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Synthesis and antiulcer activity of 2-[5-substituted-1-*H*-benzo(d) imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4-(3*H*) ones

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Abstract. 2-[5-substituted-1-*H*-benzo(d)imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4-(3*H*)-one derivatives were synthesized and tested for antiulcer activity against pylorus ligation-induced, aspirin induced and ethanol induced ulcer in rat model. All the synthesized compounds were characterized by using IR, MS and ^{1}H NMR spectral and elemental analysis. The compounds were scramed for their antiulcer activity: compounds **5k** and **5n** showed higher activity than omeprazole used as standard.

Keywords. Synthesis; 4-quinazolinone; benzimidazole; antiulcer activity.

1. Introduction

Benzimidazole sulfinyl methyl pyridine is a well-established class of H^+/K^+ATPase inhibitors, therapeutically useful in the treatment of acute and chronic ulcer conditions.[1] In the past few years, research for new antiulcer agents has focused on numerous structural patterns of benzimidazole sulfinyl methyl pyridine moiety by substitution on the benzimidazole ring, methyl sulfinyl chain and pyridine.[2] Besides this studies, another simple chemical modification was done by an insertion of pyrimidine ring instead of pyridine in the benzimidazole sulfinyl methyl pyridine moity, resulted in increase in antiulcer and antisecretory activity.[3] In addition, in recent years there has been an increasing interest in the chemistry of 4(3H)-quinazolinones because of their biological significance.[4,5] In view of these reports, it was thought worthwhile to synthesize and investigate the compounds in which the benzimidazole derivatives have been linked with the quinazoline moiety.

On the basis of the above mentioned reports, the present work is concerned with the synthesis of different 2-[5-substituted 1-*H* benzo(d)imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4-(3*H*)-one derivatives with the objective of discovering novel antiulcer agents.

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2. Experimental

2.1 *Materials, method and instruments*

Melting points were determined with Lab line melting point apparatus and are uncorrected. Infra-Red spectra were recorded on a Shimadzu 8400-s spectrophotometer using KBr pellets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varion 300 MHz spectrometer using $CDCI_3$, as solvent with TMS as an internal standard. Mass spectral data was recorded on Shimadzu QP5050 spectrophotometer. Elemental analysis (C, H, N) were performed on a FLASH EA 1112 analyzer and were within ± 0·4 of the theoretical value. The reactions were monitored by thin layer chromatography (TLC) using silica gel-G (benzene:ethanol, 1 : 5).

2.2 *General method for synthesis of compounds* **(5a–o)**

2.2a *2-((1-H Benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(3,4 dimethoxy phenyl) quinazolin 4(3H)-one* **(5a)**: To a solution of **4a** (1 g, 2 mmol) in dichloromethane (50 mL) hydrogen peroxide (30% w/v, 0·2 mL, 2 mmol) in acetic acid (5 mL) was added drop-wise in reaction mixture. The mixture was heated at 50–60°C under stirring for 8–10 h. Thereafter, the solvent was removed under reduced pressure. Residue was added in ice cold water to

yield a precipitate which was filtered and recrystallized from ethanol and shows m.p.: 240–242°C in 68% yield.

R_f = 0·79; IR:(KBr/cm^{-1}): 1514 (C=C), 1714 (C=O), 2980 (C–H alkyl), 3126 (C–H Ar), 1467 (C=N), 1543 (C–N), 3153 (N–H), 740 (C–S–C), 1033 (S=O) 1261 (C–O–C).

^{1}H NMR (300 MHz,CDCI$_3$) δ_{ppm}: 3.9 (*s*, 6H, OC<u>H</u>$_3$), 5·0 (*s*, 2H, C<u>H</u>$_2$SO), 12·4 (*s*,1H, <u>NH</u>), 6·4–8·0 (*m*, 11H, ArH). MS (*m/z*) 460[M]$^+$; Anal. Calcd. for $C_{24}H_{20}N_4O_4S_1$: C, 62·60; H, 4·34; N, 12·17. Found: C, 62·80; H, 4·61; N, 12·07. Compounds **5b–o** were obtained similarly.

2.2b *2-((1-H Benzo[d] imidazol-2-yl sulfinyl) methyl)-3-(pyridyl-2-yl) quinazolin-4(3H)- one* (**5b**): Yield: 0·64 g (62%); m.p.: 252–254°C; R_f: 0·80, IR (KBr/cm^{-1}): 1592 (C=C), 1680 (C=O), 2950 (C–H alkyl), 1668 (C=N), 1514 (C–N), 3180 (N–H), 785 (C–S–C), 1030 (S=O).

