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RESEARCH ARTICLE

Heterocyclization of barbituric acid: Synthesis of novel condensed pyrimidines

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Abstract

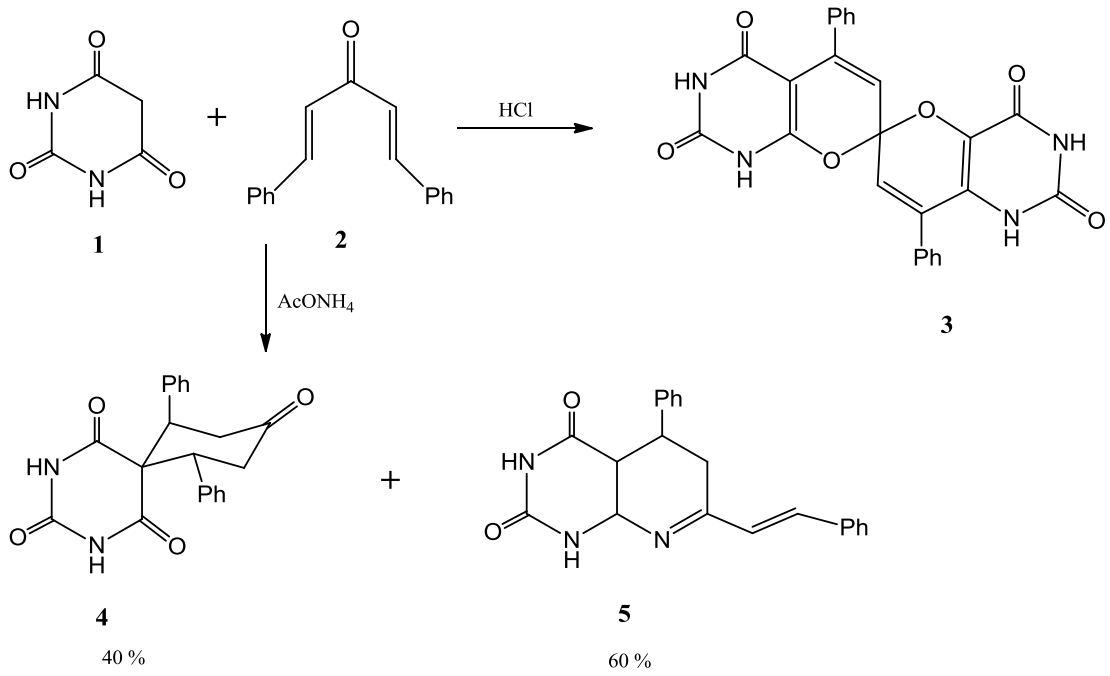
A series of heterocyclic compounds was synthesized from barbituric acid. Reaction of barbituric acid with dibenzalacetone in acidic and basic medium afforded spiro compounds **3** and **4** and pyridopyrimidine derivatives **5**, respectively. While, condensation reaction of barbituric acid with ethyl cyanoacetate and ethyl acetoacetate in presence of $AcONH_4$, gave pyridopyrimidine derivatives **7** and **8**, respectively. On the other hand, barbituric acid not condensed with dimedone to give compound **10**, but gave 2-aminopyrimidine **9**. Reaction of barbituric acid with urea and thiourea in presence of HCl and I_2 gave pyrimidopyrimidne and thiazolopyrimidine derivatives **11-13**, respectively. The structure of newly synthesized compounds was elucidated using spectral analysis (IR, ^{1}H NMR and ^{13}C NMR) and micro analysis.

