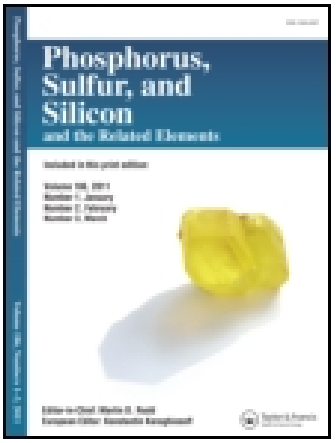


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Characterization of Nitrogen Heterocyclic Derivatives Containing Sulfur-Ether and Schiff Base

Jinyun Zheng [a] , Yujian Yu [a] , Xiaomin Zhen [a] , Erbing Yang [a] & Yufen Zhao [a b c]

[a] Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, College of Chemistry and Molecular Engineering , Zhengzhou University , Zhengzhou , China

[b] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province , Xiamen University , Xiamen , China

[c] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Ministry of Education, Department of Chemistry , Tsinghua University, Beijing , China

Accepted author version posted online: 25 Feb 2013.Published online: 20 Sep 2013.

To cite this article: Jinyun Zheng , Yujian Yu , Xiaomin Zhen , Erbing Yang & Yufen Zhao (2013) Synthesis and Characterization of Nitrogen Heterocyclic Derivatives Containing Sulfur-Ether and Schiff Base, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:11, 1564-1575, DOI: 10.1080/10426507.2012.761989

To link to this article: http://dx.doi.org/10.1080/10426507.2012.761989

Phosphorus, Sulfur, and Silicon, 188:1564–1575, 2013

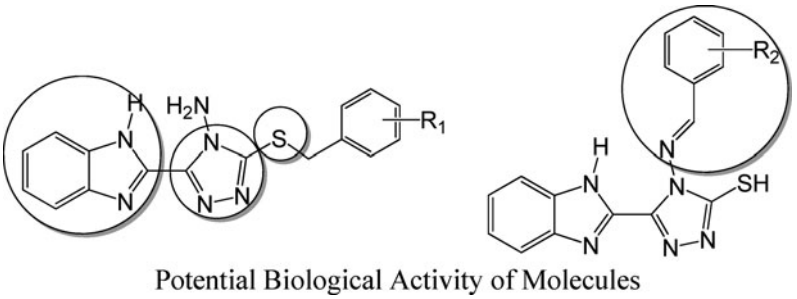
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.761989

SYNTHESIS AND CHARACTERIZATION OF NITROGEN HETEROCYCLIC DERIVATIVES CONTAINING SULFUR–ETHER AND SCHIFF BASE

Jinyun Zheng,[1] Yujian Yu,[1] Xiaomin Zhen,[1] Erbing Yang,[1] and Yufen Zhao[1,2,3]

[1]*Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, China*
[2]*Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China*
[3]*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Ministry of Education, Department of Chemistry, Tsinghua University, Beijing, China*

GRAPHICAL ABSTRACT



Potential Biological Activity of Molecules

Abstract *A series of new nitrogen heterocyclic compounds containing sulfur–ether (8a–8f) and Schiff-base (9a–9q) functionalities were synthesized by the reaction of the pharmaceutical lead compound containing both benzimidazole and 1,2,4-triazole rings. The compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, HR-MS, and ESI-MS.*

[*Supplementary materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfer, and Silicon and the Related Elements for the following free supplemental files: Additional figures.]

Received 12 November 2012; accepted 20 December 2012.
The authors would like to thank the National Natural Science Foundation Committee of China for financial support to this work (No. 20732004).
Address correspondence to Jinyun Zheng, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450052, China. E-mail: zhengjy@zzu.edu.cn

INTRODUCTION

The benzimidazole nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications.[1] Benzimidazole derivatives have varied biological activities including antimicrobial,[2] anticancer,[3] antiviral,[4] anti-inflammatory,[5] antimycobacterial,[6] anthelminthic[7] properties. Therefore, incorporating of the benzimidazole nucleus into organic molecules is an important synthetic strategy in pharmaceutical chemistry.

1,2,4-Triazole and its derivatives show a wide range of biological effects such as antibacterial,[8] antifungal,[9] anticancer,[10] anti-inflammatory,[11] analgesic,[12] anticonvulsant,[13] antiviral,[14] anti-HIV,[15] and antidepressant[16] activities. Thus, 1,2,4-triazole is a versatile lead molecule for developing potential bioactive agents.

To search new compounds with higher biological activity and lower toxicity and integrate the advantages of benzimidazole and 1,2,4-triazole, we designed a series of double heterocyclic compounds containing both benzimidazole and 1,2,4-triazole as potential pharmaceutical lead molecules. Furthermore, the lead molecules have two active groups, namely, $-NH_2$ and –SH. Because Schiff bases and thiols also play an important role in the medicinal chemistry, and they are reported to show a variety of pharmaceutical properties.[17–20] Therefore, we designed the heterocyclic derivatives containing amino and thioether (Compounds **8**) or Schiff base and thiol (Compounds **9**). The new double heterocyclic compounds were synthesized by a convenient method with high yields (Figure 1), and target compounds were prepared by the improved method with short reactive times.

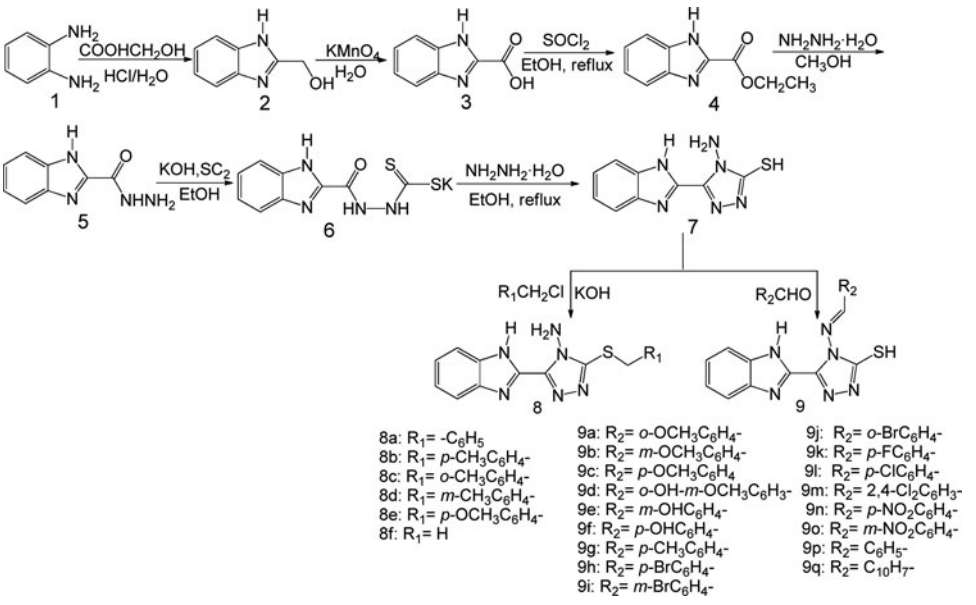


Figure 1 Synthesis of compounds.

