Simple Ultrasound-Assisted Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one and 3,4-Dihydropyrimidine-2(1*H*)-thione-Fused Steroidal Derivatives by a Three-Component Reaction

Mandakini Dutta, Junali Gogoi, Kommoori Shekarrao, Jonalee Goswami, Sanjib Gogoi,* Romesh Chandra Boruah*

Medicinal Chemistry Division, CSIR-North East Institute of Science and Technology, Jorhat 785006, India
Fax +91(376)2370011; E-mail: skgogoi1@gmail.com; E-mail: rc_boruah@yahoo.co.in

Received: 26.04.2012; Accepted after revision: 30.05.2012

Abstract: Compounds containing fused 3,4-dihydropyrimidin-2(1*H*)-one or 3,4-dihydropyrimidine-2(1*H*)-thione moieties were prepared by three-component reactions of a steroidal or nonsteroidal ketone, an alkyl or aryl aldehyde, and urea or thiourea in the presence of sodium ethoxide. The products were isolated in good yields after short reaction times under mild conditions.

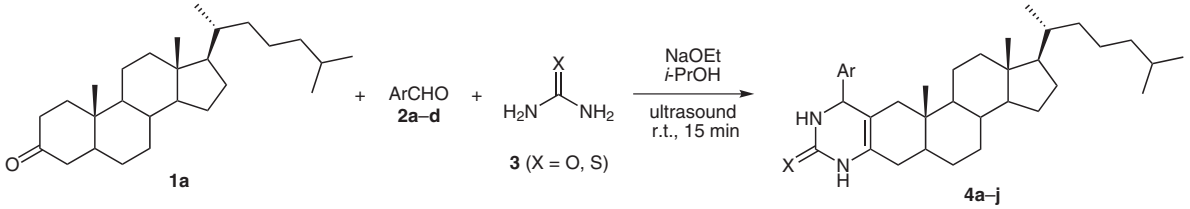
Key words: steroids, heterocycles, multicomponent reactions, ultrasound

Dihydropyrimidinones and dihydropyrimidinethiones are important classes of bioactive molecules that can exhibit a wide range of properties, such as antiviral, antitumor, antibacterial, or antiinflammatory activities.[1] These compounds can also act as calcium-channel blockers, antihypertensives, anticancer agents, neuropeptide Y antagonists, and α_{1a} adrenergic antagonists.[2] The biological activity of some recently isolated alkaloids has been attributed to the presence of a dihydropyrimidinone moiety,[1a,3] the most prominent of these alkaloids being the batzalladine alkaloids, which are potent inhibitors of HIV-gp-120-CD4.[3a]

The synthesis of dihydropyrimidinones and their thione analogues was first reported by Biginelli in 1893.[4] Improved procedures and new Biginelli-like scaffolds have been reported over the past decade, and considerable efforts have been made to develop new methods for the synthesis of such compounds because of their therapeutic and pharmacological properties.[2c,5] There are several reports on the synthesis of derivatives of dihydropyrimidinone and dihydropyrimidinethione by using protic acids,[6] Lewis acids,[7] triflates,[8] microwave irradiation,[9] ionic liquids,[10] metallic salts,[11] Dowex-50W,[12] or polyaniline, tetrafluoroboric acid, and dodecyl hydrogen sulfate.[13] Unfortunately, many of these methods suffer from major or minor limitations, such as harsh reaction conditions, low yields, expensive or toxic reagents, stoichiometric requirements for catalysts, strongly acidic conditions, long reaction times, or incompatibility with various functional groups. Therefore, the development of a milder, faster, eco-friendly, and high-yielding protocol for the synthesis of compounds containing a 3,4-dihydropyrimidin-2(1*H*)-one or a 3,4-dihydropyrimidine-2(1*H*)-thione moiety remains of great importance and represents a considerable challenge.

The recent development of synthetic protocols that use ultrasound irradiation has led to epoch-making changes in organic chemistry, as it permits the activation of substrates that have low reactivities.[14] Among the notable features of ultrasound-promoted reactions that are recognized as having value in green chemistry[14c,d] are enhanced reaction rates, the formation of purer products in improved yields, greater ease of manipulation, improved energy conservation, and minimization of wastes.[15]

Multicomponent reactions form an important class of reactions that are related to tandem reactions and that can be used to generate vast libraries of compounds with great rapidity. The highly flexible and selective nature of multicomponent reactions makes them convenient tools for the construction of many heterocyclic compounds.[16] It is known that the Biginelli reaction catalyzed by acids such as hydrochloric, trifluoroacetic, or aminosulfonic acid is accelerated by ultrasound.[17] Even Bignelli reactions catalyzed by ceric ammonium nitrate, ionic liquids, iodine, ammonium chloride, silica, or magnesium perchlorate are



Scheme 1 Ultrasound-promoted, one-pot, three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2(1*H*)-thiones

SYNTHESIS 2012, 44, 2614–2622
Advanced online publication: 13.07.2012
DOI: 10.1055/s-0032-1316564; Art ID: SS-2012-Z0392-OP

Table 1 Optimization of the Conditions for the Synthesis of the Fused 3,4-Dihydropyrimidin-2(1*H*)-One **4a**

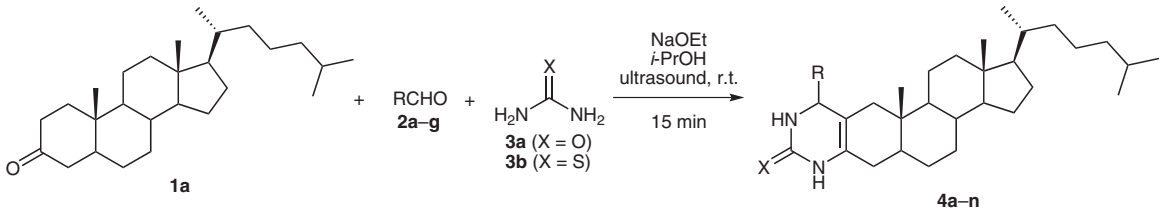
Entry	Solvent	Method[a]	Time (h)	Temp (°C)	Yield (%)[b]
1	EtOH	US	0.25	r.t.	77
2	EtOH	MW	0.25	90	50
3	EtOH	TH	6	90	56
4	*i*-PrOH	US	0.25	r.t.	94
5	*i*-PrOH	MW	0.25	90	63
6	*i*-PrOH	TH	6	90	65
7	H_2O	US	0.25	r.t.	33
8	neat	MW	0.25	90	39
9	H_2O–*i*-PrOH (8:2)	US	0.25	r.t.	70

