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IRA-International Journal of Applied Sciences
ISSN 2455-4499 Vol. 03 Issue 02 (May, 2016)
Paper DOI: https://dx.doi.org/10.21013/jas.v3.n2.p14

Biological Portfolio of 1,5-Disubstituted Tetrazoles: A Review

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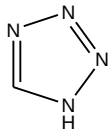
ABSTRACT

The achievement of medicinal chemistry, in the last few decades, has intensively increased due to the creation of novel drugs withe isostericnature of tetrazole ring with carboxyl group in longer chain peptides was responsible for the medicinal activity. Therefore a comprehensive search was carried out for 1, 5-disubstituted tetrazoles owing to their synthetic and effective pharmacological activities such as anti-inflammatory, antiviral, antibiotic, anti-ulcer, anti-tubercular, anti-hypertensive, etc. In spite of many research papers in the area of tetrazoles with respect to their pharmacological activity there have been no review on1, 5-disubstituted tetrazoles inthis field. The aim of present review is to classify and summarize the pharmaceutical uses of 1, 5-disubstituted tetrazole containing compounds.

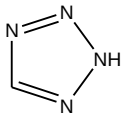
Keywords. 1, 5-disubstituted tetrazoles, biological activities, isostere.

Introduction

Tetrazoles are a representative class of poly-aza-heterocyclic compounds, consisting of a 5-memberedringoffournitrogen and one carbonatoms. They are unknown in the nature. Tetrazoles, based on the number of substituent, are divided into three categories, (i) parent tetrazoles (simplest tetrazoles), (ii) monosubstituted tetrazoles (1-or 5-substituted), and (iii) disubstituted tetrazoles (1, 5- or 2,5-disubstituted).



1-H tetrazole



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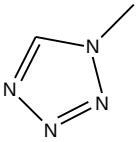
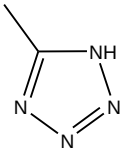
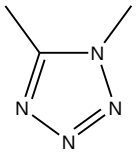


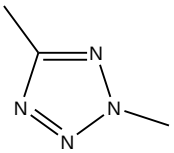
1H-substituted tetrazole



5-substituted-1H- tetrazole



1,5-disubstituted tetrazole



2,5-disubstituted tetrazole

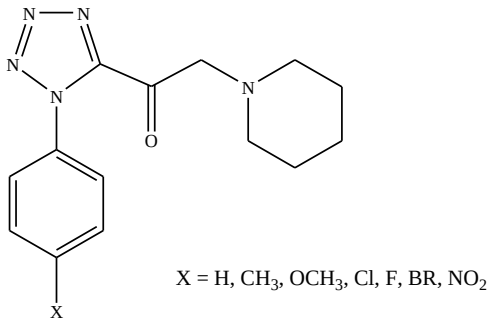
The first tetrazole was prepared by the Swedish chemist Bladin[1] in 1885. *Katritzky et al*.[2] synthesized 1,5-disubstituted tetrazoles in high yields from imidoylbenzotriazoles having short reaction time and mild reaction conditions. Tetrazoles are a class of heterocycles with a wide range of applications including rocket propellants[3] and explosives[4].The tetrazoles are representative of active pharmacophores for several therapeutic active molecules such as antiallergic[5], anti-inflammatory[6], antibiotic[7], anti-hypertensive[8] and anti-tubercular agents[9].

Isosteric nature of tetrazole ring is responsible for its use in medicinal chemistry. The 1,5-disubstituted tetrazoles were incorporated into longer peptides as isosteres for the cis-amide bond[10]. These substituents have displayed similar types of pharmacological activities because of their physicochemical properties, though they are structurally different. The replacement of *cis*-amide group by 1,5-disubstituted tetrazole enhances the metabolic stability of the molecule. Now a days, 1,5-disubstituted tetrazole containing scaffolds are found to be used as drugs for the treatment of various diseases.

Biological Portfolio of 1,5-disubstituted tetrazoles.

1. Antimicrobial Activity.

T. Elavarasan et al[11] have reported the synthesis of a new series of novel heterocyclic compounds containing both tetrazoles and piperidine nuclei together, namely, 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperidin-1-yl)ethanone**(1)**, and evaluated their antimicrobial activity using serial dilution method. The evaluation of antimicrobial activity shows that several compounds exhibit good activity when compared with the reference drug candidates and thus could be promising new lead molecules. *R.B. Uttarwar et al*[12] have reported the synthesis of benzimidazolylacetamide**(2)** and screened for their significant antimicrobial activity.



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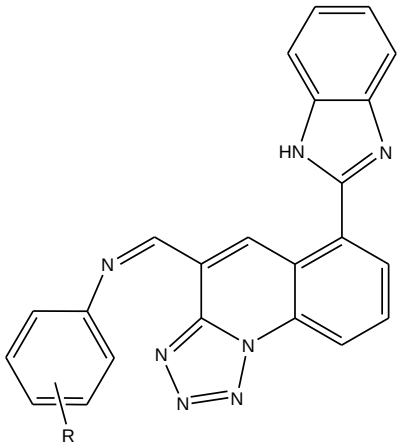

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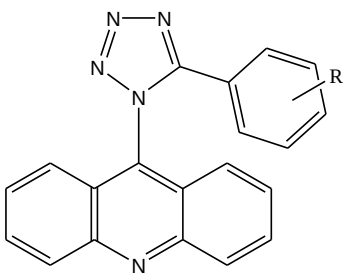
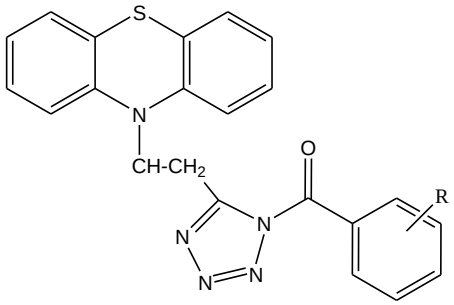
2. Analgesic Activity.

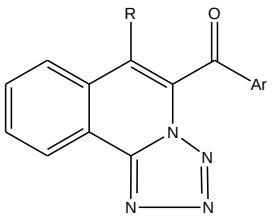
Kavitha H.P. et al[13] have reported the synthesis and analgesic activity of some novel tetrazole derivatives containing acridine ring **(3)**. Rajasekaran et al[14] have prepared a series of 5[b-(phenothiazinyl-10-yl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles **(4)** and demonstrated that these compounds possessed good analgesic activity tested both by acetic acid induced writhing method and hot plate method and anti-inflammatory activity tested by carrageenin induced paw edema method.

