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Modulation of the spacer in *N,N*-bis(alkanol)amine aryl ester heterodimers led to the discovery of a series of high potent P-glycoprotein-based multidrug-resistance (MDR) modulators

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Abstract

In this study, a new series of *N,N*-bis(alkanol)amine aryl ester heterodimers was synthesized and studied. The new compounds were designed on the basis of the structures of our previous arylamine ester derivatives endowed with high P-gp-dependent multidrug resistance reversing activity on a multidrug-resistant leukemia cell line. All new compounds were active in the pirarubicin uptake assay on the doxorubicin–resistant erythroleukemia K562 cells (K562/DOX). In particular, compounds bearing a linker made up of 10 methylenes showed unprecedented high reversal activities regardless of the combination of aromatic moieties. Docking results obtained by an *in silico* study supported the data obtained by the biological tests. Finally, a study devoted to establish the chemical stability in phosphate buffer solution (PBS) and human plasma of these compounds was planned, since the new derivatives contain two ester groups. Only a few compounds exhibited a significant degradation in the human plasma matrix. In conclusion, we have identified a new very powerful series of compounds. Three of them, **17**, **20** and **23**, appeared the most promising compounds and could represent interesting leads for the development of new potent and efficacious P-gp-dependent MDR modulators.

Keywords

P-gp modulators; MDR reversers; doxorubicin-resistant human erythroleukemia K562 cells (K562/DOX); pirarubicin uptake; molecular docking, human plasma stability.

List of Abbreviations

P-gp, P-glycoprotein; DOX, Doxorubicin; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimmide hydrochloride; DMAP, 4-dimethylaminopyridine; TPSA, topological polar surface area; PDB, Protein Data Bank; PBS, phosphate buffer solution; KEE, ketoprofene ethylester.

1. Introduction

The resistance of cancer cells to cytotoxic drugs is a significant limitation to successful chemotherapy. In particular, multidrug resistance (MDR) is a type of acquired drug resistance to multiple classes of structurally and mechanistically unrelated anticancer drugs [1].

MDR is a complex phenomenon which can derive from different biochemical mechanisms. In the case of the so called classical MDR, cells accumulate a lower intracellular concentration of drug as a result of an accelerated efflux of the antitumor agents mediated by an ATP-dependent process. The main mechanism responsible of this transport is the overexpression of integral membrane transporters such as P-glycoprotein (P-gp, ABCB1), belonging to the ABC (ATP Binding Cassette) protein family [2].

P-gp is a membrane glycoprotein present, beside cancer cells, in several important tissues and blood-tissue barriers, where it regulates some important physiological processes such as the secretion of lipophilic molecules and the extrusion of exogenous agents [3, 4]. Unfortunately, this efflux protein is overexpressed in cancer cells as a result of the upregulation of the human MDR1 gene expression and it extrudes the chemotherapeutic drug from the cells, lowering its concentration below that necessary for anticancer action. [5,6].

Since its discovery and the elucidation of the mechanism of action, P-gp has been considered a suitable target for circumventing transporter-dependent MDR. MDR reversers (chemosensitizers) are P-gp modulators that administered in combination with cytotoxic agents, which are substrates of the efflux pump, could restore their efficacy in resistant cancer cells [7,8].

Verapamil was the first compound showing P-gp modulating activity and, together with many other molecules, belongs to the first generation of P-gp modulators. However, the toxicity of this first series of compounds prevented their clinical use and, at present, verapamil is only used as gold standard in biological assays. Since then, many P-gp modulators, belonging to three generations of compounds have been identified [9,10]. Several of them have reached pre-clinical or clinical trials [11,12], but none of these compounds has been approved for therapy, because of their low potency, toxicity and inhibitory effect on isoforms of cytochrome [13], although some of the latest MDR reversing compounds show a safer profile.

The failure of pre-clinical and clinical investigational studies led to considerable pessimism regarding the validity of such therapeutic approach to overcome MDR [14]. Nevertheless, the search for new, safer, more potent and efficacious multidrug transporter modulators is still of interest. In fact, MDR occurs also in brain disorders such as epilepsy, depression, and schizophrenia: in these diseases, about 20-40 % of the patients develop resistance to current therapeutic drugs [15]. Another field of investigation regards Parkinson's and Alzheimer's diseases: recent evidences suggest that a decrease in P-gp expression and function at blood brain barrier occur in these diseases [16]. Consequently, there are several reasons for medicinal chemists to continue the search for molecules that could be used to modulate P-gp.

Information on the interaction site of P-gp suggest that it is a large, flexible drug binding domain where molecules can accommodate in a plurality of binding modes, establishing $\pi-\pi$, ion-π, hydrogen bonds and hydrophobic interactions [17]. So, in the search for efficient P-gp modulating MDR reversers, in the last years we have designed and studied several families of basic molecules bearing suitably positioned aromatic rings, assuming that the presence of aromatic moieties and of one or more protonable nitrogen atoms is an important property for the P-gp interaction. In our drug design strategy, these molecular features have been connected by linkers of different length and flexibility [18, 19]. In particular, a high structural flexibility would allow the molecules to choose the most productive binding mode within the P-gp recognition site. This approach, labeled as "polyvalency", had been already used successfully by other researchers, who synthesized several homodimers as MDR inhibitors [20-22].

Based on the polyvalency approach, we synthesized several *N,N*-bis(alkanol)amine aryl esters characterized by the presence of a basic nitrogen atom linked to two different aromatic ester portions by two polymethylenic chains of variable length as spacers. Actually, this approach

provided good results since most of the synthesized compounds showed to be very potent MDR reversers in a human leukemia cell line [18, 23-25].

The first series of compounds were characterized by different combinations of aromatic residues connected to the *N*-methylated basic portion by two identical polymethylenic chains of variable length as spacers [18, 23-25]; best results were obtained by the combination of two chains constituted by 4 or 5 methylenes, with a spacer total length corresponding to 8 or 10 methylenes and one nitrogen atom. Then, we explored the consequences of varying the relative position of the nitrogen in the chain, abandoning the symmetry of the linkers. These derivatives conserved two aromatic ester portions, and a chain of nine components, eight methylenes and one nitrogen atom, but the position of the nitrogen atom was changed according to the length of the two linkers (3- and 5-methylenes long, structure A, Chart 1) [24]. In this way the nitrogen atom was at different distances from the two aromatic moieties, according to the length of the two different spacers. The new asymmetric compounds showed an outstanding potency if compared to the symmetric isomers; in particular the combination of the *(E)*-3-(3,4,5-trimethoxyphenyl)vinyl (also named *trans*-3,4,5-trimethoxycinnamyl) moiety with the 3,4,5-trimethoxyphenyl and anthracene residues (compounds **I-IV**, structure A, Chart 1) that were already present in the most potent of the previously synthesized compounds [18, 23-24] gave rise to the best results of the series. On the bases of these unexpected results, in the present study we decided to widen the series of asymmetrical derivatives by synthesizing all the possible isomers obtained by the combination of different spacers of 2-8 units, for a total length of 8, 9 and 10 methylenes, bearing the aromatic moieties described above (compounds **1-28**, structure B, Chart 1).
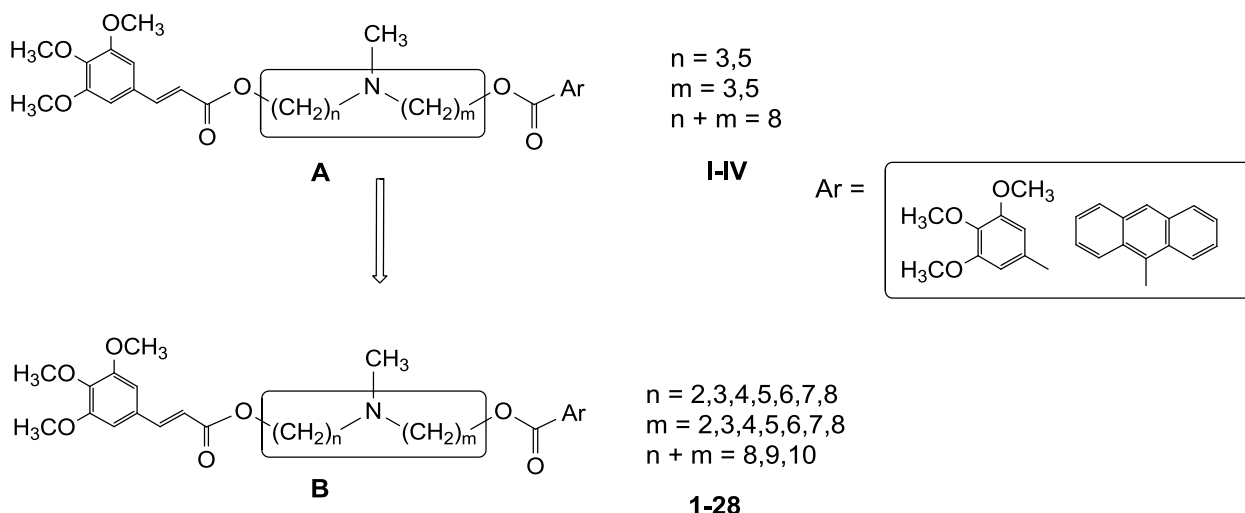
Chart 1. Structure of the reference compounds **I-IV** and of the derivatives **1-28** synthesized in this paper.
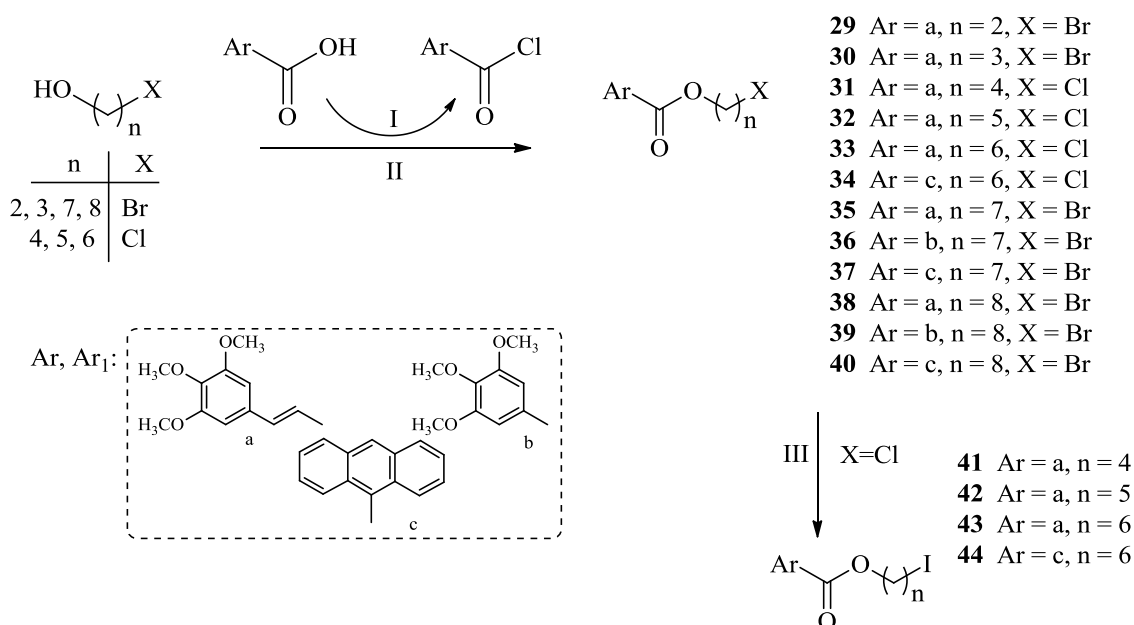
The reversal activity of the new compounds **1-28** was evaluated by the pirarubicin uptake assay in doxorubicin-resistant erythroleukemia K562 cells (K562/DOX). Moreover, a molecular docking simulation was performed in order to identify the potential binding poses of compounds and their mechanism of interaction within the P-gp binding pocket. Finally, a study devoted to establish the chemical stability of these compounds was planned. In fact, it is well known that the ester group, present in the chemical structure of studied compounds, can be susceptible to hydrolysis by the plasma enzymes. Therefore, a series of experiments concerning the stability of these compounds were performed.
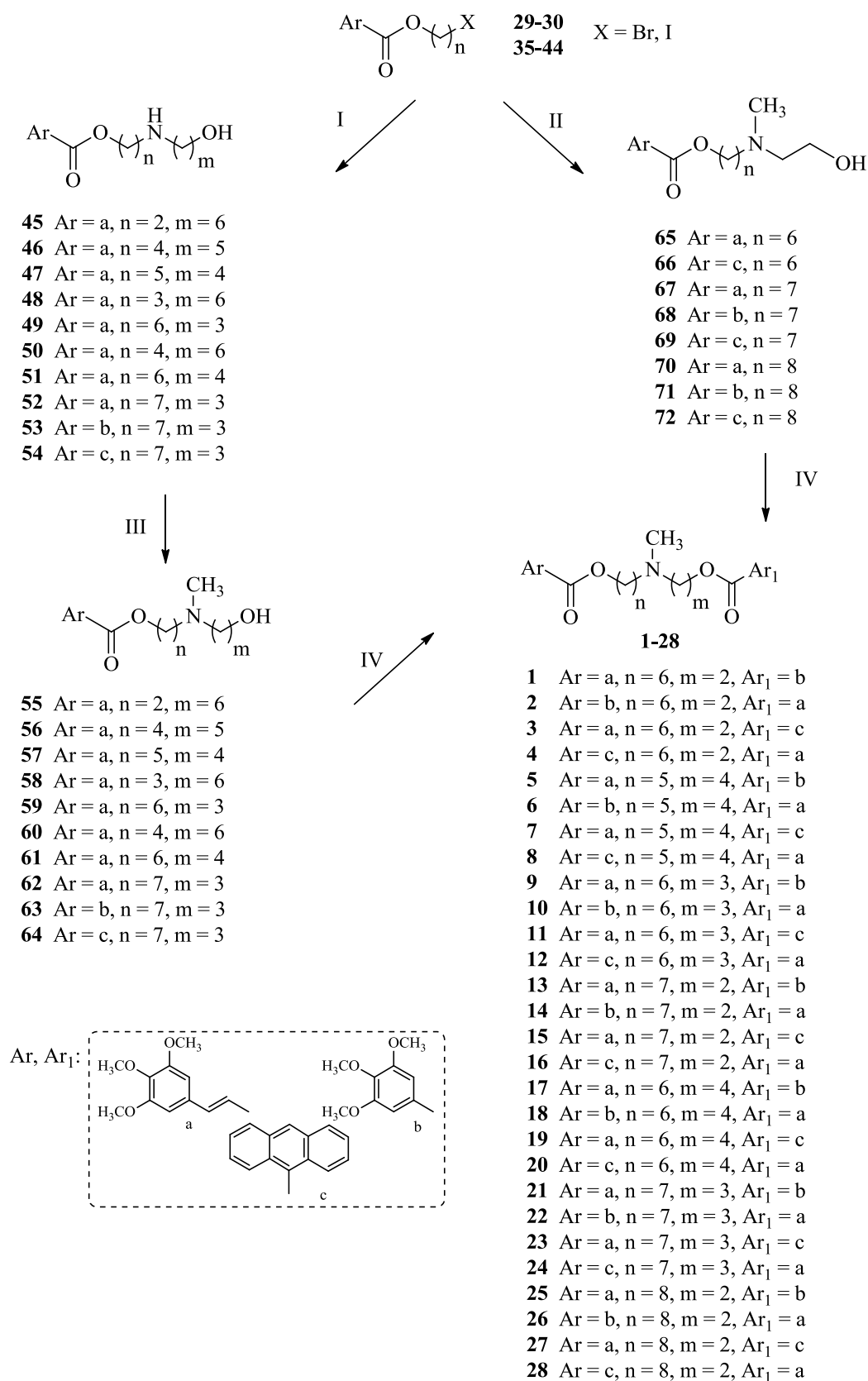
2. Chemistry

The reaction pathways used to synthesize the designed derivatives (**1-28**) are reported in Schemes 1 and 2. The haloesters **29-40** were synthesized by esterification of the suitable haloalkyl alcohol (2-bromoethan-1-ol, 3-bromopropan-1-ol, 4-chlorobutan-1-ol, 5-chloropentan-1-ol, 6-chlorohexan-1-ol, 7-bromoheptan-1-ol and 8-bromooctan-1-ol) with the commercially available (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid, 3,4,5-trimethoxybenzoic acid or anthracene-9-carboxylic acid (Scheme 1). These esters were obtained by transformation of the carboxylic acid in the corresponding acyl chloride by reaction with $SOCl_2$ in ethanol-free $CHCl_3$ (for details, see the Experimental section). Derivatives **29**, **30**, **32**, **33**, **35** had already been described by our group [18, 24].

The chloroalkyl esters **31**- **34** were transformed in the corresponding iodo derivatives **41-44** with NaI in acetone, in order to achieve higher yields in the following reaction. The bromo esters **29-30, 35-40** and the iodo esters **41-44** were then transformed into the secondary amines **45-54** by reaction with the corresponding aminoalcohol using standard procedures (Scheme 2). These compounds were alkylated by reductive methylation with HCOOH/HCHO to give the corresponding tertiary amines **55-64**. In order to obtain the (2-hydroxyethyl)methylaminoesters **65-72**, the appropriate haloester was reacted with the commercially available 2-methylaminoethan-1-ol, yielding directly the desired tertiary amines **65-72**.

Final compounds **1-28** were eventually obtained by reaction of **55-72** with the proper carboxylic acid using EDCI and DMAP in anhydrous CH_2Cl_2, or by transformation of the carboxylic acid in the corresponding acyl chloride as described before. The suitable acids are the same described previously: (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid, 3,4,5-trimethoxybenzoic acid and anthracene-9-carboxylic acid.

29	Ar = a, n = 2, X = Br
30	Ar = a, n = 3, X = Br
31	Ar = a, n = 4, X = Cl
32	Ar = a, n = 5, X = Cl
33	Ar = a, n = 6, X = Cl
34	Ar = c, n = 6, X = Cl
35	Ar = a, n = 7, X = Br
36	Ar = b, n = 7, X = Br
37	Ar = c, n = 7, X = Br
38	Ar = a, n = 8, X = Br
39	Ar = b, n = 8, X = Br
40	Ar = c, n = 8, X = Br

41	Ar = a, n = 4
42	Ar = a, n = 5
43	Ar = a, n = 6
44	Ar = c, n = 6

Scheme 1. Reagents and conditions: (I) $SOCl_2$, $CHCl_3$; (II) $CHCl_3$; (III) NaI, acetone.

Ar O—(CH₂)ₙ—X **29-30**   X = Br, I
            35-44

I

II

Ar O—(CH₂)ₙ—NH—(CH₂)ₘ—OH

45 Ar = a, n = 2, m = 6
46 Ar = a, n = 4, m = 5
47 Ar = a, n = 5, m = 4
48 Ar = a, n = 3, m = 6
49 Ar = a, n = 6, m = 3
50 Ar = a, n = 4, m = 6
51 Ar = a, n = 6, m = 4
52 Ar = a, n = 7, m = 3
53 Ar = b, n = 7, m = 3
54 Ar = c, n = 7, m = 3

65 Ar = a, n = 6
66 Ar = c, n = 6
67 Ar = a, n = 7
68 Ar = b, n = 7
69 Ar = c, n = 7
70 Ar = a, n = 8
71 Ar = b, n = 8
72 Ar = c, n = 8

III

IV

55 Ar = a, n = 2, m = 6
56 Ar = a, n = 4, m = 5
57 Ar = a, n = 5, m = 4
58 Ar = a, n = 3, m = 6
59 Ar = a, n = 6, m = 3
60 Ar = a, n = 4, m = 6
61 Ar = a, n = 6, m = 4
62 Ar = a, n = 7, m = 3
63 Ar = b, n = 7, m = 3
64 Ar = c, n = 7, m = 3

IV

1-28

1 Ar = a, n = 6, m = 2, Ar₁ = b
2 Ar = b, n = 6, m = 2, Ar₁ = a
3 Ar = a, n = 6, m = 2, Ar₁ = c
4 Ar = c, n = 6, m = 2, Ar₁ = a
5 Ar = a, n = 5, m = 4, Ar₁ = b
6 Ar = b, n = 5, m = 4, Ar₁ = a
7 Ar = a, n = 5, m = 4, Ar₁ = c
8 Ar = c, n = 5, m = 4, Ar₁ = a
9 Ar = a, n = 6, m = 3, Ar₁ = b
10 Ar = b, n = 6, m = 3, Ar₁ = a
11 Ar = a, n = 6, m = 3, Ar₁ = c
12 Ar = c, n = 6, m = 3, Ar₁ = a
13 Ar = a, n = 7, m = 2, Ar₁ = b
14 Ar = b, n = 7, m = 2, Ar₁ = a
15 Ar = a, n = 7, m = 2, Ar₁ = c
16 Ar = c, n = 7, m = 2, Ar₁ = a
17 Ar = a, n = 6, m = 4, Ar₁ = b
18 Ar = b, n = 6, m = 4, Ar₁ = a
19 Ar = a, n = 6, m = 4, Ar₁ = c
20 Ar = c, n = 6, m = 4, Ar₁ = a
21 Ar = a, n = 7, m = 3, Ar₁ = b
22 Ar = b, n = 7, m = 3, Ar₁ = a
23 Ar = a, n = 7, m = 3, Ar₁ = c
24 Ar = c, n = 7, m = 3, Ar₁ = a
25 Ar = a, n = 8, m = 2, Ar₁ = b
26 Ar = b, n = 8, m = 2, Ar₁ = a
27 Ar = a, n = 8, m = 2, Ar₁ = c
28 Ar = c, n = 8, m = 2, Ar₁ = a

Ar, Ar₁:

Scheme 2. Reagents and conditions: (I) H₂N(CH₂)ₘOH (m= 3, 4, 5, 6) an. CH₃CN; (II) CH₃NH(CH₂)₂OH, an. CH₃CN; (III) HCOOH/CH₂O, EtOH; (IV) Ar₁COCl, CHCl₃ or EDCI, DMAP, an. CH₂Cl₂

3. Results and discussion

3.1. Modulation of pirarubicin uptake

The P-gp modulating ability of compounds **1-28** was evaluated on K562/DOX doxorubicin resistant cells that overexpress only the membrane glycoprotein P-gp [26-29]. K562 is a human leukemia cell line established from a patient with chronic myelogenous leukemia in blast transformation [30]. The uptake of THP-adriamycin (pirarubicin) was measured by a continuous spectrofluorometric signal of anthracycline at 590 nm (λ_{ex} = 480 nm) after cell incubation, following the protocols reported in previous papers [31,32]. The P-gp modulating activity of the studied compounds on the pirarubicin uptake test is expressed by: *i*) $[I]_{0.5}$, which measures the potency of the modulator and represents the concentration that causes a half-maximal increase (α = 0.5) in the nuclear concentration of pirarubicin, and *ii*) α_{max}, which represents the efficacy of the modulator and is the maximum increase in the nuclear concentration of pirarubicin in resistant cells that can be obtained with a given compound. The value of α varies between 0 (in the absence of the modulator) and 1 (when the amount of pirarubicin in resistant cells is the same as in sensitive cells).

