IJPSR (2014), Vol. 5, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 February, 2014; received in revised form, 26 April, 2014; accepted, 15 June, 2014; published 01 August, 2014

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NEW 1, 6- DIPHENYL-10, 10a-DIHYDROPYRIDO[2, 3-*d*]-1, 2, 4-TRIAZOLO [4, 3-*a*]PYRIMIDIN-5(1*H*)-ONE DERIVATIVES

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Keywords:

Dimethyformamidedimethylacetal (DMFDMA), Enaminones, Pyridotriazolopyrimidin-5(1*H*)-one, Maximal Electroshock (MES), Subcutaneous pentylenetetrazole (scPTZ), Anticonvulsant activity

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ABSTRACT: In this research, a new series of total twenty derivatives (39-58) of titled compound were synthesized with the help of substituted acetophenone which undergoes Aldol condensation reaction with dimethyformamidedimethylacetal (DMFDMA) to form corresponding unsaturated carbonyl compounds such as enaminones. The compound 2-thioxo-1,3-dihydropyridino[2,3-d] pyrimidin-4(1*H*)-one were obtained by reacting enaminones with 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one in the presence of dioxane. In this reaction, 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one acts as a nucleophilic reagent. Thus, the titled compounds were obtained by cyclizing an intermediate followed by desulphuration with the liberation of hydrogen sulphide gas in the presence of acetic acid. The homogeneity and purity of synthesized compound was ascertained by physical constant determination and chromatographic methods. The structure of the synthesized derivative was further confirmed by spectral (FTIR, NMR, MS) and elemental (C, H, N) analysis. The anticonvulsant activity of the compounds (39-58) was evaluated against Maximal Electroshock (MES)-induced seizures. The compounds, those found effective, were as well tested against subcutaneous pentylenetetrazole (scPTZ)-induced seizures model in mice. Using the rotorod procedure, the neurotoxicity was assessed. The results of anticonvulsant activity (*in vivo*) indicated that the compounds (46) and (57) possessed significant activity when compared with Phenytoin as a standard.

INTRODUCTION: Pyrimidine is a heterocyclic compound in which the two nitrogen atoms are the heteroatom. A simple pyrimidine has been derived from benzene by the replacement of two of the ring carbon atoms by nitrogen.

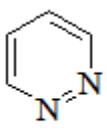
QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(8).3409-17

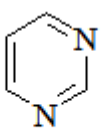
Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(8).3409-17

Pyrimidine (II), an isomeric diazine is single ring compound, with nitrogen in position one and three of a six membered benzene ring. Pyrimidine has been found to be associated with diverse biological activities and pyrimidine derivatives also play a key role in numerous biological processes [1-8].



(I)



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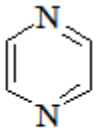
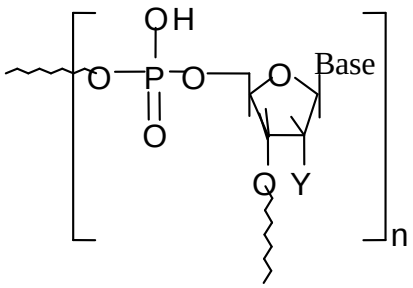


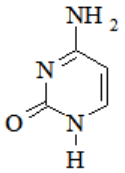
(III)

Pyrimidine and purine bases are present in all nucleic acids Y = H, OH). Nucleic acids are present in all living organisms, whether plants, animals or viruses, nucleic acids are the long chain hetero polymers made up of complex monomeric units called nucleotides. Each nucleotide is made up of one molecule of phosphoric acid, one molecule of pentose sugar and either a purine or a pyrimidine base (cytosine, uracil or thymine). There are two types of nucleic acids (IV), ribonucleic acid (RNA; Y = OH) and deoxyribonucleic acids (DNA; Y = H).

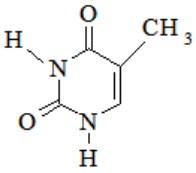


(IV)

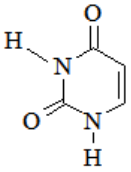
The most common pyrimidines of DNA are cytosine (V), thymine (VI) and that of RNA are cytosine, uracil (VII).



(V)



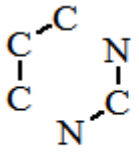
(VI)



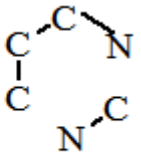
(VII)

The pyramidal nature of a few well-defined amino groups indicates that a strong correlation exists between the non-planarity of the amide and peptide torsion angles. The pyramidal nature of the amino groups might arise due to effect of lone pair of electrons at the central nitrogen atom. Amino groups are one of the various types of hydrogen bond donors, abundantly found in protein main-chain, side-chains and DNA bases. The design of pyrimidine antimetabolites has involved changes in substituent on the ring, isosteric replacement of ring atoms, changes in ring size, attached sugars and phosphate residues.

