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Review Article

TRIAZOLES - IMPINGING THE BIOACTIVITIES

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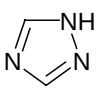
ABSTRACT

Efforts have been made in the last few decades to synthesize a different new heterocyclic compound along their derivatives which were evaluated for their various activities as antimicrobial, antiviral, antitumor, anticonvulsant and many more. The triazole moiety seems to be very small but its diversity in biological activity alone, along and as various derivatives had extraordinarily fascinated the scientists. This is a focused review on the triazole moiety and its amazingly evaluated derivatives which are under development and are sure to impinge the stream of medicinal chemistry.

Keywords: Triazole, antimicrobial, antiviral, antitumor, anticonvulsant activity

INTRODUCTION

Triazoles are the class of heterocyclic compounds[1] which are under study since many a years. Its diversity in showing the pharmacological activities is mind blowingly identified well by the medicinal chemists. Triazole, with many a compounds as incorporating with other heterocyclic nucleus, hydrazides[2], substituted triazoles[3], β-agonist[4] or incorporated with antibiotics[5] are some of great uses which fascinates the chemists to continue research on it and find out more hidden potentials of this nucleus.



1,2,4-TRIAZOLE

1,2,3-TRIAZOLE

The pharmacological properties shown by this moiety (Fig.1) includes Phosphodiesterases enzyme inhibitor[6], hepatitis C[7],anti-inflammatory[8], antimicrobials[9], β-lactamase inhibitors[10], fungicidal[11], insecticidal[12], antitumor[13], anticonvulsant[14], antidepressant[15], plant growth inhibitor[16]. Further sunthesis of various compounds as 1,2,4-triazole-C-nucleoside[17], acyclic C-nucleosides[18], pyrimidines[19], D-manno-pentitol-1-yl-1,2,4-triazoles[20], benzotriazoles[21], indoles[22], quinolones[23], triazolo thymidines[24] are in record.

Fig.1: Pharmacological activities of triazole moiety.

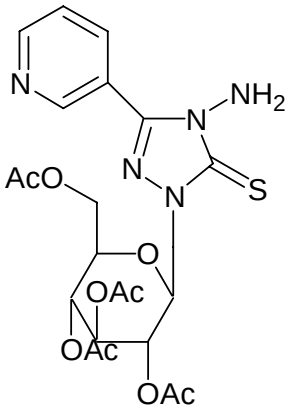
So here the spectrum of activity of this triazole nucleus is being reviewed, among the activities shared are antibacterial, antiviral, antifungal, anticonvulsant, antitumor, anti-inflammatory and antituberculosis.

Antibacterial activity

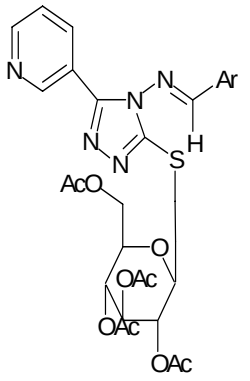
Day by day medicinal chemistry is towards its advancement, many antibiotics are now chemically modified from original compounds present naturally e.g. beta lactams[26] . Many of them are still obtained naturally named as amino glycosides and a lot more are synthetically derived as sulfonamides[27], the quinolones and the oxazolidinones. Moreover they are classified in two types based on their mode of action as bactericidal agents and bacteriostatic agent[28].

Among various triazole derivatives, base and sugar modified nucleoside derivatives reflect a potent anti-microbial activity resulting in its application in the chemotherapy of cancer and viral infection. The inhibitory effect of N-glucosides **(1), (3)** and those of S-glucosides **(2)** are manipulated by changing the position of substituent on aromatic ring.

The compound resulted higher inhibitory activity against *Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum, Staphylococcus aureus, Pseudomonas aeruginosa, and Bacillus subtilis*[29].

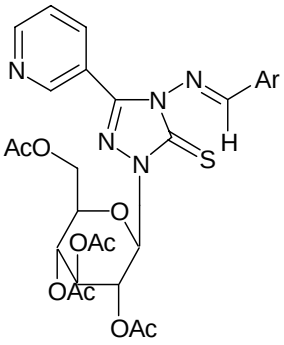


(1)



2	Ar
a	C_6H_5
b	$4\text{-}CH_3\text{-}C_6H_4$

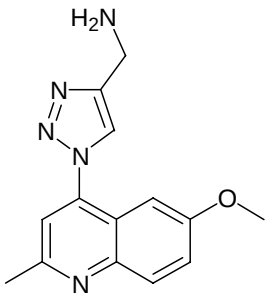
(2)



3	Ar
a	$4\text{-}CH_30C_6H_4$
b	$4\text{-}ClC_6H_4$

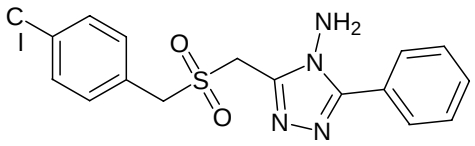
(3)

The sequential one pot synthesis assisted in cyclisation of resulting active compound named 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1H-1, 2, 3-triazol-4-yl] methanamine **(4)** which was a potent antimicrobial compound against all pathogenic strains. Active piperazine nucleus in this compound is responsive for this activity[30]



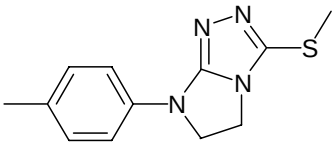
(4)

3-(4-Chlorobenzylsulfonylmethyl)-5-(2-chlorophenyl)-4H-1,2,4-triazol-4-amine **(5)** was synthesized and potent antimicrobial activity was evaluated. The compound also exhibited cytotoxic activity[31].



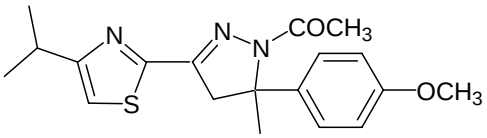
(5)

Condensation product 1-Arylimidazolidine-2-thiones directed the synthesis of 7-(4-methylphenyl)-3-methylthio-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazole **(6)** by a series of intermediate steps which showed a profound antimicrobial activity . The activity was superior to reference drug ampicillin *in-vitro*[32].



(6)

Novel 2-substituted-5-[isopropylthiazole] clubbed1,2,4-triazole (**7), (8)** were synthesized as potent antimicrobial agent. The activity was shown by the compound named 4-(4-Dimethylaminebenzylideneamino)-5-(4-isopropylthiazol-2-yl)-4H-1, 2, 4-triazole-3-thiol[33].



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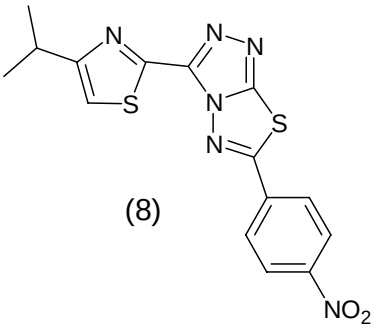
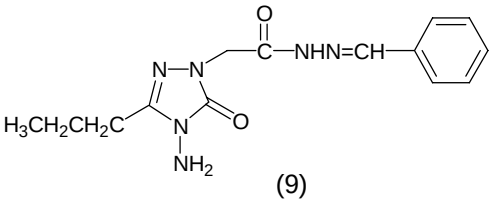


(8)

Antimicrobial activity of some newly synthesized compounds were evaluated and resulted in potent activity against many microorganisms . The compounds **(9), (10), (11), (12)** prepared belongs to 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo- [1,2,4] triazole derivatives[34].



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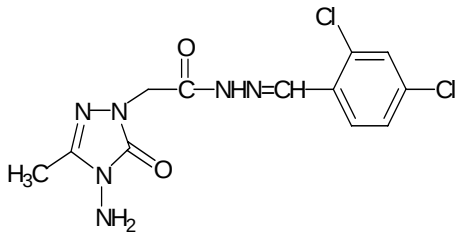

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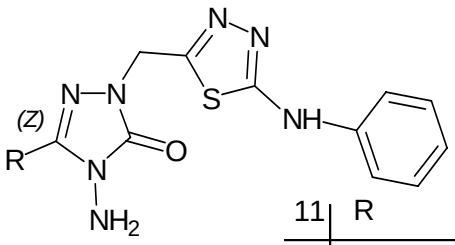
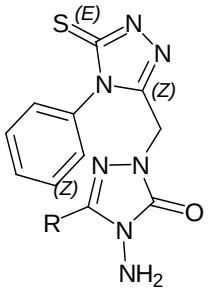


11	R
a	CH_3
b	$CH_2C_6H_5$
c	C_6H_5

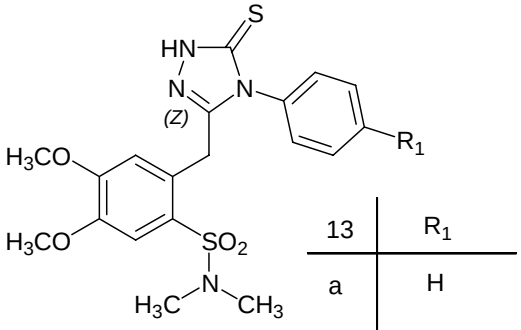
(11)



12	R
a	CH_3
b	$CH_2C_6H_5$

(12)

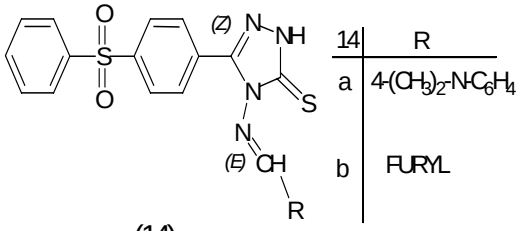
Compound from series of 5-[2-(substituted sulfamoyl)-4,5-dimethoxy-benzyl]-4aryl-s-triazole-3-thiones **(13)** were prepared and resulted in antimicrobial activity equipotent to streptomycin, giving an exception against *Enterobacter cloacae* and *Salmonella* species. The synthesized compounds were better than chloramphenicol. Moreover Gram-ve strains were sensitive rather than Gram +ve, against the activity[35].



