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Article

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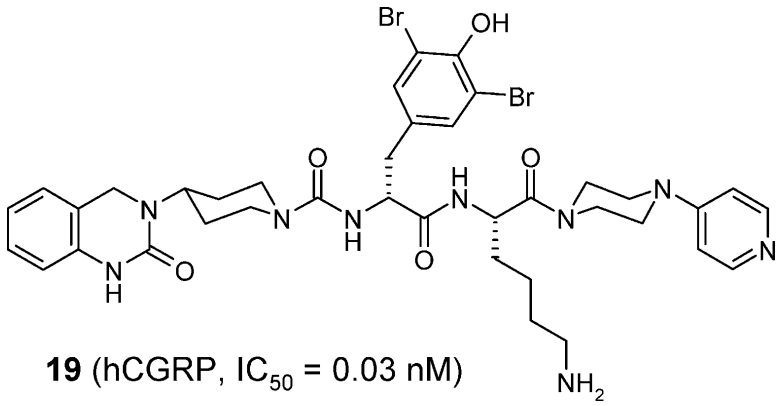

19 (hCGRP, IC_{50} = 0.03 nM)

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Development of Human Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists. 1. Potent and Selective Small Molecule CGRP Antagonists. 1-[N^2-[3,5-Dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine: The First CGRP Antagonist for Clinical Trials in Acute Migraine†

Klaus Rudolf,* Wolfgang Eberlein, Wolfhard Engel, Helmut Pieper, Michael Entzeroth, Gerhard Hallermayer, and Henri Doods

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Although the triptans have greatly improved the acute treatment of migraine headache, there are yet many shortcomings. Therefore, new strategies for the treatment of migraine are needed which offer advantages over current therapy, e.g. triptans. Our novel approach was based on the hypothesis that the release of calcitonin gene-related peptide (CGRP) could play a causative role in migraine headache. Thus we initiated a program aimed at the design and synthesis of small molecule CGRP receptor antagonists. High throughput screening led to the identification of (*R*)-Tyr-(*S*)-Lys dipeptide-like compounds that showed weak but unequivocal binding to the human CGRP receptor. Lead optimization afforded highly potent CGRP antagonists, the prototype being compound **19** (BIBN4096). This compound exhibiting a favorable biological profile was selected for initial clinical trials. A proof of concept study indicated that intravenous application of **19** was effective in the treatment of acute migraine headache. This finding strongly supports our initial working hypothesis that CGRP plays an important role in the pathophysiology of migraine.

Introduction

Migraine is a very common and painful headache disorder that is ranked among the world's most disabling medical illnesses. Approximately 12% of the adult population in the western society suffer from migraine attacks.[1]

Therapy with 5-$HT_{1B/1D}$ agonists, the so-called triptans, is presently considered the most effective treatment of migraine. Although triptans are efficacious and generally well tolerated, this class of drugs has drawbacks of therapeutic relevance. Many patients do not respond to this type of treatment and complete pain relief is the exception rather than the rule. Between 25 and 40% of responsive patients suffer from recurrent headaches within several hours. Being 5-$HT_{1B/1D}$ agonists, triptans act as potent vasoconstrictors and are therefore contraindicated in patients with hypertension or ischemic heart disease.[2] Thus, a clear demand exists for new antimigraine medication with pronounced improvement over current therapies.

Accordingly, research programs targeting different aspects of migraine pathogenesis have been described in recent years. Most companies active in this field have focused on selective 5-HT_{1F}[3] or 5-HT_{1D}[4] agonists, neurokinin antagonists,[5] or endothelin antagonists,[6] but so far such compounds have not progressed beyond phase II clinical trials.

Our strategy was to adopt a new approach that was specifically directed toward the neurovascular aspect of migraine pathogenesis. For many years it has been hypothesized that migraine headache is associated with dilatation of cranial vessels and activation of the trigeminal vascular system. The major neurotransmitter of the trigeminal vascular system is calcitonin gene-related peptide (CGRP), a 37 amino acid neuropeptide belonging to a family of peptides including calcitonin, adrenomedullin, and amylin. CGRP-containing nerves innervate blood vessels in various regions of the body, and those involved in cerebral circulation are especially densely innervated. Although CGRP has a variety of effects, its most pronounced action is vasodilatation. It is indeed one of the most potent endogenous vasodilators known, e.g. of cerebral and dural vessels.[7]

In man, stimulation of the trigeminal ganglion results in the release of CGRP. The hypothesis that CGRP could be involved in the pathogenesis of migraine came from observations by Edvinsson and Goadsby, demonstrating that the levels of the potent vasodilator CGRP in the jugular blood are elevated during the acute phase of a migraine attack.[8] Inhibition of CGRP-mediated vasodilatation by CGRP antagonists should therefore be expected to attenuate vascular headache, if CGRP is implicated in the pathogenesis of migraine headache.

At the outset of our research program rather large C-terminal fragments of CGRP, e.g., $CGRP_{8-37}$, had

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† Dedicated to Prof. Dr. Hans Machleidt on the occasion of his 78th birthday.

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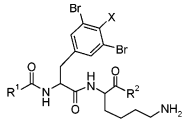
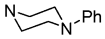
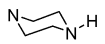
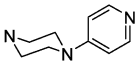
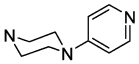
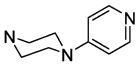
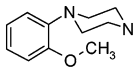
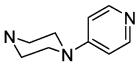
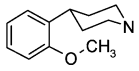
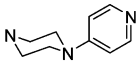
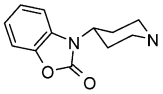
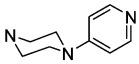
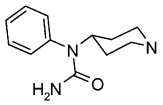
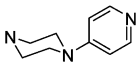
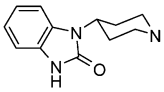
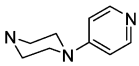
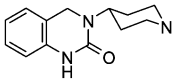
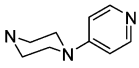
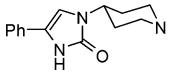
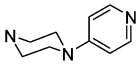
Table 1. Structural Variations of Lead Compounds **1** and **2**



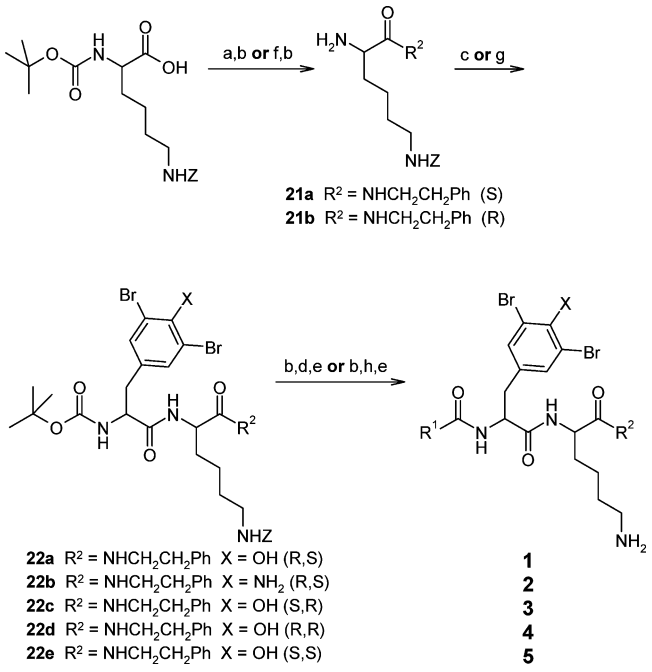
cpd	R^1	R^2	X	config AA^1	config AA^2	IC_{50} (nM)[a]
1	$PhCH_2CH_2CH_2$	$NHCH_2CH_2Ph$	OH	R	S	17000
2	$PhCH_2CH_2CH_2$	$NHCH_2CH_2Ph$	NH_2	R	S	40000
3	$PhCH_2CH_2CH_2$	$NHCH_2CH_2Ph$	OH	S	R	>300000
4	$PhCH_2CH_2CH_2$	$NHCH_2CH_2Ph$	OH	R	R	>300000
5	$PhCH_2CH_2CH_2$	$NHCH_2CH_2Ph$	OH	S	S	>300000
6	$PhCH_2CH_2CH_2$	NHPh	NH_2	R	S	50000
7	$PhCH_2CH_2CH_2$		NH_2	R	S	>300000
8	$PhCH_2CH_2CH_2$		NH_2	R	S	>300000
9	$PhCH_2CH_2CH_2$		NH_2	R	S	10300
10	$PhCH_2CH_2$	$NHCH_2CH_2Ph$	NH_2	R	S	196000
11	2-Methoxyphenyl-CH_2CH_2NH	$NHCH_2CH_2Ph$	OH	R	S	13000
12	2-Methoxyphenyl-CH_2CH_2NH		OH	R	S	1000
13	3-Methoxyphenyl-CH_2CH_2NH		OH	R	S	200
14			OH	R	S	226
15			OH	R	S	250
16			OH	R	S	44
17			OH	R	S	4.7
18			OH	R	S	0.2
19			OH	R	S	0.03
20			OH	R	S	0.05

[a] IC_{50} for inhibition of human CGRP receptor. For details, see Experimental Section.

been described in the literature as antagonists, having limited potency.[9] Due to their peptide nature, these compounds were limited in their application, especially in in vivo or clinical investigations. We initiated a synthetic program for the design and synthesis of small molecule CGRP receptor antagonists to evaluate the role of CGRP in experimental migraine models and to discover if migraine headache is indeed related to the release of CGRP in man.