[a] US: Ultrasound irradiation; MW: Microwave irradiation; TH: thermal heating.
[b] Isolated yield of isolated product.

promoted by ultrasound.[18] However, there are few reports on base-catalyzed Biginelli reactions[19] and, the best of our knowledge, there is no report of an ultrasound-assisted, base-mediated, one-pot, Biginelli-type, three-component reaction of a cyclic ketone, an aldehyde, and urea or thiourea. In a continuation of our studies on heterosteroids,[20] we present a very simple, mild, economic, and efficient strategy for the synthesis of dihydropyrimidinone- or dihydropyrimidinethione-fused steroids and nonsteroids through an ultrasound-promoted, three-component, one-pot condensation of a ketone, an aldehyde, and thiourea or urea in the presence of an equimolar amount of base using 2-propanol as an environmentally benign solvent.[21]

We began our study by investigating the reaction of cholestan-3-one (**1a**) with benzaldehyde (**2a**) and urea (**3a**) in presence of an equimolar amount of sodium ethoxide as the base (Scheme 1). We performed an extensive optimization of the three-component reaction to determine the best condition for the synthesis of the 3,4-dihydropyrimidine-2(1*H*)one-fused steroid product **4a** (Table 1). Initially, we examined the synthesis of **4a** by three different methods involving ultrasound irradiation (US), microwave irradiation (MW), and conventional thermal heating (TH), respectively. We selected the protic solvents etha-

Table 2 Ultrasound-Assisted Syntheses of Steroidal A-Ring Fused 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2(1*H*)-thiones



Entry	RCHO	X	Product (**4a–j**)	Yield (%)[a]
1	PhCHO (**2a**)	O	**4a**	94
2	4-TolCHO (**2b**)	O	**4b**	90
3	4-FC_6H_4CHO (**2c**)	O	**4c**	93
4	3-BrC_6H_4CHO (**2d**)	O	**4d**	86
5	PrCHO (**2e**)	O	**4e**	91
6	BuCHO (**2f**)	O	**4f**	88
7	$Me(CH_2)_4$CHO (**2g**)	O	**4g**	88
8	PhCHO (**2a**)	S	**4h**	90
9	4-TolCHO (**2b**)	S	**4i**	87
10	4-FC_6H_4CHO (**2c**)	S	**4j**	88
11	3-BrC_6H_4CHO (**2d**)	S	**4k**	88
12	PrCHO (**2e**)	S	**4l**	90
13	BuCHO (**2f**)	S	**4m**	91
14	$Me(CH_2)_4$CHO (**2g**)	S	**4n**	93

[a] Yield of the isolated product.

nol, 2-propanol, and water as media for the reaction. When the three-component reaction was carried in ethanol or 2-propanol under thermal condition for six hours, the product **4a** was obtained in 56 and 65% yield, respectively (Table 1, entries 3 and 6, respectively). Similarly, the microwave-mediated reaction of **1a**, **2a**, and **3a** in protic solvent under basic condition gave **4a** in 50–63% yield (entries 2 and 5), whereas the solid-phase three-component reaction with microwave heating for 15 minutes gave a 39% yield of **4a** (entry 8). Our initial attempt to carry out the three-component reaction with ultrasonication in water as the solvent gave a poor yield (33%) of **4a** (entry 7). However, we observed that the use of isopropanol as a cosolvent (20%) improved the yield of **4a** to 70% (entry 9). The best yield (94%) was, however, obtained by conducting the three-component reaction with ultrasound irradiation in 2-propanol as the solvent (entry 4).

Next, we examined the three-component reaction of cholestan-3-one (**1a**) with various aromatic or aliphatic aldehydes **2b–g** and urea (**3a**) or thiourea (**3b**) under our optimized reaction conditions (Table 2). The corresponding products **4b–n** were obtained in in 86–93% yields.

To evaluate the scope and limitations of the reaction further, we extended it to the steroidal A-ring conjugated ketone **1b**, the D-ring oxo steroid **1c**, the B-ring conjugated ketone **1d**, and the nonsteroidal cyclic ketones **1e–f** under our optimized condition, and we obtained products **4o–x** in 85–91% yields (Table 3).

Table 3 Ultrasound-Assisted Syntheses of Steroidal and Nonsteroidal 3,4-Dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2(1*H*)-thiones

