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New 1,3-dioxolane and 1,3-dioxane derivatives as effective modulators to overcome multidrug resistance

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Abstract—Multidrug resistance (MDR) to antitumor agents represents a major obstacle to a successful chemotherapy of cancer. Overexpression of P-glycoprotein (p-gp) seems to be the major factor responsible for MDR. A large number of chemically unrelated compounds are known to interact with p-gp resulting in a decreasing resistance. In our efforts related to structure–activity studies of new potential MDR reversal agents we synthesized a series of compounds that differ in the aromatic core structure, the linker, and the basic moiety. For our search of new aromatic core structures we synthesized novel 2,2-diphenyl-1,3-dioxolane, 2,2- diphenyl-1,3-dioxane, and 4,5-diphenyl-1,3-dioxolane derivatives. A range of lipophilic linker structures and protonable basic moieties were synthesized and investigated to optimize the structure of the potential MDR-modulators. The compounds were tested in vitro using human Caco-2 cells. Both the cytotoxicity of the synthons and their ability to resensitize the cells were determined with a MTT assay. The results show that at low concentration various substances reverse tumor cell MDR. Some of the new structures show better effects than established modulators like trifluoperazine.

1. Introduction

The phenomenon of multidrug resistance (MDR) is one of the main problems of a successful cancer therapy.[1] This is mainly observed at chemotherapy of malignant tumor. MDR is primarily bound to transmembranous transport-proteins, whose overexpression in tumor cells causes an increased efflux of the cytostatic drug. In consequence of the reduced concentration the cytostatic process stagnates. P-glycoprotein (p-gp) is one of the most important and well-explored transport proteins.[2] It is well known that a range of clinically used drugs are also able to reverse MDR. But the original pharmacological effect of these substances now turns into an unrequested side effect. The last decade is characterized by the development of new classes of potential modulators but actually there is no drug with MDR indication in clinical application.[3] An optimal chemosensitizer for overcoming multidrug resistance should inhibit the transport-protein, for example, p-gp, without noteworthy side effects and tolerable cytotoxicity.[4] There is no high resolution X-ray structure of p-gp and therefore novel structure-activity relationships of new modulators are still under way.[5] In the last few years various theoretical models could be developed showing the demand on steric structure of potential modulators.[6] Therefore a lipophilic domain consisting of two aromatic rings and a basic moiety with a positive charge at physiological pH value connected by an aliphatic linker should be essential requirements for active structures.[7–13] Further investigations showed the presence of two or three hydrogen donor points[14] and hydrogen acceptor points[15] with a defined steric constitution as essential structure characteristic of p-gp modulators. As a consequence of these results a range of pharmacophore models[16,17] were published such as the postulated verapamil (rhodamine123)-binding site[16] and the Hoechst 33342 model.[19] The existence of further binding sites will be

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discussed presently. Based on these results and in continuation of our work to reversal agents of phenothiazine type and other heterocyclic aromatic ring systems we synthesized a range of new potential MDR modulators and tested whether the substances reverse multidrug resistance.

2. Results

Following well-known structure–activity relationships new substance types were created that can be subdivided into three molecule domains: a lipophilic, aromatic structure, a carbon chain as linker, and a basic molecule part. We focused our special attention on investigations to the hydrophobic moiety of 2,2-diphenyl-1,3-dioxolane, 2,2-diphenyl-1,3-dioxane, and 4,5-diphenyl-1,3-dioxolane derivatives. By systematic variation of each of these domains we synthesized a multitude of new substances. The development of the synthetic strategy is described below.

2.1. Synthetic chemistry

2,2-Diphenyl-1,3-dioxolane derivatives and 2,2-diphenyl-1,3-dioxane derivatives are acetals of benzophenone with hexanetriol and 2-hydroxymethyl-2-methyl-propane-1,2-diol, respectively. Due to the low carbonyl-activity of the keto-group a direct conversion of benzophenone with the triols under acidic conditions does not lead to the desired cyclic compounds. Only previous activation of the benzophenone by transfer of the aromatic ketone in its pursuant dimethylacetal **1**, which is synthesized from benzophenone dichloride[20,21] with methanol and equimolar amounts of pyridine, makes the reaction work.

In a new modified variation[22] we converted the benzophenone dimethylacetal **1** in toluol by addition of catalytic amounts of sulfuric acid with hexanetriol **2** and 2-(hydroxymethyl)-2-methyl-1,3-propanediol **4**, respectively. Additionally we removed resulting methanol by Soxhlet equipment filled with calcium chloride. Consequently the expected compounds 4-(2,2-diphenyl-1,3-dioxolane-4-yl)butanol **3** and (5-methyl-2,2-diphenyl-1,3-dioxane-5-yl)methanol **5** were isolated in good yields.

In principle the synthesized 4,5-diphenyl-1,3-dioxolanes represent acetals of a benzaldehyde derivate with hydrobenzoine. This lipophilic structure consists of two aromatic rings of the hydrobenzoine and an aromatic ring of the 4-hydroxybenzaldehyde.

Because of the higher carbonyl-activity of the benzaldehyde derivative a direct conversion with hydrobenzoine could be achieved. We used 4-(ω-halogenalkoxy)benzaldehyde derivatives for benzaldehyde derivatives synthesized by deprotonation of 4-hydroxybenzaldehyde with sodium ethanolate in ethanol followed by reaction with 1,2-dibromoethane, 1,3-bromochloropropane, and 1,4-dibromobutane, respectively.[23–25] We received the crystalline substances 4-(2-bromoethoxy)benzaldehyde **7a,** 4-(3-chloropropoxy)benzaldehyde **7b**, and 4-(4-bromobutoxy)benzaldehyde **7c** which were converted with hydrobenzoine **6** into the 4,5-diphenyl-1,3-dioxolane derivatives **8a**–**c**.[26] As solvents and entrainer we used chloroform. For the acid catalysis we used hydrogen chloride-gas and the formed reaction water was removed by azeotrope-destillation with water trap. After purification by column chromatography we obtained the desired compounds.

Concerning stereochemistry the 4,5-diphenyl-1,3-dioxolane derivatives represent a very interesting type of substance classes. The substituted 1,3-dioxolane is characterized by two chiral centers in 4- and 5-position and in 2-position in case of (4*R*,5*S*) configuration by a pseudochirale center. At last four configuration isomers can be framed[27,28] (Fig. 1).

The *R*,*R*- and the *S*,*S*-isomers have optical activity. The others represent *meso*-forms with *R*- and *S*-configuration at the carbon atoms 4 and 5, and pseudo-chirality at position 2, respectively. Consequently two different isomers of this *meso*-form (*cis* and *trans*) are existing. Synthesis of these two *meso cis*/*trans* derivatives was achieved by the described method by acetalization with 4-(3-chloropropoxy)benzaldehyde **8b** using the *meso*-form of hydrobenzoine. The two expected diastereomers could be separated by flash chromatography. We obtained the *trans*- and *cis*-form in a ratio of 1:3. The two optically active isomers are dioxolane-derivatives which are derived from two optically active hydrobenzoine-derivatives *R*,*R* and *S*,*S*. In this case the carbon atom in 2-position does not have pseudo-chirality. We synthesized these two derivatives according to the described method using the (1*R*,2*R*)- and (1*S*,2*S*)-derivatives of the hydrobenzoines and a pure stereoisomer was obtained after flash chromatography. As a result of that it was possible to separate and synthesize the four possible configuration isomers for 2-[4-(3-chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane **8b**/*trans*, **8b**/*cis*, **8b**/*RR*, and **8b**/*SS*, respectively.

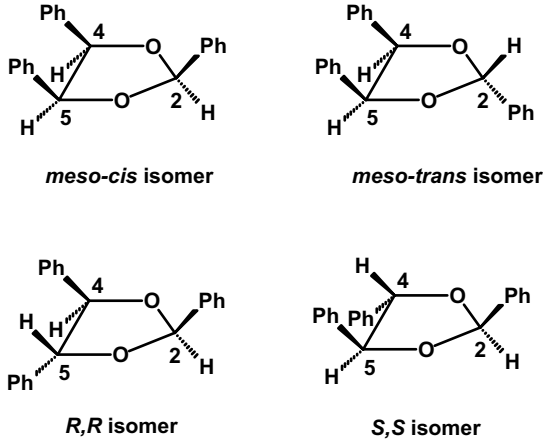


Figure 1. Configuration isomers of 4,5-diphenyl-1,3-dioxolane derivatives.

Since we used ^{1}H NMR-spectroscopy, X-ray structure analysis and polarimetry the determination of physicochemical structure of the four configuration isomers was possible. The two *meso*-forms represent diastereomers among themselves and also to the (4*R*,5*R*)- and (4*S*,5*S*)-forms. These forms are enantiomeric to each other.

In ^{1}H NMR-spectra diastereomers show anisochronous signals. Enantiomers are characterized by identical spectra in achiral medium.[29] The differentiation of the diastereomers was achieved by analyzing the signals of the protons at the dioxolane-ring in 2-, 4-, and 5-position. As expected a differentiation of the two enantiomers among themselves was not possible. A summary of the crucial ^{1}H NMR-signals of the protons in 2-, 4-, and 5-position for the isomers of 2-[4-(3-chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane is shown in Table 1.

Table 1. δ-Data (in ppm) of the ^{1}H NMR-spectra of the isomers of 2-[4-(3-chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane, solvent: $CDCl_3$

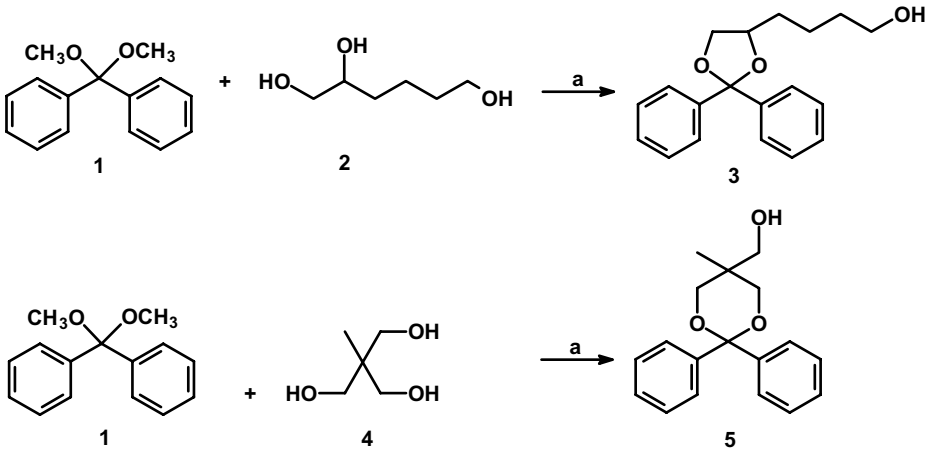
	H_2	$H_{4,5}$
meso-trans-isomer	δ = 6.76 (s)	δ = 5.40 (s)
meso-cis-isomer	δ = 6.15 (s)	δ = 5.51 (s)
(4*R*,5*R*)-isomer	δ = 6.34 (s)	δ = 4.91–4.95 (m)
(4*S*,5*S*)-isomer	δ = 6.34 (s)	δ = 4.91–4.95 (m)

The confirmation of enantiomeric purity was achieved by polarimetric investigations of *R,R*- and *S,S*-configured final compounds. We obtained the specific angle of rotation data of $[\alpha]_D^{20}$ +40 (**22**/*RR*), $[\alpha]_D^{20}$ −40 (**22**/*SS*), $[\alpha]_D^{20}$ +26 (**27**/*RR*) and $[\alpha]_D^{20}$ −26 (**27**/*SS*) proving the pure stereoisomers (Scheme 1).

