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Hetero Diels–Alder reaction: a novel strategy to regioselective synthesis of pyrimido[4,5-*d*]pyrimidine analogues from Biginelli derivative

Pratibha Sharma,* Ashok Kumar, Nilesh Rane and Vamsi Gurram

School of Chemical Sciences, Devi Ahilya University, Indore Takshila Campus, Khandwa Road, Indore, MP 452 017, India

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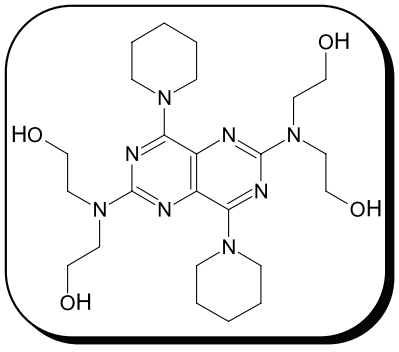
Abstract—A number of potent pyrimido[4,5-*d*]pyrimidine analogues have been efficiently synthesized by hetero Diels–Alder cycloaddition of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester, a Biginelli compound with *N*-arylidine-*N*′-methylformamidines and *N*-arylidine guanidine in dry toluene. Structures of the newly obtained cycloadducts were established on the basis of elemental and spectral (IR, NMR and Mass) data. The molecular mechanism of the observed cycloaddition reaction has been investigated theoretically by means of PM3 semiempirical method. Transition state structure determinations and activation energy calculations have shown the preference for the *endo* approach over the *exo* approach of dienophile towards the diene fragments used, which is consistent with the experimental results. The studied cycloadditions proceed via an asynchronous concerted mechanism. It was demonstrated that FMO theory could reasonably predict the relative reactivities between dienes as well as indicating that these reactions belong to normal Diels–Alder type cycloadditions.

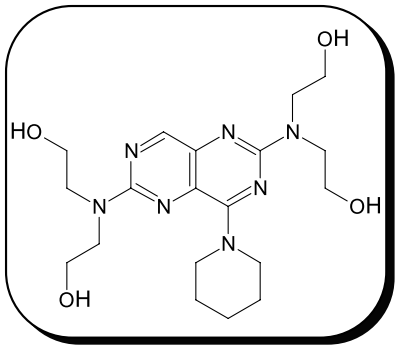
1. Introduction

In recent years, the hetero Diels–Alder (HDA) reaction has emerged as an elegant protocol for the construction of six membered heterocyclic systems.[1] HDA's ability to generate four new contiguous stereogenic centers in a single laboratory operation, with the regio- and stereo-chemical outcomes being predicted using orbital symmetry considerations enhances its synthetic utility. Moreover, an increasingly growing number of heterodienes and heterodienophiles broaden the scope of HDA reactions as a mainstay of many heterocycle and natural product syntheses.[2]

Among them, pyrimido[4,5-*d*]pyrimidine, a condensed heterocycle, represents an attractive target due to the interesting pharmacological activities of these molecules as regards the modulation of antitumor drug acitivity,[3]



Dipyridamole (RA-8)



Mopidamole (RA233)

Figure 1. Prototype of pyrimido[4,5-*d*]pyrimidine and its derivative.

Keywords: Hetero Diels–Alder cycloadditions; Pyrimido[4,5-*d*]pyrimidines; Biginelli compound; Dienophile; Semiempirical; PM3.
* Corresponding author. Tel.: +91 731 2460208; fax: +91 731 2470372; e-mail: drpratibhasharma@yahoo.com

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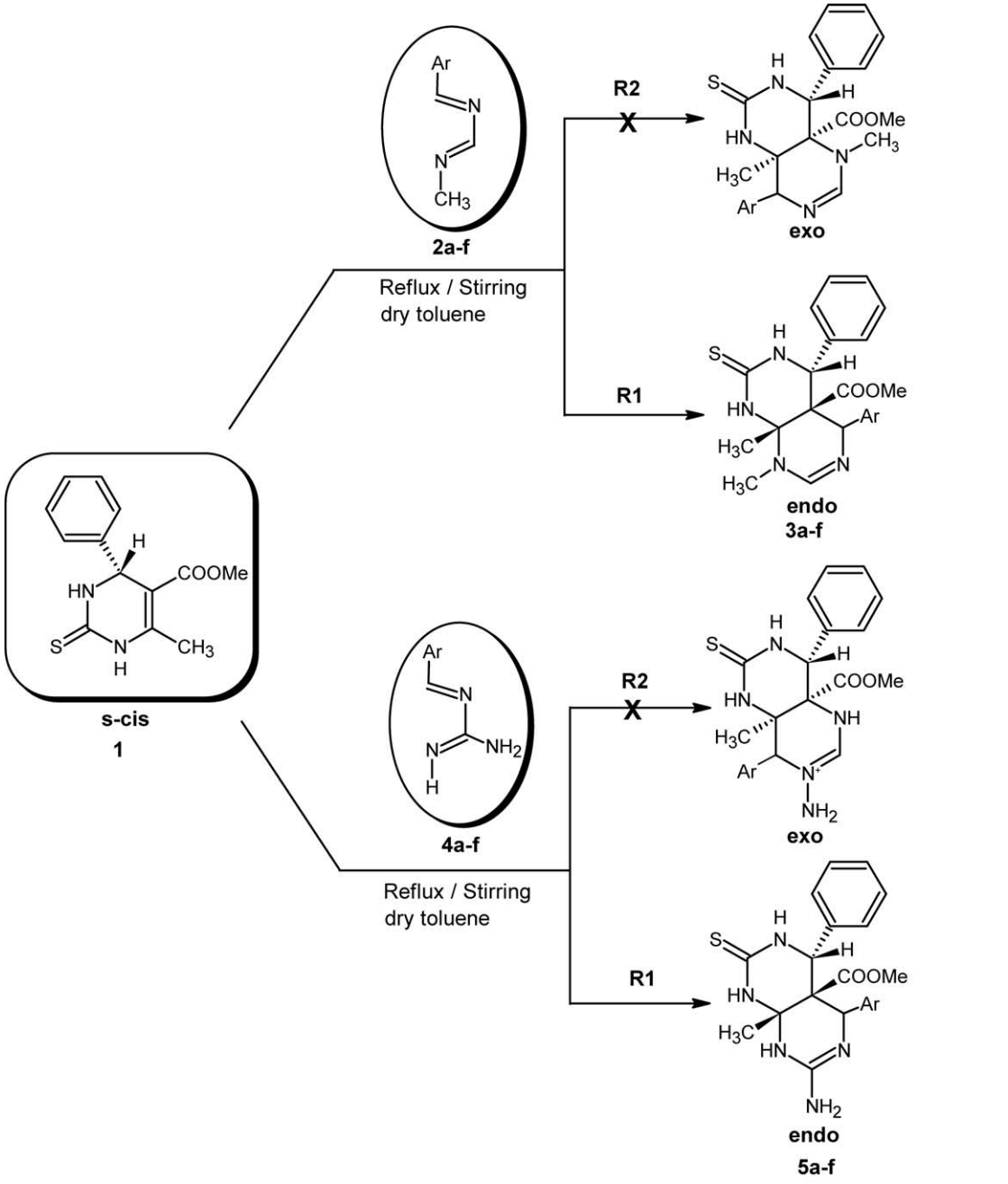
antioxidant (lipid peroxidation inhibitors),[4] antiviral,[5] and potent inhibitory action on the tyrosine kinase domain of epidermal growth factor receptor,[6] 5-phosphoribosyl-1-pyrophosphate synthetase[7] and dihydrofolate reductase.[8] Again, pyrimido[4,5-*d*]pyrimidine prototype dipyridamole (RA-8) and its derivative mopidamole (RA-233) (Fig. 1) are clinically approved effective cardiovascular[9] and anti-neoplastic agents.[10] Thus, the efficient and novel synthesis of such compounds is of prime interest and represents a highly pursued target.

Buoyed from the aforementioned information and in continuation of our previous work on versatile syntheses of heterocycles,[11–15] we herein report for the first time a novel and expeditious strategy to prepare a number of potent pyrimido[4,5-*d*]pyrimidine analogues based on the $[\pi 4_s + \pi 2_s]$ cycloaddition reaction, considering the 5,6 double bond of the Biginelli compound as a dienophile in a one pot synthesis. In addition, the transition state energy of conformers responsible for producing the selective stereo-isomers is also discussed.