^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 5·1 (*s*, 2H, C<u>H</u>$_2$SO), 11·8 (*s*, 1H, <u>NH</u> benz), 6·4–8·4 (*m*,12H, ArH). MS (*m/z*) 401 [M]$^+$; Anal. Calcd. for $C_{21}H_{15}N_5O_2S_1$: C, 62·84; H, 3·74; N, 17·45. Found: C, 62·92; H, 3·91; N, 17·28.

2.2c *2-((1-H Benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyridyl-3-yl) quinazolin-4(3H)-one* (**5c**): Yield: 0·74 g (72%); m.p.: 240–242°C, R_f: 0·81, IR (KBr/cm^{-1}): 1585 (C=C), 1670 (C=O), 2945 (C–H alkyl), 1660 (C=N), 1524 (C–N), 3210 (N–H), 782 (C–S–C), 1030 (S=O).

^{1}H NMR(300 MHz,CDCI$_3$) δ_{ppm}: 4·9 (*s*, 2H, C<u>H</u>$_2$SO), 11·8 (*s*,1H, <u>NH</u> benz), 6·4–8·2 (*m*, 12H, ArH). MS (*m/z*) 401 [M]$^+$; Anal. Calcd. for $C_{21}H_{15}N_5O_2S_1$: C, 62·84; H, 3·74; N, 17·45. Found: C, 62·72; H, 4·04; N, 17·38.

2.2d *2-((1-H Benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyrazine-2-yl) quinazolin-4(3H)-one* (**5d**): Yield: 0·72 g (70%); m.p.: 292–294°C, R_f: 0·82, IR (KBr/cm^{-1}): 1632 (C=C), 1700 (C=O), 2940 (C–H alkyl), 1642 (C=N), 1468 (C–N), 3250 (N–H), 742 (C–S–C), 1029 (S=O). ^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 4·9 (*s*, 2H, <u>CH</u>$_2$SO); 11·8 (*s*, 2H, <u>NH</u>), 6·4–8·0 (*m*, 12H, ArH). MS (*m/z*) 402 [M]$^+$; Anal. Calcd. for $C_{20}H_{14}N_6O_2S_1$: C, 59·70; H, 3·48; N, 20·89. Found: C,59·92; H, 3·78; N, 21·20.

2.2e *2-((1-H Benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(tetrazole-5-yl) quinazolin-4(3H)-one* (**5e**): Yield: 056 g (54%); m.p.: above 300°C; R_f: 0·70, IR (KBr/cm^{-1}): 1635 (C=C), 1678 (C=O), 2920 (C–H alkyl), 1642 (C=N), 1410 (C–N), 3320 (N–H), 716 (C–S–C), 1021 (S=O), 1480 (N=N).

^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 12·2 (*s*, 1H, <u>NH</u> benz), 12·5 (*s*, 1H, <u>NH</u> tetrazole), 5·3 (*s*, 2H, C<u>H</u>$_2$SO), 6·9–8·5 (*m*, 8H, ArH). MS (*m/z*) 392[M]$^+$; Anal. Calcd. for $C_{17}H_{12}N_8O_2S_1$: C, 52·04; H, 3·06; N, 28·57. Found: C, 52·32; H, 3·31; N, 28·68.

2.2f *2-((5-Methoxy benzo[d]imidazol-2-ylsulfinyl) methyl)-3-(3,4 dimethoxy phenyl) quinazolin-4(3H)-one* (**5f**): Yield: 0·66g (64%); m.p.: 236–238°C; R_f: 0·78, IR (KBr/cm^{-1}): 1521 (C=C), 1710 (C=O), 2950 (C–H alkyl), 1610 (C=N), 1467 (C–N), 3190 (N–H), 780 (C–S–C), 1265 (C–O–C), 1049 (S=O).

^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 3·8 (*s*, 9H, OC<u>H</u>$_3$), 12·0 (*s*, 1H, <u>NH</u> benz), 4·8 (*s*, 2H, <u>CH</u>$_2$SO), 6·6–7·8 (*m*, 8H, ArH). MS (*m/z*) 491 [M]$^+$; Anal. Calcd. for $C_{25}H_{22}N_4O_5S_1$: C, 61.09; H, 4·48; N, 11·40. Found: C, 61·32; H, 4·51; N, 11·30.

