*Biological Forum – An International Journal* **15(2): 42-45(2023)**

**ISSN No. (Print): 0975-1130**
**ISSN No. (Online): 2249-3239**

# Synthesis and Anticonvulsant Activity of 3,5-Bis[(5'-Substituted Phenyl) 1,3,4-Oxadiazole] 1,4-Dihydropyridine

***Honde Bharat S.**, Kadm Sai V., Shelke Pratiksha S., Chimankar Ayushi D., Kale Rutuja B. and Kanhe Nandini K.***

*Department of Pharmaceutical Chemistry, S.V.N.H.T'S College of B. Pharmacy, Shrishivajinagar (Rahuri factory), Tal-Rahuri, District-Ahmednagar (Maharashtra), India.*

*(Corresponding author: Honde Bharat S.*)*

*(Received: 20 December 2022; Revised: 24 January 2023; Accepted: 28 January 2023; Published: 04 February 2023)*
*(Published by Research Trend)*

**ABSTRACT: The reveals that the 1.4-Dihydro Pyridine and 1',3',4'-oxadiazole are pharmacologically more active units. The reaction of substituted aromatic or benzene substituted aldehydes with ethyl acetoacetate ammonia formation of diethyl 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-dicarboxylate (I), which on reaction with hydrazine hydrate formation of 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-dicarbohydrazide (II), added with substituted benzoic acid in presence of phosphorous oxychloride final formation of 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-[bis-(5'-substituted 1',3',4'-oxadiazole)] 1,4-dihydropyridine (3a-3l). Purity was checked by TLC and chemical structure of synthesized derivatives were elucidated by their IR, Proton NMR, MS analysis data. According to dose 30 mg/ml concentration as compared to Phenytoin 5mg/ml standard drug. The synthesized derivatives were screened for anticonvulsant activity.**

