

Intramolecular cyclization of 1-(2-arylethyl)tetrahydro-6-hydroxy-1H-pyrimidin-2-thiones: effect of substituents on reactivity

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Abstract Convenient synthetic procedures for 1,2,3,6,7,11*b*-hexahydro-4H-pyrimido[6,1-*a*]isoquinolin-4-thiones and 2,3,6,7,12,12*b*-hexahydro-1H-pyrimido[1',6':1,2]pyrido[3,4-*b*]indole-4-thiones have been developed. Structural factors which influence on a cascade cyclization process have been elucidated.

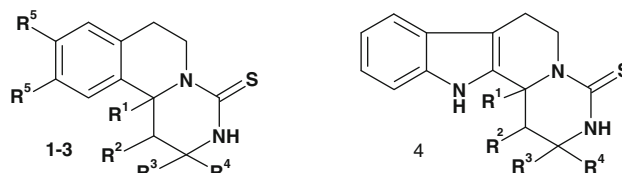
Keywords 4H-Pyrimido[6,1-*a*]isoquinolin-4-thiones · Pyrido[3,4-*b*]indole-4-thiones · Cascade cyclization · Structure–reaction conditions correlation

Introduction

Isoquinoline and indole[2,3-*c*]pyridine (β -carboline) heterocyclic systems are of ongoing interest due to their prevalence in the structure of a wide range of biologically active compounds, such as alkaloids and therapeutics. Notably, a number of active compounds incorporate a structural core in which either isoquinoline or β -carboline moieties are annealed at positions C(1)–C(2) with a pyrimidine cycle. Significant examples of such compounds are represented by alkaloid *Elaeagnifoline* comprising the structural fragment of pyrimido[6,1-*a*]- β -carboline [1], and a few pyrido[6,1-*a*]isoquinolines which display antihypertensive activity [2,3]. Known synthetic methods toward these heterocyclic systems can be divided into two groups. The first approach implies annealing of the pyrimidine cycle to an isoquinoline precursor [2,4]. The second approach comprises methods in which either the isoquinoline or carboline cycle is formed at the

final step of the synthesis [5,6]. In general, the majority of the methods for the synthesis of pyrimido[6,1-*a*]isoquinolines and pyrimido[6,1-*a*]- β -carbolines are multi-step preparations. In this regard, development of the facile methods leading to these compounds is of considerable interest with respect to combinatorial or directed syntheses of bioactive compounds.

Previously, we reported an alternative approach to the synthesis of 1,2,3,6,7,11*b*-hexahydro-4H-pyrimido[6,1-*a*]isoquinolin-4-thiones **1** and 2,3,6,7,12,12*b*-hexahydro-1H-pyrimido[6,1-*a*]- β -carboline-4-thiones **4** (Scheme 1) proceeding as a cascade cyclization of *N*-(3-oxoalkyl)-*N'*-(2-arylethyl)-thioureas [7] or their acetals [8].



1 R⁵ = OMe; **2** R⁵ = OH; **3** R⁵ = H; R¹–R⁴ = H, Alk

Also, it was shown that compounds **1** and **4** could be synthesized by the reaction between α , β -unsaturated carbonyl compounds, arylethylamines, and thiocyanic acid [7]. Unfortunately, the cyclization was studied only on few reactions, which wrongly narrowed its potential scope.

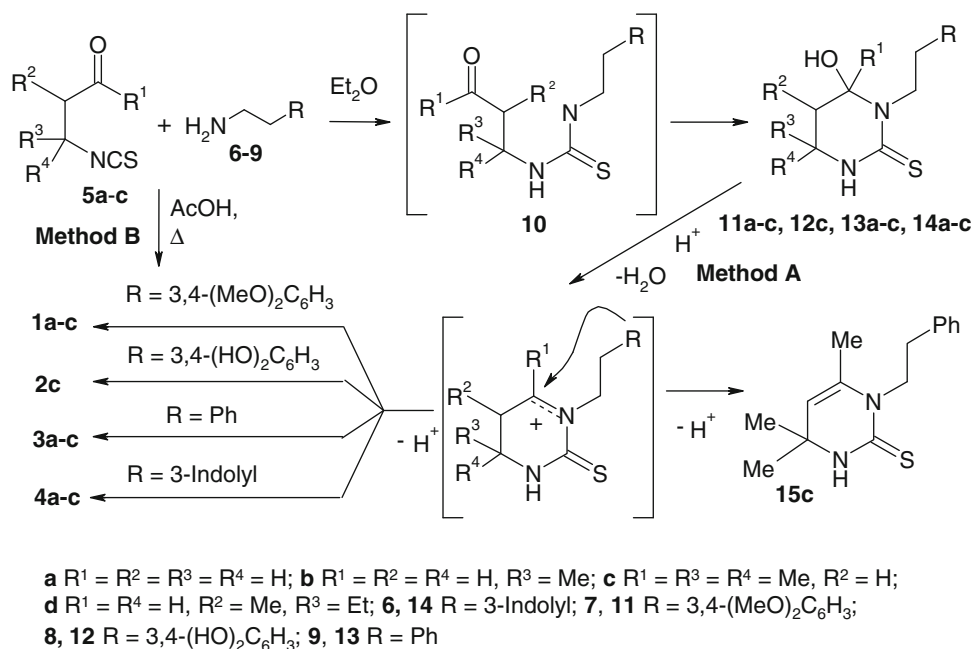
In order to elucidate the influence of the substituents' structural and electronic properties on cascade cyclization process, the substrates' set was significantly widened.

Experimental section

¹H and ¹³C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.13 and 50.3 MHz, respectively, using

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Scheme 1 Reaction of 1,3-isothiocyanatocarbonyl compounds with β -arylethylamines. Intramolecular cyclization of 6-hydroxypyrimidin-2-thiones



TMS as an internal standard ($\delta = 0.00$ ppm). IR spectra were recorded on a Specord 75IR. Melting points were determined using Kofler hot-stage melting point apparatus and are uncorrected. All reagents and solvents were purchased from Aldrich and Acros Organics and used without further purification.

