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Research Article

ONE-POT SYNTHESIS AND BIOLOGICAL STUDY OF NEW BARBITURIC ACID DERIVATIVES USING PTC TECHNIQUE

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ABSTRACT

Some novel pyrimido[4',5':4,5]furo[2,3-d]pyrimidine, pyrano[2,3-d]pyrimidine, pyrimidinyliden-3,4-dihydro-2H-1,3-thiazine, (1,3-thiazol-2-yliden)hexahydro-2,4,6-pyrimidinetrione as well as other derivatives of barbituric acid have been synthesized. The antimicrobial activity of all synthesized compounds was tested and showed a good inhibitory effect against most of employed microorganisms.

Keywords: Barbituric acid, Pyrano[2,3-d]pyrimidine, PTC, Antimicrobial activity.

1. INTRODUCTION

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecules. Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of its ability to synthesize small drug-like molecules with several degrees of structural diversity. Barbituric acid derivatives, i.e., Phenobarbital and Mephobarbital[1] are well known drugs, which are used for the treatment of epilepsy. Although these drugs are very effective in controlling seizures, they have major side-effects like sedation and hypnosis. Substituted at the 5-position of barbituric acid nucleus[2,3] remarkably increase the antiepileptic activity. Also, these compounds have a wide spectrum of biological activities such as sedatives, antitumor, antifungal, antiviral, anti-inflammatory agents, hypnotics, antisclerotics, and bacteriostatics[4-6].

Moreover, barbituric acid derivatives[7-9] have been reported to exhibit anti-cancer, analeptic, immunomodulating, anti-AIDS activity[10] and some others are reported to be selective matrix metalloproteinase (MMP) inhibitors[11]. While barbituric acid itself is used as precursor for the synthesis of some materials such as pigments[12], dyes[13] and polymers[14].

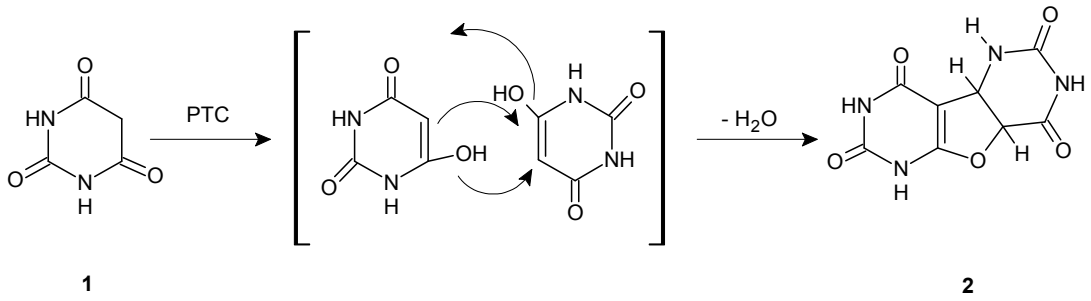
Therefore, as part of our program aimed for the preparation of new heterocyclic compounds[15-21] guided by the observation that the presence of two or more different heterocyclic moieties in a molecule often enhances the biological profile remarkably. We report herein an efficient one-pot synthesis of some barbituric acid derivatives under phase transfer catalysis conditions (PTC).

2. RESULTS AND DISCUSSION

2.1 Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1, 2, 3 and 4. 1,2,3,4,4a,6,7,8,9,9b-Decahydropyrimido[4',5':4,5]furo[2,3-d]pyrimidine-2,4,7,9-tetraone **2** was obtained by stirring of barbituric acid **1** alone under phase transfer conditions (PTC) [dioxane/ K_2CO_3 / tetrabutylammonium bromide (TBAB)] (*cf.* Scheme 1). ^{1}H-NMR of compound **2** showed the absence of

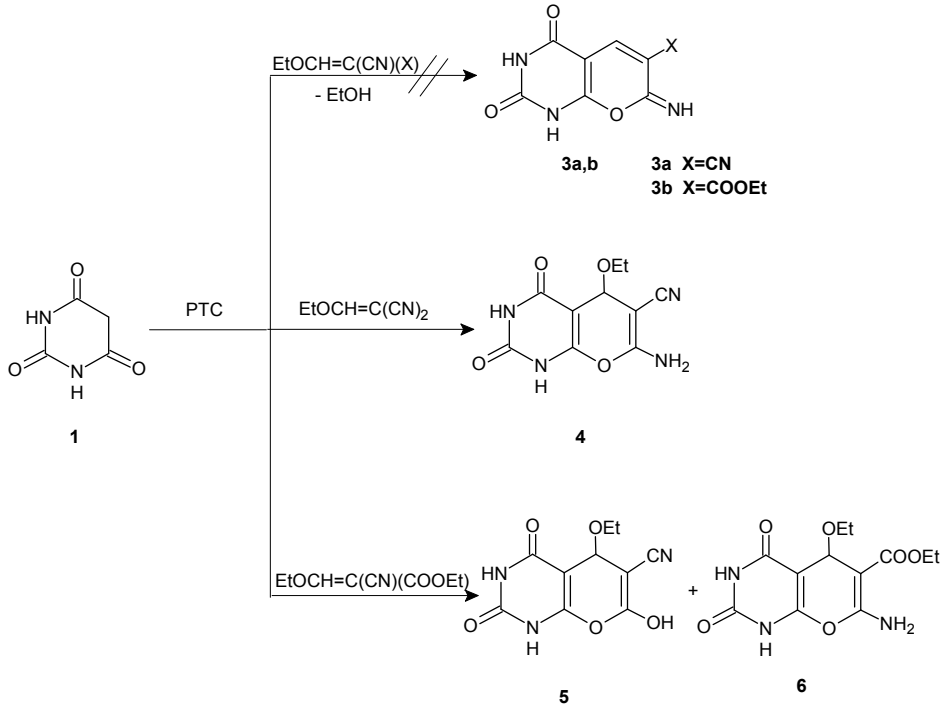
methylene group and appearance of new signals doublet of doublet at δ 4.44 and 4.21 ppm characteristic of 2CH protons.



