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"Pharmacological significance of Oxazole moiety"

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Abstract

Oxazole is one of the versatile molecules. It has been used exclusively in medicinal chemistry for various pharmacological activities. Due to binding with a good-sized spectrum of receptors and enzymes without problems in organic structures through diverse non-covalent interactions, oxazole-based molecules have become a form of tremendous heterocyclic nuclei that have acquired interest from researchers globally, mainly to synthesize various oxazole derivatives. Different pharmacological activities include anti-bacterial, anti-tuberculosis, anti-fungal, and anti-helminths. This work illustrates diversepharmacological activities exhibited by Oxazole moiety and its significance in the development of modern medicine.

Introduction

The oxazole ring, with one nitrogen atom and one oxygen atom, which might be extensively displayed in herbal merchandise and artificial molecules, is called a high skeleton for drug discovery. On the account of structural and chemical range, oxazole isan important scaffold, which permitsdifferent types of interactions with numerous receptors and enzymes, displaying extensive organic adaptability. It also has a significant impact on medicinal chemistry, demonstrating both its immense therapeutic potential and the need for the development of newer, more potent drugs.As a result, compounds are formed that contain a huge amount of oxalic salts, which play an important role in the treatment of various diseases, such as antibacterial, antifungal, anti-inflammatory, anti-viral, anti-tuberculosis, anti-cancer, anti-parasitic, anti-diabetic, etc. were often used as research candidates. Drugs containing oxazole with medicinal value are active worldwide. Various pharmacologicalchemical systems of oxazole-primarily based total molecules are enumerated are displayed in the following Table. Due to the range of pharmacological activities, the chemical synthesis of oxazole and its derivatives has emerged as a key goal and has drawn the attention of modern-day pharmacologists and chemists around the globe to be explored exhaustively for the advantage

of mankind. Until now, many inventive oxazole synthesis methodologies were advanced, inclusive of the van Leusen reaction, Cornforth reaction, Fisher reaction, Doyle reaction, Dakin–West reaction, in addition to Robinson–Gabriel r reaction, etc. Among those artificial strategies, it's famous that the van Leusen oxazole synthesis, primarily based totally on tosyl methyl isocyanides (TosMICs), is one of the most widely used chemicals for the synthesis of oxazole-based molecules, because of its extremely good virtues like easy operation, effortlessly acquired raw materials, and an extensive substrate scope, and it's synthesishas advanced in recent decades. It is worth citing that the pharmacological interest ofprimary oxazole-based moieties in Table may be acquired through van Leusen's response as a key step.

Anti-Bacterial Activity

Saloni Kakkar et al. prepared 4-substituted aryl 2- 4-disubstituted phenoxy methyl 4-oxazol-5-one derivatives and used the cup-plate method to test their antibacterial potential against Xanthomonas citri and E. coli in comparison to the common medication streptomycin.[1]

Several substituted thiazole, oxazole, and imidazole derivatives were synthesized by Argade ND et al. Using M. tuberculosis, the derivatives' in vitro antitubercular potential was investigated. Their antibacterial properties were also assessed. [2]

The antibacterial potential of a series of pyrazole derivatives of oxazole-5-one moiety was synthesized by Argade ND et.al., and evaluated against S. aureus, E. coli, and P. aeruginosa. As reference medications for antibacterial activity, ampicillin and streptomycin (10 and 25 µg/ml) were utilized. [3]

Wang et al., synthesized nitrocefin, which is used to identify bacterial resistance by determining if a bacteria produces beta-lactamase. By preventing overtreatment and treatment errors, the identification of bacterial resistance can enhance treatment quality and efficiency while lessening patient suffering and treatment costs.[4]

2, 4-disubstituted oxazoles were synthesized by Dabholkar et al., who then tested their antibacterial effectiveness against Gram-positive bacteria like S. aureus and C. diphtheriae as well as Gram-negative bacteria like E. coli and P. aeruginosa. The typical medication utilized was ampicillin trihydrate, and the inhibition zone was expressed in millimeters. Compound 28 showed strong efficacy against the different strains of bacteria.[5]

