Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 2547–2551

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel Coumarin Derivatives of Heterocyclic Compounds as Lipid-Lowering Agents☆

Gurram R. Madhavan,[a,*] Vadla Balraju,[a] Bejugam Mallesham,[a] Ranjan Chakrabarti[b] and Vidya B. Lohray[a]

[a]*Discovery Chemistry, Dr. Reddy's Discovery Research, Bollarum Road, Miyapur, Hyderabad 500050, India*
[b]*Discovery Biology, Dr. Reddy's Discovery Research, Bollarum Road, Miyapur, Hyderabad 500050, India*

Received 28 February 2003; accepted 1 May 2003

Abstract—Coumarin derivatives of different heterocycles (**5**,**7a**–**i**, **10** and **11**) were designed based on cyclisation of 2-ethoxy-3-phenylpropanoic acid and 2-benzylmalonic acid as novel lipid-lowering agents and their preliminary in vivo screening indicates **7c** has moderate triglyceride-lowering activity.

Atherosclerotic cardiovascular disease is the leading cause of death in developed countries. Epidemiological studies have identified a variety of independent risk factors that contribute to coronary artery disease (CAD); most notable are high LDL-cholesterol, triglyceride (TG) and low HDL-cholesterol. Current therapies mostly focus on lowering LDL-cholesterol and statins used for this purpose are pretty effective and also safe.[1] Yet they are not effective in lowering TG and HDL. Most patients still experience adverse coronary events despite statin therapy. In addition, recent reports of undesirable side effects of some 'super statins'[2] indicate that the scope of improving the potency of this class of drugs may be limited. Fibrate class of drugs, which are mostly used to treat hyper triglyceridemia and low HDL-cholesterol, needs very high doses to show significant efficacy.[3] In addition a combination of fibrate and statins has recently been reported to increase events of myotoxicity in patients of CAD.[2] Therefore, there is a constant need for a different class of potent compounds to treat dyslipidemia.

Oxidative stress has recently been implicated in the pathogenesis of various diseases such as diabetes and CAD. Consequently, the potential therapeutic or preventive effects of antioxidative agents have been mentioned.[4] Coumarins are known to have antioxidant potential like α-tocopherol (Vitamin-E). Previously, we had reported[5] that an 2-ethoxy-3-propanoic acid derivative showed blood glucose lowering activity in experimental animal models. We thought of changing the pharmacophore by cyclising the 2-ethoxy propanoic acid to form a coumarin moiety (Fig. 1). Similarly, we can also cyclise 2-benzylmalonic acid derivatives to coumarin carboxylic acid derivatives. In this paper, we report the synthesis of coumarin derivatives having

