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Review Article

A REVIEW ON SYNTHESIS, CHARECTIRIZATION PHARMACOLOGICAL ACTIVITY OF 1, 2, 4 TRIAZOLE DERIVATIVES CONTAINING BENZOTHIAZOLE

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Substituted benzotriazole derivatives are an important class of heterocyclic compounds. In recent years, the analogs and derivatives of heterocyclic compounds have attracted great interest due to their biological and pharmacological properties. The benzothiazole-containing compound participating in the study aims to evaluate new products with biological activity, such as antibacterial, anticancer, antifungal, anthelmintic, antidiabetic, amyloid imaging agent and anticancer agent. This review focuses on the 4,444 different synthesis methods of potentially active substituted benzothiazoles currently under development. The present review focuses on the benzothiazoles with potential activities that are now in development.

Key Words: Benzothiazole, Pharmacological activity, Antimicrobial activity, Anticonvulsant activity, Antibacterial activity.

INTRODUCTION

Heterocyclic Compound

Heterocyclic compounds are natural compounds that include a ring structure containing atoms additionally to carbon, **like sulfur, oxygen or nitrogen**, as a part of the ring. they'll be either easy aromatic rings or non-aromatic rings. Some **examples are pyrazole (C), pyrimidine (C4H4N2) and dioxane (C4H8O2).**

The compounds similar to cyclopropane, an anaesthetic with unstable properties, and cyclo-hexane, a solvent, aren't heterocyclic, they're merely cycloalkanes many heterocyclic compounds, counting some amines, are carcinogenic.[1]

These hetero atoms are mostly N,S and O Elements like P,Si,B,Sn,As,Al,Cu also are occasionally incorporated within the ring.Epoxide (eg.ethylene oxide) and lactone (eg.gama-butyrolactone) are generally excluded thanks to the relative instability of their ring systems[2]

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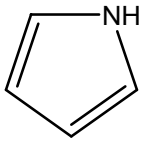
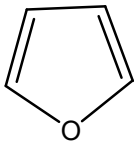
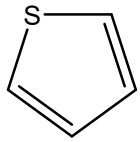
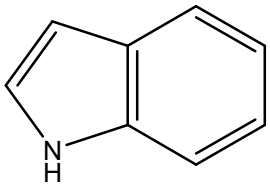
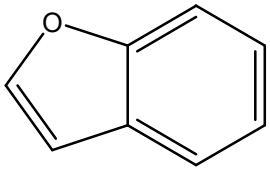
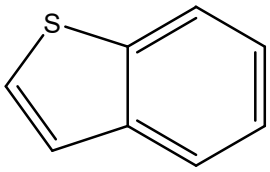
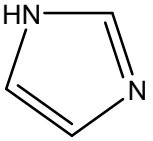
Example of hetrocyclic compound-

1.) 5-Membered Rings-

A.)One Hetero atom containing Compound,

A.)One Hetero atom containing Compound,	Stracture of Compound,
a .pyrole(azole)	 pyrrole
b.Furan(oxazole)	 Furan
c.Thiophene(thiophene)	 Thiophene
d.Indole(benzo[b]azole)	 Indole
e.Benzofuran(benzo[b]oxazole)	 Benzofuran
f.Benzothiophene(benzo[b]thiophiole)	 Benzothiophene

B.)Two hetero atom containing Compound-

a.Imidazole(1,3-diazole)	 Imidazole

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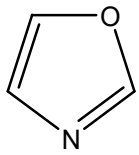
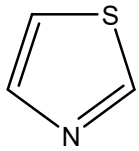
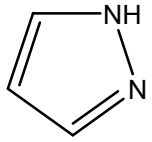
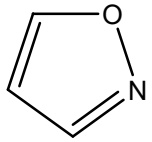
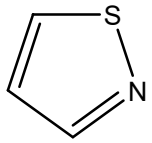
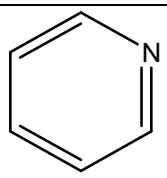
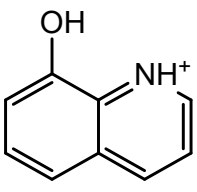
b.Oxazole(1,3-oxazole)	 Oxazole
c.Thiazole(1,3-thiazole)	 .Thiazole
d.Pyrazole(1,2-diazole)	 Pyrazole
e.Isoxazole(1,2-oxazole)	 Isoxazole
f.Isothiazole(1,2-thiazole)	 Isothiazole

2.) 6-Membered Rings-

A.) One hetro atom containing Compound	**Structure of Compound**
a.Pyridine(azine)	 Pyridine
b.Pyrilium(oxinium)	Pyrilium  oxinium Caution: A net charge appears to be present

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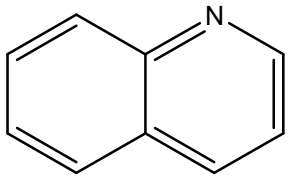
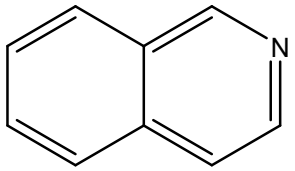
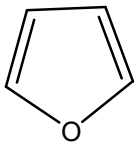
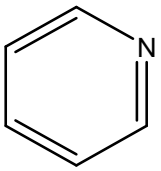
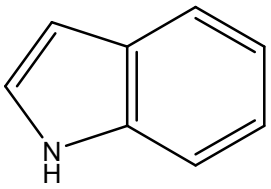
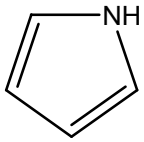
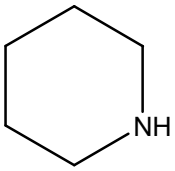
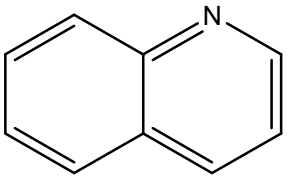
c.Quinoline(benzo[b]azine)	 Quinolin
d .Isoquinoline(benzo[c]azine)	 Isoquinoline

Classification of Hetero cyclic Compounds

Five membered Heterocyclic compound;	**Six membered Heterocyclic compound;**	**Condensed Heterocyclic compound;**
They contain five atoms within the ring out of which four are carbon atoms and one is hetero atom.	**These compounds containe six atoms within the ring, out of which five are carbon atoms and one may be a hetero atom.**	**In these compounds ,a benzene formula is fused with a five or six membered heterocycle .**
 Furan	 Pyridine	 Indole
 pyrrole	 piperidine	 Quinolin

Triazole profile

The name “triazole” was first tell by Bladin in 1855 for recitation the carbon–nitrogen ring method C2H3N3. it's a white to straw crystalline solid with a weak, char acteristic odour, soluble in water and alcohol, melts at 120 °C and boils at 260 °C. Triazole exists in two isomeric forms like 1,2,4-triazole and 1,2,3-triazole.[3]

The triazole nucleoside, ribavirin (Virazole, Virazid), was first synthesized in 1972 (Witkowski et al., 1972) and, after quite three decades, still proves to be useful for the treatment of sort of viral infections. Ribavirin could also be a broad-spectrum antiviral that

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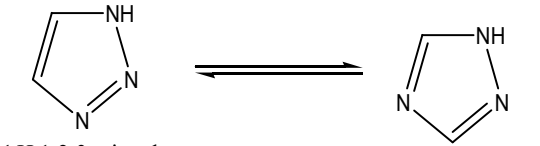
inhibits a spread of RNA viruses in vitro and in vivo (Sidwell et al., 1972). Ribavirin is permitted for clinical use for the treatment of infections with the respiratory syncytial virus (Fernandez et al., 1986), Lassa fever virus (Fernandez et al., 1986), and, more newly, along side interferon, for the action of chronic infections with the hepatitis C virus (Reichard et al., 1998). Recently, ribavirin was also publicized to cause fortification against Nipah virus–associated encephalitis and mortality (Chong et al., 2001). Although ribavirin is effective in cell culture against flaviviruses, the compound causes little or no protective effect in animal models and within the clinical.**[4]**

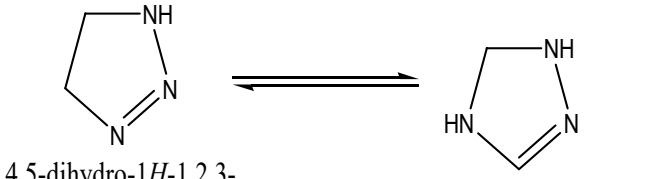
Triazole-

Nitrogenous heterocyclic compounds play a crucial role in synthetic, agrochemical and pharmaceutical fields mainly 1,2,3-triazole and 1,2,4-triazole (1). Triazoles are,



1*H*-1,2,3-triazole 1*H*-1,2,4-triazole

an important class of five-membered ring heterocyclic compounds. they're grouped into two main types, the 1,2,3-triazoles which is V-triazoles (I) and 1,2,4-triazoles or S-triazoles (II) (2). NH, **[5].** The properties of triazoles are utilized in many directions for years.



4,5-dihydro-1*H*-1,2,3-triazole 4,5-dihydro-1*H*-1,2,4-triazole

(5)

Triazole derivatives, between others propiconazole and epoxiconazole are used as plant fortification products. uniconazole and Paclobutrazole are used as plant development retardants . Some triazole, naphthotriazole and benzotriazole are used as decomposition inhibitors for copper .