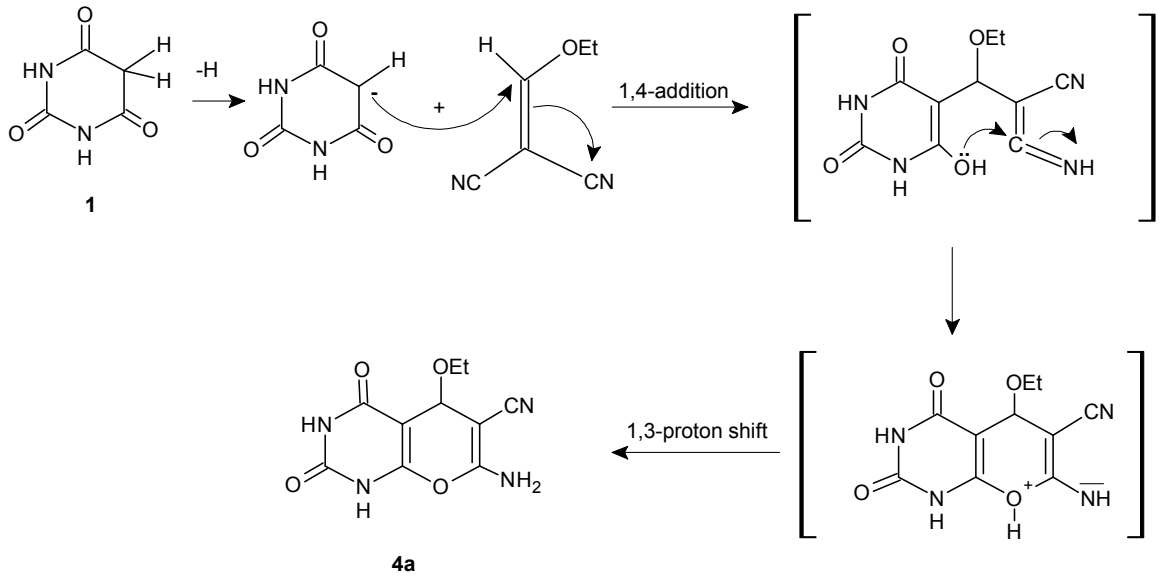
Scheme 1

Reaction of compound **1** with (ethoxymethylene)malononitrile, or ethyl 2-cyano-3-ethoxyacrylate under PTC conditions did not give the expected compounds **3a,b**. Instead of that we obtained 7-amino-5-ethoxy-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **4** and a mixture of 5-ethoxy-7-hydroxy-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **5** and ethyl 7-amino-5-ethoxy-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxylate **6**(*cf*. Scheme **2**). ^{1}H-NMR spectra showed the appearance of the signal corresponding to ethoxy group (-OEt), in addition to the signals at δ 3.12 and 1.22 ppm corresponding to ester group in compound **6**.

The reaction pathway for the formation of pyrano[2,3-d]pyrimidine derivative **4** was assumed to be proceeded *via* Michael addition reaction of active methylene group in compound **1** to the activated double bond in (ethoxymethylene)malononitrile to form the non-isolable intermediate followed by the intramolecular cyclization to furnish *o*-aminocarbonitrile of pyrano[2,3-d]pyrimidinone derivative **4** (*cf*. Scheme **3**).

