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Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Synthesis and Evaluation of Biological Activity of Imidazo[2,1-*b*]-1,3,4-thiadiazolo [2,3-*c*]-*s*-triazoles, *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo[4,5-*b*]quinoxaline and *bis*-(*s*-Triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*][imidazo[4,5-*b*]-cyclohexane]-5a,6a-diene)

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Condensation of 4-amino-5-mercapto-3-(α-naphthyl)-*s*-triazole (**1**) with cyanogen bromide gives 6-amino-3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (**2**) which on condensation with chloranil yields 3,9-di-(α-naphthyl)-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo[4,5-*b*]cyclohexane]-5a,6a-diene) (**3**). 3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo[4,5-*b*]quinoxaline (**4**) is obtained by a similar condensation of (**2**) with 2,3-dichloroquinoxaline. The reaction of (**2**) with α-haloketones followed by bromination affords 7-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles (**5**) and their 6-bromo analogues **6** respectively. The structures of all newly synthesized compounds were established on the basis of elemental analyses, IR, ^{1}H-NMR. The antibacterial and antifungal activities of all newly synthesized compounds have also been evaluated.

Key Words: Antimicrobial, Cyanogen bromide, α-Haloketones, Chloranil, 2,3-Dichloroquinoxaline

Introduction

1,2,4-Triazole motif is found in a number of chemotherapeutic agent such as conazole fungicides, triazolobenzodiazepine, rizatriptan and ribavirin (Fig. 1), that find a wide array of biological activities such as anti-fungal,[1] antibacterial,[2] anticonvulsant[3] and anticancer[4] analgesic,[5] antiinflammatory,[6] antiviral,[7] insecticide,[8] antidepressant.[9] 1,3,4-Thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial, antifungal, antiinflammatory,[10] antitubercular[11] and leishmanicidal[12] agents. In the past years, the literature survey is enriched with progressive finding about the synthesis and pharmacological evaluation of fused heterocycles.[10]

Imidazole motif is found in number of chemotherapeutic agents such as etomidate, zolpidem, nafimidone, cimetidine, clodine, pilocarpine and metronidazole (Fig. 2). Imidazole is one of the most fascinating classes of compounds possessing variety of biological activities[13,14] such as anti-HIV, anti-histamine, antibacterial, tranquillizer *etc*. Quinoxaline systems are also important class of compounds that present in certain important biological compounds[15] such as folic acid, riboflavin and pyocyanine.

Encouraged by these observation and in continuation of our earlier studies on the synthesis of biological active heterocyclic compounds,[14,16,17] we report herein, the synthesis of 3,9-di-(α-naphthyl)-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo

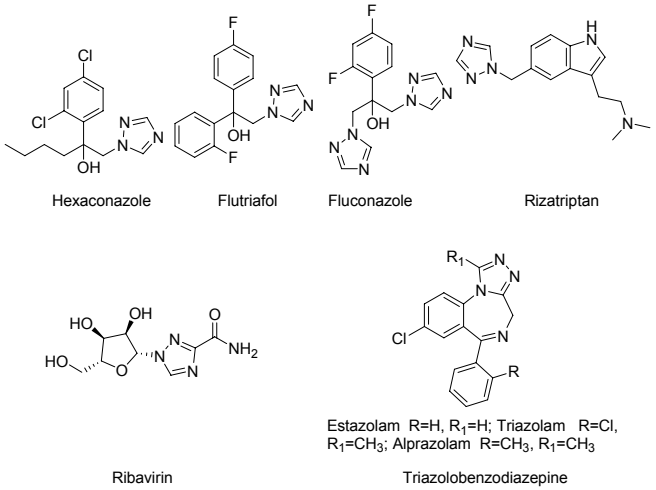


Figure 1. Known drugs having triazole ring.

