Review

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The recent progress in the field of the applications of isoxazoles and their hydrogenated analogs: mini review

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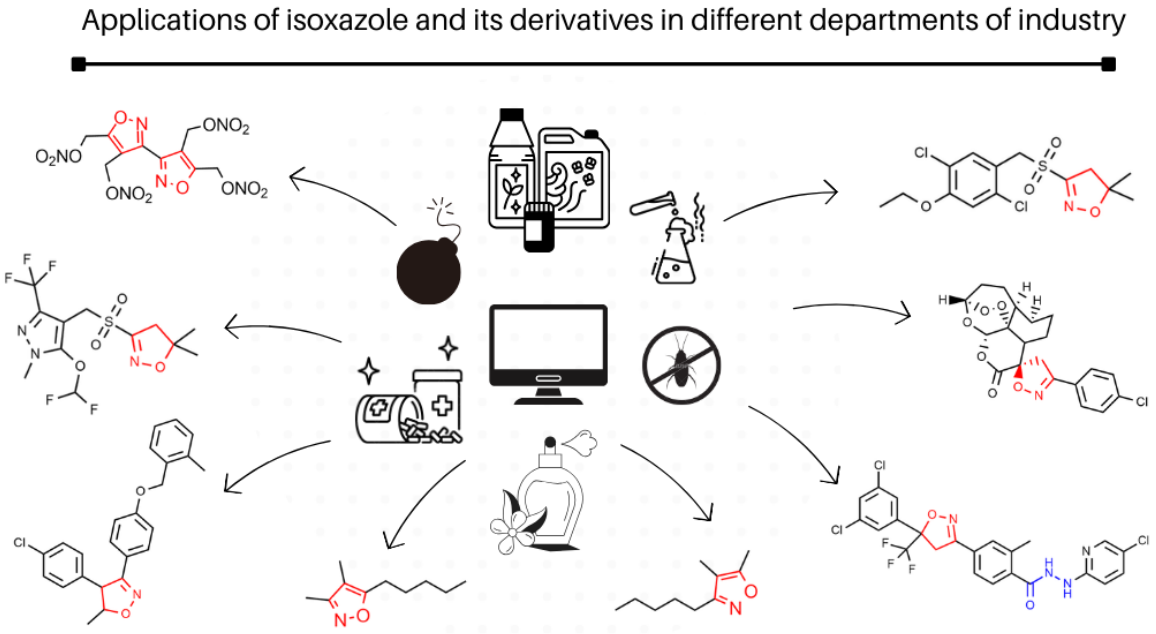

Abstract: Recent review of the general application of isoxazoles and isoxazolines has been done based on current state of the art in this area. Isoxazole and its analogues have majority of possible applications in many fields of plural branches of industry. They possess good biological activity, so most of them are being used successfully in medicine and veterinary. These heterocyclic compounds could be also very important precursors of many organic

transformation. Due to their easy modification, general interest of their development still increases.

Keywords: Isoxazole, Isoxazolines, Pharmacophores, Applications, Heterocyclic Compounds, Bio-active,

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Introduction

Heterocyclic organic compounds are the one that contain at least one heteroatom in the ring. They are widespread and represent one of the most widely described branches of organic chemistry. It is estimated that among the approximately 20 million identified and patented compounds, approximately, 1/6 are heterocycles. Due to their properties and biological activity, they are used in many industries. The great majority of pharmacophores, cosmetics, agrochemicals, plastic additives, or anticorrosive agents on the market today contain a heterocyclic ring in their structure [1-4],[5-7]. A common feature of all heterocycles, is that they easy undergo many modifications, which gives the opportunity to design their subsequent wide application via organic synthesis. The ease with which different functional groups can be inserted into the heterocyclic ring makes these compounds of great interest to scientists which causes that the chemistry of heterocyclic systems is constantly evolving.

Very prominent, among the many important heterocycles, are isoxazole and its analogs [8]. Isoxazoles are a group of heterocyclic organic compounds that contain a five-atom ring in their structure, which includes three carbon atoms, nitrogen and oxygen atoms. Inside the ring, there are two double bonds (Fig. 1a). Depending on the degree and position of saturation in the isoxazole ring, isoxazolines can be identified, as well as isoxazolidines (Fig. 1e) which are fully saturated analogs of isoxazoles [10]. Furthermore, studies have demonstrated that these structural differences have a direct influence on the broad spectrum of biological activities and therapeutic potential exhibited by these compounds [9].

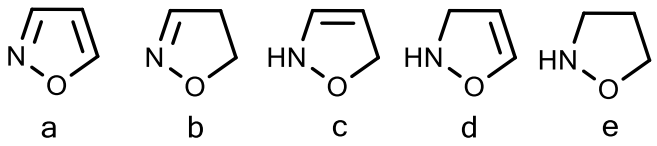


Fig 1. Isoxazole and its hydrogenated analogs.

