ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2015; 7 (1): 45 – 51

REVIEW ARTICLE

Structure Activity Relationship Studies of 5-Membered Heterocyclic Derivatives

D. Kumudha*, R.R.Reddy

Arya college of Pharmacy, Kandi, Sangareddy, Medak, Telangana, India

Received 17 Oct 2015; Revised 12 Feb 2016; Accepted 24 Feb 2016

ABSTRACT

Some novel 4-([5-amino-1,3,4-thiadiazol-2yl) methyl)-5-substituted phenyl-4*H*-1,2,4-triazol-3-thiols **(8a-d),** 5[(3-mercapto-5-substituted phenyl-4*H*-1,2,4-triazol-4-yl)methyl]1,3,4-oxadiazole-2-thiol**[9a-d]**, 4-{(5-mercapto-4-(4-substituted phenyl)-4*H*-1,2,4-triazol-3-yl]methyl}-5-substituted phenyl-4*H*-1,2,4-triazole-3-thiol **[$10a_1$-a_2 – $10d_1$-d_2],** 2-(3-mercapto-5-substituted phenyl)-4*H*-1,2,4-triazol-4-yl)-N^1-[(1*E*)-substituted phenyl methylene) acetohydrazide (Schiffs bases) **[$11a_1$-a_6-$11d_1$-d_6]** and 2-(3-mercapto-5-substituted phenyl-4*H*-1,2,4-triazol-4-yl)-N-(4-oxo-2-substituted phenyl-1,3-thiazolidin-3-yl) acetamides **[$12a_1$-a_3-$12d_1$-d_3]** were prepared and characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral analysis. Few compounds were evaluated for anticonvulsant, CNS depressant activities and neurotoxicity as reported earlier. Additionally the Structure Activity Relationship (SAR) studies have been carried out to determine the relevance of the different moieties that define the potency of triazole derivatives.

Key words:1,2,4-triazole,1,3,4-thiadiazoles,1,3,4-oxadiazole, Schiff's bases ,4-Thiazolidinones anticonvulsant, CNS depressant activity, Neurotoxicity , SAR .

INTRODUCTION

Oxadiazole is a five membered heterocyclic ring containing two nitrogen and one oxygen. 1,3,4-oxadiazoles are found to possess biological activitieslike antibacterial [1], antifungal [1], antimicrobial [2], antituberculor [5], anti-HIV [4], antidepressant [7], analgesic [3], anticancer [4], anti-inflammatory [2,3,7], anticonvulsant [6] activities etc. Also some heterocyclic moieties such as 1,2,4-triazole nucleus exhibit wide spectrum of pharmacological activities such as antibacterial [13,14], antifungal [13,14], antimycobacterial[8,12], antitumor [10,12], anti-HIV [11] , anti-inflammatory [15], analgesic [15], antiviral [12], antihistaminic[9], anticonvulsant [16], anxiolytic [15], insecticidal [14], antimicrobial [8] etc. On other hand 1,3,4-thiadiazoles are of current interest due to their broad spectrum of pharmacological activities such as antifungal [20], antituberculor [19], antimicrobial [17,21], anti-inflammatory [22], anticancer [24], anticonvulsant [23], antiviral [18], analgesic [21], antibacterial [20] activities. In addition it has been reported that 1,3,4-thiadiazoles exhibit various biological activities possibly due to the presence of =N-C-S moiety [18]. Schiff's bases are associated with various biological activities such as antibacterial [25,26], antifungal [26], antimicrobial [27], CNS depressant [31], anticonvulsant [29-31], anthelmintic [27], antioxidant [27], antituberculor[32], analgesic [28], anti-inflammatory [28], antipyretic [28] activities. Schiff's bases are also used as substrates in the synthesis of number of industrial and pharmacologically active compounds via ring closure, cycloaddition and replacement reaction. 4-thiazolidinones have been found to possess different biological activities such as antifungal [33], antituberculor [34], antimicrobial [35], anti-inflammatory [40], anticonvulsant [36], antiviral [42], anti-HIV[41], analgesic [37], antibacterial [33,34,37], antidiabetic [39], anti-parkinsonian [38] activities.

MATERIALS AND METHODS

Melting Points were in an open capillary tube and are uncorrected. IR Spectra (KBr) were recorded on a Perkin Elmer FT-IR Spectrophotometer and ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Ultra Shield NMR-Spectrophotometer 300MHz instrument using DMSO-d6/D_2O/$CDCl_3$ using TMS as an internal standard (Chemical shift in δ ppm). The mass spectra were recorded on a JOEL-Accu TOF JMS –T100LC Mass Spectrometer. Compounds were checked for their homogeneity by TLC on Silica Gel G plates and spots were visualized in iodine vapour.

