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Synthesis and evaluation of novel 2,3,5-triaryl-4*H*,2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-diones for advanced glycation end product formation inhibitory activity

Anjandeep Kaur [a], Baldev Singh [a,*], Amteshwar Singh Jaggi [b]

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

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ABSTRACT

The synthesis of some biologically interesting pyrrolo-isoxazolidine derivatives was accomplished by the 1,3-dipolar cycloaddition reaction of substituted azomethine N-oxides **1** with substituted *N*-aryl maleimides **2** leading to the formation of new stereoisomeric 2,3,5-triaryl-4*H*,2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione derivatives **3** 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. All the synthesized compounds have been found to exhibit significant activity against AGE formation.

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Diabetes is an endocrine disorder, which results from an absolute/relative deficiency of insulin or insulin resistance and is characterized by hyperglycemia. As one of the most prevalent metabolic syndromes word-wide, this disease results in short-term metabolic changes in lipid and protein metabolism and long-term irreversible vascular and connective-tissue changes due to which life expectancy of diabetic patients is only two-thirds of that of the normal population.

Non-enzymatic reaction between reducing sugar and free amino group of proteins, also known as Maillard reaction is initiated by the formation of Schiff bases between the sugar carbonyls and the free amino groups of the proteins, which is followed by isomerization (Amadori Rearrangements), generating a relatively stable aminoketose derivatives. The rearrangement, oxidation and reduction of these derivatives which are further capable of acting as protein cross linking agents, result in the formation of several high molecular weight protein aggregates and other fluorescent entities, referred as advanced glycation end products (AGEs) such as pentosidine, carboxymethyllysine, crossline and pyralline.[1,2] Thus AGEs inactivate proteins or modify their biological activities, leading to microvascular and macrovascular complications in diabetes mellitus and their accumulation on the tissues and organs results in oxidative stress, inflammation and vascular damage which further trigger a sequence of tissue dysfunction and thus are responsible for the development of atherosclerosis, retinopathy, cataract, nephropathy, neuropathy and for increased risk of myocardial infarction and stroke.[3–7] The crosslinked protein, for example, crosslinked collagen, is postulated to confer pathological conditions found in patients with diabetes and aging, such as arterial stiffness and decreased myocardial compliance, resulting from the loss of collagen elasticity.[8,9] Also the enhanced formation of AGEs exists in the blood and tissues of patients in various pathophysiological states, such as atherosclerosis, Alzheimer's disease, end-stage renal disease (ESRD), rheumatoid arthritis and liver cirrhosis.[10,11] Thus, agents that inhibit the formation of AGEs are purported to have therapeutic potentials in patients with diabetes and age-related diseases. Over the last few decades, numerous AGE-inhibitors have been identified, many of which belongs to natural products like plant extracts from various vegetative and reproductive parts of *Artocarpus lakoocha*,[12] *Cassia tora*,[13] *Cordia sinensis*,[14] *Hedyotis diffusa*[15] etc. and various kinds of chilies and spices for example, alligator pepper, ginger, nutmeg etc.[16,17] However many of them upon clinically testing as AGE-inhibitors proved to be therapeutically inadequate because of their low efficacy.

The valuable and diverse biological activity of molecules containing pyrrolo-isoxazolidines, isoxazolidine, pyrrole and pyrrolidinone moieties confers on them a high pharmacological value. Michael et al reported isoxazolidine ring fused with ring D of steroidal moieties as potential anti-inflammatory agents and such analogues have found clinical status.[18] Pyrrolo-isoxazolidine derivatives also exhibit a wide array of biological activities like

* Corresponding author. Mobile: +91 9988302741.
E-mail address: drbaldev.chem@yahoo.com (B. Singh).