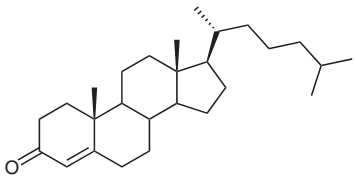
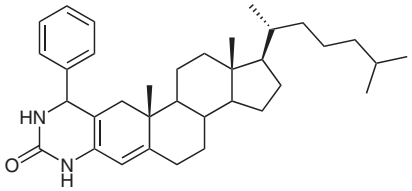
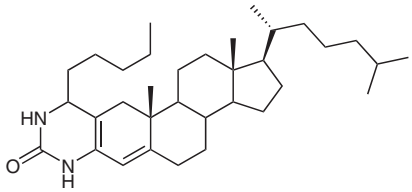
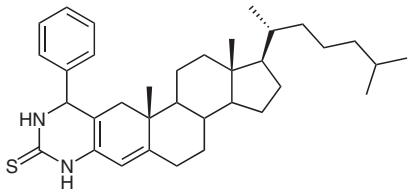
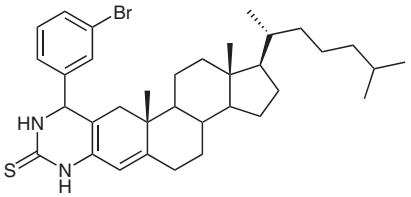
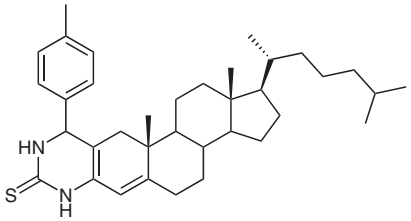
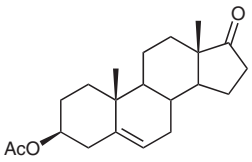
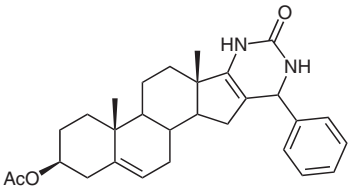
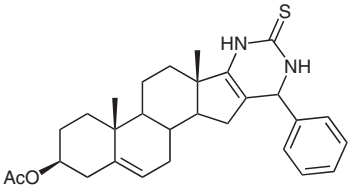
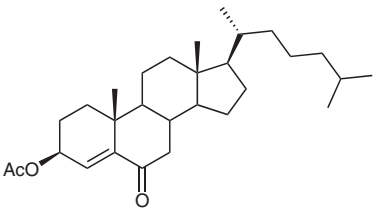
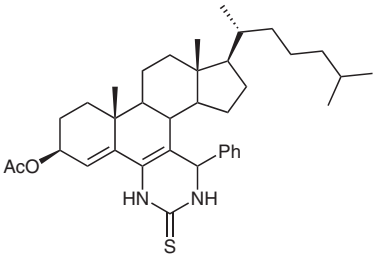
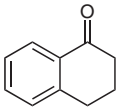
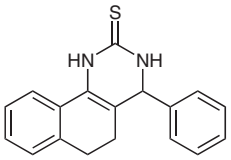
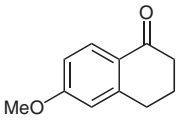
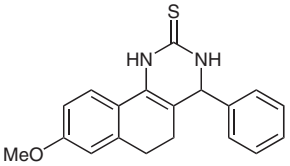
Entry	Ketone	RCHO	X	Product	Yield (%)[a]
1	**1b** 	PhCHO (**2a**)	O	**4o** 	90
2	**1b**	$Me(CH_2)_4CHO$ (**2g**)	O	**4p** 	87
3	**1b**	PhCHO (**2a**)	S	**4q** 	90
4	**1b**	3-BrC_6H_4CHO (**2d**)	S	**4r** 	91
5	**1b**	4-TolCHO (**2b**)	S	**4s** 	89

Table 3 Ultrasound-Assisted Syntheses of Steroidal and Nonsteroidal 3,4-Dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2(1*H*)-thiones (continued)

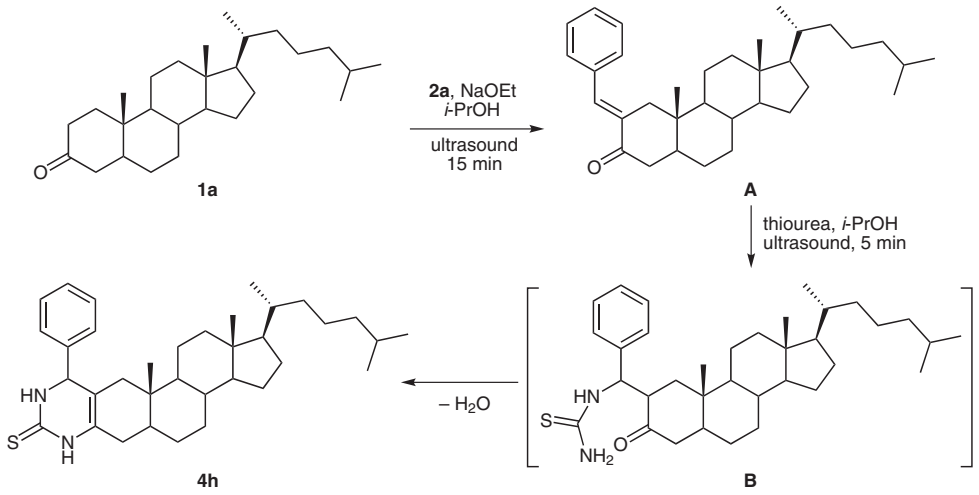
Entry	Ketone	RCHO	X	Product	Yield (%)[a]
6	**1c** 	PhCHO (**2a**)	O	**4t** 	87
7	**1c**	PhCHO (**2a**)	S	**4u** 	90
8	**1d** 	PhCHO (**2a**)	S	**4v** 	86
9	**1e** 	PhCHO (**2a**)	S	**4w** 	86
10	**1f** 	PhCHO (**2a**)	S	**4x** 	85

[a] Yield of the isolated product.

The fused steroids and nonsteroids **4a**–**x** were characterized by means of ^{1}H and ^{13}C NMR spectroscopy and GC/MS.

