COMPUTER-ASSISTED CLASSES ON MEDICINAL CHEMISTRY OF BARBITURATES AND THIOBARBITURATES

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Abstract

The purpose of this study is elaboration of computer classes for pharmacy or chemistry students on ADMET parameters of barbiturates and thiobarbiturates in the context of their molecular structure and gathering students' feedback on the classes. Barbiturates and thiobarbiturates are derivatives of barbituric acid and thiobarbituric acid, respectively. These drugs, depending on clear differences in their structure, exert a variety of effects on the central nervous system, ranging from mild sedation to total anesthesia. Barbiturates may be used as hypnotics, anxiolytics and anticonvulsants whereas thiobarbiturates can be applied for the induction of general anesthesia. At present barbiturates are usually replaced by benzodiazepines which are less dangerous at overdose. Nevertheless, they remain a model group of drugs to discuss structure-activity relationship, in particular the effect of lipophilicity on the activity profile.
The presented computer-assisted classes were designed by taking into consideration the common problems which many students experiense when they learn medicinal chemistry.The classes make use of freely available web services only and consist of the following steps: (1) calculation of lipophilicity of selected barbiturates and thiobarbiturates with several algorithms offered by Virtual Computational Chemistry Laboratory web service;(2) discussion of relationship between the lipophilicity value and activity profile;(3) calculation of other ADMET parameters (e.g. plasma protein binding, blood-brain barrier penetration, human intestinal absorption) of barbiturates and thiobarbiturates with PREADMET web service and ADMEBoxes web service (demo version) .
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

The educational value of computers is well-documented (Gladwin, Margerison & Walker, 1992). Computers make teaching more efficient and effective as they facilitate using text, graphics, animation, sound, and video during classes (Munar et al., 2006). Furthermore, computers and multimedia enable to involve students in interactive problem-solving exercises and to perform real-time calculations and data processing (Munar et al., 2006). The computer technology significantly changed the educational process (Brimberry & Riffee¸ 1995), supplying new didactic tools for teachers but also making the knowledge easy accessible. Thus, teaching natural and medical sciences, in particular chemistry and pharmacy, without the application of computers is nowadays impossible to imagine, as computers are used in the research in all their branches, from theoretical chemistry to drug analysis. It is also very likely that the chemistry or pharmacy graduates will apply computers in their professional life, e.g. for molecular modeling, instrumental analysis and data capture and control.

From the reasons mentioned above, the knowledge of computer-assisted drug design (CADD) techniques is at present a must in the education of pharmacy and chemistry students

(Kaczor, Matosiuk & Persona, 2009a, 2009b, 2009c). It is estimated that application of CADD techniques to drug discovery approaches may lead to a reduction of up to 50% in the cost of drug design (Taft et al., 2008). Among various CADD approaches, determination of the relationship between biological activity of a substance and its structure have been proved to be a useful and powerful method which may be applied for example for lead optimization. Structure-activity studies of pharmacologically active compounds have been a subject of a few educative articles (e.g. Hansch, 1971; Seybold, May & Bagal, 1987; Hansen & Jurs, 1988; Roy, 1989; Muranaka, 2001; Persona et al., 2009). It was noticed that although the axiom that "form follows function" is one of the most fundamental in science and technology, in chemistry "function follows form" (Seybold, May & Bagal, 1987). It means that properties of molecules (including biological activity) derive strictly from their structures which should be stressed in education of future chemists and pharmacists (Seybold, May & Bagal, 1987).

Nowadays, biological activity is understood in a broad manner and includes not only binding with the molecular targets or anti-targets, but also a pharmacokinetic aspect, i.e. ADMET (absorption, distribution, metabolism, excretion and toxicity) parameters of the compound. The importance of ADMET parameters for drug action may be illustrated by the fact that, among other factors, poor pharmacokinetic parameters resulted in lower than expected number of new drugs in spite of huge number of new chemical compounds (Norinder & Bergström, 2006). Hence, reliable screening filters for ADMET parameters are highly desirable. Computational screening of ADMET parameters in a designed series of compounds is a routine in the contemporary pharmaceutical industry. It often precedes synthesis and biological tests and makes it possible to save money and human effort. In spite of that, many chemistry and pharmacy students encounter problems in explaining ADMET parameters of medicinal compounds in the context of the molecular structure. In particular, the effect of the change of substituents on the lipopilicity value of a compound and the consequences of a given lipophilicity value for values of other ADMET parameters are confusing for many students.

