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NON THIAZOLIDINEDIONE ANTIHYPERGLYCAEMIC AGENTS. 2: α-CARBON SUBSTITUTED β-PHENYLPROPANOIC ACIDS[1]

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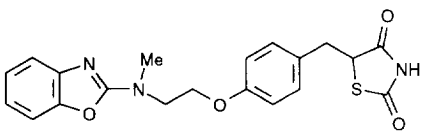
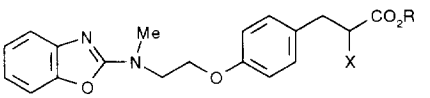
Abstract: *The thiazolidine-2,4-dione ring of insulin sensitising antidiabetic agents can be replaced by α-acyl-, α-alkyl- and α-(aralkyl)-carboxylic acids. Inclusion of an additional lipophilic moiety affords compounds* ***14*** *and* ***16****, equipotent to BRL 48482.*

In the preceding paper[1] we described a series of novel non thiazolidine-2,4-dione antidiabetic agents based on the replacement of the benzylthiazolidine-2,4-dione moiety of the insulin sensitiser BRL 48482[2] by α-heteroatom substituted-β-phenylpropanoic acids **1**. This work culminated in the discovery of a series of extremely potent α-alkoxy-carboxylic acids typified by the α-ethoxyacid SB 213068. In this paper we present an extension of this concept to include α-acyl-, α-alkyl- and α-(aralkyl)-substituted acids **2-20**.



BRL 48482



1 (X = Hal, SR^1, NR^1R^2, OR^1);
SB 213068 (X = OEt, R = H);
2-20

In an initial series of α-carbon substituted-β-phenylpropanoic acids, we examined the effect of replacing the electronegative α-ethoxy substituent of SB 213068 with a series of electron withdrawing carbon substituents[3] such as ester **2**, ketones **3**, **4** and nitrile **5** (Table). Encouragingly, both the ester **2** and the nitrile **5** retained antihyperglycaemic activity only marginally less than that shown by BRL 48482 in the ob/ob mouse model of non insulin dependent diabetes mellitus,[4] indicating that such malonate derivatives are effective replacements for the thiazolidine-2,4-dione ring. Nevertheless, since both compounds remained two orders of magnitude less potent than SB 213068, we have investigated other factors which may influence their biological activity. In particular, we decided to explore the effect of replacing the electron withdrawing group by more lipophilic alkyl groups. Examination of simple racemic α-alkyl-substituted compounds **6-10** indicated that such compounds could retain antidiabetic activity,[5] although these analogues were generally less potent than BRL 48482. Whilst the antihyperglycaemic potency of compounds **6-10** clearly varies with changes in chain length of the alkyl substituent, no consistent trend was observed. In an attempt to optimize the activity in this series, several α-aryl- and α-(aralkyl)-analogues **11-16** were prepared. The most potent compounds from this group were the α-(3-phenylpropyl)- and α-(5-phenylpentyl)-analogues **14** and **16.** Both of these compounds

had ED_{25} values of 3 μmol.kg^{-1} diet,[4] indistinguishable from that shown by BRL 48482. Interestingly, the intermediate chain length α-(4-phenylbutyl)-derivative **15** was 30-fold less potent.

Table: Antihyperglycaemic Potency of α-Carbon Substituted β-Phenylpropanoic Acid Derivatives[a]

Compound	X	R	ED_{25} (μmol.kg^{-1} diet)[b]	Compound	X	R	ED_{25} (μmol.kg^{-1} diet)[b]
2	CO_2Me	Me	10	**13**	$(CH_2)_2Ph$	Me	100
3	COMe	Me	300	**14**	$(CH_2)_3Ph$	H	3
4	COPh	Et	>1000	**15**	$(CH_2)_4Ph$	H	100
5	CN	H	10	**16**	$(CH_2)_5Ph$	H	3
6	Me	H	1000	**17**	$CH_2CH{=}CH_2$	H	30
7	Et	H	30	**18**	$CH_2CH{=}CHPh$	H	30
8	*n*-Pr	H	10	**19**	CH_2OMe	H	30
9	*i*-Pentyl	H	100	**20**	$(CH_2)_2OPh$	H	30
10	*n*-Hexyl	H	10	SB 213068	OEt	H	0.1
11	Ph	H	30	BRL 48482	-	-	3
12	CH_2Ph	Me	300	Troglitazone	-	-	400[c]