13	R_1
a	H
b	Cl

(13)

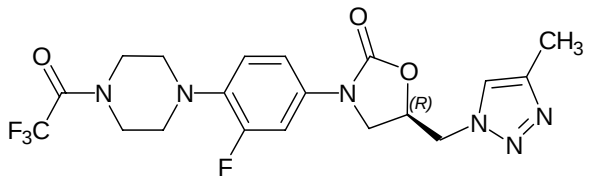
In the synthesis of new compounds containing diphenylsulfone moiety **(14),** the results revealed that incorporation of NH_2 functional group in azomethine function made a rise in antibacterial activity against *B.subtillis, P.aeruginosa* in comparison to chloramphenicol[36].



14	R
a	4-$(CH_3)_2$-N-C_6H_4
b	FURYL

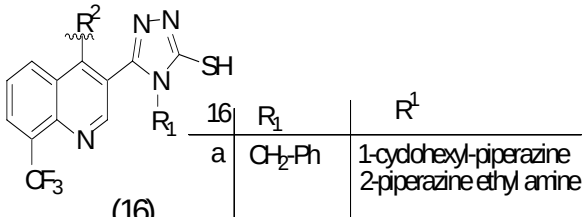
(14)

Another series of compounds bearing 5-(4-methyl-1,2,3-triazole)methyl group at C5 of oxazolidine ring were evaluated, compound containing substitution of isopropylcarbonyl group at C4 position of piperazine resulted in most active compound **(15)** striking gram +ve strains. Taking linezolid and vancomycin as standard compounds, evaluation of this new series of were performed and the compounds showed a potent antimicrobial activity. The variance of the activity depended upon the presence of 4-methyl-1,2,3-triazole moiety within the acyl-piperazine having analogues resulted in raised protein binding efficiency and lowered antimicrobial activity against *Streptococcus pneumonia* strains[37].



(15)

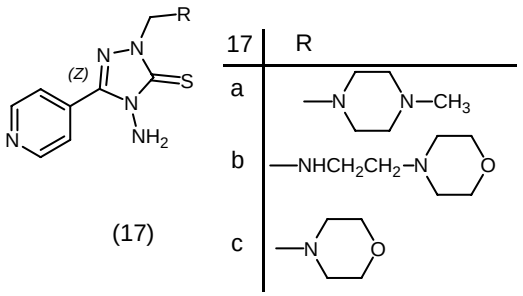
Microwave assisted reaction, involved in nucleophillic substitution reaction, resulted in reduced reaction time and improved yield. Quinoline derivatives 5-(4-amino substituted-8-(trifluoromethyl) quinolin-3-yl)-4-(un) substituted phenyl-4H-1, 2; 4- triazole-3-thiols were synthesized by this technique and were evaluated for antimicrobial activity. SAR of **(16)** reveals that presence of CF_3, active amine at 8 and 4 position of quinoline respectively, also other bioactive moieties as e.g. –SH, -$CH_2CH_2OCH_3$ and Ph moieties at triazole ring were shown responsible for the potent antimicrobial activity[38].



16	R_1	R^1
a	CH_2-Ph	1-cyclohexyl-piperazine 2-piperazine ethyl amine
b	Ph	piperidine-4-propanol 1-cyclohexyl piperazine 2-piperazine ethyl amine
c	CH_2CH_2OMe	piperidine-4-propanol 1-cyclohexyl piperazine 4-ethyl piperazine

(16)

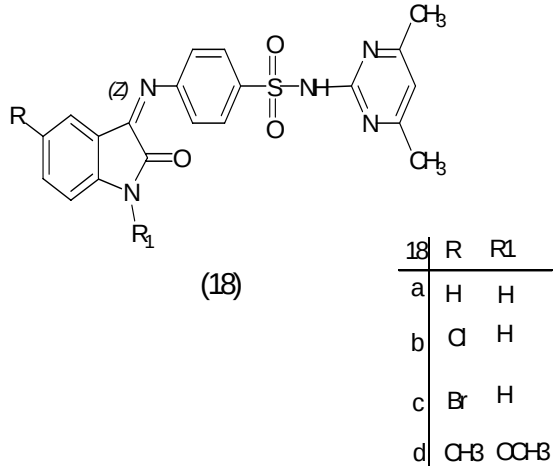
Precursor isonicotinic hydrazide resulted in 4-amino-5-pyridin-4-yl-4H-1, 2, 4- triazole-3-thiol through number of steps which was further treated, synthesized and the resulted compound **(17)** was evaluated for antimicrobial property[39].



Antiviral activity

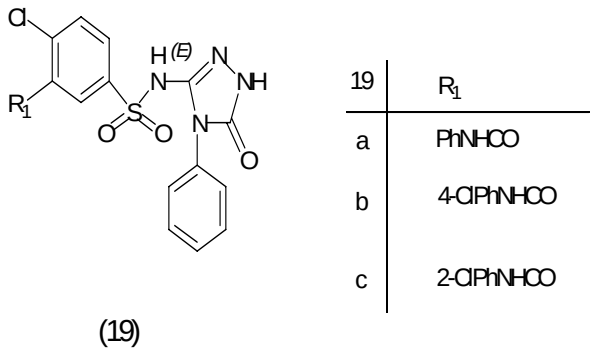
HIV (retrovirus) is a virus resulting in the slow depletion of immune system of the affected human beings resulting in opportunistic infections[40]. Contrasting from other retroviruses it is different, its single stranded RNA is attached to tightly bound proteins and enzymes for the development of the virion namely reverse transcriptase, proteases, ribonucleases and integrases. The treatment of HIV regimen HAART[41] (Highly Active Antiretroviral Therapy) is not at the best mainly due to rebound phenomenon of virus at the withdrawal of the treatment resulting in increment of CD4+ T-cells which results in AIDS[42]. The weak results of present drug regimen against HIV infection has stressed for refocusing on the biomechanisms for latency regarding HIV. Some new compounds were synthesized and evaluated for the anti-HIV activity.

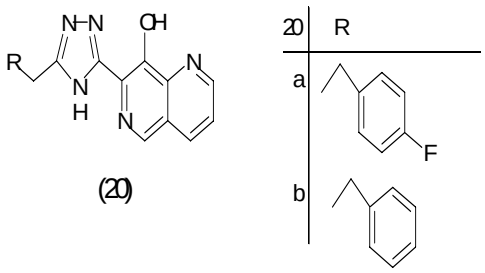
4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene) amino]-*N* (4, 6-dimethyl-2-pyrimidinyl)-benzene sulphonamide and its derivatives (**18)** were prepared and they were found active against replication of HIV-1 and HIV-2 in MT-4 cells[43].



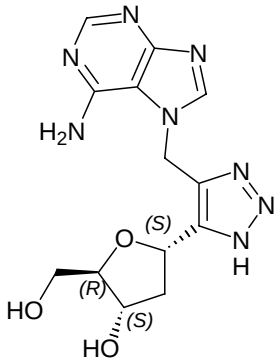
Synthesis of new 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)semicarbazide derivatives were prepared and they were found potentially active against T4-lymphocytes infected. The compounds (**19)** were successfully changed to triazolones and it also helpful in finding out SAR[44].

A new pharmacophore named 8-hydroxy-1,6-naphthyridine core and a triazole is identified. The two metal co-ordination pharmacophore patterns were selected for designing of key structural component (**20)**. In potency against enzyme system the benzyl and flourobenzyl showed equivalent activity but if the substituent was made smaller in size the activity depleted[45].



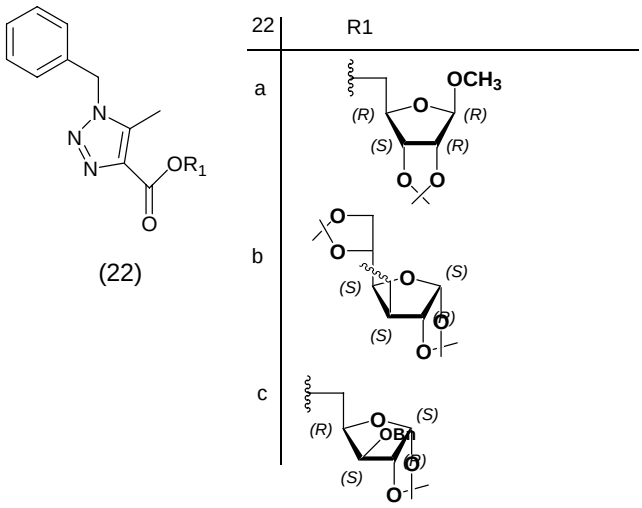


Various derivatives of trisubstituted triazoles (**21)** were prepared as inhibitors of reverse transcriptase and the two derivatives with difference in thio group position were found out to be most active compounds which were also analysed with crystallographic analysis[46].



