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L-Proline Catalyzed Synthesis of Indolylidine Barbituric Acid Derivatives and their Alternative One-Pot Approach

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*L-Proline catalyzed C-C formation between indole-3-aldehyde **(1)** and barbituric acid **(2)** in ethanol at R.T for 30 mins results in the facile formation of the α,β–unsaturated products i.e 5-(1H-Indo-3-ylmethylene)-pyrimidine-2,4,6-triones**(3)**. The latter could be synthesized alternatively by treating barbituric acid **(2)** with DMF-DMS complex, followed by addition of indole **(4)** in AcOH under one-pot conditions. The structures of products are established by IR, ^{1}H-NMR and Mass spectroscopy.*

Keywords: L-Proline, Indole-3-aldehyde, barbituric acid, DMF-DMS complex, Alternative synthesis.

Barbituric acid and its derivatives have been used predominantly for their anti-convulsant[1] and sedative–hypnotic [2] properties. Phenobarbital, the oldest of the commonly used barbiturates was first used as an anti-convulsant in 1911 [3]. It was regularly prescribed to prevent febrile seizures in infants, but is now infrequently used due to its side effects [4]. Commonly, barbiturates are somewhat effective in all seizure disorders except in the absence of (petitmal) seizures [5].

The importance of indoles is well recognized by synthetic as well as biological chemists [6]. The most ubiquitous of the known bioactive alkaloids are based on the indole moiety [7]. Medicinal chemists repeatedly turn to indole based compounds as a target pharmacophore for the development of therapeutic agents[8]. The prevalence of this moiety in natural and bioactive products continues to be a vector in the development of new methodology to find useful compounds [9].

Keeping in view the prominent biological activity of both the moieties **1** and **2,** it was considered worthwhile to synthesize their condensed product **3** i.e. indolylidine barbituric acid . However, the reported methods [10] for the synthesis of **3** suffer from multi-step approach, longer reaction times and lower yields. Jain et al.. reported synthesis of 3 using L-proline in monochlorobenzene, but the extensive study has not been done on the mechanistic aspect of the reaction.

Herein we describe an improved synthetic protocol using L-proline as an effective organo-catalyst to synthesize indolylidine barbituric acid derivatives in high yields using an eco-friendly solvent (ethanol).

L-Proline is an effective organo-catalyst[11-14] for several powerful asymmetric transformations such as aldol, Michael, Knoevenagel reactions. Proline is an abundant bifunctional molecule which is inexpensive and available in both the enantiomeric forms. The two functional groups of proline can act as both acid and base catalyst and can also facilitate chemical transformations in concert.

RESULTS & DISCUSSION:-

To realize the reaction shown in scheme-1, we have examined the condensation of barbituric acid with indole-3-aldehyde by using catalytic amount of L-proline to establish the optimum conditions . Initially, indole-3-aldehyde **(1)** and L-proline were stirred together in an