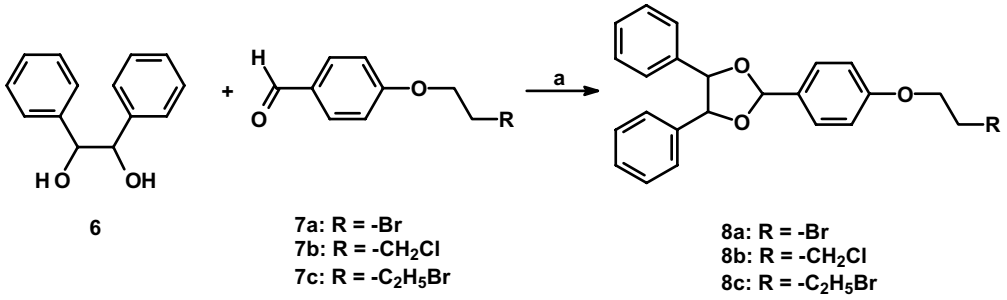
Due to the fact two *meso*-forms do not show optical activity and the protons in 2-, 4- and 5-position show identical signals with only different shift the final determination of the configuration was achieved by X-ray structure analysis (data not shown) (Scheme 2).

For investigations of the influence on structural variations in the lipophilic, aromatic domain we synthesized 4,5-diphenyl-1,3-dioxolane derivatives with substituted vicinal phenyl moieties. Synthesis of 4,4′-difluorohydrobenzoine **11b** was achieved starting from the analogous benzil derivative **10b** by reduction with sodium borohydride in 2-propanol (Scheme 3).[30] 2,2′-Dichlorohydrobenzoine **11a** was obtained by acyloine-condensation of 2-chlorobenzaldehyde **9a** and subsequent reduction.[31]

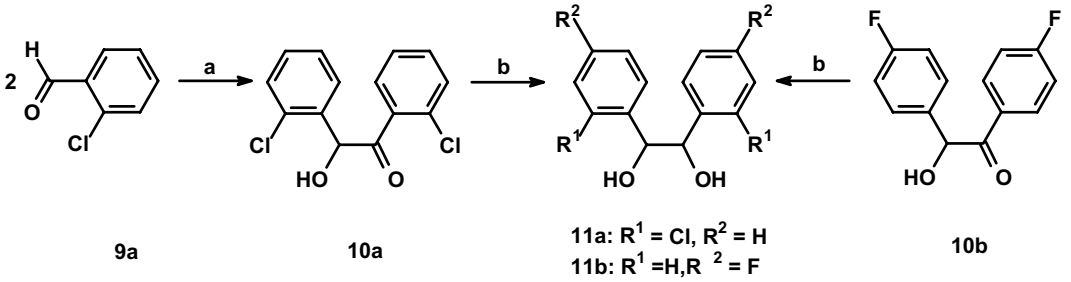
For reaction of the basic moiety with the lipophilic group containing a halogen we used two different methods: on the one hand, the reaction with an excess of base simultaneous as proton acceptor without solvent (method A) and on the other hand the conversion with sodium hydride in DMSO (method B).



Scheme 1. Transacetalizations. Reagents and condition: (a) H_2SO_4/toluene, reflux.



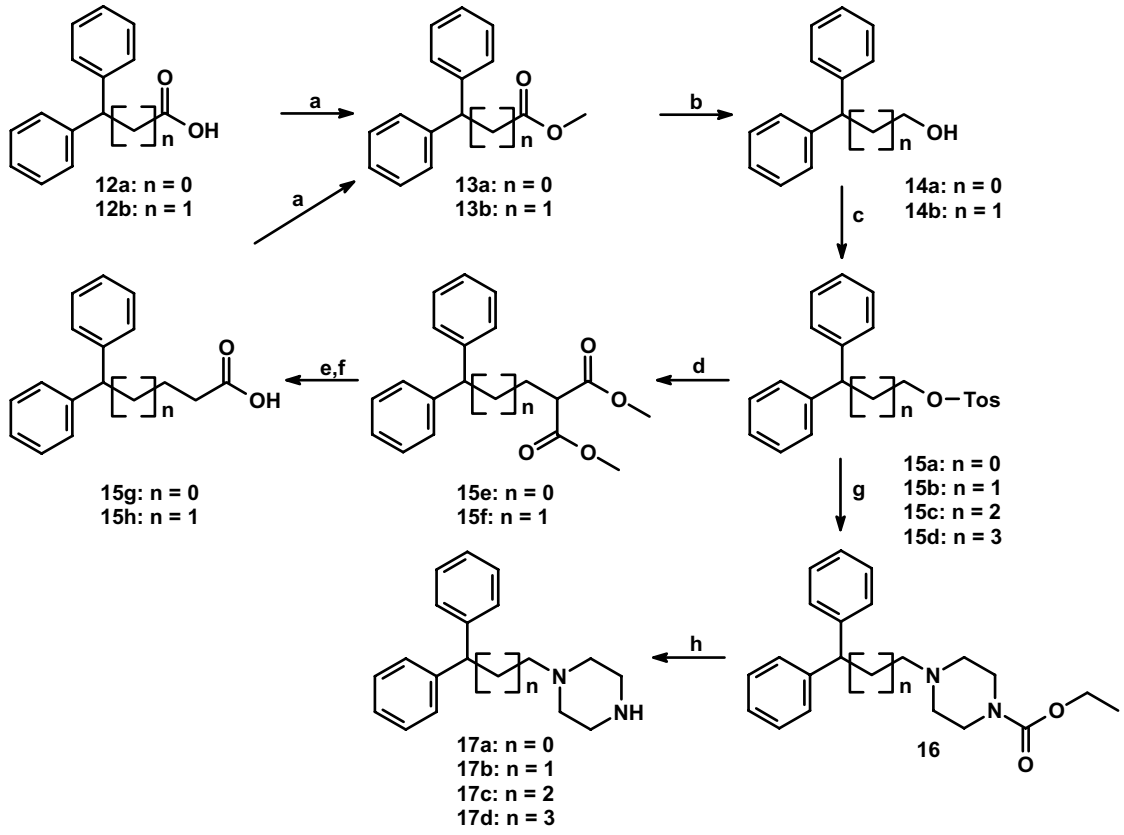
Scheme 2. Synthesis of **8a**–**c**. Reagents: (a) HCl/$CHCl_3$.



Scheme 3. Synthesis of the substituted hydrobenzoine derivatives **11**. Reagents: (a) KCN, EtOH/H_2O; (b) $NaBH_4$, *i*-PrOH.

During the synthesis of the 2,2-diphenyl-1,3-dioxolane and 2,2-diphenyl-5-methyl-1,3-dioxane derivatives the hydroxy group of the intermediates **3** and **5** was transferred into the homologous tosylates **3-T** and **5-T**. The following reaction with the basic moiety was achieved in toluol with triethylamine or potassium carbonate[32] as proton acceptor.[33] In selection of the basic molecule domain we decided to use the well-known piperidine and piperazine derivatives[34,35] and furthermore for new diphenylalkylpiperazine derivatives. The synthesis of the ω,ω-diphenylalkylpiperazine derivatives was achieved by reaction of diphenylalkyl-*p*-toluenesulfonates with ethyl *N*-piperazinecarboxylate (Scheme 4).[36,37] As base for the synthesis of the assigned diphenylalkyltosylates we used 2,2-diphenylacetic acid **12a** and 3,3-diphenylpropionic acid **12b** which were converted into the methyl ester **13**. The esters were reduced afterwards with lithium aluminum hydride to the alcohols **14** and transferred into the desired tosylates with carbon chain length C-2 **15a** and C-3 **15b**. These two products were also used as basic intermediates synthesizing the tosylates with carbon chain length of C-4 and C-5. The extension of the carbon chain was achieved by C-alkylation with dimethyl malonate. These alkylated esters **15e**,**f** were hydrolyzed to the free malonic acids and converted into the monocarbonic acids **15g**,**h** by decarboxylation. Formation of the methyl ester was followed by the reduction to the free alcohols and conversion to the tosylate yields with carbon chain length C-4 **15c** and with C-5 **15d**.

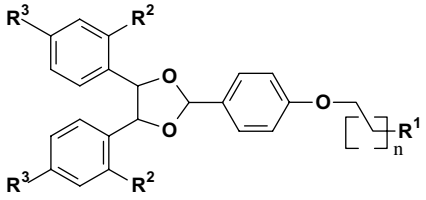
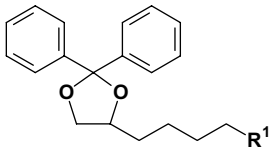
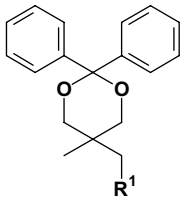
The received diphenylalkyltosylates **15** were converted without solvent and with twofold molar quantity of ethyl *N*-piperazinecarboxylate. Subsequently the protection groups were removed by basic hydrolysis leading to the diphenylalkylpiperazine residues **17a**–**d**.



Scheme 4. Synthesis of the ω,ω-diphenylalkylpiperazines **17**. Reagents and conditions: (a) MeOH, $H_2SO_4/CHCl_3$, reflux; (b) $LiAlH_4/Et_2O$, rt; (c) Tos-Cl, $NEt_3/CHCl_3$, rt; (d) NaOEt, dimethyl malonate/EtOH, reflux; (e) KOH/EtOH, reflux; (f) ΔT; (g) ethyl *N*-piperazinecarboxylate, 100 °C; (h) KOH/EtOH, H_2O, reflux.

