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A practical multi-step synthesis of ethyl *N*-functionalized β-amino benzimidazole acrylate derivatives as promising cytotoxic agents

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Abstract: A series of 16 new ethyl β-amino benzimidazole acrylate derivatives **12(a-p)** with a (2*E*)-*s*-cis/trans conformation and bearing two points of diversity was designed and synthesized by using a multi-step strategy (reductive amination, deprotection in acidic media and transamination) in moderate to good yields from ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate (**5**) and mono substituted *N*-Boc diamines (**7a**, **7b**) as starting building-blocks. Products **12** were evaluated for their *in vitro* cytotoxic potential against six selected human cell lines (Huh7-D12, Caco2, MDA-MB231, HCT116, PC3 and NCI-H727). Compounds **12a**, **12e** and **12l** exhibited selective and micromolar antitumor activities against Huh7-D12 and Caco2 cell lines.

Keywords: benzimidazole, reductive amination, transamination, microwave, cytotoxicity.

Introduction

Benzimidazole is a heterocyclic scaffold consisting of a benzene and an imidazole ring. During the last decades, benzimidazole has gained considerable attention by the pharmaceutical community, and this is confirmed by recent reports in the literature that describe the "therapeutic evolution of their derivatives in pre-clinical and clinical trials during the last quinquennial period" [1,2]. Medicinal aspects and structure activity relationship (SAR) of benzimidazole have been reviewed by Yadav and Ganguly [3]. Owing to that cancer is the second major cause of death worldwide [4], chemical and pharmaceutical researchers investigated the synthesis of bioactive benzimidazole derivatives with significant cytotoxic effects. As examples in Figure 1, bendamustine (***I***) is a benzimidazole-based drug approved for chronic lymphoid leukemia treatment [5]. Compound ***II*** developed by Sharma *et al.* [6] was identified as benzimidazole derivative that exhibited *in vitro* cytotoxic activity against MDA-MB231 cell line with a half inhibitory concentration (IC_{50}) value of 3.3 μM. The new 5-fluorine benzimidazole-4-carboxamide derivative ***III*** was reported as a promising anti-cancer agent and showed promising cell inhibitory activity against HCT116 cell with an IC_{50} of 7.4 μM [7]. Introduction of a purine moiety in benzimidazole derivative ***IV*** was found to exhibit growth inhibitory activity towards Aurora-A kinase with an IC_{50} value of 10 nM [8]. Varshney *et al.* investigated the multi-step synthesis of 1-[(5-alkenyl/hydroxyalkenyl substituted-1,3,4-oxadiazol-2-yl)-methyl]-2-methyl-1*H*-benzimidazoles and found that compound ***V*** was the most bioactive benzimidazole derivative [9] against human breast adenocarcinoma (MCF-7 cell, IC_{50} 40 μM) and human cervical carcinoma (HeLa) cell lines (IC_{50}

5.3 μM). Introduction of a 4-amino-quinolyl fragment to benzimidazole at the C-4 position in compound ***VI*** exhibited inhibitory activity against VEGFR-2 (IC_{50} = 30 nM) associated to anti-cancer activity against MCF-7 cancer cells (IC_{50} = 1.3 μM) [10].

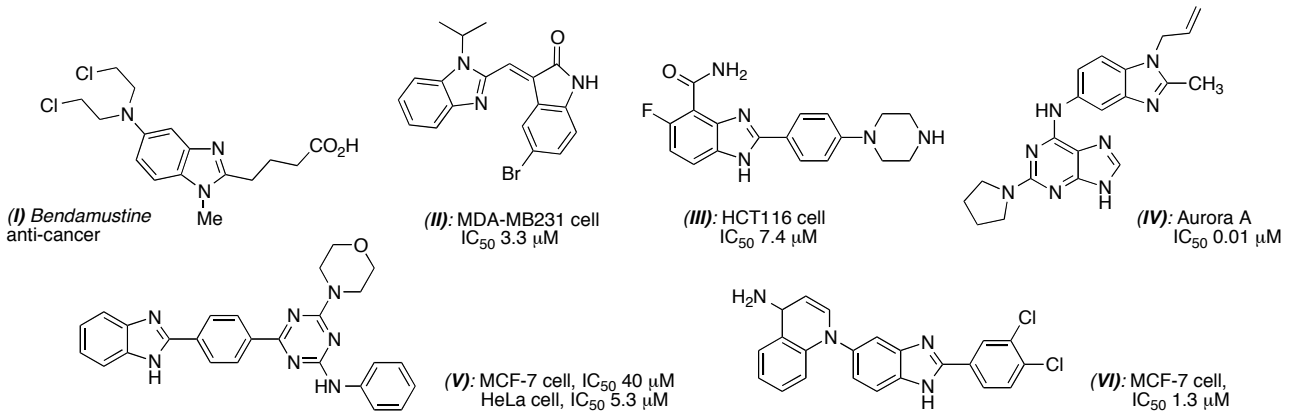


Figure 1: Examples of bioactive benzimidazole derivatives.

Stimulated by these pharmaceutical applications for benzimidazole scaffold bearing specific groups as bioactive compounds against a variety of cancer cell lines, our goal was to explore the construction of stereocontrolled β-amino benzimidazole acrylates [11] (Figure 2) bearing, a flexible diamino linker and a variable *N*-arylmethyl moiety.

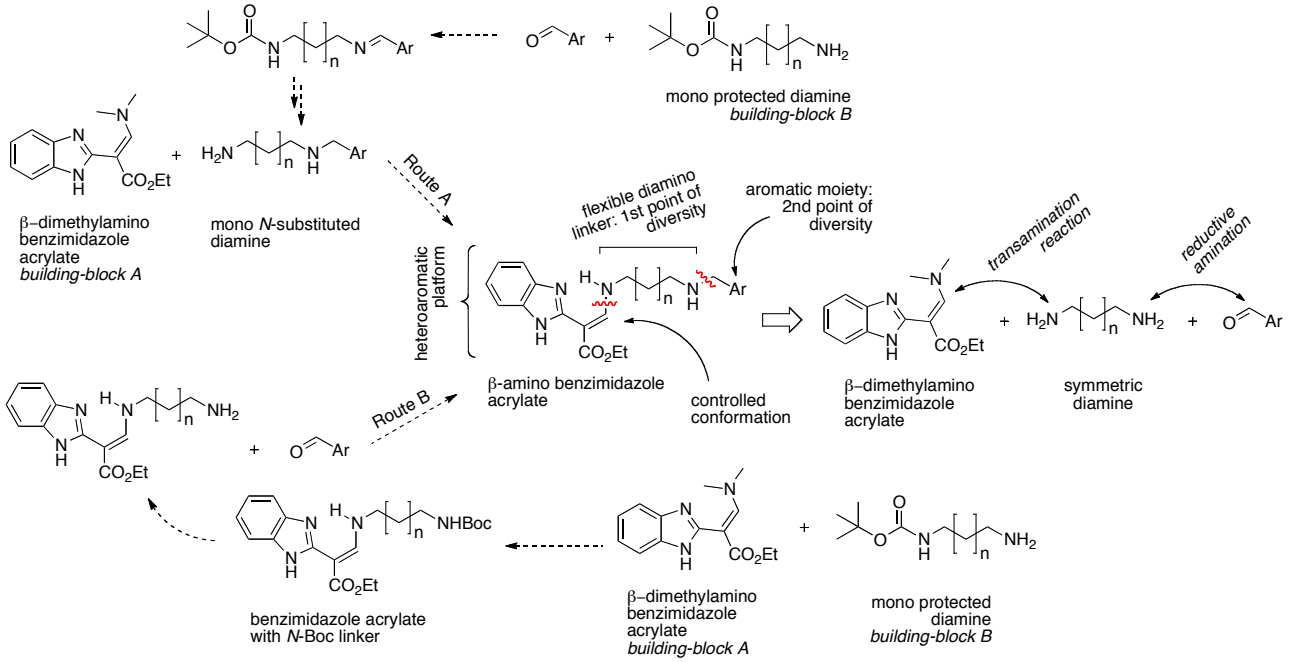


Figure 2: Retrosynthetic strategy for ethyl *N*-functionalized β-amino benzimidazole acrylates

Our retrosynthetic strategy towards new *N*-functionalized β-amino benzimidazole acrylate derivatives shows two possible routes. Route A is based on a transamination reaction between β-dimethylamino benzimidazole acrylates (building block A) and a mono *N*-substituted diamine. Route B involves the reductive amination of amino-linked benzimidazole acrylate with aromatic aldehydes. Considering these two routes to build *N*-functionalized β-amino benzimidazole acrylates for this project, it can be observed that the β-dimethylamino benzimidazole acrylate will be used as building-block for the two routes A and B. Herein, we present the synthetic results for the

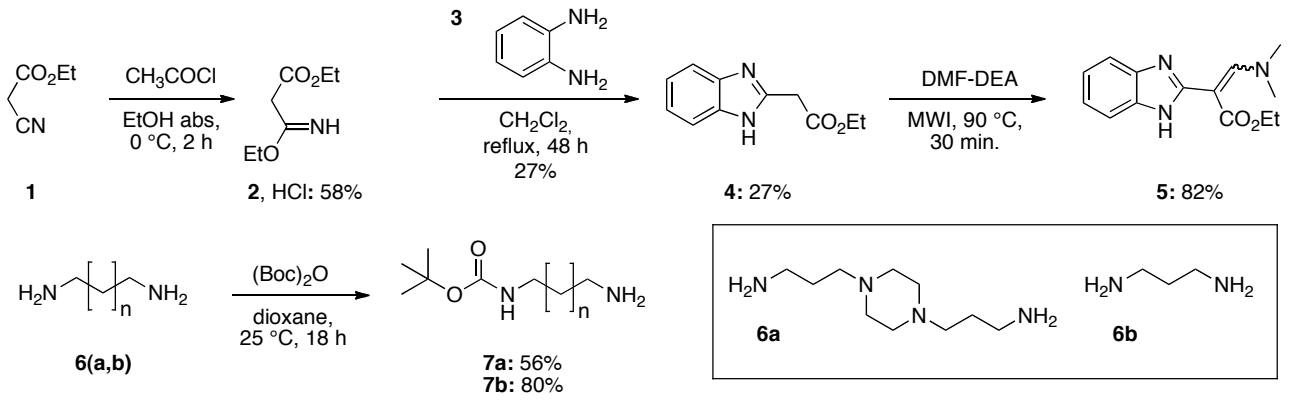
preparation of these new benzimidazole derivatives, their intermediates and their biological activities as potential cytotoxic agents.

Results and discussion

Chemistry.

Synthesis of building blocks A and B: The strategy for the synthesis of ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** as building block A and *N*-Boc diamines **7(a, b)** as building block B is outlined in Scheme 1.

Access to **5** was achieved in three steps. The first step is based on a modified protocol for the classic Pinner reaction. Ethyl cyanoacetate **1** is converted into ethyl 2-ethoxycarbonylacetimidate hydrochloride **2** in acidic conditions by addition of acetyl chloride (compound **1** in dry absolute EtOH) to generate *in situ* hydrochloric acid at 0 °C. After two hours, the reaction mixture was concentrated *in vacuum* and a product crystallized rapidly in multi-grams quantities of desired imidate hydrochloride **2** (58% yield). This salt underwent facile heterocyclocondensation with commercially available *ortho*-phenylenediamine **3** in refluxed methylene chloride during 48 hours to give ethyl 2-(1*H*-benzimidazol-2-yl)acetate **4** (27% yield) [12]. Finally, the desired building-block **5** was easily prepared according to a previous method developed in our laboratory [13]. This solvent-free protocol consisted in reacting compound **4** with *N,N*-dimethylformamide diethyl acetal (DMF-DEA) at 90°C for 30 min. under microwave irradiation conditions [14]. After purification by recrystallization from AcOEt (82% yield), the structure of ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** was ascertained by HRMS, ^{1}H and ^{13}C NMR. Building-block **5** was prepared with an overall yield of 13% in multi-gram quantities.

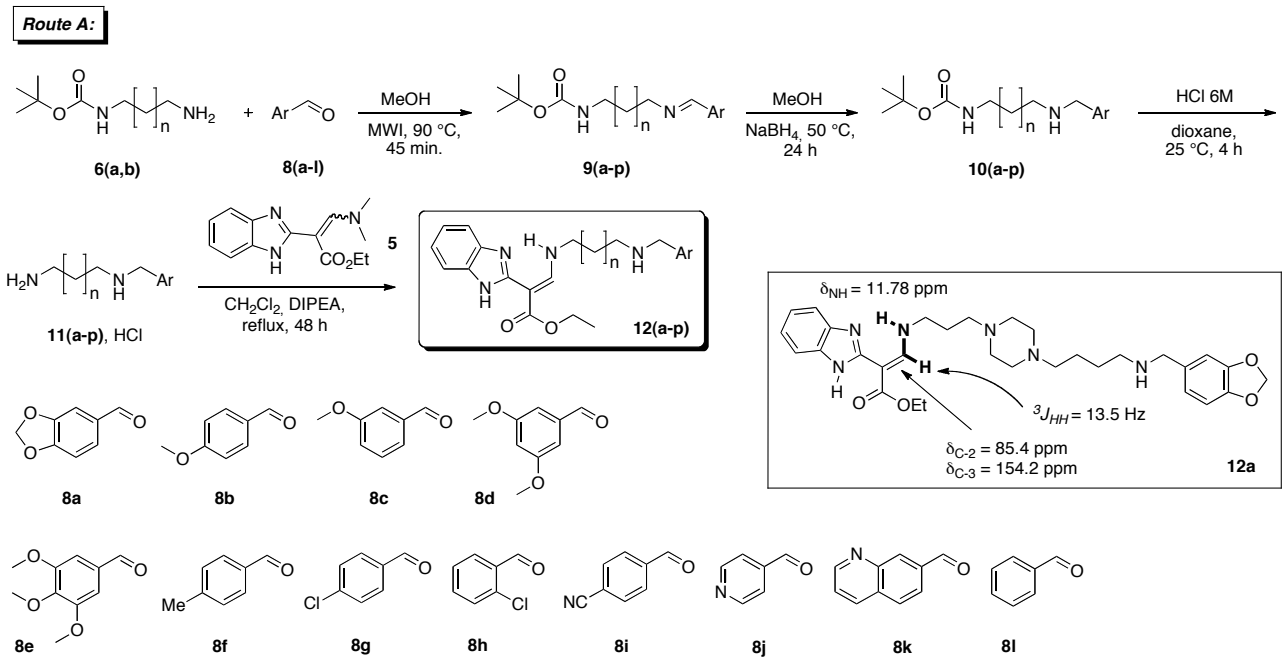


Scheme 1: Synthesis of **5** (building block A) and *N*-Boc diamine **7(a, b)** (building blocks B).

Next, the preparation of **7(a, b)** was pursued using commercially available diamines **6a** and **6b**. Routes A and B involve the use of mono-protected diamines **7(a, b)**; we chose the *N*-Boc protecting group because it is effectively removed in acid conditions. *Tert*-butyl {2-[4-(3-aminopropyl)pyperazin-1-yl]propyl}carbamate **7a** and *tert*-butyl (3-aminopropyl)carbamate **7b** were synthesized according to the literature [15, 16]. Treatment of diamines **6a** and **6b** with di-*tert*-butyldicarbonate $(Boc)_2O$ in 1,4-dioxane at room temperature for 24 hours produced mainly mono-*N*-Boc protected diamines **7a** (56% yield) and **7b** (80% yield).

*Synthesis of ethyl N-functionalized β-amino benzimidazole acrylate derivatives **12** using Route A:* In Scheme 2, our main task was to accomplish a reliable synthesis of mono *N*-substituted diamines **11** possessing two points of diversity. To obtain a sufficient number of compounds suitable for a preliminary biological screening, we selected a series of aromatic aldehydes **8** containing a variety of electron-donating substituents for **8(a-f)**, electron-withdrawing substituents for **8(g-i)**, without substituents (**8l**), and heteroaromatic aldehydes **8(j, k)** to introduce molecular diversity on the phenylmethyl moiety of the desired products **11(a-p)**. The preparation of **9** was

easily conducted by reaction of mono-*N*-Boc protected diamine **7a** or **7b** with an appropriate number of equivalents of aldehyde **8** in MeOH under microwave irradiation conditions. After 45 min. at 90°C we obtained desired arylaldimines **9(a-p)** (68-98% yields, Table 1).



Scheme 2: Route A for the preparation of ethyl *N*-functionalized β-amino benzimidazole acrylate derivatives **12(a-p)**.

Next, transforming arylaldimines **9(a-p)** into mono *N*-protected diamines **10(a-p)** was accomplished with 5 equivalents of $NaBH_4$ in MeOH at 50 °C for 24 h [17]. Compounds **10(a-p)** were obtained as crystallized or viscous products in yields ranging from 73 to 98%. For deprotection of the *N*-Boc group in compounds **10(a-p)**, we employed a solution of 6M HCl in 1,4-dioxane at room temperature for 4 h. This straight forward protocol afforded expected hydrochloride salts **11(a-p)** in good yields (63-98%) without impurities or by-products especially for compounds **11(a-d)**.

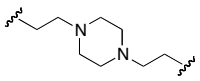
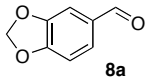
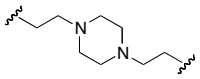
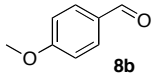
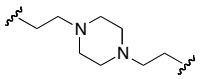
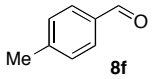
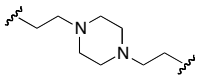
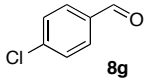
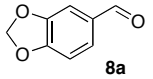
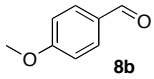
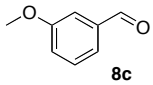
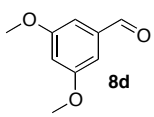
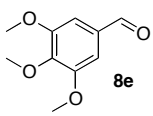
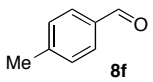
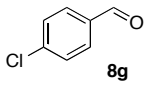
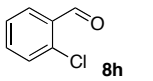
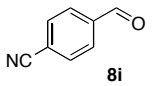
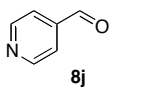
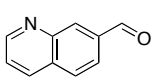
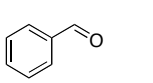
With the hydrochloride salts of mono *N*-substituted diamines **11(a-p)** in hand, our focus was the transformation of ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** into desired compounds **12** by transamination. Typically, the mechanism of this reaction is an addition-elimination [18] after the loss of dimethylamine *via* an aminal intermediate, which could not be isolated [13]. In previous work, we used **5** as an ambident synthon in a regioselective aza-annulation with isocyanate for the preparation of 1-oxo-1,2-dihydropyrimido[1,6-*a*]benzimidazole-4-carboxylates using solvent-free conditions under microwave irradiation [19]. This solvent-free aza-annulation was also extended to mono *N*-substituted hydrazines in the synthesis of new 4-(1*H*-benzimidazol-2-yl)-1,2-dihydro-(3*H*)-pyrazol-3-ones [20]. Based on these results, we decided to examine the reactivity of **5** with mono *N*-substituted diamines **11** in solution phase under microwave because microwave-assisted organic synthesis (MAOS) [21] has shown to dramatically reduce reaction times and improve product yields and ratios. Unfortunately, all microwave reaction attempts in a closed vessel using a polar or a non-polar solvent (EtOH, MeCN, CH_2Cl_2), different temperatures (40-80°C) and reaction times (40-80 min.), only afforded **12** in poor conversion (~5-10%).

