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Synthesis of Functionalized 2,3-Dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones and Their Recyclization to 2,3-Dihydrothieno[3,4-*d*]pyrimidin-4(1*H*)-ones

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ABSTRACT: *By the reaction of 6-aryl(alkyl)amino-5-cyano-2,3-dihydro-1,3-thiazin-4(10)-ones with α-halogenoketones in the presence of triethylamine, 2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones have been synthesized and their acid-catalyzed recyclization to 2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-ones has been found and studied.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:104–111, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20181

INTRODUCTION

Condensed heterocyclic systems containing the thiophene ring have captured the keen interest of medical chemists. A number of thieno[2,3-*d*]pyrimidine derivatives were reported to exhibit diverse biological activity [1–4]. At the same time, little is known about isomeric thieno[3,4-*d*]pyrimidines in which the thiophene ring is annulated through its other edge to the d-edge of the pyrimidine ring [5–7]. Previously, we described a facile synthetic route to 6-aryl(alkyl)amino-5-cyano-2,3-dihydro-1,3-thiazin-4(1*H*)-ones and demonstrated their tendency to recyclize under the action of basic agents like potassium hydroxide or triethylamine yielding the thiolates of 1-substituted 5-cyano-6-mercapto-2,3-dihydropyrimidin-4(1*H*)-ones [8]. On alkylating the latter at the sulfur atom with dimethyl sulfate or benzyl chloride, they furnished 6-alkylthio-5-cyano-2,3-dihydropyrimidin-4(1*H*)-ones. The neighboring positions of the alkylthio and cyano substituents on the heterocyclic ring enable further heterocyclization of such compounds by the intramolecular Thorp condensation using functionalized alkyl halides as alkylating agents [9]. In the present study, we carry on the research on the chemistry of 2,3-dihydro-1,3-thiazin-4(1*H*)-ones and develop some new approaches to the synthesis of functionalized partially hydrogenated thienopyrimidines.

RESULTS AND DISCUSSION

Heating 3-alkyl(aryl)amino-2-cyano-3-mercaptoacrylamides **1a, b** with aldehydes and ketones **2a–h** in the presence of a catalytic amount of acid as previously described [8], we obtained 2,3-dihydro-1,3-thiazin-4(1*H*)-ones **3a–l**. Chloroacetone **4a**, α-chloro-*tert*-butylmethylketone **4b**, and bromoacetophenone **4c** were used as alkylating agents for further heterocyclization (Scheme 1). It is found that short boiling (for 1–2 h) of compounds **3** and **4** with two equivalents of triethylamine in ethanol

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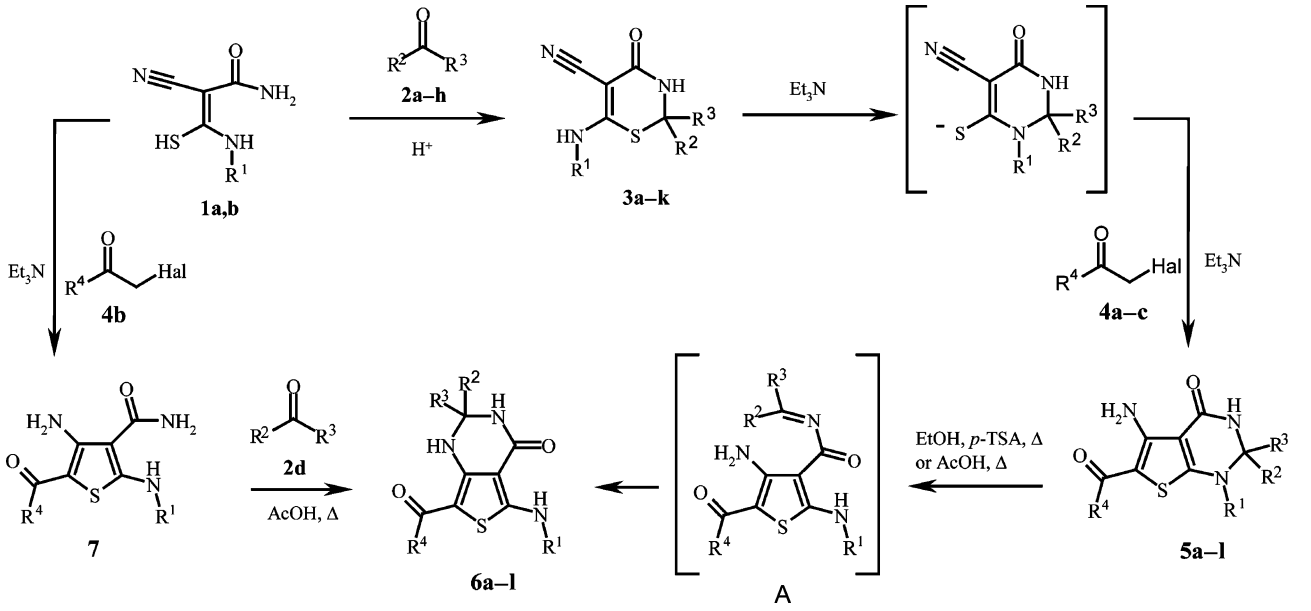


1, R^1 = Et (a), R^1 = Ph (b).

2, R^2 = H, R^3 = Me (a); R^2 = H, R^3 = Ph (b); R^2 = H, R^3 = 4-$MeOC_6H_4$ (c); R^2 = H, R^3 = 4-$CF_3C_6H_4$ (d); R^2 = H, R^3 = 2-thienyl (e); R^2 = H, R^3 = 2,3-dihydro-1,4-benzodioxin-6-yl (f); $R^2 = R^3$ = Me (g); $R^2 = R^3$ = adamantyliden (h).