2.2g *2-((5-Methoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyridyl-2-yl) quinazolin-4(3H)-one* (**5g**): Yield: 0·69 g (67%); m.p.: 260–261°C, R_f: 0·78, IR (KBr/cm^{-1}): 1570 (C=C), 1692 (C=O), 2940 (C–H alkyl), 1668 (C=N), 1514 (C–N), 3200 (N–H), 780 (C–S–C), 1265 (C–O–C), 1033 (S=O).

^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 3·9 (*s*, 3H, OC<u>H</u>$_3$), 11·9 (*s*, 1H, <u>NH</u> benz), 5·0 (s, 2H, <u>CH</u>$_2$SO), 6·5–8·5 (*m*, 8H, ArH). MS (*m/z*) 431 [M]$^+$; Anal. Calcd. for $C_{22}H_{17}N_5O_3S_1$: C, 61·25; H, 3·94; N, 16·24. Found: C, 61·52; H, 4·21; N, 16·38.

2.2h *2-((5-Methoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyridyl-3-yl) quinazolin-4(3H)-one* (**5h**): Yield: 0·66 g (65%); m.p.: 228–230°C, R_f: 0·82, IR (KBr/cm^{-1}): 1580 (C=C), 1670 (C=O), 2952 (C–H alkyl), 1660 (C=N), 1524 (C–N), 3210 (N–H), 782 (C–S–C), 1270 (C–O–C), 1033 (S=O).

^{1}H NMR (300 MHz, CDCI$_3$) δ_{ppm}: 5·0 (*s*, 2H, C<u>H</u>$_2$SO), 3·9 (*s*, 3H, OC<u>H</u>$_3$), 12·3 (*s*, 1H, <u>NH</u> benz), 6·6–7·4 (*m*, 8H, ArH). MS (*m/z*) 431 [M]$^+$; Anal. Calcd. for $C_{22}H_{17}N_5O_3S_1$: C, 61·25; H, 3·94; N, 16·24. Found: C, 61·52; H, 4·31; N, 16–38.

2.2i *2-((5-Methoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyrazine-2-yl) quinazolin-4(3H)-one* (**5i**): Yield: 0·74g (72%); m.p.: 286–288°C, R_f: 0·84, IR (KBr/cm^{-1}): 1644 (C=C), 1705 (C=O), 2932 (C–H alkyl), 1652 (C=N), 1468 (C–N), 3240 (N–H), 742 (C–S–C), 1042 (S=O), 1272 (C–O–C).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 5·0 (*s*, 2H, $\underline{CH_2}SO$), 3·9 (*s*, 3H, $O\underline{CH_3}$), 11·8 (*s*, 1H, NH), 6·6–7·9 (*m*, 8H, ArH). MS (*m/z*) 432[M]$^+$; Anal. Calcd. for $C_{21}H_{16}N_6O_3S_1$: C, 58·33; H, 3·70; N, 19·44. Found: C, 58·52; H, 3·90; N,19·22.

2.2j *2-((5-Methoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(tetrazole-5-yl) quinazolin-4(3H)-one* (**5j**): Yield: 0·61 g (59%); m.p.:above 300°C, R_f: 0·78, IR (KBr/cm^{-1}): 1622 (C=C), 1680 (C=O), 2910 (C–H alkyl), 1660 (C=N), 1422 (C–N), 3420 (N–H), 718 (C–S–C), 1268 (C–O–C), 1069 (S=O) 1482 (N=N).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 5·0 (*s*, 2H, $C\underline{H_2}SO$), 3·8 (*s*, 3H, $OC\underline{H_3}$), 11·9 (*s*, 1H, NH benz.), 12·4 (*s*, 1H, NH tetrazole), 6·6–8·2 (*m*, 8H, ArH). MS (*m/z*) 422 [M]$^+$; Anal. Calcd. for $C_{18}H_{14}N_8O_3S_1$: C, 51·18; H, 3·31; N, 26·54. Found: C, 41·52; H, 3·41; N, 26·38.