The most widely employed route to synthesize pyrimidine involves the combination of a reagent containing the N-C-N skeleton with C-C-C unit. These syntheses are typical examples of the bis-nucleophile plus bis-electrophile method of constructing heterocycles. Both the nitrogen atom of the N-C-N reagent act as nucleophiles and both the terminal carbon atoms of C-C-C reagents are electrophiles. Urea, thiourea and guanidine are commonly used as N-C-N reagents and β-dialdehyde, β-ketoaldehyde and β- ketoester are typical C-C-C reagents (XIII-XI).



(VIII)



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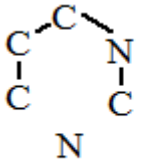
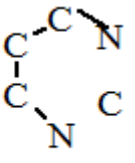


(X)



(XI)

Out of above four routes, the condensation of the three-carbon unit to a species having N-C-N linkage is most widely used. The three-carbon unit may be

a) β- dialdehyde

b) β- ketoaldehyde

c) β- ketoester

d) β- ketonitrile or other combinations of these functional groups. The nitrogen containing unit may be urea, thiourea, amidine or guanidine.

OBJECTIVE AND MECHANISM [9-16]: The compound 2-thioxo-1,3-dihydropyridin[2,3-d] pyrimidin-4 (1*H*)-one were obtained by reacting enaminones with 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one in glacial acetic acid. Following the above mentioned procedure, hydrazoloyl halides were reacted with triethylamine in the presence of chloroform to obtained tilted compound (39-58). The interesting CNS properties of several compounds with three angular fused heterocyclic systems are well known.

Antipsychotic activity of pyrazolopyrido-6(7*H*)-pyrimidinones and antidepressant effect of trizoloquinoxalines have been encouraged to synthesize pyrazolopyridopyrimidinone derivatives and further, shall be investigated for anticonvulsant activity.

Substituted acetophenone (XXXI) undergoes Aldol condensation reaction with dimethyformamidedimethylacetal (XXXII) to form corresponding enaminones, 3-(dimethylamino)-1-phenylprop-2-en-1-ones (XXXIII). The compound 2-thioxo-1,3-dihydropyridino[2,3-d] pyrimidin-4(1*H*)-one (XXXV) were obtained by reacting enaminones (XXXIII) with 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one (XXXIV) in glacial acetic acid. In this reaction, 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one (XXXIV) acts as a nucleophilic reagent. The titled compounds (XXXVI) were obtained by cyclizing an intermediate followed by desulphuration with the liberation of hydrogen sulphide gas in the presence of acetic acid (**FIG.1**).

