Synthesis and antimicrobial activity of *N*-analogous corollosporines

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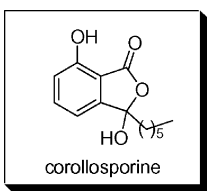
Corollosporine is an antimicrobial metabolite, which was isolated from the marine fungus *Corollospora maritima*. Owing to its basic 4-hydroxyphthalic acid anhydride structure, it has become an attractive target for a structure/activity relationship modelling of derived compounds with potential antibiotic activity. In this regard we report on the straightforward synthesis of hetero analogous corollosporines, which were easily prepared by a three-step reaction sequence, taking advantage of a novel multi-component reaction (AAD-reaction) and a subsequent aromatization/Grignard reaction protocol. Furthermore, the obtained products were tested in several biological assays to evaluate their antimicrobial activity.

Introduction

The synthesis and biological evaluation of potentially new antibiotic agents is undoubtedly an important topic in current chemical and medicinal research. Beside the design of more effective antibiotics with a lower range of unwanted side effects, this demand is especially forced by the ongoing multi-resistance of several bacterial strains against commonly used pharmaceuticals.

As a major approach, the discovery of suitable new leads is governed by the isolation of active compounds from biological resources. In a recent example, Lindequist and co-workers isolated the novel antibacterial agent corollosporine (Scheme 1) from the marine fungus *Corollospora maritima*, which was located on driftwood in the North Sea close to the island Helgoland (Germany).[1] Corollosporine [(±)-3-hexyl-3,7-dihydroxy-1(3*H*)-isobenzofuran-1-one] is a typical member of antibiotics with phthalide activity against *Staphylococcus aureus* and *Bacillus subtilis*. Owing to the rather low isolated yield of corollosporine from the culture filtrate of *Corollospora maritima*, Mori and Ohzeki[2] developed different syntheses for the desired intermediate with acceptable overall yields.



Scheme 1 Structure of corollosporine.

As a consequence of the promising activity of corollosporine in antibacterial assays, we became interested in the synthesis of hetero (nitrogen) analogous compounds to study their antibiotic behaviour. For this purpose a short synthesis protocol was developed, taking advantage of a novel multicomponent reaction (MCR), which was recently discovered by some of us.[7]

In general, multicomponent reactions offer significant advantages over stepwise procedures with respect to environmental sustainability and atom efficiency.[3] Therefore, a part of us has been interested in the development of transition metal-catalyzed three- and four-component coupling reactions, such as the hydroaminomethylation of olefins[4] and the amidocarbonylation of aldehydes.[5] With respect to the latter work a three-component reaction was discovered,[6] in which **a**mides react with **a**ldehydes and **d**ienophiles (AAD-reaction) to give a large variety of 1-acylamino-2-cyclohexene derivatives in unprecedented efficiency. Based on a simple condensation reaction of amides and aldehydes, the underlying mechanism takes advantage of the formation of 1-(*N*-acylamino)-1,3-butadienes as key intermediates, which are subsequently converted by a Diels–Alder reaction with electron-deficient dienophiles to the corresponding products (Scheme 2).[7] By comparison with their purely 'carbonic' counterparts, the resulting heteroatom-substituted dienes not only exhibit higher reactivity in most cases but also give functionalized products which are useful for further synthetic manipulations.

In addition to our work, several other groups have also demonstrated the versatility of (isolated) functionalized 1,3-butadienes for Diels–Alder chemistry.[8] In this regard, prominent examples include the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine[11] and tabersonine.[12] Furthermore, we have additionally extended the synthetic scope of the AAD-reaction by a selective amide replacement through suitable electrophilic or nucleophilic reagents like isocyanates (IAD-reaction),[13] orthoesters (ALAD-reaction) and anhydrides (ANAD-reaction).[14] Covering this range of substrates, we have actually synthesized more than 200 carbo- and hetero-cyclic compounds including highly substituted bicyclo[2.2.2]-oct-2-ene-,[15] enantiomerically pure cyclohexenol-,[14] and cyclo-hexenylamino-,[7e] phthalic acid-,[7d] phenanthridone-,[16] lactam-[17] as well as aniline-derivatives.[18] Taking account of the basic principle of the latter work, we also prepared a range of novel luminoles.[19] Here, an efficient three-step synthesis was elaborated, comprising first the AAD-reaction

