Asian Journal of Chemistry; Vol. 23, No. 12 (2011), 5471-5476

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis, Characterization and Antifungal Activity of Some 5-Substituted 4-Amino-1,2,4-triazole-3-thiols

AURANGZEB HASAN[1,*], MOHAMMAD NADEEM AKHTAR[2] and SHELLY GAPIL[1]

[1]Department of Chemistry, Faculty of Science, University of Malaya, Kuala Lumpur-50603, Malaysia
[2]Institute of Bioscience, University Putra Malaysia, Kuala Lumpur-43400, Malaysia

*Corresponding author: Fax: +60 379674193; Tel: +60 379675165; E-mail: flavonoids@hotmail.com; aurangzeb@um.edu.my

(*Received*: 10 March 2011; *Accepted*: 24 August 2011) AJC-10308

A series of 5-substituted 4-amino-1,2,4-triazole-3-thiols (**4a-i**) was synthesized by refluxing substituted organic acids (**a-i**) with methanol to the corresponding esters (**1a-i**). These esters were then converted to hydrazides (**2a-i**) by reaction with hydrazine hydrate in the presence of absolute ethanol. The hydrazides were then converted to 5-substituted 1,3,4-oxadiazole-2-thiols (**3a-i**) by cyclization reaction with carbon disulfide and KOH which was followed by reaction with hydrazine hydrate in the presence of absolute ethanol. Structure of the synthesized compounds was established by physico-chemical and spectral data analysis. Synthesized compounds were subjected to antifungal activity. Antifungal activity analysis was performed against *Aspergillus flavus*, *Mucor species*, *Aspergillus niger* and *Aspergillus fumigates*, with test compounds at a concentration of 200 µg/mL. Terbinafine was used as the standard drug.

Key Words: Oxadiazoles, Triazoles, Thiols, *in vitro* antifungal activity.

INTRODUCTION

Aromatic systems such as 1,2,4-triazoles having three nitrogen atoms at symmetrical position have been studied because of their broad spectrum of agricultural and industrial activities[1,2] as well as pharmacological properties such as antibacterial, antimicrobial[3,4], anticonvulsant[5] and antiinflammatory[6]. The synthesis of these heterocycles has received considerable attention in recent years[7-11]. In view of these facts and in continuation of our work[12] on the synthesis of biologically important heterocyclic compounds, we describe here the synthesis of some new 5-substituted 4-amino-1,2,4-triazole-3-thiols through the intramolecular cyclization of variably substituted acid hydrazides to the corresponding 5-substituted 1,3,4-oxadiazoles-2-thiols and evaluation of their antifungal activity. The structures of the compounds were assigned on the basis of their physical and spectral data.

EXPERIMENTAL

Melting points of the synthesized compounds were recorded on Gallenkamp digital melting point apparatus MFB-595-101 M in open-end capillary tubes and were uncorrected. Thin layer chromatography was carried out on pre-coated silica gel plates (0.2 mm, E. Merck, 20 cm × 20 cm, $60F_{254}$). FTIR spectral data were recorded on Bio-Red Merlin spectrophotometer using KBr discs. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.43 MHz) spectra were recorded on Bruker AM-300 spectrometer in DMSO and $CDCl_3$ solutions using TMS as internal standard. EIMS was recorded on a GCMS Agilent VG: 70 SE Mass spectrometer. Purity of the synthesized compounds was also monitored by the same instrument.

Synthetic method

Preparation of 5-(4-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (4a): Preparation of methyl-4-nitrobenzoate (**1a**), 4-nitrobenzoic acid hydrazide (**2a**), 5-(4-nitrophenyl)-1,3,4-oxadiazole-2-thiol (**3a**) have been reported earlier[12].

5-(4-Nitrophenyl)-1,3,4-oxadiazole-2-thiol (4 g, 0.017 mol) and 80 % hydrazide hydrate (6 mL, 0.124 mol) in absolute ethanol were refluxed in a 250 mL flask fitted with a condenser and a guard tube. The reaction time was monitored through TLC technique (silica; ethyl acetate:petroleum ether, 1:2). After the completion of the reaction the solvent and excess hydrazine hydrate were removed under reduced pressure using rotary evaporator. The residue left behind was washed with diethyl ether and recrystallized from ethanol. Same synthetic procedure was adopted for the synthesis of compounds (**4b-i**). Purification of synthesized compounds was achieved by recrystallization and purity of each compound was monitored by thin layer chromatography and gas chromatography.

