Synthesis and Histamine H_2-Receptor Antagonist Activity of 4-(1-Pyrazolyl)butanamides, Guanidinopyrazoles, and Related Compounds [+)]

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A series of 4-(1-pyrazolyl)butanamides, pyrazolylalkyl cyanoguanidines, and related compounds with diverse functional groups (*e.g.* nitro, amino, guanidino groups) in the 3-position of the pyrazole ring was prepared *via* 4-(3-nitro-1-pyrazolyl)butanenitrile (**5**) and the corresponding carboxylic acid **7** as central intermediates. The amides **9a–d** were prepared from the primary amines **8a–d** which represent partial structures of the H_2-receptor antagonists roxatidine, cimetidine, ranitidine, and famotidine. The roxatidine-derived 4-(3-nitro-1-pyrazolyl)butanamide (**9a**) proved to be the compound with the highest H_2-receptor antagonist activity of 23 compounds tested at the isolated guinea pig right atrium preparation, achieving about 6 times famotidine's or 160 times cimetidine's potency. By contrast, in Ghosh-Schild rats **9a** did not inhibit histamine-stimulated gastric acid secretion at a dosage of 0.1 μmol/kg *i.v.* Compounds **20a** (the 3-(trifluoroethylguanidino)pyrazole analogue of **9a**, **12a** (the cyanoguanidine analogue) and *N*-{4-[3-(trifluoroethylguanidino)-1-pyrazolyl]butyl}cyanoguanidine (**29**), which are about as active as famotidine in the atrium, turned out to be very potent inhibitors of gastric acid secretion as well (*e.g.*, **29**: 74 % inhibition at 0.025 μmol/kg). These compounds are comparable to famotidine in the rat stomach and by far superior to cimetidine and ranitidine in this test system.

Synthese und Histamin-H_2-antagonistische Aktivität von 4-(1-Pyrazolyl)butanamiden, Guanidinopyrazolen und verwandten Verbindungen

Eine Reihe von 4-(1-Pyrazolyl)butanamiden, Pyrazolylalkylcyanoguanidinen und analogen Verbindungen mit unterschiedlichen funktionellen Gruppen (z. B. Nitro, Amino, verschiedene Guanidino- gruppen) in 3-Position des Pyrazolringes wurde hergestellt über 4-(3-Nitro-1-pyrazolyl)butannitril (**5**) oder die entspr. Carbonsäure **7** als zentrale Intermediate. Zur Herstellung der Amide **9a–d** wurden die primären Amine **8a–d** eingesetzt, die Partialstrukturen der H_2-Antagonisten Roxatidin, Cimetidin, Ranitidin und Famotidin darstellen. Das von Roxatidin abgeleitete 4-(3-Nitro-1-pyrazolyl)butanamide (**9a**) erwies sich mit *ca.* 6facher Famotidin- und 160facher Cimetidinstärke unter den 23 am isolierten rechten Meerschweinchenatrium getesteten Substanzen als der potenteste H_2-Antagonist, zeigte dagegen an der Ghosh-Schild-Ratte in einer Dosierung von 0.1 μmol/kg *i.v.* keine Hemmung der Histamin-stimulierten Magensäuresekretion. Die Verbindungen **20a** (das 3-(Trifluorethylguanidino)pyrazol-Analoge von **9a**, das analoge Cyanoguanidin **12a** und *N*-{4-[3-(Trifluorethylguanidino)-1-pyrazolyl]-butyl}cyanoguanidin (**29**) die am Atrium mit pK_B-Werten um 8 etwa die Wirkstärke von Famotidin besitzen, erwiesen sich auch als sehr potente Inhibitoren der Magensäuresekretion (z. B. **29**: 74 % Hemmung bei 0.025 μmol/kg). Die Aktivität dieser Substanzen ist am Rattenmagen mit derjenigen von Famotidin vergleichbar, während die Wirkung von Cimetidin und Ranitidin in diesem Testmodell bei weitem übertroffen wird.

Since the introduction of cimetidine (Scheme 1) into the therapy of gastric and duodenal ulcers a vast number of structurally different imidazole and non-imidazole histamine H_2-receptor antagonists has been described (for a review see ref. [1)]). Regardless of chemical diversity most of these compounds have some features in common as they are characterized by an aromatic or heteroaromatic ring mostly linked with a basic substituent, a polar group which is usually called the 'urea equivalent' (*e.g.* the cyanoguanidine in cimetidine), and a flexible chain connecting both structural parts. With increasing receptor affinity of the residual molecule the polar group may be successfully varied over a wider range. For example, numerous heterocyclic and acyclic systems as polar groups proved to further increase activity in the piperidinomethylphenoxyalkylamine series [1)]. Even a simple amide group as in roxatidine (Scheme 1) is compatible with high H_2-receptor antagonist potency. ICI 162846 [2)] is another example of an amide-type H_2-receptor blocker which is described as a very effective antisecretory agent in man [3)].

The aim of this study was to synthesize potent H_2-receptor antagonists by combining crucial structural features of both ICI 162846 and roxatidine-like compounds.

[+)] Dedicated to Prof. Dr. *H. Schönenberger*, Regensburg, on the occasion of his 70th birthday.

Results and Discussion

Synthesis

The synthesis of 4-(3-nitro-1-pyrazolyl)butanenitrile (**5**), a key intermediate in the preparation of the title compounds, was accomplished starting from pyrazole (**1**) by *N*-nitration, rearrangement to 3-nitropyrazole **3**, and *N*-alkylation with 4-chlorobutanenitrile (**4**) (Scheme 2). The main product **5** could be separated from its isomer **6** by flash chromatography. Compound **5** could be easily hydrolysed in hydrochloric acid resulting in the butanoic acid **7**. The latter was converted into the corresponding imidazolide by reaction with *N,N'*-carbonyldiimidazole (CDI) and subsequently treated with the primary amines **8a–d** which represent characteristic substructures of the main classes of H_2-receptor antagonists. The nitro group of amine **9a** was hydrogenated to form the aminopyrazole **10a**, that turned out to be a useful building block for the preparation of the carbonic acid derivatives **12a**, **13a**, **15a**, **17a–20a**. The cyanoguanidines **12a**, **13a** were prepared start-

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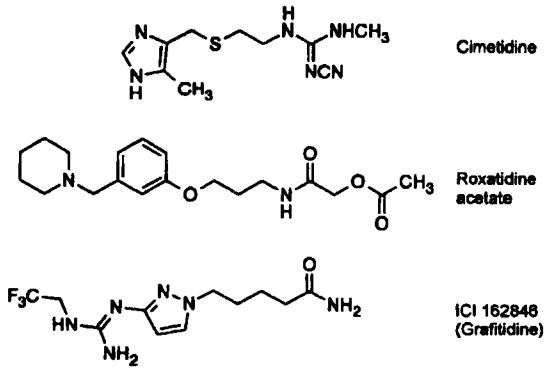
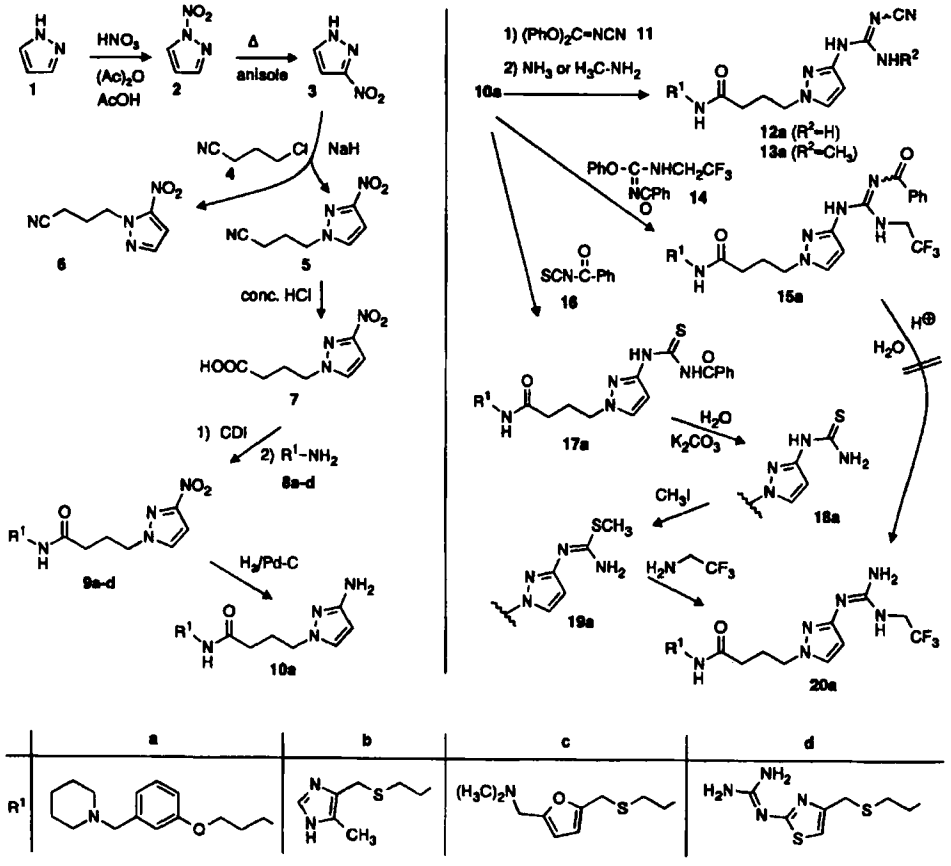


