# COMPUTER-ASSISTED CLASSES ON MEDICINAL CHEMISTRY OF NEUROLEPTICS

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## Abstract

*The purpose of this study is elaboration of computer-assisted classes for pharmacy students on medicinal chemistry and molecular pharmacology of neuroleptics and gathering of students' feedback on such a didactic approach.*

*The neuroleptics or antypsychotics are a group of drugs used for the treatment of psychosis, in particular in schizophrenia and the manic phase of bipolar disorder. According to the chemical classification, the following main groups of neuroleptics can be distinguished: tricyclic neuroleptics (phenothiazine, thioxanthene and dibenzoepine derivatives), derivatives of buthyrophenone, diphenylbutylpiperidine, indole and benzamide. Pharmacologically they can be divided into typical and atypical, taking into account the ratio of their affinity to the dopamine $D_2$ and the serotonin $5\text{-}HT_{2A}$ receptors.*

*The presented computer-assisted classes were designed by taking into account the common problems which many students encounter when they learn medicinal chemistry.The classes make use of free software and freely available web services only and consist of the following steps:(1) molecular modeling of selected neuroleptics on the level of semi-empirical AM1 method with VegaZZ;(2) discussion of the structural features of neuroleptics that affects their pharmacological profile;(3) homology modeling of dopamine $D_2$ receptor with SWISS-MODEL;(4) molecular docking of selected neuroleptics to the models of dopamine $D_2$ receptor with PatchDock.*

*The classes were highly approved by students and may be utilized in education of pharmacy and chemistry but also biology and medicine students.*

**Key words**: *computer-assisted classes, information and communication technologies in teaching, media in education; improving classroom teaching, teaching/learning strategies.*

## Introduction

Computing and communication technology continue on making a great impact on all aspects of cognition, education and training. Thus, the field of computer-assisted science teaching is extremely active nowadays. Many authors determined that involving computers in education process makes it more interesting, develops motivation of the students and helps to keep their attention during classes (Muzyka, 2009; Miller et al., 2011). Such effects can be achieved even by enriching the classes with PowerPoint slides only (Apperson, Laws & Scepansky, 2006).

Application of computers for teaching science is thus more and more common on all the levels of education, from primary to tertiary. In particular, computer-assisted classes may be of valuable help for the pharmacy or chemistry students who learn organic or medicinal chemistry. These students encounter multiple problems: they find it difficult to memorize names, formulas and synthesis of compounds and pharmacological profiles of drugs. Furthermore, linking structural information (like bioactive conformation, structure-activity relationship and interaction with molecular targets) with pharmacological activity is impossible for the majority of students when they have only two-dimensional formulas of drugs (structural formulas

drawn on paper). Among the reasons that organic and medicinal chemistry are often difficult for students is that they are not accustomed to thinking in a visual manner (Fleming, Hart & Savage, 2000; Stueker et al., 2003; Muzyka, 2009). Understanding the shapes of molecules, which is crucial for drug design, is easier for students when they can "see" the molecules (Muzyka, 2009). Thus, computer models can help to associate the hand-held models and the two-dimensional representations (Muzyka, 2009).

Interestingly, in spite of easy access to internet and multimedia technology, it was experienced by the author that the fourth year pharmacy students expressed their surprise that molecules are not flat and that chemical compounds can adopt different conformations. Next, many students were not able to distinguish between three-dimensional models of R- and S-enantiomers, to indicate polar fragments of a molecule, to build a model of a dipeptide as well as to discuss potential interactions of a drug with a target receptor or a target enzyme.

## Problem of Research

Nowadays, many tools to model and visualize three-dimensional structure of small molecules and proteins are freely available for non-commercial users (Ertl & Jelfs, 2007). However, the amount of the corresponding materials for the teachers with the proposals of computer-assisted classes on medicinal chemistry is still unsatisfactory. It is at least partially connected with the fact that the preparation of computer-assisted classes or even a PowerPoint slides-assisted lecture requires a lot of time and effort (Apperson, Laws & Scepansky, 2006).

