Synthesis and SAR Studies of Novel Triazolopyrimidine Derivatives as Potent, Orally Active Angiotensin II Receptor Antagonists

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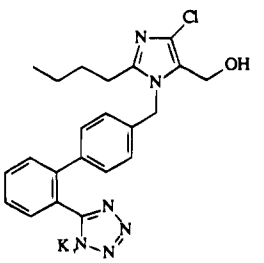
The synthesis and pharmacological activity of new nonpeptide angiotensin II (AII) receptor antagonists are presented. These [1,2,4]-triazolo[1,5-*c*]pyrimidine and 1,2,4-triazolo[4,3-*c*]-pyrimidine derivatives represent a new class of bicyclic antagonists that produced a potent, oral antihypertensive activity in the renal artery-ligated rat model. *In vitro*, they displayed a high affinity for rat adrenal AII receptors and were found to be specific for the AT_1 receptor subtype. A SAR study has shown the importance of the 8-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl for oral activity and the critical role of alkyl substituents at 5- and 7-positions. No significant differences were found between the [1,5-*c*] and [4,3-*c*] series. UP 269-6 (5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidin-2(3*H*)-one, derivative **29**) was selected as the lead compound. It was shown to be a highly potent antihypertensive derivative (decrease in mean arterial pressure of 39.6 ± 7.2 mmHg at 1 mg/kg po in renal artery-ligated rat) with a long duration of action which displayed a high affinity for adrenal AII receptors with a marked selectivity for the AT_1 receptor subtype (K_i AT_1 = 24 nM; K_i AT_2 = 79 200 nM). This compound is currently undergoing extensive pharmacological and clinical development.

Introduction

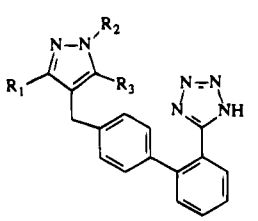
Angiotensin II (AII) is the effector molecule of the renin–angiotensin system (RAS) which plays an important role in the regulation of blood pressure and salt and water homeostasis.[1] The reduction of AII levels with angiotensin converting enzyme (ACE) inhibitors such as captopril or enalapril has been shown to be clinically effective in the treatment of hypertension and congestive heart failure.[2] However, ACE inhibitors potentiate bradykinin levels because ACE also degrades this inflammatory peptide[3a] and, as a result, may produce side effects such as coughing and angioedema.[3b] An alternative and more selective mode of inhibiting AII effects is to antagonize its interaction with its receptors in order to avoid side effects that may be related to bradykinin potentiation.

A number of peptide analogues of AII have been reported to impair its action by competitive inhibition of the binding to its receptors,[4] but their therapeutic prospects are limited due to a lack of oral bioavailability and a partial agonist activity.[1,4] Recently, several nonpeptide AII receptor antagonists have been described to be orally active and devoid of agonist activity.[5] Among them, Losartan (DuP 753, Chart 1), an imidazole derivative, is currently undergoing extensive clinical evaluation.[6] The great majority of orally active AII antagonists reported since the discovery of Losartan have included a biphenylyltetrazole moiety linked to a five-membered or six-membered heterocycle, the biphenylyltetrazole being linked to a nitrogen atom. With the aim of discovering new orally active AII antagonists, we sought to synthesize C-linked biphenylyltetrazole derivatives and we developed two C-linked heterocyclic series, namely pyrazole derivatives[7] of formula A (Chart 1) and pyrimidine derivatives[8] of formula B (Chart 1). These studies led to the discovery, in both series, of derivatives with similar oral potency to that of Losartan.

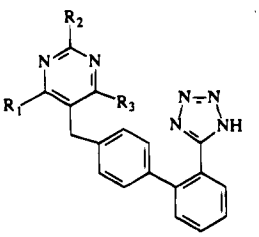
Chart 1. Structures of DuP 753 and C-Linked Pyrazole and Pyrimidine Derivatives



DuP 753[6] (LOSARTAN)



Formula A[7]



Formula B[8]

In a Merck report,[9] a bicyclic derivative (imidazo[4,5-*b*]pyridine), namely L-158,809 (Chart 2), was described to be significantly more potent than Losartan both *in vitro* and *in vivo*. L-158,809 is a biphenylyltetrazole derivative in which the biphenyl is linked to a nitrogen atom of an imidazole ring. As a part of our program to synthesize novel C-linked AII antagonists, it was interesting to study C-linked bicyclic series. We describe herein the synthesis and pharmacological activity of

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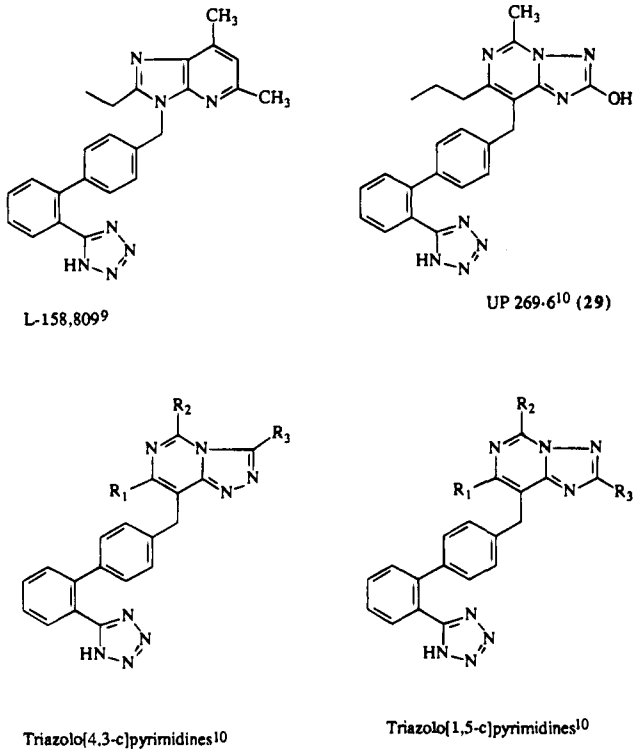
Chart 2. Structures of L-158,809, UP 269-6, and Triazolo[4,3-*c*]pyrimidine and Triazolo[1,5-*c*]pyrimidine Derivatives



new potent, orally active AII receptor antagonists, namely triazolo[1,5-*c*]pyrimidine and triazolo[4,3-*c*]pyrimidine derivatives[10] (Chart 2) which represent bicyclic structures built from our previously studied[8] pyrimidine series and in which the biphenylyltetrazole moiety is attached at the 5-position of a pyrimidine ring.

We present the pharmacological activity of UP 269-6 (5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidin-2(3*H*)-one, **29**, Chart 2) which was selected as the lead compound for further pharmacological and clinical development.

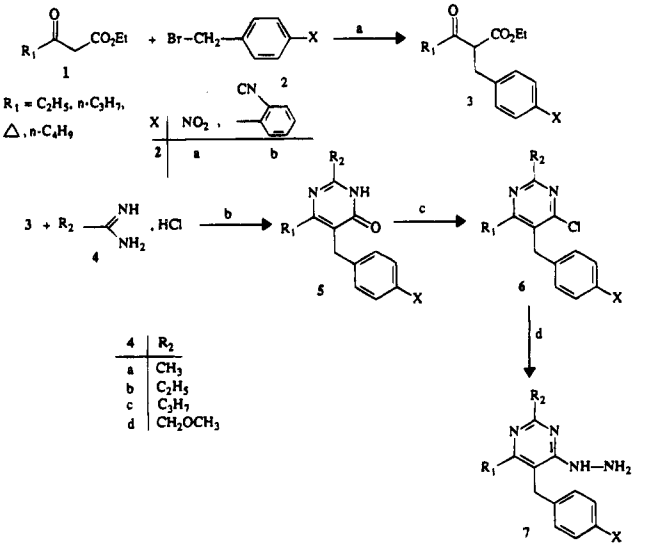
Chemistry

Triazolo[4,3-*c*]pyrimidines and triazolo[1,5-*c*]pyrimidines were generally prepared by cyclization of adequate pyrimidine derivatives, as has been reported in the literature.[11-15] The most common procedure consisted of cyclization of 4-hydrazinopyrimidines with various reagents such as orthoesters,[11] cyanogen chloride,[12] carbon disulfide,[13] isothiocyanates,[14] and ethyl chloroformate.[15] These cyclizations led either to [4,3-*c*] isomers or directly to rearranged [1,5-*c*] derivatives. When [4,3-*c*] isomers were obtained, a Dimroth rearrangement[11,15] allowed the preparation of the corresponding [1,5-*c*] derivatives.

Such an approach was used to synthesize the target triazolo[4,3-*c*]pyrimidine and triazolo[1,5-*c*]pyrimidine derivatives. The preparation of key 4-hydrazinopyrimidine intermediates **7** was required, and one synthetic pathway to these derivatives is depicted in Scheme 1.

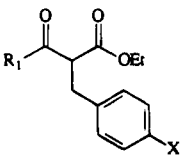
Alkylation of β-keto esters 1 with substituted benzyl bromides **2** in THF in the presence of lithium chloride and *N,N*-diisopropylethylamine[16] led to 2-benzyl derivatives **3** in 75–98% yield. The cyclization of compounds **3** was conveniently achieved by action of 1.5 equiv of

Scheme 1. Preparation of Key 4-Hydrazinopyrimidine Intermediates **7**[a]



[a] (a) LiCl, $(i\text{-Pr})_2NC_2H_5$, THF, reflux 15 h; (b) NaOMe, MeOH, room temperature, 20 h, reflux 3 h; (c) $POCl_3$, 100 °C, 6 h; (d) N_2H_4, EtOH, reflux 2 h.

Table 1. Preparation of 2-Alkylated β-Keto Esters **3**



3

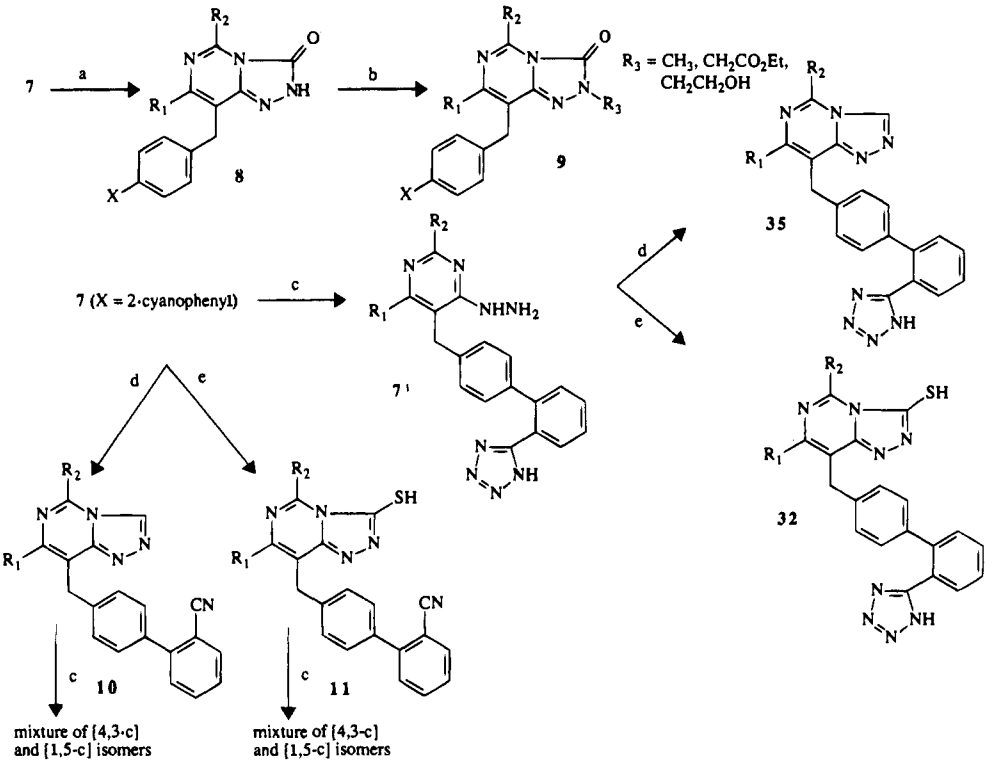
no.	R_1	X	yield[a] (%)
3a	n-C_3H_7	2-cyanophenyl	98
3b	n-C_4H_9	2-cyanophenyl	93
3c	C_2H_5	2-cyanophenyl	91
3d	cyclopropyl	2-cyanophenyl	85
3e	n-C_3H_7	NO_2	75

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

amidine hydrochlorides **4** in MeOH with 1.6 equiv of NaOMe to give pyrimidin-4(3*H*)-one derivatives **5**[17] in 36–61% yield. Chlorination of the latter in $POCl_3$ at reflux[17] afforded 4-chloropyrimidines **6**, in 84–98% yield, which upon treatment with hydrazine hydrate in EtOH gave 4-hydrazino derivatives **7**[18] in 58–93% yield.

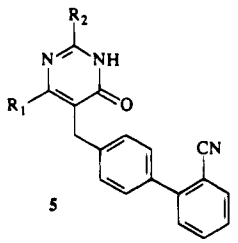
In order to study the influence of a substitution at the 2- or 3-position of the triazolo[4,3-*c*]- or triazolo[1,5-*c*]pyrimidine derivatives, we performed various cyclization reactions proceeding from **7** either according to previous literature reports or by a modified procedure. We wanted to introduce some polar groups at the 2- or 3-position of the studied triazolopyrimidines, as the presence of a hydroxymethyl or carboxy group at the 5-position of the imidazole ring was shown to be beneficial for the activity[6] in the DuPont imidazole series. In addition, consideration of the L-158,809 structure[9] could indicate that the introduction of alkyl groups at these positions (especially methyl) might be particularly favorable. Moreover, in the triazolo[4,3-*c*]-pyrimidine series, it was interesting to synthesize 3-oxo derivatives and to verify whether a substitution at the 2-nitrogen was favorable.