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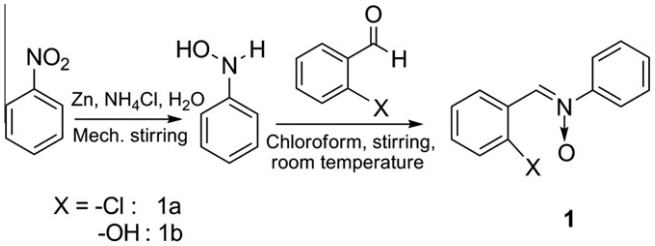
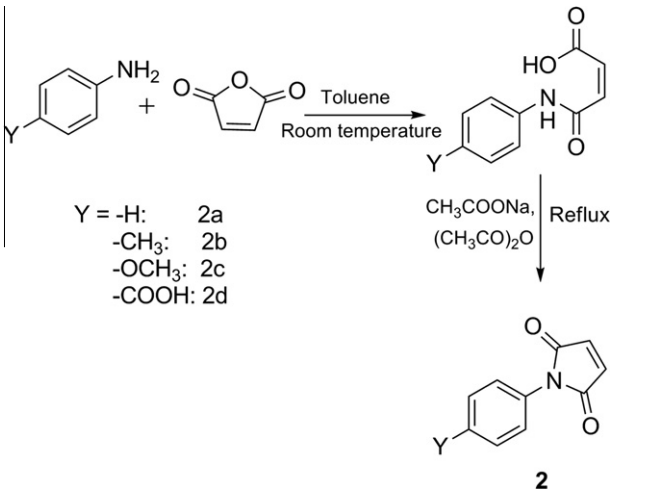
anti-HIV,[19] anti-bacterial,[20,21] anti-fungal,[22] anti-cancer,[23] anti-tuberculosis,[24,25] and have also been present as basic moiety in broad spectrum antibiotics like negamycin and 3-epinegamycin.[26] Nicolaou et al and Negoro et al have reported substituted pyrrol-1-ylacetic acids and tetrahydropyrrolo[1,2-*a*]pyrazine derivatives to be active for inhibition of aldose reductase, the enzyme responsible for diabetic complications.[27,28] Ilyin et al found a series of novel heterocyclic combinatorial libraries containing 4*H*-thieno[3,2-*b*]pyrrole, thieno[2′,3′:4,5]-pyrrolo[1,2-*d*][1,2,4]triazine and thieno [2′,3′:4,5]pyrrolo[1,2-*a*]pyrazine heterocyclic moieties to be antidiabetic in nature.[29] Uniflorine and Alexine which are polyhydroxylated pyrrolizidine alkaloids, synthesized by 1,3-dipolar cycloaddition of nitrone and alkene has also been found to be antidiabetic in nature.[30,31] The isoxazolyl-serine and isoxazole based peroxisome proliferator activated receptor agonists have antidiabetic properties and show robust insulin sensitizing and hypolipidemic activities in clinical trials.[32,33] The other isoxazole and isoxazolidine-3,5-dione derivatives have been used as antidiabetic agents.[34,35]

Thus the pyrrolo-isoxazolidine moieties serve as versatile synthetic intermediates with immense biological activities including a potential to inhibit advanced glycation end product formation. Therefore, the present study was designed to synthesize variously ortho-substituted nitrones and their cycloproducts pyrrolo-isoxazolidines and to evaluate these compounds for their advanced glycation end-product formation inhibitory activity. This is the first report on AGE-inhibitory activity exhibited by pyrrolo-isoxazolidine moieties which due to their high efficacy may open new avenues for the development of therapeutics targeted against protein glycation in hyperglycemic conditions.

