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BIOLOGICAL ACTIVITY AND ANALYTICAL CHARACTERIZATION OF BARBITURIC ACID

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ABSTRACT

Earlier literature reports imply that this scaffold is having activity on central nervous system. According to the present studies it has become an attractive target for the development of drugs, which hold variety of biological activities. Derivatives of barbituric acid have attracted the attention of researchers in synthetic organic chemistry, as well as medicinal chemistry, for a long time as a result of their exceptionally diverse biological activity. Present review highlights the importance of the barbituric acid in the present context.

Keywords*:* Barbituric acid, Biological activity, Spectral studies, X-ray Crystallography, Dye properties.

1 INTRODUCTION

Barbituric acid (BA) is documented as the parent compound of the barbiturate drugs. (Fig.1). It is used in the production of riboflavin, Nembutal, and Phenobarbital.[1-2] This class of compounds has been extensively used in medical and biological studies for many years, the best known of which is their sedative action in the central nervous system[3] (CNS).

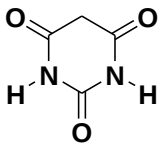

Fig.1

It was demonstrated that some barbituric acid derivatives have new and very interesting biological activities that stand apart from previous medical utilization of barbituric acid derivatives.[4] However it is a precursor to barbituric acid derivatives widely been used in the manufacturing of plastics,[5] textiles,[6] polymers,[7] and pharmaceuticals,[8-9] dental materials,[10] water thinned or oil-based inks,[11] and as polymerization catalysts.[12] In view of the above observations it is worthwhile to make a brief review on it.

2 Barbiturates

2.1 Chemistry of Barbiturates

Barbituric acid an organic compound of the pyrimidine family,[13] chemically called as 2,4,6 trioxopyrimidine, a class of compounds with a characteristic six-membered ring structure composed of four carbon atoms and two nitrogen atoms. Compounds possessing the C_2=O group are known as oxybarbiturates, and those having a C_2=S group are known as thiobarbiturates.

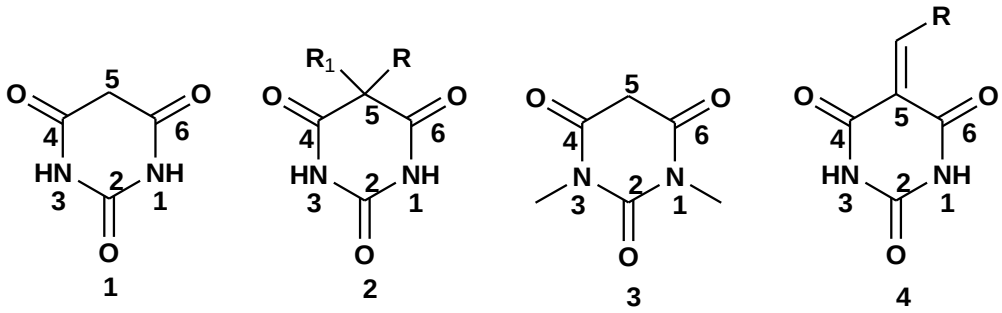

Fig.2

The thiobarbiturates generally have higher lipid solubilities than their corresponding oxybarbiturates. The α-carbon has a reactive hydrogen atom and is quite acidic, variety of barbituric acid drugs were synthesized by employing Knoevenagel condensation. Their biological activities varied when substituent's introduced on two Nitrogen atoms and 5th position of barbituric acid. (Fig. 2)

2.2 Synthesis of Barbituric acid

Several synthetic methods are available in the literature. In 1862, A. V. Baeyer accidentally discovered the barbituric acid, by combining urea and malonic acid on condensation reaction.[14]

2.3 Synthesis of Barbiturate drugs

Barbituric acid condense smoothly with aldehydes under moderate conditions,[15-17] yielding 5-ylidene.The presence of low electron density at the C-5 position in the exocyclic C=C bond, owing to conjugation with the carbonyl groups in the 4 and 6-positions, causes the nucleophilic addition reaction. Several literature procedures were reported for the Knoevenagel condensation of substituted benzaldehydes and barbituric acid.[18-19] Jursic[20] performed the condensation of barbituric acid substituted benzaldehydes in excess of methanol solution without adding any external acid or base catalyst. Uncatalysed Knoevenagel condensation of barbituric acid and substituted benzaldehydes in aqueous medium at room temperature was reported by Mohit L. et al. [21] Solvent-free Knoevenagel condensations of barbituric acid under solid state, synthesis was achieved by Gerd Kaupp et al.[22]

