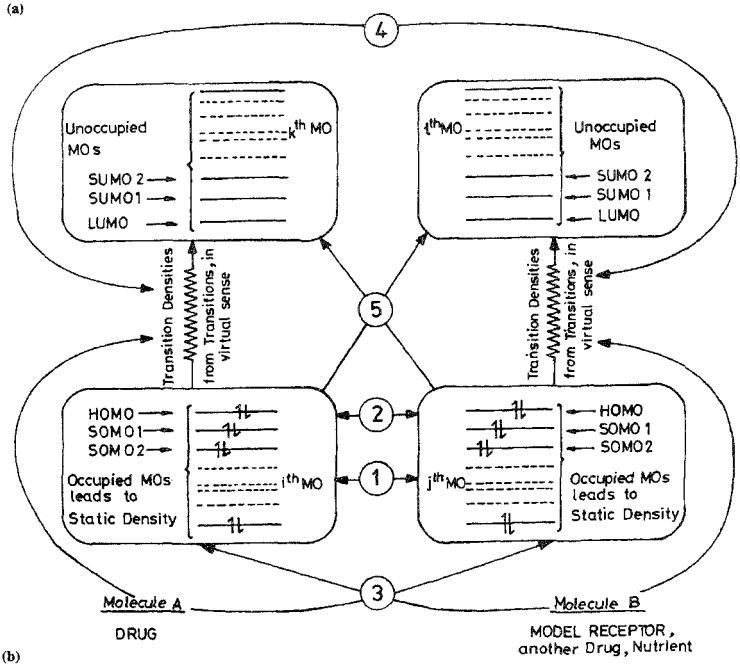
The interaction energy program in FORTRAN, developed by us, computes these terms for any given geometry of the complex, thus facilitating an explicit analysis of the relative role played by various terms in the binding process.

2.2. Starting with a crude model for a receptor, with the repeated use of the interaction energy program and varying the geometry and composition of the model receptor a self-consistent (refined) model for the receptor can be achieved!

Although the receptor as a whole could be a complex molecule, as far as the drug activity is concerned, only a portion of the molecule will be involved in the interaction with the drug. In fact, our experience with large molecules clearly suggests that at distances greater than 7 Å no significant interaction occurs between molecules, or pairs of atoms or functional groups. This important factor reduces the complexities of the systems (drug or receptor) to manageable sizes when computing their interaction energies, thereby facilitating this modelling approach.

Smaller molecular units like nucleic acid bases, free amino acids, small peptides and nucleotides, likewise, can be employed as models for the active site of the receptor.

(a)



(b)

Type	Range	Attractive/ repulsive	Pairwise additive
1. Electrostatic	long	either	yes
2. Exchange	short	repulsive*	nearly
3. Polarisation	long	attractive	no
4. Dispersion	long	attractive	yes
5. Charge-transfer	short	attractive	nearly

*Except possibly for the interaction between two anions.

FIG. 3. Features of the various components of molecular interaction, (a) in terms of interaction and mixing of Molecular Orbitals (MOs) and (b) their characteristic properties. *H*ighest *O*ccupied *M*olecular *O*rbital (HOMO), its immediate neighbours–*S*ubjacent *O*ccupied *M*olecular *O*rbitals (SOMO-1 & SOMO-2) and the *L*owest *U*noccupied *M*olecular *O*rbital (LUMO), its immediate neighbours–*S*ubjacent *U*noccupied *O*rbitals (SUMO-1 & SUMO-2), play a dominant role in interaction studies.

Consequently, a feature of the approach, is that the computational exercise forces one to think (or enhance one's understanding) of the structural features necessary for the drug as well its effector–receptor, concurrently and on equal footing. Such an advantage is non-existent in any of the currently followed drug design efforts[14,15].

The approach in quest of receptor(s) consists of two stages:

2.2.1. In the first stage, as outlined in scheme 1, the wavefunctions and energies of drugs, their derivatives or metabolites and model receptors are generated which form the zeroth order basis set for the intermolecular perturbative interaction energy calculations. These data are stored in the data base.

Another feature of the approach is that the data is computed only once and can be reused. No repetition of computations is necessary and results in a big saving in computational cost and time. This feature is essential in view of the fact that a functional group or a moiety appears in a variety of positions/situations, in the search for receptor identity.

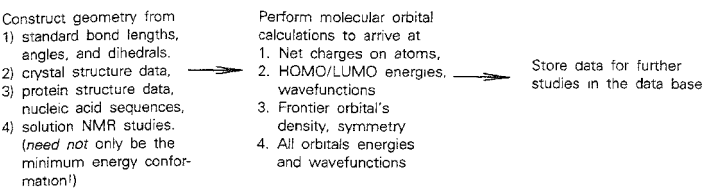
2.2.2. In the second stage (scheme 2) the interaction energy calculations between a given drug and a set of models for the active site structure of a receptor are carried out to arrive at a self-consistent model of the receptor which can lead to a new classification of receptors based on their own identity.

2.3. Not only drug-receptor interactions but also drug-interactions, drug-nutrient interactions and toxicities can be analysed using the same methodology/program.

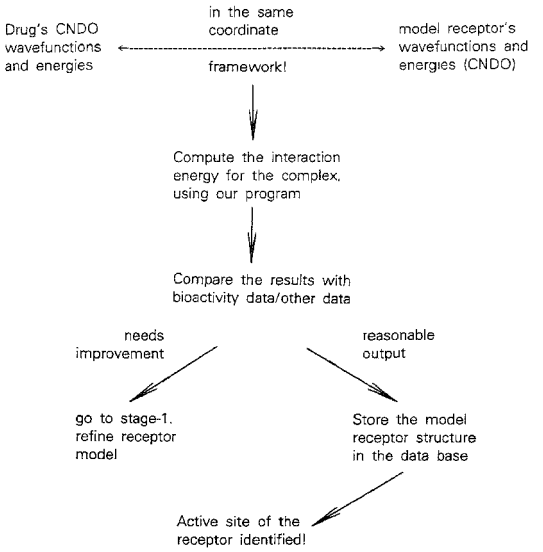
This is feasible in view of the plausibility that a given active site structure acting as a therapeutic site for one drug, could as well act as a toxicity or an antagonist or an inactive centre for another drug, its derivative(s) or metabolite(s). One can easily perform a computational exercise to see how a given receptor site interacts with various other drugs and *vice versa*. Such an effort may suggest newer experiments as a challenge to the experimentalists or can act as a complementary tool, something like Raman spectroscopy complementing infrared spectroscopy. So, as an added bonus, the approach opens the door to understanding the molecular origin of adverse effects of drugs[16,17], drug interaction[18–21], etc., all under the umbrella of the data stored in the data bank and the interaction energy program. Further, in the future it may become possible to answer questions like whether a given receptor for a drug is same in the infectious or disease state and in the normal state, *i.e.* the methodology may help in characterising, at the molecular level, the disease state and the mechanism of drug (especially antibiotics) resistance.

