Research in Pharmacy, 5: 13-21, 2015 ISSN: 2231-539X
www.researchinpharmacy.com

Regular Article

6-(substitutedbenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one Derivatives: New Class of Antihyperglycemic Agent

Deepthi. D. Kini*[1], Jessy Elizabeth Mathew[2]

*[1]Department Pharmaceutical Chemistry, Karnataka College of pharmacy, Bangalore, Karnataka, India
[2]Department Pharmaceutical Chemistry, Manipal College of pharmaceutical sciences, Manipal, Karnataka, India
*Corresponding author email: deepthikini@gmail.com

The novel compounds have been prepared in order to improve the pharmacological profiles of antihyperglycemic activity. In the present paper, series of 6-(substitutedbenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one **O1-12** were tested against hyperglycemia. Their antihyperglycemic activity was evaluated by Streptozotocin (STZ) and Sucrose-loaded (SLM) model. The results of studies indicate that, among the compounds **O1**, **O6**, **O10**, **O12**, **O8**, and **O3** displayed significant reduction in blood glucose level in streptozotocin and sucrose loaded rat models. The purity of the synthesized compounds was characterized by means of IR, ^{1}H-NMR, mass spectral and elemental analysis.

Key words: Oxazole; Aromatic aldehydes, Antihyperglycemic activity.

Diabetes mellitus is a major public health problem in the developed as well as developing countries. It is ranked seventh among the leading causes of death, and third when it's fatal complications are taken in to account (Trivedi, 2004). Recent estimations of the World Health Organization, more than 180 million people all over the world suffer from diabetes mellitus (DM). By the year 2030 their number can increase more than 2-fold and DM is a metabolic disorder which is associated with three basic pathophysiological abnormalities: impaired insulin secretion, excessive hepatic glucose production, and insulin resistance in skeletal muscle, liver, and adipose tissue. It is now clear that aggressive control of hyperglycemia in patients with diabetes can prevent or delay the onset of complications such as retinopathy, nephropathy, and neuropathy (Kumar et al., 2007). We have found that oxazolidines and related oxazolidine are classes of heterocycles that are of considerable interest because of the diverse range of their biological properties, such as like antihypertensives (Caroon, 1983), antidepressant (Pinder, 1985), antithyroid (Gardrat, 1990), leishmanicidal (Sonika, 1990), antidiabetic (Heong, 2007), anti-HIV (Kamlesh, 2003), antiarrhythmic (Kostochka, 2003), antitumor (Vara Prasad, 2006), anticonvulsant, antimicrobial (Seoung, 2003). This background information led to the design of 6-(substitutedbenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one **O1-12** derivatives

Materials and Methods

Materials

Synthetic starting material, reagents and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co., Merck Chemical Co. and were dried when necessary.

The melting points were taken in open capillary tube and are uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited Bangaluru, India). Proton (^{1}H) NMR spectra (Bruker 400 NMR spectrometer Mumbai, India) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000, Chennai, India), and microanalyses were performed using a *vario EL* V300 *elemental* analyzer (*Elemental* Analysensysteme *GmbH* Chennai, India). The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E.Merck) using ethyl acetate: benzene (1:3) and visualized in UV chamber. IR, ^{1}H-NMR, mass spectral data and elemental analyses were consistent with the assigned structures.

Synthetic Procedure

1-hydroxypropan-2-one (1.00 g,) and KSCN (1.07 g,) were dissolved in ethanol (30 mL). After cooling at -5 °C, 12M aqueous HCl (1.10 mL,) was carefully added and the mixture was stirred under reflux for 24 h, and then it was cooled by using crushed ice. After extraction with ethyl acetate (3x 25 mL), the combined organic phase was successively washed with saturated aqueous sodium bicarbonate, water, and finally it was dried using Magnesium sulphate. After filtration and concentration under reduced pressure, the residue was collected to afford compound **1.** A mixture of 5-methyloxazole-2(3H)-thione **1** chloroacetic acid (0.006 mol), sodium acetate anhydrous (6 g) in glacial acetic acid and acetic acid anhydride (120 mL, 3:1) was refluxed for 12 min. Further an equimolecular amount (0.006 mol) of the appropriate aromatic aldehyde was added. The reaction mixture was refluxed for 2 h, allowed to cool and was poured into crushed ice water; the formed precipitate was filtered off, dried and recrystallized by using ethanol to give the corresponding 6-(substitutedbenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one **O1-12**.

