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Barbituric Acids: A Review of Preparation, Reactions and Biological Applications

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ABSTRACT

Barbiturates, which are derived from the medically significant substance barbituric acid also known as malonylurea or 4-hydroxyuracil, are employed as anaesthetics, sedative-hypnotics, anticonvulsants, and depressants of the central nervous system. In recent years, researchers have paid great attention to compounds and derivatives of barbituric acid, although the first barbituric acid was discovered in 1864 by Adolf Von Baeyer. Due to its great medical and biological importance and wide applications in polymerization catalysts, plastics and textiles, aqueous or oil inks, and polymers. The background, reactions, and methods of preparing barbituric acid have been studied over the last ten years.

1. Introduction

Barbituric acid or (pyrimidine-2,4,6(1H,3H,5H)-trione), includes five hetero atoms (three Oxygen and two Nitrogen), Structure 1 (Packianathan et al., 2007). Adolf von Baeyer produced barbituric acid for the first time in 1864, using urea and diethyl malonate as a starting material (Roth et al., 2008). For his future work in organic chemistry and organic dyes, he got the Nobel Prize in Chemistry. He is supposed to have dubbed the novel substance barbituric acid after celebrating its discovery in a nearby Ghent tavern where some artillery officers were celebrating the feast day of St. Barbara, their patron saint (Figure 1) (Westhorpe et al., 2002). Barbiturates are used in a range of chemicals that affect the central nervous system in the pharmaceutical industry (Cordato, Herkes Mather, 2003). In addition to being utilized as anti-seizure (Singh, Kaur & Verma, 2009), anti-cancer (Uhlmann & Fröscher, 2009), anti-microbial (Singh, Kaur & Verma, 2009), (Morgan, et al., 2002), Nanoscience application (Bassani, 2006), anticonvulsants, anesthetics, and sedative hypnotics (Ikeda, et al., 2007), (Patrick 2013), the majority of them have hypnotic and sedative effects in larger dosages (Barakat et al., 2015).

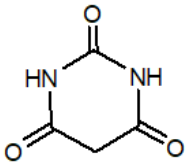

Fig. 1. Barbituric Acid

Barbituric acid is an organic building acid that can side and inside molecules when oxygen and nitrogen are present. When a (CH_2) group loses a hydrogen atom, the barbiturate anion forms, which is stabilized as a flat carbane by forming the resonant (Scheme 1), (Garcia et al., 2016).

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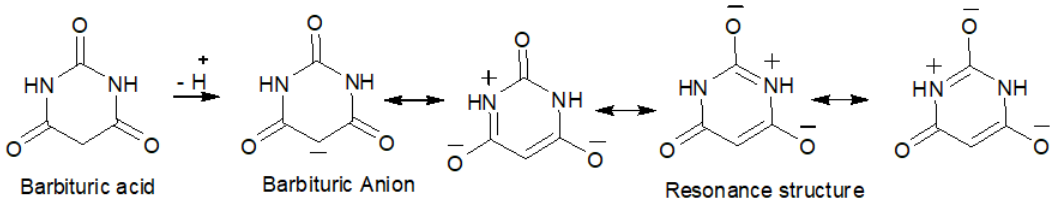
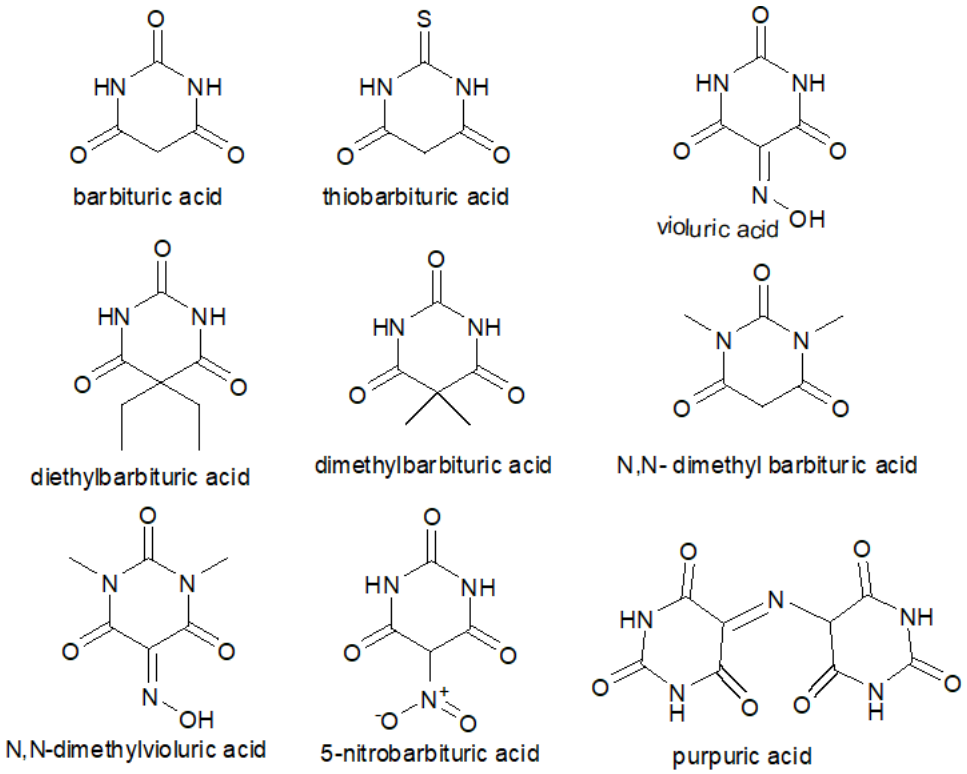


