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Anti-neuropathic and anticonvulsant activities of various substituted triazoles analogues

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Various heterocyclic compounds along their derivatives were evaluated for their biological activities as antiviral, antitumor, anticonvulsant, antibacterial, antifungal, antituberculosis, analgesic, anti-inflammatory, antidiabetic, antihistamine and other biological activities. The triazole moiety seems to be very small, but in the biological profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. The triazole derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities. This review article covers the information of triazoles derivatives having different psychopharmacological actions. Thus triazole acts as a promising medicinal agent for the scientists working over this field. This review can be helpful to develop various more new compounds possessing triazoles moiety that could be better in terms of efficacy and lesser toxicity.

Capsule Summary: The heterocyclic compounds and their derivatives were reviewed for their biological activities such as as antiviral, antitumor, anticonvulsant, antibacterial, antifungal, antituberculosis, analgesic, anti-inflammatory, antidiabetic and antihistamine.

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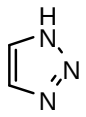
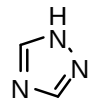
INTRODUCTION

Heterocyclic compounds are cyclic compounds with at least two different elements as ring member atoms. They are the counterparts of homocyclic compounds, which have only ring atoms from the same element. Although heterocyclic compounds may be inorganic, most contain at least one carbon atom, and one or more atoms of elements other than carbon within the ring structure, such as sulfur, oxygen or nitrogen. In organic chemistry non carbons which replace carbon atoms are called heteroatoms. Triazole and its derivatives possess a great significance in medicinal chemistry and numerous heterocyclic compounds containing triazole with different biological activities can be synthesized from them (Amir et al., 2008; Demaray et al., 2008; Demirbas, 2004). Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, having a fivemembered ring of two carbon atoms and three nitrogen atoms. The two isomers are: 1,2,3-triazole and 1,2,4-triazole (Siddiqui et al., 2011).



1,2,3-triazole



1,2,4-triazole

Out of these two, 1, 2, 4-triazole possess significant and wide variety of activity in comparison to 1, 2, 3-triazole. 1,2,3-triazole is considered to be the most stable organic compound in comparison to all other organic compounds possessing three adjacent nitrogen atoms. Aziridine was formed by flash vacuum pyrolysis from 1,2,3-triazole at 500°C which leads to loss of molecular nitrogen. Certain triazoles undergo cleavage very easily due to socalled ring-chain tautomerism such as in the

Dimroth rearrangement. 1,2,3-triazole is considered to be the most useful component, widely used in research purpose as a building block for complex chemical compounds such as pharmaceutical drugs like tazobactam (Kaplancikli et al., 2005; Karakurt et al., 2006; Karthikeyan, 2009; Kharb et al., 2012; Kokil, 2010; Lin et al., 2005; Mohamed et al., 2006; Pachuta-Stec et al., 2009). 1, 2, 4-Triazole is a basic aromatic heterocycle and its derivatives posses a wide variety of pharmacological activity such as antifungal, anticancer, anticonvulsant, antimicrobial, anti-inflammatory, antioxidant, anti-tubercular, anti-malarial, anti-nociceptive (Ali et al., 2015, Asif et al., 2015a-f; Havaldar and Patil, 2008; Ibrahim, 2009; Jadhav et al., 2009; Jordao et al., 2009. Kakefuda et al., 2002; Pandey et al., 2009; Pandey, et al., 2001; Shafiee et al., 2002**;** Shiradkar et al., 2007; Siddiqui and Arora, 2005). Some of the marketed preparation which contains triazole ring is fluconazole and itraconazole. 1,2,3-Triazole finds use in research as a building block for more complex chemical compounds, such as some antifungal drugs like tazobactam include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole. The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol (Agarwal and Singh, 2006; Sussman et al., 2001; Akbarzadeh et al., 2003; Brodie et al., 2009; Sidwell et al., 2005; Mauras et al., 2009; Sheehan et al., 2007).