3, R^1 = Et, R^2 = H, R^3 = Ph (a); R^1 = Et, R^2 = H, R^3 = 2-thienyl (b); R^1 = Et, R^2 = H, R^3 = 2,3-dihydro-1,4-benzodioxin-6-yl (c); R^1 = Et, $R^2 = R^3$ = adamantyliden (d); R^1 = Ph, R^2 = H, R^3 = Me (e); R^1 = Ph, R^2 = H, R^3 = Ph (f); R^1 = Ph, R^2 = H, R^3 = 4-$MeOC_6H_4$ (g); R^1 = Ph, R^2 = H, R^3 = 4-$CF_3C_6H_4$ (h); R^1 = Ph, $R^2 = R^3$ = Me (k); R^1 = Ph, $R^2 = R^3$ = adamantylide (l).

4, R^4 = Me (a); R^4 = *t*-Bu (b); R^4 = Ph (c).

SCHEME 1

provides high yields of 5-amino-6-aroyl(acyl)-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **5a–l** which precipitate from the reaction mixture on cooling in the form of colorless or yellow crystals and usually need no further purification (Table 1).

The structure of compounds **5a–i** was corroborated by the IR, ^{1}H NMR, and ^{13}C NMR spectral data. The IR spectra display intensive absorption bands of the CO groups at 1675–1680 cm^{-1}, NH group at 3180–3210 cm^{-1} and also narrow medium-intensive absorption bands in the regions 3440–3460 and 3300–3330 cm^{-1} referring to antisymmetric and symmetric vibrations of the NH_2 group, respectively. A ^{1}H NMR signal for the proton of the NH group in the 2,3-dihydropyrimidine ring appears in the region 8.0–8.7 ppm as a singlet or doublet (for R^2 = H, J_{CH-NH} = 1–4 Hz). Protons of the NH_2 group are magnetically nonequivalent and give rise to two strongly broadened singlets in the region 7.30–7.50 ppm, which may be attributed to the formation of an intramolecular hydrogen bond with the neighboring carbonyl group. Compounds **5a–c,f–l** are characterized by the doublet in the region 5.30–6.40 ppm (J_{CH-NH} = 1–4 Hz) which arises from the proton of the CH group in the aminal moiety. ^{13}C NMR spectra show a peak of the C^2 atom in the region 68.0–75.0 ppm.

Due to the presence of the amino and acyl (aroyl) substituents at respective positions 5 and 6, the synthesized 2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **5** are regarded as polyfunctional compounds and promising synthons both in derivatization of the corresponding heterocyclic nucleus and in the design of new condensed heterocycles. In studying the reactivity of the amino group, we have found that compound **5k**, if heated with benzaldehyde in glacial acetic acid, furnishes the only reaction product, 2-(4-methoxyphenyl)-5-phenylamino-7-pivaloyl-2,3-dihydrothieno[3,4-*d*]pyrimidin-4(1*H*)-one **6k** which is isomeric to **5k** differing by the annelation edge of the thiophene ring. This recyclization of thienopyrimidines has been studied thoroughly: as found, the reaction rate is significantly affected by the medium acidity, temperature, and the nature of substituents

TABLE 1 Elemental Analytical Data of Compounds **5**

	R^1	R^2	R^3	R^4	Formula	Calcd/(found) C	H	N	S
5a	Et	H	2-Thienyl	Me	$C_{14}H_{15}N_3O_2S_2$	52.32 (52.07)	4.70 (4.83)	13.07 (13.25)	19.95 (20.08)
5b	Et	H	Ph	*t*-Bu	$C_{19}H_{23}N_3O_2S$ 357.48	63.84 (64.03)	6.49 (6.60)	11.75 (11.91)	8.97 (8.77)
5c	Et	H	2,3-Dihydro-1,4-benzodioxin-6-yl	Ph	$C_{23}H_{21}N_3O_4S$ 435.51	63.43 (63.51)	4.86 (4.84)	9.65 (9.55)	7.36 (7.11)
5d	Ph	H	Me	*t*-Bu	$C_{18}H_{21}N_3O_2S$ 343.45	62.95 (62.74)	6.16 (6.22)	12.23 (12.01)	9.34 (9.07)
5e	Ph	Me	Me	*t*-Bu	$C_{19}H_{23}N_3O_2S$ 357.48	63.84 (63.68)	6.49 (6.40)	11.75 (11.71)	8.97 (8.71)
5f	Ph	H	Ph	*t*-Bu	$C_{23}H_{23}N_3O_2S$ 405.52	68.12 (68.33)	5.72 (5.76)	10.36 (10.48)	7.91 (8.25)
5g	Ph	H	Ph	Ph	$C_{25}H_{19}N_3O_2S$ 425.51	70.57 (70.63)	4.50 (4.52)	9.88 (9.87)	7.54 (7.58)
5h	Ph	H	4-$MeOC_6H_4$	Me	$C_{21}H_{19}N_3O_3S$ 393.47	64.11 (64.12)	4.87 (4.80)	10.68 (10.64)	8.15 (8.10)
5k	Ph	H	4-$MeOC_6H_4$	*t*-Bu	$C_{24}H_{25}N_3O_3S$ 435.55	66.18 (66.09)	5.79 (5.65)	9.65 (9.80)	7.36 (7.11)
5l	Ph	H	4-$CF_3C_6H_4$	*t*-Bu	$C_{24}H_{22}F_3N_3O_2S$ 473.52	60.88 (60.75)	4.68 (4.73)	8.87 (8.78)	6.77 (7.04)

at positions 1 and 2 of the dihydropyrimidine ring.

