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4,5-DIHYDRO-4-OXO-3*H*-IMIDAZO[4,5-c]PYRIDINES: POTENT ARYLACETIC ACID-DERIVED AT_1 ANTAGONISTS WITH IMPROVED AFFINITY FOR THE AT_2 RECEPTOR

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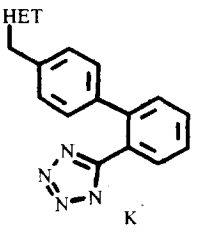
Abstract. The replacement of dimethylacetamide with arylacetic acid esters and acetamides at the imidazo[4,5-c]pyridine 5-position of EMD 66684 **2** imparts affinity for the AT_2 receptor. The highest affinity was found with the phenylacetic acid isopropylester moiety, which led to compound **7c** with an IC_{50} value of 32 nM (AT_2) and an AT_2/AT_1 ratio of 5

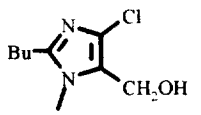
Introduction:

In recent years the development of angiotensin (ang) II receptor antagonists has become the main pharmacological approach to the regulation of the renin-angiotensin system. Losartan **1**, the most advanced ang II antagonist for the treatment of hypertension, and many others mediate their effects by blocking the ang II AT_1 receptor subtype.[1] In our group, 1,2-dihydropyridin-2-ones,[2] (6-oxo-3-pyrazinyl)-benzimidazoles,[3] 4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-ones,[4] 7-ethyl-1,2-dihydroquinolin-2-ones[5] and 1,2,3,4-tetrahydropyrimidin-2,4-diones[6] have been studied as selective AT_1 antagonists. With the discovery of the non-peptide ligand PD 123,177 the AT_2 receptor subtype has been identified in various tissues.[7] The physiological role of this receptor has not yet been clearly defined, but recent studies have indicated that it may play a role in wound healing, cardiac remodelling and cerebral blood flow.[8] Besides increased activation of the AT_2 receptor, associated with losartan-induced hyperreninaemia,[9] could have undesirable effects. Thus, it seemed reasonable to develop compounds which would bind to both ang II subtypes. Recently some compounds with affinity for both the AT_1 and AT_2 receptors have been described.[10] We previously reported the identification of EMD 66684 **2** as a potent antagonist of the AT_1 receptor.[4] During further studies of the SAR of **2** we discovered structural modifications that enhanced the binding affinity of the imidazo[4,5-c]pyridine class of antagonists to the AT_2 receptor. Our main objective was to discover ang II antagonists with AT_1 potency < 10 nM and an AT_2/AT_1 ratio ~1. In this article, we report the synthesis of arylacetic acid derivatives as potent AT_1 receptor antagonists with improved affinity for the AT_2 receptor.

