

# Applications of Quantum Chemical Methods in Drug Design

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## 1. Introduction

Quantum mechanics (QM) is an essential and widely used tool in computer-aided drug research. The comprehensive utility of QM is exemplified in this chapter via several case studies performed in our laboratory. In section 2.1 we describe a routine, which we have used to obtain accurate force field parameters from results of ab initio calculations on small model structures. Probably the most important application of QM is the explicit description of the electronic structure of a molecule. In this context, section 2.2.1 demonstrates the consequences of  $\pi$ -delocalization and atom hybridization on molecular geometry and section 2.2.2 highlights the potential importance of QM for conformational analyses. Another important area of QM application is the calculation of atomic point charges (section 2.3), which can be used to study binding properties such as intermolecular Coulomb forces, hydrogen bonding, and molecular electrostatic potentials (section 2.4). Section 2.5 presents investigations on charge-transfer complexes which may play a role in molecular recognition processes. The chapter is concluded with an outlook. It should be noted that only a subjective selection of typical and fairly simple “every day” implementations is given in this chapter; no attempt was made to survey the comprehensive literature in this field. Rather, we intend to demonstrate the general utility of QM calculations in molecular modeling.

## **2. Application Examples**

### **2.1 Force Field Parameters from Ab Initio Calculations**

Since modeling studies on drug interactions with biological targets such as receptors, enzymes or other biomacromolecules involve large chemical systems, thus molecular mechanics methods have to be applied. In molecular mechanics molecules are considered as a collection of masses (atoms) held together by elastic or harmonic forces, analogous to a ball-and-spring model. These forces can be described by potential energy functions of structural features like bond lengths, bond angles, torsional angles and non-bonded interactions [1]. Often modelers face situations in which the force field in use lacks parameters for single atoms or particular combinations of atoms. In principle, new parameters can be introduced by analogy with existing values, by trial and error adjustment to fit experimental data, or by the use of quantum mechanics. The effort which is required to develop the new parameters should be related to the weight of the scientific question under consideration. If accurate parameters are needed, quantum mechanical calculations must be performed. In studies on dopamine D<sub>3</sub>-receptor agonists, recently carried out in our group realistic molecular geometries for some of the ligands were lacking [2]. In detail several bond stretching and angle bending parameters for five-membered heterocycles were undefined in the consistent valence force field (CVFF) of INSIGHT/Discover [3]. A variety of techniques for obtaining force field parameters have been proved. They can be deduced from two main strategies, as shown in the following diagrams (Fig 1a and Fig 1b). Both strategies have been applied successfully to a large variety of molecules.

Particular problems arise in the parametrization of cyclic systems. Methods, based on geometrical distortions, like for example Hopfinger's method A [4], are unsatisfactory, because bond lengths and angles have to be treated independently. This problem is avoided applying method B. Leonard and Ashman have developed the method to parameterize force constants for bond stretching and angle bending for the MM2 force field [5]. They used the diagonal elements of an ab initio Hessian to calculate the corresponding numerical values. The Hessian is the matrix of second derivatives of the energy with respect to Cartesian coordinates of the atoms and the diagonal elements are the force constants associated with each of the variables. In this context, the variables are the bond lengths, the bond angles, and the torsion angles determined in the Z-matrix defining the molecule. If the molecule is made up of  $n$  atoms, the variables are defined as  $n - 1 =$  bond lengths,  $n - 2 =$  bond angles, and  $n - 3 =$  torsion angles. After geometry optimization of a molecule, the Hessian matrix is available as output, but only for quite small molecules (in GAUSSIAN-92 it was restricted to twenty variables, corresponding to only eight atoms). To bypass this problem, a frequency calculation must be added after geometry optimization. Examining the eigenvalues of the matrix can ensure that the geometry optimization did not locate a saddle point, but rather a minimum, which is required for any further step. Both saddle point and minimum are so-called stationary points, characterized by a zero gradient (first derivative with respect to the atom coordinates). But a minimum of a multidimensional potential energy surface is characterized by exclusively positive eigenvalues of the Hessian matrix, whereas a saddle point corresponds to at least one negative

eigenvalue (a first-order saddle point is characterized by one negative eigenvalue, a second-order saddle point by two negative eigenvalues and so forth). The easiest way to distinguish the type of stationary point, however, is to consider the number of frequencies (NIMAG) at the end of the GAUSSIAN output. "NIMAG = 0" means that no vibrational frequencies exist and a minimum has been found. The next two steps in the procedure of Leonard and Ashman are the conversion of the diagonal elements from atomic units into force field units and the calculation of scaling factors for bond lengths and angles. The calculated force constants had to be scaled down by approximately 25 % and 70 % to yield force constants comparable in numerical size to those included in MM2. Neither force constants nor scaling factors can be incorporated directly into a different force field. A modification of the described procedure that meets the requirements of CVFF was developed. Fragments with known force field parameters were chosen. After a full geometry optimization (HF/6-31G\*) second derivatives and vibrational frequencies were calculated. The force constants were extracted from the GAUSSIAN output and converted from atomic into CVFF units. Now a linear regression of the calculated values versus the original CVFF force constants was performed. The resulting correlation functions confirmed a linear relationship between the Hessian diagonal elements and the CVFF force constants, and could be used to scale newly calculated force constants. Beyond force constants, values for the unstrained, equilibrated bond lengths and angles are needed for a force field calculation. These values can be taken from crystal structures, but it must be considered that x-ray data may be deceptive. Many structural details result from interactions of the molecule with

its neighbors (packing forces), which usually do not exist in the environment of interest. A second disadvantage is the latitude in the quality of crystal structures, even at low  $R$  factors. A third limitation is that, depending on the temperature, molecules are vibrating in the crystals. Because of these “rigid body motions”, x-ray bond lengths can be substantially too short. Another problem is that x-rays measure the center of the electron density, but not the nuclear position. Force field programs, however, are based upon nuclear positions. The crystallographic measurement of electron densities tends to prolong C-N and C-O bonds, because the lone pair sticks out, so that the center of electron density is further away from the carbon than is the nucleus. Bonds to hydrogens are always too short in x-ray measurements, because the electron is pulled toward the atom to which it is bonded. Thus, to avoid the uncertainty of crystal data, one can use reference values from ab initio calculations. Nonetheless, calculated values for bond lengths of double, triple, and hydrogen bonds may be too short. Large basis sets with polarization functions and electron correlation are required for reliable descriptions.

