Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

A facile synthesis of some novel fused [1,2,4]triazolo[3,4-b][1,3,4]thiadiazol derivatives

Kerru Nagaraju [a], Yalagala Kotaiah [a], Chinnam Sampath [a], Nallapaneni Harikrishna [a] & Chunduri Venkata Rao [a]
[a] Department of Chemistry, Sri Venkateswara University, Tirupati, 517 502, Andhra Pradesh, India
Published online: 27 Nov 2012.

Journal of Sulfur Chemistry, 2013
Vol. 34, No. 3, 264–275, http://dx.doi.org/10.1080/17415993.2012.734306

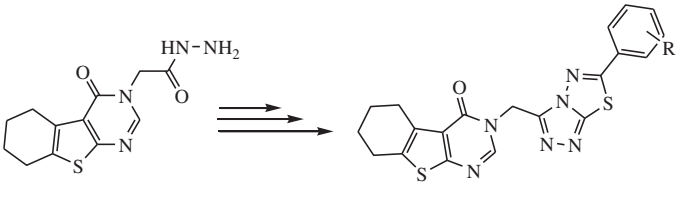
A facile synthesis of some novel fused [1,2,4]triazolo[3,4-b][1,3,4]thiadiazol derivatives

Kerru Nagaraju, Yalagala Kotaiah, Chinnam Sampath, Nallapaneni Harikrishna and Chunduri Venkata Rao*

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India

(*Received 19 July 2012; final version received 23 September 2012*)

A series of novel 3-[6-(4-substituted phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one derivatives (**7a**–**7h**) have been synthesized from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile **(1)** through a multi-step reaction sequence. The key intermediate **(6)** on condensation with various substituted aromatic carboxylic acids in the presence of phosphorus oxychloride afforded the series of title compounds (**7a**–**7h**). The structures of all newly synthesized compounds were established on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR and liquid chromatography mass spectrometry spectral data.



Keywords: thieno[2,3-d]pyrimidin-4-one; oxopyrimidine; 1,2,4-triazole; 1,3,4-thiadiazole; cyclization reaction

1. Introduction

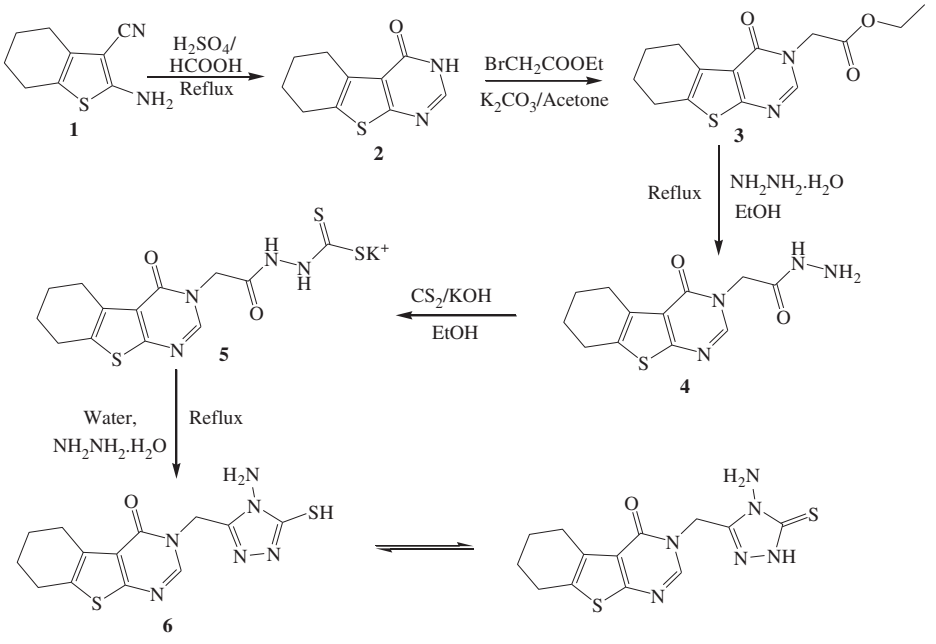
A wide variety of heterocyclic benzothiophene systems and their substituted derivatives have been extensively used for the synthesis of a very large number of biologically important molecules over many years. It is evident from the literature that certain thienopyrimidine derivatives have been found to exhibit varied biological activities such as antioxidant, antitumor (*1*), inhibitors of VEGFR-2 kinase (*2*), cytotoxicity (*3*), and antimicrobial activity (*4*, *5*). Manhas *et al*. (*6*) have synthesized various substituted thienopyrimidine derivatives and evaluated their anti-inflammatory activity (*6*). Several thienopyrimidiones were also synthesized and evaluated for their use for selective 5-HT_{1A} receptor ligands (*7*), anti-hypertensive agents (*8*), potent gonadotropin-releasing hormone receptor antagonists (*9*), and for their fungicidal activities (*10*). In addition, a large

*Corresponding author. Email: cvrsvu@gmail.com

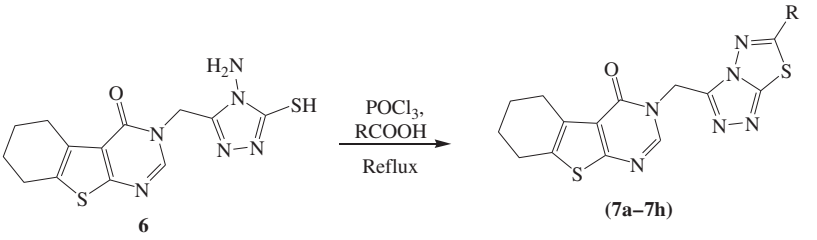
number of tetrahydrobenzothienopyrimidinone derivatives were reported for their analgesic, anti-inflammatory, antimicrobial, and anticonvulsant activities (*11–13*). In the past few years, the synthesis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives have received considerable attention as a result of their biological importance and their important roles in organic and medicinal chemistry. They show a wide range of therapeutic activities, such as antioxidant (*14*), antimicrobial (*15–17*), antiviral (*18*), anti-inflammatory (*19–22*), *in vitro* anti-HIV, antitumor (*23*), and antibacterial (*24*, *25*) activities. Moreover, much interest has also been focused on their antihypertensive (*26*), antituberculosis (*27*), antidepressant, anxiolytic (*28*), analgesic (*29*, *30*), and *in vitro* cytotoxicity (*31*) activities. The search for versatile and widely applicable methods for the synthesis of new heterocyclic compounds and novel molecules is a major topic in contemporary organic synthesis. Thus, the aim of the present work is the synthesis of thienopyrimidine derivatives containing the [1,2,4]triazolo[3,4-b][1,3,4]thiadiazol moiety.

