One-Pot Synthesis of 5,7,8,9,9a,10-Hexahydro-8-thioxotetrahydropyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-triones *via* a Four-Component Coupling Reaction of Aldehydes, Amines, Barbituric Acids, and Thiouracil

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An efficient one-pot approach to the synthesis of 5,7,8,9,9a,10-hexahydro-8-thioxopyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-triones **5** *via* a four-component reaction of an aldehyde **1**, an amine **2**, a barbituric acid **3**, and thiouracil (**4**) is reported for the first time. This new multicomponent reaction is accomplished in refluxing EtOH in the presence of tungstophosphoric acid ($H_3PW_{12}O_{40}$) as a catalyst. A variety of hexahydropyrido[2,3-*d*:6,5-*d*′]dipyrimidinetrione derivatives were successfully synthesized in excellent yields with this protocol (*Table 2*).

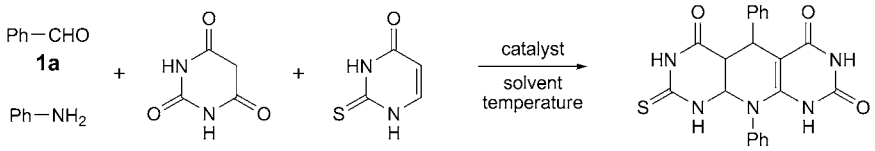
Introduction. – Pyrimidines are known as interesting heterocyclic scaffolds which exhibit various biological and pharmacologic activities [1]. Among them, fused pyrimidines have been used as a common source for the synthesis of new therapeutic agents [2]. Recent studies have shown that pyrimidine-fused heterocycles, particularly their oxo and thioxo derivatives, possess a wide range of biological activity and for this reason, they are extensively used in the design of new drugs [3]. For example, pyrimidopyrimidine derivatives have attracted considerable interest due to their tyrosine kinase inhibitory activity [4], antitumor activity [5], antiviral effect [6], and antioxidant properties [7]. In this regard, the developments of new methodologies for the synthesis of these heterocyclic compounds and new pyrimidine-containing heterocycles have received considerable interest in recent years [8–13]. The synthesis of pyrimidine derivatives by a multicomponent reaction (MCR) is an attractive approach for the construction of this class of compounds [14].

In continuation of our previous works on the synthesis of biologically active compounds [15], we would like to report a four-component sequence for the synthesis of a new pyrimidine-fused scaffold, by means of a condensation reaction of an aldehyde **1**, an amine **2**, a barbituric acid **3**, and thiouracil (=2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; **4**). This new strategy allows for the general access to new derivatives **5** of 5,7,8,9,9a,10-hexahydro-8-thioxopyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione. Structure–activity relationship (SAR) studies of 5,6-dihydropyrimidine-2,4(1*H*,3*H*)-dione derivatives showed that their biological activities are highly dependent on the substituent groups at the saturated pyrimidine moiety [16]. On the other hand, few methods for the synthesis of multiply substituted tetrahydropyrimidin-2(1*H*)-ones have been described [17]. In the present protocol, by choosing different aldehydes **1** and amines **2**, a large structural diversity can be achieved. Accordingly,

from the synthetic perspective, our convenient MCR strategy is a significant advance for the synthesis of this category of tetrahydropyrimidin-2(1*H*)-ones. To the best of our knowledge, this new approach provides the first example of an efficient access to **5**.

Results and Discussion. – To achieve proper conditions for the synthesis of derivatives **5**, we tested the reaction of benzaldehyde (**1a**), aniline (= benzenamine; **2a**), barbituric acid (= pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione; **3a**) and thiouracil (**4**) in various solvents and in the presence of an acidic catalyst. The results of the optimization study (*Table 1*) revealed that the reaction occurred without any catalyst in boiling EtOH, but compound **5a** was obtained in only 28% yield (*Entry 1*). The yield was enhanced to 90% when 2 mol-% of $H_3PW_{12}O_{40}$ were added to the reaction media (*Entry 3*). The acid $H_3PW_{12}O_{40}$ is known as an efficient catalyst for many organic transformations due to its unique properties [18]. The advantages of heteropolyacid catalysts are the following: high catalytic performance, strong acidity, recyclability, selectivity to a particular reaction product by selective stabilization of the reaction intermediate, safety, lower waste, and ease of separation [19]. Thus, we optimized the reaction conditions with $H_3PW_{12}O_{40}$ as the catalyst. Reducing the amount of catalyst led to a reduction in yield (*Entry 2*). Similar results were obtained by increasing the amount of catalyst to 2.5 mol-% (*Entry 4*), indicating that a 2.0 mol-% loading of $H_3PW_{12}O_{40}$ for this reaction was optimal. Refluxing conditions were superior to room temperature (*cf. Entry 5*), and EtOH was the best solvent tested (*Entries 3* and *4 vs. 6–10*), establishing boiling EtOH and 2 mol-% of $H_3PW_{12}O_{40}$ as the best conditions.