2.4. The methodology in relation to drug action and drug design.

Our efforts are concerned with the pharmacodynamic phase in drug action (scheme 3), the phase wherein the drug is purely or exclusively involved in interaction with the receptor. This is something similar to the interaction between two molecules in the gas

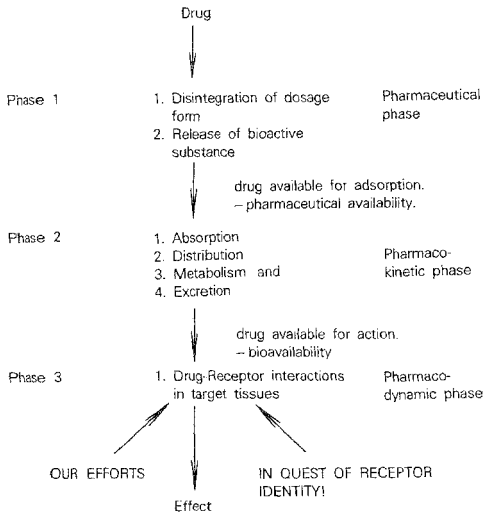


Scheme 1. The sequence of steps involved in generation and storage of molecular wavefunctions and energies of drugs, their derivatives or metabolites, nutrients and model receptors in the data base.



Scheme 2. The sequence of steps involved in arriving at the active site structure of a receptor in our approach.

phase without any interference of either media or other molecules. Although, interactions do occur *in vivo*, the classification of the term or situation – pharmacodynamic phase – refers solely to that part of events where the drug actually meets the



Scheme 3. Role of our methodology in relation to the various phases of drug action.

receptor. It is to this vital zone in drug action that the outlined theoretical methodologies apply.

What is provided here is an *alternative tool* to the conventional computational methods *viz.* QSAR[22,23] extensively used in drug design. Current QSAR methods require a series of test compounds with determined biological activity data known before hand and use complicated statistics[24] to arrive at a better candidate drug. They tell nothing about the receptor's molecular structural features. On the other hand, in the approach outlined here, it is possible to get at the active site structure of a receptor. Once this is done, it is obvious that the enormous cost and time involved in drug design efforts is reduced. Hence, the approach has the potential to aid in drug design efforts.

3. The data base

We have begun constructing a data base consisting of molecular geometries, net charges, complete CNDO[25] wavefunctions and energies for a number of compounds, drugs, and biomolecules likely to act as receptors. Currently we have the data for the following compounds:

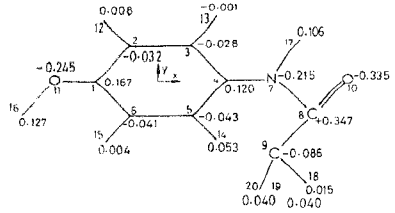
Table I
Cartesian coordinates of atoms in aspirin and paracetamol (fig. 4)

Drug	Aspirin			Paracetamol		
Atom no.	X	Y	Z	X	Y	Z
1	−1.400	0.000	0.000	−1.400	0.000	0.000
2	−0.700	1.212	0.000	−0.700	1.212	0.000
3	0.700	1.212	0.000	0.700	1.212	0.000
4	1.400	0.000	0.000	1.400	0.000	0.000
5	0.700	−1.212	0.000	0.700	−1.212	0.000
6	−0.700	−1.212	0.000	−0.700	−1.212	0.000
7	2.760	0.000	0.000	2.830	0.000	0.000
8	3.440	−1.178	0.000	3.539	−1.227	0.000
9	4.960	−1.178	0.000	5.065	−1.227	0.000
10	2.830	−2.234	0.000	2.924	−2.292	0.000
11	1.430	2.477	0.000	−2.760	0.000	0.000
12	0.820	3.533	0.000	−1.240	2.148	0.000
13	2.790	2.477	0.000	1.240	2.148	0.000
14	1.240	−2.148	0.000	1.240	−2.148	0.000
15	−1.240	−2.148	0.000	−1.240	−2.148	0.000
16	−2.480	0.000	0.000	−3.300	−0.935	0.000
17	−1.240	2.148	0.000	3.335	0.875	0.000
18	3.103	1.569	0.000	5.427	−0.199	0.000
19	5.323	−0.664	0.890	5.427	−1.741	0.890
20	5.323	−2.206	0.000	5.427	−1.741	0.890
21	5.323	−0.664	−0.890			

1. Paracetamol, $C_8H_9NO_2$, antipyretic/analgesic/anti-inflammatory.
2. Acetylsalicylic acid, $C_9O_4H_8$, antipyretic/analgesic/anti-inflammatory.
3. Phenacetin, $C_{10}H_{13}NO_2$, anti-inflammatory.
4. Naproxen, $C_{14}H_{14}O_3$, anti-inflammatory.
5. Ibuprofen, $C_{13}H_{18}O_2$, anti-inflammatory.
6. Mefenamic acid, $C_{15}H_{15}NO_2$, anti-inflammatory.
7. Flufenamic acid, $C_{14}H_{10}F_3NO_2$, anti-inflammatory.
8. Enfenamic acid*. $C_{15}H_{15}NO_2$, anti-inflammatory.
9. Naphthalene nitrenium ion, $C_{10}H_8N$, model aromaticamine carcinogen.
10. Porphin, $C_{20}H_{14}N_4$, model for heme ring current.
11. Benzene, C_6H_6, a model for aromatic ring.
12. Guanine,
13. Adenine,
14. Thymine,
15. Uracil,
16. Cytosine.

