Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Annals of Biological Research, 2010, 1 (1) : 82-89
(http://scholarsresearchlibrary.com/archive.html)

Current biological and synthetic profile of Triazoles: A review

Priyanka P. Gadhave[1], Nachiket S. Dighe*[1], Shashikant R. Pattan[1], Pravin Deotarse, Deepak S. Musmade[1] and R. V. Shete[2]

[1]Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar
[2]Department of Pharmacology, R D's College of Pharmacy, Bhor, Pune

---

Abstract

Triazole is a five membered heterocyclic system consisting of two carbon atoms and three nitrogen atoms shows wide range of biological activities. Triazoles can be synthesized using Einhorn-Brunner reaction or the Pellizzari reaction from acyl hydrazides. Triazoles posses wide spectrum of biological activities like including antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antihypertensive, analgesic, and hypoglycemic properties. The present reviews attempted to gather the various developments in synthesis and biological activities of triazole derivatives.

Key words: 1, 2, 4-Triazole, Pharmacological activity, SAR, Total synthesis.

Introduction

1,2,4-Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1, 2, 4-Triazoles can be prepared using the Einhorn-Brunner reaction or the Pellizzari reaction.

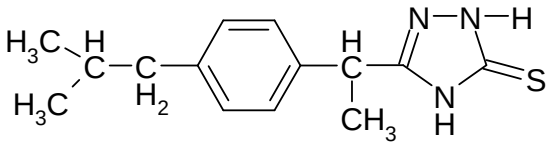
Einhorn-Brunner reaction

The Einhorn-Brunner reaction is the chemical reaction of imides with alkyl hydrazines to form a mixture of isomeric 1, 2, 4-triazoles. The Pellizzari reaction is the chemical reaction of an amide and a hydrazide to form a 1, 2, 4-triazole.

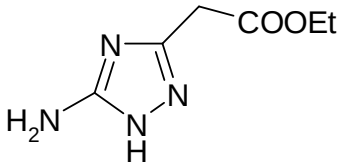
Anti-inflammatory activity

1. The synthesis of 3-[1-(4-(2-methylpropyl)phenyl)ethyl]-1,2,4-triazole-5-thione and its condensed derivatives 6-benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones are described.

The structures of the compounds were elucidated by spectral and elemental analysis. In the pharmacological studies, anti-inflammatory activities of these compounds have been screened. In gastric ulceration studies the synthesized compounds were generally found to be safe at a 200 mg/kg dose level**.** [1]

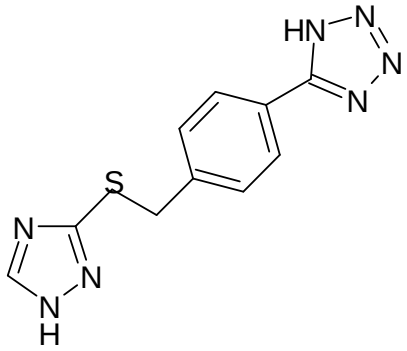


2. The synthesis of different acylated 1,2,4-triazole-3-acetates with the objective of discovering novel and potent anti-inflammatory agents. Structures of the synthesized compounds were elucidated by spectral and elemental analyses. The obtained compounds were evaluated for their anti-inflammatory activites as well as gastric ulcerogenic effects and acute toxicity.[2]



Antimycobacterial activity

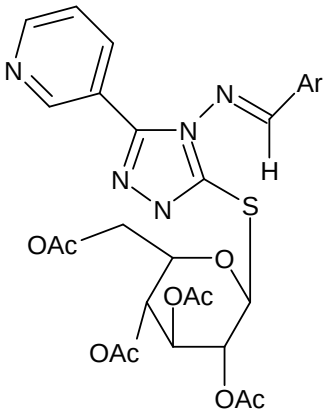
Series of 3-benzylsulfanyl derivatives of 1,2,4-triazole and 4-methyl-1,2,4-triazole were synthesized by alkylation of starting triazole-3-thiol with appropriately substituted benzyl halide. All members of the set were evaluated for in vitro antimycobacterial activity against *Mycobacterium tuberculosis, M. avium,* and two strains of *M. kansasii*. The activities were expressed as the minimum inhibitory concentration. The compounds exhibited only a moderate or slight antimycobacterial activity. Minimum inhibitory concentrations fall into a range of 32->1000 μmol/l. The most active substances bear two nitro groups or a thioamide group on the benzyl moiety. As regards the cytotoxicity effect, the evaluated compounds can be considered as moderately toxic. [3]



