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A MEDICINAL CHEMISTRY CASE STUDY: AN ACCOUNT OF AN ANGIOTENSIN II ANTAGONIST DRUG DISCOVERY PROGRAMME

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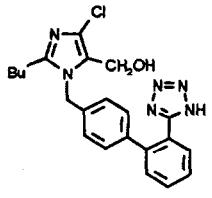
1. INTRODUCTION

The World Health Organisation estimates[1] that cardiovascular disease is responsible for the deaths of approximately 33,000 people each day worldwide. High blood pressure (hypertension) has been shown to be a major risk factor in cardiovascular disease and consequently the discovery of drugs which reduce blood pressure and decrease cardiovascular mortality has been a continuing goal of the medicinal chemist. The success of inhibitors of Angiotensin Converting Enzyme (ACE) in the treatment of hypertension has highlighted the importance of attenuating the effects of the hormone angiotensin II (AII), an octapeptide which is a very potent vasopressor agent. Consequently considerable effort has been directed at finding new ways of attenuating the effects of this hormone. One such approach has been to identify a simple molecule which would antagonise the effects of AII at its receptor. The discovery of such a compound had proved elusive. However, during 1988 and 1989 the DuPont company disclosed their results on a series of non-peptide antagonists of AII characterised by the biphenyl-terazole DuP753[2]; (Losartan). This announcement prompted an explosion of work in the AII antagonist area throughout almost the entire pharmaceutical industry.

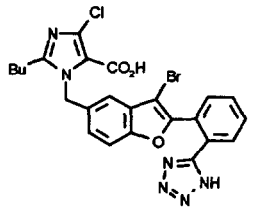
At Glaxo we have had a long standing interest in non-peptide antagonists of angiotensin II. The breakthrough at DuPont prompted us to concentrate more of our efforts in this area and also provided us with some valuable data. Indeed we have now successfully identified four potential clinical candidates, of which GR117289 and GR138950 are the furthest advanced in development.

We have taken this opportunity to review our own work in the field of non-peptide angiotensin II antagonists, paying particular attention to detailing the processes which led to the identification of our clinical candidates. Furthermore we have endeavoured to describe these processes from the perspective of the organic chemist.

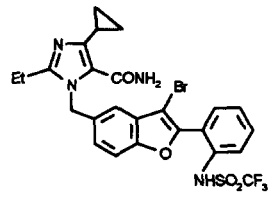
We hope that this review will afford the practising chemist some insight into the commercial drug discovery process; especially its objectives, the problems encountered and the strategies commonly employed. We anticipate that this review will be particularly informative to the younger organic chemist who may be contemplating entering the pharmaceutical industry.



DuP753



GR117289

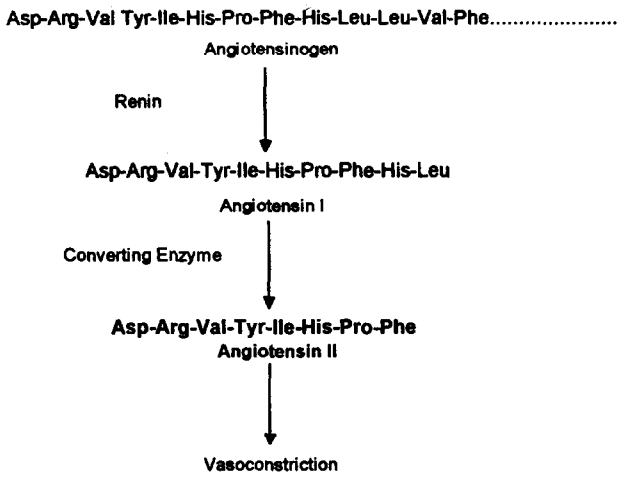


GR138950

2. THE RENIN ANGIOTENSIN SYSTEM AND ANGIOTENSIN II ANTAGONISTS

The Renin-Angiotensin System (RAS) plays a key role in the regulation of blood pressure and water and electrolyte balance in the body[3]. Angiotensin II is the effector hormone of the RAS; it stimulates cell surface receptors, primarily on vascular smooth muscle cells, which results in vasoconstriction and ultimately increases in blood pressure. It also plays a role in some of the more complex feedback mechanisms of the RAS. The RAS is depicted in a very much simplified form in Figure 1. The highly specific enzyme (angiotensinogen is its only known substrate) renin cleaves the protein angiotensinogen to release the decapeptide, angiotensin I. The two C-terminal amino acids of this peptide are further cleaved by a second less specific enzyme, Angiotensin Converting Enzyme (ACE) to give the octapeptide angiotensin II.

Figure 1: The Renin Angiotensin System



Clearly the activity of the RAS could be attenuated by inhibiting either of the enzymes ACE or renin or by antagonism of AII at its receptors.

The development of ACE inhibitors has proved a remarkable success[4]. A large number of ACE inhibitors are now on the market and the antihypertensive effectiveness of these agents is well proven. Indeed such is the effectiveness of these agents that the ACE inhibitors enalapril[4b] and captopril[4c] were respectively the third and fourth highest selling drugs in the world in 1992[5]. It is the clinical effectiveness of these agents that has highlighted the importance of the RAS in cardiovascular disease and has vindicated the pioneering work of the Squibb group[4b] and the research group of John Laragh[6] in a sceptical climate. However, ACE inhibitors are not without side effects. ACE is a non specific aminopeptidase which is, among other things, responsible for the degradation of other hormones such as the inflammatory peptide bradykinin and the neurokinins. Hence, some of the side-effects, such as the often cited 'dry cough', associated with ACE inhibitor treatment are believed to result from elevated levels of one or more of these agents[7]. Consequently alternative approaches towards attenuating the effects of the RAS, which would be without these inherent side effect liabilities, have proved attractive to the medicinal chemist.

A great deal of effort has been directed at the search for renin inhibitors as therapeutic agents. However, whilst numerous potent inhibitors of renin *in vitro* have been identified[4a] there are few examples which exhibit the oral activity desirable for the treatment of hypertension. Indeed no renin inhibitor has yet reached the market.

In principle antagonism of AII at its receptor would represent the most direct and selective method of attenuating the effects of the RAS and could offer advantages over inhibition of ACE as an antihypertensive therapy.

Peptidic antagonists of AII had been known since the early 1970's. These AII analogues (e.g. saralasin) proved effective anti-hypertensive agents when administered intra-arterially but suffered from the ubiquitous problems associated with peptidic drugs, namely very short plasma half lifes and a lack of oral activity[8].

Consequently, whilst demonstrating the therapeutic potential of an AII antagonist, these peptides were unsuitable clinical entities. The identification of a non-peptide antagonist of AII was therefore awaited.

In 1982 the Takeda company disclosed[9] the structures of a series of weakly potent non-peptide AII antagonists (1). It was these lead structures, and their subsequent refinement to afford DuP753[2], which precipitated the vast amount of research in the field of non-peptide AII antagonists.

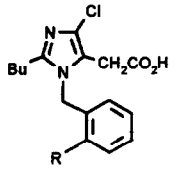
3. NON-PEPTIDE ANGIOTENSIN II ANTAGONISTS

Workers at the DuPont company pioneered the development of non-peptide angiotensin II antagonists and successfully identified the first clinical candidate Losartan (DuP753) which is currently in phase III clinical trials. A bold and imaginative approach led the DuPont group from the Takeda imidazoles (1), through a series of di-aryl analogues[10] (2) to DuP753[2], the first orally active angiotensin II antagonist. The disclosure of the identification of DuP753 precipitated a frantic search for non-peptide angiotensin II antagonists throughout almost the entire pharmaceutical industry. A plethora of analogues (3) of DuP753 in which an alternative "northern" heterocycle is linked through nitrogen to the "southern" biaryl tetrazole portion emerged.

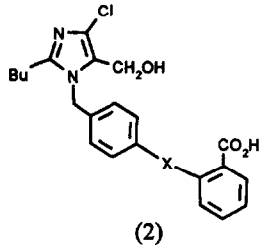
Also taking the Takeda imidazoles as a lead workers at SmithKline Beecham[11] identified a series of compounds with structures markedly different from DuP753. Via an approach based on modelling the overlap of these imidazoles and related compounds with the believed bioactive conformation of angiotensin II the SmithKline Beecham workers identified the thienylmethyl acrylate SK&F108566 which is a potent and orally active angiotensin II antagonist.

Concurrent work at the Parke-Davis company led to the identification[12] of a group of molecules characterised by the imidazopyridine PD123177. Radioligand binding studies using DuP753 and PD123177 have established[13] the presence of at least two distinct populations of angiotensin receptors, termed AT_1 (DuP753 sensitive) and AT_2 (PD123177 sensitive). It is the AT_1 receptor which is responsible for the hypertensive effects of AII, the functional role of the AT_2 receptor is still to be elucidated.

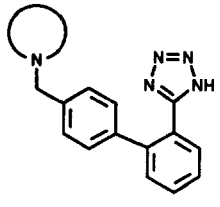
All of the AII antagonists subsequently discussed in this review are selective for the AT_1 receptor subtype.



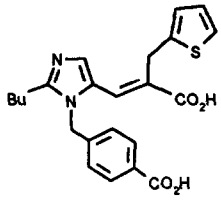
(1)



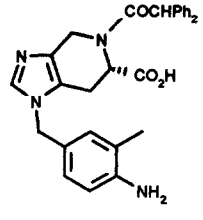
(2)



(3)



SK&F108566



PD123177

4. THE NON-PEPTIDE ANGIOTENSIN II ANTAGONIST PROGRAMME AT GLAXO

4.1 *Chemical Programme*

The objective of our programme was to identify non-peptide angiotensin II antagonists with the following properties; oral activity, ability to reduce blood pressure at doses below $1mgkg^{-1}$, durations of action suitable for once daily therapy and, preferably, good (i.e. greater than 40%) oral bioavailability. We believed that we had to identify non-peptide AII antagonists exhibiting these properties if they were to compete successfully with exisiting anti-hypertensive therapies. The medicinal chemistry strategies which we implemented led to the successful fulfilment of this objective as is described in the following pages.

The evolution of our chemical programme is shown schematically in figure 2. We too took the Takeda imidazoles[9] (1) as a lead. The diagram illustrates the evolution of our programme from these Takeda compounds through to the identification of key compounds, the bromobenzofurans GR117289[14], GR138950[15], GR159763[16] and the double ester pro-drug (4[17]), and the biphenylmethyl pyrazole (5a[18]).

As our work in this area progressed we did draw on information disclosed by other research groups, particularly the DuPont group, and this is also illustrated in figure 2. Our programme was in its infancy when DuPont published their first patent[19] on non-peptide angiotensin II antagonists. At this time we were working with an indole (6) as a lead and we used DuPont data for a series of anilides to enhance the potency of this indole. The disclosure[20] that DuP753 was orally active and undergoing development led us to initiate a strategy which led to the identification of the pyrazoles (5). Additionally during the latter stages of our programme we drew on data reported for the Merck imidazopyridine L158,809[21]. Figure 2 also depicts the fate of the Takeda imidazoles (1) at the hands of the DuPont[2] and SmithKline Beecham[11] research groups and the wealth of analogues (3) spawned by DuP753.

