A New Series of Imidazolones: Highly Specific and Potent Nonpeptide AT_1 Angiotensin II Receptor Antagonists

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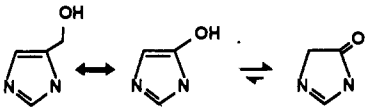
Starting from the structure of the novel nonpeptide AT_1 receptor antagonist DuP 753 (losartan), a new series of potent antagonists was designed. In these compounds the central imidazole nucleus was replaced by the dihydroimidazol-4-one structure. The most active compounds had a spirocyclopentane or a spirocyclohexane ring in position 5. Like the imidazole series, the best substituents were the linear butyl chain in position 2 and the [2'-(tetrazol-5-yl)biphenylyl]methyl group in position 3. Antagonistic activity was assessed by the ability of the compounds to competively inhibit [^{125}I]AII binding to the AT_1 subtype receptor and to antagonize AII-induced contractions in rabbit aorta rings. The most active compounds had IC_{50} values in the nanomolar range. In conscious rats, compounds 4 and 21 antagonized the AII pressor response when administered orally. Compound 21 (SR 47436) was the most active; it was recently shown to also be active in cynomolgus monkeys both intravenously and orally. This molecule is now undergoing clinical trials for the treatment of hypertension.

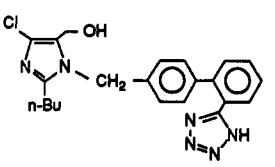
Angiotensin II (AII), an octapeptide produced by the renin-angiotensin system (RAS), is a powerful endogenous vasopressor agent. Drugs that interact with the RAS (captopril, enalapril) have been shown to be effective for the treatment of human hypertension and cardiac heart failure. These angiotensin-converting enzyme inhibitors work by blocking the production of AII from angiotensin I. An alternative approach would be to block the action of AII at the level of its receptor. Until recently, all known AII antagonists have been peptide analogues.[1] Their therapeutic use has been limited by their partial agonist activity and lack of oral bioavailability.[2] More recently, starting from a weakly active lead compound[3] patented by Takeda,[4] extensive structure–activity[5-7] investigations by the DuPont group led to potent and specific antagonists. One of these, 2-*n*-butyl-4-chloro-5-(hydroxymethyl)-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole (DuP 753, losartan) is undergoing extensive clinical evaluation.[8] This pioneer work initiated a flury of activity in pharmaceutical research, and many other nonpeptide orally active AT_1 angiotensin II receptor antagonists have since been reported.[9-11]

All these antagonists possess a central aromatic nucleus bearing the pharmacophores indispensable for activity and notably a polar function adjacent to the biphenyl substituent. While a polar function in this area of the molecule seems to be necessary to maintain activity, the role of the aromatic ring in the binding to the receptor remains uncertain. In DuPont's series, the imidazole ring often bears a hydroxymethyl group in position 5. If we put a polar hydroxy group close to the imidazole ring, we obtain a 4-hydroxyimidazole, which preferentially exists in the dihydroimidazol-4-one form.

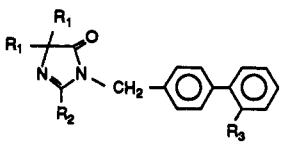
We postulated that this structure could play the same role as the 5-(hydroxymethyl)imidazole group with respect to the AII receptor. In other words, the receptor interaction played by the hydroxy group might be mimicked



by a carbonyl group. Furthermore, since the chloro substituent in position 4 in the (hydroxymethyl)imidazole series interacts with the receptor by occupying a lipophilic pocket,[7] we thought that an alkyl group could play the same role as that of the chlorine atom. We began our program with the synthesis of monosubstituted 5-alkyldihydroimidazolones. These compounds turned out to be unstable;[12] to circumvent this problem we focused our research on the 5,5-disubstituted analogs 1. These compounds constitute a new class of nonpeptide AT_1 antagonists.[13]



Losartan



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Chemistry

The dihydroimidazolone ring was first synthesized by Finger.[14,15] Three different pathways can be used for the synthesis of this ring (Scheme I): route a, condensation between an imidate and an amino ester,[16] route b, condensation of an ortho ester and an amino amide,[17] and route c, acylation of the same amino amide and basic cyclization of the resulting product.[18]

The dihydroimidazolone can exist in two tautomeric forms which can be distinguished by their infrared spectra: 1,5-dihydroimidazol-4-one (form a) ((C=O) 1700 cm^{-1}, (C=N) 1560 cm^{-1}) and 3,5-dihydroimidazol-4-one (form b) ((C=O) 1720 cm^{-1}, (C=N) 1630 cm^{-1}). These tautomeric forms have been investigated by several authors.[16,19-21] Before alkylation, all our products exist in

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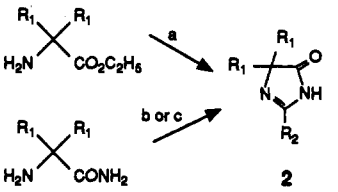
Scheme I[a]



[a] (a) $R_2C(=NH)OC_2H_5$; (b) $R_2C(OCH_3)_3$; (c) R_2COCl then KOH.

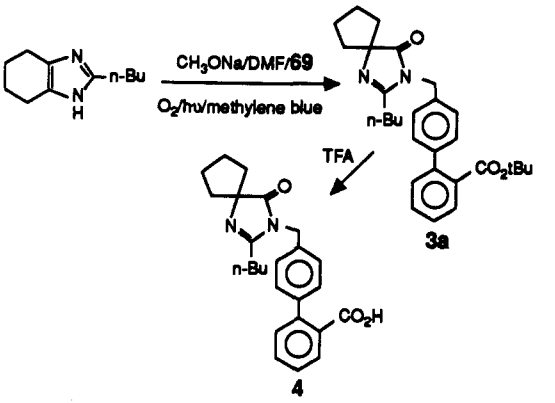
form b (IR, $CHCl_3$); some of them exist in form a in the solid state (IR); but alkylation gave only the 3,5-dihydroimidazol-4-one structure (IR, NMR).

Starting from the dihydroimidazolone prepared by one of the three pathways, a general procedure to obtain the compounds described in this paper is presented in Scheme II for the synthesis of **4**. Alkylation of **2a** with the requisite biphenyl[7] occurs in dimethylformamide in the presence of either sodium hydride at room temperature or sodium methoxide at 40 °C. Under these conditions, we obtained a single alkylation product in excellent yield (80–90%). The alkylation position was assessed by infrared and NMR–NOE (nuclear Overhauser effects) experiments. Deprotection of the acid function was obtained by trifluoroacetic acid to yield **4**.

Compound **4** was also obtained starting from 2-*n*-butyltetrahydro-4,5,6,7-benzimidazole by performing the alkylation in the presence of oxygen and light as depicted in Scheme III. The transformation involved photooxidation followed by rearrangement of the tetrahydrobenzimidazole.[22]

To confirm the structure of the alkylated product, we performed a regiospecific synthesis of **3a** (Scheme IV). The amino-1-cyclopentanecarboxylic acid was protected by an Fmoc group and coupled with 4-(aminomethyl)-