5-(4-Nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (4a): 5-(4-Nitrophenyl)-1,3,4-oxadiazole-2-thiol (4.0 g; 0.017 mol),

NH_2-NH_2 (6.12 g; 0.124 mol) were reacted according to the general procedure. Colour reddish yellow; yield: 80 % (3.20 g); recrystallization from EtOH; m.p. 158-159 ºC; m.f. $C_8H_7N_5O_2S$; m.w. 237. IR (KBr, ν_{max}, cm^{-1}): 3250 (N-H), 2606 (S-H), 1602 (C=C), 1553 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.99-8.02 (dd, *J* = 7.4, 2.4 Hz, 1H, Ar H), 8.30 (dd, *J* = 6.8, 3.1 Hz, 1H, Ar H), 8.30 (dd, *J* = 6.8, 3.1 Hz, 1H, Ar H), 7.99-8.02 (dd, *J* = 7.4, 2.4 Hz, 1H, Ar H), 9.34 (s, 1SH), 3.42 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 131.02, 126.91, 125.04, 147.01, 125.04, 126.91 (Ar C), 160.04, 182.05 (triazole moity C). MS (m/z) 237 (100 %) (M^+), 207 (58 %) (loss of N_2H_2), 148 (59 %) (loss of NCSH), 46 (70 %) (loss of NO_2), 190 (60 %). Anal. calcd. (%) for $C_8H_7N_5O_2S$: C, 40.54; H, 2.97; N, 29.55; found (%) C, 40.51; H, 2.89; N, 29.63.

5-(3-Nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (4b): 5-(3-Nitrophenyl)-1,3,4-oxadiazole-2-thiol (5.0 g; 0.021 mol), NH_2-NH_2 (6.40 g; 0.120 mol) were reacted according to the general procedure. Colour brown; yield: 82 % (4.10 g); recrystallization from EtOH; m.p. 162-164 ºC; m.f. $C_8H_7N_5O_2S$; m.w. 237. IR (KBr, ν_{max}, cm^{-1}): 3201 (N-H), 2561 (S-H), 1580 (C=C), 1530 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.28 (dd, *J* = 3.4, 5.8 Hz, 1H, Ar H), 7.84 (q, *J* = 6.8 Hz, 1H, Ar H), 8.24 (dd, *J* = 2.5, 7.2 Hz, 1H, Ar H), 8.31 (dd, *J* = 6.2, 3.3 Hz, 1H, Ar H), 12.3 (s, 1SH), 3.8 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 132.07, 128.59, 149.37, 125.66, 126.33, 127.02 (Ar C) 164.51, 181.33 (triazole moity C). MS (m/z) 237 (100 %) (M^+), 207 (58 %) (loss of N_2H_2), 148 (59 %) (loss of NCSH), 46 (70 %) (loss of NO_2), 190 (60 %). Anal. calcd. (%) for $C_8H_7N_5O_2S$: C, 40.54; H, 2.97; N, 29.55; found (%) C, 40.49; H, 2.88; N, 29.65.

5-Phenyl-4-amino-1,2,4-triazole-3-thiol (4c): 5-Phenyl-1,3,4-oxadiazole-2-thiol (7.0 g; 0.036 mol), NH_2-NH_2 (6.60 g; 0.132 mol) were reacted according to the general procedure. Colour red yellow; yield: 78 % (5.50 g); recrystallization from EtOH; m.p. 175-177 ºC; m.f. $C_8H_8N_4S$; m.w. 192. IR (KBr, ν_{max}, cm^{-1}): 3213 (N-H), 2590 (S-H), 1575 (C=C), 1515 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.37 (dd, *J* = 4.2, 3.1 Hz, 1H, Ar H), 7.61(m, 1H, Ar H), 7.89 (m, 1H, Ar H), 7.61 (m, 1H, Ar H), 13.30 (s, 1SH), 4.10 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 130.42, 127.41, 127.05, 125.01, 127.05, 127.41 (Ar C) 158.66, 185.72 (triazole moity C). MS (m/z) 192 (100 %) (M^+), 162 (58 %) (loss of N_2H_2), 103 (59 %) (loss of NCSH), 46 (70 %) (loss of NO_2), 191 (60 %). Anal. calcd. (%) for $C_8H_8N_4S$: C, 50.04; H, 4.19; N, 29.18; found (%) C, 50.11; H, 4.13; N, 29.25.

