Bioorganic & Medicinal Chemistry 26 (2018) 3065–3075

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Review article

The recent progress of isoxazole in medicinal chemistry

Jie Zhu[a], Jun Mo[a], Hong-zhi Lin[a], Yao Chen[b], Hao-peng Sun[a,*]

[a] Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 211198, China
[b] Department of Medicinal Chemistry, Nanjing University of Chinese Medicine, Nanjing 210023, China

ARTICLE INFO

Keywords:
Isoxazole
Biological activities
Anticancer
Antimicrobial
Anti-inflammation

ABSTRACT

Isoxazole compounds exhibit a wide spectrum of targets and broad biological activities. Developing compounds with heterocycle rings has been one of the trends. The integration of isoxazole ring can offer improved physical-chemical properties. Because of the unique profiles, isoxazole ring becomes a popular moiety in compounds design. In this review article, the major focus has been paid to the applications of isoxazole compounds in treating multiple diseases, including anticancer, antimicrobial, anti-inflammatory, etc. Strategies for compounds design for preclinical, clinical, and FDA approved drugs were discussed. Also, the emphasis has been addressed to the future perspectives and trend for the application.

1. Introduction

Isoxazole is a member of five-membered heterocycles. Isoxazole has two heteroatoms, oxygen atom, and a nitrogen atom, at the adjacent position. Two carbon-carbon double bonds contribute to the unsaturated property of the molecule. The structural features of isoxazole make it possible for multiple non-covalent interactions, especially hydrogen bonds (hydrogen bond acceptor N and O), pi-pi stack (unsaturated five-membered ring), and hydrophilic interactions (overall hydrophilic profile with CLogP = 0.121). There is a shared feature for the organic compounds developed in the recent decades that the majority of them may have included a heterocycle ring.[1–3] The inclusion of isoxazole may contribute to the increased efficacy, decreased toxicity, and improved pharmacokinetics profiles.[4–6] Given that there is a wide spectrum of protein targets that isoxazole compounds could interact with, isoxazole compounds possesses broad biological activities including anticancer, antibacterial, antifungal, antiviral, anti-microbial, anti-TB, anti-inflammatory, etc. Successful applications of developing isoxazole compounds have resulted in multiple corresponding drugs in the market. Sulfisoxazole has been approved for the treatment of severe, repeated, or long-lasting urinary tract infections by inhibiting the enzyme dihydropteroate synthetase. Risperidone has been approved for the treatment of schizophrenia in adults and in adolescents, ages 13–17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10–17, by blockade of dopaminergic D2 receptors in the limbic system alleviates positive symptoms of schizophrenia. And Leflunomide has been approved for the management of the signs and symptoms of active rheumatoid arthritis (RA) to improve physical function and to slow the progression of structural damage associated with the disease. In this article, the applications of developing isoxazole compounds in treating various diseases are focused. Discussions are emphasized on strategies and approaches to corresponding compounds design, as well as the limitations and future perspectives. Patents of isoxazole in the past three years are shown in Table 1.

2. Isoxazole derivatives as anticancer agents

2.1. 3,4,5-Isoxazole compounds as anticancer agents

At the top of HSP90 has been recognized as an exciting molecular target for cancer treatment since HSP90 stabilizes a variety of proteins that have been implicated in oncogenesis. Consequently, many isoxazole based HSP90 inhibitors have been developed by researchers. Here we review potential HSP90 inhibitors with 3,4,5-tri-substituted isoxazole scaffold and their designing ideas.

NVP-AUY922 (**1**) (Fig. 1) is an experimental drug candidate developed by Vernalis for treating cancer. **NVP-AUY922** has shown promising activity in preclinical testing against several different tumor types[7] and has been under 28 clinical trials for years.[8]

In 2016, Chi Zhang et al. incorporated diversified amino acid derivatives to the 3-amido motif of the isoxazole scaffold based on **NVP-AUY922** to achieve more polar and apolar interactions These compounds showed significantly different potency against HSP90. Especially, compound **2** displayed high binding potency of 14 nM against HSP90 and inhibited H3122 human lung cancer cell and BT-474

* Corresponding author.
E-mail address: author@university.edu (H.-p. Sun).

https://doi.org/10.1016/j.bmc.2018.05.013
Received 28 March 2018; Received in revised form 6 May 2018; Accepted 10 May 2018
Available online 28 May 2018
0968-0896/

Table 1
Patents of isoxazole during the past three years (2016–2018).