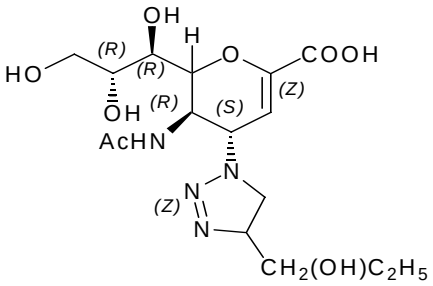
(21)

Another important compound that were active against HIV reverse transcriptase,1–benzyl-1H-1,2,3-triazole derivatives linked to carbohydrate moiety, were prepared[47]. The two new synthesized classes of compounds (**22)** consisted of carbohydrate protected and non-protected moieties. The cytotoxicity was very low as compared to AZT and SI higher than DDC and DDI. Morover it was found that the HOMO energy was similar to other classical antivirals, also their high lipophilicity and higher molecular weight made them interesting candidate as promising lead molecule for further biological evaluation.



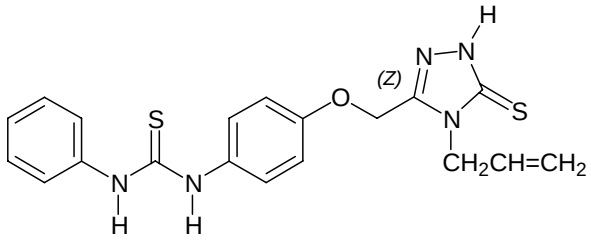
(22)

A newly derived 4-triazole modified zanamivir (**23)** was synthesized via click reaction and the inhibitory activities were found near to that of zanamivir. It was evaluated against Avian Influenza Virus (AIV, H5N1). Binding agreement between the inhibitors and the neuraminidase were provided by molecular modelling[48].



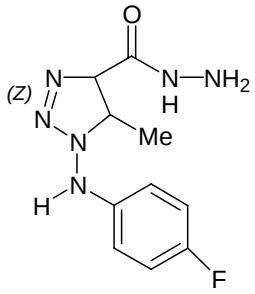
(23)

The under shown compound (**24)** were prepared as the novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4 triazole-3- thiones which proved to be having a good activity against cox sacie virus B4, also active against the thymidine kinase positive Varicella zoster virus[49].



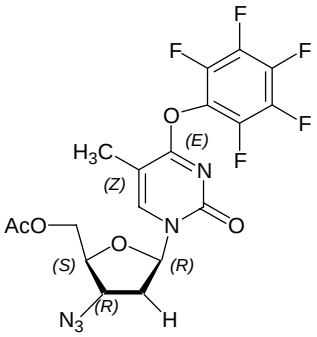
(24)

Antiviral activity against cantalago virus was derived from the compound i.e. N-amino-1, 2, 3-triazole is **(25)** shown. The structural position 4 at triazole is being further experimented for increasing potential of activities[50].



(25)

A series of triazoles and pentafluorophenyloxy-substituted pyrimidine nucleoside (**26)** were synthesized by one pot reaction. The synthesized compounds provided nominal potency as anti-viral compounds as compared to AZT[51].



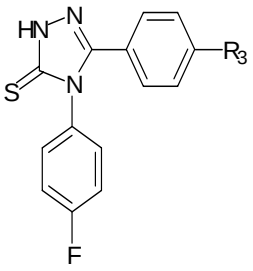
(26)

Anti-convulsant activity

Seizures initiate by the rapid and excessive firing of neurons and is controlled by the class of drugs called Anticonvulsant Drugs[52]. They act by the mechanism of mood stabilising mainly by treatment of bipolar disorder[53]. They are also called antiepileptic drugs (AED's). The other type of convulsive non-epileptic seizures are not responding to this class of drugs. In epileptic condition area of cortex is hyperirritable and this irritability is being decreased by this class of drugs. The main targets molecules of the drugs are voltage gated Na channels, GABAA receptors, GAT-1 GABA transporter and GABA transaminase[54], voltage-gated calcium channels, SV2A and α2δ[55, 56]. However antiepileptogenic treatment[57] is under human trials. Here is the review of the newly synthesized compounds showing anticonvulsant activity and they proved to be effective for further research as lead compounds.

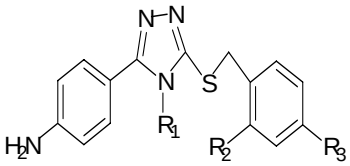
Synthesis and anticonvulsant activity of 4,5-diphenyl-2H-1,2,4-triazole was carried out on four animal models of seizures namely , viz. Maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)- induced seizure threshold tests. The various substituted compounds (**27)** showed the anticonvulsant activity[58].

Novel series of 3-{[(substituted phenyl)methyl]thio}-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles (**28),** was synthesized which were similarly evaluated by the above said technique and the two active compounds were evaluated and was concluded that the alkyl substitution or primary amino group were essential for the compound to show an activity[59].



(27)

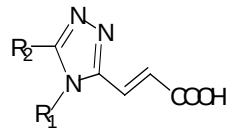
27	R_3
a	NO_2
b	NH_2
c	CH_3
e	H
f	OH



(28)

28	R1	R2	R3
a	CH_3	H	H
b	CH_2-CH=CH_2	Cl	Cl
c	"	H	H

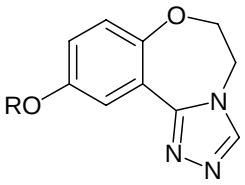
Condensation reaction of the N^3-substituted amidrazones and with malice anhydrides provided with newer derivatives (**29)** of 3-(3, 4-diaryl-1, 2, 4-triazole-5-yl_propenoic acid which were evaluated for the anticonvulsant activity[60].



(29)

29	R_1	R_2
a	2-C_5H_4N	C_6H_5

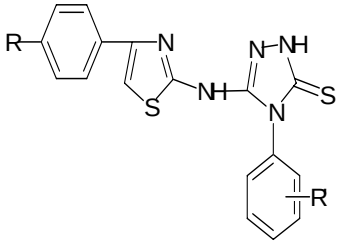
A series of novel 10-alkoxy-5,6-dihydro-triazolo[4,3-d]benzo[f][1, 4] oxazepine derivatives were synthesized and evaluated by the maximal electroshock (MES) test and their neurotoxicity was evaluated by the rota rod neurotoxicity test (Tox). The compound (**30)** was found to have better anticonvulsant activity than marketed drugs namely carbamazepine, phenytoin and it was also shown that the activity was mediated by GABA-mediated mechanism[61].



(30)

30	R
a	-n-C_7H_{15}

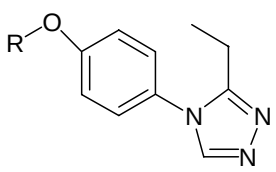
A new class of drug (**31)** incorporating triazoles to thiazoles 3-[4-(substituted phenyl)-1,3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1H-1,2,4- triazole-5-thiones were synthesized and found to have anticonvulsant activity which was designed as keeping in view the structural requirement of pharmacophore model. The figures of Protective index (PI), Median Hypnotic Dose (HD50), and Median lethal dose were higher than the standard drugs[62].



(31)

31	R	R
a	Cl	4-OCH_3
b	Br	2-CH_3

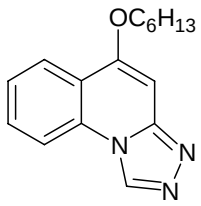
The same evaluation was also done for the other compound **(32)** named 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole which exhibited much greater PI value than of prototype drug phenytoin. It concluded that it might have effect on GABA neurotransmission and activate glutamate decarboxylase or inhibit (GABA)–a-oxoglutarate aminotransferase (GABA-T) in the brain[63].



(32)

32	R
a	-n-C_7H_{15}
b	-N-C_8H_{17}

5-hexyloxy-[1, 2, 4] triazolo [4, 3-a] quinoline (**33)** was synthesized and evaluated, found potent anticonvulsive in nature with low level of neurotoxicity[64]. All the possible mechanism of anticonvulsive activity was done in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test.



(33)

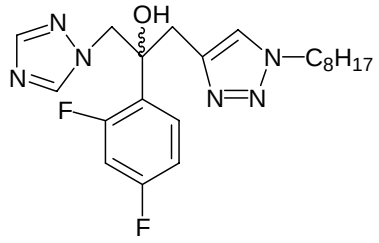
Anti-fungal activity

Antifungal are the class of drugs that are used to eradicate fungal infections from the human body. They work by exploiting differences between mammalian and fungal cells to eradicate fungal organism without harming the host cells. As both the cells are eukaryotic in nature so it is more difficult to design the drugs of antifungal activity with fine selections of the cells without causing any side effects[65].

Drugs of fungal origin include griseofulvin from *Penicillium griseofulvum*, used to treat fungal infections, Inhibitions of

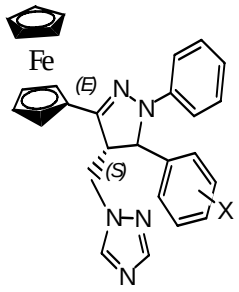
cholesterol synthesis by statins (HMG-CoA reductase inhibitors). E.g. devastating from *Penicillium citrinum,* lovastatin from *Aspergillus terreus* and the oyster mushroom[66]. So further here we are emphasising on the newly synthesized compounds including triazole moiety showing better antifungal property.

Candida fungal pathogens were impinged by the new triazole derivatives **(34),** analogous to the fluconazole both by in vivo and in vitro. The easily accessible molecules, 1, 4-disubstituted-1, 2, 3-triazole compounds with long alkyl chains displayed a good antifungal activity. It was more potent than the standard drugs namely ketoconazole, amphoterecin B and fluconazole. The enantiomers are still under process as they are supposed to have more potent activity than the racemic compounds[67].