5-(4-Chloro-3-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (4d): 5-(4-Chloro-3-nitrophenyl)-1,3,4-oxadiazole-2-thiol (4.0 g; 0.014 mol), NH_2-NH_2 (6 g; 0.120 mol) were reacted according to the general procedure. Colour yellow; yield: 80 % (3.20 g); recrystallization from EtOH; m.p. 139-140 ºC; m.f. $C_8H_6N_5O_2SCl$; m.w. 271. IR (KBr, ν_{max}, cm^{-1}): 3160 (N-H), 2575 (S-H), 1572 (C=C), 1525 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.59 (dd, *J* = 3.2, 6.7 Hz, 1H, Ar H), 8.19 (d, *J* = 3.2 Hz, 1H, Ar H), 8.34 (d, *J* = 6.3 Hz, 1H, Ar H), 12.10 (s, 1SH), 3.81 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 132.56, 130.02, 151.71, 138.37, 127.61, 129.61 (Ar C) 160.02, 180.20 (triazole moity C). MS (m/z) 271 (100 %) (M^+), 241 (58 %) (loss of N_2H_2), 182 (59 %) (loss of NCSH), 46 (70 %) (loss of NO_2), 224 (60 %). Anal. calcd. (%) for $C_8H_6N_5O_2SCl$: C, 35.45; H, 2.23; N, 25.85; found (%) C, 35.51; H, 2.12; N, 25.77.

5-(5-Chloro-2-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (4e): 5-(5-Chloro-2-nitrophenyl)-1,3,4-oxadiazole-2-thiol (6.0 g; 0.022 mol), NH_2-NH_2 (7 g; 0.140 mol) were reacted according to the general procedure. Colour brown; yield: 76 % (4.60 g); recrystallization from EtOH; m.p. 151-153 ºC; m.f. $C_8H_6N_5O_2SCl$; m.w. 271. IR (KBr, ν_{max}, cm^{-1}): 3308 (N-H), 2575 (S-H), 1572 (C=C), 1525 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.99 (d, *J* = 7.3 Hz, 1H, Ar H), 8.34 (dd, *J* = 6.1, 2.8, 1H, Ar H), 8.05 (d, *J* = 2.3 Hz, 1H, Ar H), 11.06 (s, 1SH), 4.12 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 131.66, 155.01, 127.11, 125.04, 136.33, 126.21 (Ar C) 158.88, 189.01 (triazole moity C). 271 (100 %) (M^+), 241 (58 %) (loss of N_2H_2), 182 (59 %) (loss of NCSH), 46 (70 %) (loss of NO_2), 224 (60 %). Anal. calcd. (%) for $C_8H_6N_5O_2SCl$: C, 35.45; H, 2.23; N, 25.85; found (%) C, 35.49; H, 2.15; N, 25.73.

