Bioorganic & Medicinal Chemistry Letters, Vol.3, No.6, pp. 1019-1024, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

THE SYNTHESIS OF HETEROSUBSTITUTED BENZIMIDAZOLE DERIVATIVES WITH POTENT ANGIOTENSIN II ANTAGONIST ACTIVITY

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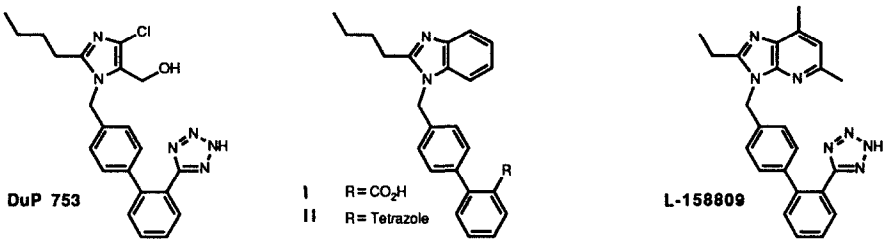
(*Received in Belgium* 1 *February* 1993; *accepted* 30 *March* 1993)

Abstract: The syntheses and biological activities of novel imidazo[4,5-d]pyridazine and imidazo[4,5-c] pyridone derivatives are reported. These series include analogues which have in vitro and in vivo Angiotensin II antagonist activities which are amongst the most potent yet recorded.

The principle of attenuating elevated blood pressure by pharmacological intervention with the renin angiotensin system (RAS) is very attractive. Intervention at the level of the inhibition of angiotensin converting enzyme (ACE) is currently well established in medical practice (1) and intervention at the level of antagonism at the angiotensin II (AII) receptor is currently undergoing clinical evaluation with investigations of the Du Pont compound, DuP 753, being most advanced (2). The structure-activity relationships around DuP 753 indicate that the key structural features of this compound are a 2-n-alkyl substituted imidazole linked by a methylene unit to a biphenyl moiety having a specifically located tetrazole unit (3). ICI Workers have previously reported the synthesis, biological properties and structure-activity relationships of 2-alkylbenzimidazole derivatives (4) in which the imidazole 4- and 5-substituents of DuP 753 have been replaced by a fused ring (I and II). Additional work related to this series was undertaken with the objective of trying to improve pharmacological properties. The introduction of heteroatoms into the benz-ring of the benzimidazole moiety was conceived as an approach which could be used to modulate physical properties and investigate structure-activity relationships with respect to this part of the molecule. It was postulated that such variations might modulate lipophilicity, basicity (of the imidazo nitrogen atom) and solubility in potentially beneficial ways possibly leading to improved oral activity. Furthermore, there was the possibility of picking up additional specific interactions with the receptor and thus increasing antagonist potency.

The synthesis and biological properties of a series of imidazo[4,5-b]pyridines has been reported; the introduction of the nitrogen atom at the 4-position (of the benzimidazole moiety) was shown to be highly beneficial for pharmacological properties. Fine tuning of the substituents on the heterocyclic ring provided the highly potent antagonist L-158809 (5).

