1. Introduction

Insomnia is most often defined by an individual's report of sleeping difficulties.[1] One definition of insomnia is difficulties in initiating and maintaining sleep, or non-restorative sleep, associated with impairments of daytime functioning or marked distress for more than 1 month. "Insomnia is most often thought of as both a sign and a symptom that can accompany several sleep, medical, and psychiatric disorders, characterized by persistent difficulty falling asleep and staying asleep or sleep with bad quality. Specialists in sleep medicine have been attempted to diagnose many different sleep disorders. Patients with various disorders including delayed sleep phase syndrome are often misdiagnosed as primary insomnia. When a person has trouble for getting to sleep but has a normal sleep pattern once asleep, circadian rhythm disorder has almost the same cause. In many cases, insomnia is co-morbid with another disease, side-effects of medications, or a psychological problem. Approximately half of all causes of insomnia are related to psychiatric disorders.[1-4] It is possible that insomnia represents a significant risk for the development of a subsequent psychiatric disorder."[1] Sleep-onset insomnia is difficulty falling asleep at the beginning of the night, often a symptom of anxiety disorders or the delayed sleep phase disorder.

There are two types of insomnia: primary insomnia and secondary insomnia. Primary insomnia means that a person having sleep problems that are not directly associated with any other health condition or problem. Secondary insomnia means that a person having sleep problems because of something else, such as a health condition (like asthma, depression, arthritis, cancer, or heartburn); pain; medication they are taking; or a substance they are using (like alcohol and other compounds).[5-9]

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Pharmacological treatments have been used mainly to reduce symptoms in acute insomnia; their role in the management of chronic insomnia remains unclear.\[1-4\] It is important to identify or rule out medical and psychological causes before deciding on the treatment for insomnia.\[1,10\] Attention to sleep hygiene is an important first line treatment strategy and should be tried before any pharmacological approach is considered.\[1,11\]

2. Barbiturates

Barbiturates are drugs that act as central nervous system depressants. By virtue of this, they produce a wide spectrum of effects, from mild sedation to total anesthesia. Barbiturates are also effective as anxiolytics, hypnotics, and anticonvulsants.\[12\] Barbiturates are still widely used in surgical anesthesia, especially to induce anesthesia. These compounds are derivatives of barbituric acid. Barbituric acid was first synthesized in 1864, by Adolf von Baeyer. The synthesis was done by condensing urea (an animal waste product) with diethyl malonate.\[12,13\] Barbiturates were first introduced for medical use in the early 1900s. More than 2,500 barbiturates have been synthesized, and at the height of their popularity, about 50 were marketed for human use. Barbiturates produce a wide spectrum of central nervous system depression, from mild sedation to coma, and have been used as sedatives, hypnotics, anesthetics, and anticonvulsants. The primary differences among many of these products are how fast they produce an effect and how long those effects last. Barbiturates are classified as ultra-short, short, intermediate, and long-acting. The Ultra-short barbiturates such as thiopental (Pentothal) produce unconsciousness within about a minute of intravenous (IV) injection. These drugs may be used to induce general anesthesia. Volatile anesthetics are then used to maintain general anesthesia until the end of the operation. Because thiopental and other ultrashort-acting barbiturates are typically used in hospital settings, they are not very likely to be abused, noted the DEA.\[12\] Barbiturate abusers prefer the short-acting and intermediate-acting barbiturates. After oral administration, the onset of action is from 15 to 40 minutes, and the effects last up to six hours. These drugs are primarily used for insomnia and preoperative sedation. Veterinarians use pentobarbital for anesthesia and euthanasia. Long-acting barbiturates include phenobarbital (Luminal) and mephobarbital (Mebaral). Effects of these drugs are realized in about one hour and last for about 12 hours, and are used primarily for daytime sedation and the treatment of seizure disorders. Barbiturates contain a “balance” of hydrophilic (2,4,6-pyrimidinetrione ring structure) and lipophilic (5,5'-substituents) functionality. The overall hydrophilic (polar) or lipophilic (non-polar) character of the barbiturates is a function of: the hydrophilicity of the pyrimidinetrione ring which is a function of the number of N-substituents and the pKa of the acidic proton(s), and the overall size and structure of the two substituents at the 5-position. (See Fig.-1).\[14-19\]
2.1 Mechanism of barbiturates action