General procedure for preparation of tetrahydro-6-hydroxy-4,4,6-trimethyl-1H-pyrimidin-2-thiones **11**, **13**, **14c**

To a stirred solution of 4-methyl-4-isothiocyanatopentane-2-one (**5c**) (0.50 g, 3.2 mmol) in 10 mL of absolute ether is added a solution of the corresponding β -arylethylamine (**6**, **7**, or **9**) (3.2 mmol) in 10 mL of absolute ether maintaining temperature of the reaction mixture around 0°C. After 5-h stirring at room temperature precipitated crystals are filtered, washed with ether, and dried to give desired product.

1-[2-(3,4-Dimethoxyphenyl)ethyl]tetrahydro-6-hydroxy-4,4,6-trimethyl-1H-pyrimidin-2-thione (**11c**)

Yield 89%. Mp (°C): 152–153. Anal. Calcd for C $_{17}$ H $_{26}$ N $_2$ O $_3$ S (338.46), %: C, 60.33; H, 7.74; N, 8.28; Found, %: C, 60.25; H, 7.78; N, 8.31. IR(CHCl $_3$, cm $^{-1}$): ν_{max} = 3600 (OH), 3420 (NH), 1510 (NC=S). 1H NMR (200 MHz, DMSO- d_6 , ppm): δ_H = 8.14 (br. s, 1H, NH), 6.79–6.91 (m, 3H, Ar), 6.00 (br. s, 1H, OH), 3.94 (m, 2H, CH $_2$ Ar), 3.73 (s, 6H, 2*OCH $_3$), 3.08–3.22 (m, 1H, NCH), 2.78–2.92 (m, 1H, NCH), 2.01 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.95 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.53 (s, 3H, 6-CH $_3$), 1.28 (s, 3H, 4-CH $_3$), 1.18 (s, 3H, 4-CH $_3$). ^{13}C NMR: δ_C = 176.7 (C=S), 148.7, 147.3, 132.5, 120.4, 112.4, 112.1 (Ar), 82.5 (C $_6$), 55.6

(OCH $_3$), 55.4 (OCH $_3$), 49.0 (NCH $_2$), 48.9 (C $_4$), 47.8 (C $_5$), 34.9 (CH $_2$ Ar), 29.6 (6-CH $_3$), 29.0 (4-CH $_3$), 28.2 (4-CH $_3$).

Tetrahydro-6-hydroxy-1-[2-(1H-indole-3-yl)ethyl]-4,4,6-trimethyl-1H-pyrimidin-2-thione (**14c**)

Yield 88%. Mp (°C): 150–151. Anal. Calcd for C $_{17}$ H $_{23}$ N $_3$ OS (317.45), %: C, 64.32; H, 7.30; N, 13.24; Found, %: C, 64.15; H, 7.28; N, 13.27. IR(CHCl $_3$, cm $^{-1}$): ν_{max} = 3550 (OH), 3300, 3150 (NH), 1480 (NC=S). 1H NMR (200 MHz, DMSO- d_6 , ppm): δ_H = 10.58 (s), 8.34–6.95 m. (6H, Indolyl), 7.82 (br. s, 1H, NH), 6.02 (br. s, 1H, OH), 3.86–4.19 (m, 2H, CH $_2$ Ind), 2.93–3.07 (m, 1H, NCH), 2.85–2.99 (m, 1H, NCH), 1.86 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.82 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.47 (s, 3H, 6-CH $_3$), 1.25 (s, 3H, 4-CH $_3$), 1.15 (s, 3H, 4-CH $_3$).

Tetrahydro-6-hydroxy-4,4,6-trimethyl-1-(2-phenylethyl)-1H-pyrimidin-2-thione (**13c**)

Yield 83%. Mp (°C): 133–134. Anal. Calcd for C $_{15}$ H $_{22}$ N $_2$ O $_2$ S (278.41), %: C, 64.71; H, 7.96; N, 10.06; Found, %: C, 60.58; H, 8.06; N, 10.17. IR(CHCl $_3$, cm $^{-1}$): ν_{max} = 3510 (OH), 3200 (NH), 1490 (NC=S). 1H NMR (200 MHz, DMSO- d_6 , ppm): δ_H = 8.18 (br. s, 1H, NH), 7.16–7.32 (m, 5H, Ar), 6.03 (br. s, 1H, OH), 4.10–3.84 (m, 2H, CH $_2$ Ar), 3.21 (m, 1H, 2J 11.6, 3J 11.6, 3J 5.3 Hz, NCH), 2.85 (m, 1H, 2J 11.6, 3J 11.6, 3J 5.3 Hz, NCH), 2.00 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.94 (d, 1H, 2J 13.8 Hz, C $_{(5)}$ H), 1.53 (s, 3H, 6-CH $_3$), 1.28 (s, 3H, 4-CH $_3$), 1.18 (s, 3H, 4-CH $_3$). ^{13}C NMR: δ_C = 176.7 (C=S), 139.9, 128.5, 128.5, 128.3, 128.3, 126.0 (Ar), 82.5 (C $_6$), 49.0

Table 1 Yields of pyrimido[6,1-*a*]isoquinolin-4-thiones **1a–d**, **2c**, **3a–c** and pyrimido[6,1-*a*]- β -carbolin-4-thiones **4a–c** prepared by Methods A, B, and C

Compd	Yield (%)		
	A	B	C
1a	–	–	21
1b	–	49	35
1c	73	84	64
1d	–	–	34
2c	–	93	–
3a	19	–	–
3b	22	–	–
3c	50	–	–
4a	49	–	–
4b	45	44	21
4c	52	73	52

(NCH₂), 49.0 (C₄), 47.8 (C₅), 35.3 (CH₂Ph), 29.6 (6-Me), 29.1 (4-CH₃), 28.9 (4-CH₃).

General procedures for preparation of 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-thiones **1–3** and 2,3,6,7,12,12*b*-hexahydro-1*H*-pyrimido[6,1-*a*]- β -carbolin-4-thiones **4**. Yields are summarized in Table 1.

Method A To a stirred solution of 1,3-isothiocyanatocarbonyl compound **5** (64.5 mmol) in 100 mL of ether is added dropwise over a period of 1 h a solution of amine (64.5 mmol) in 50 mL of absolute ether at 5–10 °C. Formed precipitate is filtered, dried, and dissolved in 100 mL of the corresponding acid. The resulting solution is refluxed for a certain period of time, cooled to room temperature, and poured on to crushed ice. Precipitated solid was collected, washed with water and, recrystallized from ethanol.

