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Synthesis and Antiulcer Activity of 2-[{5-Substituted-1*H*-benzo(d)imidazol-2-yl sulfinyl}methyl]-3-substituted Phenyl Quinazoline-4(3*H*)-one Derivatives

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The synthesis of 2-[{5-substituted-1*H*-benzo(d)imidazol-2-yl sulfinyl}methyl]-3-substituted phenyl quinazoline-4(3*H*)-one derivatives were carried out. Anthranilic acid was treated with chloroacetylchloride to give *n*-chloroacetyl anthranilic acid (**1**). **1** was then treated with amines to give 2-chloromethyl-3-aryl-4(3*H*)-one-quinazoline (**2**). **2** was condensed with 2-mercapto 5-substituted benzimidazoles **3(a-g)**, **4(a-g)** and **5(a-g)** and finally oxidation of sulfur was carried out to give **6(a-g)**, **7(a-g)** and **8(a-g)**. All compounds were characterized by their spectral studies. Antiulcer activities of **6(a-g)**, **7(a-g)** and **8(a-g)** were studied by pylorous ligation induced ulcer models in rats.

Key Words: Synthesis, 4-Quinazolinone, Benzimidazole, Antiulcer activity.

INTRODUCTION

The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-esophagitis and nonsteroidal antiinflammatory drug-induced lesions[1]. Such diseases seem to have prominent share in health disorder in current scenario of globalization and are treated by blocking acid secretion in stomach. A series of benzimidazole derivatives have exhibited proven antiulcer activity as potential inhibitors of H^+/K^+ATPase. The enzyme H^+K^+-ATPase is responsible for gastric acid production and is located in the secretary membranes of the parietal cell[2-7]. In this paper, some new derivatives of benzimidazole by combination of the quinazoline nucleus with different substituents at the 3-N of quinazoline with benzimidazole ring (**6-8**) and their antiulcer activity have been reported.

The structures of the starting compounds and novel benzimidazole derivatives (**6-8**) are given in **Scheme-I**.

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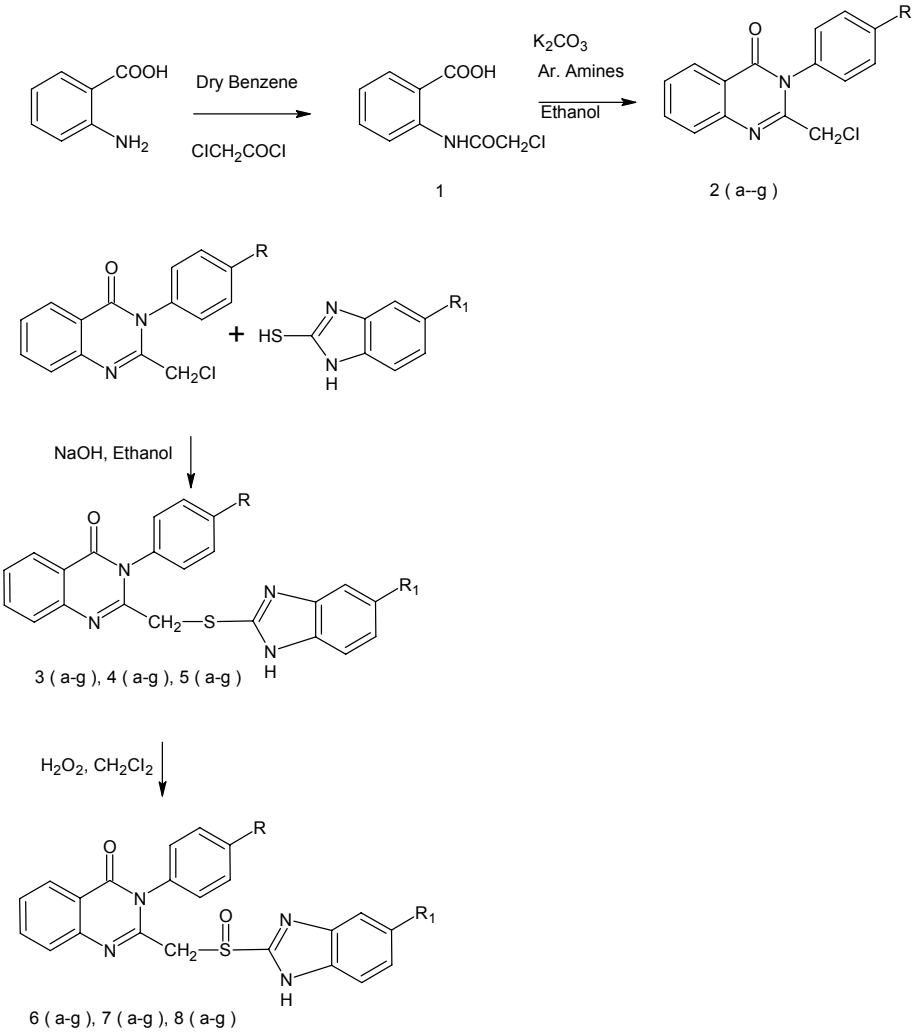


