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Original article

Exploring new selective 3-benzylquinoxaline-based MAO-A inhibitors: Design, synthesis, biological evaluation and docking studies

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ABSTRACT

In this investigation, we searched for novel MAO-A inhibitors using a 3-benzylquinoxaline scaffold based on our earlier findings. Series of *N*′-(3-benzylquinoxalin-2-yl)acetohydrazide, **4a**, *N*′-(3-benzylquinoxalin-2-yl)benzohydrazide derivatives **4b**–**f**, *N*′-[2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl) acetyl]benzohydrazide derivatives **7a**–**d**, (9*H*-fluoren-9-yl)methyl 1-[2-(2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl)acetyl)-hydrazinyl]-2-ylcarbamate derivatives **8a**–**c**, 2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*′-benzylidene acetohydrazide derivatives **9a**–**h**, and ethyl 2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl)acetate derivatives **10a**–**e** were synthesized and evaluated *in vitro* as inhibitors of the two monoamine oxidase isoforms, MAO-A and MAO-B. Most of the compounds showed a selective MAO-A inhibitory activity in the nanomolar or low micromolar range. Compounds **4e** and **9g** were the most potent derivatives with high MAO-A selectivity and their molecular docking studies were performed in order to rationalize the obtained biological result.

1. Introduction

Depression has been reported to be the fourth global burden of disease, with nearly 12% of the global disability adjusted life years [1]. In addition to the psychological stress on patients and families, depression contributes to the development and progression of systemic and organ diseases [2–5]. Anxiety disorders, which often precede and co-occur with depression, are found in 10–21% of children and adolescents [6]. In the Middle East (namely, Egypt and the Kingdom of Saudi Arabia (KSA)) changing in the socioeconomic status have been shown to be associated with increased chronic diseases including chronic mental diseases like depression [7–9].

The monoamine oxidase inhibitors (MAOIs) were the first drugs used to treat depression. They work by blocking the breakdown of a number of neurotransmitters involved in depression *via* an enzyme, MAO. MAO (EC 1.4.3.4; MAO) is a flavoprotein localized in the outer mitochondrial membrane and present in practically all mammalian tissues. The primary role of MAO lies in the metabolism of amines and in the regulation of neurotransmitter levels and intracellular amine stores [10]. Two isoforms of MAO (MAO-A and MAO-B) have been found [11]. These two forms of MAO are characterized by their different affinities to inhibitors and their different specificities to substrates [12]. MAO-A preferably metabolizes serotonin, adrenaline, and noradrenaline [13], whereas β-phenylethylamine and benzylamine are predominantly metabolized by MAO-B [14]. Tyramine, dopamine, and some other important amines are common substrates for both isoenzymes [15].

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Nowadays, the therapeutic interest of MAOIs falls into two major categories. MAO-A inhibitors have been used mostly in the treatment of mental disorders, in particular depression and anxiety [16–18], while MAO-B inhibitors could be used in the treatment of Parkinson's disease and Alzheimer's disease [19,20].

In our efforts to add to the development of novel selective MAO-A inhibitors, we have recently focused on utilizing the 3-benzylquinoxaline scaffold where compound such 3-benzyl-2-(2-morpholin-4-yl-ethyl)amino-quinoxaline **I** showed potent and high selectivity MAO-A inhibition activity [21,22]. We have also showed that a structurally related pyridazinylacetic acid derivatives synthesized in our laboratory were able to inhibit MAO-A with high selectivity index (SI) values [23]. The main goal of the present study was to synthesize a new family of hybrid quinoxaline derivatives **II**–**IV** based on the 3-benzylquinoxalin-2(1*H*)-one unit (Chart 1 and Chart 2). The rational design of the new compounds was based on the following considerations: (i) the possession of the hydrazido functionality (*e.g.* Iproniazid), (ii) the presence of the benzamido functionality (*e.g.* Moclobemide), and (iii) the keeping benzylquinoxalinyl group which seems to play a role in orientation and complex formation at the active site of the enzyme.

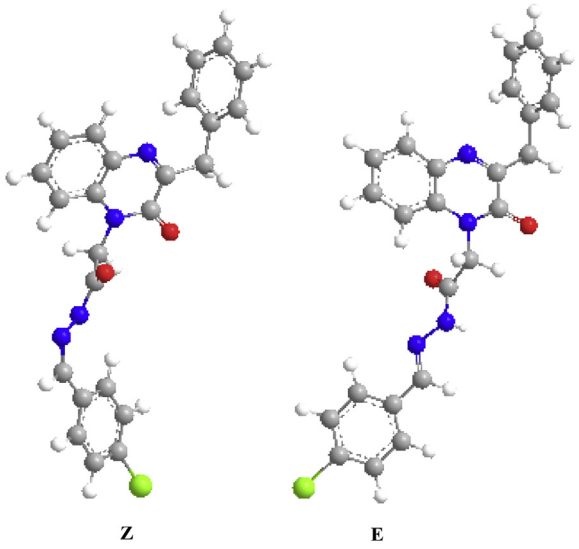

Fig. 2. The Z- and E-forms of compound **9d** using molecular mechanics MM2 and PM3 calculations.

