Synthesis and Angiotensin II Receptor Antagonist Activity of C-Linked Pyrazole Derivatives

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The synthesis and pharmacological activity of new nonpeptide angiotensin II (AII) receptor antagonists are presented. These 5-O-substituted and 5-C-substituted 3-alkylpyrazole derivatives represent a new series of antagonists and have led to to the discovery of compounds with potent oral antihypertensive activity in a renal artery-ligated rat model. *In vitro*, they displayed a high affinity for rat adrenal AII receptors. *In vivo* structure–activity relationship study has shown the importance of the 4-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl moiety for oral activity and the critical role of alkyl substituents at the 1- or 2-position. In the case of oral administration, 5-C derivatives were found to be, on the whole, more potent than 5-O derivatives. UP 221-78, 5-hydroxymethyl-3-*n*-propyl-1-(2,2,2-trifluoroethyl)-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-]methyl]-1*H*-pyrazole (79), displayed equivalent antihypertensive activity to the well known antagonist Losartan at 3 mg/kg *p.o.* in renal artery-ligated rats, with maximal decreases in mean arterial pressure of 60 and 63 mmHg for Losartan and UP 221-78, respectively.

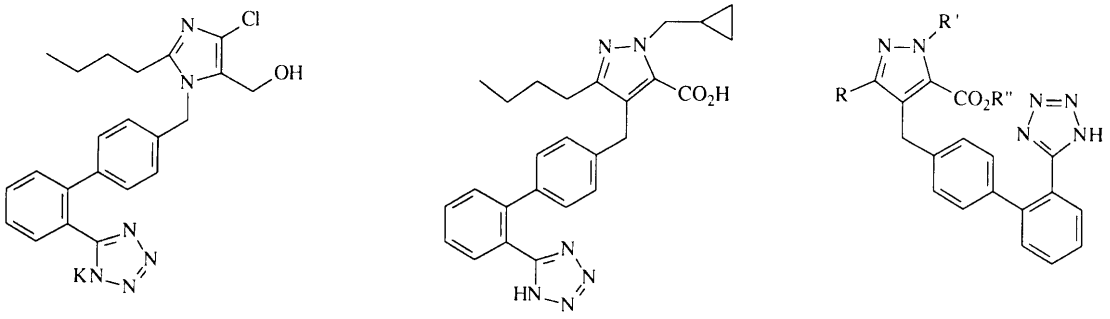
Keywords pyrazole; antihypertensive; angiotensin II; angiotensin II receptor antagonist; structure–activity relationship; 2′-(1*H*-tetrazol-5-yl)biphenyl

Angiotensin II (AII) is a powerful vasopressor peptide produced by the renin-angiotensin system.[1] Angiotensin converting enzyme (ACE) inhibitors, which reduce the AII levels, can be effective antihypertensive agents, and captopril and enalapril have taken an important part of the world market for drugs to treat hypertension and congestive heart failure.[2] However ACE inhibitors may produce side effects such as cough and angioedema,[3a-c] probably owing to their lack of selectivity, which results in an increase of bradykinin levels. Another way to inhibit the AII effects is to antagonize its action at the receptor level in order to obtain more specific drugs and to avoid side effects related to bradykinin potentiation. A first peptidic approach has led to the discovery of potent *in vitro* AII receptors antagonists,[4] but they were not orally active and displayed a partial agonistic activity.

Since the discovery of DuP 753 (Losartan, Fig. 1),[5] the first orally active nonpeptide AII receptor antagonist, numerous derivatives have been reported as potent and selective antagonists.[6] The great majority of them contain a biphenyltetrazole moiety appended to a five-membered or a six-membered heterocycle, the biphenyltetrazole being linked to a nitrogen atom.

In our first approach to obtain new orally active AII antagonists we synthesized various C-linked biphenyltetrazole derivatives. We have described the synthesis and AII antagonistic activity of C-linked triazolo[4,3-*c*]-pyrimidine and triazolo[1,5-*c*]pyrimidine derivatives, which led to the discovery of UP 269-6 (Fig. 2), a new orally potent antagonist which is currently in clinical development.[7a-c] Prior to the discovery of UP 269-6, we studied a series of C-linked pyrimidine derivatives[8] (Fig. 2) and two series of C-linked pyrazole derivatives,[9] namely 5-oxypyrazoles of formula A (Fig. 2) and 5-C-substituted pyrazoles of formula B (Fig. 2).

Independently, Glaxo have described [[3-butyl-1-cyclopropylmethyl-4-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1*H*-pyrazole-5-carboxylic acid (Fig. 1) as being a potent orally active AII receptor antagonist.[10a] More recently, a Merck report described a series of 3-alkyl-1-phenyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylic acids (Fig. 1) as potent AII



Dup 753[5] Glaxo[10a] Merck[10b]

Fig. 1. Structures of Losartan, Glaxo and Merck Pyrazole Derivatives

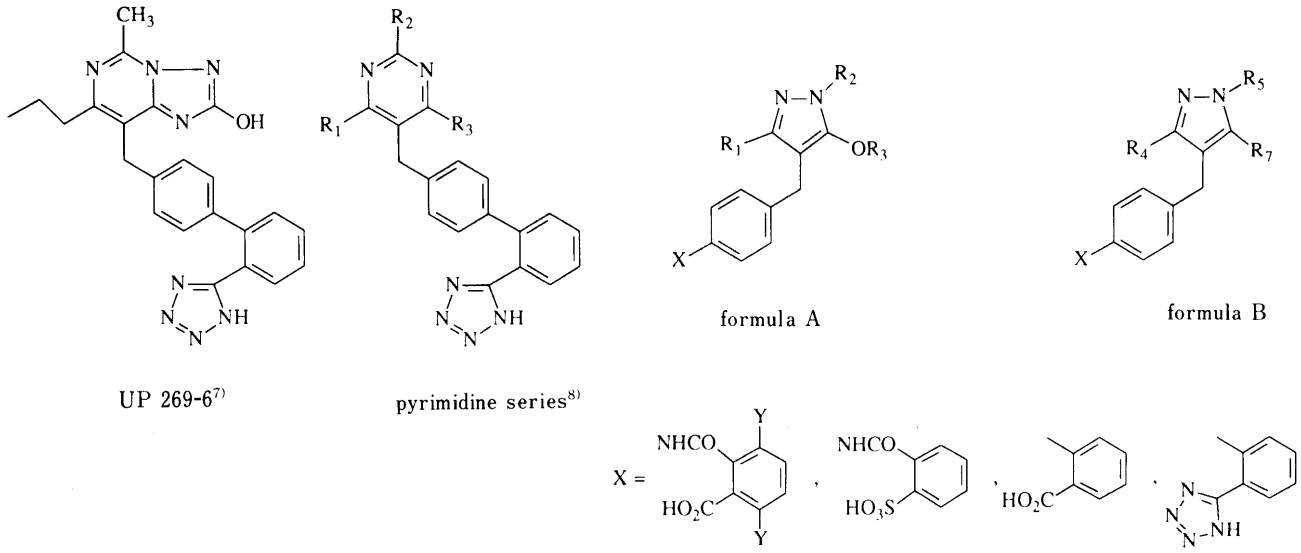
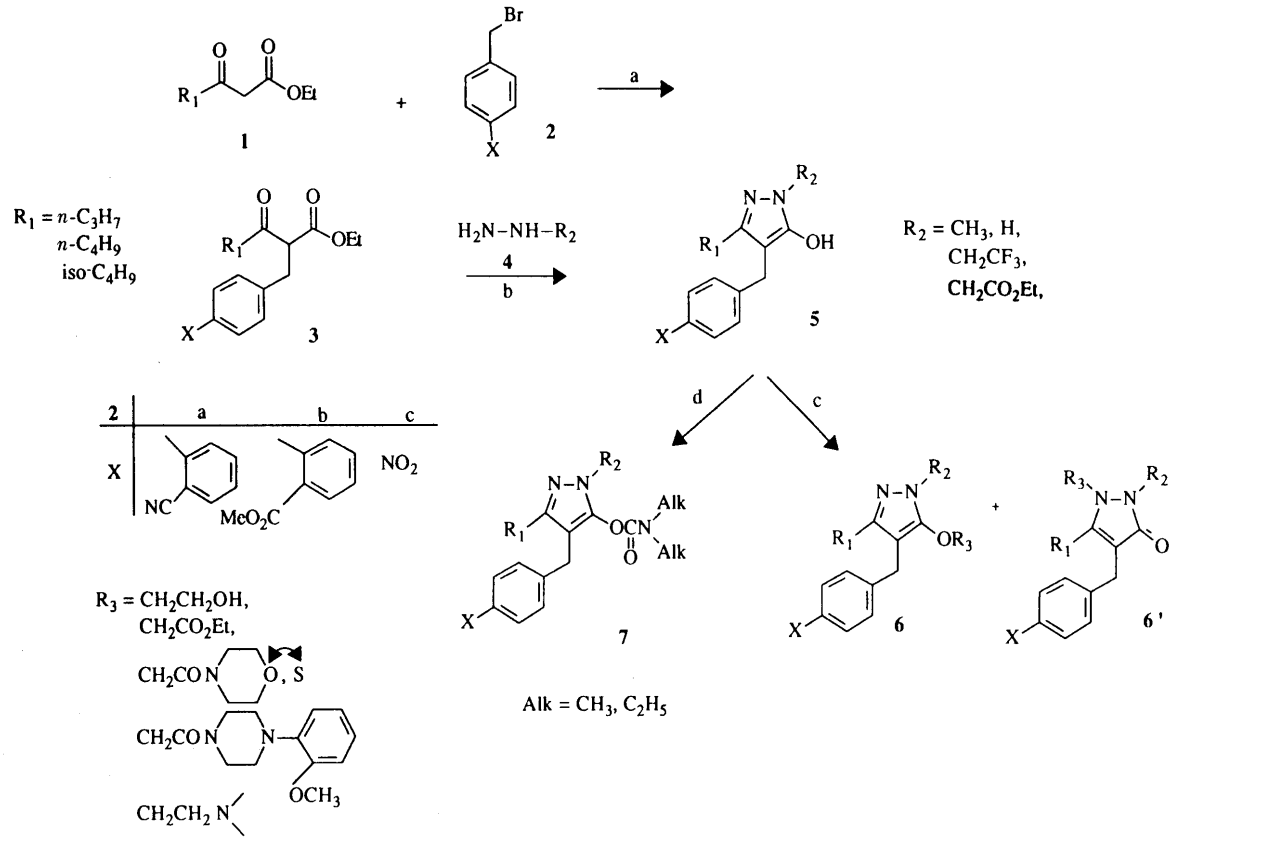


Fig. 2. Structures of UP 269-6 and of Pyrazole Derivatives of Formula A and B



(a) LiCl, (iso-Pr)$_2$ NEt, THF, reflux, 15 h (b) EtOH, reflux, 3 h (c) R_3X (X = Br or Cl), Na_2CO_3, acetone, reflux 10 h (d) (Alk)$_2$ N COCl, CH_2Cl_2, $(Et)_3N$, reflux 10 h

Chart 1

receptor antagonists.[10b] Our pyrazoles series includes not only 5-C-linked pyrazole derivatives as in Glaxo and Merck reports but also 5-O-linked derivatives which are of particular interest due to the ease of their chemical synthesis. Therefore, we would like to report herein the results of our work on the synthesis and structure–activity relationships (SARs) in the pyrazole series.

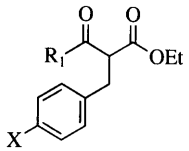
Chemistry

We have synthesized two different families of pyrazole derivatives, namely 5-oxy substituted pyrazoles of formula A and 5-C-substituted pyrazoles of formula B (Fig. 2). The preparation of all intermediates has been described.[9] The synthesis of 5-oxypyrazole derivatives **6** was achieved as shown in Chart 1. Alkylation of β-keto esters **1** with substituted benzyl bromides **2** in tetrahydrofuran (THF), in the presence of lithium chloride and *N*,*N*-diisopropyl ethylamine,[11] led to the 2-benzyl derivatives **3** (Table I). The cyclization of compounds **3** was conveniently achieved by the action of the substituted hydrazine **4** in refluxing

ethanol to give 4-benzyl-5-hydroxypyrazoles **5** (Table II). Alkylations of compounds **5** with various haloalkyl derivatives (R_3X) in acetone or 2-butanone at reflux with sodium carbonate provided mainly the O-alkylated derivatives **6** together with N-alkylated derivatives **6'** (the 2 isomers were easily separated by chromatography on silica gel or by crystallization). The action of *N,N*-dialkylcarbamoyl chlorides on **5** in methylene chloride (10 h at reflux) led to the *N,N*-dialkyl carbamoyl derivatives **7**.

