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Original article

Synthesis and antimicrobial activities of some new triazolothiadiazoles bearing 4-methylthiobenzyl moiety

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Abstract

A series of substituted triazolothiadiazoles (**6a–j** and **7a–j**) have been synthesized by condensing 4-amino-3-[4-methylthiobenzyl]-4*H*-1,2,4-triazole-5-thiol (**5**) with substituted aryl furoic acids/aromatic acids in the presence of $POCl_3$. The triazole (**5**) was obtained by the fusion of 4-methylthiophenyl acetic acid (**4**) with thiocarbohydrazide.

The structures of newly synthesized compounds are characterized by elemental analysis, IR, ^1H NMR and mass spectroscopic studies and were screened for their antimicrobial activities. The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.

Keywords: Triazolothiadiazole; Antibacterial; Antifungal; Methylthiobenzyl moiety

1. Introduction

The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention due to the synthetic and effective biological importance. A large number of ring systems containing 1,2,4-triazoles have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, anti-anxiety, antimicrobial agents [1,2] and antimycotic agents such as Fluconazole, Itraconazole and Voriconazole [3,4]. Also there are some known drugs containing 1,2,4-triazole moiety, e.g. Triazolam [5], Alprazalam [6], Etizolam [7], Furacylin [8], Ribavirin [9], Hexaconazole [10], Triadimefon [11], Mycobutanil [12], Rizatriptan [13], Propiconazole [14], and Fluotrimazole [15].

4-Amino-3-substituted-5-mercapto-1,2,4-triazoles by virtue of their ambident nucleophilic centers are good starting materials for the synthesis of several interesting *N*-bridged heterocycles. A variety of biological activities like antibacterial [16–19], antifungal [20,21], antitubercular [22], antimycobacterial [23], anticancer [24,25], diuretic [26,27] and hypoglycemic [28] activities have been reported in mercapto- and thione-substituted 1,2,4-triazole ring system. 1,3,4-Thiadiazole nucleus is associated with a broad spectrum of biological activities possibly by their virtue of pharmacophoric $\rangle$N–C=S moiety [29,30].

Review of literature indicated that *N*-bridged heterocycles derived from 1,2,4-triazoles bearing methylthiobenzyl moiety possess antimicrobial activities [31,32]. Prompted by the pharmacological importance of these molecules, it was decided to synthesize some new triazolothiadiazoles and study their biological activities. In the present investigation a new

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1,2,4-triazole system carrying 4-methylthiobenzyl moiety at position 3 was selected as the starting material and the newly synthesized compounds were screened for their antimicrobial activities. The results of such studies are discussed herein.

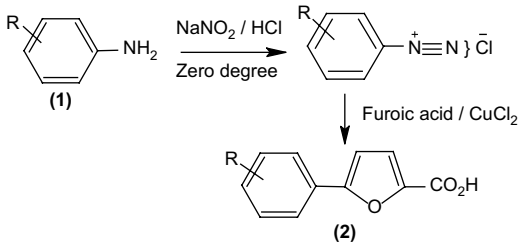
2. Chemistry

Thiocarbohydrazide was prepared from hydrazine hydrate and carbon disulfide following the literature method [33]. Substituted aryl furoic acids (**2**) were prepared according to the literature method [34] (Scheme 1). 4-Methylthiophenyl acetonitrile (**3**) was obtained commercially and converted into 4-methylthiophenyl acetic acid (**4**) by alkaline hydrolysis (Scheme 2). The acid (**4**) was fused with thiocarbohydrazide to get the triazole (**5**). Condensation of the triazole (**5**) with various substituted aromatic/aryl furoic acids in the presence of phosphorus oxychloride afforded a series of 3-[4-methylthiobenzyl]-6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**6a–j**) and 3-[4-methylthiobenzyl]-6-(5-phenyl-2-furyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**7a–j**) (Scheme 3). The newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR and mass spectral data. The characterization data has been given in Table 1.

3. Biological activity

3.1. Antibacterial activity

The newly synthesized compounds **6a–j** and **7a–j** were screened for their antibacterial activities against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25922), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumoniae* bacterial strains by the disc diffusion method [35,36]. The discs measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations such as <10 μg/ml and >10 μg/ml in *N*,*N* dimethyl formamide. One milliliter containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicates in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ciprofloxacin was used as standard drug at a concentration of 10 μg/ml. Solvent and growth controls were kept separately and the zone of inhibition was noted. The results of such studies are given in Table 2.



Scheme 1.