2. Results and discussion

In the present investigation, we have synthesized novel fused pentacyclic [1,2,4]triazolo[3,4-b][1,3,4]thiadiazolo thienopyrimidines from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**1**) using the reaction sequences shown in Schemes 1 and 2. The starting material **1** was prepared via a multicomponent condensation between elemental sulfur, cyclohexanone, and activated melanonitrile in diethyl amine using the Gewald reaction conditions reported in the literature (*32*). One of the convenient synthetic methods to construct the oxopyrimidine ring system employs treatment of amino and cyano functionality, with formic acid at refluxing temperature. Compound **1** upon refluxing with formic acid and concentrated sulfuric acid at 110°C (*5*) resulted in the formation of 5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**2**). Compound **2** on treatment with ethyl bromoacetate and potassium



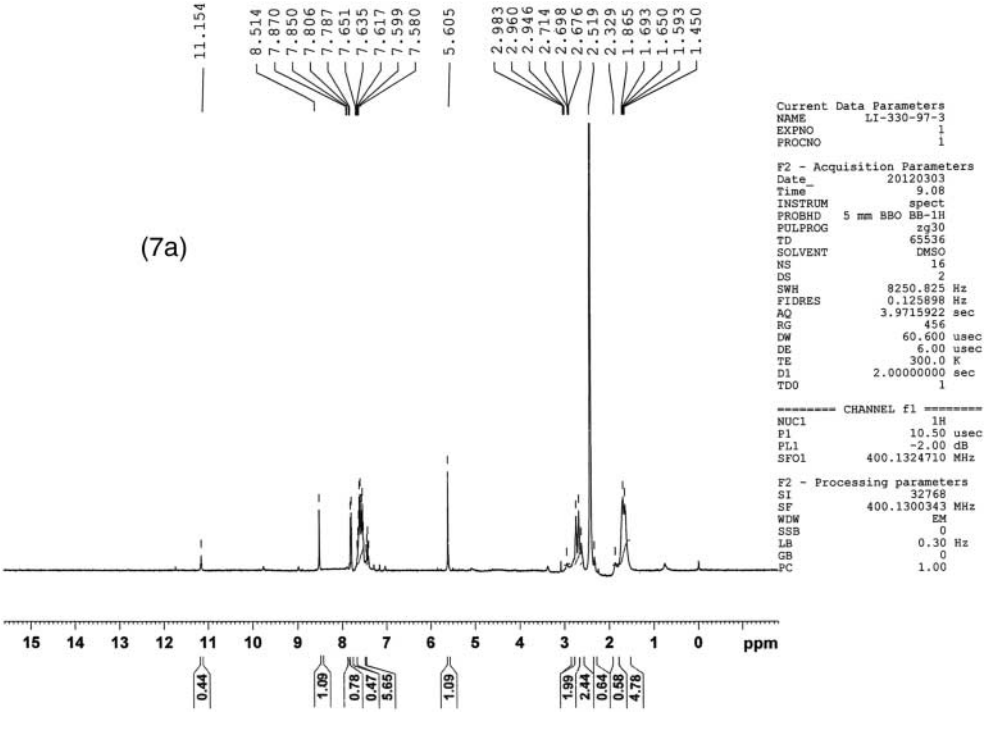
Scheme 1. Synthetic pathways to 3-(4-amino-5-mercapto-4H-[1,2,4]triazol-3-ylmethyl)-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one.