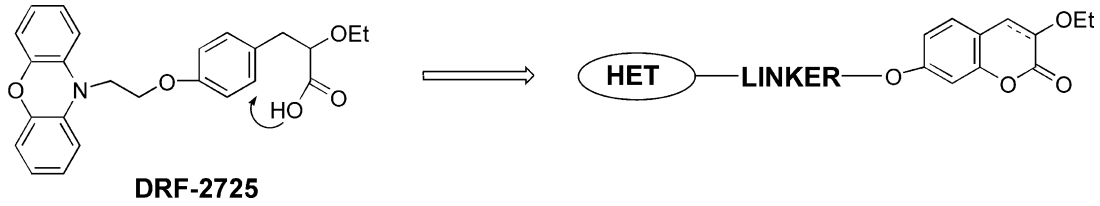
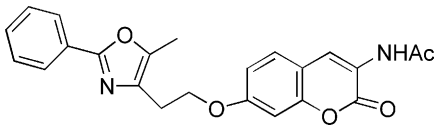
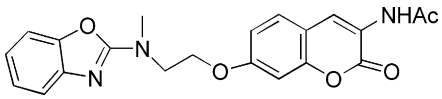
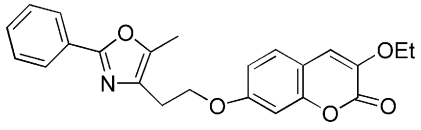
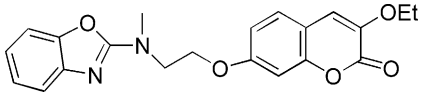
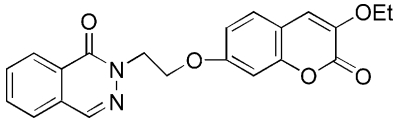
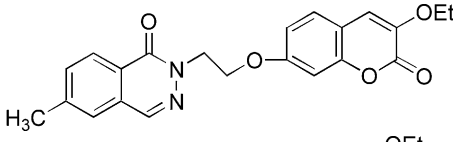
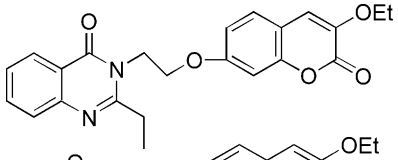
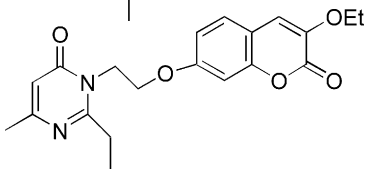
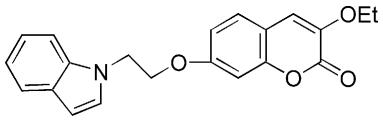
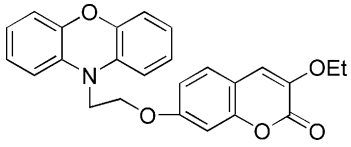
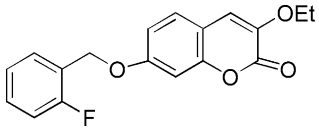
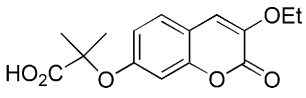


Figure 1. Conversion of 2-ethoxypropanoic acid to coumarin derivative.

☆DRL-publication no. 299
*Corresponding author. Tel.: +91-40-3045439; fax: +91-40-3045438; e-mail: madhavangr@drreddys.com

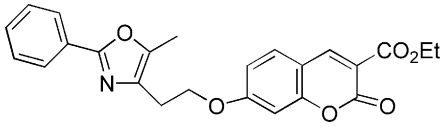
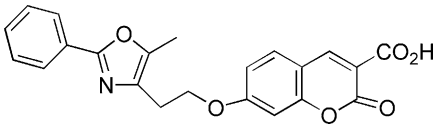
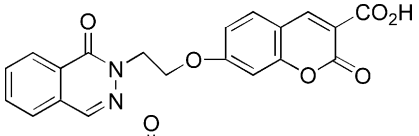
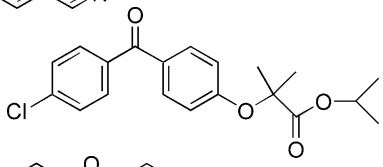
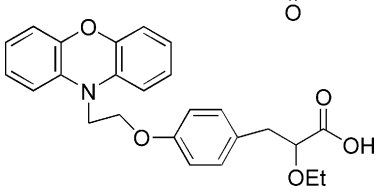
0960-894X/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00490-6

Table 1. Physical and biological data of coumarin derivatives[a]

Compd	Structure	M.P. °C	TG[b]
5a		251–252	2±0.5
5b		214–216	NE[c]
7a		153–154	31±1
7b		142–144	NE
7c		159–160	45±2
7d		168–170	NE
7e		196–198	NE
7f		122–124	26±1
7g		116–118	27±2
7h		130–132	NE
7i		142–144	25±2
8		146–148	16±1

(continued on next page)

Table 1 (*continued*)

Compd	Structure	M.P. °C	TG[b]
10a		140–142	2±0.5
11a		169–170	32±2
11c		261–262	NE
Fenofibrate		—	36 (at 30 mg/kg)
DRF-2725		—	47

[a]Checked in Swiss albino mice.
[b]Triglyceride lowering activity (%). Test compounds were administered at 3 mg/kg for 6 days.
[c]NE = Not effective.

different heterocycles, which are attached mostly with a linker of one or two carbon chain and interesting triglyceride lowering activity.

