Implementation of National Education Policy -2020: Multidisciplinary Education

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I

A review on Oxazines: Synthesis and Biological Potentials

Amol K. Kharde [1], Vinod R. Kadu[2], Somnath S. Gholap[3]

[1 2]Arts, Science and Commerce College, Kolhar Tal: Rahata Dist: Ahmednagar Dist: Ahmednagar(MS)

[3]Arts, Commerce and Science College, Rahata Tal: Rahata Dist: Ahmednagar Dist: Ahmednagar(MS)

Corresponding author: Amol K. Kharde

Email-ssgholap2002@gmail.com

Abstract:

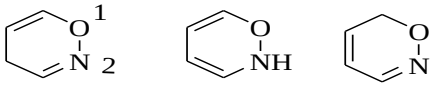
Due to their wide range of pharmacological effects, oxazine derivatives are a prominent class of heterocycle molecules that have attracted a lot of synthetic research. By appropriately substituting nitrogen and oxygen for carbon and hydrogen atoms in benzene and its reduction products, oxazine, a heterocyclic molecule, can be synthesised. Oxazine derivatives have emerged as attractive synthetic intermediates in recent years, as well as having significant biological properties like sedative, analgesic, antipyretic, anticonvulsant, antitubercular, antitumor, antimalarial, and antibacterial effects. The progress of drug resistance is currently a major challenge, and in order to address it, it is necessary to synthesise new classes of chemicals. The aim of the article's is to evaluate the generalisation of the information gathered regarding the synthesis of oxazine derivatives and their activity. For researchers interested in oxazine derivatives, we anticipate that this endeavour will be of particular interest.

Keywords: Oxazine, Biological activities, antibacterial.

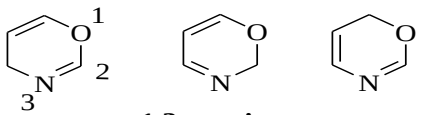
Introduction:

At least 50% of organic chemistry research is done on heterocyclic compounds. Numerous biologically active compounds with heterocyclic rings have been shown to have a variety of biological functions and to play significant roles in the drug discovery process.[1] Oxazine is important scaffold in biologically active compounds.[2]Depending upon the position of oxygen and nitrogen atom, oxazines are classified as 1,2-, 1,3- and 1,4-oxazine.[3]1,2-Oxazines are effective building blocks for the production of the novel physiologically active compounds.[4] Due to broad range of biological activities and synthetic convenience 1,3-Oxazines moiety has gained great attention from many organic and pharmaceutical chemists.[5] 1,3-oxazine derivatives shows biological active properties likeantifungal[6], antibacterial[7], antibacterial[8], antiulcer[9], antitumor[10], anticancer[11], and anti-microbial.[12]1,4-oxazines also having a wide range of biological application because of their vital bioactive nature.[13]

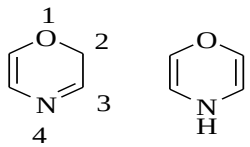
Over the past three decades, oxazines have attracted interest, but little research has been done on these molecules. One nitrogen and one oxygen are found in heterocyclic molecules called oxazines. Depending on the relative positions of the heteroatoms and double bonds, there are three different isomers1, 2-,1, 3-,and1,4-oxazines.



1,2-oxazine



1,3-oxazine



1,4-oxazine

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I

The first 1,3-oxazine derivative was synthesised by Cope and Holly in 1944 via Mannich reaction.[14]Only few reports are available regarding the antimicrobial activity of 1,3-oxazines.

