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Research paper

Synthesis and biological evaluation of 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one structural derivatives as anti-cancer and apoptosis inducing agents

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ABSTRACT

A series of thirteen 5*H*-dibenzo [*b*,*e*][1,4]diazepin-11(10*H*)-one structural derivatives has been synthesized and evaluated for anti-proliferative activity against five human cancer cell lines. Compound **9a** exhibited potent tumour growth inhibition in all cell lines with IC_{50} values in the range of 0.71–7.29 μM. Experiments on lung (A549) and breast (MDAMB-231) cancer cell lines to investigate the mechanisms of growth inhibition and apoptosis inducing effects of **9a** showed that it arrested both cancer cell lines in the G2/M phase of cell cycle in a dose dependent manner. Hoechst staining analysis revealed that **9a** inhibited tumour cell proliferation through apoptosis induction. Additionally, the mitochondrial membrane potential (ΔΨm) was affected and the levels of reactive oxygen species (ROS) were raised. The simple synthetic preparation and their biological properties make these dibenzodiazepinone-triazole scaffolds promising new entities for the development of cancer therapeutics.

1. Introduction

Cancer is the leading global health burden that at some time will directly or indirectly affect the lives of most people. Local cancer treatments, such as surgical and radiation therapies are not always viable due to the position of the tumour in the body. Furthermore, these methods are often unsuccessful in completely removing tumours. Chemotherapy is a systemic cancer treatment and chemotherapeutic drugs interfere with the cell cycle and thus cell division, angiogenesis or induce tumour cell apoptosis by several signalling pathways. However, due to the high cancer mortality rate, development of drug resistance and undesirable side effects there is an urgent need to design and synthesise new anti-cancer drugs.

The dibenzodiazepinone [5,10-dihydro-11*H*-dibenzo[*b*,*e*] [1,4] diazepin-11-one]**1**(Fig. 1) scaffold is known to exhibit wide range of biological activities including neuroleptic [1], anti-inflammatory [2], anti-depressant [3], anti-microbial [4], anti-hypertensive [5] and anti-viral [6] efficacies. Moreover, dibenzodiazepinone research led to the discovery of drug leads such as Chk1 kinase inhibitors **2** (Fig. 1) [7] and the histone deacetylase HDAC [8] inhibitor **3**. Diazepinomicin **4** is an unusual farnesylated-dibenzodiazepinone secondary metabolite isolated [3,9] from *Micromonospora* and contains dibenzodiazepinone skeleton that is unprecedented among natural products and its biosynthesis [10] has been described recently. The anti-tumour, anti-bacterial and anti-inflammatory activities of **4** have also been reported [11]. Compound **4** (Fig. 1) induces apoptosis by selectively targeting the peripheral benzodiazepine receptor (PBR) [12].

On the other hand, many triazole containing compounds exhibit extensive range of pharmacological activities including potent anticancer properties [13]. For instance, cefatrizine, tazobactam

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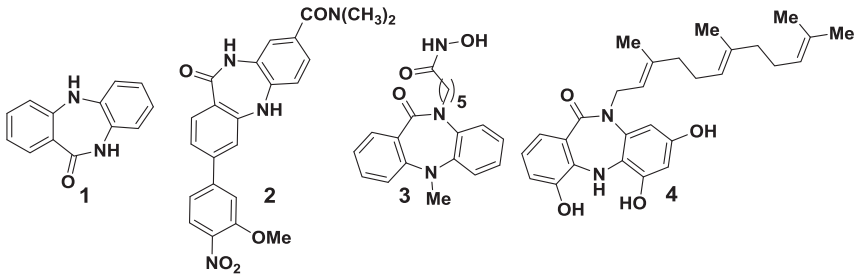

Fig. 1. Other Dibenzodiazepinones therapeutic compounds.

and carboxyamidotriazole are some of the triazole containing compounds which are in clinical or preclinical studies [14,15]. Among the triazoles, 1,2,3-triazoles are capable of interacting with the biological targets through *H*-bonding and are stable to metabolic degradation [16]. Based on these observations and inspired by the promising anticancer activities of dibezodiazepinones and 1,2,3-triazoles, we designed a series of dibezodiazepinone-triazole hybrid compounds with a view to produce promising anticancer agents.