According to the literature, the isoxazole ring ranks 33rd out of 351 heterocyclic systems in terms of applicability in popular drugs [2]. Therefore, isoxazole and its analogs

are recognized as important pharmacophores, driving significant interest in the development of new synthetic methodologies for their preparation. Current research efforts are highly focused on exploring innovative approaches to efficiently synthesize these compounds, due to their relevance in organic syntheses [10]. As mentioned before, these compounds could be used in many organic syntheses f.e. to obtain nitriles, β-hydroxy ketones, as well as α,β-unsaturated ketones and oximes, among others [8]. They are also excellent precursors in the synthesis of β-amino acids, C-disaccharides, and imino or amino polyols [14-15].

There are a number of methods for the synthesis of isoxazole and its functionalized derivatives and analogs [11]. One of the most popular and widely used methods for the synthesis of isoxazoles and their analogs includes the reaction of alkenes with nitrones, ketoazenes, carbonylimines, or N-oxides of nitriles [12-13].

General application of isoxazole and its hydrogenated analogs

Medicine and veterinary

The isoxazoles themselves, as well as their analogs exhibit a variety of biological activities. They possess antibacterial, antibiotic, anticancer, antifungal and antitumor properties, among others [16]. On the other hand, isoxazole analogs, which are isoxazolines, could be characterized by antimicrobial properties. Consequently, it is possible to use them as anti-inflammatory drugs [12-13]. Due to isoxazolines' stimulation of the central nervous system, these compounds are also classified as antidepressants [11-15]. On the other hand, nucleosides, which contain an isoxazoline ring, exhibit antiviral activity [11]. For this reason, they could be found among the wide range of pharmacophores used in many therapeutic agents [11-15]. The table 1 summarizes patents on several compounds containing an isoxazoline ring with uses consistent with their above characteristics.

In the literature, the therapeutic effects of compounds containing an isoxazole or isoxazoline ring are well described. Commercially available drugs include Zonisamide under the name Zonegran (Europe) (Fig. 2). This compound contains an isoxazole ring and exhibits anti-epileptic activity, but can also be used to treat Alzheimer's disease [21-22].

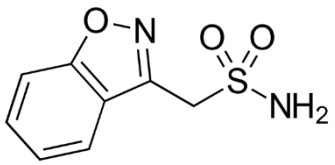
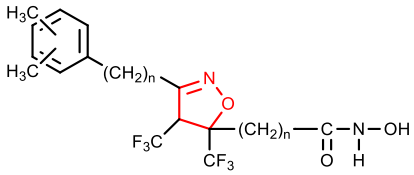
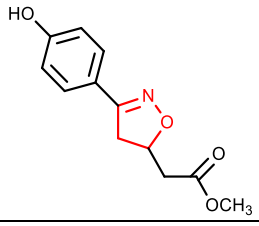
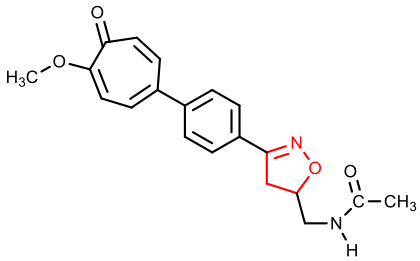
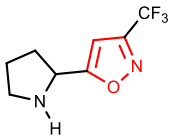


Fig. 2. Chemical structure of Zonisamide in a commercially available drug called Zonegran.

Table 1. Examples of biological activity of selected compounds based on isoxazole analogs in the patents.

	Structure	Action
US005716967A [17]		Selective inhibitors of phosphodiasterase type IV, used in the treatment of AIDS, rheumatism, anti-inflammatory effect
US007662843B2 [18]		Antitumor effects, anti-inflammatory,
US0059901.36A [19]		Antibacterial,
EP0588917A4 [20]		Inhibitor of the need for nicotine, Alzheimer's disease inhibiting drugs.

Another example of a medicine with an isoxazole ring is Seromycin, which includes the active substance Cycloserine in its composition. This drug is primarily used in the treatment of tuberculosis or mycobacteriosis of the lungs [23]. Another active substance containing an isoxazole ring is Flucloxacillin, a key component of the pharmaceutical formulation known as Floxapen (Fig. 3), which is used as an antibiotic for inflammation of the skin and soft tissues, as well as inflammation of the upper respiratory tract [24]. An interesting aspect, from the point of view of the applicability of this substance, is the research conducted by Fayomi's team. They showed that Floxapen can be used far apart from the medicinal field. According to them it could be used as an inhibitor of the electrochemical corrosion in aluminum-containing alloys [25].

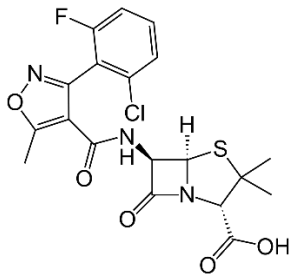


Fig. 3. The chemical structure of Flucloxacilinum in the commercially available drug Floxapen.

