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PII: S0223-5234(18)30542-7

DOI: 10.1016/j.ejmech.2018.06.051

Reference: EJMECH 10521

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 30 May 2018

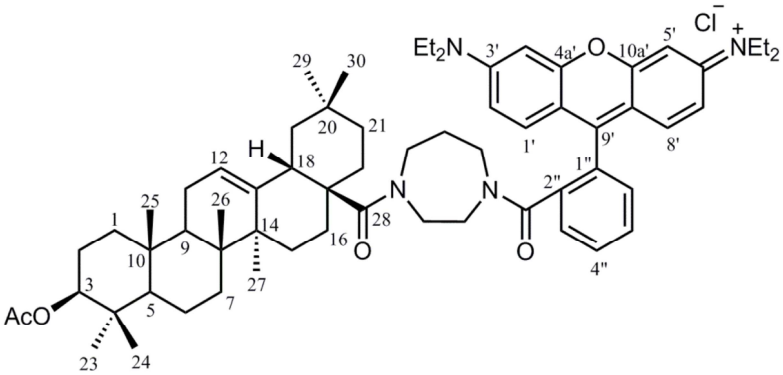
Revised Date: 18 June 2018

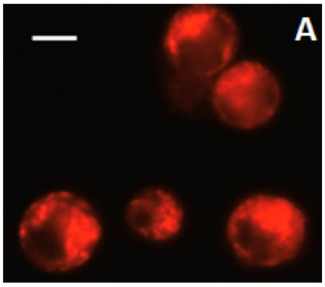
Accepted Date: 22 June 2018

Please cite this article as: R.K. Wolfram, L. Fischer, R. Kluge, D. Ströhl, A. Al-Harrasi, René. Csuk, Homopiperazine-rhodamine B adducts of triterpenoic acids are strong mitocans, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.06.051.

Mitocanic triterpenoidic homopiperazinyl-rhodamine B adduct

EC_{50} = 0.01 μM (A2780 ovarian carcinoma)





Homopiperazine-rhodamine B adducts of triterpenoic acids are strong mitocans

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Dedicated to Prof. Dr. Andrea T. Vasella, ETH Zurich, on the occasion of his 75th birthday. Ad multos annos!

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Abstract

Parent pentacyclic triterpenoic acids such as ursolic-, oleanolic, glycyrrhetinic, betulinic and boswellic acid were converted into their acetylated piperazinyl amides that were coupled with rhodamine B. SRB assays to evaluate their cytotoxicity showed all of these triterpene-homopiperazinyl-rhodamine adducts **16**-**20** being highly cytotoxic for a panel of human tumor cell lines even in nanomolar concentrations while being significantly less cytotoxic for non-malignant cells. Interestingly enough, these compounds were even more cytotoxic than previously prepared piperazinyl analogs, thus making the homopiperazinyl spacer a very interesting scaffold for the development of biologically active compounds. Extra staining experiments showed that the cytostatic effect of compounds **18** and **20** onto A2780 cancer cells is due to their ability to act as a mitocan.

Keywords: Homopiperazine, rhodamine B, mitocan; triterpenoic acids

1. Introduction

Cancer is still one of the most devastating diseases; approximately 8.9 million deaths in 2016 were caused by cancer.[1] Many therapies have been developed and help to cure patients in early stages suffering from this disease or to prolong their lifespan for months or even years. Much progress has been made especially in the development of small-molecule anticancer drugs.[2, 3] However, many of them kill healthy cells as well as targeted cancer cells. In search of higher active and more selective drugs, mitochondria have moved in the focus of scientific interest. Mitochondrial functions of cancer cells differ from those of normal cells.[4] As a consequence, mitochondria can be regarded as an interesting target for cancer therapy.[5, 6] Thus, the development of cytotoxic agents being able to impair mitochondrial functions especially in cancer cells seems most rewarding. As a consequence, the development of mitocans,[7-10] compounds that primarily target mitochondria, was called for.

Several derivatives of pentacyclic triterpenoids [11] showed an increased cytotoxic and a significant anti-tumor activity both *in vitro* and *in vivo*.[11-17] Increased cytotoxicity, however, was observed for those molecules holding an additional amino group (in)-directly attached to the carbon skeleton of the triterpenoid.[18-22] Thereby, compounds coupled to a piperazinyl residue showed significantly better anticancer activity than their parent compounds.[23-27] Triterpenoids, however, holding both a piperazinyl spacer [28, 29] as well

as a rhodamine B moiety attached to it were shown to act as mitocanic agents of high cytotoxicity.[17, 30] Interestingly enough, while SciFinder (as of 2018, May) reports 157 pentacyclic triterpenoids with a piperazinyl moiety,[31-36] there is only one report dealing with the synthesis and cytotoxic evaluation of ursolic acid derivatives holding a homopiperazinyl moiety instead of a piperazinyl group.[29] Hence, we became interested in compounds holding a homopiperazinyl moiety together with a rhodamine B group, and to investigate their ability to act as mitocanic agents.

2. Results and discussion

2.1. Chemistry

The starting materials (Fig. 1), ursolic acid (**1**), oleanolic acid (**2**), glycyrrhetinic acid (**3**) and betulinic acid (4**)** were purchased from commercial suppliers in bulk. 3-*O*-Acetyl-11-keto-β-boswellic acid (**5**) was extracted from the resin of frankincense applying a modification of Jauch's procedure.[37] Deacetylation of **5** with an aqueous solution of sodium hydroxide in EtOH gave 11-keto-β-boswellic acid (**10**) in almost quantitative yield.

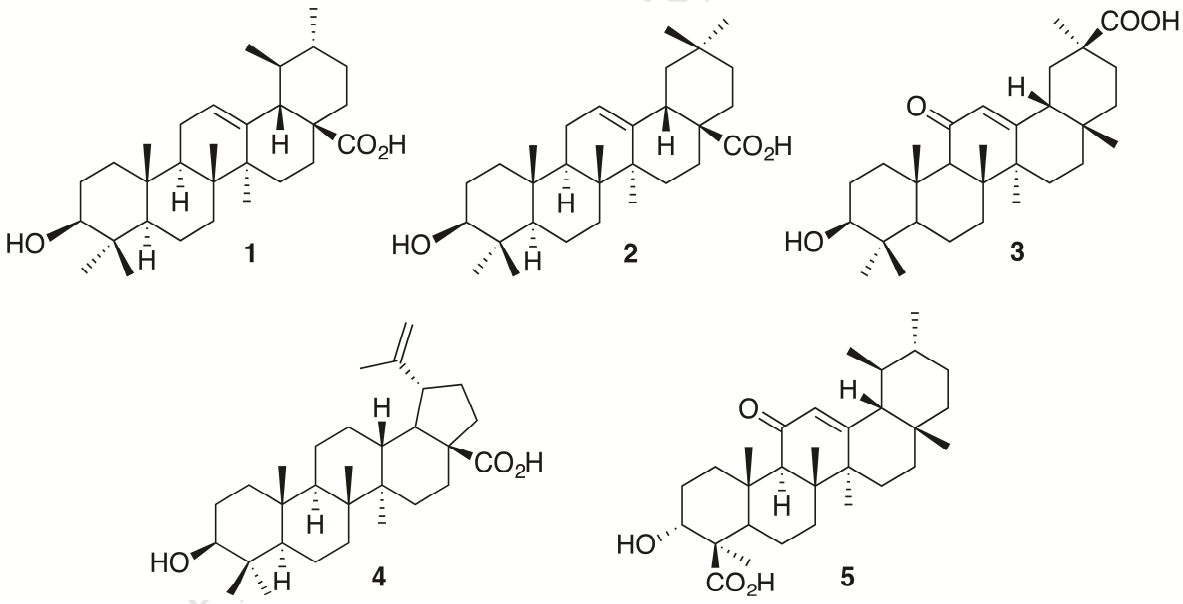
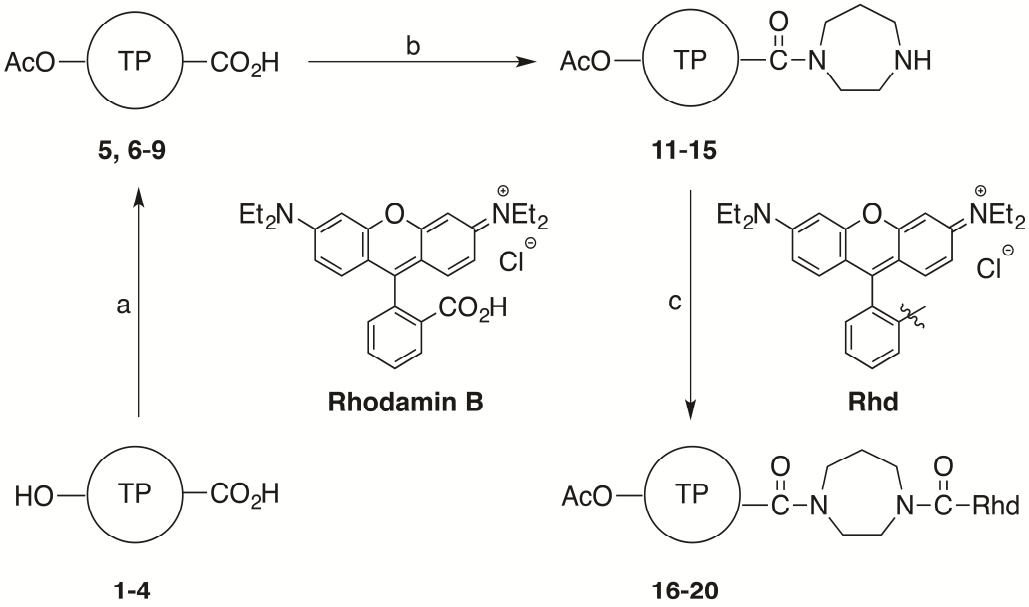


Fig. 1. Structure of parent triterpenoic acids: ursolic acid (**1**), oleanolic acid (**2**), glycyrrhetinic acid (**3**), betulinic acid (**4**), 3-*O*-acetyl-11-keto-β-boswellic acid (**5**).

Scheme 1 shows the coupling reaction of the triterpenoic acids with homopiperazine. Thus, to avoid side reactions prior to the coupling of the corresponding triterpenoic acid chloride to homopiperazine, the HO-C(3) was protected as an acetate. Acetylation of **1-4** with acetic

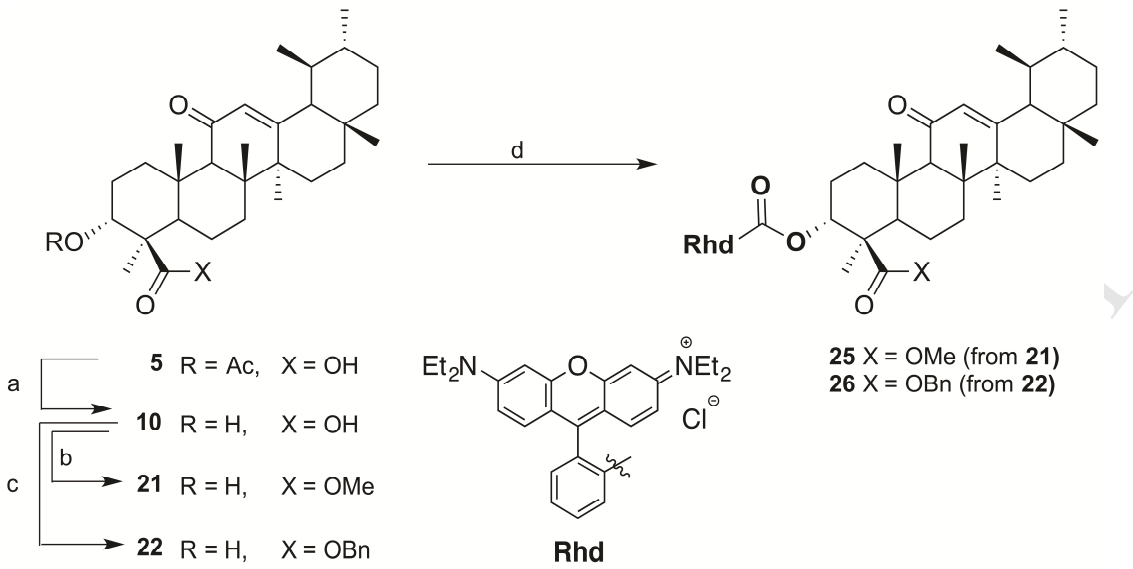
anhydride gave compounds **6-9** in good yields (70-90%). Activation of acetylated compounds **5-9** with oxalyl chloride followed by their reactions with homopiperazine gave compounds **11-15** in moderate to good isolated yields (48-95%).

To obtain the desired rhodamine B derivatives, commercially available rhodamine B was activated by its reaction with oxalyl chloride, and the resulting acid chloride was coupled with the corresponding triterpenoic acid homopiperazine derivative **11-15** to yield final target compounds **16-20** in 50-83% isolated yield.