We then decided to use classic heating by using an oil bath and magnetic stirring. For salts **11(a-d)**, two equivalents of di-*iso*-propyl ethylamine (DIPEA) and a reaction time of 24 hours were required and, for the remaining salts **11(e-p)**, 1.1 equivalent of DIPEA and a reaction time ranging

from 4 to 6 h gave good results for to the furnishing of compounds **12(e-p)** (see experimental section for details).

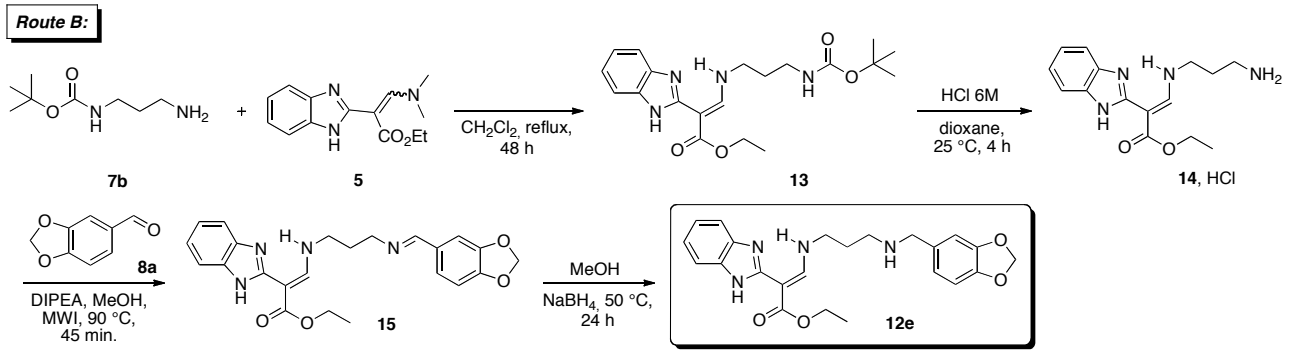
As seen from the results in Table 2, we obtained a library of 16 new β-amino benzimidazole acrylate derivatives **12** in low yields (10-38%) for **12(b, c)**, **12(f-i)**, **12k** and **12(m, n)**; in moderate yields (42-63%) for **12e**, **12j** and **12l,** and in good yields (61-93%) for **12a**, **12d** and **12(o, p)**. of the identities of these compounds **12(a-p)** were confirmed by ^{1}H, ^{13}C NMR and HRMS analyses. All the *N*-functionalized β-amino benzimidazole acrylates derivatives **12(a-p)** adopted a characteristic (2*E*)-*s*-cis/trans conformation (Scheme 1), which is stabilized by an intramolecular hydrogen bond, as indicated by the strong downfield shifted resonance of the NH group on C-3 (**12a**, δ_{NH} = 11.78 ppm in ^{1}H NMR spectrum using DMSO-d_6). It is noteworthy that a coupling constant $^{3}J_{HH}$ = 13.5 Hz in **12a** between the amino group on C-3 and H-3 ($\delta_{H\text{-}3}$ = 8.10 ppm) indicate a *trans*-relationship [22]. The shift of NH in benzimidazol-2-yl moiety (**12a**, δ_{NH} = 10.8 ppm) accounted also for an intramolecular hydrogen bound with the C=O of the acrylate ester function and enhanced the stability of the (2*E*)-*s*-cis/trans conformation. The planar character of this (2*E*)-*s*-cis/trans conformation is associated to a strong polarization of the C-2/C-3 bond (**12a**, $\delta_{C\text{-}2}$ = 85.4 ppm and $\delta_{C\text{-}3}$ = 154.2 ppm) and confirmed a "push-pull" effect [23].

Table 1: Results for the preparation of intermediates **9(a-p)**, **10(a-p)**, hydrochloride salts **11(a-p)** and products **12(a-p)** in Route A.

n	Starting aldehydes **7**	Yield (%)[a] for intermediates **9**, **10**, **11** and compounds **12**							
		9		**10**		**11**		**12**	
	 **8a**	**9a**	90	**10a**	84	**11a**	98	**12a**	93
	 **8b**	**9b**	68	**10b**	79	**11b**	98	**12b**	18
	 **8f**	**9c**	94	**10c**	84	**11c**	98	**12c**	20
	 **8g**	**9d**	87	**10d**	90	**11d**	98	**12d**	91
-CH_2-	 **8a**	**9e**	99	**10e**	80	**11e**	86	**12e**	42
-CH_2-	 **8b**	**9f**	96	**10f**	73	**11f**	82	**12f**	38
-CH_2-	 **8c**	**9g**	96	**10g**	79	**11g**	63	**12g**	34
-CH_2-	 **8d**	**9h**	92	**10h**	80	**11h**	98	**12h**	10
-CH_2-	 **8e**	**9i**	97	**10i**	74	**11i**	87	**12i**	15
-CH_2-	 **8f**	**9j**	98	**10j**	98	**11j**	98	**12j**	48
-CH_2-	 **8g**	**9k**	96	**10k**	87	**11k**	98	**12k**	36
-CH_2-	 **8h**	**9l**	95	**10l**	75	**11l**	94	**12l**	45
-CH_2-	 **8i**	**9m**	91	**10m**	70	**11m**	98	**12m**	31
-CH_2-	 **8j**	**9n**	88	**10n**	80	**11m**	98	**12n**	12
-CH_2-	 **8k**	**9o**	96	**10o**	88	**11o**	98	**12o**	63
-CH_2-	 **8l**	**9p**	97	**10p**	73	**11p**	80	**12p**	61

[a] Isolated yield after purification.

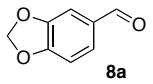
*Route B as possible alternative process for the synthesis of ethyl N-functionalized β-amino benzimidazole acrylate derivatives **12**:* In route A, the construction of compounds **12** is based on reductive-amination, deprotection transamination reactions and we think that it will be interesting to explore an alternative route according to Scheme 3. Starting ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** reacted smoothly with *tert*-butyl (3-aminopropyl)carbamate **7b** in refluxing dry methylene chloride for 48 h. After concentrating the reaction mixture *in vacuum*, the crude product **13** was directly purified by preparative chromatography (Combi Flash R_f 200 psi apparatus from Serlabo Technologies, France) on alumina gel Puriflash Interchim using a stepwise gradient from 99:1 to 90:10 of cyclohexane/AcOEt as mobile phase (**13**: 61% yield, Table 2).



Scheme 3: Route B for the preparation of ethyl *N*-functionalized β-amino benzimidazole acrylate derivative **12e.**

In the second step, carbamate **13** was deprotected in acidic conditions as used in route A (6M HCl in 1,4-dioxane at 25 °C for 4 h) affording hydrochloride salt **14** in 72% yield.

Table 2: Results for the preparation of the intermediates **13,** hydrochloride salt **14**, **15** and compound **12e** in Route B.

Starting aldehydes **8**	Yield (%)[a] for intermediates **13**, **14**, **15** and **12e**							
 **8a**	**13**	61	**14**	72	**15**	84	**12e**	(51)[b]

[a] Isolated yield after purification.
[b] Yield determined by ^{1}H NMR in DMSO-d_6 from the crude reaction mixture.

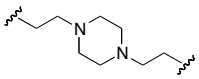
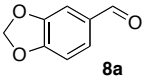
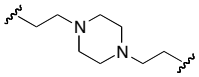
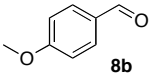
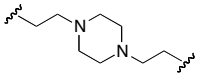
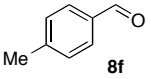
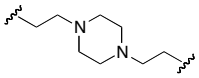
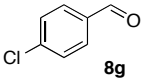
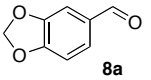
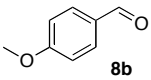
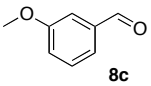
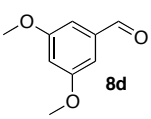
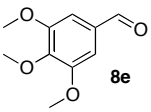
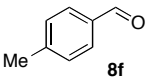
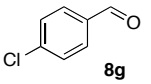
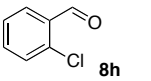
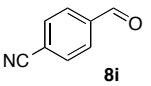
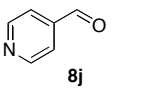
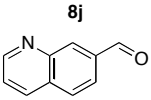
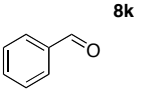
Next, the condensation of amino hydrochloride salt **14** with 3,4-(methylenedioxy)benzaldehyde **8a** was conducted under microwave irradiation at 90°C in the presence of 1.1 equivalent of DIPEA. After 45 min., this microwave process afforded **15** in 84% yield without modification of the (2*E*)-*s*-cis/trans conformation. Finally, applying the reduction reaction conditions used in route A (MeOH, 5 equivalents of $NaBH_4$, 50°C, 24 hours) to convert **15** into secondary **12e**, analysis of the crude reaction mixture by ^{1}H NMR in DMSO-d_6 solution showed a conversion of 51% for **12e** together with by-products. After purification of **12e** (~25-30% yield), we continued to explore another parameters of reaction conditions for reduction (ratio $NaBH_4$/product **15**, temperature and reaction time) and we were not able to increase the performance and the quality for this aldimine reduction. In fact, it's possible that benzimidazole and β-amino acrylate moieties of **15** do not tolerate the reduction conditions. On the basis of these results, route A is more practicable for purification of intermediates in each step.

Cytotoxic assays

All the new *N*-functionalized β-amino benzimidazole acrylates derivatives **12(a-p)** were evaluated for their in vitro cytotoxic potential against six selected human cancer cell lines, namely, hepatocellular carcinoma (Huh7 D12), colorectal adenocarcinoma (Caco 2), colorectal carcinoma (HCT 116), breast (MDA MB231), prostate (PC3) and lung (NCI-H727). The percentage of cell survival was measured at at single dose of 25 μM, and IC_{50} values were determined for those compounds exhibiting a survival percentage below 50% in 3 assays, using roscovitine as reference (Table 3).

It is observed from the primary screening results in Table 3 that compounds **12** exhibited antitumor activities in several tumor cell lines with IC_{50} lower than 10 μM. A brief survey of these results can be divided in two categories: compounds **12(a-d)** bearing a *N,N′*-bis-propyl(piperazin-1-yl) linker and products **12(e-p)** with the shorter *N*-propyl linker.

Table 2: Antiproliferative activity of compounds **12(a-p)** on six representative tumor cell lines.

Compound **12**	n	Starting aldehydes **7**	% of survival[a] and IC_{50} (μM) of selected compounds[b]					
			Huh7 D12	Caco 2	MDA-MB231	HCT 116	PC3	NCI-H727
12a		 **8a**	17 (4.1)	10 (9)	11 (8)	13 (7)	34 (10)	27 (9)
12b		 **8b**	21 (4)	11 (8)	17 (4)	9 (5)	12 (10)	23 (3)
12c		 **8f**	59 (4)	9 (8)	14 (6)	9 (7)	11 (10)	17 (5)
12d		 **8g**	18 (3)	9 (6)	12 (4)	14 (4)	13 (10)	16 (4)
12e	$-CH_2-$	 **8a**	13 (5)	15 (9)	25 (10)	20 (11)	46 (17)	32 (10)
12f	$-CH_2-$	 **8b**	13 (8)	31 (8)	24 (10)	6 (11)	66 (14)	84 (ND)[c]
12g	$-CH_2-$	 **8c**	20 (3)	48 (4)	27 (10)	11 (10)	72 (15)	85 (ND)
12h	$-CH_2-$	 **8d**	15 (7)	14 (9)	23 (9)	9 (10)	50 (13)	45 (13)
12i	$-CH_2-$	 **8e**	23 (9)	72 (10)	53 (11)	47 (10)	82 (39)	107 (ND)
12j	$-CH_2-$	 **8f**	9 (4)	2 (2)	5 (9)	0 (8)	28 (9)	26 (ND)
12k	$-CH_2-$	 **8g**	14 (9)	11 (10)	24 (10)	12 (9)	38 (10)	29 (10)
12l	$-CH_2-$	 **8h**	56 (10)	72 (3)	121 (>25)	95 (>25)	95 (31)	122 (ND)
12m	$-CH_2-$	 **8i**	44 (6)	30 (7)	88 (36)	48 (7)	72 (31)	65 (4)
12n	$-CH_2-$	 **8j**	38 (14)	10 (10)	36 (8)	22 (7)	45 (14)	45 (12)
12o	$-CH_2-$	 **8k**	18 (8)	17 (6)	67 (18)	31 (10)	56 (23)	50 (14)
12p	$-CH_2-$	 **8l**	16 (7)	28 (6)	51 (10)	17 (10)	65 (24)	59 (20)
Roscovitine	-	-	21 (15)	3 (15)	21 (12)	10 (9)	24 (13)	30 (43)
DMSO	-	-	100 (>25)	100 (>25)	100 (>25)	100 (>25)	100 (>25)	100 (>25)

[a] Percentage of survival measured at 25 μM (triplicate).
[b] IC_{50} values in brackets are expressed in μM and are the average of three assays, standard error ±0.5 μM.
[c] ND: IC_{50} not determined.

For the first group (Figure 3), only **12a** presented a selective activity against Huh7-D12 cell lines (IC_{50} = 4 μM). Compound **12c** showed also an impact on Huh7-D12 with a similar IC_{50} of 4

μM and exhibited cytotoxicity on NCI-H727 cell line (IC_{50} = 5 μM). On the other hand, **12b** and **12d** were unselective because both were found to be active on Huh7-D12, MBA-MB231, HCT116 and NCI-H727 cell lines (Table 3, Figure 3). For the second group in Table 2, it could be observed that four compounds among the series **12(e-p)** with *N*-propyl linker exhibited selective cytotoxicities. The presence of a 2-chlorophenyl moiety in compound **12l** displayed potential cytotoxicity on colorectal adenocarcinoma (Caco2) with IC_{50} 3 μM. The second selective derivative is **12e**. This one is active on Huh7-D12 cell lines with IC_{50} = 5 μM. For compounds **12g** and **12j**, the selectivity is moderate but both showed cyctotoxicity against Huh7-D12 and Caco2 cell lines (**12g**: Huh7-D12, IC_{50} = 3 μM and Caco2 IC_{50} = 4 μM; **12j**: Huh7-D12, IC_{50} = 4 μM and Caco2 IC_{50} = 2 μM). It could be noticed that derivatives **12a** and **12e** bearing a benzo[1,3]dioxo-5-yl moiety showed selective cytotoxicity against Huh7-D12 in a similar manner, which means the length and the nature of the linker had a minor role in the cytotoxic activity.

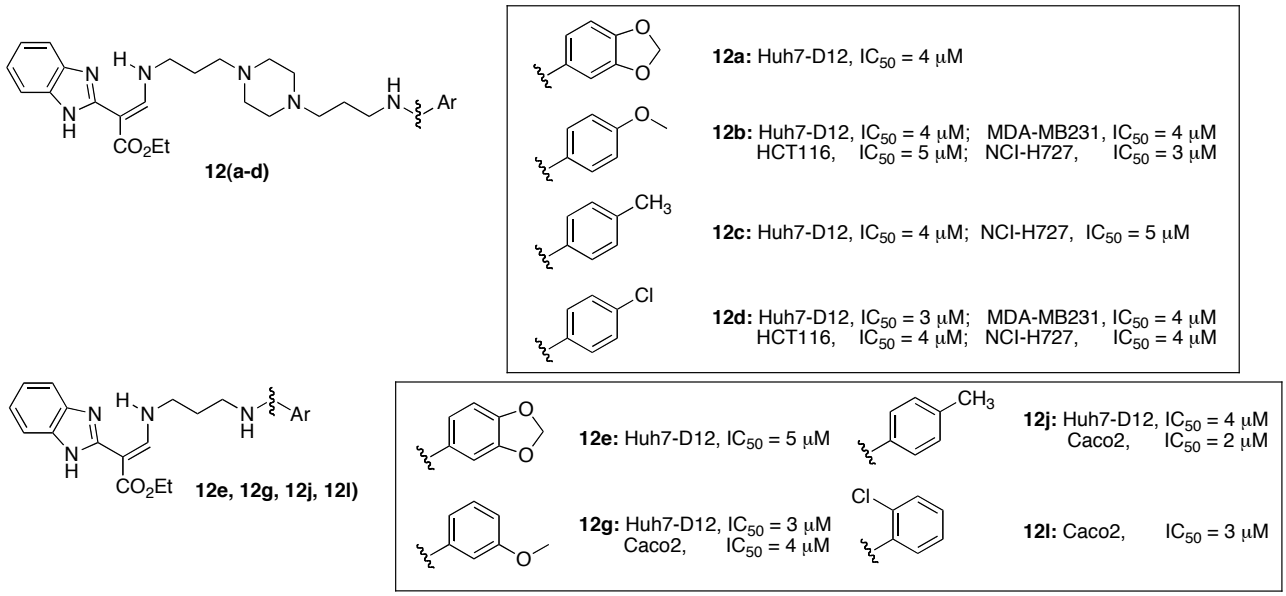


Figure 3: Compounds **12(a-e), 12g**, **12j**, **12l** and their anti-tumor activities.

Lastly, comparison of compounds **12d** and **12l** showed that the position of Cl on the phenylmethylamino group associated to the length and the nature of linker has an important effect on cytotoxicity.

Conclusion

In summary, we have developed a series of new *N*-functionalized β-amino benzimidazole acrylate derivatives from ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate and two mono-substituted *N*-Boc diamines as building-blocks. Two convergent routes were investigated with these building-blocks. Route "A" was more efficient for this multi-step synthesis of these benzimidazole derivatives based on successive reductive amination, acidic *N*-Boc deprotection and transamination. This process offered the possibility of preparing a library of sixteen *N*-functionalized β-amino benzimidazole acrylate derivatives bearing two points of diversity (the first is the linker issued from the diamine and the second is an arylmethylamino moiety). All the new benzimidazole derivatives were analyzed by ^{1}H and ^{13}C NMR and presented a (2*E*)-s-cis/trans conformation associated to a strong polarization of the C-2/C-3 double bond by a push-pull effect. The 16 new synthesized compounds were evaluated for their *in vitro* cytotoxic potential against six representative human tumoral cell lines and 8 of them were found to be active against Huh7-D12, MDA-MB231, NCI-H727, HCT116 and Caco2 with IC_{50} below 5 μM. Among the bioactive compounds, **12a**, **12e** and

12l turned out to be interesting because they presented selective micromolar inhibition activity on Huh7-D12 (**12a**: IC_{50} = 4 μM and **12e**: IC_{50} = 5 μM) and Caco2 (**12l**: IC_{50} = 3 μM). The current results for these 3 bioactive compounds have the potential to be developed as cytotoxic agents and their structural modification could lead to the generation of promising anticancer agents.

Experimental

Chemistry section

General Information. Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J is given in Hertz. High resolution mass spectra (HRMS) were recorded in positive mode using direct Electrospray infusion, on a Waters Q-Tof 2 or on a Thermo Fisher Scientific Q-Exactive spectrometers at the "Centre Régional de Mesures Physiques de l'Ouest" ScanMAT UMS 2001 (CRMPO ScanMAT UMS 2001, Rennes, France). Microwave reactions (S2 Wave platform SFS ScanMAT, Rennes) were carried out using an Anton Paar Monowave 300® microwave reactor (Anton Paar France) using 10-mL borosilicate glass vials equipped with snap caps. Preparative chromatography was carried out using a Combi Flash R_f 200 psi (Serlabo Technologies France) using pre-packed column of silica gel 60 F 254 Merck equipped with a DAD UV/Vis 200-360 nm detector. Elemental analyses were performed on a Flash Microanalyzer EA1112 CHNS/O Thermo Electron in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Solvents were evaporated using a BUCHI rotary evaporator. All reagents and solvents were purchased from Acros, Aldrich Chimie, and Fluka France and were used without further purification.

