POTENT AND SELECTIVE ABCG2 INHIBITORS DERIVED FROM TARIQUIDAR

Dissertation

Zur Erlangung des Doktorgrades der Naturwissenschaften

(Dr. rer. Nat.)

an der naturwissenschaftlichen Fakultät IV

- Chemie und Pharmazie -

der Universität Regensburg

Vorgelegt von

Cristian Ochoa Puentes

Aus Bucaramanga (Kolumbien)

2012

The experimental part of this work was carried out between October 2008 and November 2011 under the supervision of Prof. Dr. Burkhard König at the institute of Organic Chemistry, University of Regensburg.

The PhD Thesis was submitted on:	23.02.2012
The colloquium took place on:	30.03.2012

Board of Examiners:	Prof. Dr. Henri Brunner	(Chairman)
	Prof. Dr. Burkhard König	(1 st Referee)
	Prof. Dr. Armin Buschauer	(2 nd Referee)
	Prof. Dr. Oliver Reiser	(Examiner)

Acknowledgements

I would like to express my sincere thanks to my supervisor Prof. Dr. Burkhard König for the opportunity to work in his very motivated and dinamic group and for his useful synthetic hints to overcome some difficulties during my Ph.D. I am so glad that he gave me the possibility to work on an exciting and challenging project which I enjoied a lot.

I would also like to thank Prof. Dr. Armin Buschauer and Prof. Dr. Günther Bernhardt for the excellent cooperation and valuable ideas in the ABCG2 transporters project.

I am greatful to all the persons from the pharmacy department which were involved in the pharmacological part of this work, Dr. Peter Höcherl, Dr. Matthias Kühnle, Kira Bürger and specially Stefanie Bauer for the contributions, explanations and ideas that were very important to have good results during this project. Steffi thanks for proofreading my thesis.

I thank all coworkers of the central analytical department, especially Annette Schramm, Georgine Stühler, Fritz Kastner and Dr. Thomas Burgemeister for recording 2D NMR spectra, and both Wolfgang Söllner and Joseph Kiermaier for recording mass spectra.

Financial support from the Deutscher Akademischer Austauschdiens, COLCIENCIAS, ICETEX and the Universidad Nacional de Colombia are gratefully appreciated.

I would like to thank Dr. Rudi Vasold for all his valuable help with GC and HPLC problems, Simone Strauß for assisting me in preparative HPLC, Ernst Lautenschlager for his help in all technical questions and Susanne Schulze for providing me chemicals and laboratory facilities.

I also thank Carolin Falenczyk, Laura Waltl and Manuel Bause for their motivated work during their internships.

I extend my sincere thanks to all the former and actuall collegues, especially

Dr. Andreas Späth, Durga Prasada and Dr. Supratim Banerjee for the nice discussions about chemistry and life.

Dr. Michael Egger and Dr. Carolin Fisher for introducing me into the ABC transporters project, for been always helpful and for the synthetic work we made together.

The “evening club” Dr. Stefan Stadlbauer, Dr. Daniel Vomasta, Dr.Robert Lechner, Dr. Florian Schmidt, Tobi Trottmann, Benjamin Gruber, Natascha Kuzmanovic, Stefan Balk, Susanne Kümmel, Susanna Schmidbauer, Andreas Hohenleutner and Josef Herrmann, for make much more easier my integration into the German, or better the Bavarian culture. I really enjoied very much “the Friday lunch” and all the evening activities we had.

Michael Dobmeier, also an “evening club member”, for the nice discussions, especially after working time and for all the help regarding academic and non-academic issues during my stay in Regensburg.

I have also to thank my former flatmates Thomas, Johanes, Martin, Matthias and Daniel for the nice welcome and atmosphere during my first two years in Regensburg. You my friends know how to make a good party.

I owe many thanks to my parents Cristian and Maria Emma, and my brothers William and Oscar.

Finally, my deep and sincere thanks go to my little family. To my wife Liliana for her love, patience, support and encouragement during all this time in Germany, you also made my “job” easier. To our beloved and beatiful daughter Hannah, thank you my little for taking me away all the stress and for bring me an infinite happiness every single day during the last months.

To Lili and Hannah

Table of Contents

1.	**Solid Phase Synthesis of Tariquidar-Related Modulators of ABC Transporters Preferring Breast Cancer Resistance Protein (ABCG2)**	**1**
1.1	Introduction	2
1.2	Results and Discussion	3
1.3	Conclusion	7
1.4	Experimental section	7
1.5	References	19
2.	**Biaryl Tariquidar-Related Derivatives as Potent and Selective Breast Cancer Resistance Protein Modulators**	**21**
2.1	Introduction	22
2.2	Results and Discussion	23
2.3	Conclusion	28
2.4	Experimental section	28
2.5	References	38
3.	**Synthesis and Breast Cancer Resistance Protein (BCRP) Inhibitory Activity of New Multidrug Resistance Modulators Based on Tariquidar**	**40**
3.1	Introduction	41
3.2	Results and Discussion	44
	Synthesis	44
	Inhibition of ABCB1 and ABCG2 transporters	46
3.3	Conclusion	49
3.4	Experimental section	49
3.5	References	65
4.	**Summary**	**68**
5.	**Zusammenfassung**	**70**
6.	**Abbreviations**	**72**
7.	**Appendix**	**74**

1. Solid Phase Synthesis of Tariquidar-Related Modulators of ABC Transporters Preferring Breast Cancer Resistance Protein (ABCG2)[i]

Aiming at structural optimization of potent and selective ABCG2 inhibitors, such as UR-ME22-1, from our laboratory, an efficient solid phase synthesis was developed to get convenient access to this class of compounds. 7-Carboxyisatoic anhydride was attached to Wang resin to give resin bound 2-aminoterephthalic acid. Acylation with quinoline-2- or -6-carbonyl chlorides, coupling with tetrahydroisoquinolinylethylphenylamine derivatives, cleavage of the carboxylic acids from solid support and treatment with trimethylsilydiazomethane gave the corresponding methyl esters. Among these esters highly potent and selective ABCG2 modulators were identified (inhibition of ABCB1 and ABCG2 determined in the calcein-AM and the Hoechst 33342 microplate assay, respectively)[ii]. Interestingly, compounds bearing triethyleneglycol ether groups at the tetrahydroisoquinoline moiety (UR-COP77, UR-COP78) were comparable to UR-ME22-1 in potency but considerably more efficient (max inhibition 83% and 88% vs 60%, rel. to fumitremorgin C, 100%) These results support the hypothesis that solubility of the new ABCG2 modulators and of the reference compounds tariquidar and elacridar in aqueous media is the efficacy limiting factor.

---

i Puentes C. O., Höcherl, P., Kühnle M., Bauer S. Bürger K., Bernhardt G., Buschauer A., König B. *Bioorg. Med. Chem. Lett.* **2011**, 21, 3654-3657.

ii The flow cytometric calcein-AM efflux assay and the Hoechst 33342 microplate assay were carried out by Peter Höcherl, Stefanie Bauer and Kira Bürger at the Institute of Pharmacy, University of Regensburg.

1.1 Introduction

Whereas numerous inhibitors of p-glycoprotein (ABCB1) are reported in the literature,[1–9] the number of available modulators of the breast cancer resistance protein (ABCG2) is very limited.[10–15] The multidrug resistance (MDR) modulators tariquidar[16] and elacridar[17] (Figure 1) are among the most potent inhibitors of ABC transporters. They are known to inhibit both p-glycoprotein (ABCB1) and the breast cancer resistance protein (ABCG2) with a preference for ABCB1 in case of tariquidar. Recently, we synthesized a series of tariquidar analogues in which, at the benzamide core, the hetarylcarboxamido residue was shifted to the meta-position and the two methoxy groups were replaced with a carboxylic acid methyl ester. Surprisingly, compounds such as UR-ME22-1 (Figure 1) turned out to be potent and highly selective modulators of ABCG2.[18] It is noteworthy that compared to the considerably less potent but more efficient reference compound fumitremorgin C the maximum inhibitory effect was by 40–60% lower[18] (cf. concentration response curve of UR-ME22-1 in Figure 2), presumably due to limited water solubility. Regardless of the lack of drug-like properties, UR-ME22-1 and analogues are considered of potential value as PET-ligands[19] and as pharmacological tools in proof-of-concept studies, for example, to overcome the blood-brain barrier by analogy with the modulation of ABCB1.[20] Although the synthesis of the new ABCG2 inhibitors reported before[18] is relatively simple, only moderate to low yields were obtained due to solubility and purification problems.

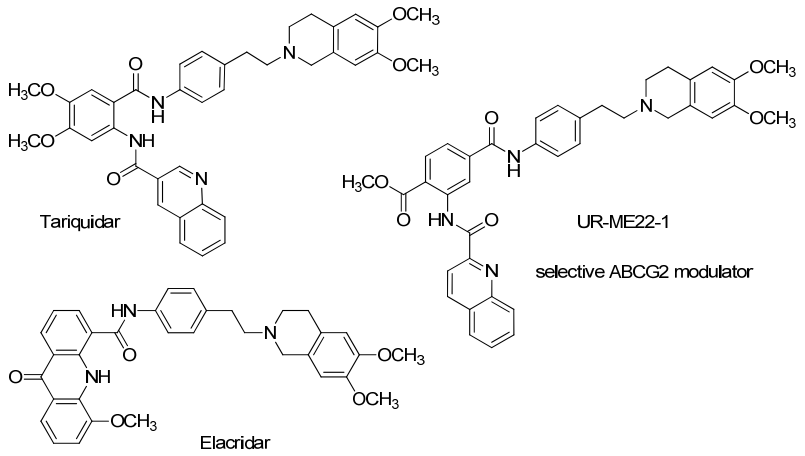
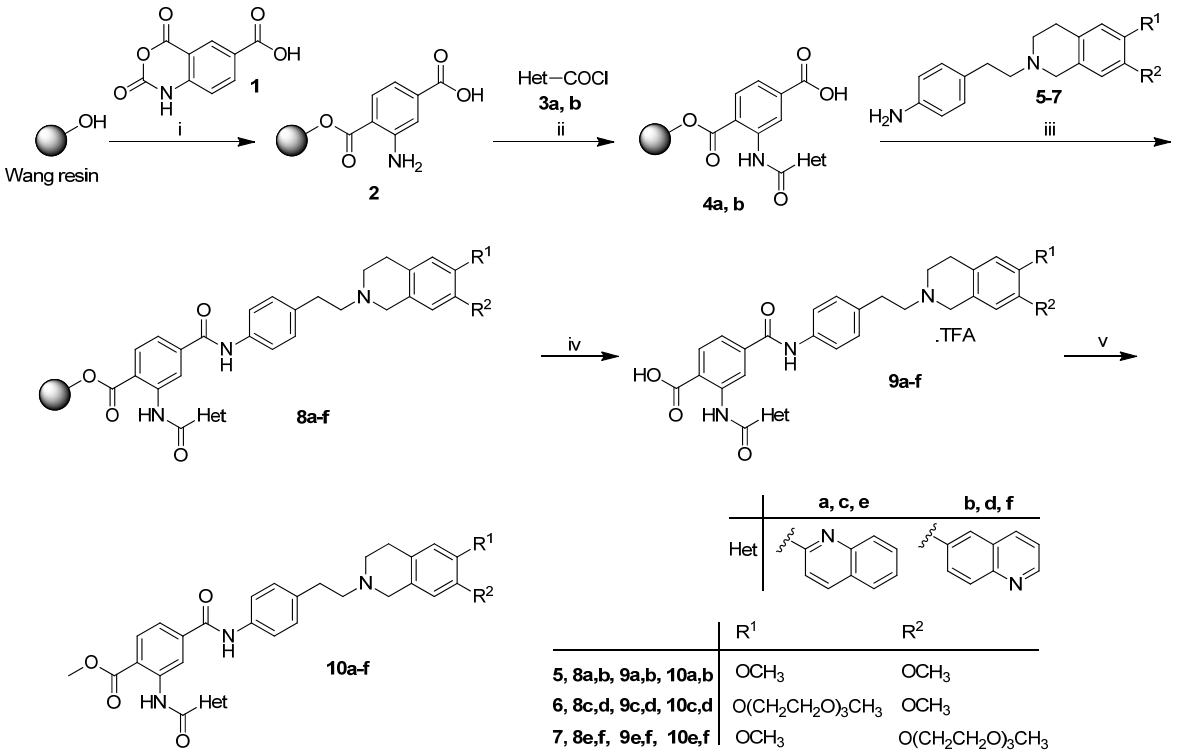


Figure 1. Structures of tariquidar (ABCB1 preferring), elacridar (combined ABCB1 and ABCG2 modulator) and the selective ABCG2 modulator UR-ME22-1.

With respect to structural optimization of the lead compound UR-ME22-1 and solving the aforementioned problems, we developed a solid phase synthesis (SPS) (Scheme 1) to get more convenient chemical access to a broader variety of analogues including more soluble ABCG2 modulators.

1.2 Results and Discussion

Wang resin was selected as polymer support, and 7-carboxyisatoic anhydride[21] as a ‘‘key’’ building block, because it can be easily linked to the resin giving a solid phase bound aminoterephthalic derivative, which is the central core structure of the target compounds. The best conditions to attach 7-carboxyisatoic anhydride **1** to the solid support were found when the resin, previously swollen in DMF, was heated overnight at 98 °C with 5 equiv of 7-carboxyisatoic anhydride and 3 equiv of DMAP.



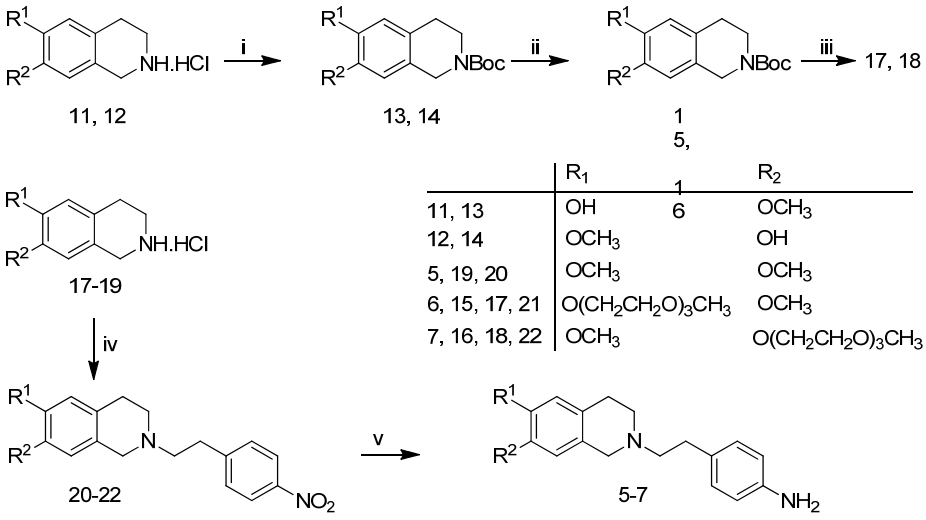
Scheme 1. SPS of tariquidar analogues **9a–f** and **10a–f**. Reagents and conditions: (i) 7-carboxyisatoic anhydride **1**, DMAP, DMF, 98 °C, overnight; (ii) quinolinecarbonyl chlorides **3a,b**, DIPEA, DCM, rt, 12 h (twice); (iii) tetrahydroisoquinolinylethylphenylamines **5–7**, HBTU, DIPEA, DMF, rt, 24 h; (iv) TFA/DCM/TES (1:1:0.05), rt, 30 min (twice); (v) $TMSCHN_2$, PhH/MeOH (1:1), rt, 1 h.

The second combinatorial step involved acylation of the resin bound aminoterephthalic derivative **2** with quinoline-2- or quinoline-6-carboxylic acids. Although different peptide coupling conditions were tested to link the heterocyclic carboxylic acids (HBTU, DIPEA; HOBt, EDC, DMAP; HOAt, DCC), only a mixture of 40% the desired amide and 60% of 2-aminoterephthalic acid was obtained as detected by ^{1}H NMR spectra of products released for analysis from solid support. However, acylation was successfully achieved, when a mixture of

the resin, freshly prepared acid chloride (**3a,b**) and DIPEA was shaken in DCM during 12 h at room temperature (this procedure was repeated once).

In the next synthetic step the tetrahydroisoquinolinylethylphenylamine derivatives **5–7** were linked to the carboxylic acids **4a,b**. Aiming at more hydrophilic analogues of UR-ME22-1, we attached a triethyleneglycol chain to the tetrahydroisoquinoline motif (building blocks **6** and **7** cf. Scheme 2). The synthesis of the resin bound tariquidar analogues **8a–f** was accomplished when **4a,b** were reacted with **5–7**, HBTU, and DIPEA in DMF for 24 h (Scheme 1). Cleavage of the resin with a ‘‘cocktail’’ of TFA/DCM/TES (1:1:0.05) gave the carboxylic acids **9a–f**, which were transformed into the methyl esters **10a–f** using trimethylsilyldiazomethane ($TMSCHN_2$).

For the synthesis of the building blocks **5–7**, the required tetrahydroisoquinolines **17** and **18** (Scheme 2) were prepared from methoxytetrahydroisoquinolinols **11** and **12** according to the procedure described by Bobbitt et al.[22] and were N-protected using di-tert-butyl dicarbonate ($(BOC)_2O$). The N-Boc protected tetrahydroisoquinolines **13** and **14** were allowed to react with 2-[2-(2-methoxyethoxy)ethoxy]ethyl 4-methylbenzenesulfonate[23] to give **15** and **16** which were deprotected with HCl in anhydrous ether yielding **17** and **18**. Finally, compounds **6** and **7** as well as the dimethoxy-substituted analogue **5**[24] were obtained by refluxing **17–19** with 4-nitrophenethyl bromide and reduction of the nitro group by catalytic hydrogenation.



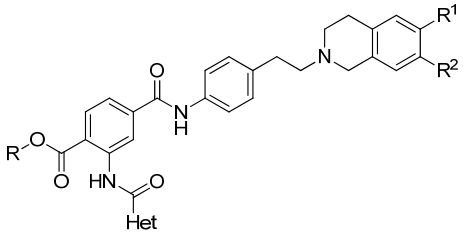
	R_1	R_2
11, 13	OH	OCH_3
12, 14	OCH_3	OH
5, 19, 20	OCH_3	OCH_3
6, 15, 17, 21	$O(CH_2CH_2O)_3CH_3$	OCH_3
7, 16, 18, 22	OCH_3	$O(CH_2CH_2O)_3CH_3$

Scheme 2. Synthesis of tetrahydroisoquinolinylethylphenylamine derivatives **5–7**. Reagents and conditions: (i) $(BOC)_2O$, TEA, DCM, rt, overnight; (ii) 2-[2-(2-methoxyethoxy)ethoxy]ethyl 4-methylbenzenesulfonate, KOH, THF, reflux, 6 h; (iii) HCl/Et_2O, DCM, overnight; (iv) 4-nitrophenethyl bromide, K_2CO_3, CH_3CN, reflux, 18 h; (v) EtOH, Pd/C, H_2, 5 bar, rt, 24 h.

As shown in Table 1, a set of 12 tariquidar analogues was obtained in moderate to high yields. Compounds **10a** and **10b** were obtained in significantly better yields compared to the previously

described route,[18,19] illustrating that the SPS methodology is superior to the synthesis in solution.

Table 1. Tariquidar analogues synthesized on solid phase Wang resin



Compound	R	R^1	R^2	Het.	Yield (%)
9a	H	OCH_3	OCH_3	2-Quinol.	81[a]
9b	H	OCH_3	OCH_3	6-Quinol.	97[a]
9c	H	$O(CH_2CH_2O)_3CH_3$	OCH_3	2-Quinol.	73[a]
9d	H	$O(CH_2CH_2O)_3CH_3$	OCH_3	6-Quinol.	87[a]
9e	H	OCH_3	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	65[a]
9f	H	OCH_3	$O(CH_2CH_2O)_3CH_3$	6-Quinol.	95[a]
10a (UR-ME22-1)	CH_3	OCH_3	OCH_3	2-Quinol.	75 (10)[b] (53)[c]
10b (UR-ME19-2)	CH_3	OCH_3	OCH_3	6-Quinol.	95 (14)[b] (86)[c]
10c (UR-COP77)	CH_3	$O(CH_2CH_2O)_3CH_3$	OCH_3	2-Quinol.	90
10d	CH_3	$O(CH_2CH_2O)_3CH_3$	OCH_3	6-Quinol.	53
10e (UR-COP78)	CH_3	OCH_3	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	95
10f (UR-COP134)	CH_3	OCH_3	$O(CH_2CH_2O)_3CH_3$	6-Quinol.	50

[a] Overall yield based on the loading of the resin. [b] Kühnle et al.[18] [c] Wang et al.[19]

The synthesized modulators and the reference compounds tariquidar and elacridar were investigated for inhibition of ABCB1 and ABCG2 in a calcein-AM (ABCB1)[25] and a Hoechst 33342 (ABCG2) microplate assay[26] using ABCB1-overexpressing Kb-V1 and ABCG2-overexpressing MCF-7/Topo cells. The data are summarized in Table 2.

Tariquidar and elacridar show IC_{50} values in the high nanomolar range and are almost equipotent at ABCB1, whereas elacridar is approximately four times more potent as an ABCG2 inhibitor. The carboxylic acids **9a–f** are inactive at both transporters, confirming preliminary results on such compounds as potential cleavage products of modulators such as **10a**.[18] By contrast, the methyl esters **10b**[18] and **10c,e** selectively modulate ABCG2 with IC_{50} values comparable to that of elacridar, being two to three fold less potent than the reference compound, UR-ME22-1 (**10a**). Interestingly, the regioisomeric triethylene glycol ethers **10c** and **10e**, bearing a quinoline-2-carboxamido substituent at the benzamide core, are superior to **10a** with respect to the maximal inhibitory effect: 83% and 88% versus 61% (Figure 2). This strongly

supports the hypothesis that limited water solubility is the major reason for submaximal efficacy of UR-ME22-1 (**10a**) and related potent ABCG2 modulators.

Table 2. Inhibition of ABC transporters by reference compounds and the tariquidar analogues **9a-f**, **10a-f** determined in the calcein-AM (ABCB1) and Hoechst 33342 (ABCG2) microplate assay unless otherwise indicated.

Compd	ABCB1 IC_{50} [nM]	ABCG2 IC_{50} [nM]	Compd	ABCB1 IC_{50} [nM]	ABCG2 IC_{50} [nM]
Tariquidar	223±8 [a]	526±85 [b]	**9f**	>50000	>50000
Elacridar	193±18 [a]	127±41 [b]	**10a** [c]	>29000 [a]	59 ± 11 [b]
9a	>50000	>5000	**10b** [d]	>10000 [a]	172 ± 45 [b,e]
9b	>1000	>100000	**10c** [f]	>50000	183 ± 32
9c	>100000	>50000	**10d**	>100000	390 ± 57 [g]
9d	>50000	>50000	**10e** [h]	>50000	130 ± 29
9e	>100000	6200	**10f** [i]	>50000	508 ± 191 [j]

[a] ref. 18: data from flow cytometric calcein-AM assay. [b] ref. 18: data from flow cytometric mitoxantron assay (% maximal inhibitory effect, relative to fumitremorgin C): IC_{50} values (% max. effect), Tariquidar: 916 ± 197 nM (39%), Elacridar 250 ± 45 nM (46%), 10a: 60 ± 10 nM (56%); 10b: 179 ± 35 nM (25%). [c] UR-ME22-1. [d] UR-ME19-2. [e] 55% maximal inhibitory effect. [f] UR-COP77. [g] 41% maximal inhibitory effect. [h] UR-COP78. [i] UR-COP134. [gj] 61% maximal inhibitory effect.

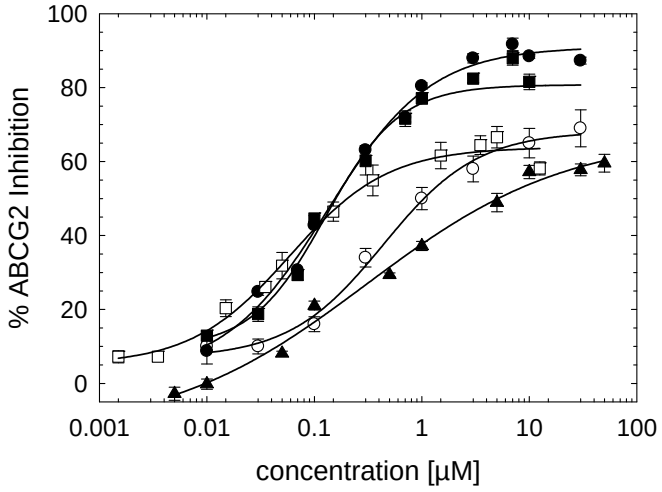


Figure 2. Concentration dependent inhibition of the ABCG2 transporter in MCF-7/Topo cells (Hoechst 33342 assay) by tariquidar (open circles) and the tariquidar analogues **10a** (UR-ME22-1; open squares), **10c** (filled squares), **10e** (UR-COP78; filled circles) and **10f** (filled triangles).

The maximal inhibition is expressed as % relative to the maximum inhibition of ABCG2 by fumitremorgin C (at a concentration of 10 μM).

1.3 Conclusion

The solid phase synthesis presented in this contribution proved to be a convenient method for the preparation of small libraries of this class of ABCG2 inhibitors due to high conversion efficiency in all reaction steps resulting in good to high yields. In particular, intrinsic difficulties in solution chemistry, due to low solubility of intermediates and target molecules, were circumvented. Compounds **10c,e** are among the most potent and selective ABCG2 modulators reported so far. The increased solubility and ABCG2 inhibitory efficacy of these compounds is very promising with respect to the development of pharmacological tools for in vivo proof-of-concept studies, provided that the drug-like properties can be further improved. Thereby, automated parallel solid phase synthesis resulting in larger substance libraries should be helpful to optimize the lead structures.

1.4 Experimental section

General. Wang resin was purchased from Fluka (100-200 mesh, 1.1 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from either Aldrich, Acros, Merck, or Fluka and used without further purification. Manual solid-phase organic syntheses were carried out at 25 °C in polypropylene syringes equipped with a porous polypropylene disk at the bottom (purchased from Roland Vetter Laborbedarf OHG). Solid phase reaction at higher temperature was carried out in an eppendorf tube with a microcentifuge tube holder. Flash column chromatograph was performed with silica gel (Merck silica gel 60M 40-63 μm); products were detected by TLC on alumina plates coated with silica gel (Merck silica gel 60 F254, thickness 0.2 mm) and visualized by UV light (λ) 254 nm). Melting points were determined with an OptiMelt MPA100 and are uncorrected. NMR spectra were measured at 298 K on a Bruker Avance 300 or Bruker Avance 600 instruments. Chemical shifts are reported in δ (ppm) relative to external standards and coupling constants J are given in Hz. Abbreviations for the characterization of the signals: s) singlet, d) doublet, t) triplet, m) multiplet, bs) broad singlet, dd) double doublet. The relative numbers of protons is determined by integration. Mass spectra were recorded with Finnigan MAT TSQ 7000 (ESI) and Finnigan MAT 90 (HRMS), IR spectra with a Bio- Rad FT-IR-FTS 155 spectrometer.

General procedure for the preparation of 13 and 14. Compound **11** (0.5 g, 2.31 mmol) and triethylamine (0.8 mL, 5.77 mmol) were dissolved in 10 mL of dry DCM, the mixture was

cooled in an ice bath and di-tert-butyl dicarbonate (0.5 g, 2.31 mmol) was added slowly. The mixture was stirred at room temperature overnight, and then washed with water and brine, dried over magnesium sulphate, filtered and the solvent evaporated. The compound was purified by flash chromatography (ethyl acetate: petroleum ether 1:1).

tert-Butyl 6-hydroxy-7-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate 13. Yield 85%, white solid, R_f= 0.55, **mp**. 119.4-120.2 ^oC. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 6.65 (s, 1H, ArH), 6.53 (s, 1H, ArH), 4.45 (s, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 3.57 (m, 2H, NCH_2CH_2), 2.67 (m, 2H, NCH_2CH_2), 1.46 (s, 9H, $C(CH_3)_3$). **^{13}C-NMR** ($CDCl_3$, 75 MHz): δ= 154.9, 145.3, 144.1, 127.3, 125.0, 114.3, 108.5, 79.7, 56.0, 45.7, 40.7, 28.5, 28.2. **IR** (KBr) [cm-1]: ν = 3024, 2906, 1622.

tert-Butyl 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate 14. Yield 80%, white solid, R_f= 0.55, **mp.** 123.6-124.2 ^oC. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ= 6.85 (s, 1H, ArH), 6.70 (s, 1H, ArH), 4.47 (s, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 3.60-3.61 (m, 2H, NCH_2CH_2), 2.75 (t, ^{3}J=5.6, 2H, NCH_2CH_2), 1.48 (s, 9H, $C(CH_3)_3$). **^{13}C-NMR** ($CDCl_3$, 75 MHz) : δ= 154.8, 151.7, 149.5, 138.5, 133.1, 120.1, 112.5, 83.4, 56.0, 45.1, 40.4, 28.9, 28.4. **IR** (KBr) [cm-1]: ν = 3024, 2976, 1685.

General procedure for the preparation of 15 and 16. A mixture of **13** (50 mg, 0.17 mmol), 2-[2-(2-methoxyethoxy)ethoxy]ethyl 4-methylbenzenesulfonate (60 mg, 0.19 mmol) and KOH (10 mg, 0.19 mmol) was refluxed in THF under N_2 atmosphere during 6 h, the solvent was evaporated and the residue was dissolved in DCM and washed with water. The organic phase was dried over magnesium sulphate, filtered and the solvent evaporated.

tert-Butyl 7-methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate 15. Yield 70%, colorless oil. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 6.65 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.41 (s, 2H, NCH_2), 4.14 (t, ^3J=5.4 Hz, 2H, CH_2), 3.85 (t, ^3J=5.4 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.72 (m, 2H, CH_2), 3.62 (m, 6H, 3 CH_2), 3.52 (m, 2H, NCH_2CH_2), 3.36 (s, 3H, OCH_3), 2.71 (t, ^3J=5.4 Hz, 2H, NCH_2CH_2), 1.47 (s, 9H, $C(CH_3)_3$). **^{13}C-NMR** ($CDCl_3$, 75 MHz): δ= 153.8, 147.2, 145.7, 113.1, 108.6, 78.6, 70.9, 69.7, 69.6, 69.5, 68.6, 67.6, 58.0, 55.0, 27.4, 27.3. **MS** (ESI; DCM/MeOH + 10 mmol/L NH_4Ac): m/z (%)= 426.1 (100) [MH^+]. **IR** (KBr) [cm^{-1}]: ν = 2918, 2873, 1689.

tert-Butyl 6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate 16. Yield 72%, colorless oil. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 6.47 (s, 1H, ArH), 6.44 (s, 1H, ArH), 4.28 (s, 2H, CH_2), 3.93 (t, ^3J=3.9 Hz, 2H, CH_2), 3.69-3.62 (m 5H, CH_2,

OCH_3), 3.56-3.52 (m, 2H, CH_2), 3.49-3.44 (m, 6H, 3 CH_2), 3.36-3.33 (m, 2H, CH_2), 3.17 (s, 3H, OCH_3), 2.53 (t, ^3J=5.6 Hz 2H, CH_2), 1.30 (s, 9H, $C(CH_3)_3$). **^{13}C-NMR** ($CDCl_3$, 75 MHz): δ= 154.6, 148.0, 146.7, 111.9, 111.6, 79.4, 71.7, 70.5, 70.4, 70.3, 69.4, 68.5, 58.7, 55.7, 28.3, 27.7. **MS** (ESI; DCM/MeOH + 10 mmol/L NH_4Ac): m/z (%)= 426.1 (100) [MH^+]. **IR** (KBr) [cm^{-1}]: ν = 2920, 2875, 1670.

General procedure for the preparation of 17 and 18. A mixture of **15** (0.2 g, 0.47 mmol) dissolved in 10 mL of dry DCM and 0.3 mL of HCl/Et_2O were stirred at room temperature overnight. The solvent was evaporated and the product was dried under vacuum.

