

Development of Substituted Dihydroisoxazoles as Potential Antioxidant Agents

Atish Babanrao Gajbhiye

Research centre, Department of Chemistry G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati

M.M. Kodape

Department of Chemistry, Sant, Gadge Baba Amravati University, Amravati

N.D. Gawhale

Department of Chemistry G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati

Abstract

Dihydroisoxazoles represent a versatile class of heterocyclic compounds with diverse biological properties, including significant antioxidant potential. In this study, a series of substituted dihydroisoxazoles were designed and synthesized using efficient and reproducible synthetic methodologies. The structures of the synthesized compounds were confirmed through spectroscopic techniques such as NMR, IR, and mass spectrometry. The antioxidant potential of these compounds was evaluated using standard in vitro assays, including DPPH radical scavenging and ABTS assays. Several derivatives exhibited notable antioxidant activity, indicating that specific substituents on the dihydroisoxazole scaffold enhance free radical scavenging ability. Structure-activity relationship (SAR) analysis suggested that the position and nature of substituents significantly influence antioxidant efficacy. These findings highlight substituted dihydroisoxazoles as promising scaffolds for the development of novel antioxidant agents and provide valuable insights for future drug discovery efforts targeting oxidative stress-related disorders.

Keywords: Dihydroisoxazoles, Antioxidant Activity, Free Radical Scavenging, Biological Evaluation

Introduction

In addition to the carbon framework, heterocyclic compounds are a class of cyclic organic molecules that contain heteroatoms such as nitrogen, sulfur, oxygen, etc. Heterocyclic compounds are used to treat a wide range of illnesses because of their varied pharmacological properties. The heterocyclic ring is the primary structural element of the majority of the medicinal drugs used in modern medicine. Nitrogen-containing heterocyclic rings stand out among these chemicals due to their broad distribution, biological characteristics, and simplicity of synthesis. Chalcones are open-chain flavonoids with two aryl rings joined to the reactive propenone linker. Chalcones and nitrogen-containing heterocycles, such as isoxazoles and dihydropyrazoles, have a wide range of biological activities, including antimicrobial, antioxidant, anticancer, antimalarial, antidepressant, antihistaminic, antitubercular, and anti-inflammatory properties, according to a review of the literature [1-22].

Therapeutic drugs such as β -lactam antibiotics, cloxacillin and dicloxacillin, sulfisoxazole and sulfamethoxazole (antibacterials), valdecoxib (selective COX-II inhibitor), and leflunomide (an immunosuppressive disease-modifying antirheumatic drug [DMARD]) contain isoxazole, a five-membered heterocyclic ring. The antifungal drug drazoxolon and the antitubercular antibiotic cycloserine both contain the fully reduced form of isoxazole, or isoxazoline and isoxazolidine scaffolds, respectively. Another intriguing heterocyclic molecule is dihydropyrazole, which has two nitrogen atoms in close proximity to a five-membered ring. By interacting with various hydrazines, this ring can be easily created from α , β -unsaturated carbonyl compounds. Drugs such as Ibipinabant (anti-obesity cannabinoid receptor type 1 (CB1) antagonist), Antipyrine, Aminopyrine, Ramifenazone, and Dipyrone (analgesics), and Muzolimine (diuretic) all include the dihydropyrazole or its oxo derivative scaffold.

Because of their deep biological action, different azoles are desirable building blocks for the creation of new anti-oxidant agents that target diseases of therapeutic importance. In light of this, the purpose of this article is to synthesize a number of 5-(1H-benzo[d]imidazol-5-yl)-Substituted 3-phenyl-4,5-dihydroisoxazole derivatives and assess their antioxidant qualities.

Material and Methods

All chemicals used in the experiments were of analytical reagent (AR) grade. Analytical thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 aluminium sheets. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in CDCl_3 on a 500 MHz spectrometer with tetramethylsilane (TMS) serving as the internal standard.

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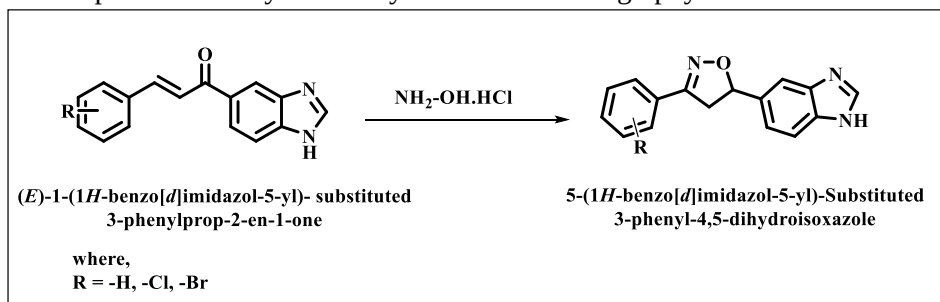
Characterization Techniques

The structure of synthesized compounds was determined by chemical properties elemental analysis and spectral data. ¹H-NMR spectra were recorded on Bruker Avance Neo 500 MHz spectrometer using CDCl₃ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatogram.