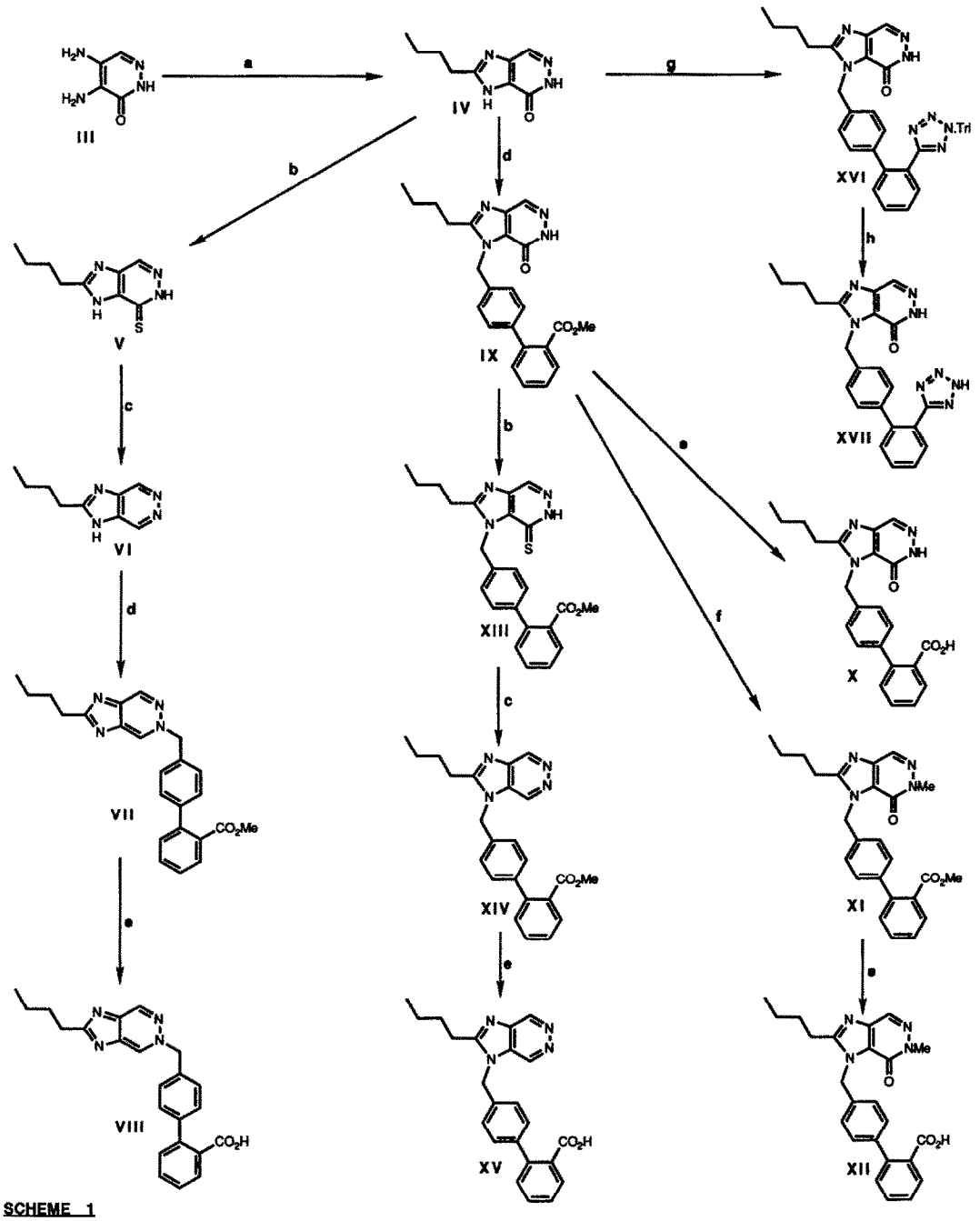
We now wish to report the synthesis of a series of imidazopyridazines which contains compounds whose in vitro and in vivo AII antagonist activities are amongst the most potent to have been reported and also the synthesis of a related imidazopyridone which provides interesting information on the structure-activity relationships (6).



