Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 999–1002

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

NOVEL EUGLYCEMIC AND HYPOLIPIDEMIC AGENTS : PART - 2 ANTIOXIDANT MOIETY AS STRUCTURAL MOTIF#

K. Anji Reddy,[a] B. B. Lohray,*[†] Vidya Bhushan,[†] A. Sekar Reddy,[†] P. Hari Kishore,[†] V. Venugopal Rao,[†] V. Saibaba,[†] A. C. Bajji,[†] B. M. Rajesh,[†] K. Vivekananda Reddy,[†] Ranjan Chakrabarti,[§] R. Rajagopalan,[§]

[†] *Deparment of Medicinal Chemistry and Drug Discovery,* [§] *Department of Pharmacology*

[a] *Dr. Reddy's Research Foundation, Hyderabad - 500 050, INDIA*

Received 9 February 1998; accepted 20 March 1998

Abstract: Several thiazolidinediones having antioxidant moities in their structural motif have been synthesised and evaluated for their euglycemic and hypolipidemic activities. A few of them have been found to be superior to troglitazone.

In most Non Insulin Dependent Diabetes Mellitus (NIDDM, type 2) patients, there is resistance to the action of insulin on target tissues and therefore, drugs that reverse the insulin resistance without stimulating release from β-cells[1] fulfil a present medical need in the treatment of NIDDM. Since the pioneering discovery of ciglitazone by Sohda *et. al.* [2] there has been a surge of interest in the development of novel antihyperglycemic agents that can control hyperglycemia without causing hypoglycemia.[3]

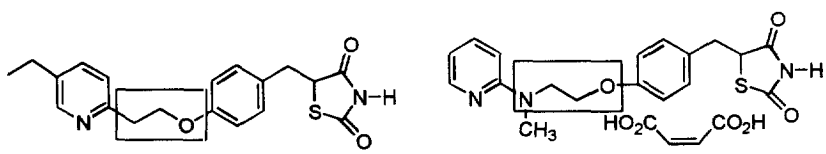


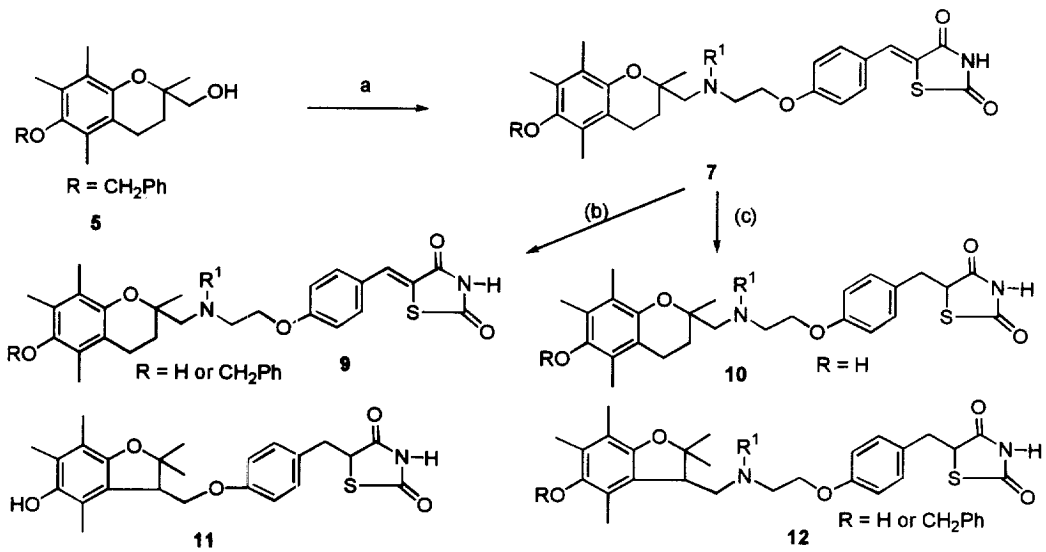
CHART I

Troglitazone[3c] which has a beneficial antioxidant moiety, has been recently withdrawn from European market due to hepatic dysfunction[4] and increase in lipoprotein a[1] (Lpa[1]).[5] However, in US and Japan, regulatory authorities have asked the change of labelling; and suggested the regular monitoring of liver enzyme, since the benefits of troglitazone outweigh its risks. But there is a definite need for a safe and efficacious antihyperglycemic agent. We focused our attention on molecules which preserve the beneficial antioxidant moiety but have superior euglycemic and hypolipedemic activities compared to troglitazone. Antioxidants are known to be interceptors of peroxy radicals and singlet oxygen that therefore inhibit lipid peroxidation,[6] (which has been implicated in the alteration of glucose transport and microangiopathic disease in diabetes).[7] Our strategy is based on comparison of euglycemic activities of pioglitazone and rosiglitazone, which suggests that introduction of N-(CH_3)- group between the pyridine ring and phenoxyethyl moiety of pioglitazone leads to several fold increase in potency (see Chart-I).