This review documents the evolution of our non-peptide angiotensin II antagonist programme as depicted in figure 2 and discusses, where appropriate, any general principles of drug discovery. An overview of relevant synthetic chemistry is presented and in a conclusion we have endeavoured to draw together these principles and assess their overall impact on the success of the programme.

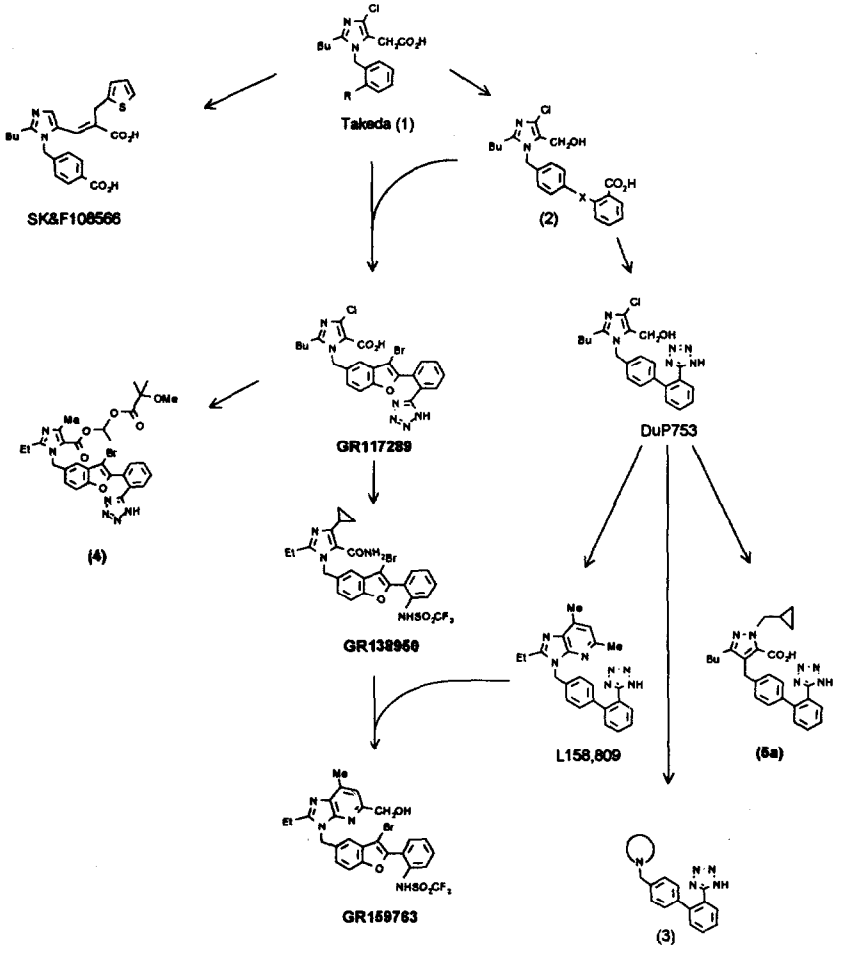
4.2 *Biological Test Methods*

Throughout this programme of work the in vitro potency of AII anatagonists was determined in a functional assay[22] using isolated rabbit aortic strips. The potency of compounds is expressed as a pK_B value, which is the negative log of the equillibrium constant for binding of the antagonist to the receptor. In this assay the contraction of a small piece of smooth muscle to ascending concentrations of AII is measured and a dose-response curve constructed. The experiment is then repeated in the presence of the test compound at a single concentration, which, for an antagonist, leads to a shift in the dose response curve to higher concentrations. Assuming reversible competitive anatagonism the pK_B value is also represented by the negative log of antagonist concentration which causes a two fold shift in the dose response curve. This value is estimated from the displacement of the two dose response curves. Throughout this review the term potency refers to potency *in vitro* determined in this manner.

Throughout this programme of work we used a rat model of hypertension to evaluate the activity of our compounds *in vivo*. In this model[23] ligation of the renal artery of a single kidney of the rat leads to activation of the RAS and a sustained elevation of diastolic blood pressure AII antagonists cause reductions in blood pressure in this model. Throughout this review *in vivo* activity and oral activiy refer to the lowering of blood pressure in this model.

The renal hypertensive rat proved a particularly informative *in vivo* model. For any given compound this model affords a measure of not only absolute *in vivo* efficacy but also duration of action and, from a comparison of falls in blood pressure after oral and intra-arterial administration, a qualitative estimate of oral absorption.

Figure 2: The Evolution of the Non-Peptide Angiotensin II Antagonist Programme at Glaxo

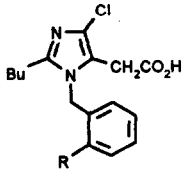


5. THE IDENTIFICATION OF THE BROMOBENZOFURAN-TETRAZOLE GR117289; A POTENT AND ORALLY ACTIVE NON-PEPTIDE ANGIOTENSIN II ANTAGONIST

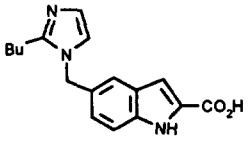
Since its discovery[24] in 1940 a great deal of medicinal chemical effort has been directed at modification of the peptide residues of AII. From these extensive investigations two key observations had emerged[25]. Firstly it had been established that a reduction in the number of amino acid residues in the peptide typically leads to a profound loss in pharmacological activity. Secondly it had been found that the imidazole and phenol side chains of the histidine and tyrosine residues and the C-terminal carboxylic acid of AII are essential for high receptor affinity. The former observation precluded any sensible approach towards a non-peptide AII

antagonist based on a much simpler di or tri-peptide. From the latter observations we formulated our initial approach towards a non-peptide AII antagonist.

The majority of agonist and antagonist molecules derive a large proportion of their receptor affinity from a coulombic interaction with the receptor protein. For example antagonists of the biogenic amines adrenaline, dopamine, histamine and 5-hydroxytryptamine typically all contain a key basic group. Given the importance of the C-terminal carboxylic acid in the binding of AII to its receptors we surmised that this carboxylic acid must be involved in a coulombic interaction and furthermore that any potent antagonist should contain an acidic group. In combination with the importance of the histidine imidazole residue of AII this suggested that an imidazole linked to a carboxylic acid by an appropriate spacer might form the basis of an approach to identifying a non-peptide AII anagonist. From a combination of this line of thinking and the known structures of the Takeda imidazoles (1) the indole (6) emerged as an early lead in our programme.

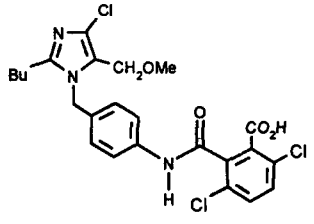


(1)
R = Cl $pIC_{50} = 5.6$



(6)
$pK_B = 5.7$

The publication of the first patent on non-peptide AII antagonists from the DuPont company[19] had a profound effect on our programme. This patent contained a substantial amount of information and it was clear that the DuPont group had been working on a similar strategy to our own for some years and furthermore, with a great deal of success. In the context of our work with the indole (6) two aspects of the data reported in the DuPont patent drew our attention. Firstly that the anilide (7), an extended carboxylic acid analogue of the Takeda imidazole (1), was a much more potent antagonist than its N-methyl counterpart[10a], and secondly that the majority of the imidazoles which they reported bore a 5-hydroxymethyl substituent. For the reasons outlined below, on the basis of this information we decided to prepare the indole (13).



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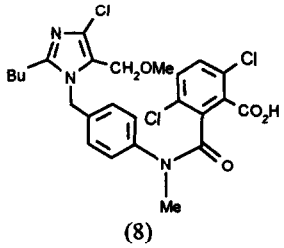
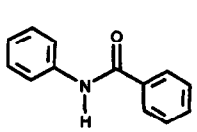


(8)

In a contemporary communication Shudo and co-workers reported[26] that N-methylation of a benzanilide leads to a profound change in conformation about the amide bond. Based on the observation of a marked fall in biological activity on methylation of a benzanilide based retinoid[27] Shudo and co-workers went on to demonstrate that both in solution and the solid state the two aryl rings of benzanilide adopt exclusively a trans conformation (9) about the amide partial double bond, whereas in N-methylbenzanilide the aryl rings adopt exclusively a cis geometry (10).



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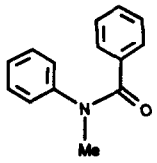
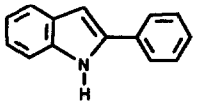
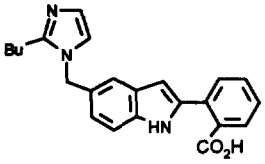


(10)

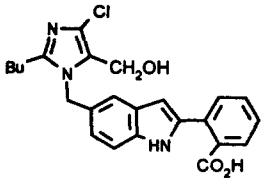


(11)

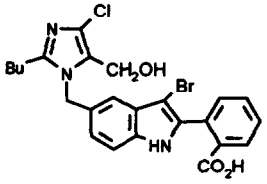
In the light of the observations of Shudo and co-workers we concluded that the fall in potency observed on methylation of the anilide (7) was due to a change to a cis type conformation (8), with a correspondingly much poorer complementarity with the receptor. We realised that the trans aryl amide geometry of a benzanilide could be mimicked by a 2-aryl indole (11). Furthermore we saw that this could be realised for the DuPont anilides by incorporating a 1,2-disubstituted aryl ring into the indole (6) to afford a 2-aryl indole (12). However, based on the preponderance of 4-chloro-5-hydroxymethyl imidazoles in the Dupont patent[19] we elected to take a more direct approach and prepare the indole (13), a molecule containing two simultaneous structural changes.



(12)



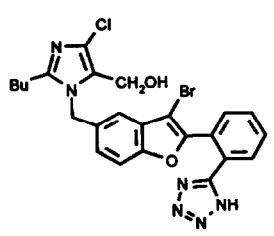
(13)



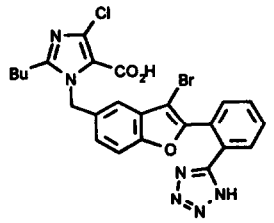
(14) $pK_B = 8.6$

Due to the vagaries of synthetic organic chemistry it transpired that the 3-bromo indole (14), rather than the indole (13) itself, was prepared. Introduction of an indole 3-bromine atom occurred as an unintended reaction in the radical bromination of a corresponding 5-methyl indole *en route* to indole (13). However it was decided to carry this 3-bromo intermediate through the remaining planned synthetic transformations, a decision which proved spectacularly successful as the molecule proved to be over a hundred times more potent than the original indole (6). Indeed the des-bromo indole (13) itself was never prepared, the project moved forward on the back of the 3-bromo indole and a strong reason to prepare its des-bromo counterpart never arose. We subsequently found that the large increase in potency reflected in the 3-bromo indole is almost certainly due to the presence of the bromine atom. However the role of this atom was subsequently investigated in an intrinsically more potent series of compounds (see section 6) rather than by preparing the des-bromo indole (13).