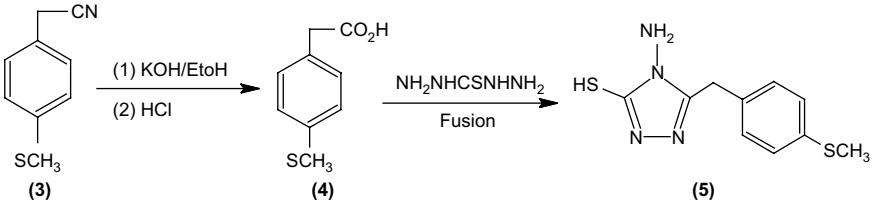
3.2. Antifungal activity

All the newly synthesized compounds **6a–j** and **7a–j** were screened for their antifungal activity against *Candida albicans* (NICM No. 300), *Aspergillus fumigatus* (NICM No. 902), *Aspergillus flavus* (NICM No. 524) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [37,38]. Sabouraud agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Agar medium of 20 ml was poured into each Petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made on this seeded agar plates and <10 μg/ml and >10 μg/ml of the test compounds in *N*,*N* dimethyl formamide were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicates and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Fluconazole as standard. The minimum inhibitory concentration (MIC) for Fluconazole in DMF was in the range of 0.01–16 μg/ml against the tested species. Results of screening studies are given in Table 3.

4. Results and discussion

The investigation of the antibacterial and antifungal screening studies revealed that all the tested compounds **6a–j** and **7a–j** showed moderate to good inhibition in DMSO. Compounds **6a**, **6b**, **6c**, **6e**, **6h**, **6j**, **7b**, **7c**, **7d**, and **7j** showed comparatively good activity against all the bacterial strains. The good activity can be attributed to the presence of pharmacologically active groups 2,3,4-trichloro, 4-methylthio, 2,4-dichloro-5-fluoro, which are directly attached to the phenyl ring of the triazole system, and the groups 4-nitro, 4-fluoro, 2-nitro-4-chloro, 2-trifluoromethyl, 4-chloro, 4-methyl which are directly attached to the arylfuryl ring. The presence of groups 4-hydroxy, 4-bromo, 2,4-dichloro on the phenyl ring and the groups 2,4,5-trichloro, 4-nitro, 4-bromo and 2-nitro-4-methoxy was responsible for the decrease in activity. Compounds **7g** and **7h** showed moderate activity due to the presence of 2,5-dichloro and 4-methoxy groups.

Compounds **6b**, **6c**, **6f**, **6j**, **7b**, **7c**, **7f**, **7h** showed comparatively good activity against all the tested fungal strains. The groups 4-methylthio, 2,4-dichloro-5-fluoro and 2-chloro-4-nitro which are directly attached to the phenyl ring of the triazole system were responsible for the good antifungal activity. The groups 4-chloro-2-nitro, 2-trifluoromethyl, 4-bromo and 4-methoxy



Scheme 2.

which are attached to the arylfuryl ring were responsible for the good antifungal activity.

5. Conclusion

The research study reports the successful synthesis and antimicrobial activity of new 1,2,4-triazolothiadiazole derivatives bearing 4-methylthiobenzyl moiety. The antimicrobial activity results indicated that some of the tested compounds showed the most promising antibacterial and antifungal activities.

6. Experimental protocols

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using Merk silica gel 60 F_{254} coated alumina plates. IR spectra were recorded on a SHIMADZU-FTIR infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ on AMX (400 MHz) spectrometer using TMS as internal standard. FAB MS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas.

*6.1. Procedure for the preparation of substituted aryl furoic acid (**2**)*

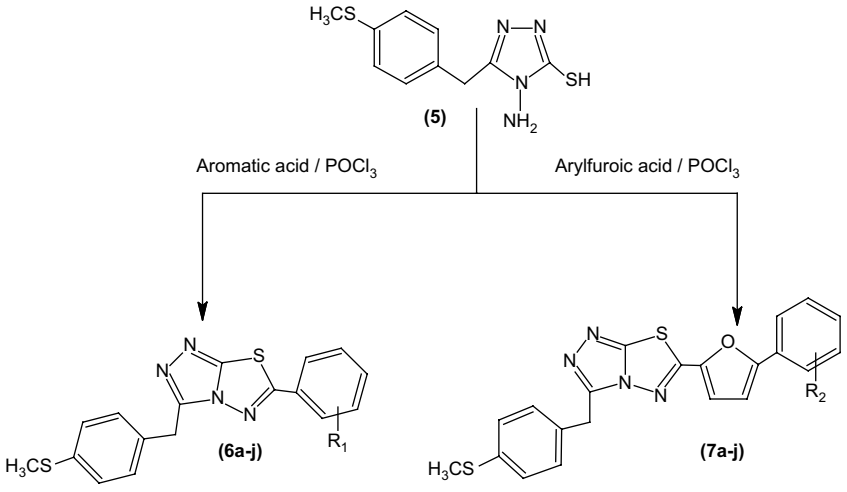
A mixture containing substituted aniline (100 mmol), hydrochloric acid (15%, 60 ml) and water (90 ml) was heated until clear solution was obtained, cooled to 0 °C, diazotized with aqueous sodium nitrite (30%, 24 ml) and filtered. To the filtered solution, water (50 ml) and furoic acid (9.6 g, 100 mmol) were added. Aqueous solution of cupric chloride (2.5 g in 10 ml of water) was added dropwise and stirred for 4 h at room temperature and kept aside for 16 h. The resulting solid was filtered off, suspended in water and purified by steam distillation in the presence of sodium carbonate to give the corresponding aryl furoic acid. These compounds were then recrystallized from a mixture of dimethyl formamide and ethanol.