An ideal method for teaching pharmacokinetics involves opportunities for problem solving accompanied by didactic and interactive instruction (Munar et al., 2006) which can be both offered by computer-assisted classes.

Problem of Research

To address the didactic problems raised above, some computer-assisted classes on determination of ADMET properties have been elaborated (Aarson et al., 1988; Mehvar, 1997; Hedaya, 1998; Woodward, 1998; Hedaya & Collins, 1999; Munar et al., 2006; Kaczor, Matosiuk & Persona, 2009b; Persona et al., 2010). The most recent proposals (Kaczor, Matosiuk & Persona, 2009b; Persona et al., 2010) are based on real research problems and hence show the students how knowledge and computer-assisted techniques work in everyday scientific practice. On the other hand, proposals of computer classes which concern the important groups of the registered drugs are complementary to those based on the series of new compounds. Lacking the aspect of compound novelty, such computer classes, thanks to focusing on the model and well-investigated group of compounds, make it possible to demonstrate the students clear and educative relationships between molecular structure and pharmacokinetics. Furthermore, working with compounds known by students gives a unique opportunity to refer to the facts the students are familiar with and to widen and strengthen students' knowledge. Thus, in this way, computer-assisted classes on ADMET parameters of some registered drugs may be a useful complement to lectures, seminars and laboratories on medicinal chemistry.

Briefly, the problem which this study addresses is still insufficient number of complete and ready-to-use proposals of computer-assisted classes on ADMET parameters of biologically active compounds in the context of molecular structure which involve currently available

PROBLEMS
OF EDUCATION
IN THE 21st CENTURY
Volume 28, 2011

software and web services and which 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 ADMET parameters of barbiturates and thiobarbiturates in the context of their molecular structure and gathering students' feedback on the classes. The classes involve: (1) calculation of lipophilicity of selected barbiturates with several algorithms; (2) discussion of relationship between the lipophilicity value and activity profile; (3) calculation of other ADMET parameters (e.g. plasma protein binding, blood-brain barrier penetration, human intestinal absorption) of barbiturates and thiobarbiturates.

Methodology of Research

General Background of Research

In spite of vast amount of literature on significance and experimental determination or calculation of ADMET parameters, there are not many proposals which can be used in computer-assited teaching students about pharmacokinetics of drugs (Aarson et al., 1988; Mehvar, 1997; Hedaya, 1998; Woodward, 1998; Hedaya & Collins, 1999; Munar et al., 2006; Kaczor, Matosiuk & Persona, 2009b; Persona et al., 2010). Thus, there is an urgent need to bridge this educational gap.

Instruments and Procedures

The proposed computer-assisted classes on ADMET parameters of barbiturates and thiobarbiturates involve a few computational procedures which are carried out by participating students, under supervision of a teacher. First, the students calculate lipophilicity (logP) with application of AlogPS, AClogP, AB/logP, milogP, AlogP, MlogP, KOWWiN, XlogP2 and XlogP3 algorithms as offered by Virtual Computational Chemistry Laboratory web service (Tetko et al., 2005). Next, they calculate other ADMET parameters, such as: pH-dependent distribution coefficient (logD), pKa, molecular weight, polar surface area and solubility in water with ADMEBoxes web service (demo version). Finally, the students calculate plasma protein binding, blood-brain barrier penetration and absorption parameters with PREADMET web service (Lee et al., 2003) and probability of side effects with ADMEBoxes web service. All the web services applied during these computer-assisted classes are very user-friendly. As the input they only require to draw a structural 2D formula of a compound with the accompanied molecular editor.