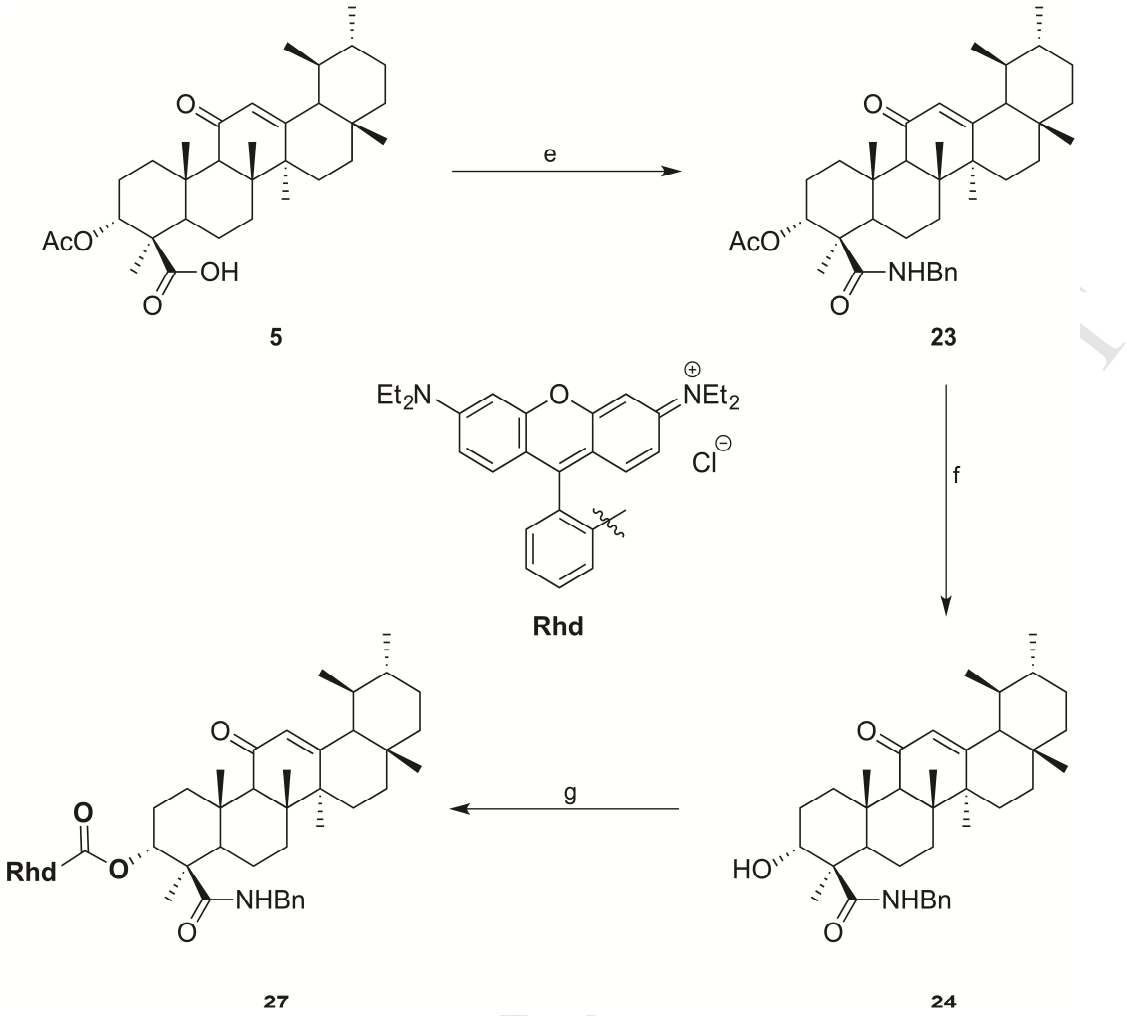
Scheme 1. Synthesis of triterpenoic acid homopiperazine derivatives. Reaction conditions: a) Ac_2O, reflux, 2 h, 70–90%, b) $(COCl)_2$, CH_2Cl_2, r.t., 3 h, then homopiperazine, NEt_3, cat. DMAP, CH_2Cl_2, r.t., 24 h, 48–99%, c) Rhd-CO_2H, $(COCl)_2$, CH_2Cl_2, r.t., 3 h, then NEt_3, cat. DMAP, CH_2Cl_2, r.t., 24 h, 50–83%.

Previous studies have shown that triterpenoic acids holding a rhodamine B moiety directly attached to the triterpene skeleton are highly cytotoxic but possess a significantly lower tumor/non-tumor selectivity [17] than derivatives where the triterpene and the rhodamine are separated by a piperazine spacer.[30] To verify if this holds true also for previously not investigated 11-keto-β-boswellic acid derivatives, the synthesis of some representative 11-keto-boswellic acid derived compounds was undertaken. Compound **5** is an ideal starting material (Scheme 2), and its reaction in dry DMF with methyl iodide or benzyl bromide in the presence of finely grounded K_2CO_3 gave the methyl ester **21** and the benzyl ester **22,** respectively.[38]



Scheme 2. Synthesis of 11-keto-β-boswellic acid derivatives **10**, **21**-**27**: a) NaOH, EtOH, r.t., 12 h; b) MeI, K_2CO_3, DMF, r.t., 24 h, 92%; c) BnBr, K_2CO_3, DMF, r.t., 24 h, 57%; d) Rhd-CO_2H, $(COCl)_2$, CH_2Cl_2, r.t., 3 h, then NEt_3, DMAP, CH_2Cl_2, r.t., 24 h, **25** 43%, **26** 58%;

Reaction of **5** with oxalyl chloride followed by the addition of benzyl amine (Scheme 3) furnished the *N*-benzyl amide **23** in good yield. Deacetylation of **23** with KOH in MeOH at ambient temperature gave **24**. Finally, coupling of **21**, **22** or **24** with activated rhodamine B as described above gave the rhodamine B esters **25**-**27**, respectively.



Scheme 3: a) $(COCl)_2$, CH_2Cl_2, r.t., 3 h, then $BnNH_2$, NEt_3, DMAP, CH_2Cl_2, r.t., 24 h, 80%; b) KOH, MeOH, r.t., 3 d, 76%; c) Rhd-CO_2H, $(COCl)_2$, CH_2Cl_2, r.t., 3 h, then NEt_3, DMAP, CH_2Cl_2, r.t., 24 h, 57%.

2.2.Biology

The cytotoxicity of the compounds was evaluated in sulforhodamine B assays (SRB), and the results are summarized in Table 1.

Table 1. Cytotoxicity of selected compounds (EC_{50} values in µM from SRB assays after 96 h of treatment, the values are averaged from three independent experiments performed each in triplicate, confidence interval CI = 95%, cut-off the assay 30 µM, n.m. not measured; mean ± standard mean error). Human cancer cell lines: A375 (epithelial melanoma), A2780 (ovarian carcinoma), HT29 (colorectal adenocarcinoma), MCF7 (breast adenocarcinoma), SW1736 (thyroidea carcinoma); non-malignant: NIH 3T3 (mouse fibroblasts); data for compounds **1**-**5** and **21** are taken from literature.[30, 39-41] Betulinic acid (**BA**) was used as a standard.

Compound	A375	A2780	HT29	MCF7	NiH3T3	SW1736
1	n. m.	11.7±0.6	10.6±0.7	12.7±0.1	18.7±1.6	n. m.
2	n. m.	14.0±2.3	38.8±3.1	>60	76.4±0.7	n. m.
3	n. m.	74.57±3.73	80.09±4.00	84.70±4.24	18.52±0.93	76.93±3.85
4	n. m.	8.8±0.9	14.4±2.3	10.2±1.2	16.1±1.4	n. m.
5	n. m.	14.4±2.0	19.4±1.1	17.4±1.7	26.4±3.0	n. m.
11	3.21±0.17	2.85±0.24	1.99±0.02	2.41±0.20	0.90±0.15	n. m.
12	1.95±0.87	2.21±0.06	1.88±0.14	1.61±0.04	1.81±0.21	n. m.
13	2.30±0.14	2.31±0.23	1.30±0.04	1.50±0.02	1.23±0.10	3.25±0.15
14	18.66±1.63	12.0±0.62	5.11±1.07	10.74±1.00	12.30±1.02	18.66±1.63
15	n. m.	1.61±0.08	1.47±0.04	1.52±0.04	1.05±0.06	1.84±0.08
16	0.51±0.05	0.45±0.03	0.50±0.07	0.39±0.04	0.40±0.03	n. m.
17	0.04±0.01	0.02±0.003	0.04±0.01	0.03±0.004	0.14±0.02	0.04±0.01
18	0.03±0.01	0.01±0.001	0.04±0.005	0.03±0.01	0.17±0.07	0.03±0.01
19	0.76±0.09	0.22±0.01	0.28±0.01	0.22±0.02	0.33±0.07	0.22±0.04
20	0.05±0.02	0.04±0.002	0.14±0.07	0.05±0.02	0.36±0.16	0.05±0.02
21	n. m.	n. m.	18.4±2.0	29.2±3.0	>30	n. m.
22	24.8±27.7	30.1±57	28.8±100	26.4±48.3	>30	24.8±27.7
23	13.7±1.1	10.8±2.2	20.2±1.8	9.8±1.2	28.1±4.9	n. m.
24	12.8±0.5	10.0±0.9	10.7±0.6	7.3±0.9	4.9±1.2	n. m.
25	0.36±0.06	0.30±0.03	0.29±0.03	0.23±0.03	0.19±0.02	n. m.
26	1.52±0.11	1.32±0.12	1.71±0.15	1.38±0.13	1.01±0.13	n. m.
27	0.59±0.09	0.53±0.08	0.55±0.07	0.49±0.03	0.40±0.04	n. m.
BA	17.1±1.7	11.0±1.9	14.4±2.3	14.8±1.9	13.1±1.1	18.3±2.0

As a result, boswellic acid derived compounds were cytotoxic but their selectivity for tumor cells (as compared to non-malignant fibroblasts NIH 3T3) was low. The presence of a keto function at the C-11 position seems to be disadvantageous for gaining good cytotoxicity. Further investigation of derivatives of **5** (OH at C-3 coupled directly with rhodamine B) showed that the cytotoxicity is highest for the methyl ester **25**. Again, selectivity was low for all of these compounds.

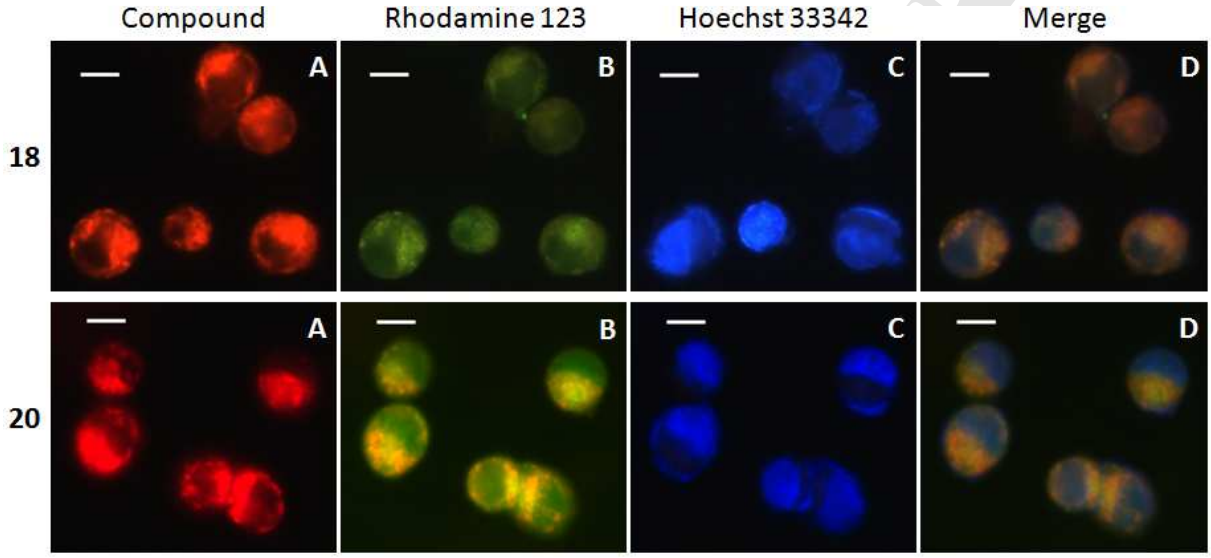


Fig. 2. Fluorescence microscopic investigations by double staining with Rhodamine 123 and Hoechst 33342: A2780 ovarian carcinoma cells were analyzed after an incubation for 24 hours with compound **18** (100 nM) and compound **20** (400 nM), respectively. Picture A was captured with the Zeiss filter set 15, picture B was captured with the Zeiss filter set 09, picture C was captured with the Zeiss filter set 02 and picture D is an overlay of A, B and C. Scale bar = 10 µm.