Taile et al. synthesized a variety of oxazol-5-ones and employed ciprofloxacin and sulphacetamide as reference medications to test their antibacterial potential against a range of harmful microorganisms. The antifungal potential of the produced compounds against Candida albicans and Aspergillus niger was also investigated. The zone of inhibition was examined with clotrimazole and gentamycin. Compounds 34 and 35 demonstrated good antibacterial activity [6]

Anti-Fungal Activity

Zhang et al. produced a chain of several derivatives of propanoic acid and used different reference medications to test their antibacterial and antifungal capabilities against different microorganisms. [7]

The antifungal potential of a series of pyrazoles connected to the oxazole-5-one moiety was synthesized and evaluated by Candida albicans. Reference drugs for antifungal activity are fluconazole, ketoconazole, and clotrimazole (10, 20, and 30 µg/ml) were used for antifungal activity. Benzoxazole-5-carboxylate derivatives were prepared and their antifungal activity was evaluated by Shamsuzzaman Khan et al. against fungal strains.[8]

Tom et al. synthesized new derivatives of five-membered heterocyclic compounds containing oxazole and benzothiazole rings, and then screened them for antifungal activity using ketoconazole as standard drugs. The novel oxazole derivatives were found to be promising compounds for antifungal activity.[9]

Padmavathi et al. synthesized a new class of amide-linked bis-heterocycles and tested their antifungal activity against coccidioidomycosis, histoplasmosis, blastomycosis, Pneumocystis pneumonia using chloramphenicol and ketoconazole as standard medications. This new class of amide-linked bis-heterocycles exhibited higher activity than standard antifungal compounds.[10]

Taile et al. synthesized a variety of oxazol-5-ones and employed ciprofloxacin and sulphacetamide as reference medications to test their antibacterial potential against a range of harmful microorganisms. The antifungal potential of the produced compounds against Candida albicans and Aspergillus niger was also investigated. The zone of inhibition was examined with clotrimazole and gentamycin. While compounds 36 and 37 demonstrated strong antifungal action, compounds 34 and 35 demonstrated good antibacterial activity.[11]

Using trimethoprim and miconazole as the conventional medication, antifungal Anand et al. synthesized a variety of substituted benzoxazoles and assessed their antibacterial potential against S. aureus, E. coli, C. albicans, and C. glabrata. Excellent antifungal activity was demonstrated by 2-ethoxy5 chlorobenzo[d]oxazole (42), and 2-methoxybenzo[d]oxazole (45) among the substances under investigation.[12]

Anti-Inflammatory Activity

Kumar. G et al., synthesized anti-inflammatory properties of synthetic substances were tested against carrageenan. Three different dosages of 25, 50, and 100 mg/kg p.o. were used in the study. The anti-inflammatory activity of thiazole derivatives (3a-3d) has been seen to range from 29.7% to 69.6%. At 25, 50, and 100 mg/kg p.o., compound 3c had greater anti-inflammatory activity (38.5, 55.4, and 69.6) than the reference medication Phenyl butanone (22.2, 35.8, and 66.5). 100 mg/kg [13]

A variety of oxazole derivatives were prepared by Dündar et al., who then assessed their ability to inhibit COX-2. The constitutive form of COX-1 is involved in homeostasis and gastroprotective effects, while COX-2 is involved in inflammatory sites. Of the compounds that were synthesized, it was discovered that 84 had the greatest selective COX-2 inhibition (70.14% ± 1.71). [14]

Shakya AK et al. synthesized A series of N-(2-(4-chlorobenzyl) benzo[d]oxazol-5-yl)-3-substituted-propanamide (3a-3n) and evaluated for their acute and chronic anti-inflammatory potential. These derivatives demonstrated excellent anti-inflammatory activity. [15]

Some oxazole derivatives were synthesized by Singh N et al., and they were assessed for their anti-inflammatory ability against carrageenan-induced edema in albino rats.[16]