Evaluation of Students' Performance

To evaluate how much knowledge and skills the students gained from the classes, they areasked to write the report on the tasks they performed. Moreover, the "Computer-assisted drug design" course ends with a final exam, consisting of theoretical and practical parts.

Students' Feedback on Computer-assisted Classes

To gain students' feedback on the computer-assisted classes, they were asked to fill in

an anonymous questionnaire. 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 Barbiturates and Thiobarbiturates

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

Barbituric acid (2,4,6-trioxohexahydropyrimidine) was synthesized for the first time by Bayer in 1864 (Obniska, 1999). Thiobarbituric acid is the analogue of barbituric acid in which the oxygen atom in position C2 is replaced by a sulfur atom. Barbituric acid itself does not have hypnotic properties. It is a strong acid, well soluble in water and barely soluble in lipids. The pharmacological activity of barbituric acid derivatives is conditioned by the presence of alkyl or aryl substituents at the carbon atom C5.

The following rules of structure-activity relationship have been found for barbiturates and thiobarbiturates (Obniska, 1999): (1) the sum of carbon atoms of the substituents at the C5 carbon atom should be between 6 and 10; (2) the branching of substituents at the C5 carbon atom decreases the duration of action; (3) the presence of unsaturated substituent at the C5 carbon atom increases the activity and decreases the duration of action; (4) an aromatic substituent promotes antiepileptic activity; (5) the presence of a halogen in alkyl substituents increases the activity; (6) alkylation of a nitrogen atom of the hexahydropyrimidinetrion increases the speed of onset, decreases the duration of action, promoting the hypnotic or even narcotic activity; (7) thiobarbiturates act quickly and shortly in comparison to barbiturates and exhibit narcotic activity. In summary, all the changes in the structure of barbiturates or thiobarbiturates which increase lipophilicity, increase the speed of onset, decrease the duration of action and promote hypnotic activity.

Taking into consideration the speed of onset and duration of action, barbiturates can be classified into ultrashort-acting, short-acting, intermediate-acting and long acting (compare below).

The mechanism of action of barbiturates is connected with the activation of γ-aminobutyric acid (GABA) ionotropic receptors. Finally, the regular use of barbiturates causes barbiturate dependence and tolerance to their effects.

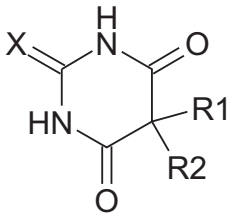
As a complement to this part of the classes, the students may be made familiar with the database DrugBank (Knox et al., 2011) where they can find more detailed information on barbiturates and thiobarbiturates and other drugs of interest.

Calculation of Lipophilicity and its Relation to the Activity Profile

During the next part of classes the students calculate lipophilicity of selected barbiturates and thiobarbiturates and discuss the obtained values in the context of molecular structure and activity profiles of these drugs. The drugs used for the studies are presented in Table 1. The values of lipophilicity which the students should obtain are collected in Table 2. The following algorithms, offered by Virtual Chemistry Laboratory web service may be applied to calculate the lipophilicity: AlogPS, AClogP, AB/logP, milogP, AlogP, MlogP, KOWWiN, XlogP2 and XlogP3. This web service also supplies the experimental values of lipophilicity (when available, Table 2). It is important to make the students aware that all the parameters calculated during the

classes are based on the 2D structure representation and thus stereochemical or conformational effects are not considered. The students should be informed about possible limitations of such an approach.

Table 1. The studied barbiturates and thiobarbiturates (1-10).



Class/drug	No.	R1	R2	X
1. Ultrashort- and short-acting				
Thiamylal	**1**	allyl	1-methylbutyl	S
Thiopental	**2**	ethyl	1-methylbutyl	S
Pentobarbital	**3**	ethyl	1-methylbutyl	O
Secbutabarbital	**4**	ethyl	1-methylpropyl	O
2. Intermediate-acting				
Allobarbital	**5**	allyl	allyl	O
Amylobarbital	**6**	ethyl	3-methylbutyl	O
Butabarbital	**7**	ethyl	buthyl	O
Cyclobarbital	**8**	ethyl	1-cyclohexenyl	O
3. Long-acting				
Barbital	**9**	ethyl	ethyl	O
Phenobarbital	**10**	ethyl	phenyl	O

Table 2. The values of lipophilicity calculated with different algorithms for barbiturates and thiobarbiturates (1-10).

