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Syntheses of C-ring modified dehydroabietylamides and their cytotoxic activity

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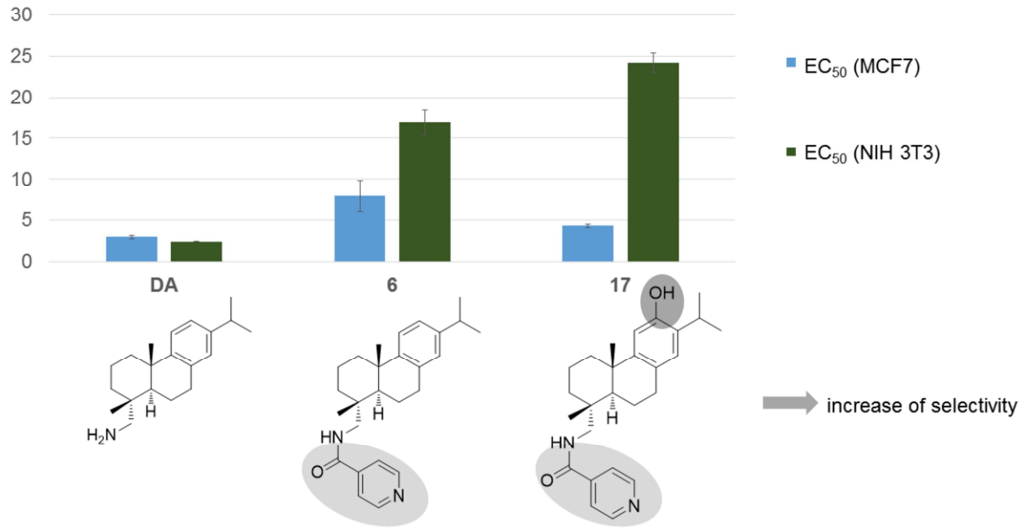
Graphical abstract



Abstract

Due to their auspicious pharmacological efficacy as future drug candidates, natural products have been attracting scientific interest for centuries. An interesting field of research concerns the natural product class of terpenes. In this regard, a multitude of studies have already shown their promising biological potential. Therefore, a set of 27 derivatives of the diterpene dehydroabietylamine was synthesized, focusing on C-ring modifications and the derivatization of the amino moiety at C-18. Subsequent screening of the compounds in colorimetric sulforhodamine B-assays revealed an *in vitro* cytotoxicity especially towards malignant cell line MCF7. Particularly, 12-hydroxy-*N*-(isonicotinoyl)dehydroabietylamine and *N*-(4-methoxybenzoyl)dehydroabietylamine showed good cytotoxic activities (EC_{50} (MCF7) = 4.3 ± 0.2 µM and EC_{50} (MCF7) = 4.5 ± 1.5 µM, respectively) and significant selectivities (SI = 6.2 and SI = 8.8, respectively) towards malignant cell lines.

1. Introduction

Since ancient times, natural products have been used in traditional folk medicine for the treatment of a wide spectrum of diseases and illnesses. References presumed that herbs and flowers were already used as drugs 60,000 years ago.[1] In the beginning of the 19th century, the isolation of morphine as the first pharmacologically active pure compound marked the revolution of modern medicine by natural products.[2] Nowadays, approximately 50% of the approved small molecule drugs are based on natural products and derivatives thereof.[3] Especially, the development of new potent anticancer agents is dominated by the use of natural product leads. The potential of these substances was already demonstrated in the 1950s with the discovery of the vinca alkaloids, vinblastine and vincristine. Today about 65% of the anticancer agents in clinical use are of natural product origin (including plants, marine organisms and microorganisms).[3, 4] The ongoing scientific interest in the discovery and the development of new anticancer agents is motivated by the limited use of common chemotherapeutic agents due to their high toxicity towards healthy tissue and strong associated side effects. Paclitaxel (Figure 1), for instance - one of the most prescript chemotherapeutic agents worldwide - is approved for the treatment of metastatic breast cancer and ovarian carcinomas[5], but is also leading to hypersensitivity[6] as well as neurotoxic and neuropathy side effects[7, 8].

Based on their inherent biological activity and their great pharmacological potential, natural substances continue to represent optimal lead structures for the discovery and the development of future drug candidates. This potential is confirmed by the large number of natural product derived compounds in the various phases of the clinical trials.[9]

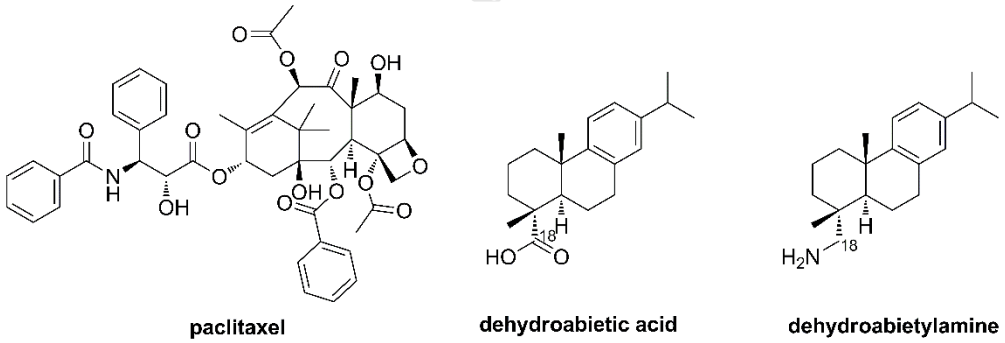


Figure 1. Structures of selected diterpenes.

In addition to Paclitaxel, other representatives of the natural product class of diterpenes are showing a multitude of pharmacological properties as well, e.g. dehydroabietic aicd (Figure 1). Dehydroabietic acid occurs widely in the natural resin of various *pinus* species.[10-15]

As the most abundant component in resin acids, dehydroabietic acid provides a protection against harmful microorganisms and covers mechanical damage. Ammonolysis and

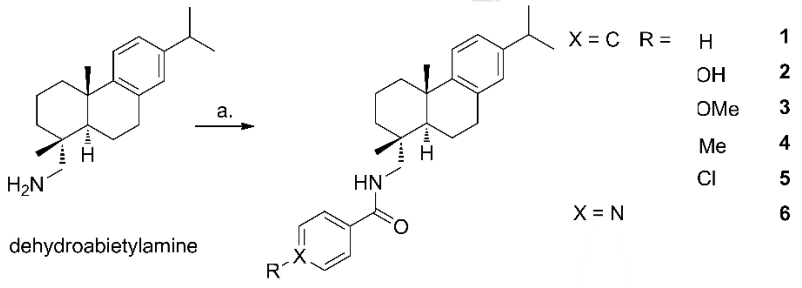
subsequent dehydration afforded dehydroabietylamine (Figure 1), another diterpene with a broad spectrum of pharmacological properties.[16] This tricyclic abietane-type diterpene is modified with an amino moiety at C-18 and derivatives thereof are showing *i.a.* an antimalarial[17], an antiinflammatory[18], an antibacterial[19], an antiviral[19] and an anticancer potential[20-23]. Several investigations on the cytotoxicity of dehydroabietylamides showed the promising potential of these derivatizations.[24-26] Hence, we synthesized a set of 22 dehydroabietylamine derived amides and determined their *in vitro* anticancer potential in the colorimetric sulforhodamine B-assay.

2. Results and discussion

2.1. Chemistry

We focused on three different groups of derivatizations starting from commercial available dehydroabietylamine: (i) "simple" amide derivatives, (ii) C-ring-modified amides and (iii) biotinylated conjugates.

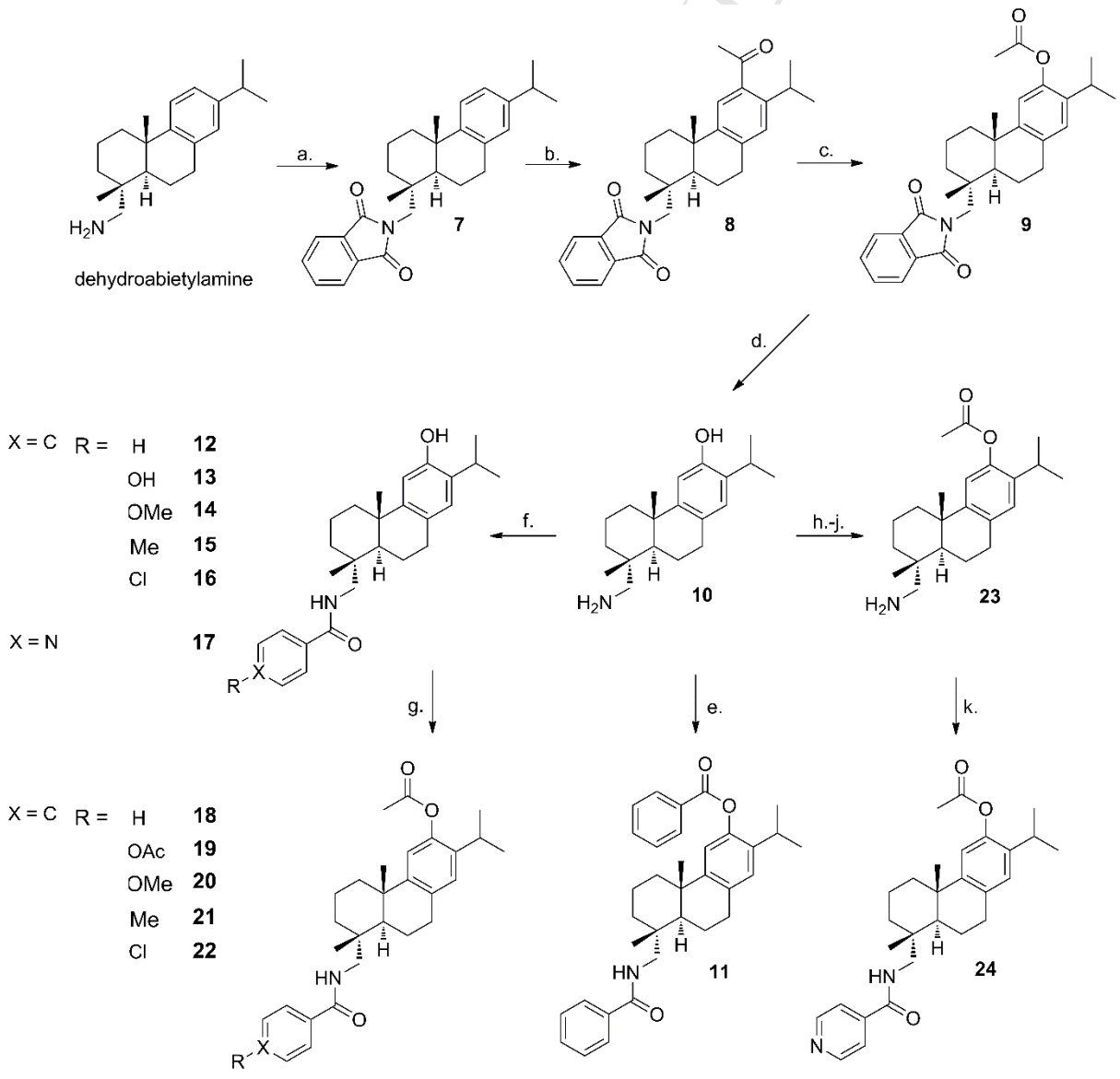
A positive influence/promising potential of amide functionalities on the *in vitro* antitumor activity of dehydroabietylamine derivatives was found in various investigations.[24-28] Therefore, we started with the derivatization of the amino moiety of dehydroabietylamine at C-18. In view of structure-activity relationships to be carried out, a set of *para*-substituted aromatic amides (**1**-**6**) was synthesized via EDC/HOBt coupling reactions in 51-77% isolated yields (Scheme 1).



Scheme 1. Synthesis of dehydroabietylamides (**1**-**6**): (a) aromatic carboxylic acid, EDC, HOBt, DCM, overnight, rt, 51-77%.

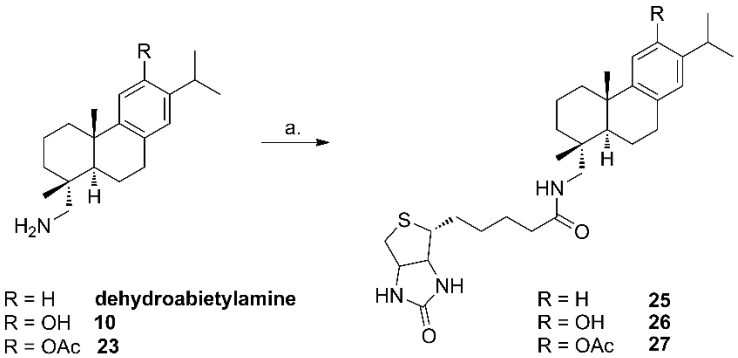
Moreover, we investigated the influence of additional C-ring modifications on the biological activity of the dehydroabietylamides. Thus, dehydroabietylamine was modified in four steps according to the procedure developed by González and Perez-Guaita[29] (Scheme 2). Initially the amino moiety at C-18 was protected by the reaction with phthalic anhydride to afford **7**.