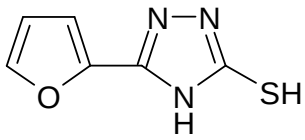
Antimicrobial activity

1. Glucosidation of some 4-amino- and 4-arylideneamino-5-(pyridin-3-yl)-2,4-dihydro-[1,2,4]-triazole-3-thiones with 2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl bromide followed by chromatographic separation gave the corresponding N- and S-b-D-glucosides. The structure of

these two regiosiomers was established chemically and spectroscopically. Deamination as well as deacetylation of some selected nucleosides have been achieved. Antimicrobial screening of 14 selected compounds resulted in their activity against Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum, Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, and Escherichia coli.[4]

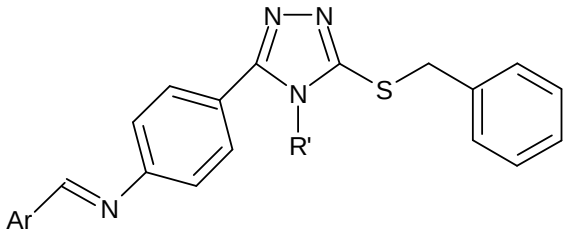


2. Ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetate, 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide and a series of new *N*-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides were synthesized and evaluated for in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Escherichia coli* ATCC 8739, *Shigella flexneri*, *Salmonella typhi*, *Proteus mirabilis* and antifungal activity against *Candida albicans* ATCC 10231 using the disk diffusion and microdilution methods. The in vitro antimycobacterial activity of the new compounds against *Mycobacterium tuberculosis* H37Rv was evaluated employing the BACTEC 460 radiometric system. The highest inhibition observed was 61% at _6.25 _g/ml.[5]

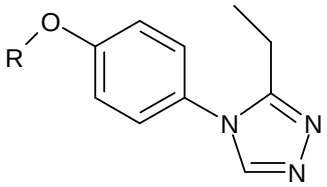


Anticonvulsant activity

1. A series of novel 3-{[(substituted phenyl)methyl]thio}-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles and several related Schiff's bases, 3-{[(substituted phenyl)-methyl]thio}-4-alkyl/aryl-5-{[[(substituted phenyl/5-nitro-2-furyl)methylene]amino]-phenyl}-4H- 1,2,4-triazoles were synthesized for evaluation of their biological properties. Structures of the synthesized compounds were confirmed by the use of their spectral data besides elemental analysis. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and neurotoxicity (NT) screens. A number of triazole derivatives, exhibited protection after intraperitoneal administration at the dose of 100 and 300 mg/kg in one or both models employed. Some of the tested compounds showed marginal activity against *M. tuberculosis H37 Rv*.[6]

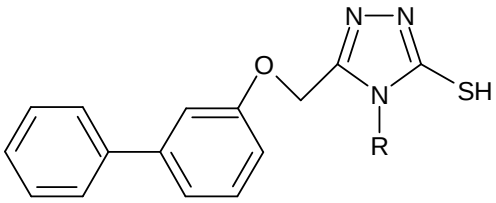


2.A series of 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazole derivatives was synthesized as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole 3q was found to be the most potent with ED50 value of 8.3 mg/kg and protective index (PI = TD50/ED50) value of 5.5, but compound 3r, 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole, exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin. For explanation of the possible mechanism of action, the compound 3r was tested in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test.[7]