INTRODUCTION

Recently, much attention has been paid to the development of new methods for the synthesis of heterocyclic compounds, due to their potential importance in the fields of pharmaceutical and agricultural drugs. Heterocyclic compounds derived from barbituric acid such as pyrano[2,3-d]pyrimidines,(1,3) pyrido[2,3-d]pyrimidines,(4) pyrimido[4,5-d]pyrimidines and other derivatives are well recognized by synthesis as well as biological chemists, and are generally used as antitumors,(5-10) analgetic substances,(11) bactericidals,(12-16) and fungicidal.(17) Barbituric acid is a pyrimidine, containing strong acid (pka = 4.01, in aqueous medium) with an active methylene group and can be involved in condensation reactions with aldehydes or ketones or δ,β-unsaturated carbonyl compounds to form other heterocyclic compounds with interested biological activity. Keeping in view the importance of barbituric acid and its derivatives, it was worth trying to get more derivatives from them and the compounds which we synthesized have been reported here.

Result and discussion

The formation of dibenzylideneacetones 2 was achieved using standard procedures (18). Treatment of barbituric acid with dibenzylidineacetone in acidic medium afforded spiropyranopyrimidine **3** in good yield (85%). While, the same reaction was proceed in presence of amm.acetate as a basic medium to afford a mixture of spiropyrimidine **4** and pyridopyrimidine **5** in 40:60 % ratio, respectively (Scheme 1).

