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A Convenient Synthesis and Hepatoprotective Activity of Imidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidine, Tetraazaacenaphthene and Tetraazaphenalene from Cyclic Ketene Aminals Through Tandem Addition-Cyclization Reactions‡

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Abstract—A novel one-pot synthesis of imidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidinones (**2**), tetraazaacenaphthene-3,6-diones (**4**), tetarazaphenalene-1,7-dione (**4d**) is delineated from the reaction of cyclic ketene aminal (**1**) and alkyl or aryl isothiocyanate through tandem addition-cyclization reactions. However, reaction of ketene aminal (**1a**) with alkyl isothiocyanate only yielded angularly cyclized product **5** which did not react further to yield **6**. The structure of **2c** and **4d** was ascertained by single crystal X-ray diffraction analysis which demonstrated a network of various inter- and intramolecular interactions, responsible for the stability and packing of the molecules in the crystalline state. Some of the compounds (**2a**–**h**) were screened for hepatoprotective activity but only **2a** was found most effective.

Introduction

The synthesis of complex naturally occurring organic compounds with high selectivity is always a challenging and fascinating undertaking. Synthesis of such compounds by domino reaction is one of the possible alternatives. Ketene aminals (**1**), by virtue of their unique electronic topography are considerably used as versatile synthon for the construction of one pot regioselective synthesis of polycyclic heterocycles and are highly significant in contemporary organic chemistry. Owing to the extended conjugation between electron donating amino groups and electron withdrawing substituents at α-carbon in ketene aminals (**1**), make the double bond highly polarized with a significant increase in bond length (1.38–1.47Å)[1–8], compared to normal olefins. Participation of lone-pair electrons of nitrogen in resonance with olefinic bond resulted in high electron density on the α-carbon atom, making it highly susceptible to electrophile. Thus, nucleophilicity of α-carbon is highly increased compared to secondary nitrogen. In heterocyclic ketene aminals α-carbon site, β-carbon, α-substituents and particularly the secondary amino groups generally participate in chemical synthesis. Among these sites, cyclization involving α-carbon atom and secondary amino groups is widely studied for the synthesis of diverse heterocycles.[4] However, annulations reaction involving α-carbon substituents and secondary nitrogen atom is meagrely exploited for the construction of fused heterocycles of therapeutic importance.[9] In this paper we wish to report one pot regioselective synthesis of a novel heterocyclic system, starting from the reaction of cyclic ketene aminals (**1**) and alkyl or aryl isothiocyanate.

Results and Discussion

So far, to our knowledge, there is only one precedent in the literature where diethyl (1,3-imidazolidin-2-ylidene)malonate[9] (**1c**) is employed for the synthesis of annulated heterocycle as oxo analogue of tetraazaacenaphthene (**3**, $n=2$) from reaction with alkyl or aryl isocyanate.

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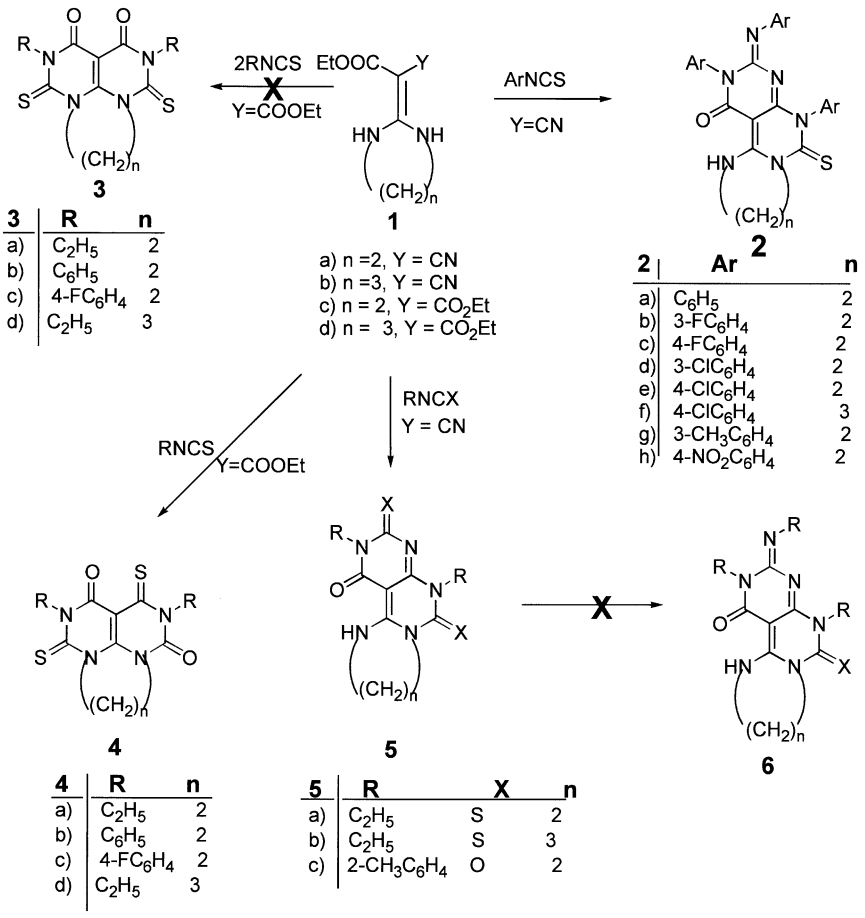