No.	AlogPS	AClogP	AB/ logP	milogP	AlogP	MlogP	KOW-WiN	XlogP2	XlogP3	Aver. logP	logP exp
1	3.11	2.49	2.92	2.62	2.87	1.33	3.23	2.53	3.23	2.70	-
2	3.05	2.33	2.66	2.59	2.81	1.14	2.87	2.33	2.85	2.54	2.85
3	2.16	1.65	1.88	2.04	1.91	0.76	2.00	2.08	2.07	1.84	2.10
4	1.70	1.19	1.39	1.49	1.45	0.47	-	1.51	1.65	1.35	-
5	1.08	0.73	1.16	0.81	0.88	0.29	-	0.84	1.05	0.85	-
6	1.87	1.65	1.88	1.78	1.91	0.76	2.00	2.08	2.07	1.78	2.07
7	1.65	1.31	1.62	1.80	1.66	0.47	1.59	1.57	1.73	1.49	1.73
8	1.96	1.24	1.96	1.97	1.74	0.95	2.30	1.61	1.77	1.72	1.77
9	0.73	0.39	0.65	0.74	0.75	-0.16	0.60	0.43	0.65	0.53	0.65
10	1.40	0.64	1.40	0.80	1.32	0.78	1.33	1.32	1.47	1.16	1.47

The students should state on the basis of Table 2 that in general the highest lipophilicity values were found for ultrashort- and short acting barbiturates and thiobarbiturates (Thiamylal, Thiopental, Pentabarbital). In case of Thiamylal and Thiopental it is caused by the presence

of a sulfur atom as well as a large and branched 1-methylbuthyl substituent. Interestingly, Secbutabarbital which is very similar to Pentabarbital (possesses 1-methylpropyl group instead of 1-methylbutyl substituent) exhibits significantly lower lipophilicity than Pentabarbital. The lowest lipophilicity in the set was obtained for Barbital and it can be explained by the presence of relatively small and not branched substituents (i.e. two ethyl groups) at the C5 carbon atom. The discrepancies between the expected order of lipophilicity values in the group of barbiturates can be caused by an error in computational approximation of lipophilicity as it may be concluded from the comparison of available experimental lipophilicity with average computed lipohilicity. Furthermore, XlogP3 algorithm was found to give the lipohilicity closest to experimental values whereas MlogP returned significantly lowered values.

In addition to lipophilicity, logP, the students may calculate pH-dependent distribution coefficient, logD, with ADMEBoxes web service (demo version). Distribution may be computed for stomach (pH=1.7), duodenum (pH=4.6), jejunum and ileum (pH=6.5), blood (pH=7.4) and colon (pH=8.0). As shown in Table 3, distribution values decrease with the increase of pH as barbiturates and thiobarbiturates are ionizable compounds of acidic character. Obviously, the highest values of distribution were found for compounds characterized with the highest lipohilicity.

Table 3. pH-dependent distribution coefficient (logD) for barbiturates and thiobarbiturates (1-10).

No.	pH = 1.7 (Stomach)	pH = 4.6 (Duodenum)	pH = 6.5 (Jejunum & Ileum)	pH = 7.4 (Blood)	pH = 8.0 (Colon)
1	2.92	2.92	2.87	2.66	2.30
2	2.66	2.66	2.62	2.41	2.04
3	1.88	1.88	1.86	1.76	1.52
4	1.39	1.39	1.38	1.27	1.04
5	1.16	1.16	1.14	1.04	0.80
6	1.88	1.88	1.86	1.76	1.52
7	1.62	1.62	1.61	1.50	1.27
8	1.96	1.96	1.94	1.84	1.61
9	0.65	0.65	0.64	0.53	0.30
10	1.40	1.39	1.35	1.14	0.78