Scheme 1. Barbiturate anion and its resonance forms

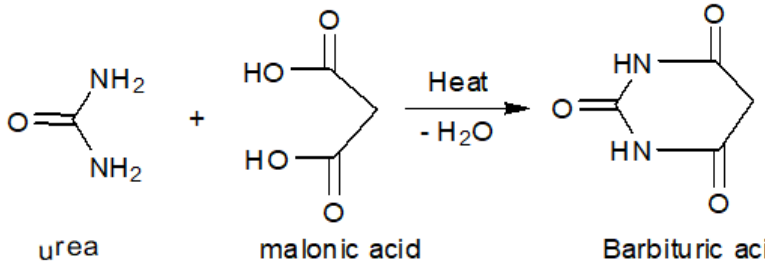
There are several types of barbituric acid, but a few of them are used as common types such as barbituric acid, thiobarbituric acid, violuric acid, diethylbarbituric acid, dimethylbarbituric acid, N,N- dimethyl barbituric acid, N,N-dimethylvioluric acid, 5-nitrobarbituric acid and purpuric acid (Scheme 2) (Mahmudov, et al., 2014).



Scheme 2. Types of Barbituric Acid

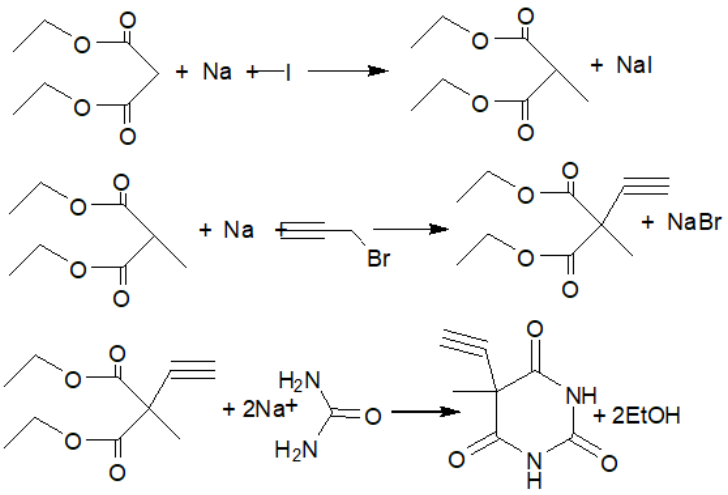
1.1. Preparation Methods of Barbituric Acid Derivatives

Generally, Barbituric acid was prepared by Adolf Johann Von Baeyer in 1864 from a combination of the urea and malonic acid (Scheme 3).