3	R	n
a)	C_2H_5	2
b)	C_6H_5	2
c)	4-FC_6H_4	2
d)	C_2H_5	3

2	Ar	n
a)	C_6H_5	2
b)	3-FC_6H_4	2
c)	4-FC_6H_4	2
d)	3-ClC_6H_4	2
e)	4-ClC_6H_4	2
f)	4-ClC_6H_4	3
g)	3-$CH_3C_6H_4$	2
h)	4-$NO_2C_6H_4$	2

4	R	n
a)	C_2H_5	2
b)	C_6H_5	2
c)	4-FC_6H_4	2
d)	C_2H_5	3

5	R	X	n
a)	C_2H_5	S	2
b)	C_2H_5	S	3
c)	2-$CH_3C_6H_4$	O	2

Scheme 1.

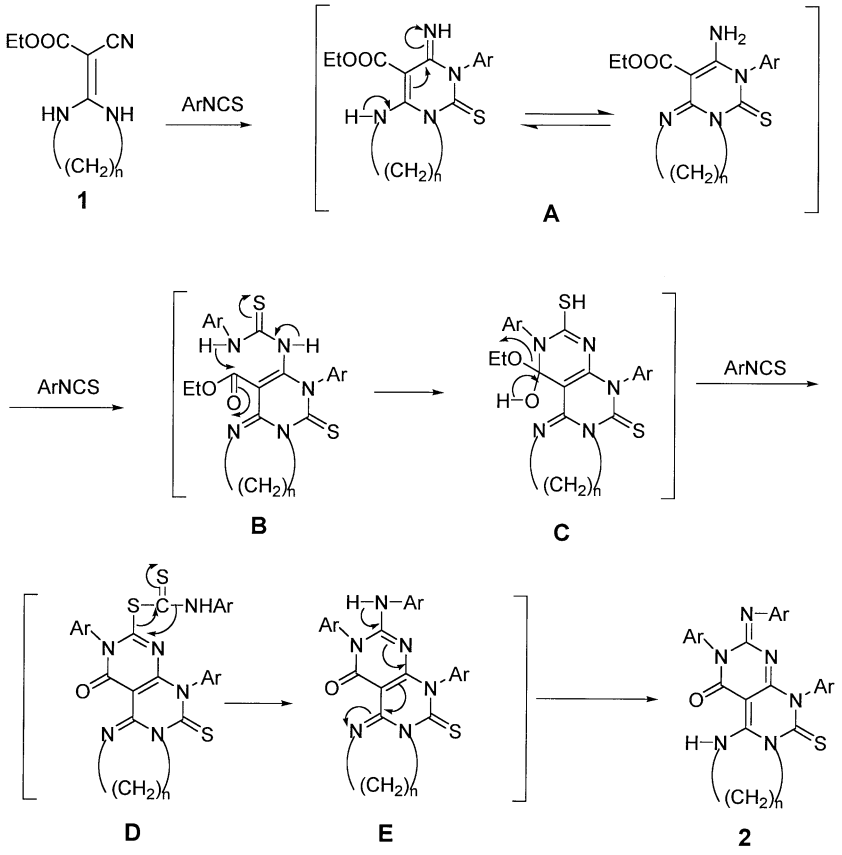
Since ketene aminal **1c**,**d** are highly polarised symmetrical molecules in which α-carbon is flanked by two ester groups while β-carbon with two adjacent secondary amino groups in a cyclic frame was expected to yield product **3** on reaction with alkyl or aryl isothiocyanate, but the structure of one of the isolated compounds was assigned by single crystal X-ray diffraction analysis as 2,8-diethyl-3,9-dithioxo-2,3,5,6,8,9-hexahydro-1*H*,4*H*,7*H*-2,3*a*,6*a*,8-tetraazaphenalene-1,7-dione (**4d**).