The results obtained are reported in Table 1 together with those of verapamil, the gold standard of P-gp activity inhibition, used as reference compound. 3,4,5-Trimethoxyphenyl derivatives **I** and **II** and their anthracene analogs **III** (GDE6) and **IV** (FRA77) [24] have been added for comparison, since they are the previously obtained asymmetric derivatives.

All the newly synthesized compounds were able to inhibit the activity of P-gp; their potencies and efficacies were higher than those of verapamil. In fact all molecules showed potency values ($[I]_{0.5}$) in the submicromolar or nanomolar range and in many cases were able to completely reverse P-gp-dependent pirarubicin extrusion (α_{max} close to 1).

A thorough evaluation of the potency values indicated that both the chain length and the combination of the aromatic residues have some influence on the activity of our compounds. In fact, in the case of derivatives **1-4**, which carried a total spacer of 8-methylenes due to the combination of two chains of 2 and 6 methylenes, the anthracene derivative **3** showed the best result, with an $[I]_{0.5}$ value of 0.04 μM, as it happened for the two anthracene regioisomers **III** and **IV** which were used as lead compounds. The other compounds of the set, **1**, **2** and **4**, had lower potencies.

In the case of a total length of 9 methylenes, which can be obtained by three different combinations of spacers, the presence of the anthracene residue conferred excellent properties to the molecules: all the isomers, with the exception of compound **16**, showed a nanomolar activity (compounds **7**, **8**, **11, 12** and **15** with $[I]_{0.5}$ values between 0.02 and 0.04 μM). The corresponding derivatives carrying the combination of *trans*-3,4,5-trimethoxycynnamyl moiety with the 3,4,5-trimethoxyphenyl residue showed a similar nanomolar activity only in the case of the two regioisomers **13** and **14**.

The best results were obtained with the isomers with a total spacer of 10 methylenes; remarkably, all the compounds (the three series **17**-**20**, **21**-**24**, **25**-**28**) showed outstanding potencies in the nanomolar range, regardless of the combination of aromatic moieties, with unprecedented results in these series of derivatives.

As regards the efficacy values, almost all the compounds were able to completely reverse P-gp-dependent pirarubicin extrusion (α_{max} = 0.90-0.99). In a little number of derivatives, some lower efficacies can be highlighted (compounds **1**, **4**, and **14** with α_{max} values of 0.77 or 0.79).

Altogether, these data seem to confirm our previous results [23-24] that the MDR modulating activity of this family of molecules can be related on the one hand to the nature of the aromatic moieties and on the other to two characteristics of the linker, both the position of the nitrogen and the total length of the tether. More interestingly, however, from these results it also comes to light that the compounds which present a total spacer of 10 methylenes (**17-28**) are a new series of very potent and efficacious compounds, regardless of the combination of aromatic moieties and of chain lengths. In these series, only the total distance of the aromatic esters seems to be the crucial factor for the activity. Therefore, we compared the potencies of these asymmetric compounds **17-28** with the results obtained by the corresponding symmetric isomers **V** and **VI** already described by us [18].

As shown in Table 1 these two analogs, in particular the 3,4,5-trimethoxyphenyl derivative **V**, showed a lower potency and efficacy. This comparison confirms the result already found in our previous paper [24]. In fact, although the nitrogen position has not a clear influence on the activity, if this atom is at the center of the spacer the activity of the compounds decreases.

Table 1

MDR-reversing activity and predictor parameters for binding free energy, drug transport properties and lipophilicity of compounds **1-28**
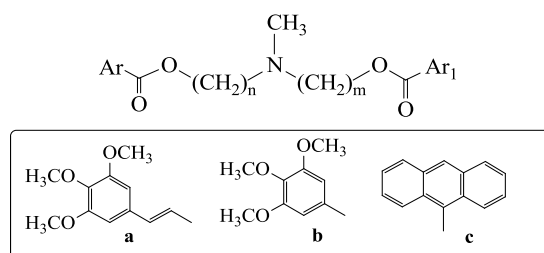
total number of methylenes in the spacer	compd	n	m	Ar	Ar$_1$	$[I]_{0.5}$ μM[a]	α_{max}[b]	ΔG (Kcal/mol)[c]	TPSA (Å^2)[d]	logP$_{o/w}$[e]
8	**I**[f]	5	3	a	b	0.12±0.02	0.99 ±0.01	-7	111.22	6.30
	II[f]	5	3	b	a	0.27±0.05	0.97±0.02	-6.2	111.22	6.26
	III GDE6[f]	5	3	a	c	0.04±0.01	0.98 ±0.02	-7.4	83.53	6.42
	IV FRA77[f]	5	3	c	a	0.04±0.02	0.94±0.03	-8.3	83.53	6.38
8	**1**	6	2	a	b	0.19+0.07	0.77+0.04	-6.4	111.22	6.31
	2	6	2	b	a	0.46±0.07	0.91±0.03	-6.3	111.22	6.38
	3	6	2	a	c	0.04+0.01	0.94+0.03	-7.9	83.53	6.30
	4	6	2	c	a	0.20±0.08	0.79±0.06	-6.9	83.53	5.86
9	**5**	5	4	a	b	0.10 + 0.04	0.94+ 0.05	-7	111.22	6.26
	6	5	4	b	a	0.27 + 0.12	0.99 + 0.01	-6.9	111.22	6.60
	7	5	4	a	c	0.03 + 0.01	0.99 + 0.01	-7	83.53	6.11
	8	5	4	c	a	0.04 + 0.01	0.94 + 0.02	-7.8	83.53	6.21
9	**9**	6	3	a	b	0.24 + 0.08	0.90 + 0.04	-6.8	111.22	6.53
	10	6	3	b	a	0.39 + 0.12	0.99 + 0.01	-6.5	111.22	6.56
	11	6	3	a	c	0.03 + 0.001	0.99 + 0.01	-8	83.53	6.35
	12	6	3	c	a	0.04 + 0.01	0.92 + 0.03	-8.4	83.53	6.22
9	**13**	7	2	a	b	0.04 + 0.01	0.99 + 0.01	-7	111.22	6.23
	14	7	2	b	a	0.07±0.02	0.79±0.04	-7.5	111.22	6.58
	15	7	2	a	c	0.02 + 0.01	0.98 + 0.02	-7.5	83.53	6.31
	16	7	2	c	a	0.17±0.08	0.88±0.08	-7	83.53	6.11
10	**17**	6	4	a	b	0.01+0.001	0.99+0.01	-8	111.22	6.91
	18	6	4	b	a	0.07 + 0.002	0.99 + 0.01	-7.4	111.22	6.89
	19	6	4	a	c	0.02+0.005	0.94+0.05	-8.7	83.53	6.66
	20	6	4	c	a	0.01 + 0.002	0.95 + 0.05	-7.7	83.53	6.74
10	**21**	7	3	a	b	0.06 + 0.02	0.99 + 0.01	-7	111.22	6.90
	22	7	3	b	a	0.08 + 0.03	0.97±0.03	-7.4	111.22	6.95
	23	7	3	a	c	0.01 + 0.003	0.93 ± 0.04	-8	83.53	6.67
	24	7	3	c	a	0.04 ± 0.01	0.88 ± 0.08	-8.3	83.53	6.71
10	**25**	8	2	a	b	0.02 ± 0.01	0.93 ± 0.03	-7.3	111.22	6.91
	26	8	2	b	a	0.04 ± 0.01	0.91 ± 0.02	-7.5	111.22	6.89

					[I]$_{0.5}$[a]	Efficacy[b]	ΔG[c]	TPSA[d]	logP[e]
	27	8	2	a	c	0.05 ± 0.02	0.99 ± 0.01	-8.1	83.53	6.81
	28	8	2	c	a	0.04 ± 0.01	0.96 ± 0.02	-7.2	83.53	6.80
10	**V**[g]	5	5	a	b	0.80 ± 0.20	0.84 ± 0.09	-6.7	111.22	6.80
	VI[g]	5	5	a	c	0.10 ± 0.02	0.80 ± 0.07	-6.9	83.53	6.90
	Verapamil[h]					1.60 ± 0.30	0.70 ± 0.07	-7.8	63.95	4.50

[a] Concentration of the inhibitor that causes a 50% increase in nuclear concentration of pirarubicin (α = 0.5). [b] Efficacy of MDR-modulator and maximum increase that can be obtained in the nuclear concentration of pirarubicin in resistant cells. Results are expressed as the mean ± SE of three independent experiments done at least three times. [c] Predicted binding affinity. [d] Predicted topological polar surface area (TPSA). [e] The n-octanol/water partition coefficient (log P$_{o/w}$) was obtained by using implicit log P method (iLOGP) [f] See within ref. [24]: compounds **I**, **II**, **III** and **IV** are labelled as 13, 12, 16, and 15 respectively. [g] See within ref. [18]: compounds **V** and **VI** are labelled as 11 and 12 respectively. [h] see ref. [24].

3.2.Molecular modeling studies

In order to elucidate the binding mode of the compounds in the P-gp interaction site, and possibly to explain their remarkable inhibitory activity, an *in silico* study was performed. Compounds were docked into the protein, and the binding energy was calculated using the Autodock/Vina XB software [33]. The crystal structure of human P-gp (PDB code 6C0V) was used as Molecular docking target [34], while, to identify the potential binding pocket of our compounds, we referred to the 3D structure of Mus musculus P-gp in complex with BDE-100 (PDB code 4XWK) [35,36]. As a matter of fact, this compound showed to be a P-gp inhibitor with a IC$_{50}$ of 23.2±2.9 μM [36]. Compounds were clustered into sets "1" and "2", on the basis of the presence (set 1) or absence (set 2) of the anthracene group. The ligand binding mode was visually analyzed: all compounds docked with similar poses (Figure 1), showing interactions that appeared similar to those established by verapamil with the binding site residues. The computation of docking energies shows that all molecules are able to interact with the binding site, displaying a good thermodynamic affinity. Nevertheless, some differences can be highlighted, depending on the aromatic residues and the total length of the spacer, which modify the binding profiles. In particular, the docking results showed that the more active compounds, which show a calculated binding free energy (ΔG value) smaller than -7.8, are decorated in most cases by the anthracene ester group; in addition, the compounds characterized by a linker of 10 methylene never exhibit ΔG higher than -7.

Figure 2 described the correlation between the calculated binding free energy (ΔG) and the experimental p[I]$_{0.5}$ values: although with a certain approximation, the performed calculations are able to partially correlate the biological activity of the new compounds, as shown by the trend found in the experimental *vs* predicted plot.

Also the analyses of predicted lipophilicity (logP) and of the topological polar surface area (TPSA), by using SwissADME [37] were performed. The parameter TPSA is defined as the sum of surfaces of polar atoms in the molecule, and is useful in order to identify the druggability of ligands, since it can be a measure of the ability of the compounds to permeate cells. Molecules with a TPSA value greater than 140 Å² tend to be poor in permeation of cell membranes, and are considered poor drug-like compounds [38].

These parameters may explain the differences between [I]$_{0.5}$ and efficacy values against ΔG, in particular as regard the standard verapamil. In fact, comparing the new synthesized compounds with verapamil, it can be observed how, despite a similar ΔG value, verapamil displays lower potency and efficacy with respect to the derivatives described in the paper. This behavior could be related to its lower lipophilicity and permeability.
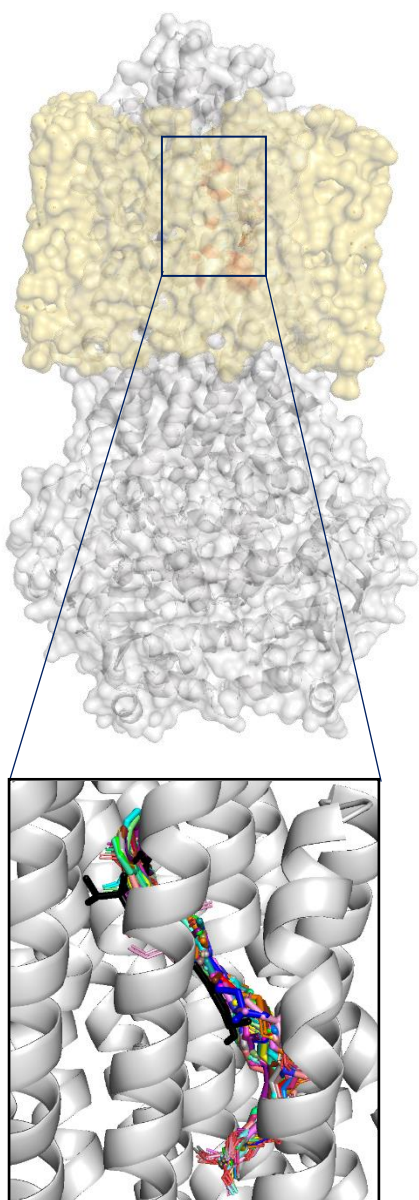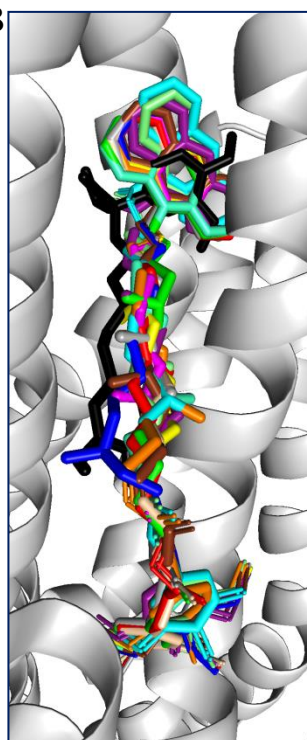
Fig. 1. Overview of molecules best poses of compounds **1-28** within the P-gp binding pocket. A) The P-gp 3D structure is shown in grey cartoon and surface representation. The bilayer is reported in yellow surface. Verapamil (black) and the studied ligands (coloured) are shown inside the P-gp binding pocket with stick models. B) and C) show a closer view of the binding mode of set "1" and set "2", respectively.
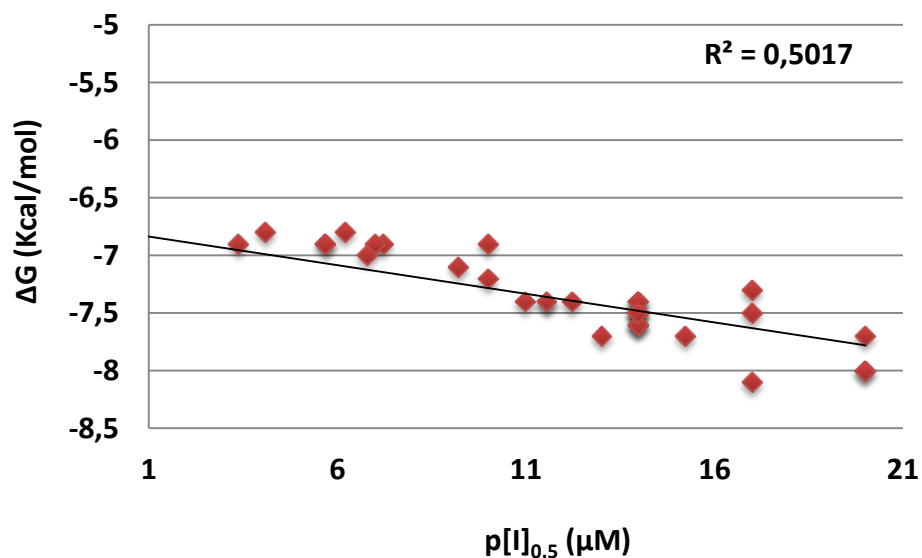
Fig. 2. Correlation between the calculated Autodock/vinaXB binding free energies (ΔG) and the experimental $p[I]_{0.5}$ values for P-gp.

In order to gain more information on the remarkable inhibitory activity of the new compounds, we also carried out a ligand-binding-site interaction network analyses on all derivatives. In fact, it could be interesting to evaluate which type of interactions could be established between the protein and all studied compounds, identifying the involved residues, and making a comparison with those formed with other known inhibitors.

Figure 3 shows the 2D molecular docking models of the interaction between P-gp and BDE-100 (panel A) used as template reference, the standard verapamil (panel B), and two of the new compounds, the potent compounds **17** and **23**, which are representative of cluster sets "2" and "1", respectively (panel C and D).

Crystal structure of the mouse P-gp complexed with BDE-100 compound (PDB code 4XWK), was used as reference point to study protein binding interactions [36]. BDE-100 (panel A) forms hydrophobic interactions with different aromatic residues but only one π-stacking bond with Tyr-303; this is sufficient for its inhibitory capacity. Verapamil, docked into the human P-gp (PDB code 6C0V) [34], is surrounded by several lipophilic or aromatic residues (panel B), but as well as BDE-100, is able to form only one π-stacking interaction. On the contrary, compounds **17** and **23** are able to form a higher number of interactions with different residues of the binding site: the presence of long polymethylenic chains allows numerous hydrophobic interactions within the binding pocket, in addition to the capability to form stronger aromatic interactions compared to BDE-100 and verapamil. For instance, for **23** the presence of the anthracene group favors the formation of three π-stacking bonds between the three rings of the aromatic moiety and Phe-335, Phe-728 and Phe-759 residues of the P-gp binding site (panel C), while both BDE-100 and verapamil are able to form only one π-stacking interaction. As regard compound **17**, the higher number of hydrophobic interactions of the spacers, compared to verapamil and BDE-100, stabilizes its binding into the active pocket despite the formation of only one π-stacking bond (panel D).