We have synthesized several coumarin derivatives (Table 1) and checked for their triglyceride lowering activity.

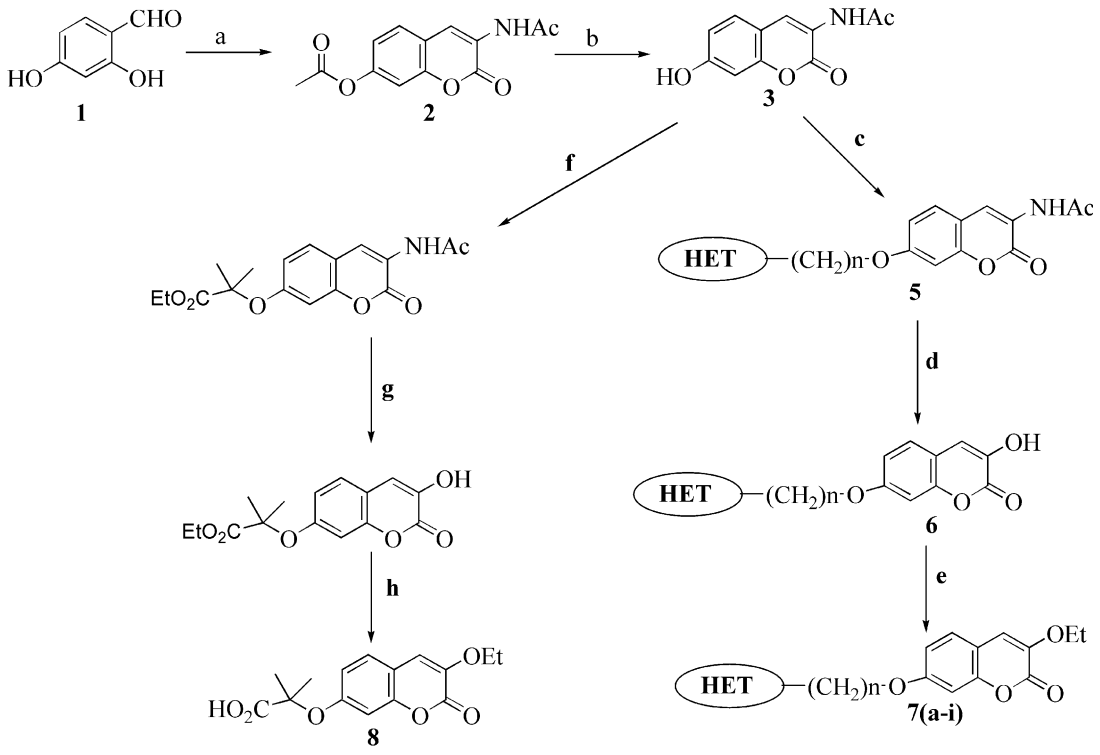
Chemistry

Initially, we synthesized 3-ethoxy coumarin starting from 2,4-dihydroxybenzaldehyde by cyclising with *N*-acetylglycine as represented in Scheme 1. Later the 3-acetylamino coumarin was linked to a heterocycle with a linker having one of the following leaving groups (compound **4**): 4-(2-methane sulphonyloxy ethyl)-5-methyl-2-phenyl oxazol;[7a] *N*-Benzoxazol-2-yl-*N*-(2-chloroethyl)methyl amine;[7b] 1-(2-bromoethyl)-1*H*-indole;[7c] 2-Phenoxazine-10-ylethyl-(methane sulfonate) ;[6] 2-(2-bromoethyl)-2*H*-phthalazinone;[7d] 3-(2-bromoethyl)-3*H*-quinazolin-4-one [7e] and 3-(2-chloroethyl)-2-ethyl-6-methyl-4(3*H*)-pyrimidinone. The acetylamino group of **5** was converted to 3-hydroxy coumarin **6** by the treatment with 3N HCl.[8] The 3-hydroxy coumarin derivative **6** was alkylated with ethyl iodide in the presence of KOH (powdered) in dry DMSO to give ethoxy derivative **7**. Well known TG lowering drugs like fibrates having 2-methyl-propanoic acid moiety as a pharmacophore. In compound **8**, we attached this moiety to comarin to explore the biological activity of such compounds.

