Synthesis and Chemical Reactivity of New Azaenamines Incorporated the 4,5,6,7-Tetrahydrobenzo[*b*]thiophene Moiety: 3+3 Atom Combination

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Abstract: Novel azaenamines incorporating a tetrahydrothiophene moiety were prepared. Michael addition of an azaenamine with α,β-unsaturated nitriles took place to give [1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine (thia-triaza-benzo[*a*]fluorene) derivatives. The condensation with malononitrile resulted in the formation of a [1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carbonitrile. The azaenamine also reacted with aldehydes and piperidine to give Mannich products.

Key words: azaenamine, tetrahydrobenzo[*b*]thiophene, Michael addition, condensation, Mannich alkylation

Compounds containing the tetrahydrobenzothiophene (THBT) moiety are selective HCV polymerase inhibitors,[1] selective versus human DNA polymerase and calf thymus.[1] These compounds also have diverse pharmacological activities including antibacterial,[2] immunodulatory,[3] anti-inflammatory,[4] antidiabetic, antiplatelet activating factor,[5] and antiviral activity.[6,7]

In continuation of our interest in azaenamine chemistry,[8–12] we report here a new synthesis of azaenamines containing the 4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate and -carboxamide moieties. Also we report the chemical reactivity of the synthesized azaenamines. Thus, it has been found that coupling acetoacetic acid with the 3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-diazonium chloride (**3a**) and the 3-carboxamide **3b** afforded the corresponding pyruvaldehyde-1-arylhydrazones **5a** and **5b** in 73% and 68% yields, respectively. Although, the appearance of NH at very low field implies the presence of an azaenamine in the *syn*-form **6**, in related work we obtained an X-ray crystal structure for an azaenamine analogue that indicated that it exists in the *anti*-form **5**.[10] The low field hydrazone NH at δ = 12 is not, thus, due to deshielding by hydrogen bonding as we believed, but most likely results from the delocalization of the nitrogen lone pair [cf. Scheme 1 structure **5(II)**]. It is clear that azaenamines can be seen as bidentate ligands since they have two nucleophilic and two electrophilic centers. Due to an interest in developing syntheses for biologically interesting fused pyridazines[8,12,13] herein, we report an efficient route for the Michael addition reaction of azaenamines **5** to α,β-unsaturated nitriles. As stated above, the CH group of the azaenamine is quite nucleophilic as a result of the hydrazone lone pair delocalization. Thus, in a preliminary study, we found that reacting compound **5a** with ethyl 2-cyano-3-phenylacrylate (**7a**) afforded a product for which several isomeric structures seemed possible. Structures involving addition on the acyl methyl group was readily ruled out on the basis of the ^{1}H NMR spectrum, which revealed a methyl signal at δ = 2.36. Acyclic structures were also excluded based on ^{1}H NMR spectra analysis, which showed in addition to the methyl signal, a singlet signal at δ = 5.09 for H4 of the pyridazine and a broad signal at δ = 11.19 for the NH group. The resulting product was assigned the tetracyclic structure **10** based on mass spectroscopy and NMR analysis, which revealed the absence of an OEt group on the thiophene ring. IR and ^{13}C NMR also indicated the absence of the CN signal and band. Compound **10a** is most likely formed via intermediacy of **8** and **9**, which could not be isolated (Scheme 2).

Formation of such tetracyclic product supports our suggestion that the reaction proceeds via initial addition of the hydrazone CH in compound **5a** to the activated double bond in **7** followed by cyclization rather that initial addition of NH in **5a** to the double bond in **7**. Repeating these reactions with carboxamide **5b** gave the same results. In an extension of our study we also found that ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (**7b**) and ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (**7c**) also added to **5a** to yield products **10b** and **10c**,respectively. The structure of **10c** was established based on spectral data. The IR spectra indicated the absence of the CN band; the ^{1}H NMR spectrum of **10c** indicated the presence of one ester group with a characteristic triplet at δ = 1.14 (*J* = 7.2 Hz) for CH_3 and quartet at δ = 4.07 (*J* = 7.2 Hz) for CH_2. It also featured characteristic set of multiplets at δ ~ 1.77 and 2.71 for the cyclohexene ring. It indicated two singlets at δ ~ 2.36 and 3.69 for (MeCO) and OMe, respectively. In addition it indicated a singlet at δ = 5.05 for H4 of the pyridazine. It also revealed aromatic protons as two doublets at δ = 6.80 and 7.11. Finally the broad singlet at δ = 11.16 was assigned to NH. Furthermore, full assignment of the ^{13}C NMR data confirmed the structure of **10c**, where the key signal at δ = 13.7 was assigned to CH_3CH_2 and signals at

