ELSEVIER

Il Farmaco 53 (1998) 357–364

IL FARMACO

Studies on propafenone-type modulators of multidrug resistance VI. Synthesis and pharmacological activity of compounds with varied spacer length between the central aromatic ring and the nitrogen atom [1]

Peter Chiba [b], Danilo Annibali [a], Manuela Hitzler [b], Elisabeth Richter [b], Gerhard Ecker [a,*]

[a] *Institut für Pharmazeutische Chemie der Universität Wien, Althanstrasse 14, A-1090 Vienna, Austria*

[b] *Institut für Medizinische Chemie der Universität Wien, Waehringer Strasse 10, A-1090 Vienna, Austria*

Received 1 September 1997; accepted 25 March 1998

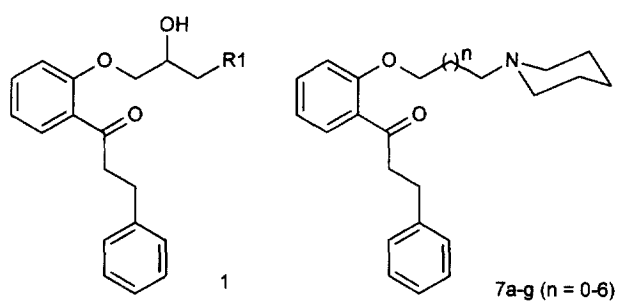
Abstract

A series of propafenone-type modulators of multidrug resistance (MDR) with varied spacer length between the central aromatic ring and the positively chargeable nitrogen atom was synthesized and tested for their ability to block P-glycoprotein-mediated transport of daunomycin out of tumor cells. Synthesis was achieved by *O*-alkylation of *o*-hydroxy-3-phenylpropiophenone with dibromoalkanes and subsequent nucleophilic substitution of the bromine with piperidine. All compounds showed high MDR-modulating activity with EC_{50} values from 1.45–0.15 μM. Generally, activity increased with increasing number of methylene groups, whereby it reaches a plateau for compounds with more than five methylene groups between the ether oxygen and the nitrogen atom.

Keywords: Multidrug resistance; Modulators; P-glycoprotein; Propafenone; Structure–activity relationship

1. Introduction

Development of unspecific mechanisms of resistance represents a major problem in tumor therapy. Several concepts for overcoming multidrug resistance (MDR) in cancer cells have been proposed in the literature [1]. One of the most investigated is inhibition of the multidrug transporter P-glycoprotein (PGP). PGP is a membrane-bound ATP-driven efflux pump which is overexpressed in a broad variety of multidrug-resistant tumor cells [2]. It shows extremely broad substrate specificity, thus pumping a wide variety of structurally and functionally diverse cytotoxic agents out of tumor cells [3]. Although there is some evidence that the major biological function of PGP is protection of the organism against toxic xenobiotics, its physiological role remains unclear. Within the past decade, numerous compounds have been identified which are able to inhibit PGP-mediated drug efflux [4,5]. Although this represents an interesting approach for overcoming multidrug resistance in tumor cells, only a few structure–activity relationship studies in the field of MDR modulators have been published. In general, it is concluded that one or more aromatic rings, a nitrogen atom which is positively charged at physiological pH and high lipophilicity are major determinants for high activity of PGP inhibitors [6]. We recently demonstrated that within homologous series of propafenone-type MDR modulators **1** (Fig. 1) there is an excellent correlation between pharmacological activity and lipophilicity of the compounds [7]. For high activity, the nitrogen atom needs to be positively chargeable at physiological pH. Additionally, bulky substituents in the vicinity of the nitrogen lead to a dramatic decrease in MDR-modulating



Propafenone (1a): R1 = propylamino

GP05 (1b): R1 = 1-piperidyl

Fig. 1. Chemical structure of compounds **1a,b** and **7a–g**.

* Corresponding author. Tel.: +43 1 31336 8571; fax: +43 1 31336 771; e-mail: ecker@speedy.pch.univie.ac.at

[1] For Part V, see Ref. [14].

0014-827X/98/$19.00
PII S0014-827X(98)00035-4

activity [8]. Thus, following our ligand-based approach for the development of highly active propafenone-type PGP inhibitors, we tried to estimate the optimal distance between the nitrogen atom and the central aromatic ring by synthesizing and testing a series of compounds **7a–g** with varied chain length (Fig. 1).

2. Chemistry

In contrast to the previously published procedure for synthesis of **7a** and **7b** [9], which is based on the reaction of 2′-hydroxy-3-phenylpropiophenone **2** with ω-chloroalkylamines, we focused on the procedure given in Scheme 1. The *o*-acylphenol **2** was reacted with an excess of corresponding α,ω-dibromoalkanes to give the arylether **3a–g**. Several reaction conditions, such as K_2CO_3/acetone, NaOEt/ethanol and reaction with the the sodium salt of **2** as educt were applied. Best results were achieved with NaOEt/ethanol, which is in accordance with the procedure given for synthesis of **7c** by Turbanti et al. [10]. In our case, small amounts of the alkenyl derivatives **4a–g** and the dimers **5a–g** (for **5c** see also Ref. [10]) were also isolated as byproducts. When sodium ethoxide was used, the formation of ethoxy analogues **6c–g** was also observed. Reaction of **3a–g** with piperidine yielded the target compounds **7a–g**.

3. MDR-modulating activity

The daunomycin efflux assay is a direct and accurate functional method to measure inhibition of PGP-mediated transmembrane transport [8]. The resistant human T-lymphoblast cell line CEM vcr1000 was used in our studies [11]. The time-dependent decrease in mean cellular fluorescence was determined in the presence of various concentrations of modifier and the first-order rate constants (V_{max}/K_m) were calculated by non-linear regression analysis. Correction for simple diffusion was achieved by subtracting the efflux rates observed in the parental line. EC_{50} values of modifiers were calculated from dose–response curves of V_{max}/K_m versus modifier concentration. Values are given in Table 1 and represent the mean (±s.d.) of at least four independently performed experiments.

