SUMMARY

More than 800 million people of the world are suffering from one and other type of arthritis which is the most distressing and disabling syndrome. This has been called the great cripler and king of human miseries. Arthritis is a type of inflammatory disorder. However, the alleviation of inflammation both acute and chronic as well as for the treatment of inflammatoryr diseases, many potent non-steriodal anti-inflammatory drugs like aspirin, indomethacin, mfenamic acid, flufenamic acid, namoyrate, sulindac, tolimetin, ibuprofen, naproxen, are available. However, these drugs possess serious inherent side effects, like gastric haemorrhage, perforation, bone marrow depression and gastric ulcers. In spite of considerable progress in the field of anti-inflammatory drugs there is not a single drug which can be termed as ideal. Since currently available drugs show variable response in different individuals and possess serious side effects, the search for the better drugs for the treatment of inflammation is the need of the day.

In the present work, we have screened some derivatives of some indole, napthalene,pyrazoline, thiazolidones, thiazolidinone and azetidinone. These compounds have shown interesting anti-inflammatory and analgesic activities.

SCHEME-I

N-(5-[(arylmethylene)amino]-1,3,4-thiadiazol-2-yl)methyl) [1,3,4]
thiadiazino[6,5-b]indol-3-amine, 2-aryl-3-{5-[(1,3,4] thiahdiazino[6,5-b]indol-3-ylamino)methyl]-1,3,4-thiazolidin-4-one, and 3-chloro-4-aryl-1-{5-[(1,3,4]thiahdiazino[6,5-b]indol-3-ylamino)methyl]-1,3,4-thiahdiazol-2-
yl]azetidin-2-one.

Acute and chronic inflammation and different type of arthritis are the inflammatory disorders. Which are a big blow to humanity and continual search for newer non-steroidal anti-inflammatory agents is the only way to fortify against this awful threat. Indole and its analogs constitute the active class of compounds possessing wide spectrum of biological activities, such as anti-inflammatory, anticonvulsant, antimicrobial antibacterial and antifungal. Moreover, azethidinones and thiazolidinones are well famed for their anti-inflammatory activities. In the light of above report and also in continuation of our laboratory work on chemoselective reaction of indole derivatives, a drug strategy has been planned to synthesize several
indole derivatives possessing azetidinone and thiazolidinone moiety with the hope to get better anti-inflammatory molecules. All compounds have been screened for their anti-inflammatory, ulcerogenic, analgesic and toxicity activities.

The chemical synthesis initiates with the reaction of indole-2,3-dione with thiosemicarbazide to yield 3-thiosemicarbazidoindole-2-one 1. 2-Amino-1,3,4-thiadiazino (6,5-b) indole 2 was prepared by the cyclization of compound 1 with cold. conc. sulphuric acid. Furthermore the compound 2 reacted with chloroethylacetate to yield 2-carboethoxymethylamino-1,3,4,-thiadiazino(6,5-b) indole 3. The later compound on reaction with thiosemicarbazide resulted into the formation of 2-(thiosemicarbazidocarbonylmethylamino)-1,3,4-thiadiazino(6,5-b) indole 4. The compound 4 on treatment with conc. H$_2$SO$_4$ and followed by neutralized with liquid NH$_3$ gave 2-[5’-aminothiadiazol-2’-yl methylamino]-1,3,4-thiadiazino (6,5-b) indole 5. Compound 5 when reacted with substituted benzaldehydes yielded N-{5’-[arylmethylene]amino}-1,3,4-thiadiazol-2-yl methyl]1,3,4-thiadiazino[6,5-b]indol-3-amine 6a-6h, 2-aryl-3-[5’-[[1,3,4] thiadiazino [6,5-b]indol-3-ylamino) methyl]-1,3,4-thiadiazol-2-yl]-1,3-thiazolidin-4-one 7a-7h, were synthesized by cyclocondensation of 6a-6h with thioglycolic acid in presence of anhydrous ZnCl$_2$, while 3-chloro-4-aryl-1-{5’-[[1,3,4]thiadiazino[6,5-b]indol-3-ylamino]methyl]-1,3,4-thiadiazol-2-yl}azetidin-2-one 8a-8h were synthesized by cycloaddition of 6a-6h with chloroacetylchloride in presence of triethyl amine The structure of all newly indole derivatives were confirmed on the basis of analytical and spectral data.