The preparation of pyrazoles of formula **B** was performed according to the procedures illustrated in Chart 2. Condensation of the ketones **8** with methyl 2-methoxyacetate, in the presence of 1 eq of sodium in toluene led to the diketones **9**. The latter were alkylated with substituted benzyl bromides **2** under the same conditions as described for the β-keto esters **1** to give the benzylated diketones **10** (Table III). The desired 1-alkyl pyrazole derivatives **13** were synthesized by two methods. The first involved direct cyclization of diketones **1** with substituted hydrazine in refluxing ethanol, leading to a mixture of isomers **12** and **13** with **12** as the main compound. A more convenient method, when it was possible, was to synthesize the unsubstituted pyrazole **11**, by treatment of **10** with hydrazine hydrate in ethanol, and to alkylate it with an appropriate alkyl halide (R_5X) in the presence of a base such as sodium bicarbonate or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in acetone at 45 °C. This second procedure allowed us to obtain predominantly the isomer **13** but it failed when $R_5 = CH_2CF_3$ because of a lack of

TABLE I. Preparation of 2-Alkylated β-Ketoesters **3**

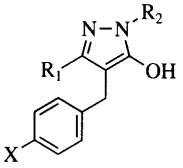


3

Compd. No.	R_1	X	Yield[a] (%)
3a	n-C_3H_7	2-Cyanophenyl	98
3b	n-C_4H_9	2-Cyanophenyl	93
3c	iso-C_3H_7	2-Cyanophenyl	91
3d	n-C_4H_9	2-Carbomethoxyphenyl	88
3e	n-C_3H_7	NO_2	75
3f	n-C_4H_9	NO_2	76

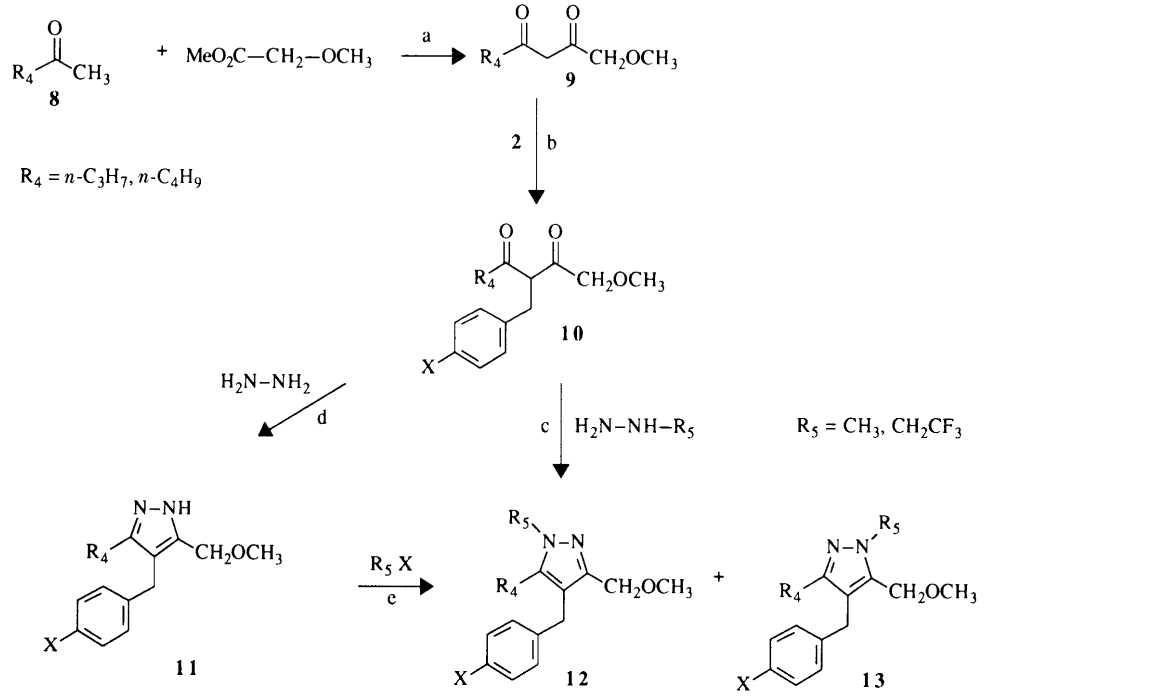
a) Yield calculated from starting substituted benzyl bromide for the crude oil used without further purification (HPLC purity 80—90%).

TABLE II. Synthesis of 3-Oxypyrazole Derivatives **5**



Compd. No.	R_1	R_2	X	Yield[a] (%)	mp (°C)
5a	n-C_3H_7	CH_3	2-Cyanophenyl	82	165
5b	n-C_4H_9	CH_3	2-Cyanophenyl	84	138
5c	iso-C_4H_9	CH_3	2-Cyanophenyl	76	163
5d	n-C_3H_7	CH_2CF_3	2-Cyanophenyl	55	154
5e	n-C_4H_9	CH_2CF_3	2-Cyanophenyl	57	137
5f	iso-C_4H_9	CH_2CF_3	2-Cyanophenyl	51	Oil
5g	n-C_3H_7	CH_3	2-Carbomethoxyphenyl	73	108
5h	n-C_3H_7	CH_3	NO_2	75	174
5i	n-C_4H_9	CH_3	NO_2	70	136
5j	n-C_3H_7	CH_2CF_3	NO_2	82	160
5k	n-C_3H_7	H	NO_2	81	196
5l	n-C_3H_7	CH_2CO_2Et[b]	NO_2	40	134

a) Yield calculated from the corresponding β-ketoester **3**. *b*) Prepared from ethyl hydrazinoacetate hydrochloride in ethanol with sodium hydrogenocarbonate.



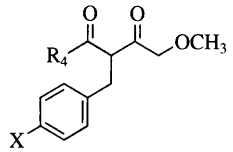
(a) Na, toluene, 60—70 °C or DBU, acetone, 45°C (b) LiBr, (iso-Pr)$_2$ NEt, THF, reflux 15 h (c) EtOH, reflux, 2 h (d) EtOH, reflux, 2 h (e) $NaHCO_3$

Chart 2

reactivity of 1-iodo-2,2,2-trifluoroethane, even at higher temperatures.

Derivatives of formula **14**—**16** were prepared from the 5-methoxymethyl derivatives **13** as depicted in Chart 3. The hydroxymethyl derivatives **14** and **14'** were obtained in a two-step procedure by treatment of **13** and **12**, respectively, with boron tribromide in chloroform at 0 °C and subsequent hydrolysis of the bromomethyl intermediates with sodium carbonate in a dioxane/water mixture at reflux. The acid derivatives **15** were obtained by oxidation of the alcohols **14** with sodium dichromate and sulfuric acid, and the corresponding esters **16** were synthesized from the acids **15** by coupling of ethanol with *N*,*N*-dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) at room temperature.

TABLE III. Preparation of 3-Benzyl Diketones of Formula **10**



10

Compd. No.	R_4	X	Yield[a] (%)	mp (°C)
10a	n-C_4H_9	2-Cyanophenyl	64	Oil
10b	n-C_3H_7	2-Cyanophenyl	72	Oil
10c	n-C_3H_7	NO_2	59	55[b]

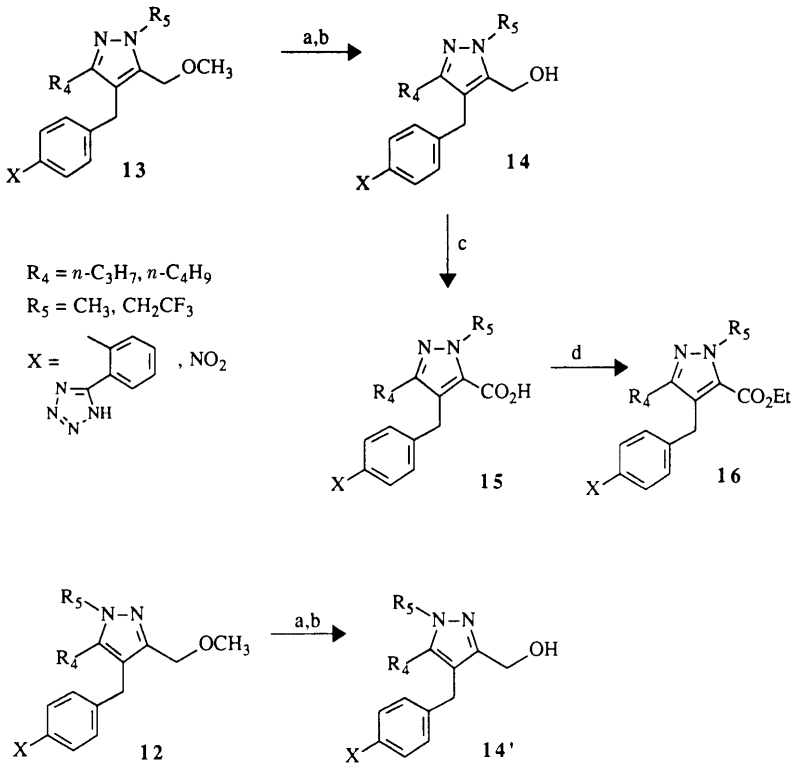
a) Yield calculated from starting substituted benzyl bromide for the crude oil used without further purification (HPLC purity 80—90%). *b*) Crystallized in diisopropyl ether.

The synthesis of target derivatives was achieved as shown in Chart 4. Phthalic acid derivatives were prepared in two steps from 4-(4-nitrobenzyl)pyrazoles **17**, by catalytic hydrogenation with palladium on carbon of the latter and subsequent condensation of the corresponding amino derivative **17'** with appropriately substituted phthalic anhydride in acetonitrile. Sulfonic acid derivatives were similarly obtained by treatment of the corresponding amino derivatives **17'** with sulfobenzoic acid cyclic anhydride in acetonitrile. The biphenyl-2'-carboxylic acid derivatives were prepared by alkaline hydrolysis of the corresponding esters **18**. The 2'-(1*H*-tetrazol-5-yl)biphenyl derivatives were synthesized in two steps from the corresponding nitriles **19** by the action of trimethyltin azide in toluene or xylene at temperatures between 120 °C and 160 °C and subsequent cleavage of the intermediary 1-trimethylstannyltetrazol-5-yl derivative by gaseous hydrogen chloride in THF. In some cases, the tetrazol-5-yl derivatives were obtained directly without isolation of trimethylstannyl intermediates.

Results and Discussion

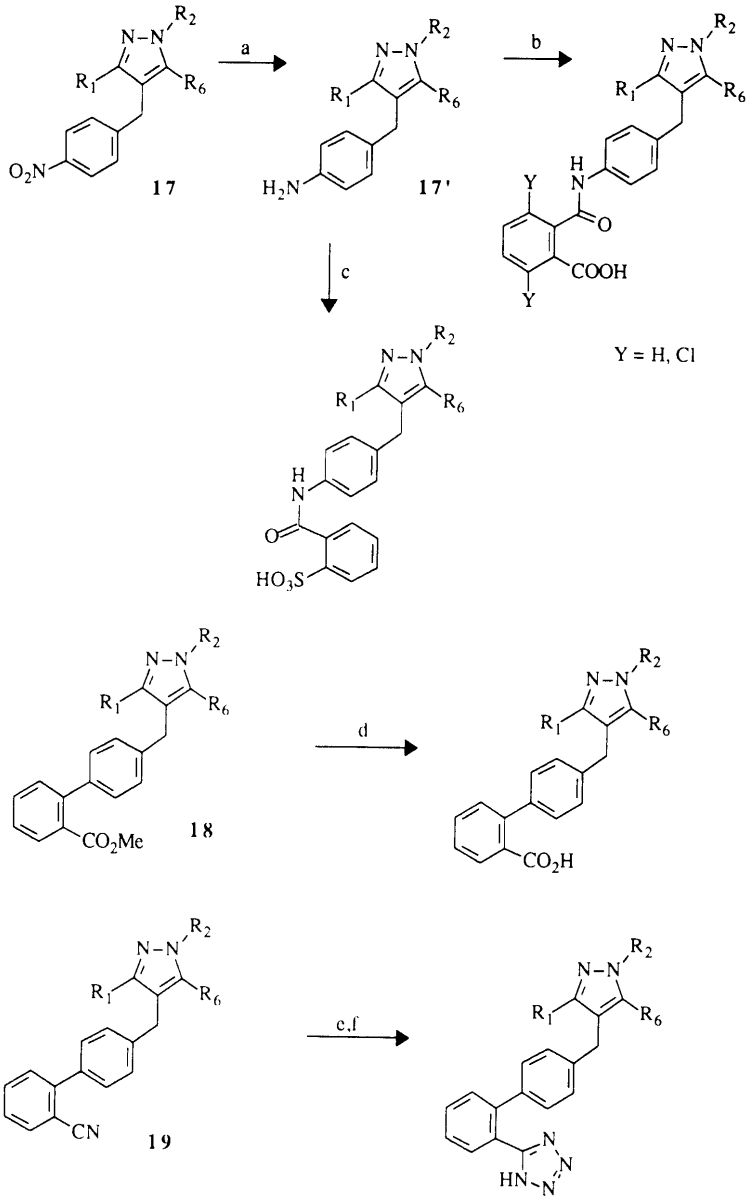
In vitro, the affinity of the compounds was measured in terms of the ability to displace the specific binding of [^{125}I]Sar 1–Ile 8–AII from rat adrenal AII receptors at 10^{-5} and 10^{-7} M. *In vivo*, some compounds in Tables IV, V and VII were tested for the ability to inhibit the AII-induced pressor response in rats, orally at 100 mg/kg and intravenously at 10 mg/kg.