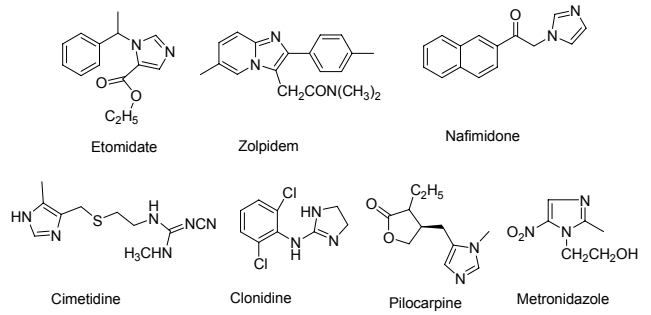


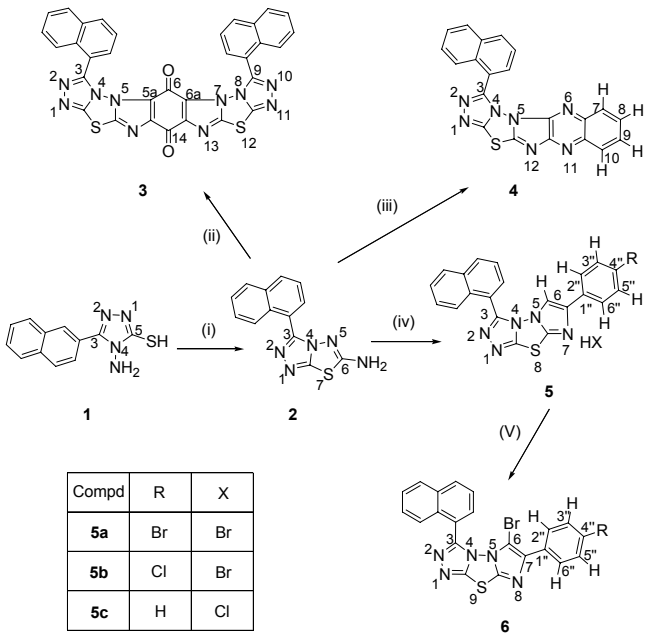
Figure 2. Known drugs having imidazole ring.

[3,2-*b*][imidazo[4,5-*b*]cyclohexane]-5a,6a-diene) (**3**) and 3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo [4,5-*b*]quinoxaline (**4**) and 7-aryl-3-(α-naphthyl)-imidazo[2, 1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole **5** derived from 6-amino-3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (**2**) and biological activity associated with them.

Result and Discussion

The synthetic route of titled compounds is shown in Scheme 1. The required compound 4-amino-3-(α-naphthyl)-5-mercapto-*s*-triazole (**1**) was prepared in excellent yield following the method of Dhaka *et al*.[18] Condensation of **1** with cyanogen bromide afforded 6-amino-3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (**2**). The structural assignment of **2** was supported by elemental analysis, IR and ^{1}H-NMR spectral data. Condensation of **2** with chloranil gave a compound, which was assigned the structure **3** on the basis of spectral data. The appearance of absorption band at 1721 cm^{-1} is in good agreement with system **3**. Condensation of **2** with 2,3-dichloroquinoxaline furnished **4**, another bridgehead heterocyclic system. The structural assignment of **4** was supported by spectral data and elemental analysis (vide Experimental). Condensation of **2** with α-haloketones furnished 7-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles (**5**). The compound **2**, being unsymmetrical, on cyclization with α-haloketones is expected to give 7-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo [2,3-*c*]-*s*-triazoles (**5**) or 6-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles (**7**) or both (Scheme 2), depending on the mode of cyclization.