6-(2-fluorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O1)

The compound was obtained as a solid; Yield: 67%; m.p.171-173 °C. IR cm^{-1}: 3122 (Ar-CH), 2929 (Alkane-CH), 1678 (C=O), 1305 (C-N), 1157 (Ether C-O-CH), 1072 (C-F).^{1}H NMR ($CDCl_3$) δ (ppm): 6.82-7.04 (m, 4H; Ar-H), 7.74 (s, 1H; Alkene-CH), 6.03 (s, 2H; Oxazole-CH), 1.69 (s, 3H; -CH_3).EI-MS m/z (M+2): 265 (calcd for $C_{13}H_{10}FNO_2S$; 263.29). Anal.calcd for $C_{13}H_{10}FNO_2S$; C, 59.30; H, 3.83; N, 5.32; Found: C, 59.34; H, 3.89; N, 5.38.

6-(3-fluorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O2)

The compound was obtained as a solid; Yield: 69%; m.p.182-184 °C. IR cm^{-1}: 3100 (Ar-CH), 2952 (Alkane-CH), 1720 (C=O), 1340 (C-N), 1297 (Ether C-O-CH), 1012 (C-F).^{1}H NMR ($CDCl_3$) δ (ppm): 7.67 (s, 1H; Alkene-CH), 6.74-7.12 (m, 4H; Ar-H), 6.14 (s, 2H; Oxazole-CH), 1.99 (s, 3H; -CH_3). EI-MS m/z (M+2): 265 (calcd for $C_{13}H_{10}FNO_2S$; 263.29).
Anal.calcd for $C_{13}H_{10}FNO_2S$; C, 59.30; H, 3.83; N, 5.32; Found: C, 59.37; H, 3.86; N, 5.39.

6-(4-fluorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O3)
The compound was obtained as a solid; Yield: 72%; m.p.196-198 °C. IR cm^{-1}: 3107 (Ar-CH), 2959 (Alkane-CH), 1724 (C=O), 1344 (C-N), 1291 (Ether C-O-CH), 1022 (C-F). ^1H NMR ($CDCl_3$) δ (ppm): 7.69 (s, 1H; Alkene-CH), 6.71-7.18 (m, 4H; Ar-H), 6.12 (s, 2H; Oxazole-CH), 2.14 (s, 3H; -CH_3). EI-MS m/z (M+2): 265 (calcd for $C_{13}H_{10}FNO_2S$; 263.29). Anal.calcd for $C_{13}H_{10}FNO_2S$; C, 59.30; H, 3.83; N, 5.32; Found: C, 59.31; H, 3.84; N, 5.32.

6-(2-cholorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O4)
The compound was obtained as a solid; Yield: 67%; m.p.176-178 °C. IR cm^{-1}: 3145 (Ar-CH), 2926 (Alkane-CH), 1726 (C=O), 1304 (C-N), 1191 (Ether C-O-CH), 594 (C-Cl). ^1H NMR ($CDCl_3$) δ (ppm): 7.71 (s, 1H; Alkene-CH), 6.62-7.06 (m, 4H; Ar-H), 6.19 (s, 2H; Oxazole-CH), 2.34 (s, 3H; -CH_3). EI-MS m/z (M+2): 281 (calcd for $C_{13}H_{10}ClNO_2S$; 279.74). Anal.calcd for $C_{13}H_{10}ClNO_2S$; C, 55.82; H, 3.60; N, 5.01; Found: C, 55.86; H, 3.64; N, 5.09.

6-(3-cholorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O5)
The compound was obtained as a solid; Yield: 69%; m.p.161-163 °C. IR cm^{-1}: 3014 (Ar-CH), 2962 (Alkane-CH), 1737 (C=O), 1354 (C-N), 1291 (Ether C-O-CH), 562 (C-Cl). ^1H NMR ($CDCl_3$) δ (ppm): 7.79 (s, 1H; Alkene-CH), 6.82-7.31 (m, 4H; Ar-H), 6.11 (s, 2H; Oxazole-CH), 2.21 (s, 3H; -CH_3). EI-MS m/z (M+2): 281 (calcd for $C_{13}H_{10}ClNO_2S$; 279.74). Anal.calcd for $C_{13}H_{10}ClNO_2S$; C, 55.82; H, 3.60; N, 5.01; Found: C, 55.83; H, 3.62; N, 5.04.