RESULTS AND DISCUSSION

Synthesis and Characterization

The new derivatives of heterocycles containing benzimidazole, 1,2,4-triazole and active groups $–NH_2$ and –SH were prepared by the typical heterocyclic synthesis method. The *o*-phenylenediamine reacted with hydroxyacetic acid in the presence of hydrochloric acid to yield 2-hydroxymethylbenzimidazole, then oxidization, esterification, hydrazinolysis, salification, and finally cyclization formed compound **7**. Due to the presence of $–NH_2$ and –SH active groups, the structure of compound **7** can be modified easily. Its derivatives of thioethers and Schiff bases were designed and synthesized, and compounds **8a**–**8f** and **9a**–**9q** were obtained with high yields (upon 85%) in a shorter time (2–4 h). It is worth mentioning, in the synthesis process of compounds 9, general transformations were catalyzed by concentrated sulfuric acid or hydrochloric acid using acetonitrile or methanol as a solvent.[21,22] The result is that using acetonitrile as solvent led to low yields and long reaction times (more than 10 h). Glacial acetic acid was used as efficient solvent and catalyst to synthesize compounds (**9a**–**9q**) in a shorter time (2–4 h, reflux) with higher yields. The compounds are all solids with high melting points, easily precipitated, and purified, and then the pure target compounds were obtained and characterized.

The ^1H NMR and ^{13}C NMR spectra of compounds **8a**–**8f** were recorded, and the ^1H NMR spectrum of **8a** is depicted in Figure 2 as a typical example. Figure 2 shows three singlets at 4.52, 6.62, and 13.48 ppm attributed to methylene ($–SCH_2$), amino ($–NH_2$), and imino group (–NH), respectively. The signals at 7.28–7.80 ppm are assigned to the aromatic protons. The ^{13}C NMR spectrum of **8a** displayed 11 singlets belonging to the different 11 carbons of the compound **8a**. The signals at 153.3 and 146.3 ppm are

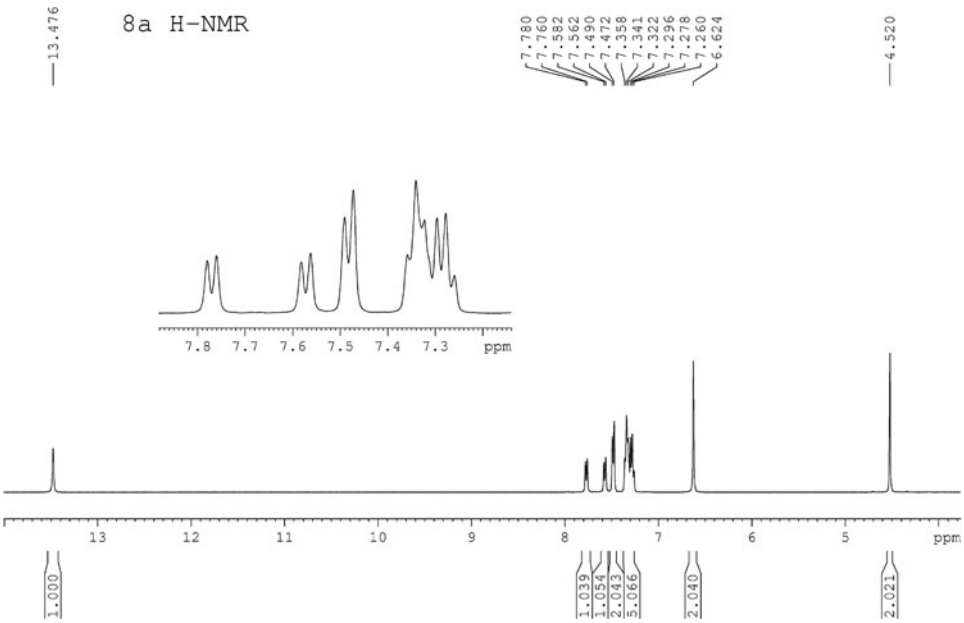


Figure 2 The ^1H NMR spectrum of compound **8a**.

assigned to the triazole's carbons, and the signal at 141.0 ppm is assigned to the imidazole's. The six singlets at 139.3, 137.8, 129.5, 128.9, 127.9, 122.8, and 112.5 ppm belonged to the aromatic carbons. The signal of the saturated carbon ($-SCH_2$) also found at 34.9 ppm.

The FT-IR spectrum of **8a** showed a broad absorptions in the region of 3418 and 3296 cm^{-1} corresponding to the stretching vibration of N–H. The characteristic absorptions for the vibration of the benzene ring were found at 1638, 1495, and 1454 cm^{-1}. The bending vibration of methylene group is also observed at 1419 cm^{-1}.

The ^1H NMR and ^{13}C NMR spectra of **9a**–**9q** were recorded, and the ^1H NMR spectrum of **9f** was depicted in Figure 3 as a typical example. There are four singlets in low field with the integral of 1 at 9.20, 10.41, 13.25, and 14.45 ppm in Figure 3 belong to –OH, –N=CH, –NH, and –SH, respectively. The two doublets at 7.57 and 7.66 ppm are assigned to the aromatic protons of benzimidazole moiety, and the remaining two doublets for benzene ring protons were observed at 6.94 and 7.81 ppm, respectively. Other aromatic protons resonated as a multiplet at 7.21–7.34 ppm. The ^{13}C NMR spectrum of **9f** showed two signals at 163.9 and 141.8 ppm are assigned to the carbons of triazole. The singlets at 162.5 and 139.4 ppm are attributed to carbon of –N=CH– and imidazole, respectively. While the other aromatic carbons also observed at 158.9, 138.9, 131.9, 124.7, 122.9, 116.5, and 112.6 ppm.

The FT-IR spectrum of **9f** showed three broad absorption bands at 3350, 3138, and 2608 cm^{-1} attributed to characteristic stretching vibration of O–H, N–H, and S–H. The absorptions for the vibration of the benzene ring were found at 1570, 1516, and 1482 cm^{-1}. The broad absorption band at 1604 cm^{-1} assigned to the stretching vibration of C=N bond was observed too.