*6.2. Procedure for the preparation of (4-methylthiophenyl) acetic acid (**4**)*

A mixture of (4-methylthiophenyl) acetonitrile (**1**) (16.3 g, 0.1 mol) and a solution of potassium hydroxide (11.2 g, 0.2 mol) in water (25 ml) was heated to reflux for 8 h. The resulting mixture was cooled to 20 °C and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from ethanol. Yield 82%, m.p. 96–98 °C.

*6.3. Procedure for the preparation of 4-amino-5-mercapto-3-[4-methylthiobenzyl]-4H-1,2,4-triazole (**5**)*

An equimolar mixture of an acid (**2**) and thiocarbohydrazide was heated on an oil bath till the contents melted. The reaction mixture was maintained at this temperature for 3 h. Then it was allowed to cool and treated with dilute sodium bicarbonate solution in order to remove any unreacted acid left. The solid was



Scheme 3.

Table 1
Characterization data of compounds **6a–j** and **7a–j**

Compound	R_1/R_2	M.F.	M.W.	Yield (%)	M.p. (°C)	Analysis (%), found (calculated)		
						C	H	N
6a	2,3,4-Cl_3–C_6H_2–	$C_{17}H_{11}N_4S_2Cl_3$	440	82	154–158	46.31, 46.22	2.57, 2.51	12.69, 12.68
6b	4-SCH_3–C_6H_4–CH_2	$C_{19}H_{18}N_4S_3$	398	91	119–124	56.24, 56.22	4.23, 4.19	12.60, 14.57
6c	2,4-Cl_2–5-F–C_6H_2	$C_{17}H_{11}N_4S_2ClF$	424	90	106–108	48.20, 48.01	2.66, 2.61	13.21, 13.17
6d	C_6H_4–CH_2–	$C_{18}H_{16}N_4S_2$	352	90	157–159	61.33, 60.21	4.58, 4.47	15.90, 14.10
6e	4-NO_2–C_6H_4–	$C_{17}H_{13}N_5S_2O_2$	383	85	106–109	53.29, 53.25	3.38, 3.42	18.31, 18.26
6f	4-OH–C_6H_4–	$C_{17}H1_4N_4S_2O$	354	89	104–107	57.68, 57.61	4.21, 3.98	16.13, 15.81
6g	4-Br–C_6H_4–	$C_{17}H_{13}N_4S_2Br$	417	90	176–179	49.07, 48.92	3.22, 3.14	13.49, 13.42
6h	4-F–C_6H_4–	$C_{17}H_{13}N_4S_2F$	356	95	190–194	57.33, 57.28	3.75, 3.68	16.83, 16.72
6i	2,5-Cl_2–C_6H_3–	$C_{17}H_{12}N_4S_2Cl_2$	407	97	173–175	50.26, 50.13	3.08, 2.97	13.85, 13.74
6j	2-Cl–4-NO_2–C_6H_3–	$C_{17}H_{12}N_5S_2O_2Cl$	417	90	166–169	49.91, 48.86	3.94, 2.89	17.83, 16.76
7a	2,4,5-Cl_3–$C_{10}H_4$–	$C_{21}H_{13}N_4S_2OCl_3$	506	95	177–181	50.23, 49.67	2.61, 2.58	11.14, 11.03
7b	4-Cl_2–NO_2–C_6H_5–	$C_{21}H_{14}N_5S_2O_3Cl$	483	89	122–125	52.19, 52.12	3.16, 2.92	14.52, 14.47
7c	2-CF_3–$C_{10}H_6$–	$C_{22}H_{15}N_4S_2OF_3$	472	89	139–144	56.17, 55.92	3.27, 3.20	12.94, 11.86
7d	4-Cl–$C_{10}H_6$–	$C_{21}H_{15}N_4S_2OCl$	437	89	162–165	57.51, 57.46	3.53, 3.44	12.87, 12.76
7e	4-NO_2–$C_{10}H_6$–	$C_{21}H_{15}N_5S_2O_3$	448/449	89	255–257	56.22, 56.11	3.42, 3.36	15.75, 15.68
7f	4-Br–$C_{10}H_6$–	$C_{21}H_{15}N_4S_2OBr$	483	90	205–209	52.29, 52.18	3.31, 3.13	12.64, 11.59
7g	2,5-Cl_2–$C_{10}H_5$–	$C_{21}H_{14}N_4S_2OCl_2$	472	89	233–237	53.33, 53.28	3.15, 2.98	12.04, 11.84
7h	4-OCH_3–$C_{10}H_6$–	$C_{22}H_{18}N_4S_2O_2$	434	85	182–186	60.97, 60.81	4.26, 4.18	13.98, 12.89
7i	2-NO_2–4-OCH_3–$C_{10}H_5$–	$C_{22}H_{11}N_5O_4S_2$	479	89	156–159	55.22, 55.10	3.63, 3.57	14.69, 14.60
7j	4-CH_3–$C_{10}H_6$–	$C_{22}H_{18}N_4S_2O$	418	89	179–181	63.17, 63.06	4.42, 4.33	13.44, 13.39

