Studies on some biologically active substituted 4(3*H*)-quinazolinones. Part 1. Synthesis, characterization and anti-inflammatory[#]-antimicrobial activity[$] of 6,8-disubstituted 2-phenyl-3-[substituted-benzothiazol-2-yl]-4(3*H*)-quinazolinones

Sachin S. Laddha*, Sudhir G. Wadodkar, and Sharad K. Meghal

Medicinal Chemistry Division, Department of Pharmaceutical Sciences, Nagpur University, Amravati Road, Nagpur-440010 (M.S.), India
E-mail: sachinladdha@indiatimes.com, pinkumanno@rediffmail.com

Abstract

Two series of 6,8-disubstituted 2-phenyl-3-[substituted benzothiazol-2-yl]-4(3*H*)-quinazolinones [**3a-m** and **4a-m**] have been synthesized and characterized by elemental analysis and spectral data. The anti-inflammatory activity of the title compounds (**3a-m** and **4a-m**) was evaluated and the most active compounds were evaluated for COX-1 and COX-2 inhibitory activity and ulcerogenic activity. All the test compounds were administered orally/intraperitoneally at a dose 50 mg/Kg body weight and percentage inhibitions were determined. Further more all the compounds were also tested against Gram negative, Gram positive bacteria and fungi. Among the compounds tested in this study, compounds 2-phenyl-3-(4-methoxybenzothiazol-2-yl)-4(3*H*)-quinazolinone (**3e**), 2-phenyl-3-(5-methylbenzothiazol-2-yl)-4(3*H*)-quinazolinone (**3f**) and 2-phenyl-3-(4-6-dimethylbenzothiazol-2-yl)-4(3*H*)-quinazolinone (**3l**) showed most prominent anti-inflammatory activity with low gastric ulceration incidence compare to reference standard Indomethacin. Further compounds, **3e, 3f** and **3l** revealed superior inhibitory profile against COX-2 enzyme, when compared with reference standard Indomethacin. Among all the compounds, compounds **4g** and **4j** posses a broad spectrum of antibacterial activities against both Gram positive and Gram negative bacteria but insignificant antifungal and anti-inflammatory activity.

Keywords: 2-Phenyl-3-[substituted-benzothiazol-2-yl]-4(3*H*)-quinazolinone, 6,8-dibromo, 2-phenyl-3-[substituted-benzothiazol-2-yl]-4(*3H*)-quinazolinone, anti-inflammatory, COX-1 and 2 inhibitory activity, antimicrobials

Introduction

Design of agents for fast and effective relief from pain and inflammation in the human being is a major challenge for the medicinal chemists. Non-steroidal anti-inflammatory drugs (NSAID's) are the most common choice for the treatment of a number of inflammatory diseases associated with a number of pathological conditions.[1] The commonly proposed mechanism of action of NSAID's is lowering prostaglandin production through inhibition of cyclo-oxygenase. This key enzyme is involved in the conversion of arachidonic acid into prostaglandins (PG's) and thromboxane.[2] The major side effects of NSAID's are their gastrointestinal ulcerogenic activity and bronchospasm.[3, 4] This is because of decreased levels of PG's which has dual functions; mediation of inflammation and cytoprotection in the stomach and intestine[5]. Recent reports suggest that cyclo-oxygenase enzyme exist in two isoforms COX-1 and COX-2, which are regulated differently[6]. COX-1 is responsible for the synthesis of gastroprotective PG's in the GI and proaggregatory thromboxane in blood platelets,[7] whereas short lived COX-2 is induced by pro-inflammatory stimuli such as endotoxin, bacterial lipopolysaccharide, growth factors, cytokines, mitogens, and tumor-promoting agents.[8, 9] It has been shown that the undesirable side effects of NSAID's are may be due to COX-1 inhibition while the beneficial effects, such as reduction of swelling and analgesia, are related to COX-2 inhibition.[10, 11] Further recent studies reveals that compounds having more COX-1 selectivity shows evidence of more gastrointestinal toxicity.[12] Hence a potent and selective COX-2 should block the production of prostaglandin in inflammatory cells without affecting in the homeostatic and gastro-protective actions mediated by COX-1.[6] The search continues to develop new drugs that have potent anti-inflammatory activity with minimum side effects. Although many NSAID's are in the market, the present therapeutic approach and chemical design of NSAID's are now targeted towards the development of selective COX-2 inhibitors and as a result, several selective COX-2 inhibitors are commercially available.[12]

The quinazoline nucleus has been found to possess varied pharmacological activities *viz.* anticonvulsant,[14, 15] bronchodilator,[16, 17] anti-inflammatory,[18-20] antimalarial,[21] antituberculous,[22] anti-HIV,[23] narcotic antagonist,[24] anti-tumor,[25] tyrosinekinase inhibitor,[26] adenosine antagonist,[27] antimicrobial,[28] etc. Similarly various substituted benzothiazoles are known to possess varied pharmacological activities like anti-tumor,[29] antimicrobials,[30, 31] anthelmintic,[32] analgesic,[33] anti-inflammatory,[34] anticonvulsant,[35, 36] and CVS agents.[37]

The simultaneous use of several drugs to treat inflammatory conditions, associated with some microbial infections may cause health problems especially in patients with impaired liver or kidney functions. Also, from the pharmaco-economic point of view, and for better patient compliance, an anti-inflammatory antimicrobial agent with minimum adverse effects and high safety margin is highly desirable.

In view of the fact that several 4-oxoquinazoline derivatives possess useful anti-inflammatory as well as antimicrobial properties,[28,38] we designed and synthesized various derivatives of 2-phenyl-3-(substituted- benzothiazol-2-yl)-4(3*H*)-quinazolinone. Also with aim

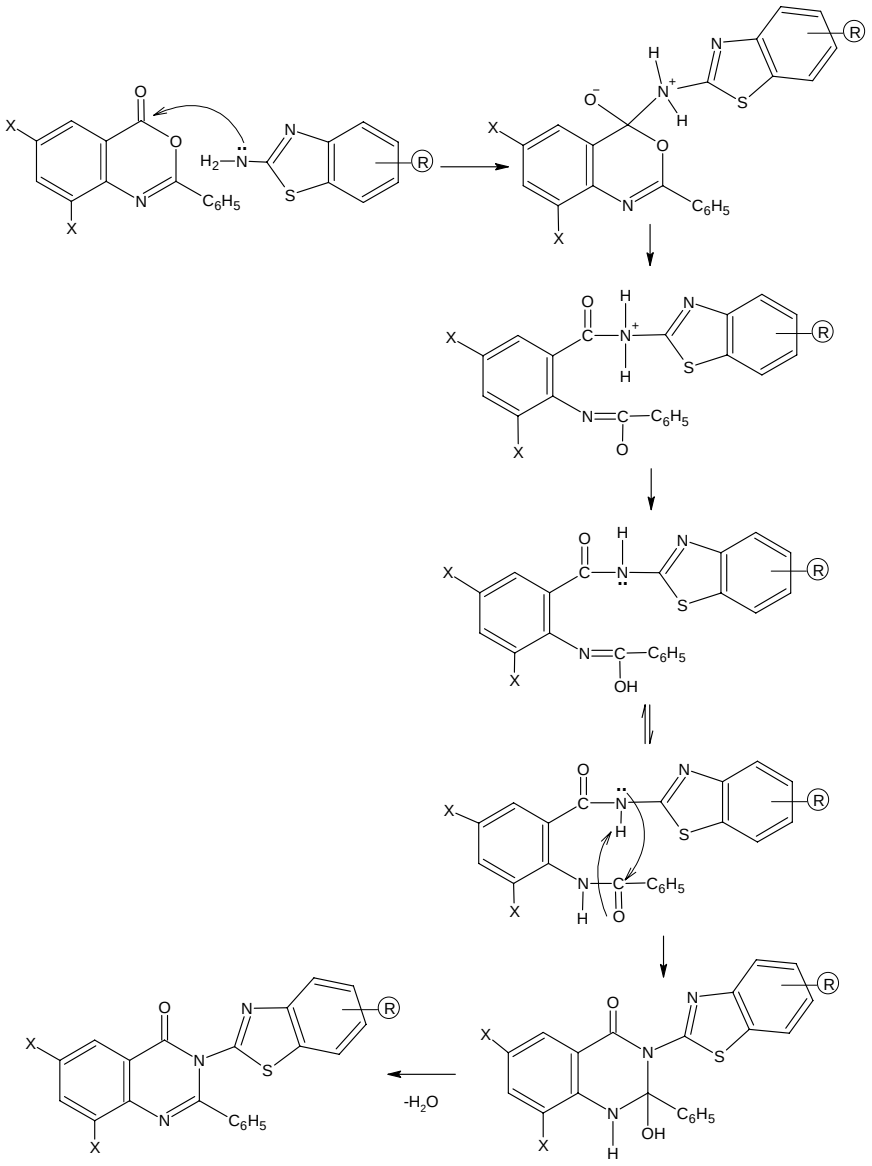
of obtaining the novel potent anti-inflammatory antimicrobial agents with fewer side effects, we decided to combine the benzothiazole nucleus with the quinazoline molecule. Moreover, it was considered of interest to substitute various groups on the benzothiazole nucleus to investigate the influence of such structural variation on the anticipated biological activities. In addition to the targeted anti-inflammatory and antimicrobial activities, the ulcerogenic toxicity profiles of newly synthesized compounds were also determined. Thus in the present investigation, twenty six different derivatives of 6,8-disubstituted, 2-phenyl-3-(substituted-benzothiazol-2-yl)-4(3*H*)-quinazolinone were synthesized and evaluated for their anti-inflammatory anti-microbial and ulcerogenic activities.

