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Journal of Chemical and Pharmaceutical Research, 2017, 9(11):132-144

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Overview of Mercapto-1,2,4-Triazoles: Synthesis and Pharmacology Comprehensive Review on Chemistry and Pharmacology of Mercapto-1,2,4-Triazoles

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ABSTRACT

The history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. After World War II, there was an enormous explosion research in the field of heterocycles. About one half of over six million compounds recorded in Chemical Abstracts are heterocyclic. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry.

Keywords: Heterocyclic compounds; Mercapto-1,2,4-triazoles

INTRODUCTION

Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. Since in heterocycles non-carbons usually are considered to replace carbon atoms, they are called heteroatoms e.g. different from carbon and hydrogen. A ring with only heteroatoms is called homocyclic compound and heterocycles are the counterparts of homocyclic compounds. Thus incorporation of oxygen, nitrogen, sulfur or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compound. These structures may comprise either simple aromatic rings or non-aromatic rings. The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or depolymerized. Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in general, stable. Those with two heteroatoms are more likely to occur as reactive intermediates. Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthrocynines and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life (Figure 1). Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs. In short, heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties and applications of heterocycles [1].

Some noteworthy developments had been done in heterocyclic chemistry [2]:

1818: Brugnatelli isolates alloxan from uric acid.
1832: Dobereiner produces furfural by treating starch with sulfuric acid.
1834: Runge obtains pyrrole by dry distillation of bones.
1906: Friedlander synthesize indigo dye, allowing synthetic chemistry to displace a large agricultural industry.
1936: Treibs isolates chlorophyl derivatives from crude oil, explaining the biological origin of petroleum.
1951: Chargraff's rules are described, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code.
Here some heterocycles are given follow:

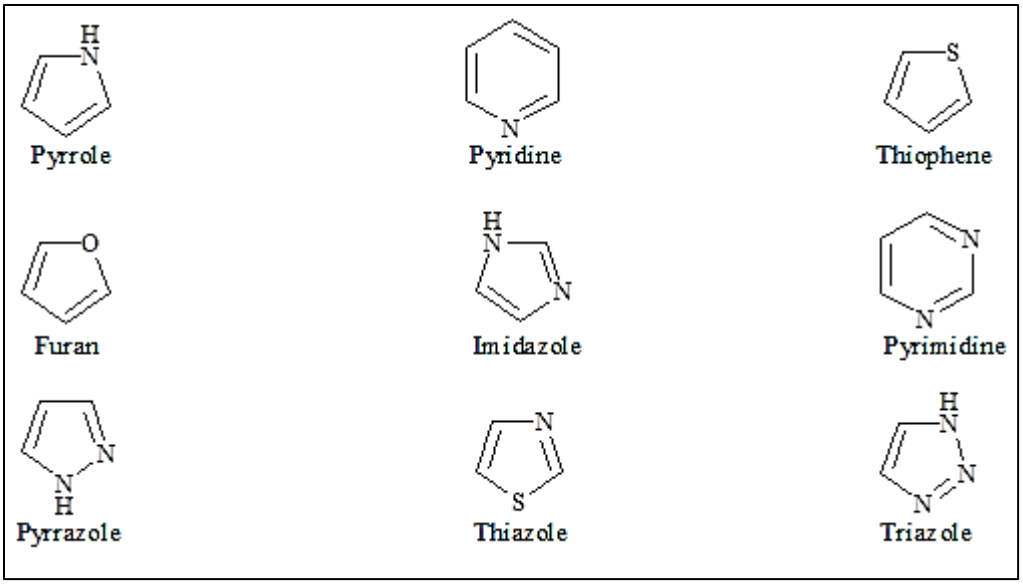


Figure 1: Heterocycles structures

1,2,4-Tiazole moiety has found usally in the various naturally obtained products [3,4] and the synthesis of the components containing 1,2,4-triazole moiety has many advantages mainly due to their diverse biological activities in pharmaceutical and agrochemical fields [5-11]. A very wast variety of 1,2,4-tiazole derivatives having antibacterial [5,6], antifungal [5,7], Antimycobacterial [8,12], antiviral [5], anti-inflammatory [6], anticonvulsant [7], antidepressant [8], antitubercular, antitumoral, antihypertensive, analgesic, enzyme inhibitor, hypoglycemic [9], sedative [10], hypnotic [11], antiparasitic [12], herbicidal [13], insecticidal [14,15] and plant growth activities. So, many drugs which containing triazole moiety had been already used in formulation of medicament, like Alprazolam (anxiolytic agent, tranquilizer), Anastrozole, Letrozole, Vorozole(antineoplastics, nonsteroidal competitive aromatase inhibitors), Estazolam (hypnotic, sedative, tranquilizer), Etoperidone (antidepressant), Fluconazole, Itraconazole, Terconazole (antifungal agents), Ribavirin (antiviral agent), Benatradin (diuretic), Rilmazafon (hypnotic,anxiolytic, used in the case of neurotic insomnia), Nefazodone (antidepressant, 5-HT2A antagonist), Rizatriptan (antimigraine agent), Trapidil (hypotensive), Trazodone (antidepressant, anxiolytic, selectively inhibits central serotonin uptake) and Triazolam (sedative and hypnotic) [3]. Schiff bases are most important class of organic compounds which have large utilization in many biological aspects [16]. Many Schiff bases containing 1,2,4-triaole moiety exhibit antibacterial, antifungal [17] and antitumoral activities [18,19].