Scheme 2. Preparation of Triazolo[4,3-*c*]pyrimidine Derivatives[a]



[a] (a) CDI, THF, reflux 1.5 h; (b) NaOEt, EtOH, R_3-hal (hal = I, Br), reflux 7 h; (c) Me_3SnN_3, xylene, 115 °C, 48 h and then HCl gas, THF; (d) $(EtO)_3CH$, reflux 4 h; (e) CS_2, MeOH, reflux 1 h and then EtOH, reflux 1 h.

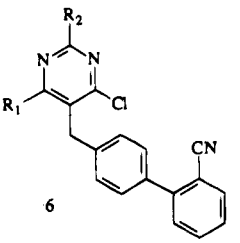
Table 2. Preparation of Pyrimidin-4(3*H*)-one **5**



no.	R_1	R_2	yield[a] (%)	mp (°C)
5a	*n*-C_3H_7	CH_3	60.8	209–210
5b	*n*-C_4H_9	CH_3	59	173
5c	C_2H_5	CH_3	60	188
5d	cyclopropyl	CH_3	54	230
5f	*n*-C_3H_7	C_2H_5	45	216
5g	*n*-C_3H_7	C_3H_7	51	150
5h	*n*-C_3H_7	CH_2OCH_3	55	134
5i	*n*-C_3H_7	SCH_3	36	218
5j	*n*-C_3H_7	H	56[b]	158

[a] Overall yield for the two steps from 4′-(bromomethyl)-2-cyanobiphenyl (**2b**). [b] Yield calculated from **5i**.

Table 3. 4-Chloropyrimidine Derivatives **6**



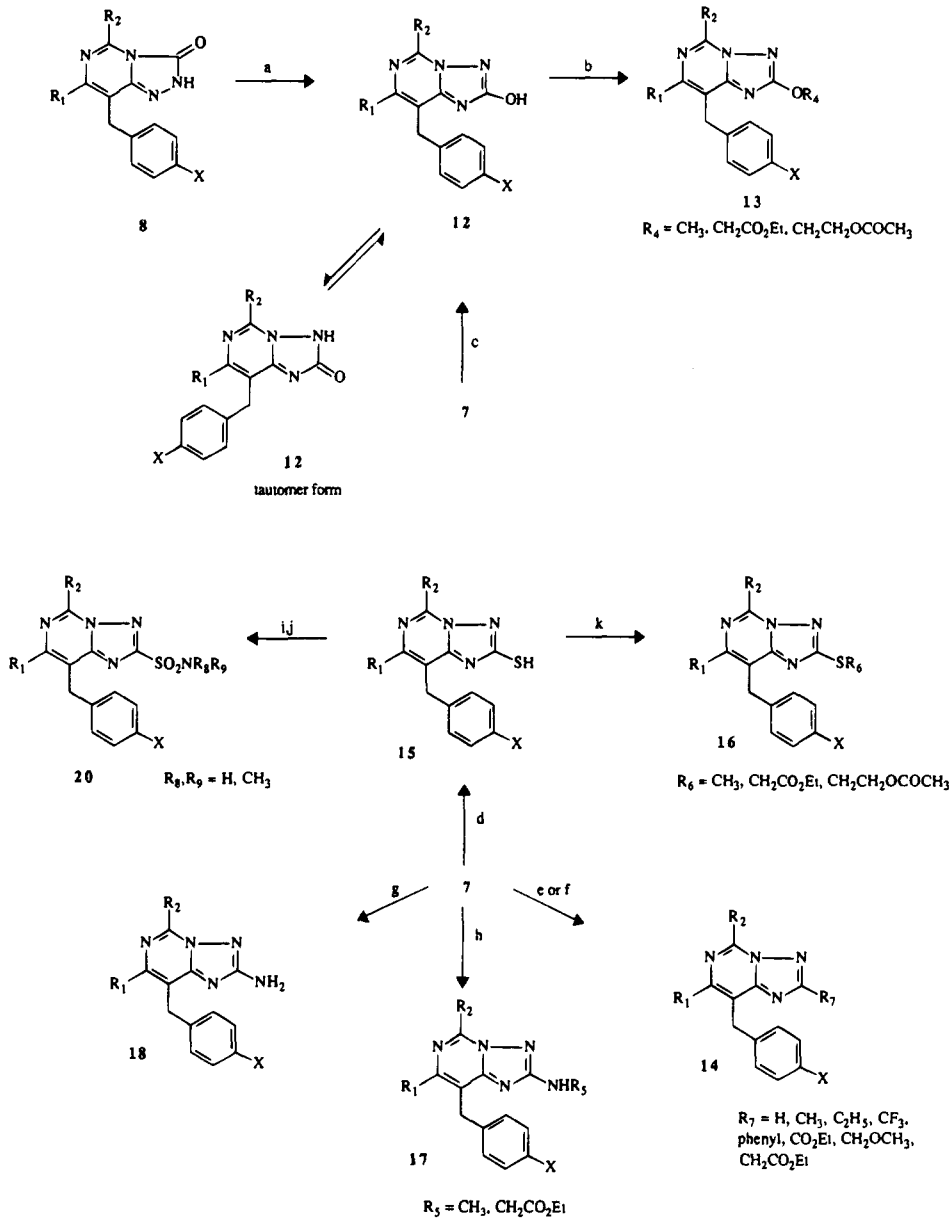
no.	R_1	R_2	yield (%)	mp (°C)
6a	*n*-C_3H_7	CH_3	98	102
6b	*n*-C_4H_9	CH_3	95	75
6c	C_2H_5	CH_3	97	80
6d	cyclopropyl	CH_3	88	oil
6f	*n*-C_3H_7	C_2H_5	90	oil
6g	*n*-C_3H_7	*n*-C_3H_7	93	oil
6h	*n*-C_3H_7	CH_2OCH_3	89	oil
6i	*n*-C_3H_7	SCH_3	84	88
6j	*n*-C_3H_7	H	91	95

As depicted in Scheme 2, the reaction of **7** with 1,1′-carbonyldiimidazole (CDI) in THF at reflux afforded triazolo[4,3-*c*]pyrimidin-3(2*H*)-one derivatives **8** in 70–76% yield. Alkylation of compound **8** with methyl iodide, ethyl bromoacetate, or 2-bromoethanol was performed in refluxing EtOH in the presence of 1 equiv of NaOEt and provided N-alkylated derivatives **9**.

The synthesis of the 3-mercapto derivative **32** and the unsubstituted derivative **35** was achieved for comparison with the 3-oxo derivative **25**. It was necessary to prepare the tetrazole derivatives **7′** before the cyclization step because when corresponding cyano derivatives **10** and **11** were treated with Me_3SnN_3 in xylene,[10] isomerization into [1,5-*c*] isomers occurred (Scheme 2). Treatment of **7′** with triethyl orthoformate at reflux led to target derivative **35**, while reaction of **7′** with CS_2 and NaOH in methanol and then in ethanol at reflux afforded the 3-mercapto derivative **32**.

In the same manner used for the [4,3-*c*] series, we sought to introduce optionally substituted polar groups (hydroxy, mercapto, sulfonamido, amino, or carboxy) or alkyl groups at the 2-position of the triazolo[1,5-*c*]-pyrimidine. Therefore, triazolo[1,5-*c*]pyrimidine derivatives were synthesized as depicted in Scheme 3. Dimroth-type isomerization of triazolo[4,3-*c*]pyrimidin-3(2*H*)-one **8** in EtOH with 3 N KOH at reflux[15] gave triazolo[1,5-*c*]pyrimidin-2(3*H*)-one derivatives **12** in 60–65% yield. The latter were more conveniently obtained in one step (90–95% yield) from hydrazino **7** by direct heating with urea in *N*-methylpyrrolidone at 160 °C.

Scheme 3. Preparation of Triazolo[1,5-*c*]pyrimidine Derivatives[a]

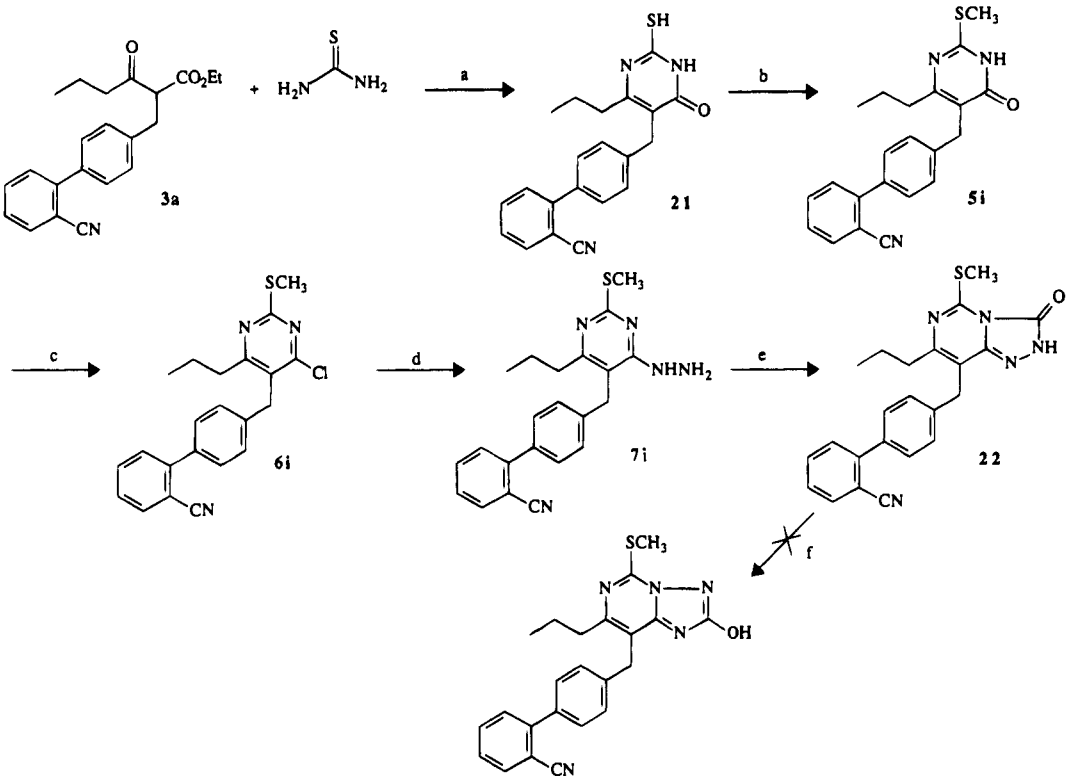


[a] (a) 3 N KOH, EtOH, 60 °C, 4 h; (b) K_2CO_3, acetone, R_4-hal (hal = I, Br), reflux 5 h; (c) urea, *N*-methylpyrrolidone, 160 °C, 6 h; (d) CS_2, *n*-BuOH, reflux 3 h; (e) $R_7C(OEt)_3$, 90 °C, 5 h and then HCO_2H, reflux 5 h; (f) R_7COCl, TEA, $CHCl_3$, reflux 2 h and then $POCl_3$, 100 °C, 6 h; (g) 2-methyl-2-thiopseudourea sulfate, H_2O, reflux 16 h; (h) $R_5N{=}C{=}S$, toluene, reflux 2 h and then ICH_3, reflux 2 h and then K_2CO_3, $EtOCH_2CH_2OH$, reflux 3 h; (i) $NaClO_3$, concentrated HCl, 0 °C, 20 min; (j) R_8R_9NH, H_2O, 50 °C, 1 h; (k) NaOEt, EtOH, R_6-hal (hal = I, Br), reflux 2 h.

O-Alkylated derivatives **13** were prepared proceeding-from **12** by reaction with methyl iodide, ethyl bromoacetate, or 2-bromoethanol, in the presence of K_2CO_3 in acetone.

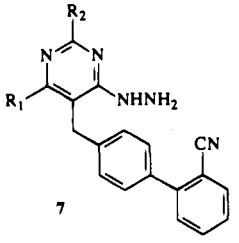
Other triazolo[1,5-*c*]pyrimidine derivatives were prepared from 4-hydrazino derivatives **7** as described in Scheme 3. The 2-alkyl derivatives **14** were synthesized by two methods. The first one consisted of heating **7** in an orthoester, $R_7C(OEt)_3$, at reflux followed by treatment with formic acid at reflux to afford [1,5-*c*] isomers **14** in 70–80% yield. A second method involved condensing an acyl chloride, R_7COCl, with hydrazino **7** to give hydrazide derivatives, which, upon treatment with $POCl_3$ at reflux, afforded directly the corresponding 2-alkyltriazolo[1,5-*c*]pyrimidine derivatives **14** in 35–70% yield. The reaction of **7** with CS_2 in *n*-butanol at reflux yielded directly the 2-mercaptotriazolo[1,5-*c*]-pyrimidine isomers **15** without isolation of [4,3-*c*] isomers in 80–90% yield. These 2-mercapto derivatives **15** were alkylated with methyl iodide, ethyl bromoacetate, or 2-bromoethyl acetate to give 2-alkylthio derivatives **16**. Sulfonamide derivatives **20** were obtained in two steps proceeding from 2-mercapto derivatives **15**. Action of sodium chlorate in concentrated hydrochloric acid at −5 °C led to sulfonyl chloride derivatives **19** which upon treatment with ammonia or appropriately substituted amines yielded the corresponding sulfonamides **20** in 45–55% yield. The preparation of the 2-amino derivatives **18** was achieved by reaction of 2-methyl-2-thiopseudourea sulfate with hydrazino derivatives **7** in water at reflux for 16 h; this procedure led directly to [1,5-*c*] isomers in 15–20% yield. The 2-alkylamino derivatives **17** were prepared by a two-step procedure:[14] reaction of hydrazino **7** with alkyl isothiocyanates afforded corresponding 4-(4′-alkyl-5-methylisothiosemicarbazido)pyrimidines which were cy-

Scheme 4. Preparation of 5-Methylthio Derivative 22[a]



[a] (a) NaOMe, MeOH, reflux 10 h; (b) KOH, ICH_3, MeOH, room temperature, 4 h; (c) $POCl_3$, 100 °C, 5 h; (d) N_2H_4, EtOH, reflux 2 h; (e) CDI, THF, reflux 2 h; (f) 3 N KOH, EtOH, reflux 10 h.

