Indian J Physiol Pharmacol 2006; 50 (4): 431–434

LETTER TO THE EDITOR

ANTIHYPERGLYCEMIC EFFECTS OF NEWLY SYNTHESIZED 6,7-BIS[2-(SUBSTITUTEDPHENYL)-4-OXOTHIAZOLIDIN-3YL] QUINOXALINE 2,3-(1 *H*, 4 *H*)-DIONES

Sir,

(Received on April 12, 2006)

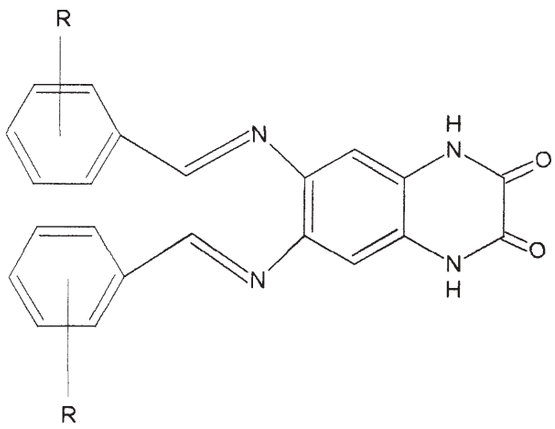
Glucagon-like peptide-1 (GLP) is an incretin secreted from the small intestine in response to food ingestion, and exhibits several biological effects including stimulation of insulin secretion, inhibition of glucagons secretion, slowing gastric emptying and induction of safety. However, GLP-1 action has a very short half life about 1 min due to the degradation by dipeptidyl peptidase-IV (DPP-IV). DPP-IV is a serine protease, which removes the dipeptide from the N-terminus of substrate proteins by cleaving post proline or alanine residues. DPP-IV is expressed in many tissues and body fluids, and exists as either a membrane bound or a soluble enzyme. Since the discovery that GLP-1 secretion is impaired in diabetes, several approaches have been employed to enhance GLP-1 action. Among them, DPP-IV inhibition has been proved to be an effective method (1). Therapeutic use of inhibitors of the enzyme responsible for the inactivation of GLP-1 as anti-diabetic agents was first proposed in 1995 (2) on the basis of the finding that GLP-1 seems uniquely sensitive to cleavage by DPP-IV; compounds of this class have now reached phase III clinical trials. With a DPP-IV inhibitor it is possible to completely prevent the N-terminal degradation of GLP-1 that occurs *in vivo,* resulting in significant enhancement of its insulinotropic activity (3, 4).

In view of this above literature the present study was undertaken to investigate the effects of some quinoxaline-2,3-dione derivatives for anti-hyperglycemic activity against alloxan induced diabetes in rats, moreover recently some of the compounds in this series have been reported in literature as inhibitors of enzyme dipeptidyl peptidase-IV (DPP-IV).

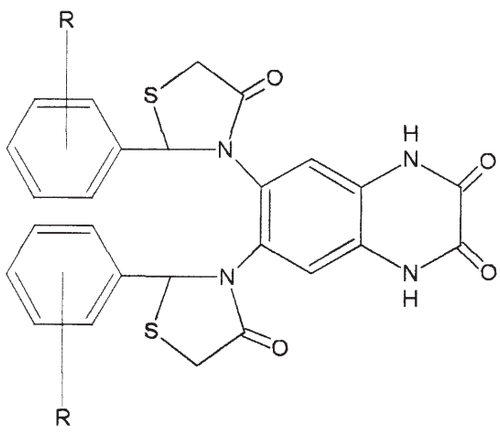
The synthesis, structure ellucidation and antibacterial activity of the compounds have been reported earlier (5) and in present study these compounds having the structure given below were tested for their acute anti-hyperglycemic activity in alloxan induced diabetic rats.

Male Wistar rats weighing 100–250 gm were used for the study. The animals were housed in propylene cages under standard laboratory conditions, maintained on a natural light and dark cycle and had free access to food and water ad libitum. Animals were fed with standard rat pellet diet [AMRUT, Laboratory Animal Feed, (Rat & Mice Feed), Pranav Agro Industries

Ltd., Sangali, Maharashtra State.]. The experimental protocol were approved by the institutional ethics committee [CPCSEA registration No: 448/01/CPCSEA, dated 25th July 2001] and conducted according to the guidelines for the use and care of experimental animals.



Compound I a-f



Compound II a-f

Where R = H, 2-OH, 2-Cl, 4-Cl, 2-OCH_3, 4-OCH_3

Alloxan monohydrate 120 mg/kg, body weight was dissolved in normal saline solution and injected intra-peritoneally after 12 hours fasting to induce hyperglycemia. Alloxan is capable of producing fatal hypoglycemia as a result of massive pancreatic insulin release, therefore the animals were treated with 20% glucose solution (15–20 mL) orally after 6 hours (6). After one hour of alloxan administration the animals were fed on standard pellets and water. The blood glucose level (BGL) was monitored after alloxanization in blood samples collected by tail tipping method using a glucometer (ACCU-CHEK, Active, Roche Diagonistics, Mannheim, Germany). It was confirmed after 48 hours (on third day). Animals found hyperglycemic, having BGL above 150 mg/dL, of blood were selected for the study and were divided into different groups. Control group received only vehicle, standard group received glibenclamide (0.50 mg/kg, i.p.) and test groups were treated with a single dose of test compounds (5 mg/kg, i.p.). The blood glucose level was monitored immediately before, and 1, 2, 3, 5 and 24 hours after administration of the test compounds.