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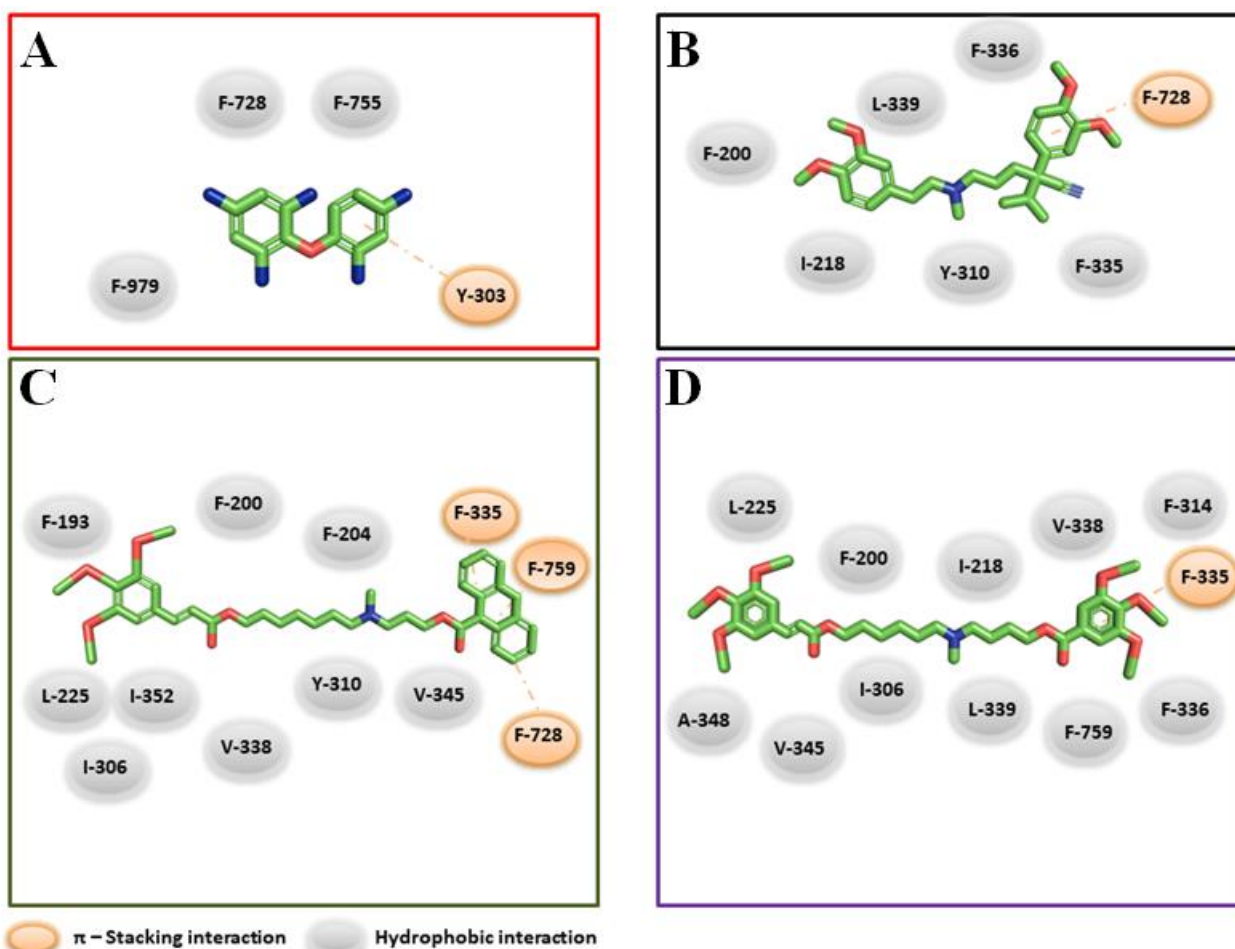
Fig. 3: 2D Molecular docking models of the interaction between compounds and P-gp: for clarity, only interacting residues are displayed. A) BDE-100, B) Verapamil, C) Compound **23**, D) Compound **17**.

In summary, the docking results supported the data obtained by the biological tests: all molecules are able to interact with the binding site with a good thermodynamic affinity: the differences in the activity can be related to the ΔG values. The good activity of the compounds bearing an anthracene ester group can be partially explained by the higher number of π-stacking bonds that these molecules are able to establish with the protein.

3.3. Chemical stability tests

The chemical stability tests on these compounds were carried out both in phosphate buffer solution (PBS) and in human plasma, in order to distinguish between spontaneous or enzymatic hydrolysis respectively.

The stability analyses were performed by LC-MS/MS methods operating in product ion scan mode, in the appropriate m/z range to ensure the fragment ions detection. The LC-MS/MS system and the parameters used in this study were reported in the Supplementary Data section.

The stability of each compound, in both reported matrices, was evaluated by monitoring the variation of its concentration at different incubation times. By plotting these data (analyte concentrations vs the incubation time) their respective degradation profiles were obtained. Generally, when the substrate concentration is smaller than its Michaelis–Menten constant (K_M), the enzymatic degradation rate is described by a first-order kinetic.

Therefore, plotting the natural logarithm of the quantitative data versus the incubation time, a linear function can be used and its slope represents the degradation rate constant (k). Therefore, the half-life ($t_{1/2}$) of each tested compound can be calculated as follows:

$$t_{1/2} = \frac{\ln(0.50\,\mu M)}{k}$$

The plots of the natural logarithm of the quantitative data versus the incubation time of all the studied compounds were analysed. The obtained results demonstrated that all the compounds were stable in PBS and most of them also in human plasma. In fact, only the degradation plots of **II**, **10**, **18** and **22** in human plasma showed a significant decay rate (k value), and their calculated half-life values ($t_{1/2}$ values between 39 min. and 123 min), were reported in Table 2. Furthermore, the half-life value of ketoprofene ethylester (KEE), used as reference compound, demonstrated that the employed human batch was enzymatically active (half-life < 2 h) [39,40]. At the contrary, the k values of the other studied compounds were close to 0; consequently for these derivatives, extremely high $t_{1/2}$ values can be calculated. Since under the proposed experimental conditions a half-life over 240 min is not measurable, it is reasonable to consider that their half-life values could be equal or greater than 240 min. The human plasma degradation profiles of compound **22** and of its stable isomer **21** are reported as an example (Figure 4); the plots of the other compounds are reported in the Supplementary Data section.

Table 2
Half-life values of reference and studied compounds.

Comp.	PBS t $_{1/2}$ ± error (min)	Human plasma t $_{1/2}$ ± error (min)
KEE	n.d.	107 ± 16
1	>240	>240
2	>240	>240
3	>240	>240
4	>240	>240
5	>240	>240
6	>240	>240
7	>240	>240
8	>240	>240
9	>240	>240
10	>240	39 ± 6
11	>240	>240
12	>240	>240
13	>240	>240
14	>240	>240
15	>240	>240

Comp.	PBS t $_{1/2}$ ± error (min)	Human plasma t $_{1/2}$ ± error (min)
16	>240	>240
17	>240	>240
18	>240	123 ± 53
19	>240	>240
20	>240	>240
21	>240	>240
22	>240	45 ± 13
23	>240	>240
24	>240	>240
25	>240	>240
26	>240	>240
27	>240	>240
28	>240	>240
I	>240	>240
II	>240	41 ± 19
V	>240	>240

n.d.: not determined
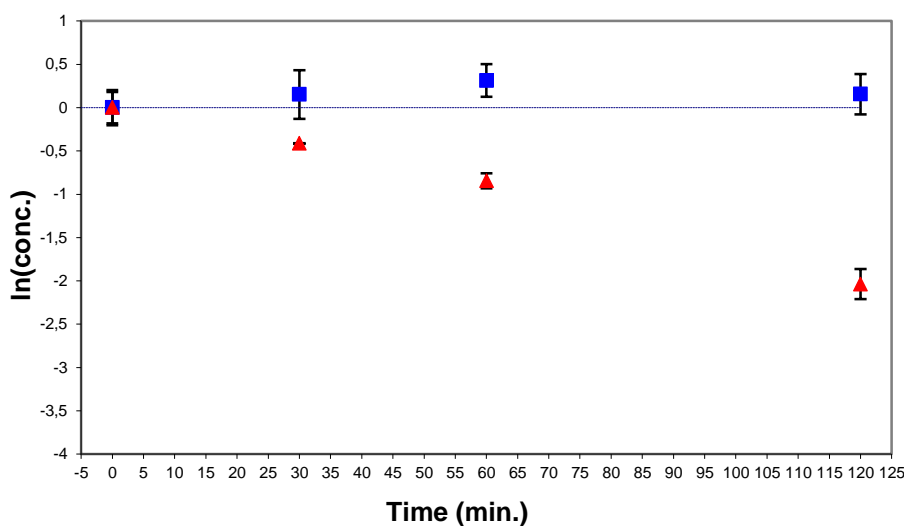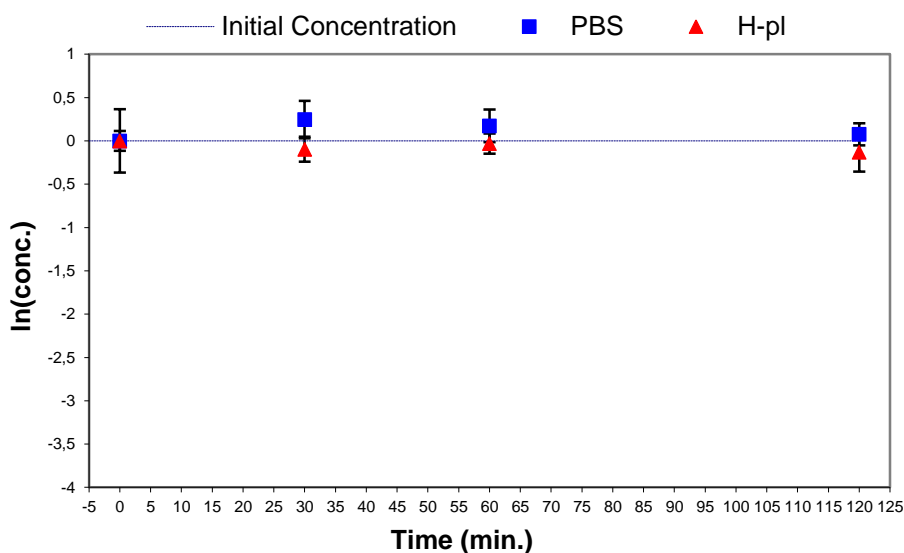
Fig. 4: Degradation profiles in PBS (blue) and human plasma (red) of compound **21** (top) and compound **22** (bottom).

The degradation products of **II**, **10**, **18** and **22** compounds were also investigated to establish the possible enzyme hydrolytic mechanism. The results confirmed that these compounds were degraded for hydrolysis of the ester group linked to the *trans*-3,4,5-trimethoxycinnamyl moiety, with formation of the corresponding *N*-alkyl alcohol and of the free trimethoxycinnamic acid. As an example, the chromatograms of compound **22** in human plasma at two incubation times (0 and 120 min respectively) is reported in Figure 5.
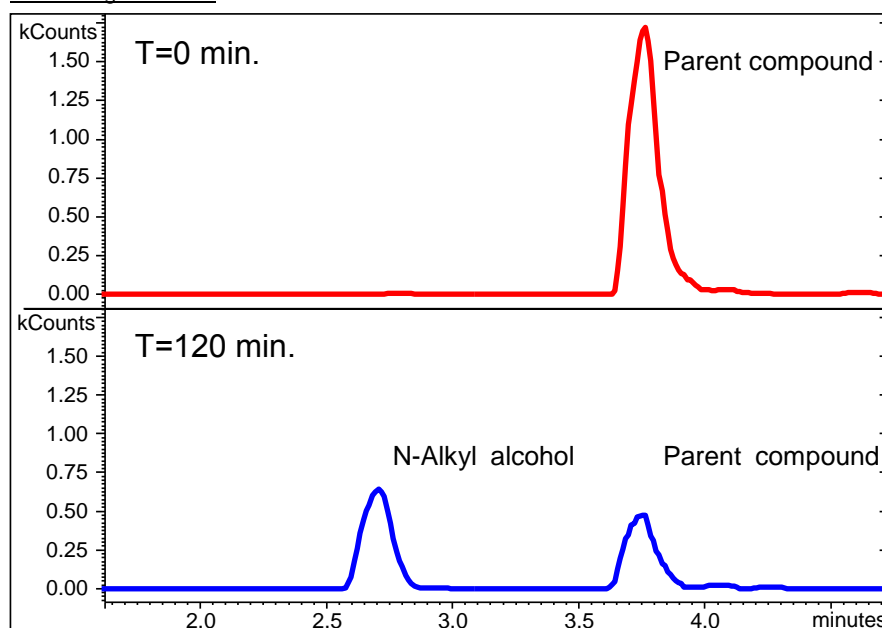
Fig. 5: LC-MS/MS chromatographic profiles of compound **22** in human plasma at the initial (up) and final (bottom) incubation time.

Interestingly, the hydrolysis occurs only when the *trans*-3,4,5-trimethoxycinnamic ester is combined with the 3,4,5-trimethoxybenzoic moiety, while the combination with the anthracene group prevents the enzyme activity (i.e. anthracene analogues **24** and/or **12**). Furthermore, hydrolysis occurs only when the *N*-alkyl chain length of the *trans*-3,4,5-trimethoxycynnamyl portion is of three methylenes: different values prevent the hydrolysis (i.e. **26** and/or **V**). Only **18**, bearing a *N*-alkyl chain length of four methylenes in the cinnamyl portion, shows a appraisable degradation, but its *k* value is three times lower with respect to the analogues carrying a chain with three methylene units. Compound **6**, characterized by the same structural feature of **18**, is instead completely stable in human plasma, indicating that the chain composed by 4 methylenes confers a higher stability.

4. Conclusions

In the present study, we designed and synthesized several new *N,N*-bis(alkanol)amine aryl ester heterodimers by modulating the combination of aromatic moieties and the length of the methylenic chain. In particular, we achieved all the possible isomers obtained by the combination of different spacers of 2-8 units, for a total length of 8, 9 and 10 methylenes, bearing the aromatic moieties described above. These derivatives were evaluated for P-gp inhibitory activity on doxorubicin-resistant erythroleukemia K562 cell line (K562/DOX). The new compounds showed good P-gp modulating ability in the pirarubicin assay: all molecules showed potency values ($[I]_{0.5}$) in the submicromolar or nanomolar range and in many cases were able to completely reverse P-gp-dependent pirarubicin extrusion (α_{max} close to 1).

The best results were obtained with the isomers showing a total spacer of 10 methylenes; in fact, all the compounds showed outstanding potencies in the nanomolar range, regardless of the combination of aromatic moieties, with unprecedented results in these series of derivatives. In this group of compounds, the nitrogen position and therefore the distance of this atom from the combined aromatic residues have not a clear influence on the activity. So, the total distance of the aromatic esters seems to be the crucial factor for the activity. However, comparing the potencies of the compounds **17-28** with the activities obtained by two already described symmetric isomers **V** and **VI** [18] (Table 1), the same result already found in our previous paper [24] was confirmed: the

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nitrogen position has not a clear influence on the activity, but if this atom is at the center of the spacer the activity of the compounds decreases.

In order to explain the remarkable inhibitory activity of the new compounds, we carried out a ligand-binding-site interaction network analyses on all the derivatives. Using a computational approach, we highlighted that all the molecules are able to interact with the protein binding site, displaying a good thermodynamic affinity. Some compounds however showed better binding outlines, characterized by smallest binding energies (ΔG) that showed a certain correlation with the experimental inhibitory activities. The good activity of the compounds bearing an anthracene ester group can be partially explained by the higher number of π-stacking bond that these molecules are able to establish with the protein.

Interesting information were obtained from the stability experiments performed on these new series of MDR inhibitors both in phosphate buffer solution (PBS) and in human plasma. The compounds, despite the presence of two ester groups, were stable in both the tested matrices. Only four compounds (**II**, **10**, **18** and **22**) exhibited a significant degradation in the human plasma matrix, showing the hydrolysis of the ester group present on the 3,4,5-trimethoxycinnamyl moiety of the molecule. Interestingly, these compounds present a common characteristic in their chemical structures which reasonably favors the enzymatic activity. In fact, it was observed that the hydrolysis occurs only in the presence of the 3,4,5-trimethoxyphenyl moiety and when the *N*-alkyl chain linked with *trans*-3,4,5-trimethoxycinnamyl portion has a length of three methylenes. Therefore, the substitution of aromatic moiety (e.g. in the case of anthracene analogues) or the modification of the length of the *N*-alkyl chain, prevents the enzymatic activity.

In conclusion, we have identified a new very powerful series of P-gp-dependent MDR inhibitors showing a *N,N*-bis(alkanol)amine aryl ester scaffold. Interestingly, all the compounds carrying a linker composed by 10 methylenes in different combination showed an excellent pharmacological profile. Docking studies confirmed that these molecules are able to interact in a fruitful manner with the P-gp binding pocket, and evaluation of their chemical stability in PBS and human plasma confirmed that these compounds are in most cases stable in both media, allowing us to predict their *in vivo* bioavailability. Three compounds, **17** (CF24), **20** (CF27) and **23** (ELF85) appear to be the most interesting of the series and could represent interesting leads for the development of new potent and efficacious P-gp-dependent MDR modulators.

5. Experimental

5.1. Chemistry

All melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR). Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063-0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040-0.063 mm; Merck). Yields are given after purification, unless otherwise stated.

ESI-MS spectra were obtained using a Varian 1200L triple quadrupole system (Palo Alto, CA, USA) equipped by Elettrospray Source (ESI) operating in both positive and negative ions.

The data were acquired in scan mode between the range 150-800 m/z by introducing the sample solution, via syringe pump at 10 μL min^{-1}. The sample solution of each analyte was freshly prepared by diluting its stock solution (1 mg mL^{-1} in acetonitrile) up to a concentration of 1.0 μg mL^{-1} in mixture of mQ water:acetonitrile 50:50 (v/v).

In the used instrumental conditions, the most abundant signal for the analytes showed to be the protonated ([M+H]$^{+}$) or deprotonated ([M-H]$^{-}$) molecule ion species.

Compounds **1-28** were obtained in a purity ≥ 95%. Their combustion analyses are indicated by symbols, and the analytical results are within ±0.4% of the theoretical values. Compounds were named following IUPAC rules as applied by ChemBioDraw Ultra 14.0 software. When reactions were performed in anhydrous conditions, the mixtures were maintained under nitrogen. Free bases

x-y were transformed into the hydrochloride by treatment with a solution of acetyl chloride (1.1 eq) in anhydrous CH_3OH. The salts were crystallized from abs. ethanol/petroleum ether.

5.1.1. General procedure for the synthesis of haloesters 29-40

A 1 mmol portion of the appropriate carboxylic acid (*trans*-3-(3,4,5-trimethoxyphenyl)acrylic acid, 3,4,5-trimethoxybenzoic acid or anthracene-9-carboxylic acid) was transformed into the acyl chloride by reaction with $SOCl_2$ (2 mmol) in 5 mL of $CHCl_3$ (free of ethanol) at 60 °C for 4-5 h. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure; the mixture was then treated twice with cyclohexane and the solvent removed under reduce pressure. The acyl chloride obtained was dissolved in $CHCl_3$ (free of ethanol), and the suitable alcohol (2-bromoethan-1-ol, 3-bromopropan-1-ol, 4-chlorobutan-1-ol, 5-chloropentan-1-ol, 6-bromoexan-1-ol, 7-bromeptan-1-ol or 8-bromooctan-1-ol) (0.9 eq) was added. The mixture was heated to 60 °C. After 4 h, the reaction mixture was cooled to rt, and treated with CH_2Cl_2. The resulting organic layer was washed with 10% NaOH solution, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The substances obtained were purified by flash chromatography in the case of **31**, **38**, **39** and **40**, otherwise were used as such for the next reaction. Compounds **29**, **30**, **32**, **33** and **35** were already synthesized by our group with the same procedure [18,24].

5.1.1.1. (E)-4-chlorobutyl 3-(3,4,5-trimethoxyphenyl)acrylate 31

Pale yellow oil. Chromatographic eluent: cyclohexane/ethyl acetate70:30. Yield: 68.0%. ^{1}H-NMR ($CDCl_3$) δ: 7.60 (d, J=16.0 Hz, 1H, *CH*=CH); 6.75 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.24 (t, J=6.0 Hz, 2H, CH_2O); 3.89 (s, 6H, OCH_3); 3.88 (s, 3H, OCH_3); 3.60 (t, J=6.0 Hz, 2H, CH_2Cl); 1.98-1.82 (m, 4H, CH_2) ppm. ^{13}C APT NMR **($CDCl_3$) δ:** 153.46 (C=O); 144.90 (CH=CH); 129.85 (C); 117.17 (CH=CH); 105.29 (CH arom.); 63.67 (CH_2); 60.97 (OCH_3); 56.18 (OCH_3); 44.50 (CH_2); 29.23 (CH_2); 26.21 (CH_2) ppm.

5.1.1.2. 6-chlorohexyl anthracene-9-carboxylate 34

Yellow oil. Yield: 87.1 %. ^{1}H-NMR ($CDCl_3$) δ: 8.52 (s, 1H, CH arom.); 8.15-7.97 (m, 4H, CH arom.); 7.62-7.42 (m, 4H, CH arom.); 4.63 (t, J=6.8 Hz, 2H, CH_2O); 3.54 (t, J=4.8 Hz, 2H, CH_2Cl); 1.96-1.85 (m, 2H, CH_2); 1.85-1.76 (m 2H, CH_2); 1.63-1.46 (m, 4H, CH_2) ppm.

5.1.1.3. 7-bromoheptyl 3,4,5-trimethoxybenzoate 36

Pale yellow oil. Yield: 37.8%. ^{1}H-NMR ($CDCl_3$) δ: 7.28 (s, 2H, CH arom.); 4.29 (t, J=6.8 Hz, 2H, CH_2O); 3.90 (s, 6H, OCH_3); 3.89 (s, 3H, OCH_3); 3.39 (t, J=6.8 Hz, 2H, CH_2Br); 1.90-1.81 (m, 2H, CH_2); 1.80-1.70 (m Hz, 2H, CH_2); 1.50-1.32 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 166.22 (C=O); 152.91 (C); 142.16 (C); 125.46 (C); 106.79 (CH arom.); 62.21 (CH_2); 60.88 (OCH_3); 56.24 (OCH_3); 33.80 (CH_2); 32.65 (CH_2); 28.63 (CH_2); 28.38 (CH_2); 28.02 (CH_2); 25.82 (CH_2) ppm.