**Keywords:** 1,4-dihydropyridine, Oxadiazole, IR, NMR, MS, Anticonvlsant.

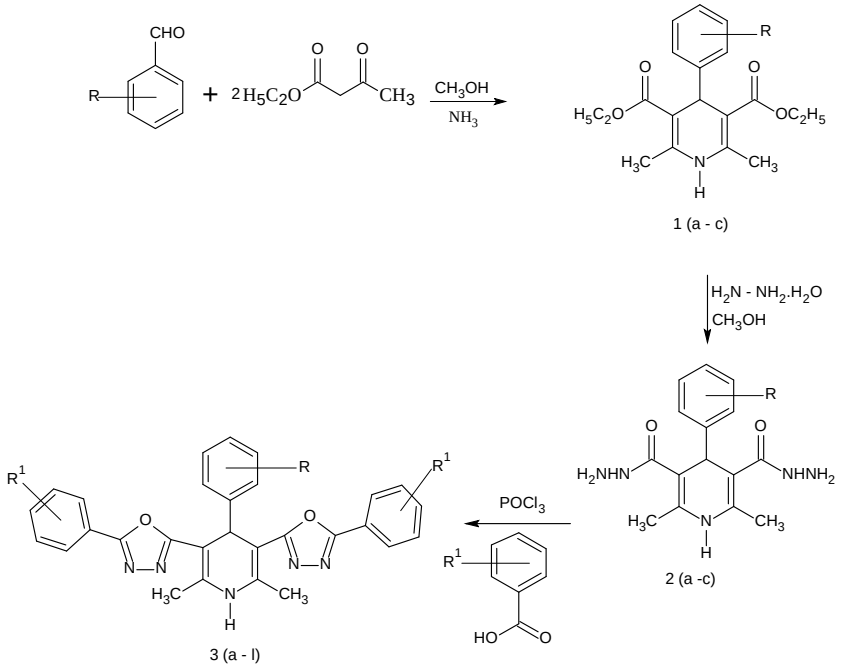
## INTRODUCTION

The compounds of 1,4-Dihydropyridine have been various pharmacological activities like analgesic (Borgarelli *et al.*, 2022), antimicrobial (Shahverdi and Shahverdi 2007), antitumour (Zidermane *et al*., 1978; Vanicha and Kanyawim 2006), antiplatelet (Cooper *et al.*, 1992), antidepressant (Shidhu and Mamatha 2013), and anti-inflammatory activities (Pattan *et al*., 2014), Moreover 1,3,4-oxadiazole compounds are also mention d in literature to have been powerful analgesic (Asif *et al.*, 2011), antimicrobial (Muhammad and Sumaira 2012), pharmacological significance (Rajeev and Prabodh 2011), pyridines with Affinity for β-Amyloid Plaques (Veroniki and Georgia 2022), C-2 fuctionalized imadazo (1,2-a) pyridine (Mousmee and Parteek 2022). On consideration the above observation, it was worthwhile to derivatives some new gives 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-[bis-(5'-substituted 1',3',4'-oxadiazole)] 1,4-dihydropyridine (3a-3l) and to activity them for anticonvulsant activity.

## MATERIALS AND METHODS

The melting point of all derivatives were determine by open capillary tubes using liquid paraffin bath and are uncorrected. The derivatives was check by using TLC on silica gel G, plates using methyl acetate: acetone (1:1) as development chamber detected by iodine vapours. The IR spectra were recorded on Jasco-ftir 4100 spectrometer, using KBR powder techniques. Proton NMR Spectra were recorded on Varian –NMR-Hg-300 MHz Spectrophotometer in $CDCl_3$ using TMS as an internal standard.

**Scheme of synthesis.**




## EXPERIMENTAL

**1. 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-dicarboxylate (I).** The mixture of substituted aromatic aldehyde (0.01mole), ethyl acetoacetae (20ml) and ammonia (6 ml) in methanol (100ml) was refluxed in R.B.F. for 3-4hrs. reaction was monitor by TLC. After completion of reaction 50 ml warm water is added and solution was allowed to cool. The precipitated solid was filtered washed with methanol and recrytallised from methanol (Yung-Yuan and Shiuh-Tzung 2022).

**IR (KBr)**: 3336(NH), 3054 (CH), 1684 (C=O), 3231 (C=C) and 2975cm$^{-1}$ ($CH_3$).

**2. 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-dicarbohydrazide (II).** A mixture of 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-dicarboxylate (I) and hydrazine hydrate 1:2 portion was mixed in methanol (30ml) and refluxed for 4-8hrs. The excess methanol was remove by distillation, the mixture was filtered and recrystillized from methanol and dried it (Orhan and Hanif 2015).

IR (KBr): 3343 (NH), 3234 (C=C), 1687 (C=O), 3055 ($CH_3$), 1369(CN).

**3. 2,6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-[bis-(5'-substituted 1',3',4'-oxadiazole)] 1,4-dihydropyridine (3a-3l).** A mixture of 2, 6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5 dicarbohydrazide (II), and substituted benzoic acid (0.02 mole) in phosphorous oxychloride (5ml) was refluxed on water bath, the rection was monitored by using TLC, after complation of reaction the mixture was slowely poured onto crushed ice and kept for overnight. Seprated solids were filtered,washed with cold water ahd was neutrilized by sodium bicarbonate solution,dreied and recrtillzed from methanol.

**IR (KBr)**: 3303 (NH), 3060 (C=C), 1687 (C=N), 1173cm$^{-1}$ (C-O-C), and 740 cm$^{-1}$ (C-Cl).

**$^1$H NMR**: δ 8.011- 8.036 (m, 8H, 2-Cl Phenyl); 7.25-7.514 (m, 5H Phenyl); 3.51 (S, 1H, pyridine) and 3.01(d, 6H, $CH_3$);

