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3-SUBSTITUTED 6-BUTYL-1,2-DIHYDROPYRIDIN-2-ONES: A NEW SERIES OF POTENT NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

Mathias Osswald*, Werner W. K. R. Mederski, Michael Schwarz#, Norbert Beier, Ingeborg Lues, Klaus-Otto Minck.

E. Merck, Preclinical Pharmaceutical Research and Central Process Development#, 64271 Darmstadt, Germany

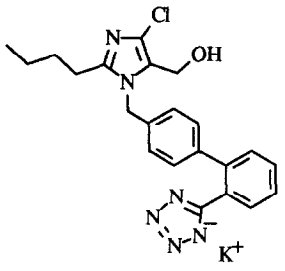
Abstract: The syntheses and biological activities of a series of novel 3-substituted 6-butyl-1,2-dihydro-pyridin-2-ones are presented. A number of these compounds are shown to be potent antagonists of angiotensin II with in vitro potencies in the nanomolar or even subnanomolar range. They also have proven their suitability as effective inhibitors of angiotensin II pressor response in vivo.

Introduction:

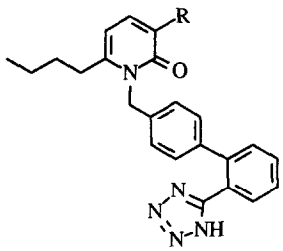
The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure and electrolyte balance.[1] The octapeptide angiotensin II (A II) is the most effective vasoconstricting agent in this pathway[2] and therefore of considerable interest for a potential treatment of hypertension and heart failure. During the past two decades several approaches to intervene in the renin-angiotensin cascade have been attempted leading to the development of inhibitors of angiotensin converting enzyme (ACE)[3] and renin.[4] Whereas the unfavourable pharmacokinetics of current renin inhibitors continue to present a great obstacle, ACE-inhibitors are already well established[5] but will also interfere with levels of other endogenous peptides (eg. bradykinin), which might account for some of their significant side effects.[6] These facts generated strong interest in the development of the potentially more specific angiotensin II receptor antagonists.

Recently researchers at Du Pont described the first potent, nonpeptide angiotensin II receptor antagonist losartan **I**.[7] This compound shows good oral bioavailability and is currently undergoing phase III clinical trials as an antihypertensive agent. In the meantime, several other A II antagonists have been reported,[8] most of them including the same structural key features: a biphenyl moiety bearing an acidic group on the ortho-position of the distal phenyl, a hydrophobic alkyl chain and a polar functional group linked to a heterocyclic ring system.

In the course of our search for novel angiotensin II receptor antagonists, we assumed that replacement of the imidazole ring in losartan with a pyridin-2-one would provide compounds with good biological activity. Herein, we report on the synthesis of a series of 3-substituted pyridin-2-ones **II**, which contain compounds exhibiting in vitro A II antagonist activities in the nanomolar or even subnanomolar range. Recently substituents related to some of those employed here in the 3-position have been introduced in the 6-position of quinazolinones leading to derivatives with excellent potency as well.[9]



I



II

Chemistry:

The synthetic routes used to prepare representative compounds of this class of angiotensin II antagonists are illustrated in Scheme 1 and 2. Treatment of hexan-2-one **1** with ethyl formate and potassium *tert*-butoxide gave the potassium salt of heptan-1,3-dione as a crude product, which could be cyclized with cyanoacetamide leading to the 6-butyl-3-cyano-pyridin-2-one **2**. Hydrogenation of the cyano group over Raney-Ni and subsequent *tert*-butoxycarbonyl (Boc) protection of the resulting amino residue yielded **3**, which was then alkylated with 4'-bromomethylbiphenyl-2-carbonitrile.[10] The N-isomer **4** was predominantly isolated but considerable amounts of the generally less polar O-alkylated regioisomer were also obtained. Phase transfer conditions[11] provided the best ratio in favour of the desired N-isomer. Regiochemistry of **4** was proven by 2D NMR and IR spectroscopy showing a significant upfield shift of the two pyridone-ring protons in comparison to the O-isomer and the characteristic IR carbonyl absorption near 1650 cm^{-1}. Transformation into tetrazole **5** by standard procedure with sodium azide[12] followed by deprotection of the amino group furnished product **6**. Alkylation of nitrile **4** with benzyl bromide, subsequent tetrazole formation and deprotection gave the target molecule **10**.

