European Journal of Medicinal Chemistry 79 (2014) 282–289

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and biological activity of 4-aryl-3-benzoyl-5-phenylspiro [pyrrolidine-2.3′-indolin]-2′-one derivatives as novel potent inhibitors of advanced glycation end product

Anjandeep Kaur [a], Baldev Singh [a,*], Bhawna Vyas [a], Om Silakari [b]

[a] Department of Chemistry, Punjabi University, Patiala 147002, India
[b] Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India

ARTICLE INFO

Article history:
Received 18 November 2013
Received in revised form
11 March 2014
Accepted 5 April 2014
Available online 8 April 2014

Keywords:
Azomethine ylide
Pyrrolidine
Cycloaddition
Stereoselective
Antiglycation

ABSTRACT

Diabetic complications and their detrimental effects caused by sugar derived substances, have been the serious issue for the last few years and have yet not been fully combated. The key point of the present study is to synthesize some newer chemical entities which can eradicate such ailments to the maximum possible extent. So with this aim synthesis of some biologically interesting spiro-indolone-pyrrolidine derivatives was accomplished by 1,3-dipolar cycloaddition reaction of azomethine ylide **6** generated *in situ* from isatin and benzyl amine with the substituted α,β-unsaturated carbonyl compounds **3** as dipolarophile, leading to the formation of new 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-one derivatives **7** stereoselectively in excellent yields. The synthesized compounds have been screened for their advanced glycation end (AGE) product formation inhibitory activity on the basis of their ability to inhibit the formation of AGEs in the bovine serum albumin (BSA)-glucose assay and have been found to exhibit significant activity against AGE formation.

1. Introduction

Diabetes mellitus (DM) is a long-term issue, characterized by a state of fasting hyperglycemia [1]. DM and its complications, arising subsequently wizard macrovascular (coronary artery disease, stroke) and microvascular (retinopathy, neuropathy, nephropathy, and other microangiopathies) are the fourth most important causes of mortality. Hyperglycemia is one of the causative factors of diabetic complications, like atheroma, hypertension and microangiopathy. Its detrimental effects are mostly attributed to the formation of sugar-derived substances called advanced glycation end products (AGEs) [2]. The presence of advanced glycation end products (AGEs) is closely related to hyperglycemia and their patho-biochemistry could explain many of the changes observed in diabetes related complications. AGEs are a heterogeneous group of molecules formed by the non-enzymatic reaction of reducing sugars and the free amino groups of proteins, lipids, and nucleic acids [3]. Sugars react reversibly with the amino groups in those macromolecules to form Schiff's base adducts which further undergo Amadori rearrangement along with subsequent oxidation, dehydration and cyclization to form stable AGEs. The consequence of AGE formation is the reticulation of proteins. This phenomenon has been observed in long-lived proteins such as tissue collagen, lens crystallin, fibronectin, tubulin, laminin, actin, hemoglobin, albumin and lipids associated with low-density lipoproteins. The formation and accumulation of increased AGEs have been implicated in the development of cataracts, uremia, atherosclerosis, Alzheimer's disease, Parkinson's disease and above all, clinical complications of type 2 diabetes, such as micro- and macroangiopathy, retinopathy, nephropathy, neuropathy and ulcer [4–12].

The valuable and diverse biological activity of molecules containing pyrrole, spiropyrrolidine, spiro-indolone-pyrrolidine, pyrrolidinone and indole moieties confers on them a high pharmacological value. Spiropyrrolidine and oxindole or indolone ring system forms the core structure of many pharmacological agents and alkaloids which find use as indigenous medicine [13–19]. Spiro-indole-pyrrolidine derivatives exhibit a wide array of biological activities like anti-bacterial [20,21] anti-fungal [22], acetylcholinesterase inhibitors [23], anti-cancer [24] anti-inflammatory [25], anti-tubercular [26,27], anti-leukemic [28] anti-convulsant [29] and anti-viral [30].