4. Calculation of lipophilicity

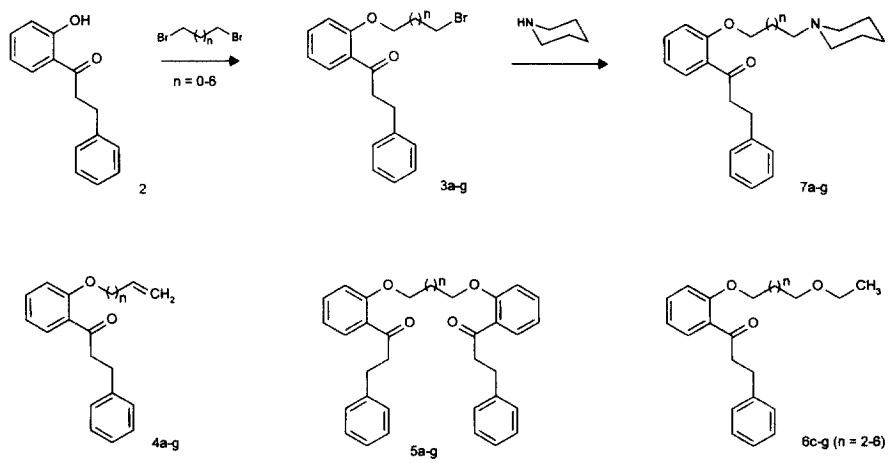
For calculation of log *P* values, the molecular modelling software package MOLGEN [12] was used. In a comparison study of five software packages, MOLGEN was shown to give excellent results when compared with experimentally determined values [13]. The compounds were built using the builder function, optimized, and the log *P* values were calculated using the option 'conformationally independent'.

5. Results and disussion

A series of propafenone-type aryloxyalkylamines was synthesized and tested for their PGP-inhibitory activity to estimate the optimal distance between the central aromatic ring and the positively chargeable nitrogen atom. Chemical structures and pharmacological activity of all compounds tested are given in Table 1. With the exception of **7a**, all derivatives show higher activity than the parent compound GP05 **1b**, with the C_8 analogue **7g** being the most active compound.

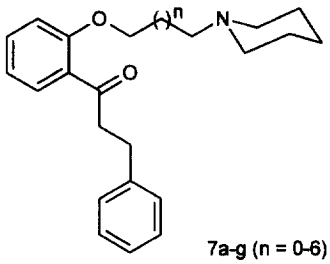
Nevertheless, this might be due to generally higher lipophilicity of the compounds due to the absence of the hydroxy group. Thus, we calculated the log *P* values of compounds **7a–g** using the software package MOLGEN, which proved to yield excellent results within the series of propafenone-type modulators of multidrug resistance [13]. Values are also given in Table 1.

All derivatives are less active than would be expected from the corresponding activity–lipophilicity correlation for propafenones (Fig. 2). This indicates that the hydroxy group is important for receptor interaction. This is also supported by



Scheme 1. Synthesis of compounds **7a–g**.

Table 1
Chemical structure, calculated log *P* values and MDR-modulating activity of compounds **7a–g**



Comp.	*n*	Formula	M.p. (°C)	Anal. [a]	log *P*	EC_{50} [b] (μM)
1a	–	$C_{21}H_{27}NO_3 \cdot HCl$	175–177	–	3.36	1.08 (±0.25)
1b	–	$C_{23}H_{29}NO_3 \cdot HCl$	153–155	–	3.67	0.68 (±0.20)
7a	0	$C_{22}H_{27}NO_2 \cdot HCl \cdot 0.75H_2O$	85–88	Ref. [9]	4.21	1.45 (±0.27)
7b	1	$C_{23}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$	157–159	Ref. [9]	4.32	0.65 (±0.16)
7c	2	$C_{24}H_{31}NO_2 \cdot HCl$	129–131	Ref. [10]	4.77	0.38 (±0.08)
7d	3	$C_{25}H_{33}NO_2 \cdot HCl \cdot 1.5H_2O$	136–138	C, H, N, Cl	5.19	0.24 (±0.08)
7e	4	$C_{26}H_{35}NO_2 \cdot HCl$	121–123	C, H, N, Cl	5.61	0.20 (±0.10)
7f	5	$C_{27}H_{37}NO_2 \cdot HCl$	141–143	C, H, N, Cl	6.02	0.17 (±0.03)
7g	6	$C_{28}H_{39}NO_2 \cdot HCl \cdot 0.5H_2O$	113–114	C, H, N, Cl	6.44	0.15 (±0.05)

[a] Satisfactory C, H, N, and Cl elemental analyses (±0.4%) were obtained.
[b] The values given represent the mean (±s.d.) of at least four independently performed experiments.

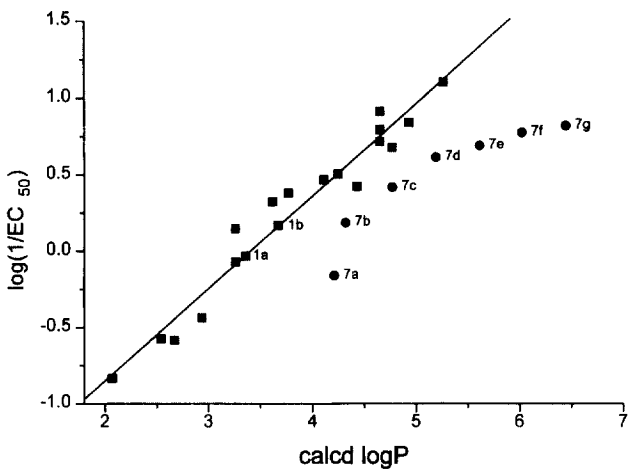


Fig. 2. Correlation of calculated log *P* values of compounds **7a–g** with MDR-modulating activity (expressed as $\log(1/EC_{50})$ values); the line and the squares (■) represent the correlation established previously for propafenone derivatives; the filled circles (●) represent compounds **7a–g**.