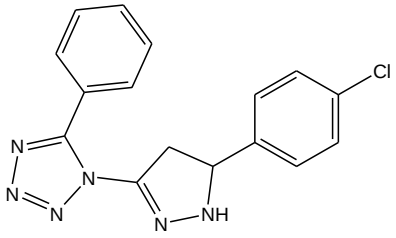




3 **4**

Koppula et al[15]have synthesized a new series of triazole / tetrazoleisoquinolines and coumarinoylisocoumarin**(5)** derivatives and evaluated their antimicrobial activity against gram positive, gram negative bacteria and different fungi namely *F. pallidoroseum, C. capsici.* Synthesized compounds were also evaluated for their analgesic activity and tested compounds showedbetter results when compared with standard drug. *V. H. Bhaskar et al*[16] have synthesized eight different derivatives of substituted 5-phenyl-1-(5-substituted phenyl) -4,5-dihydro-1*H*-pyrazol-3-yl)-1*H*-tetrazole **(6)** by reacting the chalcones with hydrazine hydrate in presence of glacial acetic acid. The compounds were screened for analgesic activity by acetic acid induced writhing method and hot plate method.



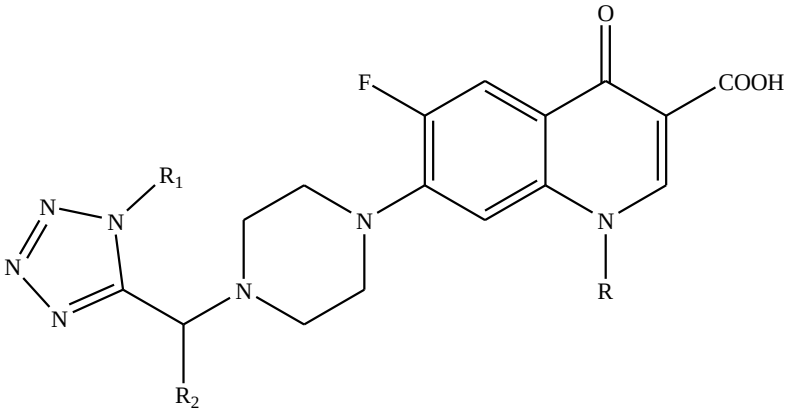


5 **6**

3. Antibacterial Activity.

It'sa potential promising new scaffold for the novel anti-inflammatory and antibacterial agents.*Chauhan et al*[17] have explored the synthesis of norfloxacin moiety by incorporating tetrazole scaffold at the N-4 position of the C-7 piperazin-1-yl group of newly developed norfloxacin entity, 1H-tetrazol-5-yl-(aryl) methyl piperazinyl-6-

fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(7)**and evaluated for their antibacterial activity against various strains of *Staphylococcus aureus*. All the synthesized compounds showed significant in vitro antibacterial activity against Gram-positive bacteria whereas some compounds displayed moderate activity against Gram-negative bacteria. *M. Sabbah et al*[18] have reported the synthesis of a new analogues of N-acyl-homoserine-lactone (AHL), in which the amide was replaced by a triazole or tetrazole ring**(8)** and tested for their activity as LuxR-dependent QS modulators. Several compounds showed a level of antagonistic or agonistic activity, notably some 1,4-triazolic and 1,5-tetrazolic derivatives.



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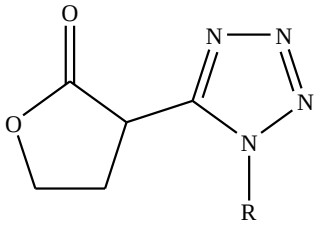

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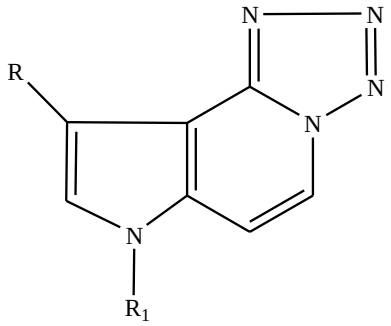
C.G. Dave et al[19] have reported the antibacterial activity of all the newly synthesized tetrazolo[1,5-*c*]pyrrolo[3,2-e]pyrimidines **(9)**by the agar plate diffusion method. *K. SudhakarBabuet al*[20]have reported the synthesis of a series of novel biphenyl tetrazoles**(10)** from the secondary amides and screened for their antibacterial activity.



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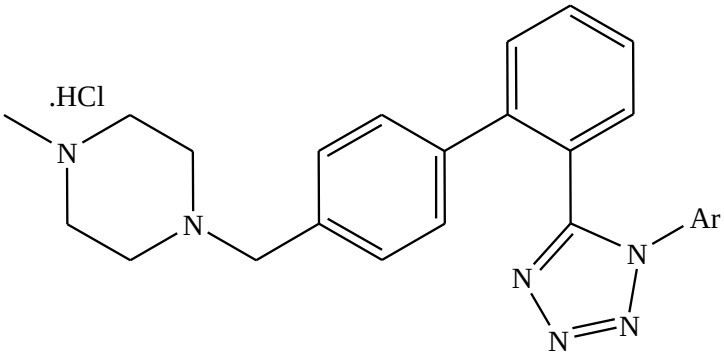

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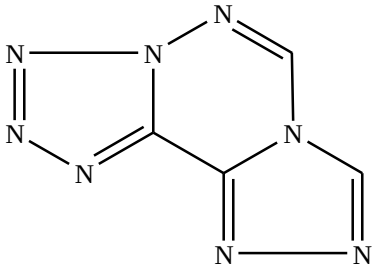
Tahaet al[21] have reported the synthesis of some heterocyclic compounds 1,2,4-Triazolo[4,3-*d*]tetrazolo[5,1-*f*]-1,2,4-triazines **(11)**utilizing Ethyl 1-Aminotetrazole-5-carboxylate and evaluated for their antimicrobial activity. Further, *Taha etal*[22] have reported the preparation of new compounds substituted aryl tetrazolo[1,5-b]1,2,5-oxadiazepin-9-ones **(12)** and evaluated for the antibacterial activities against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Escherichia coli* and *Klebsiellapeneumoniae*) bacteria using Ciprofloxacin and Norfloxacin as antibacterial standards.



