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# Synthesis and *In silco* Study of Some New Derivatives Containing Barbiturate Moiety Compounds

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**ABSTRACT**

Computational chemistry has achieved great success in the field of drug design, as it has played an effective role in shortening the effort, money and time to discover compounds with good properties as a proposed drug. The research dealt with the preparation of nine new compounds derived from barbituric acid using simple methods, seven of which are azo compounds and three are ketones prepared from some pharmaceutical carboxylic acids (Indomethacin, Ibuprofen and Mefenamic acid). The chemical formulas were confirmed by physical methods (color change and melting point measurement) and some spectroscopic methods (FT-IR and $^{1}$HNMR spectra). Theoretical tests were conducted using the programs (Swiss ADME test) and (cardiotoxicity prediction), where the two programs predicted the unsuitability of some of the prepared compounds as drugs due to their poor kinetic properties in addition to containing toxic parts that affect some functions of the heart muscle. Accordingly, they must be excluded or their composition modified before completing biological and clinical studies.

**Keywords:** Barbiturate compounds, Azo dye, Carboxylic acids, theoretical studies, Swiss ADMEE calculations, Cardiotoxicity test.

## INTRODUCTION

Barbituric acid was prepared in 1864 by Adolf von Baer, but it was found through a review of the literature that barbituric acid is pharmacologically inert, but its substituents on the C5 atom give pharmacological activity through its effect on the central nervous system, as the presence of the pyrimidine-trione ring in addition to the nature of the substituent group at the 5 position made most of its compounds hydrophobic[1]. For example, the compound (5,5-diethylbarbituric) was used clinically as a hypnotic in 1904, but the use of barbiturates in anesthesia was in the 1920s in the United States and Germany, where the compound (5-ethyl-5-(1-methylbutyl)-2,4,6(1H,3H,5H)-pyrimidinetrione) has been used in intravenous anesthesia for the past sixty years[2,3]. There are other derivatives of barbituric acid that have given many biological properties, including antimicrobial[4], antioxidant[5], and antidiabetic properties[6]. The researcher Yan *et al.,* found that 5-benzylidene barbiturate derivatives showed an inhibitory effect on fungal and bacterial tyrosinase[7]. There are other barbiturates that have

an anticancer effect[8]. As for the researcher Naguib and his group, he found that some barbituric acid derivatives have an anti-HIV effect[9]. There are other studies that concluded that some acid derivatives prevented Wistar mice from developing non-alcoholic fatty liver disease[10,11]. Also, derivatives of this acid were used in many industrial applications as catalysts for polymerization, plastics, textiles, and water-based or oil-based inks[12,13]. Azo dyes are among the most important chromophores that have applications in various fields, including industrial and medical ones. Some of them are used as food colorings, in the manufacture of dyes, and in the cosmetics industry[14]. The researchers (Beauty Kumari and Khurshid Ahmed) prepared a number of azo derivatives of barbituric acid and tested the antimicrobial activity of the prepared compounds and the results were positive[15]. In addition to the researcher (Tariq Aziz and his group) who conducted a biological examination of a number of azo dyes derived from barbituric acid against a number of bacterial strains (*B. subtilis*, *E. coli* and, *S. typhid*) and fungal strains (*C. albicans*, *A. niger*, and *C. glabrata*) in addition to the antioxidant activity, the result was the maximum inhibition compared to the standard drug (Ciprofloxacin and Fluconazole)[16].

After reviewing many literatures that confirmed that a large number of barbituric acid derivatives have biological and medical efficacy, our research focused on preparing new derivatives of this acid using simplified methods and testing some of their pharmacokinetic properties as well as testing their toxicity on heart functions to predict whether they might be suitable as proposed drugs or not through some theoretical tests such as computer modeling before testing them practically and clinically by specialists.