Results and Discussion

Chemistry

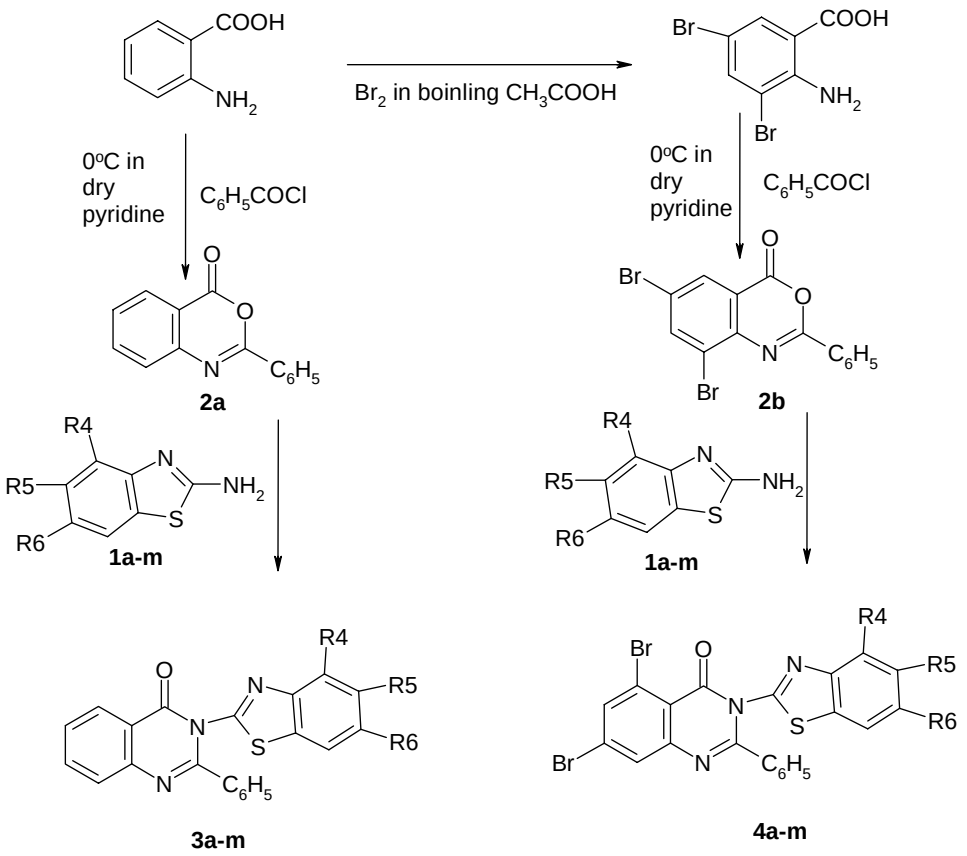
Synthesis of the title compounds **3a-m** and **4a-m** has been carried out as depicted in Scheme 2. Various substituted derivatives of 2-amino benzothiazole (**1a-m**) were prepared by a reported procedure.[42] 2-phenyl-4*H*-3,1-benzoxazin-4-one (**2a**) and 6,8-dibromo-2-phenyl-4*H*-3,1-benzoxazin-4-one (**2b**) were also prepared by reported method.[43]

Compounds **2** and **1** were condensed in dry pyridine for 6-18 hrs. The probable mechanism of the reaction involves, first the ring opening of 6,8 disubstituted-2-phenyl-4*H*-3,1-benzoxazin-4-one (**2**) by the attack of 2-aminobenzothiazole (**1**). This is the ring-opening step, followed by removal of water molecule to close the ring, and form the title compounds (Scheme 1).



Scheme 1. Reaction mechanism.

All of the synthesized compounds were characterized by their physical, analytical and spectral data. They were given separately in experimental section and Tables 1 and 2. The title compounds showed disappearance of bands at 1600-1650 cm^{-1} (N–H deformation) and 3460-3500 cm^{-1} (N–H stretching) due to conversion of free amino group into cyclic nitrogen. Halogen containing compounds **3g** and **3j** and **4a-m** showed the absorption bands at 590-760 cm^{-1} (C–X stretching) and nitro compounds **3k** and **4k** showed the bands at 1490-1550 cm^{-1} The EI MS and



Scheme 2. Synthetic route.

^{1}H NMR spectral data of all the synthesized compounds were in conformity with the structure assigned.

In the EI-MS spectra, molecular ion [M^+] peaks, which appeared at different intensities, confirmed the molecular weights of the examined compounds (**3a-m** and **4a-m**). Molecular ion peaks were the base peaks for the compound **3a-f**, **3h, 3i, 3k-m**. Appearance of an isotope peak [M^++2] as intense as the molecular ion peak confirmed the presence of halogen atom in compounds **3g, 3j** and **4a-m**

Anti-inflammatory activity

Carrageenan-induced paw edema in rats

All newly synthesized compounds were tested for their anti-inflammatory activity against carrageenan-induced edema at dose of 50 mg/kg using Indomethacin as reference standard. The percentage protection against inflammation was calculated using the formula given below:

$(V_C - V_T) / V_C \times 100$ where V_C is the increase in paw volume of control (in the absence of test compound) and V_T is the increase in paw volume after administration of the test compound. The results are recorded in Table 4.

The results revealed that all the synthesized compounds were exhibited anti-inflammatory activity. However, they were found less potent when compared with the reference standard. In general compound **3a-m** exhibited more pronounced anti-inflammatory activity than the compound **4a-m**. Among all the compounds tested, compounds **3e**, **3f** and **3l** exhibited remarkable anti-inflammatory activity as compared with the reference standard. Although it is difficult to trace a good correlation between chemical structure and anti-inflammatory activity from the result obtained, some preliminary conclusions can be drawn as follows. In general compounds **3a-m** were found to be more potent when compared with compounds **4a-m** (Table 4). The comparative anti-inflammatory data clearly showed that compounds shown higher inhibition when administer intraperitoneally. Also in both series, compounds **3g, 3j, 3k** and **4 a-m** having electron withdrawing groups (*p*-nitro and halogen) on both benzothiazole and quinazoline nucleus have shown less anti-inflammatory activity compared with the compounds having electron releasing groups (alkyl and alkoxy). Among the compounds tested in this study, compounds 2-phenyl-3-(4-methoxybenzothiazol-2-yl)-4(3*H*)-quinazolinone (**3e**), 2-phenyl-3-(5-methyl benzothiazol-2-yl)-4(3*H*)-quinazolinone (**3f**) and 2-phenyl-3-(4-6-dimethyl benzothiazol-2-yl)-4(3*H*)-quinazolinone (**3l**) showed most prominent anti-inflammatory activity (% inhibition : **3e** = 63 (2hr) and 66.3 (3hr) when administered orally, 68.2 (2hr) and 70.8 (3hr) administered intraperitoneally ; **3f** = 68.6(2hr), 69.7 (3hr) when administered orally, 70.6 (2hr) and 74.1 (3hr) administered intraperitoneally and **3l** = 68.6 (2hr), 74.17 (3hr) when administered orally, 70.6 (2hr) and 77.5 (3hr) administered intraperitoneally with low gastric ulceration incidence compare to reference standard.

