Efficient ionic liquid-catalysed synthesis and antimicrobial studies of 4,6-diaryl- and 4,5-fused pyrimidine-2-thiones

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One-pot three-component condensation of aromatic ketones (1-tetralones, acetophenones, indane-1,3-dione), substituted aromatic aldehydes and thiourea in the presence of *N*-methylpyridinium tosylate under solvent free conditions at 100–110 °C for 2–4 h afforded tetrahydrobenzo[*h*]quinazoline-2-thiones, pyridimidine-2-thiones and indeno-pyrimidine-2-thiones in excellent yields. All synthesised thiones were screened for their antimicrobial activities.

Keywords: *N*-methylpyridinium tosylate, spectral data, tetrahydrobenzo[*h*]qunazoline-2-thiones, pyrimidine-2-thiones, antimicrobial activities

The chemistry of sulfur-containing organic compounds has gained importance, since it has led to a multitude of compounds displaying interesting structural features and biologically active profiles. For example, organosulfur compounds have been reported to be useful as antibacterials,[1] antibiotics[2] and antioxidants.[3] We therefore explored the synthesis and antimicrobial properties of some fused and substituted pyrimidine thiones containing biologically active moieties such as tetrahydronaphthalene and indanone.

The quinazoline skeleton is of great importance as it is prevalent in many natural and synthetic biologically active compounds which find applications in the pharmaceutical and biochemical arenas.[4] The pharmacodynamic versatility of the quinazoline moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring alkaloids isolated from animals, families of plant kingdoms and from microorganism.[5,6] Quinazoline compounds are also useful in the treatment of cancer, inflammation and epilepsy disorders.[7] Two recently reported tetrahydrobenzo[*h*]quinazoli ne-2-thiones **I**, **II** (Fig. 1) are, respectively, inhibitors of phosphodiesterase 10A[8] and melanogenesis.[9]

Pyrimidines, variously substituted, are also important sub-structures found in a number of naturally occurring and biologically active substances. For example, pyrimidine-2-thiones find applications as antihypertensives *e.g.* SQ 32926 **III** (Fig. 1),[10] as potential calcium channel blockers,[11] antibacterial,[12] anti-inflammatory, antifungal,[13] antibiotics[14] and antitumour agents.[15]

Originally, tetrahydrobenzo[*h*]qunazoline-2-thiones and pyrimidine-2-thiones were prepared under thermal conditions[16] in two steps or in a single step by using different organic solvents. However, in spite of their potential utility, these methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time, cumbersome product isolation procedures, polar, volatile and hazardous organic solvents and often expensive catalysts. However, more recently there are reports of the synthesis of thiones using microwave irradiations[17] and ultrasonication.[18]

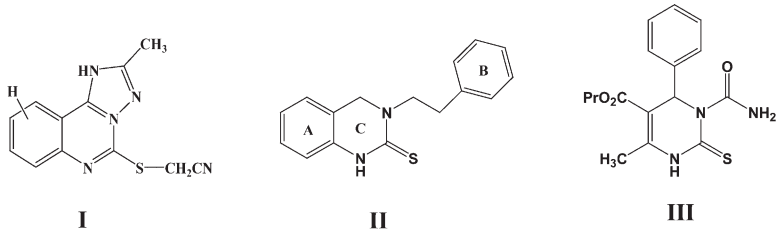
We now report the efficient synthesis of fused heterocyclic thiones using *N*-methylpyridinium tosylate, an ionic liquid, in excellent yields. The method developed has the advantage of being environmentally benign, rapid, and features an easy work up, a recyclable catalyst and affords products in excellent yields.

Results and discussion

Multicomponent reactions (MCRs) constitute a highly valuable synthetic tool for construction of heterocyclic compounds required for drug discovery programmes.[19] They provide convergent and ecofriendly assembly of three or more building blocks in practical one-pot operations.[2o] During the last decade ionic liquids have emerged as green alternatives to volatile and hazardous organic solvents. This prompted us to explore the capability of ionic liquids in the synthesis of thiones.