The formation of product **4d** is possibly initiated by addition of α-carbon (**1d**) and cyclic amino group to alkyl or aryl isothiocyanate, followed by decarboxylation and thermal cyclization. The reaction of alkyl or aryl isothiocyanate with unsymmetrical ketene aminals (**1a**,**b**) in which two different electron-withdrawing substitutents are linked to the α-carbon atom is not studied so far. We studied the course of reaction of ethyl (1,3-imidazolidin-2-ylidene)cyanoacetate (**1a**) or ethyl (tetrahydropyrimidin-2-ylidene) cyanoacetate (**1b**) with isothiocyanate or isocyanate. We anticipated the formation of an obvious linearly cyclized product but the isolated compound identified by single crystal X-ray diffraction was angularly cyclized (**2**). This reaction is possibly initiated by addition of cyclic amino function to isothiocyanate followed by Michael addition to cyano group to form an amine that further underwent addition-cyclization and rearrangement to yield **2** (Scheme 1).

It is conspicuous that the reaction of **1a**,**b** with aryl isothiocyanate exclusively yielded 8-arylimino-6,9-diaryl-5-thio-2,3-dihydro-1*H*-imidazo[1,2-*c*]pyrimido[5,4-*e*] pyrimidin-10-one (**2**). In this reaction no intermediate similar to **5** was isolated possibly due to faster rate of formation of intermediate dithiocarbamate [**C**] which in situ underwent rearrangement followed by concomitant elimination of carbon disulphide to yield angularly cyclized product **2** (Scheme 2).

However, reaction of **5** with excess of alkyl isothiocyanate did not proceed further and the NMR showed no sign of formation of **6**. Several attempts were made to isolate the compound **6** but always the starting compound (**5**) was recovered, possibly due to difference in the degree of reactivity of aryl and alkyl isothiocyanate. In conclusion, the formation of different products in this reaction is based on tandem addition-cyclization and selectivity of alkyl or aryl isothiocyanate for α-carbon substituent.

The structure of isolated products **2**, **4** and **5** was ascertained by spectroscopic and elemental analyses. The ^{1}H NMR spectra of **2a** displayed two triplets at δ 3.89 and 4.30 obviously for two methylene groups. Other multiplet at δ 7.32–7.48 was assigned for 15 aromatic protons in downfield. IR spectrum showed two peaks at ν 1670 and 3340 cm^{-1} due to C=O and NH groups, respectively. The ^{1}H NMR spectrum of **5c** displayed two



Scheme 2. Mechanism of reaction for the product **2**.

multiplets in downfield at δ 7.1–7.3 and 7.6–8.0 for eight aromatic protons. Two singlets at δ 2.38 and 3.4 were assigned for two methyl and two methylene groups, respectively. It is conspicuous from the NMR data of **5c** that none of the aromatic proton resonated in upfield as it is observed in **2a**, because of their presence in deshielding zones. The molecular ion and its fragmentation pattern unambiguously confirmed the assigned structure of the isolated compound. Finally, the structure of **2** was confirmed by single crystal X-ray diffraction of **2c** that showed the presence of two molecules in one asymmetric unit.

Some of the compounds (**2a**–**h**) were evaluated for their hepatoprotective activity against thioacetamide induced hepatic damage at 10 mg/kg dose as reported earlier.[10,11] The activity of the compounds was assessed on the basis of percent protection afforded in various levels of serum enzyme parameters such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and alkaline phosphatase (ALP). Except **2a** none of the compounds displayed significant activity in any of the enzyme parameters. Compound **2a** afforded better percent protection against GPT(72), GOT(70) and ALP (58) compared to standard drug, silymarin in all the parameters.

The ORTEP diagram (Fig. 1) shows the molecular structure of **2c** with atomic numbering scheme. The planar 4-fluorophenyl rings at N6, N8 and N9 have twisted conformations with respect to the almost planar imidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidine backbone.

