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THE SYNTHESIS OF BRL 49653 - A NOVEL AND POTENT ANTIHYPERGLYCAEMIC AGENT

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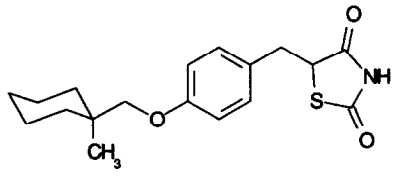
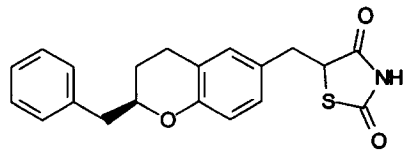
Abstract: Modifications based upon a metabolite of ciglitazone afforded BRL 49653, a novel potent insulin sensitizer. A facile synthesis of this compound is described.

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 is centred currently around a combination of diet and aerobic exercise programmes or sulphonylurea therapy.[3] The latter drugs, which are designed to stimulate insulin secretion, are often poorly effective and have the potential to induce hypoglycaemia.[4] Several new approaches to the treatment of the disease are being investigated.[5]

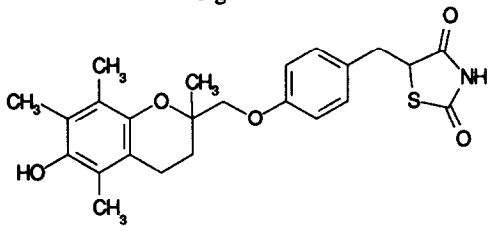
The discovery of a new antidiabetic agent, ciglitazone, that exerted its antihyperglycaemic effects by improvements in peripheral tissue insulin sensitivity was reported in 1982.[6] This elicited considerable interest within the pharmaceutical industry[7] and several analogous compounds such as pioglitazone,[8] CS-045[9] and englitazone[10] have been progressed to clinical studies.



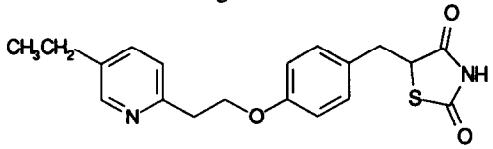
Ciglitazone



Englitazone



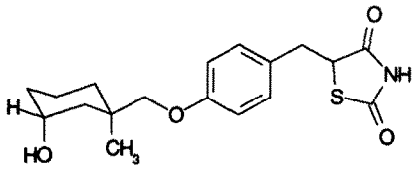
CS-045



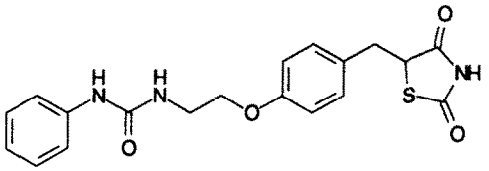
Pioglitazone

Our own interest in this area commenced with the observation that AD 4743, a metabolite of ciglitazone,[11] was more potent than ciglitazone itself. The increased activity displayed by AD 4743 may be

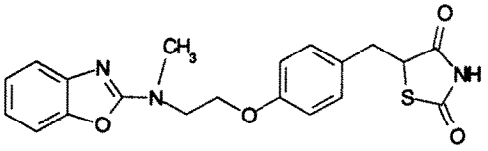
related to increased bioavailability by improved hydrophilicity of this molecule (CLog P values for ciglitazone and AD 4743 are 3.57 and 1.48 respectively[12,13]) or by fortuitous incorporation of an additional receptor binding group. Our approach was based initially around the preparation of compounds with calculated CLog P values close to that of AD 4743 and led to the discovery of a series of ureas typified by BRL 46950 (CLog P 1.37).[14] This novel ureido-ethoxy linked analogue was found to be 50-fold more potent than ciglitazone when tested in the C57Bl/6 ob/ob obese mouse model of NIDDM (Table).[15]



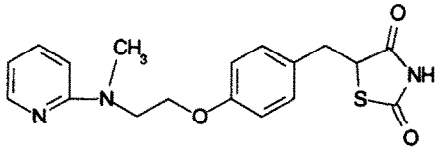
AD 4743



BRL 46950



BRL 48482



BRL 49653

Table:- Antihyperglycaemic Activity of Various 2,4-Thiazolidinediones

COMPOUND	MINIMUM EFFECTIVE DOSE (μmol.kg^{-1} diet)[a]	COMPOUND	MINIMUM EFFECTIVE DOSE (μmol.kg^{-1} diet)[a]
BRL 49653	3	Englitazone	200[b]
BRL 48482	3	AD 4743	500[c]
BRL 46950	100	CS-045	600
Pioglitazone	200	Ciglitazone	3000

Notes:- (a) See reference 15 for definition of minimum effective dose. (b) Estimated dose based on data given in reference 10. (c) Estimated dose based on data given in reference 11.

