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Synthesis and Biological Activities of Some 1,3,4-Oxadiazoles, Thiadiazoles, Triazoles and Related Compounds Possessing Benzofuran moiety

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The condensation of 5-chloro-3-methyl-2-benzofuran carbohydrazide (4) with phenylisothiocynate gave 5-chloro-3-methylbenzofuran-2-carbo-N-phenylthiosemicarbazide (5). The cyclisation of 5 under different reaction conditions furnished 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazole, thiadiazolidinone and thiopyrimidone. Their chemical structures have been assigned by IR, ^{1}HNMR, Mass and elemental analyses. All the compounds synthesized were evaluated for antibacterial and antifungal activity*.

There is considerable interest in the chemotherapeutic activity of heterocycles such as oxadiazoles, thiadiazoles, triazoles, thiadiazolidinones and pyrimidines[1-4]. Recently we have reported that biheterocycles containing benzofuran and pyrazoline ring system possessed significant antimicrobial activity[5]. In continuation of our research on synthesis of pharmacologically active benzofuran derivatives, we now report the synthesis of oxadiazoles, thiadiazoles, triazoles, thiadiazolidinones and pyrimidones coupled with benzofuran moiety and the biological activity exhibited by them.

5-Chloro-3-methyl-2-benzofuran carbohydrazide (4), an intermediate in the synthesis of title compounds was synthesized from ethyl 5-chloro-3-methyl-2- benzofuran carboxylate (3). 5-Chloro-2-hydroxy acetophenone (1) on reaction with ethyl chloroacetate in anhydrous acetone in presence of anhydrous potassium carbonate gave 5-chloro-2-ethoxycarbomethoxy acetophenone (2), the ester (2) underwent Thorpe-Zeigler cyclisation in anhydrous dimethyl formamide in presence of anhydrous potassium carbonate to afford ethyl 5-chloro-3-methyl-2-benzofuran carboxylate (3). The compound (3) on reaction with hydrazine hydrate in ethanol gave 5-chloro-3-methyl-2-benzofuran carbohydrazide (4).

The carbohydrazide (4) was subjected to condensation with phenyl isothiocynate in ethanol to produce 5-chloro-3-methylbenzofuran-2-carbo-N-phenylthiosemicarbazide (5). Thiosemicarbohydrazide (5) underwent cyclisation in boiling ethanol with iodine and potassium iodide which resulted in the formation of 5-anilino-2-(5-chloro-3-methyl benzofuran-2-yl)-1,3,4-oxadiazole(6).

Cyclisation of 5 in concentrated sulphuric acid at low temperature furnished the formation of 1,3,4-thiadiazole (7). Thiosemicarbohydrazide (5) on refluxing with aqueous sodium hydroxide offered 5-(5-chloro-3-methylbenzofuran-2-yl)-4-phenyl-2,3-dihydro(3H)1,2,4-triazol-3-thione (8). The treatment of compound 5 with chloroacetic acid in presence of sodium acetate in ethanol produced thiazolidinone

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derivative (9).

The reaction of 2-benzofuran thiosemicarbohydrazide (5) with malonic acid in acetyl chloride as solvent resulted in the formation of anticipated biheterocycle, 1-(5-chloro-3-methyl-2-benzofuronyl)-4,6-dioxo-3-phenyl-2-thioxotetrahydro-pyrimidin-1(2H)-ylcarboxamide (10).

Structures of all the cyclised compounds were assigned by their IR, ^{1}HNMR, Mass spectra and elemental analysis. All the synthesized compounds were screened for antibacterial and antifungal activity.

Melting points were determined in open capillaries and are uncorrected, they are expressed in degree celsius. The purity of all compounds was checked by TLC. Infrared spectra were recorded on a Perkin Elmer 1000 in KBr disc, ^{1}HNMR spectra were recorded on a Bruker AMX 4000 and Mass spectra were recorded on GC-Mass Spec Finnigan MAT 8230 Ms.