The biphenyl tetrazole derivatives (Tables VI and VIII) were tested orally in renal artery-ligated hypertensive rats,[12] a high renin model, at 10 or 30 mg/kg either by



(a) BBr_3, CH_2Cl_3, 0 °C, 1 h, r.t, 12 h (b) Na_2CO_3, H_2O/dioxane, reflux, 3 h (c) H_2SO_4, $Na_2Cr_2O_7$, H_2O, 5 h (d) DCC, DMAP, EtOH, r.t, 2 h

Chart 3



(a) Raney nickel, H_2, EtOH, r.t, atm. pressure (b) (substituted) phthalic anhydride, CH_3CN, r.t, 3 h (c) sulfobenzoic anhydride, CH_3CN, r.t, 5 h (d) NaOH, EtOH, reflux, 2 h (e) $Me_3Sn\ N_3$, toluene, reflux, 14 h (f) HCl gas, toluene/THF, r.t, 1 h

Chart 4

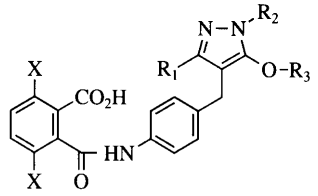
the tail-cuff method[13] or by a direct method.[14] Results are expressed as change in arterial blood pressure (systolic arterial pressure (SAP) in the tail-cuff method and mean arterial pressure (MAP) in the direct method).

The major purpose of our work was to find orally active compounds. Therefore the *in vitro* data only give % displacement at 10^{-5} and 10^{-7} M and do not allow rational discussion of the *in vitro* SAR. Nevertheless, the results in Tables IV and V show that phthalic acid and sulfobenzoic acid derivatives display a high affinity for AII receptors with several compounds (**20**, **21**, **25**, **31**—**33**, **38**—**40** and **42**) causing more than 50% displacement of [^{125}I]Sar 1–Ile 8–AII at 10^{-7} M.

Five compounds of this series (Tables IV and V), among the most active *in vitro* (**20**, **21**, **25**, **31**, **32**), were tested *in vivo* for the ability to inhibit AII-induced pressor response. The results show that if the compounds display a high activity at 10 mg/kg when administered intravenously, they have very weak oral activity at 100 mg/kg. These results highlight the lack of oral activity of the derivatives which do not have a biphenyltetrazole group, as observed in the Dupont imidazole series[5] and in the Glaxo pyrazole series.[10a]

The activity data for the biphenyl tetrazole derivatives of formula A are presented in Table VI. *In vitro*, the various modifications of R_1, R_2 and R_3 do not cause significant variations in the affinity, except when R_1 is isobutyl (see **48**, **49**, **50**), which seems to be rather unfavorable as compared to the corresponding *n*-butyl derivatives (**45**, **46**, **47**). *In vivo*, comparisons between the results for 3-*n*-propyl derivatives ($R_1 = n\text{-}C_3H_7$; **37**, **38**, **41**, **42**, **43**, **44**, **62**) and those for 3-*n*-butyl derivatives ($R_1 = n\text{-}C_4H_9$; **39**, **40**, **45**, **47**, **46**, **51**, **63**) show that, except for **37** *vs.* **39**, the *n*-propyl chain is rather more favorable than the *n*-butyl group. The replacement of the 1-methyl group ($R_2 = CH_3$) by a (1-(2,2,2-trifluoroethyl) group ($R_2 = CH_2CF_3$) does not

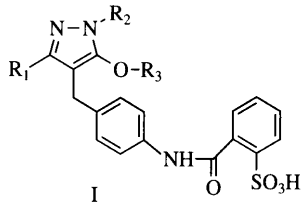
TABLE IV. Phthalic Acid Derivatives of Formula A



Compd. No.	R_1	R_2	R_3	X	Method	Yield[a] (%)	mp (°C)	Formula[b]	*In vitro* activity % displacement[c]		*In vivo* activity % inhibition of AII	
									10^{-5} M	10^{-7} M	100 mg/kg[d] (*p.o.*)	10 mg/kg[e] (i.v.)
20[f]	*n*-C_3H_7	CH_3	CH_2CO_2Et	Cl	D	36	199—200	$C_{26}H_{27}Cl_2N_3O_6$	96±1	63±1	N.A.	92.3±2.2
21	*n*-C_3H_7	CH_3	CH_2CO_2Me	Cl	E	39	150—151	$C_{25}H_{25}Cl_2N_3O_6$	93±1	60±1	20.6±7.3	83.3±3.6
22	*n*-C_4H_9	CH_3	CH_2CO_2Et	H	E	46	140—141	$C_{27}H_{31}N_3O_6$	92±1	39±1	N.T.	N.T.
23	*n*-C_3H_7	CH_3	CH_2CO_2Et	H	E	49	139—140	$C_{26}H_{29}N_3O_6$	88±1	40±1	N.T.	N.T.
24	*n*-C_3H_7	CH_2CF_3	CH_2CO_2Me	H	E	36	189—192	$C_{26}H_{26}F_3N_3O_6$	94±1	26±1	N.T.	N.T.
25	*n*-C_3H_7	CH_2CF_3	CH_2CO_2Me	Cl	E	41	169—170	$C_{26}H_{24}Cl_2F_3N_3O_6$	98±1	52±1	N.T.	76.2±2.6
26[f]	*n*-C_3H_7	CH_3	CH_2CO_2Me	H	D	39	173—174	$C_{25}H_{27}N_3O_6$	82±1	34±1	N.T.	N.T.
27[f]	*n*-C_3H_7	CH_2CO_2Et	CH_2CO_2Et	Cl	D	29	189—191	$C_{29}H_{31}Cl_2N_3O_8$	96±1	9±1	N.T.	N.T.
28	*n*-C_3H_7	H	CH_2CO_2H	H	D	31	170—171	$C_{23}H_{23}N_3O_6$	10±1	0±1	N.T.	N.T.
29	*n*-C_4H_9	CH_3	H	Cl	E-b,c	80	172—174	$C_{23}H_{23}Cl_2N_3O_4$	83±1	0±1	N.T.	N.T.
30	*n*-C_3H_7	CH_2CO_2Et	H	Cl	E-b,c	78	150—153	$C_{25}H_{25}Cl_2N_3O_6$	85±1	2±1	N.T.	N.T.

a) Overall yield for all steps of the method. *b*) All elemental analyses for C, H and N were within ±0.4% of the calculated values unless otherwise noted. *c*) Percent displacement of [^{125}I] Sar 1–Ile 8–AII bound to rat adrenal membranes by compounds at 10^{-5} and 10^{-7} M; values are mean±S.E.M. of three determinations. *d*) Percent inhibition of the initial change in AII pressor response in rat upon regular i.v. injection of AII (150—250 ng/kg) for 1 h after i.v. dosing. Values are mean±S.E.M. of three determinations. *e*) Percent inhibition of the initial change in AII pressor response on rat upon regular i.v. injection of AII (150—250 ng/kg) for 2 h after oral dosing. Values are mean±S.E.M. of three determinations. *f*) Dicyclohexylamine salt. N.A.: not active. N.T.: not tested.

TABLE V. Sulfobenzoic Acid Derivatives (I) and Biphenyl Carboxylic Acid Derivatives (II) of Formula A



I

Compd. No.	R_1	R_2	R_3	Type	Method	Yield[a] (%)	mp (°C)	Formula[b]	*In vitro* activity % displacement[c]		*In vivo* activity % inhibition of AII	
									10^{-5} M	10^{-7} M	100 mg/kg[d] (*p.o.*)	10 mg/kg[e] (i.v.)
31	*n*-C_3H_7	CH_3	CH_2CO_2Et	I	F	84	203—205	$C_{26}H_{29}N_3O_7S$	92±1	60±1	23.9±3.7	85.6± 1.1
32	*n*-C_4H_9	CH_3	CH_2CH_2OH	I	G	21	174—175	$C_{24}H_{29}N_3O_6S$	83±1	60±1	N.A.	92.8±12.4
33	*n*-C_3H_7	CH_2CF_3	CH_2CH_2OH	I	G	24	211—213	$C_{24}H_{26}F_3N_3O_6S$	91±1	64±1	N.T.	N.T.
34	*n*-C_3H_7	CH_3	CH_2CO_2H	I	I	88	170—171	$C_{23}H_{25}N_3O_7S$	85±1	48±1	N.T.	N.T.
35	*n*-C_3H_7	CH_3	CH_2CH_2OH	II	H	48	168—170	$C_{23}H_{26}N_2O_4$	63±1	5±1	N.T.	N.T.
36	*n*-C_4H_9	CH_3	H	II	H-b	91	228—230	$C_{22}H_{24}N_2O_3$	62±1	10±1	N.T.	N.T.

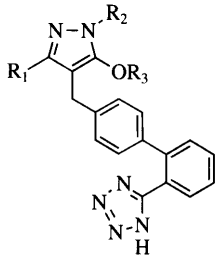
a—*e*) See footnotes of Table IV. N.A.: not active. N.T.: not tested.

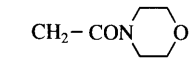
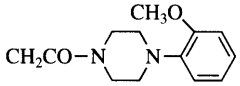
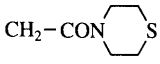
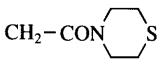
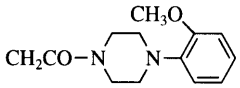
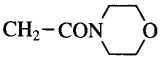
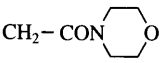
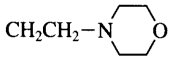
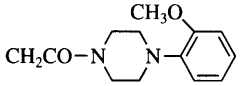
improve oral activity as we can see by comparison between **37**, **39**, **41** and **45** on the one hand, and **38**, **40**, **42**, and **47**, on the other. The nature of R_3 is not very critical for oral activity, but CH_2CO_2Et (**41**, **42**), $CON(CH_3)_2$ (**62**) and H (**38**, **39**) seem to be optimal. The introduction of long-chain substituents at the 5-position of the pyrazole ring (OR_3) is not favorable for oral activity, although it does not seem to impair the *in vitro* affinity (**52** to **61**).

The results obtained with the 5-oxypyrazole derivatives of formula A (Table IV—VI), confirm the critical role of the biphenyltetrazole group for orally active compounds. This series includes compounds which are orally active at 10 mg/kg on artery-ligated rats (**39**, **42**, **38**, **41**, **62**) even though they remain less potent than Losartan (Table VIII).

The data for the 5-C substituted pyrazoles of formula B, which are related to the Glaxo pyrazole derivatives,[10a] are presented in Tables VII and VIII. *In vitro*, the activity is significantly higher for the derivatives in which R_5 is methyl as compared to those in which R_5 is hydrogen (**66** *vs.* **68** and **69** *vs.* **71**; Table VII). More interesting is the

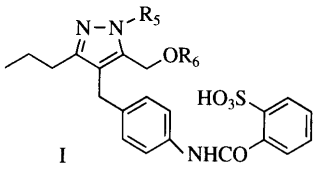
TABLE VI. Biphenyl Tetrazole Derivatives of Formula A



