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Facile Synthesis, Pure DFT Calculations, and PM3 Semiempirical MO Method Validation of Regiospecificity of Novel 1,4-Dihydropyrido[2,3-d]pyrimidine Derivatives

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FACILE SYNTHESIS, PURE DFT CALCULATIONS, AND PM3 SEMIEMPIRICAL MO METHOD VALIDATION OF REGIOSPECIFICITY OF NOVEL 1,4-DIHYDROPYRIDO[2,3-d]PYRIMIDINE DERIVATIVES

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Reaction of 6-aminothiouracil (or uracil) with equimolar amounts of different ketones or diketones and the appropriate aromatic aldehydes afforded di- and tricyclic linear pyrido[2,3-d]pyrimidine derivatives 4, 6–12, 14, 16–18, 20, and 21, and pyrimido[4,5-b]quinoline derivatives 15 and 19 in good yields. The regiospecificity, which led to the formation of compound 4 not 5, was validated using ab initio at the HF/6–31 G^{+}(d,p) level and pure density functional theory (DFT) calculations using BLYP energy functional and the basis set DNP via studying the thermodynamics of their possible conformers and regioisomers. In addition, the total energy of the transition state was calculated for compounds 12 and 13 to determine whether the reaction products were thermodynamically or kinetically controlled. Hence, the linear structures and the regiospecificities of the reactions for the structures reported in this article were established by elemental analysis, spectral data, ab initio calculations, pure DFT, and PM3 parameters.

Keywords: Ab initio validation; acetylacetone; 6-amino-uracil and thiouracil; molecular modeling; trifloroacetylacetone

INTRODUCTION

Pyrimidine is the parent heteroring of a very important group of compounds that have been extensively studied because of their occurrence in living systems. Compounds containing pyrimidine rings have been reported as antibacterial, antifungal, and anti-HIV agents.[1–4]

Substitution of a pyridine ring for a benzene ring often is compatible with retention of biological activity, and occasionally this moiety is an essential part of the pharmacophore. Such substitution of =N for CH= is an example of the common medicinal strategy known as bioisosterism. Therefore, pyridine derivatives have a

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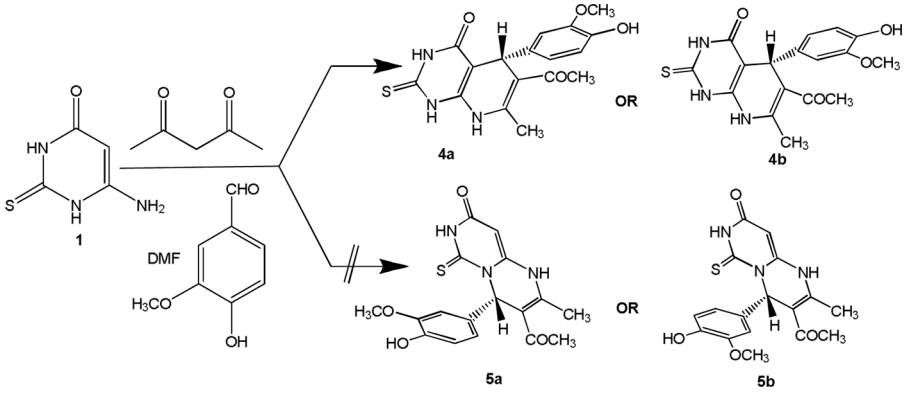
broad spectrum of biological activity, such as antihypertensive, bronchodilator, anti-inflammatory, and antifungal activities.[5–9]

Moreover, 1,4-dihydropyridines, known as nifedipine, exhibit coronary vasodilators activity, and therefore they are used for relief of the intense chest pains of angina pectoris.[10] Compounds having a combination of pyrimidine with 1,4-dihydropyridine moieties are expected to possess medicinal properties. Encouraged by these reports and in continuation of our work in this field,[11–16] we report here the synthesis of some new 1,4-dihydropyridinopyrimidine derivatives.

RESULTS AND DISCUSSION

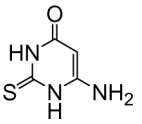
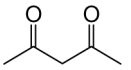
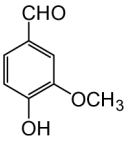
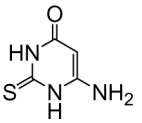
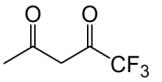
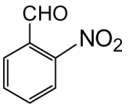
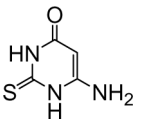
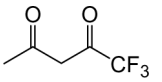
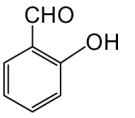
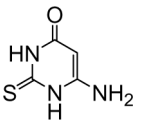
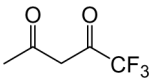
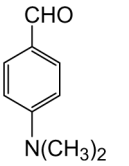
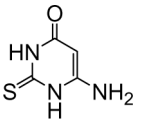
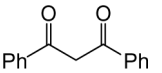
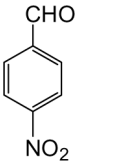
In this study, 6-aminothiouracil (**1**), 6-amino-1-methyluracil (**2**), and 6-amino-1,3-dimethyluracil (**3**), are used as starting materials for the synthesis of 1,4-dihydropyrido[2,3-d]pyrimidines.

1,4-Dihydropyrido[2,3-d]pyrimidines were synthesized by refluxing equimolar amounts of 6-aminothiouracil (**1**) in dimethylformamide (DMF) with 1,3-diketones, (namely acetylacetone, trifloroacetylacetone, dibenzoylmethane, and benzoylacetone) with appropriate aromatic aldehydes. The cyclocondensation of **1** with acetylacetone and vaniline in DMF afforded the pyridopyrimidine **4**. There are two possibilities for ring closure: if the N1-position is unsubstituted, as in compound **1**, ring closure takes place at either the N1 or the C-5 atom. Both cyclizations have been reported in the reaction of 5-aminopyrazole with 1,3-dicarbonyl compounds,[17,18] but we observed only cyclization at C-5 to give 6-acetyl-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-2-thioxo-2,3,5,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-(1*H*)one (**4**) (Scheme 1; Table 1) To gain deep understanding of the electronic structure, reactivity, and ring cyclization potential of compound **1** toward vanillin and acetylacetone, quantum mechanical calculations were performed at the density functional theory (DFT) level using the Becke–Lee–Yang–Parr (BLYP) energy functional and the basis set DNP (double-numerical basis functions with polarization functions). Moreover, ab initio calculations at the Hartree–Fock (HF) level with the basis set 6-31G^{+}, and the augmented version of these sets incorporating extra p and d functions, were performed on the possible



Scheme 1. Cyclocondensation of **1** with acetylacetone and vaniline to afford pyrido[2,3-d]pyrimidine derivative **4**.

