Pure Appl. Chem., Vol. 77, No. 1, pp. 179–184, 2005.
DOI: 10.1351/pac200577010179

Novel pyrrole-containing hypoglycemic and hypotriglyceridemic compounds*

Braj B. Lohray‡ and Vidya Lohray

Zydus Research Center, Moraiya, Ahmedabad 382 210, India

Abstract: Several substituted α-alkoxy phenyl propionic acids were synthesized, and their hypotriglyceridemic properties were evaluated in Swiss albino mice. Some of the compounds showed excellent triglyceride- and cholesterol-lowering properties even at a dose of 1 mg/kg. 2,5-Substituted pyrrole-containing heterocycles were among the most potent alkoxy propionic acid class of compounds. These compounds also showed excellent antidiabetic activities in animal models.

Cardiovascular diseases have been the general cause of death in most diabetic patients. Improper glucose homeostasis leads to a cascade of complications such as hyperglycemia, hypertriglyceredemia, hypercholesteremia, lowering of HDL, nephropathy, retinopathy, atherosclerosis, and such other cardiovascular disorders (CVDs). It has been shown that the mortality due to CVD in hyperchlolesteremic patients is reduced by treatment with statins, especially Atorvastatin (**1**) or Simvastatin (**2**) compared to that of Lovastatin (**3**) [1]. This has been attributed to the triglyceride-reducing property of these drugs in addition to the cholesterol reduction. On the other hand, it is known that the insulin sensitizers working through PPAR activation such as Pioglitazone (**4**) and Rosiglitazone (**5**) showed beneficial effect in diabetic and cardiovascular patients [2].

It has been shown in Phase II clinical trials that the PPAR α/γ dual activators such as Ragaglitazar [3] (**6**) (discontinued in Phase III clinical trials) and Tesaglitazar (**7**) (Phase III) reduced triglycerides (TGs) in diabetic patients. Therefore, a molecule that can reduce cholesterol levels and TGs in addition to glucose levels in diabetic patients will be highly desirable to reduce mortality due to CVD in diabetic patients.

With a view to introduce cholesterol-lowering activity in PPAR α/γ activator templates, we selected the pyrrole-containing compound **12** (a heterocycle moiety present in Atorvastatin) as a starting point. Several heterocyclic templates have been studied in combination with 2-alkoxy-3-phenyl propionic acid pharmacophore. The molecules having this pharmacophore have been shown to possess PPAR α/γ dual activating properties [3,4]. Such molecules reduce serum TGs and total cholesterol (TC) in Swiss albino mice, which are hypertriglyceredemic.

*Paper based on a presentation at the 24th International Symposium on the Chemistry of Natural Products and the 4th International Congress on Biodiversity, held jointly in Delhi, India, 26–31 January 2004. Other presentations are published in this issue, pp. 1–344.

‡Corresponding author: Tel: +91-2717-250801; Fax: +91-2717-250606: E-mail: braj.lohray@zyduscadila.com