5.1.1.4. 7-bromoheptyl anthracene-9-carboxylate 37

Orange oil. Yield: 41.2%. ^{1}H-NMR ($CDCl_3$) δ: 8.49 (s, 1H, CH arom.); 8.08 (d, J=8.4 Hz, 2H, CH arom.); 8.05 (d, J=8.4 Hz, 2H, CH arom.); 7.60-7.40 (m, 4H, CH arom.); 4.62 (t, J=6.4 Hz, 2H, CH_2O); 3.38 (t, J=6.8 Hz, 2H, CH_2Br); 1.92-1.78 (m, 4H, CH_2); 1.60-1.30 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 169.74 (C=O); 131.02 (C); 129.26 (CH arom.); 128.66 (CH arom.); 128.41 (C); 129.96 (CH arom.); 125.48 (CH arom.); 125.02 (CH arom.); 65.81 (CH_2); 33.88 (CH_2); 32.66 (CH_2); 29.13 (CH_2); 28.77 (CH_2); 28.70 (CH_2); 26.06 (CH_2) ppm.

5.1.1.5. (E)-8-bromooctyl 3-(3,4,5-trimethoxyphenyl)acrylate 38

Yellow oil. Chromatographic eluent: cyclohexane/ethyl acetate70:30. Yield: 40.2%. ^{1}H-NMR ($CDCl_3$) δ: 7.55 (d, J=16.0 Hz, 1H, *CH*=CH); 6.72 (s, 2H, CH arom.); 6.31 (d, J=16.0 Hz, 1H, CH=*CH*); 4.16 (t, J=6.8 Hz, 2H, CH_2O); 3.85 (s, 6H, OCH_3); 3.84 (s, 3H, OCH_3); 3.37 (t, J=6.8 Hz, 2H, CH_2Br); 1.90-1.81 (m, 2H, CH_2); 1.76-1.65 (m, 2H, CH_2); 1.44-1.24 (m, 8H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 167.07 (C=O); 153.43 (C); 144.61 (CH=CH); 129.96 (C); 117.48 (CH=CH); 105.20 (CH arom.); 64.64 (CH_2); 60.98 (OCH_3); 56.16 (OCH_3); 33.98 (CH_2); 32.74 (CH_2); 29.07 (CH_2); 28.70 (CH_2); 28.63 (CH_2); 28.05 (CH_2); 25.87 (CH_2) ppm. ESI-MS *m/z* (%): 429 (100) [*M*+H]$^+$.

5.1.1.6. 8-bromooctyl 3,4,5-trimethoxybenzoate 39

Pale yellow oil. Chromatographic eluent: cyclohexane/ethyl acetate 80:20. Yield: 37.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.27 (s, 2H, CH arom.); 4.28 (t, J=6.8 Hz, 2H, CH$_2$O,); 3.88 (s, 6H, OCH$_3$); 3.87 (s, 3H, OCH$_3$); 3.37 (t, J=6.4 Hz, 2H, CH$_2$Br); 1.86-1.80 (m, 2H, CH$_2$); 1.78-1.69 (m, 2H, CH$_2$); 1.43-1.22 (m, 8H, CH$_2$) ppm.

5.1.1.7. 8-bromooctyl anthracene-9-carboxylate 40

Yellow oil. Chromatographic eluent: cyclohexane/ethyl acetate 80:20. Yield:79.6%. ^{1}H-NMR (CDCl$_3$) δ: 8.50 (s, 1H, CH arom.); 8.07 (d, J=8.8 Hz, 2H, CH arom.); 8.00 (d, J=8.4 Hz, 2H, CH arom.,); 7.57-7.48 (m, 4H, CH arom.); 4.63 (t, J=6.8 Hz, 2H, CH$_2$O); 3.38 (t, J=4.8 Hz, 2H, CH$_2$Br); 1.95-1.77 (m, 4H, CH$_2$); 1.47-1.38 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR **(CDCl$_3$) δ:** 169.78 (C=O); 131.03 (C); 129.25 (CH arom.); 128.66 (CH arom.); 128.41 (C); 126.95 (CH arom.); 125.49 (CH arom.); 125.04 (CH arom.); 70.92 (CH$_2$); 65.91 (CH$_2$); 33.99 (CH$_2$); 32.76 (CH$_2$); 29.16 (CH$_2$); 28.66 (CH$_2$); 28.07 (CH$_2$); 26.02 (CH$_2$) ppm.

5.1.2. General procedure for the synthesis of iodoesters 41-44

A 1 mmol portion of the suitable chloroester (**31-34**) was dissolved in acetone. To this solution NaI (4 eq) was added, and the resulting mixture was maintained 24 h at reflux in the dark. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure; the residue was dissolved in CH$_2$Cl$_2$ and washed with water. The organic layer was dried with Na$_2$SO$_4$, and the solvent was removed under reduced pressure yielding a yellow oil which was used as such for the next reaction. Compound **42** was already synthesized by our group with the same procedure [24].

5.1.2.1. (E)-4-iodobutyl 3-(3,4,5-trimethoxyphenyl)acrylate 41

Yield: 94.7%. ^{1}H-NMR (CDCl$_3$) δ: 7.57 (d, J=16.0 Hz, 1H, *CH*=CH); 6.73 (s, 2H, CH arom.); 6.31 (d, J=16.0 Hz, 1H, CH=*CH*); 4.20 (t, J=6.0 Hz, 2H, CH$_2$O); 3.86 (s, 6H, OCH$_3$); 3.85 (s, 3H, OCH$_3$); 3.21 (t, J=6.8 Hz, 2H, CH$_2$I); 1.98-1.87 (m, 2H, CH$_2$); 1.84-1.74 (m, 2H, CH$_2$) ppm.

5.1.2.2. (E)-6-iodohexyl 3-(3,4,5-trimethoxyphenyl)acrylate 43

Yield: 95.9%. ^{1}H-NMR (CDCl$_3$) δ: 7.58 (d, J=16.0 Hz, 1H, CH=CH); 6.74 (s, 2H, CH arom.); 6.33 (d, J=15.6 Hz, 1H, CH=CH); 4.19 (t, J=6.8 Hz, 2H, CH$_2$O); 3.88 (s, 6H, OCH$_3$); 3.87 (s, 3H, OCH$_3$); 3.19 (t, J=6.8 Hz, 2H, CH$_2$I); 1.91-1.79 (m, 2H, CH$_2$); 1.86-1.68 (m, 2H, CH$_2$); 1.50-1.38 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 153.44 (C); 144.66 (*CH*=CH); 140.16 (C); 129.92 (C); 117.40 (CH=*CH*); 105.28 (CH arom.); 64.61 (CH$_2$); 60.95 (OCH$_3$); 56.18 (OCH$_3$); 33.13 (CH$_2$); 29.83 (CH$_2$); 26.54 (CH$_2$); 25.10 (CH$_2$); 6.79 (CH$_2$) ppm.

5.1.2.3. 6-iodohexyl anthracene-9-carboxylate 44

Yield: 90.4%. ^{1}H-NMR (CDCl$_3$) δ: 8.52 (s, 1H, CH arom.); 8.15-7.97 (m, 4H, CH arom.); 7.65-7.42 (m, 4H, CH arom.); 4.63 (t, J=6.4 Hz, 2H, CH$_2$O); 3.17 (t, J=6.8 Hz, 2H, CH$_2$I); 1.99-1.73 (m, 4H, CH$_2$); 1.60-1.37 (m, 4H, CH$_2$) ppm.

5.1.3. General procedure for the synthesis of hydroxyaminoesters 45-54

The appropriate haloester (**29, 30, 35-37, 41-43**) (1 mmol) and the suitable aminoalkylalcohol (3-aminopropan-1-ol, 4-aminobutan-1-ol , 5-aminopentan-1-ol or 6-aminohexan-1-ol) (2 mmol) were dissolved in 1 mL of anhydrous CH$_3$CN. The mixture was heated at 80 °C for 5-10 h. The reaction mixture was cooled to room temperature, treated with CH$_2$Cl$_2$ and the organic layer was washed with 10% NaOH solution. After drying with Na$_2$SO$_4$, the solvent was removed under reduced pressure and the residue purified by flash chromatography, yielding a pale-yellow oil. **52** was used as such in the next reaction.

5.1.3.1. (E)-2-((6-Hydroxyhexyl)amino)ethyl 3-(3,4,5- trimethoxyphenyl)acrylate 45

Chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 90:10:1. Yield: 26.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.56 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.27 (t,

J=4.8 Hz, 2H, CH$_2$OH); 3.85 (s, 6H, OCH$_3$); 3.83 (s, 3H, OCH$_3$); 3.61-3.53 (m, 2H, CH$_2$O); 2.89 (t, J=4.8 Hz, 2H, NCH$_2$,); 2.61 (t, J=6.4 Hz, 2H, NCH$_2$); 1.59-1.41 (m, 4H, CH$_2$); 1.40-1.23 (m, 4H, CH$_2$) ppm. ESI-MS *m/z* (%): 382 (100) [*M*+H]$^+$.

5.1.3.2. (E)-4-((5-Hydroxypentil)amino)butyl 3-(3,4,5- trimethoxyphenyl)acrylate 46

Chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 90:10:1. Yield: 35.6%. ^{1}H-NMR (CDCl$_3$) δ: 7.53 (d, J=15.6 Hz, 1H, *CH*=CH); 6.70 (s, 2H, CH arom.); 6.29 (d, J=15.6 Hz, 1H, CH=*CH*); 4.14 (t, J=6.8 Hz, 2H, CH$_2$O); 3.83 (s, 6H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 3.56 (t, J=6.4 Hz, 2H, CH$_2$OH); 3.21 (bs, 1H, OH); 2.64-2.57 (m, 4H, NCH$_2$); 1.78-1.68 (m, 2H, CH$_2$); 1.68-1.42 (m, 6H, CH$_2$); 1.42-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.95 (C=O); 153.38 (C); 144.63 (CH=CH); 140.05 (C); 129.87 (C); 117.37 (CH=CH); 105.19 (CH arom.); 64.26 (CH$_2$); 62.19 (CH$_2$); 60.91 (OCH$_3$); 56.12 (OCH$_3$); 49.52 (CH$_2$); 49.26 (CH$_2$); 29.53 (CH$_2$); 29.06 (CH$_2$); 28.57 (CH$_2$); 28.24 (CH$_2$); 26.55 (CH$_2$) ppm.

5.1.3.3. (E)-5-((4-Hydroxybutyl)amino)pentyl 3-(3,4,5- trimethoxyphenyl)acrylate 47

Chromatographic eluent: abs. ethanol/ CH$_2$Cl$_2$/petroleum ether/NH$_4$OH 65:340:60:8. Yield: 72.5%. ^{1}H-NMR (CDCl$_3$) δ: 7.53 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.29 (d, J=16.0 Hz, 1H, CH=*CH*); 4.13 (t, J=6.8 Hz, 2H, CH$_2$O); 3.83 (s, 6H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 3.51 (t, J=5.0 Hz, 2H, CH$_2$OH); 3.44 (bs, 1H, OH); 2.61-2.56 (m, 4H, NCH$_2$); 1.72-1.48 (m, 8H, CH$_2$); 1.49-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 153.38 (C); 144.61 (CH=CH); 140.04 (C); 129.91 (C); 117.39 (CH=CH); 105.21 (CH arom.); 64.36 (CH$_2$); 62.44 (CH$_2$); 60.90 (OCH$_3$); 56.12 (OCH$_3$); 49.64 (CH$_2$); 49.32 (CH$_2$); 32.39 (CH$_2$); 29.31 (CH$_2$); 26.59 (CH$_2$); 26.44 (CH$_2$); 23.73 (CH$_2$) ppm.

5.1.3.4. (E)-3-((6-Hydroxyhexyll)amino)propyl 3-(3,4,5-trimethoxyphenyl)acrylate 48

Chromatographic eluent: abs. ethanol/ CH$_2$Cl$_2$/petroleum ether/NH$_4$OH 65:340:60:8. Yield: 51.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.60 (d, J=16.0 Hz, 1H, *CH*=CH); 6.74 (s, 2H, CH arom.); 6.32 (d, J=16.0 Hz, 1H, CH=*CH*); 4.26 (t, J=6.0 Hz, 2H, CH$_2$O); 3.87 (s, 6H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 3.61 (t, J=6.8 Hz, 2H, CH$_2$OH); 2.72 (t, J=7.2 Hz, 2H, NCH$_2$); 2.61 (t, J=7.2 Hz, 2H, NCH$_2$); 1.96-1.85 (m, 2H, CH$_2$); 1.83 (bs, 1H, NH); 1.61-1.58 (m, 4H, CH$_2$); 1.40-1.30 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.99 (C=O); 153.43 (C); 144.81 (CH=CH); 140.16 (C); 129.87 (C); 117.25 (CH=CH); 105.26 (CH arom.); 62.80 (CH$_2$); 62.68 (CH$_2$); 60.96 (OCH$_3$); 56.17 (OCH$_3$); 49.81 (CH$_2$); 46.61 (CH$_2$); 32.65 (CH$_2$); 29.88 (CH$_2$); 29.22 (CH$_2$); 27.04 (CH$_2$); 25.62 (CH$_2$) ppm.

5.1.3.5. (E)-6-((3-Hydroxypropyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 49

Chromatographic eluent: abs. ethanol/ CH$_2$Cl$_2$/petroleum ether/NH$_4$OH 65:340:60:8. Yield: 80.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.50 (d, J=15.6 Hz, 1H, *CH*=CH); 6.78 (s, 2H, CH arom.); 6.27 (d, J=15.6 Hz 1H, CH=*CH*); 4.11 (t, J=6.8 Hz, 2H, CH$_2$O); 3.80 (s, 6H, OCH$_3$); 3.79 (s, 3H, OCH$_3$); 3.69 (t, J=5.6 Hz, 2H, CH$_2$OH); 3.51 (bs, 2H, NH+OH); 2.79 (t, J=6.0 Hz, 2H, NCH$_2$); 2.56 (t, J=6.8 Hz, 2H, NCH$_2$); 1.69-1.57 (m, 4H, CH$_2$); 1.52-1.41 (m, 2H, CH$_2$); 1.40-1.22 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 153.35 (C); 144.57 (CH=CH); 140.01 (C); 129.89 (C); 117.37 (CH=CH); 105.20 (CH arom.); 64.43 (CH$_2$); 63.48 (CH$_2$); 60.86 (OCH$_3$); 56.10 (OCH$_3$); 49.49 (CH$_2$); 49.37 (CH$_2$); 30.48 (CH$_2$); 29.42 (CH$_2$); 28.61 (CH$_2$); 28.81 (CH$_2$); 25.78 (CH$_2$) ppm.

5.1.3.6. (E)-4-((6-Hydroxyhexyl)amino)butyl 3-(3,4,5-trimethoxyphenyl)acrylate 50

Chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 90:10:1. Yield: 57.4%. ^{1}H-NMR (CDCl$_3$) δ: 7.50 (d, J=16.0 Hz, 1H, *CH*=CH); 6.67 (s, 2H, CH arom.); 6.25 (d, J=16.0 Hz, 1H, CH=*CH*); 4.13 (t, J=6.8 Hz, 2H, CH$_2$O); 3.80 (s, 6H, OCH$_3$); 3.78 (s, 3H, OCH$_3$); 3.50 (t, J=6.4 Hz, 2H, CH$_2$OH); 2.57 (t, J=6.8 Hz, 2H, NCH$_2$); 2.53 (t, J=7.2 Hz, 2H, NCH$_2$); 2.45 (bs, 2H, OH+NH); 1.71-1.60 (m, 2H, CH$_2$); 1.59-1.49 (m, 2H, CH$_2$); 1.58-1.45 (m, 4H, CH$_2$); 1.33-1.20 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.92 (C=O); 153.35 (C); 144.63 (CH=CH); 140.04 (C); 129.85 (C); 117.29 (CH=CH); 105.20 (CH arom.); 64.28 (CH$_2$); 62.24 (CH$_2$); 60.86 (OCH$_3$); 56.09 (OCH$_3$); 49.74 (CH$_2$); 49.40 (CH$_2$); 32.64 (CH$_2$); 29.75 (CH$_2$); 27.05 (CH$_2$); 26.55 (CH$_2$); 26.31 (CH$_2$); 25.67 (CH$_2$) ppm.

5.1.3.7. (E)-6-((4-Hydroxybutyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 51

Chromatographic eluent: $CH_2Cl_2/MeOH/NH_4OH$ 95:5:0.5. Yield: 70.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.58 (d, J=15.6 Hz, 1H, *CH*=CH); 6.75 (s, 2H, CH arom.); 6.34 (d, J=15.6 Hz, 1H, CH=*CH*); 4.19 (t, J=6.4 Hz, 2H, CH$_2$O); 3.89 (s, 6H, OCH$_3$); 3.87 (s, 3H, OCH$_3$); 3.57 (t, J=6.4 Hz, 2H, CH$_2$OH); 2.68-2.58 (m, 4H, NCH$_2$); 1.72-1.58 (m, 6H, CH$_2$); 1.60-1.51 (m, 2H, CH$_2$); 1.47-1.32 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 167.27 (C=O); 153.44 (C); 144.61 (CH=CH); 129.96 (C); 117.48 (CH=CH); 105.27 (CH arom.); 64.52 (CH$_2$); 62.58 (CH$_2$); 60.97 (OCH$_3$); 56.18 (OCH$_3$); 49.66 (CH$_2$); 49.39 (CH$_2$); 32.60 (CH$_2$); 29.53 (CH$_2$); 28.83 (CH$_2$); 28.66 (CH$_2$); 26.93 (CH$_2$); 25.85 (CH$_2$) ppm.

5.1.3.8. (E)-6-((3-Hydroxypropyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 52

Yield: 72.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.53 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.29 (d, J=16.0 Hz, 1H, CH=*CH*); 4.14 (t, J=6.8 Hz, 2H, CH$_2$O); 3.83 (s, 6H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 3.73 (t, J=5.6 Hz, 2H, CH$_2$OH); 2.91 (bs, 2H, NH+OH); 2.80 (t, J=6.0 Hz, 2H, NCH$_2$); 2.55 (t, J=7.2 Hz, 2H, NCH$_2$); 1.72-1.62 (m, 4H, CH$_2$); 1.50-1.38 (m, 2H, CH$_2$); 1.38-1.25 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 167.05 (C=O); 153.42 (C); 144.58 (CH=CH); 140.10 (C); 129.95 (C); 117.48 (CH=CH); 105.27 (CH arom.); 64.61 (CH$_2$); 64.19 (CH$_2$); 60.93 (OCH$_3$); 56.16 (OCH$_3$); 49.87 (CH$_2$); 49.71 (CH$_2$); 30.56 (CH$_2$); 29.74 (CH$_2$); 29.12 (CH$_2$); 28.68 (CH$_2$); 27.12 (CH$_2$); 25.88 (CH$_2$) ppm.

5.1.3.9. 6-((3-Hydroxypropyl)amino)hexyl 3,4,5-trimethoxybenzoate 53

Chromatographic eluent: abs. ethanol/ CH_2Cl_2/petroleum ether/NH$_4$OH 65:340:60:8. Yield: 71.4%. ^{1}H-NMR (CDCl$_3$) δ: 7.24 (s, 2H, CH arom.); 4.24 (t, J=6.8 Hz, 2H, CH$_2$O); 3.85 (s, 6H, OCH$_3$); 3.84 (s, 3H, OCH$_3$); 3.73 (t, J=5.6 Hz, 2H, CH$_2$OH); 3.21 (bs, 1H, OH); 2.80 (t, J=6.0 Hz, 2H, NCH$_2$); 2.55 (t, J=6.8 Hz, 2H, NCH$_2$); 1.76-1.67 (m, 2H, CH$_2$); 1.67-61 (m, 2H, CH$_2$); 1.48-1.23 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.21 (C=O); 152.87 (C); 142.12 (C); 125.48 (C); 106.78 (CH arom.); 65.15 (CH$_2$); 64.00 (CH$_2$); 60.84 (OCH$_3$); 56.20 (OCH$_3$); 49.76 (CH$_2$); 49.70 (CH$_2$); 30.64 (CH$_2$); 29.74 (CH$_2$); 29.30 (CH$_2$); 28.65 (CH$_2$); 27.11 (CH$_2$); 25.89 (CH$_2$) ppm.

5.1.3.10. 6-((3- Hydroxypropyl)amino)hexyl anthracene-9-carboxylate 54

Chromatographic eluent: abs. ethanol/ CH_2Cl_2/petroleum ether/NH$_4$OH 65:340:60:8. Yield: 48.4%. ^{1}H-NMR (CDCl$_3$) δ: 8.50 (s, 1H, CH arom.); 8.03 (d, J=8.8 Hz, 2H, CH arom.); 8.00 (d, J=8.4 Hz, 2H, CH arom.); 7.55-7.40 (m, 4H, CH arom.); 4.60 (t, J=6.8 Hz, 2H, CH$_2$O); 3.78 (t, J=5.2 Hz, 2H, CH$_2$OH); 3.21 (bs, 1H, OH); 2.82 (t, J=5.6 Hz, 2H, NCH$_2$); 2.56 (t, J=7.2 Hz, 2H, NCH$_2$); 1.90-1.81 (m, 2H, CH$_2$); 1.72-1.61 (m, 2H, CH$_2$); 1.50-1.20 (m, 8H, CH$_2$) ppm.