Better results were obtained for compounds derived from parent **1**-**4**. Thus, all of the acetylated triterpene-homopiperazinyl amides **11**-**15** were cytotoxic in the µM range while the triterpene-homopiperazinyl-rhodamine adducts **16**-**20** showed the highest cytotoxicity for the human tumor cell lines even in nanomolar concentrations.

Compared to previously reported piperazine-rhodamine compounds,[30] derivatives of ursolic and oleanolic acid holding each a homopiperazinyl spacer were twice as cytotoxic as their piperazinyl analogs. Interestingly enough, those analogs derived from glycyrrhetinic acid or

betulinic acid were less cytotoxic than analogs from parent ursolic or oleanolic acid. Thus, the glycyrrhetinic acid derived compound **19** exhibited the lowest cytotoxicity of all compounds of this series while compound **18** displayed the highest. These results parallel previous findings described for the piperazinyl derivatives.[30]

Furthermore, selectivity of cytotoxicity between tumor cells and nonmalignant fibroblasts (NIH 3T3) was improved for the new derivatives holding the homopiperazinyl spacer. Thus, the selectivity factor was S = EC_{50} (NIH 3T3) / EC_{50} (2780 cells) = 9 for betulinic acid derived **20**, and this selectivity is even higher (S = 17) for the oleanolic acid derived compound **18**.

Some additional experiments were performed to reveal the mode of action of these compounds (Figure 2). Major benefit of linking triterpenes to rhodamine B is the relative ease of localization of the compounds within the (cancer) cells. While staining of the cells with the bisbenzimidazole dye Hoechst 33342 allows the identification of cell nuclei, Rhodamine 123 is usually applied in living cells to stain the mitochondria. A comparison of subfigures B (Fig. 2) shows an additional orange fluorescence for compound **20** in addition to the green fluorescence. This effect is due to the higher concentration of the compound **20** (400 nM for **20**, 100 nM for **18**). However, the fluorescence microscopic studies also revealed that both compounds **18** and **20** are located not in the nucleus, but in the same area as the Rhodamine 123 dye, i.e. the mitochondria. As described above, cells treated with each of these compounds showed an inhibited growth as compared to untreated cells (control). Consequently, it can be assumed that the cytostatic effect of compounds **18** and **20** onto A2780 cancer cells is due to their ability to act as a mitocan.

3. Conclusion

Parent triterpenoic acids ursolic-, oleanolic, glycyrrhetinic, betulinic and boswellic acid were acetylated followed by the conversion into their piperazinyl amides that were coupled with rhodamine B. These compounds were subjected to RB assays to evaluate their cytotoxicity. All of these triterpene-homopiperazinyl-rhodamine adducts **16**-**20** were highly cytotoxic for a panel of human tumor cell lines even in nanomolar concentrations while being significantly less cytotoxic for non-malignant cells. Several of the homopiperazinyl-rhodamine adducts were even more cytotoxic than previously prepared piperazinyl analogs, thus making the

homopiperazinyl spacer a very interesting scaffold for the development of biologically active compounds. Extra staining experiments showed that the cytostatic effect of compounds **18** and **20** onto A2780 cancer cells is due to their ability to act as a mitocan.

Acknowledgments

We like to thank Mrs. V. Simon for measuring the IR and UV-vis spectra as well as the optical rotations. The cell lines were kindly provided by Dr. Th. Müller (Dept. of Haematology/Oncology, Martin-Luther Universität Halle-Wittenberg). Financial support by the Oman Research Council (ORG/EBR/15/007) and the ScienceCampus Halle WCR (W13004216) is gratefully acknowledged. The authors declare no conflict of interests.

4. Experimental part

4.1. General

NMR spectra were recorded using the Varian spectrometers Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz; typical experiments: H-H-COSY, HMBC, HSQC, NOESY), MS spectra were taken on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.1 kV, sheath gas nitrogen) instrument. The optical rotations were measured on a Perkin-Elmer polarimeter at 20 °C; TLC was performed on silica gel (Merck 5554, detection with cerium molybdate reagent); melting points are uncorrected (*Leica* hot stage microscope. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer Spectrum 1000. The solvents were dried according to usual procedures. The purity of the compounds was determined by HPLC and found to be >96%. The parent triterpenoic acids were obtained from Betulinines (Stříbrná Skalice, Czech Republic) in bulk quantities. Fluorescence microscopic images were recorded on an Axioskop 20 with an AxioCam MR3 (Carl Zeiss AG). Flow cytometric experiments were performed on an Attune acoustic focusing cytometer (Life Technologies GmbH). The SRB assay was performed as previously described.[20, 30, 39, 42]

4.2.Biology

4.2.1. Double-staining experiment using Rhodamine 123 and Hoechst 33342

The Hoechst 33342 dye was used for live-cell fluorescent staining of DNA, and mitochondria were stained by Rhodamine 123. Approx. $1 \cdot 10^6$ cells (A2780) were seeded in cell culture flasks (25 cm^2), and the cells were allowed to grow up for 24 h. After removing of the used

medium, the substance loaded fresh medium was reloaded (or a blank new medium as a control). After 24 h, the content of the flask was collected and centrifuged (1200 rpm, 4 °C), the pellet was gently suspended in phosphate-buffered saline (PBS (w/w), 1 ml) and centrifuged again. The PBS was removed, and the pellet gently suspended in PBS (50 µl) again. After having mixed the cell suspension with a solution of Hoechst 33342/ Rhodamine 123 (10 µg/ml, 20 µl) the cells were incubated for 30 min at 37°C in the dark and washed with PBS (w/w, 2x 500 µl). The analysis of the cells was performed with an Axioskop (Zeiss) epifluorescent microscope after re-suspending the pellet in the supernatant. Different filter sets were used for the screening: for the compounds the Zeiss filter set 15 (BP 546/12, FT 580, LP 590), for Hoechst 33342 the Zeiss filter set 02 (G 365, FT 395, LP 420) and for Rhodamine 123 the Zeiss filter set 09 (BP 450-490, FT 510, LP 515), respectively.

4.3.General procedures

4.3.1. General procedure for the acetylation of parent triterpenoic acids (GP1)

A solution of the triterpenoic acid **1-4** (10.0 g, 22 mmol, 1.0 eq.) in acetic anhydride (160 mL) was stirred under reflux for 2 h. To the hot reaction mixture, acetic acid (20 mL) was slowly added. Stirring was continued for another 10 min, then water (40 mL) was slowly added, and the precipitate was filtered off. The precipitate was washed with water (4×50 mL), cold EtOH (20 mL) and dried under reduced pressure. The desired products were obtained as off-white solids that were pure enough (as checked by TLC, NMR, MS) for the next reaction steps. Analytical samples were obtained either by re-crystallization or column chromatography.

4.3.2. General procedure for the coupling with homopiperazine (GP2)

To an ice-cold solution of acetate **5-9** (0.5 g, 1.0 mmol, 1.0 eq.) in dry CH_2Cl_2 (10 mL), oxalyl chloride (0.5 g, 0.3 mL, 4 mmol, 4.0 eq.) was slowly added, and the mixture was allowed to warm to ambient temperature, and stirring was continued for 3 h. The solvent was removed under reduced pressure, the residue dissolved in dry THF (10 mL), and the volatiles were evaporated. To a solution of the residue in dry CH_2Cl_2 (10 mL), homopiperazine (2.0 g, 2 mmol, 2.0 eq.), NEt_3 (0.2 mL, 1.5 mmol, 1.5 eq.) and DMAP (5 mol-%) were added, and stirring was continued for 2 h. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel) afforded the desired products as off-white solids.

4.3.3. General procedure for the preparation of the rhodamine B derivatives (GP3)

To an ice-cold solution of rhodamine B (0.3 g, 0.63 mmol, 1 eq.) in dry CH_2Cl_2 (6 mL), oxalyl chloride (0.32 g, 0.2 mL, 2.51 mmol, 4 eq.) was slowly added, and the mixture was allowed to warm to ambient temperature; stirring was continued for 3 h. The solvent was removed under reduced pressure, the residue dissolved in dry THF (2×10 mL), and the CH_2Cl_2 (10 mL) compounds **11-15** (0.3 g, 0.46 mmol, 1 eq.), NEt_3 (0.1 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added, and stirring was continued overnight. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel, MeCN/CH_2Cl_2/H_2O 10:1:1) afforded the desired rhodamine B derivatives as intensively violet solids.

4.4.Syntheses

4.4.1. 3-*O*-Acetyl-11-keto-β-boswellic acid (5)

This compound was isolated following a modified Jauch's procedure [8] and obtained as a colorless solid; m.p. 268–270 °C; $[\alpha]_D$ = +81.1° (*c* = 1.0, $CHCl_3$), [lit.: m.p. 271–276 °C, $[\alpha]_D$ = +82.0° (*c* = 1.25, $CHCl_3$)].[37]

4.4.2. 3-*O*-Acetyl-ursolic acid (6)

Following GP1 from ursolic acid (**1**) compound **6** was obtained in 90% yield; m.p. 280–285 °C, $[\alpha]_D$ = +65.6° (*c* 0.33, $CHCl_3$), [lit.: m.p. 285 °C,[43] $[\alpha]_D$ = +69.0° (*c* = 0.19, $CHCl_3$)].[39]

4.4.3. 3-*O*-Acetyl-oleanolic acid (7)

Following GP1 from oleanolic acid (**2**) compound **7** was obtained in 73% yield; m.p. 266–269 °C, $[\alpha]_D$ = +69.4° (*c* = 0.30, $CHCl_3$), [lit.: m.p. 265–268 °C, $[\alpha]_D$ = +65.0° (*c* = 0.33, $CHCl_3$)].[39]

4.4.4. 3-*O*-Acetyl-18β-glycyrrhetinic acid (8)

Following GP1 from glycyrrhetinic acid (**3**) compound **8** was obtained in 85% yield; m.p. 316–318 °C, $[\alpha]_D$ = +161.9° (*c* = 0.2, $CHCl_3$) [lit.: m.p. 310–313°C); $[\alpha]_D$ = +163.8° (*c* = 1.0, $CHCl_3$)]. [44]

4.4.5. 3-*O*-Acetyl-betulinic acid (9)

Following GP1 from betulinic acid (**4**) compound **9** was obtained in 70% yield; m.p. 282–285 °C, $[\alpha]_D$ = +21.0° (*c* = 0.33, $CHCl_3$), [lit.: m.p. 287–289 °C[45], $[\alpha]_D$ = +20.5° (*c* = 0.58)].[42]

4.4.6. 11-Keto-β-boswellic acid (10)

Compound **5** (10.0 g, 19.5 mmol) was dissolved in ethanol (200 mL), and an aq. solution of sodium hydroxide (4 M, 100 mL) was added. After stirring at 25 °C for 12 h, the pH was adjusted to pH 1 by addition with aq. HCl, the crude product was extracted with $CHCl_3$ (5×100 mL) and purified by column chromatography (silica gel, hexane/ethyl acetate, 98:2) to afford **10** in almost quantitative yield as a colorless solid; m.p. 192–195 °C $[\alpha]_D$ = +118.2° (*c* = 3.72, $CHCl_3$), [lit.: m.p. 194–195 °C [37], $[\alpha]_D$ = +121° (*c* = 1.11, $CHCl_3$)].[37]

4.4.7. (3α, 4β) 3-Acetyloxy-*N*-homopiperazinyl-11-oxo-urs-12-en-23-one (11)

Following GP2 from **5** followed by column chromatography ($CHCl_3$/MeOH, 9:1), **11** was obtained in 64% yield as an off-white solid; m.p. 170–173 °C; R_f 0.4 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D$ = +29.7° (*c* = 0.34, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) =278 nm (3.30); IR (KBr): ν = 3442*br*, 2927*m*, 1736*s*, 1654*m*, 1458*m*, 1381*m*, 1249*m*, 1026*m*, 755*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.62 (m, 1 H, 3-H), 5.54 (s, 1 H, 12-H), 3.84–3.64 (m, 4 H, CONCH_2), 3.23–2.90 (m, 4 H, HNCH_2), 2.54 (ddd, *J* = 13.5, 13.5, 3.4 Hz, 1 H, 1-H_a), 2.40 (s, 1 H, 9-H), 2.25 (m, 1 H, 6-H_a), 2.11 (s, 3 H, CH_3CO), 2.14–2.03 (m, 2 H, $CONCH_2CH_2$), 2.02–1.77 (m, 3 H, 2-H_a, 15-H_a, 16-H_a), 1.69–1.56 (m, 3 H, 6-H_b, 2-H_b, 7-H_a), 1.54 (d, *J* = 11.2 Hz, 1 H, 18-H), 1.51–1.33 (m, 4 H, 22-H_a, 7-H_b, 21-H_a, 19-H), 1.32 (s, 3 H, 27-H_3), 1.32–1.16 (m, 5 H, 15-H_b, 21-H_b, 1-H_b, 22-H_b, 5-H), 1.25 (s, 3 H, 23-H_3), 1.24 (s, 3 H, 26-H_3), 1.23 (s, 3 H, 25-H_3), 1.01 (m, 1 H, 16-H_b), 0.94 (s, 3 H, 30-H_3), 0.96–0.92 (m, 1 H, 20-H), 0.82 (s, 3 H, 28-H_3), 0.80 (d, *J* = 6.2 Hz, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.5 (C-11), 174.4 (C-24), 170.9 (CH_3CO), 164.7 (C-13), 130.6 (C-12), 71.6 (C-3), 61.8 (C-9), 58.9 (C-18), 54.2 (C-5), 49.6 (C-4), 48.0, 45.8 (4×CONCH_2), 45.3 (C-8), 43.7 (C-14), 40.9 (C-22), 39.3 (C-19, C-20), 38.1 (C-10), 34.1 (C-1), 33.9 (C-7), 33.8 (C-17), 30.9 (C-21), 28.8 (C-28), 27.5 (C-16), 27.3 (C-15), 24.5 (C-2), 23.0 (C-23), 21.2 (CH_3CO), 21.1 (C-30), 20.8 ($CONCH_2CH_2$), 20.6 (C-27), 19.7 (C-6), 18.6 (C-26), 17.4 (C-29), 16.2

(C-25) ppm; MS [ESI, MeOH for $C_{37}H_{58}N_2O_4$ (594.88)]: *m*/*z* (%) 1189.3 (3) $[2M+H]^+$, 595.3 (100) $[M+H]^+$.