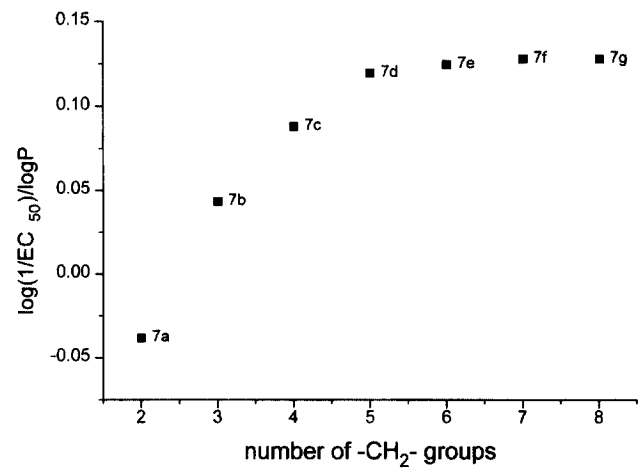


Fig. 3. Plot of the number of methylene groups vs. the activity/log *P* ratio expressed as $\log(1/EC_{50})/\log P$.

the fact that the enantiomers of propafenone showed statistically significant differences in their PGP-inhibitory potency by a factor of 2 [14].

In contrast to the series of propafenone analogues, there is no linear relationship between $\log(1/EC_{50})$ values and lipophilicity of compounds **7a–g**. As can be seen in Fig. 2, the PGP-inhibitory potency of the compounds increases with increasing lipophilicity (or number of methylene groups), until a plateau is reached. Thus, derivatives with log *P* values higher than 5.2, which corresponds to at least five methylene groups, show nearby identical activity. This is even better reflected by a plot of the log(Potency)/log *P* ratio versus the number of methylene groups, which is show in Fig. 3.

In summary, no optimal distance seems to exist within the set of compounds tested. This is somewhat contradictory to previously published results for acridone carboxamides, which showed a spacer length of three–four methylene groups between the cationic site and the lipophilic part as optimal [15]. Nevertheless, for **7a–g** it has to be taken into account that all compounds tested show extremely high flexibility. This may lead to back-folding of the nitrogen substituent in the phospholipid membrane, which was shown, for example, for a series of *N*-alkylbenzylamines [16]. Thus, synthesis and testing of conformationally constrained analogues is necessary to get further evidence on the influence of the distance between the two proposed pharmacophoric substructures on MDR-modulating activity.

6. Conclusions

A series of propafenone type aryloxyalkylamines **7a–g** with varied spacer length between the central aromatic ring and the nitrogen atom was synthesized and tested for PGP-inhibitory activity. All derivatives showed lower activity than would be expected according to their log *P* values. This indicates that the hydroxy group is important for receptor interaction. Generally, activity increases with increasing number of methylene groups and reaches a plateau for compounds with at least five methylene groups. Thus, within this series of compounds, no optimum seems to exist for the distance between the central aromatic ring and the nitrogen atom. Nevertheless, due to the high flexibility of the compounds, conformationally constrained analogues have to be synthesized to further support our findings.

7. Materials and methods

7.1. Chemistry

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer Paragon 1000 spectrophotometer. NMR spectra were recorded on a Varian Unity plus 300 system, using tetramethylsilane as internal standard. EI/MS spectra were performed on a Shimadzu QP 500 equipped with a DI 50 probe; GC/MS spectra were performed on an HP-5890A GC equipped with an HP-5970 MSD and a 59970 ChemStation data system (both by L. Jirovetz, Institute of Pharmaceutical Chemistry, University of Vienna, Austria). Microanalyses were done by J. Theiner (Institute of Physical Chemistry, University of Vienna, Austria). Analyses indicated by the symbols were within $\pm 0.4\%$ of theoretical values.

*7.2. General procedures for preparation of bromoalkylphenylethers **3a–g***

7.2.1. Procedure A

1-(2-Hydroxyphenyl)-3-phenyl-1-propanone **2** (5.00 g, 22.1 mmol) was dissolved in 35 ml of acetone and added dropwise to a suspension of 3.67 g (26.5 mmol) of K_2CO_3 and 44.2 mmol of dibromoalkane in 10 ml of acetone. The reaction mixture was heated to reflux for 20 h, cooled, filtered and evaporated to dryness. The resulting yellow oil was diluted with diethyl ether and washed with water and brine. The organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified via column chromatography (silica gel, diethyl ether/petroleum ether).

7.2.2. Procedure B

A solution of 0.51 g (22.1 mmol) of sodium in 90 ml of ethanol (dried flasks, argon atmosphere) was heated to 50°C and 5.00 g of **2** (22.1 mmol) were added. After 2 min, 66.3 mmol of dibromoalkane were added and the suspension was heated to reflux for 4 h. The reaction mixture was cooled, filtered, diluted with diethyl ether and washed with water and brine. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The resulting yellow oil was purified via column chromatography (silica gel, diethyl ether/petroleum ether).

7.2.3. Procedure C

66.3 mmol of dibromoalkane were added to a suspension of 5.54 g (22.3 mmol) of the sodium salt of **2** in toluene and the resulting mixture was heated to reflux for 23 h. The reaction mixture was cooled, filtered and concentrated. The resulting oil was dissolved in CH_2Cl_2 and washed with water and brine. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The resulting oil was purified via column chromatography (silica gel, diethyl ether/petroleum ether).

*7.3. 1-(2-(2-Bromoethyloxy)phenyl)-3-phenyl-1-propanone **3a***

Yield 19.4% (A). ^{1}H NMR ($CDCl_3$, ppm): δ 3.05 (t, 2H, $J=7.8$ Hz, –CH_2–Ph), 3.41 (t, 2H, $J=7.8$ Hz, CO–CH_2–), 3.63 (t, 2H, $J=5.7$ Hz, Br–CH_2–), 4.37 (t, 2H, $J=5.7$ Hz, O–CH_2–), 6.89 (d, 1H, $J=8.1$ Hz, arom. H-3), 7.03 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.15–7.31 (m, 5H, phenyl H), 7.44 (ddd, 1H, $J=1.8$, 7.5, 8.1 Hz, arom. H-4), 7.68 (dd, 1H, $J=1.8$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 28.82, 30.18 (CH_2–Ph, CH_2–Br), 45.38 (CO–CH_2), 68.17 (O–CH_2), 112.16, 121.38, 125.80, 128.27, 128.38, 128.74, 130.45, 133.21, 141.48, 156.70 (arom. C), 201.57 (CO); IR (KBr, cm^{-1}): ν 1661 (CO); EI/MS (70 eV): *m/e* 332, 334 (M^+, 3), 227, 229 (17), 121 (28), 91 (51), 57 (100). *Anal.* ($C_{17}H_{17}O_2Br$) C, H, Br.