filtered, washed with water, dried and recrystallized from ethanol to obtain the pure triazole. Yield 62%; m.p. 198–200 °C.

*6.4. Procedure for the preparation of 6-(4-aryl/arylfuryl)-3-[4-(methylthio)benzyl][1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**7a–j** and **8a–j**)*

A mixture of triazole (0.01 mol), substituted benzoic acids/aryl furoic acids (0.01 mol) and phosphorus oxychloric acid (10 ml) was heated for 8 h. Excess of phosphorus oxychloric acid was removed under reduced pressure. The resulting reaction mass was cooled and poured into cold water with vigorous stirring. The solid thus obtained was filtered, washed with dilute sodium bicarbonate solution followed by water, dried and recrystallized from ethanol.

*6.4.1. Compound **4***

IR (KBr, cm^{-1}): 3340 (OH), 3053 and 3011 (Ar-H), 2873 (C–H), 1715 (C=O), 1627, 1562 and 1485 (C=N, C=C);

Table 2
Antibacterial activity data of compounds **6a–j** and **7a–j**

Compound	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*E. coli*
6a	**18 (12.5)**	**17 (12.5)**	**24 (6)**	**19 (12.5)**
6b	18 (12.5)	18 (6)	13 (25)	16 (12.5)
6c	**19 (12.5)**	**17 (12.5)**	**23 (6)**	**20 (6)**
6d	11 (25)	15 (25)	14 (25)	11 (25)
6e	16 (12.5)	18 (6)	13 (12.5)	17 (12.5)
6f	12 (25)	12 (25)	17 (25)	10 (25)
6g	15 (25)	16 (25)	20 (25)	13 (25)
6h	**18 (12.5)**	**17 (12.5)**	**25 (6)**	**19 (12.5)**
6i	15 (25)	10 (25)	13 (25)	12 (25)
6j	**19 (12.5)**	**17 (12.5)**	**23 (6)**	**18 (12.5)**
7a	13 (25)	10 (25)	10 (25)	12 (25)
7b	**18 (12.5)**	**18 (6)**	**23 (6)**	**19 (6)**
7c	**19 (12.5)**	**18 (6)**	**25 (6)**	**18 (12.5)**
7d	**18 (12.5)**	**18 (6)**	**22 (12.5)**	**20 (6)**
7e	16 (25)	10 (25)	20 (12.5)	17 (25)
7f	12 (25)	11 (25)	15 (25)	11 (25)
7g	16 (25)	18 (6)	20 (12.5)	16 (12.5)
7h	14 (25)	17 (12.5)	18 (12.5)	16 (12.5)
7i	12 (25)	12 (25)	21 (6)	13 (25)
7j	**18 (12.5)**	**18 (6)**	**23 (6)**	**18 (6)**
Ciprofloxacin	19 (12.5)	18 (12.5)	25 (6)	20 (6)

Values in bracket are MIC values.

Table 3
Antifungal activity data of compounds **6a–j** and **7a–j**

Compound	*A. fumigatus*	*A. flavus*	*C. albicans*	*Penicillium marneffei*
6a	13 (25)	15 (25)	10 (25)	17 (25)
6b	**22 (6)**	**17 (25)**	**19 (6)**	**20 (6)**
6c	**21 (6)**	**18 (6)**	**20 (6)**	**19 (6)**
6d	13 (25)	10 (25)	17 (6)	12 (25)
6e	15 (25)	11 (25)	14 (25)	11 (25)
6f	**22 (6)**	**18 (12.5)**	**20 (6)**	**18 (6)**
6g	14 (25)	15 (12.5)	13 (25)	13 (25)
6h	19 (12.5)	16 (12.5)	10 (25)	17 (12.5)
6i	11 (25)	11 (25)	15 (25)	13 (25)
6j	**22 (6)**	**17 (12.5)**	**20 (6)**	**19 (6)**
7a	12 (25)	17 (**12.5**)	12 (25)	17 (25)
7b	**22 (6)**	**18 (12.5)**	**18 (12.5)**	**17 (6)**
7c	20 (6)	11 (25)	15 (25)	20 (6)
7d	17 (12.5)	10 (25)	12 (25)	16 (25)
7e	14 (25)	11 (25)	17 (12.5)	11 (25)
7f	**20 (6)**	**17 (12.5)**	**18 (6)**	**20 (6)**
7g	13 (25)	18 (6)	20 (6)	17 (12.5)
7h	**22 (6)**	**18** (12.5)	**10 (25)**	**18 (6)**
7i	19 (12.5)	12 (25)	17 (25)	15 (25)
7j	21 (12.5)	11 (25)	14 (25)	17 (12.5)
Ciclopiroxolamine	22 (6)	18 (12.5)	20 (6)	20 (6)

Values in bracket are MIC values.