2.4 Tautomerism

Barbituric acid exists in the solid state in the trioxo structure as shown by X-ray[23-24] and ^{14}N-NQR[25] methods. NMR investigation of the oxo-hydroxy equilibrium also indicates that only the oxo form is present in a solution in anhydrous DMSO.[26, 27] BA exist as single molecular species in the gas phase with trioxo tautomers being the most stable. This conclusion was reached on the basis of calculated tautomer energies and FT-IR spectra.[28] Igor Novak et al. have used G3MP2B3 method to calculate Gibbs free energies of the two possible tautomers established that keto tautomers are more stable than enols by 36.8 and 36.7 kJ/mol, respectively.[29] Recently Michale R.Chierothi et al. reported that by griding a commercial sample of Barbituric acid in its trioxo form for 24 h, a new compound has been isolated. The new phase has been identified as trihydroxy isomer. [30] Ab inito and density functional theory (DFT) methods were used to study the tautomers of barbituric acid in the gas phase and in a polar medium, this method was concluded that the triketo form of barbituric acid is found to be the most stable form in the gas phase and in solution. Tautomers, which are partially, enolized forms, have higher dipolemoments in gas phase are stabilized in polar medium.[31]

2.5 *Spectral studies on Barbituric acid*

UV-Vis, IR spectra, Raman spectroscopy, NMR and Mass spectrometry details for BA discussed by Jacek T. Bojarski et.al.[32]

2.6 X-ray studies

Crystallographic data show that barbiturates generally have low symmetric crystal systems, i.e., monoclinic or sometimes triclinic. Sadad Al-Saqqar et al. reported the X-ray diffractometric analysis of barbituric acid (1,4)-dioxane solvate confirmed the two nitrogen atoms of the acid act as hydrogen donors to two oxygen atoms, each from a different molecule of (1,4)-dioxane.[33] (Fig.3.) Maria Victoria Roux et al. reported the calorimetric, computational, and powder Crystallographic Study of barbituric acid [34] and Single crystal X-ray Crystallographic study has been done for the compound 5,5dimethyl Barbituirc acid.[35] Crystallization of Polymorphs of Phenobarbital was reported by Neslihan Zencirci et al.[36]

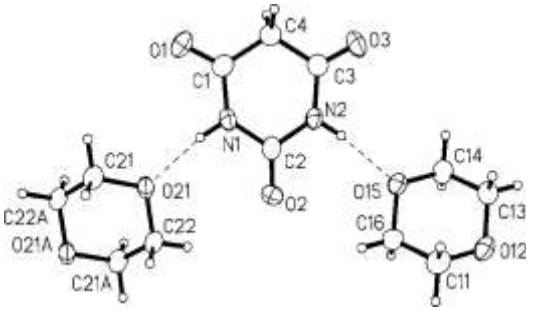

Fig. 3

Mechanically Induced Phase Change in Barbituric acid was achieved by Michele R. Chierotti, et al. By grinding a commercial sample of barbituric acid in its trioxo form (polymorph II, 99%) for 24 h, a new compound has been isolated. The new phase has been identified as the trihydroxyl isomer.

2.7 Thermogravimetric analysis and Thermophysical Study

According to Alexandre Berlin et al. made thermogravimetric characteristics of barbituric acid and its derivatives they indicates the degrees of hydration as well as the range of stabilities of the anhydrous compounds. The decomposition of barbital has also been made to study the effect of alkyl substituent's in the 5 position on the decomposition. The differential thermal analysis for dilituric acid showed a sharp exotherm at 190^{o} indicating a violent explosion.[37] Manuel Temprado et al. reports a differential scanning calorimetry (DSC) study of some of the barbituric acid derivatives.[38] Electron paramagnetic resonance study of thermal decomposition of barbituric acid can be studied by J. N. Herak et al. the structures of the detected radicals in the decomposition of the barbituric acid derivatives suggest that there are various ways of decomposition of these substances. In all the analyzed compounds a loss of the substituent group R^1 or R^2 is detected. The loss of R^1 or R^2 is not necessarily decomposition for all the molecules other competitive decomposition pathways are possible. These experiments undoubtedly prove that in thermal decomposition of molecules free radicals may be found.[39]