### **2.2.1 Equilibrium Geometry for a Dopamine-D<sub>3</sub>-Receptor Agonist**

Molecular mechanics methods achieve good structural accuracy for classical molecules, whereas their reliability for species with particular combinations of atoms may be questionable, particularly in the case of molecules containing heteroatoms, which affect geometry and conformation via the position of their lone-pairs. Force field programs for example often fail to calculate the geometry

of particular nitrogen atoms. The development of a pharmacophore model in a study on dopamine agonists required the prior optimization of the aminothiazole derivative pramipexol (Fig. 2) [6]. Force fields offer pure  $sp^3$  or pure  $sp^2$  hybridization for the classification of the nitrogen in the  $NH_2$  group. It is known, however, that the nitrogen atom in aniline (aminobenzol) exhibits an intermediate geometry between a pyramidal and a trigonal planar condition, due to a certain population of  $sp^2$  hybridization [7]. The  $NH_2$  group of the aminothiazoles is connected to a heteroaromatic five-membered ring with  $sp^2$  geometry, thus creating a similar environment as  $NH_2$  in aniline. Analyzing crystal data of aminothiazoles could not solve the problem, since the available structures show both planar and slightly tetrahedral geometries [8]. A planar geometry of the  $NH_2$  group is supported by a possible tautomeric exchange of hydrogens between the  $NH$ - and the  $NH_2$  group, whereas a more pyramidal geometry is supported by the fact that the ring-nitrogen is more electronegative than the sulfur and thus causes the sulfur to push electrons into the ring which may cause a higher percentage of  $sp^3$  hybridization on the  $NH_2$  group, since its lone pair is not that much attracted by the ring. This assumption was confirmed by quantum chemical calculations. 2-Amino-1,3-thiazole was geometry optimized starting from two different points (a: pyramidal  $NH_2$ , b: planar  $NH_2$ ) using 3-31G\* and 6-31G\*\* Hartree-Fock methods. Both basis sets yielded a slightly pyramidal geometry as energetically more favorable. It should be kept in mind however, that solvation and the formation of hydrogen bonds can lead to a change in the tautomeric forms of heterocyclic compounds. In those cases a trigonal planar arrangement at the  $NH_2$  group should be energetically more

favorable, as already mentioned. Thus, despite the result of the QM optimization which corresponds to vacuum conditions, the presence of hydrogen bonding partners may introduce a planar geometry.

### **2.2.2 Searching for a Bioactive Conformation**

This issue will be exemplified by our pharmacophore search for a series of 17 $\alpha$ -hydroxylase-17,20-lyase inhibitors [9]. 17 $\alpha$ -hydroxylase-17,20-lyase converts gestagens such as progesterone and pregnenolone to androgens by 17 $\alpha$ -hydroxylation, followed by the cleavage of the side-chain. Because of its key role in the biosynthesis of androgens, inhibition of this enzyme results in a total blockade of androgen production. Thus, the enzyme represents an interesting target in the treatment of prostate cancer. The development of potent enzyme inhibitors requires a detailed understanding of their binding mode. The ability of ligands to bind to a receptor site is reflected by the three-dimensional (3D) shape of the ligand in the receptor bound conformation (bioactive conformation). A pharmacophore hypothesis can be derived from a series of known ligands and their common 3D-features. The pharmacophore is constructed by superimposing energetically favorable conformations of all ligands according to their consensus in structural features. The template structure for the superposition should fulfill the following criteria: i) the compound should be very potent, because then its molecular structure contains all essential features for high affinity and ii) the structure should be rigid or semi-rigid to facilitate the search for the bioactive conformer. The highly potent

compound MH3, a semi-rigid 17 $\beta$ -substituted aziridiny-steroid was chosen as template (Fig. 3). In this molecule only the bond between the steroid skeleton and the aziridine moiety can freely rotate. A molecular mechanics conformational analysis resulted in two low energy conformations (Fig. 4), which both had an almost identical potential energy as calculated in the Tripos force field [10]. Both conformers differ in the position of the nitrogen lone pair, pointing in two different directions. However, the lone pair is essential for enzyme inhibition. The ligands directly interact with the heme iron of the enzyme forming a coordinative bond via the nitrogen lone pair. Accordingly, the orientation of the lone pair is critical for the pharmacophoric superposition. Both conformers were studied in more detail using a quantum mechanical approach. Applying the ab initio 3-21G\*\* basis set, a geometry optimization revealed a significant energy difference between the two conformers. Consequently, the resulting minimum-energy conformation was chosen as the template structure. Another structural feature to be investigated was the NH-group in the aziridine ring, which normally exhibits pyramidal inversion. However, this NH is part of a conformationally very restricted three-membered ring with a high inversion barrier at biological temperatures. The nitrogen inversion process of strained NH aziridine rings has been the subject of a large number of scientifically very interesting quantum chemical investigations [11]. Experimental investigations on aziridines revealed a strong inversion even at low temperatures [12]. It subsequently became apparent that NH aziridines can achieve inversion by hydrogen exchange. In the presence of water the aziridine invertomers are rapidly interconverted at room temperature by a protonation-deprotonation

process. On the basis of ab initio calculations, it was suggested that the protonation-deprotonation is effected via a NH-bonded aziridine-2 H<sub>2</sub>O complex that promotes rapid site exchange of the geminal ring hydrogen atoms [13]. An ab initio geometry optimization of the MH3 invertomers with the 3-21G\*\* basis set revealed no significant energy difference between the configurations. Thus, this problem could not be solved from calculations and both invertomers of the minimum conformation had to be considered in the following steps of our study.

### **2.3 Atomic Point Charges**

An accurate treatment of the electron density distribution is required to determine the electrostatic properties of molecules. Thus, appropriate methods for obtaining atomic charges are of particular importance. Commercial modeling software packages offer the possibility of calculating atomic charges very easily using topological methods, which are based mainly on the electronegativity of different atom types. The algorithms used combine the atomic electronegativities with experimentally derived parameters on the bond types linking the atoms. The point charge of each atom is calculated, taking into account its own electronegativity as well as the electronegativities of the directly connected neighbor atoms and the types of their covalent bonds. Clearly, geometrical and conformational influences are neglected in these algorithms, their main advantage being that they are computationally fast. But in particular in the case of polar molecules the use of topological methods to derive atomic charges can be unreliable due to the inappropriate treatment of mesomeric or

inductive effects. Where electronic effects predominate, molecular properties are best studied using quantum chemically derived atomic charges. Two general techniques are used to extract charges from wave functions: i) the Mulliken population analysis based on partitioning the electron distribution and ii) the ESP method based on fitting properties, which depend on the electron distribution to a model which replaces this distribution by a set of atomic charges. Both methods can be performed with ab initio and semi-empirical program packages. Semi-empirical calculations are fast and user friendly and therefore represent attractive methods to obtain quantum mechanical results. In our experience, however, one should carefully interpret data from semi-empirical calculations involving nitrogen atoms in unsaturated systems. In order to compare the molecular electrostatic potentials of some 17 $\alpha$ -hydroxylase-17,20-lyase inhibitors (see Section 2.2.2) we have performed semi-empirical PM3 charge calculations. In the case of ligand MH61 (Fig. 5) the Mulliken and the ESP method offered rather different results for the oxime group. The oxime contains an oxygen and a nitrogen in the same molecular segment, both of which can form a coordinative bond to the heme iron. In general, due to its higher electronegativity, oxygen is expected to be a better bonding partner than nitrogen. Nevertheless, the nitrogen in the oxime group should be able to compete as binding partner for the iron. The Mulliken method assigned a much stronger negative charge to the oxygen (-0.262) than to the nitrogen (-0.037), whereas ESP charges offer a more negative value for the nitrogen atom (O = -0.258; N = -0.390). Corresponding to the different charge distributions one will obtain different pharmacophore models. Which method provides the “better”

atomic charges? An analysis of intermolecular interactions in crystal structures of oxime molecules has been used to answer that question. In all available complex structures with one central metal ion, we found no coordinative bonds from the oxime oxygen to the metal, but exclusively coordination between the nitrogen atom and the metal ion (data were retrieved from the Cambridge Crystallographic Database [14]). In a comprehensive study, Böhm et al. investigated complexes of oxazoles, methoxypyridines and oxime ethers with water [15]. Based on interaction energies obtained from ab initio calculations, they found the oxygen atoms as rather weak hydrogen bond acceptors when  $sp^2$ -type nitrogen atoms are present in the same fragment. Thus, ESP-derived atomic point charges seem to be more appropriate to the subsequent calculations of the molecular electrostatic potential. This example shows that charges from semi-empirical calculations should not be used without validation.