Table 4. Preparation of 4-Hydrazinopyrimidines 7

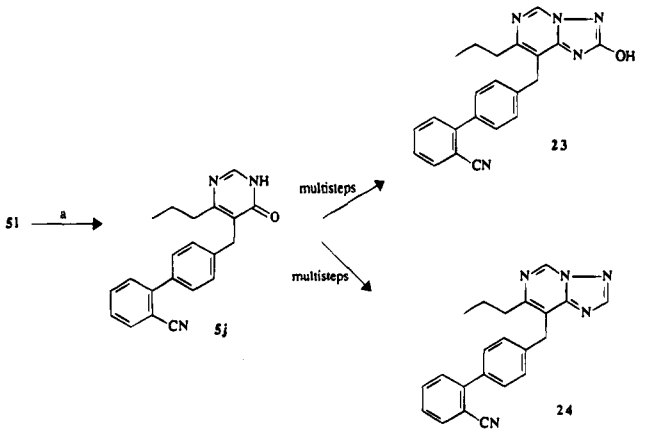


no.	R_1	R_2	yield (%)	mp (°C)
7a	*n*-C_3H_7	CH_3	92	156
7b	*n*-C_4H_9	CH_3	93	154
7c	C_2H_5	CH_3	89	190
7d	cyclopropyl	CH_3	87	170
7f	*n*-C_3H_7	C_2H_5	91	80
7g	*n*-C_3H_7	*n*-C_3H_7	82	oil
7h	*n*-C_3H_7	CH_2OCH_3	76	oil
7i	*n*-C_3H_7	SCH_3	58	106
7j	*n*-C_3H_7	H	78	120

clized in 2-ethoxyethanol at reflux in the presence of K_2CO_3; no [4,3-*c*] isomers were detected.

In L-158,809, it was shown that the methyl groups at the 5- and 7-positions played a critical role for oral activity. Thus, in order to evaluate the importance of the substitution at the 5-position in our series (which could be considered to play a similar role to that of the 7-methyl of L-158,809), it was interesting to synthesize 5-methylthio and 5-desmethyl derivatives for comparison with the 5-methyl derivatives. The 5-methylthio derivative **22** was obtained proceeding from β-keto ester **3a** as depicted in Scheme 4. Reaction of **3a** with thiourea in EtOH in the presence of NaOEt[19] yielded 2-mercaptopyrimidin-4(3*H*)-one **21** which after alkylation by methyl iodide led to 2-(methylthio)pyrimidin-4(3*H*)-one **5i**. The corresponding triazolo[4,3-*c*]pyrimidin-3(2*H*)-one **22** was then obtained by a similar reaction sequence as described above for compounds **8**. Interestingly, no rearrangement occurred when **22** was treated by 3 N KOH in EtOH at reflux. Since the reaction of **3a** with formamidine failed to give the pyrimidine-4(2*H*)-one **5j**, the latter was prepared by desulfurization of the 2-methylthio derivative **5i** with Raney nickel in refluxing diglyme (Scheme 5). Triazolo[1,5-*c*]pyrimidines **23** and **24** were obtained proceeding from the pyrimidin-4(2*H*)-one **5j** by the procedures described in Schemes 1–3.

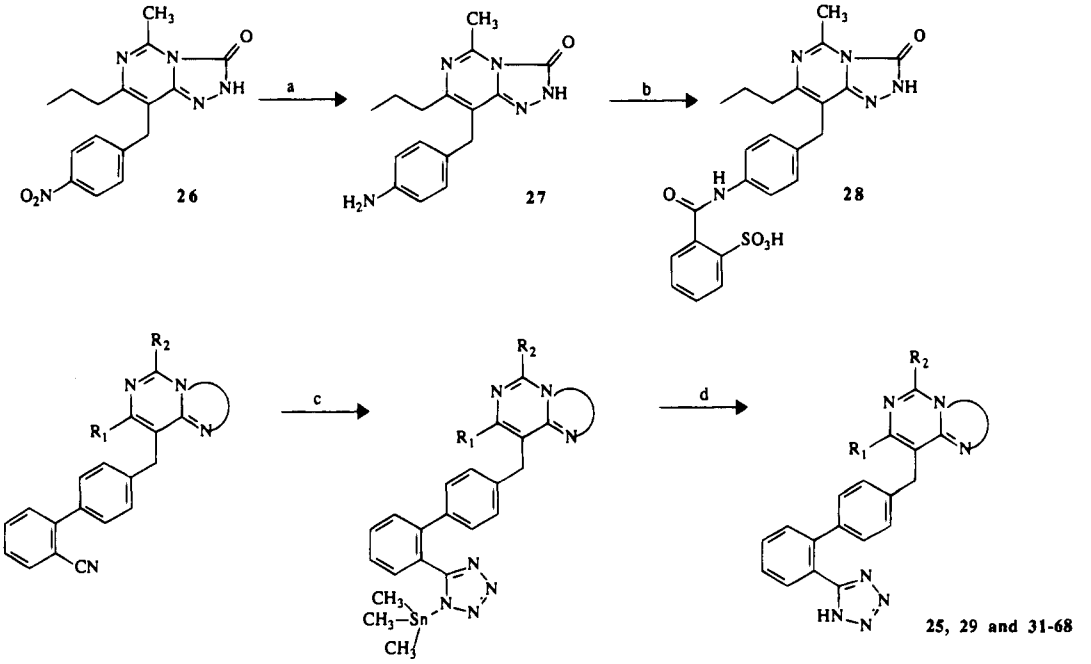
Scheme 5. Preparation of 5-Desmethyl Derivatives **23** and **24**[a]



[a] (a) Raney nickel, diglyme, reflux 3 h.

The sulfonic acid derivative **28** was prepared proceeding from the corresponding 8-(4-nitrobenzyl) derivative **26** by catalytic hydrogenation in MeOH with Raney nickel yielding the corresponding 8-(4-aminobenzyl)

Scheme 6. Preparation of Benzenesulfonic Acid and (1*H*-Tetrazol-5-yl)biphenyl Target Derivatives[a]



[a] (a) H_2, Raney nickel, MeOH, room temperature; (b) 2-sulfobenzoic acid anhydride, CH_3CN, room temperature, 15 min; (c) Me_3SnN_3, xylene, 115 °C, 48 h; (d) HCl gas, THF, room temperature, 20 min.

derivative **28**, which upon treatment with sulfobenzoic anhydride led to the target sulfonic acid **30** (Scheme 6). The biphenylcarboxylic acid derivative **30** was obtained by hydrolysis of the corresponding nitrile with NaOH in refluxing ethylene glycol. The tetrazole derivatives **25**, **29**, and **31**–**68** were obtained by reaction of the corresponding nitriles with trimethyltin azide at 115–135 °C in toluene or xylene followed in some cases by the hydrolysis of intermediary *N*-trimethylstannyl derivatives with gaseous HCl in THF as depicted in Scheme 6. The key 4′-(bromomethyl)-2-cyanobiphenyl (**2b**) was synthesized by a known procedure[10,20] from *o*-anisic acid.

Results and Discussion

In vitro, the affinities of the compounds were measured by their ability to displace the specific binding of [^{125}I]Sar^1-Ile^8-AII from rat adrenal AII receptors. K_i values for AT_1 and AT_2 receptors were determined, and dithiothreitol (DTT, 20 mM) was used to discriminate between AII receptor subtypes since it was shown to inhibit almost totally the binding to the AT_1 receptor subtype but not to affect the binding to the AT_2 one.[22] All tested compounds displayed an affinity for the AT_2 receptor superior to 10 000 nM.

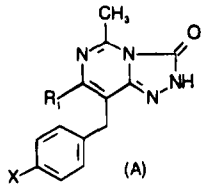
In vivo, the compounds were tested orally in renal artery-ligated hypertensive rats,[23] a high renin-dependent hypertensive animal model, either at 10 mg/kg by the tail-cuff method[24] or at 1 mg/kg by a direct method.[25] Results were expressed as the change in arterial blood pressure (systolic arterial pressure (SAP) for 10 mg/kg and mean arterial pressure (MAP) for 1 mg/kg).

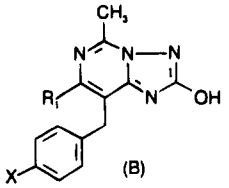
As previously reported by DuPont in the imidazole series, the results in Table 5 showed that the introduction of a biphenylyltetrazole group (**25** and **31**) led to potent, orally active derivatives in both triazolopyrimidine series (A and B). The 2-carbamoylbenzenesulfonic acid **28** was only 4-fold less active *in vitro* than **25** but was poorly active *in vivo* at 10 mg/kg. The replacement of the tetrazole group of **31** by a carboxylic acid (**30**) resulted in a significant loss of oral activity and *in vitro* affinity.

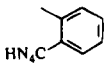
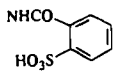
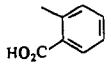
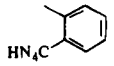
Therefore, our SAR investigations in these series were carried out exclusively with 8-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl derivatives. The results in Table 6 allowed comparison between the [4,3-*c*] and [1,5-*c*] series. Considering the 2- or 3-OH derivatives (**25**, Table 5, and **29**, Table 6), both series led to equipotent oral activity at either 10 or 1 mg/kg. Surprisingly, when R_3 = SH (**32**, **33**, and **34**), the [4,3-*c*] derivatives **32** and **34** are 10 times less potent *in vitro* than the [1,5-*c*] derivative **33** but display markedly higher oral activity at 10 mg/kg and the same activity at 1 mg/kg. Comparison between **35** and **36** showed that there is no significant difference between receptor affinity or oral activity with either isomer when R_3 = H. With regard to these findings, it was difficult to conclude which series was superior since the relative oral or *in vitro* potencies of [4,3-*c*] and [1,5-*c*] isomers depended on the nature of the R_3 substituent.

In order to study the influence of the substitution at the 7-position (R_1), we synthesized a series of 2-hydroxytriazolo[1,5-*c*]pyrimidine derivatives (see Table 7). Considering the affinity of compounds **29** (R_1 = *n*-C_3H_7), **31** (R_1 = *n*-C_4H_9, Table 5), **38** (R_1 = C_2H_5), and **39** (R_1 = cyclopropyl) for AT_1 receptors, it appeared that the *n*-propyl chain seemed to be optimal for the *in vitro* activity. Compound **39** which possesses a cyclopropyl ring at the 7-position was 4- and 2.5-fold less potent than **29** and **38**, respectively. This could indicate that a linear alkyl side chain was to be preferred to a cyclic or branched one. With regard to oral activities exhibited by these four derivatives, we can state that the *n*-C_3H_7 (**29**) and *n*-C_4H_9 (**31**) chains led to equipotent antihypertensive activities at 10 mg/kg. Nevertheless, when tested at 1 mg/kg, **29** displayed a higher antihypertensive effect than **31**. Shortening of the 7-alkyl side chain

Table 5. Effect of Substitution on the Benzyl Group

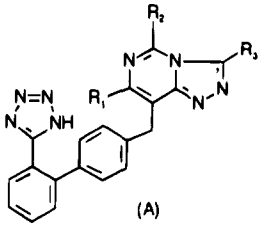


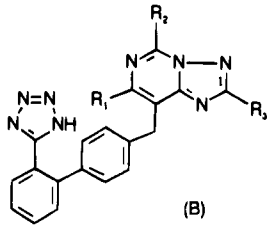


no.	R_1	X	series	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	oral activity: change in blood pressure (mmHg) 10 mg/kg[d]	oral activity: change in blood pressure (mmHg) 1 mg/kg[e]
25	*n*-C_3H_7		A	A	25	248–249	$C_{23}H_{22}N_8O$	10	−87.5 ± 7.6	−44.6 ± 7.0
28	*n*-C_3H_7		A	B	50	283–286	$C_{23}H_{23}N_5O_5S$	41	−18.3 ± 9.5	NT[f]
30	*n*-C_4H_9		B	E	60	210–211	$C_{24}H_{24}N_4O_3$	622	−23.5 ± 7.3	NT
31	*n*-C_4H_9		B	D	70	236–238	$C_{24}H_{24}N_8O$	30	−91.5 ± 4.7	−22.1 ± 2.2

[a] Overall yield for all steps described in the method. [b] All elemental analyses for C, H, and N were within ±0.4% of the calculated values unless otherwise noted. [c] K_i value represents the result of one experiment run in triplicate on rat adrenal membranes. [d] Systolic arterial pressure values are determined by the tail cuff method[24] in renal artery-ligated rats and represent the mean ± SEM of three to eight determinations. [e] Mean arterial pressure values are determined by a direct method[25] in renal artery-ligated rats and represent the mean ± SEM of three to seven determinations. [f] Not tested.