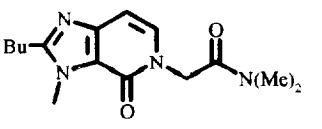


HET =

1 losartan



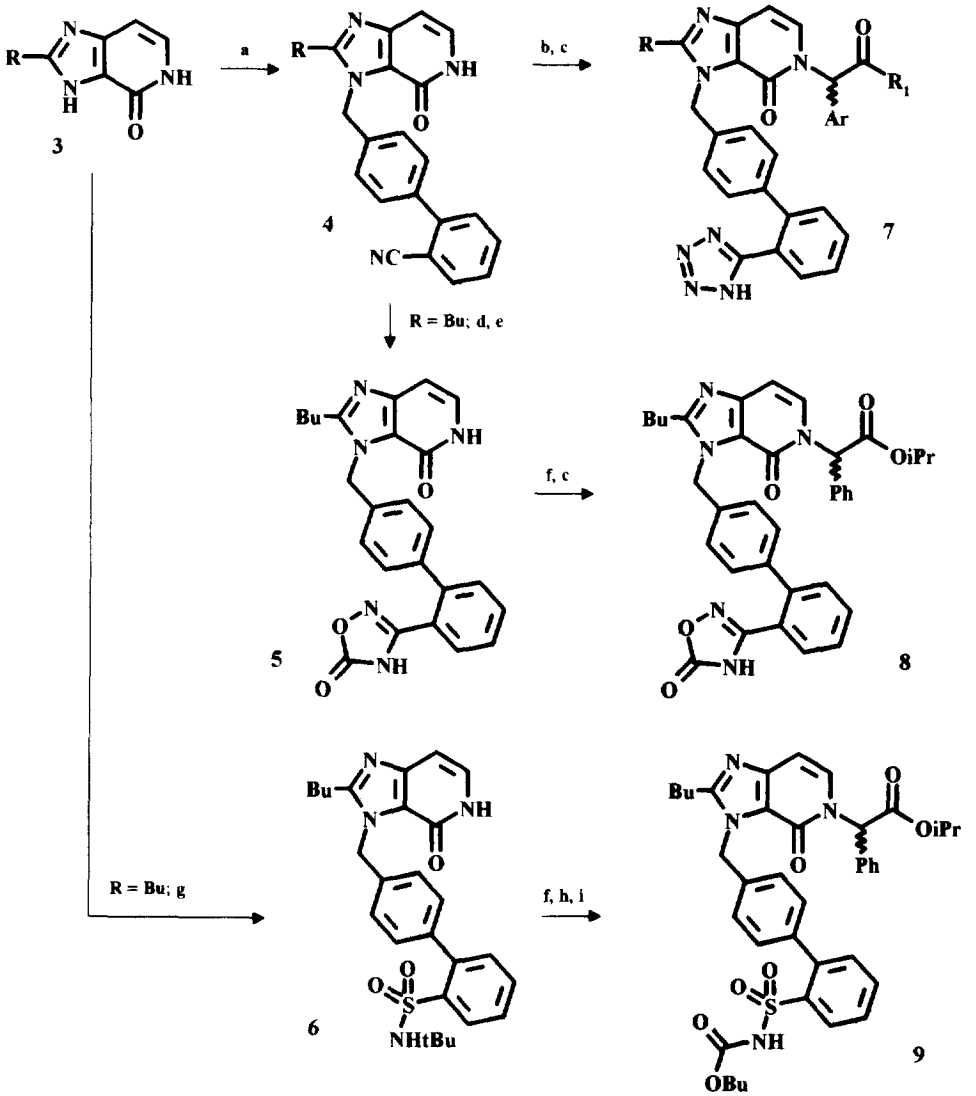
2 EMD 66684



Chemistry:

The synthesis of the various imidazo[4,5-c]pyridone-based antagonists bearing an arylacetic acid-derived moiety at the 5-position of the heterocycle is outlined in Scheme I. The parent biphenyl derivatives **4**, **5** and **6** were prepared using 2-alkyl imidazo[4,5-c]pyridones **3**[4] as starting materials.

Scheme I



Reagents: a. K_2CO_3, 4'-(bromomethyl)biphenyl-2-carbonitrile, DMF, rt; b. KO*t*Bu, $ArCHBrCOR_1$, DMF, rt; c. Me_3SnN_3, toluene, reflux; then silica gel chromatography; d. $NH_2OH{\cdot}HCl$, NEt_3, DMSO, 75°C; e. CDI, THF, reflux; f. KO*t*Bu, $PhCHBrCO_2iPr$, DMF, rt; g. K_2CO_3, 4-bromomethyl-2'-*tert*-butylamino-sulphonyl[1,1']biphenyl, DMF, rt; h. TFA, rt; i. $ClCO_2nBu$, DMAP, pyridine, rt.

For the synthesis of biphenyltetrazole compounds **7**, imidazo[4,5-c]pyridones **3** were treated with potassium carbonate and 4'-(bromomethyl)biphenyl-2-carbonitrile[11] leading to the desired 3*H*-coupled products **4** in moderate yields. Reaction of the anions of **4** with α-bromoarylacetates or amides[12] afforded the N-5 alkylated intermediates which were transformed into the final tetrazoles **7** using trimethyltin azide in refluxing toluene and subsequent silica gel chromatography of the crude tin adducts.

In addition to the variation of the N-5 position of the imidazo[4,5-c]pyridine heterocycle, we investigated various modifications of the tetrazole moiety, which led to non-tetrazole ang II antagonists.

The 1,2,4-oxadiazol-5-one group as a bioisoster of the tetrazole moiety[13] was introduced starting with biphenyl nitrile **4** (R = Bu). Addition of hydroxylamine to nitrile **4** afforded the corresponding amidoxime, which was immediately cyclised with 1,1'-carbonyldiimidazole to give oxadiazole **5**. The dianion of **5** was formed with two equivalents of potassium *tert*-butoxide and selectively alkylated at the N-5 position with isopropyl α-bromophenylacetate to provide the desired product **8** in modest yield.