To bridge this gap, several computer-assisted classes on medicinal chemistry have been elaborated (Muranaka, 2001; Kossida, Tahri & Daizadeh, 2002; Tavares de Oliveira et al., 2006; Persona et al., 2007; Tsai, 2007; Kaczor, Matosiuk & Persona, 2009a, 2009b, 2009c; Persona et al., 2009; Persona et al., 2010). These classes involve teaching protein science with application of computers, conformational analysis of natural ligands and molecular docking studies, molecular modeling and calculation of the structure-correlated parameters describing skin permeability of theaflavonoids, structure-activity studies, structure-based virtual screening for novel monoaminooxidase B (MAO-B) inhibitors and estimation of drug-likeness and calculation of ADMET properties for some series of novel compounds. The students who participated in the classes respond positively or even enthusiastically to the above computer-assisted classes on medicinal chemistry and highly approved such an educational approach. Thus, it was an encouragement and motivation to design subsequent computer-assisted classes on this branch of science.

Shortly, the problem which this study addresses is still insufficient number of complete and ready-to-use proposals of computer-assisted classes on medicinal chemistry that may be easily reproduced and applied by university teachers for education of chemistry, pharmacy, medicine and biology students.

## Research Focus

In the light of above, the purpose of this study is elaboration of computer classes for students on medicinal chemistry and molecular pharmacology of neuroleptics and gathering of students' feedback of such an didactic approach. The classes involve (1) molecular modeling of selected neuroleptics; (2) discussion of the structural features of neuroleptics that affect their pharmacological profile; (3) homology modeling of the main molecular target of typical neuroleptic, i.e. $D_2$ receptor; (4) molecular docking of selected neuroleptics to their molecular target.

## Methodology of Research

### *General Background of Research*

The quick search in PubMed and Google search engine with the keywords "computer-assisted classes" or "computer-aided classes" and "medicinal chemistry" does not return any complete proposals of such classes. Looking on the website of *Journal of Chemical Education* makes it possible to find a few proposals (e.g. Muranaka, 2001; Kossida, Tahri & Daizadeh, 2002; Tavares de Oliveira et al., 2006; Tsai, 2007). It confirms the above discussed urgent need to elaborate such classes.

### *Instruments and Procedures*

The proposed computer-assisted classes on medicinal chemistry and molecular pharmacology of neuroleptics involve a few computational procedures which are performed by participating students, under supervision of a teacher. First, the students build 3D molecular models of neuroleptics on the level of semi-empirical method AM1 with application of VegaZZ software (Pedretti, Villa & Vistoli, 2004). The charges are calculated with Gasteiger method. Next, the students perform the conformational analysis of molecules of neuroleptics for all the rotatable bonds on the level of molecular mechanics as offered by VegaZZ software. Then, they build a homology model of the dopamine $D_2$ receptor with SWISS-MODEL (Arnold, Bordoli, Kopp & Schwede, 2006). Finally, they conduct molecular docking (in rigid docking approach) of the molecules of neuroleptics (protonated on the suitable nitrogen atom) to the dopamine $D_2$ receptor with PatchDock server (Duhovny, Nussinov & Wolfson, 2002; Schneidman-Duhovny et al., 2005). Visualization of three-dimensional structures of neuroleptics, receptors and drug-receptor complexes is performed by students with PyMol software (De Lano, 2002).

### *Evaluation of Students' Performance*

To evaluate how much the students learnt from the classes, they were asked to write the report on the tasks they performed. Furthermore, the "Computer-assisted drug design" course ends with a final exam, consisting of theoretical and practical parts.

### *Students' Feedback on Computer-assisted Classes*

After the classes the students were given an anonymous questionnaire to fill, in order to evaluate the applied didactic approach. They were asked to answer the following questions: (1) What did you like in the computer-assisted classes? (2) What did not you like? (3) What is the most important thing which you learnt from the classes? (4) What was redundant? (5) Is there any aspects of the classes that should be covered in more detail?

## Results of Research

### *Basic Information about Neuroleptics*

In the introductory part of classes students are asked to recapitulate and organize their knowledge about neuroleptics. The most important facts are summarized below.