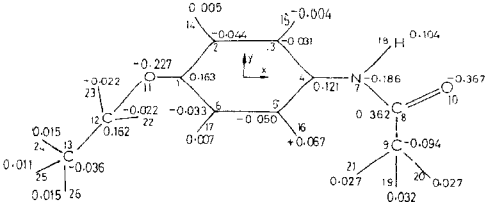
components of DNA/RNA, for modelling the 'active sites' of receptor(s).

*This drug is an Indian contribution in recent times. It was synthesized by Raiz Hashim and P. B. Sattur at the Regional Research Laboratory, Hyderabad, in 1964. After extensive clinical trials, it was released to the market, under the trade name TROMARIL by Unichem in 1981. Like the fenamates, its side effects are skin rashes, itching and diarrhoea. Many other contributions are in the offing[8].



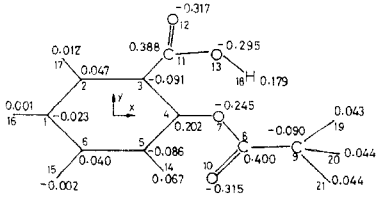
HOMO (29th MO) $\varepsilon = -10.78201$ ev (π type)
LUMO (30th MO) $\varepsilon = +3.84764$ ev (π type)

PARACETAMOL $C_8H_9NO_2$



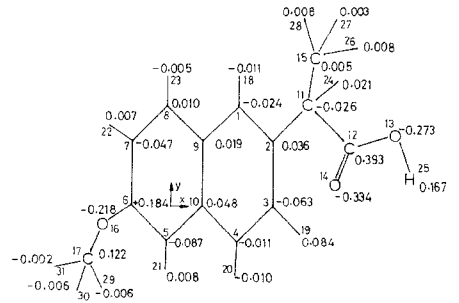
HOMO (35th MO) $\varepsilon = -10.67081$ ev (π type)
LUMO (36th MO) $\varepsilon = +3.90078$ ev (π type)

PHENACETIN $C_{10}H_{13}NO_2$



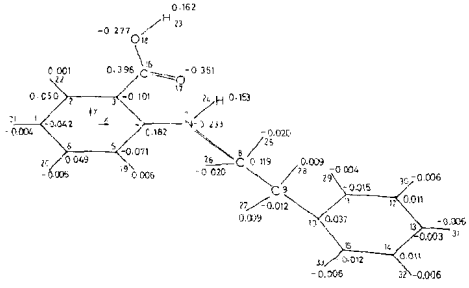
HOMO (34th MO) $\varepsilon = -12.28014$ ev (π type)
LUMO (35th MO) $\varepsilon = +2.31844$ ev (π type)

ASPIRIN $C_9H_8O_4$



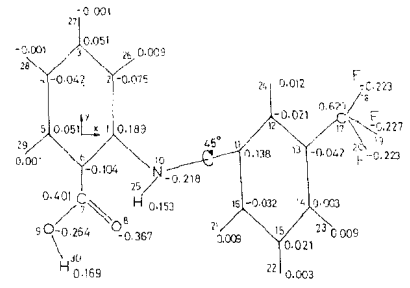
HOMO (44th MO) $\varepsilon = -10.41127$ ev (π type)
LUMO (45th MO) $\varepsilon = +2.01812$ ev (π type)

NAPROXEN $C_{14}H_{14}O_3$



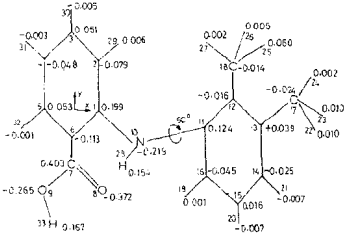
HOMO (46th MO) ε = −11.11069 ev (π type)
LUMO (47th MO) ε = +2.48474 ev (π type)

ENFENAMIC ACID $C_{15}H_{15}NO_2$



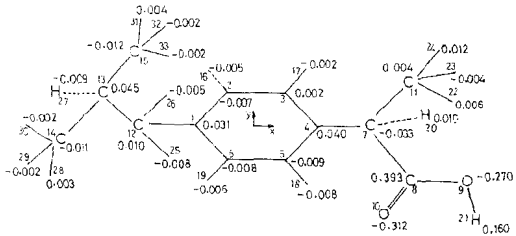
HOMO (52nd MO) ε = −10.88397 ev (π type)
LUMO (53rd MO) ε = +2.28888 ev (π type)

FLUFENAMIC ACID $C_{14}H_{10}F_3NO_2$



HOMO (46th MO) ε = −10.53285 ev (π type)
LUMO (47th MO) ε = +2.50966 ev (π type)

MEFENAMIC ACID $C_{15}H_{15}NO_2$



HOMO (41th MO) ε = −11.85714 ev (~π type)
LUMO (42th MO) ε = +3.72909 ev (~π type)

IBUPROFEN $C_{13}H_{18}O_2$

FIG. 4. The net charges on all atoms in the various drugs together with the HOMO/LUMO energies (CNDO method). See Tables I–IV for their corresponding cartesian coordinates.

Presenting a complete data file for each of the above molecules, consisting of cartesian coordinates in a convenient molecule-fixed coordinate system, complete CNDO wavefunctions and energies (not just the HOMO/LUMOs), and the net charges on all the atoms including hydrogens, would become too unwieldy to be included here*. Consequently, only a partial set of data for drugs mentioned above is given. The data given are: (a) the net charges on all the atoms (fig. 4), (b) the cartesian coordinates (Tables I–IV) and the corresponding highest occupied and lowest vacant molecular orbitals (Tables V–VIII).

Table II
Cartesian coordinates of atoms in ibuprofen and phenacetin (fig. 4)