Triazole activity has also been utilized in medicine and biochemistry. Brassinazole could even be a inhibitor brasynosteroid biosynthesis. Triazole derivatives have a actually extensive biological effect confirmed by research. they have-

1.Antimicrobial activity ,

2.Fungicidal activity ,

3. Antiviral activity ,

4.Anti-proliferative activity ,

5.Cytotoxic and antitumoractivity ,

6. Antioxidant activity ,

7.Anti-leishmanial activity ,

8. Antitubercular activity ,

9.Anti-inflammatory and,

10.Anticonvulsant activity ,

11.Analgesic activity , and

12. Antimalarial activity .

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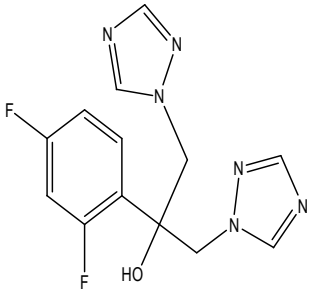
Among the triazole derivatives are also registered substances commonly utilized in antifungal therapy: fluconazole, itraconazole, voriconazole, and posaconazole **.[6]**

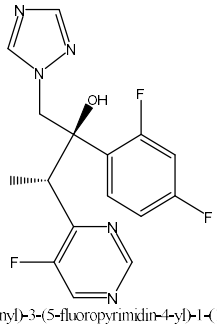
Karaca Gençer, H. et al,(2017), divided into two groups: triazoles and imidazole . the foremost frequently used triazoles are fluconazole and itraconazole that display a good spectrum of antifungal activity . Several novel triazole antifungal drugs, like voriconazole, posaconazole, ravuconazole and albaconazole,

fluconazole



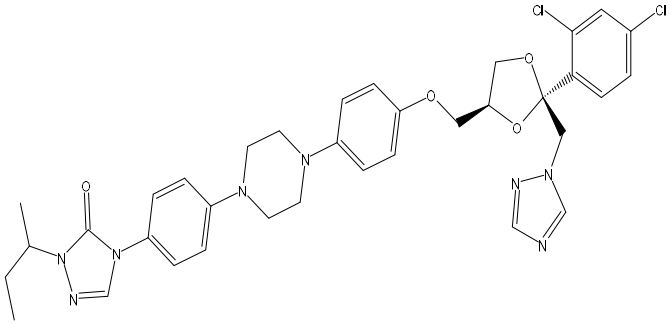
2-(2,4-difluorophenyl)-1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol

Fluconazole



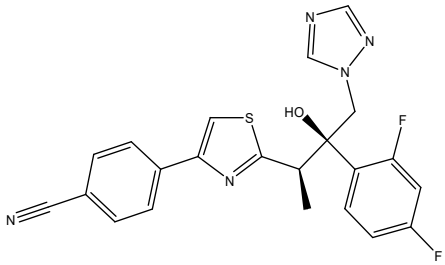
(2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol

Voriconazole



2-butan-2-yl-4-[4-[4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-1,2,4-triazol-3-one

Itraconazole-



4-[2-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl]benzonitrile

Ravuconazole

are available within the market or are at the late stages of clinical trials . These drugs act by competitive inhibition of the lanosterol 14α-demethylase (CYP51A1), which is that the key enzyme in sterol biosynthesis of fungi. Selective inhibition of CYP51A1 would cause depletion of ergosterol, a serious component of the fungal cell wall , and accumulation of lanosterol and other 14-methyl sterols leading to the expansion inhibition of fungal cells.[7] .

Genral synthesis of Triazole-[8.]

1. **Pellizzari Synthesis-** There are various 1,2,4-triazole-based drugs in scientific employ for the treatment of various diseases.Amides on response with hydrazides form acyl amidrazone as an transitional which after intramolecular cyclization delivered 1,2,4-triazoles.

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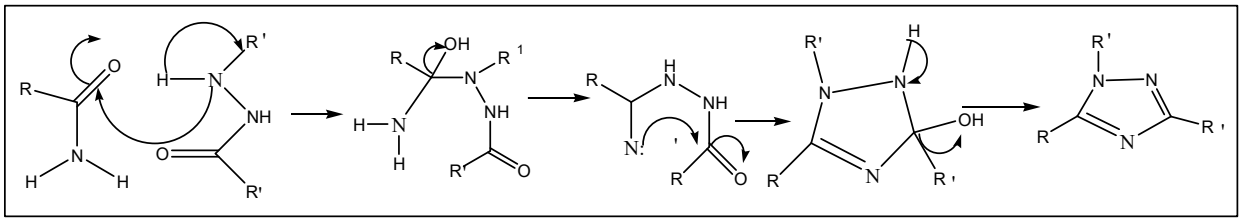
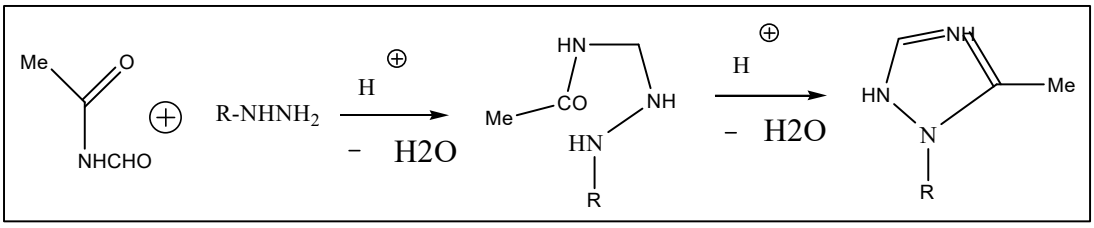
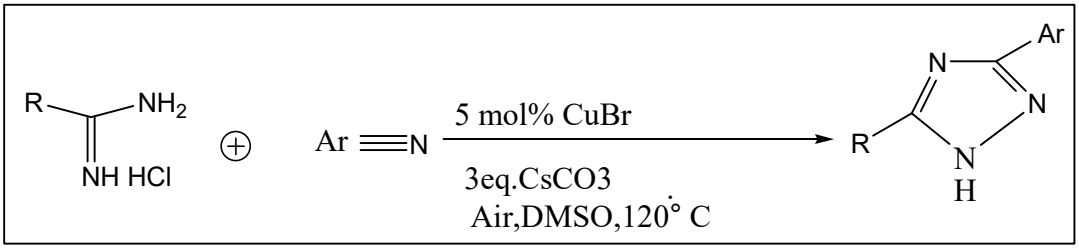


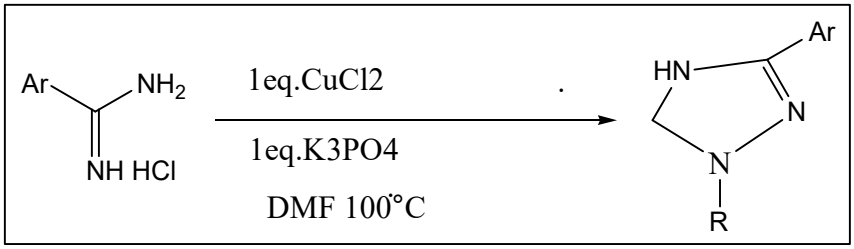
2. **Einhorn-Brunner Synthesis-** 1,2,4-triazoles as antiviral, antifungal, herbicidal, and catalase inhibitors induced profound importance to get fresh entities for his or her broader applications.Acid-catalyzed condensation of formylacetamide with alkyl hydrazines delivered 1-alkyl-5-methyl-1,2,4-triazoles.



3. **From <u>Amidines</u>- (a).** It is a weak base and therefore the pKa of 2 .19 is for protonated genus1,2,4-Triazoles are synthesized by copper-catalyzed oxidative combination of organic nitrile with amidine below atmospheric air in DMSO at 120°C.



(b). A flexible synthesis of 1,3-disubstituted-1,2,4-triazoles has been organized from amidine and tri alkyl amines in DMF at 100°C via K3PO4 as a base and oxygen as oxidant within the occurrence of copper(II) catalyst.



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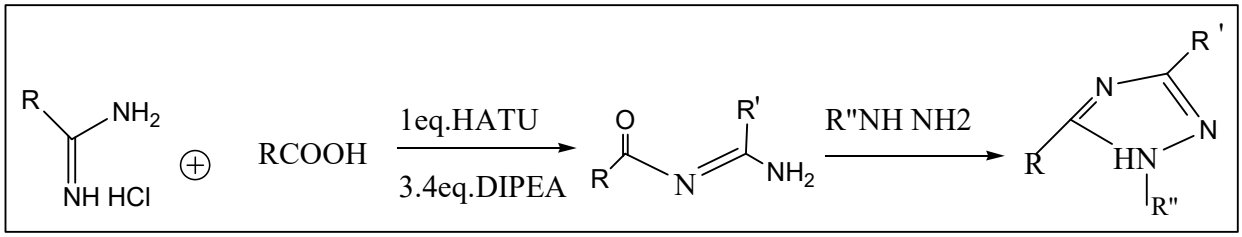
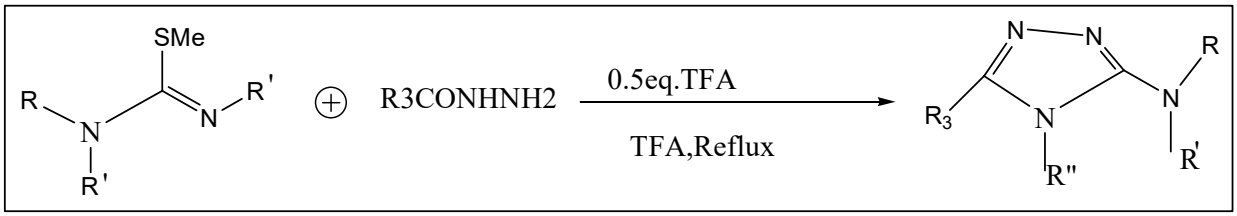
(c). A extremely regio selective synthesis of 1,3,5-tri substituted 1,2,4-triazoles from the response of acid and amidines, followed by action with monosubstituted hydrazine, has been reported.

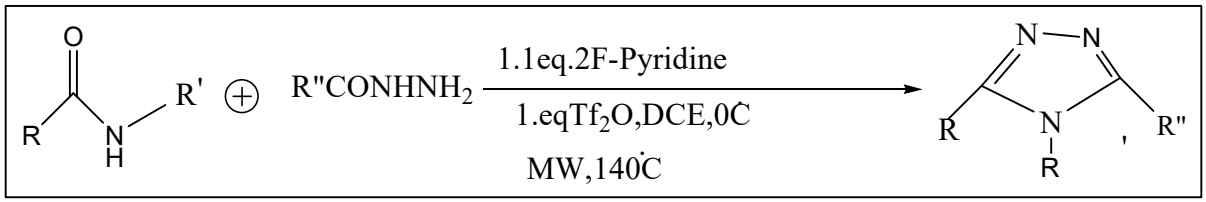


4. *From Acylhydrazide*

(a) It is these new applications of machinery to organic synthesis that possibly guide the way in 1,2,4-triazole chemistry. Acid-catalyzed reduction of acylhydrazides with S-methyl - isothioureas in THF (Tetrahydrofuran) at reflux temperature for 3–22 h gave 1,2,4-triazoles**.**



(b). 1,2,4-Triazoles contribute seriously to the pharmaceutical industry. Triflic anhydride organization followed by a microwave-induced cyclodehydration reaction of secondary amide and acylhydrazines afforded 3,4,5-trisubstituted 1,2,4-triazoles.