Followed by an acylation under Friedel-Crafts conditions to provide **8**. Compound **9** was obtained by a Bayer-Villiger oxidation in the presence of *meta*-chloroperbenzoic acid. Subsequent hydrazinolysis of **9** afforded target molecule 12-hydroxydehydroabietylamine (**10**). First, **10** was modified by the reaction with benzoyl chloride to obtain the double substituted product **11**. Further amidations of **10** were carried out via EDC/HOBt coupling reactions to preserve the hydroxy moiety at C-12 and to investigate its influence on the biological activity and further possible structure-activity relationships. The syntheses of **12**-**17** were accomplished in 48-94% isolated yield. Moreover, the hydroxy moiety at C-12 was acetylated to complete the set of the C-ring modified compounds. The acetylation of **12**-**16** was realized by the reaction with acetyl chloride and TEA to provide **18**-**22** in 61-97% isolated yield. An optimization of the acetylation of **17** was realized by preceding the acetylation of **10** in three steps to afford **23** and subsequent amidation to obtain **24**.



Scheme 2. Synthesis and derivatization of 12-hydroxydehydroabietylamine: (a) phthalic anhydride, pyridine, reflux, 2.5h, 72%; (b) AcCl, $AlCl_3$, DCM, 0 °C to rt, 2h, 92%; (c) mCPBA, TFA, DCM, 0 °C to rt, overnight, 86%; (d) $N_2H_4 \cdot H_2O$, EtOH, 80 °C, 7h, 89%; (e) benzoylchloride, TEA, DCM, 0 °C to rt, 0.5h, 54%; (f) aromatic carboxylic acid, EDC, HOBt, DCM, 0 °C to rt, overnight, 48-94%; (g) AcCl, TEA, DCM, 0 °C, 0.5h, 61-97%; (h) Boc_2O, NaOH, THF, 0 °C to rt, 2h, 74%; (i) AcCl, TEA, DCM, 0 °C to rt, 30 min, 88%; (j) TFA, DCM, 0 °C to rt, 1.5h, 95%; (k) isonicotinic acid, EDC, HOBt, DCM, 0 °C to rt, overnight, 78%.

In general, a key aspect in the development of new chemotherapeutic drugs is the optimization of the tumor specificity to avoid side effects that occur with the common chemotherapeutic agents (e.g. with doxorubicin, epirubicin, cisplatin, paclitaxel). An often discussed strategy to enhance drug uptake is the use of a vitamine-mediated targeting mechanism [30, 31]. Based on the increased vitamin requirement for cellular functions, various rapidly growing cancer cell lines show an over-expression of biotin-specific receptors at their cell surface allowing an efficient, targeted inclusion of biotin and biotinylated substances.[30, 31] Thus, the third set of dehydroabietylamine derivatives consists of three biotinylated conjugates to compare their cytotoxic activity and their tumor specificity with the dehydroabietylamides. Starting from **DA**, **10** and **23**, respectively, **25**-**27** were synthesized via EDC/HOBt coupling reactions (Scheme 3).



Scheme 3. Synthesis of biotin conjugated dehydroabietylamine derivatives (**25**-**27**): (a) biotin, EDC, HOBt, DMF, 0 °C to rt, overnight, 70-80%.

2.2. Biological evaluation

The set of dehydroabietylamine derived compounds **1**-**6** and **10**-**27** was screened in colorimetric SRB-assay to determine their *in vitro* cytotoxic activity; their EC_{50} values for

five human tumor cell lines and one nonmalignant mouse fibroblasts were measured. The results are compiled in Table 1.

Table 1. Cytotoxicity of compounds **1-6** and **10-27**, dehydroabietylamine (**DA**, for comparison) and betulinic acid (**BA,** as a standard); EC_{50} values in μM from SRB assay after 96 h of treatment; the values are averaged from three independent experiments performed each in triplicate; confidence interval CI = 95%. Human cancer cell lines: FaDu (hypopharyngeal carcinoma), A2780 (ovarian carcinoma), HT29 (colorectal carcinoma), MCF7 (breast carcinoma), SW1736 (thyroid carcinoma) and nonmalignant mouse fibroblasts (NIH 3T3).

EC_{50} [μM]	FaDu	A2780	HT29	MCF7	SW1736	NIH 3T3
DA	3.9 ± 0.1	3.8 ± 0.1	2.1 ± 0.1	3.0 ± 0.2	4.2 ± 0.3	2.4 ± 0.0
1	>30	>30	>30	>30	>30	>30
2	14.1 ± 0.2	8.7 ± 3.5	8.5 ± 1.4	8.0 ± 1.1	13.0 ± 2.1	6.9 ± 1.0
3	17.3 ± 6.2	9.1 ± 2.4	10.4 ± 3.5	4.5 ± 1.5	11.2 ± 4.2	22.8 ± 3.6
4	18.9 ± 3.4	12.5 ± 3.6	22.8 ± 3.5	10.4 ± 3.7	14.2 ± 2.1	13.5 ± 2.6
5	>30	>30	>30	>30	>30	>30
6	14.4 ± 1.4	9.8 ± 3.1	10.7 ± 1.3	7.9 ± 1.9	14.2 ± 2.7	16.9 ± 1.5
10	11.5 ± 0.4	17.3 ± 0.2	9.5 ± 0.2	8.9 ± 0.3	13.6 ± 0.5	22.0 ± 3.2
11	>30	>30	>30	>30	>30	>30
12	14.8 ± 0.3	12.5 ± 0.5	16.2 ± 0.7	4.8 ± 0.3	11.5 ± 0.9	18.1 ± 1.0
13	>30	>30	>30	>30	>30	>30
14	20.0 ± 1.8	13.2 ± 1.9	13.5 ± 3.6	11.7 ± 1.5	16.1 ± 0.3	23.2 ± 6.1
15	12.2 ± 2.4	10.0 ± 0.7	17.2 ± 1.9	8.5 ± 1.1	7.0 ± 0.3	16.8 ± 3.0
16	21.9 ± 2.1	6.6 ± 0.4	10.5 ± 1.1	5.0 ± 0.5	10.2 ± 0.4	16.0 ± 3.7
17	18.8 ± 1.1	12.9 ± 2.4	19.0 ± 2.6	4.3 ± 0.2	27.3 ± 5.5	24.2 ± 1.2
18	13.4 ± 0.9	8.1 ± 0.9	9.0 ± 0.9	4.5 ± 0.3	13.5 ± 1.8	17.3 ± 1.8
19	20.2 ± 0.8	17.9 ± 1.2	11.2 ± 0.5	10.5 ± 0.8	17.2 ± 1.2	21.4 ± 1.3
20[a]	--	--	--	--	--	--
21	12.8 ± 2.7	19.4 ± 2.2	26.7 ± 2.6	11.5 ± 2.4	10.7 ±2.6	>30
22	14.4 ± 2.4	5.0 ± 0.2	11.7 ± 2.1	6.1 ± 1.9	15.3 ± 0.9	>30
23	13.1 ± 0.9	20.0 ± 0.7	10.1 ± 0.3	10.7 ± 0.6	18.3 ± 1.3	>30
24	12.4 ± 1.2	14.4 ± 1.9	15.3 ± 1.9	5.7 ± 0.8	12.8 ± 1.4	29.5 ± 2.5

25	24.5 ± 2.6	18.6 ± 1.3	15.5 ± 1.7	11.6 ± 3.8	>30	15.7 ± 6.4
26	>30	>30	>30	>30	>30	>30
27	>30	>30	>30	>30	>30	>30
BA	10.7 ± 2.1	9.7 ± 2.0	16.0 ± 2.1	10.6 ± 0.8	14.8 ± 1.4	12.9 ± 1.5

[a] Compound **20** is not soluble under the conditions of the SRB-Assay.

In general, the dehydroabietylamine derivatives showed a moderate to good cytotoxic activity. In this context, the distinct influence of almost all compounds on the proliferation of the breast cancer cell line MCF7 is particularly noteworthy. The lowest EC_{50} values of this study can be observed for this cell line. Thus, the following discussion of possible structure-activity relationships is concentrated on the impact on the malignant cell line MCF7 and the nonmalignant mouse fibroblasts NIH 3T3. The cytotoxicity for the nonmalignant cell line is relevant in order to obtain an idea of the selectivity [characterized by the selectivity index (SI); e.g. SI = EC_{50} (NIH 3T3)/EC_{50} (MCF7)] of the compounds which is an important aspect for prospective pharmacological applications.

The pharmacological promise of **DA**, which has intensively been investigated in various studies[20, 23], is confirmed by the low EC_{50} values for all examined human cancer cell lines but the results are spoiled by a distinct low selectivity (SI = 0.8). Therefore, we investigated the influence of an amidation of the amino moiety at C-18 on the *in vitro* cytotoxic activity at first. Whereas *N*-benzoyldehydroabietylamine (**1**) showed a total loss of a cytotoxic activity (EC_{50} > 30 µM), the introduction of a substituent in *para* position of the aromatic moiety can affect the cytotoxicity significantly. In addition to *N*-(4-hydroxybenzoyl)dehydroabietylamine (**2**), *N*-(4-methylbenzoyl)dehydroabietylamine (**4**) and *N*-(isonicotinoyl)dehydroabietylamine (**6**) that showed a good (to moderate) cytotoxicity (EC_{50} (MCF7) = 8.0 ± 1.1 µM, EC_{50} (MCF7) = 10.4 ± 3.7 µM and EC_{50} (MCF7) = 7.9 ± 1.9 µM, respectively), *N*-(4-methoxybenzoyl)dehydroabietylamine (**3**) is particularly noteworthy. In this first group of compounds, **3** is characterized by the highest cytotoxic activity (EC_{50} (MCF7) = 4.5 ± 1.5 µM) - comparable to **DA** (EC_{50} (MCF7) = 3.0 ± 0.2 µM) - and an increased selectivity (SI = 8.8) - ten times higher than **DA**. The effect of C-ring modification on the cytotoxic activity of the dehydroabietylamides is inconclusive with regard to the elucidation of structure-activity relationships. Whereas a C-ring modification of **DA** led to a general decrease in cytotoxicity (from EC_{50} (MCF7) = 3.0 ± 0.2 µM to EC_{50} (MCF7) = 10.1 ± 0.3 µM) and a slight increase in selectivity (from SI = 0.9 to SI > 3.0), this trend cannot be observed after the derivatization of its amine moiety by substituted benzoic acids. Their cytotoxicity and selectivity are still

strongly influenced by the substituents of the aromatic residue. For example, no distinct cytotoxic activity can be determined for **1** and **5** (EC_{50} > 30 μM), while - in contrast to **DA** - C-ring modifications introduce a definitive improvement of their *in vitro* cytotoxicity (e.g. 12-hydroxy-*N*-benzoyldehydroabietylamine (**12**): EC_{50} (MCF7) = 4.8 ± 0.3 μM or 12-hydroxy-*N*-(4-chlorobenzoyl)dehydroabietylamine (**16**): EC_{50} (MCF7) = 5.0 ± 0.5 μM). Furthermore, 12-hydroxy-*N*-(isonicotinoyl)dehydroabietylamine (**17**), which showed the highest cytotoxic activity (EC_{50} (MCF7) = 4.3 ± 0.2 μM) combined with a high selectivity (SI = 6.2) in this study, should be mentioned. The acetylated dehydroabietylamides **18-24** show no further significant increase of their cytotoxicity or of their selectivity.

The results of the SRB assay concerning the biotinylated derivatives **25-27** do not indicate any positive effect on the cytotoxic activity; in addition to the distinct decrease in the cytotoxic activity, no significant selectivity can be observed. Accordingly, the biotinylation of dehydroabietylamine is not an appropriate method to increase its tumor specificity.

