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SYNTHESIS AND ANTI-INFLAMMATORY EVALUATION OF NOVEL BENZIMIDAZOLE ANALOGUES CONTAINING TRIAZOLE, THIAZOLE, ARYLAZETIDINONE AND ARYLTHIAZOLIDINONE MOIETIES

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ABSTRACT
In search for new leads towards potent anti-inflammatory agents, an array of novel (Z)-2-((1*H*-benzo[d]imidazol-1-yl)methyl)-5-arylidenethiazolo[3,2-b][1,2,4]triazol-6(5*H*)-one (**6-10**) have been synthesized from 3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**4**). Another potent anti-inflammatory agents 1-(5-((1*H*-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-arylazetidin-2-one (**14-16**) and 3-(5-((1*H*-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-arylthiazolidin-4-one (**17-19**) have also been synthesized from 5-((1*H*-benzo[d]imidazol-1-yl)methyl)-*N*-arylidene-1,3,4-thiadiazol-2-amine (**11-13**). Structures of all the compounds were confirmed by elemental and spectral data. Further, these compounds were subjected to screen for their toxicity profile, anti-inflammatory activity and ulcerogenic liability. Structure activity relationship results of the compounds indicates that 1-(5-((1*H*-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-chlorophenyl)azetidin-2-one (**15**) displayed better anti-inflammatory activity.

KEYWORDS
Benzimidazole, Toxicity, Anti-inflammatory, Ulcerogenic liability and Structure Activity Relationship.

INTRODUCTION
Nowadays inflammation have attracted a chemist because it is known not only as a symptom of great deal of common ailments but also as an early phase of some serious diseases such as heart vascular diseases[i-ii], cancer[iii], alzheimer disease[iv] and various kinds of rheumatoid arthritis[v]. Treatment of inflammation with steroids (i.e., glucocorticoids) is associated with severe side effects, leading at times, to hearts, kidney and liver damages[vi]. Presently, non-steroidal anti-inflammatory drugs (NSAIDs) are preferred agents for the treatment of pain and inflammation, particularly, arthritis. Currently available NSAIDs have been characterized as dual COX-1 and COX-2 inhibitors[vii]. Evan these NSAIDs are found to have some side effects, due to their inhibitory activity against COX-1 [viii]. There is not a single drug available, which can be termed as ideal in terms of risk-benefit ratio. Hence, there is still critical need for new anti-inflammatory agents. So, the discovery of novel anti-inflammatory drugs has been interacting a lot of interests.

Thus, as a part of our program of synthesizing new chemical entities possessing anti-inflammatory profile, our interests have been focussed on benzimidazole derivatives.
After reviewing literature, it has been observed that good anti-inflammatory activity was found to be associated with benzimidazole[ix-xii], triazole[xiii-xvi], thiazole[xvii-xx], thiazolidinones[xxi-xxiii] and azetidinones[xiv-xvi] rings reported by various researchers. Therefore, in view of above facts and in continuation to search for new biological active derivatives, herein, we report the synthesis and biological evaluation: anti-inflammatory activity and ulcerogenic liability along with toxicity profile, of novel class of benzimidazole scaffold with trizolylthiazoles, thiazolidinones and azetidinone.

Results and Discussion

Chemistry

The reaction sequence leading to the formation of various benzimidazole derivatives is given in the scheme-1. The reaction of benzimidazole (**1**) with ethylchloroacetate produced the desired ethyl -2-(1*H*-benzo[d]imidazol-1-yl)acetate (**2**), which was converted into 2-(2-(1*H*-benzo[d]imidazol-1-yl)acetyl)hydrazine carbothioamide (**3**) on treatment with thio semicarbazide. Compound (**3**) reacted with aq. KOH to afford 3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**4**), which was then converted into (Z)-2-((1*H*-benzo[d]imidazol-1-yl)methyl)-5-arylidenethiazolo[3,2-b][1,2,4]triazol-6(5*H*)-one (**6-10**). From all, only compound **6** is discussed here, it was synthesised from compound **4** using chloroacetic acid, benzaldehyde and anhydrous sodium acetate in acetic anhydride and acetic acid under refluxed for 6-8 hours. IR spectra have shown all expected peaks in cm^{-1} at 3357(N-H), 3078(C-H aromatic), 2939(C-H aliphatic), 1654(C=O), 1636 (C=C of aromatic ring), 1046(C-O-C) and 659(C-S-C), this was fully supported by ^{1}H-NMR have shown expected signals at ð 7.89-7.76 (m, aromatic 5H of benzimidazole), 7.75-7.74 (m, aromatic 5H of benzene), 7.26 (s, 1H, alkenyl group), 4.46 (s, 2H, of CH_2 group) and finally mass spectrometry was confirmed that compounds have shown molecular ion peak at 359[M^+,100%]. Another potent anti-inflammatory agents 1-(5-((1*H*-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-arylazetidin -2-one (**14-16**) and 3-(5-((1*H*-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-arylthiazolidin-4-one (**17-19**) have also been synthesized from 5-((1*H*-benzo[d]imidazol-1-yl)methyl)-*N*-arylidene-1,3,4-thiadiazol-2-amine (**11-13**). From all, only compound **14** and compound **17** is discussed here, compound **14** was synthesised from compound **11** by using dry dioxane, chloroacetlyl chloride and triethyl amine at temperature of 0-5^{o}C. This reaction mixture was, then refluxed for 6-8 hours. IR spectra have shown all expected peaks in cm^{-1} at 2915 (C-H aromatic), 1702 (C=O), 1606 (C=C of aromatic ring), 1018 (N-N) and 669 (C-S-C). This was fully supported by ^{1}H-NMR have shown expected signals at ð 7.37-7.09 (m, aromatic 5H of benzimidazole), 6.81-6.80 (m, aromatic 5H of benzene), 4.59 (s, 2H, of CH_2 group), 1.84 (s, 1H attached with aromatic ring) and 1.67 (s, 1H attached with of >C=O) and finally mass spectrometry was confirmed that compounds have shown molecular ion peak at 395 [M^+,100%]. Similarly, compound **17** was synthesised from compound **11** by using thioglycolic acid and anhydrous $ZnCl_2$ in DMF was refluxed for 8-11 hours. IR spectra have shown all expected peaks in cm^{-1} at 3264 (C-H aromatic), 2930 (C-H aliphatic), 1734 (C=O), 1615 (C=C of aromatic ring), 1077(N-N) and 687(C-S-C).This was fully supported by ^{1}H-NMR have shown expected signals at ð 7.77-7.46 (m, aromatic 5H of benzimidazole), 7.24-6.98 (m, aromatic 5H of benzene), 5.12 (s, 2H, of CH_2 group), 4.66 (s, 1H attached with aromatic ring) and 3.65 (s, 2H of

CH_2 attached with >C=O group).and finally mass spectrometry was confirmed that compounds have shown molecular ion peak at 393.05 [M^+,100%].
The structures of all synthesized compounds were confirmed by their spectral studies such as IR, ^{1}H NMR and Mass spectrometry and elemental analysis.