The substituted quinolyl oxazoles were found by Eren G. et al. to be very potent inhibitors of phosphodiesterase 4 (PDE4). PDE4, one of the PDE enzymes specific to cAMP, is expressed by immunological and inflammatory cells. PDE4 IC50 values of 1.4 nm and 1 nm, respectively, for compounds 86 and 87 were found to be the most efficacious among those under investigation.[17]

A series of diaryl heterocyclic derivatives were produced by Valko M. et al., who also assessed their in vitro inhibitory effects on COX-1 and COX-2 isoforms. Compound 85 was discovered to have the highest COX-2 inhibition of all the oxazole derivatives, at 47.10% ± 1.05 when compared to the conventional drugs, rofecoxib and indomethacin.[18]

Anti-cancer Activity

Chiacchio MA et al., synthesized medications based on iso/oxazoles. Additionally reported are the corresponding dehydrogenated derivatives, or iso/oxazolines and iso/oxazolidines. These derivatives exhibited excellent anti-cancer activity as compared to standard drugs.[19]

Bisoxazoles were synthesized by Cantalejo et al. and their anticancer activity was assessed against the cancer cell line HT-29. Additionally, the inhibitory potency of the derivatives towards recombinant human choline kinase (ChoK) was evaluated in an ex vivo system. These derivatives were found to display potent anti-cancer activity. [20]

Johan et al. The synthesized special sequence that encloses the thiazole moiety in Aurora kinase inhibitors (SNS-314, 24). Additionally, important binding components and SAR have been described.[21]

Semenyuta I et al, synthesized oxazole derivative based on the potential of anticancer activity. [22]

Mahal et al. investigated the antitumoral characteristics of cis-stilbene combretastatin A-4 (CA-4), a metabolite of the South African bush willow Combretum caffrum. Nevertheless, the trans-isomerization of CA-4 and its low solubility restrict its application in anticancer treatment. Different heterocycles were combined with CA-4 to alleviate these disadvantages, resulting in the development of CA-4 analogs with imidazole and oxazole rings. The oxazoles replaced with halogen exhibited increased anticancer action. Human HT-29 colon cancer, human 518A2 melanoma, and Ea.hy926 endothelial hybrid cells were among the various cell lines that were employed. [23]

Barca et al. investigated the molecular interactions of three ruthenium complexes in isolated mammalian nuclei. The antitumor medication cis-diamminedichloroplatinum (CDDP) was compared with the complexes, which were chemotherapeutic agents that reduce metastatic tumors in vivo (57). The complexes under examination were Na trans-RuCl4 (DMSO) imidazole (NAMI) (54), Na trans-RuCl4 (DMSO) oxazole (NAOX) (55) and Na trans-RuCl4 (TMSO) isoquinoline (TEQU) (56). When the Ru complexes were tested for toxicity on V79

cells, it was discovered that only TEQU decreased the cloning efficiency and caused several mutations in V79 cells grown in culture, whereas NAMI and NAOX had no effect.[24]

Using 5-fluorouracil as a reference, Liu et al. prepared a variety of trisubstituted oxazole derivatives and evaluated their antitumor potential against two cancer cells: PC-3 (human prostate cancer) and A431 (human epidermis carcinoma). These novel moieties exhibited excellent activities against the PC-3 (human prostate cancer) and A431 (human epidermis carcinoma) cell lines. [25]

Anti-diabetic

Ashton et al. synthesized a range of β-aminoacylpiperidines with fused five-membered heterocyclic rings (thiazole, oxazole, isoxazole, or pyrazole) as dipeptidyl peptidase IV inhibitors. Out of all the screened oxazole derivatives, (R)-3-amino-1-(2-cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)-4-(2,5-fluorophenyl)butane-1-one was found to possess considerable DPP-IV inhibition (IC50 = 0.18 μM) [26]

A chain of oxazole derivatives was synthesized. KolterR et al. checked for PTP-1B inhibitory activity. Protein tyrosine phosphatase-1B (PTP-1B) has been found important for the treatment of diabetes and obesity. Out of all compounds, 97 and 98 exhibited the most promising activity.[27]

