European Journal of Medicinal Chemistry 80 (2014) 295–307

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Oxazolidinone derivatives: Cytoxazone–Linezolid hybrids induces apoptosis and senescence in DU145 prostate cancer cells

Annavareddi Naresh [a], Maddimsetti Venkateswara Rao [a], Sudha Sravanti Kotapalli [b], Ramesh Ummanni [b,*], Batchu Venkateswara Rao [a,*]

[a] Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
[b] Centre for Chemical Biology, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 15 January 2014
Received in revised form
20 March 2014
Accepted 22 April 2014
Available online 24 April 2014

Keywords:
Oxazolidinones
Cytoxazone
Linezolid
Anticancer
Apoptosis
Senescence

InChIKey:
FEXZFZUCRSWTRS-PTLVDUHHSA-N

ABSTRACT

In this study, we report the synthesis of novel oxazolidinone derivatives derived from linezolid **3** having *p*-methoxyphenyl group at C-4 position. *In vitro* evaluation for their anticancer activity toward cultured A549, DU145, HELA, and MCF7 were carried out. The series of compounds prepared displayed wide range of cytotoxicity in MTT assays (10–70 μM) across the cell lines tested. Of the all tested compounds **16** and **17** displayed good anticancer potential against A549 (lung) and DU145 (prostate) cancer cells. Further, to determine their anticancer potential, in the present study we have assessed effect of **17** on DU145 cells growth in *in vitro* assays. The results clearly demonstrated that the exposure of DU145 cells to **17** inhibits cell proliferation and induces apoptosis by activation of caspase-3 and -9. Long term exposure of DU145 cells to **17** induced cellular senescence confirmed by senescence marker β-galactosidase staining of cells on post exposure to **17**. The results from this current report support that the oxazolidinone derivatives with ethyl and acryl substitutions showed promising anticancer activity which will be helpful to develop further novel anticancer agents with better therapeutic potential.

1. Introduction

The leading cause of death in the world is cancer. Over 8.0 million people died of cancer and many more going to get effected with this disease in future [1]. The preliminary cancer treatment options remains either alone or in combination of radio therapy, surgery and chemotherapy. For the last several years continuing efforts are being made by industry and academia to develop useful chemotherapeutic agents. In this connection many class of compounds have been identified for their antitumour activity.

Oxazolidinone derivatives have a novel mechanism of action on cancer, HIV, monoamine oxidize, glutamate receptor antagonist, and metabotropic [2]. These are also new class of antibacterial agents and demonstrate potent *in vitro* and *in vivo* activity against important human pathogens, including multiple antibiotic-resistant strains of gram positive organisms [3]. Design of new oxazolidinones with different structural modifications for better therapeutic activity is a very active ongoing research [4]. Some of the oxazolidinones like "3-nitro-5–methyl-2-oxazolidone, 3-(2-hydroxy-3-(2-nitro-1H-imidazol-1-yl)propyl)-2-oxazolidinone, (4-(4-(bis(2-chloroethyl)amino)-2,5-dimethoxyphenyl)methylene aminophenyl)-2-oxazolidinone" are showing anticancer activity and are in early clinical trials [5]. Posizolid **1**, torezolid **2**, linezolid **3**, cytoxazone **4** and *epi*-cytoxazone **5** are showing interesting biological activities having the basic common oxazolidinone structure (Fig. 1). Posizolid **1** is an antibiotic under investigation by AstraZeneca for the treatment of bacterial infections [6]. Torezolid **2** has been used for complicated skin infections [7]. Linezolid **3** is the first example of new class of synthetic antibacterial compounds which block protein biosynthesis and used for the treatment of serious infections caused by Gram-positive bacteria [8]. Until now a number of structural modifications of linezolid **3** have been reported. Many research groups involved in the introduction of heterocyclic moieties replacing the rings A-, B-, or C [9] (Fig. 2). Cytoxazone **4** is a natural product shows cytokine-modulating activity by inhibiting the signalling pathway of Th_2 cells [10] and its C-5-epimer *epi*-cytoxazone **5**, which is a synthetic derivative, is also showing interesting activity [11]. One of the basic structural differences between cytoxazone **4** and other above compounds is the presence

* Corresponding authors.
E-mail addresses: ummanni@iict.res.in (R. Ummanni), venky@iict.res.in, drb.venky@gmail.com (B. Venkateswara Rao).