Among many synthetic drugs which have been used nowadays containing isoxazole/isoxazoline ring in their structures, scientists carried out many attempts to modify natural substances to obtain even better biological activities [26]. One of great examples is the discovery that isoxazolines could be applied as antimaralial agents. Naykanti et al. [27], reported, that spiroisoxazoline analogues on the basis of artemisinin (the natural organic substance which is antimalarial agent) show very good activity against P. falciparum (Fig. 4a). Apart of using natural substance, but in the same area, Raval et al. [28] have evaluated some 5-imidazopyrazole-isoxazoline derivatives against malaria. The research has shown that these compounds (Fig. 4b) show prominent action toward P. falciparum comparing to commonly used quinine.

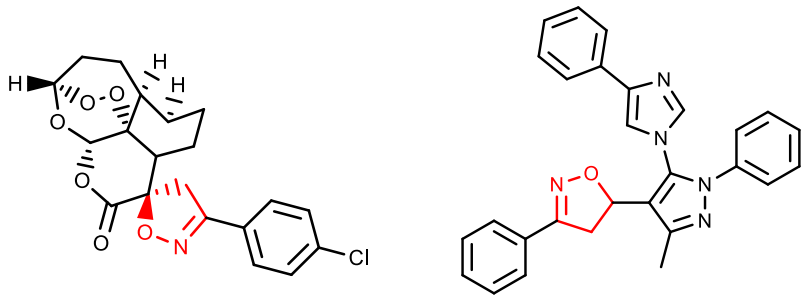
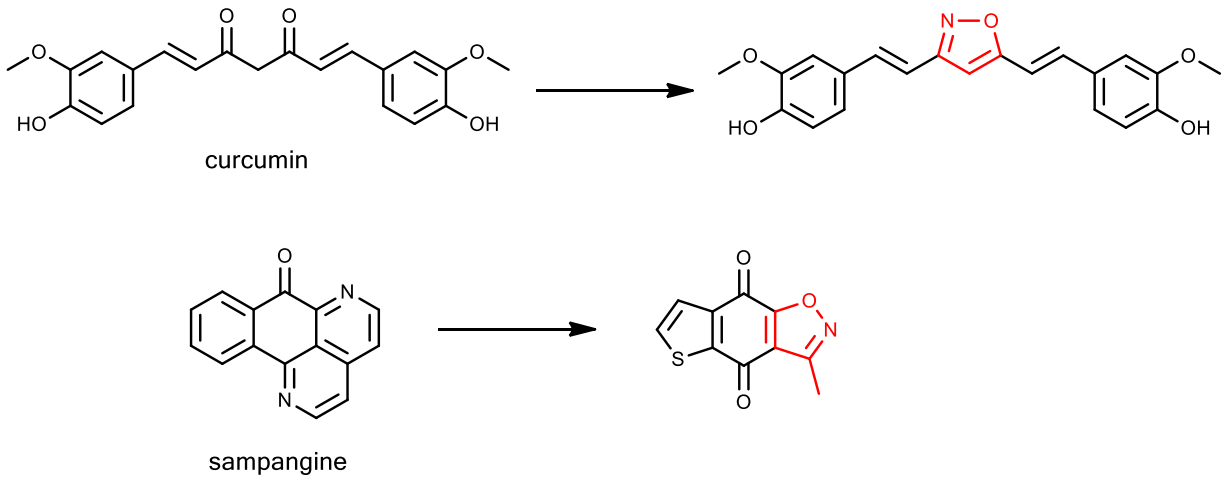


Fig. 4. Isoxazolines derivatives which shows potent antimalarial activity.

Moreover, Rodrigues et al. [29] have shown that the derivatives from curcumin containing isoxazole ring could be used as a promising agent against breast cancer, but also, the series of sampangine derivatives containing isoxazole showed strong anti-cryptococcal activity comparing to comercial voriconazole [30] (Scheme 1).



Scheme 1. Natural compounds transformations leading to isoxazole containing compounds with higher biological activity towards subsequent.

Recently, it has been found via *in silico* experiments, that tested isoxazolines and isoxazolidines (Fig. 5) could be used as a very promising anti-inflammatory agents which bonds very well with enzymes that could inhibit cyclooxygenase [31]. Research has found that these compounds could act even better than well-known anti-inflammatory agent Ketoprofen.