Method B A solution of 1,3-isothiocyanatocarbonyl compound **5** (78.0 mmol) and amine **6–8** (70.0 mmol) in 100 mL of glacial acetic acid is refluxed for a certain period of time. Separation and purification of the product is done as in method A.

Method C To a stirred solution containing α , β -unsaturated carbonyl compound **14** (67.2 mmol), dry potassium thiocyanate (6.52 g, 67.2 mmol), and catalytic amount of hydroquinone in 30 mL of glacial acetic acid is added dropwise a solution of sulfuric acid (3.30 g, 33.6 mmol) in 10 mL of glacial acetic acid at 0–10 °C. The reaction mixture is stirred at room temperature for 1.5 h and precipitated potassium sulfate is filtered out. Then the amine (60.5 mmol) was added to the filtrate and the resulting solution is refluxed for 3 h. Separation and purification of the product is done as in method A.

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-thione (1a)

Mp (°C): 195–196. Anal. Calcd for C₁₄H₁₈N₂O₂S (278.37), %: C, 60.40; H, 6.52; N, 10.06. Found, %: C, 60.51; H, 6.44; N, 10.12. IR(CHCl₃, cm⁻¹): ν_{\max} = 3450 (NH), 1510 (NC=S). ¹H NMR (200 MHz, CDCl₃, ppm): 7.21 (br. s, 1H, NH), 6.64 (s, 2H, 8-H, 11-H), 5.52 (br.d, 1H, ²*J* = 12.5 Hz, 6-He), 4.66 (dd, 1H, ³*J* = 11.2, ³*J* = 2.7 Hz, 11b-Ha), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.26–3.55 (m, 2H, 2-H₂), 3.20 (m, 1H, ²*J* = 12.5, ³*J* = 12.8, ³*J* = 2.5 Hz, 6-Ha), 3.01 (m, 1H, ²*J* = 14.6, ³*J* = 12.8, ³*J* = 3.4 Hz, 7-Ha), 2.65 (br.d, 1H, ²*J* = 14.6 Hz, 7-He), 2.52 (br.d., 1H, ²*J* = 12.1 Hz, 1-He), 1.98 (m, 1H, ²*J* = 12.1, ³*J* = 11.9, ³*J* = 11.2, ³*J* = 5.6 Hz, 1-Ha). ¹³C NMR: δ_C = 177.6 (C=S), 147.9, 147.9, 128.2, 127.3, 111.6, 108.5 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 56.2 (OCH₃), 56.0 (OCH₃), 55.4 (C_{11b}), 47.4 (C₆), 39.7 (C₂), 30.0 (C₁), 28.6 (C₇).

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-2-methyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (1b)

Mp (°C): 197–198 °C (lit.: 197–198 [7]). ¹H NMR (200 MHz, CDCl₃, ppm), **2,11b-cis-8b**: δ_H = 6.58 (br.s, 1H, NH), 6.64, 6.61 (s, 2H, 8-H, 11-H), 5.45–5.61 (m, 1H, 6-He), 4.62–4.78 (m, 1H, 11b-H), 3.87 (s, 6H, 2OCH₃), 3.71 (m, 1H, ³*J* = 11.5, ³*J* = 6.5, ³*J* = 3.3 Hz, 2-Ha), 3.25 (m, 1H, ²*J* = 12.1, ³*J* = 12.1, ³*J* = 3.1 Hz, 6-Ha), 2.92–3.12 (m, 1H, 7-Ha), 2.60–2.75 (m, 1H, 7-He), 2.51 (m, 1H, ²*J* = 13.3, ³*J* = 3.3, ³*J* = 3.3 Hz, 1-He), 1.65 (m, 1H, ²*J* = 13.3, ³*J* = 11.9, ³*J* = 11.5 Hz, 1-Ha), 1.28 (d, 3H, ³*J* = 6.5 Hz, 2-CH₃); **2,11b-trans-8b**: δ_H = 6.93 (br.s, 1H, NH), 6.64, 6.61 (s, 2H, 8-H, 11-H), 5.45–5.61 (m, 1H, 6-He), 4.62–4.78 (m, 1H, 11b-H), 3.73 (s, 6H, 2OMe), 3.50–3.66 (m, 1H, 2-He), 3.14 (m, 1H, ²*J* = 12.1, ³*J* = 12.1, ³*J* = 2.2 Hz, 6-Ha), 2.92–3.12 (m, 1H, 7-Ha), 2.60–2.75 (m, 1H, 7-He), 1.87–2.17 (m, 2H, 1-H₂), 1.35 (d, 3H, ³*J* = 6.5 Hz, 2-CH₃). ¹³C NMR (50 MHz, DMSO-d₆, ppm), **2,11b-cis-8b**: δ_C = 176.6 (C=S), 147.5, 147.4, 128.2, 126.7, 111.6, 109.3 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 55.8 (OCH₃), 55.5 (OCH₃), 51.3 (C_{11b}), 46.4 (C₆), 44.0 (C₂), 34.5 (C₁), 28.2 (C₇), 21.8 (2-CH₃); **2,11b-trans-8b**: δ_C = 176.3 (C=S), 147.5, 147.4, 128.2, 126.7, 111.6, 109.3 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 55.8 (OCH₃), 55.5 (OCH₃), 51.3 (C_{11b}), 46.0 (C₆), 45.7 (C₂), 34.5 (C₁), 28.0 (C₇), 20.4 (2-CH₃).

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-2,2,11b-trimethyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (1c)

Mp (°C): 175–176 (lit.: 166–167 [7]). ¹H NMR (200 MHz, CDCl₃, ppm): δ_H = 7.13 (br.s, 1H, NH), 6.62 (s, 2H,

8-H, 11-H), 5.63 (dd, 1H, $^2J = 12.9$, $^3J = 5.1$ Hz, 6-He), 3.88 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.35 (m, 1H, $^2J = 12.9$, $^3J = 12.7$, $^3J = 2.7$ Hz, 6-Ha), 3.05 (m, 1H, $^2J = 15.8$, $^3J = 12.7$, $^3J = 5.1$ Hz, 7-Ha), 2.65 (m, 1H, $^2J = 15.8$, $^3J = 2.7$ Hz, 7-He), 2.35 (d, 1H, $^3J = 14.0$, 1-He), 2.12 (d, 1H, $^2J = 14.0$ Hz, 1-Ha), 1.72 (s, 3H, 11b-Me), 1.46 (s, 3H, 2-CH₃), 1.18 (s, 3H, 2-CH₃). ¹³C NMR (50 MHz, CDCl₃, ppm): $\delta_C = 176.8$ (C=S), 147.8, 147.7, 134.1, 125.8, 111.6, 108.4 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 58.1 (C_{11b}), 56.3 (OCH₃), 55.8 (OCH₃), 50.3 (C₂), 48.7 (C₆), 43.8 (C₁), 31.7 (2-CH₃), 30.2 (2-CH₃), 28.2 (C₇), 28.0 (11b-CH₃).