(34)

Ferrocene is known to have a strange record for a dramatic change in the activity of compounds, was also utilised to incorporate the compound, synthesized by Mannich type reaction, sequential condensation and cyclisation reaction, resulting in ferrocenyl containing 1H-1, 2, 4-triazole derivatives **(35)**. It resulted a profound activity against five types of fungi *Penicillium zeae, Aspergillus solani, Candida fulvum, Penicillium piricola and Candida ara*. It was also proved that addition of a methyl group along ferrocene and aryl linkage resulted in flexible compounds[68]

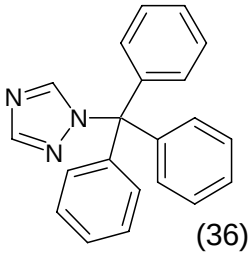


35	X
a	4-OMe
b	2-Cl
c	3,4-O-CH_2-O
d	4-Me

(35)

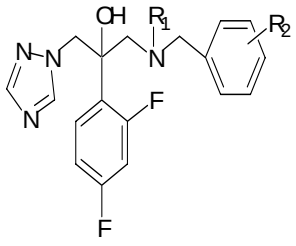
The use of Computer docking to produce a series of 1-(1H-1, 2, 4-triazole-1-yl)-2-(2, 4-difluorophenyl)-3-substituted-2-propanols, analogues to fluconazole, resulted in the screening against 8 human pathogens. *A. fumigatus* was impinged by nearly all type of synthesized compounds and showed broad spectrum activity. The compound **(36)** showed 128 times more activity against *Candida albicans*. Also it showed the positive approach to introduce a side chains consisting allyl group and benzyl bromides to interact with hydrophobic pockets and also to generate p-p stacking interaction with Tyr 118[69].

Another series of compound (**37)** were prepared as inhibitors of cytochrome P450 14 α demethylase resulting in activity better than clotrimazole and fluconazole and also a correlation between docking energy and growth inhibition between them[70].



(36)

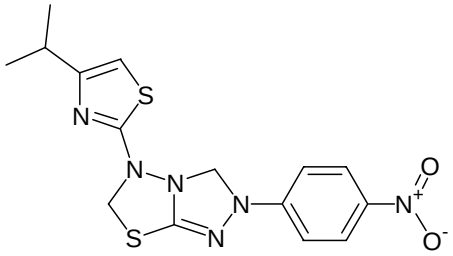
Series of CYP51 inhibitors were found, synthesized and resulted in novel 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted benzylamino-2-propanols which showed comparable activity to voriconazole. Moreover again substituted benzyl chain showed part in producing an active pharmacophore and an amine side resulted in a higher activity when shortened[71].



36	R1	R2
a	CH(CH3)2	4-Br
b	(CH2)3CH3	4-CH2CH3
c	"	2-CH3

(37)

Novel 2-substituted-5-[isopropylthiazole] clubbed 1, 2, 4-triazole were synthesized as potent antifungal agent. The activity was shown by the compound (**38),** named 3-(4-Isopropylthiazol-2-yl)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole[72].

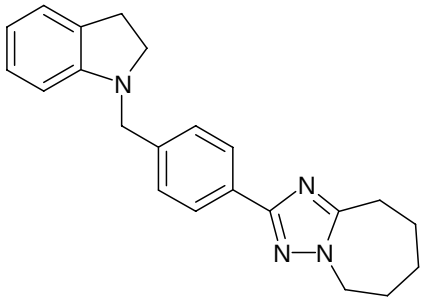


(38)

Antitumor activity

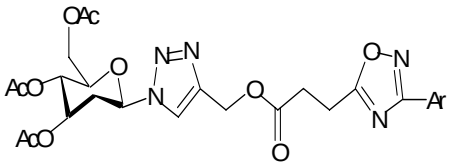
Antitumour drugs are those chemical substances that inhibits or combat the development of cancerous cells. The various classes of antitumour drugs include as Alkylating agents, Antimetabolites, Antimitotics consisting of taxol that binds to the tubulin and helps in inhibiting spindle dynmics and stops the cell divison, Topoisomerase II inhibitors which abstrain DNA from unwounding that is the requirement for both DNA replication and RNA or protein synthesis and last but not the least i.e. generating the free radicals[73].

Compound 1-(6,7,8,9-Tetrahydro-5H-[1,2,4]-triazolo[1,5,-a]-azepine-2-yl)benzyl]indole (**39),** was prepared and evaluated for anticancer activity against human tumour cell lines derived from nine cancer cell lines . The anticancer activity was moderate or weak in comparison to other lead series of compounds namely vincristine and vinblastine[74].



(39)

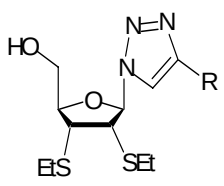
Synthesis of heterocyclic compounds containing a glycosyl function, a triazole moiety and 1, 2, 4-oxadiazole ring in which triazole ring has substituent at N-1 and C-4 atoms resulted in inhibitory properties[75].



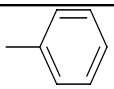
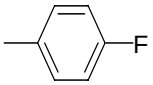
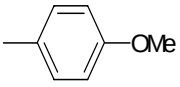
(40)

40	R
a	p-bromophenyl
b	p-nitrophenyl

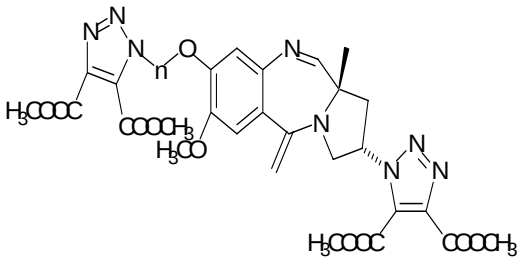
Ribonucleoside linked with triazole i.e.2',3'-dideoxy-2',3'-diethane thionucleosides (**41)** bearing triazoles, showed an excellent yield and resulting in antitumour activity. Triazole nucleosides showed activity against HepG2 cells, possible conjugations between triazole ring and benzene in nucleoside offers an improved binding potential to the target. Moreover it showed activity better than the reference marketed compound Floxuridine against HePG2, A549 and HeLa cell lines[76].



(41)

41	R
a	
b	
c	

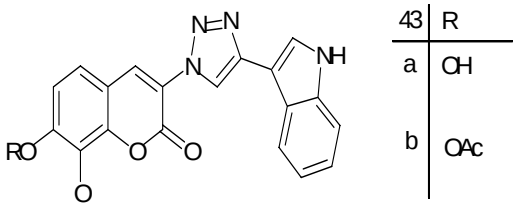
Linkage of 1, 2, 3-triazole with pyrrolobenzodiazepine by click chemistry resulted in useful pharmacophore **(42)** for several DNA-alkylating and cross linking agents. They were having a good DNA binding affinity and anticancer activity which were evaluated by thermal denaturation studies[77].



(42)

42	n
a	5

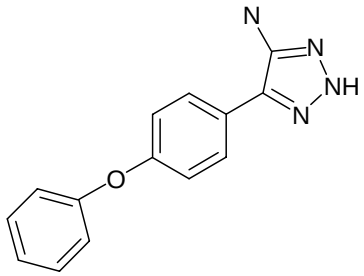
Further Novobiocin containing triazole analogues (**43)** were designed and synthesized, where triazole moiety is analogy to amide moiety of natural products. The SAR suggest that the sterically demanded side chains consisting of biaryl, indole or homologated aryl groups showed better activity than substituted aryl compounds[78].



(43)

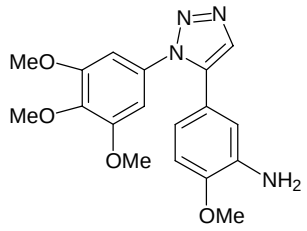
43	R
a	OH
b	OAc

4-aryl-5- cyano-2H-1, 2, 3-triazole were synthesized and found to have HER2 tyrosine kinase inhibitors. The lipophilicity of the substituting groups in (**44)** is the main bioactivities which is rational by the IC50 value. 4 Phenyl position on the triazole is the best substituting position on the for inhibitory activity[79].



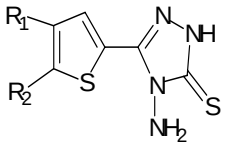
(44)

Tubulin polymerization inhibition, a key to inhibit the cancerous cells, followed by a compound named 2-methoxy-5-(1-(3, 4, 5-trimethoxyphenyl)-1H-1, 2, 3-triazol-5-yl) aniline showed potent cytotoxic activity. Molecular modelling supported that the activity of (**45)** was most likely due to binding site of α, β-tubulin in the β subunit. They were represented as cis restricted analogue of combresatin[80].



(45)

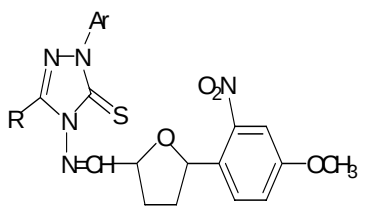
3, 4, 5-substituted -1, 2, 4 triazole were synthesized and the biological screening of (**46)** showed high toxicity against thymocytes and low toxicity against blood lymphocytes. The PFC test for the compound surpasses 29 time of that of control cells. Also shown that the incorporation of the 5-phenylthiophene-2- and tetrahydrobenzothiophene- 2-substituent at 5th position in the structure of 3- mercapto-1, 2, 4-triazoles are auspicious to the interaction of the biological targets[81].