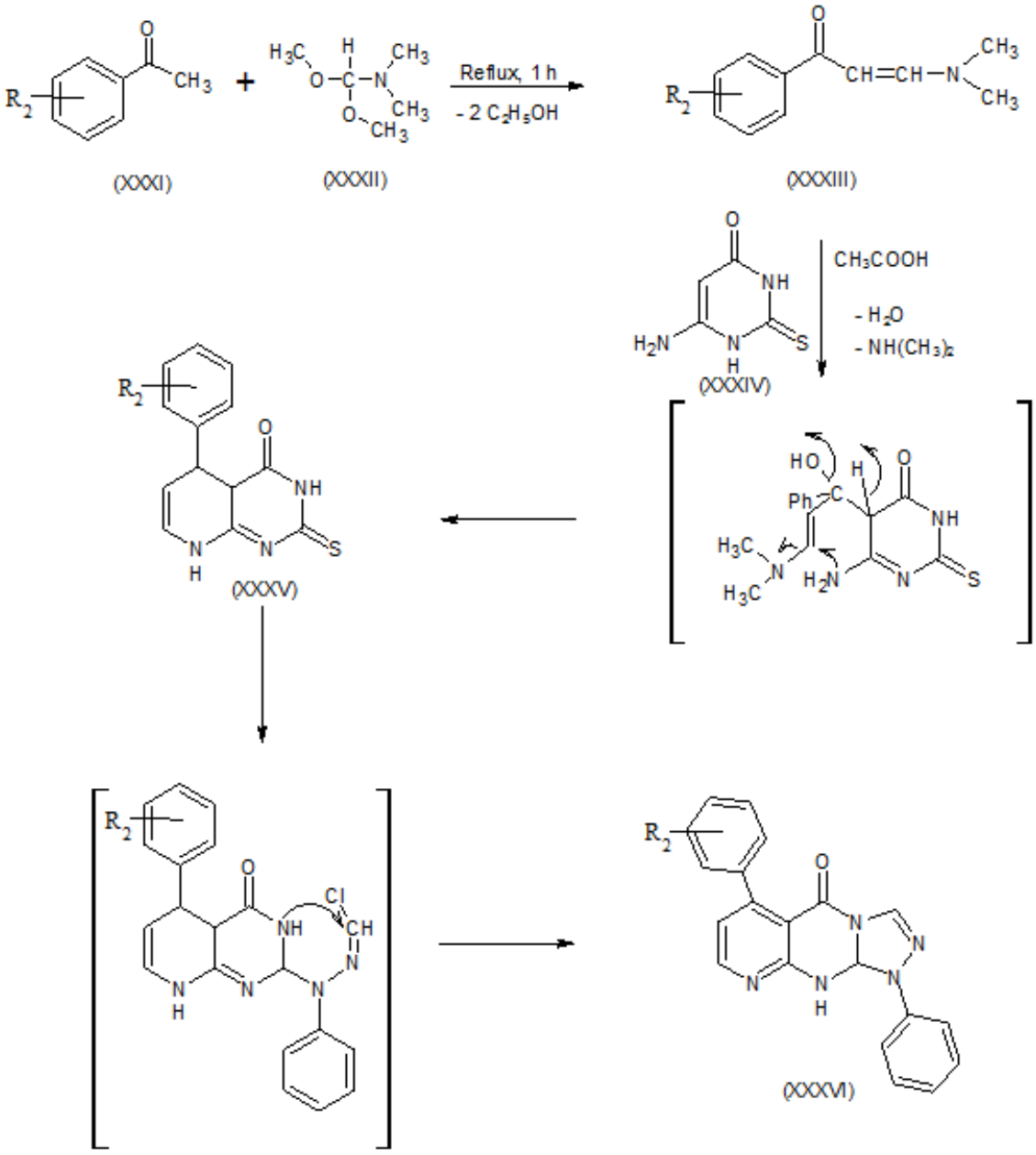
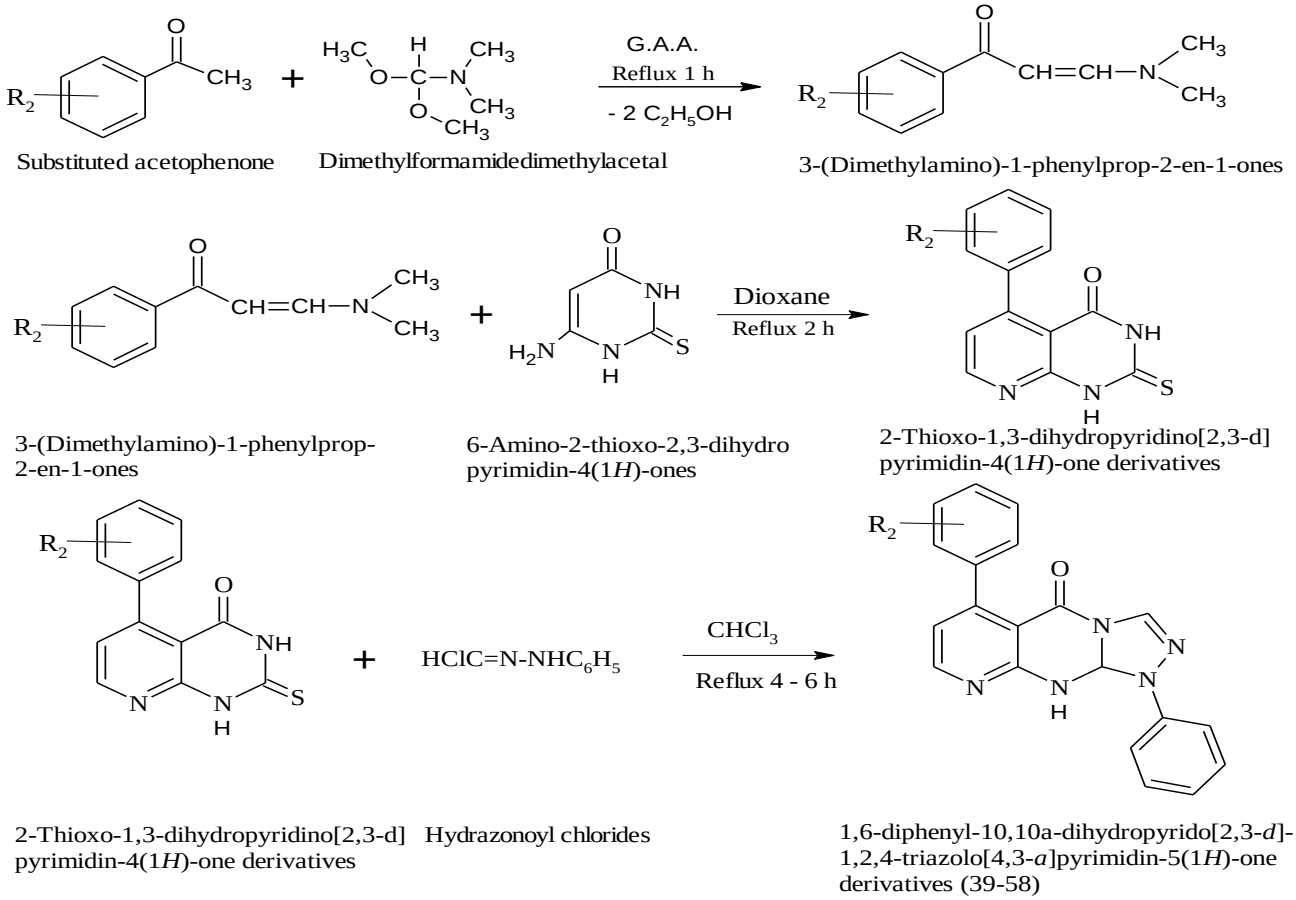