2-Ethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-1-methyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (1d)

Mp (°C): 166–167. Anal. Calcd for C₁₇H₂₄N₂O₂S (320.45), %: C, 63.72; H, 7.55. Found, %: C, 63.80; H, 7.58. IR (CHCl₃, cm⁻¹): $\nu_{\max} = 3420$ (NH), 1490 (NC=S). ¹H NMR (200 MHz, CDCl₃, ppm): $\delta_H = 6.65$ (s, 2H, 8-H), 6.63 (s, 1H, 11-H), 6.57 (br.s, 1H, NH), 5.30–5.46 (m, 1H, 6-He), 4.41 (br.s, 1H, 11b-Ha), 3.85 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.19–3.40 (m, 2H, 6-Ha, 2-H), 3.00–3.11 (m, 1H, 7-Ha), 2.58–2.80 (m, 2H, 1-H, 7-H), 1.40–1.64 (m, 2H, 1-CH₂CH₃), 1.13 (d, 3H, $^3J = 7.0$ Hz, 1-CH₃), 0.94 (t, 3H, $^3J = 7.5$ Hz, 1-CH₂CH₃).

1,2,3,6,7,11b-Hexahydro-9,10-dihydroxy-2,2,11b-trimethyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (2c)

Mp (°C): 218–219. Calcd for C₁₅H₂₀N₂O₂S (292.40), %: C, 61.61; H, 6.89. Found, %: C, 61.80; H, 6.90. IR (CHCl₃, cm⁻¹): $\nu_{\max} = 3350$ (NH), 3200 (OH), 1475 (NC=S). ¹H NMR (200 MHz, CDCl₃, ppm): $\delta_H = 8.79$ (br.s, 2H, OH), 8.14 (br.s, 1H, NH), 6.63 (s, 1H, 11-H), 6.47 (s, 1H, 8-H), 5.41 (dd, 1H, $^2J = 13.0$, $^3J = 4.0$ Hz, 6-He), 3.18 (m, 1H, $^2J = 13.0$, $^3J = 12.2$, $^3J = 2.5$ Hz, 6-Ha), 2.72 (m, 1H, $^2J = 15.2$, $^3J = 12.2$, $^3J = 4.0$ Hz, 7-Ha), 2.48 (m, 1H, $^2J = 15.2$ Hz, 7-He), 2.30 (d, 1H, $^3J = 14.1$, 1-He), 1.92 (d, 1H, $^2J = 14.1$ Hz, 1-Ha), 1.55 (s, 3H, 11b-CH₃), 1.31 (s, 3H, 11b-CH₃), 1.03 (s, 3H, 11b-CH₃). ¹³C NMR (50 MHz, CDCl₃, ppm): $\delta_C = 176.3$ (C=S), 143.8, 133.5, 126.6, 123.6, 115.1, 112.4 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 57.3 (C_{11b}), 49.5 (C₂), 48.4 (C₆), 42.9 (C₁), 31.0 (2-CH₃), 29.4 (2-CH₃), 28.2 (11b-CH₃), 28.0 (C₇).

1,2,3,6,7,11b-Hexahydro-4H-pyrimido[6,1-a]isoquinolin-4-thione (3a)

Mp (°C): 197–198. Anal. Calcd for C₁₂H₁₄N₂S (218.32), %: C, 66.02; H, 6.46. Found, %: C, 65.89; H, 6.46. IR (CHCl₃, cm⁻¹): $\nu_{\max} = 3410$ (NH), 1490 (NC=S). ¹H NMR (200 MHz, CDCl₃, ppm): $\delta_H = 7.15$ –7.21 (m, 5H,

NH and Ar), 5.48 (m, 1H, $^2J = 12.5$, $^3J = 4.2$, $^3J = 2.9$ Hz, 6-He), 4.72 (dd, 1H, $^3J = 1.2$, $^3J = 4.0$ Hz, 11b-Ha), 3.21–3.54 (m, 3H, 2-H₂, 6-Ha), 3.07 (m, 1H, $^2J = 15.6$, $^3J = 11.8$, $^3J = 4.2$ Hz, 7-Ha), 2.75 (m, 1H, $^2J = 15.6$, $^3J = 2.9$, $^3J = 2.9$ Hz, 7-He), 2.53 (m, 1H, $^2J = 13.4$, $^3J = 4.0$ 1-He), 2.02 (m, 1H, $^2J = 13.4$, $^3J = 11.2$, $^3J = 5.4$ Hz, 1-Ha).

1,2,3,6,7,11b-Hexahydro-2-methyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (3b)

Mp (°C): 161–162°C (lit.: 161–162°C [8]). ¹H NMR (200 MHz, CDCl₃, ppm), **2,11b-cis-8b**: $\delta_H = 7.13$ –7.21 (m, 4H, Ar), 6.60 (br.s, 1H, NH), 5.42–5.54 (m, 1H, 6-He), 4.70–4.80 (m, 1H, 11b-H), 3.65–3.76 (m, 1H, 2-H), 3.32 (m, 1H, $^2J = 12.2$, $^3J = 12.2$, $^3J = 2.8$ Hz, 6-Ha), 3.00–3.21 (m, 1H, 7-Ha), 2.76 (m, 1H, $^2J = 15.8$, $^3J = 5.1$, $^3J = 2.8$ Hz, 7-He), 2.53 (m, 1H, $^2J = 13.2$ Hz, 1-He), 1.67 (m, 1H, $^2J = 13.2$, $^3J = 11.2$, $^3J = 11.2$ Hz, 1-Ha), 1.26 (d, 3H, $^3J = 6.6$ Hz, 2-CH₃); **2,11b-trans-8b**: 7.13–7.21 (m, 4H, Ar), 6.95 (br.s, 1H, NH), 5.42–5.54 (m, 1H, 6-He), 4.70–4.80 (m, 1H, 11b-H), 3.53–3.62 (m, 1H, 2-H), 3.32 (m, 1H, $^2J = 12.2$, $^3J = 12.2$, $^3J = 2.8$ Hz, 6-Ha), 3.00–3.21 (m, 1H, 7-Ha), 2.76 (m, 1H, $^2J = 15.8$, $^3J = 5.1$, $^3J = 2.8$ Hz, 7-He), 2.15–2.21 (m, 2H, 1-H₂), 1.33 (d, 3H, $^3J = 6.6$ Hz, 2-CH₃).

