Academic Science Journal

Synthesis and Pharmacological Significance of Isoxazoline Derivatives: A Mini review

Nihad Kh. Ibrahim, Wijdan Amer Ibrahim and Mohammed Alwan Farhan*

Chemistry Department – College of Science – Diyala University

Alshamary_198840@yahoo.com

Received: 10 February 2023 **Accepted: 18 April 2023**

DOI: https://doi.org/10.24237/ASJ.02.01.742C

Abstract

Five-membered cyclic compound that contains (C=N–O) bond, like isoxazoline having bioorganic and pharmacological importance is considered as useful transformation intermediate to a large number of bioactive molecules. It is well known from scientific literatures that this class of hetero-compounds has biological activities. So, this discussed the synthetic methods of these building blocks targeting bioactive molecule containing isoxazoline ring with advanced and varied medical applications. A large number of research and review studies describe new synthesis pathways of isoxazolines derivatives would represent a promising matrix for the further development of the isoxazoline core which could be a leading core for future developments to obtain safer and more effective therapies.

Keywords: Heterocyclic compounds, Isoxazoline, Biological activities, Anticancer activity, Antioxidant activity.

Academic Science Journal

تحضير ودراسة الاهمية الدوائية لمشتقات Isoxazoline : مقالة مراجعة

نهاد خليل ابراهيم، وجدان عامر إبراهيم ومحمد علوان فرحان

قسم الكيمياء- كلية العلوم – جامعة ديالى – العراق

الخلاصة

المركبات الحلقية الخماسية الغير متجانسة الحاوية على الاصرة (C=N–O) مثل الايزوكسازولين تمتلك العديد من الصفات العضوية الحيوية والصيدلانية. كما أنها تعتبر مركبات وسطية مهمة في الكيمياء العضوية. من خلال الدراسات العلمية فانه من المعروف ان هذا النوع من المركبات غير المتجانسة له العديد من الفعاليات البيولوجية. لذلك في هذه المقالة، تمت مراجعة العديد من طرق ومسارات التصنيع لهذه الجزيئات التركيبية نحو أنظمة فعالة حيويا تمتلك تطبيقات طبية متقدمة ومتنوعة. وصفت الكثير من الدراسات البحثية ومقالات المراجعة مسارات تحضير مشتقات الايزوكسازولين والتي تمثل مصفوفة متنوعة اتجاه تطور هذا القالب المهم وتقود هذا المركز الى تحديثات مستقبلية نحو الحصول على معالجات آمنة واكثر فعالية.

الكلمات المفتاحية: المركبات الحلقية الغير متجانسة ، الايزوكسازولين، الفعالية البيولوجية، الفعالية المضادة للسرطان، الفعالية المضادة للأكسدة.

Introduction

Isoxazolines in medicinal chemistry are synthetic and natural occurrence compounds (Figures 1&2). They have pharmacological treatments role in the treatment of some conditions like inflammatory, cancer, bacterial, fungal, parasitic, Alzheimer, insecticidal and diabetic [1- 6].

Academic Science Journal

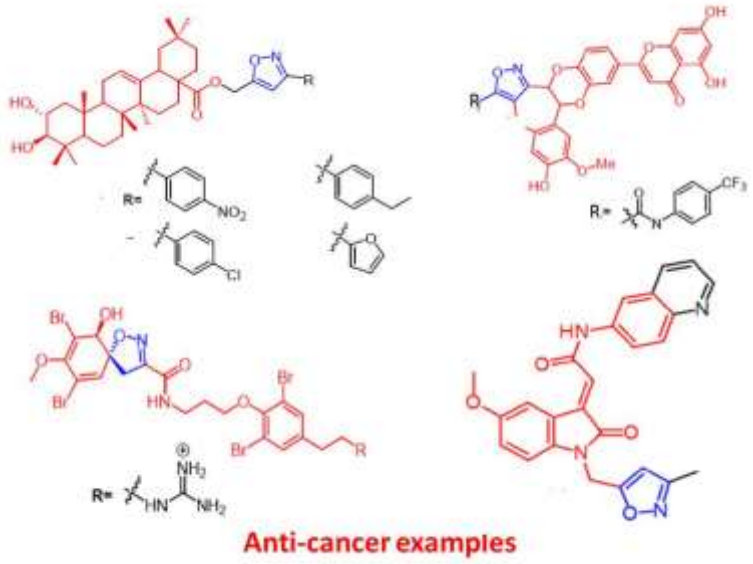


Figure 1: Isoxazoline derivatives with anti- cancer activity [6].

In research field, 1,3-dipole cycloaddition reactions generate derivatives containing this moiety even with modification of natural products. These hetero (Nitrogen and Oxygen) partially saturated compounds with electron-rich structural candidates are

of particular intermediates. These unique architectureded compounds have a high affinity binding with complementary receptors that assisted target therapeutic applications.