46	R_1	R_2
a	$(CH_2)_4$	$(CH_2)_4$
b	H	C_6H_5

(46)

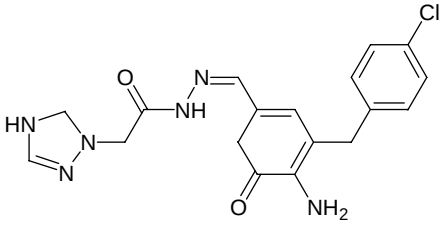
3-substituted4-[5-(4-methoxy-2-nitrophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4 triazoles **(47)**, synthesized by aminomethylation with various amines and formaldehyde resulted in various products that were active against various cell lines derived from cancer cells namely CNS, leukemia, renal, colon, ovarian, melanoma and lungs[82].



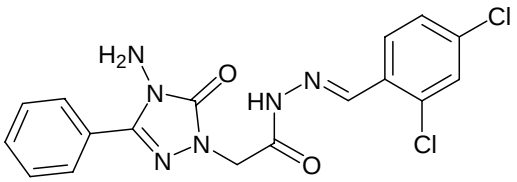
47	Ar
a	H
b	CH_3
c	$2\text{-}ClC_6H_4\text{-}OCH_2$
d	$4\text{-}ClC_6H_4\text{-}OCH_2$
e	$2,4\text{-}Cl_2C_6H_3OCH_2$

(47)

Anti-tumorous activity of some newly synthesized compounds (**48), (49)** belonging to 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives were evaluated and potent activity was found against many microorganism[83].



(48)



(49)

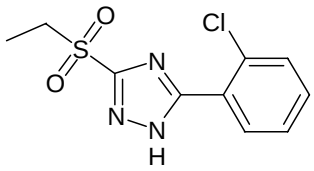
Anti-Inflammatory activity

Unlike opioids[84] (CNS acting) they act by binding to glucocorticoids or COX enzyme and resulting in reduced pain and inflammation. Exception to this, paracetamol acts by inhibiting the reuptake of endocannabinoids[85] resulting the same. Side effects associated with this class includes ulcerous stomach[86], exacerbating asthma and kidney damage[87].

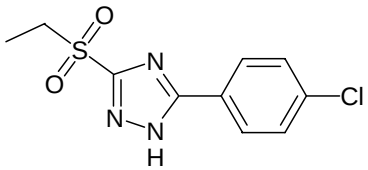
ImSAIDs[88] (Immune selective Anti-inflammatory Derivatives), unlike others, a class of peptides having diverse biological properties including anti-inflammatory, derived from the submandibular gland and saliva[89]. The activation and migration of inflammatory cells, are inhibited, which are immune cells responsible for magnifying the inflammatory response, e.g. Tripeptide FEG (Phe-Glu-Gly) and its D-isomer feG[90]

The compounds have been synthesized and evaluated and are found more potent, review study shows that the side-effects have been tried to be minimised so that a better treatment would be given to the needful.

Preparation of sulphones (**50), (51)** of 5-aryl-3-alkylthio- 1, 2, 4-triazoles showed potent anti-inflammatory activity devoid of ulcerogenic potential. The activity can be modified by substitution at phenyl ring and sulphur or oxidation of sulphur to sulphate. The compounds shown have no ulcerogenic activity and so this type of compound is of fruitful matrix for the development t of this classification[91].



(50)



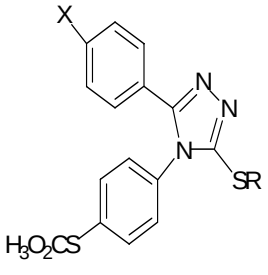
(51)

New compounds of (**52)** as shown were synthesized and evaluated to have potent anti-inflammatory activity. The SAR of class of 3-thio and alkylthio-4,5-diaryl-4H-1,2,4- triazoles was evaluated and reveals that

i) C-3 SR substituent in the diarylheterocycles provided potent and selective inhibition of COX-2 isozyme,

i. SO2Me moiety inserts deep into the COX-2 secondary pocket and the C-3 SR sulphur atom forms a weak hydrogen bond with NH2 atom of Arg12 as shown by the molecular studies.

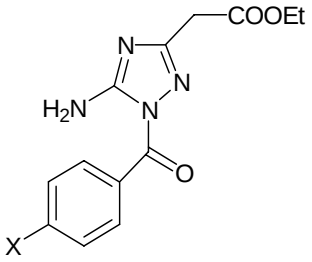
ii. C-3 alkylthio compounds is useful to study the function and catalytic activity of the COX-2 isozyme[92].



52	R	X
a	Me	H
b	Et	F
c		Me

(52)

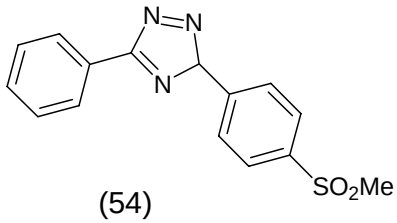
1-acyl-5-amino-1, 2, 4-triazole derivatives (**53)** were synthesized and reported for higher affinity for COX-2 active site and have the said activity. These compounds showed low gastric ulcerogenecity as compared to that of standard indomethacin[93].



53	R
a	Cl
b	Br
c	NO_2

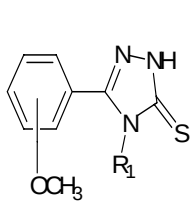
(53)

A series of compounds (aryl-1, 2, 3-triazole-1-yl)-methanesulfonylphenyl derivatives (**54)** were prepared as shown having central 1, 2, 3-triazole, having two aryl substituents on both sides of the triazole, as a novel class of COX -2 inhibitors . Compounds having vicinal diaryl pattern shows more potent COX-2 inhibition than the 1, 3-diaryl substituted compounds. A substitution of F or Cl group (electron withdrawing groups) on the para position of the aryl group displayed higher activity of COX-2 inhibition. Moreover the centrally placed triazole ring also add on to the better lipophilicity required for the activity[94].



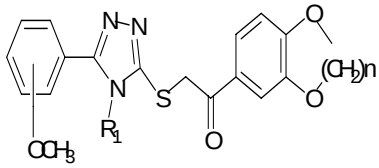
(54)

5-(2-,3- and 4-methoxyphenyl)-4*h*-1,2,4-triazole-3-thiol derivatives (**55), (56)** were prepared and were found potent with reference to acetyl salicylic acid and ibuprofen in exhibiting anti-inflammatory activity. TAK-603 (Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2, 4-triazol-1-ylmethyl) quinoline-3 carboxylate), a compound that showed anti-rheumatic activity [95].



55	position	R^1
a	ortho	C_6H_5
b	meta	"
c	para	"

(55)



56	n
a	2
b	1
c	2
d	3

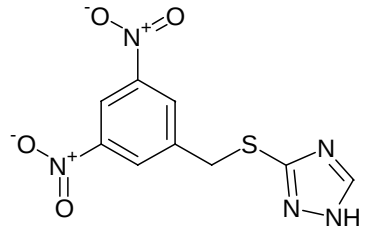
(56)

Anti-tuberculous activity

Ghon focus is the site of infection for pulmonary T.B and spreading of it is mediated by bloodstream and lymph. Monteoux tuberculin test, interferon-[96] release assay including QuantiFERON-TB Gold and T-SPOT. TB test are available.

The drug regimen of treatment includes the measures to invade the unusual structure and chemical composition of the cell wall of the mycobacterium including isoniazid, rifampin and many others. It is well treated by a combination of different drugs and eradicated assisted with the side effects of drug resistance. The DOTS treatment is also under its way to treat a number of patients successfully. So here we present a review of the latest synthesized compounds that showed promising results in the treatment of this disease.

Synthesis of 1, 2, 4-triazole 3-benezylsulphanyl derivatives (**57)** resulted in the antimycobacterial activity. It showed that the antimycobacterial activity is due to the benzylsulphonyl group on the triazole ring. The two compounds shown reflects the best activity in this reference. The presence of H-atom at position 4 is necessary for the receptor interaction[97].

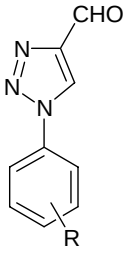


(57)

New N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**58)** were synthesized and further results revealed that the presence of hydrogen bond acceptor subunit, triazoles and phenyl rings planarity, aromatic ring position, uniform HOMO coefficient distribution, position of aromatic ring are all responsible for the activity[98].

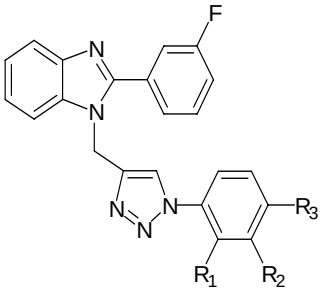
2- (3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1h-[1, 2, 3]-triazol-4-yl-methyl)-1h-benzo[d] imidazole derivatives **(59)** were efficiently synthesized by new methodology which resulted in potent antituberculous compounds. The technique clubbed triazoles along benzimidazole series for H37Rv inhibitors were

used. Activity better than rifampin was seen and the potency of the compound is due to highly electronegative part flourine and triazoles attached to benzimidazole[99].