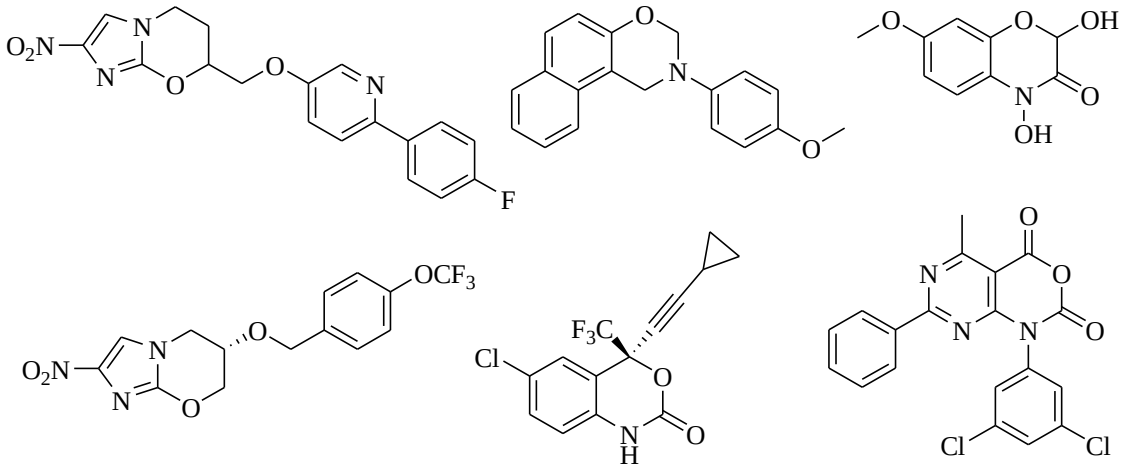
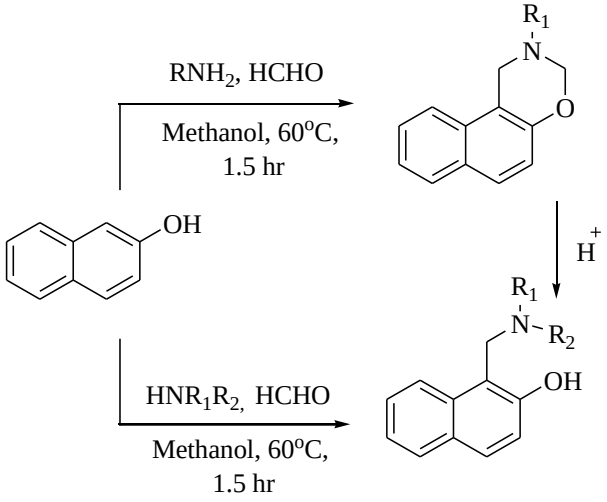


Figure 1. Some biologically activeoxazine derivatives.

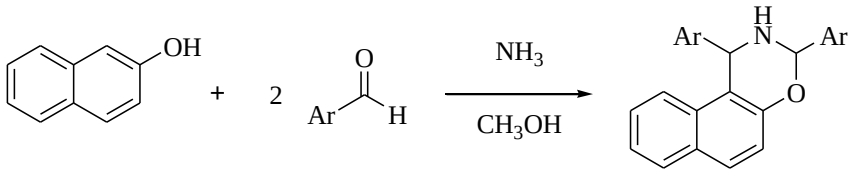
Oxazine heterocycles show useful biological activities. Its increasing importance in pharmaceutical and biological field, through this review article, we are planned to collect synthesis of some oxazine derivatives.Hence there is enough scope to explore new oxazine derivatives for their antibacterial & antifungal activity.

Shen and *co-workers* prepare a series of oxazine and 1-alkylaminomethylnaphthol analogues by addition reactions of phenol, formaldehyde, and alkylamines in methanol as a solvent at 60^{O}C. (Scheme1)[15]



Scheme 1. Synthesis of oxazine and 1-alkylaminomethylnaphthol derivatives.

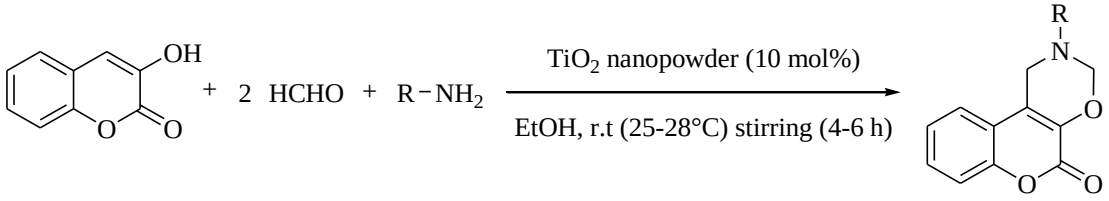
Turgut and *co-workers* developed 1,3-oxazines derivatives by ring closure reaction of naphthols, substituted aryl- and heteroaryl aldehydes and ammonia in methanol. (Scheme 2)[16]



Scheme 2. Synthesis of 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines.

