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THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF TETRAHYDROQUINOLINE ANGIOTENSIN II ANTAGONISTS CONTAINING A SUBSTITUTED BIPHENYLTETRAZOLE GROUP

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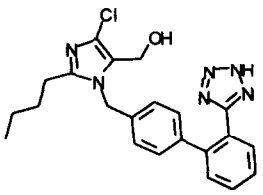
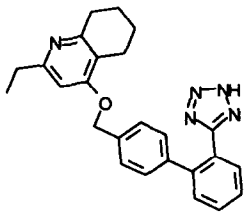
Abstract: The synthesis of analogues of tetrahydroquinoline angiotensin II antagonist, ZENECA ZD6888, bearing substituents on the biphenyl ring system is reported. Several of these compounds show comparable or superior activity to ZD6888 in an *in vitro* binding assay and in inhibition of the AII-induced pressor response in normotensive rats.

Following the clinical success of angiotensin converting enzyme (ACE) inhibitors[1], the search for agents that block the renin angiotensin system (RAS) at alternative points in the proteolytic cascade or at the angiotensin II (AII) receptor has been an area of intense research. The disclosure of potent non-peptide AII receptor antagonists by the Du Pont group[2], leading to the discovery of DuP 753, represented a significant advance and provided the stimulus for many groups to focus research on this point of intervention in the RAS[3]. The vast majority of publications arising from this work to date, report on AII antagonists where the same biphenyl tetrazole portion is retained but is linked to alternative heterocyclic rings[3]. A few examples of related AII antagonists that contain heterocyclic biaryl groups have been reported[4] and only a very limited exploration of the effect of substituents on the biphenyl group has been published[5]. One of the reasons why modification of the biphenyl tetrazole group has attracted less attention is probably the synthetic challenges faced in the construction of complex biphenyls. In the work described here, we have investigated a short series of AII antagonists that contain substituted derivatives of the biphenyl tetrazole group. Thus, we report the synthesis and biological properties of a series of analogues of the 2-ethyl tetrahydroquinoline derivative, ZD6888[6], which bear an additional substituent on the biphenyl group.



DuP 753

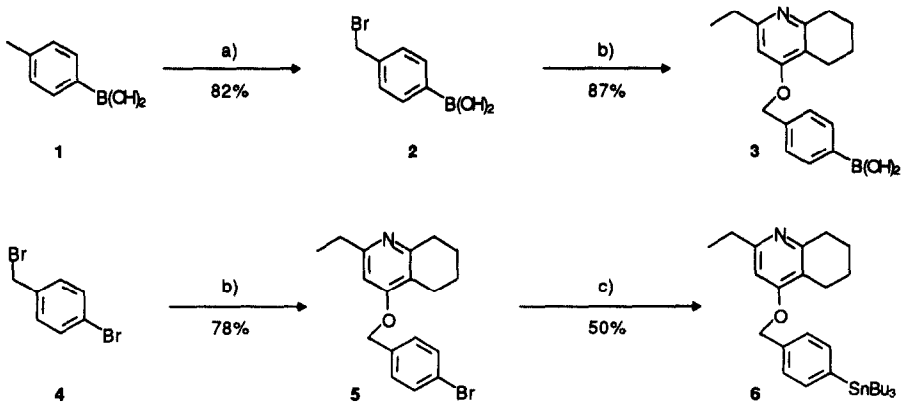


ZD6888

Finding suitable methods for the synthesis of the appropriate biphenyls was a key challenge, and in this work we have developed synthetic routes for the easy introduction of substituents into either of the phenyl rings in the biphenyl group of ZD6888. For the introduction of substituents into the terminal, tetrazole-bearing ring a

modification of the route used to prepare the unsubstituted biphenyl tetrazole was used. In this route a tolyl metal species was coupled with *o*-bromobenzonitrile under palladium catalysis. In order to simplify the synthesis of analogues, a tolyl metal which had already been coupled to the tetrahydroquinoline was seen as a key intermediate in a more convergent synthesis. This strategy also has the advantage that alkyl substituents could be introduced to the tetrazole-bearing ring without being subjected to a potentially unselective radical bromination reaction. Furthermore, as the tetrazole ring would be formed in the last step this avoids the need for the introduction and subsequent removal of a protecting group for the tetrazole. Two such tolyl metal compounds linked to a 2-ethyl tetrahydroquinoline via a methyleneoxy link were prepared, the boronic acid **3** and the tributylstannane **6** (Scheme 1).