Chemistry

Triazole is one of a class of organic heterocyclic compounds containing a five-membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at nonadjacent positions. Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$. The two isomers are: 1,2,4-Triazole and 1,2,3-Triazole (Figures 2 and 3).

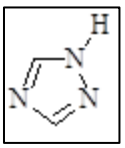


Figure 2: 1,2,4 triazole

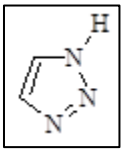


Figure 3: 1,2,3 triazole

1,2,4-Triazoles can be prepared synthetically using the Einhorn-Brunner reaction in which an imide is reacted with an alkyl hydrazine to form a mixture of isomeric (Figure 4).

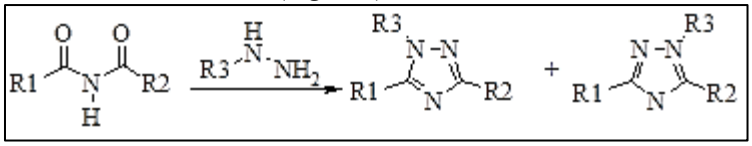


Figure 4: Einhorn-Brunner reaction, R1,R2,R3= alkyl or aryl

Physical Properties

The simplest member of the triazole family is triazole itself, white to pale yellow crystalline solids with a weak characteristic odor; soluble in water and alcohol, melts at 120°C, boils at 260°C.

Mercapto Triazole

The incorporation of mercapto group at third or fifth position of triazole moiety form mercapto triazole moiety. As the mercapto triazole is derivative of triazole moiety it possessed various biological activities and it having very broad spectrum activity. It possessed anti-inflammatory [20-27], anti-microbial [19,28,29], anti-fungal and anti-bacterial [22,30-32], anti-tubercular [33-35], anti-HIV [36,37], cytotoxic activity [38], anti-tumoral [39] and other miscellaneous activity like plant growth regulating activity etc. [40]. So, the mercapto triazole having potent activity and having broad spectrum of biological activity. The mercapto triazole having two unstable canonotical form which are continuously converted into each other (Figure 5).

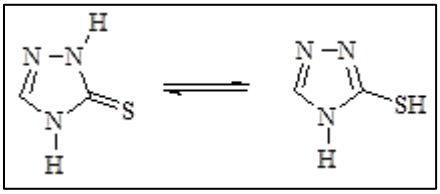


Figure 5: Mercapto trimazole

Preparation of Mercapto Triazole

Synthesis of 5-aryl-3-mercapto-1,2,4-triazoles [19]:

Reaction of 4-acylthiosemicarbazide with KOH 10% under reflux, followed by the acidification with concentrated hydrochloric acid (Figure 6).

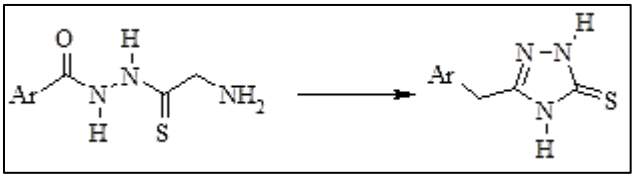


Figure 6: Synthesis of 5-aryl-3-mercapto-1,2,4-triazoles

Synthesis of 3-(3-Methoxyphenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione [20]:

A solution of 0.01 mol of 1-(3-methoxybenzoyl) thiosemicarbazide in 100 mL 2 N NaOH is reflux 3 hrs, cool it to room temp. Acidify to pH= 4 obtain. Precipitate is filter off and recrystalize from 2-propanol (Figure 7).

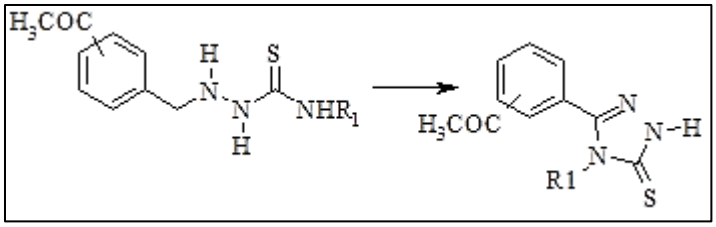


Figure 7: Synthesis of 3-(3-Methoxyphenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione

Synthesis of 3-((5,6,7,8,-Tetrahydronanphthalen-2-yl)oxymethyl)4-amino-5-mercapto-1,2,4-triazoles [21]:
A mixture of thiocarbohydrazide (0.1 mol) and (5,6,7,8-tetrahydro Naphthalen-2yl) oxyacetic acid heat in an oil bath at 160-170°C for 2 h. The fused mass thus obtain is disperse with hot water to obtain the triazole (Figure 8). The product is recrystallize from methanol; 135°C.

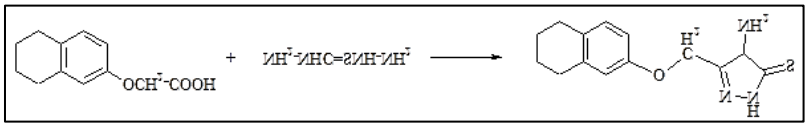


Figure 8: Synthesis of 3-((5,6,7,8,-Tetrahydronanphthalen-2-yl)oxymethyl)4-amino-5-mercapto-1,2,4-triazoles

Synthesis 4-amino-3-mercapto-5-((1H-indol-3-yl) methyl)-1,2,4-triazole [22]:
Equimolar mixture of thiocarbohydrazide (0.1 mol) and 1H-indol-3-acetic acid is heat in an oil-bath at 160-170˚C for 2h. the fused mass thus obtain is disperse with hot water to obtain the triazole (Figure 9). The product is recrystalise from methanol.