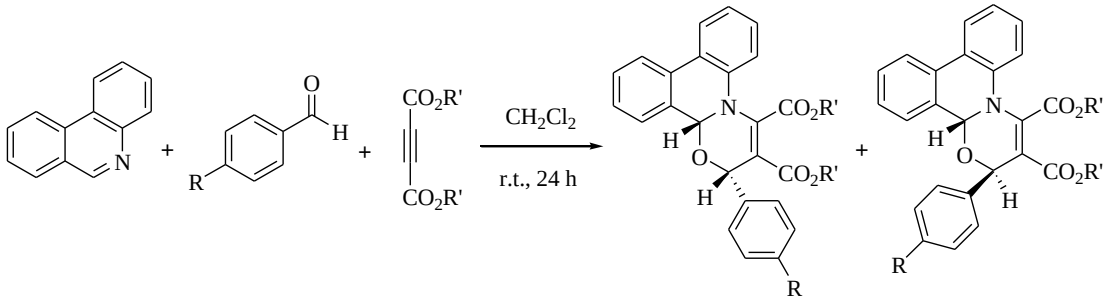
Mukhopadhyay and *co-workers* prepare coumarin-based 1,3-oxazine derivatives by the addition reaction of 3-hydroxycoumarin, primary amines, and formaldehyde at 25–28^{O}C for 4-6 hrs using TiO_2 nanoparticles as a catalyst with remarkable reusability. (Scheme 3)[17]

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I



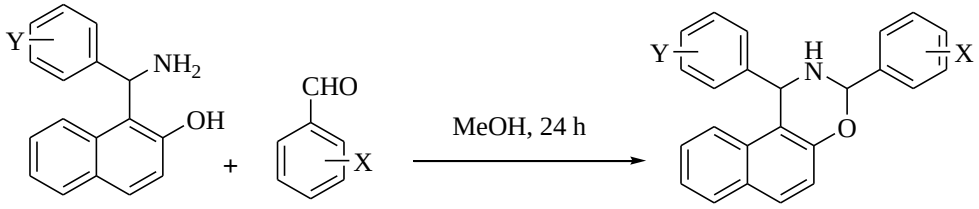
Scheme 3. Synthesis of coumarin based 1,3-oxazine derivatives catalyzed by TiO_2 nanoparticle.

Mehrabi and *co-workers* have developed the preparation of 1,3-oxazine analogues from phenantridine, dialkylacetylenedicarboxylates (DAADs) and aromatic aldehydes in DCM at ambient temperature for 24 hours (Scheme 4).[18]



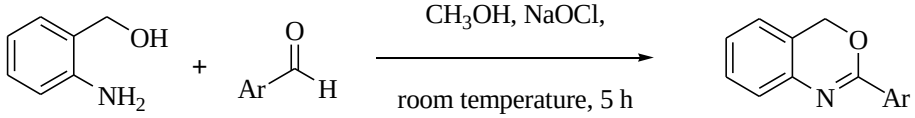
Scheme 4. Synthesis of 1,3-oxazine derivatives.

Fulop and *co-workers* have developed a Mannich-type aminoalkylation reaction of appropriate reactants to synthesize Betti base derivatives (amino naphthols) with various substituted benzaldehydes, which are three-component isomeric mixtures in $CDCl_3$ at room temperature and further give 1,3-oxazine derivatives (Scheme 5).[19]



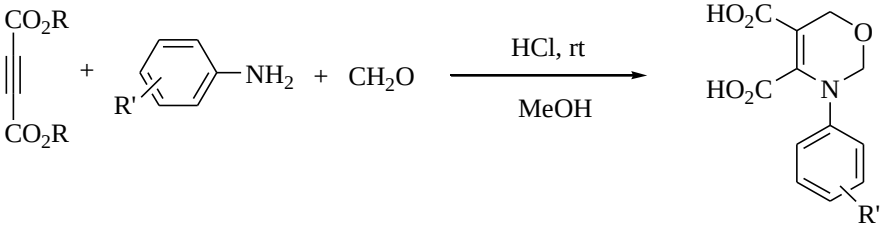
Scheme 5. Synthesis of oxazine analogues from Betti bases.