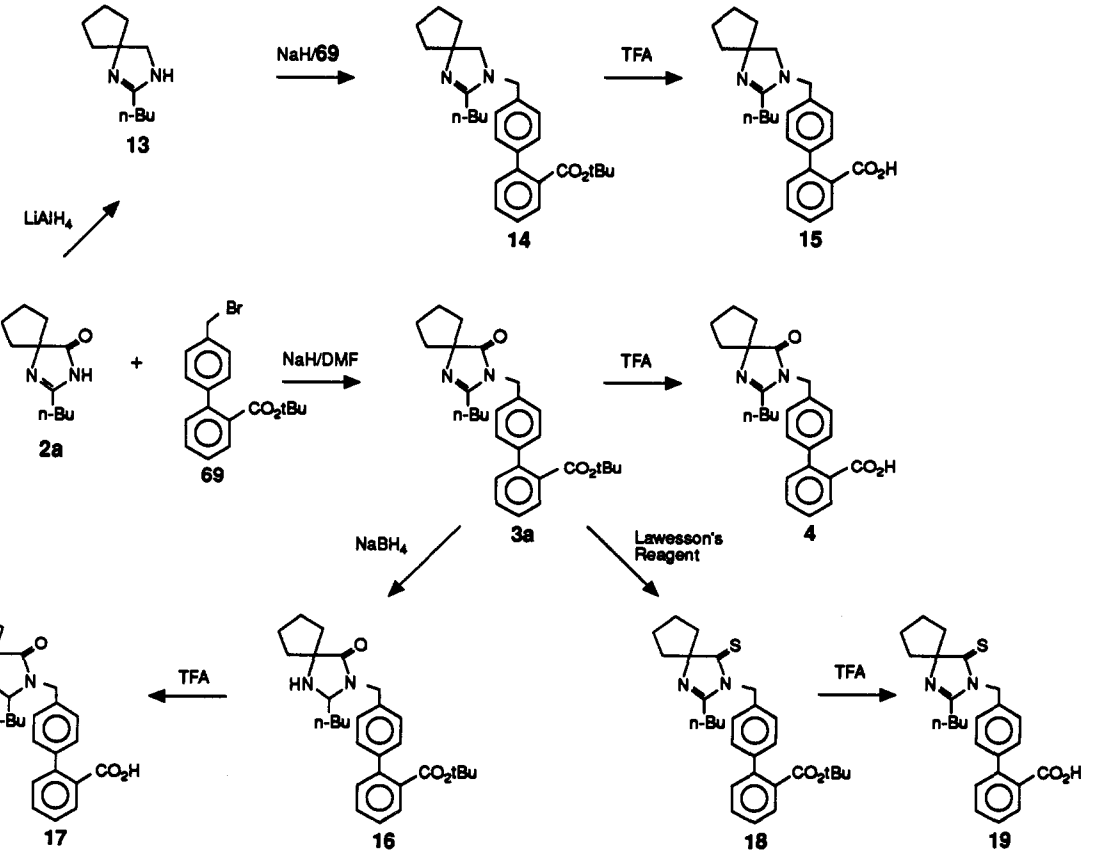
Scheme III



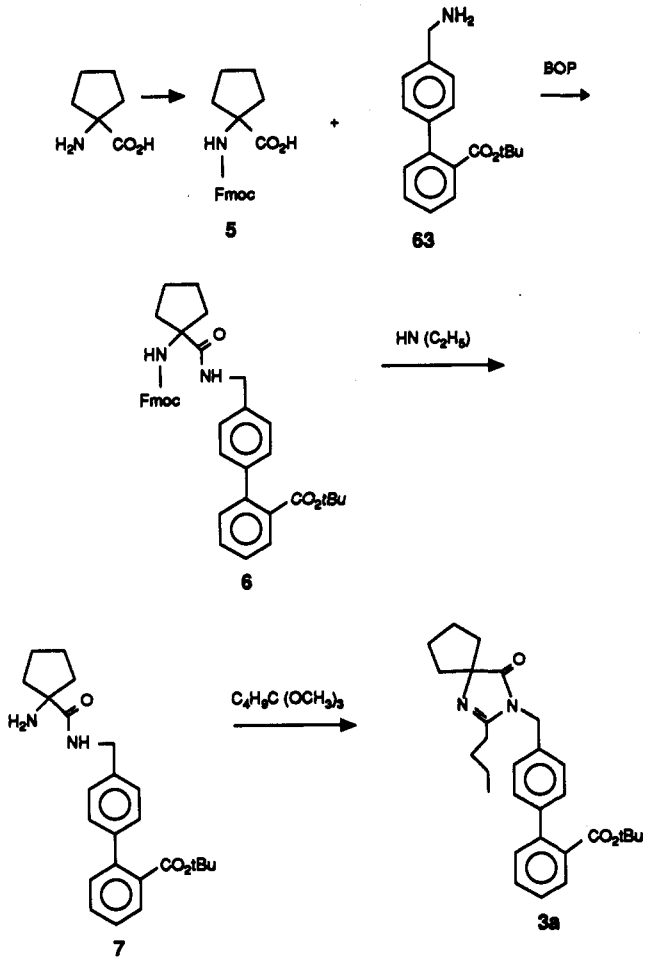
2′-(*tert*-butoxycarbonyl)biphenyl[23] in the presence of [(benzotriazol-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate (BOP).[24] The Fmoc group was removed in the presence of diethylamine to obtain **7** which was cyclized with the appropriate ortho ester to give the same compound **3a**, as above (IR, NMR, MS).

Attempts to prepare the other regioisomer starting from 1-[[2′-(*tert*-butoxycarbonyl)biphenyl-4-yl]amino]cyclopentanecarboxamide were unsuccessful. Compound **12** was, however, obtained as a secondary product during alkylation of the tetrahydroimidazolone **8** (Scheme V). This latter compound could be obtained from **2a** by reduction with sodium borohydride or by hydrogenation over platinum oxide. In contrast, upon treatment with $LiAlH_4$, **2a** was reduced to yield the corresponding 4,4-disubstituted imidazoline **13**[22] (Scheme II). Alkylation with the requisite biphenyl[7] occurred on N-1 as revealed by NMR–NOE experiments.

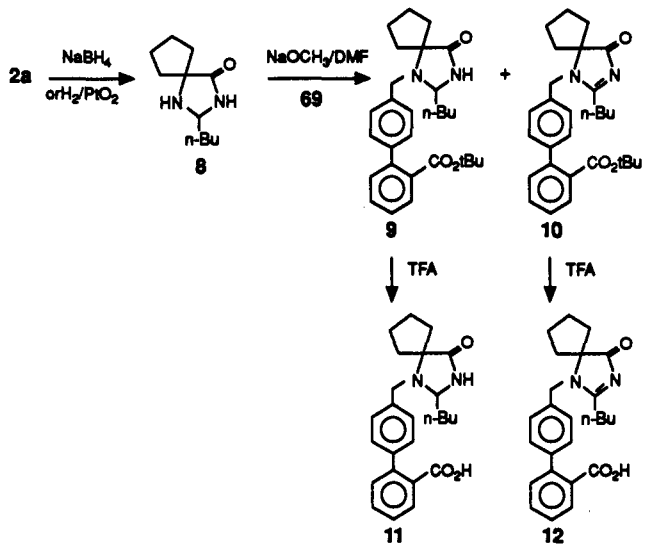
Scheme II



Scheme IV



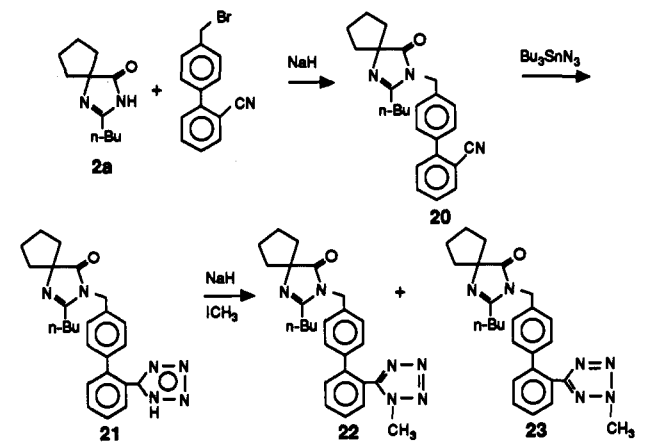
Scheme V



Sodium borohydride was also useful in the reduction of the alkylated dihydroimidazolone **3a**. In this case, double-bond reduction led to the tetrahydrimidazol-4-one **16**, closely related to **3a** (Scheme II). The second tetrahydro regioisomer was synthesized by direct alkylation of **8** (Scheme V).

Alkylated dihydroimidazol-4-thione was obtained upon thionation of the corresponding alkylated dihydroimidazol-4-one with Lawesson's reagent[25] (Scheme II). Thionation at 80 °C in toluene selectively transformed the carbonyl function of the lactam without affecting the carbonyl of the ester function. Alkylation of 5,5-disubstituted 3,5-dihydroimidazole-4-thione occurred as planned on the sulfur atom rather than on the ring nitrogen.

Scheme VI



Compounds bearing the tetrazolyl group were synthesized as described in Scheme VI. The dihydroimidazolone **2a** was alkylated with 4-(bromomethyl)-2′-cyanobiphenyl[7] under the same conditions as above. Formation of the tetrazole ring occurred with tributyltin azide in refluxing xylene. Alkylation of the tetrazole ring with methyl iodide afforded a mixture of the two isomers, which could be separated by chromatography.

All the compounds bearing the spiropiperidine ring in position 5 were prepared starting from the *N*-benzyl-protected dihydroimidazolone **65** (Scheme VII). Hydrogenolysis of the benzyl group yielded **66**. Acylation occurred by treatment with the desired acid and BOP, the acid chloride, or the acid anhydride. Alkylation of **66** with *tert*-butyl bromoacetate furnished **68**. In all cases deprotection was obtained by treatment with trifluoroacetic acid.

Discussion

The compounds reported in this paper were first tested for their affinity for the AT_1 receptor as measured by their ability to displace [^{125}I]AII from its specific binding sites in rat liver membranes. Secondly, their antagonistic properties were assessed through the inhibition of the AII-induced contractions of rabbit aortic strips.

Numerous substitutions on position five of the dihydroimidazolone ring have been described (Tables I and II). The receptor accommodates best, at this position, lipophilic substituents but with reduced mobility. For this reason the preferred substituents are the cyclic ones. Maximum activity was obtained with the three spiro substituents (**4**, **34**, **35**). Substitution of a carbon in this cycle by a heteroatom (**39**, **40**) resulted in loss of activity, especially for the basic nitrogen (**40**). The nitrogen atom of the piperidine ring in compound **40** offers the possibility to easily introduce chemical groups, with the hope of enhancing the affinity for the receptor. It was tempting to introduce amino acids, especially arginine (the amino acid in position 2 in AII) since no nonpeptide antagonists described to date bear a cationic group. Some compounds bearing a second carboxylic group were also synthesized. Unfortunately all such compounds displayed lower binding affinity than compound **4** (Table III).