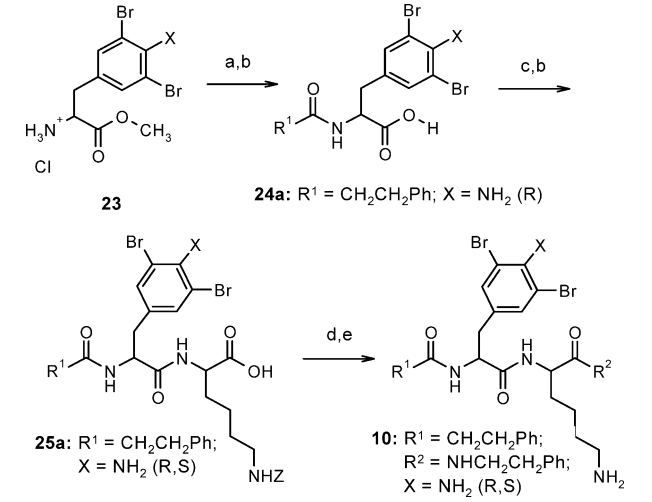
A high throughput screen was established using a human neuroblastoma cell line (SK-N-MC) constitutively expressing the human CGRP receptor, and screening parts of our corporate compound pool led to the identification of the (*R*)-Tyr-(*S*)-Lys dipeptide-like compounds **1** and **2** displaying hCGRP receptor affinities in the micromolar range. Since both compounds contained two chiral centers (*R*)-AA^1 and (*S*)-AA^2, we examined whether the interaction with the hCGRP receptor was stereospecific. We chose the 3,5-dibromo-Tyr derivative **1** as a reference compound and synthesized the three corresponding stereoisomers **3** (*S*,*R*), **4** (*R*,*R*), and **5** (*S*,*S*). As can be seen from Table 1, these compounds are devoid of any hCGRP binding affinity exhibiting IC_{50} values above 300 000 nM. This result indicated that compound **1** interacted with the hCGRP receptor in a stereospecific manner, with both chiral centers being involved in this binding process. With this basis a synthetic program was initiated aimed at

Scheme 1[a]



[a] (a) R²H, TBTU, HOBt, DIEA, DMF, room temperature; (b) TFA, CH_2Cl_2, room temperature; (c) Boc-D- or L-Phe(3,5-Br_2-4-X)-OH, TBTU, HOBt, DIEA, DMF, room temperature; (d) R^1CO_2H, TBTU, HOBt, DIEA, DMF, room temperature; (e) HBr, AcOH, anisole, room temperature; (f) R²H, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (g) Boc-D- or L-Phe(3,5-Br_2-4-X)-OH, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (h) R^1CO_2H, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature.

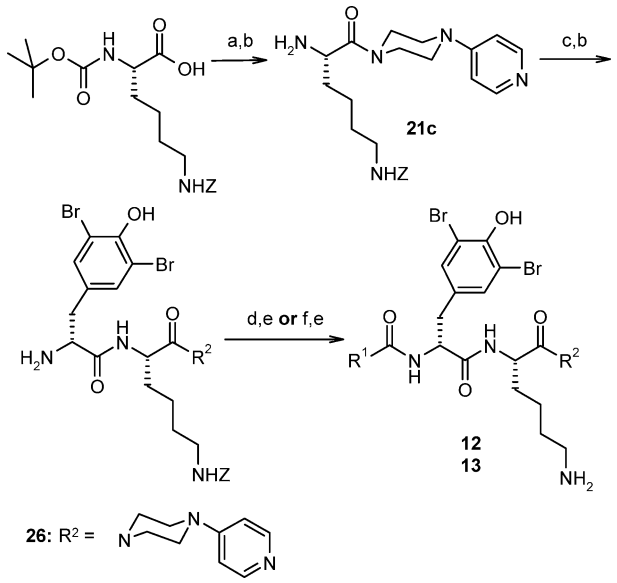
Scheme 2[a]



[a] (a) R^1CO_2H, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (b) 2 N aq NaOH, MeOH/DMF, room temperature; (c) L-Lys(Z) methyl ester hydrochloride, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (d) R²H, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (e) HBr, AcOH, anisole, room temperature.

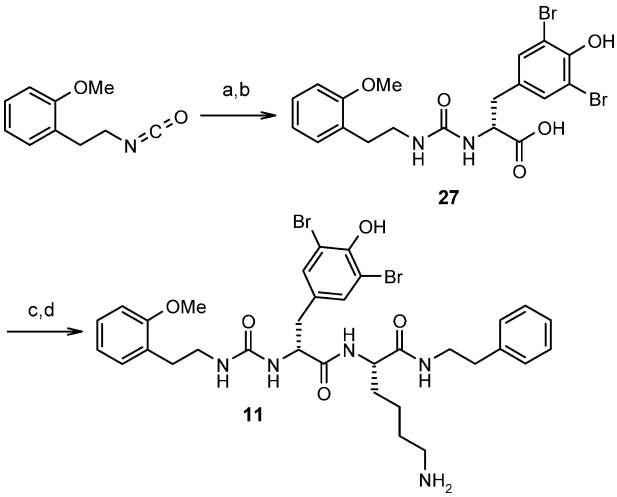
generating compounds with hCGRP receptor affinity in the submicromolar range using compounds **1** and **2** as starting structures. Since no reliable information about the three-dimensional structure of these compounds and about the binding site of the hCGRP receptor was available at the beginning of our project, we had to perform lead optimization by conventional structure activity studies.

Scheme 3[a]



[a] (a) 1-(4-Pyridinyl)piperazine, DIEA, TBTU, HOBt, DMF, room temperature; (b) TFA, CH_2Cl_2, room temperature; (c) Boc-D-Phe(3,5-Br_2-4-OH)-OH, TBTU, HOBt, DIEA, DMF, room temperature; (d) 2-(2-methoxyphenyl)ethyl isocyanate, THF, room temperature; (e) HBr, AcOH, anisole, room temperature; (f) 2-(3-methoxyphenyl)ethylamine, CDT, DIEA, THF, reflux.

Scheme 4[a]

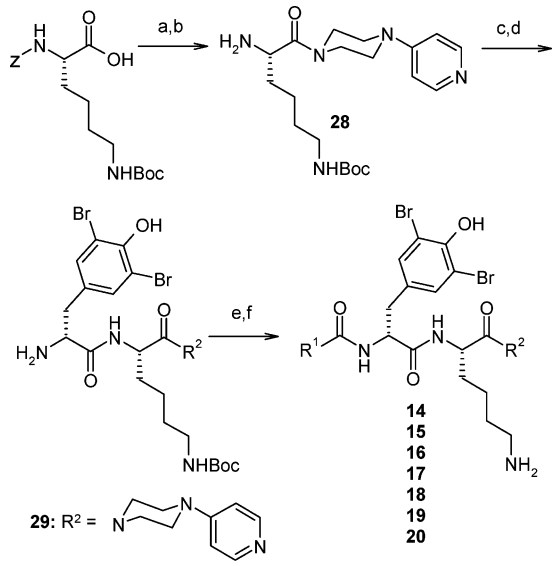


[a] (a) H-D-Phe(3,5-Br_2-4-OH)-OEt·HBr, triethylamine, THF, room temperature; (b) 2 N aq NaOH, THF, room temperature; (c) **21a**, DIEA, TBTU, HOBt, DMF, room temperature; (d) HBr, AcOH, anisole, room temperature.

Results and Discussion

Chemistry. The dipeptide-like compounds listed in Table 1 were synthesized according to Schemes 1−6, following methods known from peptide chemistry. Whereas construction of the peptide backbone of most compounds started from the C-terminus, compounds **6**, **7**, **8**, and **9** were constructed from their N-termini as shown in Scheme 6. Two different procedures were used to introduce the urea moiety characteristic for compounds **11**−**20**. Synthesis of **11** and **12** involved addition of the free α-amino group of an appropriately protected amino acid derivative to an isocyanate; for the synthesis of **13**−**20** a very general method involved the condensa-

Scheme 5[a]



[a] (a) 1-(4-Pyridinyl)piperazine, DIEA, TBTU, HOBt, DMF, room temperature; (b) H_2, Pd/C, $KHSO_4$, MeOH, room temperature; (c) *N*-(9-fluorenylmethoxycarbonyl)-3,5-dibromo-D-tyrosine, TBTU, HOBt, DIEA, THF, room temperature; (d) diethylamine, THF, room temperature; (e) R^1H, CDT, DIEA, THF, reflux; (f) TFA, CH_2Cl_2, room temperature; (g) hydrogen chloride/methanol, room temperature.

tion of a primary or secondary amine with *N*,*N*′-carbonylditriazole and the free α-amino group.