^{1}H NMR ($CDCl_3$, δ): 2.43 (s, 3H, SCH_3), 4.41 (s, 2H, $-CH_2$), 7.16 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl), 7.41 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl); FAB MS (*m/z*, %): 183 ($M^+ + 1$, 100), 182 (M^+, 64), 137 (53), 91 (33); ^{13}C NMR ($CDCl_3$, δ): 172.18 (CO_2H), 18.34 (CH_2), 27.13 (SCH_3), 129 (C_1), 116 (C_2 and C_6), 122 (C_2 and C_5), 124 (C_4).

6.4.2. Compound ***5***

IR (KBr, cm^{-1}): 3354 and 3277 (asymmetric and symmetric stretching frequencies of NH_2), 3035 (Ar, C–H), 2926 and 2854 (C–H), 1627, 1562 and 1485 (C=N, C=C); ^{1}H NMR ($CDCl_3$, δ): 2.38 (s, 3H, SCH_3), 4.43 (s, 2H, $-CH_2$), 13.51 (s, 1H, NH/SH tautomeric), 7.19 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl), 7.37 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl); FAB MS (*m/z*, %): 252 (M^+, 23), 253 ($M^+ + 1$, 100), 205 (12), 197 (46); ^{13}C NMR ($CDCl_3$, δ): 15.32 (CH_2), 28.33 (SCH_3), 131 (C_3), 136 (C_5), 114–129 (aromatic carbons of 4-methylthiophenyl).

6.4.3. Compound ***6a***

IR (KBr, cm^{-1}): 3022 (Ar-H), 2919 and 2851 (C–H), 1624, 1579, 1492 and 1476 (C=N, C=C), 843, 815 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 2.38 (s, 3H, SCH_3), 4.43 (s, 2H, $-CH_2$), 7.53 (d, 2H, $J = 8.8$ Hz, 2,3,4-trichlorophenyl), 7.75 (d, 2H, $J = 8.8$ Hz, 2,3,4-trichlorophenyl), 7.19 and 7.37 (2d, 4H, $J = 8.4$ Hz, 4-methylthiophenyl); FAB MS (*m/z*, %): 440 (M^+, 52), 441 ($M^+ + 1$, 100), 442 (M + 2, 64), 444 (M + 4, 94), 446 (M + 6, 83), 307 (73), 289 (48); ^{13}C NMR ($CDCl_3$, δ): 15.83 (CH_2), 30.85 (SCH_3), 131 (C_3), 133 (C_6), 137 (C_8), 129–134 (aromatic carbons of C7 of 2,3,4-trichlorophenyl), 126.92–129.48 (aromatic carbons of 4-methylthiophenyl).

6.4.4. Compound ***6b***

IR (KBr, cm^{-1}): 3031 (Ar-H), 2917, 2848 (C–H), 1597, 1513 and 1493 (C=N, C=C); ^{1}H NMR ($CDCl_3$, δ): 2.48 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3), 4.36 (s, 2H, $-CH_2$), 4.18 (s, 2H, $-CH_2$), 7.16–7.30 (m, 8H, 4-methylthiophenyl); FAB MS (*m/z*, %): 398 (M^+, 43), 399 ($M^+ + 1$, 100), 391 (39), 307 (22); ^{13}C NMR ($CDCl_3$, δ): 15.87 ($2CH_2$), 30.85 ($2SCH_3$), 131 (C_3), 133 (C_6), 137 (C_8), 126.90–131.68 (aromatic carbons of 4-methylthiophenyl).

6.4.5. Compound ***6c***

IR (KBr, cm^{-1}): 3014 (Ar-H), 2931, 2876 (C–H), 1627 and 1496 (C=N, C=C), 1093, 1018 (C–F), 893 and 856 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 2.50 (s, 3H, SCH_3), 4.44 (s, 2H, $-CH_2$), 7.81 (d, 1H, $J = 1.6$ Hz, dichlorofluorophenyl, meta H–F coupling), 7.65 (d, 1H, $J = 12$ Hz, dichlorofluorophenyl, ortho H–F coupling), 7.29 (d, 1H, $J = 8$ Hz, 4-methylthiophenyl), 7.33 (d, 1H, $J = 8$ Hz, 4-methylthiophenyl); FAB MS (*m/z*, %): 421 ($M^+ + 1$, 100), 420 (M^+, 23), 422 (M + 2, 71), 426 (M + 4, 27), 205 (12), 197 (46); ^{13}C NMR ($CDCl_3$, δ): 11.05 (CH_2), 26.02 (SCH_3), 150.87 (C_3), 153.37 (C_6), 156.98 (C_8), 126.47–133.06 (aromatic carbons of 2,4-dichloro-5-flurophenyl), 122.33–125.04 (aromatic carbons of 4-methylthiophenyl).