5-Chloro-2-ethoxy carbomethoxy acetophenone (2) was prepared by adding to a solution of 5-chloro-2-hydroxy acetophenone (1) (6.8 g, 0.02 mol) in anhydrous acetone (50 ml), ethyl chloroacetate (6 g, 0.02 mol) and anhydrous potassium carbonate (12 g) . The reaction mixture was heated under gentle reflux for 20 h, the potassium salts were filtered off and washed with acetone. The solvent acetone was removed under reduced pressure and the residue solidified upon cooling. It was crystallised from benzene-petroleum ether as shining plates, yield 7.2 g (70%), mp 60°, IR (KBr) cm^{-1} 1759 (ester C=O), 1664 (-$COCH_3$), ^{1}HNMR ($CDCl_3$) δ 1.3 (t, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 4.9 (s, 2H, OCH_2), 7.1-7.8 (m, 3H, Ar-H).

Ethyl 5-chloro-3-methyl-2-benzofuran carboxylate (3) was prepared by heating a mixture of 5-chloro-2-ethoxy carbomethoxy acetophenone (2) (7.2 g, 0.028 mol) and anhydrous potassium carbonate (6 g) in anhydrous dimethyl formamide (10 ml) on a steam bath for 10 h. The reaction mixture was cooled and poured into ice water with constant stirring, the solid separated was collected by filtration and crystallised from benzene-petroleum ether as light brown needles, yield- 4 g (60%), mp- 80°, IR (KBr) cm^{-1}- 1712 (C=O), ^{1}HNMR ($CDCl_3$) δ 1.25 (s, 3H, CH_3), 1.4 (t, 3H, OCH_2CH_3), 4.4 (q, 2H, OCH_2CH_3), 7.2-7.6 (m, 3H, Ar-H).