In the present investigations, one-pot three-component reactions of aromatic ketones (1-tetralones, acetophenones and 1,3-indandiones), aromatic aldehydes and thiourea at 100–110 °C for 2–4 h in the presence of *N*-methylpyridinium tosylate (prepared by a reported procedure[21]) afforded variously substituted tetrahydrobenzo[*h*]qunazoline-2-thiones **3**, pyrimidine-2-thiones **6** and indeno-pyrimidine-2-thiones **9** (Schemes 1–3) in excellent yield (80–90%). A plausible mechanism of the reaction is given in Scheme 4. A comparison of reaction times and yields of conventional methods,[16,23–26] microwave heating,[17,26] ultrasound irradiation[18] and our solvent-free method is made in Table 1.

It is pertinent to note that conventional synthesis of thiones either in one step (ketone + aldehyde + NH_2CSNH_2) or in two steps (2-benzylidene derivatives of ketone + NH_2CSNH_2) in presence of KOH and ethanol afforded products only after prolonged refluxing and in a low yield. The method reported in this paper requires only water to work up the products, was completed in less time and afforded products in excellent yields (Table 1). The ionic liquid was recovered after the reaction and it was found suitable for two more reaction cycles without any change in its efficiency.



I II III

Fig. 1 Structures of tetrahydrobenzo[*h*]quinazoline-2-thiones **I**, **II** and pyrimidine-2-thione SQ 32926 **III**.

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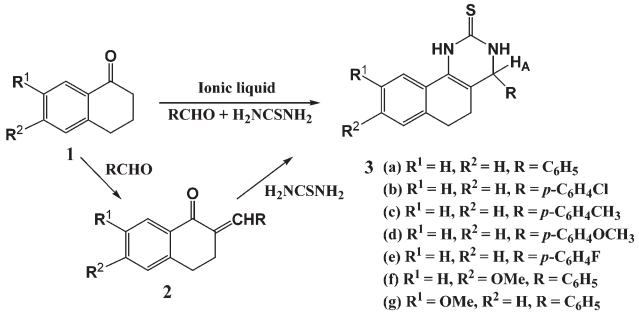
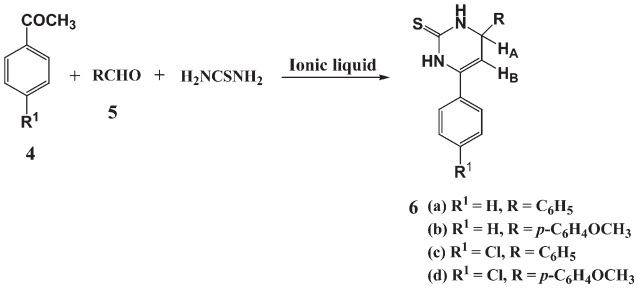


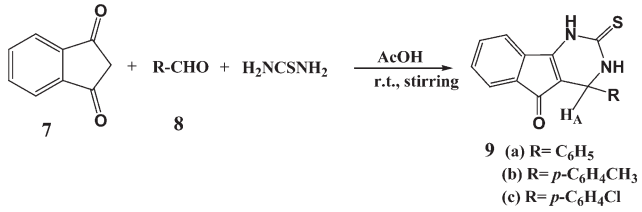
Scheme 1



Scheme 2

The products **3a–d**, **f**, **g**, and **6a**, **b**, **d** are known compounds, and were characterised by comparison of their physical and spectroscopic data with those previously reported.[16–18,23–26] The structures of the new compounds **3e**, **6c** and **9a–c** were deduced from their spectroscopic data.

The structural assignment of **3f** and **6a** as representative cases are discussed. The ^{1}H NMR spectrum of **3f** shows a singlet at δ 5.20 readily assignable to H_A (Scheme 1). Two triplets at δ 2.10, 2.78 and multiplet at δ 6.68–8.10 are assigned



Scheme 3

to the tetrahydronaphthalene ring. Similarly in the ^{1}H NMR spectrum of **6a**, appearance of a multiplet at δ 5.21 is assigned to H_A and a multiplet at δ 5.30 is assigned to H_B (Scheme 2). Aromatic protons appear as multiplet at δ 7.33–7.45 and NH protons appear at δ 6.83 and δ 7.67.