http://dx.doi.org/10.1016/j.ejmech.2014.04.062
0223-5234/

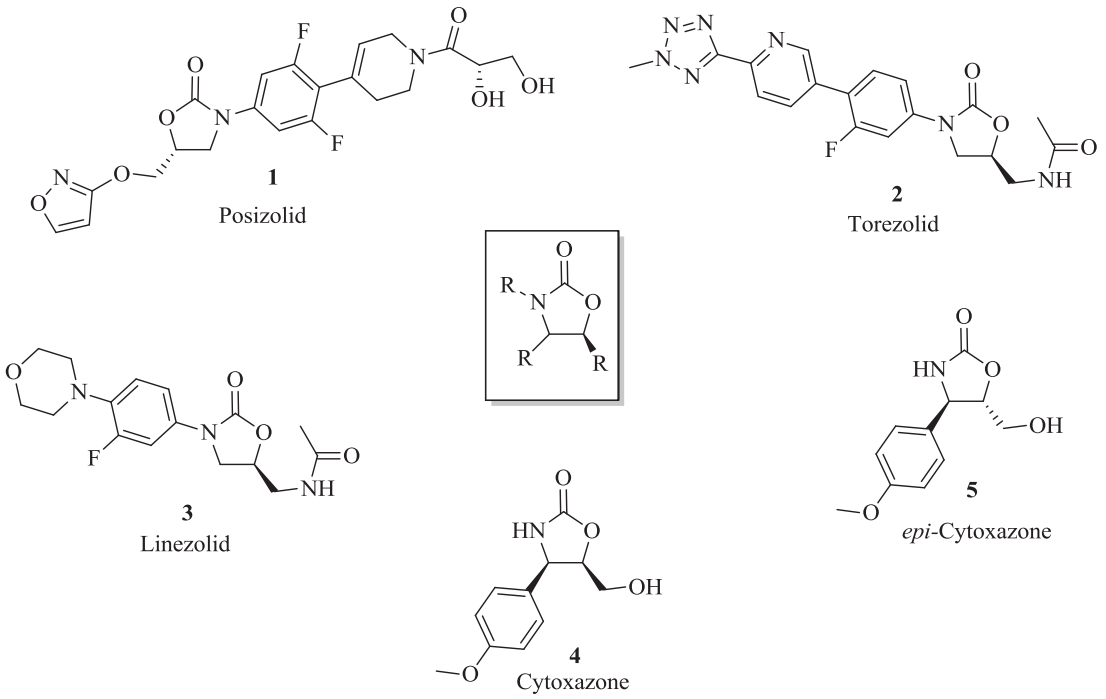

Fig. 1. Some of the active oxazolidinone derivatives.

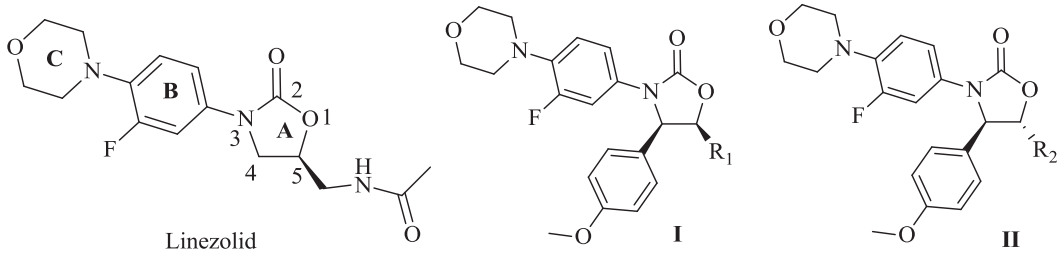

Fig. 2. Structure of linezolid **3** and new proposed structures (**I**, **II**).

of *p*-methoxyphenyl group at C-4 position in the oxazolidinone ring. We envisaged that the hybrid structures **I** & **II** of linezolid **3** & cytoxazone **4** and linezolid **3** & *epi*-cytoxazone **5** may be of some importance for new leads, since such kind of oxazolidinones to the best of our knowledge have not been synthesized. In addition a substituent at C-4 position creates a new stereo centre which gives the possibility of erythro and threo oxazolidinones and helps in studying the relation of stereochemistry with therapeutic action. In this context here in we describe the synthesis and anticancer activity of new hybrids having the *p*-methoxyphenyl functionality at the C-4 position.

2. Results and discussion

2.1. Chemistry

The retrosynthetic analysis for our new hybrid structures **I** (**9**, **10**, **11**) and **II** (**13**, **14**, **15**, **16**, **17**, **18**, **20**, **21**) were shown in Scheme 1. The required starting materials for our synthesis are cytoxazone **4** and *epi*-cytoxazone precursor **12** which have been synthesized using our earlier procedure [12]. The basic core structures of erythro **I** and threo **II** can be prepared by *N*-arylation of oxazolidinones **4** & **12** with iodo derivative **6** to give **9** & **13** and further manipulations of **9** & **13** should give the compounds **10** to **21**.

The desired iodo compound **6** (Scheme 2) for the synthesis of main scaffold for Buchwald coupling can be synthesized from **7** which in turn can be prepared from commercially available 1,2-difluoro-4-nitrobenzene [13]. The amine in compound **7** was converted to iodo by diazotization followed by iodination [14] to afford the compound **7** in 85% yield. Treatment of cytoxazone **4** with TBSCl afforded the compound **8** in 94% yield. The coupling between oxazolidinone **8** (Scheme 3) and iodo compound **6** in Buchwald conditions followed by deprotection of TBS-group with TBAF solution furnished the compound **9** in 80% yields [15]. The compound **9** was treated with benzoic anhydride to give the compound **11** in 90% yield. When **9** was treated with acrylic acid, DCC and DMAP interestingly it gave the compound **10** exclusively in 87% [16].

For preparing threo derivatives, the coupling (Scheme 4) between oxazolidinone **12** and iodo compound **6** have been achieved by Buchwald conditions to yield the scaffold **13** in 90% yield. The olefin in compound **13** was oxidized by O_3 in dichloromethane at −78 °C and then reduced by the $NaBH_4$ in methanol to afford the compound **14** in 87% yield. The compound **14** was made bezoyl derivative **15** (Scheme 5) by treating with benzoic anhydride and triethylamine in 77% yield. The compound **14** was made acryloyl derivative using acrylic acid, DCC and DMAP to give the compound **16** in 85%. The reduction of olefin in compound **13** (Scheme 6) with H_2 and Pd/C in MeOH gave the compound **17** in 85% yield and