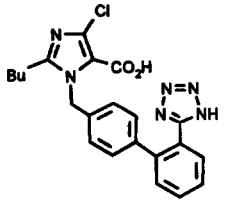
Serendipity had provided us with a great leap forward in our programme; gaining great encouragement from the improved potency of the bromo-indole (14) we identified the benzofuran (15) as our next key target, this molecule also incorporated two important structural changes. Simply for ease of synthesis we favoured replacement of the indole with a benzofuran, and we chose to replace the carboxylic acid of compound (14) with a tetrazole as data disclosed in the Dupont patent demonstrated that relative to a carboxylic acid this acid isostere greatly enhanced potency. The benzofuran (15) proved to be only slightly more potent *in vitro* than the indole (14); however it exhibited one crucial advantage over all the compounds we had so far prepared; it lowered blood pressure in the renal hypertensive rat model of hypertension after oral administration.



(15) $pK_B = 9.1$



GR117289 $pK_B = 9.8$



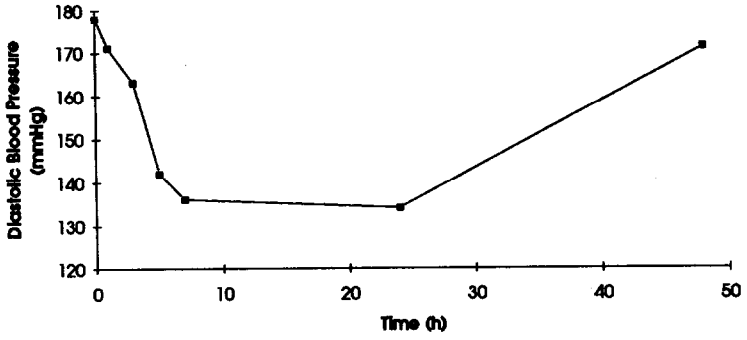
EXP3174

We considered the orally active alcohol (15) as a potential development candidate. However we found that oxidation of the imidazole-5-methanol to the corresponding imidazole-5-carboxylic acid GR117289 afforded a compound with much enhanced *in vitro* potency and oral activity. Indeed, via pharmacokinetic experiments we subsequently demonstrated that the alcohol underwent metabolic oxidation *in vivo* and acted as a pro-drug for GR117289.

It is also pertinent to note that it subsequently emerged[2,28] that the hydroxymethyl group of DuP753 is itself also oxidatively metabolised *in vivo*, affording the more potent carboxylic acid EXP3174.

GR117289 proved to be a potent AII antagonist both *in vitro* and *in vivo* and caused significant and prolonged falls in blood pressure in the renal hypertensive rats after oral administration (Figure 3). However the oral bioavailability of GR117289 is low (3% in the rat-see below).

Figure 3: The Effect of GR117289 on Diastolic Blood Pressure in Renal-Artery Ligated Hypertensive Rats after Oral Administration ($3mgkg^{-1}$)



Bioavailability[29] is determined largely by the relative efficiency of two processes, absorption into blood plasma and clearance from it. It follows that good bioavailability is obtained when the former is high and the latter low.

In the development of drugs for oral therapy good oral bioavailability[30] is desirable and advantageous as this ensures an accurate systemic exposure of drug to a patient.

Due to reasons of age, health, lifestyle and simple biological variation, the extent of absorption, metabolism and excretion of a drug substance can vary widely between individuals within a population. If a drug has intrinsically high bioavailability the differences between individuals will not greatly affect their systemic exposure to a drug from a given oral dose. However, if bioavailability is particularly low differences between individual patients can lead to very different levels of systemic exposure from a given dose. This can

lead to difficulties in administering a safe and effective dose. Additionally low bioavailability can lead to severe problems in oral toxicology studies. Unfeasibly large doses can be required to provide the systemic exposure required for correct toxicological evaluation.

Table 1: Pharmacokinetic Parameters[29] of GR117289 in the Rat.

F^{29} (%)	Vd^{29} (l/kg)	Clp^{29} (ml/min/kg)	$t_{1/2}$ [29](h)
3	0.5	0.8	8.0

Data obtained from pharmacokinetic studies[29] in the rat (table 1) had revealed that GR117289 has very low bioavailability (F = 3%) and furthermore, given that it exhibits low plasma clearance, that this results from poor oral absorption.

Hence whilst exhibiting good oral activity and duration of action GR117289 did not fulfil our initial objective of good bioavailability (i.e. >40% - see section 4). However we believed that GR117289 possessed sufficient oral activity to be an effective antihypertensive therapy and, furthermore that it held advantages over DuP753, the then furthest developed AII antagonist, in being more potent and not being subject to metabolic activation *in vivo*. Given the known intense activity of other pharmaceutical companies in the angiotensin II antagonist area we believed that we could not afford not to take the risk of developing a compound at the first opportunity (the principle of "good enough soon enough"). Hence, despite its low oral bioavailabiliy, we elected to take GR117289 into exploratory development.

With the benefit of hindsight developing GR117289 despite its low bioavailability in the rat proved a risk wisely taken as its bioavailability in man is a much more satisfactory 22%. This illustrates one of the fundamental problems encountered in medicinal chemistry, interspecies variation, and more specifically the difficulty of extrapolating from effects and parameters observed in animal models to those which would be anticipated in man.

Once it had been decided to take GR117289 into exploratory development the identification of compounds with substantially improved bioavailability became the key objective of our research programme. Thus the subsequent structure activity relationship (SAR) investigation based around GR117289, whilst designed to delineate key features of the molecule, was also performed with the aim of improving bioavailability.

A comparison of the data of table 1 and figure 3 reveals an apparent disparity between the pharmacokinetic and pharmacological half lives of GR117289. The pharmacological effect of GR117289 persists for far longer than can be accounted for purely in terms of its circulating plasma levels. This effect has been observed for a number of other AII antagonists (e.g. DuP753 and EXP3174[31]) and is indeed apparent for other compounds described in this review (e.g. GR159763 - section 9). Hilditch and co-workers[32] discuss this phenomenon in detail. They suggest that it would seem to question whether the antihypertensive effects of AII antagonists are due simply to blockade of AT_1 receptors in the vasculature or rather are due, at least in part, to AT_1 receptor blockade at some other as yet unidentified site.

6. AN INVESTIGATION OF STRUCTURE ACTIVITY RELATIONSHIPS BASED AROUND GR117289

Having identified GR117289 we sought to learn more about this class of AII antagonist and to substantially improve upon its low bioavailability (see previous section). A study of structure activity relationships (SAR) based around GR117289 was performed to address both of these issues. Although this did not provide compounds with enhanced bioavailability it did provide us with the information required to formulate a strategy which eventually led to the identification of the highly bioavailable triflamide GR138950 (see section 8).

Obtaining or improving oral bioavailability is a problem commonly encountered, or is indeed ubiquitous, in medicinal chemistry. However the quest for good oral bioavailability is a largely empirical and pragmatic exercise; simple and sometimes seemingly insignificant changes to a molecule can have profound and unpredictable effects upon bioavailability. We believed that a more detailed understanding of the key features of GR117289 would allow us to take a more informed approach to solving this problem. Thus we performed the subsequently described SAR study with the aim of enhancing bioavailability very much in mind.

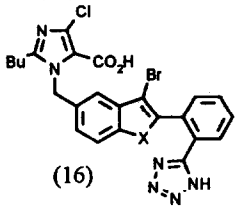
Structure activity relationships for the the benzofuran oxygen atom, the tetrazole, the benzofuran 3-substituent and the imidazole regions of GR117289 are described and discussed below

6.1 *Replacement of the Benzofuran Oxygen Atom*

The benzofuran oxygen atom of GR117289 was replaced by both nitrogen and sulphur atoms. The indole (16b) is less potent than GR117289 and the benzothiophene (16a) is less potent still (table 2). It is likely that these differences in potency arise from changes to the C-X bond lengths and C-X-C bond angles altering the geometeries of the molecules. However from the indole (16b) it is apparent that replacement of the benzofuran oxygen atom with a hydrogen bond donor offers no advantage in terms of potency.

Table 2: *In Vitro* Potency of Compounds (16)

Compound	X	pK_B
16a	S	8.7
16b	NH	9.0
GR117289	O	9.8



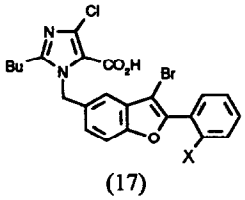
(16)

6.2 *Replacement/Modification of the Tetrazole*

The series of compounds (17a-h) was prepared to explore the role of the tetrazole in GR117289. The compounds (17a-c) which possess an acidic replacement for the tetrazole exhibit a broad range of potency *in vitro* (Table 3). As each of these alternative groups has an acid strength comparable[33] to that of a tetrazole it is likely that the differing potencies of these compounds have geometric/steric origins.

Table 3: *In Vitro* Potencies of Bromobenzofurans (17)

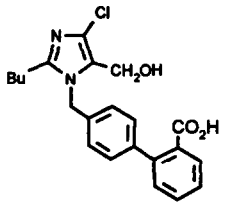
Compound	X	pK_B
17a	CO_2H	10.2
GR117289	Tetrazole	9.8
17b	CONHTetrazole	8.8
17c	$NHSO_2CF_3$	7.8
17d	CO_2Et	7.8
17e	$CONH_2$	7.2
17f	2-Me-Tetrazole	6.4
17g	1-Me Tetrazole	7.3
17h	CN	<6



(17)

Replacement of the tetrazole of GR117289 with a carboxylic acid affords a slight increase in potency. This is in contrast to the findings of the DuPont workers for DuP753 and related compounds[34]. Replacement of the tetrazole of DuP753 with a carboxylic acid, compound (18), actually leads to a ca. 1.5 orders of

magnitude fall in potency, similarly replacement of the tetrazole of the DuP753 metabolite EXP3174 with a carboxylic acid, compound (19) leads to a ca. 2 orders of magnitude fall in potency. These profound differences in SAR suggest that, whilst there is an apparent similarity between bromobenzofuran based GR117289 type and biaryl based DuP753 type AII antagonists, the two series of compounds may interact quite differently with the AT_1 receptor. We believe that these differences reflect a difference in geometry between the two structural types as discussed below.