Scheme 1

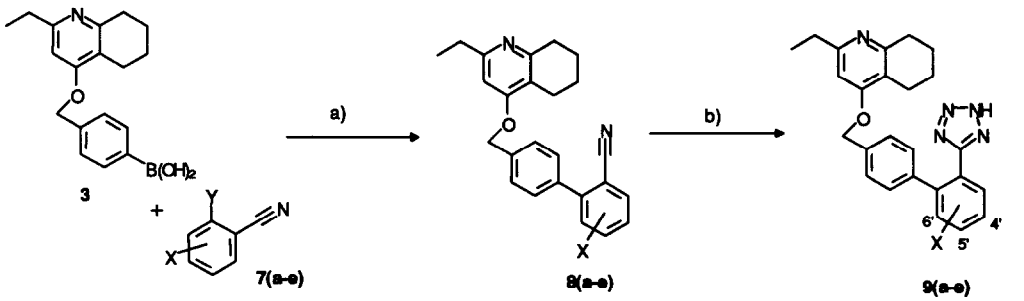


a) Br_2, CCl_4, light b) 2-Ethyl-5,6,7,8-tetrahydro-4(1*H*)-quinolone, NaH, DMF c) Bu_6Sn_2, $Pd(PPh_3)_4$, PhMe

The boronic acid intermediate **3** was prepared by O-alkylation of 2-ethyl-5,6,7,8-tetrahydro-4(1*H*)-quinolone with the bromomethyl compound **2** under standard conditions. The bromomethyl reagent **2** was prepared from *p*-tolylboronic acid following literature conditions[7]. The preparation of stannane **6** was achieved by palladium-catalysed stannylation of the bromoaryl **5**[8]. With routes to these two key intermediates in hand, we investigated their coupling reactions with *o*-bromobenzonitrile. These reactions indicated that the boronic acid **3** was the preferred reagent as it gave a cleaner, faster, higher yielding reaction than its tin counterpart. Thus, boronic acid (**3**) was selected as the reagent for further synthesis.

The conversion of **3** to the final products **9(a-e)** proceeded straightforwardly (Scheme 2). The electrophilic partner in the coupling reaction were either 2-bromobenzonitrile derivatives, prepared from the available 2-bromobenzoic acids, or 2-cyanobenzene triflate derivatives prepared from the corresponding phenol by electrophilic cyanation[9], followed by reaction with triflic anhydride. The palladium-coupling reactions of **3** proceeded in moderate to good yield (46-59%) using a modification of literature conditions[10], ($Pd(PPh_3)_4$, toluene, ethanol, 100 °C, 18 hours). The introduction of ethanol as an additional co-solvent greatly increased the dissolution of the boronic acid starting material and the yield of coupled product. Conversion of the nitriles (**8**) to the tetrazoles (**9**) was achieved by treatment with excess tributyltin azide in xylene[2a]. An alternative

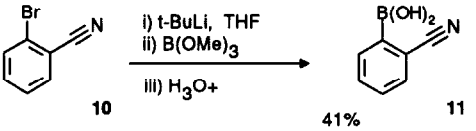
Scheme 2



a) $Pd(PPh_3)_4$, PhMe, EtOH, Na_2CO_3 (aq) b) i) Bu_3SnN_3, xylene, 140°C ii) HCl, MeOH

Analog	Y	X	Yield step a (%)	Yield step b (%)
9a	Br	4'-OMe	58	34
9b	Br	4'-Me	59	62
9c	OTf	4'-Cl	54	52
9d	OTf	5'-OMe	46	57
9e	OTf	6'-Me	49	69