The crystal packing (Fig. 2) reveals a network of various non-covalent intra-, and intermolecular interactions of the types C–H...π and H-bonding that play a fundamental role in three-dimensional organization of the molecules in solid state.[12] Currently the importance of these interactions is being realized in crystal engineering[13] and supramolecular design.[14] The C–H...π distances which also include some edge to face or T-shaped π–π interactions,[15] range from 2.792 to 2.915 Å. The strong N–H...O bonding distances range 2.792–2.915 Å while the weak H-bonding of the types C–H...F, C–H...N and C–H...S range from 3.236 to 4.176 Å. There are two F–F intermolecular short contacts of type 1[16] (distances 2.874 and 2.840 Å, respectively) in the crystal packing. It is most likely that such contacts are only a mere manifestation of close packing rather than attractive interactions.[17] Thus, the interplay of the various intermolecular forces stabilizes the structures in the crystalline state.

Experimental

Melting points are uncorrected. The reagent grade reaction solvent such as DMF was further purified and dried following literature procedures. TLC was performed on precoated silica gel plastic plates and visualized by irradiation, exposure to iodine vapours or spraying with $KMnO_4$ solution. IR spectra of liquid samples were run neat, and solids as KBr pellets. ^1H NMR spectra were recorded at 200 MHz in $CDCl_3$ and

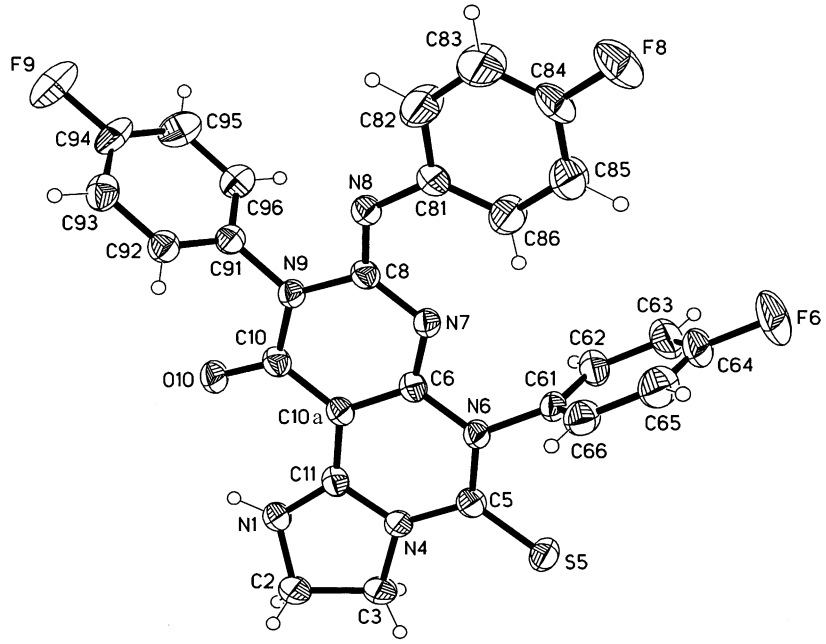


Figure 1. ORTEP diagram of **2c** showing the crystal structure of one of the two molecules in one asymmetric unit.

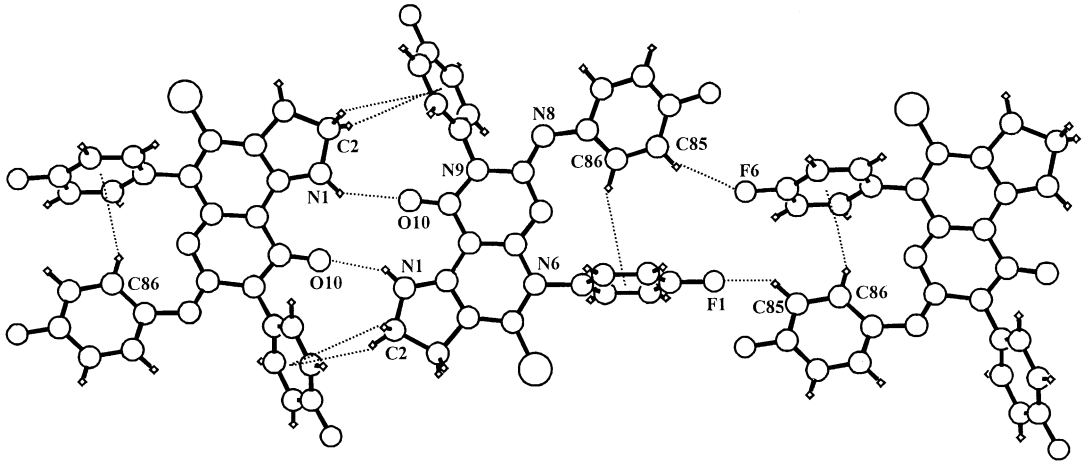


Figure 2. PLUTO packing diagram of **2c** showing C–H. . .π, N–H. . .O and C–H. . .F interactions by dotted lines.