## **2.4 Molecular Electrostatic Potentials**

The molecular electrostatic potential (MEP) can be used to investigate molecular interactions. If polar molecules approach each other, the initial contact arises from long-range electrostatic attractions. These electrostatic interactions can be either attractive or repulsive. An electropositive part of an approaching molecule will seek to dock to an electronegative region; similarly charged parts will repel each other. Due to the charges and dipole moments in a molecule, an electrostatic field is generated in its environment. Consequently, distinct molecular electrostatic potentials exist at specific distances from the

molecules. These can be represented in molecular modeling programs as interaction energy fields derived from the atomic charges and a positive point charge (a kind of proton model) which is located in a 3D grid surrounding the molecule. We applied this method for example to find a biologically relevant conformation for H<sub>2</sub>-antagonists used for ulcer therapy. The compounds occupy the histamine binding site of the histamine H<sub>2</sub>-receptor, thus inhibiting the histamine induced gastric acid secretion. Four main structural classes (Fig. 6) are utilized as drugs: imidazole derivatives (cimetidine), basically substituted furanes (ranitidine), guanidinothiazoles (famotidine) and aminoalkylphenoxy derivatives (roxatidine). All these antagonists were supposed to occupy a common receptor binding site [16]. Since the 3D-structure of the receptor is not yet known, we wanted to derive a pharmacophore model, to prove this hypothesis. Most of the H<sub>2</sub>-antagonists exhibit a high degree of conformational freedom. The evaluation of available crystal data and a systematic conformational search revealed mainly bent conformations partly with intramolecular hydrogen bonds as most favorable. This result is in accordance with an investigation on the H<sub>2</sub>-antagonist metiamide. The authors have used the Hartree-Fock method with three different basis sets (3-21G\*, 6-31G\*\* and 6-31+G\*\*) to study the conformational properties of metiamide [17]. The calculations clearly indicate the preference for a folded conformation with an hydrogen bond between the imidazole ring and one of the NH groups, similar to the crystal structure (Fig. 7). However, calculations with one isolated molecule in vacuum often result in an overestimation of intramolecular contacts, since competing interaction partners are absent. We started our investigation with the

semi-rigid guanidinothiazole ICI27032, a potent competitive H<sub>2</sub>-antagonist which adopts solely extended conformations, due to its aromatic ring system (Fig. 8). The molecular electrostatic potential of the energetically most favorable ICI27032 conformation has been calculated using AM1 ESP point charges. In a next step, we searched for energetically favorable conformations of the other antagonists which yielded MEPs similar to the MEP of the ICI27032 template. The results are displayed in Fig. 9. All the selected extended conformations exhibit an extremely similar spatial distribution of the MEP properties despite their different chemical fragments. It is therefore reasonable to suppose that all compounds could be recognized by the receptor in this extended conformation.

## 2.5 Molecular Orbital Calculations

This section deals with the application of molecular orbital (MO) calculations in structure-activity relationship (SAR) analyses. Calcium channel blocking 1,4-dihydropyridine (DHP) derivatives like nifedipine (Fig. 10) are widely used in the therapy of cardiovascular disorders. Radiolabelling experiments and site-directed mutagenesis clearly reveal the  $\alpha_1$ -subunit of L-type calcium channels as binding site. However, no experimentally derived 3D-coordinates of the receptor protein and its DHP binding site are available to elucidate the forces involved in specific binding. Hydrogen bond donor properties of the NH-group and at least one further hydrogen bond accepted by the carbonyl groups of the ester side chains combined with electrostatic attractions are indicated as the main binding forces by SAR analyses. However, it has been demonstrated that

these binding elements cannot solely account for the high affinity of some compounds. The affinity of 23 nifedipine-like DHPs (Fig. 11) has been determined in radioligand binding experiments. The  $pK_i$ -values range over more than five log units, although the single structural change has been the varied substitution pattern of the 4-phenyl ring. Until now it is not clarified whether the ring substituents interact directly with the binding site or if they influence the molecular characteristics of the DHP molecules in common. A recently used atomistic pseudoreceptor model for a series of DHPs indicated a putative charge-transfer interaction for stabilizing the DHP/binding site complex [18]. In order to prove this hypothesis, a qualitative and quantitative analysis of the molecular orbitals of nine DHP derivatives has been performed [19]. Charge-transfer (or electron-donor-acceptor) interactions indicate an electronic charge transfer from the HOMO of a donor molecule ( $HOMO_d$ ) to the LUMO of an accepting neighbor molecule ( $LUMO_a$ ). Small energy barriers between  $HOMO_d$  and  $LUMO_a$  increase the probability of charge transfer but with two further additions: The corresponding molecular orbitals must be able to overlap and  $HOMO_d$  and  $LUMO_a$  must be energetically close (Fig. 12). In the case of a charge-transfer interaction for the stabilization of the DHP/binding site complex, the electron-accepting LUMO should be located at the 4-phenyl ring of the DHPs, since highest binding affinities are found for derivatives with electron-withdrawing substituents at this position. Using the semi-empirical AM1 method, the molecular structures of the DHPs were optimized and the molecular orbitals were computed (the author had demonstrated the reliability of AM1 by comparing results from high level ab initio calculations). In order to assign

correctly the unoccupied molecular orbitals localized at the 4-phenyl ring (designed as LUMO\*) all relevant unoccupied orbitals (LUMO, LUMO+1, LUMO+2...) have been visualized. In nearly all cases the LUMO was positioned at the 1,4-dihydropyridine heterocycle. Only for compound **3NO<sub>2</sub>** (3'-NO<sub>2</sub>) and **F<sub>5</sub>** (1',2',3',4',5'-F<sub>5</sub>) the LUMOs are identical with the LUMO\*s (Fig. 13). All the other DHPs, which lack comparably potent electron-withdrawing substituents, contain only energetically less favorable LUMO\*s (LUMO+1 and LUMO+2) at the aromatic ring system. In contrast to the situation described so far, compounds **3N<sub>3</sub>** (3'-N<sub>3</sub>) and **3OMe** (3'-OCH<sub>3</sub>) have the HOMO instead located at the 4-phenyl ring. Apparently, electron-donating moieties cause an electron excess at the 4-phenyl ring, thereby inducing the formation of occupied MOs at this position. Therefore, the existence of energetically favorable LUMO\*s at the 4-phenyl ring becomes more unlikely. In order to decide whether charge-transfer interactions may play a major role in the receptor binding of DHPs, the experimentally derived free binding energies ( $\Delta G$ ) were correlated with the calculated LUMO\* energies and a highly significant correlation coefficient of 0.91 was obtained (see Fig. 14). On examining these results, one has to keep in mind that  $\Delta G$  values not only mirror charge-transfer interactions but a multitude of ligand-dependent direct (hydrogen bonding, electrostatic, van der Waals, and hydrophobic binding forces) and indirect factors (solvation energies and entropic terms). Assuming that all investigated DHPs besides the charge transfer exert almost identical direct interactions, one could argue that indirect factors narrow the interpretation of the data. However, due to the limited structural variation of the compounds (only a single functional group is modified)