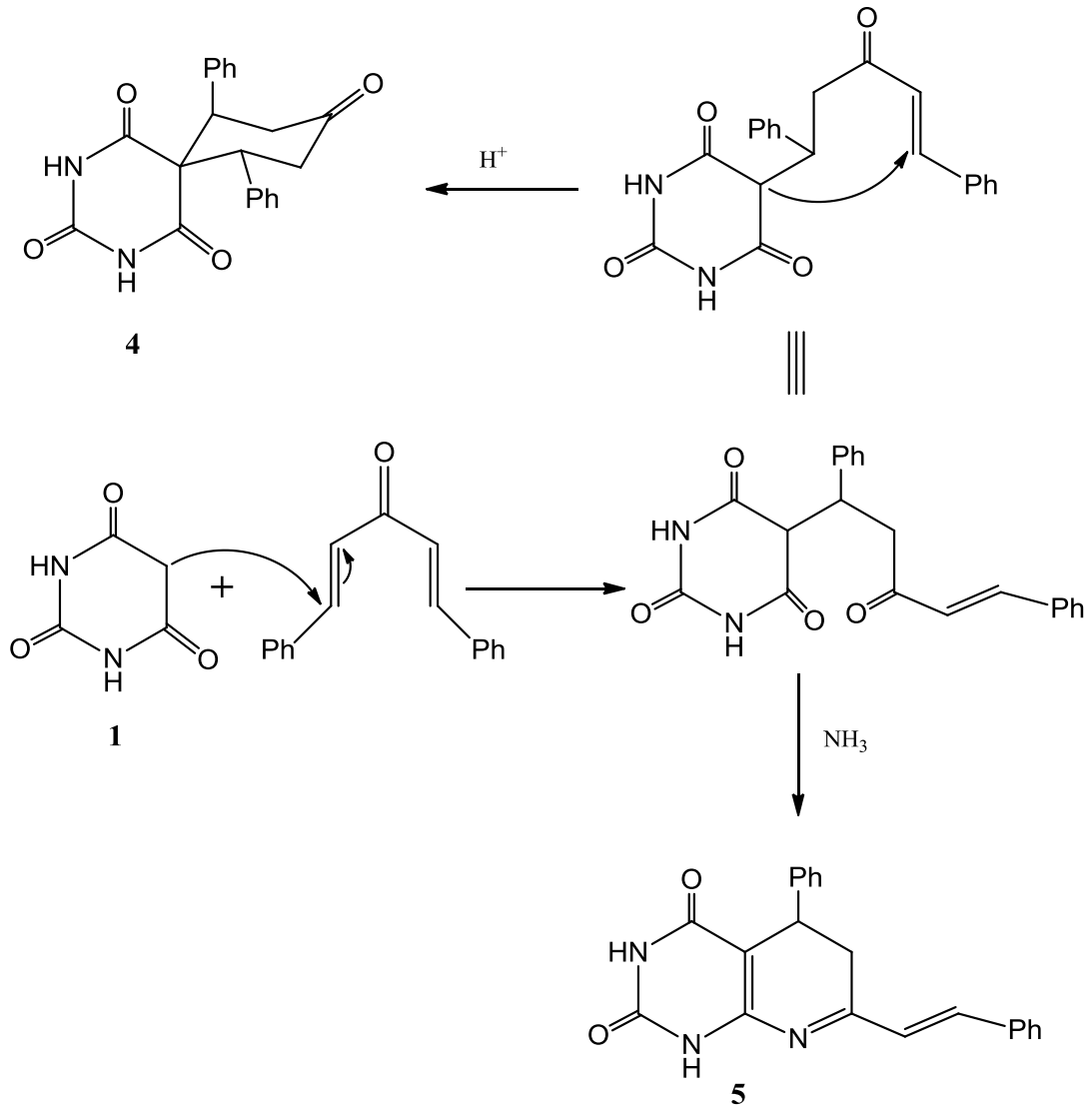


Scheme 1 Cycloaddition reaction to synthesize spiropyranopyrimidine and pyridopyrimidne derivatives.

The structure assigned for the reaction product was established form the analytical and spectral data. The ^{1}HNMR spectrum of compound **3** showed pyran ring proton at δ = 5.90 ppm as singlet, and multiplet for aromatic protons at δ = 6.98–7.16 ppm. In addition to, the two NH's at δ = 10.00, δ = 12.00 ppm as singlet.

When the reaction of compound **1** and dibenzalacetone was conducted in acetic acid and ammonium acetate, this led to formation two compounds 1,5 adduct **4** in addition to pyridopyrimidine **5**. The ^{1}HNMR of compound **4** revealed two signals at δ = 2.49 ppm as doublet for CH_2 and at δ = 3.24 ppm as triplet for CH of cyclohexyl protons. In addition to, two signals at δ = 11.20, δ = 11.40 ppm for two NH's protons. ^{1}HNMR of compound **5** showed doublet at δ = 3.25 ppm for CH_2, triplet at δ = 3.90 ppm for CH, Moreover, the NH's protons are found at δ = 11.15 and δ = 11.41 ppm (Scheme 3)