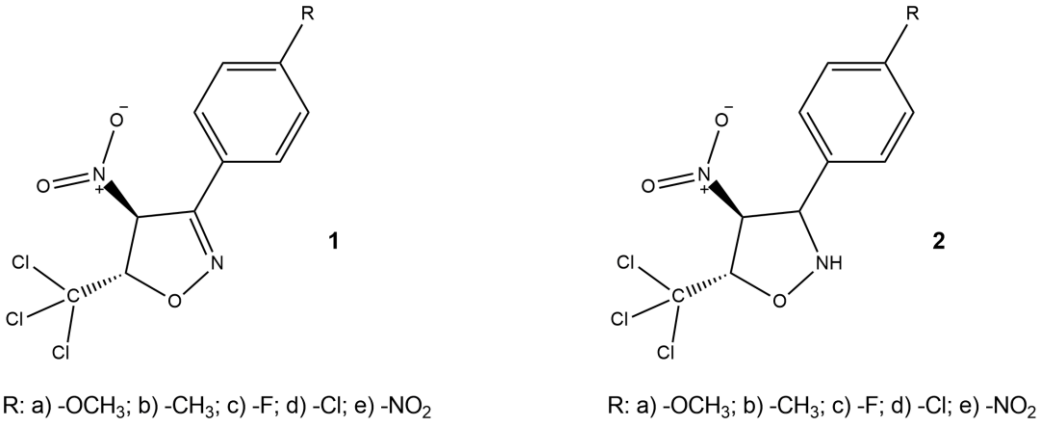


Fig. 5. The chemical structure of analyzed series of 1) isoxazolines and 2) isoxazolidines [31].

Malik et al. [32] have led the review of new isoxazole-based inhibitors of poly (ADP-ribose) polymerase (PARP), which later led to investigation *in silico* of their activity against cancer cells, but also they tested the cytotoxicity of these inhibitors. PARP inhibitors are commonly used in cancer treatments to stop the repair of cancer cells, as a consequence of which they die. The best activity against 13 different types of cancer cells has shown the 3,4-diarylisoxazole derivative (Fig. 6). It has been found that this compound, not only promotes the cleavage in breast cancer and hepatocellular carcinoma cells, but also prevents damage of treated cells.

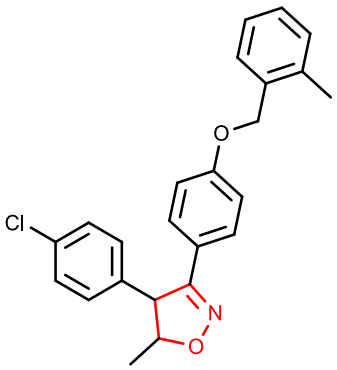
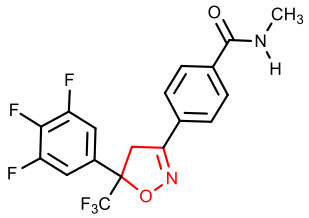
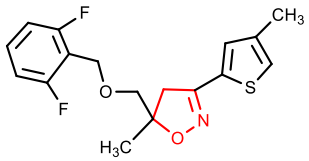
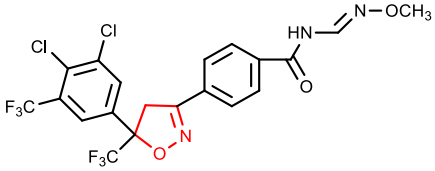


Fig. 6. Chemical structure of 3-(4-((2-methylbenzyl)oxy)phenyl)-4-(4-chlorophenyl)-5-methyl-isoxazole [32].

Isoxazoles and their analogs have also found a broad applications in veterinary medicine and the agricultural industry. These compounds exhibit insecticidal activity and can

be successfully used as animal preventatives and crop protection [33]. Examples of such compounds are shown in the Table 2.

Table 2. Examples of of properties of newly synthesized compounds based on isoxazole analogs in the patents.

	Structure	Action
US11278533B2 [34]		Insecticidal and antiparasitic activity,
US7338967 [35]		Herbicide,
US2011/0059988A1 [36]		Antiparasitic effect for animals and plants,

Compounds containing the isoxazoline ring are commonly used in therapeutics against ectoparasites, applied in veterinary medicine. Their broad spectrum of action covers many types of insects parasitizing livestock. Among the most common and popular substances present in animal drugs that contain an isoxazoline ring in their structure is Fluralaner. The compound is available in pharmaceuticals under the trade name Exzolt and Bravecto. These drugs are used preventively against ectoparasites in poultry [37] and in dogs and cats [38] (Fig. 7). In addition, the formulations are characterized by a very rapid and targeted action, even up to four months. They also show no toxic effects on animal or human health [39].

Other examples of isoxazolines commercially available as active ingredients in animal drugs are Afoxolaner (formulation name NexGard), which has a biocidal effect on fleas in dogs and cats [40], Lotilaner (formulation name Credelio), which is an effective treatment for a wide range of canine and feline ectoparasites [41], Sarolaner (formulation name Simparica), which also shows action on a broad spectrum of external parasites, controlling flea infestations, earworm, scabies, or ticks in dogs and cats [42].