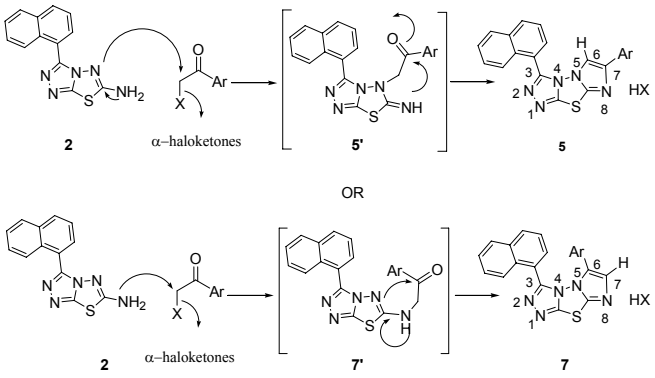
The compound **2**, however, on cyclization gave only one product (TLC). The formation of **5** or **7** could be expected via the intermediated **5′** or **7′** structural isomers, which may be obtained in principal by the initial nucleophillic attack of ring nitrogen or amine nitrogen on α-haloketones respectively. Lack of absorption band in the IR spectra of these compounds (**5** or **7**) in the region 1670 - 1700 cm^{-1} showed the absence of a carbonyl group, thereby suggesting a cyclic structure for **5** or **7**. The appearance of a singlet at δ 6.58 - 6.76 (1H, s, C_6-H) in the ^{1}H-NMR spectrum of these compounds (**5** or **7**) corroborated the cyclic structure. The ^{1}H-NMR spectral data of the cyclized product was not of much help in deciding its structure (**5** or **7**). The ring nitrogen atom, which is directly attached to another nitrogen, is more nucleophillic than amine nitrogen atom because of its greater basicity; hence, isomer **5** should be formed. To conquer this problem, it was planned to take bromination on aryl substituted imidazole ring. Imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles are condensed aromatic system and are very liable to electrophilic substitution reaction as calculated by total charge density (Fig. 3) and localization energy for electrophilic reaction (Fig. 4) (by Marvin Sketch of ChemAxon 1998 -



Compd	R	X
5a	Br	Br
5b	Cl	Br
5c	H	Cl

(i) CNBr; (ii) Chloranil, anhydrous NaOAc, AcOH; (iii) 2,3-Dichloroquinoxaline, anhydrous NaOAc; (iv) *p*-R-$C_6H_4COCH_2X$; (v) Br_2, AcOH, NaOAc

Scheme 1



Scheme 2

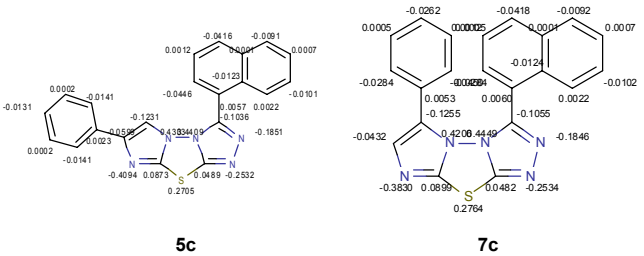


Figure 3. Total charge density of compound **5c** and **7c**.

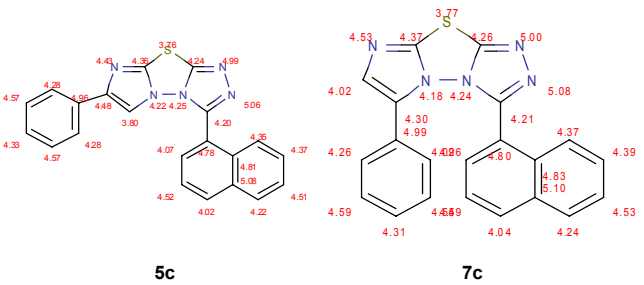


Figure 4. Localization energy of compound **5c** and **7c**.

2008).[19] Localization energy for electrophilic reaction is 3.80 for C_6-H in isomer **5c** which is lees in comparison to 4.02 for C_7-H in isomer **7c**, so **5c** is more reactive towards bromination. Further, it can be supported by the fact that total charge density at C_6-H in isomer **5c** is −0.1231 in comparison to −0.0432 for C_7-H in isomer **7c**. Thus, bromination of **5** yielded 6-bromo derivative and the structural assignment was confirmed by the disappearance of singlet at δ 6.58 - 6.76 due to the C_6-H proton. Hence, it can be claimed with certainty that structural isomer formed during the present reaction was 7-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles (**5**) not the other isomer 6-aryl-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles (**7**).