Table 6. Comparison between the [4,3-*c*] (A) and [1,5-*c*] (B) Series





no.	R_1	R_2	R_3	series	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	oral activity: change in blood pressure (mmHg) 10 mg/kg[d]	oral activity: change in blood pressure (mmHg) 1 mg/kg[e]
29	*n*-C_3H_7	CH_3	OH	B	D	72	234–235	$C_{23}H_{22}N_8O$	24	−92.2 ± 23	−39.6 ± 7.2
32	*n*-C_3H_7	CH_3	SH	A	F	9	247–248	$C_{23}H_{22}N_8S$	127	−90.2 ± 12.5	−22.4 ± 4.2
33	*n*-C_3H_7	CH_3	SH	B	G	60	223–225	$C_{23}H_{22}N_8S$	10	−57.8 ± 9.9	−19.7 ± 6.7
34	*n*-C_4H_9	CH_3	SH	A	F	11	172–174	$C_{24}H_{24}N_8S$	106	−86.3 ± 8.6	−24.3 ± 2.7
35	*n*-C_3H_7	CH_3	H	A	H	20	182–184	$C_{23}H_{22}N_8$[g]	10	−77.2 ± 11.8	−24.2 ± 14.1
36	*n*-C_3H_7	CH_3	H	B	P	54	183–184	$C_{23}H_{22}N_8$	12	−89.7 ± 10.5	−20.1 ± 7.8
37	*n*-C_3H_7	SCH_3	OH	A	A	41	259–261	$C_{23}H_{22}N_8OS$	9000	−15.6 ± 4.4	NT[f]

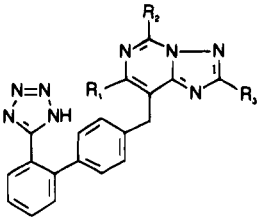
[a–f] See the corresponding footnotes of Table 5. [g] N: calcd, 27.30; found, 27.93.

resulted in a drop in oral activity as was observed with compounds **38** and **39**.

Using molecular modeling design, we have superimposed the structures of UP 269-6 (**29**) and L-158,809. The result in Figure 2 showed that the 2- and 5-positions of the triazolo[1,5-*c*]pyrimidine fitted with the 5-methyl and 7-methyl of L-158,809, respectively. Since in L-158,809 the introduction of these two methyl groups has been shown to increase appreciably the affinity and the oral antihypertensive activity,[9] it was interesting to evaluate the effect of various substitutions at the 2- and 5-positions in our series.

The nature of the substitution at the 5-position (R_2, Table 7) seemed to be critical for the receptor affinity and oral activity. When R_2 = H or alkyl, the optimal receptor affinity was obtained with the methyl group (**29**). When this 5-methyl was replaced by a longer alkyl group such as ethyl (**41**) or *n*-propyl (**42**), the receptor affinity dropped dramatically, but when it was replaced by a hydrogen (**40**), the binding was only reduced by half. On the other hand, considering the oral activity, it seemed to be very unfavorable for R_2 to be a hydrogen, whereas an ethyl group (**41**) led to similar or slight increased activity at 1 mg/kg relative to the methyl derivative (**29**) while *in vitro* **41** was 10 times less potent than **29**. Substitution with a *n*-propyl (**42**) decreased the antihypertensive activity at 1 mg/kg relative to **29** and **41**. The insertion of an oxygen atom in the 5-alkyl chain gave rise to methoxymethyl (**43**) and hydroxymethyl (**44**) derivatives which displayed significantly higher receptor affinity than *n*-propyl (**42**) and ethyl (**41**) derivatives, respectively, but exhibited a reduced oral activity at 1 mg/kg as compared to that of **41**. Comparison between compounds **57**, **60**, and **61** (Table 10) on the one hand and between **36** (Table 6) and **63** (Table 10) on the other hand confirmed the above statements,

Table 7. Influence of 7-Alkyl and 5-Alkyl Chains in the [1,5-*c*] Series



no.	R_1	R_2	R_3	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	oral activity: change in blood pressure (mmHg) 10 mg/kg[d]	oral activity: change in blood pressure (mmHg) 1 mg/kg[e]
29	*n*-C_3H_7	CH_3	OH	D	72	234–235	$C_{22}H_{22}N_8O$	24	−92.2 ± 2.3	−39.6 ± 7.2
38	C_2H_5	CH_3	OH	D	65	254	$C_{22}H_{20}N_8O{\cdot}0.25H_2O$	35	−72.8 ± 13.2	−20.1 ± 8.3
39	cyclopropyl	CH_3	OH	D	57	264–265	$C_{23}H_{20}N_8O$	82	−51.1 ± 12.4	−12.3 ± 5.1
40	*n*-C_3H_7	H	OH	D	68	190–192	$C_{22}H_{20}N_8O$	46	−38.3 ± 6.1	−17.9 ± 4.4
41	*n*-C_3H_7	C_2H_5	OH	D	65	250–251	$C_{24}H_{24}N_8O$	225	−75.8 ± 6.6	−46.5 ± 3.0
42	*n*-C_3H_7	*n*-C_3H_7	OH	D	72	258–259	$C_{25}H_{25}N_8O$	659	−72.6 ± 10.4	−22.2 ± 5.1
43	*n*-C_3H_7	CH_2OCH_3	OH	D	59	166–168	$C_{24}H_{24}N_8O_2{\cdot}0.5H_2O$	92	−88.7 ± 15.0	−18.5 ± 11.5
44	*n*-C_3H_7	CH_2OH	OH	I	62	182–183	$C_{23}H_{22}N_8O_2{\cdot}H_2O$	10	−40.6 ± 12.4	−21.5 ± 8.3

[a–e] See the corresponding footnotes of Table 5.

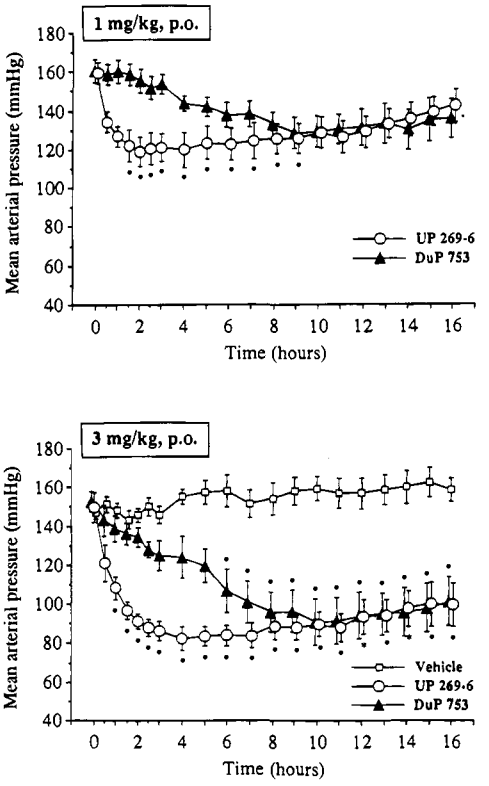


Figure 1. Time course of the antihypertensive activity of UP 269-6 (**29**), DuP 753 (Losartan), and vehicle in the conscious renal artery-ligated hypertensive rats. Hypertension in the rat was developed by renal artery ligation as described in ref 23. Compounds were administered orally by gavage at 1 and 3 mg/kg, 7 days after renal artery ligation. Vehicle was an aqueous suspension containing arabic gum, Tween 80, and NaCl. In the aim to clarify the figure, the effects of the vehicle are shown in the second part of the figure. Values represent the mean ± SEM (n = 5–6 rats/group). An asterisk indicates a different from pretreatment values (P < 0.05).

leading to the conclusion that the 5-methyl or 5-ethyl substitutions were definitely the most favorable irrespective of the 2-substitution.

Comparison between **37** (R_2 = SCH_3, Table 7) and the 5-CH_3 derivative **25** showed that the 5-position was also very critical in the [4,3-*c*] series since the replacement of the 5-CH_3 by a 5-SCH_3 induced a dramatic loss of receptor affinity and oral activity.

In order to investigate the range of functionality which could be tolerated at the 2-position of the triazolo-[4,3-*c*]pyrimidin-3(2*H*)-one **25**, we decided to attach various substituents at this point (Table 8). *In vitro*, the substitutions at the 2-nitrogen of **25** with an ethyl acetate (**45**) or hydroxyethyl (**46**) led to compounds displaying high affinities, since **45** and **46** were equipotent to **25**. Nevertheless, the introduction of a shorter substituent such as a methyl (**47**) decreased the affinity. Therefore, the modulation of the receptor affinity at this position was not correlated with steric effects but more likely with electronic effects of the substituents. *In vivo*, the substitutions with an ethyl acetate (**45**), a 2-hydroxyethyl (**46**), or a 2-methyl (**47**) decreased the activity at 1 mg/kg relative to unsubstituted **25**. Thus, the substitution at this position seemed to decrease slightly the oral efficacy.

In the triazolo[1,5-*c*]pyrimidine series, we examined a number of substitutions at the 2-position (R_3, Tables 9 and 10). The 2-amino derivative **54** (R_3 = NH_2, Table 9) displayed superior binding affinity to the corresponding 2-hydroxy (**29**) and 2-mercapto (**33**, Table 6) derivatives. It was 24- and 10-fold more potent *in vitro* than **29** and **33**, respectively. Nevertheless, the shift between receptor affinities of **54** and **29** did not result in an increased oral activity for the former, both compounds being essentially equipotent. On the other hand, the 2-mercapto derivative **33** was less orally active than **29** though it was 2-fold more potent *in vitro*. These findings indicated again that in this series, the receptor affinity was not directly correlated to the oral antihypertensive effect.

The data in Table 9 allowed evaluation of the effect of a substitution at the 2-branched heteroatom in the triazolo[1,5-*c*]pyrimidine series. Comparison between **29** (R_3 = OH) and **48** (R_3 = OCH_3) showed that the methylation of the 2-hydroxy group resulted in a significant drop in the oral activity without change in the receptor affinity. In the 2-mercapto-substituted series, the introduction of a methyl (**50**, R_3 = SCH_3) or an ethyl acetate (**49**, R_3 = SCH_2CO_2Et) decreased the oral activity and the receptor affinity relative to the

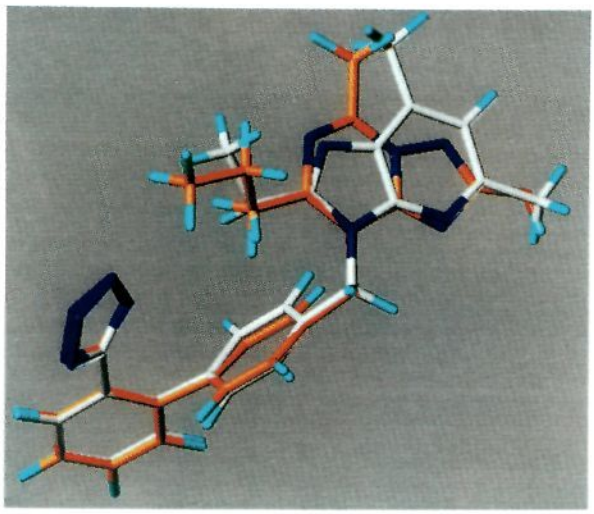
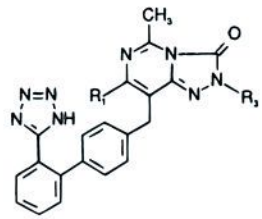


Figure 2. Superimposition of UP 269-6 (**29**, carbons in orange) and L-158,809 (carbons in white), using Sybyl software.

unsubstituted **33** (Table 6). In the 2-sulfonamido derivatives series (**51**–**53**), the unsubstituted sulfonamide **52** displayed significantly higher *in vitro* and *in vivo* potency than the *N*-methyl (**53**) and *N*-dimethyl (**51**) derivatives, the latter being completely inactive po at 10 mg/kg. In the 2-amino-substituted series (**54**–**56**), the effect of a substitution was less dramatic since the *N*-methyl derivative **55** in only 5-fold less potent *in vitro* and slightly less orally active than **54**. The substitution with an ethyl acetate group (**56**) induced a drop in the affinity and the oral activity at 1 mg/kg. Thus, these findings demonstrated that if the introduction of an heteroatom (N, S, O) at the 2-position of the triazolo-[1,5-*c*]pyrimidine ring gave rise to compounds with high affinities and potent, oral antihypertensive effects, substitutions at these heteroatoms decreased *in vivo* and *in vitro* potency.

It was particularly interesting to study the 2-alkyl-substituted derivatives in our series (the 2-position of our triazolo[1,5-*c*]pyrimidines corresponding to the 5-position of L-158,809; see Figure 2) and to compare them with the 5,7-dimethylimidazo[4,5-*b*]pyridine derivative, L-158,809[9] (Chart 2), which was reported to be one of the most potent AII receptor antagonists to date. Comparison between the 2-unsubstituted **36** (Table 6) and the 2-methyl derivative **57** (Table 10) showed that, unlike in the Merck imidazo[4,5-*b*]pyridine series, the

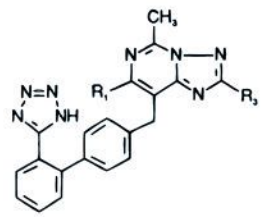
Table 8. N-Substituted Derivatives of the [4,3-*c*] Series



								oral activity	
								change in blood pressure (mmHg)	
no.	R_1	R_3	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	10 mg/kg[d]	1 mg/kg[e]
25	*n*-C_3H_7	H	A	25	248–249	$C_{23}H_{22}N_8O$	10	−87.5 ± 7.6	−44.6 ± 7.0
45	*n*-C_3H_7	CH_2CO_2Et	J	49	173–174	$C_{27}H_{28}N_8O_3$	12	−71.7 ± 18.4	−21.6 ± 7.6
46	*n*-C_3H_7	CH_2CH_2OH	J	36	149–150	$C_{25}H_{26}N_8O_2$[f]	6	−67.9 ± 7.2	−25.6 ± 5.0
47	*n*-C_3H_7	CH_3	J	54	205–206	$C_{24}H_{24}N_8O$	53	−48.8 ± 16.3	−25.1 ± 4.6

[a–e] See the corresponding footnotes of Table 5. [f] C: calcd, 63.80; found, 63.30. N: calcd, 23.82; found, 24.28.