COX-1 and COX-2 catalyzed prostaglandin biosynthesis assay (in-vitro)

Compounds **3e, 3f,** and **3l** that showed in-vivo anti-inflammatory activity compared to that of Indomethacin in carrageenan-induced paw edema in rats was further tested for their ability to inhibit COX-1 and COX-2 enzyme in-vitro applying the methodology of Wakitani *et al*. The results clearly indicated that the tested compounds exhibited very weak inhibitory activity against COX-1 enzyme (IC_{50} values between 98 - >100 μmol) when compared with Indomethacin (IC50 values 0.22 μmol). While tested compounds, **3e, 3f** and**3l** revealed superior inhibitory profile against COX-2 enzyme as indicated by their Ic_{50} values (1.57, 1.87 and 0.39 μmol respectively), when compared with reference standard Indomethacin.

Ulcerogenic effects

Compounds **3e, 3f** and **3l** which exhibited moderate to potent anti-inflammatory profiles in the animal model were evaluated for their ulcerogenic potential in rats. All the active compounds revealed a superior GI safety profiles with oral dose of 100 mg/kg/day, when compared with reference standard, Indomethacin; which was found to create 100% ulceration under same conditions. Gross observation of the isolated rat stomachs showed a normal stomach texture for all active compounds.

In vitro antimicrobial activity

Compounds **3a-m** and **4a-m** have been evaluated for their *in vitro* antimicrobial activity against *Escherichia coli* (E. coli ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) as an example of Gram negative bacteria, *Staphylococcus aureus* (ATCC 25923) and *Enterococcus faecalis* (ATCC 29212) as examples of Gram positive bacteria, and *Candida albicans* (ATCC 90018) as a representative of fungi. The microdilution susceptibility test in Muller Hinton Broth (Sigma Aldrich) was used when testing bacterial strain, while Saboureaud Liquid medium (Sigma Aldrich) was used for the determination of antifungal activity. The minimum inhibitory concentrations (MICs in μg/ml) of the tested compounds are recorded in Table 4.

The results revealed that all newly synthesized compounds were exhibited potent antibacterial activities and poor antifungal activity. In general, compounds **4a-m** exhibited more pronounced antibacterial potencies than the compound **3a-m**, with better activity against both Gram positive and Gram negative bacteria. Among all the compounds tested, **4g, 4j** and **4k** exhibited remarkable antibacterial activity against the Gram negative *Escherichia coli* (E.Coli ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) as compared with the broad spectrum antibiotic Tobramycin. Compounds **4j** and **4k** were equipotent as Tobramycin in *Pseudomonas aeruginosa* (ATCC 27853). It is worth-mentioning that, a compound **4g** was more active than Tobramycin, against the same organisms.

On the other hand, compounds **4b, 4d, 4h, 4i** and **4m** exhibited potent activity against the Gram positive *Staphylococcus aureus* ATCC 25923 and *Enterococcus faecalis* (ATCC 29212) as compared with Tobramycin. The antibacterial activities of compounds **4c, 4d,** and **4e** were 50% lower than, the standard against the *Staphylococcus aureus* and **4a, 4e,** and **4f** against *Enterococcus faecalis*. Moreover, compounds **4l** and **4m** were moderately active against the same organisms. The rest of the tested compounds were less active against all organisms with MIC values ranging between 14-48 μg/ml. All the tested compounds showed weak antifungal activity against *Candida albicans* (ATCC 90018), when compared with reference antifungal agent Fluconazole.

In short, compounds **4g** and **4j** posses a broad spectrum of antibacterial activities against both, Gram positive and Gram negative bacteria but insignificant antifungal activity.

The different substituents on the aromatic ring exert a significant influence on the biological activity. The presence of electron withdrawing groups (halogen and nitro) on the aromatic ring in general decreases the anti-inflammatory activity of test compounds compared to compounds having electron-donating groups (alkyl). Based upon the results it will also be necessary to optimize the lead compound by substituting series of electron –donating groups on aromatic ring and selectively modifying the quinazoline nucleus.

Experimental Section

General Procedures. Melting points were determined in open capillaries using a Thermonik precision melting point cum boiling point apparatus, Model C-PMB-2 (Mumbai, India) and are uncorrected. Purity of the compounds was checked by precoated TLC plates (E.Merck Kieselgel 60 F254, Mumbai, India). IR spectra were recorded using KBr pellets on a Perkin-Elmer 337 Spectrophotometer from Perkin Elmer International Incorporation, Rorkreuz, Switzerland (ν max cm^{-1}), ^1H NMR spectra on Bruker W.M. 400 Spectrometer (Bruker AG, Fallanden, Switzerland) at 360 MHz using TMS as internal standard (chemical shift in δ ppm) and mass spectra (EI-MS) were recorded on a Jeol D-300 spectrometer(Jeol Ltd.,Tokyo,Japan). Elemental analyses were carried out at using Heraeus Carlo Erba 1180 CHN analyser (from Heraeus Instrument GmbH, Hanau, Germany). All the chemicals were purchased from Aldrich Company Ltd. Dorset (UK)

Synthesis of substituted products of 2-aminobenzothiazole 1a-m. These compounds were synthesized from aniline and substituted aniline using known methods[42]. The product **1a-m** on recrystallization from ethanol was obtained in pure form.

Synthesis of substituted products of 2-phenyl-4*H*-3,1-benzoxazin-4-one 2a-m. These compounds were synthesized from anthranilic acid and 3,5-dibromoanthranilic acid using known methods[43]. The products **2a-m** on recrystallization from ethanol was obtained in pure form.

Synthesis of substituted 2-phenyl-3-[substituted benzothiazol-2-yl]-quinazolin-4-ones 3a-b A solution of 2-phenyl-4*H*-3,1-benzoxazin-4-one (1.17 g, 0.005 mole) in 15 ml of dry pyridine, 2-aminobenzothiazole (0.75 g, 0.005 mole) was added in fraction with constant stirring for 10 min. After that the reaction mixture was refluxed for 9 hrs. The hot solution was incorporated in a beaker containing 100 gms of crushed ice and 5 ml of conc. HCl. The solid separated (**3a**) was filtered, dried and recrystallised from glacial acetic acid, yield 0.91 g (78 %), m.p. 276 – 278 °C. R*f*: 0.63 (rectified spirit). Using the above procedure, thirteen such compounds **3a-m** were synthesized and characterized and their physical data are listed in **Table 1.**

Synthesis of 6,8 dibromo-2-phenyl-3-(substituted benzothiazol-2-yl)-quinazolin-4(3*H*)-one derivaties 4a-m. In a round bottom flask (50 ml) containing solution of 6,8 Dibromo- 2-phenyl-4*H*-3,1-benzoxazin-4-one (1.91 g, 0.005 mole) in 15 ml of dry pyridine, 2-aminobenzothiazole (0.75 g, 0.005 mole) was added in fraction with constant stirring for 10 min. After that the reaction mixture was refluxed on oil-bath for 12 hrs. The hot solution was incorporated in a beaker containing 100 gms of crushed ice and 5 ml of conc. HCl. The solid separated (**4a**) was filtered, dried and recrystallised from glacial acetic acid, yield 0.47 g, (40.4 %), m.p. 248-250 °C, R*f*: 0.61(rectified spirit). Using the above procedure thirteen such compounds **4a-m** were synthesized and characterized and their physical data are listed in **Table 1**.