5.1.4. General procedure for the synthesis of (hydroxyalkyl)methylaminoesters 55-64

A 1 mmol portion of the appropriate hydroxyaminoester (**45-54**) was dissolved in 5 mL of anhydrous ethanol and HCOOH (17 mmol) and 37% HCHO solution (5 mmol) were added. The mixture was heated to 80 °C for 4-5 h and concentrated in vacuo. The residue was then dissolved in CH_2Cl_2 and the organic layer was washed with 10% NaOH solution. After drying with Na$_2$SO$_4$, the solvent was removed under reduced pressure, giving a pure compound as yellow oil which was used as such for the next reaction.

5.1.4.1. (E)-2-((6-Hydroxyhexyl)(methyl)amino)ethyl 3-(3,4,5-trimethoxyphenyl)acrylate 55

Yield: 80.7%. ^{1}H-NMR (CDCl$_3$) δ: 7.61 (d, J=16.0 Hz, 1H, *CH*=CH); 6.75 (s, 2H, CH arom.); 6.37 (d, J=16.0 Hz, 1H, CH=*CH*); 4.33 (t, J=6.0 Hz, 2H, CH$_2$O); 3.88 (s, 6H, OCH$_3$); 3.87 (s, 3H, OCH$_3$); 3.62 (t, J=6.4 Hz, 2H, CH$_2$O); 2.75 (t, J=6.0 Hz, 2H, NCH$_2$); 2.47 (t, J=7.2 Hz, 2H, NCH$_2$); 2.36 (s, 3H, NCH$_3$); 1.63 -1.48 (m, 4H, CH$_2$); 1.46-1.28 (m, 4H, CH$_2$) pp

5.1.4.2. (E)-4-((5-Hydroxypentyl)(methyl)amino)butyl 3-(3,4,5-trimethoxyphenyl)acrylate 56

Yield: 92.0%. ^{1}H-NMR (CDCl$_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.30 (d, J=16.0 Hz, 1H, CH=*CH*); 4.17 (t, J=6.8 Hz, 2H, CH$_2$O); 3.84 (s, 6H, OCH$_3$); 3.83 (s, 3H, OCH$_3$); 3.58 (t, J=6.8 Hz, 2H, CH$_2$O); 2.40-2.25 (m, 4H, NCH$_2$); 2.16 (s, 3H, NCH$_3$); 1.74-1.50 (m, 6H, CH$_2$); 1.50-1.40 (m, 2H, CH$_2$); 1.40-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.99 (C=O); 153.39 (C); 144.62 (CH=CH); 140.05 (C); 129.91 (C); 117.40 (CH=CH); 105.20 (CH

arom.); 64.43 (CH$_2$); 62.62 (CH$_2$); 60.92 (OCH$_3$); 57.68 (CH$_2$); 57.35 (CH$_2$); 56.13 (OCH$_3$); 41.11 (NCH$_3$); 32.48 (CH$_2$); 28.88 (CH$_2$); 26.76 (CH$_2$); 24.14 (CH$_2$); 23.91 (CH$_2$) ppm.

5.1.4.3. (E)-5-((4-Hydroxybutyl)(methyl)amino)pentyl 3-(3,4,5-trimethoxyphenyl)acrylate 57
Yield: 85.0%. ^{1}H-NMR (CDCl$_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.30 (d, J=16.0 Hz, 1H, CH=*CH*); 4.15 (t, J=6.8 Hz, 2H, CH$_2$O); 3.84 (s, 6H, OCH$_3$); 3.83 (s, 3H, OCH$_3$); 3.51 (m, J=5.6 Hz, 2H, CH$_2$O); 2.41-2.30 (m, 4H, NCH$_2$); 2.19 (s, 3H, NCH$_3$); 1.74-1.51 (m, 6H, CH$_2$); 1.51-1.50 (m, 2H, CH$_2$); 1.48-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.96 (C=O); 153.39 (C); 144.57 (CH=CH); 140.06 (C); 129.93 (C); 117.42 (CH=CH); 105.22 (CH arom.); 64.39 (CH$_2$); 62.60 (CH$_2$); 60.90 (OCH$_3$); 58.17 (CH$_2$); 57.74 (CH$_2$); 56.13 (OCH$_3$); 41.21 (NCH$_3$); 32.54 (CH$_2$); 28.62 (CH$_2$); 26.45 (CH$_2$); 26.14 (CH$_2$); 23.89 (CH$_2$) ppm.

5.1.4.4. (E)-3-((6-Hydroxyhexyl)(methyl)amino)propyl 3-(3,4,5-trimethoxyphenyl)acrylate 58
Yield: 91.1%. ^{1}H-NMR (CDCl$_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.29 (d, J=16.0 Hz, 1H, CH=*CH*); 4.19 (t, J=6.8 Hz, 2H, CH$_2$O); 3.84 (s, 6H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 3.56 (t, J=6.8 Hz, 2H, CH$_2$O); 2.42 (t, J=7.2 Hz, 2H, NCH$_2$); 2.30 (t, J=7.6 Hz, 2H, NCH$_2$); 2.18 (s, 3H, NCH$_3$); 1.89-1.77 (m, 2H, CH$_2$); 1.54-1.49 (m, 2H, CH$_2$); 1.49-1.40 (m, 2H, CH$_2$); 1.40-1.20 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.95 (C=O); 153.40 (C); 144.68 (CH=CH); 140.11 (C); 129.88 (C); 117.31 (CH=CH); 105.25 (CH arom.); 63.03 (CH$_2$); 62.56 (CH$_2$); 60.91 (OCH$_3$); 57.58 (CH$_2$); 56.14 (OCH$_3$); 54.18 (CH$_2$); 42.09 (NCH$_3$); 32.67 (CH$_2$); 27.16 (CH$_2$); 27.08 (CH$_2$); 26.54 (CH$_2$); 25.64 (CH$_2$) ppm.

5.1.4.5. (E)-6-((3-Hydroxypropyl)(methyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 59
Yield: 96.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.49 (d, J=15.6 Hz, 1H, *CH*=CH); 6.67 (s, 2H, CH arom.); 6.26 (d, J=15.6 Hz, 1H, CH=*CH*); 4.10 (t, J=6.4 Hz, 2H, CH$_2$O); 3.79 (s, 6H, OCH$_3$); 3.78 (s, 3H, OCH$_3$); 3.69 (t, J=5.6 Hz, 2H, CH$_2$O); 2.48 (t, J=6.0 Hz, 2H, NCH$_2$); 2.27 (t, J=7.2 Hz, 2H, NCH$_2$); 2.14 (s, 3H, NCH$_3$); 1.68-1.58 (m, 4H, CH$_2$); 1.48-1.20 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.91 (C=O); 153.34 (C); 144.50 (CH=CH); 140.01 (C); 129.89 (C); 117.41 (CH=CH); 105.19 (CH arom.); 64.45 (CH$_2$); 64.42 (CH$_2$); 60.83 (OCH$_3$); 58.30 (CH$_2$); 57.97 (CH$_2$); 56.07 (OCH$_3$); 41.88 (NCH$_3$); 28.62 (CH$_2$); 27.78 (CH$_2$); 27.09 (CH$_2$); 26.91 (CH$_2$); 22.66 (CH$_2$) ppm.

5.1.4.6. (E)-4-(6-Hydroxyhexyl(methyl)amino)butyl 3-(3,4,5-trimethoxyphenyl)acrylate 60
Yield: 96.9%. ^{1}H-NMR (CDCl$_3$) δ: 7.50 (d, J=16.0 Hz, 1H, *CH*=CH); 6.68 (s, 2H, CH arom.); 6.26 (d, J=16.0 Hz, 1H, CH=*CH*); 4.13 (t, J=6.4 Hz, 2H, CH$_2$O); 3.80 (s, 6H, OCH$_3$); 3.79 (s, 3H, OCH$_3$); 3.51 (t, J=6.8 Hz, 2H, CH$_2$O); 2.86 (bs, 1H, OH); 2.30-2.22 (m, 4H, NCH$_2$); 2.12 (s, 3H, NCH$_3$); 1.65-1.59 (m, 2H, CH$_2$); 1.54-1.44 (m, 4H, CH$_2$); 1.43-1.33 (m, 2H, CH$_2$); 1.32-1.18 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.97 (C=O); 153.34 (C); 144.61 (CH=CH); 139.99 (C); 129.87 (C); 118.00 (CH=CH); 105.17 (CH arom.); 64.39 (CH$_2$); 62.40 (CH$_2$); 60.87 (OCH$_3$); 57.66 (CH$_2$); 57.25 (CH$_2$); 56.08 (OCH$_3$); 42.10 (NCH$_3$); 32.66 (CH$_2$); 27.25 (CH$_2$); 27.06 (CH$_2$); 26.73 (CH$_2$); 25.67 (CH$_2$); 23.63 (CH$_2$) ppm.

5.1.4.7. (E)-6-(4-Hydroxybutyl(methyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 61
Yield: 93.1%. ^{1}H-NMR (CDCl$_3$) δ: 7.53 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.30 (d, J=16.0 Hz, 1H, CH=*CH*); 4.14 (t, J=6.4 Hz, 2H, CH$_2$O); 3.84 (s, 6H, OCH$_3$); 3.83 (s, 3H, OCH$_3$); 3.52-3.47 (m, 2H, CH$_2$O); 2.36-2.24 (m, 4H, NCH$_2$); 2.17 (s, 3H, NCH$_3$); 1.70-1.55 (m, 6H, CH$_2$); 1.54-1.44 (m, 2H, CH$_2$); 1.53-1.23 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.96 (C=O); 153.40 (C); 144.51 (CH=CH); 140.07 (C); 129.94 (C); 117.47 (CH=CH); 105.23 (CH arom.); 64.49 (CH$_2$); 62.63 (CH$_2$); 60.88 (OCH$_3$); 58.23 (CH$_2$); 57.87 (CH$_2$); 56.12 (OCH$_3$); 41.23 (NCH$_3$); 32.66 (CH$_2$); 28.64 (CH$_2$); 27.09 (CH$_2$); 26.74 (CH$_2$); 26.30 (CH$_2$); 25.88 (CH$_2$) ppm.

5.1.4.8. (E)-6-((3-Hydroxypropyl(methyl)amino)hexyl 3-(3,4,5-trimethoxyphenyl)acrylate 62
Yield: 97.6%. ^{1}H-NMR (CDCl$_3$) δ: 7.56 (d, J=15.6 Hz, 1H, *CH*=CH); 6.73 (s, 2H, CH arom.); 6.31 (d, J=15.6 Hz, 1H, CH=*CH*); 4.16 (t, J=6.4 Hz, 2H, CH$_2$O); 3.86 (s, 6H, OCH$_3$); 3.85 (s, 3H, OCH$_3$); 3.76 (t, J=5.2 Hz, 2H, CH$_2$O); 2.56 (t, J=5.6 Hz, 2H, NCH$_2$); 2.33 (t, J=7.2 Hz, 2H, NCH$_2$); 2.21 (s, 3H, NCH$_3$); 1.72-1.63 (m, 4H, CH$_2$); 1.50-1.42 (m, 2H, CH$_2$); 1.42-1.25 (m, 6H, CH$_2$) ppm.

5.1.4.9. 6-((3-Hydroxypropyl)(methyl)amino)hexyl 3,4,5-trimethoxybenzoate 63

Yield: 79.8%. ^{1}H-NMR (CDCl$_3$) δ: 7.26 (s, 2H, CH arom.); 4.27 (t, J=6.8 Hz, 2H, CH$_2$O); 3.87 (s, 6H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 3.75 (t, J=5.4 Hz, 2H, CH$_2$O); 2.47 (t, J=5.6 Hz, 2H, NCH$_2$); 2.32 (t, J=7.6 Hz, 2H, NCH$_2$); 2.20 (s, 3H, NCH$_3$); 1.80-1.69 (m, 2H, CH$_2$); 1.68-1.62 (m, 2H, CH$_2$); 1.50-1.23 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.24 (C=O); 152.88 (C); 142.10 (C); 125.50 (C); 106.77 (CH arom.); 65.18 (CH$_2$); 64.59 (CH$_2$); 60.86 (OCH$_3$); 58.50 (CH$_2$); 58.06 (CH$_2$); 56.21 (OCH$_3$); 41.85 (NCH$_3$); 29.16 (CH$_2$); 28.67 (CH$_2$); 27.65 (CH$_2$); 27.17 (CH$_2$); 27.10 (CH$_2$); 25.92 (CH$_2$) ppm.

5.1.4.10. 6-((3-Hydroxypropyl)(methyl)amino)hexyl anthracene-9-carboxylate 64

Yield: 87.2%. ^{1}H-NMR (CDCl$_3$) δ: 8.50 (s, 1H, CH arom.); 8.03 (d, J=8.8 Hz, 2H, CH arom.); 8.00 (d, J=8.4 Hz, 2H, CH arom.); 7.55-7.42 (m, 4H, CH arom.); 4.61 (t, J=6.8 Hz, 2H, CH$_2$O); 3.78 (t, J=5.2 Hz, 2H, CH$_2$O); 2.56 (t, J=5.6 Hz, 2H, NCH$_2$); 2.34 (t, J=7.2 Hz, 2H, NCH$_2$); 2.21 (s, 3H, NCH$_3$); 1.93-1.86 (m, 2H, CH$_2$); 1.70-1.64 (m, 2H, CH$_2$); 1.50-1.20 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.77 (C=O); 131.01 (C); 129.20 (CH arom.); 128.61 (CH arom.); 128.39 (C); 129.92 (CH arom.); 125.46 (CH arom.); 125.02 (CH arom.); 65.91 (CH$_2$); 64.61 (CH$_2$); 58.45 (CH$_2$); 58.07 (CH$_2$); 41.85 (NCH$_3$); 29.15 (CH$_2$); 28.72 (CH$_2$); 27.65 (CH$_2$); 27.18 (CH$_2$); 27.03 (CH$_2$); 26.03 (CH$_2$) ppm.

5.1.5. General procedure for the synthesis of (2-hydroxyethyl)methylaminoesters 65-72

The appropriate haloester (**35-40**, **43**, **4**) (1 mmol) and 2-methylaminoethan-1-ol (2 mmol) were dissolved in 3 mL of anhydrous CH$_3$CN. The mixture was maintained at rt for 48 h. The reaction mixture was treated with CH$_2$Cl$_2$ and the organic layer was washed with 10% NaOH solution. After drying with Na$_2$SO$_4$, the solvent was removed under reduced pressure.

The substances obtained were used as such for the next reaction (**65**, **66**, **67**), or were purified by flash chromatography in the case of **68**, **69**, **70**, **71** and **72**.

5.1.5.1. (E)-6-((2- Hydroxyethyl) methylamino)hexyl 3-(3,4,5- trimethoxyphenyl)acrylate 65

Yellow oil. Yield: 91.0%. ^{1}H-NMR (CDCl$_3$) δ: 7.56 (d, J=16.0 Hz, 1H, *CH*=CH); 6.73 (s, 2H, CH arom.); 6.32 (d, J=16.0 Hz, 1H, CH=*CH*); 4.17 (t, J=6.8 Hz, 2H, CH$_2$O); 3.86 (s, 6H, OCH$_3$); 3.85 (s, 3H, OCH$_3$); 3.55 (t, J=5.6 Hz, 2H, CH$_2$OH); 2.99 (bs, 1H, OH); 2.49 (t, J=5.6 Hz, 2H, NCH$_2$); 2.37 (t, J=7.2 Hz, 2H, NCH$_2$);2.21 (s, 3H, NCH$_3$); 1.77-1.60 (m, 2H, CH$_2$); 1.53-1.42 (m, 2H, CH$_2$); 1.41-1.26 (m, 4H, CH$_2$) ppm.

5.1.5.2. 6-((2-Hydroxyethyl)methylamino)hexyl anthracene-9-carboxylate 66

Yellow oil. Yield: 94.9%. ^{1}H-NMR (CDCl$_3$) δ: 8.48 (s, 1H, CH arom.); 8.05-7.87 (m, 4H, CH arom.); 7.56-7.40 (m, 4H, CH arom.); 4.62 (t, J=6.8 Hz, 2H, CH$_2$O); 3.57 (t, J=5.6 Hz, 2H, CH$_2$OH); 2.50 (t, J=5.6 Hz, 2H, NCH$_2$); 2.39 (t, J=6.8 Hz, 2H, NCH$_2$); 2.23 (s, 3H, NCH$_3$); 1.95-1.86 (m, 2H, CH$_2$); 1.57-1.43 (m, 4H, CH$_2$); 1.42-1.30 (m, 2H, CH$_2$) ppm.

5.1.5.3. (E)-7-((2- Hydroxyethyl)methylamino)heptyl 3-(3,4,5- trimethoxyphenyl)acrylate 67

Yellow-orange oil. Yield 93.2%. ^{1}H-NMR (CDCl$_3$) δ: 7.52 (d, J=16.0 Hz, 1H, *CH*=CH); 6.69 (s, 2H, CH arom.); 6.28 (d, J=16.0 Hz, 1H, CH=*CH*); 4.13 (t, J=6.4 Hz, 2H, CH$_2$O); 3.82 (s, 6H, OCH$_3$); 3.81 (s, 3H, OCH$_3$); 3.51 (t, J=5.6 Hz, 2H, CH$_2$OH); 2.99 (bs, 1H, OH); 2.44 (t, J=5.6 Hz, 2H, NCH$_2$); 2.32 (t, J=7.2 Hz, 2H, NCH$_2$); 2.16 (s, 3H, NCH$_3$); 1.69-1.59 (m, 2H, CH$_2$); 1.48-1.20 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 153.37 (C); 144.52 (CH=CH); 140.05 (C); 129.92 (C); 117.44 (CH=CH); 105.23 (CH arom.); 64.56 (CH$_2$); 60.86 (OCH$_3$); 58.86 (CH$_2$); 58.41 (CH$_2$); 57.72 (CH$_2$); 56.10 (OCH$_3$); 41.63 (NCH$_3$); 29.13 (CH$_2$); 28.66 (CH$_2$); 27.14 (CH$_2$); 25.89 (CH$_2$) ppm.

5.1.5.4. 7-((2-Hydroxyethyl)methylamino)heptyl 3,4,5-trimethoxybenzoate 68

Oil. Chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 95:5:0.5. Yield: 77.3%. ^{1}H-NMR (CDCl$_3$) δ: 7.27 (s, 2H, CH arom.); 4.28 (t, J=6.8 Hz, 2H, CH$_2$O); 3.89 (s, 6H, OCH$_3$); 3.88 (s, 3H, OCH$_3$); 3.55 (t, J=5.6 Hz, 2H, CH$_2$OH); 2.92 (bs, 1H, OH); 2.50 (t, J=5.6 Hz, 2H, NCH$_2$); 2.38 (t, J=7.6 Hz, 2H, NCH$_2$); 2.22 (s, 3H, NCH$_3$); 1.81-1.70 (M, 2H, CH$_2$); 1.50-1.28 (m, 8H, CH$_2$) ppm.

5.1.5.5. 7-((2-Hydroxyethyl)methylamino)heptyl anthracene-9-carboxylate 69

Pale yellow oil. Chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 96:4:0.4. Yield: 66%. ^{1}H-NMR ($CDCl_3$) δ: 8.51 (s, 1H, CH arom.); 8.04 (d, J=8.8 Hz, 2H, CH arom.); 8.05 (d, J=8.4 Hz, 2H, CH arom.); 7.58-7.40 (m, 4H, CH arom.); 4.61 (t, J=6.8 Hz, 2H, CH_2O); 3.57 (t, J=5.6 Hz, 2H, CH_2OH); 2.92 (bs, 1H, OH); 2.51 (t, J=5.6 Hz, 2H, NCH_2); 2.39 (t, J=7.6 Hz, 2H, NCH_2; 2.25 (s, 3H, NCH_3); 1.94-1.83 (m 2H, CH_2); 1.50-1.20 (m, 8H, CH_2) ppm.

5.1.5.6. (E)-8-(2- Hydroxyethyl)methylamino)octyl 3-(3,4,5-trimethoxyphenyl)acrylate 70

Pale yellow oil. Chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 90:10:1. Yield: 56.1%. ^{1}H-NMR ($CDCl_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 6.71 (s, 2H, CH arom.); 6.30 (d, J=16.0 Hz, 1H, CH=*CH*); 4.15 (t, J=6.8 Hz, 2H, CH_2O); 3.84 (s, 6H, OCH_3); 3.83 (s, 3H, OCH_3); 3.54 (t, J=5.6 Hz, 2H, CH_2OH); 2.96 (bs, 1H, OH); 2.47 (t, J=5.6 Hz, 2H, NCH_2); 2.35 (t, J=7.2 Hz, 2H, NCH_2); 2.19 (s, 3H, NCH_3); 1.70-1.59 (m, 2H, CH_2); 1.47-1.38 (m, 2H, CH_2); 1.37-1.19 (m, 8H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 167.02 (C=O); 153.39 (C); 144.54 (CH=CH); 140.01 (C); 129.94 (C); 117.47 (CH=CH); 105.18 (CH arom.); 64.64 (CH_2); 60.91 (OCH_3); 58.81 (CH_2); 58.33 (CH_2); 57.74 (CH_2); 56.11 (OCH_3); 41.60 (NCH_3); 29.40 (CH_2); 29.22 (CH_2); 28.71 (CH_2); 27.21 (CH_2); 27.18 (CH_2); 25.91 (CH_2) ppm.

