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New imidazoline/α_2-adrenoceptors affecting compounds—4(5)-(2-aminoethyl)imidazoline (dihydrohistamine) derivatives. Synthesis and receptor affinity studies

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ABSTRACT

Compilation of agmatine structure and imidazoline moiety leads to a new group of imidazoline/α_2-adrenoceptor ligands, 4(5)-(2-aminoethyl)imidazoline derivatives. In this study the exploration of previously unknown 4(5)-(2-aminoethyl)imidazolines including the analogues of reported imidazoline and α_2-adrenoceptors ligands: clonidine, rilmenidine, idazoxan, efaroxan, antazoline, tracizoline is described. The synthesis of a variety of novel 4(5)-(2-aminoethyl)imidazolines and their I_1, I_2, α_2-adrenoceptors affinities are reported.

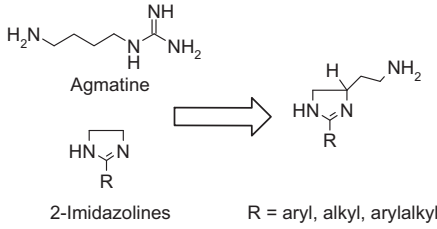
1. Introduction

Imidazolines are a numerous family of biologically active compounds known from comprehensive therapeutic applications. Most recent hypotheses connect activity of imidazolines with three types of imidazoline receptors (I_1, I_2 and I_3) and α_2-adrenoceptors in different parts of CNS and peripheral tissues. These molecular targets are responsible for the versatile biological activities of imidazolines discussed in many reviews: antihypertensive, antiallergic, antihypertensive, antidiabetic, sympatholytic, analgetic and anxiety-relieving properties.[1–3]

Several compounds were reported as the natural ligands of imidazoline receptors, including β-carbolines,[4,5] imidazolacetic acid ribotide[6] and agmatine.[7]

We have recently reported a new group of compounds (4(5)-(2-aminoethyl)imidazoline derivatives) that are structural analogues of imidazoline ring and the natural ligand of imidazoline receptors—agmatine.[8] This group of heterocyclic compounds posses much higher affinity to imidazoline receptors than agmatine itself. That study lead us to a hypothesis that the imidazoline ring derivatization of known I/α_2 ligands in 4(5) position may lead to a new group of biologically active compounds.

In this study we describe the further exploration of previously unknown 4(5)-(2-aminoethyl)imidazolines including the analogues of known synthetic imidazoline and α_2-adreno receptors ligands: clonidine, rilmenidine, idazoxan, efaroxan, antazoline and tracizoline. In this work the synthetic methods and I/α_2 receptors affinity studies are reported.



2. Results and discussion

2.1. Chemistry

The syntheses of 4(5)-(2-aminoethyl)imidazoline derivatives were performed with the modified methods reported recently.[9] The synthetic pathway began with the preparation of the selectively N^4-protected (2*S*)- and (2*R*)-1,2,4-triaminobutane (**1a** and **1b**) according to the literature procedure[10] starting from L or D-glutamic acid.

2.1.1. [4(5)*S*]-4(5)-(2-Aminoethyl)-2-benzylaminoimidazoline dihydrobromide (5)

Compound **5** was synthesized using modified method reported for 2-benzylaminoimidazoline preparation (Scheme 1).[11] In the first step the cyclic thiourea **2** was obtained from **1a** and CS_2.[12]

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Then compound **2** was reacted with EtI yielding **3**. The ethylmercapto-group of **3** was substituted with benzylamine according to the reported method[11] and further the benzyloxycarbonyl group of **4** was cleaved with HBr in AcOH yielding **5**.

2.1.2. 2-Arylamino 4(5)-(2-aminoethyl)imidazoline derivatives

A series of 4(5)-(*N*-benzyloxycarbonyl-2-aminoethyl)-2-arylaminoimidazolines (**6c–16c**, **6e–16e**) were synthesized from selectively protected triaminobutanes (**1a** or **1b**) using isothioureas iodides (**6b–16b**) as cyclisation agents (Scheme 2).[13,14] N-Substituted thioureas were purchased from commercial sources (**6a–8a**, **14a–16a**) or were prepared from appropriate amines according to the reported method (**9a–13a**).[17] The isothioureas (**6b–16b**) were prepared from appropriate thioureas and MeI or EtI in alkylation reactions according to the literature procedure.[15] The excess of diamine over isothiourea hydroiodide in cyclisation reaction was not necessary. The triaminobutane derivatives **1a** or **1b** were reacted with isothioureas in a 1:1 molar ratio. The benzyloxycarbonyl groups were cleaved with HBr in AcOH yielding (**6d–16d**, **13f–16f**).

2.1.3. [4(5)*S*]-4(5)-(2-aminoethyl)-2-[dicyclopropylmethyl)amino]imidazoline dihydrochloride (17d), a guanidine analogue of rilmenidine

Synthesis of **17d** was performed applying the isothiourea derivatives cyclisation method[13,14] of vicinal diamines to obtain triaminobutane derivative **1a** and isothiourea **17b**. Dicyclopropylm ethylamine **17a** was obtained from dicyclopropylketone as reported.[16] **17a** was converted into thiourea applying the literature method[17] and alkylated with MeI yielding **17b**.

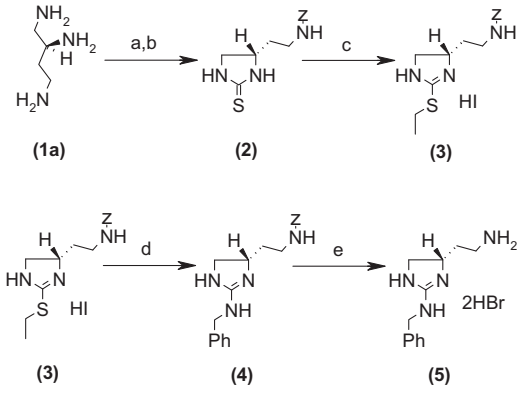
Due to the lability of dicyclopropylmethyl group in acidic conditions, HBr in glacial acetic acid was not suitable as benzyloxycarbonyl group remover. The protecting group of **17c** was cleaved with H_2/Pd/C yielding **17d** (Scheme 3).

2.1.4. Tolazoline (19) and naphazoline (21a,21b) analogues

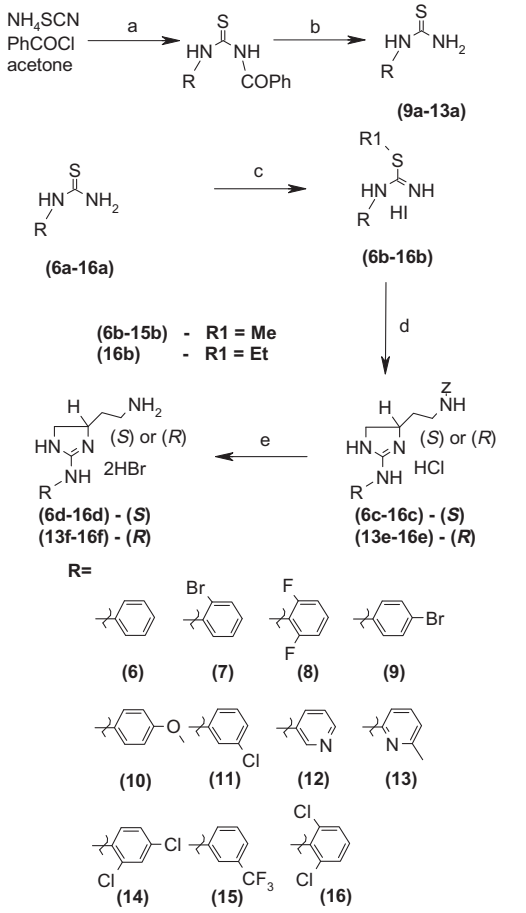
The synthesis of **19**, **21a**, **21b** was designed applying iminoesters hydrochlorides as cyclisation agents of vicinal diamines, using in this case triaminobutane derivatives **1a** and **1b**. The iminoesters of phenyl- and naphthylacetic acids were prepared as previously reported[18,19] and were reacted with selectively protected triaminobutanes **1a** or **1b** yielding **18**, **20a** or **20b**. The cleavage of benzyloxycarbonyl groups was performed with HBr in AcOH (Scheme 4).

2.1.5. [4(5)*S*]-(25a) and [4(5)*R*]-4(5)-(2-Aminoethyl)-2-(2-ethyl-2,3-dihydro-1-benzofurane-2)imidazoline dihydrobromide (25b) (efaroxane analogues)

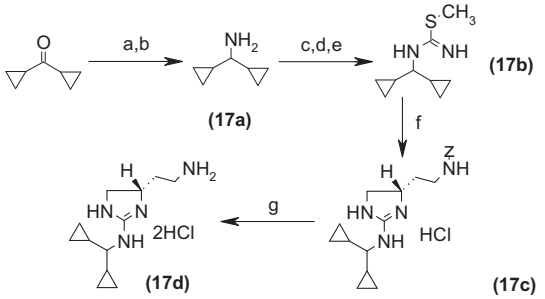
The racemic methyl ester **22** was obtained according to the reported procedure[20] and converted into corresponding amide



Scheme 1. Reagents and conditions: (a) EtOH, H_2O, Et_3N, CS_2, 5 h, 60 °C; (b) HCl, 9 h, reflux; (c) EtI, MeOH, 2 h, reflux; (d) $PhCH_2NH_2$, *t*-BuOH, 5 h, reflux; (e) HBr/AcOH, 3 h, rt.



Scheme 2. Reagents and conditions: (a) RNH_2, 30 min, reflux; (b) 2.5 M NaOH, 40 min, 90 °C; (c) MeI or EtI, MeOH, 3 h, reflux; (d) **1a** or **1b**, *n*-pentanol, 24 h, reflux; (e) HBr/AcOH, 3 h, rt.

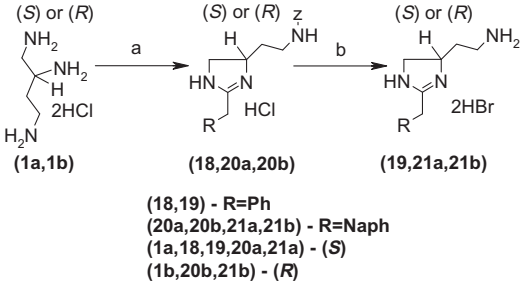


Scheme 3. Reagents and conditions: (a) NH_2OH, pyridine, 4 h, 100 °C; (b) $LiAlH_4$, THF, Et_2O, 6 h, reflux; (c) NaSCN, PhCOCl, acetone, 1.5 h, reflux; (d) 2.5 M NaOH, 1.5 h, 90 °C; (e) MeI, MeOH, 3 h, reflux; (f) **1a**, *n*-pentanol, 24 h reflux; (g) H_2, 10% Pd/C, MeOH, 4 h.

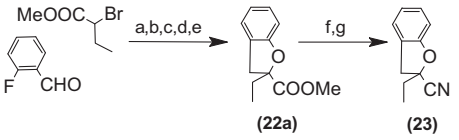
with NH_3/MeOH. Then the amide was dehydrated with $POCl_3$/pyridine[21,22] yielding **23** (Scheme 5). Nitrile **23** was converted in situ into iminoester with sodium ethoxide[21,23] and reacted with **1a** or **1b** yielding **24a** or **24b** (Scheme 6). Finally the N-protecting benzyloxycarbonyl groups were removed with HBr in AcOH.

2.1.6. 4(5)*S*]-(29a) and [4(5)*R*]-4(5)-(2-Aminoethyl)-2-(2,3-dihydro-1,4-benzodioxane-2)imidazoline (29b) dihydrobromide (idazoxane analogues)

The racemic nitrile **26** was obtained and converted into iminoester **27** according to the reported procedure (Scheme 7).[24] Then



Scheme 4. Reagents and conditions: (a) $PhCH_2(NH)OEt{\cdot}HCl$ or Naph $CH_2(NH)OEt{\cdot}HCl$, EtOH, Et_3N; (b) HBr/AcOH, 3 h, rt.



Scheme 5. Reagents and conditions: (a) *t*-BuOK, dioxane, 18 h, rt; (b) H_2 10% Pd/C, MeOH, 24 h, rt; (c) 1 M NaOH, THF, 24 h, rt; (d) NaH, DMF, $PhCH_3$, 16 h, 110–120 °C; (e) $SOCl_2$, MeOH, 24 h, rt; (f) 24% NH_3/MeOH, 48 h, rt; (g) $POCl_3$, pyridine, 3 h, reflux.

compound **27** was reacted with **1a** or **1b** yielding **28a** or **28b**. The *N*-benzyloxycarbonyl groups were cleaved with HBr in AcOH (Scheme 8).