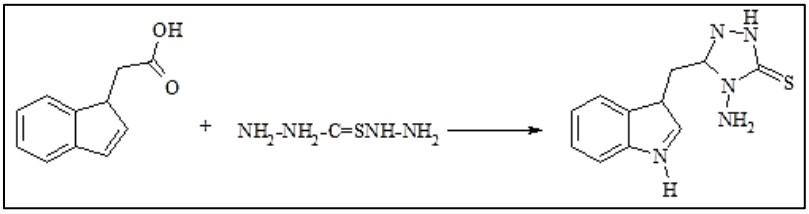


Figure 9: Synthesis 4-amino-3-mercapto-5-((1H-indol-3-yl) methyl)-1,2,4-triazole

Preparation of 5-(2-napthyloxymethyl)-4-substituted-1,2,4-triazole-3-thiones [23]:
1-(2-Napthyloxyacetyl)-4-substituted thiosemicarbazides (10 mmol) is reflux for 8 h in 40 ml 1 N aqueous sodium hydroxide. The mixture is acidifying to pH 2 and the precipited product is filter off, washe with water and crystalise from suitable solvents (Figure 10).

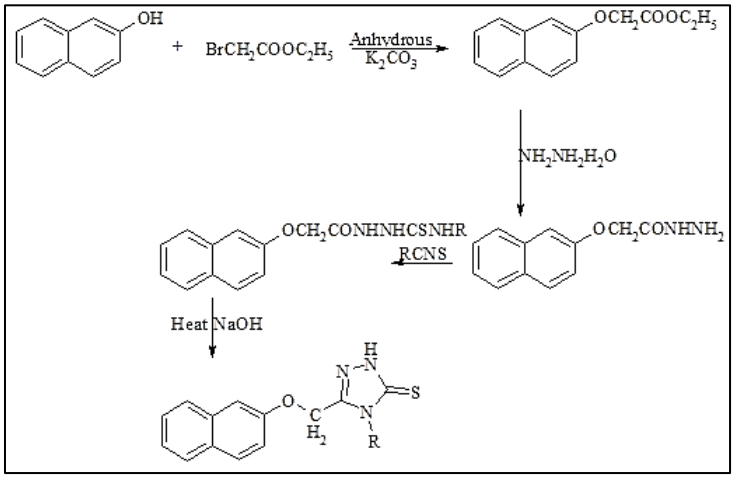


Figure 10: 5-(2-napthyloxymethyl)-4-substituted-1,2,4-triazole-3-thiones

Bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) alkanes [24]:

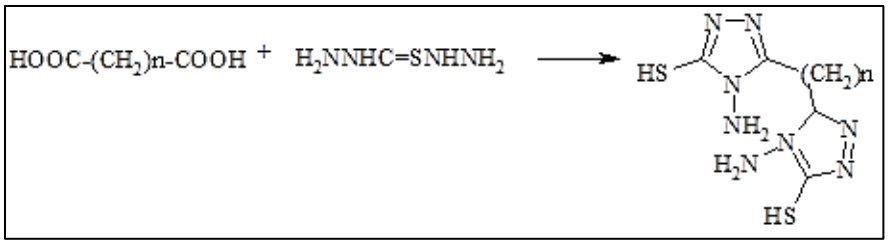


Figure 11: Bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) alkanes

A mixture of dicarboxylic acid (0.01 M) and thiocarbohydrazide (0.02 M) contained in a flat-bottomed flask heated in an oil bath until the contents will melt. The mixture is maintain at this temperature for 15 ± 20 min (Figure 11). The product will obtain on cooling it will treat with dilute sodium bicarbonate solution to remove the unreacted dicarboxylic acid if any. It wash with water and collect by filtration. The product is recrystallize from a mixture of dimethylformamide and water to afford the title compounds 3a ± c. 3a: bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)methane, m.p. 278 ± 280°C, yield 80%; 3b: bis-(4-amino-5 mercapto-1,2,4-triazol-3-yl)ethane, m.p. 242±244°C, yield 82%; 3c: bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)butane, m.p. 244 ± 246°C, yield 83%.

Review Based on Mercapto Triazole

The 1,2,4-triazole skeleton exists in many natural and synthetic biologically active materials and its derivatives are applied in various pharmaceutical and biochemical fields. A very wast variety of 1,2,4-tiazole derivatives having antibacterial, antifungal, Antimycobacterial, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antitubercular, antitumoral, antihypertensive, analgesic, enzyme inhibitor, hypoglycemic, sedative, hypnotic, antiparasitic, herbicidal, insecticidal and plant growth activities etc.

Anti-inflammatory Activity

Manikrao et al. discussed in preliminary testing of newly synthesized compound was tested for it anti-inflammatory activity. They revealed that compound (1) had showed inhibition of rat paw edema ranging from 25.94-44.44% after 90 min. it had showed equipotent activity compared to standard drug. More ever they revealed that substituting of phenyl ring with chloro, nitro, methyl and methoxy group into phenyl ring and replacement of phenyl nucleus by benzyl it was enhanced the anti-inflammatory activity (Figure 12). Among that triazoles compound (2) and (3) was more potent than other triazoles. They concluded that substitution at *para* position is more potent than the *ortho* and *meta* position [25].