Academic Science Journal

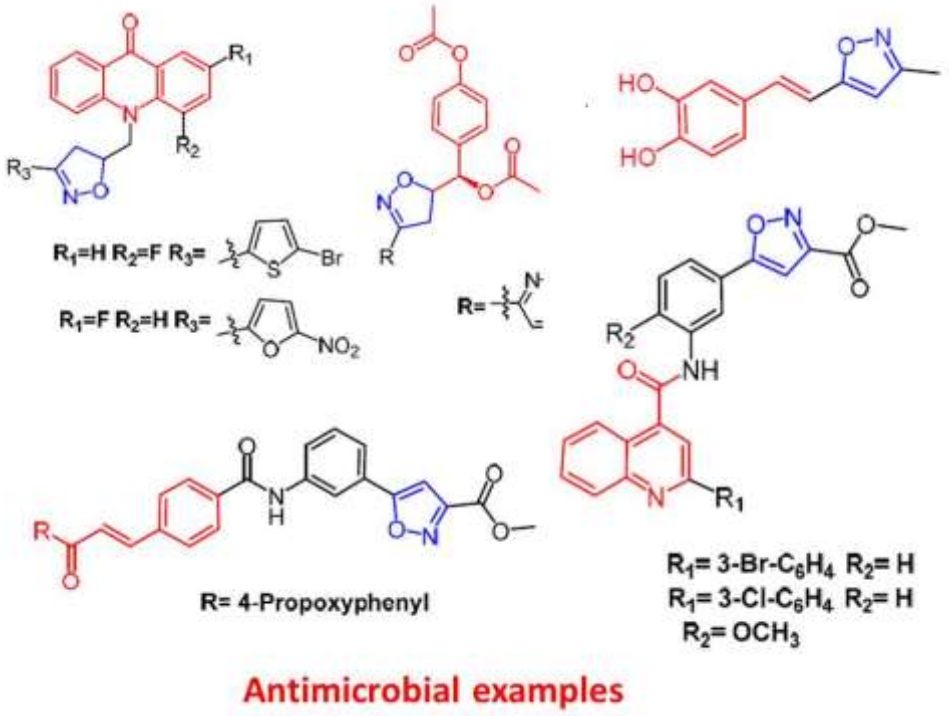


Figure 2. Antimicrobial examples having isoxazoline moiety [6].

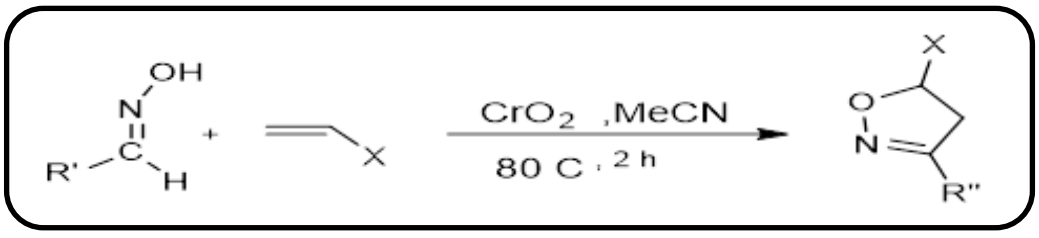
Natural isoxazoline backbone exhibits remarkable activity that is demonstrated by number of studies. However, natural components extraction, isolation then modification pointed direct usage for trial reports and clinical treatment with high pharmacological activity and physicochemical properties where their biological activity reduces side effects and improves selectivity [1,3],[7-11].

A highly appreciable number of five-membered heterocycles, containing nitrogen - oxygen bond compounds have turned out to be potential chemo- and pharmaco- therapeutic agents. Synthetic analogs of this hetero nucleus with therapeutic properties can be obtained through of lead compound relationship. Isoxazolines derivatives like other cyclic compounds systems show cis-trans structural isomerism where four stereoisomers are possible for isoxazolines containing identical substituents at C3 and C5 positions. These are the two *cis*- and two *trans*-forms [12].

A lot of modifications Were added to isoxazoline molecules during the last few years, and chemical and biological activities of these derivatives were studied during the last few years on isoxazoline molecules and chemical and biological activities of these derivatives have been studied. Isoxazoline derivatives were converted into different classes of heterocyclic molecules with different types of potential biological activities including antimicrobial, antiinflammatory, fibrinogen receptor and glycoprotein receptor antagonist, anticancer, anti-HIV, and antidepressant activities beside insecticidal, antibiotic, anti-tumor, anti-tuberculosis and ulcerogenic properties [11]. Because of these applicable importance, this study aimed to cover more important synthetic approaches to isoxazoline derivatives and their reactivities to increase researchers interesting of this scaffold in organic synthesis.

Summary of synthesis methods:

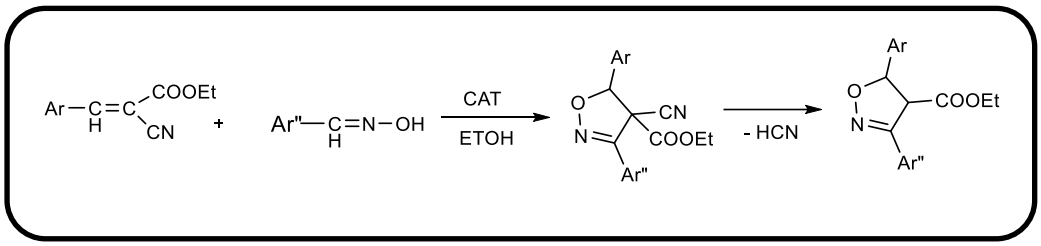
a. Quilico experiment: The reaction of Nitrile oxides with unsaturated compounds is the first path of isoxazole chemistry [13].
b. Huisgen cycloaddition: Nitrile oxides introduced in this synthetic method of isoxazolines as an example of 1,3-dipolar cycloaddition reactions [14,15]. The, alkene reacts with nitrile oxide in situ mechanism in moderate yields (Scheme - 1). The method has proven to be just as versatile for intramolecular nitrile oxide cycloaddition reactions [16].