Neuroleptics or antipsychotics are a group of drugs that are used for the treatment of schizophrenia and the manic phase of bipolar mood disorders. It is worth mentioning that

schizophrenia affects about 1% of population while bipolar mood disorder – up to 5% of population. Both illnesses are nowadays only partially curable and current therapies help only a part of patients. Thus, understanding molecular basis of the action of neuroleptics is crucial for the design of better drugs.

The neuroleptics can be classified according to their chemical structure, taking into account the characteristic chemical entity in their molecules. Thus, tricyclic neuroleptics (phenothiazine, thioxanthene and dibenzoepine derivatives), derivatives of buthyrophenone, diphenylbutylpiperidine, indole and benzamide are distinguished (Figure 1). Pharmacologically neuroleptics are divided into typical and atypical, taking into account the ratio of their affinity to the dopamine $D_2$ and the serotonin 5-$HT_{2A}$ receptors. An ideal neuroleptic should be able to treat all the three groups of symptoms of schizophrenia, namely positive (e.g. hallucinations, delusions), negative (e.g. lowered mood, social isolation) and cognitive (e.g. worse cognitive abilities, disorganized thinking) symptoms. The available drugs manage quite well with positive symptoms and to the lesser degree with negative symptoms but are unsatisfactory for the treatment of cognitive symptoms. Furthermore, the neuroleptics exhibit significant side-effects, such as extrapyrimidal symptoms, weight gain, diabetes, agranulocytosis (lower count of white blood cells) and hyperprolactinemia. As a complement of this part of the classes, the students may be made familiar with the database DrugBank (Knox et al., 2011) where they can find more detailed information on neuroleptics and other drugs of interest.
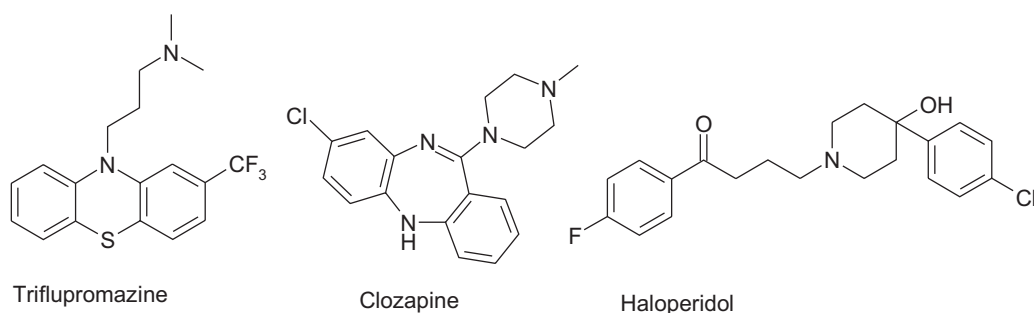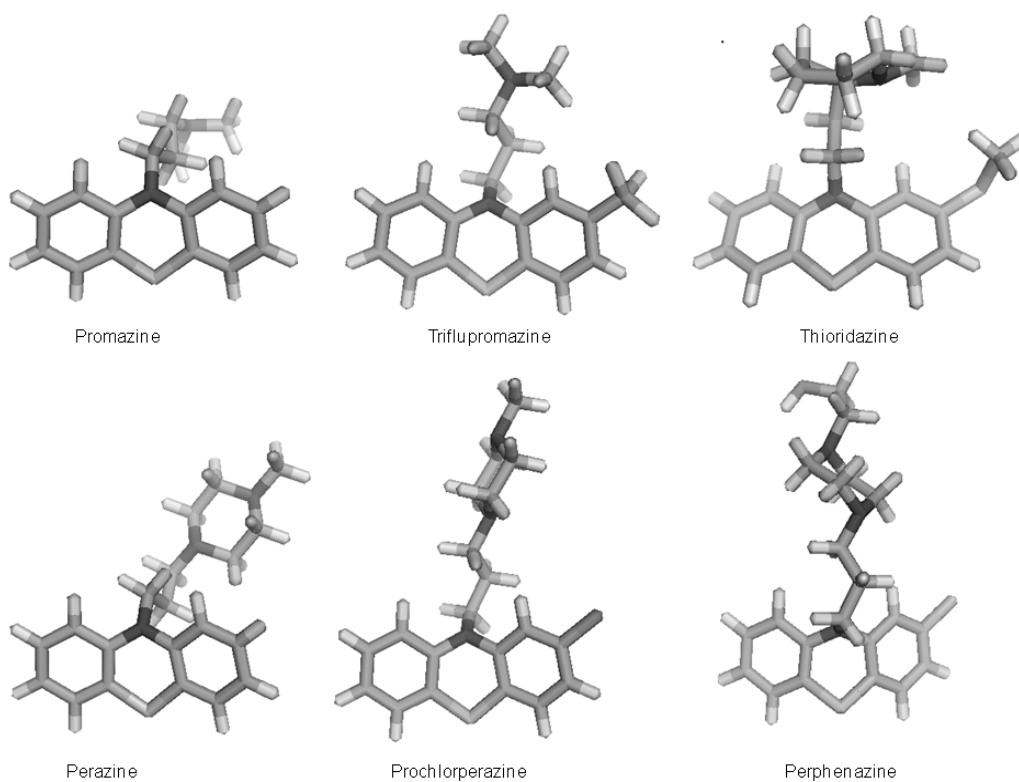


