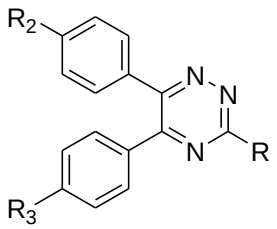
2.1. 1,2,4-TRIAZINE AS ANTI-INFLAMMATORY AND ANALGESIC AGENT

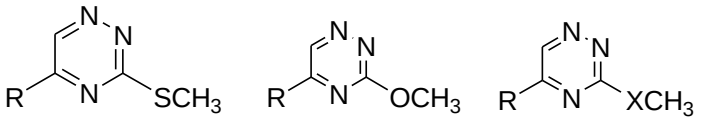
Lacefield and Ho has reported the synthesis of some 5,6-diaryl-1,2,4-triazines **1** and evaluated for anti-inflammatory potential as a substitute for topically applied steroids for symptomatic therapy. It was observed that the synthesised derivatives afforded relief by reducing the intensity of inflammation followed by a reduction in the time during which the inflammatory condition persists. Furthermore, they were devoid of the significant systemic toxicity which was a drawback of the topically applied steroids employed primarily to relieve the symptoms of inflammation (Lacefield and Ho, 1977).



1

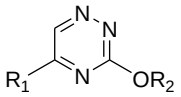
(Where R is Hydrogen or $(X)_nR_1$, in which X is either O or S, n is an integer which is either 0 or 1, and R_1 is C_1-C_8 alkyl, C_7-C_8arylalkyl, C_3-C_8cycloalkyl, or C_4-C_8 (cycloalkyl) alkyl; and R_2 and R_3 independently are C_1-C_3alkoxy or di(C_1-C_3 alkyl)amino group.)

Heilman *et al*. have synthesised a series of 3-methylthio and 3-alkoxy derivatives of asymmetric 1,2,4-triazines **2-6** and evaluated their anti-inflammatory efficacy under conditions for both acute and chronic inflammation. Out of all the synthesised derivatives the following triazine derivatives were reported to exhibit maximum activity with minimal GI complications as compared to standard indomethacin (Heilman *et al*., 1980).



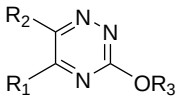
2 **3** **4**

R = substituted phenyl derivatives



5

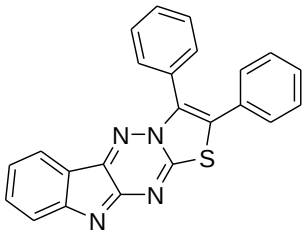
R_1 = substituted phenyl derivatives
R_2 = Ethyl, Isopropyl, Phenyl, Allyl, 4-chlorophenyl



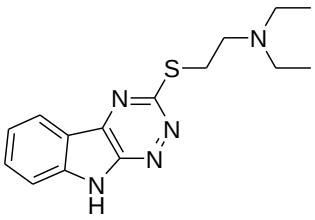
6

R_1, R_2 = substituted phenyl derivatives
R_2 = Ethyl, Isopropyl, Phenyl, Allyl,
R_3 = Ethyl, Isopropyl, Phenyl, Allyl, 4-chlorophenyl

Tomchin *et al.* have reported the synthesis of some 1,2,4-triazino[6,5-b]indole derivatives and further evaluated for anti-hypoxic and anti-inflammatory activity. The maximum activity was observed for compounds **7** and **8**, which was more effective than indomethacin. All the triazino indole derivatives studied also exceeded indomethacin on the anti-inflammatory activity in a thermal burn model (Tomchin *et al.*, 1997).

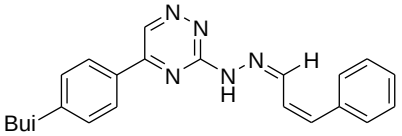


7



8

Makhlouf and Maklad, reported the synthesis and analgesic, anti-inflammatory activity of some1,2,4-triazine derivatives. The derivatives were synthesised by incorporating the isobutyl phenyl entity in the triazine heterocyclic system. Out of all the synthesised derivatives the arylidene hydrazine, derivative **9** revealed the highest anti-inflammatory activity while the hydrazine derivative **10** showed pronounced analgesic activity. The fused triazolo triazine **11** exhibited dual analgesic-anti-inflammatory activity without any ulcerogenicity (Makhlouf and Maklad, 2004).



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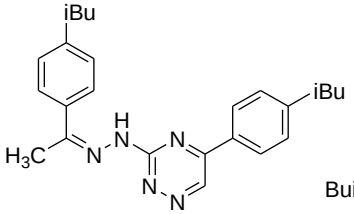

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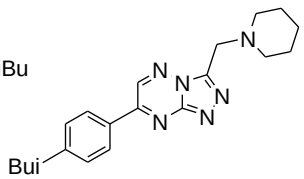
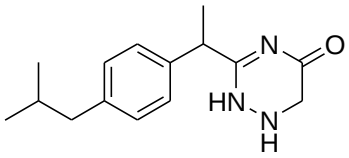


11

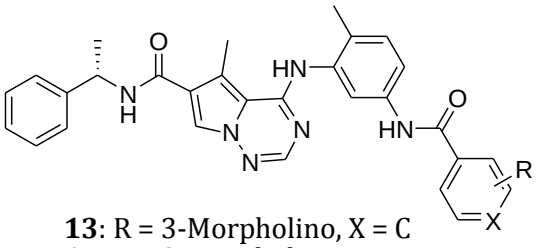
iBu = isobutyl phenyl

Amir *et al.* synthesised and evaluated anti-inflammatory activity of 1,2,4-triazine analogues. Compound **12** showed significant anti-inflammatory activity (71%) (Amir *et al.*, 2007a).

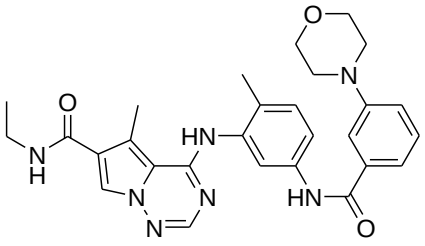


12

Wrobleski *et al.* reported the synthesis of a series of pyrrolo[2,1-f][1,2,4]triazine analogues and identified them as potent p38α MAP kinase inhibitors. All the compounds were reported to elicit significant cellular potency (IC_{50}: <100 nM) for acute *in vivo* murine model. Further, the inhibition of lipopolysaccharide-stimulated TNF-α production was measured under *in vivo* screening after oral administration of potent compounds. Compounds **13**, **14** and **15** were reported to be the most potent in this model, significantly inhibiting TNF-α production by 87%, 89% and 84% respectively (Wrobleski *et al.*, 2008).