4.4.8. 3β-Acetyloxy-28-(1-homopiperazinyl)-urs-12-en-28-one (12)

Following GP2 from **6** followed by column chromatography (hexane/ethyl acetate, 5:1) **12** was obtained in 84% yield as an off-white solid; m.p. 178–180 °C (lit.: 151–157 °C)[29]; R_f 0.2 (hexane/ethyl acetate, 5:1); $[\alpha]_D$ = +9.9° (*c* = 0.35, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 203 nm (4.04); IR (KBr): ν = 3448*br*, 2947*m*, 1734*s*, 1624*s*, 1458*m*, 1371*m*, 1247*s*, 1028*m*, 753*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.15 (m, 1 H, 12-H), 4.42 (dd, *J* = 9.1, 7.5 Hz, 1 H, 3-H), 3.96–3.49 (m, 4 H,CONCH_2), 3.34–2.97 (m, 4 H, HNCH_2), 2.37 (d, *J* = 9.9 Hz, 1 H, 18-H), 2.32–2.17 (m, 2 H, 16-H_2), 1.99 (s, 3 H, CH_3CO), 1.88 (m, 2 H, 11-H_2), 1.69 (m, 1 H, 22-H_a), 1.63–1.53 (m, 4 H, 2-H_2, 22-H_b, 1-H_a), 1.52–1.38 (m, 4 H, 6-H_a, 21-H_a, 7-H_a, 9-H), 1.39–1.20 (m, 4 H, 6-H_b, 21-H_b, 7-H_b, 19-H), 1.07–0.95 (m, 6 H, $CONCH_2CH_2$, 1-H_b, 20-H, 15-H_2), 1.04 (s, 3 H, 27-H_3), 0.93 (s, 3 H, 30-H_3), 0.90 (s, 3 H, 25-H_3), 0.85 (s, 3 H, 29-H_3), 0.82 (s, 6 H, 23-H_3, 24-H_3), 0.77 (d, *J* = 11.5 Hz, 1 H, 5-H), 0.67 (s, 3 H, 26-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C-28), 171.0 (CH_3CO), 138.4 (C-13), 125.1 (C-12), 80.9 (C-3), 55.3 (C-5), 54.8 (C-18), 49.0 (C-17), 47.5 (C-9), 46.8 (2×CH_2N), 46.4 (2×CH_2N), 42.2 (C-14, C-8), 39.4 (C-19), 38.7 (C-20), 38.2 (C-1), 37.7 (C-4), 36.9 (C-10), 34.4 (C-22), 32.9 (C-7), 30.5 (C-21), 28.2 (C-23), 28.1 ($CONCH_2CH_2$), 27.8 (C-15), 25.6 (C-16), 23.9 (C-27), 23.5 (C-2), 23.3 (C-11), 21.3 (CH_3CO), 21.2 (C-30), 18.2 (C-6), 17.4 (C-29), 17.0 (C-26), 16.7 (C-24), 15.5 (C-25) ppm; MS [ESI, MeOH for $C_{37}H_{60}N_2O_3$ (580.88)]: *m*/*z* (%) 581.4 (100) $[M+H]^+$.

4.4.9. 3β-Acetyloxy-28-(1-homopiperazinyl)-olean-12-en-28-one (13)

Following GP2 from **7** followed by column chromatography ($CHCl_3$/MeOH, 92:8) **13** was obtained in 99% yield as an off-white solid; m.p. 187–190 °C; R_f 0.25 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D$ = +16.4° (*c* = 0.30, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 203 nm (4.10); IR (KBr): ν = 3442*br*, 2946*s*, 1733*s*, 1622*s*, 1466*m*, 1371*m*, 1247*s*, 1182*m*, 1028*m*, 1007*m*, 986*m*, 753*m* cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.25 (m, 1 H, 12-H), 4.48 (dd, *J* = 9.6, 7.5 Hz, 1 H, 3-H), 3.78–3.54 (m, 4 H, CONCH_2), 3.45 (br s, 1 H, NH), 3.12–2.83 (m, 5 H, HNCH_2, 18-H), 2.11 (ddd, *J* = 14.1, 14.1, 2.6 Hz, 1 H, 16-H_a), 2.03 (s, 3 H, CH_3CO), 2.00–1.79 (m, 4 H, $CONCH_2CH_2$, 11-H_2), 1.74–1.46 (m, 10 H, 19-H_a, 22-H_2, 16-H_b, 2-H_2, 15-H_a, 1-H_a, 6-H_a, 9-H), 1.41 (m, 1 H, 6-H_b), 1.37–1.14 (m, 5 H, 7-H_2, 21-H_2, 19-H_b), 1.13 (s, 3 H, 27-H_3), 1.10–0.97 (m, 2 H, 15-H_b, 1-H_b), 0.93 (s, 3 H, 25-H_3), 0.92 (s, 3 H, 30-H_3), 0.89 (s, 3 H, 29-H_3),

0.85 (s, 3 H, 23-H_3), 0.84 (s, 3 H, 24-H_3), 0.82 (m, 1 H, 5-H), 0.74 (s, 3 H, 26-H_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9 (C-28), 171.0 (CH_3CO), 144.7 (C-13), 121.4 (C-12), 80.9 (C-3), 55.4 (C-5), 48.4 (2×CONCH_2), 47.8 (C-17), 47.7 (C-9), 47.3 (CONCH_2), 46.5 (C-19), 46.4 (CONCH_2), 43.7 (C-18), 41.9 (C-14), 39.2 (C-8), 38.1 (C-1), 37.7 (C-4), 37.0 (C-10), 34.1 (C-21), 33.0 (C-29), 32.8 (C-7), 30.4 (C-20), 30.1 (C-22), 28.8 (CONCH$_2$$CH_2$), 28.1 (C-23), 28.0 (C-15), 25.9 (C-27), 24.0 (C-30), 23.5 (C-2), 23.4 (C-11), 22.8 (C-16), 21.3 (CH_3CO), 18.2 (C-6), 17.1 (C-26), 16.7 (C-24), 15.4 (C-25) ppm; MS [ESI, MeOH for $C_{37}H_{60}N_2O_3$ (580.88)]: *m*/*z* (%) 581.3 (100) $[M+H]^+$.

4.4.10. (3β, 18β)-3-Acetyloxy-30-(1-homopiperazinyl)-olean-12-en-11,30-dione (14)

Following GP2 from **8** followed by column chromatography ($CHCl_3$/MeOH, 92:8) **14** was obtained in 48% yield as an off-white solid; m.p. 260–264 °C; R_f 0.2 (hexane/ethyl acetate, 2:1); $[\alpha]_D$ = +109.8° (*c* = 0.38, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 203 nm (3.92), 262 nm (3.93); IR (KBr): ν = 3441*br*, 2951*s*, 1730*s*, 1657*m*, 1633*m*, 1465*m*, 1385*m*, 1248*s*, 1163*m*, 1029*m*, 987*m*, 540*m* cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (br s, 1 H, NH), 5.67 (s, 1 H, 12-H), 4.50 (dd, *J* = 11.6, 4.8 Hz, 1 H, 3-H), 3.90–3.66 (m, 4 H, CONCH_2), 3.30–3.12 (m, 4 H, HNCH_2), 2.77 (ddd, *J* = 13.6, 13.6, 3.5 Hz, 1 H, 1-H_a), 2.34 (s, 1 H, 9-H), 2.27 (m, 1 H, 18-H), 2.23 (m, 2 H, CONCH$_2$CH_2), 2.09–1.97 (m, 4 H, 21-H_2, 16-H_a, 19-H_a), 2.03 (s, 3 H, CH_3CO), 1.82 (ddd, *J* = 13.6, 13.6, 3.8 Hz, 1 H, 15-H_a), 1.75–1.53 (m, 5 H, 2-H_2, 7-H_a, 19-H_b, 6-H_a), 1.47–1.30 (m, 4 H, 6-H_b, 7-H_b, 22-H_2), 1.34 (s, 3 H, 27-H_3), 1.22 (s, 3 H, 29-H_3), 1.21–1.15 (m, 1 H, 15-H_b), 1.14 (s, 3 H, 25-H_3), 1.10 (s, 3 H, 26-H_3), 1.08–0.97 (m, 2 H, 1-H_b, 16-H_b), 0.86 (s, 6 H, 23-H_3, 24-H_3), 0.80 (s, 3 H, 28-H_3), 0.78 (m, 1 H, 5-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9 (C-11), 175.2 (C-30), 171.0 (CH_3CO), 169.3 (C-13), 128.5 (C-12), 80.6 (C-3), 61.7 (C-9), 55.0 (C-5), 48.0 (C-18), 46.7 (2×CONCH_2), 45.3 (C-8), 45.0 (CONCH_2), 44.6 (CONCH_2), 44.4 (C-20), 43.9 (C-19), 43.3 (C-14), 38.8 (C-1), 38.0 (C-4), 37.7 (C-22), 36.9 (C-10), 32.9 (C-21), 32.7 (C-7), 31.8 (C-17), 28.4 (C-28), 28.0 (C-23), 26.9 (C-29), 26.8 (C-16), 26.3 (C-15), 26.1 (CONCH$_2$$CH_2$), 23.5 (C-2), 23.0 (C-27), 21.3 (CH_3CO), 18.7 (C-26), 17.4 (C-6), 16.7 (C-24), 16.4 (C-25) ppm; MS [ESI, MeOH for $C_{37}H_{58}N_2O_4$ (594.87)]: *m*/*z* (%) 595.5 (100) $[M+H]^+$.

4.4.11. 3β-Acetyloxy-28-(1-homopiperazinyl)-lup-20(29)en-28-one (15)

Following GP2 from **9** followed by column chromatography ($CHCl_3$/MeOH, 9:1) **15** was obtained in 86% yield as an off-white solid; m.p. 196–199 °C; R_f 0.24 ($CHCl_3$/MeOH, 9:1);

$[\alpha]_D$ = -6.5° (*c* = 0.34, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 201 nm (4.09); IR (KBr): ν = 3445*br*, 2945*s*, 2869*m*, 1734*s*, 1628*s*, 1456*m*, 1374*m*, 1247*s*, 1185*m*, 1029*m*, 979*m*, 881*m*, 754*m* cm^{-1}; NMR (400 MHz, $CDCl_3$): δ = 4.68 (m, 1 H, 29-H_a), 4.55 (m, 1 H, 29-H_b), 4.40 (dd, *J* = 9.6, 8.0 Hz, 1 H, 3-H), 3.67–3.50 (m, 4 H, CONCH_2), 3.04–2.89 (m, 5 H, HNCH_2, 19-H), 2.84 (m, 1 H, 13-H), 2.08 (m, 1 H, 16-H_a), 1.98 (s, 3 H, CH_3CO), 1.96–1.87 (m, 3 H, $CONCH_2CH_2$, 22-H_a), 1.78 (ddd, *J* = 10.5, 10.5, 7.5 Hz, 1 H, 21-H_a), 1.65 (s, 3 H, 30-H_3), 1.66–1.60 (m, 2 H, 12-H_a, 1-H_a), 1.57 (m, 2 H, 2-H_2), 1.53–1.47 (m, 2 H, 16-H_b, 18-H), 1.48–1.42 (m, 1 H, 6-H_a), 1.42–1.39 (m, 7 H, 6-H_b, 11-H_a, 15-H_a, 21-H_b, 7-H_2, 22-H_b), 1.25–1.18 (m, 2 H, 9-H, 11-H_b), 1.12 (m, 1 H, 15-H_b), 0.97–0.88 (m, 2 H, 12-H_b, 1-H_b), 0.92 (s, 3 H, 27-H_3), 0.90 (s, 3 H, 26-H_3), 0.82 (s, 3 H, 25-H_3), 0.79 (s, 6 H, 24-H_3, 23-H_3), 0.73 (d, *J* = 8.9 Hz, 1 H, 5-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5 (C-28), 171.0 (CH_3CO), 151.2 (C-20), 109.2 (C-29), 81.0 (C-3), 55.5 (C-5), 55.0 (C-17), 53.0 (C-18), 50.8 (C-9), 46.9 (4×CONCH_2), 45.7 (C-19), 42.0 (C-14), 40.7 (C-8), 38.4 (C-1), 37.8 (C-4), 37.1 (C-10), 36.9 (C-13), 36.1 (C-22), 34.3 (C-7), 32.3 (C-16), 31.4 (C-21), 29.9 (C-15), 29.0 ($CONCH_2CH_2$), 27.9 (C-23), 25.6 (C-12), 23.7 (C-2), 21.3 (CH_3CO), 21.2 (C-11), 19.7 (C-30), 18.2 (C-6), 16.5 (C-24), 16.2 (C-25), 16.1 (C-26), 14.7 (C-27) ppm; MS [ESI, MeOH for $C_{37}H_{60}N_2O_3$ (580.88)]: *m*/*z* (%) 581.3 (100) $[M+H]^+$.