4 *Dyes*

Many Barbituric acid derivatives such as Thiobarbituric acid and its derivatives also been used in the synthesis of dyes and pigments or

intermediates in the preparation of Dyes.[40,41] Barbituric acid has been used as disperse dyes with strong fluorescent and as yellow organic pigments,[5]and investigated as stain developers for the identification of nucleic acids.[42] Isidor greenwald investigated that by the addition of alcohol to a mixture of solutions of barbituric acid, picric acid and sodium hydroxide, a red precipitate is obtained.[43] The barbituric acid group present in the yellow and orange iso indolinone and azo pigments provides hydrogen bonding within these pigment systems giving them good durability but this still falls short of the standard required for automotive quality. The synthesis, characterisation and properties of some polycyclic barbiturate pigments are described. The pigments have been tested as colourants for plastic and paint and the results of lightfastness, heatfastness and contact bleed tests are reported by D. Thetford et al. results suggest that only the barbiturate pigments with large aromatic moieties such as the pyren-1-yl and fluoren-2-yl substituent's have good lightfastness properties at reduced shades in plastics.[5] Novel heterocyclic disazo barbituric acid dyes were synthesized and solvatochromic properties were studied (Fig.4. & Fig.5.) The effects of varying the pH and solvent on the absorption of the dyes substituted with electron-withdrawing and electron-donating groups at their o-, m-, and p-position were examined in detail.[44] Some other literature reports also well documented about the dyes properties of the barbituric acid.[45-47]

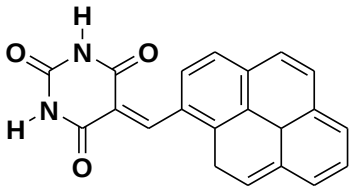

Fig.4

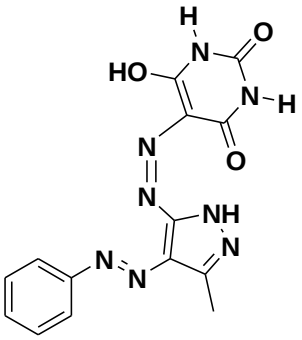

Fig.5

5 *Biological Activities of Barbituric acid*

Barbiturates are 6-oxo derivatives of uracil, a component of the nucleic acids. This similarity may be important since barbiturates have been found to associate preferentially with adenine2 analogous to the uracil-adenine binding in nucleic acids. The strong interaction observed between barbiturates and adenine led to the suggestion that the barbiturates exert their biological activity by specifically binding and inactivating a variety of molecules containing adenine, including coenzymes and adenosine 5'triphosphate,[48] they bind to specific regions of various receptors e.g. to GABA, nicotinic-acetylcholine (nAChR) or BK channel receptors which are all ligand-gated ion channels,[49] the binding to the GABA receptor requires that C5 substituted by alkyl or aryl groups. The substitution enhances lipid solubility and facilitates transport of BA towards their enzyme targets.[29]

5.1. *CNS Depressant activity*

It is important to note that Barbituric acid itself has no CNS activity. Barbituric acid ring as well as the C(5) lipophylic side chains known to be necessary for CNS activity. CNS activity obtained by substitution certain alkyl, alkenyl or aryl groups on pyrimidine ring structure.

Edwared. Smmissm et al. reported the synthesis of Acyloxy alkyl barbiturates as Potential Long-Acting Central Nervous System Depressants.[50] (Fig.6.) Recently José D. Figueroa-Villar et al. investigated the synthesis of a new family of barbiturates, 5-chloro-5-benzylbarbituric acids using a simple efficient synthetic method from aromatic aldehydes and barbituric acid, followed by reduction and chlorination with trichloro-isocyanuric acid *in vivo* evaluation with mice showed that these compounds are having tranquilizing activity. The obtained data clearly indicate that the most active compounds are those with substituent's at the *ortho* position[51] (Fig.7.)