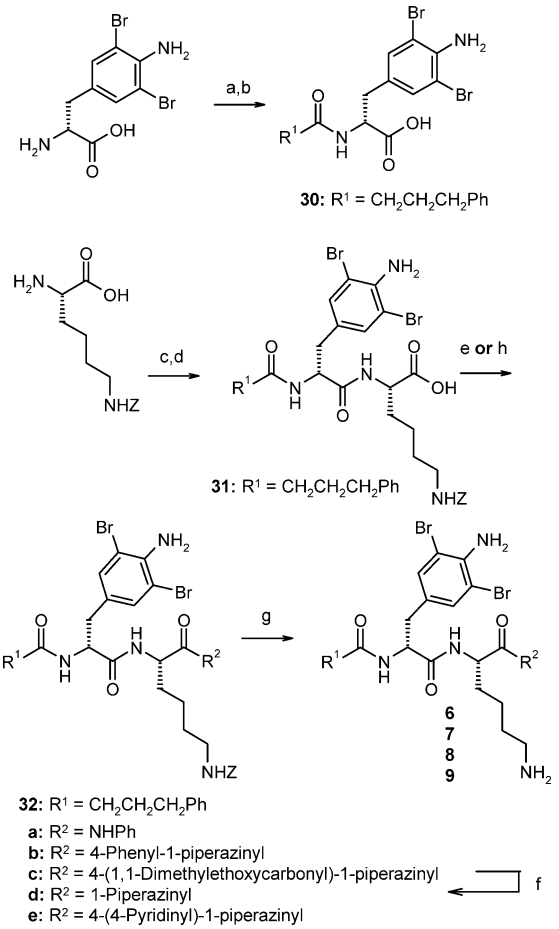
The synthesis of novel piperidine **33**, which was required as a starting material for compound **17**, is illustrated in Scheme 7. 4-Phenylamino-1-phenylmethylpiperidine was treated with sodium cyanate in the presence of trifluoroacetic acid. The benzyl protecting group of the resulting product was removed by hydrogenolysis to give **33**. Synthesis of novel piperidine **34**, an intermediate required for the preparation of test compound **20**, is depicted in Scheme 8. Boc protected 4-piperidinammonium hydrogencarbonate was treated with phenacyl bromide, followed by sodium cyanate in the presence of glacial acetic acid. Removal of the Boc group by trifluoroacetic acid gave piperidine **34**.

Biology. The binding affinities of compounds for the human CGRP receptor were determined by inhibition of ^{125}I-CGRP as previously described.[11] Species dependent CGRP receptor binding affinities of compounds **13**, **18** and **19** are reported in Table 3. CGRP receptor antagonism for compounds **13**, **16**, **17**, **18** and **19** (Table 2) was determined by measuring the formation of cyclic AMP in SK-N-MC cells, incubated with CGRP alone or in the presence of antagonist as depicted for compound **19** in Figure 1.

Discussion

The first step of lead optimization strategy was to screen selected compounds within the corporate compound pool being structurally related to the (*R*)-Tyr-(*S*)-Lys dipeptide-like leads **1** and **2**. Compounds **6** to **10** identified by this procedure exhibited CGRP receptor affinities between 10 300 nM and > 300 000 nM, as shown in Table 1. To assess the significance of the individual structural fragments, the lead compounds were arbitrarily divided into four parts: N-terminus

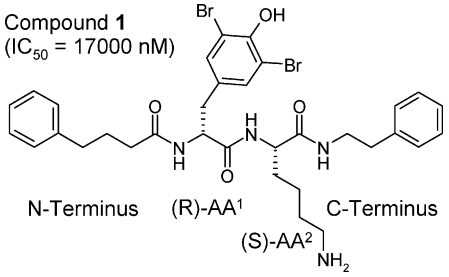
Scheme 6[a]



[a] (a) Diethylaminotrimethylsilane, 100 °C; (b) R^1CO_2H, 4-methylmorpholine, isobutyl chloroformate, THF, −15 to −20 °C; (c) chlorotrimethylsilane, 4-methylmorpholine, CH_2Cl_2, room temperature; (d) **30**, 4-methylmorpholine, isobutyl chloro-formate, THF, −15 °C; (e) R^2H, 4-methylmorpholine, isobutyl chloroformate, THF, room temperature; (f) TFA, CH_2Cl_2, room temperature; (g) HBr, AcOH, anisole, room temperature; (h) R^2H, HOBt, DCC, DMF/THF, room temperature.

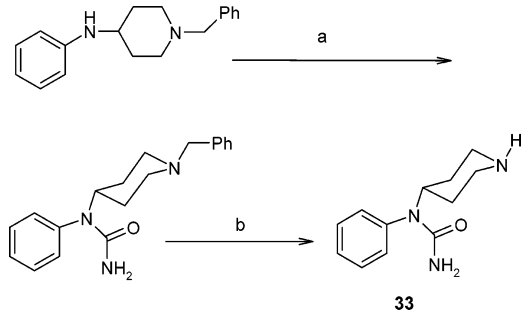
(NT), amino acid-1 (AA^1), amino acid-2 (AA^2), C-terminus (CT) (Chart I).

Chart 1



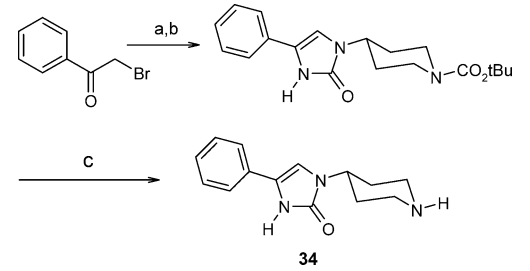
SAR studies thereafter were based on the assumption that the contribution of each structural fragment toward binding affinity was additive. Accordingly, any change in receptor affinity induced by variation of one fragment, while keeping all others constant, was taken as a hint for the significance of this fragment for receptor interaction. Analysis of the C-terminal part comprising compounds **2**, **6**, **7**, **8**, and **9** showed quite interesting results. Despite a large degree of freedom as indicated by comparable binding affinities of **2** (IC_{50} 40 000 nM) and

Scheme 7[a]



[a] (a) NaNCO, CF_3CO_2H, toluene, room temperature; (b) H_2, $Pd(OH)_2$ (Pearlman's catalyst), methanol, 50 °C.

Scheme 8[a]



[a] (a) 4-Amino-1-(1,1-dimethylethoxycarbonyl)piperidine, anhydrous sodium acetate, CH_2Cl_2, room temperature; (b) NaNCO, glacial acetic acid/water, room temperature; (c) TFA, CH_2Cl_2, room temperature.

Table 2. pA_2 and IC_{50} Values of Selected Compounds

compd	pA_2[a]	IC_{50} (nM)[b]
13	6.9	200
16	8.0	44
17	9.1	4.7
18	10.1	0.2
19	11.1	0.03

[a] CGRP receptor antagonism was determined by measuring the formation of cyclic AMP in SK-N-MC cells. Cells were incubated with CGRP alone or in the presence of at least four concentrations of antagonist. pA_2 values were determined by means of Schild-Plot analysis. The values are the mean of three individual experiments performed in triplicate. [b] Binding affinity was determined with SK-N-MC cells expressing the human CGRP-receptor using ^{125}I-CGRP as the radioligand. Data reported is derived from triplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration−response curves.

6 (IC_{50} 50 000 nM), the presence of an aromatic system at a certain distance to (*S*)-Lys seemed not to be sufficient for receptor recognition, since **7** (IC_{50} > 300 000 nM) showed no hCGRP receptor binding at all. In contrast, the incorporation of a rigidifying element bearing a negatively polarized group at the end of the aromatic fragment such as the 4-(4-pyridinyl)-piperazine moiety of **9** (IC_{50} 10 300 nM) seemed to be very suitable for a favorable interaction with the CGRP receptor, accounting for the more than 30-fold improved receptor affinity as compared to the 4-phenylpiperazine derivative **7** (IC_{50} > 300 000 nM).

For the establishment of SAR in the N-terminal part a comparison of compounds **10** and **11** with our lead **2** proved also interesting. The binding affinities of **2** (IC_{50} 40 000 nM) and **10** (IC_{50} 196 000 nM) differed by a factor of 5 indicating that the presence of an aromatic system at a certain distance to the dibromo-Tyr seemed to be important for receptor recognition. Another clue came from a comparison of **1** (IC_{50} 17 000 nM) with **11** (IC_{50} 13 000 nM). Replacement of the 3-phenylpropyl group in **1** with a (2-methoxyphenyl)ethylamino moiety (**11**), thereby creating a rigid urea bridge into the side chain seemed to be also acceptable for hCGRP receptor affinity. Finally, as **1** (X = OH) showed a 2-fold preference in binding affinity over compound **2** (X = NH_2), we decided to perform the next synthetic steps exclusively with derivatives containing the 3,5-dibromo-(*R*)-Tyr moiety.

Table 3. Species-Selective CGRP Receptor Binding of Compounds **13**, **18**, and **19**[a]

compd	human CGRP receptor affinity, IC_{50} (nM)[a]	rat CGRP receptor affinity, IC_{50} (nM)[b]	marmoset CGRP receptor affinity, IC_{50} (nM)[c]
13	200	70500	n.d.[d]
18	0.2	56.7	2.7
19	0.03	6.4	0.06

Binding affinity was determined with SK-N-MC cells expressing the human CGRP receptor,[a] rat spleen preparations,[b] or marmoset spleen preparations.[c] ^{125}I-CGRP was used as the radioligand and was incubated with increasing concentrations of the displacing compound. The IC_{50} values were obtained by nonlinear regression analysis on the basis of a one binding site model. Data reported are derived from triplicate wells and three independent experiments. Mean IC_{50} values were determined from 10-point, one-third log concentration−response curves. [d] Not determined.