3. Conclusion

In summary, a set of 27 dehydroabietylamine derivatives was synthesized by simple derivatization of the amino moiety at C-18 and by modifications of the C-ring of the abietane-framework. Subsequent screening in the colorimetric SRB-assays determined their *in vitro* cytotoxicity for several human tumor cell lines and a nonmalignant mouse fibroblast. The suitable combination of modifications lead to cytotoxic activities comparable to those of dehydroabietylamine, and additionally, to an increased selectivity towards malignant cell lines. In addition, Swisstargetprediction (http://www.swisstargetprediction.ch) shows compounds of this kind as inhibitors of 17β-hydroxysteroid dehydrogenase I. Inhibitors of this enzyme might be ideal candidates for treating cancer patients who developed aromatase inhibitor resistance.[32]

4. Experimental part

4.1 General

Dehydroabietylamine (purity > 90 %) was obtained from TCI; further reagents were bought from commercial suppliers without any further purification. The solvents were dried according to usual procedures. TLC was performed on silica gel (Macherey-Nagel, detection with ceriummolybdate spray reagent and UV absorption). Melting points are uncorrected (LEICA hot stage microscope). Microanalysis were performed with a Foss-Heraeus Vario EL (CHNS) instrument. NMR spectra were recorded using the VARIAN spectrometers Gemini

2000 or Unity 500 at 27 °C (δ given in ppm; *J* in Hz, typical experiments: ^{13}C APT, DQF-COSY, HMBC, HSQC). ESI-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 341 at 20 °C; IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000; UV-vis spectra were recorded on Perkin-Elmer Lambda 14 spectrometer.

4.2 General procedures

4.2.2 General procedures A

The carboxylic acid (1.2 eq.) was suspended in DCM (dry, 10 mL/100 mg carboxylic acid) and cooled to 0 °C. HOBt (1.4 eq.) and EDC (1.4 eq.) were added. After 30 min of stirring at 0 °C, the amine (1 eq.) was added. After completion of the reaction (as indicated by TLC) and usual aqueous work-up the residue was subjected to column chromatography.

4.2.3 General procedures B

Acetylation was achieved by reaction with AcCl (1.2 eq.) and TEA (cat.) in dry DCM (dry, 10 mL/100 mg carboxylic acid). After completion of the reaction (as indicated by TLC) and usual aqueous work-up the residue was subjected to column chromatography.

4.3 Syntheses

The syntheses of the compounds **1**-**9** were performed according to previously reported procedures.[33]

4.3.1 12-Hydroxydehydroabietylamine (**10**)

Compound **9** (1.25 g, 2.64 mmol) was dissolved in boiling ethanol (25 mL) and hydrazine monohydrate (0.78 mL, 15.91 mmol) was added. After completion of the reaction (as indicated by TLC) the suspension was filtered and the residue was washed with fresh ethanol (2 x 5 mL). The filtrate was concentrated under diminished pressure and suspended in NaOH (2 M, 30 mL). After 1 hour, the aqueous mixture was neutralized with HCl (2 M) and extracted with DCM (6 x 40 mL). The organic phase was washed with brine (50 mL), dried and concentrated under diminished pressure. Compound **10** (0.71 g, 89%) was obtained without any further purification as a colorless solid; R_F = 0.38 (silica gel, chloroform/methanol, 9:1); mp = 193-198 °C; $[\alpha]_D$ = +50.9° (*c* = 0.36, $CHCl_3$); IR (KBr): *v* = 3442*br*, 2956*s*, 2926*s*, 2862*s*, 2366*w*, 2344*w*, 1636*m*, 1612*m*, 1586*w*, 1510*w*, 1460*w*, 1422*m*, 1386*w*, 1324*w*, 1242*w*,

1168*w* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 302 nm (3.50); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (*s*, 1H,14-H), 6.62 (*s*, 1H, 11-H), 3.19 - 3.09 (*m*, 1H, 15-H), 2.90 - 2.71 (*m*, 2H, 7-H_a + 7-H_b), 2.62 (*d*, *J* = 13.3 Hz, 1H, 18-H_a), 2.44 (*dd*, *J* = 13.4, 2.6 Hz, 1H, 18-H_b), 2.20 - 2.14 (*m*, 1H, 1-H_a), 1.84 - 1.61 (*m*, 4H, 2-H_a + 2-H_b + 6-H_a + 6-H_b), 1.47 (*dd*, *J* = 11.1, 3.6 Hz, 1H, 5-H), 1.43 - 1.27 (*m*, 3H, 3-H_a + 3-H_b + 1-H_b), 1.25 - 1.19 (*m*, 9H, 16-H + 17-H + 20-H), 0.89 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 (C-13), 148.4 (C-9), 132.1 (C-12), 126.7 (C-14), 126.7 (C-8), 111.1 (C-11), 53.83 (C-18), 45.1 (C-5), 38.8 (C-1), 37.5 (C-10), 37.3 (C-4), 35.4 (C-3), 29.6 (C-7), 26.9 (C-15), 25.3 (C-20), 22.9 (C-16), 22.7 (C-17), 19.0 (C-6), 18.9 (C-2), 18.9 (C-19) ppm; MS (ESI, MeOH): m/z (%) = 302.2 ($[M+H]^+$, 100); analysis calculated for $C_{20}H_{31}NO$ (301.47): C 79.68, H 10.36, N 4.65; found: C 79.51, H 10.45, N 4.43.

4.3.2 12-Benzoyloxy-*N*-benzoyldehydroabietylamine (**11**)

Compound **10** (0.10 g, 0.33 mmol) was dissolved in DCM (10 mL), TEA (0.20 mL, 1.44 mmol) and benzoyl chloride (0.12 mL; 1.04 mmol) were added. After 30 min stirring at 0 °C followed by usual aqueous work-up, the residue was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:3). Compound **11** (0.09 g, 54%) was obtained as a colorless solid; R_F = 0.44 (silica gel, *n*-hexane/ethyl acetate, 7:3); mp = 105 °C; $[\alpha]_D$ = +43.2° (*c* = 0.33, $CHCl_3$); IR (KBr): *v* = 3424*br*, 2962*m*, 2928*m*, 2868*m*, 1736*s*, 1646*s*, 1602*m*, 1578*w*, 1540*m*, 1490*m*, 1450*m*, 1384*w*, 1312*w*, 1266*s*, 1244*s*, 1176*m*, 1164*m*, 1114*w*, 1086*m*, 1064*m*, 1024*w*, 708*s* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 240 nm (4.35), 278 nm (3.83); ^1H NMR (400 MHz, CDCl3): δ = 8.24 - 8.19 (*m*, 2H, 28-H), 7.78 - 7.72 (*m*, 2H, 23-H), 7.67 - 7.61 (*m*, 1H, 30-H), 7.55 - 7.47 (*m*, 3H, 29-H + 25-H), 7.46 - 7.40 (*m*, 2H, 24-H), 6.99 (*s*, 1H, 14-H), 6.97 (*s*, 1H, 11-H), 6.17 - 6.11 (*dd*, *J* = 6.2, 6.2 Hz, 1H, NH), 3.46 (*dd*, *J* = 13.6, 6.3 Hz, 1H, 18-H_a), 3.33 (*dd*, *J* = 13.6, 6.4 Hz, 1H, 18-H_b), 3.05 - 2.91 (*m*, 2H, 15-H + 7-H_a), 2.89 - 2.78 (K, 1H, 7-H_b), 2.25 - 2.18 (*m*, 1H, 1-H_a), 2.07 - 1.98 (*m*, 1H, 6-H_a), 1.86 - 1.73 (*m*, 2H, 6-H_b + 2-H_a), 1.72 - 1.58 (*m*, 1H, 2-H_b) 1.56 - 1.49 (*m*, 2H, 5-H + 3-H_a), 1.48 - 1.32 (*m*, 2H, 3-H_b + 1-H_b)), 1.26 (*s*, 3H, 20-H), 1.21 (*d*, *J* = 7.0 Hz, 3H, 16-H), 1.18 (*d*, *J*= 7.0 Hz, 3H, 17-H), 1.02 (s, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, CDCl3): δ = 167.8 (C-21), 165.6 (C-26), 148.4 (C-9), 146.6 (C-13), 137.2 (C-12), 135.0 (C-22), 133.6 (C-30), 133.0 (C-8), 131.5 (C-25), 130.3 (C-28), 129.9 (C-27), 128.8 (C-24), 128.7 (C-29), 127.3 (C-14), 127.0 (C-23), 118.2 (C-11), 50.4 (C-18), 45.6 (C-5), 38.5 (C-1), 37.8 (C-4), 37.8 (C-10), 36.5 (C-3), 30.1 (C-7), 27.4 (C-15), 25.5 (C-20), 23.2 (C-16), 23.1 (C-17), 19.2 (C-6), 19.0 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 510.3 ($[M+H]^+$, 32), 527.1 ($[M+NH4]^+$, 5), 532.5

([M+Na]$^+$, 15), 564.1 ([M+Na+MeOH]$^+$, 10), 1019.2 ([2M+H]$^+$, 100), 1041.1 ([2M+Na]$^+$, 70); analysis calculated for $C_{34}H_{49}NO_3$ (509.68): C 80.12, H 7.71, N 2.75; found: C 79.87, H 2.94, N 2.56.

4.3.3 12-Hydroxy-*N*-benzoyldehydroabietylamine (**12**)

Compound **12** was prepared according to general procedure A from benzoic acid (0.05 g, 0.40 mmol) and compound **10** (0.10 g, 0.33 mmol) followed by column chromatography (silica gel, *n*-hexane/ethyl acetate, 7:3). Compound **12** (0.07 g, 53%) was obtained as a colorless solid; R_F = 0.32 (silica gel, *n*-hexane/ethyl acetate, 7:3); mp = 194-196 °C; $[\alpha]_D$ = +6.6° (*c* = 0.34, $CHCl_3$); IR (KBr): *ν* = 3432*br*, 2958*s*, 2928*s*, 2868*m*, 1646*s*, 1578*w*, 1542*m*, 1534*m*, 1490*w*, 1420*w*, 1306*m*, 1292*m*, 1270*m*, 1242*m*, 1180*w*, 710*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 240 nm (4.10), 298 nm (3.53); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 - 7.70 (*m*, 2H, 23-H), 7.52 - 7.45 (*m*, 1H, 25-H), 7.45 - 7.38 (*m*, 2H, 24-H), 6.82 (*s*, 1H, 14-H), 6.64 (*s*, 1H, 11-H), 6.17 - 6.09 (*dd*, *J* = 6.2, 6.2 Hz, 1H, NH), 4.94 (*s*, 1H, OH), 3.45 - 3.30 (*m*, 2H, 18-H_a + 18-H_b), 3.12 (*hept*, *J* = 6.8 Hz, 1H, 15-H), 2.91 - 2.68 (*m*, 2H, 7-H_a + 7-H_b), 2.22 - 2.14 (*m*, 1H, 1-H_a), 1.98 - 1.90 (*m*, 1H, 6-H_a), 1.84 - 1.59 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.55 - 1.49 (*m*, 1H, 3-H_a), 1.45 (*dd*, *J* = 12.3, 1.9 Hz, 1H, 5-H), 1.42 - 1.29 (*m*, 2H, 1-H_b + 3-H_b), 1.25 - 1.19 (*m*, 9H, 16-H + 17-H + 20-H), 1.00 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (C-21), 151.1 (C-13), 148.1 (C-9), 135.0 (C-22), 131.9 (C-12), 131.6 (C-25), 128.8 (C-24), 127.0 (C-8), 127.0 (C-23), 126.9 (C-14), 111.1 (C-11), 50.6 (C-18), 46.1 (C-5), 38.5 (C-1), 37.8 (C-4), 37.7 (C-10), 36.5 (C-3), 29.8 (C-7), 27.0 (C-15), 25.5 (C-20), 22.8 (C-16), 22.7 (C-17), 19.4 (C-6), 18.9 (C-19), 18.8 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 406.3 ([M+H]$^+$, 100), 428.3 ([M+Na]$^+$, 52), 460.3 ([M+Na+MeOH]$^+$, 8); analysis calculated for $C_{27}H_{35}NO_2$ (405.57): C 79.96, H 8.70, N 3.45; found: C 79.77, H 8.95, N 3.21.