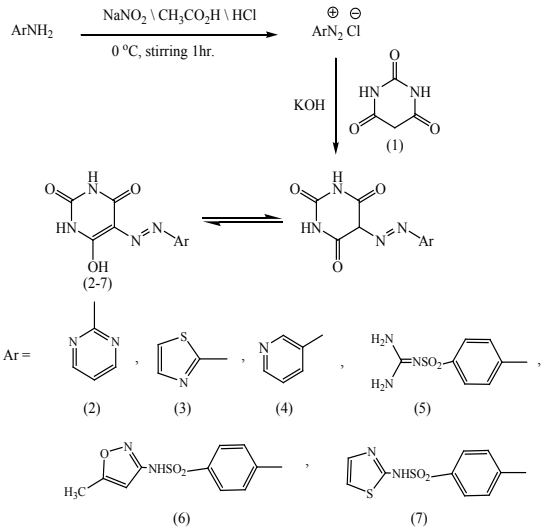
## EXPERIMENTAL

## MATERIALS AND METHODS

All compounds used in this research were used as supplied without purification from Fluka (Germany). Melting points were measured in open capillaries by using an electrothermal IA 9300 Digital-Series instrument. An Alpha platinum ATR (Germany) Bruker, FT-IR spectrophotometer has been used to determine the IR spectra. On 400 MHz Varian spectrometers, $^1$H NMR spectra were acquired with DMSO-$d_6$ as a solvent and TMS as an internal standard.

### Synthesis of 6-Hydroxy-5-(arylazo)-1H-pyrimidine-2,4-dione (2-7)[17-20]

The reaction includes two steps. In the first step, a round-bottomed flask placed inside a bowl containing ice. A mixture of (0.005 mol) of the primary aromatic amine, (5 mL) of $CH_3COOH$, and (5 mL) of conc. HCl. Stir until the amine is dissolved, then a solution is added to it, of (0.35 g, 0.005 mole) $NaNO_2$ dissolved in (5 mL) of water. The mixture stirring for an hour in the ice bath while maintaining the temperature below zero degrees Celsius to notice the formation of a colored precipitate of diazonium salt. The second step is to perform the coupling reaction with Barbituric acid, by adding of (0.64 g, 0.005 mole) of barbituric acid and (0.28 g, 0.005 mole) of potassium hydroxide with (5 mL) of water, after stirring for 3 h at room temperature, to give a colored mixture equivalent by sodium acetate to PH = 5-6 to form a colored precipitate of one of the azo dyes, which is separated by filtration, washed several times with water, and dried.




**Scheme 1. Synthesis of 6-Hydroxy-5-(arylazo)-1H-pyrimidine-2,4-dione (2-7)**

**6-Hydroxy-5-(pyrimidin-2-ylazo)-1H-pyrimidine-2,4-dione (2):** brown, yield 42%, m.p. = decomposed. IR ($\upsilon$ cm$^{-1}$): 3189 (amidic N-H), 3079 (OH), 1752 (C=O), 1601 (N=N).

**6-Hydroxy-5-(thiazol-2-ylazo)-1H-pyrimidine-2,4-dione (3):** pale yellow, 80%, m.p. = 276-281°C. IR ($\upsilon$ cm$^{-1}$): 3350 (OH), 3185

(amidic N-H), 3072 (aromatic C-H), 1674 (C=O), 1600 (N=N). $^1$H-NMR (DMSO-$d_6$, δ ppm): 14.35 (s, 1H, OH), 11.79 (s, 1H, NH), 11.52 (s, 1H, NH), 7.57-7.42 (d-d, 2H, CH=CH).

**6-Hydroxy-5-(Pyridin-3-ylazo)-1H-pyrimidine-2,4-dione (4):** pale brown, yield 53%, m.p. = 320°C. IR (υ cm$^{-1}$): 3169 (OH), 3232 (amidic N-H), 3060 (aromatic C-H), 1698 (C=O), 1587 (N=N). $^1$H-NMR (DMSO-$d_6$, δ ppm): 11.41 (s, 1H, OH), 8.83 (s, 1H,NH), 8.42 (s, 1H, NH), 7.97-7.48 (m, 4H, pyridine ring).