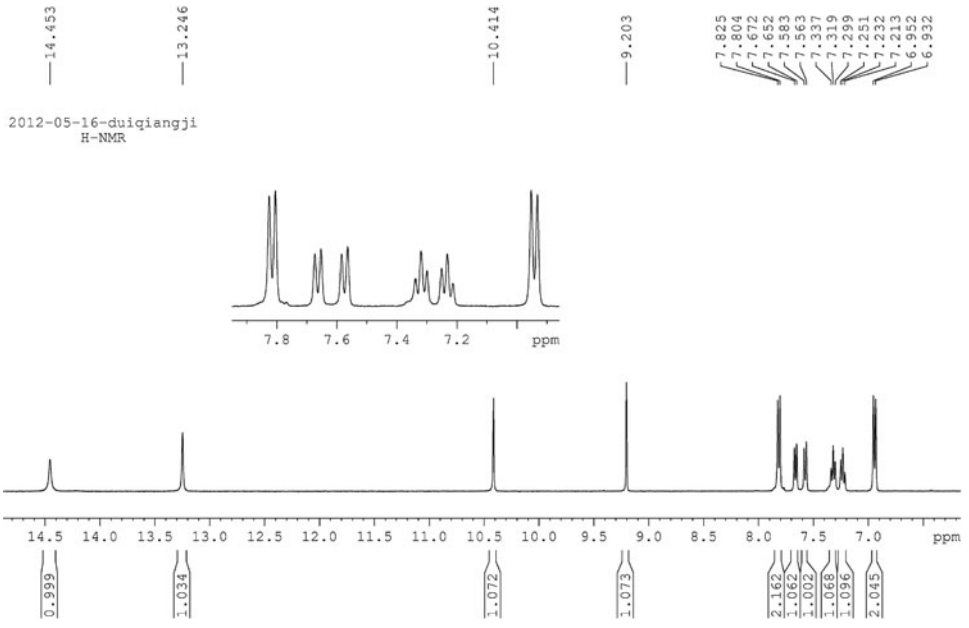


Figure 3 The ^1H NMR spectrum of compound **9f**.

Table 1 ESI-MS^n data of compounds **8a–8f**

Compounds	Precursor ions	Fragment ions (relative abundance%)				
8a	323.1 (9)	361.0 (8)	345 (100)	218.0 (9)		
(MW = 322)	323.1 (23)	307.1 (100)	229.9 (22)	217.9 (90)	143.9 (6)	91.2 (17)
	306.8 (65)	229.9 (100)	203.9 (30)	143.9 (23)		
	218.0 (90)	188.8 (100)	143.8 (33)			
8b	337.1 (83)	375.1 (13)	359.1 (100)	218.1 (25)	105.1 (23)	
(MW = 336)	337.2 (34)	321.1 (42)	232.9 (51)	217.9 (37)	143.9 (2)	105.1 (100)
	321.1 (79)	304.1 (51)	288.0 (30)	229.9 (100)	203.9 (49)	
	233.0 (33)	217.0 (100)	143.9 (38)			
8c	337.1 (100)	375.1 (10)	359.1 (76)	218.1 (17)	105.1 (14)	
(MW = 336)	337.1 (33)	321.1 (29)	288.1 (56)	233.0 (20)	217.9 (88)	
	144.0 (3)	105.1 (100)				
	320.1 (23)	288.1 (100)	229.9 (9)			
8d	337.1 (76)	375.1 (9)	359.1 (100)	218.2 (21)	105.0 (12)	
(MW = 336)	337.1 (36)	321.1 (66)	233.0 (16)	229.9 (12)	217.9 (100)	
	143.9 (4)	105.0 (47)				
	320.1 (36)	304.0 (13)	288.0 (11)	229.9 (100)	203.9 (24)	144.0 (10)
8e	353.2 (11)	375.1 (100)	218.1 (7)	121.1 (9)		
(MW = 352)	353.2 (4)	336.5 (23)	218.0 (16)	144.0 (4)	121.1 (100)	
8f	247.0 (100)	269.0 (34)	232.0 (44)	218.1 (6)	144.0 (3)	
(MW = 246)	247.0 (23)	230.9 (100)	201.9 (33)	160.9 (7)	144.0 (19)	
	230.0 (24)	201.9 (94)	160.9 (90)	143.9 (100)		

Positive Ion ESI-MS/MS Spectra of Compounds

The fragmentation experiments were performed using a Bruker Esquire 3000 electrospray ion trap mass spectrometer. Ionization of analytes was carried out using the following setting of ESI: nebulizer gas flow 7 psi, dry gas 4 L/min, dry temperature 300 °C, capillary voltage 4000 V. ESI-MS^n spectra were obtained by collision induced dissociation (CID) experiments with helium after isolation of the appropriate precursor ions, and the isolation width was 2.0 *m/z*.

Compared with the ESI-MS^n spectra of their positive molecular ions, the $[M+H]^+$ ions of compounds **8** present relatively simple and orderly spectra. The ESI-MS^n data of compounds **8a–8f** are shown in Table 1. The results showed that the $[M+H]^+$ ions mainly produced $[M+H\text{-}16]^+$, $[M+H\text{-}16\text{-}R_1]^+$, $[M+H\text{-}CHR_1]^+$, $[M+H\text{-}16\text{-}CHR_1]^+$, $[144]^+$, and $[105]^+$ six kinds of positive ions. By integrating the results of ESI-MS^n data, the fragmentation pathways were proposed as shown in Figure 4. It is worth noting that the $[M+H]^+$ ions of compounds **8a–8f** all produced ions at *m/z* 144, which might to form a tri-ring cyclic compound.

The fragmentation patterns of $[M+H]^+$ ion of compounds **9a–9q** are little different to those of compounds **8** due to the Schiff-base structure. The main fragment ions derived from $[M+H]^+$ ions were $[M+H-R_2CN]^+$, and *m/z* at 144 and 105 were also produced.

Solubility of Compounds

Because of their rigid and ring structures, compounds **8** and compounds **9** have excellent solubility in polar aprotic solvents such as DMF and DMSO, but only slight

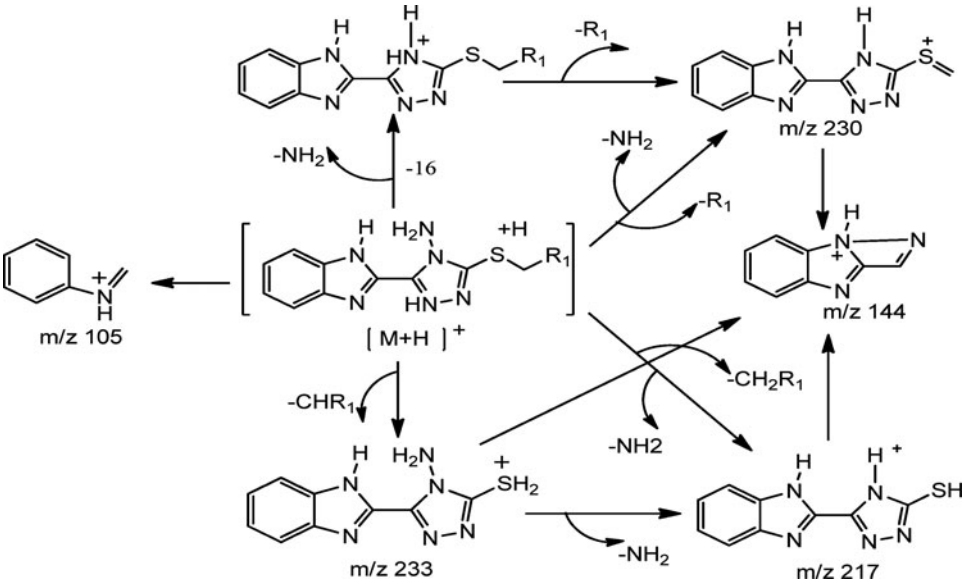


Figure 4 The proposed fragmentation pathways of compounds **8a–8f**.

solubility in protonic solvents such as water and ethanol and low-polarity solvents such as methylene chloride and chloroform. Phosphorylation of $–NH_2$ or oxidation of –SH may be improved their solubility in water and other solvents, which will be the focus of our next work.