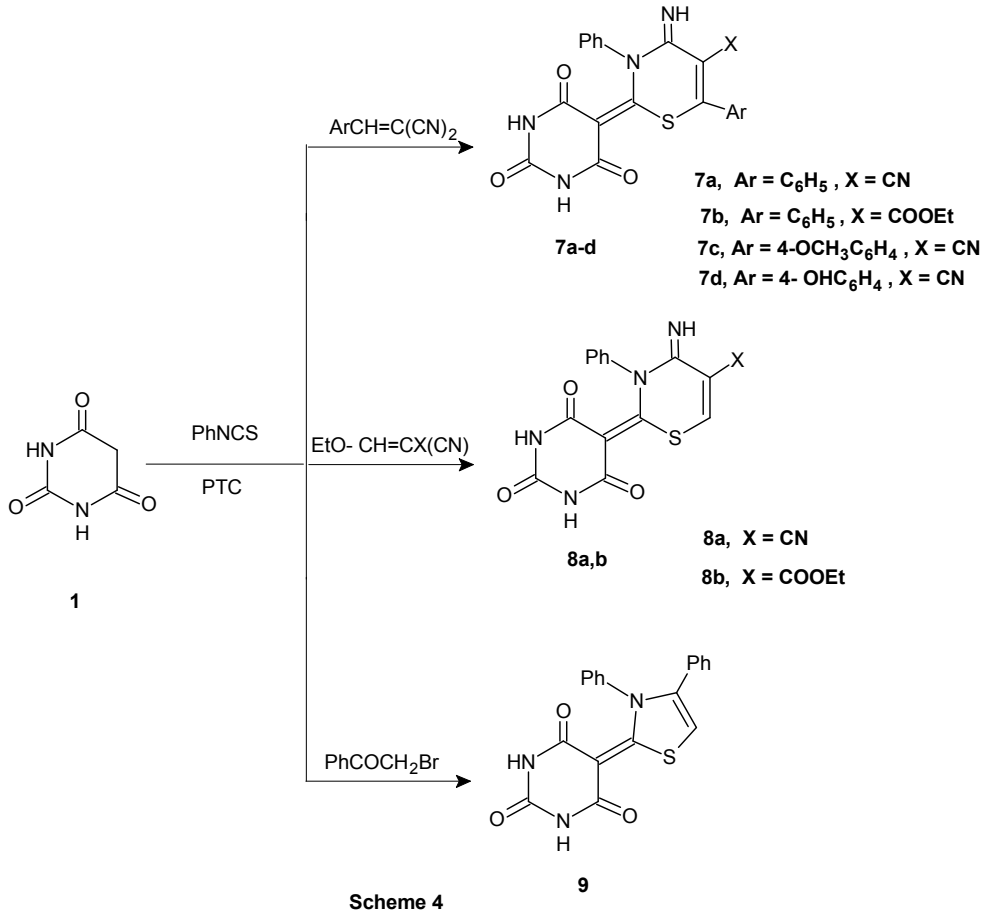


Scheme 2



Scheme 3

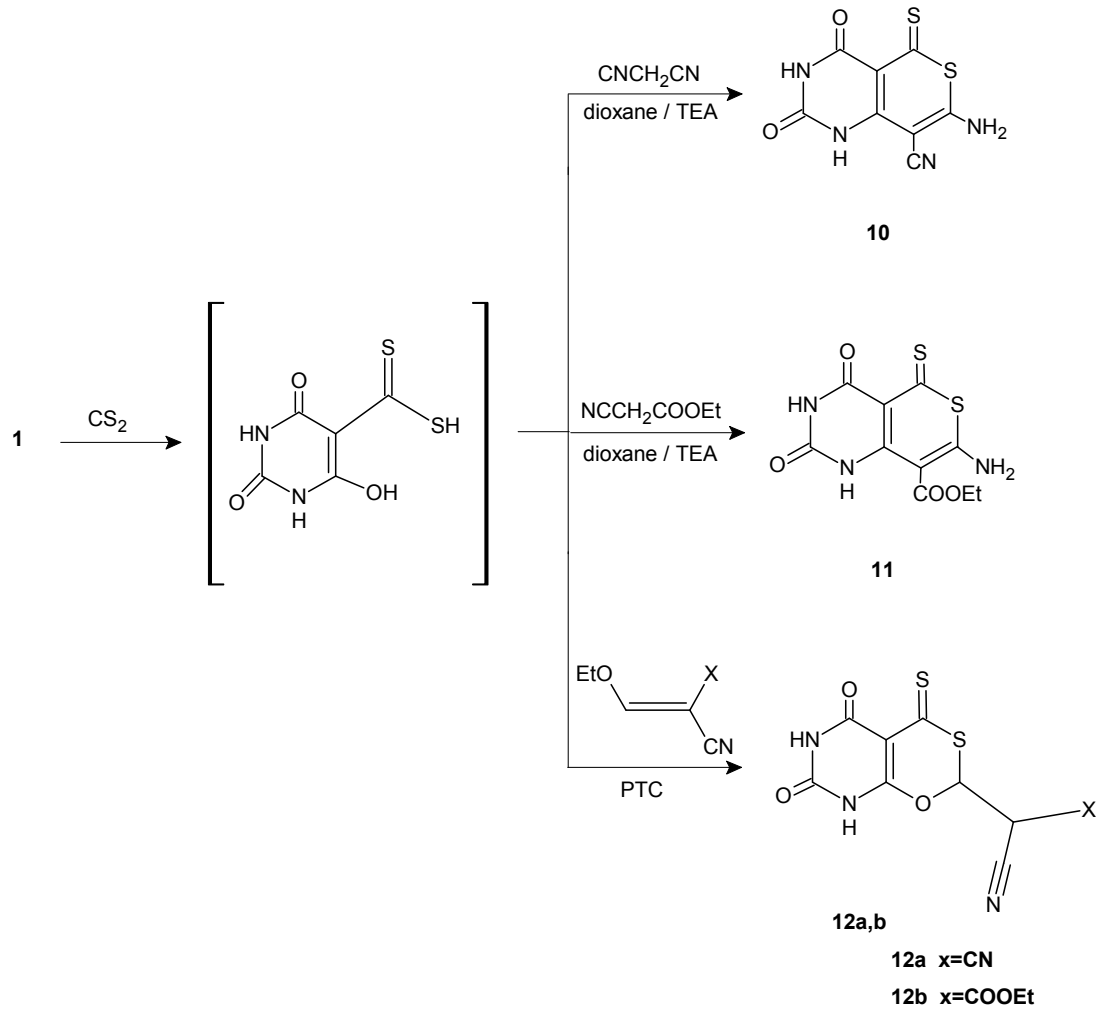
Compound **1** was allowed to react with phenylisothiocyanate and arylediene derivatives [(ethoxymethylene)malononitrile or ethyl 2-cyano-3-ethoxyacrylate] or phenacyl bromide in 1:1:1 molar ratio under phase transfer catalysis (PTC) [dioxane / K_2CO_3 / tetrabutylammonium bromide (TBAB)] to afford a class of stable heterocyclic barbiturate compounds **7a-d and 9** in good to excellent yields, respectively, (*cf*. Scheme **4**).