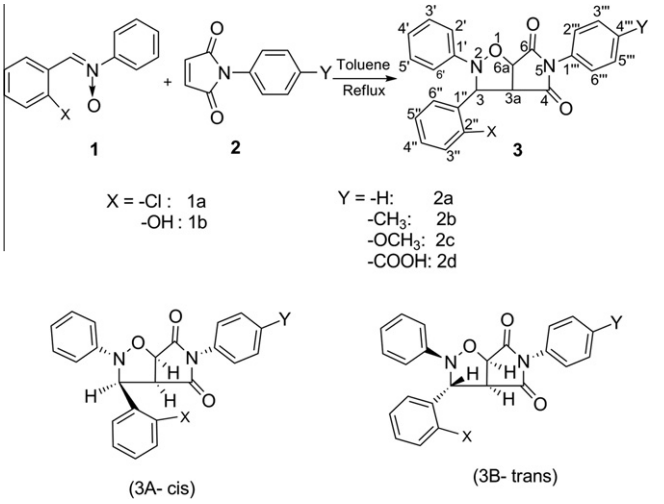
As can be seen from the results recorded (Table 1 in Supplementary data), in all examples examined, a smooth reaction proceeds to give isoxazolidines (**3a**–**h**) exclusively in moderate to good yields via regioselective cycloaddition of azomethine N-oxides and maleimides. The starting compounds, azomethine N-oxides **1** (Scheme 1) and maleimides **2** (Scheme 2) were synthesized by following the similar procedure as reported in literature.[36,37] Equimolar quantities of **1** and **2** in sodium dried toluene under refluxing conditions gave a mixture of diastereoisomers (Scheme 3) of 2,3,5-triaryl-4*H*,2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione derivatives **3a–h**, which were separated through column chromatography into two diastereomers **3–A** and **3–B** using hexane:ethyl acetate mixture in ratio of 9:1 as eluent.[38] The stereochemical assignment of the these diastereomers was made on the basis ^{1}H NMR, ^{1}H NMR COSY and ^{1}H NMR NOESY spectral data which revealed the coupling patterns for both the diastereomers that allowed for the differentiation between the two molecules using their obtained spectra. The isomers showing C^3–H and C^{6a}–H as doublets and C^{3a}–H as doublet of doublet on coupling with both protons C^3–H and C^{6a}–H were assigned as cis geometry and the isomers showing C^3–H as singlet, C^{3a}–H and C^{6a}–H as doublets in their ^{1}H NMR spectra were assigned as trans geometry.



Scheme 1. Schematic diagram describing the synthesis of differently substituted nitrones.



Scheme 2. Schematic diagram describing the steps in the synthesis of maleimides from differently substituted aniline derivatives.



Scheme 3. Schematic diagram describing the synthesis of cis and trans isomers from differently substituted diaryl nitrones and maleimides.

In their I.R. spectra these derivatives exhibit a strong absorption band (ν_{max}) in the range 1712–1717 cm^{-1} and a shoulder band in the range 1746–1792 cm^{-1} due to imide carbonyl groups. However, in the ^{1}H NMR spectra *cis*-3-(2-chlorophenyl)-2,5-bis(phenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**3a**–**A**) displays a doublet of doublet at δ 4.06 (1H, H^{3a}) due to coupling with both H^3 and H^{6a} (J = 9.00 Hz and 7.84 Hz), a doublet at δ 4.90 (1H, H^3) due to coupling with proton H^{3a} (J = 9.08 Hz), a another doublet at δ 5.28 (1H, H^{6a}) due to coupling with H^{3a} (J = 7.80 Hz), multiplet signal at δ 6.60–7.65 (14H, Ar–H). While the ^{1}H NMR spectrum of *trans*-3-(2-chlorophenyl)-2,5-bis(phenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (**3a**–**B**) displays a partially resolved doublet of doublet at δ 4.05 (1H, H^{3a}) due to coupling with H^{6a} (J = 7.40 Hz) and minor coupling with H^3, a doublet at δ 5.05 (1H, H^{6a}) due to coupling with H^{3a} (J = 7.48 Hz), a singlet at δ 6.11 (1H, H^3) and multiplet signal at δ 6.53–7.77 (equivalent to 14H, Ar–H).