2.1.7. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(*N*-benzyl-*N*-phenyl) aminomethyl]imidazoline trihydrobromide (antazoline analogue) (30c)

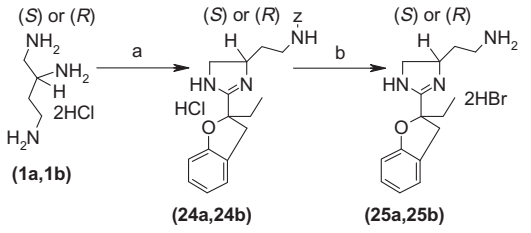
The synthesis of antazoline analogue was performed according to the reported method[25] using 2-(chloromethyl)imidazoline[26] derivative as a substrate. Chloroacetonitrile was converted into iminoacetate and reacted with **1a** yielding **30a**. Compound **30a** was next condensed with *N*-benzylaniline and further the *N*-benzyloxycarbonyl group was cleaved with HBr in AcOH yielding **30c** (Scheme 9).

2.1.8. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-phenylimidazoline dihydrobromide (31b)

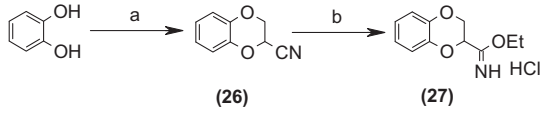
The imidazoline **31a** was synthesized from **1a** and iminoester hydrochloride obtained from benzonitrile (Scheme 10). The N-protecting group was removed using standard HBr in AcOH method yielding **31b**.

2.1.9. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-(2-fluorophenyl)imidazoline dihydrobromide (32b) and [4(5)*S*]-4(5)-(2-aminoethyl)-2-[(*E*)-2-phenylethenyl]imidazoline dihydrobromide (33b) (tracizoline analogue)

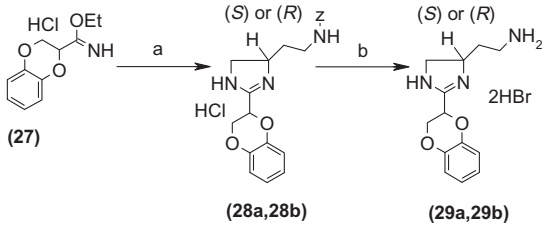
Imidazolines **32a** and **33a** were synthesized using the recently reported vicinal diamines cyclisation method into imidazoline ring with aldehydes and *N*-bromosuccinimide.[27] **1a** was reacted appropriately with 2-fluorobenzaldehyde or cinnamaldehyde yielding



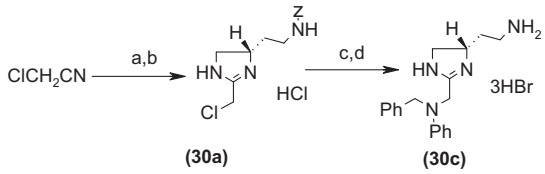
Scheme 6. Reagents and conditions: (a) **23**, EtONa, EtOH, 12 h, rt; (b) HBr/AcOH, 3 h, rt.



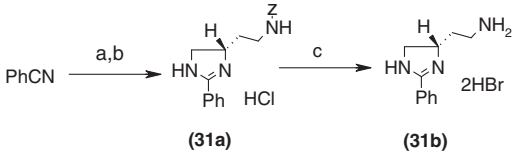
Scheme 7. Reagents and conditions: (a) CH_2CClCN, acetone, 18 h, reflux; (b) EtOH, 2 M HCl/Et_2O.



Scheme 8. Reagents and conditions: (a) **1a** or **1b**, Et_3N, EtOH, 4 h, reflux; (b) HBr/AcOH, 3 h, rt.



Scheme 9. Reagents and conditions: (a) EtOH, 2 M HCl/Et_2O; (b) **1a**, EtONa, EtOH, 1.5 h, reflux; (c) $PhCH_2(Ph)NH$, EtOH, 24 h, reflux; (d) HBr/AcOH, 3 h, rt.



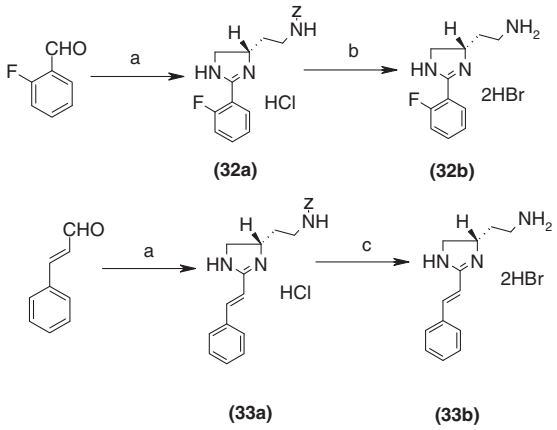
Scheme 10. Reagents and conditions: (a) EtOH, 2 M HCl/Et_2O; (b) **1a**, Et_3N, EtOH, 3 h, reflux; (c) HBr/AcOH, 3 h, rt.

32a or **33a**. The *N*-benzyloxycarbonyl groups were removed with HBr in AcOH (Scheme 11). Due to the lability of the double bond in tracizoline analogue, the HBr/AcOH treatment was shortened to 30 min.

2.2. α_2-Adrenoceptor and imidazoline I_1 and I_2 receptors affinity studies

The newly prepared imidazoline ligands were investigated for the affinity to α_2-adrenoceptor, imidazoline I_1 and imidazoline I_2 binding sites. Clonidine hydrochloride was enclosed as reference compound. The affinity studies were performed using kidney and brain male Sprague–Dawley rats P_2 membranes as was reported recently.[28] The results are shown in Table 1. Clonidine and agmatine were enclosed as reference compounds.

Looking through the reported data (e.g., for clonidine)[29–32] it is clear that affinity values are very variable to species, tissues and type of radioligand. As a conclusion form the literature studies—compound posses the affinity to I or α_2-adrenoceptors if K_i or IC_{50} is close to 1000 nM or below this value. If the reported K_i or IC_{50} were below 100 nM the affinities were described as high. The affinity values are very variable to species, tissues and type of radioligand. In this study several compounds with moderate affinities to I_1, I_2 and α_2-adrenoceptors were discovered.



Scheme 11. Reagents and conditions: (a) **1a**, SuNBr, CH_2Cl_2, 13 h, 0 °C to rt; (b) HBr/AcOH, 3 h, rt; (c) HBr/AcOH, 0.5 h, rt.

Table 1
Binding affinities to I_1, I_2 and α_2-adrenoceptors for prepared compounds, agmatine and clonidine

Compounds (configuration)	I_1 IC_{50} (nM)	I_2 K_i (nM)	α_2 K_i (nM)
5 (*S*)	100,900	7498	5539
7 (*S*)	3700	18,830	1553
8 (*S*)	93,140	21,770	13,060
9 (*S*)	59,380	81,250	25,800
10 (*S*)	79,770	24,890	9376
11 (*S*)	33,900	20,270	7018
12 (*S*)	>10,00,000	>10,00,000	19,660
13d (*S*)	7781	15,650	445
13f (*R*)	8509	39,570	4907
14d (*S*)	1482	1762	854
14f (*R*)	6334	92,520	16,920
15d (*S*)	1310	12,700	3007
15f (*R*)	1249	47,690	26,690
16d (*S*)	7749	2432	1899
16f (*R*)	2716	9564	4315
17d (*S*)	>100,000	27,980	5727
19 (*S*)	277,600	59,360	23,320
21a (*S*)	>100,000	1001	964
21b (*R*)	583,400	46,260	83,770
25a (*S*)	1008	2548	20,350
25b (*R*)	32,540	18,890	869
29a (*S*)	5112	8115	24,020
29b (*R*)	2652	9612	5412
30c (*S*)	11,620	19,060	481,800
31b (*S*)	72,860	3560	43,070
32b (*S*)	116,600	27,600	178,600
33b (*S*)	17,220	11,240	3896
Clonidine	366.2	364.5	8.7
Agmatine[a]	36,532 ± 3080	416,700 ± 118,800	31,700 ± 11,000

[a] Result drawn from the literature, [4] obtained in similar experimental conditions using Wistar rats tissues.

Compounds **14d**, **15d**, **15f**, **25a** indicate moderate affinities to I_1 receptors. In case of I_2 receptor affinity the most interesting results were obtained for **14d** and **21a**. Some of the new compounds show also interesting affinities to α_2-adrenoceptors: **14d**, **13d**, **21a**, **25b**. The other compounds indicate low or no affinity (K_i, IC_{50} >100,000 or >10,00,000 nM).

Estimation of the affinities is compared with two reference compounds—clonidine and agmatine. None of the obtained compounds show the clonidine affinity level for I and α_2-adrenoceptors but majority of them is still much above the values reported for agmatine.

Analyzing the closest analogues of clonidine (**16d**, **16f**), it is clear that the substituent in 4(5) position distinctly diminishes the affinities to both I and α_2-adrenoceptors. The same situation takes place for the other analogues of I/α_2 ligands. Compared to the reported values for different ligands and tissues there is serious drop in I_2 affinity in naphazoline (**21a**, **21b**)[33–37] and idazoxane (**29a**, **29b**).[33–37] Analogous conclusions may be drawn from the affinities to α_2-adrenoceptors. The analogues of naphazoline (**21a**, **21b**) and idazoxane (**29a**, **29b**) indicate much lower affinities to α_2-adrenoceptors than the authentic compounds.[34,35,38]

In several cases both enantiomers/diastereomeric mixtures were examined (**13d**, **13f**, **14d**, **14f**, **15d**, **15f**, **16d**, **16f**, **21a**, **21b**, **25a**, **25b**, **29a**, **29b**). We observed interesting affinity differences between the enantiomers or diastereomeric mixtures [4(5)*S*]/[4(5)*R*]. The results show strong influence of 4(5)-substituent configuration on the affinities values. In most cases [4(5)*S*] compounds indicates higher I_1 affinities, but for idazoxane analogues (**29a**, **29b**). The same situation take place for I_2 and α_2-adrenoceptor affinities, except efaroxane (**25a**, **25b**) and idazoxane (**29a**, **29b**) analogues for which better results were obtained for [4(5)*R*] diastereomeric mixtures.

3. Conclusions

In summary, we have described a new group of agmatine/imidazoline ring analogues, 4(5)-(2-aminoethyl)imidazoline derivatives. Some of the new compounds posses moderate affinities to I_1, I_2 and α_2-adrenoceptors. The obtained values of K_i, IC_{50} are lower than reported for synthetic imidazoline ligands, but much higher than the natural ligand of imidazoline receptor-agmatine itself. The most valuable results were obtained for [4(5)*S*] enantiomers or [4(5)*S*] diastereomeric mixtures. With reference to our present studies, 4(5)-(2-aminoethyl)imidazolines may be a new group of compounds that affects the cardiovascular system by I/α_2 mediated response.

4. Experimental

4.1. General

Starting materials were obtained from commercial sources and were used without further purification. Reaction process was followed by thin layer chromatography (TLC) with commercial silica gel plates (Merck, Silica Gel F_{254} on aluminium sheets). Column chromatography was done on Silica Gel 60, 0.063–0.200 mm (Merck). ^{1}H NMR spectra were recorded on Varian Unity Plus 500 MHz and Varian Gemini 200 MHz spectrometers. ^{13}C NMR spectra were recorded on Varian Gemini 200 MHz Spectrometer. MSFAB spectra were recorded on Trio-3, VG, Great Britain. Melting points are uncorrected. Microanalyses were performed on Carlo Erba CHNS-O-EA1180 instrument for C, H, N.

4.1.1. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-ethylmercaptoimidazoline hydroiodide (3)

(2*S*)-N^4-Benzyloxycarbonyl-1,2,4-triaminobutane dihydrochloride **1a** (388 mg, 1.25 mmol) was dissolved in a mixture of H_2O (4 ml) and ethanol (8 ml) and Et_3N (0.35 ml) was added. The solution was cooled in ice bath and CS_2 (0.38 ml, 5 mmol) was added dropwise. The resulting mixture was stirred for 5 h at 60 °C. After cooling concd HCl (0.2 ml) was added and the solution was refluxed for 9 h. The volatiles were removed under reduced pressure yielding an oily residue. It was suspended in 1 M $KHSO_4$ (30 ml) and extracted with $CHCl_3$ (3 × 30 ml). The organic layer was dried with Na_2SO_4 and evaporated yielding a crude yellow oil of **2**. It was purified by column chromatography on silica gel using $CHCl_3$/acetone (5:1) as an eluent. Yield of **2**: 289 mg (83%), oil.