Drug	Ibuprofen			Phenacetin		
Atom no.	X	Y	Z	X	Y	Z
1	−1.400	0.000	0.000	−1.400	0.000	0.000
2	−0.700	1.212	0.000	−0.700	1.212	0.000
3	0.700	1.212	0.000	0.700	1.212	0.000
4	1.400	0.000	0.000	1.400	0.000	0.000
5	0.700	−1.212	0.000	0.700	−1.214	0.000
6	−0.700	−1.212	0.000	−0.700	−1.213	0.000
7	2.920	0.000	0.000	2.800	0.000	0.000
8	3.427	0.717	1.241	3.460	−1.143	0.000
9	4.764	0.841	1.456	4.980	−1.143	0.000
10	2.627	1.184	2.051	2.850	−2.200	0.000
11	3.433	0.726	−1.257	−2.760	0.000	0.000
12	−2.920	0.000	0.000	−3.475	1.238	0.000
13	−3.433	0.726	1.257	−4.989	0.957	0.000
14	−4.973	0.726	−1.257	−1.240	2.148	0.000
15	−2.920	0.000	−2.515	1.240	2.148	0.000
16	−1.240	2.148	0.000	1.239	−2.149	0.000
17	1.240	2.148	0.000	−1.241	−2.148	0.000
18	1.240	−2.148	0.000	3.305	0.875	0.000
19	−1.240	−2.148	0.000	5.343	−0.629	0.890
20	3.283	−1.028	0.000	5.343	−2.171	0.000
21	5.387	0.476	0.824	5.343	−0.629	−0.890
22	3.070	1.753	−1.257	−3.212	1.810	−0.890
23	4.523	0.726	−1.257	−3.212	1.810	0.890
24	3.070	0.212	2.147	−5.252	0.385	0.890
25	−3.283	0.514	0.890	−5.534	1.901	0.000
26	−3.283	−1.027	0.000	−5.252	0.385	−0.890
27	−3.070	1.753	−1.257			
28	−5.337	1.240	−0.367			
29	−5.337	1.240	−2.147			
30	−5.336	−0.302	−1.257			
31	−3.283	−1.028	−2.515			
32	−3.283	0.514	−3.405			
33	−1.830	0.000	−2.515			

*Limited copies of the data can be had from the author on request.

Table III
Cartesian coordinates of atoms in mefenamic acid and enfenamic acid (fig. 4)

Drug	Mefenamic acid			Enfenamic acid		
Atom no.	X	Y	Z	X	Y	Z
1	1.025	0.000	0.000	−1.400	0.000	0.000
2	1.025	1.400	0.000	−0.700	1.212	0.000
3	−0.188	2.100	0.000	0.700	1.212	0.000
4	−1.400	1.400	0.000	1.400	0.000	0.000
5	−1.400	0.000	0.000	0.700	−1.212	0.000
6	−0.188	−0.700	0.000	−0.700	−1.212	0.000
7	−0.188	−2.160	0.000	2.800	0.000	0.000
8	0.878	−2.775	−0.000	3.535	−1.273	0.000
9	−1.331	−2.820	0.000	5.049	−0.992	0.000
10	2.203	−0.680	0.000	5.809	−2.308	0.000
11	3.501	−0.129	0.000	5.109	−3.520	0.000
12	3.908	0.703	1.050	5.809	−4.733	0.000
13	5.197	1.250	1.050	7.209	−4.733	0.000
14	6.078	0.965	0.000	7.909	−3.520	0.000
15	5.671	0.133	−1.050	7.209	−2.308	0.000
16	4.382	−0.414	−1.050	1.430	2.477	0.000
17	5.639	2.152	2.190	2.650	2.477	0.000
18	2.951	1.011	2.190	0.750	3.655	0.000
19	4.067	−1.055	−1.860	1.240	−2.148	0.000
20	6.350	−0.086	−1.860	−1.240	−2.148	0.000
21	7.072	1.387	0.000	−2.480	0.000	0.000
22	5.904	3.133	1.795	−1.240	2.148	0.000
23	6.506	1.714	2.685	1.380	4.379	0.000
24	4.825	2.257	2.907	3.305	0.875	0.000
25	2.781	2.087	2.240	3.272	−1.845	−0.890
26	3.383	0.668	3.130	3.272	−1.845	0.890
27	2.004	0.501	2.018	5.312	−0.420	0.890
28	2.203	−1.690	0.000	5.312	−0.420	−0.890
29	1.960	1.940	0.000	4.029	−3.520	0.000
30	−0.188	3.180	0.000	5.269	−5.668	0.000
31	−2.335	1.940	0.000	7.749	−5.668	0.000
32	−2.335	−0.540	0.000	8.989	−3.520	0.000
33	−1.146	−3.772	0.000	7.749	−1.373	0.000

Many more are in the process of being added to the above list. These include: (a) all the amino acids, (b) model di-, tri-, and penta-peptides relevant to CNS activity, (c) models of A-, B-, Z- DNAs, as possible models for receptor sites, (d) models of receptors built from amino acid sequences, (e) all the possible 200 essential drugs, (f) newer model anticarcinogens, antivirals, antibacterial drugs, etc.

With the protein data base and the nucleic acid sequence data base becoming available in India, under the National Biotechnology Board (NBTB) program, many more

Table IV
Cartesian coordinates of atoms in flufenamic acid and naproxen (fig. 4)

Drug	Flufenamic acid			Naproxen		
Atom no.	X	Y	Z	X	Y	Z
1	1.024	0.000	0.000	2.237	2.100	0.000
2	1.024	1.400	0.000	3.450	1.400	0.000
3	−0.188	2.100	0.000	3.450	0.000	0.000
4	−1.400	1.400	0.000	2.237	−0.700	0.000
5	−1.400	0.000	0.000	−0.188	−0.700	0.000
6	−0.188	−0.700	0.000	−1.400	0.000	0.000
7	−0.188	−2.170	0.000	−1.400	1.400	0.000
8	0.878	−2.785	0.000	−0.186	2.100	0.000
9	−1.331	−2.830	0.000	1.025	1.400	0.000
10	2.220	−0.690	0.000	1.025	0.000	0.000
11	3.527	−0.162	0.000	4.766	2.160	0.000
12	3.855	0.895	0.857	5.921	1.172	0.000
13	5.153	1.420	0.857	7.203	1.626	0.000
14	6.123	0.887	0.000	5.698	−0.027	0.000
15	5.796	−0.170	−0.857	4.848	3.045	−1.257
16	4.497	−0.694	−0.857	−2.578	−0.680	0.000
17	5.502	2.545	1.770	−2.578	−2.110	0.000
18	5.310	2.175	3.012	2.237	3.180	0.000
19	6.760	2.870	1.600	4.385	−0.540	0.000
20	4.743	3.578	1.500	2.237	−1.780	0.000
21	4.245	−1.510	−1.519	−0.188	−1.780	0.000
22	6.544	−0.581	−1.519	−2.335	1.940	0.000
23	7.125	1.292	0.000	−0.188	3.180	0.000
24	3.107	1.306	1.519	4.824	2.787	0.890
25	2.220	−1.700	0.000	7.807	0.879	0.000
26	1.960	1.940	0.000	4.019	3.754	−1.257
27	−0.188	3.180	0.000	5.792	3.590	−1.257
28	−2.335	1.940	0.000	4.790	2.419	−2.147
29	−2.335	−0.540	0.000	−1.550	−2.473	0.000
30	−1.146	−3.782	0.000	−3.091	−2.473	0.890
31				−3.091	−2.473	−0.890

interesting set of model receptor geometries can be built in the near future. So we foresee the need and growth of the data base for drug design in the imminent future, to a level something similar to the currently popular Cambridge crystallographic data base. The latter data base started in the 60s with crystal structure data for about 200 organic molecules, grew[26] to about 2000 entries by 1975 and currently to around 50,000 entries. This represents a collection of data from worldwide publications in the area.