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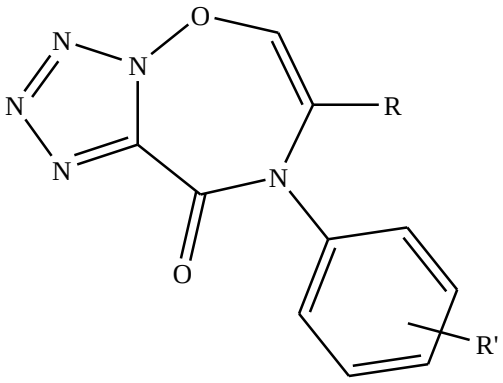

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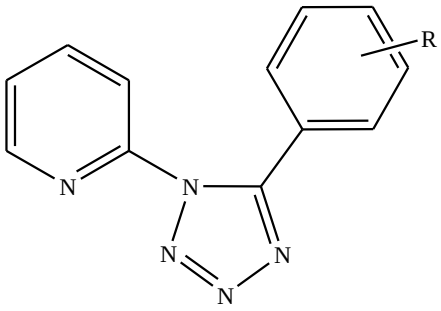
Shanmugapandiyan et al[23] have reported the synthesis a new series of 2-(5-substituted phenyl-1H-tetrazol-1-yl) pyridine **(13)** by the [3+2] cycloaddition of N-pyridyl-2-yl imidoformylchloride-benzene and sodium azide. All the synthesized compounds were screened for their antibacterial (*Staphylococcus aureus, Bacillus*

subtilis, Escherichia coli and *Pseudomonas aeruginosa*) and antifungal activities (*Aspergillusfumigatus*and *Candida albicans*) by cup plate method. *P. B. Mohite et al*[24] have reported the synthesis of various tetrazole containing new pyrimidine 4-(substituted phenyl)-6-(5-phenyl-1*H*-tetrazol-1-yl) pyrimidin-2-ol **(14)** and evaluated for their in vitro antibacterial and antifungal properties.



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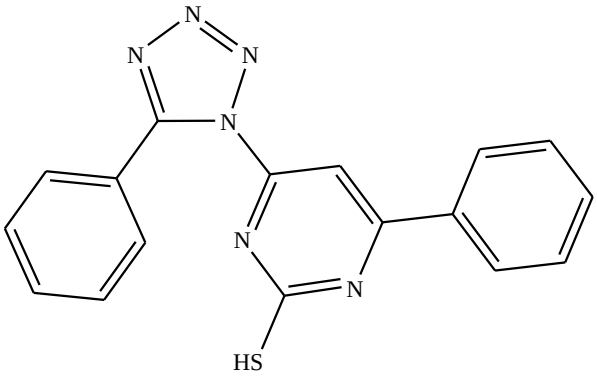

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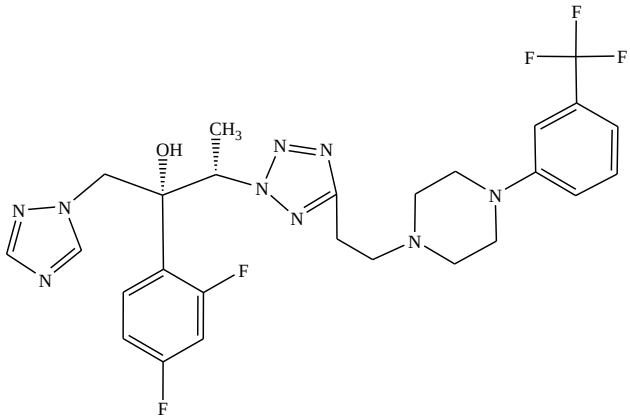
4. Antifungal Activity.

A series of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol and (2R,3S)-2-(2,4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazole-1-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol has been synthesized *by R. S. Upadhayaya et al*.[25] The antifungal activity of compounds was evaluated by *in vitro* agar diffusion and broth dilution assay. Furthermore, *R. S. Upadhayaya et al*[26] have reported the synthesis of tetrazole-based triazole derivatives bearing an ethyl chain linked with an aryl-piperazine, which are structurally similar to compounds **(15)** and **(16)**, and evaluated for their antifungal activity against the different fungal cultures such as *Candida* species, *C. neoformans*and *Aspergillus*species.



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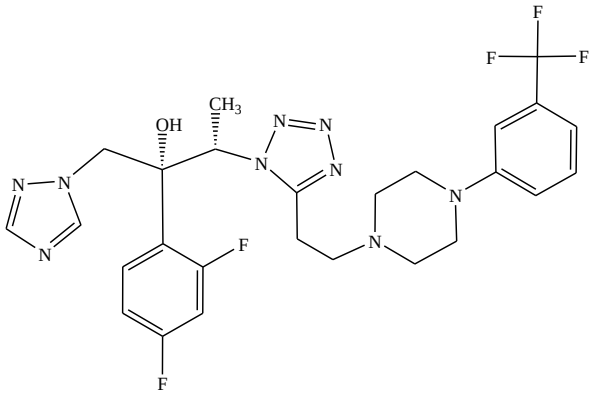

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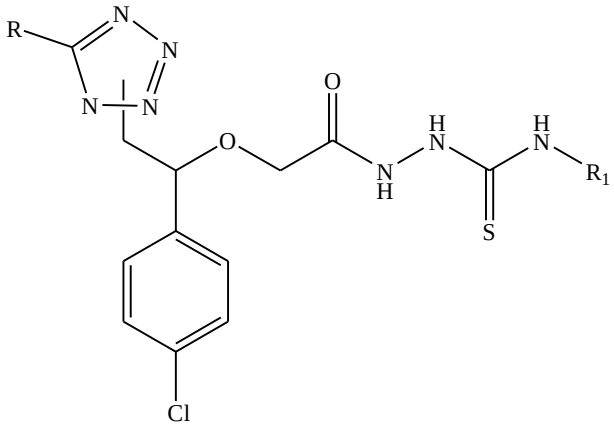
5. Anti-convulsant Activity.

S. A. F. Rostom et al[27] have reported the synthesis and antimicrobial evaluation of a new series of substituted tetrazoles**(17)** that are structurally related to the famous antimicrobial azole pharmacophore. Antimicrobial evaluation revealed that twenty compounds were able to display variable growth inhibitory effects on the tested Gram positive and Gram negative bacteria with special efficiency against the Gram positive strains. On the other hand, out of twelve compounds, two compounds were proved to be the most active anticonvulsant agents with high activity. Whereas,*Wagle S. et al*[28] have reported the synthesis of some new 4-styryltetrazolo[1,5-*a*]quinoxalines**(18)** and screened for their *in vitro* potent anticonvulsant activity.



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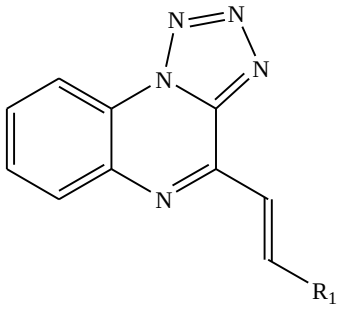

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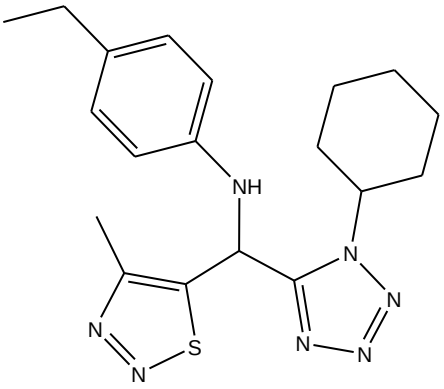
6. Antiviral Activity.