*Ethyl 2-ethoxycarbonylacetimidate hydrochloride (**2**)*

The synthesis was carried out in a 250-mL two-necked round-bottomed flask, charged with magnetic stirrer and fitted with a condenser. To a stirred (400 rpm) solution of ethyl cyanoacetate **1** (17.3443 g, 16.3 mL, 153.34 mmol) in 134 mL of ethanol cooled at 0 °C acetyl chloride (96.2975 g, 87.2 mL, 1.227 mole) was added dropwise under a stream of argon over a period of 2 hours. Stirring was continued from 0 °C to room temperature for 12 hours. Volatiles were removed using a rotary evaporator under reduced pressure. The crude residue, which crystallized rapidly by triturating in 10 mL of diethyl ether, was collected by filtration in a Büchner funnel (porosity N°4). The salt **2** was rinsed with Et_2O (4 x 10 mL), then dried under high vacuum (10^{-2} Torr) at 25 °C for 1 hour to give the desired salt **2** as white needles in 58% yield. This salt was further used without purification and was stored at 4 °C under argon. Mp = 137-139 °C. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, J = 7.5 Hz, C<u>H</u>$_3$CH$_2$O); 1.50 (t, 3H, J = 7.0 Hz, C<u>H</u>$_3$CH$_2$O); 3.88 (s, 2H, C<u>H</u>$_2$CO); 4.19 (q, 2H, J = 7.1 Hz, CH$_3$C<u>H</u>$_2$O); 4.67 (q, 2H, J = 7.0 Hz, CH$_3$C<u>H</u>$_2$O); 12.34 (br s, 2H, N<u>H</u>, <u>H</u>Cl).

*Ethyl 2-(1H-benzimidazol-2-yl)acetate (**4**)*

The synthesis was carried out in a 500-mL round-bottomed flask, charged with a magnetic stirrer and fitted with a condenser. A suspension of ethyl 2-ethoxycarbonylacetimidate hydrochloride **2** (22 g, 112.4 mmol) and orthophenylenediamine **3** (12.1603 g, 112.4 mmol) in 230 mL of dry methylene chloride was stirred vigorously (500 rpm) under reflux for 48 hours. After removing all insolubles (ammonium chloride and unreacted products) by filtration, the volatiles were removed using a rotary evaporator under reduced pressure. To the resulting crude residue (which crystallized after standing) 20 mL of diethyl ether was added and the mixture was triturated for 15-20 min. Product **4** was collected by filtration in a Büchner funnel, rinsed with Et_2O (20 x 4 mL), dried under high

vacuum (10^{-2} Torr) for 1 hour at 25 °C, and then recrystallized in toluene to give desired product as a grey powder in 27% yield. Mp = 123-125 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, *J* = 7.1 Hz, C<u>H</u>$_3$CH$_2$O); 4.70 (s, 2H, C<u>H</u>$_2$CO); 4.21 (q, 2H, *J* = 7.2 Hz, CH$_3$C<u>H</u>$_2$O); 7.22-7.27 (m, 2H, =C<u>H</u>, H-5, H-6, Ar); 7.58 (m, 2H, =C<u>H</u>, H-4, H-7, Ar); 10.55 (br s, 1H, N<u>H</u>). ^{13}C NMR ($CDCl_3$) δ: 14.2 (<u>C</u>H$_3$CH$_2$O); 34.7 (<u>C</u>H$_2$CO); 62.0 (CH$_3$<u>C</u>H$_2$O); 122.7 (C-3a, C-4, C-5, C-6, C-7, C-7a, Ar); 147.1 (<u>C</u>=N, C-2); 170.0 (<u>C</u>=O, CO_2Et). HRMS, *m/z*: 205.0978 found (calculated for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ requires 205.0977).

*Ethyl 3-dimethylamino-2-(1H-benzimidazol-2-yl)acrylate (**5**)*

In a 10-mL glass tube were placed successively ethyl 2-(1*H*-benzimidazol-2-yl)acetate **4** (2 g, 9.8 mmol) and dimethylformamide diethylacetal DMF-DEA (1.7313 g, 2 mL, 11.8 mmol, 1.2 equiv). The glass tube was sealed with a snap cap and placed in a Monowave® 300 Anton Paar microwave reaction chamber. The reaction mixture was irradiated at 90 °C (P = 800 Watt) for 30 min. under vigorous magnetic stirring. Then, the volatiles were removed using a rotary evaporator under reduced pressure. The crude residue, which crystallized after standing at room temperature, was rinsed with AcOEt (3 x 20 mL), the resulting material was collected by filtration in a Büchner funnel, and dried under high vacuum (10^{-2} Torr) at 25 °C for 2 hours. Recrystallization from AcOEt afforded ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate (**5**) in 82% yield as yellow needles. Mp = 201-203°C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, *J* = 7.1 Hz, C<u>H</u>$_3$CH$_2$O); 2.96 (s, 6H, (C<u>H</u>$_3$)$_2$N); 4.21 (q, 2H, *J* = 7.1 Hz, CH$_3$C<u>H</u>$_2$O); 7.27 (s, 1H, =C<u>H</u>); 7.19-7.49 (m, 4H, =C<u>H</u>, Ar); 7.99 (br s, 1H, N<u>H</u>). ^{13}C NMR ($CDCl_3$) δ: 14.8 (<u>C</u>H$_3$CH$_2$O); 44.9 ((<u>C</u>H$_3$)$_2$N); 60.1 (CH$_3$<u>C</u>H$_2$O); 87.4 (<u>C</u>=CH-N(CH$_3$)$_2$); 114.7 (=<u>C</u>H, C-4, C-7, Ar); 121.7 (=<u>C</u>H, C-5, C-6, Ar); 138.1 (C-3a, C-7a, Ar); 150.0 (<u>C</u>=N, C-2, Ar); 155.0 (=<u>C</u>H-N(CH$_3$)$_2$); 168.8 (<u>C</u>=O, CO_2Et). HRMS, *m/z*: 260.1400 found (calculated for $C_{14}H_{18}N_3O_2$ $[M+H]^+$ requires 260.1399).

*Tert-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate (**7a**)*

Compound **7a** was prepared in 56% yield as a colorless oil according to a previous procedure developed in our laboratory [15]. (UV: $\lambda_{max.}$ 236 nm). R_f 0.18 on alumina gel (CH_2Cl_2/MeOH 95:5 v/v as eluent). ^{1}H NMR (DMSO-d_6) δ: 1.33 (s, 9H, Me$_3$CO); 1.49-1.59 (m, 4H, CH$_2$); 2.27-2.37 (m, 12H, 6 x CH$_2$); 2.64 (t, 2H, *J* = 6.8 Hz, CH$_2$NH$_2$); 3.07 (m, 2H, CH$_2$NH); 4.88 (br s, NH$_2$); 5.21 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 26.3 (CH$_2$); 28.4 (Me$_3$CO); 30.4 (CH$_2$); 39.7 (CH$_2$NH$_2$); 40.6 (CH$_2$NH); 52.9 (CH$_2$N); 53.1 (CH$_2$N); 56.3 (NCH$_2$); 56.6 (NCH$_2$); 78.4 (Me$_3$CO); 155.9 (NHCO). HRMS, *m/z*: 301.2606 found (calculated for $C_{15}H_{33}N_4O_2$ $[M+H]^+$ requires 301.2603).

*Tert-butyl (3-aminopropyl)carbamate (**7b**)*

Compound **7b** was prepared in 80% yield according to a previous procedure developed in our laboratory [16] as a colorless oil then, it was stocked at 4 °C as a solution (2 g/mL) in dry ether. (UV: $\lambda_{max.}$ 220 nm). R_f 0.82 on alumina gel (CH_2Cl_2/MeOH 95:5 v/v as eluent). ^{1}H NMR ($CDCl_3$) δ: 1.31 (s, 2H, NH$_2$); 1.40 (s, 9H, (C<u>H</u>$_3$)$_3$CO); 1.57 (q, 2H, *J* = 6.6 Hz, H-2); 2.74 (t, 2H, *J* = 6.6 Hz, H-1); 3.14-3.18 (m, 2H, H-3); 4.97 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 28.5 ((<u>C</u>H$_3$)CO); 33.5 (C-2); 38.5 (C-3); 39.8 (C-1); 79.1 ((CH$_3$)$_3$<u>C</u>O); 156.3 (NH<u>C</u>O$_2$C(CH$_3$)$_3$). ES$^+$ (MeOH) HRMS, *m/z*: 175.1447 found (calculated for $C_8H_{19}N_2O_2$ $[M+H]^+$ requires 175.1447).

*General procedure under microwave irradiation for the solution phase synthesis of aldimines **9(a-p)** from tert-butyl (4-aminobutyl)carbamate **7(a,b)** with a series of aromatic aldehyde **8(a-l)**.*

In a 10-mL glass tube (for microwave synthesis) were placed successively *tert*-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate **7a** (0.249 g, 0.83 mmol, 1 equiv) or *tert*-butyl (3-aminopropyl)carbamate **7b** (0.113 g, 0.65 mmol, 1 equiv), aromatic aldehyde **8** (0.6-0.75 equiv with **7a** or 0.95-1 equiv with **7b**) and 1 mL of dry methanol. The glass tube was sealed with a snap cap and introduced in the microwave cavity of a Monowave® 300 Anton Paar reactor (P = 800 Watt). The reaction mixture was irradiated at 95 °C for 45 min. under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room

temperature and volatiles were removed using a rotary evaporator under reduced pressure. The desired aldimine **9** (mobile or visquous oil) was dried under high vacuum (10^{-2} Torr) at 25 °C for 20 min. and used further without purification.

*Tert-butyl [3-(4-{3-[(benzo[1,3]dioxol-5-ylmethylene)amino]propyl}piperazin-1-yl)propyl]carbamate (**9a**)*

Compound **9a** was prepared in 90% yield as a viscous orange oil from *tert*-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate **7a** (1 equiv.) and 3,4-(methylenedioxy)benzaldehyde **8a** (0.75 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3$)$_3$CO); 1.65 (quint, 2H, *J* = 6.4 Hz, H-2); 1.88 (quint, 2H, *J* = 7.2 Hz, H-7); 2.31-2.51 (m, 12H, H-3, H-4, H-5, H-6); 3.15-3.21 (m, 2H, H-1); 3.57-3.59 (m, 2H, H- 8); 5.46 (br s, 1H, NH); 5.99 (s, 2H, O$C\underline{H}_2$O); 6.80-6.83 (d, 1H, *J* = 7.9 Hz, H-5', Ar); 7.06-7.10 (dd, 1H, *J* = 1.6, 8.0 Hz, H-6', Ar); 7.32 (d, 1H, *J* = 1.5 Hz, H-2', Ar); 8.15 (s, 1H, N=C$\underline{H}$, H-9). ^{13}C NMR ($CDCl_3$) δ: 26.4 (C-7); 28.2 (C-2); 28.6 (($\underline{C}H_3$)$_3$CO); 40.1 (C-1); 53.3- 53.4 (C-4, C-5); 56.4 (C-3); 57.0 (C-6); 59.4 (C-8); 78.9 ((CH$_3$)$_3\underline{C}$O); 101.5 (O$\underline{C}$H$_2$O); 106.7 (C-5', Ar); 108.1 (C-2', Ar); 124.3 (C-6', Ar); 131.3 (C-1', Ar); 148.4 (C-3', Ar); 149.8 (C-4', Ar); 156.2 (NH$\underline{C}$OO(CH$_3$)$_3$); 160.4 (N=$\underline{C}$H, C-9). ES$^+$ HRMS, *m/z*: 433.2813 found (calculated for $C_{23}H_{37}N_4O_4$ $[M+H]^+$ requires 433.2809).

*Tert-butyl [3-(4-{3-[(4-methoxybenzylidene)amino]propyl}piperazin-1-yl)propyl]carbamate (**9b**)*

Compound **9b** was prepared in 68% yield as orange oil from *tert*-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate **7a** (1 equiv.) and 4-methoxybenzaldehyde **8b** (0.6 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H, ($C\underline{H}_3$)$_3$CO); 1.63 (quint, 2H, *J* = 6.3 Hz, H-2); 1.86 (quint, 2H, *J* = 7.2 Hz, H-7); 2.34-2.54 (m, 12H, H-3, H-4, H-5, H-6); 3.14-3.19 (m, 2H, H-1); 3.56-3.61 (m, 2H, H- 8); 3.82 (s, 3H, O$C\underline{H}_3$); 5.51 (br s, 1H, NH); 6.88-6.92 (m, 2H, H-3', H-5', Ar); 7.61-7.66 (m, 2H, H-2', H-6', Ar); 8.19 (s, 1H, N=C$\underline{H}$, H-9). ^{13}C NMR ($CDCl_3$) δ: 26.4 (C-7); 28.3 (C-2); 28.7 (($\underline{C}H_3$)$_3$CO); 40.1 (C-1); 53.3-53.4 (C-4, C-5); 55.5 (C-3); 56.4 (C-6); 57.0 (C-8); 59.7 (O$\underline{C}$H$_3$); 78.9 ((CH$_3$)$_3\underline{C}$O); 114.1 (C-3', C-5', Ar); 129.3 (C-1', Ar); 129.6 (C-2', C-6', Ar); 156.2 (NH$\underline{C}$OO(CH$_3$)$_3$); 160.6 (N=$\underline{C}$H, C-9); 161.6 (C-4', Ar). ES$^+$ HRMS, *m/z*: 419.3013 found (calculated for $C_{23}H_{39}N_4O_3$ $[M+H]^+$ requires 419.3017).

*Tert-butyl [3-(4-{3-[(4-methylbenzylidene)amino]propyl}piperazin-1-yl)propyl]carbamate (**9c**)*

Compound **9c** was prepared in 94% yield as orange oil from *tert*-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate **7a** (1 equiv.) and 4-methylbenzaldehyde **8f** (0.6 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3$)$_3$CO); 1.64 (quint, 2H, *J* = 6.6 Hz, H-2); 1.86-1.91 (m, 2H, H-7); 2.37 (s, 3H, C$\underline{H}_3$); 2.39-2.48 (m, 12H, H-3, H-4, H-5, H-6); 3.15-3.21 (m, 2H, H-1); 3.59- 3.64 (td, 2H, *J* = 0.8, 6.8 Hz, H-8); 5.49 (br s, 1H, NH); 7.19-7.21 (m, 2H, H-3', H-5', Ar); 7.58-7.61 (m, 2H, H-2', H-6', Ar); 8.23 (s, 1H, N=C$\underline{H}$, H-9). ^{13}C NMR ($CDCl_3$) δ: 21.6 ($\underline{C}H_3$); 26.4 (C-7); 28.2 (C-2); 28.5 (($\underline{C}H_3$)$_3$CO); 40.1 (C-1); 53.2-53.3 (C-4, C-5); 56.4 (C-3); 56.9 (C-6); 59.6 (C-8); 59.8 ($\underline{C}H_3$); 78.8 ((CH$_3$)$_3\underline{C}$O); 128.1 (C-2', C-6', Ar); 129.4 (C-3', C-5', Ar); 133.7 (C-1', Ar); 140.8 (C-4', Ar); 156.2 (NH$\underline{C}$OO(CH$_3$)$_3$); 161.2 (N=$\underline{C}$H, C-9). ES$^+$ HRMS, *m/z*: 403.3068 found (calculated for $C_{23}H_{39}N_4O_2$ $[M+H]^+$ requires 403.3067).

*Tert-butyl [3-(4-{3-[(4-chlorobenzylidene)amino]propyl}piperazin-1-yl)propyl]carbamate (**9d**)*

Compound **9d** was prepared in 87% yield pale brown oil from *tert*-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate **7a** (1 equiv.) and 4-chlorobenzaldehyde **8g** (0.7 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3$)$_3$CO); 1.65 (quint, 2H, *J* = 6.3 Hz, H-2); 1.89 (quint, 2H, *J* = 7.2 Hz, H-7); 2.39-2.51 (m, 12H, H-3, H-4, H-5, H-6); 3.17-3.19 (m, 2H, H-1); 3.61-3.66 (td, 2H, *J* = 1.0, 6.8 Hz, H-8); 5.46 (br s, 1H, NH); 7.35-7.39 (m, 2H, H-3', H-5', Ar); 7.62-7.67 (m, 2H, H-2', H-6', Ar); 8.24 (s,

1H, N=C<u>H</u>, H-9). ^{13}C NMR ($CDCl_3$) δ: 26.4 (C-7); 28.1 (C-2); 28.6 ((<u>C</u>H_3)$_3$CO); 40.1 (C-1); 53.2-53.3 (C-4, C-5); 56.4 (C-3); 56.7 (C-8); 59.8 (C-6); 78.9 ((CH$_3$)$_3$<u>C</u>O); 129.0 (C-3', C-5', Ar); 129.4 (C-2', C-6', Ar); 134.9 (C-1', Ar); 136.6 (C-4', Ar); 156.2 (NH<u>C</u>OO(CH$_3$)$_3$); 160.0 (N=<u>C</u>H, C-9). ES$^+$ HRMS, *m/z*: 423.2519 found (calculated for $C_{22}H_{36}N_4O_2{}^{35}Cl$ $[M+H]^+$ requires 423.2521).

*Tert-butyl {3-[(Benzo[1,3]dioxol-5-ylmethylene)amino]propyl}carbamate (**9e**)*

Compound **9e** was prepared in 99% yield as yellowish oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 3,4-(methylenedioxy)benzaldehyde **8a** (1 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, (C<u>H</u>$_3$)$_3$CO); 1.85 (quint, 2H, *J* = 6.6 Hz, H-2); 3.23-3.29 (m, 2H, H-1); 3.62 (t, 2H, *J* = 6.2 Hz, H-3); 5.18 (br s, 1H, NH); 5.99 (s, 2H, OC<u>H</u>$_2$O); 6.81 (d, 1H, *J* = 8.0 Hz, H-5', Ar); 7.08 (dd, 1H, *J* = 1.5, 8.0 Hz, H-6', Ar); 7.31 (d, 1H, J = 1.4 Hz, H-2', Ar); 8.13 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 ((<u>C</u>H_3)$_3$CO); 31.2 (C-2); 39.6 (C-1); 59.5 (C-3); 79.1 ((CH$_3$)$_3$<u>C</u>O); 101.6 (O<u>C</u>H$_2$O); 106.6 (C-2', Ar); 108.17 (C-5'); 124.5 (C-6', Ar); 131.0 (C-1', Ar); 148.4 (C-3', Ar); 150.0 (C-4', Ar); 156.2 (NH<u>C</u>OO(CH$_3$)$_3$); 160.6 (N=<u>C</u>H, C-4). ES$^+$ HRMS, *m/z*: 307.1655 found (calculated for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ requires 307.1658).

*Tert-butyl {3-[(4-methoxybenzylidene)amino]propyl}carbamate (**9f**)*

Compound **9f** was prepared in 96% yield as yellow-orange oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 4-methoxybenzaldehyde **8b** (1 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, C<u>H</u>$_3$)$_3$CO); 1.86 (quint, 2H, *J* = 6.5 Hz, H-2); 3.26-3.28 (m, 2H, H-1); 3.64 (t, 2H, *J* = 6.0 Hz, H-3); 3.84 (s, 3H, OC<u>H</u>$_3$); 5.19 (br s, 1H, NH); 6.98-7.01 (d, 2H, *J* = 8.8 Hz, H-3', H-5', Ar); 7.45-7.47 (d, 2H, *J* = 8.8 Hz, H-2', H-6', Ar); 8.19 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 ((<u>C</u>H_3)$_3$CO); 31.2 (C-2); 39.6 (C-1); 55.5 (O<u>C</u>H$_3$); 59.7 (C-3); 79.0 ((CH$_3$)$_3$<u>C</u>O); 114.1 (C-3', C-5', Ar); 129.2 (C-1', Ar); 129.8 (C-2', C-6', Ar); 156.2 (NH<u>C</u>OO(CH$_3$)$_3$); 160.8 (C-4', Ar); 161.8 (N=<u>C</u>H, C-4). ES$^+$ HRMS, *m/z*: 293.1867 found (calculated for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ requires 293.1865).