Compound **2** (788 mg, 2.82 mmol) was dissolved in MeOH (20 ml) and EtI (0.34 ml, 4.2 mmol) was added. The resulting mixture was refluxed for 2 h. The volatiles were removed under reduced

pressure yielding the oily product **3** that was used without further purification. Yield: 1229 mg, (100%), oil. ^{1}H NMR (500 MHz, CD_3OD): δ (ppm) = 1.36 (t, J = 7.0, 3H, CH_2CH_3), 1.85–2.00 (m, 2H, $CHCH_2CH_2$), 3.05–3.40 (m, 4H, SCH_2, CH_2CH_2NH), 3.45–3.60 (m, 1H, $HNCH_2CH$), 3.95–4.10 (m, 1H, $HNCH_2CH$), 4.20–4.40 (m, 1H, $CH_2CH(NH)CH_2$), 5.05 (s, 2H, OCH_2Ph), 7.15–7.40 (m, 5H, C_6H_5). Anal. Calcd for $C_{15}H_{24}IN_3O_2S$: C, 41.19; H, 5.53; N, 9.61; S, 7.33. Found: C, 41.11; H, 5.63; N, 9.56; S, 7.49.

4.1.2. 4(5)*S*]-2-Benzylamino-4(5)-(2-aminoethyl)imidazoline dihydrobromide (5)

Compound **3** (1087 mg, 2.50 mmol) was dissolved in *t*-BuOH (18 ml) and benzylamine (0.44 ml, 5 mmol) was added. The mixture was refluxed for 5 h. The volatiles were evaporated under reduced pressure and the oily residue was suspended in H_2O, alkalized with 1 M NaOH and extracted with $CHCl_3$ (4 × 30 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue of **4** was converted into hydrochloride (5.5 M HCl in MeOH) and then purified by column chromatography on silica gel using $CHCl_3$/MeOH (7:1) as eluent. Yield: 743 mg (62%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.40–1.90 (m, 2H, $CHCH_2CH_2$), 2.90–3.35 (m, 3H, CH_2CH_2NH, $HNCH_2CH$), 3.45–3.70 (m, 1H, $HNCH_2CH$), 3.75–4.05 (m, 1H, $CH_2CH(NH)CH_2$), 4.41 (d, J = 5.5, 2H, $HNCH_2Ph$), 5.01 (s, 2H, OCH_2Ar), 5.80–6.20 (br s, 1H, N*H*), 7.15–7.45 (m, 10H, $HNCH_2C_6H_5$, $OCH_2C_6H_5$), 8.10–8.70 (br s, 2H, N*H*), 10.28–10.77 (br s, 1H, N*H*).

To **4** (660 mg, 1.70 mmol) a solution of HBr in AcOH (5 ml) was added. The mixture was stirred for 3 h at rt. and then evaporated under reduced pressure. The residue was dissolved in *i*-PrOH and precipitated with Et_2O yielding a very hygroscopic creamy powder of **5**: 600 mg (93%). Mp 103–106 °C. ^{1}H NMR (200 MHz, MeOD): δ (ppm) = 1.90–2.15 (m, 2H, $CHCH_2CH_2$), 2.93–3.22 (m, 2H, CH_2CH_2NH), 3.44 (dd, J_1 = 6.6, J_2 = 9.7, 1H, $HNCH_2CH$), 3.88 (t, J = 9.7, 1H, $HNCH_2CH$), 4.14–4.33 (m, 1H, $CH_2CH(NH)CH_2$), 4.48 (s, 2H, $HNCH_2Ph$), 7.25–7.55 (m, 5H, C_6H_5). ^{13}C NMR (200 MHz, MeOD): 34.1, 37.5, 47.7, 49.5, 54.6, 128.8, 129.4, 130.3, 137.8, 160.6. MS FAB MH^+ 219 (calcd for $C_{12}H_{18}N_4$ M = 218.3). Anal. Calcd for $C_{12}H_{20}Br_2N_4$: C, 37.92; H, 5.30; N, 14.74. Found: C, 37.95; H, 5.23; N, 14.73.

4.1.3. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-phenylaminoimidazoline hydrochloride (6c). General procedure A

S-Methyl-*N*-phenylisothiourea hydroiodide (**6b**) (472 mg, 1.69 mmol) was added to (2*S*)-N^4-benzyloxycarbonyl-1,2,4-triaminobutane **1a** (400 mg, 1.69 mmol) in 1-pentanol (4 ml). The reaction mixture was refluxed for 24 h. The volatiles were removed under reduced pressure. The oily residue was suspended in H_2O (20 ml), alkalized to pH 12 with 1 M NaOH and extracted with Et_2O (4 × 30 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The crude product **6c** was converted into hydrochloride with 5.5 M HCl in MeOH and purified by column chromatography on silica gel using $CHCl_3$/MeOH (6:1) as eluent. Yield: 395 mg (62%), oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 1.60–1.95 (m, 2H, $CHCH_2CH_2$), 3.15–3.45 (m, 3H, CH_2CH_2NH, $HNCH_2CH$), 3.70–3.90 (m, 1H, $HNCH_2CH$), 3.95–4.15 (m, 1H, $CH_2CH(NH)CH_2$), 5.01 (s, 2H, OCH_2Ph), 5.55–5.85 (br s, 1H, N*H*) 7.15–7.45 (m, 10H, C_6H_5, C_6H_5), 7.80–8.30 (br s, 2H, N*H*), 10.71 (s, 1H, N*H*). Anal. Calcd for $C_{19}H_{23}ClN_4O_2$: C, 60.88; H, 6.18; N, 14.95. Found: C, 60.87; H, 6.30; N, 14.78.

4.1.4. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-phenylaminoimidazoline dihydrobromide (6d). General procedure B

Compound **6c** (127 mg, 0.34 mmol) was dissolved in HBr in AcOH (3 ml) and stirred for 3 h at rt. The volatiles were removed under reduced pressure. The oily yellowish residue was dissolved in *i*-PrOH and precipitated with Et_2O yielding an extremely hygroscopic powder of **6d**. Yield: 121 mg (97%). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 1.75–1.95 (m, 2H, $CHCH_2CH_2$), 2.77–2.95 (m, 2H, CH_2CH_2NH), 3.35–3.45 (m, 1H, $HNCH_2CH$), 3.70–3.83 (m, 1H, $HNCH_2CH$), 4.05–4.15 (m, 1H, $CH_2CH(NH)CH_2$), 7.25–7.50 (m, 5H, C_6H_5), 7.73–7.90 (br s, 3H, NH_3^+), 8.34 (s, 1H, N*H*), 8.58 (s, 1H, N*H*) 10.41 (s, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.6, 49.7, 54.7, 125.6, 128.9, 131.5, 136.8, 159.4. MS FAB MH^+ 205 (calcd for $C_{11}H_{16}N_4$ M = 204.3). Anal. Calcd for $C_{11}H_{18}Br_2N_4$: C, 36.09; H, 4.96; N, 15.30. Found: C, 36.19; H, 5.00; N, 15.23.

4.1.5. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(2-bromophenyl)amino]imidazoline hydrochloride (7c)

Preparation and purification of **7c** was achieved according to the general procedure A, starting from **7b** (610 mg, 1.70 mmol). Yield: 386 mg (50%), oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.65–1.87 (m, 2H, $CHCH_2CH_2$), 3.15–3.40 (m, 3H, CH_2CH_2NH, $HNCH_2CH$), 3.78–3.80 (m, 1H, $HNCH_2CH$), 4.02–4.15 (m, 1H, $CH_2CH(NH)CH_2$), 5.03 (AB system, J_1 = 12.2, J_2 = 21.5, 2H, OCH_2Ph), 5.75–5.95 (br s, 1H, N*H*) 7.10–7.65 (m, 9H, C_6H_5, C_6H_4Br), 7.85–8.65 (br s, 2H, N*H*), 10.10–10.25 (br s, 1H, N*H*). Anal. Calcd for $C_{19}H_{22}BrClN_4O_2$: C, 50.29; H, 4.89; N, 12.35. Found: C, 50.30; H, 5.02; N, 12.21.

4.1.6. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(2-bromophenyl)amino] imidazoline dihydrobromide (7d)

Preparation and purification of **7d** was carried out according to the general procedure B, starting from **7c** (154 mg, 0.34 mmol). Yield: 139 mg (92%), extremely hygroscopic powder. ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 1.72–2.03 (m, 2H, $CHCH_2CH_2$), 2.75–3.02 (m, 2H, CH_2CH_2NH), 3.32–3.58 (m, 1H, $HNCH_2CH$), 3.72–3.80 (m, 1H, $HNCH_2CH$), 4.05–4.23 (m, 1H, $CH_2CH(NH)CH_2$), 7.30–7.95 (m, 7H, C_6H_4Br, NH_3^+), 8.38 (s, 1H, N*H*), 8.60 (s, 1H, N*H*), 10.36 (s, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.4, 49.7, 54.9, 123.3, 130.7, 130.8, 132.0, 135.3, 135.4, 159.8. MS FAB MH^+ 283, 285 (calcd for $C_{11}H_{15}BrN_4$ M = 282.0, 284.0). Anal. Calcd for $C_{11}H_{17}Br_3N_4$: C, 29.69; H, 3.85; N, 12.59. Found: C, 26.60; H, 3.92; N, 12.47.

4.1.7. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(2,6-difluorophenyl)amino]imidazoline hydrochloride (8c)

Preparation of **8c** was carried out according to the general procedure A, starting from **8b** (537 mg, 1.70 mmol). **8c** as a hydrochloride was purified by column chromatography on Sephadex LH-20 using MeOH as eluent. Yield: 363 mg (52%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.67–2.03 (m, 2H, $CHCH_2CH_2$), 3.21–3.63 (m, 3H, CH_2CH_2NH, $HNCH_2CH$), 3.87–4.12 (m, 1H, $HNCH_2CH$), 4.12–4.33 (m, 1H, $CH_2CH(NH)CH_2$), 5.02 (s, 2H, OCH_2Ph), 5.79–6.05 (br s, 1H, N*H*), 6.75–7.03 (m, 2H, $C_6H_3F_2$), 7.32–7.50 (m, 6H, $C_6H_3F_2$, C_6H_5), 8.46–8.90 (br s, 2H, N*H*), 9.95–10.15 (br s, 1H, N*H*). Anal. Calcd for $C_{19}H_{21}ClF_2N_4O_2$: C, 55.54; H, 5.15; N, 13.64. Found: C, 55.56; H, 5.29; N, 13.47.

4.1.8. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(2,6-difluorophenyl)amino]imidazoline dihydrobromide (8d)

Preparation and purification of **8d** was completed according to the general procedure B, starting from **8c**. Yield: 131 mg, (96%), very hygroscopic powder.^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 1.70–2.05 (m, 2H, $CHCH_2CH_2$), 2.70–3.05 (m, 2H, CH_2CH_2NH), 3.25–3.50 (m, 1H, $HNCH_2CH$), 3.70–3.95 (m, 1H, $HNCH_2CH$), 4.05–4.30 (m, 1H, $CH_2CH(NH)CH_2$), 7.20–8.10 (m, 6H, $C_6H_3F_2$, NH_3^+), 8.70 (s, 1H, N*H*), 8.89 (s, 1H, N*H*), 10.31 (s, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.0, 37.4, 50.0, 55.1, 113.1, 113.4, 113.7, 113.9, 114.0, 114.3, 114.4, 132.2, 132.4, 132.6, 157.6, 157.7, 159.9, 162.6, 162.7. MS FAB MH^+ 241 (calcd for $C_{11}H_{14}F_2N_4$ M = 240.2). Anal. Calcd for $C_{11}H_{16}Br_2F_2N_4$: C, 32.86; H, 4.01; N, 13.93. Found: C, 33.98; H, 4.17; N, 13.74.

4.1.9. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(4-bromophenyl)amino]imidazoline hydrochloride (9c)

Compound **9c** was synthesized according to the general procedure A, starting from **9b** (634 mg, 1.70 mmol). The product **9c** as hydrochloride was purified by column chromatography on silica gel using $CHCl_3$/MeOH (5:1) as eluent. Yield: 324 mg (42%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.60–2.00 (m, 2H, CHCH_2CH$_2$), 3.15–3.50 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.76–3.97 (m, 1H, HNCH_2CH), 3.98–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.03 (s, 2H, OCH_2Ph), 5.60–5.95 (br s, 1H, NH), 7.10–7.60 (m, 9H, C$_6H_5$, C$_6H_4$Br), 7.95–8.40 (br s, 2H, NH), 10.78 (s, 1H, NH). Anal. Calcd for $C_{19}H_{22}BrClN_4O_2$: C, 50.29; H, 4.89; N, 12.35. Found: C, 50.24; H, 4.83; N, 12.43.