Table 1. Physical and analytical data of compounds **3a-m** and **4a-m**

Comp[a]	R4	R5	R6	Mol. formula (Mol. Wt)[b]	Mp (°C)	Yield (%)[a]	Mass (m^+)
3a	H	H	H	$C_{21}H_{13}N_3OS$ (355.4)	276-278	78	355
3b	OCH_3	H	H	$C_{22}H_{15}N_3O_2S$ (385.4)	216-218	70	385
3c	H	OCH_3	H	$C_{22}H_{15}N_3O_2S$(385.4)	190-192	66.7	385
3d	H	H	OCH_3	$C_{22}H_{15}N_3O_2S$(385.4)	192-194	70	385
3e	CH_3	H	H	$C_{22}H_{15}N_3OS$(369.4)	152-154	66.7	369
3f	H	CH_3	H	$C_{22}H_{15}N_3OS$(369.4)	180-182	70	369
3g	H	Cl	H	$C_{21}H_{12}ClN_3OS$ (389.86)	198-200	40.4	391[c]
3h	H	H	OC_2H_5	$C_{23}H_{17}N_3O_2S$(399.46)	140-142	70	399
3i	H	OC_2H_5	H	$C_{23}H_{17}N_3O_2S$(399.46)	192-194	70	399
3j	H	H	Br	$C_{21}H_{12}N_3OSBr$(434.3)	208-210	66.7	436[c]
3k	H	H	NO_2	$C_{21}H_{12}N_4O_3S$(400.4)	262-264	40.4	400
3l	CH_3	H	CH_3	$C_{23}H_{17}N_3OS$(383.4)	200-202	70	383
3m	OC_2H_5	H	H	$C_{23}H_{17}N_3O_2S$(399.46)	216-218	40.4	401
4a	H	H	H	$C_{21}H_{11}N_3OSBr_2$(513.21)	248-250	40.4	515[c]
4b	OCH_3	H	H	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	198-200	70	545[c]
4c	H	OCH_3	H	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	98-100	40.4	545[c]
4d	H	H	OCH_3	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	208-210	66.7	545[c]
4e	CH_3	H	H	$C_{22}H_{13}N_3OSBr_2$(527.2)	168-170	70	529[c]
4f	H	CH_3	H	$C_{22}H_{13}N_3OSBr_2$(527.2)	204-206	70	529[c]
4g	H	Cl	H	$C_{21}H_{10}Br_2ClN_3OS$ (547.65)	208-210	40.4	549[c]
4h	H	H	OC_2H_5	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	192-194	70	559[c]
4i	H	OC_2H_5	H	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	202-204	66.7	559[c]
4j	H	H	Br	$C_{21}H_{10}N_3OSBr_3$(592.11)	164-166	70	594[c]
4k	H	H	NO_2	$C_{21}H_{10}N_4O_3SBr_2$(558.2)	240-242	66.7	560[c]
4l	CH_3		CH_3	$C_{23}H_{15}N_3OSBr_2$(541.2)	170-172	70	543[c]
4m	OC_2H_5	H	H	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	206-208	78	559[c]

[a] Compounds **3g** and **4g** were recrystallised from ethanol, and compounds **3a-f, 3h-m, 4a-f** and **4h-m** from glacial acetic acid.

[b] CHN analysis were found to be within the limit of ±0.4%.

[c] Values represent (M^++2) due to appearance of an isotopic peak.

Table 2. Elemental analysis of compound **3a-m** and **4a-m**

Comp	Mol. formula (Mol. Wt)	Analysis %					
		Calculated			Found		
		C	H	N	C	H	N
3a	$C_{21}H_{13}N_3OS$ (355.4)	70.97	3.69	11.82	70.94	3.71	11.81
3b	$C_{22}H_{15}N_3O_2S$ (385.4)	68.55	3.92	10.90	68.58	3.93	10.87
3c	$C_{22}H_{15}N_3O_2S$(385.4)	68.55	3.92	10.90	68.54	3.94	10.94
3d	$C_{22}H_{15}N_3O_2S$(385.4)	68.55	3.92	10.90	68.58	3.91	10.87
3e	$C_{22}H_{15}N_3OS$(369.4)	71.52	4.09	11.37	71.54	4.11	11.39
3f	$C_{22}H_{15}N_3OS$(369.4)	71.52	4.09	11.37	71.55	4.12	11.36
3g	$C_{21}H_{12}ClN_3OS$ (389.86)	64.70	3.10	10.78	64.72	3.13	10.81
3h	$C_{23}H_{17}N_3O_2S$(399.46)	69.15	4.29	10.52	69.18	4.28	10.50
3i	$C_{23}H_{17}N_3O_2S$(399.46)	69.15	4.29	10.52	69.17	4.31	10.55
3j	$C_{21}H_{12}N_3OSBr$(434.3)	58.07	2.78	9.68	58.10	2.79	9.66
3k	$C_{21}H_{12}N_4O_3S$(400.4)	62.99	3.02	13.99	62.96	3.04	13.96
3l	$C_{23}H_{17}N_3OS$(383.4)	72.04	4.47	10.96	72.06	4.49	10.94
3m	$C_{23}H_{17}N_3O_2S$(399.46)	69.15	4.29	10.52	69.17	4.28	10.54
4a	$C_{21}H_{11}N_3OSBr_2$(513.21)	49.15	2.16	8.19	49.18	2.15	8.21
4b	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	48.64	2.41	7.74	48.63	2.42	7.76
4c	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	48.64	2.41	7.74	48.62	2.42	7.72
4d	$C_{22}H_{13}N_3O_2SBr_2$(543.3)	48.64	2.41	7.74	48.62	2.42	7.72
4e	$C_{22}H_{13}N_3OSBr_2$(527.2)	50.12	2.49	7.97	50.14	2.48	7.98
4f	$C_{22}H_{13}N_3OSBr_2$(527.2)	50.12	2.49	7.97	50.15	2.48	7.99
4g	$C_{21}H_{10}Br_2ClN_3OS$ (547.65)	46.06	1.84	7.67	46.09	1.85	7.65
4h	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	49.57	2.71	7.54	49.59	2.72	7.52
4i	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	49.57	2.71	7.54	49.54	2.69	7.56
4j	$C_{21}H_{10}N_3OSBr_3$(592.11)	42.60	1.70	7.10	42.62	1.71	7.12
4k	$C_{21}H_{10}N_4O_3SBr_2$(558.2)	45.19	1.81	10.04	45.21	1.82	10.07
4l	$C_{23}H_{15}N_3OSBr_2$(541.2)	51.04	2.79	7.76	51.07	2.78	7.74
4m	$C_{23}H_{15}N_3O_2SBr_2$(557.26)	49.57	2.71	7.54	49.56	2.72	7.56

Table 3. The anti-inflammatory activity and gastric ulceration effect of compounds **3a-m** and **4a-m**