Scheme 1

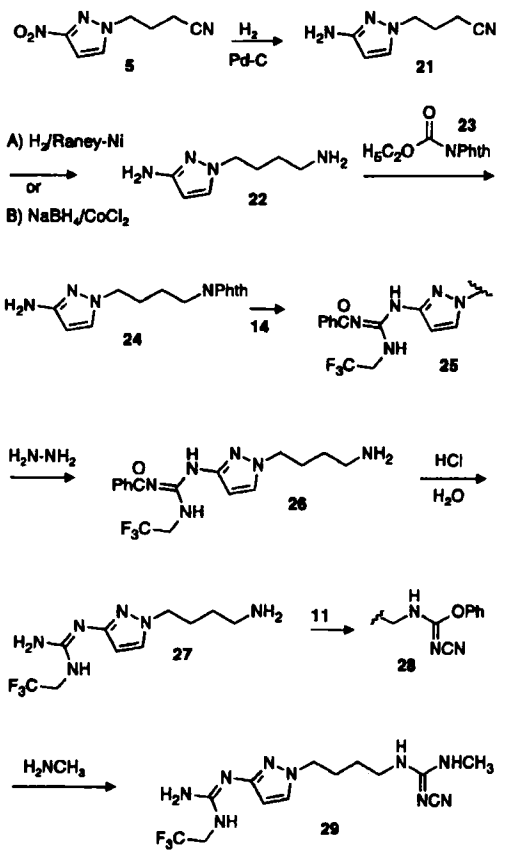
ing from equimolar amounts of **10a** and diphenyl cyanocarbonimidate (**11**) followed by treatment of the intermediate *N*-cyano-*O*-phenyl isourea with an excess of ammonia or methylamine. The benzoylguanidine **15a** was analogously prepared from **10a** and the isourea **14**. The latter was obtained by treating *N*-(diphenoxymethylene)benzamide with trifluoroethylamine. The benzoyl group in **15a** could not be removed by hydrolysis in hydrochloric acid without marked decomposition and formation of by-products. Therefore, the trifluoroethylguanidine **20a** was synthesized starting from **10a** by addition to benzoylisothiocyanate (**16**), basic hydrolysis (thiourea **18a**), *S*-methylation, and aminolysis of the isothiourea **19a**.

The nitro group and the nitrile function in **5** could be consecutively reduced by catalytic hydrogenation over Pd-C catalyst (*cf.* compd. **21**, Scheme 3) and *Raney*-nickel in liquid ammonia as the solvent, respectively (**22**) (method A). The second reduction step can also be carried out with $NaBH_4$ using $CoCl_2$ for activation (method B), however, route A was preferred owing to a higher yield. The monoprotection of **22** was achieved by using an equimolar amount of *N*-ethoxycarbonyl phthalimide (**23**), as the more nucleophilic aliphatic amino group preferably attacks **23**. Aminolysis of **14** with **24** resulted in the benzoylguanidine **25**. Hydrazinolysis of the phthalimide ring followed by acid hydrolysis of the benzoylguanidine group in **26** resulted in the guanidine-substituted pyrazolylbutylamine **27** which was then allowed to react consecutively with **11** and methylamine affording cyanoguanidine **29**.

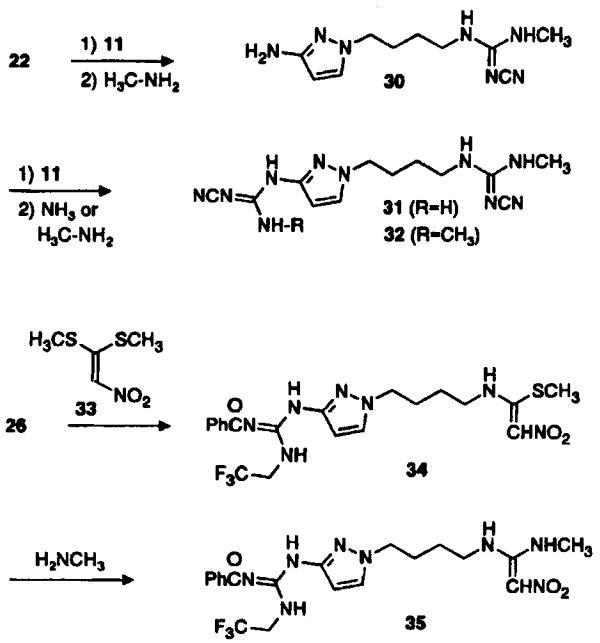
The bifunctional amine **22** could also be selectively converted into cyanoguanidine **30** by reaction with an equimolar amount of **11** and an excess of methylamine (Scheme 4). Subsequently, a second cyanoguanidine group could be introduced by treatment with an additional equivalent of **11** followed by ammonolysis or aminolysis (**31**, **32**). For the preparation of the nitroethenediamine **35**, amine **26** was first allowed to react with 1,1-bis(methylthio)-2-nitroethene (**33**) to form the ketene-*N*,*S*-acetal **34** which was subsequently treated with methylamine. For comparison, compounds **36**–**43** (Scheme 5), which are devoid of a pyrazole ring, were prepared as they show structural analogy in the so-called



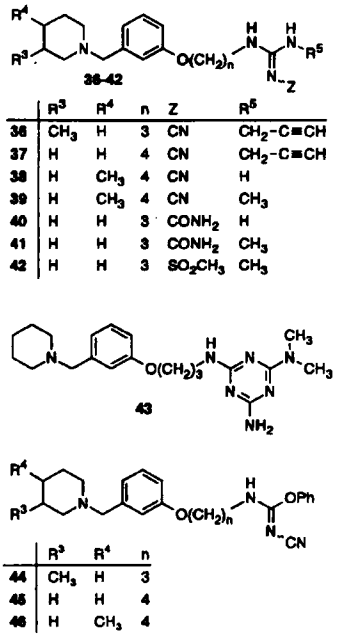
Scheme 2



Scheme 3



Scheme 4



Scheme 5

'urea equivalent' moiety and in the aminomethylphenoxyalkyl substructure of the H_2-receptor antagonists (*cf.* compds. with letter code 'a'). The cyanoguanidines **36–39** and the methanesulfonylguanidines were synthesized by successive aminolysis of the appropriate diphenyl carbonimidates, whereas the carbamoylguanidines **40** and **41** were obtained from the pertinent cyanoguanidines by hydrolysis in hydrochloric acid at room temp. The triazine **43** was synthesized by way of a described procedure [4] (analytical data *cf.* Table 1, Exper. Part).

Pharmacology

The compounds **9a–d, 10a, 12a, 13a, 15a, 18a, 20a, 29,** and **30–43** as well as some reference substances were investigated for histamine H_2-receptor antagonist activity at the isolated spontaneously beating guinea pig right atrium [5] (inhibition of the histamine-stimulated increase in heart rate). Additionally, selected substances were also tested for inhibition of the histamine-stimulated gastric acid secretion in anaesthetized rats. The results are summarized in Table 2.

For the reference antagonists, pA_2 values [6] can be determined with a slope not significantly different from unity. Of the H_2-receptor antagonists currently on the market famotidine is the most potent in the isolated guinea pig atrium preparation. Whereas cimetidine and ranitidine do not affect the maximum increase in heart rate, famotidine induces a slight depression of the histamine concentration response curve by about 10 % over the dose range used [7]. By contrast, many of the new compounds induced a pronounced dose-dependent depression of the concentration response curves. Therefore, investigations over a wider dose range were not carried out and pK_B [8] instead of pA_2 values were calculated for the antagonist concentrations tested (Table 2).

Guinea pig atrium

A series of substances showed strong H_2-receptor antagonist properties in the guinea pig atrium preparation. For example the aminopyrazolebutanamide **9a** with a roxatidine-like substituent at the amide-*N* was found to be about 6 times more potent than famotidine. The concentration response curve of histamine was shifted to the right, however, in contrast to famotidine, **9a** thereby additionally produced a considerable depression of the maximum response, indicating more pronounced non-competitive properties. The amide with cimetidine-like partial structure, **9b**, was inactive in the concentrations used whereas the activity of the furan and thiazole analogues **9c** and **9d** was in the same range as those of ranitidine and famotidine, respectively. Hydrogenation of the nitro group in **9a** induced an approximately 6-fold decrease in activity (**10a**). Incorporation of the amino-*N* into a cyanoguanidine, benzoylguanidine, thiourea, or trifluoroethylguanidine system resulted in a further more or less pronounced decrease in antagonist potency compared to **10a**. An additional 'urea equivalent' as in **12a**, **13a**, **15a**, **18a**, and **20a** does not appear to be of advantage. On the other hand, the trifluoroethylguanidine-substituted pyrazole ring may confer H_2-receptor affinity similar to the piperidinomethylphenoxy, dimethylaminomethylfuran, or the guanidinothiazole moiety in the therapeutically used drugs. Compound **29**, an analogue of ICI 162846 characterized by a cyanoguanidine instead of an amide group, displayed very strong H_2-receptor antagonist activity achieving a pK_B of about 8 in the atrium preparation. Similar activities were also found for **36**, **37**, and **43**. As demonstrated by compounds **36–43** multiple structural changes are tolerated in the polar group of piperidinomethylphenoxyalkylamine-type antagonists.

Gastric acid secretion

The shape of the histamine concentration response curve on the atrium in the presence of **9a** resembles that after dosage of 'insurmountable' H_2-receptor antagonists [9] such as the highly potent triazole derivative loxtidine [10], which is one of several long-acting antisecretory agents suspected of producing severe side-effects on neuroendocrine cells during long-term treatment [11, 12]. However, though **9a** was the most potent H_2-receptor blocker in the atrium, the substance did not affect histamine-stimulated gastric acid secretion at a dosage of 0.1 µmol/kg. Therefore, **9a** was not further investigated. Nevertheless, discrepancies between gastric and cardiac effects are frequently found and may, for instance, be associated with pharmacokinetics and metabolism or - as demonstrated *in vitro* - with the hydrophobicity of the compounds [13,14]. Comparing the cardiac effects of **9a** *versus* **12a** and **20a**, a rather low activity should be anticipated for the latter two compounds in the stomach. However, in Ghosh-Schild rats **12a** and **20a** are comparable to famotidine and by far superior to **9a**, cimetidine, and ranitidine. Acid secretion was completely blocked by 0.1 and 0.05 µmol/kg of **12a** and **20a**, respectively. The guanidinopyrazole **29** proved to be the most potent antisecretory agent tested in this series. The compound inhibited histamine-stimulated gastric acid secretion by 74 % at a dosage of 0.025 µmol/kg.