1,2,3,6,7,11b-Hexahydro-2,2,11b-trimethyl-4H-pyrimido[6,1-a]isoquinolin-4-thione (3c)

Mp (°C): 188–189. Anal. Calcd for C₁₅H₂₀N₂S (260.40), %: C, 69.19; H, 7.74. Found, %: C, 69.40; H, 7.71. IR (CHCl₃, cm⁻¹): $\nu_{\max} = 3420$ (NH), 1490 (NC=S). ¹H NMR (200 MHz, CDCl₃, ppm): $\delta_H = 7.13$ –7.29 (m, 4H, Ar), 6.74 (br.s, 1H, NH), 5.65 (m, 1H, $^2J = 12.5$, $^3J = 4.9$, $^3J = 1.9$ Hz, 6-He), 3.37 (m, 1H, $^2J = 12.5$, $^3J = 12.5$, $^3J = 2.9$ Hz, 6-Ha), 3.12 (m, 1H, $^2J = 16.1$, $^3J = 12.5$, $^3J = 4.9$ Hz, 7-Ha), 2.73 (m, 1H, $^2J = 16.1$, $^3J = 2.9$, $^3J = 1.9$ Hz, 7-He), 2.36 (d, 1H, $^3J = 14.0$ Hz, 1-He), 2.13 (d, 1H, $^2J = 14.0$ Hz, 1-Ha), 1.73 (s, 3H, 11b-CH₃), 1.43 (s, 3H, 2-CH₃), 1.13 (s, 3H, 2-CH₃). ¹³C NMR (50 MHz, CDCl₃, ppm): $\delta_C = 176.9$ (C=S), 142.2, 133.3, 129.4, 129.4, 126.6, 125.0 (C_{7a}, C₈, C₉, C₁₀, C₁₁, C_{11a}), 58.4 (C_{11b}), 50.3 (C₂), 48.7 (C₆), 43.7 (C₁), 31.7 (2-CH₃), 30.2 (2-CH₃), 29.2 (C₇), 28.1 (11b-CH₃).

2,3,6,7,12,12b-Hexahydro-1H-pyrimido[1',6':1,2]pyrido[3,4-b]indole-4-thione (4a)

Mp (°C): 205–206. Anal. Calcd for C₁₄H₁₅N₃S (257.36), %: C, 65.34; H, 5.87; N, 16.33. Found, %: C, 65.18; H, 5.89; N, 16.32. IR (CHCl₃, cm⁻¹): $\nu_{\max} = 3485$, 3415 (NH), 1500 (NC=S). ¹H NMR (200 MHz, DMSO-d₆, ppm): $\delta_H = 9.98$ (br.s, 1H, N₍₁₂₎H), 7.46 (d, 1H, $^3J = 7.0$ Hz, 8-H), 7.37

(d, 1H, $^3J = 7.0$ Hz, 11-H), 7.32 (br.s, 1H, N₍₃₎H), 7.13 (m, 1H, $^3J = 7.0$, $^3J = 7.0$ Hz, 9-H), 7.05 (m, 1H, $^3J = 7.0$, $^3J = 7.0$ Hz, 10-H), 5.74 (dd, 1H, $^2J = 12.7$, $^3J = 3.3$ Hz, 6-He), 4.74 (dd, 1H, $^3J = 10.7$, $^3J = 4.1$ Hz, 12b-H), 3.14–3.39 (m, 3H, 6-Ha, 2-H₂), 2.94 (m, 1H, $^2J = 14.5$, $^3J = 12.7$, $^3J = 3.3$ Hz, 7-Ha), 2.57–2.87 (m, 2H, 1-He, 7-He), 1.93 (m, 1H, $^2J = 13.2$, $^3J = 11.0$, $^3J = 10.7$, $^3J = 5.6$ Hz, 7-Ha). ^{13}C NMR (50 MHz, DMSO-*d*₆, ppm): $\delta_{\text{C}} = 177.6$ (C=S), 136.9 (C_{12a}), 132.7 (C_{11a}), 126.8 (C_{7b}), 122.0 (C₉), 119.5 (C₁₀), 118.5 (C₈), 111.5 (C₁₁), 109.3 (C_{7a}), 53.4 (C_{12b}), 48.5 (C₆), 39.2 (C₂), 28.0 (C₁), 21.1 (C₇).

2,3,6,7,12,12b-Hexahydro-2-methyl-1H-pyrimido[1',6':1,2]pyrido[3,4-b]indole-4-thione (4b)

Mp (°C): 266–267 (lit. 266–267 [7]). ^1H NMR (200 MHz, CDCl₃, ppm): **2,12b-cis-4b**: $\delta_{\text{H}} = 10.68$ (br.s, 1H, N₍₁₂₎H), 7.84 (br.s, 1H, N₍₃₎H), 7.01–7.10, 7.24–7.48 (m, 4H, Ar-H), 5.70–5.80 (m, 1H, 6-He), 4.80–4.90 (m, 1H, 12b-H), 3.40–3.60 (m, 1H, 2-H), 2.59–3.15 (m, 3H, 6-Ha, 7-He, 7-Ha), 2.49–2.58 (m, 1H, 1-He), 1.50 (m, 1H, $^2J = 12.7$, $^3J = 11.5$, $^3J = 11.5$ Hz, 1-Ha), 1.21 (d, 3H, $^3J = 6.6$ Hz, 2-CH₃); **2,12b-trans-4b**: $\delta_{\text{H}} = 10.68$ (br.s, 1H, N₍₁₂₎H), 8.12 (br.d, 1H, $^3J = 2.9$ Hz, N₍₃₎H), 7.01–7.10, 7.24–7.48 (m, 4H, Ar-H), 5.69 (m, 1H, $^2J = 2.2$, $^3J = 3.7$, $^3J = 1.0$ Hz, 6-He), 4.83 (m, 1H, $^3J = 9.1$, $^3J = 4.6$, 12b-H), 3.40–3.60 (m, 1H, 2-H), 3.22 (m, 1H, $^2J = 2.2$, $^3J = 11.7$, $^3J = 3.0$ Hz, 6-Ha), 2.88 (m, 1H, $^2J = 15.2$, $^3J = 11.7$, $^3J = 3.7$ Hz, 7-Ha), 2.67 (br.d, 1H, $^2J = 15.2$ Hz, 7-He), 2.38 (m, 1H, $^2J = 13.3$, $^3J = 4.6$, $^3J = 4.2$ Hz, 1-He), 2.08 (m, 1H, $^2J = 13.3$, $^3J = 9.1$, $^3J = 4.6$ Hz, 1-Ha), 1.27 (d, 3H, $^3J = 6.6$ Hz, 2-CH₃).