CONCLUSIONS

Two series of nitrogen heterocyclic compounds containing thioether or Schiff bases were synthesized by the improved reaction method with high yields. The structures of all compounds were determined by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopies. The positive ion ESI-MS/MS spectra of compounds were recorded, and the fragmentation patterns of $[M+H]^+$ were discussed. The biological activities and potential clinical applications of compounds are under study.

EXPERIMENTAL

Instruments and Reagents

Melting point was recorded on a XT4A micro melting point determination instrument. ^{1}H-NMR and ^{13}CPD-NMR spectra were on a Bruker AV 400 with deuterated DMSO as solvents. Chemical shifts (δ values) are given in parts per million with tetramethylsilane as an internal standard. ESI-MS and HR-MS were recorded on Bruker Esquire-3000 electrospray ion trap mass spectrometer and Water Q-Tof micro mass spectrometer, respectively. Infrared spectra were recorded with a Bruker-Alpha spectrophotometer in the range of 4000–400 cm^{-1}; samples were prepared as KBr pellets.

Hydroxyacetic acid, 1,2-diaminobenzene, benzyl chlorides, substituent benzaldehydes, carbon disulfide, thionyl chloride, hydrazinium hydrate (80%), and other reagents were used as supplied (AR).

The compound **2** was prepared from 1,2-diaminobenzene and hydroxyacetic acid according to the literature,[23] mp 170–171 °C. Using potassium permanganate oxidation of compound **2**, compound **3** was obtained as white solid, mp 169–171 °C.[23] Compound **3** reacted with thionyl chloride to obtain compound **4**, mp 219–220 °C. Compound **5** was prepared by the compound **4** and hydrazine hydrate in ethanol,[24] mp 242–243 °C.

Synthesis of Potassium Salt (Compound 6)

KOH (5.73 g, 102.17 mmol) was dissolved in anhydrous ethanol (200 mL), and benzimidazole-2-carboxylic acid hydrazide (12.00 g, 68.12 mmol) was added. The solution was cooled in an ice bath. Then carbon disulfide (6.12 mL, 102.17 mmol) was added in small portions, and the reaction mixture was stirred for 40 h at room temperature. The precipitated potassium dithiocarbamate was collected by filtration and was further washed with anhydrous ether (3 × 20 mL) and dried under vacuum. The potassium salt was obtained almost in quantitative yield and was used in the next step without further purification.

Synthesis of 4-Amino-5-(1H-benzimidazole-2-yl)-4H-[1,2,4]triazole-3-thiol (Compound 7)

A suspension of potassium salt (6) (12.00 g, 41.32 mmol), ethanol (100 mL) and hydrazine hydrate (80%, 11 mL) were placed in the flask and refluxed for 8 h. The reaction mixture was cooled to room temperature and diluted with water (50 mL). The solution was acidificated with concentrated hydrochloric acid, and the required triazole (6) was precipitated out. Which was filtered, washed with cold water (3 × 30 mL), and recrystallized from 90% ethanol to yield white solid of 8.85 g (yield 92.3%). Melting point: 249–250 °C.

Compound 7: ^{1}H NMR (DMSO-d_6) δ: 14.26 (s, 1H, –SH), 13.33 (s, 1H, –NH), 7.78 (d, J = 7.6 Hz, 1H, Ph–H), 7.63 (d, J = 8.0 Hz, 1H, Ph–H), 7.32 (m, 2H, Ph–H), 6.44 (s, 2H, –NH_2); ESI-MS m/z: calcd for 233.06 $[M+H]^+$, 255.04 $[M+Na]^+$, found 233.0 $[M+H]^+$, 255.0 $[M+Na]^+$.

Synthesis of 3-(Benzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8a)

Compounds **8a**–**8f** were prepared by a similar synthetic procedure; compound **8a** is reported as the typical example: Compound **7** (0.40 g, 1.72 mmol) was suspended in appropriate amount water, and KOH (0.069 g) was added under stirring at room temperature. After 30–40 min, the solution was brought to 0 °C in an ice bath, and benzyl chloride (0.44 g, 3.44 mmol) was dropped in with vigorous stirring. The reaction mixture was stirred continuously for 3 h at room temperature with the appearance of a white precipitate. The solid was filtered, washed with water, and recrystallized from methanol/DMF.

Characterization Data of Compounds 8a–8f

3-(Benzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8a): White solid; yield: 90.1%; mp: 246–247 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.48 (s, 1H, –NH), 7.77 (d, J = 8.0 Hz, 1H, Ph–H), 7.57 (d, J = 8.0 Hz, 1H, Ph–H), 7.48 (d, J = 7.2 Hz, 2H, Ph–H), 7.31 (m, 5H, Ph–H), 6.62 (s, 2H, –NH_2), 4.52 (s, 2H, –CH_2–); ^{13}C NMR

(DMSO-d_6) δ/ppm: 153.3, 146.3, 141.0, 139.3, 137.8, 129.5, 128.9, 127.9, 122.8, 112.5, 34.9; FT-IR (KBr) ν/cm^{-1}: 3418 (N–H), 3296, 2895, 1638, 1495, 1454, 745, 711, 695; ESI-MS *m*/*z*: 323.1 $[M+H]^+$, 345.1 $[M+Na]^+$; HR-MS: calcd for $C_{16}H_{15}N_6S$ $[M+H]^+$ 323.1079, found 323.1076.

3-(4-Methylbenzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8b): White solid; yield: 88.6%; mp: 237–239 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.46 (s, 1H, –NH), 7.76 (d, J = 7.6 Hz, 1H, Ph–H), 7.57 (d, J = 7.6 Hz, 1H, Ph–H), 7.31 (m, 4H, Ph–H), 7.13 (d, J = 7.2 Hz, 2H, Ph–H), 6.61 (s, 2H, –NH_2), 4.47 (s, 2H, –CH_2-), 2.28 (s, 3H, –CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.4, 146.4, 141.0, 139.3, 138.1, 132.0, 129.4, 128.6, 122.9, 112.6, 34.8, 21.2; FT-IR (KBr) ν/cm^{-1}: 3416, 3310, 3206, 2979, 1642, 1513, 1416, 784, 746; ESI-MS *m*/*z*: 337.1 $[M+H]^+$, 359.1 $[M+Na]^+$; HR-MS: calcd for $C_{17}H_{17}N_6S$ $[M+H]^+$ 337.1235, found 337.1232.