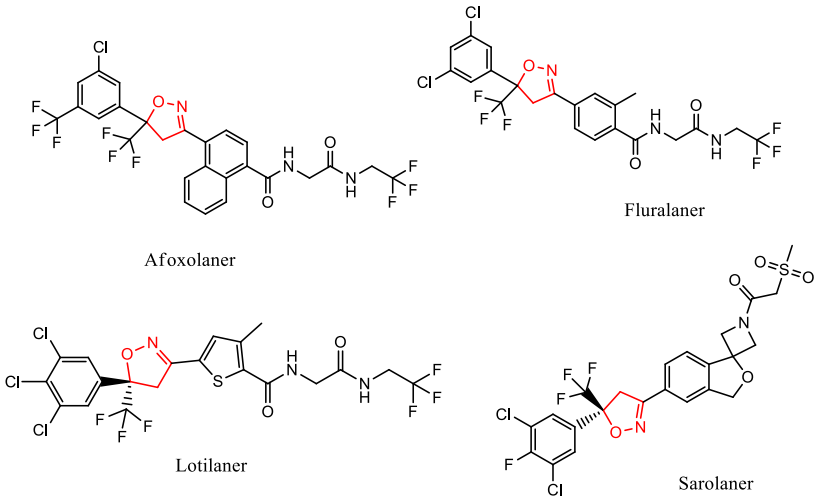


Fig. 7. Structures of the compounds that make up the active substances used in veterinary medicine.

Agriculture

In addition to medical use, isoxazolines are also successfully applied in agriculture as crop protection products. Thus, Pyroxasulfone, found commercially as Zidua, is used in cereal crops. It prevents the growth of grasses and weeds because, when absorbed by the roots, it has a thinning effect on them, allowing the growth of unwanted plants to be easily controlled [33]. Fenoxasulfone (Fig. 8) has a similar effect, and is mainly used as a control agent for hopweed in rice cultivation [43].

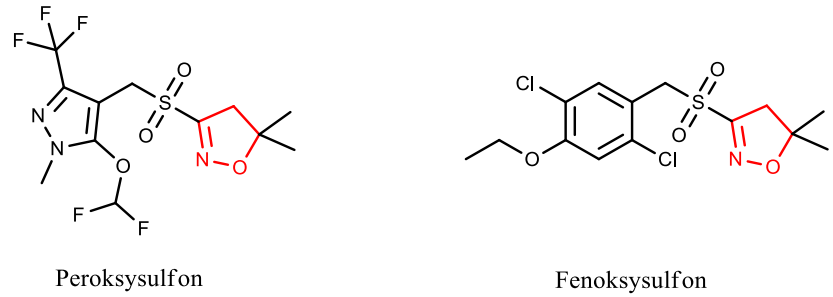


Fig. 8. Chemical structure of pyroxasulfone and their commercially available agents.

Herbicides containing an isoxazoline ring include mainly Methiozolin, which appears under the trade name PoaCure (Fig. 9).

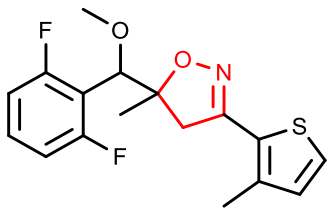


Fig. 9. Chemical structure of methiozolin and commercially available agent.

The product is mainly used in rice cultivation [42], but is also used to control the proliferation of annual panicle weeds on lawns, sports fields or golf courses. The agent has a slow and long-lasting effect and is highly resistant to weather conditions [44-45].

Jiang et al. [46] have designed the new insecticidal agent against *Spodoptera frugiperda,* which could poses a potential threat to corn, as well as tomatoes and peppers crops. It's caterpillars damage the buds and growth cones and might even bite into the fruits. The best insecticidal activities against *S. frugiperda* exhibits N-(5-chloropyridin-2-yl)-4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzohydrazide (Fig.10.) These results not only indicated that scaffold hopping is a promising tool in desing and synthesis of new potential drugs and biologically active agents, but also that synthesised isoxazoline ring containg compound could be a potential candidate agent to control populations of *S. frugiperda* in agriculture.

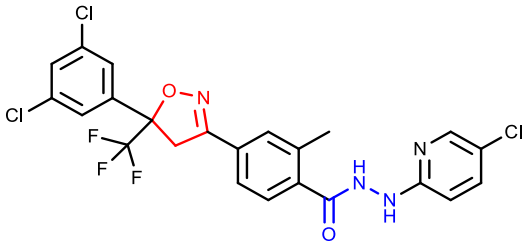
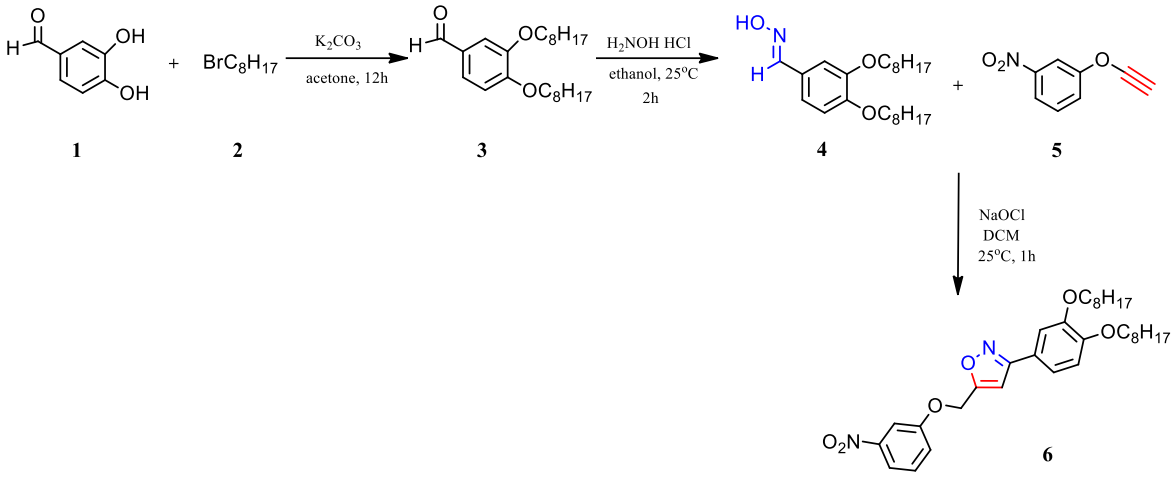