N-alkylation of the basic residue represents the last reaction step of our synthesis scheme and led to the desired final compounds which all have the essential molecular structure with lipophilic, aromatic domain, the linker, and the basic moiety. All final compounds were purified by flash chromatography and converted into the maleic acid salts to have a water-soluble form for biochemical tests. Table 2 shows the synthesized

Table 2. Scheme of the final compounds with activity

Compound	*n*	R^1	R^2	R^3	$IC_{50mod.}$ [μM ± SD]	$IC_{10tox.}$ [μM ± SD]	$In._{tox.10}$ [% ± SD]	$In._{mod.5}$ [% ± SD]
								
20	2	PIP	H	H	13.8 ± 4.8	15.3 ± 4.6	52.3 ± 3.8	34.2 ± 2.9
21	2	HEP	H	H	107,8 ± 6.1	76.6 ± 7.1	14.4 ± 3.5	<5
22/*cis*	2	MP	H	H	14.4 ± 3.9	21.1 ± 5.1	63.5 ± 4.7	34.6 ± 3.7
22/*trans*	2	MP	H	H	13.5 ± 3.6	19.5 ± 4.8	63.8 ± 3.8	33.2 ± 3.5
22/*RR*	2	MP	H	H	9.4 ± 3.1	20.4 ± 4.8	64.8 ± 4.1	41.5 ± 2.9
22/*SS*	2	MP	H	H	7.1 ± 3.4	19.9 ± 5.2	65.3 ± 3.5	45.4 ± 3.1
23	2	DP1P	H	H	64.3 ± 5.1	16.4 ± 4.6	35.5 ± 2.9	7.4 ± 1.8
24	2	DP2P	H	H	9.1 ± 5.0	6.1 ± 3.9	42.3 ± 3,3	14.2 ± 3,1
25	2	DP3P	H	H	69.6 ± 4.9	18.5 ± 4.2	37.2 ± 2.8	9.3 ± 1.5
26	2	DP4P	H	H	34.3 ± 4.2	12.4 ± 3.4	43.5 ± 3.4	11.2 ± 2.1
27/*cis*	2	DP5P	H	H	9.2 ± 3.1	16.8 ± 3.6	63.3 ± 3.8	41.5 ± 3.4
27/*trans*	2	DP5P	H	H	12.5 ± 3.5	15.9 ± 3.8	62.3 ± 3.1	35.7 ± 2.8
27/*RR*	2	DP5P	H	H	18.5 ± 3.6	16.2 ± 3.5	60.8 ± 3.9	25.2 ± 2.1
27/*SS*	2	DP5P	H	H	17.1 ± 3.7	17.1 ± 3.8	61.7 ± 3.4	27.5 ± 2.3
28	2	MP	Cl	H	12.9 ± 3.3	19.5 ± 3.6	57.3 ± 4.1	34.2 ± 2.9
29	2	MP	H	F	15.2 ± 4.1	18.8 ± 3.7	63.4 ± 3.5	30.6 ± 2.8
30	1	MP	H	H	8.7 ± 3.2	8.6 ± 3.5	57.7 ± 4.0	32.4 ± 3.2
31	1	DP5P	H	H	19.9 ± 4.3	14.7 ± 3.9	43.2 ± 2.9	22.5 ± 2.4
32	3	MP	H	H	25.4 ±. 5.8	13.8 ± 5.2	33.7 ± 3.1	16.4 ± 1.8
33	3	DP5P	H	H	27.4 ± 3.9	17.5 ± 3.9	31.4 ± 2.4	15.1 ± 2.0
								
34	—	PIP	—	—	35.8 ± 3.9	18.1 ± 4.9	27.3 ± 2.2	11.4 ± 1.7
35	—	HEP	—	—	152.3 ± 3.2	98.3 ± 5.6	13.1 ± 2.1	<5
36	—	MP	—	—	18.8 ± 4.7	10.5 ± 3.6	47.3 ± 3.2	23.7 ± 2.0
37	—	DP5P	—	—	5.7 ± 3.6	5.85 ± 3.2	62.8 ± 3.7	44.2 ± 3.5
								
38	—	MP	—	—	11.2 ± 3.4	9.7 ± 3.6	53.4 ± 3.9	32.7 ± 2.8
39	—	DP5P	—	—	8.8 ± 2.9	6.1 ± 3.2	57.5 ± 4.1	42.1 ± 3.1
Trifluoperazine	—	—	—	—	16.1 ± 3.5	11.3 ± 3.3	51.7 ± 3.7	28.4 ± 4.1
Verapamil	—	—	—	—	4.7 ± 2.1	24.9 ± 3.0	66.3 ± 3.7	48.1 ± 2.7

Abbreviations: PIP, piperidine; HEP, hydroxyethylpiperazine; MP, 4-methylpiperazine; DP1P, diphenylmethylpiperazine; DP2P, diphenylethylpiperazine; DP3P, diphenylpropylpiperazine; DP4P, diphenylbutylpiperazine; DP5P, diphenylpentylpiperazine, $IC_{50mod.}$, molar concentration [μM] of the modulator that inhibits the growth of Caco-2 cells by 50% in presence of a constant concentration of 1 μM vinblastine; $IC_{10tox.}$, subinhibitory concentration [μM] of the modulator without vinblastine where 90% of the cells appear to be viable after incubation; $In._{tox.10}$, inhibition of cell growth [%] with 1 μM vinblastine + $IC_{10tox.}$ of the modulator relative to untreated cells with 1 μM vinblastine without modulator; $In._{mod.5}$, inhibition of cell growth [%] with 1 μM vinblastine + 5 μM modulator relative to untreated cells with 1 μM vinblastine without modulator.

final compounds. The group $\mathbf{R}^1$ represents the variable basic moiety.

2.2. Biological activity

For the in vitro tests of the synthesized compounds the MTT assay was applied. This method determines the viability of cells. Consequently it is possible to quantify the antiproliferative effect of the cytostatic drug and the cytostatic drug in combination with the test substance which is a parameter of the MDR reversal activity of the test substances. The cytotoxicity of the compounds can also be analyzed by incubation of cells with different concentrations of the test substances and determination of the number of surviving cells. The MTT proliferation test bases on the conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazoliumbromide) by mitochondrial dehydrogenases of living cells into a blue-coloured formazan derivative. The absorption of the formazan whose concentration can be determined with a wavelength of 570 nm correlates with the number of living cells. This test was performed at a human Caco-2 cell line originating from a human colon carcinoma. This cell line is a well-established and stably p-gp expressing cell system with a high content of the transporter. Former experiments showed that other possible binding sites of Caco-2 cell line, like CYP 3A4, MRP, and the organic cation transporter were too low in abundance or affinity to contribute to the total binding to a relevant extent.[38] So this assay is suitable to study p-gp functionality.[39] The overexpression of p-gp was induced by growing cells in the presence of the cytostatic drug vinblastine.[40] Human Caco cells (0.5×10^4 cells/ml) were seeded in 96-well microtiter plates and preincubated for 90 min at 37 °C and 5% CO_2. For the resistant Caco cells we determined an IC_{50} value for vinblastine of 2.12 μM with a quite high standard deviation especially in the high concentration interval which is founded by the resistance phenomenon. According to clinical practices we decided to use a constant molar concentration of the cytotoxic drug vinblastine of 1 μM (IC_{75}) as standard. Therefore cells were incubated with vinblastine (1 μM), vinblastine (1 μM) + references (0.1–400 μM) and finally vinblastine (1 μM) + test substance (0.1–400 μM) for 48 h at 37 °C. The test for cytotoxicity was carried out by treatment of cells only with test substance of decreasing concentrations. Every experiment was performed 3–5 times at different days. If more than 90% of the originally used cells appear to be viable after incubation, the concentration of the compound is non-toxic. Table 2 gives the modulator concentration $IC_{10tox.}$ as a subinhibitory concentration used in reversal experiments.

For evaluation of this test the IC values were determined by the *GraphPadPrism* and *Origin* 7*G* programs. For tests with cells treated with cytostatic drug and test substance the $IC_{50mod.}$ value as quantity for MDR reversal activity of the compounds at a constant molar vinblastine concentration of 1 μM (IC_{75}) and for tests with untreated cells the cytotoxicity ($IC_{10tox.}$) were determined. Interpretation of the data point out a problem in measures of MDR reversal. In the literature there does not exist a uniform measurement method for evaluation of testing data. The mostly used criterion in the MDR reversal studies is the 'MDR ratio' (Fold reversal) defined as the ratio between the IC_{50} value of the cytotoxic agent in absence and presence of a subinhibitory concentration of the modulator ($IC_{10tox.}$). Drawback of this method is the fact that in QSAR studies data are preferred where the same molar concentration of the modifier is used instead of the same toxic IC values.[8] The 'modulator index' (MI) is defined as MDR ratio divided by the used modulator concentration and has been proposed to solve the problem of the dependence on the modulator concentration. The disadvantage of both methods is the usage of different cytostatic drug concentrations for determination of the IC_{50} value in presence of the modifier because this is not a practical concept concerning clinical practice. So we declared an $IC_{50mod.}$ which is defined as molar concentration of the modulator that inhibits the growth of Caco-2 cells by 50% in presence of a constant concentration of 1 μM vinblastine (IC_{75}). The percentage inhibition of the cell growth as $In._{tox.10}$ value (1 μM vinblastine + $IC_{10tox.}$) and $In._{mod.5}$ (1 μM vinblastine + 5 μM modulator) in relation to untreated cells with 1 μM vinblastine without modulator is also given to have a direct comparison between references and control. This method allows fast quantification of the interaction of drugs with human multidrug transporter and has the potential to serve as a high-throughput screening to detect compounds prone to p-gp mediated transport. A plot between the MDR activity ($\log IC_{50mod.}$ in presence of a subinhibitory modulator concentration) and the own cytotoxicity ($\log 1/IC_{50tox.}$) shows a poor correlation ($R^2 = 0.42$).

3. Discussion

The present results of the biochemical test contribute both a statement to structure–activity relationships and conclusions about efficiency of the separate structure domains (lipophilic aromatic structure, linker, and basic moiety) which were systematically variated and

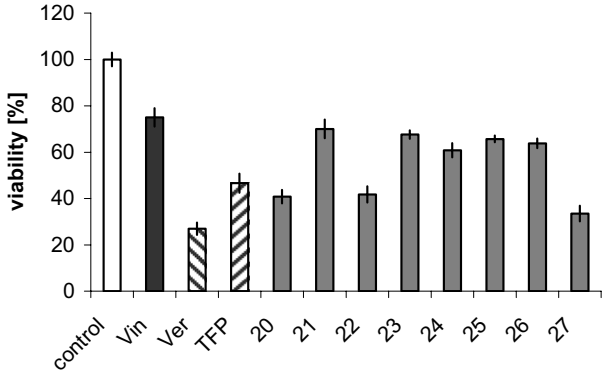


Figure 2. Influence of the basic moiety on activity of 4,5-diphenyl-1,3-dioxolane derivatives. Viability [%] of cells with 1 μM vinblastine (Vin) in comparison with a mixture of 1 μM Vin + 5 μM modulator or references verapamil (Ver) and trifluoperazine (TFP).

combined. Figure 2 shows the modulatoric effect of compounds with different basic moiety. The different basic residues are connected with 4,5-diphenyl-1,3-dioxolane (*cis*-isomer) about a C-3 chain as constant structures.

In general it can be said that the basicity of the residue has an important influence on the modulating activity. So compounds with reduced basicity (e.g., diphenylmethylpiperazine **23**) show explicit lower inhibition values compared to compounds with more basic residues (e.g., 4-methylpiperazine **22**). Additionally a hydrophilic substituent at the basic residue (e.g., 2-hydroxyethylpiperazine **21**) has negative effects. The piperidine derivative **20** with only one protonable nitrogen shows good effectivity but nevertheless exceeded those of the piperazine derivatives with two basic centers. The most potent basic residue represents 1-(5,5-diphenylpentyl)piperazine **27**. It is characterized by two basic, protonable centers and in comparison to diphenylmethylpiperazine by a higher basicity caused by the larger distance to the two phenyl rings. The positive influence on the additional lipophilic substituents is in evidence.

Figure 3 shows the influence of linker-length on the activity of the 4,5-diphenyl-1,3-dioxolane derivatives of compounds with the two most effective basic residues (4-methylpiperazine, diphenylpentylpiperazine). It is readily identifiable that for both basic residues the linker C-3 shows the best modulating activity and consequently represents the optimal distance between the lipophilic aromatic molecule part and the basic moiety.