Some interesting observations are noted from the data given in fig. 4. Consider the net charges on the various functional groups (Table IX). The charges on these groups are nearly constant, especially on the hetero atoms, independent of the position or group to

Table V
HOMO and LUMO wavefunctions and energies (CNDO) in aspirin and paracetamol

Drug		Aspirin			Paracetamol		
MO-Energy (ev)			−12.280	2.318		−10.782	3.848
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
1	S	C	0.008	−0.000	C	0.000	0.000
	PX		0.028	−0.000		0.000	0.000
	PY		−0.194	−0.000		0.000	0.000
	PZ		0.000	0.161		−0.405	−0.090
2	S	C	0.001	0.000	C	−0.000	−0.000
	PX		0.008	0.000		0.000	0.000
	PY		0.123	0.000		−0.000	−0.000
	PZ		0.000	−0.349		−0.236	−0.449
3	S	C	−0.015	−0.000	C	0.000	0.000
	PX		−0.007	−0.000		−0.000	0.000
	PY		−0.317	−0.000		0.000	0.000
	PZ		−0.000	−0.425		0.278	0.545
4	S	C	0.009	0.000	C	0.000	−0.000
	PX		−0.037	0.000		0.000	0.000
	PY		0.257	−0.000		−0.000	0.000
	PX		−0.000	0.327		0.390	−0.110
5	S	C	0.017	−0.000	C	−0.000	0.000
	PX		0.071	−0.000		−0.000	0.000
	PY		−0.314	−0.000		0.000	−0.000
	PZ		−0.000	0.195		0.271	−0.430
6	S	C	−0.026	0.000	C	0.000	−0.000
	PX		−0.088	−0.000		0.000	0.000
	PY		0.144	−0.000		−0.000	0.000
	PZ		0.000	−0.482		−0.240	0.523
7	S	O	−0.014	0.000	N	0.000	−0.000
	PX		0.057	0.000		−0.000	−0.000
	PY		−0.236	−0.000		−0.000	0.000
	PZ		0.000	−0.062		−0.490	−0.008
8	S	C	0.021	−0.000	C	−0.000	0.000
	PX		−0.119	−0.000		0.000	0.000
	PY		0.036	−0.000		−0.000	0.000
	PZ		0.000	−0.104		−0.014	0.113
9	S	C	−0.056	0.000	C	0.000	−0.000
	PX		0.160	−0.000		−0.000	0.000
	PY		0.009	−0.000		0.000	0.000
	PZ		−0.000	−0.013		0.006	0.023
10	S	O	−0.075	−0.000	O	−0.000	0.000
	PX		0.426	0.000		0.000	−0.000

Table V (*contd.*)

Drug		Aspirin			Paracetamol		
MO-Energy (ev)			−12.280	2.318		−10.782	3.848
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
	PY		−0.170	0.000		0.000	−0.000
	PZ		−0.000	0.079		0.259	−0.075
11	S	C	−0.065	0.000	O	0.000	0.000
	PX		0.076	0.000		0.000	0.000
	PY		0.185	−0.000		−0.000	−0.000
	PZ		0.000	−0.351		0.335	0.025
12	S	O	−0.004	−0.000	H	−0.000	0.000
	PX		−0.190	−0.000			
	PY		−0.277	0.000			
	PZ		0.000	0.364			
13	S	O	−0.004	0.000	H	0.000	−0.000
	PX		−0.116	−0.000			
	PY		−0.141	0.000			
	PZ		−0.000	0.126			
14	S	H	0.277	−0.000	H	−0.000	−0.000
15	S	H	−0.152	−0.000	H	0.000	0.000
16	S	H	−0.034	−0.000	H	−0.000	−0.000
17	S	H	0.169	−0.000	H	−0.000	−0.000
18	S	H	0.059	0.000	H	0.000	0.000
19	S	H	0.028	0.032	H	0.009	−0.039
20	S	H	0.016	0.000	H	−0.009	0.039
21	S	H	0.028	−0.032			

For hydrogen S is the 1*s* atomic orbital; for atoms S, PX, PY and PZ refer to the $2s$, $2p_x$, $2p_y$ and $2p_z$ valence atomic orbitals respectively.

which they are attached to in the various drugs. This result suggests that during interaction with a given receptor, the above groups interact with nearly the same strength in all the above drugs. As electrostatic interactions are of long range and as hydrogen bonds are predominantly electrostatic in nature, it is reasonable to expect that the above observation can play a significant role in simplifying the search of receptor identity.

Preliminary analysis of interaction of the above drugs with guanine as a possible active site of a receptor, indicates the possibility of formation of a rotated sandwich complex with weak binding energy. Based on this *apriori* information, we looked for possible binding of ibuprofen with DNA. It was gratifying to observe that this drug binds in a unique manner with DNA, unlike the well established minor or major groove binding

Table VI
HOMO and LUMO wavefunctions and energies (CNDO) in ibuprofen and phenacetin

