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Invited review

Isoxazoline containing natural products as anticancer agents: A review

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ABSTRACT

Isoxazolines are an important class of nitrogen and oxygen containing heterocycles that belong to the azoles family which have gained much importance in the field of medicinal chemistry as the anticancer agents. Moreover, natural products are always expectedly regarded as an important hoard of a large number of potential chemotherapeutic candidates. Therefore, this review mainly focuses on the existence of isoxazoline derivatives in natural sources, their isolation and uses there of as anticancer agents besides highlighting the synthetic pathways to achieve these compounds. Structural–activity relationship and the influence of stereochemical aspects on anticancer activity of such compounds have also been discussed. It covers the literature upto 2014 and would certainly provide a great insight to scientific community to accelerate further research for the development of some novel anticancer drugs.

1. Introduction

Nowadays, cancer has gradually become the leading cause of death worldwide and seriously endangering the health and life of humans for a long period [1]. It has been reported that cancer can be caused by one of the three ways namely, incorrect diet, genetic predisposition and environmental contaminants [2]. Consistent efforts have been made to fight against this disease in the past few years as a result of advancements in cellular and molecular biology leading to the development of potent anticancer agents capable of targeting the cancerous tissues with minimal side effects. Natural products have appreciably contributed to the development of a large number of anticancer drugs [3–10]. About 50% of all anticancer drugs approved internationally are either natural products or natural product mimics and were developed on the basis of the knowledge obtained from small or macromolecules existing in nature [11].

Recently, various azole derivatives have attracted considerable attention in the field of anticancer research [12–18]. Among them, Δ^2-isoxazoline derivatives are an important class of five membered nitrogen-oxygen containing heterocyclic compounds that exhibited promising antineoplastic properties. The general chemical structure of Δ^2-isoxazoline is shown in Fig. 1.

Some important examples of synthetic Δ^2-isoxazoline scaffolds are 3,5-diaryl-isoxazoline linked 2,3-dihydroquinazolinone hybrids **1** [19], arylisoxazoline containing anthranilic diamides **2** [1], 3,5-diaryl-isoxazoline linked pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) conjugates **3** [20] and dibenzo[*b*,*f*]azepinetethered isoxazoline derivatives **4** [21] that act as potent anticancer agents with an improved pharmacokinetics profile Fig. 2. Anticancer properties associated with isoxazole compounds are summarized in Fig. 3.Viewing the importance of natural products as well as Δ^2-isoxazoline containing pharmacores in the field of cancer research, the present review is mainly focused on those natural products which bear Δ^2-isoxazoline moiety exhibiting anticancer potential. Furthermore, we discussed about various pathways and influence of stereochemical aspects particularly on anticancer activity of such compounds.

2. Naturally occurring anticancer isoxazoline derivatives

2.1. Subereamolline A

It has been reported that methanol extract of sponge *Suberea mollis*, collected from Hurghada at the Egyptian Red Sea coast yielded a bioactive dibrominated metabolite, (+)-subereamolline A **5**. It potently inhibits the migration and invasion of metastatic human breast cancer cells i.e. MDA-MB-231 at the nanomolar dose level Fig. 4 [22,23]. From this study, it was found that the presence of terminal ethyl carbamate moiety is an important factor for the

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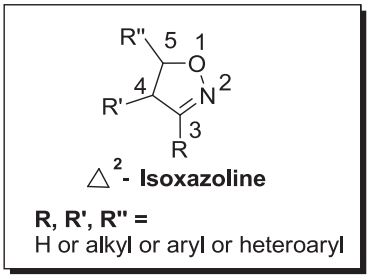

Fig. 1. General structure of Δ^2 – Isoxazoline.

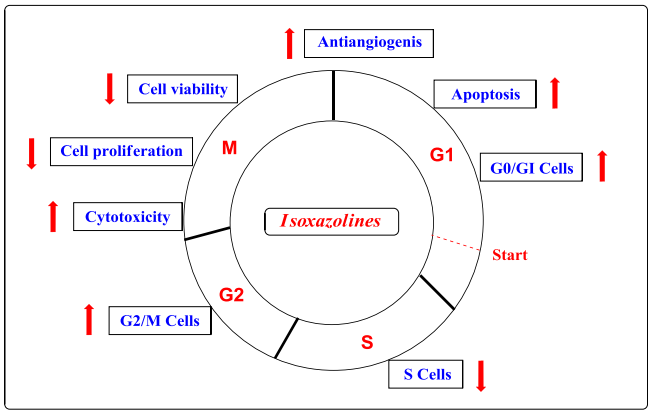

Fig. 3. Proposed anticancer properties of isoxazoline compounds.

antimigratory activity [23]. The compound (+)-**5**, having S-configuration at the spirocentre displayed high potency against cancer cells even at nanomolar dose level while anticancer effect of (−)-**5**, a non natural isoxazoline derivative having R-configuration at the same spirocentre obtained during the total synthesis has not been reported till date. Therefore, compound (+)-**5** may act as a novel scaffold for the design of more efficient breast cancer migration and invasion inhibitor to control malignant form of cancer.