4.4.12. 9-[2-[[4-[(3α,4β)-3-Acetyloxy-11,24-dioxo-urs-12-en-24-yl]-1-homopiperazinyl]carbonyl]-phenyl]-3,6-bis[diethylamino]-xanthylium chloride (16)

Following GP3 from rhodamine B and oxalyl chloride rhodamine B chloride was obtained. To a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **11** (0.22 g, 0.46 mmol, 1 eq.), NEt_3 (70 mg, 0.10 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work-up as described and purification by column chromatography afforded **16** in 83% yield; m.p. 213–215 °C; R_f 0.5 ($MeCN/CH_2Cl_2/H_2O$, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 274 nm (4.40), 647 nm (4.96); IR (KBr): ν = 3442*br*, 1732*m*, 1634*m*, 1590*m*, 1470*m*, 1413*m*, 1338*m*, 1247*m*, 1181*m*, 1074*m*, 684*m* cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71–7.59 (m, 2 H, 3″-H, 5″-H), 7.50–7.44 (m, 1 H, 4″-H), 7.35–7.20 (m, 3 H, 6″-H, 1′-H, 8′-H), 6.96–6.75 (m, 4 H, 2′-H, 7′-H, 4′-H, 5′-H), 5.55 (s, 1 H, 12-H), 5.51 (m, 1 H, 3-H), 3.95–3.21 (m, 16 H, 4×CONCH_2, N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$,), 2.51 (ddd, *J* = 13.8, 13.8, 3.0 Hz, 1 H, 1-H_a), 2.38 (s, 1 H, 9-H), 2.18 (m, 1 H, 6-H_a), 2.11 (s, 3 H, CH_3CO), 2.09 (m, 1 H, 16-H_a), 1.98–1.76 (m, 5 H, 2-H_2, 15-H_a, $CONCH_2CH_2$), 1.65 (dddd, *J* = 15.6, 15.6, 7.1, 5.6 Hz, 1 H, 6-H_b), 1.55 (d, *J* = 11.4 Hz, 1 H, 18-H), 1.53–1.37 (m, 6 H, 22-H_2, 7-H_a, 21-H_a, 19-H, 5-H), 1.34 (s, 3 H,

27-H_3), 1.33 (m, 12 H, N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$), 1.31–1.22 (m, 4 H, 21-H_b, 7-H_b, 1-H_b, 15-H_b), 1.25 (s, 3 H, 26-H_3), 1.23 (s, 3 H, 23-H_3), 1.22 (s, 3 H, 25-H_3), 1.02 (m, 1 H, 16-H_b), 0.96–0.90 (m, 4 H, 20-H, 30-H_3), 0.82 (s, 3 H, 28-H_3), 0.80 (s, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.5 (C-11), 174.4 (C-24), 170.8 (CH_3CO), 168.4 (CO-Rhd), 164.8 (C-13), 158.8 (C-9′), 157.7 (C-4a′, C-10a′), 155.7 (C-3′, C-6′), 134.0 (C-1″), 132.3 (C-1′, C-8′), 131.3 (C-2″), 130.5 (C-12), 130.0 (C-6″), 129.8 (C-3″), 129.4 (C-5″), 127.1 (C-4″), 114.7 (C-2′, C-7′), 113. 5 (C-8a′, C-9a′), 96.4 (C-4′, C-5′), 72.3 (C-3), 61.6 (C-9), 59.1 (C-18), 54.0 (C-5), 49.5 (C-4), 47.7 (4×CONCH_2), 46.3, 46.2 (N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$), 45.2 (C-8), 43.7 (C-14), 40.8 (C-22), 39.3 (C-19, C-20), 38.0 (C-10), 34.3 (C-1), 33.9 (C-7), 33.8 (C-17), 31.0 (C-21), 29.0 ($CONCH_2CH_2$), 28.7 (C-28), 27.9 (C-16), 27.4 (C-15), 23.3 (C-2), 22.7 (C-23), 21.3 (CH_3CO), 21.1 (C-30), 20.8 (C-6), 20.6 (C-27), 18.5 (C-26), 17.4 (C-29), 16.0 (C-25), 12.7 (N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$) ppm; MS [ESI, MeOH for $C_{65}H_{89}ClN_4O_5$ (1055.88)]: *m*/*z* (%) 1019.7 (100) $[M-Cl]^+$.

4.4.13. 9-[2-[[4-[(3β)-3-acetyloxy-28-oxours-12-en-28-yl]-1-homopiperazinyl]carbonyl]phenyl]-3,6-bis(diethylamino)-xanthylium chloride (17)

As described above for the synthesis of **16**, to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **12** (0.21 g, 0.46 mmol, 1 eq.), NEt_3 (70 mg, 0.10 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work up as described and purification by column chromatography afforded **17** in 74% yield; m.p. 238–245 °C; R_f 0.5 (MeCN/CH_2Cl_2/H_2O, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 275 nm (4.21), 647 nm (4.74;R (KBr): ν = 3440*br*, 2926*m*, 1729*m*, 1590*s*, 1528*m*, 1468*m*, 1413*m*, 1338*m*, 1275*m*, 1247*m*, 1181*m*, 1133*m*, 1074*m*, 1010*m*, 921*m*, 684*m* cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.56 (m, 2 H, 3″-H, 5″-H), 7.47–7.39 (m, 1 H, 4″-H), 7.31–7.27 (m, 1 H, 6″-H), 7.25–7.15 (m 2 H, 1′-H, 8′-H), 6.90–6.73 (m, 4 H, 2′-H, 7′-H, 4′-H, 5′-H), 5.17 (m, 1 H, 12-H), 4.46 (dd, *J* = 9.5, 7.8 Hz, 1 H, 3-H), 4.06–3.04 (m, 16 H, 4×CONCH_2, N″(C$H_2$$CH_3$)$_2$, N′(C$H_2$$CH_3$)$_2$), 2.40 (m, 1 H, 18-H), 2.18–2.04 (m, 2 H, 16-H_2), 2.02 (s, 3 H, CH_3CO), 1.88 (m, 2 H, 11-H_2), 1.77–1.54 (m, 3 H, 2-H_2, 1-H_a), 1.54–1.41 (m, 5 H, 6-H_a, 21-H_a, 7-H_a, 9-H, 22-H_a), 1.40–1.18 (m, 5 H, 6-H_b, 21-H_b, 7-H_b, 19-H, 22-H_b), 1.32 (t, *J* = 7.2 Hz, 6 H, N′($CH_2C$$H_3$)$_2$), 1.31 (t, *J* = 7.0 Hz, 6 H, N″($CH_2C$$H_3$)$_2$), 1.08–0.84 (m, 6 H, 1-$H_b$, 20-H, 15-$H_2$, $CONCH_2C$$H_2$), 1.02 (s, 3 H, 27-$H_3$),

0.90 (br s, 9 H, 29-H_3, 30-H_3, 25-H_3), 0.83 (s, 3 H, 23-H_3), 0.82 (s, 3 H, 24-H_3), 0.79 (m, 1 H, 5-H), 0.68 (s, 3 H, 26-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6 (C-28), 171.0 (CH_3CO), 168.6 (CO-Rhd), 168.0 (C-9′), 157.7, 157.6 (C-4a′, C-10a′), 155.7, 155.6 (C-3′, C-6′), 138.5 (C-13), 135.9 (C-1″), 132.5 (C-1′, C-8′), 130.1 (C-2″), 130.0 (C-6″), 129.6 (C-3″, C-5″), 126.8 (C-4″), 125.0 (C-12), 113.8, 113.6 (C-2′, C-7′), 113.5 (C-8a′, C-9a′), 96.4, 96.2 (C-4′, C-5′), 80.9 (C-3), 55.3 (C-5), 55.2 (C-18), 48.9 (C-17), 47.5 (C-9), 46.2, 46.1 (N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$, 4×CONCH_2), 42.3 (C-14), 39.3 (C-8), 38.7 (C-19, C-20), 38.2 (C-1), 37.6 (C-4), 36.9 (C-10), 34.8 (C-22), 33.7 (CONCH$_2$$CH_2$), 32.9 (C-7), 30.4 (C-21), 28.0 (C-23), 27.9 (C-15), 23.5 (C-2), 23.4 (C-27), 23.3 (C-11), 21.3 (CH_3CO), 21.4 (C-16), 21.2 (C-30), 18.1 (C-6), 17.5 (C-29), 16.9 (C-26), 16.7 (C-24), 15.5 (C-25), 12.7, 12.6 (N′(CH$_2$$CH_3$)$_2$, N″(CH$_2$$CH_3$)$_2$) ppm; MS [ESI, MeOH for $C_{65}H_{89}ClN_4O_5$ (1041.90)]: *m*/*z* (%) 1005.9 (100) $[M\text{-}Cl]^+$.

4.4.14. 9-[2-[[4-[(3β)-3-Acetyloxy-28-oxo-olean-12-en-28-yl]1-homopiperazinyl]carbonyl]phenyl]-3,6-bis(diethylamino)-xanthylium chloride (18)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **13** (0.27 g, 0.46 mmol, 1 eq.), NEt_3 (70 mg, 0.10 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work up as described and purification by column chromatography afforded **18** in 82% yield; m.p. 245–248 °C; R_f 0.5 (MeCN/CH_2Cl_2/H_2O, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 277 nm (4.20), 647 nm (4.76); IR (KBr): ν = 3442*br*, 2926*m*, 1629*m*, 1590*s*, 1528*m*, 1468*m*, 1413*m*, 1338*m*, 1275*m*, 1247*m*, 1181*m*, 1133*m*, 1074*m*, 1010*m*, 921*m*, 684*m* cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.55 (m, *2* H, 3″-H, 5″-H), 7.43 (m, 1 H, 4″-H), 7.32–7.28 (m, 1 H, 6″-H), 7.27–7.18 (m 2 H, 1′-H, 8′-H), 6.85–6.73 (m, 4 H, 2′-H, 7′-H, 4′-H, 5′-H), 5.22 (m, 1 H, 12-H), 4.46 (dd, *J* = 9.5, 7.6 Hz, 1 H, 3-H), 4.02–3.40 (m, 12 H, 2×CONCH_2, N′(CH_2CH$_3$)$_2$, N″(CH_2CH$_3$)$_2$), 3.38–2.95 (m, 5 H, 2×CONCH_2, 18-H), 2.16–2.04 (m, 1 H, 16-H_a), 2.02 (s, 3 H, CH_3CO), 1.96–1.78 (m, 4 H, CONCH$_2$CH_2, 11-H_2), 1.77–1.36 (m, 9 H, 2-H_2, 6-H_a, 15-H_a, 16-H_b, 7-H_a, 1-H_a ,19-Ha, 9-H), 1.35–1.14 (m, 6 H, 6-H_b, 7-H_b, 22-H_a, 19-H_b, 21-H_2), 1.31 (m, 12 H, N′(CH$_2$CH_3)$_2$, N″(CH$_2$CH_3)$_2$), 1.09 (s, 3 H, 27-H_3), 1.13–0.96 (m, 3 H, 22-H_b, 15-H_b, 1-H_b), 0.93 (s, 3 H, 30-H_3), 0.88 (s, 6 H, 29-H_3, 25-H_3), 0.83 (s, 3 H, 23-H_3), 0.82 (s, 3 H, 24-H_3), 0.79 (m, 1 H, 5-H), 0.67 (s, 3 H, 26-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (C-28), 171.0 (CH_3CO), 168.7 (CO-Rhd), 165.7 (C-9′), 157.7 (C-4a′, C-10a′), 155.6 (C-3′, C-6′), 144.7 (C-13), 136.3 (C-1″), 132.5 (C-1′, C-8′), 130.1

(C-2″), 130.0 (C-6″), 129.6 (C-3″, C-5″), 126.7 (C-4″), 121.4 (C-12), 114.8 (C-2′, C-7′), 113.6 (C-8a′, C-9a′), 96.4, 96.2 (C-4′, C-5′), 80.9 (C-3), 55.3 (C-5), 47.7 (C-17), 47.6 (C-9), 46.3 (C-19), 46.2, 46.0 (N′(*C*$H_2$$CH_3$)$_2$, N″(*C*$H_2$$CH_3$)$_2$, 4×CON*C*$H_2$), 43.6 (C-18), 42.0 (C-14), 39.0 (C-8), 38.0 (C-1), 37.7 (C-4), 37.0 (C-10), 34.0 (C-21), 33.8 (C-22), 33.0 (C-29), 32.8 (C-7), 30.3 (C-20), 28.0 (C-23), 27.9 (C-16), 27.8 (C-15), 25.7 (C-27), 24.0 (C-30), 23.7 (CONCH$_2$*C*H$_2$), 23.5 (C-2), 23.3 (C-11), 21.3 (*C*H_3CO), 18.2 (C-6), 16.9 (C-26), 16.6 (C-24), 15.4 (C-25), 12.7 (N′(CH$_2$*C*H_3)$_2$, N″(CH$_2$*C*H_3)$_2$) ppm; MS [ESI, MeOH for $C_{65}H_{89}ClN_4O_5$ (1041.90)]: *m*/*z* (%) 1005.9 (100) $[M\text{-}Cl]^+$.