The structure–activity relationships at the dihydroimidazolone 2-position are illustrated by the data summarized in Table IV. Optimal activity occurred with the linear

Scheme VII

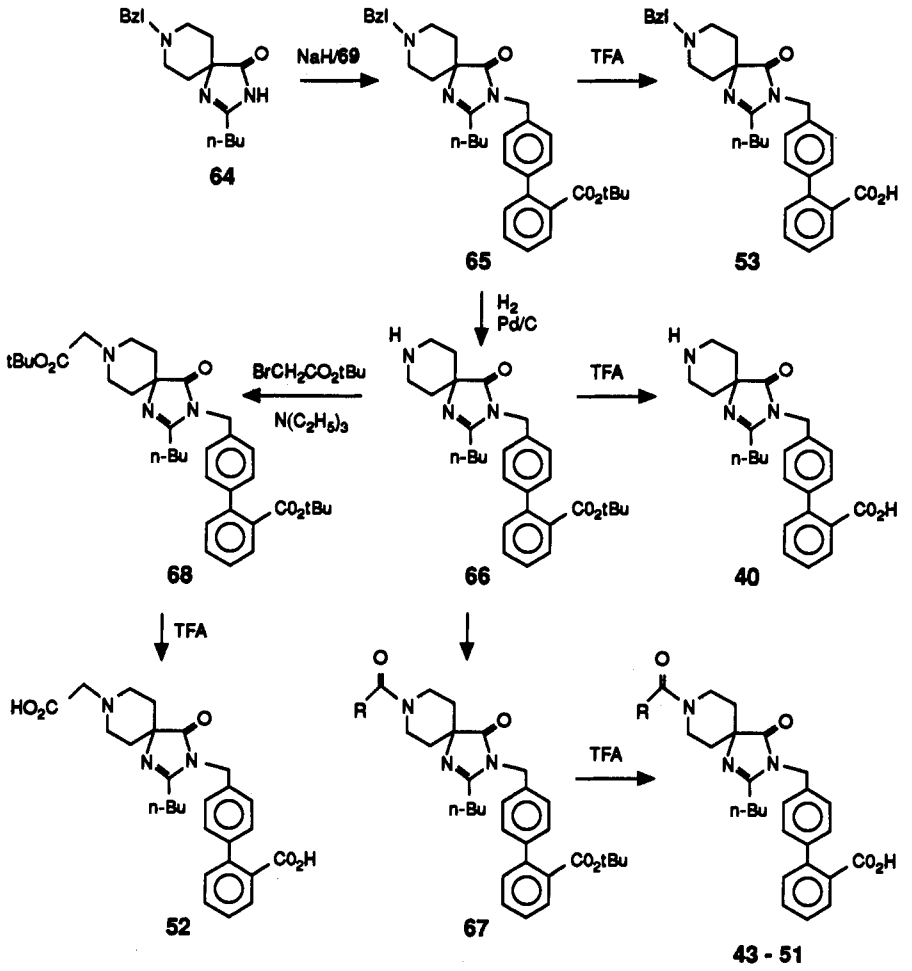
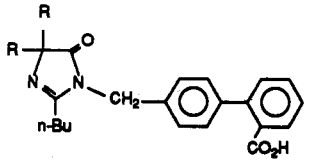


Table I. SAR at the Imidazolone 5-Position



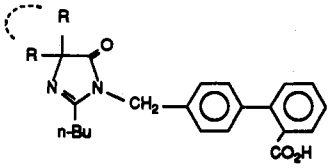
compd no.[a]	R	binding IC_{50},[b] nM	rabbit aortic ring IC_{50},[b] nM	mp, °C
24	CH_3	35	120	168–171[c]
25	C_2H_5	56	270	82–84[d]
26	n-C_3H_7	150	480	140–142
27	i-C_3H_7	20	110	120–122[c]
28	c-C_3H_5	80	110	133–135[c]
29	n-C_4H_9	1700	4000	121–122
30	i-C_4H_9	2100	5100	118–122[c]
31	C_6H_5	3000	5400	55–60[c]

[a] Acceptable C, N, H (±0.4%) combustion analyses were obtained for the new compounds. [b] For details, see the Experimental Section. [c] Monotrifluoroacetate. [d] Ditrifluoroacetate.

butyl chain (compound 4). The unsubstituted compound was inactive. The activity rose with increase of the linear carbon chain length, reaching a maximum with four C atoms. Cyclization of the carbon chain to a bulky group such as cyclohexyl (compound 59) or introduction of an aromatic ring (compounds 60, 61) gave rise to compounds of lower binding affinity.

Table V summarizes some variations at the 2′-biphenyl position. As reported[7] this position needs an acidic function. The carboxylic acid compound 4 possesses high affinity. Replacement of the carboxyl function by the isosteric tetrazole (compound 21) resulted in 10-fold greater

Table II. SAR at the Imidazolone 5-Position: Spiro Substitution



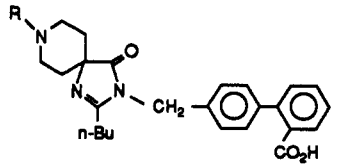
compd no.[a]	R–R	binding IC_{50},[b] nM	rabbit aortic ring IC_{50},[b] nM	mp, °C
32	$(CH_2)_2$	260	340	204
33	$(CH_2)_3$	38	42	178[c]
4	$(CH_2)_4$	10	63	176–178[c]
34	$(CH_2)_5$	7.2	38	172–174[c]
35	$(CH_2)_6$	8.7	12	160[c]
36	$(CH_2)_{11}$	350	350	130–135[c]
37	2-spiroadamantane	62	23	164–171[c]
38	2-spiroindane	60	240	217–218
39	$(CH_2)_2O(CH_2)_2$	47	200	159–162[c]
40	$(CH_2)_2NH(CH_2)_2$	890	1600	glass[d]
41	$(CH_2)_2CH(CH_3)(CH_2)_2$	66	39	198[c]
42	$(CH_2)_2CH(C_6H_5)(CH_2)_2$	260	250	155[c]

[a] Acceptable C, N, H (±0.4%) combustion analyses were obtained for the new compounds. [b] For details see the Experimental Section. [c] Monotrifluoroacetate. [d] Ditrifluoroacetate.

binding affinity as expected on the basis of DuPont's finding.[7] Methylation of the tetrazole ring, like esterification of the carboxylic function, gave rise to less active compounds.

Substitution of the oxygen atom in position 4 by a sulfur atom led to retained activity in the rabbit aortic functional test, compared with compound 4. On the other hand, the

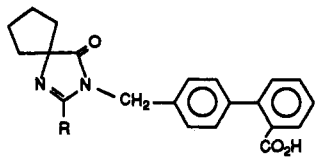
Table III. SAR at the Imidazolone 5-Position: Spiropiperidines



compd no.[a]	R	binding IC_{50},[b] nM	rabbit aortic ring IC_{50},[b] nM	mp, °C
43	$COCH_3$	18	130	90–95[c]
44	$COCF_3$	140	nt[d]	95–105[e]
45	COC_6H_5	49	70	85–90[f]
46	Arg	220	nt[d]	117 dec[g]
47	Ile	730	nt[d]	125–135[f]
48	Cys	250	nt[d]	117[f]
49	Asp	800	nt[d]	129[f]
50	$COCH_2CO_2H$	59	80	118[e]
51	$CO(2\text{-}CO_2H\text{-}C_6H_4)$	480	nt[d]	123[e]
52	CH_2CO_2H	950	nt[d]	119[f]
53	$CH_2C_6H_5$	110	420	198–200[e]

[a] Acceptable C, N, H (±0.4%) combustion analyses were obtained for the new compounds. [b] For details, see the Experimental Section. [c] Monotrifluoroacetate hydrate. [d] Not tested. [e] Monotrifluoroacetate. [f] Ditrifluoroacetate. [g] Ditrifluoroacetate monochlorohydrate.

Table IV. SAR at the Imidazolone 2-Position



compd no.[a]	R	binding IC_{50},[b] nM	rabbit aortic ring IC_{50},[b] nM	mp, °C
54	H	>10000	nt[c]	glass
55	CH_3	7000	4000	140[d]
56	$n\text{-}C_3H_7$	27	27	146[d]
57	$n\text{-}C_3F_7$	10000	nt[c]	140–142
4	$n\text{-}C_4H_9$	10	63	176–178[d]
58	$n\text{-}C_5H_{11}$	24	52	150–152[d]
59	$c\text{-}C_5H_9$	410	340	82–88[e]
60	C_6H_5	5200	5300	178[d]
61	$C_6H_5CH_2$	2500	3900	88[d]

[a] Acceptable C, N, H (±0.4%) combustion analyses were obtained for the new compounds. [b] For details, see the Experimental Section. [c] Not tested. [d] Monotrifluoroacetate. [e] Ditrifluoroacetate.

reduced compound 14 dramatically lost binding affinity, suggesting that a heteroatom was essential in position 4 of the dihydroimidazole ring.