6-(4-cholorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O6)
The compound was obtained as a solid; Yield: 72%; m.p.179-181 °C. IR cm^{-1}: 3012 (Ar-CH), 2959 (Alkane-CH), 1739 (C=O), 1351 (C-N), 1295 (Ether C-O-CH), 559 (C-Cl). ^1H NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H; Alkene-CH), 6.72-7.23 (m, 4H; Ar-H), 6.16 (s, 2H; Oxazole-CH), 2.27 (s, 3H; -CH_3). EI-MS m/z (M+2): 281 (calcd for $C_{13}H_{10}ClNO_2S$; 279.74). Anal.calcd for $C_{13}H_{10}ClNO_2S$; C, 55.82; H, 3.60; N, 5.01; Found: C, 55.87; H, 3.67; N, 5.07.

6-(2-bromobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O7)
The compound was obtained as a solid; Yield: 62%; m.p.169-171 °C. IR cm^{-1}: 3120 (Ar-CH), 2916 (Alkane-CH), 1720 (C=O), 1350 (C-N), 1153 (Ether C-O-CH), 592 (C-Br). ^1H NMR ($CDCl_3$) δ (ppm): 7.71 (s, 1H; Alkene-CH), 6.72-7.22 (m, 4H; Ar-H), 6.13 (s, 2H; Oxazole-CH), 2.24 (s, 3H; -CH_3). EI-MS m/z (M+2): 326 (calcd for $C_{13}H_{10}BrNO_2S$; 324.19). Anal.calcd for $C_{13}H_{10}BrNO_2S$; C, 48.16; H, 3.11; N, 4.32; Found: C, 48.12; H, 3.13; N, 4.34.

6-(3-bromobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O8)
The compound was obtained as a solid; Yield: 66%; m.p.166-168 °C. IR cm^{-1}: 3021 (Ar-CH), 2957 (Alkane-CH), 1737 (C=O), 1355 (C-N), 1294 (Ether C-O-CH), 616 (C-Br). ^1H NMR ($CDCl_3$) δ (ppm): 7.79 (s, 1H; Alkene-CH), 6.79-7.29 (m, 4H; Ar-H), 6.18 (s, 2H; Oxazole-CH), 2.27 (s, 3H; -CH_3). EI-MS m/z (M+2): 326 (calcd for $C_{13}H_{10}BrNO_2S$; 324.19). Anal.calcd for $C_{13}H_{10}BrNO_2S$; C, 48.16; H, 3.11; N, 4.32; Found: C, 48.16; H, 3.16; N, 4.37.

6-(4-bromobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O9)
The compound was obtained as a solid; Yield: 78%; m.p.190-192 °C. IR cm^{-1}: 3027 (Ar-CH), 2952 (Alkane-CH), 1733 (C=O), 1354 (C-N), 1297 (Ether C-O-CH), 664 (C-Br). ^1H NMR ($CDCl_3$) δ (ppm): 7.78 (s, 1H; Alkene-CH), 6.71-7.21 (m, 4H; Ar-H), 6.11 (s, 2H; Oxazole-CH), 2.23 (s, 3H; -

CH_3). EI-MS m/z (M+2): 326 (calcd for $C_{13}H_{10}BrNO_2S$; 324.19). Anal.calcd for $C_{13}H_{10}BrNO_2S$; C, 48.16; H, 3.11; N, 4.32; Found: C, 48.12; H, 3.13; N, 4.31.

6-(2-nitrobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O10)
The compound was obtained as a solid; Yield: 61%; m.p.171-173 °C. IR cm^{-1}: 3118 (Ar-CH), 2927 (Alkane-CH), 1714 (C=O), 1519 (N-O), 1342 (C-N), 1152 (Ether C-O-CH). ^1H NMR ($CDCl_3$) δ (ppm): 7.71 (s, 1H; Alkene-CH), 6.79-7.27 (m, 4H; Ar-H), 6.19 (s, 2H; Oxazole-CH), 2.25 (s, 3H; -CH_3). EI-MS m/z (M+): 290 (calcd for $C_{13}H_{10}N_2O_4S$; 290.29). Anal.calcd for $C_{13}H_{10}N_2O_4S$; C, 53.79; H, 3.47; N, 9.65; Found: C, 53.74; H, 3.42; N, 9.61.