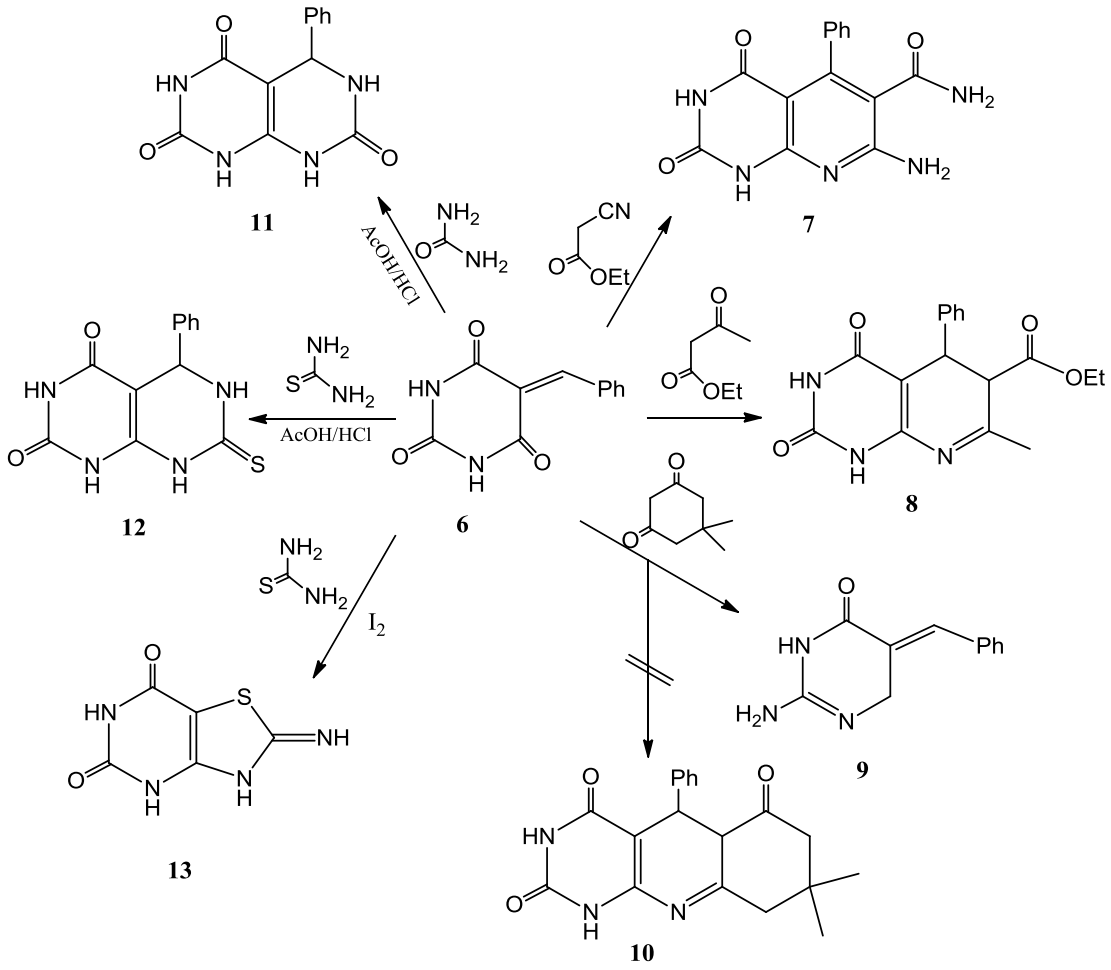
The suggested mechanism for the formation of both compound **4** and compound **5** may take place via initial Michael addition of **1** to the activated C=C of dibenzalacetone to generate the intermediate **A** which then underwent cyclohexane cyclization forming compound **4** via second intramoleculer Michael addition of methenyl barbituric acid proton to α, β unsaturated system (Scheme 3). On the other hand, compound **5** was formed by amination of **A**, followed by pyridine intramolecular cyclization giving pyridopyrimidine **5** (Scheme 3).



Scheme 2: mechanistic route for formation of compounds **4** and **5**.

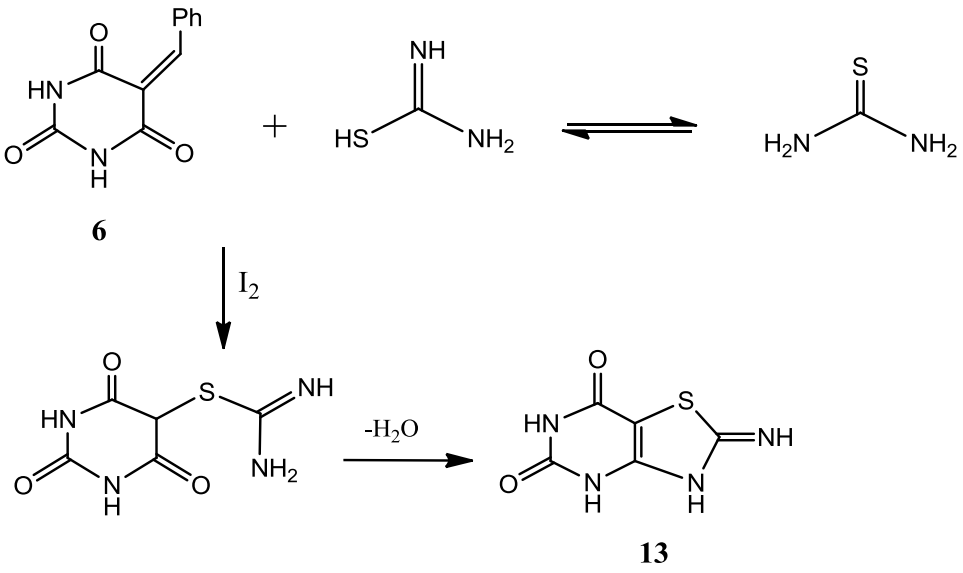
Heterocyclization of benzalbarbituric acid with ethyl cyanoacetate and ethyl acetoacetate in presence of ammonium acetate in acetic acid afforded pyridopyrimidine derivatives **7** and **8**, respectively (Scheme 3). While carring out the same reaction using dimedone, not cyclized to the desired pyrimidoquinoline derivative **10**, but gave 2-aminopyrimidine derivative **9** (Scheme 3). The formation of **12** is potentiated by the presence of one C=O group band in IR spectroscopy.