Drug		Ibuprofen			Phenacetin		
MO-Energy (ev)			−11.857	3.729		−10.671	3.901
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
1	S	C	0.011	0.002	C	−0.000	−0.000
	PX		−0.053	−0.004		−0.000	−0.000
	PY		0.007	0.000		−0.000	−0.000
	PZ		−0.445	−0.547		0.394	0.092
2	S	C	0.002	0.003	C	0.000	0.000
	PX		0.023	−0.002		−0.000	−0.000
	PY		0.003	−0.002		0.000	0.000
	PZ		−0.257	0.298		0.228	0.449
3	S	C	0.004	0.000	C	−0.000	−0.000
	PX		−0.025	0.001		−0.000	−0.000
	PY		−0.005	−0.001		−0.000	−0.000
	PZ		0.240	0.243		−0.281	−0.549
4	S	C	−0.000	0.001	C	−0.000	0.000
	PX		0.020	0.001		−0.000	−0.000
	PY		0.006	−0.000		0.000	−0.000
	PZ		0.446	−0.550		−0.381	0.118
5	S	C	0.001	0.001	C	0.000	−0.000
	PX		−0.038	−0.002		0.000	−0.000
	PY		−0.006	−0.002		0.000	0.000
	PZ		0.255	0.311		−0.257	0.426
6	S	C	−0.006	−0.003	C	−0.000	0.000
	PX		0.038	0.003		−0.000	−0.000
	PY		−0.012	−0.004		0.000	−0.000
	PZ		−0.253	0.236		0.245	−0.526
7	S	C	−0.013	−0.009	N	−0.000	0.000
	PX		−0.038	−0.005		0.000	0.000
	PY		−0.043	−0.007		0.000	−0.000
	PZ		−0.227	−0.039		0.468	0.006
8	S	C	−0.089	0.114	C	0.000	−0.000
	PX		0.063	−0.005		−0.000	−0.000
	PY		0.083	−0.048		0.000	−0.000
	PZ		0.159	−0.073		0.021	−0.100
9	S	O	−0.001	−0.023	C	0.000	0.000
	PX		−0.104	0.052		−0.000	−0.000
	PY		−0.059	0.016		−0.000	−0.000
	PY		−0.059	0.016		−0.000	−0.000
	PZ		−0.103	0.024		−0.013	−0.021

Table VI (*contd.*)

Drug		Ibuprofen			Phenacetin		
MO-Energy (ev)			−11.857	3.729		−10.671	3.901
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
10	S	O	−0.014	−0.000	O	0.000	−0.000
	PX		−0.077	−0.007		−0.000	0.000
	PY		−0.128	0.002		−0.000	0.000
	PZ		−0.106	0.014		−0.293	0.060
11	S	C	0.065	−0.083	O	−0.000	−0.000
	PX		−0.068	0.010		0.000	−0.000
	PY		−0.038	0.056		0.000	−0.000
	PZ		0.144	−0.086		−0.356	−0.022
12	S	C	−0.007	−0.013	C	0.000	0.000
	PX		0.065	0.013		0.000	0.000
	PY		−0.024	−0.020		−0.000	0.000
	PZ		0.194	−0.059		0.021	−0.017
13	S	C	−0.060	−0.073	C	−0.000	−0.000
	PX		−0.096	−0.028		−0.000	0.000
	PY		0.070	0.055		−0.000	−0.000
	PZ		−0.171	−0.081		−0.001	−0.003
14	S	C	0.018	0.021	H	0.000	−0.000
	PX		0.066	0.030			
	PY		−0.023	0.009			
	PZ		0.043	−0.014			
15	S	C	−0.003	−0.024	H	−0.000	0.000
	PX		−0.040	−0.011			
	PY		−0.006	−0.003			
	PZ		0.053	−0.010			
16	S	H	−0.015	−0.002	H	−0.000	0.000
17	S	H	−0.019	0.000	H	0.000	−0.000
18	S	H	−0.019	−0.003	H	0.000	0.000
19	S	H	−0.019	−0.002	H	−0.012	0.035
20	S	H	0.030	0.001	H	0.000	0.000
21	S	H	0.038	−0.007	H	0.012	−0.035
22	S	H	0.040	−0.005	H	−0.067	−0.003
23	S	H	−0.036	0.056	H	0.067	0.003
24	S	H	−0.066	−0.012	H	−0.007	0.006
25	S	H	0.174	0.164	H	0.000	0.000
26	S	H	−0.015	0.003	H	0.007	−0.006

Table VI (*contd.*)

Drug		Ibuprofen			Phenacetin		
MO-Energy (ev)			−11.857	3.729		−10.671	3.901
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
27	S	H	−0.001	0.003			
28	S	H	0.031	0.007			
29	S	H	−0.085	−0.035			
30	S	H	0.019	0.014			
31	S	H	0.029	0.014			
32	S	H	−0.055	0.001			
33	S	H	−0.007	−0.000			

Table VII
HOMO and LUMO wavefunctions and energies (CNDO) in mefenamic acid and enfenamic acid

Drug		Mefenamic acid			Enfenamic acid		
MO-Energy (ev)			−10.533	2.510		−11.111	2.485
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
1	S	C	−0.009	−0.004	C	−0.000	0.000
	PX		−0.010	−0.005		−0.000	0.000
	PY		0.012	0.003		−0.000	0.000
	PZ		−0.225	0.259		0.412	−0.081
2	S	C	−0.004	0.000	C	0.000	−0.000
	PX		−0.012	0.000		−0.000	0.000
	PY		−0.012	−0.001		0.000	−0.000
	PZ		−0.314	0.277		0.119	−0.408
3	S	C	0.001	−0.000	C	−0.000	0.000
	PX		0.004	−0.001		−0.000	0.000
	PY		0.004	0.000		−0.000	0.000
	PZ		0.087	−0.481		−0.344	0.383
4	S	C	−0.002	−0.000	C	−0.000	−0.000
	PX		−0.005	−0.000		−0.000	−0.000
	PY		−0.006	0.000		0.000	0.000
	PZ		0.376	0.071		−0.282	−0.262
5	S	C	−0.002	−0.001	C	0.000	0.000
	PX		−0.003	−0.001		0.000	0.000
	PY		0.005	0.001		−0.000	−0.000
	PZ		0.115	0.412		−0.312	−0.268

Table VII (*contd.*)