6-(3-nitrobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O11)
The compound was obtained as a solid; Yield: 69%; m.p.163-165 °C. IR cm^{-1}: 3002 (Ar-CH), 2939 (Alkane-CH), 1717 (C=O), 1541 (N-O), 1344 (C-N), 1292 (Ether C-O-C). ^1H NMR ($CDCl_3$) δ (ppm): 7.81 (s, 1H; Alkene-CH), 6.72-7.13 (m, 4H; Ar-H), 6.12 (s, 2H; Oxazole-CH), 2.21 (s, 3H; -CH_3). EI-MS m/z (M+): 290 (calcd for $C_{13}H_{10}N_2O_4S$; 290.29). Anal.calcd for $C_{13}H_{10}N_2O_4S$; C, 53.79; H, 3.47; N, 9.65; Found: C, 53.73; H, 3.43; N, 9.62.

6-(4-nitrobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O12)
The compound was obtained as a solid; Yield: 74%; m.p.182-184 °C. IR cm^{-1}: 3012 (Ar-CH), 2923 (Alkane-CH), 1721 (C=O), 1532 (N-O), 1337 (C-N), 1298 (Ether C-O-C). ^1H NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H; Alkene-CH), 6.92-7.19 (m, 4H; Ar-H), 6.16 (s, 2H; Oxazole-CH), 2.27 (s, 3H; -CH_3). EI-MS m/z (M+): 290 (calcd for $C_{13}H_{10}N_2O_4S$; 290.29). Anal.calcd for $C_{13}H_{10}N_2O_4S$; C, 53.79; H, 3.47; N, 9.65; Found: C, 53.74; H, 3.47; N, 9.63.

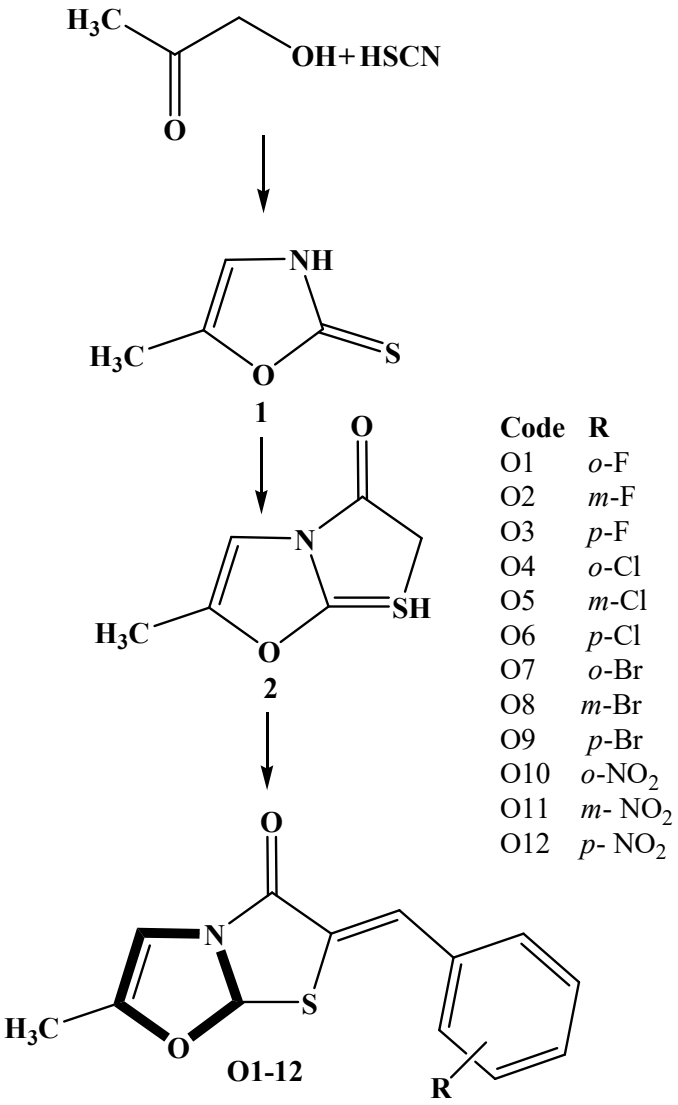
Antihyperglycemic activity
Streptozotocin (STZ) model
A solution of streptozotocin (60mg/kg) in 100 mM citrate buffer, pH 4.5 was prepared and calculated amount of the fresh solution was dosed to overnight fasted rats (60mg/kg) intraperitoneally. The blood sugar level was measured after 48 h by glucometer. Animals showing 200–400mg/dL were selected for antidiabetic screening. The diabetic animals were divided into groups of six animals each. Rats of experimental group were administered a suspension of the desired test sample (prepared in1% gum acacia) orally (100 mg/kg body weight). Controlled group animals were also fed with 1% gum acacia. The blood glucose levels were measured at 1, 2, 3, 4, 5, 6, 7 and 24 h intervals. The % fall in blood glucose from 1 to 24 h by test sample was calculated according to the area under curve (AUC) method. The average fall in AUC in experimental group compared to control group provided % antihyperglycemic activity.