Scheme 4

In a similar manner, the reaction of compound **1** with carbon disulfide and malononitrile or ethyl cyanoacetate in 1:1:1 molar ratio in refluxing dioxane and in the presence of TEA as a catalyst to afford 7-amino-2,4-dioxo-5-thioxo-1,3,4,5-tetrahydro-2H-thiopyrano[4,3-d]pyrimidine-8-carbonitrile **10** and ethyl 7-amino-2,4-dioxo-5-thioxo-1,3,4,5-tetrahydro-2H-thiopyrano[4,3-d]pyrimidine-8-carboxylate **11** respectively.

In other hand, 2-(5,7-dioxo-4-thioxo-5,6,7,8-tetrahydro-4H-[1,3]oxathiino-[6,5-d]pyrimidin-2-yl)malononitrile **12a** and ethyl 2-cyano-2-(5,7-dioxo-4-thioxo-5,6,7,8-tetrahydro-4H-[1,3]oxathiino[6,5-d]pyrimidin-2-yl)acetate **12b** were obtained by the reaction of compound **1** with a mixture of carbon disulfide and (ethoxymethylene)malononitrile or ethyl 2-cyano-3-ethoxyacrylate respectively under PTC conditions (cf. Scheme **5**).



Scheme 5

2.2 Biological Tests

2.2.1 Toxicity (Brine Shrimp Test)

All newly synthesised compounds were tested for toxicity using brine shrimp test (*Artimia salina* L.). Compounds **7- 12** had high toxicity to the brine shrimp larvae, the other compounds **2**, **4**, **5** and **6** were completely non-toxic. The results showed that compounds which containing sulfur was toxic compared to the non-containing sulfur derivatives.

2.2.2 Antibacterial Test

In vitro antimicrobial activity of the tested compounds summarized in Table **1** revealed the following: compounds **7a**, **7b**, **8a**, **8b**, **9**, **10**, **11**, and **12** were proved to be highly active 15-19 mm on *Bacillus cereus*, *Staphylococcus* ***albus*** (Gram

positive bacteria +ve) and *Psedomonas aureginosa, Escherichia coli,* (Gram negative bacteria -ve), while compounds **2**, **4**, **5** and **6** showed moderate activity 11-14 mm against the four bacterial strains.

2.2.3 Antifungal Test

All the synthesized products were evaluated *in vitro* for their antifungal activity (dermatophytes fungi) and revealed that compounds **6**, **7a**,**b**, **8a**,**b**, **9**, **10**, **11** and **12** have moderate activity against *Trichophyton mentagrophytes* and *Trichophyton verrucosum,* while the other compounds have no significant antifungal.

Table 1: Toxicity and Antimicrobial activity of the new products.

Inhibition zone diameter (mm)							
Sample	Pathogenic Bacteria				Pathogenic Fungi		Brine Shrimp (animal)
	Bacillus cereus	*Staphylococcus albus*	*Psedomonas aureginosa*	*Escherichia col*	*Trichophyton mentagrophytes*	*Trichophyton verrucosum*	
2	13	13	12	11	0	0	N
4	14	12	11	11	0	0	N
5	14	11	12	12	0	0	N
6	13	11	12	10	10	10	N
7a	16	17	18	16	11	10	H
7b	17	17	17	16	11	10	H
8a	18	17	15	14	11	11	H
8b	17	18	15	15	12	11	H
9	18	19	15	16	13	12	H
10	18	18	16	16	14	13	H
11	19	19	17	18	15	11	H
12	19	17	17	18	11	11	H

H= High toxicity, N= no toxicity, Concentration 50 ppm

3. EXPERIMENTAL

3.1 Chemistry

All melting points were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Nicolet 710 FT-IR spectrometer. ^{1}H- NMR spectra were recorded in deuterated dimethyl sulfoxide at 400 MHz on a Brucker NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 eV. The elemental analysis was carried out on an elemental analyzer 240 ºC. All compounds were checked for their purity on TLC plates.