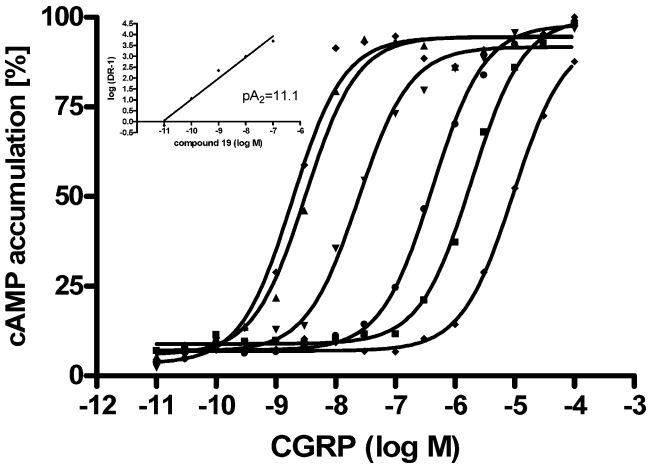


Figure 1. Concentration response curve for h-αCGRP in human SK-N-MC cells in the absence or presence of increasing concentrations of compound **19**. Values are mean of three separate experiments performed in triplicate. Inset: Schild plot analysis (determination of pA_2).

On the basis of our hypothesis that the binding affinity is the sum of individual fragment contributions, we envisaged that combining the optimal elements identified so far would lead to compounds with considerably improved binding affinity, which indeed proved to be the case. Modification of **1** by replacing the NT with the (2-methoxyphenyl)ethylamino group and the CT with the 4-(4-pyridinyl)piperazine moiety led to the identification of **12** (IC_{50} 1000 nM) that exhibited a 17-fold improved affinity toward the human CGRP receptor.

Having substantiated our hypothesis, we decided to focus next on the structural modification of the N-terminus leaving AA^1, AA^2, and CT unchanged.

In this context the presence of an urea bridge in **12** seemed to be more favorable than a carboxamide moiety present in **1** to **10**. We performed a variation of the chain

length between the distal N-atom of the urea bridge and the phenyl group as well as variation of the aromatic substitution pattern. Variation of the chain length showed no improvement in activity (data not shown), whereas a shift of the methoxy group from the ortho to the meta position led to the discovery of compound **13** (IC_{50} 200 nM) exhibiting a 5-fold increase in hCGRP receptor affinity.

Submicromolar compound **13** was used to address two important questions. First, whether the compounds obtained so far were hCGRP antagonists devoid of agonistic activity and second whether there was species dependent CGRP receptor binding. Compound **13** proved to be a competitive antagonist without any intrinsic agonistic activity exhibiting a pA_2 value of 6.9 (Table 2). Furthermore, **13** displayed a 350-fold higher affinity to human CGRP receptor compared to those of rat (rat spleen, IC_{50} 70 500 nM; Table 3). Next we reasoned that binding affinity could be further improved by introducing conformational constraints in the flexible linear linker chain between the distal N-atom of the urea bridge and the phenyl group at the end of this fragment. Replacement of the linear ethylene chain by a rigidifying piperazinyl or piperidine group yielded **14** (IC_{50} 226 nM) and **15** (IC_{50} 250 nM), which showed similar binding affinities as **13** and clearly indicated that the proximal NH group of the urea bridge was not essential for receptor binding. The existence of bulk tolerance in the spatial vicinity of the restraint linker and the aromatic system opened interesting possibilities for further design efforts, and we next extended the type of substituents in the 4-position of the piperidinyl ring to an aromatic system that was incorporated into a bicyclic ring system, as exemplified by a 2(3*H*)-benzoxazolone system (**16**, IC_{50} 44 nM, $pA_2 = 8.0$; Table 2), showing a 5-fold increase in affinity. Next we investigated the effect of a hydrogen bond donor group such as an aminocarbonyl system on affinity. This idea was realized in compound **17**, which showed high binding (IC_{50} 4.7 nM, $pA_2 = 9.1$; Table 2) emphasizing the importance of this region for receptor binding. On the basis of the results of **16** and **17**, we next synthesized the benzimidazolidinone **18** in which the NH hydrogen donor system was fixed into a planar system. Compound **18** exhibited a hCGRP receptor affinity in the subnanomolar range (IC_{50} 0.2 nM) and represented a breakthrough in our work.

In view of the favorable binding data of this compound its pharmacological and physicochemical properties have been examined in detail and will be published separately. The results so far obtained demonstrate that **18** is a high affinity and selective hCGRP antagonist (IC_{50} 0.2 nM, $pA_2 = 10.1$; Table 2); the excellent water solubility of some of its salts makes it an ideally suited tool for pharmacological and biological investigations.

Next, we investigated whether the spatial positioning of the aryl part of the benzimidazolone system could be further optimized. To get a better insight into this problem a set of benzimidazolone-like structures were designed. Comparing energy-minimized partial structures with the benzimidazolone system indicated that 3,4-dihydro-2(1*H*)-quinazolinone and 1,3-dihydro-4-phenyl-2(2*H*)-imidazolone systems display the putative key interaction points in a similar spatial arrangement, and indeed, **19** (IC_{50} 0.03 nM) and **20** (IC_{50} 0.05 nM) exhibited a significant increase in affinity. In fact, compound **19** (BIBN4096) possesses higher affinity for the human CGRP receptor than the endogenous ligand CGRP and 150-fold higher affinity compared to the peptidic antagonist $CGRP_{8-37}$.

SAR established during the described optimization work constituted a platform from which the design and synthesis of novel CGRP antagonists of reduced size and structural complexity could begin. This work already disclosed in a series of patent applications[10] will be published soon.

In view of its outstanding binding properties, compound **19** was selected for further comprehensive pharmacological, ADME, physicochemical and toxicological evaluations. A detailed report about the basic pharmacology of this compound has been recently published.[11] The results clearly show that **19** is a pure antagonist ($pA_2 = 11.1$; Figure 1) for the hCGRP receptor and is selective against a broad panel of receptors and enzymes. Moreover, **19** reverses CGRP-mediated vasodilation in human cerebral vessels and inhibits neurogenic vasodilation in a surrogate animal model of migraine pathophysiology.[11] On the basis of these encouraging results, **19** has been selected for clinical investigations. As oral bioavailability of **19** proved to be rather low in animal experiments (F_{po} (rat, dog) < 1%),[12] proof of concept studies have been performed by intravenous administration.

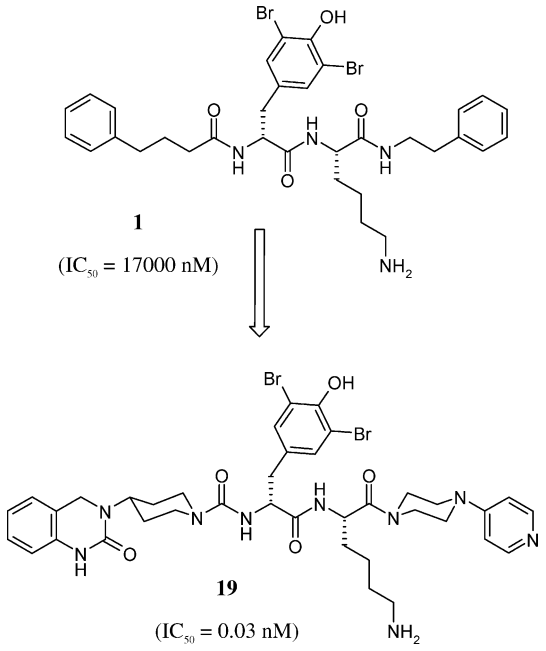
The outcome of clinical phase I and phase II studies with **19** has recently been published.[13,14] The clinical data clearly proved that **19** is efficacious for the treatment of migraine headache and thus establishes that CGRP antagonism is a safe and novel approach for the treatment of acute migraine headache.

Conclusion

A high throughput screening effort provided dipeptide-like compounds which displayed weak but unequivocal inhibition of binding to the hCGRP receptor. These compounds, characterized by a 3,5-dibromo-(*R*)-Tyr-(*S*)-Lys dipeptide fragment as the central pharmacophore, were used to design inhibitors with higher affinity to the receptor. Our strategy was to leave the dipeptidic scaffold unchanged and concentrate mainly on the C- and N-terminal parts of these molecules. The introduction of rigidifying structural elements into both terminal fragments together with an exact spatial positioning of the decisive pharmacophoric groups led to highly potent hCGRP antagonists, the prototype being compound **19** (Chart 2). Compound **19** reverses CGRP-induced vasodilation in human cerebral vessels and has proved active in an animal model related to migraine. In view of these favorable results, **19** was selected for clinical trials. In phase I studies following single intravenous administration, **19** shows good tolerability and appears to be safe.[13] In a proof of concept study, performed in a multicenter, double-blind, randomized clinical trial, **19** was effective in acute treatment of migraine headache attacks and is without cardiovascular side effects. [14]

In summary, it can be concluded that CGRP plays an important role in the pathophysiology of migraine and that CGRP receptor antagonism is a valid approach for

Chart 2



the acute treatment of migraine headache. However, further clinical studies are required before the true potential of this novel class of drug can be established.