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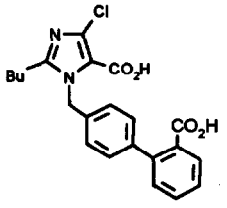


(19)

Tetrazoles are commonly used isosteres of carboxylic acids[35]. However when in their ionised states the locus of the corresponding negative charge of a tetrazole is much more extended than that of a carboxylic acid (eqn. 1). The bromobenzofuran based compounds are intrinsically longer molecules than their biaryl counterparts, i.e. one can envisage a larger distance between the imidazole and tetrazole rings in GR117289 than in DuP753 or EXP3174. Thus we propose that in the di-carboxylic acid bromobenzofuran (17a) the 2-aryl acid is a correct distance from the imidazole to allow good complimentarity with the receptor, hence the extended locus of the tetrazole offers no advantage to receptor binding. It then follows that the 2-aryl carboxylic acids and the imidazoles of the biaryls (18) and (19) are separated by too short a distance and that the extended locus of a tetrazole is required to give good complimentarity with the receptor.

Equation 1

Despite its high potency the diacid (17a) exhibits only very weak oral activity. The remaining compounds of table 3 proved orally inactive with the exception of the trifluoromethane sulphonamide (17c) which exhibits weak oral activity, perhaps surprisingly for such an intrinsically weak compound (see section 8). However, in terms of absolute potency and *in vivo* activity, we concluded that the tetrazole appeared to be the optimum group for this region of the molecule.

Rendering the tetrazole of GR117289 non acidic by methylation (compounds (17f and g)) or its replacement with a good hydrogen bonding group (amide (17e)) causes approximately a one thousand fold reduction in potency. From these data it can be inferred that the tetrazole of GR117289 is involved in an ionic, rather than a hydrogen bonded, interaction with the receptor[36].

6.3 Role of the Benzofuran 3-substituent

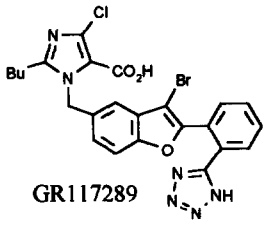
As described earlier the benzofuran 3-bromine atom appeared to play a crucial role in conferring high potency on GR117289 and its analogues, indeed des-bromo GR117289 (20d) proved to be ca. 1.5 orders of magnitude less potent than GR117289. Hence we were keen to understand the role of this substituent.

The crystal structure of GR117289 mono hydrate is depicted in Figure 4. It would be unwise to draw definitive conclusions regarding the biologically active conformation of GR117289 from X-ray data, especially

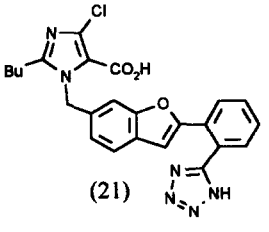
as at least one of its acidic groups would be expected to be ionized when it is bound to the receptor. However some interesting details do emerge from the X-ray data

The X-ray analysis showed the benzofuran and 2-aryl rings lying in a coplanar arrangement. We found this surprising as we had initially believed[14a] that the potency enhancing effect of the 3-bromine atom might arise from a stearic destabilization of the coplanar state restricting rotation about the benzofuran-aryl bond. However the bromine atom and tetrazole group were found to lie in a pseudo trans arrangement. It thus seemed plausible that the bromine atom and the tetrazole occupied this relationship to minimise non-bonded interactions, and that the role of the bromine atom is to force the tetrazole to adopt a cis relationship relative to the benzofuran oxygen atom. It would then follow that in the absence of the bromine atom the alternative coplanar conformation in which the tetrazole and benzofuran oxygen atom adopt a trans relationship is preferred, resulting in the lower potency of the 3-H analogue (20d).

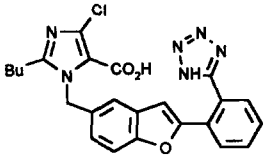
From an extension of the above conformational argument it would follow that if the fusion of the furan ring of GR117289 were reversed relative to the imidazole, and the 3-bromine atom removed, the preferred trans benzofuran oxygen-tetrazole conformation of the resulting compound (21) would offer a good correspondence with the cis oxygen-tetrazole conformation of GR117289.



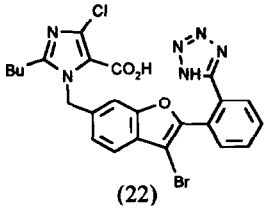
GR117289



(21)



(20d)



(22)

Thus anticipating a compound equipotent with GR117289 this reversed des-bromo benzofuran (21) was prepared, however it proved only equipotent with des-bromo GR117289 (20d) (for the sake of completeness the 3-bromo reversed benzofuran (22) was also prepared, but proved even less potent still). These findings suggested that it is unlikely that the 3-bromine atom of GR117289 enhances potency by forcing a cis relationship between the tetrazole and benzofuran oxygen atom.

Indeed the fact that the 3-bromine atom of GR117289 does not cause a significant stearic perturbation of the conformation about the benzofuran-aryl bond was confirmed by subsequent further X-ray analyses.

As GR117289 progressed through development a number of different crystalline forms of this compound were isolated. X-ray analysis of another mono hydrate of GR117289 revealed a dihedral angle of ca. 45° between the 2-phenyl and benzofuran rings. Furthermore it also revealed that the 3-bromine atom and tetrazole lay in close proximity in a psuedo cis relationship (figure 5). These findings indicated that it is unlikely that close proximity between the tetrazole and bromine atom of GR117289 is energetically unfavourable. Furthermore, as above, they also indicate that it is unlikely that the 3-bromine atom of GR117289 enhances potency by forcing a cis relationship between the tetrazole and benzofuran oxygen atom.

Figure 4: Two Views of an X-Ray Crystal Structure of GR117289 monohydrate

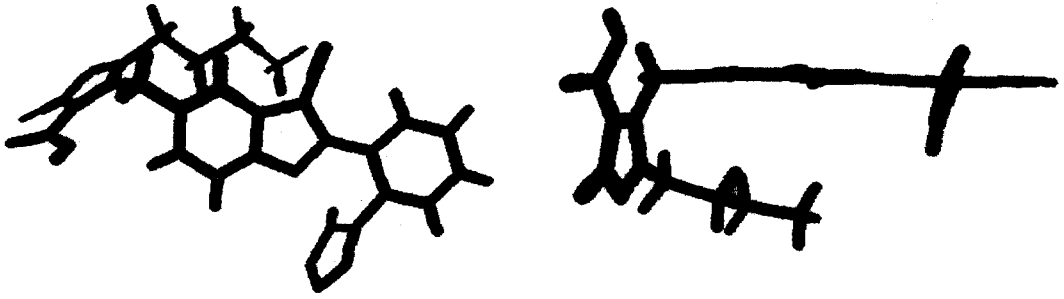
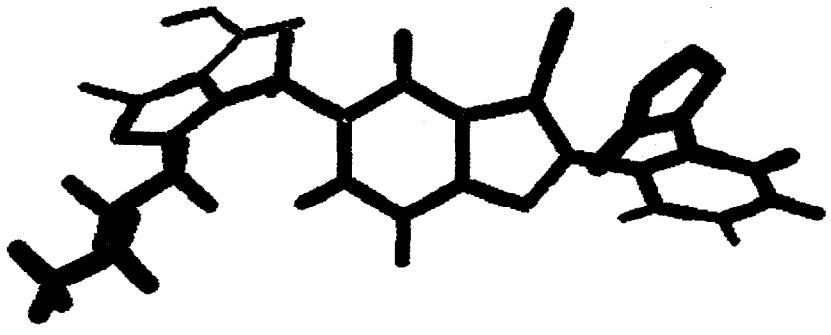


Figure 5: X-Ray Crystal Structure of an Alternative Mono Hydrate of GR117289

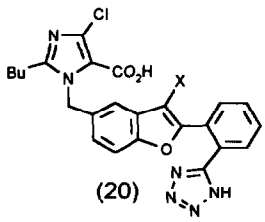


Having discounted conformational effects the role of the 3-bromine atom was probed further by way of a series of GR117289 analogues bearing alternative benzofuran 3-substituents (Table 4).

From the low potency of the 3-^{t}butyl compound (20e) it was apparent that contrary to the other of our initial suggestions it is unlikely that the bromine atom acts to enhance a lipophilic interaction with the receptor.

Table 4: *In Vitro* Potencies of Benzofurans (20)

Compound	X	pK_B	σ_I[37]
20a	Cl	10.5	0.47
20b	CF_3	10.0	0.42
GR117289	Br	9.8	0.46
20c	OMe	9.6	0.28
20d	H	8.4	0.00
20e	^{t}Bu	8.3	-0.07



(20)

Further analysis of the data of Table 4 suggests potency *in vitro* increases with increasing σ-electron withdrawing power (σ_I[37]) of the benzofuran 3-substituent. This could arise from either this substituent reducing the already low Lewis basicity of the furanyl oxygen atom or, more probably, a modulation of the electron charge distribution of the furan ring. Indeed preliminary MNDO molecular orbital calculations (SYBYL version 5.32, data not shown) indicate that the increasing potency in compounds (20) parallels an increase in electron charge density on the benzofuran 3-substituent. This trend would indicate a dipolar interaction between this substituent and the receptor.

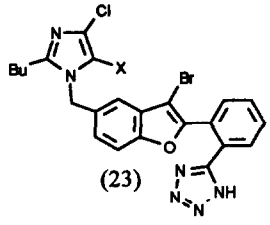
Of the various 3-substituted compounds of Table 4 only GR117289 and its chloro analogue (20a) displayed significant oral activity in renal hypertensive rats. We opted to perform further studies with 3-bromobenzofurans as synthetically a 3-bromine atom is readily introduced (via electrophilic bromination) whereas introduction of a 3-chlorine atom is problematical.

6.4 *Modification of the Imidazole Substituents*

The imidazole-5-position of GR117289 proved tolerant to a variety of alternative substituents (table 5). Introduction of non-acidic substituents, (e.g. amides (23a-c)) causes only a small potency decrease relative to GR117289. It thus appears unlikely that the imidazole 5-substituent of GR117289 participates in a full ionic interaction with the receptor, as, if this were the case, such modifications would lead to the more drastic falls in potency observed on similar modification of the tetrazole region (see section 6.2). The observed potency changes are more consistent with a hydrogen bonded interaction between the imidazole-5-substituent and the receptor. Furthermore the comparable potencies of the primary, secondary and tertiary amides (23a-c) suggest that the 5-substituent acts as a hydrogen bond acceptor.

Table 5: *In Vitro* Potencies of Bromobenzofurans (23)

Compound	X	pK_B
GR117289	CO_2H	9.8
23a	CONHMe	9.2
23b	$CONH_2$	9.0
23c	$CONMe_2$	8.8
23d	CO_2Et	8.3
23e	CH_2CO_2H	9.8
23f	$CH_2NHCONH_2$	8.8



(23)

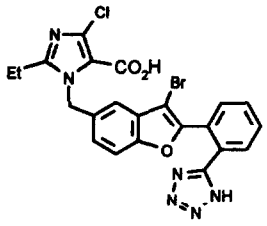
Interestingly replacement of the imidazole chlorine atom with a methyl group leaves potency unchanged, despite the fact that such a change would significantly enhance the basicity of the imidazole[38].