approximately the same entropic effects may be postulated. Thus, the obtained correlation should reflect the influence of potential 4-phenyl ring charge-transfer interactions on the binding affinities of the DHPs. To determine whether a reliable model had been found the binding energy of a novel DHP was predicted. Calculations were carried out to determine the LUMO\* of the most active DHP isradipine, a compound which carries a benzoxadiazole ring instead of the 4-phenyl ring. The LUMO\* energy indicated a very strong charge-transfer complex and ranked the compound in accordance with the experimental data as most potent (see Fig. 14).

### **3. Outlook**

It has been demonstrated with a few examples that the application of quantum mechanics is an essential tool in the molecular modeling area of medicinal chemistry. However, it is not yet playing a role in disciplines where the size of the molecular systems is too large to allow a study using ab initio methods. The development of massively parallel supercomputers should offer the potential to predict molecular properties relevant to a variety of problems in medicinal chemistry like penetration, diffusion or metabolic processes. Computational calculations have a good chance of representing “reality” if they are based on quantum theory. This makes molecular modeling more reliable and offers the opportunity to complement experimental measurements.

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## Figure legends

Figure 1a.

Schematic architecture of force field parameterization procedures for bond lengths and bond angles according to Hopfinger and Pearlstein [4]. In a first step model fragments with known parameter are slightly varied in their geometry and the resulting energy profile is calculated. The parabolic run of the energy curve allows to calculate the parabola opening constant ( $b_{2i}$ ) from a quadratic regression analysis. If a linear correlation ( $r > x$ ) of  $b_{2i}$  and the known force constant ( $k_{FF}$ ) is achieved, the method is suitable for the estimation of lacking force field parameters. Parameters for ring systems are derived from nonring model fragments.

Figure 1b.

Schematic architecture of force field parameterization procedures for bond lengths and bond angles according to Leonard and Ashman [5]. Fragments used for parameterization are optimized. A frequency calculation is included. The Hessian matrix comprises the second partial derivatives of the wave functions with respect to displacement of the atom coordinates. Diagonal elements are the force constants associated with each variable (bond lengths, angles, dihedrals). The extracted force constants have to be converted from atomic units to force field units and have to be adjusted to the force field values.

Figure 2.

Structural formula of the dopamine agonist pramipexol.

Figure 3.

Structure of the 17 $\alpha$ -hydroxylase-17,20-lyase inhibitor MH3.

Figure 4.

Two energetically favorable conformations of the MH3 aziridine ring. Both conformers differ in the position of the nitrogen lone pair (displayed in magenta).

Figure 5.

Structural formula of the 17 $\alpha$ -hydroxylase-17,20-lyase inhibitor MH61.

Figure 6.

Structural formulas of H<sub>2</sub>-receptor antagonists, which are used for ulcer therapy. The compounds can be divided into four different chemical classes: imidazole derivatives (cimetidine), furanes (ranitidine), guanidinothiazoles (famotidine), phenoxy derivatives (roxatidine).

Figure 7.

Crystal structure of the H<sub>2</sub>-antagonist metiamide with an intramolecular hydrogen bond (yellow dots) between the imidazole nitrogen and an NH group of the side chain.

Figure 8.

Chemical and conformational structure of the H<sub>2</sub>-antagonist ICI27032.

Figure 9.

Molecular electrostatic potentials of the H<sub>2</sub>-antagonists. The MEPs have been calculated on the basis of AM1 point charges and are contoured at  $-1 \text{ kcal mol}^{-1}$  (blue),  $\pm 0$  (yellow), and  $1 \text{ kcal mol}^{-1}$  (red).

Figure 10.

Structure of the calcium channel blocker nifedipine.

Figure 11.

Experimentally derived free binding energies ( $\Delta G$ ) of the investigated DHP derivatives. [Adopted from 19].

Figure 12.

Schematic representation of a charge transfer interaction. The solid arrow illustrates  $\pi$ -electron transfer between the HOMO of the donor molecule ( $\text{HOMO}_D$ ) and the LUMO of the acceptor molecule ( $\text{LUMO}_A$ ). Dashed arrows indicate interactions between corresponding HOMOs and LUMOs of one molecule. [Adopted from 19].

Figure 13.

Molecular orbital plots. The LUMO of compound **H** (left) is located on the 1,4-dihydropyridine heterocycle whereas for compound **3NO<sub>2</sub>** it is located on the 4-phenyl ring (right).

Figure 14.

Correlation of the calculated LUMO\* energies and the experimentally derived free binding energies ( $\Delta G$ ) of the investigated DHP compounds. The asterisk on the extrapolated dotted line depicts the calculated LUMO\* energy of the most active compound isradipine [adopted from 18].