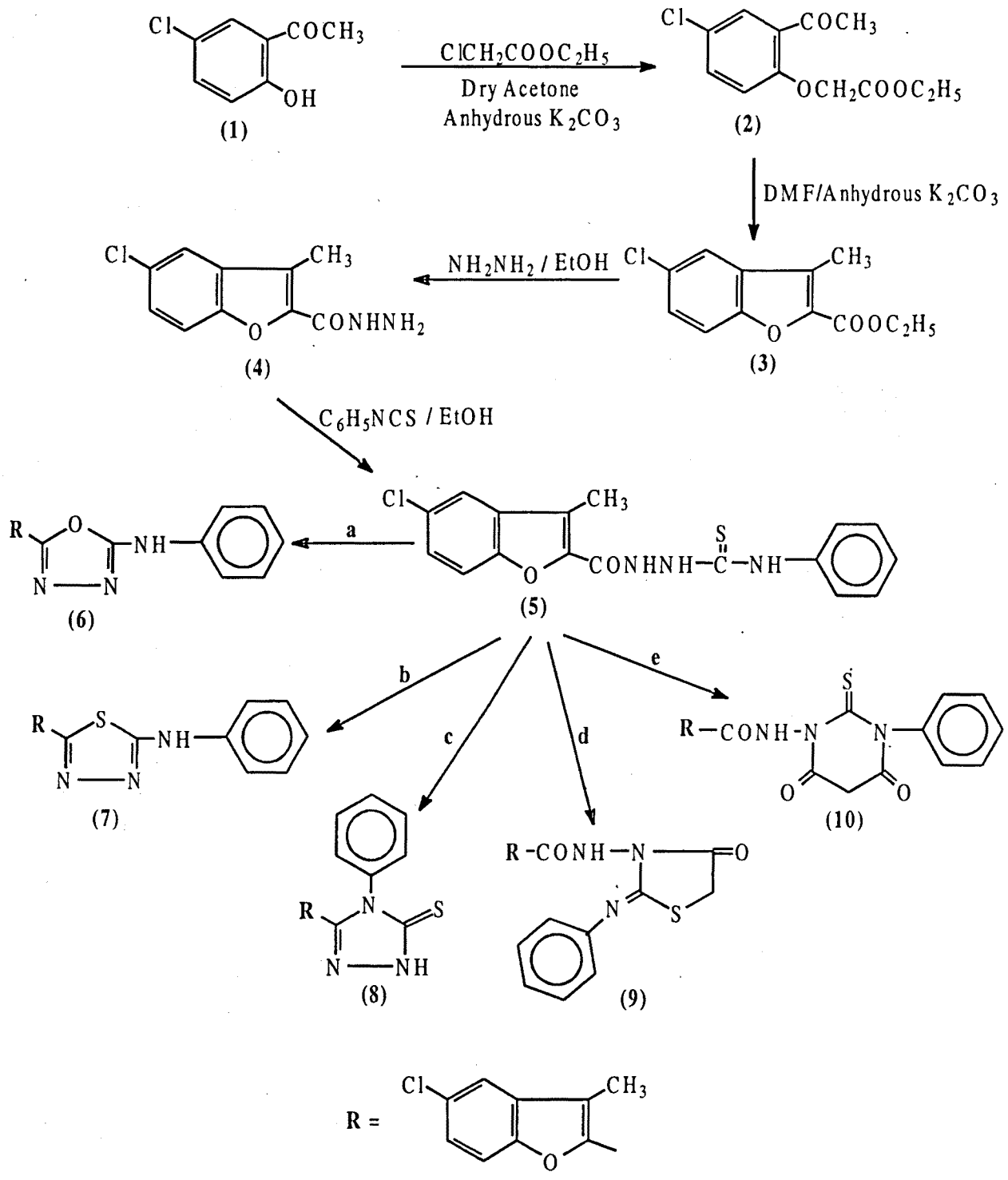
5-Chloro-3-methyl-2-benzofuran carbohydrazide (4) was synthesized by adding to a solution of ethyl 5-chloro-3-methyl-2-benzofuran carboxylate (3) (2.38 g, 0.01 mol) in anhydrous ethanol (10 ml), hydrazine hydrate (4 ml) and heating under reflux for 3 h. The solid separated after cooling was collected and crystallised from ethanol, yield- 2 g (97%), mp- 218°, IR (KBr) cm^{-1} - 3301 (NH), 1651 (C=O), ^{1}HNMR ($CDCl_3$) δ 2.5 (s, 3H, CH_3), 4.5 (s, 2H, NH_2) 7.2-7.6 (m, 3H, Ar-H), 9.9 (s, 1H, CONH).

5-Chloro-3-methylbenzofuran-2-carbo-N-phenylthiosemicarbazide (5) was prepared by adding to a suspension of 5-chloro-3-methyl-2-benzofuran carbohydrazide (4) (2.24 g, 0.01 mol) in ethanol (20 ml) phenyl isothiocynate (1.49 g, 0.01 mol). The mixture was heated at reflux for 5 h, the reaction mixture was cooled and the product separated was filtered, dried and crystallised from dioxane, yield- 1.12 g (93%), mp- 198°, IR (KBr) cm^{-1}- 3178 (NH), 1681 (C=O), 1211 (C=S), ^{1}HNMR ($CDCl_3$) □ 2.5 (s, 3H, CH_3), 7.2-7.7 (m, 8H, Ar-H), 7.9 (s, 1H, PhNH), 9.8 (s, 1H, NH NH-C=S) 10.7 (s, 1H, CONH), mass spectra m/z M^+ 359 (10%), 224 (10%), 214 (38%), 115 (30%), 121 (100%), 91 (90%), 77 (62%).