*1, 2, 3, 4, 4a, 6, 7, 8, 9, 9b-decahydropyrimido [4', 5':4, 5] furo[2,3-d]pyrimidine-2, 4, 7, 9-tetraone (**2**, $C_8H_6N_4O_5$)*

To a solution of barbituric acid **1** (0.01 mol, 1.28 g) in dioxane (20 cm^3), anhydrous potassium carbonate (3 g) and TBAB (0.005 g) were added. The reaction mixture was stirred for 5 h at 60 ^{o}C till the completion of the reaction (TLC). The reaction mixture was filtered off and the residual solid was triturated with light petroleum ether, dried and recrystallized from ethanol.

Yield (77%); mp 260 ^{o}C; IR (KBr) cm^{-1}: σ 3121 (NH), 1628 (C=O); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 11.09 (s, 4H, 4NH), 4.44-4.21 (dd, 2.2, 1.0, 2H, 2CH); ^{13}C NMR (100 MHz, DMSO): 168.52,

163.25, 161.4, 156.8, 152.0, 90.5, 72.3, 49.1; MS, m/z (%): 239(M+1) (30); Anal. Calcd. $C_8H_6N_4O_5$ (238.15): C (40.35); H (2.54); N (23.53). Found: C (40.15); H (2.66); N (23.61).

3.2 General procedure for the synthesis of compounds (4-6)

To a mixture of barbituric acid **1** (0.01 mol, 1.28 g) and ethoxy-methylenemalononitrile (0.01 mol, 1.22 g) or ethyl 2-cyano-3-ethoxyacrylate (0.01 mol, 1.69 g) in dioxane (20 cm^3), anhydrous potassium carbonate (3 g) and TBAB (0.005 g) were added. The reaction mixture was stirred for 4 h at 60 ^oC. The obtained solid product was filtered off, dried and crystallized from ethanol.

*7-Amino-5-ethoxy-2, 4-dioxo-1, 3, 4, 5-tetrahydro-2H-pyrano[2, 3-d] pyrimidine-6-carbonitrile (**4**, $C_{10}H_{10}N_4O_4$)*

Yield (85%); crystallized from EtOH; mp 270 ^oC; IR (KBr) cm^{-1}: σ 3340, 3235, 3121 (NH_2, NH), 2234 (CN), 1645 (C=O); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 10.28 (s, 2H, 2NH), 7.40 (br, 2H, NH_2), 3.99 (s, 1H, CH), 3.08 (q, 2H, CH_2), 1.20 (t, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO): 163.97, 151.46, 150.05, 121.77, 117.26, 95.30, 58.74, 46.29, 40.14, 9.09; Anal. Calcd. $C_{10}H_{10}N_4O_4$ (250.21): C (48.00); H (4.03); N (22.39). Found: C (48.15); H (4.13); N (22.14).

*5-Ethoxy-7-hydroxy-2, 4-dioxo-1, 3, 4, 5-tetrahydro-2H-pyrano[2,3-d] pyrimidine -6-carbonitrile (**5**, $C_{10}H_9N_3O_5$)*

Yield (70%); crystallized from EtOH; mp 170 ^oC; IR (KBr) cm^{-1}: σ 3476 (OH), 3192 (NH), 2215 (CN), 1667 (C=O); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 11.10 (s, 2H, 2NH), 10.80 (br, 1H, OH), 4.34 (s, 1H, CH), 3.56 (q, 2H, CH_2), 1.12 (t, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO): 203.22, 163.70, 158.54, 150.72, 117.26, 85.42, 64.81, 62.34, 56.26, 15.82; Anal. Calcd. $C_{10}H_9N_3O_5$ (251.19): C (47.82); H (3.61); N (16.73). Found: C (47.90); H (3.41); N (16.85).

*Ethyl 7-amino-5-ethoxy-2, 4-dioxo-1, 3, 4, 5-tetrahydro-2H-pyrano [2,3-d] pyrimidine-6-carboxylate (**6**, $C_{12}H_{15}N_3O_6$)*

Yield (65%); crystallized from EtOH; mp 208 ^oC; IR (KBr) cm^{-1}: σ 3300, 3135, 3190 (NH_2, NH), 1720 (C=O_{ester}), 1665 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 10.09, 9.98 (s, 2H, 2NH), 8.20 (br, 2H, NH_2), 4.14 (s, 1H, CH), 3.37 (q, 2H, CH_2), 3.12 (q, 2H, CH_2), 1.22 (t, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO): 167.58, 164.06, 151.61, 148.88, 118.71, 100.83, 93.13, 83.09, 60.22, 46.28, 39.95, 14.95. MS, m/z (%): 297(M^+) (33), 281 (24), 263 (29), 248 (25), 201 (21), 186 (20), 124 (39), 86 (100); Anal. Calcd. $C_{12}H_{15}N_3O_6$ (297.26): C (48.49); H (5.09); N (14.14). Found: C (48.30); H (5.19); N (14.23).