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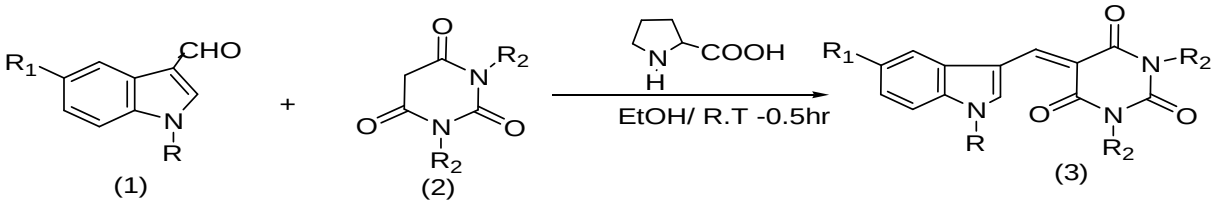
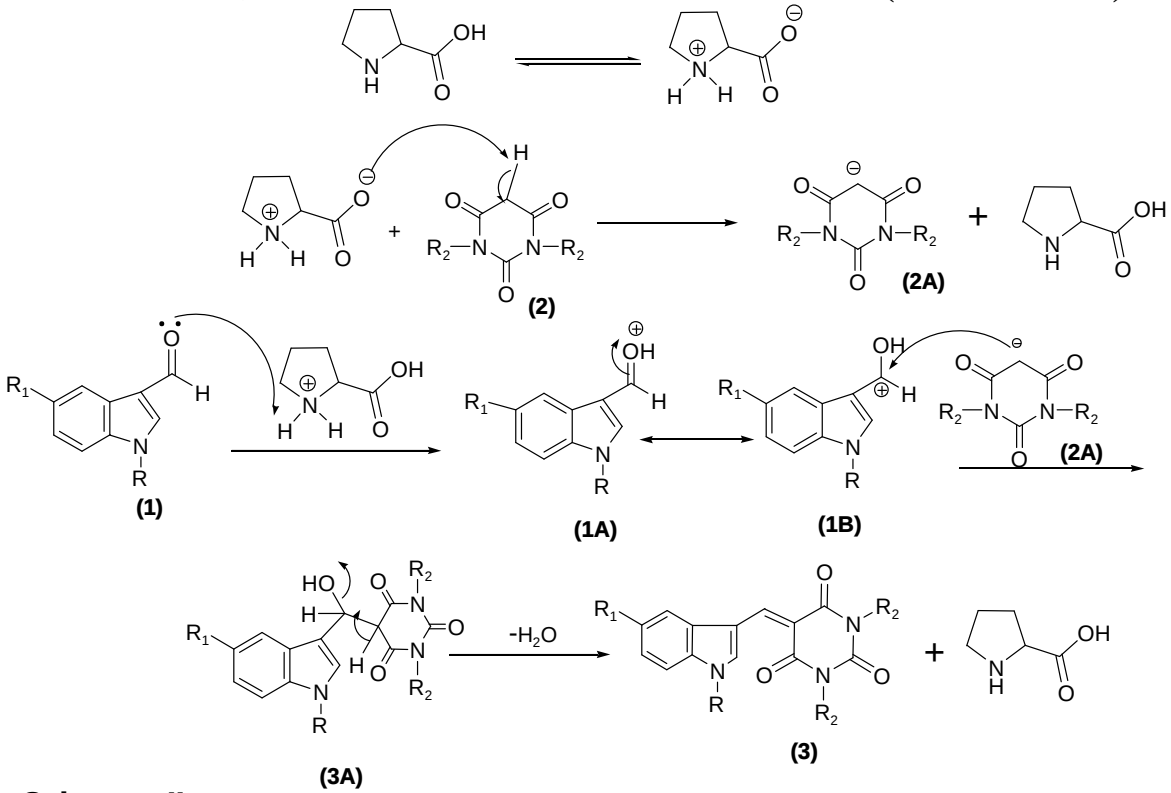


Scheme-I

R.B in EtOH as solvent. After 5 mins of stirring, barbituric acid **(2)** was added and continued stirring at R.T for another 20 mins. The reaction mixture in the R.B flask was initially off-white in colour. After 30mins of stirring, yellow colored solid separated out of the reaction which was an indication for the completion of the reaction, and the same was confirmed by TLC. The structure of the product was assigned on the basis of IR, NMR & Mass spectral data. In order to compare the suitability of the solvent, the reaction was studied in different solvents. However, ethanol seems to be the best solvent for this reaction. (Please see Table-1)



Scheme - II

Mechanisms:

Two possible mechanisms have been proposed to account for the formation of **3** from **1.** In the first possible mechanism (Scheme-II), initially, L-proline abstracts a proton from the active methylene group of **2** to afford **2A.** Later, L-proline protonates the carbonyl group of **1** to form **1A** which is a resonance hybrid of two structutres **IA** and **IB**. **2A** attacks the carbocation species **1B** to form the intermediate **3A** which loses a molecule of water to form the final product **3**. The liberated Proline brings about further condensation of **1** with **2** in a repetitive cyclical form.