Scheme 1: Efficient synthesis of the target heterocycles from aldoximes using Magtrieve (CrO_2)

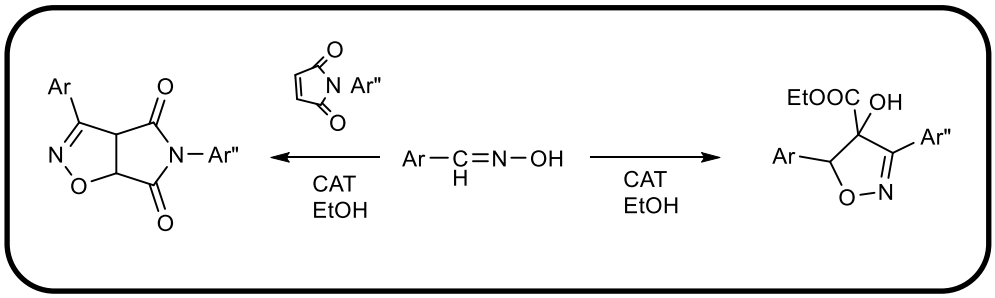
c. Oxidative dehydrogenation of aldoxims:, The nitrile where reacted with unsaturated ester substituted with nitrile group to produce ethyl 3,5-diarylisoxazole-4-carboxylates. It was

observed that peculiar reaction conditions were done for careful removal of HCN from their predicted cycloaddition reaction (CAT) isoxazolines[17]. (Scheme-2)



Scheme 2: Synthesis of cycloaddition isoxazolecompined by HCN removal.

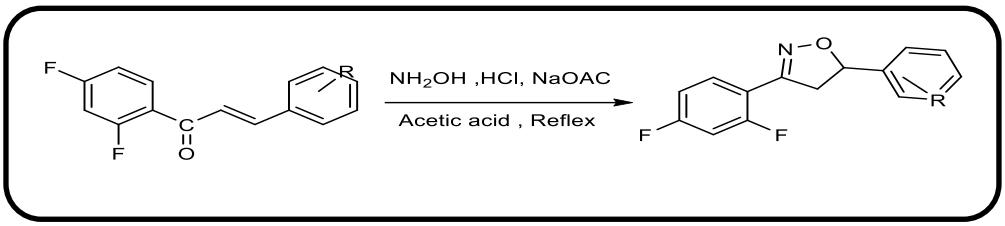
Scheme - 3 is a good example of 1,3-dipolar cycloaddition of N-aryl maleimides towards a series 3-Aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,8-dihydroisooxazolines via a dipolarophile to obtained the substituted isoxazolines in a good yield[18].



Scheme 3: Isoxazoles synthesis via 1,3-dipolar cycloaddition.

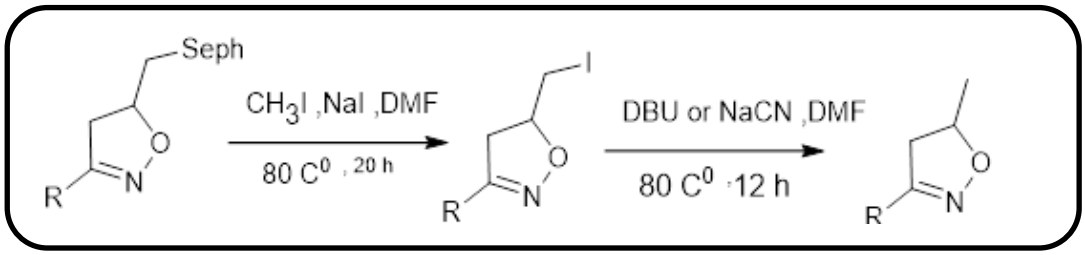
d. Condensation reaction: Three component condensation reaction in free solvent - basic medium is considered a favored path like synthesis of 4-Arylidene-3-phenylisoxazol-5-ones via combination of aromatic aldehyde in the same reaction vessel with ethyl benzoylacetate, hydroxylamine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) under reflux condition [19] .

Fluorinated chalcones condensation with hydroxylamine in acidic medium was another example of isoxazoline preparation under reflux conditions (Scheme-4). The evaluation of the final products in bacterial resistance section showed a good activity where fluorine presence altered valuable stability and lipophilicity characters towards good biological activity [20].



Scheme 4: Condensation reaction towards fluorinated derivatives

e. deselenenylation reaction: Wei Ming *et. al.* presented another isoxazoline derivatives functionalized by 3, 5 – substitution sites where aromatic selenide of isoxazoline derivative produced their substituted isoxazoles (Scheme-5) in basic medium [21].

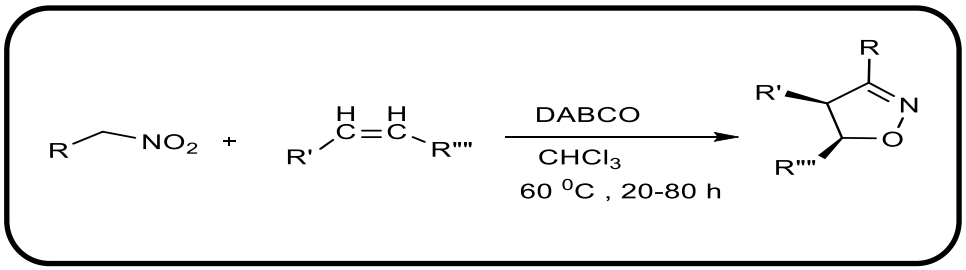


Scheme 5: Deselenenylation reaction to synthesis of disubstituted isoxazole and isoxazoline with use of 1,5-diazabicyclo [5,4,0]-undec-5-ene (DBU) or NaCN as a base under reflux condition.

f. One-step regioselective - 1,3-dipolar cycloaddition reaction: A quick, efficient and easily One-step regioselective - 1,3-dipolar cycloaddition reaction was performed to prepare 5-aminoisoxazoles using nitrile oxides and α-cyanoenamines (Scheme-6) [22].