* Corresponding author.
E-mail addresses: singhbldv52@gmail.com, drbaldev.chem@yahoo.com (B. Singh).

http://dx.doi.org/10.1016/j.ejmech.2014.04.022
0223-5234/

Differently substituted spiropyrrolidine-tetrones derivatives were reported to be active for the inhibition of aldose reductase activity, the enzyme responsible for diabetic complications [31,32]. Ko et al. and Kim et al. reported the aldose reductase inhibitory activity of spirosuccinimides which are pyrrolidine-dione derivatives [33,34]. Substituted piperidinyl glycinyl 2-cyano-4,5-methano pyrrolidines and cyano-pyrrolidine derivatives were evaluated as potent and stable dipeptidyl peptidase IV inhibitors, thus useful for the treatment of diabetes [35,36]. Many pyrrolo[1,2-*c*]imidazole-1,3-dione moieties and their analogs rosiglitazone and pioglitazone have been developed as potent inhibitors of aldose reductase and were proposed as anti-diabetic agents [37,38]. Polyhydroxylated pyrrolizidine alkaloids, Uniflorine and Alexine, and many dispiropyrrolidine derivatives synthesized through 1,3-dipoar cycloaddition of azomethine ylides have also been found to be anti-diabetic in nature [39–41].

Many hexahydro-pyridoindole derivatives serve as a potential remedy for diabetes induced abnormalities due to their aldose reductase inhibitory activity [42,43]. Li et al. evaluated the insulin sensitizing and glucose lowering abilities of indole derivatives [44]. Indolyl-carboxylate moieties act as dual action anti-diabetic agents that inhibit glycogen phosphorylase and activate glucokinase [45]. Dong et al. have also reported that indole derivatives possess potent PPARc protein binding activity comparable to rosiglitazone [46]. The anti-diabetic activity of fluorinated spiro-indole-thiazinones/thiazolidinones was also comparable to the standard drug Metformin [47]. Pyrimido[1,2-*a*]indole moieties have also been used as oral hypoglycemic agents [48].

Jang et al. reported the advanced glycation end product formation inhibitory activity of pyrrolidinone epicathechins [49]. Pyrrolidine-carboxamide and pyrrolidine-carbothioamide derivatives were also reported as advanced glycation end product inhibitors by Shantharam et al. [50]. Khan et al. reported the indolone based bis-Schiff bases of isatin to exhibit advanced glycation end product inhibitory activity [51].

Thus the spiro-indolone-pyrrolidine moieties serve as versatile synthetic intermediates with immense biological activities including a potential to inhibit advanced glycation end product formation. So in continuation with our previous research activity directed towards construction of pyrrolo-isoxazolidines as bioactive heterocycles especially those associated with advance glycation end product formation inhibitory activity [52], the present study has been designed to synthesize variously substituted spiro-indolone-pyrrolidines from azomethine ylide substrates and to evaluate these compounds for their advanced glycation end-product formation inhibitory activity. The finding that spiro-indolone-pyrrolidine moieties display high efficacy in AGE-inhibitory activity may open up new avenues for the development of therapeutics targeted against protein glycation in hyperglycemic conditions.

The theoretical calculations of frontier molecular orbital (FMO) energies have proven to be an important tool in these reactions for predicting the stability of the synthesized products and evaluating the mechanism and reactivity of azomethine ylide cycloadditions, on the basis of both thermodynamic and kinetic aspects.

2. Results and discussion

2.1. Chemistry

Our synthetic approach was based on a three-component strategy involving the 1,3-dipolar cycloaddition between α,β-unsaturated carbonyl compounds **3a–i** and non stabilized azomethine ylide, generated *in situ via* condensation of isatin and benzyl amine in refluxing methanol. The starting, α,β-unsaturated carbonyl compounds i.e. chalcones **3** (Scheme 1) were synthesized by following the procedure as reported in literature [53]. This cycloaddition proceeded in a highly regio- and stereocontrolled fashion to afford single product i.e. 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-one derivatives (**7a-i**), as indicated by TLC in excellent yields (Scheme 2). This cycloaddition is regioselective with the electron-rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of **3a-i**, and is stereoselective, affording only one diastereomer exclusively, despite the presence of three stereocenters in the product as found in many similar cycloaddition studies [54,55].