The principal mechanism of action of barbiturates is believed to be their affinity for the GABA<sub>A</sub> receptor (acts on GABA (Gamma-aminobutyric acid; H<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>COOH); benzodiazepine (BDZ) receptor Cl⁻ channel complex). The GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the vertebrate central nervous system.[14,15] There are two classes of GABA receptors: GABA<sub>A</sub> and GABA<sub>B</sub>. GABA<sub>A</sub> receptors are ligand-gated ion channels (also known as ionotropic receptors), whereas GABA<sub>B</sub> receptors are G protein-coupled receptors (also known as metabotropic receptors). Barbiturates bind to the GABA<sub>A</sub> receptor at the alpha subunit, which are binding sites distinct from GABA itself and also distinct from the benzodiazepine binding site.[20,21] Like benzodiazepines, barbiturates have similar effect of GABA at this receptor. In addition to this GABA-ergic effect, barbiturates also block the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, a subtype of glutamate receptor.[20,21] The AMPA receptor (AMPA, or quisqualate receptor) is a non ionotropic trans-membrane receptor types for glutamate that mediates fast synaptic transmission in the central nervous system (CNS). Its name is derived from its ability to be activated by the artificial glutamate analog AMPA.[21] Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the GABA<sub>A</sub> receptor, increases the efficacy of GABA, whereas benzodiazepines increase the frequency of the chloride ion channel opening at the GABA<sub>A</sub> receptor to increase the potency of GABA. The direct gating or opening of the chloride ion channel is the reason for the increased toxicity of barbiturates compared to benzodiazepines in overdose.[20-23]

Barbiturates are relatively non-selective compounds that bind to an entire super-family of ligand-gated ion channels, of which the GABA<sub>A</sub> receptor channel is only one of several representatives. While GABA<sub>A</sub> receptor currents are increased by barbiturates (and other general anaesthetic compounds), ligand-gated ion channels that are predominantly permeable for cationic ions are blocked by these compounds.[12,24] The findings implicate (non-GABA-ergic) ligand-gated ion channels in mediating some of the (side) effects of barbiturates.[12,25]

In 1988, the synthesis and binding study of an artificial receptor binding barbiturates by 6 complementary hydrogen bonds was published by Chang and Hamilton.[26] According to this study, different kinds of receptors were designed, as well as different barbiturates and cyanurates, not for their efficiencies as drugs but for applications in supramolecular chemistry, in the conception of materials and molecular devices.[12,26] The actions of the barbiturates are described in more detail in the Pharmacology Notes. General properties of these compounds relatively concern to low “lipophilicity” and low plasma protein binding.[14-20]
3. Octanol-water partition coefficient and biodegradation of barbiturates

The octanol-water partition coefficient \( (K_{ow}) \) is a measure of the equilibrium concentration of a compound between octanol and water that indicates the potential for partitioning in to soil organic matter (i.e., a high \( K_{ow} \) indicates a compound which will preferentially partition into soil organic matter rather than water). This coefficient is inversely related to the solubility of
a compound in water. The \( \log K_{ow} \) is used in models to estimate plant and soil invertebrate bioaccumulation factors. The \( \log K_{ow} \) is commonly used in QSAR studies and drug design, since this property is related to drug absorption, bioavailability, metabolism, and toxicity. This parameter is also used in many environmental studies to help determine the environmental fate of chemicals.[27,28] It has quite a lot of use in medicine and medicinal chemistry. Biodegradation (\( TB_d \) in mol/h)) is another useful and important factors in chemical and biochemical studies.[28]

It needs to use the effective and useful mathematical methods for making good concern between several data of chemical properties, medicinal chemistry and biological activity of chemicals.