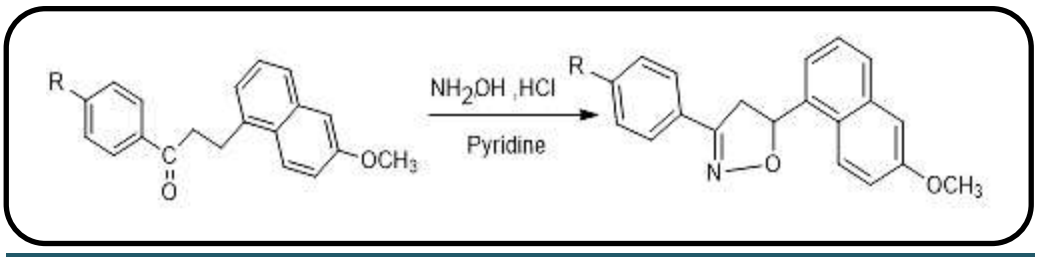
Scheme 6: One step synthesis of 5-aminoisoxazoles via 1,3-dipolar cycloaddition.

g. Dehydration reaction of primary nitro compound: In the reaction mixture aldoxims with 4-methoxy cinnamonitrile provided 1,3-Dipolar cycloaddition reaction converted to isoxazolines where dipolar primary nitrophiles (nitro compound) with 1,4-diazabicyclo[2.2.2]octane (DABCO) base presence. The reaction of activated nitro compounds affords isoxazoline in excellent yields compared to other methods (Scheme-7) where nitro alkanes have low reactivity [23]



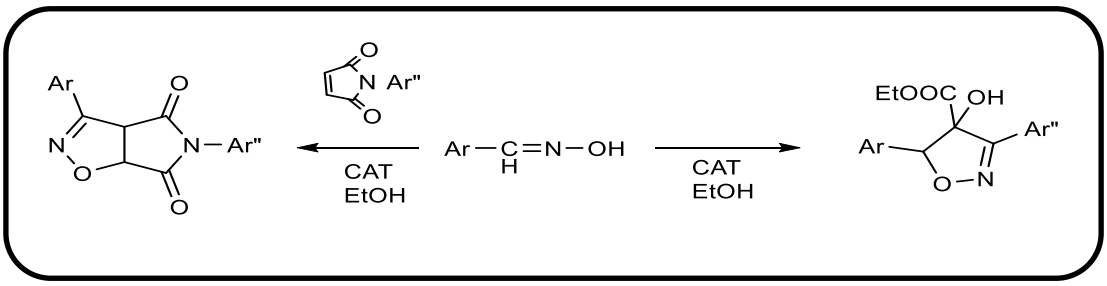
Scheme 7: Preparation of phenylisoxazol-5-one derivatives.

By returning to chalcone reaction, many isoxazoline derivatives were synthesized with fast reaction with hydroxylamine.HCl- NaOH mixture. Mannich bases and substituted primary amines (hydroxylamine. HCl) were reacted with substituted phenyl ketone under reflux conditions to produce a series of substituted methoxynaphthalene) -2-isoxazolines (Scheme 8) having a significant to moderate antimicrobial activity. [24]



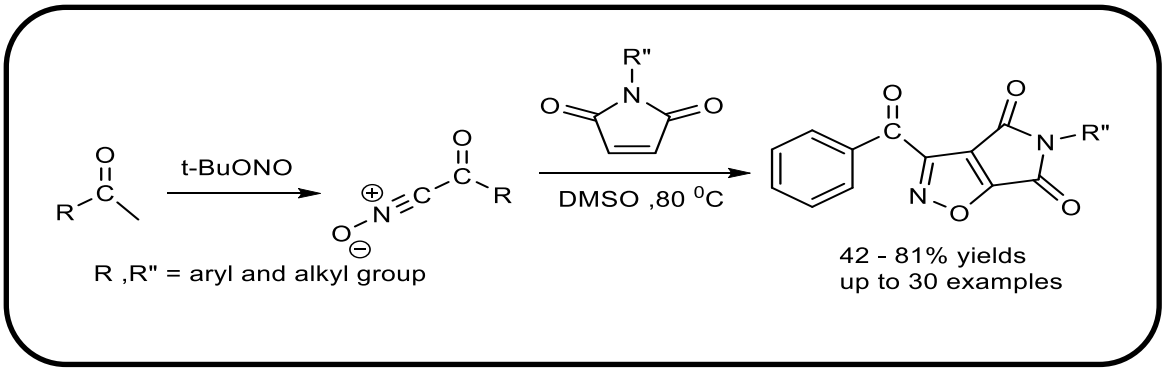
Scheme 8: Synthesis of some novel Mannich bases of isoxazolines.

The prepared cyclic nitrile oxide (or substituted isoxazolines) like Pyrrolo[3,4-d]-7,8-dihydroisooxazolines via in situ 1,3-dipolar cycloaddition of N-aryl maleimides were introduced in reaction with acetyl acetone towards novel pyroazolines with same mechanism of reaction (Scheme – 9) [25].



Scheme 9: Some novel pyrazoline- isoxazolines by 1, 3 cycloaddition (CAT) of N- aryl imides.