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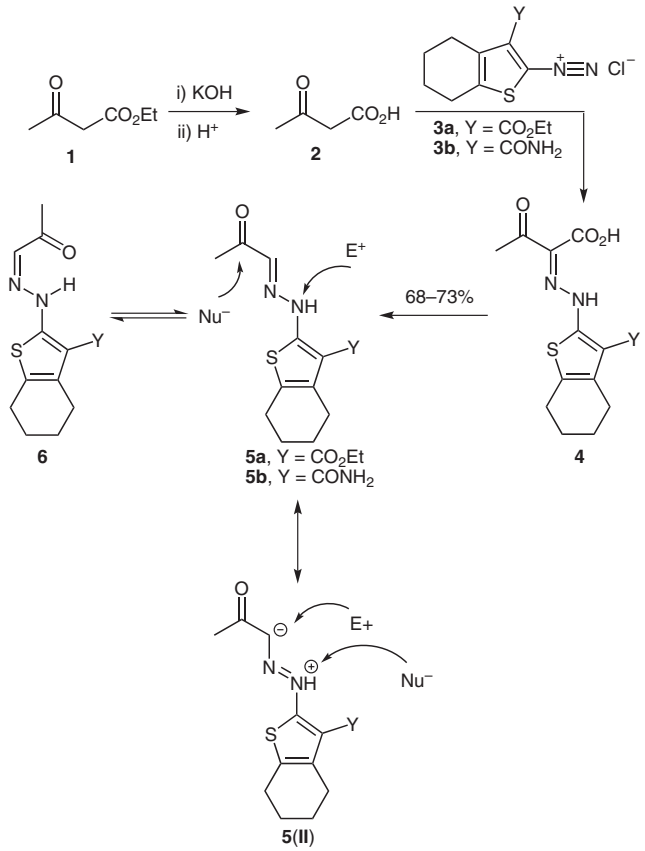


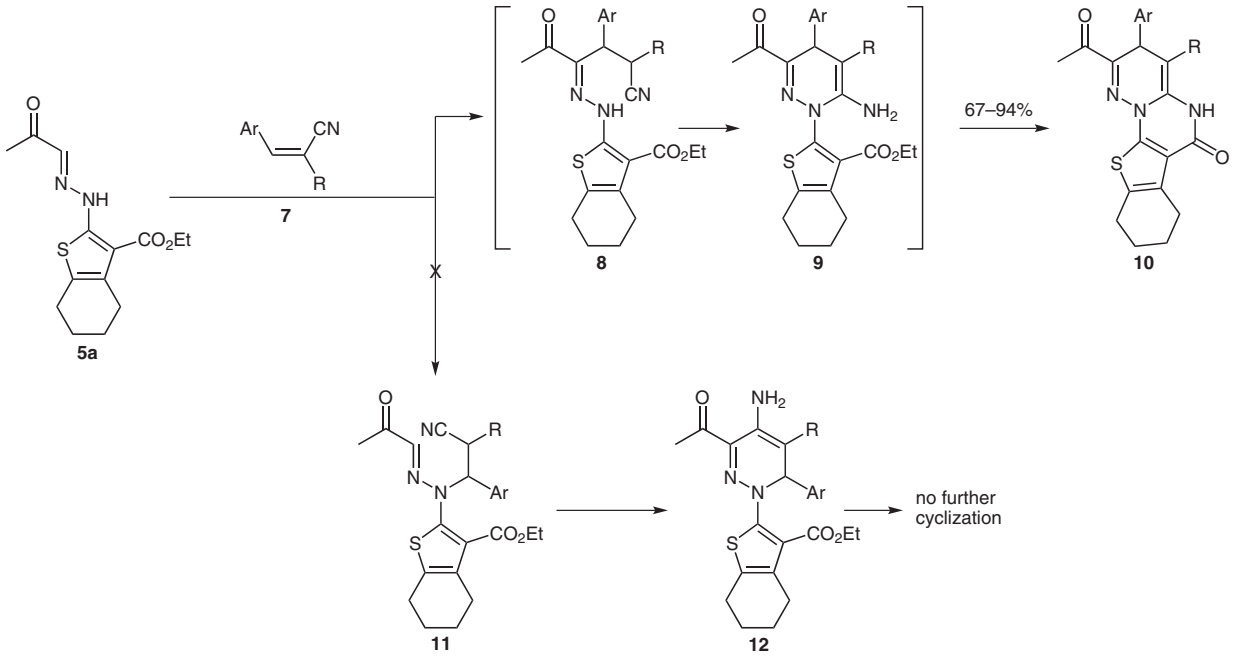
Scheme 1

δ = 21.2, 22.2, 23.6, and 24.5 were assigned to CH_2 of the cyclohexene; the following signals were also assigned: 24.6 (CH_3CO), 33.5 (CH pyridazine), 54.8 (OMe), 59.9 ($MeCH_2$), 78.2 (CCO_2Et), 167.1 (CO_2Et), and 194.5 (CO). ^{13}C NMR also indicated the absence of the CN signal. Full spectral data for all new compounds are presented in the experimental section. Also aryl-idenemalononitriles added to azaenamine **5a** and gave compounds **10d**,**e**. The structure of the products was also established based on spectral data. Moreover, 2-cyano-3-phenylacrylamide (**7f**) and 3-(4-chlorophenyl)-2-cyano-acryamide (**7g**) were added to **5a** to yield **10f** and **10g**. The reactivity of azaenamine **5a** was also tested with 2-(4-chlorobenzoyl)-3-phenylacrylonitrile (**7h**) and the product was found to be, as expected, **10h**. These syntheses have been conducted in a much shorter time by heating the reaction mixture in a microwave oven, leading also to much better yields (Table 1).