**Figure 1: Examples of common neuroleptics representing different structural classes.**

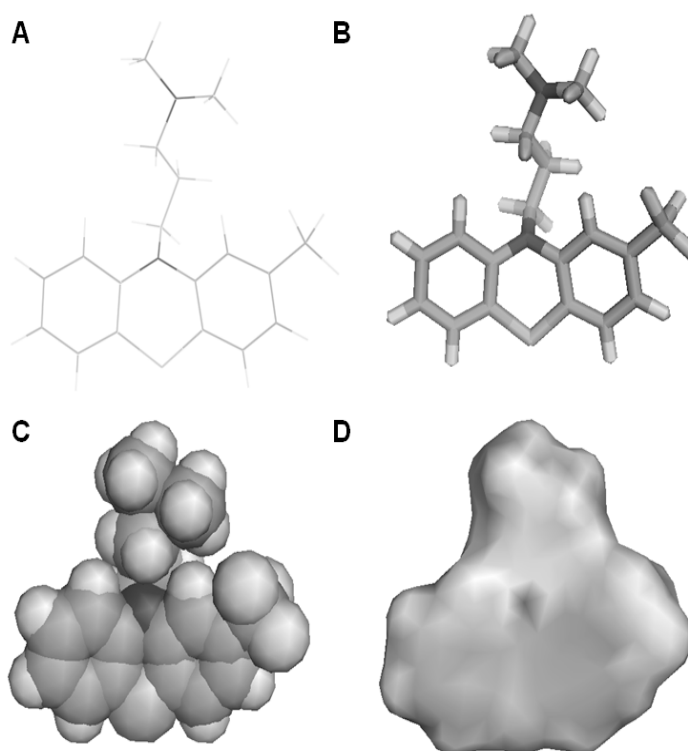*Molecular Modeling of Selected Neuroleptics*

In this part of classes the students model a three-dimensional structure of five selected neuroleptics on the level of semi-empirical AM1 method using VegaZZ software. In addition, they perform conformational analysis to investigate conformational freedom of the substituent in position 10 of the phenothiazine ring system. The modeled neuroleptics belong to the phenothiazine class and involve promazine, triflupromazine (promazine group), thioridazine (ridazine group), perazine, prochlorperazine (perazine group) and perphenazine (phenazine group). The two-dimensional formulas of the investigated neuroleptics are presented in Figure 2, whereas the three-dimensional representations of structure are given in Figure 3. The students are encouraged to try different ways of visualization of three-dimensional structure as offered by VegaZZ (wire, sticks, balls, Figure 4). Next, they might also inspect the real shape of a molecule by displaying molecular surface (Figure 4) and check the distribution of charge in the molecule. Thanks to suitable modules of VegaZZ they can also discuss lipophilicity, polar surface area and other molecular properties of neuroleptics.