Comp	Ulcer incidence	Increase in paw edema (ml)± S.E.M.[b,c]			
		Per oral (p.o.)		Intraperitoneal (i.p.)	
		2. hr (%protection)	3.5hr (%protection)	2. hr (%protection)	3.5 hr (%protection)
3a	NT[a]	0.54±0.027 (37.2)	0.43±0.015 (53.9)	0.51±0.035 (40)	0.41±0.017 (53.9)
3b	NT[a]	0.44±0.018 (48.8)	0.39±0.055 (56.2)	0.42±0.021 (50.6)	0.37±0.019 (58.40)
3c	NT[a]	0.38±0.035 (55.8)	0.34±0.012 (61.8)	0.36±0.018 (57.6)	0.33±0.035 (62.9)
3d	NT[a]	0.44±0.013 (48.8)	0.41±0.067 (53.9)	0.42±0.054 (50.6)	0.40±0.045 (55)
3e	0/6	0.31±0.022 (63)	0.30±0.027 (66.3)	0.27±0.038 (68.2)	0.26±0.029 (70.8)
3f	0/6	0.27±0.019 (68.6)	0.27±0.044 (69.7)	0.25±0.025 (70.6)	0.23±0.035 (74.1)
3g	NT[a]	0.64±0.019 (25.6)	0.64±0.027 (28.1)	0.60±0.033 (29.4)	0.62±0.043 (30.3)
3h	NT[a]	0.45±0.033 (47.7)	0.43±0.019 (51.7)	0.42±0.019 (50.6)	0.42±0.024 (52.8)
3i	NT[a]	0.45±0.028 (47.7)	0.40±0.036 (55)	0.43±0.026(49.4)	0.39±0.021 (56.2)
3j	NT[a]	0.62±0.029 (27.9)	0.62±0.037 (30.3)	0.59±0.046 (30.6)	0.60±0.037(32.6)
3k	NT[a]	0.66±0.019 (23.3)	0.67±0.039 (24.7)	0.64±0.055 (24.7)	0.67±0.051 (24.7)
3l	0/6	0.27±0.061 (68.6)	0.23±0.025 (74.1)	0.25±0.027 (70.6)	0.20±0.033 (77.5)
3m	NT[a]	0.44±0.032 (48.8)	0.38±0.055 (57.3)	0.41±0.018 (51.8)	0.38±0.044 (57.3)
4a	NT[a]	0.71±0.039 (17.4)	0.71±0.041 (20.2)	0.68±0.025 (20)	0.70±0.038 (21.3)
4b	NT[a]	0.70±0.012 (18.6)	0.71±0.023 (20.2)	0.67±0.041 (21.2)	0.69±0.052 (22.5)
4c	NT[a]	0.68±0.063 (20.9)	0.68±0.017 (23.6)	0.66±0.028 (22.4)	0.67±0.039 (24.8)
4d	NT[a]	0.69±0.034 (19.8)	0.69±0.030 (22.5)	0.67±0.019 (21.2)	0.68±0.036 (23.6)
4e	NT[a]	0.69±0.016 (19.8)	0.69±0.023 (22.5)	0.66±0.053 (22.4)	0.68±0.027 (23.6)
4f	NT[a]	0.68±0.021 (20.2)	0.68±0.034 (23.6)	0.65±0.024 (23.5)	0.67±0.019 (24.8)
4g	NT[a]	0.69±0.052 (19.8)	0.69±0.035 (22.5)	0.66±0.053 (22.4)	0.69±0.043 (22.5)
4h	NT[a]	0.68±0.022 (20.9)	0.69±0.046 (22.5)	0.66±0.031 (22.4)	0.68±0.025 (23.6)
4i	NT[a]	0.67±0.029 (22)	0.68±0.034 (23.6)	0.65±0.040 (23.5)	0.67±0.057 (24.8)
4j	NT[a]	0.70±0.034 (18.6)	0.72±0.061 (19.1)	0.68±0.019 (20)	0.71±0.029 (20.2)
4k	NT[a]	0.73±0.063 (15.1)	0.73±0.041(18)	0.71±0.052 (16.5)	0.72±0.021 (19.1)
4l	NT[a]	0.67±0.029 (22)	0.67±0.031 (24.3)	0.64±0.026 (24.7)	0.65±0.029 (27)
4m	NT[a]	0.70±0.021 (18.6)	0.70±0.052 (21.3)	0.68±0.025 (20)	0.70±0.025 (21.3)
Control	NT[a]	0.86±0.025	0.89±0.029	0.85±0.037	0.89±0.041
Stand.. indomethacin	6/6	0.26(69.8) ±0.027	0.18(79.8) ±0.025	0.22(74.1) ±0.025	0.17(80.9) ±0.025

[a] N.T., not tested.

[b] S.E.M. denotes the standard error of the mean.

[c] All data are significantly different from control ($P > 0.005$).

Table 4. MIC's (μg/ml) of test compounds **3a-m** and **4a-m**

Comp	*E. coli*	*P. aeruginosa*	*S. aureus*	*Entero. faecalis*	*C. albicans*
3a	30	24	34	34.5	150
3b	35	34.5	40	42	200
3c	35.2	37	40.5	42	212
3d	38	40	40	42.5	220
3e	32	27	35.5	37	165
3f	33	29	37	37.5	175
3g	23.5	21	28	28.5	118
3h	40	46.5	41	45	260
3i	38	45	42	45	250
3j	24	20.5	28.5	30	112
3k	27	22	28.5	28	125
3l	44	52	52	54	282
3m	42	45	47	48	266
4a	10.2	9.5	7.6	2.4	32
4b	11.2	11.5	8.5	7.5	45
4c	11.5	11.5	9	8	50
4d	12.5	12	9.2	8.5	49
4e	10.5	10.5	8.5	3.4	38
4f	11	11.2	8	3.5	40
4g	9	7.5	2	1.2	28
4h	15.2	13.5	12.5	12.8	55
4i	15	13.5	12.2	12.5	57
4j	8.5	8	1.5	1	24
4k	9.2	8.2	3.2	1.2	18
4l	20	18.5	13.5	13	62
4m	17	15.5	13	12.5	60
Fluconazole	NT[a]	NT[a]	NT[a]	NT[a]	0.25
Tobramycine	0.135	8	3.8	1.2	NT[a]

[a] N.T., not tested.

Table 5. *In vitro* human COX-2 [b] and COX-1[a] enzymes inhibitory activity of compounds 3e, 3f and 3l

Test compound	COX-2 (IC_{50} μM)[c]	COX-1 (IC_{50} μM)[c]
Indomethacin	2.64	0.22
3e	1.57	98
3f	1.87	>100
3l	0.39	>100

[a] Human recombinant COX-2 enzyme.
[b] Human COX-1 enzyme from human platelet.
[c] Values are means of at least four experiments.

Pharmacology

Locally bred Sprague-Dawley rats of either sex weighing between 120 to 160 g, obtained from National Center for Laboratory Animal Sciences, Hyderabad, India, were used in present study. Animals were kept in wire-mesh cages and maintained under constant environmental conditions [23±2°C 12-h light]. All animals had free access to standard pellet diet (Hindustan Leaver Ltd.. Mumbai) and water, in a constant light-dark cycle. During the course of experiment, the general behavior of animal was normal. All the experimental protocols were approved by the institutional animal ethical committee and experiments were conducted in accordance with the standard guidelines.

Anti-inflammatory activity

The Anti-inflammatory activity of the synthesized compounds **3a-m** and **4a-m** were evaluated by carrageenan induced rat paw edema model[39]. All the test compounds were suspended in 0.5% carboxy methyl cellulose and administered either orally or intraperitoneally (50 mg/kg) 60 min prior the injection of 0.1 ml of freshly prepared solution of carrageenan (1%) in physiological saline solution (154mM NaCl) into the sub-planter tissue of hind paw of each rat. The same volume of saline solution was injected into hind paw of the control. The volume was measured by water plethysmometer prior to the administration of carrageenan (sigma) and; 1h and 3hrs. after the injection of carrageenan. The increase in volume of the paw was adopted as a measure of oedema. The antiedmatous effects of the compounds were estimated as percentage inhibition in comparison with control.

COX-1 and COX-2 catalyzed prostaglandin biosynthesis assay

Compounds **3e, 3f and 3l** that showed in vivo anti-inflammatory activity comparable to that of Indomethacin in carrageenan induced paw edema in rats were further tested for their ability to

inhibit COX-1 and COX-2 enzymes by using the procedure described by Wakitani *et. al.*[40]. In brief, Human COX-1(0.3 mg protein/assay) or COX-2 (1mg protein/assay) was suspended in 0.2 ml of 100mMol Tris-HCl buffer (pH 8) containing cofactors, Tryptofan (5mMol) and Hematin (and 2µl µMol). The reaction mixture was pre-incubated with each test compound (indifferent concentration) for 5 min. at 24°C. To it [^{14}C] arachidonic acid (100.00dpm, 30µMol) was added and the reaction mixture again incubated for 2 (COX-1) or 45 min (COX-2) at 24°C. The reaction was terminated by the addition of 400 µl stock solution containing diethyl ether-methanol-1M citric acid (30:4:1 v/v). The reaction mixture was then centrifuged at 1700×g for 5 min at 4 °C. 50µ of the upper phase of the centrifuged mixture were applied to a thin-layer chromatography (TLC) plate. TLC was performed at 4 °C by using diethyl ether–methanol–acetic acid (90:2:0.1 v/v) as mobile phase. The COX enzyme inhibitory activity was calculated from the percent conversion of arachidonic acid to PGH_2 and its decomposition product, using a radiometric photographic system. The concentration of the compound causing 50% enzyme inhibition (Ic_{50}) was calculated. The results were given in **Table 5**.