58	R
a	3,5-Di-Cl
b	4CH_3

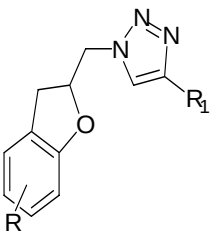
(58)



59	R1	R2	R3
a	F	F	F
b	H	F	F
c	H	F	H
d	OMe	H	H
e	F	H	F
f	H	H	H

(59)

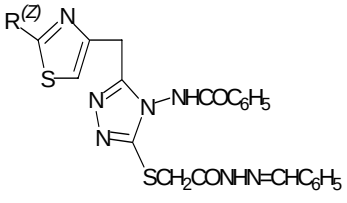
1-(2, 3-dihydronaphtho (benzo) furan-2-yl-methyl) 4-alkyl/ aryl-1, 2, 3-triazoles, (**60),** a new class of hybridised molecules was synthesized utilising the Huisgen (3+2) cycloaddition reaction of acetylenes and azides[100].



60	R	R_1
a	4-CHO	$(CH_2)_4CH_3$
b	4-CHO	$(CH_2)_5CH_3$
c	2,5-Di-Me	CH_2OH

(60)

Thiozolyl triazole derivatives **(61)** were being synthesized by the same above said method which resulted in compounds that were active against the H37Rv strain with decreased chances of resistance to be developed. Also the MORE (microwave organic reaction enhancement method) played an important role. The derivatives containing highly electronegative part at sulphahydrl group represented as new compound having the said activity.[101]



61	R
a	$NHCOCH_2Cl$
b	$NHCOCH_3$
c	$NHCOC_6H_5$

(61)

CONCLUSION

From the review of the various results shown by active compounds, we can find out that triazole moiety showed a promising results in most of the pharmacological activity and also we have fascinating results available under its belt.

Triazole showed a promising result as in clubbed mode, incorporated moieties, synthesis under microwave assisted reactions, cycloaddition and by many more mechanism reported in this review. We hope that in the future many new pharmacological profiles will be added to it as it is still unrevealed and many more would be available soon as the research is never ceases.

REFERENCES

1. Katica Colanceska Ragenovic, Vesna Dimova, Vlado Kakurinov, Dora Gabor Molnar and Aleksandra Buzarovska: Synthesis, antibacterial and antifungal activity of 4-substituted-5-aryl-1,2,4-triazole. Molecules 2001; 6: 815-824.
2. Yaseen A. Al-Soud, Mohammad N. Al-Dweri, Najim A. Al-Masoudi: Synthesis, antitumor and antiviral properties of some 1,2,4-triazole derivatives. IL FARMACO 2004; 59: 775–783.
3. Syed Azhar Nizami, Syed Azhar Nizami1, M. Gurumurthy1, Swarup jyoti Chattarjee, Debashisha Panda: Evaluation of antimicrobial potency of some synthesized thiazolidin-4-one substituted 1, 2, 4-triazoles, Journal of Advanced Pharmaceutical Research 2010; 1: 26-35.
4. M. A. Giembycz, G. Dent, J.E. Sounss: Review: theophyline and isoenzyme-selective phosphodiestrase inhibitors, Allerg. Dis 1997; 1: 531–567.
5. S Jubie Pranabesh Sikdar, R Kalirajan, B Gowramma, S Gomathy, S Sankar & K Elango: Synthesis and antimicrobial activity of some novel ciprofloxacin analogues. Journal of Pharmacy Research 2010; 3(3): 511-513.
6. S.C. Beasley, N. Cooper, L. Gowers, J. P. Gregory, A.A.F. Haughan, P.G. Hellewell, D. Macar, J.Miotla, J.G. Montana, T. Morgan, R. Taylor, K.A. Runcie, B. Tuladhar, J.B .H. Warneck: Synthesis and evaluation of a novel series of phosphodiestrase IV inhibitors. a potential treatment for asthma. Bioorg. Med. Chem. Lett. 1998; 8: 2629–2634.
7. De Clercq E: In search of a selective antiviral chemotherapy. Clin Microbiol Rev. 1997; 10: 674–693.
8. Ram Janam Singh: 1,2,3-Triazole derivatives as possible antiinflammatory agents. Rasayan J Chem 2009; Vol.2, No.3: 706-708.
9. D.A. Griffin, S.K. Mannion: Preparation of substituted triazolylbutanoates as plant growth regulators. Eur. Pat. Appl. EP 1986; 199,474.
10. Timo Weide, S. Adrian Saldanha, Dmitriy Minond, Timothy P. Spicer, Joseph R. Fotsing, Michael Spaargaren, Jean-Marie Frere, Carine Bebrone, K. Barry Sharpless, Peter S. Hodder , Valery V. Fokin: NH-1,2,3-Triazole inhibitors of the VIM-2 metallo-β-lactamase. ACS Med. Chem. Lett. 2010; 1 (4): pp 150–154.
11. G. Heubach, B. Sachse, H. Buerstell: 1,2,4-Triazole derivatives. Ger. Offen. 1979; 2: 760.
12. G. Tanaka: Triazole derivatives. Japan Kokai 1974; 7495.
13. T.C. Jenkins, I.J. Stratford, M.A. Stephens : 3-Nitro-1,2,4-triazoles as hypoxia-selective agents. Anticancer Drug Des 1989; 4 : 145–160.
14. M. I. Husain, M. Amir: Synthesis of some new substituted thiosemicarbazides and triazoles as possible anticonvulsants. J. Indian Chem. Soc. 1986; 63: 317–319.
15. S.-H.L. Chiu, S.-E.W. Huskey: Species differences in *N*-glucuronidation. Drug Metabol. Dispos1998; 26: 838–847.
16. R. Eliott, R. L. Sunley, D. A. Griffin: Preparation of plant growth regulant triazoles and imidazoles. UK Pat Appl GB 1986; 2: 175,301.
17. N. A. Al-Masoudi, N.A. Hassan, Y.A. Al-Soud, P. Schmidt, A. E. D. M. Gaafer, M.Weng, S. Marino, A . Schoch, A. Amer, J.C. Jochims: Synthesis of *C*- and *N*-nucleosides from 1-aza-2-

azoniaellene and 1,3-diaza-2-azoniaaallene salts. J. Chem. Soc. Perkin Trans. 1998; 1: 947–953.