3-(2-Methylbenzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8c): White solid, yield: 92.0%; mp: 255–257 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.51 (s, 1H, –NH), 7.68 (s, 2H, Ph–H), 7.42 (d, J = 7.2 Hz, 1H, Ph–H), 7.23 (m, 5H, Ph–H), 6.65 (s, 2H, –NH_2), 4.47 (s, 2H, –CH_2-), 2.42 (s, 3H, –CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.2, 146.3, 141.0, 139.4, 137.2, 135.2, 130.8, 130.4, 129.9, 128.3, 126.5, 122.9, 112.5, 33.5, 19.2; FT-IR (KBr) ν/cm^{-1}: 3420, 3304, 3209, 2980, 1643, 1495, 1416, 742; ESI-MS *m*/*z*: 337.1 $[M+H]^+$, 359.1 $[M+Na]^+$.

3-(3-Methbenzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8d): White solid; yield: 92.0%; mp: 230–231 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.49 (s, 1H, –NH), 7.77 (d, J = 7.2 Hz, 1H, Ph–H), 7.58 (d, J = 7.2 Hz, 1H, Ph–H), 7.28 (m, 5H, Ph–H), 7.09 (d, J = 7.2 Hz, 2H, Ph–H), 6.63 (s, 2H, –NH_2), 4.48 (s, 2H, –CH_2-), 2.29 (s, 3H, –CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.6, 146.4, 140.9, 139.3, 138.1, 134.2, 128.8, 128.5, 126.6, 124.4, 122.9, 112.5, 34.9, 21.4; FT-IR (KBr) ν/cm^{-1}: 3421, 3303, 3272, 2970, 2893, 1639, 1623, 1485, 1420, 798, 743, 692; ESI-MS *m*/*z*: 337.1 $[M+H]^+$, 359.1 $[M+Na]^+$.

3-(4-Methoxybenzylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8e): White solid; yield: 93.2%; mp: 247–249 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.46 (s, 1H, –NH), 7.76 (s, 1H, Ph–H), 7.56 (s, 1H, Ph–H), 7.39((d, J = 8.0 Hz, 2H, Ph–H), 7.30 (s, 2H, Ph–H), 6.89 (d, J = 7.6 Hz, 2H, Ph–H), 6.61 (s, 2H, –NH_2), 4.46 (s, 2H, –CH_2-), 3.73 (s, 3H, –OCH_3); ^{13}C NMR (DMSO-d_6) δ/ppm:163.5, 153.4, 146.3, 141.0, 139.4, 129.4, 127.2, 122.8, 114.8, 55.8, 33.2; FT-IR (KBr) ν/cm^{-1}: 3419, 3309, 3201, 2903, 2832, 1642, 1611, 1512, 1460, 835, 747.0; ESI-MS *m*/*z*: 353.2 $[M+H]^+$, 375.1 $[M+Na]^+$; HR-MS: calcd for $C_{17}H_{17}N_6OS$ $[M+H]^+$ 353.1185, found 353.1187.

3-(3-Methylthio)-5-(1H-benzimidazol-2-yl)-4H-[1,2,4]triazole-4-amine (Compound 8f): White solid; yield: 95.8%; mp: 253–255 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 13.47 (s, 1H, –NH), 7.76 (d, J = 7.6 Hz, 1H, Ph–H), 7.56 (d, J = 8.0 Hz, 1H, Ph–H), 7.29 (m, 5H, Ph–H), 6.58 (s, 2H, –NH_2), 2.67 (s, 3H, –CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.2, 146.4, 141.0, 139.8, 122.8, 112.5, 14.5; FT-IR (KBr) ν/cm^{-1}: 3418, 3301, 3273, 2978, 1640, 1624, 1497, 1459, 742; ESI-MS *m*/*z*: 247.0 $[M+H]^+$, 269.0 $[M+Na]^+$; HR-MS: calcd for $C_{10}H_{11}N_6S$ $[M+H]^+$ 247.0766, found 247.0768.

Synthesis of 5-(1H-Benzimidazol-2-yl)-4-((2-methoxybenzylidene) amino)-4H- [1,2,4]triazole-3-thiol (Compound 9a)

Compounds **9a**–**9q** were prepared by the similar synthesis procedure. Here, compound **9a** is reported as the typical example: A solution of compound 7 (0.40 g, 1.72 mmol)

and 2-methoxybenzaldehyde (0.35 g, 2.58 mmol) in acetic acid (15 mL) was refluxed for 2 h under electromagnetic stirring. The reaction mixture was cooled to room temperature, and the solid was slowly precipitated out. It was filtered, washed with methanol (3 × 10 mL), and recrystallized from methanol to obtain the pure compound **9a** 0.565 g (yield: 93.6%).

Characterization Data of Products 9a–9q

Compound 9a: ^{1}H NMR (DMSO-d$_6$) δ/ppm: 14.51 (s, 1H, –SH), 13.24 (s, 1H, –NH), 9.77 (s, 1H, –N=CH–), 8.06 (d, J = 7.6 Hz, 1H, Ph–H), 7.63 (m, 3H, Ph–H), 7.28 (m, 3H, Ph–H), 7.13 (t, J = 7.6 Hz, 1H, Ph–H), 3.90 (s, 3H, –OCH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm: 164.1, 163.7, 159.8, 142.1, 139.0, 138.9, 135.2, 127.9, 123.7, 121.3, 120.5, 112.6, 112.5, 56.4; FT-IR (KBr) ν/cm^{-1}: 3443, 3273, 2739, 2418, 1691, 1597, 1521, 1479, 744; ESI-MS m/z: 351.2 [M+H]$^+$, 373.2 [M+Na]$^+$; HR-MS: calcd for $C_{17}H_{15}N_6OS$ [M+H]$^+$ 351.1028, found 351.1025.