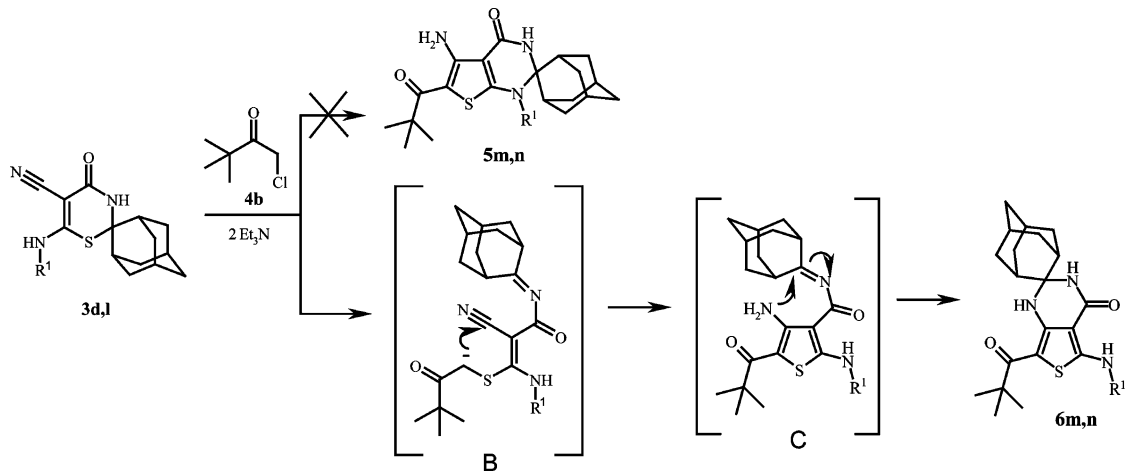
Thus, compounds **5h,k** bearing the anisyl group at the 2-position are almost quantitatively converted into compounds **6h,k** on heating them for 4–5 h in ethanol along with 5 mol% of *p*-toluenesulfonic acid (*p*-TSA). Compounds **5f,g**, 2-phenyl-substituted analogues of **5h,k**, are nearly half-converted into the corresponding products **6f,g** under the same conditions, whereas the rest of compounds **5** remain practically unchanged. As seen, the recyclization rate increases with the electron donor ability of the aryl substituent at position 2; the reaction also proceeds faster for *N*-phenyl compounds **5d–l** as against their *N*-ethyl analogues **5a–c**. The acyl (aroyl) group at 6-position exerts no effect on the reaction rate. We have found that all compounds **5a–l**, irrespective of the nature of substituents, can be converted into 2,3-dihydrothieno[3,4-*d*]pyrimidin-4(1*H*)-ones **6a–l** on heating them for 4 h in glacial acetic acid, along with the 5 mol% amount of *p*-TSA (Table 2). We suggest that the recyclization occurs via formation of the acyl imine intermediate A caused by the addition of a catalytic amount of strong acid or by acetic acid used as a solvent. This ring-opening reaction step is promoted by a donor substituent, like the anisyl group, and stabilizing the intermediate A, which accounts for the regularities revealed by us experimentally. The intramolecular recyclization pattern was demonstrated by the fact that an attempted cross-reaction did not proceed: boiling compound **5f** in acetic acid with the equivalent quantity of *p*-methoxybenzaldehyde or *p*-trifluoromethylbenzaldehyde in the presence of *p*-TSA resulted in the only product **6f**; an intermolecular reaction pathway was thus ruled out.

The structure of compounds **6a–l** was firmly established by the spectroscopic methods as well as chemical correlation. Their IR spectra display the absorption bands assigned to the groups NH (3190–3210 cm^{-1}) and C=O (1660–1670 cm^{-1}). The 2,3-dihydrothienopyrimidine ring manifests itself by the characteristic ^1H NMR spectral picture: the endocyclic NH-protons give rise to sometimes broadened singlet peaks in the region 8.1–8.9 ppm, whereas the CH-proton is responsible for a singlet in the region 5.0–6.0 ppm (for $R^2 = H$). It is noteworthy that the exocyclic NH-proton provides a signal in the most downfield region—10.4–10.6 ppm for $R^1 = Ph$ or 8.1–8.3 ppm for $R^1 = Et$; in the latter case, the peak appears as a slightly broadened triplet due to the spin–spin coupling with the protons of the neighboring CH_2 group, with the $J_{NH-CH_2} = 6–7$ Hz. In contrast to compounds **5a–l**, the carbon atom of the aminal fragment in compounds **6a–l** shows its ^{13}C NMR signal in the region 61.1–68.0 ppm. 2,3-Dihydrothieno[3,4-*d*]pyrimidin-4(1*H*)-one **6l** was obtained from the reaction of 3-mercaptoacrylamide derivative **1b** with compound **4b** to give substituted 4-amino-3-thiophenecarboxamide **7** which was treated with *p*-trifluoromethylbenzaldehyde under acidic conditions.

TABLE 2 Elemental Analytical Data of Compounds **6**

	R^1	R^2	R^3	R^4	*Formula*	*Calcd/(found)*			
						C	*H*	*N*	*S*
6a	Et	H	2-Thienyl	Me	$C_{14}H_{15}N_3OS_2$	52.32	4.70	13.07	19.95
						(52.46)	(4.75)	(13.20)	(19.72)
6b	Et	H	Ph	*t*-Bu	$C_{19}H_{23}N_3O_2S$	63.84	6.49	11.75	8.97
					357.48	(63.70)	(6.41)	(11.86)	(8.80)
6c	Et	H	2,3-Dihydro-1,4-benzodioxin-6-yl	Ph	$C_{23}H_{21}N_3O_4S$	63.43	4.86	9.65	7.36
					435.51	(63.35)	(4.82)	(9.52)	(7.59)
6d	Ph	H	Me	*t*-Bu	$C_{18}H_{21}N_3O_2S$	62.95	6.16	12.23	9.34
					343.45	(62.61)	(6.24)	(12.29)	(9.17)
6e	Ph	Me	Me	*t*-Bu	$C_{19}H_{23}N_3O_2S$	63.84	6.49	11.75	8.97
					357.48	(63.60)	(6.40)	(11.63)	(8.88)
6f	Ph	H	Ph	*t*-Bu	$C_{23}H_{23}N_3O_2S$	68.12	5.72	10.36	7.91
					405.52	(68.32)	(5.70)	(10.41)	(7.93)
6g	Ph	H	Ph	Ph	$C_{25}H_{19}N_3O_2S$	70.57	4.50	9.88	7.54
					425.51	(70.42)	(4.44)	(9.97)	(7.42)
6h	Ph	H	4-$MeOC_6H_4$	Me	$C_{21}H_{19}N_3O_3S$	64.11	4.87	10.68	8.15
					393.47	(64.27)	(4.96)	(10.55)	(8.41)
6k	Ph	H	4-$MeOC_6H_4$	*t*-Bu	$C_{24}H_{25}N_3O_3S$	66.18	5.79	9.65	7.36
					435.55	(66.00)	(5.73)	(9.58)	(7.52)
6l	Ph	H	4-$CF_3C_6H_4$	*t*-Bu	$C_{24}H_{22}F_3N_3O_2S$	60.88	4.68	8.87	6.77
					473.52	(60.63)	(4.65)	(8.79)	(6.62)
6m	Et	Adamantyliden		*t*-Bu	$C_{22}H_{31}N_3O_2S$	65.80	7.78	10.46	7.98
					401.58	(65.98)	(7.80)	(10.54)	(7.70)
6n	Ph	Adamantyliden		*t*-Bu	$C_{26}H_{31}N_3O_2S$	69.46	6.95	9.35	7.13
					449.62	(69.65)	(6.87)	(9.47)	(7.02)