Reddy and *co-workers* synthesize 1,3-oxazines derivatives using sodium hypochlorite (NaOCl) from 2-aminobenzylamine, various aldehydes in methanol as solvent (Scheme 6).[20]



Scheme 6. Synthesis of 4*H*-benzo[*d*]-[1,3]oxazines.

Jiang and *co-workers* develop a novel methodology for the preparation of 1,3-oxazine analogues by promotion of Bronsted acids such as hydrochloric acid from formaldehyde, amines, and alkynoates using an easy, experimentally developed protocol, and the final products were obtained in excellent yields under normal reaction conditions (Scheme 7).[21]

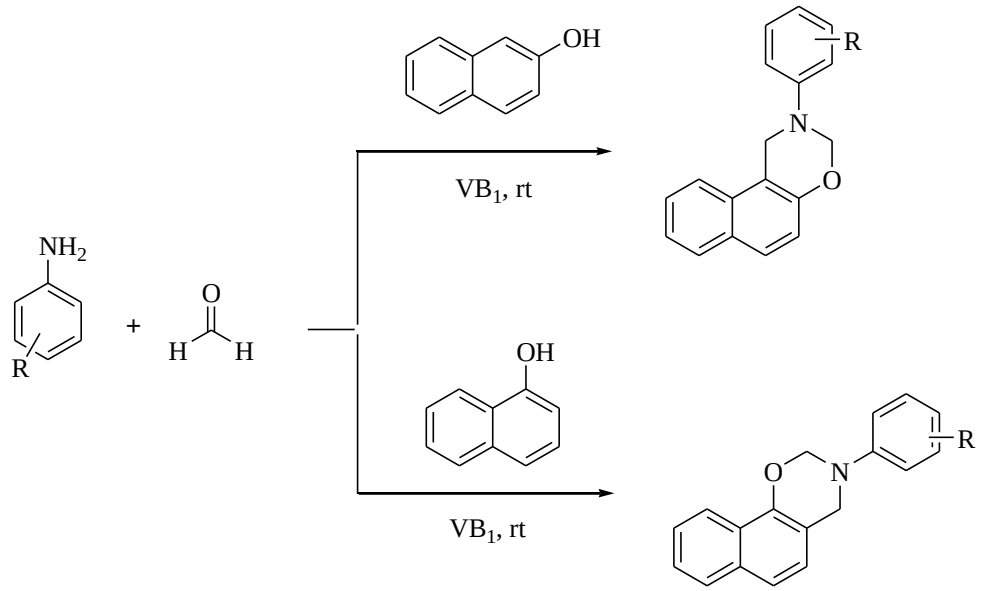


Scheme 7. 3,4,5-trisubstituted-1,3-oxazine synthesis catalyzed by Bronsted acid.

Bandgar and *co-workers* developed a multi-component, one-pot reaction of anilines, formaldehyde and α- or ß- naphthol as an efficient and suitable process for the production of a diverse of 1,3- oxazine analogues using innovative thiamine

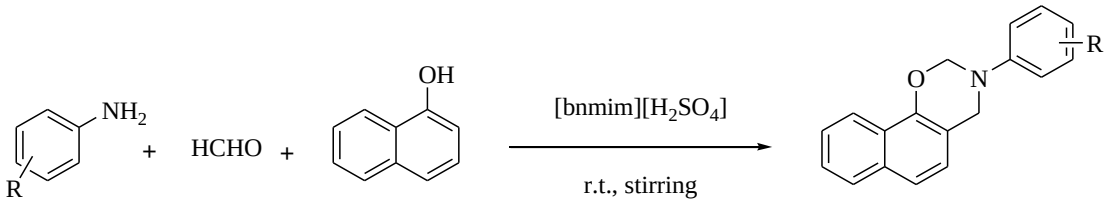
ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I

hydrochloride (VB1) as a biodegradable and greener catalyst in aqueous media (Scheme 8).[22]