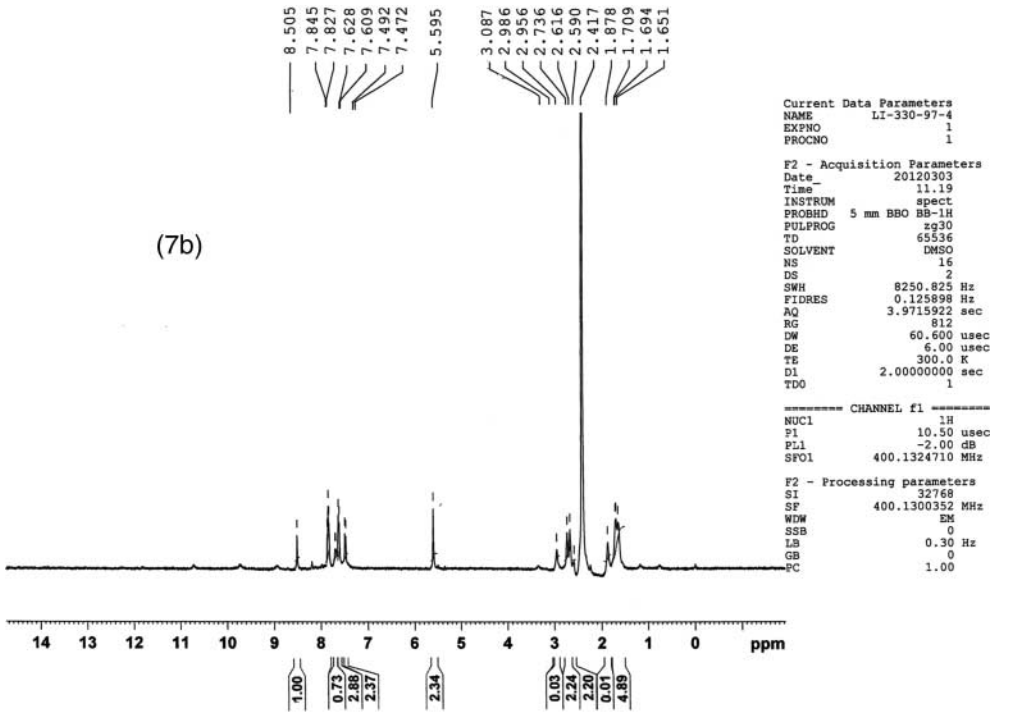


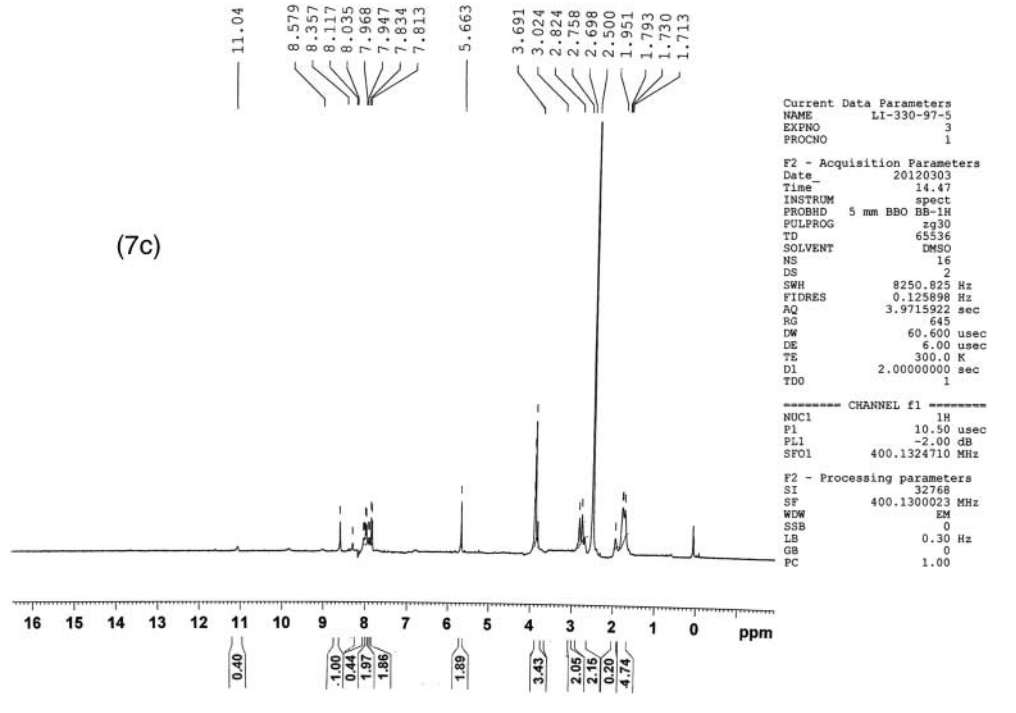
Scheme 2. Synthetic pathway to [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives. (a) R = C_6H_5; (b) R = 4-C_6H_4Cl; (c) R = 4-$C_7H_7OCH_3$; (d) R = 4-$C_6H_4NO_2$; (e) R = 4-C_6H_4OH; (f) R = 4-$C_6H_4CH_3$; (g) R = 4-C_6H_4Br; (h) R = 4-$C_6H_4NH_2$.

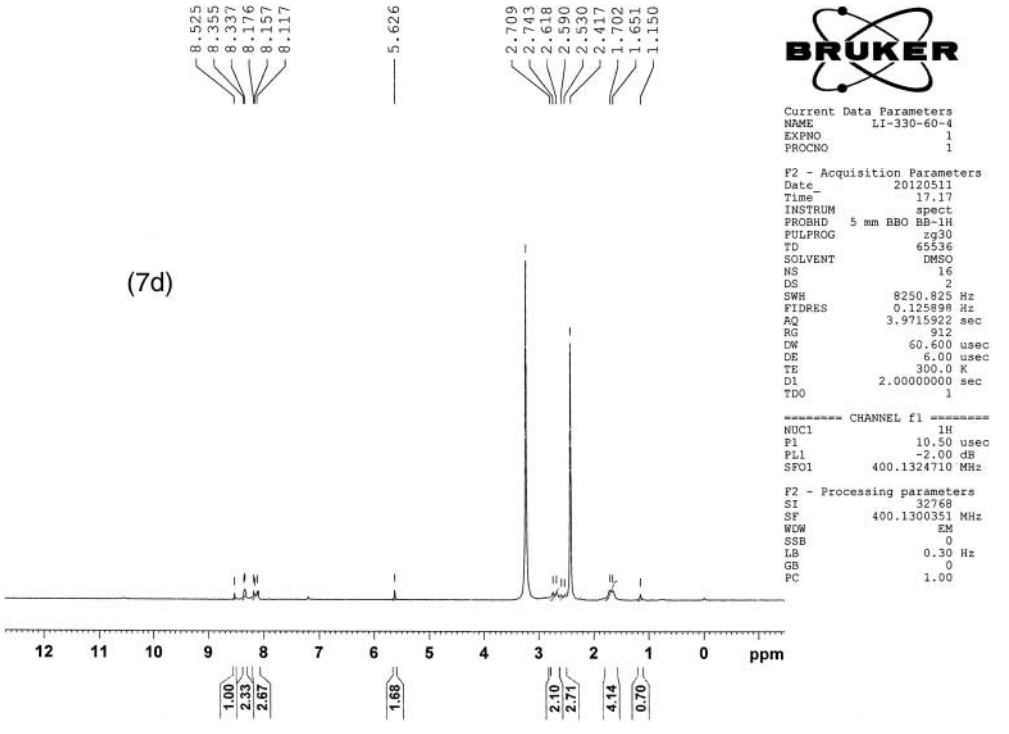
carbonate in acetone gave (4-oxo-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-3-yl)-acetic acid methyl ester (**3**). Compound **3** on treatment with hydrazine hydrate in absolute ethanol (*33*) furnished (4-oxo-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-3-yl)-acetic acid hydrazide (**4**).