The comparison of the lipophilic aromatic structures was realized by compounds each with a 4-methylpiperazine residue as standard linked by a C-3 carbon chain. The isomers of 4,5-diphenyl-1,3-dioxolane represent the most effective class of compounds. The individual isomers differ in reversal activity, whereas the optically active forms show better values than the two *meso*-forms (**22**/*SS* > **22**/*RR* > **22**/*cis* > **22**/*trans*). In the series of compounds with geminal bounded phenyl residues the 2,2-diphenyl-1,3-dioxane derivative **38** shows better activity than the 2,2-diphenyl-1,3-dioxolane derivative **36**. Introduction of substituents into the phenyl rings (**28** and **29**) leads to no significant improvement of the activity compared to the unsubstituted *cis*-isomer **22** (Fig. 4).

The results afford analogous to the 4-methylpiperazine derivatives a comparison of the reversal activity of compounds with variable lipophilic aromatic structures and constant diphenylpentylpiperazine residue as most effective basic moiety. The result of the investigation with constant methylpiperazine residue can be confirmed. Tendentious derivatives of 4,5-diphenyl-1,3-dioxolane show good reversal values. The different isomers of **27** explicitly differ in their activity but the sequence is not comparable to the results of the methylpiperazine derivatives (Fig. 5).

The present results of in vitro-tests show that a range of the synthesized compounds have MDR reversal potential. Some of the substances even exhibit a higher activity as well-known MDR modulators like trifluoperazine. However, the excellent results of verapamil can only be reached in particular cases. A

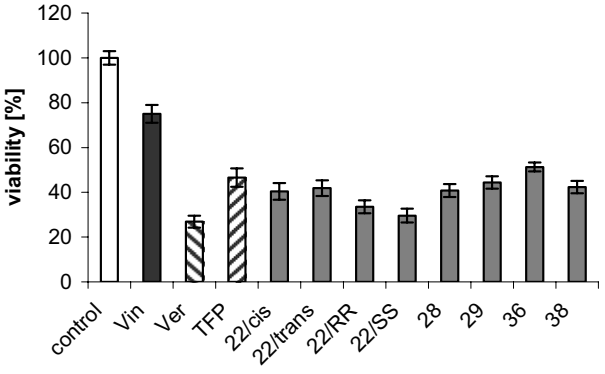


Figure 4. Influence of the lipophilic aromatic structure on activity of 4-methylpiperazine derivatives. Viability [%] of cells with 1 μM vinblastine (Vin) compared to a mixture of 1 μM Vin + 5 μM modulator or references verapamil (Ver) and trifluoperazine (TFP).

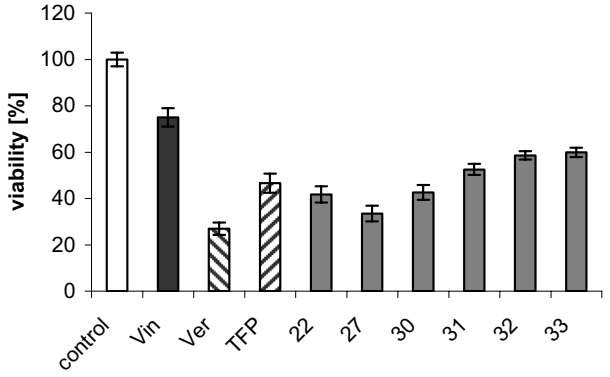


Figure 3. Influence of the linker on the activity of 4,5-diphenyl-1,3-dioxolane derivatives. Viability [%] of cells with 1 μM vinblastine (Vin) in comparison with mixture of 1 μM Vin + 5 μM modulator or references verapamil (Ver) and trifluoperazine (TFP).

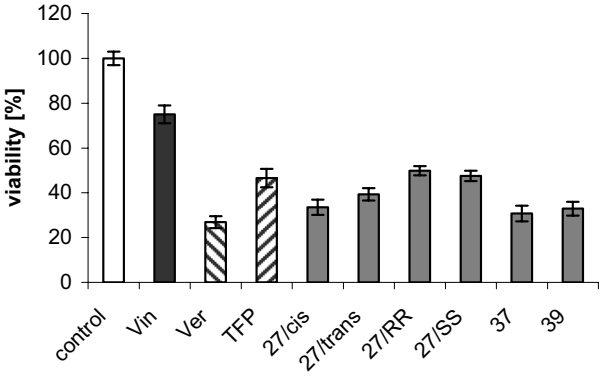


Figure 5. Influence of the lipophilic aromatic structure on activity of 5,5-diphenylpentylpiperazine derivatives. Viability [%] of cells with 1 μM vinblastine (Vin) in comparison with mixture of 1 μM Vin + 5 μM modulator or references verapamil (Ver) and trifluoperazine (TFP).

systematic variation and combination of individual molecule domains resulted in explicit differences in the effect of appropriate substances. Thereby the received results partially correlate with well-known structure–activity relationships. Concerning the most effective substances lipophilic molecules show best reversal activity without exception. Additionally it could be shown that introduction of hydrophilic domains like the 2-hydroxyethylpiperazine-residue leads to a damage of activity. The comparison shows that basic residues correlate with common acquirements[8,9] whereby multiple protonable, tertiary amines integrated into cyclic structures have a positive effect on activity of the molecule overall. In addition it could be shown that reduction of basicity (e.g., diphenylmethylpiperazine residue) affects the reversal activity negatively. Contrary to pharmacophore-models[16] which postulate multiple hydrogen acceptor/donator points the piperidine residue with only one protonable nitrogen shows an astonishing good activity on Caco-2 cells. However, the most effective residues represent piperazine derivatives with two basic centers. The optimal length of the linker determined by us for the 4,5-diphenyl-1,3-dioxolane derivatives also correlates with literature data of an optimal distance of 5 Å between lipophilic aromatic structure and basic moiety.[13] Our test results confirmed acknowledgments about the lipophilic aromatic structure of MDR-modulators.[10,11] All our lipophilic structures are represented by cyclic systems with two or three aromatics. Thereby the most effective compounds feature a defined angle between the aromatic rings and correspond to the data of Suzuki et al.[13] Generally the steric arrangement of aromatic structures seems to be significant for the reversal activity which can be demonstrated by results of the different isomers of the 4,5-diphenyl-1,3-dioxolane derivatives. Even the 5,5-diphenylpentylpiperazine residue could represent the lipophilic aromatic structure themselves which also could explain the quite good reversal effects of compounds with this basic moiety and lipophilic structures failed at other tests.

As already noted for P-gp there are two pharmacophore models—the postulated verapamil (rhodamine123)-binding site[18] and the Hoechst 33342 model.[19] For some of our compounds we could find a good correlation with these models. In initial investigations we observed a good correlation in 5 of 6 possible features for the *RR*-isomer of **22** at the verapamil binding site and in case of the Hoechst 33342 model in 4 of 5 possible features for the *SS*-isomer of **22**. It is noteworthy that in both models the respective hydrogen donor feature cannot be occupied by our compounds which offers further options for synthesis.

The used test system with Caco-2 cells proved to be a suitable method for measurement of the MDR reversal activity of the synthesized compounds and to postulate general structure–activity relationships for new potential MDR modulators. Further tests with new potential modifiers additionally on other cell lines like LLC-PK1:MDR1 are under investigation and confirm these outcomes.

4. Experimental

4.1. Materials and general methods

Mass spectra (MS) were recorded on a *Finnigan MAT-710C* spectrometer. Gas chromatography–mass spectra (GC–MS) were recorded on a *Hewlett-Packard HP 5890 II/MS: 5971 A*. Elemental analyses were performed on a *CHNS-932 microanalyzer (LECO-Corporation)*. ^{1}H NMR spectra were obtained with a *Varian Gemini 2000* spectrometer operating at 400 MHz; all values are reported in parts per million (δ) downfield from solvent. Polarimetric measurement was accomplished by an *Eloptron/Polartronic E* (*Fa. Schmid + Haensch GmbH & Co*). Flash chromatography was performed on silica gel (*Merck Kieselgel 60, 40–63 mesh*). TLC was carried out on silica gel plates (*E. Merck 60 F_{254}*); zones were detected visually by ultraviolet irradiation (254 nm). All reagents were used as purchased unless otherwise stated. All solvents were dried, according to standard procedures. All reactions were carried out under an atmosphere of dry argon. All chemicals were purchased from *Sigma–Aldrich Chemie GmbH (Germany)*.

4.2. Chemistry

4.2.1. Benzophenone dimethylacetal (1). To a solution of 0.12 mol pyridine in 100 ml methanol 0.1 mol benzophenone dichloride was added dropwise and stirred at 0 °C for 1 h and for 1 h at room temperature. The crude solid **1** was filtered in vacuo and recrystallized from methanol as white crystals. Experimental data according to the literature.[15] Yield 89%; mp 106 °C (from MeOH); MS (ES+) *m*/*z* 229.3 (M+H).

4.2.2. 4-(2,2-Diphenyl-1,3-dioxolan-4-yl)butanol (3). To 0.1 mol benzophenone dissolved in 30 ml CH_2Cl_2 0.1 mol 1,2,6-hexanetriol and 0.15 mol **1** were added. The mixture was stirred for 24 h at room temperature. Once the reaction was finished 50 ml of a saturated sodium bicarbonate solution was added. The organic layer was washed twice with 30 ml saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. Product **3** was purified by flash chromatography (heptane/Et_2O, 9:1) over silica gel as a colorless oil. Yield 62%; ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.23–2.00 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 3.60–3.74 (m, 3H, –C*H*O, –C*H*$_2$–OH), 4.09–4.33 (m, 2H, –O–C*H*$_2$–), 7.23–7.86 (m, 10H, Ar*H*); Anal. $C_{19}H_{22}O_3$ requires C, 76.48; H, 7.43. Found: C, 76.49; H, 7.47; MS (ES+) *m*/*z* 299.4 (M+H).

4.2.3. (5-Methyl-2,2-diphenyl-1,3-dioxolan-5-yl)methanol (5). Compound **5** was synthesized according to **3** from **1** and 2-(hydroxymethyl)-2-methyl-1,3-propanediol yielding a colorless oil. Yield 64%; Anal. $C_{18}H_{20}O_3$ required C, 76.48; H, 7.43. Found: C, 76.45; H, 7.44; MS (ES+) *m*/*z* 285.4 (M+H).

4.2.4. 1,2-Bis(2-chlorophenyl)ethane-1,2-diol (11a). 0.2 mol 2-chlorobenzaldehyde **9a** and 4 g potassium cyanide were dissolved in 60 ml EtOH (60%). After heating the mixture under reflux for 15 min 1 g potassium cyanide was added and heated for another 15 min. Once the reaction was

finished the solvent was evaporated in vacuo and the residue was dissolved in 50 ml AcOEt. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The intermediate **10a** was dissolved in 200 ml *i*-PrOH, 0.1 mol sodium borohydride was added, and the mixture was stirred for 12 h at room temperature. Once the reaction was finished hydrochloric acid (1 M) was added until hydrogen evolution was ceased. The mixture was extracted with Et_2O, dried (Na_2SO_4), and evaporated. Compound **11a** was given by recrystallization from heptane as white crystals. Yield 38%; mp 145–146 °C (from heptane); MS (GC/MS) *m*/*z* 283.

