Arch Pharm Res Vol 34, No 6, 887-891, 2011
DOI 10.1007/s12272-011-0604-3

Archives of Pharmacal Research
www.springer.com/12272

Synthesis, Characterization, and Antihyperglycemic Activity of Novel Oxazolidine Derivatives

Theivendren Panneer Selvam[1], Palanirajan Vijayaraj Kumar[2], Parthasarathi Ramu[3], and Arumugam Siva Kumar[4]

[1]Department of Pharmaceutical Chemistry, Srinivas College of Pharmacy, Valachil, Mangalore 574 143, Karnataka, India, [2]Faculty of Pharmaceutical Sciences, UCSI (University College Sadaya International) University, Jalan Menara Gading 56000 Cheras, Kuala Lumpur, Malaysia, [3]Department of Biotechnology, IITMadras, Chennai 600 036, Tamilnadu, India, and [4]School of Bio Science and Technology, VIT University, Vellore 632 014 Tamilnadu, India

(Received August 24, 2010/Revised November 18, 2010/Accepted November 22, 2010)

A number of compounds have been prepared in order to improve pharmacological roles of anti-hyperglycemic activity. In the present paper, a series of 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidines (**6a-e**) were tested against hyperglycemia. Their antihyperglycemic activity was evaluated by streptozotocin (STZ) and sucrose-loaded (SLM) models. Compounds **6a, b, c, d,** and **e** displayed significant reductions in blood glucose in the 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: Oxazolidine, Aromatic aldehydes substitution, Antihyperglycemic activity

INTRODUCTION

Diabetes mellitus is a major public health problem in developed as well as developing countries. It is ranked seventh among the leading causes of death, and is third when its fatal complications are taken into account (Trivedi et al., 2004). Recent estimations of the World Health Organization suggest that more than 180 million people all over the world suffer from diabetes mellitus (DM). By the year 2030, this number may increase more than 2-fold (Diabetes World Health Organization, 2006). DM is a metabolic disorder that 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 antihypertensive (Caroon et al., 1983), antidepressant (Pinder, 1985), antithyroid (Gardrat and Latxague, 1990), leishmanicidal (Sonika and Satyavan, 1990), antidiabetic (Heong et al., 2007), anti-HIV (Sharma et al., 2003), antiarrhythmic (Kostochka et al., 2003), antitumor (Vara Prasad et al., 2006), and anticonvulsant and antimicrobial (Kim et al., 2008). This background information led to the design of 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1, 3-oxazolidine derivatives (**6a-e**).

Correspondence to: Theivendren Panneer Selvam, Department of Pharmaceutical Chemistry, Srinivas College of Pharmacy, Valachil, Mangalore 574 143, Karnataka, India
Tel: 91-748-3067724, Fax: 91-824-2442766
E-mail: tpsphc@gmail.com