In conclusion, piperidinomethylphenoxypropanamine, an essential partial structure of roxatidine and related H_2-receptor antagonists, may be converted into the amide of cyanoguanidino- or trifluoroethylguanidino-substituted pyrazolylbutanoic acids resulting in potent H_2-receptor blockers (**12a**, **20a**) *in vitro* and *in vivo*. In order to obtain H_2 blockers with promising activity, it is not necessary to combine structural features of both roxatidine and ICI 162846, thereby in some way doubling the putative pharmacophores. This can be seen in compound **29**, where a cyanoguanidine group as a conventional 'urea equivalent' is incorporated instead of the amide in ICI 162846. Compound **29** is both a highly active H_2-receptor antagonist on the guinea pig right atrium and a very potent inhibitor of gastric acid secretion in the rat.

The authors are grateful to Dr. *H. Engler*, Heumann Pharma (Nuremberg, Germany), for the investigations on Ghosh-Schild rats and to *Mrs. M. Ewald* for the performance of the pharmacological experiments on the guinea pig atrium. The Fonds der Chemischen Industrie is thanked for a grant.

Experimental Part

Chemistry

M.p. (uncorrected): melting point apparatus Büchi 512.- Elemental analyses: Perkin-Elmer 240B and 240C.- ^{1}H-NMR: Bruker WM 250 (250 MHz) and Bruker AC 300 (300 MHz), TMS as internal reference.- EI-MS: Finnigan MAT CH7A (170 °C, 70 eV), Finnigan MAT 711 (200 °C, 80 eV), and Kratos MS 25 RF (250 °C, 70 eV); $^+$FAB-MS, $^-$FAB-MS: (xenon; DMSO/glycerol): Finnigan MAT CH5DF. Prep. chromatography: Chromatotron 7924T (Harrison Research); glass rotors with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck). Short path distillation: Kugelrohr apparatus (Büchi GKR-50).

4-(3-Nitro-1-pyrazolyl)butanenitrile (**5**)

N-Nitropyrazole (**2**, yield 90 %, m.p. 91–92 °C, ref. [15]: 92–93 °C) and 3-nitropyrazole (**3**, yield 94 %, m.p. 172–173 °C, ref. [16]: 174–175 °C) are prepared according to known procedures [15,16]. Compound **3** (113.08 g, 1 mol) is added in portions to a stirred suspension of NaH (1.05 mol) in DMF. After the evolution of gas has ceased a catalytic amount of KI is added and **4** is dropped into the reaction mixture. The mixture is stirred for 7 h at 50 °C, chilled, and diluted with water. The crude products **5** and **6** (174.6 g) are obtained as an oil by extraction with $CHCl_3$. Isolation of the isomer **5** is achieved by flash chromatography (1 kg of silica gel for 87.3 g of isomers **5** and **6**, column width 80 mm, EtOAc/petroleum ether (b.p. 40-60 °C), 3 + 7). Yield 128.5 g (71 %) **5**, and 20.6 g (11 %) **6**. For analytical purposes **5** is purified by Kugelrohr distillation *in vacuo* (bath temp.$_{0.05}$: 170-190 °C). The structural isomer **6** is not further investigated (^{1}H-NMR of **6** (300 MHz, $CDCl_3$): δ (ppm) = 7.56 (d, J = 2.2 Hz, 1H, Pyr-3-H), 7.10 (d, J=2.2 Hz, 1H, Pyr-4-H), 4.74 (t, J = 6.5 Hz, 2H, Pyr-C*H*$_2$), 2.47 (m, 2H, C*H*$_2$-CN), 2.31 (m, 2H, C*H*$_2$-CH_2CN)).

4-(3-Nitro-1-pyrazolyl)butanoic acid (**7**)

The nitrile **5** (12.13 g, 67 mmol) is hydrolysed by heating under reflux in 35 ml of conc. HCl for 2 h. The mixture is chilled, the precipitated product is filtered off, washed with water, and dried. Yield 12.61 g (94 %) **7**. An analytical sample is recrystallized from water.

4-(3-Nitro-1-pyrazolyl)-N-{3-[3-(1-piperidinylmethyl)phenoxy]propyl}-butanamides **9a–d**

Compound **7** (6 g, 3 mmol) is added to *N,N'*-carbonyldiimidazole (5.13 g, 31 mmol) in 20 ml anhydrous DMF and stirred for 30 min at room temp. A solution of 3 mmol of the pertinent primary amine base **8a–d** in 10 ml DMF is added dropwise and the mixture is stirred for further 6 h. Subsequently, an aqueous NaCl solution is added and the butyramides **9a–d** are isolated by extraction with either Et_2O (**9a**), EtOAc/nBuOH (50 + 50) (**9b**), or EtOAc

(**9c,d**). The main portion of **9a** may be used for further reactions without purification. The compounds are chromatographed (Chromatotron, $CHCl_3$/MeOH, 99+1 (**9a,c**) or 90 + 10 (**9b,d**), NH_3 atmosphere) affording **9a** as an oil whereas **9d** solidifies and can be recrystallized from MeCN.

4-(3-Amino-1-pyrazolyl)-N-{3-[3-(1-piperidinylmethyl)phenoxy]propyl}-butanamide (**10a**)

The nitropyrazole **9a** (9.5 g, 22 mmol) is dissolved in 150 ml THF and hydrogenated over 600 mg Pd-C (10 %) for 40 h at 1 bar. After removal of the catalyst by filtration and evaporation of the solution, **10a** is obtained as an oil which can be used for further reactions without purification. A sample for analytical and pharmacological investigation is purified chromatographically (Chromatotron, $CHCl_3$/MeOH, 99+1, NH_3 atmosphere).

Cyanoguanidines **12a**, **13a**

A mixture of **11** (0.626 g, 2.6 mmol), **10a** (1.05 g, 2.6 mmol), and 5 ml Et_3N in 25 ml MeCN is stirred for 2 h at room temp. The volatiles are removed *in vacuo* and the crude *N*-cyano-*O*-phenylisourea is directly treated with either 30 ml of methanolic NH_3 (**12a**) at room temp. for 12 h, or 20 ml of 30 % ethanolic methylamine under reflux for 5 min. The reaction mixtures are evaporated to dryness. Compound **12a** crystallizes on treating with Et_2O (recrystallization from EtOH/H_2O). Crude **13a** is dissolved in EtOAc, the org. layer is washed consecutively with 2 % aqueous NaOH and water, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining oil is chromatographed (Chromatotron, $CHCl_3$/MeOH, 98+2, NH_3 atmosphere), and compound **13a** is crystallized from $CHCl_3$ (recrystallization from EtOH/H_2O).

N-[(Phenoxy)(2,2,2-trifluoroethylamino)methylene]benzamide (**14**)

N-Diphenoxymethylene benzamide (4.76 g, 0.015 mol) [17] is dissolved in 25 ml CH_2Cl_2, 3 ml of a 50 % solution of 2,2,2-trifluoroethylamine in CH_2Cl_2 are added and the mixture is allowed to react at room temp. under control by TLC (silica gel F_{254}, $CHCl_3$). If necessary further trifluoroethylamine is added until the reaction is complete. After dilution with CH_2Cl_2 the org. layer is washed with 5 % NaOH in order to remove phenol and dried over Na_2SO_4. Evaporation of the solvent results in slowly crystallizing **14** which is recrystallized from EtOH.

N-{N-[1-[3-[N-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]carbamoyl]-propyl]-3-pyrazolyl]-N'-(2,2,2-trifluoroethyl)diaminomethylene}benzamide (**15a**)

Compounds **10a** (1.05 g, 2.6 mmol) and **14** (0.85 g, 2.6 mmol) are heated under reflux for 5 h in 25 ml of anhydrous pyridine. The mixture is chilled and evaporated to dryness, the residue is dissolved in Et_2O and washed with water. Evaporation of the solvent results in crystalline **15a**.

N-Benzoyl-N'-{1-[3-[N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-carbamoyl]propyl]-3-pyrazolyl}thiourea (**17a**)

A mixture of **10a** (2.15 g, 5.4 mmol) and **16** (0.88 g, 5.4 mmol) in 50 ml of $CHCl_3$ is stirred for 1 h at room temp. Subsequently the solution is evaporated *in vacuo*, the residue is crystallized from Et_2O and recrystallized from MeCN.

N-{1-[3-[N-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]carbamoyl]-propyl]-3-pyrazolyl}-thiourea (**18a**)

The benzoylthiourea **17a** (2.41 g, 4.3 mmol) is refluxed for 10 min with K_2CO_3 (1.24 g, 9 mmol) in MeOH (60 ml) and water (20 ml). The solution is concentrated *in vacuo*, diluted with water and extracted with $CHCl_3$. The org. layer is washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining oil is treated with Et_2O affording crystalline **18a** (recrystallization from EtOH/H_2O).

N-{3-[3-(1-Piperidinylmethyl)phenoxy]propyl}-4-{3-[N-(2,2,2-trifluoroethyl)diaminomethylene]amino-1-pyrazolyl}butanamide (**20a**)

The thiourea **18a** (1.65 g, 3.6 mmol) is stirred overnight with MeI (0.27 ml, about 4.3 mmol) in 20 ml of EtOH at room temp. The solution is concentrated and the remaining *S*-methylisothiuronium iodide **19a** is directly heated under reflux for 30 h in 20 ml of a 50 % ethanolic solution of trifluoroethylamine. The volatiles are removed *in vacuo*, the residue is dissolved in $CHCl_3$, the org. layer is washed consecutively with aqueous NH_3 and water, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining oil is chromatographed (Chromatotron, $CHCl_3$/MeOH, 98+2, NH_3 atmosphere) affording crystalline **20a**.

4-(3-Amino-1-pyrazolyl)butanenitrile (**21**)

The nitropyrazole **5** (29.93 g, 0.17 mol) is hydrogenated in 200 ml of THF over 0.9 g Pd-C (10 %) at 1 bar for 12 h. The catalyst is filtered off and the solvent is removed *in vacuo* affording **21** as a chromatographically pure oil. An analytical sample is distilled in a Kugelrohr (bath temp.$_{0.05}$: 165–180 °C).