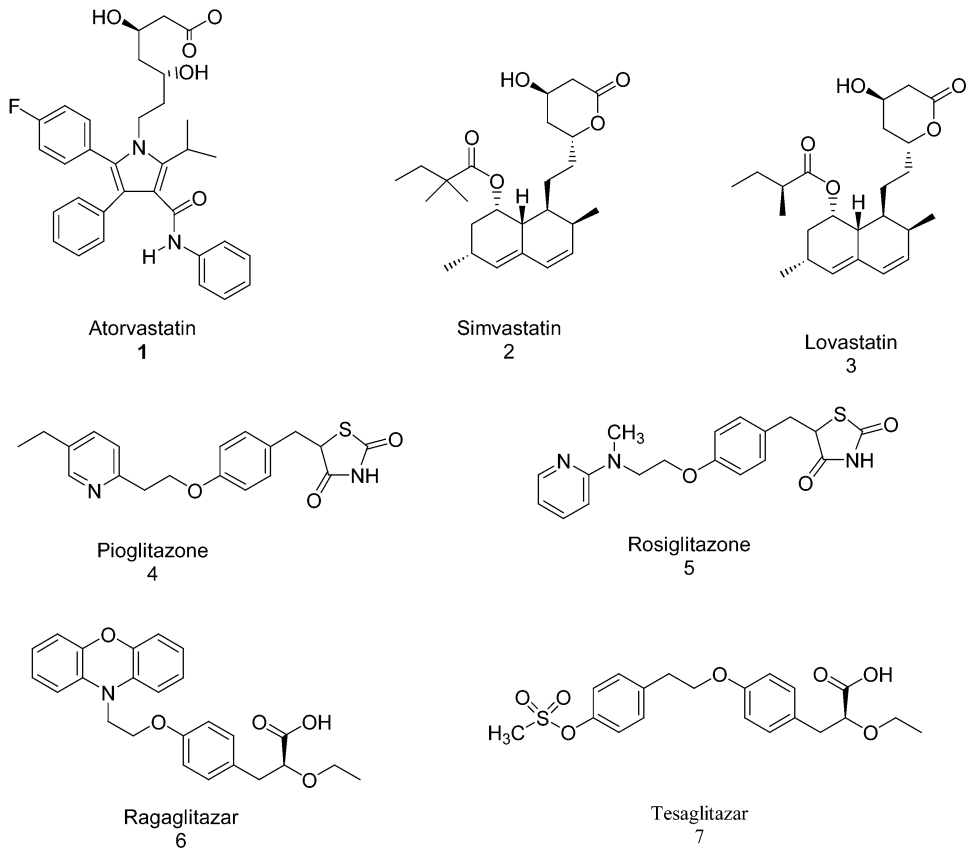
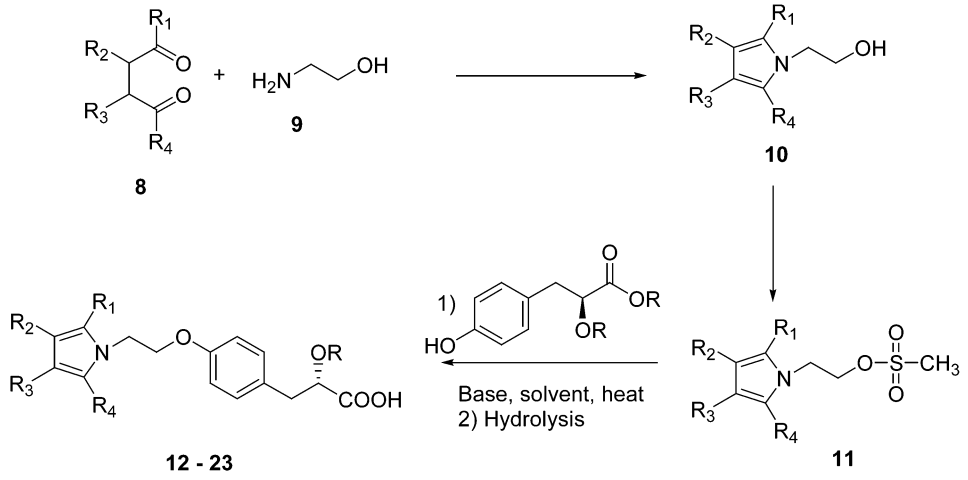


Chart 1

The compound **12** prepared according to the synthetic route depicted in Scheme 1 was tested at a dose of 50 mg/kg in male Swiss albino mice for 6 days. The compound **12** showed 15 % reduction in serum TGs. A related compound **13** also did not show any remarkable activity (Table 1).



Scheme 1

Table 1 TG- and TC-lowering activity in male Swiss albino mice after 6 days of treatment.

Sr. no.	Substitution R_1	R_2	R_3	R_4	Dose (mg/kg)	Swiss albino mice TG	TC
12	*i*-Pr	PhNHCO–	C_6H_5–	4F-C_6H_4–	50	15	3
13	*i*-Pr	H	C_6H_5–	4F-C_6H_4–	50	3	8
14	*i*-Pr	H	H	4F-C_6H_4–	10	–	+69
15	*i*-Pr	PhNHCO-	H	4F-C_6H_4–	10	+10	+9
16	C_6H_5-	H	H	4F-C_6H_4–	10	26	19
17	*i*-Pr	H	H	C_6H_5	3	+30	+36
18	*i*-Pr	H	H	4-$MeOC_6H_4$	10	31	+42
19	*i*-Pr	H	H	CH_3	10	53	4
1	6	+9					
20	*i*-Pr	H	H	C_2H_5–	3	41	+24
	1	50	2				
21	H	H	H	H	10	16	+27
22	CH_3	H	H	CH_3	50	55	18
	3	39	+33				
	1	27	+10				
23	CH_3	H	H	C_6H_5	10	65	31