Table 1. *Optimization of the Four-Component Reaction between Benzaldehyde* (**1a**), *Aniline* (**2a**), *Barbituric Acid* (**3a**), *and Thiouracil* (**4**)[a])

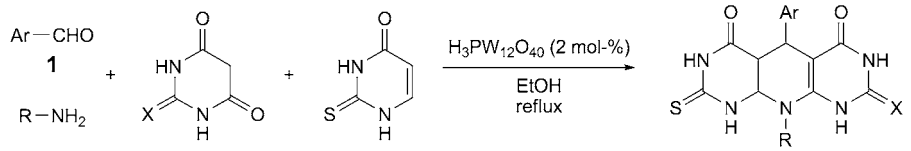


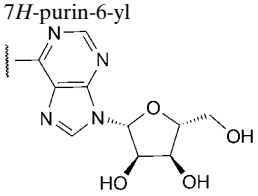
Entry	Catalyst	Solvent	Temp. [°]	Time [h]	Yield [%][b])
1	none	EtOH	reflux	12	28
2	$H_3PW_{12}O_{40}$	EtOH	reflux	10	87[c])
3	$H_3PW_{12}O_{40}$	EtOH	reflux	5	90
4	$H_3PW_{12}O_{40}$	EtOH	reflux	5	91[d])
5	$H_3PW_{12}O_{40}$	EtOH	r.t.	24	45
6	$H_3PW_{12}O_{40}$	DMSO	100	5	75
7	$H_3PW_{12}O_{40}$	none	80	12	42
8	$H_3PW_{12}O_{40}$	MeCN	reflux	5	65
9	$H_3PW_{12}O_{40}$	toluene	100	5	45
10	$H_3PW_{12}O_{40}$	H_2O	reflux	12	61

[a]) Amount of materials in all reactions: barbituric acid (**3a**; 1 mmol), benzaldehyde (**1a**; 1 mmol), thiouracil (**4**; 1 mmol), aniline (**2a**; 1 mmol), and $H_3PW_{12}O_{40}$ (2 mol-%). [b]) Yield of isolated **5a**. [c]) 0.03 g (1.5 mol-%) of catalyst. [d]) 0.05 g (2.5 mol-%) of catalyst.

Thus, we selected these optimum conditions for the preparation of other derivatives of **5** starting from commercially accessible aromatic aldehydes **1** and amines **2**, barbituric acids **3**, and thiouracil (**4**). As shown in *Table 2*, both electron-poor and electron-rich aromatic aldehydes **1** furnished excellent yields of products. In addition, the presence of electron-donating groups at the aromatic amines **2** decreased the reaction times. Different products **5** with heterocyclic substituting moieties were synthesized from heterocyclic aldehydes and amines (*Entries 3*, *10*, and *11*, and *4*–*6*, *9*, and *10*, resp.). The heterocycle compatibility of the reaction was highlighted by amine components **2** which are attached to the desired heterocyclic groups by a spacer (*Entries 9* and *10*), and the use of 2-thiobarbituric acid resulted in as good results as with barbituric acid (*Entries 2*, *6*, and *8*). The practical synthetic efficiency of the procedure was highlighted by the reaction of terephthaldehyde (= benzene-1,4-dicarboxaldehyde), yielding the structurally complex derivative **5** (*Table 2*, *Entry 7*). The structural diversity of this process was further established with adenosine [20] and adenine [21] as amine component **2**, leading to the formation of the new nucleoside base derivatives **5f** and **5e**, respectively (*Table 2*, *Entries 5* and *4*). When uracil was used instead of thiouracil, no significant progress of the reaction was observed. This is most

Table 2. *Products of the Four-Component Reaction between Aldehydes* **1**, *and Amines* **2**, *Barbituric Acids* **3**, *and Thiouracil* (**4**)[a])