Graph theory is an attractive field for the exploration of proof techniques in Discrete Mathematics and its results have applications in many areas of sciences. A graph is a topological concept rather than a geometrical concept of fixed geometry, and hence Euclidean metric lengths, angles and three-dimensional spatial configurations have no meaning.

Chemists employ various types of names and formulas when they wish to communicate information about chemicals and their structures. For the most part names and formulas have no direct, immediate or explicit mathematical meaning. Graph theory provides many different methods of characterizing chemical structures numerically.

It has been found to be a useful tool in QSAR (Quantitative Structure Activity Relationship) and QSPR (Quantitative Structure Property Relationship).[29-34] Numerous studies have been made relating to the above mentioned fields by using what are called topological indices (TI).[34,35]

In this study, will be considered the relationship of Randić index, for molecular description of structure-property relationship studies for the logarithm of calculated Octanol-Water partitioning coefficients and total biodegradation (\( \log K_{ow} \) and \( TB_d \) (mol/h), respectively) in Barbiturate compounds (1-17).

4. Mathematical operations

The branching index that was introduced by Randić is defined as the sum of certain bond contributions calculated from the degree of the bonds suppressed molecular graphs. These bond contributions, named \( C_{ij} \) are calculated as:

\[
C_{ij} = (\delta_i \delta_j)^{-0.5}
\]

Where \( \delta_i \) is the degree of the vertex representing atom “i”, i.e., the number of bonds incident to this atom. Accordingly, the Randić index is defined as: [29,35-38]

\[
\chi = \Sigma C_{ij} = \Sigma (\delta_i \delta_j)^{-0.5}
\]

Where the summation is carried out over all the bonds of 1-17.

The inverse squared-root of the vertex degree is identified here as a measure of the relative accessible perimeter of an atom from the outside. These perimeters, which have length units, are proposed to be measured in a new unit called the Randić index (\( \chi \)). On this basis, the
bond contributions to the Randić index are relative areas of bond accessibility from the environment.

All graphing operations were performed using the Microsoft Office Excel-2003 program. The data of Octanol-Water partitioning coefficients and total biodegradation (log\(K_{ow}\) and \(TB_d\), respectively) were calculated by EPI-suit v3.12 package [39].

5. Results and discussion

It was accepted that the organic compounds toxicity properties can be introduced by utilizing the log\(K_{ow}\).[40] The quantitative structural activities and properties relationship results hold true for quite a lot of organic compounds, the most commonly used for test organism, follows this standard pattern. [41] Biodegradation is usually quantified by incubating a chemical compound in presence of a degrader, and measuring some factors like oxygen or production of CO\(_2\). The biodegradation QSAR studies demonstrate that microbial biosensors are a viable alternative means of reporting on potential biotransformation. However, a few chemicals are tested and large data sets for different chemicals need for QSAR modeling [42]. This study shows the structural relationship between Randić index (\(\chi\)), \(logK_{ow}\) and total biodegradation (\(TB_d\)) for barbiturates (1-17). The values of the relative structural coefficients of the barbiturates structures (1-17), Randić index (\(\chi\)) to logarithm of Octanol-Water partitioning coefficients (log\(K_{ow}\)) and calculated total biodegradation (\(TB_d\)) in mol/h, data were shown in Table-1. The \(\chi\) values of 1-17 increase with the increasing the number of branches in the appropriate structures. The Randić index (\(\chi\)) for barbituric acid (1) in respect with the branches of the structure is equal to 2.1216. See equations 1 and 2 and the appropriate data extended in Table-1 for other members of these group.

\[
\chi = 6[(2 - 0.5)] = 2.1216
\]

![Graph showing the linear relationship between log\(K_{ow}\) and Randić Indices (\(\chi\)) for Barbiturates (1-17).](image)

Log\(\frac{K_{ow}}{K_{ow}}\) = 1.0309(\(X\)) - 3.3924

\(R^2 = 0.9248\)

Fig. 2. The linear relationship between the values of log\(K_{ow}\) versus the Randic Indices (\(\chi\)) for Barbiturates (1-17).