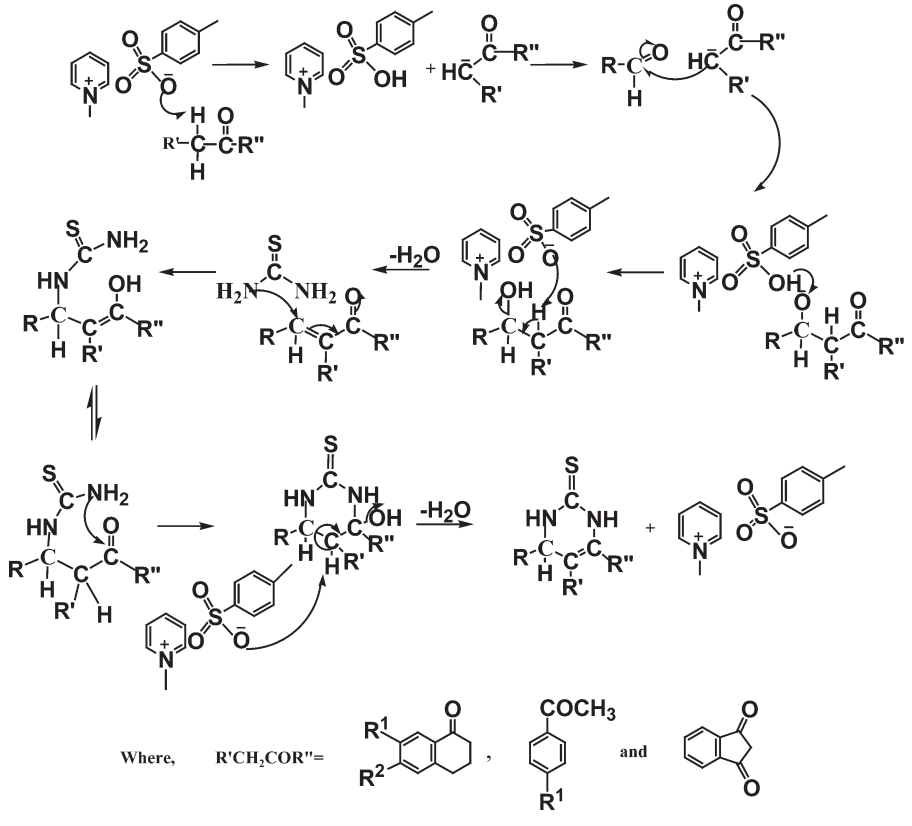
Indeno-pyrimidine-2-thiones **9a–c** were also prepared by the same method as was used for **3a–g** and **6a–d** and also under acidic conditions (using CH_3COOH) at room temperature stirring for 12–14 h which afforded thiones **9** in only moderate yield (50–60%). As a representative case, **9a** shows a singlet at δ 5.36 assigned to H_A in its ^{1}H NMR spectrum and NH protons appear as broad singlets at δ 9.77 and δ 11.68 (Scheme 3).

Antimicrobial studies

The 14 compounds, **3a–f**, **6a–d** and **9a–c**, showed a varied degree of antimicrobial activity against the test organisms employed, most showing mild to moderate antibacterial and antifungal activity (Tables 2 and 3). However, among this series of compounds **3e**, **6d**, and **9c** showed excellent activity against the gram-positive bacteria *B. Subtilis* and *S. aureus* and were the most active among their congeners in the antifungal tests.

Conclusions

In conclusion, the present procedure using an ionic liquid *N*-methylpyridinium tosylate, provides a very efficient and



Scheme 4 Plausible reaction mechanism for synthesis of pyrimidine thiones.

