Histamine Analogues, XXXV[1]:

2-Substituted Histamine Derivatives Containing Classical Moieties of H_2-Antagonists - a Novel Class of H_1-Agonists

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A new type of H_1-agonists resulted from the combination of the essential histamine structure with parts of H_2-antagonists. 2,4-Disubstituted imidazole derivatives were synthesized by reaction of imidic acid methyl esters with 1,3-dihydroxypropanone, 1,4-dihydroxybutanone or 2-oxo-4-phthalimido-1-butylacetate in liquid NH_3. The imidazole intermediates were converted into histamine analogues by simple deprotection, *Gabriel* synthesis followed by deprotection, or by side-chain elongation *via* the nitriles and final hydrogenation. The new compounds were screened for H_1-activity on the isolated guinea-pig ileum and for H_2-antagonistic activity on the isolated guinea-pig right atrium. The substances are comparably weak H_1-agonists and moderate H_2-blockers.

Histaminanaloge, 35. Mitt.: 2-Substituierte Histaminderivate mit klassischen Strukturelementen von H_2-Antagonisten - eine neue Klasse von H_1-Agonisten

Ein neuer Typ von H_1-Agonisten resultierte aus der Kombination der essentiellen Histaminstruktur mit Elementen von H_2-Antagonisten. 2,4-Disubstituierte Imidazole wurden durch Reaktion von Imidsäuremethylestern mit 1,3-Dihydroxypropanon, 1,4-Dihydroxybutanon oder 2-Oxo-4-phthalimidobutylacetat in flüssigem NH_3 erhalten. Die Imidazol-Zwischenprodukte wurden durch Abspalten der Schutzgruppe, *Gabriel*-Synthese und nachfolgende Abspaltung der Schutzgruppe, oder durch Kettenverlängerung über Nitrile und abschließende Reduktion in die gewünschten Histaminderivate überführt, die auf H_1-Aktivität am isolierten Meerschweinchendünndarm und auf H_2-Antagonismus am isolierten rechten Meerschweinchenvorhof geprüft wurden. Die Substanzen sind vergleichsweise schwache H_1-Agonisten und moderat wirksame H_2-Blocker.

In the field of histamine H_2- and H_3-receptor research numerous potent and selective agonists have been developed in the last decade[2,3], whereas in the series of H_1-agonists only a limited number of compounds with reasonable potencies have been discovered up to now. However, in respect of the wide distribution of histamine receptors in mammalians, such compounds are attractive as pharmacological tools for the study of H_1-effects, *e.g.* in human cardiology[4,5].

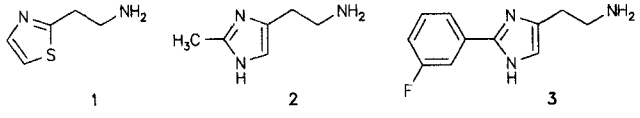

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Fig. 1

Typical H_1-agonists are heterocyclic ethanamines, *e.g.* 2-(2-thiazolyl)ethanamine (**1**; 11-32% of the potency of histamine[2]), 2-substituted histamine derivatives like 2-phenylhistamine (13%[6]) and 2-methylhistamine (**2**; 16%[2]). Recently, interest has been focussed on the class of 2-phenylhistamines. 2-(3-Fluorophenyl)histamine (**3**) and its 3-chloro analogue are the most potent highly selective H_1-agonists so far known, showing 87 and 81% relative potency compared with histamine and full efficacy at the H_1-receptor[7]. 2-Methylhistamine (**2**) was also used as a lead to develop selective H_1-agonists.

[+] Part of the PhD Thesis of *V. Zingel*, Berlin 1990.

Considering the class of 2-alkylhistamines, introduction of ethyl or propyl substituents in position 2 of the imidazole nucleus led to an increase of H_1-selectivity but always accompanied by a decrease of potency[8]. Due to this fact the aim of the present study was to enhance H_1-activity of 2-alkylhistamines by connecting them with groups bearing high affinity to histamine receptors[9], especially for the H_2-receptor, *e.g.* the piperidinomethylphenoxypropyl moiety known from the H_2-blockers lamtidine and roxatidine.

Chemistry

2-Substituted histamine derivatives are available by reaction of imidate hydrochlorides with C_3- or C_4-synthons (Fig. 2). The used imidate salts **7a-k** were synthesized according to *Pinner*[10] from the appropriate nitriles, which have been described[11] or were prepared according to similar procedures[12,13]. The reactions for **7b,d-g** were carried out in absol. CH_2Cl_2 in nearly equimolar ratio with MeOH (10% excess), whereas **7a,c,h-k** had to be prepared in absol. MeOH because of the poor solubility of the protonated nitriles in CH_2Cl_2. Route I represents the classical histamine synthesis according to *Pyman*[14] as modified by *Dziuron* and *Schunack*[15]. The imidazole synthesis is carried out in liquid ammonia with 1,3-dihydroxypropanone (**4**) as C_3-synthon under pressure of 20-22 bar. The obtained (imid-

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azol-4-yl)methanol derivatives **8e,f** were purified by column chromatography. Reaction with $SOCl_2$ at room temp. led to the 4-chloromethylimidazole derivatives **9e,f**. The following nitrile synthesis with NaCN is critical in this class of compounds because of the slight solubility of **9e,f** hydrochlorides in polar aprotic media suitable for the *Kolbe* synthesis. In addition, **9e,f** are highly reactive and very hygroscopic compounds. As a consequence the reaction had to be performed in DMSO and led to various related substances, *e.g.* isonitriles. The terminal step was the reduction to the primary amines with H_2 in liquid NH_3/Raney-Ni, followed by separation of **14e,f** by column chromatography (cc).

In order to avoid poor yields of the histamine derivatives as a result of the C-C-bond-formation in the *Kolbe* nitrile synthesis we have used a suitable C_4-synthon: Route II contains the imidazole synthesis with 1,4-dihydroxy-2-butanone[16] (**5**) in liquid NH_3 followed by a stepwise exchange of the hydroxy group for the amino group. Compound **5** had already been utilized for the synthesis of 2-substituted histamine derivatives by *Dziuron* and *Schunack*[17]. The amination of the 4-(2-chloroethyl)imidazole or 4-(2-bromoethyl)imidazole derivatives in liquid NH_3 under pressure was very difficult, resulting in the formation of secondary and tertiary amines as main impurities. Therefore, *Gabriel* synthesis should bring great improvement. Indeed the 4-(2-chloroethyl)imidazole derivatives **12a-d, g-i** are less reactive than the 4-chloromethyl imidazole derivatives **9e,f** and easy to obtain as solid bases, except **12h,i** which were used for the next step as crude oily bases. The phthalimides **13a-d, g-i** were obtained as crystalline products in good yields. In the reaction sequence of route II only the substituted 2-(imidazol-4-yl)ethanols **11a-d,g** had to be purified by cc (**11h,i** were precipitated as hygroscopic hydrochlorides and characterized as their hydrogen maleates), whereas the following intermediates and the polar histamine derivatives **14b-d, g-i** were obtained in high purity without tedious workup. In fact, route II seems to be a convenient and reliable method to obtain 2-substituted histamine derivatives. The preparation of **14a** only was difficult because only one methylene group is linking the essential histamine structure and the piperidinomethylphenoxy moiety. The precursors of **14a** were very instable, especially in alkaline solution, where a degradation to 3-(piperidinomethyl)phenol and the corresponding imidazole derivatives was observed. Concerning route I, only 10% of the desired (imidazol-4-yl)methanol derivative were obtained, followed by a complete cleavage in the ultimate step (reduction in ammonia). Regarding route II, only 27% of **11a** were obtained under mild conditions and the *Gabriel* synthesis gave only an enriched product **13a**.