4.4.15. 9-[2-[[4-[(3β, 18β)-3-Acetyloxy-11,30-dioxo-urs-12-en-30-yl]1-homopiperazinyl]carbonyl]-phenyl]-3,6-bis(diethylamino)-xanthylium chloride (19)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **14** (0.21 g, 0.46 mmol, 1 eq.), NEt_3 (70 mg, 0.10 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work up as described and purification by column chromatography afforded **19** in 50% yield; m.p. 165–170 °C; R_f 0.5 (MeCN/CH_2Cl_2/H_2O, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 271 nm (4.47), 644 nm (4.83); IR (KBr): ν = 3441*br*, 2971*m*, 1725*m*, 1590*s*, 1467*m*, 1414*m*, 1384*m*, 1338*m*, 1248*m*, 1181*m*, 1133*m*, 1074*m*, 684*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.59 (m, *2* H, 3″-H, 5″-H), 7.51–7.42 (m, 1 H, 4″-H), 7.33–7.27 (m, 1 H, 6″-H), 7.25–7.18 (m 2 H, 1′-H, 8′-H), 7.00–6.86 (m, 2 H, 2′-H, 7′-H), 6.84–6.64 (m, 2 H, 4′-H, 5′-H), 5.66 (s, 1 H, 12-H), 4.50 (m, 1 H, 3-H), 3.78–3.31 (m, 12 H, CONC*H*$_2$, N′(C*H*$_2$CH$_3$)$_2$, N″(C*H*$_2$CH$_3$)$_2$), 3.14–3.08 (m, 4 H, RhdCONC*H*$_2$), 2.77 (m, 1 H, 1-H$_a$), 2.34 (m, 1 H, 9-H), 2.23 (m, 1 H, 18-H), 2.04 (s, 3 H, CH_3CO), 2.07–1.97 (m, 5 H, 16-H$_a$, 19-H$_a$, 21-H$_a$, CONCH$_2$C*H*$_2$), 1.81 (m, 1 H, 15-H$_a$), 1.74–1.53 (m, 5 H, 2-H$_2$, 6-H$_a$, 21-H$_b$, 19-H$_b$), 1.49–1.34 (m, 5 H, 6-H$_b$, 7-H$_2$, 22-H$_2$), 1.33 (s, 3 H, 27-H$_3$), 1.31 (m, 12 H, N′(CH$_2$C*H*$_3$)$_2$, N″(CH$_2$C*H*$_3$)$_2$), 1.19 (s, 3 H, 29-H$_3$), 1.18–1.14 (m, 1 H, 15-H$_b$), 1.15 (s, 3 H, 25-H$_3$), 1.10 (s, 3 H, 26-H$_3$), 1.06–0.95 (m, 2 H, 1-H$_b$, 16-H$_b$), 0.87 (br s, 6 H, 23-H$_3$, 24-H$_3$), 0.79 (m, 1 H, 5-H), 0.76 (s, 3 H, 28-H$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.9 (C-11), 175.2 (C-30), 171.0 (CH$_3$*C*O), 169.8 (CO-Rhd), 169.5 (C-13), 158.7 (C-9′), 157.7 (C-4a′, C-10a′), 155.7 (C-3′, C-6′), 134.0 (C-1″), 133.8 (C-5″), 132.0 (C-1′, C-8′), 130.9 (C-2″), 130.0 (C-6″), 129.9 (C-3″), 128.4 (C-12), 126.9 (C-4″), 114.5, 114.3 (C-2′, C-7′), 113.5 (C-8a′, C-9a′), 96.4, 96.3 (C-4′, C-5′), 80.6 (C-3), 61.7 (C-9), 55.0 (C-5), 48.1 (C-18), 46.1 (N′(*C*$H_2$$CH_3$)$_2$, N″(*C*$H_2$$CH_3$)$_2$), 45.9 (4×CON*C*$H_2$), 45.3 (C-8), 44.4 (C-20), 44.3 (C-19), 43.3 (C-14), 38.8

(C-1), 38.0 (C-4), 37.7 (C-22), 36.9 (C-10), 32.8 (C-21, C-7), 31.8 (C-17), 29.7 ($CONCH_2CH_2$), 28.5 (C-28), 28.0 (C-23), 27.3 (C-29), 26.7 (C-16), 26.3 (C-15), 23.5 (C-2), 23.0 (C-27), 21.3 (CH_3CO), 18.7 (C-26), 17.4 (C-6), 16.7 (C-24), 16.4 (C-25), 12.6 (N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$) ppm; MS [ESI, MeOH for $C_{65}H_{87}ClN_4O_6$ (1055.88)]: *m*/*z* (%) 1019.7 (100) $[M-Cl]^+$.

4.4.16. 9-[2-[[4-[(3b)-3-Acetyloxy-20(29)en-28-oxo-lup-28-yl]-1-homopiperazinyl]carbonyl]-phenyl]-3,6-bis(diethylamino)-xanthylium chloride (20)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **15** (0.26 g, 0.46 mmol, 1 eq.), NEt_3 (70 mg, 0.10 mL, 0.69 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work-up as described and purification by column chromatography afforded **20** in 58% yield; m.p. 256–260 °C; R_f 0.5 (MeCN/CH_2Cl_2/H_2O, 10:1:1; UV-Vis (MeOH): λ_{max} (log ε) = 275 nm (4.32), 646 nm (4.84); IR (KBr): ν = 3448*br*, 2940*m*, 1590*s*, 1467*m*, 1413*m*, 1338*m*, 1247*m*, 1181*m*, 1133*m*, 1074*m*, 684*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.57 (m, *2* H, 3″-H, 5″-H), 7.47–7.42 (m, 1 H, 4″-H), 7.33–7.18 (m, 3 H, 6″-H, 1′-H, 8′-H), 7.10–6.87 (m, 2 H, 2′-H, 7′-H), 6.86–6.70(m, 2 H, 4′-H, 5′-H), 4.71 (m, 1 H, 29-H_a), 4.55 (m, 1 H, 29-H_b), 4.44 (m, 1 H, 3-H), 3.80–3.26 (m, 16 H, 4×CONCH_2, N′(C$H_2$$CH_3$)$_2$, N″(C$H_2$$CH_3$)$_2$), 2.99 (m, 1 H, 19-H), 2.84 (m, 1 H, 13-H), 2.10 (m, 1 H, 16-H_a), 2.02 (s, 3 H, CH_3CO), 1.91 (m, 1 H, 22-H_a), 1.84–1.72 (m, 3 H, $CONCH_2CH_2$, 21-H_a), 1.71–1.54 (m, 4 H, 12-H_a, 1-H_a, 2-H_2), 1.65 (s, 3 H, 30-H_3), 1.52 (m, 1 H, 18-H), 1.49–1.16 (m, 9 H, 6-H_2, 11-H_2, 15-H_a, 21-H_b, 22-H_b, 7-H_2, 9-H, 16-H_b), 1.12 (m, 1 H, 15-H_b), 1.31 (m, 12 H, $CONCH_2CH_2$, N′(C$H_2$$CH_3$)$_2$, N″(C$H_2$$CH_3$)$_2$), 0.98–0.87 (m, 2 H, 1-$H_b$, 12-$H_b$), 0.90 (s, 6 H, 27-$H_3$, 26-$H_3$), 0.81 (s, 9 H, 25-$H_3$, 24-$H_3$, 23-$H_3$), 0.76 (m, 1 H, 5-H ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (C-28), 171.0 (CH_3CO), 168.6 (CO-Rhd), 168.1 (C-9′), 157.7 (C-4a′, C-10a′), 155.7, 155.6 (C-3′, C-6′), 151.4 (C-20), 133.8 (C-1″), 132.5 (C-1′, C-8′), 130.2 (C-2″), 130.0 (C-6″), 129.9 (C-5″), 129.5 (C-3″), 126.7 (C-4″), 114.0, 113.7 (C-2′, C-7′), 113.5 (C-8a′, C-9a′), 109.2 (C-29), 96.4, 96.3 (C-4′, C-5′), 81.0 (C-3), 55.5 (C-5), 54.9 (C-17), 52.7 (C-18), 50.8 (C-9), 46.2, 46.1 (N′(*C*$H_2$$CH_3$)$_2$, N″(*C*$H_2$$CH_3$)$_2$), 45.9 (C-19), 42.8 (4×CON*C*H_2), 42.0 (C-14), 40.7 (C-8), 38.4 (C-1), 38.3 ($CONCH_2CH_2$), 37.8 (C-4), 37.1 (C-10), 36.8 (C-13), 36.1 (C-22), 34.3 (C-7), 32.3 (C-16), 31.5 (C-21), 29.9 (C-15), 27.9 (C-23), 25.5 (C-12), 23.7 (C-2), 21.3 (CH_3CO), 21.2 (C-11), 19.4 (C-30), 18.2 (C-6), 16.5 (C-24), 16.3 (C-25), 16.2

(C-26), 14.6 (C-27), 12.7 (N′(CH_2CH_3)$_2$, N″(CH_2CH_3)$_2$) ppm; MS [ESI, MeOH for $C_{65}H_{89}ClN_4O_5$ (1041.90)]: *m*/*z* (%) 1005.8 (100) $[M\text{-}Cl]^+$.

4.4.17. 11-Keto-β-boswellic acid methyl ester (21)

To a solution of **10** (6.07 g, 13 mmol, 1.0 eq.) in DMF (100 mL) finely grounded potassium carbonate (2.0 g, 14 mmol, 1.1 eq.) was added. After stirring at ambient temperature for 30 min, methyl iodide (2.2 g, 1.0 mL, 15 mmol, 1.2 eq.) was added, and stirring was continued for 24 h. The mixture was slowly added to 5% hydrochloric acid (300 mL) and a precipitate was formed. The crude product was filtered off and washed with water (2×100 mL). After purification by column chromatography (silica gel, [hexane/ethyl acetate/HOAc, 7:3:0.5%]:$CHCl_3$, 1:1) **21** (5.73 g, 92%) was obtained as a white solid; m.p. 226–228 °C $[\alpha]_D$ = +111.2° (*c* = 4.34, $CHCl_3$) [lit. m.p. 220–225 °C, $[\alpha]_D$ = +111.2° (*c* = 4.34, $CHCl_3$)][16].