4.2.5. 1,2-Bis(4-fluorophenyl)ethane-1,2-diol (11b). 0.1 mol 4,4′-difluorobenzil **10b** was reduced analogous to **10a** with sodium borohydrid yielding **11b** as white crystals. Yield 83%; mp 143–144 °C (from heptane); MS (GC/MS) *m*/*z* 246.

4.2.6. 4-(3-Chloropropoxy)benzaldehyde (7b). Fifty millimole of sodium was dissolved in 150 ml EtOH. To the mixture 50 mmol of 4-hydroxybenzaldehyde was given and the mixture was heated for 1 h under reflux. Then 0.2 mol 1,3-bromochloropropane was added dropwise, stirred, and heated for additional 3 h. The mixture was evaporated in vacuo, 150 ml saturated sodium bicarbonate solution was poured into the residue and extracted twice with 100 ml AcOEt. The organic layer was dried (Na_2SO_4) and evaporated yielding an oil. This residue was extracted with heptane and recrystallized at −10 °C. The precipitate was filtered off providing **7b** as white needles. The experimental data are in agreement with the literature.[18] Yield 62%; mp 29 °C (from heptane); Anal. $C_{10}H_{11}ClO_2$ requires C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.53; H, 5.62; Cl, 17.98; MS (GC/MS) *m*/*z* 198.

4.2.7. 4-(2-Bromoethoxy)benzaldehyde (7a). Synthesis of **7a** was achieved analogous to **7b** by reaction of 4-hydroxybenzaldehyde with dibromoethane. Experimental data correspond with the literature.[18] Yield 61%; mp 37 °C (from heptane); Anal. $C_9H_9BrO_2$ requires C, 47.19; H, 3.96; Br, 34.88. Found: C, 47.23; H, 3.98; Br, 34.92; MS (GC/MS) *m*/*z* 229.

4.2.8. 4-(4-Bromobutoxy)benzaldehyde (7c). Synthesis of **7c** was achieved analogous to **7b** by reaction of 4-hydroxybenzaldehyde with 1,4,dibromobutane. Experimental data according to the literature.[18] Yield 62%; mp 43 °C (from heptane); Anal. $C_{11}H_{13}BrO_2$ requires C, 51.38; H, 5.10; Br, 31.08. Found: C, 51.48; H, 5.05; Br, 30.97; MS (GC/MS) *m*/*z* 257.

4.2.9. (*meso*/*trans*)-2-[4-(3-Chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8b/*trans*) and (*meso*/*cis*)-2-[4-(3-chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8b/*cis*). 0.1 mol **6**/*meso* and 0.1 mol **7b** were dissolved in 200 ml $CHCl_3$ and heated for 5 h under reflux at a water trap by pumping hydrogen chloride-gas into the solution. Once the reaction was finished the organic layer was washed with 150 ml saturated sodium bicarbonate solution and 100 ml water, dried (Na_2SO_4), and evaporated in vacuo. Separation of **8b**/*trans* and **8b**/*cis* was achieved by flash chromatography (heptane/Et_2O, 9:1).

Compound (**8b**)/*trans*: Yield 23%; mp 90–92 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.21–2.27 (m, 2H, –CH_2–CH_2–CH_2–), 3.75 (t, 2H, –CH_2–Cl), 4.14 (t, 2H, O–CH_2–), 5.40 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.76 (s, 1H, –C*H*OO), 6.93–7.55 (m, 14H, –Ar*H*); Anal. $C_{24}H_{23}ClO_3$ requires C, 73.00; H, 5.87; Cl, 5.98. Found: C, 73.36; H, 5.98; Cl, 5.68; MS (GC/MS) *m*/*z* 395.

Compound (**8b**)/*cis*: Yield 65%; mp 102–103 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.25–2.31 (m, 2H, –CH_2–CH_2-CH_2–), 3.78 (t, 2H, –CH_2–Cl), 4.19 (t, 2H, O–CH_2–), 5.51 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.15 (s, 1H, –C*H*OO), 6.99–7.70 (m, 14H, –Ar*H*); Anal. $C_{24}H_{23}ClO_3$ requires C, 73.00; H, 5.87; Cl, 5.98. Found: C, 73.36; H, 5.74; Cl, 6.08; MS (GC/MS) *m*/*z* 394.

4.2.10. (4*S*,5*S*)-2-[4-(3-Chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8b/*SS*). Compound **8b**/*SS* was obtained analogous to **8b**/*trans* by reaction of *S*,*S*-hydrobenzoine with **7b**. Yield 52%; mp 96–98 °C (from heptane);^{1}H NMR ($CDCl_3$): δ [ppm] = 2.21–2.27 (m, 2H, –CH_2–CH_2–CH_2–), 3.74 (t, 2H, –CH_2–Cl), 4.15 (t, 2H, O–CH_2–), 4.91–4.95 (m, 2H, –O–C*H*Ph–C*H*Ph–O) 6.34 (s, 1H, –C*H*OO), 6.94–7.60 (m, 14H, –Ar*H*); Anal. $C_{24}H_{23}ClO_3$ requires C, 73.00; H, 5.87; Cl, 5.98. Found: C, 73.09; H, 5.76; Cl, 5.95; MS (GC/MS) *m*/*z* 394.

4.2.11. (4*R*,5*R*)-2-[4-(3-Chloropropoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8b/*RR*). Compound **8b**/*RR* was obtained analogous to **8b**/*trans* by reaction of *R*,*R*-hydrobenzoine with **7b**. Yield 54%, mp 96–98 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.21–2.27 (m, 2H, –CH_2–CH_2–CH_2–), 3.74 (t, 2H, –CH_2–Cl), 4.14 (t, 2H, O–CH_2–), 4.90–4.95 (m, 2H, –O–C*H*Ph–C*H*Ph–O), 6.34 (s, 1H, –C*H*OO), 6.95–7.59 (m, 14H, –Ar*H*); Anal. $C_{24}H_{23}ClO_3$ requires C, 73.00; H, 5.87; Cl, 5.98. Found: C, 72.89; H, 5.80; Cl, 6.06; MS (GC/MS) *m*/*z* 394.

4.2.12. (*meso*/*trans*)-2-[4-(4-Bromoethoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8a/*trans*). Compound **8a**/*trans* was obtained analogous to **8b**/*trans* by reaction of **6**/*meso* with **7a**. Yield 27%; mp 102–103 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.64 (t, 2H, –CH_2–Br), 4.33 (t, 2H, O–CH_2–), 5.39 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.75 (s, 1H, –C*H*OO), 6.94–7.60 (m, 14H, –Ar*H*); Anal. $C_{23}H_{21}BrO_3$ requires C, 64.95; H, 4.98; Br, 18.79. Found: C, 65.05; H, 4.89; Br, 18.54; MS (GC/MS) *m*/*z* 425.

4.2.13. (*meso*/*cis*)-2-[4-(4-Bromoethoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8a/*cis*). Compound **8c**/*cis* was obtained analogous to **8b**/*trans* by reaction of **6**/*meso* with **7a**. Yield 62%; mp 100–101 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 3.66 (t, 2H, –CH_2–Br), 4.34 (t, 2H, O–CH_2–), 5.49 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.14 (s, 1H, –C*H*OO), 6.98–7.70 (m, 14H, –Ar*H*); Anal. $C_{23}H_{21}BrO_3$ requires C, 64.95; H, 4.98; Br, 18.79. Found: C, 64.87; H, 4.76; Br, 18.98; MS (GC/MS) *m*/*z* 425.

4.2.14. (*meso*/*trans*)-2-[4-(4-Bromobutoxy)phenyl]-4,5-diphenyl-1,3-dioxolane (8c/*trans*). Compound **8c**/*trans* was obtained analogous to **8b**/*trans* by reaction of **6**/*meso* with**7c**. Yield 25%; mp 105–107 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.92–2.14 (m, 4H, –CH_2–CH_2–CH_2–CH_2–), 3.48 (t, 2H, –CH_2–Br), 4.04 (t, 2H, O–CH_2–), 5.40 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.75 (s, 1H, –C*H*OO), 6.91–7.54 (m, 14H, –Ar*H*); Anal. $C_{25}H_{25}BrO_3$ requires C, 66.23; H, 5.56; Br, 17.62. Found: C, 66.13; H, 5.48; Br, 17.57; MS (GC/MS) *m*/*z* 453.

4.2.15. (*meso*/*cis*)-2-[4-(4-Bromobutoxy)phenyl]-4,5-diphenyl-1,3- dioxolane (8c/*cis*). Compound **8c**/*cis* was obtained analogous to **8b**/*trans* by reaction of **6**/*meso* with**7c**. Yield 64%; mp 112–113 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.95–2.11 (m, 4H, –CH_2–CH_2–CH_2–CH_2–), 3.50 (t, 2H, –CH_2–Br), 4.05 (t, 2H, O–CH_2–), 5.49 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.13 (s, 1H, –C*H*OO), 6.97–7.67 (m, 14H, –Ar*H*); Anal. $C_{25}H_{25}BrO_3$ requires C, 66.23; H, 5.56; Br, 17.62. Found: C, 66.15; H, 5.63; Br, 17.23; MS (GC/MS) *m*/*z* 453.

4.2.16. 4,5-Bis(2-chlorophenyl)-2-[4-(3-chloropropoxy)phenyl]-1,3-dioxolane (8d/*cis*). Compound **8d**/*cis* was obtained analogous to **8b**/*trans* by reaction of **11a**/*meso* with**7b**. Yield 43%; mp 118–123 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.23–2.28 (m, 2H, –CH_2–CH_2–CH_2–), 3.73–3.78 (m, 2H, –CH_2–Cl), 4.13–4.19 (m, 2H, O–CH_2–), 6.02 (s, 2H, –O–C*H*Ph–C*H*Ph–O), 6.14 (s, 1H, –C*H*OO), 6.99–7.70 (m, 14H, –Ar*H*); Anal. $C_{24}H_{21}Cl_3O_3$ requires C, 62.15; H, 4.56; Cl, 22.93. Found: C, 62.13; H, 4.48; Cl, 22.81; MS (ES+) *m*/*z* 464.8 (M+H).

4.2.17. 4,5-Bis(4-fluorophenyl)-2-[4-(3-chloropropoxy)phenyl]-1,3-dioxolane (8e/*cis*). Compound **8e**/*cis* was obtained analogous to **8b**/*trans* by reaction of **11b**/*meso* with**7b**. Yield 29%; mp 119–121 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.20–2.28 (m, 2H, –CH_2–CH_2–CH_2–), 3.73–3.76 (m, 2H, –CH_2–Cl), 4.13–4.16 (m, 2H, O–CH_2–), 4.82–4.86 (m, 2H, –O–C*H*Ph–C*H*Ph–O), 6.33 (s, 1H, –C*H*OO), 6.98–7.57 (m, 14H, –Ar*H*); Anal. $C_{24}H_{21}F_2ClO_3$ requires C, 66.90; H, 4.91; Cl, 8.23; F, 8.82. Found: C, 66.71; H, 4.91; Cl, 8.41; F, 8.31; MS (ES+) *m*/*z* 431.9 (M+H).