2,3,6,7,12,12b-Hexahydro-2,2,12b-trimethyl-1H-pyrimido[1',6':1,2]pyrido[3,4-b]indole-4-thione (4c)

Mp (°C): 250–251 (lit. 250–251 [7]). ^1H NMR (200 MHz, DMSO-*d*₆, ppm): $\delta_{\text{H}} = 10.63$ (br.s, 1H, N₍₁₂₎H), 7.80 (br.s, 1H, N₍₃₎H), 7.41 (dd, 1H, $^3J = 7.2$, $^3J = 0.8$ Hz, 8-H), 7.31 (dd, 1H, $^3J = 7.2$, $^3J = 1.4$ Hz, 11-H), 7.08 (m, 1H, $^3J = 7.2$, $^3J = 7.2$, $^3J = 1.4$ Hz, 9-H), 6.99 (m, 1H, $^3J = 7.2$, $^3J = 7.2$, $^3J = 0.8$ Hz, 10-H), 5.72 (dd, 1H, $^2J = 12.5$, $^3J = 4.5$ Hz, 6-He), 3.44 (m, 1H, $^2J = 12.2$, $^3J = 11.5$, $^3J = 3.0$ Hz, 6-Ha), 2.90 (m, 1H, $^2J = 15.5$, $^3J = 11.5$, $^3J = 4.5$ Hz, 7-Ha), 2.70 (dd, 1H, $^2J = 15.3$, $^3J = 3.0$ Hz, 7-He), 2.46 (d, 1H, $^2J = 13.8$ Hz, 1-He), 2.25 (d, 1H, $^2J = 13.8$ Hz, 1-Ha), 1.73 (s, 3H, 12b-CH₃), 1.39 (s, 3H, 2-CH₃), 1.08 (s, 3H, 2-CH₃). ^{13}C NMR (50 MHz, DMSO-*d*₆, ppm): $\delta_{\text{C}} = 177.1$ (C=S), 138.6 (C_{12a}), 136.0 (C_{11a}), 126.2 (C_{7b}), 121.1 (C₉), 118.7 (C₁₀), 117.9 (C₈), 111.1 (C₁₁), 106.0 (C_{7a}), 56.0 (C_{12b}), 49.5

(C₂), 46.0 (C₆), 44.1 (C₁), 30.2 (2-CH₃), 29.7 (2-CH₃), 26.8 (12b-CH₃), 20.9 (C₇).

Preparation of 3,4-dihydro-4,4,6-trimethyl-1-(2-phenylethyl)-1H-pyrimidin-2-thione (15c)

A solution of 6-hydroxy-1-phenyl-4,6,6-trimethyltetrahydro-2H-pyrimidin-2-thione (**13c**) (1.24 g, 4.2 mmol) in 15 mL of glacial acetic acid is refluxed for 3 h. After cooling to room temperature the reaction mixture is poured onto crushed ice. Precipitated crystals are filtered, washed with cold water, and purified by chromatography (silica, chloroform, R_f 0.50). Combined fractions are concentrated in vacuum to give 0.97 g (83 % yield) of compound **15c**.

Mp (°C): 134–135. Anal. Calcd for C₁₅H₂₀N₂S (260.40), %: C, 69.19; H, 7.74. Found, %: C, 69.12; H, 7.80; IR (CHCl₃, cm^{−1}): $\nu_{\text{max}} = 3420$ (NH), 1510 (NC=S). ^1H NMR (200 MHz, CDCl₃, ppm): $\delta_{\text{H}} = 7.18$ –7.30 (m, 6H, NH, Ph), 4.69 (q, 1H, $^4J = 1.0$ Hz, 5-H), 4.30 (t, 2H, $^3J = 7.9$ Hz, NCH₂), 3.01 (t, 2H, $^3J = 7.9$ Hz, PhCH₂), 1.88 (d, 3H, $^4J = 1.0$ Hz, 6-CH₃), 1.27 (s, 6H, 4-(CH₃)₂). ^{13}C NMR (50 MHz, CDCl₃, ppm): $\delta_{\text{C}} = 176.7$ (C=S), 128.9, 128.5, 126.4 (Ph), 131.6 (C₆), 111.3 (C₅), 51.6 (CH₂N), 49.3 (C₄), 35.4 (CH₂Ph), 31.0 (4-CH₃), 31.0 (4-CH₃), 19.5 (6-CH₃).

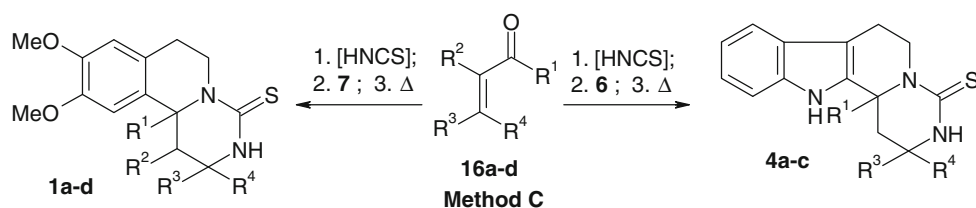
1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-4,4,5,6-tetramethyl-2(1H)-pyrimidin-2-thione (17e) is prepared by method C