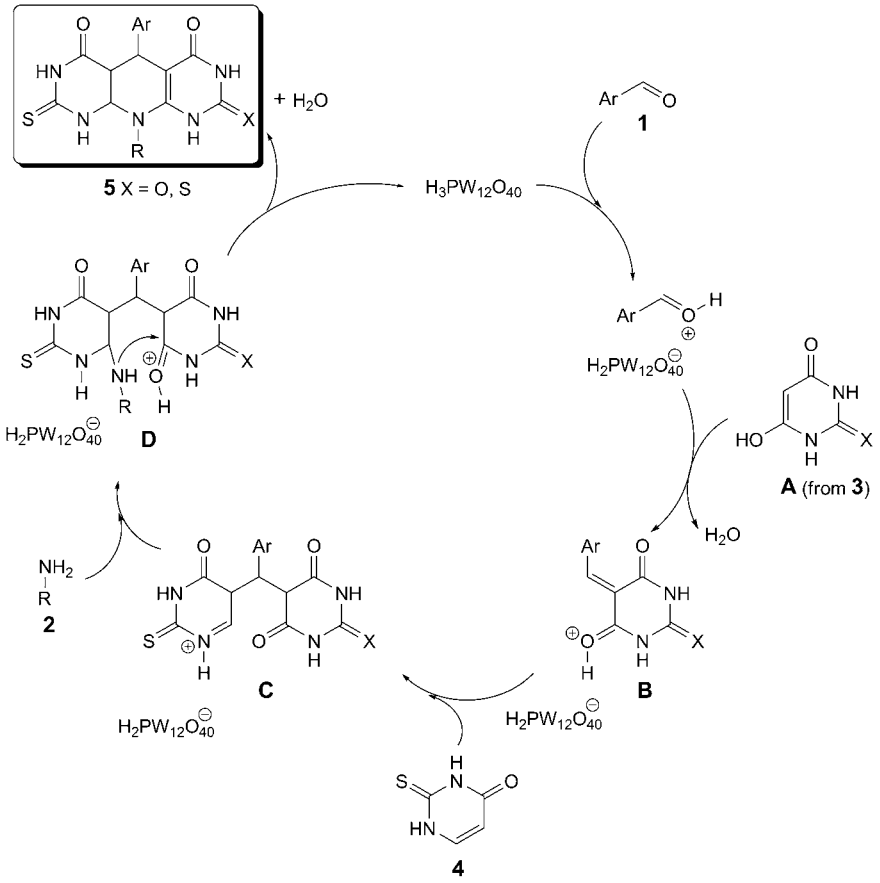
Entry	Ar	R	X	Product	Time [h]	Yield [%][b])
1	3-Me–C_6H_4	4-I–C_6H_4	O	**5b**	5	87
2	anthracen-9-yl	4-MeO–C_6H_4	S	**5c**	4	91
3	1*H*-indol-3-yl	4-MeO–C_6H_4	O	**5d**	4	93
4	4-NO_2–C_6H_4	7*H*-purin-6-yl	O	**5e**	6	84
5	4-NO_2–C_6H_4		O	**5f**	8	78
6	4-NO_2–C_6H_4	1*H*-benzimidazol-2-yl	S	**5g**	7	86
7	4-CHO–C_6H_4	4-MeO–C_6H_4	O	**5h**	12	85
8	3-OH,4-Br–C_6H_3	4-MeO–C_6H_4	S	**5i**	7	88
9	4-Cl–C_6H_4	2-(morpholin-4-yl)ethyl	O	**5j**	7	90
10	pyridin-3-yl	2-(piperazin-1-yl)ethyl	O	**5k**	8	91
11	2-thienyl	4-Br–C_6H_4	O	**5l**	5	90
12	4-Br–C_6H_4	2-MeO–C_6H_4	O	**5m**	6	89

[a]) Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), **4** (1 mmol), $H_3PW_{12}O_{40}$ (0.04 g, 2 mol-%), and EtOH (5 ml). [b]) Yield of isolated **5**.

likely due to the difference of the nucleophilicity of the C(5)-atom in the reaction with electrophilic reagents [22].

We propose a plausible mechanism for this reaction (*Scheme*): Presumably, barbituric acid **3** in its enol form **A** reacts first with the activated aldehyde to form the corresponding 5-(arylmethylidene)barbiturate **B** [23], and then thiouracil (**4**) adds to this adduct to produce the intermediate **C**. The latter can undergo a reaction with the amine component **2**, generating **D**, which is converted to the desired product **5** by an intramolecular condensation reaction.