5. *From Hydrazines*

(a). A easy and capable method for the synthesis of 1-substituted 1,2,4-triazoles has been reported from the reaction of hydrazines and formamide under microwave irradiation without a catalyst.

6. *From Amidrazone*

(a). Triazole action has also been utilized in drug and biochemistry. Ceric ammonium nitrate-catalyzed oxidative cyclization of amidrazones and aldehydes using (PEG) polyethylene glycol as response medium afforded 3,4,5-trisubstituted 1,2,4-triazoles.

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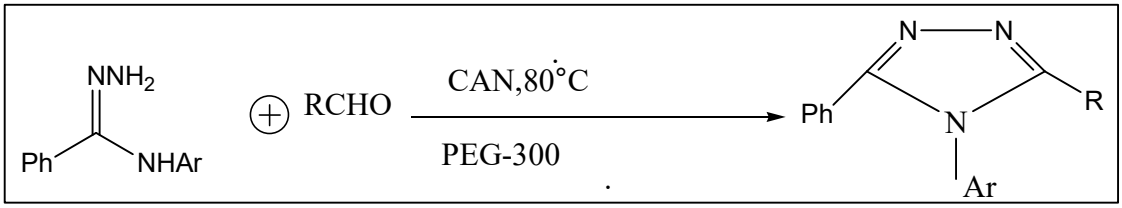
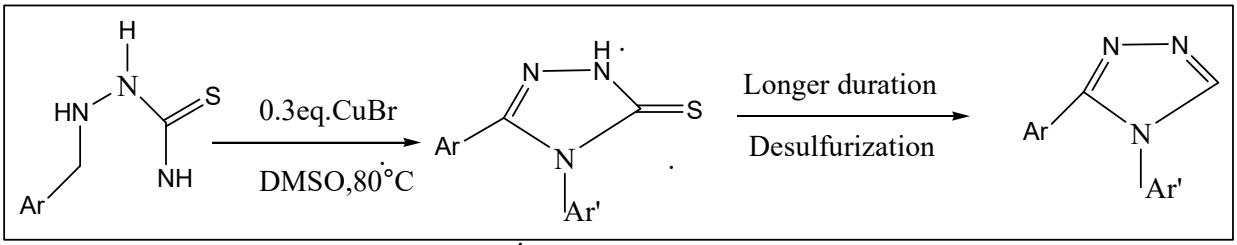
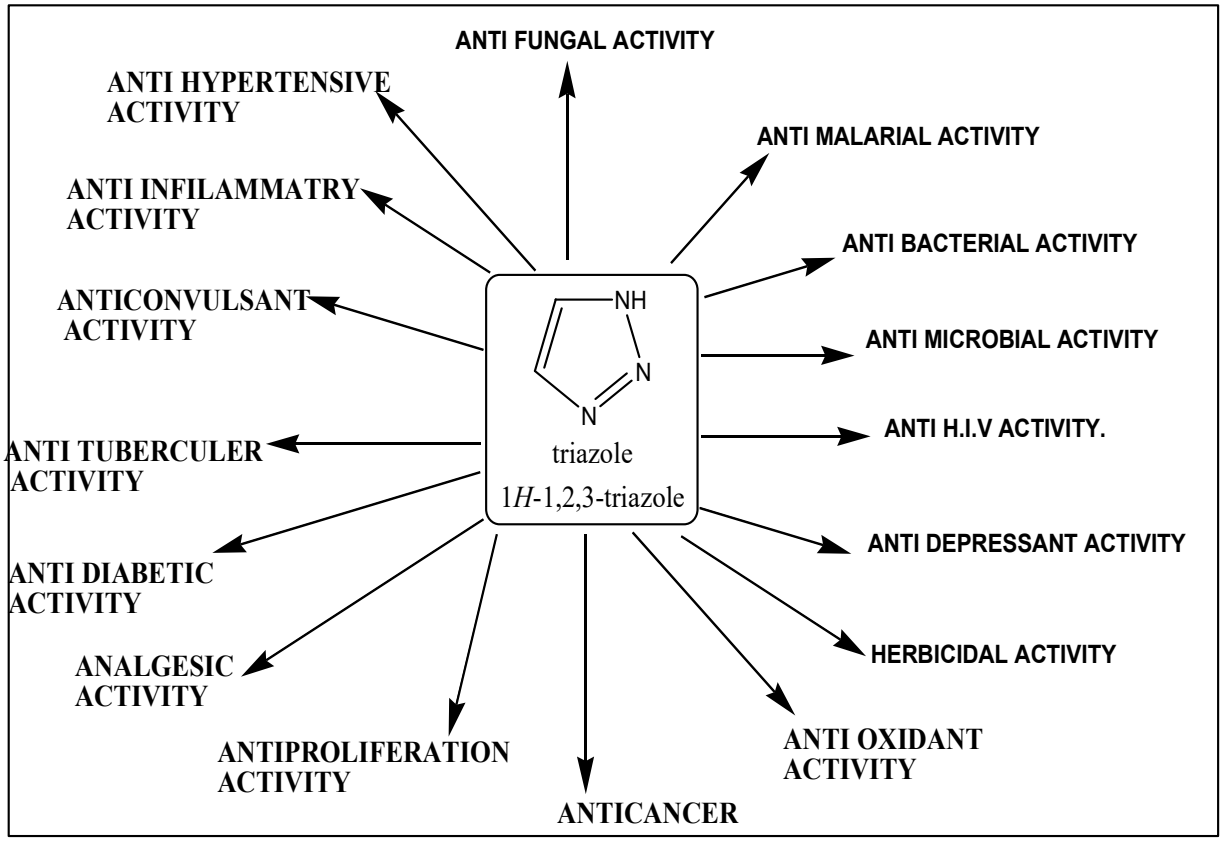


7. From Thiosemicarbazone

(a) still proves to be useful for the treatment of kind of viral infections. Oxidative cyclization of thiosemicarbazones catalyzed by (CuBr2) Copper(II) bromide in Dimethylsulfoxide (DMSO) at 80°C gave 4,5-disubstituted 1,2,4-triazol-3-thione, which was desulfurized by an extended duration of reaction



Pharmacological activity of Triazole-



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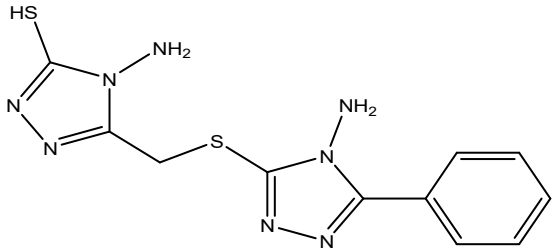
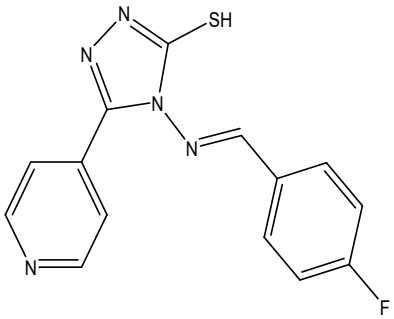
Anti- bacterial activity

Alaraji, Y. et al (2015), Novel Schiff 's bases with triazole ring **(8a and 8b)** are synthesized from 4-Amino-5-((4-amino-5-phenyl-4H 1,2,4-Triazol-3-ylthio)methyl)-4H-1,2,4-Triazole-3-thiol **(7),** which is made by numerous successive cyclization reactions initial from carboxylic acid hydrazide (1). Melting points and Infrared spectroscopy were wont to characterize the synthesized compounds. The biological activity of **compounds (7) and (8a and 8b)** were evaluated toward gram positive bacteria (staphylococcus aureus). and gram negative bacteria (Escherichia coli**).[9]**

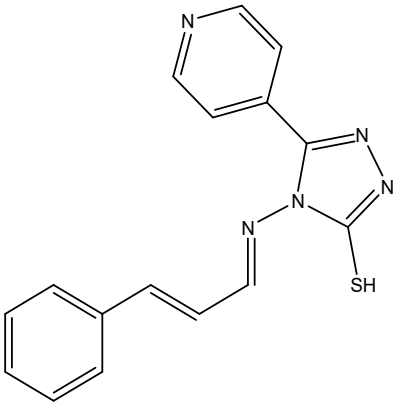


4-amino-5-((4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)methyl)-4H-1,2,4-triazole-3-thiol

Singh, R., Kashaw et.al,(2018), Antimycobacterial activity of the synthesized compounds was administered and percent reduction in comparative light units was intended using luciferase writer phage assay. Percent reduction in relative light units for isoniazid was also calculated., when tested in vitro.Tested compounds showed better antibacterial activities (minimum inhibitory concentration) against Gram-positive bacteria compared to Gram-negative. Compound , showed **4-[(4-Fluoro-benzylidene)-amino]-5-pyridin-4-yl- 4H-[1,2,4]triazole-3-thiol** better antibacterial activity than ampicillin against B. subtilis. Compound, 4-(3-Phenyl-allylideneamino)-5-pyridin-4-yl-4H-[1,2,4]triazole -3-thiol , within the series displayed most potent antifungal activity**.[10]**



4-[(4-Fluoro-benzylidene)-amino]-5-pyridin-4-yl- 4H-[1,2,4]triazole-3-thiol



4-(3-Phenyl-allylideneamino)-5-pyridin-4-yl-4H- [1,2,4]triazole-3-thiol

Al-Sa'doni et al (2020)- In this study, a sequence of 1,2,4-triazol-3-carbohydrazide compound and derivatives of 1,2,4- triazole-3-(4H)-thion are synthesized.The four tested compounds, 2,5-Dichlorobenzene sulphonic acid N'[2-(1-ethyl-5-methyl1H-[1,2,4]triazole-3-yl)-acetyl]-hydrazide and 2-Thiophene sulphonic acid N'[2-(1,5-diethyl-1H-[1,2,4]tria zole-3-yl)-acetyl]-hydrazide were the foremost active ones against P. aeruginosa (one of the foremost resistant bacteria against many drugs) and B.