An interesting reaction course was revealed by us in the attempted synthesis of **5m,n** containing an adamantene moiety. Heating compounds **3d,l** with α-chloro-*tert*-butylmethylketone **4b** in ethanol in the presence of two equivalents of triethylamine immediately leads to 5-*tert*-butyl-7-ethyl(phenyl) amino-2,3-dihydrothieno[3,4-*d*]pyrimidin-4(1*H*)-ones **6m,n** (Scheme 2) which is evidenced by the ^{1}H NMR downfield singlet signal from the NHPh-proton at 10.20 ppm for **6n** and by the corresponding triplet at 8.05 ppm for **6m** ($J_{NH-CH_2} = 4$ Hz). A straightforward formation of compounds **6m,n** in this reaction results from the steric hindrances which are caused by the *N*-ethyl(phenyl) substituent and the adamantyl moiety and preclude the 2,3-dihydrothieno[2,3-*d*]pyrimidine ring closure. Hence, the S-alkylated intermediate B first cyclizes into the *N*-alkylidene thiophenecarboxamide



SCHEME 2

intermediate C which then rapidly forms the 2,3-dihydrothieno[3,4-*d*]pyrimidine nucleus of **6m,n**.

We have thus developed a convenient synthetic access to functionalized 2,3-dihydrothieno[2,3-*d*]-pyrimidin-4(1*H*)-ones and 2,3-dihydrothieno[3,4-*d*]-pyrimidin-4(1*H*)-ones, and also revealed and investigated a novel recyclization of condensed thienopyrimidine systems.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets. ^{1}H NMR spectra were registered in the mixture $(CD_3)_2SO$:CCl_4 (2:1) on a Varian-Gemini spectrometer (300 MHz) using TMS as internal standard. ^{13}C NMR spectra were registered in $(CD_3)_2SO$ on a Varian-Gemini spectrometer (75.5 MHz) using TMS as internal standard.

General Procedure for Preparation of 5-Amino-7-acyl(aroyl)-2,3-dihidrothieno[2,3-d]pyrimidin-4(1H)-ones **5a–l** *and 2,2-Spiro(2-adamantyliden)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-ones* **6m,n**

A mixture of compound **3a–l** (10 mmol), α-chloroketone **4a–c** (11 mmol), and triethylamine (2.1 mL, 15 mmol) in ethanol (20 mL) was boiled for 2 h. On cooling the solution, resulting crystals were filtered off, dried, and recrystallized from ethanol or acetonitrile.

6-Acetyl-5-amino-1-ethyl-2-thien-2-yl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5a**. Yield 71%; mp 234–236°C; IR (ν/cm^{-1}): 3450, 3330 (NH_2), 3200 (NH), 1675 (C=O); ^{1}H NMR δ 1.22 (t, 3H, CH_3, $J = 6.9$ Hz), 2.08 (s, 3H, CH_3), 3.31 (q, 2H, CH_2, $J = 6.9$ Hz), 6.20 (d, 1H, CH, $J = 3.3$ Hz), 6.96 (t, 1H, H_{arom}, $J = 3.3$ Hz), 7.10–7.15 (m, 2H, $H_{arom} + NH_2$), 7.39 (d, 1H, H_{arom}, $J = 5.1$ Hz), 7.92 (br s, 1H, NH_2), 8.40 (d, 1H, NH, $J = 3.3$ Hz); ^{13}C NMR δ 12.38 (CH_3), 27.95 (CH_3), 45.67 (CH_2), 67.63 (CH), 95.88 (C^6), 98.91 (C^{4a}), 126.51, 126.65, 126.66 (CH_{arom}), 142.89 (C_{arom}), 154.48 (C^5), 161.30 (C^4), 161.32 (C^{7a}), 186.03 (C=O).

5-Amino-6-(2,2-dimethylpropanoyl)-1-ethyl-2-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5b**. Yield 74%; mp 215–217°C; IR (ν/cm^{-1}): 3460, 3340 (NH_2), 3200 (NH), 1675 (C=O); ^{1}H NMR δ 1.17 (t, 3H, CH_3, $J = 6.9$ Hz), 1.24 (s, 9H, *t*-Bu), 3.21 (m, 1H, CH^AH^B), 3.32 (m, 1H, CH^AH^B), 5.91 (d, 1H, CH, $J = 1.0$ Hz), 7.38–7.40 (m, 5H, H_{arom}), 8.21 (d, 1H, NH, $J = 1.0$ Hz), protons of NH_2-group are in rapid exchange; ^{13}C NMR δ 12.22 (CH_3), 27.44 ($3CH_3$), 41.87 (C, *t*-Bu), 45.71 (CH_2), 71.37 (CH), 91.18 (C^6), 97.02 (C^{4a}), 126.31, 128.86, 128.99 (CH_{arom}), 139.83 (C_{arom}), 157.42 (C^5), 161.31 (C^4), 161.63 (C^{7a}), 195.13 (C=O).