4.1.10. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(4-bromophenyl)amino] imidazoline dihydrobromide (9d)

Compound **9d** was prepared according to the general procedure B, starting from **9c** (154 mg, 0.34 mmol). Yield: 144 mg (95%), white powder. Mp 167–170 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.75–2.05 (m, 2H, CHCH_2CH$_2$), 2.75–3.05 (m, 2H, CH$_2$CH_2NH), 3.32 (dd, J_1 = 7.0, J_2 = 9.9, 1H, HNCH_2CH), 3.41 (t, J = 9.9, 1H, HNCH_2CH), 4.05–4.25 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.21 (d, J = 8.7, 2H, C$_6H_4$Br), 7.58 (d, J = 8.7, 2H, C$_6H_4$Br), 7.70–8.10 (br s, 3H, NH_3^+), 8.50 (s, 1H, NH), 8.76 (s, 1H, NH), 10.62 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.4, 49.7, 54.8, 122.2, 127.7, 134.4, 136.1, 159.5. MS FAB MH$^+$ 283, 285 (calcd for $C_{11}H_{15}BrN_4$ M = 282.0, 284.0). Anal. Calcd for $C_{11}H_{17}Br_3N_4$: C, 29.69; H, 3.85; N, 12.59. Found: C, 29.51; H, 4.00; N, 12.47.

4.1.11. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(4-metoxyphenyl)amino]imidazoline hydrochloride (10c)

Compound **10c** was obtained according to the general procedure A, starting from **10b** (551 mg, 1.70 mmol). The product **10c** was isolated by extraction with $CHCl_3$ (3 × 30 ml, drying with $MgSO_4$), converted into hydrochloride (5.5 M HCl in MeOH) and purified by column chromatography on silica gel using $CHCl_3$/MeOH (6:1) as eluent. Yield: 213 mg (31%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.60–1.95 (m, 2H, CHCH_2CH$_2$), 3.15–3.45 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.70–3.90 (m, 4H, HNCH_2CH, CH_3O), 3.95–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.01 (s, 2H, OCH_2Ph), 5.55–5.90 (br s, 1H, NH), 6.85 (d, J = 8.9, 2H, C$_6H_4$OCH$_3$), 7.15 (d, J = 8.9, 2H, C$_6H_4$OCH$_3$), 7.25–7.45 (m, 5H, C$_6H_5$), 7.60–8.40 (br s, 2H, NH), 10.25–10.45 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{25}ClN_4O_2$: C, 59.33; H, 6.22; N, 8.76. Found: C, 59.25; H, 6.34; N, 8.57.

4.1.12. 4(5)*S*]-4(5)-(2-Aminoethylo)-2-[(4-metoxyphenyl) amino]imidazoline dihydrobromide (10d)

Compound **10d** was obtained according to the general procedure B, starting from **10c** (138 mg, 0.34 mmol). Yield: 128 mg (95%), hygroscopic white powder. Mp 147–151 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.70–2.10 (m, 2H, CHCH_2CH$_2$), 2.70–3.05 (m, 2H, CH$_2$CH_2NH), 3.24–3.42 (m, 1H, HNCH_2CH), 3.65–3.85 (m, 4H, HNCH_2CH, CH_3O), 3.95–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 6.96 (d, J = 8.9, 2H, C$_6H_4$OCH$_3$), 7.17 (d, J = 8.9, 2H, C$_6H_4$OCH$_3$), 7.60–8.10 (br s, 3H, NH_3^+), 8.23 (s, 1H, NH), 8.51 (s, 1H, NH), 10.27 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.6, 49.7, 54.7, 56.6, 116.6, 128.1, 129.1, 160.0, 160.9. MS FAB MH$^+$ 235 (calcd for $C_{12}H_{18}N_4O$ M = 234.3). Anal. Calcd for $C_{12}H_{20}Br_2N_4O$: C, 36.38; H, 5.09; N, 14.14. Found: C, 36.52; H, 5.15; N, 14.03.

4.1.13. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(3-chlorophenyl)amino]imidazoline hydrochloride (11c)

Compound **11c** was prepared according to the general procedure A, starting from **11b** (558 mg, 1.70 mmol). The product **11c** was extracted with $CHCl_3$ (3 × 30 ml, drying with $MgSO_4$), converted into hydrochloride (5.5 M HCl in MeOH) and purified by column chromatography on silica gel using $CHCl_3$/MeOH (6:1) as eluent. Yield: 292 mg (42%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.80–2.00 (m, 2H, CHCH_2CH$_2$), 3.10–3.45 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.70–3.90 (m, 1H, HNCH_2CH), 3.95–4.25 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.03 (s, 2H, OCH_2Ph), 5.80–6.00 (br s, 1H, NH), 7.10–7.40 (m, 9H, C$_6H_5$, C$_6H_4$Cl), 8.09 (s, 1H, NH), 8.24 (s, 1H, NH), 10.81 (s, 1H, NH). Anal. Calcd for $C_{19}H_{22}Cl_2N_4O_2$: C, 55.75; H, 5.42; N, 13.69. Found: C, 55.63; H, 5.57; N, 13.51.

4.1.14. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(3-chlorophenyl)amino]imidazoline dihydrobromide (11d)

Compound **11d** was prepared according to the general procedure B, starting from **11c** (139 mg, 0.34 mmol). The product **11d** was precipitated from mixture of MeOH and *i*-PrOH with Et_2O. Yield: 128 mg (94%), white hygroscopic powder. Mp 203–205 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 1.75–2.10 (m, 2H, CHCH_2CH$_2$), 2.75–3.05 (m, 2H, CH$_2$CH_2NH), 3.33 (dd, J_1 = 7.0, J_2 = 9.8, 1H, HNCH_2CH), 3.77 (t, J = 9.9, 1H, HNCH_2CH), 4.02–4.24 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.16–7.48 (m, 4H, C$_6H_4$Cl), 7.65–8.10 (br s, 3H, NH_3^+), 8.56 (s, 1H, NH), 8.81 (s, 1H, NH), 10.70 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.5, 49.7, 54.8, 124.1, 125.7, 128.9, 132.7, 136.6, 138.3, 159.4. MS FAB MH$^+$ 239, 241 (calcd for $C_{11}H_{15}ClN_4$ M = 238.1, 240.1). Anal. Calcd for $C_{11}H_{17}Br_2ClN_4$: C, 32.98; H, 4.28; N, 13.99. Found: C, 32.79; H, 4.35; N, 13.90.

4.1.15. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(pyridyl-3)amino]imidazoline dihydrochloride (12c)

Preparation of **12c** was achieved according to the general procedure A, starting from **12b** (502 mg, 1.70 mmol). The product **12c** was extracted with $CHCl_3$ (3 × 20 ml, drying with $MgSO_4$), converted into hydrochloride (5.5 M HCl in MeOH) and purified by two step column chromatography. Firstly, column chromatography on silica gel using $CHCl_3$/MeOH/AcOH (4:1:0.1) as eluent and then on Sephadex LH-20 using MeOH. Yield: 154 mg (22%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.65–1.95 (m, 2H, CHCH_2CH$_2$), 3.15–3.45 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.75–3.95 (m, 1H, HNCH_2CH), 4.00–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.04 (s, 2H, OCH_2Ph), 5.65–5.85 (br s, 1H, NH), 7.28–7.38 (m, 5H, C$_6H_5$), 7.50–7.75 (m, 2H, C$_5H_4$N), 8.25–8.75 (br s, 4H, C$_5H_4$N, NH), 10.35–10.75 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{23}Cl_2N_5O_2$: C, 52.43; H, 5.62; N, 16.99. Found: C, 52.25; H, 5.80; N, 16.82.

4.1.16. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(pyridyl-3)amino]imidaz oline trihydrobromide (12d)

Compound **12d** was prepared according to the general procedure B, starting from **12c** (128 mg, 0.31 mmol). The product was precipitated form MeOH with EtO_2. Yield: 101 mg (73%), beige powder. Mp 257–259 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.70–2.10 (m, 2H, CHCH_2CH$_2$), 2.75–3.05 (m, 2H, CH$_2$CH_2NH), 3.37 (dd, J_1 = 7.1, J_2 = 9.8, 1H, HNCH_2CH), 3.80 (t, J = 9.8, 1H, HNCH_2CH), 4.05–4.30 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.65–8.25 (m, 6H, C$_5H_4$N, NH_3^+), 8.62–8.72 (m, 1H, C$_5H_4$N), 8.79 (s, 1H, NH), 9.01 (s, 1H, NH), 10.70–11.10 (br s, 1H, NH). ^{13}C NMR (200 MHz, D_2O): δ (ppm) = 34.9, 38.7, 50.1, 56.1, 131.3, 138.8, 140.1, 142.7, 143.9, 160.2. MS FAB MH$^+$ 206 (calcd for $C_{10}H_{15}N_5$ M = 205.3). Anal. Calcd for $C_{10}H_{18}Br_3N_5$: C, 26.81; H, 4.05; N, 15.63. Found: C, 26.71; H, 4.24; N, 15.75.

4.1.17. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(6-methylpyridyl-2)amino]imidazoline dihydrochloride (13c)

Compound **13c** was prepared according to the general procedure A, starting from **13b** (525 mg, 1.70 mmol). The product **13c** was extracted with $CHCl_3$ (3 × 20 ml, drying with $MgSO_4$), converted into dihydrochloride (5.5 M HCl in MeOH) and purified by column chromatography using $CHCl_3$/MeOH (7:1) as eluent. Yield:

271 mg (37%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.70–2.05 (m, 2H, CHCH_2CH$_2$), 2.51 (s, 3H, CH_3), 3.15–3.65 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.75–4.00 (m, 1H, HNCH_2CH), 4.15–4.35 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.09 (s, 2H, OCH_2Ph), 5.30–5.85 (br s, 1H, NH), 6.82–7.06 (m, 2H, C$_5H_3$N(CH$_3$)), 7.27–7.42 (m, 5H, C$_6H_5$), 7.51 (t, J = 7.8, C$_5H_3$N(CH$_3$)), 8.30–9.10 (br s, 1H, NH), 9.35–10.25 (br s, 1H, NH), 11.97 (s, 1H, NH). Anal. Calcd for $C_{19}H_{25}Cl_2N_5O_2$: C, 53.53; H, 5.91; N, 16.43. Found: C, 53.57; H, 6.04; N, 16.38.

4.1.18. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(6-methylpyridyl-2) amino]imidazoline trihydrobromide (13d)

Compound **13d** was obtained according to the general procedure B, starting from **13c** (132 mg, 0.31 mmol). The product **13d** was precipitated from mixture of MeOH and *i*-PrOH with Et_2O. Yield: 122 mg (85%), white powder. Mp 228–230 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.80–2.10 (m, 2H, CHCH_2CH$_2$), 2.51 (s, 3H, CH_3), 2.75–3.05 (m, 2H, CH$_2$CH_2NH), 3.43 (dd, J_1 = 6.6, J_2 = 10.3, 1H, HNCH_2CH), 3.87 (t, J = 10.3, 1H, HNCH_2CH), 4.10–4.30 (m, 1H, CH$_2$CH(NH)CH$_2$), 6.90 (d, J = 8.1, 1H, C$_5H_3$N(CH$_3$)), 7.01 (d, J = 7.6, 1H, C$_5H_3$N(CH$_3$)), 7.69 (t, J = 7.8, 1H, C$_5H_3$N(CH$_3$)), 7.80–8.10 (br s, 3H, NH_3^+), 9.07 (s, 2H, NH), 11.95 (s, 1H, NH) ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 24.2, 34.0, 37.4, 49.6, 54.1, 111.4, 121.1, 141.4, 151.6, 157.6, 158.8. MS FAB MH$^+$ 220 (calcd for $C_{11}H_{17}N_5$ M = 219.3). Anal. Calcd for $C_{11}H_{20}Br_3N_5$: C, 28.60; H, 4.36; N, 15.16. Found: C, 28.55; H, 4.30; N, 15.24.