3.3 General procedure for the synthesis of compounds (7a-d-9)

A mixture of compound **1** (0.01 mol, 1.28 g) in dioxane (20 cm^3), phenyl isothiocyanate (0.01 mol, 1.3 cm^3) anhydrous potassium carbonate (3 g), and a catalytic amount of TBAB was stirred for 2 h at 60 ºC. To the reaction mixture, arylidenemalononitrile derivatives (0.01 mol add weight in grams), ethyl benzylidenecyanoacetate (0.01mol, add weight in grams), ethoxy methylenemalononitrile (0.01 mol, 1.22 g), 2-cyano-3-ethoxyacrylate (0.01 mol, 1.69g) or phenacyl bromide (0.01 mol, 1.99 g) was added, then the reaction mixture was stirred for further 5 h at 60 ^oC, till the completion of the reaction (TLC). The reaction mixture was filtered off and the filtrate was evaporated under *vacuum*. The separated solid was crystallized from ethanol to give **7a-d- 9**.

*4-Imino-3,6-diphenyl-2-(2,4,6-trioxohexahydro-5-pyrimidinyliden)-3,4-dihydro-2H-1,3-thiazine-5-carbonitrile (**7a**, $C_{21}H_{13}N_5O_3S$)*

Yield (68%); crystallized from EtOH; mp 120 ^oC; IR (KBr) cm^{-1}: σ 3205 (NH), 3050 ($CH_{arom.}$), 2182 (CN) , 1672 (CO); ^{1}H-NMR(400 MHz, d_6-DMSO): δ 12.85 (s, 1H, NH), 8.98 (s, 2H, $2NH_{barbituric\ acid}$), 7.85-6.57 (m, 10H, $CH_{arom.}$); ^{13}C-NMR (100 MHz, DMSO): 163.26, 160.62, 153.11, 150.69, 142.80, 136.41, 129.00, 128.42, 127.41, 122.75, 118.13, 95.35, 89.09, 40.62; Anal. Calcd. $C_{21}H_{13}N_5O_3S$ (415.42): C (60.72); H (3.15); N (16.86); S (7.72). Found: C (60.60); H (3.25); N (16.68); S (7.92).

*Ethyl 4-imino-3,6-diphenyl-2-(2,4,6-trioxohexahydro-5-pyrimidiny-liden)-3, 4-dihydro-2H-1,3-thiazine-5-carboxylate (**7b**, $C_{23}H_{18}N_4O_5S$)*

Yield (60%); crystallized from EtOH; mp 142 °C; IR (KBr) cm^{-1}: σ 3180 (NH), 3000 ($CH_{arom.}$), 1728 (CO_{ester}) , 1659 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 12.85 (s, 1H, NH), 9.78 (s, 2H, 2NH $_{barbituric\ acid}$), 8.34-7.57 (m, 10H, $CH_{arom.}$), 3.85 (q, 2H, CH_2), 1.53 (t, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO): 167.15, 162.55, 160.14, 154.32, 152.17, 151.6 9, 142.71, 137.08, 130.32, 129.53, 128.25, 127.44, 122.77, 108.40, 95.32, 62.04, 15.22; Anal. Calcd. $C_{23}H_{18}N_4O_5S$ (462.47): C (59.73); H (3.92); N (12.11); S (6.93). Found: C (59.85); H (3.90); N (12.21); S (6.73).

*4-Imino-6-(4-methoxyphenyl)-3-phenyl-2-(2, 4, 6-trioxohexahydro-5-pyrimidinyliden)-3, 4-dihydro-2H-1, 3-thiazine-5-carbonitrile (**7c**, $C_{22}H_{15}N_5O_4S$)*

Yield (60%); crystallized from EtOH; mp 290 (dec); IR (KBr) cm^{-1}: σ 3200 (NH), 3088 ($CH_{arom.}$), 2220 (CN) , 1668 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 10.38 (s, 3H, 3NH), 8.00-7.27 (m, 9H, $CH_{arom.}$), 3.00 (s, 3H, CH_3); MS, m/z (%): 445.5 (M^+); Anal. Calcd. $C_{22}H_{15}N_5O_4S$ (445.45): C (59.32); H (3.39); N (15.72); S (7.20). Found: C (59.32); H (3.22); N (15.80); S (7.29).

*6-(4-Hydroxyphenyl)-4-imino-3-phenyl-2-(2, 4, 6-trioxohexahydro-5-pyrimidinyliden)-3, 4-dihydro-2H-1, 3-thiazine-5-carbonitrile (**7d**, $C_{21}H_{13}N_5O_4S$)*

Yield (58%); crystallized from EtOH; mp 187 °C; IR (KBr) cm^{-1}: σ 3310 (NH), 3060 ($CH_{arom.}$), 2189 (CN), 1660 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.95 (br, 2H, NH, OH), 8.98 (s, 2H, 2NH $_{barbituric\ acid}$), 8.22-6.77 (m, 10H, $CH_{arom.}$); Anal. Calcd. $C_{21}H_{13}N_5O_4S$ (431.42): C (58.46); H (3.04); N (16.23); S (7.43). Found: C (58.26); H (3.14); N (16.13); S (7.63).