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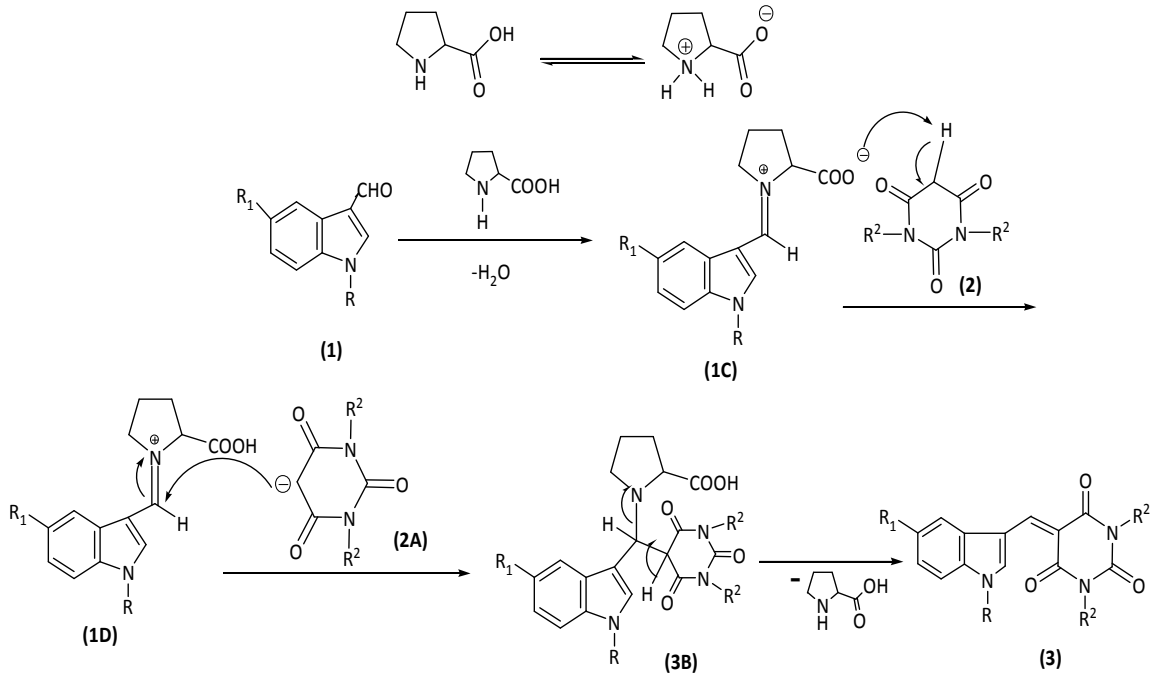

Scheme - III

In the second possible mechanism (Scheme-III), initially, **1** reacts with L-proline, in its non-zwitterionic form, to form an iminium carboxylate ion **(1C)** . Then, **1C** abstracts a proton from the active methylene group of **2** to afford the carboxylic acid containing iminium ion **1D** & barbituric acid anion **2A** as ion pairs. The ion pairs combine to form the adduct **3B** which loses Proline to form the final product **3** . The liberated Proline brings about further condensation of **1** and **2** in a repetitive cyclical form.

In substance, it can be said that the two mechanisms (shown in Scheme-**II** & Scheme-**III**) differ from one another, in that, the Scheme-**II** involves, a simple proton abstraction from the active methylene group followed by a proton transfer process catalyzed by the L-proline, whereas the Scheme-**III** involves an initial iminium ion intermediate formation and subsequent transformations leading to the final product **3**.

Table-1

Reaction of 1a with 2 resulting in 3a in different solvents:

SOLVENT	REACTION CONDITONS	TIME	Yield (%)*
EtOH	L-proline/R.T	0.5-1hr	94
MeOH	L-proline/R.T	1-2hr	85
DMF	L-proline/R.T	2-3hr	90
CH_3CN	L-proline/R.T	5hr	78
$CHCl_3$	L-proline/R.T	24hr	NIL
DMSO	L-proline/R.T	1-2hr	89

***** refers to processed yields

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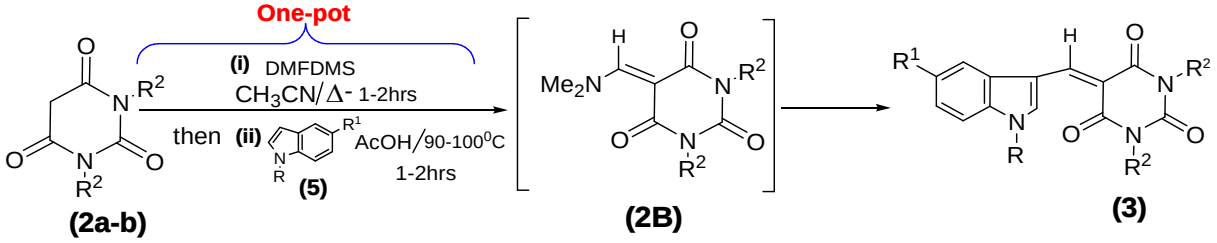
The above mentioned protocol involving condensation of **1** with **2** proved to be a general one and was extended to substituted indole-3-aldehydes to build the Knoevenagel products. (see Table-1).