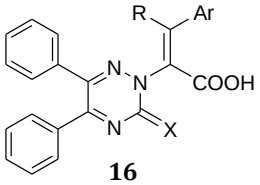


13: R = 3-Morpholino, X = C
14: R = 3-Morpholino, X = N



15

Mullick *et al.* have synthesised of a series of 1,2,4-triazine **16** and evaluated them for potential anti-anxiety and anti-inflammatory activity (Mullick *et al.*, 2009).

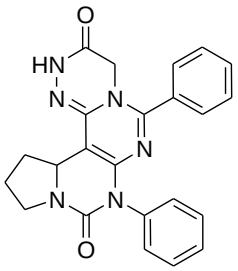


16

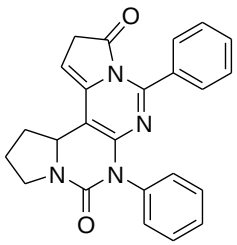
X = O or S
Ar = substituted phenyl
R = -H or -CH_3

In the case of anti-inflammatory activity, the chalcones of aldehydes give compounds with better activity as compared to acetophenones and an introduction of an allylic group on heterocyclic ring produced good anti-inflammatory activity. Secondly, compounds with an electronegative substituent at the *para* position showed better activity than other substituents.

Amin *et al.* have synthesised some 1,2,4-triazine analogues and evaluated their analgesic activity using acetic acid-induced writhing assay. All synthesised derivatives exhibited comparable activity to indomethacin. The anti-inflammatory screening of synthesised compounds was performed using carrageenan-induced rat paw oedema model. The triazino analogue **17** displayed the highest activity as compared to its 5-membered imidazo and triazolo counterpart. An IC_{50} value of the analgesic activity of compound **17** was reported to be 0.446 mg/kg. Anti-inflammatory effect of the tetracyclic imidazole analogue **18** (potency 1.06) was more than the triazine analogue **17** (potency 0.77) and standard drug indomethacin (potency 1.00) (Amin *et al.*, 2009).



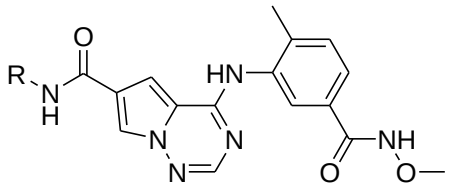
17



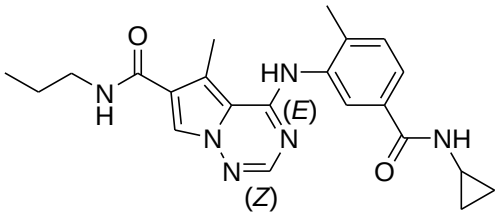
18

Liu *et al.* reported the synthesis of pyrrolo[2,1-*f*][1,2,4]triazine analogues as p38α MAP kinase inhibitor for the treatment of inflammatory conditions. With an aim to improve the pharmacokinetic properties of previously reported p38α MAP kinase inhibitors, the *N*-methoxy moiety in compounds **19** and **20** were replaced with an *N*-cyclopropyl group which result from the π character of the cyclopropyl moiety and enhanced the hydrogen bonding ability of the benzamide NH in comparison to the less potent N-alkyl analogues. Compound **21** exhibited a highly selective p38α inhibition activity along with a significantly improved pharmacokinetic profile as compared to **19** and more efficient in both the acute murine model of inflammation and rat adjuvant arthritis model. Compound **21** is

currently in phase II clinical trials for the treatment of rheumatoid arthritis (Liu *et al.*, 2010).

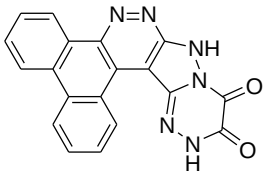


19: R = -C_2H_5
20: R = (S)-alpha-$CH_3CH_2C_6H_5$

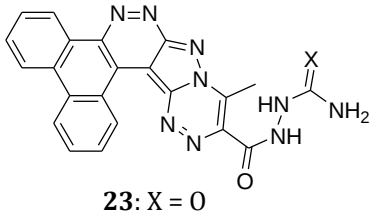


21

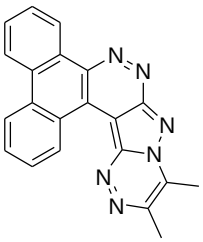
Bahashwan *et al.* reported the synthesis of a series of polycyclic analogues and evaluated their anti-inflammatory, analgesic and antimicrobial activities. Compound **22** comprising of a secondary amine of triazole showed the highest activity of anti-inflammatory. Compound **23** exhibited the highest activity of analgesic owing to the presence of methyl group. The compounds (**22-25**) and the standard drug indomethacin were found to elicit equipotent anti-inflammatory activity (6.8±1.6 to 62.4±1.2%). Also, compounds (**22-26**) and the standard drug valdecoxib possessed equipotent analgesic activity (0.15±0.01 to 0.99±0.01) (Bahashwan *et al.*, 2012).



22



23: X = O
24: X = S



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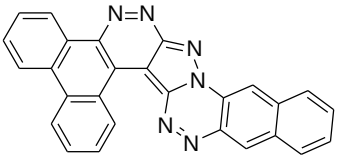
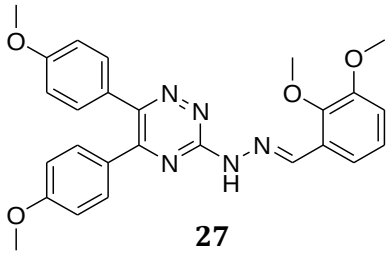


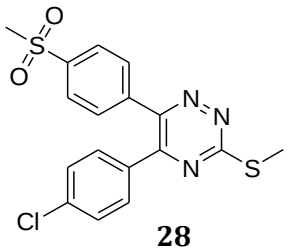
26

(Khoshneviszadeha *et al.*, 2013) have reported the synthesis of novel 1,2,4-triazine derivatives bearing hydrazone moiety synthesised and evaluated for their activity to inhibit IL-1B and TNF-α production with an aim towards the

development of a new therapeutic agent to fight against inflammatory diseases. Compound **27** exhibited a good anti-inflammatory effect in carrageenan-induced rat paw oedema. The results of western blotting demonstrated that the anti-cytokine potential of compound **27** is mainly mediated through the inhibition of p38 MAPK signalling pathway. The result reflected the promising activity of the compound **27** as an inhibitor of both cytokines with very low cytotoxicity.