Experimental Section

Chemistry. Procedures for the preparation of all final products are presented below along with representative procedures for all methods used in the preparation of intermediates. All solvents and reagents were used without purification as acquired from commercial sources.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker spectrometers at 80 MHz, 200, 400, or 600 MHz for proton (^{1}H) and 150 MHz for carbon (^{13}C) in the solvent indicated. Chemical shifts are reported in parts per million relative to tetramethysilane. Melting points were recorded on a HWS SG 2000 melting point apparatus and are uncorrected. Elemental analyses were performed on a Heraeus CHN Rapid Elemental Analyzer and are within 0.4% of the calculated values. Mass spectra were recorded on the following instruments, using the stated ionization methods: Finnigan MAT 8230 mass spectrometer, electron impact ionization; Finnigan TSQ 700 mass spectrometer, electrospray ionization.

***N*^{6}-(Phenylmethoxycarbonyl)-l-lysine-2-phenethylamide (21a).** To a mixture of Boc-Lys(Z)-OH (6.0 g, 15.7 mmol), diisopropylethylamine (2.0 g, 16 mmol), TBTU (5.2 g, 16 mmol), HOBt (2.2 g, 15.7 mmol) and 30 mL dimethylformamide (DMF) was added dropwise, with stirring, 2-phenethylamine (1.90 g, 15.7 mmol), dissolved in 13 mL of DMF, and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate. The ethyl acetate phase was then washed three times successively with 20 mL of saturated aqueous saline solution, dried over sodium sulfate, evaporated down in vacuo and triturated with diisopropyl ether to afford *N*^{2}-(1,1-dimethylethoxycarbonyl)-*N*^{6}-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (7.0 g, 92%) as colorless crystals. Anal. ($C_{27}H_{37}N_3O_5$: 483.6) C, H, N. To this intermediate, dissolved in 50 mL of dichloromethane, were added 10 mL of trifluoroacetic acid (TFA) and the reaction mixture was stirred 2 h at room temperature. After neutralization by addition of saturated aqueous sodium hydrogencarbonate solution, the organic phase was dried and evaporated down in vacuo to give the desired compound as a colorless highly viscous oil (5.5 g, 99%). Anal. ($C_{22}H_{29}N_3O_3$: 383.48) C, H, N.

***N*^{6}-(Phenylmethoxycarbonyl)-d-lysine-2-phenethylamide trifluoroacetate (21b).** The intermediate *N*^{2}-(1,1-dimethylethoxycarbonyl)-*N*^{6}-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide, prepared analogously to its (*S*)-enantiomer in a yield of 96% [Anal. ($C_{27}H_{37}N_3O_5$: 483.6) C, H, N], was treated with TFA as above. The amorphous title compound (98%) was obtained after evaporation of the solvent and trituration with ethyl acetate, followed by diethyl ether. Anal. ($C_{24}H_{30}F_3N_3O_5$: 497.51) C, H, N.

***N*^{2}-[*N*-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (22a).** *N*-Methylmorpholine (1.20 g, 12 mmol) and isobutyl chloroformate (1.7 g, 12.5 mmol) were added successively to a solution of *N*-[(1,1-dimethylethoxy)carbonyl]-3,5-dibromo-D-tyrosine (5.2 g, 11.8 mmol) in 300 mL tetrahydrofuran (THF), while stirring and maintaining a reaction temperature of −15 °C. After stirring at −15 °C for further 15 min, **21a** (4.6 g, 12 mmol) was added, batchwise, and the mixture was stirred at −15 °C for another 2 h, kept overnight at room temperature, diluted with 1.5 l of aqueous 0.5 M potassium hydrogensulfate and extracted exhaustively with ethyl acetate. The combined organic phases were dried and concentrated to dryness in vacuo. Column chromatography on silica, eluant dichloromethane/ethanol 9/1 (v/v), afforded the desired **22a** (7.5 g, 79%). Anal. ($C_{36}H_{44}Br_2N_4O_7$: 804.57) C, H, Br, N.

***N*^{2}-[4-Amino-3,5-dibromo-*N*-(1,1-dimethylethoxycarbonyl)-D-phenylalanyl]-*N*^{6}-phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (22b).** Synthesized from 4-amino-*N*-[(1,1-dimethylethoxy)carbonyl]-3,5-dibromo-D-phenylalanine and **21a** as described above for **22a**. Amorphous solid. Yield: 82%. Anal. ($C_{36}H_{45}Br_2N_5O_6$: 803.58) C, H, Br, N.

***N*^{2}-[*N*-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-L-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide (22c).** Synthesized from *N*-[(1,1-dimethylethoxy)-carbonyl]-3,5-dibromo-L-tyrosine, TBTU, HOBt, diisopropylethylamine (DIEA) and **21b** as described above. Colorless crystals. Yield: 94%. ESI-MS: $(M + H)^+$ = 803/805/807 (Br_2); $(M + Na)^+$ = 825/827/829 (Br_2). Anal. ($C_{36}H_{44}Br_2N_4O_7$: 804.57) C, H, Br, N.

***N*^{2}-[*N*-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide (22d).** Synthesized from *N*-[(1,1-dimethylethoxy)-carbonyl]-3,5-dibromo-D-tyrosine, TBTU, HOBt, DIEA and **21b** as described above. Colorless crystals. Yield: 81%. ESI-MS: $(M + H)^+$ = 803/805/807 (Br_2); $(M + Na)^+$ = 825/827/829 (Br_2). Anal. ($C_{36}H_{44}Br_2N_4O_7$: 804.57) C, H, Br, N.

***N*^{2}-[*N*-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-L-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (22e).** Synthesized from *N*-[(1,1-dimethylethoxy)-carbonyl]-3,5-dibromo-L-tyrosine, TBTU, HOBt, DIEA and **21a** as described above. Colorless crystals. Yield: 77%. ESI-MS: $(M + H)^+$ = 803/805/807 (Br_2); $(M + Na)^+$ = 825/827/829 (Br_2). Anal. ($C_{36}H_{44}Br_2N_4O_7$: 804.57) C, H, Br, N.

***N*^{2}-[3,5-Dibromo-*N*-(4-phenyl-1-oxobutyl)-D-tyrosyl]-L-lysine-2-phenethylamide Hydrobromide (1).** Treatment of **22a** with TFA in dichloromethane as described for **21a** gave amorphous *N*^{2}-[3,5-dibromo-D-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (58%) that was coupled with benzenebutanoic acid in the presence of isobutyl chloroformate and *N*-methylmorpholine as described above to afford colorless *N*^{2}-[3,5-dibromo-*N*-(4-phenyl-1-oxobutyl)-D-tyrosyl]-*N*^{6}-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (81%), mp 203−205 °C. Anal. ($C_{41}H_{46}Br_2N_4O_6$: 850.65) C, H, Br, N. A mixture of this intermediate (3.7 g, 4.35 mmol), 25 mL of glacial acetic acid, 30 mL of a 33% solution of hydrogen bromide in glacial acetic acid and 5 mL of anisole was stirred overnight at ambient temperature. The reaction mixture was stirred into diethyl ether, the solvents were decanted and the sticky precipitate formed was triturated with water, suction filtered and dried in a vacuum drier at 50 °C to afford the title compound as colorless water-insoluble crystals (2.1 g, 61%). EI-MS: M^+ = 714/716/718 (Br_2). Anal. ($C_{33}H_{40}Br_2N_4O_4$·HBr: 797.42) C, H, Br, N.

***N*^{2}-[4-Amino-3,5-dibromo-*N*-(4-phenyl-1-oxobutyl)-D-phenylalanyl]-L-lysine-2-phenethylamide Hydrobromide**

(2). The intermediate N^2-[4-amino-3,5-dibromo-*N*-(4-phenyl-1-oxobutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide was prepared from **22b** in two steps as described above (96%), mp 190−192 °C. Anal. ($C_{41}H_{47}Br_2N_5O_5$: 849.65) C, H, Br, N. Treatment with hydrogen bromide in glacial acetic acid as above gave the desired hydrobromide **2** (85%). ESI-MS: $(M + H)^+ = 714/716/718$ (Br_2); $(M + Br)^- = 792/794/796/798$ (Br_3). EI-MS: $M^+ = 713/715/717$ (Br_2). Anal. ($C_{33}H_{41}Br_2N_5O_3$·HBr: 796.43) C, H, Br, N.

***N*²-[3,5-Dibromo-*N*-(4-phenyl-1-oxobutyl)-L-tyrosyl]-D-lysine-2-phenethylamide (3).** Reaction of **22c** with TFA as above gave N^2-[3,5-dibromo-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide trifluoroacetate (67%) [Anal. ($C_{33}H_{37}Br_2F_3N_4O_7$: 818.47) C, H, Br, N], which was transformed with benzenebutanoic acid, TBTU and HOBt to colorless crystals of N^2-[3,5-dibromo-*N*-(4-phenyl-1-oxobutyl)-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide (50%). ESI-MS: $(M + Na)^+ = 871/873/875$ (Br_2). Anal. ($C_{41}H_{46}Br_2N_4O_6$: 850.64) C, H, Br, N. Removal of the benzyloxycarbonyl group by hydrogen bromide in glacial acetic acid as above and final treatment with base gave the title compound **3** (39%). Anal. ($C_{33}H_{40}Br_2N_4O_4$: 716.5) C, H, Br, N.