No.	Patent No.	Patent date	Applicant (s)	Title
1	US2018030004 (A1)[77]	1-Feb-18	Novartis	Isoxazole hydroxamic acid compounds as lpxc inhibitors
2	US2017355684 (A1)[78]	14-Dec-17	Novartis	Crystalline isoxazole hydroxamic acid compounds
3	US2017334893 (A1)[79]	23-Nov-17	Enanta Pharm Inc	Isoxazole analogs as fxr agonists and methods of use thereof
4	US2017334894 (A1)[80]	23-Nov-17	Enanta Pharm Inc	Isoxazole derivatives as fxr agonists and methods of use thereof
5	US2017326152 (A1)[81]	16-Nov-17	Vernalis (R&D) Ltd; The Institute of Cancer Res; Cancer Research Tech Limited	Isoxazole compounds as inhibitors of heat shock proteins
6	KR20170124642 (A)[82]	10-Nov-17	Novartis	Isoxazole compound for the treatment of cancer
7	CN107216322 (A)[83]	29-Sep-17	Zhangzhou Health Vocational College	Synthesis method of s-triazolothio isoxazole
8	CN107056808 (A)[84]	18-Aug-17	Univ Shanghai	3-aryl substituted isoxazole and succinimide compound and synthetic method thereof
9	PH12017500530 (A1)[85]	7-Aug-17	Nat Cancer Center; Daiichi Sankyo Co Ltd	Isoxazole derivative as mutant isocitrate dehydrogenase 1 inhibitor
10	CN107011280 (A)[86]	4-Aug-17	Chemshuttle Inc	Preparation method of 7-bromo-6-chlorobenzo[*D*]isoxazole
11	US2017190676 (A1)[87]	6-Jul-17	Epizyme Inc	Isoxazole carboxamide compounds
12	US2017172987 (A1)[88]	22-Jun-17	Univ Texas	Isoxazole treatments for frontotemporal dementia
13	WO2017089892 (A1)[89]	1-Jun-17	AstraZeneca Ab	Deuterated isoxazole derivatives and their use as metabotropic glutamate receptor potentiators
14	CN106749218 (A)[90]	31-May-17	Xinjiang Technical Inst physics & Chemistry Cas	Coumarin phenyl isoxazole derivatives and applications thereof
15	CN106674215 (A)[91]	17-May-17	Xinyi Zhongnuo New mat Tech Co Ltd	Novel nanoscale isoxazole amide pesticide synthesis method
16	CN106632119 (A)[92]	10-May-17	Univ Hubei Science & Tech	A water-phase 'one-pot' synthesis method for isoxazole ring containing compounds
17	AU2017202134 (A1)[93]	20-Apr-17	Univ Texas	Isoxazole treatments for diabetes
18	US2017002329 (A1)[94]	5-Jan-17	Ashraf Muhammad	Generating cardiac progenitor cells from pluripotent stem cells using isoxazole or isoxazole like compounds
19	TW201643158 (A)[95]	16-Dec-16	Daiichi Sankyo Co Ltd; Nat Cancer Ct	Isoxazole derivative as mutated isocitrate dehydrogenase 1 inhibitor
20	CN106188094 (A)[96]	7-Dec-16	Shenzhen Rongxin Biotechnology Co Ltd	Isoxazole ring derivatives as well as preparation method and application thereof
21	CN106117156 (A)[97]	16-Nov-16	Univ Nantong	5-Phenyl isoxazole-containing stilbenoid compound and preparation method thereof
22	KR101663662 (B1)[98]	14-Oct-16	Korea Inst Sci & Tech	1 Novel aryl isoxazole derivatives as metabotropic glutamate receptor 1 antagonists
23	CN105924405 (A)[99]	7-Sep-16	Univ Guangxi Normal	Method for synthesizing isoxazole compound from nitrine and acetylenic ketone compound
24	WO2016135749 (A1)[100]	1-Sep-16	Council Scient Ind Res	Diosgenin acetate-isoxazole derivatives, process for preparation thereof and their antifungal activity
25	MX2016002742 (A)[101]	8-Jun-16	Abbvie Inc	Diastereoselective methods for synthesizing isoxazole compounds
26	CN105622536 (A)[102]	1-Jun-16	Univ Shangqiu Normal	Trifluoromethyl alkenyl isoxazole compound and preparation method and application thereof
27	US2016137639 (A1)[103]	19-May-16	Japan Tobacco Inc	Triazole-isoxazole compound and medical use thereof
28	US2016128984 (A1)[104]	12-May-16	Flatley Discovery Lab	Isoxazole compounds and methods for the treatment of cystic fibrosis
29	US2016096829 (A1)[105]	7-Apr-16	Basf Se	Substituted Isoxazole Derivatives
30	HK1209123 (A1)[106]	24-Mar-16	Hoffmann La Roche	Substituted isoxazole amide compounds as inhibitors of stearoyl-coA desaturase 1 (SCD1) A 1(SCD1)
31	CN105418529 (A)[107]	23-Mar-16	Univ Shangqiu Normal	4-nitryl isoxazole trifluoromethyl tertiary alcohol containing compound and preparation method thereof
32	CA2960279 (A1)[108]	17-Mar-16	Epizyme Inc	Isoxazole carboxamides as irreversible smyd inhibitors
33	CN105237491 (A)[109]	13-Jan-16	Univ Shanghai	Isoxazole compounds and synthetic method thereof