18. N.A. Al-Masoudi, Y.A. Al-Soud, A. Geyer: Synthesis and spectroscopic analysis some acyclic *C*-nucleosides and the homo- *C*analogues from 1-(chloroalkyl)-1-aza-2-azoniaallene salts. Tetrahedron 1999; 55: 751–758.
19. Y.A. Al-Soud, N.A. Al- Masoudi: Synthesis and antiviral activity of some 1-(1,5-dialkyl-1*H*-1,2,4-triazol-3-yl)thymidines. Arch. Pharm. Pharm. Med. Chem. 1999; 332: 143–144.
20. Y.A. Al-Soud, N.A. Al-Masoudi, I.M. Lagoja: Synthesis and reactions of 1,5- and 1,3-dialkyl derivatives of (D-*manno*-pentitol-1-yl)-1*H*- 1,2,4-triazole nucleosides derived from 1-(chloroalkyl)-1-aza-2- azoniaallene salts. Carbohydr. Res. 1999; 318: 67–74.
21. Y.A. Al-Soud, N.A. Al-Masoudi, A.E.-R.S. Ferwanah: New potential antitumor agents: 1,2,4-triazoles bearing benzotriazoles, acetoxyhydrazides, 5-mercapto-1,2,4-triazoles and sugar hydrazone analogues. Bioorg. Med. Chem. 2003; 11: 1701–1708.
22. Y.A. Al-Soud, R.F. Halah, N.A. Al-Masoudi: Synthesis of 1-[4-(1,5- disubstituted-1H-1,2,4-triazol-3-yl)benzyl]-1*H*-indoles and 5,6-dihaloquinolones as potential antitumor agents. Org. Prep . Proced. Int. (OPPI) 2002; 34: 648–664.
23. Y.A. Al-Soud, R.F. Halah, N.A. Al-Masoudi: Synthesis of 1-[4-(1,5-disubstituted-1H-1,2,4-triazol-3-yl)benzyl]-1*H*-indoles and 5,6-dihaloquinolones as potential antitumor agents. Org. Prep. Proced.Int. (OPPI) 2002; 34: 648–664.
24. Y.A. Al-Soud, N.A. Al-Masoudi: Synthesis of 3-1,2,4-triazolo- and 3-1,3,4-thiadiazoliminothymidines. Heteroatom. Chem .2003; 14: 298–303.
25. http://www.webcitation.org/5uJysabSO.
26. Von Nussbaum F. et al: Medicinal chemistry of antibacterial natural products – exodus or revival. Angew. Chem. Int. 2006; Ed45(31): 5072–5129.
27. http://en.wikipedia.org/wiki/Antibacterial#cite_note-4
28. Sabir Hussain, Jyoti Sharma and Mohd. Amir: Synthesis and antimicrobial activities of 1,2,4-triazole and 1,3,4-thiadiazole derivatives of 5-Amino-2-Hydroxybenzoic acid. E-Journal of Chemistry 2008; Vol. 5, No.4: pp. 963-968.
29. Nasser S. A. M. Khalil: Efficient synthesis, structure and antimicrobial activity of some novel N- and S-β-D-glucosides of 5-pyridin-3-yl-1,2,4-triazoles. Carbohydrate Research 2006; 341: 2187–2199.
30. K.D. Thomas, Airody Vasudeva Adhikari, N. Suchetha Shetty: Design, synthesis and antimicrobial activities of some new quinoline derivatives carrying 1,2,3-triazole moiety. European Journal of Medicinal Chemistry 2010; 45: 3803-3810.
31. V. Padmavathi , G. Sudhakar Reddy ,A. Padmaja, P. Kondaiah, Ali-Shazia: Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles,1,3,4-thiadiazoles and 1,2,4-triazoles. European Journal of Medicinal Chemistry 2009; 44: 2106–2112.
32. Krzysztof Sztanke, Kazimierz Pasternak, Anna Sidor-Wo jtowicz, Janina Truchlinska and Krzysztof Jo zwiak: Synthesis of imidazoline and imidazo[2,1c][1,2,4]triazole aryl derivatives containing the methylthio group as possible antibacterial agents**.** Bioorganic & Medicinal Chemistry 2006; 14: 3635–3642.
33. G. V. Suresh Kumar, Y. Rajendraprasad, B.P. Mallikarjuna, S.M. Chandrashekar , C. Kistayya: Synthesis of some novel 2-substituted-5-[isopropylthiazole]clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents. European Journal of Medicinal Chemistry 2010 ; 45: 2063–2074.
34. Neslihan Demirbas, Sengul Alpay Karaoglu, Ahmet Demirbas, Kemal Sancak: Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives. European Journal of Medicinal Chemistry 2004; 39: 793–804.
35. Iraj Rahavi Ezabadi, Charalabos Camoutsis, Panagiotis Zoumpoulakis, Athina Geronikaki, Marina Sokovi Jasmina Glamocilija and Ana C iric: Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity, and conformational studies, Bioorganic & Medicinal Chemistry 2008; 16: 1150–1161.
36. Gabriela Laura Almajan, Stefania-Felicia Barbuceanu, Eva-Ruxandra Almajan, Constantin Draghici, Gabriel Saramet: Synthesis, characterization and antibacterial activity of some triazole Mannich bases carrying diphenylsulfone moieties. European Journal of Medicinal Chemistry 2009; 44: 3083–3089.
37. Oludotun A. Phillips, Edet E. Udo, Mohammed E. Abdel-Hamid, Reny Varghese: Synthesis and antibacterial activity of novel 5-(4-methyl-1H-1,2,3-triazole) methyl oxazolidinones. European Journal of Medicinal Chemistry 2009; 44: 3217–3227.
38. Sumesh Eswaran, Airody Vasudeva Adhikari, N. suchetha Shetty: Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. European Journal of Medicinal Chemistry 2009; 44: 4637–4647.
39. Hacer Bayrak, Ahmet Demirbas, Neslihan Demirbas, Sengu, Alpay Karaoglu: Synthesis of some new 1,2,4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. European Journal of Medicinal Chemistry 2009; 44: 4362–4366.
40. Weiss RA: How does HIV cause AIDS. Science 1993; 260 (5112): 1273–9.
41. Dybul M, Fauci AS, Bartlett JG, Kaplan JE, Pau AK: Panel on Clinical Practices for Treatment of HIV. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. Ann. Intern. Med. 137: 381-433.
42. Archin NM, Eron JJ, Palmer S, Hartmann-Duff A, Martinson JA, Wiegand A, Bandarenko N, Schmitz JL, Bosch RJ, Landay AL, Coffin JM, Margolis DM: Valproic acid without intensified antiviral therapy has limited impact on persistent HIV infection of resting CD4+ T cells. AIDS 2008; 22(10): 1131-1135.
43. P. Selvam, M. Chandramohan, E. De Clercq, M. Witvrouw, C. Pannecouque: Synthesis and anti-HIV activity of 4-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-N-(4,6-dimethyl-2-pyrimidinyl)benzene sulphonamide and its derivatives. Eur. J. Pharm. Sci.2001; 14: 313-316.
44. Elzbieta Pomarnacka, Iwona Kozlarska-Kedra: Synthesis of 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)semicarbazides and their transformation into 4-chloro-2-mercapto-N-(4,5-dihydro-5-oxo-4-phenyl-1H-1,2,4-triazol-3 yl)benzenesulfonamides as potential anticancer and anti-HIV agents. IL FARMACO 2003; 58: 423-429.
45. Brian A. Johns, Jason G. Weatherhead, Scott H. Allen, James B. Thompson, Edward P. Garvey, Scott A. Foster, Jerry L. Jeffrey, Wayne H. Miller : The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore. Bioorganic & Medicinal Chemistry Letters 2009; 19: 1802–1806.
46. Thorsten A. Kirschberg, Mini Balakrishnan, Wei Huang, Rebecca Hluhanich, Nilima Kutty, Albert C. Liclican, Damian J. McColl, Neil H. Squires and Eric B. Lansdon: Triazole derivatives as non-nucleoside inhibitors of HIV-1 reverse transcriptase—Structure–activity relationships and crystallographic analysis. Bioorganic & Medicinal Chemistry Letters 2008; 18: 1131–1134.
47. Fernando de C. da Silva , Maria Cecilia B.V. de Souza , Izabel I.P. Frugulhetti, Helena C. Castro , Silmara L. de O. Souza , Thiago Moreno L. de Souza ,Diego Q. Rodrigues , Alessandra M.T. Souza , Paula A. Abreu , Fabiana Passamani , Carlos R. Rodrigues, Vitor F. Ferreira: Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. European Journal of Medicinal Chemistry 2009; 44: 373-383.
48. Jian Li, Mingyue Zheng, Wei Tang: Syntheses of triazole-modified zanamivir analogues via click chemistry and anti-AIV activity. Bioorganic & Medicinal Chemistry Letters 2006; 16: 5009–5010.