Alternative method for the synthesis of 3 :-



Scheme-IV

3 could also be alternatively prepared by following the synthetic route shown in scheme-**IV**. Barbituric acid and its 1,3-dimethyl derivatives were refluxed in CH_3CN in the presence of DMF-DMS complex [15] which was prepared insitu by treating DMF and DMS in equimolar ratio, to give N,N^I-dimethylamino methylidine intermediate **(2B)**, which without isolation was further treated with indoles **(5)** in AcOH at 90-100^{0}C in one-pot resulting in the formation of

Table-2:- Characterization data of the Products (3):-

Entry	R	R^1	R^2	Product (3)	Yield (%)	
					Method A	Method B
1	H	H	H	3a	95	91
2	CH_3	H	H	3b	97	95
3	C_2H_5	H	H	3c	93	90
4	H	NO_2	H	3d	92	94
5	CH_3	NO_2	H	3e	95	92
6	H	Br	H	3f	89	87
7	CH_3	Br	H	3g	87	89
8	H	H	CH_3	3h	85	82
9	CH_3	H	CH_3	3i	88	85
10	C_2H_5	H	CH_3	3j	87	89
11	H	NO_2	CH_3	3k	93	91
12	CH_3	NO_2	CH_3	3l	94	94
13	H	Br	CH_3	3m	86	89
14	CH_3	Br	CH_3	3n	84	80
15	C_2H_5	Br	CH_3	3o	88	85

indolylidine barbituric acid derivatives **(3)** in good yields. That **2B** are the intermediates in these reactions has been shown by isolating these in two cases, when R^2=H (i.e 2a) and when R^2=CH_3(i.e **2b**), and characterizing them by spectral methods. Thus, treatment of **2a** (i.e R^2=H) with DMF-DMS complex in DMF yielded an intermediate **2B** which on subsequent treatment with indole in AcOH gave the final product **3**. Several N,N^I-dimethylamino derivatives such as DMF-DES (dimethylformamide diethylsulphate), DMF-DMA (dimethylformamide dimethylacetal), DMA-DMA (dimethylacetamide dimethylacetal) and DMF-DEA (dimethylformamide diethylacetal) were used apart from DMF-DMS to obtain the product **3**. Among all,

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DMF-DMS proved to be effective in terms of yields and reaction times (See Table-3). The products obtained were found to be identical (in M.P, M.M.P & TLC) with those prepared through Scheme-**I**.

Table-3: Synthesis of N,N^{I}-dimethylamino methylidine intermediate using different N,N^{I}-dimethyl reagent (Scheme – IV):-

Entry	Reagent used	Yield (%)	Time (mins)	M.P (ºC)
1	DMF-DMA	85	30-50	225-230
2	DMF-DEA	82	45-60	>240
3	DMF-DMS	90	10-15	>240
4	DMA-DMA	86	25-35	210-215
5	DME-DES	81	45-55	>240

CONCLUSIONS

In conclusion , we have developed an efficient , simple and eco-friendly methodology for the preparation of indolylidine barbituric acid derivatives using L-Proline as an organo catalyst in ethanol as eco-compatible solvent . The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent product yield, shorter reaction time, and the easy work-up procedure makes this approach more attractive in synthesizing avariety of such derivatives.

Experimental Section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. Thin-layer chromatography (TLC) was performed on silica gel G, and spotting was done using iodine or UV light. IR spectra were recorded with Jasco FT-IR 5300, ^{1}H NMR on Varian 400-MHz instrument , and Mass spectra on an Agilent LC-MS instrument giving only M+ values in Q+1 mode.

Preparation of 3 from 1 and 2 (General Procedure) (Method-A) : A mixture of **1** (0.735 g, 5mmole), **2** (0.640 g, 5mmole), L-proline (0.5gr) and EtOH (35ml) was stirred at R.T for 30-45 mins. At the end of this period, the reaction mass was, filtered, washed with ethanol (2X5ml) and dried to obtain crude **3**.

5-(1H-Indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3a); Yield: 0.133gr (92%) ; M.P(ºC): >220 ; IR (KBr): 3420 and 3455 cm^{-1}(broad, two -NH groups of barb.acid), 3510cm^{-1} (-NH of indole) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton),10.90 and 10.98 (S, 1H, -NH of barb.acid), 12.62 (1H,br, -NH of indole). M/Z (M^{+}+1): 256; Anal. Calcd. for ($C_{13}H_9N_3O_3$) requires C,61.21; H, 3.55; N,16.36; found C,61.67; H, 3.53; N,16.39.