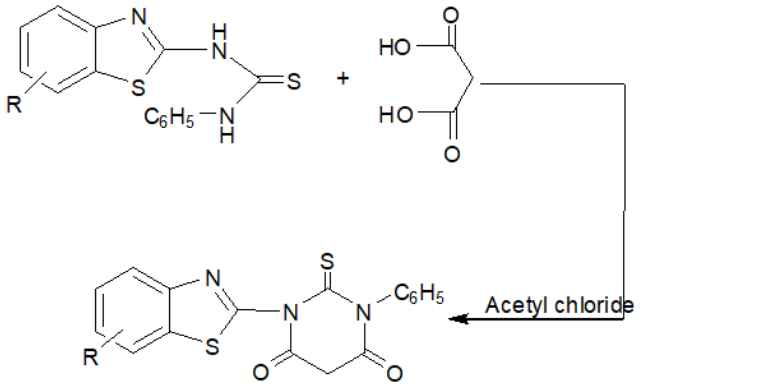
Scheme 3. Prepared method of Barbituric acid

Barbituric acid derivatives were prepared by react urea with derivatives of unsaturated malonic acids, the prepared of 5-methyl-5-propargyl-barbituric acid can be described in (Scheme 4) (Roth et al., 2008).



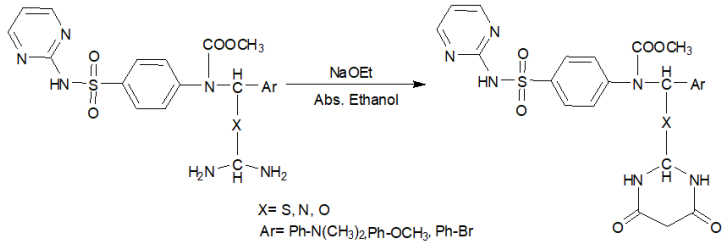
Scheme 4. Preparation of 5-methyl-5-propargyl-barbituric acid

As same side, Pareek et al (2010) synthesized thiobarbituric acid derivatives by condensation of N-(4,6-(R)-1,3-benzo[*d*]thiazole-2-yl)-N'-phenyl thiourea derivatives with malonic acid in acetyl chloride, the synthesized compounds were treated against *E. coli*, and K. species (gram negative bacteria) and against *S. aureus* and *M. lutius* (gram positive bacteria), Scheme 5.



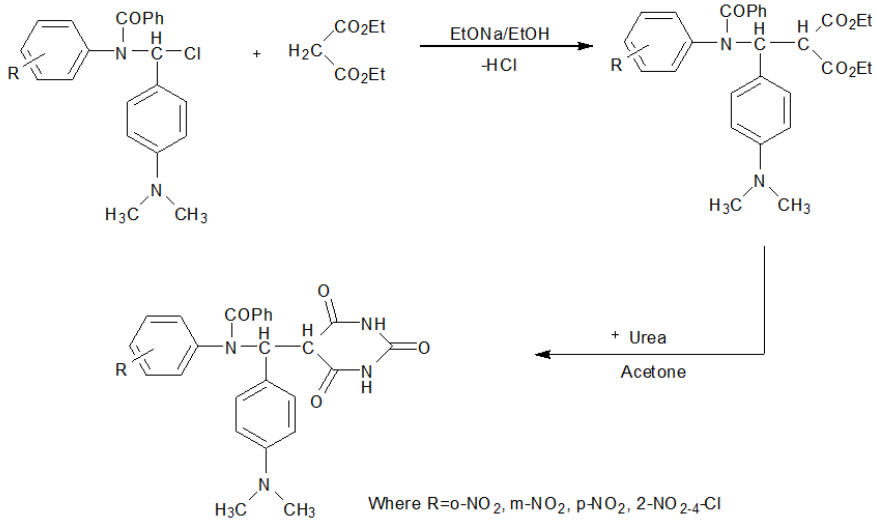
Scheme 5. Preparation of thiobarbituric acid derivatives

Salman and Zmam, (2012) synthesized of novel barbituric acid derivatives from reaction sulfadiazine derivatives with diethyl malonate in basic medium (Scheme 6).



Scheme 6. Synthesized of novel barbituric acid derivatives

For another example to synthesis of barbituric acid derivatives, N-(chloro(4-dimethylamino)phenyl) methyl)-N-phenylbenzamide derivatives was treated with diethyl malonate in basic medium to give N-[α- P-diethylmalonyl-α-p-dimethylaminobenzyl]-N-aryl-benzanilides.While the latter product was condensed with urea by nucleophilic substitution to give the pyrimidine derivatives, Scheme 7, (Zaier, 2009).