Scheme. *Proposed Mechanism for the Four-Component Coupling Reaction of Aldehyde* **1**, *Amine* **2**, *Barbituric Acid* **3**, *and Thiouracil* (**4**)



Conclusions. – We developed an efficient multicomponent approach for the preparation of 5,7,8,9,9a,10-hexahydro-8-thioxopyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione derivatives **5**. According to this protocol, when an aldehyde, an amine, and a barbituric acid were treated with thiouracil in the presence of a

catalytic amount of $H_3PW_{12}O_{40}$ in refluxing EtOH, the products were obtained in excellent yield. This strategy offers a powerful tool for preparing a new pyrimidine scaffold which has a high potential for applications in medicinal chemistry. Further studies on this structure may lead to the exploration of new drugs or biologically active compounds in the future.

We acknowledge the financial support from the Shiraz University. Also, we are thankful to Dr. *Reza Yousefi* for its helpful comments.

Experimental Part

General. Chemicals were purchased from *Fluka* and *Aldrich* chemical companies and used without further purification. TLC: silica gel *PolyGram SILG/UV254* plates. M.p.: *Barnstead-Electrothermal-9100-BZ* circulating-oil melting-point apparatus; in open capillary tubes. FT-IR Spectra: *Shimadzu-FT-IR-8300* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-Avance-250* spectrometer; in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. GC/MS: *Shimadzu-GC/MS-QP-1000-EX* apparatus; in *m/z* (rel. %).

*5,7,8,9,9a,10-Hexahydro-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione Derivatives* **5**: *General Procedure.* A mixture of thiouracil (**4**); 0.128 g, 1 mmol), barbituric acid **3** (0.13 g, 1 mmol), aldehyde **1** (1 mmol), amine **2** (1 mmol), and tungstophosphoric acid ($H_3PW_{12}O_{40}$) (0.04 g, 2 mol-%) in boiling EtOH (5 ml) was stirred for the time specified in *Table 2*. After completion of the reaction (TLC (AcOEt/hexane) monitoring), the mixture was cooled to r.t. and the precipitated product filtered and washed with H_2O (20 ml) and EtOH (10 ml): pure **5**.

*5,7,8,9,9a,10-Hexahydro-5,10-diphenyl-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5a**): Yield 90%. Yellow solid. M.p. 240–242°. IR (KBr): 3198, 2930, 1763, 17230, 1680, 1591. ^{1}H-NMR (250 MHz): 3.81 (*dd*, *J* = 6.5, 3.3, 1 H); 5.04 (*d*, *J* = 3.1, 1 H); 5.17 (*d*, *J* = 3.2, 1 H); 7.10–7.18 (*m*, 2 H); 7.29 (*dd*, *J* = 8.0, 2.9, 4 H); 7.51 (*t*, *J* = 4.3, 2 H); 7.76 (*d*, *J* = 5.4, 2 H); 9.10 (*s*, 1 H); 10.08 (*s*, 1 H); 10.52 (*s*, 1 H); 11.2 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 31.8; 71.0; 86.0; 113.8; 117.4; 130.1; 130.3; 130.7; 140.0; 145.0; 149.9; 152.6; 163.0; 176.1; 183.1. MS: 419.18 (17.9, M^+). Anal. calc. for $C_{21}H_{17}N_5O_3S$ (419.46): C 60.13, H 4.09, N 16.70, S 7.64; found: C 60.01, H 3.97, N 16.75, S 7.58.

*5,7,8,9,9a,10-Hexahydro-10-(4-iodophenyl)-5-(3-methylphenyl)-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5b**): Yield 87%. Violet solid. M.p. 230–232°. IR (KBr): 3178, 2926, 1765, 1732, 1677.1, 1581. ^{1}H-NMR (250 MHz): 2.33 (*s*, 3 H); 3.76 (*dd*, *J* = 4.9, 2.0, 1 H); 5.11 (*d*, *J* = 3.8, 1 H); 5.33 (*d*, *J* = 3.9, 1 H); 6.79 (*d*, *J* = 8.3, 2 H); 7.14 (*d*, *J* = 5.3, 2 H); 7.41 (*dd*, *J* = 6.8, 3.6, 2 H); 7.53 (*d*, *J* = 7.7, 2 H); 9.08 (*s*, 1 H); 10.12 (*s*, 1 H); 10.63 (*s*, 1 H); 11.68 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 25.0; 31.2; 50.4; 68.7; 82.2; 83.6; 116.3; 125.1; 126.6; 127.6; 128.6; 129.1; 136.3; 138.0; 140.0; 142.2; 144.3; 150.3; 163.2; 164.5; 176.0; 182.0. MS: 559.02 (14.3, M^+). Anal. calc. for $C_{22}H_{18}IN_5O_3S$ (559.38): C 47.24, H 3.24, N 12.52, S 5.73; found: C 47.29, H 3.21, N 12.58, S, 5.68.