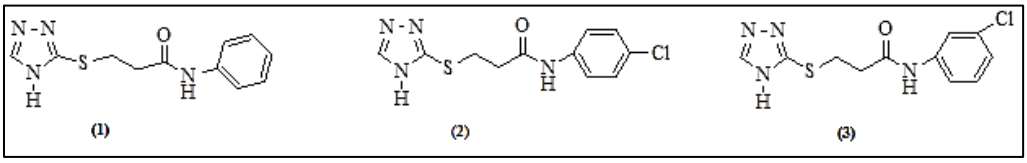


Figure 12: Triazoles

Birsen et al. revealed that the on preliminary testing all compounds were administered at 20 & 80 mg/kg doses it were possesed not more than 20% inhibition (Figure 13), but these (4-8) compounds were again tested at 10 & 40 mg/kg doses which possesed very good anti-inflammatory activity by induce gastric lesions in some mice which reduced prostaglandin synthesis [26].

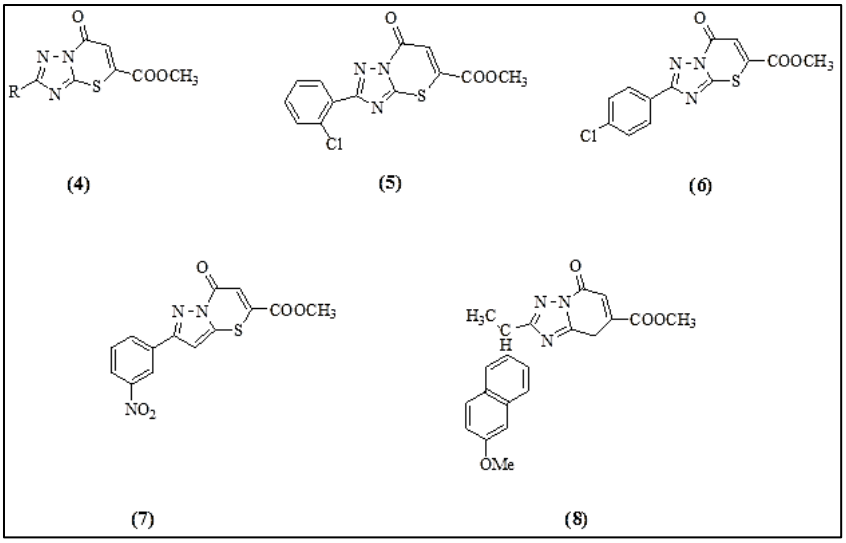


Figure 13: Anti-inflammatory activity

Palaska et al. discussed that 5-(2-napthyloxymethyl)-4-methyl-1,2,4-trazole-3-thione and 5-(2-napthyloxymethyl)-4-ethyl-1,2,4-trazole-3-thione which showed good anti-inflammatory activity with 60.62 ± 8.55 and 51.41 ± 3.98% CPE inhibition respectively (Figure 14). Where (9,10) was possessed ($32.43 \pm 3.15^{*}10^{5}/cm^{3}$) were extremely potent in inhibiting PMNL production compared with control and reference compounds (control: 122.50 ± 4.10, phenylbutazone: 53.27 ± 1.71, indomethacin: $68.80 \pm 1.80^{*}10^{5}/cm^{3}$) [20].

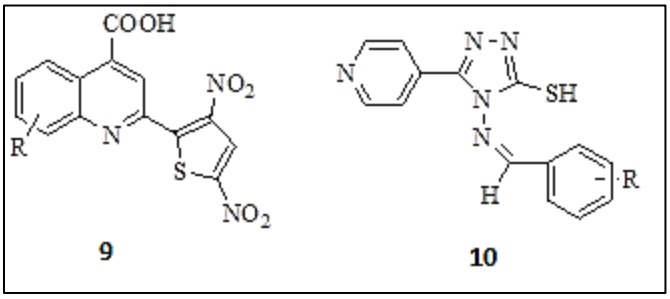


Figure 14: CPE inhibition

Turan-Zitouni et al. revealed that compound (11), (12), (13) possesed considerable analgesic activity with 65%, 56%, 67% respectively (Figure 15). They had compared those compound with aspirin 55%.With respect to SAR introduction of a chloride atom into the phenyl ring at the 6-position of the fused heterocycle led to reduction of the analgesic activity [21].

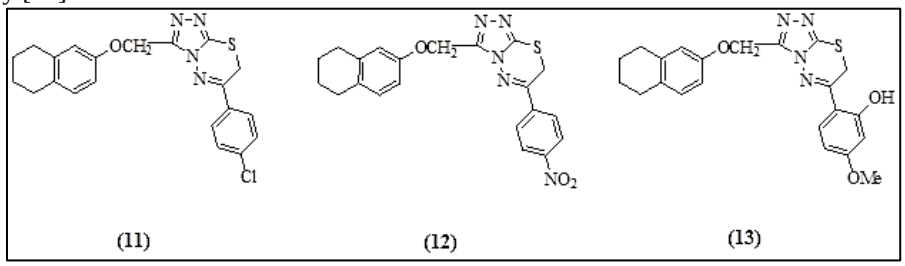


Figure 15: SAR introduction of a chloride atom

Tozkoparan et al. exhibited that preliminary investigesion showed that analgesic and antiinflammatory activity of 5-aryl-3-alkyl-thio-1,2,4-triazoles can be significantly modified by substitution on phenyl ring and sulfur or oxodation of sulfur to sulfone. Among the all synthesized compounds (14), and (15) having most prominent and consistant activity with no ulcerogenic effect (Figure 16). The compounds (14) and (15) having 2-chlorophenyl and 4-

chlorophenyl exhibited the highest analgesic and antiinflammatory activity with inhibition value 54.9%, 59.5% and 37.9%, 40.2% respectively, at 50 mg/kg dose level [23].