2 & 4	a	b	c	d	e	f
Ar	C_6H_4	4-ClC_6H_4	4-OHC_6H_4	4-$OCH_3C_6H_4$	4-$C_2H_5C_6H_4$	4-$CH_3C_6H_4$

Scheme 1. Synthetic route for pyrimido[4,5-*d*]pyrimidine derivatives.

Table 1. Kinetic results of [4+2]cycloaddtions of dienophile (**1**) with dienes

Entry	Diene[a]	Reaction conditions	Time to completion[b] (h)	Yield[c] (%)
1	**2a**	Reflux	15	72
2	**2b**	Reflux	10	76
3	**2c**	Stirring/RT	6	79
4	**2d**	Stirring/RT	4	82
5	**2e**	Reflux	19	73
6	**2f**	Reflux	9	80
7	**4a**	Reflux	17	70
8	**4b**	Reflux	11	74
9	**4c**	Stirring/RT	8	77
10	**4d**	Stirring/RT	7	80
11	**4e**	Reflux	20	71
12	**4f**	Reflux	10	78

[a] 2 equiv of diene.
[b] Monitored by TLC/HPLC.
[c] Isolated yield.

2. Results and discussion

2.1. Synthesis

The most promising methods for the construction of pyrimido[4,5-*d*] pyrimidine nucleus include multistep syntheses, starting from 1,3-disubstituted-5-cyanouracils[16] or from polymer bound 2-(alkylsulfanyl)-4-amino-pyrimidine-5-carbonitrile.[17] However, these approaches involve relatively long synthetic pathways or the use of stoichiometric amounts of expensive resin as a polymer support. Our synthetic strategy, utilizing 4-phenyl-tetrahydropyrimidine-5-carboxylate derivative with substituted methyl formamidine and guanidine affords an unprecedented and facile one-pot synthesis of pyrimido[4,5-*d*]pyrimidine analogues in good to excellent yields (Scheme 1).

The 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (**1**) herein considered as dienophile in our synthetic plan, was readily obtained by Biginelli reaction of benzaldehyde, methyl acetoacetate and

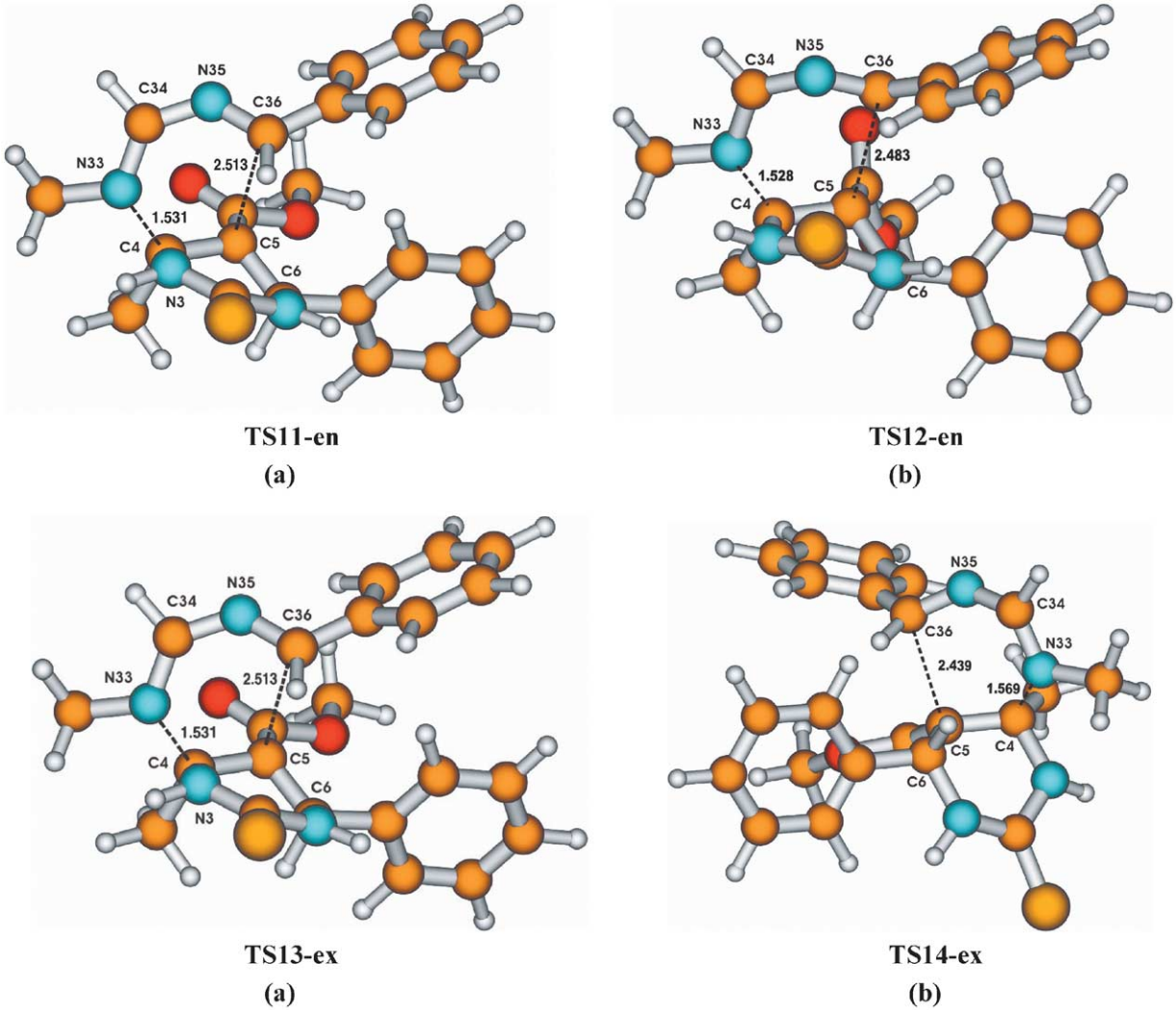


Figure 2. Transition state structures corresponding to regioisomer **1** for the [4+2]cycloaddition reaction between **1** and **2a**. (a) *trans*-approach; (b) *cis*-approach.

thiourea in refluxing ethanol. The reaction proceeds more efficiently when carried out using microwave irradiation. *N*-arylidine-*N*′-methylformamidines (**2a–f**) and *N*-arylidine guanidine (**4a–f**) were used as the diene component in the course of the reaction, which in turn were efficiently obtained from Schiff base condensation of appropriate aldehydes with *N*-methyl formamidine and guanidine, respectively. The hetero Diels–Alder reaction was carried out by refluxing/stirring these dienes (**2a–f**, **4a–f**) with dienophile (**1**) in a 2:1 molar ratio in anhydrous toluene for the required time (Table 1) in order to obtain the cycloadducts (**3a–f**, **5a–f**) bearing different substituents in 70–82% yields.

In summary, the pyrimidine nucleus, fused to the tetrahydropyrimidine ring was constructed by cycloaddition of the C–C fragment, derived from the Biginelli compound with C–N–C–N fragment of methyl formamidine and/or guanidine derivatives.

2.2. Computational studies

To unravel the understanding of mechanistic details of these cycloaddtions, we have performed the systematic quantum chemical investigations on representative HDA reactions between dienophile (**1**) and dienes (**2a** and **4a**). The SCF calculations at RHF level using PM3 semiempirical method[18] as incorporated in MOPAC 6.0 package[19] were employed.

An exhaustive exploration of the potential energy surfaces (PESs) for [4+2] cycloadditions under consideration furnished the relevant stationary points for reactants, transition state structures (TSs), and cycloadducts. Further, full geometry optimization was carried out by eigen-value following routine[20] using PM3 Hamiltonian. Finally, the nature of each stationary point was determined by diagonalizing the Hessian matrix to determine the number of imaginary frequencies (one for local minima and zero for saddle point).

In order to explicitly verify that each saddle point leads to two putative minima, the IRC pathways[21] have also been traced from all the transition states appearing on the cycloaddition energy surface profile.