Promazine

Triflupromazine

Thioridazine

Perazine

Prochlorperazine

Perphenazine
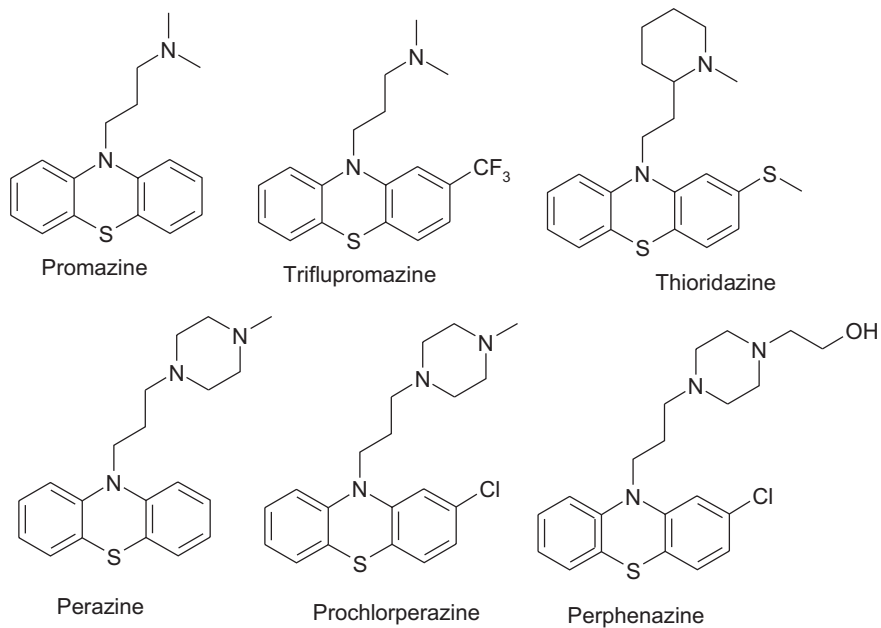
**Figure 2: The 2D structures of the investigated neuroleptics (phenothiazine derivatives).**

Promazine

Triflupromazine

Thioridazine

Perazine

Prochlorperazine

Perphenazine

**Figure 3: The 3D structures of the investigated neuroleptics (phenothiazine derivatives).**

**Figure 4: Different ways of structure representations for triflupromazine. A − wire; B − sticks; C − balls; D − molecular surface.**

*Structural Features of Neuroleptics which Affect their Pharmacological Profile*

The next part of classes is devoted to discussion of the structural features of neuroleptics that determine their pharmacological activity. Firstly, the students should notice the shape of tricyclic phenothiazine ring system, which is coplanar and bent with the respective angle value. Next, students are asked to analyze which positions in the phenothiazine system are modified by substituents, what substituents occur in these positions and how it can affect the interaction with the molecular target. The summary of essential facts which should be discussed is given below.

The neuroleptics which are derivatives of phenothiazine can be classified into three structural groups, based on the type of substituent in position 10: promazine group with N, N-dimethylaminopropyl substituent, ridazine group with piperidinyl-2-ethyl substituent and the third group constituted by the derivatives with piperidinylpropyl or piperazinylpropyl substituent, sometimes with additional hydroxylic group (perazine group and phenazine group). It was found that the conformation of aminoalkil substituent is strictly determined. It is beneficial for the neuroleptic activity if the tertiary amino group is closer to the ring bearing the substituent in position 2 (Pawłowski, 1999). The students should be able to suggest a structural modification which will favor such a conformation of aminoalkyl substituent and to give examples of respective drugs (e.g. thioxanthene derivatives). It is important to emphasize that the type of substituent in position 10 determines the pharmacological profile of phenothiazine derivatives. The members of promazine and ridazine groups are relatively weak neuroleptics in contrast to the members of perazine and phenazine groups. Nevertheless, all the derivatives share the same structural feature of the substituent in position 10, i.e. the distance of three carbon atoms

between the phenothiazine nitrogen atom and the protonable nitrogen atom of the substituent. It should be also stressed that the presence of a hydroxylic group in the compounds of phenazine group decreases the lipophilicity of the compound. On the other hand, the hydroxylic group makes it possible to transform the compound into ester prodrugs which – due to slow hydrolysis and absorption can exert the pharmacological effect for longer time.

Finally, the role of a substituent in position 2 of the phenothiazine system should be discussed: the electronoacceptor substituents in this position increase the neuroleptic activity in comparison to the unsubstituted analogs. The students ought to be able to list electronoacceptor substituents and explain the reasons of the electronoacceptor properties.