Gastrointestinal ulceration studies[44]

Compounds were **3e, 3f** and **3l** that exhibited moderate to potent anti-inflammatory profiles in the animal models were also evaluated for their ulcerogenic effects in rat. Rats were fasted for 24 h (with water ad libitum). The test compounds were suspended in a carboxymethylcellulose vehicle and administered orally by gavage at 100-mg/kg/day dose for 5 days in a volume of 0.5-ml/100 g of body weight. The animals were sacrificed with diethyl ether inhalation, their stomachs removed by cutting along the greater curvature, washed under running water and fixed in 5% formalin solution. The stomachs were then examined for lesions under a dissecting microscope.

In vitro antimicrobial activity

Compounds **3a-m** and **4a-m** have been evaluated for their in vitro antimicrobial and antifungal activity. The microdilution susceptibility test in Muller Hinton Broth (Sigma Aldrich) was used when testing bacterial strain, while Saboureaud Liquid medium (Sigma Aldrich) was used for the determination of antifungal activity. The inoculum densities were 5×10^5 cfu/ml and 0.5×10^3 cfu/ml for bacteria and fungi respectively. The minimum inhibitory concentrations (MICs in µg/ml) of the tested compounds are recorded in **Table 4**.

Compound characterization

Some representative spectral data for compounds **3a-m** and **4a-m**

2-Phenyl-3-(benzothiazol-2-yl)quinazolin-4(3*H*)-one [3a]. IR [KBr; γ] 1620cm^{-1} [C=N quinazoline] 1720 cm^{-1} [C=O] ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 7.26-8.02(m, 13H,Ar-H).

2-Phenyl-3-(4-methoxy-benzothiazol-2-yl)quinazolin-4(3*H*)-one [3b]. Recrystallised from glacial acetic acid, yield 0.81 g (70 %), m.p. 216-218 °C, R*f*: 0.73(rectified spirit). IR [KBr; γ]

1383 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH_3 stretching), ^{1}H NMR ($CDCl_3$ + DMSO,δ in ppm) 6.78-8.12(m, 12H,Ar-H), 3.76 (s-3H OCH_3)

2-Phenyl-3-(5-methoxy-benzothiazol-2-yl)quinazolin-4(3*H*)-one [3c]. Recrystallised from glacial acetic acid, yield 0.78 g, (66.7 %), m.p. 190-192 °C, R*f*: 0.72 (rectified spirit).

IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline), 1718 cm^{-1} (C=O), 2810 cm^{-1} (O-CH_3 stretching), ^{1}H NMR ($CDCl_3$ + DMSO,δ in ppm) 6.80-8.05(m, 12H,Ar-H), 3.75 (s-3H OCH_3)

2-Phenyl-3-(6-methoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [3d]. Recrystallised from glacial acetic acid, yield 0.81 g, [70 %], m.p. 192-194°C, R*f*: 0.81(rectified spirit).

IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1625cm^{-1} (C=N quinazoline) 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching) ^{1}H NMR ($CDCl_3$ + DMSO,δ in ppm) 6.55-8.11(m, 12H,Ar-H), 3.74 (s-3H OCH_3).

2-phenyl-3-(4-methylbenzothiazol-2-yl)quinazolin-4(3*H*)-one [3e]. Recrystallised from glacial acetic acid, yield 0.78 g, (66.7 %), m.p. 152-154°C, R*f*: 0.87(rectified spirit).

IR [KBr; γ] 1375 cm^{-1} (C-H deformation) 1620cm^{-1} (C=N quinazoline) 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR ($CDCl_3$ + DMSO,δ in ppm) 6.52-7.80 (m, 12H, Ar-H), 2.30 (d-3H -CH_3)

2-phenyl-3-(5-methylbenzothiazol-2-yl)quinazolin-4(3*H*)-one [3f]. Recrystallised from glacial acetic acid, yield 0.81 g, (70%), m.p. 180-182 °C, R*f*: 0.77(rectified spirit). IR [KBr; γ] 1375 cm^{-1}(C-H deformation), 1620cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR ($CDCl_3$ + DMSO,δ in ppm) δ = 6.42-7.70 (m, 12H, Ar-H), 2.35 (d-3H -CH_3)

2-Phenyl-3-(5-chlorobenzothiazol-2-yl)quinazolin-4(3*H*)-one [3g]. Recrystallised from rectified spirit, yield 0.47 g, (40.4 %), m.p. 198-200 °C, R*f*: 0.78(rectified spirit). IR [KBr; γ] 710 cm^{-1} (Ar-Cl), 1620cm^{-1} (C=N quinazoline) 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching) 1H NMR ($CDCl_3$ + DMSO,δ in ppm) 6.47-7.75 (m, 12H, Ar-H)

2-Phenyl-3-(6-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [3h]. Recrystallised from glacial Acetic acid, yield 0.73 g, (70 %), m.p. 140-142 °C, R*f*: 0.65(rectified spirit).

IR [KBr; γ] 1278 cm^{-1}(Ar-O-C Stretching), 1383 cm^{-1} (C-H in CH_3) ,1620cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C = O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.51-7.85 (m,12H,Ar-H), 1.1-1.5 (q-2H –CH_2-CH_3), 3.5-4.1 (t, 3H, CH_2-CH_3)

2-Phenyl-3-(5-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [3i]. Recrystallised from glacial acetic acid, yield 0.81 g, (70 %), m.p. 192-194 °C, R*f*: 0.82(rectified spirit).

IR [KBr; γ] 1270 cm^{-1}(Ar-O-C Stretching), 1380 cm^{-1} (C-H stretching in CH_3), 1625 cm^{-1} (C=N quinazoline), 1715 cm^{-1} (C = O), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.13-7.85 (m,12H,Ar-H), 1.1-1.6 (q-2H –CH_2-CH_3), 3.5-4.1 (t, 3H, CH_2-CH_3)

2-Phenyl-3-(6-bromobenzothiazol-2-yl)quinazolin-4(3*H*)-one [3j]. Recrystallised from glacial acetic acid, yield 0.78 g, (66.7%), m.p. 208-210 °C, R*f*: 0.76(rectified spirit).

IR [KBr; γ] 610 cm^{-1}(C - Br) 1620 cm^{-1} (C=N quinazoline) 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.40-8.10 (m, 12H, Ar-H),