Biological Result and Discussion

All the newly synthesized compounds, **4**, **5a** (R=Br), **5b** (R=Cl), **5c** (R=H), **6a** (R=Br), **6b** (R=Cl) and **6c** (R=H) were tested for antimicrobial activity against three standard bacterial strains including gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and also for antifungal activity against the fungus *Candida albicans* and *Candida tropicalis*. Antimicrobial activity tests were performed by using a broth micro dilution method.[20] The results illustrated in Table 1 revealed that, all the newly synthesized compounds displayed variable inhibitory effects on the growth of the tested bacteria (Gram positive and Gram-negative) and fungus *Candida albicans* and *Candida tropicalis*. As can be seen in Table 1, compounds **3**, **4**, **5a**, **5b**, **6a** and **6b** showed highest activity against gram-negative bacteria and compounds **4**, **6a** and **6b** showed little activity against gram-positive bacteria. Thus, compounds **4**, **6a** and **6b** exhibited broad-spectrum antibacterial profile against the tested three organisms. Compound **4** exhibited highest antifungal activity against *Candida albicans* (MIC 2 μg/mL) and *Candida tropicalis* (MIC 8 μg/mL). It is also observed that replacement of hydrogen of **5** (C_6-H) by bromine increase the biological activities.

Antimicrobial activity.

Microdilution assays: The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, **4**, **5a** (R=Br), **5b** (R=Cl), **5c** (R=H), **6a** (R=Br), **6b** (R=Cl) and **6c** (R=H), defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards.[20] The inocula of microorganisms (10^6 c.f.u./mL) were prepared from 24 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity.[21] The test compound dissolved in dimethyl sulfoxide (DMSO) was first diluted to the highest concentration (1024 μg/mL) to be tested. Then serial two-fold dilutions were made in concentration ranges from 1 to 1024 μg/mL in 10 mL sterile tubes. A prepared suspension of the standard microorganisms was added to each dilution in a 1:1 ratio. Growth (or its lack) of microorganisms was determined visually after incubation for 24 h at 37 °C. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. The minimal inhibitory concentration (MIC) values were studied for three reference bacterial (*Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*) and two fungal (*Candida albicans* and *Candida tropicalis*) strains. In this case, Ampicillin and Fluconazole were used as standard drugs for comparison in the antimicrobial study. Control experiments using dimethyl sulfoxide were done for antimicrobial activity studies.

Table 1. Minimal inhibitory concentration (MIC) of synthesized compounds against bacterial and fungal species α-halo

S. No.	Compd.	*Microorganisms and MIC (μg/mL)*				
		S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. tropicalis*
1.	**3**	8	8	256	16	32
2.	**4**	4	8	64	2	8
3.	**5a**	8	16	128	4	16
4.	**5b**	8	8	128	32	32
5.	**5c**	64	64	256	64	64
6.	**6a**	4	4	64	4	8
7.	**6b**	4	8	64	16	8
8.	**6c**	16	32	128	32	64
9.	**Ampicillin**	0.5	2	128		
10.	**Fluconazole**				0.5	4

Experimental Section

Melting points were determined on a buchi oil heated melting apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in DMSO-d_6 on Brucker (300 MHz) spectrometer using TMS as internal standard (chemical shift in δ, ppm). IR spectra were taken on a Perkin Elmer 1600, FTIR spectrophotometer using (KBr) pellets. The elemental analyses were performed on a Carlo Erba 1106 elemental analysis. TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant.

3-(α-Naphthyl)-4-amino-5-mercapto-*s*-triazole 1. It was prepared from α-naphthoic acid hydrazide according to the method of Dhaka *et al*[18] in 73% yield, mp 206 °C. (Lit[22]mp 206 °C).