*Homology Modeling of Some Molecular Targets for Neuroleptics*

This part of the classes is devoted to showing the students how they can easily obtain approximate models of the dopamine $D_2$ receptor which is the main molecular targets of typical neuroleptics. First, the students should be familiarized with the protein databases of sequences (Uniprot, Gasteiger et al. 2005) and structures (Protein Data Bank, Berman et al. 2000). They are asked to find the sequence of the target protein and to give its accession number in the Uniprot database. Next, the students check what structures of G protein-coupled receptors (GPCRs) are present in the Protein Data Bank and discuss the general pattern of GPCR architecture (seven transmembrane helices, three extracellular loops, three intracellular loops). They may also analyze the protein-ligand interaction in one of available complexes (e.g. the $\beta_2$ adrenergic receptor in complex with carazolol, PDB code 2RH1, Cherezov et al., 2007) to identify the conserved aspartate residue of the transmembrane helix 3 (TM3) as the main anchoring point.

Although SWISS-MODEL has the option to make protein models completely automatically, it is a good idea to explain the students how protein homology models are made (Kaczor, Matosiuk, Persona, 2009c). In particular, the students may try to perform some protein sequence alignment (which is the core of the homology modeling approach) and to detect evolutionary conserved residues. They should notice what templates were used by SWISS-MODEL to build the homology model. The model of the dopamine $D_2$ receptor generated with SWISS-MODEL is depicted in Figure 5. The N-terminus and the intracellular loop 3 are removed from the model as they cannot be modeled correctly due to the lack of templates.



**Figure 5: The homology model of dopamine $D_2$ receptor generated with SWISS-MODEL.**

Having GPCR models in hand, students should be able to indicate transmembrane, intracellular and extracellular parts of the receptor as well as to identify the residues forming the orthosteric binding site, necessary for the molecular docking.

Molecular docking of neuroleptics (protonated on the suitable nitrogen atom) to their molecular targets was performed with PatchDock server (Duhovny, Nussinov & Wolfson, 2002; Schneidman-Duhovny et al., 2005) which uses the rigid docking approach. Asp114 from the third transmembrane helix (TMIII) was indicated as the main residue of the binding pocket. The interested students may be encouraged to check what binding poses of neuroleptics have been published (Selent, López, Sanz & Pastor, 2008; Selent et al., 2010) and to compare literature results with the PatchDock results. All the students should be able to identify the residues forming the binding pocket and to name the type of interaction with the drug (salt bridge, hydrogen bond, hydrophobic contact etc., Figure 6). In the most probable results obtained with PatchDock, the main interaction is the salt bridge between the conserved Asp114 and the protonated nitrogen atom of a ligand.
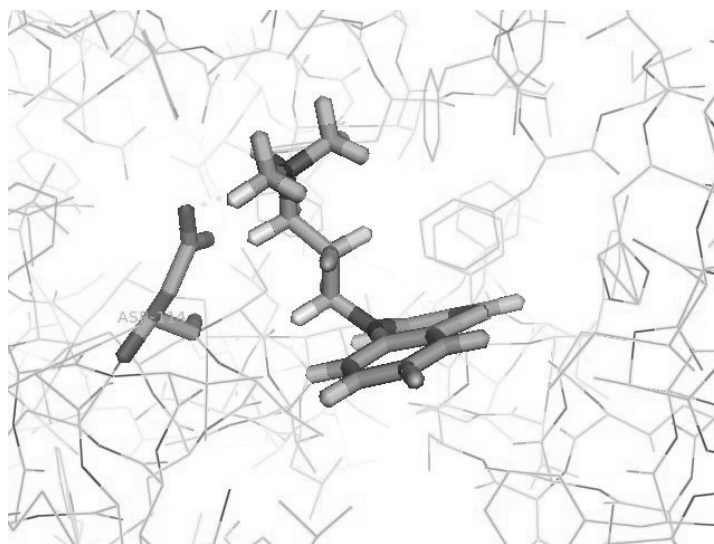


**Figure 6: The model of the dopamine D$_2$ receptor in complex with promazine.**

In summary, the proposed computer-assisted classes on medicinal chemistry and molecular pharmacology of neuroleptics give a foretaste of the most important computer-assisted drug design techniques, such as molecular modeling of small molecules, structure-activity relationship analysis, homology modeling and molecular docking.