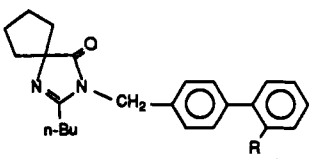
Similarly, compound 12, the regioisomer of 4, was found to be nearly 200 times less active, illustrating the importance of the relative disposition of the different pharmacophores.

Finally we also examined the influence of the double bond of dihydroimidazolone. The saturated tetrahydroimidazolones 11 and 17 showed lower activity compared with the corresponding dihydro compounds; even in this case, the regioisomer with the biphenyl close to the carbonyl group was the most active.

Biology

The activity profile of tetrazole 21 was quite similar to that reported for many second generation AII antagonists.[9-11] It had a nearly 1 order of magnitude greater binding affinity than the corresponding carboxylic acid 4 (IC_{50} = 1.3 vs 10 nM) and was also 10 times more active than losartan. In the AII-induced contractions of rabbit aortic strips we found the same hierarchy, with a 6-fold increase in potency of compound 21 over losartan.

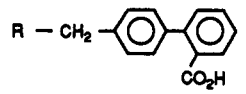
Table V. SAR at the 2'-Position of the Terminal Aromatic Ring

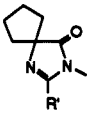
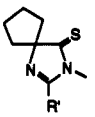
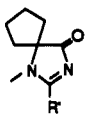
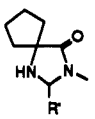
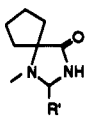
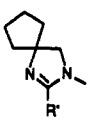


compd no.[a]	R	binding IC_{50},[b] nM	rabbit aortic ring IC_{50},[b] nM	mp, °C
4	CO_2H	10	63	176–178[c]
62	CO_2CH_3	1800	>10000	86–87
3	CO_2tBu	3200	>10000	63–65
20	CN	440	>10000	92–93
21	tetrazol-5-yl	1.3	4.0	180–181
22	1-CH_3-tetrazol-5-yl	150	200	glass
23	2-CH_3-tetrazol-5-yl	660	>10000	glass
losartan		14	25	
saralasin		2.4	2.3	

[a] Acceptable C, N, H (±0.4%) combustion analyses were obtained for the new compounds. [b] For details, see the Experimental Section. [c] Monotrifluoroacetate.

Table VI. Effect of Imidazole Ring Modification on the SAR



compd no.[a]	R[b]	binding IC_{50},[c] nM	rabbit aortic ring IC_{50},[c] nM	mp, °C
4		10	63	176–178[d]
19		80	52	185[d]
12		1800	5900	148[d]
17		190	600	180[d]
11		3300	nt[e]	215
14		>10000	nt[e]	165[d]

[a] Acceptable C, H, N (±0.4%) combustion analyses were obtained for the new compounds. [b] R' = $n\text{-}C_4H_9$. [c] For details, see the Experimental Section. [d] Monotrifluoroacetate. [e] Not tested.

Compound 21 was highly specific for the AT_1 receptor as it inhibited the binding of [^{125}I]AII to rat adrenal cortical membranes in the presence of dithiothreitol, a highly specific preparation for AT_2 subtype receptors, with an IC_{50} higher than 10^{-5} M.[26]

In conscious normotensive rats, compound 4 reduced AII-induced hypertension in a dose-related manner from

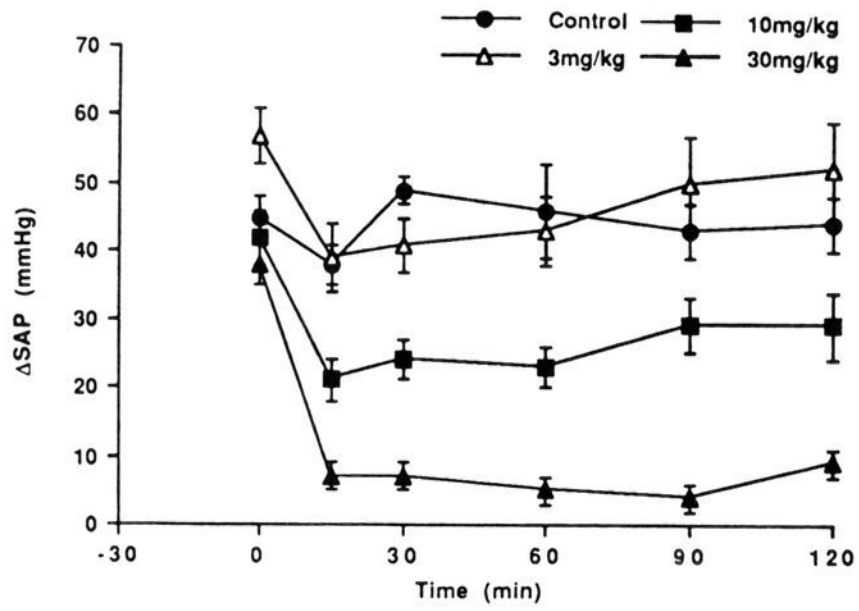


Figure 1. Effects of vehicle and compound **4** at 3, 10, and 30 mg/kg po on the pressor response to AII (40 ng/kg iv) in conscious normotensive rats. Values represent the mean increase in the systolic arterial pressure (SAP) ± SE (n = 5–6 per group).

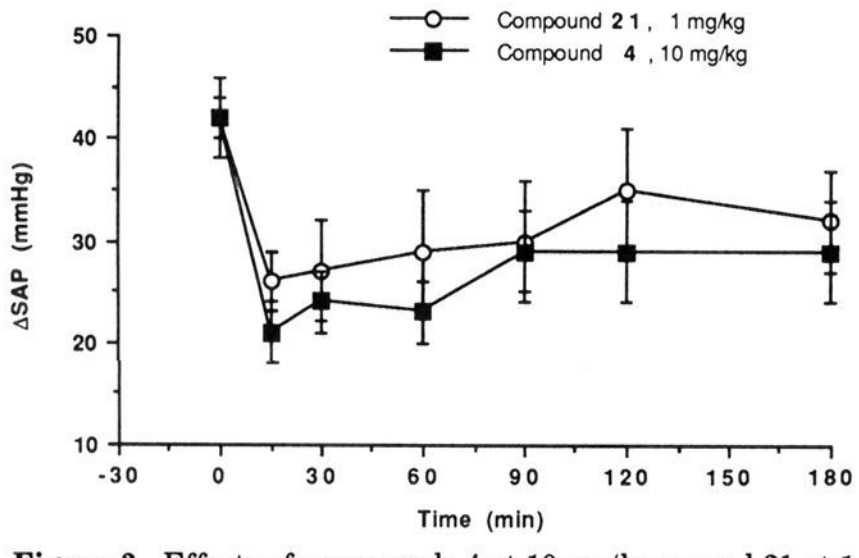


Figure 2. Effects of compounds **4** at 10 mg/kg po and **21** at 1 mg/kg po on the pressor response to AII (40 ng/kg iv) in conscious normotensive rats. Values represent the mean increase in the systolic arterial pressure (SAP) ±SE (n = 6–7 per group).

3.0 to 30 mg/kg (Figure 1). The tetrazole analogue **21**, in accordance with the binding affinities, is 10 times more active compared to **4** (Figure 2) and equipotent with losartan in the same model. The reason for the good activity observed for losartan in rats has been shown to be due to the presence of its carboxylic acid metabolite 2-*n*-butyl-4-chloro-1[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]imidazole-5-carboxylic acid (EXP3174).[27]

The high potency of compound **21** was also observed in normotensive cynomolgus monkeys where it antagonized the AII-induced pressor response after oral administration at a dose of 1 mg/kg, compound **21** being markedly more active than losartan at 10 mg/kg (Figure 3).

Conclusion

Our initial postulate that a central aromatic ring is not needed for binding to the AT_1 receptor turned out to be correct. The dihydroimidazol-4-one ring was shown to have the same function as the (hydroxymethyl)imidazole.

The structure–activity relationships around the dihydroimidazole ring are comparable to DuPont's series for positions 2 and 3, but differ for position 5. Here the receptor best accommodates lipophilic substituents, even bulky ones, but with reduced mobility.