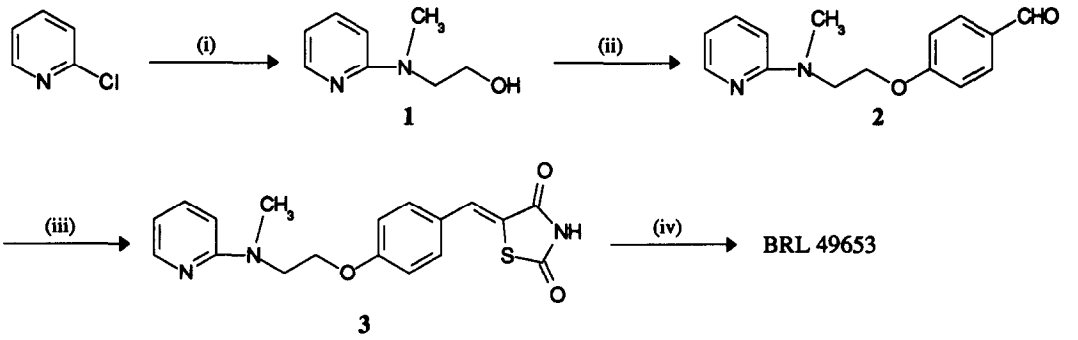
A programme based upon BRL 46950 led subsequently to the discovery of the cyclic N-(2-benzoxazolyl)amino-analogue, BRL 48482 (CLog P 2.12), the prototype of a series of heterocyclylamino-analogues.[16,17] Many of these heterocycles showed very encouraging activity, often 1000-fold greater than that of ciglitazone and from this series BRL 49653 (CLog P 1.32), a N-(2-pyridinyl)amino-analogue, was identified[17] for further study. It is noticeable that although the CLog P values of AD 4743, BRL 46950 and BRL 49653 are comparable, potency increases dramatically. These results suggest that rather than

hydrophilicity (CLogP), the important criterion for enhanced potency is the capacity for further receptor binding.

In the C57Bl/6 ob/ob obese mouse, the minimum effective dose[15] of BRL 49653 is 3 μmol.kg^{-1} of diet, approximately 60 times more potent than pioglitazone (see Table). Thus BRL 49653 is a potent antihyperglycaemic agent displaying a considerable potency advantage over competitor compounds of a similar type. Additional studies have shown that BRL 49653 enhances peripheral insulin sensitivity.[18]

The synthetic route to BRL 49653 is shown in the Scheme. Reaction of 2-chloropyridine with 2-(N-methylamino)ethanol (95%) and subsequent treatment of the product alcohol **1** with 4-fluorobenzaldehyde (72%) afforded the functionalised benzaldehyde **2**. Knöevenagel condensation[19] of **2** with 2,4-thiazolidinedione (95%) gave the highly crystalline benzylidene derivative **3** as a single (Z) geometric isomer. Finally, reduction of the double bond was achieved by means of an electron transfer reduction using dissolving magnesium metal in methanol solution (72%).[20] Racemic BRL 49653 was obtained as a white solid, mp 153-155°C, following crystallisation from methanol.[21] In common with other 5-benzyl-2,4-thiazolidinediones,[22] the proton at the chiral centre of the thiazolidinedione ring of BRL 49653 has been demonstrated to be labile. Consequently, biological evaluation of this compound has been performed using racemic material.

Scheme:- Synthesis of BRL 49653



Reagents:- (i) 2-(Methylamino)ethanol, 150°C. (ii) Sodium hydride, DMF, followed by 4-fluorobenzaldehyde, 80°C. (iii) 2,4-Thiazolidinedione, piperidinium acetate, toluene, reflux under a Dean and Stark head. (iv) Magnesium metal, methanol.

In conclusion, a programme based upon a metabolite of ciglitazone led to the discovery and facile synthesis of (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, BRL 49653, a novel potent insulin sensitizer. The results of further biological evaluation of this promising new antidiabetic agent will be presented elsewhere.

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