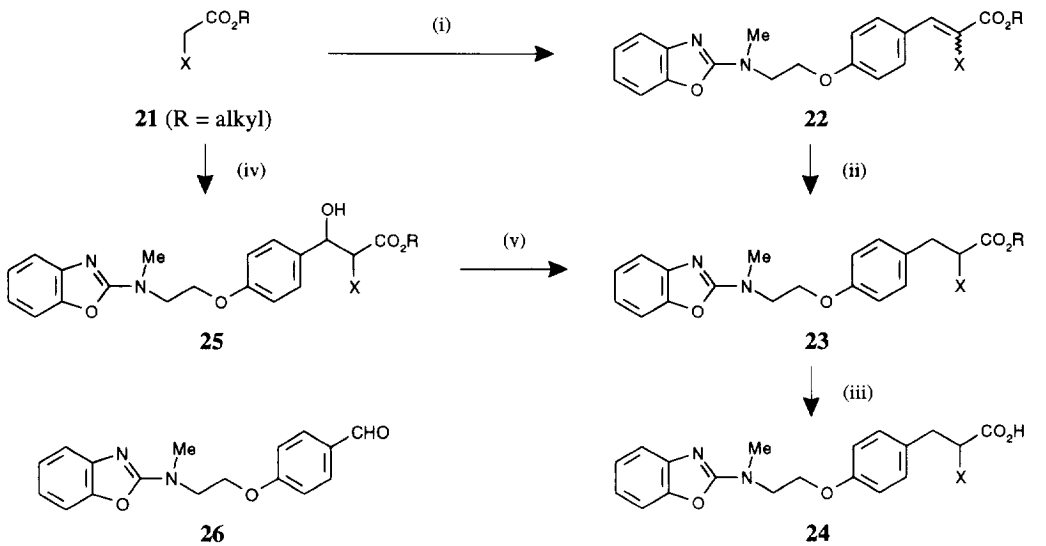
Notes: (a) Compounds were evaluated as racemates. (b) See reference 4 for definition of ED_{25}. Simple (Me, Et) esters were generally equipotent with the corresponding acids, presumably as a result of rapid in-vivo hydrolysis during chronic oral administration. (c) See references 1 and 6.

In an attempt to introduce additional functionality into two of the most potent compounds, **8** and **14**, the unsaturated analogues **17**, **18** and ethers **19**, **20** were prepared. However, whilst compounds **17** and **19** showed only a marginal reduction in potency relative to the *n*-propyl analogue **8**, the potency displayed by compounds **18** and **20** was reduced by an order of magnitude relative to **14**, suggesting that this functionality is not well tolerated within the aralkyl chain. The relatively poor potency of the ether **19** is surprising in view of the excellent antidiabetic activity[1] of the isomeric α-ethoxy-acid SB 213068 and suggests that the positioning and interaction of the oxygen atom of SB 213068 with the receptor are crucial to attaining optimal potency.

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.[7] Activation of PPARγ shows a good correlation with antidiabetic activity, suggesting that this receptor is a molecular target for this class of antidiabetic agents. PPARγ binding affinity of a small number of the compounds described in the present study has been examined.[8] Compounds **6**, **14**, BRL 48482 and SB 213068 showed K_i values of 1500, 30, 22 and 2.5 nM respectively. Whilst only limited data is available, the trend of observed binding affinities correlates with the ED_{25} values for antihyperglycaemic potency in the ob/ob mouse. In particular BRL 48482 and compound **14**, which are equipotent in the ob/ob mouse, show comparable K_i values. Taken in combination with earlier findings,[1] these data support the suggestion that these α-carbon

substituted acids 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.

Scheme: Generalised Syntheses of α-Carbon Substituted β-Phenylpropanoic Acids



Reagents:- (i) **26**, piperidinium acetate, toluene. (ii) 10% Pd-C, H_2, MeOH. (iii) Aq. LiOH. (iv) LDA, -70°C, THF, then **26**. (v) Et_3SiH, CF_3CO_2H, CH_2Cl_2.

A range of synthetic procedures have been used in the preparation of the compounds described in this paper.[3,5] Two general routes were devised and are illustrated in the Scheme. For compounds containing an electron withdrawing α-substituent **2-5**, Knoevenagel condensation[3] of an ester of the α-substituted ethanoic acid **21** with the previously described[2] aldehyde **26** afforded the propenoate derivatives **22**. Subsequent catalytic hydrogenation then gave the corresponding propanoates **23** which were subjected to basic hydrolysis to produce the desired carboxylic acids **24** as appropriate. Alternatively, for α-(aralkyl)-substituted acids[5] the most reliable procedure involved aldol reaction of the lithium enolate of an analogous ester **21** with aldehyde **26** to afford the aldol product **25**. These aldol products could be dehydrated to give propenoates **22** (not shown), or dehydroxylated by treatment with triethylsilane in trifluoroacetic acid[9] to afford the propanoates **23** directly. Other compounds were prepared by alkylation of the anion of **23** (X = H),[1] (not shown), though with variable yields.

In summary, we have further demonstrated that the thiazolidine-2,4-dione ring of insulin sensitising agents such as BRL 48482 can be replaced by simple substituted carboxylic acid derivatives with retention of antidiabetic potency. α-(Phenylalkyl)-substituted acid derivatives such as **14** and **16** show activity fully comparable with that of BRL 48482. The potency of these compounds may be dependent upon additional lipophilic interactions within the binding site of the receptor. In contrast, comparison of isomers **19** and SB 213068 suggests that the enhanced potency of the latter compound may be attributable to a favourable and

dominant interaction of the electronegative oxygen atom with the receptor and that the receptor is highly discriminatory in ligand binding.

References and Notes

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4. Antihyperglycaemic activity of the α-substituted carboxylic acid derivatives was determined in genetically obese C57Bl/6 ob/ob mice (10-12 weeks of age). This animal 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 2 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.
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8. 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.
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