4-(3-Amino-1-pyrazolyl)butanamine (**22**)

Method A: The nitrile **21** (11.88 g, 0.079 mol) is hydrogenated for 48 h at room temp. in 200 ml of liquid NH_3 over *Raney*-Ni (freshly prepared from 6 g of Al-Ni *Raney*-type alloy powder) in an autoclave (about 18 bar: H_2 pressure 10 bar + NH_3 pressure *ca.* 8 bar). After removal of the volatiles the residue is stirred with EtOH, the catalyst is filtered off, and the solvent is removed *in vacuo*. The remaining amine base **22** shows a wax-like consistency. An analytical sample is converted into the dipicrate.

Method B: $NaBH_4$ (20.08 g, 0.52 mol) is slowly (within 2 h) added at room temp. to a solution of **21** (7.80 g, 0.052 mol) and $CoCl_2.6H_2O$ (25.2 g, 0.106 mol) in 300 ml MeOH. The mixture is stirred for a further 30 min. Subsequently conc. HCl (100 ml) is added and stirring is continued until precipitated inorg. material re-dissolves. The solution is evaporated *in vacuo*, the residue is dissolved in 500 ml water, and made alkaline with aqueous NH_3. For removal of cobalt the mixture is repeatedly gassed with H_2S and filtered until the mother liquor remains colourless. The aqueous solution is evaporated, remaining water is removed by azeotropic distillation with EtOH. Amine **22** is separated from inorg. material by extraction with iPrOH and purified chromatographically (Chromatotron, $CHCl_3$/Methanol 9+1, NH_3 atmosphere) or *via* the dipicrate.

N-[4-(3-Amino-1-pyrazolyl)butyl]phthalimide (**24**)

Ethoxycarbonylphthalimide (**23**) (8.55 g, 39 mmol) is added in portions within 3–4 h to a solution of **22** (6 g, 39 mmol) in 90 % EtOH (20 ml) and stirred overnight. After addition of $CHCl_3$ compound **24** is extracted from the org. layer with cold 1M HCl. The acidic aqueous solution is washed with Et_2O, made alkaline with dil. aqueous NH_3, and extracted with $CHCl_3$. After evaporation of the org. solvent, **24** is obtained as an oil that slowly crystallizes. The compound may be recrystallized from EtOH/H_2O as fine white needles containing water which is removed on drying *in vacuo*.

N-{N-[1-(4-Phthalimidobutyl)-3-pyrazolyl]-N'-(2,2,2-trifluoroethyl)-diaminomethylene}benzamide (**25**)

The compounds **24** (2.84 g, 10 mmol) and **14** (3.22 g, 10 mmol) are dissolved in 30 ml of pyridine and refluxed for 12 h. The solution is evaporated to dryness *in vacuo*. The brown residue is treated with iPrOH and crystallized by storing in a refrigerator. Crude **25** is pure enough for further reactions. An analytical sample is recrystallized from iPrOH.

N-{N-[1-(4-Aminobutyl)-3-pyrazolyl]-N'-(2,2,2-trifluoroethyl)diamino-methylene}benzamide (**26**)

The phthalimide **25** (4.6 g, 9 mmol) is heated under reflux for 3 h with hydrazine hydrate (2 ml) in 25 ml of a 1 + 1 (*v/v*) mixture of CH_2Cl_2 and EtOH. After dilution with CH_2Cl_2 the org. layer is washed repeatedly with water, dried over Na_2SO_4 and evaporated *in vacuo*. Trituration of the remaining oil with Et_2O results in crystalline **26**. Purification for analysis may be achieved by chromatography (Chromatotron, $CHCl_3$/MeOH, 98+2, NH_3 atmosphere) followed by crystallization from Et_2O.

4-{3-[N-(2,2,2-Trifluoroethyl)diaminomethylene]amino-1-pyrazolyl}-butanamine (**27**)

The benzamide **26** (5.2 g, 13.6 mmol) is refluxed in 25 ml of 5M HCl for 1 h. The solution is chilled, washed twice with Et_2O and evaporated to dryness *in vacuo*. The residue is treated with methanolic NH_3, precipitated

inorg. material is filtered off and washed with iPrOH. The alcoholic extract of **27** is concentrated and chromatographed (Chromatotron, $CHCl_3$/MeOH, 9+1, NH_3 atmosphere) affording **27** as an oil. An analytical sample is converted into the dipicrate.

N-Cyano-O-phenyl-N'-[4-[3-[N-(2,2,2-trifluoroethyl)diamino-methylene]amino-1-pyrazolyl]-butyl]isourea (28)

Amine **27** (1 g, 3.6 mmol) is added to a suspension of **11** (0.86 g, 3.6 mmol) in 20 ml MeCN and stirred for 30 min. Subsequently the mixture is concentrated *in vacuo*, treated with Et_2O, and stored for crystallization in a refrigerator. The isourea **28** is filtered off, washed with cold Et_2O, and recrystallized from MeCN.

N-Cyano-N'-methyl-N''-[4-[3-[N-(2,2,2-trifluoroethyl)diamino-methylene]amino-1-pyrazolyl]butyl]guanidine (29)

Compound **28** (0.5 g, 1.2 mmol) is stirred for 30 min at room temp. with 30 % ethanolic methylamine (20 ml). The volatiles are removed *in vacuo*, **29** is obtained as an oil after chromatographic purification (Chromatotron, $CHCl_3$/MeOH, 90+10, NH_3 atmosphere).

N-[4-(3-Amino-1-pyrazolyl)butyl]-N'-cyano-N''-methylguanidine (30)

Diphenyl *N*-cyanocarbonimidate **11** (3.2 g, 13 mmol) is slowly added to a solution of **22** (2.07 g, 13 mmol) in a mixture of EtOH (20 ml) and Et_3N (5 ml). The mixture is stirred for 1 h and subsequently evaporated to dryness *in vacuo*. The residue is directly treated with 30 % ethanolic methylamine (25 ml) and refluxed for 5 min. The volatiles are removed *in vacuo*, compound **30** is purified chromatographically (Chromatotron, $CHCl_3$/MeOH, 95+5, NH_3 atmosphere) and recrystallized from MeCN.

Cyanoguanidines **31** *and* **32**

The compounds **30** (1.05 g, 4.5 mmol) and **11** (1.06 g, 4.5 mmol) are stirred for 6 h in 30 ml of a THF/iPrOH (2 + 1) mixture. The solution is concentrated *in vacuo* and the residue is stirred at room temp. either with 30 ml of methanolic NH_3 for 12 h or with 20 ml of 30 % ethanolic methylamine. After removal of the volatiles *in vacuo* **31** is obtained as an amorphous solid after chromatographic purification (Chromatotron, $CHCl_3$/MeOH, 95+5, NH_3 atmosphere). **32** crystallizes from Et_2O (recrystallization from MeCN).

Table 2: Histamine H_2 antagonism on the isolated guinea pig right atrium and inhibitory activity on histamine-stimulated gastric acid secretion in Ghosh-Schild rats.

	H_2 antagonism (guinea pig atrium)			acid secretion (rat)	
compd.	pK_B[a]	antagonist conc. [μM]	depression of conc. response curve. %	dosage, μmol/kg. *i.v.*	inhibition %[b]
cimetidine	6.40	0.3 – 10.0	–	0.1	0
				0.5	7
ranitidine	7.20	0.1 – 3.0	–	0.1	41
				0.5	64
famotidine	7.80	0.01 – 0.3	10	0.05	89
9a	8.59	0.03	29	0.1	0
		1.0	42		
9b	inactive	≤10.0	–		
9c	7.10	0.1	–		
9d	8.10	0.3	9		
10a	7.83	0.03	9		
		0.1	24		
12a	7.69	0.1	14	0.1	100
				0.05	71
13a	7.18	0.1	7		
15a	6.57	3.0	36		
18a	7.64	0.1	10		
20a	7.53	0.1	16	0.05	100
				0.025	50
29	8.04	0.03	13	0.025	74
				0.01	36
30	5.70	3.0	22		
31	inactive	≤1000	–		
32	inactive	≤1000	–		
35	5.70	3.0	25		
		10.0	50		
36	8.14	1.0	10		
37	8.19	1.0	12		
38	7.40	0.3	–		
39	7.99	1.0	–		
40	7.42	0.3	–		
41	inactive	1.0	–		
42	7.45	0.1	10		
43	8.05	0.3	15		

[a] mean of at least 3-5 independent experiments. SEM within ± 0.2; for cimetidine, ranitidine, famotidine: n > 10
[b] mean of 2-4 experiments.