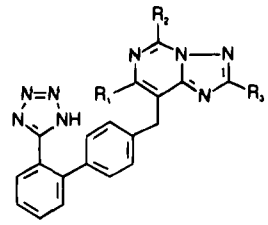
Table 9. 2-O-, 2-S-, and 2-N-Substituted Derivatives of the [1,5-*c*] Series



								oral activity	
								change in blood pressure (mmHg)	
no.	R_1	R_3	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	10 mg/kg[d]	1 mg/kg[e]
29	*n*-C_3H_7	OH	D	72	234–235	$C_{22}H_{22}N_8O$	24	−92.2 ± 2.3	−39.6 ± 7.2
48	*n*-C_3H_7	OCH_3	K	46	189–190	$C_{24}H_{24}N_8O$	27	−26.2 ± 10.1	NT[f]
49	*n*-C_3H_7	SCH_2CO_2Et	L	31	127–128	$C_{27}H_{28}N_8O_2S$	99	−26.4 ± 6.5	NT
50	*n*-C_3H_7	SCH_3	L	47	169–170	$C_{24}H_{24}N_8S$	174	−32.2 ± 5.2	−11.8 ± 3.4
51	*n*-C_3H_7	$SO_2N(CH_3)_2$	M	28	176–178	$C_{25}H_{27}N_9O_2S{\cdot}0.25H_2O$	185	−7.2 ± 4.8	NT
52	*n*-C_3H_7	SO_2NH_2	M	31	200–201	$C_{23}H_{23}N_9O_2S$	11	−61.3 ± 4.9	−14.5 ± 2.0
53	*n*-C_3H_7	SO_2NHCH_3	M	27	163–164	$C_{24}H_{25}N_9O_2S{\cdot}HCl$	139	−37.2 ± 6.1	−14.1 ± 5.9
54	*n*-C_3H_7	NH_2	N	9	170–174	$C_{23}H_{23}N_9{\cdot}H_2O$	1	−77.2 ± 13.5	−33.4 ± 5.5
55	*n*-C_3H_7	$NHCH_3$	O	53	229–230	$C_{24}H_{25}N_9{\cdot}0.25H_2O$	5	−65.3 ± 13.6	−23.6 ± 9.3
56	*n*-C_3H_7	$NHCH_2CO_2Et$	O	49	180–181	$C_{27}H_{29}N_9O_2$[g]	32	−73.6 ± 11.8	−5.7 ± 4.5

[a–f] See the corresponding footnotes of Table 5. [g] N: calcd, 24.65; found, 24.14.

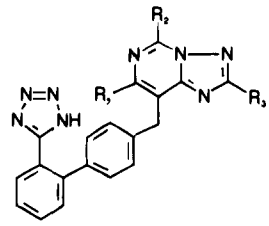
Table 10. 2-Alkyl and 2-Aryl Derivatives of the [1,5-*c*] Series



no.	R_1	R_2	R_3	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	oral activity: change in blood pressure (mmHg) 10 mg/kg[d]	oral activity: change in blood pressure (mmHg) 1 mg/kg[e]
57	*n*-C_3H_7	CH_3	CH_3	P	56	188–190	$C_{24}H_{24}N_8$	32	−71.8 ± 12.9	−17.9 ± 7.0
58	*n*-C_3H_7	CH_3	C_2H_5	P	54	190–191	$C_{25}H_{26}N_8$	8	−69.0 ± 14.9	−8.9 ± 4.0
59	*n*-C_3H_7	CH_3	CF_3	Q[f]	26	161–162	$C_{24}H_{21}F_3N_8$	147	−11.8 ± 5.3	NT[g]
60	*n*-C_3H_7	CH_2OCH_3	CH_3	P	57	137–138	$C_{25}H_{26}N_8O$	111	−44.4 ± 8.1	−21.8 ± 5.7
61	*n*-C_3H_7	CH_2OH	CH_3	I	62	190–191	$C_{24}H_{24}N_8O$	27	−21.4 ± 10.4	NT
62	*n*-C_3H_7	CH_3	phenyl	P	62	196	$C_{29}H_{25}N_8$	175	−48.2 ± 9.6	−13.3 ± 3.1
63	*n*-C_3H_7	H	H	P	54	131–133	$C_{22}H_{20}N_8$	50	−20.0 ± 5.1	NT

[a–e] See the corresponding footnotes of Table 5. [f] Proceeding from trifluoroacetic anhydride. [g] Not tested.

Table 11. [1,5-*c*] Derivatives Substituted in the 2-Position by Carboxylic Acids, Esters, Ethers, or Alcohols



no.	R_1	R_2	R_3	method	yield[a] (%)	mp (°C)	formula[b]	*in vitro* activity K_i (nM)[c] AT_1	oral activity: change in blood pressure (mmHg) 10 mg/kg[d]	oral activity: change in blood pressure (mmHg) 1 mg/kg[e]
64	*n*-C_3H_7	CH_3	CO_2Et	Q	22	168–170	$C_{26}H_{26}N_8O_2$	23	−76.7 ± 13.0	−14.9 ± 7.0
65	*n*-C_3H_7	CH_3	CO_2H	R	89	193–194	$C_{24}H_{22}N_8O_2$[f]	35	−36.4 ± 5.6	−13.4 ± 4.4
66	*n*-C_3H_7	CH_3	CH_2CO_2Et	Q	31	150	$C_{27}H_{28}N8O_2$	9	−84.0 ± 11.7	−18.1 ± 4.8
67	*n*-C_3H_7	CH_3	CH_2OCH_3	Q	41	130–131	$C_{25}H_{26}N_8O{\cdot}0.5H_2O$	15	−73.1 ± 11.3	−13.2 ± 4.3
68	*n*-C_3H_7	CH_3	CH_2OH	I	53	226–227	$C_{24}H_{24}N_8O{\cdot}0.25H_2O$[g]	5	−62.5 ± 6.9	−25.4 ± 9.3
Dup 753 (Losartan)								3.6	−104.2 ± 11	−32.9 ± 3.9

[a–e] See the corresponding footnotes of Table 5. [f] C: calcd, 63.42; found, 63.00. [g] N: calcd, 25.10; found, 24.65.

introduction of a methyl at this point failed to enhance either the receptor affinity, which was reduced by a third, or the oral activity, which was unchanged. Further lengthening of the alkyl chain (**58**, $R_3 = C_2H_5$) seemed to enhance the affinity but had no beneficial effect on the oral activity. It was noteworthy that the introduction of a 2-CF_3 group gave rise to a compound (**59**) which was 5- and 12-fold less active *in vitro* than the 2-methyl derivative **57** and the unsubstituted **36**, respectively. Moreover, when tested at 10 mg/kg po, this 2-CF_3 derivative was completely inactive. This result showed that, in our series, a very lipophilic group such as a CF_3 at this point could lead to a dramatic loss of *in vitro* and *in vivo* activities, whereas in the imidazole DuPont series, the introduction of trifluoro or pentafluoroalkyl groups has been shown to enhance the oral activity[26] due to an increased lipophilicity. Substitution at this 2-position with a bulkier group such as a phenyl (**62**) decreased both *in vitro* and oral activity as compared to the 2-unsubstituted **36**.

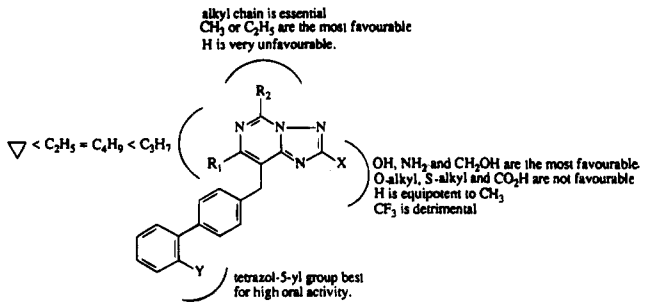
Consideration of the DuPont SAR results in the imidazole series[20,26] led us to synthesize 2-hydroxymethyl and 2-carboxy derivatives (**64**–**68**, Table 11). Contrary to that observed with Losartan and its metabolite EXP 3174, the 2-hydroxymethyl derivative **68** displayed a higher binding affinity than the corresponding 2-carboxylic acid **65**. *In vivo*, the alcohol **68** was more active than the acid **65**; nevertheless, esterification of the latter enhanced the oral activity (**64**). It was difficult to state whether the ester **64** acted as a prodrug of the corresponding acid **65**, since **64** displayed a higher binding affinity. The ethyl acetate derivative **66** was 2-fold more active *in vitro* than the ethyl carboxylate **64**, but the lengthening of the 2-carboxylate chain failed to enhance the oral activity. Etherification of the alcohol **68** led to a drop in the receptor affinity without changing the oral activity (**67**).

Compound **29** (UP 269-6; see Chart I) was selected for further pharmacological investigation and clinical evaluation after consideration of *in vitro* and *in vivo* results and due to an easier chemical synthesis as compared to that of compound **25** which had an equivalent pharmacological profile.

Pharmacological Activity of UP 269-6 (29)

In vitro, UP 269-6 displayed a high affinity for the AT_1 receptor subtype (K_i = 24 nM) and a weak affinity

Chart 3. *In Vivo* SAR Studies in the [1,5-*c*] Series



for the AT_2 receptor subtype (K_i = 79 200 nM). Under the same conditions, the K_i values for Losartan were found to be 3.6 and 74 100 nM for AT_1 and AT_2 receptor subtypes, respectively. On the other hand, the affinity of UP 269-6 was about 2-fold higher than that obtained with Losartan (8 vs 15 nM, respectively) in cultured vascular smooth muscle cells (data not shown).

In studies designed to determine the duration of action of UP 269-6 and to compare its antihypertensive activity with that of Losartan, both compounds were given orally at doses of 1 and 3 mg/kg in conscious renal artery-ligated rats. Continuous blood pressure measurements were made at least 16 h after drug administration.

When administered orally at a dose of 1 mg/kg (Figure 1), UP 269-6 had a rapid onset of action, reducing the mean arterial pressure by 40 mmHg. The decrease in blood pressure was statistically significant from 1.5 to 9 h after dosing. Losartan (1 mg/kg) lowered arterial blood pressure by 33 mmHg. This antihypertensive response occurred with a slower onset. Administration of 3 mg/kg of either UP 269-6 or Losartan to these high renin-dependent hypertensive rats resulted in significant antihypertensive responses (Figure 1). The maximal decreases in arterial blood pressure were 67 and 60 mmHg for UP 269-6 and Losartan, respectively. The maximum response to UP 269-6 occurred within 4 h following oral administration, whereas the onset of the antihypertensive response to Losartan was gradual with a maximum effect occurring at approximately 10 h. However, the duration of action of both compounds was similar with the antihypertensive response lasting for at least 16 h.

Conclusion

All compounds exhibited a high selectivity for the AT_1 receptor subtype and only a weak affinity for the AT_2 one. *In vivo*, in the triazolo[1,5-*c*] series which was more exemplified than the [4,3-*c*] series, the key structural variations investigated in our SAR study are summarized in Chart 3. The nature of the substituent beared by the biphenyl ring was shown to be very important, and the 1*H*-tetrazol-5-yl group led to the most potent compounds. The substitutions at the 5- and 7-positions (R_1 and R_2) were also shown to be critical, and alkyl substituents were the most favorable especially when $R_1 = n\text{-}C_3H_7$ and $R_2 = CH_3$. UP 269-6 (**29**) displayed high affinity and selectivity for the AT_1 receptor subtype. Furthermore, it has shown to be an efficacious, orally active, blood pressure-lowering agent in conscious renal hypertensive rats, demonstrating a dose-related and long-lasting antihypertensive effect in this model. On the basis of this profile, UP 269-6 has been selected as the lead compound in this series and is currently under phase II clinical trials for the treatment of hypertension.

Experimental Section

^{1}H NMR spectra were measured at 200 MHz on a Bruker 200 spectrometer and recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to internal reference Me_4Si. Melting points were recorded on an Electrothermal digital capillary melting point apparatus and are uncorrected. Chromatography was performed on silica gel (mesh 70–230) using the indicated solvent mixture. Elemental analyses were obtained by using a Carlo Erba Mod-106 elemental analyser. HPLC experiments were performed on a Varian liquid chromatograph with a UV detector and a suitable integration system (inverse phase C18 column). Starting materials were commercially available, or their preparation could be found in references.[10]

Ethyl 2-[(2′-Cyanobiphenyl-4-yl)methyl]-3-oxohexanoate (3a). To a solution of 863.7 g of 4′-(bromomethyl)-2-cyanobiphenyl[10,20] (**2b**) (3.17 mol) and 752 mL of ethyl butyrylacetate (4.76 mol) in 3900 mL of tetrahydrofuran were added 1117 mL of *N,N*-diisopropylethylamine and 134.6 g of lithium chloride (3.17 mol), and the mixture was refluxed for 15 h and then concentrated under vacuum. The residue was taken up with water and extracted with ethyl acetate. The organic layer was washed carefully with 1 N hydrochloric acid solution and then with water, dried over magnesium sulfate, and evaporation under vacuum. The oily brownish residue was heated at 130 °C under 20 mmHg in order to remove the residual starting materials to yield 1083 g (98%) of **3a** as a crude brown oil 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 1. The 4-nitrobenzyl bromide is commercially available, and the preparation of used β-keto esters can be found in ref 10.