The compounds described in this paper represent a new class of nonpeptide, orally active, AT_1 antagonists. The biological profile of compound **21** (SR 47436) indicates

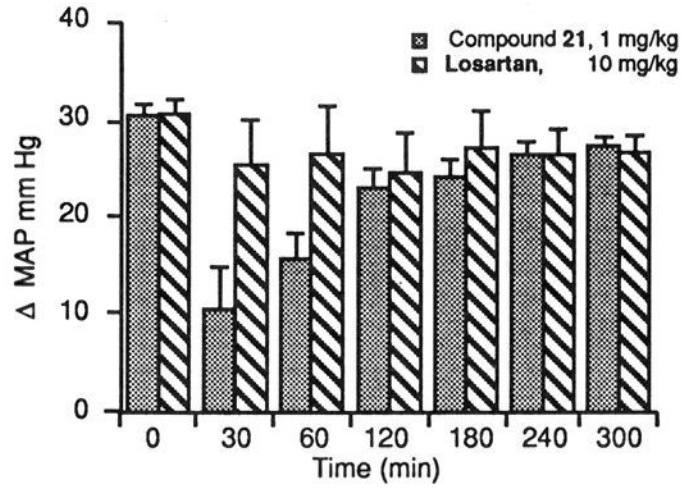


Figure 3. Comparison of effects of compound **21** at 1 mg/kg po and losartan at 10 mg/kg po on the pressor response to AII (100 ng/kg iv) in conscious normotensive cynomolgus monkeys. Values represent the mean ±SE of MAP variation (n = 4 per group).

that it is a highly potent and specific antagonist of AII both in vitro and in vivo. On the basis of this profile, **21** has been chosen as a potential candidate for clinical investigation for the treatment of hypertension, renal failure, and congestive heart failure.

Experimental Section

Physical Methods. IR spectra were obtained on a Shimadzu IR-408 or a Perkin-Elmer 298 infrared spectrophotometer and were run in methylene chloride or as KBr pellets. ^{1}H NMR spectra (200 MHz) were measured with an Bruker AC200 spectrometer; chemical shifts are expressed in ppm (δ) upfield from tetramethylsilane. Mass spectra were obtained on a Finnegan TSQ70. Melting points are uncorrected and were measured with a Tottoli melting point apparatus (Büchi). Elemental analyses were within ±0.4% of theoretical values and were determined in the Analytical Chemistry Department of Sanofi Recherche.

Angiotensin II Binding Studies on Rat Liver Membranes. Purified plasma membranes of livers from male Sprague–Dawley rats (200–250 g) were prepared by a modification of the procedure of Neville.[28] The livers were rinsed in 1 mM $NaHCO_3$ and cut into small pieces. The tissue was homogenized in ice-cold $NaHCO_3$ using a Dounce homogenizer (320 mL of 1 mM $NaHCO_3$ per 40 g of tissue). The homogenate was filtered through a gauze and spun at 1500g for 20 min. The pellets were homogenized using a Dounce homogenizer and resuspended in a solution of sucrose at 69% (wt/vol) to reach a final concentration of 44%. The resuspended pellets were layered on a discontinuous sucrose gradient (44% and 42.3%) and centrifuged for 12 min at 100000g in a Beckman SW28. After centrifugation a band of particulate material was collected at the top of the 42.3% sucrose layer and diluted in 8 mL of 1 mM $NaHCO_3$ (10 mg of proteins/mL). Aliquots of the membrane suspension were removed and stored at −20 °C. [^{125}I]AII binding assays were carried out according to an adaptation of the method described by Keppens.[29] After thawing, the membrane suspension was diluted in the incubation buffer (20 mM Tris-HCl, 10 mM $MgCl_2$, 2 g/L BSA, 145 mg/L bacitracin, pH 7.5). Aliquots of membrane suspension (20–30 μg protein/assay) were incubated for 1 h at 25 °C with [^{125}I]AII and test compound in 200 μL of incubation buffer. The incubation was stopped by rapid filtration through a Whatman GF/B filter followed by three consecutive washings in 5 mL of cold incubation buffer (the GF/B filters were preincubated for 1 h in the incubation buffer). The radioactivity bound to the filter was counted in a γ counter. Specific binding was defined as the difference between total binding and the binding in the presence of 1 μM unlabeled AII. Each assay was performed in triplicate. In competition experiments, the drug concentration producing 50% inhibition (IC_{50}) of radioligand binding and the Hill coefficient (n_H) values were determined from Hill plots of log ($B_o - B$)/B vs log (drug concentration), where B_o and B are the specific binding in the absence and present of competitor, respectively.

Rabbit Aorta: Potency Determination. Male New Zealand albino rabbits (approximately 2 kg) supplied by Elevage des

Dombes (Romans, Châtillon-sur-Chalaronne, France) were sacrificed by cervical dislocation and bled. The abdominal aorta was quickly excised and cut into rings of 2–3-mm width. Each ring was set up in an organ chamber containing 10 mL of a bathing solution kept at 37 °C, pH 7.4, and oxygenated by bubbling a 95% O_2–5% CO_2 gas mixture under a resting tension of 2 g. The modified Krebs solution used had the following composition (mM): NaCl, 137; KCl, 5.4; $MgCl_2$, 1.05; $CaCl_2$ 1.8; NaH_2PO_4, 1.2; $NaHCO_3$, 15.5; glucose, 11.5. During the 60-min equilibration period, the bathing solution was renewed several times. The antagonistic effect of the compounds, IC_{50} value (n = 2–4, per group) was evaluated by measuring their capacity to inhibit the contractile response of the preparation to 10 nM AII (which corresponded to about 90% of the maximal response). AII stimulation of the preparation was repeated at intervals of 40 min. Following the second stable response (taken as the control response), the antagonist was added to the bath. Incubation of the antagonist lasted 30 min before the next stimulation to AII. Using this procedure, four concentrations of antagonist were tested on each preparation.

Inhibition of the AII-Induced Pressor Response in Conscious Normotensive Rats. On the day before the experiment, male Sprague–Dawley rats (300–350 g) (Laboratoires Iffa Credo, L'Arbresle, France) were anesthetized with sodium pentobarbital (60 mg/kg, ip), and a catheter (PE50) was inserted into the carotid artery for measurement of blood pressure. Both catheters, filled with an aqueous solution of 40% poly(vinylpyrrolidone) and 20% heparin, were tunneled under the skin and exteriorized on the nape of the neck. Their free extremity was closed using a flame. The animals were then housed individually in cages with free access to food and water until the following morning. On the day of the experiment, each conscious rat was placed in a metabolic cage and its carotid catheter was connected by a swivel to a Statham P231a pressure transducer coupled to a Gould TA2000 polygraph. The pulsatile arterial pressure (diastolic and systolic) was continuously recorded from 1 h before to 3 h after administration of each dose compound. AII was injected (iv) in a volume of 0.05 mL/100 g at 30–50 ng/kg which elicited a rise in the systolic arterial pressure (SAP) of about 40 mmHg. AII was injected before the administration of the test drug two or three times at 15-min intervals to establish a reproducible control pressor response and subsequently at 15, 30, 60, 90, 120, and 180 min postdose. Orally administered, the compounds were dissolved in water by neutralization with a stoichiometric equivalent of KOH and then given by gavage in a volume of 1 mL/100 g. Control animals were given the corresponding solvent under the same experimental conditions. The pressor response to AII at each time was compared to that obtained for the pretreatment control.

Inhibition of the AII-Induced Pressor Response in Conscious Normotensive Cynomolgus Monkeys. Experiments were performed on conscious female animals (Macaca fascicularis) weighing 3–4 kg (Centre de Recherches Primatologiques, Le Vallon, Port-Louis, Mauritius). A chronic indwelling catheter was implanted under aseptic conditions into the thoracic aorta via a carotid artery under general anaesthesia induced by ketamine (20 mg/kg im) associated with acepromazine (0.5 mg/kg im). The catheter was filled with an aqueous solution of 40% poly(vinylpyrrolidone) and 20% heparin. Intramuscular administration of penicillin (30 000 IU/kg) and dihydrostreptomycin (0.05 g/kg) were continued for 5 days postoperation. After a recovery period of 3 weeks, the monkeys were trained to sit in a restraining chair. On the day of the experiment (at least 4 weeks after surgery), the monkey was placed on its chair. The arterial catheter was connected to a Beckman (R611) polygraph via a Gould Statham P231d pressure transducer and the pulsatile arterial pressure was recorded. AII was injected via a catheter acutely inserted into a saphenous vein, at 100 ng/kg (0.5 mL/kg) which elicited a rise in mean arterial pressure (MAP) of about 30 mmHg. SR 47436 and DUP753 were dissolved in saline by neutralization with a stoichiometric equivalent of L-arginine. These solutions were administered in a volume of 3 mL/kg by gavage. AII was injected 15 min before the administration of drugs and subsequently at 30, 60, 120, 180, 240, and 300 min. Blood pressure was recorded continuously at these times. Drug effects on the basal pressure were always noted before AII injection. The results are expressed as the mean arterial pressure (MAP) in mmHg.

Imidazolone General Synthesis: Route a. 2-*n*-Butyl-1,3-diazaspiro[4.4]non-1-en-4-one (2a). Ethyl pentanimidate[30] (1.55 g, 12 mmol), 1-amino-cyclopentanecarboxylic acid ethyl ester[31] (1.57 g, 10 mmol), 12 mL of xylene, and 6 drops of acetic acid were mixed and refluxed for 6.5 h. The mixture then was concentrated in vacuo, and the crude product was chromatographed over silica gel in 96:4:2 chloroform–methanol–acetic acid. The combined fractions were reevaporated with xylene and then benzene to remove acetic acid. A thick oil (1.85 g, 96%) was obtained: NMR (DMSO-d_6) δ 10.7 (m, 1 H), 2.33 (t, 2 H), 1.93–1.50 (m, 10 H), 1.35 (sext, 2 H), 0.92 (t, 3 H); IR ($CHCl_3$) 1720, 1635 cm^{-1}; MH^+ 195. Chlorohydrate: mp 240 °C.