Table 1: Preparative and analytical data.

no	yield %	m.p. (solvent)	formula (mol. mass)	analysis: C	H	N	calcd. found	^{1}H-NMR (δ ppm, TMS as internal reference; J in Hz) [a] MS (EI, $^+$FAB, $^-$FAB): m/z (rel. intensity, %)
5	71	oil (hygr.)	$C_7H_8N_4O_2$ (180.2)	46.67 46.47	4.48 4.36	31.10 30.89		(250 MHz, $CDCl_3$) 7.63 (d, J = 2.5, 1H, Pyr-5-H), 6.94 (d, J = 2.5, 1H, Pyr-4-H), 4.40 (t, J = 6.5, 2H, Pyr-CH_2), 2.47 (m, 2H, CH_2-CN), 2.35 (m, 2H, CH_2-CH_2CN) (EI 80 eV): 180 ($M^{+\bullet}$, 23), 163 (100)
7	95	121–123 (H_2O)	$C_7H_9N_3O_4$ (199.2)	42.21 41.96	4.55 4.52	21.10 21.05		(300 MHz, [D_6]DMSO) 12.23 (br, 1H, COOH), 8.05 (d, J = 2.5, 1H, Pyr-5-H), 7.05 (d, J = 2.5, 1H, Pyr-4-H), 4.27 (t, J = 7, 2H, Pyr-CH_2), 2.25 (t, J = 7.5, 2H, CH_2-CO), 2.04 (tt, J = 7/7, 2H, Pyr-CH_2-CH_2) ($^-$FAB): 198 ([M–H]$^-$, 92), 112 (100)
9a	94	oil	$C_{22}H_{31}N_5O_4$ (429.5)	61.52 61.53	7.27 7.37	16.31 16.10		(300 MHz, $CDCl_3$) 7.50 (d, J = 2.5, 1H, Pyr-5-H), 7.20 (dd, J = 8/8, 1H, Ph-5-H), 6.95–6.80 (m, 3H, 2Ph-H and Pyr-4-H), 6.75 (m, 1H, ar.), 6.13 (m, 1H, CO-NH), 4.30 (t, J = 6.5, 2H, Pyr-CH_2), 4.04 (t, J = 5.8, 2H, OCH_2), 3.46 (dt, J = 6/6, 2H, CH_2NH), 3.43 (s, 2H, CH_2-Ph), 2.37 (m, 4H, CH_2-N-CH_2), 2.30–2.10 (m, 4H, CO-$(CH_2)_2$), 2.0 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.56 (m, 4H, $2CH_2$), 1.43 (m, 2H, CH_2) (EI 80 eV): 429 ($M^{+\bullet}$, 9), 84 (100)
9b	90	oil	$C_{14}H_{20}N_6O_3S$ (352.4)	47.71 47.38	5.72 5.88	23.85 23.96		(300 MHz, [D_6]DMSO) 8.07 (m, 1H, CO-NH), 8.04 (d, J = 2.5, 1H, Pyr-5-H), 7.43 (s, 1H, Im-2-H), 7.06 (d, J = 2.5, 1H, Pyr-4-H), 4.25 (m, 2H, Pyr-CH_2), 3.64 (s, 2H, Im-CH_2-S), 3.22 (dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.55–2.4 (m, 2H, S-CH_2CH_2), 2.3–1.9 (m, 4H, CO-$(CH_2)_2$), 2.13 (s, 3H, Im-CH_3) (EI 80 eV): 352 ($M^{+\bullet}$, 6), 96 (100)
9c	66	oil	$C_{17}H_{25}N_5O_4S$ (395.5)	51.63 51.20	6.37 6.41	17.71 17.64		(300 MHz, [D_6]DMSO) 8.1–7.95 (m, 1H, NH), 8.05 (d, J = 2.5, 1H, Pyr-5-H), 7.06 (m, 1H, Pyr-4-H), 6.22 (1H) and 6.18 (1H) (AB-system, Fur-3-H, Fur-4-H), 4.26 (t, J = 6.5, 2H, Pyr-CH_2), 3.76 (s,2H, Fur-CH_2S), 3.37 (s, 2H, Fur-CH_2-N), 3.21 (dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.6–2.4 (t, 2H S-CH_2-CH_2), 2.2–1.95 (m, 10H, $N(CH_3)_2$ and $CO(CH_2)_2$) (EI 80 eV): 395 ($M^{+\bullet}$, 1), 137 (100)
9d	76	108–110 (MeCN)	$C_{14}H_{20}N_8O_3S_2$ (412.5)	40.77 40.96	4.89 4.91	27.16 27.15		(300 MHz, [D_6]DMSO) 8.03 (m, 1H, Pyr-5-H), 8.0 (m, 1H, CO-NH), 7.05 (d, J = 2.5, 1H, Pyr-4-H),7.2–6.5 (br, 4H, NH). 6.49 (m, 1H, Thz-5-H), 4.24 (t, J = 6.5. 2H, Pyr-CH_2), 3.6 (s, 2H, Thz-CH_2), 3.23 (dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.55–2.4 (m, 2H, S-CH_2-CH_2), 2.15–1.9 (m, 4H, CO-$(CH_2)_2$) (EI 80 eV): 412 ($M^{+\bullet}$, 2), 182 (100)
10a	88	oil	$C_{22}H_{33}N_5O_2$ (399.5)	66.14 65.88	8.32 8.57	17.53 17.61		(300 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 7.10 (d, J = 2, 1H, Pyr-5-H), 6.95–6.80 (m, 2H,ar.), 6.80–6.70 (m, 1H, ar.), 6.43 (m, 1H, CO-NH), 5.54 (d, J = 2, 1H, Pyr-4-H), 4.05 (t, J = 6, 2H, OCH_2), 3.98 (t, J = 6, 2H, Pyr-CH_2), 3.58 (m, 2H, NH_2), 3.50–3.30 (m, 2H, CH_2-NH), 3.44 (s, 2H, CH_2-Ph), 2.37 (m, 4H, CH_2-N-CH_2), 2.20–2.05 (m, 4H, CO-$(CH_2)_2$), 2.0 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.65–1.5 (m, 4H, $2CH_2$),1.43 (m, 2H, CH_2) (EI 70 eV): 399 ($M^{+\bullet}$, 13), 96 (100)
12a	57	91 (EtOH/ H_2O)	$C_{24}H_{34}N_8O_2$ •0.75 H_2O (480.1)	60.04 60.12	7.45 7.29	23.34 23.27		(300 MHz, $CDCl_3$) 10.2–8.2 (very br, 2H, NH), 7.26 (d, J = 2.5. 1H, Pyr-5-H), 7.2 (dd, J = 8/8, 1H, Ph-5-H), 6.9–6.8 (m, 2H, ar.), 6.8–6.7 (m, 1H, ar.), 6.5 (br, 1H, NH), 6.31 (m, 1H, CO-NH), 5.94(d, J = 2.5, 1H, Pyr-4-H), 4.08 (m, 2H, Pyr-CH_2), 4.02 (t, J = 5.8, 2H, OCH_2), 3.5–3.3 (m, 2H, CH_2-NH), 3.44 (s, 2H, CH_2-Ph), 2.39 (m, 4H, CH_2-N-CH_2), 2.15 (m, 4H, CO-$(CH_2)_2$), 1.98 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.6–1.45 (m, 4H, $2CH_2$),1.4 (m, 2H, CH_2) ($^+$FAB): 467 ([M+H]$^+$, 11), 98 (100)
13a	74	123–126 (EtOH/ H_2O)	$C_{25}H_{36}N_8O_2$ •0.25 H_2O (485.1)	61.33 61.59	7.62 7.59	22.89 22.97		(300 MHz, $CDCl_3$) 8.48 (br, 1H[b], NH), 8.26 (br, 1H[b], NH), 7.26 (d, J = 2.5, 1H, Pyr-5-H), 7.21 (dd, J = 8/8, 1H, Ph-5-H), 6.95–6.8 (m, 2H, ar.), 6.8–6.65 (m, 1H, ar.), 6.01 (m, 1H, CO-NH[c]),5.94 (d, J = 2.5, 1H, Pyr-4-H), 4.15–3.9 (m, 4H, OCH_2 and Pyr-CH_2), 3.5–3.3 (m, 2H, CH_2-NH), 3.47 (s, 2H, CH_2-Ph), 2.94 (d, J = 2.5, 3H, NH-CH_3), 2.4 (m, 4H, CH_2-N-CH_2), 2.3–2.05 (m, 4H, CO-$(CH_2)_2$), 1.99 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.7–1.5 (m, 4H, $2CH_2$), 1.43 (m, 2H, CH_2) ($^+$FAB): 481 ([M+H]$^+$, 15), 98 (100)
14	93	120–121 (EtOH)	$C_{16}H_{13}F_3N_2O_2$ (322.3)	59.63 59.74	4.07 3.88	8.69 8.78		(250 MHz, [D_6]DMSO) 10.13 (br, 1H[b], NH), 7.85–7.8 (m, 2H, ar.), 7.65–7.5 (m, 3H, ar.), 7.5–7.35 (m, 3H, ar.), 7.35–7.2 (m, 2H, ar.), 4.4 (m, 2H, CH_2-NH) ($^+$FAB): 323 ([M+H]$^+$, 51), 105 (100)
15a	74	73–75 (Et_2O)	$C_{32}H_{40}F_3N_7O_3$ (627.7)	61.23 61.24	6.42 6.50	15.62 15.57		(300 MHz, $CDCl_3$) 13.12 and 12.79 (m, 1H[b], NH), 9.09 and 8.68 (m, 1H[b], NH), 8.22 and 8.04(m, 2H, ar.), 7.7–7.38 (m, 3H, ar.), 7.3 (d. J = 2.5. 1H, Pyr-5-H), 7.2 (dd, J = 8/8, 1H, Ph-5-H), 6.95–6.8 (m, 2H, ar.), 6.8–6.7 (m, 1H, ar.), 5.95–5.8 (m, 1H, CO-NH[c]), 5.9 (d, J = 2.5, 1H, Pyr-4-H), 4.4 (m, 2H, NH-CH_2-CF_3[d]), 4.13 (m, 2H, Pyr-CH_2), 4.04 (m, 2H, OCH_2). 3.46 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 3.41 (s, 2H, CH_2-Ph), 2.35 (m, 4H, CH_2-N-CH_2), 2.23–2.05 (m, 4H, CO-$(CH_2)_2$), 1.99 (m, 2H, OCH_2-CH_2),1.65–1.25 (m, 6H, $3CH_2$) ($^+$FAB): 628 ([M+H]$^+$, 7), 105 (100)
17a	86	107–109 (MeCN)	$C_{30}H_{38}N_6O_3S$ (562.7)	64.03 63.53	6.81 6.77	14.93 14.97		(300 MHz, $CDCl_3$) 12.9 (br, 1H[b], NH), 9.8–8.1 (very br, 1H[b], NH), 7.87 (m, 2H, ar.), 7.7–7.4 (m, 3H, ar.), 7.35 (d, J = 2.5, 1H, Pyr-5-H), 7.18 (dd, J = 8/8, 1H, Ph-5-H), 7.07 (d, J = 2.5, 1H, Pyr-4-H), 6.95–6.6 (m, 3H, ar.), 6.32 (m, 1H, CO-NH[c]), 4.14 (m, 2H, Pyr-CH_2), 4.06 (t, J = 5.8, 2H, OCH_2), 3.47 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 3.44 (s, 2H, CH_2-Ph), 2.38 (m, 4H, CH_2-N-CH_2), 2.17 (m, 4H, CO-$CH_2)_2$), 2.01 (m, 2H, CH_2-CH_2-NH), 1.57 (m, 4H, $2CH_2$),1.43 (m, 2H, CH_2) ($^+$FAB): 562 ([M+H]$^+$, 2),105 (100)
18a	93	85 (sint.) (EtOH/ H_2O)	$C_{23}H_{34}N_6O_2S$ •0.25 H_2O (463.1)	59.65 59.54	7.51 7.69	18.15 17.88		(300 MHz, $CDCl_3$) 9.32 (br, 2H[b], NH), 7.1 (br, 1H[b], NH), 7.24 (d, J = 2.5, 1H, Pyr-5-H), 7.21 (dd, J = 8/8, 1H, Ph-5-H), 6.95–6.6 (m, 3H, ar.), 6.14 (m, 1H, CO-NH[c]), 5.8 (d, J = 2.5. 1H, Pyr-4-H), 4.3–3.8 (m, 4H, OCH_2 and Pyr-CH_2), 3.65–3.2 (m, 2H , CH_2-NH), 3.47 (s, 2H, CH_2Ph), 2.41 (m, 4H, CH_2-N-CH_2), 2.13 (m, 4H, CO-$(CH_2)_2$), 1.97 (m, 2H, OCH_2-CH_2), 1.85–1.3 (m, 6H, $3CH_2$) ($^+$FAB): 459 ([M+H]$^+$, 6), 98 (100)