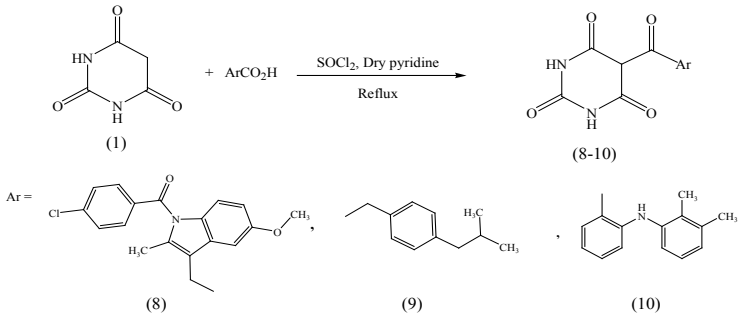
**N-Diaminomethylene-4-(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylazo)-benzenesulfonamide (5):** yellow, yield 98%, m.p. = 319°C. IR (υ cm$^{-1}$): 3326 (OH), 3234 (amidic N-H), 3326 ($NH_2$), 3077 (aromatic C-H), 1664 (C=O), 1585 (N=N),1300 (assym. $SO_2$),1130 (sym. $SO_2$).

**4-(6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylazo)-N-(5-methyl-isoxazol-3-yl)-benzenesulfonamide (6):** Dark yellow, yield 82%, m.p. = 279°C. IR (υ cm$^{-1}$): 3070 (OH), 3146 (amidic N-H), 3184 (NH), 3057 (aromatic C-H), 1642 (C=O), 1601 (N=N),1324 (assym. $SO_2$), 1146 (sym. $SO_2$), 800 (C-S).

**4-(6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylazo)-N-thiazol-2-yl-benzenesulfonamide (7):** Dark yellow, yield 84%, m.p. = 333°C. IR (υ cm$^{-1}$): 3360 (OH), 3312 (NH), 3114 (amidic N-H), 3050 (aromatic C-H), 1680 (C=O), 1608 (N=N), 1324 (assym. $SO_2$), 1120 (sym. $SO_2$). $^1$H-NMR (DMSO-$d_6$, δ ppm): 13.92 (s, 1H, OH), 11.39 (s, 2H, 2NH), 7.89-7.70 (m,6H, Ar-H & CH=CH), 6.07 (s, 1H, NH).

**Synthesis of 5-benzoylpyrimidine-2,4,6(1H,3H,5H)-trione derivatives (8-10)[21-25]**

An equimolar of (0.001mol) of one of the carboxylic acids in (10 mL) of dry pyridine, then thionyl chloride (0.12 g. 0.001 mol) was added slowly drop by drop with continuous stirring. The mixture refluxed for an hour, and after cooling, the starting material (barbituric acid)(1) was added in an amount of (0.128 g, 0.001 mol). The mixture reflux with continuous stirring for 3 hours. The solvent was evaporated to half to obtain a concentrated solution containing a gummy precipitate. Shaved ice was added to it with stirring until a precipitate was obtained. It was filtered and washed with water several times and dried.




**Scheme 2. Synthesis of 5-benzoylpyrimidine-2,4,6-trione derivatives (8-10)**

**5-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)pyrimidine-2,4,6-trione (8):** Earthy color, yield 60%, m.p.=83-86°C. IR (υ cm$^{-1}$): 3112 (amide NH), 3080(Aromatic C-H), 1690 (C=O ketone), 1674 (C=O amide), 754 (C-Cl), 1224 (assym.C-O-C), 1145 (sym. C-O-C).

**5-(2-(4-isobutylphenyl)propanoyl) pyrimidine-2,4,6-trione (9):** Pink, yield 56%, m.p. = 72°C. IR (υ cm$^{-1}$): 3120 (N-H), 3050 (aromatic C-H),1706 (C=O ketone), 1640 (C=O amide).

**5-(2-((2,3-dimethylphenyl)amino) benzoyl)pyrimidine-2,4,6-trione (10):** Gray, yield 60%, m.p.=182-188°C. IR (υ cm$^{-1}$): 3307 (NH), 3012 (N-H amide), 1691 (C=O ketone), 1637 (C=O amide). $^1$H-NMR (DMSO-$d_6$, δ ppm): 9.46 (s,2H,NH), 7.89-6.67 (m,8H,Ar-H, NH), 2.41 (s,1H,CH), 2.29 (s,3H,$CH_3$), 2.1 (s,3H,$CH_3$).

