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NON THIAZOLIDINEDIONE ANTIHYPERGLYCAEMIC AGENTS. 1: α-HETEROATOM SUBSTITUTED β-PHENYLPROPANOIC ACIDS

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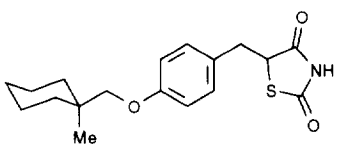
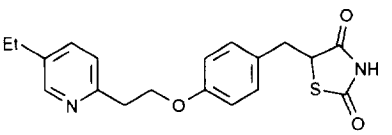
Abstract: *The 5-benzylthiazolidine-2,4-dione moiety of insulin sensitising antidiabetic agents can be replaced by a range of α-heteroatom functionalised β-phenylpropanoic acids. α-Oxy-carboxylic acids show potent antidiabetic activity and one compound, the α-ethoxyacid* ***15*** *(SB 213068), is one of the most potent antihyperglycaemic agents yet reported.* Copyright © 1996 Elsevier Science Ltd

Non-insulin dependent diabetes mellitus (NIDDM) is a complex, chronic metabolic disorder characterised by insulin resistance in the liver and peripheral tissues.[1] Insulin resistance and associated hyperinsulinaemia are being implicated increasingly in the development of other metabolic disorders such as obesity, dyslipidaemias and hypertension.[2] Treatment of NIDDM currently centres on a combination of diet and aerobic exercise programmes[3] or sulfonylurea therapy.[4] The latter drugs, which are designed to stimulate insulin secretion, are often poorly effective and have the potential to induce weight gain and hypoglycaemia.[5] Alternative approaches to the treatment of the disease are being investigated.[6]



Ciglitazone



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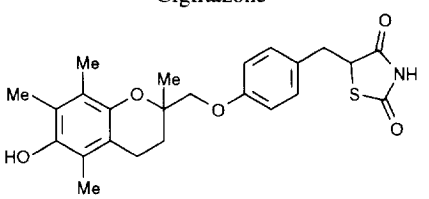
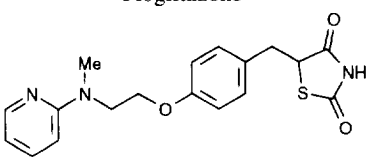


Troglitazone



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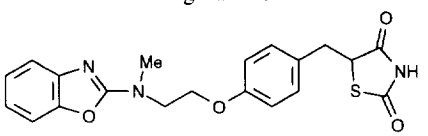
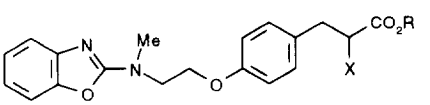


BRL 48482



1-21

During the last decade, an exhaustive search for novel, potent and selective antidiabetic agents based on the thiazolidine-2,4-dione ciglitazone[7] has yielded several development candidates. These compounds, including

pioglitazone (Takeda),[8] troglitazone (Sankyo)[9] and BRL 49653 (SmithKline Beecham),[10] exert their antidiabetic effects *via* improvements in the sensitivity of peripheral tissue to insulin. However, despite numerous attempts to replace the thiazolidine-2,4-dione ring with other heterocycles,[10b, 11] an effective modification conferring significant potency advantages over the this moiety remained elusive. More recently, we have reinvestigated the thiazolidine-2,4-dione ring as a pharmacophore for optimal[7a] antihyperglycaemic activity, and have demonstrated that this ring can be replaced very effectively by various α–functionalised carboxylic acid derivatives. In this letter we present some of our preliminary results in this new area of insulin sensitiser research.[12]

Table: α-Substituted β-Phenylpropanoic Acid Derivatives[a]

Compound	X	R	ED_{25} ($\mu mol.kg^{-1}$ diet)[b]	PPARγ K_i (nM)[c]
1	F	H	10	-
2	Cl	H	10	33
3	Cl	Me	10	-
4	Br	Me	100	-
5	SH	H	300	-
6	SMe	Me	100	600
7	SPh	H	30	37
8	SPh	Me	30	-
9	SO_2Ph	H	1000	-
10	NHMe	Me	1000	-
11	NMe_2	Me	1000	**d**
12	NHPh	H	30	-
13	OMe	H	3	15
14	OMe	Me	3	-
15	OEt	H	0.1	2.5
16	O-*n*-Pr	Na	0.3	-
17	O-*i*-Pr	Me	<0.3	-
18	OPh	H	1	0.4
19	OCH_2Ph	Na	0.3	-
20	OCH_2CH_2Ph	H	1	-
21	H	Me	>2000	6000
BRL 48482	-	-	3	22
Troglitazone	-	-	400	3800