27

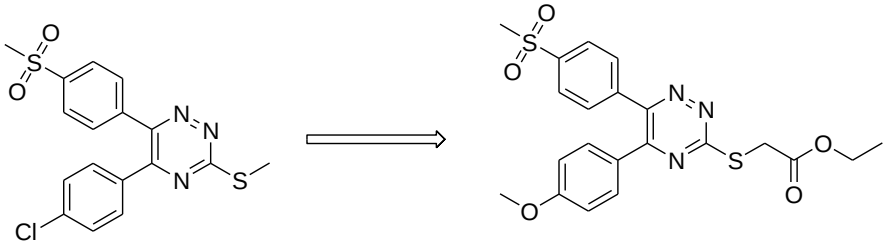


28

Irannejad *et al.* have reported the synthesis of series of 5-aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine derivatives. Synthesised compounds were evaluated for their COX-1/COX-2 inhibitory activity as well as *in vivo* anti-inflammatory and effects. All the synthesised derivatives strongly inhibited COX-2 enzyme with IC_{50} values in the range of 0.1–0.2 μM and in the most cases showed stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among all the reported compounds, compound 5-(4-Chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-3-(methylthio)-1,2,4-triazine **28** was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib (SI = 405). Evaluation of anti-inflammatory and analgesic effects of **28** showed its higher potency than indomethacin (Irannejad *et al.*, 2014).

In order to find novel cyclooxygenase (COX)-2 inhibitors for treating inflammatory-based diseases such as Alzheimer's disease (AD), Dadashpour *et al.* have reported an insertion of an ethyl carboxylate side chain to 5-(4-Chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-3-(methylthio)-1,2,4-triazine (lead compound II) to maintain residual inhibition of COX-1 through interacting with Arg 120 confirmed by preliminary molecular docking study. Accordingly, a series of ethyl 5,6-diaryl-1,2,4-triazine-3-yl thioacetate derivatives were synthesised. *In vitro* COX-1/COX-2 evaluations revealed that compound **29** (COX-2 IC_{50}: 10.1 μM,

COX-1 IC_{50}: 88.8 μM) was the most selective COX-2 inhibitor while maintaining residual inhibition of COX- 1. To evaluate their potential use against AD, an *in vitro* evaluation of β-amyloid fibril formation was performed. The results indicated that the prototype compounds are effective β-amyloid destabilising agents while compound **29** could inhibit 94% of the β-amyloid fibril formation after 48 h (Dadashpour *et al.,* 2015).



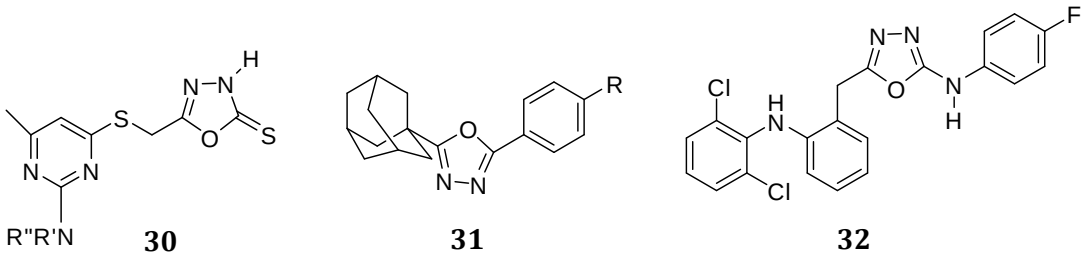
Lead Compound **II** **29**

IC_{50} COX-1 = 39.5 uM
IC_{50} COX-2 = 0.1 uM

2.2. 1,3,4-OXADIAZOLE AS ANTI-INFLAMMATORY AND ANALGESIC AGENT

Burbuliene *et al.* have reported the investigation of 5-[(2-di-substituted diamino-6-methyl-pyrimidin-4-yl)sulphanylmethyl]-3*H*-1,3,4-oxadiazol-2-thione derivatives for anti-inflammatory activity and found that compound **30** was more potent than standard ibuprofen (Burbuliene *et al.*, 2004).

Kadi *et al.* have reported the synthesis and anti-inflammatory evaluation of 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazole compounds of which, compound **31** displayed a strong dose-dependent inhibition of carrageenan-induced rat paw oedema with >50% inhibition at a concentration of 60 mg/kg. The compound consisting of the 3,4-di-MeO group was reported to be more potent than the standard indomethacin (Kadi *et al.*, 2007).



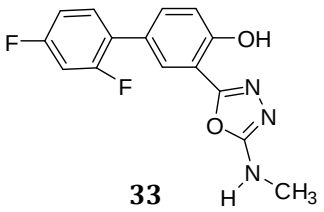
30 **31** **32**

R = 4Cl, 3,4-Di-MeO

Amir *et al.* has reported 5-(2-(2,6-Dichlorophenylamino)benzyl)-N-(4-fluorophenyl)-2-amino-1,3,4 oxadiazole **32** to be more potent than diclofenac sodium when evaluated for its analgesic activity with a maximal analgesic activity of (81.86%) (Amir *et al.*, 2007b).

(Küçükgüzel *et al.*, 2007) have reported the synthesis of series of 2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid derivatives which also comprised of 2-substituted-1,3,4-oxadiazoles and evaluated them for anti-infective and anti-inflammatory properties. Compound **33** was reported to possess comparable anti-inflammatory activity compared to standard drug diflunisal. The study also concluded that replacement of carboxylic acid function with several heterocyclic rings such as (1,2,4-triazole; 1,3,4-thiadiazole and 1,3,4-oxadiazole) lead to an increase in biological activity or a different pharmacological profile.

(Kumar *et al.*, 2008) have reported the synthesis of series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yl oxyacetic followed by their evaluation of their anti-inflammatory activity by the carrageenan-induced rat paw oedema. Derivatives possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities. Of the oxadiazole derivatives, **34** exhibited potential anti-inflammatory and analgesic effect with low ulcerogenic potential.