# METHOD A

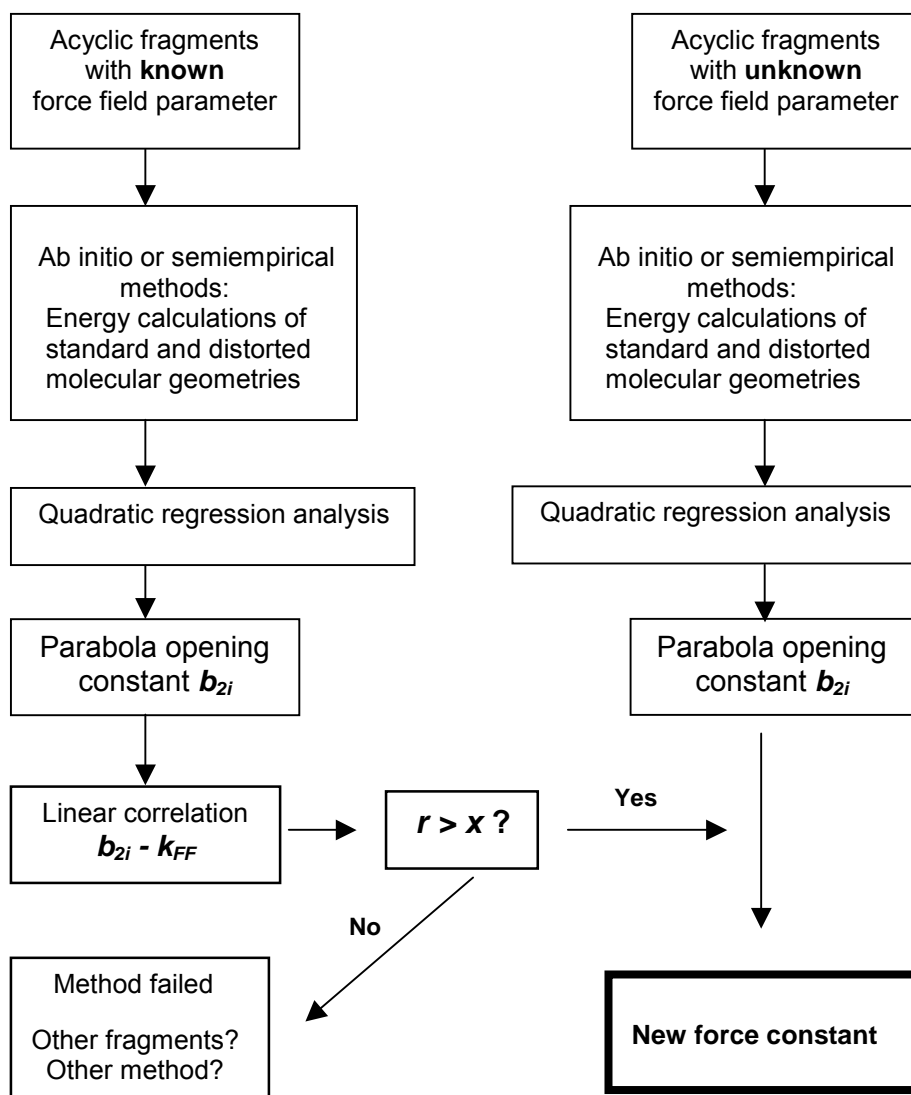


Figure 1a

## METHOD B

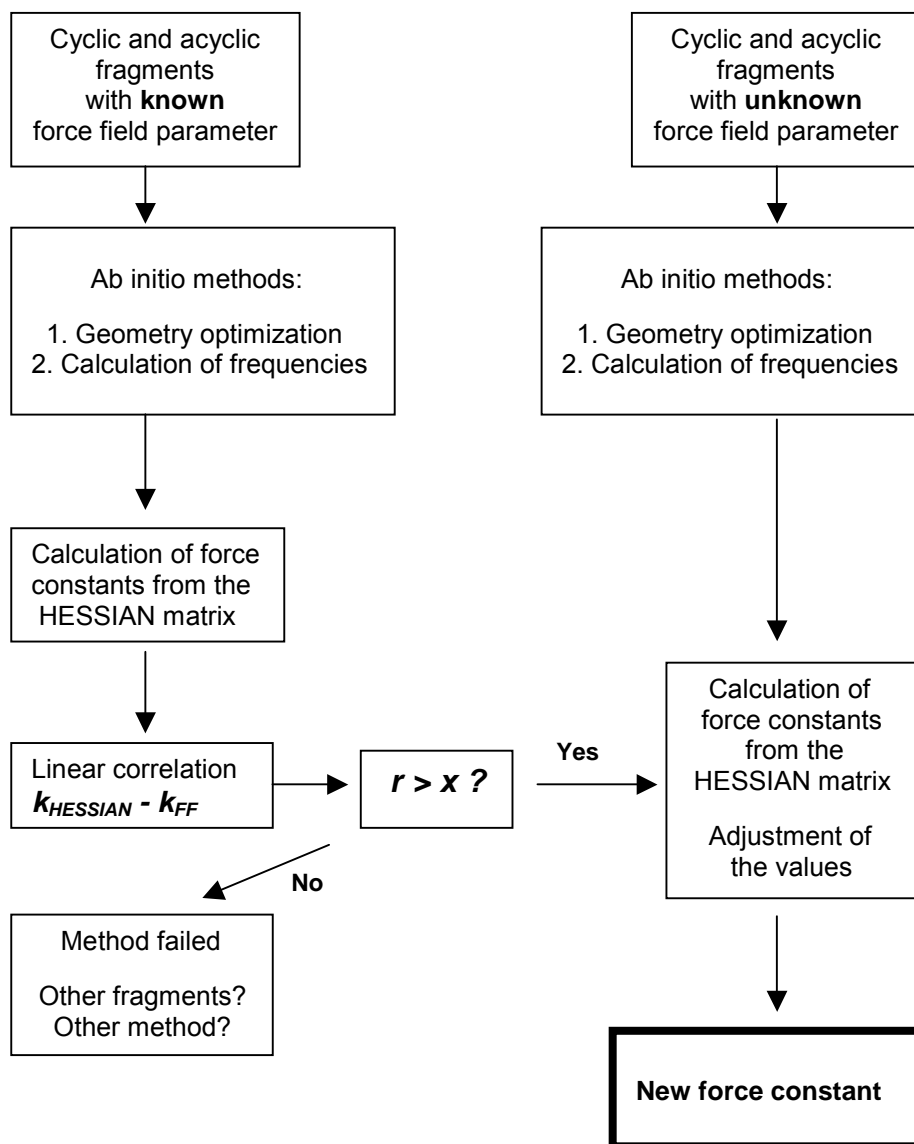
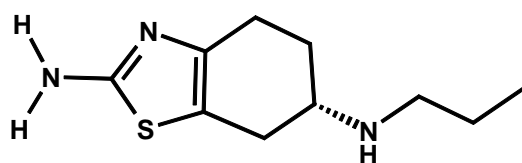
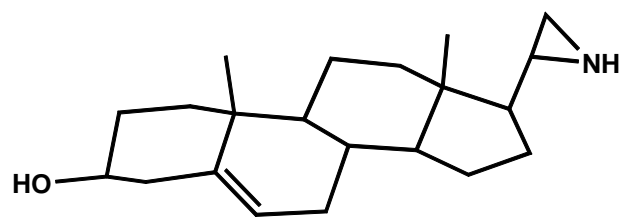