In ^{1}H NMR COSY spectra of cis isomer **3a–A** (Fig. 1), the presence of off diagonal cross peaks from protons H^{3a}/H^3 at δ 4.06/4.90 and H^{3a}/H^{6a} at δ 4.06/5.28 indicate the syn-geometry of all the three protons, while the absence of cross peaks from protons H^{6a}/H^3 at δ 5.05/6.11 and existence of very minor cross peaks from protons

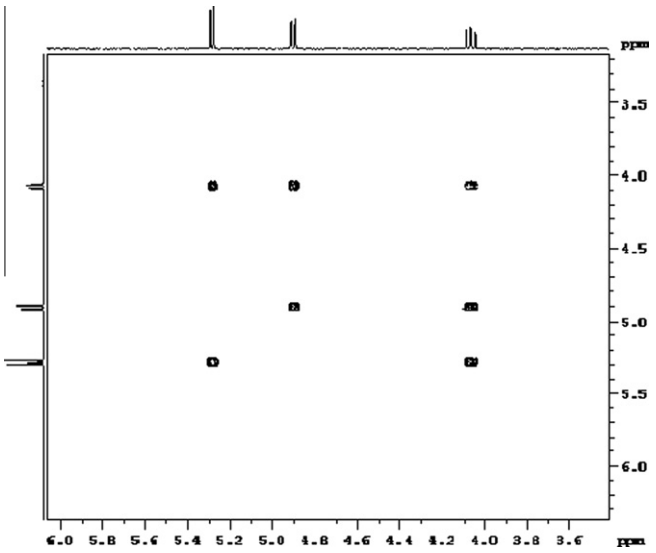


Figure 1. 400 MHz ^{1}H NMR COSY spectrum of **3a**–**A** in $CDCl_3$.

H^{3a}/H^3 at δ 4.05/6.11 in ^{1}H NMR COSY spectra of trans isomer **3a**–**B** (Fig. 2) indicates the anti-geometry of proton H^3 to the protons H^{3a} and H^{6a}. But the presence of cross peaks from the protons H^{3a}/H^{6a} in both the isomers shows the same planarity of these protons in these isomers. In the ^{1}H NMR NOESY spectra of cis isomer **3a**–**A** (Figs. 3 and 4) there exists correlation cross peaks from protons H^{3a}/H^3 at δ 4.06/4.90 and protons H^{3a}/H^{6a} at δ 4.06/5.28 but no correlation of H^{3a} with the proton of *C*-phenyl ring which signifies the 'anti' geometry of H^3 and *C*-phenyl ring and 'syn' nature of protons H^3, H^{3a} and H^{6a} protons. Cross peaks were also observed from protons H^3/(H-2′, H-6′) at δ 4.06/7.11. While in case of trans isomer **3a**–**B** (Figs. 5 and 6) cross peaks from protons H^{3a}/H^{6a} at δ 4.05/5.05 and from protons H^{3a}/H-6″ at δ 4.05/7.75 evident the 'syn' geometry of H^{3a}, H^{6a} and *C*-phenyl ring and the 'anti' geometry of H^3 proton with H^{3a} proton and *C*-phenyl ring. Besides this the cross peaks were also exhibited from protons H^3/(H-2′, H-6′) at δ 6.11/7.20. Cross peaks between protons H^{6a} and H^{3a} in both the isomers proves their 'syn' geometry. In all the reactions studied the cis and trans isomers were obtained approximately in 20:80 ratio indicating the steric interactions in endo-type transition state due to the o-substitution and more stability of the exo-type transition state.

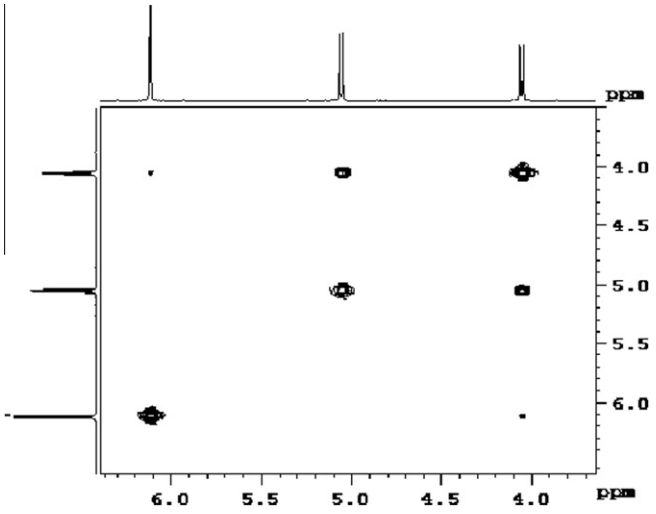


Figure 2. 400 MHz ^{1}H NMR COSY spectrum of **3a**–**B** in $CDCl_3$.