Notes: (a) All compounds were evaluated as racemates. (b) See reference 14 for definition of ED_{25}. Methyl esters were generally equipotent with the corresponding acids, presumably as a result of rapid *in-vivo* hydrolysis (cf. compounds **2-3**, **7-8** and **13-14**). (c) See reference 20 for details of the binding affinity at the PPARγ receptor. (d) 26% displacement of radioligand at 1×10^{-5} M.

Historically, the thiazolidine-2,4-dione ring of ciglitazone was derived from an earlier series of α-halo- and α–thio-carboxylic acid antihyperlipidaemic agents.[11a, 13] Using BRL 48482, a potent analogue of BRL 49653,[10] as a template and by analogy with these earlier studies, we re-examined the effect of replacing the heterocycle by various racemic α-halo- and α-thio-β-phenylpropanoic acid derivatives **1-9**. In addition, we extended our study to include α-amino- and α-oxy-substituted carboxylic acid analogues **10-12** and **13-20** respectively (Table).[14]

Initial results from the halogen series[15] of compounds **1-4** clearly demonstrated that derivatives of phenylpropanoic acid containing small electronegative α-substituents such as fluorine or chlorine, were effective replacements for the benzylthiazolidine-2,4-dione group in BRL 48482. By contrast, the corresponding α-unsubstituted phenylpropanoic acid analogue **21** was relatively inactive. In keeping with the results reported previously,[11a] the thiol **5** and methylthio analogue **6** were less potent than their heterocyclic counterpart, whereas the S-phenyl compound **7** showed reasonable potency.[15] Oxidation of **7** afforded sulfone **9** and significantly reduced activity. The activity of the amino acid derivatives **10-12** paralleled the sulfur series, with only the anilino-acid **12** having significant activity.[16] Methyl esters (e.g. **3** and **8**) displayed activities comparable to the corresponding carboxylic acids, presumably as a result of rapid *in-vivo* hydrolysis.[17]

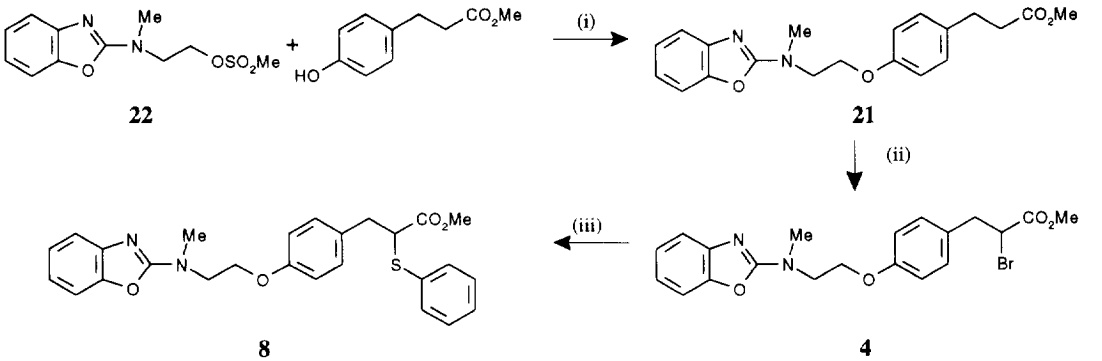
The results obtained from a study[18] of α-oxy-carboxylic acid derivatives **13-20** stand in contrast to those described above. In general, potency in this series was comparable with that of BRL 48482 and much higher than that observed in any of the other series of compounds that were investigated. These results were surprising since we had previously shown that in the heterocyclic series, the thiazolidine-2,4-dione ring was preferred over the oxazolidine-2,4-dione.[10b] Nevertheless, several α-oxy-acids (e.g. **15**, **16**, **17** and **19**) showed activities an order of magnitude more potent than BRL 48482. In particular the α-ethoxyacid **15** (SB 213068) had an ED_{25} value of 0.1 μmol.kg^{-1} diet, and is one of the most potent antihyperglycaemic agents yet reported.