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Table 1. The values of the relative structural coefficients of Barbiturates structures (1-17).

| No. | R₁ | R₂ | R₃ | R₄ | Randic Indices (χ) | Log $K_{ow}$ | $TB_d \times 10^{-5}$ (mol/h) |
|-----|----|----|----|----|-------------------|--------------|-------------------------------|
| 1   | H  | H  | H  | H  | 2.1216            | -1.2488      | 7.2                           |
| 2   | H  | H  | CH₃| CH₃| 3.0166            | -0.8264      | 5.9                           |
| 3   | CH₃| CH₃| H  | H  | 2.4144            | -0.3777      | 5.9                           |
| 4   | H  | H  | CH₃| C₂H₅| 3.4751           | -0.1289      | 5.4                           |
| 5   | CH₃| H  | C₂H₅| H  | 4.0358            | 0.6045       | 5.0                           |
| 6   | (C₂H₅)₂CH(C₂H₅)| C₂H₅| H  | H  | 5.3911            | 2.0043       | 4.2                           |
| 7   | CH(C₂H₅)CH₂CH₃| C₂H₅| C₂H₅| H  | 4.8266            | 1.7244       | 4.1                           |
| 8   | CH(CH₃)(C₂H₅):CH₃| C₂H₅| H  | H  | 4.9564            | 1.5132       | 4.4                           |
| 9   | CH(CH₃)CH₂C₂H₅| C₂H₅| H  | H  | 4.7188            | 1.5508       | 4.4                           |
| 10  | CH(CH₃)(C₂H₅):CH₃| H  | H  | H  | 5.9978            | 2.9178       | 4.4                           |
| 11  | CH(CH₃)(C₂H₅):CH₃| C₂H₅| CH₃| CH₃| 5.3152            | 2.3590       | 4.0                           |
| 12  | CH₂=CH=CH₂| CH(CH₃)(C₂H₅):CH₃| H  | H  | 4.5277            | 1.3768       | 4.4                           |
| 13  | CH₂=CH=CH₂| (CH₂)₂| H  | H  | 4.3593            | 1.8548       | 3.8                           |
| 14  | C₆H₅| C₂H₅| H  | H  | 4.8025            | 1.3301       | 4.0                           |
| 15  | C₆H₅| C₂H₅| CH₃| H  | 5.0059            | 1.5413       | 3.8                           |
| 16  | C₆H₅| C₂H₅| CH₃| CH₃| 4.8761            | 1.7525       | 3.6                           |

In Fig.-2 to Fig.-4 were shown two dimensional diagrams of the relationship between the values of Randić index, $logK_{ow}$ and $TB_d$.

The figure 2 shows a good linear relationship between the values of $log(K_{ow})$ versus the Randic Indices ($χ$) for barbiturates (1-17). The Eq.-3 is relevant to Fig.-2, and as could see by this equation can extend the linear behavior of the calculated $logK_{ow}$ and $χ$ for these compounds. The R-squared value ($R^2$) for this graph is equal to 0.9248.

$$log(K_{ow}) = 1.0309(χ) - 3.3924$$

By this way, equation 3 afford a good approximation for calculation of logarithm value of Octanol-Water partitioning coefficient ($log K_{ow}$) by the use of Randić index ($χ$) and directly for the barbiturates. The large values results for solving the first order Eq.-3 are acceptable. For achieving to $logK_{ow}$ can use directly from Eq.-3, in accordance with the structural “$χ$” values for these compounds.