S. X. Wang et al[29] have reported the synthesis of a series of novel tetrazole containing 1,2,3-thiadiazole derivatives via Ugi reaction. The preliminary bioassay indicated that most target compounds exhibited very good direct anti-TMV activity at 100 mg/mL, which was equal to or higher than that of ribavirin. Among them, compound (**19**) showed excellent anti-TMV activity with inhibition activity of 48.73%, which was higher than that of ninamycin.



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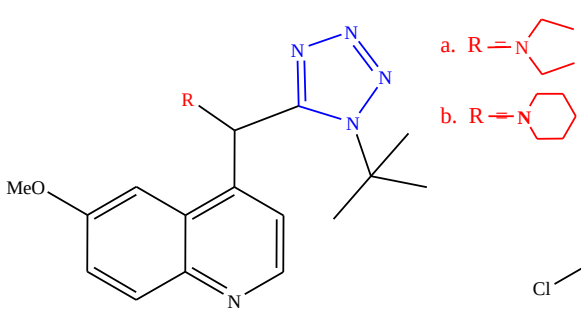
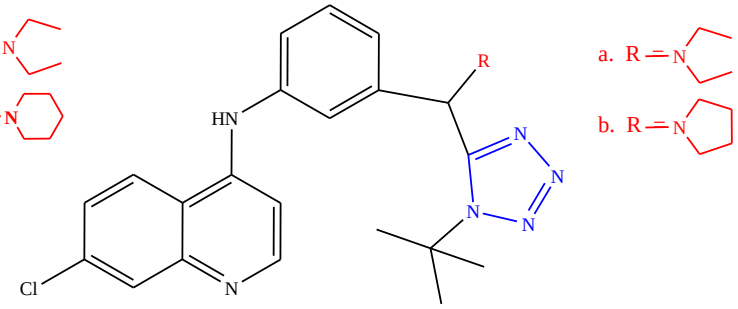
7. AntiplasmodialActivity.

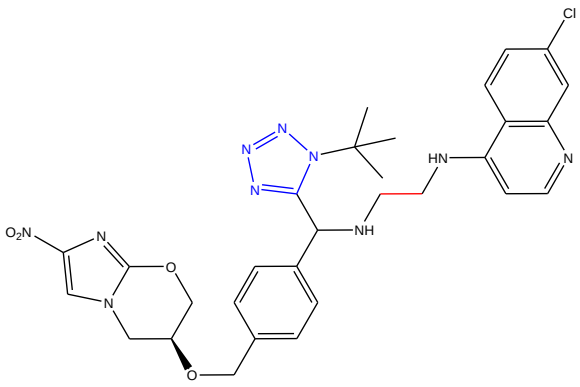
M. Tukulula et al[30] have designed and synthesized a number of new arylaminoquinolinetetrazole derivatives **(20)** using the modified $TMSN_3$-Ugi MCR and these were screened for antiplasmodial and antimycobacterial activities. The majority of these compounds exhibited modest activity against the 3D7 and K1 strains of *P. falciparum*, with IC_{50} values ranging from 0.647 to 6.737 μM. In continuation of their work, *M. Tukulula et al*[31] have reported the synthesis of a series of new deoxyamodiaquine-based compounds **(21)**and evaluated for*in vitro*antiplasmodial activity. The most potent compounds, 21a and 21b showed IC_{50} values in the range of 6–77 nM against chloroquine-resistant K1- and W2-strains of *P. falciparum*.

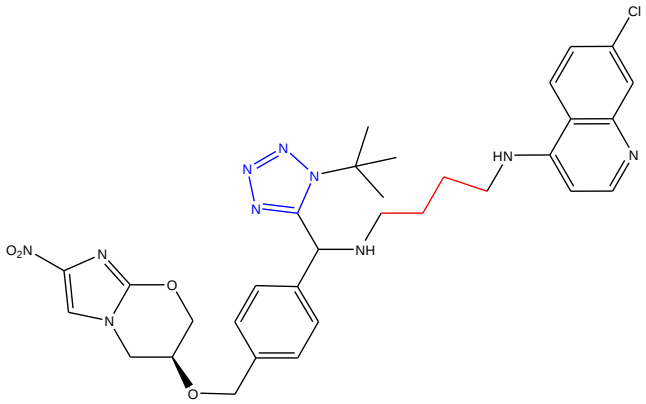




20 **21**

M. Tukulula et al[32] have also designed and synthesized new nitroimidazole and nitroimidazooxazine derivatives and screened for antiplasmodial and antimycobacterial activity. The synthesized compounds, especially hybrids **(22)** and **(23)** exhibited potent activity against the K1 strain of *P. falciparum*, with IC_{50} values in the low micromolar range.

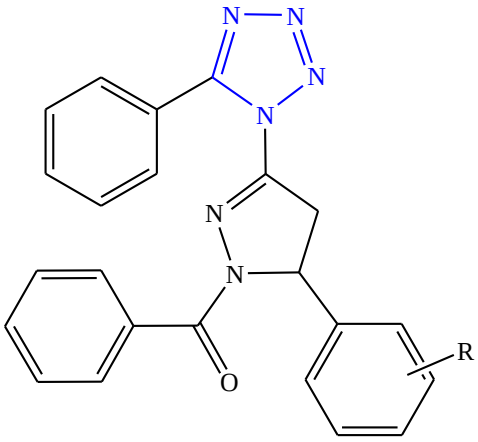




22 **23**

8. Anti-inflammatory Activity.

Mohite et al[33] have synthesized [5-substitutedphenyl-3-(5-phenyl-1H-tetrazol-1-yl)-4, 5-dihydro-1H-pyrazol-1-yl] (pyridin-4-yl) methanone**(24)** from benzonitrile and screened for in-vitro anti-inflammatory activity. *U. Natarajan et al*[34] have described a novel synthetic route for the synthesis of Schiff's bases incorporating tetrazoloquinoxalines**(25)** and screened for their in vitro antimicrobial and anti-inflammatory activity.