Scheme-I

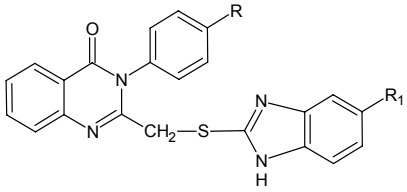
EXPERIMENTAL

The starting compounds N-chloroacetyl anthranilic acid[8,9] (**1**), 2-chloromethyl -3-aryl-4(3*H*)-one-quinazoline[8,9] (**2a-g**) and 2-[{5-substituted-1*H*-benzo(d)imidazol-2-yl thio}methyl]-3-substituted phenyl quinazoline-4(3*H*)-one derivatives[5] (**3a-g**), (**4a-g**) and (**5a-g**) were prepared according to the literature. Purity of the compounds was checked by TLC method. Melting points were determined with Lab line melting point apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu 8400-s spectrophotometer. Proton NMR spectra were recorded on a Varion 300 MHz NMR spectrometer (DMSO-d_6, δ ppm). GCMS spectra were recorded on Shimadzu QP-5050 spectrophotometer.

Synthesis of 2-[{1*H*-benzo(d)imidazol-2-yl sulfinyl]methyl}-3-phenyl quinazoline-4(3*H*)-one (6a): A solution of hydrogen peroxide 1.43 mL (0.015 mol) in dichloromethane is added in 2-[{1*H*-benzo(d)imidazol-2-yl thio}methyl]-3-phenyl quinazoline-4(3*H*)-one (0.01 mol) and stirred for 8 to 10 h. Solvent was evaporated and residue was treated with water to give solid, which was recrystallized from ethanol. IR (KBr, ν_{max}, cm^{-1}): 3157 (NH), 3035 (CH), 2920 (CH), 1647 (C=O), 1590 (C= N), 1560 (C-N), 1014 (S=O) and 742 (C-S-C). ^{1}H NMR: (DMSO-d_6) δ: 7.8 (d, 1H, quinoline-H-4), 7.4 (dd, 1H, quinoline-H-5), 7.4 (dd, 1H, quinoline-H-6), 7.3 (d, 1H, quinoline-H-7), 7.5 (d, 3H, N-C_6H_5-H-2,4,6), 6.2 (d, 2H, N-C_6H_5-H-3,5), 7.6 (d, 1H, benzimidazole-H-7), 7.4 (d, 1H, benzimidazole-H-6), 7.3 (d, 1H, benzimidazole-H-5), 7.5 (d, 1H, benzimidazole-H-4), 14.1 (s, 1H, N-H benzimidazole), 5.2 (s, 2H, CH_6-S0), MS (m/z) 400 $[M]^+$.

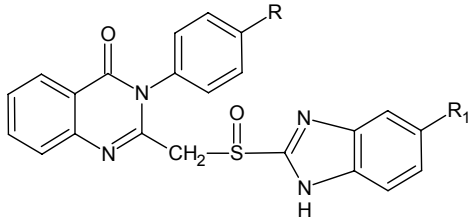
The above reaction was extended to synthesize compounds **6(b-g)**, **7(a-g)** and **8(a-g)** crystallized from ethanol. The physical data are presented in Table-2.

TABLE-1
PHYSICAL DATA OF BENZIMIDAZOLES (**3-5**)



Compd.	R	R_1	m.p. (ºC)	Yield (%)
3a	H	H	128	48
3b	CH_3	H	123	45
3c	$COCH_3$	H	131	52
3d	OCH_3	H	132	38
3e	OC_2H_5	H	136	40
3f	Br	H	161	45
3g	Cl	H	152	57
4a	H	OCH_3	125	38
4b	CH_3	OCH_3	120	48
4c	$COCH_3$	OCH_3	132	42
4d	OCH_3	OCH_3	135	42
4e	OC_2H_5	OCH_3	128	35
4f	Br	OCH_3	145	50
4g	Cl	CH_3	148	52
5a	H	$OCHF_2$	141	55
5b	CH_3	$OCHF_2$	136	41
5c	$COCH_3$	$OCHF_2$	148	52
5d	OCH_3	$OCHF_2$	142	40
5e	OC_2H_5	$OCHF_2$	130	45
5f	Br	$OCHF_2$	148	44
5g	Cl	$OCHF_2$	151	46

TABLE-2
PHYSICAL AND ANTIULCER ACTIVITY DATA OF 2-[{5-SUBSTITUTED-1*H*-BENZO (D) IMIDAZOL-2-YL SULFINYL}METHYL]-3-SUBSTITUTED PHENYL QUINAZOLINE-4(3*H*)-ONE DERIVATIVES (**6-8**)