4.2.18. 4-(2,2-Diphenyl-1,3-dioxolan-4-yl)butyl 4-methylbenzenesulfonate (3-T). To a solution of 0.1 mol **3** and 0.15 mol pyridine dissolved in 75 ml $CHCl_3$ 0.1 mol 4-methylbenzenesulfonyl chloride was given. The mixture was stirred for 24 h at room temperature. Once the reaction was finished the organic layer was washed with 50 ml saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated in vacuo. **3-T** was obtained by flash chromatography (heptane/Et_2O, 9:1) over silica gel as white crystals. Yield 62%; mp 138 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.34–1.71 (m, 6H, –CH_2–CH_2–CH_2–), 2.42 (s, 3H, –CH_3), 3.57–3.62 (m, 1H, –C*H*O–), 3.99–4.10 (m, 4H, –O–CH_2–COH, –CH_2–O–) 7.22–7.78 (m, 14H, –Ar*H*); Anal. $C_{26}H_{28}O_5S$ requires C: 69.00; H, 6.24; S, 7.08. Found C: 68.78; H, 6.14; S, 7.09; MS (ES+) *m*/*z* 453.6 (M+H).

4.2.19. (2,2-Diphenyl-5-methyl-1,3-dioxan-5-yl)methyl 4-methylbenzenesulfonate (5-T). 5-T was obtained analogous to **3-T** by use of **5**. The oily residue was recrystallized from heptane to get **5-T** as white crystals. Yield 62%; mp 125–127 °C (from heptane); ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.74 (s, 3H, –CH_3), 2.42 (s, 3H, Ar–CH_3), 3.59–3.74 (m, 2H, –O–CH_2–C–, –O–CH_2–C–), 4.22 (s, 2H, –C–CH_2–O–), 7.17–7.79 (m, 14H, –Ar*H*); Anal. $C_{25}H_{26}O_5S$ requires C, 68.47; H, 5.98; S, 7.31. Found: C, 68.32; H, 5.95; S, 7.25; MS (ES+) *m*/*z* 439.5 (M+H).

4.2.20. 2,2-Diphenylethyl 4-methylbenzenesulfonate (15a). A mixture of 1 mol **12a**, 1.5 mol MeOH, 5 g H_2SO_4, and 200 ml $CHCl_3$ was heated for 5 h under reflux using a water trap. Once the reaction was finished the organic layer was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated in vacuo to get **13a**. The untreated product was dropwise to a solution of 0.8 mol lithium aluminum hydride in Et_2O and stirred for 4 h at room temperature. The mixture was hydrolyzed with ice water. The organic layer was washed with 1 M H_2SO_4, dried (Na_2SO_4) and evaporated in vacuo to get **14a**. This residue was to a mixture of equimolar amounts of TEA and 4-methylbenzenesulfonyl chloride in 100 ml $CHCl_3$ and stirred for 24 h. Once the reaction was finished the organic layer was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated in vacuo. Compound **15a** was obtained by flash chromatography (heptane/Et_2O, 9:1) as white crystals. Yield 54%; mp 89–91 °C (from heptane); MS (GC/MS) *m*/*z* 352.

4.2.21. 3,3-Diphenylpropyl 4-methylbenzenesulfonate (15b). Compound **15b** was synthesized analogous to **15a** by use of **12b**. Yield 51%; mp 94–95 °C (from heptane); MS (GC/MS) *m*/*z* 366.

4.2.22. 4,4-Diphenylbutyl 4-methylbenzenesulfonate (15c). To a solution of 0.5 mol sodium in 300 ml EtOH 0.5 mol dimethyl malonate was given. To the mixture was given dropwise a solution of 0.5 mol **15a** in 100 ml EtOH and heated for 10 h under reflux. After evaporation the residue was dissolved in water and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated in vacuo to get **15e**. The untreated product was heated in 300 ml 5 M KOH in EtOH for 10 h under reflux. After evaporation the residue was dissolved in water and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was heated at 180 °C until for decarboxylation to get **15g**. Compound **15c** was obtained analogous to **15a** by use of **15g** as a yellow oil. Yield 50%; MS (GC/MS) *m*/*z* 380.

4.2.23. 5,5-Diphenylpentyl 4-methylbenzenesulfonate (15d). Compound **15d** was synthesized analogous to **15c** by use of **15b**. Yield 51%; MS (GC/MS) *m*/*z* 394.

4.2.24. 1-(2,2-Diphenylethyl)piperazine (17a). 0.2 mol **15a** was dissolved in 0.4 mol ethyl *N*-piperazinecarboxylate and heated for 8 h at 100 °C. To the mixture were given 100 ml AcOEt and 100 ml water. The organic layer was separated, washed with water, dried (Na_2SO_4),

and evaporated in vacuo. The crude intermediate was dissolved in 75 ml EtOH. Fifty microliters of 5 M KOH was given to the mixture and heated for 10 h under reflux. Once the reaction was finished the mixture was evaporated. The residue was extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. Compound **17a** was obtained by flash chromatography ($CHCl_3$/AcOEt, 9:1) as a colorless oil. Yield 52%; Anal. $C_{18}H_{22}N_2$ requires C, 81.16; H, 8.32; N, 10.52. Found: C, 81.09; H, 8.28; N, 10.64; MS (ES+) *m*/*z* 267.4 (M+H).

4.2.25. 1-(3,3-Diphenylpropyl)piperazine (17b). Compound **17b** was obtained analogous to **17a** by use of **15b**. Yield 54%; Anal. $C_{19}H_{24}N_2$ requires C, 81.38; H, 8.63; N, 9.99. Found: C, 81.45; H, 8.65; N, 10.06; MS (ES+) *m*/*z* 281.4 (M+H).

4.2.26. 1-(4,4-Diphenylbutyl)piperazine (17c). Compound **17c** was obtained analogous to **17a** by use of **15c**. Yield 5%; Anal. $C_{20}H_{26}N_2$ requires C, 81.59; H, 8.90; N, 9.51. Found: C, 81.53; H, 8.92; N, 9.47; MS (ES+) *m*/*z* 294.4 (M+H).

4.2.27. 1-(5,5-Diphenylpentyl)piperazine (17d). Compound **17d** was obtained analogous to **17a** by use of **15d**. Yield 52%; ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.20–1.30 (m, 2H, –CH_2–CH_2–CH_2–CH_2–), 1.46–1.54 (m, 2H, –CH_2–CH_2–CH_2–CH_2–) 2.01–2.07 (m, 2H, Ph_2–CH–CH_2–), 2.15–2.37 (m, 8H, N–CH_2–) 2.86–2.89 (m, 3H, N–CH_2, –N*H*), 3.87 (t, 1H, Ph_2–C*H*–), 7.12–7.26 (m, 10H, –Ar*H*); Anal. $C_{21}H_{28}N_2$ requires C, 81.77; H, 9.15; N, 9.08. Found: C, 81.81; H, 9.21; N, 9.03; MS (ES+) *m*/*z* 308.5 (M+H).

4.2.28. Final compounds

4.2.28.1. General method A. Ten millimoles of the hydrophobic structure/linker was dissolved in 30 mmol of the basic moiety and heated for 3 h at 120 °C. Then 50 ml water and 50 ml AcOEt were given to the mixture. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography ($CHCl_3$/MeOH, 9:1) to get the product as base which was converted into the maleic acid salts.

4.2.28.2. General method B. Ten millimoles sodium hydride was dissolved in 30 ml DMSO and stirred for 1 h at room temperature. Ten millimoles of the basic moiety was given to the mixture and stirred for another our at room temperature. Then 10 mmol of the hydrophobic structure/linker was given to the mixture and stirred for 12 h at room temperature. Once the reaction was finished it was hydrolyzed with water. The mixture was extracted with AcOEt. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography ($CHCl_3$/MeOH, 9:1) to get the product as base which was converted into the maleic acid salts.

4.2.28.3. General method for synthesis of the maleic acid salts. To a solution of the free base in Et_2O was dropped a saturated solution of maleic acid in Et_2O. Once precipitation was finished the salt was filtered off in vacuo and recrystallized from MeCN to get the maleic acid piperidine salts and the dimaleic acid piperazine salts.

4.2.28.4. *(meso/cis)*-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}piperidine (20). Compound **20** was obtained according to method A by use of **8-b**/*cis* and piperidine. Yield 79%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.45–1.59 (m, 6H, –CH_2–CH_2–CH_{2pip}–), 2.01–2.08 (m ,2H, –CH_2–), 2.41–2.49 (m ,6H, –N–CH_2–), 4.06 (t, 2H, –O–CH_2–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.98–7.66 (m, 14H, –Ar*H*); Anal. $C_{33}H_{37}NO_7$ (salt) requires C, 70.82; H, 6.66; N, 2.50. Found: C, 70.93; H, 6.58; N, 2.56; MS (ES+) *m*/*z* 444.6 (M+H).

4.2.28.5. (*meso/cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(2-hydroxyethyl)piperazine (21). Compound **21** was obtained according to method A by use of **8-b**/*cis* and *N*-(2-hydroxyethyl)piperazine. Yield 68%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 2.19–2.32 (m, 2H, –CH_2–), 2.53–2.57 (m, 12H, –N–CH_2–), 3.76 (t, 2H, –CH_2–OH), 4.17 (t, 2H, –O–CH_2–), 5.49 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.14 (s, 1H, –C*H*OO–), 6.98–7.96 (m, 14H, –Ar*H*); Anal. $C_{38}H_{44}N_2O_{12}$ (salt) requires C, 63.32; H, 6.15; N, 3.89. Found: C, 63.42; H, 6.21; N, 3.86; MS (ES+) *m*/*z* 489.6 (M+H).

4.2.28.6. *(meso/trans)*-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazin (22/*trans*). Compound **22**/*trans* was obtained according to method A by use of **8-b**/*trans* and *N*-methylpiperazine. Yield 89%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.97–2.01 (m, 2H, –CH_2–), 2.35 (s, 3H, –N–CH_3), 2.56–2.59 (m, 10H, –CH_2–), 4.03 (t, 2H, –O–CH_2–), 5.39 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.75 (s, 1H, –C*H*OO–), 6.92–7.58 (m, 14H, –Ar*H*); Anal. $C_{37}H_{42}N_2O_{11}$ (salt) requires C, 64.34; H, 6.13; N, 4.06. Found: C, 64.45; H, 6.08; N, 4.16; MS (ES+) *m*/*z* 459.6 (M+H).

4.2.28.7. *(meso/cis)*-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazine (22/*cis*). Compound **22**/*cis* was obtained according to method A by use of **8-b**/*cis* and *N*-methylpiperazine. Yield 85%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.99–2.04 (m, 2H, –CH_2–), 2.33 (s, 3H, –N–CH_3), 2.56–2.60 (m, 10H, –CH_2–), 4.06 (t, 2H, –O–CH_2–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.97–7.66 (m, 14H, –Ar*H*); Anal. $C_{37}H_{42}N_2O_{11}$ (salt) requires C, 64.34; H, 6.13; N, 4.06. Found: C, 64.15; H, 6.11; N, 4.04; MS (ES+) *m*/*z* 459.6 (M+H).