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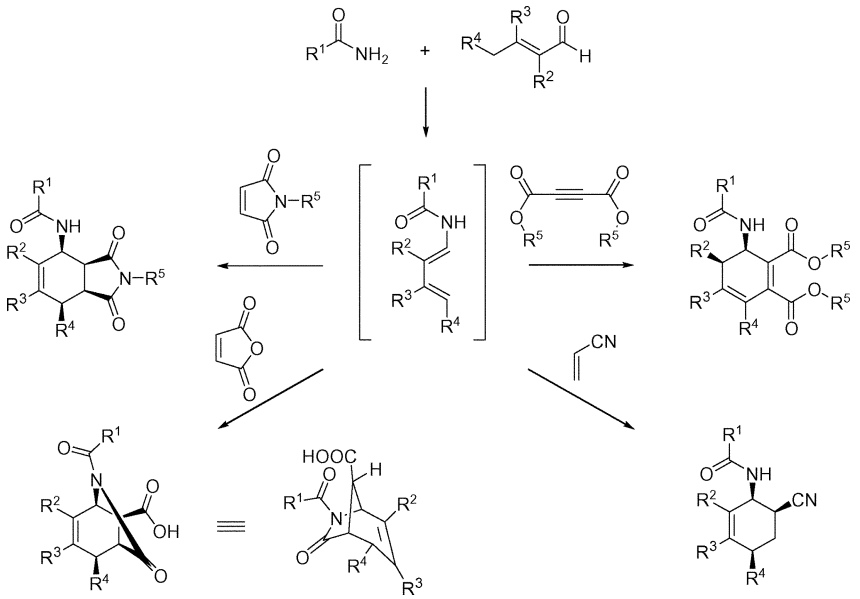
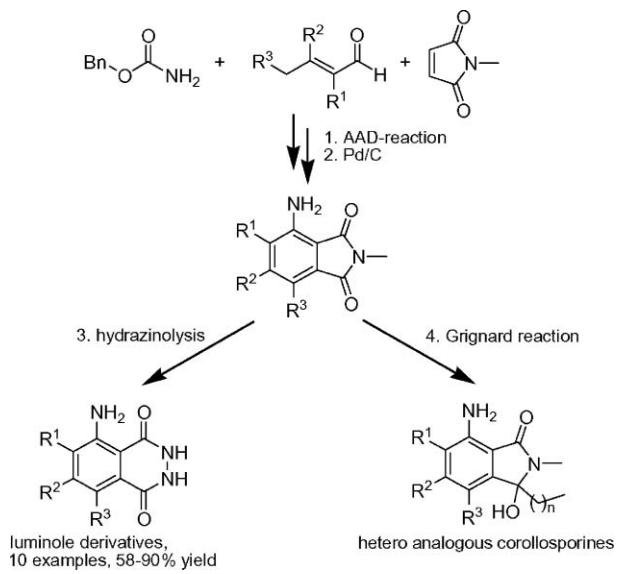


Scheme 2 Schematic representation of the AAD-reaction.

of benzyl carbamate, various aldehydes and *N*-methyl maleimide (Scheme 3, step 1). Next, the obtained products were oxidized by Pd/C to give the corresponding 4-aminophthalimides (Scheme 3, step 2). Finally, a hydrazinolysis reaction afforded the desired luminoles (Scheme 3, step 3) in good yield.



Scheme 3 Use of 4-aminophthalimides as key substrates for the synthesis of luminoles and corollosporine analogues.

Obviously, there exists a structural analogy of 4-aminophthalimides with 4-hydroxyphthalic anhydride, the precursor to corollosporine. As a result of that, we report here on the synthesis of hetero analogous corollosporine derivatives, which are easily accessible by the conversion of 4-aminophthalimides or related structures with Grignard reagents (Scheme 3, step 4). With respect to the native structure of corollosporine, the obtained compounds are somewhat bioisosteric, differing only in the substitution of oxygen – towards nitrogen atoms. Additionally, antimicrobial and antifungal assays were accomplished to determine the potential antibiotic activity of all new derivatives.