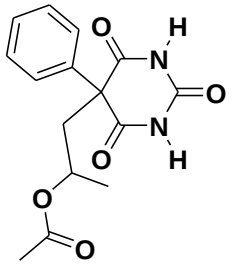

Fig.6

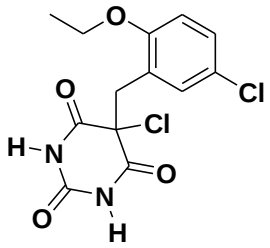

Fig.7

5.2. *Antiinflamatory activity*

A novel series of barbituric acid derivatives were identified as selective inhibitors of α4β7-MAdCAM (mucosal addressin cell adhesion molecule-1) and investigated the structure–activity relationships of the barbituric acid for their ability to inhibit the interaction between α4β7 and MAdCAM out of all the synthesized compounds 3-indolyl barbituricacid derivative (Fig.8.) exhibited potent activity at 0.06 (μM), 3-indolyl was identified as an important pharmacophore component.[52] A series of 1,3-diphenylharbituric acid derivatives has been prepared and evaluated for antiinflammatory activity by means of the Randall-Selitto test,[53] and the pleural effusion method, the compounds are found to be toxic and less active than phenylbutazone by the

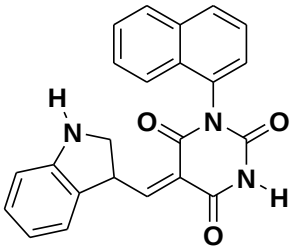

Fig.8

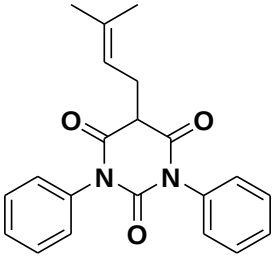

Fig.9

testing procedures used. 1,3-diphenyl-5-(3-methyl-2-butenyl)barbituricacid (Fig.9.) was identified as the most potent member of the series.[54]

5.3. *Anti cancer activity*

By combining indole and barbituric acid, new hybrid molecules were designed and synthesized. Evaluations of these molecules over 60 cell line panel of human cancer cells.

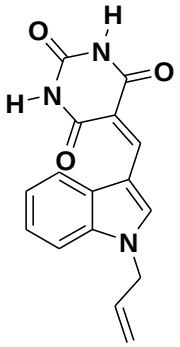

Fig.10

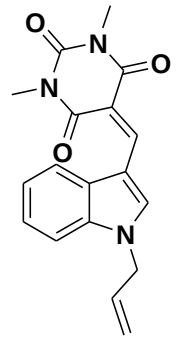

Fig.11

From all the synthesized compounds 5-((1-allyl-1H-indol-3yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (Fig.10.) and 5-((1-allyl-1H-indol-3yl)methylene)-1,3dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (Fig.11.) has shown significant anticancer activity. Dockings of these active molecules in the active sites of COX-2, thymidylate synthase and ribonucleotide reductase indicate their strong interactions with these enzymes.[55] 5-benzyl (Fig.12.) and 5-benzylidene (Fig.13.) derivatives useful in Uridine Phosphorylase inhibitors in cancer theraphy. Inhibition of Uridine Phosphorylase of these compounds equal to or greater than that of their acyclouridine counterparts.[56] Various Barbituric acid derivatives which are having significant anticancer activities were reported in the literature. [57, 58]

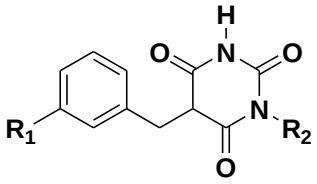

Fig.12

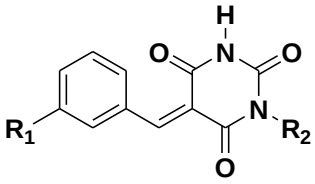

Fig.13

5.4. *Anti Bacterial Activity*

Ayoob Bazgira et al. described a one-pot and efficient method for the synthesis of pyrazolo [4',3':5,6]pyrido[2,3-d]pyrimidine-dione (Fig.14.) derivatives by condensation reaction of barbituric acids, 1H-pyrazol-5-amines and aldehydes under solvent- free conditions. All the products were evaluated for antimicrobial activity.

