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Research Article

A facile synthesis and dual inhibitor activity of novel synthesized quinazoline hydrazine-thiazoliine based Drugs

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ABSTRACT

Inflammation is a pervasive phenomenon that operates during severe perturbations of homeostasis, such as infection, injury, and exposure to contaminants, and is triggered by innate immune receptors that recognize pathogens and damaged cells. The long-term administration of nonsteroidal anti -inflammatory drugs (NSAIDs) is often limited by the emergence of gastrointestinal or cardiovascular complications . There is an indication that COX inhibition by NSAIDs enhanced synthesis of leukotrienes that occur by shunting the arachidonic acid metabolism towards the 5-lipoxygenase pathway. Dual inhibition of COX and 5 -LOX act by blocking the formation of both prostaglandins and leukotriene but do not affect lipoxin formation. Such combined inhibition avoids some of the disadvantages of selective COX-2 inhibitors and spares the gastrointestinal mucosa. 2 substituted quinazolin-4 (3H)-one was reacted with the thiosemicarbazides through the nucleophilic addition reaction to produce the quinazoline thiosemicarbazides (compound 1 & II) and the addition of various bromoketones to the com pound I & II were undergone the cyclizasation reaction to yield 2-(4-(4-substituted) thiazol-2 (3H)-ylidene)-1-(2-substituted quinazolin-4 (3H)-ylidene)hydrazine. According to the acute oral toxicity evaluation, 20 mg/kg doses of synthesized compounds were administered orally to the rats for this study. The in-vivo acute anti-inflammatory activity using a carrageenan-induced hind paw edema model and acute ulcerogenicity were studied in albino rats to show their dual inhibitor Cyclooxygenase/5 Lipooxygenase (COX/5LOX) activity. After 6h also, almost all the newly synthesized compounds showed 51-60 % edema inhibition than the standard drug and did not show any redness for ulcerogenicity. They act by blocking the formation of both prostaglandins and leucotrienes but do not affect lipoxin formation. Such combined inhibition avoids some of the disadvantages of selective COX-2 inhibitors and spares the gastrointestinal mucosa.The novel synthesised compounds can serve as COX/5 LOX dual inhibitor to reduce the burden of society.

Keywords: acute toxicity; acute inflammation; Quinazoline; thiazoliine; ulcerogenicity; Cyclooxygenase; Lipooxygenase; Dual inhibitor.

INTRODUCTION

Inflammation is a pervasive phenomenon that operates during severe perturbations of homeostasis, such as infection, injury, and exposure to contaminants, and is triggered by innate immune receptors that recognize pathogens and damaged cells. Among vertebrates, the inflammatory cascade is a complex network of immunological, physiological, and behavioral events that are coordinated by cytokines, immune signaling molecules (Noah et al., 2012). Many pathways are involved in acute inflammatory processes such as prostaglandin, histamine, bradykinin, and, more recently, platelet-activating factor (PAF) and interleukin-1 and leukotriene. The mediators and cellular effectors of inflammation are important constituents of the local environment of tumors. In some types of cancer, inflammatory conditions are present before a malignant change occurs (Alberto et al., 2008). There are three major pathways associated with the arachidonic acid (ARA) cascade, cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) pathways (Hwang et al., 2013). Non-steroidal anti-inflammatory drugs are the most commonly used drugs in the world. The long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) is often limited by the emergence of gastrointestinal (gastric mucosal erosions, ulcerations, bleeding, and perforation) or cardiovascular complications (Thais et al., 2014; Fanelli et al., 2013; Mufeed et al., 2015). There is an indication that COX inhibition by NSAIDs enhanced synthesis of leukotrienes that occur by shunting the arachidonic acid metabolism towards the 5-lipoxygenase pathway (Gilroy etal., 1998; Jenny Jacob et al., 2015). Leukotrienes are supposed to contribute to gastric mucosal injury by promoting tissue

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ischaemia and inflammation (Gandhi et al., 2012) and mainly Leukotriene B4 (LTB4) leading to development of duodenal ulcer (Martin et al., 1991).

Dual inhibition of COX and 5-LOX may limit the vascular changes seen during inflammation and leucocyte induced GI damage. They act by blocking the formation of both prostaglandins and leucotrienes but do not affect lipoxin formation. Such combined inhibition avoids some of the disadvantages of selective COX-2 inhibitors and spares the gatrointestinal mucosa (Mar- tel-Pelletier et al., 2003). Some hydrazone and Hydra- zide derivatives of benzoquinone were reported for binding study with COX-2 and 5-LOX enzymes using AutoDock-Vina software (Mansur NK et al., 2013; Misra et al., 2013). Thiazolidinone derivatives, Isatin-3-[N 2- (2-benzalaminothiazol-4-yl)] hydrazones and a series of novel 2-benzylamino-3-substituted quinazolin-4 (3H)-ones showed their antiinflammatory activity (Parul et al., 2008; Venkateshwarlu et al., 2012; Veerachamy et al., 2007; Mosaad et al., 2009). Some other quinazoline derivatives and thiazoline derivatives display a wide diversity of enzyme inhibitory activity, antimicrobial, analgesic, anti-inflammatory, anti-convulsant and so many publications expected them to be useful for patients with acquired immune deficiency syndrome (AIDS), cancer chemotherapy (Westerhof et al., 1995; Bavetsias et al., 2000; Govindaraj et al., 2010; Alagarsamy et al., 2006; Yashshree et al., 2011; Sushma et al., 2004; Liu et al., 2011; Baseem et al., 2011).