2-Phenyl-3-(6-nitrobenzothiazol-2-yl)quinazolin-4(3*H*)-one [3k]. Recrystallised from glacial acetic acid, yield 0.47 g, (40.4%), m.p. 262-264 °C, R*f*: 0.79(rectified spirit).
IR [KBr; γ] 1490 cm^{-1}(- NO_2) 1620 cm^{-1} (C=N quinazoline) 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.70-8.03(m, 12H, Ar-H),
2-Phenyl-3-(4-6-dimethylbenzothiazol-2-yl)quinazolin-4(3*H*)-one [3l]. Recrystallised from glacial acetic acid, yield 0.81 g,(70 %), m.p. 200-202 °C, R*f*: 0.69(Rectified spirit). IR [KBr; γ] 710 cm^{-1}(C-H deformation) 1380 cm^{-1} (C-H stretching in CH3), 1620 cm^{-1} (C=N quinazoline) 1725cm^{-1} (C=O), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m,11 H, Ar-H), 1.30 (s, 3H, CH_3, in 6th position of benzothiazole), 1.40 (s, 3H, CH_3, in 4th position of benzothiazole)
2-Phenyl-3-(6-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [3m]. Recrystallised from glacial acetic acid, yield 0.47 g, (40.4%), m.p. 216 – 218 °C, R*f*: 0.61(rectified spirit).
IR [KBr; γ] 1280 cm^{-1}(Ar-O-C Stretching) ,1385 cm^{-1} (C-H in CH_3),1630cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching). ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65 (m, 12H, Ar-H), 1.1-1.4 (q-2H –CH_2-CH_3), 3.4 - 4.0 (t, 3H, CH_2-CH_3)
6,8-Dibromo-2-phenyl-3-(benzothiazol-2-yl)quinazolin-4(3*H*)-one [4a]. IR [KBr; γ] 1620cm^{-1} (C=N quinazoline) 1720 cm^{-1} (C=O], ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.85-7.70(m, 11H,Ar-H), 7.9 (d, 1H, *J* =2.2, H2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H2, H_B-Ar-H*)*
6,8-Dibromo-2-phenyl-3-(4-methoxybenzothiazol-2-yl)quinazolin-4(3H)-one[4b]. Recrystallised from glacial acetic acid, yield 0.81 g, (70 %), m.p. 198 – 200 °C, R*f*: 0.69(rectified spirit). IR [KBr; γ] 1383 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline) 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH_3 stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m, 10H,Ar-H), 3.80 (s-3H OCH_3) , 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*
6,8-Dibromo-2-phenyl-3-(5-methoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [4c]. Recrystallised from glacial acetic acid, yield 0.47 g, (40.4%), m.p. 98– 100 °C, R*f*: 0.79 (rectified spirit). IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline), 1718 cm^{-1} (C=O), 2810 cm^{-1} (O-CH_3 stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m, 10H,Ar-H), 3.89 (s-3H OCH_3) , 7.9 (d, 1H, *J* =2.2, H2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*
6,8-Dibromo-2-phenyl-3-(6-methoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [4d]. Recrystallised from glacial acetic acid, yield 0.78 g, (66.7%), m.p. 208–210°C, R*f*: 0.76(rectified spirit). IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1625cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m, 10H,Ar-H), 3.80 (s-3H OCH_3), 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*
6,8-Dibromo-2-phenyl-3-(4-methylbenzothiazol-2-yl)quinazolin-4(3*H*)-one [4e]. Recrystallised from glacial acetic acid, yield 0.81 g, [70 %], m.p. 168-170 °C, R*f*: 0.82(rectified spirit). IR [KBr; γ] 1375 cm^{-1} (C-H deformation),1620cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching) ,^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.70-7.70 (m, 10H,Ar-H), 2.30 (d-3H -CH_3), 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*
6,8-Dibromo-2-phenyl-3-(5-methylbenzothiazol-2-yl)quinazolin-4(3*H*)-one[4f]. Recrystallised from glacial acetic acid, yield 0.47 g, (40.4%), m.p. 204-206°C, R*f*=0.65(rectified spirit). IR [KBr; γ] 710 cm^{-1}(Ar-Cl) ,1620cm^{-1} (C=N quinazoline),1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H

stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.75 (m,10H,Ar-H) , 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*, 2.35 (d-3H -CH_3).

6,8-Dibromo-2-phenyl-3-(5-chlorobenzothiazol-2-yl)quinazolin-4(3*H*)-one [4g]. Recrystallised from rectified spirit, yield 0.47 g, [40.4%], m.p. 208-210 °C, R*f*=0.65(rectified spirit). IR [KBr; γ] 1278 cm^{-1}(Ar-O-C Stretching), 1383 cm^{-1} (C-H in CH_3),1620cm^{-1} (C=N quinazoline) ,1722 cm^{-1} (C=O], 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65 (m,10H,Ar-H), 8.3 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 8.1 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*

6,8-Dibromo-2-phenyl-3-(6-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [4h]. Recrystallised from glacial acetic acid, yield 0.81 g, (70%), m.p. 192-194 °C, R*f*=0.77(rectified spirit). IR [KBr; γ] 1270 cm^{-1}(Ar-O-C Stretching), 1380 cm^{-1} (C-H stretching in CH_3), 1625 cm^{-1} (C=N quinazoline] ,1715 cm^{-1} (C=O), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.60 (m,10H,Ar-H), 1.1-1.6 (q-2H –CH_2-CH_3), 3.5-4.1 (t, 3H, CH_2-CH_3) , 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*

6,8-Dibromo-2-phenyl-3-(5-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [4i]. Recrystallised from glacial acetic acid, yield 0.78 g, (66.7%), m.p. 202-204 °C, R*f*= 0.87(rectified spirit). IR [KBr; γ] 610 cm^{-1}(C-Br), 1620 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-8.25 (m, 10H,Ar-H), 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*, 1.1-1.6 (q-2H –CH_2-CH_3), 3.5-4.1 (t, 3H, CH_2-CH_3)

6,8 Dibromo-2-phenyl-3-[6-bromobenzothiazol-2-yl)quinazolin-4(3*H*)-one [4j]. Recrystallised from glacial acetic acid, yield 0.81 g, (70%), m.p. 164-166 °C, R*f* =0.65 (rectified spirit).IR [KBr; γ] 1490 cm^{-1}(- NO_2), 1620 cm^{-1} (C = N quinazoline) 1720 cm^{-1} (C = O), 3050 cm^{-1}(Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.90-8.10(m,10H,Ar-H) , 8.3 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 8.1 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*

6,8-Dibromo-2-phenyl-3-[6-nitrobenzothiazol-2-yl)quinazolin-4(3*H*)-one [4k]. Recrystallised from glacial acetic acid, yield 0.78 g, [66.7 %], m.p. 240-242 °C, R*f* = 0.72(rectified spirit). IR [KBr; γ] 710 cm^{-1}(C-H deformation) ,1380 cm^{-1} (C-H stretching in CH_3), 1620 cm^{-1} (C=N quinazoline) , 1725cm^{-1} (C=O), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m,10 H, Ar-H), 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*

2-Phenyl-3-(4-6-dimethylbenzothiazol-2-yl)quinazolin-4(3*H*)-one [4l]. Recrystallised from glacial acetic acid, yield 0.81 g, [70 %], m.p. 200-202 °C, R*f*: 0.69(rectified spirit). IR [KBr; γ] 710 cm^{-1}(C-H deformation), 1380 cm^{-1} (C-H stretching in CH_3), 1620 cm^{-1} (C=N quinazoline) , 1725cm^{-1} (C=O), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65(m,9 H, Ar-H), 1.30 (s, 3H, CH_3, in 6th position of benzothiazole), 1.40 (s, 3H, CH_3, in 4th position of benzothiazole), 7.9 (d, 1H, *J* =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, *J* = 2.2, H_2, H_B-Ar-H*)*

2-Phenyl-3-(6-ethoxybenzothiazol-2-yl)quinazolin-4(3*H*)-one [4m]. Recrystallised from glacial acetic acid, yield 0.47 g, [40.4 %], m.p. 216 – 218 °C, R*f*: 0.61(rectified spirit). IR [KBr; γ] 1280 cm^{-1}(Ar-O-C Stretching), 1385 cm^{-1} (C-H in CH_3), 1630cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR [$CDCl_3$ + DMSO,δ in ppm] 6.80-7.65

(m,10H,Ar-H), 1.1-1.4 (q-2H $-CH_2-CH_3$), 3.4 - 4.0 (t, 3H, CH_2-CH_3), 7.9 (d, 1H, J =2.2, H_2, H_A-Ar-H), 7.56 (d, 1H, J = 2.2, H_2, H_B-Ar-H*)*

Acknowledgements

One of the authors [SSL] is thankful University Grants Commission, New Delhi for providing financial assistance [JRF] and Ms. Sweety Laddha for her encouragement during the project. They wish to thank CDRI Lucknow, India for recording spectra, Head, Department of Pharmaceutical Sciences, Nagpur, India, for providing facilities and Mr. Rajendra Chopade, Dr. N. J. Gaikwad, and Prof. M.R.Tajne of Nagpur University, India, for valuable suggestions.