The Fig.-3 shows a curve for relationship between the values of calculated total biodegradation ($TB_d$) versus the Randic Indices ($χ$) for 1-17. The Eq.-4 is relevant to Fig.-4,
and can see the non linear behavior of the calculated total biodegradation ($TB_d$) and $\chi$ for barbiturates (1-17). The equation has three-order structure. The R-squared value ($R^2$) for this graph shows 0.8916.

$$TB_d = 0.0825(\chi)^3 - 0.7268(\chi)^2 + 0.901(\chi) + 7.4083 \quad (4)$$

Fig. 3. A curve between values of Randić indices ($\chi$) and calculated total biodegradation ($TB_d$) for (1-17).

By the use of Randic Indices ($\chi$) for 1-17 in the Eq.-4 can achieve to an approximation for total biodegradation ($TB_d$). All values of $TB_d$ should multiply to $10^{-5}$ for achieving to calculated total biodegradation in mol/h for the compounds.

A plot of the log($K_{ow}$) versus the calculated total biodegradation ($TB_d$) for Barbiturates (1-17) was demonstrated in Fig.-4. The equation of this relationship has three-order structure and introduced by Eq.-5. The R-squared value ($R^2$) for this graph is equal to 0.9243.

$$TB_d = 0.0286(\log K_{ow})^3 + 0.1884(\log K_{ow})^2 - 1.1251(\log K_{ow}) + 5.314 \quad (5)$$

It seems that two methods were achieved for $TB_d$ calculation of barbiturates (1-17). One of these two models, is calculation of Randic Indices ($\chi$) for these important compounds by the use of Eq.-4.

The second method is the measurement of log$K_{ow}$ by the use of ($\chi$) in equations 3, then utilize the result in Eq.-5. In respect with the R-squared value ($R^2$) for these graphs it is obvious that the second model much better for this relationship. Determination of log$K_{ow}$ and $TB_d$ for the barbiturates as an important class of medicinal compounds have highly importance and the models that were demonstrated here show simple methods for this matter.
Structural Relationship Study of Octanol-Water Partitioning Coefficients and Total Biodegradation of Barbiturate Medicines by Randić Descriptor

\[ TB_d = 0.0286(\text{Log}K_{ow})^3 + 0.1884(\text{Log}K_{ow})^2 - 1.1251(\text{Log}K_{ow}) + 5.314 \]

\[ R^2 = 0.9243 \]

Fig. 4. A plot of the log($K_{ow}$) versus the calculated total biodegradation ($TB_d$) for Barbiturates (1-17).

6. Conclusion

Barbiturates are primarily used for insomnia and preoperative sedation. These drugs contain a “balance” of hydrophilic and lipophilic functionality. General properties of these compounds relatively concern to low “lipophilicity” and low plasma protein binding. Graph theory has been found to be an effective tool in QSAR and QSPR. Topological indices ($TIs$) contain valuable structural information as evidenced by the success of their widespread applications in QSAR. One of the useful descriptors for examination of structure-property relationship is Randić index. The lipophilicity and toxicity properties of organic compounds can be predicted on the basis of the $\text{log}K_{ow}$. The biodegradation QSAR studies demonstrate that microbial biosensors are a viable alternative means of reporting on potential biotransformation. In this study, we considered the relationship of Randić indices, logarithm of calculated Octanol-Water partitioning coefficients and total biodegradation ($\text{log}K_{ow}$ and $TB_d$ (mol/h), respectively) with each other for barbiturates. Randic Indices ($\chi$) show a good differences between the values of $\text{log}K_{ow}$ and $TB_d$ as two important factors in chemical and biochemical studies in these compounds.

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The word insomnia originates from the Latin "in" (no) and "somnus" (sleep). It is a disorder characterized by an inability to sleep or a complete lack of sleep. Various studies have noted insomnia to be quite a common condition, with symptoms present in about 33-50% of the adult population. This book provides a comprehensive state of the art review on the diagnosis and management of the current knowledge of insomnia and is divided into several sections, each detailing different issues related to this problem, including epidemiology, diagnosis, management, quality of life and psychopharmacology. In order to present a balanced medical view, this book was edited by a clinical psychiatrist.

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