*Evaluation of Students' Performance and the Feedback from the Students on the Classes*

In general, the student reports on the tasks carried out during these classes were more than satisfactory and some of them resembled a high-quality research papers. The results of final exam were also sufficient with a little weaker practical part which was caused most probably by the fact that some students were not comfortable with using computers. These two ways of assessment of student performance made it possible to detect the positive attitude of participants to the classes which was also confirmed by the answers for the questions in the feedback questionnaire. The most interesting remark in the questionnaires has been already mentioned in the *Introduction* section: thanks to the computer assisted classes it was possible to

find out that the molecules are not flat and can adopt different conformations.

## Discussion

The presented proposal of computer classes can be treated as a short introduction to the medicinal chemistry of neuroleptics on one hand, and a quick course on the usage of molecular modeling tools on the other one. Pharmaceutical or medicinal chemistry deals with the discovery, design, development, and preparation of drugs; the study of their kinetic and thermodynamic properties, and the interpretation of drug actions at the molecular level (Tsai, 2007). More and more often it is a part of chemistry and pharmacy curricula. The objectives of molecular modeling are nowadays similar to those listed by Dugas (Dugas, 1992) almost twenty years ago. These include different techniques of visualization, manipulation, analysis and calculation of molecular structures. The reasons why the molecular modeling skills are important for students have not changed either since then: as mentioned by Dugas (Dugas, 1992), there is increasing demand for the qualified specialists in the field. It should be thus stressed that computer-assisted medicinal chemistry becomes a must in the education of chemists and pharmacists, in particular those who intend to work in industry (Kaczor, Matosiuk & Persona, 2009a, 2009b, 2009c).

The application of computer technology, which enables the using of different molecular modeling techniques, has revolutionized the discovery, design, and optimization of drugs in pharmaceutical industries (Tsai, 2007). Personal computers (PCs) are more and more common in classroom teaching as they may be used by students to solve multiple chemical and biochemical problems (Tsai, 2000; Tsai, 2007). Using PCs has significantly improved the efficiency and breadth of teaching in science (Tsai, 2007). Surprisingly, there are not many proposals on computer-assisted medicinal chemistry classes available (Muranaka, 2001; Kossida, Tahri & Daizadeh, 2002; Tavares de Oliveira et al., 2006; Persona et al., 2007; Tsai, 2007; Kaczor, Matosiuk & Persona, 2009a, 2009b, 2009c; Persona et al., 2009; Persona et al., 2010). The proposed classes may partially bridge this gap.

After participation in the computer-assisted classes on the medicinal chemistry and molecular pharmacology of neuroleptics the students should be convinced that internet resources, such as databases, are valuable and easy accessible source of knowledge and that molecular modeling software can help them in the visualization of structure of molecules and macromolecules.

The proposed classes are also an attractive alternative to the traditional seminars on drug structure and pharmacological activity. The contemporary students are the generation for whom pictures are much more important and educative than any words, either written or spoken. Furthermore, they are generation who deals with computers in natural and obvious way. Thus, teaching them using computers is like speaking their language: it may help to motivate them and to show that science can be interesting.

It is important to emphasize that the proposed classes do not require any special computer resources and involve the application of freely available software and web services only, similarly as the earlier elaborated proposals (Kaczor, Matosiuk & Persona, 2009a, 2009b, 2009c). Thus, the classes can be easily reproduced and can be the basis of similar classes on any groups of drugs.

## Conclusions

The presented proposal of computer-assisted classes on neuroleptics is an attractive alternative to traditional teaching on structure and activity of drugs. The applied molecular modeling software enables the students to see molecules in three dimensions and to observe the real shape of molecules as the molecular surface whereas the analysis of ligand-receptor

complexes makes it possible to visualize the molecular basis of drug action. Finally, the presentation of freely available molecular modeling servers and software as well as internet databases provides the students with the tools useful in their future work.

### Acknowledgements

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