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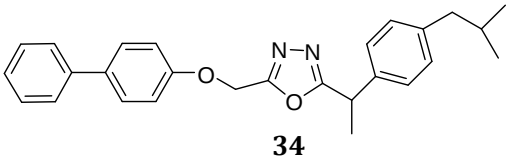

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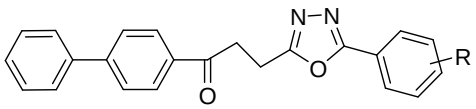


35

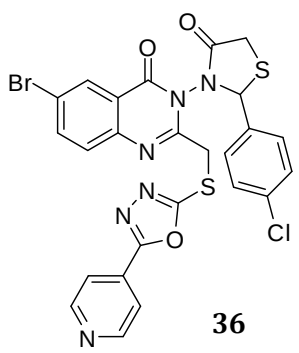
R = H, 4-Cl, 4-NO_2, 4-F, 4-MeO, 3,4-Di-MeO

(Husain *et al.*, 2009) have reported the synthesis of derivative **35** from the anti-inflammatory drug fenbufen and evaluated for anti-inflammatory activity by carrageenan induced paw oedema using diclofenac sodium and fenbufen as the

standard drugs. The compounds containing 4-Cl, 4-NO_2, 4-F and 4-MeO, were reported equipotent to fenbufen, whereas compounds with a 3,4-di-MeO group were more potent than the fenbufen and equal to diclofenac sodium. Compound **35** with the R= 4-F group also exhibited a better analgesic activity of (72.52%), than both diclofenac sodium (70.32%) and fenbufen (54.1%).

Kumar and Rajput have reported the synthesis of some quinazolin-4-one derivatives hybridised with different heterocyclic moieties at the third position of quinazolinone nucleus. Of all the said derivatives, compound **36** exhibited maximum activity, which showed 36.3% inhibition of oedema in the carrageenan-induced rat paw oedema bioassay. Interestedly the same compound elicited similar anti-inflammatory activity like standard drug phenylbutazone at the dose of 25, 50 and 100 mg/kg *p.o* (Kumar and Rajput, 2009).

(Akhter *et al.*, 2009) have reported the synthesis and biological evaluation of several aroyl propionic acid derivatives containing 1,3,4-oxadiazole nucleus. The compounds were synthesised by cyclisation of 3-aroylpropionic acids into the 1,3,4-oxadiazole nucleus by treating with various aryl acid hydrazides in the presence of $POCl_3$. The synthesised derivatives were tested *in vivo* for their anti-inflammatory activity. The compounds exhibiting activity comparable to the standard drug ibuprofen were further evaluated for their analgesic, ulcerogenic and lipid peroxidation activities. Compound **37** showed 89.50% of inhibition in paw oedema, 69.80% protection against acetic acid induced writhing and 0.7 of ulcer severity index respectively, compared to 90.12, 72.50 and 1.95 values of ibuprofen. The study concluded that the cyclisation of carboxylic group of aroyl propionic acids into a 1,3,4-oxadiazole nucleus resulted in compounds having excellent anti-inflammatory and analgesic effects with reduced gastric irritation.



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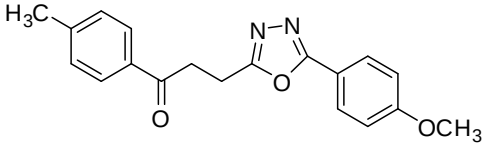
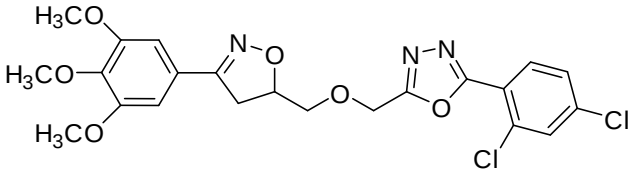


37

(Jayashankar *et al.*, 2009) have reported the synthesis of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives followed by its evaluation as anti-inflammatory and analgesic agents. The reported derivatives were synthesised *via* [3+2]-cycloaddition reaction of nitrile oxide with allyl alcohol followed by an intramolecular 1,3-diploar cycloaddition reaction of nitrile imine with a carbonyl group. Of all the evaluated derivatives, compound **38** exhibited activity comparable to ibuprofen and aspirin at the similar oral dose of 100 mg/kg.



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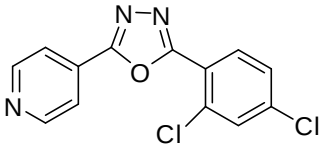
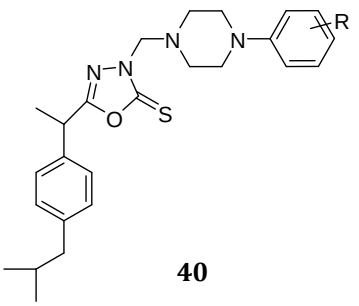


39

Based on the outcome of their study, (Gilani *et al.*, 2010) have reported that compound **39** consisting of the 2,4-dichlorophenyl group, present at the second position of the 1,3,4-oxadiazole ring, exhibited a maximal analgesic activity of (70.37±1.67%), as compared to standard ibuprofen (73.52±1.00%).

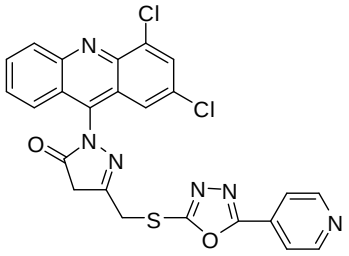
(Manjunatha *et al.*, 2010) have reported the synthesis of 1,3,4-oxadiazole derivatives **40** of ibuprofen consisting of an aryl piperazine unit at the third position of the oxadiazole ring. The reported compounds were further evaluated for anti-inflammatory activity by carrageenan induced rat paw oedema bioassay with diclofenac sodium as the standard drug. Compounds comprising of 4-Cl, 4-NO_2, 4-F and 3-Cl groups were more active than diclofenac sodium, whereas compounds with 4-MeO and 2-EtO groups exhibited less activity as compared to the standard. Compound **40** had also been reported to display analgesic activity.

Chandra *et al.* have synthesised several substituted acridinyl pyrazoline derivatives and evaluated them for the potential for anti-inflammatory activity. All of the reported derivatives exhibited anti-inflammatory and analgesic activities at the dose of 50 mg/kg, *p.o.* compared to standard phenylbutazone and aspirin. However, compound **41** showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg, *p.o* (Chandra *et al.*, 2010).