5-(1H-Benzimidazol-2-yl)-4-((3-methoxybenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9b): White solid; yield: 88.3%; mp: 229–231 °C; ^{1}H NMR (DMSO-d$_6$) δ/ppm: 14.54 (s, 1H, –SH), 13.31 (s, 1H, –NH), 9.4 (s, 1H, –N=CH–), 7.67 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 8.0 Hz, 1H, Ph–H), 7.51 (m, J = 7.4 Hz, 3H, Ph–H), 7.33 (t, J = 7.6 Hz, 1H, Ph–H), 7.24 (m, 2H, Ph–H), 3.84 (s, 3H, –OCH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm: 165.9, 163.8, 160.1, 143.2, 141.9, 138.8, 137.4, 136.8, 133.8, 130.8, 122.5, 119.6, 113.5, 55.8; FT-IR (KBr) ν/cm^{-1}: 3418, 3252, 2417, 1648, 1614, 1572, 1539,1487, 780, 735, 684; ESI-MS m/z: 351.2 [M+H]$^+$, 373.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((4-methoxybenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9c): White solid; yield: 98.0%; mp: 247–248 °C; ^{1}H NMR (DMSO-d$_6$) δ/ppm: 14.48 (s, 1H, –SH), 13.27 (s, 1H, –NH), 9.31 (s, 1H, –N=CH–), 7.93 (d, J = 8.4 Hz, 2H, Ph–H), 7.66 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 8.0 Hz, 1H, Ph–H), 7.32 (t, J = 7.4 Hz, 1H, Ph–H), 7.23 (t, J = 7.4 Hz, 1H, Ph–H), 7.14 (d, J=8.4 Hz, 2H, Ph–H), 3.87 (s, 3H, –OCH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm: 169.2, 163.9, 163.5, 141.8, 139.4, 138.9, 131.6, 124.9, 122.9, 115.1, 112.6, 56.0; FT-IR (KBr) ν/cm^{-1}: 3362, 2365, 1646, 1600, 1515, 1485, 1462, 832, 743; ESI-MS m/z: 351.1 [M+H]$^+$, 373.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((2-hydroxy-3-methoxybenzylidene)amino)-4H-[1,2,4] triazole-3-thiol (Compound 9d): Light yellow solid; yield: 88.3%; mp: 229–231 °C; ^{1}H NMR (DMSO-d$_6$) δ/ppm: 14.46 (s, 1H, –SH), 13.26 (s, 1H, –NH), 10.07 (s, 1H, –N=CH–), 9.24 (s, 1H, –OH), 7.67 (d, J = 8.0 Hz, 1H, Ph–H), 7.57 (d, J = 11.6 Hz, 2H, Ph–H), 7.38 (d, J = 7.6 Hz, 1H, Ph–H), 7.32 (t, J = 7.4 Hz, 1H, Ph–H), 7.24 (t, J = 7.4 Hz, 1H, Ph–H), 6.95 (d, J = 8.0 Hz, 1H, Ph–H), 3.84 (s, 3H, –OCH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm: 165.4, 163.9, 152.1, 148.6, 141.9, 139.4, 138.9, 125.4, 123.7, 122.5, 116.1, 115.9, 112.6, 56.1; FT-IR (KBr) ν/cm^{-1}: 3422, 3354, 2396, 1649, 1588, 1512, 1483, 729; ESI-MS m/z: 367.1 [M+H]$^+$, 377.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((3-hydroxybenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9e): White solid; yield: 85.9%; mp: 231–233 °C; ^{1}H NMR (DMSO-d$_6$) δ/ppm: 14.53 (s, 1H, –SH), 13.32 (s, 1H, –NH), 9.88 (s, 1H, –N=CH–), 9.36 (s, 1H, –OH), 7.68 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 8.0 Hz, 1H, Ph–H), 7.37 (m, 4H, Ph–H), 7.24 (t, J = 7.2 Hz, 1H, Ph–H), 7.05 (m, 1H, Ph–H); ^{13}C NMR (DMSO-d$_6$) δ/ppm: 165.9, 163.9, 158.3, 143.2, 141.9, 141.3, 138.9, 137.0, 133.6, 130.7, 121.5, 120.8, 114.8; FT-IR (KBr) ν/cm^{-1}: 3417, 3032, 2414, 1633, 1574, 1515, 1472, 786, 750; ESI-MS m/z: 337.1 [M+H]$^+$, 359.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((4-hydroxybenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9f): Light yellow solid; yield: 89.3%; mp: 236–237 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.45 (s, 1H, –SH), 13.25 (s, 1H, –NH), 10.41 (s, 1H, –N = CH–) 9.20 (s, 1H, -ArOH), 7.81 (d, J = 8.4 Hz, 2H, Ph–H), 7.67 (d, J = 8.0 Hz, 2H, Ph–H), 7.57 (d, J = 8.0 Hz, 1H, Ph–H), 7.32 (d, J = 7.6Hz, 1H, Ph–H), 7.23 (t, J = 7.6 Hz, 1H, Ph–H), 6.94 (t, J = 8.0 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 163.9, 162.5, 158.9, 141.8, 139.4, 138.9, 131.9, 124.7, 122.9, 116.5, 112.6; FT-IR (KBr) ν/cm^{-1}: 3428, 3350, 2608, 1604, 1570, 1516, 1482, 828, 745; ESI-MS m/z: 337.1 [M+H]$^+$, 359.1 [M+Na]$^+$; HR-MS: calcd for $C_{16}H_{13}N_6OS$ [M+H]$^+$ 337.0870, found 337.0879.

5-(1H-Benzimidazol-2-yl)-4-((4-methylbenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9g): Light yellow solid; yield: 91.3%; mp: 212–214 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.51(s, 1H, –SH), 13.29 (s, 1H, –NH), 9.39 (s, 1H, –N = CH–), 7.87 (d, J = 7.6 Hz, 2H, Ph–H), 7.66 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 8.0 Hz, 1H, Ph–H), 7.40 (d, J = 7.6 Hz, 2H, Ph–H), 7.32 (t, J = 7.4 Hz, 1H, Ph–H), 7.23 (t, J = 7.4 Hz, 1H, Ph–H), 2.42 (s, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6) δ/ppm: 165.9, 163.9, 143.8, 141.8, 139.3, 138.9, 130.2, 129.8, 129.6, 122.5, 112.4, 21.8; FT-IR (KBr) ν/cm^{-1}: 3362, 2367, 1648, 1600, 1566, 1534, 1479, 814, 752; ESI-MS m/z: 335.2 [M+H]$^+$, 357.2 [M+Na]$^+$; HR-MS: calcd for $C_{17}H_{15}N_6S$ [M+H]$^+$ 335.1079, found 335.1077.

5-(1H-Benzimidazol-2-yl)-4-((4-bromobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9h): Yellow solid; yield: 90.5%; mp: 193–195 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.56 (s, 1H, –SH), 13.32 (s, 1H, –NH), 9.52 (s, 1H, –N=CH–), 7.93 (d, J = 8.0 Hz, 2H, Ph–H), 7.81 (d, J = 8.4 Hz, 2H, Ph–H), 7.66 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 7.6 Hz, 1H, Ph–H), 7.33 (t, J = 7.4 Hz, 1H, Ph–H), 7.24 (t, J=7.4 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 165.9, 163.8, 141.8, 141.1, 138.8, 132.7, 131.3, 128.9, 125.6, 122.6, 112.4; FT-IR (KBr) ν/cm^{-1}: 3340, 2402, 1644, 1589, 1524, 1478, 818, 747, 527; ESI-MS m/z: 399.0, 401.0 [M+H]$^+$, 421.1, 423.0 [M+Na]$^+$; HR-MS: calcd for $C_{16}H_{12}BrN_6S$ [M+H]$^+$ 399.0028, found 399.0027.