*7.4. 1-(2-(3-Bromopropyloxy)phenyl)-3-phenyl-1-propanone **3b***

Yield 40.7% (A). ^{1}H NMR ($CDCl_3$, ppm): δ 2.30 (quin, 2H, $J=6.2$ Hz, –CH_2–), 3.03 (t, 2H, $J=7.7$ Hz, –CH_2–Ph), 3.30 (t, 2H, $J=7.7$ Hz, CO–CH_2–), 3.50 (t, 2H, $J=6.2$ Hz, –CH_2–Br), 4.19 (t, 2H, $J=6.2$ Hz, –O–CH_2–), 6.97 (d, 1H, $J=8.5$ Hz, arom. H-3), 7.01 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.15–7.34 (m, 5H, phenyl H), 7.44, (ddd, 1H, $J=1.6$, 7.5, 8.5 Hz, arom. H-4), 7.66 (dd, 1H, $J=1.6$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 29.68, 30.20, 32.03 (CH_2–CH_2–Br, CH_2–Ph), 45.37 (CO–CH_2), 65.94 (O–CH_2), 112.33, 120.94, 125.93, 128.26, 128.40, 130.26, 133.30, 141.45, 157.35 (arom. C), 201.47 (CO); GC/MS: *m/e* 348, 346 (M^+, 60), 243, 241 (100), 161 (60), 133 (50), 121 (93), 91 (45); IR (KBr, cm^{-1}): ν 1662 (CO). *Anal.* ($C_{18}H_{19}O_2Br$) C, H; Br: calc. 23.01; found 22.57%.

7.5. 1-(2-(4-Bromobutyloxy)phenyl)-3-phenyl-1-propanone 3c [10]

Yield 66.1% (B). ^{1}H NMR ($CDCl_3$, ppm): δ 1.97 (m, 4H, $-CH_2-CH_2-$), 3.03 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.30–3.38 (m, 4H, $-CH_2-Br$, $CO-CH_2-$), 4.07 (t, 2H, $J=5.4$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.1$ Hz, arom. H-3), 7.00 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.18–7.32 (m, 5H, phenyl H), 7.42 (ddd, 1H, $J=1.5$, 7.5, 8.1 Hz, arom. H-4), 7.68 (dd, 1H, $J=1.5$, 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): δ 27.80, 29.38, 30.19, 33.12 (CH_2-Ph, $CH_2-CH_2-CH_2-Br$), 45.59 ($CO-CH_2$), 67.36 ($O-CH_2$), 112.10, 120.68, 125.85, 128.24, 128.34, 130.28, 133.30, 141.54, 157.68 (arom. C), 201.07 (CO); IR (KBr, cm^{-1}): ν 1671 (CO); EI/MS (70 eV): *m/e* 360, 362 (M^+, 2), 255, 257 (13), 135, 137 (38), 121 (74), 91 (42), 77 (29), 55 (100).

7.6. 1-(2-(5-Bromopentyloxy)phenyl)-3-phenyl-1-propanone 3d

Yield 30.3% (C). ^{1}H NMR ($CDCl_3$, ppm): δ 1.53–1.59 (m, 2H, pentyl H-3), 1.75–1.87 (m, 4H, pentyl H-2, H-4), 3.03 (t, 2H, $J=8.4$ Hz, $-CH_2-Ph$), 3.30 (t, 2H, $J=6.6$ Hz, $-CH_2-Br$), 3.35 (t, 2H, $J=8.4$ Hz, $CO-CH_2-$), 4.04 (t, 2H, $J=6.0$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.4$ Hz, arom. H-3), 6.99 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.16–7.31 (m, 5H, phenyl H), 7.43 (ddd, 1H, $J=1.5$, 7.5, 8.4 Hz, arom. H-4), 7.71 (dd, 1H, $J=1.5$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 25.02, 28.42, 30.25, 32.31, 33.31 ($-CH_2-CH_2-CH_2-CH_2-Br$, $-CH_2-Ph$), 45.64 ($CO-CH_2$), 68.05 ($O-CH_2$), 112.09, 120.57, 125.86, 128.21, 128.25, 128.33, 130.35, 133.34, 141.63, 157.88 (arom. C), 201.46 (CO); IR (KBr, cm^{-1}): ν 1662 (CO); MS (70 eV): *m/e* 374, 376 (M^+, 2), 269, 271 (14), 121 (100), 91 (46), 77 (24). *Anal.* ($C_{20}H_{23}O_2Br$) C, H, Br.

7.7. 1-(2-(6-Bromohexyloxy)phenyl)-3-phenyl-1-propanone 3e

Yield 69.3% (B). ^{1}H NMR ($CDCl_3$, ppm): δ 1.35–1.83 (m, 8H, 4-hexyl $-CH_2-$), 3.03 (t, 2H, $J=8.4$ Hz, $-CH_2-Ph$), 3.32–3.38 (m, 4H, $CO-CH_2-$, $-CH_2-Br$); 4.04 (t, 2H, $J=6.3$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.1$ Hz, arom. H-3), 6.99 (dd, 1H, $J=7.2$, 7.5 Hz, arom. H-5), 7.16–7.31 (m, 5H, phenyl H), 7.43 (ddd, 1H, $J=1.5$, 7.2, 8.1 Hz, arom. H-4), 7.70 (dd, 1H, $J=1.5$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 25.53, 27.81, 29.05, 30.28, 32.45, 33.68 (hexyl $-CH_2$, CH_2-Ph, CH_2-Br), 45.59 ($CO-CH_2$), 68.20 ($O-CH_2$), 112.12, 120.51, 125.85, 128.21, 128.26, 128.34, 130.35, 133.35, 141.64, 157.98 (arom. C), 201.55 (CO); IR (KBr, cm^{-1}): ν 1665 (CO); EI/MS (70 eV): *m/e* 388, 390 (M^+, 4), 283, 285 (16), 121 (100), 91 (43), 77 (20). *Anal.* ($C_{21}H_{25}O_2Br$) C, H, Br.