*5-(Anthracen-9-yl)-2,3,5,7,8,9,10,10a-octahydro-10-(4-methoxyphenyl)-2,8-dithioxo-pyrido[2,3-*d*:6,5-*d′*]dipyrimidine-4,6(1*H*,4a*H*)-dione* (**5c**): Yield 91%. Deep red solid. M.p. > 300 (dec.). IR (KBr): 3217, 3078, 2916, 1763.5, 1674, 1566, 1435, 1381, 1319, 1211, 1165. ^{1}H-NMR (400 MHz): 3.70 (*s*, 3 H); 4.66 (*t*, *J* = 3.8, 1 H); 4.82 (*dd*, *J* = 7.6, 1.8, 1 H); 5.19 (*dd*, *J* = 7.8, 2.2, 1 H); 7.40 (*s*, 1 H); 7.49–7.95 (*m*, 6 H); 7.96 (*d*, *J* = 8.8, 2 H); 8.13 (*d*, *J* = 7.8, 2 H); 8.65 (*s*, 1 H); 9.00 (*s*, 1 H); 11.12 (*s*, 1 H); 11.57 (*s*, 1 H); 12.30 (br. *s*, 1 H); 12.48 (br. *s*, 1 H). ^{13}C-NMR (100 MHz): 27.5; 52.0; 57.7; 68.1; 89.6; 105.2; 125.3; 125.5; 125.5; 126.2; 127.6; 127.7; 128.6; 130.5; 142.1; 150.5; 151.2; 161.0; 162.4; 176.0. MS: 565.29 (15.1, M^+). Anal. calc. for $C_{30}H_{23}N_5O_3S_2$ (565.67): C 63.70, H, 4.10, N 12.38, S 11.34; found: C 63.73, H 4.07, N 12.41, S 11.31.

*5,7,8,9,9a,10-Hexahydro-5-(1*H*-indol-3-yl)-10-(4-methoxyphenyl)-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5d**): Yield 95%. Yellow solid. M.p. 308–312°. IR (KBr): 3176, 3002, 1770, 1730, 1674, 1586. ^{1}H-NMR (250 MHz): 3.80 (*s*, 3 H); 3.98 (*d*, *J* = 4.1, 1 H); 5.61 (*d*, *J* = 3.3, 1 H); 5.80 (*d*, *J* = 3.5, 1 H); 7.31 (*dd*, *J* = 10.5, 5.4, 2 H); 7.38 (*d*, *J* = 6.6, 2 H); 7.58 (*dd*, *J* = 5.9, 2.7, 2 H); 7.85 (*t*, *J* = 2.8, 2 H); 8.29 (*d*, *J* = 7.7, 1 H); 11.02 (*s*, 1 H); 11.1 (*s*, 1 H); 12.25 (*s*, 1 H); 12.42 (*s*, 1 H); 12.72 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 31.4; 51.5; 57.8; 70.1; 84.2; 105.2; 108.6; 111.3; 113.1; 117.6; 122.6; 123.6; 129.1;

136.3; 139.7; 142.0; 143.6; 150.3; 163.2; 164.5; 176.0. MS: 488.09 (23, M^+). Anal. calc. for $C_{24}H_{20}N_6O_4S$ (488.52): C 59.01, H 4.13, N 17.20, S 6.56; found: C 59.08, H 4.15, N 17.25, S 6.51.