Anticonvulsant activity of triazole derivatives

Epilepsy is a kind of disorder of central nervous system, which has affected at least 50 million people all over the world. However, most of the clinical drugs cannot control this disease effectively due to the gradually exposed side effect. In recent years, some attention has been paid to develop triazole compounds as anticonvulsant drugs due to their good activities and low toxicity. Various 3-(4-(substituted phenyl)-1,3-thiazol-2-ylamino)-4-(substituted phenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones (**1**) has been prepared by clubbing thiazole and triazole moieties for the pharmacophore model for anticonvulsant activity (Siddiqui and Ahsan, 2010). Two compounds (**1a** and **1b)** showed significant anticonvulsant activity in both maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (sc PTZ) screen along with wide safety of margin with protective index (PI), median hypnotic dose (HD 50) and median lethal dose (LD 50) much higher than standard drugs. Novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*- (1,2,4)triazolo(4,3-*a*)(1,4) benzo diazepines (**2)** were prepared by treating 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione with various aromatic acid hydrazides. Compounds were tested for anticonvulsant activity. Four of the tested compounds exhibited excellent activity in comparison with diazepam (Narayana et al, 2006). A series of 4,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one (**3)** were study the effect of cyclization of the semicarbazone moiety of aryl semicarbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant activity in animal models of seizures, viz. MES, scPTZ, subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)-induced seizure threshold tests. The compounds were also evaluated for neurotoxicity. Eight compounds exhibited anticonvulsant activity in all the animal models of seizure (Shalini et al., 2009). A series of novel 3-{((substituted phenyl)methyl)thio}-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles (**4)** and several related Schiff's bases, 3-{((substituted phenyl)-methyl)thio}-4-alkyl/aryl-5-{((((substituted phenyl/5-nitro-2-furyl)methylene)amino)-phenyl}-4*H*-1,2,4-triazoles **5** has been evaluation of their biological properties4. All compounds were evaluated for their anticonvulsant activity by MES, scPTZ and neurotoxicity (NT) screens. A number of triazole derivatives, exhibited protection at the dose of 100 and 300 mg/kg in one or both models employed. Three compounds were subjected to oral MES screening in rats at 30 mg/kg and were observed to protect 50% of the animals employed in the experiment. Analogues of 3-amino-7-(2,6-dichlorobenzyl)-6-methyltriazolo(4,3-b)pyridazine **6** containing amide or carboxylic acid function were tested for anticonvulsant activity. The compounds having the imidazole ring substituted with an amide group have been found to be generally more active against maximal electroshock-induced seizures in mice (ED_{50} = 37.5 mg/kg orally). The maximum activity was generally linked with a 2,6-dichlorobenzyl substitution pattern (Küçükgüzel et al., 2004).

The 3-Amido-7-(2,6-dichlorobenzyl)-6-methyltriazolo(4,3-b)pyridazine was also protective in the PTZ-induced seizures test (ED_{50} = 91.1 mg/kg orally) and blocked STY-induced tonic extensor seizures (ED_{50} = 62.9 mg/kg orally). A series of 4-(4-alkoxylphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives **7** and **8** 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 MES test and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 3-ethyl-4-(4-octyloxyphenyl)-4*H*-1,2,4-triazole was found to be the most potent with ED_{50} value of 8.3 mg/kg and protective index (PI = TD_{50}/ED_{50}) value of 5.5. The possible mechanism of action, it was tested in PTZ test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test (Moreau et al., 1998; Chen et al., 2007).

A series of 7-alkoxyl-4,5-dihydro-(1,2,4)triazolo(4,3-a)quinoline derivatives **9** was synthesized using 6-hydroxy-3,4-dihydro-1*H*-quinolin-2-one as a starting material (Xie et al, 2005). Their anticonvulsant activities were evaluated by the MES test and the scPTZ test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES and scMet tests show that 7-(4-fluorobenzyloxy)-4,5-dihydro-(1,2,4)triazolo(4,3-a)quinoline was found to be the most potent with ED_{50} value of 11.8 and 6.7 mg/kg respectively. A series of 5-alkoxy-(1,2,4)triazolo(4,3-a)quinoline derivatives **10**, **11** were synthesized using 4-hydroxyquinolin-2(1*H*)-one as the starting material. Their anticonvulsant activities were evaluated by the MES and their neurotoxicities were measured by the rotarod test. The results of these tests demonstrated that 5-hexyloxy-(1,2,4)triazolo(4,3-a)quinoline was the most potent anticonvulsant, with median effective dose (ED_{50}) of 19.0 mg/kg and protective index (PI=TD_{50}/ED_{50}) values of 5.8 in the MES test. Compound 5-benzyloxy-(1,2,4)triazolo(4,3-a)quinoline, exhibited a little weaker activity than previous