Looking to the medicinal importance of quinazoline, thiazoliine and hydrazine we targeted to synthesis of new class of heterocyclic molecules in which all of these moieties are present in order to develop potential dual COX/5-LOX inhibitor for better and safer treatment of inflammation and gastric ulcer.

EXPERIMENTAL SECTION

Chemicals and instruments

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. Purity of synthesized compounds was checked by thin layer chromatography using pre-coated silica gel plates. Melting points were determined by Veego VMP-1 the melting point apparatus and were uncorrected. IR spectra were recorded on Shimadzu FT-IR spectrometer model using KBr discs. The NMR spectra (DMSO-d_6) were recorded on Bruker DRX-300 spectrometer with TMS as an internal standard. The mass spectra were measured on a Shimadzu LCMS 2010A spectrometer.

Synthesis of quinazoline-thiazoline based hydrazines

The scheme of the synthetic study is shown in Fig:1.

Synthesis of (1Z)-1-(2-substituted quinazolin-4 (3H)-ylidene) thiosemicarbazides (compound 2a & 2b)

2-substituted-1, 3-benzoxazine-4 (3H)-one (0.01M) was added in ethanol to dissolve and thiosemicarbazides (0.01M) in ethanol was added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 2 h and after cooling at room temperature. The precipitate was filtered, washed with water then recrystallized from ethanol or 2-butanol and a crystalline product was obtained. The progress of the reaction was checked by thin layer chromatography (TLC). The obtained product was filtered and recrystallised from ethanol to yield the needle shaped shiny white crystals. The product was identified by TLC using Benzene: Chloroform: Methanol.

Synthesis of (1-(2-substituted quinazolin-4 (3H)-ylidene)-2-(4-substituted thiazol-2 (3H)-ylidene) hydrazine

A solution of the appropriate thiosemicarbazides derivatives (compounds 2a-2b) (0.1 mol), anhydrous sodium acetate (0.09 mol) and various bromoketones **(**0.1 mol) (a-e) in absolute ethanol (100 mL) was heated under reflux for 12-24h, concentrated and left overnight. The progress of the reaction was monitored by Thin layer chromatography (TLC). The product was filtered, dried and recrystallized from absolute ethanol to yield pale yellowish crystal. The product was identified by TLC using n-hexane: ethyl acetate.

Characterizasation

The all synthesized compounds are characterized by molecular weight, melting point, percentage yield, solubility, R_f values, Infrared, Mass, ^{13}C NMR and ^{1}H NMR spectroscopy**.**

PHARMACOLOGICAL EVALUATION

Animals

Healthy, adult albino rats of both sex male: female (1: 1) weighing 150-200 g were used for the study which was approved by the Institutional animal ethical committee and were maintained in individual polypropylene cages, with free access to ration and water. The rats were divided into groups and each groups had four animals.

Acute oral toxicity studies

The OECD guidelines 425 were followed for the acute oral toxicity study for fixing the dose. The dose level up to 100 mg/kg and 50 mg/kg of the synthesized compounds in albino rats were not produced any mortality on oral administration. So 20 mg/kg doses of synthesized compounds were administered orally to the rats for this study.

Acute Anti-inflammatory screening

Carrageenan-induced rat paw edema method as described by Winter et al (Winter et al., 1962; Akash et al., 2010) had been carried out for the evaluation of acute anti-inflammatory activity of the synthesized compounds with diclofenac sodium as a standard drug. Albino rats were divided into following groups consisting of four animals each. Animals were fastened for 12

h before the experiment and only water was allowed. Control group received 0.5 mL vehicle sodium carboxymethyl cellulose (CMC) (0.5 % w/v) per rat, and the standard group received diclofenac sodium 10 mg kg^{-1} body mass suspended in 0.5% w/v of CMC by oral route. All the remaining groups were received the test compounds at the same dose via oral route. All the suspensions for oral dose were prepared in the CMC and were administered as a constant volume of 0.5 mL per rat. After one hour of the administration of the test compounds and diclofenac sodium, 0.1 mL of 1% w/v suspension of carrageenan was injected in to the subplanatar of left paw of the test animals. The paw volume was measured using plethismometer at suitable time intervals. The difference between initial and subsequent observations gave the edema volume for the corresponding time. The anti-inflammatory activity (percentage inhibition of inflammation) of standard drug and the test compounds were calculated according to the formula. The edema is measured in the variation between the thicknesses of the two paws. The measurement was carried out at 0, 0.5, 1, 2, 3, 4 and 5 h after injection of the tested compounds, reference drug and control.

Acute ulcerogenic potential

The newly synthesized compounds were screened for ulcerogenic activity with the standard drug diclofenac and were scored by method of Cioli et al. (Cioli et al., 1979; cioli et al., 1967; Ali almasirad et al., 2014). 24 h fasted albino rats (160-180 g) were treated for a single dose of each of vehicle, standard and test compounds (20 mg/kg in 0.5% v/v CMC suspension, per oral respectively and the rats were exposed to cold stress at-20°C for 4 h and then sacrificed by ether inhalation and stomach was removed for the examination by means of a magnifying glass to assess, the incidence of redness and spot ulcers were noted. For each stomach, the scoring system of mucosal damage was as follows: 0.5: redness; 1.0: spot ulcers; 1.5: hemorrhagic streaks; 2.0: ulcers >3 but ≤5; 3.0: ulcers > 5. The mean score of each treated group minus the mean score of control group was considered as gastric mucosal ulceration score.

