A MINI REVIEW ON ISOXAZOLE

Udayan Banik*, Kuntal Manna, Partha Sakha Ghosh, Manik Das
Department of Pharmacy, Tripura University (A Central University), Suryamaninagar-799022, Tripura, India

Keywords: Isoxazole, Chemistry, synthesis, biological activity

For Correspondence: Udayan Banik
Department of Pharmacy, Tripura University (A Central University), Suryamaninagar-799022, Tripura, India
E-mail: banik.udayan89@gmail.com

ABSTRACT

Wide range of biological activity of isoxazole makes it an important anchor in the field of medicinal chemistry. Already marketed drugs like Valdecoxib as COX-2 inhibitor, Cloxacillin and Dicloxacillin as beta lactamase resistant antibiotics having isoxazole core has been proven to be efficacious drugs in present respective disease scenario. Therefore synthesis and evaluation of isoxazole containing moiety with wider therapeutic consequences is a topic of interest for the medicinal chemist. This mini review enumerates the reported synthetic strategies to synthesize isoxazole and its major therapeutic fields exploited in the literature. Thereby it is expected that this review will be beneficial for the researchers working in the same.
INTRODUCTION
Isoxazole being an azole with an oxygen atom next to the nitrogen, exhibits broad spectrum of biological activity and also forms a part of various biodynamic agents [1]. The substituted isoxazoles are also considered to be important synthons due to their versatility towards chemical transformations to useful synthetic intermediates. Isoxazole derivatives show hypoglycemic, analgesic, anti-inflammatory, antifungal, anti-bacterial and HIV-inhibitory activities [2]. Synthesis of hybrid natural products has gained momentum in recent years. It is expected that combining features of more than one biologically active natural segment in a single molecule may result in pronounced pharmacological activity while retaining high diversity and biological relevance [3-5]. The naturally occurring antibiotic cycloserine [6], the monamine oxidase inhibitor isocarboxazide, isoxazole steroids, ibotenic acid, muscimol isolated from Amanita muscaria[7] and isoxazoline-5-ones, isolated from Legume seed [8], are potential isoxazole derivatives.

STRUCTURE AND NOMENCLATURE OF ISOXAZOLE
Isoxazoles (Fig. 1) are unsaturated aromatic heterocyclic compounds containing a ring with three carbon atoms, one oxygen atom and one nitrogen atom. The trivial name for the title five-membered fully unsaturated heterocycles as “isoxazole” was originally proposed by Hantszch as it was the isomer “oxazole” discovered first. The trivial name follows the Hantszch-Widman system of nomenclature: the prefix “iso” represents isomer, “oxa” represents the oxygen atom “aza” represents the nitrogen atom the suffix “ole” denotes the ring size as five-membered; altogether the derived name is “isoxazole” [9]. This name has been accepted in IUPAC and has been used in Chemical abstracts. In Chemical Abstracts, the other systematic name 1, 2-azole, is also used.

![Fig. 1](image)

CHEMISTRY OF ISOXAZOLE
The nitrogen hetero atom is more pronounced for electron withdrawing effect, while the oxygen atom is more pronounced for electron donating effect. As neutral molecules, isoxazoles undergo electrophilic substitution rather more readily at the position 4, than benzene. Effects of substituents can modify their behavior. Substituents at the position-5 apparently have more activating and deactivating effect than substituents at the position- 3. In natural product synthesis, isoxazoles are used as latent synthons, such as masked new heterocyclic rings, masked fused...
rings, masked aromatic rings and masked aldol and related moieties [10]. The capability of isoxazole undergoing reaction is diverse: protonation, quaternization, complexation, oxidation, reduction, carbanionic condensations, thermolysis, photolysis, transformations into other heterocyclic ring systems and reaction with electrophiles, nucleophiles and Grignard reagents [6].

**Fig:** 2 Isoxazole derivative having established pharmacological activity

**GENERAL METHODS OF SYNTHESIS OF ISOXAZOLES:**


**SCHEME 1**

2. 3-Alkyl, 5-aryl isoxazoles can be prepared from aryl cyclopropanes with NaNO₂ in CF₃COOH [12].
3. Solid phase synthesis of isoxazole derivative from Diaryl 1, 3-diketones can be carried out in presence of Hydroxylamine hydrochloride and Silica gel [13].