In relation to the mechanism, we believe that the initial condensation of benzaldehyde (**2a**) on the α-position of ketone **1a** under basic condition leads to the formation of the intermediate *exo*-α,β-unsaturated ketone **A**; this readily undergoes a Michael addition reaction with thiourea to afford intermediate **B**. This intermediate then undergoes dehydrative cyclization to give the product **4h**. To substantiate this mechanism, we independently prepared the stable intermediate 2-benzylidenecholestan-3-one (**A**) by condensation of cholestan-3-one (**1a**) with benzaldehyde (**2a**), and we treated intermediate **A** with thiourea under ultrasound to give the fused derivative **4h** in high yield (88%). The most probable reason for the increase in the efficiency of the reaction in the presence of ultrasound is that cavitation creates bubbles that collapse, inducing mechanical stress that can be transmitted to a target bond.[22]

In summary, we have developed a simple, rapid, and efficient base-catalyzed one-pot procedure for the annulation of a 3,4-dihydropyrimidin-2(1*H*)-one or 3,4-dihydropyrimidine-2(1*H*)-thione moiety onto the A-, B-, or D-ring of a steroid by a three-component reaction of a steroidal ketone, an aromatic or aliphatic aldehyde, and urea or thiourea. We have compared the ultrasound-promoted Biginelli-type reaction with the corresponding reactions under conventional heating or microwave heating, and we have shown that the ultrasound-mediated reaction produces the best results. The reaction provides a new method for the preparation of A-, B- and D-ring-fused steroidal 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidin-2(1*H*)-thiones from keto steroids or endocyclic conjugated keto steroids. This new method provides significant advantages in comparison to previous methods[6–13] for



Scheme 2 Proposed mechanism for the formation of a steroidal 3,4-dihydropyrimidin-2(1*H*)-thione

synthesizing 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidin-2(1*H*)-thiones, in that the reaction is easy to perform and can be conducted at ambient temperature with short reaction times and very simple workup to give good yields (85–94%) of the required products.

Melting points were measured with a Buchi B-540 melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-2000 spectrometer by using KBr pellets. NMR spectra were recorded on a Bruker Avance DPX 300-MHz FT-NMR spectrometer with TMS as the internal standard. Mass spectra were recorded on a Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by TLC on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (60–120 mesh, Merck Chemicals). Sonication was carried in round-bottom flasks immersed in a standard ultrasonic bath producing sound waves at 44.2 kHz. All microwave reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor.

3,4-Dihydropyrimidin-2′(1*H*)-ones and 3,4-Dihydropyrimidine-2′(1*H*)-thiones; General Procedures

Method I (Ultrasound)
A mixture of the ketone (1 mmol), aldehyde (1 mmol), urea or thiourea (1 mmol), and NaOEt (1 mmol) in *i*-PrOH (10 mL) was irradiated with ultrasound for 15 min. The solvent was removed in a rotatory evaporator, and the crude residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)].

Method II (Microwave Heating)
A mixture of the ketone (1 mmol), aldehyde (1 mmol), urea or thiourea (1 mmol), and NaOEt (1 mmol) in *i*-PrOH (10 mL) was irradiated with microwaves in a closed vessel in a Synthos 3000 microwave reactor at 450 W (90 °C and 11 bar) for 15 min. The solvent was removed in a rotatory evaporator, and the crude residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)].

Method III (Thermal)
A mixture of the ketone (1 mmol), aldehyde (1 mmol), urea or thiourea (1 mmol), and NaOEt (1 mmol) was refluxed in *i*-PrOH (10 mL) for 6 h. The solvent was removed in a rotatory evaporator, and the crude residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)].

4′-Phenyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4a)
Yield: 485 mg (94%); light-yellow solid; mp 174–176 °C.

IR (KBr): 3237, 2930, 2868, 1686, 1466, 1220, 770, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.02 (m, 6 H), 5.32 (s, 1 H), 4.74 (s, 1 H), 2.00–0.50 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 143.2, 128.8, 128.7, 127.9, 127.3, 127.0, 126.9, 103.7, 61.7, 56.3, 53.3, 42.4, 40.9, 40.1, 39.8, 39.5, 36.1, 35.8, 35.4, 35.0, 31.5 (2C), 29.7, 28.2, 28.0, 24.2, 23.8 (2C), 22.8, 22.6, 21.0, 18.7 12.0, 11.9.

MS (EI): *m/z* = 516 $[M]^+$.

Anal. Calcd for $C_{35}H_{52}N_2O$: C, 81.34; H, 10.14; N, 5.42. Found: C, 81.19; H, 10.27; N, 5.73.

4′-(4-Tolyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4b)
Yield: 477 mg (90%); light-yellow solid; mp 202–204 °C.

IR (KBr): 3237, 2931, 2869, 1687, 1467, 1219, 770, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–6.88 (m, 5 H), 5.26 (s, 1 H), 4.71 (s, 1 H), 2.38–0.52 (m, 47 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 143.1, 129.3, 128.3 (2C), 128.0, 127.1 (2C), 105.1, 61.1, 56.3 (2C), 53.5, 42.3, 41.1, 40.1, 39.8 (2C), 39.4, 36.1, 35.7, 35.4, 34.1, 31.8 (2C), 28.2, 28.0, 24.2, 23.8 (2C), 22.8, 22.7, 21.0, 18.7, 12.1, 12.0.

MS (EI): *m/z* = 530.4 $[M^+]$.

Anal. Calcd for $C_{36}H_{54}N_2O$: C, 81.46; H, 10.25; N, 5.28. Found: C, 81.19; H, 10.21; N, 5.33.

4′-(4-Fluorophenyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4c)
Yield: 497 mg (93%); light-yellow solid; mp 228–229 °C.

IR (KBr): 3237, 2930, 2868, 1687, 1467, 1218, 772, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–6.76 (m, 5 H), 5.38 (s, 1 H), 4.75 (s, 1 H), 2.27–0.64 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 142.9, 129.4, 128.5 (2C), 128.2, 127.2 (2C), 105.0, 61.1, 56.2 (2C), 53.4, 42.4, 40.9, 40.1, 39.8, 39.5, 36.2, 35.7, 35.4, 34.1, 31.8 (2C), 28.2, 28.1, 24.1, 23.7 (2C), 22.8, 22.7, 21.1, 18.7, 12.1, 11.9.

MS (EI): *m/z* = 534.4 $[M^+]$.