Table 1 Synthesis of thiones by conventional method, microwave heating, ultrasound irradiation and solvent free method

Entry	Conventional method		Microwave heating		Ultrasound irradiation		Solvent free method	
	Time of reaction/h	Yield/%	Time of reaction/min	Yield/%	Time of reaction/min	Yield/%	Time of reaction/h	Yield/%
3a	5.0	72[16]	5.3	46[17]	–	–	2.5	85
3b	5.0	76[23]	–	–	–	–	2.0	87
3c	5.0	73[23]	–	–	–	–	2.5	80
3d	5.0	70[23]	5.0	40[17]	–	–	3.0	82
3e	6.0	61	–	–	–	–	3.0	84
3f	5.0	75[24]	–	–	–	–	3.5	83
3g	5.0	65[25]	–	–	–	–	2.5	81
6a	4.5	73[26]	3.0	81[26]	20	82[18]	3.0	90
6b	6.0	68[26]	4.0	80[26]	24	75[18]	2.5	85
6c	5.5	55	–	–	–	–	3.0	88
6d	6.0	68[26]	–	–	–	–	2.5	86
9a	12.0	60	–		–	–	3.0	84
9b	14.0	54	–	–	–	–	3.5	85
9c	14.0	58	–	–	–	–	2.0	81

convenient methodology for the synthesis of fused and substituted pyrimidine thiones from active methylene compounds. The significant advantages offered by this methodology are: (a) general applicability to a large number of substrates; (b) clean and fast reaction; (c) high isolated yield of products; (d) reusability of catalyst and cost effectiveness; and (e) use of ionic liquid as a catalyst as well as reaction medium avoiding hazardous organic solvents. Some of the compounds have shown moderate antimicrobial activity. Thus we believe that this simple and green procedure will be an alternative to existing procedures.

Experimental

Melting points were determined in sulfuric acid bath and are uncorrected. TLC was performed on silica gel G plates using pet ether-ethyl acetate (4:1) as eluent and iodine vapours as visualising agent. IR spectra (ν in cm^{-1}) were recorded on an ABB FTIR spectrometer. ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker Advance II 400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). The elemental analysis of compounds was performed on a Carlo Erba-1108 elemental analyser.

Synthesis of thiones **3**, **6** *and* **9***; general procedure*

a) A mixture of 2-benzylidene derivatives of compound **1** or **4** (0.01 mol), and thiourea (0.76 g, 0.01 mol) in ethanolic potash (2.0 g KOH in 25 mL ethanol) was heated under reflux for 5–6 h, and kept overnight and the volume was reduced to half. The solid, thus obtained, was filtered, washed well with water and finally crystallised from suitable solvents to afford thiones **3a–g** and **6a–d**.

b) Thiones **3a–g** and **6a–d** were also obtained directly from, respectively, compound **1** or **4** (0.01 mol), aromatic aldehydes (0.01 mol), and thiourea (0.76 g, 0.01 mol) in ethanolic potash (2g KOH in 25 mL ethanol) by refluxing for 5–6 h. The solid obtained, was filtered off, washed well with water and finally crystallised from suitable solvents to give thiones **3a–g** and **6a–d**.

c) An equimolar mixture of 1,3-indandione (1.46 g, 0.01 mol), thiourea (0.76 g, 0.01mol) and aromatic aldehydes (0.01 mol) in glacial acetic acid (10 mL) was stirred at room temperature for 12–14 h. The solid obtained was filtered off and recrystallised from suitable solvents to obtain thiones **9a–c**.

Solvent free synthesis of thiones **3**, **6** *and* **9***; general procedure*

An equimolar mixture of compound **1**, **4** or **7** (0.01 mol), thiourea (0.76 g, 0.01 mol) and aromatic aldehydes (0.01 mol) in premolten ionic liquid, N-methylpyridinium tosylate 2.0 g was stirred at 100–110 °C for 2–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was poured into ice cold water. The solid obtained was filtered off, dried and crystallised from suitable solvents.

4-Phenyl-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3a**): M.p. 254–255 °C (DMF/water) [lit.[16] 256 °C]; IR spectrum (cm^{-1}): 1138 (C=S) 1588 (C=C) 3180 (NH); ^1H NMR: δ 2.14 (t, H, CH_2, J = 6.5 Hz), 2.78 (t, 2H, CH_2, J = 6.2 Hz), 5.39 (s, 1H, H_A), 7.23–7.50 (m, 9H, ArH), 8.10 (br, 1H, NH), 8.12 (br, 1H, NH); Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.97; H, 5.48; N, 9.59; S, 10.96. Found: C, 73.90; H, 5.41; N, 9.52; S, 10.88%.

