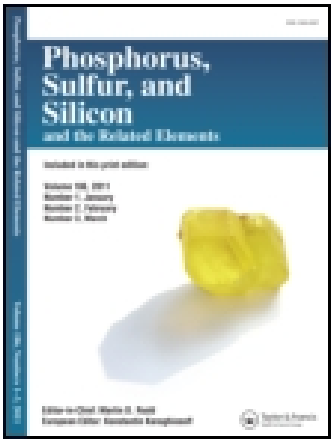

Phosphorus, Sulfur, and Silicon and the Related Elements

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Efficient Synthesis of Novel 3-[5-(1H-Benzimidazol-2-Ylmethanesulfonyl)-4-Phenyl-4H-(1,2,4)Triazol-3-Yl]-1H-(1,8)Naphthyridin-4-One Derivatives

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EFFICIENT SYNTHESIS OF NOVEL 3-[5-(1H-BENZIMIDAZOL-2-YLMETHANESULFONYL)-4-PHENYL-4H-(1,2,4)TRIAZOL-3-YL]-1H-(1,8)NAPHTHYRIDIN-4-ONE DERIVATIVES

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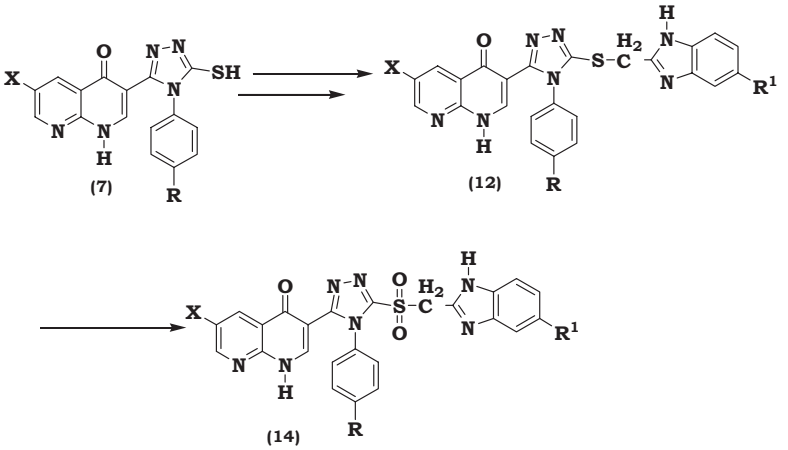
GRAPHICAL ABSTRACT



Abstract *of 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carbohydrazide (**4**) with substituted phenyl isothiocyanates (**5**) in ethanol under reflux for 30 min gave thiosemicarbazide derivatives **6**, which on cyclization in 2N NaOH under refluxing conditions for 1 h resulted in 3-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-1,8-naphthyridin-4(1H)-one (**7**). Alternatively, **7** could also be prepared from following sequence of reactions, i.e., **4** → 8 → **7**. In another sequence of reactions, condensation of **7** with chloroacetic acid in dimethylformamide (DMF) and K_2CO_3 as a mild base at 120 °C for 2 h resulted in 2-((5-(1,4-dihydro-4-oxo-1,8-naphthyridin-3-yl)-4-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl)acetic acid (**10**). The latter, on reaction with substituted o-phenylenediamine (**11**) in 6N HCl for 4 h yielded 3-(5-((1H-benzo[d]imidazol-2-yl)methylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-1,8-naphthyridin-4(1H)-one (**12**). Alternatively, **12** could also be prepared by reacting **7** with **13** in DMF and K_2CO_3 as a mild base*

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*at 120 °C for 2 h, followed by oxidation with H_2O_2 resulting in the corresponding sulfonyl derivatives **14**.*

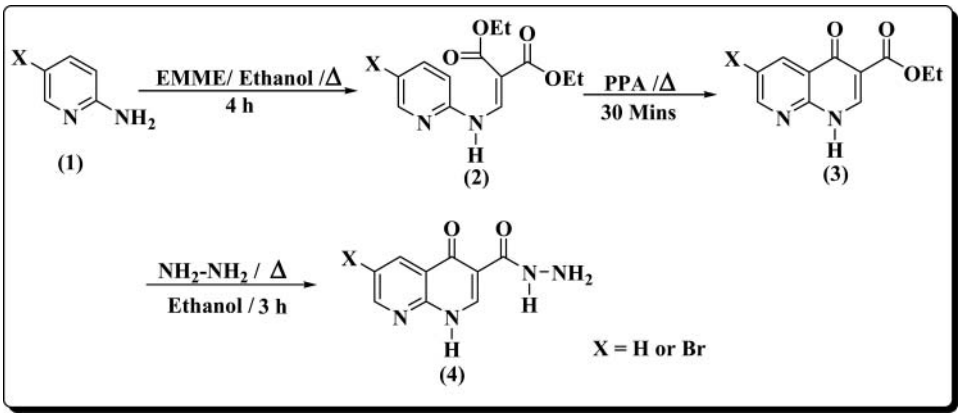
Keywords Naphthyridine acid hydrazide; phenyl isothiocyanate; thiosemicarbazide; chloroacetic acid; o-phenylenediamine; H_2O_2