Pingali et al. designed and synthesized 1,3-dioxane carboxylic acid derivatives and combined this with substituted oxazole and evaluated them for in vitro PPAR agonistic potential and in vivo sugar lowering and lipid-lowering efcacy in animal models using rosiglitazone and tesaglitazar as standard compounds. Compound 99 was found to be the most active (EC50=0.0015 μM)[28]

Raval et al. designed and synthesized novel thiophene-substituted oxazole containing α-alkoxy-phenylpropanoic acid derivatives as highly potent PPAR α/γ dual agonists. Peroxisome proliferator-activated receptors (PPARs) play a very important role in metabolic syndrome whose major manifestations are hyperglycemia, dyslipidemia, and obesity. Compound 100 was found to be the most efficacious PPAR α/γ dual agonist and showed a glucose reduction of 72%.[29].

Mariappan.G et.al., synthesized and evaluated 4-arylidine 2-[4-methoxy phenyl] oxazol-5-one derivatives of oxazole and found that 4-[3-Methoxy-benzylidene]-2-(4-methoxy-phenyl) oxazol-5-one was having activity equivalent to that of rosiglitazone.[30]

Rahim. F et.al., synthesized and evaluated new triazinoindole bearing oxazole compounds and found that compounds (E)-2-(2-(2-((5H-[1,2,4]triazino[5,6-b]indol-3-yl)thio)-1-(4-nitrophenyl) ethylidene) hydrazinyl)-4-(4-nitrophenyl) oxazole and (E)-2-(2-(2-((5H-[1,2,4]triazino[5,6-b]indol-3-yl)thio)-1-(4-nitrophenyl) ethylidene) hydrazinyl)-4-(2-nitrophenyl) oxazole displayed excellent α-amylase inhibitory activity.[31]

Anticonvulsant

The synthesis and anticonvulsant characteristics of 1,2,4-triazole-5-thione derivatives integrated with coumarin were reported by Bhat et al. Compound 63 exhibited noteworthy

anticonvulsant properties. Compound 63 demonstrated protection against seizures in the MES test at a dose of 30 mg/kg after 0.5 hours and maintained the activity at a higher dose of 100 mg/kg after 4.0 hours. Compound 63 was found to be active in the scope screen at 100 mg/kg after 0.5 hours and at a higher level of 300 mg/kg after 4.0 hours.[32]

.Effective synthesis of pharmacologically potent 1,3,4-oxadiazole compounds was reported by Kamble and Sudha (94, Figure 14), some of which contained triazoles. When compared to conventional phenytoin, it was shown that several variants containing triazoles exhibited very good effectiveness against convulsions generated by MES in rats.[33]

Cui L.J. et. al., Investigate, a series of benzoxazole derivatives containing triazolone (4a–m) that were developed and synthesized as an extension of the previous study, substituting triazolone for the triazole compounds. Based on a theory that has previously been supported by earlier research, this design aims to enhance the anticonvulsant action of the triazolone by increasing its affinity for the receptor.[34][35]

Guan LP, et al..synthesis of numbers of triazolebenzo[d]oxazoles as anticonvulsant agents. Among them, 2-phenyl-6-(4H-1,2,4-triazol-4-yl)benzo[d]oxazole (16, Figure 5) was the most active and also had the lowest toxicity. The anti-MES potency test, showed a median effective dose (ED50) of 29.5 mg/kg, a median toxicity dose (TD50) of 285 mg/kg, and a protective index (PI) of 9.7, which is greater than the reference drug, carbamazepine, whose PI value was 6.4. This attempt suggested that the mono-substituted triazoles also meet the request of the anticonvulsant activity.[36]

Guan LP, et al., synthesized triazolebenzo[d]oxazoles as anticonvulsant drugs. The most active and least hazardous of them was 2-phenyl-6-(4H-1,2,4-triazol-4-yl)benzo[d]oxazole. The anti-MES potency test yielded results that were higher than those of the reference medication, carbamazepine, including a median effective dosage (ED50) of 29.5 mg/kg, a median toxicity dose (TD50) of 285 mg/kg, and a protective index (PI) of 9.7. This attempt revealed that the mono-substituted triazoles fulfill the anticonvulsant activity's request as well.[37]

Meanwhile, another series of triazole-containing benzo[d]oxazoles were prepared by altering the position of the triazole. In this study, compound **20** was obtained with an ED_{50} of 12.7 mg/kg and 29.5 mg/kg in the MES and Sc-PTZ models, respectively. The rotarod test showed the TD_{50} of 491.0 mg/kg [36]. Sydorenko. I et.al., synthesized novel oxazole-bearing 4-thiazolidinones as potential anticonvulsant agents. It was found that these compounds exhibited promising anti-convulsant activity as compared to standard drugs [38].