40

R = 4-Cl, 4-NO_2, 4-F, 4-MeO, 2-EtO, 3-Cl



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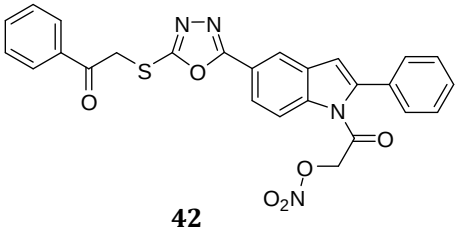

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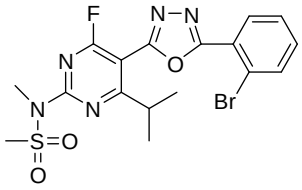


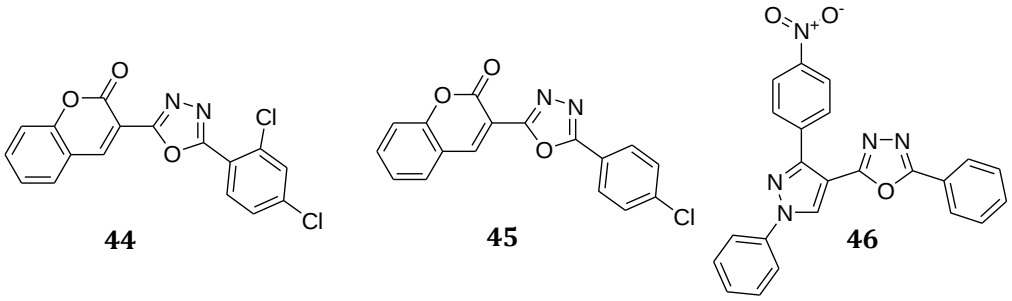
43

Bhandari *et al.* have reported the synthesis of a series of hybrid molecules having general formula 2-(5-(5-(substituted phenyl)-2-oxo-ethylthio)-1,3,4oxadiazole-2-yl)-2-phenyl-1*H*-indol-1-yl)-2-oxoethyl nitrate followed by their pharmacological screening for anti-inflammatory and analgesic activity along with an evaluation of their ulcerogenic liability. Of all the reported derivatives, compound **42** exhibited significant anti-inflammatory and analgesic effect with reduced GI ulcerogenicity. It also presented promising results in histopathological studies and devoid of mucosal injury. Compound **42** was also reported to exhibit significant nitric oxide releasing activity in an *in vitro* assay method (Bhandari *et al.*, 2010).

Palusa *et al.* have reported the synthesis and evaluation of a series of pyrimidine substituted 1,3,4-oxadiazole derivatives as antimicrobial and anti-inflammatory agents. Of all the synthesised derivatives, compound **43** exhibited good antimicrobial and anti-inflammatory activities as compared to standard ibuprofen (Palusa *et al.*, 2011).

Akhter *et al.* have reported the synthesis of a series of 3-(5-phenyl/phenylamino-[1,3,4]oxadiazol-2-yl)-chromen-2-one and *N*-[5-(2-oxo-2H chromen-3-yl)-[1,3,4] oxadiazol-2-yl]-benzamide derivatives and screened them for anti-inflammatory, analgesic activity. Compound **44** was found more potent

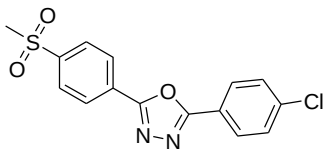
with 89% of inhibition followed by compound **45** (86%). Selected compounds were also evaluated for inhibition of COX's (COX-1 and COX-2) and LOXs (LOX-5, LOX-12, and LOX-15). Compound **44** was comparatively selective for COX-2, LOX-5, and LOX-15. The study revealed that the 1,3,4-oxadiazole derivatives were more effective than ibuprofen with reduced side effects (Akhter *et al.*, 2011).



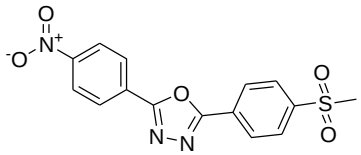
44 **45** **46**

(Bansal *et al.*, 2014) have synthesised 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles as selective COX-2 inhibitors with potent anti-inflammatory activity. Among the evaluated compounds, compound **46** (2-(3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazole) was found to be the most potent inhibitor of COX-2 with an IC_{50} value of 0.31 mM and exhibited promising degree of anti-inflammatory activity in the carrageenan-induced rat paw oedema model with ED_{50} value of 74.3 mg/kg. Compound **46** further suppressed acetic acid-induced writhes comparable to that of aspirin and gastro sparing profile superior to the aspirin. Molecular docking analysis displayed higher binding affinity of **46** towards COX-2 than COX-1.

(Grover *et al.*, 2015) have reported the synthesis of a series of 2,5-diaryl-1,3,4-oxadiazoles followed by further evaluation as potential COX-2 inhibitors. Compounds **47-51** were found to be the most potent and selective inhibitors of COX-2 (IC_{50}: 0.48–0.89 mM; SI: 67.96–132.83). Compounds **48**, **49** and **51** displayed anti-inflammatory activity superior to celecoxib in a carrageenan-induced rat paw oedema assay. The selective inhibition of COX-2 by the above compounds was well supported by molecular docking studies. Cytotoxicity studies of the most potent compounds in RAW 264.7 and J774A.1 cells revealed cell viabilities of more than 89% when tested at the concentration of 30 mM.



47



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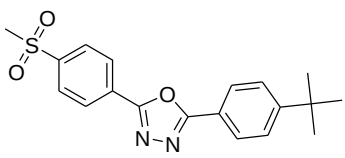

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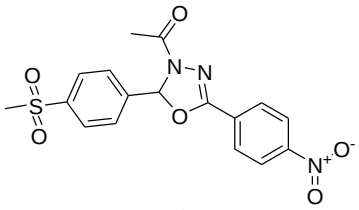

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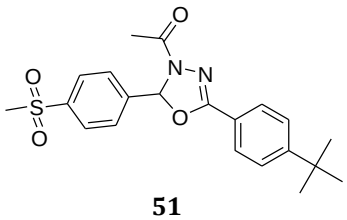


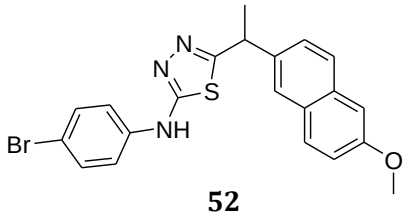
51

2.3. 1,3,4-THIADIAZOLE AS ANTI-INFLAMMATORY AND ANALGESIC AGENT

Nonsteroidal anti-inflammatory drugs (NSAIDs), comprises of molecules with a diverse set of structures, exhibit a broad spectrum of anti-inflammatory, analgesic and antipyretic effects.