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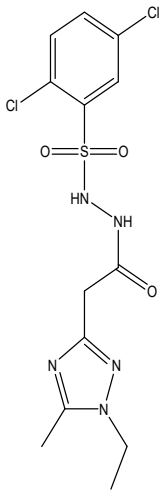
cereus ATCC11778 (MIC 0.5 µg/mL. These results suggest that compound 2,5-Dichlorobenzene sulphonic acid N'[2-(1-ethyl-5-methyl1H-[1,2,4]triazole-3-yl)-acetyl]-hydrazide and 2-Thiophene sulphonic acid N'[2-(1,5-diethyl-1H-[1,2,4]tria zole-3-yl)-acetyl]-hydrazide might be good candidates as antibacterial agents; further studies might be done on other bacterial strains also because the study of the interactions caused by these compounds with the bacterial DNA.**[11]**

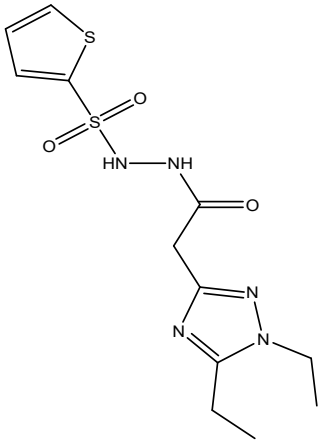


2,5-Dichlorobenzene sulfonic acid N'[2-(1-ethyl-5-methyl1H-[1,2,4]triazole-3-yl)-acetyl]-hydrazide

(6c)

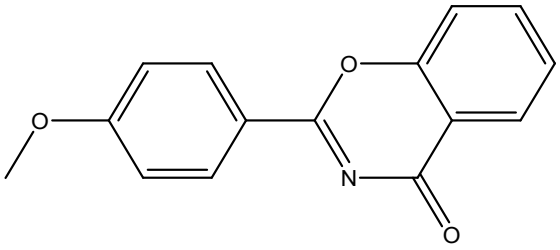
Anti-microbial Activity-

Bektaş, H .et al. 5-substitued-salicylicylic acids **(1a-e)** were transformed to acid chlorides, followed by their change to matching salicylamides **(2a-e)** [9], Scheme-1. Salicylamide on response with benzoyl chloride gave benzoxazinone **(3a-h)** [10] ,[11], Scheme-2. Benzoxazinone on response with hydrazine hydrate gave the novel compounds 3-(2-Hydroxyphenyl)-5-phenyl-1,2,4-triazoles **(4a-e)** [12].



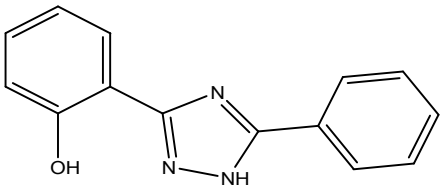
2-thiophene sulfonic acid n'[2-(1,5-diethyl-1h-[1,2,4]triazole-3-yl)-acetyl]-hydrazide

(7i)



2-(4-Methoxyphenyl)-4H-1,3-benzoxazin-4-one

[3c]



3-(2-Hydroxyphenyl)-5-phenyl-1,2,4-triazole

[4a]

Abu-Hashem, et al. (2021), Many of the recently prepared compounds during this article possess a **broad antimicrobial activity** and these heterocyclic organic compounds include many functional groups as effective antimicrobials, these compounds were obtained in good yields via using new procedures that provide fast and efficient, these compounds include- (4a) 2-

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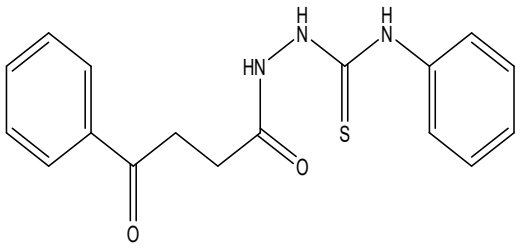
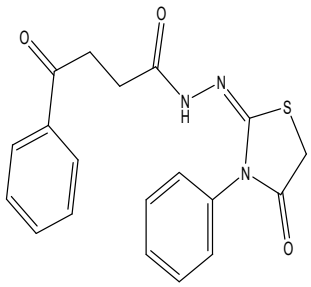
(4- oxo- 4- phenylbutanoyl) -N- phenyl hydrazine-1-carbothioamide , (5a),(6a), (7a),(8a),4-oxo-N'-(4-oxo-3-phenylthiazolidin -2-ylidene)-4-phenylbutanehydrazid-,(9a, (10a, (11a ,12a). Moreover, the simplest compounds that give effective antimicrobial activity are pyridazin-hydrazono-thiazolidinone.[13]



2-(4-oxo-4-phenylbutanoyl)-N-phenylhydrazine-1-carbothioamide

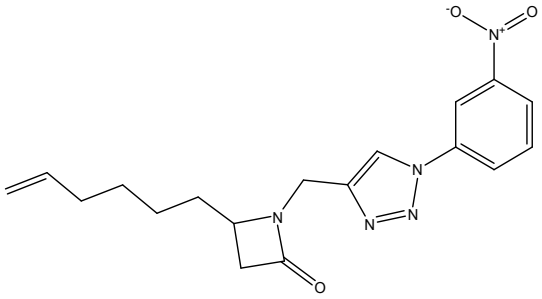
4a



4-oxo-N'-(4-oxo-3-phenylthiazolidin-2-ylidene)-4-phenylbutanehydrazid-

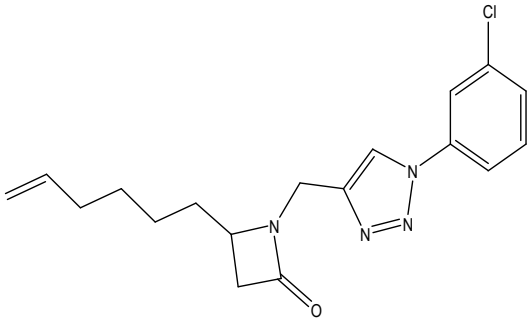
8a

Kaur, R., Singh et al (2020). A appropriate and efficient synthesis of new triazole β-lactam conjugates using tick chemistry is described. The products were finally characterized spectroscopically and tested against Gram- (þ) and Gram-(-) bacteria. Compound 4 -(hex-5-**en-**1-yl)-1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl) azetidin-2-one , and 1-((1-(3-chlorophenyl) -1H-1,2,3-triazol-4-yl)methyl)-4-(hex-5- en-1-yl)azetidin-2-one were found to be most active**.[14]**



4 -(hex-5-en-1-yl)-1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)azetidin-2-one

(7e)



, 1-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(hex-5- en-1-yl)azetidin-2-one

(7c)

Awolade, P. et al (2020)- The binding profles of compounds 9q, 10d, 10v, 10z, 16, 18, and their predecessor 8-HQ were replicated at the hemecontaining site of LDM (PjDB ID: 4WMZ). Analysis of compound 16-LDM complex ,showed that the 1H-1,2,3-triazole ring is important to strong protein binding. The ring unspecified a conformation just like the 1,2,4-triazole unit of fuconazole near the heme cofactor, thus afording compound 16 the simplest binding profle overall . [15]

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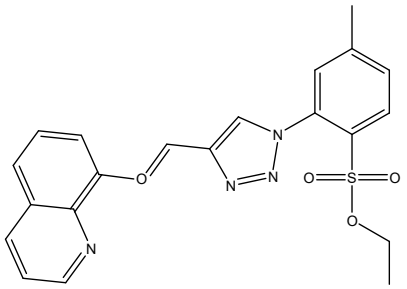
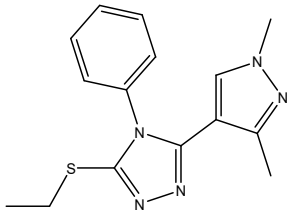


(4 ((quinolin 8 yloxy)methyl) 1H 1,2,3 triazol 1 yl) ethyl 4 methylbenzenesulfonate

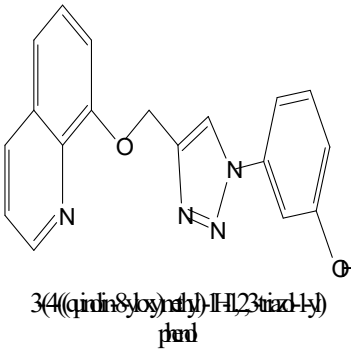
Caution: Valence appears to be exceeded

(16)



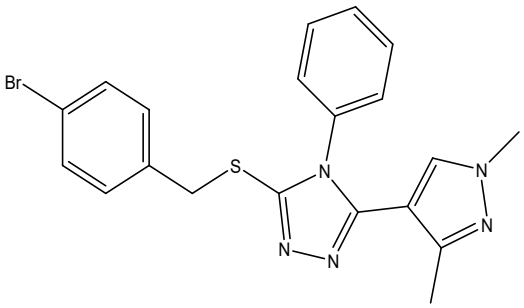
2-((5-(1,3-Dimethyl-1H-pyrazol-4-yl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetonitrile,

(5).