2. Results and discussion

2.1. Chemistry

In our synthesis, the quinoxaline scaffold was easily prepared according to the reported method in the literature (Scheme 1) [24]. The reaction of compound **1** with phosphoryl chloride afforded the rapid formation of the corresponding 2-benzyl-3-chloroquinoxaline **2** after neutralization with saturated sodium bicarbonate (Scheme 1). Further reaction of **2** with hydrazine hydrate in ethanol as a solvent afforded the 2-benzyl-3-hydrazinoquinoxaline **3** (Scheme 1) [24].

The syntheses of *N*′-(3-benzylquinoxalin-2-yl)acetohydrazide, **4a** and *N*′-(3-benzylquinoxalin-2-yl)benzohydrazide derivatives **4b**–**f** were carried out in good yield *via* amide coupling of the acids with 2-benzyl-3-hydrazinoquinoxaline **3** using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) as a coupling reagent in the presence of triethyl amine (TEA) in dimethylformamide (DMF) at 0 °C (Scheme 2). The structure of compounds **4a**–**f** was confirmed by elemental analysis, IR, and NMR spectroscopy.

The reaction of the 3-benzylquinoxalin-2(1*H*)-one **1** with ethyl bromoacetate in dimethylformamide in the presence of potassium iodide and sodium bicarbonate afforded ethyl 2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl)acetate **5** as a single product as showed by TLC using ethyl acetate/hexane (1:1) as an eluent (Scheme 3) [25]. The structure of the quinoxaline derivatives as *N*-alkylated **A** rather than *O*-alkylated products **B** (Fig. 1) [26] were secured by analyzing the HMBC spectrum of **5**. Heteronuclear correlation was observed between the singlet at δ 4.96 ppm of the methylene hydrogens of the acetic acid function and the carbons at δ 130.16 (C-10Q), 154.4 (C-2Q) and 167.18 ppm (C=O ester), while the benzyl CH_2 hydrogens at δ 4.28 ppm showed correlation to carbons at 129.62 (C-2′Ph, 6′Ph), 136.96 (C-1′Ph), 154.43 (C-3Q) and 159.18 ppm (C-2Q).

Hydrazinolysis of the ethyl ester group in **5** was carried out in methanol under reflux for 4 h to afford the corresponding hydrazide **6** in 74.4% yield (Scheme 3). Our initial studies proceed by reacting aromatic carboxylic acids and hydrazide **6** in the presence of various coupling conditions, such as 1-hydroxybenzotriazole (HOBt) in the presence of 1,1,3,3-tetramethyl-2-fluoroformamidinium hexafluorophosphate (TFFH) or HATU at 0 °C and TEA as base in DMF and recrystallize from methylene dichloride (MDC). Both methods gave satisfactory yields of the desired *N*′-(2-(3-benzyl-2-oxoquinoxalin-1(2*H*)-yl) acetyl) benzohydrazide derivatives **7** (Scheme 3).

As reported earlier such structure of type **7** could exist in four possible conformational forms (namely; EE, EZ, ZE and ZZ) due to the hindering of rotation of the C–N(1) and the C–N(2) bond [27]. However, our ^{1}H NMR spectra of compounds **7a**–**d** showed broad NH signals with no fine splitting indicated fast rate of rotation. As a prototype the ^{1}H NMR spectra of **7b** in DMSO-d_6 shows a singlet peak at δ 4.14 ppm corresponding to the benzyl CH_2 protons. Two other peaks were observed equivalent to two protons at δ 4.98 and 5.25 ppm, in ratio 2:1, corresponding to only one methylene group (CH_2) and since no definite conformers could be assigned they will just be named A and B.

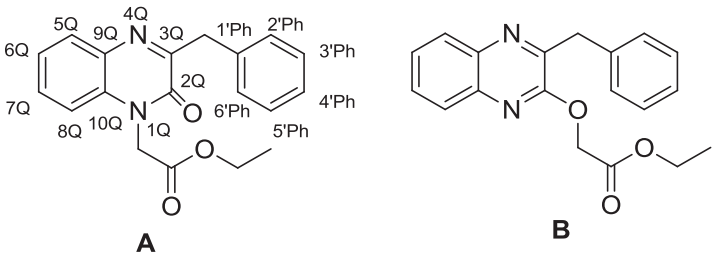

Fig. 1. The two expected structures of compound **5**.