Imidazolone General Synthesis: Route c. 2-*n*-Butyl-5,5-bis-1-methylethyl)-3,5-dihydroimidazol-4-one. *n*-Valeryl chloride (4.4 mL, 37 mmol) in 15 mL of THF was added over 30 min to a stirred solution of 2-amino-3-methyl-2-(1-methylethyl)-butanamide[32] (6.0 g, 34.4 mmol) and 4.75 mL of triethylamine in 100 mL of THF. After 2.5 h, potassium hydroxide (8.7 g, 155 mmol), 20 mL of water, and 23 mL of methanol were added, and the resulting mixture was refluxed for 2.5 h. After cooling, ammonium chloride (13.4 g) was added, and the mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was taken up in heptane to furnish a solid (4.3 g, 48%): mp 80–85 °C.

2-*n*-Butyl-5,5-diphenyl-3,5-dihydroimidazol-4-one. The title compound was prepared according to Nyitrai and Lempert:[19] mp 135 °C; NMR (DMSO-d_6) δ 7.50–7.20 (m, 10 H), 2.50 (t, 2 H), 1.65 (quint, 2 H), 1.35 (sext, 2 H), 0.90 (t, 3 H); IR (DMSO) 1730, 1635 cm^{-1}; IR ($CHCl_3$) 1725, 1640 cm^{-1}; IR (KBr) 1720, 1645 cm^{-1}.

***tert*-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (3a).** Sodium methoxide (0.27 g, 5 mmol) was added to a stirred solution of **2a** (0.97 g, 5 mmol) in DMF (10 mL) under nitrogen. After 15 min the bromo derivative **69**[7] (2.08 g, 6 mmol) was added, and the resulting mixture was stirred for 3.5 h at 40 °C. The solvent was removed in vacuo and the residue taken up in ethyl acetate and water. The organic phase was separated, washed with brine, dried (Na_2SO_4), and then concentrated. The residue was chromatographed over silica gel in 2:1 toluene–ethyl acetate to give an oil which crystallized (1.25 g, 53%): mp 63–66 °C; NMR (DMSO-d_6) δ 7.80–7.20 (m, 8 H), 4.78 (s, 2 H), 2.42 (t, 2 H), 1.95–1.65 (m, 8 H), 1.58 (quint, 2 H), 1.35 (sext, 2 H), 1.20 (s, 9H), 0.88 (t, 3 H); IR ($CHCl_3$) 1720–1710, 1625 cm^{-1}; MH^+ 461.

4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (4). 3a (1.22 g, 2.65 mmol) was stirred for 40 min in methylene choride (6 mL) and trifluoroacetic acid (8 mL). The mixture reaction was then evaporated in vacuo and the residue taken up in diethyl ether. The resulting white solid was filtered, washed with diethyl ether, and dried (1.15 g, 91%): mp 178 °C; NMR (DMSO-d_6) δ 7.75–7.20 (m, 8 H), 4.83 (s, 2 H), 2.65 (t, 2 H), 2.00–1.75 (m, 8 H), 1.50 (quint, 2 H), 1.25 (sext, 2 H), 0.78 (t, 3 H); MS MH^+ 405. Anal. ($C_{27}H_{29}F_3N_2O_5$) C, H, N.

***tert*-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (3a) (Photochemical Route).** 2-*n*-Butyl-4,5,6,7-tetrahydrobenzimidazole[33,34] (1 g, 5.6 mmol) was dissolved in DMF (45 mL) with 0.01 g of methylene blue; oxygen was passed through the magnetically stirred solution during irradiation with a UV lamp, and 0.303 g (5.6 mmol) of sodium methoxide was added followed after 0.25 h by 2.14 g (6.2 mmol) of **69**. After 1 h, the reaction mixture was taken up in ethyl acetate, water, and a few milliliters of saturated $NaHCO_3$ solution. The organic phase was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed over silica gel in 1:2 ethyl acetate–toluene to furnish **3a** (0.61 g, 23%), mp 62–65 °C. NMR, IR, and mass spectra identical with those of the product obtained by the route described in Scheme II.

1-[(Fluorenylmethyloxycarbonyl)amino]cyclopentane-1-carboxylic Acid (5). This compound was prepared by the general procedure described by Chang,[35] mp 89–91 °C.

tert-Butyl 4′-(Aminomethyl)biphenyl-2-carboxylate (63). To a stirred solution of *tert*-butyl 4′-(azidomethyl)biphenyl-2-carboxylate[23] (26 g, 84 mmol) in 120 mL of THF were added in three portions 23.4 g (89.3 mmol) of triphenylphosphine. Then the mixture was stirred at 25 °C for 3 h. Water (2.5 mL) was added, and the mixture was stirred further for 18 h. The solvent was removed in vacuo and the residue taken up in diethyl ether (200 mL). After 4 h, the mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed over silica gel in 95:5:0.2 chloroform–methanol–NH_4OH 32% to furnish a viscous oil (13.94 g, 58%).

tert-Butyl 4′-[[[[1-[(Fluorenylmethyloxycarbonyl)amino]cyclopentyl]carbonyl]amino]methyl]biphenyl-2-carboxylate (6). A solution of 5 (0.7 g, 2 mmol), 63 (0.576 g, 2 mmol), BOP (0.97 g, 2.2 mmol), and DIPEA (to adjust to pH 6, moist pH paper) in DMF (8 mL) was stirred for 1 h. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with 5% $KHSO_4$–K_2SO_4 solution, saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), filtered, and concentrated to give a gum (1.2 g, 97%).

tert-Butyl 4′-[[[(1-Aminocyclopentyl)carbonyl]amino]methyl]biphenyl-2-carboxylate (7). Compound 6 (1.1 g, 1.8 mmol) in DMF (10 mL) and diethylamine (1 mL) were stirred for 1 h. The solution was diluted with ethyl acetate and water; the organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was chromatographed over silica gel in 99:1:0.5 ethyl acetate–methanol–NH_4OH 32% to furnish 7 as an oil (0.62 g, 87%): NMR (DMSO-d_6) δ 8.60 (t, 1 H), 7.75–7.15 (m, 8 H), 4.40 (d, 1 H), 2.15–1.40 (m, 10 H), 1.25 (s, 9 H); IR ($CHCl_3$) 3450, 1700, 1650 cm^{-1}.

tert-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (3a) (from 7). A mixture of 7 (0.394 g, 1 mmol), ethyl orthopentanate (0.250 g, 1.22 mmol), and acetic acid (1 drop) were mixed in methylene chloride (2 mL), and the solution was heated at 90 °C for 1.25 h (methylene chloride was allowed to evaporate). The reaction mixture was taken up in ethyl acetate which was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel in 1:2 ethyl acetate–toluene to furnish 0.39 g (85%) of 3a: mp 63–65 °C. NMR, IR, and mass spectra identical with those of the product obtained by the route described in Scheme II.

2-*n*-Butyl-1,3-diazaspiro[4.4]nonan-4-one (8). To a solution of 2a, HCl salt (5 g, 21.7 mmol) in 100 mL of methanol was added sodium borohydride (1.64 g, 2 equiv). The mixture was stirred for 12 h; sodium borohydride (1.64 g, 2 equiv) was then added again, and the solution was stirred for an additional 12 h. The solvent was removed under vacuum: the residue was dissolved in ethyl acetate and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Column chromatography (elution: 2%, methanol–methylene chloride) furnished 2.5 g (59%) of 8 as a white solid: mp 59–62 °C; NMR (DMSO-d_6) δ 8.05 (s, 1 H), 4.25 (t, 1 H), 2.69 (s, 1 H), 1.87–1.28 (m, 14 H), 0.88 (t, 3 H).

2-*n*-Butyl-1,3-diazaspiro[4.4]nonan-4-one (8). A solution of 2a (1.5 g, 7.6 mmol) in 20 mL of methanol was hydrogenated over PtO_2 (25 mg) in a Parr apparatus at 17 psig for 18 h. The mixture was filtered through Celite and the solvent removed in vacuo to yield 1.5 g of 8 as a viscous oil. This oil was contaminated by some 2a as revealed by TLC analysis.

tert-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]nonan-1-yl)methyl]biphenyl-2-carboxylate (9) and *tert*-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-2-en-1-yl)methyl]-biphenyl-2-carboxylate (10). To a solution of the above crude 8 in 30 mL of dimethylformamide was added sodium methoxide (0.4 g, 7.4 mmol). After the mixture was stirred for 0.5 h at 25 °C, a solution of 69 (3.19 g, 9.2 mmol) in 20 mL of dimethylformamide was added. The mixture was then heated at 40 °C for 4 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel. Elution first with hexane–ethyl acetate, 3:1, afforded 0.4 g (12%) of 9 and then with hexane–ethyl acetate, 1:2, 0.25 g (7%) of 10.