Fig.10. Synthesis of N-(5-chloropyridin-2-yl)-4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-methylbenzohydrazide via scaffold hopping method. [46]

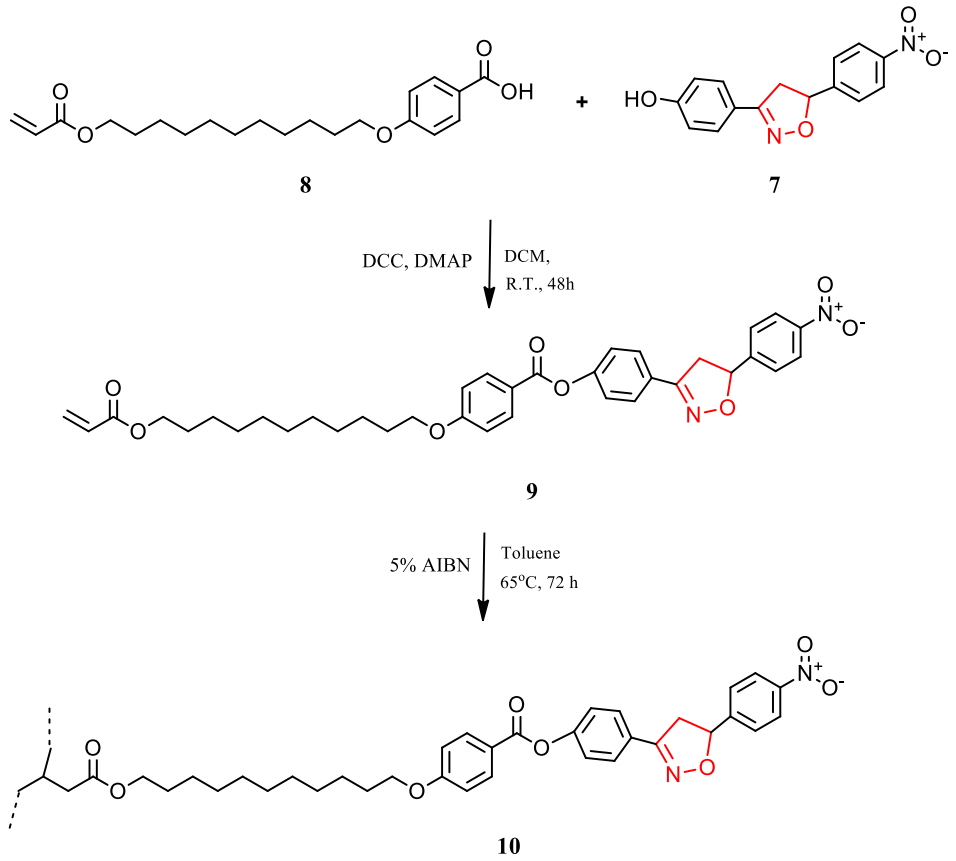
Other applications

Singh and co-workers [47] carried out a multi-step synthesis of new small-molecule gelling substances containing an isoxazoline ring in the structure (Scheme 2). The first step of this reaction consisted in the reaction of 3,4-dihydroxybenzaldehyde 1 with 1-bromooctane 2. The product of this reaction 3 was used to obtain 3,4-dioctyloxybenzoxime 4, which successively in an addition reaction with 1-nitro-3-prop-2-ynoxybenzene 5 in the presence of NaOCl, carried out in DCM allowed the preparation of 3-(3,4-di(octyloxy)phenyl)-5-((3-nitrophenoxy)methyl)isoxazole 6. This compound was tested, as a gelling agent to facilitate the separation of bisphenol A from aqueous solutions. The observed selective gelation process allows the use of this type of compound, for example, in the removal of oil spills into the seas and oceans [47].



Sch.2. Multistep synthesis of 3-(3,4-di(octyloxy)phenyl)-5-((3-nitrophenoxy)methyl)-isoxazole 6, as a gelling agent [43].

Paso and co-workers [48] to synthesize polyacrylates, used compounds containing an isoxazoline ring. The synthesis of these compounds occurs in two steps.