MATERIALS AND METHODS

Materials

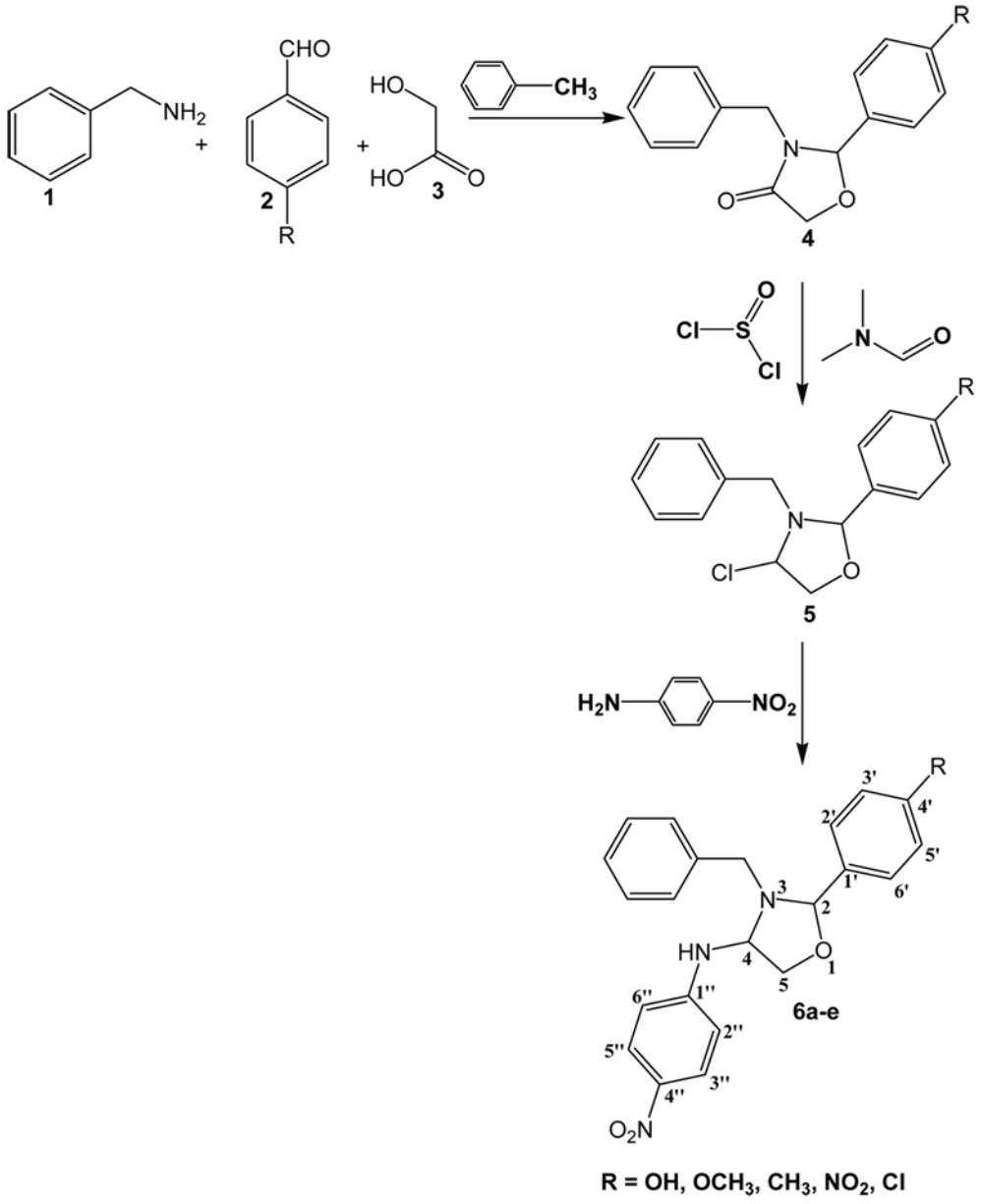
The synthetic starting material, reagents, and solvents were of analytical reagent grade or of the highest quality commercially available, and were purchased from Aldrich Chemical Co., Merck Chemical Co. and were dried when necessary.

The melting points were taken in open capillary tubes and were uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited Bangaluru). Proton (^{1}H) NMR

spectra (Bruker 400 NMR spectrometer Mumbai) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000), and microanalyses were performed using a *vario EL* V300 *elemental* analyzer (*Elemental* Analysensysteme *GmbH* Chennai). The purity of the compounds was assessed 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 a UV chamber. The IR, ^{1}H-NMR, mass spectral data and elemental analyses were consistent with the assigned structures.

General procedures

The synthetic strategy leading to the target compounds is illustrated in Scheme 1. The 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-(4''-nitrophenyl amino)-1,3-oxazolidine derivatives were synthesized by a previously reported method (Zarghi et al., 2007). Accordingly, benzylamine **1** was treated with an equimolar amount of substituted benzaldehyde **2** and hydroxy acetic acid **3** in dry toluene under reflux for 24-48 h to give 3-benzyl-2-(4'-substituted phenyl)-1,3-oxazolidine-4(5*H*)-one **4**. This was further treated with thionyl chloride and DMF to attain the chloro



Scheme 1.

derivative **5** 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-chloro-1,3-oxazolidine which was then coupled with *p*-nitro anilines in DMF at 80°C and quenched in ice-water to acquire the product. The product was separated by filtration, vaccum dried, and recrystallized from warm ethanol to yield the 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidines **6a-e**.

3-benzyl-2-phenyl-1, 3-oxazolidine-4(5*H*)-one (4)
Yellow solid, yield 82%; m.p. 172-174°C; IR (cm^{-1}): 3096 (Ar-CH), 1728 (C=O), 1468 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.96-7.54 (m, 10H, Ar-H), 6.67 (s, 1H, -CH), 4.12-4.62 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 253; (Calcd for $C_{16}H_{15}NO_2$; 253.3). Anal (%). Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.46; H, 5.61; N, 5.36.