Structural elucidation of the 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-ones was unambiguously accomplished by using one and two dimensional spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, NOESY, D_2O-exchange, ESI-MS) and elemental analyses data as described for **7a**. In the IR spectrum of 3-benzoyl-4,5-diphenylspiro[pyrrolidine-2.3′-indolin]-2′-one (**7a**) the -NH group of indolone moiety exhibited a sharp absorption peak at higher frequency i.e. 3338 cm^{-1} due to the presence of adjacent carbonyl group while the peak at lower frequency 3210 cm^{-1} was assigned to -NH group of pyrrolidine ring. A strong absorption band at 1701 cm^{-1} was due to indolone carbonyl moiety and a shoulder band at 1686 cm^{-1} due to benzoyl carbonyl. However, in the ^{1}H-NMR spectrum it displayed a singlet at δ 10.41 (1H for -NH group of indolone moiety), multiplet signal at δ 7.45-6.42 (equivalent to 19H, Ar-H), a broad doublet at δ 4.99 (1H, H-5) due to its coupling with H-4 (J = 10.24 Hz) and broad nature due to further slight interaction with ^{1}N-H proton, another doublet at δ 4.61 (1H, H-3) due to coupling with proton H-4 (J = 10.56 Hz) and a broad triplet at δ 4.04 (2H, H-4 and ^{1}N-H) due to coupling of H-4 with both the protons H-3 and H-5 (J = 10.44 Hz) and the distorted nature of triplet due to mergence of ^{1}N-H peak in this triplet. The presence of -NH protons was further supported by measuring the ^{1}H-NMR spectra in the presence of D_2O as discussed in Supporting information (Fig. 1 in Supporting information).

Further confirmation of the structure comes from the 2-dimensional ^{1}H,^{1}H-COSY spectrum (Fig. 2 in Supporting information). As evident from the ^{1}H-NMR spectrum, the most downfield doublet in the aliphatic region at δ 4.99 was assigned to proton H-5 of the pyrrolidine ring due to the presence of an adjacent nitrogen atom and its identification triggers the assignment of all the connected protons in the ring by its ^{1}H,^{1}H-COSY spectral analysis. From the ^{1}H,^{1}H-COSY correlation of H-5 (off diagonal cross peaks at δ 4.99/4.04), the triplet at δ 4.04 (J = 10.44 Hz) was assigned to the adjacent proton i.e. H-4. Further from the COSY correlation of proton H-4, as evident from the cross peaks at δ 4.04/4.61, the doublet at δ 4.61 (J = 10.56 Hz) was assigned to the adjacent H-3 proton.

In the NOESY (Fig. 3 in Supporting information and Fig. 1) spectrum, there existed correlation cross peaks from protons H-3/H-5 at δ 4.62/4.99 showing the syn-geometry of these protons. Further the cross peaks from protons H-3/(H-2‴, H-6‴) at δ 4.62/7.30 and H-5/(H-2‴, H-6‴) at δ 4.99/7.30 indicated the spatial proximity of H-3 and H-5 with the C_4-phenyl ring protons which signified the cis-relationship between H-3, H-5 and C_4-phenyl ring. The syn-geometry of H-4 and C_5-phenyl ring was evident from the off diagonal cross peaks at δ 4.04/7.34 due to protons H-4/(H-2⁗, H-6⁗). Besides this -NH proton of indolone ring also revealed the cross peak with proton H-7′ proving these protons to lie in the same plane.

The ^{13}C-NMR spectrum of **7a** exhibited the presence of two carbonyl carbons, one due to benzoyl and another due to indolone moiety at δ 196.76 and δ 181.72 respectively and the signals of aromatic carbons in the region of δ 141.36-108.90. The spiro carbon of the pyrrolidine ring appeared as the most downfield signal at