breast cancer cell with IC_{50} values of 42 and 57 nM. Molecular docking studies suggested that the central isoxazole core played a key role in their binding mode. Besides, the terminal valine moiety and the ethyleneglycol linker in compound **2** formed additional apolar and polar interaction network with a number of amino acid residues as expected.[9]

A series of new isoxazole derivatives linked by alkynes were designed and synthesized by Jian Sun et al. according to their speculation that the introduction of an alkynes group at C-4 of isoxazole could provide cation-π bond interaction with the Lys58 residue of HSP90 protein. Some compounds displayed improved anti-proliferative activity towards several human cancer cell lines with IC_{50} values in the low nanomolar range (**3**, **4** and **5**).[10]

Danqi Chen et al. conducted a fragment screening with the assistance of X-ray crystallography techniques. Compound **6** was screened out and was developed to a series of HSP90 inhibitors. Compared to **NVP-AUY922**, compound **6** is the reversed isoxazole ring. Among this series, compound **7** displayed strong inhibition of HSP90 in both molecular and cellular level. *In vivo* studies also showed statistically significant tumor growth inhibition. The T/C value of compound **7** was 18.35% at 50 mg/kg, almost twice strong than **NVP-AUY922** (T/C values was 34.06% at 50 mg/kg).[11]

Sharp discovered a novel 3,4-diarylpyrazole resorcinol HSP90 inhibitor **8** through high-throughput screening technologies and generated more potent pyrazole amide analogs by structure-based design, exemplified by compound **9**. Then, they compared the detailed biological properties of compound **9** and the corresponding isoxazole **10**. The isoxazole **10** (78 ± 15 nmol/L) displayed 9-fold antiproliferative potency greater than the corresponding pyrazole **9** (685 ± 119 nmol/L) when the mean values across the cancer cell line panel were compared. Meanwhile, isoxazole **10** also showed improved cellular uptake over pyrazole **9**.[12]

In 2016, Shi et al. designed and synthesized a series of scopoletin-isoxazole and scopoletin-pyrazole hybrids. Anticancer activities were evaluated against three human cancer cell lines including HCT-116, Hun7, and SW620 by MTT assay. Compared to scopoletin-pyrzazole hybrids, compounds with isoxazole structure exhibited better cytotoxic activities with IC_{50} values lower than 20 μM. Notably, compound **11** displayed significant anti-proliferative activity similar to sunitinib with IC_{50} values ranging from 8.76 μM to 9.83 μM and weak cytotoxicity on normal cells HFL-1 with the IC_{50} value of 90.9 μM. The results suggested that the introduction of isoxazole was an effective chemical modification to enhance the anticancer activity of scopoletin.[13]

Isoxazoles have been explored previously as BET bromodomain inhibitors.[14,15] **PNZ5 (12)**, a newly developed isoxazole, showed potent