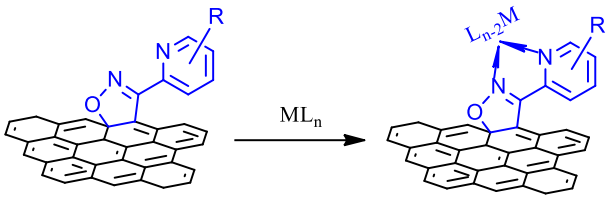


Scheme 3. Multistep synthesis of polyacrylates [48].

In the first step, monomer 9 is obtained by the esterification reaction of 3-(4-hydroxyphenyl)-5-(4-nitrophenyl)-isoxazoline 7 and 4-[11-(acryloyloxy)undecyloxy]benzoic acid 8. The resulting product is then followed by a free radical polymerization using 5% AIBN

in toluene (Scheme 3). The finished polyacrylates 10 exhibit liquid-crystalline properties and can find application in the manufacture of TVs, monitors [48].

The thriving development of nanomaterials chemistry is resulting in the next application of isoxazolines [49]. Luo et al. [50] in their study used 3-(3-pyridyl)-isoxazoline segment (Scheme 4), in the role of a functionalizer of the structure of graphene and carbon nanotubes. Introduced into the structure of the nanomaterial, the isoxazoline ring enabled the effective formation of complexes with transition group metals, which were then effectively used in the electrocatalyzed reaction to obtain molecular oxygen. The presence of isoxazoline rings was also shown to prevent the formation of nanoparticle agglomerates. This discovery provides a new solution for modern heterogeneous catalytic systems and beyond. Thanks to the presence of a functional group in the form of an isoxazoline ring, mainly existing nanofillers gain new physicochemical properties.



Scheme 4. Scheme for the formation of metal complexes with graphene functionalized with an isoxazoline-pyridine ring [50].

Moreover, it has been found the isoxazolines being agents preventing the corrosion of steel. Other organic corrosion inhibiting compounds have been used for a long time in the marine industry. However, they are not always environmentally friendly and require the use of many enhancers, or surfactants, and unfortunately, they act selectively on specific materials. Since these organic compounds show high efficiency at low concentrations and act in all environmental conditions, the development of their physicochemical properties is highly desirable. Compounds containing heteroatoms, i.e. nitrogen, oxygen or phosphorus or sulfur, but especially π-bonds, show high activity toward corrosion inhibition. Such molecules are readily adsorbed on the steel surface isolating it from direct exposure to corrosion. The adsorption phenomenon of these molecules is mainly related to the physicochemical properties of such compounds, which are determined, for example, by the aromatic nature of their structure, the presence of various functional groups, the size, or mass of the molecule, but also the π electrons, or the electron density of the atoms in the structure play a large role [51-52]. Anusuya et al. [53] synthesized and evaluated for corrosion inhibition of low-carbon steels various Δ2-isoxazoline derivatives (Fig. 11). They established the corrosion-preventing activity of this type of steel in the environment of sulfuric acid (VI)

solutions. The study confirmed that these compounds prevent the corrosion of low-carbon steels in the course of the adsorption phenomenon on the surface of the material.

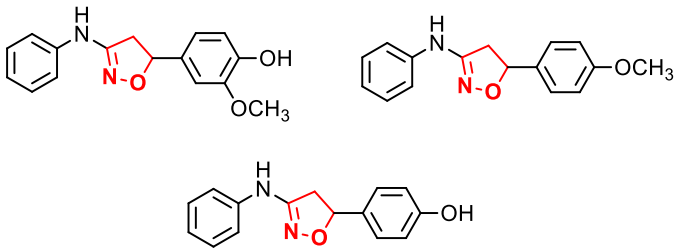


Fig. 11. Structures of 3-(phenylamino)-5-aryl-Δ^2-isoxazolines as steel corrosion inhibitors [53].

It has been found, that simple heterocyclic compound - isoxazole could play a major role in improving of working of perovskite solar cell PSC [54]. It is worth mentioning that in general, the PSC contains of hybrid organic-nonorganic compounds with lead halide as a light-collecting active layer. Thus the small heterocyclic compound was used as an additive to the perovskite precursor for improving the PSC performance. Adding the 0,4M of isoxazole can improve the PSC performance for about 2%. It all can be possible by providing lone electron pairs by the isoxazole in the results of reaction and passivation with the undercoordinated Pb clusters or Pb2+ ions of the active layer of PSC.

Noteworthy, the 3,3′-biisoxazole-4,4′,5,5′-tetrakis(methyl nitrate) TNBIO (Fig. 12) and 4,4′,5,5′-tetrakis(azidomethyl)-3,3′-bisisoxazole containing isoxazole ring, are found to be higly energetic meltcast explosives that can be used both in space and military applications [55-56].

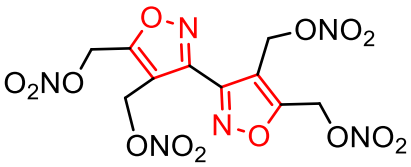


Fig. 12. Structure of 3,3′-biisoxazole-4,4′,5,5′-tetrakis(methyl nitrate) TNBIO .