4.3.4 12-Hydroxy-*N*-(4-hydroxy)benzoyldehydroabietylamine (**13**)

Compound **13** was prepared according to general procedure A from 4-hydroxybenzoic acid (0.08 g, 0.60 mmol) and compound **10** (0.20 g, 0.66 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 1:1:2) gave compound **13** (0.18 g, 65%) as a colorless solid; R_F = 0.47 (silica gel, *n*-hexane/ethyl acetate/chloroform, 1:1:2); mp = 261-263 °C; $[\alpha]_D$ = +30.7° (*c* = 0.34, DMSO); IR (KBr): *ν* = 3422*vs*, 3266*s*, 2940*m*, 2930*m*, 2868*w*, 1636*m*, 1606*s*, 1578*w*, 1558*s*, 1510*s*, 1466*w*, 1436*m*, 1418*m*; 1388*w*, 1310*m*, 1288*m*, 1232*m*, 1202*w*, 1180*m* cm^{-1}; UV-vis (DMSO): λ_{max} (log ε) = 269 nm (4.32); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.87 (*s*, 1H, OH), 8.71 (*s*, 1H, OH), 7.92 (*dd*, *J* = 6.4 Hz, 1H, NH), 7.71 - 7.66 (*m*, 2H, 23-

H), 6.78 - 6.74 (*m*, 2H, 24-H), 6.66 (*s*, 1H, 11-H), 6.60 (*s*, 1H, 14-H), 3.38 (*dd*, *J* = 13.4, 7.1 Hz, 1H, 18-H_a), 3.07 (*hept*, *J* = 6.8 Hz, 1H, 15-H), 2.94 (*dd*, *J* = 13.4, 5.8 Hz, 1H, 18-H_b), 2.73 - 2.57 (*m*, 2H, 7-H_a + 7-H_b), 2.13 - 2.05 (*m*, 1H, 1-H_a), 1.99 - 1.91 (*m*, 1H, 6-H_a), 1.76 - 1.50 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.45 (*ddd*, *J* = 13.4, 13.4, 3.8 Hz, 1H, 3-H_a), 1.36 - 1.29 (*m*, 2H, 5-H + 3-H_b), 1.20 (*ddd*, *J* = 12.6, 12.6, 3.3 Hz, 1H, 1-H_a), 1.12 (*s*, 3H, 20-H), 1.10 (*d*, *J* = 7.2 Hz, 3H, 16-H), 1.09 (*d*, *J* = 7.2 Hz, 3H, 17-H), 0.89 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (C-21), 159.9 (C-25), 152.0 (C-13), 147.4 (C-9), 131.3 (C-12), 129.2 (C-23), 125.9 (C-24), 125.5 (C-22), 124.7 (C-8), 114.6 (C-11), 110.2 (C-14), 49.2 (C-18), 44.6 (C-5), 38.2 (C-1), 37.8 (C-4), 36.9 (C-10), 35.8 (C-3), 29.2 (C-7), 26.1 (C-15), 25.3 (C-20), 22.6 (C-16), 22.5 (C-17), 18.9 (C-19), 18.9 (C-6), 18.3 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 422.2 ($[M+H]^+$, 20), 444.3 ($[M+Na]^+$, 30), 843.3 ($[2M+H]^+$, 10), 865.2 ($[2M+Na]^+$, 100); analysis calculated for $C_{27}H_{35}NO_3$ (421.57): C 76.92, H 8.37, N 3.32; found: C 76.71, H 8.55, N 3.17.

4.3.5 12-Hydroxy-*N*-(4-methoxy)benzoyldehydroabietylamine (**14**)

Compound **14** was prepared according to general procedure A from 4-methoxybenzoic acid (0.12 g, 0.79 mmol) and compound **10** (0.20 g, 0.66 mmol), followed by column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 1:1:2) to yield compound **14** (0.22 g, 77%) as a colorless solid; R_F = 0.56 (silica gel, *n*-hexane/ethyl acetate, 6:4); mp = 227-229 °C; $[\alpha]_D$ = +5.3° (*c* = 0.36, $CHCl_3$); IR (KBr): *v* = 3422*br*, 2958*s*, 2928*s*, 2868*w*, 1638*s*, 1608*s*, 1572*m*, 1546*m*, 1504*s*, 1460*m*, 1440*m*, 1418*m*, 1384*w*, 1378*w*, 1308*m*, 1256*s*, 1178*s*, 1112*w*, 1032*m*, 844*m*, 766*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 242 nm (4.16), 264 nm (4.21); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 - 7.67 (*m*, 2H, 23-H), 6.94 - 6.88 (*m*, 2H, 24-H), 6.81 (*s*, 1H, 14-H), 6.65 (*s*, 1H, 11-H), 6.07 (*dd*, *J* = 6.0, 6.0 Hz, 1H, NH), 5.28 (*s*, 1H, OH), 3.83 (*s*, 3H, 26-H), 3.41 - 3.31 (*m*, 2H, 18-H_a + 18-H_b), 3.17 - 3.08 (*hept*, *J* = 6.8 Hz, 1H, 15-H), 2.88 - 2.81 (*m*, 1H, 7-H_a), 2.76 - 2.68 (*m*, 1H, 7-H_b), 2.19 - 2.12 (*m*, 1H, 1-H_a), 1.95 - 1.89 (*m*, 1H, 6-H_a), 1.81 - 1.60 (*m*, 3H, 6-H_b + 2-H_a + 2-H_b), 1.54 - 1.47 (*m*, 1H, 3-H_a), 1.43 (*dd*, *J* = 12.3, 1.7 Hz, 1H, 5-H), 1.39 - 1.29 (*m*, 2H, 3-H_b + 1-H_b), 1.25 - 1.20 (*m*, 6H, 17-H + 16-H), 1.20 (*s*, 3H, 20-H), 0.98 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5 (C-21), 162.3 (C-25), 151.2 (C-13), 148.1 (C-9), 131.9 (C-12), 128.8 (C-23), 127.2 (C-22), 126.9 (C-8), 126.8 (C-14), 114.0 (C-24), 111.1 (C-11), 55.6 (C-26), 50.5 (C-18), 46.1 (C-5), 38.5 (C-1), 37.8 (C-4), 37.7 (C-10), 36.5 (C-3), 29.8 (C-7), 27.0 (C-15), 25.4 (C-20), 22.8 (C-16), 22.7 (C-17), 19.4 (C-6), 18.9 (C-19), 18.8 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 436.3 ($[M+H]^+$, 21), 458.3 ($[M+Na]^+$, 20), 871.2 ($[2M+H]^+$, 25), 893.3 ($[2M+Na]^+$, 100);

analysis calculated for $C_{28}H_{37}NO_3$ (435.60): C 77.20, H 8.56, N 3.22; found: C 76.99, H 8.69, N 3.10.

4.3.6 12-Hydroxy-*N*-(4-methyl)benzoyldehydroabietylamine (**15**)

Compound **15** was prepared according to general procedure A from 4-methylbenzoic acid (0.08 g, 0.60 mmol) and compound **10** (0.15 g, 0.50 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10) gave compound **15** (0.10 g, 48%) as a colorless solid;

R_F = 0.36 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 243-245 °C; $[\alpha]_D$ = +11.3° (*c* = 0.30, $CHCl_3$); IR (KBr): *v* = 3384*br*, 2954*s*, 2936*s*, 2924*s*, 2866*m*, 1626*s*, 1614*s*, 1550*s*, 1506*s*, 1466*m*, 1438*m*, 1418*s*, 1386*m*, 1376*m*, 1316*m*, 1302*s*, 1238*m*, 1188*m*, 1118*w*, 752*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 244 nm (4.20), 300 nm (3.61); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (*d*, *J* = 8.2 Hz, 2H, 23-H), 7.21 (*d*, *J* = 7.9 Hz, 2H, 24-H), 6.81 (*s*, 1H, 14-H), 6.64 (*s*, 1H, 11-H), 6.12 (*dd*, *J* = 6.1, 6.1 Hz, 1H, NH), 5.26 (*s*, 1H, OH), 3.44 - 3.30 (*m*, 2H, 18-H_a + 18-H_b), 3.13 (*hept*, *J* = 6.7 Hz, 1H, 15-H), 2.89 - 2.80 (*m*, 1H, 7-H_a), 2.78 - 2.66 (*m*, 1H, 7-H_b), 2.38 (*s*, 3H, 26-H), 2.19 - 2.12 (*m*, 1H, 1-H_a), 1.97 - 1.88 (*m*, 1H, 6-H_a), 1.82 - 1.60 (*m*, 3H, 6-H_b + 2-H_a + 2-H_b), 1.55 - 1.47 (*m*, 1H, 3-H_a), 1.43 (*dd*, *J* = 12.3, 1.9 Hz, 1H, 5-H), 1.40 - 1.29 (*m*, 2H, 3-H_b + 1-H_b), 1.23 (*d*, *J* = 5.3 Hz, 3H, 16-H), 1.21 (*d*, *J* = 5.3 Hz, 3H, 17-H), 1.20 (*s*, 3H, 20-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (C-21), 151.2 (C-13), 148.0 (C-9), 142.0 (C-25), 132.1 (C-22), 131.9 (C-12), 129.4 (C-24), 127.0 (C-23), 126.9 (C-8), 126.8 (C-14), 111.1 (C-11), 50.5 (C-18), 46.1 (C-5), 38.5 (C-1), 37.8 (C-4), 37.7 (C-10), 36.5 (C-3), 29.8 (C-7), 26.9 (C-15), 25.4 (C-20), 22.8 (C-16), 22.7 (C-17), 21.6 (C-26), 19.4 (C-6), 18.9 (C-19), 18.8 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 420.3 ($[M+H]^+$, 18), 442.3 ($[M+Na]^+$, 12), 839.3 ($[2M+H]^+$, 48), 861.3 ($[2M+Na]^+$, 100); analysis calculated for $C_{28}H_{37}NO_2$ (419.60): C 80.15, H 8.89, N 3.34; found: C 79.88, H 9.02, N 3.16.

4.3.7 12-Hydroxy-*N*-(4-chloro)benzoyldehydroabietylamine (**16**)

Compound **16** was prepared according to general procedure A from 4-chlorobenzoic acid (0.09 g, 0.60 mmol) and compound **10** (0.15 g, 0.50 mmol) followed by column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10) to yield compound **16** (0.13 g, 60%) as a colorless solid; R_F = 0.45 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 246-248 °C; $[\alpha]_D$ = +9.8° (*c* = 0.33, DMSO), IR (KBr): *v* = 3420*br*, 2956*s*, 2926*s*, 2866*m*, 1642*s*, 1630*s*, 1596*s*, 1548*s*, 1510*m*, 1486*s*, 1438*w*, 1418*m*, 1388*w*, 1308*m*,

1238*m*, 1182*m*, 1094*m*, 1048*w*, 1014*m*, 846*m*, 758*m* cm^{-1}; UV-vis (DMSO): λ_{max} (log ε) = 265 nm (6.77); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 (*s*, 1H, OH), 8.31 - 8.24 (*dd*, *J* = 6.3, 6.3 Hz, 1H, NH), 7.86 - 7.79 (*m*, 2H, 23-H), 7.52 - 7.46 (*m*, 2H, 24-H), 6.67 (*s*, 1H, 14-H), 6.61 (*s*, 1H, 11-H), 3.40 (*dd*, *J* = 13.4, 7.0 Hz, 1H,18-H_a) 3.07 (*hept*, *J* = 6.8 Hz, 1H, 15-H), 2.99 (*dd*, *J* = 13.5, 5.8 Hz, 1H, 18-H_b), 2.75 - 2.57 (*m*, 2H, 7-H_a + 7-H_b), 2.14 - 2.05 (*m*, 1H, 1-H_a), 1.99 - 1.88 (*m*, 1H, 6-H_a), 1.76 - 1.63 (*m*, 1H, 2-H_a), 1.63 - 1.50 (*m*, 2H, 6-H_b + 2-H_b), 1.50 - 1.40 (*m*, 1H, 3-H_a), 1.39 - 1.29 (*m*, 2H, 5-H + 3H_b), 1.22 (*m*, 1H, 1-H_b), 1.12 (*s*, 3H, 20-H), 1.10 (*d*, *J* = 7.0 Hz, 3H, 16-H), 1.08 (*d*, *J* = 7.0 Hz, 3H, 17-H), 0.90 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.8 (C-21), 152.0 (C-13), 147.3 (C-9), 135.7 (C-25), 133.6 (C-22), 131.3 (C-12), 129.2 (C-23), 128.2 (C-24), 125.9 (C-14), 124.7 (C-8), 110.2 (C-11), 49.5 (C-18), 44.7 (C-5), 38.1 (C-1), 37.8 (C-4), 37.0 (C-10), 35.8 (C-3), 29.1 (C-7), 26.1 (C-15), 25.3 (C-20), 22.6 (C-17), 22.5 (C-16), 18.9 (C-19), 18.9 (C-6), 18.3 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 440.2 ($[M+H]^+$, 56), 462.3 ($[M+Na]^+$, 35), 901.2 ($[2M+Na]^+$, 100); analysis calculated for $C_{27}H_{34}ClNO_2$ (440.02): C 73.70, H 7.79, N 3.18; found: C 73.50, H7.93, N 3.00.