2.2k *2-((5-Difluromethoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(3,4 dimethoxy phenyl) quinazolin-4(3H)-one* (**5k**): Yield: 0·66 g (64%); m.p.: 222–224°C, R_f: 0·76, IR (KBr/cm^{-1}): 1519 (C=C), 1757 (C=O), 2930 (C–H alkyl), 1467 (C=N), 1537 (C–N), 3110 (N–H), 802 (C–S–C), 1280 (C–O–C), 1031 (S=O).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 3·9 (*s*, 6H, $OC\underline{H_3}$), 12·6 (*s*, 1H, NH benz), 5·0 (*s*, 2H, $C\underline{H_2}SO$), 6·6 (*t*, 1H, $OC\underline{H}F_2$), 6·8–7·6 (*m*, 8H, ArH). MS (*m/z*) 526 [M]$^+$; Anal. Calcd. for $C_{25}H_{20}N_4O_5S_1F_2$: C, 57·03; H, 3·80; N, 10·64. Found: C, 57·32; H, 3·91; N, 10·78.

2.2l *2-((5-Difluromethoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyridyl-2-yl) quinazolin-4(3H)-one* (**5l**): Yield: 0·66 g (64%); m.p.:232–234°C, R_f: 0·78 IR (KBr/cm^{-1}): 1585 (C=C), 1692 (C=O), 2932 (C–H alkyl), 1668 (C=N), 1516 (C–N), 3190 (N–H), 780 (C–S–C), 1265 (C–O–C), 1010 (S=O).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 5·1 (*s*, 2H, $C\underline{H_2}SO$), 6·5 (*t*, 1H, $OC\underline{H}F_2$), 12·0 (*s*, 1H, NH benz.), 6·8–8·2 (*m*, 8H, ArH). MS (*m/z*) 467 [M]$^+$; Anal. Calcd. for $C_{22}H_{15}N_5O_3S_1F_2$: C, 56·53; H, 3·21; N, 14·98. Found: C, 56·72; H, 3·41; N, 15·28.

2.2m *2-((5-Difluromethoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3-(pyriyl-3-yl) quinazolin-4(3H)-one* (**5m**): Yield: 0·70 g (68%); m.p.: 208–210°C, R_f: 0·84, IR (KBr/cm^{-1}): 1588 (C=C), 1670 (C=O), 2910 (C–H alkyl), 1662 (C=N), 1525 (C–N), 3260 (N–H), 785 (C–S–C), 1272 (C–O–C), 1031 (S=O).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 5·1 (*s*, 2H, $C\underline{H_2}SO$), 6·4 (*t*, 1H, $OC\underline{H}F_2$), 12·2 (*s*, 1H, NH benz.), 6·4–8·4 (*m*, 8H, ArH). MS (*m/z*) 467 [M]$^+$; Anal. Calcd for $C_{22}H_{15}N_5O_3S_1F_2$: C, 56·53; H, 3·21; N, 14·98. Found: C, 56·62; H, 3·41; N, 14·78.

2.2n *2-((5-Difluromethoxy benzo[d]imidazol-2-yl sulfinyl) methyl)-3(pyrazine-2-yl) quinazolin-4(3H)-one* (**5n**): Yield: 0·72 g (70%); m.p.: 272–274°C, R_f: 0·85, IR (KBr/cm^{-1}): 1641 (C=C), 1705 (C=O), 2932 (C–H alkyl), 1655 (C=N), 1468 (C–N), 3232 (N–H), 742 (C–S–C), 1039 (S=O), 1272 (C–O–C).

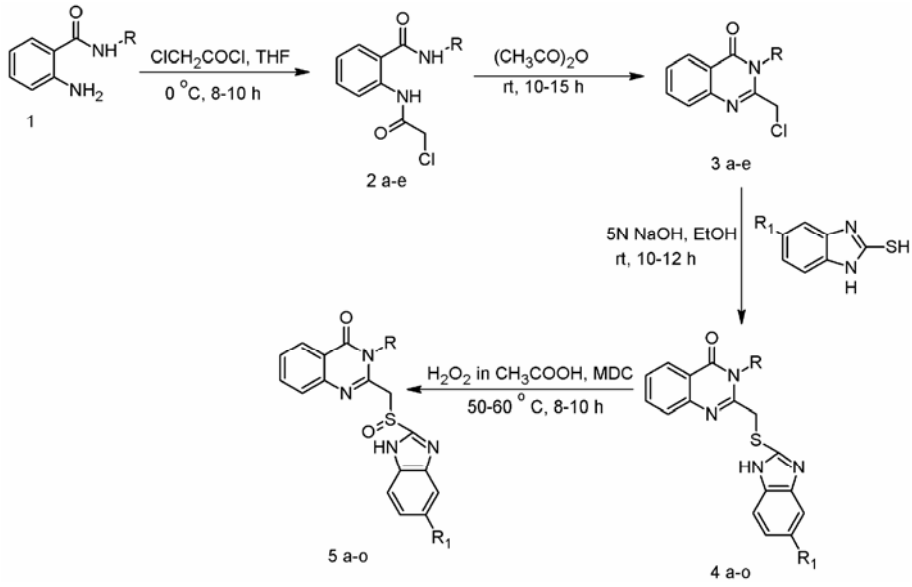
^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 5·0 (*s*, 2H, $C\underline{H_2}SO$), 12·1 (*s*, 2H, NH), 6·6 (*t*, 1H, $OC\underline{H}F_2$), 6·8–8·2 (*m*, 8H, ArH). MS (*m/z*) 468 [M]$^+$; Anal. Calcd. for $C_{21}H_{14}N_6O_3S_1F_2$: C, 53·84; H, 2·99; N, 17·94. Found: C, 53·94; H, 3·21; N, 17·98.