6.4.6. Compound ***6d***

IR (KBr, cm^{-1}): 3039 (Ar-H), 2918 (C–H, CH_3), 1600, 1525 and 1465 (C=N, C=C); ^{1}H NMR ($CDCl_3$, δ): 2.54 (s, 3H, SCH_3), 4.52 (s, 2H, 4-methylthiobenzyl), 4.47 (s, 2H, benzyl), 7.22 (d, 2H, $J = 8$ Hz, methylthiophenyl), 7.31 (d, 2H, $J = 8$ Hz, methylthiophenyl), 7.01–7.28 (m, 5H, benzyl); FAB MS (*m/z*, %): 353 ($M^+ + 1$, 100), 352 (M^+, 55), 307 (71), 281 (29), 235 (23); ^{13}C NMR ($CDCl_3$, δ): 15.23 and 18.41 ($2CH_2$), 36.45 (SCH_3), 152.33 (C_3), 155 (C_6), 166.32 (C_8), 129.76–137.10 (aromatic carbons of 4-methylthiophenyl), 126.26–129.38 (aromatic carbons of 6-methylenephenyl).

6.4.7. Compound ***6e***

IR (KBr, cm^{-1}): 3033 (Ar-H), 2912 (C–H), 1619, 1592 and 1479 (C=N, C=C), 1553, 1358 (NO_2 asymmetric and symmetric stretchings); ^{1}H NMR ($CDCl_3$, δ): 2.57 (s, 3H, SCH_3), 4.45 (s, 2H, $-CH_2$), 8.41 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl ring), 8.46 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl ring), 7.21 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl), 7.34 (d, 2H, $J = 8.4$ Hz, 4-methylthiophenyl); FAB MS (*m/z*, %): 384 ($M^+ + 1$, 100), 383 (M^+, 23), 368 (15), 338 (12), 307 (18); ^{13}C NMR ($CDCl_3$, δ): 14.96 (CH_2), 29.78 (SCH_3), 136.72 (C_3), 149.56 (C_6), 164.34 (C_8), 117.23–128.52 (aromatic carbons of 4-methylthiophenyl), 128.98–157.88 (aromatic carbons of 4-nitrophenyl).

6.4.8. Compound ***6f***

IR (KBr, cm^{-1}): 3348 (O–H), 3017 (Ar-H), 2873 (C–H), 1600, 1493 and 1459 (C=C, C=N), 1093 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.53 (S, 3H, SCH_3), 4.41 (s, 2H, $-CH_2$), 7.21 and 7.32 (2d, 4H, $J = 8$ Hz, 4-methylthiophenyl), 7.46 and 7.86 (d, 2H, $J = 8.2$ Hz, 4-hydroxyphenyl); FAB MS (*m/z*, %): 355 ($M^+ + 1$, 100), 354 (M^+, 26), 340 (12), 315 (7), 307 (38), 289 (22), 289 (48); ^{13}C NMR ($CDCl_3$, δ): 14.89 (CH_2), 29.81 (SCH_3), 137.94 (C_3), 142.76 (C_6), 148.41 (C_8), 115.43–126.28 (aromatic carbons of 4-methylthiophenyl), 127.28–133.67 (aromatic carbons of 4-hydroxyphenyl).

6.4.9. Compound ***6g***

IR (KBr, cm^{-1}): 3014 (Ar-H), 2823 (C–H), 1610, 1589 and 1487 (C=N, C=C), 1093 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.43 (S, 3H, SCH_3), 4.21 (s, 2H, $-CH_2$), 7.17 and 7.35 (2d, 4H, $J = 8.3$ Hz, 4-methylthiophenyl), 7.61 and 7.79 (d, 2H, $J = 8.1$ Hz, 4-bromophenyl); FAB MS (*m/z*, %): 417 ($M^+ + 1$, 100), 416 (M^+, 71), 418 (M + 2, 48), 236 (55), 163 (47); ^{13}C NMR ($CDCl_3$, δ): 14.83 (CH_2), 28.93 (SCH_3), 141.67 (C_3), 148.13 (C_6), 157.93 (C_8), 121–127 (aromatic carbons of 4-methylthiophenyl), 132–148 (aromatic carbons of 4-bromophenyl).