Both the compounds **12** and **13** have bulky substituents, which are not favorable for binding to the PPAR α and γ receptors (unpublished results). Therefore, we carried out a gradual structural modification to generate a structure–activity relationship. This led us to arrive at the suitable substituents around the pyrrole ring. The results, which are compiled in Table 1, show that tetra- and tri-substituted pyrroles (**12**, **13**, **15**) do not reduce serum TGs in Swiss albino mice. Thus, we synthesized 1,4-disubstituted pyrrole derivatives. Although compounds **14** and **17** did not show serum TG reduction, the TG reductions shown by **16** (26 % at 10 mg/kg dose) and **18** (31 % at 10 mg/kg dose) were encouraging. At present, we are not able to understand the rationale for certain 1,4-disubstituted compounds (**15**, **17**) to increase the serum TG levels and TC, whereas in certain other 1,4-substituted compounds, reduction of TG and TC were found in Swiss albino mice. We further studied the activity of 1,4-dialkylated pyrrole derivatives **19** and **20**, which showed 53 % reduction in TG at 10 mg/kg dose and 41 % reduction in TG at 3 mg/kg dose, respectively. The unsubstituted pyrrole derivative **21** showed very poor activity. When the isopropyl group in **19** is replaced with a methyl group, the resulting compound **22** reduced serum TG up to 27 % even at 1 mg/kg dose in contrast to compound **19** (6 % TG reduction at 1 mg/kg dose). The compound **23** having 1-methyl-4-phenyl pyrrole moiety also showed good TG- and TC-reducing activity.

This encouraged us to examine the compounds having a methyl group in the 1-position and variously substituted phenyl group in the 4-position of pyrrole moiety (Table 2).

Compound **24** with 1-methyl-4-(4-fluoro-phenyl)pyrrole moiety reduced 53 % TG at 1 mg/kg dose. Introduction of a methyl group at 4-, 3-, or 2-position in the phenyl substituent of **23** to generate **25**–**27**, respectively, led to good TG reduction. Also, methoxy group in the 3- (**28**) as well as 4-position (**29**) resulted in very good TG and TC reduction. However, the 4-OH group in compound **30** led to decreased TG-reducing activity and no cholesterol-reducing activity. When a 4-benzyloxy group was introduced in place of the 4-OH group, the TG- and TC-reducing activities were restored (**31**, 52 % TG reduction and 32 % TC reduction). On the other hand, 3-benzyloxy group in **32** as well as cyclohexylmethoxy group as in **35** destroyed such activity. Introduction of a second methoxy group at 3-position of phenyl group in **29** leading to compound **33** again destroyed the TG- and TC-reducing activity of **29**. Interestingly, compound **34** with 3,4-dioxymethylene moiety on the phenyl ring reduced both TG and TC effectively (63 % TG and 26 % TC reduction at 3 mg/kg dose). An electron-withdrawing moiety

4-mesylate (**36**) in place of 4-OH group in **30** did not alter the TG-reducing activity. Replacing the phenyl group in **23** with a pyridyl group exhibited TG-reducing activity dependent on the place of attachment of the pyridyl group to the pyrrole moiety. While 2-pyridyl group (**37**) showed 60 % reduction in TG at 3 mg/kg dose in Swiss albino mice, 4-pyridyl (**39**) reduced TG moderately (29 %) and 3-pyridyl group (**38**) showed no such activity.

Table 2 TG- and TC-lowering activity in male Swiss albino mice after 6 days of treatment.

Sr.	Substitution				Dose	Swiss albino mice	
no.	R_1	R_2	R_3	R_4	(mg/kg)	TG	TC
24	CH_3	H	H	4F-C_6H_4	1	53	+18
25	CH_3	H	H	4CH_3-C_6H_4	3	30	+43
26	CH_3	H	H	3-CH_3–C_6H_4	1	56	+25
27	CH_3	H	H	2-CH_3–C_6H_4	1	56	+9
28	CH_3	H	H	3-CH_3O–C_6H_4	3	58	17
29	CH_3	H	H	4-$MeOC_6H_4$	10	54	38
30	CH_3	H	H	4-HO-C_6H_4	3	33	+9
31	CH_3	H	H	4-$BnOC_6H_4$	3	52	32
32	CH_3	H	H	3-$BnOC_6H_4$	3	13	+11
33	CH_3	H	H	3,4-diOMe C_6H_3	10	13	+14
34	CH_3	H	H	3,4-dioxymethene phenyl	3	63	26
35	CH_3	H	H	Cy CH_2–O–C_6H_4	3	4	+22
36	CH_3	H	H	CH_3–SO_3–C_6H_4	3	34	+28
37	CH_3	H	H	2-pyridyl	3	60	+5
38	CH_3	H	H	3-pyridyl	3	+5	+4
39	CH_3	H	H	4-pyridyl	3	29	+5
40	CH_3	H	H	1-naphthyl	10	5	+10
41	CH3	H	H	2-naphthyl	3	38	+34

2-Napthyl group (**41**) in place of phenyl group in **23** gave 38 % reduction in TG, whereas 1-naphthyl group (**40**) even at 10 mg/kg dose reduced only 5 % TG.