Figure 1b





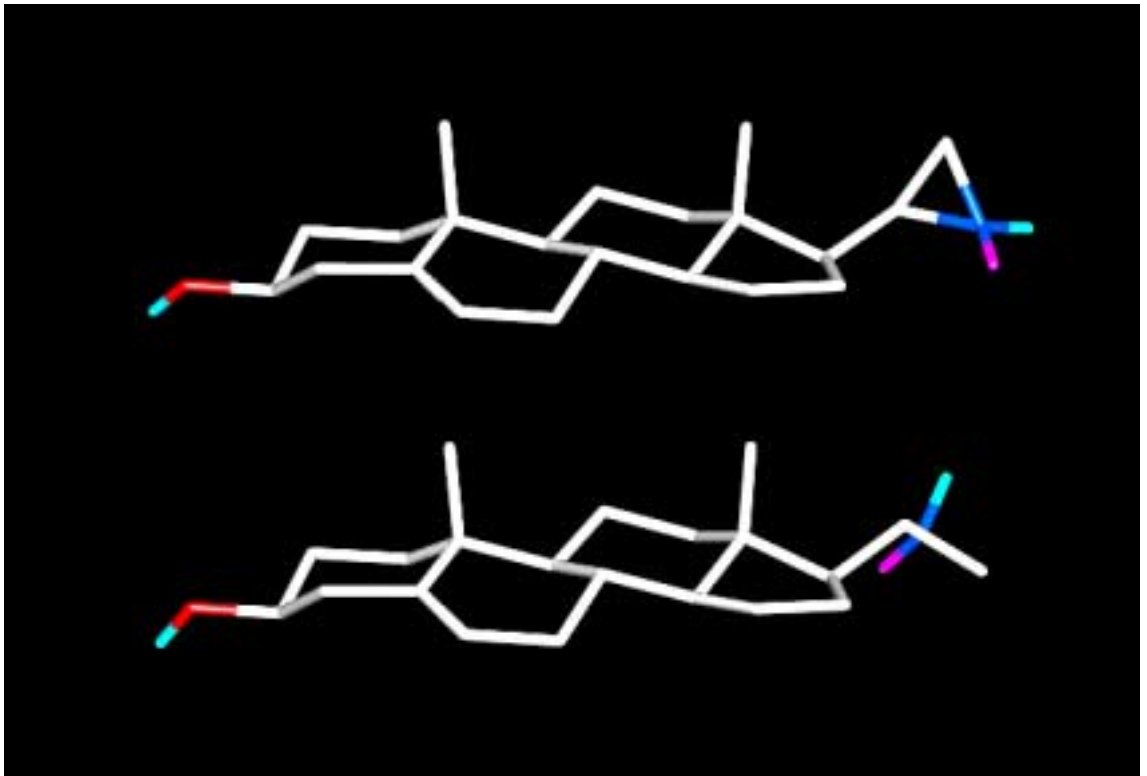
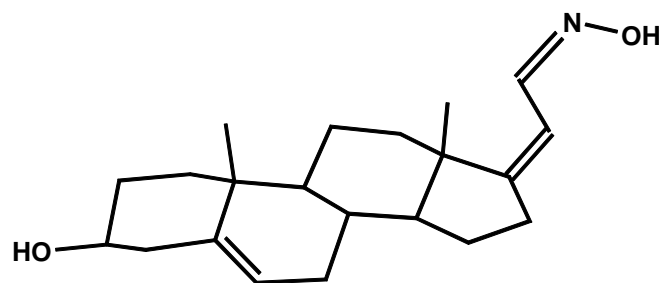
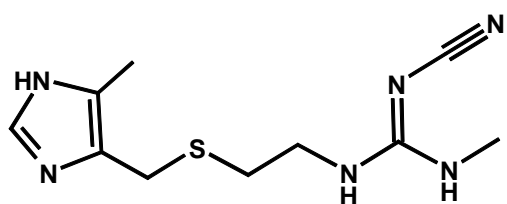
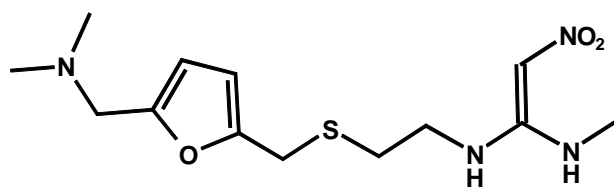