Though the dienophile (**1**) can exist in two different conformations (*s-cis* or *s-trans*), which may bind with the diene, however, only *s-cis* approach has been considered to be the most probable one as previous ab initio (HF/3–21G)

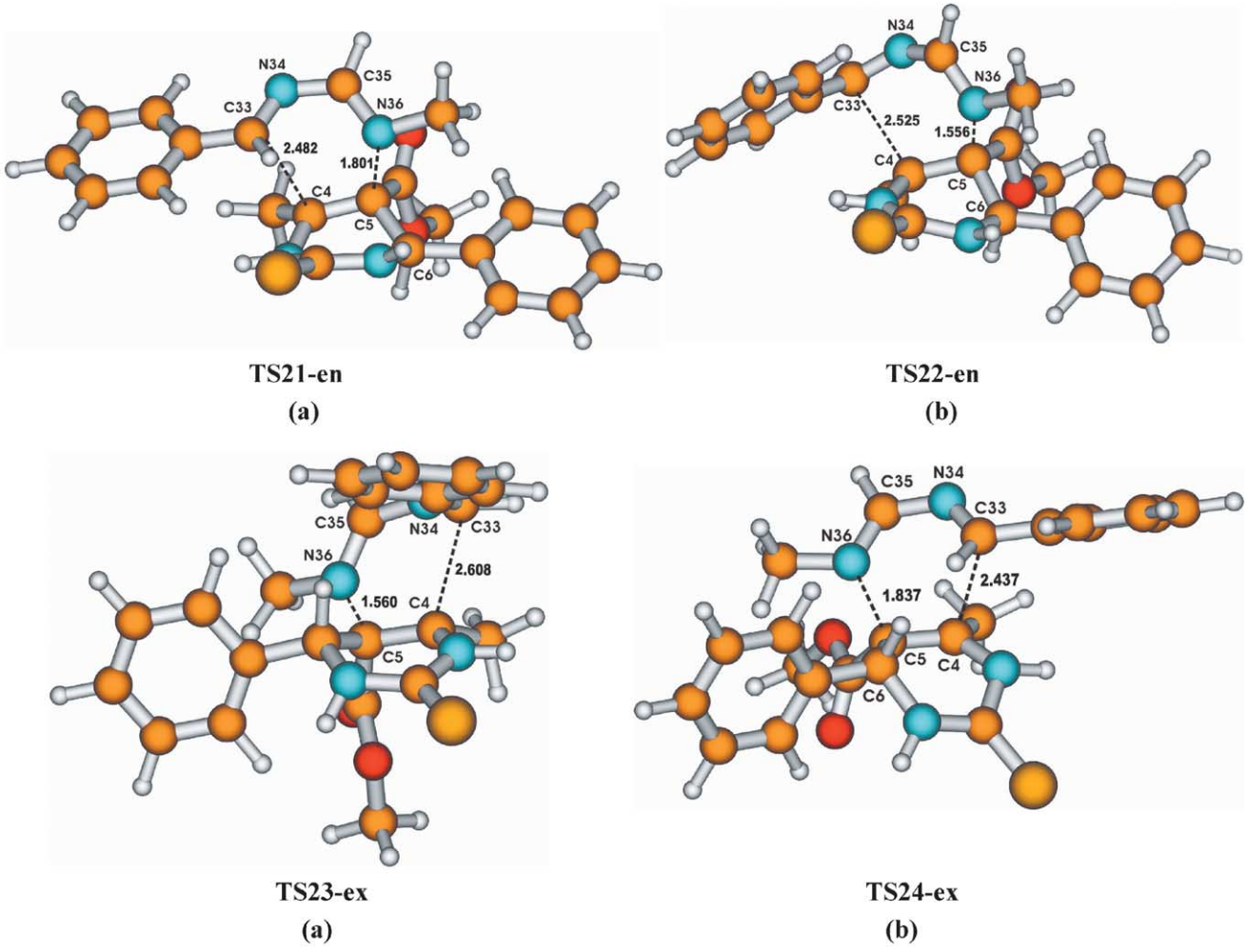


Figure 3. Transition state structures corresponding to regioisomer **2** for the [4+2]cycloaddition reaction between **1** and **2a**. (a) *trans*-approach; (b) *cis*-approach.

and semiempirical molecular orbital calculations (AM1, PM3) and X-ray crystallographic studies corroborate *s-cis* as the lower energy conformer.[22]

The results from these theoretical studies suggest that the observed cycloadditions can take place along a concerted mechanism through two reactive channels viz. *endo* and *exo* in order to generate two regioisomers (R1 and R2). Therefore, total eight transition states and eight cycloadducts have been located and characterized on PES for each representative HDA reaction corresponding to two regioisomers; two face of attack on diene (*cis* and *trans* approach) and exo/endo possibilities. For these reactions, we have labeled the transition structures as TS11–TS14 (R1) (Fig. 2) and TS21–24 (R2) (Fig. 3) for attack of **2a** on **1**. Correspondingly, TS31–TS34 (R1) (Fig. 4) and TS41–44 (R2) (Fig. 5) represent the transition states for reaction of **1** with **4a**. From these TSs, the related minima corresponding to the final cycloadducts are labeled as P11–44, respectively (Table 2).

Heat of formation for all the four TSs corresponding to R2 as compared to R1 is exceptionally large. Moreover, the *trans*-selectivity can be explained on the basis of data pertaining to Table 2, according to which, the heat of formation belonging to the endo-*trans* (TS11, 87.03 kcal mol^{-1}) conformer is 2.22 kcal mol^{-1} less than that of the endo-*cis* congener (TS12, 89.25 kcal mol^{-1}). On the other hand, the energy difference between the exo-*trans* (TS13) and exo-*cis* (TS14) conformers is 0.51 kcal mol^{-1}, but the mean difference between the energy of two sets of TSs are considerable, that is, PM3 calculated heat of formation of transition state belonging to the endo-*trans* (TS11-en, 87.03 kcal mol^{-1}) conformer is 1.53 kcal mol^{-1} less than that of the *exo* congener (TS13-ex, 88.51 kcal mol^{-1}) for the cycloaddition of **1** with **2a**. Similarly, TS31-en