5-(1-Methyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione(3b); Yield: 0.149gr (94%); M.P(ºC): >220 ; IR (KBr): 3420 and 3455 cm^{-1}(broad, two -NH groups of barb.acid) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.60 (s,3H, -NCH_3) 7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton),10.90 and 10.98 (s, 1H, -NH of barb.acid); M/Z (M^{+}+1): 270 ; Anal. Calcd. for ($C_{14}H_{11}N_3O_3$) requires C,62.21; H, 4.55; N,15.36; found C,62.27; H, 4.63; N,15.49.

5-(1-Ethyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3c); Yield: 0.150gr(88%) M.P(ºC): >220 ; IR (KBr): 3420 and 3455 cm^{-1}(broad, two -NH groups of barb.acid) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 1.60 (t, 3H, -CH_3) ,3.29 (q, 2H, -NCH_2) 7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton),10.90 and 10.98 (s, 1H, -NH of barb.acid); M/Z (M^{+}+1): 284 ; Anal. Calcd. for ($C_{15}H_{13}N_3O_3$) requires C,63.21; H, 4.65; N,14.86; found C,63.37; H, 4.63; N,14.49%.

5-(5-Nitro-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3d); Yield: 0.169gr (89%); M.P(ºC): >220 ; IR (KBr): 3420 and 3455 cm^{-1}(broad, two -NH groups of barb.acid), 3510cm^{-1} (-NH of indole) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 7.28-8.72 (m,5H) corresponds to 4H aromatic + 1H vinyl proton),10.90 and

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10.98 (S, 1H, -NH of barb.acid), 12.62 (1H,br, -NH of indole). M/Z (M^++1): 301 ; Anal. Calcd. for ($C_{13}H_8N_4O_5$) requires C,52.21; H, 2.65; N.18.66; found C,52.37; H, 2.53; N,18.69%.

5-(1-Methyl-5-nitro-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trionemethane (3e); Yield: 0.189gr (93%); M.P(ºC): >220; IR (KBr): 3420 and 3455 cm^{-1}(broad, two -NH groups of barb.acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.23 (s,3H,-NCH_3) 7.28-8.72 (m,5H) corresponds to 4H aromatic + 1H vinyl proton),10.90 and 10.98 (S, 1H, -NH of barb.acid); M/Z (M^++1): 315 ; Anal. Calcd. for($C_{14}H_{10}N_4O_5$) requires C,53.21; H, 3.25; N.17.66; found C,53.37; H, 3.33; N,17.86%.

5-(5-Bromo-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione(3f); Yield: 0.202gr (90%); M.P(ºC): >220; IR (KBr): 3430 and 3472 cm^{-1}(broad, two -NH groups of barb.acid), 3510cm^{-1} (-NH of indole) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 7.45-8.62 (m,5H) corresponds to 4H aromatic + 1H vinyl proton),10.90 and 10.98 (S, 1H, -NH of barb.acid), 12.62 (1H,br, -NH of indole). M/Z (M^++1): 333 ; Anal. Calcd. for ($C_{13}H_8BrN_3O_3$) requires C,46.51; H, 2.95; N.12.66; found C,46.67; H, 2.93; N,12.89%.

5-(5-Bromo-1-methyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione(3g); Yield: 0.217gr (91%); M.P(ºC): >220; IR (KBr): 3410 and 3465 cm^{-1}(broad, two -NH groups of barb.acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.43 (s, 3H, -NCH_3) 7.25-8.52 (m,5H) corresponds to 4H aromatic + 1H vinyl proton),10.89 and 10.98 (S, 1H, -NH of barb.acid); M/Z (M^++1): 347 ; Anal. Calcd. for ($C_{14}H_{10}Br\ N_3O_3$) requires C,48.21; H, 2.95; N.12.06; found C,48.67; H, 2.83; N,12.39%.

5-(1H-Indol-3-ylmethylene)-1,3-dimethyl-pyrimidine-2,4,6-trione (3h); Yield: 0.133gr (92%) ; M.P(ºC): >220; IR (KBr):1730,1690,1660,(-C=O of barbituric acid) 3510cm^{-1} (-NH of indole) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid),7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton) , 12.62 (1H,br, -NH of indole). M/Z (M^++1): 284 ; Anal. Calcd. for ($C_{15}H_{13}N_3O_3$) requires C,63.21; H, 4.55; N,14.36; found C,63.47; H, 4.43; N,14.59%;.