It has recently been shown that benzylthiazolidine-2,4-dione insulin sensitisers selectively activate a peroxisome proliferator-activated receptor (PPARγ), a member of the steroid nuclear receptor superfamily.[19] Activation of PPARγ shows a good correlation with antidiabetic activity, suggesting that this receptor is a molecular target for this class of antidiabetic agents. Comparison of the binding of selected α-functionalised β-phenylcarboxylic acids at PPARγ[20] with antihyperglycaemic potency also shows a general correlation between the K_i and ED_{25} values (Table). In view of this correlation and the structural similarities between compounds **1-21** and the insulin sensitisers BRL 48482 and BRL 49653, it is likely that these new analogues share a common mechanism of action with the thiazolidine-2,4-diones and that this activity is at least partly mediated via the PPARγ receptor. The differences in potency observed with the various α-functionalised phenylpropanoic acids **1-21** may thus reflect subtle changes in steric and electrostatic interactions with the receptor and may aid an understanding of the structural requirements for optimal antidiabetic activity.

A diverse range of synthetic procedures have been utilised in the preparation of the racemic compounds described.[15, 16, 18] Representative methods are illustrated in the accompanying schemes. The phenylpropanoic acid **21** was readily prepared from the previously described[10b] methanesulfonate **22** (Scheme 1). The chloro-

and bromo-acid analogues were prepared by quenching the anion of **21** with the appropriate N-halosuccinimide. Sulfur compounds were readily prepared from the corresponding halogen derivative.

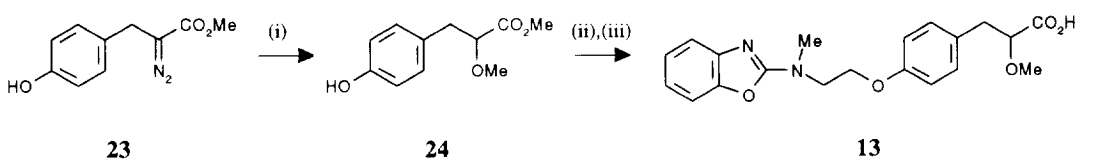
Scheme 1:- Representative Syntheses of Halogen and Sulfur Analogues



Reagents:- (i) NaH, 76%. (ii) LDA, NBS, 70%. (iii) PhSH, NaH, 66%.

Simple α-oxy-carboxylic acids were prepared from diazoester **23** by a rhodium carbenoid mediated insertion reaction[21] and subsequent alkylation of the insertion product **24** (Scheme 2). However, a more versatile method for the synthesis of these compounds utilised substituted phosphonoacetates **25** in an olefination and reduction sequence[22] with the previously described[10b] aldehyde **26** (Scheme 3). Amino acid derivatives were prepared by alkylation of an appropriate tyrosine derivative (not shown) or by rhodium carbenoid chemistry similar to that shown in Scheme 2.

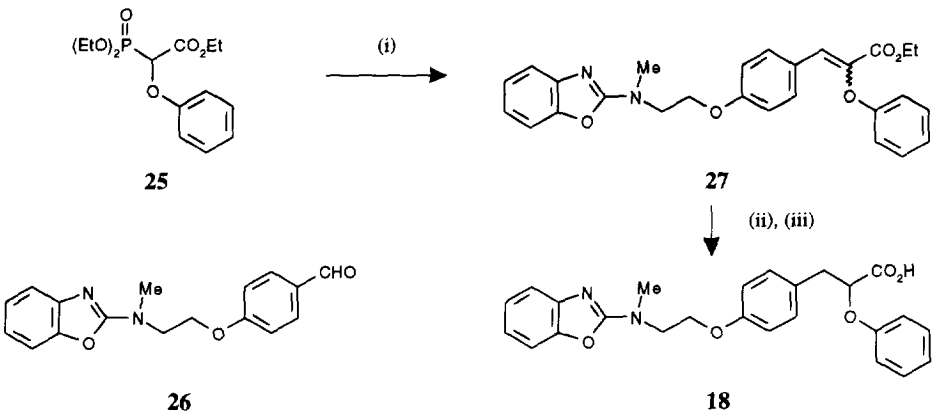
Scheme 2:- Representative Synthesis of α-Oxy-β-Phenylpropanoic Acids (Route 1)