The desired histamine structure is also obtainable in one step using the bifunctional C_4-synthon 2-oxo-4-phthalimido-1-butyl acetate (**6**)[7,18] (synthesized as described[7] from 2-oxo-3-buten-1-yl acetate[16] and phthalimide; route III). The conditions applied for the imidazole synthesis were the same as for route I or II but the work up had to be replaced by a modified one to separate **14j,k** from the major impurities. After removal of the ammonium salts the reaction mixture was treated with *N*-ethoxycarbonylphthalimide to derivatize the primary amines. The appropriate phthalimides were separated by cc and submitted to hydrazinolysis. The pure bases **14j,k** were treated with maleic acid to form salts which were recrystallized from absol. ethanol/ether. It can be concluded that, by comparing route I to III, the latter has the advantage of velocity although only fair yields are attainable.

Pharmacological Results and Discussion

All new compounds were tested for H_1-histaminergic activity in the classical isolated guinea-pig ileum assay according to a modified procedure of *Lennartz* et al.[19] and screened for H_2-antagonism of the histamine stimulated tachycardia on the spontaneously beating guinea-pig right atrium[20]. Compounds **14a-k** were tested as watersoluble hydrochlorides or hydrogen maleates. In each case a minimum of two (maximum 4 for **14b** on the ileum) determinations were carried out. The presented data (pD_2 and pA_2) are mean values.

The majority of the compounds represent a new class of histamine derivatives: H_1-agonists combined with H_2-antagonistic activity (Tab. 1). On the guinea-pig ileum all compounds show H_1-agonistic activity, but none of them is acting as a full agonist. The relative potency compared with histamine of the partial agonists **14a-k** is ranging from 0.2 to 6.9%, pD_2-values and relative potencies of **14a,f,g** were not determined. On the guinea-pig right atrium all compounds show H_2-antagonistic activity, which is weaker than

Tab. 1. H_1-agonistic and H_2-antagonistic activity of 2-substituted histamines

compound	H_1 (ileum) i.a.[a]	pD_2[b]	rel. pot.[%]	H_2 (atrium) pA_2[c]	rel. pot [%]
histamine	1.00	6.85	100	--	--
cimetidine	--	--	--	6.40	100
ranitidine	--	--	--	7.20	631
lamtidine	--	--	--	7.82[d]	2630
14a	0.12	--	--	4.80	2.5
14b	0.74	5.69	6.9	6.28	75.9
14c	0.74	4.95	1.3	5.14	5.5
14d	0.79	4.45	0.4	5.47	11.8
14e	0.98	4.15	0.2	5.94	34.7
14f	0.34	--	--	5.04	4.4
14g	0.28	--	--	5.90	31.6
14h	0.51	4.32	0.3	--	--
14i	0.57	4.18	0.2	--	--
14j	0.73	4.77	0.8	4.78	2.4
14k	0.91	4.64	0.6	3.62	0.2

[a] Intrinsic activity. [b] pD_2-value[21]. [c] pA_2-value[21]. [d] -log K_B-value reported[22].

reported for the parent molecules lamtidine, ranitidine and cimetidine. For the cimetidine analogues **14h,i** no H_2-antagonistic activity could be detected up to $0.3 \cdot 10^{-3}$ M.

Considering both qualities, these compounds are only weak H_1-agonists with moderate H_2-antagonistic activity. Highest activity was found for compound **14b**: 6.9% on the ileum (compared with histamine) and 75.9% on the atrium (compared with cimetidine). Starting out from **14b**, H_1-activity decreased if the flexible chain between the essential histamine structure and the piperidinomethyl-phenoxy group was shortened (**14a**) or lengthened (**14e-g**). Interestingly, on the atrium the H_2-antagonistic potency clearly depends on the nature of the basic function of **14b-d**. The sequence of potency (piperidino > pyrrolidino > dimethylamino substituent) is in good agreement with that reported by *Bays* and *Price*[23] in a series of H_2-antagonistic diaminotriazoles by measuring the inhibition of acid secretion on the *Heidenhain* pouch dog. Surprisingly, on the ileum higher activity was found for the dimethylamino derivative **14c** as compared with the pyrrolidino analogue **14d**. Looking at **14a-k**, H_2-antagonistic activity decreased by the replacement of the "polar moiety" of lamtidine (diaminotriazole) and ranitidine (nitroethenediamine) by a [4-(2-aminoethyl)imidazol-2-yl] group. The cimetidine analogues **14h,i** are devoid of H_2-antagonistic activity. This is also reflected in the strong decrease of potency by connecting the {[(5-methylimidazol-4-yl)methyl]thio}alkyl group with diaminotriazoles[24], thiadiazoloxides[25], or oxadiazoldiamines[26].

These data indicate that a significant increase of H_1-activity of 2-alkylhistamines cannot be successfully achieved by introduction of H_2-antagonistic side chains. Sterical requirements for H_1-agonists seem to be very different from compounds showing high affinity but no intrinsic activity at H_2-receptors. Compounds with both qualities (H_1-agonist and H_2-antagonist) may be of interest in the case of pharmacological experiments where highly selective histamine H_1-effects are desirable.

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Experimental Part

Melting points: Büchi 512 melting point apparatus, uncorrected.- ^{1}H-NMR spectra: Bruker AC 300 or Bruker WM 250 spectrometer, TMS as internal reference.- Mass spectra: Finnigan MAT CH7A (EI/70 eV), MAT 711 (EI/80 eV), and MAT CH5DF ($^+FAB_{(Xenon;\ DMSO/Glycerin)}$) or Kratos MS 25 RF (EI/70 eV).- Analytical results for compounds indicated by the molecular formula are within ± 0.4% of the theoretical values (Perkin-Elmer elemental analyzer 240 C). Stationary phase for column chromatography: Baker silicagel type 0253 (0.05-0.2 mm). Dichloromethane (DCM)/methanol saturated with ammonia (MA) mixtures were used as eluants.- Reactions under pressure were performed in a 1000 ml autoclave.- Representative examples of the reactions referred to in fig. 2 are given below. All other compounds were prepared according to the given examples.

{2-[4-(3-(Piperidinomethyl)phenoxy)butyl]imidazol-4-yl}methanol (**8e**)

12.3 g (33 mmol) 5-[3-(Piperidinomethyl)phenoxy]pentanimidic acid methylester · 2 HCl[27] and 3.0 g (33 mmol) **4** were mixed with 200 ml of liquid ammonia. The autoclave was sealed, stirred overnight at room temp. and then heated for 5 h to 60°C (22 bar). After evaporation of ammonia, the slurry was suspended in ethanol and NH_4Cl was filtered off. The solvent was removed under reduced pressure and the residue was purified by cc (400 g silica gel; 90% DCM/10% MA). The pure base was treated with ethanolic HCl to form a salt, which was crystallized under stirring with absol. ether. For analytical purpose a picrate was prepared.

4-Chloromethyl-2-{4-[3-(piperidinomethyl)phenoxy]butyl}imidazole (**9e**)

9.2 g (22 mmol) **8e** · 2 HCl were stirred with 50 ml of $SOCl_2$ for 4 h at room temp. Excess of $SOCl_2$ was removed *in vacuo* and the residue was crystallized under intensive stirring with absol. ether. The hygroscopic product had to be isolated under N_2.