DMSO-d_6 with tetramethylsilane as internal reference. Chemical shifts and coupling constants (J) were reported in δ (ppm) and in Hz, respectively. Mass spectra were collected at 70 eV by electron impact. Elemental analyses (C, H, and N) were determined at RSIC, Central Drug Research Institute, Lucknow 226001, India.

General procedure for the synthesis of 2a–h

A mixture of 1 (10 mmol) and aryl isothiocyanate (10 mmol) was heated in an oil bath at 160 °C for 4 h and cooled. The reaction mixture was treated with methanol and filtered. The precipitate thus obtained was washed several times by methanol to remove phenyl isothiocyanate and finally crystallized from DMF.

6,9-Bis(phenyl)-8-phenylimino-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido [5,4-*e*]pyrimidin-10(1*H*)-one (2a). Yield 3.7 g (80%), mp > 280 °C, IR (KBr): ν 1670 cm^{-1} (CO), 3340 cm^{-1} (NH), MS (EI): 464 (M^+, 53), 363 (100), 387 (3.4), 325 (3), 232 (13.9), ^{1}H NMR (DMSO-d_6): δ 3.89 (t, 2H, J = 8.4 Hz, CH_2), 4.30 (t, 2H, J = 8.5 Hz, CH_2), 6.58–6.80 (m, 5H, ArH), 7.20–7.26 (m, 5H, ArH), 7.32–7.52 (m, 5H, ArH), 9.63 (bs, 1H, NH). Anal. calcd for $C_{26}H_{20}N_6OS$: C, 67.22; H, 4.34; N, 18.09. Found: C, 67.56; H, 4.43; N, 18.34.

6,9-Bis(3-fluorophenyl)-8-(3-fluorophenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo [1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10(1*H*)-one (2b). Yield 0.78 g (76%), mp > 280 °C, IR (KBr): ν 1675 cm^{-1} (CO), 3345 cm^{-1} (NH), MS (EI): 518 (M^+, 100), 306 (60), 153(70), ^{1}H NMR (DMSO-d_6): δ 3.89 (t, 2H, J = 8.4 Hz, CH_2), 4.31 (t, 2H, J = 8.4 Hz, CH_2), 6.34–6.47 (m, 3H, ArH), 6.81–6.87 (m, 1H, ArH), 7.04–7.25 (m, 6H, ArH), 7.42–7.49 (m, 2H, ArH), 9.05 (bs, 1H, NH), Anal. calcd for $C_{26}H_{17}F_3N_6OS$: C, 60.23; H, 3.31; N, 16.21. Found: C, 60.52; H, 3.45; N, 16.38.

6,9-Bis(4-fluorophenyl)-8-(4-fluorophenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10(1*H*)-one (2c). Yield 0.88 g (86%), mp >280 °C, IR (KBr): ν 1670 cm^{-1} (CO), 3340 cm^{-1} (NH), MS (EI): 518 (M^+, 100), 459 (15), 306 (50), 153 (60), ^1H NMR (DMSO-d_6): δ 3.87 (t, 2H, $J=8.6$ Hz, CH_2), 4.31 (t, 2H, $J=8.5$ Hz, CH_2), 6.56–6.62 (m, 4H, ArH), 7.20–7.34 (m, 8H, ArH), 9.65 (bs, 1H, NH), Anal. calcd for $C_{26}H_{17}F_3N_6OS$: C, 60.23; H, 3.31; N, 16.21. Found: C, 60.52; H, 3.56; N, 16.38.

6,9-Bis(3-chlorophenyl)-8-(3-chlorophenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10(1*H*)-one (2d). Yield 1.0 g (89%), mp >280 °C, IR (KBr): ν 1680 cm^{-1} (CO), 3340 cm^{-1} (NH), MS (EI): 567 (M^+, 49), 359 (100), 135 (92.2), ^1H NMR (DMSO-d_6): δ 3.90 (t, 2H, $J=8.5$ Hz, CH_2), 4.32 (t, 2H, $J=8.6$ Hz, CH_2), 6.58–6.62 (m, 3H, ArH), 6.95–7.18 (m, 7H, ArH), 7.34–7.46 (m, 2H, ArH), 9.65 (bs, 1H, NH), Anal. calcd for $C_{26}H_{17}Cl_3N_6OS$: C, 54.99; H, 3.02; N, 14.82. Found: C, 54.65; H, 3.23; N, 15.05.