Calculation of other ADMET Parameters

In this part of the classes students apply two web services: ADMEBoxes and PREADMET to calculate selected ADMET parameters. Most parameters are collected in Table 4. The students are expected to draw the following general conclusions on the basis of the data presented in Table 4: (1) barbiturates and thiobarbiturates are acids and thiobarbiturates are stronger acids than barbiturates; (2) lipophilicity increases with the increase in molecular mass of a compound; (3) thiobarbiturates have larger polar surface area (PSA) than barbiturates as the radius of sulfur atom is greater than the radius of oxygen atom; (4) solubility of a compound in water decreases with increasing lipophilicity. Furthermore, the consequences of the increasing lipophilicity are higher values of human intestinal absorption (%HIA) and blood-brain barrier crossing coefficient (BBB). Barbiturates exhibit good absorption in intestines as confirmed by the values of % HIA which are greater than 70%. Barbiturates exhibit also very high values of plasma protein binding (%PPB, much greater than 32% which is considered a strong binding). This results in the fact that only a small part of a compound occurs in blood as free fraction which

PROBLEMS
OF EDUCATION
IN THE 21st CENTURY
Volume 28, 2011

may permeate to tissues and exert pharmacological effect. As acidic compounds, barbiturates predominantly bind in plasma to human serum albumin.

Table 4. Selected ADMET parameters of barbiturates and thiobarbiturates (1-10).

No.	pKa	Molecular weight	PSA, Å^2	Solubility mg/cm^3	HIA, %	PPB, %	BBB
1	7.50	254.35	90.29	0.151	93.28	87.06	1.37
2	7.50	242.34	90.29	0.370	92.40	80.75	1.31
3	7.90	226.27	75.27	0.504	82.10	80.99	1.01
4	7.90	212.24	75.27	0.972	79.99	77.67	0.71
5	7.90	208.21	75.27	1.550	85.24	72.14	0.48
6	7.90	226.27	75.27	0.400	82.10	81.03	1.01
7	7.90	212.24	75.27	1.120	80.01	74.33	0.83
8	7.90	236.27	75.27	0.810	86.38	79.76	0.89
9	7.90	184.19	75.27	4.890	75.15	27.57	0.45
10	7.50	232.23	75.27	0.438	89.42	85.27	0.50

Table 5 refers to possible side effects of barbiturates and thiobarbiturates (estimated by students with ADMEBoxes) and collects probability values of undesired effects on blood, cardiovascular and gastrointestinal systems, kidneys, liver and lungs. The highest probability was found for side effects on gastrointestinal system and on liver which is in accordance with experimental data. Much lower probability values were obtained for potential cardiotoxicity or nephrotoxicity of barbiturates and thiobarbiturates.

Table 5. The probability of side effects for barbiturates and thiobarbiturates (1-10).

No.	Blood	Cardiovascular	Gastrointestinal	Kidney	Liver	Lungs
1	0.49	0.29	0.41	0.59	0.81	0.25
2	0.42	0.22	0.50	0.29	0.64	0.40
3	0.26	0.12	0.96	0.12	0.70	0.64
4	0.23	0.12	0.95	0.05	0.71	0.60
5	0.51	0.14	0.73	0.15	0.87	0.62
6	0.26	0.12	0.78	0.08	0.70	0.64
7	0.27	0.12	0.67	0.09	0.71	0.65
8	0.22	0.03	0.71	0.11	0.80	0.86
9	0.24	0.12	0.71	0.04	0.62	0.62
10	0.41	0.41	0.90	0.06	0.44	0.58

In summary, the proposed computer-assisted classes on medicinal chemistry of barbiturates and thiobarbiturates makes it possible to recapitulate and organize the students' knowledge on this group of compounds but also to familiarize the students with modern computer-aided methods to assess ADMET parameters of drugs under development and registered drugs.