7-Methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline hydrochloride 17. Yield 98%, sticky white solid. **^{1}H-NMR** (DMSO *d*6, 300 MHz) δ= 6.81 (s, 1H, ArH), 6.79 (s, 1H, ArH), 4.12 (s, 2H, CH_2), 4.03 (m, 2H, CH_2), 3.71 (m, 5H, CH_2, OCH_3), 3.56 (m, 2H, CH_2), 3.51 (m, 4H, 2 CH_2), 3.46 (s, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.22 (s, 3H, OCH_3). **^{13}C-NMR** (DMSO *d*6, 75 MHz): δ= 147.6, 147.1, 123.6, 120.3, 112.9, 109.6, 71.1, 69.8, 69.6, 69.4, 68.7, 67.7, 55.9, 55.4, 42.9, 40.3, 23.9. **MS** (ESI; DCM/MeOH + 10 mmol/L NH_4Ac): m/z (%)= 326 (100) [MH^+]. **IR** (KBr) [cm^{-1}]: ν = 3334, 2927, 2879, 1516.

6-Methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline hydrochloride 18. Yield 98%, sticky light yellow solid. **^{1}H-NMR** ($CDCl_3$, 300MHz): δ= 6.79 (s, 1H, ArH), 6.77 (s, 1H, ArH), 4.25 (s, 2H, CH_2), 4.09-4.08 (m, 2H, CH_2), 3.82-3.80 (m, 5H, CH_2, OCH_3), 3.69-3.62 (m, 6H, 3 CH_2), 3.53-3.45 (m, 4H, 2 CH_2), 3.34 (s, 3H, OCH_3), 3.06-3.02 (m, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$,75 MHz): δ= 150.9, 148.9, 125.4, 121.0, 113.3, 113.0, 72.9, 71.7, 71.5, 71.3, 70.8, 70.0, 59.1, 56.0, 45.1, 43.0, 25.7. **HRMS** (EI) calcd. for $C_{17}H_{27}NO_5$ [$M^{\bullet+}$]: 325.1889; found: 325.1881. **IR** (KBr) [cm^{-1}]: ν = 3330, 2939, 2879, 1517.

General procedure for the preparation of 21 and 22. A mixture of the tretrahydroisoquinoline derivative **17** (0.17 g, 0.47 mmol,), 4-nitrophenethyl bromide (0.11 g, 0.5 mmol) and potassium carbonate (0.2 g, 1.5 mmol) was refluxed during 18 h in CH_3CN, the solvent was evaporated, the residue taken up in 30 mL water and extracted with DCM (3X15 mL). The solution was dried over $MgSO_4$, filtered and concentrated to give the crude product which was purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$).

7-Methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-2-(4-nitrophenethyl)-1,2,3,4-tetrahydroisoquinoline 21. Yield 58.1%, brown oil, R_f= 0.47. **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 8.14 (d, ^3J=8.8 Hz, 2H, *AA´*BB´ ArH), 7.39 (d, ^3J=8.8 Hz, 2H, AA´*BB´* ArH), 6.65 (s, 1H, ArH), 6.52 (s, 1H, ArH), 4.14 (m, 2H, CH_2), 3.86 (t, ^3J=5.0, 2H, CH_2), 3.80 (s, 3H, OCH_3),

3.74-3.72 (m, 2H, CH_2), 3.68-3.64 (m, 4H, 2 CH_2), 3.63 (s, 2H, CH_2), 3.55-3.53 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.01-2.98 (m, 2H, CH_2), 2.81-2.77 (m, 6H, 3 CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz): δ= 148.3, 147.9, 146.8, 146.5, 129.7, 126.9, 126.0, 123.6, 114.1, 110.8, 71.9, 70.7, 70.6, 70.5, 69.6, 68.6, 59.1, 59.0, 56.0, 55.6, 50.9, 33.8, 28.5. **HRMS** (EI) calcd. for $C_{25}H_{34}N_2O_7$ [$M^{\bullet+}$]: 474.2366; found: 474.2363. **IR** (KBr) [cm^{-1}]: ν = 2881, 1672, 1517, 1195.

6-Methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-2-(4-nitrophenethyl)-1,2,3,4-tetrahydroisoquinoline 22. Yield 54%, brown oil, R_f= 0.44. **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 8.13 (d, ^3J=8.7 Hz, 2H, *AA´*BB´ ArH), 7.38 (d, ^3J=8.7 Hz, 2H, AA´*BB´* ArH), 6.59 (s, 1H, ArH), 6.57 (s, 1H, ArH), 4.13-4.11 (m, 2H, CH_2), 3.86-3.84 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.73-3.72 (m, 2H, CH_2), 3.67-3.63 (m, 4H, 2 CH_2), 3.61 (s, 2H, CH_2), 3.54-3.53 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 3.01-2.98 (m, 2H, CH_2), 2.82-2.76 (m, 6H, 3 CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz): δ= 148.3, 148.2, 146.4, 146.4, 129.5, 126.7, 126.2, 123.6, 112.2, 111.9, 71.8, 70.7, 70.5, 70.4, 69.6, 68.7, 59.0, 58.9, 55.9, 55.5, 50.9, 33.8, 28.6. **HRMS** (EI) calcd. for $C_{25}H_{34}N_2O_7$ [$M^{\bullet+}$]: 474.2366; found: 474.2360. **IR** (KBr) [cm^{-1}]: ν = 2895, 1610, 1521, 1261, 1222.

General procedure for the preparation of 6 and 7. Nitro compound **21** was dissolved in ethanol, palladium on activated charcoal (10% m/m) was added, and the solution was stirred under 5 bar H_2 atmosphere during 1 d. The catalyst was filtered off, the solvent removed and the amines were purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$).

4-(2-(7-Methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)aniline 6. Yield 83%, yellow solid, **mp.** 43.5-44.5 °C, R_f= 0.31. **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 7.01 (d, ^3J=8.4 Hz, 2H, *AA´*BB´ ArH), 6.64 (s, 1H, ArH), 6.62 (d, ^3J=8.3 Hz, 2H, AA´*BB´* ArH), 6.52 (s, 1H, ArH), 4.14 (t, ^3J=5.5, 2H, CH_2), 3.86 (t, ^3J=5.5, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.74-3.72 (m, 2H, CH_2), 3.68-3.66 (m, 2H, CH_2), 3.66-3.64 (m, 2H, CH_2), 3.62 (s, 2H, CH_2), 3.55-3.53 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 2.81-2.78 (m, 4H, 2 CH_2), 2.77-2.75 (m, 2H, CH_2), 2.71-2.68 (m, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz) δ= 147.8, 146.7, 144.4, 130.3, 129.4, 127.3, 126.0, 115.2, 114.1, 110.1, 71.9, 70.7, 70.6, 70.5, 69.6, 68.6, 60.6, 59.0, 56.0, 55.7, 51.0, 33.1, 28.5. **HRMS** (EI) calcd. for $C_{25}H_{37}N_2O_7$ [$MH^{\bullet+}$]: 445.2702; found: 445.2696. **IR** (KBr) [cm^{-1}]: ν = 2920, 1645, 1516.

4-(2-(6-Methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)aniline 7. Yield 87%, brown sticky oil, R_f= 0.33. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 6.89 (d, ^3J=7.6 Hz, 2H, *AA´*BB´ ArH), 6.53-6.49 (m, 3H, 3 ArH), 4.04-4.01 (m, 2H, CH_2), 3.78-3.75 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2), 3.64-3.62 (m, 2H, CH_2), 3.59-3.54 (m, 4H, 2 CH_2), 3.47-3.44 (m, 2H, CH_2), 3.28 (s, 3H, OCH_3), 2.84-2.78 (m, 8H, 4 CH_2). **^{13}C-NMR**

($CDCl_3$, 75 MHz): δ= 147.4, 146.8, 145.6, 128.4, 127.6, 124.8, 123.2, 114.2, 111.0, 110.8, 70.8, 69.6, 69.5, 69.4, 68.5, 67.6, 58.3, 57.9, 54.9, 53.5, 49.4, 31.0, 26.3. **MS** (ESI; DCM/MeOH + 10 mmol/L NH_4Ac): m/z (%)= 445.0 (100) [MH^+]. **IR** (KBr) [cm^{-1}]: ν = 3300, 2929, 1693, 1516.

General procedure for SPS of tariquidar analogues 9. A polypropylene 2.0-ml fritted syringe was charged with 50 mg of Wang resin (1.1 mmol/g loading) and the resin was swollen in 1 ml of DMF during 1 h. The resin was transferred to an eppendorf tube and a mixture of 7-carboxyisatoic anhydride (57 mg, 0.27 mmol, 5 equiv) and DMAP (19 mg, 0.16 mmol, 3 equiv) in 1 mL of DMF was added. The resin was heated at 98 °C overnight, then transferred to a polypropylene 2.0-ml syringe and washed three times with 5% AcOH/DCM, DCM, MeOH, DMF and DCM. The syringe was fritted and a solution of DIPEA (47 μL, 0.27 mmol, 5 equiv) in DCM was added and the resin was shaken during 5 min, after that, quinoline-2(6)-carbonyl chloride (freshly prepared, 52 mg, 0.27 mmol, 5 equiv) was added and the resin was shaken at room temperature during 12 h, washed three times with DCM, MeOH, DMF, MeOH and DMF (this coupling was repeated once more). The resin was cooled down and a solution of DIPEA (95 μL, 0.55 mmol, 10 equiv) and HBTU (102 mg, 0.27 mmol, 5 equiv) in 1 mL of DMF was added, the resin was shaken for two minutes and compound **5** (0.27 mmol, 5 equiv) was added. The resin was shaken at room temperature for 24 h and then washed three times with DCM, MeOH and DMF.

Cleavage. The resin was dried under vacuum and a mixture of TFA/DCM/TES 1/1/0.05 was added (1 ml). The resin was shaken for 1 h, the cleavage cocktail was collected and the content of the syringe was washed two times with fresh 50% TFA in DCM (this procedure was repeated once more). Combined washes were evaporated and residual oil was washed with fresh diethyl ether, the precipitated solid was filtered and dried.

N-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid ·TFA 9a.

Yield 80.6%, yellow solid, **mp.** 242.7 °C dec. **^{1}H-NMR** (DMSO *d*6, 600 MHz): δ= 13.48 (s, 1H, NHCO), 10.54 (s, 1H, NHCO), 10.21 (bs, 1H, COOH), 9.42 (d, ^4J=1.0 Hz, 1H, ArH), 8.67 (d, ^3J=8.6 Hz, 1H, ArH), 8.30 (d, ^3J=8.3 Hz, 1H, ArH), 8.20 (d, ^3J=8.2 Hz, 1H, ArH), 8.15-8.14 (m, 2H, ArH), 7.92 (dt, ^3J=8.2 Hz, ^4J=1.0 Hz, 1H, ArH), 7.80-7.74 (m, 4H, ArH), 7.31 (d, ^3J=7.3 Hz, 2H, ArH), 6.82 (s, 1H, ArH), 6.79 (s, 1H, ArH), 4.52 (bs, 1H, C*H*H), 4.30 (bs, 1H, CH*H*), 3.76-3.73 (m, 7H, 2 OCH_3, C*H´*H), 3.46 (bs, 2H, CH_2), 3.36 (bs, 1H, CH*H´*), 3.10-3.07 (m, 3H, CH_2, C*H´´*H), 3.00 (bs, 1H, CH*H´´*). **^{13}C-NMR** (DMSO-*d*6, 151 MHz): δ= 168.6, 164.6, 162.9, 158,2 (TFA), 158,0 (TFA), 149.3, 148.4, 147.7, 145.8, 140.2, 140.1, 138.5, 137.7, 132.2, 131.5,

130.9, 129.1, 129.0, 128.6, 128.3, 123.1, 121.7, 120.7, 119.8, 119.3, 119.1, 118.5, 111.4, 109.6, 55.7, 55.4, 55.4, 51.6, 49.1, 29.1, 24.4. **HRMS** (LSI) calcd. for $C_{37}H_{35}N_4O_6$ [MH^+]: 631.2557; found: 631.2549. **IR** (KBr) [cm^{-1}]: ν = 2926, 1672, 1612, 1570, 1512.

N-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid ·TFA 9b.

Yield 97%, yellow solid, **mp.** 227 °C dec. **^{1}H-NMR** (DMSO *d*6, 600 MHz): δ= 12.32 (s, 1H, NHCO), 10.53 (s, 1H, NHCO), 10.11 (bs, 1H, COOH), 9.16 (d, ^4J=1.5 Hz, 1H, ArH), 9.04 (dd, ^3J=4.1 Hz ^4J=1.5 Hz, 1H, ArH), 8.66 (d, ^4J=1.5 Hz, 1H, ArH), 8.57 (d, ^3J=7.7 Hz, 1H, ArH), 8.26 (dd, ^3J=8.8 Hz ^4J=1.9 Hz, 1H, ArH), 8.21 (d, ^3J=8.7 Hz, 1H, ArH), 8.18 (d, ^3J=8.1 Hz, 1H, ArH), 7.78 (d, ^3J=8.4 Hz, 2H, ArH), 7.75 (dd, ^3J=8.2 Hz, ^4J=1.6 Hz, 1H, ArH), 7.66 (dd, ^3J=8.2 Hz, ^4J=4.2 Hz, 1H, ArH), 7.31 (d, ^3J=8.5 Hz, 2H, ArH), 6.83 (s, 1H, ArH), 6.79 (s, 1H, ArH), 4.52 (d, ^2J=14.0 Hz, 1H, C*H*H), 4.28 (d, ^2J=12.1 Hz, 1H, CH*H*), 3.76-3.73 (m, 7H, 2 OCH_3, C*H´*H), 3.45 (bs, 2H, CH_2), 3,34 (bs, 1H, CH*H´*), 3.09-3.06 (m, 3H, 1 CH_2, C*H´´*H), 2.99 (bs, 1H, CH*H´´*). **^{13}C-NMR** (DMSO-*d*6, 151 MHz) δ 169.4, 164.8, 164.4, 158.3, 158.1, 157.9, 152.6, 148.8, 148.4, 147.7, 140.6, 139.96, 137.7, 137.4, 132.2, 132.1, 131.3, 129.8, 129.0, 128.3, 127.3, 127.0, 123.1, 122.5, 121.9, 120.7, 119.8, 119.8, 111.4, 109.6, 55.8, 55.6, 55.5, 51.7, 49.2, 29.2, 24.5. **HRMS** (LSI) calcd. for $C_{37}H_{36}N_4O_6$ [MH^+]: 632.2635; found: 631.2619. **IR** (KBr) [cm^{-1}]: ν = 3104, 1670, 1612, 1579, 1517.

N-{4-[2-(7-Methoxy-6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid ·TFA 9c.

Yield 72.9%, yellow-brown solid, **mp.** 239.3 °C dec. **^{1}H-NMR** (MeOD *d*4, 600 MHz): δ= 9.34 (s, 1H, ArH), 8.39 (d, ^3J=8.2 Hz, 1H, ArH), 8.19-8.15 (m, 3H, ArH), 7.93 (d, ^3J=7.9 Hz, 1H, ArH), 7.77 (t, ^3J=7.6 Hz, 1H, ArH), 7.70 (d, ^3J=5.4 Hz, 1H, ArH), 7.63 (t, ^3J=7.5 Hz, 1H, ArH), 7.60 (d, ^3J=7.4 Hz, 1H, ArH), 7.29 (d, ^3J=5.1 Hz, 1H, ArH), 6.68 (s, 1H, ArH), 6.64 (s, 1H, ArH), 4.51 (bs, 1H, C*H*H), 4.25 (bs, 1H, CH*H*), 3.98 (t, ^3J=4.4 Hz, 2H, CH_2), 3.76-3.73 (m, 6H, OCH_3, CH_2, C*H´*H), 3.65-3.64 (m, 2H, CH_2), 3.60-3.58 (m, 4H, 2 CH_2), 3.50-3.49 (m, 4H, 2 CH_2), 3.39 (bs, 1H, CH*H´*), 3.31 (s, 3H, OCH_3), 3.13 (bs, 3H, CH_2, C*H´´*H), 3.00 (bs, 1H, CH*H´´*). **^{13}C-NMR** (MeOD *d*4, 151 MHz) δ 169.7, 167.7, 165.1, 162.3 (TFA), 162.1 (TFA), 150.6, 150.2, 149.8, 147.8, 141.8, 141.2, 139.0, 138.96 133.7, 133.1, 131.5, 131.0, 130.8, 130.3, 129.6, 128.9, 124.1, 122.7, 122.6, 120.9, 120.8, 120.3, 119.5, 114.3, 110.9, 72.9, 71.7, 71.5, 71.3, 70.6, 69.7, 59.0, 58.2, 56.4, 54.0, 51.5, 31.0, 26.6. **HRMS** (LSI) calcd. for $C_{43}H_{47}N_4O_9$ [MH^+]: 763.3343; found: 763.3326. **IR** (KBr) [cm^{-1}]: ν = 3219, 1672, 1602, 1570, 1517.

N-{4-[2-(7-Methoxy-6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid ·TFA 9d.

Yield 87%, yellow-orange solid, **mp.** 217 °C dec. **^{1}H-NMR** (DMSO *d*6, 600 MHz): δ=12.31 (s, 1H, NHCO), 10.53 (s, 1H, NHCO), 10.06 (bs, 1H, COOH), 9.15 (s, 1H, ArH), 9.04 (s, 1H, ArH), 8.65 (s, 1H), 8.56 (d, ^{3}J=8.1 Hz, 1H, ArH), 8.26 (d, ^{3}J=8.6 Hz, 1H, ArH), 8.20 (d, ^{3}J=8.5 Hz, 1H, ArH), 8.20 (d, ^{3}J=8.2 Hz, 1H, ArH), 7.78-7.75 (m, 3H, ArH), 7.66 (dd, ^{3}J=7.9 Hz, ^{4}J=3.7 Hz, 1H, ArH), 7.31 (d, ^{3}J=8.0 Hz, 2H, ArH), 6.85 (s, 1H, ArH), 6.80 (s, 1H, ArH), 4.52 (d, ^{2}J=12.7 Hz, 1H, C*H*H), 4.26 (d, ^{2}J=11.8 Hz, 1H, CH*H*), 4.05 (s, 2H, CH_2), 3.74-3.70 (m, 6H, OCH_3, CH_2, C*H´*H), 3.57 (m, 2H, CH_2), 3.52-3.50 (m, 6H, 3 CH_2), 3.42-3.41 (m, 2H, CH_2), 3.34 (bs, 1H, CH*H´*), 3,22 (s, 3H, OCH_3), 3.08-3.06 (m, 3H, CH_2, C*H´´*H), 2.97 (bs, 1H, CH*H´´*). **^{13}C NMR** (DMSO-*d*6, 151 MHz) δ 169.4, 164.8, 164.4, 158.1, 157.9, 152.6, 148.8, 147.9, 147.6, 140.6, 139.9, 137.7, 137.4, 132.2, 131.3, 129.8, 129.0, 128.3, 127.3, 127.0, 123.1, 122.5, 122.0, 120.7, 120.1, 119.8, 119.8, 112.8, 109.8, 71.2, 69.9, 69.7, 69.5, 68.8, 67.9, 58.0, 55.8, 55.6, 51.7, 49.2, 29.2, 24.5. **HRMS** (LSI) calcd. for $C_{43}H_{47}N_4O_9$ [MH^+]: 763.3343; found: 763.3329. **IR** (KBr) [cm^{-1}]: ν = 2914, 1672, 1598, 1581, 1517.

N-{4-[2-(6-Methoxy-7-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid ·TFA 9e.

Yield 64.5%, yellow-brown solid, **mp.** 250 °C dec. **^{1}H-NMR** (DMSO *d*6, 600 MHz): δ= 13.53 (s, 1H, NHCO), 10.53 (s, 1H, NHCO), 9.40 (d, ^{4}J=1.5 Hz,, 1H, ArH), 8.66 (d, ^{3}J=8.4 Hz, 1H, ArH), 8.30 (d, ^{3}J=8.4 Hz, 1H, ArH), 8.14-8.13 (m, 2H, ArH), 7.91 (dt, ^{3}J=8.2 Hz, ^{4}J=1.2 Hz, 1H, ArH), 7.78-7.76 (m, 3H, ArH), 7.73 (dd, ^{3}J=8.1 Hz, ^{4}J=1.5 Hz, 1H, ArH), 7.31 (d, ^{3}J=8.4 Hz, 2H, ArH), 6.83 (s, 1H, ArH), 6.80 (s, 1H, ArH), 4.38 (bs, 2H, CH_2), 4.02 (t, ^{3}J=4.9 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.72 (t, ^{3}J=4.6 Hz, 2H, CH_2), 3.58-3.56 (m, 2H, CH_2), 3.53-3.50 (m, 6H, CH_2), 3.44 (bs, 2H, CH_2), 3.44-3.40 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 3.06 (m, 2H, CH_2), 3.02 (bs, 2H, CH_2). **^{13}C-NMR** (DMSO *d*6, 151 MHz): δ= 168.6, 165.0, 162.9, 158.0 (TFA), 157.8 (TFA), 149.3, 148.6, 146.8, 145.8, 140.2, 140.0, 138.5, 137.7, 137.5, 132.3, 131.5, 130.9, 130.5, 129.1, 129.1, 129.0, 128.6, 128.2, 123.5, 121.7, 120.7, 119.1, 118.5, 111.7, 111.0, 71.2, 69.9, 69.7, 69.5, 68.8, 68.0, 58.0, 55.96, 55.5, 51.8, 49.2, 29.3, 24.6. **HRMS** (LSI) calcd. for $C_{43}H_{47}N_4O_9$ [MH^+]: 763.3343; found: 763.3346. **IR** (KBr) [cm^{-1}]: ν = 3296, 2875, 1689, 1654, 1570, 1514.

N-{4-[2-(6-Methoxy-7-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid ·TFA 9f.

Yield 95.4%, yellow solid, **mp.** 218 °C dec. **^{1}H-NMR** (DMSO *d*6, 600 MHz): δ= 12.31 (s, 1H, NHCO), 10.53 (s, 1H, NHCO), 10.17 (bs, 1H, COOH), 9.16 (d, ^{4}J=1.5 Hz, 1H, ArH), 9.04 (dd, ^{3}J=4.2 Hz, ^{4}J=1.5 Hz, 1H, ArH), 8.66 (d, ^{4}J=1.9 Hz, 1H, ArH), 8.58 (d, ^{3}J=8.4 Hz, 1H, ArH), 8.26 (dd, ^{3}J=8.8 Hz, ^{4}J=2.0 Hz, 1H, ArH), 8.21 (d, ^{3}J=8.8 Hz, 1H, ArH), 8.17 (d, ^{3}J=8.1 Hz, 1H, ArH), 7.79-7.75 (m, 3H, ArH), 7.67 (dd, ^{3}J=8.2 Hz, ^{4}J=4.2 Hz, 1H, ArH), 7.31 (d, ^{3}J=8.4 Hz, 2H, ArH), 6.84 (s, 1H, ArH), 6.81 (s, 1H, ArH), 4.50 (d, ^{2}J=14.6 Hz, 1H, C*H*H), 4.27 (d, ^{2}J=14.3 Hz, 1H, CH*H*), 4.04-4.02 (m, 2H, CH_2), 3.77-3.72 (m, 6H, OCH_3, CH_2, C*H´*H), 3.58-3.57 (m, 2H, CH_2), 3.53-3.50 (m, 4H, 2 CH_2), 3.46 (m, 2H, CH_2), 3.42-3.41 (m, 2H, CH_2), 3.33 (bs, 1H, CH*H´*), 3,22 (s, 3H, OCH_3), 3.06 (m, 3H, CH_2, C*H´´*H), 2.97 (d, ^{2}J=15.6 Hz 1H, CH*H´´*). **^{13}C NMR** (DMSO-*d*6, 151 MHz) δ: 169.4, 164.8, 164.4, 158.3 (TFA), 158.1 (TFA), 152.5, 148.7, 148.6, 146.8, 140.6, 139.9, 137.7, 137.6, 132.2, 131.3, 129.6, 129.0, 128.3, 127.3, 127.1, 123.4, 122.5, 122.0, 120.7, 119.8, 119.8, 119.7, 111.7, 111.0, 71.2, 69.9, 69.7, 69.5, 68.8, 68.0, 58.0, 55.8, 55.5, 51.7, 49.1, 29.2, 24.5. **HRMS** (LSI) calcd. for $C_{43}H_{47}N_4O_9$ [MH^+]: 763.3343; found: 763.3334. **IR** (KBr) [cm^{-1}]: ν = 2902, 1670, 1600, 1579, 1517.

General procedure for the esterification of compounds 9. The carboxylic acid derivative (1 equiv) was dissolved in 3 mL of a mixture PhH/MeOH 2/1 and trimethylsilyldiazomethane solution (2 M in diethyl ether) was added dropwise until no evolution of N_2 was observed. The reaction was stirred during 1 h at room temperature. The solvent was evaporated and the solid was purified by flash chromatography ($CHCl_3$:MeOH 5% or 10%).

N-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid methyl ester 10a.

Yield 75%, yellow solid, **mp.** 174 °C (decomposition), R_f= 0.35 ($CHCl_3$:MeOH 5%). **^{1}H-NMR** (CD_2Cl_2, 300 MHz): δ= 13.19 (s, 1H, NHCO), 9.41 (d, ^{4}J=0.70 Hz, 1H, ArH), 8.33 (d, ^{3}J=8.4 Hz, 1H, ArH), 8.28-8.20 (m, 3H, ArH), 8.13 (d, ^{3}J=8.2 Hz, 1H, ArH), 7.89 (d, ^{3}J=8.0 Hz, 1H, ArH), 7.77 (t, ^{3}J=7.3 Hz, 1H, ArH), 7.67-7.58 (m, 4H, ArH), 7.23 (d, ^{3}J=8.2 Hz, 1H, ArH), 6.55 (s, 1H, ArH), 6.50 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.74 (s, 6H, 2 OCH_3), 3.58 (s, 2H, CH_2), 2.88-2.71 (m, 8H, 4 CH_2). **^{13}C-NMR** (CD_2Cl_2, 75 MHz) δ: 167.7, 165.0, 164.1, 150.1, 148.0, 147.7, 146.9, 141.3, 140.6, 138.2, 136.4, 132.1, 130.8, 130.3, 129.6, 128.7, 128.2, 126.6, 122.1, 122.1, 122.0, 121.0, 119.2, 119.1, 118.7, 112.0, 110.1, 60.3, 56.2, 56.1, 55.9, 51.4, 33.6, 29.0.

HRMS (LSI) calcd. for $C_{38}H_{37}N_4O_6$ [$M^{\bullet+}$]: 645.2713; found: 645.2709. **IR** (KBr) [cm^{-1}]: ν = 3296, 2949, 1691, 1654, 1570, 1517.

N-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid methyl ester 10b. Yield 95%, yellow solid, **mp.** 199 °C (decomposition), R_f= 0.26 ($CHCl_3$:MeOH 5%). **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 12.30 (s, 1H, NHCO), 9.38 (s, 1H, ArH), 9.01 (d, ^4J=1.9 Hz, 1H, ArH), 8.52 (s, 1H, ArH), 8.41 (s, 1H, NHCO), 8.31 (d, ^3J=8.1 Hz, 1H, ArH), 8.28 (d, ^3J=8.7 Hz, 1H, ArH), 8.22 (d, ^3J=8.5 Hz, 1H, ArH), 8.17 (d, ^3J=8.5 Hz, 1H, ArH), 7.72 (d, ^3J=7.7 Hz, 1H, ArH), 7.63 (d, ^3J=7.6 Hz, 2H, ArH), 7.50-7.48 (m, 1H, ArH), 7.23 (d, ^3J=8.4 Hz, 1H, ArH), 6.59 (s, 1H, ArH), 6.53 (s, 1H, ArH), 4.01 (s, 3H, OCH_3), 3.83 (s, 6H, 2 OCH_3), 3.66 (s, 2H, CH_2), 2.92-2.89 (m, 2H, CH_2), 2.85-2.84 (m, 2H, CH_2), 2.81-2.77 (m, 4H, 2 CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz): δ= 168.5, 168.5, 165.2, 164.5, 164.5, 152.4, 149.6, 147.5, 147.2, 141.6, 140.6, 137.3, 136.9, 135.8, 132.1, 131.6, 130.4, 129.2, 128.5, 127.6, 127.0, 126.9, 126.0, 122.5, 122.0, 120.7, 117.7, 117.3, 111.3, 109.4, 77.2, 77.0, 76.7, 60.0, 55.9, 55.8, 55.6, 52.9, 50.9, 33.4, 28.5, 28.5, 20.4. **HRMS** (LSI) calcd. for $C_{38}H_{37}N_4O_6$ [MH+]: 645.2713; found: 645.2805. **IR** (KBr) [cm^{-1}]: ν = 3273, 2941, 1678, 1645, 1577, 1517.

N-{4-[2-(7-Methoxy-6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid methyl ester 10c.

Yield 90%, yellow solid, **mp.** 103.2 °C (decomposition), R_f= 0.46 ($CHCl_3$:MeOH 10%). **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ=13.24 (s, 1H, NHCO), 9.38 (d, ^4J=0.6 Hz, 1H, ArH), 8.54 (s, 1H, NHCO), 8.30 (d, ^3J=8.4 Hz, 1H, ArH), 8.25 (d, ^3J=8.3 Hz, 1H, ArH), 8.11 (d, ^3J=8.2 Hz, 1H, ArH), 7.86 (d, ^3J=8.0 Hz, 1H, ArH), 7.77 (t, ^3J=7.3 Hz, 1H, ArH), 7.65-7.61 (m, 4H, ArH), 7.22 (d, ^3J=8.1 Hz, 2H, ArH), 6.63 (s, 1H, ArH), 6.52 (s, 1H, ArH), 4.12 (t, ^3J=5.2 Hz, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.84 (t, ^3J=5.1 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.73-3.71 (m, 2H, CH_2), 3.67-3.63 (m, 6H, 3 CH_2), 3.54-3.53 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 2.91-2.88 (m, 2H, CH_2), 2.82-2.75 (m, 6H, 3 CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz): δ= 167.2, 164.8, 163.7, 149.4, 147.7, 146.7, 146.4, 140.6, 140.1, 137.6, 136.6, 136.0, 131.7, 130.2, 130.1, 129.3, 129.1, 128.3, 127.6, 126.0, 122.5, 120.7, 118.6, 118.6, 117.8, 113.9, 110.0, 71.8, 70.7, 70.5, 70.4, 69.5, 68.5, 60.0, 58.9, 55.9, 55.5, 52.6, 50.9, 33.3, 28.4. **HRMS** (LSI) calcd. for $C_{44}H_{49}N_4O_9$ [MH^+]: 777.3500; found: 777.3501. **IR** (KBr) [cm^{-1}]: ν = 3292, 2926, 1685, 1654, 1570, 1516.

N-{4-[2-(7-Methoxy-6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid methyl ester 10d.

Yield 53%, yellow solid, **mp.** 131.4 °C (decomposition), R_f= 0.37 ($CHCl_3$:MeOH 10%). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ=12.30 (s, 1H, NHCO), 9.39 (d, ^4J=1.3 Hz, 1H, ArH), 9.00 (dd, ^3J=4.2 Hz, ^4J=1.5 Hz, 1H, ArH), 8.51 (d, ^4J=1.4 Hz, 1H, ArH), 8.33-8.21 (m, 4H, NHCO, 3 ArH), 8.15 (d, ^3J=8.3 Hz, 1H, ArH), 7.70 (dd, ^3J=8.4 Hz, ^4J=1.5 Hz 1H, ArH), 7.62 (d, ^3J=8.3 Hz, 2H, ArH), 7.47 (dd, ^3J=8.2 Hz, ^3J=4.2 Hz 1H, ArH), 7.22 (m, 2H, ArH), 6.64 (s, 1H, ArH), 6.53 (s, 1H, ArH), 4.12 (t, ^3J=5.4 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.84 (t, ^3J=4.8 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.74-3.71 (m, 2H, CH_2), 3.68-3.63 (m, 6H, 3 CH_2), 3.55-3.52 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 2.94-2.89 (m, 2H, CH_2), 2.83-2.76 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ= 167.5, 164.2, 163.5, 151.4, 148.5, 146.9, 145.8, 140.7, 139.5, 136.4, 135.7, 134.8, 131.1, 130.6, 129.3, 128.2, 127.5, 126.6, 126.6, 125.9, 124.9, 121.5, 121.0, 119.6, 116.6, 116.3, 113.0, 109.0, 76.4, 76.0, 75.5, 70.9, 69.7, 69.6, 69.5, 68.6, 67.5, 58.7, 58.0, 55.0, 54.3, 51.9, 49.7, 32.1, 27.1. **HRMS** (LSI) calcd. for $C_{44}H_{49}N_4O_9$ [MH^+]: 777.3500; found: 777.3523. **IR** (KBr) [cm^{-1}]: ν = 3290, 2900, 1674, 1577, 1514.