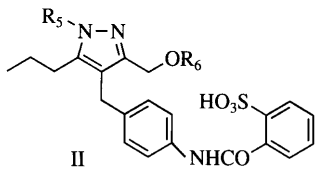
Compd. No.	R_1	R_2	R_3	Method	Yield[a] (%)	mp (°C)	Formula[b]	*In vitro* activity % displacement 10^{-5} M	10^{-7} M	Oral activity change in BP (mmHg)[d] 10 mg/kg
37	n-C_3H_7	CH_3	H	A	61	150—153	$C_{21}H_{22}N_6O$	58±1	24±1	−30.8± 5.1[e]
38	n-C_3H_7	CH_2CF_3	H	A	57	218—220	$C_{22}H_{21}F_3N_6O$	66±2	58±1	−47.4±10.8
39	n-C_4H_9	CH_3	H	A	59	176—178	$C_{22}H_{24}N_6O$	69±1	55±2	−56.0±15.1
40	n-C_4H_9	CH_2CF_3	H	A	56	210—211	$C_{23}H_{23}F_3N_6O$	74±1	66±1	−21.1± 9.3
41	n-C_3H_7	CH_3	CH_2CO_2Et	B	32	187—189	$C_{25}H_{28}N_6O_3$[f]	67±1	49±1	−44.9± 4.9[e]
42	n-C_3H_7	CH_2CF_3	CH_2CO_2Et	B	34	146	$C_{26}H_{27}F_3N_6O_3$	65±2	51±2	−50.5± 6.8[e]
43	n-C_3H_7	CH_3	CH_2CH_2OH	B	37	120—122	$C_{23}H_{26}N_6O_2$	60±1	38±2	−29.6±14.5[e]
44	n-C_3H_7	CH_2CF_3	CH_2CH_2OH	B	29	161	$C_{24}H_{25}F_3N_6O_2$	75±1	70±1	−42.3± 9.2[g]
45	n-C_4H_9	CH_3	CH_2CO_2Et	B	26	142—143	$C_{26}H_{30}N_6O_3$	64±1	40±1	−27.2± 6.4
46	n-C_4H_9	CH_3	CH_2CH_2OH	B	25	105—108	$C_{24}H_{28}N_6O_2$	68±2	38±2	−13.3± 5.3
47	n-C_4H_9	CH_2CF_3	CH_2CO_2Et	B	38	140—141	$C_{27}H_{29}F_3N_6O_3$	73±2	58±1	−26.7±11.6
48	iso-C_4H_9	CH_3	CH_2CO_2Et	B	34	172—173	$C_{26}H_{30}N_6O_3$	80±1	17±2	−34.9± 6.0[g]
49	iso-C_4H_9	CH_2CF_3	CH_2CH_2OH	B	27	145—146	$C_{25}H_{27}F_3N_6O_2$	68±1	22±3	−19.3± 4.6
50	iso-C_4H_9	CH_2CF_3	CH_2CO_2Et	B	34	114—115	$C_{27}H_{29}F_3N_6O_3$	75±1	35±3	−21.0± 5.3
51	n-C_4H_9	CH_2CF_3	CH_2CH_2OH	B	33	107—110	$C_{25}H_{27}F_3N_6O_2$	68±1	59±1	−19.7± 7.4[g]
52	n-C_3H_7	CH_2CF_3		B	41	129—131	$C_{28}H_{30}F_3N_7O_3$	71±1	66±2	−15.8± 4.2
53	n-C_3H_7	CH_2CF_3		B	28	158—160	$C_{35}H_{37}F_3N_8O_3$	82±1	65±1	−19.4± 4.4
54	n-C_3H_7	CH_2CF_3		B	32	127—128	$C_{28}H_{30}F_3N_7O_3S$	72±1	64±1	−40.1±11.3
55	n-C_3H_7	CH_3		B	24	140—141	$C_{27}H_{40}N_8O_3$	72±1	64±1	−25.5±11.4
56	n-C_4H_9	CH_3		B	25	153—155	$C_{35}H_{40}N_8O_3$	84±1	56±1	−17.8± 9.7
57	n-C_3H_7	CH_3		B	28	106—110	$C_{27}H_{31}N_7O_3$	71±2	59±3	−16.0± 6.8
58	n-C_4H_9	CH_3		B	30	140—141	$C_{28}H_{33}N_7O_3$	73±2	65±3	−21.9±12.7
59	n-C_3H_7	CH_3		B	21	132—134	$C_{27}H_{33}N_7O_2$	69±1	38±1	−22.5± 7.1
60	n-C_3H_7	CH_3		B	27	139—141	$C_{34}H_{38}N_8O_3$	80±1	59±1	−24.8±10.9
61	n-C_3H_7	CH_3	$CH_2CH_2N(CH_3)_2$	B	33	88—90	$C_{25}H_{31}N_7O$	67±1	23±1	−14.2± 7.5
62	n-C_3H_7	CH_3	$CON(CH_3)_2$	C	46	103—105	$C_{24}H_{27}N_7O_2$	58±1	41±1	−40.1±12.8
63	n-C_4H_9	CH_3	$CON(CH_3)_2$	C	44	160	$C_{25}H_{29}N_7O_2$	71±2	47±1	−34.6±12.1
64	n-C_4H_9	CH_2CF_3	$CON(CH_3)_2$	C	50	151—152	$C_{26}H_{28}F_3N_7O_2$	69±1	48±1	−19.8±10.4
65	n-C_3H_7	CH_3	$CON(C_2H_5)_2$	C	41	134—135	$C_{26}H_{33}N_7O_2$	70±1	38±1	−27.4±14.7

a—*c*) See footnotes of Table IV. *d*) SAP values were determined by the tail-cuff method in renal artery-ligated rats and represent the mean±S.E.M. of 3—7 determinations. *e*) MAP values were determined by the direct method in renal artery-ligated rats and represent the mean±S.E.M. of 3—7 determinations. *f*) N: Calcd 18.20; Found 17.73. *g*) SAP values were determined at 30 mg/kg as described in *d*).

TABLE VII. Sulfobenzoic Acid Derivatives of Formula B



I

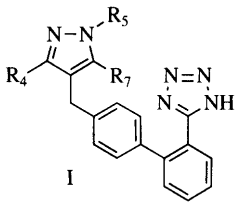


II

Compd. No.	Type	R_5	R_6	Method	Yield[a] (%)	mp (°C)	Formula[b]	*In vitro* activity % displacement		*In vivo* activity % inhibition of AII	
								10^{-5} M	10^{-7} M	100 mg/kg[d] (*p.o.*)	10 mg/kg[e] (i.v.)
66	I	H	CH_3	J	50	253—256	$C_{22}H_{25}N_3O_5$	86±1	19±1	N.T.	N.T.
67	II	CH_3	CH_3	K	29	216—218	$C_{23}H_{27}N_3O_5S$	82±1	28±2	N.T.	N.T.
68	I	CH_3	CH_3	K	15	237—238	$C_{23}H_{27}N_3O_5S$	88±1	62±1	36.4±13.1	77.8±5.5
69	I	H	H	L	30	168—172	$C_{21}H_{23}N_3O_5S$	82±1	12±2	N.T.	N.T.
70	II	CH_3	H	L	32	216—219	$C_{22}H_{25}N_3O_5S$	59±1	0±1	N.T.	N.T.
71	I	CH_3	H	L	34	255—257	$C_{22}H_{25}N_3O_5S$	80±1	57±1	N.A.	84.5±7.9

a—e) See footnotes of Table IV. N.T.: not tested. N.A.: not active.

TABLE VIII. Biphenyl Tetrazole Derivatives of Formula B



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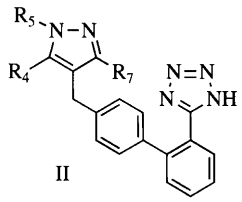

II

Compd. No.	Type	R_4	R_5	R_7	Method	Yield[a] (%)	mp (°C)	Formula[b]	*In vitro* activity % displacement[c]		Oral activity change in BP (mmHg)[d]
									10^{-5} M	10^{-7} M	10 mg/kg
72	I	*n*-C_3H_7	CH_3	CH_2OCH_3	M	24	128—130	$C_{23}H_{26}N_6O$	61±1	35±2	−63.8±11.1
73	II	*n*-C_3H_7	CH_3	CH_2OCH_3	M	8	133—134	$C_{23}H_{26}N_6O$	57±1	7±1	N.T.
74	I	*n*-C_4H_9	CH_3	CH_2OCH_3	M	17	134—135	$C_{24}H_{28}N_6O$	67±1	35±2	−42.5±15.5
75	I	*n*-C_3H_7	CH_2CF_3	CH_2OCH_3	N	15	177—178	$C_{24}H_{25}F_3N_6O$	72±1	55±1	−35.8±13.9
76	I	*n*-C_4H_9	CH_2CF_3	CH_2OCH_3	N	16	172—173	$C_{25}H_{27}F_3N_6O$	70±1	54±1	−28.6±12.9
77	I	*n*-C_4H_9	CH_3	CH_2OH	O	30	110—112	$C_{23}H_{26}N_6O$	69±1	47±1	−57.9±13.6
78	I	*n*-C_4H_9	CH_2CF_3	CH_2OH	O	27	121—122	$C_{24}H_{25}F_3N_6O$	72±1	60±1	−57.8±10.5
79	I	*n*-C_3H_7	CH_2CF_3	CH_2OH	O	32	115—116	$C_{23}H_{23}F_3N_6O$	70±1	63±2	−69.3±11.4
80	I	*n*-C_3H_7	CH_3	CH_2OH	O	31	136—139	$C_{22}H_{24}N_6O$	65±2	35±1	−75 ±26.8
81	I	*n*-C_4H_9	CH_3	CO_2Et	P	16	128—129	$C_{25}H_{28}N_6O_2$	64±1	9±1	−39.6±13.7
82	I	*n*-C_4H_9	CH_3	CO_2H	Q	78	147—148	$C_{23}H_{24}N_6O_2$	64±1	37±1	−67.6±11.6
83	I	*n*-C_3H_7	CH_2CF_3	CO_2Et	P	18	145—147	$C_{25}H_{25}F_3N_6O_2$	66±1	20±2	−23.6±12.2
DuP 753		—	—	—	—	—	—	—	—	—	−104 ±11.1

a—d) See footnotes of Table VI. N.T.: not tested.

observation that compounds of type II (**67** and **70**) display significantly lower affinities than corresponding type I derivatives (**68** and **71**), which indicates either that the electronic nature of the two nitrogen atoms is critical for the activity or that steric hindrance at the 2-position is unfavorable. These results are in agreement with those of Glaxo.[10a] *In vivo*, the two tested compounds (**68** and **71**) have no or weak oral activity for inhibition of AII-induced pressor response at 100 mg/kg, while they display high activity at 10 mg/kg i.v., which confirms the poor oral bioavailability of sulfobenzoic derivatives.

The comparison between **72** and **73** in Table VIII confirms that the substitution at the nitrogen adjacent to the alkyl side chain of the pyrazole ring is unfavorable for *in vitro* activity. When R_7 is methoxymethyl, the most favorable combination for oral antihypertensive activity on renal artery-ligated rats is $R_4 = n\text{-}C_3H_7$ and $R_5 = CH_3$ (**72**). In this case the introduction of a 2,2,2-trifluoroethyl group (**75** and **76**) decreases the oral activity, though it seems to increase the *in vitro* affinity. When R_7 is hydroxymethyl (**77** to **80**), the optimal oral activity is obtained when $R_4 = n\text{-}C_3H_7$ and $R_5 = CH_2CF_3$ or CH_3 (**79** and **80**). In the Glaxo study,[10a] it was shown that 5-carboxylic acid derivatives ($R_7 = CO_2H$) were significantly more potent *in vitro* than 5-hydroxymethyl and 5-methoxymethyl derivatives. In our study we found no

significant variation in *in vitro* activity when a 5-hydroxymethyl group was replaced by a 5-carboxylic acid (see **77** *vs.* **82**); on the contrary, the replacement by an ethyl carboxylate ($R_7 = CO_2Et$) results in a significant decrease of the affinity (**77** *vs.* **81** and **79** *vs.* **83**). The comparison of the oral activities of **81** and **82** indicates that the presence of a 5-ethyl carboxylate group is unfavorable as compared to a 5-carboxylic acid group, confirming the *in vitro* results.

In conclusion, the SAR study on biphenyl tetrazole derivatives of formula B indicates that the nature of the R_7 substituent at the 5-position of the pyrazole ring is likely to modulate the oral antihypertensive activity since the simple replacement of an ethyl carboxylate group by a carboxy group improves sensibly the antihypertensive effect. The influence of R_4 and R_5 seems to be less clear, though comparison between **72** and **75** tends to imply that the nature of R_5 could be critical. Therefore further investigations in this series could lead to the discovery of more potent derivatives. The oral antihypertensive activity of the best derivatives (**72**, **79**, **80**, **82**) could be considered as being in the same range as that of Losartan. As an illustration, the oral antihypertensive activity of UP 221-78 (**79**) is presented below together with that of Losartan.