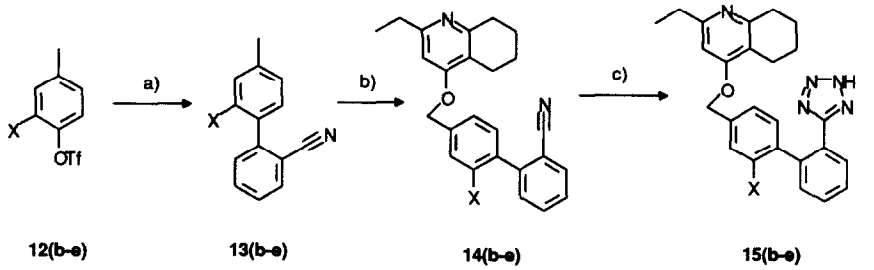
modification to the original route was developed for the introduction of substituents into the linking phenylene ring. The key limitation of the established route was the restriction that any substituent in the linking ring would need to tolerate the conditions used to prepare the aryl metal bond and indeed that the resulting aryl metal would be both suitably stable and be appropriately reactive to take part in the biaryl coupling reaction. These considerations led us to investigate a complementary synthetic strategy where the electrophilic and organometallic portions in the key coupling reaction were interchanged. Thus, it was found that metallation of *o*-bromobenzonitrile (**10**) with *t*-butyllithium at -78 °C in THF proceeded to give the relatively unstable organolithium. Reaction with tributyltin chloride did not proceed satisfactorily and transmetallation with zinc chloride followed by attempted Pd-catalysed coupling resulted in very poor and variable yields of coupled products. However, reaction with trimethyl borate proceeded in moderate yield on a reasonable scale (25 mmole) to give the boronic acid derivative (**11**).



Initial reaction of the boronic acid (**11**), under the two phase conditions employed in the earlier synthesis, resulted in a moderate yield of a single coupled biphenyl product. However, the nitrile group was hydrolysed to the amide in the presence of aqueous sodium carbonate. The hydrolysis presumably occurs prior to the coupling reaction, as this hydrolysis was not seen in the biphenyls prepared from a tolylboronic acid derivative, and probably occurs due to partitioning of the boronate anion into the aqueous carbonate solution. Alternative conditions, where the aqueous base was replaced by a tertiary amine base in a non-aqueous solvent, were tried[11]. Thus, the use of triethylamine in DMF was found to give moderate to good yields of the desired biaryl nitrile products (Scheme 3). The electrophilic partners chosen for the Pd-catalysed

reaction were aryl triflates (**12**), which were readily prepared from the available substituted *p*-cresols. The resulting biphenyl products were brominated and allowed to react with the tetrahydroquinolone under standard conditions. As in the previous series, the nitrile was converted to a tetrazole ring by reaction with the tin azide reagent under the reaction conditions established earlier (Scheme 3). Finally, the methyl ester (**15e**) was hydrolysed with aqueous sodium hydroxide to give the corresponding carboxylic acid (**15f**).

Scheme 3

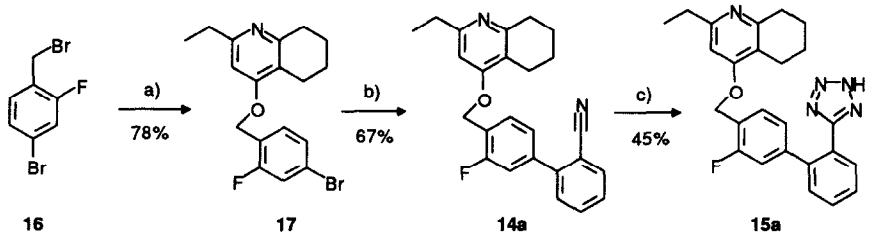


a) **11**, $Pd(PPh_3)_4$, Et_3N, DMF b) i) NBS, AIBN, CCl_4 ii) 2-Ethyl-5,6,7,8-tetrahydro-4(1*H*)-quinolone, NaH, DMF c) i) Bu_3SnN_3, xylene, 140°C ii) HCl, MeOH

Analog	X	Yield step a (%)	Yield step b (%)	Yield step c (%)
15b	Cl	55	38	59
15c	OMe	96	32	39
15d	COMe	51	30	32
15e	COOMe	49	53	29

A more convergent strategy was adopted for the synthesis of the 3-fluoro derivative (**15a**) (Scheme 4). This route utilised the aryl bromide (**17**) and followed an analogous route to that used earlier in Scheme 2, but where the organometal and electrophilic reaction centres have been interchanged.