Shearman et al. reported the first total synthesis of (+)-subereamolline A **5** and (−)-subereamolline A **5** by using preparative chiral HPLC separation of the corresponding racemates [24]. In this approach, 2-hydroxy-4-methoxybenzaldehyde **6** reacted with *N*-bromosuccinimide (NBS) followed by benzyl protection of the phenolic oxygen to obtain aldehyde **7** in 92% yield. The compound **7** so obtained was further converted into the azlactone **8** by treating **7** with *N*-acetylglycine and sodium acetate in the presence of acetic anhydride. Azlactone **8** on further saponification with barium hydroxide and subsequent condensation with *O*-benzylhydroxylamine yielded carboxylic acid **9** with 49% yield along with an oxime **10** (22% yield) as a side product. The treatment of **9** with trimethylsilyldiazomethane gave corresponding methyl ester which on subsequent hydrogenolysis over palladium black gave oxime methyl ester **11** as a cyclization precursor. Oxidative cyclization of **11** with iodobenzene diacetate using acetonitrile as a solvent gave (±)-**12** which underwent diasteroselective reduction with $Zn(BH_4)_2$ to produce trans isomer (±)-**13** as the major product along with cis isomer (±)-**15** as the minor one. Alkaline hydrolysis of methyl ester (±)-**13** with lithium hydroxide gave spiroacid (±)-**15** in an overall yield of 11% starting from aldehyde **6**. The coupling of spiroacid (±)-**14** with amine **16** in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) afforded (±)-subereamolline A **5** with 91% yield. However, improved yield (96%) of (±)-subereamolline A **5** was obtained by using propylphosphonic anhydride (T3P) as a coupling agent. The resolution of (±)-subereamolline A **5** was carried out by using preparative chiral HPLC which gave (+)-**5** having absolute configuration R and S at C-1 and C-6 chiral centre, respectively and (−)-**5**, having S and R configuration at C-1 and C-6 chiral centre, respectively (Scheme 1).

2.2. Aerothionin and 11-oxoaerothionin

(+)-Aerothionin **17**, a tetra bromo compound having spirohexadienylisoxazoline pharmacore was first isolated from the acetone extract of marine sponges, *Aplysina aerophoba* and *Verongia thiona* Fig. 5 [25,26]. Kernan et al. have isolated (+)-**17** from the dichloromethane extract of verongid sponge, *Pseudoceratina durissima* collected from Bowl Reef and Great Barrier Reef Australia [27]. The compound (+)-**17** was also isolated from the methanol/dichloromethane extract of Carribbean sponge *Aplysina fistularis insularis* [28], methanol extract of the Red Sea sponge *Suberea mollis* [22], methanol extract of Great Barrier Reef sponge *Pseudoceratina* sp. (order Veronida, family Drinellidae) [29], dichloromethane/methanol extract of sponge *Psammaplysilla purpurea* [30], methanol/chloroform extract of Caribbean sea sponge *Aplysina lacunosa* [31], dichloromethane extract of *Aplysina gerardogreeni* [32],

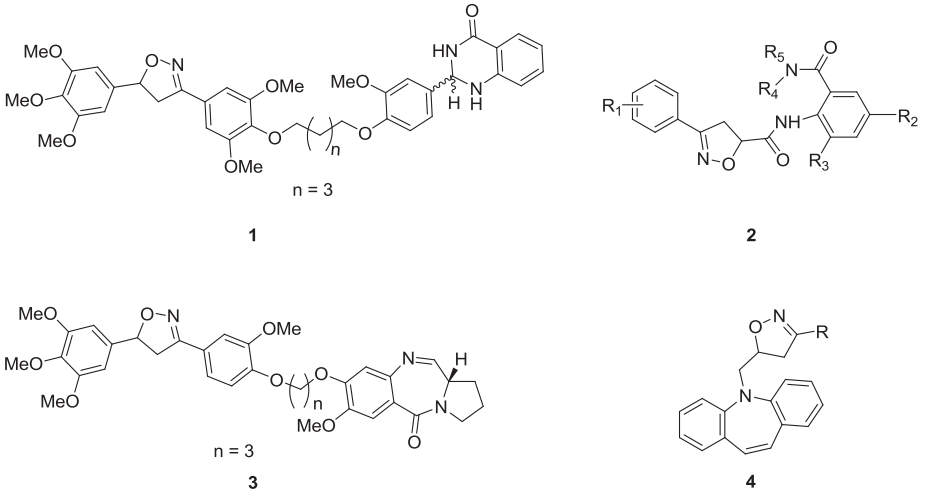

Fig. 2. Anticancer synthetic isoxazolines.