Table 1: Continued

no	yield %	m.p. (solvent)	formula (mol. mass)	analysis: C	H	N	calcd. found	^{1}H-NMR (δ ppm, TMS as internal reference; J in Hz) [a] MS (EI, $^+$FAB, $^-$FAB): m/z (rel. intensity, %)
20a	51	94 (MeCN)	$C_{24}H_{36}F_3N_7O_2$ (523.6)	57.35 57.57	6.93 7.07	18.73 18.69		(300 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 7.18 (d, J = 2.5, 1H, Pyr-5-H), 6.9–6.8 (m, 2H, ar.), 6.75 (m, 1H, ar.), 6.16 (m, 1H, CO-NH[c]), 6.0–3.8 (very br, 3H[b], NH), 5.85 (d, J = 2.5, 1H, Pyr-4-H), 4.2–3.8 (m, 6H, OCH_2, Pyr-CH_2 and NH-CH_2-CF_3[d]), 3.5–3.3 (m, 2H, CH_2NH), 3.43 (s, 2H, CH_2-Ph), 2.38 (m, 4H, CH_2-N-CH_2), 2.2–2.0 (m, 4H, CO-CH_2)$_2$), 1.95 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.55 (m, 4H, $2CH_2$), 1.43 (m, 2H, CH_2) (EI 80 eV): 523 ($M^{+\bullet}$, 39), 234 (100)
21	96	oil (hygr.)	$C_7H_{10}N_4$ (150.2)	55.98 55.45	6.71 6.77	37.31 37.00		(250 MHz, $CDCl_3$) 7.16 (d, J = 2, 1H, Pyr-5-H), 5.58 (d, J = 2, 1H, Pyr-4-H), 4.05 (t, J = 6, 2H, Pyr-CH_2), 3.70 (br, 2H[b], NH_2), 2.3 (m, 2H, CH_2-CN), 2.16 (m, 2H, CH_2-CH_2CN) (EI 80 eV): 150 ($M^{+\bullet}$, 36), 96 (100)
22	A 96 B 58	176–179 (dec.) (H_2O)	$C_7H_{14}N_4$ •2 $C_6H_3N_3O_7$ (612.4)	37.26 37.06	3.29 3.29	22.87 23.09		(300 MHz, [D_6]DMSO) 7.26 (d, J = 2, 1H, Pyr-5-H), 5.33 (d, J = 2, 1H, Pyr-4-H), 4.49 (br, 2H[b], Pyr-NH_2), 3.79 (t, J = 6.8, 2H, Pyr-CH_2), 2.50 (m, 2H, CH_2-NH), 1.88 (br, 2H[b], CH_2-NH_2), 1.67 (m, 2H, Pyr-CH_2-CH_2), 1.25 (m, 2H, CH_2-CH_2NH_2) (EI 70 eV[e]): 154 ($M^{+\bullet}$, 54). 96 (100)
24	87	106–107 (EtOH/ H_2O)	$C_{15}H_{16}N_4O_2$ (284.3)	63.37 63.03	5.67 5.63	19.71 19.53		(300 MHz, $CDCl_3$) 8.1–7.8 (m, 2H, ar.), 7.8–7.6 (m, 2H, ar.), 7.12 (d, J = 2, 1H, Pyr-5-H), 5.55 (d, J = 2, 1H, Pyr-4-H), 3.95 (t, J = 6.8, 2H, Pyr-CH_2), 3.7 (t, J = 7, 2H, CH_2-NPhth), 3.54 (very br, 2H[b], NH), 2.1–1.5 (m, 4H, $2CH_2$) (EI 70 eV[e]): 284 ($M^{+\bullet}$, 54), 96 (100)
25	93	159–160 (i-PrOH)	$C_{25}H_{23}F_3N_6O_3$ (512.5)	58.59 58.37	4.52 4.40	16.40 16.17		(300 MHz, $CDCl_3$) 13.15 and 12.95 (2m, 1H[b], NH), 9.08 and 8.72 (2m, 1H[b], NH), 8.4–7.2 (m, 9H, ar.), 7.3 (d, J = 2.5, 1H, Pyr-5-H), 6.02 and 5.9 (2m, J = 2.5, 1H, Pyr-4-H), 4.5–4.25 (m, 2H, NH-CH_2-CF_3[d]), 4.09 (t, J = 6.8, 2H, Pyr-CH_2), 3.73 (t, J = 7, 2H, CH_2-NPhth), 2.1–1.45 (m, 4H, $2CH_2$) (EI 80 eV): 512 ($M^{+\bullet}$, 72), 105 (100)
26	80	91–92 (Et_2O)	$C_{17}H_{21}F_3N_6O$ (382.4)	53.40 53.41	5.54 5.55	21.98 21.96		(300 MHz, $CDCl_3$) 13.1 and 12.8 (m, 1H[b], NH), 9.14 and 8.65 (m, 1H[b], NH), 8.23 and 8.06 (m, 2H, ar.), 7.7–7.2 (m, 3H, ar.), 7.28 (d, J = 2.5, 1H, Pyr-5-H), 5.98 and 5.91 (m, 1H, Pyr-4-H), 4.42 and 4.2 (m, 2H, NH-CH_2-CF_3[d]), 4.05 (t, J = 6.8, 2H, Pyr-CH_2), 2.72 (m, 2H, CH_2-NH_2), 1.89 (m, 2H, Pyr-CH_2-CH_2), 1.6–1.0 (m, 4H, CH_2-CH_2-NH_2[b]) (EI 70 eV[e]): 382 ($M^{+\bullet}$, 20). 105 (100)
27	40	179–181 (H_2O)	$C_{10}H_{17}F_3N_6$ $2C_6H_3N_3O_7$ (736.5)	35.88 35.84	3.15 3.10	22.82 22.64		(300 MHz, $CDCl_3$, H-D-exchange with D_2O) 7.19 (d, J = 2.5, 1H, Pyr-5-H), 5.86 (d, J = 2.5, 1H, Pyr-4-H), 4.1–3.8 (m, 4H, PyrCH_2 and NH-CH_2-CF_3[d]), 2.69 (t, J = 7, 2H, CH_2-CH_2-NH), 1.85 (m, 2H,Pyr-CH_2-CH_2), 1.42 (m, 2H, CH_2-CH_2-NH_2) (EI 80 eV): 278 ($M^{+\bullet}$, 100)
28	80	131–132 (MeCN)	$C_{18}H_{21}F_3N_8O$ (422.4)	51.18 51.15	5.01 4.97	26.53 26.54		(300 MHz, [D_6]DMSO, H-D-exchange with D_2O) 7.6–7.05 (m, 6H, 5Ph-H and Pyr-5H), 5.64 (d, J = 2.5, 1H, Pyr-4H), 4.2–3.8 (m, 4H, Pyr-CH_2 and NH-CH_2-CF_3[d]), 3.31 and 3.21 (m, 2H, CH_2-NH). 1.9–1.6 (m, 2H, Pyr-CH_2-CH_2), 1.6–1.3 (m, 2H, CH_2-CH_2-NH) ($^+$FAB): 423 ([M+H]$^+$, 100)
29	81	oil	$C_{13}H_{20}F_3N_9$ (359.4)	43.45 43.54	5.61 5.69	35.08 34.36		(300 MHz, [D_6]DMSO) 7.44 (d, J = 2.5, 1H, Pyr-5-H), 7.2–5.8 (br, 5H[b], NH), 5.65 (d, J = 2.5, 1H, Pyr-4-H), 4.03 (q, J = 10, 2H, NH-CH_2-CF_3[d]), 3.94 (t, J = 6.5, 2H, Pyr-CH_2), 3.09 (m, 2H, CH_2-NH), 2.65 (d, J = 2.5, 3H, NH-CH_3), 1.7 (m, 2H, Pyr-CH_2-CH_2), 1.39 (m, 2H, CH_2-CH_2-NH) (EI 80 eV): 359 ($M^{+\bullet}$, 72), 96 (100)
30	90	132–134 (MeCN)	$C_{10}H_{17}N_7$ (235.3)	51.05 51.37	7.28 7.42	41.67 41.27		(300 MHz, [D_6]DMSO) 7.66 and 7.28 (2d, J = 2, 1H, Pyr-5-H), 7.0–6.9 (m, 2H[b], NH), 6.05 and 5.34 (2d, J = 2, 1H, Pyr-4-H), 4.51 (s, 2H[b], Pyr-NH_2), 4.03 and 3.81 (2t, J = 6.8, 2H, Pyr-CH_2), 3.26 and 3.07 (2dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.82 and 2.65 (2d, J = 5, 3H, NH-CH_3); 1.65 (m, 2H, Pyr-CH_2-CH_2), 1.36 (m, 2H, CH_2-CH_2-NH) (EI 70 eV[e]): 235 ($M^{+\bullet}$, 8), 41 (100)
31	46	217 (dec.)	$C_{12}H_{18}N_{10}$ (302.3)	47.67 47.79	6.00 5.99	46.33 45.69		(300 MHz, [D_6]DMSO) 9.91 (br, 1H[b], NH), 7.91 (br, 2H[b], NH), 7.65 (d, J = 2.5, 1H, Pyr-5-H), 7.0-6.85 (m, 2H[b], NH), 5.91 (d, J = 2.5, 1H, Pyr-4-H), 4.02 (t, J = 6.8, 2H, Pyr-CH_2), 3.09 (dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.65 (d, J = 4.5, 3H, NH-CH_3), 1.71 (m, 2H, Pyr-CH_2-CH_2), 1.38 (m, 2H, CH_2-CH_2-NH) ($^+$FAB): 303 ([M+H]$^+$, 100)
32	69	182–184 (MeCN)	$C_{13}H_{20}N_{10}$ (316.4)	49.35 49.50	6.37 6.35	44.27 44.44		(300 MHz, [D_6]DMSO) 9.72 (br, 1H[b], NH), 8.37 (br, 1H[b], NH), 7.66 (d, J = 2.5, 1H, Pyr-5-H), 7.0-6.85 (m, 2H[b], NH), 6.06 (d, J = 2.5, 1H, Pyr-4-H), 4.04 (t, J = 6.8, 2H, Pyr-CH_2) 3.1 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 2.82 (d, J = 4.5. 3H, NH-CH_3), 2.65 (d, J = 4.5. 3H, NH-CH_3), 1.73 (m, 2H, Pyr-CH_2-CH_2), 1.38 (m, 2H, CH_2-CH_2-NH) ($^+$FAB): 317 ([M+H]$^+$, 52), 177 (100)
34	84	67 (EtOH)	$C_{20}H_{24}F_3N_7O_3S$ (499.5)	48.09 47.87	4.84 4.86	19.63 19.83		(300 MHz, $CDCl_3$) 13.15 and 12.8 (2s, 1H[b], Pyr-NH), 10.54 (br, 1H[b], CH_2-CH_2-N*H*), 9.06 and 8.68 (2m, 1H[b], F_3C-CH_2-N*H*), 8.23 and 8.04 (2m, 2H, ar.), 7.52–7.3 (m, 3H, ar.), 7.31 (d, J = 2.5, 1H, Pyr-5-H), 6.56 and 6.51 (2s, 1H, =CH-NO_2), 5.98 and 5.94 (2d, J = 2.5, 1H, Pyr-4-H), 4.44 and 4.13 (2m, 2H, NH-CH_2-CF_3[d]), 4.1 (t, J = 6.5, 2H, Pyr-CH_2), 3.42 and 3.33 (2dt, J = 6.5/6.5, 2H, CH_2-CH_2-NH), 2.43 (s, 3H, SCH_3), 1.98 (m, 2H, Pyr-CH_2-CH_2), 1.7 (m, 2H, CH_2-CH_2-NH) (EI 80 eV): 499 ($M^{+\bullet}$, 9), 105 (100)
35	72	122 (Et_2O/ Me_2CO)	$C_{20}H_{25}F3N_8O_3$ (482.3)	49.79 49.85	5.22 5.25	23.23 23.11		(300 MHz, $CDCl_3$) 13.07 and 12.72 (2m, 1H[b], NH), 10.14 (br, 1H[b], NH), 9.06and 8.7 (2m, 1H[b], NH), 8.21 and 8.02 (2m, 2H, ar.), 7.7–7.3 (m, 3H, ar.), 7.3–7.2 (m, 2H, Pyr-5-H and =CH-NO_2), 6.7–6.2 (m, 1H[b], NH), 5.95 and 5.88 (2d, J = 2.5, 1H, Pyr-4-H), 4.41 and 4.21 (2m, 2H, NH-CH_2-CF_3[d]), 4.03 (m, 2H, Pyr-CH_2), 3.28 and 3.16 (2m, 2H, CH_2-NH), 2.93 and 2.8 (2m, 3H, NH-CH_3), 2.1–1.4 (m, 4H, $2CH_2$) ($^+$FAB): 483 ([M+H]$^+$, 6), 105 (100)
36	84	oil	$C_{21}H_{29}N_5O$ (367.5)	68.64 68.36	7.95 8.04	19.06 18.91		(300 MHz, $CDCl_3$) 7.22 (dd, J = 8/8, 1H, Ph-5-H), 7.0–6.7 (m, 3H, ar.), 6.1 (br, 2H[b], NH), 4.08 (m, 2H, OCH_2), 3.95 (m, 2H, CH_2-C≡CH), 3.6–3.3 (m, 2H, CH_2-NH), 3.45 (s, 2H, CH_2-Ph), 2.79 (m, 2H[f]), 2.28 (m, 1H, C≡CH), 2.06 (m, 2H, OCH_2-CH_2), 1.87 (m, 1 H[f]), 1.8–1.4 (m, 5H[f]), 0.95–0.7 (m, 1H[f]), 0.83 (d, J = 6, 3H, CH_3) ($^+$FAB): 368 ([M+H]$^+$, 46), 112 (100)