Experimental

General Reaction for Synthesis of substituted Dihydrisoxazoles

Well proportioned reaction mixture of substituted chalcones in presence of catalyst and in solvent at suitable temperature for suitable time will be refluxed. The reaction is monitored by TLC. The product is recrystallised by column chromatography.



Scheme 1.

General Reaction for Synthesis of 5-(1H-benzo[d]imidazol-5-yl)-Substituted 3-phenyl-4,5-dihydroisoxazole

Table 1. Scope of Synthesis of substituted diazoles

Sr. No	Substrate	Reagent	Product	Time in Hrs.	Yield
1		NH ₂ OH.HCl I		8	76
2		NH ₂ OH.HCl I		8	82
3		NH ₂ OH.HCl I		8	87

Table 2. Structural Analysis

Sr. No	Structure of Products	Structural analysis by ¹ HNMR and GCMS
1		¹ HNMR(500MHz,CDCl ₃): δ 12.33 (s,1H), 8.15 (s,1H), 7.60-7.63 (m, 4H), 7.52 (m, 1H), 7.19 (m, 1H), 5.90 (s,1H), 3.82-3.56 (dd,2H) GCMS: Cal m/z:263.30, Found m/z: 263.26
2		¹ HNMR(500MHz,CDCl ₃): δ 12.35 (s,1H), 8.19 (s,1H), 7.61-7.65 (m, 5H), 7.54 (m, 1H), 7.21 (m, 1H), 5.94 (s,1H), 3.86-3.61 (dd,2H) GCMS: Cal m/z: 297.94 Found m/z:297.90
3		¹ HNMR(500MHz,CDCl ₃): δ 12.36 (s,1H), 8.18 (s,1H), 7.60-7.64 (m, 5H), 7.52 (m, 1H), 7.20 (m, 1H), 5.93 (s,1H), 3.85-3.60 (dd,2H) GCMS: Cal m/z:342.20, Found m/z: 342.18

Biological Investigation of 5-(1H-benzo[d]imidazol-5-yl)-Substituted 3-phenyl-4,5-dihydroisoxazole

Method: DPPH Free Radical Scavenging Assay

$$= \frac{(\%) \text{Free radical scavenging effect}}{\text{Absorbance of control (Ac)}} \times 100$$

$$= \frac{[\text{Absorbance of control (Ac)} - \text{Absorbance of sample (As)}]}{\text{Absorbance of control (Ac)}} \times 100$$

Conclusion

In present work, synthesized the series of 5-(1H-benzo[d]imidazol-5-yl)-Substituted 3-phenyl-4,5-dihydroisoxazole (a-c) structure is promising moiety that are able to shows the strong biological activity. Furthermore, the benzo ring inflection of the structure intentionally incorporation of chlorine (-Cl) and bromine (-Br) group over the ring. Which shows the promising and the strong anti-oxidant activities. As a conclusion, our results reveals and participate significantly to create a structural moiety and interactive relationship shows strong activity against microbes. Which is useful in drug design strategy in future.

Conflict of Interest: Authors have declared that no competing interests exist.

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References

1. Gibson, M.Z.; Nguyen, M.A.; Zingales, S.K. Design, synthesis and evaluation of (2-(Pyridinyl)methylene)-1-tetralone chalcones for Anticancer and Antimicrobial Activity. *Med. Chem.* 2018, 14, 333–343.
2. Gao, Z.; Hurst, W.J.; Czechtizky, W.; Hall, D.; Moindrot, N.; Nagorny, R.; Pichat, P.; Stefany, D.; Hendrix, J.A.; George, P.G. Identification and profiling of 3,5-dimethyl-isoxazole-4-carboxylic acid [2-methyl-4-((2S,30S)-2-methyl-[1,30]bipyrrolidinyl-10 -yl)phenyl] amide as histamine H(3) receptor antagonist for the treatment of depression. *Bioorg. Med. Chem. Lett.* 2013, 23, 6269–6273.
3. Afzal, B.S.; Lohitha, S.V.K.; Puttagunta, S.B.; Shaik, A.; Supraja, K.; Sai, H.K. Synthesis and screening of novel lipophilic diarylpropeones as prospective antitubercular, antibacterial and antifungal agents. *Biointerface Res. Appl. Chem.* 2019, 9, 3912–3918.
4. RamirezPrada, J.; Robledo, S.M.; Velez, I.D.; Crespo, M.D.P.; Quiroga, J.; Abonia, R.; Montoya, A.; Svetaz, L.; Zacchino, S.; Insuasty, B. Synthesis of novel quinoline-based 4,5-dihydro-1-H-pyrazoles as potential anticancer, antifungal, antibacterial, antiprotozoal agents. *Med. Chem.* 2017, 131, 237–254.
5. Sowmya, D.V.; Lakshmi Teja, A.; Padmaja, A.; Kamala Prasad, V.; Padmavathi, V. Green approach for the synthesis of thiophenyl pyrazoles and isoxazoles by adopting 1,3-dipolar cycloaddition methodology and their antimicrobial activity. *Eur. J. Med. Chem.* 2018, 143, 891–898. [CrossRef]
6. Chunlin, Z.; Wen, Z.; Chunquan, S.; Wannian, Z.; Chengguo, X.; Zhenyuan, M. Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev.* 2017, 117, 7762–7810.
7. Puja, J.; Dharam, P.P.; Himangini, B.; Uma, A. Chalcone and their Heterocyclic Analogue: A Review Article. *J. Chem. Pharm. Res.* 2018, 10, 160–173.
8. Ahmet, Ö.; Mehlika, D.A.; Belgin, S.; Hülya, K.G.; Handan, A.K.; Özlem, A.; Merve, B. A New Series of Pyrrole-Based Chalcones: Synthesis and Evaluation of Antimicrobial Activity, Cytotoxicity, and Genotoxicity. *Molecules* 2017, 22, 2112.
9. Pallepati, K.; Venkata, R.K.; Afzal, B.S. Antitubercular evaluation of isoxazole appended 1-carboxamido-4,5-dihydro-1H-pyrazoles. *J. Res. Pharm.* 2019, 23, 156–163.
10. Afzal, B.S.; Yejella, R.P.; Shaik, S. Design, Facile Synthesis, Characterization and Computational Evaluation of Novel Isobutylchalcones as Cytotoxic Agents: Part-A. *FABAD J. Pharm. Sci.* 2015, 40, 7–22.

