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SUBSTITUTED 4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONE ANGIOTENSIN II RECEPTOR ANTAGONISTS.

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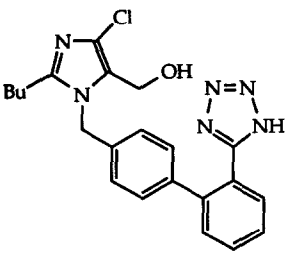
Abstract: Several substituted 4H-pyrido[1,2-a]pyrimidin-4-ones have been synthesized and investigated as potential angiotensin II receptor antagonists.

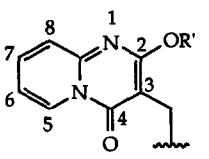
Angiotensin II (AII), an endogenous octapeptide, is a potent vasoconstrictor.[1] Angiotensin converting enzyme inhibitors (ACE), which prevent the conversion of angiotensin I into AII, have now been shown to be effective agents for the treatment of essential hypertension and congestive heart failure.[2] Unfortunately, ACE inhibitors can cause unwanted side effects, such as cough, presumably due in part to their effects on enzymes other than ACE. Angiotensin II receptor antagonists should be devoid of these side effects due to an extremely specific mode of action.

The discovery of potent, specific, orally active, non-peptide angiotensin II receptor antagonists for the treatment of hypertension and congestive heart failure by DuPont[3,4,5] has led to an avalanche of over 200 papers and patent applications by various pharmaceutical companies.[6] Herein, we describe our work. A 4H-pyrido[1,2-a]pyrimidin-4-one has been used as a replacement for the imidazole ring of DuP 753, resulting in compounds with good activity as AII receptor antagonists both *in vitro* and *in vivo*.

The 4H-pyrido[1,2-a]pyrimidin-4-one ring system appeared to be ideally suited as a "head" piece for a non-peptide AII antagonist, since it possessed the same 1,3 arrangement of nitrogens found in DuP 753, and could easily accommodate the requisite lipophilic side chain. It would also allow us to investigate the effect of linking the heterocyclic head piece to the biphenyl tetrazole through a C-C bond rather than the C-N bond of DuP 753. Thus, we embarked on a program to synthesize a variety of 4H-pyrido[1,2-a]pyrimidin-4-ones and examine their structure-activity relationships.