***Corresponding Author:**D.Kumudha**; Email:**kumudhachem@gmail.com

RESULTS AND DISCUSSION

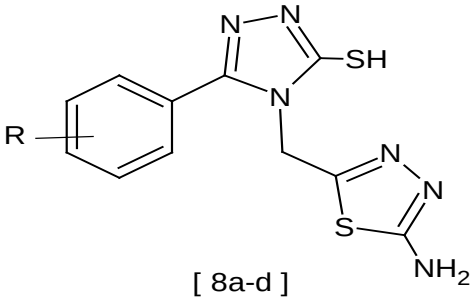
Structure activity relationship:

Literature review revealed that 1, 2, 4-triazole nucleus and their derivatives emerge rapidly with the advance of modern heterocyclic chemistry promising a variety of biological activities. 1, 2, 4-Triazole nucleus has been incorporated into wide variety of therapeutically interesting molecules to transform them into better drugs.

A study of structure activity relationship revealed that compound bearing triazole moiety possess excellent anticonvulsant activity. Likewise 5 membered heterocyclic moieties such as oxadiazole, thiadiazole and thiazolidinones possess good anticonvulsant activity. In addition to this, Schiff's base (Imino moiety) also possesses good anticonvulsant activity. The above said moieties are incorporated into 5-Substituted phenyl-1, 2, 4-triazole-3-thiol, the resulting compounds may possess synergistic anticonvulsant activity at the dose of 20mg/Kg compared with standard drug Phenytoin (30mg/Kg).

In **(8a-c),** the 5-Substituted phenyl-4*H*-1, 2, 4-triazole-3-thiol is incorporated with 2-amino 1,3,4-thiadiazole moiety through methylene bridge (-CH_2-). The newly synthesized compounds **(8a-d)** possess good anticonvulsant activity in MES and PTZ animal models. The compounds **8b, 8c, 8d** showed good activity in which the phenyl ring is substituted with R=2-Cl, 3-CH_3, 4-CH_3 respectively, than the unsubstituted compound **8a** where R=H. Among all the compounds, **8c** showed excellent anticonvulsant activity.

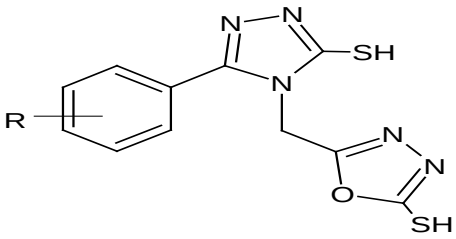
General Structure:



[8a-d]

In **(9a-c),** the 5-Substituted phenyl-4*H*-1, 2, 4-triazole-3-thiol is incorporated with 1,3, 4 oxadiazole-2 thiol possess excellent anticonvulsant activity at the dose of 20 mg/Kg when compared with Phenytoin (30mg/Kg). The newly synthesized compounds **9a, 9b, 9c** has a substituent R at phenyl ring in which R=H, 2-Cl, 3-CH_3 respectively. Among these compounds, **9b** showed excellent activity in MES and PTZ animal model due to the presence of 2-Cl on the phenyl ring.

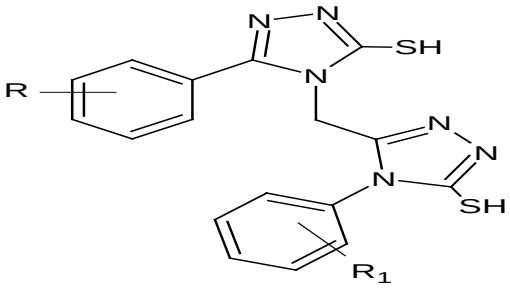
General structure:



[9a-d]

In **$10a_1$, $10b_1$, $10c_2$,** the 5-Substituted phenyl-4*H*-1, 2, 4-triazole-3-thiol is incorporated with 5-mercapto-4-(4-Substituted phenyl)-4*H*-1, 2, 4-Triazole moiety through the methylene bridge. All the compounds showed significant activity in MES and PTZ method. This may be due to the presence of substituted phenyl rings attached to triazole moiety. Among these compounds, **$10a_1$, $10c_2$** showed highest % of inhibition compared to **$10b_1$**.

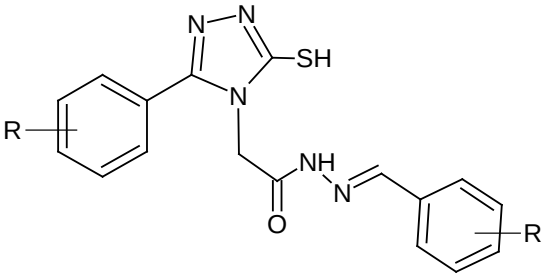
General Structure:



[$10a_1$-a_2 - $10d_1$-d_2]

In **$11a_1$, $11b_2$, $11c_3$,** the 5-Substituted phenyl-4*H*-1, 2, 4-triazole-3-thiol is incorporated with imino group (-CONHN=C-C_6H_4R) through methylene bridge. These compounds possess significant anticonvulsant activity in MES and PTZ methods. **$11b_2$** possess excellent activity may be due to the presence of R=2-Cl, R1= 4-OH substituents on phenyl ring at the dose of 20 mg/Kg.