4.2.28.8. (4*R*,5*R*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazine (22/*RR*). Compound **22**/*RR* was obtained according to method A by use of **8-b**/*RR* and *N*-methylpiperazine. Yield 88%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.97–2.01 (m, 2H, –CH_2–), 2.35 (s, 3H, –N–CH_3), 2.55–2.59 (m, 10H, –CH_2–), 4.04 (t, 2H, –O–CH_2–), 4.91–4.95 (m, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.34 (s, 1H, –C*H*OO–), 6.95–7.58 (m, 14H, –Ar*H*); Anal. $C_{37}H_{42}N_2O_{11}$ (salt) requires C, 64.34; H, 6.13; N, 4.06. Found: C, 64.42; H, 6.06; N, 4.13; MS (ES+) *m*/*z* 459.6 (M+H).

4.2.28.9. (4*S*,5*S*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazine (22/*SS*). Compound **22**/*SS* **36** was obtained according to method A by use of **8-b**/*SS* and *N*-methylpiperazine. Yield 84%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.98–2.01 (m, 2H, –C*H*$_2$–), 2.38 (s, 3H, –N–C*H*$_3$), 2.58–2.61 (m, 10H, –C*H*$_2$–), 4.04 (t, 2H, –O–C*H*$_2$–), 4.91–4.94 (m, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.34 (s, 1H, –C*H*OO–), 6.93–7.58 (m, 14H, –Ar*H*); Anal. $C_{37}H_{42}N_2O_{11}$ (salt) C, 64.34; H, 6.13; N, 4.06. Found: C, 64.37; H, 6.19; N, 4.05; MS (ES+) *m*/*z* 459.6 (M+H).

4.2.28.10. (*meso*/*cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(diphenylmethyl)piperazine (23). Compound **23** was obtained according to method B by use of **8-b**/*cis* and *N*-(diphenylmethyl)piperazine. Yield 52%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.94–2.00 (m, 2H, –C*H*$_2$–), 2.43–2.55 (m, 10H, –N–C*H*$_2$–), 4.04 (t, 2H, –O–C*H*$_2$–), 4.21 (s, 1H, –N–C*H*-Ph$_2$), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.96–7.65 (m, 20H, –Ar*H*); Anal. $C_{49}H_{50}N_2O_{11}$ (salt) requires C, 69.82; H, 5.98; N, 3.32. Found: C, 69.75; H, 6.06; N, 3.21; MS (ES+) *m*/*z* 611.8 (M+H).

4.2.28.11. (*meso*/*cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(2,2-diphenylethyl)piperazine (24). Compound **24** was obtained according to method B by use of **8-b**/*cis* and **17a**. Yield 68%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.92–1.97 (m, 2H, –C*H*$_2$–), 2.40–2.49 (m, 10H, –N–C*H*$_2$–), 2.97 (d, 2H, –N–C*H*$_2$–CH–), 4.04 (t, 2H, –O–C*H*$_2$–), 4.19 (t, 1H, –C*H*–Ph$_2$), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.90–7.65 (m, 20H, –Ar*H*); Anal. $C_{50}H_{52}N_2O_{11}$ (salt) requires C, 70.08; H, 6.12; N, 3.27. Found: C, 70.15; H, 6.11; N, 3.30; MS (ES+) *m*/*z* 625.8 (M+H).

4.2.28.12. (*meso*/*cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(3,3-diphenylpropyl)piperazine (25). Compound **25** was obtained according to method B by use of **8-b**/*cis* and **17b**. Yield 62%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.94–1.97 (m, 2H, –O–CH$_2$–C*H*$_2$–), 2.22–2.26 (m, 2H, –N–CH$_2$–C*H*$_2$–), 2.34–2.52 (m, 12H, –N–C*H*$_2$–), 3.96 (t, 1H, –C*H*–Ph$_2$), 4.05 (t, 2H, –O–C*H*$_2$–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.96–7.66 (m, 20H, –Ar*H*); Anal. $C_{51}H_{54}N_2O_{11}$ (salt) requires C, 70.33; H, 6.25; N, 3.22. Found: C, 70.36; H, 6.19; N, 3.24; MS (ES+) *m*/*z* 639.8 (M+H).

4.2.28.13. (*meso*/*cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(4,4-diphenylbutyl)piperazine (26). Compound **26** was obtained according to method B by use of **8-b**/*cis* and **17c**. Yield 69%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.45–1.48 (m, 2H, –C*H*$_2$–CH$_2$–CH–), 1.94–2.07 (m, 4H, –O–CH$_2$–C*H*$_2$–, –C*H*$_2$–CH–), 2.33–2.53 (m, 12H, –N–C*H*$_2$–), 3.88 (t, 1H, –C*H*–Ph$_2$), 4.05 (t, 2H, –O–C*H*$_2$–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.97–7.66 (m, 20H, –Ar*H*); Anal. $C_{52}H_{56}N_2O_{11}$ (salt) requires C, 70.57; H, 6.38; N, 3.17. Found: C, 70.63; H, 6.36; N, 3.23; MS (ES+) *m*/*z* 653.9 (M+H).

4.2.28.14. (*meso*/*trans*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(5,5-diphenylpentyl)piperazine (27/*trans*). Compound **27**/*trans* was obtained according to method B by use of **8-b**/*trans* and **17d**. Yield 63%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.31 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–CH–), 1.52–1.56 (m, 2H, –C*H*$_2$–CH$_2$–CH$_2$–CH–), 1.95–2.07 (m, 4H, –O–CH$_2$–C*H*$_2$–, –C*H*$_2$–CH–), 2.28–2.53 (m, 12H, –N–C*H*$_2$–), 3.87 (t, 1H, –C*H*–Ph$_2$), 4.02 (t, 2H, –O–C*H*$_2$–), 5.39 (s, 2H, –O–C*H*Ph–C*H*PhO–), 6.75 (s, 1H, –C*H*OO–), 6.92–7.52 (m, 20H, –Ar*H*); Anal. $C_{53}H_{58}N_2O_{11}$ (salt) requires C, 70.81; H, 6.50; N, 3.12. Found: C, 70.76; H, 6.53; N, 3.14; MS (ES+) *m*/*z* 667.9 (M+H).

4.2.28.15. (*meso*/*cis*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(5,5-diphenylpentyl)piperazine (27/*cis*). Compound **27**/*cis* was obtained according to method B by use of **8-b**/*cis* and **17d**. Yield 65%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.30 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–CH–), 1.53–1.56 (m, 2H, –C*H*$_2$–CH$_2$–CH$_2$–CH–), 1.97–2.07 (m, 4H, –O–CH$_2$–C*H*$_2$–, –C*H*$_2$–CH–), 2.29–2.57 (m, 12H, –N–C*H*$_2$–), 3.87 (t, 1H, –C*H*–Ph$_2$), 4.05 (t, 2H, –O–C*H*$_2$–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.97–7.66 (m, 20H, –Ar*H*); Anal. $C_{53}H_{58}N_2O_{11}$ (salt) requires C, 70.81; H, 6.50; N, 3.12. Found: C, 70.89; H, 6.56; N, 3.20; MS (ES+) *m*/*z* 667.9 (M+H).

4.2.28.16. (4*R*,5*R*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(5,5-diphenylpentyl)piperazine (27/*RR*). Compound **27**/*RR* was obtained according to method B by use of **8-b**/*RR* and **17d**. Yield 63%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.30 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–CH–), 1.53–1.58 (m, 2H, –C*H*$_2$–CH$_2$–CH$_2$–CH–), 1.95–2.07 (m, 4H, –O–CH$_2$–C*H*$_2$–, –C*H*$_2$–CH–), 2.29–2.54 (m, 12H, –N–C*H*$_2$–), 3.87 (t, 1H, –C*H*–Ph$_2$), 4.03 (t, 2H, –O–C*H*$_2$–), 4.91–4.95 (m, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.34 (s, 1H, –C*H*OO–), 6.93–7.57 (m, 20H, –Ar*H*); Anal. $C_{53}H_{58}N_2O_{11}$ (salt) requires C, 70.81; H, 6.50; N, 3.12. Found: C, 70.83; H, 6.52; N, 3.08; MS (ES+) *m*/*z* 667.9 (M+H).

4.2.28.17. (4*S*,5*S*)-1-{3-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]propyl}-4-(5,5-diphenylpentyl)piperazine (27/*SS*). Compound **27**/*SS* was obtained according to method B by use of **8-b**/*SS* and **17d**. Yield 62%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.23–1.29 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–CH–), 1.52–1.57 (m, 2H, –C*H*$_2$–CH$_2$–CH$_2$–CH–), 1.93–2.07 (m, 4H, –O–CH$_2$–C*H*$_2$–, –C*H*$_2$–CH–), 2.26–2.53 (m, 12H, –N–C*H*$_2$–), 3.87 (t, 1H, –C*H*–Ph$_2$), 4.03 (t, 2H, –O–C*H*$_2$–), 4.91–4.95 (m, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.34 (s, 1H, –C*H*OO–), 6.93–7.57 (m, 20H, –Ar*H*); Anal. $C_{53}H_{58}N_2O_{11}$ (salt) requires C, 70.81; H, 6.50; N, 3.12. Found: C, 70.75; H, 6.46; N, 3.20; MS (ES+) *m*/*z* 667.9 (M+H).

4.2.28.18. (*meso*/*cis*)-1-{3-[4-(4,5-Bis[2-chlorophenyl]-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazine (28). Compound **28** was obtained according to method A by use of **8-d**/*cis* and *N*-methylpiperazine. Yield 82%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.93–2.00 (m, 2H, –C*H*$_2$–), 2.28 (s, 3H, –N–C*H*$_3$), 2.50–2.54 (m, 10H, –C*H*$_2$–), 4.03 (t, 2H, –O–C*H*$_2$–), 6.02 (s, 2H, –O–

C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.92–7.69 (m, 14H, –Ar*H*); Anal. $C_{37}H_{40}Cl_2N_2O_{11}$ (salt) requires C, 58.50; H, 5.31; Cl, 9.33; N, 3.69. Found: C, 58.41; H, 5.25; Cl, 9.28; N, 3.76; MS (ES+) *m*/*z* 528.5 (M+H).

4.2.28.19. (*meso*/*cis*)-1-{3-[4-(4,5-Bis[4-fluorophenyl]-1,4-dioxolan-2-yl)phenoxy]propyl}-4-methylpiperazine (29). Compound **29** was obtained according to method A by use of **8-e**/*cis* and *N*-methylpiperazine. Yield 89%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.96–1.99 (m, 2H, –CH_2–), 2.29 (s, 3H, –N–CH_3), 2.50–2.55 (m, 10H, –CH_2–), 4.04 (t, 2H, –O–CH_2–), 4.81–4.86 (m, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.32 (s, 1H, –C*H*OO–), 6.91–7.54 (m, 14H, –Ar*H*); Anal. $C_{37}H_{40}F_2N_2O_{11}$ (salt) requires C, 61.15; H, 5.55; F, 5.23; N, 3.85. Found: C, 60.97; H, 5.54; F, 5.38; N, 3.79; MS (ES+) *m*/*z* 495.6 (M+H).