4.1.19. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-[(6-methylpyridyl-2) amino]imidazoline trihydrobromide (13f)

Compound **13f** was synthesized according to the procedures for **13c** and **13d**, starting from **1b** (470 mg, 1.98 mmol). Yield of **13f**: 400 mg (43%), white powder. Mp 232–235 °C. ^{1}H NMR (200 MHz, MeOD): δ (ppm) = 2.00–2.24 (m, 2H, CHCH_2CH$_2$), 2.58 (s, 3H, CH_3), 3.02–3.22 (m, 2H, CH$_2$CH_2NH), 3.62 (dd, J_1 = 6.6, J_2 = 10.3, 1H, HNCH_2CH), 4.04 (t, J = 10.3, 1H, HNCH_2CH), 4.27–4.48 (m, 1H, CH$_2$CH(NH)CH$_2$), 6.97 (d, J = 8.1, 1H, C$_5H_3$N(CH$_3$)), 7.08 (d, J = 7.5, 1H, C$_5H_3$N(CH$_3$)), 7.74 (t, J = 7.9, 1H, C$_5H_3$N(CH$_3$)). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 24.2, 34.1, 37.4, 49.6, 54.2, 111.5, 121.1, 141.5, 151.5, 157.6, 158.8. MS FAB MH$^+$ 220 (calcd for $C_{11}H_{17}N_5$ M = 219.3). Anal. Calcd for $C_{11}H_{20}Br_3N_5$: C, 28.60; H, 4.36; N, 15.16. Found: C, 28.51; H, 4.26; N, 15.19.

4.1.20. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(2,4-dichlorophenyl)amino]imidazoline hydrochloride (14c)

Compound **14c** was prepared according to the general procedure A, starting from **14b** (593 mg, 1.70 mmol). Yield: 279 mg (37%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.75–2.00 (m, 2H, CHCH_2CH$_2$), 3.10–3.50 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.85–4.00 (m, 1H, HNCH_2CH), 4.00–4.30 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.00 (s, 2H, OCH_2Ph), 5.70–6.10 (br s, 1H, NH), 7.10–7.60 (m, 8H, C$_6H_5$, C$_6H_3$Cl$_2$), 8.10–8.60 (br s, 2H, NH), 9.90–10.40 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{21}Cl_3N_4O_2$: C, 51.43; H, 4.77; N, 12.63. Found: C, 51.37; H, 4.83; N, 12.69.

4.1.21. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(2,4-dichlorophenyl) amino]imidazoline dihydrobromide (14d)

Compound **14d** was obtained according to the general procedure B, starting from **14c** (151 mg, 0.34 mmol). Yield: 133 mg (90%), white powder. Mp 260–263 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 1.72–2.05 (m, 2H, CHCH_2CH$_2$), 2.70–3.05 (m, 2H, CH$_2$CH_2NH), 3.30–3.50 (m, 1H, HNCH_2CH), 3.70–3.92 (m, 1H, HNCH_2CH), 4.05–4.25 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.42–7.66 (m, 2H, C$_6H_3$Cl$_2$), 7.75–8.06 (br s, 4H, NH_3^+, C$_6H_3$Cl$_2$), 8.47 (s, 1H, NH), 8.68 (s, 1H, NH), 10.43 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 33.8, 37.1, 49.3, 54.6, 130.0, 131.3, 131.5, 132.5, 133.8, 136.2, 159.5. MS FAB MH$^+$ 273, 275 (calcd for $C_{11}H_{14}Cl_2N_4$ M = 272.1, 274.1). Anal. Calcd for $C_{11}H_{16}Br_2Cl_2N_4$: C, 30.37; H, 3.71; N, 12.88. Found: C, 30.30; H, 3.60; N, 12.70.

4.1.22. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-[(2,4-dichlorophenyl) amino]imidazoline dihydrobromide (14f)

Compound **14f** was obtained according to the procedures A and B, starting from **1b** (390 mg, 1.65 mmol). Yield: 244 mg (34%), white powder. Mp 263–265 °C. ^{1}H NMR (200 MHz, MeOD): δ (ppm) = 1.96–2.24 (m, 2H, CHCH_2CH$_2$), 2.94–3.22 (m, 2H, CH$_2$CH_2NH), 3.52 (dd, J_1 = 6.6, J_2 = 10.1, 1H, HNCH_2CH), 3.94 (t, J = 9.9, 1H, HNCH_2CH), 4.20–4.40 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.45–7.59 (m, 2H, C$_6H_3$Cl$_2$), 7.66–7.74 (m, 1H C$_6H_3$Cl$_2$). ^{13}C NMR (200 MHz, MeOD): 34.1, 37.4, 49.3, 54.9, 130.3, 131.6, 131.8, 132.8, 134.0, 136.5, 159.8. MS FAB MH$^+$ 273, 275 (calcd for $C_{11}H_{14}Cl_2N_4$ M = 272.1, 274.1). Anal. Calcd for $C_{11}H_{16}Br_2Cl_2N_4$: C, 30.37; H, 3.71; N, 12.88. Found: C, 30.29; H, 3.76; N, 12.70.

4.1.23. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(3-trifluoromethylphenyl)amino]imidazoline hydrochloride (15c)

Compound **15c** was prepared according to the general procedure A, starting from **15b** (592 mg, 1.70 mmol). Yield: 308 mg (41%), oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.68–1.93 (m, 2H, CHCH_2CH$_2$), 3.17–3.45 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.70–3.92 (m, 1H, HNCH_2CH), 4.06–4.25 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.00 (s, 2H, OCH_2Ph), 5.68–5.80 (br s, 1H, NH), 7.20–7.55 (m, 9H, C$_6H_5$, C$_6H_4$CF$_3$), 8.15–8.35 (br s, 2H, NH), 11.00–11.12 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{22}ClF_3N_4O_2$: C, 54.24; H, 5.01; N, 12.65. Found: C, 54.35; H, 5.03; N, 12.57.

4.1.24. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(3-trifluoromethylphenyl) amino]imidazoline dihydrobromide (15d)

Compound **15d** was prepared according to the general procedure B, starting from **15c** (150 mg, 0.34 mmol). Yield: 134 mg (91%), extremely hygroscopic powder. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.78–1.98 (m, 2H, CHCH_2CH$_2$), 2.78–2.95 (m, 2H, CH$_2$CH_2NH), 3.35–3.45 (m, 1H, HNCH_2CH), 3.80 (t, J = 9.8, 1H, HNCH_2CH), 4.08–4.16 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.55–7.75 (m, 4H, C$_6H_4$CF$_3$), 7.77–7.95 (br s, 3H, NH_3^+), 8.57 (s, 1H, NH), 8.77 (s, 1H, NH), 10.62 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.5, 49.7, 54.9, 122.3, 122.4, 122.5, 122.6, 122.7, 125.2, 125.3, 125.4, 125.5, 128.0, 129.5, 132.5, 133.1, 133.8, 137.8, 159.6. MS FAB MH$^+$ 273 (calcd for $C_{12}H_{15}F_3N_4$ M = 272.3). Anal. Calcd for $C_{12}H_{17}Br_2F_3N_4$: C, 33.20; H, 3.95; N, 12.91. Found: C, 33.19; H, 3.98; N, 12.95.

4.1.25. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-[(3-trifluoromethyl phenyl)amino]imidazoline hydrochloride (15f)

Compound **15f** was prepared according to the general procedures A and B, starting from **1b** (202 mg, 0.852 mmol). Yield: 156 mg (36%), extremely hygroscopic powder. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.78–1.98 (m, 2H, CHCH_2CH$_2$), 2.78–2.98 (m, 2H, CH$_2$CH_2NH), 3.37 (dd, J_1 = 7.3, J_2 = 9.8, 1H, HNCH_2CH), 3.81 (t, J = 9.8, 1H, HNCH_2CH), 4.08–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.55–7.75 (m, 4H, C$_6H_4$CF$_3$), 7.77–8.00 (br s, 3H, NH_3^+), 8.65 (s, 1H, NH), 8.89 (s, 1H, NH), 10.80 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.5, 50.1, 54.9, 122.3, 122.4, 122.5, 122.6, 122.7, 125.3, 125.4, 125.4, 125.5, 128.0, 129.5, 132.5, 133.1, 133.8, 137.8, 159.6. MS FAB MH$^+$ 273 (calcd for $C_{12}H_{15}F_3N_4$ M = 272.3). Anal. Calcd for $C_{12}H_{17}Br_2F_3N_4$: C, 33.20; H, 3.95; N, 12.91. Found: C, 33.27; H, 4.12; N, 12.99.

4.1.26. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(2,6-dichlorophenyl) amino]imidazoline dihydrobromide (16d)

Compound **16d** was obtained according to the general procedures A and B, starting from **16b** (924 mg, 2.45 mmol). Yield of **16d**: 341 mg (32%), extremely hygroscopic white powder.

^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 1.76–1.93 (m, 2H, CHCH_2CH$_2$), 2.78–2.95 (m, 2H, CH$_2$CH_2NH), 3.37–3.45 (m, 1H, HNCH_2CH), 3.77–3.87 (m, 1H, HNCH_2CH), 4.04–4.18 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.45–7.55 (m, 1H, C$_6H_3$Cl$_2$), 7.60–7.70 (m, 2H, C$_6H_3$Cl$_2$), 7.67–7.95 (br s, 3H, NH_3^+), 8.59 (s, 1H, NH), 8.78 (s, 1H, NH), 10.55 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.3, 49.7, 55.0, 130.9, 132.8, 136.3, 159.5. MS FAB MH$^+$ 273, 275 (calcd for $C_{11}H_{14}Cl_2N_4$ M = 272.1, 274.1). Anal. Calcd for $C_{11}H_{16}Br_2Cl_2N_4$: C, 30.37; H, 3.71; N, 12.88. Found: C, 30.19; H, 3.90; N, 12.75.

4.1.27. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-[(2,6-dichlorophenyl) amino]imidazoline dihydrobromide (16f)

Compound **16f** was prepared according to the general procedures A and B, starting from **1b** (200 mg, 0.844 mmol). Yield: 111 mg (30%), extremely hygroscopic white powder. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.75–1.92 (m, 2H, CHCH_2CH$_2$), 2.75–2.95 (m, 2H, CH$_2$CH_2NH), 3.37–3.45 (m, 1H, HNCH_2CH), 3.77–3.87 (m, 1H, HNCH_2CH), 4.08–4.20 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.42–7.67 (m, 4H, C$_6H_4$Cl$_2$), 7.70–8.00 (br s, 3H, NH_3^+), 8.66 (s, 1H, NH), 8.75–9.03 (br s, 1H, NH), 10.63 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.3, 49.7, 55.0, 130.9, 132.8, 136.3, 159.6. MS FAB MH$^+$ 273, 275 (calcd for $C_{11}H_{14}Cl_2N_4$ M = 272.1, 274.1). Anal. Calcd for $C_{11}H_{16}Br_2Cl_2N_4$: C, 30.37; H, 3.71; N, 12.88. Found: C, 30.22; H, 3.90; N, 12.70.

4.1.28. *N*-(Dicyclopropylmethyl)-*S*-methylisothiourea hydroiodide (17b)

NaSCN (1230 mg, 16.18 mmol) was dissolved in acetone (40 ml) and benzoyl chloride was added (1.81 ml, 16.18 mmol). The reaction mixture was refluxed for 40 min. Then dicyclopropylmethylamine **17a** (1710 mg, 15.41 mmol) in acetone (40 ml) was added dropwise. The reaction mixture was refluxed for 90 min and then poured into cold water (400 ml). The product—*N*-benzoyl-*N*′-(dicyclopropylmethyl)urea was extracted with $CHCl_3$ (4 × 75 ml, drying with $MgSO_4$). Yield: 3980 mg (94%), yellowish oil.

To (3980 mg, 14.49 mmol) of *N*-benzoyl-*N*′-(dicyclopropylmethyl)urea 2.5 M NaOH (180 ml) was added. The reaction mixture was heated at 90 °C for 90 min. After cooling, the solution was first acidified with concd HCl then thoroughly alkalized with 20% NH_3 (aq). The resulting viscous precipitate of thiourea was used in the next step without further purification.

N-(Dicyclopropylmethyl)urea (680 mg, 4.0 mmol) was dissolved in MeOH (12 ml) and MeI (0.3 ml, 4.8 mmol) was added. The reaction mixture was refluxed for 3 h. Then the volatiles were evaporated under reduced pressure and the residue of (**17b**) was crystallized from MeOH/Et_2O. Yield: 774 mg (62%), white crystals. Mp 145–147 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 0.20–0.65 (m, 8H, 2 × C$_2H_4$CH), 0.95–1.18 (m, 2H, 2 × C$_2$H$_4$CH), 2.61 (s, 3H, SCH_3), 2.95–3.10 (t, J = 7.7, 1H, (C$_3$H$_5$)$_2$CH), 8.30–9.80 (br s, 3H, NH). Anal. Calcd for $C_9H_{17}IN_2S$: C, 34.62; H, 5.49; N, 8.97; S, 10.27. Found: C, 34.75; H, 5.63; N, 8.82; S, 10.18.