In order to prepare the 3-carboxylic derivatives **11** (Scheme 2), 3-ethoxycarbonyl-7-hydroxy coumarin (compound **9**) used as a starting material and obtained from 2,4-dihydroxybenzaldehyde, was alkylated at the 7-hydroxy group of **9** with **4** to give **10** in good yield. The ester **10** was hydrolysed with 10% NaOH solution in methanol to give carboxylic acid **11**.

Biological Activity

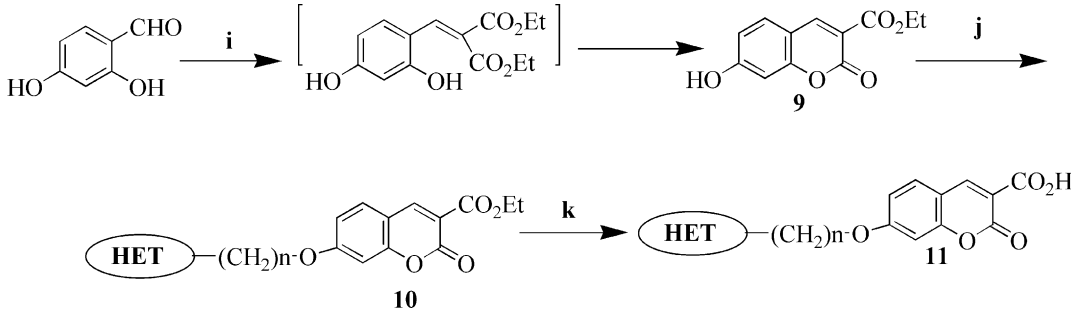
Plasma triglyceride lowering activity of **5a**, **5b**, **7a**–**i**, **8**, **10a**, **11a** and **11c** was determined in SAM [9] at 3 mg/kg oral dose as shown in Table 1. **7c** showed maximum (45%) activity and **11a** also showed good (32%) triglyceride lowering activity. **7a** (25%), **7g** (27%) and **7f** (26%) showed moderate plasma triglyceride lowering activity. In the same model, the reference standard fenofibrate, showed a 36% reduction in plasma triglyceride levels at 30 mg/kg/day, but the other compounds failed to show any significant reduction in TG at 3 mg/kg/day dose.



HET resembles for:

a) 2-phenyl-5-methyl oxazole; **b**) 2-Methylamino benzoxazole; **c**) 1(2H)-Phthalazinone **d**) 6-Methyl-1(2H)-phthalazinone **e**) 2-Methyl-4(3H)-quinazolinone **f**) 2-Ethyl-6-methyl-4(3H) pyrimidinone **g**) 1H-Indole **h**) 9H-Phenoxazine **i**) 2-Fluorophenyl.

Scheme 1. (a) *N*-acetylglycine, Ac_2O, NaOAc, reflux, 2 h; (b) 25% aq NH_3, MeOH, rt, 0.5 h; (c) HET-(CH_2) n–X [X = Cl, Br, OSO_2CH_3, etc.] (**4**), K_2CO_3, DMF, 80 °C, 24 h; (d) 3N HCl, EtOH, reflux, 1.5 h; (e) EtI, KOH, DMSO, RT, 12 h; (f) ethyl-2-bromoiso butyrate, K_2CO_3, 80 °C, 18 h; (g) 3N HCl, EtOH, 80 °C, 2 h; (h) (1) EtI, KOH, DMSO, rt, 12 h, (2) H_2O, rt, 4 h.



Scheme 2. (i) Diethyl malonate, piperidine, AcOH, EtOH, reflux, 4 h. (j) **4**, NaH, DMF, 0 °C–rt, 12 h. (k) 10% NaOH, MeOH, rt, 24 h.