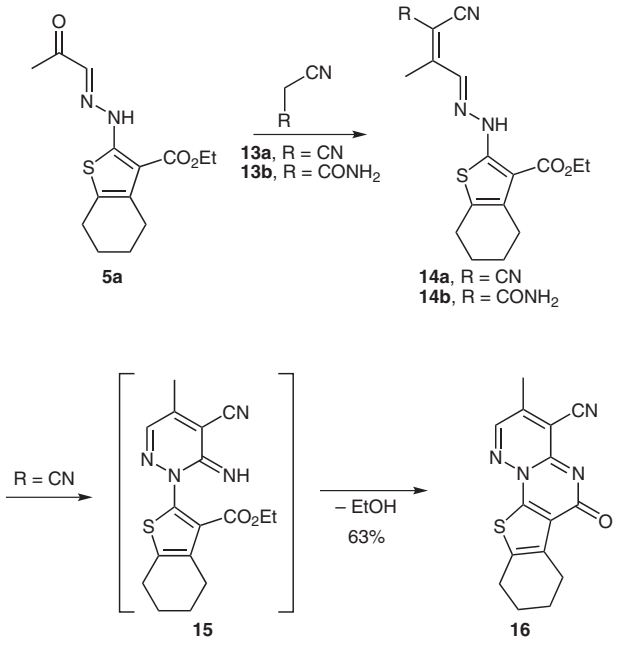
Compound **5a** was condensed with malononitrile (**13a**) in dioxane–piperidine to yield the tetracyclic compound **16** (Scheme 3). Compound **16** is believed to be formed via the acyclic intermediate **14**, which cyclized into **15** fol-

Table 1 Reaction of **5a** with Various Acrylonitriles **7a**–**h** by Conventional Heating and Microwave Irradiation (MWI)

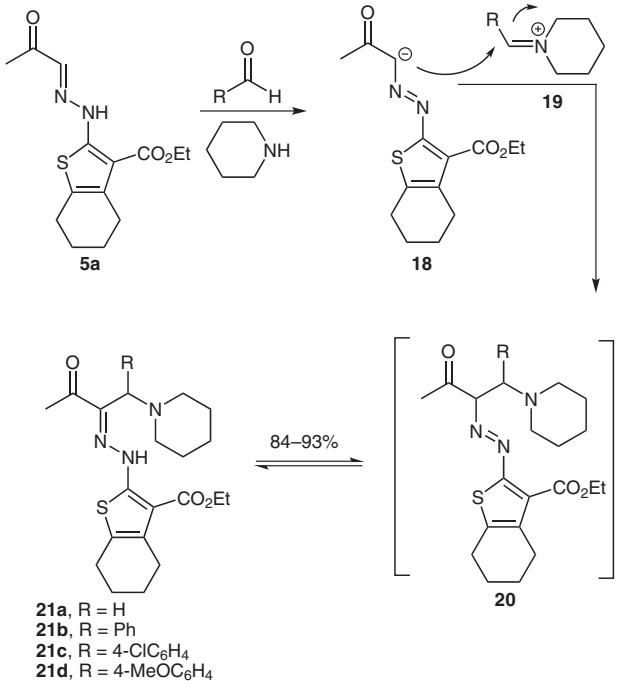
Acrylonitrile	R	Ar	Product	Yield (%)	
				Thermal	MWI
7a	CO_2Et	Ph	**10a**	67	81
7b	CO_2Et	4-ClC_6H_4	**10b**	71	85
7c	CO_2Et	4-$MeOC_6H_4$	**10c**	66	79
7d	CN	Ph	**10d**	70	92
7e	CN	4-MeC_6H_4	**10e**	68	87
7f	$CONH_2$	Ph	**10f**	78	94
7g	$CONH_2$	4-ClC_6H_4	**10g**	80	92
7h	COPh	4-ClC_6H_4	**10h**	72	86



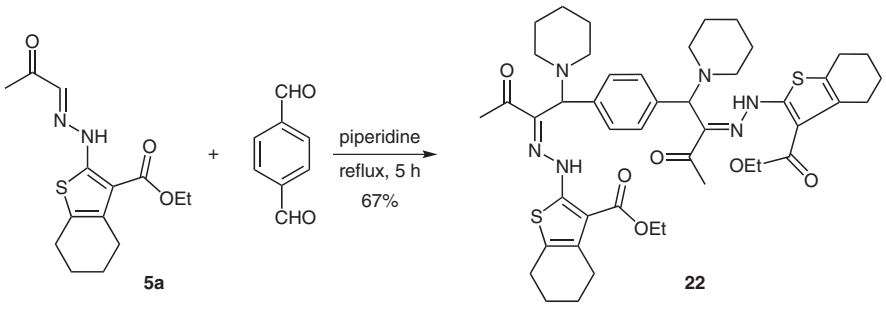
Scheme 2



Scheme 3



Scheme 4



Scheme 5

lowed by ethanol elimination. The structure of **16** was elucidated based on mass spectroscopy and ^{1}H and ^{13}C NMR, which revealed the absence of the OEt group. Thus the IR spectrum showed two bands at 2223.8 and 1682.4 cm^{-1} for CN and CO, respectively. The ^{1}H NMR spectrum showed a singlet at δ = 2.58 (CH_3), a singlet at δ = 8.69 (H2 of the pyridazine), and multiplets at δ = 1.78 and 2.91–2.93 ($H_{c\text{-hexene}}$). Furthermore, full assignment of the ^{13}C NMR data confirmed the structure **16**; the following key signals at δ = 18.3, 21.3, 22.1, 24.4 ($C_{c\text{-hexene}}$), 24.9 (CH_3), and 112.2 (CN) were assigned while the signals at 112.7, 123.8, 132.5, 134.6, 142.9, 144.3, 146.1, 146.8 were assigned to olefinic and aromatic carbons. The signal at 162.7 was assigned to (CO).