FIG. 1: REACTION MECHANISM OF 1,6-DIPHENYL-10,10a-DIHYDRO PYRIDO[2,3-d]-31,2,4TRIAZOLO[4,3-*a*] PYRIMIDIN-5(1*H*)-ONE DERIVATIVES

MATERIALS AND METHODS: The chemicals, solvents, drugs employed for synthetic work were of BDH/Hi-Media/E-Merck/Laboratory grade. The solvents were further purified by established methods [3]. The starting material used in the synthesis was obtained from SD Fine. All the residues have been dried in vacuum desiccator and crystallized. The percentage yields are based upon the products obtained after purification through crystallization. The solvent used for crystallization has been mentioned within brackets after melting point. The melting points of the compounds were determined in open capillaries using Thermonik Precision Melting point apparatus (C-PMB-2, Mumbai) method and reported here-in are in the Celsius scale and are uncorrected. All the reactions were monitored by TLC performed on aluminium plates precoated with silica gel 60(HF-254, E. Merck, India). The precoated plates were developed with iodine vapors after TLC. Solvent system (Chloroform: ethanol 3:1) was employed for thin layer chromatography and their R_f values has been reported in the preceding text.

The ultraviolet absorptions spectra were measured on Shimadzu 1601 spectrophotometer (methanol HPLC Grade). IR spectra were recorded on FTIR 8400s spectrophotometer (Kyto, Japan) from Shimadzu using KBr optics (cm^{-1}) at Sharad Pawar College of Pharmacy, Nagpur. ^{1}H-NMR spectra were recorded on Varian EM 390 spectro-photometer (chemical shift in δ ppm), at Department of Chemistry, Pune University, Pune, using tetramethylsilane (TMS) as internal standard. The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS in $CDCl_3$ solution. Signal multiplicities are presented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), bs (broad singlet) and m (multiplet). Mass spectra (EIMS) were recorded at 70 eV on JEOL D-300 spectrophotometer (Jeol Ltd., Tokyo, Japan). Elemental analysis were carried out using FLASH EA 1112 CHN analyzer (Thermo Finnigan, Italy) and found within limit of ± 0.4% of the theoretical values were taken into consideration.

SCHEME:



SYNTHESIS OF 1, 6-DIPHENYL-10,10a-DIHYDRO PYRIDO [2,3-*d*]-1,2,4-TRIAZOLO [4,3-*a*]PYRIMIDIN-5(1*H*)-ONE DERIVATIVES (39-58)

Synthesis of 1,6-diphenyl-10,10a-dihydropyrido [2,3-*d*]-31,2,4triazolo[4,3-*a*]pyrimidin-5(1*H*)-one derivatives (39-58):

1. **Synthesis of 3-(dimethylamino)-1-phenylprop-2-en-1-ones:** The reaction of dimethylformamide dimethylacetal (DMFDMA) (0.01 mol) with substituted acetophenones (0.01 mol) were carried out under reflux for 1 h in the presence of dioxane afforded the 3-(dimethylamino)-1-phenylprop-2-en-1-ones.