Table 1. Synthesis of 2-thioxo-2,3,5,8-tetrahydropyrido[2,3-d]pyrimidin-4-(1*H*)one derivatives (**4, 6–9**)

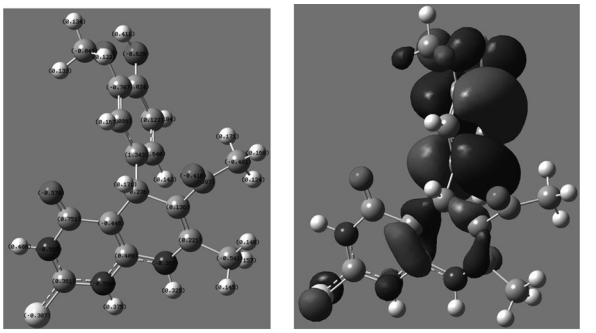
Entry	Substrate	1,3-Diketone	Aldehyde	Product	R	Y(X)	Yield (%)
1				**4a**	3-OCH_3, 4-OH	$CF_3(CH_3)$	75
2				**6**	2-NO_2	$CF_3(CH_3)$	70
3				**7**	2-OH	$CF_3(CH_3)$	80
4				**8**	4-$N(CH_3)_2$	$CF_3(CH_3)$	67
5				**9**	4-NO_2	Ph(Ph)	73

conformers of compounds **4a, b** and **5a, b** to determine the thermodynamically favorable regiospecificity and the most stable conformer. First, the equilibrium molecular geometries of conformers **4a, b** and **5a, b** were calculated, and key thermodynamic descriptors were computed. Table 2 shows the calculated total energy for the conformers **4a, b** and **5a, b** and HOMO-LUMO gap of the constitutional isomers **4a** and **5a** using ab initio calculations. The data show clearly that the reaction of compound **1** with acetylacetone and vanillin thermodynamically favors conformers **4a, b** rather than conformers **5a, b**. Hence, the reaction is regiospecific and furnishes the linear compound **4**, which was confirmed experimentally. Moreover, the data also show that conformer **4a** is more stable than conformer **4b**, inferred from the lower total energy values. However, both ab initio and DFT methods predicted smaller HOMO-LUMO energy gaps for compounds **4a, 4b, 5a**, and **5b** to follow the trend **4a** < **4b** < **5a** < **5b**, which could be attributed to the fact that DFT and ab initio methods are not sensitive to the HOMO-LUMO gap of sulfur-containing compounds.[19] Figures 1a and 1b show the equilibrium molecular geometry of conformer **4a** with the atomic charge superimposed on each atom and the HOMO isosurface of the conformer **4a** superimposed on its equilibrium molecular geometry, respectively.

Table 2. Calculated total energy [HF/6-31G^{+}(d, p)] for conformers **4a, b** and **5a, b** and HOMO-LUMO gap for conformers **4a** and **5a**

Compound	Energy (RHF), Hartree	Energy difference between conformers (a & b) (kcal/mol)	HOMO-LUMO energy gap (eV)
4a	−1514.050	$E_{4a} = E_{4b} - 1.158$	9.092
4b	−1514.048		9.113
5a	−1514.0334	$E_{5a} = E_{5b} - 0.0627$	9.215
5b	−1514.0333		9.219

Notes. Hartree = 627.51 kcal/mol; RHF, restricted Hartree–Fock.



(a) (b) **(HOMO, 8.176 eV)**

Figure 1. (a) Equilibrium molecular geometry of conformer **4a** and (b) calculated HOMO superimposed on the isosurface of the equilibrium molecular geometry of conformer **4a**.

Table 3 shows the total energy and binding energy of conformers **4a, b** and **5a, b** computed using DFT utilizing BLYP energy functional and the basis set DNP, which are consistent with the data shown in Table 2 and are in agreement with the experimental data.

The ^{1}H NMR spectrum of the product, compound **4**, showed signals due to CH_3, $COCH_3$, and OCH_3 at δ 2.73, 2.88, and 3.65 ppm, respectively, in addition to two sharp singlets at δ 5.27 and 8.61 ppm for 5-H and 8-NH, respectively, and additional NH signals at δ 11.75 and 11.97 ppm corresponding to 1,3-NH protons.

Table 3. Calculated total energy and binding energy (BLYP/DNP) for compounds (**4a, b**) and (**5a, b**) using DFT

Compound	Energy (RHF), Hartree	Binding energy, Hartree	Energy difference between conformers (a & b) (kcal/mol)
4a	−1521.514	−7.514	$E_a = E_b - 1.883$
4b	−1521.511	−7.511	
5a	−1521.505	−7.505	$E_a = E_b - 5.647$
5b	−1521.496	−7.496	

On the bases of experimental results coupled with the ab initio and DFT validations, isomeric structure **5** was discarded. Moreover, the infrared (IR) spectrum showed stretching frequencies at 3374 cm^{-1} attributable to the OH function; 3316, 3214, 3168 cm^{-1} attributable to NH groups; 1700 cm^{-1} attributable to α,β-unsaturated ketone; 1660 cm^{-1} attributable to amidic carbonyl; and 1597 cm^{-1} attributable to C=C function. The structure was further confirmed by measuring its mass spectrum, which showed molecular ion peak at m/z 358 ($M^+ - 1$, 45%).

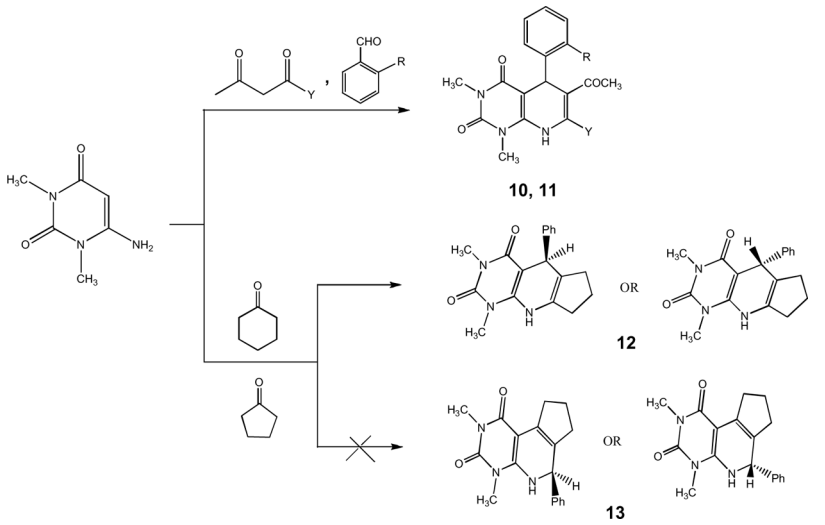
Similarly, **1** reacts with trifloroacetylacetone and *o*-nitrobenzaldehyde in refluxing DMF to afford 1,4-dihydropyrido[2,3-d]pyrimidine **6**. The IR spectrum of **6** showed frequencies at 3350–3187 cm^{-1} for (NH) groups, 1715–1699 cm^{-1} for amidic and ketonic carbonyls, 1371 cm^{-1} for C=S, and 1530, 1350 cm^{-1} for NO_2 function.

Moreover, the mass spectroscopic measurement showed the molecular ion peak at m/z 410 ($M^+ - 2$, 15%). The ^1H NMR showed singlet signals at δ 2.88 ppm for acetyl protons, 5.87 ppm for C_5-H, 8.09 for 8-NH, and 12.02 (b, 2H, 2NH).

On the other hand, **1** reacted with trifloroacetylacetone and salicyaldehyde (or *p-N,N*-dimethylaminobenzaldehyde) to give the corresponding 1,4-dihydropyridopyrimidines **7** and **8**, respectively. Structures **7** and **8** were established based on both elemental analysis and spectral data. In general, the IR spectra of **7** and **8** showed bands at 3377–3190 cm^{-1} for (NH groups), 1700–1630 cm^{-1} for carbonyl groups, and 1355 cm^{-1} for C=S function. The ^1H NMR of compound **7** showed singlet signals at δ 2.88, 5.87, 8.20, 11.65, and 12.21 ppm due to $COCH_3$, C_5-H, 8-NH, and 1.3-NH protons, respectively. On the other hand, ^1H NMR of compound **8** showed signals at δ 2.73, 2.88, 4.88, 7.94, 12.14, and 13.16 ppm due to *N,N*-$(CH_3)_2$, $COCH_3$, C_5-H, 8-NH, and 1,3-NH protons, respectively.