Results and discussion

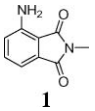
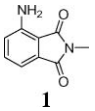
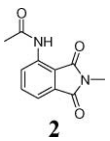
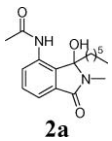
In a first set of experiments, we investigated the conversion of previously prepared *N*-methyl-4-aminophthalimide (**1**; Table 1) with different equivalents of hexylmagnesium bromide as a model reaction.[20] Thereby, the best conversion was observed using an excess of 3 equiv. hexylmagnesium bromide (Table 1, entry 3). In this case, the desired product (**1a**) was isolated in 62% yield. Interestingly, the initial application of 1 or 2 equiv. of Grignard reagent was accompanied with decreased product yields of **1a** of less than 1% and 33%, respectively (Table 1, entries 1, 2).

We explain these results by the selective formation of a magnesium complex, which is formed initially in the presence of 2 equiv. of Grignard reagent. Owing to the lower electrophilic character of the vinylogous amide unit, the nucleophilic attack of the third equivalent of hexylmagnesium bromide is favoured for the opposite carbonyl group. In agreement with this proposal, a further conversion of **1a** with hexylmagnesium bromide afforded no double alkylated product (Table 1, entry 5), and the starting material was isolated back. Not surprisingly, an increase of reaction temperature to 25 °C resulted in lower selectivity of the desired product **1a** (Table 1, entry 4). Finally, we examined the reactivity and regioselectivity of the Grignard reaction of *N*-methyl-4-acetamidophthalimide (**2**; Table 1, entry 6). Obviously, the corresponding magnesium complex cannot be formed in this case. Therefore, the regioselectivity even changed in favour of the unwanted isomer **2a** (Table 1, entry 6; **2a**/**2b** = 2 : 1).

For both the *N*-analogous corollosporine **1a** and the 'wrong' regioisomer **2a** we were able to obtain suitable crystals for X-ray analysis. In Scheme 4 the molecular structures obtained are shown.[21]

Using the optimized set of conditions for the model substrate **1a**, we prepared 22 differently substituted hetero analogous

Table 1 Orientation and selectivity of the Grignard reaction of *N*-methyl-4-aminophthalimide (**1**) with hexylmagnesium bromide[a]

Entry	Educt	Grignard reagent (equiv.)	Conversion (%)	*T*/°C	Yield[b] (%)		Selectivity *syn*/*anti*
1	 **1**	1	3	0	 **1a**	<1	—
2	 **1**	2	70	0	 **1a**	33	1 : 6[c]
3	 **1**	3	100	0	 **1a**	62	1 : 6[c]
4	 **1**	3	100	25	 **1a**	50	1 : 4[c]
5	 **1a**	3	—	0	 **1a**	80[e]	—
6	 **2**	2	100	0	 **2a**	67	2 : 1[d]

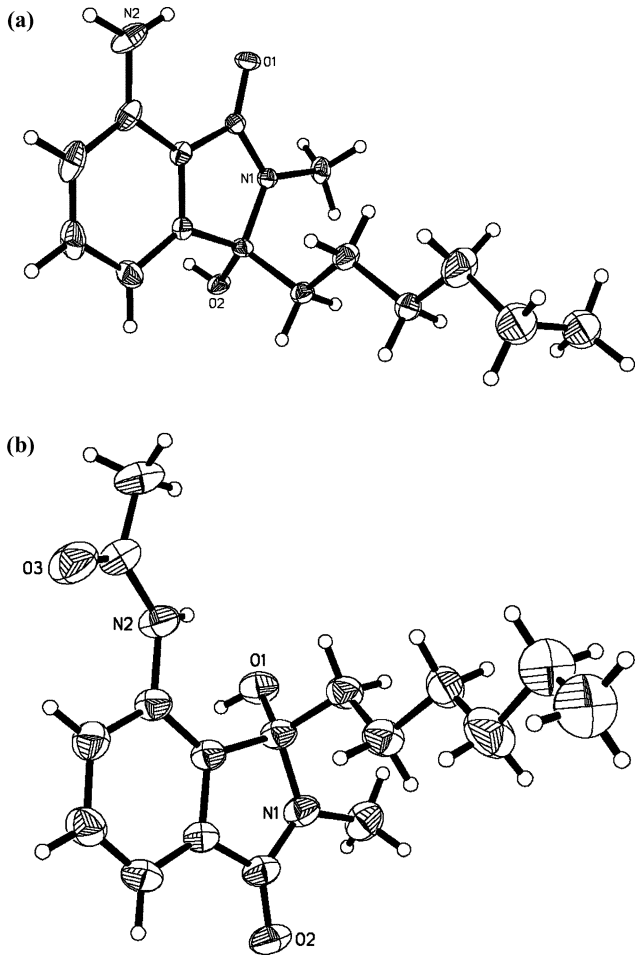
[a] Reaction conditions: 0.5 mmol educt was dissolved in 5 mL THF and Grignard reagent was slowly added. The solution was warmed up within 1 h and quenched with 1 mL water. The solvent was removed and the residue was extracted with EtOAc (3 times). Then the extract was purified by chromatography. [b] Isolated yield. [c] Selectivity determined by ^{1}H NMR. [d] Selectivity determined by yield. [e] Recovered yield.