2.2o *2-((5-Difluromethoxybenzo[d]imidazol-2-yl-sulfinyl) methyl)-3-(tetrazole-5-yl) quinazolin-4(3H)-one* (**5o**): Yield: 0·56 g (55%); m.p.: 297–298°C, R_f: 0·70, IR (KBr/cm^{-1}): 1506 (C=C), 1695 (C=O), 2950 (C–H alkyl), 1660 (C=N), 1460 (C–N), 3450 (N–H), 740 (C–S–C), 1284 (C–O–C), 1041 (S=O) 1470 (N=N).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 12·4 (*s*, 1H, NH tetrazole), 12·0 (*s*, 1H, NH benz), 5·1 (*s*, 2H, $C\underline{H_2}SO$), 6·8 (*t*, 1H, $O\underline{CH}F_2$), 7·0–8·6 (*m*, 8H, ArH). MS (*m/z*) 458[M]$^+$; Anal. Calcd. for $C_{18}H_{12}N_8O_3S_1F_2$: C, 47·16; H, 2·62; N, 24·45. Found: C, 47·42; H, 2·81; N, 24·38.

2.3 *Antiulcer screening*

2.3a *Pylorus ligation-induced gastric ulcer:* The different doses were screened for antiulcer activity by pylorus ligation in shay rat method using Omeprazole as standard.[6] Wistar Albino rats of either sex (150–200 g) were kept in the departmental animal house at room temperature 25–30°C. Rats were divided into various groups. Omeprazole (10 and 20 mg/kg) and pure compounds **5a–o** (10 and 20 mg/kg), were suspended in 1% suspension of CMC (Carboxy methyl cellulose) in distilled water and administered by oral route. The animals were fasted for 48 h prior to the experiment, but had free access to water. After the fasting period, the animals were given the drug samples p.o, 1 h prior to the ligation. Thereafter, the rats were anaesthetized with anesthetic ether. An incision of 1 cm length in the abdomen just below the sternum was made. The



Scheme 1. Reagents and conditions: (i) $ClCH_2COCl$, THF, 0°C, 8–10 h; (ii) acetic anhydride, rt, 10–15 h; (iii) 5N NaOH, EtOH, rt, 10–12 h; (iv) H_2O_2 in acetic acid, MDC, 50–60°C, 8–10 h.

stomach was exposed. A thread was passed around the pyloric sphincter and a light knot was applied to it taking due care that no blood vessel was tied along the knot. Then incision was closed by stitching the abdominal wall by a thread. The underlying skin was cleaned of any bleeding. An antiseptic cream was applied over the wound. Thereafter, the animal was kept in a separate cage and allowed to recover. Four hours later these animals were sacrificed and the stomach of each of the animals was isolated and cut open through its greater curvature. Its contents emptied into graduated test tube, volume was recorded. pH was measured by pH meter. Ulcer score were observed and ulcer index were calculated by One Way ANOVA analysis and results were compared with control by student's t test.

2.3b *Aspirin induced gastric ulcer:* Wistar Albino rats weighing between (150–200 g) were divided into five animals in group.[6] The animals are fasted for 24 h. The test drugs were administered orally in 1% CMC solution 30 min prior to aspirin at dosage of 200 mg/kg. Four hours later the rats are sacrificed by using anaesthetic ether and their stomachs dissected for the determination of gastric lesions. Ulcer score were observed and ulcer index were calculated by One Way ANOVA analysis and results were compared with control by student's *t* test.