All the newly synthesized compounds of this series were tested for anti-inflammatory, analgesic, and ulcerogenic activity, at a dose of 50 mg/kg p.o. The most active compound of this Scheme was 2,3-choro-4-(2-methoxyphenyl) 1-{5-[1,3,4] thiadiazino [6,5-b indole-3- ylamino] methyl}-1,3,4-,thiadiazol-2-yl] azetidin-2-one (8g) has shown most active anti-inflammatory and analgesic activities with better ulcerogenic activity than phenyl butazone, while this compound was found to be associated with lesser degree of anti-inflammatory and analgesic activities as compared to indomethacin. ALD$_{50}$ of all compounds was high, indicating a good safety margin.
Indole derivatives are important source of compounds of pharmacological interest as they have shown a wide spectrum of biological activities viz. antibacterial, antifungal, anti-inflammatory, antidepressant and antimicrobial activities. Furthermore, substitution of heterocyclic moiety at 3<sup>rd</sup> position markedly influenced the anti-inflammatory activity. Moreover, several azetidinone and thiazolidinone are well famed for their anti-inflammatory activities with a view to achieve anti-inflammatory activity we have synthesized some new derivatives of 5-bromo indole by in corporating different neterocyclic moierties at 3<sup>rd</sup> position of 5-bromo indole with the hope to develop and were screened for anti-inflammatory and analgesic ulcerogenic and acute toxicity activities.

The reaction sequence leading to the formation of different indole derivatives is outlined in Scheme compound 1 i.e. 5-bromo-3-chloro-acetylamino indole was prepared by reacting 5-bromo-3-aminoindole with chloro acetyl chloride in methanol. compound 1 was then reacted with hydrazine hydrate in absolute ethanol to give compound 2, i.e., 5-bromo-3-hydrazinoacetyl amino indole. Reaction of compound 2 with various aromatic aldehydes in presence of glacial acetic acid to yielded the 5-bromo-3-[(4-substituted phenyl)methylene amino amido methylene amino]indole 3a-3f. Diazotiration of compounds 3a-3f with thioglycolic acid in the presence of anhydrous ZnCl<sub>2</sub> afforded the 5-bromo-3-[4'o xo-(2'-substituted aryl-1'-thiazolinyl)amido amino methylenes]indoles 4a-4f. Further the reaction between compounds 3a-3f and chloro acetyl chloride in the presence of 2-3 drops of triethyl amine yielded the cyclized product, i.e. 5-bromo-3[2-{3'-chloro-2'-o xo-(4-substituted phenyl)-1'-azetidinyl}amido amino methylene]indole 5a-5f respectively. The structure of all compounds have been evaluated by elemental analysis (C,H,N) and spectral analysis (IR, <sup>1</sup>HNMR and mass spectrometry).
The newly synthesized compounds were evaluated for their anti-inflammatory activity against carrageen an-induced oedema. The most potent compounds of this series 4 e 5-bromo-3-[4'-oxo-2'-(4-hydroxyphenyl)-1'-thiazoliyl] amidoamino methylene indole and 5e 5-bromo-3-[2-{3'-chboro-2'-oxo-4'- (4-hydroxyphenyl)-1'-azetidinyl}amidoamino methylene] indole have shown the better anti-inflammatory activity i.e. 40.63 and 44.82% at a dose of 50 mg/kg p.o as compared to phenylbutazone. UD$_{50}$ of the most potent compounds 4 e and 5 e were found to be 160.6 and 190.9 mg/kg i.p. ALD$_{50}$ values of the compounds were quite high indicates good safety margin.