{2-[4-(3-(Piperidinomethyl)phenoxy)butyl]imidazol-4-yl}ethannitrile (**10e**)

1.8 g (36 mmol) dry NaCN were slurried in 80 ml absol. DMSO and slowly treated with a solution of 4.7 g (10.9 mmol) **9e** · 2 HCl in 40 ml of absol. DMSO. The suspension was stirred for 15 h at 35-40°C. After the reaction was finished, DMSO was removed *in vacuo* (oil vacuum pump) and the residue dissolved in water. In weak alkaline solution, the product was extracted three times with ether, dried (Na_2SO_4), followed by the removal of the solvent under reduced pressure. Crystallization from petroleum ether/toluene.

2-{2-[4-(3-(Piperidinomethyl)phenoxy)butyl]imidazol-4-yl}ethanamine (**14e**)

An autoclave was charged with 1.6 g (4.5 mmol) **10e**, 5.0 g activated Raney-Ni, 100 ml of liquid NH_3 and 10 bar H_2. The reaction mixture was intensively stirred for 2 days at ambient temp. After evaporation of H_2 and NH_3, the residue was treated with ethanol/water and subsequently filtrated. The filtrate was gassed with H_2S at pH = 9. After that, the suspension was filtrated again to remove precipitated Ni-sulphides. The filtrate was acidified, filtrated and two times extracted with each a small portion of CH_2Cl_2. The alkalized water layer was extracted with several portions of mixtures of CH_2Cl_2/isopropanol (3:1). After evaporation of the solvents under reduced pressure, the base was purified by cc (200 g silicagel; 84% DCM/16% MA). The pure base was converted into its hydrochloride, which was crystallized from absol. ether/ethanol/isopropanol. A small quantity of the base was treated, as an alternative, with dry maleic acid in absol. ether/ethanol to form a hydrogen maleate.

4-[3-(N,N-Dimethylaminomethyl)phenoxy]butanimidic acid methylester (**7c**)

Dry HCl was passed at -5 to 0°C into a solution of 8.1 g (37.1 mmol) 4-[3-(N,N-dimethylaminomethyl)phenoxy]butannitrile[11] in 150 ml of absol. methanol until saturation. The flask was tightly stoppered and the solution was allowed to stand in a freezer for at least 24 h. After that, the solvent was removed *in vacuo* (bath temp. below 25°C) to give a dry foam. This material was used for the next step without further purification.

7-[3-(Piperidinomethyl)phenoxy]heptanimidic acid methylester (**7g**)

9.0 g (30 mmol) 7-[3-(Piperidinomethyl)phenoxy]heptannitrile (prepared from 3-(piperidinomethyl)phenol[20] and 7-bromoheptannitrile) and 1.1

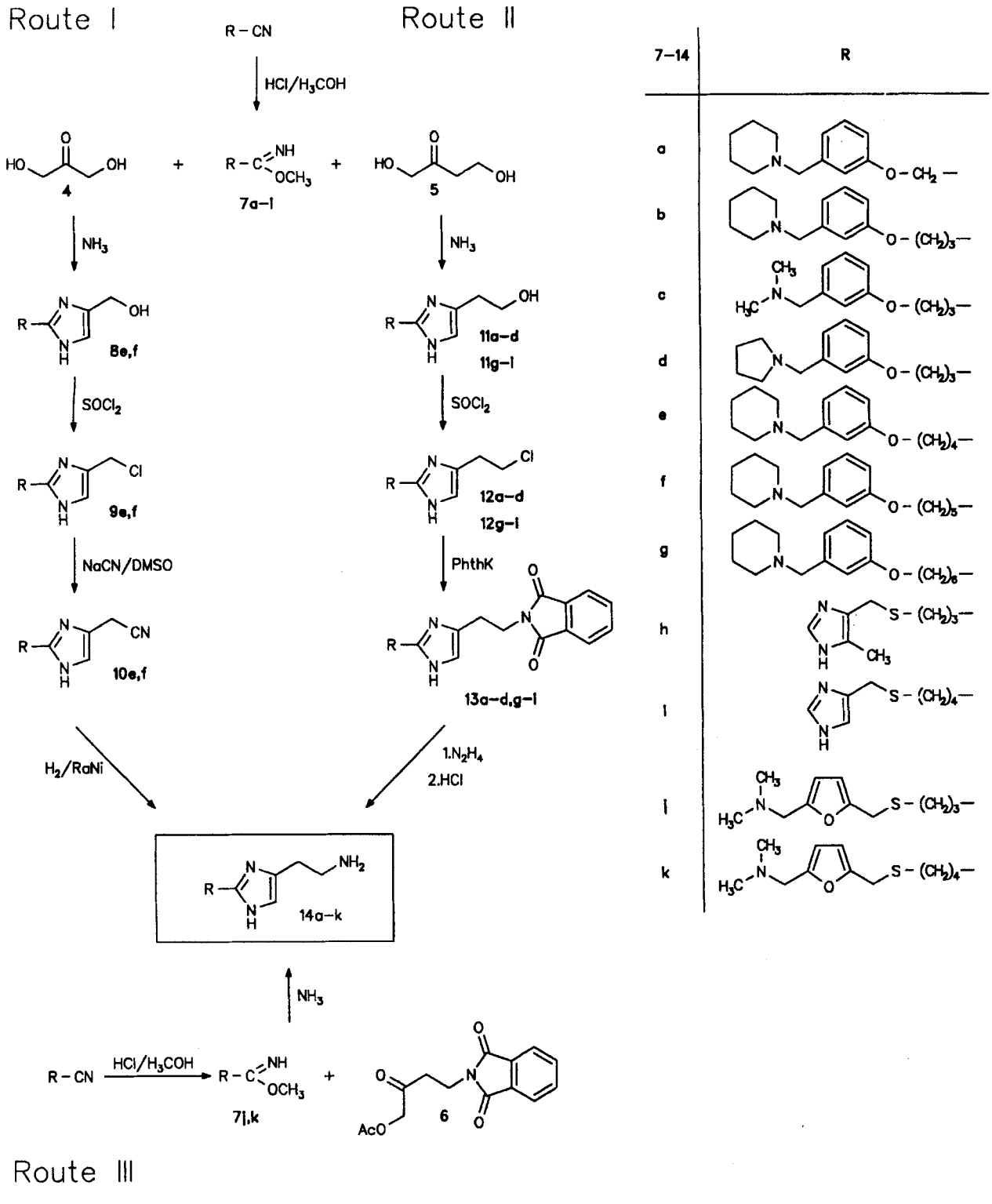

Figure 2

g (33 mmol) absol. methanol were dissolved in 150 ml of dry CH_2Cl_2. The solution was treated with dry HCl at 0 to 5°C until saturation. The reaction mixture was stirred for another two days at room temp., filtered and the solvent removed *in vacuo* (bath temp. < 25°C). A white powder was obtained under these conditions.