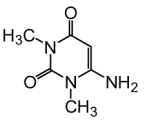
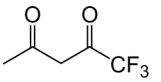
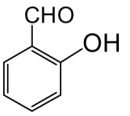
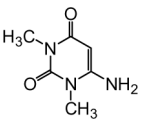
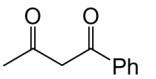
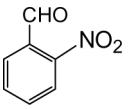
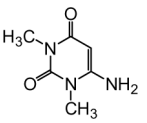
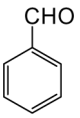
In a similar manner, **1** reacted with dibenzoylmethane to give the corresponding 1,4-dihydropyridopyrimidine derivative **9**. Compound **9** was proved by elemental and spectral data. In general, the IR showed signals at 3450–3195 cm^{-1} for the NH stretching frequencies, 1720–1700 cm^{-1} for ketonic and amidic carbonyl groups, 1530, 1350 cm^{-1} for nitro group, and a band at 1300 cm^{-1} for C=S. Moreover, the mass spectrum of **9** showed the molecular ion beaks at m/z 479 ($M^+ - 3$, 14%).

In addition, it was found that refluxing compound **3** in boiling dimethylformamide (DMF) with trifloroacetylacetone and salicyaldehyde yielded a single product, the elemental analysis of which confirmed the molecular formula ($C_{18}H_{16}N_3O_4F_3$). This product was formulated as 6-acetyl-5-[2-hydroxyphenyl]-1,3-dimethyl-7-[trifloro-methyl]-5,8-dihydropyrido[2,3-d]pyrimidine-4-[1*H*]-2,4-dione (**10**) (Scheme 2; Table 4), and the structure was confirmed by IR, ^1H NMR, and mass spectra. Its ^1H NMR spectrum revealed five singlet signals at δ 2.91, 3.35, 3.46, 5.06, and 6.94 ppm attributable to the CH_3CO, 2(N-CH_3), C5-H-pyridine ring, and OH protons and a multiplet at δ 7.07–7.21 ppm for aromatic protons, but the NH proton was not observed. This could be because the NH exists between one α,β-unsaturated ketone and one α,β-unsaturated amidic carbonyl. It is very likely that the NH could undergo tautomerization with one or two α,β-unsaturated carbonyls, in which case the dynamic equilibrium could be so fast that it cannot been seen in an ^1H NMR experiment at room temperature. The NH proton can be resolved by running a temperature-dependent ^1H NMR experiment at temperatures less than room temperature to freeze out the NH proton conformer. In addition, the mass spectrum



Scheme 2. Synthesis of pyrido[2,3-d]pyrimidine-4-[1*H*]-2,4-dione analogs **10–12**.

Table 4. Synthesis of 1,3-dimethyl-5,8-dihydropyrido[2,3-d]pyrimidin-4-(1*H*)-2,4-dione derivatives (**10–12**)

Entry	Substrate	Ketone	Aldehyde	Product	Y	Yield (%)
6				**10**	CF_3	78
7				**11**	Ph	71
8				**12**	—	69

showed the molecular ion peak at m/z 376 ($M^+ - F$, 35%) and the base peak at m/z 172 resulting from the loss of two methyl groups, carbon monoxide, OH, and $HN{-}\overset{\overset{C{-}COCH_3}{\|}}{C}{-}CF_3$ fragments.

Moreover, the IR spectrum showed absorption frequencies at 3449 cm^{-1} for the OH group, 3337 cm^{-1} for NH, 1700 cm^{-1} for the ketonic carbonyl function, and 1630 cm^{-1} for the amidic carbonyl.

In addition, reaction of **3** with benzoylacetone and *o*-nitrobenzaldehyde in refluxing DMF afforded a single product of structure **11**. Structure **11** was also proved on the base of both analytical and spectral data. The IR spectrum showed absorption frequencies at 3400 cm^{-1} for NH function, 1707 cm^{-1} for ketonic carbonyl, 1614 cm^{-1} for amidic carbonyl, 1568, and 1361 cm^{-1} for symmetric and asymmetric nitro group. Moreover, the ^1H NMR revealed five singlet signals at δ 2.77, 3.35, 3.70, 5.12, and 9.08 ppm due to CH_3, 2(N-CH_3), C-5H-pyridine ring, and 8-NH protons, respectively, besides a multiplet at δ 7.55–8.20 ppm for aromatic protons. The mass spectrum of **11** showed the molecular ion peak as base peak at m/z 386.4 ($M^+ - NO_2$, 100%), whereas the fragment at m/z 342 corresponds to the loss of acetyl group from the molecular ion.

In continuation of this work, the 1,4-dihydropyido[2,3-d]pyrimidin-4-one **12** has been also synthesized by refluxing equimolar amounts of 1,3-dimethyl-6-aminouracil (**3**) in boiling DMF with cyclopentanone and benzaldehyde derivatives. Of two possible structures, **12** and **13**, that can be proposed for such a product, compound **13** was ruled out on the bases of both the elemental and spectral data (Scheme 2; Table 4).

The cyclocondensation of enamine **3** with cyclopentanone and benzaldehyde regiospecifically gave the linear isomer pyrido[2,3-d]pyrimidin-4-one **12**.

The support for the linear structure for **12** was proved by the ^1H NMR spectrum, in particular the chemical shift for the H-5 proton and a singlet for the 9-NH proton.[20] The ^1H NMR spectrum of compound **12** contains four singlet signals at δ 3.31, 3.64, 4.51, and 9.49 ppm for 2-(N-CH_3), 5-H, and 9-NH, respectively. The 5-H and 9-NH protons are not coupled; this confirms the linear structure **12** and not the angular structure **13**. The signals at δ 3.10, 3.44 ppm for 6- and 8-CH_2 are doublets with $J = 16.0 \pm 0.2$ and 17.15 ± 0.2 Hz, whereas those for the 7-CH_2 at δ 2.12 resonated as a multiplet (see the IR and mass spectra in the Experimental section). The reaction may proceed via the attack of the active methylene group of the ketone on the carbonyl group of the aldehyde. Then, subsequent nucleophilic attack by the amino group of the uracil derivative on the carbonyl carbon of the α,β-unsaturated ketone intermediate, followed by cyclization and elimination of water, could furnish the linear structure. The alternative attack of the amino of the uracil derivative on the methylenic carbon of the α,β-unsaturated ketone followed by cyclization could lead to the angular structure. The latter case corresponds to the Skraup synthesis and Doebner–Miller synthesis of pyridines and quinolines. Ab initio calculations at the HF level with the basis set 6-31G^+(d, p) showed that compounds **12** and **13** are thermodynamically equivalent, which was inferred from their total energy. This might indicate that both isomers are in thermodynamic equilibrium. However, the HOMO-LUMO energy gap of compound **12** was greater than that of compound **13** (Table 5), which confirms that compound **12** is more thermodynamically stable than compound **13**. To understand the reaction kinetics and gain deep insights on the formation of compounds **12** versus **13**, the transition state for each compound was predicted, refined, and verified using PM3 parameters. Following the refinement and verification of both transition states, it was found that the total energy of the transition state of compound **12** is less than that of compound **13** by 4.206 kcal/mol (Table 5). These new and interesting findings confirm that the formation of compound **12** was thermodynamically (greater HOMO-LUMO gap)