INTRODUCTION

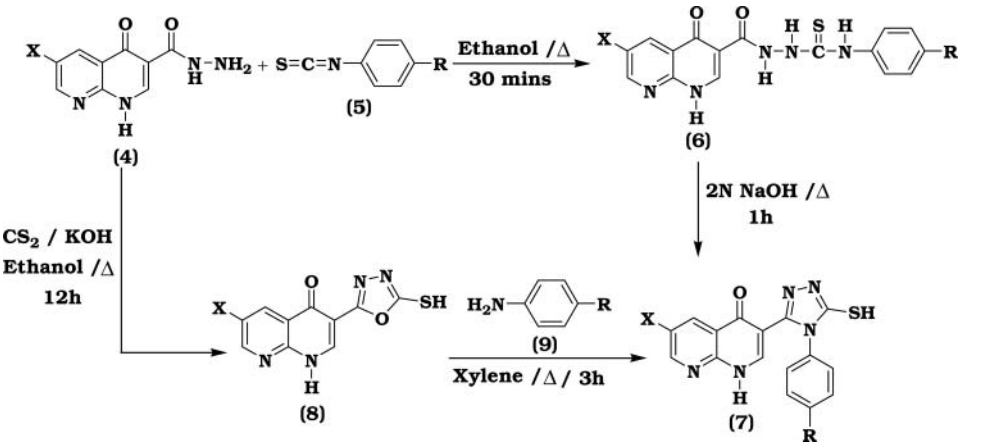
Naphthyridine derivatives have a wide spectrum of biological activity.[1] Drugs containing naphthyridine nucleus are being widely used for the diagnostics and chemotherapy of various infectious diseases.[2] The 1,2,4-triazole derivatives possess a large number of biological activities such as antibacterial,[3] antifungal,[4] diuretic,[5] and anticonvulsant.[6] These compounds have a wide range of applications in the area of pharmacology.[7] Therefore, a variety of methods have been reported[8] for the synthesis of these type of heterocyclic compounds. New challenging problems have prompted researchers to develop more efficient molecules, among which 1,2,4-triazoles play a prominent role.[9,10] According to literature reports, compounds having a benzimidazole moiety are reported to possess a number of interesting biological activities, such as antimicrobial,[11] anticancer,[12] and anthelmentic.[13] In view of these observations, we report herein, the syntheses of novel naphthyridine-appended 1,2,4-triazole derivatives, as new chemical entities that may posses useful biological activities.

RESULTS AND DISCUSSION

Commercially available 2-aminopyridine (**1**, i.e., X = H or Br) was condensed with ethoxymethylenemalonic ester (also commercially available) in ethanol under refluxing conditions for 4 h yielding the previously known[14] 4-ethoxy-3-oxo-2(pyridine-2-ylaminomethylene)-butyric acid ethyl ester (**2**, i.e., X = H or Br), which on thermal cyclization in freshly prepared hot polyphosphoric acid (PPA) for 30 min resulted in 4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (**3**, i.e., X = H or Br), also known earlier.[14] Treatment of **3** with hydrazine hydrate in ethanol for 3 h yielded **4**[15] (i.e., X = H or Br) (Scheme 1), the starting material used for further transformations in the present work.