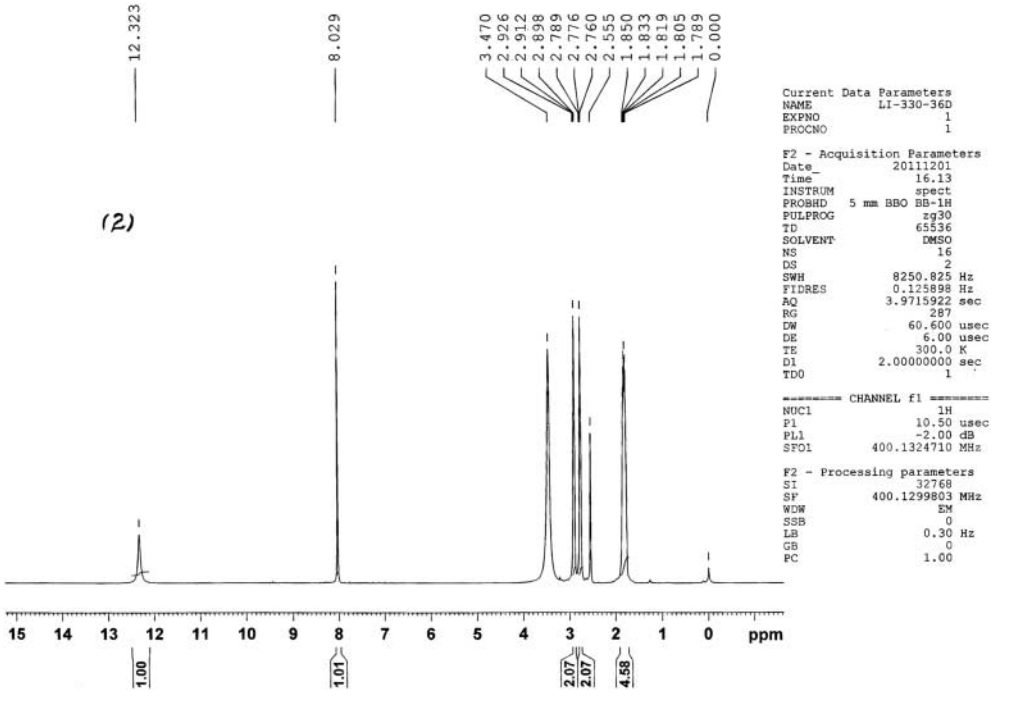
The key intermediate **4** was treated with carbon disulfide in the presence of potassium hydroxide in ethanol to afford the corresponding intermediated potassium dithiocarbazinate salt **5**, which underwent ring closure with an excess of 80% hydrazine hydrate upon reflux to give 3-(4-amino-5-mercapto-4H-[1,2,4]triazol-3-ylmethyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-4(3H)-one (**6**). The IR spectra of **6** showed characteristic absorption bands at 3456, 2896, 1658 and 1573 cm^{-1} for the NH_2, CH, C=O and C=N stretching vibrations, respectively, and its ^{1}H-NMR showed a broad one proton singlet for the SH group at $\delta = 12.74$ and the -NH_2 group as a two proton singlet at $\delta = 5.70$. Furthermore,

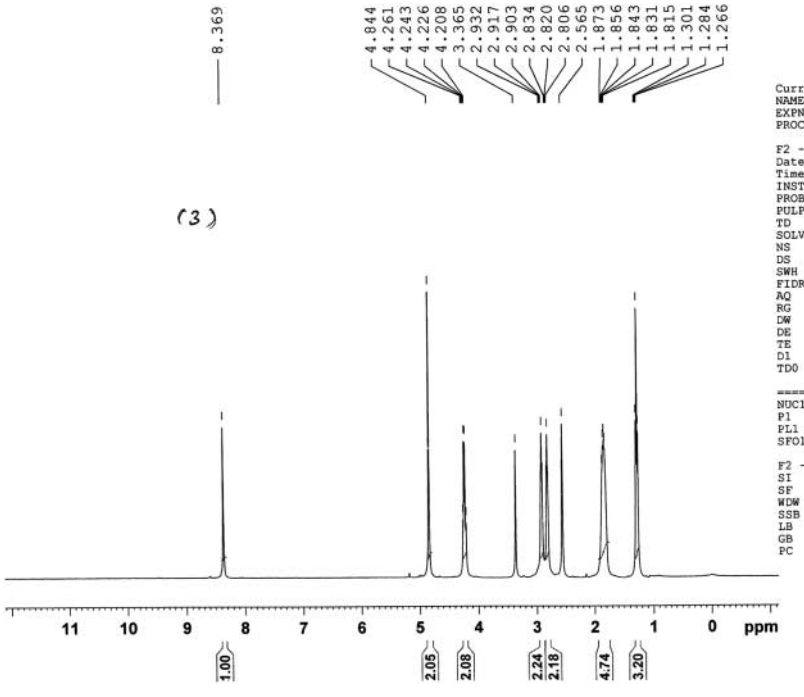










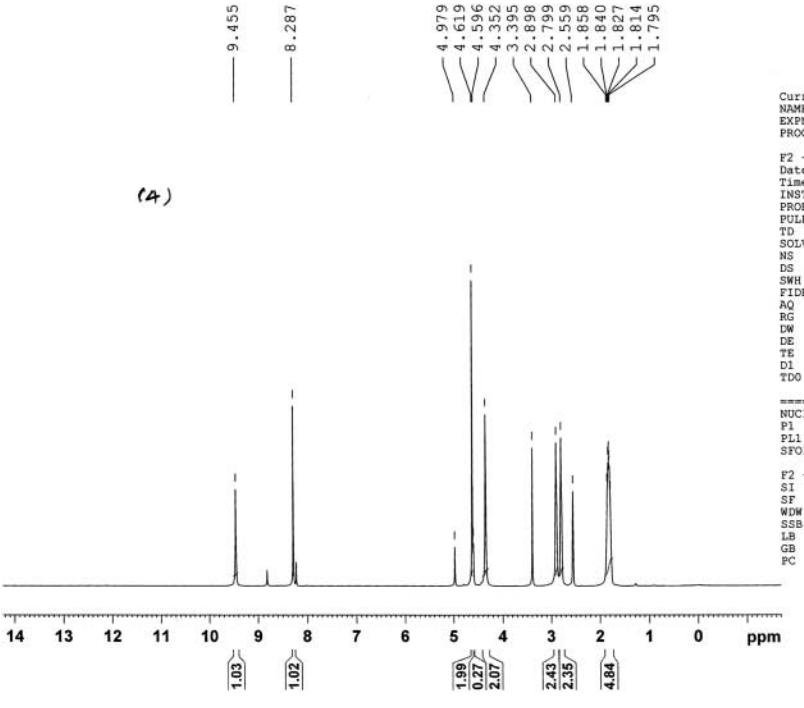



```
Current Data Parameters
NAME                  LI-330-36E
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111201
Time                       16.47
INSTRUM                    spect
PROBHD    5 mm BBO BB-1H
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                    8250.825 Hz
FIDRES                 0.125898 Hz
AQ                     3.9715922 sec
RG                           406
DW                        60.600 usec
DE                         6.00 usec
TE                        300.0 K
D1                     2.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        10.50 usec
PL1                       -2.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1299760 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```

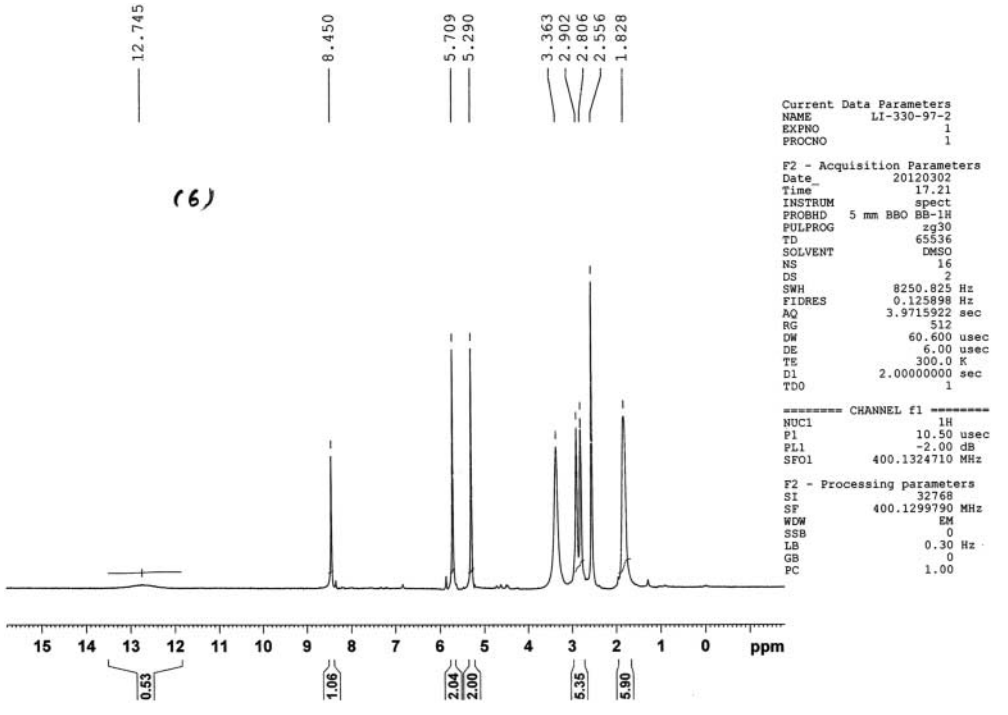