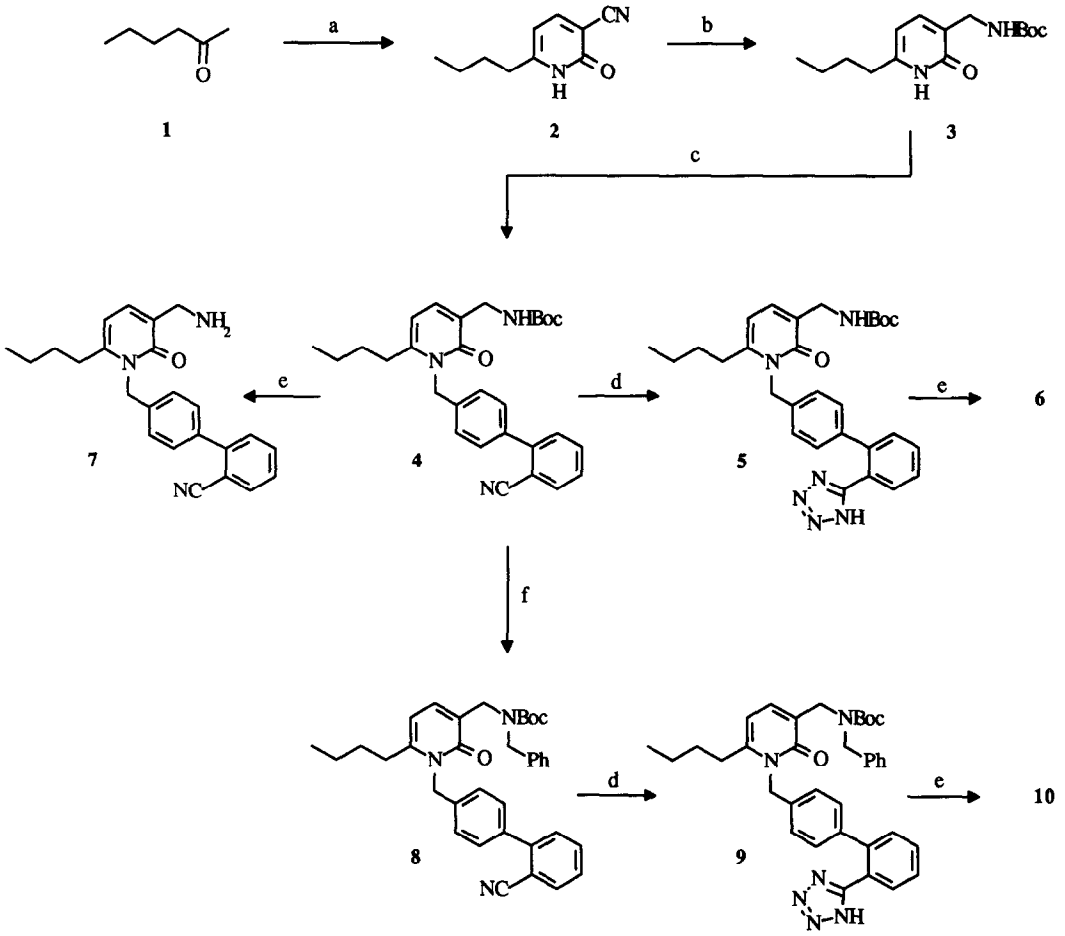
The free amino derivative **7**, obtained by acid cleavage of the Boc group was the starting material for the synthesis of the other compounds in this series (Scheme 2). The nitriles **11**, **15** and **19** were obtained by treatment of **7** with N,N-dimethylcarbamoyl chloride, acetic anhydride and methanesulfonyl chloride, respectively. Replacement of the proton at the nitrogen atom with an alkyl or benzyl residue under basic conditions led to products **13**, **17** and **21**. All nitriles were transformed into the final tetrazoles with sodium azide or trimethyltin azide.[13] Other compounds mentioned in this report were synthesized similar to these examples unless otherwise noted.

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[14] and for functional antagonism in isolated rabbit aortic rings precontracted by A II.[15] Additionally, they were evaluated in vivo for inhibition of A II induced increase in diastolic blood pressure in pithed rats.[16] The results for Losartan are given in order to provide direct comparison with those of the compounds reported here.