5.1.5.7. 8-(2- Hydroxyethyl)methylamino)octyl 3-(3,4,5- trimethoxybenzoate 71

Pale yellow oil. Chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 95:5:0.5. Yield: 75.6%. ^{1}H-NMR ($CDCl_3$) δ: 7.28 (s, 2H, CH arom.); 4.29 (t, J=6.8 Hz, 2H, CH_2O); 3.89 (s, 6H, OCH_3); 3.88 (s, 3H, OCH_3); 3.56 (t, J=5.2 Hz, 2H, CH_2OH); 2.50 (t, J=5.2 Hz, 2H, CH_2N); 2.37 (t, J=7.2 Hz, 2H, CH_2N); 2.22 (s, 3H, NCH_3); 1.81-1.70 (m, 2H, CH_2); 1.50-1.22 (m, 10H, CH_2) ppm.

5.1.5.8. 8-(2- Hydroxyethyl)methylamino)octyl anthracene-9-carboxylate 72

Yellow oil. Chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 90:10:0.1. Yield: 32.4%. ^{1}H-NMR ($CDCl_3$) δ: 8.50 (s, 1H, CH arom.); 8.05-8.00 (m, 4H, CH arom.); 7.61-7.47 (m, 4H, CH arom.); 4.61 (t, J=6.8 Hz, 2H, CH_2O); 3.57 (t, J=5.2 Hz, 2H, CH_2OH); 2.50 (t, J=5.2 Hz, 2H, NCH_2); 2.37 (t, J=7.2 Hz, 2H, NCH_2); 2.20 (s, 3H, NCH_3); 1.93-1.82 (m, 2H, CH_2); 1.53-1.42 (m, 2H, CH_2); 1.51-1.20 (m, 8H, CH_2) ppm.

5.1.6. General procedures for the synthesis of diester compounds *1-28*

Diester compounds were synthesized using two different general procedures.

General procedure A.

A solution of the suitable (hydroxyalkyl)methylaminoester (0.250 mmol) in 5 mL of an. CH_2Cl_2 was cooled at 0 °C and 0.360 mmol of the appropriate carboxylic acid, 0.083 mmol of 4-dimethylaminopiridine (DMAP) and 0.500 mmol of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCl) were added. The reaction mixture was stirred for 1 h at 0 °C and 48 h at room temperature. Then CH_2Cl_2 was added and the organic layer was washed twice with a saturated solution of $NaHCO_3$. After drying with Na_2SO_4, the solvent was removed under reduced pressure. The crude product was then purified by flash chromatography using the appropriate eluting system, yielding the desired compound as an oil. All the compounds were transformed into the corresponding hydrochloride as white solid. The salts were crystallized from abs. ethanol/petroleum ether.

General procedure B.

A 0.250 mmol portion of the appropriate carboxylic acid ((*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid, 3,4,5-trimethoxybenzoic acid or anthracene-9-carboxylic acid) was transformed into the acyl chloride by reaction with $SOCl_2$ (2 eq) in 3 mL of $CHCl_3$ (free of ethanol) at 60 °C for 4-5 h.

The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure; the mixture was then treated twice with cyclohexane and the solvent removed under reduce pressure. The acyl chloride obtained was dissolved in $CHCl_3$ (free of ethanol), and the suitable (hydroxyalkyl)methylaminoester (1 eq) was added. The mixture was heated to 60 °C. After 4 h, the reaction mixture was cooled to rt, and treated with CH_2Cl_2. The resulting organic layer was washed with 10% NaOH solution, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The substances obtained were purified by flash chromatography using the appropriate eluting

system, yielding the desired compound as an oil. All the compounds were transformed into the corresponding hydrochloride as white solid. The salts were crystallized from abs. ethanol/petroleum ether.

5.1.6.1. (E)-2-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy))hexyl)amino)ethyl 3,4,5-trimethoxybenzoate 1

Procedure A, starting from **65** and 3,4,5-trimethoxybenzoic acid.
Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 69.1.%.
^{1}H-NMR (CDCl$_3$) δ: 7.58 (d, J=15.6 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.35 (d, J=15.6 Hz, 1H, CH=*CH*); 4.35-4.20 (m, 4H, CH$_2$O); 3.87 (s, 6H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 3.84 (s, 3H, OCH$_3$); 2.72 (t, J=6.0 Hz, 2H, NCH$_2$); 2.45 (t, J=7.6 Hz, 2H, NCH$_2$); 2.33 (s, 3H, NCH$_3$); 1.80-1.70 (m, 2H, CH$_2$); 1.80-1.70 (m, 2H, CH$_2$); 1.60-1.48 (m, 2H, CH$_2$); 1.48-1.30 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.85 (C=O); 166.21 (C=O); 153.42 (C); 152.91 (C); 144.97 (CH=CH); 142.16 (C); 140.17(C); 129.83 (C); 125.46 (C); 117.15 (CH=CH); 106.84 (CH arom.); 105.31 (CH arom.); 65.07 (CH$_2$); 61.88 (CH$_2$); 60.92 (OCH$_3$); 60.87 (OCH$_3$); 57.80 (NCH$_2$); 56.23 (OCH$_3$); 56.14 (OCH$_3$) ; 55.60 (NCH$_2$); 42.53 (NCH$_3$); 28.71 (CH$_2$); 27.03 (CH$_2$); 26.87 (CH$_2$) ; 25.92 (CH$_2$) ppm.
Hydrochloride: mp 90-92 °C. **Anal:** $C_{31}H_{44}ClNO_{10}$ (C, H, N).

5.1.6.2. (E)-6-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)hexyl 3,4,5-trimethoxybenzoate 2

Procedure A, starting from **55** and 3,4,5-trimethoxybenzoic acid.
Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 68.8.%.
^{1}H-NMR (CDCl$_3$) δ: 7.58 (d, J=16.0 Hz, 1H, *CH*=CH); 7.27 (s, 2H, CH arom.); 6.73 (s, 2H, CH arom.); 6.36 (d, J=16.0 Hz, 1H, CH=*CH*); 4.35-4.24 (m, 4H, CH$_2$O); 3.97-3.80 (m, 18H, OCH$_3$); 2.70 (t, J=6.0 Hz, 2H, NCH$_2$); 2.43 (t, J=7.6 Hz, 2H, NCH$_2$); 2.31 (s, 3H, NCH$_3$); 1.80-1.70 (m, 2H, CH$_2$); 1.58-1.43 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.85 (C=O); 166.21 (C=O); 153.42 (C); 152.91 (C); 144.97 (CH=CH); 142.16 (C); 140.17(C); 129.83 (C); 125.46 (C); 117.15 (CH=CH); 106.84 (CH arom.); 105.31 (CH arom.); 65.07 (CH$_2$); 61.88 (CH$_2$); 60.92 (OCH$_3$); 60.87 (OCH$_3$); 57.80 (NCH$_2$); 56.23 (OCH$_3$); 56.14 (OCH$_3$); 55.60 (NCH$_2$); 42.53 (NCH$_3$); 28.71 (CH$_2$); 27.03 (CH$_2$); 26.87 (CH$_2$); 25.92 (CH$_2$) ppm.
Hydrochloride: mp 97-98 °C. **Anal:** $C_{31}H_{44}ClNO_{10}$ (C, H, N).

5.1.6.3. (E)-2-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)hexyl)amino)ethyl anthracene-9- carboxylate 3

Procedure B, starting from **65** and anthracene-9-carboxylic acid.
Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 32.8.%.
^{1}H-NMR (CDCl$_3$) δ: 8.49 (s, 1H, CH arom.); 8.14 (d, J=8.8 Hz, 2H, CH arom.); 7.98 (d, J=8.4 Hz, 2H, CH arom.); 7.58 (d, J=15.6 Hz, 1H, *CH*=CH); 7.53-7.43 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.33 (d, J=15.6 Hz, 1H, CH=*CH*); 4.75 (t, J=5.6 Hz, 2H, CH$_2$O); 4.14 (t, J=6.8 Hz, 2H, CH$_2$O); 3,87 (s, 3H, OCH$_3$); 3,85 (s, 6H, OCH$_3$); 2.90 (t, J=5.6 Hz, 2H, NCH$_2$); 2.51 (t, J=7.6 Hz, 2H, NCH$_2$); 2.39 (s, 3H, NCH$_3$); 1.69-1.51 (m, 4H, CH$_2$); 1.43-1.18 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.45 (C=O); 167.02 (C=O); 153.42 (C); 144.59 (CH=CH); 130.96 (C); 129.95 (C); 129.37 (CH arom.); 128.47 (CH arom.); 128.18 (C); 126.91 (CH arom.); 125.46 (CH arom.); 125.22 (CH arom.); 117.47 (CH=CH); 105.21 (CH arom.); 64.54 (CH$_2$); 62.97 (CH$_2$); 60.96 (OCH$_3$); 57.78 (CH$_2$); 56.13 (OCH$_3$); 55.91 (CH$_2$); 42.36 (NCH$_3$); 28.83 (CH$_2$); 27.19 (CH$_2$); 25.90 (CH$_2$) ppm.
Hydrochloride: mp 84-86 °C. **Anal:** $C_{36}H_{42}ClNO_7$ (C, H, N).

5.1.6.4. (E)-6-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)hexyl anthracene-9- carboxylate 4

Procedure A, starting from **66** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.
Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 99:1:0.1. Yield: 39.7.%.

^{1}H-NMR (CDCl$_3$) δ: 8.47 (s, 1H, CH arom.); 8.02 (d, J=8.8 Hz, 2H, CH arom.); 7.97 (d, J=8.4 Hz, 2H, CH arom.); 7.60 (d, J=16.0 Hz, 1H, *CH*=CH); 7.55-7.43 (m, 4H, CH arom.); 6.72 (s, 2H, CH arom.); 6.37 (d, J=16.0 Hz, 1H, CH=*CH*); 4.59 (t, J=6.8 Hz, 2H, CH$_2$O); 4.29 (t, J=6.0 Hz, 2H, CH$_2$O); 3,85 (s, 3H, OCH$_3$); 3,82 (s, 6H, OCH$_3$); 2.68 (t, J=5.6 Hz, 2H, NCH$_2$); 2.40 (t, J=7.2 Hz, 2H, NCH$_2$); 2.29 (s, 3H, NCH$_3$); 1.91-1.78 (m, 2H, CH$_2$); 1.54-1.41 (m, 4H, CH$_2$); 1.40-1.33 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.69 (C=O); 166.93 (C=O); 153.41 (C); 144.86 (CH=CH); 140.11 (C); 130.97 (C); 129.89 (C); 129.22 (CH arom.); 128.62 (CH arom.); 128.36 (C); 126.92 (CH arom.); 125.46 (CH arom.); 124.98 (CH arom.); 117.30 (CH=CH); 105.24 (CH arom.); 65.80 (CH$_2$); 62.15 (CH$_2$); 60.94 (OCH$_3$); 57.86 (CH$_2$); 56.11 (OCH$_3$); 55.72 (CH$_2$); 42.66 (NCH$_3$); 28.75 (CH$_2$); 27.04 (CH$_2$); 26.05 (CH$_2$) ppm.

Hydrochloride: mp 61-63 °C. **Anal:** C$_{36}$H$_{42}$ClNO$_7$ (C, H, N).

5.1.6.5. ***(E)-4-(Methyl-(5-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)pentyl)amino)butyl 3,4,5-trimethoxybenzoate 5***

Procedure B, starting from **57** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 95:5:0.5. Yield: 83.1.%.

^{1}H-NMR (CDCl$_3$) δ: 7.57 (d, J=16.0 Hz, 1H, *CH*=CH); 7.28 (s, 2H, CH arom.); 6.74 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.31 (t, J=6.8 Hz, 2H, CH$_2$O); 4.19 (t, J=6.4 Hz, 2H, CH$_2$O); 3,89 (s, 3H, OCH$_3$); 3,88 (s, 6H, OCH$_3$); 3,86 (s, 6H, OCH$_3$); 3,85 (s, 3H, OCH$_3$); 2.48-2.30 (m, 4H, NCH$_2$); 2.21 (s, 3H, NCH$_3$); 1.83-1.78 (m, 2H, CH$_2$); 1.78-1.68 (m, 2H, CH$_2$); 1.68-1.55 (m, 2H, CH$_2$); 1.55-1.48 (m, 2H, CH$_2$); 1.48-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.96 (C=O); 166.20 (C=O); 153.41 (C); 152.90 (C); 144.59 (CH=CH); 142.19 (C); 140.10 (C); 129.91 (C); 125.42 (C); 117.42 (CH=CH); 106.82 (CH arom.); 105.23 (CH arom.); 65.03 (CH$_2$); 64.50 (CH$_2$); 60.91 (OCH$_3$); 60.86 (OCH$_3$); 57.68 (CH$_2$); 57.30 (CH$_2$); 56.22 (OCH$_3$); 56.13 (OCH$_3$); 42.10 (NCH$_3$); 28.70 (CH$_2$); 26.96 (CH$_2$); 26.75 (CH$_2$); 23.95 (CH$_2$); 23.80 (CH$_2$) ppm. ESI-MS *m/z* (%): 604 (100) [*M*+H]$^+$.

Hydrochloride: mp 98-100 °C. **Anal:** C$_{32}$H$_{46}$ClNO$_{10}$ (C, H, N).

5.1.6.6. ***(E)-5-(Methyl-(4-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)butyl)amino)pentyl 3,4,5-trimethoxybenzoate 6***

Procedure A, starting from **56** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 96:4:0.4. Yield: 89.2.%.

^{1}H-NMR (CDCl$_3$) δ: 7.55 (d, J=16.0 Hz, 1H, *CH*=CH); 7.25 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.30 (d, J=16.0 Hz, 1H, *CH*=CH); 4.27 (t, J=6.8 Hz, 2H, CH$_2$O); 4.18 (t, J=6.2 Hz, 2H, CH$_2$O); 3,86 (s, 9H, OCH$_3$); 3,85 (s, 6H, OCH$_3$); 3,83 (s, 3H, OCH$_3$); 2.39-2.30 (m, 4H, NCH$_2$); 2.19 (s, 3H, NCH$_3$); 1.80-1.63 (m, 4H, CH$_2$); 1.63-1.48 (m, 4H, CH$_2$); 1.48-1.32 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.95 (C=O); 166.21 (C=O); 153.40 (C); 152.89 (C); 144.63 (CH=CH); 142.29 (C); 140.07 (C); 129.90 (C); 125.44 (C); 117.38 (CH=CH); 106.80 (CH arom.); 105.21 (CH arom.); 65.09 (CH$_2$); 64.49 (CH$_2$); 60.92 (OCH$_3$); 60.87 (OCH$_3$); 57.65 (CH$_2$); 57.29 (CH$_2$); 56.22 (OCH$_3$); 56.13 (OCH$_3$); 42.05 (NCH$_3$); 28.70 (CH$_2$); 26.91 (CH$_2$); 26.73 (CH$_2$); 23.94 (CH$_2$); 23.75 (CH$_2$) ppm. ESI-MS *m/z* (%): 604.2 (100) [*M*+H]$^+$.

Hydrochloride: mp 89-91 °C. **Anal:** C$_{32}$H$_{46}$ClNO$_{10}$ (C, H, N).

5.1.6.7. ***(E)-4-(Methyl-(5-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)pentyl)amino)butyl anthracene-9-carboxylate 7***

Procedure B, starting from **57** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 97:3:0.3. Yield: 23.1.%.

^{1}H-NMR (CDCl$_3$) δ: 8.49 (s, 1H, CH arom.); 8.14 (d, J=8.8 Hz, 2H, CH arom.); 7.98 (d, J=8.4 Hz, 2H, CH arom.); 7.58 (d, J=15.6 Hz, 1H, *CH*=CH); 7.53-7.43 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.33 (d, J=15.6 Hz, 1H, CH=*CH*); 4.75 (t, J=5.6 Hz, 2H, CH$_2$O); 4.14 (t, J=6.8 Hz, 2H, CH$_2$O); 3,87 (s, 3H, OCH$_3$); 3,85 (s, 6H, OCH$_3$); 2.90 (t, J=5.6 Hz, 2H, NCH$_2$); 2.51 (t, J=7.6 Hz, 2H, NCH$_2$); 2.39 (s, 3H, NCH$_3$); 1.95-1.86 (m, 2H, CH$_2$); 1.73-1.62 (m, 4H, CH$_2$); 1.56-1.47 (m, 2H, CH$_2$); 1.43-1.33 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.45 (C=O); 167.02 (C=O); 153.42 (C); 144.62 (CH=CH); 130.96 (C); 129.95 (C); 129.26 (CH arom.); 128.63 (CH arom.);

128.38 (C); 126.94 (CH arom.); 125.47 (CH arom.); 124.99 (CH arom.); 117.45 (CH=CH); 105.22 (CH arom.); 64.75 (CH_2); 64.54 (CH_2); 60.98 (OCH_3); 57.56 (CH_2); 57.21 (CH_2); 56.15 (OCH_3); 42.10 (NCH_3); 28.70 (CH_2); 26.78 (CH_2); 23.94 (CH_2); 23.78 (CH_2); 21.29 (CH_2) ppm. ESI-MS m/z (%): 614.2 (100) $[M+H]^+$.

Hydrochloride: mp 112-114 °C. **Anal:** $C_{37}H_{44}ClNO_7$ (C, H, N).

5.1.6.8. **(E)-5-(Methyl-(4-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)butyl)amino)pentyl anthracene-9-carboxylate 8**

Procedure B, starting from **56** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 97:3:0.3. Yield: 51.3.%.

^{1}H-NMR ($CDCl_3$) δ: 8.52 (s, 1H, CH arom.); 8.10-8.00 (m, 4H, CH arom.); 7.58 (d, J=15.6 Hz, 1H, *CH*=CH); 7.55-7.43 (m, 4H, CH arom.); 6.74 (s, 2H, CH arom.); 6.32 (d, J=15.6 Hz, 1H, CH=*CH*); 4.62 (t, J=6.8 Hz, 2H, CH_2O); 4.20 (t, J=6.4 Hz, 2H, CH_2O); 3,87 (s, 9H, OCH_3); 2.50-2.35 (m, 4H, NCH_2); 2.24 (s, 3H, NCH_3); 1.96-1.86 (m, 2H, CH_2); 1.70-1.50 (m, 8H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 169.75 (C=O); 167.01 (C=O); 153.42 (C); 144.64 (CH=CH); 131.00 (C); 129.93 (C); 129.22 (CH arom.); 128.62 (CH arom.); 128.37 (C); 126.92 (CH arom.); 125.46 (CH arom.); 125.00 (CH arom.); 117.44 (CH=CH); 105.20 (CH arom.); 65.86 (CH_2); 64.46 (CH_2); 60.97 (OCH_3); 57.76 (CH_2); 57.35 (CH_2); 56.14 (OCH_3); 42.14 (NCH_3); 28.76 (CH_2); 27.19 (CH_2); 26.79 (CH_2); 26.08 (CH_2); 23.83 (CH_2) ppm. ESI-MS m/z (%): 614.3 (100) $[M+H]^+$.

Hydrochloride: mp 70-72°C. **Anal:** $C_{37}H_{44}ClNO_7$ (C, H, N).

5.1.6.9. **(E)-3-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)hexyl)amino)propyl 3,4,5-trimethoxybenzoate 9**

Procedure A, starting from **59** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 97:3:0.3. Yield: 62.2.%.

^{1}H-NMR ($CDCl_3$) δ: 7.53 (d, J=15.6 Hz, 1H, *CH*=CH); 7.24 (s, 2H, CH arom.); 6.70 (s, 2H, CH arom.); 6.29 (d, J=15.6 Hz, 1H, CH=*CH*); 4.31 (t, J=6.4 Hz, 2H, CH_2O); 4.14 (t, J=6.4 Hz, 2H, CH_2O); 3,85 (s, 3H, OCH_3); 3,84 (s, 6H, OCH_3); 3,83 (s, 6H, OCH_3); 3,82 (s, 3H, OCH_3); 2.45 (t, J=7.2 Hz, 2H, NCH_2); 2.32 (t, J=7.2 Hz, 2H, NCH_2); 2.20 (s, 3H, NCH_3); 1.96-1.83 (m, 2H, CH_2); 1.71-1.59 (m, 2H, CH_2); 1.51-1.40 (m, 2H, CH_2); 1.49-1.20 (m, 4H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 166.96 (C=O); 166.14 (C=O); 153.38 (C); 152.88 (C); 144.55 (CH=CH); 142.15 (C); 129.91 (C); 125.36 (C); 122.13 (C); 117.42 (CH=CH); 106.76 (CH arom.); 105.18 (CH arom.); 64.50 (CH_2); 63.52 (CH_2); 60.85 (OCH_3); 57.67 (CH_2); 56.19 (OCH_3); 56.11 (OCH_3); 54.16 (CH_2); 42.14 (NCH_3); 28.70 (CH_2); 27.18 (CH_2); 27.11 (CH_2); 26.64 (CH_2); 25.90 (CH_2) ppm.