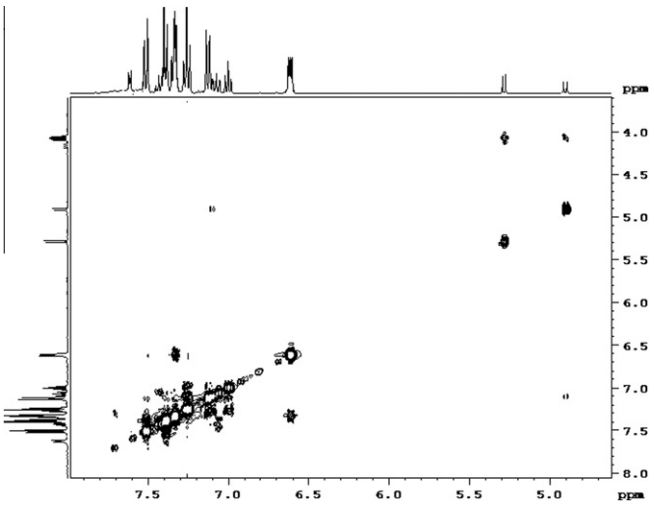


Figure 3. 400 MHz ^{1}H NMR NOESY spectrum of **3a**–**A** in $CDCl_3$.

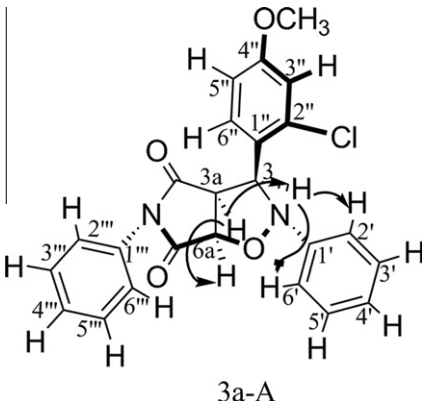


Figure 4. Structure of compound **3a**–**A** and NOE correlation.

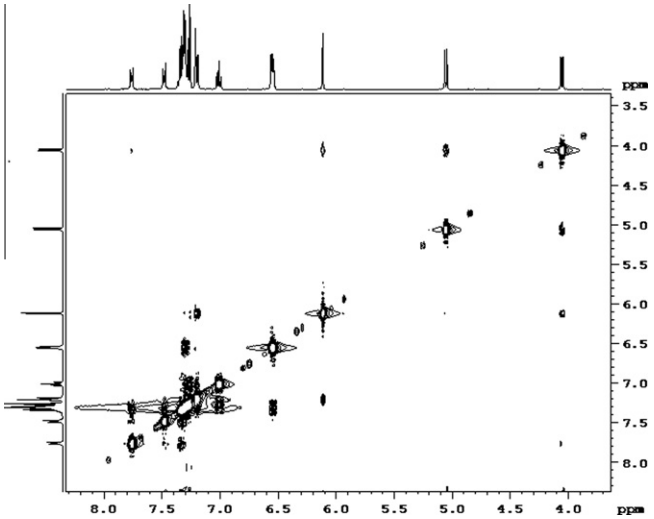


Figure 5. 400 MHz ^{1}H NMR NOESY spectrum of **3a**–**B** in $CDCl_3$.