General Structure:

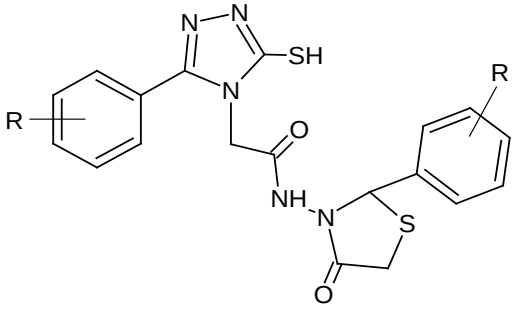


[$11a_1$-a_6 - $11d_1$- $11d_6$]

In **$12a_1$, $12b_2$, $12b_3$**, the 5-Substituted phenyl-4*H*-1,2,4-triazole-3-thiol is incorporated with

substituted with TDZ ring. All these compounds exhibited good anticonvulsant activity at the dose of 20 mg/Kg. This may be due to the presence of aryl substituents R, R1 such as (H, 4-Cl), (2-Cl, 2-OH), (3-CH_3, (3-OCH_3, 4-OH)) respectively.

General Structure:



[$12a_1$-a_3 - $12d_1$-d_3]

In **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12b_3$** are tested *in vivo* for anticonvulsant activity at the dose of 20 mg/Kg. The Standard drug Phenytoin (30mg/Kg) showed 81% inhibition in duration of extensor phase, whereas the test drugs **8b, 8c, 8d, 9a, 9b, $10a_1$, $10b_1$, $10c_2$, $11a_1$,$11b_2$, $11d_1$, $12a_1$, $12b_2$, $12b_3$** showed 68-78 % inhibition, other compounds **8a, 9c, $11c_3$** showed 61- 68 % inhibition respectively. The results are tabulated in (**Table 1**).

Table 1: Anticonvulsant activity of *s*-triazole derivatives by MES method

Code No	Dose	Duration of tonic hind limb extensor in sec(Mean ±SEM)	% inhibition
Control	DMSO	13.52±0.72NS	00
Phenytoin sodium	30mg/kg	2.45±0.431**	81.87
8a	20mg/kg	5.22 ± 0.96*	61.39
8b	20mg/kg	4.12 ± 0.90**	69.52
8c	20mg/kg	3.25±0.25**	75.96
8d	20mg/kg	3.75± 0.65**	72.26
9a	20mg/kg	4.81 ± 0.56*	64.42
9b	20mg/kg	3.78 ± 0.32**	72.04
9c	20mg/kg	5.01± 0.72*	62.94
$10a_1$	20mg/kg	3.01± 0.12**	77.73
$10b_1$	20mg/kg	4.32±0.41**	68.04
$10c_2$	20mg/kg	4.17±0.23**	69.15
$11a_1$	20mg/kg	3.21 ± 0.71**	76.25
$11b_2$	20mg/kg	3.01 ± 0.82**	77.73
$11c_3$	20mg/kg	4.53 ± 0.11*	66.49
$11d_1$	20mg/kg	3.12±0.31**	76.92
$12a_1$	20mg/kg	2.91± 0.23**	78.47
$12b_2$	20mg/kg	3.72±0.98**	72.48
$12c_3$	20mg/kg	3.11±0.77**	76.99

Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns = Non significant compared with the respective control

Test drug showed excellent anticonvulsant activity (75-97%) of phenytoin activity even at less dose of 20 mg/Kg when compared to phenytoin 30 mg/Kg.

In PTZ animal model, **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$,$11b_2$, $11c_3$, $12a_1$, $12b_2$, $12b_3$** are screened *in vivo* for anticonvulsant activity at the dose of 20 mg/Kg b.w. Standard drug diazepam(4mg/Kg) significantly prolongs the onset of seizure and protected 100% against PTZ induced convulsions. All the newly synthesized compounds significantly prolongs the time required to produce PTZ induced seizures as discussed above and showed excellent protection (83.33%) against PTZ seizures whereas **8a, 8d** afforded moderate protection (66.66%) against PTZ seizures. The results are given in (**Table 2**).