Conclusion

In summary, under the in-depth research and application in oxazole-based medicinal chemistry and the progress in other related disciplines such as cell biology, molecular biology, pharmacology, and organic chemistry, the synthesis of oxazole-based drugs will be still an active field in medicinal research and development industries for a long time. In the future, increasing researcher interests will be focused on the design, synthesis, bioactive evaluation, and action mechanism of unusual types of oxazole-based heterocyclic compounds with completely novel chemical scaffolds, which help overcome drug resistances, increase bioactivities, and will make remarkable contributions to the prevention and protection of human health. Hence, we could focus on changing the starting materials including different aldehydes

and TosMICs to modify oxazole-containing derivatives, utilizing a new synthesis technology like the MWassisted condition to improve the synthesis efficiency, or uniting other typical name reaction to synthesize the special and complex oxazole-based compounds in the future. Above all, these have clearly and strongly suggested the infinite potentiality of van Leusen oxazole synthesis in medicinal chemistry. Additionally, we hope that this review will build a full foundation and reference source, which will open up new thoughts for researchers to focus on oxazole-based medicinal molecule design and synthesis chemistry.

References

1. Aagalwe, Saloni Kakkar BMC chemistry volume 13, Article number: 16 (2019) A comprehensive review on biological activities of oxazole derivatives.
2. Argade ND, Kalrale BK, Gill CH (2008) Microwave-assisted improved method for the synthesis of pyrazole containing 2,4,-disubstituted oxazole-5-one and their antimicrobial activity. E-J Chem 5(1):120–129.
3. Argade ND, Gill CH (2008) Microwave-assisted improved method for the synthesis of pyrazole containing 2,4,-disubstituted oxazol-5-one and their antimicrobial activity. E-J Chem 5(1):120–129.
4. Li, N.N.; Xu, Y.T.; Xia, Q.; Bai, C.G.; Wang, T.Y.; Wang, L.; He, D.D.; Xie, N.N.; Li, L.X.; Wang, J.; et al. Simplified captopril analogues as NDM-1 inhibitors. *Bioorgan. Med. Chem. Lett.* **2014**, *24*, 386–389.
5. Dabholkar VV, Ali Syed SAS. Synthesis of novel oxazoles and their hydrazones. Rasayan J Chem. 2010;3(4):761–765.
6. Taile V, Hatzade K, Gaidhane P, Ingle V (2009) Synthesis and biological activity of –(4-hydroxybenzylidene)-2-(substituted styryl) oxazol-5-ones and their o-glucosides. Turk J Chem 33(2):295–305
7. Zhang W, Liu W, Jiang X, Jiang F, Zhuang H, Fu L (2011) Design, synthesis and antimicrobial activity of chiral 2-(substituted-hydroxyl)-3-(benzo[*d*]oxazol-5-yl)propanoic acid derivatives. Eur J Med Chem 46(9):3639–3650.
8. Shamsuzzaman Khan MS, Alam M, Tabassum Z, Ahmad A, Khan AU. Synthesis, antibacterial and antifungal activities of 6,5 fused steroidal oxazoles in cholestane series. *Eur J Med Chem.* 2010;45:1094–1097. doi: 10.1016/j.ejmech.2009.12.004
9. Tomi IHR, Tomma JH, Al-Daraji AHR, Al-Dujaili AH. Synthesis, characterization, and comparative study of the microbial activity of some heterocyclic compounds containing oxazole and benzothiazole moieties. *J Saudi Chem Soc.* 2015;19:392–398. doi: 10.1016/j.jscs.2012.04.010.
10. Padmavathi V, Kumara CP, Venkatesh BC, Padmaja A. Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles. *Eur J Med Chem.* 2011;46(11):5317–5326.doi: 10.1016/j.ejmech.2011.08.032.
11. Taile V, Hatzade K, Gaidhane P, Ingle V (2009) Synthesis and biological activity of –(4-hydroxybenzylidene)-2-(substituted styryl) oxazol-5-ones and their o-glucosides. Turk J Chem 33(2):295–305.