Reagents:- (i) $Rh_2(OAc)_4$, MeOH, 49%. (ii) NaH, **22** (Scheme 1), 72%. (iii) Aq. NaOH, 82%

In summary, we have now established that using potent thiazolidine-2,4-dione analogues such as BRL 48482 as a framework on which to explore modifications, this heterocyclic moiety can be replaced by various α-heteroatom functionalised β-phenylpropanoic acid derivatives. Such compounds possess a range of antidiabetic potencies reflecting subtle changes in structure-activity relationships within each series. A collection of α-oxy-acids was shown to be particularly potent, with several members of the series having potencies exceeding that of the template BRL 48482 by an order of magnitude. These analogues thus have the potential to provide the next generation of antihyperglycaemic drugs, having a profile superior to that of the existing thiazolidine-2,4-dione agents.

Scheme 3:- Representative Synthesis of α-Oxy-β-Phenylpropanoic Acids (Route 2)



Reagents:- (i) NaH, **26**, 80%. (ii) H_2, 10% Pd-C, 91%. (iii) Aq. NaOH, 71%

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References and Notes

1. Reaven, G. M., *Diabetes*, **1988**, *37*, 1595-1607.
2. (a) Epstein, M. and Sowers, J. R., *Hypertension*, **1992**, *19*, 403-418. (b) Landsberg, L., *Hypertension*, **1992**, *19 (Suppl. I)*, I61-I66.
3. Ruderman, N. B. and Schneider, S. H., *Diabetes Care*, **1992**, *15 (Suppl. 4)*, 1787-1793.
4. Bailey, C. J., *Proc. Nutrition Soc.*, **1991**, *50*, 619-630.
5. Ferner, R. E. and Neil, H. A. W., *Br. Med. J.*, **1988**, *296*, 949-950.
6. (a) Larson, E. R.; Clark, D. A. and Stevenson, R. W., *Ann. Reports Med. Chem.*, **1989**, *25*, 205-213. (b) Colca, J. R. and Tanis, S. P., *Ann. Reports Med. Chem.*, **1992**, *27*, 219-226. (c) Dow, R. L. and Kreutter, D. K., *Ann. Reports Med. Chem.*, **1995**, *30*, 159-168.
7. (a) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T. and Kawamatsu, Y., *Chem. Pharm. Bull.*, **1982**, *30*, 3580-3600. (b) Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H. and Suzuoki, Z., *Diabetes*, **1983**, *32*, 804-810.
8. Momose, Y.; Meguro, K.; Ikeda, H.; Ot, S. and Sohda, T., *Chem. Pharm. Bull.*, **1991**, *39*, 1440-1445.
9. Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K. and Horikoshi, H., *J. Med. Chem.*, **1989**, *32*, 421-428.
10. (a) Cantello, B. C. C.; Cawthorne, M. A.; Haigh, D.; Hindley, R. M.; Smith, S. A. and Thurlby, P. L., *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 1181-1184. (b) Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A. and Thurlby, P. L., *J. Med. Chem.*, **1994**, *37*, 3977-3985.
11. See for example, (a) Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T. and Kawamatsu, Y., *Chem. Pharm. Bull.*, **1982**, *30*, 3563-3573. (b) Dow, R. L; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B. and Stevenson, R. W., *J. Med. Chem.*, **1991**, *34*, 1538-1544. (c) Kees, K. L.; Smith, T. M.;