On the other hand attempts to react compound **5a** with cyanoacetamide (**13b**) resulted in the formation of acyclic product **14b**; attempts to cyclize compound **14b** failed. The structure of compound **14b** was established based on its mass spectrum, which indicated molecular ion peak as base peak at *m/z* 360. ^{1}H NMR revealed the presence of an ester group with a characteristic triplet at δ = 1.12 (*J* = 7.2 Hz, CH_3) and a quartet at δ = 4.23 (*J* = 7.2 Hz, CH_2). It featured a characteristic set of multiplets at δ ~ 1.69 and 2.65 ($H_{c\text{-hexene}}$), in addition it showed a singlet at δ = 8.61 (H_{vinyl}) and a singlet at 7.91 (NH_2); the NH signal appeared at δ = 11.62.

The reactivity of the CH group in the azaenamine could be also examined via the Mannich reaction, which is one of the most widely used reactions for the formation of carbon–carbon bonds.[14–16] In its initial form, it utilizes the addition of an aldehyde to a ketone in the presence of an amine. Herein, the scope of the Mannich reaction was extended to the addition of azaenamine **5a** to different aldehydes in presence of piperidine. The CH group of compound **5a** can be easily deprotonated under basic conditions. The resulting salt can be viewed as an aza-substituted carbanion and, as such, may react in the Mannich reaction leading to C–C bond formation (Scheme 4). Thus, the reaction of **5a** with formaldehyde and piperidine resulted in the formation of Mannich product **21a**. The IR spectrum of **21a** showed two bands at 1668.1 and 1532.2 cm^{-1} for two CO groups and a broad band at 3450.9 cm^{-1} for NH. The ^{1}H NMR spectrum showed a triplet at δ = 1.25 (CH_3CH_2), multiplets at δ = 1.3, 2.32 ($H_{piperidine}$), multiplets at δ = 1.55 and 2.56 ($H_{c\text{-hexene}}$), and a singlet signal at δ = 3.53 (CH_2). In addition it indicated a quartet at

δ = 4.24 (CH_2, ester). In a similar fashion, benzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde reacted with azaenamine **5a** to give compounds **21b–d**.

In an extension of this reaction we found that terephthalaldehyde reacted with **5a** to give bis-Mannich product **22** (Scheme 5). The structure was confirmed based on spectral data.

We report a new simple and efficient route to new azaenamines incorporated the tetrahydrobenzothiophene moiety. The prepared azaenamines are valuable precursors for synthesis of fused pyridazine derivatives via 3+3 atom combination reaction of azaenamines with unsaturated nitriles.

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a Bruker-vector 22 spectrophotometer FTIR. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 MHz and 75 MHz, respectively, on a Varian Gemini NMR spectrometer using TMS as internal standard. Mass spectra were measured on a Shimadzu GMSS-QP-1000 EX mass spectrometer at 70 eV. Microwave experiments were conducted in domestic microwave. The reactants were placed in a glass conical container and the oven was placed in an efficient hood. No special precautions were used as we did not experience any bumping during our experiments.

2-[2-(2-Oxopropylidene)hydrazino]benzo[*b*]thiophenes 5a,b; General Procedure

A mixture of KOH (3.5 g) in H_2O (100 mL) and ethyl acetoacetate (**1**, 6.5 mL) was allowed to stir at r.t. for 24 h. This soln was then cooled to 0 °C and acidified with concd HCl (4.5 mL) in ice water (15 mL). The resulting soln was treated with aryldiazonium chloride [prepared from the corresponding aromatic amine (0.05 mol) and the appropriate quantities of both HCl and $NaNO_2$]. The mixture was made basic by addition of NaOAc (8.0 g). The solid product, so formed was collected by filtration.

Ethyl 2-[2-(2-Oxopropylidene)hydrazino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5a)

Yellow solid (from EtOH); yield: 73%; mp 116–118 °C.

IR (KBr): 3445.4 (NH), 1664.7, 1659.1 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.35–1.70 (m, 4 H, $H_{c\text{-hexene}}$), 2.24 (s, 3 H, CH_3CO), 2.54–2.66 (m, 4 H, $H_{c\text{-hexene}}$), 4.24 (q, J = 7.2 Hz, 2 H, CH_2), 7.65 (s, 1 H, H_{vinyl}), 11.48 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1, 22.0, 22.4, 23.9, 25.9, 59.7, 66.3, 106.8, 123.2, 132.4, 139.0, 156.3, 163.7, 196.4.