Figure 4

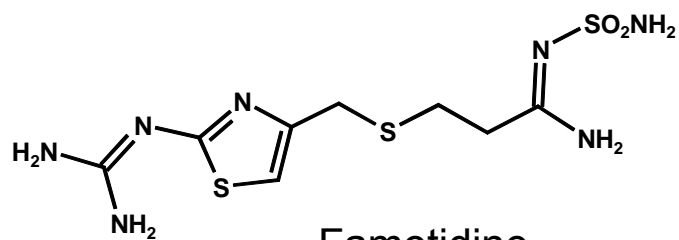




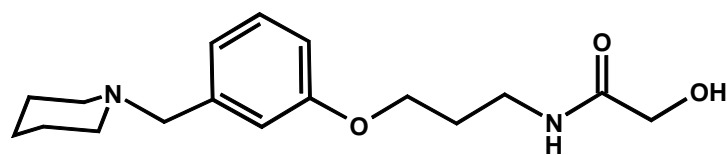
Cimetidine



Ranitidine



Famotidine



Roxatidine

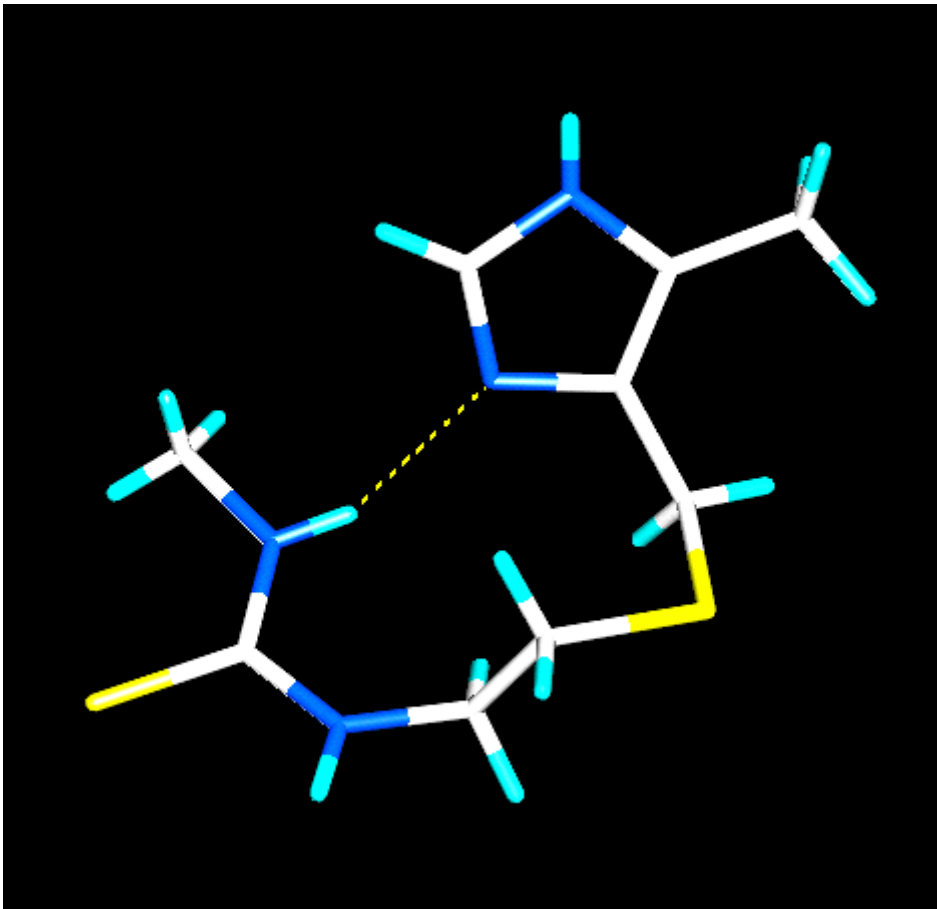


Figure 7

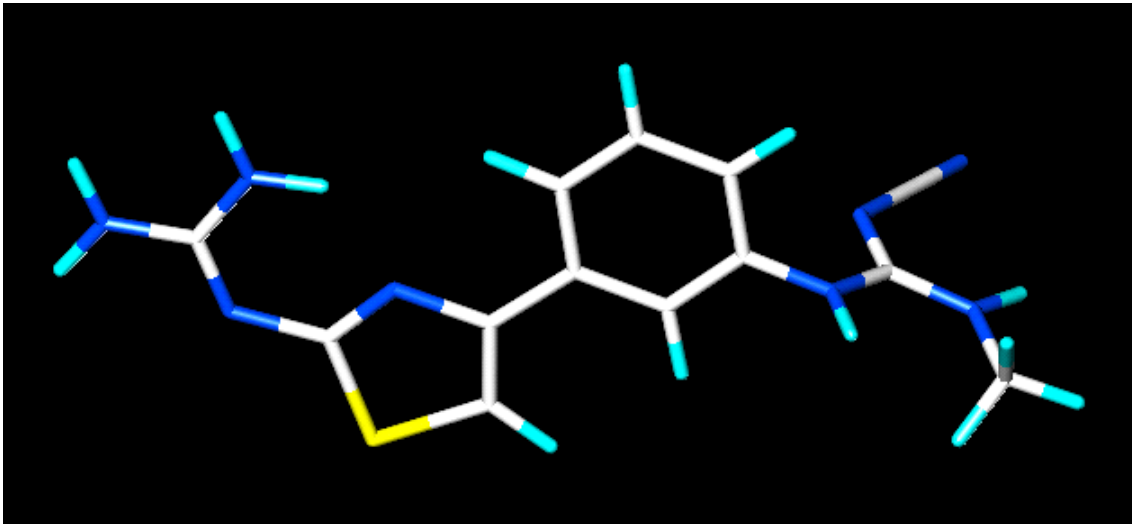
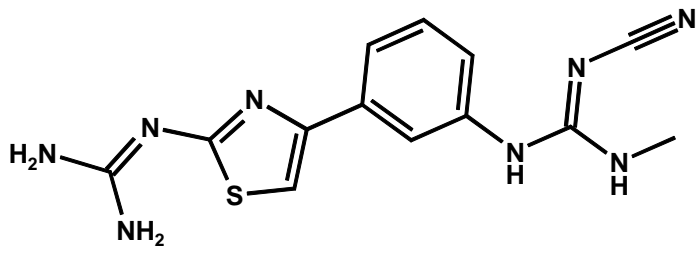
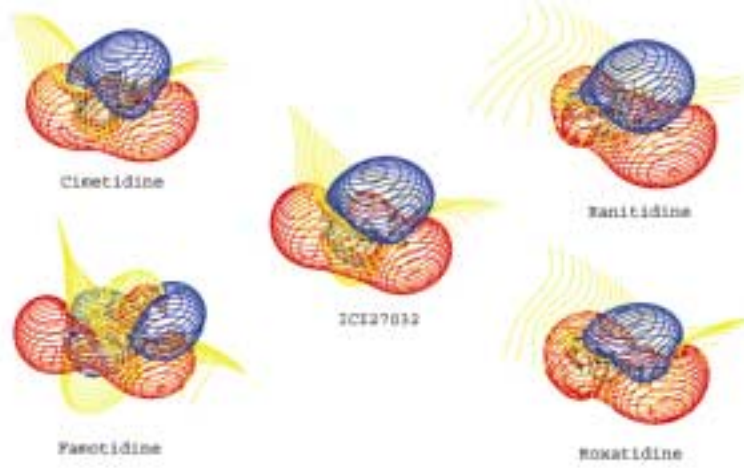


Figure 8



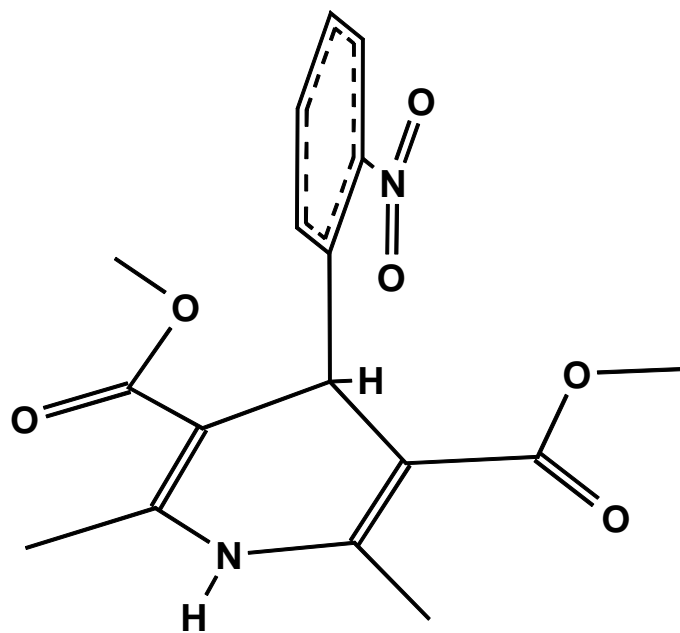
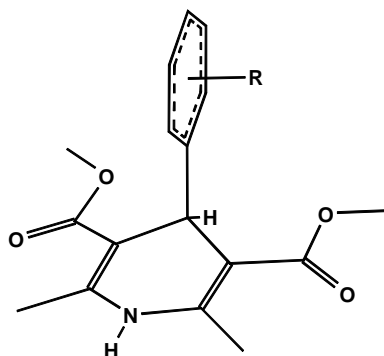
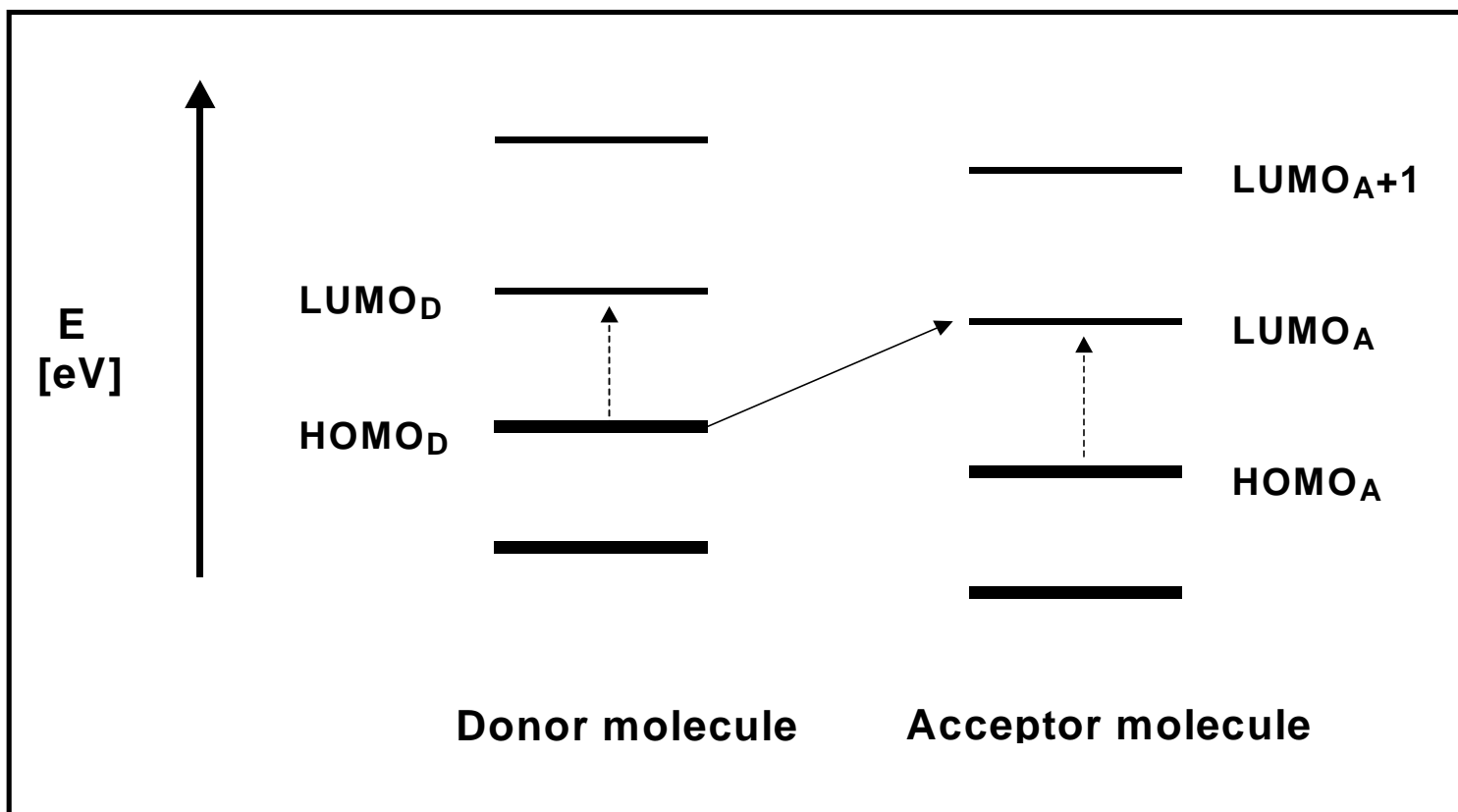