5-Amino-6-benzoyl-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5c**. Yield 72%; mp 218–220°C; IR (ν/cm^{-1}): 3440, 3310 (NH_2), 3200 (NH), 1675 (C=O); ^{1}H NMR δ 1.12 (t, 3H, CH_3, $J = 6.9$ Hz), 3.21 (m, 2H, CH_2), 4.22 (s, 4H, $2CH_2$), 5.81 (d, 1H, CH, $J = 3.0$ Hz), 6.80–6.86 (m, 3H, H_{arom}), 7.39–7.47 (m, 4H, $H_{arom} + NH_2$), 7.55–7.61 (m, 2H, H_{arom}), 8.22 (d, 1H, NH, $J = 3.0$ Hz), 8.39 (br s, 1H, NH_2); ^{13}C NMR δ 12.15 (CH_3), 45.80 (CH_2), 64.09 (OCH_2), 71.04 (CH), 94.73 (C^6), 97.70 (C^{4a}), 115.08, 117.43,119.08, 126.78, 128.40, 130.15 (CH_{arom}), 132.79, 141.62, 143.32, 143.93 (C_{arom}), 156.87 (C^5), 161.29 (C^4), 163.78 (C^{7a}), 183.91 (C=O).

5-Amino-6-(2,2-dimethylpropanoyl)-2-methyl-1-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5d**. Yield 67%; mp 250–252°C; IR (ν/cm^{-1}): 3400, 3310 (NH_2), 3200 (NH), 1680 (C=O); ^{1}H NMR δ 1.14 (s, 9H, $3CH_3$), 1.32 (d, 3H, CH_3, $J = 6.6$ Hz), 5.34 (m, 1H, CH), 7.34–7.68 (m, 6H, $H_{arom} + NH_2$), 8.01 (d, 1H, NH, $J = 1.5$ Hz), 8.45 (br s, 1H, NH_2); ^{13}C NMR δ 19.82 (CH_3), 27.33 ($3CH_3$), 41.91 (C, *t*-Bu), 68.87 (CH), 92.15 (C^6), 99.75 (C^{4a}), 126.23, 128.44, 130.22 (CH_{arom}), 140.79 (C_{arom}), 157.01 (C^5), 161.87, 162.08 (C^4, C^{7a}), 195.61 (C=O).

5-Amino-2,2-dimethyl-6-(2,2-dimethylpropanoyl)-1-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5e**. Yield 70%; mp 251–253°C; IR (ν/cm^{-1}): 3450, 3340 (NH_2), 3210 (NH), 1680 (C=O); ^{1}H NMR δ 1.09 (s, 9H, $3CH_3$), 1.45 (s, 6H, $2CH_3$), 7.35–7.61 (m, 6H, $H_{arom} + NH_2$), 8.02 (s, 1H, NH), 8.44 (br s, 1H, NH_2); ^{13}C NMR δ 26.87 ($2CH_3$), 27.30 ($3CH_3$), 41.70 (C, *t*-Bu), 74.96 (C^2), 92.36 (C^6), 98.11 (C^{4a}), 129.56, 129.80, 131.42 (CH_{arom}), 138.89 (C_{arom}), 157.27 (C^5), 161.85, 162.55 (C^4, C^{7a}), 195.29 (C=O).

5-Amino-6-(2,2-dimethylpropanoyl)-1,2-phenyl-2,3-dihydrothieno[2, 3-d]pyrimidin-4(1H)-one **5f**. Yield 78%; mp 247–249°C; IR (ν/cm^{-1}): 3440, 3300 (NH_2), 3180 (NH), 1680 (C=O); ^{1}H NMR δ 1.16 (s, 9H, $3CH_3$), 6.25 (d, 1H, CH, $J = 2.1$ Hz), 7.25–7.42 (m, 11H, $H_{arom} + NH_2$), 8.59 (br s, 2H, $NH + NH_2$); ^{13}C NMR δ 27.39 ($3CH_3$), 42.03 (C, *t*-Bu), 74.19 (CH), 92.17, 100.79 (C^6, C^{4a}), 124.73, 126.86, 127.58, 128.64, 128.92, 129.92 (CH_{arom}), 138.92, 141.57 (C_{arom}), 156.69 (C^5), 160.61, 161.45 (C^4, C^{7a}), 195.90 (C=O).

5-Amino-6-benzoyl-1,2-diphenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5g**. Yield 80%; mp 246–248°C; IR (ν/cm^{-1}): 3450, 3330 (NH_2), 3180 (NH), 1680 (C=O); ^{1}H NMR δ 6.27 (d, 1H, CH, $J = 1.9$ Hz), 7.21–7.72 (m, 16H, $H_{arom} + NH_2$), 8.40 (br s, 1H, NH_2), 8.65 (d, 1H, NH, $J = 1.9$ Hz); ^{13}C NMR δ 74.35 (CH), 95.62 (C^6), 101.21 (C^{4a}), 124.28, 126.73, 126.84, 127.76, 128.42, 128.69, 128.97, 129.92, 130.33 (CH_{arom}), 138.89, 141.28, 141.33 (C_{arom}), 156.24 (C^5), 161.38, 163.07 (C^4, C^{7a}), 184.69 (C=O).

6-Acetyl-5-amino-2-(4-methoxyphenyl)-1-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5h**. Yield 79%; mp 250–252°C; IR (ν/cm^{-1}): 3460, 3330 (NH_2), 3200 (NH), 1675 (C=O); ^{1}H NMR δ 2.03 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.22 (d, 1H, CH, $J = 2.7$ Hz), 6.86 (d, 2H, H_{arom}, $J = 8.1$ Hz), 7.11–7.45 (m, 8H, $H_{arom} + NH_2$), 7.88 (br s, 1H, NH_2), 8.50 (d, 1H, NH, $J = 2.7$ Hz); ^{13}C NMR δ 27.95 (CH_3), 55.09 (OCH_3), 73.89 (CH), 96.69 (C^6), 101.77 (C^{4a}), 113.90, 124.78, 127.59, 128.29, 129.89 (CH_{arom}), 130.74, 141.56 (C_{arom}), 153.95 (C^5), 159.49, 161.55 (C^4, C^{7a}), 186.63 (C=O).