Biological Results

Acute toxicity study

All the compounds **6-10**, **14-16** and **17-19** were investigated *in vivo* for acute toxicity profile (LD_{50}) in albino mice and the results of the study are as follows : Results of the study revealed that all the compounds exhibited LD_{50} > 800 mg kg^{-1} p.o., except compounds **9** and **10** which showed LD_{50} > 600 mg kg^{-1} p.o. So the compound **9** and **10** were found to be more toxic (LD_{50} >600 mg kg^{-1} p.o.) as compared to rest compound of the present study (Table-1).

Anti-inflammatory activity

All the compounds **6-10**, **14-16** and **17-19** along with reference drug: indomethacin was assayed for their anti-inflammatory activity at a dose of 50 mg kg^{-1} p.o. All these tested compounds displayed varying degree of inhibition of oedema and results were found to be statistically significant anti-inflammatory activity (Table-1). Out of eleven compounds tested compounds **15** and **18** were found to possess more potent anti-inflammatory activity (57.30% and 57.45%, respectively) as compared to indomethacin (56.31%) at a dose of 50 mg kg^{-1} p.o. while compound **7** showed comparable anti-inflammatory activity with standard drug (Table-1). By considering the potentiality of compounds **15** and **18**, these compounds along with indomethacin were subjected to screening at two more doses of 25 and 100 mg kg^{-1} p.o. for anti-inflammatory activity. Interestingly, compounds **15** and **18** yielded improved anti-inflammatory profile than indomethacin. However, compound **18** exhibited maximal anti-inflammatory activity of the present study (Table-1).

Ulcerogenic activity

Two most active compounds **15**, **18** and reference standard drugs, indomethacin were screened for their ulcerogenic liability. Compound **15** was found to be less ulcerogenic as compared to compound **18** and reference drugs.

Cyclooxygenase assay

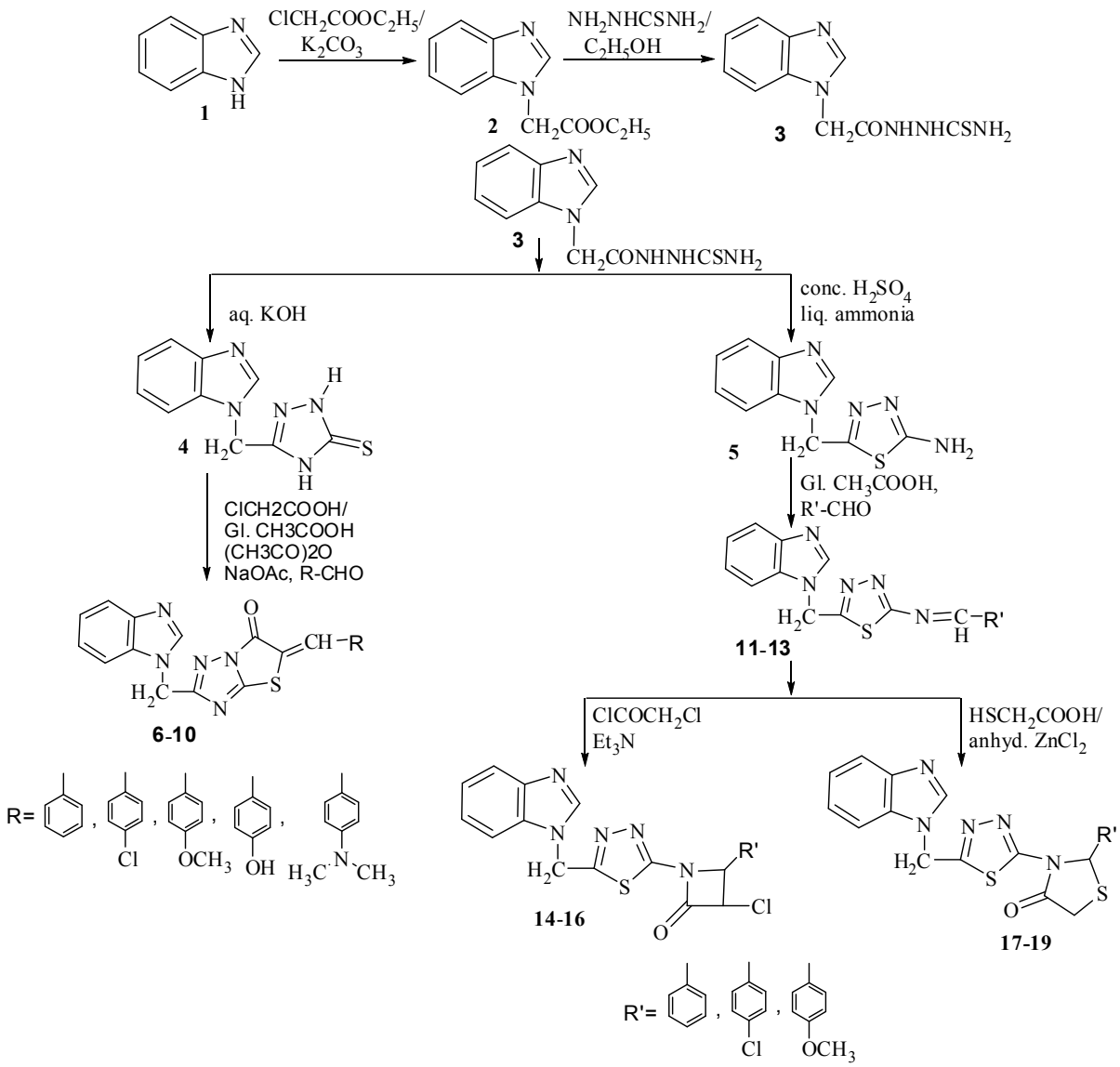
The most promising compounds **15**, **18** and reference drugs were underwent a cyclooxygenase assay to explore their most likely mechanism of action. Results given in Table-1 suggested that these compounds reduce the inflammatory response by inhibiting the prostaglandins' (PG) synthesis by inhibiting the cyclooxygnease (COX) enzyme.

Discussion

All the compounds exhibited statistically significant anti-inflammatory activity ranging from 29.10 -57.45% (Table-1). All eleven compounds showed statistically significant anti-inflammatory activity (Table-1). Structure feature showed that substituted aryl substituent remarkably increase the inflammation inhibiting property of the compounds.

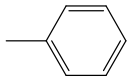
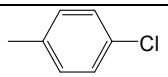
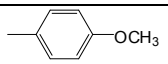
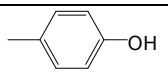
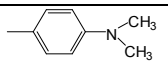
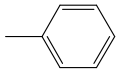
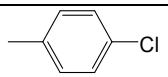
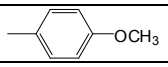
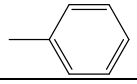
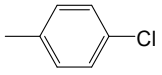
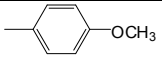
It is significant to note from the observations that when the compounds **15** and **18** bearing *p*-chlorophenyl group, as a substituent showed most potent anti-inflammatory activity, where as substitution with *p*-chlorophenyl as seen in the compound **7**, substitution with *p*-methoxyphenyl as seen in compounds **8**, **16** and **19** produced appreciable activity. The *p*-hydroxyphenyl substituent as seen in compounds **9**, *p*-aminodimethylphenyl substituent as seen in compounds **10** and phenyl substituent as seen in compounds **6**, **14** and **17** also yielded interesting anti-inflammatory profile.