Compd.	R	R_1	m.p. (ºC)	Yield (%)	Ulcer index ± SEM (10 mg)	Ulcer index ± SEM (30 mg)
6a	H	H	135	45	2.167 ± 0.3801**	1.333 ± 0.2108***
6b	CH_3	H	130	40	2.167 ± 0.2108**	1.750 ± 0.3096*
6c	$COCH_3$	H	138	48	2.667 ± 0.3333*	2.000 ± 0.1826***
6d	OCH_3	H	141	35	2.417 ± 0.5231*	1.833 ± 0.3073*
6e	OC_2H_5	H	140	46	2.333 ± 0.2789**	1.833 ± 0.2472***
6f	Br	H	168	41	2.833 ± 0.2472*	2.250 ± 0.2814**
6g	Cl	H	159	42	2.833 ± 0.2472*	2.083 ± 0.2713*
7a	H	OCH_3	127	35	1.750 ± 0.4233**	1.250 ± 0.1708***
7b	CH_3	OCH_3	124	45	1.833 ± 0.2108***	1.500 ± 0.1800***
7c	$COCH_3$	OCH_3	137	40	2.750 ± 0.4233*	2.250 ± 0.2500**
7d	OCH_3	OCH_3	139	38	2.000 ± 0.2582**	1.417 ± 0.2007***
7e	OC_2H_5	OCH_3	133	42	2.330 ± 0.3073**	1.500 ± 0.2887***
7f	Br	OCH_3	149	42	2.667 ± 0.3073*	2.000 ± 0.2582*
7g	Cl	CH_3	154	46	2.167 ± 0.2472**	1.667 ± 0.1667***
8a	H	$OCHF_2$	145	42	1.660 ± 0.3801***	1.250 ± 0.2141***
8b	CH_3	$OCHF_2$	130	40	1.833 ± 0.3073***	1.250 ± 0.1708***
8c	$COCH_3$	$OCHF_2$	152	48	2.417 ± 0.4167*	1.833 ± 0.1667***
8d	OCH_3	$OCHF_2$	144	38	1.500 ± 0.2887***	1.000 ± 0.1826***
8e	OC_2H_5	$OCHF_2$	134	38	1.917 ± 0.2386**	1.500 ± 0.3416***
8f	Br	$OCHF_2$	153	42	2.667 ± 0.2472*	2.000 ± 0.3416**
8g	Cl	$OCHF_2$	154	43	2.333 ± 0.2108**	1.667 ± 0.1054***
	Omeprazole				0.500 ± 0.28***	0.000 ± 0.0000***
	Control				3.5 ± 0.28	

n = 6, Values are expressed as mean ± SEM.
*p < 0.1 compared to control group (Student's t test).
**p < 0.01 compared to control group (Student's t test).
***p < 0.001 compared to control group (Student's t test).

RESULTS AND DISCUSSION

The synthesis of 2-[{5-substituted-1*H*-benzo(d)imidazol-2-yl sulfinyl}methyl]-3-substituted phenyl quinazoline-4(3*H*)-one derivatives **6**, **7** and **8** were carried out. N-Chloroacetyl anthranilic acid **1** and **2**-chloromethyl, 3-substituted aryl, 4(3*H*)-one quinazoline of type **2** were prepared according to literature[8,9]. **2** was then condensed with 2-mercapto 5-substituted benzimidazoles of type **3**, **4** and **5** following the

method reported in literature[5]. Finally oxidation of sulfur in the compounds of type **3**, **4** and **5** was carried out to give compounds of type **6**, **7** and **8**. All compounds were characterized by their spectral studies. IR spectra of compound showed expected bands for the different functional groups. Quinazoline ring showed strong band at 1668 cm^{-1} indicating the presence of an

group. Bands at 742 and 1014 were observed which were attributed to C-S-C and S=O vibration, respectively. ^{1}H NMR spectra of compound **6-8(a-g)** exhibited a singlet at 5.2 and 14.1 integrating for two and one protons, respectively and assigned to a methylene of the chain (-CH_2-S--) and N-H of benzimidazole. Other signals appeared in the aromatic region ranging from 6.2 to 7.8 integrating for the protons of quinazoline, aryl and benzimidazole nucleus.

The newly synthesized compounds **6-8(a-g)** in different doses were screened for antiulcer activity by pylorus ligation in shay rat method using omeprazole as standard[10]. At doses of 30 mg/kg oral administration in rats most of the compounds showed antiulcer activity. **7a**, **7b**, **8a**, **8b**, **8d** and **8e** showed highest activity at the doses 10 mg/kg after per oral administration in rat. However, none of the compounds had greater activity than omeprazole. It was concluded that difluromethoxy compounds showed maximum activity.

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