Table 2 Antibacterial activities of variously substituted pyrimidine-2-thiones **3a–g, 6a–d** and **9a–c**

Sr. no.	Entry	Zone of inhibition/mm			
		Gram Positive		Gram Negative	
		B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
1	**3a**	10	11	8	9
2	**3b**	19	18	14	16
3	**3c**	12	12	10	11
4	**3d**	15	16	12	13
5	**3e**	22	23	12	13
6	**3f**	16	15	12	14
7	**3g**	17	16	15	16
8	**6a**	11	10	16	17
9	**6b**	12	12	5	16
10	**6c**	13	14	8	9
11	**6d**	19	22	13	12
12	**9a**	9	10	6	8
13	**9b**	15	14	10	11
14	**9c**	21	24	12	14
	Ampicillin trihydrate	26	28	24	21
	DMSO	00	00	00	00

Table 3 Antifungal activities of variously substituted pyrimidine-2-thiones **3a–g, 6a–d** and **9a–c**

Sr.no.	Entry	Zone of inhibition/mm		
		A. niger	*C. albicans*	*A. fumigatus*
1	**3a**	8	7	10
2	**3b**	18	15	17
3	**3c**	11	12	14
4	**3d**	14	13	15
5	**3e**	20	19	18
6	**3f**	16	13	16
7	**3g**	15	14	14
8	**6a**	7	8	9
9	**6b**	9	11	10
10	**6c**	14	16	11
11	**6d**	21	20	17
12	**9a**	8	10	11
13	**9b**	12	14	17
14	**9c**	19	17	19
	Ampicillin trihydrate	24	25	22
	DMSO	0	0	0

4-(4-Chloro-phenyl)-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3b**): M.p. 246–248 °C (DMF/water) [lit.[23] 250–251 °C]; IR (cm^{-1}): 1141 (C=S), 1579 (C=C), 3200 (NH); ^1H NMR: δ 2.20 (t, 2H, CH_2, J = 6.8 Hz), 2.84 (t, 2H, CH_2, J = 6.5 Hz), 5.43 (s, 1H, H_A), 7.25–7.55 (m, 8H, ArH), 8.00 (br, 1H, NH), 8.02 (br, 1H, NH); Anal. Calcd for $C_{18}H_{15}N_2SCl$: C, 66.16; H, 4.59; N, 8.58; S, 9.80. Found: C, 66.30; H, 4.67; N, 8.63; S, 9.72%.

4-p-Tolyl-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3c**): M.p. 228–230 °C (DMF/water) [lit.[23] 230–232 °C]; IR (cm^{-1}): 1214 (C=S), 1568 (C=C); ^1H NMR: δ 2.18 (t, 2H, CH_2, J = 6.9 Hz), 2.38 (s, 3H, CH_3), 2.84 (t, 2H, CH_2, J = 6.1 Hz), 5.36 (s, 1H, H_A), 7.20–7.50 (m, 8H, ArH), 7.55 (br, 1H, NH), 7.62 (br, 1H, NH); Anal. Calcd for $C_{19}H_{18}N_2S$: C, 74.51; H, 5.88; N, 9.15; S, 10.46. Found: C, 74.57; H, 5.81; N, 9.00; S, 10.40%.

4-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3d**): M.p. 226–228 °C (DMF/water) [lit.[23] 220–222 °C]; IR (cm^{-1}): 1210 (C=S), 1611 (C=C), 3200 (NH); ^1H NMR: δ 2.18 (t, 2H, CH_2, J = 6.5 Hz), 2.83 (t, 2H, CH_2, J = 6.4 Hz), 4.0 (s, 3H, OCH_3), 5.43 (s, 1H, H_A), 7.28 (m, 4H, ArH), 7.26–7.54 (m, 4H, ArH), 7.90 (br, 1H, NH), 7.98 (br, 1H, NH); Anal. Calcd for $C_{19}H_{18}N_2SO$: C, 70.80; H, 5.59; N, 8.69; S, 9.94. Found: C, 70.86; H, 5.52; N, 8.65; S, 9.90%.

