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 compounds1 which are under study since many a years. Its diversity in showing the pharmacological activities is mind blowing identified well by the medicinal chemists. Triazole, with many a compounds as incorporating with other heterocyclic nucleus, hydrazides2, substituted triazoles3, β-agonist4 or incorporated with antibiotics5 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 inhibitor6, hepatitis C-antivirals7, antifungal, anti-bacterial, β-lactamase inhibitor8, fungicidal9, insecticidal10, antitumor11, anticonvulsant12, antidepressant13, plant growth inhibitor14. Further synthesis of various compounds as 1,2,4-triazole-C-nucleoside15, acyclic C-nucleosides16, pyrimidines17, D-manno-pentitol-1-yl-1,2,4-triazoles18, benzotriazoles19, indoles20, quinolones21, triazole thymidines22 are in record.

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-lactams23. Many of them are still obtained naturally named as amino glycosides and a lot more are synthetically derived as sulfonamides24, the quinolones and the oxazolidinones. Moreover they are classified in two types based on their mode of action as bactericidal agents and bacteriostatic agent25.

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 subtilis26.
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.

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.

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.

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.
In the synthesis of new compounds containing diphenylsulfone moiety (14), the results revealed that incorporation of NH₂ functional group in azomethine function made a rise in antibacterial activity against *B. subtilis*, *P. aeruginosa* in comparison to chloramphenicol.

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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.

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 CF₃, active amine at 8 and 4 position of quinoline respectively, also other bioactive moieties as e.g. –SH, -CH₂CH₂OCH₃ and Ph moieties at triazole ring were shown responsible for the potent antimicrobial activity.
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.

Antiviral activity

HIV (retrovirus) is a virus resulting in the slow depletion of immune system of the affected human beings resulting in opportunistic infections. 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 (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. 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.

Synthesis of new 1-[(6-chloro-1,1-dioxo-1,4,2-benzothiazin-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.

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 fluoro benzyl showed equivalent activity but if the substituent was made smaller in size the activity depleted.

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

Another important compound that were active against HIV reverse transcriptase, 1-benzyl-1H-1,2,3-triazole derivatives linked to carbohydrate moiety, were prepared. 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. Moreover 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.
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\(^{48}\).

The under shown compound (24) were prepared as the novel thiourea derivatives obtained from 5-[[4-aminophenoxoy)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\(^{49}\).

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\(^{50}\).

A series of triazoles and pentafluorophenoxy-substituted pyrimidine nucleoside (26) were synthesized by one pot reaction. The synthesized compounds provided nominal potency as anti-viral compounds as compared to AZT\(^{51}\).

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, GABA\(_A\) 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 pentylentetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPCT) 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\(^{59}\).

\(^{22}\) \(^{23}\) \(^{24}\) \(^{25}\) \(^{26}\)
Condensation reaction of the N3-substituted amidrazones and with malice anhydrides provided with newer derivatives (29) of 3-[3, 4-dialyl-1, 2, 4-triazole-5-yl]propenoic acid which were evaluated for the anticonvulsant activity60.

A series of novel 10-alkoxy-5,6-dihydro-triazolo[4,3-a]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 mechanism61.

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 brain63.

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 effects65.
cholesterol synthesis by statins (HMG-CoA reductase inhibitors). E.g. devasting from *Penicillium citrinum*, lovastatin from *Aspergillus terreus* and the oyster mushroom. So further here we are emphasizing 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-1,2,5-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.

Another series of compound (36) 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.

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 126 times more activity against *Candida albicans*. Also it showed the positive approach to introduce a side chains consisting alkyl group and benzyl bromides to interact with hydrophobic pockets and also to generate p-p stacking interaction with Tyr 118.

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

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.

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 dynamics and stops the cell division. Topoisomerases II inhibitors which abstrain DNA from unwinding, 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.

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.
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 properties75.

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 lines76.

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 compounds78.

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 studies77.

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 combresatin80.
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.

3-substituted 4-[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.

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.

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 of this classification.

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 C-3 SR substituent in the diarylhetarocycles 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.

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 ulcerogenicity as compared to that of standard indomethacin.

A series of compounds (aryl-1, 2, 3-triazole-1-yl)-methanesulphonylphenyl 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.

Anti-tubercular activity

Ghon focus is the site of infection for pulmonary T.B and spreading of it is mediated by bloodstream and lymph. Montoux 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-benzylsulphanyl 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.

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.

2-(3-fluoro-phenyl)-1-[1-(substituted-phenyl)-1h-[1, 2, 3]-triazol-4-yl-methyl]-1h-benz[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 benzimidazole101.

[Diagram of compound 58]

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1-(2, 3-dihyronaphtho (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 azides100.

[Diagram of compound 59]

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Thiazolyl 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 activity101.

[Diagram of compound 60]

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<td>c</td>
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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.

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