MS: m/z = 294 (M^+).

Anal. Calcd for $C_{14}H_{18}N_2O_3S$ (294.38): C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 57.02; H, 5.98; N, 9.43; S, 10.78.

2-[2-(2-Oxopropylidene)hydrazino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (5b)

Green solid (from EtOH); yield: 68%; mp 150–152 °C.

IR (KBr): 3441.2 (NH), 1659.4, 1630.7 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.72 (m, 4 H, $H_{c\text{-hexene}}$), 2.23 (s, 3 H, CH_3CO), 2.58–2.73 (m, 4 H, $H_{c\text{-hexene}}$), 7.06 (br s, 2 H, NH_2), 7.5 (s, 1 H, H_{vinyl}), 11.52 (s, 1 H, NH).

MS: m/z = 265 (M^+).

Anal. Calcd for $C_{12}H_{15}N_3O_2S$ (265.34): C, 54.32; H, 5.70; N, 15.84; S, 12.08. Found: C, 54.19; H, 5.61; N, 15.82; S, 11.86.

[1]Benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazines 10a–h; General Procedures

Method A: A mixture of azaenamine **5a** or **5b** (10 mmol) and α,β-unsaturated nitrile **7a–h** was refluxed in dioxane (20 mL) in presence of piperidine (0.5 mL) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized (dioxane).

Method B: A soln of **5a** or **5b** (10 mmol) was treated with α,β-unsaturated nitriles **7a–h** (10 mmol) in pyridine (2 mL) and irradiated in a microwave oven for 2 min, then poured onto H_2O and acidified with dil HCl. The solid product obtained was crystallized (dioxane).

Ethyl 2-Acetyl-6-oxo-3-phenyl-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carboxylate (10a)

Yield: 67% (thermal), 81% (microwave); mp 220–222 °C.

IR (KBr): 3452.9 (NH), 1690.3, 1667.1, 1624.7 cm^{-1} (3 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (t, J = 7.2 Hz, 3 H, CH_3), 1.79 (m, 4 H, $H_{c\text{-hexene}}$), 2.36 (s, 3 H, CH_3CO), 2.71–2.79 (m, 4 H, $H_{c\text{-hexene}}$), 4.07 (q, J = 7.2 Hz, 2 H, CH_2), 5.09 (s, 1 H, H3), 7.21–7.27 (m, 5 H, H_{Ar}), 11.19 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.7, 21.3, 22.2, 23.7, 24.5, 34.5, 59.9, 66.2, 78.1, 113.1, 120.5, 127.1, 127.7, 128.4, 132.0, 141.1, 141.9, 149.1, 150.2, 154.7, 167.1, 194.5.

MS: m/z = 449 (M^+).

Anal. Calcd for $C_{24}H_{23}N_3O_4S$ (449.53): C, 64.13; H, 5.16; N, 9.35; S, 7.13. Found: C, 64.00; H, 5.03; N, 9.11; S, 6.97.

Ethyl 2-Acetyl-3-(4-chlorophenyl)-6-oxo-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carboxylate (10b)

Yield: 71% (thermal), 85% (microwave); mp 202–204 °C.

IR (KBr): 3453.3 (NH), 1690.6, 1669.1, 1632.3 cm^{-1} (3 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.11 (t, J = 7.2 Hz, 3 H, CH_3), 1.77 (m, 4 H, $H_{c\text{-hexene}}$), 2.35 (s, 3 H, CH_3CO), 2.68–2.77 (m, 4 H, $H_{c\text{-hexene}}$), 5.06 (q, J = 7.2 Hz, 2 H, CH_2), 5.06 (s, 1 H, H3), 7.25–7.33 (m, 4 H, H_{Ar}), 11.17 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.7, 21.2, 22.2, 23.6, 24.4, 24.6, 34.2, 59.9, 66.1, 77.7, 113.1, 120.4, 128.4, 129.7, 131.8, 132.0, 140.8, 141.1, 148.6, 154.6, 167.0, 194.4.

MS: m/z = 483 (M^+).

Anal. Calcd for $C_{24}H_{22}ClN_3O_4S$ (483.98): C, 59.56; H, 4.58; N, 8.68; S, 6.63. Found: C, 59.53; H; 4.46; N, 8.62; S, 6.44.

Ethyl 2-Acetyl-3-(4-methoxyphenyl)-6-oxo-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carboxylate (10c)

Yield: 66% (thermal), 79% (microwave); mp 216–218 °C.

IR (KBr): 3442.2 (NH), 1685.1 1669.0, 1632.7 cm^{-1} (3 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.14 (t, J = 7.2 Hz, 3 H, CH_3), 1.77–1.79 (m, 4 H, $H_{c\text{-hexene}}$), 2.36 (s, 3 H, CH_3CO), 2.71–2.79 (m, 4 H, $H_{c\text{-hexene}}$), 3.69 (s, 3 H, OCH_3), 4.07 (q, J = 7.2 Hz, 2 H, CH_2), 5.05 (s, 1 H, H3), 6.80 (d, J = 9 Hz, 2 H, H_{Ar}), 7.11 (d, J = 9 Hz, 2 H, H_{Ar}), 11.16 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.7, 21.2, 22.2, 23.6, 24.5, 24.6, 33.5, 43.2, 54.8, 59.9, 66.1, 78.2, 113.4, 128.8, 132.0, 134.1, 140.9, 149.3, 150.2, 154.6, 158.3, 167.1, 194.5.