Scheme-1



Synthetic scheme for benzimidazole derivatives

Table-1: Pharmacological results of compounds **6-10** and **14-19**:

Compd.	R	Acute toxicity LD_{50} (mg Kg^{-1} p.o.)	Anti-inflammatory activity		Ulcerogenic activity UD_{50} (mg kg^{-1} i.p.)	Cyclooxygenase assay (% inhibition 10 µM)
			Dose (mg/kg^{-1} p.o.)	% inhibition of oedema		
Control [d]		-	1 mL	0.0	-	-
6		>800	50	37.5[a]	-	-
7		>800	50	55.20 [a]	-	-
8		>800	50	48.55[a]	-	-
9		>600	50	39. 55[a]	-	-
10		>600	50	38.50 [b]	-	-
14		>800	50	29.10 [b]	-	-
15		>800	25 50 100	36.45 [b] 57.30 [a] 79.21 [b]	115	77
16		>800	50	45.24 [b]	-	-
17		>800	50	31.50 [a]	-	-
18		>800	25 50 100	36.53 [b] 57.45 [b] 79.82 [a]	110	72
19		>800	50	42.01 [a]	-	-
Indomethacin		-	25 50 100	35.5 [b] 56.31 [c] 78.0 [b]	90	86

[a] $P< 0.05$; [b] $P< 0.01$; [c] $P < 0.001$; n = 6

[d] Propylene glycol served as control; - denotes that activity was not performed.

Experimental

General

All the reagents and solvents were generally received from commercial supplier *viz*. Spectochem, Rankem, RFCL, Merck, Qualigens and Sigma-aldrich. All melting points are in centigrade scale, uncorrected and taken on digital melting point apparatus. All organic solvents were dried and distilled before use; petroleum ether used had a boiling range 60-80°C. All ethereal or ethyl

acetate extracts were dried over anhydrous sodium sulphate. Solvents were generally removed under reduced pressure. R_f values were recorded for TLC that was carried out on glass plates coated with 0.2 mm layer of silica gel-G and also on Merck plates. The compounds on the TLC plate were visualized in UV light (254 and 366 nm) or developed in iodine atmosphere and also located by spraying various reagents. Spraying agents used for TLC were 5% aqueous sulphuric acid and 1% ethanolic ferric chloride. Infra-red (IR) spectra were recorded on Shimadzu model 435 spectrophotometer using KBr pallets and only major absorption bands are quoted in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on JEOL (400MHz) spectrometers with reference to tetramethylsilane as the internal standard. The chemical shifts are expressed in δ values and coupling constant (*J*) in Hertz. The abbreviation s, brs, d, t and m indicate the signals as singlet, broad singlet, doublet, triplet and multiplet respectively. The Mass spectra were recorded on a Varian MAT 311A instrument by using electron ionization (EI) at 70ev and TOF MS on LCT micromass and only the major peaks are quoted. Apparatus was dried in electrical oven at 120°C, flushed with nitrogen prior to use. The carbon, hydrogen and nitrogen analysis were performed on Carlo Erba-1108 (Carlo Erba, Milan, Italy), and the results were found within + 0.4% of the theoretical values. All spectral analysis was analyzed in Department of Chemistry, University of Delhi.

General procedure for the synthesis of ethyl-2-(1H-benzo[d]imidazol-1-yl)acetate (**2**)

A mixture of benzimidazole (**1**), (30g, 254mmol), ethyl chloroacetate (34.1 g, 279mmol) and anhydrous K_2CO_3 (38.56g, 279 mmol) in acetone (150ml) was refluxed for 15 hours. Progress and completion of the reaction was monitored by TLC. Then, excess of the solvent was distilled off under reduced pressure and the resulting solid mass poured into ice-water, filtered and the separated solid crystallized from methanol to yield compound **2**.

Yield: 24.5g (47.2%),MP : 172-174ºC, IR[cm^{-1}, KBr]: 3073(C-H aromatic), 2941(C-H aliphatic), 1717 (C=O), 1615 (C=C of aromatic ring), ^1H-NMR [400 MHz, $CDCl_3$-ppm]: ð7.72-7.11(m, aromatic 4H of benzimidazole), 5.43 (s,1H of benzimidazole attached with N), 4.62 (s, 2H of CH_2 attached with >C=O), 4.16-4.08 (q, 2H of CH_2 attached with CH_3), 1.17-1.15 (t, 3H of CH_3 attached with CH_2), MS: in m/z [rel.%]: 204.1 [M^+100%], Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72, Found: C, 64.29; H, 5.72; N, 13.42.

Genearal procedure for the synthesis of 2-(2-(1H-benzo[d]imidazol-1-yl)acetyl)hydrazine carbothioamide (**3**)

To a mixture of compound **2 (**22.0g, 108mmol) in ethanol (110ml), thiosemicarbazide (10.8g, 119 mmol) is added and the resulting mixture was heated under refluxed for 10 hours. After completion of the reaction, excess of the solvent was removed under reduced pressure and the formed precipitate were filtered, recrystalized from absolute ethanol to give the compound **3**.

Yield: 19.8g (73.8 %), MP: 195-197ºC, IR [cm^{-1}, KBr]: 3062(N-H), 2924(C-H aromatic), 2852(C-H aliphatic), 1685(C=O), 1649(C=C of aromatic ring), ^1H-NMR[400 MHz, DMSO-D_6-ppm]: ð12.41 (s, 1H of NH attached with >C=O, exchangeable with D_2O), 11.28 (bs, 1H of NH attached with >C=S, exchangeable with D_2O), 7.50-7.08 (m, aromatic 4H of benzimidazole), 6.81 (s, 1H of benzimidazole attached with N), 5.85 (s, 2H of CH_2 attached with >C=O), 3.33 (s, 2H of NH_2, exchangeable with D_2O), MS: in m/z[rel.%]: 249.05[M^+, 100%], Anal.Calcd for $C_{10}H_{11}N_5OS$: C, 48.18; H, 4.45; N, 28.09, Found: C, 48.01; H, 4.25; N, 28.0.