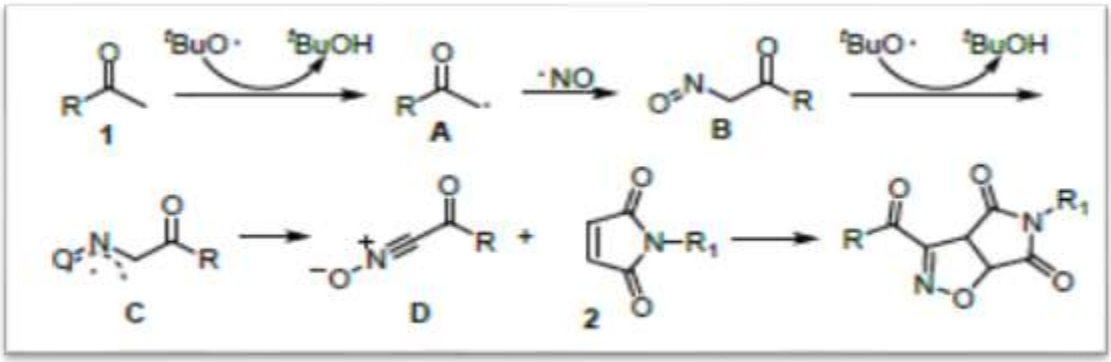
h. Cycloaddition of ketone, O- alkyl nitrite and maleimide (1,3-dipolar cycloaddition reaction) (Scheme 10): An effective approach in the subject of isoxazole and isoxazoline derivatives were constructed by nitrile oxides, alkynes or alkenes bound to a resin and performed on solid supports bonded (Ar) or (alkyl) building blocks with some limitations in structural diversity[26]. Also, substituted pyrrolo [3,4-d] isoxazolines have been synthesized with absence of metallic catalyst [27].



Scheme 10: One-pot radical - cycloaddition of alkyl ketone by tert-Butyl nitrite (t-BuONO), and N- substituted maleimide

Mechanism of this constructed reaction (Scheme -11) was confirmed by X-rays crystallography, and it was the generation of tert-Butyl nitrite (t-BuO) radical from tert-butyl nitrite, subtraction of methyl hydrogen in methyl ketone, providing a radical (A) centered at carbon atom, attacking of NO radical to radical carbon and producing nitrosoketone (B), then reacting with t-BuO radical presented acyl nitrile oxide (D).

This mechanism ended by 1,3-dipolar cycloaddition of (D) and N- substituted maleimide towards pyrrolo[3,4- d]isoxazoline product. DMSO as a good solvent and abstracter hydrogen atom that required lower energy compared to t-BuO radical [28].



Scheme 11: Mechanism details of hydrogen abstraction – cycloaddtion towards pyrrolo[3,4-d]isoxazolines.

i. Three-Component 1,3-Dipolar Cycloaddition by Spirooxindole-Fused with Triazole: Acetophenone reaction with aryl nitrile and aryl azide yielded isoxazoline and isoxazole cycles combined by spiro-oxindoles or triazole using Cu (I) as a catalyst. X-rays diffraction verified the regiochemistry and stereochemistry while various antibacterial and antifungal testing confirmed biological behavior of the resulted derivatives compared to conventional medicines [29].

Discovering and development of antimicrobial agents are goals of scientific community now days with high ability to resist known infections through multi-step, multi-components, one -pot and combinational chemistry [30] towards effective therapies [31]. These powerful tools in

organic and medicinal chemistry [32] are targeting simplicity in reaction conditions and economy especially in N-heterocyclic synthesis with high regio – stereo selectivity, environmental mode, time and yield.

Pharmacological effect of isoxazoline and its derivatives

A new series of phenol – isoxazolines derivatives was synthesized and their analgesic effects were testing [33], Figure 3.

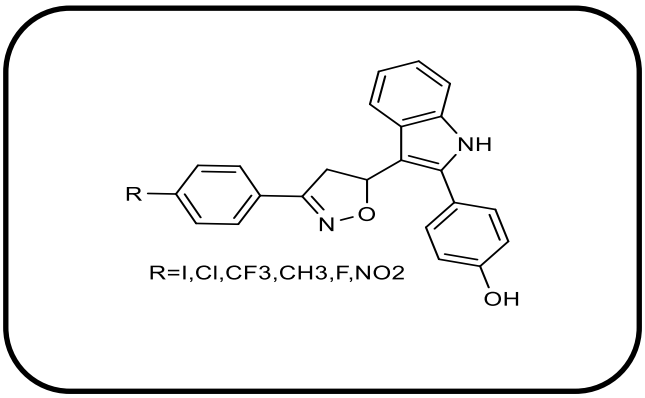


Figure 3: Indole derivatives linked to isoxazole moiety.

New dibenzoazepine isoxazoline with Dibenzoazepine cycle was synthesized, characterized by 2D NMR, then their biological inhibition or resistance effects were compared to cisplatin and suramin in murine osteosarcoma cells (LM8G7), human ovarian cancer cells (OVSAHO) breast cancer cells (MCF-7), and Myeloma cells (RPMI8226-LR5) [34], Figure 4.

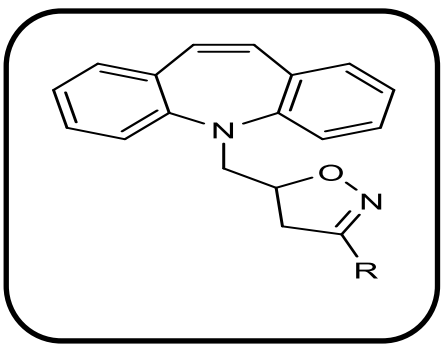


Figure 4: Chemical structure of dibenzo[b,f]azepine – N- linked isoxazoline derivatives.

1,3-dipolar cycloaddition was the applied path in generation of lactone linked to isoxazoline or isoxazolidine ring and their anticancer activity of these novel spiro derivatives related to prostate cancer cell (PC-3) and MCF-7 cell lines were evaluated with (0.01- 0.3) mM [35], Figure 5.

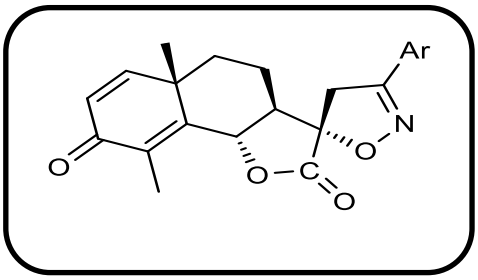


Figure 5: Spiro-isoxazoline derivatives having good anticancer activity.