3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-chloro -1,3-oxazolidine (5)
Pale Yellow solid, yield 71%; m.p. 146-148°C; IR (cm^{-1}) : 3084 (Ar-CH), 827 (C-Cl), 1412 (C=C); ^{1}H-NMR ($CDCl_3$): δ 6.18-7.42 (m, 10H, Ar-H), 4.98-5.27 (s, 2H, -CH), 3.46-4.22 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 273; (Calcd for $C_{16}H_{16}ClNO$; 273.09). Anal (%). Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.41; H, 5.96; N, 5.72.

3-benzyl-2-(4'-hydroxy phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (6a)
Pale yellow solid, yield 76%; m.p. 156-158°C; IR (cm^{-1}): 3464 (O-H), 3027 (Ar-CH), 1494 (C=C), 1564 (N=O), 1306 (N-H bending), 3396 (N-H stretching); ^{1}H-NMR ($CDCl_3$): δ 9.87 (s, 1H, Ar-OH), 6.76-7.27 (m, 13H, Ar-H), 6.31 (s, 2H, -CH), 7.21 (s, 1H, N-H), 3.44-3.67 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 391; (Calcd for $C_{22}H_{21}N_3O_4$; 391.42). Anal (%). Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.57; H, 5.44; N, 10.79.

3-benzyl-2-(4'-methoxy phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (6b)
White solid, yield 89%; m.p. 184-186°C; IR (cm^{-1}): 3026 (Ar-CH), 1524 (C=C), 1567 (N=O), 1316 (N-H bending), 3319 (N-H stretching); ^{1}H-NMR ($CDCl_3$): δ 6.72-7.23 (m, 13H, Ar-H), 6.36 (s, 2H, -CH), 3.78 (s, 3H, -OCH_3), 7.15 (s, 1H, N-H), 3.54-3.72 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 405; (Calcd for $C_{23}H_{23}N_3O_4$; 405.45). Anal (%). Calcd for $C_{23}H_{23}N_3O_4$; C, 68.13; H, 5.72; N, 10.36; Found: C, 68.19; H, 5.76; N, 10.31.

3-benzyl-2-(4'-methyl phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (6c)
Paleyellow solid, yield 77%; m.p. 170-123°C; IR (cm^{-1}): 3027 (Ar-CH), 1413 (C=C), 1570 (N=O), 1334 (N-H bending), 3313 (N-H stretching); ^{1}H-NMR ($CDCl_3$): δ 6.62-7.18 (m, 13H, Ar-H), 6.29 (s, 2H, -CH), 3.69 (s, 3H, -CH_3), 7.21 (s, 1H, N-H), 3.49-3.63 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 389; (Calcd for $C_{23}H_{23}N_3O_3$; 389.45). Anal (%). Calcd for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.95; H, 5.91; N, 10.83.

3-benzyl-2-(4'-nitro phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (6d)
Pale solid, yield 71%; m.p. 181-183°C; IR (cm^{-1}): 3027 (Ar-CH), 1413 (C=C), 1546 (N=O), 1334 (N-H bending), 3313 (N-H stretching); ^{1}H-NMR ($CDCl_3$): δ 6.79-7.33 (m, 13H, Ar-H), 6.21 (s, 2H, -CH), 7.27 (s, 1H, N-H), 3.46-3.78 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 420; (Calcd for $C_{22}H_{20}N_4O_5$; 420.42). Anal (%). Calcd for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4,79; N, 13.33. Found: C, 62.87; H, 4.75; N, 13.37.

3-benzyl-2-(4'-chloro phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (6e)
Brown solid, yield 81%; m.p. 184-186°C; IR (cm^{-1}): 3026 (Ar-CH), 1524 (C=C), 1532 (N=O), 1316 (N-H bending), 3319 (N-H stretching), 749 (C-Cl); ^{1}H-NMR ($CDCl_3$): δ 6.71-7.37 (m, 13H, Ar-H), 6.34 (s, 2H, -CH), 7.31 (s, 1H, N-H), 3.48-3.81 (m, 4H, 2 × CH_2); EI-MS (*m/z*): $[M]^+$ 409; (Calcd for $C_{22}H_{20}ClN_3O_3$; 409.87). Anal (%). Calcd for $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.43; H, 4.99; N, 10.29.

Antihyperglycemic activity
Streptozotocin (STZ) model

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

Sucrose-loaded (SLM) model

Overnight fasted male Sprague-Dawley rats were used for the sucrose-loaded experiment. Blood was collected initially and thereafter test compounds were given to the test group consisting of five rats by oral gavage at a dose of 100 mg/kg of body weight. After half an hour post-test treatment, a sucrose load of 10 gm/kg of body weight was given to each rat. Blood was collected at 30, 60, 90, and 120 min post sucrose load. The % decrease in blood glucose level was calculated according to the AUC method.