2-{2-[6-(3-(Piperidinomethyl)phenoxy)hexyl]imidazol-4-yl}ethanol (11g)

9.7 g (24 mmol) **7g** · 2 HCl and 2.5 g (24 mmol) **5**[16] were mixed with 150 ml of liquid NH_3 in an autoclave, sealed and stirred overnight at room temp. The reaction vessel was heated to 55-60°C, until the pressure rose up

Tab. 2. Preparative and analytical data

cpd.	yield [%]	mp [°C] (solvent)	formula (molecular mass)	analysis: calc. found C	H	N	mass[a] m/z (%)
7g	88	126	$C_{20}H_{32}N_2O_2 \cdot 2HCl$	59.3	8.45	6.91	332 ($M^{+\cdot}$, 20)
		(CH_2Cl_2)	(405.4)	59.4	8.67	6.84	
8e	81[b]	167	$C_{20}H_{29}N_3O_2 \cdot 2C_6H_3N_3O_7$	47.9	4.40	15.7	343 ($M^{+\cdot}$, 72)[c]
		(EtOH/H_2O)	(801.7)	48.0	4.40	15.7	
8f	86[d]	129	$C_{21}H_{31}N_3O_2 \cdot 2C_6H_3N_3O_7$	48.6	4.57	15.5	357 ($M^{+\cdot}$, 4)[c]
		(MeOH)	(815.7)	48.5	4.56	15.5	
9e	58	151[e]	$C_{20}H_{28}ClN_3O \cdot 2HCl \cdot 2H_2O$	51.0	7.28	8.92	362 ($M^{+\cdot}$, 2)
		Et_2O[f]	(470.8)	50.7	7.51	9.12	
9f	96	119[e]	$C_{21}H_{30}ClN_3O \cdot 2HCl \cdot 3H_2O$	50.2	7.62	8.36	375 ($M^{+\cdot}$, 2)
		Et_2O[f]	(502.9)	49.9	7.40	8.42	
10e	45[d]	145	$C_{21}H_{28}N_4O \cdot 2C_6H_3N_3O_7 \cdot 0.5\ H_2O$	48.4	4.30	17.1	352 ($M^{+\cdot}$, 14)[g]
		(EtOH/H_2O)	(819.7)	48.4	4.43	16.7	
11a	27[b]	200	$C_{18}H_{25}N_3O_2 \cdot 2C_6H_3N_3O_7$	46.8	4.04	16.3	315 ($M^{+\cdot}$, 22)[c]
		(H_2O)	(773.6)	46.6	4.01	16.5	
11b	61[d]	138	$C_{20}H_{29}N_3O_2 \cdot 2C_6H_3N_3O_7$	47.9	4.40	15.7	
		(EtOH/H_2O/Me_2CO)	(801.7)	47.8	4.37	15.7	
11c	54	77	$C_{17}H_{25}N_3O_2$	67.3	8.31	13.9	303 ($M^{+\cdot}$, 83)
		(Pe/Bz/Me_2CO)	(303.4)	67.1	8.50	13.7	
11c		79	$C_{17}H_{25}N_3O_2 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	44.7	4.27	16.2	
		(H_2O/MeOH)	(779.6)	44.6	4.19	16.0	
11d	64[h]	128	$C_{19}H_{27}N_3O_2 \cdot 2C_6H_3N_3O_7$	47.3	4.22	16.0	329 ($M^{+\cdot}$, 14)[c]
		(H_2O/EtOH)	(787.7)	47.1	4.23	16.0	
11g	56[d]	132	$C_{23}H_{35}N_2O_2 \cdot 2C_6H_3N_3O_7$	49.8	4.90	14.9	385 ($M^{+\cdot}$, 70)[g]
		(H_2O)	(843.8)	49.5	5.01	14.8	
11h	55[b]	111	$C_{13}H_{20}N_4OS \cdot 2C_4H_4O_4$	49.2	5.51	10.9	280 ($M^{+\cdot}$, 2)
		(Et_2O/EtOH)[f]	(512.5)	49.3	5.66	10.9	
11i	52[b]	98	$C_{13}H_{20}N_4OS \cdot 2C_4H_4O_4$	49.2	5.51	10.9	280 ($M^{+\cdot}$, 6)
		(Et_2O/EtOH)[f]	(512.5)	48.9	5.66	10.9	
12a	65	123	$C_{18}H_{24}ClN_3O$	64.8	7.25	12.6	333 ($M^{+\cdot}$, 3)
		(Pe/Bz)	(333.9)	64.7	7.37	12.6	
12b	73	105	$C_{20}H_{28}ClN_3O$	66.4	7.80	11.6	362 ($[M+H]^+$, 100)
		(Pe/Bz)	(361.9)	66.5	8.04	11.5	
12c	69	66	$C_{17}H_{24}ClN_3O$	63.4	7.52	13.1	321 ($M^{+\cdot}$, 12)
		(Pe/Cyh)	(321.9)	63.2	7.83	13.1	
12d	63	100	$C_{19}H_{26}ClN_3O$	65.6	7.53	12.1	347 ($M^{+\cdot}$, 20)
		(Pe/Bz)	(347.9)	65.3	7.64	11.8	
12g	74[d]	65	$C_{23}H_{34}ClN_3O \cdot 2C_4H_4O_4$	58.5	6.66	6.61	404 ($M^{+\cdot}$, 7)[g]
		(Et_2O/EtOH)[f,i]	(636.2)	58.3	6.65	6.65	
13b	68	125	$C_{28}H_{32}N_4O_3$	71.2	6.83	11.9	
		(Pe/Bz)	(472.6)	71.0	6.89	11.6	
13c	60	86	$C_{25}H_{28}N_4O_3$	69.4	6.53	13.0	432 ($M^{+\cdot}$, 4)
		(Et_2O)	(432.5)	69.1	6.46	12.8	
13d	63	103	$C_{27}H_{30}N_4O_3$	70.7	6.60	12.2	458 ($M^{+\cdot}$, 7)
		(Et_2O)[f]	(458.6)	70.6	6.88	11.9	
13g	69	107	$C_{31}H_{38}N_4O_3$	72.4	7.44	10.9	514 ($M^{+\cdot}$, 41)
		(i-Pr)$_2$O	(514.7)	72.0	7.49	10.7	
13g		156	$C_{31}H_{38}N_4O_3 \cdot 2C_4H_4O_4$	62.7	6.21	7.50	
		(Et_2O/EtOH)[f]	(746.8)	62.3	6.21	7.62	