Chemistry

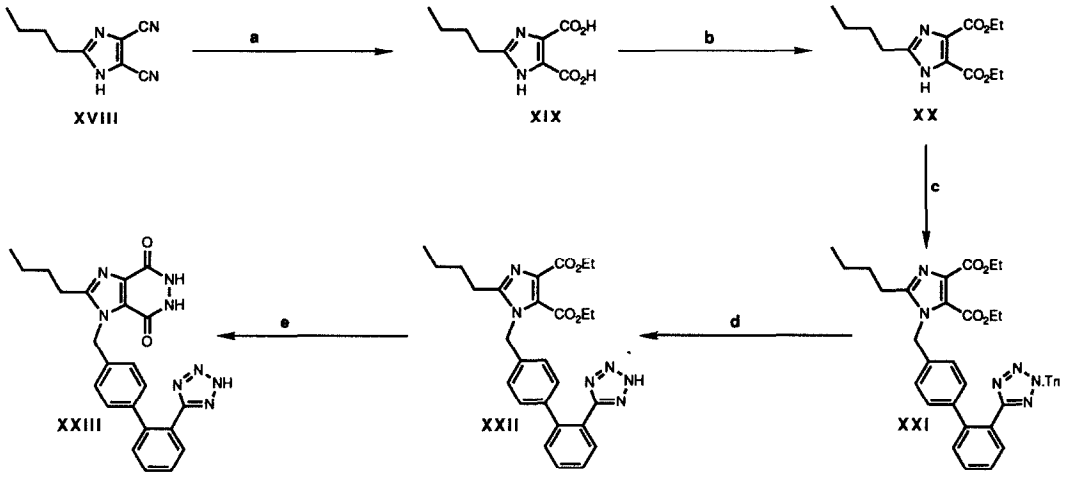
The compounds were synthesised by the routes shown in Schemes 1, 2 and 3. The synthesis of 2-alkylimidazo[4,5-d]pyridazine was based on a procedure reported by Martin and Castle (7). Treatment of 4,5-diamino-6-pyridazinone (III) with valeric anhydride under reflux gave 2-butylimidazo[4,5-d]pyridazin-4-one (IV) in good yield. The reaction of IV with phosphorus pentasulphide in refluxing pyridine solution gave 2-butylimidazo[4,5-d]pyridazine-4-thione (V; 65%) and dethiation of V with Raney nickel afforded 2-butylimidazo[4,5-d]pyridazine (VI) in 43% yield. Attempted alkylations of VI with methyl 4'-(bromomethyl)biphenyl-2-carboxylate(8)/potassium carbonate under standard conditions gave, as the major product, the undesired isomer (VII; 72%) which was the result of alkylation on the pyridazine nitrogen. The structure of this product was confirmed by ^{13}C nmr [The chemical shift of the C-2 carbon atom (182ppm) is consistent only with structure VII]. This product (VII) was deesterified under standard conditions to give the acid (VIII; 52%). Alkylation of IV gave the desired product (IX; 49%) resulting from alkylation on an imidazo nitrogen atom and the structure of this product was also established by ^{13}C nmr [Coupling from NH to C-4, C-7 and C-7a was proved by deuteration. Therefore NH is present at position 6, which also confirms the tautomeric form shown. C-7a (126ppm) couples to NCH_2, and C-3a (141ppm) couples to C-4H. Additional, long range carbon hydrogen correlation (COLOC) experiments confirmed this assignment]. Hydrolysis of the ester (IX) gave the biphenylcarboxylic acid product (X; 65%). Alkylation of IX with methyl iodide/potassium carbonate gave the expected N-methylation product (XI; 31%) which was hydrolysed to the corresponding acid (XII; 59%). Reaction of IX with phosphorus pentasulphide in refluxing pyridine gave the corresponding thione (XIII; 76%) which was reduced with Raney nickel to give XIV (42%). Hydrolysis of XIV gave the required product (XV; 50%). IV was alkylated with 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole (8) to give XVI (52%) which was then de-tritylated (MeOH/c.HCl) to give the tetrazole (XVII; 53%).

The 2-butylimidazo[4,5-d]pyridazo-4,7-dione derivative (XXIII) was prepared as shown in Scheme 2. 2-Butyl-4,5-dicyanoimidazole (XVIII) was prepared as described by Carini *et al* (9). Hydrolysis of the nitrile groups gave the dicarboxylic acid (XIX) which was esterified to the diester (XX; 32% from XVIII). Alkylation of XX with 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole gave the intermediate (XXI; 54%). De-tritylation of XXI (MeOH/c.HCl) gave XXII (40%) which was heated under reflux with hydrazine in ethanol to give the final product (XXIII; 55%).



SCHEME 1

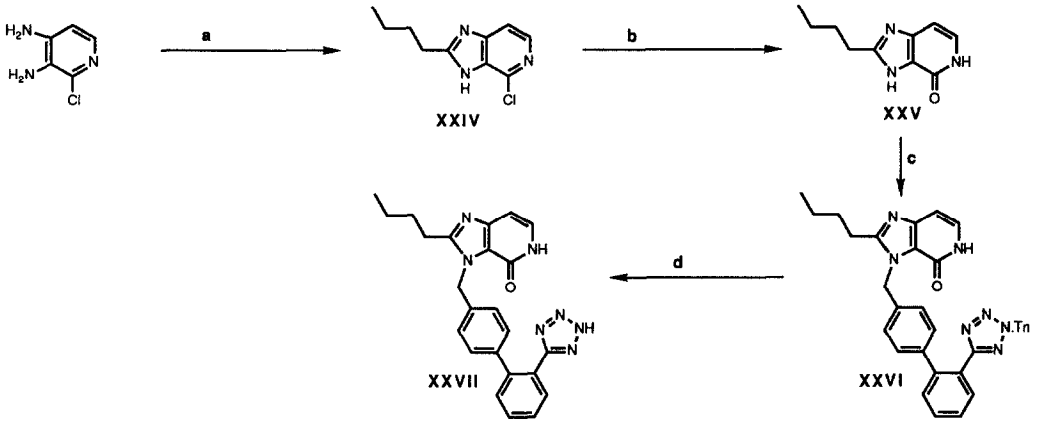
Reagents: (a) valeric anhydride; (b) P_2S_5; (c) Raney nickel; (d) K_2CO_3/methyl 4'-(bromomethyl)biphenyl-2-carboxylate; (e) NaOH/MeOH; (f) K_2CO_3/MeI; (g) K_2CO_3/5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole; (h) MeOH/c.HCl.