**MS**: 542(100 %, base peak); 542(36.85%); 420(78.07%); 200(40.7%); 120(78.0%); 90(98.4%); 85(98.14%);

**3**IR (KBr): 3402 (N-H), 3355 (unsaturated aromatic C=C), 1249 (C-O-C)

**IR (KBr):** 3388 (N-H), 3067cm$^{-1}$ (C=C), 1611 (N=C stretching), 1592 (C=N), and 1101 (C-O-C)

**IR (KBr):** 3054 (C=C), 1197(C=N), 1265 (C-O-C), 1402 ($N0_2$).

**IR (KBr):** 3381(N-H), 3060 (C=C), 1681 (C=N), 1297 (C-O-C), 859 (C-Cl)

**IR (KBr):** 3343 (N-H), 3205 (C=C), 1081 (C-O-C), 1599 (C-N), 773 (C-Cl).

**IR (KBr):** 3343cm$^{-1}$ (N-H), 2989 (C=C), 1545 (C-O-C), 695(C-Cl).

**IR (KBr):** 3120 (N-H), 2982 (C=C), 1691 (C=N), 1540 ($NO_2$), 714 (C-Cl) and 1114cm$^{-1}$ (C-O-C).

**IR (KBr):** 3093 (C=C), 1049 (C-O-C), 1481 ($NO_2$), 740 (C-Cl), 1684 (C=N).

**IR (KBr):** 3067(C=C), 1232 (C-O-C), 1525 ($NO_2$), 1691 (C=N).

**IR (KBr):** 3336 (N-H), 2982 (C=C), 1101 (C-O-C), 1534.1 ($NO_2$), 1644 (C=N).

**IR (KBr):** 3115 (N-H), 2989 (C=C), 1109 (C-O-C), 1535 ($NO_2$), 1700 (C=N).

**Anticonvulsant activity.** The proposal has been considered and approved by the IAEC for conducting the research work (CPCSEA Approval no.1211/PO/ac/08/CPCSEA). The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) and was conducted according to the guidelines for use and care of

experimental animals. Adults, healthy, overnight fasted, male albino mice, weight between 22-28gms were used. They were housed under standard environmental condition of temperature (24±2°C), humidity of 30-70% and 12hrs. light/dark cycle as per CPCSEA guideline. All animal had free to access to water and standard pelletized laboratory animal diet *ad libitum.*

The animals were divided into 14 groups with each group consisting of six animals. After 30 min. of administration, animals were stimulated through corneal electrodes with 50MA current at a pulse of 60Hz alternating current for 0.2 second. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsants activity. The above procedure was repeated after 30, 60, 90 and 120 min of administration (Ambavade *et al.*, 2006).

## RESULTS AND DISCUSSION

Periodic and unpredictable occurrence of seizures. Seizures refer to transient alteration of behavior due to the disordered, synchronous and rhythmic firing of populations of brain neurons. Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic in that available drugs inhibit seizures, but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem, because of the need for long-term therapy together with unwanted effects of many drugs. Anticonvulsant is an agent that blocks experimentally produced seizures in laboratory animals and an antiepileptic drug is a drug used medically to control the epilepsies.

**Table 1: Physical data of synthesized derivatives.**

| Derivatives Code | R | $R^1$ | Molecular formula | Molecular weight | Melting point | Yield (%) |
|---|---|---|---|---|---|---|
| 3a | H | 2-Cl | $C_{29}H_{21}N_5O_2Cl_2$ | 542 | 124-126 | 69.44 |
| 3b | H | H | $C_{29}H_{23}N_5O_2$ | 473 | 110-112 | 76.43 |
| 3c | H | 4-$NH_2$ | $C_{29}H_{25}N_7O_2$ | 503 | 218-220 | 86.82 |
| 3d | H | 4-$NO_2$ | $C_{29}H_{21}N_7O_6$ | 563 | 224-226 | 70.58 |
| 3e | 4-Cl | 2-Cl | $C_{29}H_{20}N_5O_2Cl_3$ | 576.5 | 184-186 | 89.71 |
| 3f | 4-Cl | H | $C_{29}H_{22}N_5O_2Cl$ | 507.5 | 300-302 | 95.23 |
| 3g | 4-Cl | 4-$NH_2$ | $C_{29}H_{20}N_7O_2Cl$ | 537.5 | 210-212 | 95.0 |
| 3h | 4-Cl | 4-$NO_2$ | $C_{29}H_{20}N_7O_6Cl$ | 597.5 | 230-232 | 58.55 |
| 3i | 3-$NO_2$ | 2-Cl | $C_{29}H_{20}N_6O_4Cl_2$ | 587 | 186-188 | 72.18 |
| 3j | 3-$NO_2$ | H | $C_{29}H_{22}N_6O_4$ | 518 | 176-178 | 80.53 |
| 3k | 3-$NO_2$ | 4-$NH_2$ | $C_{29}H_{24}N_8O_4$ | 548 | 280-282 | 69.62 |
| 3l | 3-$NO_2$ | 4-$NO_2$ | $C_{29}H_{20}N_8O_8$ | 608 | 238-240 | 85.71 |