3(4((quinolin8yloxy)methyl)1H1,23triazol1yl)
phenol

9q



3-((4-Bromobenzyl)thio)-5-(1,3-dimethyl-1H-pyrazol-4-yl)-4- phenyl-4H-1,2,4-triazole

(6f)

Herbicidal activity-

Mu, J. X., Zhai,et al (2019). The herbicidal activities of those compounds were experienced against lettuce and bentgrass. surrounded by them, compounds 2-((5-(1,3-Dimethyl-1H-pyrazol-4-yl)-4-phenyl-4H-1,2,4-triazol-3-yl) thio) acetonitrile, and 3-((4-Bromobenzyl)thio)-5-(1,3-dimethyl-1H-pyrazol-4-yl)-4-phenyl-4H-1,2, 4-triazole, had the very greatest herbicidal activity (80% inhibitory) against lettuce and bentgrass.**[16]**

Anticancer activity-

Pragathi, Y. J . et al, (2020)-All compounds were evaluated for his or her anticancer activities against four different neoplastic cell lines including carcinoma (MCF-7, MDA MB-231), carcinoma, and prostatic adenocarcinoma (DU-145) by MTT reduction assay method, and etoposide acts as a typical drug. . Among the synthesized compounds, 6-(4-Nitrophenyl)-3-(pyridine-4-yl)-7H-[1,2,4]tria zolo[3,4-b][1,3,4]thiadiazine , 6-(4-Chlorophenyl)-3-(pyridin-4-yl)-7H-[1,2,4]tri azolo[3,4-b][1,3,4]thiadi , (4-Bromophenyl)-3-(pyridin-4-yl)-7H-[1,2,4]tria z, ,and 6-(4-Methoxyphenyl)-3-(pyridin-4-yl)-7H-[1,2,4]tri azolo[3,4-b] [1,3,4]thiadia and displayed stronger activity along side inhibitory concentration values starting from 0.10±0 , [17].

Luo, L., Jia et al . (2021), Building on our preceding work that discovered 1,2,4-triazole–

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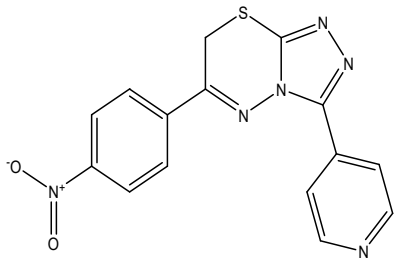
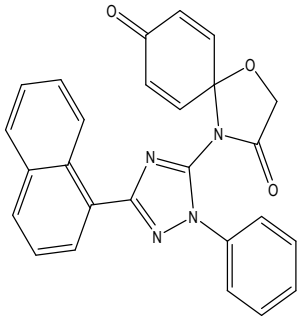


6-(4-nitrophenyl)-3-(pyridine-4-yl)-7h-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine

spirodienone as a capable pharmacophore for anticancer activity, we've further diversified 1,2,4– triazole-spirodienone derivatives and synthesized a series of novel naphthalene-substituted triazole spirodienones to explore their antineoplastic activity. Of these, compound-(6b) ,4-(3-(Naphthalen-1-yl)-1-phenyl-1H-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro [4.5] de ca-6,9-diene-3,8-dione, possesses notable in vitro cytotoxic activity by arresting cell cycle and inducing apoptosis in MDA-MB-231 cells. afterward, acute toxicity assay showed that (6b)at 20mg/kg has no apparent toxicity to the most organ in mice. additionally, compound –(6b) in vivo suppressed carcinoma 4T1 tumor growth. Taken together, these results specify that compound**–(6b)** , could also be a possible anticancer agent for further development**.[18]**

Antifungal Activity

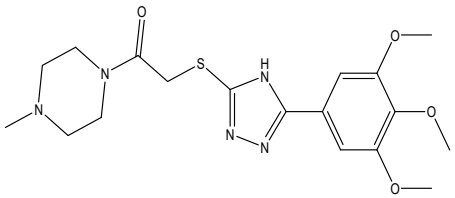
Wu, W. N., Jiang, et al. (2020), A sequence of fresh 1,2,4-triazol derivatives containing an) ethanone,(6b) 1-(4-[Pyridin-4-yl]piperazin-1-yl)-2-((5-[3,4,5-trimethoxyphenyl]-4H-1,2,4- triazol-3-yl)thio)ethanone, and 1-(4-Benzylpiperazin-1-yl)- 2-((5-[3,4,5-trimethoxy phenyl]-4H1,2,4-triazol-3,showed excellent antifungal activities



4-(3-(naphthalen-1-yl)-1-phenyl-1h-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione

(6b)

against Botrytis cinerea, at a concentration of 50 µg/amide moiety were synthesized and their antifungal activities were evaluated. The results indicated that some of the objective compounds possessed good antifungal activities. Among them, compounds –(6a),1-(Piperazin-1-yl)- 2-((5-[3,4,5-trimethoxyphenyl]-4H1,2,4-triazol-3-yl) thio) ethanone, (6g) 1-(4-[4-Hydroxy phenyl] piperazin1-yl)-2-((5-[3,4,5-trimethoxy phenyl]-4H-1, 2, 4-triazol-3-yl)thio ethanonemL, which were higher to that of Pyrimethanil (82.8%). Meanwhile, compound-(6b) ,1-(4-methyl piperazin-1-yl)- 2-((5-[3,4,5-trimethoxy phenyl] -4H1,2,4-triazol-3-yl) thio) ethanone , showed better antifungal activity against Phompsis sp, with an inhibition rate of 92.4%, in comparison with that of Pyrimethanil (85.1.) [19]



1-(4-methylpiperazin-1-yl)- 2-((5-[3,4,5-trimethoxyphenyl]-4H 1,2,4-triazol-3-yl)thio)ethanone

(6b)

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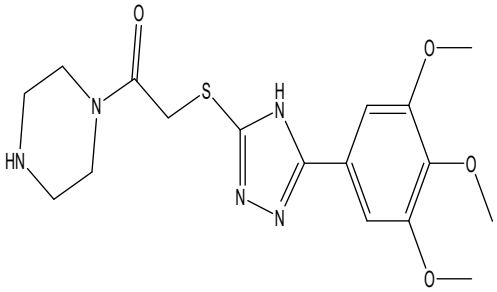
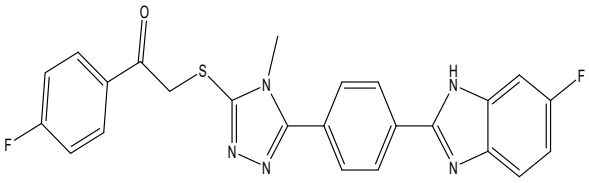


1-(Piperazin-1-yl)- 2-((5-[3,4,5-trimethoxyphenyl]-4H 1,2,4-triazol-3-yl)thio) ethanone

(6a)

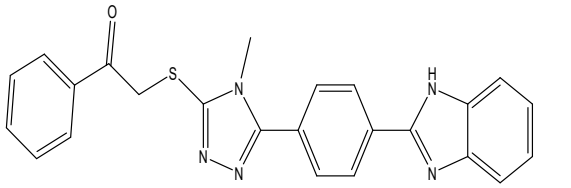
Karaca Gençer et al (2020), The Candida group are definitely the foremost important opportunistic fungal pathogens for people .In summary, introduction evaluation of latest 2-((5-(4-(5-substituted-1H-benzimidazol-2-yl)phenyl)-4-substituted-4H-1,2,4-triazol-3-yl)thio)-1-(sub stitutedphenyl)ethan-1-one derivatives as antifungal agents end in promising findings. Compounds-(**5w),** 2-((5-(4-(6-Fluoro-1H-benzimidazol-2-yl)phenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)-1-(4-fluorophenyl)ethan 1-one and 5a, 2-((5-(4-(1H-Benzimidazol-2-yl)phenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)-1-phenyl ethan -1-one , 5d , exerted an honest antifungal profile. Furthermore, toxicological and toxicological ADME studies indicated the relative potency of compounds- 5w and 5a, ,5d, Results of ergosterol level quantification assay and microscopy studies revealed that the mechanism of action of compounds is related to the inhibition of ergosterol biosynthesis.[20]

Wu, W., Lan et al (2021), This study provided a practical instrument for guiding the planning and



2-((5-(4-(6-Fluoro-1H-benzimidazol-2-yl)phenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)-1-(4-fluorophenyl)ethan 1-one

5w



2-((5-(4-(1H-Benzimidazol-2-yl)phenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)-1-phenylethan-1-one

5a

synthesis of latest and more capable active small molecules of pyrimidine derivatives for controlling Phompsis sp.Then their in vitro antifungal activities against Botryosphaeria dothidea (B. dothidea), Phomopsis sp., and Botrytis cinereal (B. cinereal) were determined. A preliminary biological test showed that compounds (5f) 5-bromo-2-fluoro-N-(2-((2-methyl-6-(trifluoromethyl) pyrimidin-4-yl)oxy)phenyl)benzamide and (5o) 5-bromo-2-fluoro-N-(3-((2-methyl-6- (trifluoromethyl) pyrimidin-4-yl)oxy)phenyl) benzamide exhibited higher antifungal activity against Phomopsis sp., with an inhibition rate of 100% compared thereto of Pyrimethanil at 85.1%. especially , compound 5o exhibited excellent antifungal activity against Phompsis sp., with the EC50 value of 10.5 μg/ml, which was even better than that of Pyrimethanil (32.1 μg/ml).[21]

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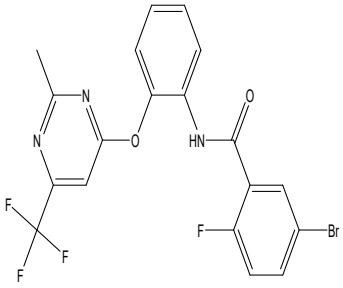
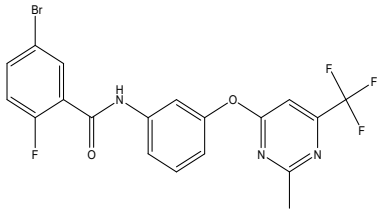


5-bromo-2-fluoro-N-(2-((2-methyl-6-(trifluoromethyl) pyrimidin-4-yl)oxy)phenyl)benzamide

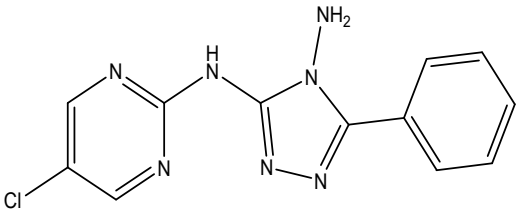
(5f)