Analgesic Activity

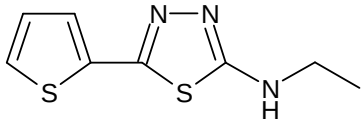
A series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid were synthesized in order to obtain new compounds with potential anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. All compounds were evaluated for their anti-inflammatory activity by the carrageenan induced rat paw edema test method. The compounds possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities. These compounds showed significant analgesic effect and at an equimolar oral doses relative to flurbiprofen were also found to be non-gastrotoxic in rats. (81.81%) than the reference drug (79.54%), low ulcerogenic potential and protective effect on lipid peroxidation.[8]



Cytotoxic activity

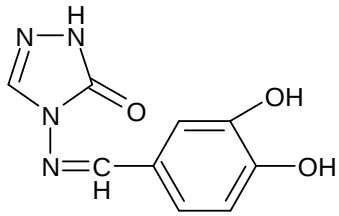
Novel derivatives of 4,5-substituted-1,2,4-triazole-thiones and 2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for their cytotoxicity. The biological study indicated that compounds 4-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-

thione, N-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazol-2-amine, 4-amino-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione and 4-amino-5-(5-phenylthien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione possessed high cytotoxicity in vitro against thymocytes. The corresponding IC50 values were 0.46 mM, 5.2 _ 10_6 mM, 0.012 mM and 1.0 _ 10_6 mM. The tested compounds showed a general stimulation effect on B-cells' response.[9]



Antioxidant activity

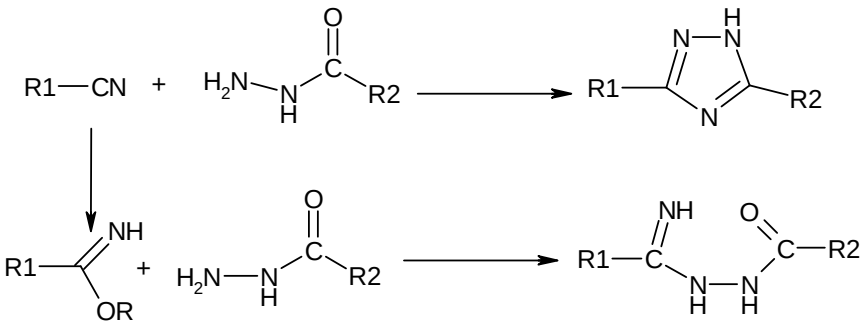
Some 4-benzyl-idenamino-4,5-dihydro1H-1,2,4-triazol-5-one derivatives were prepared and investigated for their antioxidant activity also the pKa in Non aqueous solvent is also determined.[10]



Methods of Synthesis

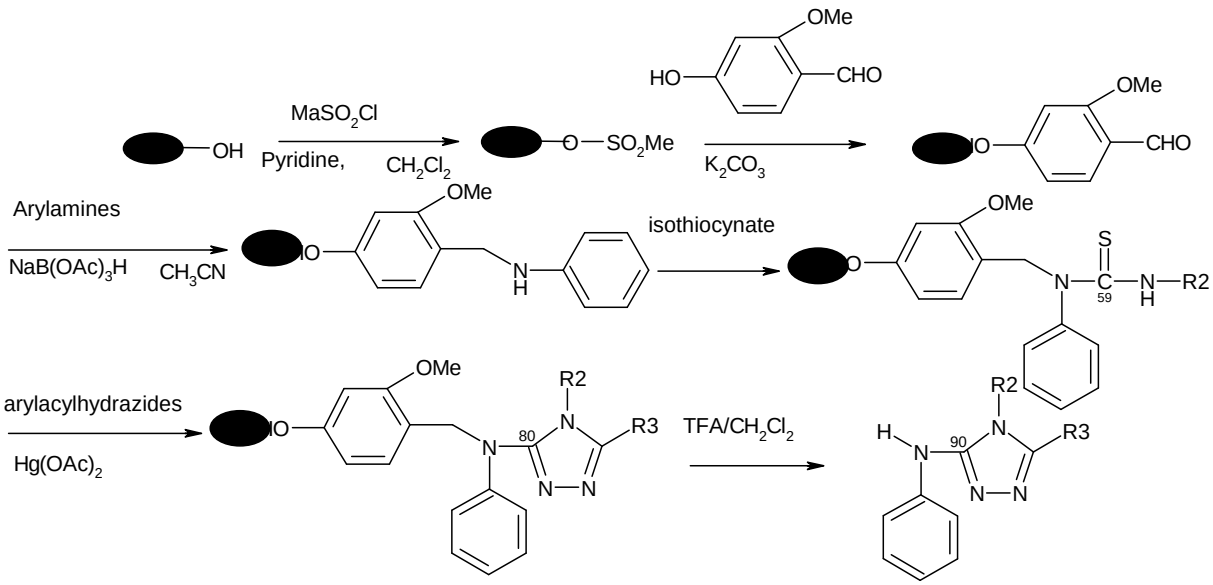
Base-catalyzed, direct synthesis of 3,5-disubstituted 1,2,4-triazoles