N-{4-[2-(6-Methoxy-7-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-2-carbonyl)-amino]-terephthalamic acid methyl ester 10e.

Yield 95.5%, yellow-brown solid, **mp.** 123.3 °C (decomposition), R_f= 0.43 ($CHCl_3$:MeOH 10%). **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ=13.24 (s, 1H, NHCO), 9.38 (s, 1H, ArH), 8.55 (s, 1H, NHCO), 8.30 (d, ^3J=8.4 Hz, 1H, ArH), 8.25 (d, ^3J=8.4 Hz, 1H, ArH), 8.12 (d, ^3J=8.2 Hz, 1H, ArH), 7.86 (d, ^3J=8.1 Hz, 1H, ArH), 7.76 (t, ^3J=8.0 Hz, 1H, ArH), 7.66-7.61 (m, 4H, ArH), 7.22 (d, ^3J=8.2 Hz, 2H, ArH), 6.58 (s, 2H, ArH), 4.11 (t, ^3J=5.2 Hz, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.84 (t, ^3J=5.1 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.73-3.71 (m, 2H, CH_2), 3.67-3.62 (m, 6H, 3 CH_2), 3.54-3.53 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 2.90-2.88 (m, 2H, CH_2), 2.83-2.82 (m, 2H, CH_2), 2.79-2.74 (m, 4H, 2 CH_2). **^{13}C-NMR** ($CDCl_3$,151 MHz): δ= 167.2, 164.7, 163.7, 149.4, 148.1, 146.4, 146.3, 140.6, 140.1, 137.6, 136.7, 135.9, 131.7, 130.2, 130.1, 129.3, 128.3, 127.6, 126.8, 126.4, 120.6, 118.6, 117.8, 112.2, 111.9, 71.8, 70.7, 70.5, 70.4, 69.5, 68.6, 60.0, 58.97, 55.9, 55.5, 52.6, 50.9, 33.4, 28.6. **HRMS** (LSI) calcd. for $C_{44}H_{49}N_4O_9$ [MH^+]: 777.3500; found: 777.3485. **IR** (KBr) [cm^{-1}]: ν = 3284, 2906, 1693, 1654, 1570, 1516.

N-{4-[2-(7-Methoxy-6-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-phenyl}-2-[(quinoline-6-carbonyl)-amino]-terephthalamic acid methyl ester 10f.

Yield 50%, yellow solid, **mp.** 136.8 °C (decomposition), R_f= 0.37 ($CHCl_3$:MeOH 10%). **^{1}H-NMR** (CD_2Cl_2, 300 MHz): δ=12.16 (s, 1H, NHCO), 9.30 (s, 1H, ArH), 8.93 (d, ^3J=4.2 Hz, 1H, ArH), 8.55 (s, 1H, NHCO), 8.44 (d, ^4J=1.7 Hz, 1H, ArH), 8.28-8.07 (m, 4H, ArH), 7.62-7.59 (m, 3H, ArH), 7.42 (dd, ^3J=8.2 Hz, ^3J=4.2 Hz 1H, ArH), 7.21 (d, ^3J=8.3 Hz, 2H, ArH), 6.56 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.04-4.01 (m, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 3.75 (s, 6H, 2 OCH_3), 3.62-3.61 (m, 2H, CH_2), 3.59-3.53 (m, 6H, 3 CH_2), 3.48-3.45 (m, 2H, CH_2), 3.29 (s, 3H, OCH_3), 2.87-2.82 (m, 2H, CH_2), 2.76-2.69 (m, 6H, 3 CH_2), 2.79-2.74 (m, 4H, 2 CH_2). **^{13}C NMR** (CD_2Cl_2, 75 MHz): δ= 167.7, 164.1, 163.9, 151.6, 148.8, 147.1, 145.5, 140.9, 139.9, 136.4, 136.3, 135.3, 131.4, 130.6, 129.4, 128.4, 127.6, 126.8, 126.6, 126.3, 125.9, 121.3, 120.9, 119.8, 117.4, 116.5, 111.0, 110.8, 71.1, 69.9, 69.7, 69.6, 68.9, 67.6, 59.1, 57.8, 54.9, 54.7, 52.0, 50.2, 32.4, 27.9. **HRMS** (LSI) calcd. for $C_{44}H_{49}N_4O_9$ [MH^+]: 777.3500; found: 777.3523. **IR** (KBr) [cm^{-1}]: ν = 3290, 2900, 1674, 1577, 1514.

ABCB1 assay.[25] ABCB1-overexpressing Kb-V1 cells[18] were seeded into flat-bottomed 96-well plates (Greiner, Frickenhausen, Germany) at a density of 20,000 cells per well (total volume: 100µL). On the following day, cells were washed with loading buffer (120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2 \cdot 6\ H_2O$, 1.5 mM $CaCl_2 \cdot 2\ H_2O$, 25 mM HEPES, 10 mM glucose, pH 7.4) in order to remove unspecific serum esterases. Afterwards, cells were incubated with loading suspension (loading buffer, 5 mg/mL BSA, 1.25 µL/mL pluronic F127 (20 % in DMSO)) containing 0.5 µM calcein-AM and the test compound at increasing concentrations for 10 min (37 °C/5 % CO_2). Subsequently, the loading suspension was discarded and cells were fixed with 4 % paraformaldehyde (PFA) solution in PBS for 20 min under light protection. After three washing circles with loading buffer, fixed cells were overlaid with 100 µL loading buffer and relative fluorescence intensities were determined at 535/25 nm at a GENios Pro microplate reader (Tecan Deutschland GmbH, Crailsheim, Germany) after excitation at 485/20 nm. The obtained mean fluorescence intensities were related to the controls and plotted against the various concentrations of test compounds.

TECAN instrument settings were as follows: Measurement mode: fluorescence top; excitation filter (Calcein-AM): 485/20; emission filter (Calcein-AM): 535/25; number of reads: 10; integration time: 40 µs; lag time: 0 µs; mirror selection: Dichroic 3 (e.g.Fl); plate definition file GRE96ft.pdf; multiple reads per well (Circle): 3x3; time between move and flash: 100 ms.

ABCG2 assay. The standard protocol for the performance of Hoechst 33342 was as follows: 3-5 days after passaging (70-90 % confluency), MCF-7/Topo cells were seeded into 96-well plates at a density of 20000 cells/well (total volume 100µL). The cells were incubated over night in a water saturated atmosphere (95 % air, 5 % carbondioxide) at 37 °C. The next day, pre-mixtures of the test compounds at increasing concentrations were prepared in 1.5 mL reaction vessels: 800 µL of pre-heated (37 °C) EMEM (Eagle's Minimum Essential Medium, Sigma, Munich, Germany) containing L-glutamine, 2.2 g/L $NaHCO_3$ (Merck, Darmstadt, Germany) and 110 mg/L sodium pyruvate (Serva, Heidelberg, Germany) supplemented with 10 % FCS, were transferred into the cups. Subsequently, 8 µL of a 0.8 mM Hoechst 33342 dye solution and 8 µL of the test compound stock solutions in different conctentrations were added to the mixture. The samples were immediatley vortexed. The incubation medium of the microplate was removed and replaced by 100 µL per well of the pre-mixtures by means of a multichannel pipette, achieving a final concentration of 10 µM fumitremorgin C (positive control) and 8 µM Hoechst 33342. The microplates were incubated (37 °C, 5 % carbondioxide) for 120 min. The supernatants were drained, and the cells were fixed for 30 min under light protection using 100 µL per well of a 4 % paraformaldehyde solution. Finally, MCF-7/Topo cells were washed three times with 250 µL PBS for each well in order to get rid of residual dye. Afterwards cells were overlaid with 100 µL PBS and the relative fluorescence intensities were determined using a GENios Pro microplate reader (TECAN Deutschland GmbH, Crailsheim, Germany). The obtained mean fluorescence intensities were related to the controls and plotted against the various concentrations of test compounds.

TECAN instrument settings were as follows: Measurement mode: fluorescence top; excitation filter (Hoechst 33342): 340/35; emission filter (Hoechst 33342): 485/20; number of reads: 10; integration time: 40 µs; lag time: 0 µs; mirror selection: user defined mirror 1; plate definition file GRE96ft.pdf; multiple reads per well (Circle): 3x3; time between move and flash: 50 ms.

On each plate, the optimal gain was calculated by determination of the fluorescence intensity in the presence of the control substance, fumitremorgin C. After measurements, the microtiter plates were stored at 4 °C for the following cell quantification procedures. As a loss of cells and unspecific toxic effects of the test compounds during the incubation phase are to be considered, the obtained fluorescence values had to be normalized to the cell number of each well. Therefore, the microplates were processed with a 0.02 % aqueous crystal violet solution (100 µL / well) for 20 min. Excess dye was removed by rinsing the trays with water for 20 min. Crystal violet bound by the cells was re-dissolved in 70 % ethanol (180 µL / well) while shaking the microplates for 2-4 h. Subsequently, the absorbance as a parameter proportional to cell mass was measured at the TECAN plate reader. For normalization of the fluorescence intensities to

the cell mass, detected fluorescence values were divided through the obtained absorbance data of each well. All values were corrected to the unspecific uptake of the dye (DMSO control value) and the data were referred to the maximal signal caused by 10 μM of the reference compound fumitremorgin C. Addition of increasing concentrations of the modulators led to sigmoidal concentration response curves. IC_{50} values were calculated using SIGMA PLOT 9.0, "Four parameter logistic curve" fitting. Errors were expressed as standard error of the mean (SEM). The required concentration of 10 μM fumitremorgin C in the final assay protocol, as a reference value for maximal transporter inhibition, was determined via the performance of the H33342 and pheophorbide assay according to the standard protocol.

1.5 References

1. Colabufo, N. A.; Berardi, F.; Perrone, M. G.; Capparelli, E.; Cantore, M.; Inglese, C.; Perrone, R. *Curr. Top. Med. Chem.* **2010,** *10,* 1703.
2. Teodori, E.; Dei, S.; Martelli, C.; Scapecchi, S. *Curr. Top. Med. Chem.* **2010,** *10*, 1715.
3. Fruttero, R.; Crosetti, M.; Chegaev, K.; Guglielmo, S.; Gasco, A.; Berardi, F.; Niso, M.; Perrone, R.; Panaro, M. A.; Colabufo, N. A. *J. Med. Chem.* **2010,** *53*, 5467.
4. Avendano, C.; Menendez, J. C. *Med Chem Reviews* **2004,** *1*, 419.
5. Baumert, C.; Hilgeroth, A. *Anti-Cancer Agents Med. Chem.* **2009,** *9*, 415.
6. Müller, H.; Pajeva, I. K.; Globisch, C.; Wiese, M. *Bioorg. Med. Chem.* **2008,** *16*, 2456.
7. Colabufo, N. A.; Berardi, F.; Cantore, M.; Perrone, M. G.; Contino, M.; Inglese, C.; Niso, M.; Perrone, R.; Azzariti, A.; Simone, G. M.; Paradiso, A. *Bioorg. Med. Chem.* **2008,** *16*, 3732.
8. Pleban, K.; Ecker, G. F. *Mini-Rev. Med. Chem.* **2005,** *5*, 153.
9. Varma, M. V. S.; Ashokraj, Y.; Dey, C. S.; Panchagnula, R. *Pharmacol. Res.* **2003,** *48*, 347.
10. Ahmed-Belkacem, A.; Pozza, A.; Macalou, S.; Pérez-Victoria, J. M.; Boumendjel, A.; Pietro, A. D. *Anti-Cancer Drugs* **2006,** *17*, 239.
11. Pick, A.; Müller, H.; Wiese, M. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 180.
12. Nicolle, E.; Boccard, J.; Guilet, D.; Dijoux-Franca, M.-G.; Zelefac, F.; Macalou, S.; Grosselin, J.; Schmidt, J.; Carrupt, P.-A.; Pietro, A. D.; Boumendjel, A. *Eur. J. Pharm. Sci.* **2009,** *38*, 39.
13. Sim, H.-M.; Lee, C.-Y.; Ee, P. L. R.; Go, M.-L. *Eur. J. Pharm. Sci.* **2008,** *35*, 293.
14. Takada, K.; Imamura, N.; Gustafson, K. R.; Henrich, C. J. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 1330.
15. Boumendjel, A.; Macalou, S.; Ahmed-Belkacem, A.; Blanc, M.; Pietro, A. D. *Bioorg. Med. Chem.* **2007,** *15*, 2892.

16. Mistry, P.; Stewart, A. J.; Dangerfield, W.; Okiji, S.; Liddle, C.; Bootle, D.; Plumb, J. A.; Templeton, D.; Charlton, P. *Cancer Res.* **2001,** *6*, 749.
17. Planting, A. S. T.; Sonneveld, P.; Gaast, A. v. d.; Sparreboom, A.; Burg, M. E. L. v. d.; Luyten, G. P. M.; Leeuw, K. d.; Boer-Dennert, M. d.; Wissel, P. S.; Jewell, R. C.; Paul, E. M.; Jr., N. B. P.; Verweij, J. *Cancer Chemother. Pharmacol.* **2005,** *55*, 91.
18. Kühnle, M.; Egger, M.; Müller, C.; Mahringer, A.; Bernhardt, G.; Fricker, G.; König, B.; Buschauer, A. *J. Med. Chem.* **2009,** *52*, 1190.
19. Wang, M.; Zheng, D. X.; Luo, M. B.; Gao, M.; Miller, K. D.; Hutchins, G. D.; Zheng, Q.-H. *Appl. Radiat. Isot.* **2010,** *68*, 1098.
20. Hubensack, M.; Müller, C.; Höcherl, P.; Fellner, S.; Spruss, T.; Bernhardt, G.; Buschauer, A. *J. Cancer. Res. Clin. Oncol.* **2008,** *134*, 597.
21. Clark, A. S.; Deans, B.; Stevens, M. F. G.; Tisdale, M. J.; Wheelhouse, R. T.; Denny, B. J.; Hartley, J. A. *J. Med. Chem.* **1995,** *38*, 1493.
22. Bobbit, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967,** *32*, 2225.
23. Snow, A. W.; Foos, E. E. *Synthesis* **2003**, 509.
24. Klinkhammer, W.; Müller, H.; Globisch, C.; Pajeva, I. K.; Wiese, M. *Bioorg. Med. Chem.* **2009,** *17*, 2524.
25. Höcherl, P. Ph. D. Thesis, Universität Regensburg, June 2010.
26. Kühnle, M. Ph. D. Thesis, Universität Regensburg, February 2010.

2. Biaryl Tariquidar-Related Derivatives as Potent and Selective BCRP Modulators*

Starting from the lead structure **2** synthesized in our laboratory, and aiming at more stable and better soluble compounds, a new series of biaryl tariquidar derivatives was synthesized by solid phase and solution synthesis. The biaryl fragment was constructed via Suzuki coupling starting from resin bound 4-bromo-2-nitrobenzoic acid and 4-(hydroxymethyl)benzeneboronic acid for compounds **15a-h** or methyl 2-amino-4-bromo benzoate and (4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)boronic acid for compounds **20a-d**. Sequential steps of reduction, amide bond formation, deprotection, mesylation and nucleophilyc substitution led to the desired structures. Inhibition of ABCB1 and ABCG2 determined in the calcein-AM and the Hoechst 33342 microplate assay, respectively, showed that analogues **15b**,**g**,**h** and **20c,d** selectively inhibit the ABCG2 transporter at nanomolar concentrations with a maximal inhibitory effect over 90%, being compound **15g** the most potent and selective ABCG2 modulator with an IC_{50} value of 590 nM, and I_{max} 109% relative to FTC. Stability of compound **15g** was also evaluated in mouse plasma.

* Patent and paper in preparation. All the synthesis and spectroscopical investigations (except compound **14**) were done by Cristian Ochoa Puentes. Compound **14** was synthesized by Manuel Bause at the Institute of Organic Chemistry, University of Regensburg. Inhibition assays for ABCB1 and ABCG2 were performed by Stefanie Bauer at the Institute of Pharmacy, University of Regensburg.

2.1 Introduction

The Breast Cancer Resistance Protein (BCRP, ABCG2), identified simultaneously by Doyle et al.[1] Allikmets et al.[2] and Miyake et al.[3] is a member of the ABC transporter superfamily.[4] The overexpression of this transporter is associated with the multidrug resistance phenomena which is one of the causes for failure in cancer chemotherapy.[4]

As well as the P-glycoprotein, the most known and studied ABC transporter, ABCG2 has caught the attention of different research groups around the globe and several efforts have been focused on understanding the structure and function of this transporter together with its substrates. It is known that ABCG2 is a 72-kDa protein composed of 665 amino acids. It has an N-terminal ATP-binding domain (or nucleotide binding fold, NBF) and a C-terminal transmembrane domain (TMD), a structure half the size and in reverse configuration to most other ABC proteins comprising two NBFs and two TMDs.[5,6] Like the other ABC transporters, ABCG2 uses the energy of ATP-hydrolysis to transport substrates across the cell membrane. However, little is known about its transport mechanism, in particular, how it recognizes and transports a broad variety of structurally and chemically unrelated compounds, including anti-cancer drugs, thus conferring drug resistance to cancer cells.

One approach to overcome BCRP mediated drug resistance involves the use of potent inhibitors of this transporter such as fumitremorgin C and its analogues Ko134 and Ko143,[7-9] novobiocin,[10] camptothecins derivatives,[11] flavonoids,[12,13] Elacridar[10] and Tariquidar and its analogues,[14,15] some anti-HIV drugs,[16] and some tyrosine kinase inhibitors[17,18] (Fig 1).

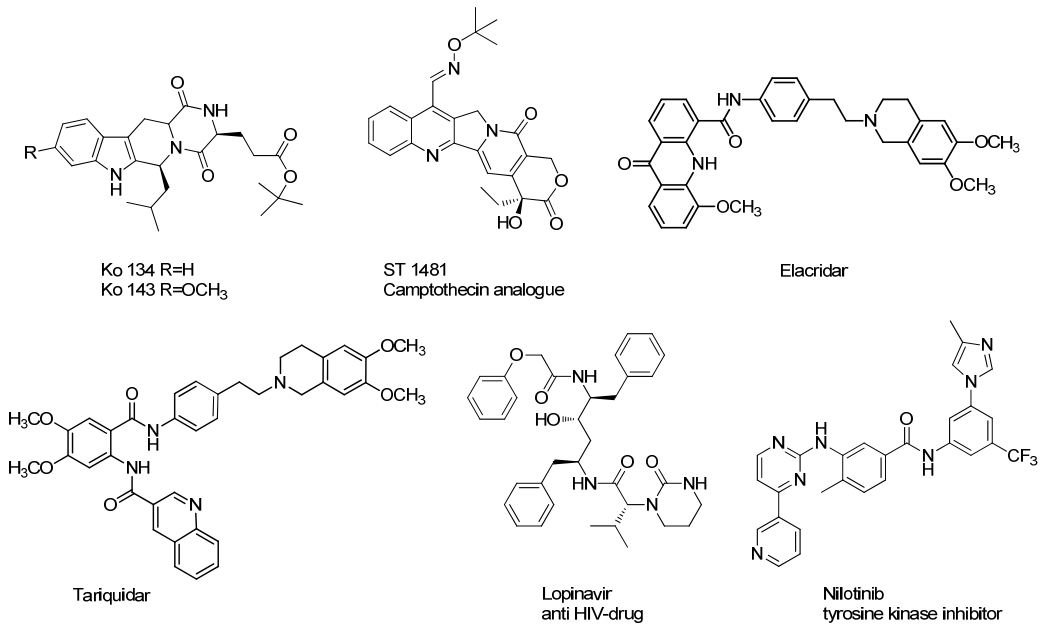


Figure 1. Structures of the main ABCG2 inhibitors.

Recently, we described the synthesis of a new class of potent and selective ABCG2 inhibitors derived from tariquidar (Figure 2).[19,20] Compound **1**, in which at the benzamide core, the hetarylcarboxamido residue was shifted to the meta-position and the two methoxy groups were replaced with a carboxylic acid methyl ester showed an IC_{50} value in the nanomolar range (59 ± 11) and a maximal inhibitory effect of 63% (Hoechst 33342 assay).[21] Interestingly, when a methoxy group on the tetrahydroisoquinoline core was replaced by a triethylenglycol chain an increase in potency was observed (IC_{50} 130 ± 29, I_{max}. 88%). Compound **2** is among the most potent and selective ABCG2 modulator reported so far.

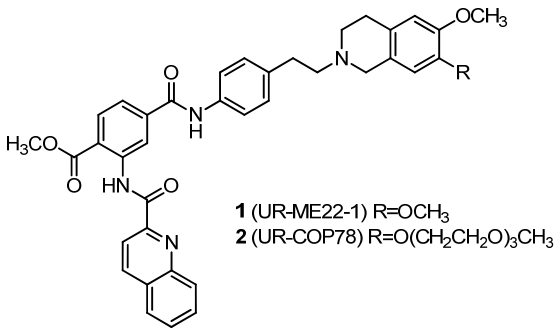


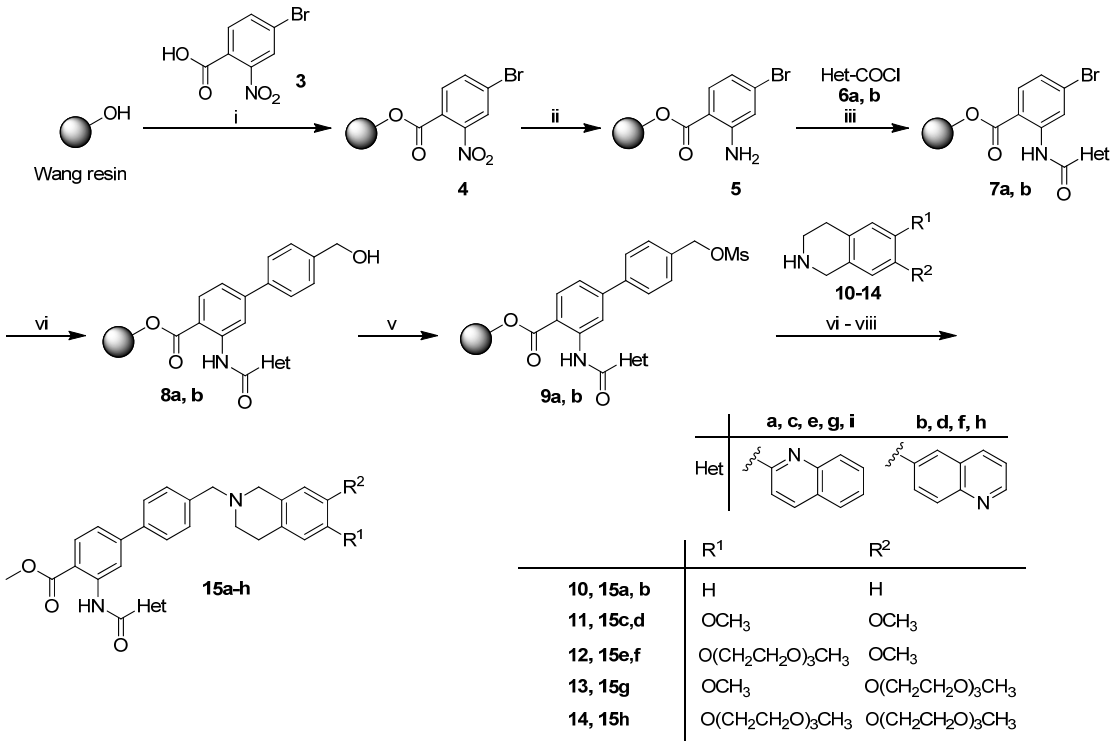
Figure 2. Structure of selective and potent ABCG2 inhibitors.

Although compounds **1** and **2** are potent and selective ABCG2 inhibitors, stability test performed in mouse plasma revealed that these compounds are hydrolyzed at the amide bond bearing the phenethyl tetrahydroisoquinoline fragment.[21] Unfortunately, these results showed that the reported compounds lack drug-like properties. Encouraged by these results we decided to design and synthesize a new class of more stable and better soluble derivatives. Our design is based on a two aryl fragment connection, by a C-C bond, as alternative to have compounds enzimatically more stable. In addition, and based in our previous experience,[20] we developed a solid phase synthesis protocol as a good alternative to have a small library of these derivatives.

2.2 Results and Discussion

As shown in Scheme 1, Wang resing was selected as solid support and 4-bromo-2-nitrobenzoic acid **3**, was attached to the resin using EDC·HCl. Reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ and acylation with quinoline-2 or quinoline-6-carbonyl chloride **6a,b** (freshly prepared) led to the resin bound amides **7a,b**. In the next step the biphenyl system was constructed by Suzuki coupling between **7a,b** and commercially available 4-(hydroxymethyl)benzeneboronic acid. Biphenyl derivatives **8a,b** were mesylated at the hydroxy group and substituted by the tetrahydroisoquinolines **10**-**14**. Compound **14** was synthesized in similar manner than **12**[20] from 1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrobromide. Finally, cleavage of the resin with

TFA/DCM (1:1) and transformation of the obtained carboxylic acids into the methyl esters with trimethylsilyldiazomethane ($TMSCHN_2$) led to the desired biphenyl tariquidar analogues **15a-h**.

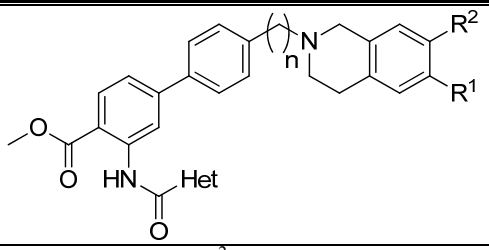


Scheme 1. SPS of tariquidar derivatives. Reagents and conditions: (i) 4-bromo-2-nitrobenzoic acid **3**, EDC·HCl, DMAP, DMF/DCM 1/1, rt, overnight; (ii) $SnCl_2 \cdot 2H_2O$, DMF, 80 °C, overnight; (iii) quinolinecarbonyl chlorides **6a, b**, DIPEA, DCM, rt, 12 h (twice); (iv) 4-(hydroxymethyl)benzeneboronic acid, $Pd(PPh_3)_4$, K_3PO_4, DME, 80 °C, 21 h; (v) MsCl, DIPEA, DCM, rt, 6 h; (vi) tetrahydroisoquinolines **10** - **14**, THF, 80 °C, 21 h; (vii) TFA/DCM (1:1), rt, 30 min (twice); (viii) $TMSCHN_2$, PhH/MeOH (1:1), rt, 1 h.

As shown in Table 1, a set of 8 tariquidar analogues was obtained in low to acceptable overall yields, mainly due to incomplete coupling between **7a, b** and the boronic acid as confirmed by analysis of by-products by NMR. All analogues bearing a tetrahydroisoquinoline with a triethylenglycol chain showed increased hydrophilic character and better solubility.

ABCB1 and ABCG2 inhibitory activity of compounds **15a-h**, as well as the reference compounds tariquidar and elacridar were investigated in a calcein-AM (ABCB1)[22] and a Hoechst 33342 (ABCG2) microplate assay[21] using ABCB1-overexpressing Kb-V1 and ABCG2-overexpressing MCF-7/Topo cells. The data are summarized in Table 2.

Table 1. Biphenyl tariquidar derivatives synthesized by SPS and in solution.



Compound	n	R^1	R^2	Het.	Yield (%)
15a	1	H	H	2-Quinol.	51[a]
15b	1	H	H	6-Quinol.	27[a]
15c	1	OCH_3	OCH_3	2-Quinol.	40[a]
15d	1	OCH_3	OCH_3	6-Quinol.	23[a]
15e	1	$O(CH_2CH_2O)_3CH_3$	OCH_3	2-Quinol.	44[a]
15f	1	$O(CH_2CH_2O)_3CH_3$	OCH_3	6-Quinol.	23[a]
15g	1	OCH_3	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	40[a]
15h	1	$O(CH_2CH_2O)_3CH_3$	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	41[a]
20a	2	H	H	2-Quinol.	14[b]
20b	2	OCH_3	OCH_3	2-Quinol.	17[b]
20c	2	OCH_3	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	12[b]
20d	2	$O(CH_2CH_2O)_3CH_3$	$O(CH_2CH_2O)_3CH_3$	2-Quinol.	4[b]

[a] Overall yield based on the loading of the resin.

[b] Overall yield for compounds synthesized in solution.

Table 2. Inhibition of ABC transporters by reference compounds and the tariquidar analogues **15a**–**i**, **20a**–**d** determined in the calcein-AM (ABCB1) and Hoechst 33342 (ABCG2) microplate assay unless otherwise indicated

Compd.	ABCB1	ABCG2	
	IC_{50} (nM)	IC_{50} (nM)	I_{max}[a] (%)
Tariquidar	223 ± 8	526 ± 85	69[c]
Elacridar	193 ± 18	127 ± 41	63[c]
Ko143	Inactive[b]	117 ± 53	103 ± 7[c]
2	>50000	130 ± 29	88[d]
15a	n.d.	1460	85
15b	4490	655	94
15c	n.d.	943 ± 79	87
15d	10900 ± 1700	1540 ± 110	92
15e	n.d	1030 ± 139	114
15f	18000 ± 1560	237 ± 65	67
15g	1230 ± 105	591 ± 87	109
15h	n.d.	913 ± 144	101
20a	>100000	1100	90
20b	>150000	3215± 490	126
20c	5420 ± 230	760	98
20d	5990 ± 1220	581 ± 80	99

[a] Relative to Fumitremorgin C (100%). [b] 1.6% inhibition at 10 μM. [c] ref 21. [d] ref 20. n.d. = not determined

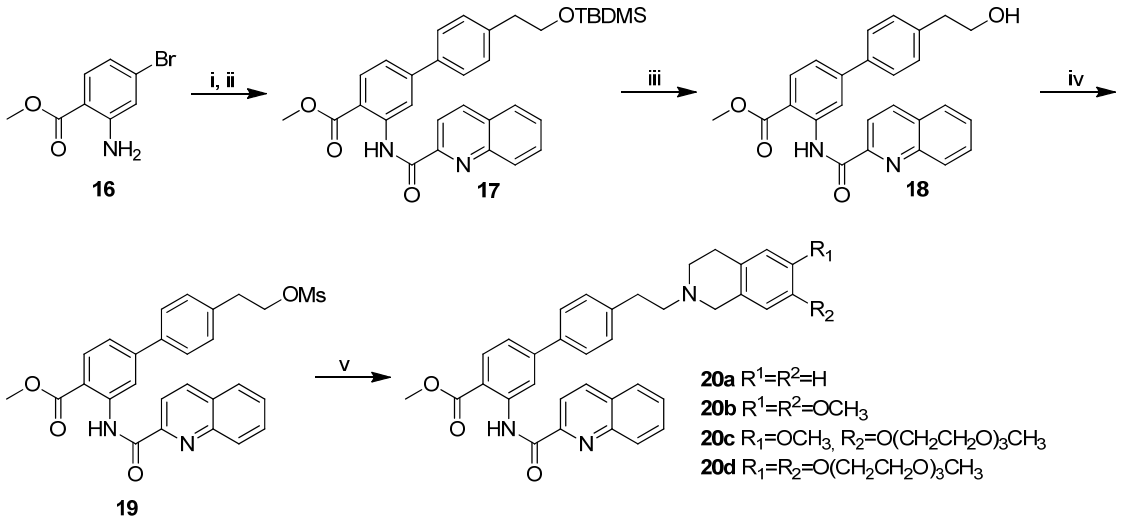
Elacridar strongly inhibits both transporters without a preference to one of the two targets, whereas tariquidar was about equipotent with elacridar at ABCB1 but about four times less potent at ABCG2. The most potent ABCG2 inhibitor reported so far, **Ko143**,[9] is inactive at

ABCB1 transporter and has an IC_{50} of 117 nM ± 53 with a maximal inhibitory effect of 103 nM ± 7, relative to fumitremorgin C.

Compounds **15b**, **15d**, **15f** and **15g** are inactive at ABCB1 transporter, were as compounds **15b**, **15c**, **15f**, **15g** and **15h** showed values in the nanomolar range for ABCG2 inhibition and are approximately 5, 7.5, 2, 5 and 7.2 fold higher than elacridar, the reference compound **2** and **Ko143**. However, **15b**, **15g** and **15h** are superior to elacridar and **2** with respect to the maximal inhibitory effect: 94%, 109% and 101% versus 66% and 88%, being **15g** and **15h** as efficient as **Ko143** (Figure 3). Compound **15g** which is the best in this series also has an IC_{50} value comparable with tariquidar, but its efficience is higher at ABCG2 inhibition (109% vs 69%).