49. Ilkay kucukguzel, Esra Tatar: Synthesis of some novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3- thiones and evaluation as antiviral/anti-HIV and anti-tuberculosis agents. European Journal of Medicinal Chemistry 2008; 43: 381-392.
50. Alessandro K. Jordao, Priscila P. Afonso: Antiviral evaluation of N-amino-1,2,3-triazoles against Cantagalo virus replication in cell culture. European Journal of Medicinal Chemistry 2009; 44: 3777–3783.
51. Mark P. Wallis, Naheed Mahmood, William Fraser: Synthesis and anti-HIV activity of C4-modified pyrimidine Nucleosides. IL FARMACO 1999: 54: 83–89.
52. Dimmock JR, Vashishta SC, Stables JP: Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. Eur J Med Chem 2000; 35: 241-249.
53. Basco, Monica Ramirez: The Bipolar Workbook- Tools for Controlling Your Mood Swings. 162-6: 2006.
54. Rogawski MA, Loscher W: The neurobiology of antiepileptic drugs. Nat Rev Neurosci. 2004; 5(7): 553-564
55. Rogawski MA, Bazil CW: New molecular targets for antiepileptic drugs: α2δ, SV2A, and K(v)7/KCNQ/M potassium channels. Curr Neurol Neurosci Rep. 2008; 8(4): 345-352.
56. Meldrum BS, Rogawski MA, Molecular targets for antiepileptic drug development. Neurotherapeutics, 2007; 4(1): 18-61.
57. Abou-Khalil BW: Comparative monotherapy trials and the clinical treatment of epilepsy. Epilepsy currents – American Epilepsy Society 2007; 7 (5): 127–9.
58. M. Shalini, P. Yogeeswari, D. Sriram, J.P, Stables Cyclization of the semicarbazone template of aryl semicarbazones: Synthesis and anticonvulsant activity of 4,5-diphenyl-2H-1,2,4-triazol-3(4H)-one. Biomedicine & Pharmacotherapy 2009; 63: 187-193.
59. Ilkay Kucukguzel, Sq. Guniz Kucukguzel: Synthesis of some 3-(Arylalkylthio)-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazole derivatives and their anticonvulsant activity. IL FARMACO 2004; 59: 893–901.
60. Bozena Modzelewska- Banachiewicz, Jacek Banachiewicz: Synthesis and biological activity of new derivatives of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid. European Journal of Medicinal Chemistry 2004; 39: 873–877.
61. Xian-Qing Deng , Cheng-Xi Wei, Fu-Nan Li, Zhi-Gang Sun , Zhe-Shan Quan: Design and synthesis of 10-alkoxy-5,6-dihydro-triazolo[4,3-d]benzo[f][1,4]oxazepine derivatives with anticonvulsant activity. European Journal of Medicinal Chemistry 2010; 45: 3080-3086.
62. Nadeem Siddiqui, Waquar Ahsan, Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and in vivo screening, European Journal of Medicinal Chemistry 2010 ;45: 1536–1543.
63. Jing Chen, Xian-Yu Sun, Kyu-Yun Chai, Jin-Seok Lee, Mi-Sun Song and Zhe-Shan Quan: Synthesis and anticonvulsant evaluation of 4-(4-alkoxylphenyl)- 3-ethyl-4H-1,2,4-triazoles as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Bioorganic & Medicinal Chemistry 2007; 15: 6775–6781.
64. Li-Jun Guo , Cheng-Xi Wei, Jing-Hao Jia , Li-Ming Zhao, Zhe-Shan Quan: Design and synthesis of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives with anticonvulsant activity. Bioorganic & Medicinal Chemistry 2007; 15: 6775–6781.
65. http://en.wikipedia.org/wiki/Antifungal_drug.
66. Daniel J. Sheehan, Christopher A. Hitchcock, Carol M. Sibley: Current and emerging azole antifungal agents. Clinical Microbiology Reviews 1999; Vol. 12, No. 1: p. 40-79.
67. Nilkanth G. Aher , Vandana S. Pore , Nripendra N. Mishra , Awanit Kumar, Praveen K. Shukla , Aanchal Sharma, Manoj K. Bhat: Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. Bioorganic & Medicinal Chemistry Letters 2009; 19: 759–763
68. Zhong Jin, Aihong Huo, Tao Liu, Yan Hu, Jianbing Liu, Jianxin Fang: Synthesis, structures and biological activity research of novel ferrocenyl-containing 1H-1,2,4-triazole derivatives. Journal of Organometallic Chemistry 2005; 690: 1226–1232.
69. Xiaoyun Chai, Jun Zhang, Honggang Hu, Shichong Yu, Qingyan Sun, Zhigang Dan, Yuanying Jiang , Qiuye Wu. Design, Synthesis and biological evaluation of novel triazole derivatives as inhibitors of cytochrome P450 14a-demethylase. European Journal of Medicinal Chemistry 2009; 24 :1913–1920.
70. Zahra Rezaei, Soghra Khabnadideh , Keyvan Pakshir , Zahra Hossaini , Fatemeh Amiri, Elham Assadpour. Design, Synthesis and antifungal activity of triazole and benzotriazole derivatives. European Journal of Medicinal Chemistry 2009; 44: 3064–3067.
71. Xiaoyun Chai, Jun Zhang, Shichong Yu, Honggang Hu, Yan Zou, Qingjie Zhao, Zhigang Dan, Dazhi Zhang, Qiuye Wu: Design, synthesis and biological evaluation of novel 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted benzylamino-2 propanols. Bioorganic & Medicinal Chemistry Letters 2009; 19:1811–1814.
72. Mitscher LA :Bacterial topoisomerase inhibitors- quinolone and pyridone antibacterial agents. Chem. Rev. 2005;105 (2): 559–92.
73. http://www.cdc.gov/niosh/topics/antineoplastic/.
74. H. Mujagic, S.-S. Chen, R. Geist, S.J. Occhipinti, B.M. Conger, C.A. Smith,W.H. Schuette, S.E. Schackney: Effects of Vincristine on cell survival, cell cycle progression and miotic accumulation in asynchronously growing Sarcoma 180 cells, Cancer Res.1983; 43: 3591– 3597.
75. Janaina V dos Anjos , Ricardo A.W. Neves Filho: Synthesis and cytotoxic profile of glycosyl–triazole linked to 1,2,4-oxadiazole moiety at C-5 through a straight-chain carbon and oxygen atoms. European Journal of Medicinal Chemistry2009;44: 3571–3576.
76. Jin-Lan Yu, Qin-Pei Wu, Qing-Shan Zhang, Yan-Hong Liu, Yun-Zheng Li, Zi-Ming Zhou: Synthesis and antitumor activity of novel 2',3'-dideoxy-2',3'-diethane thionucleosides bearing 1,2,3-triazole residues. Bioorganic & Medicinal Chemistry Letters 2010; 20: 240–243.
77. Ahmed Kamal, N. Shankaraiah,V. Devaiah, K. Laxma Reddy, Aarti Juvekar, Subrata Sen,Nisha Kurian and Surekha Zingde.Synthesis of 1,2,3-triazole-linked pyrrolobenzodiazepine conjugates employing 'click' chemistry: DNA- binding affinity and anticancer activity. Bioorganic & Medicinal Chemistry Letters 2008; 18: 1468–1473.
78. Laura B. Peterson, Brian S. J. Blagg: Click chemistry to probe Hsp90: Synthesis and evaluation of a series of triazole-containing novobiocin analogues. Bioorganic & Medicinal Chemistry Letters 2010; 20 : pp 3957-3960.
79. Zhi-Yi Cheng, Wen-Jie Li, Feng He, Jun-Min Zhou and Xiao-Feng Zhu: Synthesis and biological evaluation of 4-aryl-5-cyano-2H-1,2,3-triazoles as inhibitor of HER2 tyrosine kinase. Bioorganic & Medicinal Chemistry 2007; 15: 1533–1538.
80. Kristin Odlo, Jean Hentzen, Jeremie Fournier dit Chabert, Sylvie Ducki,, Osman A. B. S. M. Gani, Ingebrigt Sylte, Martina Skrede, Vivi Ann Florenes and Trond Vidar Hansen: 1,5 Disubstituted 1,2,3-triazoles as cis-restricted analogues of combretastatin A-4: Synthesis, molecular modelling and evaluation as cytotoxic agents and inhibitors of tubulin. Bioorganic & Medicinal Chemistry 2008; 16: 4829–4838.
81. Anelia Ts.Mavrova, Diana Wesselinova, Yordan A. Tsenov, Pavletta Denkova: Synthesis, cytotoxicity and effects of some 1,2,4-triazole and 1,3,4-thiadiazole derivatives on immunocompetent cells. European Journal of Medicinal Chemistry 2009; 44: 63-69.
82. B. Shivarama Holla , B. Veerendra, M.K. Shivananda, Boja Poojary: Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1,2,4-triazoles. European Journal of Medicinal Chemistry 2003; 38: 759-767.

83. A. Foroumadi, F. Soltani, M.H. Moshafi, R.Ashraf-Askari: Synthesis and in vitro antibacterial activity of some N-(5-aryl-1,3,4-thiadiazole-2-yl)piperazinyl quinolone derivatives. IL FARMACO 2003; 58: 1023–1028.
84. Ottani A, Leone S, Sandrini M, Ferrari A and Bertolini A: The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol 2006; 531: 280-281.
85. Lambert DM, Fowler CJ: The endocannabinoid system-drug targets, lead compounds and potential therapeutic applications. J. Med. Chem 2005; 48 (16): 5059–87.
86. http://www.medicine.ox.ac.uk/bandolier/booth/painpag/nsae/nsae.html
87. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm168830.htm
88. Mathison RD, Befus AD, Davison JS, Woodman RC: Modulation of neutrophil function by the tripeptide feG. BMC Immunol . 2003; 4: 3
89. Bao F, John SM, Chen Y, Mathison RD, Weaver LC: The tripeptide phenylalanine-(D) glutamate-(D) glycine modulates leukocyte infiltration and oxidative damage in rat injured spinal cord. Neuroscience 2006;140(3):1011-22.
90. Mathison R, Davison JS, Befus AD: Neuroendocrine regulation of inflammation and tissue repair by submandibular gland factors. Immunol Today 1994;15(11): 527-32.
91. Birsen Tozkoparan, Esra Kupeli, Erdem Yes¸ilada, Mevlut Ertan: Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with antiinflammatory–analgesic activity. Bioorganic & Medicinal Chemistry 2007; 15: 1808–1814
92. Latifeh Navidpour, Hamed Shafaroodi, Khosrou Abdi, Mohsen Amini, Mohammad H. Ghahremani, Ahmad Reza Dehpour and Abbas Shafiee. Design: synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4H-1,2,4-triazoles as selective COX-2 inhibitors. Bioorganic & Medicinal Chemistry 2006; 14: 2507–2517.
93. Ashraf M. Abdel-Megeed, Hamdy M. Abdel-Rahman, Gamal-Eldien S. Alkaramany, Mahmoud A. El-Gendy: Design, synthesis and molecular modeling study of acylated 1,2,4-triazole-3-acetates with potential anti-inflammatory activity. European Journal of Medicinal Chemistry 2009; 44: 117-123.
94. Frank Wuest, Xinli Tang, Torsten Kniess , Jens Pietzsch, Mavanur Suresh .Synthesis and cyclooxygenase inhibition of various (aryl-1,2,3-triazole-1-yl)-methanesulfonylphenyl derivatives. Bioorganic & Medicinal Chemistry 2009; 17: 1146–1151.
95. L. Labanauskas , E. Udrenaite , P. Gaidelis, A. Brukstus: Synthesis of 5-(2-,3- and 4-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol derivatives exhibiting anti-inflammatory activity. IL FARMACO 2004; 59: 255–259.
96. http://www.cdc.gov/tb/?404;http://www.cdc.gov:80/tb/pubs/corecurr/default.htm
97. Vera Klimesova , Lenka Zahajska, KarelWaisser, Jarmila Kaustova, Ute Mollmann: Synthesis and antimycobacterial activity of 1,2,4-triazole 3-benzylsulfanyl derivative. IL FARMACO 2004; 59: 279–288.
98. Marilia S. Costa, Nubia Boechat: Synthesis, tuberculosis inhibitory activity and SAR study of N-substituted-phenyl-1,2,3-triazole derivatives. Bioorganic & Medicinal Chemistry 2006; 14: 8644–8653.
99. Charansingh Gill, Ganesh Jadhav, Mohammad Shaikh , Rajesh Kale, Anant Ghawalkar, Deepak Nagargoje, Mahendra Shiradkar*:* Clubbed [1,2,3] triazoles by fluorine benzimidazole, A novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. Bioorganic & Medicinal Chemistry Letters 2008; 18: 6244–6247.
100. Rama P. Tripathi, Amit Kumar Yadav, Arya Ajay, Surendra Singh Bisht, Vinita Chaturvedi ,Sudhir Kumar Sinha: Application of Huisgen (3+2) cycloaddition reaction: Synthesis of 1-(2,3-dihydrobenzofuran-2-yl-methyl [1,2,3]-triazoles and their antitubercular evaluations. European Journal of Medicinal Chemistry 2010;45: 142–148.
101. Mahendra Shiradkar, Gorentla Venkata Suresh Kumar, Varaprasad Dasari , Suresh Tatikonda, Kalyan Chakravarthy Akula, Rachit Sha: Clubbed triazoles: A novel approach to antitubercular drugs. European Journal of Medicinal Chemistry 2007; 42:807-816.