Sucrose-loaded (SLM) model
Overnight fasted male Sprague–Dawleyrats were used for sucrose-loaded experiment. Blood was collected initially and there after test compounds were given to the test group consisting of five rats by oral gavage at a dose of 100mg/kg body weight. After half an hour post-test treatment, a sucrose load of 10 gm/kg body weight was given to each rat. Blood was collected at 30, 60, 90 and 120 min post sucrose load. The % fall in blood glucose level was calculated according to the Area under Curve method.

Results and discussion

Chemistry

The chemical structure of chlorogenic acid was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. In 6-(substitutedbenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one **O1-12**, Ar-CH stretching band appears in the range of 3150-3050 cm^{-1} and the appearance of a strong intensity band in the IR spectra of Alkane-CH in the range of 3000-2850 cm^{-1}. The appearance of 1740-1705, 1300-1000 cm^{-1} range was attributable to ester C=O, Ether C-O-CH respectively.



Code	R
O1	*o*-F
O2	*m*-F
O3	*p*-F
O4	*o*-Cl
O5	*m*-Cl
O6	*p*-Cl
O7	*o*-Br
O8	*m*-Br
O9	*p*-Br
O10	*o*-NO_2
O11	*m*- NO_2
O12	*p*- NO_2

Scheme 1. The formation of 6-(substituted benzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one

In addition the halogen peaks range which provides a strong evidence and also confirms the proposed structure. The ^{1}H NMR spectra of compound have been recorded by using DMSO. In this ^{1}H NMR, the δ value of Alkene-CH signals appears in the range of 7.74, 7.67, 7.69, 7.71, 7.79,

7.72, 7.71, 7.79, 7.78, 7.83, 7.89 and 7.62 followed by the appearance of Ar-CH in the range of 6.69-7.27, and mainly Oxazole-CH appears in the range 6.03-6.19. Most importantly aliphatic -CH_3 proton in the range of 1.6-2.3 ppm respectively. All these observed position and presence of proton signals in the ^1H NMR spectra clearly envisages that the final structure of oxazol-5(6*H*)-one. Further in mass spectrum M+2 peaks confirmed presence of halogens in the structure and its molecular weight. All these observed facts clearly demonstrate that the 5th position methyl group and 3rd position keto group in oxazole ring as well as the presence of benzylidene formation as indicated in **scheme** and also it was conforms the proposed structure (**O1-12**) **Fig 1**.

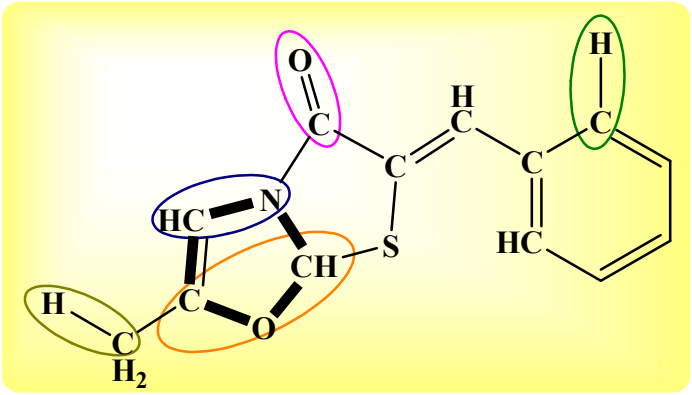


Figure 1.The characteristic feature of title compounds

Table 1. *In vivo* antihyperglycemic activity of various oxazolidines derivatives (**O1-12**) in streptozotocin (STZ) and sucrose-loaded (SLM) rat models

Compounds	**R**	**% Blood sugar lowering activity (100mg/kg)**	
		STZ model	**SLM model**
O1	***o*-F**	69.0	56.4
O2	*m-F*	NIL	NIL
O3	***p-F***	43.4	41.2
O4	*o*-Cl	NIL	NIL
O5	*m-Cl*	NIL	NIL
O6	***p-Cl***	51.4	62.1
O7	*o*-Br	NIL	NIL
O8	***m-Br***	46.4	44.2
O9	*p-Br*	NIL	NIL
O10	***o*-NO_2**	51.2	48.7
O11	*m*- NO_2	NIL	NIL
O12	***p*- NO_2**	49.1	42.4
Metformin		77.4	63.2
Glybenclamide		75.9	59.8