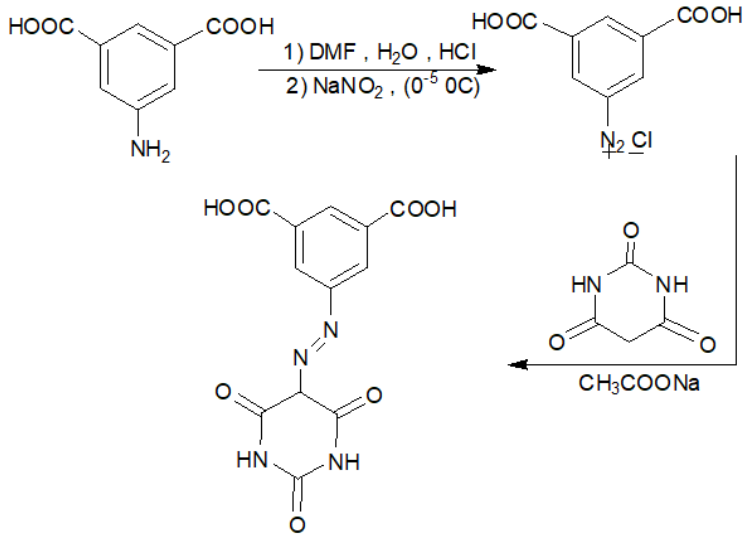


Scheme 7. Synthesis of barbituric acid derivatives by Zaier et al., 2009

2. Reactions of Barbituric Acid

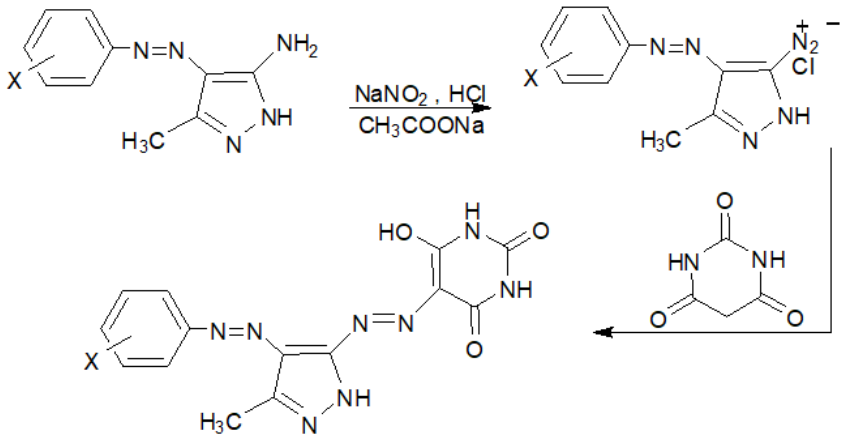
2.1. Reaction with Diazonium Compounds

In the Scheme 8, Diazonium salt is Prepared from 5-aminoisophthalic acid with sodium nitrite, the salt react with barbituric acid to form 5-[(3,5-dicarboxy phenyl) azo]-barbituric acid (Zamanloo et al., 2012).



Scheme 8. Synthesis of 5-[(3,5-dicarboxy phenyl) azo]-barbituric acid

Also, the diazotized and coupled of compound (5-Amino-4-arylazo-3-methyl-1H-pyrazoles) with (pyrimidine-2,4,6(1H,3H,5H)-trione) to form a new series of heterocyclic disazo barbituric acid dyes (Scheme 9), (Karcı & Karcı, 2008).

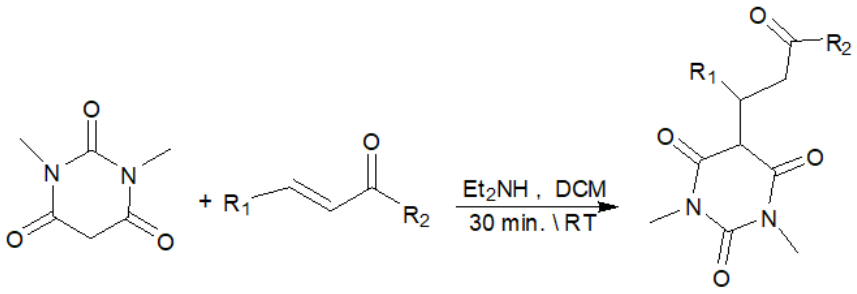


X : H ,p-NO_2 ,p-OCH_3 ,p-Cl , p-CH_3, m-NO_2 ,m OCH_3 , m-Cl ,m-CH_3 ,o-NO_2 ,o-OCH_3 , o-Cl , o-CH_3

Scheme 9. New series of heterocyclic disazo barbituric acid dyes

2.2. Reaction with Chalcone Compounds

Barakat et al., (2017) synthesized 5-monoalkylbarbiturate derivatives from reaction equimolar of N,N-dimethyl barbituric acid with chalcone derivatives in dichloromethane and in the presence of diethylamine at room temperature, (Scheme 10).