***N*²-[3,5-Dibromo-*N*-(4-phenyl-1-oxobutyl)-D-tyrosyl]-D-lysine-2-phenethylamide (4).** Starting from **22d**, the title compound was synthesized following the procedures described above. Anal. (Calcd for $C_{33}H_{40}Br_2N_4O_4$: 716.5) C, H, Br, N.

***N*²-[3,5-Dibromo-*N*-(4-phenyl-1-oxobutyl)-L-tyrosyl]-L-lysine-2-phenethylamide (5).** Starting from **22e**, the title compound was synthesized following the procedures described above. Anal. (Calcd for $C_{33}H_{40}Br_2N_4O_4$: 716.5) C, H, Br, N.

***(R)*-4-Amino-3,5-dibromophenylalanine Methyl Ester Hydrochloride (23).** To a solution of d-4-aminophenylalanine hydrate (125.0 g, 0.631 mol) in a mixture of 2.1 l of glacial acetic acid, 300 mL of water and 2 mL of concentrated hydrobromic acid a solution of anhydrous bromine (64.2 mL, 1.261 mol) in 100 mL of glacial acetic acid was added dropwise, with stirring and while maintaining a reaction temperature of 20 to 25 °C. The mixture was stirred for 1 h at ambient temperature, diluted with 2.2 l of water, and adjusted to pH 5 by addition of ca. 2.2 l of 10 N aq sodium hydroxide solution, while cooling with a mixture of crushed ice and methanol. The precipitated crystals were suction filtered, thoroughly washed with water and dried in vacuo to afford the intermediate (*R*)-4-amino-3,5-dibromophenylalanine (171.2 g, 80%); mp 265−266 °C (decomposition). To −10 °C cold anhydrous methanol (600 mL) was added dropwise thionyl chloride (27.4 mL, 0.377 mol), while maintaining a reaction temperature below −5 °C, and the resulting solution combined batchwise with the above intermediate (85 g, 0.251 mol). The mixture was stirred for a further 90 min at 50 °C and overnight at room temperature, then evaporated down in vacuo and the residue dissolved in 500 mL of hot methanol. After cooling, 1.5 L of diethyl ether was added with stirring. The resulting precipitate was suction filtered and dried in vacuo to yield the title compound (82.9 g, 85%), mp 223−224 °C (decomposition). Anal. ($C_{10}H_{13}Br_2ClN_2O_2$: 388.48) C, H, Br, N.

4-Amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanine (24a). The intermediate 4-amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanine methyl ester was prepared from **23**, benzenepropanoic acid, *N*-methylmorpholine and isobutyl chloroformate by the method described above: mp 155−156 °C. Yield: 95%. A mixture of this intermediate (46.0 g, 0.095 mol), 700 mL of THF and 48 mL 2 N aq sodium hydroxide solution was stirred for 3 h at room temperature, then adjusted to pH 2.5 by addition of 0.5 M aq potassium hydrogensulfate solution and extracted twice with ethyl acetate. The combined ethyl acetate phases were dried and evaporated down. The residue was triturated with diethyl ether, suction filtered, washed with ether and dried in a circulating air drier to give the title compound (40.3 g, 90%); mp 148−150 °C. Anal. ($C_{18}H_{18}Br_2N_2O_3$: 470.16) C, H, Br, N.

***N*²-[4-Amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysine (25).** **24a**, N^6-(phenylmethoxycarbonyl)-L-lysine methyl ester hydrochloride, *N*-methylmorpholine and isobutyl chloroformate were reacted as described above to give N^2-[4-amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysine methyl ester (92%); mp 183−186 °C Anal. ($C_{33}H_{38}Br_2N_4O_6$: 746.49) C, H, Br, N. The title compound was prepared from this intermediate by saponification with aq sodium hydroxide solution as described above (94%); mp 150−153 °C. Anal. ($C_{32}H_{36}Br_2N_4O_6$: 732.46) C, H, Br, N.

***N*²-[4-Amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-L-lysine-2-phenethylamide Hydrochloride (10).** The acid **25** was reacted with 2-phenethylamine in the presence of *N*-methylmorpholine and isobutyl chloroformate as described above to afford N^2-[4-amino-3,5-dibromo-*N*-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (81%); mp 232−234 °C. Anal. ($C_{40}H_{45}Br_2N_5O_5$: 835.62) C, H, Br, N. This intermediate was treated with a solution of hydrogen bromide in acetic acid as described above; the obtained hydrobromide was converted via its base into the desired title hydrochloride (89%); amorphous solid. ESI-MS: $(M + H)^+ = 700/702/704$ (Br_2). EI-MS: $M^+ = 699/701/703$ (Br_2). Anal. ($C_{32}H_{40}Br_2ClN_5O_3$: 737.95) C, H, Br, Cl, N.

1-[N^6-(Phenylmethoxycarbonyl)]-L-lysyl]-4-(4-pyridinyl)-piperazine (21c). Starting from Boc-Lys(Z)-OH and 1-(4-pyridinyl)-piperazine, the title compound was synthesized in two steps as described above for **21a** and **21b**. Anal. ($C_{23}H_{31}N_5O_3$: 425.52) C, H, N.

1-[N^2-(3,5-Dibromo-D-tyrosyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (26). As described above for **21a**, the title compound was prepared by coupling of **21c** with *N*-[(1,1-dimethylethoxycarbonyl]-3,5-dibromo-D-tyrosine, followed by treatment with TFA. Anal. ($C_{32}H_{38}Br_2N_6O_5$: 746.49) C, H, Br, N.

1-[N^2-[3,5-Dibromo-*N*-[[[2-(2-methoxyphenyl)ethyl]-amino]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (12). To a solution of **26** (1.0 g, 1.34 mmol) in 80 mL of tetrahydrofuran (THF) was added 2-methoxyphenethyl isocyanate (0.28 g 1.6 mmol), and the mixture was stirred for 3 days at room temperature. The reaction mixture was evaporated down in vacuo, and the residue was purified by column chromatography (MN-silica gel 60, Macherey-Nagel, 70−230 mesh ASTM, eluant: dichloromethane/methanol/cyclohexane/ammonia = 350/75/75/10 (v/v/v/v)). 0.5 g (40%) of a colorless amorphous solid was obtained. ESI-MS: $(M + H)^+ = 922/924/926$ (Br_2). Anal. ($C_{42}H_{49}Br_2N_7O_7$: 923.69) C, H, Br, N. This intermediate (0.5 g, 0.54 mmol), presumably 1-[N^2-[3,5-dibromo-*N*-[[[2-(2-methoxyphenyl)ethyl]-amino]carbonyl]-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine, was treated with hydrogen bromide in glacial acetic acid as described above for **22a** and converted to its base in the usual manner to yield the title compound **12** as a colorless, amorphous solid (0.2 g, 47%). ESI-MS: $(M + H)^+ = 788/790/792$ (Br_2); $(M + 2H)^{2+} = 394/395/396$ (Br_2). Anal. ($C_{34}H_{43}Br_2N_7O_5$: 789.56) C, H, Br, N.

1-[N^2-[3,5-Dibromo-*N*-[[[2-(3-methoxyphenyl)ethyl]-amino]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (13). A tetrahydrofuran solution (50 mL) of **26** (1.0 g, 1.34 mmol) was added dropwise over a period of 60 min to a suspension of CDT (0.22 g, 1.34 mmol) in THF (30 mL) while cooling to −5 °C and stirring. The reaction mixture was then stirred for 3 h at ambient temperature and mixed with a solution of 3-methoxybenzeneethanamine (0.20 g, 1.34 mmol) in THF (5 mL). Then the mixture was refluxed for 2 h and stirred overnight at ambient temperature. The reaction mixture was evaporated down in vacuo. Column chromatography of the residue on silica, eluant dichloromethane/cyclohexane/methanol/ammonia 7/1.5/1.5/0.2 (v/v/v/v), afforded 0.5 g (40%) of 1-[N^2-[3,5-dibromo-*N*-[[[2-(3-methoxyphenyl)ethyl]amino]-carbonyl]-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine as an amorphous foam. ESI-MS: $(M + H)^+ = 922/924/926$ (Br_2); $(M + Na)^+ = 944/946/948$ (Br_2). Anal. ($C_{42}H_{49}Br_2N_7O_7$: 923.69) C, H, Br, N. This intermediate (0.5 g, 0.54 mmol) was treated with hydrogen bromide in glacial

acetic acid as described above for **22a** and converted to its base in the usual manner to give the title compound **13** as a colorless, amorphous solid (0.42 g, 99%). ESI-MS: $(M + H)^+$ = 788/790/792 (Br_2); $(M + 2H)^{2+}$ = 395.7. Anal. ($C_{34}H_{43}Br_2N_7O_5$: 789.56) C, H, Br, N.