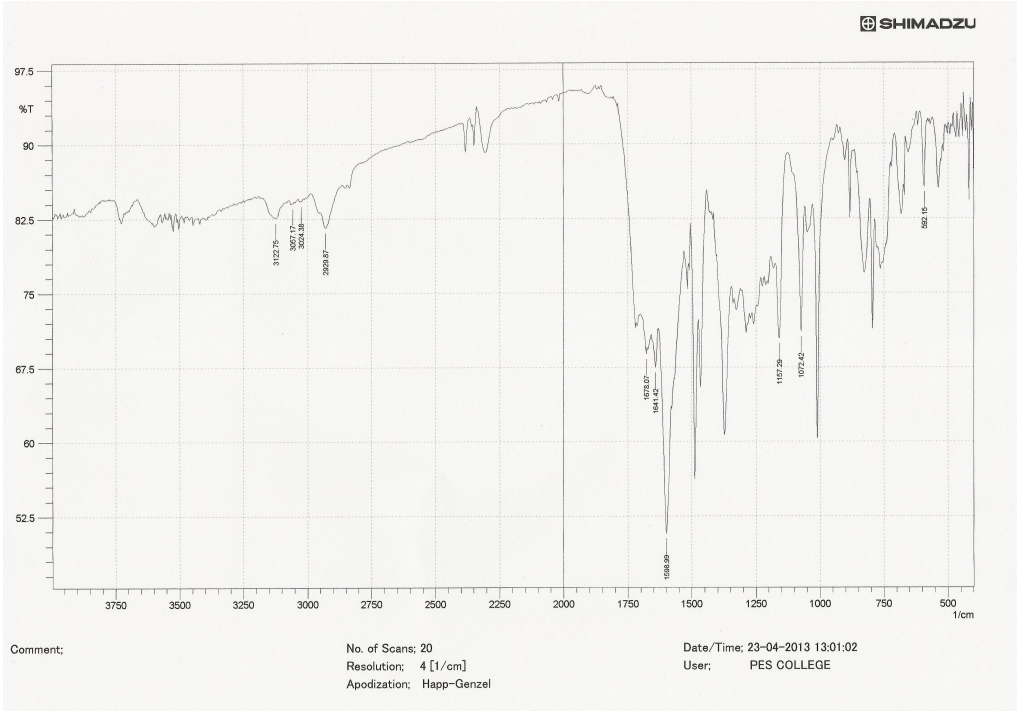


Figure 2. IR spectra of compound O1

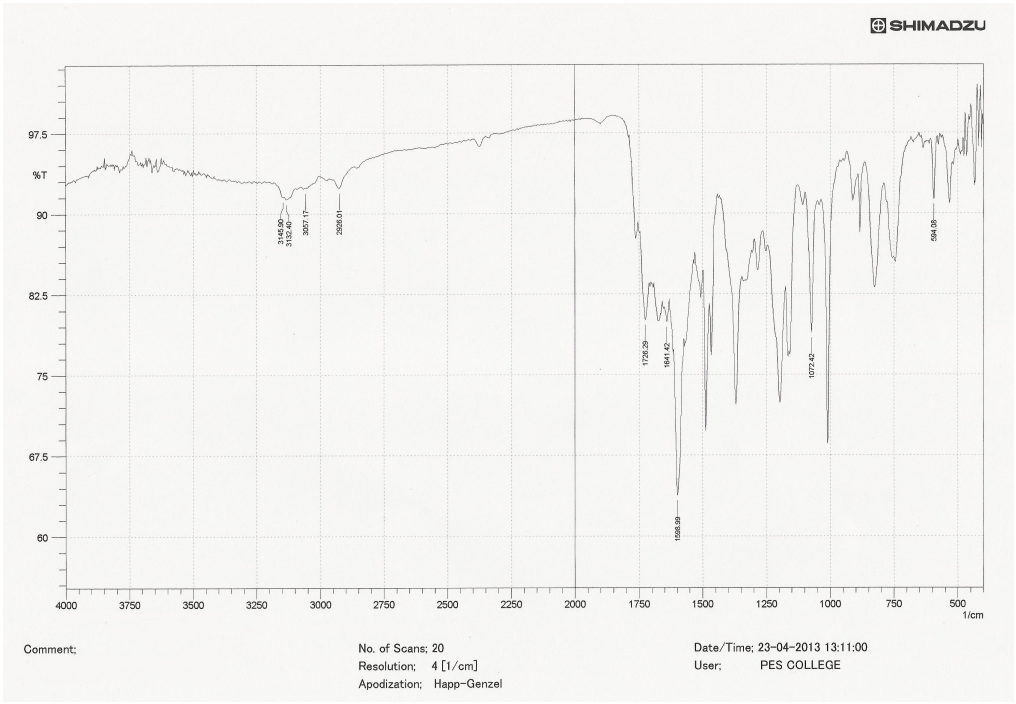


Figure 3. IR spectra of compound O4

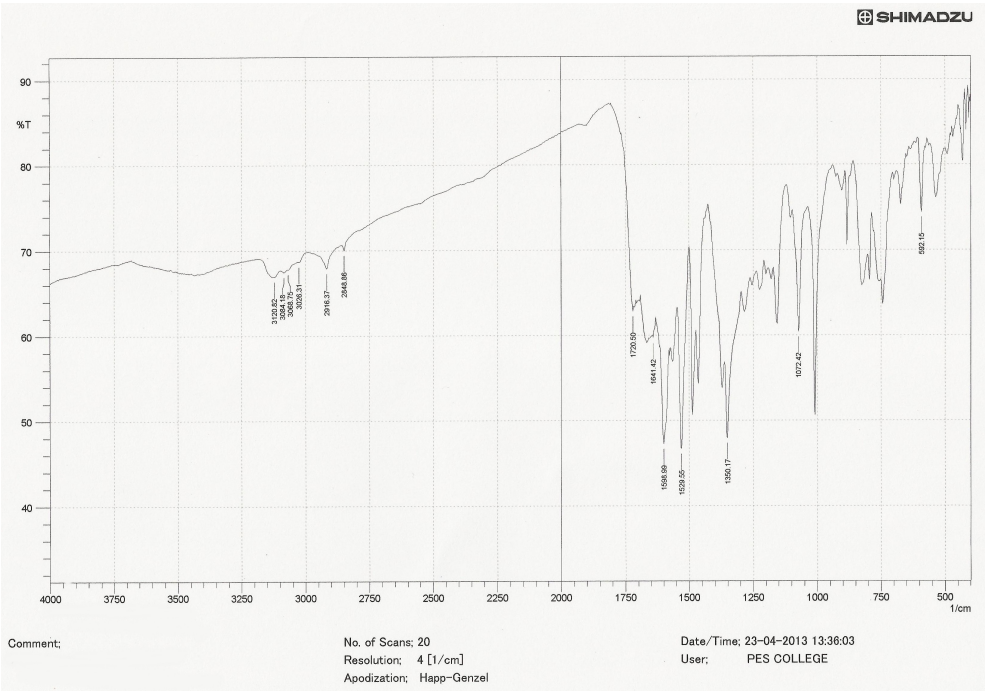


Figure 4. IR spectra of compound O7

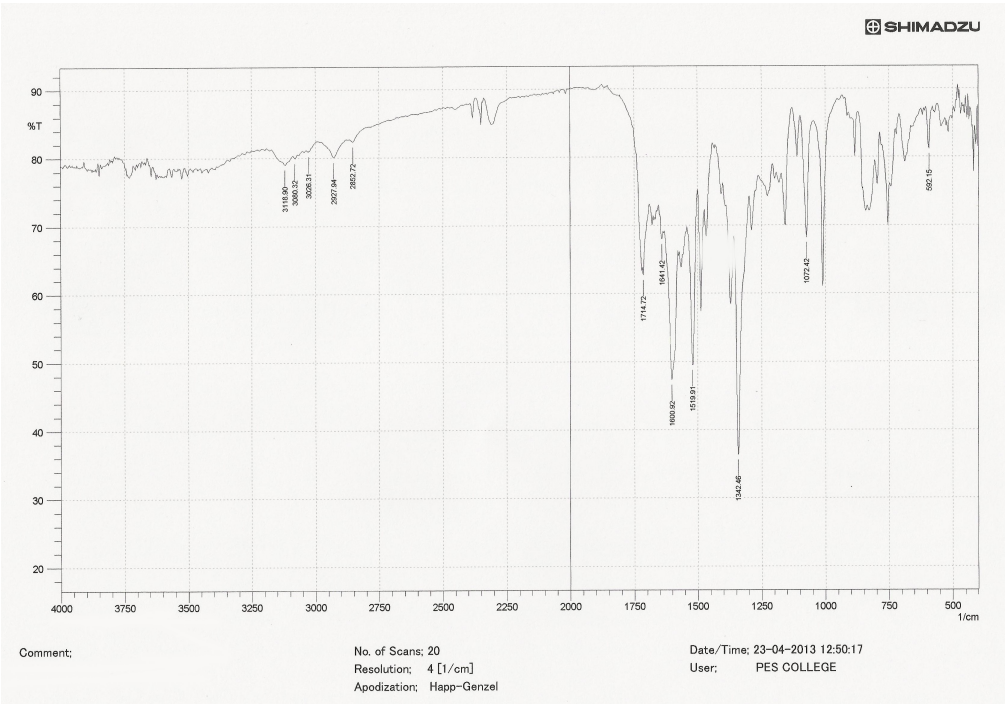


Figure 5. IR spectra of compound O10

Antihyperglycemic activity

Among the **12** screened compounds **O1-12** demonstrated antihyperglycemic activity in STZ and SLM model. In these compounds, 6-(2-fluorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (**O1**) and 6-(4-fluorobenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (**O3**) reduced blood glucose level to (69%, 56.4%) and (43.4%, 41.2%) respectively, in STZ and SLM models. The other active compounds such as **O2, O4, O5, O7, O9,** and **O11** and **O12** displayed inactive antihyperglycemic activity in both STZ model and SLM model, this is possibly due to its slow transformation than other highly active metabolites **O1, O3, O6, O8** and **O12**. A Compound with fluorine substitution displayed a significant blood glucose lowering activity in both the SLM and STZ model. Compound **(O6)** reduced blood glucose level