2. **Synthesis of 2-thioxo-1, 3-dihydropyridino[2, 3-d] pyrimidin-4(1*H*)-one derivatives:** 3-(Dimethylamino)-1-phenylprop-2-en-1-ones (0.01 mol) was refluxed for 2 h with 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1*H*)-one (0.01 mol) in dioxane (20 mL) to give 2-thioxo-1, 3-dihydropyridino[2, 3-d] pyrimidin-4(1*H*)-one derivatives.

3. **Synthesis of 1,6-diphenyl-10,10a-dihydropyrido [2,3-*d*]-1,2,4-triazolo [4,3-*a*] pyrimidin-5(1*H*)-one derivatives:** 2-Thioxo-1,3-dihydropyridino [2,3-d]pyrimidin-4(1*H*)-ones, hydrazonoyl chlorides (1.25 g, 0.005 mol) and triethylamine (0.7 mL, 0.005 mol) in the presence of chloroform (40 mL) was added. The reaction mixture was refluxed until the hydrazonoyl chlorides disappeared (4-6 h) as indicated by TLC analysis. The solvent was evaporated under reduced pressure and the residue was treated with methanol (10 mL) afforded the 1,6-diphenyl-10,10a-dihydropyrido[2,3-*d*]-1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one derivatives.

   Similarly, adopting the above procedures twenty derivatives of titled compounds were prepared by using different acetophenones (as per derivative table on p. 45) and characterized accordingly. The characterization data of synthesized compounds are as follows;

A. **1,6-Diphenyl-10,10a-dihydropyrido[2,3-*d*]-1,2,4-triazolo[4,3-*a*] pyrimidin 5(1*H*)-one (39):** Yield: 2.65 g (65 %); mp: 281-82^0(DMSO), Found: $C_{20}H_{15}N_5O$; C(69.96 %) H(4.99 %) N(20.40 %)O(4.66 %), Anal.: C(69.86 %) H(4.88 %) N(20.30 %)O(4.55 %).

B. **6-(2-Methylphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (40):** Yield: 2.55 g (55%); mp: 283-85^0(DMSO), Found: $C_{21}H_{17}N_5O$; C(70.57 %) H(5.36 %) N(19.59 %) O(4.48 %), Anal. : C(70.44 %) H(5.24 %) N(19.48 %) O(4.38 %)

C. **6-(2,6-Dimethylphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (41):** Yield: 2.35 g (45 %); mp: 280-81^0(DMSO), Found : $C_{22}H_{20}N_5O$; C(71.14 %) H(5.70 %) N(18.85 %),O(4.31 %), Anal. : C(71.02 %) H(5.64 %) N(18.75 %),O(4.21 %)

D. **6-(2-Chlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (42):** Yield: 2.66 g (77 %); mp: 289-92^0(DMSO), Found : $C_{22}H_{14}ClN_5O$; C(75.10 %) H(4.08 %), CI(9.38 %) N(16.75 %), O(4.23 %), Anal.: C(75.03 %) H(4.02 %) CI(9.35 %) N(16.65 %)

E. **6-(4-Chlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (43):** Yield: 2.60 g (70 %); mp: 285-87^0(DMSO), Found: $C_{22}H_{14}CIN_5O$; C(63.58 %) H(4.27 %) CI(9.38 %) N(18.54 %) O(4.23 %), Anal.: C(63.46 %) H(4.14%) CI(9.28 %) N(18.45 %) O(4.12 %)

F. **6-(2,4-Dichlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (44):** Yield: 2.20 g (58 %); mp: 278-80^0(DMSO), Found: $C_{20}H_{13}CI_2N_5O$; C(58.27 %) H(3.67 %) CI(17.20 %) N(16.99 %) O(3.88 %), Anal.: C(58.17 %) H(3.54 %) CI(17.10 %) N(16.85 %) O(3.77 %)

G. **6-(4-Methoxyphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (45)**: Yield: 2.62 g

(68 %); mp: 280-81^0(DMSO), Found: $C_{21}H_{17}N_5O_2$; C(67.55 %) H(5.13 %) N(18.16 %) O(8.57 %), Anal.: C(67.45 %) H(5.10 %) N(18.06 %) O(8.47 %)

H. **6-(3-Hydroxyphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (46)**: Yield: 2.85 g (82 %); mp: 285-87^0(DMSO); IR: 3382-3270 (C-N stretching of primary amine), 1125-1074 (C-N stretching of secondary amine), 3361-3240 (Ar-N-H stretching), 1650 (C=O stretching), 3107-3082 (secondary N-H stretching) cm^{-1}, 1270-1250 cm^{-1} (C-O stretching of phenolic group) ^{1}H-NMR: δ 8.9-9.6 (s, 1H, Ar-NH), 7.26-8.06 (m, 12H, Ar-H), 5.40-6.42 (s, 2H, Ar-NH_2) ppm; EIMS (m/z) :358.14 (M^+, 100). Found: $C_{20}H_{15}N_5O_2$; C(66.84 %) H(4.77 %) N(19.49 %) O(8.90 %), Anal.: C(66.77 %) H(4.65 %) N(19.38 %) O(8.80 %)