Table 5. Calculated total energy and HOMO-LUMO gap using HF/6-31G^{+}(d, p) and total energy of the transition state using PM3 parameters for compounds **12** and **13**

Compound	Energy (RHF), Hartree	HOMO-LUMO energy gap (EV)	Energy of the transition state (kcal/mol)
12	−1005.867	9.575	145.074
13	−1005.867	8.846	149.280

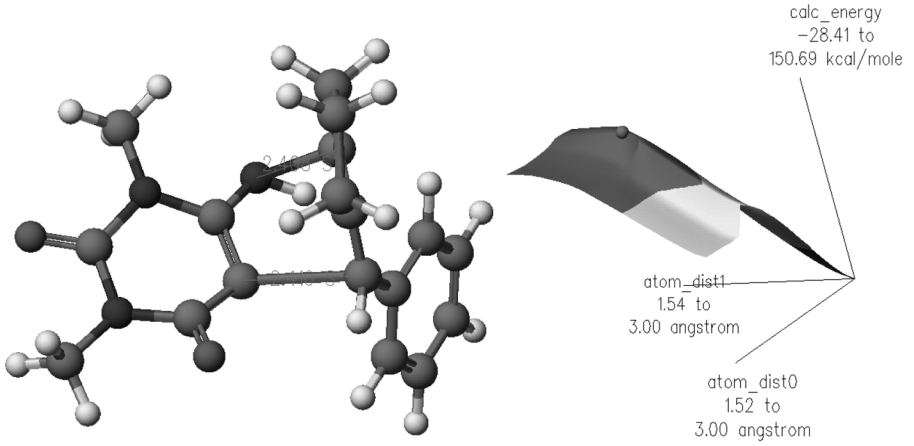
Note. Hartree = 627.5 kcal/mol.

and kinetically controlled. Figures 2 and 3 show the refined equilibrium molecular geometry of the transition state (Figs. 2a and 3a) and the potential energy surface of the optimized geometry of the transition state (Figs. 2b and 3b) of compounds **12** and **13**, respectively. The optimized geometry for the transition states of compounds **12** and **13** (Figs. 2a and 3a) show the bond distance at which bonds start to form (Figs. 2b and 3b), and the potential energy surface of the saddle point of compounds **12** and **13** (Figs. 2b and 3b) are shown with the ball cursor in the red band. Scheme 2 shows the potential enantiomers for compounds **12** and **13** and that the enantiomers do have the same energy.

The linear structure is in accordance with the reported results where the 5-H and 9-NH protons appeared at δ 4.00–6.00 and at δ 7.50–10.00 ppm, respectively.[21]

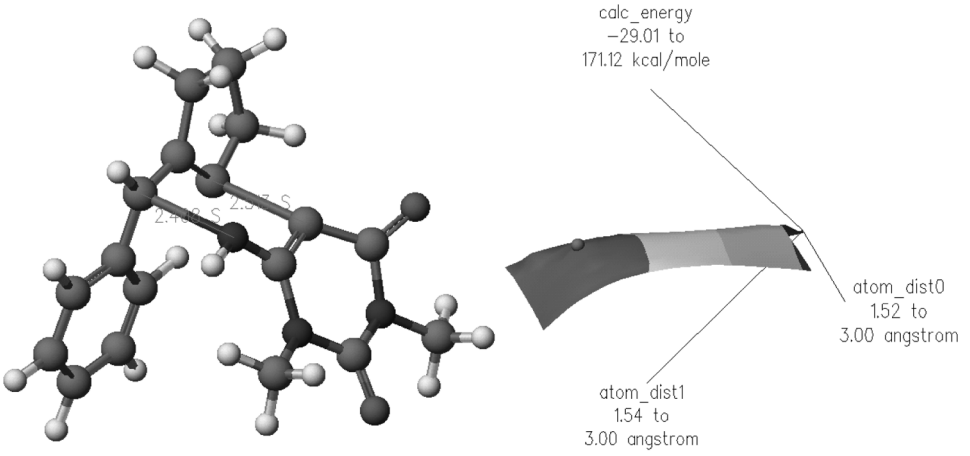
In addition, the use of the nuclear Overhauser effect (NOE) technique[22] and the assignment of the signals in the ^{1}H and ^{13}C NMR by the ^{1}H, ^{1}H COSY (correlation spectroscopy) technique and ^{1}H, ^{13}C shift correlation were reported for similar systems, which all supported the linear structure.[20,23,24]

Moreover, x-ray crystal studies and two-dimensional ^{1}H and ^{13}C NMR spectra of a product of a similar cyclocondensation reaction indicated the linear structure



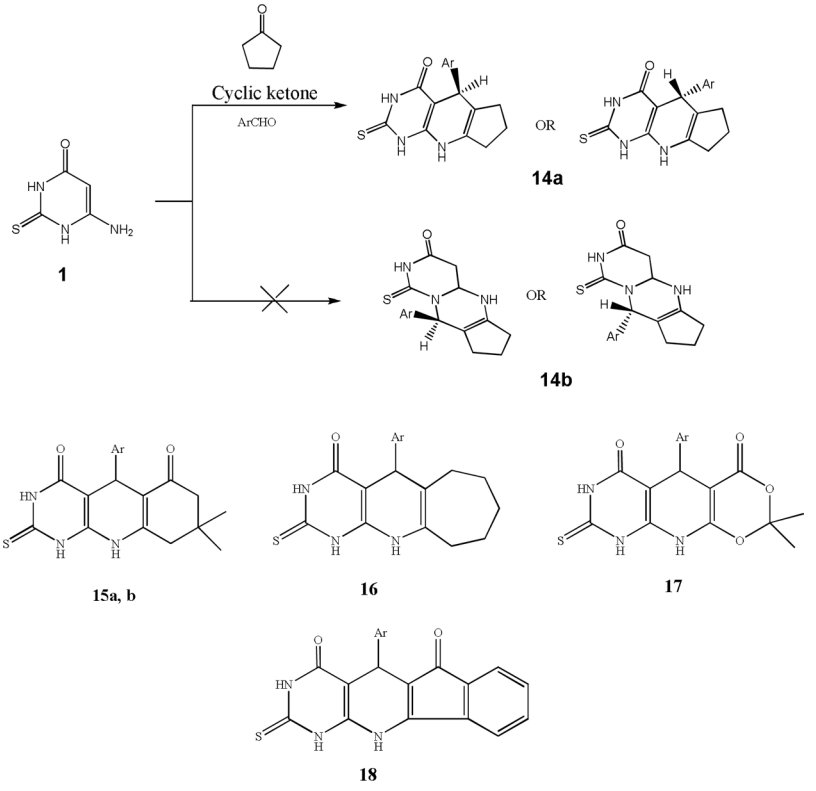
(a) (b)

Figure 2. (a) The optimized geometry of the transition state of compound **12** and (b) the potential energy surface showing the location of the transition state of compound **12**, indicated by the black cursor ball.



(a) (b)

Figure 3. (a) The optimized geometry of the transition state of compound **13** and (b) the potential energy surface showing the location of the transition state of compound **13**, indicated by the black cursor ball.