All the synthesized compounds **3a**–**h** were subjected to in vitro bioassay to Advanced Glycation End Product formation inhibitory activity by following the similar procedure as reported in literature.[39] The potential of the compounds **3a**–**h** to inhibit AGEs-formation is summarized in Table 1. All the synthesized compounds

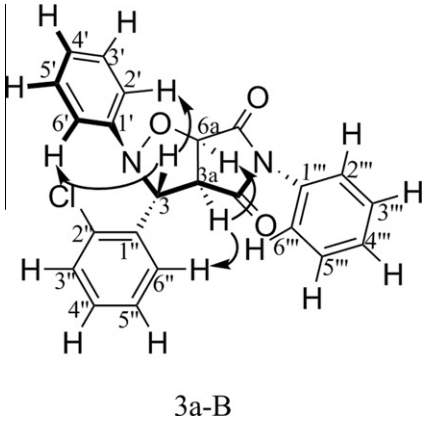
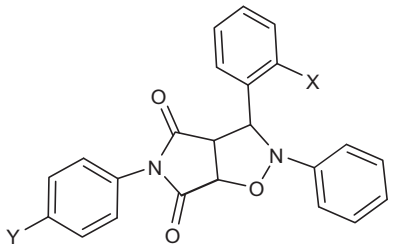


Figure 6. Structure of compound **3a–B** and NOE correlation.

have shown considerable advanced glycation end product formation inhibitory activity as the fluorescence of AGEs was shown to be remarkably inhibited by the all the synthesized compounds. Among the variously synthesized pyrrolo-isoxazolidines the compounds **3a–A, 3a–B, 3b–A, 3c–A, 3c–B, 3d–A, 3e–A, 3f–A, 3g–A** and **3h–A** were more potent than the standard drug aminoguanidine. The most active compounds **3a–A** (IC_{50} = 7.40 ± 1.3 μM), **3b–A** (IC_{50} = 7.18 ± 1.4 μM) and **3c–A** (IC_{50} = 8.63 ± 1.6 μM) were sixfolds more active than the standard drug aminoguanidine (IC_{50} = 40.54 ± 2.0 μM). The compounds **3a–B, 3b–B**, **3c–B, 3d–A, 3e–A, 3g–A** and **3h–A** (IC_{50} value ranging from 18.76 ± 1.8 to 33.05 ± 2.1 μM) also exhibited significant inhibitory activity comparable to the standard drug. However the compounds **3d–B, 3e–B, 3f–B, 3g–B** and **3h–B** exhibited lower anti-glycation activity than the standard drug (IC_{50} value ranging from 63.90 ± 2.2 to 126.67 ± 2.3 μM). The graphical representation of this data has also been shown in the form of bar graphs in Figures 7 and 8.

Table 1
Advanced glycation end-product formation inhibitory activity of pyrrolo-isoxazolidine derivatives (**3**)



Compounds	X	Y	IC_{50} (μM)
3a-A	Cl	H	7.40 ± 1.30
3a-B	Cl	H	30.91 ± 2.20
3b-A	Cl	CH_3	7.18 ± 1.45
3b-B	Cl	CH_3	23.92 ± 1.92
3c-A	Cl	OCH_3	8.63 ± 1.61
3c-B	Cl	OCH_3	24.17 ± 1.80
3d-A	Cl	COOH	33.05 ± 2.11
3d-B	Cl	COOH	126.67 ± 2.31
3e-A	OH	H	25.90 ± 1.60
3e-B	OH	H	64.77 ± 2.30
3f-A	OH	CH_3	18.76 ± 1.82
3f-B	OH	CH_3	75.00 ± 2.00
3g-A	OH	OCH_3	26.60 ± 2.11
3g-B	OH	OCH_3	90.10 ± 1.80
3h-A	OH	COOH	24.40 ± 1.91
3h-B	OH	COOH	63.90 ± 2.21
Aminoguanidine	—	—	40.54 ± 2.0