11. Kishor, P.; Venkata, K.; Afzal, B.S. Antitubercular Evaluation of Isoxazolyl Chalcones. *RJPBCS* 2017, 8, 730–735.
12. Lokesh, B.V.S.; Prasad, Y.R.; Shaik, A.B. Novel pyrimidine derivatives from 2,5-dichloro-3-acetylthienyl chalcones as antifungal, antitubercular and cytotoxic agents: Design, synthesis, biological activity and docking study. *Asian J. Chem.* 2019, 19, 310–321.
13. Afzal, B.S.; Yejella, R.P.; Shaik, S. Synthesis, Antimicrobial, and Computational Evaluation of Novel Isobutylchalcones as Antimicrobial Agents. *Int. J. Med. Chem.* 2017, 2017, 1–14.
14. Lavanya, G.; Mallikarjunareddy, L.; Padmavathi, V.; Padmaja, A. Synthesis and antimicrobial activity of (1,4-phenylene)bis(arylsulfonylpyrazoles and isoxazoles). *Eur. J. Med. Chem.* 2014, 73, 187–194.
15. Abdelhamid, A.O.; EI Sayed, I.E.; Zaki, Y.H.; Hussein, A.M.; Mangoud, M.M.; Hosny, M.A. Utility of 5-(furan-2-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide in the synthesis of heterocyclic compounds with antimicrobial activity. *Biorg. Med. Chem.* 2019, 13, 48.
16. Hassan, S.Y. Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. *Molecules* 2013, 18, 2683–2711. [CrossRef]
17. Caliskan, B.; Sinoplu, E.; Ibis, K.; Akhan Guzelcan, E.; Cetin Ataly, R.; Banoglu, E. Synthesis and cellular bioactivities of novel isoxazole derivatives incorporating an arylpiperazine moiety as anticancer agents. *J. Enzyme Inhib. Med. Chem.* 2018, 33, 1352–1361.
18. Filali, I.; Romdhane, A.; Znati, M.; Jannet, H.B.; Bouajila, J. Synthesis of new harmine isoxazoles and evaluation of their potential anti-alzheimer, anti-inflammatory, and anticancer activities. *Med. Chem.* 2016, 12, 184–190.
19. Jiabing, W.; Lili, H.; Chanchan, C.; Ge, L.; Jingwen, X.; Mengya, S.; Qian, C.; Wulan, L.; Wenfei, H.; Peihong, Q.; et al. Design, synthesis and biological evaluation of chalcone analogues with novel dual antioxidant mechanisms as potential anti-ischemic stroke agents. *Acta Pharm. Sin. B* 2019, 9, 335–350.
20. Elfi, S.V.H.; Widiastuti, A.E.S. A green synthesis of chalcones as an antioxidant and anticancer. *IOP Conf. Ser. Mater. Sci. Eng.* 2018, 299, 012077.
21. Yesseny, A.V.M.; Maurico, E.O.; Diego, A.S.M.; Marcela, A.C.; Alejandra, P.V.; Elizabeth, S.; Marcela, R.; Susana, A.Z.; Carolina, M.; Claudia, T.; et al. Antimicrobial, Anti-Inflammatory and Antioxidant Activities of Polyoxygenated Chalcones. *J. Braz. Chem. Soc.* 2019, 30, 286–304.
22. Chandrabose, K.; Narayana, S.H.; Narayana, M.; Sakthivel, R.; Uma, V.; Elangovan, M.; Devarajan, K.; Piyush, T. Advances in chalcones with anticancer activities. *Recent Pat Anticancer Drug Discov.* 2015, 10, 97–115.