Oral Antihypertensive Activity of UP 221-78 (79) In studies designed to determine the duration of action of UP 221-78 and to compare its antihypertensive activity with that of Losartan (DuP 753), both compounds were given orally at doses of 1 and 3 mg/kg in conscious renal artery-ligated rats. Continuous measurements of blood pressure by the direct method[14] were performed for at least 16 h after drug administration. Administration of 3 mg/kg of either UP 221-78 or Losartan to these renin-dependent hypertensive rats resulted in a significant

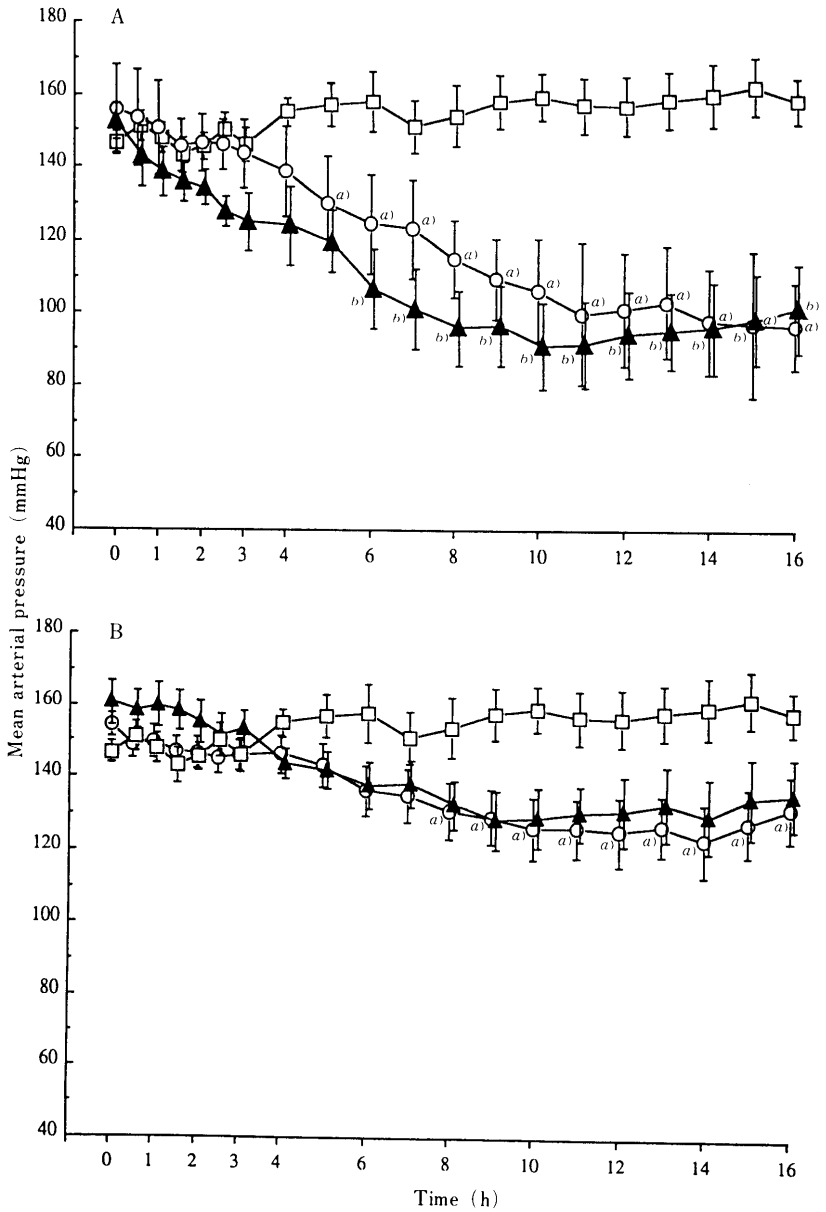

Fig. 3. Oral Antihypertensive Activity of UP 221–78 (**79**) and Losartan

Time-course of the antihypertensive activity of UP 221-78 (derivative **79**, —○—), Losartan (DuP 753, —▲—) and vehicle (—□—) in the conscious renal hypertensive rats. Hypertension in the rat was developed by renal artery ligation as described.[12] Compounds were administered orally by gavage at 1 mg/kg (B) and 3 mg/kg (A), 7 d after renal artery ligation. Vehicle was an aqueous suspension containing gum arabic, Tween 80 and NaCl. Values represent the means ± S.E.M. ($n = 5$—6 rats/group). *a*, *b*) Indicate a difference from pretreatment values (Dunnett's test, $p < 0.05$ *vs.* time 0).

antihypertensive response (Fig. 3).

The maximal decrease in arterial blood pressure was approximately 63 and 60 mmHg for UP 221-78 and Losartan, respectively. The onset of the antihypertensive response after both drugs was gradual, with a maximum effect occurring at approximately 10 h. The duration of action of the two compounds was similar, with the antihypertensive response lasting for at least 16 h. At the 1 mg/kg dose, UP 221-78 induced a statistically significant drop of 30 mmHg in mean arterial blood pressure, whereas the decrease (30 mmHg) induced by Losartan was found to be not statistically significant. In conclusion, we can assume that UP 221-78 is equipotent to Losartan for oral antihypertensive activity and presents a similar pharmacokinetic pattern.

Conclusion

Comparisons between pyrazoles of formula A and B showed that overall, the 5-oxy substituted derivatives synthesized in our study were less orally potent than the 5-C-substituted derivatives. Nevertheless, it is not clear whether this is due to the nature of the linkage (O- or C-) or to the chain length and functionality since there has been no direct comparison between similarly substituted O- and C-linked derivatives (*i.e.* O–CH_2CH_3 *vs.* CH_2–OCH_3). Moreover, among the O-substituted derivatives, compounds **39** and **42** display equivalent *in vitro* and oral activities to the C-linked compounds of Table VIII. Thus, it would be particularly interesting to investigate further the O-linked pyrazole series with the aim of improving the oral activity of these derivatives, since their synthesis is definitely easier than that of the C-linked derivatives.

The observation that substitution at the nitrogen adjacent to the alkyl side chain is detrimental to the activity whereas substitution at the other nitrogen improves the activity, is consistent with data previously reported for bicyclic compounds such as L-158,809,[15] TCV-116[16] or our triazolo [1,5-*c*]pyrimidine derivative, UP 269-6,[7a-c] in which the cyclization takes place on the opposite side to the alkyl side chain. Among the C-linked derivatives, UP 221-78 (**79**) was shown to display similar activity to Losartan when given orally at 3 mg/kg in conscious renal artery-ligated rats, which indicates that a potential candidate for further development is likely to be discovered in this series.

Experimental

^{1}H-NMR spectra were recorded at 200 MHz on a Bruker 200 spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to internal Me_4Si. Melting points were recorded on an Electrothermal digital capillary melting point appratus and are uncorrected. Chromatography was performed on silica gel (mesh 70—230) using the indicated solvent mixtures. Elemental analyses were obtained by using a Carlo Erba MOD-106 elemental analyzer. HPLC experiments were performed on a Varian liquid chromatograph with a UV detector and a suitable integration system (reverse-phase C18 column). Starting materials were commercially available or were prepared as reported.[9]

Ethyl 2-[(2′-Cyanobiphenyl-4-yl)methyl]-3-oxohexanoate (3a) *N,N*-Diisopropylethylamine (1117 ml, 6.4 mol) and LiCl (134.6 g, 3.17 mol) were added to a solution of 4′-(bromomethyl)-2-cyanobiphenyl[7-9] (**2b**, 863.7 g, 3.17 mol) and ethyl butyrylacetate (752 ml, 4.76 mol) in 3900 ml of THF. The mixture was refluxed for 15 h and concentrated *in vacuo*. The residue was taken up with water and extracted with AcOEt. The organic layer was washed carefully with 1 N HCl solution and then with water, dried over $MgSO_4$ and evaporated *in vacuo*. The oily brownish residue was heated to 130 °C under 20 mmHg in order to remove the residual starting materials, affording **3a** (1083 g, 98%) as a crude brown oil, which was used without further purification for the next step (HPLC purity: 85.5%; 4.3% of dialkylated derivative was detected). ^{1}H-NMR ($CDCl_3$) δ: 7.75 (d, 1H, J=8 Hz), 7.63 (t, 1H, J=8 Hz), 7.49—7.39 (m, 4H), 7.30 (d, 2H, J=8 Hz), 4.16 (q, 2H, J=7 Hz), 3.84 (t, 1H, J=7.5 Hz), 3.22 (d, 2H, J=7.5 Hz), 2.65—2.29 (m, 2H), 1.57 (sext, 2H, J=7.4 Hz), 1.22 (t, 3H, J=7.5 Hz), 0.86 (t, 3H, J=7.4 Hz).

All compounds of formula **3** were prepared according to this procedure and are listed in Table I. 4-Nitrobenzyl bromide is commercially available and the preparation of the β-ketoesters has been reported.[9]

4-[(2′-Cyanobiphenyl-4-yl)methyl]-5-hydroxy-1-methyl-3-*n*-propylpyrazole (5a) A solution of **3a** (60 g, 146 mmol, HPLC purity 85.5%) in 150 ml of EtOH was treated with methylhydrazine (15 ml, 282 mmol). The mixture was heated to reflux for 3 h and then concentrated *in vacuo*. The residue was taken up with water and extracted with CH_2Cl_2. The organic layer was extracted twice with a dilute NaOH solution and the aqueous layer was acidified with SO_2 and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a residue, which was crystallized from Et_2O–AcOEt to afford **5a** (40 g, 82%), mp 165 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.70—7.22 (m, 8H), 3.64 (s, 2H), 3.29 (s, 3H), 2.29 (t, 2H, J=7.5 Hz), 1.46 (sext, 2H, J=7.5 Hz), 0.78 (t, 3H, J=7.5 Hz).

All compounds of formula **5** were synthesized by this procedure from the appropriate substituted hydrazine. The data are summarized in Table II.

Method A. 5-Hydroxy-1-methyl-3-*n*-propyl-4-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]pyrazole (37) A solution of **5a** (5 g, 15 mmol) in 50 ml of toluene was treated with trimethyltin azide (4 g, 19 mmol). The mixture was heated to reflux for 14 h, then cooled and 10 ml of $CHCl_3$ and 10 ml of MeOH were added. The obtained crystals were filtered off and taken up into 40 ml of toluene and 10 ml of THF. Gaseous HCl was bubbled in for 10 min and the reaction mixture was stirred for 1 h at room temperature. The solvents were evaporated off *in vacuo* and the residue was taken up with a dilute NaOH solution and washed with AcOEt. The aqueous layer was acidified by bubbling of SO_2 and the obtained crystals were collected by filtration and washed with acetone to give **37** (3.1 g, 61%), mp 150—153 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.61—7.56 (m, 4H), 7.10 (d, 2H, J=7.5 Hz), 6.98 (d, 2H, J=7.5 Hz), 3.54 (s, 2H), 3.34 (s, 3H), 2.25 (t, 2H, J=7.5 Hz), 1.40 (sext, 2H, J=7.5 Hz), 0.81 (t, 3H, J=7.5 Hz).

Method B. a) Ethyl 2-[4-[(2′-Cyanobiphenyl-4-yl)methyl]-1-methyl-3-*n*-propylpyrazol-5-yl]oxyacetate (6a) Sodium carbonate (5.3 g, 50 mmol) and ethyl bromoacetate (61 ml, 55 mmol) were added to a solution of **5a** (16.5 g, 50 mmol) in 200 ml of acetone. The mixture was heated to reflux for 10 h and then concentrated *in vacuo*. The residue was taken up with 50 ml of water and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a residue, which was chromatographed on silica gel with a mixture of $CHCl_3$ and acetone (95 : 5) as eluent to give **6a** (12 g, 58%), oil. ^{1}H-NMR ($CDCl_3$) δ: 7.62 (d, 1H, J=7.5 Hz), 7.50 (t, 1H, J=7.5 Hz), 7.36—7.25 (m, 4H), 7.14 (d, 2H, J=7.8 Hz), 4.31 (s, 2H), 4.05 (q, 2H, J=6.5 Hz), 3.71 (s, 2H), 3.62 (s, 3H), 2.33 (t, 2H, J=7.8 Hz), 1.48 (sext, 2H, J=7.8 Hz), 1.10 (t, 3H, J=6.5 Hz), 0.80 (t, 3H, J=7.8 Hz).

b) Ethyl 2-[1-Methyl-3-*n*-propyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazol-5-yl]oxyacetate (41) Prepared according to method A from **6a** and chromatographed on silica gel with a mixture of $CHCl_3$–MeOH (90 : 10), yield 55%, mp 187—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.71—7.49 (m, 4H), 7.06 (d, 2H, J=7.5 Hz), 6.98 (d, 2H, J=7.5 Hz), 4.64 (s, 2H), 4.10 (q, 2H, J=7.0 Hz), 3.68 (s, 2H), 3.60 (s, 3H), 2.24 (t, 2H, J=7.5 Hz), 1.43 (sext, 2H, J=7.5 Hz), 1.26 (t, 3H, J=7.0 Hz), 0.81 (t, 3H, J=7.5 Hz).