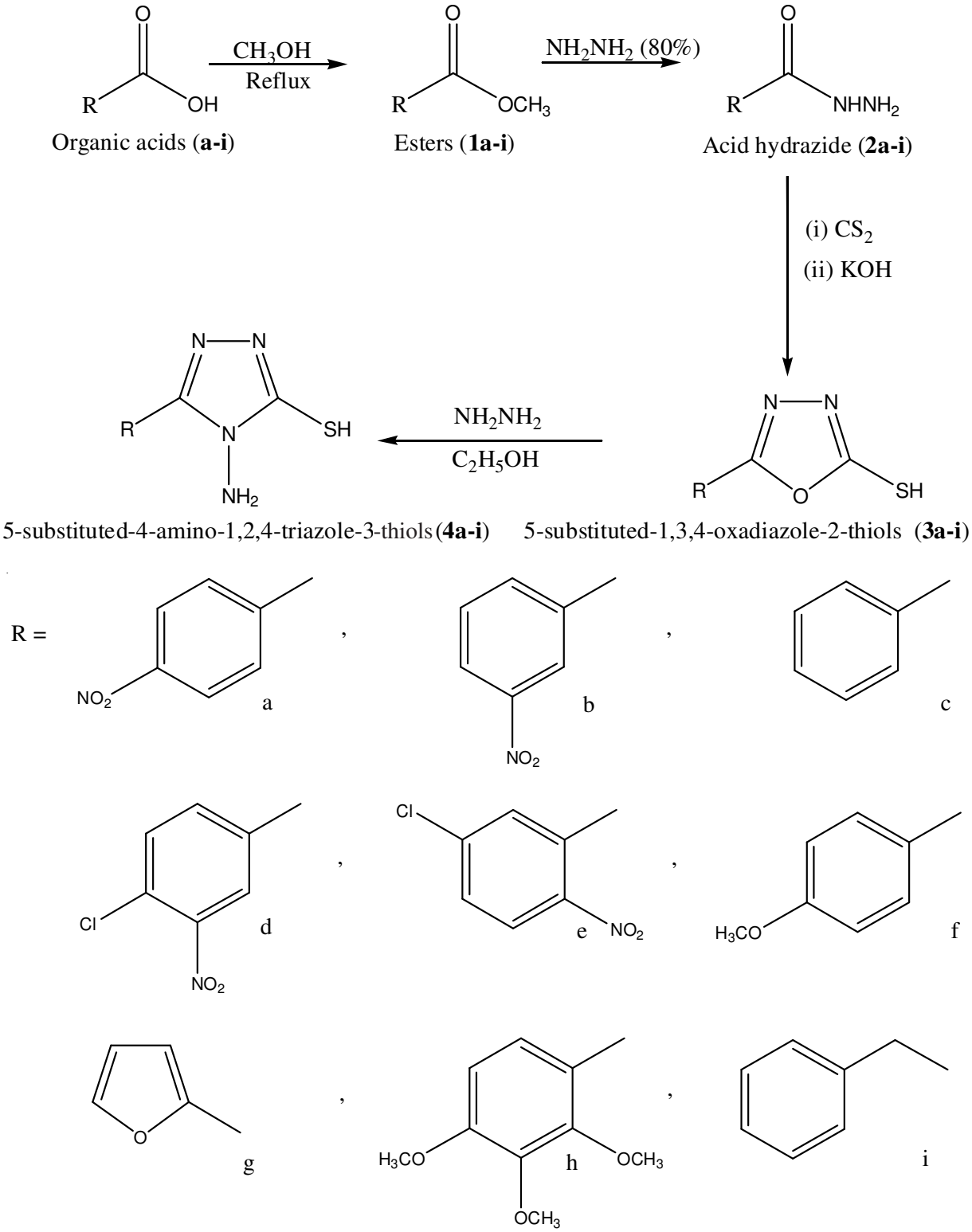
5-(4-Methoxybenzyl)-4-amino-1,2,4-triazole-3-thiol (4f): 5-(4-Methoxybenzyl)-1,3,4-oxadiazole-2-thiol (3.0 g; 0.012 mol), NH_2-NH_2 (4 g; 0.080 mol) were reacted according to the general procedure. Colour orange; yield: 79 % (2.40 g); recrystallization from EtOH; m.p. 180-182 ºC; m.f. $C_{10}H_{12}N_4OS$; m.w. 236. IR (KBr, ν_{max}, cm^{-1}): 3250 (N-H), 2536 (S-H), 1590 (C=C), 1528 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.29 (dd, *J* = 2.4, 6.7 Hz, 1H, Ar H), 7.59 (dd, *J* = 3.2, 7.1 Hz, 1H, Ar H), 7.59 (dd, *J* = 3.2, 7.1 Hz, 1H, Ar H), 7.29 (dd, *J* = 2.4, 6.7 Hz, 1H, Ar H), 10.34 (s, 1SH), 3.89 (s, 2H of NH_2), 3.20 (s, 3H, methoxyl H), 2.80 (s, 2H, methylene H); ^{13}C NMR (DMSO-d_6) δ (ppm): 130.21, 128.12, 126.61, 135.66, 126.61, 128.12 (Ar C) 162.44, 179.64 (triazole moity C), 25.12 (methylene C), 54.81 (methoxyl C). MS (m/z) 236 (100 %) (M^+), 206 (58 %) (loss of N_2H_2), 177 (59 %) (loss of NCSH), 235 (60 %). Anal. calcd. (%) for $C_{10}H_{12}N_4OS$: C, 50.87; H, 5.10; N, 23.74; found (%) C, 50.51; H, 5.12; N, 23.68.

