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URACIL-BASED ANGIOTENSIN II RECEPTOR ANTAGONISTS

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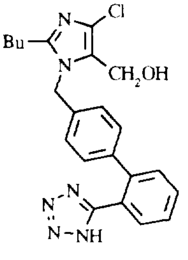
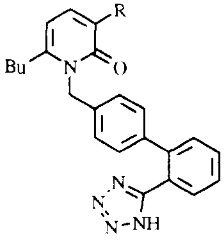
Abstract: 1,2,3,4-Tetrahydro-2,4-pyrimidinedione (uracil) is a valuable nucleus for the construction of potent antagonists of the AT_1 angiotensin II receptor. Various synthetic routes were applied in order to introduce a wide range of different groups at the N^3-nitrogen and to obtain condensed uracil derivatives as well. **12l** with a N,N-dimethylacetamide residue at N^3 was the most potent compound with an IC_{50} of 0.65 nM.

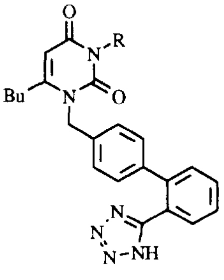
Introduction:

The blockade of the renin-angiotensin system (RAS) has become a major target in the therapy of hypertension.[1] Subsequent to angiotensin converting enzyme (ACE) inhibitors that are well established as antihypertensive drugs,[2] and renin inhibitors[3] to which extensive research has been devoted, angiotensin II receptor antagonists are now in the centre of attention. The lead compound for most of the competitive nonpeptide angiotensin II antagonists that have been found so far is losartan,[4] a potent AT_1-selective receptor antagonist which is being introduced as an antihypertensive drug in several countries.

Various heterocyclic systems have been employed as replacements for the imidazole moiety in losartan. In our group, 4,5-dihydro-3*H*-imidazo[4,5-*c*]pyridin-4-ones,[5] (6-oxo-3-pyridazinyl)-benzimidazoles,[6] 7-ethyl-1,2-dihydro-2-quinolinones[7] and 1,2-dihydro-2-pyridinones[8] (**I**) have been studied. The excellent AII antagonistic properties of the pyridones **I** encouraged us to examine other six-membered heterocycles. The replacement of the substituted double bond in **I** by an isosteric substituted amide bond in order to obtain 1,2,3,4-tetrahydro-1,3-pyrimidinedione (uracil) derivatives (**II**) seemed attractive since it was anticipated that a wide range of different substituents R could easily be introduced at the N^3-nitrogen.