Staying in the field explosives, Deng et al. synthesized the isoxazoline-based porous (Fig. 13) polymer that has been found to be very promising, reusable adsorbent of 2,4,6-trinitrotoluene TNT with a maximum adsorption capacity of 177.3 mg/g at 298 K [57].

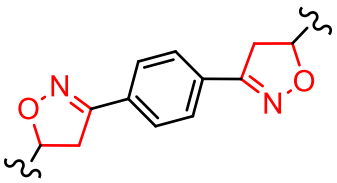


Fig. 13. Structure of isoxazole-based mer.

Zhong et al. decided to enhance the effect of adsorbing TNT with isoxazoline based polymers. They introduced to the structure of such polymer the siloxane groups. By this action they achieved the synergestic effect of the synergistic effect of Lewis acid-base(siloxane groups) and dipole-π, and π-π interactions coming from isoxazole ring interactions with TNT [58].

The interest in developing a new group of anion receptors has become a very challenging field among scientists. Recently, the activity in this field has shown the 3-amino-5-(4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazole-4-carboxamide (Fig.14.), which can easily take a role of the receptor with high selectivity for fluoride detection. It has been found that this compound not only can exhibit the changes in its UV–vis absorption but also in fluorescence emission spectra while adding the ions F-. This finding can improve the quality of treatment of industrial wastewater from fluorine ions [59].

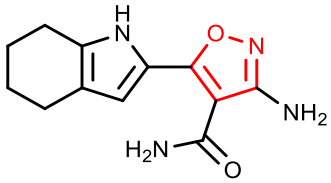


Fig. 14. Structure of chemoreceptor 3-amino-5-(4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazole-4-carboxamide.

Isoxazoles and isoxazolines can be successfully in a fragrance industry as it was confirmed by Kaiser et al [60]. They discovered that in many new volatile Constituents of Flower Michelia champaca that they achieved via the three isoxazoles are present. 5-amyl-3,4-dimethylisoxazole (Fig. 15A.) exhibits a characteristic green-herbaceous odor which can be associated with mix of estragon, celery and jasmine. Another detected was 3-amyl-4,5-dimethylisoxazole (Fig.15B) which shows similar green-herbaceous in which anise-like and nutty aspects are noticeable.

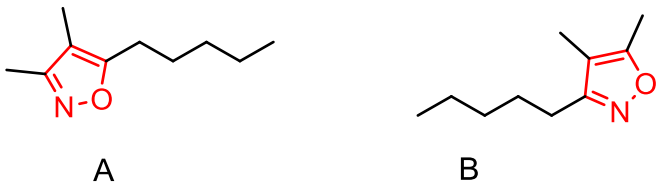
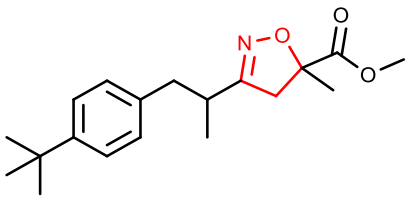
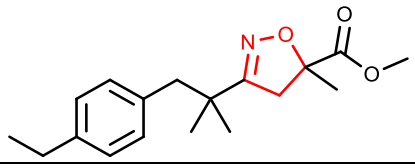
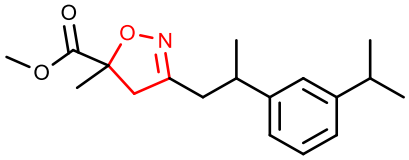


Fig. 15. Structure of isoxazoles with potential use in fragrance.

The evaluation of possible application in fragrance industry of isoxazoline carboxylate derivatives was led by Büyükbayram et al. [61] Analysis of odour durability and olfactory description has shown that few of the synthesized compounds are promising fragrants Tab.3.

Table 3. Examples of isoxazoline carboxylate derivatives examined by Büyükbayram et al.

Name	Structure	Scent
Methyl 3-(1-(4-(tert-butyl)phenyl)propan-2-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate		Citrus, aldehydic, waxy, metallic
Methyl 3-(1-(4-ethylphenyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydroisoxazole-5- carboxylate		Vanillic, anisic
Methyl 3-(2-(3-isopropylphenyl)propyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate		Watery, floral, muguet

Conclusions

Isoxazole and its hydrogenated analogs are a group of heterocyclic organic compounds with a wide range of applications. Due to their easy synthesis, which is often compliant with green chemistry principles, as well as an easy modification, the application could become various. This work proved that isoxazole and its hydrogenated derivatives can occur not only in the broad spectrum of pharmacophores or herbicides, but also can be applied in electronics, military and space industry, cosmetics, marine, analytics as adsorbents or anion receptors etc. Numerous potential applications of these compounds remain undiscovered, presenting significant opportunities for future research and innovation. This is the main reason why the interest in developing new methods of synthesis as well designing new structures, is still growing.

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