7.8. 1-(2-(7-Bromoheptyloxy)phenyl)-3-phenyl-1-propanone 3f

Yield 59.8% (B). ^{1}H NMR ($CDCl_3$, ppm): δ 1.26–1.45 (m, 6H, 3-heptyl $-CH_2-$), 1.75–1.83 (m, 4H, 2-heptyl $-CH_2-$), 3.02 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.34 (t, 2H, $J=8.1$ Hz, $CO-CH_2$), 3.37 (t, 2H, $J=6.6$ Hz, $-CH_2-Br$), 4.02 (t, 2H, $J=6.3$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.4$ Hz, arom. H-3), 6.97 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.17–7.27 (m, 5H, phenyl H), 7.42 (ddd, 1H, $J=1.8$, 7.5, 8.4 Hz, arom. H-4), 7.69 (dd, 1H, $J=1.8$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 26.12, 27.94, 28.42, 29.09, 30.29, 32.62, 33.75 (5-heptyl CH_2, CH_2-Br, CH_2-Ph), 45.47 ($CO-CH_2$), 68.35 ($O-CH_2$), 112.15, 120.48, 125.81, 128.26, 128.31, 130.32, 133.30, 141.63, 158.01 (arom. C), 201.65 (CO); IR (KBr, cm^{-1}): ν 1674 (CO); EI/MS (70 eV): *m/e* 402, 404 (M^+, 1), 297, 299 (11), 121 (100), 91 (36), 55 (86). *Anal.* ($C_{22}H_{27}O_2Br$) H; C: calc. 65.51, found 66.23; Br: calc. 19.81, found 18.90%.

7.9. 1-(2-(8-Bromooctyloxy)phenyl)-3-phenyl-1-propanone 3g

Yield 59.2% (B). ^{1}H NMR ($CDCl_3$, ppm): δ 1.19–1.88 (m, 12H, 6-octyl $-CH_2-$), 3.03 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.33–3.42 (m, 4H, $CO-CH_2-$, $-CH_2-Br$), 4.03 (t, 2H, $J=6.6$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.4$ Hz, arom. H-3), 6.98 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.16–7.30 (m, 5H, phenyl H), 7.43 (ddd, 1H, $J=1.5$, 7.5, 8.4 Hz, arom. H-4), 7.69 (dd, 1H, $J=1.5$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 20.38, 26.20, 28.03, 28.56, 29.10, 29.15, 30.28, 32.69, 33.90 (octyl CH_2, CH_2-Ph, CH_2-Br), 45.45 ($CO-CH_2$), 68.39 ($O-CH_2$), 112.13, 120.44, 125.80, 128.26, 128.29, 130.32, 133.31, 141.62, 158.04 (arom. C), 201.08 (CO); IR (KBr, cm^{-1}): ν 1672 (CO); EI/MS (70 eV): *m/e* 416, 418 (M^+, 14), 311, 313 (14), 147, 149 (14), 121 (100), 91 (49), 55 (45). *Anal.* ($C_{23}H_{29}O_2Br$) H; C: calc. 66.19, found 66.98; Br: calc. 19.14, found 18.67%.

7.10. 3-Phenyl-1-(2-(2-propenyloxy)phenyl)-1-propanone 4b

Yield 6.5%. ^{1}H NMR ($CDCl_3$, ppm): δ 3.02 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.34 (t, 2H, $J=8.1$ Hz, $CO-CH_2-$), 4.61 (dd, 2H, $J=1.4$, 5.4 Hz, $-O-CH_2-$), 5.29 (dd, 1H, $J=1.4$, 10.5 Hz, $=CH_a$), 5.39 (dd, 1H, $J=1.4$, 17.3 Hz, $=CH_b$), 6.03 (ddt, 1H, $J=10.5$, 17.3, 5.4 Hz, $-CH=$), 6.93 (d, 1H, $J=8.6$ Hz, arom. H-3), 6.99 (dd, 1H, $J=7.4$, 7.6 Hz, arom. H-5), 7.13–7.32 (m, 5H, phenyl H), 7.41 (ddd, 1H, $J=1.7$, 7.4, 8.6 Hz, arom. H-4), 7.66 (dd, 1H, $J=1.7$, 7.6 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 30.37 (CH_2-Ph), 45.30 ($CO-CH_2$), 69.36 ($-O-CH_2$), 118.19 ($=CH_2$), 112.73, 120.85, 125.82, 128.30, 128.36, 128.78, 130.30, 133.15, 141.56, 157.40 (arom. C), 132.56 ($-CH=$), 201.85 (CO); IR (KBr, cm^{-1}): ν 1660 (CO); GC/MS: *m/e* 266 (M^+, 66),

225 (46), 161 (100), 133 (37), 121 (51), 91 (53), 77 (31). *Anal.* ($C_{18}H_{18}O_2$) C, H.

*7.11. 1,3-Bis-(2-(3-phenylpropionyl)phenyloxy)-butylene **5c** [10]*

Yield 5.4%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.82–1.91 (m, 4H, $-CH_2-CH_2-$), 2.99 (t, 4H, $J=7.8$ Hz, $-CH_2-Ph$), 3.27 (t, 4H, $J=7.8$ Hz, $CO-CH_2-$), 3.91–3.98 (m, 4H, $-O-CH_2-$), 6.87 (d, 2H, $J=8.3$ Hz, arom. H-3), 7.01 (dd, 2H, $J=7.4$, 7.6 Hz, arom. H-5), 7.14–7.29 (m, 10H, phenyl H), 7.42 (ddd, 2H, $J=1.7$, 7.4, 8.3 Hz, arom. H-4), 7.71 (dd, 2H, $J=1.7$, 7.6 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 26.24 ($-CH_2-CH_2-$), 30.19 (CH_2-Ph), 45.72 ($CO-CH_2$), 67.73 ($O-CH_2-$), 112.11, 120.64, 125.81, 128.06, 128.19, 128.29, 130.34, 133.39, 141.59, 157.80 (arom. C), 201.65 (CO); IR (KBr, cm^{-1}): ν 1660 (CO).