5-[(2′-Cyanobiphenyl-4-yl)methyl]-2-methyl-6-*n*-propylpyrimidin-4(3*H*)-one (5a). A sodium methylate solution, prepared from 120.6 g (5.24 mol) of sodium in 1.5 L of methanol, was added dropwise to a solution of 466 g (4.92 mol) of acetamidine hydrochloride in 4.3 L of methanol. The mixture was stirred for 15 min at room temperature, and 1148 g of **3a** (3.28 mol; HPLC purity 85.5%) in solution in 1.15 L of methanol was added rapidly. After stirring for 20 h at room temperature, the reaction mixture was refluxed for 3 h and concentrated under vacuum (5 L of methanol was distilled). To the mixture were added 4 L of water and 1 L of diisopropyl ether, and after vigorous stirring the crystals were filtered off, washed with water and diisopropyl ether, dried, and recrystallized in 3.5 volumes of 2-methoxyethanol to give 684.5 g (60.8%) of pure **5a**, mp 209–210 °C. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.44–7.35 (m, 6H), 3.97 (s, 2H), 2.60 (t, 2H, J = 7.5 Hz), 2.40 (s, 3H), 1.62 (sext, 2H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz).

Compounds **5a–d,f–h** were synthesized by this method starting from the appropriate 2-alkylated β-keto esters **3** and the corresponding amidine hydrochlorides **4** that are commercially available or can be prepared according to ref 21. Corresponding data are shown in Table 2.

2-Methyl-5-(4-nitrobenzyl)-6-*n*-propylpyrimidin-4(3*H*)-one (5e). To a solution of 3.5 g (152 mmol) of sodium in 175 mL of ethanol was added 9.5 g (100 mmol) of acetamidine hydrochloride. The mixture was stirred for 5 min at room temperature, and 20 g (68 mmol) of **3e** was added. After 4 days at room temperature, the solvent was evaporated off under vacuum and the residue was taken up with 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated under vacuum to give an oily residue which

crystallized in an acetone/diethyl ether mixture. The crystals were filtered off and dried to give 10.9 g (56%) of **5e**, mp 200 °C. ^{1}H NMR (DMSO-d_6): δ 8.15 (d, 2H, J = 9 Hz), 7.46 (d, 2H, J = 9 Hz), 3.91 (s, 2H), 2.42 (t, 2H, J = 7.5 Hz), 2.27 (s, 3H), 1.48 (sext, 2H, J = 7.5 Hz), 0.82 (t, 3H, J = 7.5 Hz).

5-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(methylthio)-6-*n*-propylpyrimidin-4(3*H*)-one (5i). To a solution of 5.7 g (248 mmol) of sodium in 150 mL of methanol was added 18.9 g (248 mmol) of thiourea. The mixture was stirred for 5 min, and 58 g (166 mmol) of **3a** was added. After refluxing for 10 h, the mixture was cooled and the methanol was evaporated off under vacuum. The residue was taken up with water and washed with ether, the aqueous layer was neutralized by adding dilute hydrochloric acid, and the crystals obtained were filtered off and washed with water and ether to give 26 g of the 2-mercapto derivative (mp 191 °C) which was dissolved in a solution of 5 g of potassium hydroxide in 100 mL of methanol. Iodomethane (6 mL, 96 mmol) was added, and the mixture was stirred for 4 h at room temperature. The crystals were filtered off and washed with water and ether to give 23 g (36% from **2b**) of **5i**, mp 218 °C. ^{1}H NMR (DMSO-d_6): δ 7.76–7.60 (m, 2H), 7.50–7.39 (m, 4H), 7.31 (d, 2H, J = 8 Hz), 3.88 (s, 2H), 2.56–2.47 (m, 5H), 1.64 (sext, 2H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.5 Hz).

5-[(2′-Cyanobiphenyl-4-yl)methyl]-6-*n*-propylpyrimidin-4(3*H*)-one (5j). To a solution of 29 g (77 mmol) of **5i** in 250 mL of diglyme was added 20 g of Raney nickel. The mixture was heated to reflux for 3 h, and after cooling, the catalyst was filtered off and washed with ethanol. The filtrate was evaporated under vacuum, and the residue was chromatographed on silica gel with acetone/chloroform (2/8) as eluent to give 14.2 g (56%) of **5j**, mp 158 °C. ^{1}H NMR (DMSO-d_6): δ 8.17 (s, 1H), 7.92 (d, 1H, J = 8 Hz), 7.77 (t, 1H, J = 8 Hz), 7.58 (t, 2H, J = 8 Hz), 7.48 (d, 2H, J = 8 Hz), 7.33 (d, 2H, J = 8 Hz), 3.88 (s, 2H), 2.53 (t, 2H, J = 7.5 Hz), 1.64 (sext, 2H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.5 Hz).

4-Chloro-5-[(2′-cyanobiphenyl-4-yl)methyl]-2-methyl-6-*n*-propylpyrimidine (6a). To 167 mL of phosphorus oxychloride was added portionwise in 30 min 104.8 g (305 mmol) of **5a**; a slightly exothermic effect occurred, and the temperature rose to 43 °C. At the end of the addition, the reaction mixture was allowed to return to room temperature and slowly heated to 100 °C. After 6 h at this temperature, the excess of phosphorus oxychloride was evaporated under vacuum and 100 mL of toluene was added. The solvent was removed under vacuum and the residue taken up in 500 mL of dichloromethane and washed with water. The organic layer was then dried over magnesium sulfate and evaporated to give 108.1 g of **6a** (98%), mp 102 °C. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 1H, J = 7.7 Hz), 7.64 (t, 1H, J = 7.7 Hz), 7.51–7.43 (m, 4H), 7.21 (d, 2H, J = 8 Hz), 4.23 (s, 2H), 2.77–2.69 (m, 5H), 1.65 (sext, 2H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz).

All compounds **6a–d,f–j** were prepared according to this procedure, and corresponding data are shown in Table 3.

4-Chloro-2-methyl-5-(4-nitrobenzyl)-6-*n*-propylpyrimidine (6e): prepared according to the same procedure, yield 95%, mp 95 °C. ^{1}H NMR (DMSO-d_6): δ 8.17 (d, 2H, J = 8 Hz), 7.39 (d, 2H, J = 8 Hz), 4.32 (s, 2H), 2.70 (t, 2H, J = 7.5 Hz), 2.60 (s, 3H), 1.55 (sext, 2H, J = 7.5 Hz), 0.86 (t, 3H, J = 7.5 Hz).

5-[(2′-Cyanobiphenyl-4-yl)methyl]-4-hydrazino-2-methyl-6-*n*-propylpyrimidine (7a). A mixture of 108.1 g (299 mmol) of **6a** and 183 mL of hydrazine hydrate was heated to reflux in 240 mL of ethanol for 2 h. The mixture was then cooled to room temperature with stirring, and the stirring was continued for 3 h. The crystals were filtered off, washed with water, and dried to give 98.3 g (92%) of pure **7a** (HPLC purity 99.8%), mp 156 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.8 Hz), 7.51–7.44 (m, 4H), 7.20 (d, 2H, J = 8 Hz), 5.77 (s, 1H), 3.98 (br s, 2H), 3.90 (s, 2H), 2.68 (t, 2H, J = 7.5 Hz), 2.57 (s, 3H), 1.69 (sext, 2H, J = 7.5 Hz), 0.98 (t, 3H, J = 7.5 Hz).

4-Hydrazino-2-methyl-5-(4-nitrobenzyl)-6-*n*-propylpyrimidine (7e): prepared according to the same procedure as **7a**, yield 90%, mp 126 °C.

Compounds **7b–d,f–j** were prepared according to the same procedure, and corresponding data are shown in Table 4.

Method A. **(a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-1,2,4-triazolo[4,3-*c*]pyrimidin-3(2*H*)-one (8a).** To a solution of 33.4 g (93.5 mmol) of **7a** in 600 mL of tetrahydrofuran was added 15.1 g (93.5 mmol) of 1,1′-carbonyldiimidazole, and the mixture was heated to reflux for 1.5 h. The solvent was removed under vacuum; the residue was taken up with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated off under vacuum and the residue crystallized in an ethyl acetate/diethyl ether mixture to give 26.4 g (73%) of **8a**, mp 196 °C. ^{1}H NMR ($CDCl_3$): δ 10.81 (s, 1H), 7.44 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.40–7.36 (m, 6H), 4.06 (s, 2H), 2.91 (s, 3H), 2.63 (t, 2H, J = 7.4 Hz), 1.65 (sext, 2H, J = 7.4 Hz), 0.96 (t, 3H, J = 7.4 Hz).

(b) 5-Methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,2,4-triazolo[4,3-*c*]pyrimidin-3(2*H*)-one (25). To a solution of 4 g (10.4 mmol) of **8a** in 100 mL of toluene was added 2.8 g (14.2 mmol) of trimethyltin azide. The mixture was refluxed for 24 h, and the crystals were filtered off from the hot reaction mixture, washed with ether, and suspended in 100 mL of tetrahydrofuran. Hydrogen chloride gas was bubbled into the mixture, and after complete dissolution, a precipitate began to appear. The mixture was allowed to stand overnight at room temperature, and the crystals were filtered off and dissolved in dilute sodium hydroxide solution. The latter was washed with ether and then acidified by sulfur dioxide and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated under vacuum to give a residue which crystallized from a diethyl ether/ethyl acetate mixture to provide 1.5 g (34%) of **25**, mp 248–249 °C. ^{1}H NMR (DMSO-d_6): δ 7.66–7.49 (m, 4H), 7.19 (d, 2H, J = 8 Hz), 6.99 (d, 2H, J = 8 Hz), 3.92 (s, 2H), 2.72 (s, 3H), 2.43 (t, 2H, J = 7.2 Hz), 1.48 (sext, 2H, J = 7.2 Hz), 0.83 (t, 3H, J = 7.2 Hz).

5-Methyl-8-(4-nitrobenzyl)-7-*n*-propyl-1,2,4-triazolo-[4,3-*c*]pyrimidin-3(2*H*)-one (26): prepared according to method A (a) proceeding from **7e**, yield 76%, mp 225 °C. ^{1}H NMR (DMSO-d_6): δ 8.12 (d, 2H, J = 9 Hz), 7.50 (d, 2H, J = 9 Hz), 4.09 (s, 2H), 2.73 (s, 3H), 2.49 (t, 2H, J = 7.5 Hz), 1.52 (sext, 2H, J = 7.5 Hz), 0.85 (t, 3H, J = 7.5 Hz).

Method B. **(a) 8-(4-Aminobenzyl)-5-methyl-7-*n*-propyl-1,2,4-triazolo[4,3-*c*]pyrimidin-3(2*H*)-one (27).** A solution of 5.4 g (16.5 mmol) of **26** in 100 mL of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.8 g of Raney nickel. When the uptake of hydrogen had ceased, the catalyst was filtered off and the solvent evaporated off under vacuum to give 4.6 g (94%) of **27**, mp 180 °C. ^{1}H NMR (DMSO-d_6): δ 6.88 (d, 2H, J = 8.4 Hz), 6.44 (d, 2H, J = 8.4 Hz), 4.86 (s, 2H), 3.73 (s, 2H), 2.71 (s, 3H), 2.46 (t, 2H, J = 7.5 Hz), 1.50 (sext, 2H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz).

(b) 2-[[[4-[(2,3-Dihydro-5-methyl-7-*n*-propyl-3-oxo-1,2,4-triazolo[4,3-*c*]pyrimidin-8-yl)methyl]phenyl]amino]carbonyl]benzenesulfonic Acid (28). To a solution of 4.6 g (15.5 mmol) of **27** in 300 mL of acetonitrile was added a solution of 2.9 g (15.7 mmol) of 2-sulfobenzoic acid cyclic anhydride in 30 mL of acetonitrile. The mixture was stirred for 15 min, and the crystals were collected and washed with diethyl ether and then dissolved in an aqueous sodium bicarbonate solution. This solution was washed with diethyl ether and ethyl acetate and then acidified with sulfur dioxide. The crystals were filtered off, washed with water and diethyl ether, and dried to give 4 g (53%) of **28**, mp 283–286 °C. ^{1}H NMR (DMSO-d_6): δ 7.92–7.87 (m, 1H), 7.76–7.70 (m, 1H), 7.59–7.50 (m, 4H), 7.24 (d, 2H, J = 8.5 Hz), 3.94 (s, 2H), 2.83 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.57 (sext, 2H, J = 7.5 Hz), 0.91 (t, 3H, J = 7.5 Hz).

Method C. **(a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-2-hydroxy-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (12a).** A solution of 13.8 g (36 mmol) of **8a** in 40 mL of ethanol and 150 mL of 3 N potassium hydroxide solution was heated to 60 °C for 4 h, and 100 mL of water was added. The solution was acidified with concentrated hydrochloric acid, and the crystals were filtered off, washed with water, and

taken up in chloroform. The chloroform solution was dried over magnesium sulfate and evaporated under vacuum to give 10.6 g of crude **12a** which was chromatographed on silica gel with chloroform/methanol (9/1) as eluent to yield 8.4 g (61%) of pure **12a**, mp 226 °C. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.49–7.30 (m, 6H), 4.30 (s, 2H), 2.87 (s, 3H), 2.81 (t, 2H, J = 7 Hz), 1.69 (sext, 2H, J = 7 Hz), 0.96 (t, 3H, J = 7 Hz).