2.3c *Ethanol-induced gastric ulcer:* Male Albino wistar rats weighing between 150 and 200 g were divided into five animals in group.[6] The animals were fasted for 24 h with free access to water. Animals were given 10 mg and 20 mg/kg test compounds and Omeprazole 10 mg, 20 mg/kg orally in 1% CMC solution. 1 h later, 1 mL/200 g of 99·00% alcohol was administered p.o. (per oral – drug doses given to animals orally) to each animal. Animals were sacrificed 1 h after alcohol administration, stomachs were isolated and cut open along the greater curvature and pinned on a soft board. The gastric mucosa was examined for ulcers. Ulcer scores were observed and ulcer index were calculated by One Way ANOVA analysis and results were compared with control by student's *t* test.

2.4 *Acute toxicity (LD_{50})*

Healthy adult Albino mice (20–25 g) of either sex, starved overnight were subjected to acute toxicity studies as per guidelines (AOT No. 425) suggested by Organization for Economic Co-operation and Development (OECD) 2001. The mice were observed continuously for 2 h for behavioural, neurological and autonomic profiles for any lethality or death for next 48 h.

3. Results and discussion

3.1 *2-((5-Substituted benzo[d]imidazol-2-yl sulfinyl) methyl)-3-substituted quinazolin-4-(3H)-one* **(5a–o)**:

Table 1a. *In vivo* pylorus ligation-induced antiulcer activity of test compounds (**5a–o**).

			Pylorus ligated antiulcer activity					
			Ulcer index ± SEM		PH of gastric juice ± SEM		Volume of gastric juice ± SEM	
Comp. No.	*R*	R_1	10 mg (***)	20 mg (***)	10 mg	20 mg (***)	10 mg	20 mg (***)
5a	3,4-Dimethoxy phenyl	H	1.0 ± 0.2236	0.68 ± 0.07348	2.86 ± 0.09798***	3.7 ± 0.1881	8.46 ± 0.3709***	6.5 ± 0.3356
5b	2-Pyridyl	H	1.4 ± 0.1871	0.7 ± 0.05477	2.56 ± 0.1123*	3.9 ± 0.1241	9.56 ± 0.4167**	7.3 ± 0.2694
5c	3-Pyridyl	H	1.6 ± 0.3317	0.9 ± 0.06633	2.5 ± 0.1*	3.8 ± 0.2354	12.22 ± 0.6264	8.0 ± 0.5481
5d	2-Pyrazine	H	0.9 ± 0.1871	0.6 ± 0.05831	3.3 ± 0.01517***	4.4 ± 0.2083	8.46 ± 0.3709***	5.3 ± 0.3234
5e	5-Tetrazole	H	1.5 ± 0.4183	1.06 ± 0.1806	2.58±0.1744*	4.02 ± 0.1715	12.8 ± 0.251	7.7 ± 0.2672
5f	3,4-Dimethoxy phenyl	OCH_3	1.2 ± 0.1213	0.6 ± 0.07071	3.48±0.06633***	4.8 ± 0.1761	10.46 ± 0.41*	6.2 ± 0.2786
5g	2-Pyridyl	OCH_3	1.2 ± 0.1236	0.7 ± 0.05831	2.44±0.06782*	3.7 ± 0.1319	10.24 ± 0.2786*	6.4 ± 0.2358
5h	3-Pyridyl	OCH_3	1.5 ± 0.1512	0.7 ± 0.05099	2.82±0.1068*	4.0 ± 0.2888	11.78 ± 0.6296	7.1 ± 0.5016
5i	2-Pyrazine	OCH_3	0.9 ± 0.1871	0.4 ± 0.03162	3.34±0.36*	5.0 ± 0.2916	7.76 ± 0.7626***	5.3 ± 0.3353
5j	5-Tetrazole	OCH_3	1.4 ± 0.3317	0.7 ± 0.03742	2.64±0.2379	4.5 ± 0.1844	11.3 ± 0.5215***	7.3 ± 0.3435
5k	3,4-Dimethoxy phenyl	$OCHF_2$	0.6 ± 0.1871	0.3 ± 0.03742	3.62±0.1562***	5.08 ± 0.2557	5.44 ± 0.20***	3.3 ± 0.2561
5l	2-Pyridyl	$OCHF_2$	0.9 ± 0.1823	0.5 ± 0.04472	2.84±0.2421**	4.3 ± 0.3899	7.72 ± 0.5054***	5.6 ± 0.2786
5m	3-Pyridyl	$OCHF_2$	1.2 ± 0.1213	0.6 ± 0.05099	3.38±0.2709***	4.9 ± 0.2205	10.76 ± 0.4707***	7.1 ± 0.2891
5n	2-Pyrazine	$OCHF_2$	0.7 ± 0.2212	0.3 ± 0.04	3.56±0.2657**	5.12 ± 0.2922	6.48 ± 0.4224*	4.2 ± 0.2441
5o	5-Tetrazole	$OCHF_2$	1.0 ± 0.2236	058 ± 0.05831	2.8±0.2966**	4.5 ± 0.3415	8.2 ± 0.437***	5.0 ± 0.2973
Omeprazole	0.4 ± 0.08124	0.0 ± 0.0	7.4 ± 0.337***	7.6 ± 0.2417	1.2 ± 0.1897***	1.0 ± 0.1562		
Control			4.2 ± 0.1939		2.1 ± 0.1327		13.0 ± 0.725	