Table 2: Anticonvulsant activity of *s*-triazole derivatives by PTZ animal model

Code No	Dose	Onset of Seizure (min) (Mean ± SEM)	% Protection
Control	DMSO	2.10± 0.27^{ns}	0
Diazepam	4mg/Kg	13.52±0.52***	100
8a	20mg/kg	09.13±0.75*	66.6
8b	20mg/kg	11.01±0.37**	83.33
8c	20mg/kg	11.32±0.27**	83.33
8d	20mg/kg	08.01±0.49*	66.66
9a	20mg/kg	10.21±0.52**	83.33
9b	20mg/kg	11.53±0.61**	83.33
9c	20mg/kg	8.58±0.14*	66.66
$10a_1$	20mg/kg	11.20±0.75**	83.33
$10b_1$	20mg/kg	9.32±0.79*	66.66
$10c_2$	20mg/kg	10.03±0.42**	83.33
$11a_1$	20mg/kg	11.45±0.31**	83.33
$11b_2$	20mg/kg	11.98±0.46**	83.33
$11c_3$	20mg/kg	12.01±0.73***	83.33
$12a_1$	20mg/kg	10.35±0.74**	83.33
$12b_2$	20mg/kg	11.67±0.86**	66.66
$12c_3$	20mg/kg	10.79±0.27**	83.33

Results are expressed in Mean ± SEM (n=6); Significance levels ***P<0.001, **P<0.01, *P<0.05, ns = Non significant compared with the respective control

CNS Depressant activity:

All the compounds **8a-c, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12b_3$** are evaluated for CNS depressant activity by using actophotometer scoring technique and swim pool technique.

In behavioral study of *s*-triazole derivatives using actophotometer, the synthesized compounds **8a-c, 9a-c, $10a_1$, $10b_1$, $10c_2$, $12a_1$, $12b_2$, $12b_3$** do not show any decrease in locomotor activity. Only the test compounds **8d, $11a_1$, $11b_2$, $11c_3$** showed poor CNS depressant activity as compared to Phenytoin, the results are given in (**Table 3**).

Table 3: Behavioral study of *s*-triazole derivatives using actophotometer

Code No	Control (24Hrs Prior)	Post Treatment		% inhibition
		0.5Hr	1Hrs after	
Phenytoin	474.84±0.21	220.22±0.50	173.19±0.41**	64
8a	415.09±0.76	365.65±0.91	352.62±0.18^{ns}	15
8b	441.17±0.72	401.71±0.25	373.26±0.23^{ns}	15
8c	387.42±0.53	367.27±0.70	351.07±0.33^{ns}	9
8d	394.48±0.17	285.51±0.37	261.07±0.41*	32
9a	481.13±1.31	476.51±0.23	430.61±0.38^{ns}	11
9b	470.03±0.92	450.62±0.64	382.91±0.29^{ns}	19
9c	466.15±0.70	459.29±0.79	400.31±0.31^{ns}	15
$10a_1$	532.33±0.21	520.15±0.66	468.14±1.52^{ns}	13
$10b_1$	489.47±0.39	436.25±0.17	412.14±0.13^{ns}	16
$10c_2$	459.63±0.91	431.29±0.29	390.72±0.69^{ns}	15
$11a_1$	475.12±0.73	407.56±0.91	325.26±0.56**	32
$11b_2$	483.14±0.17	410.23±0.73	350.57±0.32*	26
$11c_3$	463.18±0.16	415.72±0.23	358.47±0.37*	22
$12a_1$	512.21±0.24	500.27±0.47	466.34±0.36^{ns}	09
$12b_2$	493.41±0.27	480.71±0.71	440.48±0.76^{ns}	11
$12c_3$	461.73±0.72	440.31±0.34	401.13±0.86^{ns}	13

Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns = Non significant compared with the respective control

The test compounds were tested at a dose of 20mg/kg (i.p), Phenytoin tested at 30mg/kg (i.p.).

In a similar study, using forced swim pool test, the immobility period after the administration of synthesized compounds are compared to Carbamazepine (Standard Drug). The compounds **8d, $11a_1$, $11b_2$, $11c_3$** showed little increase in immobility period when compared to standard indicating poor CNS depressant activity. The results are given in (**Table 4**).