Both ways of assessment of students' performance during computer-assisted classes, i.e. reports on the performed tasks and the final exam, indicated a positive attitude of participants to this didactic approach. It was also confirmed by the analysis of evaluating questionnaires filled by the students after classes. It is worth stressing that some participants got truly interested in the calculation of pharmacokinetics parameters. They suggested in the questionnaires that broadened discussion of the algorithms behind the web-services used during the classes could improve their understanding of the subject. Surprisingly, other student stated that they would appreciate some homework tasks to practice the knowledge and skills acquired during the computer-assisted classes.

Discussion

The presented proposal of computer-assisted classes can be treated as a short introduction to the medicinal chemistry of barbiturates and thiobarbiturates on one hand, and a quick course on the computation of ADMET parameters (pharmacokinetics) of pharmacologically active compounds on the other one. Pharmacokinetics applies complex mathematics to investigate, model, and predict how drugs are absorbed, distributed, metabolized, and eliminated by the body (Munar et al, 2006). Knowledge of pharmacokinetic concepts and equations are valuable tools in the elaboration of optimal drug-dosing regimens (Munar et al, 2006). Among other reasons, tight connections with mathematics makes pharmacokinetics an ideal material for computer-assisted classes (Hedaya, 1998) and such classes have been elaborated (Aarson et al., 1988; Mehvar, 1997; Hedaya, 1998; Woodward, 1998; Hedaya & Collins, 1999; Munar et al., 2006; Kaczor, Matosiuk & Persona, 2009b; Persona et al., 2010). The presented proposal may be considered as an update on current freely available web services that may be used in education of students.

Noteworthy, in spite of dealing with computers in everyday life, most students do not realize how useful computers can be in estimation of ADMET parameters of medicinal substances and how quickly it can be done. It should be stressed, however, that computational ADMET data is only a rough approximation of experiment and cannot replace it. Nowadays, computation can be used to make decision not to synthesize a particular derivative but they cannot be applied to gain exact values of ADMET parameters of a substance. In particular, in the field of drug metabolism prediction there is still a lot of work to be done.

The tendency in pharmaceutical (and in general scientific) education is toward greater involvement of the students in the learning process (LeBlanc & Aiache, 1995). The teacher-centered approach has several drawbacks, e.g. the lack of students motivation as the students are just passive recipients of compartmentalized knowledge whose retention is low (LeBlanc & Aiache, 1995). In this context, computer-assisted teaching/learning may be considered as a step towards student-centered approach in which students are active participants of the classes. In parallel to significant changes in the teaching of science there has been a great increase in the possibilities offered by computer-assisted learning which may help meet the new challenges to scientific/medical education (Aarson et al., 1988; Brimberry & Riffee¸ 1995; LeBlanc & Aiache, 1995). Contemporary computer technologies, in particular the internet, may open the way for the development of modern educational environments.

Three aspects of the proposed computer-assisted classes should be also emphasized. Firstly, as it has been already mentioned, the classes are based on a group of compounds well-known by students with all the advantages of this fact. Secondly, the author's intention is to perform these classes in the way resembling a real scientific work to evolve creativity and problem-solving skills of the students as suggested by other authors (Mehvar, 1997). Such an

approach is opposite to conventional classes with necessity to memorize factual information and to conduct tasks according to specific procedures. Thirdly, using modern computational tools enables the students, who are on the threshold of selection of their future career to gain a foretaste of a medicinal chemist's job at a university or in pharmaceutical industry.

It is also important to stress 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 earlier proposed computer-assisted classes (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 medicinal chemistry of barbiturates and thiobarbiturates is an attractive alternative to traditional teaching on ADMET parameters of this group of drugs. The students learn how to estimate ADMET parameters of drugs and potential drugs with application of computers. They are also made aware about the importance of pharmacokinetics in action of drugs. Importantly, the classes are intended to develop creativity and problem-solving skills of the students. The students who are on the threshold of selection of their future career, gain a foretaste of a medicinal chemist's job at a university or in pharmaceutical industry. Finally, the presentation of freely available web services provides the students with the tools useful in their future work.

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