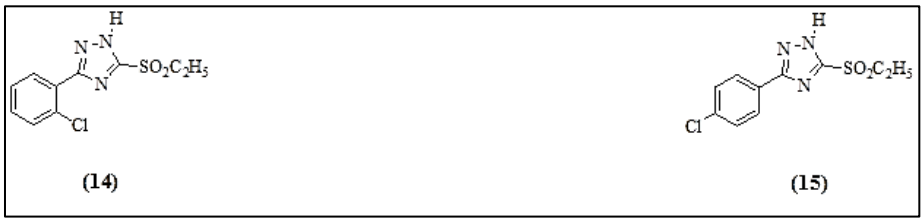


Figure 16: Analgesic and antiinflammatory activity

Labanauskas et al. they had studied anti-inflammatory activity using carrageenin- and bentonite-induced paw edema in rats. The comparision of paw volume measured with an electric onkograph immediately before 1, 2, 3 and 5 hrs after injection of carrageenin or bentonite (Figure 17). The compounds (16,17) are more active than ibuprofen. The acute toxicity of these compounds was less than acute toxicity of acetyl salicylic acid and it also exhibited very less toxicity than ibuprofen [24].

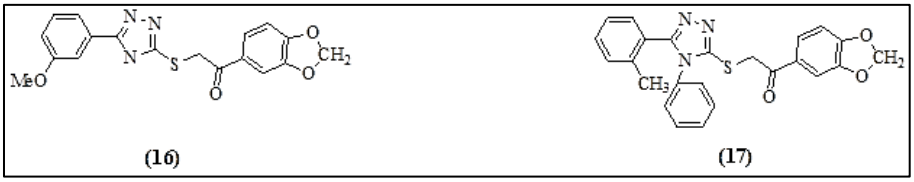


Figure 17: Acute toxicity of acetyl salicylic acid

Kalluraya et al. exhibited that the compound having dinitro chinchoninic acid had good anti-inflammatory activity than chinchoninic acid (Figure 18) [27].

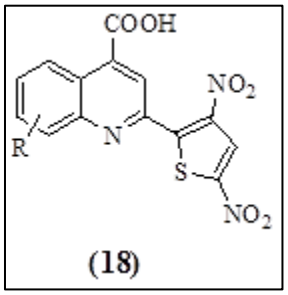


Figure 18: Anti-inflammatory activity dinitro chinchoninic acid

Antimicrobial Activity

Hamid Khanmohammadia et al. discussused (Figure 19). The Activity of the compound (19) possesed antimicrobial activity due to 4-Cl, 4-Me, 4-MeO, 2,4-di-Cl and 2-OH substituted in phenyl ring which gives good inhibition against *S. aureus* as compared to penicillin zone of inhibition. The anti *S. aureus* activity of compounds 4-Cl and 2-OH substituted with zone of 13 mm and 18 mm, respectively [28].

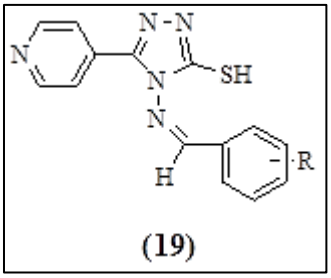


Figure 19: Antimicrobial activity, R`= 4-Cl, 4-Me, 4-MeO, 2,4-di-Cl, 2-OH

Shivarama Hollaa et al. discussused (Figure 20). The activity of the compounds (20) and (21) due to 2-Cl, 4-NO_2 particularly showed very good antimicrobial activity against *B. subtilis* [19].

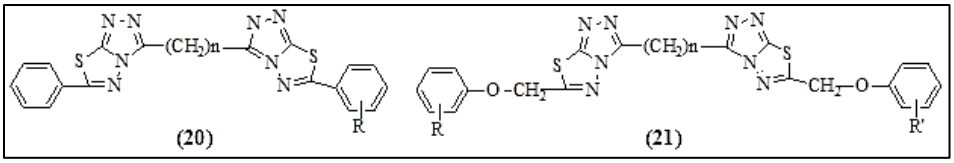


Figure 20: B.subtilis, R= 4-Cl, n = 4, R= 2-Cl, n=2

Kumar et al. had been discussed that all the newly synthesized compounds displayed variable inhibitory effects on the growth of the tested bacteria (Gram positive and Gram-negative) and fungus *Candida* albicans and *Candida tropicalis* (Figure 21). They also revealed that compounds (22), (23) and (24) exhibited broad-spectrum antibacterial profile against the tested three organisms. Compound (22) exhibited highest antifungal activity against *Candida albicans* (MIC 2 μg/mL) and *Candida tropicalis* (MIC 8 μg/mL). It had also observed that replacement of hydrogen of by bromine increase the biological activities [29].