Yield 55%. Mp (°C): 125–126. Anal. Calcd for C₁₈H₂₆N₂O₂S (334.48), %: C, 64.64; H, 7.84. Found, %: C, 64.50; H, 7.81. IR (CHCl₃, cm^{−1}): $\nu_{\text{max}} = 3410$ (NH), 1515 (NC=S). ^1H NMR (200 MHz, C₆D₆, ppm): $\delta_{\text{H}} = 7.63$ (br. s, 1H, NH), 6.95 (d, 1H, $^4J = 2.0$ Hz, Ar-2'-H), 6.85 (dd, 1H, $^3J = 8.1$, $^4J = 2.0$ Hz, Ar-6'-H), 6.63 (d, 1H, $^4J = 8.1$ Hz, Ar-5'-H), 4.42–4.60 (m, 2H, NCH₂), 3.02 (t, 2H, $^3J = 7.9$ Hz, CH₂Ar), 1.43 (s, 3H, 5-CH₃), 1.21 (s, 3H, 6-CH₃), 1.01 (s, 6H, 4-(CH₃)₂). ^{13}C NMR (50 MHz, C₆D₆, ppm): $\delta_{\text{C}} = 178.1$ (C=S), 150.4, 149.0, 131.9, 121.2, 113.6, 112.9 (Ar), 127.0 (C₆), 116.0 (C₅), 55.9 (OCH₃), 55.8 (OCH₃), 53.8 (CH₂N), 50.0 (C₄), 35.7 (CH₂Ar), 27.5 (4-CH₃), 27.5 (4-CH₃), 14.6 (6-CH₃), 13.1 (5-CH₃).

Preparation of ethyl 1-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thio-5-pyrimidinecarboxylate (19)

A mixture of ethyl acetoacetate (1.73 g, 13.3 mmol), benzaldehyde (1.41 g, 13.3 mmol), *N*-[2-(3,4-dimethoxyphenyl)ethyl]thiourea (**18**) (2.98 g, 13.3 mmol), catalytic amount of p-TSA, and 30 mL of ethanol is refluxed for 6 h. Then the reaction mixture is kept at 0°C for 2 days.

Scheme 2 Simplified synthesis of pyrimido[6,1-*a*]isoquinolines and pyrimido [6,1-*a*]- β -carbolines



a $R^1 = R^2 = R^3 = R^4 = H$; **b** $R^1 = R^2 = R^4 = H$, $R^3 = Me$; **c** $R^1 = R^3 = R^4 = Me$, $R^2 = H$;
d $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = Et$; **6**. $H_2NCH_2CH_2-3\text{-Indolyl}$; **7**. $H_2NCH_2CH_2C_6H_3-3,4\text{-(OMe)}_2$;

Precipitated crystals are filtered. The filtrate is evaporated in vacuum to half volume and cooled to furnish the precipitate which is collected and combined with the first fraction. Combined solid is washed with cold ethanol to give 1.74 g (30 % yield) of compound **19**.

Mp ($^{\circ}C$): 143–144. Anal. Calcd for $C_{24}H_{28}N_2O_4S$ (440.56), %: C, 65.43; H, 6.41. Found, %: C, 65.25; H, 6.40; IR ($CHCl_3$, cm^{-1}): $\nu_{max} = 3415$ (NH), 1700 (C=O), 1630 (C=C), 1510 (NC=S). 1H NMR (200 MHz, $CDCl_3$, ppm): $\delta_H = 7.91$ (d, 1H, $^3J = 3.2$ Hz, NH), 7.20–7.40 (m, 5H, 4-Ph), 6.70–6.82 (m, 3H, Ar), 5.39 (d, 1H, $^3J = 3.2$ Hz, 4-H), 4.80 (br. s, 1H, NCH), 4.14 (br. s, 1H, NCH), 4.14 (q, 2H, $^3J = 7.0$ Hz, OCH_2CH_3), 3.86 (s, 6H, $2OCH_3$), 2.90 (t, 2H, $^3J = 7.6$ Hz, CH_2Ar), 2.56 (s, 3H, 6- CH_3), 1.21 (t, 3H, $^3J = 7.6$ Hz, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): $\delta_C = 178.5$ (C=S), 165.7 (C=O), 149.0, 147.8, 130.5, 120.6, 111.9, 111.3 (Ar), 142.0, 128.8, 128.8, 128.0, 126.5, 126.5 (4-Ph), 145.3 (C_6), 108.2 (C_5), 60.7 (OCH_2CH_3), 55.9 (OCH_3), 55.9 (OCH_3), 53.9 (C_4), 49.8 (NCH₂), 35.1 (CH_2Ar), 16.6 (6- CH_3), 14.1 (OCH_2CH_3).

Results and discussion

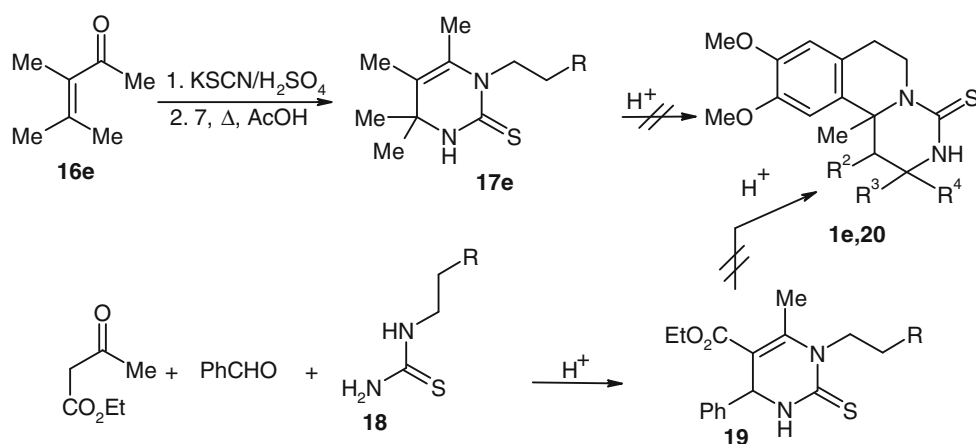
Synthesis of compounds **1–4** was accomplished by three methods. Reaction of 1,3-isothiocyanatocarbonyl compounds **5a–c** [9] with β -arylethylamines **6**, **7**, **9** in ether [10] lead to the transient *N*-(3-oxoalkyl)-*N'*-(2-arylethyl)thioureas **10** undergoing spontaneous cyclization into 6-hydroxypyrimidin-2-thiones **11c**, **13a–c**, **14a–c**. It was shown that upon heating compounds **11c**, **14a–c**, and **13a–c** underwent intramolecular amidoalkylation (particularly, thiouridoalkylation) converting into 1,2,3,6,7,11*b*-hexahydro-4*H*-pyrimido[6,1-*a*] isoquinoline-4-thiones **1c**, **3a–c**, and 2,3,6,7,12,12*b*-hexahydropyrimido[6,1-*a*]- β -carbolin-4(1*H*)-thione **4c**. Hydroxypyrimidinethiones **11c**, **13c**, **14c** were isolated and characterized, whereas compounds **11a,b** and **14a,b** were involved into further reactions without purification. Overall yields of compounds **1**, **3**, **4** were of 19–73% (Method A) (Scheme 1; Table 1).