```
Current Data Parameters
NAME                  LI-330-83-1
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20120214
Time                        9.51
INSTRUM                    spect
PROBHD    5 mm BBO BB-1H
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                    8250.825 Hz
FIDRES                 0.125898 Hz
AQ                     3.9715922 sec
RG                           256
DW                        60.600 usec
DE                         6.00 usec
TE                        300.0 K
D1                     2.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        10.50 usec
PL1                       -2.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1299782 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



the formation of **6** was also supported by its mass spectrum which exhibited a molecular ion (M^+) peak at $m/z = 334$ with 100% relative abundance corresponding to the molecular formula $C_{13}H_{14}N_6OS_2$.

Interestingly, the resultant triazole **6** was further converted into [1,2,4]-trizolo-[3,4-b][1,3,4]-thiadiazoles (**7a**–**7h**) in a one-pot reaction by condensation with various substituted aromatic acids in the presence of phosphorus oxychloride followed by an intramolecular ring closure to form the five-membered ring in very good yield (Scheme 2). The structures of the synthesized compounds **7a**–**7h** were assigned on the basis of spectral studies. The physical data, IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and mass spectral data for all the synthesized compounds are reported in the experimental section. The IR spectra of the title compounds **7a**–**7h** showed absorption bands at 2943–2857, 1696–1651, and 1593–1473 cm^{-1} for the CH, C=O, and C=N stretching vibrations, respectively. The absence of the $-NH_2$ and –SH proton signals in the ^{1}H-NMR spectrum of **7a**–**7h** is indicative of the conversion of **6** to [1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiadiazoles (**7a**–**7h**) on treatment with RCOOH in $POCl_3$.

3. Conclusions

In summary, we have developed a synthesis of novel substituted phenyl [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole derivatives. The structures of the synthesized compounds were conformed with their spectral data. In the present investigation, thin layer chromatography (TLC) monitoring reveals that a mixture of products is not formed.

4. Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. All the reactions were monitored by TLC on precoated silica gel 60 F254 (mesh); spots were

visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography. The IR spectra were recorded on a Perkin-Elmer BX1 FTIR Spectrophotometer as KBr pellets and the wave numbers were given in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer in $CDCl_3$/DMSO-d_6 solution using TMS as an internal standard. The mass spectra were recorded on an Agilent 1100 LC/MSD instrument with the method API-ES at 70 eV. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer.

4.1. *Procedure for the preparation of 5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-4(3H)-one (2)*

Concentrated sulfuric acid (4 ml) at 0–5°C was added to a mixture of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**1**) (1 g, 5.6 mmol) in formic acid (10 ml). The mixture was refluxed for 2 h and allowed to cool to room temperature (rt). The mixture was poured into ice cold water. The solid separated was filtered and purified by recrystallization with ethanol.

Yield: 91% (brown color solid); mp 188–200°C; IR (KBr) (ν_{max} cm^{-1}): 2836 (CH), 1651 (C=O), 1581 (C=N); ^1H NMR (400 MHz; DMSO-d_6): δ_H 1.78–1.85 (m, 4H, CH_2), 2.77 (t, $J_{HH} = 5.2$ Hz, 2H, CH_2), 2.91 (t, $J_{HH} = 5.6$ Hz, 2H, CH_2), 8.02 (s, 1H, CH-pyrimidine), 12.32 (br s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.73, 22.43, 24.40, 25.29, 122.68, 130.79, 132.09, 144.75, 157.62, 162.38; liquid chromatography mass spectrometry (LCMS) (70 eV): $m/z = 205$ $(M–H)^-$. Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58; O, 7.76; S, 15.55; found: C, 58.12; H, 4.76; N, 13.45; O, 7.71; S, 15.97%.

4.2. *Procedure for the preparation of (4-oxo-5,6,7,8-tetrahydro[1]benzothieno [2,3-d]pyrimidin-3-yl)-acetic acid methyl ester (3)*

A solution of compound **2** (2.06 g, 10 mmol), ethyl bromo acetate (1.3 ml, 12 mmol), and potassium carbonate (3.45 g, 25 mmol) in 20 ml acetone was stirred for 2 h. The precipitated solid obtained after the evaporation of acetone was washed with cold water and recrystallized from ethanol.