Conclusion

We have designed and synthesized 3-ethoxy and 3-carboxyl derivatives of coumarins with different heterocycles which are attached with a linker of a one or two carbon chain, leading to a general structure **7a**–**i** and **11a**–**c** based on the cylisation of the pharmacophore of 2-ethoxypropanoic acid derivatives. Of all the compounds, ethoxy coumarin derivative with phthalazinone was the most potent (compound **7c**) showing 45% of triglyceride lowering activity at 3 mg/kg/day in the Swiss albino mouse model and was several times better than that of the reference standard fenofibrate. Further studies on **7c** are in progress, and will be published in the future.

Acknowledgements

The authors are thankful to the management of Dr Reddy's group for their encouragement. We thank Dr. R. Rajagopalan, President, for his constant encouragement.

References and Notes

1. La Rosa, J. C.; Hi, J.; Vupputuri, S. *J. Am. Med. Assoc.* **1999**, *282*, 2340.
2. Evans, M.; Rees, A. *Curr. Opin. Lipidol.* **2002**, *13*, 415.
3. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J. C. *Circulation* **1998**, *98*, 2088.
4. Balz, F. *Natural Antioxidants in Human Health and Disease*; Acedamic Press: San Diego, CA, 1994.
5. Lohray, B. B.; Lohray, V. B.; Bajji, A. C.; Kalchar, S.; Poondra, R. R.; Padakanti, S.; Chakrabarthi, R.; Vikramidithyan, R. K.; Misra, P.; Juluri, S.; Mamidi, N. V. S. R.; Rajagopalan, R. *J. Med. Chem.* **2001**, *44*, 2675.
6. Shirley, D. A.; Sen, K.; Glimer, J. C. *J. Org. Chem.* **1961**, *26*, 3587.
7. (a) Hisashi, S.; Syoji, O.; Mashiro, T.; Tsutomu, S.; Megumi, I.; Korekiyo, W.; Itsuo, U. *J. Med. Chem.* **1998**, *41*, 1927. (b) Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K.; Faller, A.; Haigh, D.; Hindley, R. M.; Jefcott, L. J.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Smith, D. G.; Smith, S. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2127. (c) Lohray, B. B.; Vidya, B.; Rao, P. B.; Madhavan, G. R.; Murali, N.; Rao, K. N.; Reddy, A. K.; Rajesh, B. M.; Reddy, P. G.; Chakraborthy, R.; Vikramadithyan, R. K.; Rajagopalan, R.; Mamidi, N. V. S. R.; Jajoo, H. K.; Subramaniam, S. *J. Med. Chem.* **1998**, *41*, 1619. (d) Csampai, A.; Koermendy, K.; Sohar, P.; Ruff, F. *Tetrahedron* **1989**, *45*, 5539. (e) Ranganathan, D.; Farooqui, F.; Mehrotra, S.; Kesavan, K. *Heterocycles* **1986**, *24*, 2493 and in house prepared.
8. Shin, C.; Nakajima, Y.; Sato, Y. *Chem. Lett.* **1984**, 1301.
9. An inbreed colony (at our own animal house) of Swiss Albino Mice (SAM) of 21–29 g body weight, moderately hypertriglycerimic, has been used for screening the compounds. Animals (5 per group) were treated orally with 3 mg/kg/day of **5a**–**b**, **7a**–**i**, **8**, **10a**, **11a**, **11c** for 6 days. The control animals were treated with the vehicle (0.25% carboxymethyl cellulose, 3 mL/kg) only. Animals were bled through retro orbital sinus on day-1 and day-6 of the experiment. Plasma samples were prepared and triglyceride levels were measured by using a commercial kit (Pointe Scientific, USA). For calculating of percentage reduction of triglycerides, the standard method published previously (Reddy, K. A.; Lohray, B. B.; Reddy, A. S.; Mamidi, N. V. S. R.; Reddy, P. P.; Saibaba, V.; Jaipal Reddy, N.; Suryaprakash, A.; Misra, P.; Vikramidithyan, R. K.; Rajapopalan, R. *J. Med. Chem.* **1999**, *42*, 3265 and Saibal, K. D.; Krorrida, V. L. N.; Jagadhesan, H; Iqbal, J. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 3579.) was applied.