*4-Imino-3-phenyl-2-(2, 4, 6-trioxohexahydro-5-pyrimidinyliden)-3, 4-dihydro-2H-1, 3-thiazine-5-carbonitrile (**8a**, $C_{15}H_9N_5O_3S$)*

Yield (87%); crystallized from EtOH; mp 330 °C; IR (KBr) cm^{-1}: σ 3267 (NH), 3028 ($CH_{arom.}$), 2210 (CN), 1679 (CO); ^{1}H-NMR (400 MHz, d_6 -DMSO): δ 11.11 (s, 1H, NH), 10.18 (s, 2H, 2NH $_{barbituric\ acid}$), 7.44-6.86 (m, 5H, $CH_{arom.}$), 6.25 (s, 1H, CH); ^{13}C-NMR (100 MHz, DMSO): 168.25, 163.16, 151.10, 150.09, 148.88, 130.10, 118.87, 58.88, 56.53, 40.95, 18.92, 13.92; Anal. Calcd. $C_{15}H_9N_5O_3S$ (339.32): C (53.09); H (2.67); N (20.64); S(9.45). Found: C (53.39); H (2.45); N (20.54); S (9.47).

*Ethyl 4-imino-3-phenyl-2-(2,4,6-trioxohexahydro-5-pyrimidinyliden)-3,4-dihydro-2H-1,3-thiazine-5-carboxylate (**8b**, $C_{17}H_{14}N_4O_5S$)*

Yield (85%); crystallized from EtOH; mp 212 °C; IR (KBr) cm^{-1}: σ 3200 (NH), 1730 (CO_{ester}) , 1650 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 12.70 (s, 1H, NH), 9.48 (s, 2H, 2NH $_{barbituric\ acid}$), 7.77-7.00 (m, 5H, $CH_{arom.}$), 6.11 (s, 1H, CH), 4.12 (q, 2H, CH_2), 1.23 (t, 3H, CH_3); MS, m/z (%): 385(M-1); Anal. Calcd. $C_{17}H_{14}N_4O_5S$ (386.37): C (52.85); H (3.65); N (14.50); S (8.30). Found: C (52.71); H (3.77); N (14.62); S (8.20).

*5-(3, 4-Diphenyl-2, 3-dihydro-1, 3-thiazol-2-yliden)hexa hydro-2, 4, 6- Pyrimidinetrione (**9**, $C_{19}H_{13}N_3O_3S$)*

Yield (75%); crystallized from EtOH; mp 265 °C; IR (KBr) cm^{-1}: σ 3247 (NH), 3000 ($CH_{arom.}$), 1695 (CO); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 9.88 (s, 2H, 2NH $_{barbituric\ acid}$), 7.98-6.87 (m, 10H, $CH_{arom.}$), 5.45 (s, H, CH). ^{13}C-NMR (100 MHz, DMSO): 165.1, 162.9, 160.2, 152.4, 141.2, 138.7, 104.6, 132.0, 129.5, 128.6, 127.3, 123.6; MS, m/z (%): 363(M^+) (20), 270 (11), 127 (100), 77 (34); Anal. Calcd. $C_{19}H_{13}N_3O_3S$ (363.39): C (62.80); H (3.61); N (11.56); S (8.82). Found: C (62.90); H (3.71); N (11.58); S (8.60).

3.4 General procedure for the synthesis of compounds (10 and 11)

A mixture of compound **1** (0.01 mol, 1.28 g) in dioxane (20 cm^3), carbon disulfide (0.01 mol, 0.76 cm^3), and a catalytic amount of TEA were stirred for 2 h at r. t. followed by addition of malononitrile (0.01 mol, 1.32 g) or ethyl cyanoacetate (0.01 mol, add weight in grams). The reaction mixture was refluxed for 9 h, then filtered off. The filtrate was evaporated under *vacuum* and the separated solid was crystallized from ethanol to give **10** and **11**, respectively.

*7-Amino-2,4-dioxo-5-thioxo-1,3,4,5-tetrahydro-2H-thiopyrano[4,3-d]-pyrimidine-8-carbonitrile (**10**, $C_8H_4N_4O_2S_2$)*

Yield (78%); crystallized from EtOH; mp 220 °C; IR (KBr) cm^{-1}: σ 3370, 3255, 3198 (NH_2, NH), 2207 (CN), 1657 (C=O), 1210 (C=S); ^{1}H-NMR (400 MHz, d_6 -DMSO): δ 11.16 (s, 2H, $2NH_{barbituric\ acid}$), 6.70 (s, 2H, NH_2); ^{13}C-NMR (100 MHz, DMSO): 195.20,

163.23, 158.46, 160.52, 151.24, 117.20, 95.11, 90.00; Anal. Calcd. $C_8H_4N_4O_2S_2$ (252.26): C (38.09); H (1.60); N (22.21); S (25.42). Found: C (38.15); H (1.41); N (22.22); S (25.41).