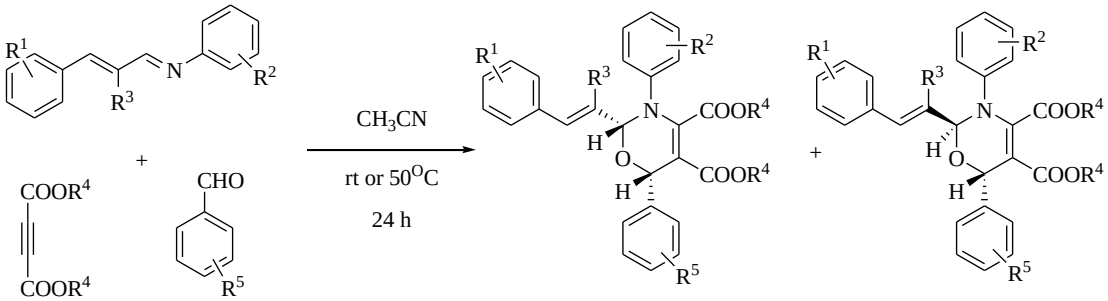
Scheme 8. Thiamine hydrochloride (VB1) catalysed synthesis of 1,3- oxazine analogues.

Shingare and *co-workers* have developed the one-pot procedure for the synthesis of 1,3-oxazine analogues using novel [bnmim] [HSO_4] as an ionic liquid at room temperature and stirring (Scheme 9).[23]



Scheme 9. Synthesis 3,4-dihydro-3-substituted-2*H*-naphtho[2,1-e][1,3]oxazine analogues.

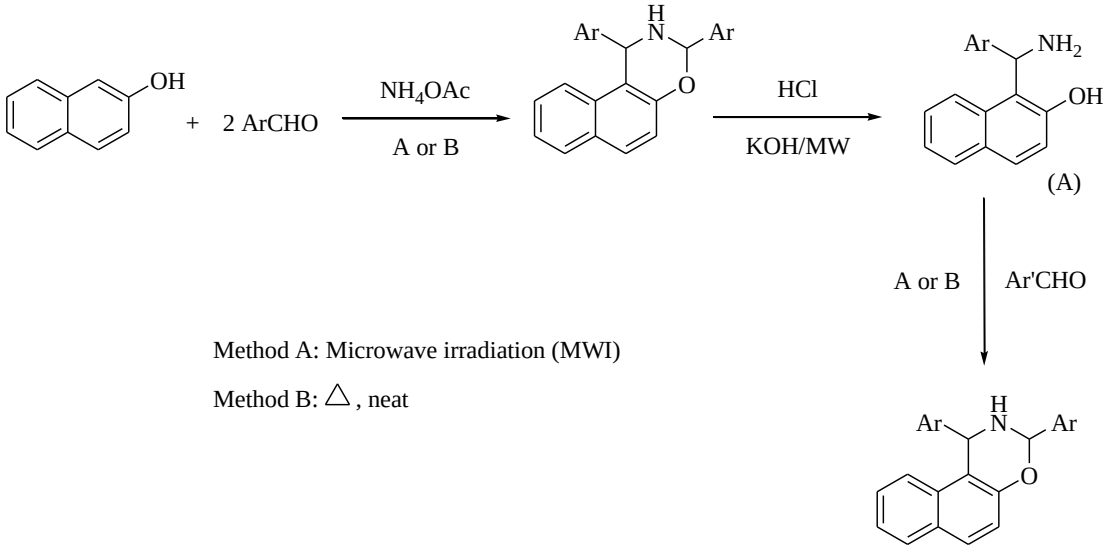
Lei and *co-workers* have synthesized structurally diversified 1,3-oxazine analogues by multi-component reaction involving α,ß-unsaturated imines, acetylenedicarboxylate and benzaldehyde in acetonitrile at 50^{O}C for 24 h (Scheme 10).[24]



Scheme 10. Synthesis ofstructurally diversified 1,3-oxazine analogues.