12. Anand M, Ranjitha A, Himaja M (2011) Silica sulfuric acid catalyzed microwave-assisted synthesis of substituted benzoxazoles and their antibacterial activity. Int Res J Pharm 2(4):211–213

13. Gajendra Kumar Volume 107,Synthesis, anti-inflammatory and analgesic evaluation of thiazole/oxazole substituted benzothiazole derivatives

14. Dündar Y, Ünlü S, Banoğlu E, Entrena A, Costantino G, Nunez MT, Ledo F, Şahin MF, Noyanalpan N (2009) Synthesis and biological evaluation of 4,5-diphenyloxazolone derivatives on route towards selective COX-2 inhibitors. Eur J Med Chem 44:1830–1837.

15. Ashok K. Shakya ` Volume 24, Issue 5 Pages 616-624 Molecular modeling, synthesis, characterization and pharmacological evaluation of benzo[d]oxazole derivatives as non-steroidal anti-inflammatory agents

16. Singh N, Bhati SK, Kumar A (2008) Thiazolyl/oxazolyl formazanyl indoles as potent anti-inflammatory agents. Eur J Med Chem 43(11):2597–2609. .Kuang R, Shue HJ, Blythin DJ, Shih NY, Gu D, Chen X, Schwerdt J, Lin L, Ting PC, Zhu X, Aslanian R, Piwinski JJ, Xiao L, Prelusky D, Wu P, Zhang J, Zhang X, Celly CS, Minnicozzi M, Billah M, Wang P (2007) Discovery of a highly potent series of oxazole-based phosphodiesterase 4 inhibitors. Bioorg Med Chem Lett 17:5150–5154

17. Eren G, Ünlü S, Nuñezv MT, Labeaga L, Ledo F, Entrena A, Ea Banoğlu, Costantino G, Şahin MF (2010) Synthesis, biological evaluation, and docking studies of novel heterocyclic diaryl compounds as selective COX-2 inhibitors. Bioorg Med Chem 18:6367–6376.

18. Valko M., Leibfritz D., Moncol J., Cronin M. T., Mazur M., Telser J. Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry & Cell Biology. 2007;39(1):44–84. doi: 10.1016/j.biocel.2006.07.001.

19. Chiacchio M.A., Lanza G., Chiacchio U., Giofre S.V., Romeo R., Iannazzo D., Legnani L. Oxazole-based compounds as anticancer agents. *Curr.Med.Chem.* 2019;26:73377371.doi: 10.2174/0929867326666181203130402.

20. Cantalejo YM, Sáez B, Monterde MI, Murillo MT, Braña MF (2011) Synthesis and biological activity of new bis pyridinium salts 4,4′ bispyridyl-5-5′-perflouroalkyl-2,2′-bisoxazoles. Eur J Med Chem 46:5662–5667.

21. Johan D.O, et. al. Discovery of a potent and selective Aurora kinase inhibitor, Bioorg. Med. Chem. Lett.: 2008. p. 4880 - 4884. DOI: 10.1016/j.bmcl.2008.07.073.

22. Vladimir Zyabrev, Stepan Pilyo, Bohdan Demydchuk, Maryna Kachaeva, Ivan Semenyuta, Victor Zhirnov, Yevheniia Velihina, Volodymyr Brovarets,*ChemMedChem* **2023**.

23. Mahal K, Biersack B, Schobert R (2013) New oxazole-bridged combretastatin A-4 analogs as potential vascular-disrupting agents. Int J Clin Pharmacol Ther 15(1):41–43

24. Barca A, Pani B, Tamaro M, Russo E (1999) Molecular interactions of ruthenium complexes in isolated mammalian nuclei and cytotoxicity on V-79 cells in culture. Mutat Res 423(1–2):171–181.