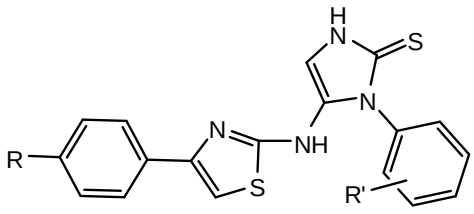
compound in controlling the seizure induced by MES test at the dose of 22.8 mg/kg, but it possessed lower neurotoxicity with PI value of 12.0, which was safer than marketed drug carbamazepine. To explain the possible mechanism of anticonvulsant activity, the compounds were tested in PTZ test, isoniazid test, thiosemicarbazide test; 3-mercaptopropionic acid and STY test (Guo et al., 2009). To further investigate anticonvulsant activity of quinoline derivatives, a series of 7-alkoxy-4,5-dihydro-(1,2,4)triazolo (4,3-a)quinoline-1(2*H*)-one derivatives **12** was synthesized starting from 7-hydroxyl-3,4-dihydro-2(1*H*)-quinoline (Jin et al., 2006). In initial (phase I) screening and quantitative (phase II) evaluation, compound 7-benzyloxyl-4,5-dihydro-(1,2,4)thiazolo(4,3-a)quinoline-1(2*H*)-one was among the most active and also has the lowest toxicity. In the anti-MES potency test, it showed median effective dose (ED_{50}) of 12.3 mg/kg, median toxicity dose (TD_{50}) of 547.5 mg/kg. Thus demonstrating much greater margin of safety compared to prototype drugs. It also showed significant oral activity against MES-induced seizures and low oral neurotoxicity in mice.

Thiazolyl-containing triazoles 13a and 13b both showed comparable anticonvulsant activity and higher protective index than the standard drugs phenytoin, ethosuximide and phenobarbital. Compound 13a possessed strong anti-maximal MES activity with effective dose (ED_{50}) of 13.4 mg/kg which was close to phenytoin and carbamazepine and better than phenobarbital and valproate. Compound 13b also displayed a better profile of anticonvulsant activity with lesser neurotoxicity (PI = 18.3). Both of the triazoles showed wide range of safe profile as the hypnotic dose $(HD)_{50}/ED_{50}$ values of 13a and 13b were found to be 36.27 and 47.16 against MES induced seizures, which were much higher than those showed by phenytoin. Moreover, they also gave a significant safety profile in PTZ induced seizure indicating the compounds as broad anticonvulsant spectrum. Notably, the ED50 and toxic dose (TD_{50}) values demonstrated that both of them exhibited adequate absorption in mice orally with lesser neurotoxic effects (Siddiqui, and Ahsan. 2010). Benzo(*d*)oxazolyl-derived triazole 14 showed an ED50 of 29.5 mg/kg, a TD_{50} of 285 mg/kg, in the anti-MES potency test, which was greater than the reference drug carbamazepine (Wei et al., 2009). Oxadiazolyl-substituted triazole 15 and its analogues exhibited considerable activity in both PTZ and MES models. Compound 15 was protective in the PTZ model in rats with an oral ED_{50} of 25.5 mg/kg and in the MES model in rats with an oral ED_{50} of 14.6 mg/kg. Neurotoxicity was observed with an ED_{50} of 335 mg/kg. The research also manifested that these triazoles acted as selective γ-aminobutyricacid (GABA) potentiating compounds with no interaction to the benzodiazepine binding site (Lankau et al., 2007). The results indicated that compound 15 was potential to be developed as selective GABA potentiating drugs. A series of phenyl-substituted triazoles were showed that compound 16a was the most potent one with ED_{50} value of 8.3 mg/kg and PI (TD_{50}/ED_{50}) value of 5.5, whereas compound 16b exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin (Chen et al., 2007). The anticonvulsant evaluation of indolyl-substituted triazoles indicated that compound 17a was more potent than carbamazepine after 4 h in the MES model and compounds 17b-d displayed lower neurotoxicity than phenytoin (Siddiqui, et al, 2008). Pyridyl-containing triazole 18 showed good anticonvulsant activity with total recovery time and time for hind limb extension recovery less than the standard drug phenytoin (Kshirsagar et al, 2009).