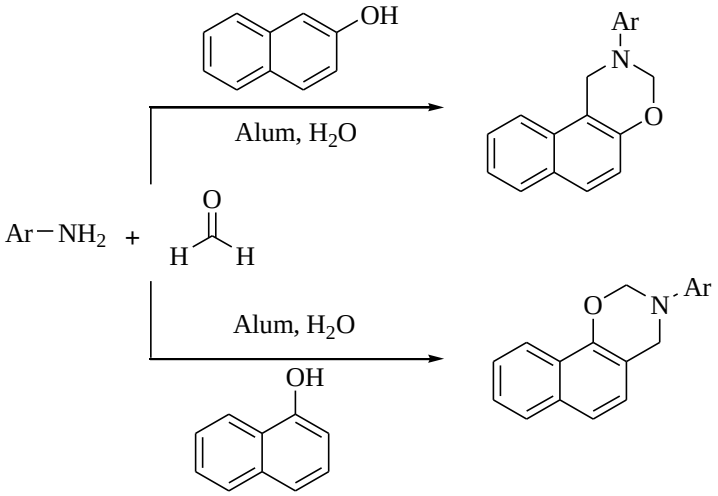
Sapkal and *co-workers* have developed a solvent-free protocol for the preparation of 1,3-oxazine derivatives using "ammonium acetate" as a catalyst in microwave irradiation. They have highlighted the reaction's progress for the formation of Betti bases (A) (Scheme 11).[23]

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I



Scheme 11. Synthesis of 1,3-oxazine derivatives.

Shingare and *co-workers* have developed 1,3-oxazine derivatives by using "$KAl(SO_4)_2.12H_2O$ (alum)" as a green catalyst by reaction of α- or ß-naphthol, various amines and formaldehydes. (Scheme 12).[25]



Scheme 12. Synthesis of various oxazine derivatives.

Conclusions:

Oxazine and related heterocyclic compounds have antimycobacterial, antibacterial, antifungal, anticoagulant, anticancer, antioxidant, and cytotoxic activities. It has been found that oxazine derivatives can be synthesized in a number of ways. So, this review article can extend the synthetic utility of new heterocyclic oxazine derivatives. Therefore, biological significance of oxazine compounds could be utilized for the development of new chemical entities to various diseases. We can therefore draw the conclusion that numerous more oxazine derivatives can be produced and are likely to exhibit strong pharmacological activity. We believe that our succinct review will help everyone who is interested in this exciting family of heterocyclic compounds make decisions regarding the selection of targets and objectives for more research.

References:

(1) Article, R. Green Synthesis Of Thiazine And Oxazine Derivatives - A Short Review Sayaji S. Didwagh and Pravina B. Piste* P.G. Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara-415 001, Maharashtra, India. **2013**, *4* (6), 2045–2061. https://doi.org/10.13040/IJPSR.0975-8232.4(6).2045-61.

(2) Sindhu, T.; Arikkatt, S.; Vincet, G.; Chandran, M.; Bhat, A.; Krishnakumar, K. Biological Activities of Oxazine and Its Derivatives. *Int. J.*

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I

*Pharma Sci. Res.***2013**, *4* (11), 134–143.

(3) Králová, P.; Ručilová, V.; Soural, M. Polymer-Supported Syntheses of Heterocycles Bearing Oxazine and Thiazine Scaffolds. *ACS Comb. Sci.***2018**, *20* (9), 529–543. https://doi.org/10.1021/acscombsci.8b00076.

(4) Gaonkar, S. L.; Nagaraj, V. U.; Nayak, S. A Review on Current Synthetic Strategies of Oxazines. *Mini. Rev. Org. Chem.***2018**, *16* (1), 43–58. https://doi.org/10.2174/1570193x15666180531092843.

(5) Mathew George , Lincy Joseph, H.; Raj.Sadananda. A Review on Screening of Novel Oxazine Derivatives for Certain Pharmacological Activities. *Hum. J.***2016**, No. 1, 1–6.