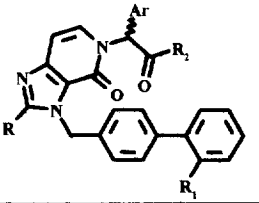
Acylsulphonamides are well-known as bioisosters of the tetrazole unit in ang II receptor antagonists.[14] Again, imidazo[4,5-c]pyridine **3** (R = Bu) served as the starting material for the synthesis of acylsulphonamide **9**. The *tert*-butyl protected sulphonamide **6** was prepared in reasonable yield from **3** on treatment with potassium carbonate and 4-bromomethyl-2'-*tert*-butylamino-sulphonyl[1,1']biphenyl in dimethylformamide. Replacement of the N-5 hydrogen with isopropyl phenylacetate was accomplished by reacting intermediate **6** with potassium *tert*-butoxide and the corresponding electrophile. Removal of the N-*tert*-butyl group in the subsequent product with trifluoroacetic acid and acylation of the resultant primary sulphonamide with butyl chloroformate furnished the final compound **9** in good overall yield.

Biological results and discussion:

The biological data of the target compounds are outlined in Table 1. These compounds were tested for their *in vitro* binding affinity to angiotensin II AT_1 receptors in a rat adrenal cortex preparation[15] or AT_2 receptors in rat adrenal medulla.[16] The results for losartan **1** and EMD 66684 **2** are given in order to provide direct comparison with those of the compounds reported here.

The introduction of a methyl phenylacetate in the N-5 position of the 4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one resulted in the discovery of the first compound in this series (**7a**) with a modest affinity for the AT_2 receptor. However, the ester functionality is required for AT_2 activity since the corresponding acid (**7b**) showed markedly less AT_2 affinity. At the outset of our further studies, we introduced more lipophilic alkoxy substituents (R_2 in Table I) into the parent compound **7a**. These modifications led to ester derivatives (**7c-7f**) with increased affinities for the AT_2 receptor from which the isopropyl acetate **7c** showed an 8-fold improvement compared with the methyl acetate **7a**. Substitution of the various positions of the phenyl ring (Ar in Table I) in the optimised isopropyl ester **7c** had a negative effect on the AT_2 - as well as the AT_1 binding (**7k-7m**). Other aryl and heteroaryl substituents not shown in Table I had a similar effect on binding behaviour. Keeping the isopropyl phenylacetate moiety constant, the effect of the R substituent was also examined in this series. Comparison of compounds **7g**, **7c**, **7h** and **7i** differing in the lengths of the aliphatic sidechains at the C-2 position indicated that alkyl groups shorter than butyl enhanced AT_1 affinity while a maximum of AT_2 affinity was observed with the butyl chain. Replacement of the alkoxy substituents by various alkyl groups (R_2 in Table I)

Table 1: *In Vitro* Binding Data of 3-(4-biphenylylmethyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-c]pyridines



Compound	R	R_1	R_2	Ar	Binding[AT_1], IC_{50}(nM)[15]	Binding[AT_2], IC_{50}(nM)[16]	AT_2/AT_1
7a	Bu	CN_4H [a]	OMe	Ph	4.0	250	63
7b	Bu	CN_4H	OH	Ph	28	17,000	607
7c	Bu	CN_4H	O*i*Pr	Ph	6.5	32	5
7d	Bu	CN_4H	OcycloPn [b]	Ph	8.8	120	14
7e	Bu	CN_4H	OPn	Ph	14	150	11
7f	Bu	CN_4H	OCH_2*i*Pr	Ph	6.5	95	15
7g	Pn	CN_4H	O*i*Pr	Ph	7.1	47	7
7h	Pr	CN_4H	O*i*Pr	Ph	3.1	58	19
7i	Et	CN_4H	O*i*Pr	Ph	3.1	150	48
7k	Bu	CN_4H	O*i*Pr	Ph(o-Cl)	11	570	52
7l	Bu	CN_4H	O*i*Pr	Ph(m-Cl)	11	360	33
7m	Bu	CN_4H	O*i*Pr	Ph(p-Cl)	9	165	18
7n	Bu	CN_4H	Me	Ph	4.1	320	78
7o	Bu	CN_4H	Ph	Ph	8	330	41
7p	Bu	CN_4H	tBu	Ph	6.6	300	46
7q	Bu	CN_4H	NH2	Ph	3	950	317
7r	Bu	CN_4H	NMe2	Ph	3.6	125	35
7s	Bu	CN_4H	NEt2	Ph	4.2	58	14
7t	Bu	CN_4H	NHiPr	Ph	5.6	300	54
7u	Bu	CN_4H	morpholinyl	Ph	2.9	70	24
7v	Bu	CN_4H	pyrrolidinyl	Ph	3.7	100	27
7w	Bu	CN_4H	piperidinyl	Ph	4.4	220	50
7x	Bu	CN_4H	NMePh	Ph	19	150	8
8	Bu	$C_2N_2O_2H$ [c]	O*i*Pr	Ph	11	140	13
9	Bu	SO_2NHCO_2Bu	O*i*Pr	Ph	21	430	20
1	---	---	---	---	8.2	>10,000	>1220
2	---	---	---	---	0.7	>10,000	>14286