RESULT AND DISCUSSION

Chemistry

The novel series of Quinazoline-hydrazine-Thiazoline based compounds were prepared by the conventional method as shown in the scheme. 2 substituted quinazolin-4 (3H)-one was reacted with the thiosemicarbazides through the nucleophilic addition reaction to produce the quinazoline thiosemicarbazides (compound 1 & II) and the addition of various bromoketones to the com pound I & II were undergone the cyclizasation reaction to yield 2-(4-(4-substituted) thiazol-2 (3H)-ylidene)-1-(2-substituted quinazolin-4 (3H)-ylidene) hydrazine. The percentage yield of the synthesized compounds was 60-70%. The all synthesized compounds were characterized by Molecular weight, melting point, Percentage yield, solubility, R_f values, Infrared spectroscopy, ^1H NMR,^{13}C NMR spectroscopy and mass spectroscopy as follows.

(1Z)-1-(2-methylquinazolin-4 (3H)-ylidene) thiosemicarbazides ($C_{10}H_{11}N_5S$) (I)

Yield-71%; m.p. 250-260°C; R_f-0.61; IR (KBr, cm^{-1}): 1620.9 (C=N str), 1235.1 (C-N str). 3481 (N-H), 895 ((Ar C-H bend, 1571 (Ar C=C str), 3108 (Ar C-H str), 825 and 1227 (C=S), 3335 (NH_2), 2888 (CH_3 str); ^1H-NMR (DMSO-d_6) δ: 7.5-7.8 (m, 4H, Ar-H), 9.5 (s, NHof quinazoline, 1H), 8.5, 8.41 (m, 2H, NH_2), 0.97-1.02 (t, 3H, CH_3), 11.52 (s, 2H=N-NH); ^{13}C (DMSO-d_6) δ: 157.4 (C2), 141.0 (C_4=N), 127.9 (C5 &C6), 132.8 (C7), 124.1 (C8), 145.6 (C9), 120.5 (C10), 178. 6 (C=S), 18.9 (CH_3).MS (m/z): M^+ calculated 233.29, found 233.75

(1Z)-1-(2-phenylquinazolin-4 (3H)-ylidene) thiosemicarbazide ($C_{15}H_{13}N_5S$) (II)

Yield-73%; m.p. 220-225°C; R_f-0.59; IR (KBr, cm^{-1}): 1617.6 (C=N str), 1241 (C-N str). 3432 (N-H), 899 ((Ar C-H bend, 1592 (Ar C=C str), 3080 (Ar C-H str), 827 and 1232 (C=S), 3405 (NH_2); ^1H-NMR (DMSO-d_6) δ: 7.85-7.98 (m, 4H, Ar-H), 8.7 (s, NH of quinazoline,1H), 8.5, 8.75 (m, 2H, NH_2), 7.2-7.6 (m, 5H, Ar), 7.9 (s, 2H=N-NH); ^{13}C (DMSO-d_6) δ: 155.24 (C2), 143.1 (C4=N), 129.5 (C5 &C6), 131.4 (C7), 125.2 (C8), 144.2 (C9), 121.5 (C10), 180. 9 (C=S), 18.7 (CH_3), Ar-C (phenyl)-123.07, 126.36, 127.33, 127.67, 134.91, 145.93. MS (m/z): M^+ calculated 295.36, found 295.15

(10Z, 12E)-1-(2-methylquinazolin-4 (3H)-ylidene)-2-(4-methylthiazol-2 (3H)-ylidene) hydrazine ($C_{13}H_{13}N_5S$) (Ia)

Yield-67%; m.p. 225°C; R_f-0.71; IR (KBr, cm^{-1}): 2202 (C=N str), 1181 (C-N str). 3435 (N-H), 894 ((Ar C-H bend), 1590 (Ar C=C str), 3180 (Ar C-H str), 2890 (CH_3 str), 2068 (S-C=N), 3352 (NH of thiazoline ring) ; ^1H-NMR (DMSO-d_6) δ: 6.46-7.40 (m, 4H, Ar-H in quinazoline), 10.3 (s, NHof quinazoline,1H), 0.97-1.02 (t, 3H, CH_3), 2.3 (t,3H,4 CH_3 in thiazole), 12.25 (NH of thiazole), 6.5 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: 155.2 (C2), 143.1 (C4=N), 129.5 (C5 &C6), 131.4 (C7), 125.2 (C8), 144.2 (C9), 121.5 (C10), 165. 9, 18.9 (CH_3 attached in C2 in Quinazoline), (C'2-S in thiazole), 157.2 (C'4 in thiazole), 99.8 (C'5 in thiazole), 20.8 (CH_3 attached in C'4 in thiazoline) MS (m/z): M^+ calculated 271.34, found 271.39

(10E, 12E)-1-(2-methylquinazolin-4 (3H)-ylidene)-2-(4-phenylthiazol-2 (3H)-lidene) hydrazine ($C_{18}H_{15}N_5S$) (Ib)