Genearal procedure for the synthesis of 3-((1H-benzo[d]imidazol-1-yl)methyl)-1H-1,2,4-triazole-5(4H)-thione (**4**)

A solution of compound **3** (9g, 36.1mmol),10% aq. KOH (23ml), (2.23g, 39.7mmol) and water (135ml) of was heated for 3hours, cooled, filtered and the filtrate was acidified with HCl (37%).The precipitated solid was filtered and washed with water. Then, the product was crystallized from methanol-ether to furnish compound **4.**

Yield: 6.5g (77.66%), MP: 189-191ºC, IR [cm^{-1}, KBr]: 3401(N-H), 2924(C-H aromatic), 2852(C-H aliphatic), 1628(C=C of aromatic ring), 1464(C=S), ^{1}H-NMR [400 MHz, DMSO-D_6-ppm]: ð 12.43 (s, 1H of NH attached with >C=S, exchangeable with D_2O), 11.24 (brs, 1H of NH attached with >C=S, exchangeable with D_2O), 7.50-7.06 (m, aromatic 4H of benzimidazole), 6.81 (s, 1H of benzimidazole attached with N), 5.85 (s, 2H of CH_2 attached with N of benzimidazole), MS: in m/z [rel.%]: 231[M^+,100%], Anal. Calcd for $C_{10}H_9N_5S$: C, 51.93; H, 3.92; N, 30.28, Found: C, 51.34; H, 3.52; N, 30.02.

Genearal procedure for the synthesis of (Z)-2-((1H-benzo[d]imidazol-1-yl)methyl)-5-benzylidenethiazolo[3,2-b][1,2,4]triazol-6(5H)-one (**6**)

A solution of compound **4** (1g, 4.32mmol), chloroacetic acid (0.82g, 8.64mmol), benzaldehyde (0.50g, 4.75mmol), anhydrous sodium acetate (0.43g, 5.18mmol), acetic anhydride (1.7ml, 18.1mmol) and acetic acid (2.95ml, 51.8mmol) was refluxed for 6-8 hours. Then, after refluxing, the mixture was poured into ice water. The precipitated solid was filtered and dissolved in dichloromethane. The organic layer was washed using 6% $NaHCO_3$ and brine and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized from ethanol solvents to produce compound **6**.

Yield: 0.70g (45.16%), MP: 209-211ºC, IR [cm^{-1}, KBr]: 3357(N-H), 3078 (C-H aromatic), 2939 (C-H aliphatic), 1654 (C=O), 1636 (C=C of aromatic ring), 1046 (C-O-C), 659 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.89-7.76 (m, aromatic 5H of benzimidazole), 7.75-7.74 (m, aromatic 5H of benzene), 7.26 (s, 1H, alkenyl group), 4.46 (s, 2H, of CH_2 group), MS: in m/z [rel.%]: 359[M^+,100%], Anal. Calcd for $C_{19}H_{13}N_5OS$: C, 63.49; H, 3.65; N, 19.49, Found: C, 63.09; H, 3.45; N, 19.09.

Genearal procedure for the synthesis of (Z)-2-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-chlorobenzylidene)thiazolo[3,2-b][1,2,4]triazol-6(5H)-one (**7**)

A solution of compound **4** (1g, 4.32mmol), chloroacetic acid (0.82g, 8.64mmol), 4-chlorobenzaldehyde (0.67g, 4.75mmol), anhydrous sodium acetate (0.43g, 5.18mmol), acetic anhydride (1.7ml,18.1mmol) and acetic acid (2.95ml,51.8 mmol) was refluxed for 6-8 hours. Then, after refluxing, the mixture was poured into ice water. The precipitated solid was filtered and dissolved in dichloromethane. The organic layer was washed using 6% $NaHCO_3$ and brine and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystalized from benzene-petroleum ether solvent to produce compound **7**.

Yield: 0.65g (38.2%), MP: 234-236ºC, IR [cm^{-1}, KBr]: 3433 (N-H), 2994 (C-H aromatic), 2933 (C-H aliphatic), 1648 (C=O), 1578 (C=C of aromatic ring), 1038 (C-O-C), 1002 (N-N), 753 (C-Cl), 628 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.64-7.32 (m, aromatic 5H of benzimidazole), 7.24-7.17 (m, aromatic 4H of benzene), 6.93 (s, 1H, alkenyl group), 4.81 (s, 2H, of CH_2 group), MS: [M^+] at m/z 393.05 [M^+, 100%], Anal.Calcd for $C_{19}H_{12}N_5OSCl$: C, 57.94; H, 3.05; N, 17.15, Found: C, 57.04; H, 2.95; N, 17.01.

Genearal procedure for the synthesis of (Z)-2-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-methoxybenzylidene)thiazolo[3,2-b][1,2,4]triazol-6(5H)-one (**8**)

A solution of compound **4** (1g, 4.32mmol), chloroacetic acid (0.82g, 8.64mmol), 4-methoxybenzaldehyde (0.65g, 4.75mmol), anhydrous sodium acetate (0.43g, 5.18mmol), acetic anhydride (1.7ml, 18.1mmol) and acetic acid (2.95ml, 51.8mmol) was refluxed for 6-8 hours. Then, after refluxing, the mixture was poured into ice water. The precipitated solid was filtered and dissolved in dichloromethane. The organic layer was washed using 6% $NaHCO_3$ and brine and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized from ethanol solvent to produce compound **8**.

Yield: 0.68g (40.48%), MP: 241-243ºC, IR [cm^{-1}, KBr]: 3432 (N-H), 2994 (C-H aromatic), 2934 (C-H aliphatic), 1685 (C=O), 1648 (C=C of aromatic ring), 1069 (C-O-C), 1003 (N-N), 700 (C-Cl), 628 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.91-7.57 (m, aromatic 5H of benzimidazole), 7.34-7.30 (m, aromatic 4H of benzene), 7.27 (s, 1H, alkenyl group), 5.67 (s, 2H, of CH_2 group), 4.77 (s, 3H of $–OCH_3$), MS: [M^+] at m/z 389, Anal. Calcd for $C_{20}H_{15}N_5O_2S$: C, 61.68; H, 3.85; N, 17.95, Found: C, 61.08; H, 3.35; N, 17.15.

Genearal procedure for the synthesis of (Z)-2-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-hydroxybenzylidene)thiazolo[3,2-b][1,2,4]triazol-6(5H)-one (**9**)

A solution of compound **4** (1g, 4.32mmol), chloroacetic acid (0.82g, 8.64mmol), 4-hydroxybenzaldehyde (0.58g, 4.75mmol), anhydrous sodium acetate (0.43g, 5.18mmol), acetic anhydride (1.7ml, 18.1mmol) and acetic acid (2.95ml, 51.8mmol) was refluxed for 6-8 hours. Then, after refluxing, the mixture was poured into ice water. The precipitated solid was filtered and dissolved in dichloromethane. The organic layer was washed using 6% $NaHCO_3$ and brine and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized from acetone solvent to produce compound **9**.

Yield: 0.62 (38.27%), MP: 264-266ºC, IR [cm^{-1}, KBr]: 3357 (N-H), 3077 (C-H aromatic), 2939 (C-H aliphatic), 1636 (C=O), 1614 (C=C of aromatic ring), 1107(C-O-C), 1013 (N-N), 658 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 12.83 (s, 1H of –OH group exchangeable with D_2O), 7.88-7.46 (m, aromatic 5H of benzimidazole), 7.05-7.03 (m, aromatic 4H of benzene), 6.86 (s, 1H, alkenyl group), 5.39 (s, 2H, of CH_2 group), MS: in m/z [rel.%]: 375 [M^+,100%], Anal.Calcd for $C_{19}H_{13}N_5O_2S$: C, 60.65; H, 3.41; N, 18.64, Found: C, 60.05; H, 3.14; N, 18.16.