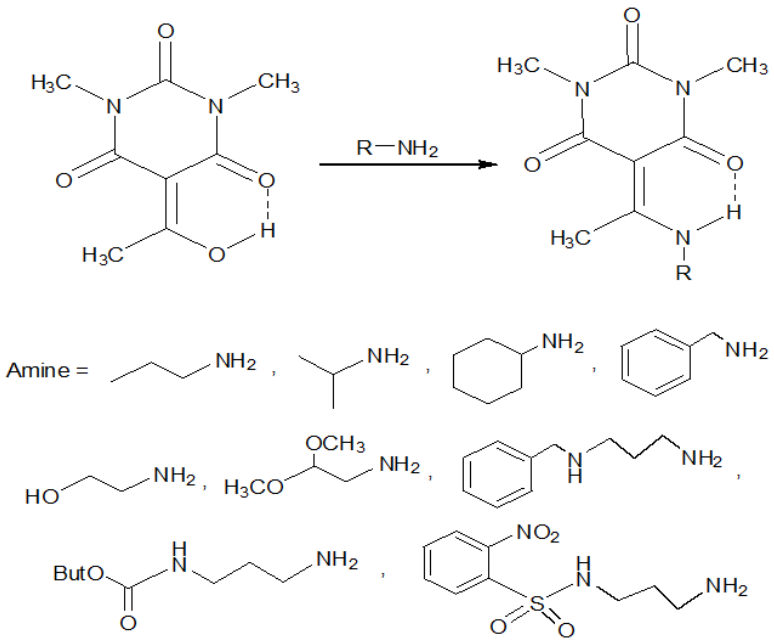
$R_2 = C_6H_5$, $R_1 = C_6H_5$
$R_2 = C_6H_5$, R_1= P-NO_2-C_6H_5
R_2= C_6H_5, R_1 = O-NO_2-C_6H_5
R_2= C_6H_5, R_1 = M-Br-C_6H_5
R_2= C_6H_5, R_1 =
R_2= C_6H_5, R_1= Para-F-C_6H_5

R_2= P-CF_3-C_6H_5 , R_1= P-CF_3-C_6H_5
R_2= P-F-C_6H_5 , R_1= P-CF_3-C_6H_5
R_2= P-Cl-C_6H_5 , R_1= P-F-C_6H_5
R_2= P-Cl-C_6H_5 , R_1= P-Br-C_6H_5
R_2= P-F-C_6H_5 , $R_1 = C_6H_5$
$R_2 = C_6H_5$, R_1= P-Cl-C_6H_5

Scheme 10. Synthesized of 5-monoalkylbarbiturate derivatives

2.3. Reaction with Primary Amines

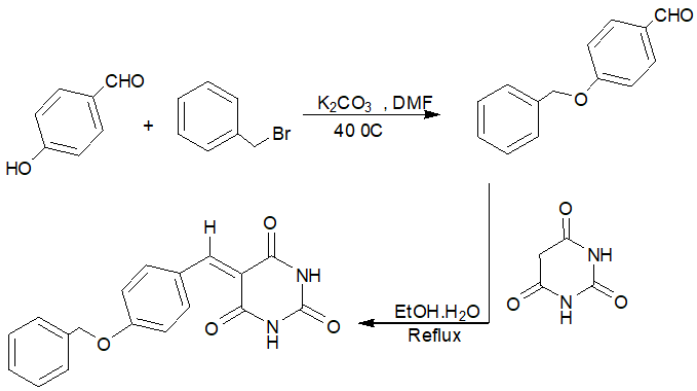
da Silva and Lima (2003) synthesized enamine derivatives in good yields and under moderate conditions from reaction 5-acetyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione with a group of primary amines (Scheme 11).