Yield-64%; m.p. 241°C; R_f-0.65; IR (KBr, cm^{-1}): 2214 (C=N str), 1185 (C-N str). 3430 (N-H), 897 ((Ar C-H bend, 1595 (Ar C=C str), 3170 (Ar C-H str), 2885 (CH_3 str) 2030 (S-C=N), 3343 (NH of thiazoline ring) ; ^1H-NMR (DMSO-d_6) δ: 7.2-7.6 (m, 4H, Ar-H), 10.8 (s, NHof quinazoline,1H), 0.97-1.02 (t, 3H, CH_3), 6.8-7.1 (m,5H,Ar-H), 12.1 (NH of thiazole), 6.5 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: 155.24 (C2), 143.2 (C4=N), 129.3 (C5

&C6), 131.4 (C7), 125.2 (C8), 144.2 (C9), 121.5 (C10), 18.7 (CH_3 attached in C2 of quinozoline), 160. 9 (C'2-S in thiazole), 157.7 (C'4 in thiazole), 100.2 (C'5 in thiazole), Ar-C (phenyl at C'4)-123.7, 126.6, 127.3, 127.7, 134.1, 137.9. MS (m/z): M^+ calculated 333.41, found 333.29.

(10E, 12E)-1-(2-methylquinazolin-4 (3H)-ylidene)-2-(4- p-tolylthiazol-2 (3H)-ylidene) hydrazine ($C_{19}H_{17}N_5S$)(Ic)

Yield-68%; m.p. 294°C; R_f-0.71; IR (KBr, cm^{-1}): 2217 (C=N str), 1190 (C-N str). 3431 (N-H), 895 ((Ar C-H bend, 1599 (Ar C=C str), 3170 (Ar C-H str), 2870 (CH_3 str), 2030 (S-C=N), 3343 (NH of thiazoline ring) ; ^{1}H-NMR (DMSO-d_6) δ: 7.2-7.6 (m, 4H, Ar-H), 11.8 (s, NHof quinazoline,1H), 0.8-1.0 (t, 3H, CH_3), 12.2 (NH of thiazole), 6.8-7.1 (m,4H,Ar-H), 6.5 (s, 1H=CH), 2.5 (t,3H, CH_3 attached with aromatic ring at 4 thiazole); ^{13}C (DMSO-d_6) δ: 155.4 (C2), 143.2 (C4=N), 129.3 (C5 &C6), 131.4 (C7), 125.2 (C8), 144.2 (C9), 121.5 (C10), 20.7 (CH_3 attached in C2 of quinazoline), 162.8 (C'2-S in thiazole), 158.1 (C'4 in thiazole), Ar-C (phenyl attached to C'4)-123.07, 126.3, 128.3, 127.7, 134.1, 137.3, 24.2 (attached with aromatic ring at C'4of thiazole), 99.8 (C'5 in thiazole) . MS (m/z): M^+ calculated 347.44, found 347.81.

(10E, 12E)-2-(4-(4-chlorophenyl) thiazol-2 (3H)-ylidene)-1-(2-methylquinazolin-4 (3H)-ylidene) hydrazine ($C_{18}H_{14}ClN_5S$) (Id)

Yield-59%; m.p. 215°C; R_f-0.69; IR (KBr, cm^{-1}): 2225 (C=N str), 1100 (C-N str). 3420 (N-H), 901 ((Ar C-H bend, 1600 (Ar C=C str), 3200 (Ar C-H str), 2895 (CH_3 str), 2051 (S-C=N), 3370 (NH of thiazoline ring), 570 (P-Cl); ^{1}H-NMR (DMSO-d_6) δ: 7.3-7.6 (m, 4H, Ar-H), 11.6 (s, NHof quinazoline,1H), 0.9-1.5 (t, 3H, CH_3), 11.7 (NH of thiazole), 6.8-7.1 (m,4H,Ar-H), 6.5 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: 155.2 (C2), 141.8 (C4=N), 129.8 (C5 &C6), 132.4 (C7), 125.5 (C8), 140.2 (C9), 124.5 (C10), 20.7 (CH_3 attached in C2 of quinozoline), 162.8 (C'2-S in thiazole), 155.1 (C'4 in thiazole), Ar-C (phenyl at C'4 of thiazole)-123.07, 126.3, 128.3, 127.7, 134.1, 137.3, 97.2 (C'5 in thiazole) . MS (m/z): M^+ calculated 367.86, found 367.51.

(10E, 12E)-2-(4-(4-methoxyphenyl) thiazol-2 (3H)-ylidene)-1-(2-methylquinazolin-4 (3H)-ylidene) hydrazine ($C_{19}H_{17}N_5OS$) (Ie)

Yield-70%; m.p. 239°C; R_f-0.81; IR (KBr, cm^{-1}): 2225 (C=N str), 1102 (C-N str). 3420 (N-H), 901 ((Ar C-H bend, 1600 (Ar C=C str), 3200 (Ar C-H str), 2892 (CH_3 str), 2051 (S-C=N), 3381 (NH of thiazoline ring), 2838 (P-OCH_3); ^{1}H-NMR (DMSO-d_6) δ: 7.3-7.6 (m, 4H, Ar-H), 11.4 (s, NH of quinazoline,1H), 0.9-1.5 (t, 3H, CH_3), 11.5 (NH of thiazole), 6.8-7.1 (m,4H,Ar-H), 6.5 (s, 1H=CH), 3.5 (t, 3H, OCH_3); ^{13}C (DMSO-d_6) δ: 155.2 (C2), 141.8 (C4=N), 129.8 (C5 &C6), 132.4 (C7), 125.5 (C8), 140.2 (C9), 124.5 (C10), 20.7 (CH_3 attached in C2 of quinozoline), 162.8 (C'2-S in thiazole), 157.3 (C'4 in thiazole), Ar-C (phenyl at C'4 of thiazole)-123.07, 126.3, 128.3, 127.7, 134.1, 137.3, 52.9 (OCH_3), 96.4 (C'5 in thiazole) . MS (m/z): M^+ calculated 367.86, found 367.51.