Nikam research team [36] synthesized a series of isoxazolines by applying sonochemistry field, starting from chalcones. The *in vitro* microbial behaviors, molecular docking and antioxidant of these isoxazolines with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) were performed, Figure 6.

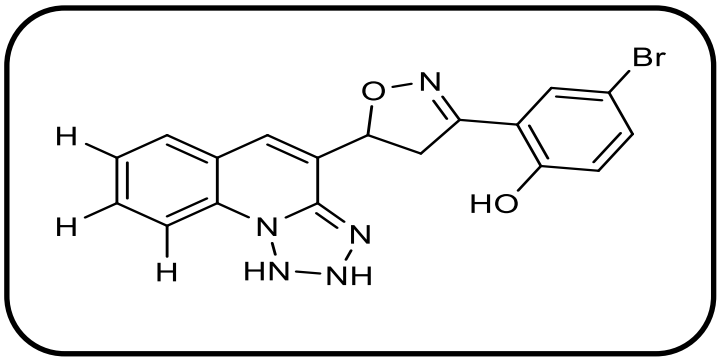


Figure 6: Strucuture of isoxazoline derivatived from chalcone.

Isoxazoline derivatives based on chalcones were prepared from substituted benzaldehyde and substituted acetophenone, condensed with $NH_2OH.HCl$ then selected to evaluate *in vitro*

antibacterial studies against (*S. aureus, B. subtilis,, E. coli* and *P. aureginosa*) and antioxidant - DPPH radical scavenging [37], Figure 7.

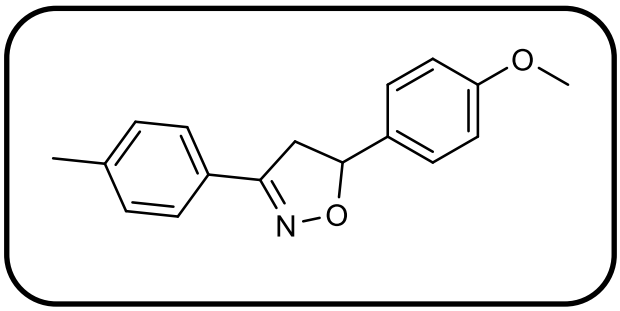


Figure 7: New Indolo[3,2-c]isoquinoline having very good activity against *P. aeruginosa*.

Thirty isoxazoline derivatives including 3,5-substituted-4,5-dihydroisoxazoline and 3,5-substituted aryl-4,5-dihydroisoxazoline were prepared by H_2SO_4 catalyzed cyclization of hydroxylamine hydrochloride and aryl chalcones under solvent-free conditions. The antimicrobial, antioxidant and insecticidal activities of the synthesized isoxazolines were evaluated [38].

Synthesis of new heterocyclic fluorene – Isoxazoline derivatives were made up from 2-acetyl fluorene with aromatic aldehyde in basic medium (NaOH) [39], Figure 8. These prepared derivatives can be suggested as building blocks of pharmaceuticals, thermosetting plastics, lubricants and unusual optical or electrical materials such as organic light-emitting diodes, solar cells and flat panel.

Academic Science Journal

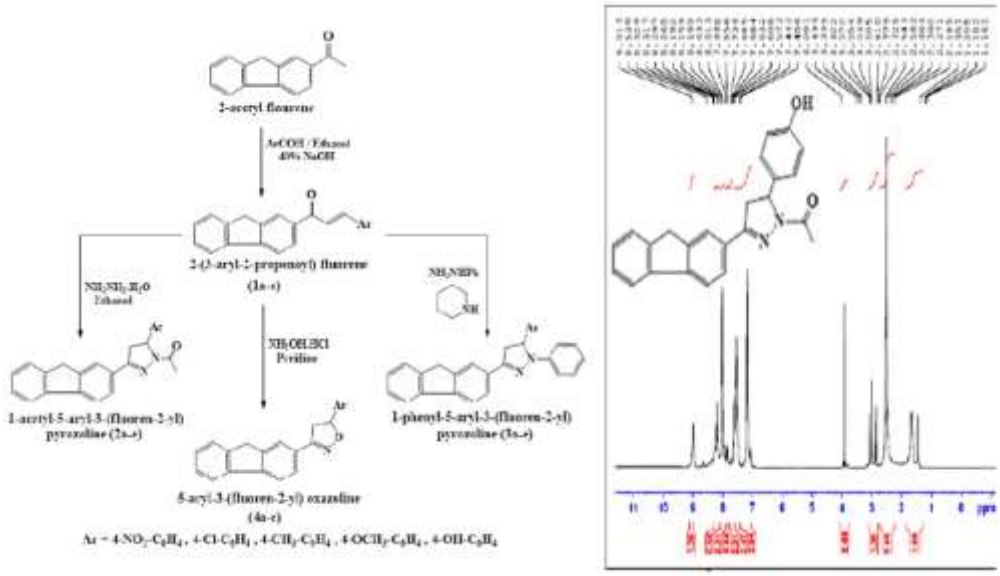


Figure 8: New fluorene – Isoxazoline derivatives starting from Claisen-Schmidt condensation.

New quinazolinone– isoxazoline hybrids were targeted compounds via 1,3-dipolar cycloaddition of aromatic nitrile oxides and quinazolinones with no effect of phenyl ring substituents through experimental and theoretical (Density Functional Theory (DFT)) studies [40], Figure 9. These studied can be with further investigation as new drug candidates in fungal, bacterial, tubercular, malarial and SARS-CoV-2 subjects.