$n = 5$, Values are expressed as mean ± SEM. *$P < 0{\cdot}1$ compared to control group (Student's *t* test). **$P < 0.01$ compared to control group (Student's *t* test). ***$P < 0{\cdot}001$ compared to control group (Student's t test)

Table 1b. *In vivo* aspirin induced antiulcer activity of some test compounds.

Compound no.	*R*	R_1	Ulcer index ± SEM 10 mg (***)	Ulcer index ± SEM 20 mg (***)
5a	3,4-Dimethoxy phenyl	H	0·6 ± 0·1	0·4 ± 0·1
5d	2-Pyrazine	H	0·7 ± 0·1225	0·3 ± 0·1225
5i	2-Pyrazine	OCH_3	0·5 ± 0·1581	0·2 ± 0·1225
5k	3,4-Dimethoxy phenyl	$OCHF_2$	0·4 ± 0·1871	0·2 ± 0·1225
5l	2-Pyridyl	$OCHF_2$	0·4 ± 0·1871	0·5 ± 0·0
5n	2-Pyrazine	$OCHF_2$	0·5 ± 0·1581	0·1 ± 0·1
5o	5-Tetrazole	$OCHF_2$	0·8 ± 0·2	0·1 ± 0·1
Omeprazole			0.5 ± 0.1581	0·0 ± 0·0
Control				3·8 ± 0·1225

$n = 5$, 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).

Table 1c. *In vivo* ethanol induced antiulcer activity of some test compounds.

Compound no.	*R*	R_1	Ulcer index ± SEM 10 mg (***)	Ulcer index ± SEM 20 mg (***)
5a	3,4-Dimethoxy phenyl	H	2·8 ± 0·1225	2·0 ± 0·1581
5d	2-Pyrazine	H	2·7 ± 0·1225	2·0 ± 0·1581
5i	2-Pyrazine	OCH_3	2·4 ± 0·1871	1·8 ± 0·2
5k	3,4-Dimethoxy phenyl	$OCHF_2$	2·2 ± 0·1225	1·5 ± 0·1581
5l	2-Pyridyl	$OCHF_2$	2·6 ± 0·1871	1·6 ± 0·1
5n	2-Pyrazine	$OCHF_2$	2·4 ± 0·1	1·3 ± 0·1225
5o	5-Tetrazole	$OCHF_2$	2·4 ± 0·1871	1·6 ± 0·2915
Omeprazole			0·3 ± 0·1225	0·0 ± 0·0
Control				6·0 ± 0·2236

$n = 5$, 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).

The syntheses of the compounds were performed using the route shown in scheme 1. 2-(2-chloroacetamido)-N-substituted benzamide **2a–e** were synthesized by condensation of 2-amino *N*-substituted benzamide **1** with chloroacetyl chloride by stirring for 8–10 h at 0°C. The 2-chloromethyl-3-N-substituted quinazoline 4(3H) one(R = 3,4 dimethoxy phenyl, 2-pyridyl, 3-pyridyl, 2-pyrazine, 5-tetrazole) **3a–e** were synthesized by cyclisation of 2-(2-chloroacetamido)-N-substituted benzamide refluxing with acetic anhydride for 10–12 h.[7,8] Compounds were confirmed by IR spectral data. Quinazoline ring showed band at 1668–1678 cm^{-1} indicating the presence of an N-CO group. NH of benzamide ($NHCOCH_2Cl$) showed band at 3190–3220·2–(2-chloroacetamido)-N-substituted benzamide cyclized to form 2-chloromethyl compound showed band for C=N at 1605–1668, C–N at 1514–1550, C–Cl at 759–768, alkyl C–H (CH_2CI) at 2930–2940.