(10E, 17E)-2-(4-methylthiazol-2 (3H)-ylidene)-1-(2-phenylquinazolin-4 (3H)-ylidene) hydrazine (II a) ($C_{18}H_{15}N_5S$)

Yield-70%; m.p. 239°C; R_f-0.81; IR (KBr, cm^{-1}): 2231 (C=N str), 1082 (C-N str). 3480 (N-H), 931 ((Ar C-H bend, 1604 (Ar C=C str), 3108 (Ar C-H str), 2858 (CH_3 str), 1453 (CH_3 bend), 2051 (S-C=N), 3299 (NH of thiazoline ring); ^{1}H-NMR (DMSO-d_6) δ: 7.3-7.8 (m, 9H, Ar-H), 11.8 (s, NH of quinazoline,1H), 10.6 (NH of thiazole), 1.5 (t, 3H, CH_3 attached to thiazoline ring at 4), 6.3 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: ^{13}C (DMSO-d_6) δ: 158.5 (C2), 162.8 (C4=N), 126.2 (C5 &C6), 130.5 (C7), 134.5 (C8), 143.7 (C9), 120.3 (C10), Ar-C (phenyl attached to C2 of quinazoline)-121.7, 124.3, 123.3, 127.5, 131.3, 137.1, 164.2 (C'2-S in thiazole), 153.5 (C'4 in thiazole), 24.1 (CH_3 attached to C'4 of Thiazole), 98.7 (C'5 in thiazole); MS (m/z): M^+ calculated 333.41, found 333.25.

(10E, 12E)-1-(2-phenylquinazolin-4 (3H)-ylidene)-2-(4-phenylthiazol-2 (3H)-ylidene) hydrazine (II b) ($C_{23}H_{17}N_5S$)

Yield-69%; m.p. 280°C; R_f-0.73; IR (KBr, cm^{-1}): 2233 (C=N str), 1085 (C-N str). 3484 (N-H), 938 ((Ar C-H bend), 1628 (Ar C=C str), 3110 (Ar C-H str), 2059 (S-C=N), 3305 (NH of thiazoline ring); ^{1}H-NMR (DMSO-d_6) δ: 7.3-7.8 (m, 14H, Ar-H), 11.5 (s, NH of quinazoline,1H), 12.6 (NH of thiazole), 6.5 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: ^{13}C (DMSO-d_6) δ: 158.5 (C2), 162.8 (C4=N), 126.2 (C5 &C6), 130.5 (C7), 134.5 (C8), 143.7 (C9), 120.3 (C10), Ar-C (phenyl attached to C2 of quinazoline)-121.7, 124.3, 123.3, 127.5, 131.3, 137.1, 164.2 (C'2-S in thiazole), 153.5 (C'4 in thiazole), Ar-C (phenyl attached to C'4 of thiozoline)-124.7, 125.3, 128.1, 129.5, 130.5, 137.1, 104.7 (C'5 in thiazole); MS (m/z): M^+ calculated 395.48, found 395.63.

(10E, 12E)-1-(2-phenylquinazolin-4 (3H)-ylidene)-2-(4-p-tolylthiazol-2 (3H)-ylidene) hydrazine (II c) ($C_{24}H_{19}N_5S$)

Yield-70.5%; m.p. 280°C; R_f-0.73; IR (KBr, cm^{-1}): 2233 (C=N str), 1085 (C-N str). 3484 (N-H), 938 ((Ar C-H bend), 1628 (Ar C=C str), 3110 (Ar C-H str), 2059 (S-C=N), 3305 (NH of thiazoline ring); ^{1}H-NMR (DMSO-d_6) δ: 7.1-7.9 (m, 13H, Ar-H), 11.7 (s, NH of quinazoline,1H), 12.3 (NH of thiazole), 6.1 (s, 1H=CH), 2.7 (t, 3H,CH_3 attached to C'4 of thiazole); ^{13}C (DMSO-d_6) δ: ^{13}C (DMSO-d_6) δ: 159.2 (C2), 162.7 (C4=N), 126.8 (C5 &C6), 131.5 (C7), 133.2 (C8), 146.7 (C9), 120.3 (C10), Ar-C (phenyl attached to C2 of quinazoline)-121.4, 123.8, 121.9, 128.5, 130.3, 136.1, 163.2 (C'2-S in thiazole), 158.2 (C'4 in thiazole), Ar-C (phenyl attached to C'4 of thiozoline)-125.7, 125.9, 127.1, 129.5, 130.5, 137.1, 25.2 (t, 3H, CH_3 attached to Ar phenyl with C'4 of thiazole), 105.2 (C'5 in thiazole); MS (m/z): M^+ calculated 409.14, found 408.87.