5-(2-Furoyl)-4-amino-1,2,4-triazole-3-thiol (4g): 5-(2-Furoyl)-1,3,4-oxadiazole-2-thiol (5 g; 0.028 mol), NH_2-NH_2 (6.30 g; 0.126 mol) were reacted according to the general procedure. Colour dull yellow; yield: 81 % (4.00 g); recrystallization from EtOH; m.p. 172-173 ºC; m.f. $C_6H_6N_4OS$; m.w. 182. IR (KBr, ν_{max}, cm^{-1}): 3220 (N-H), 2529 (S-H), 1577 (C=C), 1524 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.20 (d, *J* = 3.4 Hz, 1H, Ar H), 8.01 (m, 1H, Ar H), 8.34 (d, *J* = 3.7Hz, 1H, Ar H), 11.50 (s, 1SH), 4.11 (s, 2H of NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 134.01, 128.61, 125.21, 129.61 (Ar C) 160.28, 185.77 (triazole moity C). MS (m/z) 182 (100 %) (M^+), 152 (58 %) (loss of N_2H_2), 123 (59 %) (loss of NCSH), 181 (60 %). Anal. calcd. (%) for $C_6H_6N_4OS$: C, 39.58; H, 3.31; N, 30.76; found (%) C, 39.51; H, 3.12; N, 30.55.

5-(2-Phenethyl)-4-amino-1,2,4-triazole-3-thiol (4h): 5-(2-Phenethyl)-1,3,4-oxadiazole-2-thiol (4.00 g; 0.018 mol), NH_2-NH_2 (6.2 g; 0.124 mol) were reacted according to the general procedure. Colour light brown; yield: 83 % (3.30 g); recrystallization from EtOH; m.p. 160-162 ºC; m.f. $C_{10}H_{12}N_4S$; m.w. 220. IR (KBr, ν_{max}, cm^{-1}): 3330 (N-H), 2568 (S-H), 1568 (C=C), 1524 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.21 (dd, *J* = 2.5, 6.7 Hz, 1H, Ar H), 7.95 (m, 1Hz, 1H, Ar H), 7.25 (m, 1H, Ar H),7.95 (m, 1H, Ar H), 12.01 (s, 1SH), 3.96 (s, 2H of

NH_2), 3.21 (t, J = 6.1, 3.8 Hz, 2H, methylene H), 2.82 (t, J = 6.1 Hz, 2H, methylene H); ^{13}C NMR (DMSO-d_6) δ (ppm): 132.05, 128.41, 126.01, 125.11, 126.01, 128.41 (Ar C) 160.09, 178.06 (triazole moity C), $0.21, 46.21 (methylene C). MS (m/z) 220 (100 %) (M^+), 190 (58 %) (loss of N_2H_2), 161 (59 %) (loss of NCSH), 219 (60 %). Anal. calcd. (%) for $C_{10}H_{12}N_4S$: C, 54.56; H, 5.47; N, 25.47; found (%) C, 54.63; H, 5.33; N, 25.59.

5-(3,4,5-Trimethoxyphenyl)-4-amino-1,2,4-triazole-3-thiol (4i): 5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol (5 g; 0.017 mol), NH_2-NH_2 (6.10 g; 0.122 mol) were reacted according to the general procedure. Colour red; yield: 80 % (4 g); recrystallization from EtOH; m.p. 210-212 ºC; m.f. $C_{11}H_{14}O_3N_4S$; m.w. 282. IR (KBr, ν_{max}, cm^{-1}): 3315 (N-H), 2529 (S-H), 1577 (C=C), 1533 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.25 (d, J = 6.8 Hz, 1H, Ar H), 7.25 (d, J = 6.8Hz,