*7.12. 1-(2-(4-Ethoxy-butyloxy)phenyl)-3-phenyl-1-propanone **6c***

Yield 2.9%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.21 (t, 3H, $J=6.9$ Hz, $-CH_3$), 1.63–1.92 (m, 4H, $-CH_2-CH_2-$), 3.03 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.30–3.48 (m, 6H, $-CH_2-O-CH_2-$, $CO-CH_2-$), 4.07 (t, 2H, $J=7.8$ Hz, $-O-CH_2-$), 6.92 (d, 1H, $J=8.7$ Hz, arom. H-3), 6.98 (dd, 1H, $J=7.2$, 7.8 Hz, arom. H-5), 7.12–7.27 (m, 5H, phenyl H), 7.42 (ddd, 1H, $J=1.8$, 7.2, 8.7 Hz, arom. H-4), 7.68 (dd, 1H, $J=1.8$, 7.8 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 15.17 (CH_3), 26.20, 26.50 ($-CH_2-CH_2-$), 30.29 (CH_2-Ph), 45.44 ($CO-CH_2$), 66.10, 68.30, 69.90 ($O-CH_2-$, $-CH_2-O-CH_2-$), 112.20, 120.50, 125.80, 128.31, 128.47, 130.30, 130.83, 133.28, 141.64, 157.96 (arom. C), 201.74 (CO); IR (KBr, cm^{-1}): ν 1673 (CO); GC/MS: *m/e* 326 (M^+, 1), 121 (32), 101 (100), 91 (32), 55 (61). *Anal.* ($C_{21}H_{26}O_3$) C, H.

*7.13. General procedure for preparation of amines **7a–g***

The bromoalkoxypropiophenone **3** (2.5 mmol) was dissolved in 5 ml of piperidine and heated to reflux for 30 min. The reaction mixture was cooled, diluted with 2N HCl and extracted several times with diethyl ether. The aqueous phase was alkalized with NaOH and extracted several times with diethyl ether. The combined organic layers from the second extraction step were dried over Na_2SO_4 and evaporated to dryness. The resulting oil was purified via column chromatography (silica gel, CH_2Cl_2/methanol/NH_4OH conc. 200:10:1).

Formation of the hydrochlorides was carried out by dissolving the amine in ethyl acetate and adding a 1 M solution of HCl in diethyl ether. The hydrochloride was filtered off and purified via crystallization.

*7.14. 3-Phenyl-1-(2-(2-(1-piperidyl)ethyloxy)phenyl)-1-propanone **7a** [9]*

Yield 87.7%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.35–1.58 (m, 6H, 3-piperidine $-CH_2-$), 2.34–2.47 (m, 4H, $N-(CH_2)_2-$), 2.73 (t, 2H, $J=5.7$ Hz, $-CH_2-N$), 3.02 (t, 2H, $J=7.8$ Hz, $-CH_2-Ph$), 3.38 (t, 2H, $J=7.8$ Hz, $CO-CH_2-$), 4.16 (t, 2H, $J=5.7$ Hz, $O-CH_2-$), 6.93 (d, 1H, $J=8.1$ Hz, arom. H-3), 6.99 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.15–7.30 (m, 5H, phenyl H), 7.43 (ddd, 1H, $J=1.8$, 7.5, 8.1 Hz, arom. H-4), 7.68 (dd, 1H, $J=1.8$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 24.06 (piperidine C-4), 25.88 (piperidine C-3, C-5), 30.27 (CH_2-Ph), 45.51 ($CO-CH_2$), 54.94 (piperidine C-2, C-6), 57.76 (CH_2-N), 66.56 ($O-CH_2$), 112.35, 120.64, 125.78, 128.28, 128.32, 130.29, 133.28, 141.66, 157.78 (arom. C), 201.08 (CO); IR (KBr, cm^{-1}): ν 1661 (CO); EI/MS (70 eV): *m/e* 337 (M^+, 0.2), 121 (2), 111 (24), 98 (100), 91 (10), 55 (13).

7a-hydrochloride: yield 80.0%; m.p. 85–88°C (i-PrOH).

*7.15. 3-Phenyl-1-(2-(3-(1-piperidyl)propyloxy)phenyl)-1-propanone **7b** [9]*

Yield 94.4%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.38–1.60 (m, 6H, 3-piperidine $-CH_2-$), 1.97 (quin, 2H, $J=6.3$ Hz, $-CH_2-$), 2.18–2.40 (m, 4H, $N(CH_2)_2$), 2.41 (t, 2H, $J=6.3$ Hz, $-CH_2-N$), 3.02 (t, 2H, $J=7.5$ Hz, $-CH_2-Ph$), 3.34 (t, 2H, $J=7.5$ Hz, $CO-CH_2$), 4.08 (t, 2H, $J=6.3$ Hz, $-O-CH_2-$), 6.94 (d, 1H, $J=7.8$ Hz, arom. H-3), 6.98 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.41 (ddd, 1H, $J=1.8$, 7.5, 7.8 Hz, arom. H-4), 7.68 (dd, 1H, $J=1.8$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 24.28, 25.88, 26.70 (3-piperidine CH_2, $-CH_2-$), 30.28 (CH_2-Ph), 45.60 ($CO-CH_2$), 54.47 ($N(CH_2)_2$), 56.10 (CH_2-N), 66.98 ($O-CH_2$), 112.14, 120.45, 125.77, 128.29, 130.31, 133.30, 141.58, 157.97 (arom. C), 201.51 (CO); IR (KBr, cm^{-1}): ν 1664 (CO); EI/MS (70 eV): *m/e* 351 (M^+, 0.2), 124 (15), 98 (100), 91 (8), 55 (11).

7b-hydrochloride: yield 21.3%; m.p. 157–159°C (EtOAc/i-PrOH).

*7.16. 3-Phenyl-1-(2-(4-(1-piperidyl)butyloxy)phenyl)-1-propanone **7c** [10]*

Yield 84.5%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.38–1.85 (m, 10H, 3-piperidine $-CH_2-$, 2-butyl $-CH_2-$), 2.24–2.41 (m, 6H, $-CH_2-N(CH_2)_2$), 3.02 (t, 2H, $J=8.1$ Hz, $-CH_2-Ph$), 3.35 (t, 2H, $J=8.1$ Hz, $CO-CH_2-$), 4.06 (t, 2H, $J=6.3$ Hz, $-O-CH_2-$), 6.93 (d, 1H, $J=8.1$ Hz, arom. H-3), 6.98 (t, 1H, $J=7.5$ Hz, arom. H-5), 7.16–7.30 (m, 5H, phenyl H), 7.42 (ddd, 1H, $J=1.5$, 7.5, 8.1 Hz, arom. H-4), 7.67 (dd, 1H, $J=1.5$, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 23.46, 24.36, 25.87, 27.31, 30.28 (3-piperidine CH_2, 2 butyl CH_2, $-CH_2-Ph$), 45.35 ($CO-CH_2$), 54.43 ($N(CH_2)_2$), 58.79 (CH_2-N), 68.32 ($O-CH_2$), 112.17, 120.46, 125.80, 128.28, 128.30, 130.28, 133.26, 141.60, 157.92 (arom. C), 201.72 (CO); IR (KBr, cm^{-1}): ν 1673 (CO); EI/MS (70 eV): *m/e* 365 (M^+, 0.1), 274 (5), 121 (4), 98 (100), 91 (9), 55 (16).