A convenient and efficient one step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles by the condensation of a nitrile and a hydrazide is presented. A diverse range of functionality and heterocycles are tolerated under the reaction conditions developed, and the reactivity of the nitrile partner is relatively insensitive to electronic effects.[11]



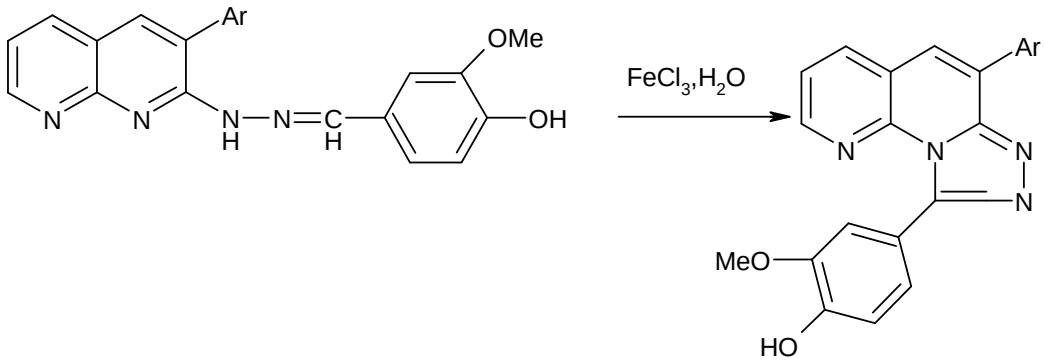
Traceless liquid-phase synthesis

A liquid-phase route to 3-alkylamino-4,5-disubstituted-1,2,4-triazoles has been developed, which permits the incorporation of three elements of diversity. The heterocycle was constructed upon PEG6000 (soluble polymer) modified by 4-hydroxy-2-methoxybenzaldehyde, from which a traceless cleavage could be realized with TFA/CH2Cl2. This method provided a library of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles with reasonable yields and excellent purity.[12]

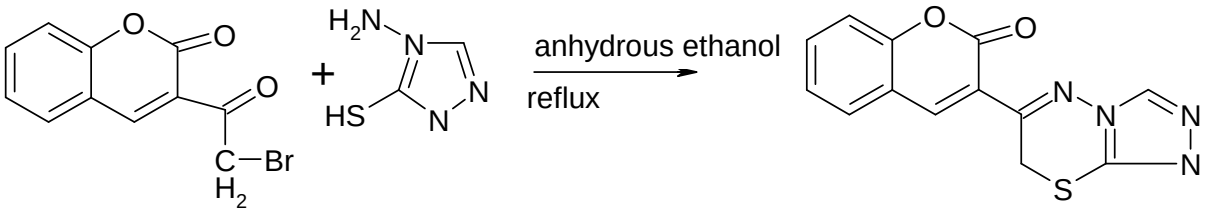


Solid phase synthesis of Triazole using $FeCl_3$ using Oxidative cyclization.