Based on the TG- and TC-reducing activities observed in single-dose studies, compounds **23**, **29**, **31**, and **34** were selected for a multiple-dose study to evaluate their effect with increasing dose. Male Swiss albino mice were treated for 6 days with the selected compounds, and their effect on TG and serum TC reduction is tabulated in Table 3. Both TG and serum TC were reduced in a dose-dependent manner. It is interesting to note that although the effect on TG lowering is seen starting from the lowest dose of 0.1 mg/kg, the reduction in cholesterol is observed at the highest dose taken in all the cases except **31**, wherein 18.9 % reduction in serum cholesterol is found even at 1 mg/kg dose. The cholesterol reduction achieved with these four compounds is quite high (20–25 %) in this animal model.

Table 3 Hypotriglyceredemic and hypocholesterolemic effects of selected compounds in Swiss albino mice after 6 days of treatment.

Compound	Dose (mg/kg)	Triglyceride % reduction	Cholesterol % reduction	Triglyceride reduction
23	0.1	25.2 ± 3.9	–13.7 ± 5.7	ID_{50} = 1.2 mg/kg
	1	46.8 ± 3.0	–9.8 ± 6.2	
	10	64.6 ± 2.4	20.7 ± 4.7	
29	0.1	18.0 ± 7.4	–8.9 ± 4.6	ID_{50} = 1.4 mg/kg
	1	38.7 ± 5.3	2.1 ± 7.9	
	10	64.5 ± 1.5	46.9 ± 3.2	
31	0.1	41.3 ± 6.8	–11.7 ± 3.8	ID_{50} = 0.24 mg/kg
	1	67.2 ± 4.0	18.9 ± 2.0	
	10	74.7 ± 1.3	38.7 ± 4.7	
34	0.1	27.8 ± 6.2	–26.5 ± 7.7	ID_{50} = 0.97 mg/kg
	1	50.7 ± 1.6	–0.7 ± 9.1	
	10	63.5 ± 1.2	45.6 ± 2.9	

Looking at the very good activity in hypertriglyceredemic mice, we decided to study these compounds **29**, **31**, and **34** in genetic models of diabetes and obesity. Thus, hyperglycemic male db/db mice (6–8 weeks old) were treated at 1 mg/kg dose for 6 days with **29**, **31**, and **34**. All of the compounds showed comparatively very good activities of serum glucose reduction and serum TG reduction (Table 4).

Table 4 Antihyperglycemic and hypotriglyceredemic effect of compounds in db/db mice after 6 days of treatment.

Compound	Dose (mg/kg)	Glucose % reduction	Triglyceride % reduction
29	1	61.9 ± 1.7	48.9 ± 6.3
31	1	58.2 ± 1.5	50.5 ± 5.7
34	1	65 ± 2	54.9 ± 3.2

The compounds **29**, **31**, and **34** have been taken for further studies in other animal models of diabetes, obesity, and insulin resistance. Studies to establish the mechanism of action of these drugs through which they lower serum TG, glucose, and TC are under progress.

ACKNOWLEDGMENT

We wish to thank Mr. P. R. Patel, CMD of Zydus Cadila for encouragement and support.

REFERENCES

1. E. J. Schaefer, J. R. McNamara, T. Tayler, J. A. Daly, J. L. Gleason, L. J. Seman, A. Ferrari, J. J. Rubenstein. *Am. J. Cardiol*. **93** (1), 31–39 (2004).
2. B. B. Lohray and Vidya Bhushan. *Curr. Med. Chem*. **11**, 763–771 (2004) and references cited therein.
3. B. B. Lohray, V. B. Lohray, A. C. Bajji, S. Kalchar, R. R. Poondra, S. Padakanti, R. Chakrabarti, R. K. Vikramadithyan, P. Misra, S. Juluri, N. V. S. R. Mamidi, R. Rajagopalan. *J. Med. Chem.* **44**, 2675 (2001).

4. (a) B. B. Lohray, R. Ramanujam, R. Chakrabarti, V. B. Lohray, R. B. Paraselli. WO patent 9908501 (1999); (b) B. B. Lohray, R. Ramanujam, B. A. Channaveerappa, R. Chakrabarti, S. Kalchar, V. B. Lohray. WO patent 9920614 (1999); (c) B. B. Lohray, R. Ramanujam, B. A. Channaveerappa, R. Chakrabarti, S. Kalchar, V. B. Lohray. WO patent 9919313 (2000); (d) B. B. Lohray, R. Ramanujam, R. Chakrabarti, V. B. Lohray, R. B. Paraselli. U.S. patent 6130214 (2000); (e) R. M. Gurram, B. B. Lohray, R. Rajagopalan, R. Chakrabarti, A. B. Channaveerappa, V. B. Lohray, B. R. Paraselli, K. Shivaramayya. WO patent 0050414 (2000); (f) B. B. Lohray, V. K. G. Barot, V. B. Lohray. WO patent 0153257 (2001).