6,9-Bis(4-chlorophenyl)-8-(4-chlorophenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10(1*H*)-one (2e). Yield 0.98 g (86%), mp >280 °C, IR (KBr): ν 1680 cm^{-1} (CO), 3330 cm^{-1} (NH), MS (EI): 567 (M^+, 90), 307 (8), 232 (10), 153 (50), 135 (52), ^1H NMR (DMSO-d_6) : δ 3.92 (t, 2H, $J=8.2$ Hz, CH_2), 4.34 (t, 2H, $J=8.0$ Hz, CH_2), 6.60 (d, 2H, $J=8.0$ Hz, CH_2), 6.85 (d, 2H, $J=8.2$ Hz, ArH), 7.23 (d, 2H, $J=8.8$ Hz, ArH), 7.27 (d, 2H, $J=8.8$ Hz, ArH), 7.53 (d, 2H, $J=8.4$ Hz, ArH), 7.60 (d, 2H, $J=8.4$ Hz, ArH), 9.67 (bs, 1H, NH), Anal. calcd for $C_{26}H_{17}Cl_3N_6OS$: C, 54.99; H, 3.02; N, 14.82. Found: C, 55.12; H, 3.15; N, 14.53.

7,10-Bis(4-chlorophenyl)-9-(4-chlorophenylimino)-6-thioxo-1,2,3,4,6,7,9,10-octahydro-11*H*-dipyrimido[1,2-*c*:5,4-*e*]pyrimidin-11-one (2f). Yield 0.8 g (69%), mp >260 °C, IR (KBr): ν 1680 cm^{-1} (CO), 3340 cm^{-1} (NH), MS (EI): 581 (M^+, 40), 391 (70), 345 (35), ^1H NMR (DMSO-d_6): δ 1.85–1.95 (m, 2H, CH_2), 3.80–3.36 (m, 4H, $2CH_2$), 6.65 (d, 2H, $J=8.2$ Hz, ArH), 6.9 (d, 2H, $J=8.2$ Hz, ArH), 7.30–7.36 (m, 4H, ArH), 7.57–7.67 (m, 4H, ArH), 9.67 (bs, 1H, NH), Anal. calcd for $C_{27}H_{19}Cl_3N_6OS$: C, 55.73; H, 3.29; N, 14.45. Found: C, 55.45; H, 3.52; N, 14.63.

6,9-Bis(3-methylphenyl)-8-(3-methylphenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10(1*H*)-one (2g). Yield 0.8 g (74%), mp >260 °C, IR (KBr): ν 1685 cm^{-1} (CO), 3335 cm^{-1} (NH), MS (EI): 506 (M^+, 10.5), 462 (23.1), 407 (63), 406 (48.5), ^1H NMR (DMSO-d_6): δ 2.13 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 3.98 (t, 2H, $J=8.5$ Hz, CH_2), 4.5 (t, 2H, $J=8.5$ Hz, CH_2), 6.75–6.80 (m, 2H, ArH), 7.00–7.14 (m, 4H, ArH), 7.28–7.51 (m, 6H, ArH), 9.68 (bs, 1H, NH), Anal. calcd for $C_{29}H_{26}N_6OS$: C, 68.75; H, 5.17; N, 16.59. Found: C, 68.53; H, 5.34; N, 16.82.

6,9-*Bis*(4-nitrophenyl)-8-(4-nitrophenylimino)-5-thioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]-pyrimidin-10(1*H*)-one (2 h). Yield 0.94 g (73%), mp >260 °C, IR (KBr): ν 1678 cm^{-1} (CO), 3268 cm^{-1} (NH), MS (EI): 599 (M^+, 10), 180 (39.9), 164 (55.7), ^1H NMR (DMSO-d_6): δ 3.95 (t, 2H, $J=8.8$ Hz, CH_2), 4.35 (t, 2H, $J=8.2$ Hz, CH_2), 6.62 (d, 2H, $J=9$ Hz, ArH), 7.52 (d, 2H, $J=8.8$ Hz, ArH), 7.64 (d, 2H, $J=8.6$ Hz, ArH), 7.63 (d, 2H, $J=9$ Hz, ArH), 8.27–8.33 (m, 4H, ArH), 9.65 (bs, 1H, NH), Anal. calcd for $C_{26}H_{17}N_9O_7S$: C, 52.08; H, 2.86; N, 21.03. Found: C, 52.35; H, 2.68; N, 21.45.