*Tert-butyl {3-[(3-methoxybenzylidene)amino]propyl}carbamate (**9g**)*

Compound **9g** was prepared in 96% yield as yellow oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 3-methoxybenzaldehyde **8c** (0.95 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.45 (C<u>H</u>$_3$)$_3$CO); 1.90 (quint, 2H, *J* = 6.6 Hz, H-2); 3.26-3.32 (m, 2H, H-1); 3.67-3.71 (m, 2H, H-3); 3.86 (s, 3H, OC<u>H</u>$_3$); 5.10 (br s, 1H, NH); 6.97-7.01 (ddd, 1H, *J* = 1.2, 2.6, 8.1 Hz, H-2', Ar); 7.24-7.28 (dt, 1H, *J* = 1.2, 7.6 Hz, H-4', Ar); 7.31-7.36 (m, 2H, H-5', H-6'; Ar); 8.26 (t, 1H, *J* = 1.3 Hz, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 ((<u>C</u>H_3)$_3$CO); 31.1 (C-2); 39.5 (C-1); 55.49 (OC<u>H</u>$_3$); 59.8 (C-3); 79.1 ((CH$_3$)$_3$<u>C</u>O); 111.7 (C-2', Ar); 117.5 (C-4', Ar); 121.5 (C-6', Ar); 129.7 (C-5', Ar); 137.6 (C-1', Ar); 156.2 (NH<u>C</u>OO(CH$_3$)$_3$); 160.0 (C-3', Ar); 161.4 (N=<u>C</u>H, C-4). ES$^+$ HRMS, *m/z*: 293.1867 found (calculated for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ requires 293.1865).

*Tert-butyl {3-[(3,5-dimethoxybenzylidene)amino]propyl}carbamate (**9h**)*

Compound **9h** was prepared in 92% yield as amorphous yellowish oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 3,5-dimethoxybenzaldehyde **8d** (0.98 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, (C<u>H</u>$_3$)$_3$CO); 1.88 (quint, 2H, *J* = 6.6 Hz, H-2); 3.24-3.3 (m, 2H, H-1); 3.64-3.69 (td, 2H, *J* = 0.83, 6.5 Hz, H-3); 3.82 (s, 6H, 2 x OCH$_3$); 5.00 (br s, 1H, NH); 6.52 (t, 1H, *J* = 2.3 Hz, H-4', Ar); 6.86-6.87 (d, 1H, *J* = 2.3 Hz, H-2', H-6', Ar); 8.19 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 ((<u>C</u>H_3)$_3$CO); 31.1 (C-2); 39.5 (C-1); 55.6 (2 x OCH$_3$); 59.7 (C-3); 79.1 ((CH$_3$)$_3$<u>C</u>O); 103.5 (C-4'); 105.9 (C-2', C-6', Ar); 138.2 (C-1', Ar); 156.2 (NH<u>C</u>OO(CH$_3$)$_3$); 160.1 (C-3', C-5', Ar); 161.4 (N=<u>C</u>H, C-4). ES$^+$ HRMS, *m/z*: 323.1974 found (calculated for $C_{17}H_{27}N_2O_4$ $[M+H]^+$ requires 323.1971).

*Tert-butyl {3-[(3,4,5-trimethoxybenzylidene)amino]propyl}carbamate (**9i**)*

Compound **9i** was prepared in 97% yield as yellow oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 3,4,5-trimethoxybenzaldehyde **8e** (0.95 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1. 87 (quint, 2H, *J* = 6.6 Hz, H-2); 3.23-3.29 (m, 2H, H-1); 3.66 (t, 2H, *J* = 6.5 Hz, H-3); 3.87 (s, 3H, $OC\underline{H}_3$); 3.9 (s, 6H, 2 x OCH_3); 4.96 (br s, 1H, NH); 6.96 (s, 2H, H-2', H-6', Ar); 8.17 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 31.2 (C-2); 39.5 (C-1); 56.3 (2 x $O\underline{C}H_3$); 59.7 ($O\underline{C}H_3$); 61.1 (C-3); 79.2 (($CH_3)_3\underline{C}O$); 105.1 (C-2', C-6', Ar); 131.7 (C-1', Ar); 140.4 (C-4', Ar); 153.6 (C-3', C-5', Ar); 156.1 ($NH\underline{C}OO(CH_3)_3$); 161.1 (N=<u>C</u>H, C-4). ES^+ HRMS, *m/z*: 353.2077 found (calculated for $C_{18}H_{29}N_2O_5$ $[M+H]^+$ requires 353.2076).

*Tert-butyl {3-[(4-methylbenzylidene)amino]propyl}carbamate (**9j**)*

Compound **9j** was prepared in 98% yield as yellow-orange oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 4-methylbenzaldehyde **8f** (0.95 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.86 (quint, 2H, *J* = 6.5 Hz, H-2); 2.38 (s, 3H, $C\underline{H}_3$); 3.19_3.37 (m, 2H, H-1); 3.65 (t, 2H, *J* = 6.0 Hz, H-3); 5.20 (br s, 1H, NH); 7.19-7.22 (d, 2H, *J* = 7.8 Hz, H-3', H-5', Ar); 7.59-7.61 (d, 2H, *J* = 8.1 Hz, H-2', H-6', Ar); 8.23 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 21.6 ($\underline{C}H_3$); 28.6 (($\underline{C}H_3)_3CO$); 31.1 (C-2); 39.6 (C-1); 59.8 (C- 3); 79.0 (($CH_3)_3\underline{C}O$); 128.2 (C-2', C-6', Ar); 129.5 (C-3', C-5', Ar); 133.5 (C-1', Ar); 141.1 (C-4', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$); 161.4 (N=<u>C</u>H, C-4). ES^+ HRMS, *m/z*: 277.1915 found (calculated for $C_{16}H_{25}N_2O_2$ $[M+H]^+$ requires 277.1916).

*Tert-butyl {3-[(4-chlorobenzylidene)amino]propyl}carbamate (**9k**)*

Compound **9k** was prepared in 96% yield as yellowish oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 4-chlorobenzaldehyde **8g** (0.98 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.87 (quint, 2H, *J* = 6.6 Hz, H-2); 3.26 (m, 2H, H-1); 3.66 (t, 2H, *J* = 6.1 Hz, H-3); 5.07 (br s, 1H, NH); 7.37 (m, 2H, H-2', H-6', Ar); 7.65 (m, 2H, H-3', H-5', Ar); 8.23 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.4 (($\underline{C}H_3)_3CO$); 30.9 (C-2); 39.31 (C-1); 59.5 (C-3); 79.0 (($CH_3)_3\underline{C}O$); 128.9 (C-3', C-5', Ar); 129.3 (C-2', C-6', Ar); 134.5 (C-1', Ar); 136.6 (C-4', Ar); 156.0 ($NH\underline{C}OO(CH_3)_3$); 160.0 (N=<u>C</u>H, C-4). ES^+ HRMS, *m/z*: 297.1372 found (calculated for $C_{15}H_{22}N_2O_2{}^{35}Cl$ $[M+H]^+$ requires 297.1370).

*Tert-butyl {3-[(2-chlorobenzylidene)amino]propyl}carbamate (**9l**)*

Compound **9l** was prepared in 95% yield as yellowish oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 2-chlorobenzaldehyde **8h** (1 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.89 (quint, 2H, *J* = 6.6 Hz, H-2); 3.27-3.29 (m, 2H, H-1); 3.72 (td, 2H, *J* = 1.1, 6.5 Hz, H-3); 5.09 (br s, 1H, NH); 7.27-7.40 (m, 3H, H-4', H-5', H-6', Ar); 7.99 (dd, 1H, *J* = 1.6, 7.6 Hz, H-3', Ar); 8.71 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.5 (($\underline{C}H_3)_3CO$); 31.1 (C-2); 39.43 (C-1); 59.9 (C-3); 79.1 (($CH_3)_3\underline{C}O$); 127.1 (C-5', Ar); 128.3 (C-3', Ar); 129.9 (C-6', Ar); 131.7 (C-4', Ar); 133.1 (C-2', Ar); 135.2 (C-1', Ar); 156.1 ($NH\underline{C}OO(CH_3)_3$); 158.3 (N=<u>C</u>H, C-4). ES^+ HRMS, *m/z*: 297.1369 found (calculated for $C_{15}H_{22}N_2O_2{}^{35}Cl$ $[M+H]^+$ requires 297.1370).

*Tert-butyl {3-[(4-cyanobenzylidene)amino]propyl}carbamate (**9m**)*

Compound **9m** was prepared in 91% yield as yellowish viscous oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and 4-cyanobenzaldehyde **8i** (1 equiv.) according to the standard procedure under microwave irradiation. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H, ($C\underline{H}_3)_3CO$); 1.88 (quint, 2H, *J* = 6.6 Hz, H-2); 3.22-3.27 (m, 2H, H-1); 3.68-3.73 (m, 2H, H-3); 4.95 (br s, 1H, NH); 7.67-7.7 (m, 2H, H-3', H-5', Ar); 7.80-7.83 (m, 2H, H-2', H-6', Ar); 8.30 (s, 1H, N=C<u>H</u>, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.5 (($\underline{C}H_3)_3CO$); 31.1 (C-2); 39.2 (C-1); 59.6 (C-3); 79.2 (($CH_3)_3\underline{C}O$); 114.0 (C-4', Ar); 118.6 (CN); 128.6 (C-2', C-6', Ar); 132.5 (C-3', C-5', Ar); 139.9 (C-1', Ar); 156.1

(NHCOO$(CH_3)_3$); 159.6 (N=CH, C-4). ES^+ HRMS, *m/z*: 310.1530 found (calculated for $C_{16}H_{21}N_3O_2Na$ $[M+Na]^+$ requires 310.1531).

*Tert-butyl {3-[(pyridin-4-ylmethylene)amino]propyl}carbamate (**9n**)*

Compound **9n** was prepared in 88% yield as orange viscous oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and pyridine-4-carbaldehyde **8j** (0.98 equiv.) according to the standard procedure under microwave irradiation. ^1H NMR ($CDCl_3$) δ: 1.42 (s, 9H, $(CH_3)_3CO$); 1.89 (quint, 2H, *J* = 6.6 Hz, H-2); 3.23-3.29 (m, 2H, H-1); 3.71 (t, 2H, *J* = 6.1 Hz, H-3); 4.98 (br s, 1H, NH); 7.56-7.58 (dd, 2H, *J* = 1.5, 4.5 Hz, H-3', H-5', Ar); 8.26 (s, 1H, N=CH, H-4); 8.67-8.69 (dd, 2H, *J* = 1.4, 4.5 Hz, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.5 ($(CH_3)_3CO$); 31.0 (C-2); 39.2 (C-1); 59.6 (C-3); 79.2 ($(CH_3)_3CO$); 122.0 (C-3', Ar); 122.6 (C-5', Ar); 142.9 (C-4', Ar); 150.3 (C-2', Ar); 150.5 (C-6', Ar); 156.1 (NHCOO$(CH_3)_3$); 159.6 (N=CH, C-4). ES^+ HRMS, *m/z*: 286.1536 found (calculated for $C_{14}H_{21}N_3O_2Na$ $[M+Na]^+$ requires 286.1531).

*Tert-butyl {3-[(quinolin-8-ylmethylene)-amino]-propyl}carbamate (**9o**)*

Compound **9o** was prepared in 96% yield as brownish deliquescent powder from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and quinoline-8-carbaldehyde **8k** (0.95 equiv.) according to the standard procedure under microwave irradiation. ^1H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(CH_3)_3CO$); 1.95 (quint, 2H, *J* = 6.5 Hz, H-2); 3.31-3.33 (m, 2H, H-1); 3.84 (t, 2H, *J* = 6.0 Hz, H-3); 5.25 (s, 1H, NH); 7.42-7.46 (dd, 1H, *J* = 4.2, 8.3 Hz, H-3', Ar); 7.60 (t, 1H, J = 7.7 Hz, H-6', Ar); 7.90 (dd, 1H, *J* = 1.4, 8.1 Hz, H-5', Ar); 8.19 (dd, 1H, *J* = 1.8, 8.3 Hz, H-4', Ar); 8.39 (dd, 1H, *J* = 1.4, 7.3 Hz, H-7', Ar); 8.96 (dd, 1H, *J* = 1.8, 4.2 Hz, H-2', Ar); 9.64 (s, 1H, N=CH, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.6 ($(CH_3)_3CO$); 31.3 (C-2); 39.7 (C-1); 60.1 (C-3); 78.9 ($(CH_3)_3CO$); 121.4 (C-3', Ar); 126.6 (C-6', Ar); 127.6 (C-4a', Ar); 128.4 (C-7', Ar); 130.5 (C-5', Ar); 133.1 (C-4', Ar); 136.5 (C-8', Ar); 146.7 (C-8a', Ar); 150.2 (C-2', Ar); 156.2 (NHCOO$(CH_3)_3$); 159.3 (N=CH, C-4). ES^+ HRMS, *m/z*: 314.1853 found (calculated for $C_{18}H_{24}N_3O_2$ $[M+H]^+$ requires 314.1868).

*Tert-butyl [3-(benzylidene-amino)propyl]carbamate (**9p**)*

Compound **9p** was prepared in 97% yield as dark orange viscous oil from *tert*-butyl (3-aminopropyl)carbamate **7b** (1 equiv.) and benzaldehyde **8l** (0.98 equiv.) according to the standard procedure under microwave irradiation. ^1H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(CH_3)_3CO$); 1.88 (quint, *J* = 6.5 Hz, 2H, H-2); 3.24-3.31 (m, 2H, H-1); 3.65-3.7 (m, 2H, H-3); 5.15 (br s, 1H, NH); 7.39-7.43 (m, 3H, H-4', H-5', H-6', Ar); 7.70-7.73 (m, 2H, H-2', H-3', Ar); 8.27 (s, 1H, N=CH, H-4). ^{13}C NMR ($CDCl_3$) δ: 28.5 ($(CH_3)_3CO$); 31.2 (C-2); 39.6 (C-1); 59.7 (C-3); 79.0 ($(CH_3)_3CO$); 128.1 (C-3', Ar); 128.2 (C-5', Ar); 128.7 (C-2', Ar); 129.6 (C-6', Ar); 130.8 (C-4', Ar); 136.2 (C-1', Ar); 156.2 (NHCOO$(CH_3)_3$); 161.5 (N=CH, C-4). ES^+ HRMS, *m/z*: 263.1756 found (calculated for $C_{15}H_{23}N_2O_2$ $[M+H]^+$ requires 263.1759).

*Standard procedure for reduction of aldimines **9(a-p)** into N-Boc monoprotected diamines **10(a-p)**.*

All the reduction reactions were conducted in a 10-mL two-necked round-bottomed flask, charged with a magnetic stirrer and fitted with a condenser. Aldimine **9** (0.5 mmol, 1 equiv.) was solubilized in methanol (6-8 mL) under vigorous stirring (500 rpm) and cooled at 0 °C. To this solution was added small portions of $NaBH_4$ (0.094 g, 2.5 mmol, 5 equiv.) over a period of 10 minutes. The resulting suspension was stirred at 50 °C for 24 h (monitored by TLC on 0.2-mm precoated plates of silica gel 60 F-254, Merck). After cooling down to room temperature, volatiles were removed under reduced pressure using a rotary evaporator. Deionized water (8-12 ml) was added to the residue and the resulting mixture was transferred into a separating funnel. An extraction was conducted using dichloromethane (3 x 6-8 mL), the combined organic phases were dried over magnesium sulphate $MgSO_4$, filtered using a filter paper and the solvent was removed *in vacuo*. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h. The desired *N*-Boc monoprotected diamines **10** were obtained as viscous oils that crystallized on standing and was used further without purification.

*Tert-butyl [3-(4-{3-[(benzo[1,3]dioxol-5-ylmethyl)amino]propyl}piperazin-1-yl)propyl]carbamate **(10a)***

Compound **10a** was prepared in 84% yield as orange-yellowish oil from **9a** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(C\underline{H}_3)_3CO$); 1.59-1.73 (m, 4H, H-2, H-7); 2.36-2.45 (m, 12H, H-3, H-4, H-5, H-6); 2.64 (t, 2H, J = 6.9 Hz, H-8); 3.15-3.20 (m, 2H, H-1); 3.68 (s, 2H, H-9); 5.47 (br s, 1H, NH); 5.93 (s, 2H, $OC\underline{H}_2O$); 6.74 (d, 2H, J = 1.0 Hz, H-5', H-6', Ar); 6.82 (s, 1H, H-2', Ar). ^{13}C NMR ($CDCl_3$) δ: 26.5 (C-2); 27.1 (C-7); 28.6 ($(CH_3)_3CO$); 40.2 (C-1); 48.1 (C-8); 53.3-53.5 (C-4, C-5); 53.9 (C-9); 57.0-57.2 (C-3; C-6); 78.8 ($(CH_3)_3\underline{C}O$); 101.0 ($O\underline{C}H_2O$); 108.2 (C-2', Ar); 108.7 (C-5', Ar); 121.2 (C-6', Ar); 134.6 (C-1', Ar); 146.6 (C-4', Ar); 147.8 (C-3', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 435.2968 found (calculated for $C_{23}H_{39}N_4O_4$ $[M+H]^+$ requires 435.2965).

*Tert-butyl (3-{4-[3-(4-methoxybenzylamino)propyl]piperazin-1-yl}propyl)carbamate (**10b**)*

Compound **10b** was prepared in 79% yield as yellowish oil from **9b** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(C\underline{H}_3)_3CO$); 1.59-1.73 (m, 4H, H-2, H-7); 2.35-2.41 (m, 12H, H-3, H-4, H-5, H-6); 2.65 (t, 2H, J = 6.9 Hz, H-8); 3.16-3.18 (m, 2H, H-1); 3.70 (s, 2H, H-9); 3.79 (s, 3H, $OC\underline{H}_3$); 5.48 (br s, 1H, NH); 6.83-6.86 (m, 2H, H-3', H-5', Ar); 7.19-7.24 (m, 2H, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 26.5 (C-2); 27.0 (C-7); 28.6 ($(\underline{C}H_3)_3CO$); 40.2 (C-1); 48.2 (C- 8); 53.3-53.5 (C-4, C-5); 53.4 (C-9); 55.4 ($O\underline{C}H_3$); 57.0-57.2 (C-3, C-6); 78.9 ($(CH_3)_3\underline{C}O$); 113.9 (C-3', C-5', Ar); 129.4 (C-2', C-6', Ar); 132.6 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$); 158.8 (C-4', Ar). ES^+ HRMS, *m/z*: 421.3173 found (calculated for $C_{23}H_{41}N_4O_3$ $[M+H]^+$ requires 421.3173).