In order to have a diverse library of compounds, we decided to synthesize a second series of derivatives leaving the methyl ester and the quinoline-2-carboxamido substituents in the structure which is a characteristic of the best inhibitors we have reported before including compound **15g**.[19,20]

Compounds **20a-d**, in which the length of the linker between the tetrahydroisoquinoline moiety and the biphenyl motif was modified by adding a second methylene group, were synthesized in solution in similar fashion starting from methyl 2-amino-4-bromobenzoate **16** and (4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)boronic acid[23] (Scheme 2, Table 1).



Scheme 2. Solution synthesis of tariquidar analogues. Reagents and conditions: (i) methyl 2-amino-4-bromobenzoate **15**, (4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)boronic acid, $Pd(PPh_3)_4$, K_3PO_4, THF, 80 °C, 15 h; (iii) quinoline-2-carbonyl chloride **6a**, TEA, DCM, 40 °C, overnight; (iv) TBAF, THF, rt, 3 h; (iv) MsCl, TEA, DCM, rt, 5 h; (v) tetrahydroisoquinolines **10**, **11**, **13** and **14**, CH_3CN, 80 °C, overnight.

As shown in table 2, compounds **20a-d** are also selective for the inhibition of the ABCG2 transporter, but the insertion of an additional methylene group in the linker did not lead to a

more potent compound when compared to analogue **15g.** These results suggest that the distance between the tetrahydroisoquinoline core and the biaryl moiety may influence the inhibitory activity of this class of analogues. Compounds **20c** and **20d** have higher IC_{50} values compared with all the reference compounds, but with respect to the maximal inhibitory effect, these compounds are superior to tariquidar, elaquidar and **2**, and are comparable to **Ko143** (Figure 3). Here is noteworthy to mention that the addition of one or two triethylen glycol chains at the tetrahydroisoquinoline core of the synthesized derivatives having a quinoline-2-carboxamido moiety increases the inhibitory activity over the transporter (compounds **15g**, **15h**, **20c** and **20d**).

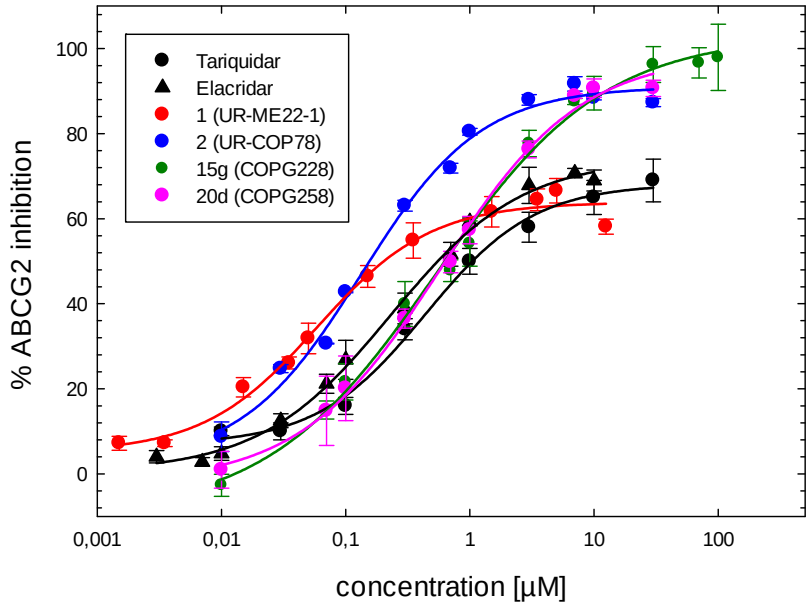


Figure 3. Concentration dependent inhibition of the ABCG2 transporter in MCF-7/Topo cells (Hoechst 33342 assay) by tariquidar (filled black circles), elacridar (filled black triangles) and the tariquidar analogues **1** (UR-ME22-1; filled red circles), **2** (UR-COP78; filled blue circles), **15g** (COPG228; filled green circles) and **20d** (COPG258; filled pink circles). The maximal inhibition is expressed as % relative to the maximum inhibition of ABCG2 by fumitremorgin C (at a concentration of 10 µM).

With respect to future *in vivo* studies, compound **15g** was selected to evaluate its stability under physiological conditions.[21] The stability test, performed in mouse plasma, revealed that this compound is more stable than compound **2**, which is completely decomposed after 15 min (data not shown). Enzymatic degradation of the new compound started after 30 min, and after 24h around 60% of the compound still remains. HPLC/MS analysis showed that the methyl ester of the anthranilic ring is hydrolyzed affording the corresponding carboxylic acid derivative which

is not active in the inhibition of the ABCG2. This result shows that compound **15g** might be used to perform further studies *in vivo*.

2.3 Conclusion

In conclusion, the solid phase synthesis herein presented is a straightforward method to conveniently obtain a small library of biaryl tariquidar related derivatives. A second set of compounds was also synthesized in solution following a similar procedure for the compounds obtained on solid phase. Compound **15g**, which is the most active tariquidar analogue here obtained with a selective inhibitory activity over ABCG2, has a higher IC_{50} value compared to the most active inhibitor reported K**o143** (590 nM vs 117 nM ± 53), but has about the same maximal inhibitory effect (109% vs 103% ± 7 relative to fumitremorgin C). The structural characteristics of the compounds obtained here together with their activities and the improved stability may lead to a new class of active and more stable tariquidar derivatives.

2.4 Experimental Section

General. Wang resin was purchased from Fluka (100-200 mesh, 1.1 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from either Aldrich, Acros, Merck, or Fluka and used without further purification. Manual solid-phase organic syntheses were carried out at 25 °C in polypropylene syringes equipped with a porous polypropylene disk at the bottom (purchased from Roland Vetter Laborbedarf OHG). Solid phase reaction at higher temperature was carried out in an eppendorf tube with a microcentifuge tube holder. Flash column chromatograph was performed with silica gel (Merck silica gel 60M 40-63 μm); products were detected by TLC on alumina plates coated with silica gel (Merck silica gel 60 F254, thickness 0.2 mm) and visualized by UV light (λ) 254 nm). Melting points were determined with an OptiMelt MPA100 and are uncorrected. NMR spectra were measured at 298 K on a Bruker Avance 300 or Bruker Avance 600 instruments. Chemical shifts are reported in δ (ppm) relative to external standards and coupling constants J are given in Hz. Abbreviations for the characterization of the signals: s) singlet, d) doublet, t) triplet, m) multiplet, bs) broad singlet, dd) double doublet. The relative numbers of protons is determined by integration. Mass spectra were recorded with Finnigan MAT TSQ 7000 (ESI) and Finnigan MAT 90 (HRMS), IR spectra with a Bio- Rad FT-IR-FTS 155 spectrometer.

General procedure for SPS of tariquidar analogues 15. A polypropylene 5.0-ml fritted syringe was charged with 200 mg of Wang resin (0.9 mmol/g loading) and the resin was swollen in 3 mL of DCM/DMF (4/1) during 1 h. A mixture of 4-bromo-2-nitrobenzoic acid

(0.45 mmol, 2.5 equiv) and EDC·HCl (0.45 mmol, 2.5 equiv) in 2 mL of DCM/DMF (4/1) was added, the resin was cooled down and shaken for 5 min. then, DMAP (20% mol) was added and the resin was shaken at room temperature overnight. After washing the resin with DMF, MeOH and DCM (3X each), $SnCl_2 \cdot 2H_2O$ (1.8 mmol, 10 equiv) in DMF was added and the resin was heated at 80 °C overnight, then the resin was washed again with the same solvents and swollen in dry DCM. Quinoline-2(6)-carbonyl chloride (freshly prepared 0.9 mmol, 5 equiv) and DIPEA (0.9 mmol, 5 equiv) were added and the resin was shaken at room temperature during 12 h and washed three times with DCM, MeOH, DMF, MeOH and DMF (this coupling step was repeated). DME was added and the resin was swollen during 1 h. 4-(Hydroxymethyl)benzeneboronic acid (0.54 mmol, 3 equiv), $Pd(PPh_3)_4$ (5% mol), and K_3PO_4, (2 M sln. 0.54 mmol, 3 equiv) were added and the resin was heated at 80 °C during 21 h, then several washes with DMF, MeOH and DCM were done. Dry DCM was added and the resin was cooled down, then mesyl chloride (0.9 mmol, 5 equiv) and DIPEA (0.45 mmol, 2.5 equiv) were added and the resin was shaken at room temperature for 6 h. After several washes with DCM and THF, the resin was swollen in dry THF and the tetrahydroisoquinoline derivative (0.9 mmol, 5 equiv) was added, after this, the resin was heated at 70 °C during 21 h. Finally, the resin was washed with DMF, MeOH and DCM and dry under vacuum.

Cleavage. The resin was dried under vacuum and a mixture of TFA/DCM 1/1 was added (3 ml) and the resin was shaken for 30 min., the cleavage cocktail was collected and the content of the syringe was washed 2 times with fresh 50% TFA in DCM (this procedure was repeated). Combined washes were evaporated and residual oil was washed with fresh diethylether, the precipitated solid was filtered and dried.

Esterification. The carboxylic acid derivative (1 equiv) was dissolved in 3 mL of a mixture PhH/MeOH 2/1 and trimethylsilyldiazomethane solution (2 M in diethyl ether) was added dropwise until no evolution of N_2 was observed. The reaction was stirred during 1 h at room temperature. The solvent was evaporated and the solid was purified by flash chromatography ($CHCl_3$/MeOH 95/5).

Methyl 4'-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15a.

Yield 51%, yellow solid, R_f = 0.25 ($CHCl_3$/MeOH 95/5), **mp.** 154-156 °C dec. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 13.33 (s 1H, NHCO), 9.37 (d, ^4J=1.6 Hz, 1H, ArH), 8.41-8.33 (m, 3H, ArH), 8.16 (d, ^3J=8.2 Hz, 1H, ArH), 7.89 (d, ^3J=7.9 Hz, 1H, ArH), 7.82 (dt, ^4J=1.1 Hz, ^3J=8.2 Hz, 1H, ArH), 7.71 (d, ^3J=8.1 Hz, 2H, ArH), 7.65 (t, ^3J=7.4 Hz, 1H, ArH), 7.49 (d, ^3J=8.1 Hz,

2H, ArH), 7.39 (dd, ^4J=1.8 Hz, ^3J=8.3 Hz, 1H, ArH), 7.12-7.10 (m, 3H, ArH), 7.01-6.99 (m, 1H, ArH), 4.07 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 3.68 (s, 2H, CH_2), 2.92 (t, ^3J=5.7 Hz, 2H, CH_2), 2.78 (t, ^3J=5.6 Hz, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ: 167.9 (C=O), 163.7 (C=O), 150.1 (Cquat.), 146.7 (Cquat.), 146.6 (Cquat.), 141.2 (Cquat.), 138.8 (Cquat.), 138.6 (Cquat.), 137.7 (+), 134.8 (Cquat.), 134.4 (Cquat.), 131.7 (+), 130.3 (+), 130.2 (+), 129.6 (+), 129.4 (Cquat.), 128.7 (+), 128.2 (+), 127.6 (+.), 127.4 (+), 126.6 (+), 126.1 (+), 125.6 (+), 121.3 (+), 119.0 (+), 118.9 (+), 115.1 (Cquat.), 62.4 (-), 56.1 (-), 52.4 (+), 50.6 (-), 29.1 (-). **HRMS** (EI-MS) calcd. for $C_{34}H_{29}N_3O_3$ [$M^{\bullet+}$]: 527.2209; found: 527.2202. **IR** (KBr) [cm^{-1}]: ν = 2958, 1681, 1550, 1500.

Methyl 4'-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-6-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15b.

Yield 27%, yellow solid, R_f = 0.47 ($CHCl_3$/MeOH 95/5), **mp.** 100-102 °C dec. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ= 12.40 (s, 1H, NHCO), 9.36 (d, ^4J=1.6 Hz, 1H, ArH), 9.06 (dd, ^4J=1.6 Hz, ^3J=4.2 Hz, 1H, ArH), 8.65 (d, ^4J=1.8 Hz, 1H, ArH), 8.44-8.38 (m, 2H, ArH), 8.29 (d, ^3J=8.8 Hz, 1H, ArH), 8.20 (d, ^3J=8.3 Hz, 1H, ArH), 7.75 (d, ^3J=8.1 Hz, 2H, ArH), 7.54 (d, ^3J=8.1 Hz, 2H, ArH), 7.53 (d, ^3J=8.2 Hz, 1H, ArH), 7.45 (dd, ^4J=1.8 Hz, ^3J=8.3 Hz, 1H, ArH), 7.17-7.15 (m, 3H, ArH), 7.06-7.04 (m, 1H, ArH), 4.06 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2), 3.73 (s, 2H, CH_2), 2.96 (t, ^3J=5.7 Hz, 2H, CH_2), 2.81 (t, ^3J=5.6 Hz, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ: 169.1 (C=O), 165.1 (C=O), 152.2 (+), 149.6 (Cquat.), 147.3 (Cquat.), 142.1 (Cquat.), 138.8 (Cquat.), 138.5 (Cquat.), 137.4 (+), 134.7 (Cquat.), 134.3 (Cquat.), 132.7 (Cquat.), 131.5 (+), 130.3 (+), 129.6 (+), 128.7 (+), 128.4 (+), 127.7 (Cquat.), 127.4 (+), 127.2 (+), 126.6 (+), 126.1 (+), 125.6 (+), 121.9 (+), 121.3 (+), 118.8 (+), 113.8 (Cquat.), 62.3 (-), 56.1 (-), 52.6 (+), 50.6 (-), 29.0 (-). **HRMS** (EI-MS) calcd. for $C_{34}H_{29}N_3O_3$ [$M^{\bullet+}$]: 527.2209; found: 527.2198. **IR** (KBr) [cm^{-1}]: ν = 2966, 1674, 1566, 1500.

Methyl 4'-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15c.

Yield 40%, yellow solid, R_f = 0.28 ($CHCl_3$/MeOH 95/5), **mp.** 162-164 °C dec. **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 13.33 (s, 1H, NHCO), 9.36 (d, ^4J=1.7 Hz, 1H, ArH), 8.40-8.38 (m, 2H, ArH), 8.35 (d, ^3J=8.4 Hz, 1H, ArH), 8.17 (d, ^3J=8.2 Hz, 1H, ArH), 7.90 (dd, ^4J=0.6 Hz, ^3J=8.1 Hz, 1H, ArH), 7.84-7.81 (m, 1H, ArH), 7.72 (d, ^3J=8.1 Hz, 2H, ArH), 7.67-7.64 (m, 1H, ArH), 7.50 (d, ^3J=8.1 Hz, 2H, ArH), 7.40 (dd, ^4J=1.8 Hz, ^3J=8.2 Hz, 1H, ArH), 6.61 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.74 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 2.84 (t, ^3J=5.7 Hz, 2H, CH_2), 2.71 (t, ^3J=5.9 Hz, 2H, CH_2). **^{13}C-NMR**

($CDCl_3$, 151 MHz) δ: 167.9 (C=O), 163.7 (C=O), 150.1 (Cquat.), 147.5 (Cquat.), 147.2 (Cquat.), 146.7 (Cquat.), 146.6 (Cquat.) 141.2 (Cquat.), 138.7 (Cquat.), 138.6 (Cquat.), 137.6 (+), 131.7 (+), 130.2 (+), 130.1 (+), 129.6 (+), 129.3 (Cquat.), 128.2 (+), 127.6 (+.), 127.3 (+), 126.6 (Cquat.), 126.1 (Cquat.), 121.3 (+), 119.0 (+), 118.8 (+), 115.1 (Cquat.), 114.4 (+), 109.5 (+), 62.3 (-), 55.9 (+), 55.9 (+), 55.6 (-), 52.3 (+), 50.8 (-), 28.6 (-). **HRMS** (EI-MS) calcd. for $C_{36}H_{33}N_3O_5$ [$M^{\bullet+}$]: 587.2420; found: 587.2407. **IR** (KBr) [cm^{-1}]: ν = 2962, 1681, 1608, 1516.

Methyl 4'-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-6-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15d.

Yield 23%, yellow solid, R_f = 0.54 ($CHCl_3$/MeOH 95/5), **mp.** 120-122 °C dec. **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 12.35 (s, 1H, NHCO), 9.31 (d, ^4J=1.8 Hz, 1H, ArH), 9.01 (dd, ^4J=1.6 Hz, ^3J=4.1 Hz, 1H, ArH), 8.60 (d, ^4J=1.9 Hz, 1H, ArH), 8.35 (dt, ^4J=2.1 Hz, ^3J=8.8 Hz, 2H, ArH), 8.25 (d, ^3J=8.8 Hz, 1H, ArH), 8.16 (d, ^3J=8.3 Hz, 1H, ArH), 7.71 (d, ^3J=8.1 Hz, 2H, ArH), 7.55-7.49 (m, 3H, ArH), 7.40 (dd, ^4J=1.8 Hz, ^3J=8.2 Hz, 1H, ArH), 6.61 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.01 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 3.59 (s, 2H, CH_2), 2.84 (t, ^3J=5.7 Hz, 2H, CH_2), 2.77 (t, ^3J=5.6 Hz, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz) δ: 169.1 (C=O), 165.0 (C=O), 152.2 (+), 149.5 (Cquat.), 147.5 (Cquat.), 1447.3 (Cquat.), 147.2 (Cquat.), 142.1 (Cquat.), 138.5 (Cquat.), 137.4 (+), 132.7 (Cquat.), 131.4 (+), 130.2 (+), 129.6 (+), 128.4 (+), 127.7 (Cquat.), 127.4 (+), 127.2 (+), 126.5 (Cquat.), 126.1 (Cquat.), 121.9 (+), 121.3 (+), 118.8 (+), 115.4 (Cquat.), 113.8 (Cquat.), 111.4 (+),109.5 (+), 62.3 (-), 55.9 (+), 55.6 (-), 52.5 (+), 50.8 (-), 28.6 (-). **HRMS** (EI-MS) calcd. for $C_{36}H_{33}N_3O_5$ [$M^{\bullet+}$]: 587.2420; found: 587.2417. **IR** (KBr) [cm^{-1}]: ν = 2958, 1674, 1566, 1500.

Methyl 4'-((7-methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15e.

Yield 44%, sticky yellow oil, R_f = 0.35 ($CHCl_3$/MeOH 95/5). **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ= 13.33 (s, 1H, NHCO), 9.36 (d, ^4J=1.7 Hz, 1H, ArH), 8.39-8.33 (m, 3H, ArH), 8.15 (d, ^3J=8.2 Hz, 1H, ArH), 7.88 (d, ^3J=8.2 Hz, 1H, ArH), 7.82-7.80 (m, 1H, ArH), 7.71 (d, ^3J=8.1 Hz, 2H, ArH), 7.65-7.62 (m, 1H, ArH), 7.48 (d, ^3J=8.1 Hz, 2H, ArH), 7.39 (dd, ^4J=1.7 Hz, ^3J=8.2 Hz, 1H, ArH), 6.66 (s, 1H, ArH), 6.50 (s, 1H, ArH), 4.13 (t, ^3J=5.4 Hz, 2H, CH_2), 4.06 (s, 3H, OCH_3), 3.85 (t, ^3J=5.0 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.73-3.72 (m, 4H, 2 CH_2), 3.67-3.63 (m, 4H, 2 CH_2), 3.56 (s, 2H, CH_2), 3.54-3.53 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 2.81 (t, ^3J=5.6 Hz, 2H, CH_2), 2.74 (t, ^3J=5.5 Hz, 2H, CH_2). **^{13}C-NMR** ($CDCl_3$, 151 MHz) δ: 167.8 (C=O), 163.5 (C=O), 150.0 (Cquat.), 147.7 (Cquat.), 146.6 (Cquat.), 146.6 (Cquat.), 146.5 (Cquat.) 141.1 (Cquat.), 138.6 (Cquat.), 138.5 (Cquat.), 137.6 (+), 131.6 (+), 130.2 (+), 130.1 (+), 129.5

(+), 129.3 (Cquat.), 128.1 (+), 127.5 (+), 127.3 (+), 127.3 (Cquat.), 126.1 (Cquat.), 121.2 (+), 118.8 (+), 118.8 (+), 115.0 (Cquat.), 114.1 (+), 110.0 (+), 71.8 (-), 70.7 (-), 70.5 (-), 70.4 (-), 69.5 (-), 68.6 (-), 62.3 (-), 58.9 (+), 55.9 (+), 55.6 (-), 52.3 (+), 50.7 (-), 28.5 (-). **HRMS** (EI-MS) calcd. for $C_{42}H_{45}N_3O_8$ [$M^{\bullet+}$]: 719.3207; found: 719.3222. **IR** (KBr) [cm^{-1}]: ν = 2960, 2918, 1685, 1608, 1560, 1514.

Methyl 4'-((7-methoxy-6-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-6-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15f.

Yield 23%, sticky yellow oil, R_f = 0.25 ($CHCl_3$/MeOH 95/5). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 12.35 (s, 1H, NHCO), 9.31 (d, ^4J=1.7 Hz, 1H, ArH), 9.01 (dd, ^3J=4.2, ^4J=1.7 Hz, 1H, ArH), 8.59 (d, ^4J=1.9 Hz, 1H, ArH), 8.39-8.31 (m, 2H, ArH), 8.25 (d, ^3J=8.9 Hz, 1H, ArH), 8.15 (d, ^3J=8.4 Hz, 1H, ArH), 7.71 (d, ^3J=8.2 Hz, 2H, ArH), 7.49 (d, ^3J=8.2 Hz, 2H, ArH), 7.48 (d, J=8.2 Hz, 1H, ArH) 7.40 (dd, ^3J=8.4, ^4J=1.8 Hz, 1H, ArH), 6.67 (s, 1H, ArH), 6.50 (s, 1H, ArH), 4.14 (t, ^3J=5.3 Hz, 2H, CH_2), 4.00 (s, 3H, OCH_3), 3.86 (t, ^3J=5.3 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.76-3.71 (m, 4H, 2 CH_2), 3.69-3.63 (m, 4H, 2 CH_2), 3.59-3.52 (m, 4H, 2 CH_2), 3.37 (s, 3H, OCH_3), 2.82-2.76 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 168.1 (C=O), 164.0 (C=O), 151.2 (+), 148.6 (Cquat.), 146.8 (Cquat.), 146.2 (Cquat.), 145.7 (Cquat.), 141.1 (Cquat.), 137.9 (Cquat.), 137.4 (Cquat.), 136.3 (+), 131.6 (Cquat.), 130.4 (+), 129.3 (+), 128.6 (+), 127.4 (+), 126.7 (Cquat.), 126.3 (+), 126.1 (+), 125.1 (Cquat.), 120.9 (+), 120.2 (+), 117.7 (+), 113.1 (+), 112.7 (Cquat.), 109.0 (+), 70.9 (-), 69.7 (-), 69.6 (-), 69.5 (-), 68.6 (-), 67.6 (-), 61.3 (-), 58.0 (+), 54.9 (+), 54.6 (-), 51.5 (+), 49.8 (-), 27.5 (+). **HRMS** (EI-MS) calcd. for $C_{42}H_{45}N_3O_8$ [$M^{\bullet+}$]: 719.3207; found: 719.3211. **IR** (KBr) [cm^{-1}]: ν = 2931, 1672, 1612, 1566, 1514.

Methyl 4'-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15g.

Yield 40%, sticky yellow oil, R_f = 0.16 ($CHCl_3$/MeOH 95/5). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.31 (s, 1H, NHCO), 9.32 (d, ^4J=1.7 Hz, 1H, ArH), 8.34-8.29 (m, 3H, ArH), 8.14 (d, ^3J=8.3 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.82-7.75 (m, 1H, ArH), 7.68 (d, ^3J = 8.2 Hz, 2H, ArH), 7.65-7.58 (m, 1H, ArH), 7.46 (d, ^3J=8.2 Hz, 2H, ArH), 7.37 (dd, ^3J=8.3, ^4J=1.8 Hz, 1H, ArH), 6.56 (s, 1H, ArH), 6.52 (s, 1H, ArH), 4.08 (t, ^3J=5.2 Hz, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.83-3.75 (m, 5H, OCH_3, CH_2), 3.68 (m, 4H, 2 CH_2), 3.63-3.57 (m, 4H, 2 CH_2), 3.53 (s, 2H, CH_2), 3.48 (m, 2H, CH_2), 3.31 (s, 3H, OCH_3), 2.79 (m, 2H, CH_2), 2.71 (m, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz,) δ: 168.0 (C=O), 163.7 (C=O), 150.1 (Cquat.), 148.1 (Cquat.), 146.8 (Cquat.), 146.6 (Cquat.), 146.4 (Cquat.), 141.2 (Cquat.), 138.7 (Cquat.), 138.6 (Cquat.), 137.7 (+), 131.7

(+), 130.3 (+), 130.2 (+), 129.6 (+), 129.4 (Cquat.), 128.2 (+), 127.6 (+), 127.4 (+), 126.9 (Cquat.), 126.7 (Cquat.), 121.3 (+), 119.0 (+), 118.9 (+), 115.1 (Cquat.), 112.2 (+), 112.0 (+), 71.96 (-), 70.86 (-), 70.66 (-), 70.56 (-), 69.66 (-), 68.66 (-), 62.36 (-), 59.0 (+), 56.0 (+), 55.76 (-), 52.4 (+), 50.76 (-), 28.76 (-). **HRMS** (EI-MS) calcd. for $C_{42}H_{45}N_3NaO_8$ $[M+Na]^+$: 742.3099; found: 742.3107. **IR** (KBr) [cm^{-1}]: ν = 2926, 1612, 1517.

Methyl 4'-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 15h.

Yield 41%, sticky light yellow oil, R_f = 0.3 (DCM/MeOH 100/1). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.31 (s, 1H, NHCO), 9.35 (d, ^4J=1.6 Hz, 1H, ArH), 8.39-8.29 (m, 3H, ArH), 8.14 (d, ^3J=8.3 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.83-7.76 (m, 1H, ArH), 7.70 (d, ^3J=8.2 Hz, 2H, ArH), 7.65-7.58 (m, 1H, ArH), 7.47 (d, ^3J=8.1 Hz, 2H, ArH), 7.38 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 6.65 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.12-4.07 (m, 4H, 2 CH_2), 4.04 (s, 3H, OCH_3), 3.81 (dd, ^3J=9.9, ^4J=4.7 Hz, 4H, 2 CH_2), 3.75-3.69 (m, 6H, 3 CH_2), 3.67-3.60 (m, 8H, 4 CH_2), 3.55-3.49 (m, 6H, 3 CH_2), 3.36 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.80-2.72 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 167.9 (C=O), 163.6 (C=O), 150.1 (Cquat.), 147.4 (Cquat.), 147.1 (Cquat.), 146.7 (Cquat.), 146.6 (Cquat.), 141.2 (Cquat.), 138.8 (Cquat.), 138.6 (Cquat.), 137.6 (+), 131.7 (+), 130.2 (+), 130.2 (+), 129.6 (+), 129.3, 128.2 (+), 127.7, 127.6 (+), 127.3 (+), 127.2, 121.3 (+), 118.9 (+), 118.8 (+), 115.1 (+), 115.0 (Cquat.), 113.2 (+), 71.9 (-), 70.7 (-), 70.6 (-), 70.5 (-), 69.7 (-), 69.7 (-), 69.0 (-), 62.4 (-), 59.0 (+), 55.7 (-), 52.4 (+), 50.7 (-), 28.7 (-). **HRMS** (EI-MS) calcd. for $C_{48}H_{58}N_3O_{11}$ $[M+H]^+$: 852.4066; found: 852.4072. **IR** (KBr) [cm^{-1}]: ν = 2875, 1685, 1500.

Methyl 4'-(2-hydroxyethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 18.

A mixture of methyl 2-amino-4-bromobenzoate **16** (3.24 g, 14.1 mmol), (4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)boronic acid (3.95 g, 14.1 mmol), $Pd(PPh_3)_4$ (808 mg, 0.7 mmol, 5%mol) and K_3PO_4 (7.0 mL 2M solution, 14.1 mmol) in 25 mL of THF was stirred and heated at 80 ^oC for 15h. The solvent was evaporated and DCM was added. After washing with brine, the organic layer was separated and dried over $MgSO_4$. The compound was purified by flash chromatograpy (PE:AcOEt 10:1) and the fraction containing the product (3.7 g) was collected and used for the next step. Quinoline-2-carbonyl chloride (1.83 g, 9.59 mmol) was added to a mixture of the biaryl derivative above obtained (3.7 g) and TEA (4.01 mL, 28.7 mmol) in dry DCM. The mixture was heated at 40 ^oC and stirred overnight. 1N HCl was added and the organic phase separated, washed with 1N $NaHCO_3$ and dried over $MgSO_4$. The compound was purified by flash chromatograpy (PE:AcOEt 10:1) and the fraction containing

the product (4.07 g) was collected and used for the next step. TBAF (1.8 mL 1M solution in THF) was added to a cold solution of **17** (1.0 g) in 5 mL THF and the mixture was stirred at rt for 3 h. The solvent was evaporated, saturated NH_4Cl was added and the compound extracted with DCM. The compound was purified by flash chromatograpy (PE:AcOEt 1.5:1, R_f = 0.20). Yield 27.2% over three steps, white solid, **mp.** 188-190 °C dec. **^{1}H NMR** (DMSO, 300 MHz): δ= 13.12 (s, 1H, NHCO), 9.23 (d, ^4J=1.8 Hz, 1H, ArH), 8.65 (d, ^3J=8.5 Hz, 1H, ArH), 8.29 (d, ^3J=8.5 Hz, 1H, ArH), 8.19 (d, ^3J=8.4 Hz, 1H, ArH), 8.14-8.08 (m, 2H, ArH), 7.98-7.91 (m, 1H, ArH), 7.81-7.75 (m, 1H, ArH), 7.67 (d, ^3J=8.2 Hz, 2H, ArH), 7.51 (dd, ^3J=8.4, ^4J=1.8 Hz, 1H, ArH), 7.40 (d, ^3J=8.2 Hz, 2H, ArH), 4.75 (t, ^3J=5.2 Hz, 1H, OH), 4.02 (s, 3H, OCH_3), 3.72-3.66 (m, 2H, CH_2), 2.83 (t, ^3J=6.9 Hz, 2H, CH_2). **^{13}C NMR** (DMSO, 75 MHz) δ: 166.9 (C=O), 162.7 (C=O), 149.2 (Cquat.), 145.6 (Cquat.), 140.3 (Cquat.), 138.2 (+), 136.3 (Cquat.), 131.6 (+), 130.7 (+), 129.6 (+), 129.2 (+), 128.9 (Cquat.), 128.4 (+), 128.0 (+), 126.5 (+), 121.0 (+), 118.3 (+), 117.4 (+), 114.5 (Cquat.), 61.9 (-), 52.4 (+), 38.5 (-). **HRMS** (EI-MS) calcd. for $C_{26}H_{23}N_2O_4$ $[M+H]^+$: 427.1652; found: 427.1662. **IR** (KBr) [cm^{-1}]: ν = 3331, 3221, 2947, 1689, 1500, 1247.

Methyl 4'-(2-((methylsulfonyl)oxy)ethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 19.

To a cold mixture of **18** (150 mg, 0.35 mmol) and TEA (0.12 mL, 0.7 mmol) in dry DCM, mesyl chloride (40.8 μL, 0.52 mmol) was added dropwise. The mixture was stirred at rt for 5h, saturated $NaHCO_3$ solution was added and the organic layer was separated and dried over $MgSO_4$. The compound was purified by flash chromatograpy (PE:AcOEt 1.5:1, R_f = 0.25). Yield 90%, white solid, **mp.** 184-186 °C dec. **^{1}H NMR** ($CDCl_3$, 300 MHz,): δ= 13.33 (s, 1H, NHCO), 9.35 (d, ^4J=1.7 Hz, 1H, ArH), 8.39-8.32 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 7.90 (d, ^3J=8.0 Hz, 1H, ArH), 7.86-7.79 (m, 1H, ArH), 7.72 (d, ^3J=8.2 Hz, 2H, ArH), 7.69-7.62 (m, 1H, ArH), 7.41-7.31 (m, 3H, ArH), 4.47 (t, ^3J=6.8 Hz, 2H, CH_2), 4.07 (s, 3H, OCH_3), 3.12 (t, ^3J=6.8 Hz, 2H, CH_2), 2.90 (s, 3H, OCH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.9 (C=O), 163.7 (C=O), 150.1 (Cquat.), 146.6 (Cquat.), 146.3 (Cquat.), 141.2 (Cquat.), 138.6 (Cquat.), 137.7 (+), 136.6 (Cquat.), 131.7 (+), 130.2 (+), 130.2 (+), 129.5 (+), 129.4 (Cquat.), 128.2 (+), 127.7 (+), 127.6 (+), 121.2 (+), 118.8 (+), 115.2 (Cquat.), 70.0 (-), 52.4 (+), 37.4 (+), 35.3 (-). **HRMS** (EI-MS) calcd. for $C_{27}H_{25}N_2O_6S$ $[M+H]^+$: 505.1428; found: 505.1442. **IR** (KBr) [cm^{-1}]: ν = 3026, 3221, 2929, 1697, 1672, 1500, 1251.