Reaction between β -arylethylamines **6–8** and 1,3-isothiocyanatocarbonyl compounds **5b,c** also occurred upon

heating in acetic acid. In this case, a cascade cyclization of the transient thioureas **10** lead to compounds **1b**, **c**, **2c**, and **4b,c** in yields of 44–93% (Method B) (Scheme 1; Table 1). Since the starting 1,3-isothiocyanatocarbonyl compounds **5** are formed as a result of addition of isothiocyanic acid to α , β -unsaturated aldehydes and ketones in acidic conditions [9], we simplified synthesis of pyrimido[6,1-*a*]isoquinolines **1** and pyrimido[6,1-*a*]- β -carbolines **4** further. Successive treatment of α , β -unsaturated carbonyl compounds **16a–d** in acetic acid with isothiocyanic acid, generated in situ from KNCS and H_2SO_4 , and amines **6**, **7** furnished compounds **4a–c**, **1a–d** in 21–64% yields (Method C). This procedure represents a facile synthesis of the target compounds due to both experimental convenience and commercial availability of the starting materials. However, it was via Method B that the highest yields were achieved. For instance, yields of compound **1c**, obtained by methods A, B, and C, were of 73 (total for two steps, calculated on the starting amine), 84, and 64, respectively (Scheme 2; Table 1).

It is noteworthy that success of the isoquinoline ring closure depends on electronic properties of the aryl substituent in a β -arylethyl fragment. Thus, 3 h of refluxing in acetic acid of compound **13c**, which has no electron donating groups in the aromatic ring, does not lead to the cyclization product, but stops at the dehydration step giving 3,4-dihydro-4, 4, 6-trimethyl-1-(2-phenylethyl)-1*H*-pyrimidin-2-thione **15c** (Scheme 1). Similarly, compounds **13a,b** do not undergo cyclization under these conditions. Cyclization of compounds **13a–c** proceeds only upon heating in 85% phosphoric acid for 2 h, affording compounds **3a,c** in 19, 22 and 50% yields correspondingly (Scheme 1; Table 1). Therefore, Method A is applicable even in the absence of electron-donating substituents in the aromatic ring, whereas Methods B and C can be successfully used only if such substituents are present.

Apparently, presence of the substituents at positions of C(5) and C(6) in the pyrimidine ring should impede formation of isoquinoline or β -carboline fragment of compounds **1–4**. Previously, we reported that compounds **1c** and **4c**, which are formed through the pyrimidine intermediates bearing no alkyl substituents at positions C(5) and C(6), could be obtained under very mild conditions. For instance, cascade

Scheme 3 Attempts to cyclize 5-substituted 3,6-dihydropyrimidin-2(1H)-thiones

17e, 18, 19 R = 3,4-(OMe)₂C₆H₃; **1e** R¹ = R² = R³ = Me, X = S; **20** R² = CO₂Et, R³ = H, R⁴ = Ph

cyclization of the thioureas **10** occurs even in aqueous oxalic acid at room temperature [9]. At the same time, successive treatment of α , β -unsaturated ketone **16e** with isothiocyanic acid and amine **7** followed by a 3-h reflux in acetic acid did not give expected pyrimidoisoquinoline, but 3,4-dihydro-1H-pyrimidin-2-thione **17e** (Scheme 3).

An attempt to involve into cyclization Biginelli pyrimidine **19**, obtained from *N*-[2-(3,4-dimethoxyphenyl)ethyl]thiourea **18**, benzaldehyde and ethyl acetoacetate, was also unsuccessful (Scheme 3). Noteworthy, compounds **17e** and **19** did not convert into the corresponding pyrimidoisoquinolines **1e, 20** by neither prolonged reflux in acetic acid (10 h) nor replacing acetic acid with trifluoroacetic or phosphoric acid (Scheme 3). On the other hand, cyclization was observed for compounds **1–4c, 1d**, which only have a substituent at position C(1) or C(11b).

Pyrimidine ring annealing process can be easily monitored by ¹H NMR spectroscopy. Particularly, ¹H NMR spectra of compounds **1–4** have a distinct signal from an equatorially oriented proton at C(6) with an abnormally high chemical shift (5.34–5.74 ppm) due to the deshielding effect by the adjacent thiourea group. Signals of the structurally related protons in *N*-arylethyl-substituted 1H-pyrimidine-2-thiones **11–13, 17, 19** are shifted to higher field on 1–2 ppm. Consequently, according to ¹H NMR data, compounds **1b, 3b, 4b** are formed as diastereomeric mixtures of 2,11b-*trans*/2,11b-*cis* and 2,12b-*trans*/2,12b-*cis* in 1:1, 1:1, 4:1 ratios correspondingly. However, an overlapping of the signals in the spectrum of compound **1d** did not allow determining its diastereomeric composition.

Conclusion

Convenient procedures for synthesis of 1,2,3,6,7,11b-hexahydro-4H-pyrimido[6,1-*a*]isoquinolin-4-thiones and 2,

3,6,7,12,12 *b*-hexahydro-1H-pyrimido[1', 6': 1, 2]pyrido[3, 4-*b*] indole-4-thiones have been developed. The described synthetic approach is mostly restricted by the reactivity of the transient *N*-arylethyl-substituted 1H-pyrimidine-2-thiones in an intramolecular amidoalkylation, which is influenced by both sterical and and electronic factors. Increasing the effective volume of the substituents at positions C(5) and C(6) of the pyrimidine ring disfavors intramolecular amidoalkylation. Increased electron density in the aromatic ring of the *N*-arylethyl moiety facilitates isoquinoline ring closure process.

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