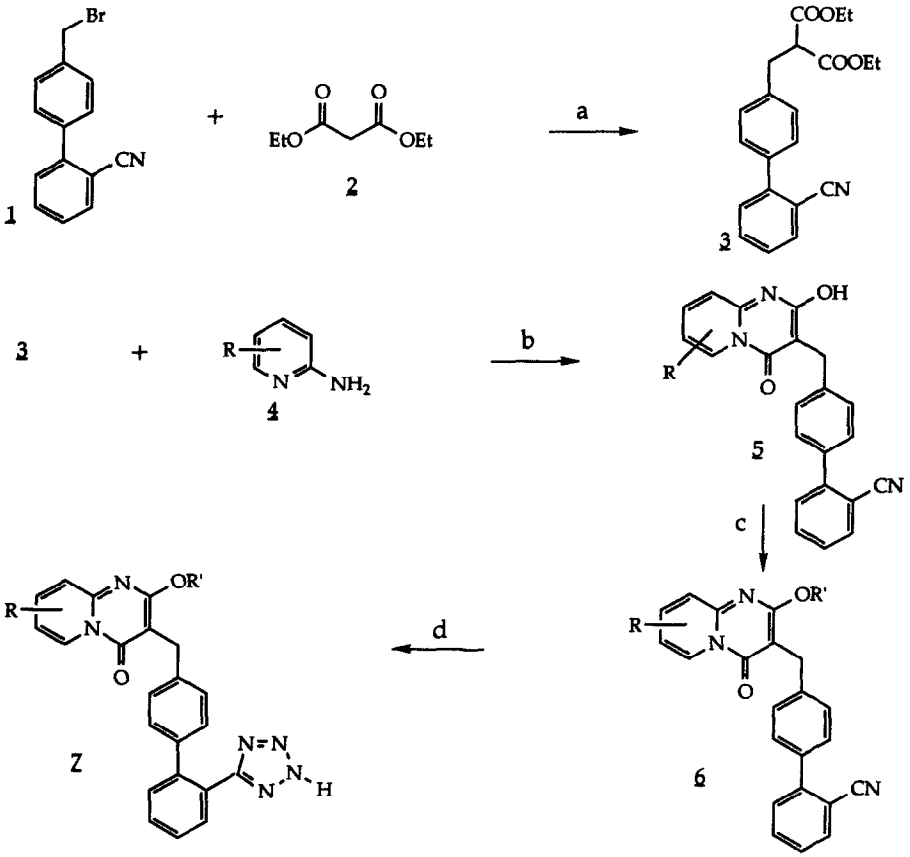
DuP 753



4H-pyrido(1,2a)-pyrimidin-4-one

The desired compounds were prepared by the procedure depicted in **Scheme 1**. The known biphenylnitrile[5b] **1** was reacted with diethyl malonate anion **2** to give diester **3** in 50% yield along with a small amount of the O-alkylated compound. The C-alkylated compound **3** was then reacted with the appropriately substituted 2-aminopyridine derivative at 180° C to yield **5**.[7] Next, **5** was alkylated with various alkyl bromides by refluxing with K_2CO_3 in acetone. Subsequently, the nitrile moiety in compound **6** was converted to the tetrazole by refluxing with NaN_3/tributyltin chloride in xylenes.[4,5]

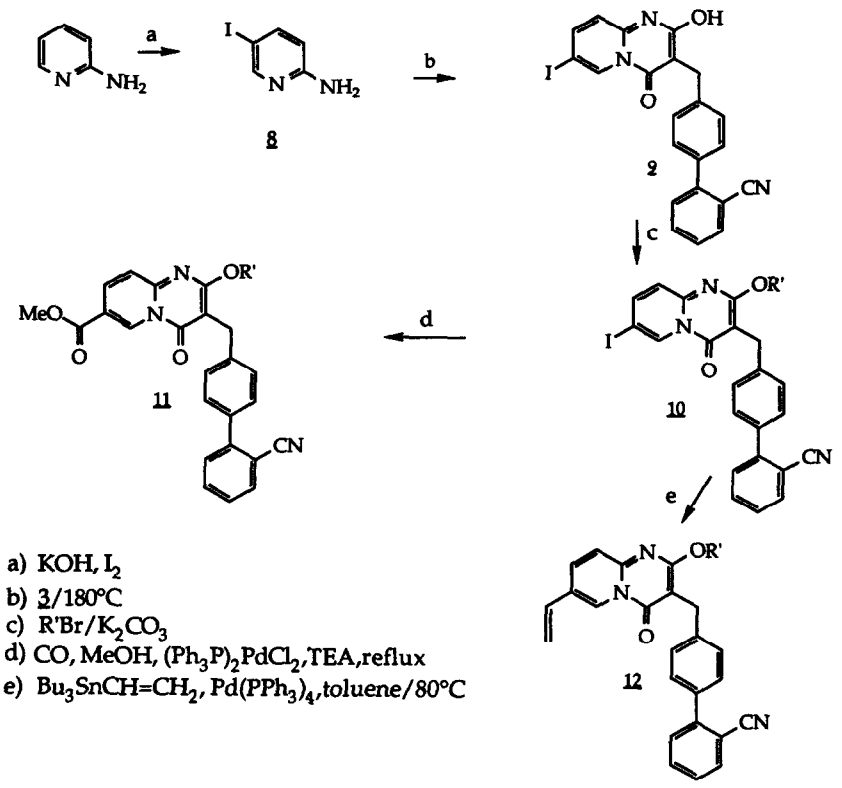
SCHEME 1



a) NaOMe/EtOH/reflux; b) 180° C/2 h; c) R'Br/K_2CO_3 /acetone/reflux;
d) Bu_3SnCl/NaN_3/xylene/reflux

In order to obtain substituted 4H-pyrido(1,2-a)-pyrimidin-4-ones where the starting 2-aminopyridines **4** were not readily available, the 6-iodo compound **9** was prepared from 5-iodo-2-amino-pyridine[8] **8** (**Scheme 2**). Alkylation of **9** followed by palladium catalyzed carboxylation[9] produced ester **11**. Iodo compound **10** could also be converted into olefin **12** *via* a Stille coupling.[10]