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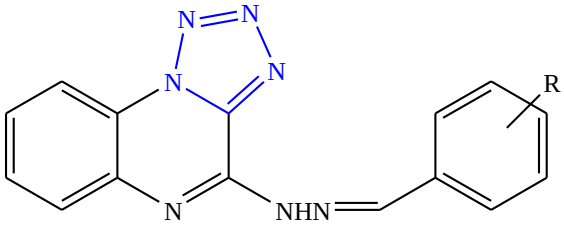

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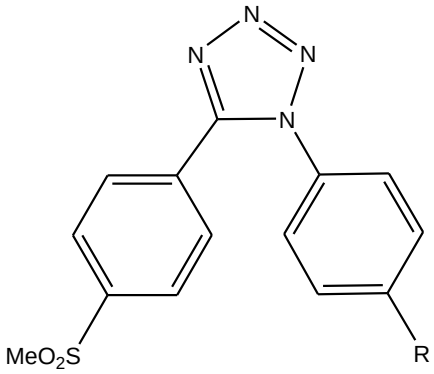
9. COX-1 & 2 Inhibitor Activities.

Selective COX-2 inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) that directly target cyclooxygenase-2, COX-2, an enzyme responsible for inflammation and pain. *Hourani et al*[35] have synthesized a series of 1,5-diaryl-substituted tetrazole derivatives **(26)** via conversion of readily available diaryl amides into corresponding imidoylchlorides followed by reaction with sodium azide and all compounds were evaluated for cyclooxygenase (COX) assays *in vitro* to determine COX-1 and COX-2 inhibitory potency and selectivity. In continuation of their work, *B.J. Al-Hourani et al*[36]have prepared a series of novel 5-substituted 1H-tetrazoles as cyclooxygenase-2 (COX-2) inhibitors via treatment of various diaryl amides with tetrachlorosilane/sodium azide.



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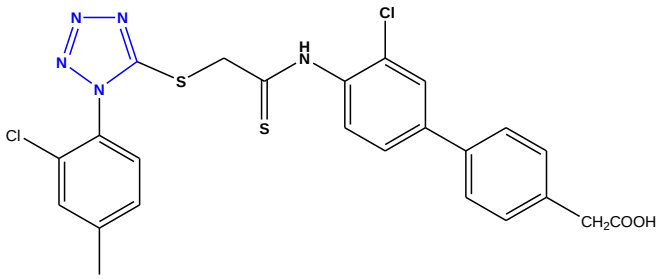
10. Anti-HIV Activity.

The role of tetrazolyl group in the binding of the thiotetrazole acetanilide inhibitors with the HIV-1 reverse transcriptase has been studied through the design of different cyclic and acyclic tetrazole**(27)** replacements by *A. Gagnon et al*.[37a]Furthermore, *A. Gagnon et al*[37b] have also reported the synthesis of a series of aryl thiotetrazolylacetanilides and evaluated as a potent inhibitors of the HIV-1 wild type and K103N/Y181C double mutant reverse transcriptases.*W. Li et al*[19c] have reported the discovery of potent HIV-1 non-nucleoside reverse transcriptase inhibitors from arylthioacetanilide**(28)** structural motif.



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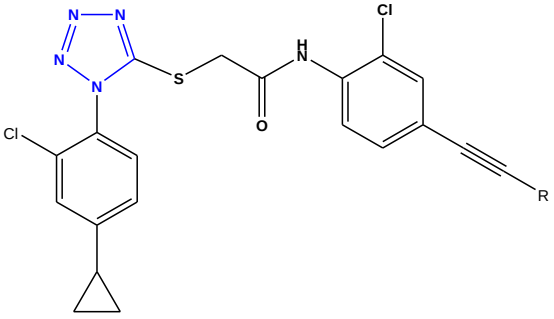

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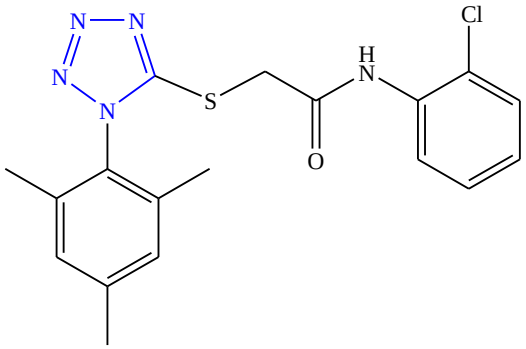
E. Muraglia et al[38] have reported a series of aryltetrazolylacetanilides**(29)** and evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors on wild-type virus and on the clinically relevant K103N mutant strain. *B. C. H. Mayet al*[39] have synthesized a core dipeptidomimetic**(30)**, by replacing cis-amide bond of peptides with 1,5-disubstituted tetrazoles as isosteres, and evaluated for the potent HIV-protease inhibitors.



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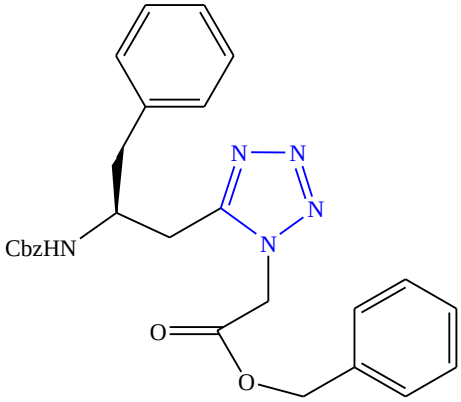
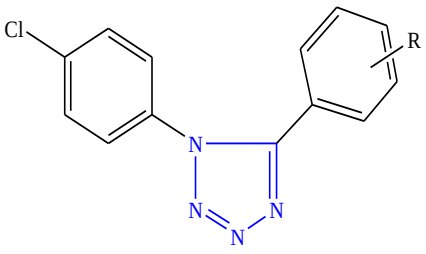


30

11. Anti-tubercular Activity.

P. Shanmugapandiyan et al[40] have synthesized several new 5-chloro-2-(5-(substituted phenyl)-1H-tetrazol-1-yl) pyridines **(31)**from 2- amino pyridine derivatives. All the synthesized compounds were screened for their antitubercular activity by Microplate Alamar Blue assay (MABA) method and have exhibited significant activity against *Mycobacterium tuberculosis* H37Rv. *Mohite P.B. et al*[41] have reported the antimycobacterial activity of different tetrazoles**(32)** having different aryl substituents on azetidinone core against *Mycobacterium tuberculosis* strain H37Rv.