Method C. a) 4-[(2′-Cyanobiphenyl-4-yl)methyl]-5-[(*N,N*-dimethylcarbamoyl)oxy]-1-methyl-3-*n*-propylpyrazole (7a) *N,N*-Dimethylcarbamoyl chloride (3.2 ml, 34.7 mmol) was added dropwise to a solution of **5a** (10 g, 30.3 mmol) in 100 ml of CH_2Cl_2 and 5 ml of triethylamine. The mixture was then heated to reflux for 10 h. After it had cooled, water was added and the whole was washed with a $KHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give **7a** (9.1 g, 75%), oil. H-NMR ($CDCl_3$) δ: 7.74 (d, 1H, J=7.5 Hz), 7.62 (t,

1H, J=7.5 Hz), 7.50—7.38 (m, 4H), 7.30 (d, 2H, J=7.5 Hz), 3.72 (s, 2H), 3.62 (s, 3H), 2.92 (s, 3H), 2.85 (s, 3H), 2.47 (t, 2H, J=7.8 Hz), 1.60 (sext, 2H, J=7.8 Hz), 0.92 (t, 3H, J=7.8 Hz).

b) 5-[*N*,*N*-Dimethylcarbamoyl)oxy]-1-methyl-3-*n*-propyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazole (62) Prepared according to method A from **7a**, yield 62%, mp 103—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.08 (d, 1H, J= 7.5 Hz), 7.61—7.38 (m, 3H), 7.11 (d, 2H, J=7.8 Hz), 7.01 (d, 2H, J=7.8 Hz), 3.63 (s, 2H), 3.43 (s, 3H), 2.97 (s, 3H), 2.82 (s, 3H), 2.47 (t, 2H, J=7.5 Hz), 1.54 (sext, 2H, J=7.5 Hz), 0.85 (t, 3H, J=7.5 Hz).

Method D. a) Ethyl 2-[1-Methyl-4-(4-nitrobenzyl)-3-*n*-propylpyrazol-5-yl]oxyacetate (6b) Prepared according to method B-a from **5h**, chromatographed on silica gel with CH_2Cl_2–acetone (90 : 10), yield 51%, mp 60—61 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 2H, J=9 Hz), 7.28 (d, 2H, J=9 Hz), 4.38 (s, 2H), 4.13 (q, 2H, J=6.5 Hz), 3.84 (s, 2H), 3.70 (s, 3H), 2.32 (t, 2H, J=7.8 Hz), 1.51 (sext, 2H, J=7.8 Hz), 1.29 (t, 3H, J=6.5 Hz), 0.88 (t, 3H, J=7.8 Hz).

b) Ethyl 2-[4-[4-[(2-Carboxy-3,6-dichlorobenzoyl)amino]benzyl-1-methyl-3-*n*-propylpyrazol-5-yl]oxyacetate (20) A solution of **6b** (3.4 g, 9.4 mmol) in 50 ml of EtOH was hydrogenated at room temperature and ordinary pressure over 500 mg of Raney nickel until hydrogen uptake has ceased. The catalyst was filtered off and the solvent was evaporated *in vacuo* to give ethyl 2-[4-(4-aminobenzyl)-1-methyl-3-*n*-propylpyrazol-5-yl]oxyacetate (**17′a**, 3 g, 93%), mp 103 °C. Compound **17′a** (3 g, 9 mmol) was dissolved in 50 ml of CH_3CN, and 3,6-dichlorophthalic anhydride (1.9 g, 9 mmol) was added. The mixture was stirred at room temperature for 3 h and the solvent was evaporated *in vacuo*. The residue was taken up with 20 ml of acetone and 15 ml of Et_2O and *N*,*N*-dicyclohexylamine (1.6 g, 9 mmol) was added. The mixture was stirred for 1 h at room temperature, then the crystals were filtered off, washed with Et_2O and dried to give **20**, dicyclohexylamine salt (5 g, 77%), mp 199—200 °C. ^{1}H-NMR (DMSO-d_6) δ: 10.25 (s, 1H), 7.55 (d, 2H, J=8.4 Hz), 7.39—7.26 (m, 2H), 7.00 (d, 2H, J=8.4 Hz), 4.62 (s, 2H), 4.10 (q, 2H, J=7 Hz), 3.65 (s, 2H), 3.60 (s, 3H), 3.00—2.80 (m, 2H), 2.26 (t, 2H, J=7.5 Hz), 1.92—1.85 (m, 4H), 1.64—1.39 (m, 8H), 1.29—1.04 (m, 13H), 0.84 (t, 3H, J=7.5 Hz).

Method E. a) Methyl 2-[1-Methyl-4-(4-nitrobenzyl)-3-*n*-propylpyrazol-5-yl]oxyacetate (6c) Prepared according to method B-a from **5h** and methyl 2-bromoacetate, chromatographed on silica gel with CH_2Cl_2–acetone (90 : 10), yield 48%, mp 57 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 2H, J=9 Hz), 7.27 (d, 2H, J=9 Hz), 4.36 (s, 2H), 3.83 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.32 (t, 2H, J=7.8 Hz), 1.51 (sext, 2H, J=7.8 Hz), 0.87 (t, 3H, J=7.8 Hz).

b) Methyl 2-[4-[4-[(2-Carboxy-3,6-dichlorobenzoyl)amino]benzyl]-1-methyl-3-*n*-propylpyrazol-5-yl]oxyacetate (21) The methyl 2-[4-(4-aminobenzyl)-1-methyl-3-*n*-propylpyrazol-5-yl]oxyacetate (**17′b**) was prepared according to method D-b from **6c**, yield 96%; this oil was used without further purification. Compound **17′b** (3.2 g, 10 mmol) was dissolved in 50 ml of CH_3CN, and 3,6-dichlorophthalic anhydride (2.1 g, 10 mmol) was added. The mixture was stirred for 5 h at room temperature and the solvent was evaporated off *in vacuo*. The residue was crystallized from acetone–Et_2O to give **21** (3.8 g, 84%), mp 150—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 10.63 (s, 1H), 7.65 (s, 2H), 7.53 (d, 2H, J=8.2 Hz), 7.07 (d, 2H, J=8.2 Hz), 4.65 (s, 2H), 3.68 (s, 2H), 3.63 (s, 3H), 3.61 (s, 3H), 2.29 (t, 2H, J=7.5 Hz), 1.47 (sext, 2H, J=7.5 Hz), 0.84 (t, 3H, J= 7.5 Hz).

Method F. 2-[[4-[[5-[(Ethoxycarbonylmethyl)oxy]-1-methyl-3-*n*-propylpyrazol-4-yl]methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (31) Compound **17′a** (3 g, 8.3 mmol) was dissolved in 30 ml of CH_3CN, and 2-sulfobenzoic acid cyclic anhydride (1.5 g, 8.1 mmol) was added. The mixture was stirred at room temperature for 5 h and concentrated *in vacuo*. The residue was crystallized from AcOEt–Et_2O to give **31** (3.8 g, 84%), mp 203—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 11.35 (s, 1H), 7.91 (m, 1H), 7.73 (m, 1H), 7.61—7.42 (m, 4H), 7.10 (d, 2H, J=8 Hz), 4.80 (s, 2H), 4.10 (q, 2H, J=6.5 Hz), 3.79 (s, 2H), 3.71 (s, 3H), 2.42 (t, 2H, J=7.5 Hz), 1.50 (sext, 2H, J=7.5 Hz), 1.17 (t, 3H, J=6.5 Hz), 0.87 (t, 3H, J=7.5 Hz).

Method G. a) 2-[3-*n*-Butyl-1-methyl-4-(4-nitrobenzyl)pyrazol-5-yl]-oxyethanol (6d) Sodium carbonate (4.6 g, 43.4 mmol) and 2-bromoethanol (5.5 g, 44 mmol) were added to a solution of **5i** (12 g, 41.5 mmol) in 150 ml of 2-butanone. The mixture was refluxed for 12 h and concentrated *in vacuo*. The residue was taken up with a dilute solution of NaOH and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*, then the residue was chromatographed on silica gel with AcOEt–acetone (6 : 4) to give **6d** (4.5 g, 32%), mp 81 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.17 (d, 2H, J=8 Hz), 7.42 (d, 2H, J=8 Hz), 4.97 (t, 1H, J=5 Hz), 3.96 (t, 2H, J=4 Hz), 3.85 (s, 2H), 3.60 (m, 2H), 3.58 (s, 3H), 2.27 (t, 2H, J=7.8 Hz), 1.37 (sext, 2H, J=7.8 Hz), 1.21 (sext, 2H, J=7.8 Hz), 0.76 (t, 3H, J=7.8 Hz).

b) 2-[[4-[[3-*n*-Butyl-5-[(hydroxyethyl)oxy]-1-methylpyrazol-4-yl]-methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (32) The 2-[4-(4-aminobenzyl)-3-*n*-butyl-1-methylpyrazol-5-yl]oxyethanol (**17′c**) was prepared according to method D-b, from **6d**, yield 94%; this oil was used without further purification. The treatment of **17′c** according to method F gave **32** in 68% yield, mp 174—176 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.93—7.85 (m, 1H), 7.76—7.68 (m, 1H), 7.58 (d, 2H, J=8 Hz), 7.51—7.45 (m, 2H), 7.12 (d, 2H, J=8 Hz), 4.11 (t, 2H, J=4 Hz), 3.79 (s, 2H), 3.62 (d, 2H, J=4 Hz), 2.49 (t, 2H, J=7.5 Hz), 1.44 (sext, 2H, J=7.5 Hz), 1.27 (sext, 2H, J=7.5 Hz), 0.85 (t, 3H, J=7.5 Hz).

Method H. a) 2-[4-[(2′-Carbomethoxybiphenyl-4-yl)methyl]-1-methyl-3-*n*-propylpyrazol-5-yl]oxyethanol (6e) Sodium carbonate (2.5 g, 23.5 mmol) and 2-bromoethanol (3 g, 23.5 mmol) were added to a solution of **5g** (8 g, 22 mmol) in 100 ml of 2-butanone. The mixture was refluxed for 16 h and the solvent was evaporated off *in vacuo*. The residue was taken up with water and extracted with $CHCl_3$. The organic layer was washed twice with water, dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel with AcOEt–acetone (1 : 1) to give **6e** (4.8 g, 53%), as an oil, which was used without further pruification. ^{1}H-NMR (DMSO-d_6) δ: 7.70 (d, 1H, J=7.6 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.49—7.37 (m, 2H), 7.18 (s, 4H), 4.98 (t, 1H, J=5 Hz), 3.98 (t, 2H, J=4 Hz), 3.75 (s, 2H), 3.65—3.52 (m, 8H), 2.29 (t, 2H, J=7.8 Hz), 1.49 (sext, 2H, J=7.8 Hz), 0.84 (t, 3H, J=7.8 Hz).

b) 2-[4-[2′-Carboxybiphenyl-4-yl)methyl]-1-methyl-3-*n*-propylpyrazol-5-yl]oxyethanol (35) A solution of **6e** (4.8 g, 11.7 mmol) in 50 ml of EtOH was treated with 1.8 g (45 mmol) of NaOH in pellets. The mixture was heated to reflux for 2 h and concentrated *in vacuo*. The residue was taken up with water, washed with AcOEt, acidified by bubbling of SO_2 and extracted with $CHCl_3$. After evaporation *in vacuo* the residue was crystallized from AcOEt–Et_2O to give **35** (4.1 g, 90%), mp 168—170 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.68 (d, 1H, J=7.6 Hz), 7.54 (t, 1H, J=7.6 Hz), 7.43 (d, 1H, J=7.6 Hz), 7.33 (d, 1H, J=7.6 Hz), 7.25—7.13 (m, 4H), 4.95 (br s, 1H), 3.95 (t, 2H, J=4 Hz), 3.73 (s, 2H), 3.61—3.52 (m, 5H), 2.28 (t, 2H, J=7.5 Hz), 1.48 (sext, 2H, J=7.5 Hz), 0.86 (t, 3H, J=7.5 Hz).

Method I. 2-[4-[[5-[(Carboxymethyl)oxy]-1-methyl-3-*n*-propylpyrazol-4-yl]methyl]phenylaminocarbonyl]benzenesulfonic Acid (34) A solution of **31** (3 g, 5.8 mmol) in 30 ml of EtOH was treated with NaOH (0.7 g, 17.4 mmol). The mixture was stirred for 2 h at 50 °C and then allowed to return to room temperature. The solvent was evaporated off *in vacuo*, the residue was taken up with water, the solution was acidified with SO_2 and $CHCl_3$ was added. An oil separated from the water–$CHCl_3$ mixture and crystallized after 2 d at room temperature. The crystals were filtered off and washed with water and Et_2O to give **34** (2.5 g, 88%), mp 170—171 °C. ^{1}H-NMR (DMSO-d_6) δ: 10.84 (s, 1H), 7.94—7.82 (m, 1H), 7.78—7.71 (m, 1H), 7.61—7.41 (m, 4H), 7.10 (d, 2H, J=8 Hz), 4.71 (s, 2H), 3.78 (s, 2H), 3.72 (s, 2H), 2.45 (t, 2H, J=7.5 Hz), 1.51 (sext, 2H, J=7.5 Hz), 0.84 (t, 3H, J=7.5 Hz).

1-Methoxyoctane-2,4-dione (9a) Sodium (26.9 g, 1169 mmol) was suspended in 400 ml of refluxing toluene. The mixture was allowed to cool to 60 °C and a mixture of 2-hexanone (200 ml, 1621 mmol) and methyl 2-methoxyacetate (102 ml, 1029 mmol) was added dropwise, the temperature being ketp between 60 °C and 70 °C during the addition. On completion of the addition the mixture was stirred for 2 h at 55 °C. After cooling, 20 ml of MeOH were added, and the mixture was stirred and mixed with a dilute NaOH solution. The aqueous layer was washed with Et_2O, acidified with HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was distilled to give **9a** (98.6 g, 56%), bp 115—120 °C (15 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 5.78 (s, 1H), 3.98 (s, 2H), 3.44 (s, 3H), 2.32 (t, 2H, J=7.7 Hz), 1.59 (sext, 2H, J=7.7 Hz), 1.38 (sext, 2H, J=7.7 Hz), 0.94 (t, 3H, J=7.7 Hz).