Tab. 2. Continued

cpd.	yield [%]	mp [°C] (solvent)	formula (molecular mass)	analysis: calc. found C	H	N	mass[a] m/z (%)
13h	53[d]	154	$C_{21}H_{23}N_5O_2S \cdot 2C_4H_4O_4$	54.3	4.87	10.9	
		(Et_2O/EtOH)[f]	(641.7)	54.0	4.95	10.7	
13i	56[d]	144	$C_{21}H_{23}N_5O_2S \cdot 2C_4H_4O_4$	54.3	4.87	10.9	409 ($M^{+\cdot}$, 6)
		(Et_2O/EtOH)[f]	(641.7)	53.9	4.90	11.0	
14a	14	110[e]	$C_{18}H_{26}N_4O \cdot 3C_4H_4O_4 \cdot H_2O$	52.9	5.92	8.23	314 ($M^{+\cdot}$, 4)
		(Et_2O/EtOH)[f]	(680.7)	52.6	6.05	8.15	
14b	70[b]	131	$C_{20}H_{30}N_4O \cdot 3C_4H_4O_4$	55.7	6.13	8.11	342 ($M^{+\cdot}$, 21)[c]
		(Et_2O/EtOH)[f]	(690.7)	55.4	6.13	8.04	
14c	68[b]	126	$C_{17}H_{26}N_4O \cdot 3C_4H_4O_4$	53.5	5.89	8.61	302 ($M^{+\cdot}$, 100)[c]
		(Et_2O/EtOH)[f]	(650.4)	53.4	5.99	8.62	
14d	42[b]	128	$C_{19}H_{28}N_4O \cdot 3C_4H_4O_4$	55.0	5.96	8.28	328 ($M^{+\cdot}$, 2)
		(Et_2O/EtOH)[f]	(676.7)	54.8	6.01	8.26	
14e	24[b]	126	$C_{21}H_{32}N_4O \cdot 3C_4H_4O_4$	56.2	6.29	7.95	356 ($M^{+\cdot}$, 24)[c]
		(Et_2O/EtOH)[f]	(704.7)	56.1	6.42	7.93	
14f	22[h]	103	$C_{22}H_{34}N_4O \cdot 3C_4H_4O_4$	56.8	6.45	7.80	370 ($M^{+\cdot}$, 3)
		(Et_2O/EtOH)[f]	(718.8)	56.3[j]	6.59	7.52	
14g	59[b]	120	$C_{23}H_{36}N_4O \cdot 3C_4H_4O_4$	57.4	6.60	7.65	384 ($M^{+\cdot}$, 15)
		(Et_2O/EtOH)[f]	(732.8)	57.4	6.86	7.66	
14h	51	124	$C_{13}H_{21}N_5S \cdot 3C_4H_4O_4$	47.8	5.30	11.2	
		(Et_2O/EtOH)[f]	(627.6)	47.7	5.37	11.0	
14i	33	123	$C_{13}H_{21}N_5S \cdot 3C_4H_4O_4$	47.8	5.30	11.2	279 ($M^{+\cdot}$, 3)
		(Et_2O/EtOH)[f]	(627.6)	47.8	5.57	11.2	
14j	22	115	$C_{16}H_{26}N_4OS \cdot 3C_4H_4O_4$	50.1	5.71	8.35	
		(Et_2O/EtOH)[f]	(670.7)	49.9	5.70	8.39	
14k	33	96	$C_{17}H_{28}N_4OS \cdot 3C_4H_4O_4$	50.9	5.89	8.18	
		(Et_2O/EtOH)[f]	(684.7)	50.6	5.93	8.18	

[a] All mass spectra were recorded on a 70 eV-spectrometer, except **7g**, **11g** (80 eV) and **12b** (FAB). [b] Calculated as hydrochloride. [c] Hydrochloride measured. [d] Calculated as base. [e] Hygroscopic. [f] Absolute solvents used. [g] Base measured. [h] Crude product. [i] Cold solvents used. [j] Elemental analysis out of limit. Solvents: Bz: benzene, Cyh: cyclohexane, Pe: petroleum ether.

Tab. 3. ^{1}H-NMR-spectra

cpd.	[solvent] δ (ppm, TMS internal standard, J [Hz])
8e	[DMSO-d_6[a]][c] 14.23 (br; 2H, ImNH$^{+\bullet}$), 10.99 (br; 1H, PipNH$^{+\bullet}$), 7.40-6.97 (m; 5H, ArH), 5.64 (br; 1H, OH$^{\bullet}$), 4.47 (s; 2H, C$\underline{H}_2$-OH), 4.20 (s; 2H, CH_2-Ph), 4.04 (t; J=6.1 Hz, 2H, O-CH_2), 3.25-3.21 (m; 2H, PipH), 3.00 (t; J=7.5 Hz, 2H, CH_2-ImC2), 2.83 (m; 2H, PipH), 1.93-1.36 (m; 10H, 6PipH, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2).
8f	[D_2O[b]][c] 7.48 (dd; J=7.8/7.8, 1H, ArH), 7.29 (s; 1H, Im5-H), 7.15-7.10 (m; 3H, ArH), 4.67 (s; 2H, C$\underline{H}_2$-OH), 4.28 (s; 2H, CH_2-Ph), 4.13 (t; J=6.3 Hz, 2H, O-CH_2), 3.51-3.47 (m; 2H, PipH), 3.03 (t; J=7.3 Hz, 2H, CH_2-ImC2), 3.00-2.93 (m; 2H, PipH), 1.99-1.46 (m; 12H, 6PipH, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2).
9e	[DMSO-d_6[a]][c] 15.20-14.50 (br; 2H, ImNH$^{+\bullet}$), 10.97 (br; 1H, PipNH$^{+\bullet}$), 7.64 (s; 1H, Im5-H), 7.38-6.98 (m; 4H, ArH), 4.86 (s; 2H, CH_2-Cl), 4.20 (s; 2H, CH_2-Ph), 4.04 (t; J=6.1 Hz, 2H, O-CH_2), 3.25-3.21 (m; 2H, PipH), 3.03 (t; J=7.5 Hz, 2H, CH_2-ImC2), 2.84-2.80 (m; 2H, PipH), 1.93-1.36 (m; 10H, 6PipH, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2).
9f	[DMSO-d_6[b]][c] 10.81 (br; 1H, PipNH$^{+\bullet}$), 7.64 (s; 1H, Im5-H), 7.37-7.11 (m; 4H, ArH), 4.86 (s; 2H, CH_2-Cl), 4.21 (s; 2H, CH_2-Ph), 4.04 (t; 2H, O-CH_2), 3.40-3.33 (m; 2H, PipH), 3.21 (t; 2H, CH_2-ImC2), 3.00-2.85 (m; 2H, PipH), 1.86-1.37 (m; 12H, 6PipH, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2).
10e	[$CDCl_3$[a]][d] 11.00-10.40 (br; 1H, ImNH$^{\bullet}$), 7.20 (dd; J=7.8/7.7, 1H, ArH), 6.89 (m; 1H, Im5-H), 6.87-6.74 (m; 3H, ArH), 3.91 (t; J=5.7 Hz, 2H, O-CH_2), 3.66 (s; 2H, CH_2-CN), 3.45 (s; 2H, CH_2-Ph), 2.72 (t; J=7.3 Hz, 2H, CH_2-ImC2), 2.43 (m; 4H, PipH), 1.89-1.79 (m; 4H, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2), 1.60-1.30 (m; 6H, PipH).
11a	[D_2O[b]][c] 7.50 (dd; 1H, ArH), 7.30 (s; 1H, Im5-H), 7.22-7.16 (m; 3H, ArH), 5.47 (s; 2H, O-CH_2), 4.27 (s; 2H; CH_2-Ph), 3.95 (t; J=6.5 Hz, 2H, C$\underline{H}_2$-OH), 3.48-3.43 (m; 2H, PipH), 3.01-2.90 (m; 4H, CH_2-ImC4, 2PipH), 1.97-1.43 (m; 6H, PipH).
11b	[CD_3OD[b]][d] 7.24 (dd; J=7.7/7.2, 1H, ArH), 6.93-6.82 (m; 3H, ArH), 6.71 (s; 1H, Im5-H), 4.00 (t; J=6.2 Hz, 2H, O-CH_2), 3.74 (t; 2H, C$\underline{H}_2$-OH), 3.61 (s; 2H, CH_2-Ph), 2.86 (t; J=7.6 Hz, 2H, CH_2-ImC2), 2.74 (t; 2H, CH_2-ImC4), 2.70-2.55 (m; 4H, PipH), 2.21-2.10 (m; 2H, CH_2-C$\underline{H}_2$-CH_2), 1.69-1.50 (m; 6H, PipH).

Table 3. Continued

11c [$CDCl_3$[a)]][d)] 7.20 (dd; J=7.8/7.9, 1H, ArH), 6.90-6.76 (m; 3H, ArH), 6.67 (s; 1H, Im5-H), 3.95 (t; J=5.9 Hz, 2H, O-CH_2), 3.82 (t; 2H, J= 5.6 Hz, CH_2-OH), 3.38 (s; 2H, CH_2-Ph), 2.86 (t; J=7.2 Hz, 2H, CH_2-ImC2), 2.76 (t; J=5.6 Hz, CH_2-ImC4), 2.25 (s; 6H, $(CH_3)_2N$), 2.20-2.11 (m; 2H, CH_2-CH_2-CH_2).