5-Anilino-2-(5-chloro-3-methyl benzofuran-2-yl)-1,3,4-oxadiazole (6) was synthesized by adding to a solution of 5 (0.268 g, 0.75 mmol) in ethanol (10 ml), 0.3 ml of aqueous sodium hydroxide (6 N). To this solution iodine in potassium iodide (10%) was added dropwise while the reaction mixture was kept at 0°. The addition of iodine was continued until the colour of iodine persisted. The reaction mixture was refluxed for 4 h, the solid that separated after cooling was filtered and dried, it was crystallised from benzene-petroleum ether, yield- 0.210 g (87%), mp- 230, IR (KBr) cm^{-1} - 3100 (NH), 1612 (C=N), ^{1}HNMR (DMSO) δ 2.5 (s, 3H, CH_3), 7.0-7.8 (m, 8H, Ar-H), 10.8 (s, 1H, NH).

5-Anilino-2-(5-chloro-3-methyl benzofuran-2-yl)-1,3,4-thiadiazole (7) was prepared by slowly adding 2-Benzofuran thiosemicarbohydrazide (5) (0.268 g, 0.75 mmol) to concentrated sulphuric acid (1.5 ml) with stirring and the temperature was kept below 0°, the temperature was maintained at 0° for another 1 h after which the reaction mixture was allowed to stand at room temperature overnight. The contents were warmed to 50°, cooled and poured into crushed ice. The solid separated was filtered, washed with water and neutralised with dilute solution of ammonia, the solid obtained was collected and crystallised from ethanol, yield 0.250 g (98%), mp 269°, IR (KBr) cm^{-1} 3050 (NH), 1600 (C=N), ^{1}HNMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3), 7.3-7.8 (m, 8H, Ar-H), 9.9 (s, 1H, NH), mass spectra m/z M^+ 341 (100%), 326 (8%), 214 (20%), 121(40%), 91(38%), 77(60%).

5-(5-chloro-3-methylbenzofuran-2-yl)-4-phenyl- 2,3-



a. I_2/KI/EtOH /reflux, 4hr b.Conc. H_2SO_4/RT, 24hr c. 5% NaOH /reflux, 1hr
d. CH_3COONa / $ClCH_2COOH$/EtOH /reflux, 5hr e. Malonic acid/acetyl chloride/Δ at 40°, 6hr

Scheme 1: Synthesis of bicyclic heterocycles.

dihydro(3H)1,2,4-triazol-3-thione (8) was prepared by heating a solution of 5 (0.268 g, 0.75 mmol) in sodium hydroxide (5%, 10 ml) at reflux for 1 h. The solution was cooled filtered and the filtrate acidified with dilute hydrochloric acid to a pH of 5. The solid that separated was collected, dried and crystallised using ethanol, yield 0.230 g (89%), mp 290°, IR (KBr) cm^{-1} 3055 (NH), 1612 (C=N), 1164 (C=S), ^{1}HNMR (DMSO) δ 2.3 (s, 3H, CH_3), 7.2-7.8 (Ar-H), 7.2-7.4 (m, 8H, Ar-H), 7.8 (s, 1H, NH).

3-(5-Chloro-3-methylbenzofuran-2-yl)-4-oxo-2-phenylimino-1,3-thiazolidin-3-yl-carboxamide (9) was prepared by adding to a solution of 5 (0.268 g, 0.75 mmol) in acetic acid (10 ml), chloroacetic acid (0.075 g) and anhydrous sodium acetate (0.075 g) The reaction mixture was refluxed for 5 h, cooled and poured into crushed ice. The solid separated was filtered, washed with water dried and crystallised from ethanol, yield 0.190 g (81%), IR (KBr) cm^{-1} 3263 (NH), 1700 (C=O), 1650 (C=O), 1612 (C=N), ^{1}HNMR ($CDCl_3$) δ 2.5 (s, 3H, CH_3), 3.4 (s, 2H, CH_2), 7.3-7.8 (m, 8H, Ar-H), 9.9 (s, 1H, NH), mass spectra m/z M^+ 399 (5%), 214 (30%), 121 (100%), 91 (70%), 77 (25%).