(b) 2-Hydroxy-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (29): prepared from **12a** according to method A (b), yield 45%, mp 234 °C. ^{1}H NMR (DMSO-d_6): δ 7.67–7.49 (m, 4H), 7.15 (d, 2H, J = 8 Hz), 6.99 (d, 2H, J = 8 Hz), 4.16 (s, 2H), 2.71 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 1.53 (sext, 2H, J = 7.5 Hz), 0.84 (t, 3H, J = 7.5 Hz).

Method D. (a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-2-hydroxy-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (12a). A mixture of 97.3 g (273 mmol) of **7a** and 43.4 g (722 mmol) of urea in 97.3 mL of *N*-methylpyrrolidone was progressively heated, and the temperature was maintained at 160 °C for 6 h. After cooling, the mixture was poured into 700 mL of cold water containing 12 g of sodium hydroxide in pellets and extracted with ethyl acetate. The aqueous layer was acidified to pH = 5 with acetic acid (40 mL), and the crystals were filtered off, washed with water and diisopropyl ether, and dried to give 98.1 g (94%; HPLC purity 99.8%) of **12a**, mp 225–226 °C. ^{1}H NMR ($CDCl_3$): see method C.

(b) 2-Hydroxy-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (29). A mixture of 5.1 g (24.7 mmol) of trimethyltin azide and 4.98 g (13 mmol) of **12a** was heated to 115 °C for 48 h in 50 mL of xylene. The temperature was then allowed to return to 80 °C, and the precipitate was filtered off, washed with hot xylene, and suspended in 75 mL of tetrahydrofuran. Hydrochloric acid gas was bubbled into this suspension until complete dissolution and then again during another 20 min. A white precipitate was formed which was filtered off after stirring for 1 h and then taken up in 100 mL of 2-butanone. This suspension was stirred at reflux for 4 h, and after cooling, the crystals were filtered off and washed with 2-butanone. Recrystallization from ethanol (95%) gave 4.27 g (77%; HPLC purity 99.9%) of **29**, mp 234–235 °C. ^{1}H NMR (DMSO-d_6): see method C.

Method E. 4′-[(7-*n*-Butyl-2-hydroxy-5-methyl-[1,2,4]-triazolo[1,5-*c*]pyrimidin-8-yl)methyl]-2-biphenylcarboxylic Acid (30). A solution of 8 g (20 mmol) of 7-*n*-butyl-8-[(2′-cyanobiphenyl-4-yl)methyl]-2-hydroxy-5-methyl-1,2,4-triazolo[1,5-*c*]pyrimidine prepared according to method D (a) proceeding from **7b** and in 6 g (150 mmol) of sodium hydroxide in 30 mL of ethylene glycol and 2 mL of water was heated to reflux for 10 h. After cooling, the solution was acidified to pH = 5 with hydrochloric acid and the crystals were collected, washed with water and acetone, and dried to give 5 g (60%) of **30**, mp 210–211 °C. ^{1}H NMR (DMSO-d_6): δ 7.69 (d, 1H, J = 8 Hz), 7.52 (t, 1H, J = 8 Hz), 7.41 (t, 1H, J = 8 Hz), 7.31 (d, 1H, J = 8 Hz), 7.25 (br s, 4H), 4.20 (s, 2H), 2.71 (m, 5H), 1.48 (sext, 2H, J = 8 Hz), 1.29 (sext, 2H, J = 8 Hz), 0.85 (t, 3H, J = 8 Hz).

Method F. (a) 4-Hydrazino-2-methyl-6-*n*-propyl-5-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidine (7′a): prepared according to the procedure of method A (b) proceeding from **7a**, yield 56%, mp 183–185 °C. ^{1}H NMR (DMSO-d_6): δ 7.58–7.40 (m, 4H), 6.99 (br s, 4H), 6.90–4.70 (br signal, 4H), 3.83 (s, 2H), 2.43 (t, 2H, J = 7.2 Hz), 2.35 (s, 3H), 1.47 (sext, 2H, J = 7.2 Hz), 0.82 (t, 3H, J = 7.2 Hz).

(b) 3-Mercapto-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,2,4-triazolo[4,3-*c*]pyrimidine (32). To a solution of 8 g of **7′a** (20 mmol) and 2.4 g (60 mmol) of sodium hydroxide in 75 mL of methanol and 7 mL of water was added dropwise 2.5 mL (41.5 mmol) of carbon disulfide, and the mixture was heated to reflux for 1 h and then evaporated to dryness under vacuum. The residue was taken up with 100 mL of ethanol, and the mixture was refluxed for 1 h. The solvent was removed under vacuum, and the residue was taken up with water. On addition of acetic acid, the pH was brought to 5, and the crystals were filtered off and chromatographed on silica gel with ethyl acetate as eluent to give 1.4 g (16%) of **32**, mp 247–248 °C. ^{1}H NMR (DMSO-d_6): δ 7.72–7.50 (m, 4H), 7.20 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 4.06 (s, 2H), 3.17 (s, 3H), 2.53 (t, 2H, J = 7 Hz), 1.52 (sext, 2H, J = 7 Hz), 0.84 (t, 3H, J = 7 Hz).

Method G. (a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-2-mercapto-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (15). To a solution of 4.38 g (12.2 mmol) of **7a** in 50 mL of *n*-butanol was added 1.5 mL of carbon disulfide. The mixture was heated to reflux for 3 h and then cooled. The crystals were filtered off, washed with diethyl ether, and dried to give 4.2 g (86%) of **15a**, mp 210 °C. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.47–7.29 (m, 6H), 4.45 (s, 2H), 2.88 (s, 3H), 2.77 (t, 2H, J = 7.5 Hz), 1.67 (sext, 2H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz).

(b) 2-Mercapto-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-tetrazolo[1,5-*c*]pyrimidine (33): prepared according to the procedure of method D (b) from **15a**, yield 69%, mp 223–225 °C. ^{1}H NMR (DMSO-d_6): δ 7.64–7.41 (m, 4H), 7.10–6.97 (m, 4H), 4.24 (s, 2H), 2.78 (s, 3H), 2.69 (t, 2H, J = 7.5 Hz), 1.44 (sext, 2H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz).

Method H. 5-Methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,2,4-triazolo[4,3-*c*]pyrimidine (35). A mixture of 4.8 g of **7′a** (12 mmol) and 40 mL of triethyl orthoformate was heated to reflux for 4 h. The mixture was evaporated under vacuum, and the residue was crystallized from an ethyl acetate/diisopropyl ether mixture to give 1 g (20%) of **35**, mp 182–184 °C. ^{1}H NMR ($CDCl_3$): δ 8.91 (s, 1H), 7.66 (d, 1H, J = 7 Hz), 7.57–7.42 (m, 3H), 7.22 (d, 2H, J = 8 Hz), 7.03 (d, 2H, J = 8 Hz), 4.36 (s, 2H), 2.87 (s, 3H), 2.73 (t, 2H, J = 7.2 Hz), 1.66 (sext, 2H, J = 7.2 Hz), 0.94 (t, 3H, J = 7.2 Hz).

Method I. 5-(Hydroxymethyl)-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]-pyrimidin-2(3*H*)-one (44). To a solution of 1 g (2.2 mmol) of 5-methoxymethyl derivative **43** (Table 7, prepared according to method D) in 50 mL of chloroform stabilized with amylene was added 0.7 mL (7.4 mmol) of boron tribromide. The mixture was stirred for 8 h at room temperature, 10 mL of 0.1 N sodium hydroxide solution was added, and the mixture was stirred again for 6 h at room temperature. The aqueous layer was separated and acidified by bubbling of sulfur dioxide. The crystals were collected, washed with acetone, and dried to give 0.6 g (62%) of **44**, mp 182–183 °C. ^{1}H NMR (DMSO-d_6): δ 7.70–7.50 (m, 4H), 7.17 (d, 2H, J = 8 Hz), 7.00 (d, 2H, J = 8 Hz), 4.83 (s, 2H), 4.20 (s, 2H), 2.70 (t, 2H, J = 7.3 Hz), 1.57 (sext, 2H, J = 7.3 Hz), 0.87 (t, 3H, J = 7.3 Hz).

Method J. (a) Ethyl [8-[(2′-Cyanobiphenyl-4-yl)-methyl]-2,3-dihydro-5-methyl-7-*n*-propyl-3-oxo-1,2,4-triazolo[4,3-*c*]pyrimidin-2-yl]acetate (9a). To a solution of 3.8 g (9.88 mmol) of **8a** in 50 mL of ethanol was added a solution of sodium ethylate, prepared from 0.25 g (10.8 mmol) of sodium in 10 mL of ethanol. The mixture was stirred for 10 min at room temperature, 1.3 mL (11.7 mmol) of ethyl bromoacetate was added dropwise, and the mixture was refluxed for 7 h. The solvent was evaporated under vacuum, and the residue was taken up with water and extracted with diethyl ether. The organic layer was washed with cold dilute sodium hydroxide solution, dried, and evaporated under vacuum to give 4.3 g (92%) of **9a**, an oil used directly for the next step. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 1H, J = 7 Hz), 7.60 (t, 1H, J = 7 Hz), 7.48–7.31 (m, 6H), 4.65 (s, 2H), 4.24 (q, 2H, J = 7.5 Hz), 4.03 (s, 2H), 2.88 (s, 3H), 2.60 (t, 2H, J = 7.5 Hz), 1.65 (sext, 2H, J = 7.5 Hz), 1.29 (t, 3H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz).

(b) Ethyl [2,3-dihydro-5-methyl-7-*n*-propyl-3-oxo-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,2,4-triazolo[4,3-*c*]pyrimidin-2-yl]acetate (45): prepared according to method D (b) from **9a**, yield 53%, mp 173–174. ^{1}H NMR (DMSO-d_6): δ 7.65 (d, 1H, J = 7 Hz), 7.57–7.55 (m, 1H), 7.47 (t, 2H, J = 7 Hz), 7.16 (d, 2H, J = 8 Hz), 7.03 (d, 2H, J = 8 Hz), 4.67 (s, 2H), 4.23 (q, 2H, J = 7.5 Hz), 3.94 (s, 2H), 2.85 (s, 3H), 2.52 (t, 2H, J = 7.5 Hz), 1.36 (sext, 2H, J = 7.5 Hz), 1.29 (t, 3H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz).

Method K. **(a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-2-methoxy-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (13a).** To a solution of 4.4 g (11.4 mmol) of **12a** in 50 mL of acetone was added 2 g of potassium carbonate. After addition of 2 mL of methyl iodide, the mixture was refluxed for 5 h, cooled to room temperature, and concentrated under vacuum and the residue was then treated with water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and evaporated under vacuum; the residue was chromatographed on silica gel in chloroform/acetone (80/20) as eluent to give 3.2 g (70%) of **13a**, mp 89 °C. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 1H, J = 7.5 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.43–7.32 (m, 6H), 4.29 (s, 2H), 4.12 (s, 3H), 2.82 (s, 3H), 2.73 (t, 2H, J = 7.5 Hz), 1.64 (sext, 2H, J = 7.5 Hz), 0.93 (t, 3H, J = 7.5 Hz).

(b) 2-Methoxy-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (48): prepared proceeding from **13a**, according to method D (b), yield 65%, mp 189–190 °C. ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 1H, J = 7 Hz), 7.61–7.41 (m, 3H), 7.05 (q, 4H, J = 8 Hz), 4.15 (s, 2H), 4.05 (s, 3H), 2.81 (s, 3H), 2.75 (t, 2H, J = 7.3 Hz), 1.68 (sext, 2H, J = 7.3 Hz), 0.96 (t, 3H, J = 7.3 Hz).

Method L. **(a) Ethyl [[8-[(2′-Cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidin-2-yl]thio]acetate (16a).** To a solution of 4 g (10 mmol) of **15a** in 40 mL of ethanol was added a solution of sodium ethoxide, obtained by adding 0.3 g (13 mmol) of sodium to 5 mL of ethanol. The mixture was stirred for 10 min at room temperature, and 1.5 mL (13 mmol) of ethyl bromoacetate was added. The mixture was then heated for 2 h to reflux, the solvent was evaporated under vacuum, and the residue was taken up with water and extracted with ethyl acetate. The organic layer was dried and evaporated under vacuum and the resulting oil crystallized in a diethyl ether/pentane mixture to give 2.9 g (60%) of **16a**, mp 103 °C. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.46–7.33 (m, 6H), 4.32 (s, 2H), 4.19 (q, 2H, J = 7.5 Hz), 4.06 (s, 2H), 2.84 (s, 3H), 2.78 (t, 2H, J = 7.5 Hz), 1.65 (sext, 2H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.5 Hz), 0.93 (t, 3H, J = 7.5 Hz).

(b) Ethyl [[5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidin-2-yl]thio]acetate (49): prepared according to method D (b), proceeding from **16a**, yield 51%, mp 127–128 °C. ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 1H, J = 8 Hz), 7.63 (m, 2H), 7.47 (d, 1H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 4.28 (s, 2H), 4.19 (q, 2H, J = 6.5 Hz), 4.05 (s, 2H), 2.88 (s, 3H), 2.82 (t, 2H, J = 8 Hz), 1.74 (sext, 2H, J = 8 Hz), 1.27 (t, 3H, J = 6.5 Hz), 0.99 (t, 3H, J = 8 Hz).