4.3.8 12-Hydroxy-*N*-(isonicotinoyl)dehydroabietylamine (**17**)

Compound **17** was prepared according to general procedure A from isonicotinic acid (0.07 g, 0.57 mmol) and compound **10** (0.15 g, 0.50 mmol). Column chromatography (silica gel, ethyl acetate/chloroform, 1:1) afforded compound **17** (0.16 g, 78%) as a colorless solid; R_F = 0.27 (silica gel, ethyl acetate/chloroform, 1:1); mp = 120-125 °C; $[\alpha]_D$ = +8.8° (*c* = 0.38, $CHCl_3$); IR (KBr): *v* = 3422*br*, 2958*s*, 2928*s*, 2868*m*, 1652*s*, 1618*m*, 1552*s*, 1510*m*, 1418*m*, 1306*m*, 1240*m*, 1184*m*, 1066*w*, 1000*w*, 756*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 242 nm (3.96), 297 nm (3.66); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (*d*, *J* = 4.9 Hz, 2H, 24-H), 7.58 (*d*, *J* = 5.2 Hz, 2H, 23-H), 6.82 (*s*, 1H, 14-H), 6.65 (*s*, 1H, 11-H), 6.32 (*t*, *J* = 5.8 Hz, 1H, NH), 3.47 - 3.30 (*m*, 2H, 18-H_a + 18-H_b), 3.15 (*hept*, *J* = 6.7 Hz, 1H, 15-H), 2.92 - 2.82 (*m*, 1H, 7-H_a), 2.78 - 2.67 (*m*, 1H, 7-H_b), 2.21 - 2.08 (*m*, 1H, 1-H_a), 1.95 - 1.88 (*m*, 1H, 6-H_a), 1.83 - 1.57 (*m*, 3H, 6-H_b + 2-H_a + 2-H_b), 1.55 - 1.46 (*m*, 1H, 3-H_a), 1.42 (*dd*, *J* = 10.5, 1.8 Hz, 1H, 5-H), 1.39 - 1.26 (*m*, 2H, 3-H_b + 1-H_b), 1.25 - 1.18 (*m*, 9H, 16-H + 17-H + 20-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (C-21), 151.5 (C-13), 150.4 (C-24), 147.9 (C-9), 142.2 (C-22), 132.2 (C-12), 126.8 (C-14), 126.6 (C-8), 121.1 (C-23), 111.0 (C-11), 50.7 (C-18), 46.0 (C-5), 38.4 (C-1), 37.9 (C-4), 37.6 (C-10), 36.5 (C-3), 29.7 (C-7), 26.9 (C-15), 25.4 (C-20), 22.8 (C-16), 22.7 (C-17), 19.4 (C-6), 18.9 (C-19), 18.7 (C-2) ppm; MS (ESI,

MeOH): m/z (%) = 407.4 ($[M+H]^+$, 100), 813.2 ($[2M+H]^+$, 26), 835.2 ($[2M+Na]^+$, 6); analysis calculated for $C_{26}H_{34}N_2O_2$ (406.56): C 76.81, H 8.43, N 6.89; found: C 76.62, H 8.69; N 6.59.

4.3.9 12-Acetoxy-*N*-benzoyldehydroabietylamine (**18**)

Compound **18** was prepared according to general procedure B from compound **12** (0.14 g, 0.35 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8.5:1.5:10) afforded compound **18** (0.15 g, 96%) as a colorless solid; R_F = 0.5 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8.5:1.5:10); mp = 87-92 °C; $[\alpha]_D$ = +29.9° (*c* = 0.33, $CHCl_3$); IR (KBr): *v* = 3422*s*, 2962*s*, 2928*s*, 2868*m*, 1758*s*, 1644*s*, 1580*m*, 1540*s*, 1492*m*, 1458*m*, 1368*m*, 1304*m*, 1290*m*, 1208*vs*, 1176*m*, 1018*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 286 nm (3.11); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (*d*, *J* = 7.3 Hz, 2H, 23-H), 7.48 (*dd*, *J* = 7.2, 7.2 Hz, 1H, 25-H), 7.42 (*dd*, *J* = 7.3, 7.3 Hz, 2H, 24-H), 6.93 (*s*, 1H, 14-H), 6.82 (*s*, 1H, 11-H), 6.19 - 6.12 (*m*, 1H, NH), 3.45 (*dd*, *J* = 13.6, 6.1 Hz, 1H, 18-H_a), 3.31 (*dd*, *J* = 13.5, 6.2 Hz, 1H, 18-H_b), 2.96 - 2.85 (*m*, 2H, 7-H_a + 15-H), 2.85 - 2.74 (*m*, 1H, 7-H_b), 2.30 (*s*, 3H, 27-H) 2.22 - 2.16 (*m*, 1H, 1-H_a), 2.02 - 1.95 (*m*, 1H, 6-H_a), 1.82 - 1.64 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.55 - 1.45 (*m*, 1H, 3-H_a), 1.45 - 1.31 (*m*, 2H, 1-H_b + 3-H_b), 1.23 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.16 (*d*, *J* = 6.9 Hz, 3H, 17-H), 1.00 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C-26), 167.8 (C-21), 148.3 (C-13), 146.3 (C-9), 137.0 (C-12), 135.0 (C-22), 133.0 (C-8), 131.5 (C-25), 128.7 (C-24), 127.2 (C-14), 127.0 (C-23), 118.0 (C-11), 50.4 (C-18), 45.5 (C-5), 38.4 (C-1), 37.8 (C-4), 37.8 (C-10), 36.5 (C-3), 30.1 (C-7), 27.3 (C-15), 25.5 (C-20), 23.1 (C-16), 23.1 (C-17), 21.1 (C-27), 19.2 (C-6), 18.9 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 448.2 ($[M+H]^+$, 64), 465.0 ($[M+NH_4]^+$, 10), 467.3 ($[2M+Ca]^{2+}$, 20), 470.3 ($[M+Na]^+$, 100); analysis calculated for $C_{31}H_{39}NO_5$ (447.61): C 77.82, H 8.33, N 3.13; found: C 77.49, H 8.57, N 2.96.

4.3.10 12-Acetoxy-*N*-(4-acetoxy)benzoyldehydroabietylamine (**19**)

Compound **19** was prepared according to general procedure B from compound **13** (0.08 g, 0.19 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 6:4:10) gave compound **19** (0.09 g, 94%) as a colorless solid; R_F = 0.47 (silica gel, *n*-hexane/ethyl acetate/chloroform, 6:4:10); mp = 95-98 °C; $[\alpha]_D$ = +24.2° (*c* = 0.33, $CHCl_3$); IR (KBr): *v* = 3422*m*, 2962*m*, 2928*m*, 2868*w*, 1758*s*, 1648*m*, 1606*m*, 1542*m*, 1498*s*, 1466*w*, 1458*w*, 1438*w*, 1370*w*, 1306*w*, 1288*w*, 1204*vs*, 1166*s*, 1104*w*, 1016*m*, 914*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 246 nm (4.11); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (*d*, *J* = 8.4 Hz, 1H, 23-H), 7.14 (*d*, *J* = 8.4 Hz, 1H, 24-H), 6.93 (*s*, 1H, 14-H), 6.82 (*s*, 1H, 11-H), 6.12 (*dd*, *J* = 5.6, 5.6 Hz, 1H,

NH), 3.42 (*dd*, *J* = 13.6, 6.1 Hz, 1H, 18-H_a), 3.30 (*dd*, *J* = 13.6, 6.2 Hz, 1H, 18-H_b), 2.98 - 2.72 (*m*, 3H, 15-H + 7-H_a + 7-H_b), 2.30 (*s*, 3H, 27-H), 2.29 (*s*, 3H, 29-H), 2.23 - 2.16 (*m*, 1H, 1-H_a), 2.01 - 1.93 (*m*, 1H, 6-H_a), 1.84 - 1.62 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.54 - 1.44 (*m*, 2H, 5-H + 3-H_a), 1.44 - 1.28 (*m*, 2H, 3-H_b + 1-H_a), 1.23 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.16 (*d*, *J* = 7.0 Hz, 3H, 17-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C-28), 169.1 (C-26), 167.0 (C-21), 153.1 (C-25), 148.3 (C-13), 146.3 (C-9), 137.0 (C-12), 133.0 (C-8), 132.6 (C-22), 128.4 (C-23), 127.2 (C-14), 121.9 (C-24), 118.0 (C-11), 50.5 (C-18), 45.6 (C-5), 38.4 (C-1), 37.8 (C-4), 37.7 (C-10), 36.5 (C-3), 30.0 (C-7), 27.3 (C-15), 25.5 (C-20), 23.1 (C-16), 23.1 (C-17), 21.3 (C-29), 21.1 (C-27), 19.2 (C-6), 18.9 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 506.2 ($[M+H]^+$, 45), 522.9 ($[M+NH_4]^+$, 10), 528.3 ($[M+Na]^+$, 30), 1011.3 ($[2M+H]^+$, 95), 1033.1 ($[2M+Na]^+$, 100); analysis calculated for $C_{31}H_{39}NO_5$ (505.65): C 73.63, H 7.77, N 2.77; found: C 73.41, H, N.

4.3.11 12-Acetoxy-*N*-(4-methoxy)benzoyldehydroabietylamine (**20**)

Compound **20** was prepared according to general procedure B from compound **14** (0.08 g, 0.18 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10) yielded compound **20** (0.08 g, 93%) as a colorless solid; R_F = 0.30 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 94-96 °C; $[\alpha]_D$ = +28.2° (*c* = 0.35, $CHCl_3$); IR (KBr): *ν* = 3424*s*, 2962*m*, 2928*m*, 2868*m*, 1758*s*, 1640*s*, 1608*s*, 1576*w*, 1542*m*, 1504*vs*, 1462*m*, 1368*m*, 1310*m*, 1300*m*, 1292*m*, 1254*vs*, 1210*s*, 1176*s*, 1110*w*, 1018*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 265 nm (4.19); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (*d*, *J* = 8.7 Hz, 2H, 23-H), 6.93 (*s*, 1H, 14-H), 6.90 (*d*, *J* = 8.7 Hz, 1H, 24-H), 6.82 (*s*, 1H, 11-H), 6.06 (*dd*, *J* = 5.7, 5.7 Hz, 1H, NH), 3.83 (*s*, 3H, 26-H), 3.43 (*dd*, *J* = 13.7, 6.2 Hz, 1H, 18-H_a), 3.29 (*dd*, *J* = 13.6, 6.3 Hz, 1H, 18-H_b), 2.95 - 2.85 (*m*, 2H, 15-H + 7-H_a), 2.85 - 2.73 (*m*, 1H, 7-H_b), 2.30 (*s*, 3H, 28-H), 2.22 - 2.15 (*m*, 1H, 1-H_a), 2.02 - 1.94 (*m*, 1H, 6-H_a), 1.85 - 1.63 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.53 - 1.45 (*m*, 2H, 5-H + 3-H_a), 1.45 - 1.30 (*m*, 2H, 3-H_b + 1-H_b), 1.23 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.16 (*d*, *J* = 6.9 Hz, 3H, 17-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C-27), 167.3 (C-21), 162.2 (C-25), 148.4 (C-13), 146.3 (C-9), 137.0 (C-12), 133.1 (C-12), 128.8 (C-23), 127.2 (C-22), 127.2 (C-14), 118.0 (C-11), 113.9 (C-24), 55.5 (C-26), 50.3 (C-18), 45.5 (C-5), 38.4 (C-1), 37.8 (C-4), 37.8 (C-10), 36.5 (C-3), 30.1 (C-7), 27.3 (C-15), 25.5 (C-20), 23.1 (C-16), 23.1 (C-17), 21.1 (C-28), 19.2 (C-6), 19.0 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 478.3 ($[M+H]^+$, 50), 497.5 ($[2M+Ca]^{2+}$, 5), 500.3 ($[M+Na]^+$, 30), 955.2 ($[2M+H]^+$, 85), 977.1 ($[2M+Na]^+$, 100); analysis calculated for $C_{30}H_{39}NO_4$ (477.64): C 75.44, H 8.23, N 2.93; found: C 75.33, H 8.46, N 2.77.