1-(5-Chloro-3-methyl-2-benzofuronyl)-4,6-dioxo-3-phenyl-2-thioxo tetrahydropyrimidin-1(2H)-yl carboxamide (10) was prepared by heating a mixture of 5 (0.268 g, 0.75 mmol) and malonic acid (1.5 m mol) in acetyl chloride (10 ml) was heated for 6 h at 40°. The reaction mixture was cooled and poured into crushed ice, the solid separated was collected and crystallised from aqueous dimethyl formamide, yield 0.186 g (76%), mp 162°, IR (KBr) cm^{-1} 3260 (NH), 1697 (C=O), 1087 (C=S), ^{1}HNMR (DMSO) δ 2.5 (s, 3H, CH_3), 2.7 (s, 2H, CH_2), 7.3-7.8 (m, 8H, Ar-H), 8.0 (s, 1H, NH), disappearance of two singlets at δ 7.9 and 9.8 due to PhNH and NHNH-C=S, mass spectra m/z M^+ 427 (5%), 341 (5%), 214 (30%), 121 (90%), 91 (100%), 77 (60%).

All the compounds synthesized were tested for *in vitro* antibacterial activity by Cup-plate diffusion method against *Staphylococcus aureus* and *Escherichia coli*, procured from the Department of microbiology, Gulbarga University, Gulbarga. The concentration of the compounds was 1 mg/ml and ciprofloxacin was used as standard drug. The compounds 3, 5, 6 and 9 showed moderate activity against *S. aureus* only and compounds 3,5,8 and 9 exhibited moderate activity against pathogenic organisms, *S. aureus* and *E. coli*.

The compounds synthesized were screened for their antifungal activity against *Aspergillus niger* and *Candida albicans* at a concentration 1 mg/ml using griseofulvin as standard drug, by cup-plate diffusion method. The compounds 4, 7 and 8 showed marked activity against *A. niger*. The benzofuran triazole 8 was as potent as the standard drug griseofulvin and the compound 10 showed high activity against *C. albicans*. The remaining compounds were either moderately or weakly active against *A. niger* and *C. albicans*. The *in vitro* antibacterial and antifungal activities are reported in Table 2.

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TABLE 1 PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound No	M.P. °	Yield (%)	Solvent of Crystallisation	Molecular Formula
2	60	70	Benzene-pet. Ether	$C_{12}H_{13}O_4Cl$
3	80	60	Benzene-pet. Ether	$C_{12}H_{11}O_3Cl$
4	218	97	Ethanol	$C_{10}H_9O_2N_2Cl$
5	198	93	Dioxane	$C_{17}H_{14}O_2N_3SCl$
6	230	87	Benzene-pet. Ether	$C_{17}H_{12}O_2N_3Cl$
7	269	98	Ethanol	$C_{17}H_{12}ON_3SCl$
8	290	89	Ethanol	$C_{19}H_{14}O_3N_3SCl$
9	248	81	Ethanol	$C_{20}H_{14}O_4N_3SCl$
10	262	76	Aq-DMF	

The compounds gave satisfactory C, H and N analyses.

TABLE 2: RESULTS OF *IN VITRO* ANTIMICROBIAL ACTIVITY

Compound No.	Zone of inhibition in mm*			
	Antibacterial		Antifungal	
	S. aureus	*E. coli*	*A. niger*	*C. albicans*
2	14	13	14	14
3	15	15	13	15
4	13	14	18	14
5	15	15	16	17
6	16	13	16	17
7	09	13	22	16
8	14	16	22	25
9	15	15	13	15
10	15	10	13	18
Ciprofloxacin	20	21	-	-
Griseofulvin	-	-	26	25
Control DMF	Nil	Nil	Nil	Nil

*Including diameter of the well – 8 mm.

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Antihypertensive Drug Utilization In Patients Attending Panjab University Health Centre

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The pilot study was carried out to assess prescribing practice of antihypertensive drugs at Panjab University Health Centre, Chandigarh. Prescriptions of hypertensive patients were monitored

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