Table 1: Continued

no	yield %	m.p. (solvent)	formula (mol. mass)	analysis: C	H	N	calcd. found	^{1}H-NMR (δ ppm, TMS as internal reference; J in Hz) [a] MS (EI, $^+$FAB, $^-$FAB): m/z (rel. intensity, %)
37	74	oil	$C_{21}H_{29}N_5O$ (367.5)	68.64 68.59	7.95 8.05	19.06 18.82		(300 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 6.9–6.8 (m, 2H, ar.), 6.75 (m, 1H, ar.), 6.15 (br, 1H[b], NH), 5.75 (br, 1H[b], NH), 4.1–3.9 (m, 4H, OCH_2 and CH_2-C≡CH), 3.45 (s, 2H, CH_2-Ph),3.33 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 2.39 (m, 4H, CH_2-N-CH_2), 2.33 (t, J= 2.5, 1H, C≡CH), 1.95–1.65 (m, 4H, OCH_2-(CH_2)$_2$), 1.58 (m, 4H, $2CH_2$), 1.44 (m, 2H, CH_2) ($^+$FAB): 368 ([M+H]$^+$, 16), 98 (100)
38	66	120 (MeCN)	$C_{19}H_{29}N_5O$ (343.5)	66.44 66.01	8.51 8.87	20.39 20.30		(300 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 7.0–6.85 (m, 2H, ar.), 6.85–6.75 (m, 1H, ar.), 5.98 (br, 1H[b], NH), 5.65 (br, 2H[b], NH), 3.99 (t, J = 5.8, 2H, OCH_2), 3.45 (s, 2H, CH_2-Ph), 3.27 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 2.95–2.78 (m, 2H[f]), 2.25–1.05 (m, 11H[f]), 0.91 (d, J = 6, 3H, CH_3) (EI 80 eV): 343 (M$^{+\bullet}$, 7), 98 (100)
39	78	131 (MeCN)	$C_{20}H_{31}N_5O$ (357.5)	67.19 66.79	8.74 8.78	19.59 19.39		(250 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 7.01–6.69 (m, 3H, ar.), 5.51 (br, 1H[b], NH), 5.22 (br, 1H[b], NH), 4.02 (m, 2H, OCH_2), 3.45 (s, 2H, CH_2-Ph), 3.33 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 2.98–2.64 (m, 2H, CH_2), 2.82 (d, J = 4.5, 3H, NH-CH_3), 2.25–1.06 (m, 11H, CH_2), 0.91 (d, J = 6, 3H, CH_3) (EI 80 eV): 357 (M$^{+\bullet}$, 5), 98 (100)
40	41	81–84 (EtOH/H_2O)	$C_{17}H_{27}N_5O_2$ •H_2O (351.5)	58.10 58.35	8.32 8.44	19.93 20.09		(250 MHz, $CDCl_3$) 7.21 (dd, J = 8/8, 1H, Ph-5-H), 7.1–6.74 (m, 3H, ar.), 6.8–4.5 (very br, 3H[b], NH), 4.79 (br, 2H[b], NH), 4.04 (t, J = 5.8, 2H, OCH_2), 3.42 (s, 2H, CH_2-Ph), 3.36 (t, J = 6.5, 2H, CH_2-CH_2-NH), 2.36 (m, 4H, CH_2-N-CH_2), 2.02 (m, 2H, OCH_2-CH_2), 1.77–1.22 (m, 6H, $3CH_2$) ($^+$FAB): 334 ([M+H]$^+$, 33), 291 (100)
41	52	oil	$C_{18}H_{29}N_5O_2$ •0.25 H_2O (352.0)	61.43 61.75	8.45 8.46	19.90 19.66		(300 MHz, $CDCl_3$) 10.0–4.0 (3H[b], NH), 7.22–7.05 (m, 1H, Ph-5-H), 6.9–6.6 (m, 3H, ar.), 4.71 (br, 1H[b], NH), 4.07 (m, 2H, OCH_2), 3.45–3.25 (m, 2H, CH_2-NH), 3.43 (s, 2H, CH_2-Ph), 2.9–2.7 (m, 3H, NH-CH_3), 2.36 (m, 4H, CH_2-N-CH_2), 2.04 (m, 2H, OCH_2-CH_2), 1.7–1.25 (m, 6H, $3CH_2$) ($^+$FAB): 338 ([M+H]$^+$, 5), 305 (100)
42	68	oil	$C_{18}H_{30}N_4O_3S$ (382.5)	56.52 56.66	7.90 8.01	14.65 14.56		(300 MHz, $CDCl_3$) 7.22 (dd, J = 8/8, 1H, Ph-5-H), 6.9–6.8 (m, 2H, ar.), 6.72 (m, 1H, ar.), 6.4–4.2 (very br, 2H[b], NH), 4.09 (t, J = 5.5, 2H, OCH_2), 3.6–3.3 (m, 2H, CH_2-NH), 3.45 (s, 2H, CH_2-Ph), 2.93 (s, 3H, SO_2CH_3), 2.8 (d, J = 4.5, 3H, NH-CH_3). 2.38 (m, 4H, CH_2-N-CH_2), 2.05 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.58 (m, 4H, $2CH_2$), 1.44 (m, 2H, CH_2) ($^+$FAB): 383 ([M+H]$^+$, 37), 98 (100)
43	35	110 (EtOAc)	$C_{20}H_{31}N_7O$ •0.25 H_2O) (390.0	61.59 61.62	8.14 8.15	25.14 25.19		(300 MHz, $CDCl_3$) 7.22 (dd, J = 8/8, 1H, Ph-5-H), 6.9–6.82 (m, 2H, ar.), 6.78 (m, 1H, ar.), 5.23 (m, 1H[b], NH), 4.91 (m, 2H[b], NH), 4.04 (t, J = 6, 2H, OCH_2), 3.56 (dt, J = 6/6, 2H, CH_2-CH_2-NH), 3.45 (s, 2H, CH_2Ph), 3.07 (s, 6H, N(CH_3)$_2$), 2.39 (m, 4H, CH_2-N-CH_2), 2.04 (tt, J = 6/6, 2H, OCH_2-CH_2), 1.58 (m, 4H, $2CH_2$), 1.43 (m, 2H, CH_2)
46		101–102 (MeCN)	$C_{25}H_{32}N_4O_2$ (420.6)	71.40 71.64	6.67 7.78	13.32 13.41		(250 MHz, $CDCl_3$) 7.6–6.6 (m, 10H; 9H ar., 1NH[b]), 4.02 (m, 2H, OCH_2), 3.65–3.35 (m, 2H, CH_2NH), 3.45 (s, 2H, CH_2-Ph), 2.95–2.75 (m, 2H[f]), 2.15–1.7 (m, 6H[f]), 1.7–1.45 (m, 2H[f]), 1.45–1.2 (m, 2H[f]), 0.91 (d, J = 6, 3H, CH_3) ($^+$FAB): 421 ([M+H]$^+$, 100)