Figure 10



Compound	R	$\Delta G$
<b>H</b>	H	-10.7074
<b>3Me</b>	3'-CH <sub>3</sub>	-9.9299
<b>3F</b>	3'-F	-11.5804
<b>3Cl</b>	3'-Cl	-12.6852
<b>3NO<sub>2</sub></b>	3'-NO <sub>2</sub>	-13.5991
<b>3CN</b>	3'-CN	-11.8395
<b>3N<sub>3</sub></b>	3'-N <sub>3</sub>	-11.8259
<b>3OMe</b>	3'-OCH <sub>3</sub>	-9.9163
<b>F<sub>5</sub></b>	2',3',4',5',6'-F <sub>5</sub>	-14.1447



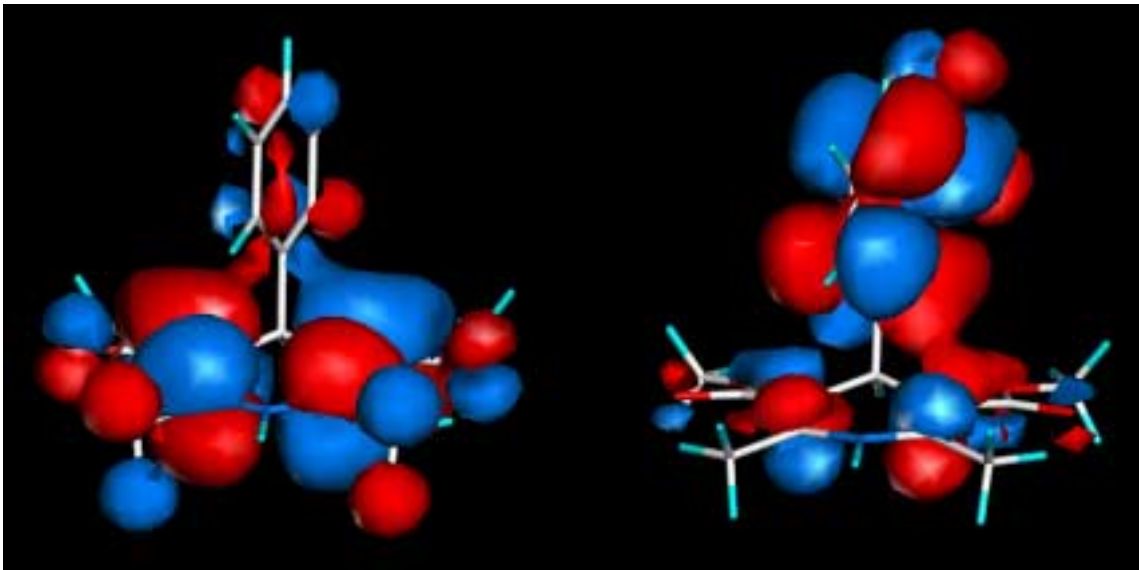


Figure 13

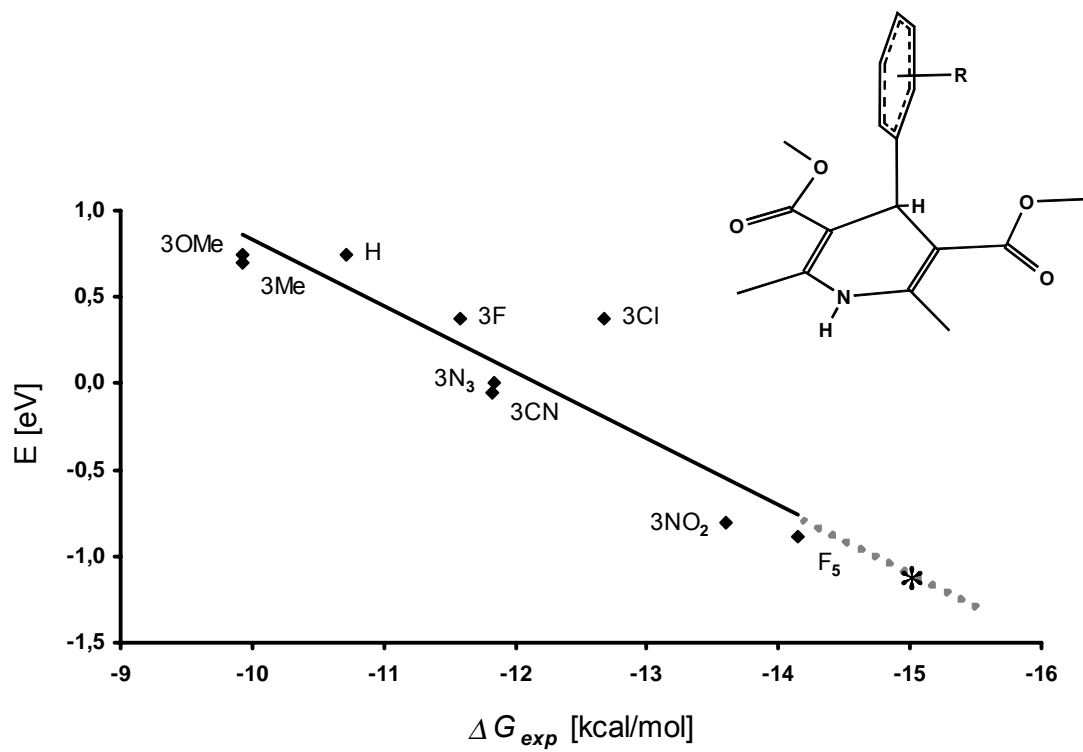


Figure 14