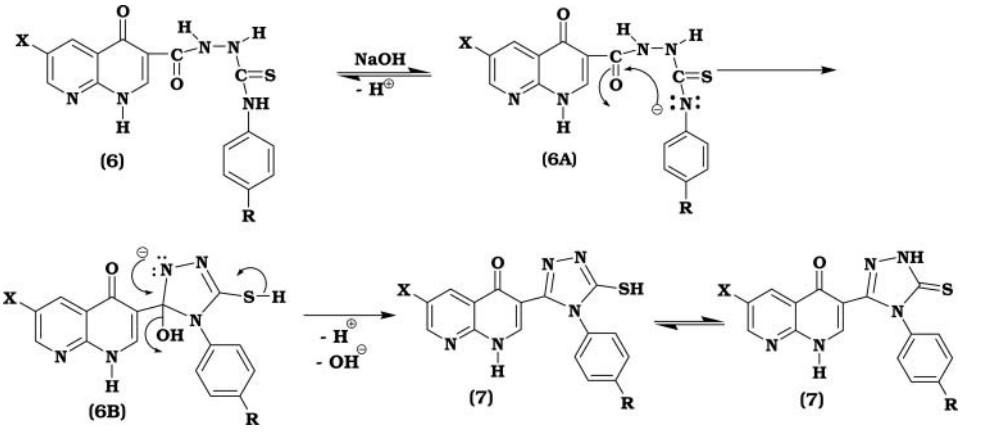
Scheme 1



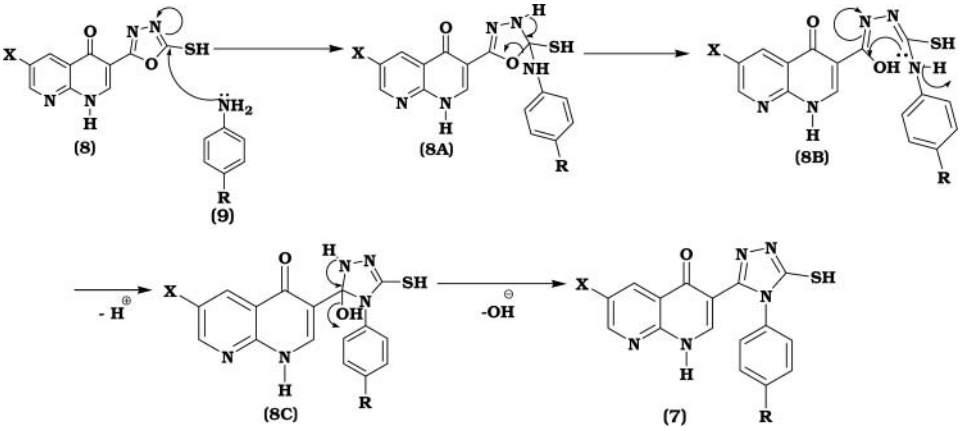
Scheme 2

The reaction of 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carbohydrazide (**4**) with phenyl isothiocyanate (**5**) in refluxing ethanol for 30 min gave the corresponding thiosemicarbazide derivatives **6**. The structures of the products obtained were assigned on the basis of their spectral and analytical data (see Experimental Section). **6** on treatment with 2N NaOH under refluxing conditions for 1 h gave products, which have been characterized as 3-(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-1,8-naphthyridin-4(1H)-one (**7**). The latter could also be prepared by the reaction of 1,8-naphthyridine acid hydrazide (**4**) with CS_2 in ethanolic KOH under refluxing conditions for 12 h giving the previously reported[16] 3-(5-mercapto-1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1H)-one (**8**), which on reaction with substituted anilines (**9**) in xylene under refluxing conditions for 3 h gave **7**. The structures of the products thus obtained were assigned on the basis of their identity (i.e., m.p., m.m.p, Co-TLC, and IR) with those of the same compounds obtained in the earlier route (i.e., $\mathbf{4} + \mathbf{5} \rightarrow \mathbf{6} \rightarrow \mathbf{7}$) .

The conversion of **6** to **7** might appear to follow the mechanism shown in Scheme 3. The mechanism, probably, involves the reversible formation of the intermediary anion



Scheme 3



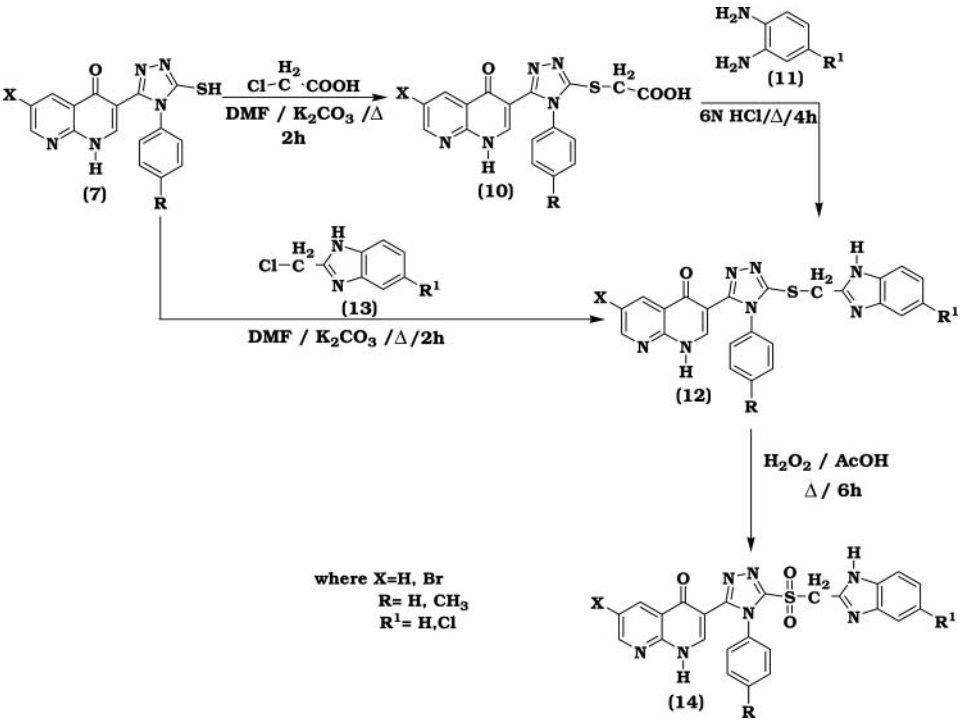
Scheme 4

6A that undergoes intramolecular electrophilic attack by the carbonyl carbon leading to the cyclic intermediate **6B**. The latter, then, loses a molecule of water giving **7**, aromatization being the driving force for the last step of the reaction (a similar mechanism was reported[17] in the literature by Cretu et al. for the synthesis of 1,2,4-triazole-3-thiones).

Once again, the conversion of **8** to **7** by reaction with **9** seems to follow the mechanism given in Scheme 4. This mechanism, probably, involves the nucleophilic attack of aniline (**9**) on α-carbon atom of the oxadiazole ring of **8** resulting in the formation of the intermediate **8A** that cyclizes intra-molecularly to form the intermediates **8B** and then **8C**, which, of course, loses a molecule of water to form **7**, aromatization leading to stability being the driving force for the last step of this mechanism sequence (Similar mechanism was reported[18] in the literature by Padmavathi et al. for the synthesis of 3,5-bis(arylsulfonylmethyl)-4-amino-1,2,4-triazoles).

In another sequence of reactions, **7** on treatment with chloroacetic acid in dimethylformamide (DMF) containing K_2CO_3 as a mild base at 120 °C for 2 h followed by simple processing gave a product that has been characterized as 2-((5-(1,4-dihydro-4-oxo-1,8-naphthyridin-3-yl)-4-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl)acetic acid (**10**). The structure of **10** was assigned on the basis of their spectral and analytical data (see Experimental Section). The compound **10** on reaction with substituted o-phenylenediamines (**11**) in 6N HCl under refluxing conditions for 4h resulted in 3-(5-((1H-benzo[d]imidazol-2-yl)methylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-1,8-naphthyridin-4(1H)-one (**12**). Alternatively, **12** could also be synthesized by reacting **7** with 2-chloromethylbenzimidazole (**13**) in DMF containing K_2CO_3 as a mild base at 120 °C for 2h. The structures of the products obtained in this route were assigned based on their identity (i.e., m.p., m.m.p., Co-TLC, and IR) with those of the same compounds obtained in the earlier route (**7** → **10** → **12**). the compound **13** required in this work were obtained from **11** and chloroacetic acid using a previously reported method.[19]

Oxidation of **12** with H_2O_2 (30%) in acetic acid at 100 °C for 6 h gave 3-(5-((1H-benzo[d]imidazol-2-yl)methylsulfonyl)-4-phenyl-4H-1,2,4-triazol-3-yl)-1,8-naphthyridin-4(1H)-one (**14**). The structures of **14** were assigned on the basis of their spectral and analytical data (see Experimental Section) .