(6) Tafti, A. D.; Fatemeh Mirjalili, B. B. Nano-Fe3O4@walnut Shell/Cu(Ii) as a Highly Effective Environmentally Friendly Catalyst for the One-Potpseudothree-Component Synthesis of 1,3-Oxazine Derivatives under Solvent-Free Conditions. *RSC Adv.***2020**, *10* (53), 31874–31880. https://doi.org/10.1039/d0ra04282j.

(7) Sharma, S.; Nath, M. Synthesis of Meso-Substituted Dihydro-1, 3-Oxazinoporphyrins. *Beilstein J. Org. Chem.***2013**, *9*, 496–502. https://doi.org/10.3762/bjoc.9.53.

(8) Chylińska, J. B.; Janowiec, M.; Urbański, T. Antibacterial Activity of Dihydro-1,3-Oxazine Derivatives Condensed with Aromatic Rings in Positions 5,6. *Br. J. Pharmacol.***1971**, *43* (3), 649–657. https://doi.org/10.1111/j.1476-5381.1971.tb07194.x.

(9) Katsura, Y.; Nishino, S.; Takasugi, H. Studies on Antiulcer Drugs. I. Synthesis and Antiulcer Activities of Imidazo[1,2-α]Pyridinyl-2-Oxobenzoxazolidines-3-Oxo-2H-1: 4-Benzoxazines and Related Compounds. *Chem. Pharm. Bull.***1991**, *39* (11), 2937–2943. https://doi.org/10.1248/cpb.39.2937.

(10) Tang, Z.; Chen, W.; Zhu, Z.; Liu, H. SnCl 4-Catalyzed Aza-Acetalization of Aromatic Aldehydes: Synthesis of Aryl Substituted 3,4-Dihydro-2H-1,3-Benzoxazines. *Synth. Commun.***2012**, *42* (9), 1372–1383. https://doi.org/10.1080/00397911.2010.540691.

(11) Nongrum, R.; Kharkongor, M.; Nongthombam, G. S.; Rani, J. W. S.; Rahman, N.; Kharmawlong, G. K.; Nongkhlaw, R. [1,3]Oxazines: Green Synthesis By Sonication Using a Magnetically-Separable Basic Nano-Catalyst and Investigation of Its Activity Against the Toxic Effect of a Pesticide on the Morphology of Blood Cells. *Environ. Chem. Lett.***2019**, *17* (3), 1325–1331. https://doi.org/10.1007/s10311-019-00857-1.

(12) Babaei, E.; Mirjalili, B. B. F. One Pot Aqueous Media Synthesis of 1,3-Oxazine Derivatives Catalyzed by Reusable Nano-Al2O3/BF3/Fe3O4 at Room Temperature. *Polycycl. Aromat. Compd.***2021**, *41* (3), 518–525. https://doi.org/10.1080/10406638.2019.1600561.

(13) Rombouts, F. J. R.; Tresadern, G.; Delgado, O.; Martínez-Lamenca, C.; Van Gool, M.; García-Molina, A.; Alonso De Diego, S. A.; Oehlrich, D.; Prokopcova, H.; Alonso, J. M.; Austin, N.; Borghys, H.; Van Brandt, S.; Surkyn, M.; De Cleyn, M.; Vos, A.; Alexander, R.; Macdonald, G.; Moechars, D.; Gijsen, H.; Trabanco, A. A. 1,4-Oxazine ß-Secretase 1 (BACE1) Inhibitors: From Hit Generation to Orally Bioavailable Brain Penetrant Leads. *J. Med. Chem.***2015**, *58* (20), 8216–8235. https://doi.org/10.1021/acs.jmedchem.5b01101.

(14) Holly, F. W.; Cope, A. C. Condensation Products of Aldehydes and Ketones with O-Aminobenzyl Alcohol and o-Hydroxybenzylamine. *J. Am. Chem. Soc.***1944**, *66* (11), 1875–1879. https://doi.org/10.1021/ja01239a022.