Yield: 80% (yellow color solid); mp 189–191°C; IR (KBr) (ν_{max} cm^{-1}): 2945 (CH), 1736 (COOEt), 1674 (C=O), 1558 (C=N) ; ^1H NMR (400 MHz; DMSO-d_6): δ_H 1.28 (t, $J_{HH} = 8.0$ Hz, 3H, CH_2 $\underline{CH_3}$) 1.81–1.87 (m, 4H, CH_2), 2.82 (t, $J_{HH} = 5.6$ Hz, 2H, CH_2), 2.93 (t, $J_{HH} = 6.0$ Hz, 2H, CH_2), 4.24 (q, $J_{HH} = 8.0$ Hz, 2H, $\underline{CH_2}CH_3$), 4.84 (s, 2H, CH_2CO), 8.36 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 13.97, 21.69, 22.34, 24.50, 25.22, 46.78, 61.22, 121.57, 130.78, 133.36, 147.49, 156.71, 161.66, 167.82; LCMS (70 eV): $m/z = 293$ $(M+H)^+$. Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; O, 16.42; S, 10.97; found: C, 57.45; H, 5.58; N, 9.57; O, 16.46; S, 10.95%.

4.3. *Procedure for the synthesis of (4-oxo-5,6,7,8-tetrahydro[1]benzothieno [2,3-d]pyrimidin-3-yl)-acetic acid hydrazide (4)*

A mixture of **3** (2.92 g, 10 mmol) and hydrazine hydrate (1.4 ml, 30 mmol) in ethanol (30 ml) was refluxed for 3 h. The reaction mixture was concentrated, cooled, and poured into ice cold water. The separated solid was filtered, dried, and recrystallized from ethanol.

Yield: 88% (pale yellow color solid); mp 243–245°C; IR (KBr) (ν_{max} cm^{-1}): 3278 (NH_2), 2916 (CH), 1658 (CONH), 1620 (C=O), 1558 (C=N) ; ^1H NMR (400 MHz; DMSO-d_6): δ_H 1.79–1.85 (m, 4H, CH_2), 2.79 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 2.89 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 4.35 (s, 2H, CH_2CO), 4.61 (s, 2H, NH_2), 8.28 (s, 1H, CH-pyrimidine), 9.45 (s, 1H, CONH); ^{13}C NMR

(100 MHz; DMSO-d_6): δ_C 21.73, 22.38, 24.50, 25.27, 46.36, 121.62, 130.76, 132.76, 148.08, 156.81, 161.63, 166.06; LCMS (70 eV): $m/z = 277$ $(M–H)^-$. Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13; O, 11.50; S, 11.52; found: C, 51.65; H, 5.12; N, 20.07; O, 11.57; S, 11.59%.

4.4. *Procedure for the synthesis of potassium dithiocarbazinate (5)*

To a solution of **4** (5.56 g, 20 mmol) and potassium hydroxide (1.68 g, 30 mmol) in 20 ml of cool ethanol was added (1.5 ml, 25 mmol) carbon disulfide and the mixture was stirred for 12 h. The obtained solid was filtered, washed with anhydrous ether (50 ml), and dried in vacuum.

4.5. *Procedure for the preparation of 3-(4-amino-5-mercapto-4H-[1,2,4]triazol-3-ylmethyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (6)*

Hydrazine hydrate (1.9 ml, 40 mmol) was added to a suspension of potassium compound (7.84 g, 20 mmol) in water (25 ml). The suspension was refluxed for 18 h until a green color was obtained. Then, the reaction mixture was cooled, diluted, and acidified with acetic acid. The precipitated solid was filtered off, washed, and recrystallized from ethanol.

Yield: 63% (pale brown color solid); mp 254–256°C; IR (KBr) (ν_{max} cm^{-1}): 3456 (NH_2), 2896 (CH), 2736 (SH), 1658 (C=O), 1573 (C=N); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.78–1.82 (m, 4H, CH_2), 2.80 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 2.90 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 5.29 (s, 2H, CH_2), 5.70 (s, 2H, NH_2), 8.45 (s, 1H, CH-pyrimidine), 12.74 (br s, 1H, SH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.69, 22.34, 24.51, 25.25, 40.20, 121.67, 130.85, 133.30, 147.65, 148.11, 156.53, 161.56, 166.82; LCMS (70 eV): $m/z = 333$ $(M–H)^-$. Anal. Calcd for $C_{13}H_{14}N_6OS_2$: C, 46.69; H, 4.22; N, 25.13; O, 4.78; S, 19.18; Found: C, 49.56; H, 4.32; N, 25.07; O, 3.04; S, 18.01%.

4.6. *General procedure for the synthesis of 3-[6-(4-subtituted phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (7a–7h)*

An equimolar mixture of compound **6** (3.34 g, 10 mmol) and aromatic acids (10 mmol) in phosphorus oxychloride (10 ml) was refluxed for 5–8 h. The reaction mixture was cooled to rt and then gradually poured onto crushed ice with stirring. The mixture was allowed to stand overnight and the separated solid was filtered, treated with dilute sodium hydroxide solution, washed thoroughly with cold water, dried, and recrystallized from ethanol.

4.6.1. *3-(6-Phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7a**)*

Yield: 84% (brown color solid); mp 266–268°C; IR (KBr) (ν_{max} cm^{-1}): 2857 (CH), 1683 (C=O), 1481 (C=N), 763 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.65–1.86 (m, 4H, $2CH_2$), 2.67 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 2.94 (t, $J_{HH} = 8.0$ Hz, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.58–7.65 (m, 5H, Ar–H), 8.51 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.68, 21.91, 22.34, 22.72, 24.51, 119.57, 121.36, 127.03, 128.50, 129.67, 130.91, 133.00, 147.68, 148.72, 157.09, 160.86, 162.39, 187.16; LCMS (70 eV): $m/z = 421$ $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_6OS_2$: C, 57.12; H, 3.84; N, 19.99; found: C, 57.22; H, 3.76; N, 19.85%.