11d [DMSO-d_6[a)]][c)] 14.30-14.13 (br; 2H, ImNH^{+*}), 11.28 (br; 1H, PyrrNH^{+*}), 7.49-6.90 (m; 5H, ArH), 4.29 (s; 2H, CH_2-Ph), 4.07 (t; 2H, O-CH_2), 3.65 (t; J=6.2 Hz, 2H, CH_2-OH), 3.34-3.04 (m; 6H, 4PyrrH, CH_2-ImC2), 2.73 (t; J=6.2 Hz, 2H, CH_2-ImC4), 2.24 (m; 2H, CH_2-CH_2-CH_2), 2.20-1.90 (m; 4H, PyrrH).

11g [$CDCl_3$[b)]][d)] 7.20 (dd; J=7.8/7.8, 1H, ArH), 6.89-6.78 (m; 3H, ArH), 6.66 (s; 1H, Im5-H), 3.95 (t; J= 6.4 Hz, 2H, O-CH_2), 3.73 (t; J=7.0 Hz, 2H, CH_2-OH), 3.44 (s; 2H, CH_2-Ph), 2.73 (t; J=7.0 Hz, 2H, CH_2-ImC4), 2.65 (t; J=7.5 Hz, CH_2-ImC2), 2.40 (m; 4H, PipH), 1.81-1.65 (m; 4H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2), 1.63-1.35 (m; 10H, 6PipH, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2).

11h [DMSO-d_6[a)]][e)] 8.71 (s; 1H, Im2-H), 7.31 (s; 1H, Im5-H), 6.06 (s; 4H, Mal), 3.79 (s; 2H, ImCH_2-S), 3.64 (t; J=6,4 Hz, 2H, CH_2-OH), 2.94 (t; J=7.6 Hz, 2H, CH_2-ImC2), 2.73 (t; J=6.3 Hz, 2H, CH_2-ImC4), 2.48 (t; 2H, S-CH_2-CH_2), 2.23 (s; 3H, CH_3), 2.01-1.94 (m; 2H, CH_2-CH_2-CH_2).

11i [DMSO-d_6[b)]][e)] 8.67 (s; 1H, Im2-H), 7.40 (s; 1H, Im5-H), 7.31 (s; 1H, Im5-H), 6.08 (s; 4H, Mal), 3.77 (s; 2H, ImCH_2-S), 3.64 (t; J=6.4 Hz, 2H, CH_2-OH), 2.87 (t; J=7.6 Hz, 2H, CH_2-ImC2), 2.73 (t; J=6.3 Hz, 2H, CH_2-ImC4), 2.48 (t; 2H, S-CH_2-CH_2), 1.78-1.69 (m; 2H, CH_2), 1.58-1.49 (m; 2H, CH_2).

12a [$CDCl_3$[b)]][d)] 10.20 (br; 1H, ImNH*), 7.36-7.17 (m; 2H, ArH), 6.96-6.80 (m; 3H, ArH), 5.08 (s; 2H, O-CH_2), 3.77 (t; J=7.0 Hz, 2H, CH_2-Cl), 3.45 (s; 2H, CH_2-Ph), 3.05 (t; J=6.9 Hz, 2H, CH_2-ImC4), 2.38-2.36 (m; 4H, PipH), 1.60-1.43 (m; 6H, PipH).

12b [$CDCl_3$[b)]][d)] 7.19 (dd; J=7.9/8.1, 1H, ArH), 7.00-6.76 (m; 3H, ArH), 6.75 (s; 1H, Im5-H), 3.97 (t; 2H, O-CH_2), 3.75 (t; J=7.1 Hz, 2H, CH_2-Cl), 3.44 (s; 2H, CH_2-Ph), 3.02 (t; J=7.0 Hz, 2H, CH_2-ImC4), 2.95 (t; J=7.3 Hz, 2H, CH_2-ImC2), 2.47-2.40 (m; 4H, PipH), 2.22-2.12 (m; 2H, CH_2-CH_2-CH_2), 1.62-1.43 (m; 6H, PipH).

12c [$CDCl_3$[b)]][d)] 7.21 (dd; J=8.1/7.9, 1H, ArH), 6.89-6.75 (m; 4H, ArH), 3.98 (t; J=6.0 Hz, 2H, O-CH_2), 3.75 (t; J=6.5 Hz, 2H, CH_2-Cl), 3.40 (s; 2H, CH_2-Ph), 3.02 (t; J=7.0 Hz, 2H, CH_2-ImC4). 2.86 (t; J=7.4 Hz, 2H, CH_2-ImC2), 2.25 (s; 6H, $(CH_3)_2N$), 2.20-2.14 (m; 2H, CH_2-CH_2-CH_2).

12d [$CDCl_3$[b)]][d)] 7.26-7.17 (m; 1H, ArH), 6.91-6.73 (m; 4H, ArH), 3.97 (t; J=5.9 Hz, 2H, O-CH_2), 3.74 (t; J=6.5 Hz, 2H, CH_2-Cl), 3.59 (s; 2H, CH_2-Ph), 3.01 (t; J=7.0 Hz, 2H, CH_2-ImC4), 2.84 (t; J=7.4 Hz, 2H, CH_2-ImC2), 2.56-2.51 (m; 4H, PyrrH), 2.21-2.10 (m; 2H, CH_2-CH_2-CH_2), 1.81-1.76 (m; 4H, PyrrH).

12g [$CDCl_3$[b)]][d)] 7.30-7.19 (m; 1H, ArH), 6.96-6.76 (m; 3H, ArH), 6.74 (s; 1H, Im5-H), 3.94 (t; 2H, O-CH_2), 3.76 (t; J=7.0 Hz, 2H, CH_2Cl), 3.47 (s; 2H, CH_2-Ph), 3.03 (t; J=7.0 Hz, 2H, CH_2-ImC4), 2.70 (t; J=7.7 Hz, CH_2-ImC2), 2.65 (m; 4H, PipH), 1.96-1.34 (m; 14H, 6PipH, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2).

13b [$CDCl_3$[b)]][d)] 7.80-7.63 (m; 4H, PhthH), 7.17 (dd; J=8.1/7.7, 1H, ArH), 6.87-6.71 (m; 3H, ArH), 6.66 (s; 1H, Im5-H), 3.97-3.89 (m; 4H, O-CH_2, CH_2-Phth), 3.41 (s; 2H, CH_2-Ph), 2.95 (t; J=7.2 Hz, 2H, CH_2-ImC4), 2.80 (t; J=7.3 Hz, CH_2-ImC2), 2.37 (m; 4H, PipH), 2.15-2.05 (m; 2H, CH_2-CH_2-CH_2), 1.59-1.41 (m; 4H, PipH).

13c [$CDCl_3$[b)]][d)] 7.84-7.66 (m; 4H, PhthH), 7.27-7.17 (m; 1H, ArH), 6.88-6.75 (m; 3H, ArH), 6.68 (s; 1H, Im5-H), 3.98-3.92 (m; 4H, O-CH_2, CH_2-Phth), 3.39 (s; 2H, CH_2-Ph), 2.97 (t; J=7.2 Hz, 2H, CH_2-ImC4), 2.82 (t; J=7.2 Hz, CH_2-ImC2), 2.24 (s; 6H, $(CH_3)_2N$), 2.17-2.09 (m; 2H, CH_2-CH_2-CH_2).