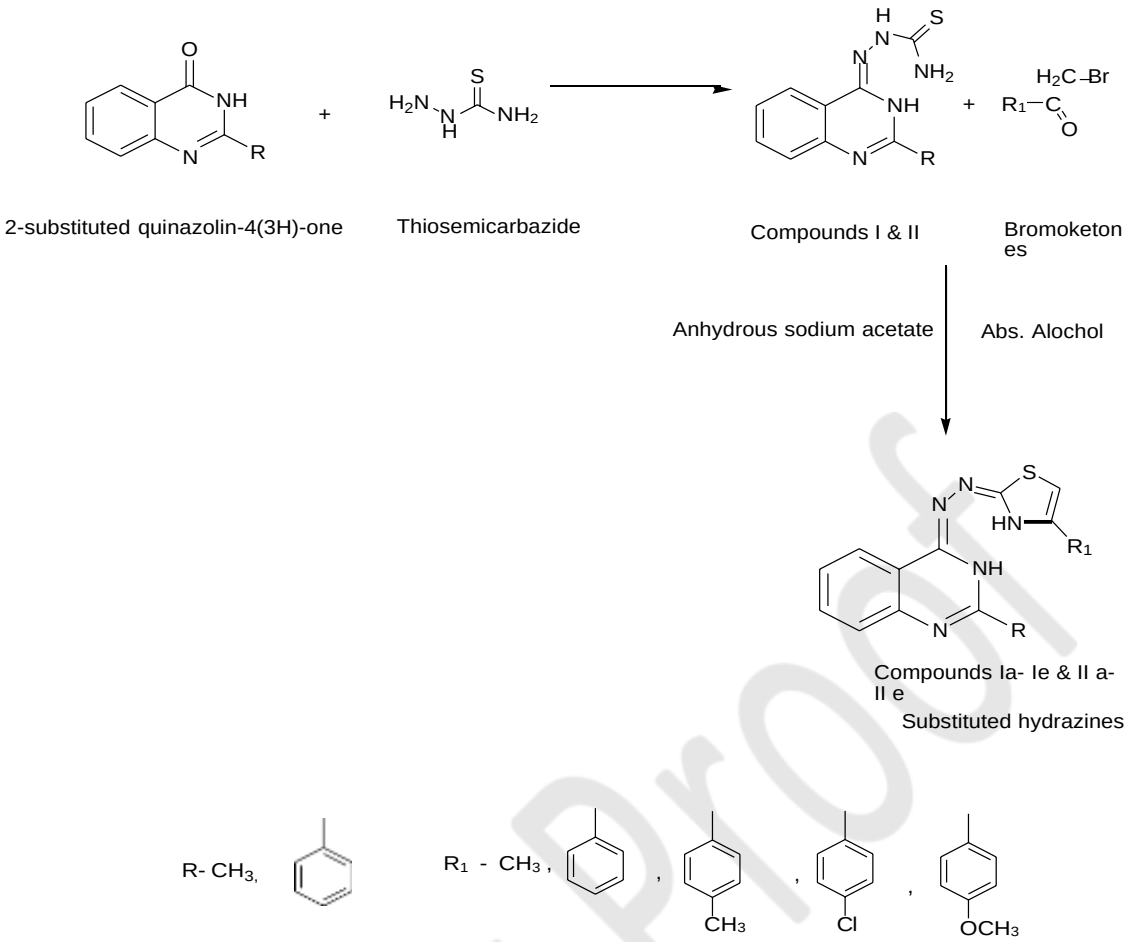

Figure 1: Scheme of the synthetic work

Table 1: Acute Anti-inflammatory screening of synthesized compounds using a carrageenan-induced hind paw edema model

Compounds	Edema (% inhibition)				
	30 minutes	1 h	2 h	4 h	6h
Control	----	---------	-------	------	-----
Standard Diclofenac sodium	45.71	59.16	75.30	89.67	40.17
Compound Ia	38.8 5	46.6 1	56.5 2	69.70	51.65
Compound Ib	44.21	54.17	63.89	72.50	59.95
Compound Ic	47.72	58.38	64.95	76.90	57.90
Compound Id	41.60	53.51	58.33	73.25	49.80
Compound Ie	48.15	54.63	62.04	78.37	52. 25
Compound IIa	42.50	50.24	59.60	67.49	48.94
Compound IIb	46.32	55.21	65.57	71.45	56.25
Compound IIc	48.68	54.68	69.34	74.28	54.27
Compound IId	45.71	57.29	63.87	72.15	50.82
Compound IIe	49.25	59.35	69.27	75.71	53.63

Significance levels * $p < 0.5$, ** $p < 0.01$, *** $p < 0.001$.