3,5-Dibromo-*N*-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosine (27). To a suspension of ethyl 3,5-dibromo-D-tyrosinate hydrobromide (20.0 g, 44.65 mmol) in THF (300 mL) was added successively triethylamine (4.52 g, 44.65 mmol) and the solution of 2-methoxyphenethyl isocyanate (8.0 g, 53.7 mmol) in THF (50 mL), and the mixture was stirred overnight at ambient temperature. The precipitate was filtered off, the filtrate was evaporated down in vacuo and the residue was added to 2 N aq sodium hydroxide solution (200 mL, 400 mmol) and stirred overnight. The reaction mixture was diluted with water (200 mL) and extracted four times with 100 mL of ethyl acetate each. The aqueous phase was acidified to pH 6 with diluted aq hydrochloric acid and the resulting colorless precipitate dried in a circulating air drier at 60 °C to afford the title compound (17.0 g, 74%) as colorless crystals; mp >196 °C (dec). ESI-MS: $(M - H)^-$ = 513/515/517 (Br_2). Anal. ($C_{19}H_{20}Br_2N_2O_5$: 516.18) C, H, Br, N.

***N*²-[3,5-Dibromo-*N*-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-L-lysine-2-phenethylamide (11).** **21a** and **27** were reacted as described above for **21a** to give *N*²-[3,5-dibromo-*N*-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-*N*⁶-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide Anal. ($C_{41}H_{47}Br_2N_5O_7$: 881.65) C, H, Br, N. This intermediate was treated with hydrogen bromide in glacial acetic acid as described above for **22a** and converted to its base in the usual manner to give the title compound **11** as a colorless, amorphous solid. ESI-MS: $(M + H)^+$ = 746/748/750 (Br_2). Anal. ($C_{33}H_{41}Br_2N_5O_5$: 747.52) C, H, Br, N.

1-[*N*⁶-(1,1-Dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (28). A solution of intermediate 1-[*N*⁶-(1,1-dimethylethoxycarbonyl)-*N*²-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (120 g, 0.2283 mol) [EI-MS: M^+ = 525. Anal. ($C_{28}H_{39}N_5O_5$: 525.64) C, H, N], prepared from Z-Lys(Boc)-OH and 1-(4-pyridinyl)piperazine as described above for **21a**, in a mixture of methanol (1 L) and 1 M aq potassium hydrogensulfate (240 mL) was hydrogenated in the presence of 10% palladium/charcoal (30 g) at room temperature and 3 bar of hydrogen pressure until the uptake of hydrogen had ceased. After working up in the usual way the title compound **28** was obtained as a colorless oil; 87.0 g, 97%. Anal. ($C_{20}H_{33}N_5O_3$: 391.51) C, H, N.

1-[*N*²-(3,5-Dibromo-D-tyrosyl)-*N*⁶-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (29). As described above for **21a**, *N*-(9-fluorenylmethoxycarbonyl)-3,5-dibromo-D-tyrosine was coupled with compound **28** to give 1-[*N*²-[3,5-dibromo-*N*-(9-fluorenylmethoxycarbonyl)-D-tyrosyl]-*N*⁶-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine. A mixture of this intermediate (50 g, 53.5 mmol) and 300 mL of diethylamine was heated to 60 °C with stirring; 100 mL of methanol were added and stirring was continued for a further 5 h at 60 °C. The reaction mixture was evaporated down in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate/methanol 6/4 (v/v)) to afford compound **29** as a colorless foam (26 g, 68%). EI− MS: M^+ = 710/712/714 (Br_2). Anal. ($C_{29}H_{40}Br_2N_6O_5$: 712.47) C, H, Br, N.

1-[*N*²-[3,5-Dibromo-*N*-[[4-(2-methoxyphenyl)-1-piperazinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (14). Analogously to the method described above for compound **13**, 1-(2-methoxyphenyl)piperazine, CDT, and **29** were transformed to 1-[*N*²-[3,5-dibromo-*N*-[[4-(2-methoxyphenyl)-1-piperazinyl]carbonyl]-D-tyrosyl]-*N*⁶-(1,1-dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine. To this intermediate (1.35 g, 1.45 mmol) was added methanol saturated with hydrogen chloride (30 mL), and the mixture was stirred overnight at ambient temperature, then evaporated down in vacuo and the residue purified by chromatography (silica gel, ethyl acetate/methanol/ammonia 7/3/0.5 (v/v/v)) to give the title compound **14** (41%). ESI-MS: $(M + H)^+$ = 829/831/833 (Br_2); $(M + 2H)^{2+}$ = 415/416/417. Anal. ($C_{36}H_{46}Br_2N_8O_5$: 830.61) C, H, Br, N. Instead of methanolic hydrogen chloride solution, TFA in dichloromethane may be used to split off the *tert*-butoxycarbonyl group.

1-[*N*²-[3,5-Dibromo-*N*-[[4-(2-methoxyphenyl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine Bis(trifluoroacetate) (15). As described for compound **14**, the title compound was prepared from 4-(2-methoxyphenyl)-piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 828/830/832 (Br_2); $(M + 2H)^{2+}$ = 414/415/416.7. Anal. (Calcd for $C_{41}H_{49}Br_2F_6N_7O_9$: 1057.67) C, H, Br, N.

1-[*N*²-[3,5-Dibromo-*N*-[[4-[2(3*H*)-oxobenzoxazol-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine Bis(trifluoroacetate) (16). As described for compound **14**, the title compound was prepared from 4-[2(3*H*)-oxobenzoxazol-3-yl]piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 855/857/859 (Br_2); $(M + 2H)^{2+}$ = 428/429/430. Anal. ($C_{41}H_{46}Br_2N_8O_{10}$: 1084.65) C, H, Br, N.

1-[*N*²-[*N*-[[4-[*N*-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine Bis(trifluoroacetate) (17). As described for compound **14**, the title compound was prepared from 4-[*N*-(aminocarbonyl)-phenylamino]piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 856/858/860 (Br_2); $(M + 2H)^{2+}$ = 428/429/430.6 (Br_2). Anal. ($C_{41}H_{49}Br_2F_6N_9O_9$: 1085.68) C, H, Br, N.

1-[*N*²-[3,5-Dibromo-*N*-[[4-(1,3-dihydro-2(2*H*)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (18). As described for compound **14**, the title compound was prepared from 4-(1,3-dihydro-2(2*H*)-oxobenzimidazol-1-yl)piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 854/856/858 (Br_2); $(M + 2H)^{2+}$ = 427/428/429.6. Anal. ($C_{37}H_{45}Br_2N_9O_5$: 855.62) C, H, Br, N.

1-[*N*²-[3,5-Dibromo-*N*-[[4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (19). As described for compound **14**, the title compound was prepared from 4-(3,4-dihydro-2(1*H*)-oxoquinazolin-3-yl)piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 868/870/872 (Br_2); $(M + 2H)^{2+}$ = 434/435/436.7. Anal. ($C_{38}H_{47}Br_2N_9O_5$: 869.65) C, H, Br, N.

1-[*N*²-[3,5-Dibromo-*N*-[[4-(1,3-dihydro-4-phenyl-2(2*H*)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (20). As described for compound **14**, the title compound was prepared from 4-(1,3-dihydro-4-phenyl-2(2*H*)-oxoimidazol-1-yl)piperidine, CDT, and **29**. ESI-MS: $(M + H)^+$ = 880/882/884 (Br_2); $(M + 2H)^{2+}$ = 440.5/441.5/442.5. Anal. ($C_{39}H_{47}Br_2N_9O_5$: 881.66) C, H, Br, N.

4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanine (30). A suspension of 4-amino-3,5-dibromo-D-phenylalanine (138.4 g, 0.41 mol) in diethylaminotrimethylsilane (250 mL) was heated to ca. 75 °C, while the diethylamine being formed was distilled off. When the theoretical amount of diethylamine had been collected, the reaction was interrupted and the surplus of diethylaminotrimethylsilane was removed using a vacuum rotatory evaporator. The residue was taken up in THF (250 mL) to give reaction mixture A. To a solution of benzenebutanoic acid (67.2 g, 0.41 mol) in dichloromethane (650 mL) were added dropwise isobutyl chloroformate (53,2 mL, 0.41 mol) and *N*-methylmorpholine (45 mL, 0.41 mol), while cooling to −15 to −20 °C. The mixture was kept at this temperature for another 3 h. Then reaction mixture A was poured into this solution drop by drop while stirring and maintaining the same temperature. After stirring at −15 °C for a further 2 h, the mixture was allowed to come back slowly to room temperature. The precipitate was filtered off, and the filtrate concentrated in vacuo. The residue was taken up in dichloromethane (500 mL) and stirred into aq concentrated potassium hydrogensulfate solution. The formed crystalline product was suction filtered, washed twice with acetone and air-dried to give 134 g (68%) of the title compound; mp 214 °C. Anal. ($C_{19}H_{20}Br_2N_2O_3$: 484.18) C, H, Br, N.