1,3-Dimethyl-5-(1-methyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3i); Yield: 0.149gr (94%); M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 3.60 (s,3H, -NCH_3), 7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton); M/Z (M^++1): 298 ; Anal. Calcd. for ($C_{16}H_{15}N_3O_3$) requires C,64.21; H, 5.55; N,14.36; found C,64.37; H, 5.93; N,14.59%;

5-(1-Ethyl-1H-indol-3-ylmethylene)-1,3-dimethyl-pyrimidine-2,4,6-trione (3j); Yield: 0.150gr(88%) ; M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 1.60 (t, 3H, -CH_3) , 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 3.29 (q, 2H, -NCH_2) 7.28-8.72 (m,6H) corresponds to 5H aromatic + 1H vinyl proton); M/Z (M^++1): 312 ; Anal. Calcd. for ($C_{17}H_{17}N_3O_3$) requires C,65.21; H, 5.65; N,13.86; found C,65.67; H, 5.63; N,13.49%;.

1,3-Dimethyl-5-(5-nitro-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trionemethane (3k); Yield: 0.169gr (89%); M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid) 3510cm^{-1} (-NH of indole) ; ^{1}H-NMR (400MHz, DMSO-d_6/TMS): δ3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 7.28-8.72 (m,5H) corresponds to 4H aromatic + 1H vinyl proton), 12.62 (1H,br, -NH of indole). M/Z (M^++1): 329 ; Anal. Calcd. for ($C_{15}H_{12}N_4O_5$) requires C,54.21; H, 3.65; N.17.66; found C,54.47; H, 3.93; N,17.89%;.

1,3-Dimethyl-5-(1-methyl-5-nitro-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (3l); Yield: 0.189gr (93%); M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 3.60 (s,3H, -NCH_3),7.28-8.72 (m,5H) corresponds to 4H aromatic + 1H vinyl proton); M/Z (M^++1): 343 ; Anal. Calcd. for($C_{16}H_{14}N_4O_5$) requires C,56.21; H, 4.25; N.16.66; found C,56.67; H, 4.93; N,16.89%.

5-(5-Bromo-1H-indol-3-ylmethylene)-1,3-dimethyl-pyrimidine-2,4,6-trione (3m); Yield: 0.202gr (90%); M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid) 3510cm^{-1} (-NH of indole),3510cm^{-1} (-NH of indole) ; ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 7.45-8.62 (m,5H) corresponds to 4H aromatic + 1H vinyl proton) , 12.62 (1H,br, -NH of indole). M/Z (M^++1): 362 ; Anal. Calcd. for ($C_{15}H_{12}BrN_3O_3$) requires C,49.21; H, 3.45; N.11.66; found C,49.67; H, 3.53; N,11.89% .

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5-(5-Bromo-1-methyl-1H-indol-3-ylmethylene)-1,3-dimethyl-pyrimidine-2,4,6-trione (3n); Yield: 0.217gr (91%); M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 3.60 (s,3H, -NCH_3),7.25-8.52 (m,5H) corresponds to 4H aromatic + 1H vinyl proton); M/Z (M^++1): 377 ; Anal. Calcd. for ($C_{16}H_{14}BrN_3O_3$) requires C,51.21; H, 3.95; N.11.06; found C,51.47; H, 3.83; N,11.39% .

5-(5-Bromo-1-ethyl-1H-indol-3-ylmethylene)-1,3-dimethyl-pyrimidine2,4,6trione (3o);Yield: 0.150gr(88%) ; M.P(ºC): >220; IR (KBr): 1730,1690,1660,(-C=O of barbituric acid); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 1.60 (t, 3H, -CH_3) , 3.21 and 3.23 (3H,s, -NCH_3 of barbituric acid), 3.29 (q, 2H, -NCH_2) 7.28-8.72 (m,5H) corresponds to 4H aromatic + 1H vinyl proton); M/Z (M^++1): 312 ; Anal. Calcd. for ($C_{17}H_{17}N_3O_3$) requires C,52.21; H, 4.65; N,10.86; found C,52.67; H, 4.93; N,10.59% .

Preparation of 3 from 2 and 5 (General Procedure) (Method-B) ; To a suspension of barbituric acid **2** (0.640gr,5mmol) in CH_3CN, DMF-DMS complex, which was prepared insitu by stirring DMF (10mM) and DMS (10nM) in equimolar ratio at R.T, was added and the mixture was refluxed for 1-2hrs at 85^{0}C. After checking the completion of the reaction by TLC, indole **5** (0.747gr, 6.5mmol) in AcOH was added to the same solution and continued refluxing for another 1-2hrs. At the end of this period, the reaction mass was poured in to ice-cold water (100ml), the separated solid was filtered, washed with water (2X10ml) and dried to obtain crude **3**. The latter, were recrystallized from DMF-EtOH to get pure **3**.

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