5-Amino-6-(2,2-dimethylpropanoyl)-2-(4-methoxyphenyl)-1-phenyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one **5k**. Yield 76%; mp 229–231°C; IR (ν/cm^{-1}): 3450, 3330 (NH_2), 3200 (NH), 1680 (C=O); ^{1}H NMR δ 1.16 (s, 9H, $3CH_3$), 3.72 (s, 3H, OCH_3), 6.20 (d, 1H, CH, $J = 1.2$ Hz), 6.83 (d, 2H, H_{arom}, $J = 8.1$ Hz), 7.29–7.43 (m, 8H, $H_{arom} + NH_2$), 8.01 (br s, 1H, NH_2), 8.48 (d, 1H, NH, $J = 1.2$ Hz); ^{13}C NMR δ 27.39 ($3CH_3$), 42.01 (C, *t*-Bu), 55.10 (OCH_3), 74.00 (CH), 92.16 (C^6), 100.56 (C^{4a}), 113.90, 125.03, 127.64, 128.37, 129.89 (CH_{arom}), 130.66, 141.53, 156.77 (C_{arom}), 159.53 (C^5), 160.93, 161.57 (C^4, C^{7a}), 195.82 (C=O).

5-Amino-6-(2,2-dimethylpropanoyl)-1-phenyl-2-(4-trifluoromethylphenyl)-2,3-dihydrothieno[2,3-d]-pyrimidin-4(1H)-one **5l**. Yield 81%; mp 268–270°C; IR (ν/cm^{-1}): 3450, 3320 (NH_2), 3200 (NH), 1680 (C=O); ^{1}H NMR δ 1.18 (s, 9H, $3CH_3$), 6.40 (d, 1H, CH, $J = 1.5$ Hz), 7.34–7.46 (m, 6H, $H_{arom} + NH_2$), 7.56 (d, 2H, H_{arom}, $J = 7.8$ Hz), 7.70 (d, 2H, H_{arom}, $J = 7.8$ Hz), 8.05 (br s, 1H, NH_2), 8.70 (d, 1H, NH, $J = 1.5$ Hz); ^{13}C NMR δ 27.35 ($3CH_3$), 42.04 (C, *t*-Bu), 73.35 (CH), 92.34 (C^6), 101.12 (C^{4a}), 124.48, 125.12 (CF_3, $^1J_{C-F} = 286$ Hz), 125.64, 127.61, 127.81, 128.75 (C_{arom}, $^2J_{C-F} = 39$ Hz), 130.00 (CH_{arom}), 141.43, 143.75 (C_{arom}), 156.51 (C^5), 160.51, 161.25 (C^{4a}, C^{7a}), 195.99 (C=O).

7-(2,2-Dimethylpropanoyl)-5-ethylamino-2,2-spiro(2-adamantyliden)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6m**. Yield 57%; mp 293–295°C; IR (ν/cm^{-1}): 3220 (NH), 1660 (C=O); ^{1}H NMR δ 1.21–1.28 (m, 12H, $4CH_3$), 1.42–1.95 (m, 12H, H_{aliph}), 2.20–2.23 (m, 2H, H_{aliph}), 3.28 (q, 2H, CH_2, $J = 6.6$ Hz), 7.61 (s, 1H, NH), 8.05 (br t, 1H, NH, $J = 6.6$ Hz), 9.46 (s, 1H, NH); ^{13}C NMR δ ($CDCl_3$) 14.53 (CH_3), 26.06, 26.39 (CH_{aliph}), 27.61 ($3CH_3$), 32.80, 33.45, 37.35 (CH_{2aliph}), 37.79 (CH_{aliph}), 41.52 (CH_2), 42.12 (C, *t*-Bu), 73.71 (C^2), 92.03, 94.36 (C^{4a}, C^7), 154.87 (C^{7a}), 163.41 (C^5), 164.80 (C^4), 196.99 (C=O).

7-(2,2-Dimethylpropanoyl)-5-phenylamino-2,2-spiro(2-adamantyliden)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6n**. Yield 60%; mp 294–296°C; IR (ν/cm^{-1}): 3250 (NH), 1660 (C=O); ^{1}H NMR δ 1.25 (s, 9H, $3CH_3$), 1.45–2.00 (m, 12H, H_{aliph}), 2.10–2.29 (m, 2H, H_{aliph}), 7.14 (t, 1H, H_{arom}, $J = 7.1$ Hz), 7.34–7.43 (m, 4H, H_{arom}), 8.08 (s, 1H, NH), 9.40 (s, 1H, NH), 10.45 (s, 1H, NH); ^{13}C NMR δ ($CDCl_3$) 26.00, 26.31 (CH_{aliph}), 27.62 ($3CH_3$), 32.72, 33.43, 37.46 (CH_{2aliph}), 37.73 (CH_{aliph}), 42.39 (C, *t*-Bu), 73.88 (C^2), 92.78 (C^7), 97.44 (C^{4a}), 118.76, 123.92, 129.52 (CH_{arom}), 139.32 (C_{arom}), 153.32 (C^{7a}), 158.56 (C^5), 163.55 (C^4), 197.92 (C=O).

General Procedure for Preparation of 7-Alkyl(aryl)amino-5-acyl(aroyl)-2,3-dihidrothieno[3,4-d]pyrimidin-4(1H)-ones **6a–l**

Method A. A mixture of compound **5h,k** (10 mmol) and *p*-TSA (0.5 mmol) in ethanol (20 mL) was boiled for 5 h. On cooling the solution, resulting precipitate was filtered off, washed with ethanol, dried, and recrystallized from ethanol.

Method B. A mixture of compound **5a–l** (10 mmol) and *p*-TSA (0.5 mmol) in glacial acetic acid (20 mL) was boiled for 4 h. On cooling the solution, mixture was diluted with 40 mL of water, resulting precipitate was filtered off, dried, and recrystallized from ethanol.

Method C. A mixture of compound **7** (10 mmol), *n*-trifluorobenzaldehyde (11 mmol) and *p*-TSA (0.5 mmol) in glacial acetic acid (20 mL) was boiled for 2 h. On cooling the solution, mixture was diluted with 40 mL of water, resulting precipitate was filtered off, dried, and recrystallized from ethanol.