DRF Publication No. : 33 e.mail : drf@hd1.vsnl.net.in.

PII: S0960-894X(98)00159-0

Thus, we envision that if we can introduce -NR- group between chroman ring and phenoxyethyl moiety, we might improve its plasma glucose and triglyceride lowering activities compared to troglitazone. With these views in mind, we prepared several compounds having N-alkyl moiety between chroman ring and phenoxyethyl linker. A general synthetic strategy is outlined in scheme-1.



Scheme-1

(a) (i) $MeSO_2Cl$ (98 %) (ii) $R^1NHCH_2CH_2OH$, Δ, Neat, 120 °C **6** (95 %) (iii) $SOCl_2$ (98 %) (iv) 4-hydroxybenzaldehyde **8** (97 %). (v) 2,4-Thiazolidinedione, piperidine, benzoic acid, toluene, Δ, **7** (98 %). (b). AcOH-HCl, Δ, 2h, 60 °C **9** (98 %). (c) (i) Mg-MeOH (ii) AcOH - HCl, 60 °C, 2h (90 %).

2,5,7,8-Tetramethyl-6-benzyloxy chroman-2-methanol (**5**) was prepared by known method.[8] Treatment of **5** with CH_3SO_2Cl in pyridine at 0 °C gave 98 % of mesylate derivative which is treated with 2-(methylamino)ethanol to afford 95 % of 2-[N-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethanol (**6**). Reaction of **6** with $SOCl_2$ followed by *p*-hydroxybenzaldehyde afforded 4-[2-(N-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethoxy]benzaldehyde (**8**) (97 %). The aldehyde **8** was condensed with 2,4-thiazolidinedione in the presence of piperidine benzoate in toluene to furnish 98 % of 5-[4-[2-N-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethoxy] phenyl methylene] thiazolidine-2,4-dione (**7**). The later can be reduced using Mg/MeOH (12 - 15 h, *ca* 25 °C) followed by treatment with AcOH-HCl (2 h, 60 °C) to give 5-[4-[2-N-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4,-dione (**10**). On the other hand, the benzyl protecting group can be removed from unsaturated compound **7** by simple treatment with acetic acid-hydrochloric acid for 2 h at 60 °C to give 98 % of 5-[4-[2-N-(6-Benzyloxy-2,5,7,8-tetramethyl chroman-2-ylmethyl)-N-methylamino]ethoxy]benzyl]thiazolidine-2,4-dione (**9**).

Similar synthetic route was followed to prepare dihydrobenzofuran analogs 5-[4-(2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethyl-1-benzofuran-3-methoxy]phenylmethyl]thiazolidine-2,4-dione (**11**) and 5-[4-[2-N-(5-

benzyloxy-2,2,4,6,7-pentamethyl-1-benzofuran-3-ylmethyl)-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4-dione (**12**) using 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethyl-1-benzofuran-3-methanol.[9] Both unsaturated and saturated thiazolidinedione derivatives were evaluated in db/db mice at 200 mg / kg / day / p.o. for 9 days.[3g] The results are summerized in Table-1. The effect of protection on phenolic OH group of benzofuran and chroman moiety were studied. The antioxidant properties of OH free and protected compounds **7** *vs* **9a** and **12a** *vs* **12d** were evaluated. The O-benzylated compound did not show any antioxidant activity.[10] However, comparing their *in vivo* activities, compound **9a** with **7**, we did not observe differences in plasma glucose lowering activity (Table 1, entry **9a** *vs* **7**) although there is considerable change in triglyceride lowering activities. Similar effect on plasma glucose and triglyceride activities were observed for dihydrobenzofuran analog (Table 1, entry **12a** *vs* **12d**). Unfortunately, contrary to our expectations, saturation of C=C bond in **9a** (i.e. **10**) lead to the complete loss of plasma glucose and triglyceride lowering activities. Thus, we find that compound **9a** and **12a** are superior to troglitazone in both plasma glucose and triglyceride lowering activities. If we compare dihydrobenzofuran analog **11** with **12a**, here also there is a considerable improvement in euglycemic and hypolipidemic activities.