Table 4: CNS Depressant activity of *s*-triazole derivatives by Swim pool test

Code No	Immobility time(s) Control (24Hrs Prior)	Post treatment (60min after)
Control	170.42 ±12.01	174.62±07.12^{ns}
Carbamazepine	138.94±19.09	241.60±13.62***
8a	133.12±8.31	154.32±08.63^{ns}
8b	126.47±13.12	147.01±06.14^{ns}
8c	118.16±7.03	130.34±05.27^{ns}
8d	148.76±6.72	183.70±01.14*
9a	115.12±9.14	120.17±10.24^{ns}
9b	124.17±8.17	130.17±09.17^{ns}
9c	100.14±13.17	117.28±16.32^{ns}
$10a_1$	114.16±16.12	132.66±8.21^{ns}
$10b_1$	168.19±8.72	140.41±9.35^{ns}
$10c_2$	125.19±16.42	105.61±15.40^{ns}
$11a_1$	120.54±12.45	180.50±12.51**
$11b_2$	145.21±8.01	178.61±17.12*
$11c_3$	124.13±9.12	160.71±09.12*
$12a_1$	127.15±13.45	145.33±10.22^{ns}
$12b_2$	135.23±15.53	157.38±9.25^{ns}
$12c_3$	160.73±9.34	180.11±08.32^{ns}

Results are expressed in Mean ± SEM (n=6); Significance levels ***P<0.001, *P<0.05, ns = Non significant compared with the respective control

In Hole board test, Injection of test compounds **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12c_3$** at 20mg/kg showed not significantly decrease in nose poking except the compounds **8d, $11a_1$, $11b_2$, $11c_3$** indicating poor CNS depressant activity. The results are given in (**Table 5**).

Table 5: Anxiolytic activity of *s*-triazole derivatives hole board test in mice

Treated group	Dose mg/kg	No. of nose poking in 5 min (Mean±SEM)	%decrease in nose pose
Control	10ml/kg	30.13 ± 3.132^{ns}	-
Diazepam	3	15.95 ± 2.011**	47.06
8a	20	27.36 ± 0.726^{ns}	10.12
8b	20	28.12 ± 1.263^{ns}	06.67
8c	20	27.01 ± 0.926^{ns}	10.35
8d	20	22.16 ± 0.327*	26.45
9a	20	28.15 ± 0.003^{ns}	06.57
9b	20	29.00 ± 0.721^{ns}	03.75
9c	20	27.97 ± 0.132^{ns}	07.16
$10a_1$	20	26.92 ± 0.175^{ns}	10.65
$10b_1$	20	28.56 ± 0.731^{ns}	05.21
$10c_2$	20	26.98 ± 0.631^{ns}	10.45
$11a_1$	20	21.07 ± 0.221*	30.07
$11b_2$	20	23.06 ± 1.729*	23.46
$11c_3$	20	23.79 ± 0.771*	21.04
$12a_1$	20	25.98 ± 0.231^{ns}	13.77
$12b_2$	20	26.52 ± 0.718^{ns}	11.98
$12c_3$	20	28.14 ± 0.237^{ns}	06.60

Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns = Non significant compared with the respective control

In Staircase test, the test compounds **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12c_3$** screened for anxiolytic activity at the dose of 20mg/kg did not show any significant effect on anxiolytic activity expect the **8d, $11a_1$, $11b_2$, $11c_3$** showed slight decrease in number of rearing indicates the presence of mild anxiolytic activity when compared to diazepam. The results are given in (**Table 6**).

Table 6: Anxiolytic activity of *s*-triazole derivatives by Staircase test in mice

Treated group	Dose mg/kg	No. of steps climbed in 5min (Mean±SEM)	No. of rearing in 5min (Mean±SEM)	% Decrease in rearing
Control	10ml/kg	25.76 ± 1.320	23.62 ± 1.091^{ns}	-
Diazepam	2	36.26 ± 0.920	14.12 ± 1.152**	40.22
8a	20	26.45 ± 0.728	21.26 ± 0.327^{ns}	09.99
8b	20	27.32 ± 0.125	22.81 ± 0.325^{ns}	03.42
8c	20	24.12 ± 0.326	20.97 ± 0.472^{ns}	11.21
8d	20	27.12 ± 0.727	18.08 ± 0.321*	23.43
9a	20	23.32 ± 0.126	20.78 ± 0.126^{ns}	12.02
9b	20	20.45 ± 0.267	20.18 ± 0.276^{ns}	14.56
9c	20	24.26 ± 0.712	21.71 ± 0.912^{ns}	08.08
$10a_1$	20	21.82 ± 0.615	20.99 ± 0.213^{ns}	11.13
$10b_1$	20	20.14 ± 0.222	19.91 ± 0.137^{ns}	15.70
$10c_2$	20	22.46 ± 0.121	20.12 ± 0.243^{ns}	17.39
$11a_1$	20	28.54 ± 0.279	17.01 ± 0.721*	27.98
$11b_2$	20	27.47 ± 0.172	18.52 ± 0.173*	21.63
$11c_3$	20	29.13 ± 0.542	17.85 ± 0. 712*	24.42
$12a_1$	20	26.14 ± 0.312	21.01 ± 0.781^{ns}	11.05
$12b_2$	20	27.14 ± 0.124	20.75 ± 0.561^{ns}	12.15
$12c_3$	20	24.15 ± 0.745	21.56 ± 0.124^{ns}	08.72

Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns= Non significant compared with the respective control

The SAR of the synthesized compounds revealed that **8d, $11a_1$, $11b_2$, $11c_3$** possess little CNS depressant activity and others are non-significant. The compounds were shown CNS depressant activity due to the presence of 4-CH_3 group on

phenyl ring in **8d**, and imino moiety attached to the 5-Substituted phenyl 1, 2, 4-triazole-3- thiol **($11a_1$, $11b_2$, $11c_3$)** (Schiffs bases).