7c-hydrochloride: yield 35.0%; m.p. 129–131°C (i-PrOH).

7.17. 3-Phenyl-1-(2-(5-(1-piperidyl)pentyloxy)phenyl)-1-propanone 7d

Yield 59%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.41–1.84 (m, 12H, 3-pentyl $-CH_2-$, 3-piperidyl $-CH_2-$), 2.44–2.72 (m, 6H, $-CH_2-N(CH_2)_2$), 3.02 (t, 2H, J = 8.1 Hz, $-CH_2-Ph$), 3.32 (t, 2H, J = 8.1 Hz, $CO-CH_2-$), 4.04 (t, 2H, J = 6.0 Hz, $-O-CH_2-$), 6.92 (d, 1H, J = 8.1 Hz, arom. H-3), 6.98 (t, 1H, J = 7.5 Hz, arom. H-5), 7.18–7.28 (m, 5H, phenyl H), 7.43 (ddd, 1H, J = 1.5, 7.5, 8.1 Hz, arom. H-4), 7.66 (dd, 1H, J = 1.5, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 23.26, 24.01, 24.21, 24.87, 28.78, 30.25 (3-pentyl CH_2, 3-piperidyl CH_2, CH_2-Ph), 45.32 ($CO-CH_2$), 53.81 ($N(CH_2)_2$), 58.11 (CH_2-N), 68.01 ($O-CH_2$), 112.02, 120.55, 125.81, 128.27, 128.32, 130.19, 133.31, 141.63, 157.76 (arom. C), 201.66 (CO); IR (KBr, cm^{-1}): ν 1664 (CO); EI/MS (70 eV): *m/e* 379 (M^+, 0.2), 154 (24), 121 (6), 98 (100), 91 (8), 55 (12).

7d-hydrochloride: yield 60.7%; m.p. 136–138°C (i-PrOH). *Anal.* ($C_{25}H_{34}NO_2Cl \cdot 1.5H_2O$) C, H, N, Cl.

7.18. 3-Phenyl-1-(2-(6-(1-piperidyl)hexyloxy)phenyl)-1-propanone 7e

Yield 94.1%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.15–1.82 (m, 14H, 4- hexyl $-CH_2-$, 3 piperidyl $-CH_2-$), 2.24–2.42 (m, 6H, $-CH_2-N(CH_2)_2$), 3.03 (t, 2H, J = 8.1 Hz, $-CH_2-Ph$), 3.35 (t, 2H, J = 8.1 Hz, $CO-CH_2$), 4.03 (t, 2H, J = 6.3 Hz, $-O-CH_2-$), 6.92 (d, 1H, J = 8.4 Hz, arom. H-3), 6.98 (t, 1H, J = 7.5 Hz, arom. H-5), 7.15–7.29 (m, 5H, phenyl H), 7.42 (ddd, 1H, J = 1.8, 7.5, 8.4 Hz, arom. H-4), 7.68 (dd, 1H, J = 1.8, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 24.31, 25.76 (2C), 26.18, 26.61, 27.33, 29.08, 30.24 (4-hexyl CH_2, 3-piperidyl CH_2, CH_2-Ph), 45.37 ($CO-CH_2$), 54.52 ($N(CH_2)_2$), 59.30 (CH_2-N), 68.35 ($O-CH_2$), 112.13, 120.40, 125.76, 128.24, 128.28, 130.27, 133.27, 141.58, 157.99 (arom. C), 201.68 (CO); IR (KBr, cm^{-1}): ν 1667 (CO); EI/MS (70 eV): *m/e* 393 (M^+, 0.2), 168 (5), 121 (8), 98 (100), 91 (6), 55 (9).

7e-hydrochloride: yield 48.5%; m.p. 121–123°C (EtOAc). *Anal.* ($C_{26}H_{36}NO_2Cl$) C, H, N, Cl.

7.19. 3-Phenyl-1-(2-(7-(1-piperidyl)heptyloxy)phenyl)-1-propanone 7f

Yield 76.0%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.20–1.81 (m, 16H, 5-heptyl $-CH_2-$, 3-piperidyl $-CH_2-$), 2.27–2.48 (m, 6H, $-CH_2-N(CH_2)_2$), 3.02 (t, 2H, J = 8.1 Hz, $-CH_2-Ph$), 3.35 (t, 2H, J = 8.1 Hz), 4.02 (t, 2H, J = 6.6 Hz, $-O-CH_2-$), 6.92 (d, 1H, J = 8.4 Hz, arom. H-3), 6.97 (t, 1H, J = 7.5 Hz, arom. H-5), 7.17–7.30 (m, 5H, phenyl H), 7.42 (ddd, 1H, J = 1.5, 7.5, 8.4 Hz, arom. H-4), 7.69 (dd, 1H, J = 1.5, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 24.27, 25.71 (2C), 26.20, 26.62, 27.47, 29.10, 29.19, 30.25 (5-heptyl CH_2, 3-piperidyl CH_2, CH_2-Ph), 45.39 ($CO-CH_2$), 54.51 ($N(CH_2)_2$), 59.38 (CH_2-N), 68.40 ($O-CH_2$), 112.11, 120.38, 125.77, 128.22, 128.26, 130.28, 133.28, 141.59, 158.03 (arom. C), 201.66 (CO); IR (KBr, cm^{-1}): ν 1670 (CO); EI/MS (70 eV): *m/e* 408 ($M+1^+$, 3), 121 (14), 98 (100), 91 (8), 55 (13).

7f-hydrochloride: yield 73.4%; m.p. 141–143°C (i-PrOH). *Anal.* ($C_{27}H_{38}NO_2Cl$) C, H, N, Cl.