13d [$CDCl_3$[b)]][d)] 7.81-7.65 (m; 4H, PhthH), 7.19 (dd; J=7.7/7.8, 1H, ArH), 6.90-6.74 (m; 3H, ArH), 6.66 (s; 1H, Im5-H), 4.01-3.92 (m; 4H, O-CH_2, CH_2-Phth), 3.57 (s; 2H, CH_2-Ph), 2.96 (t; J=7.2 Hz, 2H, CH_2-ImC4), 2.81 (t; J=7.2 Hz, CH_2-ImC2), 2.59-2.51 (m; 4H, PyrrH), 2.16-2.08 (m; 2H, CH_2-CH_2-CH_2), 1.83-1.76 (m; 4H, PyrrH).

13g [$CDCl_3$[a)]][d)] 9.70-9.20 (br; 1H, ImNH*), 7.82-7.67 (m; 4H, PhthH), 7.21 (dd; J=8/8, 1H, ArH), 6.88-6.75 (m; 3H, ArH), 6.67 (s; 1H, Im5-H), 3.97-3.89 (m; 4H, O-CH_2, CH_2-Phth), 3.43 (s; 2H, CH_2-Ph), 2.97 (t; J=7.0 Hz, 2H, CH_2-ImC4), 2.65 (t; J=7.7 Hz, CH_2-ImC2), 2.38 (m; 4H, PipH), 1.77-1.41 (m; 14H, 6PipH, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2).

13h [DMSO-d_6[a)]][e)] 8.73 (s; 1H, Im2-H), 7.85 (m; 4H, PhthH), 7.34 (s; 1H, Im5-H), 6.06 (s; 4H, Mal), 3.84 (t; J=6.6 Hz, 2H, CH_2-Phth), 3.79 (s; 2H, ImCH_2-S), 2.93-2.89 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.44 (t; 2H, S-CH_2-CH_2), 2.23 (s; 3H, CH_3), 1.95-1.90 (m; 2H, CH_2-CH_2-CH_2).

13i [DMSO-d_6[a)]][e)] 8.68 (s; 1H, Im2-H), 7.85 (m; 4H, PhthH), 7.40 (s; 1H, Im5-H), 7.35 (s; 1H, Im5-H), 6.07 (s; 4H, Mal), 3.84 (t; 2H, CH_2-Phth), 3.78 (s; 2H, ImCH_2-S), 2.94 (t; 2H, CH_2-ImC2), 2.84 (t; J=7.2 Hz, 2H, CH_2-ImC4), 2.47 (t; 2H, S-CH_2-CH_2), 1.72-1.50 (m; 4H, CH_2-CH_2-CH_2-CH_2).

14a [DMSO-d_6[a)]][e)] 8.26-7.82 (br; 3H, NH_3^{+*}), 7.43 (m; 1H, ArH), 7.17 (s; 1H, Im5-H), 7.13-7.10 (m; 3H, ArH), 6.11 (s; 6H, Mal), 5.10 (s; 2H, O-CH_2), 4.26 (s; 2H, CH_2-Ph), 3.07 (m; 4H, CH_2-NH_3^+, 2PipH), 2.82 (br; 4H, CH_2-ImC4, 2PipH), 1.95-1.30 (m; 6H, PipH).

14b [DMSO-d_6[a)]][c)] 14.80-14.30 (br; 2H, ImNH^{+*}), 10.88 (br; 1H, PipNH^{+*}), 8.34 (br; 3H, NH_3^{+*}), 7.40-6.93 (m; 5H, ArH), 4.21 (s; 2H, CH_2-Ph), 4.09 (t; J=5.9 Hz, 2H, O-CH_2), 3.48-3.41 (m; 2H, PipH), 3.26-2.97 (m; 6H, CH_2-NH_3^+, CH_2-ImC2, CH_2-ImC4), 2.85 (m; 2H, PipH), 2.27 (m; 2H, CH_2-CH_2-CH_2), 1.78-1.20 (m; 6H, PipH).

14c [DMSO-d_6[b)]][c)] 14.54 (br; 2H, ImNH^{+*}), 10.96 (br; 1H, $(CH_3)_2NH^{+*}$), 8.40-8.37 (br; 3H, NH_3^{+*}), 7.40-7.32 (m; 1H, ArH), 7.26 (s; 1H, Im5-H), 7.14-6.94 (m; 3H, ArH), 4.25 (s; 2H, CH_2-Ph), 4.09 (t; J=6.0 Hz, 2H, O-CH_2), 3.18-2.97 (m; 6H, CH_2-NH_3^+, CH_2-ImC2, CH_2-ImC4), 2.67 (s; 6H, $(CH_3)_2N$), 2.30-2.25 (m; 2H, CH_2-CH_2-CH_2).

14d [DMSO-d_6[a)]][e)] 8.40-7.60 (br; 3H, NH_3^{+*}), 7.38 (dd; J=8.1/8.1, 1H, ArH), 7.29 (s; 1H, Im5-H), 7.07-6.96 (m; 3H, ArH), 6.06 (s; 6H, Mal), 4.31 (s; 2H, CH_2-Ph), 4.06 (t; J=5.9 Hz, 2H, O-CH_2), 3.22 (m; 4H, PyrrH), 3.10 (br; 2H, CH_2-NH_3^+), 2.99 (t; J=7.5 Hz, 2H, CH_2-Im), 2.87 (t; J=7.4 Hz, 2H, CH_2-Im), 2.17 (m; 2H, CH_2-CH_2-CH_2), 1.95 (m; 4H, PyrrH).

14e [DMSO-d_6[a)]][c)] 15.00-14.20 (br; 2H, ImNH^{+*}), 10.91 (br; 1H, PipNH^{+*}), 8.33 (br; 3H, NH_3^{+*}), 7.40-6.99 (m; 5H, ArH), 4.21 (s; 2H, CH_2-Ph), 4.04 (t; J=6.0 Hz, 2H, O-CH_2), 3.24 (m; 2H, PipH), 3.17-3.12 (br; 2H, CH_2-NH_3^+), 3.01-2.96 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.88 (m; 2H, PipH), 1.91-1.38 (m; 10H, 6PipH, CH_2-CH_2-CH_2-CH_2).

14f [DMSO-d_6[a)]][e)] 8.20-7.70 (br; NH_3^{+*}), 7.40-7.35 (m; 2H, ArH), 7.07-7.00 (m; 3H, ArH), 6.08 (s; 6H, Mal), 4.24 (s; 2H, CH_2-Ph), 3.98 (t; J=6.1 Hz, 2H, O-CH_2), 3.39-3.37 (m; 2H, PipH), 3.11-2.88 (m; 10H), 1.76-1.45 (m; 12H, 6PipH, CH_2-CH_2-CH_2-CH_2-CH_2).

14g [DMSO-d_6[a)]][e)] 8.20-7.70 (br; NH_3^{+*}), 7.38 (dd; J=7.8/7.8, 1H, ArH), 7.32 (s; 1H, Im5-H), 7.07-7.00 (m; 3H, ArH), 6.06 (s; 6H, Mal), 4.23 (s; 2H, CH_2-Ph), 3.97 (t; J=6.4 Hz, 2H, O-CH_2), 3.40 (m; 2H, PipH), 3.11 (m; 4H, CH_2-NH_3^+, 2PipH), 2.91-2.51 (m; 4H, CH_2-ImC2, CH_2-ImC4), 1.80-1.30 (m; 14H, 6PipH, CH_2-CH_2-CH_2-CH_2-CH_2-CH_2).