9: NMR (DMSO-d_6) δ 7.4–7.0 (m, 9 H), 4.0–3.7 (m, 3 H), 2.3 (m, 2 H), 1.8 (m, 8 H), 1.6–1.1 (m, 4 H), 1.1 (s, 9 H), 0.8 (t, 3 H).

10: NMR (DMSO-d_6) δ 7.8–7.3 (m, 9 H), 4.8 (s, 2 H), 2.5 (t, 2 H), 1.8 (m, 8 H), 1.7–1.1 (m, 4 H), 1.1 (s, 9 H), 0.9 (t, 3 H).

4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]nonan-1-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (11). The title compound was prepared from 9 by the procedure described for the preparation of 4: mp 215 °C; NMR (DMSO-d_6) δ 12.6 (s, 1 H), 8.1 (s, 1 H), 7.6–7.1 (m, 8 H), 4.0 (m, 1 H), 3.9–3.5 (m, 2 H), 1.9–1.0 (m, 12 H), 0.7 (t, 3 H). Anal. ($C_{27}H_{31}F_3N_2O_5$), C, H, N.

4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]non-2-en-1-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (12). This compound was prepared from 10 according to the procedure described for the preparation of 4: mp 148 °C; NMR (DMSO-d_6) δ 7.8–7.4 (m, 8 H), 5.1 (s, 2 H), 2.8–2.7 (m, 2 H), 2.1–1.9 (m, 4 H), 1.9–1.7 (m, 4 H), 1.7–1.5 (m, 2 H), 1.4–1.2 (m, 2 H), 0.8 (t, 3 H); MS MH^+ 405. Anal. ($C_{27}H_{29}F_3N_2O_5$) C, H. N.

2-*n*-Butyl-1,3-diazaspiro[4.4]non-1-ene (13). A solution of 2a (HCl salt) (2 g, 8.6 mmol) in ethyl acetate was washed with a saturated sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting oil was dissolved in 70 mL of anhydrous tetrahydrofuran under N_2 atmosphere, lithium aluminum hydride (1 g, 26 mmol) was added, and the solution was refluxed for 3 h. After cooling, 10 mL of ethyl acetate and then 10 mL of H_2O were added dropwise, and the mixture was filtered. The precipitate was washed with ethyl acetate. The filtrate was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide 1.5 g (97%) of 13 as an oil: NMR (DMSO-d_6) δ 3.3 (s, 2 H), 2.1 (t, 2 H), 1.8–1.4 (m, 10 H), 1.35 (sext, 2 H), 0.9 (t, 3 H).

tert-Butyl 4′-[(2-*n*-Butyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (14). To a solution of 13 (763 mg, 4.23 mmol) in 15 mL of dimethylformamide at 0 °C under argon was added sodium hydride (80% in oil, 134 mg; 1.1 equiv). The resulting mixture was stirred at 25 °C for 0.25 h, and then a solution of 69 (1.76 g, 1.2 equiv) in 10 mL of dimethylformamide was added. The reaction mixture was stirred 0.25 h and concentrated in vacuo. The residue was dissolved in ethyl acetate, and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Column chromatography (elution: 10% methanol–methylene chloride with 0.1% concentrated ammonia) furnished 1.08 g (97%) of compound 14 as a colorless glass: NMR (DMSO-d_6) δ 7.7–7.25 (m, 8 H), 4.3 (s, 2 H), 3.0 (s, 2 H), 2.25 (t, 2 H), 1.7–1.2 (m, 12 H), 1.15 (s, 9 H), 0.9 (t, 3 H).

4′-[(2-*n*-Butyl-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid (15). A mixture of 14 (1.02 g, 2.28 mmol) in 15 mL of methylene chloride and 10 mL of trifluoroacetic acid was stirred at 25 °C for 1.25 h. The solution was concentrated under vacuum, and the residue was triturated with diethyl ether to afford 1.11 g (96%) of 15 as a white solid: mp 165–167 °C; NMR (DMSO-d_6) δ 7.8–7.35 (m, 8 H), 4.8 (s, 2 H), 3.7 (s, 2 H), 2.75 (t, 2 H), 2.0–1.55 (m, 10 H), 1.4 (sext, 2 H), 0.95 (t, 3H); MS MH^+ 391. Anal. ($C_{27}H_{31}F_3N_2O_4$) C, H, N.

tert-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]nonan-3-yl)methyl]biphenyl-2-carboxylate (16). A solution of compound 3a (5.02 g, 10.9 mmol) and sodium borohydride (0.83 g, 2 equiv) in methanol (60 mL) was stirred at room temperature for 12 h. Sodium borohydride (0.83 g, 2 equiv) was added again, and the mixture was stirred another 12 h. The solution was adjusted to pH 7 with acetic acid and concentrated under vacuum. The resulting residue was dissolved in ethyl acetate and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Compound 16 was obtained as a clear oil: 5.0 g (99%); NMR (DMSO-d_6) δ 7.60–7.10 (m, 8 H), 4.65–4.0 (quart, 2 H), 4.0 (d, 1 H), 1.90–1.05 (m, 14 H), 0.79 (t, 3 H).

4′-[(2-*n*-Butyl-4-oxo-1,3-diazaspiro[4.4]nonan-3-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (17). A solution of compound 16 (0.2 g, 0.43 mmol), 3 mL of trifluoroacetic acid and 10 mL of methylene chloride was stirred at 25 °C for 1 h. The solution was concentrated under vacuum and the residue triturated with diethyl ether to afford 0.199 g (89%) of 17 as a white solid: mp 185–190 °C; NMR (DMSO-d_6) δ 7.70–7.10 (m, 8 H), 4.65–4.30 (quart, 2 H), 4.00 (d, 1 H), 2.10–1.05 (m, 14 H), 0.75 (t, 3 H). Anal. ($C_{27}H_{31}F_3N_2O_5$) C, H, N.

tert-Butyl 4′-[(2-*n*-Butyl-4-thioxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (18). A solution of 3a (5.63 g, 12.2 mmol), Lawesson's reagent (3 g, 6.1 mmol), and toluene was stirred under N_2 at 80 °C for 6 h. The solution was filtered and concentrated under vacuum. Column chromatography (elution: 5% ethyl acetate–methylene chloride) provided 4.5 g (78%) of 18 as a white solid: mp 77–79 °C; NMR (DMSO-d_6) δ 7.8–7.25 (m, 8 H), 5.35 (s, 2 H), 2.60 (t, 2 H), 2.1–1.8 (m, 8 H), 1.6 (quint, 2 H), 1.35 (sext, 2 H), 1.2 (s, 9 H), 0.9 (t, 3 H).

4′-[(2-*n*-Butyl-4-thioxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (19). A mixture of 18 (0.229 g, 0.47 mmol) in 10 mL of methylene chloride and 10 mL of trifluoroacetic acid was stirred at 25 °C for 0.5 h. The solution was concentrated under vacuum and the residue triturated with hexane to afford 0.16 g (64%) of 19 as a white solid: mp 185–190 °C; NMR (DMSO-d_6) δ 7.65–7.0 (m, 8 H), 5.2 (s, 2 H), 2.40 (t, 2 H), 2.0–1.75 (m, 8 H), 1.50 (quint, 2 H), 1.20 (sext, 2 H), 0.78 (t, 3 H); MS MH^+ 421. Anal. ($C_{27}H_{29}F_3N_2O_4S$) C, H, N.

2-*n*-Butyl-3-[(2′-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (20). To a suspension of sodium hydride (250 mg, 80% dispersion in mineral oil) in 5 mL of anhydrous dimethylformamide was added dropwise under a nitrogen atmosphere a solution of 2a (970 mg, 5 mmol) in 10 mL of dimethylformamide. After the mixture was stirred for 0.5 h at room temperature a solution of 4-(bromomethyl)-2′-cyanobiphenyl[7] (1.5 g, 5.5 mmol) in 10 mL of dimethylformamide was added dropwise. The reaction mixture was then stirred at room temperature for 1 h. The solvent was removed under vacuum. The residue was dissolved in ethyl acetate, and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Column chromatography over silica gel (elution: 10% ethyl acetate–methylene chloride) furnished 1.68 g (87%) of 20: mp 92–93 °C; NMR (DMSO-d_6) δ 7.95–7.25 (m, 8 H), 4.75 (s, 1 H), 2.3 (t, 2 H), 1.85–1.65 (m, 8 H), 1.5 (m, 2 H), 1.25 (m, 2 H), 0.75 (t, 3 H). Anal. ($C_{25}H_{27}N_3O$) C, H, N.