Methyl 4'-(2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 20a.

A mixture of **19** (700 mg, 1.38 mmol), 1,2,3,4-tetrahydroisoquinoline **10** (0.22 mL, 1.8 mmol) and DIPEA (0.48 mL, 2.76 mmol) in 25 mL of CH_3CN was refluxed overnight. The solvent was evaporated, water was added and the compound was extracted with DCM. After purification by flash chromatograpy ($CHCl_3$:MeOH 10:0.3, R_f = 0.23) 431 mg of a white solid was obtained. Yield 57%, **mp.** 98-100 °C dec. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 9.37 (d, ^4J=1.8 Hz, 1H, ArH), 8.37 (d, ^3J=8.4 Hz, 1H, ArH), 8.32 (d, ^3J=8.4 Hz, 1H, ArH), 8.28 (d, ^3J=8.4 Hz, 1H, ArH), 8.12 (d, ^3J=8.2 Hz, 1H, ArH), 7.83 (d, ^3J=8.1 Hz, 1H, ArH), 7.77 (t, ^3J=7.6 Hz, 1H, ArH), 7.69 (d, ^3J=8.1 Hz, 2H, ArH), 7.59 (t, ^3J=7.5 Hz, 1H, ArH), 7.36-7.33 (m, 3H, ArH), 7.16-7.10 (m, 3H, ArH), 7.06-7.04 (m, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 3.00-2.93 (m, 4H, 2 CH_2), 2.86-2.80 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.4 (C=O), 149.8 (Cquat.), 146.4 (Cquat.), 146.3 (Cquat.), 141.0 (Cquat.), 140.5 (Cquat.), 137.4 (+), 137.2 (Cquat.), 134.4 (Cquat.), 134.0 (Cquat.), 131.5 (+), 130.0 (+), 129.9 (+), 129.1 (+), 129.1 (Cquat.), 128.5 (+), 127.9 (+), 127.4 (+), 127.4, 127.2 (+), 126.4 (+), 126.0 (+), 125.4 (+), 120.9 (+), 118.6 (+), 118.5 (+), 114.7 (Cquat.), 59.8 (-), 55.8 (-), 52.1 (+), 50.7 (-), 33.4 (-), 28.9 (-). **HRMS** (EI-MS) calcd. for $C_{35}H_{31}N_3$ $[M+H]^+$: 542.2438; found: 542.2454. **IR** (KBr) [cm^{-1}]: ν = 2954, 1681, 1560, 1500, 1249.

Methyl 4'-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 20b.

Compound **20b** was obtained from compounds **19** and **11** following the same procedure described above. Yield 71%, white solid, **mp.** 126-128 °C dec., R_f = 0.25 ($CHCl_3$:MeOH 10:0.3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.33 (s, 1H, NHCO), 9.35 (d, ^4J=1.7 Hz, 1H, ArH), 8.41-8.33 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 7.90 (d, ^3J=8.1 Hz, 1H, ArH), 7.82 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.73-7.62 (m, 3H, ArH), 7.39 (dd, ^3J=8.4, ^4J=1.8 Hz, 1H, ArH), 7.35 (d, ^3J=8.2 Hz, 2H, ArH), 6.61 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.07 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2), 3.02-2.93 (m, 2H, CH_2), 2.89-2.77 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.8 (C=O), 163.6 (C=O), 150.0 (Cquat.), 147.5 (Cquat.), 147.2 (Cquat.), 146.6 (Cquat.), 146.5 (Cquat.), 141.1 (Cquat.), 140.6 (Cquat.), 137.6 (+), 137.5 (Cquat.), 131.6 (+), 130.2 (+), 130.1 (+), 129.3 (Cquat.), 129.2 (+), 128.1 (+), 127.5 (+), 127.4 (+), 126.2 (Cquat.), 126.0 (Cquat.), 121.1 (+), 118.8 (+), 118.7 (+), 114.9 (Cquat.), 111.3 (+), 109.4 (+), 59.8 (-), 55.8, 55.8, 55.5 (-), 52.3, 50.9 (-), 33.5 (-), 28.5 (-). **HRMS** (EI-MS) calcd. for $C_{37}H_{35}N_3NaO_5$ $[M+Na]^+$: 624.2469; found: 624.2472. **IR** (KBr) [cm^{-1}]: ν = 2953, 1678, 1560, 1502, 1251, 771, 750.

Methyl 4'-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 20c.

Compound **20c** was obtained from compounds **19** and **13** following the same procedure described above. Yield 48%, white solid, **mp.** 109-111 °C dec., R_f = 0.27 ($CHCl_3$:MeOH 10:0.3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.27 (s, 1H, NHCO), 9.32 (d, ^4J=1.7 Hz, 1H, ArH), 8.34-8.26 (m, 3H, ArH), 8.09 (d, ^3J=8.3 Hz, 1H, ArH), 7.82 (d, ^3J=8.2 Hz, 1H, ArH), 7.78-7.71 (m, 1H, ArH), 7.65 (d, ^3J=8.1 Hz, 2H, ArH), 7.60-7.53 (m, 1H, ArH), 7.36-7.27 (m, 3H, ArH), 6.58 (s, 1H, ArH), 6.57 (s, 1H, ArH), 4.12 (t, ^3J=5.2 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.83 (t, ^3J=4.9 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.73-3.69 (m, 2H, CH_2), 3.67-3.60 (m, 6H, 3 CH_2), 3.51 (dd, ^3J=5.9, ^3J=3.4 Hz, 2H, CH_2), 3.34 (s, 3H, OCH_3), 2.96-2.90 (m, 2H, CH_2), 2.86-2.72 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.8 (C=O), 163.6 (C=O), 150.0 (Cquat.), 148.2 (Cquat.), 146.6 (Cquat.), 146.5 (Cquat.), 146.4 (Cquat.), 141.1 (Cquat.), 140.7 (Cquat.), 137.6 (+), 137.4 (Cquat.), 131.7 (+), 130.2 (+), 130.1 (+), 129.3 (Cquat.), 129.2 (+), 128.2 (+), 127.6 (+), 127.4 (+), 126.8 (Cquat.), 126.4 (Cquat.), 121.1 (+), 118.8 (+), 118.7 (+), 114.9 (Cquat.), 112.3 (+), 111.9 (+), 71.9 (-), 70.7 (-), 70.6 (-), 70.5 (-), 69.6 (-), 68.7 (-), 59.9 (-), 59.0, 55.9, 55.6 (-), 52.3, 50.9 (-), 33.6 (-), 28.7 (-). **HRMS** (EI-MS) calcd. for $C_{43}H_{47}N_3NaO_8$ $[M+Na]^+$: 756.3255; found: 756.3258. **IR** (KBr) [cm^{-1}]: ν = 3296, 2922, 1689, 1560, 1502, 1251, 769.

Methyl 4'-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-3-(quinoline-2-carboxamido)-[1,1'-biphenyl]-4-carboxylate 20d.

Compound **20d** was obtained from compounds **19** and **14** following the same procedure described above. Yield 18%, sticky yellow oil solid, R_f = 0.25 ($CHCl_3$:MeOH 100:1). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.32 (s, 1H, NHCO), 9.35 (d, ^4J=1.8 Hz, 1H, ArH), 8.41-8.34 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 7.91 (d, ^3J=7.9 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.3, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.69 (d, ^3J=8.2 Hz, 2H, ArH), 7.67-7.64 (m, 1H, ArH), 7.40 (dd, ^3J=8.3, ^4J=1.8 Hz, 1H, ArH), 7.35 (d, ^3J=8.1 Hz, 2H, ArH), 6.66 (s, 1H, ArH), 6.61 (s, 1H, ArH), 4.15-4.11 (m, 4H, 2 CH_2), 4.07 (s, 3H, OCH_3), 3.86-3.82 (m, 4H, 2 CH_2), 3.74 (dd, ^3J=5.8, ^3J=3.8 Hz, 4H, 2 CH_2), 3.68-3.64 (m, 10H, 5 CH_2), 3.55 (dd, ^3J=5.6, ^3J=3.9 Hz, 4H, 2 CH_2), 3.37 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.99-2.95 (m, 2H, CH_2), 2.86-2.78 (m, 6H, 3 CH_2). **^{13}C NM**R ($CDCl_3$, 151 MHz) δ: 167.9, 163.6, 150.1, 147.5, 147.1, 146.7, 146.6, 141.1, 140.7, 137.6 (+), 137.5, 131.6, 130.2 (+), 130.1 (+), 129.3, 129.2 (+), 128.2 (+), 127.6 (+), 127.4 (+), 127.1, 121.2 (+), 118.8 (+), 118.8 (+), 115.0 (+), 115.0 (Cquat.), 113.3 (+), 71.9 (-), 70.7 (-), 70.6 (-), 70.5 (-), 69.7 (-), 69.0 (-), 68.9 (-), 60.0 (-), 59.0 (+), 55.6 (-), 52.3 (+), 50.9 (-), 33.6 (-), 28.6 (-).

HRMS (EI-MS) calcd. for $C_{49}H_{59}N_3O_{11}$ $[M]^{+2}$: 431.7069; found: 432.7075. **IR** (KBr) [cm^{-1}]: ν = 2872, 1683, 1502, 1103.

Modulation of ABCB1 and ABCG2 was performed as decribed.[20]

Stability Investigations in Mouse Plasma. Preparation of mouse plasma and determination of esterase activity: Blood of BL6 mice was collected by heart puncture in deep anesthesia using heparin-coated syringes. Samples were immediately centrifuged for 7 min at 7000 rpm (Eppendorf centrifuge 5415R, Eppendorf, Hamburg, Germany) and the supernatant was carefully removed. After pooling, the plasma was fractioned into small aliquots for long-term storage at -80 °C. The enzymatic activity of esterases in the plasma samples was measured spectrophotometrically. The coloured product *o*-nitrophenol, formed by enzymatic cleavage of the chromogenic substrate nitrophenyl butyrate was determined as a function of time. Absorbance was plotted against time, the linear slope at the beginning of the reaction was determined and used for the calculation of volume activity:

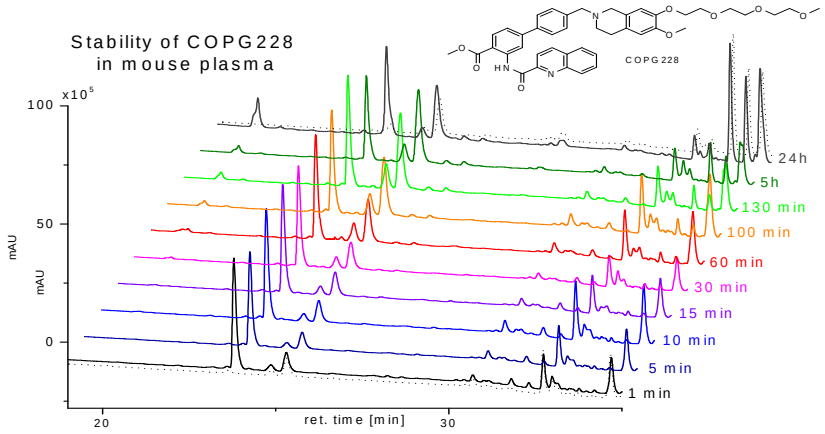
$$V_A = \frac{\frac{\Delta A \cdot V}{t}}{\varepsilon \cdot d \cdot \nu}$$

The abbreviations of the present equation define the following parameters: V_A=volume activity [$U \cdot mL^{-1}$] multiplied with 1000 for [$U \cdot L^{-1}$], ΔA=absorbance of *o*-nitrophenol at 414 nm, t=time [min], V=total volume [mL], $\varepsilon_{o\text{-nitrophenol}}$=3190 [$L \cdot mol^{-1} \cdot cm^{-1}$], d=path length [cm], ν=plasma volume [mL].

The test compounds were dissolved in DMSO at a concentration of 3 mM. Subsequently, test compound stocks, mouse plasma, deproteinated plasma, culture medium and phosphate buffered saline were equilibrated on a Wealtec heat plate (Wealtec, Sparks, USA) to 37 °C for approximately 15 min. Thereafter, a 1:50 dilution of the substances with the corresponding medium was prepared in 1.5-mL polypropylene reaction vessels (Eppendorf, Hamburg, Germany). The samples were shortly vortexed and immediately incubated at 37 °C. After increasing periods of time, aliquots were taken, and the reaction was stopped by the addition of two parts of ice-cold acetonitrile. For quantitative precipitation of the denatured proteins, the samples were efficiently vortexed and stored at 4 °C for 30 min. Finally, samples were centrifuged for 5 min at 17000 g, using an Eppendorf MiniSpin plus centrifuge, and the supernatants were transferred into new plastic cups. For HPLC analysis the samples were further diluted (1:2) with acetonitrile and stored at -80 °C until the measurement. For HPLC analysis samples were unfrozen at room temperature and injected into the HPLC system (Waters, Eschborn, Germany). Analysis was accomplished by gradient elution with water containing TFA (0.05 %) and acetonitrile (0 min, 15 %; 25 min, 80 %; 26 min, 95 %; 36 min,

95 %; 37 min, 15 %; 45 min, 15 %), at a constant flow rate of 1.0 mL/min. The HPLC system was equipped with a Luna RP-18 (2), 3 µm, 150 mm x 4.6 mm column. Analysis was carried out via UV-detection at a wavelength of 210 nm.

HPLC/MS analysis for the blank (mouse plasma, dotted lines) and for **15g** (COPG228, solid line) after mouse plasma stability test.



1.5 References

1. Doyle, L. A.; Yang, W.; Abruzzo, L. V.; Krogmann, T.; Gao, Y.; Rishi, A. K.; Ross, D. D. *Proc. Natl. Acad. Sci. USA* **1998,** *95*, 15665.
2. Allikmets, R.; Schriml, L. M.; Hutchinson, A.; Romano-Spica, V.; Dean, M. *Cancer Res.* **1998,** *58*, 5337.
3. Miyake, K.; Mickley, L.; Litman, T.; Zhan, Z.; Robey, R.; B. Cristensen; Brangi, M.; Greenberger, L.; Dean, M.; Fojo, T.; Bates, S. E. *Cancer Res.* **1999,** *59*, 8.
4. Han, B.; Zhang, J.-T. *Curr. Med. Chem. – Anti-Cancer Agents* **2004,** *4*, 31.
5. Robey, R. W.; To, K. K. K.; Polgar, O.; Dohse, M.; Fetsch, P.; Dean, M.; Bates, S. E. *Adv. Drug Delivery Rev.* **2009,** *61*, 3.
6. Ni, Z.; Bikadi, Z.; Rosenberg, M. F.; Mao, Q. *Curr. Drug. Metab.* **2010,** *11*, 603.
7. Rabindran, S. K.; Ross, D. D.; Doyle, L. A.; Yang, W.; Greenberger, L. M. *Cancer Res.* **2000,** *60*, 47.
8. Loevezijn, A. v.; Allen, J. D.; Schinkel, A. H.; Koomen, G.-J. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 29.

9. Allen, J. D.; Loevezijn, A. v.; Lakhai, J. M.; Valk, M. v. d.; Tellingen, O. v.; Reid, G.; Schellens, J. H. M.; Koomen, G.-J.; Schinkel, A. H. *Mol. Cancer Ther.* **2002,** *1*, 417.
10. Ahmed-Belkacem, A.; Pozza, A.; Macalou, S.; Pérez-Victoria, J. M.; Boumendjel, A.; Pietro, A. D. *Anti-Cancer Drugs* **2006,** *17*, 239.
11. Perego, P.; Cesare, M. D.; Isabella, P. D.; Carenini, N.; Beggiolin, G.; Pezzoni, G.; Palumbo, M.; Tartaglia, L.; Pratesi, G.; Pisano, C.; Carminati, P.; Scheffer, G. L.; Zunino, F. *Cancer Res.* **2001,** *61*, 6034.
12. Versiani, M. A.; Diyabalanage, T.; Ratnayake, R.; Henrich, C. J.; Bates, S. E.; McMahon, J. B.; Gustafson, K. R. *J. Nat. Prod.* **2011,** *74*, 262.
13. Pick, A.; Müller, H.; Mayer, R.; Haenisch, B.; Pajeva, I. K.; Weigt, M.; Bönisch, H.; Müller, C. E.; Wiese, M. *Bioorg. Med. Chem.* **2011,** *19*, 2090.
14. Mistry, P.; Stewart, A. J.; Dangerfield, W.; Okiji, S.; Liddle, C.; Bootle, D.; Plumb, J. A.; Templeton, D.; Charlton, P. *Cancer Res.* **2001,** *61*, 749.
15. Pick, A.; Müller, H.; Wiese, M. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 180.
16. Weiss, J.; Rose, J.; Storch, C. H.; Ketabi-Kiyanvash, N.; Sauer, A.; Haefeli, W. E.; Efferth, T. *J. Antimicrob. Chemother.* **2007,** *59*, 238.
17. Shi, Z.; Tiwari, A. K.; Shukla, S.; Robey, R. W.; Kim, I.-W.; Parmar, S.; Bates, S. E.; Si, Q.-S.; Goldblatt, C. S.; Abraham, I.; Fu, L.-W.; Ambudkar, S. V.; Chen, Z.-S. *Biochem. Pharmacol.* **2009,** *77*, 781.
18. Tiwari, A. K.; Sodani, K.; Wang, S.-R.; Kuang, Y.-H.; Jr., C. R. A.; Chen, X.; Chen, Z.-S. *Biochem. Pharmacol.* **2009,** *78*, 153.
19. Kühnle, M.; Egger, M.; Müller, C.; Mahringer, A.; Bernhardt, G.; Fricker, G.; König, B.; Buschauer, A. *J. Med. Chem.* **2009,** *52*, 1190.
20. Puentes, C. O.; Höcherl, P.; Kühnle, M.; Bauer, S.; Bürger, K.; Bernhardt, G.; Buschauer, A.; König, B. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 3654.
21. Kühnle, M. Ph.D. Thesis, Universität Regensburg, February **2010**.
22. Höcherl, P. Ph.D. Thesis, Universität Regensburg, June **2010**.
23. Pizzirani, D.; Roberti, M.; Cavalli, A.; Grimaudo, S.; Cristina, A. D.; Pipitone, R. M.; Gebbia, N.; Tolomeo, M.; Recanatini, M. *ChemMedChem* **2008,** *3*, 345.

3. Synthesis and Breast Cancer Resistance Protein (BCRP) Inhibitory Activity of New Multidrug Resistance Modulators Based on Tariquidar*

A new class of potent and selective multidrug resistance modulators based on tariquidar is reported. The central core of the new compounds was synthesized via Sonogashira coupling and a palladium-copper mediated domino coupling-cyclization process. Sequential steps of acylation, deprotection, mesylation and nucleophylic substitution led to compounds **22a-h** which were deprotected at the nitrogen of the indole core with TBAF. Compounds **22a-h** and **23a-h** were evaluated for inhibition of the P-glycoprotein (ABCB1) and the Breast Cancer Resistance Protein (BRCP) determined in the calcein-AM and the Hoechst 33342 microplate assay, respectively. All compounds showed to be selective for ABCG2, however compounds **23a-h** are more active that their analogues **22a-h**. The most promising compound is more potent that the most active ABCG2 inhibitor reported so far **Ko143**, and showed an IC_{50} value of 59 ± 14 nM and a maximal inhibitory effect of 100%.

* Patent and paper in preparation. All the synthesis and spectroscopical investigations (except compound **21**) were done by Cristian Ochoa Puentes. Compound **21** was synthesized by Manuel Bause at the Institute of Organic Chemistry, University of Regensburg. Inhibition assays for ABCB1 and ABCG2 were performed by Stefanie Bauer at the Institute of Pharmacy, University of Regensburg

3.1 Introduction

Cancer is one of the leading causes of death in the world. According with the International Agency for Research on Cancer (IARC), in 2008 about 12.7 million cancer cases and 7.6 million cancer deaths were estimated to occurred worldwide[1,2] and the number of cancer deaths is estimated to be 15.5 millions in 2030 due to population growth and adoption of cancer-associated lifestyle like tobacco and alcohol use, physical inactivity and obesity.

The increase in cancer incidence and mortality has motivated the development of prevention, screening and early detection programs as well as the development of new drugs and treatments to be used in chemotherapy. Although these strategies could reduce the mortality rates, a very important factor to be considered is the efficacy of the chemotherapy, which is influenced by different factors including the occurrence of drug-resistant tumor cells. The multi-drug resistance (MDR)[3] is a phenomenon in which cancer cells develop resistance to a variety of non related chemotherapeutic drugs, and is known that altered cell membrane ABC transporters are involved in this resistance phenomenon.

ABC transporters are large membrane-bound proteins with evolutionarily conserved structure-function features.[4] There are in total 48 known ABC transporters which are divided into seven distinct subfamilies of proteins, namely ABCA (12 members), ABCB (11 members), ABCC (12 members), ABCD (4 members), ABCE (1 member), ABCF (3 members) and ABCG (5 members).[5] These proteins have the ability to transport a wide diversity of large hydrophobic or amphipatic molecules, various xenobiotics and endobiotics over biological barriers.[6] However, in overexpressed membrane ABC transporters an increased drug efflux of chemotherapeutic agents is presented and thereby the intracellular drug level is reduced causing drug resistance.[7]

From all the ABC transporters, P-glycoprotein (P-gp or ABCB1, ABCB subfamily), the multidrug resistance-associated proteins (MRPs, in the ABCC subfamily) and breast cancer resistance protein (BCRP or ABCG2, in the ABCG subfamily) are the best known extrusion pumps. These proteins have the same energy-dependent transport system which uses the energy of ATP hydrolysis as their energy source.[7]

P-glycoprotein (ABCB1, P-gp), the first drug efflux pump found to contribute to multidrug resistance, is expressed in only a limited number of tissues with barrier function, including epithelia of the liver, kidney, small and large intestine and capillary endothelial cells in brain, ovary, and testis, and is able to pump out a broad range of cytotoxic drugs including anthracyclines, *Vinca* alkaloids, epipodophyllotoxins, and taxanes.[8] The expression of the multidrug resistance-associated proteins (MRPs) is induced by cytotoxic drugs. Most of its members are involved in pharmacotherapy resistance and its preferred substrates are anionic

drugs (e.g. methotrexate) and neutral drugs conjugated to acidic ligands, such as glutathione (GSH), glucuronate, or sulfate.[9]

Breast cancer resistance protein is a half transporter found in high levels in the placenta, liver, central nervous system, adrenal gland, prostate, testes, uterus, and breast, and in low levels in blood and blood brain barrier, gastrointestinal tract, lung, kidney and pancreas.[10] The overexpression of this transporter confers resistance to a broad range of anticancer drugs like methotrexate, mitoxantrone, camptothecin derivatives, anthracyclines and flavopiridol.[11]

One alternative to overcome the MDR in these transporters is to develop new compounds to be used in cancer treatment. However in some cases the new drugs also become substrates of the efflux pump, therefore the discovery of specific inhibitors of the drug-efflux activity is the most promising alternative to reverse the MDR phenomenon.[9] P-glycoprotein inhibitors are well known due to the extensive research done with this transporter during the past two decades.[12,13] The first generation of P-gp inhibitors consists of drugs, not developed to reverse MDR, which have another pharmacological activity like verapamil, cyclosporine A and tamoxifen. The second generation of P-gp inhibitors is mainly composed of analogues of the first generation with improved potency, specificity and less toxicity, together with compounds with new structures. Some examples include dexverapamil, trans-flupentixol and valspodar. Finally, the third generation of P-gp inhibitors was developed with a more rational drug design approach and is expected to have a specific and potent interaction with the P-gp transporter without inhibiting other ABC family transporters.[14] Biricodar (VX-710), tetrandrine, FG020326, S-9788, elacridar (GF-120918), zosuquidar (LY-335979), laniquidar (R101933), tariquidar (XR9576, Figure 2)[15] and its derivatives[16] are some examples of these inhibitors (Figure 1).

Based on the experience acquired with ABCB1, different approaches to develop ABCG2 inhibitors have been explored. Fumitremorgin C was the first ABCG2 inhibitor described[17] but its neurotoxic effects preclude its use *in vivo*, however some synthetic derivatives were obtained[18] and its analogue Ko143 (Figure 1) was found to be nontoxic *in vitro* at useful concentrations and evinced no signs of toxicity in mice at high oral doses. This compound appears to be the most potent BCRP inhibitor known so far.[19] Some other reported inhibitors include camptothecins derivatives,[20] flavonoids,[21,22] anti-HIV drugs,[23] and tyrosine kinase inhibitors[24,25] and also inhibitors of of P-gp or MRP1 such as elacridar, tariquidar (Figure 2) and biricodar (VX-710) (Figure 1).

Recently, new ABCG2 inhibitors have been reported based on tariquidar.[26,27] Several structural variations made on the basic structure led to one promising inhibitor in which no methoxy groups are attached to the benzamide core and the quinoline-3-carboxamide moiety was replaced by a 1-(4-nitrophenyl)urea fragment.[27]

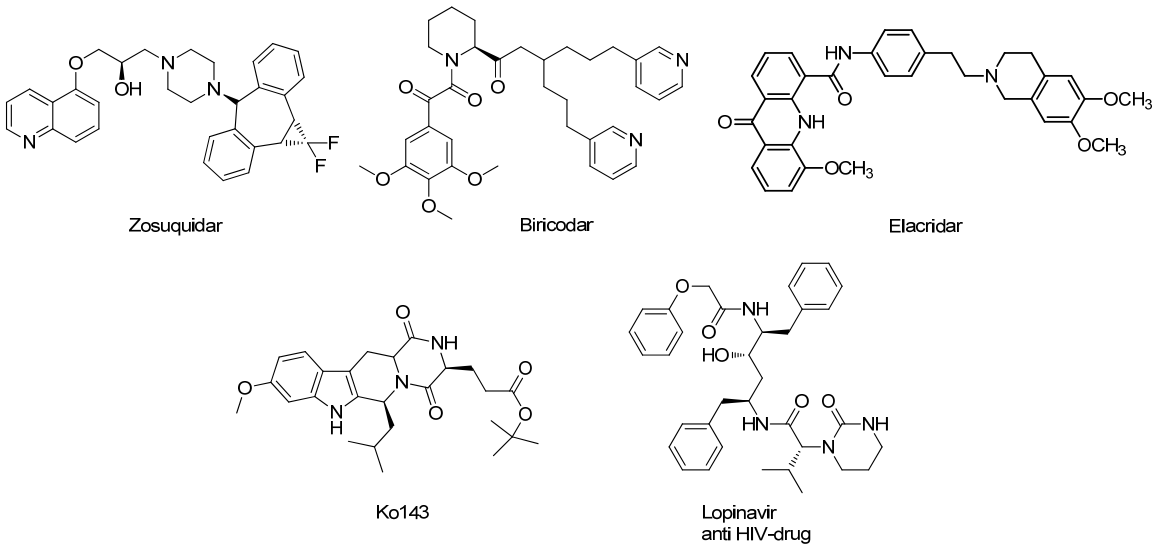


Figure 1. Structures of zosuquidar (ABCB1 modulator), biricodar, elacridar (dual ABCB1 and ABCG2 modulators), Ko143 and lopinavir (ABCG2 modulators)

During our studies on tariquidar based inhibitors[16,28] we discovered that when the two methoxy groups attached to the benzamide were replaced by a carboxylic acid methyl ester and the hetarylcarboxamido residue was shifted to the meta-position a potent and highly selective ABCG2 modulator was obtained (UR-ME-22-1, Figure 2).[29] In addition, the inclusion of a triethylenglycol ether group at the tetrahydroisoquinoline moiety, in order to increase the solubility, led to a compound (UR-COP78) comparable in potency to UR-ME-22-1 but considerably more efficient (max. inhibition 88% rel. to fumitremorgin C, 100%) (Figure 2).[30] Further stability studies performed in plasma mouse revealed that these compounds are not stable enough and the amide bond bearing the phenethyl tetrahydroisoquinoline fragment is hydrolyzed.[31] These previous results prompted us to design, synthesize and evaluate the ABCG2 inhibitory activity of a new class of tariquidar like derivatives. The design of the new compounds was based on the structural characteristics that lead to the best modulators UR-ME-22-1 and UR-COP78 (dashed squares, Figure 2). In addition, we introduced an indole core linked to the anthranilamide fragment in order to improve the stability of the compounds (Figure 2, target compounds).

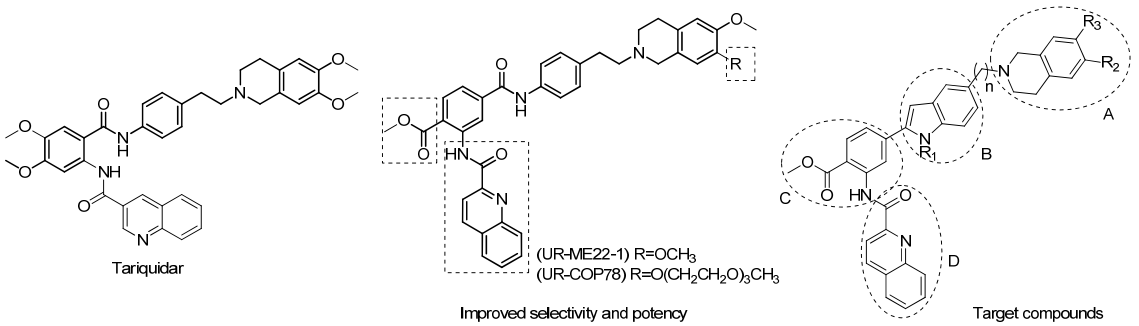
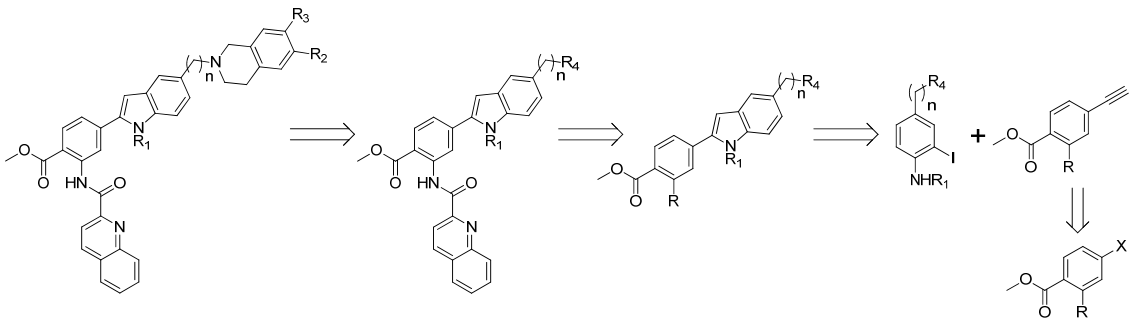


Figure 2. Structures of tariquidar (ABCB1 preferring modulator), the selective ABCG2 modulators UR-ME22-1 and UR-COP78 and the target compounds

3.2 Results and Discussion

Synthesis. As shown in Figure 2, the structure of the target compounds is composed from four fragments: the tetrahydroisoquinoline moiety (fragment A), the indole motif (fragment B), the methyl aminobenzoate moiety (fragment C) and the quinoline-2-carbonyl core (fragment D) (dashed ovals, Figure 2). First our synthetic efforts focussed on the indole core. There are different methodologies for the synthesis of indole derivatives;[32-35] and we sought a strategy that would allow us to obtain the indole substituted at the position 2 with the methyl aminobenzoate core (fragments B and C) in a few sequential steps. A Sonogashira coupling followed by a palladium-copper mediated domino coupling-cyclization process[36-39] was envisaged as good pathway to obtain this motif.

