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NOTE

Synthesis of some new thiosemicarbazide and 1,2,4-triazoles heterocycles bearing thiophene nucleus as a potent antitubercular and antimicrobial agents

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Abstract : The starting compound 2-hydrazino carbonyl-3-chloro-5-phenoxy-benzo(*b*)thiophene on reaction with different substituted phenyl isothiocyanates to give *N*-substituted arylthiosemicarbazide derivatives (1a-h). 1,2,4-Triazole derivatives (2a-h) have been prepared by the cyclization of arylthiosemicarbazides (1a-h) with sodium hydroxide. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$) and some other microbes.

Keywords : Thiosemicarbazide, triazoles.

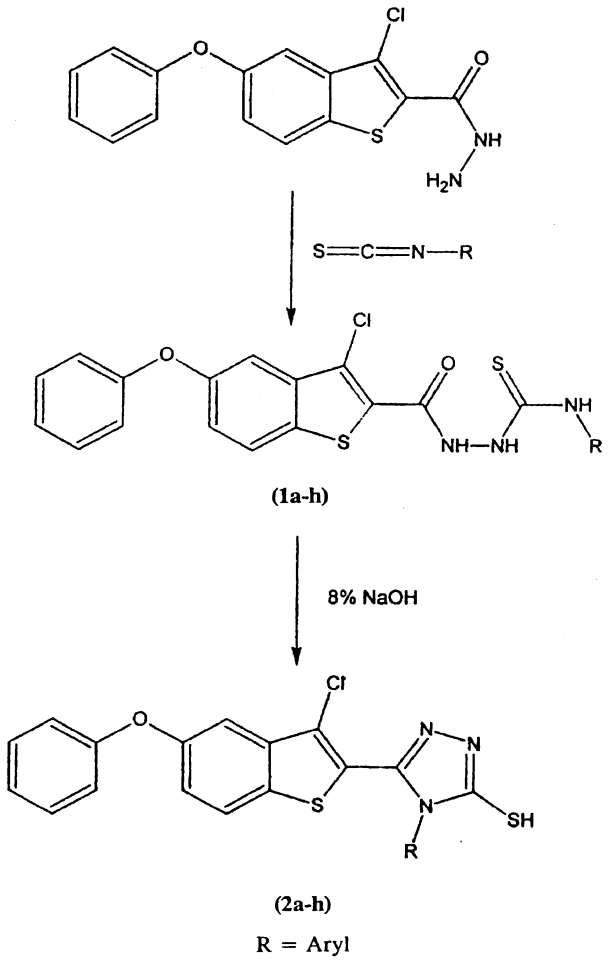
1,2,4-Triazole and its derivatives possess wide range of therapeutic activities[1]. The *N*-substituted arylthiosemicarbazide derivatives **(1a-h)** were prepared by the reaction of 2-hydrazino carbonyl-3-chloro-5-phenoxy-benzo(*b*)thiophene with different substituted phenyl isothiocyanates. 1,2,4-Triazole derivatives **(2a-h)** have been prepared by the reaction of arylthiosemicarbazides with sodium hydroxide.

The antitubercular evaluation of the compound was carried out at Tuberculosis Antimicrobial Acquisition Coordination Facility (TAACF), Alabama, USA, primary screening of the compounds for antitubercular activity has been conducted at minimum inhibition concentration 6.25 μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the ALAMAR radiometric system. The antimicrobacterial activity data were compared with standard drug Rifampin at 0.25 μg/ml concentration which showed 96% inhibition. Compounds having 4-bromo, 4-methyl, 4-methoxy and 4-chloro showed higher activity than the others. The antimicrobial activity was assayed by using the cup-plate agar diffusion method[2] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against varieties of bacterial strains such as *E. coli*, *B. magaterium*, *S. aureus* and fugi *A. niger* at 40 μg/ml concentration. Standard drugs like amoxycillin, ampicillin, ciprofloxacin, erythromycin and griseofulvin were used for the comparison purpose. It could be observed that compounds **1a** (18), **1d** (20), **1g** (20) and **2g** (20) were active against *E. coli*. Compounds **1a** (19), **1d** (25), **1g** (25), **2h** (17), were active against *P. vulgaris*. Compounds **1a** (20), **1d** (21), **1f** (26), **2d** (20) and **2f** (18) were active against *B. mega*. Compounds **1b** (21), **1d** (29), **1e** (31), **2e** (14), **3b** (20) and **3f** (18) were active against *S. aureus*. Compounds **1a** (23), **1b** (27), **1d** (30), **2a** (18), **3b** (21) and **3h** (18) displayed maximum activity against *A. niger*.