Genearal procedure for the synthesis of (Z)-2-((1H-benzo[d]imidazol-1-yl)methyl)-5-(4-(dimethylamino)benzylidene)thiazolo[3,2-b][1,2,4]triazol-6(5H)-one (**10**)

A solution of compound **4** (1g, 4.32mmol), chloroacetic acid (0.82g, 8.64mmol), 4-aminodimethylbenzaldehyde (0.71g, 4.75mmol), anhydrous sodium acetate (0.43g, 5.18mmol), acetic anhydride (1.7ml, 18.1mmol) and acetic acid (2.95ml, 51.8mmol) was refluxed for 6-8 hours. Then, after refluxing, the mixture was poured into ice water. The precipitated solid was filtered and dissolved in dichloromethane. The organic layer was washed using 6% $NaHCO_3$ and brine and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized from DMF solvent to produce compounds **10**.

Yield: 0.60g (34.48%), MP: 206-208 ºC, IR [cm^{-1}, KBr]: 3269 (N-H), 3086 (C-H aromatic), 2928 (C-H aliphatic), 1628 (C=O), 1605 (C=C of aromatic ring), 1117 (C-O-C), 1053 (N-N), 643 (C-S-C), ^{1}H-NMR [400 MHz, DMSO-D_6-ppm]: ð 8.77-7.70 (m, aromatic 5H of benzimidazole), 7.34-7.11 (m, aromatic 4H of benzene), 7.02 (s, 1H, alkenyl group), 4.94 (s,

2H, of CH_2 group) and 3.29 (s, 6H of $-N(CH_3)_2$), MS: in m/z[rel.%]: 402.1 [M^+ ,100%], Anal.Calcd for $C_{21}H_{18}N_6OS$: C, 62.68; H, 4.51; N, 20.86, Found: C, 62.08; H, 4.11; N, 20.06.

Genearal procedure for the synthesis of 5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-amine (**5**)

A fine powder of the compound **3** (9.0g, 36.1 mmol) was gradually added to cold concentrated sulphuric acid (27 ml) at 0-5ºC and the mixture was stirred at room temperature for 30 min. Then the reaction mixture was poured into ice-water mixture, filtrated after the ice melting and the filtrate made alkaline to pH 8 with liq. ammonia. The precipitated product was filtered, washed with cold water, dried and recrystallized from ethanol to afford the desired product **5**.

Yield: 6.5g (77.66%), MP: 181-183ºC, IR [cm^{-1}, KBr]: 3423 (NH_2), 2926 (C-H aromatic), 2868 (C-H aliphatic), 1692 (C=C of aromatic ring), 956(N-N), 640 (C-S-C), ^{1}H-NMR [400 MHz, DMSO-D_6-ppm]: ð 7.49-6.80 (m, aromatic 5H of benzimidazole), 5.86 (s, 2H, of CH_2 group) and 3.35 (brs, 2H of NH_2 group exchangeable with D_2O), MS: in m/z [rel.%]: 231.0 [M^+ , 100%], Anal. Calcd for $C_{10}H_9N_5S$: C, 51.53; H, 3.92; N, 30.28, Found: C, 51.03; H, 3.52; N, 30.02.

Genearal procedure for the synthesis of 5-((1H-benzo[d]imidazol-1-yl)methyl)-N-benzylidene-1,3,4-thiadiazol-2-amine (**11**)

A solution of compound **5** (2g , 8.65mmole) and benzaldehyde (1.01g,9.51mmole) in absolute ethanol (20 ml) in presence of few drops of glacial acetic acid was refluxed for 8-12 hours. Progress and completion of the reaction was followed by TLC. After completion of reaction, excess of solvent was distilled off, cooled and then poured onto crushed ice and filtered. The solid thus separated was recrystallized form the ethanol solvent to give compound **11**.

Yield: 1.2g(43.48%), MP: 218-220 ^oC, IR [cm^{-1}, KBr]: 2989 (C-H aromatic), 2907 (C-H aliphatic), 1606 (C=C of aromatic ring), 1012 (N-N), 673 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.83-7.55 (m, aromatic 5H of benzimidazole), 7.34-7.27 (m, aromatic 5H of benzene), 7.26 (s, 1H, alkenyl group) and 5.67 (s, 2H, of CH_2 group), MS: $[M]^+$ at m/z 319, Anal Cacld for $C_{17}H_{13}N_5S$: C, 63.93; H, 4.10; N, 21.92, Found: C, 63.09; H, 4.01; N, 21.39.

Genearal procedure for the synthesis of 5-((1H-benzo[d]imidazol-1-yl)methyl)-N-(4-chlorobenzylidene)-1,3,4-thiadiazol-2-amine (**12**)

A solution of compound **5** (2g, 8.65mmole) and 4-chlorobenzaldehyde, (1.32g, 9.51mmole) in absolute ethanol (20 ml) in presence of few drops of glacial acetic acid was refluxed for 8-12 hours. Progress and completion of the reaction was followed by TLC. After completion of reaction, excess of solvent was distilled off, cooled and then poured onto crushed ice and filtered. The solid thus separated was recrystallized form the methanol solvent to give compound **12**.

Yield: 1.30g (42.48%), MP: 242-245ºC, IR [cm^{-1}, KBr]: 3089 (C-H aromatic), 2931 (C-H aliphatic), 1615 (C=C of aromatic ring), 1023 (N-N), 677 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.57-7.33 (m, aromatic 5H of benzimidazole), 7.32-7.28 (m, aromatic 4H of benzene), 7.27 (s, 1H, alkenyl group) and 5.67 (s, 2H, of CH_2 group), MS: in m/z [rel.%]: 353.05 [M^+ , 100%], Anal.Calcd for $C_{17}H_{12}N_5SCl$: C, 57.7; H, 3.42; N, 19.79, Found: C, 57.07; H, 3.04; N, 19.29.

Genearal procedure for the synthesis of 5-((1H-benzo[d]imidazol-1-yl)methyl)-N-(4-methoxybenzylidene)-1,3,4-thiadiazol-2-amine (**13**)

A solution of compound **5** (2g, 8.65mmole) and *p*-methoxybenzaldehyde, (1.3g, 9.51mmole) in absolute ethanol (20 ml) in presence of few drops of glacial acetic acid was refluxed for 8-12 hours. Progress and completion of the reaction was followed by TLC. After completion of reaction, excess of solvent was distilled off, cooled and then poured onto crushed ice and filtered. The solid thus separated was recrystallized form the ethanol solvent to give compound **13**.
Yield: 1.27g (42.05%), MP: 214-216ºC, IR [cm^{-1}, KBr]: 3079 (C-H aromatic), 2976 (C-H aliphatic), 1606 (C=C of aromatic ring), 1043 (C-O-C), 1024 (N-N), 673 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.91-7.55 (m, aromatic 5H of benzimidazole), 7.34-7.30 (m, aromatic 4H of benzene), 7.27 (s, 1H, alkenyl group), 5.67 (s, 2H, of CH_2 group) and 4.77 (s, 3H of $–OCH_3$), MS: in m/z [rel.%]:349.1 [M^+, 100%], Anal.Calcd for $C_{18}H_{15}N_5OS$: C, 61.87; H, 4.33; N, 20.01, Found: C, 61.43; H, 4.03; N, 19.91.