Academic Science Journal

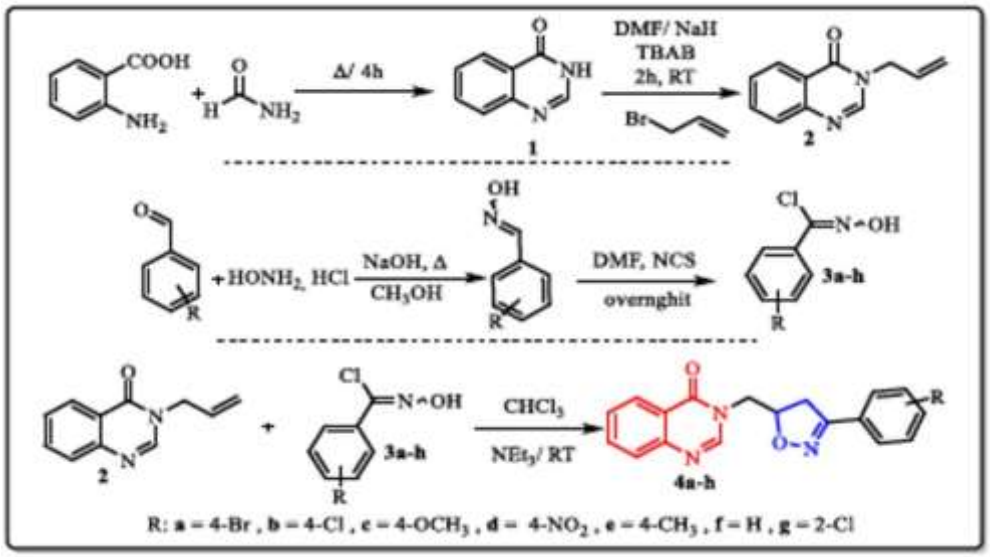


Figure 9: New quinazolinone– isoxazoline hybrids preparation pathways starting from anthanilic acid.

For human use, many isoxazolines were structural drug administrated for specific treatment such as Oxacillin that defines as semi-synthetic antibacterial related to penicillin (Figure 10). Clinical studies of available isoxazolines such as Afoxolaner, Sarolaner and others had been reported as veterinarian options like demodicosis treatment of dog and cat or other treatment with successful use after Food and Drug Administration (FDA) approval [41-43], Figure 11.

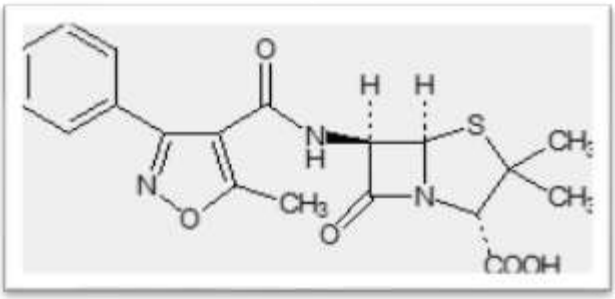


Figure 10: Oxacillin as semi-synthetic antibacterial related to penicillin contains isoxazolines moiety.

Academic Science Journal

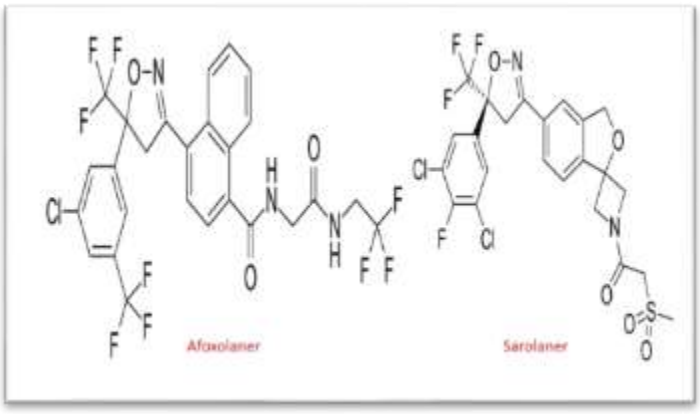


Figure 11: Isoxazoline derivatives for flea prevention and treatment.

Conclusion

Isoxazoline derivatives are building blocks in organic synthesis for a number cyclic and acyclic heterocyclic materials can be obtained according to cyclization and rearrangement. Isoxazoline chemistry remains a unique model associated with various pharmacological activities. They represent a great interest to the research community for further development for safer and more effective therapeutics.

Acknowledgements

The authors wish to thank Department of Chemistry, College of Science, University of Diyala, Iraq, for supporting this work.

References

1. K. Kaur, V. Kumar, A. Sharma, G. Gupta, Eur. J. Med. Chem. 77, 121–133 (2014)
2. T. Zhang, M. Dong, J. Zhao, X. Zhang, X. Mei, J. Pestic. Sci. 44, 181–185 (2019)
3. P. Patil, A. Thakur, A. Sharma, S. Flora, Drug Dev. Res. 81, 165–183 (2020)
4. M. Aarjane, S. Slassi, A. Ghaleb, B. Tazi, A. Amine, Arabian J. Chem. 14, 103057 (2021)
5. G. Kumar, R. Shankar, Chemmedchem 16, 430–447 (2021)

6. X. Wang, Q. Hu, H. Tang, X. Pan, Pharmaceu. 16, 228 (2023)

7. Y. Guo, Q. Zhang, Z. Liu, C. Bao, J. Fan, R. Yang, Ind. Crops Prod. 140, 111706 (2019)

8. H. Xu, K. Zhang, M. Lv, M. Hao, J. Agric. Food Chem. 69, 8098–8109 (2021)

9. Z. Liu, M. Han, X. Yan, W. Cheng, Z. Tang, L. Cui, R. Yang, Y. Guo, J. Agric. Food Chem. 70, 7921–7928 (2022)

10. A. Oubella, A. Taia, S. Byadi, M. Lahcen, A. Bimoussa, M. Essaber, C. Podlipnik, H. Morjani, M. Itto, A. Aatif, J. Biomol. Struct. Dyn. 40, 1–13 (2022).