**SCHEME-III**

- β-(Carbethoxymethyl)aminonapthalene, β-(Thiosemicarbozido carbonylmethyl) aminonapthalene, β-(2'-Amino-1',3',4'-thiadiazole-5'-yl) methylaminonaphthaline

The napthalene derivatives naproxen and nabumetone are currently used for the treatment of inflammatory disorders. The discovery of Nabumetone exoploled the napthalene nucleus for the synthesis of its derivatives with the hope to possess better activity than Nabumetone. Furthermore, napthalene derivative have also been found various biological activitiyes like antibacterial cardiovascular and anti-inflammatory. The substitution of different heterocyclic nuclei at β-napthalene has been reported to possess potent anti-inflammatory activities. A large number of thiazolidinones, azetidinones and thiadiazoles were reported to possess potent anti-inflammatory activity. In view above facts it was thought worthwhile to synthesis some newer napthalene derivative by incorporating the azetidinone and thiazolidinone moiety at position of napthalene nucleus with the aim to get better molecule with anti-inflammatory activity. All the compounds have been screened for their anti-inflammatory activity. (The structure of all compounds have been evaluated by elemental and spectral analysis. (I.R, 'H NMR and mass spectrometry)

Compound 1, i.e. (carbethoxymethyl)aminonaphthalene was prepared by reacting β-amino naphthalene with chloroethylacetate in methanol. Compound 1 was
then reacted with thiosemicarbazide in absolute methanol-water to give compound 2, i.e. β-(thiosemicarbazido-carbonylmethyl)aminonaphthalene. Reaction of compound 2 with H$_2$SO$_4$ and liquid ammonia in ethanol water to yield compound 3, β-(2′-amino-1′,3′,4′-thiadiazol-5′-yl methylamino naphthalene. On further reaction of compound 3 with various aromatic aldehyde in the presence of glacial acetic acid afforded the corresponding β-[2′-(p-methoxybenzylidene) amino-1′,3′,4′-thiadiazol-5′-yl)methyl]amino- naphthalenes 4a-4j, further undergoes cycloaddition with thioglycolic acid in presence of anhydrous ZnCl$_2$ to afforded 2′-[2″-(p-methoxyaryl)-4″-oxo-thiazolidin-3″-yl-1′,3′,4′-thiadiazol-5′-ylmethyl]aminonaphthalenes 5a-5j. On the other hand, reaction between compounds 4a-4j and chloro acetyl chloride in the presence of 2-3 drops of triethylamine to yielded a cyclized product, i.e. azetidinones 6a-6j, respectively.

All the newly synthesized compounds have evaluated for anti-inflammatory, activity in rats. Some compounds of the present series have shown interesting anti-inflammatory activity among these compound 6 e i.e. β-2′-[3″-chloro-2″-(p-chloro phenyl)-4″-oxo-azetidin-1′,3′,4′-thiadiazol-5′-yl methyl]aminonaphthalene was the most active compound of this series having 54.75% activity. It was also tested for ulcerogenic liability and was found to be ulcerogenic than phenylbutazone. ALD$_{50}$ of the compounds were high, indicating a good safety margin.

**SCHEME-IV**

5-Substitutedbenzylideneamino-1,3,4,- thiazole-2-thiols, 5 substituted-benzylideneamino-2 thiocarboxethoxy- methyl-1,3,4-thiadiazoles, 5- substituted-benzylideneamino-2-(thiosemicarbazidomethyl-thio)-1,3,4-thiadiazoles, 5- substitutedbenzylideneamino-2-[5′-amino-1′,3′,4′-thiadiazole-2′-ylthiomethyl]-1,3,4-thiadiazoles, 5-substitutedbenzylidene amino-2-[5′-(substituted benzylideneamino-1′,3′,4′- thiazolid-2′-yl)-thiomethyl]-1,3,4- thiazoles, 5-[4′-oxo-3′-chloro-2′-substitutedphenyl-azetidin-1′-yl]-2-[5"-(4"'-oxo-3"'-chloro-2"'-arylazetidin-1"'-yl)-1"',3"',4"'-thiadiazol-2"'-yl]-thiomethyl]-1,3,4-thiadiazoles.