1-Methoxyheptane-2,4-dione (9b) Prepared according to the same procedure as described for **9a**, yield 60%, bp 105—110 °C (15 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 5.77 (s, 1H), 3.98 (s, 2H), 3.42 (s, 3H), 2.29 (t, 2H, J=7.5 Hz), 1.64 (sext, 2H, J=7.5 Hz), 0.94 (t, 3H, J=7.5 Hz).

3-[(2′-Cyanobiphenyl-4-yl)methyl]-1-methoxyheptane-2,4-dione (10b) Compound **2a** (41.1 g, 151 mmol), *N*,*N*-diisopropylethylamine (52 ml, 298 mmol) and lithium bromide (13.1 g, 151 mmol) were added to a

solution of **9b** (35.9 g, 227 mmol) in 400 ml of THF. The mixture was heated to reflux for 15 h, cooled to room temperature and evaporated *in vacuo*. The residue was taken up in a dilute HCl solution and extracted twice wth AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to afford an oil, which was heated to 100 °C under 0.5 mmHg in order to eliminate the starting materials. The residue was chromatographed on silica gel with $CHCl_3$–acetone (95 : 5) to give **10b** (37.8 g, 72%), oil. ^{1}H-NMR ($CDCl_3$) δ: 7.67 (d, 1H, J=7.5 Hz), 7.56 (t, 1H, J=7.5 Hz), 7.43—7.30 (m, 4H), 7.18 (d, 2H, J=7.8 Hz), 4.13 (t, 1H, J=7.4 Hz), 3.92—3.71 (m, 2H), 3.23 (s, 3H), 3.21—2.91 (m, 2H), 2.53—2.07 (m, 2H), 1.44 (sext, 2H, J=7.5 Hz), 0.76 (t, 3H, J=7.5 Hz).

All compounds of formula **10** were prepared according to this procedure and are listed in Table III.

Method J. a) 5-Methoxymethyl-4-(4-nitrobenzyl)-3-*n*-propylpyrazole (11a) Hydrazine hydrate (2 ml, 41 mmol) was added to a solution of **10c** (10 g, 34 mmol) in 200 ml of EtOH, and the mixture was heated to reflux for 2 h. The solvent was evaporated off *in vacuo* and the residue was taken up with diisopropyl ether and triturated until it crystallized. The solid material was collected by filtration and washed with Et_2O to give **11a** (7.6 g, 77%), mp 129 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.67 (br s, 1H), 8.10 (d, 2H, J=8 Hz), 7.39 (d, 2H, J=8 Hz), 4.33 (s, 2H), 3.91 (s, 2H), 3.29 (s, 3H), 2.48 (t, 2H, J=7.5 Hz), 1.55 (sext, 2H, J=7.5 Hz), 0.89 (t, 3H, J=7.5 Hz).

b) 2-[[4-[(5-Methoxymethyl-3-*n*-propylprazol-4-yl)methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (66) The 4-(4-aminobenzyl)-5-methoxymethyl-3-*n*-propylpyrazole (**17'd**) was prepared according to method D-b from **11a**, yield 93%, mp 126 °C. The treatment of **17'd** according to method F, afforded **66**, in 70% yield, mp 253—256 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.97—7.81 (m, 1H), 7.78—7.67 (m, 1H), 7.61—7.40 (m, 4H), 7.14 (d, 2H, J=8 Hz), 4.58 (s, 2H), 3.83 (s, 2H), 3.31 (s, 3H), 2.59 (t, 2H, J=7.5 Hz), 1.53 (sext, 2H, J=7.5 Hz), 0.85 (t, 3H, J=7.5 Hz).

Method K. a) 5-Methoxymethyl-1-methyl-4-(4-nitrobenzyl)-3-*n*-propylpyrazole (13a) and 3-Methoxymethyl-1-methyl-4-(4-nitrobenzyl)-5-*n*-propylpyrazole (12a) A solution of **10c** (13.5 g, 46 mmol) in 270 ml of EtOH was treated with methylhydrazine (3 ml, 56 mmol). The mixture was heated to reflux for 2 h and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–pentane (7 : 3) to give **13a** (first eluted product, 4.5 g, 32%), mp 75 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 2H, J=8.5 Hz), 7.31 (d, 2H, J=8.5 Hz), 4.31 (s, 2H), 3.92 (s, 2H), 3.79 (s, 3H), 3.30 (s, 3H), 2.49 (t, 2H, J=7.5 Hz), 1.41 (sext, 2H, J=7.5 Hz), 0.89 (t, 3H, J=7.5 Hz) and **12a** (second eluted product, 9.3 g, 67%), mp 84 °C. ^{1}H-NMR ($CDCl_3$): δ: 8.12 (d, 2H, J=8.5 Hz), 7.29 (d, 2H, J=8.5 Hz), 4.31 (s, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.28 (s, 3H), 2.42 (t, 2H, J=7.5 Hz), 1.53 (sext, 2H, J=7.5 Hz), 0.88 (t, 3H, J=7.5 Hz).

b) 2-[[4-[(5-Methoxymethyl-1-methyl-3-*n*-propylpyrazol-4-yl)methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (68) The 4-(4-aminobenzyl)-5-methoxymethyl-1-methyl-3-*n*-propylpyrazole (**17'e**) was prepared according to method D-b from **13a**, yield 93%, oil. The treatment of **17'e** according to method F afforded **68** in a yield of 50%, mp 237—238 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.94—7.81 (m, 1H), 7.77—7.66 (m, 1H), 7.59—7.41 (m, 4H), 7.07 (d, 2H, J=7.8 Hz), 4.43 (s, 2H), 3.77 (br s, 5H), 3.25 (s, 3H), 2.39 (t, 2H, J=7.5 Hz), 1.50 (sext, 2H, J=7.5 Hz), 0.83 (t, 3H, J=7.5 Hz).

c) 2-[[4-[[(3-Methoxymethyl-1-methyl-5-*n*-propylpyrazol-4-yl)-methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (67) The 4-(4-aminobenzyl)-3-methoxymethyl-1-methyl-5-*n*-propylpyrazole was prepared according to method D-b from **12a**, yield 95%, mp 91 °C. The treatment of the latter according to method F afforded **67** in a yield of 45%, mp 216—218 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.94—7.82 (m, 1H), 7.76—7.64 (m, 1H), 7.56—7.42 (m, 4H), 7.09 (d, 2H, J=7.8 Hz), 4.31 (s, 2H), 3.76 (s, 3H), 3.74 (s, 2H), 3.24 (s, 3H), 2.56 (t, 2H, J=7.5 Hz), 1.36 (sext, 2H, J=7.5 Hz), 0.84 (t, 3H, J=7.5 Hz).

Method L. a) 3-Hydroxymethyl-1-methyl-4-(4-nitrobenzyl)-5-*n*-propylpyrazole (14'a) A solution of **12a** (11.7 g, 38.6 mmol) in 360 ml of CH_2Cl_2, cooled to 0 °C, was treated dropwise with BBr_3 (7.3 ml, 77.2 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 12 h, then a dilute solution of ammonium hydroxide was added dropwise, and the organic layer was decanted, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give the 5-bromomethyl derivative (12.4 g, mp 93 °C). The latter was dissolved in 90 ml of water and 90 ml of dioxane. To this solution was added Na_2CO_3 (9.3 g, 87 mmol). The mixture was heated to reflux for 3 h and concentrated to half its volume *in vacuo*. The residue was taken up with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give **14'a** (7.2 g, 66%), mp 129 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.11 (d, 2H, J=8 Hz), 7.46 (d, 2H, J=8 Hz), 4.91 (t, 1H, J=5 Hz), 4.32 (d, 2H, J=5 Hz), 3.94 (s, 2H), 3.68 (s, 3H), 2.47 (t, 2H, J=7.5 Hz), 1.29 (sext, 2H, J=7.5 Hz), 0.82 (t, 3H, J=7.5 Hz).

b) 4-(4-Aminobenzyl)-3-hydroxymethyl-1-methyl-5-*n*-propylpyrazole Prepared according to method D-b from **14'a**, yield 60%, mp 115 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.90 (d, 2H, J=7.5 Hz), 6.60 (d, 2H, J=7.5 Hz), 4.48 (s, 2H), 3.73 (s, 3H), 3.67 (s, 2H), 3.33 (br s, 3H), 2.48 (t, 3H, J=7.5 Hz), 1.44 (sext, 2H, J=7.5 Hz), 0.89 (t, 3H, J=7.5 Hz).

c) 2-[[4-[[3-Hydroxymethyl-1-methyl-5-*n*-propylpyrazol-4-yl]methyl]phenyl]aminocarbonyl]benzenesulfonic Acid (70) Prepared according to method F, from the amino derivative obtained by method L-b, yield 80%, mp 216—218 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.97—7.84 (m, 1H), 7.78—7.67 (m, 1H), 7.60—7.44 (m, 4H), 7.13 (d, 2H, J=7.8 Hz), 6.95—6.45 (br s, 3H), 4.47 (s, 2H), 3.83 (s, 3H), 3.78 (s, 2H), 2.62 (t, 2H, J=7.5 Hz), 1.40 (sext, 2H, J=7.5 Hz), 0.86 (t, 3H, J=7.5 Hz).

Method M. a) 4-[(2'-Cyanobiphenyl-4-yl)methyl]-5-methoxymethyl-1-methyl-3-*n*-propylpyrazole (13b) and 4-[(2'-Cyanobiphenyl-4-yl)methyl]-3-methoxymethyl-1-methyl-5-*n*-propylpyrazole (12b) Hydrazine hydrate (2.8 ml, 57 mmol) was added to a solution of **10b** (17.8 g, 51 mmol) in 100 ml of EtOH and the mixture was refluxed under stirring for 2 h. The solvent was evaporated off and the residue was chromatographed on silica gel with CH_2Cl_2–acetone (8 : 2) to give 16.1 g of 4-[(2'-cyanobiphenyl-4-yl)methyl]-5-methoxymethyl-3-propylpyrazole as an oil. The latter (16.1 g, 47 mmol) was dissolved in 160 ml of acetone, and DBU (8.3 ml, 56 mmol) and iodomethane (8 ml, 128 mmol) were added. The mixture was heated to 45 °C for 8 h and the solvent was removed *in vacuo*. The residue was taken up with dilute HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily residue. Chromatography on silica gel with Et_2O gave **13b** (first eluted compound, 8.7 g, 51%), oil. ^{1}H-NMR ($CDCl_3$) δ: 7.73 (d, 1H, J=7.5 Hz), 7.62 (t, 1H, J=7.5 Hz), 7.51—7.36 (m, 4H), 7.22 (d, 2H, J=8 Hz), 4.32 (s, 2H), 3.865 (s, 5H), 3.26 (s, 3H), 2.50 (t, 2H, J=7.5 Hz), 1.57 (sext, 2H, J=7.5 Hz), 0.90 (t, 3H, J=7.5 Hz). Further elution with Et_2O–acetone (9 : 1) gave **12b** (2.7 g, 16%), oil.

b) 5-Methoxymethyl-1-methyl-3-*n*-propyl-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazole (72) A solution of **13b** (5.6 g, 16.6 mmol) in 100 ml of toluene was treated with trimethyltin azide (5.2 g, 25 mmol). The mixture was refluxed for 20 h, cooled to room temperature, taken up with 100 ml of water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a residue, which crystallized from AcOEt–Et_2O to afford a solid (3.4 g, 6.1 mmol), mp 182 °C, which was identified as the trimethylstannyl derivative by ^{1}H-NMR. The product was dissolved in 90 ml of dioxane and 6 ml of water, then benzylamine (1.36 g, 12.2 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was taken up with dilute HCl and extracted with AcOEt. The organic layer was extracted with an ammonium hydroxide solution and the aqueous layer was separated, filtered and acidified by bubbling of SO_2. The obtained crystals were collected by suction and dried to give **72** (3.0 g, 48%), mp 128—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.90 (d, 2H, J=7.6 Hz), 7.62—7.35 (m, 3H), 6.98 (br s, 4H), 4.21 (s, 2H), 3.74 (s, 2H), 3.56 (s, 3 H), 3.22 (s, 3H), 2.26 (t, 2H, J=7.5 Hz), 1.42 (sext, 2H, J=7.5 Hz), 0.80 (t, 3H, J=7.5 Hz).

c) 3-Methoxymethyl-1-methyl-5-*n*-propyl-4-[[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]pyrazole (73) Prepared according to b) from **12b**, yield 50%, mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.92 (d, 1H, J=7.6 Hz), 7.64—7.39 (m, 3H), 7.08—6.97 (m, 4H), 4.10 (s, 2H), 3.78 (s, 2H), 3.62 (s, 3H), 3.16 (s, 3H), 2.49 (t, 2H, J=7.5 Hz), 1.47 (sext, 2H, J=7.5 Hz), 0.81 (t, 3H, J=7.5 Hz).