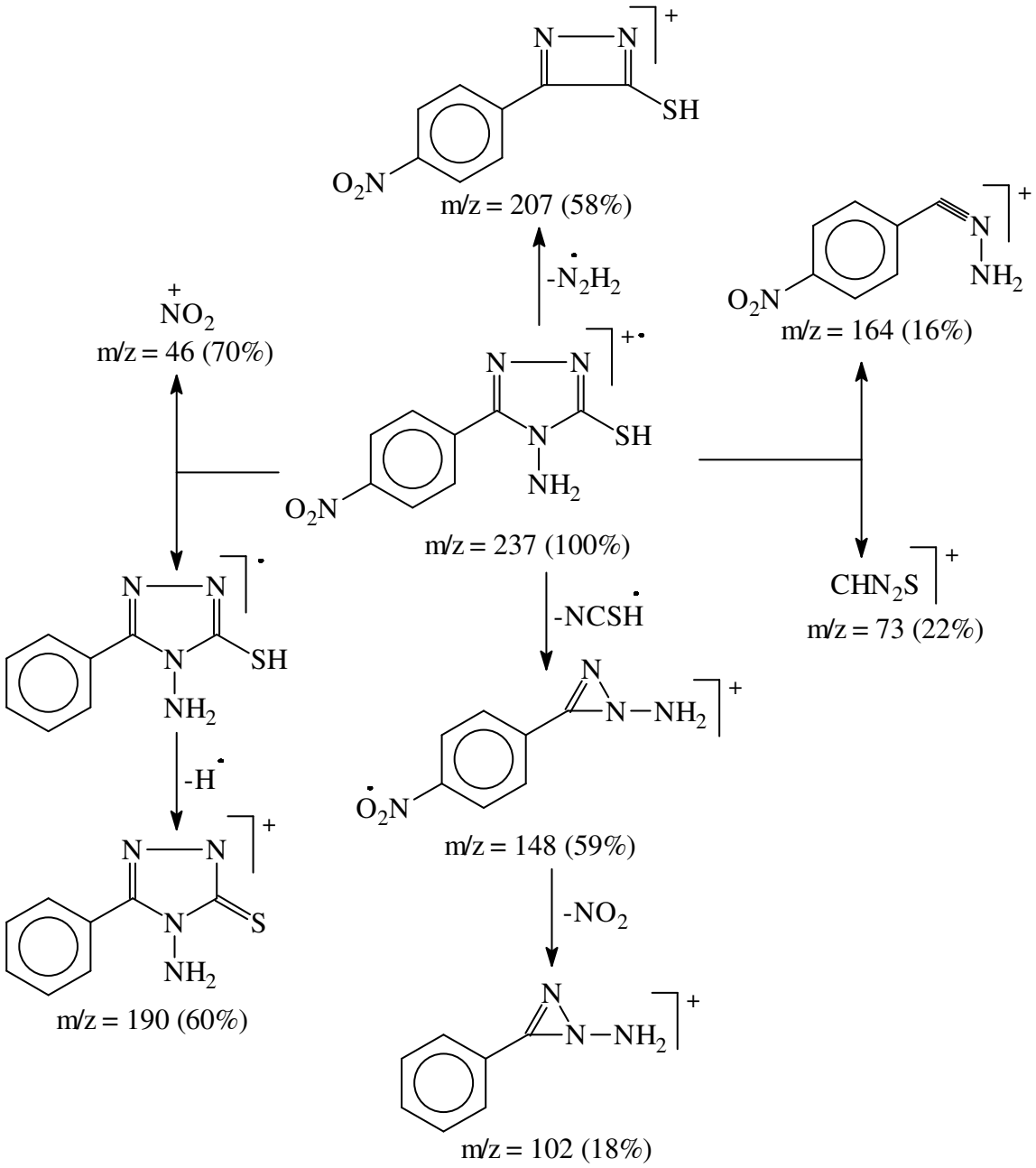
Scheme-1: General scheme for the synthesis of 5-substituted 4-amino-1,2,4-triazol-3-thiols

1H, Ar H), 7.25 (s, 1H, Ar H), 11.89 (s, 1SH), 4.21 (s, 2H of NH_2), 3.90 (s, 9H, 3Methoxyl H); ^{13}C NMR (DMSO-d_6) δ (ppm): 130.01, 130.66, 136.01, 136.01, 136.01, 130.66 (Ar C) 158.32, 186.44 (triazole moity C) 54.33 (Methoxyl C). MS (m/z) 282 (100 %) (M^+), 252 (58 %) (loss of N_2H_2), 223 (59 %) (loss of NCSH), 281 (60 %). Anal. calcd. (%) for $C_{11}H_{14}N_4O_3S$: C, 46.82; H, 4.98; N, 19.87; found (%) C,46.93; H, 4.85; N, 19.87.

Antifungal activity evaluation: The synthesized compounds were tested by agar tube dilution method[13] for their *in vitro* fungicidal activity. Terbinafine (200 µg/mL) was used as positive control. All experiments were done in three replicates. Four fungal strains: *Aspergillus flavus*, *Mucor species*, *Aspergillus niger* and *Aspergillus fumigatus* were used. All fungal strains were grown on 6.5 % Sabouraud dextrose agar (SDA), pH 5.7) at 28 °C and preserved at 4 °C in a refrigerator. 100 mm slants with sterilized SDA were prepared by adding each compound in 200 µg/mL concentration. Terbinafine (200 µg/mL) was used as standard drug while DMSO was used as negative control. Each slant was inoculated with 4 mm piece of respective fungal strain and incubated at 28 °C for 7-10 days. Fungal growth was compared with negative control to get the percentage inhibition.