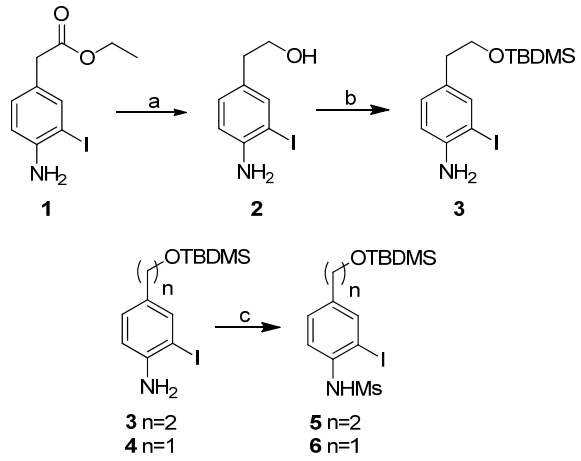
According with our retrosynthetic approach (Scheme 1), an *ortho*-iodoaniline derivative with a suitable functional group that allow a further modification to attach the fragment A of the molecule, and a phenylacetylene derivative are the coupling partners needed to synthesize the desired indole.



Scheme 1. Retrosynthetic approach for the synthesis of the target compounds.

The *ortho*-iodoaniline derivative was obtained from ethyl 2-(4-amino-3-iodophenyl)acetate **1**[40] by sequential steps of reduction with BH_3·THF, protection of the obtained amino alcohol **2** with

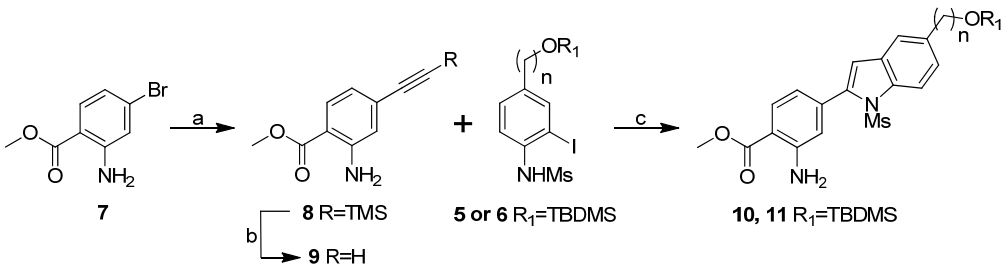
TBDMS-Cl and mesylation with MsCl to give **5**. In order to have a set of diverse structures, compound **6** was synthesized in similar fashion starting from **4**[41] (Scheme 2).



Scheme 2. Synthesis of the *ortho*-iodoaniline derivatives **5** and **6**. Reagents and conditions: (a) BH_3·THF, THF, rt. (b) Imidazole, TBDMS-Cl, DCM, rt. (c) MsCl, Py, rt.

Phenylacetylene derivative **9** was synthesized from commercially available methyl 2-amino-4-bromobenzoate **7** and trimethylsilylacetylene under standard Sonogashira conditions. The trimethylsilyl group was removed with TBAF (Scheme 3).

The so obtained aryl alkynes were converted into indoles **10** and **11** by reacting **9** with **5** or **6** in a palladium-copper mediated domino coupling-cyclization process (Scheme 3).



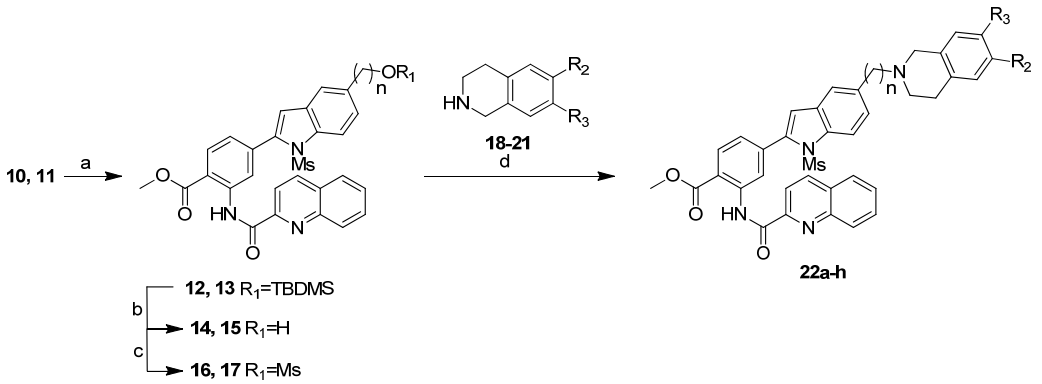
Scheme 3. Synthesis of indoles **10** and **11**. Reaction conditions: (a) Methyl 2-amino-4-bromobenzoate **7**, trimethylsilylacetylene, CuI, $Pd(PPh_3)_2Cl_2$, THF/TEA 2/1, 60°C. (b) TBAF, THF, rt. (c) $Pd(PPh_3)_2Cl_2$, CuI, DMF/TEA 2/1, 90°C.

Next, fragment D of the target structure was attached to the indoles **10** and **11**. Acylation of **10** and **11** with freshly prepared quinoline-2-carbonyl chloride, obtained from commercially available quinoline-2-carboxylic acid, led to compounds **12** and **13** which were converted into

16 and **17** by deprotection and mesylation, in order to have a structure that allows the attachment of fragment A (Scheme 4).

Finally, fragment A was coupled to the structure using commercially available 1,2,3,4-tetrahydroisoquinoline **18**, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **19**, 6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline **20** previously reported[30] and 6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline **21**[42] synthesized analogously than **20** starting from 1,2,3,4-tetrahydroisoquinoline-6,7-diol (Scheme 4).

Several derivatives were prepared by reaction of compounds **22a-h** with TBAF to remove the mesyl group at the nitrogen atom of the indole core affording compounds **23a-h** (Scheme 4).



	n=1	n=2	R_2	R_3
	6, 11, 13, 15, 17	**5, 10, 12, 14, 16**		
18	**22b, 23b**	**22a, 23a**	H	H
19	**22d, 23d**	**22c, 23c**	OCH_3	OCH_3
20	**22f, 23f**	**22e, 23e**	OCH_3	$O(CH_2CH_2O)_3CH_3$
21	**22h, 23h**	**22g, 23g**	$O(CH_2CH_2O)_3CH_3$	$O(CH_2CH_2O)_3CH_3$

Scheme 4. Synthesis of target compounds **22a-h** and **23a-h**. Reaction conditions: (a) Quinoline-2-carbonyl chloride, TEA, DCM, 40°C. (b) TBAF, THF, rt. (c) MsCl, TEA, DCM, rt. (d) Tetrahydroisoquinolines **18-21**, DIPEA, CH_3CN, reflux. (e) TBAF, THF, rt.

Inhibition of ABCB1 and ABCG2 transporters. The synthesized compounds **22a-h** and **23a-h** together with the reference compounds Ko143, tariquidar and elacridar were investigated for their inhibition of ABCB1 and ABCG2 in a calcein-AM (ABCB1)[43] and a Hoechst 33342 (ABCG2) microplate assay[31] using ABCB1-overexpressing Kb-V1 and ABCG2-overexpressing MCF-7/Topo cells (Table 1).

Table 1. Inhibition of ABCB1 and ABCG2 transporters by reference compounds (Ko143, tariquidar and elacridar) and the derivatives **22a–h**, and **23a–h** determined in the calcein-AM (ABCB1) and Hoechst 33342 (ABCG2) microplate assay unless otherwise indicated

Compd	ABCB1	ABCG2	
	IC_{50} (nM)	IC_{50} (nM)	I_{max} [a] (%)
Ko143	inactive[b]	117 ± 53	103 ± 7[c]
Tariquidar	223 ± 8	526 ± 85	69[c]
Elacridar	193 ± 18	127 ± 41	63[c]
UR-COP78	>50000	130 ± 29	88[d]
22a	>150000	947 ± 121	45
22b	n.d.	2090 ± 270	22
22c	2010 ± 510	992 ± 89	45
22d	n.d.	458 ± 35	63
22e	n.d.	504 ± 40	56
22f	n.d.	629 ± 26	38
22g	n.d.	n.d.	n.d.
22h	1580 ± 80	1020 ± 70	50
23a	>150000	374 ± 27	103
23b	>100000	350 ± 35	99
23c	>100000	159 ± 24	99
23d	7480 ± 790	412 ± 24	99
23e	n.d.	59 ± 14	100
23f	1620 ± 230	140 ± 33	99
23g	n.d.	n.d.	n.d.
23h	n.d.	136 ± 48	107

[a] Relative to Fumitremorgin C (100%). [b] 1.6% inhibition at 10 μM.

[c] ref 31. [d] ref 30. n.d = not determined

All tested compounds showed no inhibitory activity over ABCB1 transporter, whereas the ABCG2 inhibitory activity is in the nanomolar range (except compound **22b** and **22h**). In the first series of compounds, in which a mesyl group is attached at the nitrogen of the indole core, two derivatives (**22d**, **22e**) have similar IC_{50} values compared to tariquidar but are slightly less effective (63% and 56% vs 69%)

The second set of compounds, with an unprotected N-H group at the indole core, is more effective that the analogues having the mesyl group at the same position. This result suggests that the unprotected N-H group is fundamental for the activity. Compounds **23a-f** and **23h** are more potent and efficient than tariquidar (lower IC_{50} values and higher maximal inhibitory effect) at ABCG2 inhibition. With respect to elacridar and **UR-COP78**, analogues **23a,b** and **23d** have IC_{50} values approximately 2.8 and 3.2 fold higher, but the maximal inhibitory effect is superior (103% and 99% vs 63% and 88%). Compounds **23c**, **23f** and **23h** have IC_{50} values in the same range but are more efficient (I_{max} of 99%, 100% and 107%, respectively) (Figure 3).
Compared to the most potent and selective ABCG2 inhibitor reported so far **Ko143**,[19] compounds **23a**,**b** and **23d** have IC_{50} values 3 and 3.5 fold higher and a comparable maximal

inhibitory effect. More interesting, analogues **23c**,**f** and **23h** have about the same IC_{50} values and maximal inhibitory effect.

The most potent and promising compound, however, is **23e**, which has an improved potency compared to **Ko143**,(59 ± 14 nM vs 117 ± 53 nM) and a very close maximal inhibitory effect (100% vs 103%).

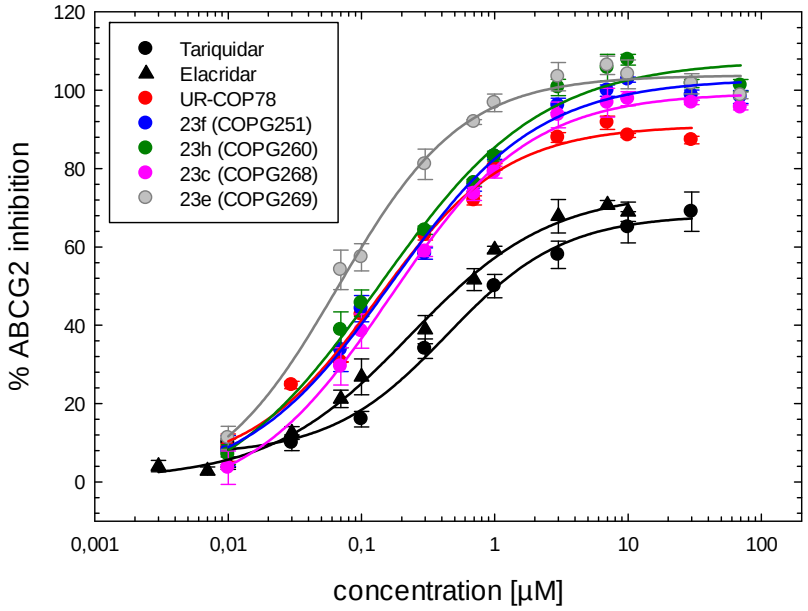


Figure 3. Concentration dependent inhibition of the ABCG2 transporter in MCF-7/Topo cells (Hoechst 33342 assay) by tariquidar (filled black circles), elacridar (filled black triangles) and the tariquidar analogues UR-COP78 (filled red circles), **23f** (COPG251; filled blue circles), **23h** (COPG260; filled green circles), **23c** (COPG268; filled pink circles) and **23e** (COPG269; filled gray circles). The maximal inhibition is expressed as % relative to the maximum inhibition of ABCG2 by fumitremorgin C (at a concentration of 10 µM).

In order to evaluate the biological stability of the synthesized analogues, compound **23f**, was selected for a stability test in mouse plasma.[31] In this test, the compound and mouse plasma were incubated at 37 °C and after increasing periods of time, aliquots were taken, the reaction was stopped and the protein was removed. Analysis of the sample by HPLC showed that the compound is stable after one hour and after 24 hours around 50% of the compound is degradated. HPLC/MS analysis confirmed that the fragments obtained correspond to the enzymatic hydrolysis of the methyl ester located at the anthranilic ring.

3.3 Conclusion

A new class of potent and selective multidrug resistance modulators derived from tariquidar was synthesized via Sonogashira coupling and a palladium-copper mediated domino coupling-cyclization process. All tested compounds showed no inhibitory activity over ABCB1 transporter, whereas the ABCG2 inhibitory activity is in the nanomolar range, except for compound **22b** and **22h**.

The most potent and promising compound, **23e**, has a lower IC_{50} value and a very close maximal inhibitory effect (59 ± 33 nM, I_{max} 100%) compared to the most potent and selective ABCG2 inhibitor reported so far **Ko143**, (117 ± 53, I_{max} 103 ± 7%).

The selectivity, the increased activity and the biological stability of derivatives **23e**,**f** and **23h**, show that these compounds are good candidates for *in vivo* studies in order to overcome drug resistance of tumor cells associated to ABCG2 transporters.

3.4 Experimental Section

General. Commercial reagents and starting materials were purchased from Aldrich, Fluka, or Apollo Scientific and used without further purification. Compounds **1**, **4** and $PdCl_2(PPh_3)_2$ were prepared by reported methods. Flash chromatography was performed on silica gel (Merck silica gel Si 60 40-63 μm); products were detected by TLC on alumina plates coated with silica gel (Merck silica gel 60 F254, thickness 0.2 mm) and visualized by UV light (λ) 254 nm). Melting points were determined with an OptiMelt MPA100 apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance 300 (1H: 300.1 MHz; 13C: 75.5 MHz; *T* = 300 K), Bruker Avance 400 (1H: 400.1 MHz; 13C: 100.6 MHz; *T* = 300 K), and Bruker Avance 600 (1H: 600.1 MHz; 13C: 150.1 MHz; *T* = 300 K) instruments. Chemical shifts are reported in δ/ppm relative to external standards and coupling constants *J* are given in Hz. Abbreviations for the characterization of the signals: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet, dd = double doublet. The relative numbers of protons is determined by integration. Error of reported values: chemical shift 0.01 ppm (1H NMR), 0.1 ppm (13C NMR), coupling constant 0.1 Hz. The used solvent for each spectrum is reported. Mass spectra were recorded with Finnigan MAT TSQ 7000 (ESI) and Finnigan MAT 90 (HRMS), and the IR spectra with a Bio-Rad FT-IR-FTS 155 spectrometer.

2-(4-Amino-3-iodophenyl)ethanol 2.

Ethyl 2-(4-amino-3-iodophenyl)acetate **1**[40] (100 mg, 0.32 mmol) was dissolved in dry THF, the solution was cooled in an ice bath and BH_3·THF complex (0.97 mL, 0.97 mmol, 3 equiv) was

added dropwise. After the addition, the reaction was stirred at rt during 3 h and quenched with MeOH, diluted with water and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporating the solvent, the compound was purified by recrystalization from PE:AcOEt 1:1. Yield 77%, white solid, **mp.** 81.4-82.0°C. **^{1}H NMR** (MeOD, 300 MHz): δ= 7.47 (d, ^4J=1.9 Hz, 1H, ArH), 6.98 (dd, ^3J=8.1, ^4J=2.0 Hz, 1H, ArH), 6.73 (d, ^3J=8.1 Hz, 1H, ArH), 3.65 (t, ^3J=7.0 Hz, 2H, CH_2), 2.64 (t, ^3J=7.0 Hz, 2H, CH_2). **^{13}C NMR** (MeOD, 75 MHz): δ= 147.4 ($C_{quat,}$), 140.1 (+), 131.6 ($C_{quat,}$), 131.0 (+), 116.1 (+), 84.6 ($C_{quat,}$), 64.3 (–), 38.8 (–). **HRMS** (EI-MS) calcd. for $C_8H_{10}INO$ $[MH]^+$: 262.9807; found: 262.9809. **IR** (KBr) [cm^{-1}]: ν = 3372, 3267, 2947, 2860, 1601, 1495, 665, 584.

4-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-2-iodoaniline 3.

Imidazole (140 mg, 2.09 mmol, 1.1 equiv) was added to a mixture of 2-(4-amino-3-iodophenyl)ethanol **2** (500 mg, 1.9 mmol, 1 equiv) and TBDMS -Cl (310 mg, 2.09 mmol, 1.1 equiv) in 10 mL of dry DCM. The reaction was stirred at rt for 4 h, water was added and the organic phase was separated, wahed with brine and dried over $MgSO_4$. After evaporating the solvent, the compound was purified by flash chromatography (PE:AcOEt 10:1, R_f= 0.22). Yield 99%, light yellow solid, **mp.** 81.4-82.0°C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 7.51 (d, ^4J=1.7 Hz, 1H, ArH), 6.98 (dd, ^3J=8.1, ^4J=1.8 Hz, 1H, ArH), 6.67 (d, ^3J=8.1 Hz, 1H, ArH), 3.98 (s, 2H, NH_2), 3.73 (t, ^3J=6.9 Hz, 2H, CH_2), 2.67 (t, ^3J=6.9 Hz, 2H, CH_2), 0.89 (s, 9H, 3 CH_3), -0.00 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ= 144.9 ($C_{quat,}$), 139.3 (+), 131.0 ($C_{quat,}$), 130.1 (+), 114.5 (+), 84.1 ($C_{quat,}$), 64.5 (–), 38.0 (–), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). **HRMS** (EI-MS) calcd. for $C_{14}H_{25}INOSi$ $[M+H]^+$: 378.0745; found: 378.0750. **IR** (KBr) [cm^{-1}]: ν = 3448, 3207, 2951, 2856, 1616, 1498, 665.

General procedure for the preparation of the methanesulfonamides 5 and 6. Methanesulfonyl chloride (0.36 mmol) was added dropwise to a solution of the aromatic amines **3** or **4**[41] (0.36 mmol) in 5 mL of pyridine at 0°C. After the addition, the reaction was stirred at room temperature overnight. Water and AcOEt were added and the organic phase separated, washed with 1 N HCl, 1 N $NaHCO_3$ and dried over $MgSO_4$. After evaporating the solvent, the compound was recristalized from PE:DCM 1:1 (compound **5**) or used without any further purification (compound **6**).

N-(4-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-2-iodophenyl)methanesulfonamide 5.

Yield 83%, viscous orange oil. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 7.75 (d, ^4J=1.8 Hz, 1H, ArH), 7.58 (d, ^3J=8.3 Hz, 1H, ArH), 7.25 (dd, ^3J=8.3, ^4J=1.5 Hz, 1H, ArH), 6.62 (s, 1H, NH), 3.82 (t,

^3J=6.4 Hz, 2H, CH_2), 3.01 (s, 3H, CH_3), 2.78 (t, ^3J=6.4 Hz, 2H, CH_2), 0.89 (s, 9H, 3 CH_3), -0.00 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 140.0 (+), 139.5 ($C_{quat,}$), 135.6 ($C_{quat,}$), 130.7 (+), 122.8 (+), 92.5 ($C_{quat,}$), 63.7 (–), 39.9 (+), 38.1 (–), 25.8 (+), 18.2 ($C_{quat,}$), -5.4 (+). **HRMS** (EI-MS) calcd. for $C_{15}H_{27}INO_3SSi$ $[M+H]^+$: 456.0520; found: 456.0513. **IR** (KBr) [cm^{-1}]: ν =2926, 2856, 1332, 1161, 632.

N-(4-(((tert-Butyldimethylsilyl)oxy)methyl)-2-iodophenyl)methanesulfonamide 6.

Yield 80%, white solid, **mp.** 100.3-101.8°C, **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 7.81-7.78 (m, 1H, ArH), 7.59 (d, ^3J=8.3 Hz, 1H, ArH), 7.31 (dd, ^3J=8.4, ^4J=1.6 Hz, 1H, ArH), 6.57 (s, 1H, NH), 4.67 (s, 2H, CH_2), 2.99 (s, 3H, CH_3), 0.94 (s, 9H, 3 CH_3), 0.11 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 141.1 ($C_{quat,}$), 136.8 (+), 136.1 ($C_{quat,}$), 127.5 (+), 122.6 (+), 92.4 ($C_{quat,}$), 63.4 (–), 40.0 (+), 25.9 (+), 18.4 ($C_{quat,}$), -5.2 (+). **HRMS** (EI-MS) calcd. for $C_{14}H_{24}INO_3SSi$ $[MH]^+$: 441.0291; found: 441.0290. **IR** (KBr) [cm^{-1}]: ν = 3273, 2953, 1327, 1149, 1089, 775.

Methyl 2-amino-4-((trimethylsilyl)ethynyl)benzoate 8

A mixture of methyl 2-amino-4-bromobenzoate **7** (100 mg, 0.43 mmol), trimethylsilylacetylene (73µL, 0.52 mmol, 1.2 equiv.), CuI (8.1 mg, 430 µmol, 10% mol) and $Pd(PPh_3)_2Cl_2$ (15 mg, 21.5 µmol, 5%mol) in 5 mL of THF/TEA 2/1 was stirred and heated at 60 °C for 6 h. Water and DCM were added, the organic layer separated and washed with 1N HCl, 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:1. Yield 73%, Yellow solid, **mp.** 69-73.1°C, R_f= 0.27. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 7.72 (d, ^3J=8.3 Hz, 1H, ArH), 6.73 (d, ^4J=1.4 Hz, 1H, ArH), 6.67 (dd, ^3J=8.3, ^4J=1.5 Hz, 1H, ArH), 5.68 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 0.20 (s, 9H, 3 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ= 168.2 (C=O), 150.1 ($C_{quat,}$), 131.2 (+), 128.6 ($C_{quat,}$), 119.9 (+), 119.7 (+), 110.6 ($C_{quat,}$), 104.5 ($C_{quat,}$), 96.5 ($C_{quat,}$), 51.7 (+), -0.01 (+). **MS** (CI-MS NH_3): m/z (%)= 247.1 (75) $[MH]^{+\cdot}$. **IR** (KBr) [cm^{-1}]: ν = 3460, 3354, 2949, 2160, 1689, 1244, 837, 758.

Methyl 2-amino-4-ethynylbenzoate 9.

A solution of methyl 2-amino-4-((trimethylsilyl)ethynyl)benzoate **8** (77 mg, 0.31 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.31 mL, 0.31 mmol, 1M in THF) was added and the reaction was stirred for 10 min. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:1. Yield 74%, Yellow solid, **mp.** 75.1-76.8°C, R_f= 0.22.

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.82 (d, ^3J=8.3 Hz, 1H, ArH), 6.81 (d, ^4J=1.5 Hz, 1H, ArH), 6.76 (dd, ^3J=8.2, ^4J=1.5 Hz, 1H, ArH), 5.77 (s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.16 (s, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ= 168.0 (C=O), 149.9 ($C_{quat,}$), 131.2 (+), 127.5 ($C_{quat,}$), 120.0 (+), 119.7 (+), 110.8 ($C_{quat,}$), 83.0 ($C_{quat,}$), 79.0 (+), 51.6 (+). **MS** (EI-MS): m/z (%)= 175.1 (100) $[MH]^{+\cdot}$. **IR** (KBr) [cm^{-1}]: ν = 3479, 3375, 3244, 2949, 1689, 1244, 1099, 769.

General procedure for the synthesis of compounds 10 and 11.

A mixture of methyl 2-amino-4-ethynylbenzoate **9** (0.57 mmol), Methanesulfonamides **5** or **6** (0.57 mmol), CuI (10.8 mg, 57 µmol, 10% mol) and $Pd(PPh_3)_2Cl_2$ (20 mg, 28.5 µmol, 5%mol) in 5 mL of DMF/TEA 2/1 was stirred and heated at 90°C for 24 h. Water was added and the compound was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The compound was purified by flash chromatography PE:AcOEt 10:3.

Methyl 2-amino-4-(5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1H-indol-2-yl)benzoate 10.

Yield 54%, Yellow solid, **mp.** 132-134°C, R_f = 0.36. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 8.01 (d, ^3J=8.5 Hz, 1H, ArH), 7.90 (d, ^3J=8.1 Hz, 1H, ArH), 7.44 (d, ^4J=1.0 Hz, 1H, ArH), 7.26 (dd, ^3J=8.9, ^4J=1.9 Hz, 1H, ArH), 6.91-6.84 (m, 2H, ArH), 6.73 (s, 1H, ArH), 5.83 (bs, 2H, NH_2), 3.91-3.83 (m, 5H, OCH_3, CH_2), 2.94 (t, ^3J=6.9 Hz, 2H, CH_2), 2.70 (s, 3H, SO_2CH_3), 0.89 (s, 9H, 3 CH_3), 0.00 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 168.3 (C=O), 149.7 ($C_{quat,}$), 141.4 ($C_{quat,}$), 137.5 ($C_{quat,}$), 137.0 ($C_{quat,}$), 136.0 ($C_{quat,}$), 130.5 (+), 130.4 ($C_{quat,}$), 126.9 (+), 121.5 (+), 118.1 (+), 117.9 (+), 115.6 (+), 113.8 (+), 110.7 ($C_{quat,}$), 64.6 (–), 51.6 (+), 39.3 (–), 38.7 (+), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). **HRMS** (EI-MS) calcd. for $C_{25}H_{35}N_2O_5SSi$ $[M+H]^+$: 503.2030; found: 503.2035. **IR** (KBr) [cm^{-1}]: ν = 3495, 3379, 2951, 2854, 1689, 773.

Methyl 2-amino-4-(5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1H-indol-2-yl)benzoate 11.

Yield 69%, Yellow solid, **mp.** 112-114.8°C, R_f = 0.29. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 8.03 (d, ^3J=8.6 Hz, 1H, ArH), 7.87 (d, ^3J=8.2 Hz, 1H, ArH), 7.54 (d, ^4J=0.8 Hz, 1H, ArH), 7.31 (dd, ^3J=8.6, ^4J=1.6 Hz, 1H, ArH), 6.87-6.80 (m, 2H, ArH), 6.73 (s, 1H, ArH), 5.49 (bs, 2H, NH_2), 4.83 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.69 (s, 3H, SO_2CH_3), 0.95 (s, 9H, 3 OCH_3), 0.12 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 168.3 (C=O), 149.6 ($C_{quat,}$), 141.5 ($C_{quat,}$), 138.2 ($C_{quat,}$), 137.5 ($C_{quat,}$), 137.4 ($C_{quat,}$), 130.5 (+), 130.3 ($C_{quat,}$), 123.9 (+), 118.6 (+), 118.2 (+), 117.9 (+), 115.7 (+), 113.9 (+), 110.7, 64.8 (–), 51.6 (+), 38.9 (+), 26.0 (+), 18.4 ($C_{quat,}$), -5.1 (+). **MS** (EI-

MS): m/z (%)= 530 (100) $[M+NH_4]^+$, 489 (10) $[MH]^+$. **IR** (KBr) [cm^{-1}]: ν = 3496, 3381, 2953, 2858, 1678 775.

General procedure for the preparation of compounds 12 and 13. To a mixture of **10** or **11** (0.38 mmol) and TEA (1.66 mmol, 3 equiv.) in dry DCM, quinoline-2-carbonyl chloride (0.45 mmol, 1.2 equiv.) was added. The mixture was stirred and heated at 40°C overnight. 1N HCl was added and the compound was extracted with DCM, washed with 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:3.

Methyl 4-(5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 12.

Yield 92%, Yellow solid, **mp.** 81-83°C, R_f = 0.45. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.39 (s, 1H, NHCO), 9.30 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.33 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz, 1H, ArH), 7.90 (d, ^3J=8.2 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.4 Hz, 1H, ArH), 7.69-7.62 (m, 1H, ArH), 7.46 (d, ^4J=1.1 Hz, 1H, ArH), 7.41 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.27 (dd, ^3J=8.5, ^4J=1.7 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.88 (t, ^3J=6.8 Hz, 2H, CH_2), 2.95 (t, ^3J=6.8 Hz, 2H, CH_2), 2.84 (s, 3H, SO_2CH_3), 0.89 (s, 9H, 3 CH_3), 0.00 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.0 ($C_{quat,}$), 140.4 ($C_{quat,}$), 138.0 ($C_{quat,}$), 137.7 (+), 137.1 ($C_{quat,}$), 136.0 ($C_{quat,}$), 130.4 ($C_{quat,}$), 130.3 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 127.1 (+), 125.3 (+), 121.6 (+), 120.6 (+), 118.8 (+), 116.1 ($C_{quat,}$), 115.5 (+), 114.5 (+), 64.6 (–), 52.5 (+), 39.3 (–), 39.2 (+), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). **HRMS** (EI-MS) calcd. for $C_{35}H_{40}N_3O_6SSi$ $[M+H]^+$: 658.2402; found: 658.2402. **IR** (KBr) [cm^{-1}]: ν = 2953, 2856, 1685, 771.

Methyl 4-(5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 13.

Yield 76%, Yellow solid, **mp.** 165-167°C, R_f = 0.50. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.34 (s, 1H, NHCO), 9.25 (d, ^4J=1.6 Hz, 1H, ArH), 8.34-8.29 (m, 3H, ArH), 8.13 (d, ^3J=8.3 Hz, 1H, ArH), 8.01 (d, ^3J=8.6 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.79 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.65-7.59 (m, 1H, ArH), 7.54 (s, 1H, ArH), 7.37 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.31 (dd, ^3J=8.6, ^4J=1.4 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 4.82 (s, 2H, CH_2), 4.03 (s, 3H, OCH_3), 2.81 (s, 3H, SO_2CH_3), 0.93 (s, 9H, 3 CH_3), 0.09 (s, 6H, 2 CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.1 ($C_{quat,}$), 140.4 ($C_{quat,}$),

138.2 ($C_{quat,}$), 137.9 ($C_{quat,}$), 137.7 (+), 137.5 ($C_{quat,}$), 130.3 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 125.3 (+), 124.0 (+), 120.6 (+), 118.8 (+), 118.7 (+), 116.2 ($C_{quat,}$), 115.6 (+), 114.7 (+), 64.9 (–), 52.5 (+), 39.4 (+), 26.0 (+), 18.4 ($C_{quat,}$), -5.1 (+). **HRMS** (EI-MS) calcd. for $C_{34}H_{37}N_3NaO_6SSi$ $[M+Na]^+$: 666.2065; found: 666.2066. **IR** (KBr) [cm^{-1}]: ν = 2949, 2852, 1705, 1676, 767.

Synthesis of compounds 14 and 15. General procedure. A solution of **12** or **13** (0.15 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.15 mmol, 1M in THF) was added and the reaction was stirred for 10 min. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 1:1.5

Methyl 4-(5-(2-hydroxyethyl)-1-(methylsulfonyl)-1H-indol-2-yl)-2-(quinoline-2-carbox amido)benzoate 14.

Yield 61%, Yellow solid, **mp.** 198-200°C, R_f = 0.32. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.39-8.32 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.03 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.70-7.62 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.29-7.24 (m, 1H, ArH), 6.86 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.93 (t, ^3J=6.5 Hz, 2H, CH_2), 2.99 (t, ^3J=6.5 Hz, 2H, CH_2), 2.89 (s, 3H, SO_2CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.1 ($C_{quat,}$), 140.3 ($C_{quat,}$), 137.9 ($C_{quat,}$), 137.7 (+), 137.1 ($C_{quat,}$), 135.1 ($C_{quat,}$), 130.6 ($C_{quat,}$), 130.4 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 126.6 (+), 125.3 (+), 121.5 (+), 120.7 (+), 118.8 (+), 116.2 ($C_{quat,}$), 115.8 (+), 114.2 (+), 63.8 (–), 52.5 (+), 39.7 (+), 39.0 (–). **HRMS** (EI-MS) calcd. for $C_{29}H_{26}N_3O_6S$ $[M+H]^+$: 544.1537; found: 544.1541. **IR** (KBr) [cm^{-1}]: ν = 2937, 2883, 1683, 769.

Methyl 4-(5-(hydroxymethyl)-1-(methylsulfonyl)-1H-indol-2-yl)-2-(quinoline-2-carbox amido)benzoate 15.