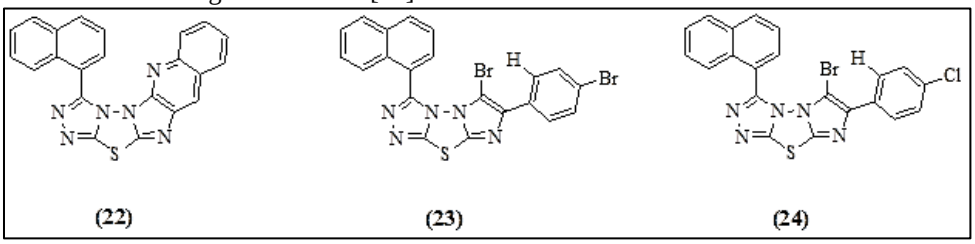


Figure 21: Compounds displayed variable inhibitory effects on the growth of the tested bacteria

Antifungal and Antibacterial Activity

Collin et al. revealed that antifungal activity of synthesized compounds (25) and (26) were determined by the disk diffusion method, using following yeast strains: C. *albicans, C. tropicalis* and *Saccharomyces cerevisiae.* They studied SAR might be interpreted like this: overall electron density present on both the aromatic and heterocyclic rings seems to be responsible for the activity (Figure 22). They also revealed that attachment of an alkylnitrile group to thiol function enhanced the antifungal activity. For the antimicrobial activity SH and NH_2 group should be free in form [30].

Figure 22: Antifungal activity of synthesized compounds

Kaplancikli et al. discussed that when MICs were recorded of the compounds for anti-fungal and anti-microbial activity, the compound (27) possessed similar antifungal activity against *C. globrata,* when it was compared with ketoconazole. When all synthesized compounds were compared with chloramphenicol, compound (28) gives similar activity against *S. aureus* (Figure 23). Among these compounds compound (27) including the methyl on phenyl showed significant antifungal activity [22].

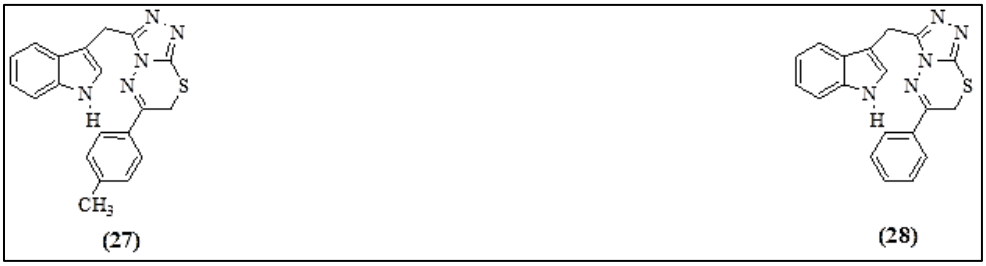


Figure 23: Anti-fungal and anti-microbial activity MICs

Isloor et al. had done antibacterial and antifungal screening revealed that some of the tested compound showed good inhibition at 3 μg/ml concentration. The antibacterial testing indicated the compound (29) showed exellent activity

againts all tested bacterial strains, *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa.* The MIC of compound (30) having p-chloro substitution showed maximum inhibition againts all the tested microorganisms (Figure 24). The antifungal sreening revealed that among the tested compound (29), (30) possesed very good activity againts fungal strins *Candida albicans* at 3 µg/ml concentration [31].

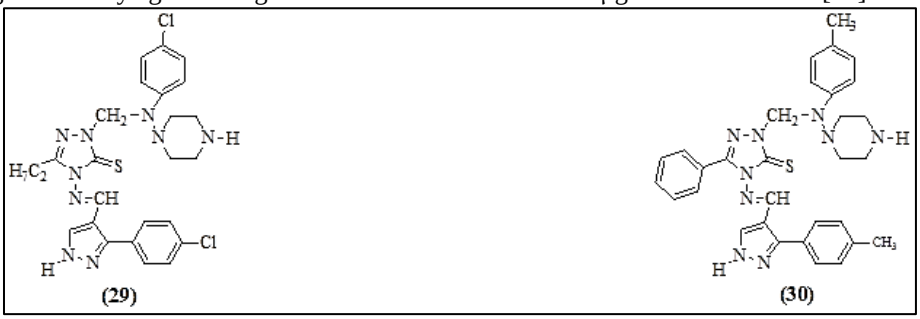


Figure 24: Antibacterial and antifungal screening

Ulusoy et al. discussused (Figure 25). The activity of the compound (31) due to incorporating the 5-nitro-2-furyl moiety which stressed the importance of this residue in antibacterial action [32].

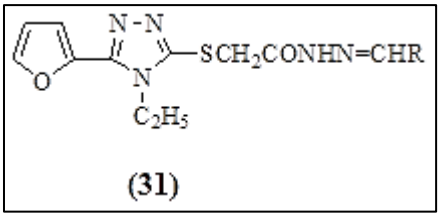


Figure 25: 5-nitro-2-furyl moiety, R=5-nitro-2-furylethenyl

Anti-tubercular Activity

Bayrack et al. revealed that preliminary testing possesed that some compound exhibited activity against *Mycobacterium smegmatis* that is atipic tuberculosis factor (Figure 26). According to the result of test that concluded that conversion of carbothiomide moity into 5-mercapto-1,3,4-oxadiazole nucleus and further ring fusion into compound (32) afforded an increase in the anti-tubercular and antimicrobial activity [33].