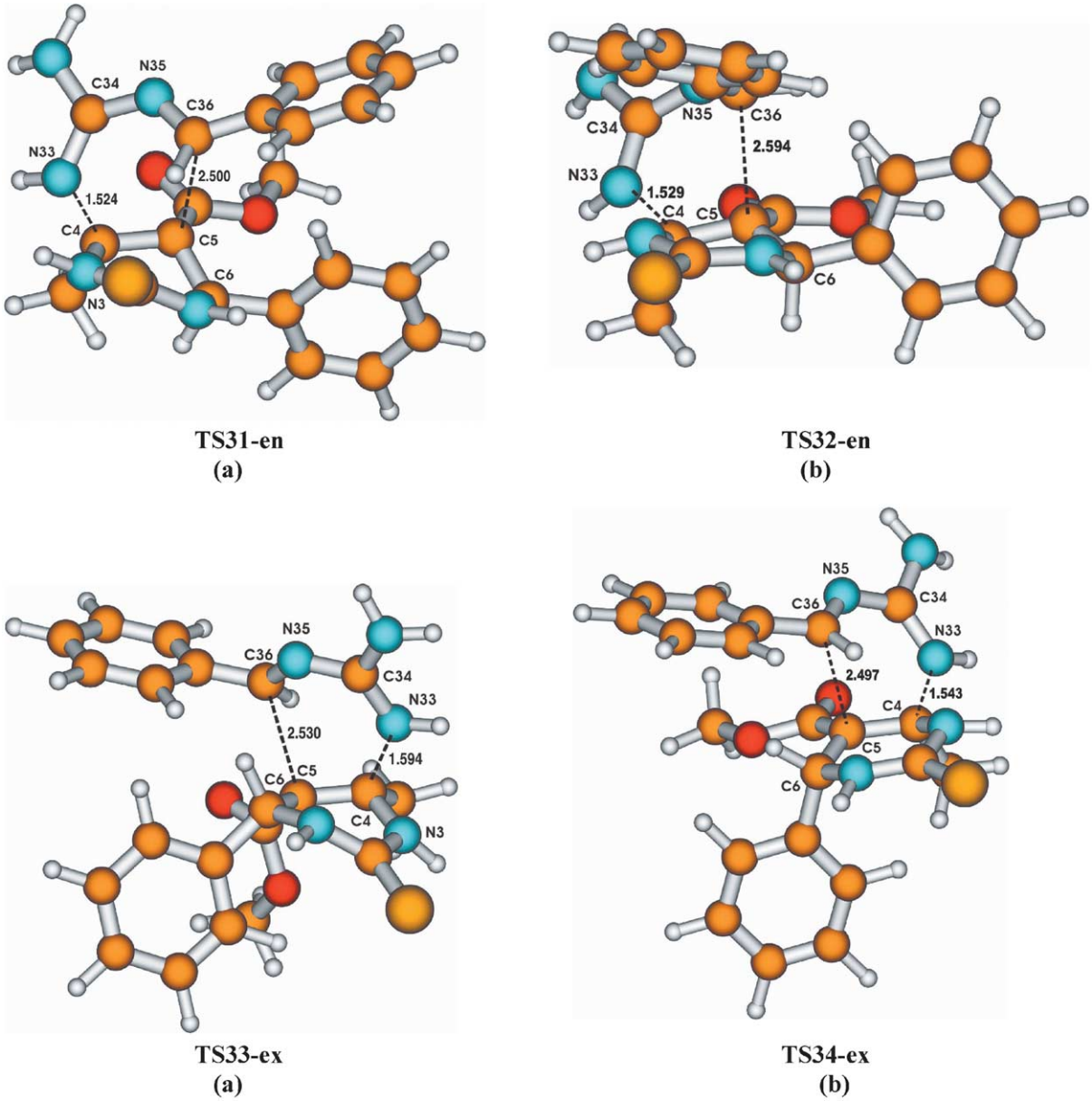


Figure 4. Transition state structures corresponding to regioisomer **1** for the [4+2]cycloaddition reaction between **1** and **4a**. (a) *trans*-approach; (b) *cis*-approach.

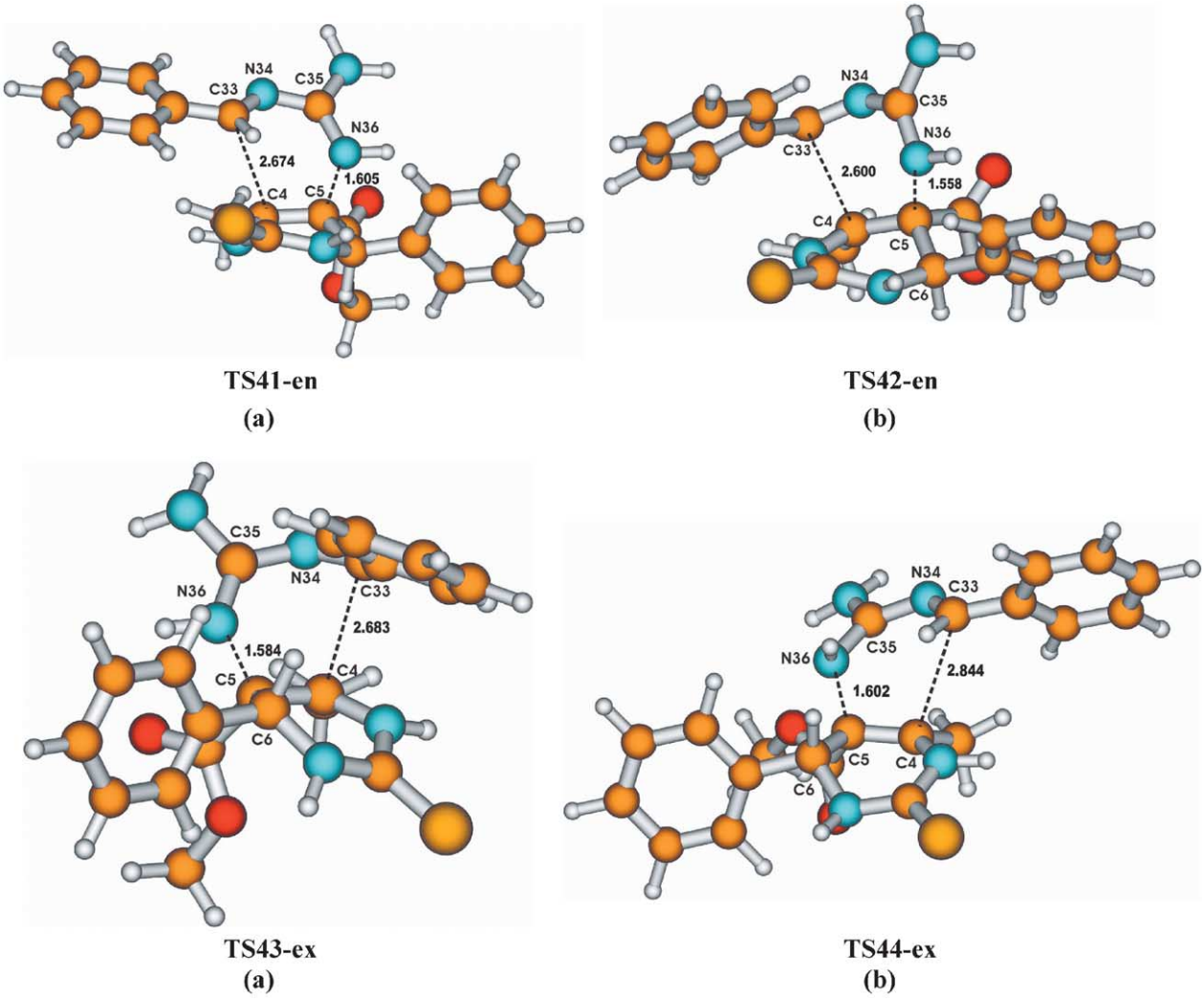


Figure 5. Transition state structures corresponding to regioisomer **2** for the [4+2]cycloaddition reaction between **1** and **4a**. (a) *trans*-approach; (b) *cis*-approach.

Table 2. PM3 relative energies (kcal mol^{-1}) to reactants[a] for the stationary points of the reactions

S. no.	Stationary points	Rel. energies	Stationary points	Rel. energies
1	TS11-en	48.23	P11-en	6.05
2	TS12-en	50.45	P12-en	5.92
3	TS13-ex	49.71	P13-ex	3.79
4	TS14-ex	50.22	P14-ex	2.49
5	TS21-en	60.22	P21-en	4.72
6	TS22-en	65.27	P22-en	0.84
7	TS23-ex	64.35	P23-ex	4.62
8	TS24-ex	57.63	P24-ex	2.29
9	TS31-en	32.91	P31-en	−1.57
10	TS32-en	38.86	P32-en	−2.78
11	TS33-ex	37.36	P33-ex	−1.06
12	TS34-ex	38.03	P34-ex	−6.66
13	TS41-en	37.30	P41-en	−11.62
14	TS42-en	43.23	P42-en	−14.79
15	TS43-ex	46.25	P43-ex	−8.57
16	TS44-ex	49.15	P44-ex	−10.19

[a] PM3 heat of formation (kcal mol^{-1}) for the reactants are: **1**+**2a**=38.80; **1**+**4a**=44.34.

(77.25 kcal mol^{-1}) is 4.45 kcal mol^{-1} lower as compared to the TS33-ex (81.70 kcal mol^{-1}) for the HDA reaction between **1** and **4a**.

Moreover, it has been inferred from the relative energies of stationary points summarized in Table 2 that, though the calculated difference in energies of the alternative products is small, but it is highly significant. Hence, reaction pathway along the *endo* approach experiences the relatively smaller activation barrier (48.23 kcal mol^{-1} and 32.91 kcal mol^{-1} for the formation of **3a** and **5a**, respectively) as compared to the corresponding *exo* approach and thus is the favourable route. The PM3 optimized geometries of **3a** and **5a** is shown in Figure 6. The predicted regiochemistry agrees quite well with the experimental outcome.