corollosporines with moderate to good yield (11–73%; Table 2, compounds **1a**–**18b**). To evaluate their antibiotic activity, all compounds were employed within agar diffusion assays to test their antibiotic activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*, respectively (Table 2). To our delight, the *N*-analogous corollosporine (**1a**) was found to be as active as the natural corollosporine against *Staphylococcus aureus* (inhibition zone: 10 mm; Table 2, entry 1) (data not shown). More surprisingly, the corresponding isomer (**1b**) revealed the same activity as well (inhibition zone: 10 mm; Table 2, entry 2).

Next, we examined the influence of different alkyl and aromatic moieties attached to the aromatic scaffold. With the exception of the dimethylated derivative (**3**), which also revealed activity against *Staphylococcus aureus* (inhibition zone: 10 mm; Table 2, entry 3), a diethyl-, diisopropyl-, or dibenzyl-substitution was found to be ineffective (Table 2, entries 4–6). This may be explained by a lower cell permeability of the test compounds or the lack of binding to target enzymes.

Our further examinations concentrated on the replacement of the amino group towards other substituents in diverse aromatic positions. A monochlorination of the aromatic scaffold led to compounds with stronger activity against the gram positive *Staphylococcus aureus*. For instance, the 7-chloro-substituted corollosporine derivate (**8a**) revealed good activity against *S. aureus* (inhibition zone: 13 mm; Table 2, entry 8), whereas the corresponding isomer (**8b**) displayed one of the highest activities (inhibition zone: 14 mm; Table 2, entry 9). In contrast to these results, a monochlorination in 5- or 6-position afforded compounds (**9b**,**a**, respectively) with a comparable activity against *Staphylococcus aureus* (inhibition zones: 13–14 mm; Table 2, entries 10–11), but no antimicrobial effect was found comprising strains of *Bacillus subtilis* and *Escherichia coli*. In another example, the dichlorinated compound (**10**) was found to be active against *Staphylococcus aureus* and *Bacillus subtilis*. Additionally, we tested the bioactivity of fluorinated corollosporine derivatives. Here, an inseparable mixture of isomers (**11a**,**b**) showed only weak antimicrobial activity. Moreover, the antimicrobial evaluation of the tetrafluorinated derivative (**12**) revealed no activity against all employed strains (Table 2, entry 14).

In addition, we examined the influence of different alkyl chains and aromatic substituents attached to the tertiary hydroxy group. It is important to note that neither chain-shortened, nor chain-elongated derivatives displayed any activity against the tested bacterial strains (Table 2, entries 15–19). Furthermore, both isomers with attached *p*-tolyl substituents were found to be ineffective as well (Table 2, entries 20, 21). Consistently, the natural



Scheme 4 Molecular structure of: (a) **1a**, and (b) **2a** (for both, the thermal ellipsoids correspond to the 30% probability level).

3-hexyl-3-hydroxy motif seems to have an essential influence on the antimicrobial activity.

In a second approach we investigated the minimal inhibitory concentration (MIC) of two chlorinated compounds. Compounds **8b** and **9b** showed activity according to the screening results with MIC values of 83.5 and 28.5 μg mL^{-1} against *Bacillus subtilis*. These experiments show that the antibacterial activity is concentrated on gram positive bacteria.