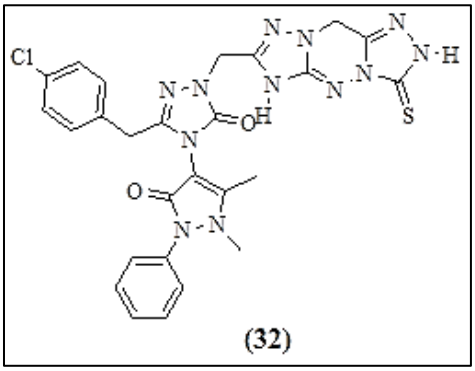


Figure 26: 5-mercapto-1,3,4-oxadiazole nucleus and further ring fusion

Klimesova et al. revealed that antimycobacterium assessment triazole derivatives possess only a moderate activity. The MIC value generally within range of 32>1000 µmol/l. By comparing their MIC value with INH, triazoles derivatives less active against *M. tuberculosis* 331/88 and *M. kansasii* 6509/96 than INH. They also revealed that antimycobacterial activity is connected with benzylsulfanyl group on triazole ring. The substitution on phenyl ring it has been observed that electron withdrawing group reduce the MICs values. So compounds 3-(3,5-dinitrobenzylthio)-4H-1,2,4triazole (33), 3-(2,4-dinitrobenzylthio)-4H-1,2,4triazole (34) most active compound their activities ranging from 32 to 500 µmol/l. So the triflurometlhyl group possess the more active derivatives. The thioamide derivatives the 4-substituted derivative (35) showed good activity (Figure 27). The presence of H atom at 4 positions necessary for receptor interaction [34].

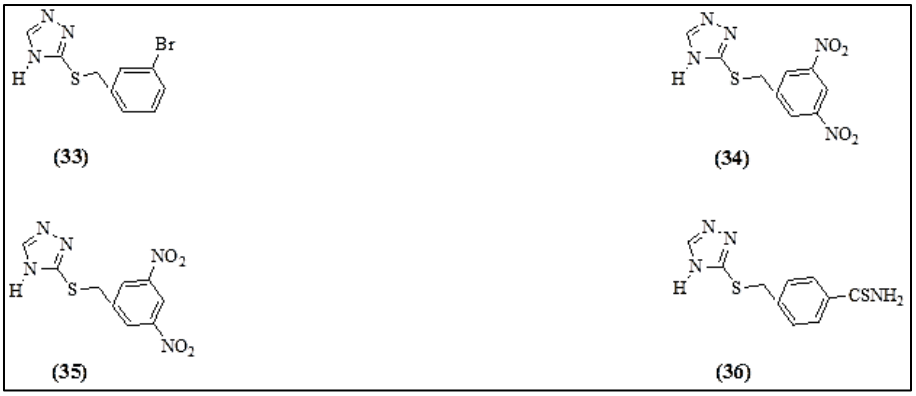


Figure 27: Receptor interaction

Shiradkar et al. synthesised compounds were tested for their antitubercular activity against *M. tuberculosis* $H_{37}RV$. The antituberculosis activity had been carried out tuberculosis antimicrobial acquisition and coordinating facility, USA (Figure 28). The primary activity has been carried out using CABTEc 460 radiometric system [37-39]. The data had been compared with standard drug Rifampin at 0.03 mg/mL concentration with 97% inhibition effect [35].

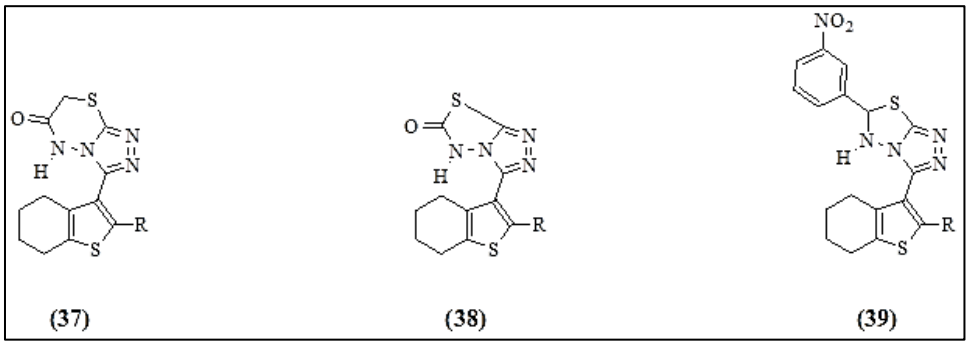


Figure 28: Antitubercular activity

Anti HIV Activity

Pomarnacka et al. discussused compound (40) had showed moderate activity (IC_{50}>200 µM, EC_{50}=28.8 µM, TI_{50}>6.94) Activity of the compound due to phNHCO particularly showed very good anti-HIV activity (Figure 29) [36].

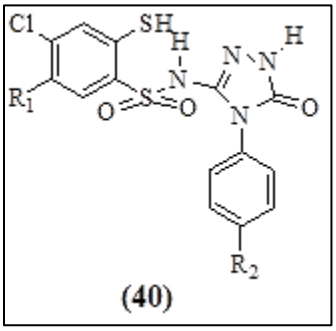
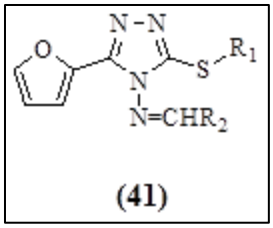


Figure 29: Moderate activity R1= phNHCO, R2= H

Liu et al. revealed that Compound (41**)** was found to be the most active inhibitor against HIV^{-1} replication in cell culture (EC50=12 µM) and against HIV^{-1} reverse transcriptase (IC50=43.5 µM) (Figure 30), which provided a good lead for further optimization on structure based molecular modification [37].