4.1.29. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[dicyclopropylmethyl)amino]imidazoline hydrochloride (17c)

Compound **17c** was prepared according to the general procedure A, starting from **17b** (530 mg, 1.70 mmol). The product **17c** was extracted with Et_2O (3 × 30 ml, drying with $MgSO_4$), converted into hydrochloride (5.5 M HCl in MeOH) and purified by two step column chromatography. Firstly, column chromatography on silica gel using $CHCl_3$/MeOH (4:1) as eluent and next on Sephadex LH-20 using MeOH. Yield: 147 mg (22%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 0.20–0.70 (m, 8H, 2 × C$_2H_4$CH), 0.80–1.13 (m, 2H, 2 × C$_2$H$_4$CH), 1.55–2.00 (m, 2H, CHCH_2CH$_2$), 2.86–3.08 (m, 1H, (C$_3$H$_5$)$_2$CH), 3.10–3.48 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.54–3.78 (m, 1H, HNCH_2CH), 3.85–4.10 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.07 (s, 2H, OCH_2Ph), 5.80–6.30 (br s, 1H, NH), 7.20–7.45 (m, 5H, C$_6H_5$), 7.55–8.40 (br s, 3H, NH). Anal. Calcd for $C_{20}H_{29}ClN_4O_2$: C, 61.14; H, 7.44; N, 14.26. Found: C, 60.98; H, 7.43; N, 14.13.

4.1.30. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(dicyclopropylmethyl) amino]imidazoline dihydrochloride (17d)

Compound **17c** (122 mg, 0.311 mmol) was dissolved in MeOH (15 ml) and hydrogenated over 10% Pd/C (20 mg) for 4 h. Then the catalyst was filtered off, the product was converted into dihydrochloride (5.5 M HCl in MeOH) and precipitated from MeOH with Et_2O. Yield: 84 mg (92%), oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 0.15–0.60 (m, 8H, 2 × C$_2H_4$CH), 0.95–1.05 (m, 2H, 2 × C$_2$H$_4$CH), 1.65–1.78 (m, 2H, CHCH_2CH$_2$), 2.65–2.83 (m, 3H, (C$_3$H$_5$)$_2$CH, CH$_2$CH_2NH), 3.21 (dd, J_1 = 6.8, J_2 = 9.3, 1H, HNCH_2CH), 3.66 (t, J = 9.3, 1H, HNCH_2CH), 3.97–4.05 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.90–8.90 (br s, 6H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 2.9, 3.0, 3.9, 4.0, 16.5, 16.6, 34.1, 37.5, 49.8, 54.4, 62.7, 160.0. MS FAB MH$^+$ 223 (calcd for $C_{12}H_{22}N_4$ M = 222.3). Anal. Calcd for $C_{12}H_{24}Br_2N_4$: C, 37.52; H, 6.30; N, 14.58. Found: C, 37.39; H, 6.44; N, 14.50.

4.1.31. 4(5)*S*]-2-Benzyl-4(5)-(*N*-benzyloxycarbonylo-2-aminoethyl)imidazoline hydrochloride (18)

Ethyl phenyliminoacetate hydrochloride (319 mg, 1.6 mmol) was added to the solution of **1a** and Et_3N (0.17 ml, 1.25 mmol) in 99.9% anhyd EtOH (3 ml). The reaction mixture was refluxed for 2 h and the volatiles were evaporated under reduced pressure. The residue was suspended in H_2O (20 ml), alkalized with 1 M NaOH and extracted with $CHCl_3$ (3 × 15 ml, drying with Na_2SO_4). The organic layer was evaporated yielding an oil of crude (**42**). The product was converted into hydrochloride (5.5 M HCl in MeOH) and purified by column chromatography on silica gel using $CHCl_3$/MeOH (7:1) as eluent. Yield: 320 mg (68%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.50–1.95 (m, 2H, CHCH_2CH$_2$), 3.10–3.45 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.65–4.25 (m, 4H, HNCH_2CH, CH$_2$CH(NH)CH$_2$, CCH_2C$_6H_5$), 5.04 (s, 2H, OCH_2Ph), 5.90–6.30 (br s, 1H, NH), 6.95–7.75 (m, 10H, C$_6H_5$, C$_6H_5$), 8.40–9.10 (br s, 1H, NH), 10.20–10.60 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{24}ClN_3O_2$: C, 64.25; H, 6.47; N, 11.24. Found: C, 64.22; H, 6.33; N, 11.43.

4.1.32. 4(5)*S*]-4(5)-(2-Aminoethylo)-2-benzylimidazoline dihyd robromide (19)

Compound **19** was prepared according to the general procedure B. The product was crystallized from MeOH/*i*-PrOH/Et_2O. Yield: 314 mg (88%), white powder. Mp 222–225 °C. ^{1}H NMR (200 MHz, MeOD): δ (ppm) = 1.95–2.25 (m, 2H, CHCH_2CH$_2$), 2.90–3.25 (m, 2H, CH$_2$CH_2NH_3^+), 3.67 (dd, J_1 = 7.4, J_2 = 11.4, 1H, HNCH_2CH), 4.00 (s, 2H, CH_2C$_6H_5$), 4.07 (t, J = 11.4, 1H, HNCH_2CH), 4.40–4.60 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.20–7.60 (m, 5H, C$_6H_5$). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.0, 34.2, 37.3, 51.4, 56.7, 129.7, 130.6, 130.7, 133.6, 171.4. MS FAB MH$^+$ 204 (calcd for $C_{12}H_{17}N_3$ M = 203.3). Anal. Calcd for $C_{12}H_{19}Br_2N_3$: C, 39.48; H, 5.25; N, 11.51. Found: C, 39.30; H, 5.09; N, 11.43.

4.1.33. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(naphthyl-1)methylene]imidazoline hydrochloride (20a)

Ethyl (naphthyl-1)iminoacetate hydrochloride (380 mg, 1.52 mmol) was added to a solution of **1a** (464 mg, 1.50 mmol) and Et_3N (208 μl, 1.50 mmol) in 99.9% EtOH (8 ml). The reaction mixture was refluxed for 3 h and the volatiles were evaporated under reduced pressure. The oil residue was suspended in H_2O (15 ml), alkalized with 1 M NaOH and extracted with $CHCl_3$ (4 × 20 ml, drying with $MgSO_4$). The organic layer was evaporated yielding an oil of crude (**46a**). The product was converted into hydrochloride (5.5 M HCl in MeOH) and purified by column chro-

matography on silica gel using $CHCl_3$/MeOH (20:3) as eluent. Yield: 391 mg (62%), oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.48–1.84 (m, 2H, $CHCH_2CH_2$), 3.00–3.20 (m, 2H, CH_2CH_2NH), 3.27–3.43 (m, 1H, $HNCH_2CH$), 3.70–3.85 (m, 1H, $HNCH_2CH$), 4.00–4.12 (m, 1H, $CH_2CH(NH)CH_2$), 4.34 (s, 2H, $CH_2C_{10}H_7$), 4.92 (s, 2H, OCH_2Ph), 5.80–6.05 (br s, 1H, NH), 7.16–7.25 (m, 5H, C_6H_5), 7.33–8.05 (m, 7H, $C_{10}H_7$), 10.00–10.40 (br s, 2H, NH). Anal. Calcd for $C_{24}H_{26}ClN_3O_2$: C, 68.00; H, 6.18; N, 9.91. Found: C, 67.94; H, 6.15; N, 9.79.

4.1.34. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(naphthyl-1)methylene] imidazoline dihydrobromide (21a)

Compound **21** was obtained according to the general procedure B, starting from **20a**. The product was crystallized from MeOH/Et_2O. Yield: 40 mg (96%), beige powder. Mp 294–297 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) = 1.70–2.00 (m, 2H, $CHCH_2CH_2$), 2.75–3.05 (m, 2H, $CH_2CH_2NH_3^+$), 3.55 (dd, J_1 = 7.6, J_2 = 11.4, 1H, $HNCH_2CH$), 3.92 (t, J = 11.4, 1H, $HNCH_2CH$), 4.25–4.47 (m, 3H, $CH_2CH(NH)CH_2$), $C_{10}H_7CH_2$), 7.55–8.15 (m, 10H, $C_{10}H_7$, NH_3^+). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 31.7, 34.0, 37.2, 51.3, 56.7, 124.1, 127.1, 127.7, 128.7, 129.1, 130.1, 130.5, 130.8, 133.2, 135.8, 171.8. MS FAB MH^+ 254 (calcd for $C_{16}H_{19}N_3$ M = 253.3). Anal. Calcd for $C_{16}H_{21}Br_2N_3$: C, 46.29; H, 5.10; N, 10.12. Found: C, 46.33; H, 5.17; N, 10.06.

4.1.35. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-[(naphthyl-1)methylene] imidazoline dihydrobromide (21b)

Compound **21b** was synthesized according to the procedure for **20a** and **21a**, starting from **1b** (533 mg, 1.72 mmol). Yield: 414 mg (58%), beige powder. Mp 307–309 °C. ^{1}H NMR (200 MHz, MeOD): δ (ppm) = 1.90–2.20 (m, 2H, $CHCH_2CH_2$), 2.90–3.18 (m, 2H, $CH_2CH_2NH_3^+$), 3.65 (dd, J_1 = 7.4, J_2 = 11.6, 1H, $HNCH_2CH$), 4.04 (t, J = 11.4, 1H, $HNCH_2CH$), 4.35–4.55 (m, 3H, $CH_2CH(NH)CH_2$), $C_{10}H_7CH_2$), 7.45–7.72 (m, 4H, $C_{10}H_7$), 7.86–8.40 (m, 3H, $C_{10}H_7$). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 31.8, 34.0, 37.1, 51.3, 56.7, 124.1, 127.1, 127.7, 128.7, 129.1, 130.1, 130.5, 130.8, 133.2, 135.8, 171.8. MS FAB MH^+ 254 (calcd for $C_{16}H_{19}N_3$ M = 253.3). Anal. Calcd for $C_{16}H_{21}Br_2N_3$: C, 46.29; H, 5.10; N, 10.12. Found: C, 46.38; H, 5.07; N, 9.99.

4.1.36. 2-Ethyl-2,3-dihydro-1-benzofurane-2-carboxylic acid amide (22b)

To 2-ethyl-2,3-dihydro-1-benzofurane-2-carboxylic acid methyl ester **22a** (2050 mg, 9.95 mmol), 24% NH_3 in MeOH (60 ml) was added. The reaction mixture was stirred for 48 h in rt. The volatiles were evaporated under reduced pressure and the residue was crystallized from AcOEt/hexane. Yield: 1730 mg (91%), white powder. Mp 95–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.96 (t, J = 7.5, 3H, CH_2CH_3), 1.91–1.98 (m, 1H, CCH_2CH_3), 2.10–2.17 (m, 1H, CCH_2CH_3), 3.18 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 3.58 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 5.61–5.78 (br s, 1H, $CONH_2$), 6.61–6.76 (br s, 1H, $CONH_2$), 6.83–6.95 (m, 2H, $C_6H_4(O)CH_2$), 7.13–7.20 (m, 2H, $C_6H_4(O)CH_2$).

4.1.37. 2-Ethyl-2,3-dihydro-1-benzofurane-2-carboxylic acid nitrile (23)

To **22b** anhydrous pyridine (20 ml) was added. The solution was cooled in ice bath and $POCl_3$ (2.75 ml, 30.01 mmol) was added dropwise. The reaction mixture was refluxed for 3 h. The volatiles were removed under reduced pressure and the oily residue was suspended in 1 M $KHSO_4$ and extracted with CH_2Cl_2 (4 × 40 ml, drying with $MgSO_4$). The organic layer was evaporated. The oily residue was dissolved in minimal volume of hexane: AcOEt (10:1) and left in refrigerator overnight. The dark precipitate was filtrated, washed with hexane and discarded. The filtrate was evaporated under reduced pressure yielding an oil of **23**, 1460 mg (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, J = 7.3, 3H, CH_2CH_3), 2.03–2.22 (m, 2H, CCH_2CH_3), 3.31 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 3.63 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 6.84–6.99 (m, 2H, $C_6H_4(O)CH_2$), 7.18–7.24 (m, 2H, $C_6H_4(O)CH_2$).