*Tert-butyl (3-{4-[3-(4-methylbenzylamino)propyl]piperazin-1-yl}propyl)carbamate (**10c**)*

Compound **10c** was prepared in 84% yield as yellowish oil from **9c** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(C\underline{H}_3)_3CO$); 1.59-1.72 (m, 4H, H-2, H-7); 2.33 (s, 3H, $C\underline{H}_3$); 2.36-2.45 (m, 12H, H-3, H-4, H-5, H-6); 2.66 (t, 2H, J = 6.9 Hz, H-8); 3.15-3.21 (m, 2H, H-1); 3.73 (s, 2H, H-9); 5.48 (br s, 1H, NH); 7.11-7.13 (m, 2H, H-3', H-5', Ar); 7.18-7.21 (m, 2H, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 21.2 ($\underline{C}H_3$); 26.5 (C-2); 27.1 (C-7); 28.6 ($(\underline{C}H_3)_3CO$); 40.2 (C-1); 48.2 (C-8); 53.3-53.5 (C-4, C-5); 53.8 (C-9); 57.0-57.2 (C-3, C-6); 78.9 ($(CH_3)_3\underline{C}O$); 128.2 (C-2', C-6', Ar); 129.2 (C-3', C-5', Ar); 136.6 (C-1', Ar); 137.4 (C-4', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 405.3228 found (calculated for $C_{23}H_{41}N_4O_3$ $[M+H]^+$ requires 405.3224).

*Tert-butyl (3-{4-[3-(4-chlorobenzylamino)propyl]piperazin-1-yl}propyl)carbamate (**10d**)*

Compound **10d** was prepared in 90% yield as orange-yellow oil from **9d** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, $(C\underline{H}_3)_3CO$); 1.59-1.73 (m, 4H, H-2, H-7); 2.35-2.44 (m, 12H, H-3, H-4, H-5, H-6); 2.64 (t, 2H, J = 6.8 Hz, H-8); 3.14-3.20 (m, 2H, H-1); 3.73 (s, 2H, H-9); 5.48 (br s, 1H, NH); 7.22-7.29 (m, 4H, H-2', H-3', H-5', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 26.4 (C-2); 27.1 (C-7); 28.6 ($(\underline{C}H_3)_3CO$); 40.1 (C-1); 48.2 (C- 8); 53.3-53.5 (C-4, C-5); 53.4 (C-9); 57.0-57.1 (C-3, C-6); 78.9 ($(CH_3)_3\underline{C}O$); 128.6 (C-3', C-5', Ar); 129.5 (C-2', C-6', Ar); 132.6 (C-4', Ar); 139.2 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 425.2678 found (calculated for $C_{22}H_{38}N_4O_2{}^{35}Cl$ $[M+H]^+$ requires 425.2678).

*Tert-butyl {3-[(benzo[1,3]dioxol-5-yl)methylamino]propyl}carbamate (**10e**)*

Compound **10e** was prepared in 80% yield as orange-yellow oil from **9e** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, $(C\underline{H}_3)_3CO$); 1.60-1.69 (m, 2H, H-2); 1.51 (br s, 1H, NH); 2.70 (t, 2H, J = 6.5 Hz, H-3); 3.19-3.21 (m, 2H, H-1); 3.67 (s, 2H, H-4); 5.32 (br s, 1H, NH); 5.93 (s, 2H, $OC\underline{H}_2O$); 6.74 (d, 2H, J = 0.86 Hz, H-5', H-6', Ar); 6.83 (s, 1H, H-2'). ^{13}C NMR ($CDCl_3$) δ: 28.56 ($(\underline{C}H_3)_3CO$); 29.78 (C-2); 39.57 (C-1); 47.32 (C-3); 53.94 (C- 4); 79.09 ($(CH_3)_3\underline{C}O$); 101.0 ($O\underline{C}H_2O$); 108.2 (C-2', Ar); 108.8 (C-5', Ar); 121.3 (C-6', Ar); 134.4 (C-1', Ar); 146.6 (C-4', Ar); 147.8 (C-3', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 309.1814 found (calculated for $C_{16}H_{25}N_2O_4$ $[M+H]^+$ requires 309.1814).

*Tert-butyl [3-(4-methoxybenzylamino)propyl]carbamate (**10f**)*

Compound **10f** was prepared in 73% yield as dark orange-yellow oil from **9f** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, ($C\underline{H}_3)_3CO$); 1.66 (m, 2H, H-2); 1.78 (br s, 1H, NH); 2.69 (t, 2H, *J* = 6.5 Hz, H-3); 3.21 (m, 2H, H-1); 3.71 (s, 2H, H-4); 3.79 (s, 3H, $OC\underline{H}_3$); 5.34 (br s, 1H, NH); 6.85 (d, 2H, *J* = 8.7 Hz, H-3', H-5', Ar); 7.24 (d, 2H, *J* = 8.7 Hz, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 29.3 (C-2); 39.1 (C-1); 46.8 (C-3); 53.1 (C- 4); 55.4 ($O\underline{C}H_3$); 79.3 (($CH_3)_3\underline{C}O$); 114.0 (C-3', C-5', Ar); 129.9 (C-2', C-6', Ar); 132.3 (C-1', Ar); 156.5 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 295.2021 found (calculated for $C_{16}H_{27}N_2O_3$ $[M+H]^+$ requires 295.2022).

*Tert-butyl [3-(3-methoxybenzylamino)propyl]carbamate (**10g**)*

Compound **10g** was prepared in 79% yield as yellowish oil from **9g** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, ($\underline{C}H_3)_3CO$); 1.68 (m, 2H, H-2); 1.82 (br s, 1H, NH); 2.70 (t, 2H, *J* = 6.5 Hz, H-3); 3.21 (m, 2H, H-1); 3.76 (s, 2H, H-4); 3.81 (s, 3H, $OC\underline{H}_3$); 5.24 (br s, 1H, NH); 6.77-6.92 (m, 3H, H-4', H-5', H-6', Ar); 7.21-7.23 (d, 1H, *J* = 7.8 Hz, H-2', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.5 (($\underline{C}H_3)_3CO$); 29.9 (C-2); 39.5 (C-1); 47.4 (C-3); 54.1 (C- 4); 55.3 ($O\underline{C}H_3$); 79.1 (($CH_3)_3\underline{C}O$); 112.6 (C-4', Ar); 113.7 (C-2', Ar); 120.5 (C-6', Ar); 129.5 (C-5', Ar); 141.9 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$); 159.8 (C-3', Ar). ES^+ HRMS, *m/z*: 295.2024 found (calculated for $C_{16}H_{27}N_2O_3$ $[M+H]^+$ requires 295.2022).

*Tert-butyl [3-(3,5-dimethoxybenzylamino)propyl]carbamate (**10h**)*

Compound **10g** was prepared in 80% yield as yellowish oil from **9h** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H, ($C\underline{H}_3)_3CO$); 1.66-1.74 (m, 2H, H-2); 2.42 (br s, 1H, NH); 2.70 (t, 2H, *J* = 6.6 Hz, H-3); 3.18-3.22 (m, 2H, H-1); 3.73 (s, 2H, H-4); 3.78 (s, 6H, (2 x $OC\underline{H}_3$); 5.17 (br s, 1H, NH); 6.35 (t, 1H, *J* = 2.3 Hz, H-4', Ar); 6.50-6.51 (d, 2H, *J* = 2.3 Hz, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.5 (($\underline{C}H_3)_3CO$); 29.6 (C-2); 39.1 (C-1); 47.0 (C-3); 54.0 (C-4); 55.5 (2 x OCH_3); 79.3 (($CH_3)_3\underline{C}O$); 99.4 (C-4', Ar); 106.3 (C-2', C-6', Ar); 141.7 (C-1', Ar); 156.4 ($NH\underline{C}OO(CH_3)_3$); 161.0 (C-3',C-5', Ar). ES^+ HRMS, *m/z*: 325.2131 found (calculated for $C_{17}H_{29}N_2O_4$ $[M+H]^+$ requires 325.2127).

*Tert-butyl [3-(3,4,5-trimethoxybenzylamino)propyl]carbamate (**10i**)*

Compound **10i** was prepared in 74% yield as pale yellow oil from **9i** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.68-1.72 (m, 2H, H-2); 1.89 (br s, 1H, NH); 2.71 (t, 2H, *J* = 6.6 Hz, H-3); 3.21-3.24 (m, 2H, H-1); 3.72 (s, 2H, H-4); 3.83 (s, 3H, $OC\underline{H}_3$); 3.86 (s, 6H, 2 x $OC\underline{H}_3$); 5.06 (br s, 1H, NH); 6.56-6.59 (m, 2H, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 30.1 (C-2); 39.3 (C-1); 47.5 (C-3); 54.6 (C- 4); 56.2 (2 x $O\underline{C}H_3$); 61.0 ($O\underline{C}H_3$); 79.2 (($CH_3)_3\underline{C}O$); 105.0 (C-2', C-6', Ar); 136.2 (C-1', Ar); 136.9 (C-4', Ar); 153.3 (C-3', C-5', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 355.2232 found (calculated for $C_{18}H_{31}N_2O_5$ $[M+H]^+$ requires 355.2233).

*Tert-butyl [3-(4-methylbenzylamino)propyl]carbamate (**10j**)*

Compound **10j** was prepared in 98% yield as pale yellow oil from **9j** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, ($C\underline{H}_3)_3CO$); 1.57 (br s, 1H, NH); 1.61-1.70 (m, 2H, H-2); 2.33 (s, 3H, $C\underline{H}_3$); 2.69 (t, 2H, *J* = 6.5 Hz, H-3); 3.20-3.22 (m, 2H, H-1); 3.72 (s, 2H, H-4); 5.38 (br s, 1H, NH); 7.16 (m, 4H, H-2', H-3', H-5', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 21.2 ($C\underline{H}_3$); 28.6 (($\underline{C}H_3)_3CO$); 29.7 (C-2); 39.6 (C-1); 47.5 (C-3); 53.83 (C-4); 79.0 (($CH_3)_3\underline{C}O$); 128.2 (C-2', C-6', Ar); 129.2 (C-3', C-5', Ar); 136.6 (C-1', Ar); 137.3 (C-4', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 279.2071 found (calculated for $C_{16}H_{27}N_2O_2$ $[M+H]^+$ requires 279.2072).

*Tert-butyl [3-(4-chlorobenzylamino)propyl]carbamate (**10k**)*

Compound **10k** was prepared in 87% yield as pale yellow oil from **9k** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H, ($C\underline{H}_3)_3CO$); 1.59-1.70 (m, 2H, H-2); 2.47

(br s, 1H, NH); 2.67 (t, 2H, *J* = 6.4 Hz, H-3); 3.19-3.21 (m, 2H, H-1); 3.73 (s, 2H, H-4); 5.22 (br s, 1H, NH); 7.25 (m, H-2', H-3', H-5', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.4 (($\underline{C}H_3)_3CO$); 29.6 (C-2); 39.2 (C-1); 47.1 (C-3); 53.2 (C-4); 79.1 ($(CH_3)_3\underline{C}O$); 128.5 (C-2', C-6', Ar); 129.6 (C-3', C-5', Ar); 132.7 (C-4', Ar); 138.3 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES$^+$ HRMS, *m/z*: 299.1523 found (calculated for $C_{15}H_{24}N_2O_2{}^{35}Cl$ $[M+H]^+$ requires 299.1526).

*Tert-butyl [3-(2-chlorobenzylamino)propyl]carbamate (**10l**)*

Compound **10l** was prepared in 75% yield as pale yellow oil from **9l** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.65-1.71 (m, 3H, H-2, NH); 1.74 (br s, 1H, NH); 2.68 (t, 2H, *J* = 6.6 Hz, H-3); 3.20-3.22 (m, 2H, H-1); 3.85 (s, 2H, H-4); 5.23 (br s, 1H, NH); 7.18-7.36 (m, H-3', H-4', H-5', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.5 (($\underline{C}H_3)_3CO$); 29.9 (C-2); 39.5 (C-1); 47.3 (C-3); 51.4 (C- 4); 79.1 ($(CH_3)_3\underline{C}O$); 126.9 (C-5', Ar); 128.4 (C-4', Ar); 129.6 (C-3', Ar); 130.3 (C-6', Ar); 133.8 (C-2', Ar); 137.6 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES$^+$ HRMS, *m/z*: 299.1523 found (calculated for $C_{15}H_{24}N_2O_2{}^{35}Cl$ $[M+H]^+$ requires 299.1526).

*Tert-butyl [3-(4-cyanobenzylamino)propyl]carbamate (**10m**)*

Compound **10m** was prepared in 70% yield as yellowish oil from **9m** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.58 (br s, 1H, NH); 1.65 (quint, 2H, *J* = 6.3 Hz, H-2); 2.67 (t, 2H, *J* = 6.5 Hz, H-3); 3.18-3.24 (m, 2H, H-1); 3.82 (s, 2H, H-4); 5.10 (br s, 1H, NH); 7.47-7.40 (m, H-2', H-6', Ar); 7.57-7.62 (m, H-3', H-5', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 30.0 (C-2); 39.2 (C-1); 47.3 (C-3); 53.7 (C- 4); 79.2 ($(CH_3)_3\underline{C}O$); 110.8 (C-4', Ar); 119.1 (CN); 128.8 (C-2', C-6', Ar); 132.3 (C-3', C-5', Ar); 146.1 (C-1', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES$^+$ HRMS, *m/z*: 290.1871 found (calculated for $C_{16}H_{24}N_3O_2$ $[M+H]^+$ requires 290.1868).

*Tert-butyl {3-[(pyridin-4-yl)methylamino]propyl}carbamate (**10n**)*

Compound **10n** was prepared in 80% yield as pale yellow oil from **9n** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9H, ($C\underline{H}_3)_3CO$); 1.70 (quint, 2H, *J* = 6.5 Hz, H-2); 2.31 (s, 1H, NH); 2.71 (t, 2H, *J* = 6.5 Hz, H-3); 3.22-3.24 (m, 2H, H-1); 3.81 (s, 2H, H-4); 5.14 (s, 1H, NH); 7.27-7.29 (d, 2H, *J* = 6 Hz, H-3', H-5', Ar); 8.53-8.55 (dd, 2H, *J* = 1.6, 4.4 Hz, H-2', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 29.9 (C-2); 39.1 (C-1); 47.2 (C-3); 52.8 (C- 4); 79.3 ($(CH_3)_3\underline{C}O$); 123.2 (C-3', C-5', Ar); 148.9 (C-4', Ar); 150.0 (C-2', C-6', Ar); 156.4 ($NH\underline{C}OO(CH_3)_3$). ES$^+$ HRMS, *m/z*: 288.1682 found (calculated for $C_{14}H_{23}N_3O_2Na$ $[M+Na]^+$ requires 288.1688).

*Tert-butyl {3-[(quinolin-8-ylmethyl)amino]propyl}carbamate (**10o**)*

Compound **10o** was prepared in 88% yield as brownish oil from **9o** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H, ($C\underline{H}_3)_3CO$); 1.69 (quint, 2H, *J* = 6.6 Hz, H-2); 2.18 (br s, 1H, NH); 2.73 (t, 2H, *J* = 6.7 Hz, H-3) 3.18-3.24 (m, 2H, H-1); 4.34 (s, 2H, H-4); 5.31 (br s, 1H, NH); 7.38-7.43 (dd, 1H, *J* = 4.2, 8.3 Hz, H-3', Ar); 7.45-7.50 (dd, 1H, *J* = 7.1, 8.1 Hz, H-6', Ar); 7.65-7.67 (d, 1H, *J* = 7.0 Hz, H-7', Ar); 7.71-7.74 (dd, 1H, *J* = 1.4, 8.2 Hz, H-5', Ar); 8.13-8.17 (dd, 1H, *J* = 1.8, 8.3 Hz, H-4', Ar); 8.90-8.92 (dd, 1H, *J* = 1.8, 4.2 Hz, H-2', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6 (($\underline{C}H_3)_3CO$); 29.8 (C-2); 39.6 (C-1); 47.5 (C-3); 51.0 (C-4); 79.0 ($(CH_3)_3\underline{C}O$); 121.2 (C-3', Ar); 126.4 (C-5', Ar); 127.3 (C-6', Ar); 128.5 (C-4a', Ar); 129.2 (C-7', Ar); 136.6 (C-8', Ar); 138.1 (C-4', Ar); 147.0 (C-8a', Ar); 149.6 (C-2', Ar); 156.2 ($NH\underline{C}OO(CH_3)_3$). ES$^+$ HRMS, *m/z*: 316.2020 found (calculated for $C_{18}H_{26}N_3O_2$ $[M+H]^+$ requires 316.2025).

*Tert-butyl (3-benzylaminopropyl)carbamate (**10p**)*

Compound **10p** was prepared in 73% yield as dark orange oil from **9p** according to the standard procedure for reduction. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, ($C\underline{H}_3)_3CO$); 1.63-1.72 (m, 2H, H-2); 1.77 (br s, 1H, NH); 2.71 (t, 2H, *J* = 6.5 Hz, H-3); 3.21-3.23 (m, 2H, H-1); 3.77 (s, 2H, H-4); 5.34 (br s, 1H, NH); 7.22-7.33 (m, 5H, H-2', H-3', H-4', H-5', H-6', Ar). ^{13}C NMR ($CDCl_3$) δ: 28.6

(($\underline{C}H_3)_3CO$); 29.7 (C-2); 39.5 (C-1); 47.5 (C-3); 54.1 (C- 4); 79.1 (($CH_3)_3\underline{C}O$); 127.1 (C-4', Ar); 128.3 (C-2', C-6', Ar); 128.5 (C-3', C-5', Ar); 140.2 (C-1', Ar); 156.3 ($NH\underline{C}OO(CH_3)_3$). ES^+ HRMS, *m/z*: 287.1736 found (calculated for $C_{15}H_{24}N_2O_2Na$ $[M+Na]^+$ requires 287.1735).

*Standard procedure for deprotection of N-Boc monoprotected diamines **10(a-p)** into their hydrochloride salts **11(a-p)**.*

Deprotection of *N*-Boc compounds **10(a-p)** was realized according to a method of literature [15], which involved the use of a solution of 6M HCl in 1,4-dioxane. After acidic treatment and work-up, the desired hydrochloride salt **11** was dried under high vacuum (10^{-2} Torr) at 25 °C, then was stocked at 4 °C under nitrogen.

*{3-[4-(3-Aminopropyl)piperazin-1-yl]-propyl}benzo[1,3]dioxol-5-yl methylamine hydrochloride (**11a**)*

Hydrochloride salt **11a** was prepared from **10a** in 98% yield as tannish yellow powder. Mp = 209-211 °C. ^{1}H NMR (DMSO-d_6) δ: 2.00-2.23 (m, 4H, H-2, H-7); 2.89-2.97 (m, 4H, H-1, H-8); 3.26-3.69 (m, 12H, H-3, H-4, H-5, H-6); 4.04 (s, 2H, H-9); 6.05 (s, 2H, $OC\underline{H}_2O$); 6.94-6.97 (d, 1H, J = 7.9 Hz, H-5', Ar); 7.02-7.05 (dd, 1H, J = 0.8, 8.0 Hz, H-6', Ar); 7.22 (d, 1H, J = 0.7 Hz, H-2', Ar); 8.18 (br s, 3H, $N\underline{H}_2$, $\underline{H}Cl$); 9.47 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.1 (C-7); 21.5 (C-2); 36.2 (C-1); 43.3 (C-8); 48.1 (C-4, C-5); 49.7 (C-9); 52.8 (C-3; C-6); 101.3 ($O\underline{C}H_2O$); 108.3 (C-2', Ar); 110.4 (C-5', Ar); 124.2 (C-6', Ar); 125.3 (C-1', Ar); 147.3 (C-4', Ar); 147.7 (C-3', Ar). ES^+ HRMS, *m/z*: 335.2445 found (calculated for $C_{18}H_{31}N_4O_2$ $[M+H]^+$ requires 335.2447).