by (51.4%) in STZ model while latter demonstrated significant activity (62.1%) in SLM model. The transformation order of screened compounds is **O1 > O6 > O10 > O12 > O8> O3** Metformin and Glybenclamide were used as standard antidiabetic drug in both the models. All values are represented in **Table 1**.

References

Caroon JM, Clark RD, Kluge AF, Strosberg A M.1983. Synthesis and antihypertensive activity of a series of spiro [1,3,4,6,7b-hexahydro-2H-benzo [a] quinoline-2,5'oxazolidin-2'-ones]. *J Med Chem*. 26: 1426-1433.

Diabetes. 2006. *World Health Organization. Information Bulletin* No.312.

Gardrat C, Latxague L. 1990. A new synthesis of DL-5-vinyl oxazolidine-2-thione, anatural antityroid factor. *J Org Chem*, 27: 1534-1541.

Heong SO, Hoh GH, Seung HC. 2007. Solid phase synthesis of 1, 3-oxazolidine derivatives, *Tetrahedron Lett*, 41: 5069-5072.

Kamlesh S, Kishwar S, Anwar S. 2003. Stereo selective formation of steroidal (6R)-spiro oxazolidines. *Indian J Chem*, 42B: 2866-2868.

Kostochka LM, Lezina VP, Kostochka M L. 2003. Synthesis of 3-(2-Aryloxazolidin-3yl)tropanes. *Chem of Heterocycl Compounds*, 39: 1227-1230.