**Table 2: Duration of hind limb extensor of synthesized derivatives.**

| Group | Treatment | Dose (mg/kg) | Duration of hind limb extensor in seconds (mean±S.E.M) | | | |
|---|---|---|---|---|---|---|
| | | | 30 minutes | 60 minutes | 90 minutes | 120 minutes |
| I | Control | 0.1ml/10 gm | 71±0.577 | 74±2.082 | 71±1.155 | 72.33±1.202 |
| II | Standard (Phenytoin) | 5 mg | 25±2.646** | 19.66±0.882** | 11.66±1.202** | 8.66±1.202** |
| III | 3a | 30 mg | 43.98±0.577** | 25.67±1.856** | 40.66±1.453** | 41.33±1.764** |
| IV | 3b | 30 mg | 40.1±0.577** | 26±1.155** | 29.66±1.202** | 37.66±1.202** |
| V | 3c | 30 mg | 46.66±0.882** | 29±0.577** | 31.66±1.202** | 39.33±1.202** |
| VI | 3d | 30 mg | 46±0.577** | 28±0.577** | 32.33±1.202** | 40±1.732** |
| VII | 3e | 30 mg | 49±1.155** | 29.66±1.453** | 31±0.577** | 34±0.577** |
| VIII | 4f | 30 mg | 63.66±1.856ns | 25.66±0.882** | 26±2.082** | 30±1.155** |
| X | 4g | 30 mg | 42.33±1.202** | 28±1.000** | 33.66±1.202** | 30±1.732** |
| XI | 4h | 30 mg | 45.33±2.186** | 27.66±0.882** | 29.66±1.453** | 39.66±1.202** |
| XII | 4i | 30 mg | 40±1.155** | 29.33±0.882** | 35.66±0.882** | 53.33±2.404** |
| XIII | 4j | 30 mg | 60±1.528ns | 31±1.528** | 28.33±1.856** | 36.33±1.453** |
| X | 4k | 30 mg | 41.33±1.202** | 29±1.000** | 34.66±1.202** | 31±1.732** |
| XIII | 4l | 30 mg | 61±1.528ns | 32±1.528** | 29.33±1.856** | 37;.33±1.453** |
| | | | | | | |

**Statistical analysis.** Data obtained from pharmacological experiments are expressed as means ± S.E.M. At the end of experiments test groups were compared with control and were tested for its significance using ANOVA followed by Dunnetts test. Valves of $P<0.05$ or lower were regarded as significant. The results of anticonvulsant activity of all the synthesized derivatives is presented above.

## CONCLUSIONS

After 30 mins derivatives 3b, 3i, 3k showed better activity. After 60 mins. Derivatives 3a, 3b, 3f showed better activity. After 90 mins. Derivatives 3f, 3j, 3k showed better activity. After 120 mins. Derivatives 3f, 3g, 3k showed better activity. We're as the remaining derivatives exhibited moderate activity. From the anticonvulsant data of the synthesized derivatives, we can conclude that the derivatives 3a, 3f and 3k have exhibited excellent anticonvulsant activity in MES model and hold promise as anticonvulsant agents after further development.

## FUTURE SCOPE

- The result of the research work proves that 2,6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-[bis-(5'-substituted 1',3',4'-oxadiazole)] 1,4-dihydropyridine derivatives can lead to a potential drug candidate in coming future. Research can be further done with a hope to develop the lead molecule to get a better drug candidate with better activity and lesser side effects.
- Furthermore in the future, more number of possible derivatives of 2,6-dimethyl-4-(substituted Phenyl)1,4-dihydropyridine 3,5-[bis-(5'-substituted 1',3',4'-oxadiazole)] 1,4-dihydropyridine derivatives can be synthesized and evaluated for their possible pharmacological activities.