Scheme 11. Synthesized of enamine derivatives

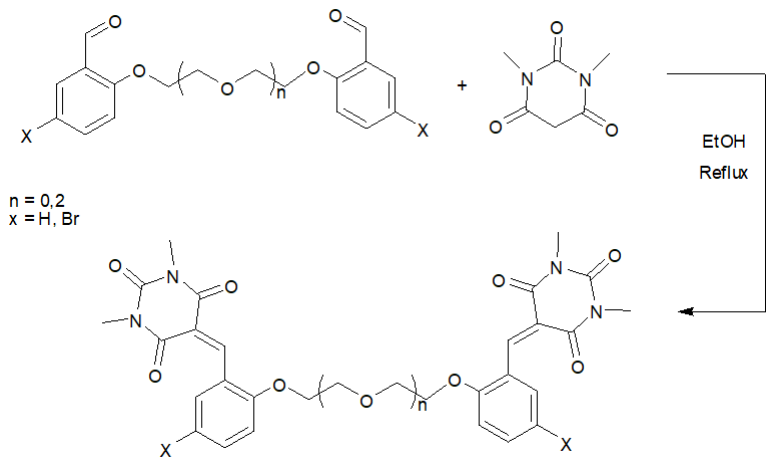
2.4. Other Reactions

Zheng et al., (2011) prepared 5-(4-(benzyloxy)benzylidene)-barbituric acid from condensation aldehyde intermediate and barbituric acid by the Knoevenagel reaction (Scheme 12).



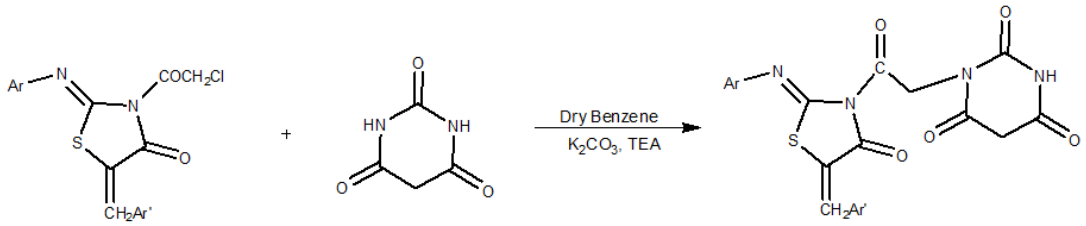
Scheme 12. Synthesized of 5-(4-(benzyloxy)benzylidene)- barbituric acid

Sheikhhosseini, Farrokhi and Bigdeli (2016) synthesized of benzylidene barbituric derivatives containing ethylene ether spacers from reaction ethylene ether based di-aldehyde derivatives with barbituric acid derivatives under mild reaction conditions (Scheme 13).



Scheme 13. Synthesis of benzylidene barbituric derivatives containing ethylene ether

The researchers Shiradkar, et al., (2007) prepared a babituric acid derivative from reacted 3-(2-chloroacetyl)-2-arylimino-5-[(*Z*)-arylmethylidene]-1,3-thiazolan-4-ones with barbituric acid compound in presence of triethylamine (Scheme 14).



Scheme 14. Synthesis of babituric acid by Shiradkar, et al., (2007)

3. Application of Barbituric Acid

Barbituric acids can be thought of as multipurpose building blocks with interesting and challenging chemistry. They are frequently used as synthones in the rational design of various fused pyrimidine derivatives, including synthetic analogs of naturally occurring compounds as well as other systems with potential biological benefits (Levina & Velichko, 1960; Bojarski et al., 1985).

3.1. Complexes as Potent Urease Inhibitor

Barakat et al., (2020) was reported the synthesis of new [CoL_2] NO3 complex of the barbituric acid based ligand 5-((benzylamino) methylene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione as shown in Figure 2.