(15) Shen, A. Y.; Tsai, C. T.; Chen, C. L. Synthesis and Cardiovascular Evaluation of N-Substituted 1-Aminomethyl-2-Naphthols. *Eur. J. Med. Chem.***1999**, *34* (10), 877–882. https://doi.org/10.1016/S0223-5234(99)00204-4.

ISBN: 978-93-94819-23-8
Pub. Date: 12/02/2023
Volume: I

(16) Turgut, Z.; Pelit, E.; Köycü, A. Synthesis of New 1,3-Disubstituted-2,3-Dihydro-1H-Naphth-[1,2e][1,3] Oxazines. *Molecules***2007**, *12* (3), 345–352. https://doi.org/10.3390/12030345.

(17) Mondal, A.; Rana, S.; Mukhopadhyay, C. One-Pot, Expeditious and Chromatography-Free Synthesis of New Chromeno[4,3-e][1,3]Oxazine Derivatives Catalyzed by Reusable TiO2 Nanopowder at Room Temperature. *Tetrahedron Lett.***2014**, *55* (24), 3498–3502. https://doi.org/10.1016/j.tetlet.2014.04.099.

(18) Mehrabi, H.; Hatami-Pour, M. Facile, One-Pot Synthesis of New Phenanthridine Derivatives through 1,4-Dipolar Cycloaddition of Phenantridine, Activated Acetylenes, and Aromatic Aldehydes. *Chinese Chem. Lett.***2014**, *25* (11), 1495–1498. https://doi.org/10.1016/j.cclet.2014.05.024.

(19) Szatmári, I.; Martinek, T. A.; Lázár, L.; Fülöp, F. Substituent Effects in the Ring-Chain Tautomerism of 1,3-Diaryl-2,3-Dihydro-1H-Naphth[1,2-e][1,3]Oxazines. *Tetrahedron***2003**, *59* (16), 2877–2884. https://doi.org/10.1016/S0040-4020(03)00331-4.

(20) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. Highly Efficient One-Pot Synthesis of 2-Substituted Quinazolines and 4H-Benzo[d][1,3]Oxazines via Cross Dehydrogenative Coupling Using Sodium Hypochlorite. *Adv. Synth. Catal.***2010**, *352* (2–3), 341–346. https://doi.org/10.1002/adsc.200900715.

(21) Cao, H.; Jiang, H. F.; Qi, C. R.; Yao, W. J.; Chen, H. J. Brønsted Acid-Promoted Domino Reactions: A Novel One-Pot Three-Component Synthesis of 3,4,5-Trisubstituted-3,6-Dihydro-2H-1,3-Oxazines. *Tetrahedron Lett.***2009**, *50* (11), 1209–1214. https://doi.org/10.1016/j.tetlet.2009.01.002.

(22) Dhakane, V. D.; Gholap, S. S.; Deshmukh, U. P.; Chavan, H. V.; Bandgar, B. P. An Efficient and Green Method for the Synthesis of [1,3]Oxazine Derivatives Catalyzed by Thiamine Hydrochloride (VB1) in Water. *Comptes Rendus Chim.***2014**, *17* (5), 431–436. https://doi.org/10.1016/j.crci.2013.06.002.

(23) Kategaonkar, A. H.; Sonar, S. S.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. Ionic Liquid Catalyzed Multicomponent Synthesis of 3,4-Dihydro-3-Substituted-2H-Naphtho[2,1-e][1,3]Oxazine Derivatives. *Org. Commun.***2010**, *3* (1), 1–7.

(24) Lei, M.; Zhan, Z.; Tian, W.; Lu, P. One-Pot, Three-Component Synthesis of Highly Functionalized 1,3-Oxazine Derivatives from α,ß-Unsaturated Imine, Alkyne, and Aldehyde. *Tetrahedron***2012**, *68* (16), 3361–3367. https://doi.org/10.1016/j.tet.2012.02.041.

(25) Sadaphal, S. A.; Sonar, S. S.; Shingate, B. B.; Shingare, M. S. Water Mediated Synthesis of Various [1,3]Oxazine Compounds Using Alum as a Catalyst. *Green Chem. Lett. Rev.***2010**, *3* (3), 213–216. https://doi.org/10.1080/17518251003709522.