The relationship between potency and chain-length of the alkyl group at the imidazole 2-position was investigated in both 4-chloro and 4-methyl imidazole analogues of GR117289. A 2-ethyl imidazole substituent was found to confer the highest potency in both series (see below).

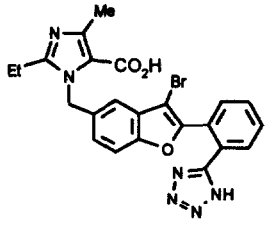
The studies based around the GR117289 template furnished valuable knowledge of structure activity relationships and led to some increases in *in vitro* potency. However few of the modifications led to compounds with any oral activity in renal hypertensive rats, the exceptions being the weakly active N-methyl amide (23a) and triflamide (17c), the 3-chloro benzofuran (20a) and the 2-alkyl chain shortened imidazoles (24 and 25)

The 2-ethyl-4-chloro and 2-ethyl-4-methyl imidazole analogues of GR117289 (24 and 25) proved significantly more potent than the parent molecule (pK_B = 10.5 and 10.6 respectively) and considerably more orally active. However this improved oral activity reflected enhanced absolute potency and not improved bioavailability. The 2-ethyl-4-methyl imidazole (25) was used in a subsequent pro-drug study (see following section).

Information gathered from these SAR studies was however subsequently put to effective use in the strategy leading to the identification of GR138950 (see section 8).



(24) $pK_B = 10.5$



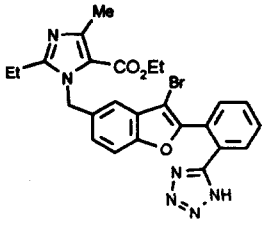
(25) $pK_B = 10.6$

7. AN EFFORT TO ENHANCE THE ORAL BIOAVAILABILITY OF GR117289 TYPE COMPOUNDS BY THE FORMATION OF ESTER PRO-DRUGS

As outlined earlier whilst GR117289 is a highly potent AII antagonist *in vitro* and exhibits good oral activity in renal hypertensive rats, its oral bioavailability is low (table 1). Data obtained from pharmacokinetic studies in the rat (table 1) revealed that the plasma clearance of GR117289 is low and therefore that the low bioavailability of this compound results from its poor absorption.

A strategy that is commonly employed to enhance drug absorbtion is pro-drug formation[39]. The drug is administered as a derivative which is metabolically converted into the active entity after absorbtion. In the case of carboxylic acids, esters are commonly used as pro-drugs.

An ester pro-drug strategy was pursued in an effort to enhance the bioavailability of GR117289 type compounds. The 2-ethyl-4-methyl imidazole (25), which is intrinsically more potent than GR117289 (see previous section), was used in this pro-drug exercise. Of the simple esters prepared, the ethyl ester (26) exhibited the best oral activity. However pharmacokinetic analysis showed that, although the ester (26) is well absorbed, metabolic conversion into the active entity (25) is inefficient, resulting in practice in only a small enhancement in the bioavailability of the acid. These findings suggested that formation of an ester pro-drug could indeed enhance oral absorption but that we should focus our efforts onto esters which would be more efficiently converted into the parent acid *in vivo*.



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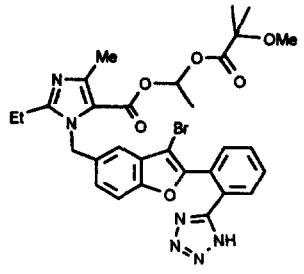


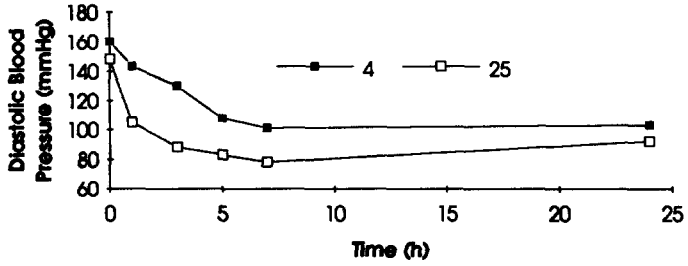
(4)

Amongst other properties, such as aqueous solubility at differing acidities and rate of dissolution, the absorption of a drug molecule is very much dependent upon its lipophilicity. Potent di-acidic isolipophilic[40] analogues of the ethyl ester (26) exhibit very poor oral activity. This suggests that the superior absorption of the ethyl ester (26) relative to these di-acids results from its being mono-acidic and not from any lipophilicity effect. However experiments with other esters of the acid (25) and esters of related compounds suggested that the lipophilicity of the ester (26) is around the optimum for oral absorption in the rat. Thus when designing subsequent pro-drugs we concentrated on those which would be isolipophilic with the ethyl ester (26).

The use of double ester pro-drugs of carboxylic acids is well precedented[41], typically these esters enhance oral absorption but are rapidly cleaved in plasma to afford their parent acids. We prepared a series of double ester pro-drugs of the acid (25), the majority of which demonstrated oral efficacy superior to that of the ethyl ester. An extensive series (over 30 compounds) of double ester pro-drugs of the acid (25) and its 4-chloro imidazole counterpart (24) was prepared, the majority of these double esters demonstrated oral activity enhanced over that of the ethyl ester (26). The double esters isolipophilic with the ethyl ester (26) proved the most effective. The methoxy pivolyl derived species (4), the most orally efficacious of these double esters exhibits blood pressure lowering effects comparable to those obtained on intra-arterial administration of the parent acid (figure 6).

Whilst the relative oral and inta-arterial activities of the double ester (4) and its parent acid (25) (figure 6) were suggestive of improved bioavailability it transpired that such data were misleading. For example, pharmacokinetic experiments in the dog revealed that the time integrated plasma concentration of the parent acid (25) afforded by oral administration of the double ester (4) is only ca. 10% of that afforded by i.a. administration of the acid itself - an effective bioavailability of only ca. 10%. Similar results were obtained for other related pro-drugs.

Figure 6: A Comparison of the Hypotensive Effects of Orally Administered Double Ester (4) and Intra-Arterially Administered Acid (25) in Renal-Artery Ligated Hypertensive Rats (Both 0.3 mgkg^{-1})



In light of the poor pharmacokinetics observed for the the double ester (4) and related compounds we took the decision to abandon the pro-drug approach to enhancement of bioavailability and to seek to identify compounds with good bioavailability in their own right.(see following section). With the benefit of hindsight it would appear that we devoted far too much effort to this pro-drug exercise. We were misled by the remarkable oral activities of these compounds which did not reflect improved bioavailability.

8. THE IDENTIFICATION OF THE BROMOBENZOFURAN-TRIFLAMIDE GR138950; A NON PEPTIDE ANGIOTENSIN II ANTAGONIST WITH HIGH INTRINSIC ORAL BIOAVAILABILITY

The approach of forming pro-drugs of analogues of GR117289 had led to compounds with improved oral activity, however it had not afforded the desired enhancement of oral bioavailability.

If a pro-drug is to enhance the bioavailability of its parent compound a fine balance needs to be struck between the stability of the pro-drug in the gut, its absorption from the gut and its conversion into the active species in the plasma. This balance is notoriously difficult to obtain. Indeed we chose to abandon a pro-drug approach and set ourselves the objective of identifying a potent orally active AII antagonist with high bioavailability in its own right. From the work with ester/double ester pro-drugs of GR117289 we concluded that diacidic bromobenzofurans are more poorly absorbed than monoacidic species. Furthermore, on this

basis, we adopted a strategy of working solely with monoacidic species in aiming towards this objective of high bioavailability.

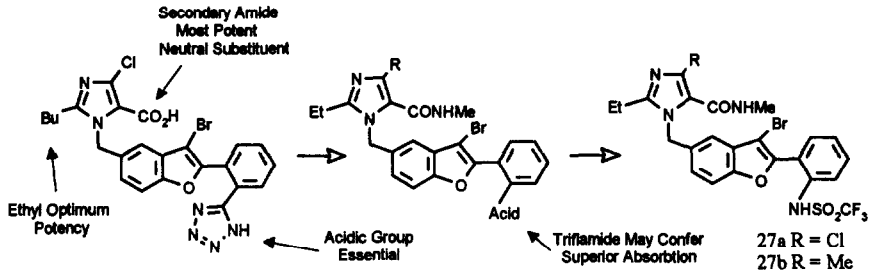
Taking GR117289 as a starting point the triflamides (27a and b) emerged as initial targets following this mono-acid strategy. The choice of these compounds as initial targets arose from three key aspects of the SAR we had established around GR117289 (see section 6) and on the crucial observation of surprising oral activity in a compound with only modest *in vitro* potency.

SAR studies around GR117289 had demonstrated that an acidic group in the pendant aromatic ring is crucial for high potency *in vitro*. In contrast, the carboxylic acid in the imidazole ring, although important, is not crucial for high potency *in vitro*. Clearly, under the monoacid strategy, the imidazole carboxylic acid needed to be replaced by a neutral group. In this context we favoured a secondary amide as we had shown this substituent retained the highest potency *in vitro* relative to a carboxylic acid. Additionally we felt that any drop in potency associated with replacing the carboxylic acid could be offset by replacing the butyl group with the potency enhancing ethyl group. We thus anticipated that replacement of the imidazole of GR117289 with a 2-ethyl-5-carboxamidoimidazole would afford a monoacidic species retaining good potency *in vitro* (Figure 7).

The key advance towards improved bioavailability was serendipitous. As part of our biological strategy we had adopted a policy of evaluating all our compounds in renal hypertensive rats *via* the oral route. The triflamide analogue of GR117289 compound (17c) exhibits only weak oral activity, however given the low potency of this compound we concluded that it must be particularly well absorbed. From this observation we extrapolated that in this type of compound a triflamide confers better oral absorbtion than a corresponding tetrazole.

Thus, drawing on a combination of the above observations we anticipated that the triflamides (27a and b) would exhibit good oral absorption with little accompanying fall in potency *in vitro*.

Figure 7: A Strategy Towards Identifying a Bromobenzofuran with High Intrinsic Bioavailability



The two triflamides (27a and b) indeed fulfilled our expectations. Compounds (27a and b) are potent antagonists of angiotensin II $pK_B = 9.2$ and 9.0 respectively and in renal hypertensive rats both compounds are essentially equally effective at lowering blood pressure after intra-arterial or oral administration.