Though a carboxylic acid (COOH) group is essential for anti-inflammatory activity; however, (Amir and Kumar, 2005; Amir *et al.*, 2007b) had reported that some compounds were still able to elicit anti-inflammatory activity when this carboxylic acid group was replaced by a thiadiazole ring. This could be attributed to the weakly basic nature of thiadiazoles as compared to other azoles due to the inductive effect of the additional heteroatom.

Amir and Kumar have synthesised by replacing the carboxyl group in naproxen, a standard drug, with *N*-(4-bromophenyl)-1,3,4-thiadiazol-2-amine to yield compound **52** wherein compound **52** and naproxen exhibited values of 75% and 74% inhibition, respectively in the carrageenan-induced rat paw oedema test (Amir and Kumar, 2005).



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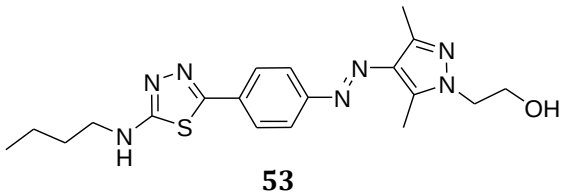
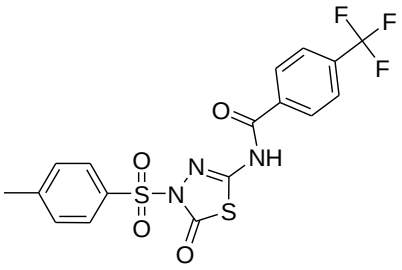


53

1,3,4-thiadiazoles have also been reported for their advantage as analgesics compared to other heterocycles. (Oruc *et al.*, 2006) have synthesised a series of compounds containing 1,3,4-thiadiazole or 1,2,4-triazole as analgesics, wherein the thiadiazole containing compound **53** exhibited good analgesic activity.

Compounds reported being designed by Schenone *et al.* exhibited good analgesic activity in the acetic acid-induced writhing test. Some compounds of this series also elicited similar anti-inflammatory activity in the carrageenan rat paw oedema test. The best was, however, compound **54**, with an inhibition value of 48.8% at a dose of 12.5 mg/kg (Schenone *et al.*, 2006).



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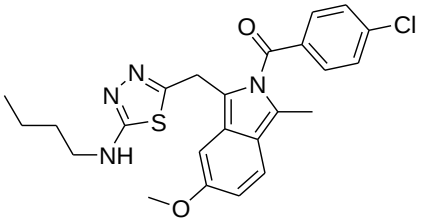

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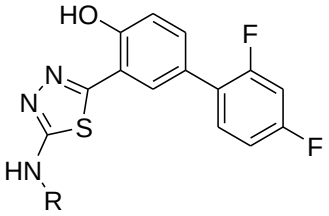
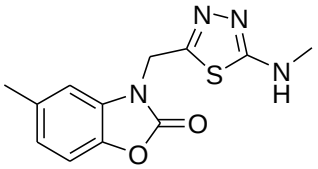
Amir *et al.* have also reported the design and synthesis of a series of indomethacin derivatives with different heterocycles in an attempt circumvent the undesired gastric toxicity associated with these derivatives. Of the potent compounds, compound **55**, generated by replacement of the carboxylic acid group of indomethacin with substituted amino-1,3,4-thiadiazole, produced a distinct advantage in anti-inflammatory and analgesic activity. The outcome thus indicated the effectiveness of the 1,3,4-thiadiazole nucleus in the design of anti-inflammatory and analgesic agents (Amir *et al.*, 2007b).

(Küçükgüzel *et al.*, 2007) have reported that thiadiazol derivatives of salicylic acid exhibited significant anti-inflammatory activity. Compound **56**, obtained by replacement of the the carboxyl group in diflunisal with *N*-(p-tolyl)-1,3,4-thiadiazol-2-amine, produced improved anti-inflammatory activity over the parent compound diflunisal, a marketed NSAID in clinical use, with percentage inhibition values of 55% (compound **56**) and 24% (diflunisal) in the carrageenan-induced rat paw oedema test. Compound **56** was also assessed *in*

vivo for analgesic activity (paw withdrawal latency in seconds ± SEM), yielding a value of 19.2±0.91 as compared to diflunisal which was 19.1±1.18.



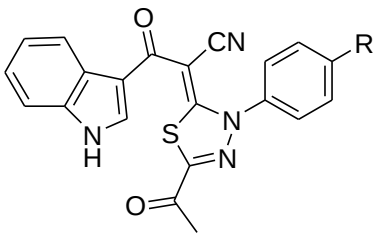
56: R = 4-OMe-Ph



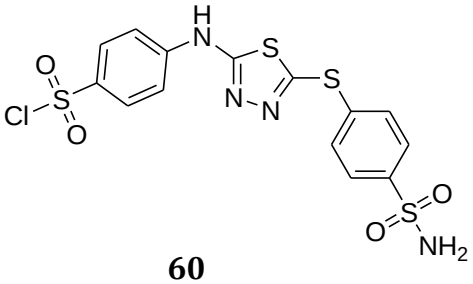
57

In a study reported by Salgin-Goksen *et al.* several of the synthesised compounds, exhibited potent anti-inflammatory and analgesic activity. In the acetic-acid-induced abdominal writhing test, **57** displayed the most potent inhibition (74%) as compared to aspirin (66%). In the hot plate test, **57** demonstrated 54% inhibition where morphine exhibited 51% inhibition in the same assay (Salgin-Goksen *et al.*, 2007).

Radwan *et al.* have reported the compound **58** as the most potent anti-inflammatory of the compounds tested, inhibiting carrageenan-induced oedema of the hind paw in mice (33%). Compound **59** was also reported to exhibit enhanced analgesic activity in a hot-plate test in mice, with a 3.1-fold efficacy about standard indomethacin (Radwan *et al.*, 2007).