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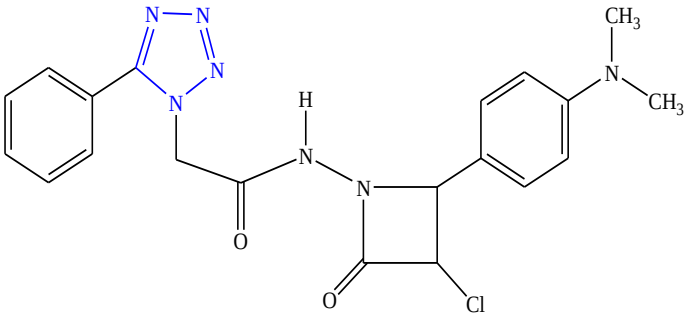
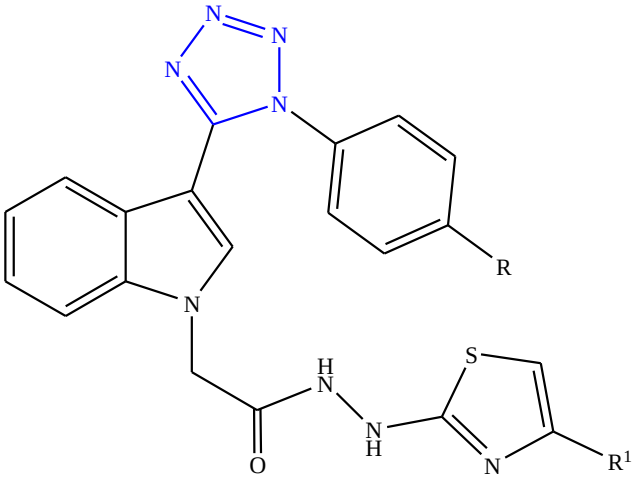


32

12. Antitumor Activity.

S. Muralikrishnaet al[42]have reported the synthesis of1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted

phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one**(33)**and tested for *in vitro* antitumor activity using the Alamar Blue assay. *R. Romagnoli et al*[43] have concisely synthesized two series of 1,5-diaryl substituted tetrazoles**(34)**as rigid analogues of Combretastatin and identified as potent antiproliferative and antitumor agents. Several of these compounds were found having potent activity in inhibiting the growth of multidrug resistant cells over expressing P-glycoprotein. Active compounds induced apoptosis through the mitochondrial pathway with activation of caspase-9 and caspase-3.



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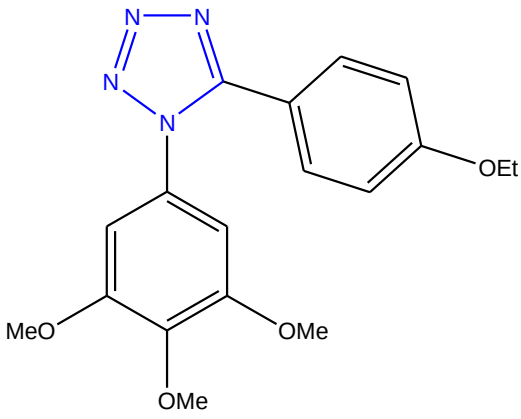


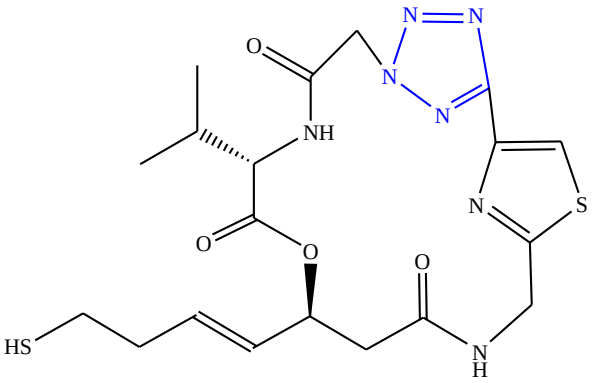
34

13. Anticancer Activity.

The current scenario highlights the need for the discovery and development of new lead compounds, exhibiting optimal *in vivo* antitumor potency and new mechanisms of action. Recent advances in clinical techniques, including large co-operative studies are allowing more rapid and reliable evaluation of new drugs. The combination of these advantages with improved preliminary screening systems is enhancing the emergence of newer and more potent compounds.Surprisingly it is found that the tetrazole derivatives possess high degree of anticancer activities.

X. Li et al[44]have reported the design, synthesis, and biological evaluation of a new series of largazole analogues in which a 4-methylthiazoline moiety was replaced

with a triazole and tetrazole rings. Compound **(35)** bearing a tetrazole ring was identified to show much better selectivity for HDAC1 over HDAC9 than largazole (10-fold). On the other hand, *G. S. Jedhe et al*[45] have developed a series of 1,5-disubstituted tetrazole analogues of combretastatin with extended hydrogen-bond donors at the ortho-positions of the aryl A and B rings and evaluated for their inhibition of the growth of four different human cancer cell lines, that is, human cervix carcinoma (HeLa), human non-small-cell lung carcinoma (A549 and H1299), and breast adenocarcinoma (MCF-7). Compound **(36)**bearing ortho-hydroxyl group in the B-ring was shown to enhance antiproliferative activity.



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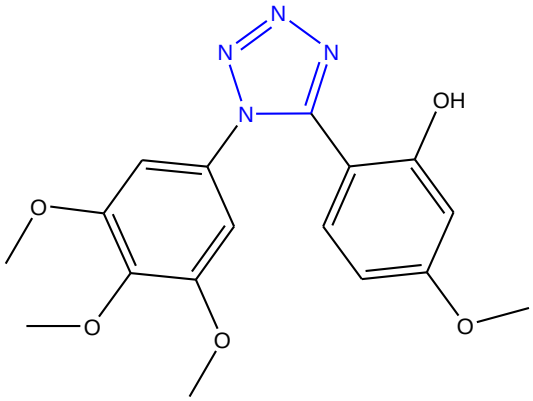
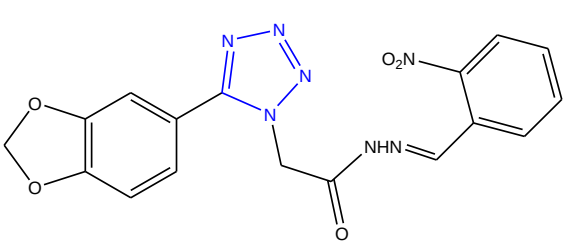
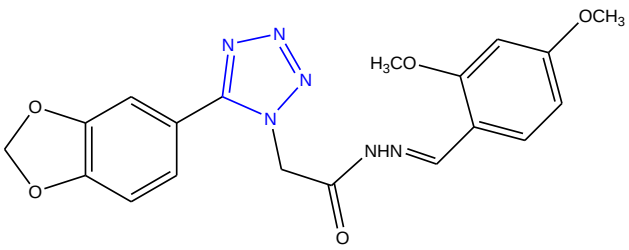