The diverse therapeutic application of dibenzodiazepine derivatives and related compounds in medicinal chemistry has stimulated considerable synthesis interest in the construction of this tricyclic ring privileged scaffold. Eight chemical retro synthetic approaches are presented in Fig. 2. In 1985, a one-step synthesis delivered in a modest 30% yield the dibenzodiazepine scaffold [17,18] by refluxing 2-chlorobenzoic acid and *o*-phenylendiamine in the presence of copper as catalyst and chlorobenzene as solvent that is denoted as route I. The reaction product from 2-iodoaniline and a substituted1-fluoro-2-nitrobenzene was then employed in a palladium mediated intramolecular carbonylation reaction [19] to provide the 1,4-benzodiazepine product identified as route II. The ring closing reductive lactamization methodology [20] using the dissolving-metal condition of iron and acetic acid was another synthesis approach [route III]. The amine ring closure path gave an efficient synthesis of 1,4-benzodiazepines [21] *via* the double amination of ortho-substituted aryl bromides is shown as route IV. The one step preparation of dibenzodiazepines [22] and related derivatives illustrated as route V was accomplished by the palladium-catalyzed reaction between alkyl 2-(2-chlorophenylamino)benzoate and ammonia. The utilization of $POCl_3$ enabled substituted ethyl 2-(phenylamino)phenylcarbamate to participate in an intramolecular lactamization *via* the electrophilic aromatic substitution to furnish route VI to the desired 1,4-benzodiazepine [23]. The synthesis of the target compound was also achieved through a high temperature, Cs_2CO_3 driven, double nucleophilic aromatic substitution reaction [24] of anthranilamide with 2,5-dichloronitrobenzene depicted as route VII. Recently, route VIII, the 1,4-benzodiazepine core [25] structure was assembled from the substituted *N*-methoxy-2- (methylphenylamino) benzamide through an intramolecular PIDA-mediated oxidative C—N bond synthesis in 82% yield in this cyclisation step.

2. Results and discussion

2.1. Chemistry

We utilized a slightly modified one step dibenzodiazepine synthesis [route I in Fig. 2]. Our dibenzodiazepinone-triazole analogues were prepared following the reaction sequence depicted in Scheme 1. Initially, ethyl-2-iodobenzoate **5** was reacted with *o*-phenylenediamine **6** in presence of 10 mol% CuI in a pressure tube at 100 °C to give the dibenzodiazepinone **1** in 50% yield [26].

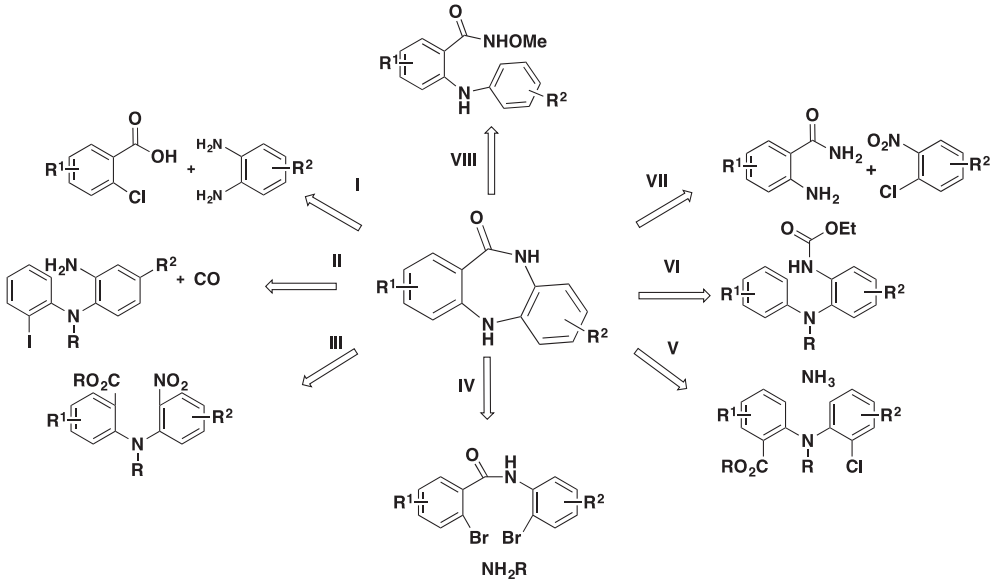

Fig. 2. Retrosynthetic routes I to VIII providing the medicinal dibenzodiazepine scaffold.