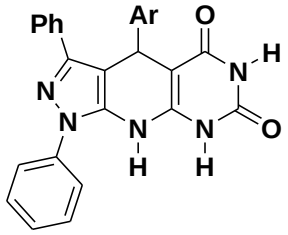

Fig.14

Almost most of the compounds exhibited good to excellent antibacterial activity against all the tested strains.[59] Huacan Song et al. reported the synthesis and antimicrobial activity of 5-(4-hydroxybenzylidene)-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (Fig.15.) and 5-(4-hydroxybenzyledene)pyrimidine-2,4,6(1H,3H,5H)-triones (Fig.16.) and found to be most potent inhibitors with IC50 value of 14.49 μM and, 13.98 μM respectively.[60]

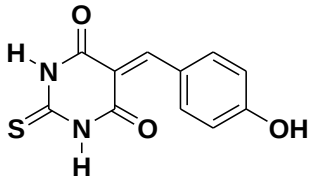

Fig.15

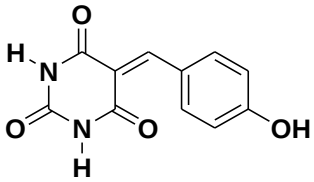

Fig.16

5.5. *Antituberculosis activity*

Recently we reported the synthesis of novel barbiturates and thiobarbiturate analogs of Furano chromene carbaldehydes and dihydropyranochromenes and evaluated for their antitubercular activities against *Mycobacterium tuberculosis* H37RV, and cytotoxicity (CC50) in the VERO cell MABA assay. The results indicate pyranochromene analog showed good antitubercular activity (IC_{90}: 5.9 μg/mL) and cytotoxicity (CC_{50}: 14.27 μg/mL). antitubercular activity of 5-(6,10-Dimethyl-4,8-dioxo-4,8-dihydropyrano[3,2-*g*]chromen-3-yl)methylene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (Fig.17.) was superior to the antituberculosis drug, pyrazinamide (PZA; IC_{90}: >20 μg/mL).[61]

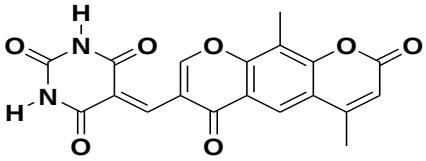

Fig.17

5.6. *Analgesic activity*

In Analgesics 1 Julius A. Vida et al. reported the synthesis of 5-substituted 5-propionoxybarbituric and evaluated for analgesic activity. One compound, 5-propionoxy-5-(1-phenylethy1)barbituric acid, (Fig.18.) displayed better analgesic activity than codeine orally and had half the analgesic potency of morphine when administered subcutaneously.[62] In Analgesics 2 same authors (Julius A. Vida et al.) synthesized the acyloxy, trialkylsilyloxy, triphenylsilyloxy, and tosyloxy derivatives of 5-**(**1-phenylethy1)barbituric acids from all the synthesized compounds 5-acetoxy-5-(l-phenylethyl)barbituricacid (Fig.19) and 5-cyclopropylcarbonyl-oxy-5-(l-phenylethyl)barbituricacid (Fig.20.) exhibited better analgesic activity than codeine orally.[63]

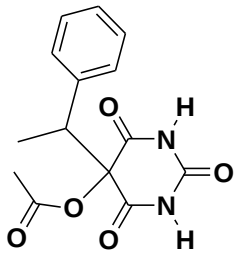

Fig.18

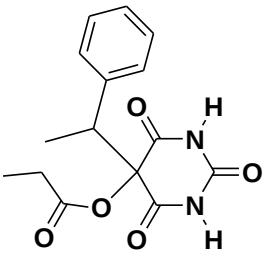

Fig.19

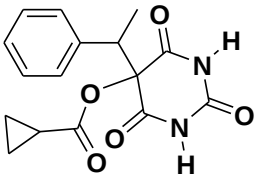

Fig.20

5.7. *Protein Tyrosine Phosphatase Inhibitor*

protein tyrosine phosphatase are key regulators of the phosphorylation of proteins involved in cellular signal transduction pathways. New series of barbituric acid derivatives synthesized and evaluated protein tyrosine phosphate inhibitory activity. 5-(2,4bis(4-(trifluoromethyl)benzyloxy)benzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (Fig.21.) was proved most potent with an IC50 value of 10μM. [64]