36

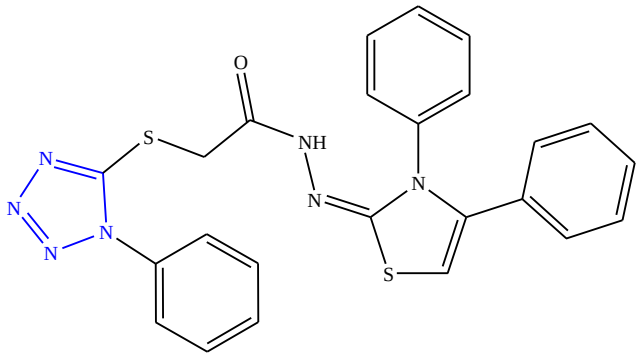
M. Arshad et al[46].have reported the synthesis of a series of tetrazolohydrazones starting from the simple molecules. All the compounds were screened against the ER+/- breast cancer cell lines. Out of these, five compounds were found to retard the growth of breast cancer cells. Based on the gene study the compound **(37)** and two other were found more effective in retarding the growth of MCF-7 cells. While compound **(38)** showed more growth retarding effects in ER negative MDA-MB-231 and ZR-75 cell lines.

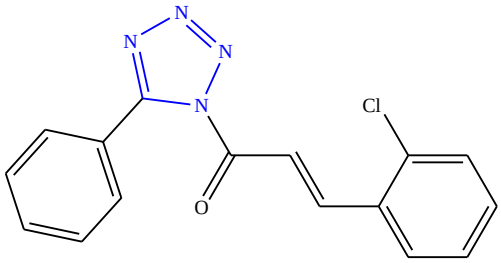




37 **38**

M. D. Altıntop et al[47] have described the synthesis of thiazoline derivatives bearing a hydrazone moiety along with tetrazole ring and evaluated for their antibacterial activity against *P. aeruginosa*. Furthermore,the most effective derivatives were also evaluated for their cytotoxicity against C6 rat glioma cells. The compound **(39)** bearing 1-phenyl-1H-tetrazole was found to be the most promising anticancer agent against C6 glioma cell lines with an IC_{50} value of 8.3 +- 2.6 µg/ml when compared with cisplatin (IC_{50} = 13.7 +- 1.2 µg/ml). The synthesis of 5-phenyl tetrazolechalcones were reported by Bhaskar*et al.*[48]The synthesized chalcones were screened for anticancer activity against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. The compound **(40)**was found to be active with selective influence on ovarian cancer cell lines.

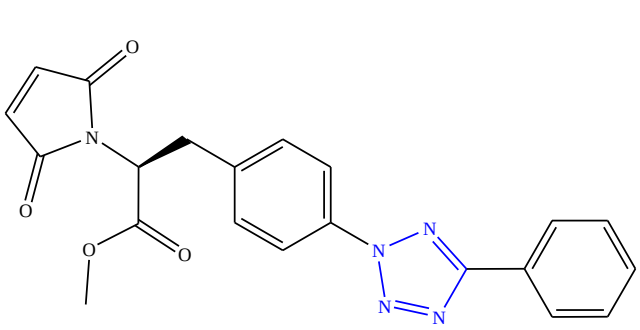




39 **40**

B. Zhu et al[49] have developed two types of novel chemical tools for the study of DNAmethyltransferases (DNMT1s). Among these compounds, one of them (41) possessed reasonable inhibitory activity against DNMT1 in both *in vitro* enzymatic

assays and cell growth proliferation experiments. Both T1 and **41** showed effective labeling of endogenous DNMT1 from mammalian cells by using *in vitro* competitive pull-down and live-cell bioimaging experiments. *S.C. Kohler et al*[50] have synthesized derivatives of the third-generation P-gp inhibitor HM30181**(42)**. The compounds were tested for their inhibitory activities against the breast cancer resistance protein (BCRP) and screened against P-glycoprotein (P-gp, ABCB1) and multidrug resistance protein 1 (MRP1, ABCC1) to confirm the selectivity toward BCRP.



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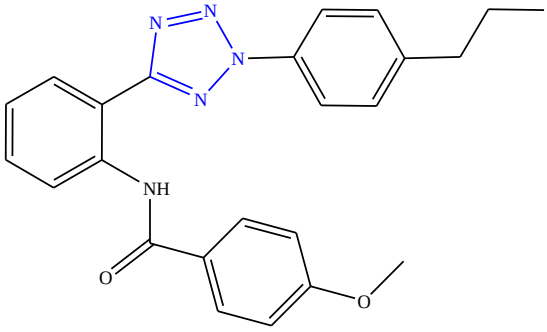
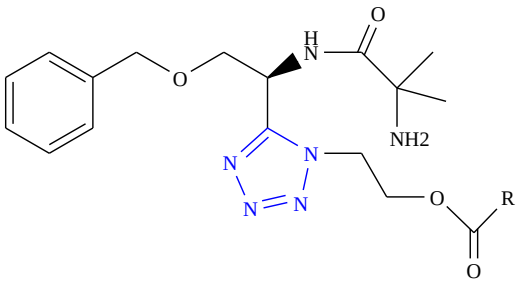
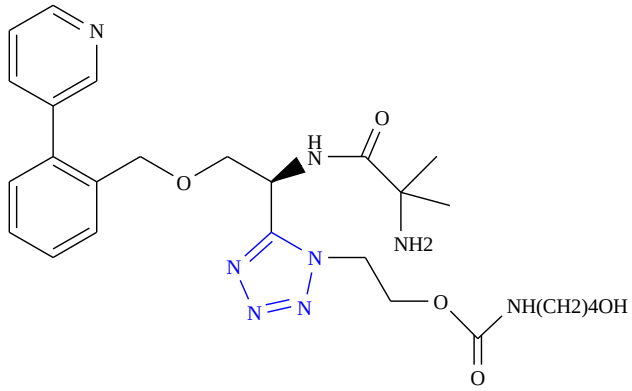


42

14. Human Growth Hormone Secretagogue (GHS)

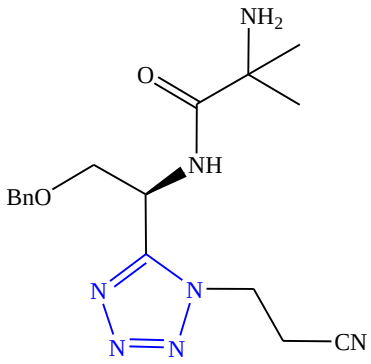
A tetrazole-based peptidomimeticester (BMS-317180)**43** was discovered as a human growth hormone secretagogue (GHS) by Jun Li et al.[51] Furthermore, *Jun Li et al*[52] have synthesized a series of ortho-substituted compounds and evaluated for the SAR studies of the O-benzyl serine side chain with improved *in-vitro* and *in-vivo* activity. Among them, the biphenyl compound **(44)** shows twofold improvement in potency compared to its parent compound BMS-317180.