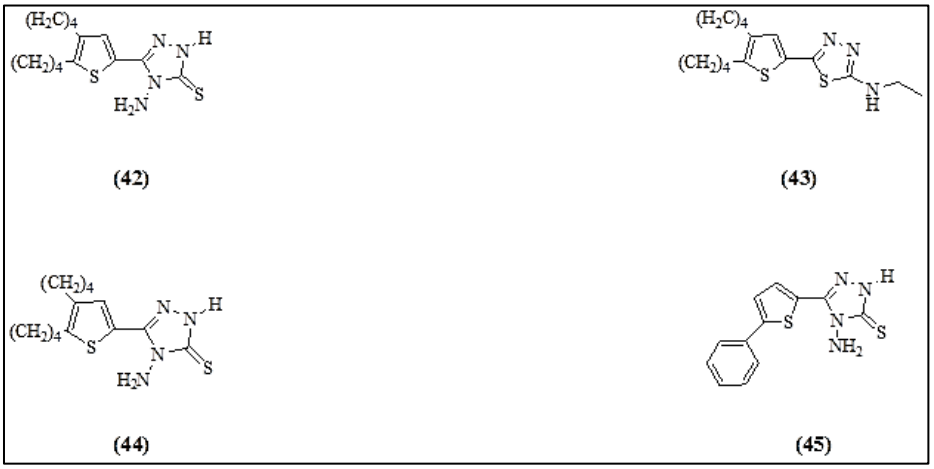


(41)

Figure 30: Active inhibitor against HIV-1 replication in cell culture, R1= phenyl, R2= 3,4-dimethoxyphenyl

Cytotoxic Activity

Anelia et al. performed the exclusive trypan blue test for estimation of cytotoxicity with compound (42), (43), (44), on thymocytes and blood lymphocytes derived from sexually mature hamsters. They showed IC_{50} values were in the range of 0.46-1.0 × 10^{-6}. With respect to blood lymphocytes the most cytotoxic compound was compound (44), its IC_{50} value was 0.012 µM. The PFC, LIF and the migration tests studied indicated that the compound exhibited a general stimulating effect on the B-cells response (Figure 31). The compound (45) showed highest value number of PFC, which had affinity to supress 29 times than that of the controll cells [38].



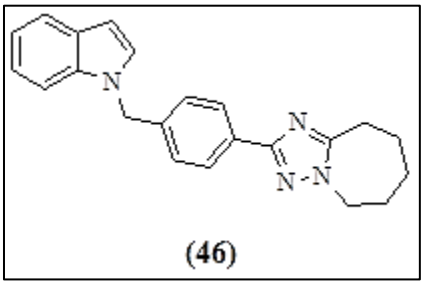
(42) **(43)**

(44) **(45)**

Figure 31: Exclusive trypan blue test for estimation of cytotoxicity with compound

Anti Tumorial Activity

Mausoudi et al. tested all compound for antitumor activity acording to NCL *in vitro* protocols (Figure 32). They were evaluated for three cancer types: breast, lung and CNS cancer. Whereas compound (46) was tested against 60 human tumor cell lines, at five, 10-fold dilutions from a maximum of 10^{-4} M. Among all tested compound only compound (46) exhibited marked activity against colon (HCC-2998), and melanoma (UACC-257) cancers, with low percentage growth of log_{10} concentration= -2.0 at 10^{-5} and -83 at 10^{-4} M, respectively. It also possesed good activity against individual cell lines melanoma (LOX IMVI), ovarian (OVCAR-3); prostate (PC-3) and breast (NCI/ADR-RES) cancer with log_{10} values of -69, -62, -64, -68 respectively [39].



(46)

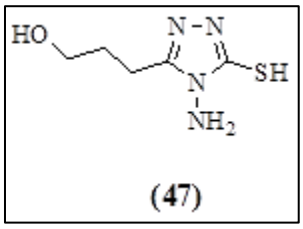
Figure 32: Compound for antitumor activity acording to NCL *in vitro* protocols

Miscllenius Activity

Plant growth regulating activity:

Zhang et al. showed that compounds 39, 40 on sprouting of wheat and radish seeds have been investigated. After treating with solutions of 100 μg/mL and 10 μg/mL of the title compounds for 7 days, the germination percentages have been determined, and from the difference in length between stems and radicles of seedlings treated with the title compounds and those treated with distilled water, the plant growth regulating activities have also been calculated. A positive result represents a growth increase (Figure 33), whereas a negative result implies an inhibition [40]:

$$\text{Effect} = \frac{\text{The length of sample's stem/radicle} - \text{the reference's length}}{\text{The length of reference's stem/radicle}} \times 100\%$$



(47)

Figure 33: Compounds 39, 40 on sprouting of wheat and radish seeds

Other application of mercapto triazole:

- The mercapto triazoles having very wast application as pharmacological application as described above, It having also use as de masking agents.
- It also using in lipidperoxidation.
- Plant growth regulators regulation in seed germination [40].
- It having widespread use as corrosion inhibitor agents.
- It having anti-consultant activity [41].

CONCLUSION

About one half of over six million compounds recorded in Chemical Abstracts are heterocyclic. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.

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