The ^{1}HNMR of compound **8** showed signals at $\delta = 0.95$ as triplet for CH_3, at $\delta = 4.10$ as quartet for CH_2, at $\delta = 4.20$ as doublet for CH, at $\delta = 4.90$ as doublet for CH and two signals to NH's at $\delta = 11.40$ and $\delta = 11.60$ ppm.



Scheme 3: Heterocyclization of 5-benzyledine barbituric acid.

The reaction of benzalbarbituric acid **6** with urea and thiourea in presnce of HCl gave the corresponding pyrimidopyrimidine derivatives **11** and **12**, respectively (Scheme 3). While, the reaction of banzalbarbituric acid **6** with thiourea in presence of iodine gave thiazolopyrimidine **13** (Scheme 3). The spectral analysis of **11-13** was agreement with their structures. The preparation of thiazolopyrimidine **13** may occur within the formation of alkyl thiourea derivative through an oxidative alkylation followed by thiazolcyclization by intramolecular dehydration as in (Scheme 4).



Scheme 4: Proposed mechanism of thiazolopyrimidine **13** cyclization.

Experimental

All melting points were determined with electro thermal IA 9100 series digital melting point apparatus and are uncorrected. All experiments were carried out using drying solvents. The IR spectra were recorded on a Parkin-Elmer model 1600 FTIR spectrometer as KBr discs (USA). ^{1}H, ^{13}C NMR spectra were recorded with Brucker AC-300 MHz spectrometer. Chemical shift are expressed as δ (ppm) scale relative to TMS as an internal standard and DMSO-d6 as solvent. The elemental analyses were determined on a Parkin-Elmer model 240 at Micro-analytical Center Cairo University.

5,5'-diphenyl-7,7'-spirobi[pyrano[2,3-d]pyrimidine]-2,2',4,4' (1H,1'H,3H,3'H)-tetraone (3) To a solution of barbituric acid (**1**) (5.00 mmol), dibenzalacetone (5.00 mmol) and HCl (5.00 mmol) in ethanol (16 mL) and the contents were refluxed for 6 h. The reaction mixture were concentrated by evaporation, cooled and poured into crushed ice. The solid thus separated was filtered, washed with water, dried and crystallized from ethanol to give compound **2** in 85 % yield as yellow crystals, Mp. 290–291 °C. IR (KBr): 3273 cm^{-1} (NH), 1623 cm^{-1} (C=O). ^{1}H NMR (300 MHz, DMSO-d6): δ = 5.90 (s, 1H, CH olefenic), 6.98–7.16 (m, 10H, ArH's), 10.00 (s, 1H, NH), 12.00 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d6): 21.1, 73.0, 91.0, 126.7, 127.4, 145.0, 150.7, 169.2, 172.1, 189.2, 190.1. Anal Calcd for $C_{25}H_{16}N_4O_6$ (468.42): C, 64.10; H, 3.44; N, 11.96. Found: C, 63.85; H, 3.29; N, 11.64.