5-(1H-Benzimidazol-2-yl)-4-((3-bromobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9i): Yellow solid; yield: 88.3%; mp: 170–172 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.58 (s, 1H, –SH), 13.31 (s, 1H, –NH), 9.49 (s, 1H, –N=CH–), 8.19 (s, 1H, Ph–H), 7.98 (d, J = 7.6 Hz, 1H, Ph–H), 7.88 (m, 1H, Ph–H), 7.68 (d, J = 8.4 Hz, 1H, Ph–H), 7.56 (m, 2H, Ph–H), 7.34 (t, J = 7.6 Hz, 1H, Ph–H), 7.25 (t, J = 7.8 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 166.0, 163.8, 141.9, 141.1, 138.7, 135.8, 134.7, 131.6, 129.7, 128.7, 124.4, 122.7, 111.7; FT-IR (KBr) ν/cm^{-1}: 3320, 2419, 1649, 1592, 1534, 1482, 793, 731, 528; ESI-MS m/z: 399.0,401.0 [M+H]$^+$, 421.1,423.0 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((2-bromobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9j): Light yellow solid; yield: 90.8%; mp: 179–181 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.60 (s, 1H, –SH), 13.28 (s, 1H, –NH), 10.13 (s, 1H, –N=CH–), 8.24 (t, J = 4.2 Hz, 1H, Ph–H), 7.85 (t, J = 4.0 Hz, 1H, Ph–H), 7.72 (d, J = 8.0 Hz, 1H, Ph–H), 7.59 (d, J = 5.2 Hz, 3H, Ph–H), 7.34 (t, J = 7.6 Hz, 1H, Ph–H), 7.26 (t, J = 7.6 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 165.2, 163.5, 142.2, 139.4, 138.8, 134.9, 134.0, 131.7, 129.3, 128.9, 126.1, 123.0, 112.7; FT-IR (KBr) ν/cm^{-1}: 3383, 3246, 2424, 1645, 1588, 1529, 1479, 748, 528; ESI-MS m/z: 399.0, 401.0 [M+H]$^+$, 421.1, 423.0 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((4-fluorobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9k): White solid; yield: 94.6%; mp: 203–204 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.54 (s, 1H, –SH), 13.31 (s, 1H, –NH), 9.49 (s, 1H, –N=CH–), 8.06 (dd, J_1 = 6.0 Hz, J_2 = 8.4 Hz, 2H, Ph–H), 7.66 (d, J = 8.0 Hz, 1H, Ph–H), 7.58 (d, J = 8.0 Hz, 1H, Ph–H), 7.45 (t, J = 8.8 Hz, 2H, Ph–H), 7.33 (t, J = 7.6 Hz, 1H, Ph–H), 7.22

(t, J = 8.2 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 167.9, 163.6, 163.4, 141.4, 139.4, 138.4, 131.7, 128.7, 122.5, 116.5, 112.5; FT-IR (KBr) ν/cm^{-1}: 3405, 2418, 1602, 1585, 1510, 1475, 1151, 834, 745; ESI-MS m/z: 339.1 [M+H]$^+$, 361.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((4-chlorobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9l): Yellow solid; yield: 89.9%; mp: 153–159 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.54 (s, 1H, –SH), 13.32 (s, 1H, –NH), 9.53 (s, 1H, –N=CH–), 8.01 (d, J = 8.4 Hz, 2H, Ph–H), 7.68 (d, J = 8.4 Hz, 2H, Ph–H), 7.44 (m, 1H, Ph–H), 7.33 (t, J = 7.6 Hz, 1H, Ph–H), 7.24 (t, 1H, J = 8.4 Hz, Ph–H), 7.22 (t, J = 8.4 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 166.0, 163.8, 141.8, 141.1, 138.8, 138.1, 131.3, 131.2, 129.8, 123.0, 111.8; FT-IR (KBr) ν/cm^{-1}: 3385, 3251, 2415, 1657, 1593, 1564, 1531, 1488, 827, 745; ESI-MS m/z: 355.1 [M+H]$^+$, 389.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((2,4-dichlorobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9m): Yellow solid; yield: 94.0%; mp: 167–169 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.54 (s, 1H, –SH), 13.29 (s, 1H, –NH), 10.17 (s, 1H, –N=CH–), 8.25 (d, J = 8.4 Hz, 1H, Ph–H), 7.90 (s, 1H, Ph–H), 7.69 (m, 3H, Ph–H), 7.33 (d, J = 6.8 Hz, 1H, Ph–H), 7.28 (d, J = 7.6 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 163.5, 161.7, 142.2, 139.3, 138.7, 136.5, 134.7, 130.2, 130.1, 129.2, 128.8, 121.1, 112.6; FT-IR (KBr) ν/cm^{-1}: 3399, 3132, 2361, 1649, 1587, 1555, 1513, 1489, 864, 825, 737; ESI-MS m/z: 389.1 [M+H]$^+$, 411.1 [M+Na]$^+$; HR-MS: calcd for $C_{16}H_{11}Cl_2N_6S$ [M+H]$^+$ 389.0143, found 389.0144.

5-(1H-Benzimidazol-2-yl)-4-((4-nitrobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9n): Red brown solid; yield: 95.6%; mp: 198–199 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.63 (s, 1H, –SH), 13.36 (s, 1H, –NH), 9.80 (s, 1H, –N=CH–), 8.42 (d, J = 8.4 Hz, 2H, Ph–H), 8.25 (d, J = 8.4 Hz, 2H, Ph–H), 7.67 (d, J = 7.6 Hz, 1H, Ph–H), 7.58 (t, J = 7.6 Hz, 1H, Ph–H), 7.33 (t, 1H, J = 7.6 Hz, Ph–H), 7.25 (t, J = 7.4 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 166.4, 163.8, 150.1, 141.9, 139.4, 138.7, 138.2, 128.2, 124.7, 124.5, 111.8; FT-IR (KBr) ν/cm^{-1}: 3396, 2361, 1646, 1516, 1476, 1341, 846, 749; ESI-MS m/z: 366.1 [M+H]$^+$, 388.1 [M+Na]$^+$; HR-MS: calcd for $C_{16}H_{12}N_7O_2S$ [M+H]$^+$ 366.0773, found 366.0771.