4.1.38. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-(2-ethyl-2,3-dihydro-1-benzofurane-2)imidazoline hydrochloride (24a)

Compound **23** (216 mg, 1.25 mmol) was dissolved in 99.9% EtOH (2 ml) and 2.68 M EtONa in EtOH (70 μl, 0.188 mmol) was added. The reaction mixture was stirred at rt overnight. Then the resulting mixture of iminoester was added to **1a** (387 mg, 1.25 mmol) in 99.9% EtOH (5 ml). The reaction mixture was refluxed for 4 h. The volatiles were evaporated and the crude **24a** was purified by column chromatography on silica gel using $CHCl_3$/MeOH (7:1) as eluent. Yield: 451 mg (84%), oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.95–1.05 (m, 3H, CH_2CH_3), 1.63–1.79 (m, 1H, $CHCH_2CH_2$), 1.91–2.02 (m, 1H, $CHCH_2CH_2$), 2.13–2.27 (m, 1H, CCH_2CH_3), 2.35–2.52 (m, 1H, CCH_2CH_3), 3.27–3.39 (m, 1H, CH_2CH_2NH), 3.43–3.53 (m, 1H, CH_2CH_2NH), 3.56–3.63 (m, 2H, $HNCH_2CH$, $C_6H_4(O)CH_2C$), 3.71–3.82 (m, 1H, $C_6H_4(O)CH_2C$), 3.98–4.08 (m, 1H, $HNCH_2CH$), 4.20–4.38 (m, 1H, $CH_2CH(NH)CH_2$), 5.03 (AB system, J_1 = 12.2, J_2 = 26.4, 2H, $OCH_2C_6H_5$), 6.05–6.23 (br s, 1H, NH), 6.89–6.98 (m, 2H, $C_6H_4(O)CH_2$), 7.10–7.19 (m, 2H, $C_6H_4(O)CH_2$), 7.26–7.40 (m, 5H, C_6H_5), 9.60–11.00 (br s, 2H, NH). Anal. Calcd for $C_{23}H_{28}ClN_3O_3$: C, 64.25; H, 6.56; N, 9.77. Found: C, 64.07; H, 6.58; N, 9.90.

4.1.39. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-(2-ethyl-2,3-dihydro-1-benzofurane-2)imidazoline dihydrobromide (25a)

Compound **25a** was obtained according to the general procedure B, starting from **24a** (400 mg, 0.931 mmol). Product was crystallized from MeOH/*i*-PrOH/Et_2O. Yield: 364 mg (93%), white powder. Mp 207–210 °C. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 0.91 (t, J = 7.3, 3H, CH_2CH_3), 1.78–1.98 (m, 2H, $CHCH_2CH_2$), 1.98–2.19 (m, 2H, CCH_2CH_3), 2.78–3.03 (m, 2H, CH_2CH_2NH), 3.38 (d, J = 16.6, 1H, $C_6H_4(O)CH_2C$), 3.56 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 3.61–3.72 (m, 1H, $HNCH_2CH$), 3.98 (dd, J_1 = 11.2, J_2 = 22.5, 1H, $HNCH_2CH$), 4.33–4.46 (m, 1H, $CH_2CH(NH)CH_2$), 6.85–6.97 (m, 2H, $C_6H_4(O)CH_2$), 7.12–7.27 (m, 2H, $C_6H_4(O)CH_2$), 7.70–8.10 (br s, 3H, NH_3^+), 10.40–10.65 (br s, 2H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 8.3, 33.5, 33.6, 34.0, 34.1, 37.2, 41.4, 41.6, 51.5, 57.2, 87.8, 111.4, 123.6, 125.8, 126.4, 130.1, 159.0, 175.0. MS FAB MH^+ 260 (calcd for $C_{15}H_{21}N_3O$ M = 259.3). Anal. Calcd for $C_{15}H_{23}Br_2N_3O$: C, 42.78; H, 5.50; N, 9.98. Found: C, 42.60; H, 5.67; N, 9.79.

4.1.40. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-(2-ethyl-2,3-dihydro-1-benzofurane-2)imidazoline dihydrobromide (25b)

Compound **25b** was prepared according to the procedure applied for **24a** and **25a**, starting from **1b** (360 mg, 1.16 mmol). Yield 355 mg (73%), white powder. Mp 206–208 °C. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 0.91 (t, J = 7.3, 3H, CH_2CH_3), 1.80–1.97 (m, 2H, $CHCH_2CH_2$), 1.98–2.19 (m, 2H, CCH_2CH_3), 2.79–3.04 (m, 2H, CH_2CH_2NH), 3.38 (d, J = 16.6, 1H, $C_6H_4(O)CH_2C$), 3.57 (d, J = 16.1, 1H, $C_6H_4(O)CH_2C$), 3.62–3.70 (m, 1H, $HNCH_2CH$), 3.98 (dd, J_1 = 11.2, J_2 = 22.4, 1H, $HNCH_2CH$), 4.33–4.48 (m, 1H, $CH_2CH(NH)CH_2$), 6.85–6.98 (m, 2H, $C_6H_4(O)CH_2$), 7.12–7.28 (m, 2H, $C_6H_4(O)CH_2$), 7.70–8.10 (br s, 3H, NH_3^+), 10.40–10.65 (br s, 2H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 8.3, 33.5, 33.6, 34.0, 34.1, 37.3, 41.5, 41.7, 51.6, 57.2, 87.8, 87.9, 111.4, 123.6, 125.9, 126.5, 130.1, 159.0, 175.0. MS FAB MH^+ 260 (calcd for $C_{15}H_{21}N_3O$ M = 259.3). Anal. Calcd for $C_{15}H_{23}Br_2N_3O$: C, 42.78; H, 5.50; N, 9.98. Found: C, 42.64; H, 5.47; N, 9.84.

4.1.41. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-(2,3-dihydro-1,4-benzodioxane-2)imidazoline hydrochloride (28a)

To a solution of **26** in 99.9% EtOH (253 μl), 2 M HCl in anhyd Et_2O (10 ml) were added. The reaction mixture was kept in a refrigerator (4 °C) for 3 days. The resulting precipitate was filtered, washed with anhyd Et_2O and dried in desiccator. Yield of iminoester hydrochloride **27**: 771 mg (73%), white powder. Mp 122–125 °C.

To **1a** 99.9% EtOH (5 ml) and Et_3N (162 μl, 1.16 mmol) were added. To the resulting solution the iminoester hydrochloride **27** (283 mg, 1.16 mmol) was added. The reaction mixture was refluxed for 4 h. Then the volatiles were evaporated and the residue was suspended in 1 M NaOH (20 ml) and extracted with Et_2O (4 × 40 ml, drying with $MgSO_4$). The organic layer was evaporated under reduced pressure. The crude product **28a** was converted into hydrochloride (5.5 M HCl in MeOH) and purified by column chromatography on silica gel using $CHCl_3$/MeOH (7:1) as eluent. Yield: 281 mg (58%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.55–1.95 (m, 2H, CHC*H*$_2$CH$_2$), 3.15–3.45 (m, 2H, CH$_2$C*H*$_2$NH), 3.65–3.78 (m, 1H, HNC*H*$_2$CH), 3.95–4.15 (m, 1H, HNC*H*$_2$CH), 4.18–4.35 (m, 1H, CH$_2$C*H*(NH)CH$_2$), 4.45–4.60 (m, 1H, OC*H*$_2$CH), 4.90–5.03 (m, 1H, OC*H*$_2$CH), 5.09 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.45–5.55 (m, 1H, OC*H*(C)CH$_2$), 6.60–6.80 (br s, 1H, N*H*), 6.80–7.00 (m, 4H, C$_6$*H*$_4$O$_2$), 7.25–7.40 (m, 5H, C$_6$*H*$_5$), 10.10–10.65 (br s, 2H, NH). Anal. Calcd for $C_{21}H_{24}ClN_3O_4$: C, 60.36; H, 5.79; N, 10.06. Found: C, 60.40; H, 5.85; N, 10.15.

4.1.42. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-(2,3-dihydro-1,4-benzodioxane-2)imidazoline dihydrobromide (29a)

Compound **29a** was obtained according to the general procedure B, starting from **28a**. The product was crystallized from *i*-PrOH/Et_2O. Yield: 272 mg (85%), white powder. Mp 188–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.70–2.03 (m, 2H, CHC*H*$_2$CH$_2$), 2.78–3.05 (m, 2H, CH$_2$C*H*$_2$NH), 3.62 (dd, J_1 = 8.1, J_2 = 19.2, 1H, HNC*H*$_2$CH), 4.00 (t, J = 11.7, 1H, HNC*H*$_2$CH), 4.35–4.05 (m, 3H, CH$_2$C*H*(NH)CH$_2$, OC*H*$_2$CH), 5.57–5.65 (m, 1H, OC*H*(C)CH$_2$), 6.80–7.05 (m, 4H, C$_6$*H*$_4$O$_2$), 7.75–8.10 (br s, 3H, N*H*$_3^+$), 10.56 (s, 1H, N*H*), 10.66 (d, J = 12.7, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 33.9, 37.1, 51.6, 57.2, 65.9, 66.0, 69.9, 70.0, 119.0, 119.1, 124.0, 124.3, 142.8, 144.5, 168.6. MS FAB MH$^+$ 248 (calcd for $C_{13}H_{17}N_3O_2$ M = 247.3). Anal. Calcd for $C_{13}H_{19}Br_2N_3O_2$: C, 38.16; H, 4.68; N, 10.27. Found: C, 38.19; H, 4.50; N, 10.21.

4.1.43. 4(5)*R*]-4(5)-(2-Aminoethyl)-2-(2,3-dihydro-1,4-benzodioxane-2)imidazoline dihydrobromide (29b)

Synthesis of **29b** was carried out according to the procedures for **28a** and **29a**, starting from (**1b**) (381 mg, 1.23 mmol). Yield: 256 mg (51%), white powder. Mp 191–193 °C. ^{1}H NMR (500 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.79–2.03 (m, 2H, CHC*H*$_2$CH$_2$), 2.77–3.03 (m, 2H, CH$_2$C*H*$_2$NH), 3.60–3.73 (m, 1H, HNC*H*$_2$CH), 4.00 (t, J = 11.7, 1H, HNC*H*$_2$CH), 4.37–4.05 (m, 3H, CH$_2$C*H*(NH)CH$_2$, OC*H*$_2$CH), 5.57–5.65 (m, 1H, OC*H*(C)CH$_2$), 6.80–7.05 (m, 4H, C$_6$*H*$_4$O$_2$), 7.75–8.10 (br s, 3H, N*H*$_3^+$), 10.56 (s, 1H, N*H*), 10.65 (d, J = 13.7, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 33.9, 37.1, 51.6, 57.2, 66.0, 66.1, 69.9, 70.0, 119.0, 119.1, 124.0, 124.3, 142.8, 144.5, 168.6. MS FAB MH$^+$ 248 (calcd for $C_{13}H_{17}N_3O_2$ M = 247.3). Anal. Calcd for $C_{13}H_{19}Br_2N_3O_2$: C, 38.16; H, 4.68; N, 10.27. Found: C, 38.20; H, 4.54; N, 10.09.

4.1.44. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-(chloromethyl)imidazoline hydrochloride (30a)

Chloroacetonitrile (316 μl, 5 mmol) was added to 99.9% EtOH (291 μl, 5 mmol) in 2 M HCl in Et_2O. The reaction mixture was kept for 2 days in 4 °C. The precipitate of iminoester was filtered off, washed with anhyd Et_2O and dried in a desiccator. Yield: 699 mg (88%), white powder. Mp 85–86 °C.

2.68 M EtONa in EtOH (380 μl, 1.02 mmol) and 99.9% EtOH (5 ml) were added to **1a** (318 mg, 1.02 mmol). To the resulting mixture, the iminoester obtained as above (161 mg, 1.02 mmol) was added. The reaction mixture was refluxed for 1.5 h. The volatiles were evaporated under reduced pressure and the product **30a** was purified by column chromatography on silica gel using $CHCl_3$/MeOH (3:1) as eluent. Yield: 144 mg (42%), oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.77–1.98 (m, 2H, CHC*H*$_2$CH$_2$), 3.25–3.40 (m, 2H, CH$_2$C*H*$_2$NH), 3.52–3.62 (m, 1H, HNC*H*$_2$CH), 3.97–4.08 (m, 1H, HNC*H*$_2$CH), 4.27–4.39 (m, 1H, CH$_2$C*H*(NH)CH$_2$), 4.61 (s, 2H, ClC*H*$_2$C), 5.02 (AB system, J_1 = 12.8, J_2 = 17.7, 2H, OC*H*$_2$C$_6$H$_5$), 6.22–6.33 (br s, 1H, N*H*), 7.25–7.40 (m, 5H, C$_6$*H*$_5$), 10.75–10.95 (br s, 2H, N*H*). Anal. Calcd for $C_{14}H_{19}Cl_2N_3O_2$: C, 50.61; H, 5.76; N, 12.65. Found: C, 50.58; H, 5.71; N, 12.76.