Scheme 5

EXPERIMENTAL SECTION

All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points are uncorrected and were determined using open capillary tubes in a sulfuric acid bath. TLC analyses were done on silica gel G and spotting was done using Iodine/UV lamp. IR spectra were recorded on a Perkin–Elmer model 1000 instrument in KBr phase. ^{1}H NMR were recorded in $CDCl_3$/DMSO using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on Agilent – LC-MS instrument giving only $M^{+\cdot}+1$ or $M^{+\cdot}-1$. Elemental analyses were performed by Varian 3LV analyzer series CHN analyzer and are reported in terms of percentage for C, H, and N only.

Preparation of 6 from 4 and 5

A mixture of **4** (10 mM), **5** (10 mM), and ethanol (25 mL) was refluxed for 1 h. At the end of this period, the reaction mixture was poured into ice-cold water (25 mL) and stirred for 10 min. The separated solid was filtered, washed with water (25 mL) and dried. The crude product was recrystallized from hot ethanol to obtain pure **6**.

6a (i.e., 6, X = H, R = H): Yield: 2.40 g (70%); m.p. 184–186 °C; IR (KBr): 3520–2810 cm^{-1} (broad, medium, –NH), 1724 cm^{-1} and 1700 cm^{-1}(strong, sharp, twin peaks due to symmetric and asymmetric stretchings of –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 7.09–8.30 (m, 8H, Ar–**H**, five protons of the phenyl ring and three protons of the pyridine ring), 8.74 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 9.05 (s, 1H, –N**H**), 9.68 (s,

1H, –N**H**), 9.80 (s, 1H, –N**H**), 10.55 (s, 1H, pyridine –N**H**, D_2O exchangeable); ^{13}C NMR (DMSO d_6/TMS): δ 94.90, 108.31, 117.69, 125.95, 126.30, 126.45, 126.55, 128.50, 128.63, 134.63, 140.26, 140. 91, 144.92, 163.19, 166.34, 177. 75; MS: *m/z* 340 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}N_5O_2S$: C, 56.63; H, 3.86; N, 20.64, Found: C, 56.59; H, 3.84; N, 20.60.

6b (i.e., 6, X = Br, R = H): Yield: 2.90 g (69%); m.p. 191–193 °C; IR (KBr): 3550–3005 cm^{-1} (broad, medium, –NH–), 1736 and 1724 cm^{-1} (strong, sharp, twin peaks due to symmetric and asymmetric stretchings of –CO–); ^1H NMR (DMSO d_6/TMS): δ 7.19–8.34 (m, 7H, Ar–**H**), 8.72 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 9.15 (s, 1H, –N**H**), 9.70 (s, 1H, –N**H**), 9.82 (s, 1H, –N**H**), 10.25 (s, 1H, pyridine –N**H**, D_2O exchangeable); MS: *m/z* 419 $[M+H]^+$. Anal. Calcd for $C_{16}H_{12}$ BrN_5O_2S: C, 45.94; H, 2.89; N, 16.74. Found: C, 45.90; H, 2.84; N, 16.70.

6c (i.e., 6, X = H, R = CH_3): Yield: 2.48 g (70%); m.p. 200–202 °C; IR (KBr): 3492–3210 cm^{-1} (broad, medium, –NH–), 1720 and 1702 cm^{-1} (strong, sharp, twin peaks due to symmetric and asymmetric stretchings of –CO–); ^1H NMR (DMSO d_6/TMS): δ 2.70 (s, 3H, –C**H**$_3$), 7.29–8.45 (m, 8H, Ar–**H**), 8.66 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 9.20 (s, 1H, –N**H**), 9.65 (s, 1H, –N**H**), 9.89 (s, 1H, –N**H**), 10.40 (s, 1H, pyridine –N**H**, D_2O exchangeable); MS: *m/z* 354 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82. Found: C, 57.72; H, 4.23; N, 19.80.

6d (i.e., 6, X = Br, R = CH_3): Yield: 3.11 g (72%); m.p. 208–210 °C; IR (KBr): 3360–2912 cm^{-1} (broad, medium, –NH–), 1710 and 1699 cm^{-1} (strong, sharp, twin peaks due to symmetric and asymmetric stretchings of –CO–); δ 2.74 (s, 3H, –C**H**$_3$), 7.10–8.18 (m, 7H, Ar–**H**), 8.54 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 9.18 (s, 1H, –N**H**), 9.78 (s, 1H, –N**H**), 9.90 (s, 1H, –N**H**), 11.20 (s, 1H, pyridine –N**H**, D_2O exchangeable); MS: *m/z* 432 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}$ BrN_5O_2S: C, 47.23; H, 3.26; N, 16.26. Found: C, 47.18; H, 3.21; N, 16.21.

Preparation of 7 from 6

A solution of **6** (10 mM) in 2N NaOH (25 mL) was refluxed at 100 °C for 1 h. At the end of this period, the reaction mixture was cooled to RT and neutralized with conc. HCl (5 mL). The separated solid was filtered, washed with water (20 mL) and dried. The crude product was recrystallized with ethanol to obtain pure **7**.