(10E, 12E)-2-(4-(4-chlorophenyl) thiazol-2 (3H)-ylidene)-1-(2-phenylquinazolin-4 (3H)-ylidene) hydrazine (II d) ($C_{23}H_{16}ClN_5S$)

Yield-57.5%; m.p. 205°C; R_f-0.55; IR (KBr, cm^{-1}): 2239 (C=N str), 1185 (C-N str). 3394 (N-H), 918 ((Ar C-H bend), 1618 (Ar C=C str), 311 (Ar C-H str), 2059 (S-C=N), 3305 (NH of thiazoline ring), 592 (P-Cl); ^{1}H-NMR (DMSO-d_6) δ: 7.1-7.9 (m, 13H, Ar-H), 11.5 (s, NH of quinazoline,1H), 11.9 (NH of thiazole), 6.9 (s, 1H=CH); ^{13}C (DMSO-d_6) δ: 158.9 (C2), 165.3 (C4=N), 125.5 (C5 &C6), 132.1 (C7), 127.2 (C8), 148.7 (C9), 119.9 (C10), Ar-C (phenyl attached to C2 of quinazoline)-121.4, 123.8, 121.9, 128.5, 130.3, 136.1, 161.1 (C'2-S in thiazole), 155.6 (C'4 in thiazole), Ar-C (phenyl attached to C'4 of thiozoline)-125.7, 125.9, 127.1, 129.5, 130.5, 131.1, 104.9 (C'5 in thiazole); MS (m/z): M^+ calculated 429.92, found 430.09.

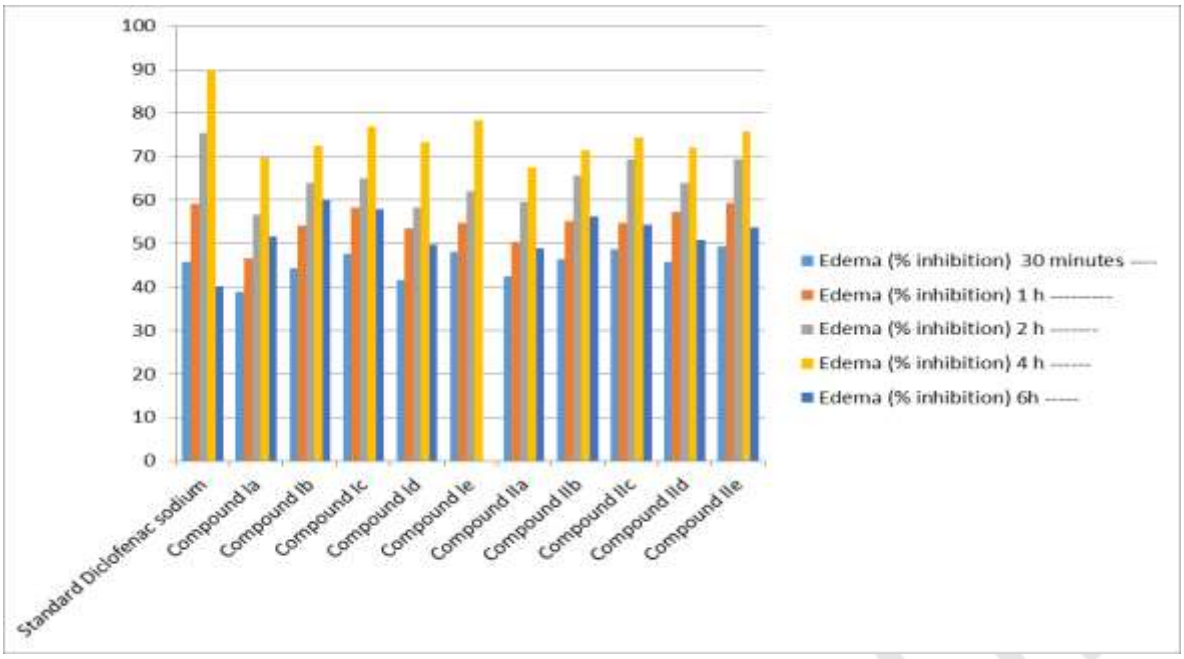

Figure 2: Acute Anti-inflammatory screening of synthesized compounds using a carrageenan-induced hind paw edema model

Table 2: Acute ulcerogenic potential of synthesized compounds

Compounds	Ulcer index (mean ± S.E)
Control	0
Standard Diclofenac sodium	1.97 ± 0.43
Compound Ia	0
Compound Ib	0
Compound Ic	0
Compound Id	0.35 ± 0.57
Compound Ie	0.12± 0.44
Compound IIa	0
Compound IIb	0. 1 ± 0.23
Compound IIc	0.13 ± 0.15
Compound IId	0.34 ± 0.32
Compound IIe	0. 18± 0.44

Significance levels * $p < 0.5$, ** $p < 0.01$, *** $p < 0.001$ as compared with control