6-Amino-3-(α-naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole 2. A mixture of **2** (6.05 g, 0.025 mole) and cyanogen bromide (5.30 g, 0.05 mole) in absolute ethanol (150 mL) was heated under reflux on a water bath for 6 hr, cooled to room temp, concentrated to one fourth of its original volume and neutralized with potassium carbonate solution. The solid thus separated was filtered and recrystallized from ethanol to give white shiny crystals mp 148 °C, yield 3.5 g (52.43%). IR (KBr): 771,792 (α-substituted naphthyl), 1522 (C-N stretching); 1603, 1627 (C=C & C=N); 3057 (aromatic C-H stretching); 3321, 3412 (N-H stretching). ^{1}H-NMR δ 6.99 (2H, s, NH_2 protons), 7.42 (1H, dd, J = 2.7 Hz, 7.3 Hz), 7.61-7.74 (4H, m), 8.07 (1H, dd, J = 2.0 Hz, 8.1 Hz), 8.46 (1H, dd, J = 2.5 Hz, 7.1 Hz). Anal. Calcd. for $C_{13}H_9N_5S$: C, 58.41; H, 3.39; N, 26.20. Found: C, 58.21; H, 3.60; N, 26.01%.

3,9-Di-(α-naphthyl)-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*][imidazo[4,5-*b*] cyclohexane]-5*a*,6*a*-diene) 3. A solution of **2** (1.335 g, 0.005 mole) in acetic acid (25 mL) was added to a solution of chloranil (0.615 g, 0.0025 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in acetic acid (20 mL) The reaction mixture was heated under reflux for 4 hr. The mixture acquired brownish colouration and a brown colour-

ed solid started separating after about 30 min. after completion of reaction, cooled the reaction mixture and the solid thus separated was filtered, washed thoroughly with water and finally recrystallized from glacial acetic acid, to get brown coloured crystals mp 223 °C, yield 1.0 g (31.55%). IR (KBr): 771, 802 (α-substituted naphthyl), 1518 (C-N stretching); 1571, 1627 (C=C & C=N); 1721 (C=O); 3057 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 7.51 (2H, dd, J = 2.7 Hz, 7.3 Hz), 7.66-7.85 (8H, m), 8.10 (2H, dd, J = 2.3 Hz, 7.5 Hz), 8.45 (2H, dd, J = 2.3 Hz, 7.5 Hz). Anal. Calcd. for $C_{32}H_{14}N_{10}S_2O_2$: C, 60.57; H, 2.21; N, 22.08. Found: C, 60.82; H, 2.14; N, 22.32%.

3-(α-Naphthyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*] imidazo[4,5-*b*]quinoxaline 4. A solution of **2** (1.068 g, 0.004 mole), 2,3-dichloroquinoxaline (0.796 g, 0.004 mole) and anhydrous sodium acetate (0.656 g, 0.008 mole) in absolute ethanol (75 mL) was heated under reflux for 6 hr. The reaction mixture was concentrated, cooled and poured into ice-cold water. A yellow precipitate thus obtained, was filtered off, dried and recrystallized from ethanol to get cream coloured crystals mp 146 °C, yield 0.5 g (31.81%). IR (KBr): 635, 763, 793 (α-substituted naphthyl and 1,2-disubstituted benzene ring); 1577, 1624 (C=C & C=N); 3045 (C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 7.51-8.11 (10H, m), 8.45 (1H, dd, J = 2.3 Hz, 7.5 Hz). Anal. Calcd. for $C_{21}H_{11}N_7S$ C, 64.11; H, 2.82; N, 24.92. Found: C, 64.41; H, 2.90; N, 24.72%.