*Genearal procedure for the synthesis of 1-(5-((*1*H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-arylazetidin-2-one* (**14-16**)
To a solution of compound **11-13**, (0.5g each) in dry dioxane, chloroacetlyl chloride and triethyl amine were added with constant stirring at temperature of 0-5^{o}C. This reaction mixture was, then, refluxed for 6-8 hours, the progress and completion of reaction was checked by TLC. After completion of the reaction, excess of solvent was removed by distillation, residue was poured on crushed ice and then filtered. The separated product was recrystallized form proper solvent to furnish compound **14-16**. By following above method, compounds **14**, **15** and **16** were obtained from compounds **11**, **12** and **13** respectively. Their physical, analytical and spectral data are given below:

*Genearal procedure for the synthesis of 1-(5-((*1*H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-phenylazetidin-2-one* (**14**)
To a solution of compound **11** (0.5g, 1.57mmol) in dry dioxane (5ml), chloroacetyl chloride (0.19g, 1.72mmol) and triethylamine (0.24ml, 1.72mmol) were added with constant stirring at temperature of 0-5^{o}C. This reaction mixture was, then, refluxed for 6-8 hours, the progress and completion of reaction was checked by TLC. After completion of the reaction, excess of solvent was removed by distillation; residue was poured on crushed ice and then filtered. The separated product was recrystallized by using DMF solvent to furnish compound **14**.
Yield: 0.33g (53.22%), MP: 232-236ºC, IR [cm^{-1}, KBr]: 2915 (C-H aromatic), 1702 (C=O), 1606 (C=C of aromatic ring), 1018 (N-N), 669 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.37-7.09 (m, aromatic 5H of benzimidazole), 6.81-6.80 (m, aromatic 5H of benzene), 4.59 (s, 2H, of CH_2 group), 1.84 (s, 1H attached with aromatic ring) and 1.67 (s, 1H attached with of >C=O), MS: in m/z[rel.%]: 395 [M^+,100%], Anal.Calcd for $C_{19}H_{14}N_5OSCl$: C, 57.65; H, 3.56; N, 17.61, Found: C, 57.05; H, 3.16; N, 17.06.

*Genearal procedure for the synthesis 1-(5-((*1*H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-chlorophenyl)azetidin-2-one* (**15**)
To a solution of compound **12** (0.5g , 1.41 mmol) in dry dioxane (5ml), chloroacetyl chloride (0.18g, 1.55mmol) and triethylamine (0.22ml , 1.55mmol) were added with constant stirring at temperature of 0-5^{o}C. This reaction mixture was, then, refluxed for 6-8 h, the progress and completion of reaction was checked by TLC. After completion of the reaction, excess of solvent was removed by distillation, residue was poured on crushed ice and then filtered. The separated product was recrystallized by using DMF solvent to furnish compound **15**.

Yield: 0.34g (55.74%), MP: 241- 144ºC, IR [cm^{-1}, KBr]: 3062 (C-H aromatic), 2925 (C-H aliphatic), 1727 (C=O), 1602 (C=C of aromatic ring), 1073 (N-N), 700 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.36-7.32 (m, aromatic 5H of benzimidazole), 7.05-6.77 (m, aromatic 4H of benzene), 4.60 (s, 2H, of CH_2 group), 1.66 (s, 1H attached with aromatic ring) and 1.44 (s, 1H, attached with of >C=O), MS: in m/z [rel.%]: 429.01 [M^+ , 100%], Anal.Calcd for $C_{19}H_{13}Cl_2N_5OS$: C, 53.03; H, 3.04; N, 16.23, Found: C, 52.93; H, 3.00; N, 16.02.

Genearal procedure for the synthesis of 1-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-methoxyphenyl)azetidin-2-one (**16**)

To a solution of compound **13** (0.5g**,** 1.43 mmol) in dry dioxane (5ml), chloroacetlyl chloride (0.18g , 1.57mmol) and triethyl amine (0.22ml, 1.57mmol) were added with constant stirring at temperature of 0-5ºC. This reaction mixture was, then, refluxed for 6-8 hours, the progress and completion of reaction was checked by TLC. After completion of the reaction, excess of solvent was removed by distillation, residue was poured on crushed ice and then filtered. The separated product was recrystallized by using DMF solvent to furnish compound **16**.

Yield: 0.31g (50.82%), MP: 254-257ºC, IR [cm^{-1}, KBr]: 3229 (C-H aromatic), 2925 (C-H aliphatic), 1741 (C=O), 1602 (C=C of aromatic ring), 1108 (C-O-C), 1060 (N-N), 674 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.36-7.32 (m, aromatic 5H of benzimidazole), 7.05-6.77 (m, aromatic 4H of benzene), 4.60 (s, 2H, of CH_2 group), 4.28 (s, 3H of –OCH_3), 1.66 (s, 1H attached with aromatic ring) and 1.44 (s, 1H attached with of >C=O), MS: in m/z [rel.%]: 425.01 [M^+ , 100%], Anal.Calcd for $C_{20}H_{16}ClN_5O_2S$: C, 56.40; H, 3.79; N, 16.44, Found: C, 56.10; H, 3.07; N, 16.04.

General procedure for the synthesis 3-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-arylthiazolidin-4-one (**17-19**)

A solution of compound **11-13** (0.5g each), thioglycolic acid and anhydrous $ZnCl_2$ in DMF as a solvent was refluxed for 8-11 hours, then concentrated, cooled and poured into ice-water and then filtered. The product obtained was purified by recystallization from appropriate solvent to get compound **17-19**, and the homogeneity of these was checked by TLC. By using above method, compounds **17**, **18** and **19** were procured form compounds **11**, **12** and **13** respectively. The physical, analytical and spectral data of compounds **17-19** are furnished below:

General procedure for the synthesis 3-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-phenylthiazolidin -4-one (**17**)

A solution of compound **11** (0.5g, 1.57mmol), thioglycolic acid (0.16g, 1.72mmol) and anhydrous $ZnCl_2$ (0.26g, 1.88mmol) in DMF (5 ml) was refluxed for 8-11 hours. The progress of the reaction was checked by TLC, then concentrated, cooled and poured into ice-water and then filtered. The product obtained was purified by recystallization by using benzene solvent to get compound **17**.