7-Acetyl-5-ethylamino-2-thien-2-yl-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6a**. Yield 75% (method B); mp 239–241°C; IR (ν/cm^{-1}): 3200 (NH),

1670 (C=O); ^{1}H NMR δ 1.24 (t, 3H, CH_3, $J = 7.2$ Hz), 2.06 (s, 3H, CH_3), 3.25 (m, 2H, CH_2), 6.02 (s, 1H, CH), 6.92 (t, 1H, H_{arom}, $J = 3.9$ Hz), 7.00–7.07 (m, 1H, H_{arom}), 7.34 (d, 1H, H_{arom}, $J = 3.9$ Hz), 8.17 (br t, 1H, NH, $J = 6.0$ Hz), 8.26 (s, 1H, NH), 8.39 (s, 1H, NH); ^{13}C NMR δ 14.20 (CH_3), 27.81 (CH_3), 41.53 (CH_2), 66.40 (CH), 89.65, 94.33 (C^{4a}, C^7), 1243.31, 128.10, 128.36 (CH_{arom}), 139.23 (C_{arom}), 157.87 (C^{7a}), 162.70, 163.05 (C^5, C^4), 186.67 (C=O).

7-(2,2-Dimethylpropanoyl)-5-ethylamino-2-phenyl-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6b**. Yield 79% (method B); mp 203–205°C; IR (ν/cm^{-1}): 3360, 3200 (NH), 1670 (C=O); ^{1}H NMR δ 1.96 (m, 12H, $4CH_3$), 3.26 (q, 2H, CH_2, $J = 6.6$ Hz), 5.86 (s, 1H, CH), 7.29–7.41 (m, 5H, H_{arom}), 8.21 (m, 2H, NH + NHEt), 8.94 (s, 1H, NH); ^{13}C NMR δ 14.22 (CH_3), 27.25 ($3CH_3$), 41.47 (CH_2), 41.62 (C, *t*-Bu), 66.46 (CH), 89.88, 94.24 (C^{4a}, C^7), 126.10, 128.40, 128.55 (CH_{arom}), 142.26 (C_{arom}), 154.86 (C^{7a}), 163.09, 163.66 (C^5, C^4), 195.05 (C=O).

7-Benzoyl-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-ethylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4-(1H)-one **6c**. Yield 73% (method B); mp 233–235°C; IR (ν/cm^{-1}): 3350, 3200 (NH), 1670 (C=O); ^{1}H NMR δ 1.21 (t, 3H, CH_3, $J = 7.2$ Hz), 3.73 (s, 4H, $2CH_2$), 3.22 (m, 2H, CH_2), 5.79 (s, 1H, CH), 6.79–6.92 (m, 3H, H_{arom}), 7.40–7.47 (m, 3H, H_{arom}), 7.62–7.66 (m, 2H, H_{arom}), 8.13 (s, 1H, NH), 8.27 (t, 1H, NH, $J = 6.3$ Hz), 8.80 (s, 1H, NH); ^{13}C NMR δ 14.07 (CH_3), 41.64 (CH_2), 64.09 (OCH_2), 65.92 (CH), 92.88, 95.10 (C^{4a}, C^7), 114.78, 117.09, 118.73, 126.87, 128.42, 130.40 (CH_{arom}), 135.54, 140.98, 143.14, 143.45 (C_{arom}), 154.34 (C^{7a}), 162.96 (C^5), 165.59 (C^4), 183.10 (C=O).

7-(2,2-Dimethylpropanoyl)-2-methyl-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6d**. Yield 64% (method B); mp 231–235°C; IR (ν/cm^{-1}): 3310, 3200 (NH), 1660 (C=O); ^{1}H NMR δ 1.24 (s, 9H, $3CH_3$), 1.39 (d, 3H, CH_3, $J = 6.3$ Hz), 4.97 (m, 1H, CH), 7.10–7.49 (m, 5H, H_{arom}), 8.06 (s, 1H, NH), 8.47 (s, 1H, NH), 10.58 (s, 1H, NH); ^{13}C NMR δ 22.72 (CH_3), 27.24 ($3CH_3$), 41.84 (C, *t*-Bu), 61.57 (CH), 90.86, 97.70 (C^{4a}, C^7), 119.04, 124.02, 129.71 (CH_{arom}), 139.20 (C_{arom}), 153.89 (C^{7a}), 157.26 (C^5), 162.74 (C4), 195.81 (C=O).

2,2-Dimethyl-7-(2,2-dimethylpropanoyl)-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6e**. Yield 68% (method B); mp 257–259°C; IR (ν/cm^{-1}): 3340, 3200 (NH), 1660 (C=O); ^{1}H NMR δ 1.22 (s, 9H, $3CH_3$), 1.48 (s, 6H, $2CH_3$), 7.08–7.40 (m, 5H, H_{arom}), 8.14 (s, 1H, NH), 8.53 (s, 1H, NH), 10.60 (s, 1H, NH); ^{13}C NMR δ 27.26 ($3CH_3$), 30.00 ($2CH_3$), 41.82 (C, *t*-Bu), 68.75 (C^2), 90.50, 96.91 (C^{4a}, C^7), 119.07, 124.06, 129.71 (CH_{arom}), 139.22 (C_{arom}), 152.96 (C^{7a}), 157.29 (C^5), 162.50 (C^4), 195.84 (C=O).

7-(2,2-Dimethylpropanoyl)-2-phenyl-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6f**. Yield 86% (method B); mp 271–273°C; IR (ν/cm^{-1}): 3200 (NH), 1670 (C=O); ^{1}H NMR δ 1.23 (s, 9H, $3CH_3$), 5.91 (s, 1H, CH), 7.13 (t, 1H, H_{arom}, $J = 6.0$ Hz), 7.29–7.45 (m, 9H, H_{arom}), 8.52 (s, 1H, NH), 8.88 (s, 1H, NH), 10.57 (s, 1H, NH); ^{13}C NMR δ 27.26 ($3CH_3$), 41.92 (C, *t*-Bu), 66.41 (CH), 90.97, 97.72 (C^{4a}, C^7), 119.30, 124.25, 126.09, 128.52, 128.66, 129.77 (CH_{arom}), 139.19, 142.11 (C_{arom}), 153.06 (C^{7a}), 157.04 (C^5), 163.10 (C^4), 196.11 (C=O).