I. **6-(3-Nitrophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (47)**: Yield: 2.65 g (72 %); mp: 281-83^0(DMSO), Found: $C_{20}H_{14}N_6O_3$; C(61.85 %) H(4.15 %) N(21.69 %) O(12.36 %), Anal.: C(61.77 %) H(4.10 %) N(21.59 %) O(12.25%)

J. **6-(3-Aminophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (48)**: Yield: 2.68 g (74 %); mp: 278-80^0(DMSO), Found: $C_{20}H_{16}N_6O$; C(67.02 %) H(5.06 %) N(23.45 %) O(4.46 %), Anal.: C(66.99 %) H(5.01 %) N(23.35 %) O(4.36 %)

K. **6-(2-Bromophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (49)**: Yield : 2.25 g (63 %); mp: 278-80^0(DMSO), Found: $C_{20}H_{15}BrN_5O$; C(75.10 %) H(4.08 %) N(16.75 %) O(4.46 %), Anal.: C(75.01 %) H(4.02 %) N(16.65 %) O(4.50 %)

L. **6-(3-Methylphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (50)**: Yield : 2.85 g (85 %); mp: 288-89^0(DMSO), Found: $C_{21}H_{17}N_5O$; C(75.10 %) H(4.08 %) N(16.75 %) O(4.56 %), Anal.: C(75.02 %) H(4.01%) N(16.65 %) O(4.50 %)

M. **6-(2,4-Dimethylphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo [4,3-*a*]pyrimidin-5(1*H*)-one (51)**: Yield: 2.78 g (76 %); mp: 274-76^0(DMSO), Found: $C_{22}H_{20}N_5O$; C(75.10 %) H(4.08 %) N(16.75 %) O(4.46 %), Anal.: C(74.99 %) H(4.00 %) N(16.64 %) O(4.48 %)

N. **6-(3-Chlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (52)**: Yield: 2.45 g (65 %); mp: 284-86^0(DMSO), Found: $C_{22}H_{14}ClN_5O$; C(75.10 %) H(4.08 %) CI(9.38 %) N(16.75 %) O(3.13 %), Anal.: C(74.98 %) H(3.97 %) CI(9.38 %) N(16.66 %) O(3.13 %)

O. **6-(5-Chlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (53)**: Yield: 2.10 g (61 %); mp: 268-69^0(DMSO), Found: $C_{22}H_{14}ClN_5O$; C(75.10 %) H(4.08 %) N(16.75 %) CI(9.38 %) O(3.13 %), Anal. : C(74.98 %) H(4.00 %) N(16.68 %) CI(9.35 %) O(3.10 %)

P. **6-(2,6-Dichlorophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (54)**: Yield: 2.85 g (85 %); mp: 288-90^0(DMSO), Found: $C_{20}H_{13}N_5Cl_2O$; C(75.10 %) H(4.08 %) N(16.75 %) CI(17.38 %) O(3.24 %), Anal.: C(75.00 %) H(4.01 %) N(16.58 %) CI(17.40 %) O(3.26 %)

Q. **6-(2-Methoxyphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (55)**: Yield : 2.69 g (69 %); mp: 286-88^0(DMSO), Found: $C_{21}H_{17}N_5O_2$; C(75.10 %) H(4.08 %) N(16.75 %), O (4.52 %), Anal.: C(75.02 %) H(4.03 %) N(16.69 %) O (4.50 %)

R. **6-(2-Hydroxyphenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (56)**: Yield : 2.15 g (58 %); mp: 280-82^0(DMSO), Found:

$C_{20}H_{15}N_5O_2$; C(75.10 %) H(4.08 %) N(16.75 %) O(3.42 %), Anal. : C(75.01 %) H(4.04 %) N(16.59 %) O(3.40 %)

S. **6-(2-Nitrophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (57)**: Yield: 2.60 g (71 %); mp: 278-79^0(DMSO); IR: 3382-3270 (C-N stretching of primary amine), 1125-1074 (C-N stretching of secondary amine), 3361-3240 (Ar-N-H stretching), 1425-1410 (C-NO_2 stretching), 1650 (C=O stretching), 3107-3082 (secondary N-H stretching) cm^{-1}, ^{1}H-NMR: δ 8.9-9.5 (s, 1H, Ar-NH), 7.26-8.06 (m, 12H, Ar-H), 5.40-6.42 (s, 2H, Ar-NH_2) ppm; EIMS (m/z) :388.10 (M^+, 100). Found: $C_{20}H_{15}N_6O_3$; C (75.10 %) H (4.08 %) N (16.75 %) O(9.13 %), Anal. : C (74.95 %) H (3.96 %) N (16.58 %) O(9.10 %)

