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Review article

Isoxazole ring as a useful scaffold in a search for new therapeutic agents

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ABSTRACT

Due to its relatively easy synthesis, isoxazole ring has been as an object of interest for chemists and pharmacologists from research groups all over the world. Its chemical modifications include both connection of isoxazole with other aromatic, heteroaromatic or non aromatic rings and substitution with different alkyl groups. Thanks to their usually low cytotoxicity, isoxazole derivatives are still popular scaffolds for the development of new agents with variable biological activities, such as antimicrobial, antiviral, anticancer, anti-inflammatory, immunomodulatory, anticonvulsant or anti-diabetic properties. This review discusses the chemical structure of recently developed isoxazole derivatives with regards to their activity and potential therapeutic use.

Contents

1. Introduction

Development of organic chemistry permanently contributes to the progress in multiple fields of science. A common feature of majority of newly synthesized organic compounds is the presence of at least one heterocyclic ring. Thus, heterocyclic chemistry is an important tool in the search for new active substances with a number of potential applications. One of the most interesting heterocyclic rings is an isoxazole that is a five membered ring containing oxygen and nitrogen atoms. A widely used isoxazole

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ring synthesis method is 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides and the reaction of hydroxylamine with a three-carbon atom component, such as 1,3-diketone or α,β-unsaturated ketone [1]. Beam et al. [2] described synthesis of substituted isoxazoles using oxime of a ketone with α hydrogen from an aromatic ester (Fig. 1). Although there are many methods for modification and substitution of the isoxazole ring, most of the resulting compounds show some biological activity. In this review, we report on the diversity of isoxazole derivative structures with focus on their structure-activity relationship (SAR).

2. Biological activity of isoxazole derivatives

2.1. Antimicrobial agents

Kang et al. [3] described synthesis of a series of new 1β-methylcarbapenems with 5'-isoxazolopyrrolidin-3'ylthio moiety in C2 position with potent antibacterial activity. The synthesized isoxazolidine, isoxazoline and isoxazole derivatives (**1a-1c**) (Fig. 2) showed a similarly potent antibacterial properties against different Gram-positive and Gram-negative organisms. The most active isoxazole derivative (**1c**) displayed comparable activity (MIC values 0.013–0.391 μg/ml) to meropenem (MIC values 0.013–0.195 μg/ml) against most of the examined bacteria except *P. aeruginosa*. Furthermore, the compounds featured high, comparable to that of meropenem (**2**), stability to dehydropeptidase-I, a renal enzyme responsible for degradation of carbapenems.

Bacterial peptide deformylase (PDF) has recently gained considerable attention as a potential target for antibacterial therapy. This enzyme is essential for protein biosynthesis and maturation. It is not present in mammalian cells, which may reduce the potential risk of side effects in patients treated with PDF inhibitors. Calí et al. [4] synthesized a series of isoxazole-3-hydroxamic acid derivatives and evaluated their *in vitro* ability to inhibit PDF activity in *Escherichia coli* and *Staphylococcus aureus*. It turned out that the most effective PDF inhibitor was the derivative with *meta*-substitution in the phenyl group. In addition, small electronegative substituents like chlorine or fluorine were more favored than more bulky and polar moieties like methyl, methoxy or N-acetyl groups (**3**–**6**). The IC_{50} values against *E. coli* and *S. aureus* of the most active derivatives were determined as 9.8 and 2.3 μM for compound **3**, 6.5 and 2.2 μM for compound **4**, 4.4 and 2.0 for compound **5**, 7.0 and 2.0 μM for compound **6,** respectively.

Padmaja et al. [5] obtained a new series of heterocycle derivatives by cyclocondensation and evaluated their antimicrobial activities towards Gram-positive and Gram-negative bacteria. The highest activity among the obtained pyrazoles, isoxazoles, pyrimidines and thioxopyrimidines was determined for amino-iminoisoxazole derivatives **7** and **8**. Furthermore, compound **8** with sulfone moieties possessed stronger antimicrobial activity than **7** one with diaroyl units. The study also demonstrated that the compounds with the highest activity preferably contained a chloro

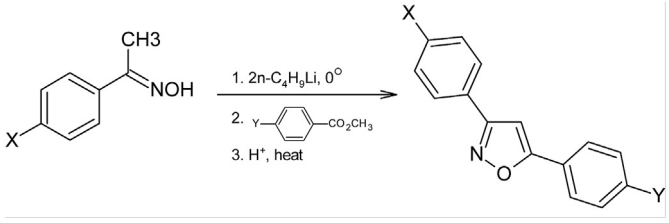

Fig. 1. Synthesis of 3,5-diarylisoxazoles by acid cyclisation of *para*-substituted acetophenone oxime dianion with methyl *para*-substituted benzoate.