Scheme 3. Cyclocondensation of **1** with aromatic aldehydes and cyclic ketones to afford pyridopyrimidine derivatives **14a**, **16–18**, and pyrimido[4,5-b]quinoline analogs **15a–b**.

rather than angular product was formed.[25] This recent publication provides additional support for the linear structure.[26]

As we mentioned, there are two possibilities for ring closure of reaction of **1** with cyclopentanone and benzaldehyde derivatives to give compound **14a** (Ar = C_6H_5) (Scheme 3; Table 6). Structure of 9-phenyl-1-thioxo-1,2,6,7,8, 9-hexahydrocyclopenta[d]pyrimido[1,6-a]pyrimidin-3(5*H*)-one (**14b**) was ruled out based on the spectral data. In addition, ab initio calculations at the HF level with

Table 6. Synthesis of 1,4-dihydropyrido[2,3-d]thiopyrimidine derivatives (**14a, 14b, 15a, 15b, 16–18**)

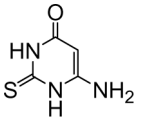
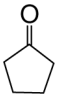
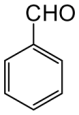
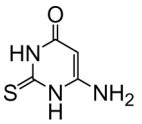
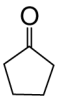
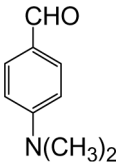
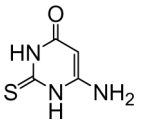
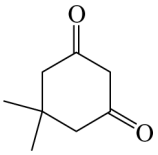
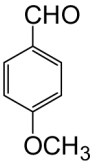
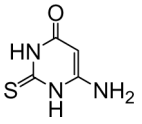
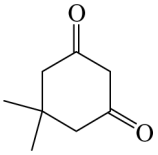
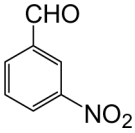
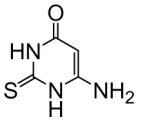
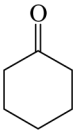
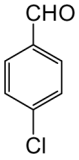
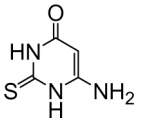
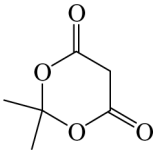
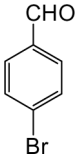
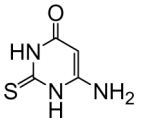
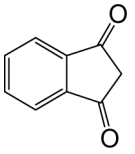
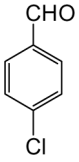
Entry	Substrate	Ketone	Aldehyde	Product	Ar	Yield (%)
9				**14a**	Ph	80
10				**14b**	C_6H_4-*N,N*-$(CH_3)_2$	76
11				**15a**	C_6H_4-OCH_3-*p*	81
12				**15b**	C_6H_4-NO_2-*m*	79
13				**16**	C_6H_4-Cl-*p*	69
14				**17**	C_6H_4-Br-*p*	64
15				**18**	C_6H_4-Cl-*p*	73

Table 7. Calculated total energy and HOMO-LUMO gap using HF/6-31G$^+$(d, p) for compounds **14a** and **14b**

Compound	Energy (RHF), Hartree	HOMO-LUMO energy gap, (EV)
14a	−1250.441	9.630
14b	−1250.423	9.687

the basis set 6-31G$^+$(d, p) showed clearly that the formation of compound **14a** is thermodynamically more favorable than that of compound **14b**, which was inferred from the lower total energy of compound **14a**. However, the HOMO-LUMO of compounds **14b** was greater than that of compound **14a**, which is a known problem with sulfur-containing compounds (Table 7).

The ^{1}H NMR spectrum of compound **14a** showed signals for the 6- and the 8-CH_2 as doublet of doublets with $J = 16.0 \pm 0.2$ and 17.5 ± 0.2 Hz, in addition to two sharp singlets at δ 5.37 and δ 7.95 ppm for 5-H and 9-NH, respectively, a multiplet at δ 7.07–7.24 for aromatic protons, and NH signals at δ 11.70 and 11.91 ppm corresponding to the 1,3-NH protons.

Structure **14b** should show three singlet signals at δ 6.81, 8.01, and 13.50 ppm corresponding to C-H and two NH protons, which is not the case. Furthermore, the mass spectrum of compound **14a** has a molecular ion peak at m/z 296 ($M^+ - 1$, 18.3%), which confirms that the product should be the structure of compound **14a** not **14b**.

Similarly, 4-dihydropyrido[4,5-d]thiopyrimidine **14c** was synthesized by the reaction of 6-aminothiouracil (**1**) with cyclopentanone and *p*-(*N,N*-dimethylamino) benzaldehyde in boiling DMF. The mass spectrum of compound **14c** showed a molecular ion peak at m/z 321 (M^+-CH_3, $2H_2$, 77%) corresponding to the loss of CH_3 fragment plus H_2 (cf. Experimental section).

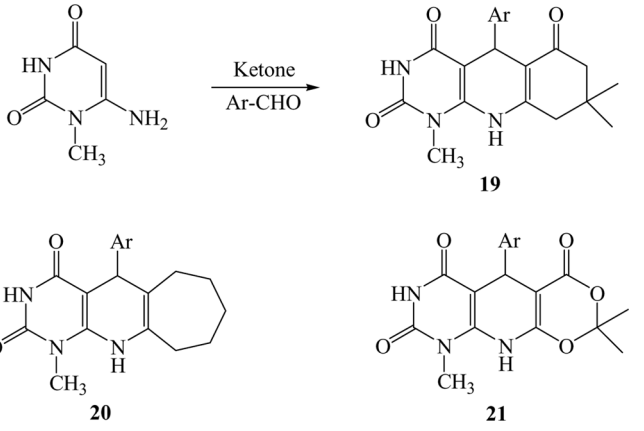
On the other hand, 1,4-dihydropyrido[4,5-d]thiopyrimidines **15a, b** were obtained by using dimedone instead of cyclopentanone. Moreover, the reaction of **1** with cycloheptanone, Meldrum's acid, and indandione in the presence of benzaldehyde derivatives afforded the formation of pyrido[4,5-d]thiopyrimidine derivatives **16**–**18**.

Analogously, 6-amino-1-methyluracil (**2**) underwent a similar reaction with dimidone and benzaldehyde derivatives and gave the corresponding pyrido[4,5-d] pyrimidines **19a, b** (Scheme 4; Table 8).

On the other hand, **2** reacted with cycloheptanone in the presence of *p*-chlorobenzaldehyde to give the corresponding pyrido[4,5-d]pyrimidine **20**, whereas the reaction of **2** with meldrum's acid and *p*-bromobenzaldehyde afforded the pyrido[4,5-d]pyrimidine **21**.