7.20. 3-Phenyl-1-(2-(8-(1-piperidyl)octyloxy)phenyl)-1-propanone 7g

Yield 73.8%. ^{1}H NMR ($CDCl_3$, ppm): δ 1.23–1.82 (m, 18 H, 6-octyl $-CH_2-$, 3-piperidyl $-CH_2-$), 2.30–2.48 (m, 6H, $-CH_2-N(CH_2)_2$), 3.02 (t, 2H, J = 7.5 Hz, $-CH_2-Ph$), 3.35 (t, 2H, J = 7.5 Hz, $CO-CH_2-$), 4.02 (t, 2H, J = 6.6 Hz, $-O-CH_2-$), 6.92 (d, 1H, J = 8.4 Hz, arom. H-3), 6.97 (t, 1H, J = 7.5 Hz, arom. H-5), 7.17–7.27 (m, 5H, phenyl H), 7.42 (ddd, 1H, J = 1.8, 7.5, 8.4 Hz, arom. H-4), 7.68 (dd, 1H, J = 1.8, 7.5 Hz, arom. H-6); ^{13}C NMR ($CDCl_3$, ppm): δ 24.20, 25.56 (2C), 26.20, 26.47, 27.55, 29.15, 29.19, 29.33, 30.27 (6-octyl CH_2, 3-piperidyl CH_2, CH_2-Ph), 45.39 ($CO-CH_2$), 54.41 ($N(CH_2)_2$), 59.32 (CH_2-N), 68.45 ($O-CH_2$), 112.15, 120.40, 125.77, 128.24, 128.28, 130.28, 133.27, 141.60, 158.05 (arom. C), 201.74 (CO); IR (KBr, cm^{-1}): ν 1670 (CO); EI/MS (70 eV): *m/e* 421 (M^+, 0.2), 121 (8), 98 (100), 91 (7), 55 (17).

7g-hydrochloride: yield 88.0%; m.p. 113–114°C (EtOAc/i-PrOH). *Anal.* ($C_{28}H_{40}NO_2Cl \cdot 0.5H_2O$) C, H, N, Cl.

Acknowledgements

The present work was generously supported by the Austrian Science Fund (grant #P11760-MOB). D. Annibali thanks the ERASMUS program for financial support.

References

[1] P.R. Twentyman, Multidrug resistance: strategies for circumvention, Drug News Persp. 6 (1993) 647–654.
[2] S.E. Kane, Multidrug resistance of cancer cells, Adv. Drug Res. 28 (1996) 182–252.
[3] J.A. Kellen, Multidrug Resistance, in: J.A. Kellen (Ed.), Reversal of Multidrug Resistance in Cancer; CRC Press, Boca Raton, FL, 1994, pp. 1–19.
[4] J.M. Ford, W.N. Hait, Pharmacology of drugs that alter multidrug resistance in cancer, Pharmacol. Rev. 42 (1990) 155–199.
[5] G. Ecker, P. Chiba, Recent developments in overcoming tumour cell multi-drug resistance, Exp. Opin. Ther. Patents 7 (1997) 589–599.
[6] G. Ecker, P. Chiba, Structure–activity-relationship studies on modulators of the multidrug transporter P-glycoprotein — an overview, Wien. Klin. Wochenschr. 107 (1995) 681–686.
[7] G. Ecker, P. Chiba, M. Hitzler, D. Schmid, K. Visser, H.P. Cordes, J. Csöllei, J.K. Seydel, K.J. Schaper, Structure–activity relationship studies on benzofurane analogs of propafenone-type modulators of tumor cell multidrug resistance, J. Med. Chem. 39 (1996) 4767–4774.
[8] P. Chiba, M. Hitzler, E. Richter, M. Huber, C. Tmej, E. Giovagnoni, G. Ecker, Studies on propafenone-type modulators of multidrug resistance, III. Variations on the nitrogen, Quant. Struct. Activity Relat. 16 (1997) 361–366.

[9] L. Turbanti, G.F. Di Paco, Nuovi dialchilamino e ciclometilenaminoalcossi-β-fenilpropiofenoni ad azione coronarodilatatrice ed antispastica (Novel dialkylamino- and cyclomethyleneaminoalkoxy-β-phenylpropiophenones with coronardilating and antispastic activity), Farmaco Ed. Sci. 17 (1962) 651–659.

[10] L. Turbanti, C.S. Tauro, G. Garzelli, Alcuni nuovi dialchilamino- e ciclometilenaminoalcossi-β-fenilpropiofenoni ad azione coronarodilatatrice ed antispastica (A series of novel dialkylamino- and cyclomethyleneaminoalkoxy-β-phenylpropiophenones with coronardilating and antispastic activity), Farmaco Ed. Sci. 18 (1963) 149–169.

[11] V. Gekeler, G. Frese, A. Noller, R. Handgretinger, A. Wilisch, H. Schmidt, C. Muller, R. Dopfer, T. Klingbiel, H. Diddens, H. Probst, D. Niethammer, Mdr1/P-glycoprotein, topoisomerase and glutathione-*S*-transferase gene expression in primary and relapsed state adult and childhood leukemias, Br. J. Cancer 66 (1992) 507–517.

[12] P. Baricic, M. Mackov, MOLGEN, distributed by Milan Hudecek, P. Horova 18, 841 07 Bratislava, Slovakia.

[13] S. Prets, A. Jungreithmair, P. Chiba, G. Ecker, Comparison of different methods for estimation of propafenone-type modulators of multidrug resistance, Sci. Pharm. 64 (1996) 627–636.

[14] P. Chiba, S. Rebitzer, E. Richter, M. Hitzler, G. Ecker, Synthesis and pharmacological activity of the stereoisomeres of GP88, a propafenone-type modulator of multidrug resistance, Bioorg. Med. Chem. Lett. 8 (1998) 829–832.

[15] N. Dodic, B. Dumaitre, A. Daugan, P. Pianetti, Synthesis and activity against multidrug resistance in Chinese hamster ovary cells of new acridone-4-carboxamides, J. Med. Chem. 38 (1995) 2418–2426.

[16] E.A. Coats, M. Wiese, H.-L. Chi, H.P. Cordes, J.K. Seydel, Computer modelling and NMR studies of interactions between phospholipids and benzylamines, Quant. Struct. Activity Relat. 11 (1992) 364–369.