11. A. Phanumartwiwath, C. Kesornpun, S. Sureram, P. Hongmanee, P. Pungpo, P. Kamsri, A. Punkvang, C. Eurtivong, P. Kittakoop, S. Ruchirawat, J. Chem. Res. 45, 1003–1015 (2021)

12. D. Patil, M. Chincholkar, and N. Dighade, Asian J. Chem.,15, 1, 450 (2003)

13. K. Kumar and P. Jayaroopa, Int. J. Pharm. Chem. Biol. Sci, 3, 294–304 (2013)

14. A. Quilico, G. Alcontres, and P. Grünanger, Nature, 166, 4214, 226–227, (1950)

15. K. Kumar, M. Govindaraju, N. Renuka, and G. Vasanth Kumar, J. Chem. Pharm. Res., 7, 3, 250–257 (2015)

16. S. Bhosale, S. Kurhade, U. Prasad, V. Palle, and D. Bhuniya, Tetrahedron Lett., 50, 27, 3948–3951 (2009)

17. V. Govindappa, J. Prabhashankar, B. Khatoon, M. Nigappa, and A. Kariyappa, Der Pharma Chem., 4, 6, 2283–2287 (2012)

18. K. Umesha, K. Ajay Kumar, and K. Lokanatha Rai, Synth. Commun., 32, 12, 1841–1846 (2002)

19. A. Kumar and P. Jayaroopa, Int. J. Pharm. Chem. Biol. Sci., 3, 2, 294–304 (2013)

20. V. Kadnor, G. Pandhare, A. Gadhave, and B. Uphade, Rasayan J. Chem.,4, 2, 437–441 (2011)

21. G. Wang, Z. Chen, and X. Huang, Chinese Chem. Lett., 16, 8, 995 (2005)

22. A. Saad, M. Vaultier, and A. Derdour, Molecules, 9, 7, 527–534, (2004)

23. M. Mirzazadeh and G. Mahdavinia, E-Journal Chem., 9, 1, 425–429 (2012)

24. S. Gosavi, D. Nandal, and S. Pawar, Asian J. Chem., 31,12, 1760–1772 (2019)

25. N. Shah, A. Biradar, S. Habib, J. Dhole, M. Baseer, and P. Kulkarni, Der Pharma Chem., 3, 1, 167–171 (2011)

26. S. Dadiboyena and A. Nefzi, Tetrahedron Lett., 53, 16, 2096–2099, (2012)

27. H. Wang, R. Cheng , G. Wang, Y. Shi, J. Wang, H. Guo, L. Trigoura, Y. Xing, S. sun, Tetrahedron Lett., 61, 12, 151652 (2020)

28. Y. Lin, K. Zhang, M. Gao, Z. Jiang, J. Liu, Y. Ma, H. Wang, Org. Biomol. Chem., 17, 22, 5509–5513 (2019)

29. R. Sakly, H. Edziri, M. Askri, M. Knorr, K. Louven, C. Strohmann, M. Mastouri, J. Heterocycl. Chem., 54, 6, 3554–3564 (2017)

30. K. Kaur, M. Jain, R. Reddy, and R. Jain, Eur. J. Med. Chem., 45, 8, 3245–3264 (2010)

31. D. Mungra, M. Patel, D. Rajani, and R. Patel, Eur. J. Med. Chem., 46, 9, 4192–4200 (2011)

32. H. Pellissier, Chem. Rev., 113, 1, 442–524 (2013)

33. E. Dilli, M. Mastan, and T. Sobha, Der Pharm. Lett., 4, 5, 1431–1437 (2012)

34. M. Panchegowda, S. Nanjunda, K. Aryan, M. Sengottuvelan, D. Shivaramu, N. Chikkagundagal, G. Sethi, K. Sugahara, K. Subbegowda, BMC Chem. Biol., 12, (2012)

35. J. Khazir, P. Pal, D. Mahendhar, I. Hyder, S. Shafi, S. Sawant, G. Chashoo, A. Mahajan, M. Alam, A. Saxena, S. Arvinda, B. Gupta, H. Sampath Eur. J. Med. Chem., 63, 279–289 (2013)

36. M. Nikam, P. Mahajan, M. Damale, J. Sangshetti, S.. Dabhade, D. Shinde & C. Gill, Med. Chem. Res., 24, 9, 3372–3386, (2015)

37. V. Verma, Russ. J. Gen. Chem., 88, 12, 2628–2645 (2018)

38. K. Chikkula, Int. J. Pharm. Pharm. Sci., 9, 7, 13 (2017)

39. R. Dawood, K. Ahmed, Tikrit J. Pure Sci. 20, 2, 121- 127 (2015)

40. Y. Rhazi, M. Chalkha, A. Nakkabi, I. Hammoudan, M. Akhazzane, M. Bakhouch, S. Chtita, M. El Yazidi, Chem. 4, 969–982 (2022)

41. X. Zhou, A. Hohman, W. Hsu, J. Am. Vet. Med. Assoc. 256, 1342–1346 (2020)

42. V. Palmieri,| W. Dodds, J. Morgan, E. Carney, H. Fritsche, J. Jeffrey, R. Bullock, J. Kimball, Vet Med Sci. 6, 933–945(2020)

43. X. Zhou, A. Hohman, W. Hsu, J. Vet. Pharmacol. Therap. 45, 1–15 (2022)