*{3-[4-(3-Aminopropyl)piperazin-1-yl]propyl}-(4-methoxybenzyl)amine hydrochloride (**11b**)*

Hydrochloride salt **11b** was prepared from **10b** in 98% yield as orange needles. Mp = 183-185 °C. ^{1}H NMR (DMSO-d_6) δ: 2.02-2.17 (m, 4H, H-2, H-7); 2.89-3.01 (m, 4H, H-1, H-8); 3.25- 3.80 (m, 12H, H-3, H-4, H-5, H-6); 3.77 (s, 3H, $OC\underline{H}_3$); 4.06 (t, 2H, J = 5.3 Hz, H-9); 6.96-7.01 (m, 2H, H-3', H-5', Ar); 7.47-7.52 (m, 2H, H-2', H-6', Ar); 8.12 (br s, 3H, $N\underline{H}_2$, $\underline{H}Cl$); 9.35 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 19.9 (C-7); 21.4 (C-2); 36.2 (C-1); 43.3 (C-8); 48.0 (C-4, C-5); 49.4 (C-9); 52.9 (OCH3); 55.2 (C-3, C-6); 114.0 (C-3', C-5', Ar); 123.7 (C-2', C-6', Ar); 131.7 (C-1', Ar); 159.7 (C-4', Ar). ES^+ HRMS, *m/z*: 321.2650 found (calculated for $C_{18}H_{33}N_4O$ $[M+H]^+$ requires 321.2648).

*{3-[4-(3-Aminopropyl)piperazin-1-yl]propyl}-(4-methylbenzyl)amine hydrochloride (**11c**)*

Hydrochloride salt **11c** was prepared from **10c** in 98% yield as tannish yellow powder. Mp = 198-200 °C. ^{1}H NMR (DMSO-d_6) δ: 2.02-2.15 (m, 4H, H-2, H-7); 2.32 (s, 3H, $C\underline{H}_3$); 2.89-2.99 (m, 4H, H-1, H-8); 3.24-3.69 (m, 12H, H-3, H-4, H-5, H-6); 4.08 (t, 2H, J = 5.3 Hz, H-9); 7.22-7.25 (m, 2H, H-3', H-5', Ar); 7.44-7.47 (m, 2H, H-2', H-6', Ar); 8.15 (br s, 3H, $N\underline{H}_2$, $\underline{H}Cl$); 9.44 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.0 ($C\underline{H}_3$); 20.8 (C-7); 21.4 (C-2); 36.2 (C-1); 40.4 (C-8); 43.5 (C-4, C-5); 48.1 (C-9); 49.7 (C-3); 52.8 (C-6); 128.9 (C-2, C-6', Ar); 129.2 (C-3', C-5', Ar); 130.1 (C-1', Ar); 138.4 (C-4', Ar). ES^+ HRMS, *m/z*: 305.2701 found (calculated for $C_{18}H_{33}N_4$ $[M+H]^+$ requires 305.2700).

*{3-[4-(3-Aminopropyl)piperazin-1-yl]propyl}-(4-chlorobenzyl)amine hydrochloride (**11d**)*

Hydrochloride salt **11d** was prepared from **10d** in 98% yield as yellow-orange powder. Mp = 200-204 °C. ^{1}H NMR (DMSO-d_6) δ: 2.03-2.23 (m, 4H, H-2, H-7); 2.90-3.04 (m, 4H, H-1, H-8); 3.31-3.74 (m, 12H, H-3, H-4, H-5, H-6); 4.13 (t, 2H, J = 5.3 Hz, H-9); 7.48-7.50 (m, 2H, H-2', H-6', Ar); 7.62-7.65 (m, 2H, H-3', H-5', Ar); 8.24 (br s, 3H, $N\underline{H}_2$, $\underline{H}Cl$); 9.69 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 19.9 (C-7); 21.3 (C-2); 36.1 (C-1); 43.6 (C-8); 47.9 (C-4, C-5); 49.1 (C-9); 52.8 (C-3, C-6); 128.6 (C-3', C-5', Ar); 130.9 (C-2', C-6', Ar); 132.2 (C-4', Ar); 133.7 (C-1', Ar). ES^+ HRMS, *m/z*: 325.2155 found (calculated for $C_{17}H_{30}N_4{}^{35}Cl$ $[M+H]^+$ requires 325.2153).

*3-[(Benzo[1,3]dioxol-5-yl)methylamino]propylamine hydrochloride (**11e**)*

Hydrochloride salt **11e** was prepared from **10e** in 86% yield as tannish yellow powder. Mp > 250 °C. ^{1}H NMR (D_2O) δ: 2.03-2.13 (m, 2H, H-2); 3.05-3.18 (m, 4H, H-1, H-3); 4.18 (s, 2H, H-4); 6.03 (s, 2H, OC<u>H</u>$_2$O); 6.96-6.99 (m, 3H, H-2', H-6', H-5', H-6', Ar). ^{13}C NMR (D_2O) δ: 23.7 (C-2); 36.5 (C-1); 43.7 (C-3); 51.1 (C-4); 101.6 (O<u>C</u>H$_2$O); 108.9 (C-2', Ar); 109.9 (C-5', Ar); 123.9 (C-6', Ar); 124.2 (C-1', Ar); 147.7 (C-4', Ar); 148.2 (C-3', Ar). ES$^+$ HRMS, *m/z*: 209.1292 found (calculated for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ requires 209.1290).

*3-(4-Methoxybenzylamino)propylamine hydrochloride (**11f**)*

Hydrochloride salt **11f** was prepared from **10f** in 82% yield as brown needles. Mp > 250 °C. ^{1}H NMR (D_2O) δ: 2.03-2.13 (m, 2H, H-2); 3.05-3.18 (m, 4H, H-1, H-3); 3.85 (s, 3H, OC<u>H</u>$_3$); 4.21 (s, 2H, H-4); 7.05-7.08 (d, 2H, *J* = 8.7 Hz, H-3', H-5', Ar); 7.41-7.44 (d, 2H, *J* = 8.7 Hz, H-2', H-6', Ar). ^{13}C NMR (D_2O) δ: 23.7 (C-2); 36.5 (C-1); 43.6 (C-3); 50.7 (C-4); 55.4 (OC<u>H</u>$_3$); 114.6 (C-3', C-5', Ar); 122.9 (C-1', Ar); 131.5 (C-2', C-6', Ar); 159.8 (C-4', Ar). ES$^+$ HRMS, *m/z*: 195.1498 found (calculated for $C_{11}H_{19}N_2O$ $[M+H]^+$ requires 195.1497).

*3-(3-Methoxybenzylamino)propylamine hydrochloride (**11g**)*

Hydrochloride salt **11g** was prepared from **10g** in 63% yield as brown yellow powder. Mp = 198-200 °C. ^{1}H NMR (DMSO-d_6) δ: 2.02-2.05 (m, 2H, H-2); 2.88-2.98 (m, 4H, H-1, H-3); 3.77 (s, 3H, OC<u>H</u>$_3$); 4.08 (t, 2H, *J* = 5.5 Hz, H-4); 6.94-6.98 (m, 1H, H-2', Ar); 7.09-7.12 (d, 1H, *J* = 7.6 Hz, H-4', Ar); 7.22-7.23 (m, 1H, H-6', Ar); 7.30-7.35 (m, 1H, H-5', Ar); 8.13 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.43 (br s, 1H, N<u>H</u>). ^{13}C NMR (DMSO-d_6) δ: 23.8 (C-2); 36.3 (C-1); 43.9 (C-3); 50.2 (C-4); 55.4 (O<u>C</u>H$_3$); 114.8 (C-4', Ar); 115.7 (C-2', Ar); 122.3 (C-6', Ar); 130.0 (C-5', Ar); 133.4 (C-1', Ar); 159.5 (C-3', Ar). ES$^+$ HRMS, *m/z*: 195.1497 found (calculated for $C_{11}H_{19}N_2O$ $[M+H]^+$ requires 195.1497).

*3-(3,5-Dimethoxybenzylamino)propylamine hydrochloride (**11h**)*

Hydrochloride salt **11h** was prepared from **10h** in 98% yield as brown yellow powder. Mp = 205-207 °C. ^{1}H NMR (D_2O) δ: 2.04-2.14 (m, 2H, H-2); 3.05-3.18 (m, 4H, H-1, H-3); 3.82 (s, 6H, (2 x OC<u>H</u>$_3$); 4.19 (s, 2H, H-4); 6.67 (m, 3H, H-2', H-4', H-6', Ar). ^{13}C NMR (D_2O) δ: 23.7 (C-2); 36.5 (C-1); 44.0 (C-3); 51.0 (C-4); 55.5 (2 x O<u>C</u>H$_3$); 101.1 (C-4', Ar); 108.1 (C-2', C-6', Ar); 132.8 (C-1', Ar); 160.7 (C-3', C-5', Ar). ES$^+$ HRMS, *m/z*: 225.1603 found (calculated for $C_{12}H_{21}N_2O_2$ $[M+H]^+$ requires 225.1603).

*[3-(3,4,5-Trimethoxybenzylamino)propylamine hydrochloride (**11i**)*

Hydrochloride salt **11i** was prepared from **10i** in 87% yield as brown powder. Mp = 200-202 °C. ^{1}H NMR (DMSO-d_6) δ: 2.01-2.06 (m, 2H, H-2); 2.89-2.94 (m, 4H, H-1, H-3); 3.65 (s, 3H, OC<u>H</u>$_3$); 3.79 (s, 6H, 3 x OC<u>H</u>$_3$); 4.04 (s, 2H, H-4); 7.01 (s, 2H, H-2', H-6', Ar); 8.17 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.59 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.7 (C-2); 36.2 (C-1); 43.5 (C-3); 50.3 (C-4); 56.1 (2 x O<u>C</u>H$_3$); 60.1 (O<u>C</u>H$_3$); 107.7 (C-2', C-6', Ar); 127.3 (C-1', Ar); 137.6 (C-4', Ar); 152.8 (C-3', C-5', Ar). ES$^+$ HRMS, *m/z*: 255.1706 found (calculated for $C_{13}H_{23}N_2O_3$ $[M+H]^+$ requires 255.1709).

*3-(4-Methylbenzylamino)propylamine hydrochloride (**11j**)*

Hydrochloride salt **11j** was prepared from **10i** in 98% yield as brown powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 1.99-2.04 (m, 2H, H-2); 2.31 (s, 3H, C<u>H</u>$_3$); 2.87-2.95 (m, 4H, H-1, H-3); 4.05 (s, 2H, H-4); 7.21-7.24 (d, 2H, *J* = 7.8 Hz, H-2', H-6', Ar); 7.45-7.46 (d, 2H, *J* = 8.0 Hz, H-3', H-5', Ar); 8.19 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.50 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.9 (CH3); 23.6 (C-2); 36.2 (C-1); 43.5 (C-3); 49.8 (C-4); 128.9 (C-1', Ar); 129.2 (C-2', C-6', Ar); 130.2 (C-3', C-5', Ar); 138.4 (C-4', Ar). ES$^+$ HRMS, *m/z*: 179.1547 found (calculated for $C_{11}H_{19}N_2$ $[M+H]^+$ requires 179.1548).

*3-(4-Chlorobenzylamino)propylamine hydrochloride (**11k**)*

Hydrochloride salt **11k** was prepared from **10k** in 98% yield as tannish yellow powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 1.99-2.09 (m, 2H, H-2); 2.88-2.98 (m, 4H, H-1, H-3); 4.11 (t, 2H, J = 5.2 Hz, H-4); 7.48-7.51 (m, 2H, H-2', H-6', Ar); 7.62-7.66 (m, 2H, H-3', H-5', Ar); 8.22 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.68 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.6 (C-2); 36.1 (C-1); 43.6 (C-3); 49.2 (C-4); 128.6 (C-3', C-5', Ar); 130.9 (C-4', Ar); 132.2 (C-2', C-6', Ar); 133.7 (C-1', Ar). ES$^+$ HRMS, *m/z*: 199.1001 found (calculated for $C_{10}H_{16}N_2{}^{35}Cl$ $[M+H]^+$ requires 199.1002).

*3-(2-Chlorobenzylamino)propylamine hydrochloride (**11l**)*

Hydrochloride salt **11l** was prepared from **10l** in 94% yield as tannish yellow powder. Mp = 177-179 °C. ^{1}H NMR (DMSO-d_6) δ: 2.03-2.13 (m, 2H, H-2); 2.87-2.92 (m, 2H, H-1); 3.08 (m, 2H, H-3); 4.24 (t, 2H, J = 5.1 Hz, H-4); 7.40-7.85 (m, 4H, H-3', H-4', H-5', H-6', Ar); 8.23 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.77 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.6 (C-2); 36.1 (C-1); 43.1 (C-3); 47.0 (C-4); 127.5 (C-5', Ar); 129.6 (C-4', Ar); 129.8 (C-3'); 130.8 (C-6', Ar); 132.0 (C-2', Ar); 133.6 (C-1', Ar). ES$^+$ HRMS, *m/z*: 199.1002 found (calculated for $C_{10}H_{16}N_2{}^{35}Cl$ $[M+H]^+$ requires 199.1002).

*[3-(4-Cyanobenzylamino)propylamine hydrochloride (**11m**)*

Hydrochloride salt **11m** was prepared from **10m** in 98% yield as tannish orange powder. Mp = 224-226 °C. ^{1}H NMR (D_2O) δ: 2.04-2.15 (m, 2H, H-2); 3.07-3.25 (m, 4H, H-1, H-3); 4.36 (s, 2H, H-4); 7.63-7.66 (d, 2H, J = 8.3 Hz, H-2', H-6', Ar); 7.85-7.88 (d, 2H, J = 8.4 Hz, H-3', H-5', Ar). ^{13}C NMR (D_2O) δ: 23.7 (C-2); 36.5 (C-1); 44.3 (C-3); 50.6 (C-4); 112.4 (C-4'); 118.9 (CN); 130.4 (C-2', C-6', Ar); 133.2 (C-3', C-5', Ar); 135.8 (C-1', Ar). ES$^+$ HRMS, *m/z*: 190.1345 found (calculated for $C_{11}H_{16}N_3$ $[M+H]^+$ requires 190.1344).

*3-[(Pyridin-4-yl)methylamino]propylamine hydrochloride (**11n**)*

Hydrochloride salt **11n** was prepared from **10n** in 98% yield as pale orange powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 1.87-2.11 (m, 2H, H-2); 2.85-2.94 (m, 2H, H-1); 3.07 (m, 2H, H-3); 4.27 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 4.42 (s, 2H, H-4); 8.19-8.21 (d, 2H, J = 6.4 Hz, H-3', H-5', Ar); 8.93-8.95 (d, 2H, J = 6.4 Hz, H-2', H-6', Ar); 10.30 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.6 (C-2); 36.1 (C-1); 44.1 (C-3); 48.4 (C-4); 127.0 (C-3', C5', Ar); 143.4 (C-2', C-6', Ar); 149.5 (C-4', Ar). ES$^+$ HRMS, *m/z*: 166.1344 found (calculated for $C_9H_{16}N_3$ $[M+H]^+$ requires 166.1344).

*3-[(Quinolin-8-yl)methylamino]propylamine hydrochloride (**11o**)*

Hydrochloride salt **11o** was prepared from **10o** in 98% yield as dark brown powder. Mp = 204-206 °C. ^{1}H NMR (DMSO-d_6) δ: 2.04-2.14 (m, 2H, H-2); 2.87-2.92 (m, 2H, H-1); 3.14 (m, 2H, H-3); 4.76 (t, 2H, J = 4.9 Hz, H-4); 7.70-7.76 (m, 2H, H-3', H-6', Ar); 8.11-8.16 (m, 2H, H-5', H-7', Ar); 8.24 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 8.59-8.62 (dd, 1H, J = 1.6, 8.3 Hz, H-4', Ar); 9.05-9.07 (dd, 1H, J = 1.6, 4.4 Hz, H-2', Ar); 9.55 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.7 (C-2); 36.2 (C-1); 44.2 (C-3); 46.0 (C-4); 122.3 (C-3', Ar); 126.8 (C-5', Ar); 128.2 (C-6', Ar); 128.9 (C-4a', Ar); 129.8 (C-7', Ar); 132.7 (C-8', Ar); 138.5 (C-4', Ar); 144.5 (C-8a', Ar); 150.0 (C-2', Ar). ES$^+$ HRMS, *m/z*: 238.1323 found (calculated for $C_{13}H_{17}N_3Na$ $[M+Na]^+$ requires 238.1320).

*3-Benzylaminopropylamine hydrochloride (**11p**)*

Hydrochloride salt **11p** was prepared from **10p** in 80% yield as tannish orange powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 2.00-2.05 (m, 2H, H-2); 2.87-2.99 (m, 4H, H-1, H-3); 4.11 (t, 2H, J = 5.4 Hz, H-4); 7.40-7.59 (m, 5H, H-2', H-3', H-4', H-5', H-6', Ar); 8.16 (br s, 3H, N<u>H</u>$_2$, <u>H</u>Cl); 9.46 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 23.7 (C-2); 36.3 (C-1); 43.9 (C-3); 50.2 (C-4); 128.8 (C-2', C-6', Ar); 129.1 (C-4', Ar); 130.3 (C3', C-5', Ar); 132.0 (C-1', Ar). ES$^+$ HRMS, *m/z*: 165.1390 found (calculated for $C_{10}H_{17}N_2$ $[M+H]^+$ requires 165.1392).

*Standard procedure for the preparation of ethyl β-amino 2-(1H-benzimidazol-2-yl)acrylate **12(a-d)** by transamination from {3-[4-(3-aminopropyl)piperazin-1-yl]propyl}-arylamine hydrochloride **11(a-d)**.*

To a suspension of {3-[4-(3-aminopropyl)piperazin-1-yl]propyl}-arylamine hydrochloride **11(a-d)** (0.19 mmol., 1 equiv.) in 10 mL of dry CH_2Cl_2 under vigorous magnetic stirring (30 min. to 1 h, 500 rpm) was added dropwise a solution of *N,N*-di-*iso*-propylethylamine DIPEA (49 mg, 0.38 mmol., 2 equiv.) in 6 mL of CH_2Cl_2 over a period of 15-20 min. at room temperature. After stirring at 25 °C during 1-2 h, ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** (49 mg, 0.19 mmol., 1 equiv.) was added in one portion in the reaction mixture, then the resulting suspension was refluxed for 24 h. After cooling down to room temperature, the yellow or yellow-orange reaction mixture was concentrated under reduced pressure in a rotary evaporator. To the crude residue was added appropriate volume of cooled deionized water (4 °C), and then mixing or triturating was pursued until complete precipitation. The insoluble compound **12** was collected by filtration on a Büchner funnel (porosity N°4) and rinsed successively with deionized water (10-20 x 2 mL) and hexane (10-20 x 2 mL). *For more information's on work-up, see description for each product.* The desired product **12** was dried under high vacuum (10^{-2} Torr) during 1 h at 25 °C that gave a powder and was analyzed by ^1H, ^{13}C NMR and HRMS.