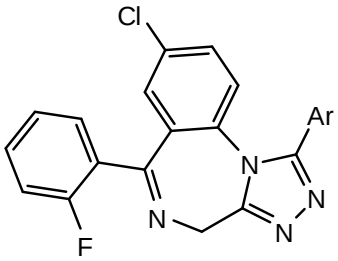
Anti-neuropathic activity of triazole derivatives

Triazole compounds as anti-neuropathic agents were developed early. Some triazole antidepressant drugs like trazodone (**19**), etoperidone (**20**) and nefazodone (**21**) as well as hypnotic/sedative drugs alprazolam (**22**) and estazolam (**23**) are prevalently used in clinic. Triazole derivatives have been demonstrated to possess good biological activities against some neuropathic-relative diseases such as Alzheimer's disease (AD), Parkinson's disease, schizophrenia, dementia, anxiety, depression and so on. Several literatures reported that many triazoles had potential activities for treating AD (Fischer et al., 2011). Triazolylthiophene derivatives **24a** and **24b** were good inhibitors of cdk5/p25 with the IC_{50} values of 32 and 0.035μmol/l (Shiradkar, et al, 2011), thus they had potential as possible treatments for AD. Another purinebased fluoroaryl-triazole **25** was also found to bind to the ATP binding site of cdk5/p25 with comparable binding energies (Nair, et al, 2011). Berberine is a major constituent of many natural drugs, which possesses various biological activities (Fang et al., 2010). Triazole-containing berberine derivatives **26a** and **26b** were inhibitors of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Compound **26a** with a diisopropylamino moiety substituted on the triazole ring, displayed the best inhibitory activity (IC_{50} = 0.044 μmol/L) against AChE. Meanwhile, the butyl derivative **26b** showed good inhibitory activity with IC_{50} value of 0.201μmol/l against AChE and gave the highest potency of abnormal aggregation of β-amyloid (Aβ) aggregation inhibition (77.9%).

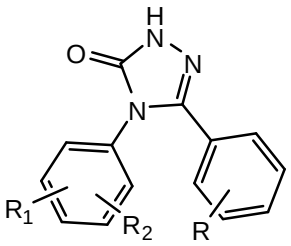
Molecular modeling simulations showed that the triazole moieties actually contributed to the inhibitory activities through interacting with the catalytic sites of AChE (Shi et al., 2011), which manifested that the triazole ring is beneficial for their biological activity. These compounds are potential candidates for treating AD. Aβ Peptides into toxic aggregates have been identified as a key event in AD. Inhibition of this process has thus emerged as a major therapeutic track against AD (Ouberai, et al, 2009). The prepared series of 1,4-diphenyltriazoles as probes targeting β-Amyloid aggregates in AD showed excellent binding affinities to Aβ aggregates (Ki = 0.004-0.03 μmol/L). Compounds **27a** and **27b** exhibited very good *in vivo* properties-high initial uptake and fast washout in normal mice (Qu et al., 2007). Taken together, these diphenyltriazole probes demonstrate promising *in vitro* and *in vivo* characteristics and they may provide a convenient platform for development of new imaging agents targeting amyloid plaques in the brain Very recently, a great many of tacrine-derived triazole compounds have been attracting much attention as AChE inhibitors (Bourne et al., 2010).



(**1**)



(**2**)

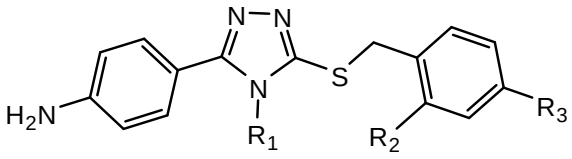


(**3**)

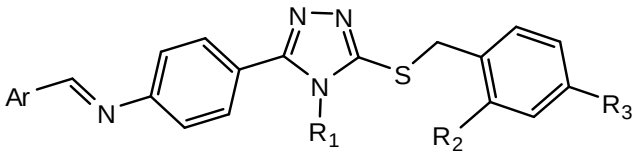
1a R=Cl, R'=4-OCH_3 **Ar**=Pyridin-4-yl, 4-NO_2-1H-indol-2-yl, R=H, NO_2, CH_3, OH