T. **6-(2-Aminophenyl)-1-phenyl-10,10a-dihydro-pyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (58)**: Yield: 2.55 g (66 %); mp: 275-76^0(DMSO), Found: $C_{20}H_{16}N_6O_3$; C(75.10 %) H(4.08 %) N(16.75 %) O(3.13 %), Anal.: C(74.97 %) H(3.99 %) N(16.60 %) O(3.15 %)

RESULT AND DISCUSSION [17-24]:

Pharmacological Studies:

Anticonvulsant activity [25, 26]: The compounds under **scheme** (39-58) were evaluated for their anticonvulsant activity against Maximum Electroshock (MES) induced seizures while the selected compounds were evaluated against subcutaneous pentylenetetrazole (scPTZ) induced seizure model in mice. The minimal motor impairment was measured by the rotarod (neurotoxicity) test.

All the test compounds were administered intraperitoneally (ip) at various dose levels ranging from 20-1000 µmol/kg body weight and the median effective dose (ED_{50}, dose of the compounds required to assure anticonvulsant protection in 50 % of animals from hind limp tonic extension), median toxic dose (TD_{50}) and protection index (PI) values were determined.

The anticonvulsant activity was carried out on albino mice (20-25g) of either sex or male albino rats (100-150 g) as experimental animals. The animals were divided into two groups (control and test) and each experimental group consisted of six animals (N=6). The animals were housed under standard conditions and allowed free access to standard pellet diet and water (ab libitum). Phenytoin was used as standard drug. The test compounds and standard drug were suspended in methyl cellulose in water (0.5%).

1. **Maximum Electroshock (MES) Test:** The test compounds (39-58) were administered intraperitoneally (ip) at a dose of 20-1000 µmol / kg body weight. Maximum electroshock seizure were elicited using electroconvulsometer with a 60 cycle altering current of 50 mA for 0.25 sec via ear clip electrode as per the procedure described by Swinyard et. At 171 effects was assessed at 0.5 h after administration by recording the tonic extension of the hind limbs at different doses. The reduction in time or absence of hind limb tonic extension of seizure is defined as protection.

   Median effective dose (ED_{50}) was calculated at the doses of test compounds until at least three points were established in the range of 10-90 % seizure protection or minimal observed neurotoxicity. The results are presented in Table 3 Subcutaneous pentylenetetrazole (scPTZ) seizure threshold test. Further, the most active compounds were evaluated against scPTZ model in mice pentylenetetrazole dissolved in saline solution was administered in the posterior midline of the mice and the onset and severity of convulsion was noted for the control group. The test group was administered with the selected compounds 30 min prior to the administration of PTZ and the anticonvulsant activity was detected in terms of ED_{50} {i.e. dose of the compounds required to assure anti-convulsant protection in 50 % of animals from hind limb tonic extension (tonic phase) and is presented in **Table 1**.

2. **Neurotoxicity screening:** The neurotoxicity of all the test compounds was evaluated using rotorod test. Mice were trained to balance on the rotating rod (3.2 cm diameter) that rotates at 6 rpm and was allowed three attempts to remain on the rotating rod for 20 sec. Trained animals were treated with test compounds at a dose of 20-1000 µmol/kg administered intraperitoneally. Neurotoxicity was determined by the inability of the animal to remain on the rod for 1 min. Each of the trained animals was tested in this manner at 30 min after the administration of drug. The results are represented as mean toxic dose TD_{50} [i.e. dose eliciting minimal neurological toxicity in 50 % of animals as assessed by the rotorod test (locomotor deficit)], which are further used in the calculation of PI (TD_{50} / ED_{50}) **Table 1**.