losartan

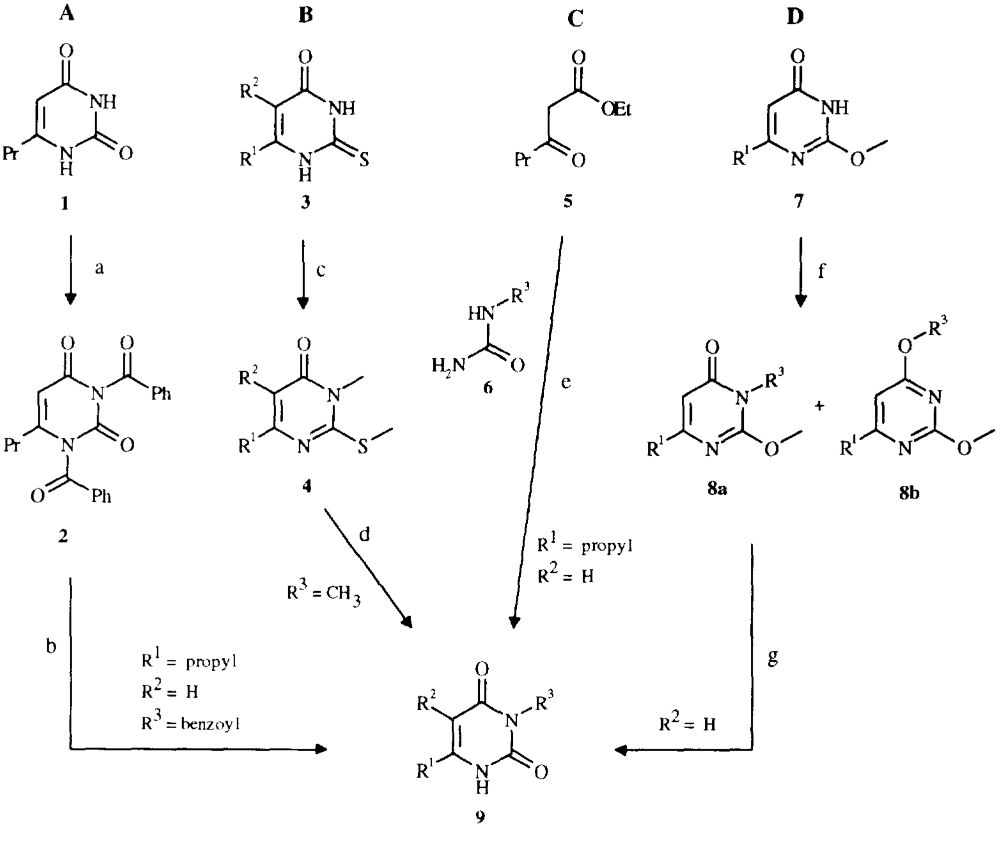

I


II

Synthesis:

The parent uracil derivatives **9** were prepared following well-known synthetic routes (see Scheme 1). For the synthesis of an N^3-benzoyl-protected uracil (route **A**) 6-propyluracil **1**[9] was dibenzoylated and selectively debenzoylated according to Cruickshank et al.[10] For the preparation of various 3-methyluracil derivatives (route **B**) 2-thiouracils **3**[11] were first treated with dimethyl sulphate to give N,S-dimethylated products **4** (contaminated with approx. 15% O,S-dimethylated compounds)[12] which were then hydrolysed.[12] Some 3,6-disubstituted uracil derivatives could be obtained in low yield by condensation of ethyl butyrylacetate **5** with substituted ureas (route **C**).[13] Methoxypyrimidinones **7**[14] were alkylated to yield 1 : 1 mixtures of N- and O-alkylated products **8a** and **8b** (route **D**). After chromatographic isolation the N-alkylated compounds **8a** were hydrolysed to obtain several 3-substituted uracil derivatives **9**.

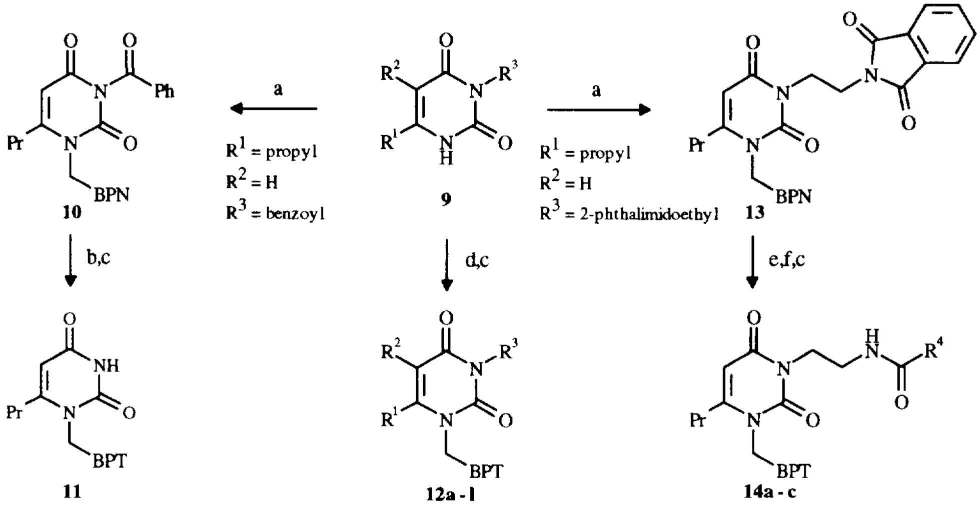
Scheme 1



A: a: 2.2 equivalents PhCOCl, CH_3CN, pyridine, 51%; b: K_2CO_3, dioxane/water, 28%; **B**: c: 2.3 equivalents dimethyl sulphate, NaOH, 45-86%; d: conc. HCl, reflux, 57-80%; **C**: e: 1. 85% phosphoric acid, toluene, Dean-Stark trap; 2. NaOEt, ethanol; 19-26%; **D**: f: dimethylchloroacetamide, NaH, DMF, 46% or f: methyl 2-bromomethylbenzoate, NaOH, CH_2Cl_2, $Bu_4N^+ Br^-$, 81% or f: N-(2-bromoethyl)-phthalimide, Cs_2CO_3, DMF, 40%; chromatographic separation of 1 : 1 mixture of **8a** and **8b**; g: 1N HCl, 44-100%;