[a] CN_4H = 1*H*-tetrazole-5-yl; [b] Pn =pentyl; [c] $C_2N_2O_2H$ = 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-yl

resulted in weaker AT_2 binding derivatives (**7n-7p**). In this case a ten-fold loss of AT_2 binding affinity was observed compared with **7c**. In the search for more stable ester derivatives, phenyl acetamides were introduced in the N-5 position (R_2 in Table I). A variety of amides were synthesised starting from the unsubstituted compound **7q** to the more sterically demanded methylphenyl analogue **7x**. In general, these amides had a higher potency for the AT_1 receptor except for the bulky methylphenyl analogue **7x**. Hydrogen atoms at the amide position were unfavourable for the AT_2 binding. This was observed with **7q** and to some extent with **7t**. The diethylacetamide substituent, employed successfully in the AT_1-selective 4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one antagonist series,[4] was similar in the AT_2 binding affinity but showed a two-fold increase in AT_1 potency relative to compound **7c**. This is also true for the morpholino derivative **7u**. Recognizing that the isopropyl phenylacetate moiety had a remarkable effect on the AT_2 affinity, the bioisosteric oxadiazole **8** and acylsulphonamide **9** were examined as tetrazole replacements in **7c** (R_1 in Table I). Both compounds showed a modest decrease in AT_2 affinity together with a small loss in AT_1 potency.

In conclusion, it has been shown that angiotensin II antagonists with AT_1 potencies that are equal or superior to losartan and with significant affinity for the AT_2 site can be derived from the 4,5-dihydro-3*H*-imidazo[4,5-c]pyridin-4-one nucleus. Optimum affinity was observed with isopropyl phenylacetate at N-5 and a butyl chain at C-2. This compound, **7c**, exibited an AT_2/AT_1 ratio of 5 along with a nanomolar affinity for the AT_1 receptor. The AT_2 value of **7c** (32 nM) is in the range of the selective AT_2 compound PD 123,177 (30 nM).

The most potent AT_2 binding compound **7c** was tested for functional AT_1 antagonism *in vitro* in isolated rabbit aortic rings precontracted by ang II[1] and evaluated *in vivo* for inhibition of ang II induced increase in diastolic blood pressure in pithed rats.[17] The functional potency of **7c** is in the nanomolar range (IC_{50} = 2.0 nM) and the *in vivo* inhibition in the pithed rat modell is excellent (95 % at 3mg/kg, 2h).

Orientating studies of the pharmacokinetics were carried out in order to examine the stability of the isopropyl ester **7c** *in vivo*. Preliminary *in vitro* studies with **7c** in rat plasma at 37°C showed that only 39% of the parent compound could be detected after 4 hours by means of HPLC. After a single *i.v.* and *p.o.* administration of **7c** (1 mg/kg and 10 mg/kg, respectively) in rats concentrations were determined for **7c** as well as for the corresponding acid **7b** (using an HPLC method). Although the bioavailability of the ester was determined with about 60% the acid **7b** was observed in each plasma sample in substantial amounts. 5 minutes after *i.v.* injection the plasma concentrations of **7c** and **7b** were already similar to each other (measured in ng/ml).

Because of this negative outcome and the need for lower AT_2/AT_1 IC_{50} ratios, other approaches to the incorporation of AT_2 affinity in non-peptide ang II antagonists were pursued.

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