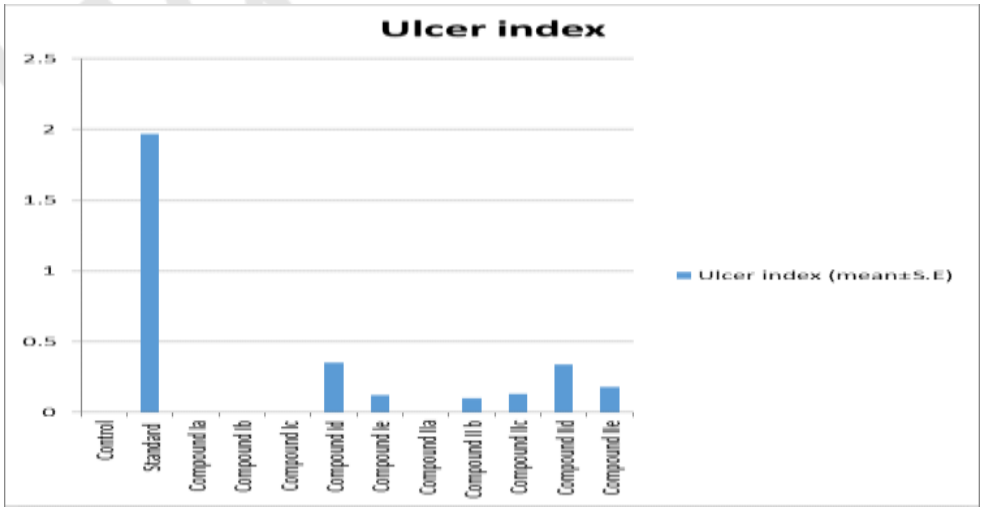

Figure 3: Acute ulcerogenic potential of synthesized compounds

(10E, 12E)-2-(4-(4-methoxyphenyl) thiazol-2 (3H)-ylidene)-1-(2-phenylquinazolin-4 (3H)-ylidene) hydrazine (II e) ($C_{24}H_{19}N_5OS$)

Yield-59.5%; m.p. 235°C; R_f-0.63; IR (KBr, cm^{-1}): 2239 (C=N str), 1191 (C-N str). 3397 (N-H), 923 ((Ar C-H bend), 1628 (Ar C=C str), 315 (Ar C-H str), 2059 (S-C=N), 3313 (NH of thiazoline ring), 2831 (P-OCH_3); ^{1}H-NMR (DMSO-d_6) δ: 7.1-7.9 (m, 13H, Ar-H), 11.5 (s, NH of quinazoline,1H), 11.9 (NH of thiazole), 6.9 (s, 1H=CH), 3.6 (t, 3H,OCH_3 attached to C'4 of thiazole); ^{13}C (DMSO-d_6) δ: 158.9 (C2), 165.3 (C4=N), 125.5 (C5 &C6), 132.1 (C7), 127.2 (C8), 148.7 (C9), 119.9 (C10), Ar-C (phenyl attached to C2 of quinazoline)-121.4, 123.8, 121.9, 128.5, 130.3, 136.1, 163.1 (C'2-S in thiazole), 157.6 (C'4 in thiazole), Ar-C (phenyl attached to C'4 of thiozoline)-114.7, 128.9, 58.2 (OCH_3), 110.9 (C'5 in thiazole); MS (m/z): M^+ calculated 425.13, found 425.15.

The disappearance of C=O in the 2 substituted quinazolin-4 (3H)-one and the presence of C=N band at 1620 region confirmed the formation of quinazoline thiosemicarbazides. The presence of S-C=N peak confirmed the synthesis of 2-(4-(4-substituted) thiazol-2 (3H)-ylidene)-1-(2-substituted quinazolin-4 (3H)-ylidene) hydrazine.

Pharmacological evaluation

According to the acute oral toxicity evaluation, 20 mg/kg doses of synthesized compounds were administered orally to the rats for this study. The *In-vivo* acute anti-inflammatory activity using a carrageenan-induced hind paw edema model and acute ulcerogenicity of the synthesized compounds were studied in albino rats to show their dual inhibitor COX/5LOX activity. The results are shown in Table 1, Figure 2 and Table 2, Figure 3 respectively. Anti-inflammatory activity data revealed that all the synthesized compounds protected the rats from carrageenan-induced inflammation slowly at 30 min of reaction time with increased activity at 1 h that reached a peak level at 4 h. The activity falls at after 4 h. After 6 h also, almost all the newly synthesized compounds showed 51-60 % edema inhibition than the standard drug. From the synthesized compounds, the compounds Ic, Ie and II e showed good activity. In addition all the test compounds are evaluated by gastri c ulcerogenicity in albinorats and the results are summarized in Table 2. The close inspection of all test compounds, the compounds Ia, Ib, Ic, IIa and IIb did not show any redness, the compounds Ie, IIb and II c showed minimal ulcer index, the compounds Id, IId showed high ulcer index than the other tested compounds. Currently available nonsteroidal anti - inflammatory drugs (NSAIDs) exhibit gastric toxicity. So there is greater need for newer NSAIDs devoid of such side effects. Thus dual COX/5 LOX inhibitors are proven to be effective in inflammatory diseases including bronchial asthma without causing gastrointestinal damage. Rather the inhibition of leukotriene synthesis may lead to protective effects on the gastrointestinal mucosa (Luca et al., 2003). In addition quinazoline and hydrazine derivatives resulted in potent anti - inflammatory activity (Govindaraj et al., 2012).

CONCLUSION

Pain and inflammation are the symptoms of wide range of musculoskeletal diseases and disorders. These symptoms causes the big socio economic crisis in developing as well as developed countries. Alleviate those symptoms without any side effects like gastric mucosal erosion which leads to gastritis, is the prime challenge in pain therapies. Our study shown that the novel Quinazoline-hydrazine-Thiazoliine based synthesised compounds can serve as COX/5-LOX dual inhibitors. By inhibiting those enzymes our synthesized compounds inhibit the pain and inflammation without affecting gastric mucosa. These compounds will reduce the burden of society from pain without any harmful side effects like gastritis. Further studies are needed to evaluate the molecular mechanism of the novel compounds.

CONFLICT OF INTEREST STATEMENT

This research report had no conflict of interest.

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