TABLE 1: ANTICONVULSANT ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

Compd. No.[a]	Intraperitoneal administration to mice			PI[d]
	MES[a]	scPTZ[b]	NT[c]	
39	106	111	265	1.49
40	667	ND	653	3.10
41	517	615	125	1.78
42	335	ND	140	1.24
43	295	660	156	1.12
44	181	ND	198	1.15
45	180	ND	134	1.40
46	**152**	**550**	**108**	**3.95**
47	271	ND	187	1.42
48	209	ND	168	1.24
49	271	ND	221	1.18
50	205	ND	203	1.19
51	225	ND	270	1.34
52	204	ND	276	2.82
53	322	715	213	1.28
54	259	ND	225	1.79
55	320	ND	270	1.46
56	244	ND	158	1.20
57	**585**	**425**	**633**	**4.05**
58	259	ND	787	1.03
Phenytoin	646	ND	732	4.28

[a]All compounds were administered by ip injection at doses of 20-1000 µmol/kg and values were determined at t=30 min. MES indicates maximum electroshock test and the data are represented in terms of ED_{50}. [b] Subcutaneous pentylenetetrazole test. [C] Neurotoxicity screening using rotorod test and values are expressed in terms of TD_{50}. [d] Protection index ($PI=TD_{50}/ED_{50}$). [e]ND: activity not determined . All the activity data reaches the statistical significance $p<0.05$ (One way ANOVA ; Dunnet's test).

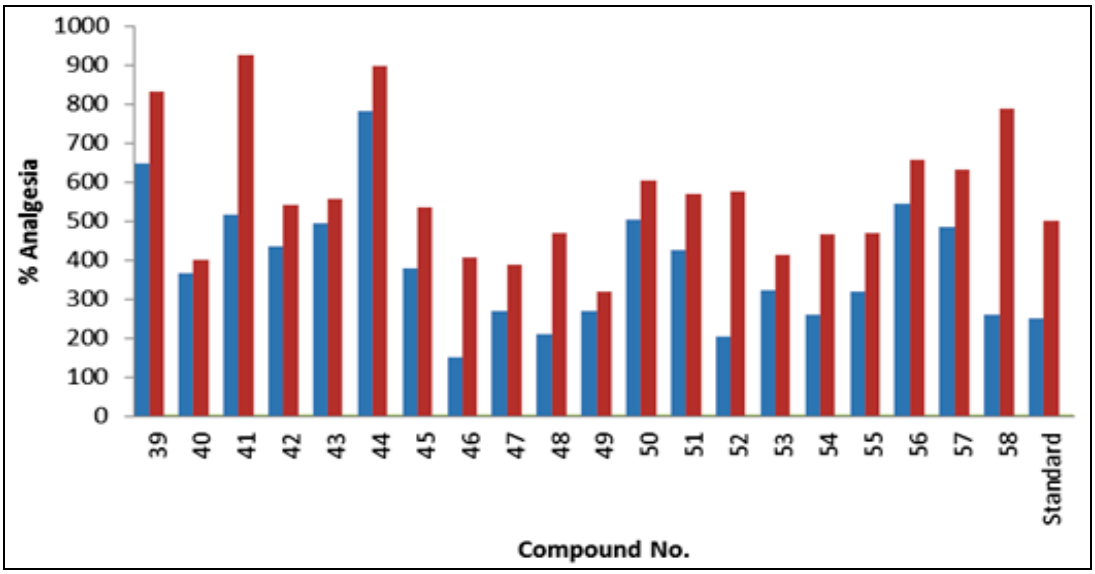


FIG. 3: ANTICONVULSANT ACTIVITY OF SYNTHESIZED COMPOUNDS (39-58)

CONCLUSION: The compounds (39-58) were obtained with a good yield **Scheme**. These compounds exhibited expected anticonvulsant activity comparable with Phenytoin. The results of anticonvulsant activity (*in vivo*) indicated that the compounds (**46**) and (**57**) possessed significant anticonvulsant activity. The presence of electron withdrawing groups on the aromatic ring, in general, decreases the potency of the compounds compared to compounds having electron-donating groups. This may be because of low lipophilicity which in turn may decrease the permeability across the biological membranes. Further, it has been found that the ED_{50} and TD_{50} values of test compounds increase significantly at t=4 h, compared to t=30 min, in contrast to the standard, indicating that the compounds were metabolized with time in the biological environment. This trend was found to be more pronounced in the compounds (42), (43), (44), (47), (48), (49), (52), (53), (54) and (57) (having electron withdrawing groups) as compared to compounds (40), (41), (50), (51) and (55) (having electron -donating groups).

ACKNOWLEDGEMENT: Authors are thankful to Principal, Sharad Pawar College of Pharmacy, Nagpur for providing necessary facilities for carrying out this research work successfully**.**

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How to cite this article:
Kawade DP and Khedekar PB: Synthesis and anticonvulsant activity of some new 1,6- diphenyl-10,10a-dihydropyrido[2,3-d]-1,2,4-triazolo[4,3-a]pyrimidin-5(1h)-one derivatives. Int J Pharm Sci Res 2014; 5(8): 3409-17.doi: 10.13040/IJPSR.0975-8232.5(8).3409-17