In conclusion, it can be said that compounds possess good to significant anticonvulsant activity even at the less dose when compared to standard. Hence a detailed study on these derivatives may be quite desirable. All the synthesized compounds were also screened for CNS Depressant activity. The result indicated that almost all the tested compounds possess less CNS depressant activity in comparison with standard. Hence further optimization and development of these compounds is required for drug development.

ACKNOWLEDGEMENTS

Authors are thankful to the Principal Dr. R. Rajareddy, Arya College of Pharmacy, Kandi, Sangareddy, Medak, for providing laboratory facilities and Dr. Chidhambaranathan, Department of Pharmacology, K. M. College of Pharmacy for his help in carrying out biological activity studies. The authors are also thankful to the Head, SAIF, CDRI, Lucknow for providing spectral data.

REFERENCES

1. Dundappa S Donawade, A.V.Raghu and Guru S Gadagimath. Synthesis and antimicrobial activity of some new-1-substituted-3-pyrrolyl aminocarbonyl/ oxadiazolyl/triazolyl/5-methoxy-2-methylindoles and benz[g]indoles. Indian J Chem. 2006; 45B. 689-696.
2. K.C.Ravindra, H.M.Vagdevi, V.P.Vaidya and Basavaraj Padmashali. Synthesis, antimicrobial and anti-inflammatory activities of 1,3,4-oxadiazoles linked to naptho[2,1-b]furan. Indian J Chem. 2006; 45B. 2506-2511.
3. Shivanandha Wagle, Airody Vasudeva Adhikari and Nalilu Suchetha Kumari. Synthesis of some new 2(3-methyl-7-substituted-2-oxo quinoxalinyl)-5-(aryl)-1,3,4-oxadiazoles as potential non-steroidal anti-inflammatory and analgesic agents. Indian J Chem. 2008; 45B. 439-448.
4. Maryam Zahid, Khawaja A.Yasin, Tashfeen Akhtar, Nasim H.Rama, Shalid Hameed, Najim A.Al.Masoudi, 5. Roberta Laddo and Paolo La Colla. Synthesis and invitro antiproliferative activity of new adamantylthiazolyl-1,3,4-oxadiazoles. ARKIVOC, General Papers. 2009; (xi). 85-93.
5. Shashikanth R Pattan, P A Rabara, Jayashri S Pattan, A A Bukitagar, V S Wakale and D S Musmade. Synthesis and evaluation of some novel substituted 1,3,4-oxadiazoles and pyrazole derivatives for antituberculor activity. Indian J Chem. 2009; 48B. 1453-1456.
6. Ali Almasirad, Sayyed A Tabatabai, Mehrdad Faizi, Abbas Kebriaee Zadeh, Nazila Mehrai, Afshin Dalvandi and Abbas Shafiee. Synthesis and anticonvulsant activity of new 2-substituted -5-[2-(2-fluoro phenoxy) phenyl]-1,3,4-oxadiazoles and 1,24-triazoles. Bioorganic & Medicinal Chemistry Letters. 2004; 14. 6057-6059.
7. U.Misra, A.Hitkari, A.K.Saxena, S.Gurtu, K.Shanker. Biologically active indolylmethyl-1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 4*H*-1,3,4-triazoles and 1,24-triazines. Eur.J Med.Chem. 1996; 31. 629-634.
8. Mahendra Shiradkar, Unnat Pandit, Kalyan Chakravarthy Akula, Abhay Meheta and Gorentla Venketa Suresh Kumar. Microwave assisted synthesis and antimicrobial screening of fused triazoles. General Papers. AKIVOC. 2006; (xiv). 141-154.
9. Walid Fathalla, S. M. Ei Rayer and Ibrahim A. I. Ali. Convenient synthesis of 1-substituted -4-methyl-5-oxo [1,2,4] triazolo[4,3a]quinazolines. General Papers, ARKIVOC. 2007; (xvi). 173-186.
10. Xiang-Li Zhao, Shu Chun Guo, Hai-Sheng Song, Ding Wang and Ping Gong. Synthesis and antitumor activities of novel [1,2,4]triazolo[1,5a]pyrimidines. Molecules. 2007; 12. 1136-1146.
11. Jing de Wu, Xin Yong Liu, Xianchao Cheng, Yuan Cao, Defeng Wang, Zhong Li, Wenfong Xu Christophe Pannecouque, Myriam Witrvrouw and Erik De Clereq. Synthesis of novel derivatives of 4-amino-3-(2-furyl)-5-mercapto-1,2,4-triazole as potential HIV-1 NNRTIs. Molecules. 2007; 12. 2003-2016.
12. P.Vijayakumar and V.Rajeswar Rao. Synthesis and antituberculor, antiviral and anticancer activity of 3-(3-mercapto alkyl-7*H*[1,2,4-triazolo[3,4b][1,3,4]thiadiazin-6-yl]chromen-2-one and its derivatives. Indian J Chem. 2008; 47B. 106-111.