SCHEME 2



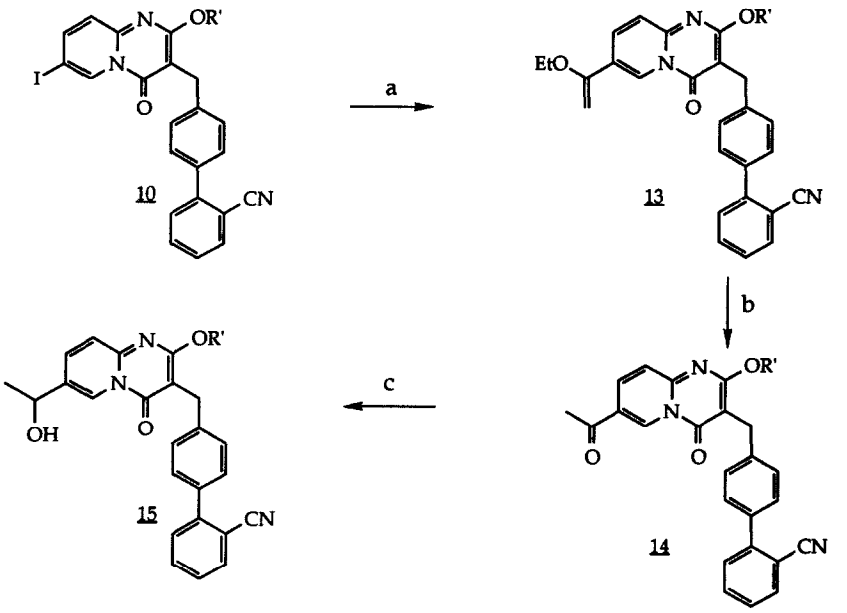
a) KOH, I_2
b) 3/180°C
c) R'Br/K_2CO_3
d) CO, MeOH, $(Ph_3P)_2PdCl_2$,TEA,reflux
e) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$,toluene/80°C

As shown in **Scheme 3**, the methyl ketone **14** was produced by palladium catalyzed coupling of (1-ethoxyvinyl)tributyltin to **10** followed by acid hydrolysis of enol ether **13**. The nitrile derivatives were then converted to the tetrazole as before. Unfortunately, we were unable to synthesize compounds with electron donating substituents, such as alkoxy or amino, on the pyrido-pyrimidinone ring.

The *in vitro* binding constants for the analogs shown were obtained using bovine adrenal cortex preparations.[11] Examination of the IC_{50} values in **Table 1** show that the most active compound in this series is **7l** (IC_{50}=0.25μM *vs.* DuP 753 IC_{50}=0.30μM), the unsubstituted pyrido-pyrimidinone. The

presence of an acidic functionality at C-6 (**7g**) decreased activity considerably. However, conversion of

SCHEME 3



a) $Bu_3SnC(OEt)=CH_2$, $(Ph_3P)_2PdCl_2$, toluene, 80° C;
b) 5N HCl/THF, 2 h, RT;
c) $NaBH_4$/EtOH/$CeCl_3$

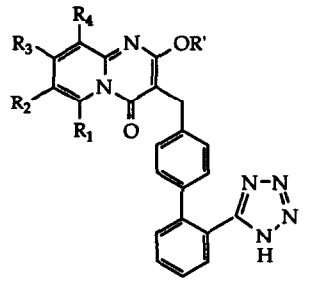
the acid to the ethyl ester (**7f**) counteracts this increase. Placement of an alkyl substituent at R_2, R_3 or R_4 decreases binding affinity relative to the unsubstituted compound. However, increasing the hydrophilicity of the side chain by introducing a hydroxyl group (**7c**) has a favorable affect on binding, increasing affinity four-fold over the methyl compound **7h**.

It is also evident from **Table 1** that the length of the side chain governs the *in vitro* activity to a large extent with an n-propyl group attached to oxygen showing the best activity. When the carbon chain is an n-butyl unit, **7k**, activity decreases. Shorter side chains also decrease activity (**7a, 7b**). On the other hand, branched alkyl chains at R' have little effect on activity.

Compound **7l** was also tested *in vivo* in a high renin rat model of hypertension.[12] Although **7l** was equipotent with DuP 753 *in vitro* , it was roughly one half as active *in vivo*, producing a 50 mm Hg drop in blood pressure over 5 hours when administered orally at 10 mg/kg.