Pharmacokinetic studies of compound (27b) in the rat (table 6) revealed excellent bioavailability but disappointingly high plasma clearance and a correspondingly short plasma half-life. An extensive programme of systematic variation of the amide nitrogen substituent and imidazole 4-substituent of triflamides (27) was undertaken in an effort to reduce plasma clearance whilst maintaining potency and good bioavailability. Over 50 compounds were prepared in this study, however it would be inappropriate to discuss the data in detail in this review. Suffice to say that this exercise led to the identification of GR138950, a highly bioavailable compound with much reduced plasma clearance (table 6).

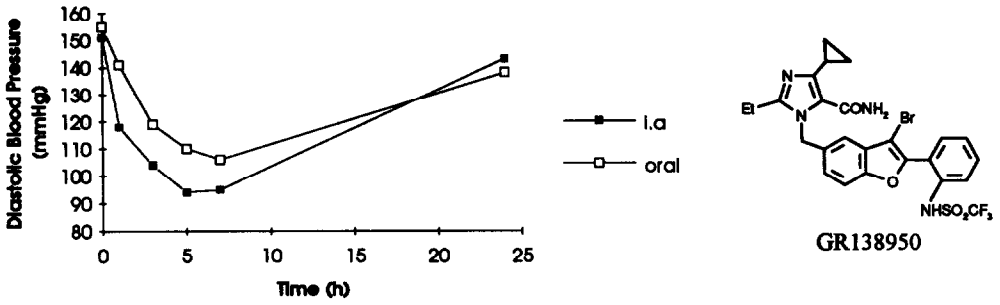
Table 6: Pharmacokinetic Parameters[29] of Triflamides 27b and GR138950 in the Rat.

Compound	F (%)	Vd (l/kg)	Clp (ml/min/kg)	$t_{1/2}$ (h)
27b	95	4.3	42.0	1.2
GR138950	79	2.4	8.9	3.2

GR138950 is a potent antagonist of angiotensin II *in vitro*, pK_B = 9.0, and causes marked and prolonged falls in blood pressure in renal hypertensive rats after oral administration (Figure 8). The compound has an excellent pharmacokinetic profile in the rat with a bioavailability of 79% and relatively low plasma clearance (Table 6).

In GR138950 we realised our objective of identifying a highly orally bioavailable angiotensin II antagonist. GR138950 duly entered clinical development as a treatment for hypertension.

Figure 8: The Hypotensive Effect of GR138950 in Renal Artery Ligated Hypertensive Rats after Oral and Intra-Arterial (i.a.) Administration (both 0.3mgkg^{-1})

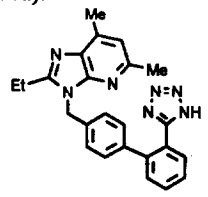


9. THE IDENTIFICATION OF THE BROMOBENZOFURAN-TRIFLAMIDE GR159763; AN IMIDAZOPYRIDINE CONTAINING NON-PEPTIDE ANGIOTENSIN II ANTAGONIST WITH HIGH INTRINSIC ORAL BIOAVAILABILITY

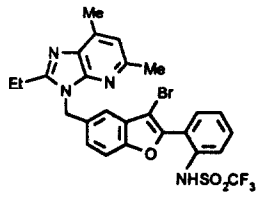
As a potent, orally active and highly bioavailable AII antagonist GR138950 fulfilled the initial objectives of our research programme. However, we still wished to identify a subsequent clinical candidate with these properties.

As outlined earlier, DuP753[2] can be regarded as the prototype non-peptide angiotensin II antagonist. The literature is replete with analogous angiotensin II antagonists (3) in which an alternative "northern" heterocycle is linked through nitrogen to the "southern" biaryl tetrazole portion of DuP753. Although we had shown that different SAR exists for bromobenzofuran and biaryl based AII antagonists we explored the possibility of replacing the imidazole of GR138950 with some of these alternative "northern" heterocycles. However, given its success in leading to the identification of GR138950 we adhered to our "mono-acid" strategy (see section 8) and used only non-acidic heterocyclic units. The majority of alternative "northern" heterocycles we examined afforded bromobenzofurans with potency substantially reduced relative to their biaryl counterparts. Similarly incorporation of the "northern" heterocycle of our own C-linked pyrazole biaryl tetrazoles into a bromobenzofuran led to a significant fall in potency (see section 10). We ascribed these

differences in potency to differences in the manner in which the two types of compound bind to the receptor which had become apparent from SAR studies (section 6). In contrast incorporation of the "northern" imidazopyridine of the Merck compound L158,809[21] led to the potent bromobenzofuran based angiotensin II antagonist, compound (28a).



L158,809

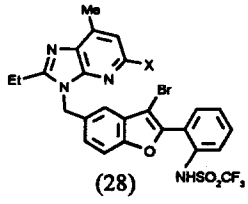


(28a)

The imidazopyridine (28a) proved to be a potent AII antagonist, pK_B = 9.3, with excellent oral activity. This compound exhibits an extremely long duration of action in renal hypertensive rats, blood pressure had not even begun to return to the initial hypertensive levels 50h after administration (figure 9). We had previously only observed prolonged durations of action (i.e. >24h) for diacidic bromobenzofuran based compounds, hence our prejudices suggested that *in vivo* the imidazopyridine (28a) might be metabolically oxidised to a potent di-acidic species. Moreover we anticipated that oxidation of the 5-methyl, rather than 7-methyl, group would be more likely to lead to a compound with high receptor affinity and hence that compound (28c) would be the diacidic metabolite. To investigate the possibility of this oxidative metabolism we prepared the diacid (28c), the 5-H imidazopyridine (28b) and also the 5-hydroxymethyl imidazopyridine and examined their pharmacological profiles (figure 9).

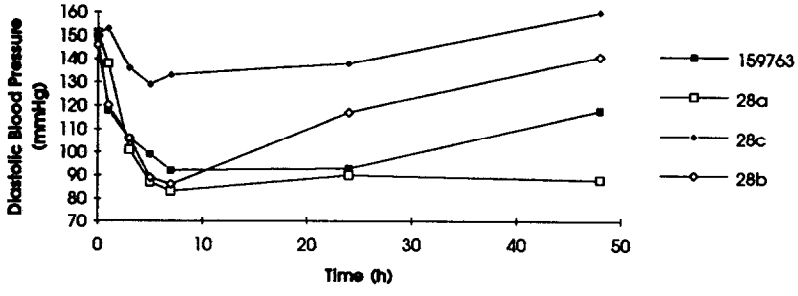
Table 7: *In Vitro* Potencies of Imidazopyridines (28)

Compound	X	pK_B
28a	Me	9.3
GR159763	CH_2OH	8.6
28b	H	8.3
28c	CO_2H	9.3



(28)

Figure 9: The Hypotensive Effects of Imidazopyridines (28) in Renal Artery Ligated Hypertensive Rats after Oral Administration (1mgkg^{-1})



All of the imidazopyridines (28a-c and GR159763) proved to be potent AII antagonists (table 7). In terms of oral activity the diacid (28c) proved relatively weak, which is consistent with our hypothesis of poor absorption of diacidic species (see earlier), and the 5-H compound exhibits a relatively short duration of action (figure 9). However like its methyl analogue (28a), the hydroxymethyl imidazopyridine (GR159763) exhibits excellent oral activity and an extended duration of action. On the basis of their excellent oral activities both the 5-methyl and the 5-hydroxymethyl imidazopyridines (28a and GR159763) were subject to pharmacokinetic evaluation.

Experiments in the rat revealed excellent pharmacokinetic profiles for both the 5-methyl and 5-hydroxymethyl imidazopyridines (28a and GR159763) (table 8). Furthermore, in contrast to our initial prejudice, these experiments demonstrated that neither of these compounds experiences simple oxidative metabolism of its 5-substituent. HPLC analysis revealed that none of the 5-hydroxymethyl or 5-carboxyl acid imidazopyridines appeared in plasma samples from experiments performed with the 5-methyl imidazopyridine (28a) and similarly that none of the 5-acid appeared in samples obtaining from the 5-hydroxymethyl compound (GR159763). Indeed the relatively low values for the plasma clearances of compounds (28a and 159763) are indicative of high metabolic stability.

Table 8: Pharmacokinetic Parameters[29] of GR159763 and (28a) in the Rat.

Compound	F (%)	Vd (l/kg)	Clp (ml/min/kg)	$t_{1/2}$ (h)
28a	70	1.33	5.5	2.8
GR159763	115	2.4	4.8	5.7

In exhibiting such good *in vivo* activities and pharmacokinetic profiles both of the imidazopyridines (GR159763 and 28a) fulfilled all the objectives of our non-peptide angiotensin II antagonist programme (see section 4.1).

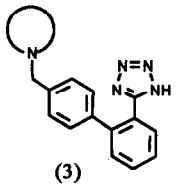
10. THE IDENTIFICATION OF C-LINKED PYRAZOLE BIARYL TETRAZOLES; POTENT ANGIOTENSIN II ANTAGONISTS, SOME OF WHICH EXHIBIT GOOD ORAL ACTIVITY AND BIOAVAILABILITY

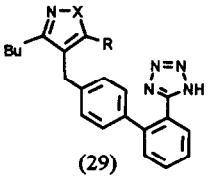
As outlined earlier DuP753[2] represented the first potent and orally active non-peptide angiotensin II antagonist. Once its structure had been disclosed a whole host of analogous compounds (3) in which an alternative "northern" heterocycle is linked through nitrogen to the "southern" biaryl tetrazole portion of DuP753 were reported. Given the good oral activity[20] of DuP753 we considered that it would be prudent to devote a limited amount of our effort into work with biaryl tetrazoles. We endeavoured to identify a novel structural class by attempting to link a "northern" heterocycle to the "southern" biaryl tetrazole through carbon.

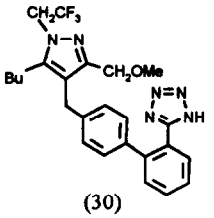
We believed that the 2 and 5 imidazole substituents and the unsubstituted sp^2 imidazole N-3 atom to be important in conferring potency to DuP753. We thus envisaged that a biaryl tetrazole with a C-linked northern heterocycle would have to take the the form of structure (29). To maintain aromaticity X would have to be a heteroatom and furthermore, if that heteroatom were nitrogen it could be substituted so as to mimic the imidazole 4-chlorine atom of DuP753.

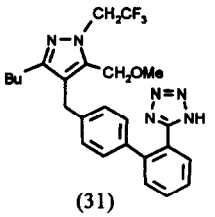
Application of this analysis led us to prepare the two pyrazoles (30 and 31). Whilst clearly the analysis would have only suggested preparation of the β-nitrogen[42] substituted regioisomer (the β-regioisomer) the α-nitrogen[42] substituted regioisomer (the α-regioisomer) was generated as a consequence of a non-

regioselective pyrazole ring synthesis. The two regioisomeric pyrazoles (30 and 31) displayed modest potency. More encouragingly the β-regioisomer exhibited modest oral activity indicative of good oral absorption for a compound of such modest *in vitro* potency. Consequently further related compounds were prepared.