5-bromo-2-fluoro-N-(3-((2-methyl-6- (trifluoromethyl)pyrimidin-4-yl)oxy)phenyl)benzamide

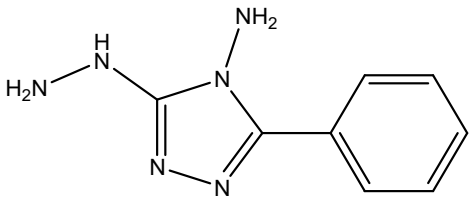
(5o)

El-Reedy, A. A., et al .(2020), Diferent new 1,2,4-triazolo[4,3-b][1,2,4,5]tetrazines and 1,2,4-triazolo[4,3-b][1,2,4]triazines are obtained from heterocyclization of 3-substituted-4-amino-5-substituted-amino-1,2,4-triazoles (3a),(N3 -(5-chloropyrimidin-2-yl)-5-phenyl-4H-1,2,4-triazole-3,4-diamine) , (N3 -(5-bromopyrimidin-2-yl)-5-(pyridin-4-yl)-4H-1,2,4-triazole-3,4-diamine) and 3-substituted-4-amino-5-hydrazino-1,2,4-triazoles (9a) , (3-hydrazinyl-5-phenyl-4H-1,2,4-triazol-4-amine) b, 3-hydrazinyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-4-amine): with (α and β) bifunctional. The recently prepared compounds were examined as an antibacterial agents, anti-infammatory (against E. coli (Escherichia coli) and Gram-positive bacteria), also as antifungal (against C. albicans (Candida albicans)) agents. The recently prepared compound showed high antifungal, antibacterial, and anti-infammatory activities in comparing with the profitable antibiotics, NegGram , Indomethacin, , Nystatin. and, Imipenem.**[22]**



(N3 -(5-chloropyrimidin-2-yl)-5-phenyl-4H-1,2,4-triazole-3,4-diamine)

(3a)



(3-hydrazinyl-5-phenyl-4H-1,2,4-triazol-4-amine)

(9a)

Anti-Diabetic Activity

Mohamed, M.et al.(2020),The obtained compounds were reacted with p-toluinesulfonyl chloride 2 to provide the equivalent sulfonamides 3a-h. Compound 1b was allowed to respond with dissimilar cyclic ketone or aromatic aldehydes under alkaline situation to afford the probable imino compounds 4a-d and 6a-c, respectively. These compounds were suitable to react with ethyl glycolate to yield the predictable thiazolidinone derivatives 7a-c, or 7a-c, correspondingly .The obtained compounds exhibited very important in vivo and in vitro antihyperglycemic effect at a dose of 40 mg/kg body weight compared to the standard drug

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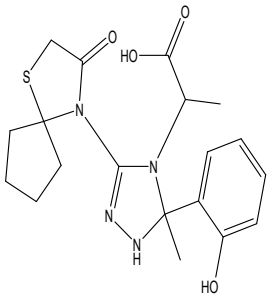
gliclazide and control. The antidiabetic effect was investigated using oral glucose tolerance test in standard and non-insulin-dependent diabetes mellitus (NIDDM) in STZ-rat model. Compounds 3a-h, 5b, 5c, 5d, 7a, 7b, and 7c showed significant activity in lowering blood glucose (more than 80%) compared to the NIDDM control.**[23]**



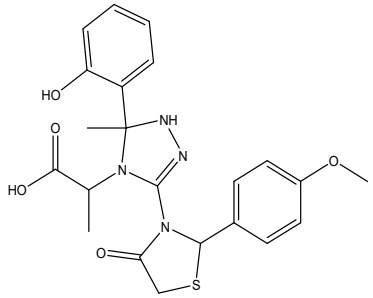
2-[5-(2-HYDROXY-phenyl)- 5-methyl-3-(3-oxo-1-thia-4-aza-spiro[4.4] non-4-yl)-1,5-dihydro-[1,2,4]triazol-4-yl]- propionic acid

(7a)

2-(1,5-dihydro5-(2-hydroxyphenyl)- 3-(2-[4-methoxyphenyl]-4-oxothiazolidin3-yl)-5-methyl-1,2,4-triazol-4-yl)propanoic acid (5d)

Tubercular activity

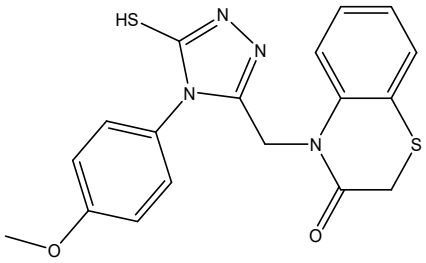
Karczmarzyk, Z., et al . (2020), Synthesized molecules have publicized good antitubercular activity with regard to the quality antitubercular drugs. The , 4-((5-mercapto-4-(4-methoxyphenyl)-4H-1, 2, 4-triazol-3-yl) methyl)-2H-benzo[b][1, 4]thiazin-3(4H)-one , 4-((4-(4-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl) methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one and -(4-(4-methoxyphenyl)-5-((3-oxo-2,3-dihydro-4H benzo[b][1,4]thiazin-4-yl)methyl)-4H-1,2,4-triazol -3-yl) 4-nitrobenzothioate are the foremost active antitubercular compounds having a least



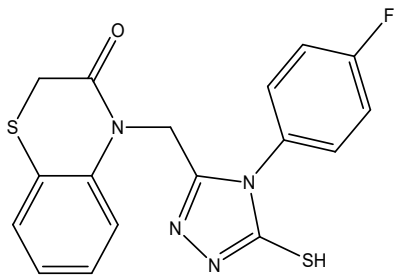
2-(1,5-dihydro 5-(2-hydroxyphenyl)- 3-(2-[4-methoxyphenyl]-4-oxothiazolidin 3-yl)-5-methyl-1,2,4-triazol-4-yl)propanoic acid

(5d)

inhibitory concentration of 12.5 µg/ml. The synthesized molecules' cytotoxic data expose that tested compounds exhibited low in vitro cytotoxicity (higher IC50 values) in human embryonic kidney 293 (HEK293T) cells.[24]



4-((5-mercapto-4-(4-methoxyphenyl)-4H-1, 2, 4-triazol-3-yl) methyl)-2H-benzo[b][1, 4]thiazin-3(4H)-one



4-((4-(4-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl) methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one

Analgesic and Anti-infilammatory activity

Sert-Ozgur, S., Tel, et al. (2017), Formerly demonstrated that assured heterocyclic compounds derived from 3-substituted-1,2,4-triazole-5-thiones had promising analgesic/anti-inflammatory activities along side low ulcerogenic properties. Therefore, we sought to

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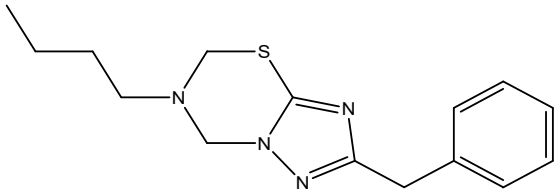
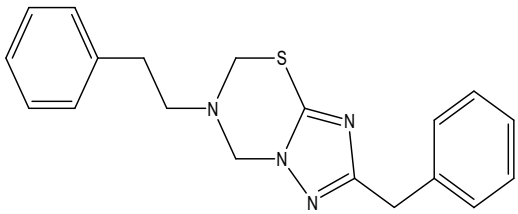
style and synthesize new derivatives of triazol-5-thiones-fused heterocycles. within the present study, a cycle of novel bis-Mannich bases, namely(1a-c),(2a-c)(3a-d), and 2-Benzyl-6-phenethyl-6,7-dihydro-5H-1,2,4-triazolo[3,2- b]-1,3,5-thiadiazine .The majority of the prepared compounds caused comparatively smaller amount gastrointestinal (GI) side effects than the reference drugs indomethacin and naproxen did.[25]



2-Benzyl-6-butyl-6,7-dihydro-5H-1,2,4-triazolo[3,2-b]-1,3,5-thiadiazine

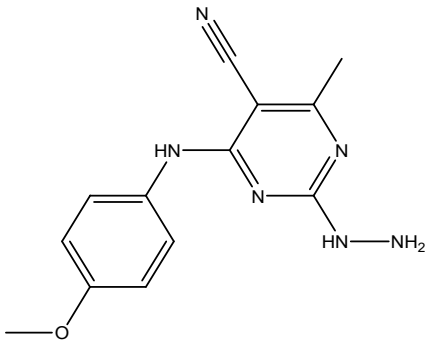
(2a)



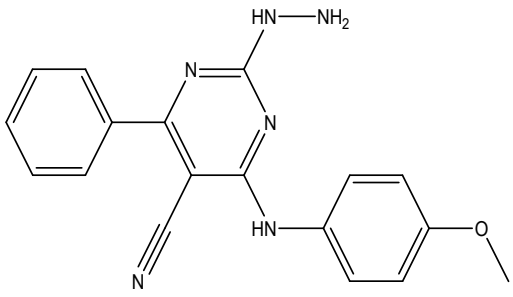
2-Benzyl-6-phenethyl-6,7-dihydro-5H-1,2,4-triazolo[3,2- b]-1,3,5-thiadiazine

(2c)

Farghaly et al. (2019), The present work is an addition of an on going attempt toward the development and classification of fresh molecules with antihypertensive activity. In the present examination bioisosterism, and hybrid pharmacophorebased drug design led to the classification of multifunctional non-chiral C4-pyrimidine derivatives with antihypertensive potency. Compounds , **2-Hydrazinyl-6-methyl-4-(4-methoxyanilino)-pyrimidine-5-carbonitrile , 2-Hydrazinyl-6-phenyl-4-(4-methoxyanilino)-pyrimidine-5- carbonitrile ,** 2-(4-Cyano-5-oxo-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-6-methyl-4-(4-methoxyanilino)-pyrimidine-5-carbonitrile , 2-(4-Cyano-5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-6- phenyl-4-(4-methoxyanilino)-pyrimidine-5-carbonitrile , exhibited promising lowering on MABP, calcium channel blocking action and decrease in heart rate.The impact of structural variation on activity was examined leading to that changes in positions could be important in receptor binding.**[26]**