Yield: 0.35g (56.9%), MP: 256- 258ºC, IR [cm^{-1}, KBr]: 3264 (C-H aromatic), 2930 (C-H aliphatic), 1734 (C=O), 1615 (C=C of aromatic ring), 1077(N-N), 687(C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.77-7.46 (m, aromatic 5H of benzimidazole), 7.24-6.98 (m, aromatic 5H of benzene), 5.12 (s, 2H, of CH_2 group), 4.66 (s, 1H attached with aromatic ring) and 3.65 (s, 2H of CH_2 attached with >C=O group), MS: in m/z [rel.%]: 393.05 [M^+, 100%], Anal.Calcd for $C_{19}H_{15}N_5OS_2$: C, 58.0; H, 3.84; N, 17.8, Found: C, 57.60; H, 3.74; N, 17.58.

General procedure for the synthesis 3-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-chlorophenylthiazolidin -4-one (**18**)

A solution of compound **12** (0.5g, 1.41mmol), thioglycolic acid (0.14g, 1.55mmol) and anhydrous $ZnCl_2$ (0.23g, 1.7mmol) in DMF (5 ml) was refluxed for 8-11 hours. The progress of the reaction was checked by TLC, then concentrated, cooled and poured into ice-water and then filtered. The product obtained was purified by recystallization by using benzene solvent to get compound **18**.

Yield: 0.37g (61.16%), MP: 237-239ºC, IR [cm^{-1}, KBr]: 2937 (C-H aromatic), 2840 (C-H aliphatic), 1717 (C=O), 1617 (C=C of aromatic ring), 1027 (N-N), 619 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.34-6.50 (m, aromatic 5H of benzimidazole), 6.50-6.33 (m, aromatic 4H of benzene), 5.01 (s, 2H, of CH_2 group), 4.54 (s, 2H of $–CH_2$- attached with >C=O group) and 4.17 (s, 2H of CH_2 attached with aromatic ring), MS: in m/z [rel.%]: 427.01 [M^+ , 100%], Anal.Calcd for $C_{19}H_{14}ClN_5O_2S$: C, 53.33; H, 3.3; N, 16.37, Found: C, 53.13; H, 3.03; N, 16.09.

General procedure for the synthesis 3-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-methoxyphenylthiazolidin -4-one (**19**)

A solution of compound **13** (0.5g, 1.43mmol), thioglycolic acid (0.14g, 1.57mmol) and anhydrous $ZnCl_2$ (0.23g, 1.71mmol) in DMF (5ml) was refluxed for 8-11 hours. The progress of the reaction was checked by TLC, then concentrated, cooled and poured into ice-water and then filtered. The product obtained was purified by recystallization by using benzene solvent to get compound **19**.

Yield: 0.32g (52.89%), MP: 260- 263ºC, IR [cm^{-1}, KBr]: 3026 (C-H aromatic), 2951 (C-H aliphatic), 1729 (C=O), 1608 (C=C of aromatic ring), 1072 (C-O-C), 1025 (N-N), 635 (C-S-C), ^{1}H-NMR [400 MHz, $CDCl_3$-ppm]: ð 7.88-7.75 (m, aromatic 5H of benzimidazole), 7.75-6.82 (m, aromatic 4H of benzene), 5.64 (s, 2H, of CH_2 group), 4.46 (s, 2H of $–CH_2$- attached with >C=O group), 3.49 (s, 1H of –CH- attached with aromatic ring) and 2.59 (s, 3H of $–OCH_3$), MS: in m/z [rel.%]: 423.01 [M^+, 100%], Anal. Calcd for $C_{20}H_{17}N_5O_2S_2$: C, 56.72; H, 4.07; N, 16.44, Found: C, 56.72; H, 4.07; N, 16.44.

Pharmacology

All the compounds **6-10** and **14-19** were evaluated for their anti-inflammatory and acute toxicity. The experiments were performed on albino rats of Charles Foster strain of either sex, excluding pregnant females, of 70 to 90 days weighing 68-115g. Acute toxicity of numerous compounds was tested in albino mice (22–28 g). (Rats and mice were purchased from LABO-AIDS, Meerut, U.P., India). Food (chaw pallet) and water were given to the animals *ad libitum*. The test compounds were dissolved in propylene glycol. Indomethacin (from commercial source) was used as reference drugs. The biological activities were carried out in Late Dr. Ashok Kumar's (ex supervisor) lab, Medicinal Chemistry Division, Department of Pharmacology, Lala Lajpat Rai Memorial Medical College, Meerut (U.P.), India and the protocol was approved by the ethical committee of Lala Lajpat Rai Memorial Medical College, Meerut (U.P.), India.

Acute toxicity study

The test compounds were investigated for acute toxicity profile (LD_{50}) in albino mice, according to the method of Smith Q. E.[xxvii]. The test compounds were given orally at different dose levels in separate groups of animals. After 24 hours of drug administration, percent mortality in each group was observed. LD_{50} was calculated from the data obtained.

Anti-inflammatory activity

This activity was done according to the given procedure given by Winter *et al.,*[xxviii]. Indomethacin were used as reference drugs. The rats were divided into three groups (control, drug treated, and standard drug) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL was injected under planter aponeurosis of right hind paw of each rat. One group was kept as control and treated with propylene glycol. Test compounds and standard drugs were administered to the animals of drug treated and standard drug group, respectively, 1 h before to carageenan injection. The paw volume of each rat was measured before 1 and 3 h after carrageenan treatment with the help of Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below-

Percentage of inhibition of oedema = $(1 - V_t / V_c) \times 100$

Where, V_t and V_c are the mean increase in paw volume of rats of treated group and the control group, respectively. Results obtained were statistically analyzed.

Ulcerogenic Activity

The ulcerogenic activity was done on albino rats according to the procedure of Verma *et al*.,[xxix] . The rats were fasted for 24 hours prior to the administration of the test compounds. Water was given to the animals *ad libitum*. The most promising compounds **15**, **18** and reference drugs were given intraperitoneally, and then these animals were sacrificed 8 hours after drug treatment. The stomach, duodenum and jejunum were removed and examined with a hand lens for any evidence of the following: (a) shedding of epithelium, (b) petechial or frank hemorrhage, (c) erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic liability.