4.4.18. 11-Keto-β-boswellic acid benzyl ester (22)

As described for the synthesis of **21**, from **10** (10.0 g, 22 mmol, 1.0 eq.) and benzyl bromide (4.1 g, 2.9 mL, 24 mmol, 1.1 eq.) followed by aqueous workup and re-crystallisation from MeOH, compound **22** was obtained as a white solid in 57% yield; m.p. 202–204 °C; R_f 0.23 (hexane/ethyl acetate, 5:1); $[\alpha]_D$ = +111.0° (*c* = 0.37, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 264 nm (3.97); IR (KBr): ν = 3448*br*, 2928*m*, 1726*s*, 1644*s*, 1456*m*, 1385*m*, 1214*m*, 1169*m*, 1107*m*, 1056*m*, 968*m*, 754*m*, 698*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5 H, Ph), 5.53 (s, 1 H, 12-H), 5.15 (d, *J* = 12.3 Hz, 1 H, CH_aPh), 5.09 (d, *J* = 12.3 Hz, 1 H, CH_bPh), 4.13 (m, 1 H, 3-H), 2.49 (ddd, *J* = 13.4, 13.4, 3.3 Hz, 1 H, 1-H_a), 2.41 (s, 1 H, 9-H), 2.30 (dddd, *J* = 14.8, 14.8, 4.3, 2.6 Hz, 1 H, 2-H_a), 2.09 (ddd, *J* = 13.7, 13.7, 4.8 Hz, 1 H, 16-H_a), 1.87 (ddd, *J* = 13.7, 13.7, 5.2 Hz, 1 H, 15-H_a), 1.82 (m, 1 H, 6-H_a), 1.72 (m, 1 H, 6-H_b), 1.65 (ddd, *J* = 13.0, 13.0, 3.8 Hz, 1 H, 7-H_a), 1.58–1.51 (m, 2 H, 2-H_b, 18-H), 1.51–1.38 (m, 5 H, 22-H_a, 5-H, 21-H_a, 7-H_b, 19-H), 1.36–1.24 (m, 3 H, 22-H_b, 1-H_b, 21-H_b), 1.32 (s, 3 H, 23-H_3), 1.31 (s, 3 H, 27-H_3), 1.20 (m, 1 H, 15-H_b), 1.12 (s, 3 H, 26-H_3), 1.00 (m, 1 H, 16-H_b), 0.97 (s, 3 H, 25-H_3), 0.95 (s, 3 H, 30-H_3), 0.94 (m, 1 H, 20-H), 0.82 (s, 3 H, 28-H_3), 0.80 (d, *J* = 6.6 Hz, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.5 (C-11), 176.4 (C-24), 164.9 (C-13), 135.7 (C_i-Ph), 130.5 (C-12), 128.5 (C_m-Ph), 128.4 (C_o-Ph), 128.2 (C_p-Ph), 70.7 (C-3), 66.2 (CH_2Ph), 60.4 (C-9), 59.0 (C-18), 48.9 (C-5), 47.5 (C-4), 45.1 (C-8), 43.8 (C-14), 40.9 (C-22), 39.3 (C-19, C-20), 37.4 (C-10), 34.0 (C-1, C-17), 32.9 (C-7), 30.9 (C-21), 28.8 (C-28), 27.5 (C-16), 27.2 (C-15), 26.3 (C-2), 24.2 (C-23), 21.1 (C-30), 20.5 (C-27), 18.9

(C-6), 18.2 (C-26), 17.4 (C-29), 13.3 (C-25) ppm; MS [ESI, MeOH for $C_{37}H_{52}O_4$ (560.82)]: *m*/*z* (%) 1143.3 (100) $[2M+Na]^+$, 1121.2 (29) $[2M+H]^+$, 583.3 (11) $[M+Na]^+$, 561.4 (22) $[M+H]^+$.

4.4.19. 3-*O*-Acetyl-11-keto-β-boswellic acid benzylamide (23)

To an ice-cold solution of **5** (2.0 g, 4.0 mmol, 1.0 eq.) in dry CH_2Cl_2 (20 mL), oxalyl chloride (2.0 g, 1.4 mL, 16 mmol, 4.0 eq.) was slowly added, and the mixture was allowed to warm to ambient temperature, and stirring was continued for 3 h. The solvent was removed under reduced pressure, the residue dissolved in dry THF (10 mL), and the volatiles were again evaporated. To a solution of the residue in dry CH_2Cl_2 (15 mL), benzyl amine (1.3 g, 1.3 mL, 12 mmol, 3.0 eq.), NEt_3 (0.6 g, 0.3 mL, 5.8 mmol, 1.5 eq.) and DMAP (5 mol-%) were added, and stirring was continued overnight. Evaporation of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, hexane/ethyl acetate, 5:1) afforded **23** as a white solid in 80% yield; m.p 173–178 °C; R_f 0.4 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D$ = +52.2° (*c* = 0.36, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 280 nm (3.35); IR (KBr): ν = 3442*br*, 2927*m*, 1737*m*, 1654*m*, 1522*m*, 1455*m*, 1372*m*, 1247*m*, 1027*m*, 699*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H, Ph), 5.74 (dd, *J* = 5.5, 5.1 Hz, 1 H, N*H*), 5.56 (s, 1 H, 12-H), 5.33 (m, 1 H, 3-H), 4.47 (dd, *J* = 14.4, 5.7 Hz, 1 H, CH_aPh), 4.37 (dd, *J* = 14.4, 4.9 Hz, 1 H, CH_bPh), 2.55 (ddd, *J* = 13.2, 13.2, 3.5 Hz, 1 H, 1-H_a), 2.41 (s, 1 H, 9-H), 2.31 (dddd, *J* = 14.6, 14.6, 4.2, 2.5 Hz, 1 H, 2-H_a), 2.10 (m, 1 H, 16-H_a), 2.09 (s, 3 H, C*H*$_3$CO), 1.89 (m, 1 H, 15-H_a), 1.81–1.60 (m, 4 H, 6-H_2, 7-H_a, 2-H_b), 1.55 (d, *J* = 11.4 Hz, 1 H, 18-H), 1.53–1.44 (m, 3 H, 22-H_a, 7-H_b, 21-H_a), 1.42 (m, 1 H, 5-H), 1.40 (m, 1 H, 19-H), 1.35 (s, 3 H, 27-H_3), 1.39–1.19 (m, 4 H, 22-H_b, 21-H_b, 15-H_b, 1-H_b,), 1.18 (s, 3 H, 23-H_3), 1.17 (s, 3 H, 26-H_3), 1.11 (s, 3 H, 25-H_3), 1.02 (m, 1 H, 16-H_b), 0.96 (s, 3 H, 30-H_3), 0.88 (m, 1 H, 20-H), 0.83 (s, 3 H, 28-H_3), 0.81 (d, *J* = 6.4 Hz, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.0 (C-11), 174.9 (C-24), 170.1 (CH_3CO), 164.6 (C-13), 138.1 (C_i-Ph), 130.6 (C-12), 128.8 (C_m-Ph), 128.0 (C_o-Ph), 127.6 (C_p-Ph), 73.5 (C-3), 60.3 (C-9), 59.0 (C-18), 50.5 (C-5), 46.7 (C-4), 45.0 (C-8), 43.8 (CH_2Ph), 43.7 (C-14), 40.9 (C-22), 39.3 (C-19), 39.2 (C-20), 37.4 (C-10), 34.9 (C-1), 34.0 (C-17), 33.1 (C-7), 30.9 (C-21), 28.8 (C-28), 27.5 (C-16), 27.2 (C-15), 24.7 (C-23), 24.0 (C-2), 21.3 (*C*H_3CO), 21.1 (C-30), 20.5 (C-27), 19.5 (C-6), 18.3 (C-26), 17.4 (C-29), 13.5 (C-25) ppm; MS [ESI, MeOH for $C_{39}H_{55}NO_4$ (601.41)]: *m*/*z* (%) 1225.3 (54) $[2M+Na]^+$, 922.4 (8) $[3M+Ca]^+$, 624.4 (67) $[M+Na]^+$, 602.3 (100) $[M+H]^+$.

4.4.20. 11-Keto-β-boswellic acid benzylamide (24)

To a solution of **23** (1.8 g, 3.1 mmol, 1 eq.) in MeOH (50 mL), KOH (0.9 g, 15.7 mmol, 5 eq.) was added, and the mixture was stirred at ambient temperature for 3 d. The mixture was slowly added to hydrochloric acid (1 M, 15 mL). The aqueous phase was extracted with CH_2Cl_2 (4×15 mL), the combined organic phases were washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel, hexane/ethyl acetate, 5:1) afforded **24** as a white solid in 76% yield; m.p. 216–218 °C; R_f 0.13 (hexane/ethyl acetate, 2:1); $[\alpha]_D$ = +118.0° (*c* = 0.35, $CHCl_3$); UV-Vis (MeOH): λ_{max} (log ε) = 266 nm (3.83); IR (KBr): ν = 3423*br*, 2925*m*, 2869*m*, 1728*m*, 1655*s*, 1511*m*, 1455*m*, 1382*m*, 1234*m*, 1200*m*, 1057*m*, 966*m*, 700*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H, Ph), 5.75 (dd, *J* = 5.5, 5.2 Hz, 1 H, N*H*), 5.55 (s, 1 H, 12-H), 4.48 (dd, *J* = 14.6, 5.5 Hz, 1 H, CH_aPh), 4.37 (dd, *J* = 14.6, 5.2 Hz, 1 H, CH_bPh), 4.13 (m, 1 H, 3-H), 2.50 (ddd, *J* = 13.7, 13.7, 3.5 Hz, 1 H, 1-H_a), 2.43 (s, 1 H, 9-H), 2.42 (dddd, *J* = 14.4, 14.4, 4.5, 2.5 Hz, 1 H, 2-H_a), 2.09 (ddd, *J* = 13.7, 13.7, 4.7 Hz, 1 H, 16-H_a), 1.86 (ddd, *J* = 13.7, 13.7, 4.7 Hz, 1 H, 15-H_a), 1.75–1.66 (m, 3 H, 6-H_2, 7-H_a), 1.56 (m, 1 H, 2-H_b), 1.53 (d, *J* = 11.0 Hz, 1 H, 18-H), 1.51–1.42 (m, 4 H, 5-H, 22-H_a, 7-H_b, 21-H_a), 1.41–1.30 (m, 4 H, 22-H_b, 19-H, 1-H_b, 21-H_b), 1.31 (s, 3 H, 27-H_3), 1.29 (s, 3 H, 23-H_3), 1.19 (m, 1 H, 15-H_b), 1.15 (s, 3 H, 26-H_3), 1.09 (s, 3 H, 25-H_3), 1.00 (m, 1 H, 16-H_b), 0.95 (s, 3 H, 30-H_3), 0.94 (m, 1 H, 20-H), 0.82 (s, 3 H, 28-H_3), 0.79 (d, *J* = 6.5 Hz, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.2 (C-11), 176.2 (C-24), 164.7 (C-13), 138.3 (C_i-Ph), 130.5 (C-12), 128.7 (C_m-Ph), 127.9 (C_o-Ph), 127.5 (C_p-Ph), 70.8 (C-3), 60.4 (C-9), 59.0 (C-18), 48.8 (C-5), 47.4 (C-4), 45.0 (C-8), 43.8 (C-14), 43.7 (CH_2Ph), 40.9 (C-22), 39.3 (C-19), 39.2 (C-20), 37.6 (C-10), 34.2 (C-1), 34.0 (C-17), 33.2 (C-7), 30.9 (C-21), 28.8 (C-28), 27.5 (C-16), 27.2 (C-15), 26.6 (C-2), 25.1 (C-23), 21.1 (C-30), 20.5 (C-27), 19.7 (C-6), 18.3 (C-26), 17.4 (C-29), 13.5 (C-25) ppm; MS [ESI, MeOH for $C_{37}H_{53}NO_3$ (559.84)]: *m*/*z* (%) 1141.4 (87) $[2M+Na]^+$, 1119.2 (48) $[2M+H]^+$, 859.5 (8) $[3M+Ca]^+$, 582.3 (6) $[M+Na]^+$, 560.3 (100) $[M+H]^+$, 542.3 (11) $[M+H-H_2O]^+$.

4.4.21. 3,6-Bis(diethylamino)-9-[2-[3α,4β)-[24-methoxy-11,24-dioxours-12-en-3-oxycarbonyl]-phenyl]-xanthylium chloride (25)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **21** (0.44 g, 0.91 mmol, 1 eq.), NEt_3 (0.14 g, 0.15 mL, 1.38 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work up as described and purification by column chromatography afforded **25** in 43% yield; m.p. 165–170 °C; R_f 0.5 (MeCN/ CH_2Cl_2/H_2O, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 270 nm (4.40), 641 nm (4.97); IR (KBr): δ = 3441*br*, 2973*m*, 1723*m*, 1648*m*, 1590*s*,