1bR=Br, R'=2-CH_3 6-OCH_3-2-naphthyl-4-C_6H_4, R_1=H, 2-CH_3

2-Br-5-$OCH_3C_6H_3$, pyridine-3-yl R_2=4-CH_3, 5-CH_3, 6-CH_3, 4-H

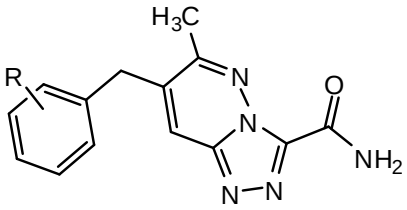


(**4**)

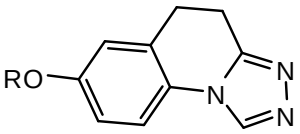


(**5**)

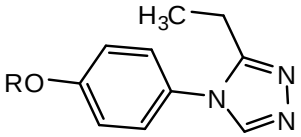
R_1=H, CH_3, R2=R3=H, halo, alkyl, Ar= phenyl, cyclohexyl, pyridyl



(**6**)

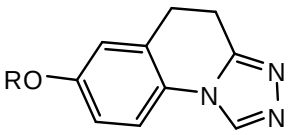


(**7**)

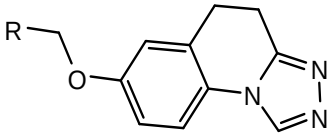


(**8**)

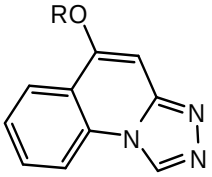
R=H, 2,6,-Cl R=$CH_2C_6H_5$, $CH_2C_6H_5$(p-F), $CH_2C_6H_5$(p-CH_3)



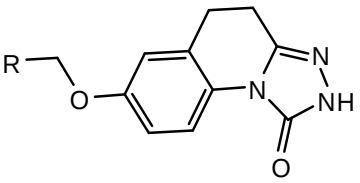
(**9**)



(**10**)



(**11**)

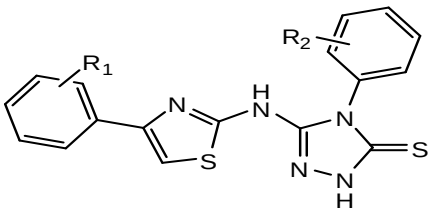


(**12**)

R=n-C_2H_5, n-C_3H_7, $CH_2C_6H_5$ **R**=CH_3, C_2H_5, C_3H_7, C_4H_9, $CH_2C_6H_5$, $CH_2C_6H_5$(4-F)

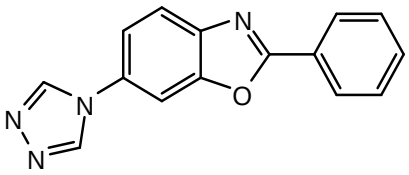
R=C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}

The series of compound **28**, the most potent noncovalent AChE inhibitors known, are in pre-clinical trials (Krasinski et al., 2005). Parkinson's disease (PD) is a neurodegenerative disorder, more and more people are infected in the world. There are currently no drugs to treat neurodegeneration in PD, and all existing medications only treat symptoms, lose efficacy over time, and produce untoward side effects. The first highly selective, orally bioavailable c-jun-N-terminal kinase (JNK) inhibitor **29** for protection of dopaminergic neurons *in vitro* and *in vivo*. At 0.3μmol/l, this compound showed statistically significant protection of primary dopaminergic neurons, had pharmacokinetic properties in rodents consistent with twice daily dosing, and was orally efficacious at 30 mg/kg in a mouse model of PD (Chambers et al., 2011). Collectively, these results suggested that this triazole JNK inhibitor could be a promising therapeutic neuroprotective agent in the treatment of PD.



13a, R_1 = Br, R_2 = 2-CH_3

13b, R_1 = Cl, R_2 = 4-OCH_3



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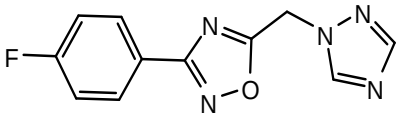