Drug		Mefenamic acid			Enfenamic acid		
MO-Energy (ev)			−10.533	2.510		−11.111	2.485
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
6	S	C	0.001	0.001	C	−0.000	−0.000
	PX		−0.001	0.001		−0.000	0.000
	PY		−0.010	0.001		0.000	0.000
	PZ		−0.318	−0.377		0.135	0.482
7	S	C	0.005	0.001	N	−0.000	−0.000
	PX		0.001	0.000		0.000	−0.000
	PY		0.007	0.000		0.000	0.000
	PZ		−0.007	−0.377		0.627	0.102
8	S	O	−0.005	−0.001	C	0.000	0.000
	PX		−0.013	−0.001		−0.000	−0.000
	PY		−0.021	−0.002		0.000	0.000
	PZ		0.187	0.353		−0.086	0.024
9	S	O	−0.003	−0.000	C	0.000	0.000
	PX		−0.008	−0.000		−0.000	−0.000
	PY		−0.004	−0.000		−0.000	0.000
	PZ		0.022	0.140		0.005	0.001
10	S	N	0.000	0.002	C	0.000	0.000
	PX		0.005	0.001		0.000	−0.000
	PY		−0.028	0.001		0.000	0.000
	PZ		0.597	−0.106		0.020	0.001
11	S	C	−0.007	−0.000	C	0.000	0.000
	PX		−0.021	−0.013		−0.000	−0.000
	PY		−0.054	0.035		0.000	−0.000
	PZ		−0.184	−0.023		0.021	−0.001
12	S	C	−0.048	0.008	C	−0.000	−0.000
	PX		−0.014	0.004		0.000	0.000
	PY		0.206	−0.021		0.000	−0.000
	PZ		0.023	−0.002		0.011	0.001
13	S	C	0.015	−0.005	C	0.000	0.000
	PX		−0.005	0.016		−0.000	−0.000
	PY		−0.062	−0.027		−0.000	−0.000
	PZ		−0.021	0.017		−0.014	0.000
14	S	C	0.001	−0.000	C	0.000	0.000
	PX		0.055	−0.015		−0.000	−0.000
	PY		−0.126	0.036		−0.000	−0.000
	PZ		0.137	−0.024		−0.021	−0.001
15	S	C	−0.016	0.003	C	0.000	−0.000
	PX		0.051	−0.001		−0.000	0.000
	PY		−0.069	−0.003		−0.000	0.000
	PZ		0.000	0.001		−0.000	0.001

Table VII (*contd.*)

Drug		Mefenamic acid			Enfenamic acid		
MO-Energy (ev)			−10.533	2.510		−11.111	2.485
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
16	S	C	0.056	−0.010	C	−0.000	−0.000
	PX		−0.131	0.022		0.000	−0.000
	PY		0.137	−0.037		0.000	0.000
	PZ		0.020	0.015		0.008	0.381
17	S	C	−0.021	0.001	O	−0.000	−0.000
	PX		0.014	0.002		−0.000	0.000
	PY		0.045	−0.005		0.000	−0.000
	PZ		0.038	−0.001		0.216	−0.366
18	S	C	0.031	−0.022	O	−0.000	0.000
	PX		0.003	0.021		−0.000	0.000
	PY		−0.046	0.013		0.000	−0.000
	PZ		−0.039	−0.000		0.012	−0.131
19	S	H	−0.049	0.001	H	0.000	−0.000
20	S	H	0.063	−0.004	H	−0.000	0.000
21	S	H	0.003	−0.000	H	−0.000	0.000
22	S	H	0.024	0.010	H	0.000	0.000
23	S	H	−0.004	−0.011	H	−0.000	−0.000
24	S	H	0.006	0.001	H	0.000	0.000
25	S	H	−0.059	0.001	H	0.162	0.021
26	S	H	0.002	0.019	H	−0.162	−0.021
27	S	H	0.050	−0.006	H	0.019	−0.006
28	S	H	0.024	0.010	H	−0.019	0.006
29	S	H	−0.013	0.002	H	0.000	0.000
30	S	H	0.008	0.001	H	−0.000	−0.000
31	S	H	−0.000	−0.000	H	−0.000	−0.000
32	S	H	−0.003	0.001	H	0.000	−0.000
33	S	H	0.002	0.000	H	−0.000	−0.000

drugs. Further studies are underway to elucidate the exact nature, strength and geometry of this binding process.

4. Other features

Apart from its use in receptor identification and drug design, the data base can also be profitably utilised in a variety of situations, some of which are:

Table VIII
HOMO and LUMO wavefunctions and energies (CNDO) in flufenamic acid and naproxen

Drug		Flufenamic acid			Naproxen		
MO-Energy (ev)			−10.884	2.289		−10.411	2.018
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
1	S	C	0.005	0.007	C	−0.000	0.001
	PX		0.001	0.008		−0.010	0.001
	PY		−0.018	−0.004		0.002	−0.001
	PZ		0.230	−0.277		−0.379	0.427
2	S	C	0.008	0.000	C	0.005	0.001
	PX		0.026	−0.000		0.017	0.001
	PY		0.023	0.000		0.007	0.001
	PZ		0.298	−0.249		−0.340	−0.263
3	S	C	−0.003	0.001	C	−0.006	−0.002
	PX		−0.011	0.001		−0.016	0.000
	PY		−0.005	−0.000		−0.002	−0.002
	PZ		−0.092	0.477		0.115	−0.267
4	S	C	0.003	0.000	C	0.003	0.001
	PX		0.010	0.000		0.013	0.001
	PY		0.010	−0.000		0.003	0.000
	PZ		−0.363	−0.095		0.385	0.400
5	S	C	0.002	0.002	C	0.002	0.000
	PX		−0.000	0.001		0.007	0.000
	PY		−0.007	−0.001		0.001	−0.000
	PZ		−0.114	−0.392		−0.439	−0.391
6	S	C	0.002	−0.002	C	−0.001	0.000
	PX		0.009	−0.003		−0.003	0.000
	PY		0.015	−0.001		0.002	−0.000
	PZ		0.303	0.386		−0.325	0.248
7	S	C	−0.007	−0.001	C	0.001	−0.000
	PX		−0.001	−0.000		0.003	−0.000
	PY		−0.010	−0.000		0.000	−0.000
	PZ		0.003	0.375		0.073	0.303
8	S	O	0.004	0.002	C	−0.002	0.000
	PX		0.015	0.001		−0.006	0.000
	PY		0.023	0.002		0.001	−0.000
	PZ		−0.177	−0.353		0.347	−0.439
9	S	O	0.004	0.000	C	0.001	−0.000
	PX		0.010	0.001		0.007	−0.000
	PY		0.006	0.000		0.001	0.000
	PZ		−0.018	−0.140		0.136	−0.026
10	S	N	−0.002	−0.002	C	−0.001	0.000
	PX		0.007	−0.003		−0.007	0.000
	PY		0.028	−0.001		0.001	−0.000

Table VIII (*contd.*)