Cyclooxygenase activity

This test was carried out *in vitro* on the microsmal fraction of mucosal preparations of rabbit distal colon in order to search out the possible mechanism of action of the test compounds by Calderano *et al.,*[xxx]. Colonic mucosa (=2-3g), stripped as previously described, was minced and homogenized (Potter homogenizer) in 3 volumes of Tris buffer, 0.1 M, pH 8.0. The homogenate was centrifuged for 30 min at 10 000 g. The resulting supernatent was centrifuged for 1 hour at 100 000 g. The precipitate was suspended in Tris buffer, 0.1M, pH 8.0, and re-centrifuged for 1 hour at 100 000 g. The microsomal pellet was used immediately for an enzyme assay; cyclooxygenase activity was assayed by measuring the rate of conversion of arachidonic acid to PGE_2. Microsomal fractions (50 µ L) were incubated with test agents for 5 min at 37^oC in 30 mL Tris HCl, pH 8.0 containing 2 mM reduced glutathione, 5mM L-tryptophan, and 1µM hematin. The substrate, 20 µM arachidonic acid with tracer amount of [1- ^{14}C] arachidonic acid [=20 000 cpm] was then added and the reaction proceeded for 3 min at 37 ^oC. The reaction was stopped by addition of 0.2 mL of ethyl ether/methanol /citric acid 0.2 M (30:4:1), which was pre-cooled at -25 ^oC. PGE_2 was extracted twice into the same mixture. The solvent was evaporated under a N_2 stream and radilabelled arachidonic acid was separated from radio-labeled PGE_2 by RP-HPLC. HPLC analysis was performed on a Hitachi spectrophotometer (Hitachi High Technologies America, San Jose, CA, USA) equipped with a flow cell. The sample was injected on an ultra sphere column (Beckman Coulter Ltd., High Wycombe, Buckinghamshire, UK) ODS 5 mm, 4.6 mm X 25 cm with 2 mmol unlabelled PGE_2 as an internal standard, PG chromatographic profile was obtained by isocratic elution with 150 mM H_3PO_4 in water, pH 3.5, containing 30% acetonitrile a flow rate of 1mL min^{-1} monitoring the UV absorption at 214 nm. Radioactivity that coeluted with authentic PGE_2 was quantified by liquid scintillation spectrometry. Test samples

were compared to parried control incubations. The percentage of inhibition was calculated as follows:
[(cpm control – cpm test / (cpm control)) X 100]

Conclusion

Out of eleven compound examined, compound **15** and **18** were found to be the most promising compounds of the present study. LD_{50} of these compounds was very high suggesting good safety margin, and also these compounds possessing less ulcerogenic liability as compared to standard drugs indomethacin. However, compound **15** yielded outstanding biological results as compared compound **18**.

At the end, following conclusion can be drawn:

- Presence of *o*- or *p*-chlorophenyl group as a substituent may elicit a remarkable increase in anti-inflammatory activity.
- *o*- or *p*-methoxyphenyl substitution showed significant activity.
- Presence of electronegative atom may play an important role in the modulation of activity.
- Compounds bearing *p*-substitution showed better activity as compared to *o*- substitution.

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References

i. Anderson S. E., Edvinsson M. L. and Edvinsson L.; Clin. Sci., 105, (2003), 699.
ii. Omoigui S.; Med. Hypotheses, 65, (2005), 559.
iii. Blasko I. and Grubeck-Loebenstein B.; Drugs Aging, 20(2), (2003), 101.
iv. Charles P., Elliott M. J., Davis D., Potter A., Kalden J. R., Antoni C., Ebrel G., Feldmann M. and Maini R. N.; J. Immunol., 163(3), (1999), 1521.
v. Theodoropopoulos G., Papaconstantinou I., Felekouras E., Nikiteas N., Karakitsos P., Panoussopoulos D., Ch Lazaris A., Patsouris E., Bramis J. and Gazouli M.; World J. Gastroenterol., 12, (2006), 5037.
vi. Parfitt K.; Martindale- The Complete Drug Reference, Pharmaceutical Press, 32, (1999), 1010.
vii. (a) Kargman S., Wong E., Greig G. M., Falgueyret J. P., Cromlish W., Ethier D., Yergey J. A., Evan J. F., Kennedy B., Tagari P., Francis D. and Neill G. P.O.; Biochem. Pharmacol., 52(7), (1996), 1113. (b) Bridean C., Kargman S., Dallob A. L., Ehrich E. W., Rodger I. W. and Chan C. C.; Inflamm. Res., 45, (1996), 68.
viii. Richardson C. and Emery P.; Drug safety, 15, (1996), 249.
ix. Lazer E. S., Matteo M. R. and Possanza G. J.; J. Med. Chem., 30(4), (1987), 726.
x. Marriapan G., Bhuyan N.R., Kumar P., Kumar D. and Murali K.; Indian J. Chem., 50B, (2011), 1216.

xi. Nirmal R., Shanmugapandiyan P., Denshing K.S., Ilavarasan R. and Anbalagan N.; IJPSDR, 2(2), (2010), 115.
xii. Tupe A. P., Pawar P. Y., Mane B. Y. and Magar S. D.; RJPBCS, 4(2), (2013), 928.
xiii. Shiradhkar M. and Kale R.; Indian J. Chem., 45B, (2006), 1009.
xiv. Kalluraga B. and Rahimann M. A.; Indian J. Chem., 41B, (2002), 1712.
xv. Braccio M. D., Grossi G., Roma G., Piras D., Mattaioli F. and Gosmar M.; Eur. J. Med. Chem., 43(3), (2008), 584.
xvi. Cao Z. P., Dong W. J. and Dong H. S.; Indian J. Chem., 48B, (2009), 873.
xvii. Franklin P. X., Pillai A. D., Rathod P. D., Yarande S., Nivsarkar M., Padh H., Vasu K. K. and Suduranam, V.; Eur. J. Med. Chem., 43, (2008), 129.
xviii. Bansal E., Kumar A., Verma R. S., Saxena K. K. and Srivastava V. K.; Indian J. Heterocycl. Chem., 9, (2000), 301.
xix. Dundar Y., Cakir B., Kupeli E., Sahin M. F. and Noyanalpan N.; Turk. J. Chem., 31, (2007), 301.
xx. Franklin P. X., Pillai A. D., Rathod P. D., Yerande S., Nivsarkar M., Padh H., Vasu K. K. and Sudersanam V.; Eur. J. Med. Chem., 43(1), (2008), 129.
xxi. Dundar Y., Cakir B., Kupeli E., Sahin M. F. and Noyanalpan N.; Turk. J. Chem., 31, (2007), 301.
xxii. Ottana R., Mecari R., Barreca M. L., Bruno G., Rotondo A., Rossi A., Chiricosta G., Paola R. D., Sautebin L., Cuzzocrea S. and Vigorita M. G.; Bioorg. Med. Chem., 13(13), (2005), 4243.
xxiii. Yadav R., Srivastava S. D. and Srivastava S. K.; Indian J. Chem., 44B, (2005), 1262.
xxiv. Srivastava S. K., Srinivasta S. K. and Srivastava S. D.; Indian J. Chem., 39B, (2000), 464.
xxv. Srivastava S. K., Srivastava S. and Srivastava S. D.; Indian J. Chem., 41B, (2002), 2357.
xxvi. Bansal G., Sharma A. and Singh M.; Bioorg. Med. Chem. Lett., 15, (2005), 3962.
xxvii. Smith Q. E.; Pharmacol. Screening Tests Progress Medi. Chem., Butterworth, London, 1, (1960), 1.
xxviii. Winter C. A., Risley E. A. and Nuss G. W.; Proc. Soc. Exp. Biol., 111, (1962), 544.
xxix. Verma M., Sinha J. N. and Gujrati V. R.; Pharma. Res. Commun., 13, (1981), 967.
xxx. Calderaro C., Parrillo C., Giovane A., Greco R., Matera M. G., Berrino L. and Rossi R.; J. Pharmacol. Exp. Ther., 263, (1992), 579.

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