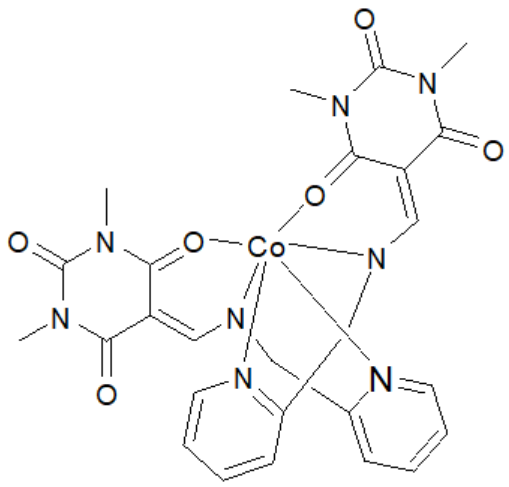


Fig. 2. Structure of [CoL_2] NO_3

Yilmaz, Aksoy, and Sahin (2009) have created three new copper (II) complexes of of 5,5-diethlybarbiturate (barb), [$Cu(barb)_2(dmen)$] $0.5H_2O$ (dmen = N,N-dimethylethylenediamine), [$Cu(barb)_2(bapa)$] (bapa= bis (3-aminopropyl)amine), and [Cu(barb)(apen)](barb) $2H_2O$ (apen

= N,N-bis(3-aminopropyl) ethylenediamine) and studied them using chemical, spectroscopic, and thermal techniques, Figure 3.

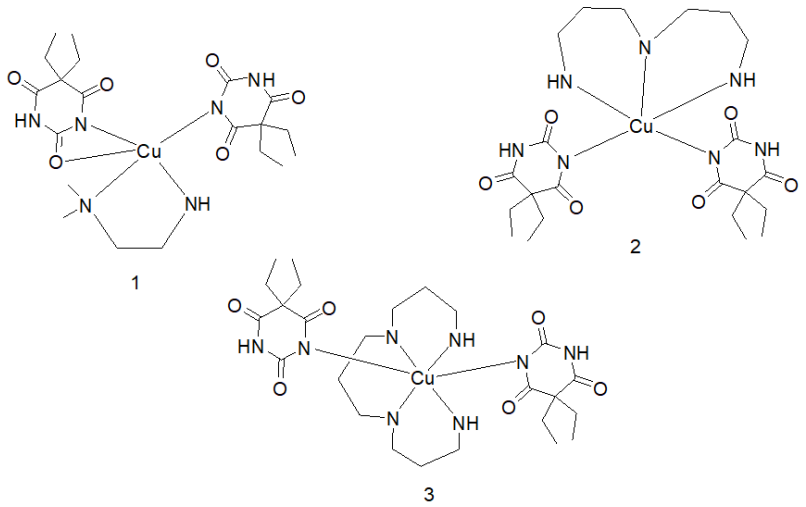


Fig. 3. Structure of three new copper(II) complexes

3.2. Antimicrobial Activity

Fahad, et al., (2019a; 2019b; 2022) were prepared a series of barbituric acid derivatives from sulfadiazine as starting material. The synthesized compounds were tested for their antimicrobial properties against two species of fungi, *Aspergillus flavus* and *Candida Albicans*, as well as three different types of bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The synthetic chemicals' effects on biological applications had a stronger antibacterial effect than the standard, Figure 4.

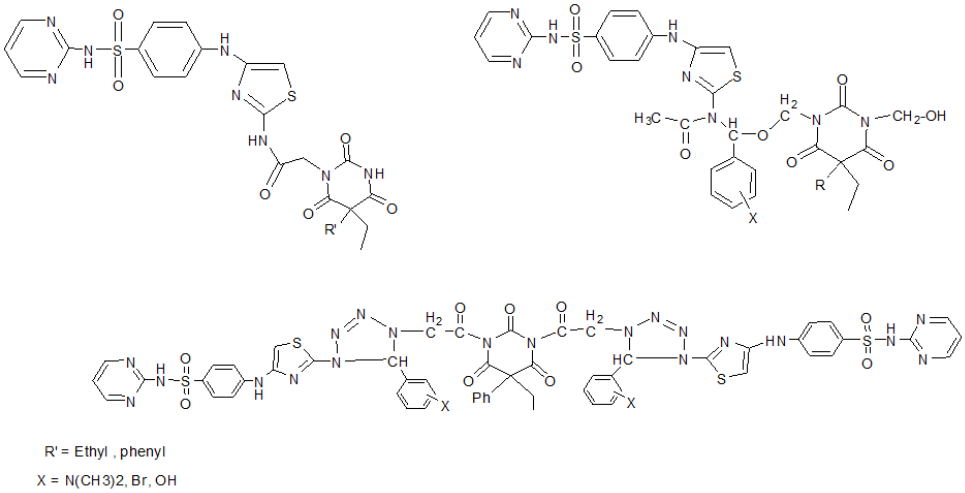


Fig. 4. Structure of barbituric acid derivatives containing sulfa moiety

Phenobarbital is a drug that has been used in a variety of medical settings as a hypnotic, anxiolytic, and anticonvulsant. It also has active functional groups that can be converted into colors, polymers, antibacterial, and anti-antioxidant agents. Phenobarbital was used to create a number of derivatives of barbituric acid that had a 1,2,3,4-tetrazoline moiety as shown in Figure 5, (Fahad et al., 2021).