RESULTS AND DISCUSSION

Chemistry

The synthesized series of heterocycles, **6a-e**, by the reaction of **5** with appropriate *p*-nitro anilines in the presence of DMF are presented in Scheme 1. The IR, ^{1}H-NMR, mass spectroscopy, and elemental analysis results for the new compounds are in accordance with the assigned structures. The IR spectra of compound **4** showed stretching bands of a keto group at 1728 cm^{-1}. In **5**, stretching bands of a chloro group at 749 cm^{-1} is evidence for the conversion of oxazolidinone. For the title compounds **6a-e** stretching and bending NH bands appeared at 3300-3400 cm^{-1} and 1300-1350 cm^{-1} respectively. The recorded IR spectrum of representative compounds **6a-e** showed missing chloro group bands. This clearly suggests that the chloro group of **5** was converted into secondary NH. The proton magnetic resonance spectra of oxazolidine and its corresponding derivatives were recorded in $CDCl_3$. For **6a-e,** the NH signal of the 3-benzyl-2-(4'-substituted phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine moiety appeared at 7.26 (s), 7.15 (s), 7.21 (s), 7.27 (s), 7.34 (s), ppm, respectively. The position and presence of the NH signal in the ^{1}H-NMR spectra of the final compounds confirms the secondary NH proton in the oxazolidine moiety. This clearly indicates that the oxazolidine-4(5*H*)-one moiety was involved in 4(5*H*)-chloro-1,3-oxazolidine as well as (4"-nitrophenyl amino)-1,3-oxazolidine formation. All these observed facts clearly demonstrate that the 4th position of the keto group in the oxazolidine ring was converted into a secondary amino group as indicated in Scheme 1 and confirms the proposed structures (**6a-e**) Fig. 1.

Antihyperglycemic activity

Among the **5** screened compounds, **6a-e** demonstrated antihyperglycemic activity in the STZ and SLM models, For these compounds, 3-benzyl-2-(4'-hydroxy phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (**6a**) and 3-benzyl-2-(4'-nitro phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (**6d**) reduced