Literature survey revealed that 1,3,4 thiazole derivatives are associated with various biological activities such as anti-inflammatory, anticonvulsant, antibacterial and antifungal. The incorporation of azetidinone moiety in different heterocyclic nuclei markedly modulates the anti-inflammatory activity. Therefore, it
was thought worthwhile to synthesized some new azetidinone derivatives of thia diazole by incorporating it at 2 and 5-position of 1,3,4- thia diazoles nucleus with the hope to get better anti-inflammatory molecule with improved anti-inflammatory activities. All the compounds have been screened for their anti-inflammatory, ulcerogenic, analgesic and toxicity activities. The structures of all compounds have been evaluated by elemental and spectral analysis (IR, and $^1$HNMR spectrometry).

The substituted benzyldehyde in presence of glacial acetic acid on reaction with 5-amino-1,3,4-thiadiazole-2-thiol, it was converted into compound, 5-substituedbenzylidenamino-1,3,4,-thiadiazole-2-thiols. The compound reacted when with chloroethylacetate gave compound, 5-substituted- benzylideneamino-2-(thiocarbethoxymethyl)-1,3,4,-thiadiazoles. Furthermore, the compound when treated with thiosemicarbazide resulted into the formation of the compound, 5-substitutedbenzylideneamino-2-(thiosemicarbazidomethyl-thio)-1,3,4-thiadiazoles. These compounds, on dehydrocyclsation with conc H$_2$SO$_4$ and ammonia solution gave compounds. The compounds, when further reacted with substitutedbenzyldehyde yielded the, substituted-benzylidene- amino-2-[(5'-substitutedbenzylideneamino)-1',3',4'-thiadiazol-2'-yl) homethyl]-1,3,4- thiazdizoles. The later compounds on cycocondensation with monochloroacetyl chloride and triethylamine furnished the compound, 5-[4'-oxo-3' -chloro-2'-substitutedphenyl-azetidin-1'-yl]-2-[{5"-(4'''-oxo-3''-chloro-2"'-aryl-azetidin-1"'-yl)-1"',3"',4"'-thiadizol-2"'-yl}thiomethyl]-1,3,4- thidiazoles.

All the twenty-four newly synthesized compounds of this series were tested for anti-inflammatory and analgesic activity, at a dose of 50 mg/ kg p.o. All the compounds of the series showed good response with respect to the anti-inflammatory activity. Moreover, the most potent compounds 5j and 6j have exhibited 36.95 and 37.64% inhibition of oedema at 50 mg/ kg p.o. and it was found to be less ulcerogenic in the comparison of the standard drug. ALD$_{50}$ of the compounds were quite high thereby indicating a good safety margin.

**SCHEME-V**

5-Methoxy-3-substituted chalconylindoles, 5-Methoxy-3-[1-acetyl-5-(substitutedphenyl)-2'-pyrazolin-3-yl]indoles, 5-Methoxy-3-[1-acetyl-5-(substitutedphenyl)-4-phenylazo-2-pyrazolin-3-yl]indoles, and 5-Methoxy-1'-
Indomethacin and tenidap are indole derivatives, which are successfully utilized by the clinicians for the treatment of different inflammatory disorders like different type of arthritis. Indole, the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties like anti-inflammatory, analgesic, antimicrobial, cardiovascular and anticonvulsant activities etc. Furthermore, substitution of heterocyclic moiety at 3rd position markedly influenced the anti-inflammatory activity. Moreover, several pyrazoline and azo derivatives have also been reported to possess promising anti-inflammatory activity. In view of above observations we have synthesized a new series of 5-methoxy indole by incorporating different heterocyclic moieties at 3rd position of 5-methoxy indole with the hope to develop better anti-inflammatory and analgesic agents with lesser side effects. All the compounds were tested pharmacologically for their anti-inflammatory, analgesic, ulcerogenic and acute toxicity evaluation.