Anal. Calcd for $C_{35}H_{51}FN_2O$: C, 78.61; H, 9.61; N, 5.24. Found: C, 78.66; H, 9.73; N, 5.50.

4′-(3-Bromophenyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4d)
Yield: 511 mg (86%); light-yellow solid; mp 232–234 °C.

IR (KBr): 3236, 2930, 2869, 1686, 1467, 1219, 770, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–6.69 (m, 5 H), 5.37 (s, 1 H), 4.71 (s, 1 H), 2.28–0.54 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 144.0, 130.0, 128.5, 128.2, 127.4, 126.6, 126.4, 104.3, 61.0, 56.2, 53.5, 42.4, 41.0, 40.1, 39.8, 39.5 (2C), 36.1, 35.8, 35.4, 34.1, 31.8 (2C), 28.2, 28.0, 24.2, 23.8 (2C), 22.9, 22.6, 21.1, 18.7, 12.1, 12.0.

MS (EI): *m/z* = 516.4 $[M - Br]^+$.

Anal. Calcd for $C_{35}H_{51}BrN_2O$: C, 70.57; H, 8.63; N, 4.70. Found: C, 70.77; H, 8.69; N, 4.75.

4′-Propyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4e)
Yield: 439 mg (91%); light-yellow solid; mp 183–184 °C.

IR (KBr): 3249, 2929, 2868, 1715, 1467, 1222, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 5.67 (s, 1 H), 3.73 (m, 1 H), 2.19–0.66 (m, 51 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 142.2, 105.4, 56.9, 56.3 (2C), 54.2, 44.6, 42.4, 39.8, 39.5 (2C), 36.2, 35.8, 35.4, 35.3, 31.8 (2C), 31.5, 29.8, 28.2, 28.0 (2C), 24.2 (2C), 23.9 (2C), 22.5, 18.7, 14.2, 11.9, 11.8.

MS (EI): *m/z* = 482.4 $[M^+]$.

Anal. Calcd for $C_{32}H_{54}N_2O$: C, 79.61; H, 11.27; N, 5.80. Found: C, 79.82; H, 11.30; N, 5.73.

4′-Butyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4f)
Yield: 437 mg (88%); light-yellow solid; mp 187 °C.

IR (KBr): 3249, 2929, 2868, 1716, 1467, 1222, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.04 (s, 1 H), 5.66 (s, 1 H), 3.74 (m, 1 H), 2.20–0.68 (m, 53 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 142.2, 105.4, 56.9, 56.3 (2C), 54.3, 44.8, 42.4, 39.8, 39.5 (2C), 36.1, 35.8, 35.4, 35.3, 31.8 (2C), 31.5, 29.7, 28.2, 28.0 (2C), 24.2 (2C), 23.8 (2C), 23.3, 22.6, 18.7, 14.1, 11.9, 11.8.

MS (EI): *m/z* = 496.4 $[M^+]$.

Anal. Calcd for $C_{33}H_{56}N_2O$: C, 79.78; H, 11.36; N, 5.64. Found: C, 79.83; H, 11.20; N, 5.79.

4′-Pentyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestan-2′(1′*H*)-one (4g)
Yield: 449 mg (88%); light-yellow solid; mp 194–195 °C.

IR (KBr): 3249, 2929, 2868, 1716, 1467, 1221, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.03 (s, 1 H), 5.70 (s, 1 H), 3.79 (s, 1 H), 2.19–0.66 (m, 55 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 142.2, 105.4, 56.9, 56.2 (2C), 54.4, 44.9, 42.4, 39.9, 39.5 (2C), 36.1, 35.8, 35.4, 35.3, 31.8 (2C), 31.5, 29.7, 28.2, 28.0 (2C), 24.2 (2C), 23.9 (2C), 23.3, 22.9, 22.6, 18.7, 14.2, 11.9, 11.8.

MS (EI): *m/z* = 510.4 $[M^+]$.

Anal. Calcd for $C_{34}H_{58}N_2O$: C, 79.94; H, 11.44; N, 5.48. Found: C, 79.78; H, 11.25; N, 5.72.

4′-Phenyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4h)
Yield: 479 mg (90%); light-yellow solid; mp 201–203 °C.

IR (KBr): 3190, 2928, 2868, 1567, 1468, 1208, 758, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.13 (m, 6 H), 6.48 (s, 1 H), 4.77 (s, 1 H), 1.87–0.63 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 141.8, 130.1, 129.8, 128.9, 128.4, 127.2, 126.0, 107.0, 61.3, 56.3, 53.3, 42.4, 41.8, 39.8 (2C), 36.1, 35.8, 35.4, 35.3, 31.5 (2C), 29.8, 28.2, 28.0, 24.2, 23.8 (2C), 22.8, 22.6, 21.1, 18.7, 12.1, 12.0, 11.9.

MS (EI): *m/z* = 532.4 $[M^+]$.

Anal. Calcd for $C_{35}H_{52}N_2S$: C, 78.89; H, 9.84; N, 5.26. Found: C, 78.95; H, 9.90; N, 5.23.

4′-(4-Tolyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4i)
Yield: 475 mg (87%); light-yellow solid; mp 212–214 °C.

IR (KBr): 3192, 2929, 2869, 1570, 1490, 1220, 756, 666 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1 H) 7.38–7.01 (m, 5 H), 4.55 (s, 1 H), 1.99–0.43 (m, 47 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 141.6, 129.0, 128.1 (2C), 127.1 (2C), 125.5, 106.8, 61.9, 56.3 (2C), 53.3, 42.4, 40.9, 39.8 (2C), 39.5, 36.1, 35.8, 35.0, 31.4, 30.0, 28.1, 28.0 (2C), 24.2 (2C), 23.8 (2C), 22.8, 22.6, 21.0, 18.6, 12.0, 11.9.

MS (EI): *m/z* = 546 $[M^+]$.

Anal. Calcd for $C_{36}H_{54}N_2S$: C, 79.06; H, 9.95; N, 5.12. Found: C, 78.85; H, 9.80; N, 5.36.