4-(4-Fluoro-phenyl)-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3e**): M.p. 228–230 °C (DMF/water); IR (cm^{-1}): 1215 (C=S), 1650 (C=C), 3170 (NH); ^1H NMR: δ 2.16 (t, 2H, CH_2, J = 7.0 Hz), 2.40 (t, 2H, CH_2, J = 6.7 Hz), 5.40 (s, 1H, H_A), 7.35–7.60 (m, 8H, ArH), 8.12 (br, 1H, NH), 8.14 (br, 1H, NH); Anal. Calcd for $C_{18}H_{15}N_2SF$: C, 69.67; H, 4.84; N, 9.03; S, 10.32. Found: C, 69.60; H, 4.90; N, 9.10; S, 10.39%.

8-Methoxy-4-phenyl-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3f**): M.p. 244–246 °C (EtOH) [lit.[24] 248–250 °C]; IR (cm^{-1}): 1304 (C=S), 3202 (NH); ^1H NMR: δ, 2.10 (t, 2H, CH_2, J = 7.7 Hz), 2.78 (t, 2H, CH_2, J = 7.2 Hz), 3.80 (s, 3H, OCH_3), 5.20 (s, 1H, H_A), 6.68–8.10 (m, 8H, ArH), 8.14 (br, 1H, NH), 8.16 (br, 1H, NH); Anal. Calcd for $C_{19}H_{18}N_2SO$: C, 70.80; H, 5.59; N, 8.69; S, 9.94. Found: C, 70.88; H, 5.54; N, 8.62; S, 9.88%.

9-Methoxy-4-phenyl-3,4,5,6-tetrahydro-1H-benzo[h]quinazoline-2-thione (**3g**): M.p. 232–233 °C (EtOH) [lit.[25] 230–235 °C]; IR (cm^{-1}): 1315 (C=S), 1558 (C=C); ^1H NMR: δ 2.12 (t, 2H, CH_2, J = 6.1 Hz), 2.76 (t, 2H, CH_2, J = 6.6 Hz), 3.82 (s, 3H, OCH_3), 5.25 (s, 1H, H_A), 6.77–8.16 (m, 8H, ArH), 8.18 (br, 1H, NH), 8.20 (br, 1H, NH); Anal. Calcd for $C_{19}H_{18}N_2SO$: C, 70.80; H, 5.59; N, 8.69; S, 9.94. Found: C, 70.86; H, 5.56; N, 8.63; S, 9.90%.

4,6-Diphenyl-3,4-dihydro-1H-pyrimidine-2-thione (**6a**): M.p. 160–162 °C (EtOH); IR (cm^{-1}): 1180 (C=S), 1558 (C=C), 3171 (NH); ^1H NMR: δ 5.21 (m, 1H, H_A), 5.30 (m, 1H, H_B), 6.83 (br, 1H, NH), 7.33–7.45 (m, 10H, ArH), 7.67 (br, 1H, NH); Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.18; H, 5.26; N, 10.53; S, 12.03. Found: C, 72.10; H, 5.32; N, 10.58; S, 12.09%.

4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydro-1H-pyrimidine-2-thione (**6b**): M.p. 175–176 °C (DMF/water); IR (cm^{-1}): 1250 (C=S), 1558 (C=C), 3202 (NH); ^1H NMR: δ 3.78 (s, 3H, OCH_3), 5.12–5.14 (m, 1H, H_A), 5.18–5.20 (m, 1H, H_B), 6.87–6.90 (m, 2H, ArH), 7.27–7.30 (m, 2H, ArH), 7.34–7.38 (m, 3H, ArH), 7.48–7.50 (m, 2H, ArH), 8.75 (br, 1H, NH), 9.05 (br, 1H, NH); Anal. Calcd for $C_{17}H_{16}N_2SO$: C, 68.91; H, 5.41; N, 9.46; S, 10.81. Found: C, 68.99; H, 5.48; N, 9.40; S, 10.87%.