4,7-Diethyl-5,8-dithioxo-1,2,4,5,7,8-hexahydro-3*H*,6*H*-2*a*,4,7,8*a*-tetraazaacenaphthene-3,6-dione (4a). A mixture of **1c** (0.46 g, 2 mmol) and ethyl isothiocyanate (1.39 g, 16 mmol) was heated at 160–170 °C. The reaction mixture was cooled, diluted with ether and filtered. It was crystallized from DMF. Yield 0.49 g (80%), mp >280 °C, IR (KBr): ν 1660 cm^{-1} (CO), MS (EI): 310 (M^+, 37), 281 (25), 253 (14), 239 (8), 223 (19), ^1H NMR (DMSO-d_6): δ 1.28 (t, 6H, $J=7.2$ Hz, $2CH_3$), 4.46–4.52 (m, 8H, $4CH_2$), Anal. calcd for $C_{12}H_{14}N_4O_2S_2$: C, 46.45; H, 4.51; N, 18.06. Found : C, 46.56; H, 4.58; N, 18.19.

4,7-Diphenyl-5,8-dithioxo-1,2,4,5,7,8-hexahydro-3*H*,6*H*-2*a*,4,7,8*a*-tetraazaacenaphthene-3,6-dione (4b). It was prepared from **1c** (0.46 g, 2 mmol) and phenyl isothiocyanate (2.1 g, 16 mmol) as described above. The crude product was crystallized from DMF. Yield 0.64 g (78%), mp >260 °C, IR (KBr): ν 1660 cm^{-1} (CO), MS (EI): 406 (M^+, 100), 374 (10), ^1H NMR (DMSO-d_6): δ 4.4 (s, 4H, $2CH_2$), 7.2–7.5 (m, 10H, ArH), Anal. calcd for $C_{20}H_{14}N_4O_2S_2$: C, 59.11; H, 3.45 ; N, 13.78. Found: C, 59.36; H, 3.62; N, 14.03.

4,7-Di(4-fluorophenyl)-5,8-dithioxo-1,2,4,5,7,8-hexahydro-3*H*,6*H*-2*a*,4,7,8*a*-tetraazaacenaphthene-3,6-ione (4c). It was synthesized by thermal cyclization of **1c** (0.46 g, 2 mmol) and 4-fluorophenyl isothiocyanate (2.4 g, 16 mmol) and the product was isolated as described earlier. It was crystallized from DMF. Yield 0.68 g (76%), mp >280 °C, IR (KBr): ν 1665 cm^{-1} (CO), MS (EI): 442 (M^+, 49), 410 (41), 289 (24), ^1H NMR (DMSO-d_6): δ 4.42 (s, 4H, $2CH_2$), 7.2–7.4 (m, 8H, ArH), Anal. calcd for $C_{20}H_{12}F_2N_4O_2S_2$: C, 54.29; H, 2.71; N, 12.66. Found: C, 54.45; H, 3.09; N, 12.36.

2,8-Diethyl-3,9-dithioxo-2,3,5,6,8,9-hexahydro-1*H*,4*H*,7*H*-2,3*a*,6*a*,8-tetraazaphenalene-1,7-dione (4d). It was obtained by thermal cyclization of **1d** (0.48 g, 2 mmol) and ethyl isothiocyanate (1.4 g, 16 mmol) as described above. Yield 0.42 g (65%), mp >190 °C, IR (KBr): ν 1660 cm^{-1} (CO), MS (EI): 324 (M^+, 100), 295 (26), 268 (16), 237 (10), ^1H NMR (DMSO-d_6): δ 1.18 (t, 6H, $J=7.2$ Hz, $2CH_3$), 2.15–2.17 (m, 2H, CH_2), 3.9 (t, 2H, $J=7.2$ Hz), 4.36 (t, 2H, $J=7.0$ Hz), 4.4–4.5 (m, 4H, $2CH_2$), Anal. calcd for $C_{13}H_{16}N_4O_2S_2$: C, 48.14; H, 4.93; N, 17.28. Found: C, 47.82; H, 4.91; N, 17.10.