14h [DMSO-d_6[b)]][e)] 8.73 (s; 1H, Im2-H), 8.40-7.50 (br; NH_3^+), 7.31 (s; 1H, Im5-H), 6.07 (s; 4H, Mal), 3.80 (s; 2H, ImCH_2-S), 3.10 (br; 2H, CH_2-NH_3^+), 2.92-2.84 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.47 ((t); 2H, S-CH_2-CH_2), 2.23 (s; 3H, CH_3), 1.97-1.93 (m; 2H, CH_2-CH_2-CH_2).

14i [DMSO-d_6[a)]][e)] 8.66 (s; 1H, Im2-H), 8.50-7.50 (br; NH_3^{+*}), 7.40 (s; 1H, Im5-H), 7.36 (s; 1H, Im5-H), 6.08 (s; 6H, Mal), 3.77 (s; 2H, ImCH_2-S), 3.10 (t; 2H, CH_2-NH_3^+), 2.92-2.85 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.51 (t; 2H, S-CH_2-CH_2), 1.75-1.55 (m; 4H, CH_2-CH_2-CH_2-CH_2).

14j [DMSO-d_6[a)]][e)] 8.40-7.50 (br; NH_3^{+*}), 7.30 (s; 1H, Im5-H), 6.60 (d; J=3.1 Hz, 1H,

Table 3. Continued

	FurH), 6.36 (d; J=3.1 Hz, 1H, FurH), 6.07 (s; 6H, Mal), 4.32 (s; 2H, N-CH_2-Fur), 3.81 (s; 2H, Fur-CH_2-S), 3.10 (br; 2H, C$\underline{H}_2$-NH_3^+), 2.92-2.85 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.71 (s; 6H, $(CH_3)_2N$), 2.54 (t; 2H, S-C$\underline{H}_2$-CH_2), 2.00-1.93 (m; 2H, CH_2-C$\underline{H}_2$-CH_2).
14k	[DMSO-d_6[a)]][e)] 8.40-7.50 (br; NH_3^{+*}), 7.31 (s; 1H, Im5-H), 6.60 (d; J=3.1 Hz, 1H, FurH), 6.36 (d; J=3.1 Hz, 1H, FurH), 6.06 (s; 6H, Mal), 4.31 (s; 2H, N-CH_2-Fur), 3.78 (s; 2H, Fur-CH_2-S), 3.10 (br; 2H, C$\underline{H}_2$-NH_3^+), 2.90-2.80 (m; 4H, CH_2-ImC2, CH_2-ImC4), 2.71 (s; 6H, $(CH_3)_2N$), 2.48 (t; 2H, S-C$\underline{H}_2$-CH_2), 1.77-1.53 (m; 2H, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2).

[a)] 300 MHz-spectra. [b)] 250 MHz-spectra. [c)] Hydrochloride measured. [d)] Base measured. [e)] Hydrogen maleate measured. Abbreviations used: Im = imidazole, Pip = piperidine, Ph = phenyl, Pyrr = pyrrolidine, Fur = furane, Mal = maleic acid, ArH = protons of aromatic or heterocyclic moieties, Phth = phthalimide, br = broad, * = exchangeable with D_2O.

to 20 bar for 5 h. After opening and evaporation of NH_3 at room temp., the slurry was suspended in ethanol and liberated from inorganic material. Further work up was realized by prep. cc (400 g silica gel; 90% DCM/10% MA). The product was an oily base, for analytical purposes a picrate was prepared.

2-{2-[(3-(Piperidinomethyl)phenoxy)methyl]imidazol-4-yl}ethanol (**11a**)

The reaction was carried out as for compound **11g** with 13.5 g (58.6 mmol) 2-[3-(piperidinomethyl)phenoxy]ethanimidic acid methylester · 2 HCl (**7a**) and 6.1 g (58.6 mmol) **5**[16] in 200 ml of liquid NH_3, with the exception, that the autoclave was heated immediately after closing until the pressure rose up to 14-15 bar. After 16 h the reaction was terminated and **11a** was purified by cc (conditions see **11g**), followed by the formation of a hydrochloride and of a picrate.

4-(2-Chloroethyl)-2-{6-[3-(piperidinomethyl)phenoxy]hexyl}imidazole (**12g**)

3.9 g **11g** · 2 HCl (10 mmol) were treated with 50 ml of $SOCl_2$ and stirred for 4 h at room temp. under the exclusion of moisture. After evaporation of remainder $SOCl_2$ the residue was dissolved in water. The acidic layer was extracted three times with ether, alkalized with a few drops of 2 N-NaOH and then 3-4 times extracted with cold ether. The org. layer was washed with water and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, a clear oil was obtained. For analytical purposes, a small probe was treated with dry maleic acid in cold absol. ether/ethanol to form a hydrogen maleate.

N-{2-[2-[6-(3-(Piperidinomethyl)phenoxy)hexyl]imidazol-4-yl]ethyl}phthalimide (**13g**)

1.3 g (6.8 mmol) potassium phthalimide were suspended in 40 ml of dry DMF and under stirring heated to 120°C. 2.5 g (6.2 mmol) **12g** (base) in 20 ml absol. DMF were added dropwise. The reaction was finished after about 3 h. The cold solution was poured into 300 ml of water, extracted three times with ether and the ether phase was dried over Na_2SO_4. The drying material was filtered off and the solvent was removed *in vacuo*. The residue solidified immediately after short storage in a freezer and was recrystallized from diisopropylether.

2-{2-[6-(3-(Piperidinomethyl)phenoxy)hexyl]imidazol-4-yl}ethanamine (**14g**)

1.6 g (3.1 mmol) **13g** were suspended in a small quantity of ethanol, refluxed with 0.17 g (3.4 mmol) hydrazine hydrate for 2-3 h (TLC-control necessary!), and subsequently treated with a surplus of 2 N-HCl. The suspension was refluxed for another 30 min and then allowed to cool. After filtration, the acidic layer was extracted twice with each a small portion of CH_2Cl_2 and then alkalized with 2 N-NaOH. The inorganic layer was repeatedly extracted with mixtures of CH_2Cl_2/*i*-PrOH (3:1). After evaporation of the solvents *in vacuo*, the pure base was transformed into the appropriate hydrochloride and, as an alternative, into the hydrogen maleate.

2-{2-{3-[[(5-(N,N-Dimethylaminomethyl)furan-2-yl)methyl]thio]propyl}-imidazol-4-yl}ethanamine (**14j**)

The reaction was performed as described for compound **11g** from 12.6 (36.7 mmol) 4-{[(5-*N,N*-dimethylaminomethyl)furan-2-yl)methyl]thio}-butanimidic acid methylester · 2 HCl (**7j**) and 10.1 g (36.7 mmol) 2-oxo-4-phthalimido-1-butyl acetate[7] (**6**) in 150 ml of liquid NH_3. After complete removal of NH_3 at room temp., the residue was suspended with ethanol and inorganic material was filtered off. The filtrate was evaporated to dryness *in vacuo* and then again dissolved in a small quantity of ethanol. The solution was slowly treated with 4.2 g (19 mmol) *N*-ethoxycarbonylphthalimide. The appropriate phthalimide of **14j** was directly purified by prep. cc (stationary phase: 400 g silicagel; 92% DCM/8% MA). Subsequent hydrazinolysis afforded the pure amine **14j**, which was treated with dry maleic acid in absol. ether/ethanol to form a hydrogen maleate.

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