4.6.2. *3-[6-(4-Chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7b**)*

Yield: 78% (brown color solid); mp 210–212°C; IR (KBr) (ν_{max} cm^{-1}): 2879 (CH), 1696 (C=O), 1473 (C=N), 833 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.65–1.70 (m, 4H, 2CH$_2$), 2.59 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 2.95 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 5.59 (s, 2H, CH$_2$), 7.49 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.62 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.50 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.81, 22.64, 22.96, 24.08, 38.16, 119.03, 121.83, 126.68, 129.50, 130.73, 132.01, 136.19, 147.42, 149.95, 157.38, 161.43, 164.82, 173.59; LCMS (70 eV): m/z = 455 (M+H)$^+$. Anal. Calcd for $C_{20}H_{15}ClN_6OS_2$: C, 52.80; H, 3.32; N, 18.47; found: C, 52.68; H, 3.28; N, 18.31%.

4.6.3. *3-[6-(4-Methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7c**)*

Yield: 73% (brown color solid); mp 218–220°C; IR (KBr) (ν_{max} cm^{-1}): 2894 (CH), 1688 (C=O), 1573 (C=N), 802 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.71–1.79 (m, 4H, 2CH$_2$), 2.75 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 2.82 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 3.69 (s, 3H, OCH$_3$), 5.66 (s, 2H, CH$_2$), 7.83 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.96 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.57 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 20.00, 20.63, 22.80, 24.23, 38.49, 54.06, 113.47, 122.06, 127.12, 128.28, 130.65, 133.86, 138.07, 148.44, 149.29, 156.81, 163.11, 167.09, 178.23; LCMS (70 eV): m/z = 451 (M+H)$^+$. Anal. Calcd for $C_{21}H_{18}N_6O_2S_2$: C, 55.98; H, 4.03; N, 18.65; found: C, 55.86; H, 4.12; N, 18.46%.

4.6.4. *3-[6-(4-Nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7d**)*

Yield: 81% (orange color solid); mp 280–282°C; IR (KBr) (ν_{max} cm^{-1}): 2943 (CH), 1682 (C=O), 1527 (C=N), 856 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.65–1.70 (m, 4H, 2CH$_2$), 2.59 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 2.74 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 5.62 (s, 2H, CH$_2$), 8.17 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.35 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.52 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.59, 21.74, 22.23, 25.68, 37.11, 116.36, 121.72, 125.53, 127.94, 130.52, 132.38, 137.61, 148.25, 149.05, 158.93, 160.28, 164.64, 171.49; LCMS (70 eV): m/z = 466 (M+H)$^+$. Anal. Calcd for $C_{20}H_{15}N_7O_3S_2$: C, 51.60; H, 3.25; N, 21.06; found: C, 51.76; H, 3.21; N, 21.15%.

4.6.5. *3-[6-(4-Hydroxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-one (**7e**)*

Yield: 79% (brown color solid); mp 246–248°C; IR (KBr) (ν_{max} cm^{-1}): 3417 (OH), 2943 (CH), 1682 (C=O), 1527 (C=N), 856 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.68–1.73 (m, 4H, 2CH$_2$), 2.46 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 2.69 (t, J_{HH} = 8.0 Hz, 2H, CH$_2$), 5.48 (s, 2H, CH$_2$), 7.68 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.84 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.05 (s, 1H, CH-pyrimidine), 10.36 (s, 1H, Ar–OH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.16, 22.69, 23.85, 24.43, 38.60, 117.74, 119.82, 126.95, 128.48, 131.04, 133.53, 138.24, 149.37, 151.99, 159.31, 161.93, 162.26, 169.18; LCMS (70 eV): m/z = 437 (M+H)$^+$. Anal. Calcd for $C_{20}H_{16}N_6O_2S_2$: C, 55.03; H, 3.69; N, 19.25; found: C, 55.21; H, 3.61; N, 19.12%.

4.6.6. *3-[6-(4-Methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7f**)*

Yield: 66% (brown color solid); mp 212–214°C; IR (KBr) (ν_{max} cm^{-1}): 2892 (CH), 1664 (C=O), 1536 (C=N), 796 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.71–1.76 (m, 4H, $2CH_2$), 2.38 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 2.52 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 3.04 (s, 3H, Ar–CH_3), 5.51 (s, 2H, CH_2), 7.28 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.61 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.37 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 20.37, 21.88, 23.16, 24.92, 26.08, 37.53, 115.26, 120.18, 124.11, 129.63, 129.98, 132.49, 139.28, 147.72, 153.57, 159.26, 162.01, 165.35, 171.48; LCMS (70 eV): m/z = 433 $(M–H)^-$. Anal. Calcd for $C_{21}H_{18}N_6OS_2$: C, 58.04; H, 4.18; N, 19.34; found: C, 58.12; H, 4.23; N, 19.27%.

4.6.7. *3-[6-(4-Bromophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7g**)*

Yield: 73% (yellow color solid); mp 264–266°C; IR (KBr) (ν_{max} cm^{-1}): 2941 (CH), 1672 (C=O), 1593 (C=N), 764 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.68–1.74 (m, 4H, $2CH_2$), 2.42 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 2.68 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 5.04 (s, 2H, CH_2), 7.31 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.73 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.68 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 20.92, 21.48, 22.10, 24.28, 38.44, 118.76, 121.59, 125.06, 130.23, 132.47, 133.61, 138.80, 146.39, 149.33, 154.53, 159.78, 162.95, 168.89; LCMS (70 eV): m/z = 467 $(M+H)^+$. Anal. Calcd for $C_{20}H_{15}BrN_6OS_2$: C, 51.40; H, 3.24; N, 17.98; found: C, 51.32; H, 3.14; N, 17.72%.

4.6.8. *3-[6-(4-Amino-phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylmethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**7h**)*

Yield: 81% (brown color solid); mp 283–285°C; IR (KBr) (ν_{max} cm^{-1}): 3428 (NH_2), 2859 (CH), 1651 (C=O), 1527 (C=N), 829 (C−S); ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.71–1.75 (m, 4H, CH_2), 2.52 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 2.74 (t, J_{HH} = 8.0 Hz, 2H, CH_2), 5.04 (s, 2H, NH_2), 5.51 (s, 2H, CH_2), 7.42 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 7.96 (d, J_{HH} = 8.0 Hz, 2H, Ar–H), 8.26 (s, 1H, CH-pyrimidine); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 21.04, 21.42, 23.91, 25.18, 38.73, 118.38, 120.69, 124.28, 127.51, 130.17, 137.36, 139.52, 147.01, 149.99, 157.38, 160.64, 162.75, 172.93; LCMS (70 eV): m/z = 436 $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_6O_2S_2$: C, 55.03; H, 3.69; N, 19.25; found: C, 55.12; H, 3.61; N, 19.36%.