4.3.12 12-Acetoxy-*N*-(4-methyl)benzoyldehydroabietylamine (**21**)

Compound **21** was prepared according to general procedure B from compound **15** (0.06 g, 0.14 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10) afforded compound **21** (0.04 g, 62%) as a colorless solid; R_F = 0.56 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 92-95 °C; $[\alpha]_D$ = +28.3° (*c* = 0.31, $CHCl_3$); IR (KBr): *v* = 3424*br*, 2962*s*, 2928*s*, 2868*m*, 1758*s*, 1642*s*, 1614*m*, 1542*s*, 1500*s*, 1458*m*, 1368*m*, 1302*m*, 1208*s*, 1176*m*, 1018*m*, 752*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 242 nm (4.15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (*d*, *J* = 8.1 Hz, 2H, 24-H), 7.22 (*d*, *J* = 7.9 Hz, 2H, 23-H), 6.93 (*s*, 1H, 14-H), 6.82 (*s*, 1H, 11-H), 6.10 (*dd*, *J* = 5.9, 5.9 Hz, 1H, NH), 3.43 (*dd*, *J* = 13.7, 6.3 Hz, 1H, 18-H_a), 3.30 (*dd*, *J* = 13.7, 6.4 Hz, 1H, 18-H_b), 2.97 - 2.85 (*m*, 2H, 7-H_a + 15-H), 2.84 - 2.73 (*m*, 1H, 7-H_b), 2.38 (*s*, 3H, 26-H), 2.30 (*s*, 3H, 28-H), 2.23 - 2.15 (*m*, 1H, 1-H_a), 2.03 - 1.94 (*m*, 1H, 6-H_a), 1.83 - 1.62 (*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.55 - 1.44 (*m*, 2H, 5-H + 3-H_a), 1.44 - 1.28 (*m*, 2H, 3-H_b + 1-H_b), 1.23 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 7.0 Hz, 3H, 16-H), 1.16 (*d*, *J* = 6.9 Hz, 3H, 17-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C-27), 167.7 (C-21), 148.4(C-9), 146.3 (C-12), 141.9 (C-25), 137.0 (C-13), 133.1 (C-8), 132.1 (C-22), 129.4 (C-23), 127.2 (C-14), 127.0 (C-24), 118.0 (C-11), 50.3 (C-18), 45.5 (C-5), 38.4 (C-1), 37.8 (C-4), 37.8 (C-10), 36.5 (C-3), 30.1 (C-7), 27.3 (C-15), 25.5 (C-20), 23.1 (C-16), 23.1 (C-17), 21.6(C-26), 21.1 (C-28), 19.2 (C-6), 18.9 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 462.3 ($[M+H]^+$, 42), 479.1 ($[M+NH_4]^+$, 4), 484.4 ($[M+Na]^+$, 38), 923.3 ($[2M+H]^+$, 72), 945.2 ($[2M+Na]^+$, 100); analysis calculated for $C_{30}H_{39}NO_3$ (461.64): C 78.05, H 8.52, N 3.03; found: C 77.78, H 8.76, N 2.81.

4.3.13 12-Acetoxy-*N*-(4-chloro)benzoyldehydroabietylamine (**22**)

Compound **22** was prepared according to general procedure B from compound **16** (0.06 g, 0.14 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10) afforded compound **22** (0.06 g, 89%) as a colorless solid; R_F = 0.36 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 94-98 °C; $[\alpha]_D$ = +25.3° (*c* = 0.33, $CHCl_3$); IR (KBr): *v* = 3420*br*, 2962*s*, 2928*s*, 2868*m*, 1758*s*, 1646*s*, 1596*m*, 1542*m*, 1486*s*, 1368*m*, 1306*m*, 1210*s*, 1176*m*, 1092*m*, 1016*m*, 758*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 242 nm (4.26); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 - 7.63 (*m*, 2H, 23-H), 7.42 - 7.36 (*m*, 2H, 24-H), 6.93 (*s*, 1H, 14-H), 6.82 (*s*, 1H, 11-H), 6.09 (*dd*, *J* = 6.4, 6.4Hz, 1H, NH), 3.44 (*dd*, *J* = 13.7, 6.5 Hz, 1H, 18-H_a), 3.28 (*dd*, *J* = 13.7, 6.4 Hz, 1H, 18-H_b), 2.97 - 2.85 (*m*, 2H, 7-H_a + 15-H), 2.84 - 2.72 (*m*, 1H, 7-H_b), 2.30 (*s*, 3H, 27-H), 2.23 - 2.15 (*m*, 1H, 1-H_a), 2.01 - 1.92 (*m*, 1H, 6-H_a), 1.85 - 1.59

(*m*, 3H, 2-H_a + 2-H_b + 6-H_b), 1.54 - 1.44 (*m*, 2H, 3-H_a + 5-H), 1.43 - 1.31 (*m*, 2H, 1-H_b + 3-H_b), 1.23 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.16 (*d*, *J* = 6.9 Hz, 3H, 17-H), 0.99 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C-26), 166.7 (C-21), 148.3 (C-9), 146.3 (C-13), 137.8 (C-25), 137.0 (C-12), 133.3 (C-22), 133.0 (C-8), 129.0 (C-24), 128.4 (C-23), 127.2 (C-14), 118.0 (C-11), 50.4 (C-18), 45.5 (C-5), 38.4 (C-1), 37.8 (C-4), 37.8 (C-10), 36.5 (C-3), 30.0 (C-7), 27.3 (C-15), 25.5 (C-20), 23.1 (C-16), 23.1 (C-17), 21.1 (C-27), 19.2 (C-6), 19.0 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 482.3 ($[M+H]^+$, 34), 499.1 ($[M+NH_4]^+$, 12), 504.3 ($[M+Na]^+$, 42). 965.1 ($[2M+H]^+$, 58), 984.9 ($[2M+Na]^+$, 100); analysis calculated for $C_{29}H_{36}ClNO_3$ (482.05): C 72.26, H 7.53, N 2.91; found: C 71.94, H 7.75, N 2.71.

4.3.14 12-Acetoxydehydroabietylamine (**23**)

Compound **10** (0.45 g, 1.59 mmol) was dissolved in THF (30 mL) and the solution was cooled to 0 °C. Sodium hydroxide (1 N, 7 mL) and di-*tert*-butyl dicarbonate (0.35 mg, 1.61 mmol) were added. After 2h of stirring at room temperature the solvent was removed under vacuum and sodium dihydrogen phosphate (1 N, 20 mL) was added. The aqueous phase was extracted with DCM (4 x, 40 mL). The combined organic phases were washed with brine (30 mL), dried and concentrated in vacuum. For analysis a sample was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); R_F = 0.43 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8:2:10); mp = 96-98 °C; $[\alpha]_D$ = +27.4° (*c* = 0.33, $CHCl_3$); IR (KBr): ν = 3422*vs*, 2962*m*, 2928*m*, 2868*m*, 1690*s*, 1618*m*, 1510*s*, 1472*w*, 1458*m*, 1418*m*¸1368*m*, 1324*w*, 1308*w*, 1246*m*, 1166*s*, 1052*w* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 307 nm (3.24); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (*s*, 1H, 14-H), 6.64 (*s*, 1H, 11-H), 4.53 (*dd*, *J* = 6.0, 6.0 Hz, 1H, NH), 3.17 - 3.04 (*m*, 2H, 15-H + 18-H_a), 2.96 (*dd*, *J* = 13.9, 7.0 Hz, 1H, 18-H_b), 2.84 (*dd*, *J* = 16.1, 6.0 Hz, 1H, 7-H_a), 2.74 (*ddd*, *J* = 17.1, 11.4, 7.3 Hz, 1H, 7-H_b), 2.21 - 2.14 (*m*, 1H, 1-H_a), 1.87 - 1.78 (*m*, 1H, 6-H_a), 1.79 - 1.71 (*m*, 1H, 2-H_a), 1.71 - 1.61 (*m*, 2H, 6-H_b + 2-H_b), 1.43 (*s*, 9H, 23-H), 1.44 - 1.32 (*m*, 2H, 1-H_b + 3-H_a), 1.28 - 1.24 (*m*, 1H, 3-H_b), 1.24 (*d*, *J* = 4.1 Hz, 3H, 16-H), 1.23 (*d*, *J* = 4.1 Hz, 3H, 17-H), 1.20 (*s*, 3H, 20-H), 0.90 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C-21), 151.0 (C-9), 148.4 (C-13), 131.8 (C-12), 127.2 (C-8), 126.8 (C-14), 111.1 (C-11), 79.3 (C-22), 51.3 (C-18), 45.1 (C-5), 38.5 (C-1), 37.6 (C-4), 37.5 (C-10), 36.1 (C-3), 29.7 (C-7), 28.6 (C-23), 27.0 (C-15), 25.4 (C-20), 22.9 (C-16), 22.7 (C-17), 19.1 (C-6), 18.8 (C-2), 18.8 (C-19) ppm; MS (ESI, MeOH): m/z (%) = 424.2 ($[M+Na]^+$, 100), 456.2 ($[M+Na+MeOH]^+$, 15); analysis calculated for $C_{25}H_{39}NO_3$ (401.58): C 74.77, H 9.79, N 3.49; found: C 74.55, H 9.93, N 3.21.

N-Boc-dehydroabietylamine was acetylated according to general procedure B to yield 12-acetoxy-*N*-Boc-dehydroabietylamine. Column chromatography (silica gel, *n*-hexane/ethyl acetate/chloroform, 8.5:1.5:10) afforded 12-acetoxy-*N*-Boc-dehydroabietylamine (0.45 g, 64% over two steps) as a colorless solid; R_F = 0.48 (silica gel, *n*-hexane/ethyl acetate/chloroform, 8.5:1.5:10; mp = 65-66 °C; $[\alpha]_D$ = +31.3° (*c* = 0.34, $CHCl_3$); IR (KBr): v = 3442*vs*, 2966*m*, 2930*m*, 2868*w*, 1758*m*, 1718*m*, 1702*m*, 1636*m*, 1508*m*, 1498*m*, 1458*w*, 1384*w*¸1366*m*, 1246*m*, 1208*m*, 1170*s*, 1016*w* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 296 nm (3.00); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94 (*s*, 1H, 14-H), 6.83 (*s*, 1H, 11-H), 4.52 (*dd*, *J* = 6.0, 6.0 Hz, 1H, NH), 3.11 (*dd*, *J* = 13.8, 6.5 Hz, 1H, 18-H_a), 2.95 - 2.86 (*m*, 2H, 15-H + 7-H_a), 2.79 (*ddd*, J = 17.4, 11.2, 7.5 Hz, 1H, 7-H_b), 2.30 (*s*, 3H, 25-H), 2.20 - 2.14 (*m*, 1H, 1-H_a), 1.90 - 1.83 (*m*, 1H, 6-H_a), 1.79 - 1.60 (*m*, 3H, 6-H_b + 2-H_a + 2-H_b), 1.46 (*dd*, *J* = 12.5, 2.2 Hz, 1H, 5-H), 1.43 (*s*, 9H, 23-H), 1.42 - 1.34 (*m*, 2H, 1-H_b + 3-H_a), 1.27 - 1.21 (*m*, 1H, 3-H_b), 1.20 (*s*, 3H, 20-H), 1.19 (*d*, *J* = 7.3 Hz, 3H, 16-H), 1.17 (*d*, *J* = 7.3 Hz, 3H, 17-H), 0.90 (*s*, 3H, 19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1 (C-24), 156.3 (C-21), 148.6 (C-9), 146.3 (C-13), 137.0 (C-12), 133.2 (C-8), 127.1 (C-14), 118.1 (C-11), 79.3 (C-22), 51.2 (C-18), 44.6 (C-5), 38.4 (C-1), 37.7 (C-4), 37.5 (C-10), 36.1 (C-3), 29.9 (C-7), 28.5 (C-23), 27.3 (C-15), 25.4 (C-20), 23.2 (C-16), 23.1 (C-17), 21.1 (C-25), 19.0 (C-6), 18.8 (C-19), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 466.2 ($[M+Na]^+$, 100), 909.1 ($[2M+Na]^+$, 10); analysis calculated for $C_{27}H_{41}NO_4$ (443.62): C 73.10, H 9.32, N 3.16; found: C 72.97, H 9.52, N 2.87. 12-Acetoxy-*N*-Boc-dehydroabietylamine was dissolved in DCM (20 mL), cooled to 0 °C and TFA (5 mL) was added. After 2.5 h of stirring at room temperature, the solution was diluted with DCM (30 mL) and was washed with aqueous sodium hydrogen carbonate solution (saturated, 3 x, 20 mL). The organic phase was washed with brine (20 mL), dried and concentrated in vacuo. Compound **23** (0.32 g, 92 %) was obtained as a colorless solid; R_F = 0.29 (silica gel, chloroform/methanol, 9:1); mp = 103-104 °C; $[\alpha]_D$ = +18.4 (*c* = 0.32, $CHCl_3$); IR(KBr): v = 3181*w*, 2970*w*, 2925*w*, 1790*w*, 1749*m*, 1620*w*, 1514*m*, 1464*w*, 1378*w*, 1220*m*, 1195*s*, 1143*vs*, 1020*m*, 809*m*, 784*s*, 707*vs* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 296 nm (2.75) ; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (*br s*, 2H, NH_2), 6.94 (*s*, 1H, 14-H), 6.78 (*s*, 1H, 11-H), 2.97 - 2.74 (*m*, 5H, 18-H_a + 18-H_b + 15-H + 7-H_a + 7-H_b), 2.28 (*s*, 3H, 22-H), 2.22 - 2.17 (*m*, 1H, 1-H_a), 1.84 - 1.64 (*m*, 4H, 6-H_a + 6-H_b + 2-H_a + 2-H_b), 1.55 - 1.49 (*m*, 1H, 3-H_a), 1.42 - 1.34 (*m*, 2H, 1-H_b + 5-H), 1.31 - 1.21 (*m*, 1H, 3-H_b), 1.20 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.15 (*d*, *J* = 6.9 Hz, 3H, 17-H), 1.02 (*s*, 3H, 19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (C-21), 147.8 (C-9), 146.3 (C-13), 137.4 (C-12), 132.6 (C-8), 127.2 (C-14), 117.7 (C-11), 51.6 (C-18), 45.6 (C-5), 37.8 (C-1), 37.5 (C-10), 35.8 (C-4), 35.1 (C-3),

28.6 (C-7), 27.3 (C-15), 24.8 (C-20), 23.1 (C-16), 23.0 (C-17), 21.1 (C-22), 18.8 (C-6), 18.1 (C-2), 17.6 (C-19) ppm; MS (ESI, MeOH): m/z (%) = 344.1 ($[M+H]^+$, 100), 687.2 ($[2M+H]^+$, 5); analysis calculated for $C_{22}H_{33}NO_2$ (343.50): C 76.92, H 9.68, N 4.08; found: C 76.84, H 9.51, N3.85.