58: R = Me
59: R = Cl

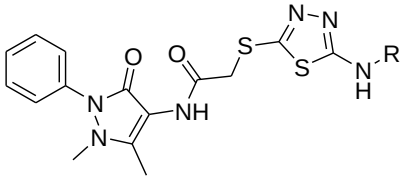


60

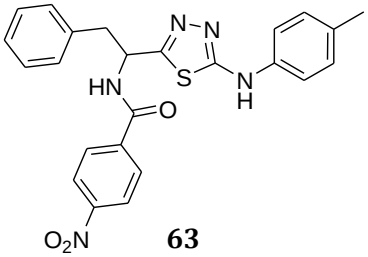
1,3,4-thiadiazoles are also said to possess good anti-inflammatory and analgesic activities, with some exhibiting high selective index for COX-2, which can reduce the side effects associated with the long-term clinical administration of traditional NSAIDs. Employing the colorimetric COX inhibitor screening assay, all compounds reported by Sharma *et al.* were evaluated for COX-1 and COX-2 inhibition. Compound **60** exhibited the most potent COX-2 inhibition (42%) with

a significant anti-inflammatory and analgesic activity (inhibition of paw oedema after 3 h 56 mg/kg: 53.48±0.02%) as compared to standard indomethacin and tramadol hydrochloride (Sharma *et al.*, 2008).

Rostom *et al.* have reported the anti-inflammatory and antimicrobial activities of a series of compounds including **61** and **62**. These derivatives were evaluated using the formalin-induced paw oedema and the turpentine oil-induced granuloma pouch bioassays, with diclofenac sodium as a standard drug. Recording the anti-inflammatory activity after three hours as a criterion for the formalin-induced paw oedema bioassay (acute inflammatory model), compounds **61** and **62** exhibited more efficacies (49% and 46%, respectively) than the standard drug (44%) (Rostom *et al.*, 2009).



61: R = H
62: R = COMe



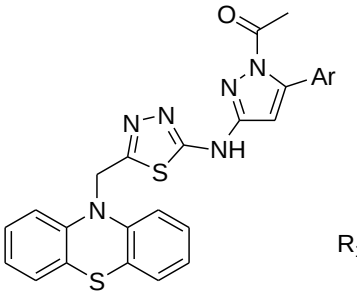
63

In another study, Moise *et al.* had reported that all compounds with anti-inflammatory activity synthesised exhibited less toxicity than the corresponding compounds without thiadiazole ring, with compound **63** exhibiting the lowest (Moise *et al.*, 2009).

Pluta *et al.* have reported the design and synthesis of compounds in which a 10*H*-phenothiazine scaffold was linked with varied heterocycles to obtain compounds possessing diverse biological activities. Compound **64**, with a 1,3,4-thiadiazole ring substituted in position 10, elicited significant *in vivo* anti-inflammatory activity and fewer ulcerogenic side effects compared with standard phenylbutazone (Pluta *et al.*, 2011).

Özadalı *et al.* have reported the synthesis a series of compounds containing 1,3,4-thiadiazole or 1,2,4-triazole. *In vitro* assessment studies indicated that thiadiazole **65** exhibited comparatively better inhibition of 5-lipoxygenase (5-LOX) than the corresponding triazole (Özadalı *et al.*, 2012).

Verma *et al.* have reported the synthesis of some *N*-phenyl thiosemicarbazide which was further condensed with aromatic carboxylic acid in the presence of conc. sulphuric acid to form the 1,3,4-thiadiazole analogues. The compounds were screened for anti-inflammatory activity by carrageenan induced rat paw oedema method wherein the compound **66** exhibited significant to moderate anti-inflammatory activity (Verma *et al.*, 2014).



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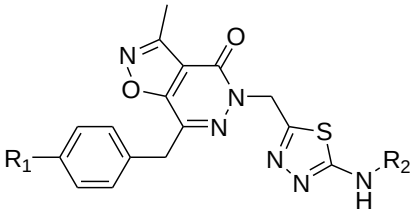

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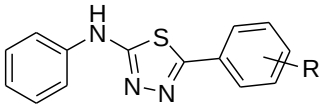
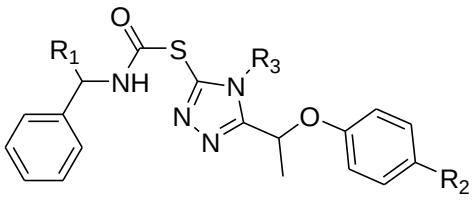


66

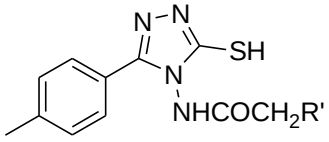
2.4. 1,2,4-TRIAZOLE AS ANTI-INFLAMMATORY AND ANALGESIC AGENT

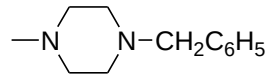
Turan-Zitouni *et al.* have reported the synthesis of 1,2,4-triazole derivatives by alkali cyclisation condition of thiosemicarbazides obtained by reacting acetic or propionic acid hydrazides with various aryl/alkyl isothiocyanates. It was followed by their pharmacological evaluation for anti-inflammatory activity using the carrageenan bioassay model in rats. Among all the reported derivatives, compound **67** (70.5%), **68** (73.1%), **69** (73.8%) and **70** (72.1%) showed maximum inhibition of carrageenan-induced rat paw oedema as compared to standard indomethacin (67.3%) (Turan-Zitouni *et al.*, 2007).

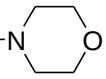
Upmanyu *et al.* have synthesised fifteen new substituted 1,2,4-triazoles using 4-methylbenzoic acid as a starting reactant. The reported derivatives were evaluated for anti-inflammatory and anti-nociceptive effects by the carrageenan-induced paw oedema method, and hot plate method and tail immersion method. Compounds **71** and **72** were reported to exhibit significant anti-inflammatory activity compared to other synthesised compounds, with **72** also showing superior anti-nociceptive activity as compared to standard indomethacin (Upmanyu *et al.*, 2011).



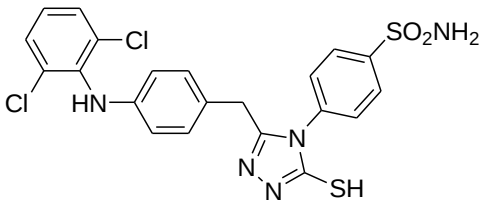
67 $R_1 = C_6H_5$; $R_2 = H$; $R_3 = C_6H_5$
68 $R_1 = CH_3$; $R_2 = Cl$; $R_3 = C_6H_5$
69 $R_1 = CH_3$; $R_2 = H$; $R_3 = C_6H_{11}$
70 $R_1 = CH_3$; $R_2 = Cl$; $R_3 = C_6H_{11}$



71 R' = 

72 R' = 

(Pattan *et al.*, 2012) have reported the synthesis of a series of 1,2,4-triazole derivatives followed by its evaluation for antimicrobial, anti-tubercular and anti-inflammatory activities. Compound **73** exhibited maximal anti-inflammatory effect (40.26%) as compared to standard diclofenac sodium (44.47%).