We also found that the three-carbon atoms involved in the bond formation are significantly pyramidalized, as it can be seen from the bond angles shown in Table 3, which are in close proximity to the sp^3 geometry. In addition, the carbon atom of the diene **2a**, which is not involved in the bond formation, is slightly pyramidal, with the attached hydrogen (H44) laying 7.3° out of the diene plane. This distortion

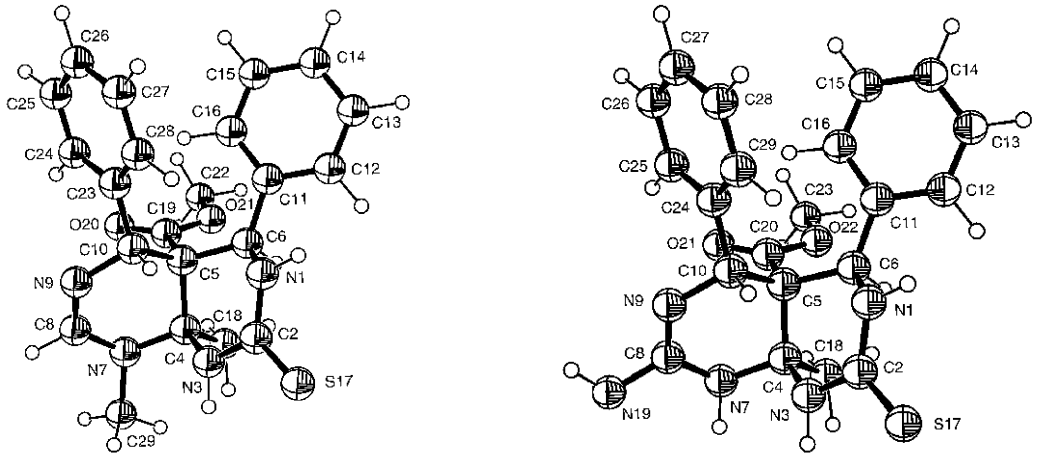


Figure 6. The ORTEP plot of **3a** and **5a** with atom numbering. Thermal ellipsoids are scaled to 50% probability. The atom numbering is arbitrary and has nothing to do with the IUPAC nomenclature.

probably allows for better overlap between the diene π-system and the new forming bonds.

Furthermore, the transition vector (TV),[23] that is, the eigen-vector associated to the unique negative eigen-value of the force constant matrix is dominated by the motion of new forming C–C and C–N bond and the extent of asynchronicity (Δr) can be measured by means of difference between the distances of the bonds that are being formed in the cycloaddition reactions, that is, $\Delta r = d(\text{C36–C5}) - d(\text{N33–C4})$ at different TSs obtained for the studied reactions. The corresponding Δr-values are found in the range of 0.982–0.936 and shown in Table 3 along with selected geometrical parameters for the different TSs.

Likewise, two TSs for diastereomeric reaction between **1** and **4a** with hydrogen at N33 in *syn* and *anti* conformation has been determined. The diastereomeric TSs for the reaction under study differ by the location of nitrogen lone pair. In syn approach the lone pair rotates inward toward the diene fragment, while in anti approach, the lone pair rotates away from the diene fragment. The relief of lone pair-π-electron repulsion in *anti* approach compared to *syn* leads to a shorter N-C4 distance (1.524 Å) at transition state structure (TS31) and consequently results lower energy in the former (32.91 kcal mol^{-1}). The same effect was noticed by the Houk in the Diels–Alder reaction of formaldimine with 1,3-butadiene[24] and Bachrach in DA reaction of 1-aza-1,3-butadiene.[25] This implies that even though two-orbitals on the nitrogen (the π- and the lone pair orbital) can interact with the dienophile; the preferred path rotates the lone pair away from the reaction zone. Only the π-orbital participates in the formation of new C–N bond.

Thus, on the basis of the above rationalization the observed HDA cycloadditions can be predicted as the asynchronous concerted ones, vis-à-vis in good agreement with the experimental evidences.

2.3. Frontier molecular orbital analysis

The reaction studied in this work can also be understood through the frontier molecular orbital (FMO)[26] model based on the energy gap of HOMO and LUMO. The FMO model can be appropriate to explain the observed reaction rate for the cycloaddition reactions of **1** with different dienes, that is,

Table 3. Selected geometrical parameters and asynchronicity (Δr) for the TSs located on cycloaddition reaction profile

	TS11-en	TS13-ex	TS31-en	TS33-ex
C4–N33[a]	1.53	1.59	1.52	1.59
C5–C36[a]	2.51	2.57	2.50	2.53
C4–C5[a]	1.51	1.48	1.51	1.46
N3–C4–N33[b]	101.37	104.06	105.29	099.91
C6–C5–C36[b]	112.68	109.86	114.53	100.50
C5–C4–N33[b]	113.21	111.58	114.097	113.91
N3–C4–N33[b]	101.37	104.06	105.29	99.91
C6–C5–C36[b]	112.68	108.86	114.53	100.50
C4–C5–C36[b]	97.70	96.42	97.03	100.28
C5–C36–N35[b]	93.09	90.91	93.18	93.08
N3–C4–N33–C34[c]	85.84	−146.23	106.71	−114.46
C6–C5–C36–N35[c]	−170.71	051.02	−178.09	060.49
N33–C34–N35–C36[c]	−23.43	−28.37	−16.76	−18.88
Δr	0.982	0.983	0.976	0.936

[a] Distances in Å.
[b] Angles in degrees.
[c] Torsion angles in degrees; $\Delta r = d(\text{C5–C36}) - d(\text{C4–N33})$.

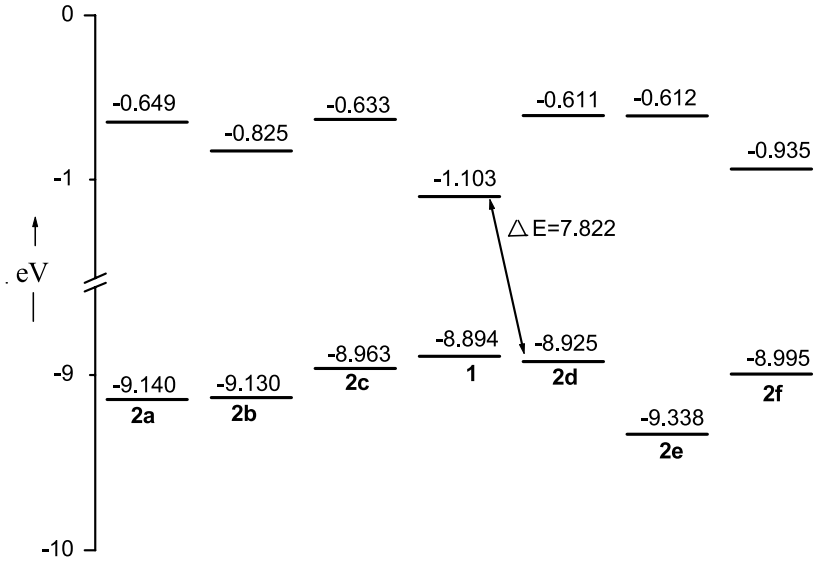


Figure 7. Frontier molecular orbitals of dienophile **1** and dienes **2a–f**.

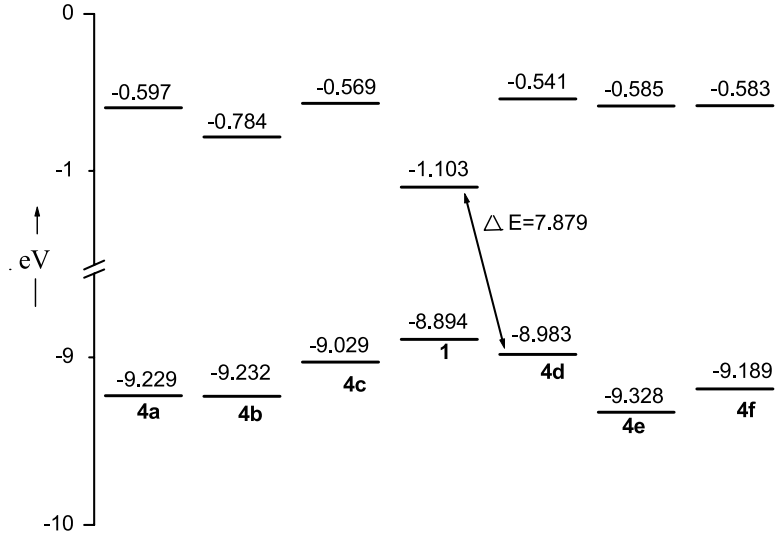


Figure 8. Frontier molecular orbitals of dienophile **1** and dienes **4a–f**.