MS: m/z = 479 (M^+).

Anal. Calcd for $C_{25}H_{25}N_3O_5S$ (479.56): C, 62.62; H, 5.25; N, 8.76; S, 6.69. Found: C, 62.57; H, 5.12; N, 8.66; S, 6.63.

2-Acetyl-6-oxo-3-phenyl-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carbonitrile (10d)

Yield: 70% (thermal), 92% (microwave); mp 238–240 °C.

IR (KBr): 3445.8 (NH), 2223.7 (CN), 1668.9, 1634.2 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81–1.93 (m, 4 H, $H_{c\text{-hexene}}$), 2.12 (s, 3 H, CH_3CO), 2.82–2.94 (m, 4 H, $H_{c\text{-hexene}}$), 5.11 (s, 1 H, H3), 7.66–8.06 (m, 5 H, H_{Ar}), 11.78 (s, 1 H, NH).

MS: *m*/*z* = 402 (M^+).

Anal. Calcd for $C_{22}H_{18}N_4O_2S$ (402.48): C, 65.65; H, 4.51; N, 13.92; S, 7.97. Found: C, 65.60; H, 4.39; N, 13.86; S, 7.91.

2-Acetyl-3-(4-methylphenyl)-6-oxo-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carbonitrile (10e)

Yield: 68% (thermal), 87% (microwave); mp 172–174 °C.

IR (KBr): 3442.5 (NH), 2221.2 (CN), 1664.1, 1624.2 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.81–1.93 (m, 4 H, $H_{c\text{-hexene}}$), 2.12 (s, 3 H, CH_3CO), 2.38 (s, 3 H, CH_3), 2.82–2.94 (m, 4 H, $H_{c\text{-hexene}}$), 4.81 (s, 1 H, H3), 7.37–7.47 (m, 4 H, H_{Ar}), 14.02 (s, 1 H, NH).

MS: *m*/*z* = 416 (M^+).

Anal. Calcd for $C_{23}H_{20}N_4O_2S$ (416.51): C, 66.33; H, 4.84; N, 13.45; S, 7.70. Found: C, 66.20; H, 4.78; N, 13.31; S, 7. 59.

2-Acetyl-6-oxo-3-phenyl-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carboxamide (10f)

Yield: 78% (thermal), 94% (microwave); mp 280–282 °C.

IR (KBr): 3466.4, 3344.9, 3143.4 (NH, NH_2), 1664.2, 1567.8 cm^{-1} (3 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.76–1.77 (m, 4 H, $H_{c\text{-hexene}}$), 2.36 (s, 3 H, CH_3CO), 2.68–2.78 (m, 4 H, $H_{c\text{-hexene}}$), 5.35 (s, 1 H, H3), 7.19–7.35 (m, 7 H, H_{Ar}, NH_2), 12.98 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4, 22.4, 23.8, 24.7, 33.7, 79.4, 109.2, 113.1, 120.6, 127.2, 127.7, 128.5, 132.2, 139.9, 141.4, 147.8, 155.1, 155.9, 169.6, 194.7.

MS: *m*/*z* = 420 (M^+).

Anal. Calcd for $C_{22}H_{20}N_4O_3S$ (420.49): C, 62.84; H, 4.79; N, 13.32; S, 7.63. Found: C, 62.52; H, 4.63; N, 13.12; S, 7.60.

2-Acetyl-3-(4-chlorophenyl)-6-oxo-5,6,7,8,9,10-hexahydro-3*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carboxamide (10g)

Yield: 80% (thermal), 92% (microwave); mp 264–266 °C.

IR (KBr): 3467.1, 3346.3, 3143.9 (NH, NH_2), 1664.3, 1571.2 cm^{-1} (CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.75 (m, 4 H, $H_{c\text{-hexene}}$), 2.35 (s, 3 H, CH_3CO), 2.67–2.77 (m, 4 H, $H_{c\text{-hexene}}$), 5.36 (s, 1 H, H3), 7.26–7.39 (m, 6 H, H_{Ar}, NH_2), 13.01 (s, 1 H, NH).

MS: *m*/*z* = 454 (M^+).

Anal. Calcd for $C_{22}H_{19}ClN_4O_3S$ (454.94): C, 58.08; H, 4.21; N, 12.32; S, 7.05. Found: C, 57.92; H, 4.03; N, 12.17; S, 6.88.

2-Acetyl-4-benzoyl-3-(4-chlorophenyl)-3,5,7,8,9,10-hexahydro-6*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazin-6-one (10h)

Yield: 72% (thermal), 86% (microwave); mp 180–182 °C.

IR (KBr): 3452.9 (NH), 1692.2, 1626.7 cm^{-1} (3 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78 (m, 4 H, $H_{c\text{-hexene}}$), 2.37 (s, 3 H, CH_3CO), 2.74–2.84 (m, 4 H, $H_{c\text{-hexene}}$), 5.24 (s, 1 H, H3), 6.80–7.49 (m, 9 H, H_{Ar}), 11.17 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.4, 22.4, 23.9, 24.7, 24.8, 53.8, 86, 120.5, 120.7, 126.1, 128.3, 128.6, 129.6, 130.2, 132.1, 132.3, 139.4, 140.3, 143.1, 145.5, 150.5, 155.1, 194.4, 194.6.