2-*n*-Butyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (21). A solution of 20 (1.85 g, 4.8 mmol), crude tributylin azide[38] (2.4 g) and 25 mL of xylene was refluxed for 88 h. After cooling, the mixture was extracted three times with 1 N sodium hydroxide solution (20 mL). The basic extracts were washed with ethyl ether and the pH adjusted to 5 with a 3 N hydrochloric acid solution. The precipitated product was extracted with methylene chloride, and the extracts were dried over sodium sulfate. After evaporation, the solid residue was recrystallized from 96% ethyl alcohol to provide 1.41 g (68%) of 21: mp 180–181 °C; NMR (DMSO-d_6) δ 7.7–7.35 (m, 4 H), 7.0 (s, 4 H), 4.6 (s, 2 H), 2.2 (t, 2 H), 2.0–1.5 (m, 8 H), 1.2 (m, 2 H), 1.1 (m, 2 H), 0.75 (t, 3 H). Anal. ($C_{25}H_{28}N_6O$) C, H, N.

2-*n*-Butyl-3-[[2′-(1-methyltetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (22) and 2-*n*-Butyl-3-[[2′-(2-methyltetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (23). To a suspension of sodium hydride (58 mg, 80% dispersion in mineral oil) in 5 mL of anhydrous dimethylformamide was added dropwise, under nitrogen, a solution of 21 (514 mg, 1.2 mmol) in 5 mL of dimethylformamide. After the mixture was stirred for 0.5 h at room temperature, methyl iodide (185 mg, 1.3 mmol) was added. The reaction mixture was then stirred at room temperature for 4 h. The solvent was removed under vacuum. The residue was taken up with water and extracted with ethyl acetate. This was dried over sodium sulfate and the solvent evaporated in vacuo. Column chromatography over silica gel (elution: 40% ethyl acetate–hexane) yielded a faster eluting isomer, 23 (92 mg, 17%) and a slower eluting isomer, 22 (189 mg, 36%).

22: NMR (DMSO-d_6) δ 7.8–7.4 (m, 4 H), 7.0 (m, 4 H), 4.6 (s, 2 H), 3.35 (s, 3 H), 2.2 (t, 2 H), 1.9–1.5 (m, 8 H), 1.38 (m, 2 H), 1.15 (m, 2 H), 0.7 (t, 3 H). Anal. ($C_{26}H_{30}N_6O$) C, H, N.

23: NMR (DMSO-d_6) δ 7.75–7.3 (m, 4 H), 7.0 (m, 4 H), 4.6 (s, 2 H), 4.15 (s, 3 H), 2.25 (t, 2 H), 1.9–1.5 (m, 8 H), 1.4 (m, 2 H), 1.2 (m, 2 H), 0.7 (t, 3 H). Anal. ($C_{26}H_{30}N_6O$) C, H, N.

2-*n*-Butyl-8-(phenylmethyl)-1,3,8-triazaspiro[4.5]dec-1-en-4-one (64). The title compound was prepared from ethyl 4-amino-1-(phenylmethyl)piperidine-4-carboxylate using the procedure described for the preparation of 2a: mp 170–172 °C.

tert-Butyl 4′-[(2-*n*-Butyl-8-(phenylmethyl)-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylate (65). The title compound was prepared from 64 using the procedure described for the preparation of 3a: mp 133 °C.

4′-[[2-*n*-Butyl-8-(phenylmethyl)-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (53). The title compound was prepared from 65 using the procedure described for the preparation of 4: mp 198–200 °C. Anal. ($C_{34}H_{36}F_3N_3O_5$) C, H, N.

tert-Butyl 4′-[(2-*n*-Butyl-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylate (66). Palladium on carbon (10%, 2 g) was added to a stirred solution of 65 (4.3 g, 7.6 mmol) in methanol (100 mL). The resulting mixture was stirred under hydrogen at atmospheric pressure for 18 h. The reaction mixture was filtered and the solution evaporated in vacuo to give a viscous oil (3.33 g, 92%).

4′-[(2-*n*-Butyl-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (40). The title compound was prepared from 66 using the procedure described for the preparation of 4 and was obtained as a glass: NMR (DMSO-d_6) δ 7.80–7.15 (m, 8 H), 4.75 (S, 2 H), 3.20–3.10 (m, 4 H), 2.40 (t, 2 H), 2.20–1.60 (m, 4 H), 1.50 (quint, 2 H), 1.30 (sext, 2 H), 0.80 (t, 3 H). Anal. ($C_{27}H_{30}F_3N_3O_5$)·(CF_3CO_2H)$_{0.5}$) C, H, N.

tert-Butyl 4′-[[2-*n*-Butyl-4-oxo-8-[(*tert*-butoxycarbonyl)methyl]-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]biphenyl-2-carboxylate (68). Compound 66 (0.6 g, 1.26 mmol), triethylamine (0.175 mL), and *tert*-butyl bromoacetate (0.21 mL, 1.28 mmol) were mixed in toluene (5 mL) and stirred for 18 h. The reaction mixture was diluted with ethyl acetate and a 5% $KHSO_4$–K_2SO_4 solution; the organic layer was separated, washed with a saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed over silica gel in 100:3:1 chloroform–methanol–acetic acid to give an oil (0.47, 64%).

4′-[[2-*n*-Butyl-8-(carboxymethyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]biphenyl-2-carboxylic Acid, Ditrifluoroacetate (52). The title compound was prepared from 68 using the procedure described for the preparation of 4: mp 119 °C. Anal. ($C_{31}H_{33}F_6N_3O_9$) C, H, N.

tert-Butyl 4′-[(8-Acetyl-2-*n*-butyl-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylate (67, R = CH_3). To a stirred solution of 66 (0.20 g, 0.42 mmol) in methylene chloride (5 mL) at 0 °C were added 0.073 mL (0.42 mmol) of diisopropylethylamine and 0.032 mL (0.45 mmol) of acetyl chloride. After 0.5 h, the reaction mixture was diluted with ethyl acetate and water; the organic layer was washed with 1% $KHSO_4$–K_2SO_4 solution, water, and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed over silica gel in 95.5 ethyl acetate–methanol to furnish 67 (R = CH_3) as a glass.

4′-[(8-Acetyl-2-*n*-butyl-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate Monohydrate (43). The title compound was prepared from 67 (R = CH_3) by using the procedure described for the preparation of 4: mp 90–95 °C; NMR (DMSO-d_6) δ 2.05 (s, 3 H, CH_3CO). Anal. ($C_{29}H_{34}F_3N_3O_7$) C, H, N.

tert-Butyl 4′-[[2-*n*-butyl-4-oxo-8-(trifluoroacetyl)-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]biphenyl-2-carboxylate (67, R = CF_3). To a stirred solution of 66 (0.60 g, 1.26 mmol) in methylene chloride (20 mL) at 0 °C were added triethylamine (0.19 mL, 1.3 mmol) and then trifluoroacetic anhydride (0.19 mL, 1.38 mmol). After 0.5 h, water was added; the organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed over silica gel in 1:2 ethyl acetate–hexane to furnish a solid (0.37 g, 51%): mp 126 °C.

4′-[[2-*n*-Butyl-4-oxo-8-(trifluoroacetyl)-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]biphenyl-2-carboxylic Acid, Trifluoroacetate (44). The title compound was prepared from 67 (R = CF_3) by using the procedure described for the preparation of 4: mp 95–105 °C; MS MH^+ 516. Anal. ($C_{29}H_{29}F_6N_3O_6$) C, H. N.

tert-Butyl 4′-[[2-*n*-Butyl-4-oxo-8-[*N*-(*tert*-butoxycarbonyl)arginyl]-1,3,8-triazaspiro[4.5]dec-1-en-3-yl]methyl]bi-

phenyl-2-carboxylate, Hydrochloride (67, RCO = Boc-Arg). A mixture of **66** (0.60 g, 1.26 mmol), Boc-Arg-OH, HCl (0.493 g, 1.5 mmol), BOP (0.666 g, 1.5 mmol), and diisopropylethylamine to adjust the pH to 7 (moist pH paper) in methylene chloride (10 mL) and DMF (15 mL) was stirred for 18 h. The mixture was evaporated in vacuo and the residue taken up in ethyl acetate and water; the organic layer was washed with 5% $KHSO_4$–K_2SO_4 solution, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel in 85:15 chloroform–methanol to furnish 0.8 g (95%) of an oil which crystallized: mp 60–65 °C.

4′-[(8-Arginyl-2-*n*-butyl-4-oxo-1,3,8-triazaspiro[4.5]dec-1-en-3-yl)methyl]biphenyl-2-carboxylic Acid, Hydrochloride Ditrifluoroacetate (46). The title compound was prepared from **67** (RCO = Boc-Arg) by using the procedure described for the preparation of **4**: mp 117 °C dec; MS MH^+ 576. Anal. ($C_{35}H_{44}ClF_6N_7O_8$) C, H, N.

Methyl 4′-[(2-*n*-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]biphenyl-2-carboxylate (62). The title compound was prepared from **2a** by using the procedure described for the preparation of **3a**: mp 86–87 °C. Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

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