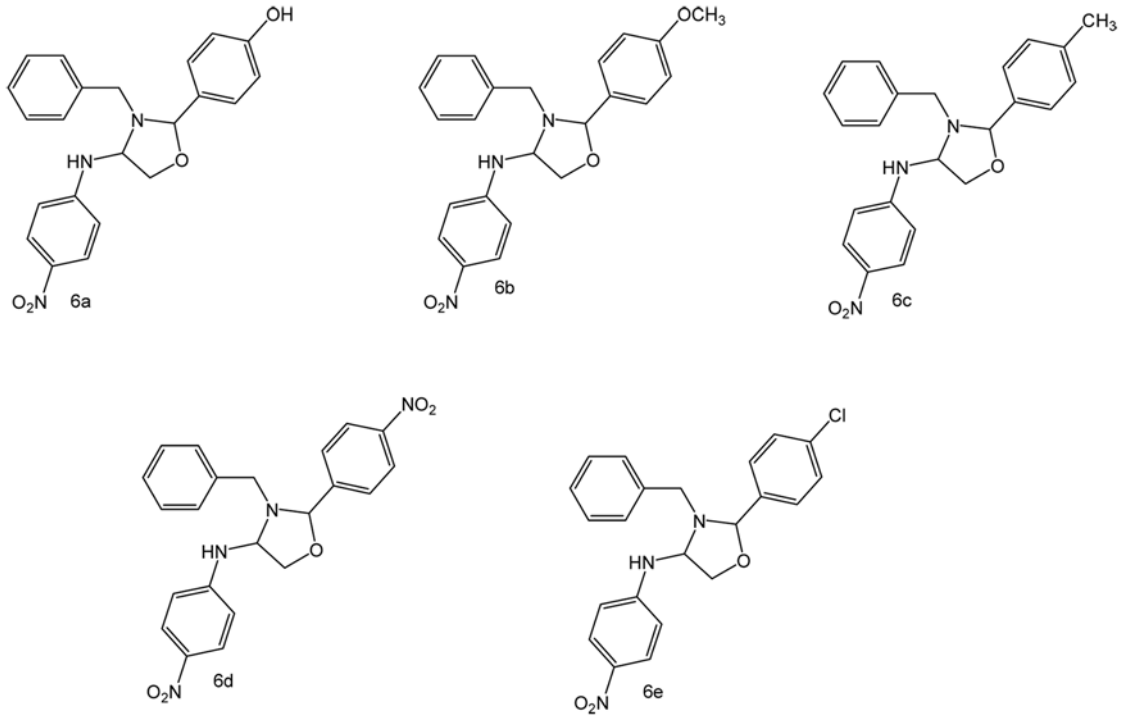


Fig. 1. Schematic structure for the synthesized oxazolidine derivatives

Table I. *In vivo* antihyperglycemic activity of various oxazolidines derivatives (**6a–e**) in streptozotocin (STZ) and sucrose-loaded (SLM) rat models

Compounds	% Blood sugar lowering activity (100 mg/kg)	
	STZ model	SLM model
6a	52.0	72.0
6b	19.6	NIL
6c	13.4	33.2
6d	48.5	66.4
6e	10.9	43.6
Metformin	19.7	13.5
Glybenclamide	31.2	39.4

blood glucose to 52% and 72%, and 48.5% and 66.4%, in the STZ and SLM models, respectively. The other active compound 3-benzyl-2-(4'-mehoxy phenyl)-4(5*H*)-(4"-nitrophenyl amino)-1,3-oxazolidine (**6b**) displayed moderate antihyperglycemic activity in the STZ model (19.6%) and was inactive in the SLM model, this is possibly due to its slower transformation than the other highly active metabolites (**6a, 6d, 6e,** and **6c**). The compound with a chloro substituent at position 4′ in the phenyl ring (**6e**) displayed signicant blood glucose lowering activity (43.6%) in the SLM model while only a 10.9% reduction in blood glucose in the STZ model. Compound **6c** reduced blood glucose by 13.4% in the STZ model while later demonstrated signicant activity (33.2%) in the SLM model. The transformation order of screened compounds was **6a > 6d > 6e > 6c > 6b.** Metformin and glybenclamide were used as standard antidiabetic drugs in both models. All values are presented in Table I.

REFERENCES

Caroon, J. M., Clark, R. D., Kluge, A. F., and Strosberg, A. M., Synthesis and antihypertensive activity of a series of spiro [1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine-2,5'-oxazolidin-2'-one]s. *J. Med. Chem.*, 26, 1426-1433 (1983).

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

Gardrat, C., Latxague, L., and Picard, J. P., A new synthesis of DL-5-vinyl oxazolidine-2-thione, a natural antithyroid factor. *J. Heterocycl. Chem.*, 27, 811-812 (1990).

Heong, S. O., Hoh, G. H., and Seung, H. C., Solid phase synthesis of 1, 3-oxazolidine derivatives, *Tetrahedron Lett.*, 41, 5069-5072 (2007).

Kim, S. J., Jung, M.-H., Yoo, K. H., Cho, J.-H., and Oh, C.-H., Synthesis and antibacterial activities of novel oxazolidinones having cyclic sulfonamide moieties. *Bioorg. Med. Chem. Lett.*, 18, 5815-5818 (2008).

Kostochka, L. M., Lezina, V. P., and Kostochka, M. L., Synthesis of 3-(2-Aryloxazolidin-3yl)tropanes. *Chemistry of Heterocyclic Compounds*. 39, 1227-1230 (2003).

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

Pinder, R. M., A2 adrenoceptor antagonists as anti-depressants. *Drugs of the Future*, 10, 841-857 (1985).

Sharma, K., Saleem, K., and Salim, A., Stereoselective formation of steroidal (6R)-spiro oxazolidines. *Indian J. Chem.*, 42B, 2866-2868 (2003).

Sonika, B. and Satyavan, S., 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 (1990).

Trivedi, N. A., Mazumdar, B., Bhatt, J. D., and Hemavathi, K. G., Effect of Shilajit on blood glucose and lipid profile in alloxan-induced diabetic rats. *Indian J. Pharmacol.*, 36, 373-376 (2004).

Vara Prasad, J. V. N., Boyer, F. E., Chupak, L., Dermyer, M., Ding, Q., Gavardinas, K., Hagen, S. E., Huband, M. D., Jiao, W., Kaneko, T., Maiti, S. N., Melnick, M., Romero, K., Patterson, M., and Wu, X., Synthesis and structure-activity studies of novel benzocycloheptanone oxazolidinone antibacterial agents. *Bioorg. Med. Chem. Lett.*, 16, 5392-5397 (2006).

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