RESULTS AND DISCUSSION

Nine 5-substituted 4-amino-1,2,4-triazole-3-thiols were obtained in 76-83 % yield by converting variably substituted organic acids (**a-i**) to the corresponding esters (**1a-i**) and acid hydrazides (**2a-i**) by reaction with methanol and hydrazine hydrate, respectively. The hydrazides were converted to 5-substituted 1,3,4-oxadiazole-2-thiols (**3a-i**) as described[12]. 5-Substituted 1,3,4-oxadiazole-2-thiols were subsequently converted

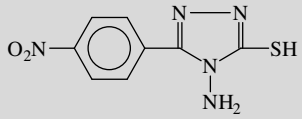
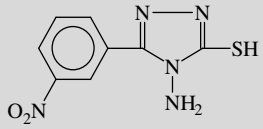
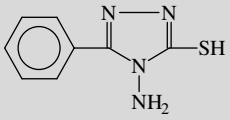
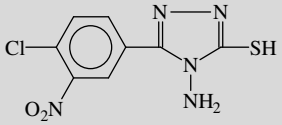
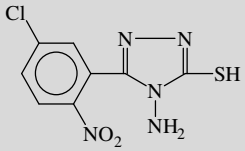
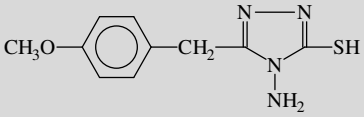
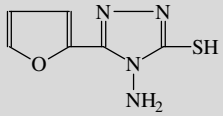
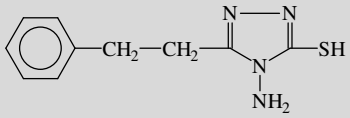
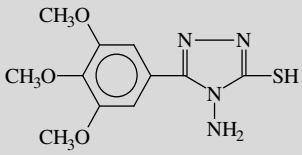
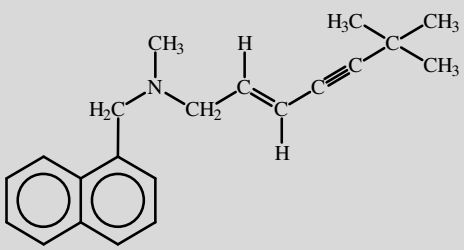


Scheme-II: Mass fragmentation of 5-(4-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (**4a**)

to 5-substituted 1,2,4-triazole-3-thiols (**4a-i**) by refluxing in the presence of 80 % hydrazine hydrate and absolute ethanol. The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in **Scheme-I**.

Mass spectral data support the proposed structures. **Scheme-II** shows the fragmentation pattern for 5-(4-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (**4a**) which serves as an example for all the compounds mutatis mutandis. The mass

TABLE-1
ANTIFUNGAL ACTIVITY OF 5-SUBSTITUTED 4-AMINO-1,2,4-TRIAZOLE-3-THIOLS (**4a-i**)

Compd.	Structure of 5-substituted 4-amino-1,2,4-triazole-thioester	Fungal strains/Inhibition (%)			
		Aspergillus flavus	*Mucor species*	*Aspergillus niger*	*Aspergillus fumigatus*
4a		96.22	87.66	74.79	97.20
4b		84.12	91.32	81.20	89.83.00
4c		69.00	40.90	65.20	57.00
4d		81.00	78.36	79.19	93.60
4e		71.00	85.89	89.99	75.37
4f		27.00	15.58	24.39	55.19
4g		63.21	48.44	38.27	53.11
4h		54.00	21.22	20.00	42.17
4i		50.00	19.48	51.99	38.31
Terbinafine standard drug		100.00	90.00	110.80	98.40

spectrum of (**4a**) showed characteristic peaks. The molecular ion peak is the base peak, which appeared at m/z 237. A peak at m/z 207 is due to the loss of N_2H_2 fragment. A peak at m/z 148 appeared due to the loss of CNSH fragment. Similarly, the loss of nitrogen gives a characteristic peak at m/z 190.