4.3.15 12-Acetoxy-*N*-(isonicotinoyl)dehydroabietylamine (**24**)

Compound **24** was prepared according to general procedure A from compound **23** (0.10 g, 0.29 mmol) and isonicotinic acid (0.05 g, 0.4 mmol). Column chromatography (silica gel, *n*-hexane/ethyl acetate 3:7) gave compound **24** (0.10 g, 77%) as a colorless solid; R_F = 0.3 (silica gel, *n*-hexane/ethyl acetate, 3:7); mp = 85-89 °C; $[\alpha]_D$ = +29.6° (*c* = 0.34, $CHCl_3$); IR (KBr): *v* = 3406*s*, 2962*s*, 2930*s*, 2868*m*, 1758*s*, 1654*s*, 1542*s*, 1496*m*, 1458*m*, 1438*m*, 1408*m*, 1370*m*, 1300*m*, 1210*vs*, 1176*m*, 1162*m*, 1066*w*, 1018*m*, 756*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 298 nm (3.21); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (*d*, *J* = 4.8 Hz, 2H, 26-H), 7.58 (*d*, *J* = 5.0 Hz, 2H, 25-H), 6.93 (*s*, 1H, 14-H), 6.81 (*s*, 1H, 11-H), 6.26 (*dd*, *J* = 5.0, 5.0 Hz, 1H, NH), 3.46 (*dd*, *J* = 13.7, 6.4 Hz, 1H, 18-H_a), 3.29 (*dd*, *J* = 13.7, 6.3 Hz, 1H, 18-H_b), 2.96 - 2.85 (*m*, 2H, 7-H_a + 15-H), 2.78 (*ddd*, *J* = 17.7, 11.2, 7.5 Hz, 1H, 7-H_b), 2.29 (*s*, 3H, 22-H), 2.22 - 2.16 (*m*, 1H, 1-H_a), 1.99 - 1.93 (*m*, 1H, 6-H_a), 1.82 - 1.71 *(m*, 2H, 6-H_b + 2-H_a), 1.71 - 1.64 (*m*, 1H, 2-H_b), 1.53 - 1.47 (*m*, 1H, 3-H_a), 1.45 (*dd*, *J* = 12.3, 1.9 Hz, 1H, 5-H), 1.42 - 1.30 (*m*, 2H, 1-H_b + 3-H_b), 1.22 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.15 (*d*, *J* = 6.9 Hz, 3H, 17-H), 1.00 (*s*, 3H, 19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2 (C-21), 165.8 (C-23), 150.6 (C-26), 148.2 (C-9), 146.3 (C-13), 142.1 (C-24), 137.1 (C-12), 132.9 (C-8), 127.2 (C-14), 121.1 (C-25), 118.0 (C-11), 50.5 (C-18), 45.4 (C-5), 38.3 (C-1), 37.9 (C-4), 37.7 (C-10), 36.5 (C-3), 29.9 (C-7), 27.3 (C-15), 25.4 (C-20), 23.1 (C-16), 23.1 (C-17), 21.1 (C-22), 19.2 (C-6), 19.0 (C-19), 18.6 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 449.3 ($[M+H]^+$, 100), 471.3 ($[M+Na]^+$, 5), 897.1 ($[2M+H]^+$, 30), 918.9 ($[2M+Na]^+$, 10); analysis calculated for $C_{28}H_{36}N_2O_3$ (448.60): C 74.97, H 8.09, N 6.24; found: C 74.81, H 8.23, N 5.87.

4.3.16 *N*-Biotinyldehydroabietylamine (**25**)

Compound **25** was prepared according to general procedure A from dehydroabietylamine (0.15 g, 0.52 mmol) and biotin (0.13 g, 0.53 mmol) using DMF as solvent. Column chromatography (silica gel, chloroform/methanol, 9:1) afforded compound **25** (0.22 g, 81%) as a colorless solid; R_F = 0.36 (silica gel, chloroform/methanol, 9:1); mp = 128-130 °C; $[\alpha]_D$ = +41.3° (*c* = 0.32, $CHCl_3$); IR (KBr): *v* = 3406*m*, 3312*s*, 3076*m*, 2956*s*, 2926*s*, 2866*m*, 1704*vs*, 1654*s*, 1648*s*, 1550*m*, 1508*w*, 1498*m*, 1458*m*, 1382*m*, 1326*w*, 1266*m*,

1216*w*, 1172*w* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 285 nm (3.21); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.16 (*d*, *J* = 8.2 Hz, 1H, 11-H), 6.99 (*dd*, *J* = 8.2, 1.6 Hz, 1H, 12-H), 6.90 (*d*, *J* = 1.4 Hz, 1H, 14-H), 6.28 (*br s*, 1H, NH), 6.00 (*br s*, 1H, NH), 4.43 (*dd*, *J* = 4.9, 4.9 Hz, 1H, 29-H), 4.19 (*dd*, *J* = 4.8, 4.8 Hz, 1H, 27-H), 3.22 (*dd*, *J* = 13.6, 5.3 Hz, 1H, 18-H_a), 3.11 (*dd*, *J* = 13.6, 5.8 Hz, 1H, 18-H_b), 3.07 - 3.01 (*m*, 1H, H-26), 2.94 - 2.78 (*m*, 4H, 7-H_a + 7-H_b + 15-H + 30-H_a), 2.69 (*d*, *J* = 12.8 Hz, 1H, 30-H_b), 2.32 - 2.26 (*m*, 1H, 1-H_a), 2.21 (*t*, *J* = 7.3 Hz, 2H, 22-H_a + 22-H_b), 1.93 - 1.87 (*m*, 1H, 6-H_a), 1.81 - 1.57 (*m*, 8H, 2-H_a + 2-H_b + 6-H_b + 25-H_a + 25-H_b + 24-H_a + 24-H_b + 23-H_a), 1.45 - 1.37 (*m*, 3H, 23-H_b + 3-H_a + 5-H), 1.37 - 1.32 (*m*, 1H, 1-H_b), 1.32 - 1.24 (*m*, 1H, 3-H_b), 1.23 (*d*, *J* = 6.9 Hz, 6H, 16-H + 17-H), 1.21 (*s*, 3H, 20-H), 0.93 (*s*, 3H, 19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6 (C-21), 163.9 (C-28), 147.3 (C-13), 145.7 (C-9), 135.0 (C-8), 127.1 (C-14), 124.3 (C-11), 123.9 (C-12), 61.9 (C-27), 60.4 (C-28), 55.6 (C-26), 49.9 (C-18), 45.4 (C-5), 40.5 (C-30), 38.5 (C-1), 37.6 (C-4), 37.6 (C-10), 36.3 (C-3), 36.3 (C-22), 33.5 (C-15), 30.3 (C-7), 28.3 (C-23), 28.2 (C-24), 26.0 (C-25), 25.5 (C-20), 24.1 (C-16), 24.1 (C-17), 19.1 (C-6), 19.0 (C-19), 18.8 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 512.3 ($[M+H]^+$, 10), 534.4 ($[M+Na]^+$, 10), 1023.3 ($[2M+H]^+$, 15), 1045.3 ($[2M+Na]^+$, 100); analysis calculated for $C_{30}H_{45}N_3O_2S$ (511.76): C 70.41, H 8.86, N 8.21, S 6.27; found: C 70.13, H 8.96, N 8.65, S 6.03.

4.3.17 *N*-Biotinyl-12-hydroxydehydroabietylamine (**26**)

Compound **26** was prepared according to general procedure A from compound **10** (0.15 g, 0.50 mmol) and biotin (0.17 g, 0.70 mmol) using DMF as solvent. Column chromatography (silica gel, chloroform/methanol, 9:1) afforded compound **26** (0.19 g, 72%) as a colorless solid; R_F = 0.39 (silica gel, chloroform/methanol, 9:1); mp = 154-156 °C; $[\alpha]_D$ = +55.4° (*c* = 0.35, MeOH); IR (KBr): *ν* = 3404*s*, 2928*s*, 2866*m*, 1696*vs*, 1654*s*, 1550*m*, 1510*m*, 1458*m*, 1380*m*, 1308*m*, 1268*m*, 1242*m*, 1184*m*, 1164*m*, 1088*w*, 1048*w* cm^{-1}; UV-vis (MeOH): λ_{max} (log ε) = 303 nm (3.47); ^1H NMR (500 MHz, CD_3OD): δ = 6.75 (*s*, 1H, 14-H), 6.61 (*s*, 1H, 11-H), 4.38 (*dd*, *J* = 7.8, 4.5 Hz, 1H, 29-H), 3.83 (*dd*, *J* = 7.8, 4.4 Hz, 1H, 27-H), 3.63 – 3.56 (*m*, 1H, 18-H_a), 3.15 (*hept*, *J* = 6.9 Hz, 1H, 15-H), 2.81 (*dd*, *J* = 12.7, 5.0 Hz, 1H, 30-H_a), 2.73 (*dd*, *J* = 10.2, 5.2 Hz, 2H, 7-H_a + 7-H_b), 2.63 – 2.59 (*m*, 2H, 18-H_b + 30-H_b), 2.51 (*ddd*, *J* = 7.3, 4.5 Hz, 1H, 26-H), 2.24 – 2.18 (*m*, 3H, 1-H_a + 22-H_a + 22-H_b), 2.04 – 1.97 (*m*, 1H, 6-H_a), 1.80 (*dddd*, *J* = 16.3, 13.1, 8.2, 3.0 Hz, 1H, 2-H_a), 1.72 – 1.62 (*m*, 3H, 2-H_b + 6-H_b + 25-H_a), 1.61 – 1.51 (*m*, 1H, 25-H_b), 1.50 – 1.40 (*m*, 4H, 24-H_a + 24-H_b + 3-H_a + 5-H), 1.40 – 1.23 (*m*, 4H, 1-H_b + 3-H_b + 23-H_a + 23-H_b), 1.19 (*s*, 3H, 20-H), 1.19 (*d*, *J* = 6.9 Hz, 3H, 16-H), 1.16 (*d*, *J* = 6.9 Hz, 3H, 17-H), 0.92 (*s*, 3H, 19-H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 176.0 (C-

21), 166.1 (C-28), 153.3(C-13), 149.2 (C-9), 133.2 (C-12), 127.4 (C-14), 127.1 (C-8), 111.5 (C-11), 63.2 (C-27), 61.5 (C-29), 57.0 (C-26), 50.5 (C-18), 45.4 (C-5), 40.9 (C-30), 39.7 (C-1), 39.0 (C-4), 38.6 (C-10), 37.2 (C-3), 36.8 (C-22), 30.7 (C-7), 29.8 (C-23), 29.4 (C-24), 27.8 (C-15), 27.0 (C-25), 25.9 (C-20), 23.6 (C-16), 22.8 (C-17), 20.5 (C-6), 19.8 (C-2), 19.7 (C-19) ppm; MS (ESI, MeOH): m/z (%) = 528.4 ($[M+H]^+$, 74), 550.5 ($[M+Na]^+$, 100); analysis calculated for $C_{30}H_{45}N_3O_3S$ (527.76): C 68.27, H 8.59, N 7.96, S 6.08; found: C 67.96, H 8.73, N 7.75, S 5.86.