7a (i.e., 7, X = H, R = H): Yield: 2.20 g (69%); m.p. 174–176 °C; IR (KBr): 3420–3205 cm^{-1} (broad, medium, –NH and –SH) and at 1663 cm^{-1}(strong, sharp, –CO–); ^1H– NMR spectrum (DMSO/d_6/TMS) δ 5.40 (s,1H, –S**H**), 7.40–8.30 (m, 8, Ar–**H**, five aryl protons of the phenyl ring and three aryl protons of the pyridine ring), 8.85 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 11.50 (s, 1H, –N**H**, D_2O exchangeable); MS: *m/z* 322 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}N_5OS$: C, 59.80; H, 3.45; N, 21.79. Found: C, 59.72; H, 3.41; N, 21.75.

7b (i.e., 7, X = Br, R = H): Yield: 2.28 g (71%); m.p. 191–193 °C; IR (KBr): 3444–3120 cm^{-1} (broad, medium, –NH– and –SH), 1710 cm^{-1} (strong, sharp, –CO–); ^1H NMR (DMSO d_6/TMS): δ 5.48 (s, 1H, –S**H**), 7.10–8.30 (m, 7**H**, two aryl protons of the pyridine ring + five aryl protons of the benzene ring), 8.70 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 12.58 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 400 $[M+H]^+$. Anal. Calcd for $C_{16}H_{10}$ BrN_5OS: C, 48.01; H, 2.52; N, 17.50. Found: C, 47.98; H, 2.45; N, 17.46.

7c (i.e., 7, X = H, R = CH_3): Yield: 2.35 g (72%); m.p. 180–182 °C; IR (KBr): 3460–3218 cm^{-1} (broad, medium, –NH– and –SH), 1725cm^{-1} (strong, sharp, –CO–); ^1H

NMR (DMSO d_6/TMS): δ 2.43 (s, 3H, –CH_3), 5. 46 (s, 1H, –S**H**), 7.06–8.29 (m, 7**H**, three aryl protons of the pyridine ring + four aryl protons of the benzene ring), 8.88 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 12.15 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 336 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}N_5OS$: C, 60.88; H, 3.91; N, 20.88. Found: C, 60.81; H, 3.88; N, 20.83.

7d (i.e., 7, X = Br, R = CH_3): Yield: 3.15 g (70%); m.p. 196–198 °C; IR (KBr): 3340–2910 cm^{-1} (broad, medium, –NH– and –SH), 1690 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 2.47 (s, 3H, –CH_3), 5. 50 (s, 1H, –S**H**), 7.06–8.38 (m, 6**H**, two aryl protons of the pyridine ring + four aryl protons of the benzene ring), 8.54 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 12.15 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}BrN_5OS$: C, 49.29; H, 2.92; N, 16.90. Found: C, 49.22; H, 2.90; N, 16.86.

Alternate Preparation of 7 from 8 and 9

A mixture of **8** (10 mM), **9** (10 mM) and xylene (25 mL) was refluxed for 3 h. At the end of this period, the excess of xylene was distilled off under reduced pressure. The separated solid was filtered, washed with hexane and dried. The crude product was recrystallized from ethanol to obtain pure **7**.

Preparation of 10 from 7

A mixture of **7** (10 mM), chloroacetic acid (10 mM), DMF (20 mL), and K_2CO_3 (5 mM) was refluxed at 120 °C for 2 h. At the end of this period, the reaction mixture was cooled to RT and diluted with water (20 mL). The separated solid was filtered, washed with water (20 mL) and dried. The crude product was recrystallized from ethanol (20 mL) to obtain pure **10**.

10a (i.e., 10, X = H, R = H): Yield: 2.46 g (65%); m.p. 112–114 °C; IR (KBr): 3605–2821 cm^{-1} (broad, medium, –NH), 1730 cm^{-1} (strong, sharp, –O–C=O–), 1698 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO/d_6/TMS) δ 4.13 (s, 2H, –C**H**$_2$), 7.16–7.95 (m, 8H, Ar–**H**, five aryl protons of the phenyl ring and three aryl protons of the pyridine ring), 8.77 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 10.25 (s, 1H, –O**H**, D_2O exchangeable), 11.30 (s,1H, –N**H**, D_2O exchangeable); MS: *m/z* 380 $[M+H]^+$. Anal. Calcd for $C_{18}H_{13}N_5O_3S$: C, 56.98; H, 3.45; N, 18.46. Found: C, 56.93; H, 3.40; N, 18.40.

10b (i.e., 10, X = Br, R = H): Yield: 3.00 g (67%); m.p. 136–138 °C; IR (KBr): 3412–3060 cm^{-1} (broad, medium, –NH– and –OH), 1712cm^{-1} (strong, sharp, –O–C=O), 1697 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 4.15 (s, 3H, –CH_3), 7.16–8.39 (m, 7**H**, two aryl protons of the pyridine ring + five aryl protons of the benzene ring), 8.56 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 10.15 (s, 1H, –O**H**, D_2O exchangeable), 11.55 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 459 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}BrN_5O_3S$: C, 47.17; H, 2.64; N, 15.28. Found: C, 47.10; H, 2.60; N, 15.22.

10c (i.e., 10, X = H, R = CH_3): Yield: 2.48 g (63%); m.p. 156–158 °C; IR (KBr): 3320–2817 cm^{-1} (broad, medium, –NH– and –OH), 1716 cm^{-1} (strong, sharp, –O–C = O), 1680 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 2.43 (s, 3H, –C**H**$_3$), 4.20 (s, 2H, –C**H**$_2$), 7.06–8.29 (m, 7**H**, three aryl protons of the pyridine ring + four aryl protons of the benzene ring), 8.48 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 10.20 (s, 1H, –O**H**, D_2O exchangeable), 11.99 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 394

$[M+H]^+$. Anal. Calcd for $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80. Found: C, 57.97; H, 3.79; N, 17.73.