(3)


(29)

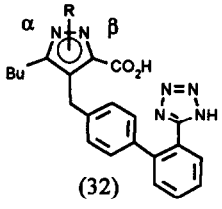

(30)


(31)

We proceeded to replace the methoxy methyl γ-substituent[42] of pyrazoles (30 and 31) with a carboxylic acid as we had found that an analogous change to the imidazole-5-substituent in with bromobenzofuran based AII antagonists led to a marked increase in potency (see earlier). This modification led to a substantial increase in potency in the β-isomer (32c) and only a slight increase in potency in the α-isomer (32a). Furthermore the β-regioisomer exhibits good oral activity. Interestingly the N-unsubstituted pyrazole (32b) exhibited potency intermediate between the two regioisomers. The relative potencies of the regioisomeric pyrazoles (32a and c) were consistent with our structural analysis (see above) which would have suggested higher potency in the β-regioisomer.

Table 9 ***In Vitro*** **Potencies of Pyrazoles (32)**

Compound	R[42]	pK_B
32a	α-CH_2CF_3	7.7
32b	H	8.8
32c	β-CH_2CF_3	9.8


(32)

Gaining great encouragement from having identified the potent and orally active pyrazole (32c) we set about exploring the structure activity relationships of this class of molecule in more detail. We found that replacement of the trifluoroethyl group of pyrazole (32c) with a simple ethyl group (5b) left potency effectively unchanged, we then used this nitrogen substituent to perform SAR studies.

We found that variation of the pyrazole γ–substituent failed to afford compounds with potency comparable to that of (5b). However only modest falls in potency were associated with replacing the carboxylic acid of (5b) with neutral substituents such as amides which suggests that the carboxylic acid, like the corresponding carboxylic acid of GR117289, is involved in a hydrogen bonded interaction with the receptor.

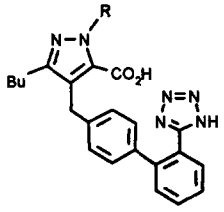
Replacement of the tetrazole of pyrazole (5b) with either a carboxylic acid or a triflamide both lead to a ca. 100 fold fall in potency. This effect mirrors that observed on replacement of the tetrazole of DuP753

with either of these other acidic groups, but is in contrast to the findings for bromobenzofurans (see earlier) where the replacement of the tetrazole of GR117289 with a carboxylic acid causes a slight increase in potency. This suggests that the interaction of the pyrazolobiaryl tetrazoles (5) with the AT_1 receptor is similar to that of DuP753 rather than that of GR117289 (see earlier). Indeed further differences between the modes of binding of pyrazolobiaryl tetrazoles (5) and bromobenzofurans emerged subsequently when attempts were made to combine features of both types of structure (see later).

Having established the optimum combination of a β N-substituent a γ-carboxylic acid and a southern biaryl tetrazole the β-substituent itself was briefly examined. Potency proved largely insensitive to changes in the β substituent, even introduction of aryl groups or relatively large alkyl groups left potency essentially unchanged. The relative potencies of the α and β regioisomer pairs (5c and d) confirmed the initial finding of superior potency in β-regioismers.

Table 10: *In Vitro* Potencies of Pyrazoles (5)

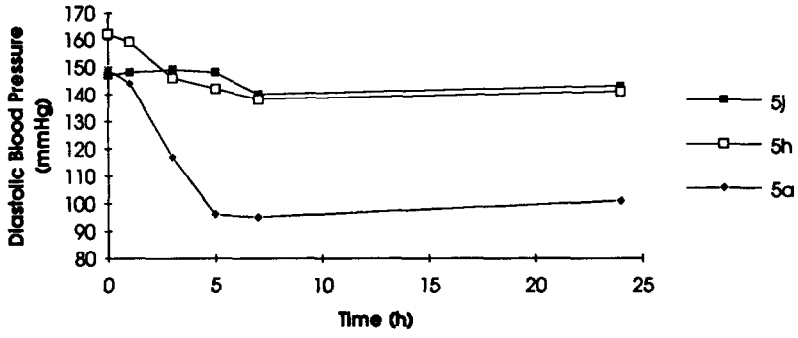
Compound	R	pK_B	
		α	β
5a	CPM[43]		10.5
5b	Et		9.8
5c	^{n}Bu	8.0	10.0
5d	^{i}Pr	8.0	10.0
5e	Me		9.8
5f	^{n}Pr		10.5
5g	$CH_2{}^t$Bu		10.6
5h	cyclo-Bu		10.9
5i	^{i}Bu		11.0
5j	Ph		



(5)

The majority of the β-substituted γ-carboxylic acid pyrazoles (5) exhibit oral activity. However, even amongst these compounds oral activity proves subtly dependent on the nature of the N-substituent. For example the N-cyclopropylmethyl pyrazole (5a) exhibits large and prolonged falls in blood pressure whilst the N-phenyl species (5j) is orally inactive (figure 10).

Figure 10: A Comparison of the Hypotensive Effects of Pyrazoles (5a, h and j) in Renal Artery Ligated Hypertensive Ratsafter Oral Administration (1mgkg^{-1})



As discussed in section 7 the oral absorption of a molecule can be very much dependent upon its lipophilicity. The N-cyclobutyl pyrazole (5h), which is isolipophilic[40] with the N-cyclopropylmethyl pyrazole (5a) has only very weak oral activity (figure 10) despite its very high *in vitro* potency. This suggests that the oral activity of pyrazoles (5) is not dependent simply upon lipophilicity.

The N-cyclopropylmethyl and N-n-butyl compounds (5a and c) proved to be the most orally efficacious pyrazoles we identified. On this basis these compounds were selected for bioavailability determination to assess their potential as development candidates.

Data obtained from pharmacokinetic studies in the rat (Table 11) demonstrate that both pyrazoles (5a and c) exhibit long plasma half lifes and furthermore that these result from low clearance rather than from high volume of distribution. The low clearances are indicative of high metabolic stability and a low rate of excretion, the low volumes of distribution indicate that these molecules are held largely within the plasma compartment. Most importantly the two compounds are well orally absorbed resulting in respectively good (58%) and modest (26%) bioavailability for pyrazoles (5a and c).

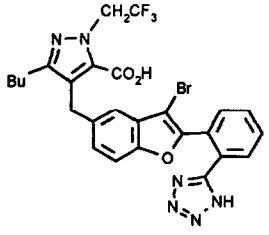
Table 11: Pharmacokinetic Parameters[29] of Pyrazoles (5a and c) in the Rat

Compound	F (%)	Vd (l/kg)	Cl_P (ml/min/kg)	$t_{1/2}$ (h)
5a	58	0.20	0.20	12.3
5c	26	0.16	0.12	14.8

In our work with bromobenzofuran based non-peptide AII antagonists we had concluded that di-acidic species are poorly absorbed (see section 8). To enhance the oral absorption of di-acidic bromobenzofurans initially we had had to resort to formation of pro-drugs of one of the acidic functions and ultimately we adopted a strategy of working exclusively with mono-acidic species. (a strategy which proved highly successful - see section 8). The fact that a number of the other then known[2,44] AII antagonists were mono-acidic prodrugs which are converted into more potent diacidic species *in vivo* lent credibility to our hypothesis concerning absorption and di-acidicity. Consequently in the light of the above evidence we found the 58% bioavailability of the diacidic N-cyclopropylmethyl pyrazole (5a) particularly gratifying. It would, however, be fatuous to speculate as to what is responsible for such surprisingly high bioavailability when very close analogues of the N-cyclopropylmethyl pyrazole (5a) have very poor oral activity and, by inference, bioavailability (see above).

In exhibiting good potency *in vitro*, good oral activity in the renal hypertensive rat model of hypertension and good pharmacokinetics the cycloproylmethyl pyrazole (5a) also fulfilled all the objectives of our non-peptide angiotensin II antagonist programme (see section 4.1).

We did attempt to combine some features of both pyrazolobiaryl tetrazoles and our bromobenzofuran tetrazoles. The C-linked pyrazole bromobenzofuran tetrazole (33), a hybrid of pyrazole (5b) and GR117289 proved to be a disappointingly weak AII antagonist.



(33) $pK_B = 7.8$

It has been mentioned earlier that differences in SAR suggest that GR117289 and DuP753 bind to the AT_1 receptor differently, and furthermore that the C-linked pyrazoles (5) bind in a manner akin to DuP753. The low potency of the pyrazole-bromobenzofuran hybrid (33) serves to further illustrate the differences in receptor binding between bromobenzofuran tetrazole and biaryl tetrazole AII antagonists.

It is worthy of note that workers at Merck independently identified[45] C-linked pyrazoles (5), although their work focused primarily on N-aryl species. The Merck group arrived at these structures through a somewhat different line of reasoning.

Having identified the pyrazole (5a) we took the decision to perform no further medicinal chemistry with compounds so closely related to DuP753 (i.e. with biaryl tetrazoles).

11. SYNTHETIC CHEMISTRY

In a typical medicinal chemistry project once a core structural template has been identified an efficient synthesis of this core structural template is essential if rapid progress is to be made. Armed with such a synthesis the preparation of analogues for an SAR study or a fine tuning exercise becomes straightforward and large quantities of key compounds can be prepared quickly. It is particularly advantageous if the synthesis provides a late stage intermediate from which appropriate analogues can be made in relatively few steps As our non-peptide Angiotensin II antagonist programme evolved it became necessary for us to develop efficient and versatile syntheses of both bromobenzofurans and C-linked pyrazole bi-iaryls.