Method N. 4-[(2'-Cyanobiphenyl-4-yl)methyl]-5-methoxymethyl-3-*n*-propyl-1-(2,2,2-trifluoroethyl)pyrazole (13c) 2,2,2-Trifluoroethylhydrazine (21.5 g, 113 mmol; 60% in water) was added to a solution of **10b** (30.1 g, 86 mmol) in 350 ml of EtOH. The mixture was refluxed for 4 h and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with AcOEt–cyclohexane (2 : 8) to give **13c** (first eluted compound, 10.7 g, 29%), oil. ^{1}H-NMR ($CDCl_3$) δ: 7.74 (d, 1H, J=7.6 Hz), 7.62 (t, 1H, J=7.6 Hz), 7.52—7.36 (m, 4H), 7.20 (d, 2H, J=8 Hz), 4.80 (q, 2H, J=8.3 Hz), 4.40 (s, 2H), 3.89 (s, 2H), 3.26 (s, 3H), 2.51 (t, 2H, J=7.5 Hz), 1.58 (sext, 2H, J=7.5 Hz), 0.90 (t, 3H, J=7.5 Hz).

Further elution afforded 18.4 g (51%) of the 1-(2,2,2-trifluoroethyl)isomer **12c**, as an oil.

b) 5-Methoxymethyl-3-*n*-propyl-1-(2,2,2-trifluoroethyl)-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazole (75) A solution of **13c** (3.2 g, 7.5 mmol) in 50 ml of xylene was treated with trimethyltin azide (1.8 g, 8.6 mmol) and the mixture was heated to reflux for 30 h. The solution was then cooled and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was taken up into 30 ml of THF and gaseous HCl was bubbled in for 10 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (97 : 3) to give **75** (1.8 g, 50%), mp 177—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.57—7.31 (m, 4H), 6.93 (s, 4H), 4.67 (q, 2H, J=8.3 Hz), 4.30 (s, 2H), 3.68 (s, 2H), 3.14 (s, 3H), 2.32 (t, 2H, J=7.5 Hz), 1.42 (sext, 2H, J=7.5 Hz), 0.77 (t, 3H, J=7.5 Hz).

Method O. a) 4-[(2′-Cyanobiphenyl-4-yl)methyl]-5-hydroxymethyl-1-methyl-3-*n*-propylpyrazole (14a) Prepared according to method L-a as an oil, which was chromatographed on silica gel with CH_2Cl_2–acetone (8 : 2), yield 80%. ^{1}H-NMR (DMSO-d_6) δ: 7.94 (d, 1H, J=7.5 Hz), 7.78 (t, 1H, J=7.5 Hz), 7.65—7.43 (m, 4H), 7.29 (d, 2H, J=8 Hz), 5.20 (t, 1H, J=5 Hz), 4.49 (d, 2H, J=5 Hz), 3.33 (s, 2H), 3.27 (s, 3H), 2.32 (t, 2H, J=7.5 Hz), 1.42 (sext, 2H, J=7.5 Hz), 0.81 (t, 3H, J=7.5 Hz).

b) 5-Hydroxymethyl-1-methyl-3-*n*-propyl-4-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]pyrazole (80) A solution of **14a** (12 g, 34.7 mmol) in 120 ml of acetic anhydride was refluxed for 2 h. The solvent was evaporated off to give 12.7 g of the 5-acetoxymethyl derivative as an oil. The latter was dissolved in 200 ml of toluene and trimethyltin azide (8 g, 38 mmol) was added. The mixture was refluxed for 30 h and then the solvent was evaporated off. The residue was taken up with 100 ml of EtOH and 100 ml of water and NaOH (1.9 g, 46 mmol) was added. The mixture was heated to 50 °C for 3 h and the solvents were evaporated off *in vacuo*. The residue was chromatographed on silica gel with AcOEt–MeOH (97 : 3) to give **80** (5 g, 37%), mp 136—139 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.68—7.44 (m, 4H), 7.12—6.98 (m, 4H), 5.00 (br s, 1H), 4.50 (s, 2H), 3.84 (s, 3H), 3.78 (s, 2H), 2.38 (t, 2H, J=7.5 Hz), 1.48 (sext, 2H, J=7.5 Hz), 0.86 (t, 3H, J=7.5 Hz).

Method P. Ethyl 3-*n*-Butyl-1-methyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazole-5-carboxylate (81) A solution of sodium dichromate dihydrate (7.2 g, 24 mmol) in 16 ml of water was added dropwise to a suspension of the hydroxymethyl derivative **77** (26 g, 72 mmol; prepared according to method L from **74**) in 65 ml of water and 65 ml of sulfuric acid, at a temperature below 30 °C. On completion of the addition the temperature raised to 35 °C and the mixture was stirred for 5 h at this temperature. The mixture was then poured into iced water, made alkaline by addition of NaOH (pH = 8) and filtered on Celite before being washed with AcOEt. The aqueous layer was acidified with SO_2 to pH 6 and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give an oily residue, which was crystallized from isopropyl ether to afford 3-*n*-butyl-4-[(2′-cyanobiphenyl-4-yl)methyl]-1-methylpyrazole-5-carboxylic acid (**15a**, 8.7 g, 32%), mp 181 °C. The latter was dissolved in 200 ml of $CHCl_3$. The solution was cooled to 0 °C, then *N*,*N*-dicyclohexylcarbodiimide (5.2 g, 25 mmol) and 4,6-dimethyl-2-aminopyridine (0.2 g, 1.6 mmol) were added, followed by 4 ml of EtOH added dropwise. The mixture was stirred at room temperature for 2 h, filtered and washed with dilute NaOH solution and acetic acid. The organic layer was dried and evaporated *in vacuo* and the residue was chromatographed on silica gel with AcOEt–cyclohexane (1 : 1) to give ethyl 3-*n*-butyl-4-[(2′-cyanobiphenyl-4-yl)methyl]-1-methylpyrazole-5-carboxylate (**16a**, 7.1 g, 77%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 7.72 (d, 1H, J=7.5 Hz), 7.60 (t, 1H, J=7.5 Hz), 7.50—7.34 (m, 4H), 7.19 (d, 2H, J=7.5 Hz), 4.26 (q, 2H, J=6.5 Hz), 4.12 (s, 5H), 2.54 (t, 2H, J=7.5 Hz), 1.62—1.46 (m, 2H), 1.42—1.29 (m, 2H), 1.22 (t, 3H, J=6.5 Hz), 0.89 (t, 3H, J=7.5 Hz). The treatment of **16a** (7.1 g, 17.7 mmol) with trimethyltin azide (4 g, 19.1 mmol) according to method N-b gave **81** (4.3 g, 54%), mp 128—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.09 (d, 2H, J=7.5 Hz), 7.63—78.47 (m, 2H), 7.39 (d, 2H, J=7.5 Hz), 7.17 (m, 4H), 4.24 (1, 2H, J=6.5 Hz), 4.05 (s, 2H), 3.97 (s, 3H), 2.41 (t, 2H, J=7.5 Hz), 1.57—1.39 (m, 2H), 1.35—1.14 (m, 5H), 0.85 (t, 3H, J=7.5 Hz).

Method Q. 3-*n*-Butyl-1-methyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrazole-5-carboxylic Acid (82) A solution of **81** (2.2 g, 4.9 mmol) in a mixture of 20 ml of water, 20 ml of EtOH and NaOH (0.5 g, 12.5 mmol) was heated to reflux for 2 h. The solvents were removed by evaporation *in vacuo* and the residue was taken up with water, washed with AcOEt and acidified with SO_2 (pH = 5.5). The obtained crystals were collected by suction, and washed with water and Et_2O to give **82** (1.6 g, 78%), mp 147—148 °C. ^{1}H-NMR (DMSO-d_6): 7.70—7.49 (m, 4H), 7.05—6.95 (m, 4H), 4.02 (s, 2H), 4.00 (s, 3H), 2.39 (t, 2H, J=7.5 Hz), 1.46—1.13 (m, 4H), 0.79 (t, 3H, J=7.3 Hz).

Biology. Angiotensin II Receptor Binding Assay Rat adrenal membranes were obtained as described.[12] Rats were decapitated and the whole adrenals were rapidly dissected and freed from fatty tissue. They were rapidly dried and weighed. Adrenal tissue were homogenized in 100 volumes of ice-cold buffer (Tris–HCl 10 mM, saccharose 0.2 M, EDTA 1 mM, pH 7.4) with a glass-Teflon homogenizer. The homogenate was centrifuged at 3000 *g* for 10 min at 4 °C. The supernatant was further centrifuged at 12000 *g* for 13 min at 4 °C, and this supernatant was ultracentrifuged in a polycarbonate tube at 102000 *g* for 60 min at 4 °C. The resulting pellet was resuspended in 50 volumes of ice-cold incubation buffer (Tris–HCl 50 mM, $MgCl_2$ 5 mM, BSA 0.25%, pH 7.2) and homogenized in the glass-Teflon homogenizer. Receptor binding studies were carried out as previously described[17,18] with slight modifications. Total reaction volume was 500 μl, consisting of 100 μl of membranes (25—40 μg protein), 50 μl of [^{125}I]Sar 1–Ile 8–AII (0.2 nM, final concentration), 50 μl of various concentrations of the drugs (10^{-5} and 10^{-7} M for screening test) and 300 μl of incubation buffer. Incubation time was 60 min at 25 °C. Non-specific binding was measured in the presence of 1 μM (final concentration) unlabelled AII and was about 4—11% of total binding. The reaction was terminated by addition of 3 ml of cold washing buffer (Tris–HCl 50 mM, $MgCl_2$ 5 mM, pH 7.2), followed by rapid filtration through Whatman GF/B glass fiber, filters which were washed twice with the washing buffer. Each assay was performed in triplicate.

Data Analytis Competition data were analyzed using the non linear regression program LIGAND[19] adapted for an IBM-PC[20] and obtained from Elsevier-Biosoft (Cambridge, England).

Antihypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats Male CD Sprague Dawley rats (250—270 g) were anesthetized with ketamine (100 mg/kg, i.p.) and the left renal artery was completely ligated by means of a 4.0 silk suture, taking care not to damage the left kidney or left renal vein.[12] Seven days after the ligation, two procedures were performed to record the blood pressure in conscious hypertensive rats. To estimate the oral antihypertensive potency of the AII receptor antagonists, groups of renal artery-ligated rats (n=3—7 rats/dose) were dosed orally by gavage with the test compound at 10 or 30 mg/kg. The SAP was measured before and 3 h after dosing by the indirect tail-cuff method[13] using a sphygmomanometer (PE 300 Narco) coupled to a polygraph (Beckman R411). The change in SAP was expressed as the decrease in SAP 3 h postdose. The MAP was measured by the direct method as described by Smits.[14] Two or three days before the experiment, the animals were anesthetized as above for surgical preparation. The left femoral artery was cannulated and the catheter was passed subcutaneously to the dorsal side of the neck and exteriorized. The catheter was connected to a Statham pressure transducer coupled to a polygraph (Beckman R411) for monitoring arterial blood pressure. The signal output was analyzed with a digital computer (Buxco Electronics, Sharon, U.S.A.). MAP was recorded before and 20 h after dosing. The change in MAP was expressed as maximal decrease in MAP observed during the experiment. When the decrease in MAP was less than −15 mmHg, the drug was considered without effect.

Inhibition of AII-Induced Vasopressor Effects in Conscious Normotensive Rats Male CD Sprague Dawley rats (280—300 g) were anesthetized with ketamine (100 mg/kg i.p.) and the right femoral artery and the left femoral vein were cannulated. After a one-week period, the femoral catheter was connected to a Statham pressure transducer coupled to a polygraph (Beckman R411) for monitoring arterial blood pressure. The signal output was analyzed with a digital computer (Buxco Electronics, Sharon, U.S.A.). To determine the effect of the compound (*p.o.* and i.v.) on the AII-induced pressor response, AII was injected i.v. (150 to 250 ng/kg) in conscious normotensive rats (n=6) before the administration of test compound and subsequently at regular intervals after oral dose for 2 h and after i.v. dose for 1 h. The vasopressor response to AII after each dose of test compound was expressed as percent inhibition of the initial change in AII pressor response. The *in vivo* potency of the new antagonists was assessed in terms of their ability to inhibit the AII-induced vasopressor response based on the maximal % inhibition of AII after oral or i.v. administration. When the maximal % inhibition of AII was less than 20%, the drug was considered without effect.

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