References and Notes

[#] Part of the work is presented in International symposium on Drug Discovery and Process Research, Kolhapur University, Kolhapur, Feb2002

[$] Part of the work is presented at Indian Pharmaceutical Congress, Pune, 2002

1. Allison, M.C.; Howatson, A.G.; Torrance, C.J.; Lee, F.D., Russell, R.I *N.Engl. J. Medi.* **1992,** *327*, 749.
2. Vane, J.R. *Nat.New.Biol*. **1971,** *231*, 232.
3. Amadio, P.; Cummings, D.M. *Prosgrad. Med*. **1993,** *93*,73.
4. Wallace, J.L.; Carter, E.; Mcknight, G.W.; Le, T.; McCafferty, D.M.; Aregentierh, D.; Capetola, R. *Gastroenterology* **1993,** *104*,(A), 221.
5. Ronald, F.; Borne Non sterodial anti-inflammatory agents. In *Foye's Principle of Medicinal chemistry, 5th Edn*., Lemke, T.L.; Williams, D.A., Eds., International student edn., Lippincott, Williams and Wilkins, 2002, pp 751-793.
6. Song, Y.; Connor, D.T. ; Sercel, A.D. ; Sorenson, R.J. ; Doubleday. R.; Unangst, P.C.; Roth. B.D.; Beylin, V.G. ; Gilbertsen, R.B. ; Chan, K. ; Schrier, D.J.; Guglietta, A.; Bornemeier, D.A.; Dyer, R.D. *J.Med.Chem.***1999**,*42*, 1161.
7. Puig, C. ; Crespo, M.I.; Godessart, N.; Feixas, J.; Iharzo, J.; Jimenez, J.M.; Soca, L.; Cardelus, I.; Heredia, A.; Miralpeix, M.; Puig, J.; Beleta, J.; Huerta, J.M.; Lopez, M.; Segarra, V.; Ryder H.; Palacios, J.M. *J.Med.Chem.* **2000,** *43,* 214.
8. Vane, J.R.; Bakhle, Y.S.; Botting, R.M. *Annu. Rev. Pharmacol. Toxicol*. **1998,** *38,* 97.
9. Fu, J-Y.; Maferrer, J.L.; Seibert, K.; Raj, A.; Needleman, P. *J.Biol. Chem*. **1990**, *265*,16737.
10. Mitchell, J.A.; Akarasereenont, P.; Thiemermann, C.; Flower, R.J.; Vane, J.R. *Proc. Natl. Acad. Sci. USA.* **1993**, *90,* 11693
11. Smith, W.L.; Garavito, M.; DeWitt, D.L. *J. Biol. Chem.* **1996,** *271*, 33157

12. Gerd, D.; Werner, K. *E. J. Med. Chem*. **2001,** *36,*109
13. Giuseppe, C.; Vincenzo, S.; Elisa, P.; Beatrice, S.; Ferdinando, F.; Timothy, D.W.; John, L.W.; Demian, R.I.; Edson, A.; Giuseppe, C.; Gilberto, De. N. *Eur. J. Med. Chem*. **2001,** *36,* 517.
14. Wolfe, J.F.; Rathman, T.L.; Sleevi, M.C.; Campbell, J.A.; Greenwood, T.D. *J. Med. Chem.* **1990,** *33*, 161.
15. Rastogi, V.K.; Parmar, S.S.; Sing, S.P.; Akers, T.K. *J. Heterocycl. Chem.* **1978**, 15, 497.
16. Rao A.R.R.; Bahekar, R.H. *Ind. J. Chem. 38B* **1999,** 4, 434
17. Bahekar, R.H.; Rao A.R.R. *Arzneim.-Forsch./Drug Res.* **2001,** 51, 284.
18. Bansal, E.; Ram, T.; Sharma, S.; Tyagi, M.; Preeti Rani, A.; Bajaj, K.; Tyagi, R.; Goel, B.; Srivastava, V.K.; Guru, J.N.; Kumar, A. *Ind. J. Chem.* **2001,** *40B*, 307.
19. Okumura, K., Oine, T., Yamada,Y., Hayashi, G., Nakama, M., Nose, T. *J. Med. Chem.* **1968,** 11, 788.
20. Ozaki, K.; Yamada, Y.; Oine, T., Ishizuka, T.; Iwasawa, Y. *J.Med.Chem*. **1985,** 28, 568.
21. Bhargava, P.N.; Chaurasia, M.R. *J.Med.Chem*. **1968,** 11, 404.
22. Parmar, S.S.; Kumar, R. *J.Med.Chem*. **1968,** 11, 635.
23. Alagarsamy, V.; Pathak, V.S.; Venkateshperumul, R.; Meena, S.; Thirumurugan, K.; Solomon, R.; Declercq, E. *Indian. J. Pharm. Sci*. **2003,** 65, 293.
24. Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Heterocyclic. Chem*. **1980,** 17, 155.
25. Skibo, E.B.; Huang, X.; Martinez, R.; Lemus, R.H.; Craigo, W.A.; Dorr, R.T. *J.Med.Chem.* **2002,** 45, 5543.
26. Pandey, A.; Volkots, D.L.; Seroogy, J.M.; Rose, J.W.; Yu Jin-chen, Lambing, J.L.; Hutchaleelaha, A.; Hollenbach, S.J.; Abe, K.; Giese, N.A.; Scarborough, R.M. *J. Med. Chem*. **2002,** 45, 3772.
27. Webb, T.R.; Lvovskiy, D.; Kim, S.; Xiago-duo, Ji.; Melman, N.; Linden, J.; Jacobson, K.A. *J. Biorg. Med. Chem.* **2003,** 2, 77.
28. Pannerselvam, P.; Pradeepchandran, R.V.; Sridhar, S.K. *Indian J. Pharm. Sci*. **2003,** 65, 268.
29. Beneteau, V.B.T.; Guillard, J.; Leance, S.M.; Pfeiffer, B. *Eur. J. Med. Chem*. **1999,** 34, 1053.
30. Kabeer, A.S.; Baseer, M.A.; Mote, N.A. *Asian J. Chem*. **2001,** 13, 496.
31. Hassan, K.H.M.; Mahmoud, A.M.; El-Sherief, A. *Z. Naturforsch IV*. **1978,** 33B, 1005.
32. Nadkarni, A.B.; Kamath, R.V.; Khadse, G.B.; *Indian J. Heterocycl. Chem*. **2000,** 9, 309
33. Mruthyunjayasawmy, B.H.M.; Shanthaveerappa, B.K. *Indian J. Chem. Sec-B* **2000,** 39, 433.
34. Miyamatsn, H.; Ueno, S.; Shimizu, M.; Hosono, J.; Tomari, M.; Seida, K.; Suzuki, T.; Wada, J. *J. Med. Chem*. **1974,** 17, 491.
35. Hays, J.S.; Rice, M.J.; Ortwine, D.F.; Johnson, G.; Schwarz, R.D.; Boyd, D.K.; Copceland, F.L.; Vartanian, M.J.; Boxer, P.A . *J.Pharm. Sci.* **1994,** 833, 1425.

36. Chopade, R.S.; Bahekar, R.H.; Khedekar, P.B.; Bhusari, K.P.; Rao, A.R.R. *Arch. Pharm*. **2002,** 8, 381.
37. Rose, U *J. Heterocyclic Chem*., **1992,** 29, 551.
38. Gineinath, M.M.; El-Sherbeny A.E.I.; Nasr, M.N.; Maarouf, A.R. *Arch. Pharm. Med. Chem*. **2002,** 11, 556.
39. Winter, C.A.; Edwin, A.R.; Nuss, G.W. *Proc. Soc. Exp. Biol. Med. III*. **1962,** 544.
40. Wakitani, T.; Nanayama, M.; Masaki, M.; Matsushita, *Jpn. J. Pharmacol*. **1998,** 78, 365.
41. Sancilio, L.F.; Nolan, J.C.; Wagner, L.E. *Arzneim.-Forsch./Drug Res*. **1987,** 37, 513.
42. Trefouel, J.; Trefouel, M.; Nitti, F.; Bovet, D. *Chem. Res. Soc. Bio.* **1935,** 120, 756.
43. Zentmyr, D.T.; Wagner, E.C. *J. Org. Chem.* **1949,** 14, 967.