10d (i.e., 10, X = Br, R = CH_3): Yield: 3.31 g (70%); m.p. 167–169 °C; IR (KBr): 3330–2922 cm^{-1} (broad, medium, –NH– and –OH), 1710 cm^{-1} (strong, sharp, –O–C=O), 1697 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 2.55 (s, 3H, –CH_3), 4.46 (s, 2H, –C**H**$_2$), 7.12–8.38 (m, 6**H**, two aryl protons of the pyridine ring + four aryl protons of the benzene ring), 8.50 (s, 1H, –C**H**, α-proton to the enamine nitrogen), 11.00 (s, 1H, –O**H**, D_2O exchangeable), 12.15 (s, 1**H**, –N**H**, D_2O exchangeable); MS: *m/z* 473 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}$ BrN_5O_3S: C, 48.32; H, 2.99; N, 14.83. Found: C, 48.29; H, 2.95; N, 14.80.

Preparation of 12 from 10 and 11

A mixture of **10** (10 mM), **11** (10 mM), and 6N HCl (25 mL) was refluxed at 100 °C for 4 h. At the end of this period, the reaction mixture was cooled to RT and neutralized with aq. NH_3 (10 mL). The separated solid was filtered, washed with water (25 mL) and dried. The crude product was recrystallized from hot ethanol to obtain **12**.

12a (i.e., 12, X = H, R = H, R^1 = H): Yield: 3.38 g (75%); m.p. 236–238 °C; IR (KBr) 3100–3000 cm^{-1} (broad, medium, –NH), 1692 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO/d_6/TMS) δ 4.50 (s, 2H, –C**H**$_2$), 7.05–8.39 (m, 12H, Ar–**H**), 8.62 (s, 1H, –C**H**, α-proton to enamine nitrogen), 12.20 (s, 1H, pyridine –N**H,** D_2O exchangeable), 14.10 (s, 1H, benzimidazole – N**H**, D_2O exchangeable); ^{13}C NMR (DMSO d_6/TMS): δ 37.29, 111.71, 112.06, 114.91, 124.76, 126.08, 126.42, 126.80, 127.41, 128.02, 128.23, 128.47, 128.56, 132.59, 139.53, 142.94, 144.23, 150.08, 150. 42, 162.66, 164.10, 176.24, 176.54; MS: *m/z* 452 $[M+H]^+$. Anal. Calcd for $C_{24}H_{17}N_7OS$: C, 63.84; H, 3.80; N, 21.72. Found: C, 63.80; H, 3.77; N, 21.70.

12b (i.e., 12, X = Br, R = H, R^1 = H): Yield: 4.00 g (76%); m.p. >250 °C; IR (KBr): 3415–3100 cm^{-1} (broad, medium, –NH–), 1675 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 4.62 (s, 2H, –C**H**$_2$), 7.06–8.39 (m, 11H, Ar–**H**), 8.55 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.95 (s,1H, pyridine –N**H,** D_2O exchangeable), 12.20 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 531 $[M+H]^+$. Anal. Calcd for $C_{24}H_{16}$ BrN_7OS: C, 54.35; H, 3.04; N, 18.49. Found: C, 54.30; H, 2.98; N, 18.46.

12c (i.e., 12, X = H, R = CH_3, R^1 = H): Yield: 3.35 g (72%); m.p. 242–244 °C; IR (KBr): 3490–3050 cm^{-1} (broad, medium, –NH–), 1666 cm^{-1} (strong, sharp, –CO– stretching); ^{1}H NMR (DMSO d_6/TMS): δ 1.23 (s, 3H, –C**H**$_3$), 4.68 (s, 2H, –C**H**$_2$), 7.16–8.39 (m, 11H, Ar–**H**), 8.57 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.55 (s, 1H, pyridine –N**H**, D_2O exchangeable), 12.99 (s, 1H, benzimidazole – N**H**, D_2O exchangeable); MS: *m/z* 466 $[M+H]^+$. Anal. Calcd for $C_{25}H_{19}N_7OS$: C, 64.50; H, 4.11; N, 21.06. Found: C, 64.47; H, 4.02; N, 21.00.

12d (i.e., 12, X = Br, R = CH_3, R^1 = H): Yield: 3.70 g (69%); m.p. 246–248 °C; IR (KBr): 3410–3218 cm^{-1} (broad, medium, –NH–), 1690 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 1.14 (s, 3H, –C**H**$_3$), 4.54 (s, 2H, –C**H**$_2$), 7.16–8.23 (m, 10H, Ar–**H**), 8.59 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.25 (s, 1H, pyridine –N**H**, D_2O exchangeable), 12.45 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 545 $[M+H]^+$. Anal. Calcd for $C_{25}H_{18}$ BrN_7OS: C, 55.15; H, 3.33; N, 18.01. Found: C, 55.12; H, 3.29; N, 17.96.

12e (i.e., 12, X = H, R = H, R^1 = Cl): Yield: 3.88 g (80%); m.p. >250 °C; IR (KBr) 3455–3110 cm^{-1} (broad, medium, –NH), 1690 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR

(DMSO/d_6/TMS) δ 4.56 (s, 2H, –C**H**$_2$), 7.15–8.40 (m, 11H, Ar–**H**), 8.60 (s, 1H, –C**H**, α-proton to enamine nitrogen), 12.00 (s, 1H, pyridine –N**H**, D_2O exchangeable), 13.20 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 486 $[M+H]^+$. Anal. Calcd for $C_{24}H_{16}ClN_7OS$: C, 59.32; H, 3.32; N, 20.18. Found: C, 59.30; H, 3.31; N, 20.15.