6,9-Diethyl-5,8-dithioxo-2,3,5,6,8,9-hexahydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidin-10 (1*H*)-one (5a). A mixture of **1a** (0.36 g, 2 mmol) and ethyl isothiocyanate (1.4 g, 16 mmol) was heated at 160 °C for 8 h and cooled. The solid thus obtained was filtered, washed with ether to

remove the unreacted isothiocyanate. The crude product was crystallized from DMF. Yield 0.4 g (65%), mp > 218 °C, IR (KBr): ν 1670 cm^{-1} (CO), 3260 cm^{-1} (NH), MS (EI): 309 (M^+, 33), 281 (100), 249 (16), ^1H NMR (DMSO-d_6): δ 1.17 (t, 6H, $J = 6.8$ Hz, $2CH_3$), 4.24 (s, 4H, $2CH_2$), 4.35 (q, 2H, CH_2), 4.52 (q, 2H, CH_2), 9.28 (s, 1H, NH), Anal. calcd for $C_{12}H_{15}N_5OS_2$: C, 46.58; H, 4.89; N, 22.64. Found: C, 46.79; H, 5.23; N, 22.35.

7,10-Diethyl-6,9-dithioxo-1,2,3,4,6,7,9,10-octahydro-11*H*-dipyrimido[1,2-*c*:5,4-*e*] pyrimidin-11-one (5b). It was prepared from the fusion of **1b** (0.39 g, 2 mmol) and ethyl isothiocyanate (1.39 g, 16 mmol) at 160 °C for 10 h. The solid thus obtained was purified on silica gel column using chloroform as eluent. Yield 0.42 g (65%), mp > 210 °C, IR (KBr): ν 1650 cm^{-1} (CO), 3240 cm^{-1} (NH), MS (EI): 323 (M^+, 15), 295 (27), 236 (21), ^1H NMR ($CDCl_3$): δ 1.3 (t, 6H, $J = 7$ Hz, $2CH_3$), 1.97–1.99 (m, 2H, CH_2), 4.1 (q, 4H, $2CH_2$), 4.5 (t, 2H, $J = 7.5$ Hz), 4.7 (t, 2H, $J = 7.5$ Hz, CH_2), 8.5 (bs, 1H, NH), Anal. calcd for $C_{13}H_{17}N_5OS_2$: C, 48.29; H, 5.29; N, 21.60. Found: C, 48.44; H, 5.34; N, 21.72.

6,9-Bis(2-methylphenyl)-2,3-dihydroimidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidine-5,8,10 (1*H*,6H,9*H*)-trione (5c). It was synthesized from the reaction of **1a** (0.18 g, 1 mmol) and 2-tolyl isocyanate (0.8 g, 6 mmol) as described in the preceding experiment. Yield 0.3 g (75%), mp > 260 °C, IR (KBr): ν 1650 cm^{-1} (CO), 3310 cm^{-1} (NH), MS (EI): 401 (M^+, 25), 386 (11), 311 (42), 13 (100), ^1H NMR (DMSO-d_6): δ 2.38 (s, 6H, $2CH_3$), 3.4 (s, 4H, $2CH_2$), 7.1–7.3 (m, 4H, ArH), 7.6–8.0 (m, 4H, ArH), 8.3 (s, 1H, NH), Anal. calcd for $C_{22}H_{19}N_5O_3$: C, 65.82; H, 4.77; N, 17.44. Found: C, 66.13; H, 4.99; N, 17.64.

Crystal data for 2c. $C_{26}H_{17}F_3ON_6S$, monoclinic, space group $P2_1/c$, $a = 15.4414$ (8), $b = 17.3720$ (9), $c = 17.9836$ (9) Å, $\beta = 96.100$ (1)°, $V = 4796.8$ (4) $Å^3$, $Z = 8$, MoK_α, $\lambda = 0.7103$, $\mu = 0.19$ mm^{-1}, $d_{calc} = 1.436$ g/cm^3 F (000) = 2128, $T = -50$ °C. The 20413 reflections measured on a Siemens SMART CCD Area Detector yielded 6822 unique data ($2\theta_{max} = 47$, $R_{int} = 0.0325$). The structure was solved by direct methods and refined anisotropically on non-H atoms by full matrix least-squares method on F^2 with statistical weighting, geometrically ideally placed H-atoms by riding model to give $R = 0.0474$ for 5657 reflections with $I > 2\sigma$ (I) [$WR_2 = 0.1162$, $(\triangle/\sigma)_{max} = 0.000$, $S = 1.109$, 667 parameters refined]. The final difference Fourier map showed no significant peaks ($\triangle\rho_{max,\ min} = 0.222$, -0.2222 e/$Å^{-3}$). All the crystallographic calculations were performed with SHELXS86,[18] SHELXL93[19] and NRCVAX[20] program suit. Full details are available in the supporting information.

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