25. Liu XH, Lv PC, Xue JY, Song BA, Zhu HL (2009) Novel 2,4,5-trisubstituted oxazole derivatives: synthesis and antiproliferative activity. Eur J Med Chem 44(10):3930–3935

26. Ashton WT, Sisco RM, Dong H, Lyons KA, He H, Doss GA, Leiting B, Patel RA, Wu JK, Marsilio F, Thornberry NA, Weber AE (2005) Dipeptidyl peptidase IV inhibitors derived

from *β*-aminoacylpiperidines bearing a fused thiazole, oxazole, isoxazole, or pyrazole. Bioorg Med Chem Lett 15(9):2253–2258.

27. Y.-M. Li, J. C. Milne, L. L. Madison, R. Kolter, and C. T. Walsh, Science, 1996, 274, 1188.

28. Pingali H, Jain M, Shah S, Makadia P, Zaware P, Goel A, Patel M, Giri S, Patel H, Patel P (2008) Design and synthesis of novel oxazole containing 1,3-Dioxane-2-carboxylic acid derivatives as PPAR α/γ dual agonists. Bioorg Med Chem 16(15):7117–7127.

29. Raval P, Jain M, Goswami A, Basu S, Gite A, Godha A, Pingali H, Raval S, Giri S, Suthar D, Shah M, Patel P (2011) Revisiting guitars: thiophene substituted oxazole containing α-ethoxy phenylpropanoic acid derivatives as highly potent PPAR α/γ dual agonists devoid of adverse effects in rodents. Bioorg Med Chem Lett 21(10):3103–3109

30. Mariappan.G et.al., Design, synthesis and antidiabetic evaluation of oxazolone derivatives, J. Chem. Sci, 2011, 123(3), 335-341.

31. Rahim. F et.al., New triazinoindole bearing thiazole/oxazole analogues: Synthesis, αamylase inhibitory potential and molecular docking study, Bioorganic Chemistry, 2019, 92, 1-7.

32. Bhat MA, Al-Omar MA.. Coumarin incorporated triazoles: a new class of anticonvulsants. Acta Pol Pharm 2011;68:889–95.

33. Kamble RR, Sudha BS, Ravindra RK, Belagur SS. An efficient synthesis of pharmacologically active derivatives of 1,3,4-oxadiazoles. J Heterocycl Chem 2006;43:345–51.

34. Cui L.J., Xie Z.F., Piao H.R., Li G., Chai K.Y., Quan Z.S. Synthesis and anticonvulsant activity of 1-substituted-7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline. Biol. Pharm. Bull. 2005;28:1216–1220. doi: 10.1248/bpb.28.1216.

35. Jin H.G., Sun X.Y., Chai K.Y., Piao H.R., Quan Z.S. Anticonvulsant and toxicity evaluation of some 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1(2H)-ones. Bioorg. Med. Chem. 2006;14:6868–6873. doi: 10.1016/j.bmc.2006.06.044.

36. Wei CX, Guan LP, Jia JH, et al.. Synthesis of 2-substituted-6-(4H-1,2,4-triazol-4-yl)benzo[d]oxazoles as potential anticonvulsant agents. Arch Pharmacal Res 2009;32:23–31.

37. Tan YD, XY He, Rao BQ, et al.. Synthesis and evaluation of the anticonvulsant activities of triazole-containing benzo[d]oxazoles. *Chin J Org Chem* 2016;36:2449–55.

38. Song MX, Rao BQ, Cheng BB, et al.. Design, synthesis, and evaluation of the antidepressant and anticonvulsant activities of triazole-containing benzo[d]oxazoles. *CNS Neurol Disord Drug Targets* 2017;16:187–98.

39. Sydorenko. I, The synthesis and the anticonvulsant activity screening of new 5-substituted 2-imino-4-thiazolidinone derivatives, Original Researches, 2022, 20 (1), 77