Yield 73%, Yellow solid, **mp.** 172.6-174°C, R_f = 0.25. **^{1}H NMR** (DMSO, 300 MHz): δ= 13.12 (s, 1H, NHCO), 9.12 (d, ^4J=1.6 Hz, 1H, ArH), 8.62 (d, ^3J=8.5 Hz, 1H, ArH), 8.25 (d, ^3J=8.5 Hz, 1H, ArH), 8.18 (d, ^3J=8.4 Hz, 1H, ArH), 8.09 (m, 2H, ArH), 7.92 (m, 2H, ArH), 7.75 (td, ^3J=7.1, ^4J=0.8 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.43 (td, ^3J=8.3, ^4J=1.5 Hz, 2H, ArH), 7.05 (s, 1H, ArH), 5.32 (s, 1H, OH), 4.64 (s, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.22 (s, 3H, SO_2CH_3). **^{13}C NMR** (75 MHz, DMSO) δ: 166.8 (C=O), 162.7 (C=O), 149.1 ($C_{quat,}$), 145.6 ($C_{quat,}$), 140.0

($C_{quat,}$), 139.0 ($C_{quat,}$), 138.7 ($C_{quat,}$), 138.3 (+), 137.8 ($C_{quat,}$), 136.6 ($C_{quat,}$), 130.7 (+), 130.3 (+), 129.5 ($C_{quat,}$), 129.2 (+), 128.9 ($C_{quat,}$), 128.5 (+), 128.0 (+), 124.3 (+), 124.1 (+), 120.5 (+), 119.0 (+), 118.4 (+), 115.6 ($C_{quat,}$), 114.7 (+), 113.6 (+), 62.6 (–), 52.6 (+), 40.1 (+). **HRMS** (EI-MS) calcd. for $C_{28}H_{24}N_3O_6S$ $[M+H]^+$: 530.1380; found: 530.1382. **IR** (KBr) [cm^{-1}]: ν = 3267, 1681, 1249, 765.

Synthesis of compounds 16 and 17. General procedure. A mixture of **14** or **15** (0.18 mmol) and TEA (0.47 mmol, 2.5 equiv.) in 10 mL of dry DCM was stirred and cooled in an ice bath. Mesyl chloride (0.18 mmol) was added dropwise and the reaction was stirred at rt overnight. Water was added, the organic layer separated and washed with 1N HCl, 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography (Ethyl ether:PE 10:1). Compound **17** was used in the next step without any further purification.

Methyl 4-(1-(methylsulfonyl)-5-(2-((methylsulfonyl)oxy)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 16.

Yield 81%, Yellow solid, **mp.** 220-222°C, R_f = 0.40. **^{1}H NMR** ($CDCl_3$, 300 MHz)= δ: 13.39 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.40-8.32 (m, 3H, ArH), 8.18 (d, ^3J=8.3 Hz, 1H, ArH), 8.06 (d, ^3J=8.6 Hz, 1H, ArH), 7.92 (d, ^3J=8.2 Hz, 1H, ArH), 7.84 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.71-7.64 (m, 1H, ArH), 7.49 (d, ^4J=1.2 Hz, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.27 (dd, ^3J=8.6, ^4J=1.7, 1H, ArH), 6.86 (s, 1H, ArH), 4.49 (t, ^3J=6.8 Hz, 2H, CH_2), 4.09 (s, 3H, OCH_3), 3.19 (t, ^3J=6.8 Hz, 2H, CH_2), 2.93 (s, 3H, SO_2CH_3), 2.92 (s, 3H, SO_2CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.3 ($C_{quat,}$), 140.4 ($C_{quat,}$), 137.7 ($C_{quat,}$), 137.7 (+), 137.3 ($C_{quat,}$), 132.8 ($C_{quat,}$), 130.5 ($C_{quat,}$), 130.5 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 126.4 (+), 125.2 (+), 121.6 (+), 120.8 (+), 118.8 (+), 116.3 ($C_{quat,}$), 115.9 (+), 113.8 (+), 70.2 (–), 52.5 (+), 40.0 (+), 37.5 (+), 35.5 (–). **HRMS** (EI-MS) calcd. for $C_{30}H_{28}N_3O_8S_2$ $[M+H]^+$: 622.1312; found: 622.1315. **IR** (KBr) [cm^{-1}]: ν = 2949, 1683, 769.

General procedure for the synthesis of indol derivatives 22a-h. A mixture **16** or **17** (56µmol), DIPEA (67µmol, 1.2 equiv.) and the tetrahydroisoquinolines **18-21** in CH_3CN was refluxed overnight. The solvent was evaporated, 1N HCl was added and the compound was extracted with AcOEt. The organic layer was washed with 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography.

Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 22a.

Yield 62%, yellow solid, **mp.** 121-123 °C, R_f = 0.21 (DCM/MeOH 100/3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.38 (s, 1H, NHCO), 9.29 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.34 (m, 3H, ArH), 8.17 (d, ^3J=8.2 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=7.7 Hz, 1H, ArH), 7.85-7.82 (m, 1H, ArH), 7.67-7.65 (m, 1H, ArH), 7.49 (d, ^4J=0.9 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.30 (dd, ^3J=8.5, ^4J=1.6 Hz, 1H, ArH), 7.16-7.10 (m, 3H, ArH), 7.07-7.04 (m, 1H, ArH), 6.87 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2), 3.05 (dd, ^3J=9.5, ^3J=6.6 Hz, 2H, CH_2), 2.96 (t, ^3J=5.8 Hz, 2H, CH_2), 2.88 (s, 3H, SO_2CH_3), 2.86-284 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.9 (Cquat.), 146.6 (Cquat.), 140.9 (Cquat.), 140.3 (Cquat.), 137.9 (Cquat.), 137.6 (+), 137.0 (Cquat.), 136.9 (Cquat.), 134.2 (Cquat.), 130.5 (+), 130.3 (+), 130.3 (+), 130.2 (Cquat.), 129.3 (Cquat.), 128.6 (+), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 126.1 (+), 125.6 (+), 125.3 (+), 121.0 (+), 120.6 (Cquat.), 118.7 (+), 116.1 (Cquat.), 115.6 (+), 114.3 (+), 77.2 (–), 77.0 (–), 76.7 (–), 60.4 (–), 56.1 (–), 52.4 (+), 50.9 (–), 39.5 (+), 33.7 (–), 29.0 (–). **HRMS** (EI-MS) calcd. for $C_{38}H_{35}N_4O_5S$ $[M+H]^+$: 659.2323; found: 659.2329. **IR** (KBr) [cm^{-1}]: ν = 2931, 1685, 1519, 773.

Methyl 4-(5-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 22b.

Yield 79%, yellow solid, **mp.** 135-137 °C, R_f = 0.23 (DCM/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.37 (s, 1H, NHCO), 9.29 (d, ^4J=1.6 Hz, 1H, ArH), 8.37-8.34 (m, 3H, ArH), 8.18 (d, ^3J=8.2 Hz, 1H, ArH), 8.06 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.3, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.68-7.64 (m, 2H, ArH), 7.47 (dd, ^3J=8.6, ^4J=1.6 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.15-7.09 (m, 3H, ArH), 7.00 (d, ^3J=6.9 Hz, 1H, ArH), 6.88 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.82 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 2.96-2.92 (m, 5H, SO_2CH_3, CH_2), 2.81 (t, ^3J = 5.9 Hz, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.7 (C=O), 149.8 (Cquat.), 146.5 (Cquat.), 140.9 (Cquat.), 140.3 (Cquat.), 137.9 (Cquat.), 137.6 (+), 137.5 (Cquat.), 134.8 (Cquat.), 134.6 (Cquat.), 134.2 (Cquat.), 130.3 (+), 130.2 (+), 130.2 (Cquat.), 130.2 (+), 129.3 (Cquat.), 128.6 (+), 128.2 (+), 127.6 (+), 126.7 (+), 126.5 (+), 126.1 (+), 125.5 (+), 125.2 (+), 121.6 (+), 120.7 (+), 118.7 (+), 116.1 (Cquat.), 115.4 (+), 114.1 (+), 62.4 (–), 56.0 (–), 52.4 (+), 50.6 (–), 39.8 (+), 29.0 (–). **HRMS** (EI-MS) calcd. for $C_{37}H_{33}N_4O_5S$ $[M+H]^+$: 645.2166; found: 645.2161. **IR** (KBr) [cm^{-1}]: ν = 1683, 1504, 775.

Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl) -1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 22c. Yield 86%, yellow solid, **mp.** 124-126 °C, R_f = 0.24 (DCM/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.5 Hz, 1H, ArH), 8.40-8.31 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.86-7.80 (m, 1H, ArH), 7.68-7.63 (m, 1H, ArH), 7.48 (s, 1H, ArH), 7.40 (dd, ^3J=8.3, ^4J=1.6 Hz, 1H, ArH), 7.29 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2), 3.04 (dd, ^3J=9.7, ^3J=6.0 Hz, 2H, CH_2), 2.88-2.82 (m, 9H, SO_2CH_3, 6 CH_2).**^{13}C NMR** (75 MHz, $CDCl_3$) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (Cquat.), 147.5 (Cquat.), 147.2 (Cquat.), 146.6 (Cquat.), 141.0 (Cquat.), 140.4 (Cquat.), 137.9 (Cquat.), 137.7 (Cquat.), 137.0 (+), 136.9 (Cquat.), 130.5 (Cquat.), 130.4 (+), 130.3 (+), 130.2 (+), 129.4 (Cquat.), 128.3 (+), 127.6 (+), 126.6 (+), 126.3 (Cquat.), 126.1 (Cquat.), 125.3 (+), 121.1 (+), 120.6 (+), 118.8 (+), 116.2 (Cquat.), 115.7 (+), 114.3 (+), 111.3 (+), 109.4 (+), 60.3 (–)55.9 (+), 55.9 (+), 55.7 (–), 52.5 (+), 51.0 (–), 39.6 (+), 33.8 (–), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{40}H_{39}N_4O_7S$ $[M+H]^+$: 719.2534; found: 719.2532. **IR** (KBr) [cm^{-1}]: ν = 2931, 1683, 1518, 773.

Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl) -1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 22d.

Yield 52%, light yellow solid, **mp.** 140-142 °C, R_f = 0.29 ($CHCl_3$/MeOH 100/3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.5 Hz, 1H, ArH), 8.39-8.32 (m, 3H, ArH), 8.18 (d, ^3J=8.2 Hz, 1H, ArH), 8.06 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=7.9 Hz, 1H, ArH), 7.86-7.81 (m, 1H, ArH), 7.69-7.64 (m, 2H, ArH), 7.46 (dd, ^3J=8.5, ^4J=1.1 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.6 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.61 (s, 1H, ArH), 6.50 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83-3.80 (m, 5H, OCH_3, CH_2), 3.61 (s, 2H, CH_2), 2.94 (s, 3H, SO_2CH_3), 2.88-2.84 (m, 2H, CH_2), 2.83-2.79 (m, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (Cquat.), 147.5 (Cquat.), 147.2 (Cquat.), 146.6 (Cquat.), 140.9 (Cquat.), 140.3 (Cquat.), 137.9 (Cquat.), 137.6 (+), 137.5 (Cquat.), 130.4 (+), 130.3 (+), 130.2 (Cquat.), 130.2 (+), 129.3 (Cquat.), 128.3 (+), 127.6 (+), 126.8 (+), 126.0 (Cquat.), 125.2 (+), 121.7 (+), 120.7 (+), 118.7 (+), 116.2 (Cquat.), 115.5 (+), 114.1 (+), 111.4 (+), 109.4 (+), 62.4 (–), 55.8 (+), 52.4 (+), 50.7 (–), 39.9 (+), 29.6 (–), 28.5 (–). **HRMS** (EI-MS) calcd. for $C_{39}H_{37}N_4O_7S$ $[M+H]^+$: 705.2377; found: 705.2376. **IR** (KBr) [cm^{-1}]: ν = 1687, 1518, 769.

Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido) benzoate 22e.

Yield 82%, yellow solid, **mp.** 93-96 °C, R_f = 0.22 (DCM/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.36 (s, 1H, NHCO), 9.27 (d, ^4J=1.6 Hz, 1H, ArH), 8.35-8.33 (m, 3H, ArH), 8.16 (d, ^3J=8.2 Hz, 1H, ArH), 8.01 (d, ^3J=8.5 Hz, 1H, ArH), 7.90 (d, ^3J=7.4 Hz, 1H, ArH), 7.83-7.81 (m, 1H, ArH), 7.67-7.64 (m, 1H, ArH), 7.48 (d, ^4J=0.6 Hz, 1H, ArH), 7.39 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.29 (dd, ^3J = 8.6, ^4J=1.6 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 6.61 (s, 2H, ArH), 4.13 (t, ^3J=5.0 Hz, 2H, CH_2), 4.07 (s, 3H, OCH_3), 3.85 (t, ^3J=5.3 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.73 (m, 2H, CH_2), 3.69-3.63 (m, 6H, 3 CH_2), 3.55-3.53 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.06-3.03 (m, 2H, CH_2), 2.89-2.84 (m, 9H, SO_2CH_3, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.8 (Cquat.), 148.2 (Cquat.), 146.5 (Cquat.), 146.4 (Cquat.), 140.9 (Cquat.), 140.3 (Cquat.), 137.9 (Cquat.), 137.6 (+), 136.9 (Cquat.), 136.7 (Cquat.), 130.4 (+), 130.3 (+), 130.2 (+), 130.2 (Cquat.), 129.3 (Cquat.), 128.2 (+), 127.6 (+), 126.7 (Cquat.), 126.5 (+), 125.2 (+), 121.0 (+), 120.6 (+), 118.7 (+), 116.1 (Cquat.), 115.6 (+), 114.2 (+), 112.2 (+), 111.9 (+), 71.8 (–), 70.7 (–), 70.5 (–), 70.4 (–), 69.6 (–), 68.6 (–), 60.1 (–), 58.9 (+), 55.9 (+), 55.4 (–), 52.4 (+), 50.8 (–), 39.5 (+), 33.5 (–), 28.4 (–). **HRMS** (EI-MS) calcd. for $C_{46}H_{51}N_4O_{10}S$ $[M+H]^+$: 851.3320; found: 851.3326. **IR** (KBr) [cm^{-1}]: ν = 2922, 1685, 1518, 771.

Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido) benzoate 22f.

Yield 63%, yellow solid, **mp.** 115-117 °C, R_f = 0.16 (DCM/MeOH 100/3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.35 (s, 1H, NHCO), 9.28 (d, ^4J=1.7 Hz, 1H, ArH), 8.36-8.31 (m, 3H, ArH), 8.16 (d, ^3J=8.2 Hz, 1H, ArH), 8.05 (d, ^3J=8.6 Hz, 1H, ArH), 7.88 (d, ^3J=8.2 Hz, 1H, ArH), 7.81 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.66-7.62 (m, 2H, ArH), 7.44 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 7.39 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 6.60 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.10 (t, ^3J=5.4 Hz, 2H, CH_2), 4.06 (s, 3H, OCH_3), 3.83 (t, ^3J=5.1 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 3.71 (dd, ^3J=5.9, ^3J=3.7 Hz, 2H, CH_2), 3.66-3.61 (m, 4H, 2 CH_2), 3.57 (s, 2H, CH_2), 3.54-3.51 (m, 2H, CH_2), 3.35 (s, 3H, OCH_3), 2.93 (s, 3H, SO_2CH_3), 2.83 (t, ^3J=5.6 Hz, 2H, CH_2), 2.76 (t, ^3J=5.7 Hz, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.6 (C=O), 149.8 (Cquat.), 148.1 (Cquat.), 146.5 (Cquat.), 146.3 (Cquat.), 140.8 (Cquat.), 140.2 (Cquat.), 137.8 (Cquat.), 137.5 (+), 137.4 (Cquat.), 134.8 (Cquat.), 130.3 (+), 130.2 (+), 130.1 (Cquat.), 130.1 (+), 129.2 (Cquat.), 128.2 (+), 127.5 (+), 126.8 (Cquat.),

126.7 (+), 126.5 (Cquat.), 125.1 (+), 121.5 (+), 120.6 (+), 118.6 (+), 116.1 (Cquat.), 115.3 (+), 114.1 (+), 112.2 (+), 111.9 (+), 71.8 (–), 70.6 (–), 70.5 (–), 70.4 (–), 69.5 (–), 68.6 (–), 62.4 (–), 58.9 (+), 55.9 (+), 55.5 (–), 52.4 (+), 50.6 (–), 39.7 (+), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{45}H_{49}N_4O_{10}S$ $[M+H]^+$: 837.3164; found: 837.3174. **IR** (KBr) [cm^{-1}]: ν = 2931, 1681, 1518, 767.

Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 22g.

Yield 38%, sticky yellow solid, R_f = 0.27 (DCM/MeOH 100/5). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.35 (s, 1H, NHCO), 9.26 (d, ^4J=1.6 Hz, 1H, ArH), 8.35-8.29 (m, 3H, ArH), 8.14 (d, ^3J=8.3 Hz, 1H, ArH), 8.00 (d, ^3J=8.6 Hz, 1H, ArH), 7.88 (d, ^3J=8.2 Hz, 1H, ArH), 7.80 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.67-7.59 (m, 1H, ArH), 7.46 (s, 1H, ArH), 7.37 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.30-7.25 (m, 1H, ArH), 6.85 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.60 (s, 1H, ArH), 4.11 (t, ^3J=5.0 Hz, 4H, 2 CH_2), 4.05 (s, 3H, OCH_3), 3.82 (t, ^3J=5.1 Hz, 4H, 2 CH_2), 3.75-3.70 (m, 4H, 2 CH_2), 3.66-3.62 (m, 10H, 5 CH_2), 3.53 (dd, ^3J=5.9, ^3J=3.3 Hz, 4H, 2 CH_2), 3.36 (s, 6H, 2 OCH_3), 3.03-2.98 (m, 2H, CH_2), 2.86 (s, 3H, SO_2CH_3), 2.88-2.75 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.9 (Cquat.), 147.5 (Cquat.), 147.1 (Cquat.), 146.6 (Cquat.), 141.0 (Cquat.), 140.3 (Cquat.), 137.9 (Cquat.), 137.7 (+), 137.0 (Cquat.), 136.9 (Cquat.), 130.5 (Cquat.), 130.4 (+), 130.3 (+), 130.2 (+), 129.3 (Cquat.), 128.3 (+), 127.6 (+), 127.5 (+), 127.2 (Cquat.), 126.5 (+), 125.2 (+), 121.1 (+), 120.6 (+), 118.8 (+), 116.1 (Cquat.), 115.6 (+), 115.0 (+), 114.3 (+), 113.3 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.1 (–), 69.0 (–), 60.4 (–), 59.0 (+), 55.7 (–), 52.5 (+), 51.0 (–), 39.5 (+), 33.8 (–), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{52}H_{63}N_4O_{13}S$ $[M+H]^+$: 983.4107; found: 983.4109. **IR** (KBr) [cm^{-1}]: ν = 2926, 2879, 1683, 1518.

Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido) benzoate 22h.

Yield 80%, sticky yellow solid, R_f = 0.27 ($CHCl_3$/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.37 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.32 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.05 (d, ^3J=8.6 Hz, 1H, ArH), 7.90 (d, ^3J=8.2 Hz, 1H, ArH), 7.82 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.67-7.62 (m, 2H, ArH), 7.44 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.15-4.05 (m, 7H, OCH_3, 2 CH_2), 3.86-3.76 (m, 6H, 3 CH_2), 3.75-3.69 (m, 4H, 2 CH_2), 3.68-3.61 (m, 8H, 4 CH_2), 3.56-3.51 (m, 6H, 3 CH_2), 3.36 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.93

(s, 3H, SO_2CH_3), 2.81-2.75 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (Cquat.), 147.5 (Cquat.), 147.1 (Cquat.), 146.6 (Cquat.), 140.9 (Cquat.), 140.3 (Cquat.), 138.0 (Cquat.), 137.7 (+), 137.5 (Cquat.), 135.0 (Cquat.), 130.4 (+), 130.3 (+), 130.3 (Cquat.), 130.2 (+), 129.4 (Cquat.), 128.3 (+), 127.6 (+), 127.2 (Cquat.), 126.8 (+), 125.2 (+), 121.6 (+), 120.7 (+), 118.8 (+), 116.2 (Cquat.), 115.5 (+), 115.1 (+), 114.2 (+), 113.2 (+), 71.9 (-), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.7 (–), 69.0 (–), 69.0 (–), 62.6 (–), 59.0 (+), 55.7 (–), 52.5 (+), 50.7 (–), 39.8 (+), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{51}H_{61}N_4O_{13}S$ $[M+H]^+$: 969.395; found: 969.3954. **IR** (KBr) [cm^{-1}]: ν = 2877, 1685, 1518, 769.

General procedure for the synthesis of indol derivatives 23a-h. A solution of **22a** (0.15 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.15 mmol, 1M in THF) was added and the reaction was stirred for 72 h at room temperature. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography.

Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23a.

Yield 57%, yellow solid, **mp.** 116-118 °C R_f = 0.29 (DCM/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 5% MeOD, 300 MHz): δ= 13.39 (s, 1H, NHCO), 9.99 (s, 1H, NH), 9.19 (d, ^4J=1.5 Hz, 1H, ArH), 8.36-8.29 (m, 3H, ArH), 8.10 (d, ^3J=8.4 Hz, 1H, ArH), 7.89 (d, ^3J=8.2 Hz, 1H, ArH), 7.81 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.67-7.61 (m, 1H, ArH), 7.51 (dd, ^3J=8.4, ^4J=1.7 Hz, 1H, ArH), 7.46 (s, 1H, ArH), 7.42-7.31 (m, 2H, ArH), 7.13-7.02 (m, 4H, ArH), 6.92 (s, 1H, ArH), 4.05 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2), 3.06-2.93 (m, 4H, 2 CH_2), 2.91-2.76 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 5% MeOD, 75 MHz) δ: 167.7 (C=O), 163.9 (C=O), 149.9 (Cquat.), 146.6 (Cquat.), 141.4 (Cquat.), 137.8 (Cquat.), 137.7 (+), 136.6 (Cquat.), 136.1 (Cquat.), 134.2 (Cquat.), 132.2 (Cquat.), 131.9 (+), 130.2 (+), 129.4 (Cquat.), 128.6 (+), 128.3 (+), 128.0 (Cquat.), 127.6 (+), 127.2 (Cquat.), 126.6 (+), 126.1 (+), 125.6 (+), 124.5 (+), 120.5 (+), 119.6 (+), 118.8 (+), 115.6 (+), 114.8 (Cquat.), 111.2 (+), 101.9 (+), 56.1 (–), 52.4 (+), 51.0 (–), 40.3 (–), 34.0 (–), 28.3 (–). **HRMS** (EI-MS) calcd. for $C_{37}H_{33}N_4O_3$ $[M+H]^+$: 581.2547; found: 581.2545. **IR** (KBr) [cm^{-1}]: ν = 1681, 1519, 771, 740.

Methyl 4-(5-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23b.

Yield 34%, yellow solid, **mp.** 204-206 °C R_f = 0.20 ($CHCl_3$/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.40 (s, 1H, NHCO), 9.36 (d, ^4J=1.6 Hz, 1H, ArH), 8.95 (s, 1H, NH), 8.39-8.30 (m, 3H, ArH), 8.13 (d, ^3J=8.3 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.82 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.70-7.64 (m, 1H, ArH), 7.63 (s, 1H, ArH), 7.48 (dd, ^3J=8.4, ^4J=1.7 Hz, 1H, ArH), 7.39 (d, ^3J=8.3 Hz, 1H, ArH), 7.29 (dd, ^3J=8.3, ^4J=1.3 Hz, 1H, ArH), 7.10-7.07 (m, 3H, ArH), 7.02-6.94 (m, 2H, ArH), 4.07 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2), 3.69 (s, 2H, CH_2), 2.92 (t, ^3J=5.5 Hz, 2H, CH_2), 2.80 (t, ^3J=5.7 Hz, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (C=O), 163.9 (C=O), 146.6 (Cquat.), 137.7 (+), 136.8 (Cquat.), 136.6 (Cquat.), 134.9 (Cquat.), 134.4 (Cquat.), 131.9 (+), 131.6 (Cquat.), 130.2 (+), 129.4 (Cquat.), 129.3 (Cquat.), 128.9 (Cquat.), 128.7 (+), 128.3 (+), 127.6 (+), 126.6 (+), 126.0 (+), 125.5 (+), 125.0 (+), 121.5 (+), 119.7 (+), 118.8 (+), 115.7 (+), 114.9 (+), 111.1 (+), 102.1 (+), 63.2 (–), 56.0 (–), 52.4 (+), 50.5 (–), 29.1 (–). **HRMS** (EI-MS) calcd. for $C_{36}H_{31}N_4O_3$ $[M+H]^+$: 567.2391; found: 567.240. **IR** (KBr) [cm^{-1}]: ν = 3408, 1683, 1514, 773.

Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23c.

Yield 70%, yellow solid, **mp.** 118-120 °C R_f = 0.24 (DCM/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 5% MeOD, 300 MHz): δ= 13.35 (s, 1H, NHCO), 10.18 (s, 1H, NH), 9.14 (d, ^4J=1.4 Hz, 1H, ArH), 8.30-8.27 (m, 3H, ArH), 8.06 (d, ^3J=8.4 Hz, 1H, ArH), 7.85 (d, ^3J=8.1 Hz, 1H, ArH), 7.81-7.75 (m, 1H, ArH), 7.61 (t, ^3J=7.5 Hz, 1H, ArH), 7.51-7.43 (m, 2H, ArH), 7.36 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.3, ^4J=1.2 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.59 (s, 1H, ArH), 6.54 (s, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3), 3.70 (s, 2H, CH_2), 3.00 (dd, ^3J=10.6, ^3J=5.4 Hz, 2H, CH_2), 2.85-2.80 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 5% MeOD, 75 MHz) δ 167.6 (C=O), 163.7 (C=O), 149.6 (Cquat.), 147.5 (Cquat.), 147.2 (Cquat.), 146.5 (Cquat.), 140.8 (Cquat.), 138.1 (Cquat.), 137.6 (+), 136.6 (Cquat.), 136.3 (Cquat.), 131.8 (+), 131.5 (Cquat.), 130.2 (+), 130.2 (+), 129.3 (Cquat.), 129.1 (Cquat.), 128.3 (+), 127.6 (+), 126.1 (Cquat.), 125.9 (Cquat.), 124.2 (+), 120.3 (+), 120.0 (+), 118.7 (+), 115.5 (+), 114.7 (Cquat.), 111.3 (+), 111.3 (+), 109.4 (+), 101.4 (+), 60.8 (–), 55.9 (+), 55.8 (+), 55.5 (–), 52.4 (+), 50.9 (–), 33.8 (–), 28.3 (–). **HRMS** (EI-MS) calcd. for $C_{39}H_{37}N_4O_5$ $[M+H]^+$: 641.2758; found: 641.2763. **IR** (KBr) [cm^{-1}]: ν = 3520, 1668, 1518, 775.

Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23d.

Yield 75%, yellow solid, **mp.** 168-170 °C R_f = 0.23 ($CHCl_3$/MeOH 100/5). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.31 (s, 1H, NHCO), 9.31 (d, ^4J=1.6 Hz, 1H, ArH), 9.13 (s, 1H, NH), 8.30-8.25 (m, 3H, ArH), 8.04 (d, ^3J=8.4 Hz, 1H, ArH), 7.84 (d, ^3J=8.1 Hz, 1H, ArH), 7.80-7.73 (m, 1H, ArH), 7.64-7.57 (m, 2H, ArH), 7.39 (dd, ^3J=8.4, ^4J=1.6 Hz, 1H, ArH), 7.32 (d, ^3J=8.3 Hz, 1H, ArH), 7.25 (dd, ^3J=8.4, ^4J=1.2 Hz, 1H, ArH), 6.92 (d, ^4J=1.5 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 6.47 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2), 3.57 (s, 2H, CH_2), 2.81 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.6 (C=O), 163.8 (C=O), 149.8 (Cquat.), 147.4 (Cquat.), 147.1 (Cquat.), 146.5 (Cquat.), 141.3 (Cquat.), 137.7 (Cquat.), 137.6 (+), 136.8 (Cquat.), 136.7 (Cquat.), 131.8 (+), 130.2 (+), 130.1 (+), 130.0 (Cquat.), 129.3 (Cquat.), 128.9 (Cquat.), 128.2 (+), 127.6 (+), 126.8 (Cquat.), 126.3 (Cquat.), 124.9 (+), 121.5 (+), 119.6 (+), 118.7 (+), 115.7 (+), 114.8 (Cquat.), 111.4 (+), 111.2 (+), 109.5 (+), 102.0 (+), 63.2 (–), 55.9 (+), 55.8 (+), 55.6 (–), 52.4 (+), 50.7 (–), 28.7 (–). **HRMS** (EI-MS) calcd. for $C_{38}H_{35}N_4O_5$ $[M+H]^+$: 627.2602; found: 627.2608. **IR** (KBr) [cm^{-1}]: ν = 3408, 1683, 1516, 771.

Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydro isoquino lin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23e.

Yield 65%, yellow solid, **mp.** 128-130 °C R_f = 0.20 (DCM/MeOH 100/5). **^{1}H NMR** ($CDCl_3$, 5% MeOD, 300 MHz): δ= 13.35 (s, 1H, NHCO), 9.96 (s, 1H, NH), 9.18 (d, ^4J=1.2 Hz, 1H, ArH), 8.30-8.27 (m, 3H, ArH), 8.06 (d, ^3J=8.4 Hz, 1H, ArH), 7.86 (d, ^3J=8.2 Hz, 1H, ArH), 7.82-7.75 (m, 1H, ArH), 7.62 (t, ^3J=7.5 Hz, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 7.35 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.3, ^4J=1.2 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.59 (s, 2H, ArH), 4.12 (t, ^3J=5.2 Hz, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.85 (t, ^3J=5.1 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.74-3.70 (m, 2H, CH_2), 3.67-3.62 (m, 6H, 3 CH_2), 3.54 (dd, ^3J=5.8, ^3J=3.3 Hz, 2H, CH_2), 3.36 (s, 3H, OCH_3), 2.99 (dd, ^3J=10.5, ^3J=5.4 Hz, 2H, CH_2), 2.82 (dd, ^3J=9.9, ^3J=6.0 Hz, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 5% MeOD, 75 MHz,) δ: 167.7 (C=O), 163.8 (C=O), 149.7 (Cquat.), 148.1 (Cquat.), 146.5 (Cquat.), 146.4 (Cquat.), 141.0 (Cquat.), 138.1 (Cquat.), 137.6 (+), 136.7 (Cquat.), 136.4 (Cquat.), 131.8 (+), 131.7 (Cquat.), 130.2 (+), 129.3 (Cquat.), 129.1 (Cquat.), 128.3 (+), 127.6 (+), 126.8 (Cquat.), 126.4 (Cquat.), 124.2 (+), 120.3 (+), 119.9 (+), 118.7 (+), 115.6 (+), 114.7 (Cquat.), 112.2 (+), 111.9 (+), 111.4 (+), 101.5 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.6 (–), 68.6 (–), 60.9 (–), 59.0 (+), 55.9 (+), 55.6 (–), 52.4 (+), 51.0 (–), 33.9 (–), 28.5 (–). **HRMS** (EI-MS) calcd. for $C_{45}H_{49}N_4O_8$ $[M+H]^+$: 773.3545; found: 773.3544. **IR** (KBr) [cm^{-1}]: ν = 3533, 2916, 2833, 1681, 1516, 771.

Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23f.

Yield 18%, light yellow solid, **mp.** 110-112 °C R_f = 0.15 ($CHCl_3$/MeOH 100/4). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ= 13.34 (s, 1H, NHCO), 9.32 (d, ^4J=1.7 Hz, 1H, ArH), 9.18 (s, 1H, NH), 8.31-8.29 (m, 3H, ArH), 8.08 (d, ^3J=8.3 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.79 (ddd, ^3J=8.3, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.65-7.61 (m, 1H, ArH), 7.59 (s, 1H, ArH), 7.44 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.36 (d, ^3J=8.3 Hz, 1H, ArH), 7.27-7.25 (m, 1H, ArH), 6.95 (d, ^4J=1.5 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 6.52 (s, 1H, ArH), 4.07 (t, ^3J=5.4 Hz, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.81 (t, ^3J=5.1 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2), 3.70 (dd, ^3J=5.9, ^3J=3.7 Hz, 2H, CH_2), 3.65-3.61 (m, 4H, 2 CH_2), 3.56 (s, 2H, CH_2), 3.53-3.50 (m, 2H, CH_2), 3.35 (s, 3H, OCH_3), 2.82 (t, ^3J=5.5 Hz, 2H, CH_2), 2.76 (t, ^3J=5.6 Hz, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.7 (C=O), 149.8 (Cquat.), 148.0 (Cquat.), 146.5 (Cquat.), 146.3 (Cquat.), 141.2 (Cquat.), 137.7 (Cquat.), 137.6 (+), 136.8 (Cquat.), 136.6 (Cquat.), 131.8 (+), 130.1 (+), 130.1 (+), 129.9 (Cquat.), 129.3 (Cquat.), 128.8 (Cquat.), 128.2 (+), 127.5 (+), 127.0 (Cquat.), 126.8 (Cquat.), 124.8 (+), 121.4 (+), 119.5 (+), 118.7 (+), 115.7 (+), 114.7 (Cquat.), 112.2 (+), 111.9 (+), 111.1 (+), 101.9 (+), 71.8 (–), 70.7 (–), 70.5 (–), 70.4 (–), 69.5 (–), 68.5 (–), 63.1 (–), 58.9 (+), 55.9 (+), 55.5 (–), 52.3 (+), 50.5 (–), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{44}H_{47}N_4O_8$ $[M+H]^+$: 759.3394; found: 759.3408. **IR** (KBr) [cm^{-1}]: ν = 2900, 2875, 1681, 1516, 771.

Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23g.

Yield 53%, sticky light yellow oil, R_f = 0.23 (DCM/MeOH 100/5). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.33 (s, 1H, NHCO), 9.31 (d, ^4J=1.5 Hz, 1H, ArH), 9.25 (s, 1H, NH), 8.33-8.26 (m, 3H, ArH), 8.07 (d, ^3J=8.4 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.82-7.75 (m, 1H, ArH), 7.66-7.59 (m, 1H, ArH), 7.46-7.43 (m, 2H, ArH), 7.33 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.4, ^4J=1.3 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.58 (s, 1H, ArH), 4.11 (t, ^3J=5.0 Hz, 4H, 2 CH_2), 4.04 (s, 3H, OCH_3), 3.82 (t, ^3J=5.1 Hz, 4H, 2 CH_2), 3.75-3.70 (m, 4H, 2 CH_2), 3.69-3.61 (m, 10H, 5 CH_2), 3.54 (dd, ^3J=5.9, ^3J=3.3 Hz, 4H, 2 CH_2), 3.36 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.99 (dd, ^3J=10.1, ^3J=5.6 Hz, 2H, CH_2), 2.83-2.77 (m, 6H, 3 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 167.7 (C=O), 163.8 (C=O), 149.8 (Cquat.), 147.4 (Cquat.), 147.0 (Cquat.), 146.5 (Cquat.), 141.3 (Cquat.), 137.9 (Cquat.), 137.6 (+), 136.6 (Cquat.), 136.2 (Cquat.), 132.0 (Cquat.), 131.8 (+), 130.2 (+), 129.3 (Cquat.), 129.2 (Cquat.), 128.2 (+), 127.6 (+), 127.2 (Cquat.), 124.3 (+), 120.4 (+), 119.5 (+), 118.7 (+), 115.7 (+), 114.9 (+), 114.7 (Cquat.), 113.2 (+), 111.3 (+), 101.7 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.0 (–),

68.9 (–), 61.0 (–), 59.0 (+), 55.7 (–), 52.4 (+), 51.0 (–), 34.1 (–), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{51}H_{61}N_4O_{11}$ $[M+H]^+$: 905.4331; found: 905.4333. **IR** (KBr) [cm^{-1}]: ν = 2870, 1683, 1516, 771.

Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1H-indol-2-yl)-2-(quinoline-2-carboxamido)benzoate 23h.

Yield 55%, light yellow oil, R_f = 0.18 ($CHCl_3$/MeOH 100/6). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ= 13.37 (s, 1H, NHCO), 9.34 (d, ^4J=1.5 Hz, 1H, ArH), 9.15 (s, 1H, NH), 8.36-8.28 (m, 3H, ArH), 8.11 (d, ^3J=8.4 Hz, 1H, ArH), 7.89 (d, ^3J=8.1 Hz, 1H, ArH), 7.84-7.76 (m, 1H, ArH), 7.66-7.59 (m, 2H, ArH), 7.48 (dd, ^3J=8.4, ^4J=1.5 Hz, 1H, ArH), 7.38 (d, ^3J=8.3 Hz, 1H, ArH), 7.26 (dd, ^3J=8.3, ^4J=1.1 Hz, 1H, ArH), 6.96 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.12-4.05 (m, 5H, OCH_3, CH_2), 3.82-3.60 (m, 20H, 10 CH_2), 3.55-3.49 (m, 6H, 3 CH_2), 3.36 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.82-2.71 (m, 4H, 2 CH_2). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (Cquat.), 147.3 (Cquat.), 147.0 (Cquat.), 146.6 (Cquat.), 141.4 (Cquat.), 137.8 (Cquat.), 137.7 (+), 136.8 (Cquat.), 136.7 (Cquat.), 131.9 (+), 130.2 (+), 130.0 (+), 129.4 (Cquat.), 128.9 (Cquat.), 128.3 (+), 127.9 (Cquat.), 127.6 (+), 127.3 (Cquat.), 124.9 (+), 121.4 (+), 119.6 (+), 118.8 (+), 115.7 (+), 115.1 (+), 114.8 (Cquat.), 113.1 (+), 111.2 (+), 102.0 (+), 77.2 (–), 71.9 (–), 70.7 (–), 70.7 (–), 70.6 (–), 70.6 (–), 70.5 (–), 70.5 (–), 69.7 (–), 69.7 (–), 68.9 (–), 63.2 (–), 59.0 (+), 55.6 (–), 52.4 (+), 50.6 (–), 28.6 (–). **HRMS** (EI-MS) calcd. for $C_{50}H_{59}N_4O_{11}$ $[M+H]^+$: 891.4175; found: 891.4178. **IR** (KBr) [cm^{-1}]: ν = 2872, 1685, 1516, 771.

Drugs and chemicals used for analysis.

A Milli-Q system (Millipore, Eschborn, Germany) was used for the purification of water in aqueous drug solutions. All chemicals used were of analytical grade, if not otherwise mentioned. Hoechst 33342 (Invitrogen, Karlsruhe, Germany) was dissolved in sterile water to produce a 0.8 mM working solution. Test compounds were dissolved in DMSO (Merck, Darmstadt, Germany) at a concentration of 10 mM. All stocks were stored at -20 °C. Topotecan (Sigma, Munich,Germany) was diluted in 70 % ethanol to a concentration of 0.1 mM and stored at 4 °C. PBS (phosphate buffered saline) was made of 8.0 g/L NaCl, 1.0 g/L $Na_2HPO_4 \cdot 2\ H_2O$, 0.20 g/L KCl, 0.20 g/L KH_2PO_4 and 0.15 g/L $NaH_2PO_4 \cdot H_2O$. The pH-value was adjusted to 7.3 - 7.4 by using a 1 M NaOH or HCl solution. Phosphate buffered saline with calcium and magnesium was made by dissolving 0.2 g/L KCl, 0.2 g/L KH_2PO_4, 8.0 g/L NaCl, 1.15 g/L $Na_2HPO_4 \cdot 2\ H_2O$ in water followed by adding 0.132 g/L of $CaCl_2 \cdot 2\ H_2O$ and 0.10 g/L of $MgCl_2 \cdot 6\ H_2O$. Adjusting the pH-value to 7.3 was performed by the dropwise addition of a 1 M NaOH solution. Fumitremorgin C (FTC, Merck, Darmstadt, Germany) was also dissolved in

DMSO and diluted to a concentration of 1 mM. A solution of 4 % (m/m) of paraformaldeyde (Merck, Darmstadt, Germany) in PBS was made by stirring 1.5 g of paraformaldehyde per 50 g total solution while heating on a magnetic stirrer for approximately 30 min. Tariquidar (free base) was synthesized according to the literature with slight modifications.[43] Elacridar was kindly provided by GlaxoSmith-Kline (Research Triangle Park, NC). Calcein-AM, purchased from Biotrend (Cologne, Germany), was dissolved in DMSO (Merck, Darmstadt, Germany) to achieve a final concentration of 100 μM.

Cell lines and culture condition.

Kb-V1 cells, an ABCB1 overexpressing subclone of KB cells (ATCC CCL-17), were maintained in Dulbecco's modified Eagle's medium (Sigma, Deisenhofen, Germany) supplemented with 10% FCS (Biochrom, Berlin, Germany) and 270 ng/mL vinblastine.

MCF-7/Topo cells, an ABCG2 overexpressing subclone of MCF-7 breast cancer adenocarcinoma cells (ATTC HTB-22) were obtained by passaging the MCF-7 cells with increasing concentrations of topotecan in the culture medium to a maximum concentration of 0.50 μM. Having reached the final concentration of topotecan, the cells were passaged after trypsinization using 0.05% trypsin/0.02% EDTA (PAA Laboratories, Pasching, Austria) every 3-5 days. The treated cells showed sufficient quantities of the ABCG2 transporter after three passages in Eagle's minimum essential medium (Sigma, Deisenhofen, Germany) containing L-glutamine, 2.2 g/L $NaHCO_3$ (Merck, Darmstadt, Germany), 0.11 g/L sodium pyruvate (Serva, Heidelberg, Germany), 10% fetal calf serum (Biochrom, Berlin, Germany), and topotecan at a concentration of 0.50 μM.

Modulation of ABCB1 (P-gp) by the flow cytometric calcein-AM assay and ABCG2 by Hoechst 33342 assay.

These assay were performed as described before.[30]

Stability Investigations in Mouse Plasma.

These assay were performed as described before.[31]

3.5 References

1. Ferlay, J.; Shin, H. R.; Bray, F.; Forman, D.; Mathers, C.; Parkin, D. M. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Available at: http://globocan.iarc.fr (Last accessed 15/12/2011).
2. Jemal, A.; Bray, F.; Center, M. M.; Ferlay, J.; Ward, E.; Forman, D. *Cancer J. Clin.* **2011,** 61, 69.

3. Mitscher, L. A.; Pillai, S. P.; Gentry, E. J.; Shankel, D. M. *Med. Res. Rev.* **1999,** 19, 477.
4. Hegedűs, C.; Szakács, G.; Homolya, L.; Orbán, T. I.; Telbisz, Á.; Jani, M.; Sarkadi, B. *Adv. Drug Delivery Rev.* **2009,** 61, 47.
5. Dean, M.; Rzhetsky, A.; Allikmets, R. *Genome Res.* **2001,** 11, 1156.
6. Glavinas, H.; Krajcsi, P.; Cserepes, J.; Sarkadi, B. *Curr. Drug Deliv.* **2004,** 1, 27.
7. Mayur, Y. C.; Peters, G. J.; Prasad, V. V. S. R.; Lemos, C.; Sathish, N. K. *Curr. Cancer Drug Targets* **2009,** 9, 298.
8. Ambudkar, S. V.; Dey, S.; Hrycyna, C. A.; Ramachandra, M.; Pastan, I.; Gottesman, M. M. *Annu. Rev. Pharmacol. Toxicol.* **1999,** 39, 361.
9. Gatti, L.; Beretta, G. L.; Cossa, G.; Zunino, F.; Perego, P. *Mini-Rev. Med. Chem.* **2009,** 9, 1102.
10. Robey, R. W.; To, K. K. K.; Polgar, O.; Dohse, M.; Fetsch, P.; Dean, M.; Bates, S. E. *Adv. Drug Deliv. Rev.* **2009,** 61, 3.
11. Noguchi, K.; Katayama, K.; Mitsuhashi, J.; Sugimoto, Y. *Adv. Drug Deliv. Rev.* **2009,** 61, 26.
12. Pleban, K.; Ecker, G. F. *Mini-Rev. Med. Chem.* **2005,** 5, 153.
13. Baumert, C.; Hilgeroth, A. *Anti-Cancer Agents Med. Chem.* **2009,** 9, 415.
14. Yang, K.; Wu, J.; Li, X. *Biosci. Trends* **2008,** 2, 137.
15. Mistry, P.; Stewart, A. J.; Dangerfield, W.; Okiji, S.; Liddle, C.; Bootle, D.; Plumb, J. A.; Templeton, D.; Charlton, P. *Cancer Res.* **2001,** 61, 749.
16. Egger, M.; Li, X.; Müller, C.; Bernhardt, G.; Buschauer, A.; König, B. *Eur. J. Org. Chem.* **2007**, 2643.
17. Rabindran, S. K.; Ross, D. D.; Doyle, L. A.; Yang, W.; Greenberger, L. M. *Cancer Res.* **2000,** 60, 47.
18. Loevezijn, A. v.; Allen, J. D.; Schinkel, A. H.; Koomen, G.-J. *Bioorg. Med. Chem. Lett.* **2001,** 11, 29.
19. Allen, J. D.; Loevezijn, A. v.; Lakhai, J. M.; Valk, M. v. d.; Tellingen, O. v.; Reid, G.; Schellens, J. H. M.; Koomen, G.-J.; Schinkel, A. H. *Mol. Cancer Ther.* **2002,** 1, 417.
20. Perego, P.; Cesare, M. D.; Isabella, P. D.; Carenini, N.; Beggiolin, G.; Pezzoni, G.; Palumbo, M.; Tartaglia, L.; Pratesi, G.; Pisano, C.; Carminati, P.; Scheffer, G. L.; Zunino, F. *Cancer Res.* **2001,** 61, 6034.
21. Versiani, M. A.; Diyabalanage, T.; Ratnayake, R.; Henrich, C. J.; Bates, S. E.; McMahon, J. B.; Gustafson, K. R. *J. Nat. Prod.* **2011,** 74, 262.
22. Pick, A.; Müller, H.; Mayer, R.; Haenisch, B.; Pajeva, I. K.; Weigt, M.; Bönisch, H.; Müller, C. E.; Wiese, M. *Bioorg. Med. Chem.* **2011,** 19, 2090.

23. Weiss, J.; Rose, J.; Storch, C. H.; Ketabi-Kiyanvash, N.; Sauer, A.; Haefeli, W. E.; Efferth, T. *J. Antimicrob. Chemother.* **2007,** 59, 238.
24. Shi, Z.; Tiwari, A. K.; Shukla, S.; Robey, R. W.; Kim, I.-W.; Parmar, S.; Bates, S. E.; Si, Q.-S.; Goldblatt, C. S.; Abraham, I.; Fu, L.-W.; Ambudkar, S. V.; Chen, Z.-S. *Biochem. Pharmacol.* **2009,** 77, 781.
25. Tiwari, A. K.; Sodani, K.; Wang, S.-R.; Kuang, Y.-H.; Jr., C. R. A.; Chen, X.; Chen, Z.-S. *Biochem. Pharmacol.* **2009,** 78, 153.
26. Pick, A.; Müller, H.; Wiese, M. *Bioorg. Med. Chem.* **2008,** 16, 8224.
27. Pick, A.; Müller, H.; Wiese, M. *Bioorg. Med. Chem. Lett.* **2010,** 20, 180.
28. Müller, C. PhD Thesis, Universität Regensburg, Regensburg, **2007**.
29. Kühnle, M.; Egger, M.; Müller, C.; Mahringer, A.; Bernhardt, G.; Fricker, G.; König, B.; Buschauer, A. *J. Med. Chem.* **2009,** 52, 1190.
30. Puentes, C. O.; Höcherl, P.; Kühnle, M.; Bauer, S.; Bürger, K.; Bernhardt, G.; Buschauer, A.; König, B. *Bioorg. Med. Chem. Lett.* **2011,** 21, 3654.
31. Kühnle, M. PhD Thesis, Universität Regensburg, Regensburg, **2010**.
32. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
33. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005,** 105, 2873.
34. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006,** 106, 2875.
35. Taber, F. D.; Tirunahari, K. P. *Tetrahedron* **2011,** 67, 7195.
36. Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988,** 36, 1305.
37. Chouzier, S.; Gruber, M.; Djakovitch, L. *J. Mol. Catal. A: Chem.* **2004,** 212, 43.
38. Oskooie, H. A.; Heravi, M. M.; Behbahani, F. K. *Molecules* **2007,** 12, 1438.
39. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007,** 107, 874.
40. Blurton, P.; Burkamp, F.; Churcher, I.; Harrison, T.; Neduvelil, J. WO 2006/008558 A1, **2006**.
41. Weinstain, R.; Sagi, A.; Karton, N.; Shabat, D. *Chem. Eur. J.* **2008,** 14, 6857.
42. Bause, M. MS Thesis, Universität Regensburg, Regensburg, **2011**.
43. Höcherl, P. PhD Thesis, Universität Regensburg, Regensburg, **2010**.
44. Hubensack, M. PhD. Thesis, Universität Regesnburg, Regensburg, **2005**.

4. Summary

Three different classes of selective ABCG2 modulator (BCRP, breast cancer resistance protein) derived from the lead structure tariquidar have been prepared in this thesis.

In chapters one and two the solid phase synthesis approach was used to obtain new derivatives of the lead structure and two different methodologies were developed. A very simple, effective and straightforward method of synthesis using Wang resing as solid support was developed in chapter one. A small library of new tariquidar derivatives was obtained in very good yields, improving thus the solution synthesis previously reported. Some of the new compounds bearing a triethylenglycol chain at the tetrahydroisoquinoline core proved to be better soluble in comparison to the other analogs. The inhibitory activity against ABCB1 and ABCG2 transporters were evaluated for all the compounds synthesized. During this work it was discovered that the methyl esters bearing both, a triethylene glycol ether and a quinoline-2-carboxamido substituent, showed selectivity for ABCG2 over ABCB1 and are superior compared to the lead structure with respect to the maximal inhibitory effect. These compounds are among the most potent and selective ABCG2 modulators reported so far and might be useful to reverse the multidrug phenomenon in cancer cells.

The second chapter, in which Wang resing was also used as solid support, describes a methodology more elaborated for the synthesis of new tariquidar-like derivatives. In order to obtain more stable compounds, the amide bond between the amino anthranilic ring and the tetrahydroisoquinolineethylphenylamine moiety was replaced and the two fragments of the molecule were linked by a C-C bond using Suzuki coupling. A set of eight compounds were obtained using the solid phase methodology, and four compounds were synthesized in solution. ABCB1 and ABCG2 inhibitory activity of the analogues were determined in the calcein-AM and the Hoechst 33342 microplate assay, respectively, and its result showed that all tested compounds are selective to ABCG2. The most potent compound in this series has an IC_{50} value of 591± 87 nM, and I_{max} 109% relative to FTC. Stability test, performed in mouse plasma, revealed that the enzymatic degradation of this derivative starts after 30 min, but after 24 h, around 60% of the compound still remains intact. The structural characteristics of the compounds here obtained together with their activity may contribute to design a new class of active and more stable tariquidar derivatives.

The last chapter describes the synthesis of another class of ABCG2 inhibitors bearing an indole core unit. The modifications were done to overcome stability problems and to improve the solubility of the compounds. In the new compounds, that share structural characteristics of the

best inhibitors previously synthesized, an indole fragment was introduced as central core in order to increase the stability of the compound. The indole fragment was synthesized by a Sonogashira coupling followed by palladium catalyzed cyclization to the heterocycle. The mesyl group at the nitrogen of the indole was removed and the selectivity and inhibitory activity of the compounds for ABCG2 was determined. The most potent and promising compound has a lower IC_{50} value (59 ± 14 nM) and a very close maximal inhibitory effect (I_{max} 100%) compared to the most potent and selective ABCG2 reported so far **Ko143**, (117 ± 53 nM, I_{max} 103 ± 7%). The selectivity, the increased activity and the biological stability of some analogues render these compounds good candidates for *in vivo* studies in order to overcome drug resistance of tumor cells associated to ABCG2 transporters.

5. Zusammenfassung

In dieser Arbeit wurden ausgehend von Tariquidar (Leitstruktur) drei verschiedene Klassen von ABCG2 selektiven Modulatoren (BCRP, breast cancer resistance protein) erhalten.

Kapitel 1 und 2 beschreiben die Entwicklung von zwei verschiedenen Methoden an Festphasensystemen, welche anschließend zur Synthese von neuen Derivaten der Leitstruktur eingesetzt wurden. Kapitel 1 beschäftigt sich mit einer sehr einfachen, effektiven und geradlinigen Synthesestrategie unter Verwendung von Wang Harz als Festphasenmaterial. Mit dieser Strategie wurde eine kleine Bibliothek von Tariquidar analogen Verbindungen in sehr guten Ausbeuten hergestellt , was eine Optimierung gegenüber der Synthese in Lösung darstellt. Die Einführung einer Triethylenglykol-Kette an der Tetrahydroisochinolin-Einheit einiger der neuen Verbindungen führte zu einer deutlichen Verbesserung der Löslichkeit im Vergleich zu den nicht substituierten Derivaten. Für alle dargestellten Verbindungen wurde die Aktivität für die Hemmung des ABCB1- und ABCG2-Transporter ermittelt. Während diesen Untersuchungen stellte sich heraus, dass die Verbindungen mit Methylester, welche sowohl eine Triethylenglykol-Kette als auch einen Chinolin-2-carboxamid Substituenten tragen, eine Selektivität für den ABCG2- gegenüber den ABCB1-Transporter aufweisen. Des Weiteren sind diese im Hinblick auf den maximalen inhibitorischen Effekt der Leitstruktur überlegen. Diese Verbindungen zählen zu den wirksamsten und selektivsten bekannten ABCG2- Modulatoren und könnten zur Behandlung von multiwirkstoffresistenten Krebszellen beitragen.

Kapitel 2 beschreibt eine sorgfältig ausgearbeitete Methode, die ebenfalls auf dem Einsatz von Wang Harz als Festphase basiert und zur Synthese von neuen Tariquidar-ähnlichen Verbindungen geeignet ist. Um die Stabilität der Verbindungen gegenüber enzymatischer Hydrolyse zu erhöhen, wurde die Amidbindung zwischen der dreifach substituierten aromatischen Teilstruktur und der Tetraisochinolin-ethylphenylamin Einheit mittels einer Suzuki Kupplung durch eine direkte C-C–Verknüpfung der beiden Fragmente ersetzt. Der Einsatz der festphasengestützten Synthese führte zu einer Serie von acht verschiedenen Verbindungen, sowie eine konventionelle Synthese in Lösung zu weiteren vier Derivaten. Anschließend wurden alle Verbindungen mit Hilfe eines Calcein-AM-Assays bzw. eines Hoechst 33342 Microplate Assays auf ihre Aktivität als ABCB1- und ABCG2-Inbihitor untersucht. Alle Derivate zeigten im Test eine Selektivität für den ABCG2-Transporter, wobei die wirksamste Verbindung dieser Serie einen IC_{50} Wert von 591± 87 nM und eine maximale Inhibition I_{max} von 109% relativ zu FTC erreichte. Weitergehende Studien zur Stabilität dieser Verbindung gegenüber enzymatischer Zersetzung in Mäuseplasma zeigten zum einen den Beginn des Abbaus nach bereits 30 min und zum anderen, dass nach 24 Std. noch 60% der

Verbindung intakt vorhanden waren. Die strukturellen Eigenschaften der Tariquidar-ähnlichen Verbindungen zusammen mit ihrer Aktivität könnten zum Design einer neuen Klasse von stabileren und aktiven Derivaten beitragen.

Das letzte Kapitel der Arbeit handelt von der Synthese einer weiteren Klasse von ABCG2-Inhibitoren, welche als Modifikation eine zentrale Indol-Einheit zur Verbesserung der Löslichkeit und zur Reduzierung des Stabilitätsproblems beinhalten. Diese neuen Verbindungen vereinen strukturelle Eigenschaften der aktivsten Inhibitoren aus Kapitel 1 und 2 mit einem zentralen Indol-Fragment zur Erhöhung der Stabilität gegenüber enzymatischer Zersetzung. Die Synthesestrategie zum Aufbau der Indol-Einheit besteht aus einer Sonogashira Kupplung gefolgt von einer weiteren Palladium katalysierten Reaktion zur Zyklisierung. Nach dem Entfernen der Mesyl-Schutzgruppe am Indol-Stickstoff wurde wiederum die Selektivität und Aktivität als Inhibitor für den ABCG2-Transporter bestimmt. Die vielversprechendste und wirksamste Verbindung aus dieser Serie besitzt einen besseren IC_{50} Wert von 59 ± 14 nM und einen nahezu maximalen inhibitorischen Effekt I_{max} von 100% im Vergleich zum bekannten, wirksamsten und selektivsten ABCG2-Inhibitor **Ko143** (117 ± 53 nM, Imax 103 ± 7%).
Die erhöhte Aktivität und Selektivität sowie die erhöhte biologische Stabilität von einigen Derivaten machen diese zu guten Kandidaten für in vivo Studien um das Problem von multiwirkstoffresistenten Tumorzellen, welche in Verbindung mit ABCG2-Transporter auftreten, zu überwinden.

6. Abbreviations

ABC	ATP binding cassette
ABCB1	ABC transporter B1, pgylocoprotein 170
ABCG2	ABC transporter G2, breast cancer resistance protein
ATP	Adenosine triphosphate
BBB	Blood brain barrier
BCRP	Breast cancer resistance protein
$(Boc)_2O$	t-Butyloxycarbonyl
Calcein-AM	Calcein-acetoxymethylester
Calcd	Calculated
CI	Chemical ionization
DCC	Dicyclohexylcarbo diimide
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DME	1,2-Dimethoxyethan
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	*N*-(3-Dimethylamino propyl)-*N*′-ethylcarbo diimide
Et_2O	Diethylether
EMEM	Eagels minimum essential medium
eq	Equivalent
EI-MS	Electron-impact ionization mass spectrometry
ESI	Electronspray ionisation
EtOAc	Ethyl acetate
EtOH	Ethanol
FCS	Fetal calf serum
FTC	Fumitremorgin C
FT	Fourier transformed
GHS	Glutathione
HBTU	(2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HIV	Human immunodeficiency virus
HOAt	(1-Hydroxy-7-azabenzotriazole).
HOBt	1-Hydroxy benzotriazole
HPLC	High pressure liquid chromatography
HR-MS	High resolution mass spectrometry
5-HT	5-Hydroxytryptamin
IARC	International agency for research on cancer
IC_{50}	Half maximal inhibitory concentration
I_{max}	Maximal inhibitory effect
IR	Infrared spectroscopy
J	Coupling constant

MCF-7/Topo	Topotecan resistant human breast cancer cells
MDR	Multidrug resistance
MRPs	Multidrug resistance-associated proteins
Me	Methyl
MeOH	Methanol
MF	Molecular formula
Mp	Melting point
MS	Mass spectrometry
MsCl	Mesyl chloride
MW	Molecular weight
NBF	Nucleotide binding fold
NMR	Nuclear magnetic resonance
PBS	Phosphate buffered saline
PE	Petrol ether (hexanes)
PET	Proton emission tomography
P-gp	P-glycoprotein
PhH	Benzene
R_f	Retention factor
RP	Reversed phase
rt	Room temperature
SEM	Standard error of the mean
SPS	Solis phase synthesis
TBAF	Tetrabutylammonium fluoride
TBDMS-Cl	*tert*-Butyldimethylsilyl chloride
TES	triethylsilane
TFA	Trifluorous acetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMD	Transmembrane domain
$TMSCHN_2$	trimethylsilyl diazomethane
Topo	Topotecan
t_r	Retention time
UV	Ultraviolett
Vis	Visible

7. Appendix

Curriculum Vitae

Cristian Ohcoa Puentes

21.07.1977, Bucaramanga, Colombia

Education

10/2008-03/2012	Dissertation: "Potent and selective ABCG2 inhibitors derived from tariquidar", University of Regensburg.
07/2001-02/2004	M.Sc.: "Straightforward Synthesis of Indeno[2,1-c]quinolines and N-(butenyl)chloroalquilamides With Pyridinyl Components as Possible Antitumoral Compounds", Universidad Industrial de Santander, Colombia.
02/1994-02/2001	B.Sc. "Synthesis of 4-N-Benzyl(α-phenylethyl)amino-4-pyridil-1-butenes and Their N-acil and N-Oxides Derivatives", Universidad Industrial de Santander, Colombia.

Teaching experience

01/2005-02/2008	Associate instructor. Universidad Nacional de Colombia, Bogotá, Colombia.
05/2004-12/2004	Associate instructor. Universidad de Pamplona, Pamplona, Colombia.

Poster presentations

Ochoa P. C, Höcherl P., Kühnle M., Bauer S., Bürger K., Bernhardt G., Buschauer A, König B. "Solid phase synthesis of tariquidar-related modulators of ABC transporters preferring breast cancer resistance protein (ABCG2)". Wissenschaftsforum Chemie, Bremen 2011

Ochoa P. C, Höcherl P., Kühnle M., Bauer S., Bürger K., Bernhardt G., Buschauer A, König B. "Solid phase synthesis of tariquidar-related modulators of ABC transporters preferring breast cancer resistance protein (ABCG2)". 47th RICT 2011 Drug Discovery and Selection, Lyon, France 2011

Ochoa, P. C. and König, B. "Solid phase synthesis of new analogues of p-Glycoprotein (ABCB1) Modulator Tariquidar", 3rd EuChemMS Chemistry Congress, Nürnberg 2010

Publications

Biaryl Tariquidar-Related Derivatives as Potent and Selective Breast Cancer Resistance Protein Modulators. Cristian Ochoa Puentes, Stefanie Bauer, Günther Bernhardt, Armin Buschauer and Burkhard König. (Manuscript in preparation).

Synthesis and Breast Cancer Resistance Protein (BCRP) Inhibitory Activity of New Multidrug Resistance Modulators Based on Tariquidar. Cristian Ochoa Puentes, Stefanie Bauer, Günther Bernhardt, Armin Buschauer and Burkhard König. (Manuscript in preparation).

Solid phase synthesis of tariquidar-related modulators of ABC transporters preferring breast cancer resistance protein (ABCG2). Cristian Ochoa Puentes, Peter Höcherl, Matthias Kühnle, Stefanie Bauer, Kira Bürger, Günther Bernhardt, Armin Buschauer and Burkhard König. *Bioorg. Med. Chem. Lett.* **2011**, 21, 3654-3657.

New Antitrichomonal Drug-like Chemicals Selected by Bond (Edge)-Based TOMOCOMD-CARDD Descriptors. Alfredo Mneses-Marcel, Oscar M. Rivera-Borroto, Yovani Marrero-Ponce, Alina Montero, Yanetsy Machado Tugores, José Antonio Escario, Alicia Gómez Barrio, David Montero Pereira, Juan José Nogal, Vladimir V. Kouznetsov, Cristian Ochoa Puentes, Arnold R. Bohórquez, Ricardo Grau, Francisco Torrens, Froylán Ibarra-Velarde and Vicente J. Arán. *J. Biomol. Screen.* **2008**, 13, 785-794

A Straightforward Synthetic Approach to Antitumoral Pyridinyl Substituted 7H-Indeno[2,1-c]Quinoline Derivatives Via Three-Component Imino Diels-Alder Reaction. Vladimir V. Kouznetsov, Cristian Ochoa Puentes, Arnold R. Romero Bohórquez, Susana A. Zacchino, Maximiliano Sortino, Mahabir Gupta, Yelkaira Vázquez, Ali Bahsas and Juan Amaro-Luis. Letters in Organic Chemistry, **2006**, 3, 300-304.

Synthesis and Antiparasitic Properties of New 4-N-Benzylamino-4-Hetarylbut-1-enes. Vladimir V. Kouznetsov, Juliette Rivero Castro, Cristian Ochoa Puentes, Elena E. Stashenko, Jairo Rene´ Martínez, Carmen Ochoa, David Montero Pereira, Juan J. Nogal Ruiz, Carlos Fernández Portillo, Susana Muelas Serrano, Alicia Gómez Barrio, Alí Bahsas, and Juan Amaro-Luis. *Arch. Pharm. Chem. Life Sci.* **2005**, 338, 32−37.

X-ray powder diffraction analysis of 2-exo-(β-pyridyl)-6-exo-phenyl-7-oxa-1-azabicyclo[2.2.1]heptanes. Poveda J. C., Henao J. A., Pinilla J. A., Kouznetsov V. V. and Ochoa C. *Powder Diffr.* **2003**, 18, 47-49.

4-N-aryl(benzyl)amino-4-heteroaryl-1-butenes as building blocks in heterocyclic synthesis. Synthesis of new tetrahidro-2-benzazepine derivatives and related compounds containing a pyridine ring. Juliette Rivero Castro, Cristian Ochoa Puentes, Vladimir V. Kouznetsov Elena E. Stashenko, juan C. Poveda, Alí Bahsas, and Juan Amaro-Luis. Heterocycl. Commun. **2002**, 34, 365-368.

Recent Advancements in the Homoallylamine Chemistry. Cristian Ochoa Puentes and Vladimir Kouznetsov. J. Heterocyclic Chem. **2002**, 39, 595-614.