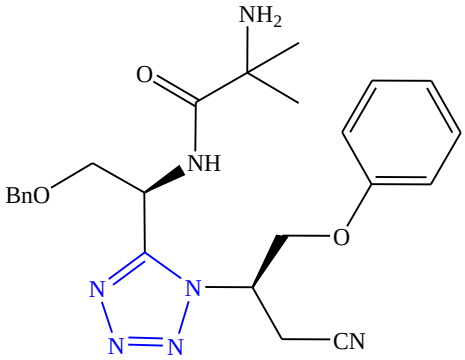




43 **44**

A.S. Hernandez et al[53] have discovered a novel class of Growth Hormone Secretagogues (GHS) based on a tetrazole template**(45)**. In vitro SAR and in vivo potency within this new class of GHS were described. In continuation of their work, *A.S. Hernandez et al*[54] have developed an enantiospecific route for the synthesis of nitriles.The potency of nitrile **(46)** has been optimized by introducing 2-arylethyl moiety which provides an additional interaction with the GHS receptor.



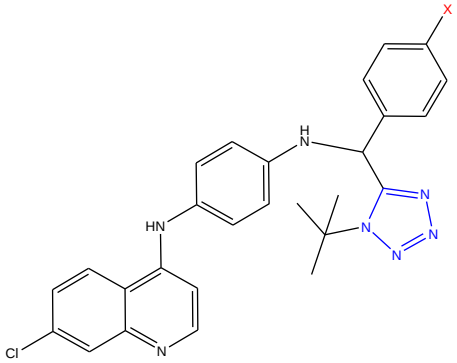


45 **46**

15. Antimalarial and Antiprotozoal activity.

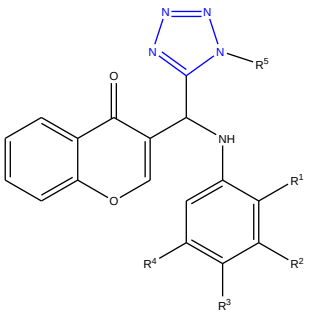
Pandey et al[55] have designed and synthesized some tetrazole embedded chloroquine (CQ) derivatives joined through variable linkers. Interestingly, compounds **47a** and **47b** showed promising *in vitro* activity against both CQ-S as well as CQ-R strain of *P. falciparum* and also excellent *in vivo* antimalarial activity against

P. yoelli.P. A. Cano et al[56] have reported the synthesis of novel 3-tetrazolylmethyl-4H-chromen-4-ones **(48)** and evaluated for antiprotozoal activity against Entamoebahistolytica, Giardia lamblia and Trichomonavaginalis.



a X = Cl

b X = Br

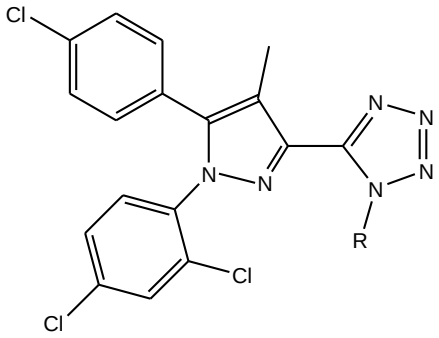


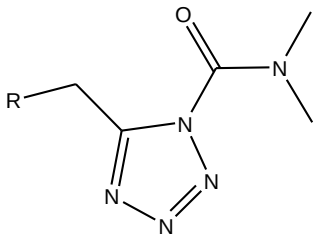
R^1 = H, Br, I, NO_2
R^2 = H, OMe
R^3 = H, Cl, OMe, NO_2
R^4 = H, OMe
R^5 = t-Bu, Cy, 2,6-diMePh

47 **48**

16. Cannabinoid Inhibitors.

S. Y. Kang et al[57]investigated a series of tetrazole-biarylpyrazole derivatives **(49)** for their inhibition of binding for cannabinoid CB1 and CB2 receptors. Several compounds in this series exhibited potent CB1 receptor binding affinities, validating the hypothesis that tetrazole could replace amide functionality to act as a bioisostere of amide moiety of rimonabant. *G. Ortar et al*[58] have synthesized a series of eighteen 1,5- and 2,5-disubstituted carbamoyl tetrazoles**(50)** and evaluated as inhibitors of endocannabinoid inactivation.



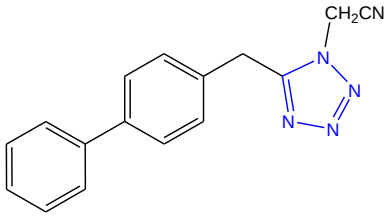


R = $PhCH_2$, $Ph(CH_2)_2$

49 **50**

17. Miscellaneous biological activities.

Ortar et al[59] have reported a new series of 1,5-disubstituted tetrazoles**(51)** and evaluated as inhibitors of anandamide cellular uptake. Some of them inhibit the uptake process with a relatively high potency (IC_{50} = 2.3–5.1 μM) and selectively over other proteins involved in endocannabinoid action and metabolism. *P.M. O'Brien et al*[60] have examined the structure-activity relationship for a series of retroamidetetrazole derivatives where they found that, out of the substituents evaluated on the benzamide ring, the 3-nitro derivative **(52)**, provided optimal activity in vitro, but the 2,6-dimethyl substituted compound **(53)**, was considerably more efficacious in vivo, in the cholesterol-fed rat model.



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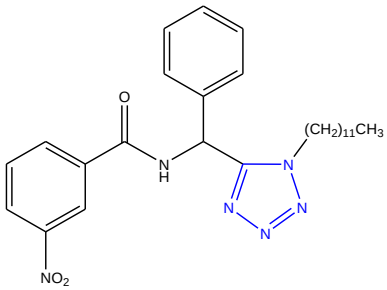

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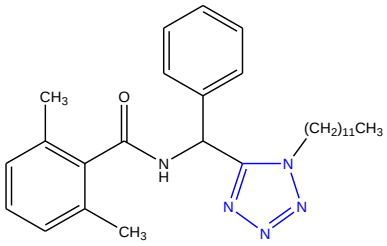

53

Conclusion

1,5-DisubstitutedTetrazoles are nitrogen-rich heterocyclic structures that possess a wide range of chemical, biological and medicinal applications. Recently, the synthesis of 1, 5-DSTs has been of great interest in the literature. In this review, we have described numerous pharmacological aspects for the synthesis of 1,5-DSTs with most of them being reported in recent years.

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