Drug		Flufenamic acid			Naproxen		
MO-Energy (ev)			−10.884	2.289		−10.411	2.018
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
	PZ		−0.602	0.092		0.121	0.027
11	S	C	0.003	0.003	C	0.000	−0.008
	PX		0.007	0.021		−0.020	−0.001
	PY		−0.045	−0.057		−0.010	−0.010
	PZ		0.180	0.064		0.089	−0.017
12	S	C	0.032	0.001	C	−0.007	0.002
	PX		0.048	−0.010		0.007	−0.003
	PY		−0.211	0.025		−0.003	0.002
	PZ		0.071	−0.002		−0.001	0.006
13	S	C	−0.003	−0.001	O	0.003	−0.000
	PX		−0.021	−0.016		−0.011	−0.000
	PY		0.070	0.047		−0.006	−0.000
	PZ		−0.012	−0.048		−0.004	−0.002
14	S	C	−0.004	0.003	O	0.005	−0.001
	PX		−0.043	0.023		−0.022	0.001
	PY		0.125	−0.059		−0.001	−0.003
	PZ		−0.193	0.068		−0.049	0.015
15	S	C	0.013	−0.002	C	−0.046	−0.030
	PX		−0.046	−0.002		0.031	−0.005
	PY		0.057	0.009		0.053	0.032
	PZ		−0.026	−0.008		−0.073	−0.039
16	S	C	−0.046	0.008	O	0.000	−0.000
	PX		0.128	−0.028		0.004	−0.000
	PY		−0.157	0.057		−0.000	−0.000
	PZ		0.074	−0.055		0.281	−0.079
17	S	C	0.024	−0.003	C	0.000	0.000
	PX		−0.010	−0.003		−0.000	0.000
	PY		−0.032	0.011		0.001	−0.000
	PZ		−0.027	−0.008		−0.023	−0.010
18	S	F	0.001	0.007	H	−0.001	−0.001
	PX		0.005	0.003			
	PY		0.014	−0.001			
	PZ		0.004	−0.014			
19	S	F	−0.003	0.000	H	−0.013	−0.000
	PX		0.011	0.000			
	PY		0.011	−0.003			
	PZ		0.013	0.002			
20	S	F	−0.005	−0.006	H	−0.001	−0.001
	PX		−0.008	−0.007			

Table VIII (*contd.*)

Drug		Flufenamic acid			Naproxen		
MO-Energy (ev)			−10.884	2.289		−10.411	2.018
Atom no.	AOs	Atom	HOMO	LUMO	Atom	HOMO	LUMO
	PY		0.027	0.011			
	PZ		0.012	0.001			
21	S	H	0.033	−0.001	H	0.001	−0.000
22	S	H	−0.052	0.003	H	−0.004	0.000
23	S	H	0.006	−0.003	H	−0.000	−0.000
24	S	H	−0.061	0.001	H	0.110	0.074
25	S	H	−0.022	−0.015	H	−0.002	0.001
26	S	H	0.027	−0.001	H	−0.023	0.003
27	S	H	−0.013	−0.001	H	0.046	0.015
28	S	H	−0.003	0.000	H	0.007	−0.008
29	S	H	0.009	−0.002	H	−0.001	0.000
30	S	H	−0.004	−0.000	H	−0.047	0.018
31					H	0.048	−0.018

For a given drug/model receptor, in a given geometry, one can have from the data base the following information:

(i) Cartesian coordinates of all the atoms, including hydrogens.

(ii) The net charges on all atoms, which enables one to guess the electrophilic or nucleophilic sites of attack.

(iii) The energies of HOMO (SOMO1, SOMO2) and LUMO (SUMO1, SUMO2) data enables us to make predictions regarding the relative propensities of involvement of these orbitals with other molecules. It may be recalled here that much of the success of the now famous Woodward-Hoffmann rules on conservation of orbital symmetry during reactions in organic chemistry, is essentially based on the symmetries of the HOMO/LUMOs. It may be useful to apply the HOMO, LUMO data available from the point of the above rules, to understand the mechanism of drug-receptor interactions at the molecular level.

(iv) The availability of all the MOs of molecules, from the data base facilitates us to set up easily molecular orbital interaction patterns with any other drug or receptor molecule. Questions like stereoselectivity (d/l isomer binding), or specificities of interaction in complex formation, of which hydrogen bonding is a popular case, can be analysed using the data bank and the interaction energy program.

Table IX
The net charges on the various functional groups in the given series of drugs

(i) the $-C-O-R$ group

Drug	$-C$	$-O$	$-R$
Paracetamol	0.167	−0.245	0.127(H)
Naproxen	0.184	−0.218	0.123(CH_3)
Phenacetin	0.163	−0.227	0.162(CH_2)
Aspirin	0.202	−0.245	0.400(C = 0)

(ii) the $-COOH$ group

Drug	$-C$ (ar)	$-C(CO)-$	$O(CO)$	$-O(OH)$	$-H(OH)$
Aspirin	−0.091	0.388	−0.317	−0.295	0.179
Enfenamic acid	−0.101	0.396	−0.351	−0.277	0.162
Mefenamic acid	−0.113	0.403	−0.372	−0.265	0.167
Naproxen	−0.026(CH_2)	0.393	−0.334	−0.273	0.167
Ibuprofen	−0.033	0.393	−0.312	−0.270	0.160

(iii) the $-NH-$ group

Drug	$-C$	$-N(H)$	$H(N)$	$-C$
Paracetomol	0.120	−0.215	0.106	0.347($C_{C=O}$)
Phenacetin	0.121	−0.186	0.104	0.362($C_{C=O}$)
Enfenamic acid	0.182	−0.233	0.153	0.119(C_{ar})
Mefenamic acid	0.199	−0.219	0.154	0.124(C_{ar})

(v) The data base can serve as an educational aid as well. It can help biochemists, pharmacologists, chemists and molecular physicists to understand the concepts and features of molecular orbital theory and methods.

5. Conclusions

We have outlined a new computational molecular modelling approach, based on drug-(model) receptor interaction studies, to arrive at a self-consistent model for the active site structure of a receptor. Unlike the current QSAR methods, our approach is based on a sound theory, *viz.* quantum mechanics, and possesses the potential to provide a molecular level interpretation of drug action, interaction and design. The need and features of the associated data base are also highlighted. Our own results utilizing the data base will be discussed elsewhere.

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