6.4.10. Compound ***6h***

IR (KBr, cm^{-1}): 3066 (Ar-H), 2891 (C–H), 1612, 1575 and 1469 (C=N, C=C), 1126 (C–F); ^{1}H NMR ($CDCl_3$, δ): 2.45 (S, 3H, SCH_3), 4.46 (s, 2H, $-CH_2$), 7.21 and 7.43 (2d, 4H, $J = 8.6$ Hz, 4-methylthiophenyl), 7.73–7.92 (m, 4H, 4-flurophenyl); FAB MS (*m/z*, %): 357 ($M^+ + 1$, 100), 356

(M^+, 65), 235 (48), 163 (53); ^{13}C NMR ($CDCl_3$, δ): 14.58 (CH_2), 28.17 (SCH_3), 137 (C_3), 141 (C_6), 145 (C_8), 115–128 (aromatic carbons of 4-methylthiophenyl), 135–142 (aromatic carbons of 4-flurophenyl).

6.4.11. Compound ***7a***

IR (KBr, cm^{-1}): 3057 (Ar-H), 2912 and 2818 (C–H), 1596 and 1491 (C=N, C=C), 892, 875 and 840 (C–Cl); ^1H NMR ($CDCl_3$, δ): 2.43 (s, 3H, SCH_3), 4.49 (s, 2H, $-CH_2$), 7.57 (d, 1H, $J = 3.8$ Hz, furan-H), 7.82 (d, 1H, $J = 3.8$ Hz, furan-H), 8.20 (s, 1H, 2,4,5-trichlorophenyl), 8.07 (s, 1H, 2,4,5-trichlorophenyl), 7.12 and 7.25 (2d, 4H, $J = 8$ Hz, 4-methylthiophrenyl); FAB MS (*m/z*, %): 507 ($M^+ + 1$, 100), 506 (M^+), 508 (M + 2, 72), 510 (M + 4, 83), 512 (M + 6, 75), 307 (73), 289 (48); ^{13}C NMR ($CDCl_3$, δ): 16.32 (CH_2), 30.43 (SCH_3), 139.61 (C_3), 147.43 (C_6), 152.12 (C_8), 121–129 (aromatic carbons of 4-methylthiophenyl), 126–133 (carbons of furan ring), 132–147 (aromatic carbons of 2,4,5-trichlorophenyl).

6.4.12. Compound ***7b***

IR (KBr, cm^{-1}): 3068 (Ar-H), 2917 and 2849 (C–H), 1592 and 1493 (C=N, C=C), 1535, 1348 (NO_2 asymmetric and symmetric stretching frequencies), 898, 879 (C–Cl); ^1H NMR ($CDCl_3$, δ): 2.45 (s, 3H, SCH_3), 4.41 (s, 2H, $-CH_2$), 6.85 (d, 1H, $J = 4$ Hz, furan-H), 7.23 (d, 1H, $J = 4$ Hz, furan-H), 7.13 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.34 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.82 (d, 1H, $J = 2$ Hz, 2-nitro-4-chlorophenyl), 7.73 (d, 1H, $J = 8.4$ Hz, 2-nitro-4-chlorophenyl), 7.67 (d, 1H, $J = 2$ Hz, 2-nitro-4-chlorophenyl); FAB MS (*m/z*, %): 484 ($M^+ + 1$, 100), 483 (M^+), 485 (M + 2, 47), 487 (29), 307 (15), 279 (21), 250 (18); ^{13}C NMR ($CDCl_3$, δ): 14.96 (CH_2), 30.83 (SCH_3), 132 (C_3), 141 (C_6), 148 (C_8), 117.17–126.32 (aromatic carbons of 4-methylthiophenyl), 119–131 (carbons of furan ring), 137–159 (aromatic carbons of 2-nitro-4-chlorophenyl).

6.4.13. Compound ***7c***

IR (KBr, cm^{-1}): 3033 (Ar-H), 2917, 2848 (C–H), 1596, 1577, 1493 and 1478 (C=N, C=C), 1074, 1031 (C–F of CF_3); ^1H NMR ($CDCl_3$, δ): 2.45 (s, 3H, SCH_3), 4.42 (s, 2H, $-CH_2$), 6.89 (d, 1H, $J = 3.6$ Hz, furan-H), 7.26 (d, 1H, $J = 3.6$ Hz, furan-H), 7.21 (d, 1H, $J = 8.4$ Hz, 4-methylthiophenyl), 7.35 (d, 1H, $J = 8.4$ Hz, 4-methylthiophenyl), 7.53–7.83 (m, 4H, 2-trifluoromethylphenyl); FAB MS (*m/z*, %): 473 ($M^+ + 1$, 100), 472 (M^+, 48), 431 (47), 391 (53), 307 (47); ^{13}C NMR ($CDCl_3$, δ): 14.77 (CH_2), 29.75 (SCH_3), 143 (C_3), 153 (C_6), 155 (C_8), 113.17–126.54 (aromatic carbons of 4-methylthiophenyl), 132–138 (aromatic carbons of 2-trifluromethylphenyl), 127–130 (carbons of furan ring).