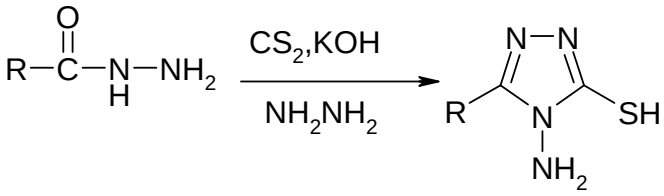
An efficient and mild method for the synthesis of 1,2,4-Triazole by the Oxidative cyclization in the solid state by grinding at room temperature has been described.[13]



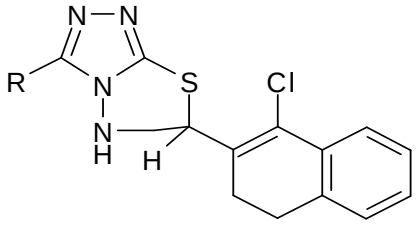
Reactions of various coumarins with anhydrous ethanol and hydrazins furnishes corresponding Triazole. [14]



1, 2, 4-Triazole derivatives can also be prepared using Hydrazides, Carbon disulfide in presence of Base. [15]



Microwave assisted synthesis of 1, 2, 4-Triazole derivatives
The 1,2,4-Triazoles can be synthesized using catalytic amount of p-TsOH under Microwave irradiation rate enhancement and improvement in yields.[16]



Conclusion

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by 1, 2, 4 Triazole derivatives. The biological profiles of these new generations of 1, 2, 4 Triazoles would represent a fruitful matrix for further development of better medicinal agents. An attempt is made to focus on some synthetic methods of triazoles including Base catalyzed synthesis and Traceless synthesis. It can act as an important tool for medicinal chemists to develop newer compounds possessing Triazole moiety that could be better agents in terms of efficacy and safety.

References

[1] Birsen Tozkoparana, Nesrin Gökhana, Göknur Aktayb, Erdem Yes¸iladac, Mevlüt Ertan, *Eur. J. Med. Chem*. 35 ;**2000;** 743−750.
[2] Ashraf M. Abdel-Megeed, Hamdy M. Abdel-Rahman, *European Journal of Medicinal Chemistry* 44 ;**2009** ;117-123.
[3] Veˇra Klimešová , Lenka Zahajská , KarelWaisser , Jarmila Kaustová , Ute Möllmann, *IL Farmaco* 59 ;**2004** ;279–288.
[4] Nasser S. A. M. Khalil, *Carbohydrate Research* 341; **2006**; 2187–2199.
[5] Nuray Ulusoy, Aysel Gu¨rsoy, *Il Farmaco* 56; **2001**; 947–952.
[6] I˙lkay Küçükgüzel, Sq. Güniz Küçükgüzel, *IL Farmaco* 59; **2004;** 893–901.
[7] Jing Chen, Xian-Yu Sun, *Bioorganic & Medicinal Chemistry* 15; **2007;** 6775–6781.
[8] Suroor A. Khan, Mohammad Amir, *European Journal of Medicinal Chemistry*, 43; **2008**; 2688-2698.

[9] Anelia Ts. Mavrova, Diana Wesselinova, *European Journal of Medicinal Chemistry* 44; **2009;** 63-69.
[10] H. Yuksek, S. Kolagh, *Ind.J.Chem*.; **2006**: 45B: 3: 175-178.
[11] Kap-Sun Yeung, Michelle E. Farkas, *Tetrahedron Letters*, 46; **2005;** 3429–3432.
[12] Ying-Xiao Zong, Jun-Ke Wang, *Tetrahedron Letters* 46; **2005;** 5139–5141.
[13] K.Mogilaiah, K.Vidya and T.Kumara Swamy,.*Ind J Chem*; **2009**, 48B: 599-601**.**
[14] P.Vijaya Kumar, V.Reyswar Rao, *Ind.J.Chem*. ; **2008**; 48B; 1: 106-10.
[15] Refat-El-Sayed, *Ind.J.Chem*. ; **2006**; 45B; 3; 738-746.
[16] P.Kamothra, A.Gupta, *Ind.J.Chem*.; **2007:** 46: 980-984.