*Ethyl-7-amino-2, 4-dioxo-5-thioxo-1, 3, 4, 5-tetrahydro-2H-thio-pyrano[4,3-d]-pyrimidine-8-carboxylate (**11**, $C_{10}H_9N_3O_4S_2$)*

Yield (84%); crystallized from EtOH; mp 260 °C; IR (KBr) cm^{-1}: σ 3379, 3260, 3190 (NH_2,NH), 1740 (CO_{ester}), 1687 (C=O), 1238 (C=S); ^{1}H-NMR (400 MHz, d_6 -DMSO): δ 11.16 (s, 2H, $2NH_{barbituric\ acid}$), 6.63 (s, 2H, NH_2), 4.21 (q, 2H, CH_2), 1.28 (t, 3H, CH_3); MS, m/z (%): 299(M^+); Anal. Calcd. $C_{10}H_9N_3O_4S_2$ (299.31): C (40.13); H (3.03); N (14.04); S (21.42). Found: C (40.24); H (3.14); N (14.14); S (21.10).

3.5 General procedure of the synthesis of compounds (12a, b)

A mixture of compound **1** (0.01 mol, 1.28 g) in dioxane (20 cm^3), carbon disulfide (0.01 mol, 0.76 cm^3), anhydrous potassium carbonate (3 g), and a catalytic amount of TBAB were stirred for 2 h at r.t. To the reaction mixture, ethoxy methylenemalononitrile (0.01 mol, 1.22 g) or 2-cyano-3-ethoxyacrylate (0.01 mol, 1.69 g) was added and stirred for further 4 h at 70 °C till the completion of the reaction (TLC). The reaction mixture was filtered off and the filtrate was evaporated under *vacuum*. The separated solid was crystallized from ethanol to give **12a, b** respectively.

*2-(5, 7-Dioxo-4-thioxo-5, 6, 7, 8-tetrahydro-4H-[1,3]oxathieno[6, 5-d]- pyrimidin-2-yl) malononitrile (**12a**, $C_9H_4N_4O_3S_2$)*

Yield (80%); crystallized from EtOH; mp 300 °C; IR (KBr) cm^{-1}: σ 3271 (NH), 3000 ($CH_{arom.}$), 2211 (CN), 1647 (C=O), 1144 (C=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 10.16 (s, 2H, $2NH_{barbituric\ acid}$), 6.3 (d, 1H, CH), 4.78 (d, 1H, CH); ^{13}C-NMR (100 MHz, DMSO): 180.0, 164.2, 162.0, 151.1, 114.2, 79.1, 62.4, 21.5; Anal. Calcd. $C_9H_4N_4O_3S_2$ (280.27): C (38.57); H (1.44); N (19.99); S (22.88). Found: C (38.47); H (1.40); N (20.14); S (22.78).

*2.1.5.2. Ethyl 2-cyano-2-(5, 7-dioxo-4-thioxo-5, 6, 7, 8-tetrahydro-4H-[1,3]-oxathiino[6, 5-d]pyrimidin-2-yl)acetate (**12b**, $C_{11}H_9N_3O_5S_2$)*

Yield (84%); crystallized from EtOH; mp 280 °C; IR (KBr) cm^{-1}: σ 3179 (NH), 2205 (CN), 1722 ($C=O_{ester}$), 1647 (C=O), 1194 (C=S); ^{1}H-NMR (400 MHz, d_6-DMSO): δ 11.16 (s, 2H, $2NH_{barbituric\ acid}$), 5.63 (d, 7.0, 1H, CH), 4.49 (d, 8.0, 1H, CH), 4.11 (q, 2H, CH_2), 1.34 (t, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO): 175.5, 168.2, 163.0, 152.1, 118.7, 93.0, 84.4, 63.7, 59.5, 38.4, 14.8; Anal. Calcd. $C_{11}H_9N_3O_5S_2$ (327.32): C (40.36); H (2.77); N (12.84); S (19.59). Found: C (40.46); H (2.65); N (12.96); S (19.49).

3.6 Microbiological studies

Inhibition zone was used for testing the activity of the new compounds against toxigenic bacteria and dermatophytes fungi based on the method previously described by Speer and Sussmuth, 1987[22]. 50 µg of the appropriated compounds were dissolved in DMSO, evaporation of the solvent and the disc put on surface inoculated medium. The dishes were incubated at 28-37 ºC for 48 h to 15 days for bacteria and fungi, respectively. At the end of incubation period, the diameter of no growth was measured

4. CONCLUSIONS

A series of new pyrimidofuropyrimidine, pyranopyrimidine, pyrimidinylidenthiazine, and thiazolopyrimidinetrione derivatives incorporating barbituric acid moiety were synthesized from barbituric acid. Analytical and spectral data (IR, NMR, MS) of all the synthesized compounds were in full agreement with the proposed structure. Comparison of the toxicity results of synthesized compounds has revealed that the compounds which contain sulfur more toxic than that not containing sulfur. Most of the compounds were found to be active against tested micro-organisms.

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