6-(4-Chlorophenyl)-4-phenyl-3,4-dihydro-1H-pyrimidine-2-thione (**6c**): M.p. 180–182 °C (EtOH); IR (cm^{-1}): 1234 (C=S), 1566 (C=C); ^1H NMR: δ 5.19 (s, 1H, H_A), 5.28 (s, 1H, H_B), 7.35–7.50 (m, 5H, ArH), 7.56 (br, 1H, NH), 7.80 (br, 1H, NH), 8.02–8.06 (m, 2H, ArH), 8.07–8.09 (m, 2H, ArH); Anal. Calcd for $C_{16}H_{13}N_2SCl$: C, 63.89; H, 4.33; N, 9.32; S, 10.65. Found: C, 63.81; H, 4.39; N, 10.58; S, 9.37%.

6-(4-Chlorophenyl)-4-(methoxyphenyl)-3,4-dihydro-1H-pyrimidine-2-thione (**6d**): M.p. 225–226 °C (DMF/water); IR (cm^{-1}): 1227 (C=S), 1566 (C=C); ^1H NMR: δ 5.17 (s, 1H, H_A), 5.30 (s, 1H, H_B), 7.30–7.52 (m, 5H, ArH), 7.58 (br, 1H, NH), 7.82 (br, 1H, NH), 8.05–8.08 (m, 2H, ArH), 8.03–8.08 (m, 2H, ArH); Anal. Calcd for $C_{17}H_{15}N_2SClO$: C, 61.72; H, 4.54; N, 8.47; S, 9.68. Found: C, 61.79; H, 4.58; N, 8.40; S, 9.60%.

4-Phenyl-1,3,4,4a,5,9b-hexahydroindeno[1,2-d]pyrimidine-2-thione (**9a**): M.p. 224–226 °C (EtOH); IR (cm^{-1}): 1173 (C=S), 1636 (C=C), 1674 (C=O); ^1H NMR: δ 5.36 (s, 1H, H_A), 7.25–7.39 (m, 8H, ArH), 7.80–7.86 (m, 1H, ArH), 9.77 (br, 1H, NH), 11.68 (br, 1H, NH); Anal. Calcd for $C_{17}H_{12}N_2SO$: C, 69.86; H, 4.11; N, 9.59; S, 10.96. Found: C, 69.80; H, 4.18; N, 9.51; S, 10.89%.

4-p-Tolyl-1,3,4,4a,5,9b-hexahydroindeno[1,2-d]pyrimidine-2-thione (**9b**): M.p. 170–172 °C (EtOH); IR (cm^{-1}): 1270 (C=S), 1640 (C=C), 1670 (C=O); ^1H NMR: δ 2.52 (s, 3H, CH_3), 5.38 (s, 1H, H_A), 7.48–7.49 (m, 2H, ArH), 7.74–7.76 (m, 2H, ArH), 7.80–7.84 (m, 4H, ArH), 8.41 (br, 1H, NH), 8.62 (br, 1H, NH); Anal. Calcd for $C_{18}H_{14}N_2SO$: C, 70.59; H, 4.58; N, 9.15; S, 10.46. Found: C, 70.51; H, 4.63; N, 9.08; S, 10.54%.

4-(4-Chlorophenyl)-1,3,4,4a,5,9b-hexahydroindeno[1,2-d]pyrimidine-2-thione (**9c**): M.p. 200–202 °C (DMF/water); IR (cm^{-1}): 1312 (C=S), 1630 (C=C), 1680 (C=O); ^1H NMR: δ 5.32 (s, 1H, H_A), 7.40–7.43 (m, 2H, ArH), 7.72–7.75 (m, 2H, ArH), 7.84–7.86 (m, 4H, ArH), 8.50 (br, 1H, NH), 8.72 (br, 1H, NH); Anal. Calcd for $C_{17}H_{11}N_2SClO$: C, 62.48; H, 3.37; N, 8.58; S, 9.80. Found: C, 62.40; H, 3.42; N, 8.50; S, 9.88%.

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