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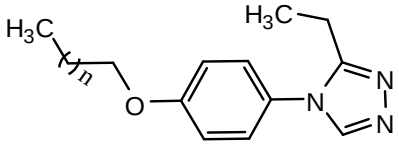
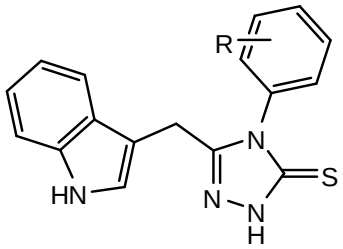
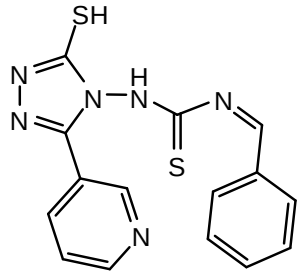


16a, n = 5 **16b**, n = 6



17a, R = 2-Cl; **17b**, R = H

17c, R = 2-OCH_3; **17d**, R = 3-CH_3



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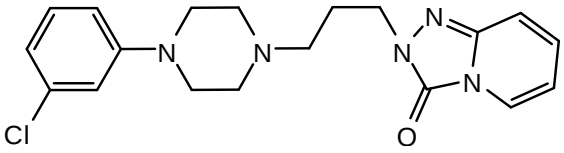
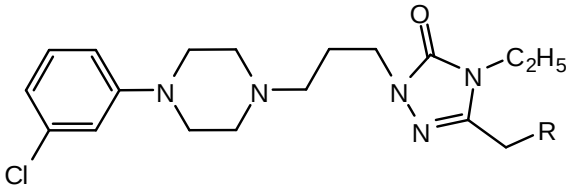
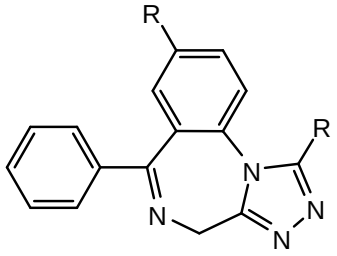


19 Trazodone

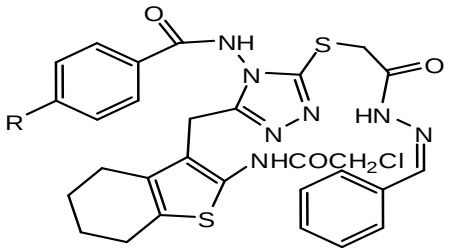


20 R = CH_3 Etoperidone **21** R = CH_2OPh Nefazodone

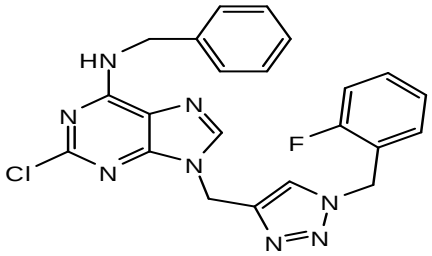


22 R = H Alprazolam

23 R = CH_3 Estazolam



24a, R = Cl **24b**, R = H



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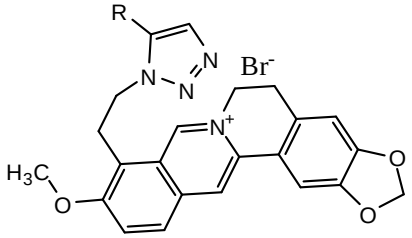
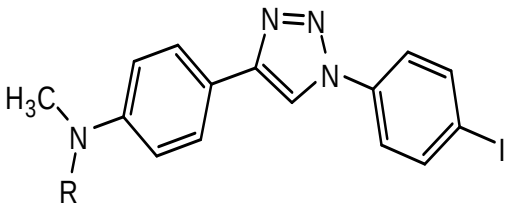
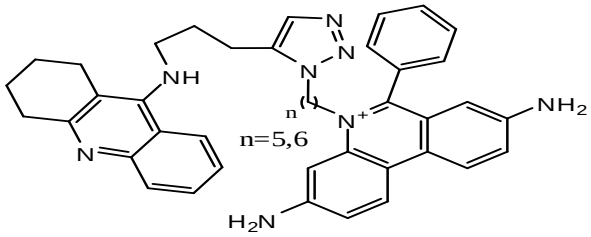


26a, R = N(*i*-Pr)$_2$ **26b**, R = $(CH_2)_3CH_3$

Corticotropin-releasing factor (CRF), a 41 amino acid neuropeptide isolated from mammalian brain, plays an important role within the brain, especially during stress. Therefore, CRF receptor antagonists ultimately play a major