Method M. **(a) *N,N*-Dimethyl-8-[(2′-cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-sulfonamide (20a).** To a solution of 9.3 g (23.3 mmol) of **15a** in 80 mL of concentrated hydrochloric acid at −5 °C was added dropwise, in the course of 15 min, 3.5 g (37.6 mmol) of sodium chlorate dissolved in 15 mL of water, the temperature being maintained between −5 and 0 °C. The mixture was then stirred for 20 min at 0 °C and thereafter poured into an ice/water mixture; the crystals formed were drained and washed with water and then taken up in 250 mL of ether, stirred for 5 min, filtered off, and air-dired to give 8 g of 8-[(2′-cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-sulfonyl chloride (**19a**), mp 141 °C. A mixture of 8 g (17 mmol) of **19a** and 40 mL of a 40% aqueous solution of dimethylamine was stirred for 1 h at 50 °C. The mixture was then extracted with chloroform, and the organic layer was dried over magnesium sulfate and then concentrated under vacuum to give 5.5 g (50%) of **20a**, mp 158 °C. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 1H, J = 7.5 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.48–7.36 (m, 6H), 4.43 (s, 2H), 3.00 (br s, 9H), 2.98 (t, 2H, J = 7.5 Hz), 1.73 (sext, 2H, J = 7.5 Hz), 0.99 (t, 3H, J = 7.5 Hz).

(b) *N,N*-Dimethyl-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-sulfonamide (51): prepared according to method D (b) from **20a**, yield 56%, mp 176–178 °C. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, J = 7.5 Hz), 7.63–7.43 (m, 2H), 7.34 (d, 1H, J = 7.5 Hz), 7.21 (d, 2H, J = 7.5 Hz), 7.02 (d, 2H, J = 7.5 Hz), 4.32 (s, 2H), 3.01 (s, 6H), 2.87 (s, 3H), 2.85 (t, 2H, J = 7.5 Hz), 1.73 (sext, 2H, J = 7.5 Hz), 0.96 (t, 3H, J = 7.5 Hz).

Method N. **(a) 2-Amino-8-[(2′-cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (18).** A solution of 10 g (28 mmol) of **7a** and 5 g (18 mmol) of 2-methyl-2-thiopseudourea sulfate in 40 mL of water was heated to reflux for 16 h. After adding water, the crystals formed were filtered off, washed with diethyl ether and ethyl acetate, taken up in dilute sodium hydroxide solution, and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated off under vacuum to give a residue which crystallized in a diisopropyl ether/ethyl acetate mixture to give 1.8 g (17%) of **18**, mp 150 °C. ^{1}H NMR (DMSO-d_6): δ 7.91 (d, 1H, J = 7.5 Hz), 7.77 (t, 1H, J = 7.5 Hz), 7.68 (d, 2H, J = 7.5 Hz), 7.48 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8 Hz), 6.42 (s, 2H), 4.24 (s, 2H), 2.69 (s, 3H), 2.68 (t, 2H, J = 7.5 Hz), 1.58 (sext, 2H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.5 Hz).

(b) 2-Amino-5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (54): prepared according to method E (b) from **18**, yield 51%, mp 170–174 °C. ^{1}H NMR (DMSO-d_6): δ 7.70–7.48 (m, 4H), 7.17 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 4.14 (s, 2H), 2.68 (s, 3H), 2.62 (t, 2H, J = 7.5 Hz), 1.53 (sext, 2H, J = 7.5 Hz), 0.84 (t, 3H, J = 7.5 Hz).

Method O. **(a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-5-methyl-2-(methylamino)-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]-pyrimidine (17a).** To a solution of 10 g (28 mmol) of **7a** in 100 mL of toluene was added 2.1 g (28 mmol) of methyl isothiocyanate, and the mixture was heated to reflux for 2 h and left overnight at room temperature. Iodomethane (2 mL, 32 mmol) was added, and the mixture was refluxed for 2 h. After cooling, the crystals were filtered off and washed with diethyl ether to give 14 g of a 5-methylisothiosemicarbazido derivative as a hydroiodide (mp 220 °C dec). The latter was heated to reflux for 3 h in 100 mL of 2-ethoxyethanol with 4.2 g of potassium carbonate. The solvent was then evaporated off under vacuum, and the residue was taken up with water. The crystals formed were filtered off and washed with water and diethyl ether to give 9.24 g (83%) of **17a**, mp 159 °C. ^{1}H NMR (DMSO-d_6): δ 7.92 (d, 1H, J = 7.5 Hz), 7.77 (t, 1H, J = 7.5 Hz), 7.57 (d, 2H, J = 7.5 Hz), 7.49 (d, 2H, J = 8 Hz), 7.38 (d, 2H, J = 8 Hz), 6.90 (q, 1H, J = 5 Hz), 4.22 (s, 2H), 2.84 (d, 3H, J = 5 Hz), 2.71 (s, 3H), 2.68 (t, 2H, J = 7.5 Hz), 1.58 (sext, 2H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.5 Hz).

(b) 5-Methyl-2-(methylamino)-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (55): prepared from **17a**, according to method E (b), yield 63%, mp 229–230 °C. ^{1}H NMR (DMSO-d_6): δ 7.69–7.48 (m, 4H), 7.15 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 6.81 (q, 1H, J = 5 Hz), 4.15 (s, 2H), 2.84 (d, 3H, J = 5 Hz), 2.71 (s, 3H), 2.62 (t, 2H, J = 7.5 Hz), 1.54 (sext, 2H, J = 7.5 Hz), 0.84 (t, 3H, J = 7.5 Hz).

Method P. **(a) 8-[(2′-Cyanobiphenyl-4-yl)methyl]-2,5-dimethyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine (14a).** A mixture of 6 g (16.8 mmol) of **7a** and 25 mL of triethyl orthoacetate was heated to 90 °C for 5 h. The mixture was evaporated under vacuum and the residue taken up in 75 mL of formic acid. The solution was heated to reflux for 5 h, and the formic acid was evaporated under vacuum. The residue was crystallized in a diethyl ether/pentane mixture to give 5 g (78%) of **14a**, mp 132 °C. ^{1}H NMR (DMSO-d_6): δ 7.91 (d, 1H, J = 8 Hz), 7.78 (d, 1H, J = 8 Hz), 7.58 (d, 2H, J = 8 Hz), 7.48 (d, 2H, J = 8 Hz), 7.37 (d, 2H, J = 8 Hz), 4.46 (s, 2H), 2.81 (s, 3H), 2.75 (t, 2H, J = 7.5 Hz), 2.50 (s, 3H), 1.60 (sext, 2H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.5 Hz).

(b) 2,5-Dimethyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (57): prepared according to method D (b) from **14a**, yield 72%, mp 188–190 °C. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J = 8 Hz), 7.58–7.40 (m, 2H), 7.34 (d, 1H, J = 8 Hz), 6.94 (br s, 4H), 4.15 (s, 2H), 2.86 (s, 3H), 2.72 (t, 2H, J = 7.5 Hz), 2.44 (s, 3H), 1.68 (sext, 2H, J = 7.5 Hz), 0.93 (t, 3H, J = 7.5 Hz).

Method Q. **(a) Ethyl 8-[(2′-Cyanobiphenyl-4-yl)methyl]-5-methyl-7-*n*-propyl-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-carboxylate (14b).** To a solution of 34.6 g (97 mmol) of **7a** and 11.9 g (118 mmol) of triethylamine in 500 mL of chloroform

stabilized with amylene was added dropwise 13.2 mL (118 mmol) of ethyl oxalyl chloride, and the mixture was stirred for 1 h at room temperature and then for 2 h to reflux. After washing with water, the chloroform layer was dried over magnesium sulfate and evaporated under vacuum; the residue was crystallized in an ethyl acetate/diethyl ether mixture to give 25 g of hydrazide, mp 176 °C. The latter was then heated to 100 °C for 6 h in 60 mL of phosphorus oxychloride. The mixture was concentrated under vacuum and the residue taken up with chloroform and washed with an aqueous sodium bicarbonate solution before being dried over magnesium sulfate and evaporated under vacuum. The residue crystallized in diethyl ether/diisopropyl ether to give 15.7 g (37%) of **14b**, mp 108 °C. ^{1}H NMR (DMSO-d_6): δ 7.92 (d, 1H, J = 7.8 Hz), 7.77 (t, 1H, J = 7.8 Hz), 7.57 (d, 2H, J = 7.8 Hz), 7.49 (d, 2H, J = 7.8 Hz), 7.38 (d, 2H, J = 7.8 Hz), 4.49–4.38 (m, 4H), 2.90 (s, 3H), 2.77 (t, 2H, J = 8 Hz), 1.60 (sext, 2H, J = 8 Hz), 1.47 (t, 3H, J = 7 Hz), 0.87 (t, 3H, J = 8 Hz).

(b) Ethyl 5-methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-carboxylate (64): prepared according to method D (b) from **14b**, yield 58%, mp 168–170 °C. ^{1}H NMR (DMSO-d_6): δ 7.71–7.49 (m, 4H), 7.18 (d, 2H, J = 8 Hz), 7.00 (d, 2H, J = 8 Hz), 4.45 (s, 2H), 4.44 (q, 2H, J = 7.5 Hz), 2.88 (s, 3H), 2.70 (t, 2H, J = 7.5 Hz), 1.56 (sext, 2H, J = 7.5 Hz), 1.47 (t, 3H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.5 Hz).

Method R. 5-Methyl-7-*n*-propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-[1,2,4]-triazolo[1,5-*c*]pyrimidine-2-carboxylic Acid (65). A mixture of 2.8 g (6.3 mmol) of **64** and 1.8 g of sodium carbonate was dissolved in 30 mL of water. The mixture was stirred for 30 h at room temperature and then acidified by bubbling of sulfur dioxide and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to dryness under vacuum. The residue crystallized in acetone/diethyl ether to give 2.3 g (89%) of **65**, mp 193–194 °C. ^{1}H NMR (DMSO-d_6): δ 7.69–7.48 (m, 4H), 7.18 (d, 2H, J = 8 Hz), 6.99 (d, 2H, J = 8 Hz), 4.30 (s, 2H), 2.98 (s, 3H), 2.70 (t, 2H, J = 7.5 Hz), 1.48 (sext, 2H, J = 7.5 Hz), 0.86 (t, 3H, J = 7.5 Hz).

Biology. Angiotensin II Receptor Binding Assay. Rat adrenal membranes were obtained according to a previously described method.[27] Rats were decapitated, and whole adrenals were rapidly dissected from fatty tissue. They were rapidly dried and weighed. Adrenal tissues 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 3000g for 10 min at 4 °C. The supernatant was centrifuged again at 12000g for 13 min at 4 °C. The supernatant was then ultracentrifuged in a polycarbonate tube at 102000g 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 with the glass-Teflon homogenizer. Receptor binding studies were carried out as previously described[27,28] with slight modifications. Total reaction volume was 500 μL consisting of 100 μL of membranes (25–40 μg of protein), 50 μL of [^{125}I]Sar^1-Ile^8-AII (0.2 nM), 50 μL of various concentrations of the drugs (10^{-9}–10^{-4} M for K_i values determination), and 300 μL of incubation buffer with or without 20 mM DTT to characterize whether drugs preferentially interact with AT_1 or AT_2 receptor subtypes. Incubation time was 60 min at 25 °C. Nonspecific binding was measured in the presence of 1 μM unlabeled 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 washing buffer. Each assay was performed in triplicate.

Data Analysis. Competition data were analyzed using the nonlinear regression program LIGAND[29] adapted for an IBM-PC[30] and obtained from Elsevier-Biosoft (Cambridge, England). The concentration of unlabeled tested drug causing 50% displacement of [^{125}I]Sar^1-Ile^8-AII from its binding site (IC_{50} value) was calculated by log–logit linear regression analysis of data (EBDA). The latter were then analyzed assuming models of one and two independent binding sites. A two-site model was accepted over a one-site fit only if it was preferred ($P < 0.05$) using the partial F-test of the program. The inhibition constant (K_i) value was calculated according to the Cheng–Prusoff equation: $K_i = IC_{50} \div (1 + L/K_d)$, in which L and K_d correspond to the concentration and dissociation constant of [^{125}I]Sar^1-Ile^8-AII, respectively. Each K_i value was determined from one experiment, each assay being performed in triplicate.

Antihypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats. Male CD Sprague–Dawley rats (250–270 g) were anesthetized with Ketamine (100 mg/kg, ip), and the left renal artery was completely ligated by means of a 4.0 silk suture, being careful not to damage the left kidney or the left renal vein.[23] Several 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 = 3–8 rats/dose) were dosed orally by gavage of the test compound at 10 or 1 mg/kg. The systolic arterial pressure (SAP) in the 10 mg/kg treated group was measured before and 3 h after dosing by the indirect tail-cuff method[24] 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 after oral administration. The arterial blood pressure in the 1 mg/kg treated group was measured by a direct method as described by Smits.[25] Two or three days before the experiment, the animals were anesthetized as above for the 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). The mean arterial pressure (MAP) was recorded before and for 16 after dosing. The change in MAP was expressed as the maximal decrease in MAP observed during the experiment. When the decrease in MAP was less than −15 mmHg, the drug was considered without effect.

Molecular Modeling. Experiments were performed with the Sybyl software package[31] on a Vaxstation 2000 with a PS 390 and on a Silicon Graphics 4D/340 VGX using the "fit atoms" option of Sybyl.

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