MS: *m*/*z* = 515 (M^+).

Anal. Calcd for $C_{28}H_{22}ClN_3O_3S$ (516.02): C, 65.17; H, 4.30; N, 8.14; S, 6.21. Found: C, 64.97; H, 4.26; N, 8.09; S, 5.95.

2-(2-But-2-enylidenehydrazino)benzo[*b*]thiophenes 14b and 16; General Procedure

A mixture of azaenamine **5a** (10 mmol), and active methylene compound **7a**,**b** was refluxed in dioxane (20 mL) in presence of piperidine (0.5 mL) for 5 h (10 min for **16**). The solvent was evaporated under vacuum and the crude product was collected and crystallized (dioxane).

Ethyl 2-[2-(4-Amino-3-cyano-2-methyl-4-oxobut-2-enylidene)hydrazino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (14b)

Yield: 65%; mp 120–122 °C.

IR (KBr): 3423.3, 3341.2, 3184.8 (NH, NH_2), 2259.2 (CN), 1673.9, 1624.7 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.12 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.69 (m, 4 H, $H_{c\text{-hexene}}$), 1.90 (s, 3 H, CH_3), 2.65 (m, 4 H, $H_{c\text{-hexene}}$), 4.23 (q, 2 H, CH_2), 8.61 (s, 1 H, H_{vinyl}), 7.91 (s, 2 H, NH_2), 11.62 (s, 1 H, NH).

MS: *m*/*z* = 360 (M^+).

Anal. Calcd for $C_{17}H_{20}N_4O_3S$ (360.44): C, 56.65; H, 5.59; N, 15.54; S, 8.90. Found: C, 56.29; H, 5.34; N, 15.31; S, 8.69.

3-Methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-[1]benzothieno[3′,2′:5,6]pyrimido[1,2-*b*]pyridazine-4-carbonitrile (16)

Yield: 63%; mp 292–294 °C.

IR (KBr): 2223.8 (CN), 1682.4 cm^{-1} (CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78 (m, 4 H, $H_{c\text{-hexene}}$), 2.58 (s, 3 H, CH_3), 2.91–2.93 (m, 4 H, $H_{c\text{-hexene}}$), 8.69 (s, 1 H, H2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.3, 21.3, 22.1, 24.4, 24.9, 112.2, 112.7, 123.8, 132.5, 134.6, 142.9, 144.3, 146.1, 146.8, 162.8.

MS: *m*/*z* = 296 (M^+).

Anal. Calcd for $C_{15}H_{12}N_4OS$ (296.35): C, 60.79; H, 4.08; N, 18.91; S, 10.82. Found: C, 60.43; H, 3.82; N, 18.66; S, 10.65.

Mannich Products 21a–d; General Procedure

To a soln of hydrazone **5** (1 mmol) in piperidine (5 mL) was added aldehyde (1 mmol) and the mixture refluxed for 3–4 h. Evaporation of the solvent afforded the crude product which was crystallized (EtOH) in a good yield.

Ethyl 2-{2-[2-Oxo-1-(piperidin-1-ylmethyl)propylidene]hydrazino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (21a)

Yield: 84%; mp 140–142 °C.

IR (KBr): 3450.9 (NH), 1668.1, 1532.2 cm^{-1} (2 CO).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.30 (m, 4 H, $H_{piperidine}$), 1.55–1.57 (m, 4 H, $H_{c\text{-hexene}}$), 2.32 (m, 6 H, $H_{piperidine}$), 2.48 (s, 3 H, CH_3), 2.56–2.68 (m, 4 H, $H_{c\text{-hexene}}$), 3.53 (s, 2 H, CH_2), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 13.25 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1, 22.2, 22.5, 23.6, 23.7, 24.1, 24.4, 26.0, 52.6, 53.5, 59.6, 107.2, 123.0, 132.2, 141.7, 163.9, 195.3.

MS: m/z = 391 (M^+).

Anal. Calcd for $C_{20}H_{29}N_3O_3S$ (391.54): C, 61.35; H, 7.47; N, 10.73; S, 8.19. Found: C, 61.13; H, 7.17; N, 10.49; S, 7.95.

Ethyl 2-(2-{2-Oxo-1-[phenyl(piperidin-1-yl)methyl]propylidene}hydrazino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (21b)
Yield: 93%; mp 152–154 °C.

IR (KBr): 3441.5 (NH), 1667.9, 1623.1 cm^{-1} (2 CO).

^1H NMR (300 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.39 (m, 4 H, $H_{piperidine}$), 1.69 (m, 4 H, $H_{c\text{-hexene}}$), 2.31 (m, 6 H, $H_{piperidine}$), 2.48 (s, 3 H, CH_3CO), 2.67–2.72 (m, 4 H, $H_{c\text{-hexene}}$), 4.23 (q, J = 7.2 Hz, 2 H, CH_2), 4.76 (s, 1 H, CH), 7.35–7.43 (m, 5 H, H_{Ar}), 12.62, (s, 1 H, NH).