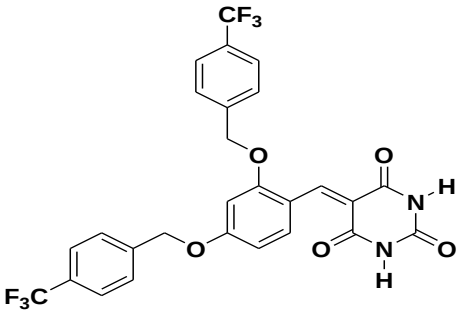

Fig.21

5.8. Radio-sensitizing agents

Y. Thirupathi Reddy et al. have been synthesized a series of Novel substituted (Z)-5-((N-benzyl-1H-indol-3-yl)methylene)imidazolidine-2,4-diones and 5-((N-benzyl-1H-indol-3-yl)methylene) pyrimidine-2,4,6(1H,3H,5H)-triones.(Fig.22.) These analogs were evaluated for their radio sensitization activity against the HT-29 cell line. SAR studies reveals that 2,4,6 (1H,3H,5H) trione derivatives exhibited greater activity over the corresponding imidazolidine-2,4-dione derivatives.[65]

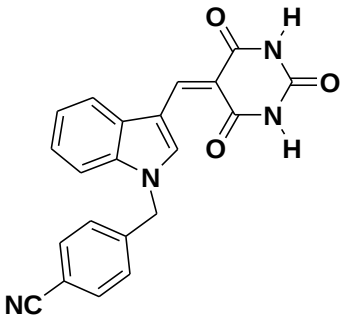

Fig.22

5.9. *Anti Diabetic activity*

Peroxisome proliferator-activated receptor (PPAR) belongs to the nuclear hormone receptor (NHR) superfamily.1 Three subtypes, PPARα, PPARγ and PPARδ, for this receptor has been identified and found to be important targets for the treatment of type 2 diabetes, dyslipidemia, atherosclerosis. Etc[66] A new series of PPARγ ligands based on barbituric acid (BA) has been designed for virtual screening and molecular docking. Out of the total 14 molecules, 6 were found to bind to the murine PPARγ with IC50 ranging from 0.1 to 2.5 μM as compared to reference standard, pioglitazone (IC50 = 0.7μM).[67] Lijuan Chen et al. evaluate the protective effect and the mechanism of the novel agonist of PPARγ on NAFLD model using one of the compounds, [68] 5-(4-(benzyloxy)benzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (Fig.23.) Same authors in another report synthesized forty-four novel barbituric and thiobarbituric acid derivatives against non-alcoholic fatty liver disease (NAFLD) This disease is closely associated with insulin resistance and metabolic syndromes including obesity, type II diabetes.

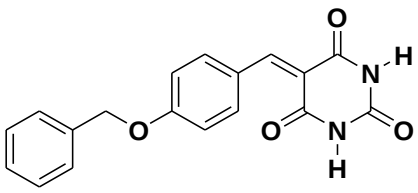

Fig.23

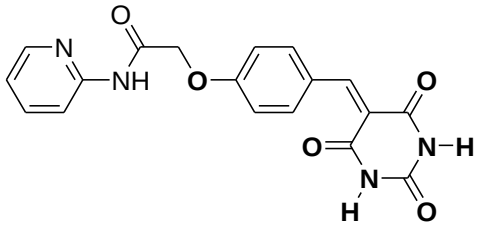

Fig.24

From all the synthesized compounds four compounds were found to increase the expression of adiponectin and lower the leptin level in 3T3-L1 adipocytes at respective concentration of 10 μM. Among them, N-(Pyridin-2-yl)-2-(4-((2,4,6-trioxotetrahydropyrimidin-5(6H)-ylidene)methyl)phenoxy)acetamide (Fig.24.) showed the most efficacious and orally active molecule for reducing fat deposition against non-alcoholic fatty liver disease.[69]

6 ACKNOWLEDGEMENTS

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7 CONCLUSION

From these observations it clearly indicates barbituric acid not only having CNS depressant activity but acts as an important pharmacophore having new and very interesting biological activities such as anti cancer, antitubercular,

anti inflammatory, analgesic, and antimicrobial activities and also functioned as dyes and pigments. This review will give scope for the future investigations on this scaffold.

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