12f (i.e., 12, X = Br, R = H, R^1 = Cl): Yield: 4.62 g (82%); m.p. >250 °C; IR (KBr): 3315–3087 cm^{-1} (broad, medium, –NH–), 1680 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 4.58 (s, 2H, –C**H**$_2$), 7.25–8.35 (m, 10H, Ar–**H**), 8.50 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.90 (s,1H, pyridine –N**H**, D_2O exchangeable), 12.65 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 565 $[M+H]^+$. Anal. Calcd for $C_{24}H_{15}BrClN_7OS$: C, 51.03; H, 2.68; N, 17.36. Found: C, 51.00; H, 2.66; N, 17.33.

12g (i.e., 12, X = H, R = CH$_3$, R^1 = Cl): Yield: 3.60 g (72%); m.p. 239–240 °C; IR (KBr): 3410–3034 cm^{-1} (broad, medium, –NH–), 1696 cm^{-1} (strong, sharp, –CO–stretching); ^{1}H NMR (DMSO d_6/TMS): δ 1.21 (s, 3H, –C**H**$_3$), 4.63 (s, 2H, –C**H**$_2$), 7.10–8.45 (m, 10H, Ar–**H**), 8.55 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.00 (s, 1H, pyridine –N**H**, D_2O exchangeable), 13.15 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 500 $[M+H]^+$. Anal. Calcd for $C_{25}H_{18}ClN_7OS$: C, 60.06; H, 3.63; N, 19.61. Found: C, 60.04; H, 4.00; N, 18.98.

12h (i.e., 12, X = Br, R = CH$_3$, R^1 = Cl): Yield: 4.68 g (81%); m.p. >250 °C; IR (KBr): 3210–2987 cm^{-1} (broad, medium, –NH–), 1691 cm^{-1} (strong, sharp, –CO–); ^{1}H NMR (DMSO d_6/TMS): δ 1.16 (s, 3H, –C**H**$_3$), 4.50 (s, 2H, –C**H**$_2$), 7.16–8.26 (m, 9H, Ar–**H**), 8.52 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.55 (s,1H, pyridine –N**H,** D_2O exchangeable), 12.50 (s,1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 579 $[M+H]^+$. Anal. Calcd for $C_{25}H_{17}BrClN_7OS$: C, 51.87; H, 2.96; N, 16.94. Found: C, 51.85; H, 2.93; N, 16.91.

Alternate Synthesis of 12 from 7 and 13

A mixture of **7** (10 mM), **13** (10 mM), DMF (20 mL), and K_2CO_3 was heated in a temperature controlled oil-bath at 120 °C for 2 h. At the end of this period, the reaction mixture was cooled to RT and diluted with water (20 mL). The separated solid was filtered, washed with water (20 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **12**.

Preparation of 14 from 13

To a suspension of **13** (10 mM) in acetic acid (20 mL) was added H_2O_2 (30%) drop-wise at 5–10 °C. After completion of addition, the reaction mixture was heated on water-bath at 100 °C for 6 h. At the end of this period, the reaction mixture was poured into ice-cold water (25 mL). The separated solid was filtered, washed with water (50 mL) and dried. The crude product was recrystallized from hot ethanol to obtain pure **14**.

14a (i.e., 14, X = H, R = H, R^1 = H): Yield: 2.95 g (61%); m.p. 162–164 °C; IR (KBr) 3470–2999 cm^{-1} (broad, medium, –NH), 1662 cm^{-1} (strong, sharp, –CO–), 1332 and 1127 cm^{-1} (strong, sharp, twin peaks due to symmetric and asymmetric stretching vibrations of –SO_2 grouping); ^{1}H NMR (DMSO/d_6/TMS) δ 4.40 (s, 2H, –C**H**$_2$), 7.00–8.40 (m, 12H, Ar–**H**), 9.15 (s, 1H, –C**H**, α-proton to enamine nitrogen), 10.40 (s, 1H, pyridine –N**H**, D_2O exchangeable), 11.00 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); ^{13}C NMR (DMSO d_6/TMS): δ 55.38, 111.87, 118.18, 121.00, 121.71, 123.79, 125.90, 126.72, 126.84, 127.36, 127.51, 130.65, 133.74, 137.67, 139.41, 145.45, 148.19, 148.93, 150.08, 150.42, 162.66,

172.22, 176.54, 176.82; MS: *m/z* 484 $[M+H]^+$. Anal. Calcd for $C_{24}H_{17}N_7O_3S$: C, 59.62; H, 3.54; N, 20.28. Found: C, 59.58; H, 3.49; N, 20.20.

14b (i.e., 14, X = Br, R = H, R^1 = H): Yield: 3.60 g (65%); m.p. 210–212 °C; IR (KBr): 3443–3150 cm^{-1} (broad, medium, –NH–), 1675 cm^{-1} (strong, sharp, –CO–), 1334 and 1128 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 4.68 (s, 2H, –C**H**$_2$), 7.12–8.43 (m, 11H, Ar–**H**), 8.54 (s, 1H, –C**H**), 11.55 (s, 1H, pyridine –N**H**, D_2O exchangeable), 12.55 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 563 $[M+H]^+$. Anal. Calcd for $C_{24}H_{16}BrN_7O_3S$: C, 51.25; H, 2.87; N, 17.43. Found: C, 51.20; H, 2.81; N, 17.38.