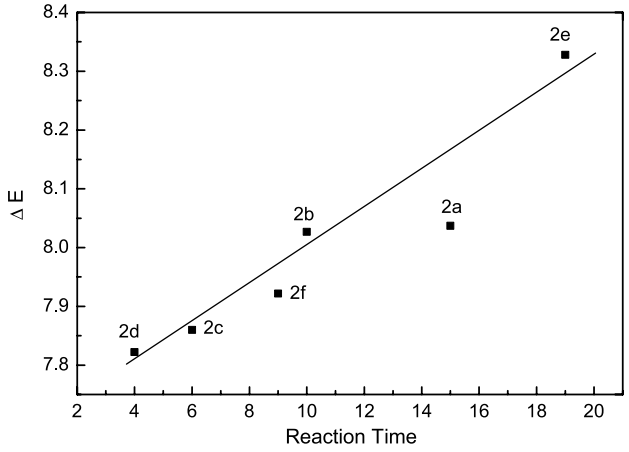


Figure 9. Plot between the reaction time and energy difference of frontier molecular orbital for reaction of **1** and dienes **2a–f** (ΔE=HOMO−LUMO).

2a–f and **4a–f** (Table 1). It has been realized from the Figures 7 and 8 that the observed reactions are E_{HOMO}(diene)−E_{LUMO}(dienophile) controlled, as is the case for normal Diels–Alder cycloaddition (NDAC). An overview of the data presented in Table 1 shows that the reaction between **1** and **2d** occur at much faster rate, which is also supported by the least $HOMO_{diene}-LUMO_{dienophile}$ energy gap in the series as depicted in the Figure 9. However, the insertion of electron donating group such as –OH and –Cl at the 4-phenyl ring of **2** increases the energy gap and subsequently retards the reaction rate (Fig. 9). In general observed reaction rate follows the pattern: **2d**>**2c**>**2f**>**2b**>**2a**>**2e**. Conversely, cycloadditions with the guanidine derivative, that is, unsubstituted *N*-terminal of diene fragment bearing NH_2 at neighbouring carbon atom give rise to lower HOMO as compared to corresponding formamidine derivatives. Hence, the $HOMO_{diene}-LUMO_{dienophile}$ energy gap

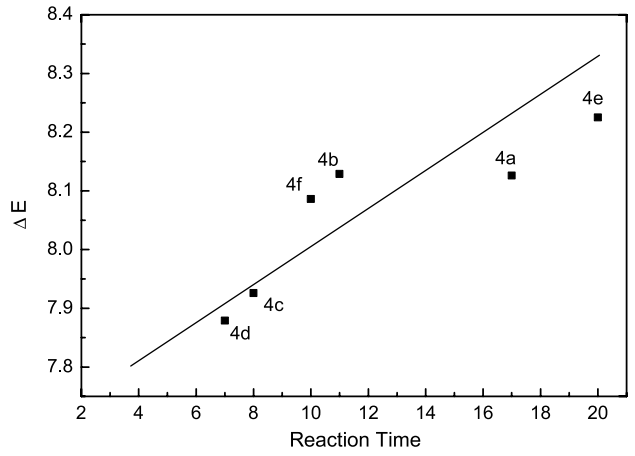


Figure 10. Plot between the reaction time and energy difference of frontier molecular orbital for reaction of **1** and dienes **4a–f** (ΔE=HOMO−LUMO).

increases, which resulted in the increase reaction time (Fig. 10).

3. Conclusion

Present studies demonstrated the HDA reaction as an expeditious and efficient procedure for the synthesis of potent pyrimido[4,5-*d*]pyrimidine conformers bearing different substituents on the C-5 phenyl ring, after successfully exploiting for the first time the dienophilic behaviour of the Biginelli compound.

As per the theoretical calculations, the studied HDA reaction of 4-phenyl-tetrahydropyrimidine-5-carboxylate derivative with substituted methyl formamidine and guanidine can be considered as an asynchronous concerted process.

Semiempirical PM3 studies supported the experimental results, suggesting a preference for the *endo* reaction pathway over the *exo* approach of the dienophile towards the diene fragment to obtain the target compounds owing to lower activation barrier of 48.23 kcal mol^{-1} and 32.91 kcal mol^{-1} for adduct formation (**3a** and **5a**, respectively). The diastereomeric reactions of (*E*)- and (*Z*)-*N*-benzylidine-guanidine displayed lower activation energy, that is, 32.91 kcal mol^{-1} for the former, which is attributed to the build-up of lone pair-π-bond repulsion during the DA reaction of *Z*-isomer. Moreover, FMO analysis reasonably predicts the observed reaction rate for the investigated cycloaddition reactions.

Therefore, normal electron demand hetero Diels–Alder reaction with the unusual dienophile and dienes presented in this work can be translated into a facile route for the construction of structurally diverse novel heterocycles of pharmacological importance, which can be envisaged as new lead compounds. In due course, the biological screening studies of all the synthesized compounds will be the subject of further investigation.

4. Experimental

Melting points (mp) were determined on an electrothermal apparatus by open capillary method and are uncorrected. All the chemicals used were of AR grade purity from E Merck. Solvents were freshly distilled and dried prior to use. IR spectra were recorded as KBr pellets on a Shimadzu 460 FTIR-spectrometer. Frequencies are reported in cm^{-1}. The NMR spectra were recorded on a Jeol NMR 200 MHz (^1H) and Bruker DRX 400 MHz (^{13}C) spectrometers in $CDCl_3$. Chemical shifts (δ) are reported in ppm value relative to tetramethylsilane (TMS) and coupling constants (*J*) in Hz. Mass spectra were taken with a Jeol D-300 spectrometer. Purity of all the synthesized compounds were ascertained by TLC resolution studies on silica gel G (E Merck) using ethyl acetate–xylene (4:6, v/v) as eluent and HPLC analysis, performed on Shimadzu LC10AS using L7 phenyl packing column, a 254 nm UV Shimadzu ASVP detector and acetonitrile/methanol/water (60:30:10) as eluent with a flow rate of 1 ml/min. Compounds **1**,[27] **2a–f** [28] and **4a–f**[28] were synthesized by modified literature method.

4.1. General procedure for the synthesis of 5-aryl-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3a–f)

To a solution of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid methyl ester **1** (6.1 g, 10 mmol) in anhydrous toluene (15 ml), was added substituted *N*-arylidene-*N*′-methyl-formamidine **2a–f** (20 mmol) at room temperature and the mixture was allowed to reflux or stirring for the required time (see Table 1). After the completion of reaction, the solvent was distilled off under reduced pressure and the residue was recrystallized from chloroform:petroleum ether (1:2) affording the corresponding pyrimido[4,5-*d*]pyrimidines in good to excellent yields.

4.1.1. 5-Phenyl-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3a). Mp (°C) 154–156. White solid. Anal. Calcd for $C_{22}H_{24}N_4O_2S$ (408.52): C, 64.68; H, 5.92; N, 13.71. Found: C, 64.60; H, 5.85, N, 13.65. IR (KBr) (ν, cm^{-1}) 3216 (NH), 3012 (CH sp^2), 2850 (CH sp^3), 1750 (C=O, ester), 1595 (C=C/C=N), 1530, 1473, 1400 (C⎓C ring str.), 1302 (C–N), 1070 (C=S); ^1H NMR (δ ppm) 2.42 (s, 3H, CH_3) 2.52 (s, 3H, N–CH_3), 3.71 (s, 3H, $COOCH_3$) 4.93 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.2 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.1 (s, 10H, 2×C_6H_5), 7.75 (br s, 1H, NH), 8.2 (s, 1H, N=CH), 9.15 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.6 (C=S), 174.4 (C=O), 145.5 (C=N), 141.4, 139.4, 132.6, 129.5, 129.4, 125.4, 123.6, 123.0 (2×Ph), 76.1 (C_{4a}), 74.0 (C_{8a}), 51.5 (C_4), 51.0 (CH_3, ester), 45.9 (C_5), 28.7 (N–CH_3) 20.8 (CH_3); FAB-MS *m*/*z* (RA %) 408 (M^+, 12).