In summary, we have replaced the imidazole of DuP 753 with 4H-pyrido[1,2-a]pyrimidine-4-one and found it to be as active as DuP753 *in vitro*. However, these compounds are less active than DuP 753 *in vivo*.

Table I



Compound No.	R_1	R_2	R_3	R_4	R	$IC_{50}\mu M$
7a	H	H	H	H	$-CH_3$	14
7b	H	H	H	H	$-CH_2CH_3$	4.4
7c	H	$-CH(OH)CH_3$	H	H	$-CH_2CH(CH_3)_2$	1.0
7d	H	H	H	$-CH_3$	$-CH_2CH_2CH_3$	6
7e	H	$-CH_3$	H	H	$-CH(CH_3)_2$	6
7f	H	$-COOC_2H_5$	H	H	$-CH(CH_3)_2$	4.9
7g	H	-COOH	H	H	$-CH(CH_3)_2$	69.3
7h	H	$-CH_3$	H	H	$-CH_2CH(CH_3)_2$	4
7i	H	$-CH_3$	H	H	$-CH_2CH_2CH_3$	1.6
7j	H	H	$-CH_3$	H	$-CH_2CH_2CH_3$	4
7k	H	H	H	H	$-CH_2(CH_2)_2CH_3$	2.4
7l	H	H	H	H	$-CH_2CH_2CH_3$	0.25

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References:

1. Vallotton, M.B. *Trends Pharmacol. Sci.* **1987**, *8*, 69.

2. Johnson, C.I. in *Handbook of Hypertension*, Vol. 5, *Clinical Pharmacology of Antihypertensive Drugs.* Doyle, A.E., Ed.; Elsevier; Amsterdam, **1984**; p 2.

3. Wong, P.C.; Chiu, A.T.; Price, W.A.; Thoolen, M.J.M.C.; Carini, D.J.; Johnson, A.L.; Taber, R.I.; Timmermanns, P.B.M.W.M. *J.Pharmacol. Exp. Ther.* **1988**, 1, 247.; Chiu, A.T., et al, *J.Pharmacol. Exp. Ther.* **1988**, 13, 157.
4. Duncia, J.V.; Chiu, A.T.; Carini, D.J.; Gregory, G.B.; Johnson, A.L.; Price, W.A.; Wells, G.J.; Wong, P.C.; Calabrese, J.C.; Timmermanns, P.B.M.W.M.; *J.Med.Chem.* **1990**, 33, 1312.
5. a) Carini, D.J.; Duncia, J.V., Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, B. M. W.; *J. Med. Chem.* 1990, 33, 1330.
   b) Carini, D.J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T., Johnson, A.L.; Pierce, M.E.; Price, W.A., Santella, J.B.; Wells, G.J.; Wexler, R.R.; Wong, P.C.; Yoo, S.-E.; Timmermans, B.M.W.M; *J.Med.Chem.* **1991**, 34, 2525.
6. For recent patent update reference:
   J. J. Baldwin, *Current Opinion in Therapeutic Patents* **1993**, 1, 137.
   Dudley, D.T.; Hamby, J.M.; *Current Opinion in Therapeutic Patents* **1993**, 5, 581.
7. Giulla, M.; Razack, L.A.; King, R.J.; White, G.R.; Utley, J.H.P.; *Tetrahedron* **1991**, 47, 675.
8 Tschitschibabin, R.; *Chem.Ber.* **1925**, 58, 115.
9. Schoenberg, A.; Bartoletti, I.; Heck, R.F.; *J. Org. Chem.* **1974** 39, 3318.
10. Trost, B.M.; Metzner, P.J.; *J. Amer. Chem. Soc.* **1980** 102, 3572.
11. Wong, P.C.; Chiu, A.T.; Price, W.A.; Thoolen, M.J.M.C.; Duncia, J.V.; Carini, D.J.; Johnson, A.L.; Taber, R.I.; Timmermanns, P.B.M.W.M.; *J.Pharmacol. Exp. Ther.* **1989**, 250, 867.
12. Chan, P.S.; Cervoni P., Ronsberg, M.A.; Scully, P.A.; Quirk, G.J.; McLendon, T.K.; *Drug Development Res.* **1989**, 18, 75.

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