11.1 *Bromobenzofurans*

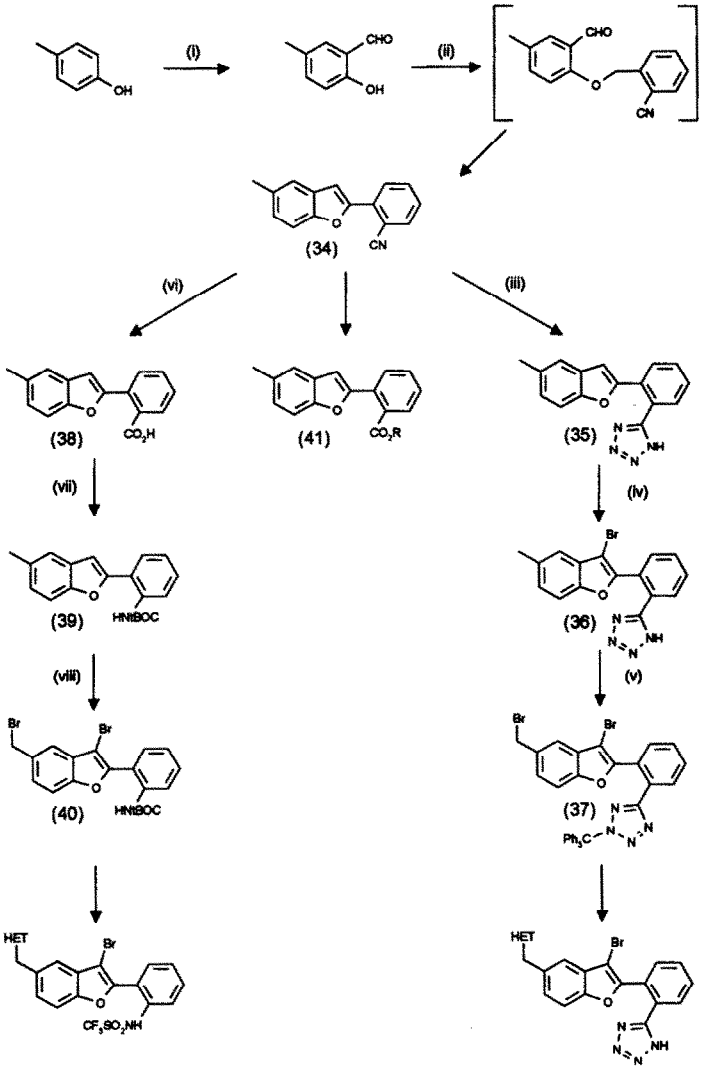
Once we had identified the key 2-aryl-3-bromobenzofuran structural element a versatile synthesis of this type of system had to developed. We had initially employed[14a] a synthesis involving a palladium(0) catalysed boronic acid/halide coupling, however this synthesis was low yielding, capricious and unsuitable for the preparation of a large quantiities of material.

We successfully developed a synthetic regime which gave ready access to large quantities of versatile late stage intermediates. The essence of this regime is shown in figure 11 .The cyanophenyl benzofuran (34) is readily prepared from p-cresol. Treatment of this cyanide with tri-butyltin azide leads to the benzofuran tetrazole (35). Electrophilic bromination of (35) affords the 3-bromobenzofuran (36) which after successive tetrazole tritylation and radical bromination, affords the dibromide (37) Similarly hydrolysis of the cyanide (34) to afford the acid (38) followed by Curtius rearrangement in t-butanol affords the t-butyl carbamate (39). Successive electrophilic bromination and radical bromination of carbamate (39) gives the dibromide (40). The two di-bromides (37 and 40) served as key intermediates in our medicinal chemistry programme.

Simple alkylation of the appropriate heterocycle with the di-bromide (37) followed by any required transformations of the heterocycle and subsequent deprotection of the tetrazole afforded a myriad of bromobenzofuran tetrazoles. Similarly alkylation with di-bromide (40), appropriate heterocycle transformation followed by deprotection of the aniline and formation of a triflamide, afforded a wide range of bromobenzofuran triflamides. In addition some bromobenzofuran acids were prepared from the corresponding ester (41) by an analogous procedure.

The two bromides (37 and 40) could be readily prepared in hundred gramme quantities. Using these intermediates we were able to easily and rapidly prepare a vast range of analogues for SAR studies (see section 6) and for extensive fine tuning exercises such as that leading to the identification of GR138950 (see section 8). The development of the chemistry of figure 11 played a key role in the success of our chemical programme in allowing such ready access to a large number of analogues.

Figure 11: Syntheses of Bromobenzofurans



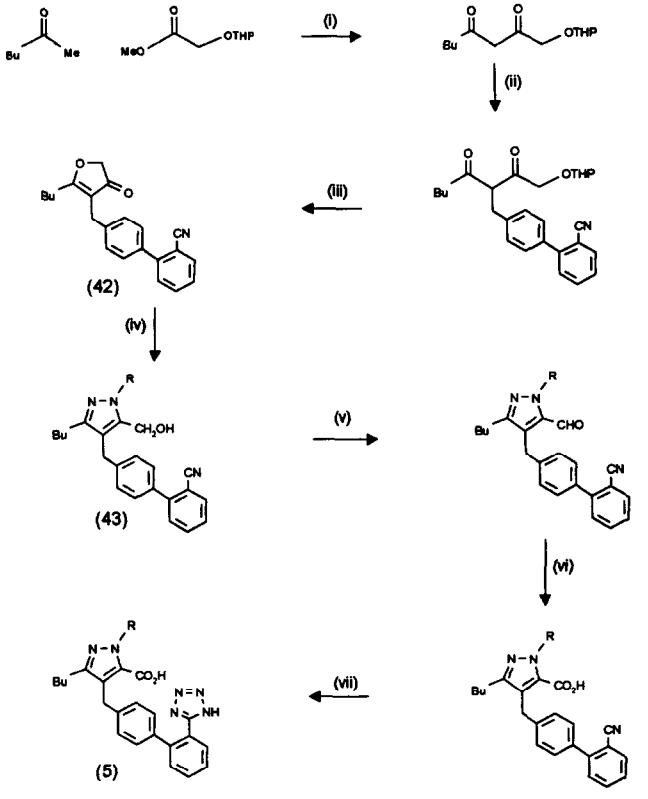
Reagents and Conditions: (i) $EtMgBr/(H_2CO)_n$,52% ; (ii) $ArCH_2Br$/Base,67% ; (iii) Bu_3SnN_3,93% ; (iv) Br_2,89% (v) a. Et_3N/Ph_3CCl, b.NBS/AIBN,68% ; (vi) KOH,87%; (vii) a. Ph_3PN_3 b.tBuOH/Δ,86% (viii) a. Br_2 b. NBS/AIBN,53%

11.2 *C-Linked pyrazole Biaryl tetrazoles*

We have published the details of our synthesis of C-linked pyrazole biaryl tetrazoles elsewhere[46]. Herein it is sufficient to say that regioselective synthesis of 3,4,5-trisubstituted pyrazoles is problematical and that we had to devise a regioselective synthesis of β-substituted γ-carboxylic acids and methanols. This synthesis is depicted in figure 12, the key step involves the reaction of the furanone (42) with an alkyl hydrazine to regioselectively afford the β-substituted[42] pyrazole methanol (43) in high yield . Using this synthesis gramme quantities of pyrazoles (5) could be prepared with relative ease.

In comparison with our work in the bromobenzofuran area only a relatively small number of C-linked pyrazoles was prepared and the development of an efficient synthesis was not so crucial in fulfilling our medicinal chemistry objective. However this regioselective and relatively straightforward synthesis was invaluable when large quantities of pyrazoles (5a and c) were required as these compounds progressed through pharmacokinetic evaluation and beyond.

Figure 12: Synthesis of C-Linked Pyrazole Biaryl Tetrazoles

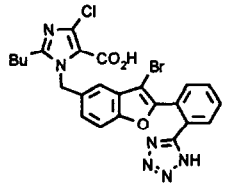
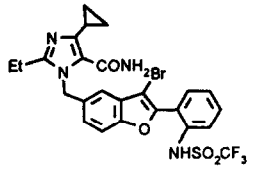
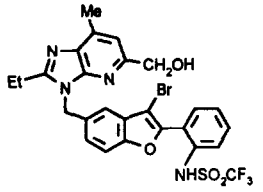
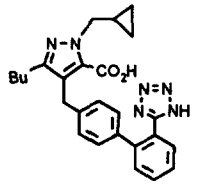


Reagents and Conditions : (i) LDA,61% ; (ii) NaH / RBr,74% ; (iii) Dowex WX4 ion exchange resin, 93% ; (iv) $RNHNH_2$ 68-92% ; (v) MnO_2 or TPAP,80-85% ; (vi) NaOCl/2-methylbut-2-ene/t-BuOH/NaH_2PO_4,100% ; (vii) Bu_3SnN_3/Δ,75-82%

12. CONCLUSION

The defined objective of the non-peptide Angiotensin II antagonist programme at Glaxo was to identify compounds which are orally active , significantly lower blood pressure at doses of $1mgkg^{-1}$, exhibit durations of action suitable for once daily therapy, and have greater than 40% oral bioavailability (see section 4). This objective was successfully achieved in the identification of the clinical candidates bromobenzofurans GR117289,GR138950 and GR159763 and the pyrazole (5a) (table 12).

Table 12: Properties of Clinical Candidates

Compound	pK_B	Oral Activty*	Duration of Action**	Rat Oral Bioavailability (%)
 GR117289	9.8	20	24	3
 GR138950	9.0	67	7	79
 GR159763	8.6	57	24	115
 5a	10.5	54	24	58

* Maximum Fall in Diastolic Blood Pressure in Renal Artery Ligated Hypertensive Rats after Oral Administration at $1mgkg^{-1}$ (mmHg)

** Time After Oral Dosing Before Diastolic Blood Pressure of Renal Artery Ligated Hypertensive Rats Begins to Increase (h)

A number of key aspects of the practise of medicinal chemistry and drug discovery are illustrated by the evolution of the project described in this review.

A lead structure as a starting point is of paramount importance to any medicinal chemical programme, indeed the generation of lead structures has latterly almost become a science in itself. The Takeda imidazoles (1) served as a lead structure in the embryonic stages of this project and indeed formed the starting point for the work which led to the identification of DuP753 and related compounds by the DuPont group and that leading to the identification of SK&F108566 by the Smithkline Beecham group. Without this lead structure it is certain that the work reported in this review would not have taken place. Furthermore the importance of a good awarness of the work of other research groups and the influence of data from other research groups is clearly illustrated at several points in this review.

Typically, in comparison with the difficulties inherent in enhancing oral activity and pharmacokinetic parameters, the *in vitro* potency of a lead structure can be enhanced with relative ease. This is clearly illustrated simply by the relatively small number of compounds required to progress from the lead indole (6) to GR117289 compared to the large number required to subsequently progress to GR138950, a compound with a good pharmacokinetic profile.

Within the medicinal chemical community the practise of fine tuning a structure by preparing a series of closely related analogues is commonly derided, indeed the term "methyl ethyl butyl futile" is often applied to this process. However elements of this project exemplify how small and seemingly insignificant structural modifications to a molecule can lead to profound and unpredictable changes in its oral activity and pharmacokinetic parameters, For example seemingly minor changes to the β-nitrogen substituent of the pyrazoles (5) had profound effects upon the oral activities of these compounds, illustrating that, at the appropriate time, a fine tuning analogue programme can prove extremely valuable.

The role of luck, or expressed less perjoratively, serendipity, in drug discovery is clearly illustrated by the unintentional introduction of a 3-bromine atom into the benzofuran (14). Introduction of this atom provided us with a major leap forward in our programme and the 3-bromine atom proved to be a key element in the all the benzofuran based compounds with which we subsequently worked.

Above all, the success of the Glaxo non-peptide angiotensin II antagonist programme illustrates the value of hard work and commitment. The results of in excess of 100 man years of work are reported in this review Without the dedication, perseverence and enthusiasm of all those involved in this project it would undoubtably not have reached its successful conclusion.

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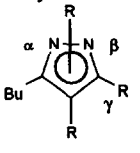

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