27a, R = H; **27b**, R = CH3



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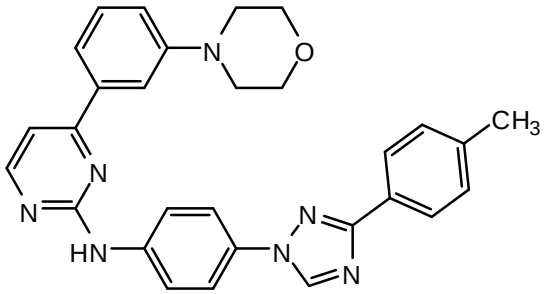

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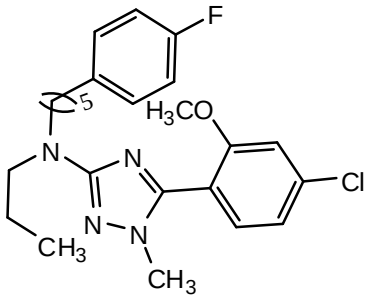

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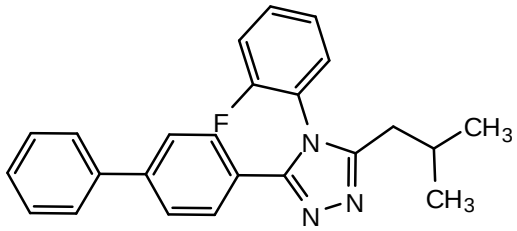

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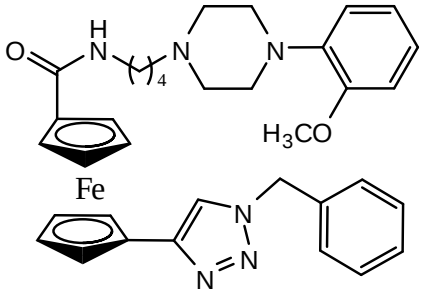

32

role in the management of some stress-related disorders such as anxiety and depression. Aryltriazole **30** showed very potent binding affinity (Ki = 0.0027 µmol/L) to CRF1 receptors with an IC_{50} of 0.049 µmol/L (Lowe et al., 2005). Several findings suggest that medications aimed at inhibiting the activity of glycine transporter 1 (GlyT1) may be useful as therapeutic agents for schizophrenia, dementia, and related disorders (Sugane et al., 2011). A series of 3-biphenyl-4-yl-4-phenyl-4*H*-1,2,4-triazoles were evaluated as novel GlyT1 inhibitors and found that fluorophenyl-substituted triazole derivative **31** was the most potent one, which had improved GlyT1 inhibitory activity and selectivity against GlyT2. In addition, triazole **32** had high membrane permeability, high oral bioavailability in mice and ameliorated learning impairment in passive avoidance tasks in mice. Triazole-derived ferrocene was a unique neutral antagonist of the dopamine receptors D3 and D4 and a potent partial agonist of the D2 subtype with EC_{50} value of 0.0025µmol/l which could be a potential lead as anti-neuropathic agent (Huber et al., 2009).

DISCUSSION

In the previous years the synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. The triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclics are found in abundance in most of the medicinal compounds. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue. Now a day's research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The success of imidazole as an important moiety of number of medicinal agents led to introduction of the triazoles. The triazoles are said

to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazoles nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti inflammatory, cns stimulants, sedatives, antianxiety and antimicrobial agents, Anti fungal activity. They are used as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other functions. Many dye stuffs and pigments have heterocyclic. The Triazole derivative possess a wide a range of pharmacological such as antimicrobial, analgesic, anti-Inflammatory, anti convulsant, anti neoplastic, anti malarial, anti viral, anti proliferative, and anti cancer activities (Zhou and Wang, 2012; Ebdrup et al., 2004; Sun et al., 2006; Upadhayaya et al., 2009; Vishnumurthy et al., 2011; Wuest et al., 2009; Zhai et al., 2008; Zhu et al., 2008). The importance of triazole derivatives lies in the field that these have good position in heterocyclic chemistry, due to its various biological activities.

CONCLUSION

In the previous years the synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. The triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclics are found in abundance in most of the medicinal compounds. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. They are predominantly among the type of compounds used such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antihypertensive, antimalarial, antianxiety, antidepressant, and antihistaminic, antitubercular agents etc. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue.

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