Acknowledgements

One of the authors (KN) is gratefully acknowledge the CSIR New Delhi for the financial assistance.

References

(1) Ameen, A.A.H.; Mohamed, F.E.S.; Farid, A.E.B. *Acta Pharm.* **2010,** *60,* 311–323.
(2) Michael, J.M.; Jean, S.B.; Jeffery, M.C.; Beth, A.C.; Jonathan, L.D.; Carla, H.R.; Stephen, M.H.; Catherine, I.S.; Elisabeth, A.K.; Matthew, A.M.; Ann, M.K.R.; Susan, B.S.; Jianmin, S. *Bioorg. Med. Chem. Lett.* **2004,** *14,* 21–24.
(3) Khulud, M.A.; Hassan, M.A.A.; Shar, S.A. *Molecules* **2010,** *15,* 3932–3957.
(4) Bothaina, A.F.; Manal, M.K.; Maha, A.H.; Zeinab, M.F. *J. Chin. Chem. Soc.* **2006,** *53,* 403–412.
(5) Nitinkumar, S.S.; Ravi, S.L.; Imtiyaz, A.M.K. *J. Chem. Sci.* **2009,** *121,* 301–307.
(6) Manhas, M.S.; Sharma, S.D.; Amin, S.G. *J. Med. Chem.* **1971,** *15,* 106–107.
(7) Maria, M.; Maria, S.; Filippo, R.; Luca, P.; Luca, D.G.; Carlo, S.; Mario, S.; Tiziana, M. *J. Med. Chem.* **1997,** *40,* 574–585.

(8) Ronald, K.R.; Jeffery, B.P.; Richard, A.R.; James, J.M.; Robert, F.; Joan, A.K.; David, A.B.; Alfonso, T. *J. Med. Chem.* **1988,** *31,* 1786–1793.
(9) Zhiqiang, G.; Yongsheng, C.; Dongpei, W.; Yun-Fei, Z.; Scott, S.R.; John, S.; Qiu, X.; Chen, C. *Bioorg. Med. Chem. Lett.* **2003,** *13,* 3617–3622.
(10) Yong, S.; Jing, W.; Ling-Ling, F.; Ming-Wu, D. *ARKIVOC* **2009,** *7,* 111–118.
(11) Veerachamy, A.; Durairaj, S.; Viswas, R.S. *ARKIVOC* **2006,** *16,* 149–159.
(12) Narayana, B.; Ashalatha, B.V.; Vijaya, R.K.K.; Suchetha, K.N. *Indian J. Chem.* **2006,** *45B,* 2696–2703.
(13) Narayana, B.; Ashalatha, B.V.; Vijaya, R.K.K.; Suchetha, K.N. *Eur. J. Med. Chem.* **2007,** *42,* 719–728.
(14) Imtiaz, K.; Sajid, A.; Shahid, H.; Nasim, H.R.; Muhammad, T.H.; Abdul, W.; Reaz, U.; Zaheer, U.H.; Ajmal, K.; Sajjad, A.; Iqbal, C.M. *Eur. J. Med. Chem.* **2010,** *45,* 5200–5207.
(15) Nuray, U.G.; Omer, K. *Eur. J. Med. Chem.* **2010,** *45,* 63–68.
(16) Sahar, M.I.B.; Rasha, M.B. *Bioorg. Med. Chem.* **2011,** *19,* 4506–4512.
(17) Karabasanagouda, T.; Airody, V.A.; Suchetha, S.N. *Eur. J. Med. Chem.* **2007,** *42,* 521–529.
(18) Abdel-Rahman, F.; Erik, D.C.; Hussein, E.K. *Acta Chim. Slov.* **2011,** *58,* 53–59.
(19) Birsen, T.; Esra, K.; Erdem, Y.; Mevlut, E. *Bioorg. Med. Chem.* **2007,** *15,* 1808–1814.
(20) Michael, D.M.; Michael, W.W.; David, T.C.; Catherine, R.K.; Denis, J.S.; Richard, D.D. *J. Med. Chem.* **1993,** *36,* 1090–1099.
(21) Sadaf, J.G.; Suroor, A.K.; Nadeem, S. *Bioorg. Med. Chem. Lett.* **2010,** *20,* 4762–4765.
(22) Mohd, A.; Harish, K.; Javed, S.A. *Eur. J. Med. Chem.* **2008,** *43,* 2056–2066.
(23) Yaseen, A.A.S.; Najim, A.A.M.; Robert, L.; Paola, L.C. *Arch. Pharm. Chem. Life Sci.* **2008,** *341,* 365–369.
(24) Xin-Ping, H.; Lin-Mei, Z.; Zi-Yi, Z.; Qin, W.; Fang, W. *J. Chin. Chem. Soc.* **2000,** *47,* 535–539.
(25) Mathew, V.; Keshavayya, J.; Vaidya, V.P. *Eur. J. Med. Chem.* **2006,** *41,* 1048–1058.
(26) Stephen, T.; Malcolm, M.; Brian, G.; Anthony, J.N.; Robin, P.; John, F.S.; John, C.D.; Timothy, L.B. *J. Med. Chem.* **1988,** *31,* 902–906.
(27) Elcin, E.O.; Sevim, R.; Fatma, K.; Nathaly, S.; Anatholy, S.D. *J. Med. Chem.* **2004,** *47,* 6760–6767.
(28) Francesca, C.; Donato, P. *J. Med. Chem.* **2001,** *44,* 931–936.
(29) Umut, S.G.; Nesrin, G.K.; Ozgur, G.; Yavuz, K.; Ekrem, K.; Samil, I.; Goknur, A.; Meral, O. *Bioorg. Med. Chem.* **2007,** *15,* 5738–5751.
(30) Mohammad, A.; Harish, K.; Sadique, A.J. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 4504–4508.
(31) Anelia, T.M.; Diana, W.; Yordan, A.T.; Pavletta, D. *Eur. J. Med. Chem.* **2009,** *44,* 63–69.
(32) Zita, P.; Anita, A.; Daniel, V. *Tetrahedron* **2008,** *64,* 11262–11269.
(33) Jiangping, L.; Zhen, L.; Yan, L.; Mi, Z.; Zhengxi, Z.; Shu, Z.; Renxiao, W.; Jian, L. *Bioorg. Med. Chem. Lett.* **2011,** *21,* 6662–6666.