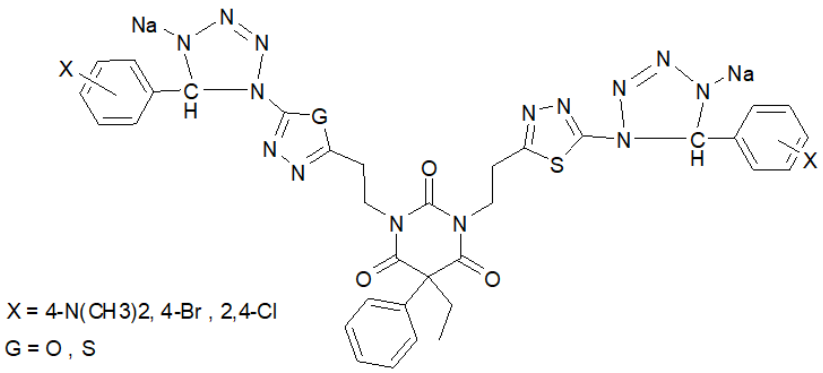


Fig. 5. Structure of barbituric acid derivatives containing 1,2,3,4-tetrazoline moiety

3.3. Anticancer Activity

Both industrialized and developing nations continue to struggle with a serious cancer epidemic. It has surpassed heart disease as the leading cause of death because of numerous global variables. Worldwide, there are several anticancer medications in clinical use, including taxol, vinblastine, vincristine, etoposide, camptothecin and its derivatives (topotecan and irinotecan), mitoxantrone, 5-fluorouracil, indomethacin, etc. Nevertheless, these medications have a number of undesirable side effects, including low blood pressure, bone marrow suppression, gastrointestinal toxicity, diarrhea, and hair loss. As a result, the scientific community is constantly motivated to look into novel chemical entities in order to develop effective and secure cancer treatments (Shoeb, 2006; Zee-Cheng & Cheng, 1978) By combining the structural features of indole and barbituric acid, new hybrid molecules were designed and synthesized by Singh, Kaur, and Verma (2009) (Figure 6).

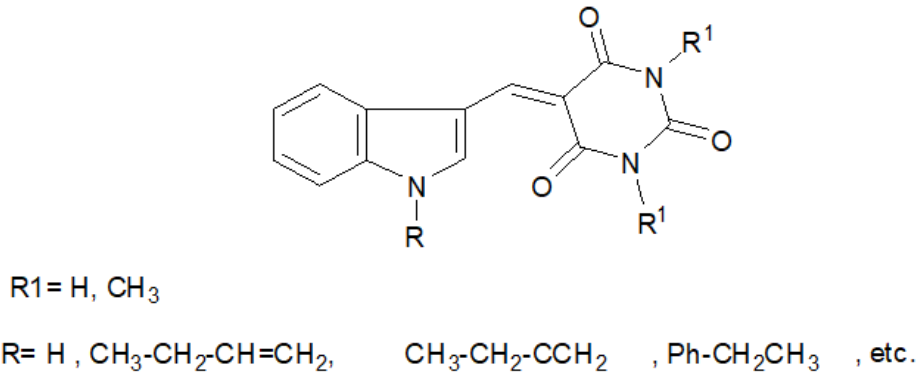


Fig. 6. Barbituric acid derivatives as anticancer

4. Conclusion

Barbituric acids and their derivatives are chemical compounds used in pharmacology as hypnotics, sedatives, anesthetics, antihypertensive medications, antioxidants, anticancer agents, anticonvulsants, antifungal agents, antibacterial, and inhibitors of the Alpha-glycosidase enzyme. This review focuses on the background, reactions, and methods of preparing barbituric acid and its biological uses. This study will aid future researchers in their analysis of earlier research and exploration of novel chemicals such as complexes, antimicrobial, and anticancer medications.

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Competing Interests

The authors have declared that no competing interests exist.

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