**Acknowledgement.** The thankful department of chemistry, SPPU Pune university, Pune for spectral data, President, Principal, SVNHTS College of Pharmacy Rahuri factory Rahuri, Ahmednagar for providing laboratory and animal activity facilities.
**Conflict of Interest.** None.

## REFERENCES

Ambavade, S. D. and Mhetre, V. D. (2006). Pharmacological evaluation of the extracts of *Sphaeranthus indicus* flowers on anxiolytics activity in mice. *Indian Journal of Pharmacology, 38*(4), 254.

Asif, M., Singh, D. and Singh, A. (2011). Analgesic activity of some 6-phenyl-4-substituted benzylidene tetrahydro pyridazin-3 (2H)-ones. *Global Journal of Pharmacology*, *5*(1), 18-22.

Borgarelli, C., Lenaers, S., De Borggraeve, W. M. and Ismalaj, E. (2022). 3-Methyl 5-{3-[(4-Methylbenzenesulfonyl) oxy] propyl} 4-(2, 3-Dichlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicarboxylate. *Molbank*, *2022*(4), M1460.

Cooper, K., Fray, M. J. and Parry, M. J. (1992). 1,4-dihydropyridine as antagonists of platelets activating factors. *J. of Med. Chem., 15*.17, 3115-3129.

Mousmee Sharma and Parteek Prasher (2022). C-2 fuctionalized imadazo(1,2-a) pyridine, synthesis and medicinal relevances. *Synthetic Communications, 52*, 1-11.

Muhammad , J. I. and Sumaira, H. (2012). Antioxidant and Antimicrobial activities of chowlai leaf and seed extracts. *Journal of medicinal plants research, 6*(27), 4450-4455.

Orhan, M. P. and Hanif, S. (2015). Synthesis and evaluation of antioxidant Activity of new quinoline-2-carbaldehyde hydrazone derivatives bioisosteric melatonin. *J. Enzyme Inhib. Med. Chem.*, 1–5.

Rajeev, K. and Prabodh, C. (2011). Pharmacological significance of triazole scaffold. *Journal of enzyme inhabitation and medicinal chemistry, 26*(1), 1-21.

Pattan, S. R., Wable, N. B. and Musmade, D. S. (2014). Synthesis and some evaluation of some novel triazolo beta-lactum derivatives for their antiinflammatory activity. *Indian Drugs Journal, 51*, 48-54.

Shahverdi, A. R. and Shahverdi, H. R. (2007). Synthesis and effect of sliver nano particales on the antibacterial activity of different antibiotics aginst staphylococus aurous and E.coil, Nonomedicine:nonotechnology. *Biology and Medicine, 3*(2), 168-171-29.

Shidhu, T. and Mamatha, A. (2013). Antidepressent activity of pyrimidine derivatives in mice. *Hygeia Journal of Drugs and Medicine, 5*(1), 129-134.

Vanicha, V. and Kanyawim, K. (2006). Sulforhodamine B colorimetric assay for cytotoxicity screening. *Nature Protocols*, 1112-1116.

Veroniki, P. K. and Georgia, N. (2022). Synthesis of Novel Pyrazolo[3,4-b] pyridines with Affinity for β-Amyloid Plaques, Molbank, 2-11.

Yung-Yuan, L. and Shiuh-Tzung, L. (2022). Reaction, Preparation of Substituted Pyridines via a Coupling of β-Enamine Carbonyls with Rongalite. *Application for Synthesis of Terpyridine*, 415–422.

Zidermane, A., Dubens, G., Zilbeers, A. and Verpele, R. (1978). Antitumar activity of nitrofuroan derivatives. *Pharmaceutical Chemical Journal, 12*, 357-360.

**How to cite this article:** Honde Bharat S., Kadm Sai V., Shelke Pratiksha S., Chimankar Ayushi D., Kale Rutuja B. and Kanhe Nandini K. (2023). Synthesis and Anticonvulsant Activity of 3,5-Bis[(5'-Substituted Phenyl) 1,3,4-Oxadiazole] 1,4-Dihydropyridine. *Biological Forum – An International Journal*, *15*(2): 42-45.