4.1.2. 5-(4-Chlorophenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3b). Mp (°C) 152–154. White solid. Anal. Calcd for $C_{22}H_{23}ClN_4O_2S$ (442.96): C, 59.65; H, 5.23; N, 12.65. Found: C, 59.58; H, 5.17; N, 12.57. IR (KBr) (ν, cm^{-1}) 3219 (NH), 3010 (CH

sp^2), 2860 (CH sp^3), 1752 (C=O, ester), 1592 (C=C/C=N), 1523, 1470, 1410 (C⋯C ring str.), 1307 (C–N), 1050 (C=S), 585 (C-Cl); ^{1}H NMR (δ ppm) 2.47 (s, 3H, CH_3) 2.51 (s, 3H, N–CH_3), 3.79 (s, 3H, $COOCH_3$) 4.89 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.21 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.82 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.19 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.8 (C=S), 174.1 (C=O), 144.2 (C=N), 142.1, 139.2, 131.7, 129.4, 129.3, 128.6, 128.4, 121.3 (Ph/Ar), 77.1 (C_{4a}), 72.8 (C_{8a}), 51.2 (C_4), 49.7 (CH_3, ester), 45.7 (C_5), 28.1 (N–CH_3) 20.7 (CH_3); FAB-MS *m/z* (RA %) 443 (M^+, 15), 445 (M^++2, 5).

4.1.3. 5-(4-Hydroxyphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3c). Mp (°C) 157–159. Reddish solid. Anal. Calcd for $C_{22}H_{24}N_4O_3S$ (424.51): C, 62.24; H, 5.70; N, 13.20. Found: C, 62.18; H, 5.62; N, 13.12. IR (KBr) (ν, cm^{-1}) 3560 (OH), 3234 (NH), 3017 (CH sp^2), 2857 (CH sp^3), 1750 (C=O, ester), 1590 (C=C/C=N), 1522, 1475, 1402 (C⋯C ring str.), 1305 (C–N), 1060 (C=S); ^{1}H NMR (δ ppm) 2.42 (s, 3H, CH_3), 2.54 (s, 3H, N–CH_3), 3.72 (s, 3H, $COOCH_3$), 4.84 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.24 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.62 (br s, 1H, NH), 7.81 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.2 (s, 1H, N=CH), 9.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), 10.2 (br s, 1H, OH); ^{13}C NMR (δ ppm) 185.2 (C=S), 175.2 (C=O), 145.5 (C=N), 141.1, 139.4, 132.0, 129.4, 129.1, 128.9, 128.7, 115.2 (Ph, Ar), 76.6 (C_{4a}), 73.5 (C_{8a}), 53.4 (C_4), 51.2 (CH_3, ester), 46.1 (C_5), 28.7 (N–CH_3) 20.9 (CH_3), FAB-MS *m/z* (RA %) 424 (M^+, 18).

4.1.4. 5-(4-Methoxyphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3d). Mp (°C) 161–163. Yellow-brown solid. Anal. Calcd for $C_{23}H_{26}N_5O_3S$ (438.54): C, 62.99; H, 5.98; N, 12.78. Found: C, 62.92; H, 5.91; N, 12.70. IR (KBr) (ν, cm^{-1}) 3220 (NH), 3015 (CH sp^2), 2850 (CH sp^3), 1760 (C=O, ester), 1600 (C=C/C=N), 1550, 1440, 1410 (C⋯C ring str.), 1300 (C–N), 1072 (C=S); ^{1}H NMR (δ ppm) 2.45 (s, 3H, CH_3), 2.51 (s, 3H, N–CH_3), 3.4 (s, 3H, OCH_3), 3.82 (s, 3H, $COOCH_3$), 4.97 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.1 (s, 5H, C_6H_5), 7.22 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.64 (br s, 1H, NH), 7.83 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.14 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.4 (C=S), 174.1 (C=O), 150.5 (C=N), 146.4, 137.5, 132.1, 128.4, 128.3, 120.6, 120.4, 113.4 (Ph/Ar), 76.1 (C_{4a}), 74.4 (C_{8a}), 56.0 (OCH_3), 51.5 (C_4), 51.0 (CH_3, ester), 45.9 (C_5), 28.6 (N–CH_3) 21.4 (CH_3); FAB-MS *m/z* (RA %) 438 (M^+, 13).

4.1.5. 5-(4-Ethylphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3e). Mp (°C) 153–155. Yellow solid. Anal. Calcd for $C_{24}H_{28}N_4O_2S$ (436.57): C, 66.03; H, 6.46; N, 12.83. Found: C, 62.98; H, 6.40; N, 12.76. IR (KBr) (ν, cm^{-1}) 3210 (NH), 3015 (CH sp^2), 2862 (CH sp^3), 1750 (C=O, ester), 1595 (C=C/C=N), 1500, 1472, 1400 (C⋯C ring str.), 1306 (C–N), 1050 (C=S), 722 (CH_2); ^{1}H NMR (δ ppm) 0.9 (t, 3H, CH_3, $^3J_{HH}$=8.0 Hz), 2.41 (s, 3H, CH_3), 2.52 (s, 3H, N–CH_3), 3.74 (s, 3H, $COOCH_3$), 4.35 (q, 2H, CH_2, $^3J_{HH}$=8.0 Hz), 4.92 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.22 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.21 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.62 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.2 (s, 1H, N=CH), 9.21 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.7 (C=S), 174.3 (C=O), 145.5 (C=N), 139.4, 137.2, 136.4, 128.3, 127.5, 127.1, 126.4, 125.5 (Ph/Ar), 76.6 (C_{4a}), 72.7 (C_{8a}), 49.3 (C_4), 48.6 (CH_3, ester), 45.9 (C_5), 28.9 (N–CH_3), 28.6 (CH_2) 20.8 (CH_3), 16.1 (CH_3); FAB-MS *m/z* (RA %) 436 (M^+, 15).

4.1.6. 5-(4-Methylphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3f). Mp (°C) 151–153. Pale yellow solid. Anal. Calcd for $C_{23}H_{26}N_4O_2S$ (422.54): C, 65.38; H, 6.20; N, 13.26. Found: C, 65.31; H, 6.13; N, 13.20. IR (KBr) (ν, cm^{-1}) 3240 (NH), 3010 (CH sp^2), 2855 (CH sp^3), 1758 (C=O, ester), 1592 (C=C/C=N), 1540, 1434, 1410 (C⋯C ring str.), 1310 (C–N), 1054 (C=S); ^{1}H NMR (δ ppm) 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3) 2.54 (s, 3H, N–CH_3), 3.81 (s, 3H, $COOCH_3$) 4.94 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.2 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 10H, C_6H_5), 7.24 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.64 (br s, 1H, NH), 7.81 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.3 (C=S), 176.4 (C=O), 140.4 (C=N), 139.6, 136.4, 134.9, 129.2, 129.1, 128.7, 128.4, 119.6 (Ph/Ar), 76.7 (C_{4a}), 72.9 (C_{8a}), 51.2 (C_4), 49.4 (CH_3, ester), 46.2 (C_5), 28.7 (N–CH_3), 21.8 (CH_3), 20.7 (CH_3); FAB-MS *m/z* (RA %) 422 (M^+, 14).

4.2. General procedure for the synthesis of 7-amino-5-aryl-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5a–f)

To a solution of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid methyl ester **1** (6.1 g, 10 mmol) in anhydrous toluene (15 ml), was added substituted *N*-arylidene-guanidine **4a–f** (20 mmol) at room temperature and the mixture was allowed to reflux or stirring for the required time (see Table 1). After the completion of reaction, the solvent was distilled off under reduced pressure and the residue was recrystallized from chloroform:petroleum ether (1:2) affording the corresponding desired pyrimido[4,5-*d*]pyrimidines in good to excellent yields.