2-Hydrazinyl-6-methyl-4-(4-methoxyanilino)-pyrimidine-5- carbonitrile



2-Hydrazinyl-6-phenyl-4-(4-methoxyanilino)-pyrimidine-5- carbonitrile

Antitumor activity-

Pragathi, Y. J., et.al.(2021), The fresh library of 1,2,4-thiadiazole-1,2,4-triazole derivatives having amide functionality was designed, synthesized, and examined for his or her

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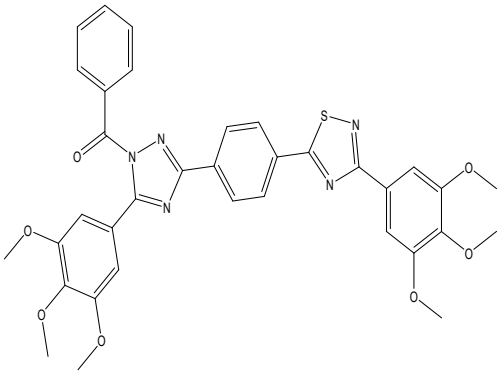
anticancer activities against four different human neoplastic cell lines counting carcinoma (MCF-7, MDA MB-231), carcinoma (A549), and prostatic adenocarcinoma (DU-145) by making use of MTT assay. Here, Etoposide acts as standard drug, and therefore the obtained results were presented as IC50 (μM) values. Among them, compounds 8b, 8c, 8d 8e, (5-(3,4,5-Trimethoxyphenyl) -3-(4-(3-(3,4,5- Tri methoxyphenyl) -1,2,4-Thiadiazol-5-yl) Phenyl) -1H 1,2,4 Triazol-)1-yl)(Phenyl Methanone -, 8g (4-Chlorophenyl) (5-(3,4,5-Trimethoxy phenyl)-3-(4-(3- (3,4,5-Trimethoxy phenyl)-1,2,4-Thiadiazol-5- yl)Phenyl)-1H-1,2,4-Triazol-1-yl)Methanone, with IC50 values starting from 0.10 ± 0.084 to 11.5 ± 6.49 μM and standard showed IC50 value ranges from 1.91 ± 0.84 μM to three .08 ± 0.135 μM.[27]

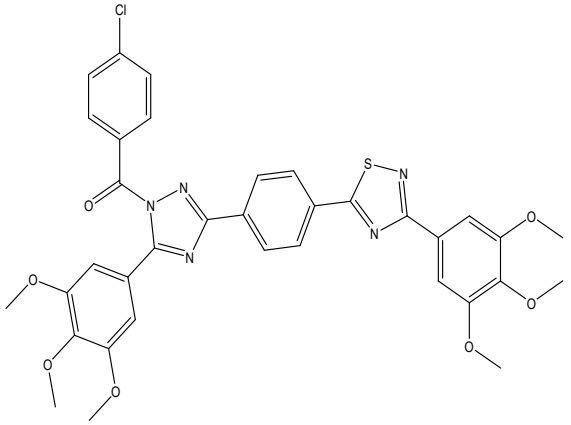


(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1H-1,2,4-Triazol-1-yl)(Phenyl)Methanone

(8e)

Antiproliferation activity

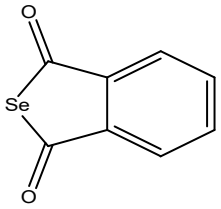
Domínguez-Álvarez et al(2014), which were used as reference drugs. due to their prominent potency and/or selectivity, four analogues (5, 21, 28 and 30), were selected in plan to charge their



(4-Chlorophenyl)(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3- (3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1H-1,2,4-Triazol-1-yl)Methanone

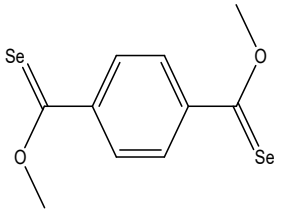
(8g)

redox properties correlated to a possible redox modulating activity. The peroxidase (GPx) examine showed slight activity for compound 30 and therefore the 2,2-diphenyl-1-picrylhydrazyl-(DPPH) assay showed a weak activity for compounds 5 and 28. this results exposed that analogues 5, 21, 28 and 30 might function a useful initial point for the planning of enhanced anti-tumour agents. (28)



Benzo[c]selenophen-1,3-dione

(5)



Dimethyl benzene-1,4-dicarboselenoate

(28)

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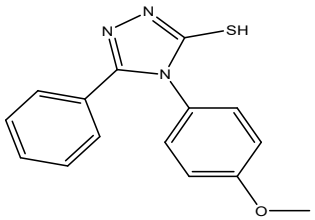
Antiprolifiration

Ghanaat, J et al (2020), during this study, a predictable methodology has been developed for the synthesis of a sequence of latest 3-mercapto-1,2,4-triazole derivatives 4a ,4 (4 Methoxyphenyl) 5 phenyl 4H 1,2,4 triazole 3 thiol , 4 (4 Methoxyphenyl) 5 p tolyl 4H 1,2,4 triazole 3 thiol, 4,5 Bis(4 methoxyphenyl) 4H 1,2,4 triazole 3 thiol ,The purity and structure of the synthesized molecules were confrmed by 13C NMR, 1 H NMR, and elemental analysis. additionally , the prepared compounds were screened for his or her anti-proliferative activity against human neoplastic cell lines including A549 (lung cancer), SKOV3 (ovarian cancer) and MCF7 (breast cancer) using MTT reduction assay. The heterocyclic bearing 3,4,5-trimethoxy moiety was found to be the foremost efective among the sequence displaying an IC50 of three .02 μM specifcally against the ovarian carcinoma neoplastic cell line.**[29]**

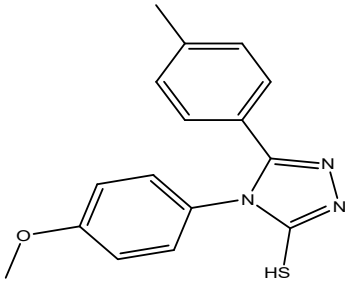
Anticonvulsant Activity

The present therapy of epilepsy is said with variety of side effects including sedation and hypnosis. All the compounds except 6a, 4-(2-methylphenyl)-5-(2-phenyl-1,3-benzoxazol-5-yl)-2,4- dihydro-3H-1,2,4-triazole-3-thione , and 6c, ,The triazole derivatives displayed reasonable to good anticonvulsant activity.All these compounds were screened for anticonvulsant activity using Maximal subcutaneous pentylene tetrazole and Electroshock method. Among the tested compounds 6g, 5-[2-(4-chlorophenyl)-1,3-benzoxazol-5-yl]-4-(2-methyl phenyl)- 2,4-dihydro-3H-1,2,4-triazole-3-thione, 6h,)and 6m ,showed potent activity like that of ordinary drugs phenytoin and carbamazepine.**[30]**

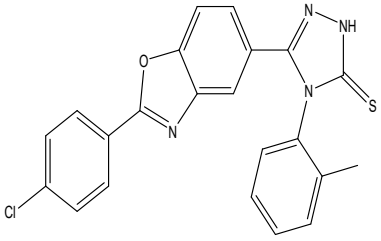


4a 4 (4 Methoxyphenyl) 5 phenyl 4H 1,2,4 triazole 3 thiol
Caution: Stereochemical terms discarded: 4a

[4a]

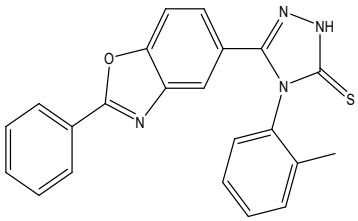


4 (4 Methoxyphenyl) 5 p tolyl 4H 1,2,4 triazole 3 thiol,



5-[2-(4-chlorophenyl)-1,3-benzoxazol-5-yl]-4-(2-methylphenyl)- 2,4-dihydro-3H-1,2,4-triazole-3-thione,

(6g)



4-(2-methylphenyl)-5-(2-phenyl-1,3-benzoxazol-5-yl)-2,4- dihydro-3h-1,2,4-triazole-3-thione

(6a)

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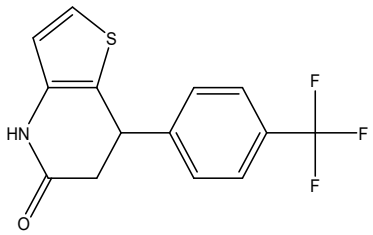
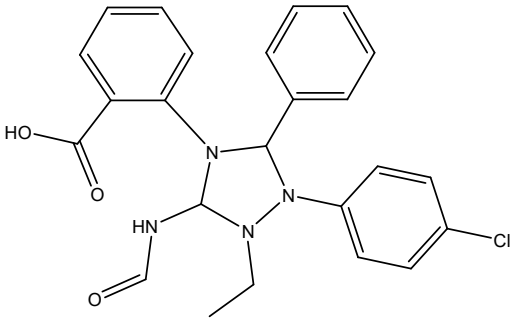
Wang, S. B., Liu et al. (2020). The occurrence of epilepsy, a nervous disorder , has exceeded 50 million universal. at the present , drug therapy (anticonvulsant drugs or antiepileptic) is that the main method of treatment of epilepsy .Compound 7-[4-(trifluoromethyl)phenyl]-6,7-dihydrothieno[3,2-b]pyridin-5-(4H)- one, showed the simplest anticonvulsant activity. The results of in vivo -aminobutyric Acid (GABA) showed that compound 7-[4-(trifluoromethyl)phenyl]-6,7-dihydrothieno[3,2-b]pyridin-5-(4H)-one may have an impact on the GABA system. Most objective compounds have favorable blood brain barrier (BBB) permeability and oral bioavailability in predictions using silico molecular properties. [31]