**Theoretical calculations technique**

Recently, many researchers have turned to some theoretical tests of organic compounds in order to discover new drugs and preparations that may be useful in several fields, as such techniques save time, effort and costs in preparing new compounds that show their benefits theoretically according to specific criteria that are prepared and examined practically in light of the calculated theoretical results that may be difficult to determine experimentally,

especially for unstable and complex molecules. In this research, some biochemical properties of the prepared compounds were tested, then the toxic activity of these compounds and their effect on the heart muscle was tested using the applications SwissADME and CardioToxCSM, respectively. The first predicts how the prepared compounds will behave inside the body in terms of (absorption, distribution, metabolism, and excretion) to give preliminary information about the possibility of using them as a medicine or not. As for the cardiotoxicity test, it gives information and predictions about the effect of the compounds on the functions of the heart muscle, for example, whether they cause (Heart failure, heart block, arrhythmia, hERG toxicity, Hypertension, Myocardial Infarction).[26-28]

## RESULTS AND DISCUSSION

### Chemically

In this research, nine compounds were prepared, six of them are azo compounds (2-7) which are characterized as colored compounds that can be used as dyes, as they were made by coupling the barbituric acid (1) with six diazonium salts. The coupling was done in the presence of potassium hydroxide which removed the acidic hydrogen from the C5 atom of the starting material to form the carbanion ion which reacted as a nitrogen-loving nucleus that attacked the diazonium salt to form six new derivatives of barbiturate (2-7). As for the three compounds, they are ketones (8-10) prepared by reaction of one of the pharmaceutical carboxylic acids (Indomethacin, Ibuprofen and Mefenamic acid) with barbituric acid in the presence of $SOCl_2$ in pyridine. The structures of the prepared compounds were established by physical and spectral measurements.

### Theoretically

### Cardiotoxicity Assay[29-30]

Cardiotoxicity test gave some predictions about the effect of compounds (1-10) on some heart functions. From Table (1) it was found that only compound (5) is likely to cause heart palpitations at levels higher or lower than normal, which may cause a disturbance in the transmission of the electrical signal regulating the heartbeat. As for the effect of compounds on blood pressure, it was found that compounds (4-10) are likely to raise blood pressure. The most dangerous effect is the effect of compounds (5,8-10) on myocardial infarction, which may cause a decrease in the amount of blood nourishing the heart muscle, which causes damage to its tissues and then a heart attack.

On the other hand, there are safe results given by all tested compounds, as it was found that they do not affect the efficiency of the heart in pumping blood to all parts of the body, i.e. they do not cause heart failure. Also, all compounds do not affect the normal heart rhythm of blood transfer from the atria to the ventricles, so they do not cause Heart Block. Finally, the theoretical test HERG Toxicity gave an expectation that all compounds do not bind to the potassium channel responsible for repolarization of the cardiac action potential, so they are safe and do not cause an extension of the period between contraction and relaxation of the heart to pump blood regularly.

**Table 2: Toxicity of compounds (1-10) on some heart functions**

| Compound No | Smiles | Arrhythmia | Cardiac failure | Heart block | HERG toxicity | Hypertension | Myocardial infarction |
|---|---|---|---|---|---|---|---|
| 1 | O=C1CC(=O)NC(=O)N1 | S | S | S | S | S | S |
| 2 | O=C1NC(=O)NC(=O)C1/N=N/c1ncccn1 | S | S | S | S | S | S |
| 3 | O=C1NC(=O)C(C(=O)N1)/N=N/c1nccs1 | S | S | S | S | S | S |
| 4 | O=C1NC(=O)C(C(=O)N1)/N=N/c1cccnc1 | S | S | S | S | T | S |
| 5 | O=C1NC(=O)C(C(=O)N1)/N=N/c1ccc(cc1)S(=O)(=O)N=C(N)N | T | S | S | S | T | T |
| 6 | O=C1NC(=O)NC(=O)C1/N=N/c1ccc(cc1)S(=O)(=O)Nc1noc(c1)C | S | S | S | S | T | S |
| 7 | O=C1NC(=O)C(C(=O)N1)/N=N/c1ccc(cc1)S(=O)(=O)Nc1nccs1 | S | S | S | S | T | S |
| 8 | COc1ccc2c(c1)C(CC(=O)C1C(=O)NC(=O)NC1=O)C(N2C(=O)c1ccc(cc1)Cl)C | S | S | S | S | T | T |
| 9 | CC(c1ccc(cc1)CC(C)C)C(=O)C1C(=O)NC(=O)NC1=O | S | S | S | S | T | T |
| 10 | O=C1NC(=O)C(C(=O)N1)C(=O)c1ccccc1Nc1cccc(c1C)C | S | S | S | S | T | T |