4.2.1. 7-Amino-5-phenyl-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5a). Mp (°C) 148–150. White solid. Anal. Calcd for $C_{21}H_{23}N_5O_2S$ (409.51): C, 61.59; H, 5.66; N, 17.10. Found: C, 61.52; H, 5.60; N, 17.02. IR (KBr) (ν, cm^{-1}) 3410 (NH_2-sym), 3365 (NH_2-asy), 3216 (NH), 2900 (CH sp^3), 1760 (C=O, ester), 1590 (C=C/C=N), 1522, 475, 1401 (C⋯C ring str.), 1312 (C–N), 1053 (C=S); ^{1}H NMR (δ ppm) 2.41 (s, 3H, CH_3), 3.81 (s, 3H, $COOCH_3$), 4.91 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.0 (s, 2H, NH_2), 7.0 (s, 10H, 2×C_6H_5), 7.7 (br s, 1H, NH), 9.2 (br s, 1H, NH), 10.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) ^{13}C NMR (δ

ppm) 183.8 (C=S), 176.1 (C=O), 145.3 (C=N), 141.2, 139.2, 129.8, 129.6, 127.4, 127.1, 124.6, 123.9 (2×Ph), 78.6 (C_{4a}), 61.5 (C_{8a}), 51.2 (C_4), 51.0 (CH_3, ester), 42.5 (C_5), 20.8 (CH_3); FAB-MS *m/z* (RA %) 409 (M^+, 15).

4.2.2. 7-Amino-5-(4-chlorophenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]-pyrimidine-4a-carboxylic acid methyl ester (5b). Mp (°C) 144–146. White solid. Anal. Calcd for $C_{21}H_{22}ClN_5O_2S$ (443.95): C, 56.81; H, 4.99; N, 15.78. Found: C, 56.74; H, 4.92; N, 15.71. IR (KBr) (ν, cm^{-1}) 3420 (NH_2-sym), 3361 (NH_2-asy), 3215 (NH), 2865 (CH sp^3), 1752 (C=O, ester), 1595 (C=C/C=N), 1534, 1481, 1407 (C⎓C ring str.), 1302 (C–N), 1062 (C=S), 580 (C-Cl); ^{1}H NMR (δ ppm) 2.44 (s, 3H, CH_3), 3.83 (s, 3H, $COOCH_3$), 4.95 (d, 1H, CH, $^4J_{HH}$= 1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.1 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.22 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.83 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.0 (br s, 1H, NH), 10.14 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 185.0 (C=S), 177.2 (C=O), 142.8 (C=N), 139.4, 137.2, 131.2, 129.2, 129.2, 127.6, 127.2, 125.6 (Ph/Ar), 78.3 (C_{4a}), 61.7 (C_{8a}), 52.1 (C_4), 51.2 (CH_3, ester), 43.6 (C_5), 24.2 (CH_3); FAB-MS *m/z* (RA %) 444 (M^+, 12), 446 (M^++2, 4).

4.2.3. 7-Amino-5-(4-hydroxyphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido-[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5c). Mp (°C) 148–150. Reddish solid. Anal. Calcd for $C_{21}H_{23}N_5O_3S$ (425.51): C, 59.28; H, 5.45; N, 16.46. Found: C, 59.23; H, 5.38; N, 16.39. IR (KBr) (ν, cm^{-1}) 3492 (OH), 3425 (NH_2-sym), 3367 (NH_2-asy), 3210 (NH), 2870 (CH sp^3), 1760 (C=O, ester), 1592 (C=C/C=N), 1534, 1451, 1425 (C⎓C ring str.), 1306 (C–N), 1060 (C=S); ^{1}H NMR (δ ppm) 2.42 (s, 3H, CH_3), 3.82 (s, 3H, $COOCH_3$), 4.91 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.12 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.26 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.61 (br s, 1H, NH), 7.8 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.1 (br s, 1H, NH), 10.18 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), 12.45 (s, 1H, OH); ^{13}C NMR (δ ppm) 183.7 (C=S), 175.1 (C=O), 146.8 (C=N), 145.1, 139.2, 132.0, 129.7, 129.5, 128.7, 126.1, 115.3 (Ph/Ar), 78.7 (C_{4a}), 62.3 (C_{8a}), 51.5 (C_4), 51.0 (CH_3, ester), 42.8 (C_5), 23.3 (CH_3); FAB-MS *m/z* (RA %) 425 (M^+, 16).

4.2.4. 7-Amino-5-(4-methoxyphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido-[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5d). Mp (°C) 143–145. Yellow-brown solid. Anal. Calcd for $C_{22}H_{25}N_5O_3S$ (439.53): C, 60.12; H, 5.73; N, 15.93. Found: C, 60.04; H, 5.67; N, 15.87. IR (KBr) (ν, cm^{-1}) 3415 (NH_2-sym), 3305 (NH_2-asy), 3215 (NH), 2875 (CH sp^3), 1752 (C=O, ester), 1590 (C=C/C=N), 1561, 1470, 1401 (C⎓C ring str.), 1305 (C–N), 1057 (C=S); ^{1}H NMR (δ ppm) 2.48 (s, 3H, CH_3), 3.4 (s, 3H, OCH_3), 3.86 (s, 3H, $COOCH_3$), 4.92 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$= 3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.17 (s, 2H, NH_2), 7.1 (s, 5H, C_6H_5), 7.28 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.67 (br s, 1H, NH), 7.82 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.3 (br s, 1H, NH), 10.21 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), ^{13}C NMR (δ ppm) 184.2 (C=S), 178.4 (C=O), 145.8 (C=N), 143.1, 139.6, 134.5, 129.4, 129.1, 126.6, 126.2, 117.9 (Ph/Ar), 77.8 (C_{4a}), 61.1 (C_{8a}), 56.1 (OCH_3), 52.7 (C_4), 51.2 (CH_3, ester), 42.7 (C_5), 23.1 (CH_3); FAB-MS *m/z* (RA %) 439 (M^+, 10).

4.2.5. 7-Amino-5-(4-ethylphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5e). Mp (°C) 141–143. Yellow solid. Anal. Calcd for $C_{23}H_{27}N_5O_2S$ (437.56): C, 63.13; H, 6.22; N, 16.01. Found: C, 63.06; H, 6.14; N, 15.93. IR (KBr) (ν, cm^{-1}) 3425 (NH_2-sym), 3310 (NH_2-asy), 3217 (NH), 2869 (CH sp^3), 1757 (C=O, ester), 1600 (C=C/C=N), 1507, 1480, 1400 (C⎓C ring str.), 1310 (C–N), 1050 (C=S), 725 (CH_2); ^{1}H NMR (δ ppm) 0.9 (t, 3H, CH_3, $^3J_{HH}$=8.0 Hz), 2.43 (s, 3H, CH_3), 3.87 (s, 3H, $COOCH_3$), 4.45 (q, 2H, CH_2, $^3J_{HH}$=8.0 Hz), 4.74 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.12 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.22 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.26 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.2 (br s, 1H, NH), 10.17 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 185.1 (C=S), 176.4 (C=O), 141.1 (C=N), 139.6, 137.2, 136.6, 128.5, 128.3 127.7, 126.2, 125.8 (Ph/Ar), 78.5 (C_{4a}), 61.7 (C_{8a}), 51.9 (C_4), 51.0 (CH_3, ester), 42.6 (C_5), 28.4 (CH_2), 24.2 (CH_3), 16.1 (CH_3); FAB-MS *m/z* (RA %) 437 (M^+, 13).

4.2.6. 7-Amino-5-(4-methylphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]-pyrimidine-4a-carboxylic acid methyl ester (5f). Mp (°C) 146–148. Pale yellow solid. Anal. Calcd for $C_{22}H_{25}N_5O_2S$ (423.53): C, 62.39; H, 5.95; N, 16.54. Found: C, 62.32; H, 5.88; N, 16.48. IR (KBr) (ν, cm^{-1}) 3417 (NH_2-sym), 3347 (NH_2-asy), 3215 (NH), 2872 (CH sp^3), 1760 (C=O, ester), 1585 (C=C/C=N), 1572, 1453, 1408 (C⎓C ring str.), 1300 (C–N), 1048 (C=S); ^{1}H NMR (δ ppm) 2.37 (s, 3 h, CH_3), 2.41 (s, 3H, CH_3), 3.84 (s, 3H, $COOCH_3$), 4.86 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.23 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$= 1.3 Hz), 6.28 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.23 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.61 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.3 (br s, 1H, NH), 10.46 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.7 (C=S), 178.1 (C=O), 142.3 (C=N), 139.4, 137.9, 135.7, 129.7, 129.1, 128.4, 127.5, 125.6 (Ph/Ar), 78.2 (C_{4a}), 62.3 (C_{8a}), 51.7 (C_4), 51.2 (CH_3, ester), 43.1 (C_5), 23.3 (CH_3), 20.9 (CH_3); FAB-MS *m/z* (RA %) 423 (M^+, 16).

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