The reaction sequence leading to the formation of different title compounds is outlined in scheme. The starting compound 5-Methoxy-3-acetylindole on refluxing with various aromatic aldehydes in the presence of 2% NaOH solution for 8–10 h yielded 5-Methoxy-3-chalconylindoles (1a–1f), these chalcones on cyclisation with hydrazine hydrate in the presence of glacial acetic acid resulted into corresponding 5-Methoxy-3-[1-acetyl-5-(substitutedphenyl)-2-pyrazolyl]indoles (2a–2f). Diazotisation of compounds 2a–2f with aniline yielded 5-Methoxy-3-[1–acetyl-5–(substituted phenyl)-4-phenylazo-2-pyrazolin]-3-indoles (3a–3f). 5-Methoxy-[1’–acetylmethylamino (substituted phenyl)-5’-(substitutedphenyl)-4-phenylazo]-2-pyrazoline-3’-yl] indoles (4a–4l) were synthesized by manich reaction using different substituted aromatic amines. The structure of all these newly synthesized compounds was confirmed on the basis of spectral (IR, 1HNMR and mass) and analytical data. The compounds were evaluated for their anti-inflammatory, analgesic and ulcerogenic activities.

All the newly thirty compounds were tested for their anti-inflammatory and analgesic activities. Some compounds of this scheme have shown mild to moderate anti-inflammatory activity and some compounds have shown more potent anti-
inflammatory activity as compared to the phenylbutazone. The anti-inflammatory activity of the most active compounds 4b and 4h i.e. 45.76 and 52.68% at the 50 mg/kg p.o. UD$_{50}$ of the potent compounds 4b and 4h 165.5 and 199.9 mg/kg i.p. Compounds 4b and 4h were found to be associated with lesser degree of anti-inflammatory and analgesic activities as compared to indomethacin. ALD$_{50}$ of the compounds were quite high, indicating a good safety margin.

**SERIES-VI**

β-(2-Arylideneamino thiazol-4-yl) amino-β'-methoxy napthalenes, β-[2-(3''-chloro-2''-oxo-4''-substitutedaryl-1''-azetidinyl)thiazol-4'-yl]amino-β'-methoxy napthalenes and β-[2-(1',3'-disubstituted phenyl-3'-substituted arylformazan-4'-yl)thiazol-4-yl]amino-β'-methoxynapthalenes.

The napthalene derivatives naproxen and nubumetone are currently used for clinical treatment of inflammatory disorders. Further, substitution of aryl heterocyclic moieties at β-position of the napthalene nucleus greatly influence the anti-inflammatory activity and analgesic activity. Thiazoles, thiazolidinones, azetidinones and formazans are also well known for their anti-inflammatory as well as analgesic properties. It was therefore thought worthwhile to synthesize some newer napthalene derivatives by incorporating azetidinyl-thiazolyl and formazanyl-thiazolyl moieties at β-position of napthalene nucleus with the hope to develop better anti-inflammatory agents. These newly synthesized compounds were tested for their anti-inflammatory, analgesic and ulcerogenic activities and acute toxicity.

The reaction sequence leading to the formation of different napthalene derivatives is outlined in **Scheme**. Compound 1, i.e. β-(chloroacetyl) amino-β'-methoxy napthalene, was prepared by reacting -amino-β'-methoxy napthalene with chloroacetyl chloride in methanol. Compound 1 was then reacted with thiourea in absolute methanol to give compound 2, i.e. β-(2-aminothiazol-4-yl)amino-β'-methoxynaphthalene. Reaction of compound 2 with various aromatic aldehydes in the presence of glacial acetic acid afforded the corresponding β-(2-arylideneaminothiazol-4-yl) amino-β'-methoxy naphthalenes 3a-3h. Furthermore, the reaction between compounds 3a-3h and chloroacetyl chloride in the presence of 2-3 drops of triethyl amine afforded a cyclized product, i.e. azetidinones 4a-4h. Diazotisation of compounds 3a-3h with aniline/substituted aniline yielded the
corresponding formazans 5a-5p respectively, the structure of all compounds has been evaluated by elemental analysis (C, H, N) and spectral analysis (IR. $^1$H NMR and mass spectrometry).

All the newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities. All the compounds showed transient mild to moderate activity. The most potent compound 5g and 50 were found to be less ulcerogenic as compared to the reference drug phenylbutazone and its anti-inflammatory activity were found to be 54.22 and 58.89% at a dose of 50 mg/kg p.o. ALD$_{50}$ of these compounds were quite high suggesting a good safety margin.