7-(*p*-Bromophenyl)-3-(α-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole hydrobromide (5a, R=Br, X=Br). A mixture of **2** (2.67 g, 0.01 mole), *p*-bromophenacyl bromide (2.78 g, 0.01 mole) in absolute alcohol (100 mL) was heated under reflux for 6 hr., half concentrated and cooled to room temp. The solid thus separated was filtered and recrystallized from methanol to give yellow crystals. mp > 240 °C, yield 2.35 g (44.59%). IR (KBr): 744, 772, 804 (α-substituted naphthyl and 1,4-disubstituted benzene ring); 1532 (C-N stretching); 1592, 1610 (C=C and C=N); 3046 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6): 6.58 (1H, s, C_6-H); 7.68-8.37 (11H, m, aromatic protons), 8.74 (1H, s, H-Br). Anal. Calcd. for $C_{21}H_{13}Br_2N_5S$: C, 47.82; H, 2.47; N, 13.28. Found: C, 47.69; H, 2.39; N, 13.5%.

Others compounds prepared similarly were **5b (R=Cl, X=Br)** yield 51.87%, mp 236 °C. IR (KBr): 740, 775, 800 (α-substituted naphthyl and 1,4-disubstituted benzene ring); 1522 (C-N stretching); 1588, 1613 (C=C and C=N); 3086 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 6.76 (1H, s, C_6-H); 7.71-8.38 (11H, m, aromatic protons), 8.74 (1H, s, H-Br). Anal. Calcd. for $C_{21}H_{13}BrClN_5S$: C, (52.28); H, (2.70); N, (14.52). Found C, 52.03; H, 2.75; N, 14.72%.

5c (R=H, X=Cl): Yield 55.56%, mp 240 °C. IR (KBr) 740, 805 (α-substituted naphthyl); 1529 (C-N stretching); 1582, 1604 (C=C and C=N); 3075 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 6.72 (1H, s, C_6-H); 7.70-8.38 (11H, m, aromatic protons), 8.56 (1H, s, H-Br). Anal. Calcd. for $C_{21}H_{14}ClN_5S$: C, 62.53; H, 3.47; N, 17.37. Found C, 62.38; H, 3.42; N, 17.30%.

6-Bromo-7-(*p*-bromophenyl)-3-(*α*-naphthyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole (6a, R=Br). To a well stirred solution of **5a** (1.022 g, 0.00194 mole) and anhydrous sodium acetate (0.318 g, 0.00388 mole) in gl. acetic acid (20 mL), bromine (0.1 mL, 0.00194 mole) was added drop wise with constant stirring. The stirring was continued for 30 min. The reaction mixture was cooled and poured onto crushed ice. A yellow coloured solid thus separated was filtered and recrystallized from ethanol to get yellow coloured crystals. Yield 0.1 g (41.6%), mp 208 °C. IR(KBr): 740,778, 810 (α-substituted naphthyl and 1,4-disubstituted benzene ring); 1532 (C-N stretching); 1610, 1628 (C=C and C=N); 3056 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6): 7.5-8.4 (11H, m, aromatic protons). Anal. Calcd. for $C_{21}H_{11}Br_2N_5S$: C, 48.02; H, 2.11; N, 13.33. Found: C, 48.29; H, 2.19; N, 13.18%.

Compounds **6b** and **6c** were prepared similarly. Their characterization data are given below.

6b (R=Cl): yield 67.71%, mp 222 (dec). IR (KBr) 740, 777, 810 (α-substituted naphthyl and 1,4-disubstituted benzene ring); 1510 (C-N stretching); 1599, 1622 (C=C and C=N); 3036 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 7.45-8.44 (11H, m, aromatic protons). Anal. Calcd. for $C_{21}H_{11}BrClN_5S$: C, 52.46; H, 2.31; N, 14.57. Found C, 52.13; H, 2.15; N, 14.72%.

6c (R=H): Yield 67.26%, mp 202 °C. IR (KBr) 736, 781, 813 (α-substituted naphthyl and 1,4-disubstituted benzene ring); 1503 (C-N stretching); 1602, 1617 (C=C and C=N); 3061 (aromatic C-H stretching). ^{1}H-NMR (DMSO-d_6) δ 7.33-8.41 (12H, m, aromatic protons). Anal. Calcd. for $C_{21}H_{12}BrN_5S$: C, 56.51; H, 2.71; N, 15.69. Found C, 56.39; H, 3.03; N, 15.72%.

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