McCaleb, M. L.; Prozialeck, D. H.; Cheeseman, R. S.; Christos, T. E.; Patt, W. C. and Steiner, K. E., *J. Med. Chem.*, **1992**, *35*, 944-953. (d) Ellingboe, J. W.; Alessi, T. R.; Dolak, T. M.; Nguyen, T. T.; Tomer, J. D.; Guzzo, F.; Bagli, J. F. and McCaleb, M. L., *J. Med. Chem.*, **1992**, *35*, 1176-1183. (e) Goldstein, S. W.; McDermott, R. E.; Gibbs, E. M. and Stevenson, R. W., *J. Med. Chem.*, **1993**, *36*, 2238-2240. (f) Ellingboe, J. W.; Lombardo, L. J.; Alessi, T. R.; Nguyen, T. T.; Guzzo, F.; Guinosso, C. J.; Bullington, J.; Browne, E. N. C.; Bagli, J. F.; Wrenn, J.; Steiner, K. and McCaleb, M. L, *J. Med. Chem.*, **1993**, *36*, 2485-2493. (g) Kees, K. L.; Caggiano, T. J.; Steiner, K. E.; Fitzgerald, J. J.; Kates, M. J.; Christos, T. E.; Kulishoff, J. M.; Moore, R. D. and McCaleb, M. L., *J. Med. Chem.*, **1995**, *38*, 617-628.

12. During the course of our work we became aware of similar studies being conducted by the Pfizer group. Hulin, B., *International Patent Appl., Publication No.* WO91/19702, **1991**.
13. (a) Kawamatsu, Y.; Asakawa, H.; Saraie, T.; Imamiya, E.; Nishikawa, K. and Hamuro, Y., *Arzneim.-Forsch.*, **1980**, *30*, 585-589. (b) Kawamatsu, Y.; Asakawa, H.; Saraie, T.; Mizuno, E.; Imamiya, E.; Nishikawa, K. and Hamuro, Y., *Arzneim.-Forsch.*, **1980**, *30*, 751-758..
14. Antihyperglycaemic activity was determined in genetically obese C57Bl/6 ob/ob mice (10-12 weeks of age). This model of NIDDM is insulin resistant, hyperinsulinaemic and glucose intolerant. Compounds were administered by dietary admixture for 8 days and antihyperglycaemic activity was determined from the reduction in the area under the blood glucose versus time curve following administration of an oral glucose load (3g/kg body weight) to 5 hr fasted mice. See reference 10b for further details. The ED_{25} dose is defined as the dose ($\mu mol.kg^{-1}$ diet) which reduces the area under the glucose tolerance curve by 25% relative to controls.
15. Haigh, D., *International Patent Appl., Publication No.* WO93/21166, **1993**.
16. Faller, A., *International Patent Appl., Publication No.* WO94/29285, **1994**.
17. Hydrolysis of simple esters *in vivo* is known to be a facile process. Caldwell, J. and Mitchell, S. C. in *Comprehensive Medicinal Chemistry*, ed. Taylor, J. B., Pergamon, **1990**, vol. 5, p. 151.
18. Haigh, D. and Sime, J. T., *International Patent Appl., Publication No.* WO94/01420, **1994**.
19. (a) Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. and Kliewer, S. A., *J. Biol. Chem.*, **1995**, *270*, 12953-12956. (b) Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M. and Evans, R. M., *Cell*, **1995**, *83*, 803-812. (c) Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A. and Lehmann, J. M., *J. Med. Chem.*, **1996**, *39*, 665-668.
20. Binding assays were performed in 96 well plates on crude extracts of XL-1 blue *E.Coli.* cells expressing a fusion protein comprising GST and the ligand binding domain of human PPARγ (GST-hPPARγLBD). 1.43 μg of total protein was present in a final volume of 50 μL. Radioligand [^{125}I]-SB 236636 {3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-3-iodophenyl]-2-ethoxypropanoic acid, K_d 8 nM at GST-hPPARγLBD, ED_{25} 3 $\mu mol.kg^{-1}$ diet in ob/ob mice} was present at 145 pM. Competing compounds were dissolved in DMSO (concentration of DMSO did not exceed 0.1%). Binding was allowed to reach equilibrium by incubation for 18 hours at 4°C. Bound ligand was separated from free on mixed cellulose ester filters. Each assay was performed in triplicate.
21. Cox, G. G.; Haigh, D.; Hindley, R. M.; Miller, D. J. and Moody, C. J., *Tetrahedron Lett.*, **1994**, *35*, 3139-3142.
22. Haigh, D., *Tetrahedron*, **1994**, *50*, 3177-3194.

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