4′-(4-Fluorophenyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4j)
Yield: 484 mg (88%); light-yellow solid; mp 221–223 °C.

IR (KBr): 3192, 2926, 2868, 1570, 1493, 1219, 762, 664 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1 H) 7.67–6.96 (m, 5 H), 4.55 (s, 1 H), 1.99–0.43 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 141.7, 129.1, 128.2 (2C), 127.2 (2C), 125.4, 106.9, 61.4, 56.1 (2C), 54.0, 42.8, 41.9, 39.9 (2C), 39.5, 36.1, 35.7, 34.8, 31.5, 30.0, 28.6, 28.0 (2C), 24.9, 23.1, 30.0, 22.6, 21.1, 18.5, 12.7, 12.0, 11.9.

MS (EI): *m/z* = 550 $[M^+]$.

Anal. Calcd for $C_{35}H_{51}FN_2S$: C, 76.31; H, 9.33; N, 5.09. Found: C, 76.55; H, 9.54; N, 5.16.

4′-(3-Bromophenyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4k)
Yield: 537 mg (88%); light-yellow solid; mp 231–232 °C.

IR (KBr): 3186, 2932, 2869, 1570, 1471, 1219, 770, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 7.46–7.19 (m, 4 H), 6.87 (s, 1 H), 4.73 (s, 1 H), 1.90–0.55 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 144.0, 131.5, 130.6, 130.2, 126.6, 126.4, 122.9, 106.3, 60.8, 59.5, 56.2, 53.5, 53.2, 42.4, 40.9, 40.1, 39.8, 39.5, 36.1, 35.8, 35.4, 35.0, 31.4, 28.2, 28.0, 24.2, 23.8, 22.9, 22.6, 21.1, 18.7, 12.1, 12.0, 11.9.

MS (EI): *m/z* = 531.4 $[M - Br]^+$.

Anal. Calcd for $C_{35}H_{51}BrN_2S$: C, 68.72; H, 8.40; N, 4.58. Found: C, 68.70; H, 8.20; N, 4.21.

4′-Propyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4l)
Yield: 449 mg (90%); light-yellow solid; mp 187 °C.

IR (KBr): 3162, 2929, 2868, 1587, 1465, 1221, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1 H), 6.58 (s, 1 H), 3.81 (m, 1 H), 2.17–0.64 (m, 51 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 126.1, 106.4, 71.3, 56.9, 56.2 (2C), 54.3, 44.8, 41.9, 39.8, 39.5 (2C), 36.2, 35.7, 35.4, 35.3, 31.7, 31.5, 29.0, 28.2, 28.2, 24.2, 23.8 (2C), 23.3, 22.8, 22.6, 18.7, 14.1, 12.0, 11.7.

MS (EI): *m/z* = 498.4 $[M^+]$, 455.4 $[M - C_3H_7]^+$.

Anal. Calcd for $C_{32}H_{54}N_2S$: C, 77.05; H, 10.91; N, 5.62. Found: C, 77.35; H, 10.98; N, 5.75.

4′-Butyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4m)
Yield: 466 mg (91%); light-yellow solid; mp 192 °C.

IR (KBr): 3172, 2928, 2868, 1583, 1467, 1222, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 6.96 (s, 1 H), 3.51 (m, 1 H), 2.56–0.58 (m, 53 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 126.0, 106.5, 71.3, 56.8, 56.2 (2C), 54.4, 44.7, 42.4, 39.5 (2C), 39.1, 36.3, 35.8, 35.4, 35.2, 31.8, 31.5, 29.7, 28.2, 28.0 (2C), 24.2, 23.8 (2C), 23.3, 22.8, 22.6, 18.7, 14.2, 11.8, 11.6.

MS (EI): *m/z* = 512.4 $[M^+]$, 455.4 $[M - C_4H_9]^+$.

Anal. Calcd for $C_{33}H_{56}N_2S$: C, 77.28; H, 11.01; N, 5.46. Found: C, 77.39; H, 10.94; N, 5.25.

4′-Pentyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4n)
Yield: 489 mg (93%); light-yellow solid; mp 188–190 °C.

IR (KBr): 3171, 2929, 2868, 1583, 1467, 1222, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1 H), 6.64 (s, 1 H), 3.82 (m, 1 H), 2.17–0.64 (m, 55 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 126.1, 106.4, 71.3, 56.9, 56.3 (2C), 54.3, 44.8, 42.4, 39.9, 39.5 (2C), 36.2, 35.8, 35.4, 35.3, 31.8 (2C), 31.5, 29.7, 28.2, 28.0 (2C), 24.2, 23.8 (2C), 23.3, 22.8, 22.6, 18.7, 14.2, 12.0, 11.8.

MS (EI): *m/z* = 526.4 $[M^+]$, 455.4 $[M - C_5H_{11}]^+$.

Anal. Calcd for $C_{34}H_{58}N_2S$: C, 77.50; H, 11.10; N, 5.32. Found: C, 77.48; H, 11.03; N, 5.27.

4′-Phenyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholest-4-en-2′(1′*H*)-one (4o)
Yield: 463 mg (90%); light-yellow solid; mp 202–204 °C.

IR (KBr): 3189, 2929, 2869, 1600, 1569, 1467, 1208, 759, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.19 (m, 6 H), 6.82 (s, 1 H), 5.31(s, 1 H), 4.98 (s, 1 H), 2.03–0.61 (m, 41 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 142.1, 137.8, 129.1, 128.9, 128.2, 128.0, 127.0, 126.7, 120.4, 107.9, 57.1, 56.1, 48.4, 47.9, 42.3, 39.7, 39.5, 36.2, 35.8, 35.4, 31.9, 31.1, 28.2, 28.0, 24.1, 23.8, 22.8, 22.7, 21.2, 19.0, 18.7, 18.6, 11.9, 11.8.