4.1.45. 4(5)*S*]-2-[(*N*-Benzyl-*N*-phenyl)aminomethyl]-4(5)-(*N*-benzyloxycarbonyl-2-aminoethyl)imidazoline hydrochloride (30b)

N-Benzylaniline (564 mg, 3.08 mmol) and 99.9% EtOH (5 ml) were added to **30a** (155 mg, 0.467 mmol). The reaction mixture was refluxed for 24 h., then cooled and 5.5 M HCl in MeOH (1.5 ml) was added. The volatiles were evaporated under reduced pressure and the product was purified by column chromatography on silica gel using $CHCl_3$/MeOH (6:1) as eluent. Yield: 90 mg (38%).^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.40–2.15 (m, 2H, CHC*H*$_2$CH$_2$), 2.93–3.22 (m, 2H, CH$_2$C*H*$_2$NH), 3.25–3.50 (m, 1H, HNC*H*$_2$CH), 3.75–3.93 (m, 1H, HNC*H*$_2$CH), 3.95–4.18 (m, 1H, CH$_2$C*H*(NH)CH$_2$), 4.28–4.78 (m, 4H, NC*H*$_2$C, NC*H*$_2$C$_6$H$_5$), 5.00 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.78–6.00 (br s, 1H, N*H*), 6.63–6.98 (m, 3H, NC$_6$*H*$_5$), 7.07–7.60 (m, 13H, OCH$_2$C$_6$*H*$_5$, NCH$_2$C$_6$*H*$_5$, NC$_6$*H*$_5$, N*H*), 10.04 (s, 1H, N*H*), 10.68 (s, 1H, N*H*). Anal. Calcd for $C_{27}H_{32}Cl_2N_4O_2$: C, 62.91; H, 6.26; N, 10.87. Found: C, 62.88; H, 6.23; N, 10.93.

4.1.46. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(*N*-benzyl-*N*-phenyl) aminomethyl]imidazoline trihydrobromide (30c)

Compound **30c** was prepared according to the general procedure B, starting from **30b** (78 mg, 0.151 mmol). The product was crystallized from *i*-PrOH/Et_2O. Yield: 69 mg (83%). Mp 205–207 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.75–2.10 (m, 2H, CHC*H*$_2$CH$_2$), 2.75–3.10 (m, 2H, CH$_2$C*H*$_2$NH), 3.57 (dd, J_1 = 7.3, J_2 = 11.4, 1H, HNC*H*$_2$CH), 3.94 (t, J = 11.4, 1H, HNC*H*$_2$CH), 4.28–4.48 (m, 1H, CH$_2$C*H*(NH)CH$_2$), 4.61 (s, 2H, NC*H*$_2$C$_6$H$_5$), 4.72 (s, 2H, NC*H*$_2$C), 6.55–6.85 (m, 3H, NC$_6$*H*$_5$), 7.18–7.50 (m, 8H, OCH$_2$C$_6$*H*$_5$, NCH$_2$C$_6$*H*$_5$, NC$_6$*H*$_5$, N*H*), 7.80–8.15 (br s, 3H, N*H*$_3^+$), 10.20 (s, 1H, N*H*), 10.33 (s, 1H, N*H*). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 33.9, 37.2, 49.9, 51.4, 56.4, 56.6, 56.9, 115.2, 116.8, 120.5, 128.8, 130.1, 130.8, 133.5, 149.4, 172.2. MS FAB MH$^+$ 309 (calcd for $C_{19}H_{24}N_4$ M = 308.4). Anal. Calcd for $C_{19}H_{27}Br_3N_4$: C, 41.40; H, 4.94; N, 10.17. Found: C, 41.29; H, 5.15; N, 10.29.

4.1.47. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-phenylimidazoline hydrochloride (31a)

99.9% EtOH (93 μl, 1.60 mmol) and 2 M HCl in Et_2O (1.5 ml) were added to benzonitrile (164 μl, 1.60 mmol). The reaction mixture was kept at 4–5 °C for 10 days. The precipitate of iminoester was filtered off, washed with anhyd Et_2O and dried in desiccator. Yield: 100 mg (34%).

Compound **1a** (167 mg, 0.54 mmol) dissolved in 99.9% EtOH (5 ml) and Et_3N (75 μl, 0.54 mmol) was added to the iminoester obtained as above (100 mg, 0.544 mmol). The reaction mixture was refluxed for 3 h. The volatiles were removed under reduced pressure. The oily residue was suspended in 1 M NaOH (10 ml) and extracted with $CHCl_3$ (4 × 10 ml, drying with $MgSO_4$). The organic layer was evaporated and the crude (**31a**) was converted into hydrochloride with 5.5 M HCl in MeOH. The product was purified by column chromatography on silica gel using $CHCl_3$/MeOH (5:1). Yield:

107 mg (55%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.60–2.00 (m, 2H, CHCH_2CH$_2$), 3.20–3.70 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.85–4.10 (m, 1H, HNCH_2CH), 4.15–4.40 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.05 (s, 2H, OCH_2C$_6$H$_5$), 6.20–6.45 (br s, 1H, NH), 7.20–8.30 (m, 10H, C$_6H_5$, C$_6H_5$), 10.62 (s, 1H, NH), 10.93 (s, 1H, NH). Anal. Calcd for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68. Found: C, 63.48; H, 6.23; N, 11.61.

4.1.48. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-phenylimidazoline dihydrobromide (31b)

Preparation and purification of **31b** was carried out according to the general procedure B, starting from **31a** (75 mg, 0.21 mmol). The product was crystallized from *i*-PrOH with Et_2O. Yield: 68 mg (93%). Mp 195–197 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.80–2.20 (m, 2H, CHCH_2CH$_2$), 2.75–3.20 (m, 2H, CH$_2$CH_2NH), 3.71 (dd, J_1 = 8.06, J_2 = 11.4, 1H, HNCH_2CH), 4.06 (t, J = 11.4, 1H, NCH_2CH), 4.35–4.65 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.57–8.12 (m, 8H, C$_6H_5$, NH_3^+), 10.70 (s, 2H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.2, 37.4, 51.5, 56.9, 130.0, 130.8, 131.0, 136.5, 167.6. MS FAB MH$^+$ 190 (calcd for $C_{11}H_{15}N_3$ M = 189.3). Anal. Calcd for $C_{11}H_{17}Br_2N_3$: C, 37.63; H, 4.88; N, 11.97. Found: C, 37.49; H, 5.03; N, 11.93.

4.1.49. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-(2-fluorophenyl)imidazoline hydrochloride (32a)

Compound **1a** (271 mg, 1.14 mmol) was dissolved in CH_2Cl_2 (4 ml) and the mixture was cooled in an ice bath. Then 2-fluorobenzaldehyde (115 μl, 1.09 mmol) was added and the resulting mixture was stirred for 40–50 min at 0 °C. Then *N*-bromosuccinimide (194 mg, 1.09 mmol) was added and the reaction mixture was stirred for additional 12 h at rt. The volatiles were evaporated under reduced pressure. The residue was suspended in 1 M NaOH (20 ml) and extracted with CH_2Cl_2 (4 × 40 ml, drying with $MgSO_4$). The organic layer was evaporated. The crude product (**32a**) was converted into hydrochloride with 5.5 M HCl in MeOH and purified by column chromatography on silica gel using $CHCl_3$/MeOH (7:1). Yield: 254 mg (62%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.70–2.15 (m, 2H, CHCH_2CH$_2$), 3.15–3.75 (m, 3H, CH$_2$CH_2NH, 1H, HNCH_2CH), 3.95–4.20 (m, 1H, HNCH_2CH), 4.25–4.50 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.07 (s, 2H, OCH_2C$_6$H$_5$), 6.10–6.30 (br s, 1H, NH), 7.10–7.70 (m, 9H, C$_6H_5$, C$_6H_4$F), 8.25–8.50 (br s, 2H, NH). Anal. Calcd for $C_{19}H_{21}ClFN_3O_2$: C, 60.40; H, 5.60; N, 11.12. Found: C, 60.31; H, 5.52; N, 11.02.

4.1.50. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-(2-fluorophenyl)imidaz oline dihydrobromide (32b)

Compound **32b** was obtained according to the general procedure B, starting from **32a** (221 mg, 0.585 mmol). The product was crystallized form *i*-PrOH/Et_2O. Yield: 212 mg (98%). Mp 238–240 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.80–2.25 (m, 2H, CHCH_2CH$_2$), 2.83–3.18 (m, 2H, CH$_2$CH_2NH), 3.75 (dd, J_1 = 7.5, J_2 = 11.4, 1H, HNCH_2CH), 4.13 (t, J = 11.4, 1H, HNCH_2CH), 4.47–4.68 (m, 1H, CH$_2$CH(NH)CH$_2$), 7.42–8.28 (m, 7H, C$_6H_4$F, NH_3^+), 10.63 (s, 1H, NH), 10.73 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.1, 37.3, 51.5, 56.8, 112.2, 112.6, 118.3, 118.8, 127.0, 127.1, 132.0, 138.5, 138.7, 159.7, 163.3, 164.8. MS FAB MH$^+$ 208 (calcd for $C_{11}H_{14}FN_3$ M = 207.2). Anal. Calcd for $C_{11}H_{16}Br_2FN_3$: C, 35.80; H, 4.37; N, 11.39. Found: C, 35.77; H, 4.51; N, 11.22.

4.1.51. 4(5)*S*]-4(5)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-[(*E*)-2-phenylethenyl]imidazoline hydrochloride (33a)

Compound **33a** was obtained according to the procedure applied for **32a**, starting from cinnamaldehyde (251 μl, 1.99 mmol). Yield 254 mg (33%), oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.55–2.05 (m, 2H, CHCH_2CH$_2$), 3.10–3.55 (m, 3H, CH$_2$CH_2NH, HNCH_2CH), 3.75–3.95 (m, 1H, HNCH_2CH), 4.05–4.25 (m, 1H, CH$_2$CH(NH)CH$_2$), 5.05 (s, 2H, OCH_2C$_6$H$_5$), 6.10–6.15 (m, 1H, NH), 6.85 (d, J = 16.5, 1H, CHCHC), 7.18–7.58 (m, 10H, CHC$_6H_5$, CH$_2$C$_6H_5$), 8.25 (d, J = 16.5, 1H, C$_6$H$_5$CHCH), 10.00–10.80 (br s, 2H, NH). Anal. Calcd for $C_{21}H_{24}ClN_3O_2$: C, 65.36; H, 6.27; N, 10.89. Found: C, 65.08; H, 6.34; N, 10.73.

4.1.52. 4(5)*S*]-4(5)-(2-Aminoethyl)-2-[(*E*)-2-phenylethenyl] imidazoline dihydrobromide (33b)

A solution of HBr in AcOH (5 ml) was added to **33a** (240 mg, 0.623 mmol). The reaction mixture was stirred for 30 min at rt. Then the volatiles were evaporated under reduced pressure and the crude product was crystallized from MeOH/Et_2O. Yield: 216 mg (92%), white powder. Mp 264–266 °C. ^{1}H NMR (200 MHz, DMSO-d_6 + TFA): δ (ppm) = 1.80–2.15 (m, 2H, CHCH_2CH$_2$), 2.80–3.15 (m, 2H, CH$_2$CH_2NH), 3.64 (dd, J_1 = 7.4, J_2 = 11.4, 1H, HNCH_2CH), 3.75–3.95 (t, J = 11.4, 1H, HNCH_2CH), 4.35–4.60 (m, 1H, CH$_2$CH(NH)CH$_2$), 6.83 (d, J = 16.5, 1H, CHCHC), 7.20–8.40 (m, 9H, CHC$_6H_5$, C$_6$H$_5$CHCH, NH_3^+), 10.36 (s, 1H, NH), 10.51 (s, 1H, NH). ^{13}C NMR (200 MHz, MeOD): δ (ppm) = 34.2, 37.4, 51.1, 56.5, 109.8, 130.1, 130.7, 133.3, 135.0, 149.1, 165.9. MS FAB MH$^+$ 216 (calcd for $C_{13}H_{17}N_3$ M = 215.3). Anal. Calcd for $C_{13}H_{19}Br_2N_3$: C, 41.40; H, 5.08; N, 11.14. Found: C, 41.40; H, 5.00; N, 11.19.

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