S = safe ; T = toxic

**Swiss ADME Calculations**[31,32]

The ADME test was chosen for the theoretical study because it is simple and can give a prediction of how a compound will behave in the body in terms of absorption, distribution, metabolism and excretion. The results are based on established principles to predict whether a compound is a promising drug or not.

The ADME test was chosen in the theoretical study for its simplicity and ability to predict how the compound behaves in the body in terms of absorption, distribution, metabolism and excretion. The results are based on established basic rules to predict whether the compound can be a promising drug or not. Table (2) shows that the TPSA(Topological polar surface area) values were in the range (206.91-75.27) and the highest value was for compound (5). This indicates that this compound contains an active functional group that is subject to rapid metabolic transformation, which reduces the possibility of absorption and permeability of the compound in the body. As for the values of (iLOGP) (Intuitive Logarithm of Partition Coefficient) ranged between (2.02-(-0.08)), where the highest value was for compound (8) and this indicates that it has lipophilic properties and the reason is that its structure contains three hydrophobic aromatic rings. As for the absorption of compounds (1-10) by the digestive system, it was found that only compounds (1,2,4,8,9,10) are expected to be absorbed in the GI system. while all compounds (1-10) cannot cross the blood-brain barrier and the reason may be attributed to either their high molecular weight or that they may be strongly hydrophobic compounds that combine with fats and hinder their passage through this barrier or they may be electrically charged in a way that hinders their passage and association with the transport proteins in the brain barrier, so it is unlikely that they have an effect on the central nervous system.

It was also found through the results of Pgp substrate (p-glycoprotein) that only the two compounds (6, 8) have a high ability to be secreted quickly before they are well absorbed in the digestive system, so they are not suitable as proposed drugs and it is preferable to modify their composition. Through the results of Lipinsky's rule, it was found that all compounds followed the rule except for compounds (6-7) that violated one of its conditions, but remained within the acceptable limit. The highest value was 1, which indicates that all compounds are active when taken orally, noting that the same compounds had a low ability to be absorbed in the digestive system.

As expected, the starting material (1) has weak ADME properties and is not suitable to be a pharmaceutical compound because it violated more than one rule in the test (Ghose-Crippen-Viswanathan model) and therefore has properties similar to narcotic substances. This was confirmed by previous research[33-35] where it was found that barbituric acid has an effect on the central nervous system and has narcotic properties.

As for the values of Bioavailabiliyt score, they were 0.05 for all the tested compounds, which confirms that if these compounds are found to be pharmaceutical compounds, they may be active orally, and this is consistent with the results given by the Lipinsky rule.

While the values of (Pan-Assay Interference Compounds) (PAINS alert) ranged between (0.1) and are within the acceptable limit, as all the prepared compounds do not give incorrect results when tested biologically, and do not contain parts that may cause problems in biological tests.

While, the values of (Brenk alert) or called as (Rapid Elimination of Swill)(REOS) they were different as they ranged between (1-4) and the highest value was for compound (5) which contains quinidine moiety in its structure and it is believed that this compound may cause a problem in metabolism because it contains a toxic group that is undesirable in drug discovery and may give properties similar to narcotic substances.[36,37]

Finally, the values (Leadlikeness) that provide information about the physical and chemical properties of compounds that could be drug candidates with good pharmacokinetic properties in terms of solubility, permeability and metabolic stability. All tested compounds gave the value (1) except for compound (9), which had the value (0), which is the best, noting that values (0,1) are considered within the acceptable limit.