1467*m*, 1413*m*, 1338*m*, 1274*m*, 1181*m*, 1133*m*, 1075*m*, 683*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 7.8, 0.9 Hz, 1 H, 3″-H), 7.87 (dt, *J* = 7.6, 1.2 Hz, 1 H, 5″-H), 7.78 (dt, *J* = 7.8, 1.2 Hz, 1 H, 4″-H), 7.38 (dd, *J* = 7.6, 1.0 Hz, 1 H, 6″-H), 7.10, 7.09 (2×d, *J* = 9.5 Hz, 2 H, 1′-H, 8′-H), 6.97, 6.84 (2×dd, *J* = 9.5, 2.4 Hz, 2 H, 2′-H, 7′-H), 6.78, 6.77 (2×d, *J* = 2.4 Hz, 2 H, 4′-H, 5′-H), 5.57 (s, 1 H, 12-H), 5.29 (m, 1 H, 3-H), 3.62 (s, 3 H, OMe), 3.63 (m, 8 H, $N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$), 2.59 (ddd, *J* = 13.3, 13.3, 3.3 Hz, 1 H, 1-H_a), 2.47 (s, 1 H, 9-H), 2.20–2.09 (m, 2 H, 2-H_a, 16-H_a), 1.92 (ddd, *J* = 13.2, 13.2, 4.7 Hz, 1 H, 15-H_a), 1.85–1.71 (m, 3 H, 6-H_2, 7-H_a), 1.56 (d, *J* = 11.0 Hz, 1 H, 18-H), 1.54–1.43 (m, 6 H, 7-H_b, 22-H_a, 21-H_a, 5-H, 19-H, 2-H_b), 1.42 (s, 3 H, 27-H_3), 1.37–1.22 (m, 4 H, 22-H_b, 21-H_b, 1-H_b, 15-H_b), 1.32 (t, *J* = 7.2 Hz, 12 H, $N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$), 1.20 (s, 3 H, 26-H_3), 1.14 (s, 3 H, 23-H_3), 1.06 (m, 1 H, 16-H_b), 1.03 (s, 3 H, 25-H_3), 0.97 (s, 3 H, 30-H_3), 0.96 (m, 1 H, 20-H), 0.84 (s, 3 H, 28-H_3), 0.83 (d, *J* = 6.0 Hz, 3 H, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1 (C-11), 175.7 (C-24), 165.4 (C-13), 164.2 (CO-Rhd), 158.9 (C-9′), 157.8, 157.7 (C-4a′, C-10a′), 155.7, 155.4 (C-3′, C-6′), 133.9 (C-1″), 133.3 (C-5″), 131.2, 131.1 (C-1′, C-8′), 130.6 (C-6″, C-2″), 130.5 (C-4″), 130.4 (C-12), 130.2 (C-3″), 114.5, 113.9 (C-2′, C-7′), 113.6, 113.5 (C-8a′, C-9a′), 96.4, 96.3 (C-4′, C-5′), 75.0 (C-3), 60.5 (C-9), 59.1 (C-18), 51.6 (OMe), 51.1 (C-5), 46.8 (C-4), 46.2, 46.1 ($N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$), 45.1 (C-8), 43.8 (C-14), 40.9 (C-22), 39.3 (C-19, C-20), 37.2 (C-10), 35.0 (C-1), 34.0 (C-17), 32.9 (C-7), 30.9 (C-21), 28.9 (C-28), 27.5 (C-16), 27.2 (C-15), 24.0 (C-23), 23.6 (C-2), 21.1 (C-30), 20.5 (C-27), 18.8 (C-6), 18.4 (C-26), 17.5 (C-29), 13.1 (C-25), 12.6 ($N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$) ppm; MS [ESI, MeOH for $C_{59}H_{77}N_2O_6Cl$ (945.72)]: *m*/*z* (%) 909.5 (100) $[M-Cl]^+$.

4.4.22. 3,6-Bis(diethylamino)-9-[2-[(3α,4β)-[24-benzyloxy-11,24-dioxours-12-en-3-oxycarbonyl]-phenyl]-xanthylium chloride (26)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **22** (0.32 g, 0.57 mmol, 1 eq.), NEt_3 (87 mg, 0.18 mL, 0.86 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work-up as described and purification by column chromatography afforded **26** in 58% yield; m.p. 175–180 °C; R_f 0.5 (MeCN/ CH_2Cl_2/H_2O, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 273 nm (4.42), 641 nm (4.99); IR (KBr): ν = 3442*br*, 2974*m*, 1720*m*, 1648*m*, 1590*s*, 1467*m*, 1413*m*, 1338*m*, 1274*m*, 1181*m*, 1133*m*, 1075*m*, 683*m* cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.17 (dd, *J* = 7.9, 0.8 Hz, 1 H, 3″-H), 7.86 (dt, *J* = 7.6, 1.2 Hz, 1 H, 5″-H), 7.76 (dt, *J* = 7.8, 1.1 Hz, 1 H, 4″-H), 7.36 (dd, *J* = 7.6, 1.0 Hz, 1 H, 6″-H), 7.32–7.25 (m, 5 H, Ph),

7.08, 7.07 (2×d, *J* = 9.7 Hz, 2 H, 1′-H, 8′-H), 6.95, 6.82 (2×dd, *J* = 9.7, 2.4 Hz, 2 H, 2′-H, 7′-H), 6.77, 6.76 (2×d, *J* = 2.4 Hz, 2 H, 4′-H, 5′-H), 5.54 (s, 1 H, 12-H), 5.28 (m, 1 H, 3-H), 5.09 (d, *J* = 12.2 Hz, 1 H, CH_aPh), 5.00 (d, *J* = 12.2 Hz, 1 H, CH_bPh), 3.62 (q, *J* = 7.2 Hz, 4 H, NCH_2CH_3), 3.61 (q, *J* = 7.2 Hz, 4 H, $N'CH_2CH_3$), 2.56 (ddd, *J* = 13.1, 13.1, 3.2 Hz, 1 H, 1-H_a), 2.45 (s, 1 H, 9-H), 2.15 (m, 1 H, 2-H_a), 2.12 (ddd, *J* = 13.7, 13.7, 4.7 Hz, 1 H, 16-H_a), 1.89 (ddd, *J* = 13.7, 13.7, 4.8 Hz, 1 H, 15-H_a), 1.79 (m, 2 H, 6-H_2), 1.73 (ddd, *J* = 12.7, 12.7, 3.7 Hz, 1 H, 7-H_a), 1.55 (d, *J* = 11.2 Hz, 1 H, 18-H), 1.52–1.41 (m, 6 H, 22-H_a, 5-H, 7-H_b, 21-H_a, 19-H, 2-H_b), 1.40 (s, 3 H, 27-H_3), 1.38–1.20 (m, 4 H, 22-H_b, 21-H_b, 1-H_b, 15-H_b), 1.31 (t, *J* = 7.0 Hz, 12 H, $N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$), 1.15 (s, 3 H, 23-H_3), 1.13 (s, 3 H, 26-H_3), 1.04 (m, 1 H, 16-H_b), 0.96 (s, 3 H, 30-H_3), 0.95 (m, 1 H, 20-H), 0.94 (s, 3 H, 25-H_3), 0.82 (br s, 6 H, 28-H_3, 29-H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1 (C-11), 174.9 (C-24), 165.4 (C-13), 164.1 (CO-Rhd), 158.8 (C-9′), 157.8, 157.7 (C-4a′, C-10a′), 155.6, 155.4 (C-3′, C-6′), 135.1 (C_i-Ph), 133.9 (C-1″), 133.3 (C-5″), 131.2, 131.1 (C-1′, C-8′), 130.6 (C-6″), 130.5 (C-2″, C-4″), 130.4 (C-12), 130.2 (C-3″), 128.6 (C_m-Ph), 128.5 (C_o-Ph), 128.4 (C_p-Ph), 114.5, 113.9 (C-2′, C-7′), 113.6, 113.5 (C-8a′, C-9a′), 96.4, 96.3 (C-4′, C-5′), 75.0 (C-3), 66.7 (CH_2Ph), 60.4 (C-9), 59.1 (C-18), 51.2 (C-5), 46.9 (C-4), 46.2, 46.1 ($N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$), 45.0 (C-8), 43.7 (C-14), 40.9 (C-22), 39.3 (C-19, C-20), 37.3 (C-10), 35.0 (C-1), 34.0 (C-17), 32.9 (C-7), 30.8 (C-21), 28.8 (C-28), 27.5 (C-16), 27.2 (C-15), 24.0 (C-23), 23.6 (C-2), 21.1 (C-30), 20.5 (C-27), 18.8 (C-6), 18.2 (C-26), 17.5 (C-29), 13.3 (C-25), 12.6 ($N(CH_2CH_3)_2$, $N'(CH_2CH_3)_2$) ppm; MS [ESI, MeOH for $C_{65}H_{81}N_2O_6Cl$ (1021.82)]: *m*/*z* (%) 985.6 (100) $[M\text{-}Cl]^+$.

4.4.23. 3,6-Bis(diethylamino)-9-[2-[(3α,4β)-[24-benzylamino-11,24-dioxours-12-en-3-oxycarbonyl]-phenyl]-xanthylium chloride (27)

As described above for **16** to a solution of rhodamine B chloride in dry CH_2Cl_2 (10 mL), **24** (0.20 g, 0.29 mmol, 1 eq.), NEt_3 (44 mg, 0.06 mL, 0.44 mmol, 1.5 eq.) and DMAP (5 mol-%) were added. Work-up as described and purification by column chromatography afforded **27** in 57% yields; m.p. 195–205 °C; R_f 0.5 ($MeCN/CH_2Cl_2/H_2O$, 10:1:1); UV-Vis (MeOH): λ_{max} (log ε) = 270 nm (4.21), 640 nm (4.76); IR (KBr): δ = 3442*br*, 2926*m*, 1718*m*, 1648*m*, 1590*s*, 1466*m*, 1413*m*, 1338*m*, 1247*m*, 1181*m*, 1075*m*, 923*m*, 683*m* cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.9, 0.9 Hz, 1 H, 3″-H), 7.82 (dt, *J* = 7.5, 1.0 Hz, 1 H, 5″-H), 7.75 (dt, *J* = 7.9, 1.0 Hz, 1 H, 4″-H), 7.34 (dd, *J* = 7.9, 1.0 Hz, 1 H, 6″-H), 7.30–7.16 (m, 5 H, Ph), 7.10, 7.07 (2×d, *J* = 9.8 Hz, 2 H, 1′-H, 8′-H), 6.97, 6.85 (2×dd, *J* = 9.6, 2.4 Hz, 2 H, 2′-H,

7′-H), 6.76, 6.74 (2×d, *J* = 2.4 Hz, 2 H, 4′-H, 5′-H), 6.06 (m, 1 H, N*H*), 5.54 (s, 1 H, 12-H), 5.30 (m, 1 H, 3-H), 4.37–4.32 (m, 2 H, CH_2Ph), 3.62 (m, 8 H, N′CH_2CH$_3$, N″CH_2CH$_3$), 2.56 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1 H, 1-H$_a$), 2.44 (s, 1 H, 9-H), 2.34 (m, 1 H, 2-H$_a$), 2.11 (ddd, *J* = 13.6, 13.6, 4.6 Hz, 1 H, 16-H$_a$), 1.89–1.82 (m, 1 H, 15-H$_a$), 1.77 (m, 1 H, 6-H$_a$), 1.61–1.34 (m, 11 H, 6-H$_b$, 2-H$_b$, 21-H$_a$, 7-H$_2$, 1-H$_b$, 22-H$_2$, 18-H, 5-H, 19-H), 1.39 (s, 3 H, 27-H$_3$), 1.31 (t, *J* = 7.0 Hz, 12 H, N′(CH$_2$CH_3)$_2$, N″(CH$_2$CH_3)$_2$), 1.28–1.18 (m, 2 H, 21-H$_b$, 1-H$_b$), 1.12 (s, 3 H, 26-H$_3$), 1.11 (s, 3 H, 23-H$_3$), 1.05–0.84 (m, 3 H, 15-H$_b$, 16-H$_b$, 20-H), 0.99 (s, 3 H, 25-H$_3$), 0.95 (s, 3 H, 30-H$_3$), 0.82 (d, *J* = 6.2 Hz, 3 H, 29-H$_3$), 0.80 (s, 3 H, 29-H$_3$) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ = 199.1 (C-11), 175.2 (C-24), 165.2 (C-13), 164.0 (CO-Rhd), 159.0 (C-9′), 157.8 (C-4a′, C-10a′), 155.4 (C-3′, C-6′), 138.3 (C$_i$-Ph), 133.7 (C-2″), 132.8 (C-5″), 131.3, 131.2 (C-1′, C-8′), 130.9 (C-1″), 130.5 (C-4″), 130.4 (C-12), 130.3 (C-6″, C-3″), 129.0 (C$_p$-Ph), 128.5 (C$_o$-Ph), 128.0 (C$_m$-Ph), 114.6, 114.4 (C-2′, C-7′), 113.8, 113.5 (C-8a′, C-9a′), 96.2 (C-4′, C-5′), 75.7 (C-3), 60.6 (C-9), 59.0 (C-18), 51.0 (C-5), 47.2 (C-4), 46.8, 46.2 (N′(*C*H$_2$CH$_3$)$_2$, N″(*C*H$_2$CH$_3$)$_2$), 45.0 (C-8), 43.7 (*C*H$_2$Ph), 43.6 (C-14), 40.1 (C-22), 39.3 (C-19, C-20), 37.4 (C-10), 35.4 (C-1), 33.8 (C-17), 33.1 (C-7), 31.1 (C-21), 28.7 (C-28), 27.5 (C-16), 27.2 (C-15), 24.5 (C-23), 23.7 (C-2), 21.1 (C-30), 20.4 (C-6), 20.4 (C-27), 18.2 (C-26), 17.5 (C-29), 13.3 (C-25), 12.5 (N′(CH$_2$*C*H$_3$)$_2$, N″(CH$_2$*C*H$_3$)$_2$) ppm; MS [ESI, MeOH for C$_{65}$H$_{82}$N$_3$O$_5$Cl (1020.84)]: *m*/*z* (%) 984.5 (100) [M-Cl]$^+$.

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Highlights

* Homopiperazinyl-rhodamine B adducts of triterpenoids were designed and synthesized
* These compounds were cytotoxic (SRB assays) in low nanomolar concentrations
* Extra staining experiments showed these compounds to act as mitocans