*Ethyl 3-[3-(4-{3-[(benzo[1,3]dioxol-5-ylmethyl)amino]propyl}piperazin-1-yl)propylamino]-2-(1H-benzimidazol-2-yl)acrylate (**12a**)*

Compound **12a** was synthesized in 93% yield as grey powder according to the standard procedure (precipitation in 2 mL of deionized water and after filtration, washing with (10 x 2 mL) of deionized water and (3 x 2 mL) of hexane). Mp = 90-92 °C. ^1H NMR (DMSO-d_6) δ: 1.28 (t, 3H, J = 6.9 Hz, $CH_2C\underline{H}_3$); 1.74-1.81 (m, 4H, H-2', H-7'); 2.33-2.73 (m, 12H, H-3', H-4', H-5', H-6'); 3.51 (m, 4H, H-1', H-8'); 3.84 (s, 2H, H-9'); 4.18-4.25 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$); 6.00 (s, 2H, $OC\underline{H}_2O$); 6.88-7.09 (m, 3H, H-2", H-5", H-6", Ar); 7.44-7.56 (m, 4H, H-4, H-5, H-6, H-7, Ar); 8.09-8.13 (d, 1H, J = 13.5 Hz, =C<u>H</u>); 10.80 (br s, 2H, NH); 11.78 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 26.2 (C-7'), 46.4 (C-8'); 52.6 (C-1'); 52.7 (C-4', C-5'); 53.6 (C-9'); 54.1 (C-3', C-6'); 59.0 ($\underline{C}H_2CH_3$); 85.4 (<u>C</u>=); 107.4 ($O\underline{C}H_2O$); 111.4 (C-2"); 116.5 (C-5"); 117.7 (C-4, C-7, Ar); 120.9 (C-5, C-6, Ar); 121.0 (C-6", Ar); 132.5 (C-1", Ar); 141.7 (C-3a, C-7a, Ar); 143.8 (C-4", Ar); 145.9 (C-3", Ar); 152.0 (C-2, Ar); 154.2 (C=<u>C</u>H); 166.7 (<u>C</u>=O, CO_2Et). ES^+ HRMS, *m/z*: 549.3188 found (calculated for $C_{30}H_{41}N_6O_4$ $[M+H]^+$ requires 549.3189).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-(3-{4-[3-(4-methoxybenzylamino)propyl]piperazin-1-yl}-propylamino)acrylate (**12b**)*

Compound **12b** was synthesized in 18% yield as grey powder according to the standard procedure (precipitation in 3 mL of deionized water and after filtration, washing with (10 x 2 mL) of deionized water and (10 x 2 mL) of hexane). Mp = 89-91 °C. ^1H NMR (DMSO-d_6) δ: 1.36 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 1.84-1.89 (m, 4H, H-2', H-7'); 2.41-2.52 (m, 12H, H-3', H-4', H-5', H-6'); 3.47-3.58 (m, 4H, H-1', H-8'); 3.78 (s, 2H, H-9'); 3.79 (s, 3H, $OC\underline{H}_3$); 4.24-4.31 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 6.82-6.89 (m, 2H, H-3", H-5", Ar); 7.15-7.18 (m, 2H, H-4, H-7, Ar); 7.29-7.40 (m, 2H, H-5, H-6, Ar); 7.56-7.58 (m, 2H, H-2", H-6", Ar); 8.02-8.06 (d, 1H, J = 11.6 Hz, =C<u>H</u>); 10.89 (br s, 1H, NH); 11.14 (br s, 1H, NH); 11.25 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.8 ($CH_2\underline{C}H_3$); 28.1 (C-2', C-7'); 47.4 (C-8'); 53.1 (C-1'); 53.3 (C-4', C-5'); 54.7 (C-9'); 54.7 (C-3', C-6'); 55.5 ($O\underline{C}H_3$); 59.8 ($\underline{C}H_2CH_3$); 86.5 (<u>C</u>=); 110.3 (C-4, C-7, Ar); 114.3 (C-3", C-5", Ar); 117.4 (C-5, C-6, Ar); 121.5 (C-2", Ar); 121.7 (C-6", Ar); 132.0 (C-1", Ar); 142.5 (C-3a, C-7a, Ar); 153.0 (C-2, Ar); 154.1 (=<u>C</u>H); 154.2 (C-4", Ar); 168.3 (<u>C</u>=O, CO_2Et). ES^+ HRMS, *m/z*: 535.3398 found (calculated for $C_{30}H_{43}N_6O_3$ $[M+H]^+$ requires 535.3397).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-(3-{4-[3-(4-methylbenzylamino)propyl]piperazin-1-yl}-propylamino)acrylate (**12c**)*

Compound **12c** was synthesized in 20% yield as grey powder according to the standard procedure (precipitation in 4 mL of deionized water and after filtration, washing with (20 x 2 mL) of deionized water and (20 x 2 mL) of hexane). Mp = 92-94 °C. ^1H NMR (DMSO-d_6) δ: 1.36 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$); 1.82-1.88 (m, 4H, H-2', H-7'); 2.33 (s, 3H, $C\underline{H}_3$); 2.44-2.79 (m, 12H, H-3', H-

5', H-6'); 3.52 (m, 4H, H-1', H-8'); 3.79 (s, 2H, H-9'); 4.24-4.31 (q, 2H, J = 6.9 Hz, C$\underline{H}_2$CH$_3$); 7.13-7.21 (m, 4H, H-4, H-5, H-6, H-7, Ar); 7.38-7.39 (d, 2H, J = 5.3 Hz, H-3", H-5", Ar); 7.56-7.58 (d, 2H, J = 5.6 Hz, H-2", H-6", Ar); 8.02-8.05 (d, 1H, J = 9.7 Hz, =C$\underline{H}$); 10.88 (br s, 1H, NH); 11.14 (br s, 1H, NH); 11.72 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.8 (CH$_2\underline{C}$H$_3$); 21.2 ($\underline{C}$H$_3$); 28.1 (C-2', C-7'); 47.3 (C-8'); 53.1 (C-1'); 53.3 (C-4', C-5'); 54.7 (C-3', C-6'); 59.8 ($\underline{C}$H$_2$CH$_3$); 86.4 ($\underline{C}$=); 110.3 (C-4, C-7, Ar); 117.3 (C-5, C-6, Ar); 121.5 (C-2", Ar); 121.6 (C-6", Ar); 128.4 (C-3", Ar); 129.4 (C-5", Ar); 131.9 (C-1", Ar); 132.5 (C-4", Ar); 142.4 (C-3a, C-7a, Ar); 153.0 (C-2, Ar); 154.2 (=$\underline{C}$H); 168.3 (C=O, CO$_2$Et). ES$^+$ HRMS, *m/z*: 519.3448 found (calculated for $C_{30}H_{43}N_6O_2$ $[M+H]^+$ requires 519.3447).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-(3-{4-[3-(4-chlorobenzylamino)propyl]piperazin-1-yl}-propylamino)acrylate (**12d**)*

Compound **12d** was synthesized in 91% yield as grey powder according to the standard procedure (using precipitation in 2 mL of deionized water and after filtration, washing with (10 x 2 mL) of deionized water and (10 x 2 mL) of hexane). Mp = 83-85 °C. ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, 3H, J = 7.0 Hz, CH$_2$C$\underline{H}_3$); 1.72-1.80 (m, 4H, H-2', H-7'); 2.39-2.41 (m, 12H, H-3', H-4', H-5', H-6'); 2.83-2.87 (m, 4H, H-1', H-8'); 4.04 (s, 2H, H-9'); 4.19-4.26 (q, 2H, J = 7.2 Hz, C$\underline{H}_2$CH$_3$); 7.07-7.10 (m, 4H, H-2", H-3", H-5", H-6", Ar); 7.44␣7.70 (m, 4H, H-4, H-5, H-6, H-7, Ar); 8.09-8.13 (d, 1H, J = 11.2 Hz, =C$\underline{H}$); 10.80 (br s, 2H, 2xNH); 11.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 (CH$_2\underline{C}$H$_3$); 23.8 (C-7'); 27.3 (C-2'); 46.5 (C-8'); 52.6 (C-1'); 52.7 (C-4', C-5'); 54.2 (C-9'); 55.5 (C-3', C-6'); 59.1 ($\underline{C}$H$_2$CH$_3$); 85.5 ($\underline{C}$=); 111.5 (C-4, Ar); 116.6 (C-7, Ar); 121.1 (C-5, C-6, Ar); 128.6 (C-3", C-5", Ar); 131.1 (C-2", C-6"); 132.6 (C-4", Ar); 132.8 (C-1", Ar); 141.8 (C-3a, C-7a, Ar); 152.1 (C-2, Ar); 154.3 (=$\underline{C}$H); 166.8 (C=O, CO$_2$Et). ES$^+$ HRMS, *m/z*: 539.2902 found (calculated for $C_{29}H_{40}N_6O_2{}^{35}Cl$ $[M+H]^+$ requires 539.2901).

*Standard procedure for the preparation of ethyl β-amino 2-(1H-benzimidazol-2-yl)acrylate **12(e-p)** by transamination from 3-(arylmethylamino)propylamine hydrochloride **11(e-p)**.*

To a suspension of 3-(arylmethylamino)propylamine hydrochloride **11(a-d)** (0.2 mmol., 1 equiv.) in 10 mL of dry CH_2Cl_2 under vigorous magnetic stirring (30 min. to 1 hour, 500 rpm) was added dropwise a solution of *N,N*-di-*iso*-propylethylamine DIPEA (28 mg, 0.22 mmol., 1.075 equiv.) in 6 mL of CH_2Cl_2 over a period of 15-20 min. at room temperature. After stirring at 25 °C during 1-2 h, ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** (52 mg, 0.2 mmol., 1 equiv.) was added in one portion in the reaction mixture, then the resulting suspension was refluxed for 24-48 h. After cooling down to room temperature, the yellow or yellow-orange reaction mixture was concentrated under reduced pressure in a rotary evaporator. To the crude residue was added appropriate volume of specified solvent to produce precipitation and triturating was pursued until complete precipitation. The insoluble compound **12** was collected by filtration on a Büchner funnel (porosity N°4) and rinsed with appropriate solvent (5-30 x 1 mL) or recrystallized. *For more information's on work-up, see description for each product.* The desired product **12** was dried under high vacuum (10^{-2} Torr) during 2-3 h at 40 °C that gave a powder and was analyzed by ^{1}H, ^{13}C NMR and HRMS.

*Ethyl {3-[(benzo[1,3]dioxol-5-ylmethyl)amino]propylamino}-2-(1H-benzimidazol-2-yl)acrylate (**12e**)*

Compound **12e** was synthesized in 42% yield as yellow powder according to the standard procedure (precipitation in 3.5 mL of acetone under reflux for 1 hour; mixing in 2 mL of Et_2O during 5.5 h at 500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12e** was rinsed with 10 x 1 mL of Et_2O). Mp = 206-208 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, CH$_2$C$\underline{H}_3$); 1.98-2.03 (m, 2H, H-2'); 2.91-2.96 (m, 2H, H-3'); 3.60 (t, 2H, J = 6.4 Hz, H-1'); 4.06 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.0 Hz, C$\underline{H}_2$CH$_3$); 6.02 (s, 2H, OC$\underline{H}_2$O); 6.91-6.93 (d, 1H, J = 7.9 Hz, H-5", Ar); 6.99-7.03 (dd, 1H, J = 1.4, 8.0 Hz, H-6", Ar); 7.07-7.13 (m, 2H, H-5, H-6, Ar); 7.17 (d, 1H, J = 1.3 Hz, H-2", Ar); 7.48-7.57 (m, 2H, H-4, H-7, Ar); 8.12 (s, 1H, =C$\underline{H}$); 9.15 (br s, 1H, NH); 10.80 (br s, 1H, NH); 11.81 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.6 (CH$_2\underline{C}$H$_3$); 27.4 (C-2'); 43.5 (C-3');

45.7 (C-1'); 49.7 (C-4'); 59.1 ($CH_2\underline{C}H_3$); 86.1 (<u>C</u>=); 101.3 (OCH_2O); 108.3 (C-2", Ar); 110.3 (C5", Ar); 121.0 (C-4, C-7, Ar); 124.1 (C-6", Ar); 125.6 (C-5, C-6, Ar); 132.6 (C-1", Ar); 141.6 (C-3a, C-7a, Ar); 147.3 (C-4", Ar); 147.7 (C-3", Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 166.6 (<u>C</u>=O, CO_2Et). ES^+ HRMS, *m/z*: 423.2036 found (calculated for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ requires 423.2032).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(4-methoxybenzylamino)propylamino]acrylate (**12f**)*

Compound **12f** was synthesized in 38% yield as tannish yellow-orange powder according to the standard procedure (precipitation in 4 mL of acetone under reflux during 6 h with mixing (500 rpm); and after filtration on a Büchner funnel, the insoluble compound **12f** was rinsed with 8 x 1 mL of acetone). Mp = 183-185 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 1.96-2.01 (m, 2H, H-2'); 2.92-2.97 (m, 2H, H-3'); 3.61 (t, 2H, J = 6.7 Hz, H-1'); 3.73 (s, 3H, $OC\underline{H}_3$); 4.09 (s, 2H, H-4'); 4.28 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 6.93-6.96 (d, 2H, J = 8.7 Hz, H-3", H-5", Ar); 7.09-7.12 (dd, 2H, J = 3.1, 5.9 Hz, H-5, H-6, Ar); 7.42-7.45 (d, 2H, J = 8.6 Hz, H-2", H-6", Ar); 7.45-7.58 (m, 2H, H-4, H-7, Ar); 8.11 (s, 1H, =C<u>H</u>); 8.85 (br s, 1H, NH); 10.80 (br s, 1H, NH); 11.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.4 (C-2'); 43.5 (C-3'); 49.3 (C-4); 55.2 ($O\underline{C}H_3$); 59.2 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 111.5 (C-4, C-7, Ar); 114.0 (C-3", C-5", Ar); 121.1 (C-1", Ar); 123.9 (C-5, C-6, Ar); 131.6 (C-2", C-6", Ar); 142.3 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 159.7 (C-4", Ar); 166.6 (<u>C</u>=O, CO_2Et). ES^+ HRMS, *m/z*: 409.2236 found (calculated for $C_{23}H_{29}N_4O_3$ $[M+H]^+$ requires 409.2234).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(3-methoxybenzylamino)propylamino]acrylate (**12g**)*

Compound **12g** was synthesized in 34% yield as tannish orange powder according to the standard procedure (precipitation in 3 mL of AcOEt, then reflux in AcOEt (10 mL) for 4 h under mixing at 500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12g** was rinsed with 8 x 1 mL of AcOEt). Mp = 150-152 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$); 1.99-2.04 (m, 2H, H-2'); 2.98 (m, 2H, H-3'); 3.61 (m, 2H, J = 6.6 Hz, H-1'); 4.14 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$); 6.95-6.98 (dd, 1H, J = 1.9, 8.3 Hz, H-4", Ar); 7.08-7.11 (m, 2H, H-5, H-6, Ar); 7.19 (s, 1H, H-2", Ar); 7.32 (t, 1H, J = 7.8 Hz, H-5", Ar); 7.50-7.56 (d, 2H, J = 18.9 Hz, H-4, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 8.48 (d, 1H, J = 4.5 Hz, H-6", Ar); 9.19 (br s, 1H, NH); 10.81 (br s, 1H, NH); 11.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.4 (C-2", Ar); 43.9 (C-3'); 45.7 (C-1'); 49.9 (C-4'); 55.2 ($O\underline{C}H_3$); 59.2 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 114.5 (C-4", Ar); 115.5 (C-2"); 121.1 (C-4, C-7, Ar); 122.1 (C-6", Ar); 129.8 (C-5, C-6, Ar); 132.6 (C-5", Ar); 141.7 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 159.4 (C-3", Ar); 166.6 (<u>C</u>=O, CO_2Et). ES^+ HRMS, *m/z*: 409.2244 found (calculated for $C_{23}H_{29}N_4O_3$ $[M+H]^+$ requires 409.2240).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(3,5-dimethoxybenzylamino)propylamino]acrylate (**12h**)*

Compound **12h** was synthesized in 10% yield as tannish yellow powder according to the standard procedure (precipitation in a mixture of Et_2O-acetone 1:2 v/v at 0 °C followed by mixing (500 rpm) for 6 h at 0 °C; and after filtration on a Büchner funnel, the insoluble compound **12h** was rinsed with 3 x 1 mL of acetone). Mp = 166-168 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$); 2.00-2.04 (m, 2H, H-2'); 2.96-3.00 (m, 2H, H-3'); 3.61 (t, 2H, J = 6.5 Hz, H-1'); 3.74 (s, 6H, $(OC\underline{H}_3)_2$); 4.09 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 6.52 (t, 1H, J = 2.2 Hz, H-4", Ar); 6.75-6.76 (d, 2H, J = 2.2 Hz, H-2", H-6", Ar); 7.07-7.13 (m, 2H, H-5, H-6, Ar); 7.50-7.55 (d, 2H, J = 15.7 Hz, H-4, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 9.17 (br s, 1H, NH); 10.79 (br s, 1H, NH); 11.80 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.4 (C-2'); 44.0 (C-3'); 45.7 (C-1'); 50.0 (C-4'); 55.4 ($O\underline{C}H_3$); 59.2 ($\underline{C}H_2CH_3$); 86.2 (<u>C</u>=); 100.5 (C-4", Ar); 107.8 (C-2", C-6", Ar); 121.1 (C-4, C-7, Ar); 129.8 (C-5, C-6, Ar); 134.1 (C-1", Ar); 143.9 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 160.6 (C-3", C-5", Ar); 166.6 (C=O, CO_2Et). ES^+ HRMS, *m/z*: 439.2343 found (calculated for $C_{24}H_{31}N_4O_4$ $[M+H]^+$ requires 439.2340).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(3,4,5-trimethoxybenzylamino)propylamino]acrylate (**12i**)*

Compound **12i** was synthesized in 15% yield as tannish yellow powder according to the standard procedure (precipitation in 2 mL of acetone, then reflux in acetone (6 mL) for 13 h under mixing at

500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12i** was rinsed with 7 x 1 mL of acetone). Mp = 191-193 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 1.96-2.05 (m, 2H, H-2'); 2.98 (t, 2H, J = 8.1 Hz, H-3'); 3.60-3.62 (m, 2H, H-1'); 3.64 (s, 3H, $OC\underline{H}_3$); 3.78 (s, 6H, 2 x $OC\underline{H}_3$); 4.08 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 6.89 (s, 2H, H-2", H-6", Ar); 7.07-7.13 (m, 2H, H-5, H-6, Ar); 7.47-7.58 (m, 2H, H-4, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 8.97 (br s, 1H, NH); 10.78 (br s, 1H, NH); 11.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.5 (C-2'); 43.9 (C-3'); 45.7 (C-1'); 50.3 (C-4'); 56.0 (2 x $O\underline{C}H_3$); 59.2 ($O\underline{C}H_3$); 60.0 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 107.4 (C-2", C-6", Ar); 111.5 (C-4, C-7, Ar); 121.0 (C-5, C-6, Ar); 127.6 (C-1", Ar); 141.6 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 152.9 (C-3", C-5", Ar); 153.9 (=<u>C</u>H); 166.6 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 469.2450 found (calculated for $C_{25}H_{33}N_4O_5$ $[M+H]^+$ requires 469.2451).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(4-methylbenzylamino)propylamino]acrylate (**12j**)*

Compound **12j** was synthesized in 48% yield as white powder according to the standard procedure (precipitation in 4 mL of acetone, then reflux for 1 h under mixing at 500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12j** was rinsed with 10 x 1 mL of acetone). Mp = 206-208 °C. ^{1}H NMR (DMSO-d_6) δ: 1.36 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 2.21 (s, 3H, $C\underline{H}_3$); 2.27 (t, 2H, J = 7.6 Hz, H-2'); 2.87-2.92 (m, 2H, H-3'); 3.51(t, 2H, J = 6.7 Hz, H-1'); 3.96 (s, 2H, H-4'); 4.23-4.30 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 7.09-7.10 (d, 2H, J = 7.9 Hz, H-2", H-6", Ar); 7.13-7.19 (m, 2H, H-4, H-7, Ar); 7.38-7.40 (d, 2H, J = 8 Hz, H-5, H-6, Ar); 7.51-7.55 (br s, 2H, 2 x NH); 7.94 (s, 1H, =C<u>H</u>); 11.08 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 20.9 ($\underline{C}H_3$); 27.4 (C-2'); 43.6 (C-3'); 45.8 (C-1'); 49.6 (C-4'); 59.2 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 111.6 (C-4, C-7, Ar); 116.7 (C-5, C-6, Ar); 121.1 (C-13, Ar); 129.0 (C-2", Ar); 129.2 (C-6", Ar); 130.1 (C-3", Ar); 132.6 (C-5", Ar); 138.4 (C-4", Ar); 141.7 (C-3a, C-7a, Ar); 151.9 (C-2, Ar); 154.0 (=<u>C</u>H); 166.7 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 393.2289 found (calculated for $C_{23}H_{29}N_4O_2$ $[M+H]^+$ requires 393.2290).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(4-chlorobenzylamino)propylamino]acrylate (**12k**)*