Table 1 : Thiazolidinediones **9** and **12** and their biological activity[a]

Compound	R	R^1	DB	Dose mg / kg	X^-	BG ↓ (9 days)[b]	TG ↓[c]
7	Bn	Me	Yes	200	-	39	32
9a	H	Me	Yes	200	-	43	70
9b	H	Et	Yes	200	-	2	76
9c	H	H	Yes	200	-	06	29
9d	H	Me	Yes	200	CH_3COO^-	11	31
9e	H	Me	Yes	200	HCl	31	30
9f	H	Me	Yes	200	Maleate	20	60
9g	H	Me	Yes	200	$CH_3SO_3^-$	20	70
10	H	Me	No	200	-	4	NA
	Troglitazone			200	-	24	50
11	H	-	No	200	-	19	40
12a	H	Me	Yes	200	-	46	71
12b	H	Me	No	200	-	17	33
12c	H	Me	Yes	200	Maleate	35	33
12d	Bn	Me	Yes	200	-	23	NA

(a) Biological protocol, ref. 3g. (b) % Reduction in plasma blood glucose. (c) % Reduction in plasma triglyceride. NA : Not Applicable ; DB = double bond, X^- = counter ion for salt formation.

Further, we examined the possibility of formation of various salts of **9a** and **12a**, which might affect biological profiles, however, none of the salts exhibited improvement in plasma glucose or triglyceride activity (Table 1, entry 9d - 9g and 12c).

It is also interesting to note that methyl group is an optimum substituent on N in both the chroman series and benzofuran series of compounds. Replacement of N-Me by N-H (Table 1, entry 9c) or N-Et (Table 1, entry 9b) leads to the reduction of activities.

We believe that compounds **9a** and **12a** would be superior in potency to troglitazone in both plasma glucose and triglyceride lowering activities with antioxidant moiety.

Acknowledgement : We thank Dr. A. Venkateswarlu, President, DRF, for encouragement and Analytical Deparment for analytical support.

References :

1. (a) Steiner, K. E.; Lien, E. L., *Progress in Medicinal Chemistry;* Ellis, G. P.; West, C. B. Eds Elsevier, Oxford **1987**, vol. 24, p 209 - 248. (b) Larson, E. R. Clark, D. A. and Stevenson, R. W. *Ann. Reports Med. Chem.* **1989**, *25*, 205-213. (c) Colea, J. R.; Tanis, S. P. *Ann. Reports Med. Chem.* **1992**, *27*, 219 - 226. (d) Dow, R. L.; Kreutter, D. K. *Annu. Reports Med. Chem.* **1995**, *30*, 159-168. (e) Hulin, B.; McCarthy, P. A.; Gibbs, E. M. *Curr. Pharma. Design* **1996**, *2*, 85-102. (f) Hulin, B. *Prog. Med. Chem.* **1994**, *31*, 1-58.
2. Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawanatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3563 - 3573 and 3580 - 3600.
3. (a) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T., *Chem. Pharm. Bull.* **1991**, *39*, 1440 - 1445. (b) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita,T.; Meguro, K. *J. Med. Chem.* **1992**, 35, 2617-2626. (c) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421-428. (d) Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N. Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E Hutson, N. J. and Johnson, M. R. *J. Med. Chem.* **1991**, *34*, 319 - 325. (e) Cantello, B. C. C.; Cawthorne, M. A.; Haigh, D.; Hindley, R. M.; Smith, S. A.; Thurlby, P. L. *Bioorganic & Medicinal Chemistry Lett.* **1994**, *4*, 1181 - 1184. (f) Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D ; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977 - 3985. (g) Lohray, B. B.; Bhushan, V.; Rao, P. B.; Madhavan, G. R.; Murali, N.; Rao, K. N.; Reddy, K. A.; Rajesh, B. M.; Reddy, P. G.; Chakrabarti, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 785.
4. Scrips (**1997**), 2282, p21, Scrips (**1997**), 2292, p20.
5. Matsumoto, K.; Miyake, S,; Yano, M.; Ueki, Y.; Tominaga, Y. *Lancet* **1997**, *350*, 1748 - 1749.
6. (a) Cablero, B. *Nutrition Reviews*, vol *51* (11), 339. (b) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y., Kurumada, T.; Hasegawa. K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421. (c) Aizawa, Y.; Kanai, T.; Hasegawa, K.; Yamaguchi, T.; Iizuka, Y.; Iwaoka, T.; Yoshioka, T. *J. Med. Chem.* **1990**, *33*, 1491.
7. Oberley, L. W.; *Free Rad. Biol. Med.* **1988**, *5*, 113 - 124.
8. Takebayashi, T.; Onodera. T.; Hasegawa, K.; Fujita, T.; Yoshioka, T. E.P. 454 501 (1991); *Chem. Abstr.* **1992**, *116*, 59361k.
9. Grisar, J. M.; Bolkenius, F. N.; Petty, M. A.; Verne, J. *J. Med. Chem.* **1995**, *38*, 453.
10. Whitehead, T. P.; Thorpe, G. H. G.; Maxwell, S. R. J. *Analytica Chemica, Acta.* **1992**, *266*, 265.