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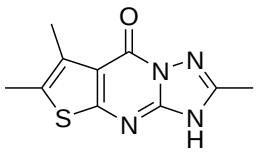

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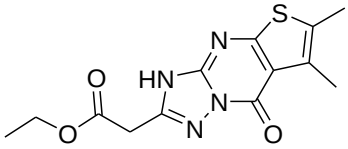

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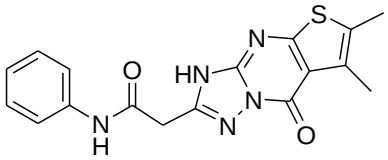

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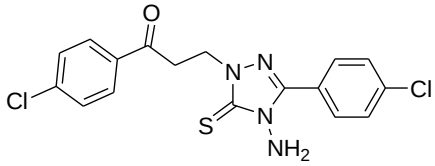
Ashour *et al.* have synthesised a series of thieno[2',3':4,5]pyrimido[1,2-b][1,2,4]triazines and thieno[2,3 d][1,2,4]triazolo[1,5-a] pyrimidines followed by their evaluation for anti- inflammatory and analgesic activity using diclofenac sodium as a reference standard. Collectively, the thienotriazolopyrimidine derivatives **74**, **75** and **76** exhibited distinctive anti-inflammatory activity at the acute and sub-acute models as well as good analgesic profile with a delayed onset of action. Moreover, they revealed good gastrointestinal safety profile and were well tolerated by experimental animals with a high safety margin in acute oral toxicity studies (ALD_{50} > 0.3 g/kg) (Ashour *et al.*, 2013).

(El-Serwy *et al.*, 2013) have reported the synthesis of series of new 1,2,4-triazole derivatives starting from 4-Amino-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4 triazole-3-thione. Compounds **77** (188.2%) and **78** (118.8%) exhibited significant anti-inflammatory potency after 4 h greater than that of indomethacin (100%) whereas other derivatives had less potency than indomethacin.



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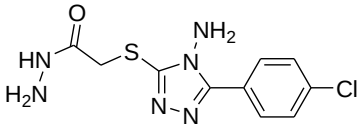

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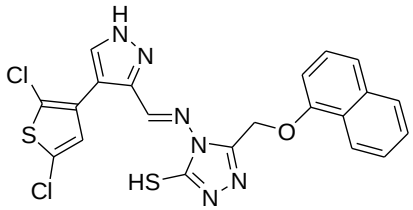


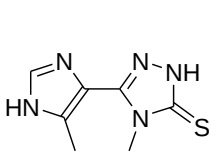
79

Vijesh *et al.* have reported the synthesis and pharmacological evaluation of pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. The synthesised compounds were screened for their analgesic activity by the tail flick method. The outcome of the study revealed that the compound **79** comprising of a 2,5-dichlorothiophene substituent on pyrazole moiety and a triazole ring showed significant analgesic activity as compared to standard pentazocine (Vijesh *et al.*, 2013).

Almasirad *et al.* have reported the preparation of new methyl-imidazolyl-1,3,4-oxadiazoles and 1,2,4-triazoles. The analgesic and anti-inflammatory profile of the synthesised compounds were evaluated by writhing and carrageenan induced rat paw oedema tests respectively. Compounds **80-82** and **83** were active analgesic agents and also showed a significant anti-inflammatory response in comparison with control. Compounds **80** and **82** were further screened for ulcerogenic activities and were found devoid of ulcerogenic liability (Almasirad *et al.*, 2014).

Jiang *et al.* have reported the synthesis of a series of hybrids from diaryl-1,2,4-triazole and hydroxamic acid or *N*-hydroxyurea. These hybrids were

further evaluated as anti-inflammatory agents. Results of their study showed that all the compounds showed dual COX-2/5-LOX inhibitory activities *in vitro*. Compound **83** showed optimal inhibitory activities (COX-2: IC_{50} = 0.15 μM, 5-LOX: IC_{50} = 0.85 μM), and also selectively inhibited COX-2 relative to COX-1 with selectivity index (SI = 0.012) comparable to celecoxib (SI = 0.015). Compound **84** also exhibited potent anti-inflammatory activity (inhibition: 54.1%) comparable to celecoxib (inhibition: 46.7%) in a xylene-induced ear oedema assay. Compound **84** also displayed promising analgesic activity in acetic acid-induced writhing response and hot-plate assay (Jiang *et al.*, 2014).



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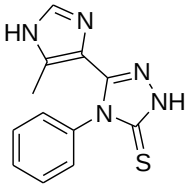

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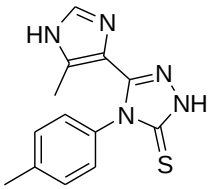

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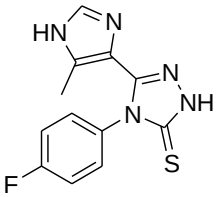

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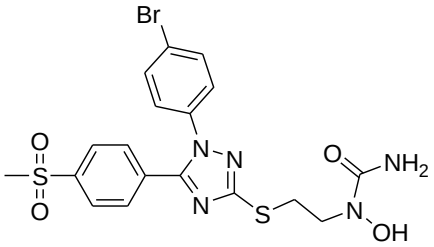

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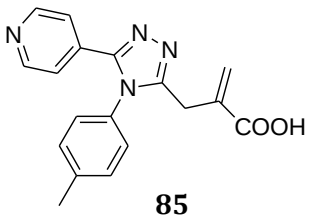

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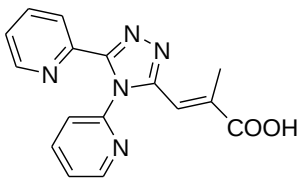

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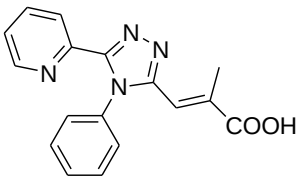

87

Paprocka *et al.* have reported the synthesis and anti-inflammatory activity of new 1,2,4-triazole derivatives comprising of a methacrylic acid moiety. The influence of the reported compounds on inflammation, the level of cytokine production and the proliferation of human peripheral blood mononuclear cells (PBMC) were experimentally evaluated. The triazoles obtained showed anti-proliferative activity and diverse effects on cytokine production. Compounds **85**, **86** and **87** exhibited the strongest anti-inflammatory potential and comparable effects with ibuprofen (Paprocka *et al.*, 2015).