7-Benzoyl-2-phenyl-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6g**. Yield 79% (method B); mp 288–292°C; IR (ν/cm^{-1}): 3300, 3200 (NH), 1670 (C=O); ^{1}H NMR δ 5.99 (s, 1H, CH), 7.12 (t, 1H, H_{arom} $J = 6.0$ Hz), 7.27–7.49 (m, 13H, H_{arom}), 7.64 (d, 1H, H_{arom}, $J = 7.0$ Hz), 8.61 (s, 1H, NH), 8.89 (s, 1H, NH), 10.60 (s, 1H, NH); ^{13}C NMR δ 66.49 (CH), 93.90, 98.42 (C^{4a}, C^7), 119.80, 124.64, 125.98, 126.98, 128.52, 128.64, 129.68, 130.72 (CH_{arom}), 139.06, 140.60, 142.26 (C_{arom}), 152.62 (C^{7a}), 160.00 (C^5), 162.91 (C^4), 184.20 (C=O).

7-Acetyl-2-(4-methoxyphenyl)-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6h**. Yield 92% (method A); mp 269–271°C; IR (ν/cm^{-1}): 3190 (NH), 1670 (C=O); ^{1}H NMR δ 2.13 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.83 (s, 1H, CH), 6.88 (d, 2H, H_{arom}, $J = 6.8$ Hz), 7.13 (t, 1H, H_{arom}, $J = 6.0$ Hz), 7.31–7.43 (m, 6H, H_{arom}), 8.24 (s, 1H, NH), 8.47 (s, 1H, NH), 10.54 (s, 1H, NH); ^{13}C NMR δ 27.71 (CH_3), 55.10 (OCH_3), 66.06 (CH), 95.06, 98.93 (C^{4a}, C^7), 113.85, 119.25, 124.23, 127.19, 129.64 (CH_{arom}), 134.21, 139.18, 153.22 (C_{arom}), 157.74 (C^{7a}), 159.26 (C^5), 163.01 (C^4), 186.74 (C=O).

7-(2,2-Dimethylpropanoyl)-2-(4-methoxyphenyl)-5-phenylamino-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6k**. Yield 95% (method A); mp 268–270°C; IR (ν/cm^{-1}): 3300, 3200 (NH), 1670 (C=O); ^{1}H NMR δ 1.24 (s, 9H, $3CH_3$), 3.76 (s, 3H, OCH_3), 5.87 (s, 1H, CH), 6.93 (d, 2H, H_{arom}, 8.9 Hz), 7.14 (t, 1H, H_{arom}), 7.30–7.47 (m, 6H, H_{arom}), 8.43 (s, 1H, NH), 8.77 (s, 1H, NH), 10.58 (s, 1H, NH); ^{13}C NMR δ 27.29 (3 CH_3), 41.92 (C, *t*-Bu), 55.22 (OCH_3), 66.27 (CH), 91.05, 97.83 (C^{4a}, C^7), 113.99, 119.24, 124.21, 127.52, 129.76 (CH_{arom}), 133.88, 139.22, 153.23 (C_{arom}), 157.61 (C^{7a}), 159.50 (C^5), 163.19 (C^4), 196.13 (C=O).

7-(2,2-Dimethylpropanoyl)-5-phenylamino-2-(4-trifluoromethylphenyl)-2,3-dihydrothieno[3,4-d]pyrimidin-4(1H)-one **6l**. Yield 80% (method B), 71% (method C); mp 283–285°C; IR (ν/cm^{-1}): 3300, 3200 (NH), 1670 (C=O); ^{1}H NMR δ 1.24 (s, 9H, $3CH_3$), 5.97 (s, 1H, CH), 7.13 (t, 1H, H_{arom}, $J = 6.0$ Hz), 7.29–7.44 (m, 4H, H_{arom}), 7.63–7.69 (m, 4H, H_{arom}), 8.64 (s, 1H, NH), 9.05 (s, 1H, NH), 10.53 (s, 1H, NH); ^{13}C NMR δ 27.21 ($3CH_3$), 41.90 (C, *t*-Bu), 65.71 (CH), 91.10, 97.60 (C^{4a}, C^7), 119.32, 123.61, 124.27 (CH_{arom}), 125.66 (q, CF_3, $^1J_{C-F} = 288$ Hz), 126.90 (CH_{arom}), 128.60 (q, C_{arom}, $^2J_{C-F} = 39$ Hz), 129.70 (CH_{arom}), 139.12, 147.22 (C_{arom}), 152.63 (C^{7a}), 157.79 (C^5), 162.93 (C^4), 196.12 (C=O).

4-Amino-5-(2,2-dimethylpropanoyl)-2-phenylaminothiophene-3-carboxamide **7**. A mixture of compound **1b** (10 mmol), α-chloroketone **4b** (11 mmol), and triethylamine (2.1 mL, 15 mmol) in ethanol (20 mL) was boiled for 2 h. On cooling the solution, resulting crystals were filtered off, dried, and recrystallized from ethanol. Yield 82%; mp 175–177°C; IR (ν/cm^{-1}): 3200 (NH), 1660 (C=O); ^{1}H NMR δ 1.23 (s, 9H, $3CH_3$), 7.08 (t, 1H, H_{arom}, $J = 6.0$ Hz), 7.29–7.39 (m, 6H, $H_{arom} + NH_2$), 7.91 (s, 2H, NH_2), 10.14 (s, 1H, NH); ^{13}C NMR δ 27.52 ($3CH_3$), 42.30 (C, *t*-Bu), 92.16, 104.32 (C^3, C^5), 119.78, 123.64, 129.45 (CH_{arom}), 140.90 (C_{arom}), 157.32, 157.38, 166.29 (C^2, C^4, $CONH_2$), 195.92 (C=O).

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