***N*²-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-*N*⁶-(phenylmethoxycarbonyl)-L-lysine (31).** To a suspension of H-Lys(Z)-OH (16.8 g, 0.06 mol) in dichloromethane (150 mL) were added dropwise, while cooling with

ice−water, trimethylchlorosilane (13.1 g, 0.12 mol) and *N*-methylmorpholine (12.1 g, 0.12 mol). This mixture A was stirred at ambient temperature for a further 12 h. A solution of **30** (29.0 g, 0.06 mol) in THF (300 mL) was cooled to −15 °C, cautiously admixed with isobutyl chloroformate (8.2 g, 0.06 mol) and *N*-methylmorpholine (0.06 mol) and kept at the same temperature for 30 min. To this solution was added slowly, while maintaining a reaction temperature of ca. −15 °C, the above mixture A. Stirring at this temperature was continued for 2 h, whereupon the mixture was allowed to come back to room temperature, then poured into cold aq 0.5 M potassium hydrogensulfate solution (2 L) and exhaustively extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated in vacuo to give 37.0 g (87%) of the title compound; mp 168−172 °C. Anal. ($C_{33}H_{38}Br_2N_4O_6$: 746.49) C, H, Br, N.

N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysine-phenylamide (32a). Prepared as described above for **22a** from **31** and aniline; mp 206−215 °C. Anal. ($C_{39}H_{43}Br_2N_5O_5$: 821.6) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-phenylpiperazine (32b). Prepared as described above for **22a** from **31** and 1-phenylpiperazine; mp 170−175 °C. ESI-MS: $(M + H)^+$ = 889/891/893 (Br_2). Anal. ($C_{43}H_{50}Br_2N_6O_5$: 890.7) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(1,1-dimethylethoxycarbonyl)piperazine (32c). Prepared as described above for **22a** from **31** and 1-(1,1-dimethylethoxycarbonyl)piperazine hydrochloride. Anal. ($C_{42}H_{54}Br_2N_6O_7$: 914.72) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]piperazine Trifluoroacetate (32d). Prepared as described above for **21a** from **32c** and TFA. Anal. ($C_{39}H_{47}Br_2F_3N_6O_7$: 928.63) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (32e). Prepared as described above for **22a** from **31** and 1-(4-pyridinyl)piperazine. ESI-MS: $(M + H)^+$ = 890/892/894 (Br_2). Anal. ($C_{42}H_{49}Br_2N_7O_5$: 891,69) C, H, Br, N.

N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysine-phenylamide Hydrobromide (6). Prepared, as described above for **1,** from **32a** and hydrogen bromide. ESI-MS: $(M + H)^+$ = 686/688/690 (Br_2). EI-MS: M^+ = 685/687/689 (Br_2). Anal. ($C_{33}H_{37}Br_2N_5O_3$·HBr: 768.38) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-4-phenyl-piperazine Hydrobromide (7). Prepared as described above for **1** from **32b** and hydrogen bromide. ESI-MS: $(M + H)^+$ = 755/757/759 (Br_2). Anal. ($C_{35}H_{44}Br_2N_6O_3$·HBr: 837.48) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-piperazine Dihydrobromide (8). Prepared as described above for **1** from **32d** and hydrogen bromide. ESI-MS: $(M + H)^+$ = 679/681/683 (Br_2). Anal. ($C_{29}H_{40}Br_2N_6O_3$·2HBr: 842.3) C, H, Br, N.

1-[N^2-[4-Amino-3,5-dibromo-*N*-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)piperazine (9). Prepared as described above for **1** from **32e** and hydrogen bromide. ESI-MS: $(M + H)^+$ = 756/758/760 (Br_2); $(M + 2H)^{2+}$ = 378.6/379.6/380.6 (Br_2). Anal. ($C_{34}H_{43}Br_2N_7O_3$: 757.56) C, H, Br, N.

4-[*N*-(Aminocarbonyl)phenylamino]piperidine (33). To the suspension of 4-phenylamino-1-phenylmethylpiperidine (7.3 g, 0.027 mol), toluene (100 mL) and sodium cyanate (1.8 g, 0.027 mol) was added dropwise, while stirring, TFA (3.1 g, 0.027 mol). Stirring was continued for 2 h, same amount as above both of sodium cyanate and TFA added and stirring continued overnight at ambient temperature. The mixture was concentrated in vacuo, the residue washed successively with water, aq sodium hydroxide solution, water and diethyl ether. The remaining colorless crystals (2.92 g, 34%) were identified to be 4-[*N*-(aminocarbonyl)phenylamino]-1-phenylmethylpiperidine; mp 158−162 °C. ESI-MS: $(M + H)^+$ = 310. Anal. ($C_{19}H_{23}N_3O$: 309.41) C, H, N. A solution of this intermediate (13.0 g, 0.042 mol) in methanol (150 mL) was hydrogenated at 50 °C and in the presence of palladium(II) hydroxide [Pearlman's catalyst] (12 g). When the hydrogen uptake had ended, the catalyst was removed and the filtrate concentrated in vacuo to give after trituration with diethyl ether the desired title compound as colorless crystals (9.2 g, 100%). ESI-MS: $(M + H)^+$ = 220. Anal. ($C_{12}H_{17}N_3O$: 219.28) C, H, N.

4-(1,3-Dihydro-2(2*H*)-oxo-4-phenyl-imidazol-1-yl)piperidine Trifluoroacetate (34). To a solution of 1-(1,1-dimethylethoxycarbonyl)-4-piperidinammonium hydrogencarbonate (55.794 g, 0.213 mol) and diisopropylethylamine (87.365 mL, 0.5 mol) in dichloromethane (500 mL) was added dropwise, while stirring, phenacyl bromide (50.00 g, 0.251 mol). After stirring a further 7 h at ambient temperature, sodium cyanate (28.665 g, 0.441 mol) was added. The mixture was acidified with acetic acid, while cooling with a mixture of crushed ice and water, and stirred overnight at ca. 0 °C, whereupon the mixture was allowed to come back to room temperature, thoroughly washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was triturated with ether, suction filtered and dried at ambient temperature in a circulating air drier to afford the intermediate 4-(1,3-dihydro-2(2*H*)-oxo-4-phenyl-imidazol-1-yl)-1-(1,1-dimethylethoxycarbonyl)piperidine (51.0 g, 70%). EI-MS: M^+ = 343. Anal. ($C_{19}H_{25}N_3O_3$: 343.19) C, H, N. This was converted into the title compound following the procedure described above for **21a**. Anal. ($C_{16}H_{18}F_3N_3O_3$: 357.33) C, H, N.

Determination of Binding Affinity with SK-N-MC Cells Expressing Human CGRP-Receptor. SK-N-MC cells were cultivated in Dulbecco's modified Eagle Medium. The medium of confluent cultures was removed. The cells were washed twice with PBS-buffer (Gibco 041−04190 M), detached by the addition of PBS-buffer, mixed with 0.02% EDTA, and isolated by centrifuging. After resuspension in 20 mL of Balanced Salts Solution [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-glucose 5.5, HEPES 30, pH 7.40] the cells were centrifuged twice at 100*g* and resuspended in BSS. After the cell number had been determined, the cells were homogenized using an Ultra-Turrax and centrifuged for 10 min at 3000*g*. The supernatant was discarded and the pellet was recentrifuged, resuspended (1 mL/1 000 000 cells) in Tris buffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and enriched with 1% bovine serum albumine and 0.1% bacitracine. The homogenate was frozen at −80 °C. The membrane preparations were stable for more than 6 weeks under these conditions.

After thawing, the homogenate was diluted 1:10 with assay buffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and homogenized for 30 s with an Ultra-Turrax. 230 μL of the homogenate was incubated at ambient temperature for 180 min with 50 pM of ^{125}I-iodotyrosyl-calcitonin-gene-related peptide (Amersham) and increasing concentrations of the test substances in a total volume of 250 μL. Incubation was ended by rapid filtration using GF/B-glass fiber filters treated with polyethyleneimine (0.1%) by means of a cell harvester. The protein-bound radioactivity was measured using a gamma counter. The nonspecific binding is defined as the radioactivity bound in the presence of 1 μM of human α-CGRP during incubation.

The concentration-binding curves were analyzed using a computer-aided nonlinear curve adaptation. All data are the mean of at least three independent experiments performed in triplicate (SEM < 5%).

Determination of Binding Affinity for Rat and Marmoset CGRP-Receptor. In separate studies, homogenates of marmoset or rat spleen were used instead of SK-N-MC cells (see above) to determine the binding affinities of compounds for rat and marmoset CGRP receptors.

Determination of CGRP Antagonism in SK-N-MC Cells. SK-N-MC cells (1 million cells) were washed twice with

250 μL of incubation buffer (Hanks's HEPES, 1 mM 3-isobutyl-1-methylxanthine, 1% BSA, pH 7.4) and preincubated at 37 °C for 15 min. After the addition of CGRP (10 μL) as agonist in increasing concentrations (10^{-11} to 10^{-6} M) or additionally of substance in three to four different concentrations, incubation was continued for a further 15 min. Intracellular cAMP was then extracted by the addition of 20 μL of 1 M HCl and centrifugation (2000*g*, 4 °C for 15 min). The supernatants were frozen in liquid nitrogen and stored at −20 °C. The cAMP contents of the samples were determined by radioimmunoassay (Amersham), and the pA_2 values of antagonistically acting substances were determined graphically.

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Supporting Information Available: Nuclear magnetic resonance (NMR) spectra and combustion analyses of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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