**Table 2: Some pharmacokinetic properties of compounds (1-10)**

| Molecule No | Formula | MW | TPSA | iLOGP | GI absorption | BBB permeant | Pgp substrate | Lipinski# violations | Ghose# violations | Bioavailability score | PAINS# alerts | Brenk# alerts | Synthetic accessibility |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_4H_4N_2O_3$ | 128.09 | 75.27 | -0.08 | High | No | No | 0 | 4 | 0.55 | 0 | 1 | 1.34 |
| 2 | $C_8H_6N_6O_3$ | 234.17 | 125.77 | 0.34 | High | No | No | 0 | 1 | 0.55 | 1 | 2 | 2.25 |
| 3 | $C_7H_5N_5O_3S$ | 239.21 | 141.12 | 0.6 | Low | No | No | 0 | 1 | 0.55 | 1 | 2 | 2.45 |
| 4 | $C_9H_7N_5O_3$ | 233.18 | 112.88 | 0.55 | High | No | No | 0 | 1 | 0.55 | 1 | 2 | 2.45 |
| 5 | $C_{11}H_{11}N_7O_3S$ | 353.31 | 206.91 | 0.13 | Low | No | No | 1 | 1 | 0.55 | 1 | 4 | 2.94 |
| 6 | $C_{14}H_{12}N_6O_6S$ | 392.35 | 180.57 | 0.71 | Low | No | Yes | 1 | 0 | 0.55 | 1 | 2 | 3.2 |
| 7 | $C_{13}H_{10}N_6O_5S_2$ | 394.39 | 195.67 | 1.08 | Low | No | No | 1 | 0 | 0.55 | 1 | 2 | 3.15 |
| 8 | $C_{23}H_{20}ClN_3O_6$ | 469.87 | 121.88 | 2.02 | High | No | Yes | 0 | 0 | 0.55 | 0 | 1 | 3.64 |
| 9 | $C_{17}H_{20}N_2O_4$ | 316.35 | 92.34 | 1.7 | High | No | No | 0 | 0 | 0.55 | 0 | 1 | 2.65 |
| 10 | $C_{19}H_{17}N_3O_4$ | 351.36 | 104.37 | 1 | High | No | No | 0 | 0 | 0.55 | 0 | 1 | 2.54 |

## CONCLUSION

After preparing the compounds (2-10) and proving their chemical formulas with some physical and spectral measurements, it was found necessary to study them theoretically using some software to study their toxicity on six heart functions and study some of their pharmacokinetic properties, which is an important step to test the suitability of using these compounds as drug candidates before conducting expensive biological tests on them to exclude toxic compounds on the most important organ in the body, which is the heart, or modifying their composition to obtain safe compounds with good ADME results.

The cardiotoxicity test predicted that compound (5) causes myocardial infarction which may cause heart attack, followed by ketone compounds (8-10) prepared from pharmaceutical carboxylic acids of the type of non-steroidal anti-inflammatory drugs (indomethacin, ibuprofen and mefenamic acid), which confirms the importance of the presence of the free carboxylic group in their structure and not being linked to groups that may affect their metabolism and may cause cardiotoxicity of these pharmaceutical compounds. As for the SwissADME tests of the prepared compounds (2-10), compared to the starting material (1), compound (5) gave poor pharmacokinetic results. It is believed that the reason is the presence of free amino groups in the guanidine group, which previous studies have shown to be toxic[38,39], which are active groups that undergo rapid metabolic transformation before the compound penetrates and is absorbed in the gastrointestinal tract. They are followed in toxicity by compounds (8-10), especially compound (8), which violated some ADME rules. This is thought to be due to their high molecular weight, and the loss of the carboxyl group in compounds n (8-10) affected their pharmacokinetics.[40,41] Therefore, it is better to exclude compounds (5, 8-10) as drug candidates.

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### Conflict of interest

The author declare that we have no conflict of interest.

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