7,11-diphenyl-2,4-diazaspiro[5,5]undecane-1,3,5,9-tetraone (4) and (E)-5-phenyl-7-styryl-1,5,6,8a-tetrahydropyrido[2,3-d]pyrimidine-2,4 (3H,4aH)-dione (5) To a solution of barbituric acid (**1**) (50.0 mmol) and dibenzalacetone (50.0 mmol) in glacial acetic acid (60 mL) ammonium acetate (50.0 mmol) was added. The reaction mixture was refluxed for 6 h. Then it was concentrated, cooled and poured into crushed ice to give solid product which was boiled in ethanol and filtered. The filtrate was left to cool then the formed precipitate was filtred and crystallized from ethanol to give compound **4** in 40 % yield as white crystals, Mp. 240–241 °C. IR (KBr): 3402 cm^{-1} (NH), 1710 (C=O), 1599 (C=O). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.49 (d, 1H, CH_2), 3.24 (t, 1H, CH), 6.93–7.37 (m, 10H, ArH's), 11.20 (s, 1H, NH), 11.40 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 49.0, 59.0, 127.9, 128.2, 128.8, 137.6, 148.9, 171.0, 172.0, 207.4. Anal Calcd for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73. Found: C, 69.34; H, 4.81; N, 7.61.

The residue was crystallized from DMF to give compound **5** in 60 % yield as pale yellow, Mp 270–271 °C. IR (KBr): 3402 cm^{-1} (NH), 1710 (C=O), 1599 (C=O). ^1H NMR (300 MHz, DMSO-d6): δ =3.25 (d, 2H, CH_2), 3.90 (t, 2H, CH), 6.90–7.37 (m, 5H, ArH's), 11.10 (s, 1H, NH), 11.40 (s, 1H, NH). Anal Calcd for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.25; H, 4.72; N, 12.11.

7-amino-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxamide (7) A mixture of benzalbarbituric acid (**6**) (5.00 mmol) and ethylcyanoacetat (5.00 mmol) in glacial acetic acid (25 mL) was added to ammonium acetate (50.0 mmol). The reaction mixture was refluxed for 6 h and left to cool at room temperature. The filtrated product was crystallized from ethanol to give compound **7** in 73 % yield as yellow crystals, Mp >300 °C. IR (KBr): 3402 cm^{-1} (NH), 1689 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d6): δ = 5.90 (s, 2H, NH_2), 7.00–7.20 (m, 5H, ArH's, and NH_2), 9.90 (s, 1H, NH), 10.10 (s, 1H, NH). Anal Calcd for $C_{14}H_{11}N_5O_3$ (297.27): C, 56.56; H, 3.73; N, 23.56. Found: C, 56.49; H, 3.50; N, 23.44.

Ethyl 7-methyl-2,4-dioxo-5-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-d] pyrimidine-6-carboxylate (8) A mixture of benzalbarbituric acid (**6**) (10.0 mmol) and ethyl acetoacetat (10.0 mmol) in glacial acetic acid (30 mL) ammonium acetate (50.0 mmol) was added. The reaction mixture was refluxed for 6 h. Then it was cooled and poured into crushed ice to give solid product which was crystallized from acetic acid to give compound **8** in 80 % yield as yellow crystals, Mp >300 °C. IR (KBr): 1712 cm^{-1} (C=O), 1660 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d6): δ = 0.95 (t, 3H, CH_3), 4.10 (q, 2H, CH_2O), 4.20 (d, 1H, CH), 4.90 (d, 1H, CH-C_6H_5), 7.10–7.30 (m, 5H, ArH's), 11.40 (s, 1H, NH), 11.60 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d6): δ = 13.8, 42.8, 49.0, 50.8, 58.9, 60.5, 127.8, 128.4, 136.6, 138.0, 148.8, 167.8, 170.9, 203.2, 207.3. Anal Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.13; H, 5.04; N, 12.71.