Kumar R, Mittal A, Ramachandran U. 2007. Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives as PPAR*c* activators. *Bioorg Med Chem Letts*, 17(16): 4613–4618.

Pinder RM. 1985. A2 adrenoceptor antagonists as antidepressants. *Drugs of the Future*, 10: 841-857.

Seoung J K, Myung H J, Kyung HY, Jung HC, Chang HO. 2008. Synthesis and antibacterial activities of novel oxazolidinones having cyclic sulfonamide moieties. *Bioorg & Med Chem Lett*, 18: 5815-5818.

Sonika B, Satyavan S.1990. Studies in antiparasitic agents, A convenient synthesis of 4phenyl-1-(2-substituted ethyl)imidazolidin-2-ones as potential leishmanicidal agents. *Indian J Chem*, 29B: 855-858.

Trivedi B, Mazumdar JD, Hemavathi KG. 2004. Effect of Shilajit on blood glucose and lipid profile in alloxan-induced diabetic rats. *Indian J Pharmacol*, 36(6): 373-376.

Vara Prasad JVN, Frederick EB, Lou C, Michael D, Qizhu Ding K. 2006 Synthesis and structure–activity studies of novel benzocycloheptanone oxazolidinone antibacterial agents. *Bioorg & Med Chem Lett*, 15: 5392-5397.

Zarghi A, Najafnia L, Daraie B, Dadrass OG, Hedayati M. 2007. Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg Med Chem Lett*. 17: 5634–5637.