2-chloromethyl-3-substituted quinazoline-4 (3H) ones **3a–e** were then reacted with 2-mercapto benzimidazoles (R_1 = H, OCH_3, $OCHF_2$) by stirring for 10–15 h in NaOH solution by substitution reaction to give-2-[1-*H*-benzo(d)imidazol-2-yl thio]methyl-3-substituted quinazoline-4-(3*H*)ones.[9] **4a–o**. Mild oxidation of sulphur was carried out using 30% w/v of hydrogen peroxide in acetic acid in presence of dichloromethane and stirred for 3–5 h at 50–60°C to give targeted sulfinyl derivatives **5a–o**. Chlorine atom of quinazoline, substituted by mercapto proton showed C–S–C peak in between 712 and 744 with disappearance of C–Cl band. Oxidation of sulphur showed peak at 1021–1033 and shifts C–S–C peak to 716–785. ^{1}H NMR spectra of compounds **5a–o**

Table 2. Percentage of inhibition of gastric acid (**5a–o**).

Compound no.	*R*	R_1	Percentage of inhibition of acid secretion (20 mg) Aspirin induced ulcer	Pylorus ligation-induced ulcer	Ethanol-induced ulcer
5a	3,4-Dimethoxy phenyl	H	90	84	67
5b	2-Pyridyl	H	–	83	–
5c	3-Pyridyl	H	–	79	–
5d	2-Pyrazine	H	92	84	67
5e	5-Tetrazole	H	–	76	–
5f	3,4-Dimethoxy phenyl	OCH_3	–	84	–
5g	2-Pyridyl	OCH_3	–	83	–
5h	3-Pyridyl	OCH_3	–	83	–
5i	2-Pyrazine	OCH_3	95	90	70
5j	5-Tetrazole	OCH_3	–	83	–
5k	3,4-Dimethoxy phenyl	$OCHF_2$	95	92	75
5l	2-Pyridyl	$OCHF_2$	87	88	73
5m	3-Pyridyl	$OCHF_2$	–	83	–
5n	2-Pyrazine	$OCHF_2$	97	92	78
5o	5-Tetrazole	$OCHF_2$	97	88	73
Omeprazole			100	100	100

exhibited a singlet at 4·8–5·1 and 11·8–12·4 integrating for two and one protons respectively and assigned to methylene proton of the chain (–CH_2–S–) and N–H of benzimidazole. A singlet for 6 protons at 3·8–3·9 is shown for OCH_3 of 3,4 dimethoxy. Other signals appeared in the aromatic region ranging from 7·0 to 8·6 integrating for the protons of quinazoline, and benzimidazole nucleus.

3.2 *Antiulcer screening*

All the quinazoline-4(3*H*)-ones were evaluated for their antiulcer activity in pylorus ligation-induced ulcers in rats with ulcer index, pH and volume of gastric juice as shown in table 1a. Compounds which showed higher antiulcer and antisecretory activity were subjected to different screening methods such as aspirin and ethanol-induced ulcers in rats. Results are shown in tables 1b and c. Compounds **5k** and **5n** showed most potent activity as compared to Omeprazole at the dose level of 10 and 20 mg/kg. Compounds **5a**, **5d**, **5i**, **5l** and **5o** showed moderate activity at the same doses. Compounds **5i**, **5k**, **5n** at 20 mg/kg dose showed less ulcer index. Mostly compounds **5d**, **5i**, **5l**, **5n** and **5o** at 10 mg/kg and compounds **5i**, **5k**, **5n**, **5o** and **5l** at 20 mg/kg doses inhibited acid secretion and overall results are as shown in table 2.

The perusal of the overall results have shown that benzimidazole sulfinyl methyl quinazoline substituted with 3-N pyrazine, dimethoxy phenyl with difluromethoxy showed maximum activity. By observing the toxicity study, arbitrarily 10, 20 mg/kg doses of test compounds were selected. Further studies are in progress to optimize these lead compounds and to characterize the mode of action.

3.3 *Acute toxicity (LD_{50})*

The synthesized compounds were tested in different doses in Albino mice as per guidelines (AOT No. 425) suggested by Organization for Economic Co-operation and Development (OECD) 2001 and did not produce any toxicity. The doses of the test compounds for antiulcer activity have been selected arbitrarily.

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