Our initial efforts to replace the imidazole nucleus in losartan with a 6-butyl-pyridin-2-one system led to the discovery of the A II antagonists **23**, **24** and **25**. We recognized that substitution in the 3-position offered a great variety of active compounds. Transformation of the 3-cyano group in **25** to the 3-aminomethyl group

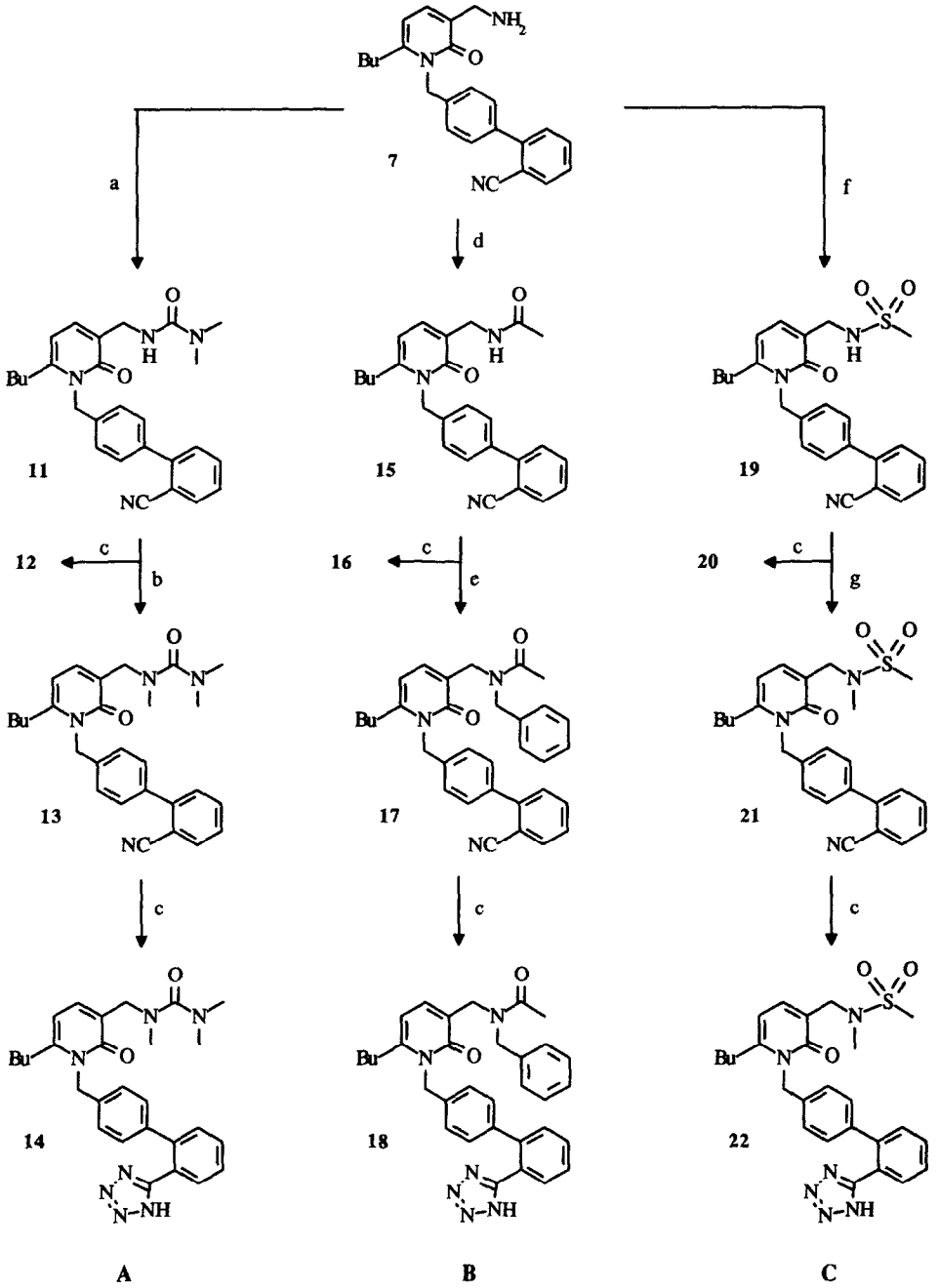
Scheme 1



Reagents: a: 1. HCOOEt/t-BuOK; 2: $NCCH_2CONH_2$; b: 1. Raney Ni/H_2/10% NH_3 in MeOH; 2. Boc_2O/THF; c: 4'-bromomethylbiphenyl-2-carbonitrile/NaOH/NBu_4I/toluene; d: NaN_3/$NHEt_3Cl$; e: HCl/dioxane; f: BnBr/NaH/THF.

suggested a very effective starting point for the synthesis of potentially interesting derivatives. Being only moderately potent, compound **6** was not the substance of choice. Introduction of a benzyl group at the amino nitrogen gave a more than 10-fold improvement in binding affinity (**10**, IC_{50} = 1.5 nM), which indicated that a primary amino residue was detrimental to activity. However, **10** showed only weak inhibition of A II pressor response, which might reflect metabolism at the benzylic methyl group in vivo. The Boc protected compounds **5** and **9** were less active probably due to their larger steric requirements but **5** unexpectedly displayed in vivo activity in the range of losartan. The ureas **12a-e** and **14** demonstrated a wide spectrum of potencies. The decisive factor for higher activity was apparently the introduction of an additional alkyl group at the terminal nitrogen (**12e** vs **12c**). This might be accounted for in terms of a favourable interaction with a lipophilic pocket on the