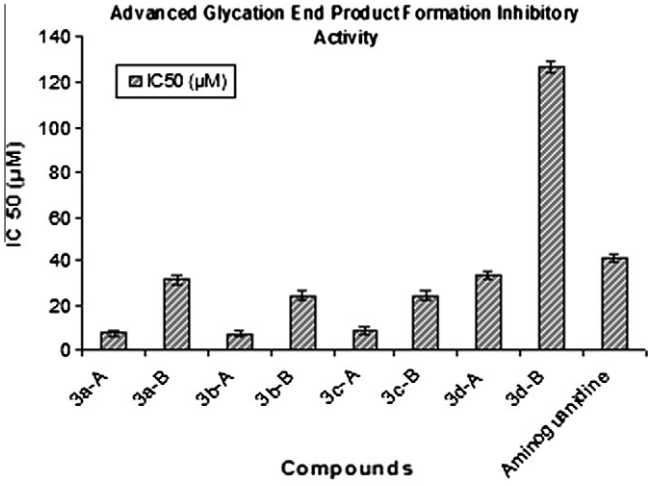


Figure 7. Graphical representation of IC_{50} (μM) values of *o*-Cl substitution on *C*-phenyl ring of pyrrolo-isoxazolidine derivatives with the standard drug aminoguanidine.

As evident from the results, among all the synthesized compounds, the cis isomers (**3**–**A**) were find out to be more active than the trans isomers (**3**–**B**). The compounds having *o*-Cl substituent on *C*-phenyl ring (**3a**–**A**) were more active than the corresponding compounds having *o*-OH group on *C*-phenyl moiety (**3e**–**A**). It suggests that the compounds with stronger electron withdrawing group (EWG) (–Cl) at ortho position of *C*-phenyl ring are more active than compounds with weaker EWG that is, –OH group. Among all the synthesized compounds the compound with *p*-CH_3 substituent on the *N*-phenyl ring of the succinimide moiety (**3b**–**A**) was most active, followed by the compound with no substitution on this ring (**3a**–**A**). The compounds with *p*-OCH_3 group exhibited moderate and the compounds with *p*-COOH group were find out to be least active anti-glycating agents. However the compounds with EWGs (–OCH_3 and –COOH) on the *N*-phenyl ring of the succinimide moiety (**3c**, **3d**, **3g** and **3h**) were less active than the corresponding compounds with no substitution (**3a** and **3e**) or substitution with electron donating group *p*-CH_3 (**3b** and **3f**) on this ring. Furthermore, among –OCH_3 and –COOH substituted compounds, the compounds with –COOH group (stronger electron withdrawing) on the *N*-phenyl ring were comparatively less potent

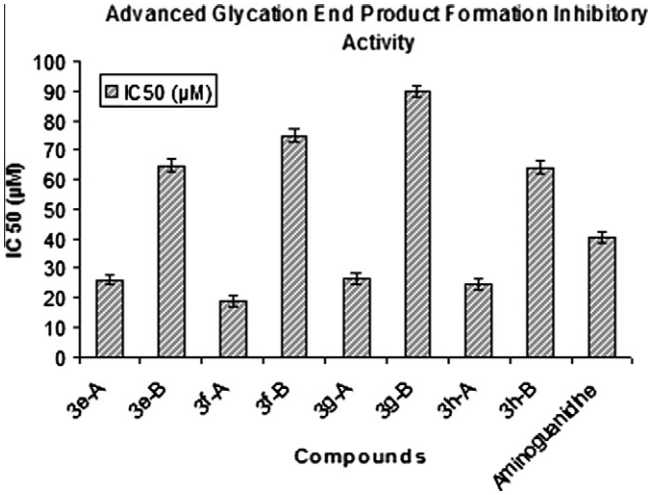


Figure 8. Graphical representation of IC_{50} (μM) values of *o*-OH substitution on *C*-phenyl ring of pyrrolo-isoxazolidine derivatives with the standard drug aminoguanidine.

than the corresponding compounds with $-OCH_3$ (weaker electron withdrawing) group.

Thus we concluded that novel pyrrolo-isoxazole derivatives exhibited significant anti AGE product formation activity. The activity was mainly influenced by stereochemistry of the compounds (*cis* being more potent) and presence of electron withdrawing/releasing groups on the *C*-phenyl ring and *N*-phenyl ring of succinimide moiety. It is concluded that hexahydropyrrolo-isoxazolidine derivatives may serve as a template for the synthesis of potent aldose reductase inhibitors. The future studies shall be directed for more complete biological activity of these synthesized compounds in in vivo model of diabetic complication in rodents.

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Supplementary data

Supplementary data (supplementary table) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.11.080.

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