[a] abbreviations: ar. = aromatic, Fur = furanyl, Ph = phenyl, Phth = phthaloyl, Pyr = pyrazolyl, Thz = thiazolyl
[b] exchangeable with D_2O
[c] exchangeable with CF_3COOD
[d] after H-D-exchange with D_2O: q, J_{H-F} 10 Hz
[e] Kratos MS 25 RF
[f] piperidine-H

N-[N-[1-[4-(1-Methylthio-2-nitroethenyl)aminobutyl]-3-pyrazolyl]-N'-(2,2,2-trifluoroethyl)diaminomethylene}benzamide (**34**)

Amine **26** (0.91 g, 2.4 mmol) is refluxed for 5 h with **33** [18] (0.393 g, 2.4 mmol) in 30 ml of MeCN. The volatiles are removed *in vacuo*, and **34** is crystallized from Et_2O (recrystallization from EtOH).

N-[N-[1-[4-(1-Methylamino-2-nitroethenyl)aminobutyl]-3-pyrazolyl]-N'-(2,2,2-trifluoroethyl)diaminomethylene}benzamide (**35**)

Compound **34** (0.87 g, 1.7 mmol) is stirred for 2 h at room temp. with 30 % ethanolic methylamine (20 ml). The mixture is evaporated to dryness *in vacuo*, **35** is purified chromatographically (Chromatotron, $CHCl_3$/MeOH, 98+2, NH_3 atmosphere) and crystallized from Et_2O/Me_2CO.

Cyanoguanidines **36-39**

Intermediate N-cyano-O-phenylisoureas: The pertinent piperidinomethylphenoxyalkylamines (10 mmol), prepared according to described methods [19,20], are allowed to react with an equimolar amount of **11** in 30 ml of Et_2O at room temp. Concentration of the solution results in partial crystallization of the corresponding *N*-cyano-*O*-phenylisoureas. Samples are filtered off and recrystallized for analysis: *N*-Cyano-*N'*-{3-[3-(3-methyl-1-piperidinylmethyl)phenoxy]propyl}-*O*-phenylisourea (**44**) m.p. 89 °C (EtOH/H_2O) [20]; *N*-cyano-*O*-phenyl-*N'*-{4-[3-(1-piperidinylmethyl)phenoxy]butyl}isourea (**45**), m.p. 95 °C (EtOH/H_2O) [20]; *N*-cyano-*N'*-{4-[3-(4-methyl-1-piperidinylmethyl)phenoxy]butyl}-*O*-phenylisourea (**46**, data *cf.* Table 1).

Cyanoguanidines: Compounds **44–46** (9.5 mmol) are treated with an excess of the pertinent amine. For the synthesis of **36** and **37** the isoureas **44** and **45** are heated under reflux for 5 h with 2.5 ml of propargylamine in MeCN (30 ml), whereas **46** is either stirred with methanolic NH_3 for 12 h at room temp. or refluxed for 10 min with 30 % ethanolic methylamine (30 ml), to obtain **38** or **39**, respectively. The volatiles are removed *in vacuo*, the residue is dissolved in Et_2O, washed consecutively twice with 5 % NaOH solution and water, and dried over Na_2SO_4. The solvent is distilled off, affording crystalline **38** and **39**, whereas **36** and **37** are obtained as oils (purification: Chromatotron, $CHCl_3$/MeOH, 98+2, NH_3, atmosphere).

Diaminomethylene ureas **40** *and* **41**

N-Cyano-*N'*-{3-[3-(1-piperidinylmethyl)phenoxy]propyl}guanidine [21] or *N*-cyano-*N'*-methyl-*N''*-{3-[3-(1-piperidinylmethyl)phenoxy]propyl}-guanidine [21] (2 g) are dissolved in 25 ml of 10 M HCl and stirred for 48 h at room temp. The mixture is evaporated *in vacuo* to dryness, the remaining salt is dissolved in water and converted into the free base by basification with

aqueous NH_3. Compound **40** precipitates from the solution and is recrystallized from EtOH/H_2O, whereas **41** is obtained as an oil after extraction with $CHCl_3$ and chromatographic purification (Chromatotron; $CHCl_3$/MeOH, 95+5, NH_3 atmosphere).

{N-Methyl-N'-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]diaminomethylene}methane sulfonamide (**42**)

A solution of diphenyl methanesulfonyl carbonimidate[17] (1.4 g, 4.8 mmol) and **8a** [19] (1.19 g, 4.8 mmol) in 30 ml of CH_2Cl_2 is stirred for 30 min at room temp. and subsequently evaporated. After addition of an excess of 30 % ethanolic methylamine (25 ml) the mixture is stirred for a further 30 min. Removal of the volatiles affords **42** as an oil which is purified chromatographically (Chromatotron, $CHCl_3$/MeOH, 99+1, NH_3 atmosphere).

2-Amino-4-dimethylamino-6-[3-[3-(1-piperidinylmethyl)phenoxy]-propyl]amino-1,3,5-triazine (**43**)

A mixture of 2-amino-4-chloro-6-{3-[3-(1-piperidinylmethyl)phenoxy]propylamino}-1,3,5-triazine [20] (3 g, 8 mmol), dimethylamine hydrochloride (13 g, 0.16 mol) and KOtBu (17.94 g, 0.16 mol) in 250 ml of EtOH is autoclaved for 10 h at 70 °C/3 bar. Subsequently, precipitated KCl is filtered off, the solvent is removed *in vacuo*, the residue is dissolved in $CHCl_3$, the org. layer is consecutively washed twice with a 1 % NaOH and water, dried over Na_2SO_4, and evaporated *in vacuo*. The remaining oil is treated with EtOAc affording crystalline **43** which may be recrystallized from EtOH/H_2O.

Pharmacology

Histamine H_2-receptor antagonist activity on the isolated guinea pig right atrium [5]

Male guinea pigs (350–400 g) were killed by a blow on the head and exsanguinated. Right atria were rapidly removed, attached to a tissue holder in an organ bath (32.5 °C) containing 20 ml of Krebs-Henseleit solution gassed with 95 % O_2/5 % CO_2. The antagonistic potency was determined from isometrically recorded cumulative concentration response curves using histamine dihydrochloride (0.1–10 μM) as the reference substance. The time of incubation was generally 30 min for the antagonists. For the pharmacological screening most compounds were tested at one or two concentrations (*cf.* Table 2) and pK_B values (mean of 3–5 independent experiments) were calculated from the expression $pK_B = -\log$ [antagonist] + log (concentration ratio – 1) [8], as the compounds produced a dose-dependent depression of the concentration response curves.

Investigation of gastric acid secretion in anaesthetized rats

The inhibition of histamine-stimulated gastric acid secretion was determined as described in detail [19]. In brief, male Sprague-Dawley rats (180–240 g) (fasting for 48h, water *ad libitum*) were anaesthetized with urethane (1.5 g/kg *i.m.*). The preparation was carried out as described by *Ghosh* and *Schild* [22]. After tracheotomy two catheters (one through the oesophagus and the other through the duodenum) were introduced into the stomach and fixed by ligature. The stomach was perfused with a 0.9 % NaCl solution (37 °C) at constant volume (1 ml/min). The perfusate was collected in fractions (15 min), the volume was measured, and the H^+ concentration was determined by end-point (pH 7) titration. For stimulation of gastric acid secretion histamine (11 $\mu mol \cdot kg^{-1} \cdot h^{-1}$) was continuously infused *via* the jugular vein. After achieving plateau secretion (90 min), solutions of the test compounds were administered *i.v.* The inhibition of acid secretion was determined as a % of the maximum histamine response (mean of 2–4 experiments).

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[Ph 303]