Scheme 2



Reagents: a: Me_2NCOCl/NEt_3; b: NaH/MeI; c: $NaN_3/NHEt_3Cl$; d: Ac_2O/NEt_3; e: NaH/BnBr; f: $MeSO_2Cl/NEt_3$; g: Cs_2CO_3/MeI

Table 1: In Vitro Data of II and Inhibition of A II Pressor Response in Pithed Rats

No.	Route	R	IC_{50} (nM)[a]	IC_{50} (nM)[b]	% inhibition[c]
5		CH_2NHBoc	6	10	68.9
6		CH_2NH_2	19	20	2.8
9		$CH_2N(Bn)Boc$	20	-	-
10		CH_2NHBn	1.5	1.0	12.4
12a#		$CH_2NHCONHPh$	18	30	0
12b#		$CH_2NHCONH$-cyclohexyl	21	90	0
12c#		$CH_2NHCONHBu$	9.0	10	10.3
12d	A	$CH_2NHCONEt_2$	6.5	-	-
12e*	A	$CH_2NHCONMe_2$	2.9	2.0	28
14*	A	$CH_2N(Me)CONMe_2$	13	-	-
16a	B	$CH_2NHCOMe$	3.8	3.0	8.6
16b	B	$CH_2NHCOPr$	5.7	-	-
16c	B	$CH_2NHCOBn$	4.1	-	-
18*	B	$CH_2N(Bn)COMe$	2.8	1.0	76.3
20a	C	CH_2NHSO_2Ph	4.1	7.0	25.2
20b	C	$CH_2NHSO_2Ph(4\text{-}Me)$	3.3	9.0	-
20c	C	$CH_2NHSO_2CF_3$	22	-	-
20d	C	CH_2NHSO_2Me	2.2	2.0	54.8
22a*	C	$CH_2N(Bn)SO_2Ph(4\text{-}Me)$	16.5	60	36.6
22b	C	$CH_2N(Me)SO_2Ph(4\text{-}Me)$	4.2	8.0	-
22c*	C	$CH_2N(Bn)SO_2Ph$	12.0	20	75.7
22d*	C	$CH_2N(Me)SO_2Ph$	4.2	2.0	68.7
22e*	C	$CH_2N(Bn)SO_2Me$	3.8	2.0	41.2
22f*	C	$CH_2N(Et)SO_2Me$	3.5	2.0	-
22g*	C	$CH_2N(iPr)SO_2Me$	1.9	0.9	82.7
22h*	C	$CH_2N(Me)SO_2Me$	1.2	0.2	83.4
23#		H	18	4.0	-
24#		Me	6.1	7.0	-
25#		CN	18	-	-
I			8.2	3.0	73.6

*: K-salt; #: for synthesis see ref.[17]; a: binding affinity rat adrenal cortex;[14] b: functional antagonism rabbit aorta;[15] c: inhibition of A II induced increase in diastolic blood pressure in pithed rats (3 mg/kg i. d.).[16]

receptor. A similar effect could be seen with amides (**16a** vs **18**), especially in vivo. Surprisingly incorporation of a third methyl group in **12e** (→**14**) resulted in 2-fold loss in binding affinity.

Among the substituents we introduced, sulfonamides **20** and **22** gave the best results, which can be summarized as follows: In the series of the secondary sulfonamides the methanesulfonyl group provided the highest potency. The strong electron withdrawing CF_3-substituent was detrimental to binding affinity (**20c**). An important step was the incorporation of an additional benzyl or alkyl group leading to tertiary sulfonamides. Whereas the differences in binding affinity were only moderate (**22g** vs **20d**), the improvement in inhibition of A II pressor response in vivo was conspicuous. In addition, decreased potency of **22a** and **22c** pointed out that the size of substituents was a critical factor. The best results were obtained with the combination of a methanesulfonyl group and a small alkyl rest. These compounds (**22g**, **22h**) displayed potencies up to subnanomolar range and their inhibitory effect on A II pressor response in pithed rats was superior to that of losartan.

In conclusion, sulfonamides **22** as well as ureas **12** and amides **18** have proven their suitability as potent nonpeptidic A II antagonists in vitro, with the first being favoured. Because of this encouraging activity compounds of the sulfonamido series were chosen for further biological evaluation and also appeared to be potent angiotensin II antagonists in vivo.

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