All the uracil derivatives **9** that had been prepared by one of the procedures described above could easily be alkylated with 4'-bromomethylbiphenyl-2-carbonitrile either in the presence of caesium carbonate in dimethyl formamide or under phase transfer conditions (Scheme 2). The uracil derivative **11** with no substituent at the N^3-nitrogen was obtained via debenzoylation of **10** and subsequent treatment with trimethyltin azide. Most of the other target compounds **12** were obtained by direct treatment with trimethyltin azide after the alkylation step. The phthalimido derivative **13** was deprotected and the resulting amine acylated to afford several amide and urea derivatives that were converted to the respective tetrazoles **14**.

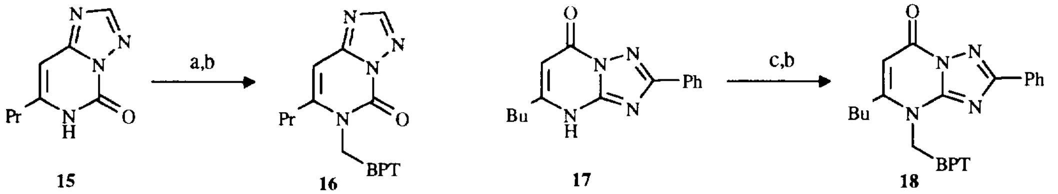
Scheme 2



BPN = 2'-cyano-4-biphenylyl, BPT = 2'-(1H-tetrazol-5-yl)-4-biphenylyl.
a: 4'-bromomethylbiphenyl-2-carbonitrile, Cs_2CO_3, DMF, 90%. b: NH_3, MeOH, 69%. c: 1. Me_3SnN_3, toluene, reflux; 2. silica gel, 14 - 100%. d: 4'-bromomethylbiphenyl-2-carbonitrile, NaOH, CH_2Cl_2, Bu_4N^+ Br^-, 45 - 90%; e: hydrazine, 100%. f: acetic anhydride, toluene, 100% or f: cyclohexylisocyanate, dioxane, 52% or f: diphenylacetic acid, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (DAPECI), N-methylmorpholine, DMF, 63%.

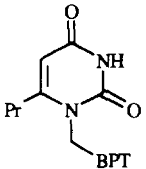
In addition, two pyrimidinone derivatives with annellated triazole rings were prepared (Scheme 3). The parent compounds **15**[15] and **17**[16] were alkylated using standard procedures and converted to the tetrazoles **16** and **18**.

Scheme 3



a: 4'-bromomethylbiphenyl-2-carbonitrile, Cs_2CO_3, DMF, 43%. b: Me_3SnN_3, toluene, reflux, followed by silica gel, 15 - 55%. c: 4'-bromomethylbiphenyl-2-carbonitrile, KO^tBu, DMF, 63%.

Table 1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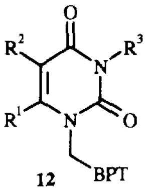
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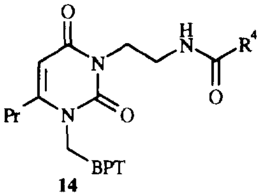
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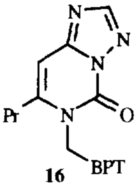
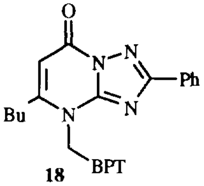