The FTIR spectrum showed absorption bands at 3250, 2606, 1602 and 1553 cm^{-1} which indicate the presence of N-H (amino), S-H (mercapto), C=C (aromatic) and C=N, respectively. The ^1H NMR spectrum of 5-(4-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (**4a**) showed characteristic signals at 7.99-8.02 (dd) and 8.30-8.33 (dd) ppm which were assigned to the aromatic protons. A signal at 3.42-3.44 ppm was attributed to the amino proton. The prominent signal at 8.34 ppm was assigned to the mercapto proton.

The ^{13}C NMR spectrum of 5-(4-nitrophenyl)-4-amino-1,2,4-oxadiazole-3-thiol (**4a**) showed characteristic peaks at 130.02, 126.91, 125.04 and 147.01 ppm which were attributed to aromatic carbon atoms. The peaks at 160.04 and 182.05 were assigned to the carbon atoms of triazole moiety. On the basis of physical and spectral data the structure of compound (**4a**) was assigned the following structure:

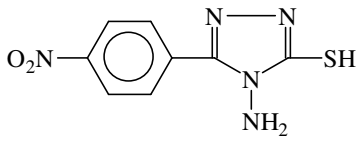


Fig. 1. Structure of 5-(4-nitrophenyl)-4-amino-1,2,4-triazole-3-thiol (**4a**)

Similarly other members of the series of 5-substituted 4-amino-1,2,4-triazole-3-thiols (**4b-i**) were synthesized by refluxing 5-substituted 1,3,4-oxadiazole-2-thiols (**3b-i**) with 80 % hydrazine hydrate in the presence of absolute ethanol.

In the *in vitro* antifungal bioassay, the compounds **4a**, **4b**, **4d** and **4e**, were found to have significant antifungal activities against four fungal strains (Table-1). In particular **4d** and **4e** had high inhibitory effects on the growth of *Aspergillus flavus*, *Mucor species, Aspergillus niger* and *Aspergillus fumigatus*. Structure activity relationship comparison shows that the presence of aromatic electron withdrawing groups present at the 5-position of the triazole-3-thiol enhances the activity of the compounds. The antifungal assay results also show that the activity of the compounds **4c**, **4f**, **4g**, **4h** and **4i** is relatively low as compared to other members of the series due to the absence of this type of grouping.

ACKNOWLEDGEMENTS

The financial support for the research project No. RG095/10AFR from the Universiti Malaya Research Grant (UMRG), University of Malaya is highly appreciated.

REFERENCES

1. A. Ikízler, F. Gümüs, S. Ozden and U. Abbasoglu, *Biol. Pharm.*, **44**, 506 (1989).
2. A. Prasad, R.J. Ramalingam, A.B. Rao, P.V. Diwan and P.B. Sattur, *Eur. J. Med. Chem.*, **24**, 199 (1989).
3. A.H. El-Masry, H.H. Fahmy, S.H. Ali and A. Waheed, *Molecules*, **5**, 1429 (2000).
4. A.S. Orabi, M.A. Moneim, E. El-Din Salem and M. El-Din Abdel-Fattah, *Polish J. Chem.*, **74**, 1675 (2000).
5. A. Al-Masirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **14**, 6057 (2004).
6. T. George, D.V. Mehta, R. Tahilramani, J. Davvid and P.K. Talwalker, *J. Med. Chem.*, **14**, 335 (1971).
7. K. Paulvannan, T. Chen and R. Hale, *Tetrahedron*, **56**, 8071 (2000).
8. D. Catarzi, V. Colotta, F. Varano, L. Cecchi, G. Filacchioni, A. Galli, C. Costagli and V. Carla, *J. Med. Chem.*, **43**, 3824 (2000).
9. D.V. Batchelor, D.M. Beal, T.B. Brown, D. Ellis, D.W. Gordon, P.S. Johnson, H.J. Mason, M.J. Ralph, T.J. Underwood and S. Wheeler, *Synlett*, 2421 (2008).
10. H. Huntsman and J. Balsells, *Eur. J. Org. Chem.*, **20**, 3761 (2005).
11. A.R. Katritzky, M.Q.D.F.G. Zhang, M.C. Griffith and K. Watson, *Org. Lett.*, **1**, 1189 (1999).
12. A. Hasan, S. Gapil and I. Khan, *Asian J. Chem.*, **23**, 2007 (2011).
13. M.I. Choudhary, Dur-e-Shahwar, Z. Parveen, A. Jabbar, I. Ali, Atta-Ur-Rahma, *Phytochemistry*, **40**, 1243 (1995).