Hydrochloride: mp 78-80 °C. **Anal:** $C_{32}H_{46}ClNO_{10}$ (C, H, N).

5.1.6.10. **(E)-6-(Methyl-(3-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)propyl)amino)hexyl 3,4,5-trimethoxybenzoate 10**

Procedure A, starting from **58** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 97:3:0.3. Yield: 71.2.%.

^{1}H-NMR ($CDCl_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 7.24 (s, 2H, CH arom.); 6.70 (s, 2H, CH arom.); 6.29 (d, J=16.0 Hz, 1H, CH=*CH*); 4.25 (t, J=6.4 Hz, 2H, CH_2O); 4.20 (t, J=6.4 Hz, 2H, CH_2O); 3,85 (s, 3H, OCH_3); 3,84 (s, 6H, OCH_3); 3,83 (s, 6H, OCH_3); 3,82 (s, 3H, OCH_3); 2.42 (t, J=6.8 Hz, 2H, NCH_2); 2.31 (t, J=7.2 Hz, 2H, NCH_2); 2.18 (s, 3H, NCH_3); 1.89-1.77 (m, 2H, CH_2); 1.78-1.67 (m, 2H, CH_2); 1.46-1.30 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 166.88 (C=O); 166.18 (C=O); 153.40 (C); 152.88 (C); 144.64 (CH=CH); 142.13 (C); 140.10 (C); 129.87 (C); 125.47 (C); 117.31 (CH=CH); 106.78 (CH arom.); 105.22 (CH arom.); 65.10 (CH_2); 62.95 (CH_2); 60.89 (OCH_3); 60.84 (OCH_3); 57.63 (CH_2); 56.20 (OCH_3); 56.11 (OCH_3); 54.22 (CH_2); 42.08 (NCH_3); 28.70 (CH_2); 27.18 (CH_2); 27.10 (CH_2); 26.66 (CH_2); 25.94 (CH_2) ppm.

Hydrochloride: mp 95-97 °C. **Anal:** $C_{32}H_{46}ClNO_{10}$ (C, H, N).

5.1.6.11. **(E)-3-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)hexyl)amino)propyl anthracene-9-carboxylate 11**

Procedure B, starting from **59** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 50.9.%.

^{1}H-NMR (CDCl$_3$) δ: 8.48 (s, 1H, CH arom.); 8.04 (d, J=8.8 Hz, 2H, CH arom.); 7.98 (d, J=8.4 Hz, 2H, CH arom.); 7.53 (d, J=16.0 Hz, 1H, *CH*=CH); 7.52-7.46 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.34 (d, J=16.0 Hz, 1H, CH=*CH*); 4.67 (t, J=6.4 Hz, 2H, CH$_2$O); 4.17 (t, J=6.8 Hz, 2H, CH$_2$O); 3.87 (s, 3H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 2.53 (t, J=6.8 Hz, 2H, NCH$_2$); 2.35 (t, J=7.6 Hz, 2H, NCH$_2$); 2.24 (s, 3H, NCH$_3$); 2.12-2.02 (m, 2H, CH$_2$); 1.74-1.61 (m, 2H, CH$_2$); 1.54-1.43 (m, 2H, CH$_2$); 1.38-1.33 (m, 4H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.65 (C=O); 167.02 (C=O); 153.43 (C); 144.57 (CH=CH); 130.99 (C); 129.95 (C); 129.25 (CH arom.); 128.62 (CH arom.); 128.39 (C); 128.10 (C); 126.91 (CH arom.); 125.46 (CH arom.); 125.02 (CH arom.); 117.50 (CH=CH); 105.24 (CH arom.); 64.59 (CH$_2$); 64.20 (CH$_2$); 60.95 (OCH$_3$); 57.80 (CH$_2$); 56.14 (OCH$_3$); 54.18 (CH$_2$); 42.17 (NCH$_3$); 28.74 (CH$_2$); 27.24 (CH$_2$); 27.15 (CH$_2$); 26.68 (CH$_2$); 25.96 (CH$_2$) ppm.

Hydrochloride: mp 57-58°C. **Anal:** C$_{37}$H$_{44}$ClNO$_7$ (C, H, N).

5.1.6.12.　(E)-6-(Methyl-(3-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)propyl)amino)hexyl anthracene-9-carboxylate 12

Procedure B, starting from **58** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 96:4:0.4. Yield: 51.8.%.

^{1}H-NMR (CDCl$_3$) δ: 8.48 (s, 1H, CH arom.); 8.10-7.95 (m, 4H, CH arom.); 7.59 (d, J=16.0 Hz, 1H, *CH*=CH); 7.52-7.40 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.61 (t, J=6.4 Hz, 2H, CH$_2$O); 4.24 (t, J=6.8 Hz, 2H, CH$_2$O); 3.87 (s, 3H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 2.45 (t, J=7.2 Hz, 2H, NCH$_2$); 2.35 (t, J=7.2 Hz, 2H, NCH$_2$); 2.22 (s, 3H, NCH$_3$); 1.95-1.80 (m, 4H, CH$_2$); 1.60-1.48 (m, 4H, CH$_2$); 1.47-1.33 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.73 (C=O); 166.96 (C=O); 153.43 (C); 144.70 (CH=CH); 140.12 (C); 131.00 (C); 129.91 (C); 129.22 (CH arom.); 128.62 (CH arom.); 128.38 (C); 128.17 (C); 126.92 (CH arom.); 125.46 (CH arom.); 125.00 (CH arom.); 117.36 (CH=CH); 105.24 (CH arom.); 65.84 (CH$_2$); 63.02 (CH$_2$); 60.96 (OCH$_3$); 57.63 (CH$_2$); 56.15 (OCH$_3$); 54.29 (CH$_2$); 42.11 (NCH$_3$); 28.76 (CH$_2$); 27.16 (CH$_2$); 27.11 (CH$_2$); 26.68 (CH$_2$); 26.06 (CH$_2$) ppm.

Hydrochloride: mp 72-73°C. **Anal:** C$_{37}$H$_{44}$ClNO$_7$ (C, H, N).

5.1.6.13.　(E)-2-(Methyl-(7-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy))heptyl)amino)ethyl 3,4,5-trimethoxybenzoate 13

Procedure B, starting from **67** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 97:3:0.3. Yield: 69.2.%.

^{1}H-NMR (CDCl$_3$) δ: 7.55 (d, J=15.6 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.31 (d, J=15.6 Hz, 1H, CH=*CH*); 4.38 (t, J=6.0 Hz, 2H, CH$_2$O); 4.15 (t, J=6.8 Hz, 2H, CH$_2$O); 3.86 (s, 6H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 3.84 (s, 6H, OCH$_3$); 2.75 (t, J=6.0 Hz, 2H, NCH$_2$); 2.42 (t, J=7.2 Hz, 2H, NCH$_2$); 2.29 (s, 3H, NCH$_3$); 1.70-1.61 (m, 2H, CH$_2$); 1.51-1.40 (m, 2H, CH$_2$); 1.40-1.20 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 166.13 (C=O); 153.42 (C); 152.90 (C); 144.54 (CH=CH); 142.27 (C); 140.11 (C); 129.93 (C); 125.24 (C); 117.46 (CH=CH); 106.92 (CH arom.); 105.25 (CH arom.); 64.57 (CH$_2$); 63.10 (CH$_2$); 60.91 (OCH$_3$); 60.86 (OCH$_3$); 58.02 (CH$_2$); 56.20 (OCH$_3$); 56.14 (OCH$_3$); 55.66 (CH$_2$); 42.78 (NCH$_3$); 29.18 (CH$_2$); 28.69 (CH$_2$); 27.35 (CH$_2$); 27.26 (CH$_2$); 25.91 (CH$_2$) ppm.

Hydrochloride: mp 111-113 °C. **Anal:** C$_{32}$H$_{46}$ClNO$_{10}$ (C, H, N).

5.1.6.14.　(E)-7-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)heptyl 3,4,5-trimethoxybenzoate 14

Procedure A, starting from **68** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 98:2:0.2. Yield: 71.1.%.

^{1}H-NMR (CDCl$_3$) δ: 7.54 (d, J=16.0 Hz, 1H, *CH*=CH); 7.23 (s, 2H, CH arom.); 6.69 (s, 2H, CH arom.); 6.32 (d, J=16.0 Hz, 1H, CH=*CH*); 4.29-4.39 (m, 4H, CH$_2$O); 3.84 (s, 6H, OCH$_3$); 3.83 (s, 3H, OCH$_3$); 3.82 (s, 6H, OCH$_3$); 3.81(s, 3H, OCH$_3$); 2.64 (t, J=6.0 Hz, 2H, NCH$_2$); 2.36 (t, J=7.2 Hz, 2H, NCH$_2$); 2.26 (s, 3H, NCH$_3$); 1.76-1.65 (m, 2H, CH$_2$); 1.44-1.25 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.84 (C=O); 166.16 (C=O); 153.39 (C); 152.87 (C); 144.77 (CH=CH); 142.13 (C); 140.12 (C); 129.85 (C); 125.47 (C); 117.27 (CH=CH); 106.78 (CH arom.); 105.24 (CH

arom.); 65.13 (CH$_2$); 62.15 (CH$_2$); 60.87 (OCH$_3$); 60.82 (OCH$_3$); 57.92 (CH$_2$); 56.19 (OCH$_3$); 56.10 (OCH$_3$); 55.69 (CH$_2$); 42.66 (NCH$_3$); 29.39 (CH$_2$); 29.16 (CH$_2$); 27.28 (CH$_2$); 27.08 (CH$_2$); 25.93 (CH$_2$) ppm.

Hydrochloride: mp 106-108 °C. **Anal:** C$_{32}$H$_{46}$ClNO$_{10}$ (C, H, N).

5.1.6.15.   (E)-2-(Methyl-(7-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)heptyl)amino)ethyl anthracene-9-carboxylate 15

Procedure B, starting from **67** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 98:2:0.2. Yield: 56.4.%.

^{1}H-NMR (CDCl$_3$) δ: 8.47 (s, 1H, CH arom.); 8.14 (d, J=8.4 Hz, 2H, CH arom.); 7.97 (d, J=8.4 Hz, 2H, CH arom.);7.58 (d, J=16.0 Hz, 1H, *CH*=CH); 7.53-7.43 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.72 (t, J=6.4 Hz, 2H, CH$_2$O); 4.15 (t, J=6.8 Hz, 2H, CH$_2$O); 3,87 (s, 3H, OCH$_3$); 3,84 (s, 6H, OCH$_3$); 2.85 (t, J=6.0 Hz, 2H, NCH$_2$); 2.46 (t, J=7.2 Hz, 2H, NCH$_2$); 2.36 (s, 3H, NCH$_3$); 1.64-1.60 (m, 2H, CH$_2$); 1.52-1.48 (m, 2H, CH$_2$); 1.48-1.33 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.51 (C=O); 167.04 (C=O); 153.42 (C); 144.57 (CH=CH); 140.04 (C); 130.97 (C); 129.96 (C); 129.32 (CH arom.); 128.56 (CH arom.); 128.48 (C); 127.98 (C); 126.87 (CH arom.); 125.44 (CH arom.); 125.29 (CH arom.); 117.51 (CH=CH); 105.19 (CH arom.); 65.66 (CH$_2$); 63.17 (CH$_2$); 60.96 (OCH$_3$); 58.00 (CH$_2$); 56.13 (OCH$_3$); 56.09 (CH$_2$); 42.47 (NCH$_3$); 29.23 (CH$_2$); 28.69 (CH$_2$); 27.32 (CH$_2$); 27.29 (CH$_2$); 25.93 (CH$_2$) ppm.

Hydrochloride: low melting solid. **Anal:** C$_{37}$H$_{44}$ClNO$_7$ (C, H, N).

5.1.6.16.   (E)-7-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)heptyl anthracene-9-carboxylate 16

Procedure A, starting from **69** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 98:2:0.2. Yield: 33.8.%.

^{1}H-NMR (CDCl$_3$) δ: 8.49 (s, 1H, CH arom.); 8.02 (d, J=8.8 Hz, 2H, CH arom.); 7.99 (d, J=8.4 Hz, 2H, CH arom.);7.59 (d, J=15.6 Hz, 1H, *CH*=CH); 7.53-7.43 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.37 (d, J=15.6 Hz, 1H, CH=*CH*); 4.59 (t, J=6.8 Hz, 2H, CH$_2$O); 4.30 (t, J=6.0 Hz, 2H, CH$_2$O); 3,86 (s, 3H, OCH$_3$); 3,85 (s, 6H, OCH$_3$); 2.69 (t, J=5.6 Hz, 2H, NCH$_2$); 2.46 (t, J=7.2 Hz, 2H, NCH$_2$); 2.30 (s, 3H, NCH$_3$); 1.94-1.81 (m, 2H, CH$_2$); 1.52-1.20 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.72 (C=O); 166.95 (C=O); 153.43 (C); 144.83 (CH=CH); 140.16 (C); 131.00 (C); 129.90 (C); 129.20 (CH arom.); 128.61 (CH arom.); 128.38 (C); 128.18 (C); 126.90 (CH arom.); 125.45 (CH arom.); 125.00 (CH arom.); 117.33 (CH=CH); 105.28 (CH arom.); 65.86 (CH$_2$); 62.20 (CH$_2$); 60.95 (OCH$_3$); 57.98 (CH$_2$); 56.14 (OCH$_3$); 55.71 (CH$_2$); 42.68 (NCH$_3$); 29.17 (CH$_2$); 28.73 (CH$_2$); 27.32 (CH$_2$); 27.07 (CH$_2$); 26.06 (CH$_2$) ppm.

Hydrochloride: mp 71-73 °C. **Anal:** C$_{37}$H$_{44}$ClNO$_7$ (C, H, N).

5.1.6.17.   (E)-4-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)hexyl)amino)butyl   3,4,5-trimethoxybenzoate 17

Procedure B, starting from **61** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH$_2$Cl$_2$/MeOH/NH$_4$OH 97:3:0.3. Yield: 65.6%.

^{1}H-NMR (CDCl$_3$) δ: 7.56 (d, J=16.0 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.31 (d, J=16.0 Hz, 1H, *CH*=CH); 4.30 (t, J=6.8 Hz, 2H, CH$_2$O); 4.16 (t, J=6.4 Hz, 2H, CH$_2$O); 3.87 (s, 9H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 3.84 (s, 3H, OCH$_3$); 2.36 (t, J=7.6 Hz, 2H, NCH$_2$,); 2.31 (t, J=7.6 Hz, 2H, NCH$_2$); 2.19 (s, 3H, NCH$_3$); 1.81-1.74 (m, 2H, CH$_2$); 1.70-1.65 (m, 2H, CH$_2$); 1.61-1.55 (m, 2H, CH$_2$); 1.49-1.28 (m; 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 166.98 (C=O); 166.21 (C=O); 153.42 (C); 152.90 (C); 144.56 (CH=CH); 142.20 (C); 140.11 (C); 129.93 (C); 125.43 (C); 117.45 (CH=CH); 106.83 (CH arom.); 105.24 (CH arom.); 65.05 (CH$_2$); 64.55 (CH$_2$); 60.92 (OCH$_3$); 60.87 (OCH$_3$); 57.80 (CH$_2$); 57.31 (CH$_2$); 56.23 (OCH$_3$); 56.14 (OCH$_3$); 42.14 (NCH$_3$); 28.72 (CH$_2$); 27.21 (CH$_2$); 26.77 (CH$_2$); 25.95 (CH$_2$); 23.83 (CH$_2$) ppm.

Hydrochloride: mp 64-66 °C. **Anal:** C$_{34}$H$_{49}$ClNO$_{10}$ (C, H, N).

5.1.6.18.   (E)-6-(Methyl-(4-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)butyl)amino)hexyl   3,4,5-trimethoxybenzoate 18

Procedure A, starting from **60** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 50.3%.

^{1}H-NMR (CDCl$_3$) δ: 7.59 (d, J=16.0 Hz, 1H, *CH*=CH); 7.29 (s, 2H, CH arom.); 6.75 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.30 (t, J=6.8 Hz, 2H, CH$_2$O); 4.21 (t, J=6.8 Hz, 2H, CH$_2$O); 3.92 (s, 9H, OCH$_3$); 3.87 (s, 6H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 2.42-2.29 (m, 4H, NCH$_2$); 2.22 (s, 3H, NCH$_3$); 1.79-1.67 (m, 4H, CH$_2$); 1.62-1.58 (m, 2H, CH$_2$); 1.52-1.42 (m, 4H, CH$_2$); 1.41-1.39 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 167.00 (C=O); 166.23 (C=O); 153.43 (C); 152.91 (C); 144.65 (CH=CH); 129.92 (C); 125.50 (C); 117.41 (CH=CH); 106.79 (CH arom.); 105.21 (CH arom.); 65.17 (CH$_2$); 64.42 (CH$_2$); 60.97 (OCH$_3$); 60.91 (OCH$_3$); 57.77 (CH$_2$); 57.31 (CH$_2$); 56.24 (OCH$_3$); 56.16 (OCH$_3$); 42.09 (NCH$_3$); 28.74 (CH$_2$); 27.23 (CH$_2$); 27.17 (CH$_2$); 26.77 (CH$_2$); 26.00 (CH$_2$); 23.77 (CH$_2$) ppm.

Hydrochloride: mp 79-81 °C**. Anal:** C$_{34}$H$_{49}$ClNO$_{10}$ (C, H, N).

5.1.6.19.　(E)-4-(Methyl-(6-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)hexyl)amino)butyl anthracene-9-carboxylate 19

Procedure B, starting from **61** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 35.4%.

^{1}H-NMR (CDCl$_3$) δ: 8.50 (s, 1H, CH arom.); 8.04-7-98 (m, 4H, CH arom.); 7.58 (d, J=16.0 Hz, 1H, *CH*=CH); 7.55-7.45 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.63 (t, J=6.4 Hz, 2H, CH$_2$O); 4.18 (t, J=6.4 Hz, 2H, CH$_2$O); 3,87 (s, 3H, OCH$_3$); 3,86 (s, 6H, OCH$_3$); 2.41 (t, J=7.2 Hz, 2H, NCH$_2$); 2.32 (t, J=7.6 Hz, 2H, NCH$_2$); 2.20 (s, 3H, NCH$_3$); 1.97-1.86 (m, 2H, CH$_2$); 1.74-1.60 (m, 4H, CH$_2$); 1.48-1.32 (m, 6H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) **δ:** 169.71 (C=O); 167.03 (C=O); 153.43 (C); 144.58 (CH=CH); 140.11 (C); 131.00 (C); 129.96 (C); 129.24 (CH arom.); 128.62 (CH arom.); 128.38 (C); 126.92 (CH arom.); 125.46 (CH arom.); 125.00 (CH arom.); 117.49 (CH=CH); 105.25 (CH arom.); 65.78 (CH$_2$); 64.60 (CH$_2$); 60.96 (OCH$_3$); 57.70 (CH$_2$); 57.18 (CH$_2$); 56.15 (OCH$_3$); 42.13 (NCH$_3$); 28.74 (CH$_2$); 27.19 (CH$_2$); 26.81 (CH$_2$); 25.96 (CH$_2$); 23.82 (CH$_2$) ppm.

Hydrochloride: mp 68-69 °C**. Anal:** C$_{38}$H$_{46}$ClNO$_7$ (C, H, N).

5.1.6.20.　(E)-6-(Methyl-(4-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)butyl)amino)hexyl anthracene-9-carboxylate 20

Procedure B, starting from **60** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 63.4%.

^{1}H-NMR (CDCl$_3$) δ: 8.50 (s, 1H, CH arom.); 8.02 (t, J=9.2 Hz, 4H, CH arom.); 7.59 (d, J=15.6 Hz, 1H, *CH*=CH); 7.56-7.44 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.34 (d, J=15.6 Hz, 1H, CH=*CH*); 4.61 (t, J=6.8 Hz, 2H, CH$_2$O); 4.21 (t, J=6.4 Hz, 2H, CH$_2$O); 3.87 (s, 3H, OCH$_3$); 3.86 (s, 6H, OCH$_3$); 2.38-2.29 (m, 4H, NCH$_2$); 2.20 (s, 3H, NCH$_3$); 1.93-1.84 (m, 2H, CH$_2$); 1.73-1.66 (m, 2H, CH$_2$); 1.62-1.46 (m, 6H, CH$_2$); 1.43-1.37 (m, 2H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 169.75 (C=O); 167.01 (C=O); 153.42 (C); 144.64 (CH=CH); 131.00 (C); 129.93 (C); 129.22 (CH arom.); 128.62 (CH arom.); 128.37 (C); 128.15 (C); 126.92 (CH arom.); 125.46 (CH arom.); 125.00 (CH arom.); 117.44 (CH=CH); 105.20 (CH arom.); 65.86 (CH$_2$); 64.46 (CH$_2$); 60.97 (OCH$_3$); 57.76 (CH$_2$); 57.35 (CH$_2$); 56.14 (OCH$_3$); 42.14 (NCH$_3$); 28.76 (CH$_2$); 27.19 (CH$_2$); 26.79 (CH$_2$); 26.08 (CH$_2$); 23.83 (CH$_2$) ppm.