Data obtained was subjected to statistical analysis to determine the statistical significance using student's 't' test, $P<0.05$ was considered as significant. The anti-hyperglycemic activity data is presented in Table I. All the values are expressed as mean ± SEM; n = 6.

Present study concluded that these compounds have significant anti-

TABLE I: Anti-hyperglycemic effect of synthesized compounds in alloxan-induced diabetic rats.

Compd.	*Blood glucose level in mg/dL*					
	0 hour	*1 hour*	*2 hour*	*3 hour*	*5 hour*	*24 hour*
I a	331±5.96*#	328±4.65*	318±4.95*	309±4.93*	291±5.38*#	189±6.81*#
I b	316±4.27*	305±5.38*	264±6.03*#	201±5.93*#	189±6.43*#	139±5.75*#
I c	271±8.46*#	267±7.10*#	251±8.62*#	240±8.20*#	215±9.67*#	198±11.35*#
I d	234±8.33*#	229±8.16*#	211±8.65*#	203±10.02*#	200±8.44*#	184±7.04*#
I e	294±8.11*	288±7.93*#	271±6.89*#	254±7.64*#	239±6.73*#	201±7.22*#
I f	309±9.14*	285±6.94*#	266±10.29*#	234±10.90*#	224±9.87*#	184±9.17*#
II a	289±8.13*#	272±8.86*#	258±9.06*#	231±9.56*#	218±9.92*#	198±10.04*#
II b	287±10.63*	255±9.86*#	223±9.77*#	207±10.31*#	202±9.11*#	186±7.66*#
II c	301±7.93*	297±7.55*#	284±10.39*#	279±12.02*#	258±9.40*#	204±8.16*#
II d	279±9.25*#	275±9.70*#	261±9.18*#	253±10.52*#	239±12.32*#	186±9.24*#
II e	312±10.17*	307±10.49*	297±9.43*	276±9.93*#	260±9.13*#	215±4.48*#
II f	310±4.68*	294±10.07*	277±11.17*#	263±10.82*#	239±7.99*#	129±8.77*#
Std.	311±3.79*	224±11.90*#	203±12.88*#	178±10.96*#	132±5.37*#	85±4.22#
Control	310±4.56*	319±5.37*	317±5.02*	323±6.86*	329±7.8**	331±7.16*
Normal	78±3.84#	80±3.50#	82±2.40#	79±3.75#	85±2.61#	81±4.23#

All the values are expressed as mean±SEM; n=6 in each group; *P<0.05 significant, compared to normal and #P<0.05 significant, compared to diabetic control.

hyperglycemic effect. Compounds I f, II f, I a and I b showed the highest anti-hyperglycemic effect with 60%, 59%, 43% and 44% reduction in blood glucose level respectively. Further studies are required to reveal the mechanism of action.

ACKNOWLEDGMENTS

The authors would like to thank Principal, P.R.C.O.P. Loni, for permitting and providing the necessary facilities to carry out this study.

P. Y. PAWAR* AND S. B. BHISE**

*Department of Pharmaceutical Chemistry,
College of Pharmacy,
Ahmednagar – 414 111 (M.S.)
E-mail : pawarpy2001@yahoo.co.in
and
**Department of Pharmacology,
Government College of Pharmacy,
Karad – 415 124 (M.S.)

*Corresponding Author

REFERENCES

1. Cheon HG, Lee CM, Kim BT, Hwang KJ. Lead discover} of quinoxalinediones as an inhibitor of dipeptidyl peptidase-IV (DPP-IV) by high-throughput screening. *Bioorganic & Medicinal Chemistry Letters* 2004; 14: 2661–2664.
2. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Hoist JJ. Both subcutaneously and intravenously administeried glucagons-like peptide 1 are rapidly degraded from the NH2-terminus in type II diabetes patients and in healthy subjects. *Diabetes* 1995; 44: 1126–1131.
3. Deacon CF, Hughes TE, Hoist JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagons-like peptidite 1 in the anesthetized pig. *Diabetes* 1998; 47: 764–769.
4. Hoist JJ, Deacon CF, Glucagon-like peptide 1 and inhibitors of dipeptidyl peptidase IV in the treatment of type 2 diabetes mellitus. *Current Opinion in Pharmacology* 2004; 4: 589–596.
5. Pawar PY, Bhise SB. Synthesis and antibacterial activity of some 6,7-bis[2-(substitutedphenyl)-4-oxothiazolidin-3yl]quinoxaline-2,3(1*H*, 4*H*)-diones. *Indian Journal of Heterocyclic Chemistry* (Paper No: 1862/05).
6. Pari L, Ramakrishnan R, Venkateswaran S. Antihyperglycemic effect of Diamed, a herbal formulation, in experimental diabetes in rats. *Journal of Pharmacy & Pharmacology* 2001; 53: 1139–1143.