4.3.18 12-Acetoxy-*N*-biotinyldehydroabietylamine (**27**)

Compound **27** was prepared according to general procedure A from compound **23** (0.10 g, 0.29 mmol) and biotin (0.09 g, 0.37 mmol) using DMF as solvent. Column chromatography (silica gel, chloroform/methanol, 9:1) afforded compound **27** (0.09 g, 55%) as a colorless solid; R_F = 0.27 (silica gel, chloroform/methanol, 9:1); mp = 130-132 °C; $[\alpha]_D$ = +53.4° (*c* = 0.31, $CHCl_3$); IR (KBr): *v* = 3284*w*, 2958*w*, 2926*m*, 2866*w*, 1754*m*, 1697*s*, 1648*s*, 1539*m*, 1496*m*, 1455*m*, 1368*m*, 1207*vs*, 1016*m*, 912*m*, 729*m* cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (log ε) = 296 nm (3.03);^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (*s*, 1H, 14-H), 6.80 (*s*, 1H, 11-H), 6.13 (*s*, 1H, NH), 5.99 (*dd*, *J* = 6.3, 6.3 Hz, 1H, NH), 4.41 (*dd*, *J* = 7.5, 4.7 Hz, 1H, 31-H), 4.18 (*dd*, *J* = 7.5, 4.7 Hz, 1H, 29-H), 3.24 (*dd*, *J* = 13.7, 5.9 Hz, 1H, 18-H_a), 3.09 - 3.00 (*m*, 2H, 18-H_b + 28-H), 2.95 - 2.85 (*m*, 2H, 15-H + 7-H_a), 2.85 - 2.74 (*m*, 2H, 7-H_b + 32-H_a), 2.62 (*d*, *J* = 12.8 Hz, 1H, 32-H_b), 2.29 (*s*, 3H, 22-H), 2.23 - 2.12 (*m*, 3H, 24-H_a + 24-H_b + 1-H_a), 1.94 - 1.85 (*m*, 1H, 6-H_a), 1.80 - 1.54 (*m*, 7H, 6-H_b + 2-H_a + 2-H_b + 25-H_a + 25-H_b +27-H_a + 27-H_b), 1.46 - 1.34 (m, 5H, 26-H_a + 26-H_b + 3-H_a + 1-H_b + 5-H), 1.34 - 1.22 (*m*, 1H, 3-H_b), 1.19 (*s*, 3H, 20-H), 1.18 (*d*, *J* = 6.7 Hz, 3H, 16-H) 1.16 (*d*, *J* = 6.7 Hz, 3H, 17-H), 0.91 (*s*, 3H, 19-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5 (C-23), 170.2 (C-21), 163.8 (C-30), 148.5 (C-13), 146.3 (C-9), 137.0 (C-12), 133.2 (C-8), 127.2 (C-14), 118.0 (C-11), 62.0 (C-29), 60.3 (C-31), 55.6 (C-28), 49.7 (C-18), 44.8 (C-5), 40.5 (C-32), 38.4 (C-1), 37.7 (C-4), 37.6 (C-10), 36.2 (C-3), 36.2 (C-24), 29.8 (C-7), 28.3 (C-25), 28.2 (C-26), 27.3 (C-15), 25.9 (C-27), 25.4 (C-20), 23.2 (C-16), 23.1 (C-17), 21.1 (C-22), 19.0 (C-19), 19.0 (C-6), 18.7 (C-2) ppm; MS (ESI, MeOH): m/z (%) = 304.8 ($[M+Ca]^{2+}$, 10), 570.5 ($[M+H]^+$, 50), 589.5 ($[2M+Ca]^{2+}$, 5), 592.5 ($[M+Na]^+$, 10), 1139.2 ($[2M+H]^+$, 80), 1161.3 ($[2M+Na]^+$, 100); analysis calculated for $C_{30}H_{45}N_3O_3S$ (569.80): C 67.45, H 8.31, N 7.37, S 5.63; found: C 67.31, H 8.60, N 7.52, S 5.52.

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References

1. Solecki, R. S., Shanidar IV, a Neanderthal Flower Burial in Northern Iraq. *Science* **1975,** *190*, 880-881.

2. Huxtable, R. J.; Schwarz, S. K., The isolation of morphine - First principles in science and ethics. *Mol. Interv.* **2001,** *1*, 189-191.

3. Newman, D. J.; Cragg, G. M., Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* **2016,** *79*, 629-61.

4. Cragg, G. M.; Newman, D. J., Plants as a source of anti-cancer agents. *J. Ethnopharmacol.* **2005,** *100*, 72-9.

5. Nobili, S.; Lippi, D.; Witort, E.; Donnini, M.; Bausi, L.; Mini, E.; Capaccioli, S., Natural compounds for cancer treatment and prevention. *Pharmacol. Res.* **2009,** *59*, 365-78.

6. Weiss, R. B.; Donehower, R. C.; Wiernik, P. H.; Ohnuma, T.; Gralla, R. J.; Trump, D. L.; Baker, J. R.; Van Echo, D. A.; Von Hoff, D. D.; Leyland-Jones, B., Hypersensitivity reactions from taxol. *J. Clin. Oncol.* **1990,** *8*, 1263-1268.

7. Scripture, C. D.; Figg, W. D.; Sparreboom, A., Peripheral Neuropathy Induced by Paclitaxel: Recent Insights and Future Perspectives. *Curr. Neuropharmacol.* **2006,** *4*, 165-172.

8. Velasco, R.; Bruna, J., Taxane-Induced Peripheral Neurotoxicity. *Toxics* **2015,** *3*, 152-169.

9. Mishra, B. B.; Tiwari, V. K., Natural products: an evolving role in future drug discovery. *Eur. J. Med. Chem.* **2011,** *46*, 4769-807.

10. Masendra; Ashitani, T.; Takahashi, K.; Lukmandaru, G., Lipophilic extractives of the inner and outer barks from six different Pinus species grown in Indonesia. *Journal of Forestry Research* **2017**.

11. Fengel, D.; Wegener, G., *Wood: chemistry, ultrastructure, reactions*. De Gruyter1983.

12. Wijayanto, A.; Dumarçay, S.; Gérardin-Charbonnier, C.; Sari, R. K.; Syafii, W.; Gérardin, P., Phenolic and lipophilic extractives in Pinus merkusii Jungh. et de Vries knots and stemwood. *Ind. Crops Prod.* **2015,** *69*, 466-471.

13. Valentin, L.; Kluczek-Turpeinen, B.; Willfor, S.; Hemming, J.; Hatakka, A.; Steffen, K.; Tuomela, M., Scots pine (Pinus sylvestris) bark composition and degradation by fungi: potential substrate for bioremediation. *Bioresour. Technol.* **2010,** *101*, 2203-9.

14. Hafizoğlu, H.; Holmbom, B.; Reunanen, M., Chemical Composition of Lipophilic and Phenolic Constituents of Barks from Pinus nigra, Abies bornmülleriana and Castanea sativa. In *Holzforschung*2002; Vol. 56, p 257.

15. Yang, N. Y.; Liu, L.; Tao, W. W.; Duan, J. A.; Tian, L. J., Diterpenoids from Pinus massoniana resin and their cytotoxicity against A431 and A549 cells. *Phytochemistry* **2010,** *71*, 1528-33.

16. Gonzalez, M. A., Synthetic derivatives of aromatic abietane diterpenoids and their biological activities. *Eur. J. Med. Chem.* **2014,** *87*, 834-42.

17. Sadashiva, M. P.; Gowda, R.; Wu, X.; Inamdar, G. S.; Kuzu, O. F.; Rangappa, K. S.; Robertson, G. P.; Gowda, D. C., A non-cytotoxic N-dehydroabietylamine derivative with potent antimalarial activity. *Exp. Parasitol.* **2015,** *155*, 68-73.

18. Wilkerson, W. W.; Galbraith, W.; DeLucca, I.; Harris, R. R., Topical antiinflammatory dehydroabietylamine derivatives. IV. *Bioorg. Med. Chem. Lett.* **1993,** *3*, 2087-2092.

19. Kovaleva, K. S.; Yarovaya, O. I.; Shernyukov, A. V.; Zarubaev, V. V.; Shtro, A. A.; Orshanskaya, Y. R.; Salakhutdinov, N. F., Synthesis of new heterocyclic dehydroabietylamine derivatives and their biological activity. *Chem. Heterocycl. Compd.* **2017,** *53*, 364-370.

20. Gowda, R.; Madhunapantula, S. V.; Kuzu, O. F.; Sharma, A.; Robertson, G. P., Targeting multiple key signaling pathways in melanoma using leelamine. *Mol. Cancer Ther.* **2014,** *13*, 1679-89.

21. Chen, Y. C.; Gowda, R.; Newswanger, R. K.; Leibich, P.; Fell, B.; Rosenberg, G.; Robertson, G. P., Targeting cholesterol transport in circulating melanoma cells to inhibit metastasis. *Pigment Cell Melanoma Res.* **2017,** *30*, 541-552.

22. Sehrawat, A.; Kim, S. H.; Hahm, E. R.; Arlotti, J. A.; Eiseman, J.; Shiva, S. S.; Rigatti, L. H.; Singh, S. V., Cancer-selective death of human breast cancer cells by leelamine is mediated by bax and bak activation. *Mol. Carcinog.* **2017,** *56*, 337-348.

23. Kuzu, O. F.; Gowda, R.; Sharma, A.; Robertson, G. P., Leelamine mediates cancer cell death through inhibition of intracellular cholesterol transport. *Mol. Cancer Ther.* **2014,** *13*, 1690-703.

24. Chen, Y.; Lin, Z.-X.; Zhou, A.-M., Synthesis and antitumour activities of a novel class of dehydroabietylamine derivatives. *Nat. Prod. Res.* **2012,** *26*, 2188-2195.

25. Mustufa, M. A.; Aslam, A.; Ozen, C.; Ali Hashmi, I.; Naqvi, N. u. H.; Ozturk, M.; Ali, F. I., Phenacyl group containing amide derivative of dehydroabietylamine exhibiting enhanced cytotoxic activity against PLC and MCF7 cancer cell lines. *Med. Chem. Res.* **2017,** *26*, 1367-1376.

26. Ling, T.; Tran, M.; Gonzalez, M. A.; Gautam, L. N.; Connelly, M.; Wood, R. K.; Fatima, I.; Miranda-Carboni, G.; Rivas, F., (+)-Dehydroabietylamine derivatives target triple-negative breast cancer. *Eur. J. Med. Chem.* **2015,** *102*, 9-13.

27. Mustufa, M. A.; Ozen, C.; Hashmi, I. A.; Aslam, A.; Baig, J. A.; Yildiz, G.; Muhammad, S.; Solangi, I. B.; Ul Hasan Naqvi, N.; Ozturk, M.; Ali, F. I., Synthesis and bio-molecular study of (+)-N-Acetyl-alpha-amino acid dehydroabietylamine derivative for the selective therapy of hepatocellular carcinoma. *BMC Cancer* **2016,** *16*, 883.

28. Lin, L.-Y.; Bao, Y.-L.; Chen, Y.; Sun, L.-G.; Yang, X.-G.; Liu, B.; Lin, Z.-X.; Zhang, Y.-W.; Yu, C.-L.; Wu, Y.; Li, Y.-X., N-Benzoyl-12-nitrodehydroabietylamine-7-one, a novel dehydroabietylamine derivative, induces apoptosis and inhibits proliferation in HepG2 cells. *Chem. Biol. Interact.* **2012,** *199*, 63-73.

29. González, M. A.; Pérez-Guaita, D., Short syntheses of (+)-ferruginol from (+)-dehydroabietylamine. *Tetrahedron* **2012,** *68*, 9612-9615.

30. Russell-Jones, G.; McTavish, K.; McEwan, J.; Rice, J.; Nowotnik, D., Vitamin-mediated targeting as a potential mechanism to increase drug uptake by tumours. *J. Inorg. Biochem.* **2004,** *98*, 1625-33.

31. Ren, W. X.; Han, J.; Uhm, S.; Jang, Y. J.; Kang, C.; Kim, J.-H.; Kim, J. S., Recent development of biotin conjugation in biological imaging, sensing, and target delivery. *Chem. Commun.* **2015,** *51*, 10403-10418.

32. Hilborn, E.; Stål, O.; Jansson, A., Estrogen and androgen-converting enzymes 17β-hydroxysteroid dehydrogenase and their involvement in cancer: with a special focus on 17β-hydroxysteroid dehydrogenase type 1, 2, and breast cancer. *Oncotarget* **2017,** *8*, 30552-30562.

33. Wiemann, J.; Loesche, A.; Csuk, R., Novel dehydroabietylamine derivatives as potent inhibitors of acetylcholinesterase. *Bioorg. Chem.* **2017,** *74*, 145-157.

Highlights

* Dehydroabietylamine shows a broad spectrum of biological activities
* “Simple” amides, C-ring-modified and biotinylated amides were prepared
* These compounds were screened in SRB assays for cytotoxic activity
* Several compounds showed high cytotoxicity and good selectivity for human tumor cells