14c (i.e., 14, X = H, R = CH_3, R^1 = H): Yield: 3.28 g (66%); m.p. 194–196 °C; IR (KBr): 3450–3100 cm^{-1} (broad, medium, –NH–), 1696 cm^{-1} (strong, sharp, –CO–), 1345 and 1129 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 1.46 (s, 3H, –C**H**$_3$), 4.62 (s, 2H, –C**H**$_2$), 7.10–8.25 (m, 11H, Ar–**H**), 8.61 (s, 1H, –C**H**), 11.25 (s, 1H, pyridine –N**H**, D_2O exchangeable), 13.15 (s, 1H, benzimidazole – N**H**, D_2O exchangeable); MS: *m/z* 498 $[M+H]^+$. Anal. Calcd for $C_{25}H_{19}N_7O_3S$: C, 60.35; H, 3.85; N, 19.71. Found: C, 60.30; H, 3.81; N, 19.67.

14d (i.e., 14, X = Br, R = CH_3, R^1 = H): Yield: 3.90 g (68%); m.p. 206–208 °C; IR (KBr): 3505–3150 cm^{-1} (broad, medium, –NH–), 1690 cm^{-1} (strong, sharp, –CO–), 1332 and 1124 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 1.26 (s, 3H, –C**H**$_3$), 4.54 (s, 2H, –C**H**$_2$), 7.16–8.23 (m, 10H, Ar–**H**), 8.54 (s, 1H, –C**H**), 11.55 (s,1H, pyridine –N**H**, D_2O exchangeable), 12.99 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 577 $[M+H]^+$. Anal. Calcd for $C_{25}H_{18}BrN_7O_3S$: C, 52.09; H, 3.15; N, 17.01. Found: C, 52.06; H, 3.10; N, 16.97.

14e (i.e., 14, X = H, R = H, R^1 = Cl): Yield: 3.60 g (70%); m.p. 189–191 °C; IR (KBr) 3460–3114 cm^{-1} (broad, medium, –NH), 1670 cm^{-1} (strong, sharp, –CO–), 1330 and 1125 cm^{-1} (strong, sharp, twin peaks due to symmetric and asymmetric stretching vibrations of $–SO_2$ grouping); ^{1}H NMR (DMSO/d_6/TMS) δ 4.36 (s, 2H, –C**H**$_2$), 7.10–8.41 (m, 11H, Ar–**H**), 9.11 (s, 1H, –C**H**, α-proton to enamine nitrogen), 10.55 (s, 1H, pyridine –N**H**, D_2O exchangeable), 11.10 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 518 $[M+H]^+$. Anal. Calcd for $C_{24}H_{16}ClN_7O_3S$: C, 55.65; H, 3.11; N, 18.93. Found: C, 55.62; H, 3.10; N, 18.90.

14f (i.e., 14, X = Br, R = H, R^1 = Cl): Yield: 4.35 g (73%); m.p. 210–212 °C; IR (KBr): 3323–3125 cm^{-1} (broad, medium, –NH–), 1685 cm^{-1} (strong, sharp, –CO–), 1332 and 1130 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 4.63 (s, 2H, –C**H**$_2$), 7.10–8.40 (m, 10H, Ar–**H**), 8.55 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.33 (s, 1H, pyridine –N**H**, D_2O exchangeable), 12.55 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 597 $[M+H]^+$. Anal. Calcd for $C_{24}H_{15}BrClN_7O_3S$: C, 48.30; H, 2.53; N, 16.43. Found: C, 48.28; H, 2.50; N, 16.41.

14g (i.e., 14, X = H, R = CH_3, R^1 = Cl): Yield: 3.66 g (69%); m.p. 196–198 °C; IR (KBr): 3430–3120 cm^{-1} (broad, medium, –NH–), 1699 cm^{-1} (strong, sharp, –CO–), 1340 and 1127 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 1.43 (s, 3H, –C**H**$_3$), 4.60 (s, 2H, –C**H**$_2$), 7.15–8.20 (m, 10H, Ar–**H**), 8.60 (s, 1H, –C**H,** α-proton to enamine nitrogen), 11.21 (s, 1H, pyridine –N**H**, D_2O exchangeable), 13.55 (s, 1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 532 $[M+H]^+$. Anal. Calcd for $C_{25}H_{18}ClN_7O_3S$: C, 56.44; H, 3.41; N, 18.43. Found: C, 56.41; H, 3.40; N, 18.42.

14h (i.e., 14, X = Br, R = CH_3, R^1 = Cl): Yield: 4.57 g (75%); m.p. 221–223 °C; IR (KBr): 3420–3105 cm^{-1} (broad, medium, –NH–), 1695 cm^{-1} (strong, sharp, –CO–), 1343 and 1128 cm^{-1} (strong, sharp, due to symmetric and asymmetric stretching vibrations of $–SO_2–$ grouping); ^{1}H NMR (DMSO d_6/TMS): δ 1.24 (s, 3H, –C**H**$_3$), 4.51 (s, 2H, –C**H**$_2$), 7.18–8.29 (m, 9H, Ar–**H**), 8.75 (s, 1H, –C**H**, α-proton to enamine nitrogen), 11.10 (s,1H, pyridine –N**H**, D_2O exchangeable), 13.10 (s,1H, benzimidazole –N**H**, D_2O exchangeable); MS: *m/z* 611 $[M+H]^+$. Anal. Calcd for $C_{25}H_{17}BrClN_7O_3S$: C, 49.15; H, 2.81; N, 16.05. Found: C, 49.11; H, 2.78; N, 16.03.

CONCLUSION

In conclusion, herein this communication, we report, a simple, efficient, and alternate methods for the synthesis of naphthyridinoyl-[1,2,4] triazoles and their subsequent products using different conditions and their oxidation studies in good yields.

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