2-Amino-5-benzylidenedihydropyrimidine-4,6-(1H,5H)-dione (9) A mixture of benzalbarbituric acid (**6**) (5.00 mmol) and dimedone (5.00 mmol) in glacial acetic acid (15 mL) was added to ammonium acetate (50.0 mmol). The reaction mixture was refluxed for 5 h, then left to cool at room temperature. The mixture was poured into ice cooled water. The separated solid was collected by filtration and crystallized from ethanol to give compound **9** in 78 % yield as yellow crystals, Mp. >300 °C. IR (KBr): 3184 cm^{-1} (NH), 1691 cm^{-1} (C=O) 1604 (C=O). ^1H NMR (300 MHz, DMSO-d6): δ =5.90 (S, 1H, CH), 7.00–7.16 (m, 5H, ArH's), 9.90 (s, 1H, NH_2), 11.10 (s, 1H, NH), 12.30 (s, 1H, NH). Anal Calcd for $C_{11}H_{11}N_3O_2$ (217.22): C, 60.82; H, 5.10; N, 19.34. Found: C, 60.58; H, 4.88; N, 19.12.

General procedure for synthesis of compounds (11 and 12) A mixture of benzalbarbituric acid (**6**) (10.0 mmol) and urea (10.0 mmol) or thiourea (10.0 mmol) in the presence of HCl (0.53 mL) and acetic acid (10 mL) was refluxed for 6 h. The mixture was concentrated and poured into crushed ice. The solid formed was filtred for recrystallization.

5-Phenyl-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (11) The filtrated product was crystallized from ethanol to give compound **11** in 80 % yield as white crystals, Mp >300 °C. IR (KBr): 3190.32 cm^{-1} (NH), 1691.52 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d6): δ = 5.90 (s, 1H, CH-C_6H_5), 6.90–7.60 (m, 5H, ArH's), 8.00 (s, 1H, NH), 8.20 (s, 1H, NH), 10.00 (s, 1H, NH), 11.40 (s, 1H, NH). Anal Calcd for $C_{12}H_{10}N_4O_3$ (258.23): C, 55.81; H, 3.90; N, 18.59. Found: C, 55.63; H, 3.82; N, 21.45.

5-Phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (12) The compound **12** was obtained in similar way just replacement urea by thiourea and crystallized from ethanol to give compound **12** in 88 % yield as brown crystals, Mp >300 °C. IR (KBr): 3431.34 cm^{-1} (NH), 1693.86 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d6): δ =5.90 (s, 1H, CH-C_6H_5), 6.80–7.60 (m, 5H, ArH's), 8.20 (s, 1H, NH), 10.00 (s, 1H, NH), 10.30 (s, 1H, NH), 10.70 (s, 1H, NH). Anal Calcd for $C_{12}H_{10}N_4O_2S$ (274.30): C, 52.54; H, 3.67; N, 20.43. Found: C, 52.42; H, 3.48; N, 20.24.

Imino-2,3-dihydrothiazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (13)

A mixture of benzalbarbituric acid (**6**) (10.0 mmol), thiourea(10.0 mmol) and iodine (10.0 mmol) in ethanol (15 mL) was refluxed for 6 h. The reaction mixture was concentrated, cooled and poured into crushed ice. The seprated solid was filtrated, washed with water and crystallized from ethanol to give compound **13** in 55 % yield as yellow crystals, Mp. = 299–300 °C. IR (KBr): 3328 cm^{-1} (NH), 1704 cm^{-1} (C=O). ^1H NMR (300 MHz, DMSO-d6): δ = 2.80 (s, 1H, NH), 9.40 (s, 1H, NH), 10.20 (s, 1H, NH), 11.00 (s, 1H, NH). Anal Calcd for $C_5H_4N_4O_2S$ (184.18): C, 32.61; H, 2.19; N, 30.42. Found: C, 32.45; H, 2.10; N, 30.26.

Conclusion

In summary, some novel condensed pyrimidine derivatives that are structurally related to known drugs pyrimidine were synthesized via multicomponent one-pot reaction starting from barbituric acid and dibenzalacetone to produce spiropyranopyrimidine, pyridopyrimidine, thiazolopyrimidine derivatives The experimental simplicity, excellent product yield, shorter reaction time, and easy work-up procedure of MCRs make this approach more attractive for synthesis a variety of such derivatives.

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