EXPERIMENTAL

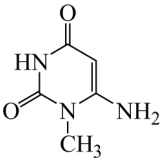
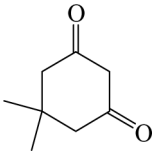
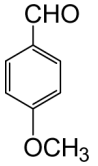
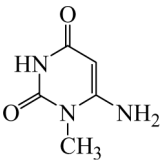
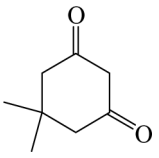
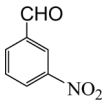
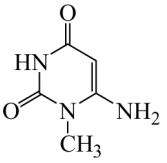
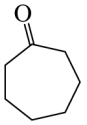
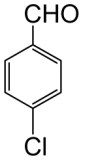
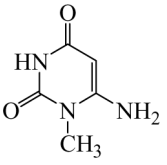
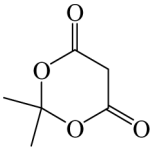
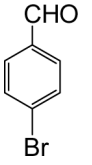
Melting points were measured with a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded for KBr discs on a Mattson 5000 Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AC 300 (300-MHz) instrument in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) as solvent,



Scheme 4. Synthesis of pyrimido[4,5-b]quinoline derivative **19** and pyridopyrimidine derivatives **20–21**.

using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as δ ppm. Mass spectra were determined on a Finnigan COS 500 instrument (70 ev). All reactions were followed by thin-layer chromatography (TLC; silica gel, aluminum sheets 60 F_{254}, Merck). Elemental analyses (C, H, and N) were carried

Table 8. Synthesis of pyrimido[4,5-b]quinoline derivatives (**19–21**)

Entry	Substrate	Ketone	Aldehyde	Product	Ar	Yield (%)
16				**19a**	C_6H_4-OCH_3-*p*	68
17				**19b**	C_6H_4-NO_2-*m*	59
18				**20**	C_6H_4-Cl-*p*	77
19				**21**	C_6H_4-Br-*p*	82

out at the Microanalytical Center of Cairo University, Giza, Egypt, and the results were found to be in good agreement (±0.3%) with the calculated values.

Molecular Modeling

All molecular geometries were fully optimized using either Gaussian 03 W, DMol3 (Wallingford, CT) implemented in Material Studio 4.2 (Accelrys, CA) or CAChe 12.12.33 (Fujitsu America Inc., Beaverton, OR). In the case of Gaussian, ab initio calculations were performed using HF/6-31G*(d, p),[27] and in the case of DMol3, BLYP energy functional with the basis set DNP were performed. In the case of transition-state calculations, harmonic vibration frequencies were calculated using PM3 parameters implemented in CAChe for all stationary points to verify that for energy minima all frequencies are real but for the transition state there is only one imaginary frequency.

General Procedure for the Preparation of Pyrido[2,3-d]pyrimidine and Pyrimido[4,5-b]quinoline

A mixture of 6-aminothiouracil (**1**) (1.43 g, 10 mmol) or 6-amino-1-methyluracil (**2**) (1.41 g, 10 mmol) or 6-amino-1,3-dimethyluracil (**3**) (1.55 g, 10 mmol) with 1,3-diketone (10 mmol) and 10 mmol of the appropriate aldehyde in DMF (30 cm^3) was refluxed for 5 h, cooled, and poured into ice water. The solid that formed was filtered off and crystallized from mixed solvent, ethanol/DMF (1:2).

Selected Data

6-Acetyl-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-2-thiooxo-2,3,5,8-tetrahydropyrido[2,3-d]pyrimidin-4-(1*H*)-one (4). Pale yellow crystal; yield 75%; mp 225 °C; IR (KBr) ν_{max} cm^{-1}: 3374 (OH), 3316, 3214, and 3168 (NH), 1700 (α,β-unsaturated ketone), 1660 (C=O) and 1597 (C=C); ^{1}H NMR (DMSO-d_6) δ ppm: 2.73 (s, 3H, CH_3), 2.88 (s, 3H, $COCH_3$), 3.65 (s, 3H, OCH_3), 5.27 (s, 1H, C_5-H), 6.44–6.79 (m, 3H, Ar-H), 7.95 (s, 1H, OH), 8.61 (s, 1H, 8-NH), 11.75 (s, 1H, NH) and 11.97 (s, 1H, NH); MS: *m/z* (%), 358 ($M^+ - 1$, 45%), 221 (73%), 220 (23), 204 (17%), 203 (22%), 202 (83%), 188 (34%), 187 (33%), 174 (22%), 173 (39%), 159 (33%), 158 (22%), 130 (66%), 105 (50%), 91 (45%), 81 (56%), 78 (100%), 77 (10%), 76 (33%), 69 (89%). Anal. calc. for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.57; H, 4.52; N, 11.56.

6-Acetyl-5-(2-nitrophenyl)-2-thioxo-7-trifluoromethyl-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-d]pyrimidin-4-one (6). Orange crystal; yield 70%; mp 223 °C; IR (KBr) ν_{max} cm^{-1}: 3350–3187 (NH), 1715–1699 (ketonic and amidic carbonyl), 1371 (C=S) and 1530, 1350 (NO_2); ^{1}H NMR (DMSO-d_6) δ ppm: 2.88 (s, 3H, $COCH_3$), 5.87 (s, 1H, C_5-H), 7.35–7.65 (m, 4H, Ar-H), 8.09 (s, 1H, 8-NH) and 12.02 (b, 2H, 2NH); MS: *m/z* (%),410 ($M^+ - 2$, 15%), 409 (37%), 408 (100%), 407 (72%), 406 (43%), 392 (13%), 387 (27%), 365 (25%), 277 (15%), 236 (15%), 205 (20%), 195 (15%), 205 (20%), 196 (15%), 143 (13%), 128 (10%). Anal. calc. for $C_{16}H_{11}F_3N_4O_4S$: C, 46.60; H, 2.69; N, 13.59. Found: C, 46.42; H, 2.32; N, 13.14.

6-Acetyl-5-(2-hydroxyphenyl)-2-thioxo-7-trifluoromethyl-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-d]pyrimidin-4-one (7). Yellow powder; yield 80%; mp >300 °C; IR (KBr) ν_{max} cm^{-1}: 3377–3190 (NH), 1700–1630 (2C=O) and 1355 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 2.88 (s, 3H, $COCH_3$), 5.87 (s, 1H, C_5-H), 6.65 (b, 1H, OH), 7.35–7.82 (m, 4H, Ar-H), 8.20 (s, 1H, NH), 11.65 (s, 1H, NH) and 12.21 (s, 1H, NH). Anal. calc. for $C_{16}H_{12}F_3N_3O_3S$: C, 50.13; H, 3.16; N, 10.96. Found: C, 49.85; H, 2.87; N, 10.64.

6-Acetyl-5-(4-dimethylaminophenyl)-2-thioxo-7-trifluoromethyl-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-d]pyrimidin-4-one (8). Pale brown powder; yield 67%; mp >300 °C; IR (KBr) ν_{max} cm^{-1}: 3377–3190 (NH), 1700–1630 (2C=O) and 1355 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 2.73 [s, 6H, $N(CH_3)_2$], 2.88 (s, 3H, $COCH_3$), 4.88 (s, 1H, C_5-H), 6.65–7.17 (m, 4H, Ar-H), 7.94 (s, 1H, 8-NH), 12.14 (s, 1H, NH) and 13.16 (s, 1H, NH). Anal. calc. for $C_{18}H_{17}F_3N_4O_2S$: C, 52.68; H, 4.18; N, 13.65. Found: C, 52.38; H, 3.84; N, 13.36.

6-Benzoyl-5-(4-nitrophenyl)-7-phenyl-2-thioxo-2,3,5,8-tetrahydro-1*H*-pyrido[2,3-d]pyrimidin-4-one (9). Yellow powder; yield 73%; mp 83 °C; IR (KBr) ν_{max} cm^{-1}: 3450–3195 (NH), 1720–1700 (2C=O) 1530, 1350 (NO_2) and 1300 (C=S); MS: m/z (%): 479 ($M^+ - 3$, 14%), 478 (17%), 375 (11%), 374 (15%), 360 (23%), 359 (84%), 357 (25%), 282 (44%), 214 (20%), 172 (14%), 165 (17%), 140 (21%), 136 (26%), 121 (58%), 120 (100%), 79 (25%), 78 (40%), 77 (80%), 76 (11%). Anal. calc. for $C_{26}H_{18}N_4O_4S$: C, 64.72; H, 3.76; N, 11.61. Found: C, 64.93; H, 3.63; N, 11.82.