MS (EI): *m/z* = 530.4 $[M]^+$.

Anal. Calcd for $C_{35}H_{50}N_2O$: C, 81.66; H, 9.79; N, 5.44. Found: C, 81.78; H, 9.73; N, 5.47.

4′-Pentyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholest-4-en-2′(1′*H*)-one (4p)
Yield: 442 mg (87%); white solid; mp 180–181 °C.

IR (KBr): 3249, 2928, 2867, 1716, 1467, 1221, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 6.90 (s, 1 H), 5.33 (s, 1 H), 4.96 (s, 1 H), 2.23–0.61 (m, 52 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 144.1, 126.0, 122.0, 107.5, 71.3, 56.8, 56.1 (2C), 54.4, 44.7, 42.4, 39.6 (2C), 39.1, 36.3, 35.8, 35.4 35.2, 31.8, 31.5, 29.7, 28.2, 28.0, 24.4, 23.8 (2C), 23.3, 22.8, 22.6, 18.7, 14.2, 11.8, 11.7.

MS (EI): *m/z* = 508.4 $[M]^+$.

Anal. Calcd for $C_{34}H_{56}N_2O$: C, 80.26; H, 11.09; N, 5.51. Found: C, 80.28; H, 11.14; N, 5.57.

4′-Phenyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholest-4-ene-2′(1′*H*)-thione (4q)
Yield: 477 mg (90%); white solid; mp 209–210 °C.

IR (KBr): 3189, 2929, 2869, 1600, 1569, 1467, 1208, 759, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.19 (m, 6 H), 6.82 (s, 1 H), 5.31 (s, 1 H), 4.98 (s, 1 H), 2.03–0.61 (m, 41 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 142.1, 137.8, 129.1, 128.9, 128.2, 128.0, 127.0, 126.7, 120.4, 107.9, 57.1, 56.1, 48.4, 47.9, 42.3, 39.7, 39.5, 36.2, 35.8, 35.4, 31.9, 31.1, 28.2, 28.0, 24.1, 23.8, 22.8, 22.6, 21.2, 19.0, 18.7, 18.6, 11.9, 11.8.

MS (EI): *m/z* = 530.4 $[M]^+$.

Anal. Calcd for $C_{35}H_{50}N_2S$: C, 79.19; H, 9.49; N, 5.28. Found: C, 79.38; H, 9.41; N, 5.54.

4′-(3-Bromophenyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholest-4-ene-2′(1′*H*)-thione (4r)
Yield: 553 mg (91%); yellow solid; mp 226–228 °C.

IR (KBr): 3186, 2931, 2869, 1571, 1471, 1219, 771, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.40–7.18 (m, 4 H), 6.86 (s, 1 H), 5.30 (s, 1 H), 4.78 (s, 1 H), 2.01–0.65 (m, 41 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 143.9, 137.5, 130.2, 129.2, 128.0, 127.0, 126.6, 126.4, 122.9, 106.3, 56.2, 53.5, 53.2, 42.4, 40.9, 40.1, 39.8, 39.5, 36.1, 35.8, 35.4, 35.0, 31.4, 28.2, 28.0, 24.2, 23.9, 22.8, 22.6, 21.0, 18.7, 12.1, 12.0, 11.9.

MS (EI): *m/z* = 529.4 $[M - Br]^+$.

Anal. Calcd for $C_{35}H_{49}BrN_2S$: C, 68.94; H, 8.10; N, 4.59. Found: C, 68.74; H, 8.18; N, 4.33.

4′-(4-Tolyl)-3′,4′-dihydropyrimidino[6′,5′:2,3]cholest-4-ene-2′(1′*H*)-thione (4s)
Yield: 485 mg (89%); light-yellow solid; mp 208–210 °C.

IR (KBr): 3192, 2929, 2867, 1569, 1490, 1220, 756, 666 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.36–7.04 (m, 5 H), 5.31 (s, 1 H), 4.56 (s, 1 H), 1.98–0.43 (m, 44 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 141.6, 137.2, 129.0, 128.1 (2C), 127.1 (2C), 125.5, 120.0, 106.8, 56.3 (2C), 53.1, 42.4, 40.9, 39.9 (2C), 39.8, 39.5, 36.2, 35.8, 34.9, 31.4, 30.0, 28.1, 28.0 (2C), 24.1, 23.8, 22.8, 22.5, 21.0, 18.5, 12.0, 11.9.

MS (EI): *m/z* = 544 $[M^+]$.

Anal. Calcd for $C_{36}H_{52}N_2S$: C, 79.35; H, 9.62; N, 5.14. Found: C, 79.70; H, 9.78; N, 5.10.

3β-Acetoxy-3′,4′-dihydropyrimidino[6′,5′:16,17]androst-5-en-2′(1′*H*)-one (4t)
Yield: 400 mg (87%); gum.

IR (KBr): 2928, 2853, 1732, 1612, 1245, 1037 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.03 (m, 7 H), 6.73 (d, *J* = 6.0 Hz, 1 H), 5.50–5.33 (m, 1 H), 4.63–4.50 (m, 1 H), 2.50–0.85 (m, 26 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 154.6, 139.9, 137.1, 129.5, 128.4 (2C), 127.8 (2C), 125.2, 122.0, 73.7, 51.7, 50.1, 47.5, 38.1, 36.9 (2C), 35.9, 31.5, 30.8, 29.7, 27.7, 21.9, 21.4, 20.3, 19.6, 13.6, 11.6.

MS (EI): *m/z* = 400.6 $[M - CH_3COOH]^+$.

Anal. Calcd for $C_{29}H_{36}N_2O_3$: C, 75.62; H, 7.88; N, 6.08. Found: C, 75.72; H, 7.74; N, 6.16.

3β-Acetoxy-3′,4′-dihydropyrimidino[6′,5′:16,17]androst-5-ene-2′(1′*H*)-thione (4u)
Yield: 429 mg (90%); gum.