13. Lingappa B, Girisha K S, Balakrishna Kalluraya, N.Sathesh Rai, Nailu Suchetha Kumari. Regioselective reaction: synthesis of novel Mannich bases derived from 3-(4,6-di-mercapto-1,2,4-triazoles and their antimicrobial properties. Indian J Chem, 2008; 47B. 1858-1864.
14. T Nidhi Gautham and O.P.Chouraria. Synthesis antimicrobial and insecticidal activity of some 4*H*-1,2,4-triazole derivatives. Indian J Chem. 2010; 49B. 956-959.
15. Anil M Manikrao, Ravindra A Fursule, K.S.Rajesh, Harish K.Hunj Wani and Prafulla M Sabale. Synthesis and biological screening of novel derivatives of 3-(N-substituted carboxamidoethylthio)-4*H*-1,2,4-triazoles. Indian J Chem. 2010; 49B. 1642-1647.
16. Jing Chen, Xian-Yu Sun, Kyu-Yun Chai, Jin-Seok Lee, Mi-Sun Song and Zhe-Shan Quan. Synthesis and anticonvulsant evaluation of 4(4-alkoxyphenyl)-3-ethyl-4*H*-1,2,4-triazoles as open–chain analogues of 7-alkoxy-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Bioorganic & Medicinal Chemistry. 2007; 15. 6775-6781.
17. Neslihan Demirbas, Ahmet Demirbas, Sengul Alpay Karaoglu and Elif Celik. Synthesis and antimicrobial activities of some new [1,2,4] triazolo[3,4-b][1,3,4]thiadiazoles and [1,2,4] triazolo[3,4b][1,3,4]thiadiazoles. General Papers. Arkivoc. 2005; (i). 75-91.
18. Abdel Rahman Farghaly, Erik De Clerq, and Hussein El-Karhef. Synthesis and antiviral activity of novel [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines. General Papers. Arkivoc. 2006; (x). 137-151.
19. Nilufer Solak and Sevim Rollas. Synthesis and antituberculosis activity of 2-(aryl/alkylamino)-5-(4-aminophenyl)-1,3,4-thiadiazoles and their schiffs bases. General Papers. Arkivoc. 2006; (xii). 173-181.
20. D.K.Sukla and S.D.Srivastava. Synthesis of some new 5-[{1,2,3-benzotriazole) -1-yl-methyl}-1'-(4'-substituted aryl-3'-choloro-2'-oxoazetidine)}amino-1,3,4-thiadiazoles: antifungal and antibacterial agents. Indian J Chem. 2008; 47B. 463-469.
21. K.C.Ravichandra, H.M. Vagdevi, .V.P.Vaidya. Synthesis, characterization and pharmacological studies on some triazolothiadiazines and triazolothiadiazoles containing naptho [2,b]furan. Indian J Chem. 2008; 47B. 1271-1276.
22. Mihaela Moise, Valesiu Sunel, Lenuta Profire, Mareel Popa Jacques Debrieses and Cristian Poptu. Synthesis and biological activity of some new 1,3,4-thiadiazole and 1,2,4-triazole compounds containing a phenylalanine moiety. Molecules. 2009; 14. 2621-2631.
23. Priyabrata Pattanayak, Rajesh Sharma. 2-amino-5-sulphanyl 1,3,4-thiadiazole derivatives as anticonvulsant agents: Synthesis and Evaluation. Indian J Chem. 2010; 49B. 1531-1534.
24. Jonna Matysiak, Anna Nasulewicz, Marzena Pelczynska, Marta Switalska, Iwona Jaroszewicz, Adam Opolski. Synthesis and antiproliferative activity of some 5-substituted 2-(2,4-dihydroxyphenyl) 1,3,4-thiadiazoles. European Journal of Medicinal Chemistry. 2006; 41. 475-482.
25. Shipra Baluja, Ashish Patel and Sumitra Chanda. Schiff's bases- Synthesis, characterization, antibacterial activity. RJPBS. 2011; 2(4). 296-304.
26. S. Ramachandran. Synthesis and antimicrobial evaluation of some novel Schiff's and Mannich bases of isatin derivatives. IJRPC. 2011; 1(3). 289-294.
27. V.Shankaranath, K. K. Raja Sekar, Y. Rajendra Prasad, M.Nirosha, K.Narender Reddy and J.Jayaprakash. Synthesis and biological evaluation of novel Schiff's bases. Journal of Pharmacy Research. 2011; 4(4). 1277-1278.
28. P. Mondal, M. Banerjee, S. Jana, A. Bose J. Synthesis and evaluation of 1,3-disubstituted Schiff's, Mannich bases and spiro-isatin derivatives. Young Pharmacists. 2010; 2(2). 169-172.
29. Chinnasamy Rajaram Prakash, Sundararajan Raja, Govindaraj Saravanan. Synthesis, characterization and anticonvulsant activity of novel Schiff's bases of isatin derivatives. International

Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(4). 177 - 181.
30. Prince P Sharma, S N Pandeya, R. K. Roy, Anurag, Krishan Verma, S Gupta. Synthesis and anticonvulsant activity of some novel isatin Schiff's bases. International Journal of ChemTech Research. 2009; 1(3). 758-763.
31. Jain, Jainendra. S, Srivastava, Radheshyam S, Aggarwal, Navneet, Sinha, Reema. Synthesis and evaluation of Schiff's bases for anticonvulsant and behavioral, depressant properties. Central nervous system agents in medicinal chemistry. 2007; 7(3). 200-204.
32. Hemant Panwar, R.S.Verma, V.K.Srivastava and Ashok Kumar. Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. Indian J. Chem. 2006; 45B. 2099-2104.
33. Esra Tatar, Ilkay Kucukguzel, Erik De Clercq, Fikrettin Sahin and Medine Gulluce. Synthesis, characterization and screening of antimicrobial, antituberculosis, antiviral and anticancer activity of novel 1,3-thiazolidine-4-ones derived from 1-[2-(benzoylamino)-4-(methylthio)butyryl]-4-alkyl/arylalkyl thiosemicarbazides. ARKIVOC. 2008; (xiv). 191-210.
34. Tumul Srivastava, Anil K Gaikwad, Wahajul Haq, Sudhir Sinha and Setu.B. Katti. Synthesis and biological evaluation of 4-thiazolidinone derivatives as potential antimycobacterial agents. ARKIVOC. 2005; (ii). 120-130.
35. Mahendra R.Shiradkar, Mangesh Ghodake, Kailash G.Bothara, Shashikanth V.Bhandari, Ana Nikalje, Kalyan Chakravarthy Akula, Nisheeth C.Desai and Prashanth J.Burange. Synthesis and anticonvulsant activity of clubbed thiazolidinone-barbituric acid and thiazolidinone –triazole derivatives. ARKIVOC. 2007; (xiv). 58-74.
36. Rama Ganesh C.K, Yadav D Bodke and Venkatesh K.B. Synthesis and biological evaluation of some innovative coumarin derivatives containing thiazolidin-4-one ring. Indian J. Chem. 2010; 49B. 1151-1154.
37. Sunil Kumar, Hemalatha Kaur, K.K.Saxena, Navica Sharma, Pinkivishwakarma and Ashok Kumar. Synthesis and antiparkinsonian activity of some new adamantyl thiazolidinonyl/azetidinonyl indole derivatives. Indian J Chem. 2010; 49B. 1398-1405.
38. S. R. Pattan, Ch. Suresh, V. D. Pujar, V. V. K. Reddy, V. P. Rasai and B. C. Koti, Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-choloro-6-fluorobenzothiazole. Indian J Chem. 2005; 44B. 2404-2408.
39. V. H. Bhaskar, K. Sharath and M. Kumar. Synthesis and anti-inflammatory activity of some 2-substituted phenyl)-3-4,5-diphenyl-1*H*-imidazol-2-yl)-1,3-thiazolidin-4-one derivatives. Asian Journal of Chemistry. 2008; 20(7). 5133-5138.
40. Jan Balzarini, Barbara Orzerzko, Jan K. Maurin, Andrezej Orzesko. Synthesis and anti- HIV studies of 2-adamantyl-substituted thiazolidin-4-ones. Eur. J. Med. Chem. 2007; 42. 993-1003.
41. Guniz Kucukguzel, Ayla Kocatepe, Erik De Clercq, Filcrettin Sahin, Medine Gulluce. Synthesis and biological activity of 4-thiazolidinones, thiosemicarbazides derived from diflunisal hydrazide. Eur.J.Med.Chem. 2006; 41. 353-359.