5-(1H-Benzimidazol-2-yl)-4-((3-nitrobenzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9o): Light yellow solid; yield: 87.3%; mp: 186–187 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.63 (s, 1H, –SH), 13.38 (s, 1H, –NH), 9.79 (s, 1H, –N=CH–), 8.81 (s, 1H, Ph–H), 8.49 (d, J = 8.4 Hz, 1H, Ph–H), 8.42 (d, J = 8.0 Hz, 1H, Ph–H), 7.90 (t, J = 8.0 Hz, 1H, Ph–H), 7.67 (t, J = 8.4 Hz, 1H, Ph–H), 7.58 (t, 1H, J = 8.0 Hz, Ph–H), 7.34 (t, J = 7.6 Hz, 1H, Ph–H), 7.25 (t, J = 7.6 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 166.6, 163.8, 148.7, 143.2, 139.5, 138.7, 135.4, 134.1, 131.3, 127.4, 123.7, 121.7, 111.7; FT-IR (KBr) ν/cm^{-1}: 3377, 3269, 2361, 1648, 1618, 1535, 1487, 1335, 806, 769, 692; ESI-MS m/z: 366.1 [M+H]$^+$, 388.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-(benzylideneamino)-4H-[1,2,4]triazole-3-thiol (Compound 9p): Light yellow solid; yield: 90.4%; mp: 197–199 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.55 (s, 1H, –SH), 13.32 (s, 1H, –NH), 9.49 (s, 1H, –N=CH–), 7.98 (d, J = 7.2 Hz, 2H, Ph–H), 7.67 (m, 2H, Ph–H), 7.61 (d, J = 7.6 Hz, 2H, Ph–H), 7.34 (m, 2H, Ph–H), 7.24 (t, J = 7.6 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 165.9, 163.9, 141.9, 141.2, 138.8, 133.4, 132.4, 129.6, 129.4, 124.0, 111.9; FT-IR (KBr) ν/cm^{-1}: 3378, 3269, 2362, 1648, 1597, 1572, 1482, 746, 723; ESI-MS m/z: 321.2 [M+H]$^+$, 343.1 [M+Na]$^+$.

5-(1H-Benzimidazol-2-yl)-4-((1-naphthalzylidene)amino)-4H-[1,2,4]triazole-3-thiol (Compound 9q): Light yellow solid; yield: 86.7%; mp: 234–235 °C; ^{1}H NMR (DMSO-d_6) δ/ppm: 14.60 (s, 1H, –SH), 13.42 (s, 1H, –NH), 10.16 (s, 1H, –N=CH–),

9.05 (d, J = 8.0 Hz, 1H, Ph–H), 8.24 (d, J = 8.4 Hz, 1H, Ph–H), 8.20 (d, J = 7.2 Hz, 1H, Ph–H), 8.09 (t, J = 4.8 Hz, 1H, Ph–H), 7.71 (m, 4H, Ph–H), 7.60 (d, J = 8.0 Hz, 1H, Ph–H), 7.34 (t, J = 7.4 Hz, 1H, Ph–H), 7.26 (t, J = 7.8 Hz, 1H, Ph–H); ^{13}C NMR (DMSO-d_6) δ/ppm: 168.2, 163.9, 144.4, 141.8, 139.8, 133.9, 133.7, 131.2, 130.8, 129.3, 128.4, 128.3, 127.2, 126.0, 125.4, 123.8, 112.6; FT-IR (KBr) ν/cm^{-1}: 3383, 3230, 2410, 1651, 1604, 1574, 1516, 1467, 745; ESI-MS m/z: 371.1 $[M+H]^+$, 393.1 $[M+Na]^+$.

REFERENCES

1. Narasimhan, B.; Sharma, D.; Kumar, P. *Med. Chem. Res.* **2012,** 21(3), 269-283.
2. Patel, R. V.; Patel, P. K.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. *Eur. J. Med. Chem.* **2012,** 53, 41-51.
3. Mavrova, A. T.; Wesselinova, D.; Vassilev, N.; Tsenov, J. A. *Eur. J. Med. Chem.* **2011,** 46, 3362-3367.
4. Tonelli, M.; Simone, M.; Tasso, B.; Novelli, F.; Boido, V.; Sparatore, F.; Paglietti, G.; Pricl, S.; Giliberti, G.; Blois, S.; Ibba, C.; Sanna, G.; Loddo, R.; La Colla, P. *Bioorg. Med. Chem.* **2010,** 18(8), 2937-2953.
5. Kaushik, D.; Khan, S. A.; Chawla, G. *Med. Chem. Res.* **2012,** 21(4), 459-467.
6. Kazimierczuk, Z.; Andrzejewska, M.; Kaustova, J.; Klimešova, V. *Eur. J. Med. Chem.* **2005,** 40, 203-208.
7. Hazelton, J. C.; Iddon, B.; Suschitzky, H.; Woolley Ley, H. *Tetrahedron* **1995,** 51, 10771-10794.
8. Sahoo, P. K.; Sharma, R.; Pattanayak, P. *Med. Chem. Res.* **2010,** 19, 127-135.
9. Gupta, A. K.; Prachand, S.; Patel, A.; Jain, S. *Int. J. Pharm. & Life Sci.* **2012,** 3, 1848-1857.
10. Demirbas, N.; Ugurluoglu, R.; Demirbas, A. *Bioorg. Med. Chem.* **2002,** 10, 3717-3723.
11. Upmanyu, N.; Gupta, J. K.; Shah, K.; Mishra, P. *J. Pharm. Biomed. Anal.* **2011,** 3, 259-265.
12. Almasirad, A.; Shafiee, A.; Abdollahi, M.; Noeparast, A.; Shahrokhinejad, N.; Vousooghi, N.; Tabatabai, S. A.; Khorasani, R. *Med. Chem. Res.* **2011,** 20(4), 435-442.
13. Aniket, K.; Mrunmayee, P. T.; Vithal, M. K.; Shweta, D.; Vilasrao, K. *Int. J. Chem. Tech. Res.* **2009,** 1, 696-701.
14. Todoulou, O. G.; Papadakivaliraki, A. E.; Ikeda, S.; Declercq, E. *Eur. J. Med. Chem.* **1994,** 29, 611-620.
15. Al-Soud, Y. A. *Phosphorus Sulfur Silicon Relat. Elem.* **2008,** 183, 2021-2036.
16. Kane, J. M.; Dudley, M. W.; Sorensen, S. M.; Miller, F. P. *J. Med. Chem.* **1988,** 31, 1253-1258.
17. Joseph, J.; Nagashri, K. *Appl. Biochem. Biotechnol.* **2012,** 167, 1446-1458.
18. Alam, M. S.; Choi, J.-H.; Lee, D.-U. *Bio. Med. Chem.* **2012,** 20, 4103-4108.
19. Jhaumeer-Laulloo, S.; Bhowon, M. G.; Mungur, S.; Maho-moodally, M. F.; Subratty, A. H. *Med. Chem.* **2012,** 8, 409-414.
20. Al-Masoudi, N. A.; Aziz, N. M.; Mohammed, A. T. *Phosphorus Sulfur Silicon Relat. Elem.* **2009,** 184, 2891-2901.
21. Cansız, A.; Koparır, M.; Demirdağ, A. *Molecules* **2004,** 9, 204-212.
22. Hu, G. Q.; Dong, X. L.; Xie, S. Q.; Huang, W. L. *Acta Pharm. Sinica.* **2008,** 43, 50-53.
23. Thakurdesai, P. A.; Wadodkar, S. G.; Chopade, C. T. *Pharmacologyonline*. **2007,** 1, 314-329.
24. Sabri, S. S.; El-Abadelah, M. M.; Yasin, H. A. *J. Heterocycl. Chem.* **1987,** 24, 165-169.