Compound **12k** was synthesized in 36% yield as orange powder according to the standard procedure (precipitation in 2 mL of acetone, and after filtration on a Büchner funnel, the insoluble compound **12k** was rinsed with 10 x 1 mL of acetone). Mp = 178-180 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 2.00-2.05 (m, 2H, H-2'); 2.94-2.96 (m, 2H, H-3'); 3.61 (t, 2H, J = 6.7 Hz, H-1'); 4.15 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 7.07-7.13 (m, 2H, H-5, H-6, Ar); 7.46-7.61 (m, 6H, H-2", H-3", H-5", H-6", H-4, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 9.27 (br s, 1H, NH); 10.79 (br s, 1H, NH); 11.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.6 ($\underline{C}H_2CH_3$); 27.5 (C-2'); 43.9 (C-3'); 45.7 (C-1'); 49.2 (C-4'); 59.1 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 121.0 (C-4, C-5, C-6, C-7, Ar); 128.6 (C-3", C-5", Ar); 131.3 (C-4", Ar); 132.0 (C-2", C-6", Ar); 133.6 (C-1", Ar); 141.7 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.8 (=<u>C</u>H); 166.6 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 413.1742 found (calculated for $C_{22}H_{26}N_4O_2{}^{35}Cl$ $[M+H]^+$ requires 413.1744).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(2-chlorobenzylamino)propylamino]acrylate (**12l**)*

Compound **12l** was synthesized in 45% yield as tannish orange powder according to the standard procedure (precipitation in 2 mL of acetone, then reflux in acetone (6 mL) for 1 hour under mixing at 500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12l** was rinsed with 6 x 1 mL of acetone). Mp = 206-208 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 2.03-2.05 (m, 2H, H-2'); 3.03-3.08 (m, 2H, H-3'); 3.63 (t, 2H, J = 6.6 Hz, H-1'); 4.20-4.25 (m, 2H, $C\underline{H}_2CH_3$); 4.28 (s, 2H, H-4'); 7.07-7.12 (m, 2H, H-5, H-6, Ar); 7.38-7.77 (m, 6H, H-3", H-4", H-5", H-6", H-4, H-7, Ar); 8.13 (s, 1H, =C<u>H</u>); 9.42 (br s, 1H, NH); 10.81 (br s, 1H, NH); 11.83 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.5 (C-2'); 44.5 (C-3'); 45.7 (C-1'); 47.2 (C-4'); 59.2 ($CH_2\underline{C}H_3$); 86.1 (<u>C</u>=); 121.1 (C-4, C-5, C-6, C-7, Ar); 127.6 (C-5", Ar); 129.7 (C-4", Ar); 130.2 (C-3", Ar); 130.9 (C-6", Ar); 132.0 (C-2", Ar); 133.6 (C-1", Ar); 141.8 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 166.6 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 413.1747 found (calculated for $C_{22}H_{26}N_4O_2{}^{35}Cl$ $[M+H]^+$ requires 413.1744).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-[3-(4-cyanobenzylamino)propylamino]acrylate (**12m**)*

Compound **12m** was synthesized in 31% yield as tannish yellow-orange powder according to the standard procedure (precipitation in a mixture of 2 mL of acetone and 2 mL of Et_2O at 0 °C followed by mixing (500 rpm) for 4 h at 0 °C; and after filtration on a Büchner funnel, the insoluble compound **12m** was rinsed with 6 x 1 mL of acetone). Mp = 186-188 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$); 2.01-2.06 (m, 2H, H-2'); 2.98-3.02 (m, 2H, H-3'); 3.62 (t, 2H, J = 6.2 Hz, H-1'); 4.21-4.25 (m, 2H, $C\underline{H}_2CH_3$); 4.27 (s, 2H, H-4'); 7.09-7.65 (m, 4H, H-4, H-5, H-6, H-7, Ar); 7.76-7.92 (m, 4H, H-2", H-3", H-5", H-6", Ar); 8.12 (s, 1H, =C<u>H</u>); 9.45 (br s, 1H, NH); 10.73 (br s, 1H, NH); 11.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.4 (C-2'); 44.2 (C-3'); 45.7 (C-1'); 49.3 (C-4'); 59.2 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 111.6 (C-4", Ar); 118.5 (<u>C</u>N); 121.1 (C-4, C-5, C-6, C-7, Ar); 130.9 (C-2", C-6", Ar); 132.5 (C-3", C-5", Ar); 137.6 (C-1", Ar); 143.8 (C-3a, C-7a, Ar); 151.8 (C-2, Ar); 153.9 (=<u>C</u>H); 166.6 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 426.1911 found (calculated for $C_{23}H_{25}N_5O_2Na$ $[M+Na]^+$ requires 426.1906).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-{3-[(pyridin-4-yl)methylamino]propylamino}acrylate (**12n**)*

Compound **12n** was synthesized in 12% yield as tannish yellow powder according to the standard procedure (precipitation in a mixture of 2 mL of Et_2O and 1 mL of EtOH at 0 °C; and after filtration on a Büchner funnel, the insoluble compound **12m** was rinsed with 5 x 1 mL of EtOH). Mp = 236-238 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 1.85-1.95 (m, 2H, H-2'); 2.01-2.06 (m, 2H, H-3'); 2.88 (t, 2H, J = 7.2 Hz, H-1'); 4.17 (s, 2H, H-4'); 4.21-4.25 (m, 2H, $C\underline{H}_2CH_3$); 7.09-7.62 (m, 4H, H-4, H-5, H-6, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 8.59-8.64 (m, 4H, H-2", H-3", H-5", H-6", Ar); 9.70 (br s, 1H, NH); 11.71 (br s, 1H, NH); 13.35 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.6 ($CH_2\underline{C}H_3$); 25.1 (C-2'); 36.1 (C-3'); 44.0 (C-1'); 48.8 (C-4'); 57.9 ($\underline{C}H_2CH_3$); 86.2 (<u>C</u>=); 121.1 (C-4, C-7, Ar); 124.4 (C-5, C-6, Ar); 124.5 (C-3",C-5", Ar); 140.8 (C-3a, C-7a, Ar); 141.0 (C-4", Ar); 149.9 (C-2", C-6", Ar); 150.3 (C-2, Ar); 153.9 (=<u>C</u>H); 166.6 (<u>C</u>=O, C O_2Et). ES$^+$ HRMS, *m/z*: 380.2088 found (calculated for $C_{21}H_{26}N_5O_2$ $[M+H]^+$ requires 380.2086).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-{3-[(quinolin-8-yl)methylamino]propylamino}acrylate (**12o**)*

Compound **12o** was synthesized in 63% yield as brownish powder according to the standard procedure (precipitation in 2 mL of deionized water at 0 °C; and after filtration on a Büchner funnel, the insoluble compound **12o** was rinsed with 30 x 1 mL of deionized water). Mp = 112-114 °C. ^{1}H NMR (DMSO-d_6) δ: 1.28 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$); 1.91-1.95 (m, 2H, H-2'); 2.89 (t, 2H, J = 5.4 Hz, H-3'); 3.61 (t, 2H, J = 6.8 Hz, H-1'); 4.19-4.26 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$); 4.55 (s, 2H, H-4'); 7.07-7.10 (m, 2H, H-5, H-6, Ar); 7.44-7.98 (m, 6H, H-2", H-3", H-4", H-5", H-6", 7", Ar); 8.11 (s, 1H, =C<u>H</u>); 8.40-8.97 (m, 2H, H-4, H-7, Ar); 9.17 (br s, 1H, NH); 10.91 (br s, 1H, NH); 11.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.6 ($CH_2\underline{C}H_3$); 28.9 (C-2'); 45.05 (C-3'); 46.2 (C-1'); 47.9 (C-4'); 59.1 ($\underline{C}H_2CH_3$); 85.9 (<u>C</u>=); 111.4 (C-4, C-7, Ar); 116.7 (C-5, C-6, Ar); 121.1 (C-3", Ar); 121.8 (C-5", Ar); 126.3 (C-6", Ar); 128.0 (C-4a", Ar); 128.4 (C-7", Ar); 136.8 (C)-8", Ar); 141.7 (C-3a, C-7a, Ar); 145.5 (C-8a", Ar); 150.2 (C-2, Ar); 151.9 (=<u>C</u>H); 154.0 (C-2", Ar); 166.7 (<u>C</u>=O, CO_2Et). ES$^+$ HRMS, *m/z*: 430.2246 found (calculated for $C_{25}H_{28}N_5O_2$ $[M+H]^+$ requires 430.2246).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-(3-benzylaminopropylamino)acrylate (**12p**)*

Compound **12p** was synthesized in 61% yield as tannish yellow powder according to the standard procedure (precipitation in 2 mL of acetone, then reflux in acetone for 1 hour under mixing at 500 rpm, and after filtration on a Büchner funnel, the insoluble compound **12p** was rinsed with 10 x 1 mL of acetone). Mp = 234-236°C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$); 2.00-2.05 (m, 2H, H-2'); 2.96-3.01 (m, 2H, H-3'); 3.62 (t, 2H, J = 6.5 Hz, H-1'); 4.17 (s, 2H, H-4'); 4.21-4.28 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$); 7.07-7.13 (m, 2H, H-2", H-6", Ar); 7.32-7.63 (m, 7H, H-3", H-4", H-5", H-4, H-5, H-6, H-7, Ar); 8.12 (s, 1H, =C<u>H</u>); 9.23 (br s, 1H, NH); 10.80 (br s, 1H, NH); 11.81 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.7 ($CH_2\underline{C}H_3$); 27.4 (C-2'); 43.8 (C-3'); 45.7 (C-1'); 49.9 (C-4'); 59.1 ($\underline{C}H_2CH_3$); 86.1 (<u>C</u>=); 111.5 (C-4, Ar); 116.7 (C-7, Ar); 121.0 (C-5, C-6, Ar); 128.6 (C-2", C-6", Ar); 128.9 (C-4", Ar); 130.1 (C-3", C-5", Ar); 132.1 (C-1", Ar); 141.6 (C-3a, C-

7a, Ar); 151.8 (C-2, Ar); 153.9 (=CH); 166.6 (C=O, CO_2Et). ES^+ HRMS, *m/z*: 379.2130 found (calculated for $C_{22}H_{27}N_4O_2$ $[M+H]^+$ requires 379.2128).

*Ethyl 2-(1H-benzimidazol-2-yl)-3-(3-tert-butyloxycarbonylaminopropylamino)acrylate (**13**)*

To a solution of *tert*-butyl (3-aminopropyl)carbamate **7b** (0.11 g, 0.63 mmol., 1 equiv.) in dry methylene chloride (8 mL) was added in one portion ethyl 3-dimethylamino-2-(1*H*-benzimidazol-2-yl)acrylate **5** (0.1633 g, 0.63 mmol., 1 equiv.). Then the resulting reaction mixture was refluxed under vigorous magnetic stirring for 48 h. After cooling down to room temperature, the reaction mixture was concentrated under reduced pressure in a rotary evaporator. The crude residue was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of alumina gel Puriflash Interchim (5 g, 32-63 μm, P_{max} 22 bar) using a stepwise gradient of cyclohexane/AcOEt eluent from 99:1 to 90:10. Pooling and evaporation of solvents in *vacuo* gave the expected compound **13** which, was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. White needles. Yield = 61%. ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 3H, *J* = 7.1 Hz, CH_2CH_3); 1.44 (s, 9H, **(**$CH_3)_3CO$); 1.90-1.95 (m, 2H, H-2'); 3.26-3.29 (m, 2H, H-1'); 3.49-3.52 (m, 2H, H-3'); 4.29 (q, 2H, *J* = 7.1 Hz, CH_2CH_3); 7.16-7.62 (m, 4H, H-4, H-5, H-6, H-7, Ar); 8.00-8.04 (d, 1H, *J* = 12.5 Hz, =CH); 10.93 (br s, 1H, NH); 11.03 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 14.8 (CH_2CH_3); 28.5 (($CH_3)_3CO$); 29.6 (C-2'); 30.9 (C-3'); 31.9 (C-1'); 47.2 (CH_2CH_3); 79.6 (($CH_3)_3CO$); 82.2 (C=); 110.4 (C-4, C-7); 117.5 (C-5, C-6); 133.7 (C-3a, C-7a); 153.8 (C-2); 156.4 (=CH); 157.8 ($NHCO_2(CH_3)_3$); 168.3 (CO_2Et).

*Ethyl 3-(3-aminopropylamino)-2-(1H-benzimidazol-2-yl)acrylate hydrochloride (**14**)*

Ethyl 2-(1*H*-benzimidazol-2-yl)-3-(3-*tert*-butyloxycarbonylaminopropylamino)acrylate **13** (0.1056 g, 0.27 mmol., 1 equiv.) was solubilized in 2 mL of dry 1,4-dioxane at 25 °C under vigorous stirring (550 rpm) during 20 min. Then a solution of 6M HCl (2 mL) was added dropwise for 30 min. in the homogeneous solution. The resulting mixture was stirred at 500 rpm during 4 h at 25 °C. and was concentrated in a rotary evaporator under reduced pressure for elimination of volatile compounds. To the crude reaction mixture was added 2 mL of anhydrous Et_2O and after triturating, the insoluble salt **14** was collected by filtration on a Büchner funnel (porosity N°4) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 4 h and gave the desired compound **14** in 72% yield as white powder. ^{1}H NMR (D_2O) δ: 1.37 (t, 3H, *J* = 7.1 Hz, CH_2CH_3); 2.04-2.14 (m, 2H, H-2'); 3.08-3.13 (m, 2H, H-3'); 3.62 (t, 2H, *J* = 6.9 Hz, H-1'); 4.38-4.45 (q, 2H, *J* = 6.9 Hz, CH_2CH_3); 7.38-7.41 (m, 2H, H-5, H-6, Ar); 7.52-7.55 (m, 2H, H-4, H-7, Ar); 8.00 (s, 1H, =CH). ^{13}C NMR (D_2O) δ: 13.8 (CH_2CH_3); 27.9 (C-2'); 30.2 (C-3'); 36.7 (C-1'); 47.2 (CH_2CH_3); 82.3 (C=); 112.3 (C-4, C-7); 124.9 (C-5, C-6); 130.0 (C-3a, C-7a); 149.3 (C-2); 157.0 (=CH); 166.79 (CO_2Et).

*Ethyl 3-{3-[(benzo[1,3]dioxol-5-ylmethylene)amino]propylamino}-2-(1H-benzimidazol-2-yl)acrylate (**15**)*

In a 10 mL glass tube (for microwave synthesis) were placed successively ethyl 3-(3-aminopropylamino)-2-(1*H*-benzimidazol-2-yl)acrylate hydrochloride **14** (14.2 mg, 0.044 mmol., 1 equiv.), *N,N*-di-*iso*-propylethylamine DIPEA (8 μL, 6.1 mg, 0.0473 mmol., 1.075 equiv.), 3,4-(methylenedioxy)benzaldehyde **8a** (6.6 mg, 0.044 mmol., 1 equiv.) and 1 mL of dry methanol. The glass tube was sealed with a snap cap and introduced in the microwave cavity of Monowave® 300 Anton Paar reactor (P = 800 Watt). The reaction mixture was irradiated during 45 min. at 90 °C under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and volatile compounds were eliminated in a rotary evaporator under reduced pressure. The desired aldimine **15** as yellowish viscous oil was dried under high vacuum (10^{-2} Torr) at 25°C for 20 min. and further used without purification. Yield = 84%. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, CH_2CH_3); 1.44-1.59 (m, 2H, H-2'); 3.09 (m, 2H, H-3'); 3.67 (m, 2H, H-1'); 4.39-4.46 (q, 2H, *J* = 6.9 Hz, CH_2CH_3); 6.08 (s, 2H, OCH_2O); 6.92-6.95 (d, 1H, *J* = 7.9 Hz, H-5'', Ar); 7.34 (d, 1H, *J* = 1.5 Hz, H-2'', Ar); 7.40- 7.43 (dd, 1H, *J* = 1.5, 7.9 Hz, H-6'', Ar); 7.61 (s, 1H, =CH); 7.86 (br s, 1H, NH); 9.82 (s, 1H, H-4'); 11.19 (br s, 1H, NH).

*Preparation of ethyl {3-[(benzo[1,3]dioxol-5-ylmethyl)amino]propylamino}-2-(1H-benzimidazol-2-yl)acrylate (**12e**) by reduction of ethyl 3-{3-[(benzo[1,3]dioxol-5-ylmethylene)amino]propylamino}-2-(1H-benzimidazol-2-yl)acrylate (**15**)*

Ethyl 3-{3-[(benzo[1,3]dioxol-5-ylmethylene)amino]propylamino}-2-(1*H*-benzimidazol-2-yl)acrylate **15** (24.9 mg, 0.06 mmol., 1 equiv.) was solubilized in methanol (6-8 mL) under vigorous stirring (500 rpm) and cooled at 0 °C. To this solution was added by small portions commercial $NaBH_4$ (11.3 mg, 0.3 mmol, 5 equiv.) over a period of 20 minutes. The resulting suspension was stirred at 50 °C for 24 h. After cooling down to room temperature, volatile compounds were eliminated under reduced pressure with a rotary evaporator. To the crude residue was added 5 mL of deionized water and the resulting mixture was transferred into a separating funnel. Extraction was conducted with CH_2Cl_2 (3 x 3 mL) and the combined organic phases were dried over magnesium sulphate $MgSO_4$, filtered on filter paper and solvent was eliminated *in vacuo*. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h. The desired compound **12e** was obtained as yellowish viscous oil and crystallized on standing. **12e** was analyzed by ^{1}H, ^{13}C NMR. Yield = 51%.

Biology section

Cell culture and survival assays. Skin diploid fibroblastic cells were provided by BIOPREDIC International Company (Rennes, France). Caco2 (differentiated colorectal adenocarcinoma, Ref ECACC: 86010202), Huh-7D12 (differential hepatocellular carcinoma, Ref ECACC: 01042712), MDA-MB-231 (breast carcinoma, Ref ECACC: 92020424), HCT-116 (actively proliferating colorectal adenocarcinoma, Ref ECACC: 91091005), PC3 (prostate carcinoma, Ref ECACC: 90112714), NCI-H727 (lung carcinoma, Ref ECACC: 94060303) cell lines were obtained from the ECACC collection and HaCaT (keratinocyte from Cell Lines Service, Eppelheim, Germany). Cells were grown according to ECACC recommendations [24]. The toxicity test of the compounds on these cells was as follows: 2 x 10^3 cells for HCT-116 cells or 4 x 10^3 for the other cells were seeded in 96 multiwell plates in triplicate and left for 24 h for attachment, spreading and growing. Then, cells were exposed for 48 h to increasing concentrations of the compounds, ranging from 0.1 to 25 mM in a final volume of 120 mL of culture medium. Cells were fixed in cooled solution of EtOH/AcOH 90:5 v/v, nuclei were stained with Hoechst 3342 (Sigma) and counted using automated imaging analysis (Cellomics Arrayscan VTI/HCS Reader, Thermo/Scientific). The IC_{50} were graphically determined.

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Conflicts of Interest:

The authors declare no conflict of interest.

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