SCHEME 2

Reagents: (a) 6N HCl; (b) EtOH/HCl; (c) K_2CO_3/5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole; (d) MeOH/HCl; (e) NH_2NH_2/EtOH.

The imidazopyridone (XXVII) was synthesised by the route shown in Scheme 3. 2-Chloro-3,4-diaminopyridine (10) reacted with valeric anhydride under reflux to give imidazopyridine (XXIV; 67%) which was hydrolysed by formic acid under reflux to give the imidazopyridone (XXV; 89%). Alkylation of XXV with 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole gave XXVI (25%) which was de-tritylated to give the product (XXVII; 50%). The structure of XXVI was assigned as shown because the ^{13}C spectrum was consistent with both the calculated spectrum based on reference compounds (11), and with the spectrum of IX; also, irradiation of the benzylic methylene gave no NOE effect to H-4 or H-5 of the imidazopyridone.



SCHEME 3

Reagents: (a) valeric anhydride; (b) HCO_2H; (c) K2CO3/5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2-H-tetrazole; (d) EtOH/c.HCl.

Biological Results

Evaluation of in vitro AII receptor binding was undertaken using a conventional ligand binding assay based on the displacement of monoiodinated angiotensin II from a washed membrane fraction prepared from guinea-pig adrenal glands. This assay has been described in detail elsewhere (4). ED_{50} Values were obtained by measuring inhibition of the pressor response induced by infusion of AII in male Alderley Park Wistar rats after a single intravenous dose of the compounds, as described elsewhere (4).

Results are shown in Table 1. The results for DuP 753 and L-158809 were obtained in the tests described above and are given in order to provide direct comparison with those of the compounds reported here.

Discussion

As can be seen from the results in Table 1, XVII and XXIII are potent AII antagonists in vitro having IC_{50} values of 22nM and 17nM respectively. In vivo results show that XXIII is about ten times more potent than XVII having ED_{50} values of 0.04mg/kg and 0.6mg/kg respectively. It is interesting to note that X, having a carboxylic acid in place of the tetrazole moiety in XVII, is about 100 times less potent in the in vitro assay (IC_{50} 2.13μM). Also structural variations which involve removal of the 7-carbonyl function (XV) or methylation of N-6 (XII) result in significant loss of in vitro activity relative to X. The related imidazopyridone (XXVII) shows that the presence of the nitrogen atom at the 5-position does not appear to be essential for potent activity because this compound shows potent in vitro (IC_{50} 16nM) and in vivo (ED_{50} 0.35mg/kg) activity.

It is possible that the carbonyl group at the 7-position of the imidazopyridazinedione (XXIII) and the imidazopyridone (XXVII) is performing a similar function to the nitrogen atom at this position in the imidazopyridine (L-158809). However, it should be noted that the introduction of the methyl group at the 6-position produces the opposite effect in the imidazopyridazinedione series (XII) to the effect in the imidazopyridine series (5).

The significant biological advantage of some of these compounds over the corresponding benzimidazole (II; 3) can be seen in Table 1, by comparing entries XVII, XXIII and XXVII with II. In particular, it can be seen that, in vivo, XXIII is more than 100x as potent as the corresponding benzimidazole.

The product arising from the alkylation on pyridazine nitrogen (VIII) showed only very weak activity in the binding assay.

Because of the encouraging activity shown in these early tests, XXIII was chosen for further biological evaluation. However, XXIII showed very poor activity when dosed orally to rats. Further experiments were undertaken aimed at determining whether this poor oral activity was due to poor absorption or due to rapid clearance or metabolism. This involved the modification of the intravenous dosing regime in order to follow the time course of activity after an intravenous dose. These experiments showed that an intravenous dose of XXIII indeed had very short duration of activity suggesting that rapid systemic clearance was occurring.

Table 1

Compound	In vitro (IC_{50} μM)	In vivo (ED_{50} mg/kg, i.v. route)
VIII	ca.100	NT
X	2.13	6.7
XII	ca.10	47
XV	ca.10	5.2
XVII	0.022	0.62
XXII	0.255	NT
XXIII	0.017	0.04
XXVII	0.016	0.35
I	2.3	13.8
II	0.096	5.2
DuP 753	0.018	0.65
L-158809	0.006	0.22

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