4.2.28.20. (*meso*/*cis*)-1-{2-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]ethyl}-4- methylpiperazine (30). Compound **30** was obtained according to method A by use of **8-a**/*cis* and *N*-methylpiperazine. Yield 85%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 2.29 (s, 3H, –N–CH_3), 2.48 (s, 4H, –N–CH_2–), 2.63 (s, 4H, –N–CH_2–), 2.84 (t, 2H, –N–CH_2–), 4.16 (t, 2H, –O–CH_2–), 5.49 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.92–7.67 (m, 10H, –Ar*H*); Anal. $C_{36}H_{40}N_2O_{11}$ (salt) requires C, 63.90; H, 5.96; N, 4.14. Found: C, 63.82; H, 6.01; N, 4.08; MS (ES+) *m*/*z* 445.6 (M+H).

4.2.28.21. (*meso*/*cis*)-1-{2-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]ethyl}-4-(5,5-diphenylpentyl)piperazine (31). Compound **31** was obtained according to method B by use of **8-a**/*cis* and **17d**. Yield 60%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.30 (m, 2H, –CH_2–CH_2–CH_2–CH–), 1.53–1.58 (m, 2H, –CH_2–CH_2–CH_2–CH–), 2.01–2.07 (m, 2H, –CH_2–CH–), 2.29–2.61 (m, 12H, –N–CH_2–), 3.87 (t, 1H, –C*H*–Ph_2), 4.16 (t, 2H, –O–CH_2–), 5.39 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.74 (s, 1H, –C*H*OO–), 6.89–7.52 (m, 20H, –Ar*H*); Anal. $C_{52}H_{56}N_2O_{11}$ (salt) requires C, 70.57; H, 6.38; N, 3.17. Found: C, 70.61; H, 6.43; N, 3.11; MS (ES+) *m*/*z* 653.9 (M+H).

4.2.28.22. (*meso*/*cis*)-1-{4-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]butyl}-4-methylpiperazine (32). Compound **32** was obtained according to method A by use of **8-c**/*cis* and *N*-methylpiperazine. Yield 87%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.65–1.72 (m, 2H, –O–CH_2–CH_2–CH_2–), 1.77–1.86 (m, 2H, –O–CH_2–CH_2–CH_2–), 2.28 (s, 3H, –N–CH_3), 2.29–2.46 (m, 10H, –N–CH_2–), 4.03 (t, 2H, –O–CH_2–), 5.48 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.13 (s, 1H, –C*H*OO–), 6.91–7.68 (m, 10H, –Ar*H*); Anal. $C_{38}H_{44}N_2O_{11}$ (salt) requires C, 64.76; H, 6.29; N, 3.97. Found: C, 64.80; H, 6.32; N, 3.99; MS (ES+) *m*/*z* 473.6 (M+H).

4.2.28.23. (*meso*/*cis*)-1-{4-[4-(4,5-Diphenyl-1,4-dioxolan-2-yl)phenoxy]butyl}-4-(5,5-diphenylpentyl)piperazine (33). Compound **33** was obtained according to method B by use of **8-c**/*cis* and **17d**. Yield 62%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.30 (m, 2H, –CH_2–CH_2–CH_2–CH–), 1.53–1.58 (m, 2H, –CH_2–CH_2–CH_2–CH–), 1.64–1.72 (m, 2H, –O–CH_2–CH_2–CH_2–), 1.78–1.82 (m, 2H, –O–CH_2–CH_2–CH_2–), 2.01–2.07 (m, 2H, –CH_2–CH–), 2.29–2.61 (m, 12H, –N–CH_2–), 3.87 (t, 1H, –C*H*–Ph_2), 3.99 (t, 2H, –O–CH_2–), 5.39 (s, 2H, –O–C*H*Ph–C*H*Ph–O–), 6.74 (s, 1H, –C*H*OO–), 6.89–7.52 (m, 20H, –Ar*H*); Anal. $C_{54}H_{60}N_2O_{11}$ (salt) requires C, 71.03; H, 6.62; N, 3.07. Found: C, 71.09; H, 6.69; N, 3.01; MS (ES+) *m*/*z* 681.9 (M+H).

4.2.28.24. *N*-[4-(2,2-Diphenyl-1,3-dioxolan-4-yl)butyl]piperidine (34). Compound **34** was obtained according to method A by use of **3-T** and piperidine. Yield 78%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.78 (m, 12H, –CH_2–CH_2–CH_2–, –CH_2–CH_2–CH_{2pip}–), 2.27–2.41 (m, 6H, –N–CH_2–), 3.64 (t, 1H, –C*HO*–), 4.06–4.16 (m, 2H, –O–CH_2–), 7.12–7.51 (m, 10H, –Ar*H*); Anal. $C_{28}H_{35}NO_6$ (salt) requires C; 69.83; H, 7.33; N, 2.91. Found: C, 69.87; H, 7.45; N, 2.86; MS (ES+) *m*/*z* 366.5 (M+H).

4.2.28.25. 1-[4-(2,2-Diphenyl-1,3-dioxolan-4-yl)butyl]-4-(2-hydroxyethyl)piperazine (35). Compound **35** was obtained according to method A by use of **3-T** and *N*-(2-hydroxyethyl)piperazine. Yield 75%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.18–1.78 (m, 6H, –CH_2–CH_2–CH_2–), 2.29–2.53 (m, 12H, –N–CH_2–), 3.57–3.66 (m, 3H, –C*H*O–, –CH_2–OH), 4.06–4.16 (m, 2H, –O–CH_2–), 7.21–7.50 (m, 10H, –Ar*H*); Anal. $C_{33}H_{42}N_2O_{11}$ (salt) requires C, 61.67; H, 6.59; N, 4.36. Found: C, 61.58; H, 6.57; N, 4.25; MS (ES+) *m*/*z* 411.5 (M+H).

4.2.28.26. 1-[4-(2,2-Diphenyl-1,3-dioxolan-4-yl)butyl]-4-methylpiperazine (36). Compound **36** was obtained according to method A by use of **3-T** and *N*-methylpiperazine. Yield 79%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.23–1.75 (m, 6H, –CH_2–CH_2–CH_2–), 2.26 (s, 3H, N–CH_3), 2.29–2.43 (m, 10H, N–CH_2–), 3.64 (t, 1H, -C*H*O-), 4.06–4.16 (m, 2H, –O–CH_2–), 7.21–7.50 (m, 10H, –Ar*H*); Anal. $C_{32}H_{40}N_2O_{10}$ (salt) requires: C, 62.73; H, 6.58; N, 4.57. Found: C, 62.62; H, 6.32; N, 4.69; MS (ES+) *m*/*z* 381.5 (M+H).

4.2.28.27. 1-[4(2,2-Diphenyl-1,3-dioxolan-4-yl)butyl]-4-(5,5-diphenylpentyl)piperazine (37). Compound **37** was obtained according to method B by use of **3-T** and **17d**. Yield 43%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 1.24–1.58 (m, 10H, –CHO–CH_2–CH_2–CH_2–, –CH_2–CH_2–CH_2–CH–Ph_2), 2.01–2.05 (m, 2H, –CH_2–CH–Ph_2), 2.28–2.58 (m, 12H, –N–CH_2–), 3.64 (t, 1H, –C*H*O–), 3.86 (t, 1H, –C*H*–Ph_2), 4.06–4.14 (m, 2H, –O–CH_2–), 6.98–7.50 (m, 20H, –Ar*H*); Anal. $C_{48}H_{56}N_2O_{10}$ (salt) requires C, 70.22; H, 6.88; N, 3.41. Found: C, 70.25; H, 6.73; N, 3.36; MS (ES+) *m*/*z* 589.8 (M+H).

4.2.28.28. 1-[(2,2-Diphenyl-4-methyl-1,3-dioxan-5-yl)methyl]-4-methylpiperazine (38). Compound **38** was obtained according to method A by use of **5-T** and *N*-methylpiperazine. Yield 65%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 0.74 (s, 3H, –C–CH_3–), 2.25 (s, 3H, –N–CH_3), 2.39–2.62 (m, 10H, –N–CH_2–), 3.56–3.77 (m, 4H, –O–CH_2–C–, –O–CH_2–C–), 7.19–7.51 (m, 10H, –Ar*H*); Anal. $C_{31}H_{38}N_2O_{10}$ (salt) requires C,

62.20; H, 6.40; N, 4.68. Found: C, 62.25; H, 6.36; N, 4.61; MS (ES+) *m/z* 367.5 (M+H).

4.2.28.29. 1-[(2,2-Diphenyl-4-methyl-1,3-dioxan-5-yl)-methyl]-4-(5,5-diphenylpentyl)piperazine (39). Compound **39** was obtained according to method B by use of **5-T** and **17d**. Yield 51%; ^{1}H NMR (base in $CDCl_3$): δ [ppm] = 0.74 (s, 3H, –C–C*H*$_3$–), 1.24–1.30 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–CH–), 1.53–1.56 (m, 2H, –C*H*$_2$–CH$_2$–CH$_2$–CH–), 2.01–2.05 (m, 2H, –C*H*$_2$–CH–Ph$_2$), 2.38–2.65 (m, 12H, –N–C*H*$_2$–), 3.56–3.77 (m, 4H, –O–C*H*$_2$–C–, –O–C*H*$_2$–C–), 3.86 (t, 1H, –C*H*–Ph$_2$), 7.01–7.58 (m, 10H, –Ar*H*); Anal. $C_{47}H_{54}N_2O_{10}$ (salt) requires C, 69.96; H, 6.74; N, 3.47. Found: C, 69.92; H, 6.69; N, 3.46; MS (ES+) *m/z* 575.8 (M+H).

4.3. Biological evaluation

4.3.1. Cell culture and drugs. Caco-2 cell line which was obtained from American Type Culture Collection (ATCC), Rockville, USA (passage 36), was kept under standard culture conditions (Dulbecco's modified Eagle's medium, 10% fetal calf serum, 1.78 mmol/L L-glutamine and 44.56 mg/L gentamicin). at 37 °C in the presence of 5% CO_2. Caco cells were subcultured by trypsinization every week and the medium was replaced twice a week. The resistant lines were obtained by stepwise selection in 10 nM vinblastine containing medium. Cell culture reagents were obtained from *Gibco–BRL*. Vinblastine was obtained from *Universitätsapotheke Klinikum Kröllwitz (Halle)*. Trifluoperazine was obtained from *Sigma–Aldrich Chemie GmbH (Germany)*.

4.3.2. MTT assay.[41] Caco cells were seeded in 96-well plates (*Millipore, Eschborn, Germany)* at a density of 5×10^3 cells per well. After incubation at 37 °C and 5% CO_2 for 90 min, cells were left unloaded (control, 0.1% DMSO) or treated with vinblastine (1 μM); vinblastine (1 μM) + trifluoperazine (0.1–400 μM) and vinblastine + test substance (0.1–400 μM) for 48 h at 37 °C. After the completion of drug exposure, 100 μg MTT in 20 μL of aqueous solution was added into each well for an additional 4 h. The absorbance of formazan at λ = 570 nm was measured on a *Polarstar Galaxy plate reader (BMG LabTechnologies GmbH)*. The percentage of viable cells was calculated to get IC_{50}-values.

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