4. Reaction of various substituted acetophenones with diethyl oxalate in the presence of sodium ethoxide forms resulting 2, 4-diketo esters which on treatment with hydroxylamine hydrochloride furnishes substituted 3-isoxazole esters [14].

**PHARMACOLOGICAL ASPECTS OF ISOXAZOLE ANTI-CONVULSANT ACTIVITY**

The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry [15]. Many patients with epilepsy fail to experience adequate control of their seizures, despite the optimal use of available antiepileptic drugs. Other patients do so only at the expense of significant toxic side effects. In recent years it has been established that inhibitors of GABA transport and in particular astroglial uptake can act as anticonvulsant agents and several isoxazole derivative synthesised has been proven to be so [16]. Compound A shown in Fig. 11 is an example for this. Compound B is also a synthesised isoxazole derivative which affects the sodium channel to show its activity [17].
ANTI-CANCER ACTIVITY
The effects of curcumin and of its isoxazole analogue in breast cancer cell line and in its multidrug-resistant (MDR) variant were examined. The isoxazole analogue Compound A has shown more potent antitumor and molecular activities both in parental and in MDR tumor cells. Isoxazole derivatives produce significantly higher direct inhibition of the COX-2 catalytic activity than curcumin. The isoxazole derivatives proved better because of minimum metal chelation when compared to curcumin [18]. The compound B has been found highly effective against human tumor cell lines especially on renal cancer, CNS cancer cell and ovarian cancer cell lines [19]. Recently NO-NSAID has been established as potent anti-cancer agents rather than their anti-inflammatory property [20]. Compound C is a NO donating compound used as anti-cancer agent.

ANTI-MICROBIAL ACTIVITY
Drazoxolon is a commonly used fungicidal agent. Acetyl Sulfisoxazole is another important antimicrobial agent from the isoxazole family which is widely used in paediatric suspensions. Cycloserine is a well-established molecule widely known for its potency against Mycobacterium tuberculosis [21-23].
CONCLUSION
Emerging research interest on isoxazole moiety already has been proven by various search group in the literature. Though many procedures are established for the synthesis of isoxazole core, but very few of them yield isoxazole with better percentage of product. But much more effort yet to be given to develop new synthetic strategies. Furthermore biological activity with new dimension need to be explored for isoxazole. Therefore this review may be helpful for medicinal chemist.

REFERENCES
[14] Ronald Palin; Lynn Abernethy; Nasrin Ansari; Kenneth Cameron; Tom Clarkson; Maureen Dempster; David Dunn; Anna-Marie Easson; Darren Edwards; John Maclean; Katy Everett;
Helen Feilden; Koc-KanHo; Steve Kultgen; Peter Littlewood; Duncan McArthur; Deborah McGregor; Hazel McLuskey; Irina Neagu; Stuart Neale; Lesley-Anne Nisbet; Michael Ohlmeyer; QuynhchiPham, Paul Ratcliffe; Yajing Rong; Andrew Roughton; Melanie Sammons; Robert Swanson; Heather Tracey; Glenn Walker. Structure–activity studies of a novel series of isoxazole-3-carboxamide derivatives as TRPV1 antagonists, Bioorganic & Medicinal Chemistry Letters, 2011, Vol. 21, pages 892–898.


[18] Paola P; Monica N; Manuela L; Annamaria M; Valeria C; Alessandra A; Michele R; Daniele S; D'Alessandro N. The antitumor activities of curcumin and of its isoxazole analogue are not affected by multiple gene expression changes in an MDR model of the MCF-7 breast cancer cell line: analysis of the possible molecular basis, Int j mol med, 2007, Vol. 20, pages 329-335.


[20] Sanja Mijatovic; Danijela Maksimovic-Ivanic; Marija Mojic; Graziella Malaponte; Massimo Libra; Vera Cardile; Djordje Miljkovic; Ljubica Harhaji; Darrin Dadineen; Kai Fan Cheng; Ylenia Bevelacqua; Marco Donia; Gianni Garotta; Yousef Al-Abed; Stanislava Stosic-Grujicic; Ferdinando Nicoletti. Novel nitric oxide-donating compound (S,R)-3-phenyl-4,5-dihydro-5-isoxazole acetic acid–nitric oxide (GIT-27NO) induces p53 mediated apoptosis in human A375 melanoma cells, Nitric Oxide, 2008, Vol. 19, Page 177–183.