MS: m/z = 467 (M^+).

Anal. Calcd for $C_{26}H_{33}N_3O_3S$ (467.64): C, 66.78; H, 7.11; N, 8.99; S, 6.86. Found: C, 66.23; H, 6.75; N, 8.57; S, 6.61.

Ethyl 2-(2-{1-[(4-Chlorophenyl)(piperidine-1-yl)methyl]-2-oxopropylidene}hydrazino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (21c)
Yield: 93%; mp 176–178 °C.

IR (KBr): 1673.9 cm^{-1} (2 CO).

^1H NMR (300 MHz, DMSO-d_6): δ = 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.32 (m, 6 H, $H_{piperidine}$), 1.71 (m, 4 H, $H_{c\text{-hexene}}$), 2.24 (s, 3 H, CH_3CO), 2.32 (m, 4 H, $H_{piperidine}$), 2.70–2.75 (m, 4 H, $H_{c\text{-hexene}}$), 4.28 (q, J = 7.2 Hz, 2 H, CH_2), 4.81 (s, 1 H, CH), 7.37–7.47 (m, 4 H, H_{Ar}), 13.46 (s, 1 H, NH).

MS: m/z = 502 (M^+).

Anal. Calcd for $C_{26}H_{32}ClN_3O_3S$ (502.08): C, 62.20; H, 6.42; N, 8.37; S, 6.39. Found: C, 61.92; H, 6.11; N, 8.12; S, 6.15.

Ethyl 2-(2-{1-[(4-Methoxyphenyl)(piperidine-1-yl)methyl]-2-oxopropylidene}hydrazino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (21d)
Yield: 87%; mp 120–122 °C.

IR (KBr): 3438.5 (NH), 1666.2, 1609.3 cm^{-1} (2 CO).

^1H NMR (300 MHz, DMSO-d_6): δ = 1.29 (t, J = 7.2 Hz, 3 H, CH_3), 1.40–149 (m, 4 H, $H_{piperidine}$), 1.72 (m, 4 H, $H_{c\text{-hexene}}$), 2.24 (s, 3 H, CH_3CO), 2.55 (m, 2 H, $H_{c\text{-hexene}}$), 2.70 (m, 2 H, $H_{c\text{-hexene}}$), 3.12–3.30 (m, 6 H, $H_{piperidine}$), 3.7 (s, 3 H, OCH_3), 4.26 (q, J = 7.2 Hz, 2 H, CH_2), 4.74 (s, 1 H, CH), 6.87 (d, J = 8.8 Hz, 2 H, H_{Ar}), 7.36 (d, J = 8.8 Hz, 2 H, H_{Ar}), 13.32 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.6, 22.6, 22.9, 24.4, 24.6, 24.7, 24.6, 25.0, 26.6, 52.6, 55.4, 60.3, 67.5, 107.7, 114.8, 123.7, 129.5, 132.9, 143.2, 157.4, 159.2, 164.6, 195.8.

MS: m/z = 497 (M^+).

Anal. Calcd for $C_{27}H_{35}N_3O_4S$ (497.66): C, 65.16; H, 7.09; N, 8.44; S, 6.44. Found: C, 64.94; H, 6.86; N, 8. 21; S, 6.20.

Ethyl 2-[2-(1-{[4-(2-{[3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl]hydrazono}-3-oxo-1-(piperidin-1-yl)butyl)phenyl](piperidin-1-yl)methyl}-2-oxopropylidene)hydrazino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (22)
To a soln of hydrazone **5a** (1 mmol) in piperidine (2 mL) was added benzene-1,4-dicarbaldehyde (2 mmol) and the mixture refluxed for 3–4 h. Evaporation of the solvent afforded the crude product which was crystallized (EtOH); yield: 67%; mp 248–250 °C.

IR (KBr): 1723.3, 1667.6 cm^{-1} (4 CO).

^1H NMR (300 MHz, DMSO-d_6): δ = 1.25–142 (t, J = 7.2 Hz, 6 H, $2CH_3$), 1.42–1.58 (m, 12 H, $H_{piperidine}$), 1.60 (m, 8 H, $H_{c\text{-hexene}}$), 2.59–2.78 (m, 8 H, $H_{c\text{-hexene}}$), 2.33 (s, 6 H, 2 CH_3CO), 3.12–3.30 (m, 8 H, $H_{piperidine}$), 4.34 (q, J = 7.2 Hz, 4 H, 2 CH_2), 4.80 (s, 2 H, CH), 7.14 (m, 4 H, H_{Ar}).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.4, 22.7, 23.0, 24.7, 25.1, 26.6, 44.0, 52.9, 59.8, 68.1, 107.9, 123.4, 125.9, 128.5, 132.9, 136.9, 142.2, 157.7, 164.5, 196.6.

MS: m/z = 857 (M^+).

Anal. Calcd for $C_{46}H_{60}N_6O_6S_2$ (857.14): C, 64.46; H, 7.06; N, 9.80; S, 7.48. Found: C, 64.33; H, 6.87; N, 9.71; S, 7.34.

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