6-Acetyl-5-(2-hydroxy-phenyl)-1,3-dimethyl-7-trifluoromethyl-5,8-dihydro-1*H*-pyrido[2,3-d]pyrimidine-2,4-dione (10). White needles; yield 78%; mp 255 °C; IR (KBr) ν_{max} cm^{-1}: 3449 (OH), 3337 (NH), 1700 (ketonic carbonyl), and 1630 (amidic carbonyl); ^{1}H NMR (DMSO-d_6) δ ppm: 2.91 (s, 3H, $COCH_3$), 3.35, 3.46 [s, s, 6H, $2N(CH_3)$], 5.06 (s, 1H, C_5-H), 6.94 (s, 1H, OH), 7.07–7.21 (m, 4H, Ar-H), and unobserved NH proton; MS: m/z (%): 376 (M^+-F, 35%), 338 (23%), 308 (12%), 250 (48%), 237 (19%), 214 (20%), 173 (15%), 172 (100%), 171 (20%), 168 (15%), 156 (18%), 143 (16%), 127 (5%), 119 (11%), 111 (10%), 108 (28%), 98 (10%), 84 (11%), 76 (12%), 65 (26%). Anal. calc. for $C_{18}H_{16}F_3N_3O_4$: C, 54.69; H, 4.08; N, 10.63. Found: C, 54.51; H, 3.92; N, 10.45.

6-Acetyl-1,3-dimethyl-5-(2-nitrophenyl)-7-phenyl-5,8-dihydro-1*H*-pyrido[2,3-d]pyrimidine-2,4-dione (11). Brown crystals; yield 71%; mp 182 °C; IR (KBr) ν_{max} cm^{-1}: 3400 (NH), 1707 (ketonic carbonyl), 1614 (amidic carbonyl), and 1568, 1361 (symmetric and asymmetric nitro group); ^{1}H NMR (DMSO-d_6) δ ppm: 2.77 (s, 3H, $COCH_3$), 3.35, 3.70 [s, s, 6H, $2N(CH_3)$], 5.12 (s, 1H, C_5-H), 7.55–8.20 (m, 4H, Ar-H) and 9.08 (s, 1H, NH); MS m/z (%): 386 (M^+-NO_2, 100%), 343 (31%), 342 (69%), 308 (12%), 242 (14%), 212 (15%), 157 (14%), 143 (8%), 128 (10%), 127 (5%), 115 (8%), 105 (30%), 101 (10%), 90 (7%), 88 (8%), 77 (23%), 76 (10%), 75 (13%), 64 (11%). Anal. calc. for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.59; H, 4.37; N, 12.61.

1,3-Dimethyl-5-phenyl-5,6,7,8,9-pentahydro-4*H*-cyclopenta[5,6]pyrido[2,3-d]pyrimidine-2,4-dione (12). Yellow powder; yield 69%; mp 150 °C; IR (KBr) ν_{max} cm^{-1}: 3421 (NH), 1700, 1660 (2C=O) and 1586 (C=C); ^{1}H NMR

(DMSO-d_6) δ ppm: 2.12, 3.10, 3.44 (m, 6H, $3CH_2$), 3.31, 3.64 [s, s, 6H, $2N(CH_3)$], 4.51 (s, 1H, C_5-H), 7.52–7.84 (m, 5H, Ar-H), and 9.49 (s, 1H, NH); MS *m/z* (%): 281 ($M^+ - CH_2 = CH_2$ or $M^+ - CO$, 41.7%), 261 (68%), 259 (88%), 247 (100%), 223 (75%), 218 (48%), 204 (52%), 196 (17%), 194 (77%), 177 (19%), 167 (54%), 166 (27%), 164 (38%), 155 (52%), 146 (85%), 140 (20%), 133 (19%), 132 (43%), 130 (27%), 126 (14%), 119 (25%), 109 (13%), 97 (8%), 84 (12%), 80 (22%), 71 (35%), 69 (45%), 55 (17%), 54 (24%). Anal. calc. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.57; H, 5.84; N, 13.29.

5-Phenyl-2-thioxo-1,2,3,5,6,7,8,9-octahydro-4*H*-cyclopenta[5,6]pyrido [2,3-d]pyrimidin-4-one (14a). Yellow powder; yield 80%; mp 194 °C; IR (KBr) ν_{max} cm^{-1}: 3407, 3186 (NH), 1619 (C=O), 1550 (C=C) and 1387 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12, 2.74, 2.89 (m, 6H, $3CH_2$), 5.37 (s, 1H, C_5-H), 7.07–7.24 (m, 5H, Ar-H), 7.95 (s, 1H, 9-NH), 11.70 (s, 1H, NH), 11.91 (s, 1H, NH); MS: *m/z* (%): 296 ($M^+ - 1$, 18.3%), 295 (100%), 294 (88%), 171 (10%), 144 (9%), 143 (13%), 125 (10%), 105 (11%), 76 (8%), 75 (10%), 68 (10%), 67 (5%), 64 (9%), 51 (15%). Anal. calc. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.43; H, 4.91; N, 13.97.

5-(4-Dimethylaminophenyl)-2-thioxo-1,2,3,5,6,7,8,9-octahydro-4*H*-cyclopenta[5,6]pyrido[2,3-d]pyrimidin-4-one (14b). Red powder; yield 76%; mp 240 °C; IR (KBr) ν_{max} cm^{-1}: 3402, 3146 (NH), 1659 (C=O), 1590 (C=C) and 1365 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12 (m, 2H, CH_2), 2.83 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 2.98, 3.04 [s, s, 6H, $2N(CH_3)$], 5.35 (s, 1H, C_5-H), 6.80–7.86 (d.d, 4H, Ar-H), 9.85 (s, 1H, 9-NH) and 12.01–12.80 (br, 2H, 2NH); MS: *m/z* (%): 321 ($M^+ - CH_3$, $2H_2$, 77.0%), 305 (38%), 294 (33%), 250 (32%), 220 (14%), 215 (48%), 214 (35%), 190 (54%), 184 (24%), 172 (54%), 167 (15%), 159 (34%), 150 (77%), 149 (100%), 148 (74%), 144 (72%), 133 (26%), 130 (24%), 108 (31%), 105 (52%), 103 (15%), 94 (27%), 92 (23%), 79 (29%), 77 (32%), 65 (21%), 64 (14%), 59 (15%). Anal. calc. for $C_{18}H_{20}N_4OS$: C, 63.50; H, 5.92; N, 16.46. Found: C, 63.76; H, 6.14; N, 16.73.

5-(4-Methoxyphenyl)-8,8-dimethyl-2-thioxo-2,3,7,8,9,10-hexahydro-pyrimido[4,5-b]quinolin-4,6-(1*H*,5*H*)-dione (15a). White crystal; yield 81%; mp 296 °C; IR (KBr) ν_{max} cm^{-1}: 3402, 3146 (NH), 1700, 1643 (2C=O), 1612 (C=C) and 1378 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 0.90 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99 (d, 2H, CH_2), 2.17 (d, 2H, CH_2), 3.66 (s, 3H, OCH_3), 4.69 (s, 1H, C_5-H), 6.75–7.10 (d, d, 4H, Ar-H), 7.94 (s, 1H, NH), 8.53 (s, 1H, NH), 12.11 (s, 1H, NH). Anal. calc. for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.96. Found: C, 62.75; H, 5.83; N, 11.24.