16


18

Compound	R^1	R^2	R^3	R^4	parent uracil synthesised via	IC$_{50}$/M$^{a)}$	IC$_{50}$/M$^{b)}$
11	-	-	-	-	route **A**	$1.0 \cdot 10^{-7}$	$4.3 \cdot 10^{-9}$
12a	ethyl	H	methyl	-	route **B**	$1.0 \cdot 10^{-6}$	
12b	cyclopropyl	H	methyl	-	route **B**	$2.4 \cdot 10^{-6}$	
12c	propyl	H	methyl	-	route **B**	$5.5 \cdot 10^{-8}$	$1.7 \cdot 10^{-8}$
12d	butyl	H	methyl	-	route **B**	$4.4 \cdot 10^{-8}$	$4.5 \cdot 10^{-9}$
12e	propyl	methyl	methyl	-	route **B**	$6.6 \cdot 10^{-6}$	
12f	propyl	H	butyl	-	route **C**	$1.6 \cdot 10^{-8}$	
12g	propyl	H	allyl	-	route **C**	$3.4 \cdot 10^{-8}$	$3.3 \cdot 10^{-9}$
12h	propyl	H	benzyl	-	route **C**	$2.5 \cdot 10^{-8}$	
12i	propyl	H	2-(methoxy-carbonyl)-benzyl	-	route **D**	$2.0 \cdot 10^{-8}$	$2.3 \cdot 10^{-9}$
12j	butyl	H	2-(methoxy-carbonyl)-benzyl	-	route **D**	$2.7 \cdot 10^{-8}$	$2.4 \cdot 10^{-9}$
12k	propyl	H	2-phthalimidoethyl	-	route **D**		$4.4 \cdot 10^{-9}$
12l	propyl	H	$CH_2CON(CH_3)_2$	-	route **D**	$9.3 \cdot 10^{-9}$	$6.5 \cdot 10^{-10}$
14a	-	-	-	methyl	route **D**	$4.0 \cdot 10^{-8}$	$3.4 \cdot 10^{-9}$
14b	-	-	-	cyclohexyl-amino	route **D**	$2.3 \cdot 10^{-8}$	$1.4 \cdot 10^{-9}$
14c	-	-	-	diphenyl-methyl	route **D**		$1.4 \cdot 10^{-8}$
16	-	-	-	-	ref. 15	$6.2 \cdot 10^{-8}$	$6.2 \cdot 10^{-9}$
18	-	-	-	-	ref. 16	$5.2 \cdot 10^{-7}$	$8.3 \cdot 10^{-8}$
losartan	-	-	-	-	-	$1.6 \cdot 10^{-7}$	$8.2 \cdot 10^{-9}$

a) binding affinity bovine adrenal cortex;[17] b) binding affinity rat adrenal cortex.[17]

Results and discussion:

The biological data of the target compounds are shown in Table 1. They were tested for their binding affinity to angiotensin II receptors in a bovine and rat adrenal cortex preparation,[17] respectively. The A II receptor binding data of similar uracil derivatives have been reported by Naka and Nishikawa,[18] but the synthetic pathway to these compounds is not described.

First, compound **11** with no substituent in position 3 of the uracil nucleus showed only modest binding activity in the bovine adrenal cortex assay, but surprisingly bound with nanomolar activity to the rat adrenal cortex preparation. Next, the most suitable residues R^1 and R^2 were sought among the compounds **12** with R^3 = methyl. In marked contrast to findings with five-membered[4] and condensed five-six-membered heterocycles,[5,19] an ethyl group in the 6-position (**12a**) was detrimental to activity.[20] Likewise, **12b** with a cyclopropyl group that imparts high activity to condensed five-six-membered heterocycles[5,6,19b] was only weakly active. Compounds **12c** and **12d** with butyl and propyl groups in the 6-position both showed similar good activity. A methyl group in the 5-position (**12e**) again dramatically weakened the potency.

In the next step, the methyl group at N^3 was replaced by more lipophilic groups such as butyl (**12f**), allyl (**12g**) and benzyl (**12h**). These three compounds showed no improved activity in the bovine adrenal cortex assay compared to the methyl derivative. Then, a 2-methoxycarbonylbenzyl group, that had revealed good activity in the 4,5-dihydro-3*H*-imidazo[4,5-*c*]pyridine-4-one series,[5] was introduced (**12i** and **12j**). Again, the potency was not significantly altered. Nor did a pthalimidoethyl group (**12k**) influence the binding.

But the activity was drastically increased to a subnanomolar IC_{50} value by introducing an N,N-dimethylacetamide substituent (**12l**). The good angiotensin II antagonistic properties of this specific residue had already been shown in our 4,5-dihydro-3*H*-imidazo[4,5-*c*]pyridine-4-one series.[5] Therefore, we prepared other compounds with amide containing substituents. However, acylaminoethyl derivatives **14a-c** could not reach a similar potency.

The two annellated uracil compounds **16** and **18** differed in their binding activity: Whereas **16** showed a nanomolar IC_{50}, **18** was only weakly active, presumably due to the bulky phenyl group attached to the ring system.

In conclusion, it has been shown that angiotensin II antagonists with potencies that are equal or superior to losartan can be derived from the uracil nucleus, and that the N,N-dimethylacetamide residue can significantly enhance the affinity to the AT_1 receptor.

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