Scheme 4



a) 2-Ethyl-5,6,7,8-tetrahydro-4(1*H*)-quinolone, NaH, DMF b) **11**, $Pd(PPh_3)_4$, Et_3N, DMF c) i) Bu_3SnN_3, xylene, 140°C ii) HCl, MeOH

Compounds **9(a-e)** and **15(a-f)** were evaluated as AII antagonists *in vitro* in a radioligand binding assay using a guinea-pig adrenal membrane preparation, which displays only the AT_1 receptor subtype[12]. The compounds were tested *in vivo* by determining their ED_{50} values for inhibition of the pressor response induced by infusion of AII in conscious normotensive rats[12]. The IC_{50} and ED_{50} values for DuP 753 and ZD6888 in these tests are included in Table 1 for comparision.

As the results in Table 1 show, substitution in either ring is at least moderately tolerated in that some activity is retained for all compounds. Thus, it would seem that there is reasonable spacial flexiblity in the binding of the biphenyl portion of these antagonists to the AII receptor. However, as all 4'- and 5'-substitutions made in the terminal ring (**9a-d**) cause a significant fall in activity *in vitro*, it is possible that substitution in these positions does result in unfavourable steric interactions with the AII receptor. The good activity of those compounds bearing substituents *ortho* to the linking bond between the two rings of the biphenyl group (**9e** and

Table 1

No	R	IC_{50} μM[a]	i.v. ED_{50}, mg/kg[b]
DuP 753		0.018	0.65
ZD6888	H	0.005	0.39
9a	4'-OMe	0.14	NT[c]
9b	4'-Me	0.054	NT[c]
9c	4'-Cl	0.093	NT[c]
9d	5'-OMe	0.067	NT[c]
9e	6'-Me	0.029	0.48
15a	2-F	0.009	0.22
15b	3-Cl	0.007	0.52
15c	3-OMe	0.008	0.39
15d	3-COMe	0.006	0.10
15e	3-COOMe	0.020	0.11
15f	3-COOH	0.027	0.24

[a]IC_{50} for inhibiton of specific binding of [^{125}I]AII to a guinea pig adrenal membrane preparation (n = 1-3)

[b]ED_{50} following iv administration to conscious rats for inhibition of AII-induced pressor response (n = 3-10)

[c]Not tested

15b-f) confirms that these rings must be effectively orthogonal when bound to the receptor. Introduction of the sterically undemanding fluoro substituent in the 2-position (compound **15a**) had little effect on activity, but results for a closely related series (data not shown) indicated that larger substituents in the 2-position of the linking phenylene ring cause a large fall in activity. Large substituents in the 2-position could be expected to unfavourably effect the conformation about the benzylic methylene group. The 3-substitutions made in the linking ring (**15b-f**) are very well tolerated, having no detrimental effect on activity *in vitro* or *in vivo*. Indeed, the 3-carbonyl compounds (**15e** and **15f**) are more potent than the parent ZD6888 in the acute i.v. *in vivo* assay.

However, these and the other potent compounds described here show no advantage over ZD6888 in an orally-dosed AII-infused, conscious, normotensive rat model.

In conclusion, general and convergent synthetic routes have been developed to prepare variously substituted biphenyl derivatives of ZD6888. Moderate to good AII antagonist activity is retained by all such compounds prepared. Those compounds bearing substituents in the 3-position show comparable or better activity than the parent ZD6888 in an acute i.v. dosed rat model.

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