*5,7,8,9,9a,10-Hexahydro-5-(4-nitrophenyl)-10-(7*H*-purin-6-yl)-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5e**): Yield 84%. Pale yellow solid. M.p. >300 (dec.). IR (KBr): 3179, 2974, 1778, 1731, 1680, 1585. ^{1}H-NMR (250 MHz): 3.78 (*dd*, *J* = 4.7, 2.5, 1 H); 5.03 (*d*, *J* = 2.6, 1 H); 5.57 (*d*, *J* = 2.8, 1 H); 7.77 (*d*, *J* = 8.7, 2 H); 7.85 (*s*, 1 H); 8.3 (*d*, *J* = 10.0, 2 H); 8.39 (*s*, 1 H); 9.22 (*s*, 1 H); 10.16 (*s*, 1 H); 10.36 (*s*, 1 H); 11.33 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 32.4; 52.4; 67.2; 75.3; 87.3; 122.1; 123.3; 131.0; 137.1; 147.2; 150.0; 151.1; 153.5; 155.6; 157.5; 168.2; 178.5; 181.0. MS: 522.21 (12.5, M^+). Anal. calc. for $C_{20}H_{14}N_{10}O_4S_2$ (522.52): C 45.97, H 2.70, N 26.81, S 12.27; found: C 46.01, H 2.72, N 26.87, S 12.21.

*5,7,8,9,9a,10-Hexahydro-5-(4-nitrophenyl)-10-{9-[(2*R*,3*R*,4*S*,5*R*)-tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)furan-2-yl)-9*H*-purin-6-yl}-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5f**): Yield 78%. Yellow solid. M.p. 234–236°. IR (KBr): 3530, 3328, 2956, 1745, 1722, 1673, 1571. ^{1}H-NMR (250 MHz): 3.36–3.39 (*m*, 3 H); 4.21–4.23 (*m*, 1 H); 4.42–4.44 (*m*, 1 H); 4.81–4.83 (*m*, 1 H); 5.02 (*s*, 1 H); 5.53 (*s*, 1 H); 6.30 (*s*, 3 H); 7.41–7.43 (*m*, 2 H); 7.67 (*dd*, *J* = 6.8, 2.2, 2 H); 7.86 (*t*, *J* = 1.5, 1 H); 7.87 (*s*, 1 H); 7.89 (*s*, 1 H); 9.14 (*s*, 1 H); 9.98 (*s*, 1 H); 11.02 (*s*, 1 H); 12.40 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 32.7; 50.2; 58.2; 61.0; 73.1; 76.0; 83.1; 85.2; 90.0; 91.9; 118.9; 120.3; 129.0; 140.0; 146.3; 150.4; 151.1; 153.4; 154.7; 155.4; 162.1; 176.3. Anal. calc. for $C_{25}H_{22}N_{10}O_9S$ (638.57): C 47.02, H 3.47, N 21.93, S 5.02; found: C 47.08, H 3.49, N 21.99, S 5.00.

*10-(1*H*-Benzimidazol-2-yl)-2,3,4,5,7,8,9,9a,10-octahydro-5-(4-nitrophenyl)-2,8-dithioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-4,6(1*H*,4a*H*)-dione* (**5g**): Yield 86%. Yellow solid. M.p. 263–265°. IR (KBr): 3180, 2970, 1779, 1735, 1676, 1584. ^{1}H-NMR (250 MHz): 3.72 (*dd*, *J* = 8.1, 3.6, 1 H); 4.90 (*d*, *J* = 7.6, 1 H); 5.87 (*d*, *J* = 6.3, 1 H); 6.98 (*d*, *J* = 7.5, 2 H); 7.19 (*d*, *J* = 2.0, 1 H); 7.22 (*d*, *J* = 4.0, 1 H); 7.79 (*d*, *J* = 8.1, 2 H); 8.20 (*d*, *J* = 5.7, 2 H); 11.68 (*s*, 1 H); 12.26 (*s*, 1 H); 12.42 (*s*, 1 H); 14.02 (*s*, 2 H). ^{13}C-NMR (62.5 MHz): 31.0; 67.9; 81.0; 116.7; 121.1; 123.0; 130.0; 136.5; 145.6; 150.5; 154.3; 162.8; 174.5; 179.1. MS: 520.12 (21, M^+). Anal. calc. for $C_{22}H_{16}N_8O_4S_2$ (520.54): C 50.76, H 3.10, N 21.53, S 12.32; found: C 50.81, H 3.13, N 21.59, S 12.28.