Experimental

Thin layer chromatography was used to access the reactions and purity of the compounds. The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 instrument in KBr disk, ^1H NMR spectra were recorded on Bruker AC-300 MHz FT NMR using TMS as an internal standard. Mass spectra were recorded on Jeol-D300 spectrometer. All the compounds gave satisfactory elemental analysis.

Preparation of N^1-(3′-chloro-5′-phenoxy benzo(b)-thiophen-2′-yl)-N^4-(o-methoxyphenyl)thiosemicarbazide **(1a-h)** : An ethanolic solution of 2-hydrazinocarbonyl-3-chloro-5-phenoxy benzo(*b*)thiophene (3.23 g, 0.01 mol) and (*o*-methoxyphenyl isothiocyanate) (1.65 g, 0.01 mol) was reflux for 6 h. The resulting solution poured onto crushed ice. The solid separated was isolated and crystallized from ethanol. **1h** : yield 60%, m.p. 223 °C (Found : C, 57.05; H, 3.70; N, 8.66. Required for $C_{23}H_{18}N_3O_3S_2Cl$: C, 57.08; H, 3.72; N, 8.68%); IR KBr (cm^{-1}) : 3062 (-CH=CH str., vinyl), 2927 ($-CH_3$ sym.), 1626 (-C=O str., ketone), 1222 (C-O-C str.), 745 (C-S-C str.); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm : 3.86 (3H, s, $-OCH_3$), 6.91 (2H, d, Ar-H), 6.96 (2H, d, Ar-H), 7.16 (3H, m, Ar-H), 7.25 (2H, d, Ar-H), 7.87 (2H, d, Ar-H). The mass spectrum pointed out the molecular ion peak at *m/z* 483.



Similarly, other compounds : **1a,** m.p. 231°; **b,** 215°; **c,** 209°; **d,** 169°; **e,** 179°; **f,** 223°; **g,** 256° (yields 54-68%) were prepared.

Preparation of 3-(3′-chloro-5′-phenoxy benzo(b)-thiophen-2′-yl)-4-(o-methoxyphenyl)-5-mercapto-1,2,4-triazole **(2a-h)** : A solution of N^1-(3′-chloro-5′-phenoxy benzo(*b*)thiophen-2′-yl)-N^4-(*o*-methoxyphenyl)thio-semicarbazide (4.83 g, 0.01 mol) was refluxed in sodium hydroxide solution (20 ml, 8%) for 5 h. The content was cooled, poured into cold water and neutralized with diluted acid. The product was isolated and crystallized from ethanol. Yield 58%, m.p. 208 °C (Found : C, 59.29; H, 3.40; N, 8.98. Required for $C_{23}H_{16}N_3O_2S_2Cl$: C, 59.29; H, 3.43; N, 9.02%); IR KBr (cm^{-1}) : 3064 (-CH=CH str. vinyl), 2925 ($-CH_3$ sym.), 1220 (C-O-C str.), 750 (C-S-C str.); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm : 3.37 (3H, s, $-OCH_3$), 6.28-8.43 (12H, m, Ar-H), 7.45 (1H, s, Ar-H), 7.72 (1H, s, Ar-H_c), 7.78 (1H, d, Ar-H_b). The mass spectrum pointed out the molecular ion peak at *m/z* 465.

Similarly, other compounds : **1a,** m.p. 184°; **b,** 192°; **c,** 198°; **d,** 149°; **e,** 220°; **f,** 208°; **g,** 180°; **h,** >300° (yields 55-75%) were prepared.

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