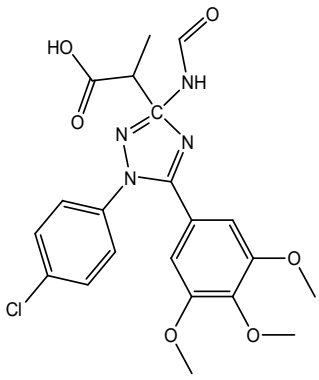


7-[4-(Trifluoromethyl)phenyl]-6,7-dihydrothieno [3,2-b]pyridin-5(4H)-one

Abuelhassan, A. H., et al,(2018), The anticonvulsant and neurotoxicity of the target compounds as compared with phenytoin and valproate revealed that compounds with 4-chlorophenyl moiety at N1 (compounds- Ethyl 4-(1-(4-chlorophenyl)-5-phenyl-1H-1,2,4-triazole -3- carboxamido)benzoate , and 3-(1-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H1, 2,4-triazole-3-carboxamido)propanoic acid triazole ring showed more protection specially against electroshock than that with unsubstituted phenyl group like compound 3-(1-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H1,2,4-triazole-3-carboxamido)propanoic acid**.** On the opposite hand, compound 4e that of 4-phenyl ethanoic acid group at N of the carboxamido ,group showed excellent anticonvulsant activity against both electroshock



Ethyl 4-(1-(4-chlorophenyl)-5-phenyl-1H-1,2,4-triazole-3-carboxamido)benzoate



3-(1-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H1,2,4-triazole-3-carboxamido)propanoic acid

Caution: Valence appears to be exceeded

and chemoshock. last , the prepared 1-(4-chlorophenyl)-5- phenyl-1H-1,2,4-triazole-3-carboxamide derivatives are revealed as promising anticonvulsant agents, stimulating the study of their full structure–activity relationship**.[32]**

Anti-Inflammatory-

Arif, M. N., Nadeem(2019), "In the nearby study

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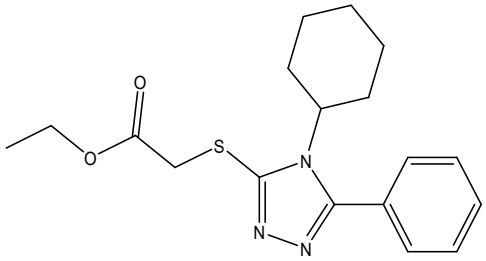
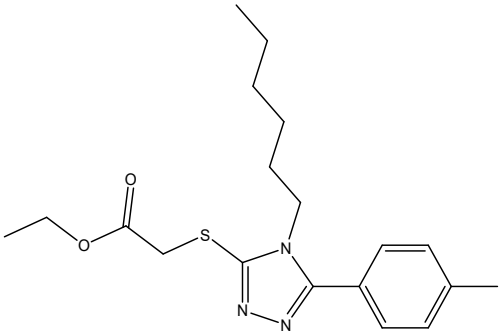
synthesis and biological assessment of nine novel ethyl [(4,5-disubstituted- 4H-1,2,4-triazol-3-yl)sulfanyl]acetate derivatives 2(a-i) is performed. All the recently synthesized acetate derivatives were screened for their antiinflammatory, and antifungal and antibacterial potential. The best activity was exposed by compound- (2g) Ethyl [(4-cyclohexyl-5-phenyl-4H-1,2,4-triazol-3- yl) sulfanyl] acetate ,which produced strong



Ethyl [(4-cyclohexyl-5-phenyl-4H-1,2,4-triazol-3- yl)sulfanyl]acetate

(2g)



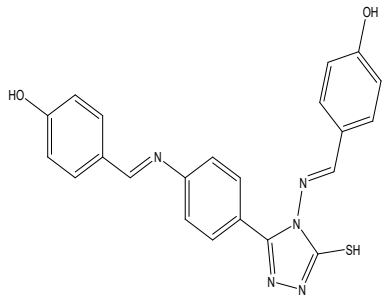
Ethyl {[4-hexyl-5-(4-methylphenyl)-4H-1,2,4- triazole-3-yl]sulfanyl}acetate

(2f)

inhibition of carrageenan-induced paw edema of 62.5% at 30 mg/kg dose. Ethyl [(4-cyclohexyl-5-phenyl-4H-1,2,4-triazol-3- yl)sulfanyl]acetate and (2f), Ethyl {[4-hexyl-5-(4-methylphenyl)-4H-1,2,4- triazole-3-yl]sulfanyl}acetate also exhibited moderate antiinflammatory effect.[33]

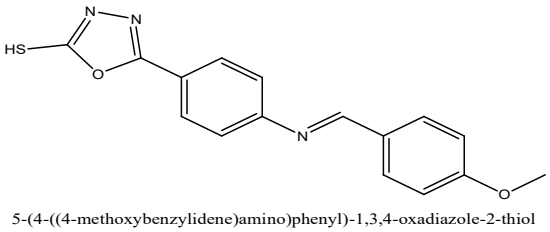
Antimalarial activity-

Thakkar, S.et al(2017), 1,2,4-Triazole and 1,3,4-oxadiazole analogues are of awareness thanks to their potential activity against malarial and microbial infections. In search of appropriate antimalarial and antimicrobial compounds, we report here the synthesis, characterization and biological activities of 1,2,4-triazole and 1,3,4-oxadiazole ana logues , 4-((Thiophen-2-ylmethylene)amino)-5-(4-((-thiophen- 2-ylmethy lene)amino)phenyl)-4H-1,2,4-triazole-3- thiol, (SS-2), 4-(((4-(4-((4-



4-(((4-(4-((4-Hydroxybenzylidene)amino)-5-mercapto-4H 1,2,4-triazol-3-yl)phenyl)imino) methyl) phenol

(SS 2)



5-(4-((4-methoxybenzylidene)amino)phenyl)-1,3,4-oxadiazole-2-thiol

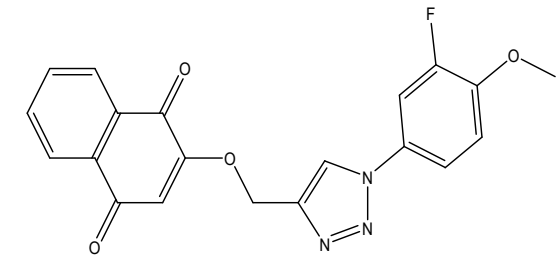
(SS-10)

Hydroxybenzylidene)amino)-5-mercapto-4H 1,2, 4-triazol-3-yl)phenyl)imino) methyl) phenol , thiol 5-(4-((4-Methoxybenzylidene) amino) phenyl)-1,3,4-oxadia zole-2-thiol. The in vitro antimicrobial activity was investigated against

pathogenic strains, the results were explained with the assistance of DFT and PM6 molecular orbital calculations.[34]

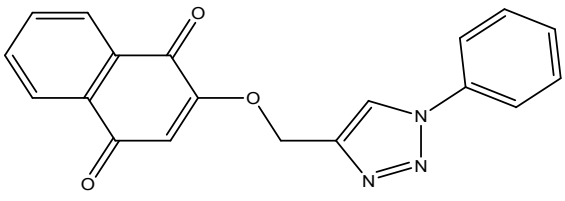
Antiplasmodial Activity –

Oramas-Royo, et al (2019), They were evaluated for his or her in vitro antimalarial activity against strains of Plasmodium falciparum and against different tumor cell lines (SKBr-3, MCF-7, HEL). the foremost vigorous antimalarial compounds showed a coffee antiproliferative activity. Simplified analogues were also obtained and a few structure–activity relationships were outlined. the simplest activity was obtained by compounds-(3s), 2-[(1-(3-Fluoro-4-methoxyphenyl)-triazol-4-yl)methoxy]-



2-[(1-(3-Fluoro-4-methoxyphenyl)-triazol-4-yl)methoxy]-naphthalene-1,4-dione

(3s)



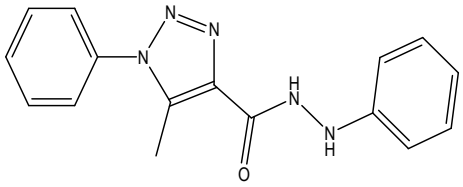
2-[(1-Phenyltriazol-4-yl)methoxy]-naphthalene-1,4-dione

(3j)

naphthalene-1,4-dione and(3j) 2-[(1-Phenyltriazol-4-yl)methoxy]-naphthalene-1,4-dione , having IC50 of 0.8 and 1.2 µM, respectively. Molecular dockings were also carried on Plasmodium falciparum enzyme dihydroorotate dehydrogenase (PfDHODH) so as to scale back the result**.[35]**

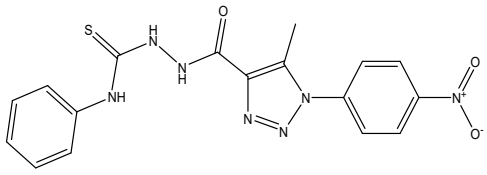
Antioxidant And Antibacterial Activity

Razzaq, A et al (2021). The antibacterial activity of the synthesized compounds (2a) ,2-(5-methyl-1-phenyl-1H-1,2,3-triazole-4- carbonyl)-N-phenylhydrazine,- 2-(1-(4-nitrophenyl)-5-methyl-1H-1,2,3- triazole-4-carbonyl)-N-phenylhydrazine-1- carbothioamide, and 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)- 4-phenyl-4H-1,2,4-triazole-3-thiol , 5-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3- triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol , were screened beside the negative bacterial strains of Helicobacter Pylori, Klebsiella pneumonia, Escherichia coli O157 and therefore the positive bacterial strain of Staphylococcus aureus using by well diffusion method. Practically, the agar and therefore the nutrient broth cultures were prepared consistent with the manufactures' instructions, which were then incubated at 37 °C.[36]



2-(5-methyl-1-phenyl-1H-1,2,3-triazole-4- carbonyl)-N-phenylhydrazine

(2a)



2-(1-(4-nitrophenyl)-5-methyl-1H-1,2,3- triazole-4-carbonyl)-N-phenylhydrazine-1- carbothioamide

(2d)

Conclusion

From the above literature review accomplished that the benzothiazoles and their derivatives have shown a broad spectrum of biological activities. it's a flexible nucleus within the ground of medicinal chemistry. Hence this exclusive molecule must function potential therapeutic leads of developing various biological agents. The biological profiles of this novel generation of benzothiazoles represent much progress with concede to the older compounds.

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