*4-[1,2,3,4,4a,5,6,7,8,9,10,10a-Dodecahydro-10-(4-methoxyphenyl)-4,6-dioxo-2,8-dithioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidin-5-yl]benzaldehyde* (**5h**): Yield 85%. Yellow solid. M.p. >300 (dec.). IR (KBr): 3190, 2972, 1771, 1728, 1679, 1588. ^{1}H-NMR (250 MHz): 3.88 (*s*, 6 H); 4.0 (*dd*, *J* = 10.0, 4.1, 2 H); 5.78 (*d*, *J* = 7.6, 2 H); 6.05 (*s*, 2 H); 7.36 (*t*, *J* = 10.0, 4 H); 7.78 (*d*, *J* = 4.5, 2 H); 7.82 (*d*, *J* = 4.0, 2 H); 8.12 (*t*, *J* = 4.5, 4 H); 10.87 (*s*, 2 H); 11.68 (*s*, 2 H); 12.26 (*s*, 2 H); 12.42 (*s*, 2 H). ^{13}C-NMR (62.5 MHz): 31.3; 45.3; 45.7; 66.3; 84.4; 110.5; 128.3; 133.0; 147.3; 150.4; 151.1; 153.5; 155.7; 157.4; 166.2; 168.3; 178.3; 181.2. Anal. calc. for $C_{38}H_{32}N_{10}O_8S_2$ (820.85): C 55.60, H 3.93, N 17.06, S 7.81; found: C 55.64, H 3.95, N 17.12, S 7.78.

*2,3,5,7,8,9,10,10a-Octahydro-5-(3-hydroxy-4-methoxyphenyl)-10-(4-methoxyphenyl)-2,8-dithioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-4,6(1*H*,4a*H*)-dione* (**5i**): Yield 85%. Yellow solid. M.p. >300 (dec.). IR (KBr): 3182, 2970, 1781, 1739, 1685, 1587. ^{1}H-NMR (250 MHz): 3.75 (*s*, 3 H); 3.78 (*s*, 3 H); 4.02 (*dd*, *J* = 4.9, 2.5, 1 H); 4.66 (*d*, *J* = 2.4, 1 H); 5.82 (*d*, *J* = 7.3, 1 H); 6.86 (*d*, *J* = 8.7, 2 H); 7.13 (*d*, *J* = 8.1, 1 H); 7.22 (*d*, *J* = 8.7, 2 H); 7.36–7.41 (*m*, 2 H); 9.27 (br. *s*, 1 H); 10.28 (br. *s*, 1 H); 11.10 (br. *s*, 1 H); 11.47 (br. *s*, 1 H). ^{13}C-NMR (62.5 MHz): 33.0; 50.8; 54.9; 68.1; 100.1; 131.2; 132.4; 134.8; 138.4; 149.8; 150.2; 154.4; 163.4; 168.4; 174.2; 179.2. MS: 511.24 (12.8, M^+). Anal. calc. for $C_{23}H_{21}N_5O_5S_2$ (511.57): C 54.00, H 4.14, N 13.69, S 12.54; found: C 54.05, H 4.18, N 13.73, S 12.50.

*5-(4-Chlorophenyl)-5,7,8,9,9a,10-hexahydro-10-[2-(morpholin-4-yl)ethyl]-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5j**): Yield 91%. Yellow solid. M.p. 258–260°. IR (KBr): 3172, 2968, 1783, 1742, 1689, 1587. ^{1}H-NMR (250 MHz): 2.36–2.40 (*m*, 4 H); 2.85–2.92 (*m*, 2 H); 3.37 (*d*, *J* = 7.1, 2 H); 3.42 (*d*, *J* = 5.8, 2 H); 3.50 (*d*, *J* = 8.3, 1 H); 3.56 (*d*, *J* = 9.5, 2 H); 5.13 (*d*, *J* = 13.5, 2 H); 7.41 (*d*, *J* = 3.4, 2 H); 7.65 (*d*, *J* = 3.2, 2 H); 9.13 (*s*, 1 H); 10.10 (*s*, 1 H); 10.62 (*s*, 1 H); 11.20 (br. *s*, 1 H). ^{13}C-NMR (62.5 MHz): 31.4; 50.0; 51.1; 66.3; 67.1; 79.5; 129.3; 131.0; 137.5; 150.5; 157.4; 162.1; 176.2; 181.6. MS: 500.54 (24, M^+). Anal. calc. for $C_{21}H_{23}ClN_6O_4S$ (490.96): C 51.37, H 4.72, N 17.12, S 6.53; found: C 51.41, H 4.74, N 17.18, S 6.50.