IR (KBr): 2929, 2856, 1738, 1666, 1246, 1031 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.00 (m, 7 H), 6.71 (d, *J* = 6.0 Hz, 1 H), 5.50–5.30 (m, 1 H), 4.63–4.50 (m, 1 H), 2.47–0.85 (m, 26 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 170.6, 140.1, 137.4 (2C), 129.7, 128.2 (2C), 127.8 (2C), 125.1, 122.4, 73.9, 51.5, 50.1, 47.7, 38.8, 36.8, 35.8, 31.8, 30.5, 29.7, 27.4, 21.9, 21.4, 20.1, 19.7, 13.5, 11.4.

MS (EI): *m/z* = 416.6 [M – CH_3COOH]$^+$, 359.2.

Anal. Calcd for $C_{29}H_{36}N_2O_2S$: C, 73.07; H, 7.61; N, 5.88. Found: C, 73.32; H, 7.74; N, 5.93.

3β-Acetoxy-4′-phenyl-3′,4′-dihydropyrimidino[6′,5′:6,7]cholest-4-ene-2′(1′*H*)-thione (4v)
Yield: 506 mg (86%); white solid; mp 182 °C.

IR (KBr): 2950, 2932, 2868, 1706, 1566, 1450, 1381, 1238, 765 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.08 (m, 8 H), 6.15 (m, 1 H), 4.23 (m, 1 H), 2.82–0.6 (m, 42 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 170.8, 141.2, 133.5, 130.2, 129.7, 129.2, 128.6 (2C), 128.2, 127.0 (2C), 82.0, 65.3, 56.1, 44.1, 42.9, 41.5, 39.5 (2C), 37.4, 36.1, 35.7, 31.0 (2C), 29.7, 28.0 (2C), 27.7 (2C), 23.8, 22.8, 22.6, 21.7, 18.7, 14.2, 11.7.

MS (EI): *m/z* = 528.4 [M – CH_3COOH]$^+$.

Anal. Calcd for $C_{37}H_{52}N_2O_2S$: C, 75.46; H, 8.90; N, 4.76. Found C, 75.68; H, 8.82; N, 4.56.

4-Phenyl-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione (4w)
Yield: 251 mg (86%); gum.

IR (KBr): 2927, 1692, 1566, 1493, 1453, 1192, 1026 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.79 (s, 1 H), 9.12 (s, 1 H), 7.96 (d, *J* = 9.0 Hz, 1 H), 7.82–6.54 (m, 8 H), 4.96 (d, *J* = 2.4 Hz, 1 H), 2.62 (t, *J* = 7.2 Hz, 2 H), 2.08 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.5, 143.2, 135.9, 129.7, 129.1, 128.5 (2C), 128.3, 128.1, 128.0, 127.4, 126.9 (2C), 121.8, 111.7, 58.9, 27.7, 23.0.

MS (EI): *m/z* = 292 [M]$^+$.

Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 73.75; H, 5.72; N, 9.68.

8-Methoxy-4-phenyl-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione (4x)
Yield: 274 mg (85%); gum.

IR (KBr): 2927, 1692, 1601, 1538, 1493, 1251 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.72 (s, 1 H), 9.06 (s, 1 H), 8.20–6.50 (m, 8 H), 4.92 (s, 1 H), 3.5 (s, 3 H), 2.68 (t, *J* = 7.2 Hz, 2 H), 2.14 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.7, 142.8, 135.5, 129.9, 129.6, 128.1, 128.6 (2C), 128.0 (2C), 127.1 (2C), 127.0, 121.9, 111.8, 59.4, 55.9, 27.5, 23.3.

MS (EI): *m/z* = 322.0 [M]$^+$.

Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.42; H, 5.70; N, 8.78.

2-Benzylidenecholestan-3-one (A)
A mixture of ketone **1a** (400 mg, 1.04 mmol), PhCHO (110 mg, 1.04 mmol), and NaOEt (71 mg, 1.04 mmol) in *i*-PrOH (10 mL) was irradiated with ultrasound for 10 min. The solvent was removed in a rotatory evaporator and the crude residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)] to give a light-yellow solid; yield: 443 mg (90%); mp 176 °C.

IR (KBr): 2929, 1678, 1445, 1193, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.28 (m, 5 H), 7.26 (s, 1 H), 3.13–3.08 (m, 2 H), 2.49–0.64 (m, 42 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.7, 137.1, 135.7, 135.4, 129.7, 129.6, 128.9, 128.6, 128.4, 66.7, 66.3, 56.4, 53.6, 42.9, 42.4, 39.9, 39.5 (2C), 36.2, 35.9, 35.8, 35.4, 31.5 (2C), 28.7, 28.3, 24.3, 23.9 (2C), 22.9, 21.4, 18.7, 12.0, 11.9.

MS (EI): *m/z* = 474.4 [M]$^+$.

Anal. Calcd for $C_{34}H_{50}O$: C, 86.01; H, 10.62. Found: C, 86.27; H, 10.75.

Conversion of 2-Benzylidenecholestan-3-one (A) into 4′-Phenyl-3′,4′-dihydropyrimidino[6′,5′:2,3]cholestane-2′(1′*H*)-thione (4h)
A mixture of ketone **A** (200 mg, 0.42 mmol) and thiourea (32 mg, 0.42 mmol) in *i*-PrOH (10 mL) was irradiated with ultrasound for 5 min. The solvent was removed in a rotatory evaporator and the crude residue was purified by column chromatography [silica gel, EtOAc–hexane (1:10)] to give **4h**; yield: 195 mg (87%). The analytical and spectral data for this compound were similar to those reported above.

Acknowledgment

We thank the Department of Science and Technology, New Delhi, for financial support. M.D. thanks CSIR, New Delhi, for the award of a senior research fellowship (SRF). We are grateful to the Director of CSIR-NEIST for his keen interest.

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