Hydrochloride: mp 80-81 °C**. Anal:** C$_{38}$H$_{46}$ClNO$_7$ (C, H, N).

5.1.6.21.　(E)-3-(Methyl-(7-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)heptyl)amino)propyl 3,4,5-trimethoxybenzoate 21

Procedure B, starting from **62** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 72.6%.

^{1}H-NMR (CDCl$_3$) δ: 7.55 (d, J=15.6 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.31 (d, J=15.6 Hz, 1H, CH=*CH*); 4.43 (t, J=6.4 Hz, 2H, CH$_2$O); 4.15 (t, J=6.8 Hz, 2H, CH$_2$O); 3.87 (s, 9H, OCH$_3$); 3.85 (s, 6H, OCH$_3$); 3.84 (s, 3H, OCH$_3$); 2.46 (t, J=7.2 Hz, 2H, NCH$_2$); 2.31 (t, J=7.2 Hz, 2H, NCH$_2$); 2.21 (s, 3H, NCH$_3$); 1.97-1.85 (m, 2H, CH$_2$); 1.72-1.60 (m, 2H, CH$_2$); 1.53-1.20 (m, 8H, CH$_2$) ppm. ^{13}C APT NMR (CDCl$_3$) δ: 167.00 (C=O); 166.16 (C=O); 153.41 (C); 152.90 (C); 144.54 (CH=CH); 142.17 (C); 140.06 (C); 129.94 (C); 125.41 (C); 117.47

(CH=CH); 106.79 (CH arom.); 105.21 (CH arom.); 64.60 (CH_2); 63.58 (CH_2); 60.92 (OCH_3); 60.87 (OCH_3); 57.97 (CH_2); 56.21 (OCH_3); 56.13 (OCH_3); 54.20 (CH_2); 42.21 (NCH_3); 29.69 (CH_2); 29.22 (CH_2); 27.37 (CH_2); 27.30 (CH_2); 26.69 (CH_2); 25.93 (CH_2) ppm.

Hydrochloride: mp 77-79 °C. **Anal:** $C_{33}H_{48}ClNO_{10}$ (C, H, N).

5.1.6.22. (E)-7-(Methyl-(3-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)propyl)amino)heptyl 3,4,5-trimethoxybenzoate 22

Procedure B, starting from **63** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 53.7.%.

^{1}H-NMR ($CDCl_3$) δ: 7.56 (d, J=16.0 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.72 (s, 2H, CH arom.); 6.31 (d, J=16.0 Hz, 1H, CH=*CH*); 4.27 (t, J=6.8 Hz, 2H, CH_2O); 4.22 (t, J=6.8 Hz, 2H, CH_2O); 3.88 (s, 6H, OCH_3); 3.87 (s, 3H, OCH_3); 3.86 (s, 6H, OCH_3); 3.85 (s, 3H, OCH_3); 2.43 (t, J=7.2 Hz, 2H, NCH_2); 2.31 (t, J=7.2 Hz, 2H, NCH_2); 2.20 (s, 3H, NCH_3); 1.93-1.82 (m, 2H, CH_2); 1.80-1.69 (m, 2H, CH_2); 1.50-1.37 (m, 2H, CH_2); 1.50-1.23 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 166.91 (C=O); 166.23 (C=O); 153.43 (C); 152.91 (C); 144.65 (CH=CH); 142.19 (C); 140.17 (C); 129.90 (C); 125.51 (C); 117.36 (CH=CH); 106.84 (CH arom.); 105.28 (CH arom.); 65.19 (CH_2); 63.03 (CH_2); 60.92 (OCH_3); 60.86 (OCH_3); 57.74 (CH_2); 56.23 (OCH_3); 56.15 (OCH_3); 54.26 (CH_2); 42.13 (NCH_3); 29.22 (CH_2); 28.69 (CH_2); 27.38 (CH_2); 27.24 (CH_2); 26.70 (CH_2); 25.97 (CH_2) ppm.

Hydrochloride: mp 89-90 °C. **Anal:** $C_{33}H_{48}ClNO_{10}$ (C, H, N).

5.1.6.23.   (E)-3-(Methyl-(7-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)heptyl)amino)propyl anthracene-9-carboxylate 23

Procedure B, starting from **62** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 68.5%.

^{1}H-NMR ($CDCl_3$) δ: 8.49 (s, 1H, CH arom.); 8.04 (d, J=8.4 Hz, 2H, CH arom.); 7.98 (d, J=8.4 Hz, 2H, CH arom.); 7.59 (d, J=16.0 Hz, 1H, *CH*=CH); 7.55-7.43 (m, 4H, CH arom.); 6.73 (s, 2H, CH arom.); 6.34 (d, J=16.0 Hz, 1H, CH=*CH*); 4.67 (t, J=6.4 Hz, 2H, CH_2O); 4.18 (t, J=6.8 Hz, 2H, CH_2O); 3.87 (s, 3H, OCH_3); 3.84 (s, 6H, OCH_3); 2.52 (t, J=7.2 Hz, 2H, NCH_2); 2.33 (t, J=7.6 Hz, 2H, NCH_2); 2.23 (s, 3H, NCH_3); 2.09-2.00 (m, 2H, CH_2); 1.72-1.63 (m, 2H, CH_2); 1.49-1.43 (m, 2H, CH_2); 1.39-1.29 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 169.67 (C=O); 167.04 (C=O); 153.41 (C); 144.56 (CH=CH); 140.04 (C); 130.98 (C); 129.96 (C); 129.25 (CH arom.); 128.62 (CH arom.); 126.38 (C); 128.10 (C); 126.92 (CH arom.); 125.46 (CH arom.); 125.02 (CH arom.); 117.51 (CH=CH); 105.19 (CH arom.); 64.66 (CH_2); 64.25 (CH_2); 63.25 (CH_2); 60.96 (OCH_3); 57.88 (CH_2); 56.12 (OCH_3); 54.23 (CH_2); 42.19 (NCH_3); 29.24 (CH_2); 28.73 (CH_2); 27.39 (CH_2); 27.29 (CH_2); 26.70 (CH_2); 25.96 (CH_2) ppm.

Hydrochloride: mp 61-63°C. **Anal:** $C_{38}H_{46}ClNO_7$ (C, H, N).

5.1.6.24.   (E)-7-(Methyl-(3-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)propyl)amino)heptyl anthracene-9-carboxylate 24

Procedure B, starting from **64** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 42.8.%.

^{1}H-NMR ($CDCl_3$) δ: 8.51 (s, 1H, CH arom.); 8.02 (t, J=8.8 Hz, 4H, CH arom.); 7.59 (d, J=16.0 Hz, 1H, *CH*=CH); 7.54-7.45 (m, 4H, CH arom.); 6.74 (s, 2H, CH arom.); 6.33 (d, J=16.0 Hz, 1H, CH=*CH*); 4.60 (t, J=6.8 Hz, 2H, CH_2O); 4.24 (t, J=6.4 Hz, 2H, CH_2O); 3.87 (s, 3H, OCH_3); 3.86 (s, 6H, OCH_3); 2.48 (t, J=7.2 Hz, 2H, NCH_2); 2.36 (t, J=7.6 Hz, 2H, NCH_2); 2.24 (s, 3H, NCH_3); 1.95-1.82 (m, 4H, CH_2); 1.60-1.48 (m, 4H, CH_2); 1.48-1.38 (m, 2H, CH_2); 1.38-1.30 (m, 2H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 169.73 (C=O); 166.94 (C=O); 153.45 (C); 144.73 (CH=CH); 140.18 (C); 131.01 (C); 129.20 (CH arom.); 128.61 (CH arom.); 128.19 (C); 126.90 (CH arom.); 125.45 (CH arom.); 125.01 (CH arom.); 117.33 (CH=CH); 105.29 (CH arom.); 65.88 (CH_2); 62.97 (CH_2); 60.96 (OCH_3); 57.65 (CH_2); 56.17 (OCH_3); 54.22 (CH_2); 42.01 (NCH_3); 29.16 (CH_2); 28.72 (CH_2); 27.35 (CH_2); 27.01 (CH_2); 25.56 (CH_2); 26.07 (CH_2) ppm.

Hydrochloride: low melting solid. **Anal:** $C_{38}H_{46}ClNO_7$ (C, H, N).

5.1.6.25. *(E)-2-(Methyl-(8-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)octyl)amino)ethyl 3,4,5-trimethoxybenzoate 25*

Procedure A, starting from **70** and 3,4,5-trimethoxybenzoic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 96:4:0.4. Yield: 44.5%.

^{1}H-NMR ($CDCl_3$) δ: 7.58 (d, J=16.0 Hz, 1H, *CH*=CH); 7.29 (s, 2H, CH arom.); 6.74 (s, 2H, CH arom.); 6.34 (d, J=16.0 Hz, 1H, CH=*CH*); 4.40 (t, J=6.0 Hz, 2H, CH_2O); 4.18 (t, J=6.8 Hz, 2H, CH_2O); 3.88 (s, 9H, OCH_3); 3.86 (s, 6H, OCH_3); 3.85 (s, 3H, OCH_3); 2.76 (t, J=6.0 Hz, 2H, NCH_2); 2.43 (t, J=7.6 Hz, 2H, NCH_2); 2.33 (s, 3H, NCH_3); 1.71-1.63 (m, 2H, CH_2); 1.53-1.45 (m, 2H, CH_2); 1.44-1.22 (m, 8H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 167.01 (C=O); 166.15 (C=O); 153.40 (C); 152.88 (C); 144.54 (CH=CH); 142.17 (C); 140.02 (C); 129.94 (C); 125.25 (C); 117.47 (CH=CH); 106.84 (CH arom.); 105.17 (CH arom.); 64.64 (CH_2); 63.14 (CH_2); 60.93 (OCH_3); 60.88 (OCH_3); 58.08 (CH_2); 56.19 (OCH_3); 56.12 (OCH_3); 55.62 (CH_2); 42.82 (NCH_3); 29.45 (CH_2); 29.23 (CH_2); 28.72 (CH_2); 27.41 (CH_2); 27.33 (CH_2); 25.91 (CH_2) ppm.

Hydrochloride: mp 90-93 °C. **Anal:** $C_{33}H_{48}ClNO_{10}$ (C, H, N).

5.1.6.26. *(E)-8-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)octyl 3,4,5-trimethoxybenzoate 26*

Procedure A, starting from **71** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 95:5:0.5. Yield: 44.2%.

^{1}H-NMR ($CDCl_3$) δ: 7.56 (d, J=15.6 Hz, 1H, *CH*=CH); 7.26 (s, 2H, CH arom.); 6.71 (s, 2H, CH arom.); 6.35 (d, J=15.6 Hz, 1H, CH=*CH*); 4.30-4.24 (m, J=6.0 Hz, 4H, CH_2O); 3.87 (s, 6H, OCH_3); 3.86 (s, 3H, OCH_3); 3.85 (s, 6H, OCH_3); 3.84 (s, 3H, OCH_3); 2.67 (t, J=5.6 Hz, 2H, NCH_2); 2.38 (t, J=7.2 Hz, 2H, NCH_2); 2.28 (s, 3H, NCH_3); 1.79-1.66 (m, 2H, CH_2); 1.50-1.19 (m, 10H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 166.94 (C=O); 166.24 (C=O); 153.41 (C); 152.89 (C); 144.78 (CH=CH); 142.14 (C); 140.13 (C); 129.90 (C); 125.51 (C); 117.33 (CH=CH); 106.80 (CH arom.); 105.25 (CH arom.); 65.22 (CH_2); 62.24 (CH_2); 60.91 (OCH_3); 60.87 (OCH_3); 58.02 (CH_2); 56.22 (OCH_3); 56.13 (OCH_3); 55.70 (CH_2); 42.72 (NCH_3); 29.46 (CH_2); 29.24 (CH_2); 28.71 (CH_2); 27.37 (CH_2); 27.16 (CH_2); 25.94 (CH_2) ppm.

Hydrochloride: mp 77-78°C. **Anal:** $C_{33}H_{48}ClNO_{10}$ (C, H, N).

5.1.6.27. *(E)-2-(Methyl-(8-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)octyl)amino)ethyl anthracene-9-carboxylate 27*

Procedure B, starting from **70** and anthracene-9-carboxylic acid.

Free base: chromatographic eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:0.2. Yield: 47.2%.

^{1}H-NMR ($CDCl_3$) δ: 8.51 (s, 1H, CH arom.); 8.15 (d, J=8.8 Hz, 2H, CH arom.); 8.00 (d, J=8.0 Hz, 2H, CH arom.); 7.59 (d, J=16.0 Hz, 1H, *CH*=CH); 7.54-7.45 (m, 4H, CH arom.); 6.75 (s, 2H, CH arom.); 6.34 (d, J=16.0 Hz, 1H, CH=*CH*); 4.72 (t, J=5.6 Hz, 2H, CH_2O); 4.17 (t, J=6.4 Hz, 2H, CH_2O); 3.88 (s, 3H, OCH_3); 3.87 (s, 6H, OCH_3); 2.86 (t, J=5.6 Hz, 2H, NCH_2); 2.46 (t, J=7.6 Hz, 2H, NCH_2); 2.36 (s, 3H, NCH_3); 1.71-1.61 (m, 2H, CH_2); 1.69-1.45 (m, 2H, CH_2); 1.39-1.24 (m, 8H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) δ: 167.06 (C=O); 153.43 (C); 144.55 (CH=CH); 131.00 (C); 129.97 (C); 129.29 (CH arom.); 128.54 (CH arom.); 126.84 (CH arom.); 125.43 (CH arom.); 125.31 (CH arom.); 117.53 (CH=CH); 105.22 (CH arom.); 64.71 (CH_2); 63.29 (CH_2); 60.98 (OCH_3); 58.09 (CH_2); 56.16 (OCH_3); 56.12 (CH_2); 42.53 (NCH_3); 29.49 (CH_2); 29.25 (CH_2); 28.74 (CH_2); 27.40 (CH_2); 25.92 (CH_2) ppm.

Hydrochloride: mp 64-66 °C. **Anal:** $C_{38}H_{46}ClNO_7$ (C, H, N).

5.1.6.28. *(E)-8-(Methyl-(2-((3-(3,4,5-trimethoxyphenyl)acryloyl)oxy)ethyl)amino)octyl anthracene-9-carboxylate 28*

Procedure A, starting from **72** and (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid.

Free base: chromatographic eluent: cyclohexane/ethyl acetate 10:90. Yield: 51.9%.

^{1}H-NMR ($CDCl_3$) δ: 8.52 (s, 1H, CH arom.); 8.09-7.99 (m, 4H, CH arom.); 7.60 (d, J=16.0 Hz, 1H, *CH*=CH); 7.55-7.46 (m, 4H, CH arom.); 6.74 (s, 2H, CH arom.); 6.38 (d, J=16.0 Hz, 1H, CH=*CH*); 4.60 (t, J=6.8 Hz, 2H, CH_2O); 4.30 (t, J=6.0 Hz, 2H, CH_2O); 3.87 (s, 3H, OCH_3); 3.86 (s, 6H, OCH_3); 2.70 (t, J=5.6 Hz, 2H, NCH_2); 2.40 (t, J=7.2 Hz, 2H, NCH_2); 2.31 (s, 3H, NCH_3); 1.93-1.73

(m, 2H, CH_2); 1.55-1.40 (m, 4H, CH_2); 1.39-1.23 (m, 6H, CH_2) ppm. ^{13}C APT NMR ($CDCl_3$) **δ:** 167.28 (C=O); 153.44 (C=O); 144.81 (CH=CH); 131.01 (C); 129.93 (C); 129.20 (CH arom.); 128.61 (CH arom.); 128.39 (C); 126.90 (CH arom.); 125.46 (CH arom.); 125.03 (CH arom.); 117.37 (CH=CH); 105.25 (CH arom.); 65.91 (CH_2); 62.26 (CH_2); 60.97 (OCH_3); 58.06 (CH_2); 56.15 (OCH_3); 55.72 (CH_2); 42.73 (NCH_3); 29.47 (CH_2); 29.21 (CH_2); 28.76 (CH_2); 27.38 (CH_2); 27.15 (C); 26.05 (CH_2) ppm.
Hydrochloride: mp 58-60 °C. **Anal:** $C_{38}H_{46}ClNO_7$ (C, H, N).

5.2. Biology.

5.2.1. Cell lines and cultures.
The K562 is an undifferentiated erythroleukemia cell line originally derived from a patient with chronic myelogenous leukemia.[30] The K562 leukemia cells and the P-gp over-expressing K562/DOX cells were obtained from Prof. J.P. Marie (Hopital Hotel-Dieu, Paris, France). The cells were cultured following a previously reported protocol.[41]

5.2.2. Drugs and chemicals.
Purified verapamil and pirarubicin were purchased by Sigma-Aldrich (Milan - Italy). Concentrations were determined by diluting stock solutions to approximately 10^{-5} M and using ε_{480} = 11500 M^{-1} cm^{-1}. Stock solutions were prepared just before use. Buffer solutions were HEPES buffer containing 5 mM HEPES, 132 mM NaCl, 3.5 mM $CaCl_2$, 5 mM glucose, at pH 7.3.
The uptake of pirarubicin in cells was followed by monitoring the decrease in the fluorescence signal at 590 nm (λ_{ex} = 480 nm) according to the previously described method.[42,43]

5.3. Molecular modeling
The crystal structure of human P-gp with in the ATP-bound, outward-facing conformation (PDB ID: 6C0V) [34], and the mouse P-gp complexed with BDE100 inhibitor (PDB code 4XWK) [36], were downloaded from PDB database [44]. The molecular structures of synthetized compounds were optimized prior to docking procedure, by using the Dock Prep application [45], The program performs optimization of ligand structures and conversion of them from 2D to 3D, also providing correction of improper bond distances, bond orders, adding hydrogens and assigning Gasteiger partial charges. Before Docking simulation, a Steepest descent minimization (100 steps at 0.02 Å step size) was taken to remove highly unfavourable clashes, followed by 10 steps of conjugate gradient minimization (0.02 Å step size) to further minimize the energy of the structure, and the "minimize structure UCSF Chimera tool" of UCSF Chimera package [46] was used to analyse their molecular graphics. In order to prepare the ligands and receptor for docking calculation, AutoDock/VinaXB was used [33], then for each compound, the molecular docking study was carried out by the software. The grid box was set to 20Å × 20 Å × 28 Å with a grid space value of 1 Å. The binding box was centred at the previously reported helix TM4 (W232), TM5 (R296, I299, I306), TM6 (Y310, F336), TM7 (F928), TM8 (F303, Y307, F770) and TM12 (M986, Q990, F994), involved in the substrate-binding region [35]. By default, a maximum of 10 poses per ligand were collected. For Autodock/VinaXB program, the parameters used were default. Within the P-gp we performed the Docking simulations on the compounds detailed in Table 1. Docking systems were set up and the results were analysed using PyMOL v2.0 [47]. In order to identify the network of interaction we used Ligplot+ v.1.4.5 [48] and Protein-Ligand Interaction Profiler [49], all the sets were by default.

5.4. Stability test

5.4.1. Chemicals
Acetonitrile (Chromasolv), formic acid and ammonium formate (MS grade), NaCl, KCl, Na_2HPO_4 $2H_2O$, KH_2PO_4 (Reagent grade) and verapamil hydrochloride (analytical standard, used as internal standard), ketoprofen (analytical standard) were purchased by Sigma-Aldrich (Milan, Italy). Ketoprofen Ethyl Ester (KEE) were obtained by Fisher's reaction from ketoprofen and ethanol.
MilliQ water 18 MΩ cm^{-1} was obtained from Millipore's Simplicity system (Milan - Italy).

Phosphate buffer solution (PBS) was prepared by adding 8.01 g L^{-1} of NaCl, 0.2 g L^{-1} of KCl, 1.78 g L^{-1} of Na$_2$HPO$_4$ 2H$_2$O and 0.27 g L^{-1} of KH$_2$PO$_4$. Human plasma was collected from healthy male volunteer and kept at -80 °C until use.

5.4.2. Sample preparation
Each sample was prepared adding 10 μL of working solution 1 to 100 μL of tested matrix (PBS or human plasma) in microcentrifuge tubes. The obtained solutions correspond to 1 μM of analyte.
Each set of samples was incubated in triplicate at four different times, 0, 30, 60 and 120 min. at 37 °C. Therefore the degradation profile of each analyte was represented by a batch of 12 samples (4 incubation times x 3 replicates). After the incubation, the samples were added with 300 μL of ISTD solution and centrifuged (room temperature for 5 min at 10000 rpm). The supernatants were transferred in autosampler vials and dried under a gentle stream of nitrogen.
The dried samples were dissolved in 1.0 mL of 5 mM of ammonium formate and 10 mM formic acid in mQ water:acetonitrile 70:30 (v/v) solution. The obtained sample solutions were analysed by LC-MS/MS methods described in the Supplementary Data section.

Supplementary data
Supplementary data related to this article can be found in the online version.

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