*5,7,8,9,9a,10-Hexahydro-10-[2-(piperazin-1-yl)ethyl]-5-(pyridin-3-yl)-8-thioxopyrido[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5k**): Yield 92%. Yellow solid. M.p. 266–268°. IR (KBr): 3378, 3188, 2965, 1786, 1747, 1681, 1583. ^{1}H-NMR (250 MHz): 2.78 (*t*, *J* = 1.8, 4 H); 3.23 (*t*, *J* = 8.3, 2 H); 3.54 (*t*, *J* = 6.2, 2 H); 3.76–3.79 (*m*, 3 H); 4.14 (*s*, 2 H); 4.47 (*s*, 1 H); 5.28 (*d*, *J* = 5.2, 1 H); 6.41 (br. *s*, 2 H); 7.35

(*dd*, *J* = 4.7, 2.0, 1 H); 7.75 (*d*, *J* = 8.0, 1 H); 8.17 (*d*, *J* = 9.0, 1 H); 8.39 (*s*, 1 H); 10.07 (*s*, 1 H); 11.55 (*s*, 1 H); 11.72 (*s*, 1 H). ^{13}C-NMR (62.5 MHz): 32; 37.1; 41.5; 51.2; 55.0; 67.3; 79.5; 123.1; 136.4; 137.1; 147.3; 150.4; 151.1; 158.1; 163.1; 176.1; 182.8. MS: 456 (27, M^+). Anal. calc. for $C_{20}H_{24}N_8O_3S$ (456.52): C 52.62, H 5.30, N 24.55, S 7.02; found: C 52.67, H 5.33, N 24.59, S 6.68.

10-(4-Bromophenyl)-5,7,8,9,9a,10-hexahydro-5-(2-thien-yl)-8-thioxopyrido[2,3-d*:6,5*-d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5l**): Yield 89%. Yellow solid. M.p. 235–237°. IR (KBr): 3210, 2971, 1790, 1751, 1678, 1579. ^{1}H-NMR (250 MHz): 3.51–3.53 (*m*, 1 H); 4.77 (*d*, *J* = 2.7, 1 H); 5.10 (*d*, *J* = 2.4, 1 H); 7.02 (*d*, *J* = 9.8, 1 H); 7.16–7.19 (*m*, 3 H); 7.38 (*d*, *J* = 3.0, 1 H); 7.41 (*d*, *J* = 3.1, 1 H); 9.66 (br. *s*, 1 H); 10.59 (*s*, 1 H); 11.09 (*s*, 1 H); 12.04 (br. *s*, 1 H). ^{13}C-NMR (62.5 MHz): 22.0; 45.7; 71.3; 91.5; 110.9; 116.4; 123.1; 124.0; 125.0; 133.3; 143.5; 146.4; 157.2; 163.1; 176.2; 178.1; 181.8. MS: 504.06 (19, M^+). Anal. calc. for $C_{19}H_{14}BrN_5O_3S_2$ (504.38): C 45.24, H 2.80, N 13.89, S 12.71; found: C 45.29, H 2.83, N 13.93, S 12.68.

5-(4-Bromophenyl)-5,7,8,9,9a,10-hexahydro-10-(2-methoxyphenyl)-8-thioxopyrido[2,3-d*:6,5*-d′*]dipyrimidine-2,4,6(1*H*,3*H*,5a*H*)-trione* (**5m**): Yield 90%. Yellow solid. M.p. >300 (dec.). IR (KBr): 3195, 2965, 1787, 1753, 1670, 1573. ^{1}H-NMR (250 MHz): 3.31–3.41 (*m*, 1 H); 3.72 (*s*, 3 H); 4.72 (*d*, *J* = 11.1, 1 H); 5.27 (*d*, *J* = 7.4, 1 H); 5.81 (br. *s*, 2 H); 7.09 (*d*, *J* = 8.2, 2 H); 7.14–7.22 (*m*, 2 H); 7.24 (*d*, *J* = 4.2, 1 H); 7.29–7.34 (*m*, 1 H); 7.43 (*dd*, *J* = 10.4, 5.4 Hz, 2 H); 9.40 (br. *s*, 1 H); 9.69 (br. *s*, 1 H). ^{13}C-NMR (62.5 MHz): 31.4; 50.0; 55.0; 68.1; 90.0; 105.2; 108.6; 111.3; 117.6; 122.6; 123.6; 128.3; 140.0; 144.4; 150.3; 157.1; 162.2; 173.6; 174.5; 179.6. MS: 528.08 (12, M^+). Anal. calc. for $C_{22}H_{18}BrN_5O_4S$ (528.38): C 50.01, H 3.43, N 13.25, S 6.07; found: C 50.07, H 3.47, N 13.29, S 6.02.

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