6.4.14. Compound ***7d***

IR (KBr, cm^{-1}): 3041 (Ar-H), 2892 (C–H), 1590, 1570, 1493 and 1478 (C=N, C=C), 1276, 1093 (C–O), 897 and 829 (C–Cl); ^1H NMR ($CDCl_3$, δ): 2.43 (s, 3H, SCH_3), 4.41 (s, 2H, $-CH_2$), 7.35 (d, 1H, $J = 3.4$ Hz, furan-H), 7.50 (d, 1H, $J = 3.4$ Hz, furan-H), 7.53 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.62 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.55 (d, 2H, $J = 8.1$ Hz, 4-chlorophenyl), 8.95 (d, 2H, $J = 8.1$ Hz, 4-chlorophenyl); FAB MS (*m/z*, %): 438 ($M^+ + 1$, 100), 437 (M^+, 47), 440 (M + 2, 49), 380 (61), 298 (38); ^{13}C NMR ($CDCl_3$, δ): 15.33 (CH_2), 29.69 (SCH_3), 133 (C_3), 136 (C_6), 144 (C_8), 109–121 (aromatic carbons of 4-methylthiophenyl), 122–127 (carbons of furan ring), 132–155 (aromatic carbons of 4-chlorophenyl).

6.4.15. Compound ***7e***

IR (KBr, cm^{-1}): 3048 (Ar-H), 2896 (C–H), 1602, 1592, 1496 and 1470 (C=N, C=C), 763 (C–Cl); ^1H NMR ($CDCl_3$, δ): 2.42 (s, 3H, SCH_3), 4.44 (s, 2H, $-CH_2$), 7.07 (d, 1H, $J = 3.6$ Hz, furan-H), 7.30 (d, 1H, $J = 3.6$ Hz, furan-H), 7.21 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.34 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.91 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.32 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl); FAB MS (*m/z*, %): 450 ($M^+ + 1$, 100), 449 (M^+, 57), 391 (47), 307 (36), 289 (21); ^{13}C NMR ($CDCl_3$, δ): 15.39 (CH_2), 30.08 (SCH_3), 136 (C_3), 139 (C_6), 143 (C_8), 116–128 (aromatic carbons of 4-methylthiophenyl), 127–132 (carbons of furan ring), 129–165 (aromatic carbons of 4-nitrophenyl).

6.4.16. Compound ***7f***

IR (KBr, cm^{-1}): 3061 (Ar-H), 2892 (C–H), 1612, 1589 and 1468 (C=N, C=C), 1542 and 1361 (NO_2 asym. and sym.); ^1H NMR ($CDCl_3$, δ): 2.41 (s, 3H, SCH_3), 4.39 (s, 2H, $-CH_2$), 6.65 (d, 2H, $J = 3.6$ Hz, furan-H), 6.73 (2d, 2H, $J = 3.6$ Hz, furan-H), 7.28 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.31 (d, 2H, $J = 8$ Hz, 4-methylthiophenyl), 7.51 (d, 2H, $J = 8.2$ Hz, 4-bromophenyl), 7.55 (d, 2H, $J = 8.2$ Hz, 4-bromophenyl); FAB MS (*m/z*, %): 483 (M^+, 91), 485 (M + 2, 49), 350 (22), 248 (38), 157 (13); ^{13}C NMR ($CDCl_3$, δ): 15.33 (CH_2), 30.21 (SCH_3), 133 (C_3), 137 (C_6), 149 (C_8), 110–126 (aromatic carbons of 4-methylthiophenyl), 127–135 (carbons of furan ring), 132–152 (aromatic carbons of 4-nitrophenyl).

6.4.17. Compound ***7g***

IR (KBr, cm^{-1}): 3076 (Ar-H), 2845 (C–H), 1615, 1566 and 1481 (C=N, C=C), 873 and 844 (C–Cl); ^1H NMR ($CDCl_3$, δ): 2.46 (s, 3H, SCH_3), 4.36 (s, 2H, $-CH_2$), 6.91 and 7.18 (2d, 2H, $J = 3.6$ Hz, furan-H), 7.23 and 7.46 (2d, 4H, $J = 8.2$ Hz, 4-methylthiophenyl), 7.57 (dd, 1H, 2,5-dichlorophenyl), 7.62 and 7.88 (2d, 2H, $J = 8.2$ Hz, 2,5-dichlorophenyl); FAB MS (*m/z*, %): 473 ($M^+ + 1$, 100), 472 (M^+, 79), 474 (M + 2, 64), 476 (M + 4, 26), 365 (33), 237 (17); ^{13}C NMR ($CDCl_3$, δ): 15.18 (CH_2), 29.32 (SCH_3), 135 (C_3), 143 (C_6), 155 (C_8), 115–128 (aromatic carbons of 4-methylthiophenyl), 128–136 (carbons of furan ring), 131–158 (aromatic carbons of 4-nitrophenyl).

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