substituent in the aryl group. Diameter of microbial growth inhibition zones in the agar-disc diffusion assay for **8** derivative (*S. aureus* - 32 mm, *B. subtilis* - 31 mm, *K. pneumoniae*- 26 mm, *P. vulgaris* - 28 mm in diameter) was comparable to that of chloramphenicol (**9**) (*S. aureus* - 35 mm, *B. subtilis* - 38 mm, *K. pneumoniae*- 37 mm, *P. vulgaris* - 42 mm).

Compounds obtained by a fusion of isoxazole ring with benzene also exert a wide range of biological activities. Lamani et al. [6] reported synthesis of a new series of benzisoxazolyl imidazothiadiazoles and evaluated their antibacterial potential. The most active derivatives **10** and **11** contained an electron withdrawing chloro or bromo moieties. Their antibacterial activity toward *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* (MIC values 0.5–3 μg/ml) was very close to that of ampicilin (**12**) (MIC values 0.5–2 μg/ml) used as a reference drug.

Changtam et al. [7] synthesized isoxazole analogs of curcumin (**13a**) (Fig. 3) that occurs naturally in *Curcuma longa* extracts. Curcuminoids, the structure of which is completely different than that of presently used antitubercular drugs, may prevent development of cross resistance in bacteria isolated from treated patients. One of the 55 obtained derivatives (**13b)** showed very high activity against *Mycobacterium tuberculosis* strains. Its MIC value towards *M. tuberculosis* H37Ra strain was as low as 0.09 μg/ml and it was 1111-fold lower than that of the parent compound curcumin (MIC 100 μg/ml) and 28-fold lower than of a standard drug kanamycin (**14**) (MIC 2.5 μg/ml). Furthermore, derivative **13b** was very active against multidrug-resistant (MDR) *M. tuberculosis* isolated from patients (MICs 0.195–3.125 μg/ml).

Yamuna et al. [8] also described a synthesis and biological properties of compounds with potential antimycobacterial activity. In a series of pyrazolo-, isoxazolo- and pyrimidocyclohepta[*b*]indoles, the best effects against *M. tuberculosis* strain H37Rv were reported for an isoxazole derivative **15** with MIC value 3.12 μg/ml. This chloro-substituted compound exerted also pronounced antimicrobial activity towards other investigated Gram-positive (*S. aureus*, *B. subtilis*) and Gram-negative (*K. pneumoniae*, *P. vulgaris*) bacteria. Other candidates for antitubercular drugs were synthesized by Naidu et al. [9]. Among a series of 3-(4-(substitutedsulfonyl)piperazin-1-yl)benzo[*d*]isoxazole analogs the strongest effects against *M. tuberculosis* H37Rv strain were determined for derivative **16** with benzenosulfonyl moiety that inhibited growth of 99% investigated bacteria at 3.125 μg/ml. The most active compounds were further investigated in a toxicity assay against murine macrophage (RAW264.7) cell line. The results were used to calculate the selectivity index (SI) that was also the highest (>130) for compound **16**. This indicated potentially high therapeutic index of this derivative and its utility for further drug development.

Lilienkampf et al. [10] synthesized a series of 5-phenyl-3-isoxazolecarboxylic acid ethyl ester derivatives with excellent antitubercular properties. In this group of compounds crucial for their activity was presence of isoxazole ring and C3 ester moiety. They differed in the substituents in the side-chain aryl moiety on the oxymethylene linker. The best activity in all experiments showed compound **17** with $-CF_3$ group at the meta position of the benzene ring with the MIC value against the *M. tuberculosis* strain H37Rv of 0.6 μM. It was also very active toward the nonreplicating bacteria (NRP-TB) in oxygen-deprived conditions (MIC 8 μM) as well as against strains resistant to the commonly used antitubercular drugs (MIC 0.9–1.0 μM). Condensation of isoxazolyl cyanoacetamide synthon with o-nitro benzaldehyde or salicylaldehyde yielded isoxazolyl pyrimido[4,5-*b*]quinolines and isoxazolyl chromeno[2,3-*d*]pyrimidin-4-ones [11]. Investigation of antimicrobial properties of the obtained compounds by means of broth dilution method showed a correlation between the highest activity and the presence of chloro or bromo group in the benzene ring. The most