5-(2-Nitrophenyl)-8,8-dimethyl-2-thioxo-2,3,7,8,9,10-hexahydro-pyrimido [4,5-b]quinolin-4,6-(1*H*,5*H*)-dione (15b). Buff sheets; yield 79%; mp 182 °C; IR (KBr) ν_{max} cm^{-1}: 3402, 3146 (NH), 1700, 1643 (2C=O), 1612 (C=C), 1530, 1350 (NO_2) and 1378 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 0.90 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99 (d, 2H, CH_2), 2.17 (d, 2H, CH_2), 4.69 (s, 1H, C_5-H), 7.07–7.20 (m, 4H, Ar-H), 8.59 (s, 1H, NH), 9.18 (s, 1H, NH), 11.53 (s, 1H, NH). Anal. calc. for $C_{19}H_{18}N_4O_4S$: C, 57.27; H, 4.55; N, 14.06. Found: C, 57.00; H, 4.22; N, 13.77.

5-(4-Chlorophenyl)-2-thioxo-1,2,3,5,6,7,8,9,10,11-decahydro-4*H*-cyclopenta [5,6]pyrido[2,3-d]pyrimidin-4-one (16). Yellow crystal; yield 69%; mp 317–319 °C; IR (KBr) ν_{max} cm^{-1}: 3339, 3151 (NH), 1650 (C=O), 1542 (C=C) and 1378 (C=S); MS: *m/z* (%): 359 (M^+, 26%), 315 (15%), 266 (10%), 210 (13%), 143 (65%), 138 (12%), 137 (15%), 127 (10%), 115 (24%), 113 (17%), 101 (32%), 98 (11%), 89 (20%), 87 (30%), 84 (13%), 77 (21%), 76 (17%), 75 (53%), 74 (26%), 70 (15%), 68 (100%). Anal. calc. for $C_{18}H_{18}ClN_3OS$: C, 60.07; H, 5.04; N, 11.68. Found: C, 59.87; H, 4.71; N, 11.40.

5-(4-Bromophenyl)-2,2-dimethyl-8-thioxo-5,8,9,10-tetrahydro-4*H*-[1,3] dioxino[5′,4′:5,6]pyrido[2,3-d]pyrimidin-4,6-(7*H*)-dione (17). Yellow crystal; yield 64%; mp 309–311 °C; IR (KBr) ν_{max} cm^{-1}: 3350, 3230 (NH), 1690, 1650 (2C=O), 1600 (C=C) and 1320 (C=S); ^{1}H NMR (DMSO-d_6) δ ppm: 1.57 (s, 6H, $2CH_3$), 5.29 (s, 1H, C_5-H), 7.02–7.42 (d. d, 4H, Ar-H), 8.20 (s, 1H, 9-NH), 11.80 (s, 1H, NH), 12.02 (s, 1H, NH). Anal. calc. for $C_{17}H_{14}BrN_3O_4S$: C, 46.80; H, 3.23; N, 9.63. Found: C, 46.49; H, 2.91; N, 9.33.

5-(4-Chlorophenyl)-2-thioxo-1,2,3,5,6,11-hexahydro-indino[5,6]pyrido [2,3-d]pyrimidin-4,6-dione (18). Colorless crystal; yield 73%; mp > 300 °C; IR (KBr) ν_{max} cm^{-1}: 3350, 3230 (NH), 1710, 1680 (2C=O); ^{1}H NMR (DMSO-d_6) δ ppm; 4.05 (s, 1H, C_5-H), 7.20–7.45 (d, d, 4H, Ar-H), 7.61–7.89 (m, 4H, Ar-H), 12.50 (s, 1H, NH), 12.50 (s, 1H, NH), 13.51 (s, 1H, NH). Anal. calc. for $C_{20}H_{12}ClN_3O_2S$: C, 60.99; H, 3.07; N, 10.67. Found: C, 60.73; H, 2.75; N, 10.39.

5-(4-Methoxyphenyl)-1,8,8-trimethyl-3,7,8,9,10-pentahydro-pyrimido [4,5-b]quinolin-2,4,6-(5*H*)-trione (19a). White sheets; yield 68%; mp 327 °C; IR (KBr) ν_{max} cm^{-1}: 3275, 3216 (NH), 2960 (CH_3), 1720, 1650, 1639 (3C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 0.88 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.05 (d, 2H, CH_2), 2.23 (d, 2H, CH_2), 3.66 (s, 3H, N-CH_3), 4.05 (s, 3H, O-CH_3), 4.77 (s, 1H, C_5-H), 6.71–7.11 (d, d, 4H, Ar-H), 8.90 (s, 1H, 10-NH), 10.92 (s, 1H, NH). Anal. calc. for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 65.84; H, 5.73; N, 10.72.

5-(3-Nitrophenyl)-1,8,8-trimethyl-3,7,8,9,10-pentahydro-pyrimido[4,5-b]quinolin-2,4,6-(5*H*)-trione (19b). Faint brown crystal; yield 59%; mp 296 °C; IR (KBr) ν_{max} cm^{-1}: 3275, 3219 (NH), 2963 (CH_3), 1710, 1665, 1634 (3C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 0.88 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.05 (d, 2H, CH_2), 2.23 (d, 2H, CH_2), 3.66 (s, 3H, N-CH_3), 4.40 (s, 1H, C_5-H), 7.07–7.24 (m, 4H, Ar-H), 9.61 (s, 1H, 10-NH), 11.62 (s, 1H, NH). Anal. calc. for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.42; H, 4.98; N, 13.96.

5-(4-Chlorophenyl)-1-methyl-3,5,6,7,8,9,10,11-octahydro-4*H*-cyclo-hepta [5,6]pyrido[2,3-d]pyrimidin-2,4-dione (20). Brown crystal; yield 77%; mp 268 °C; IR (KBr) ν_{max} cm^{-1}: 3411, 3197 (NH), 2929 (CH_3), 1710, 1675 (2C=O); MS: *m/z* (%): 355 ($M^+ - 2$, 45%), 326 (42%), 308 (31%), 264 (23%), 220 (23%), 218 (23%), 167 (20%), 163 (43%), 152 (23%), 140 (27%), 128 (23%), 117 (20%), 94 (70%), 79 (30%), 75 (93%), 74 (39%), 67 (50%), 63 (53%), 62 (50%), 57 (39%), 55 (54%). Anal. calc. for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.65; H, 5.30; N, 11.46.

5-(4-Bromophenyl)-2,2,9-trimethyl-5,7,10-trihydro-4*H*-[1,3]dioxino-[5′,4′: 5,6]pyrido[2,3-d]pyrimidin-4,6,8-trione (21). Brown crystal; yield 82%; mp

280 °C; IR (KBr) ν_{max} cm^{-1}: 3275, 3220 (NH), 2965 (CH_3), 1720, 1650, 1639 (3C=O); ^1H NMR (DMSO-d_6) δ ppm: 1.62 (s, 6H, $2CH_3$), 3.86 (s, 3H, N-CH_3), 5.29 (s, 1H, C_5-H), 7.02–7.40 (d, d, 4H, Ar-H), 9.29 (s, 1H, NH), 11.77 (s, 1H, 10-NH). Anal. calc. for $C_{18}H_{16}BrN_3O_5$: C, 49.56; H, 3.71; N, 9.68. Found: C, 49.56; H, 3.63; N, 9.66.

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