In summary, we have developed an easy and straightforward synthesis route to a variety of aza analogous corollosporines. Advantageously, the presence of the 4-amino group results in high regioselectivity of the final Grignard reaction.

Some of the obtained products revealed antibiotic activity, which is comparable to the natural product corollosporine. Here, the presence of a hexyl side chain represents an important feature for antimicrobial activity. Substitution in the aromatic moiety with chlorine results in an increase of the activity.

Experimental

Antimicrobial testing

Antimicrobial screening. The bacterial cultures were obtained from the ATCC.

Assay for antimicrobial activity: a modified disc diffusion method was used to determine the antimicrobial activity. A sterile filter disc of 6 mm diameter (B & D research) was impregnated with the test compounds. The paper disc was placed on the agar plate seeded with respective micro organisms. The plates were kept in the refrigerator at 4 °C for 4 h. The plates were then turned over to incubate overnight at 37 °C in an inverted position. At the end of the incubation period the clear zones of inhibition around the paper disc were measured. Negative control experiments were performed by using paper discs loaded with an equivalent volume of solvent, and positive control experiments were performed by the use of an equivalent amount of Ampicillin (in the case of *S. aureus* and *B. subtilis*) or Gentamicin (in the case of *E. coli*). The amount of the compounds tested during the experiments was 1000 nmol per paper disc. All experiments were done in triplicate.

Determination of minimal inhibitory concentrations (MICs) of compounds by dilution method

Sample preparation. The compound (1 mg) was dissolved in 1 mL of DMSO and serially diluted with nutrient agar medium to obtain the final concentrations.

Culture of microorganisms. A column of 3 mL sterile broth was inoculated with about a pinhead size of respective bacteria and 100 μL of the bacterial suspension was further inoculated into 10 mL of sterile broth. The final inoculated bacterial suspension was placed on an orbital shaker (175 rpm) and incubated overnight at 25 °C. For the test, the bacterial suspension was diluted in the ratio of 1 : 100.

Antibacterial assay. The minimal inhibitory concentration (MIC) was measured by the 10-fold serial broth dilution method. The assay was carried out in a 96-well tray. The wells of the first row of the tray (A1 to H1) were filled with 150 μL of diluted test substances in duplicate. From the second to eleventh row (A2, H2 to A11, H11) the wells were first filled with 100 μL of PBS (phosphate-buffered saline). Then 10 μL of the test substance from the first row was pipetted out in a stepwise manner from left to right up to the eleventh row. Finally, 10 μL of the diluted substance was discarded from the eleventh row. Each and every well from the row 1–11 was finally filled with 100 μL of diluted bacterial suspension.

The wells A12–D12 were filled with 100 μL PBS and 100 μL bacterial suspension without test substance as control wells. The wells E12–G12 were filled with 100 μL PBS and 100 μL bacterial suspension without the test substance as control wells. The well H12 was kept empty for photometric blank. The plate was shaken carefully and then incubated for 16 h at 35 °C. After incubation, the absorbance was measured at 620 nm in a plate reader (Anthos HT-II). The MIC corresponds to the lowest concentration of the test compound that still produces bacterial growth inhibition. It was determined by spectrophotometry by measuring the turbidity of the inoculated liquid broth in the presence and absence of the test compound. The highest concentration of the test substance for the assay was 5000 μg mL^{-1} and lowest concentration was 0.85 μg mL^{-1}.

Chemical synthesis

THF was distilled from Na; furthermore, Grignard solutions were bought from Aldrich. *N*-Methyl-4-aminophthalimide derivatives

Table 2 Results of the antimicrobial screening[a]

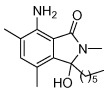
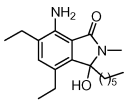
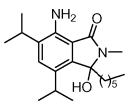
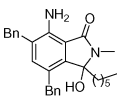
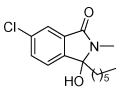
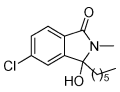
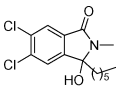
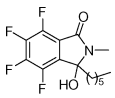
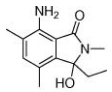
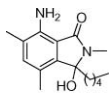
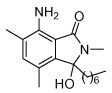
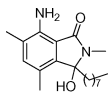
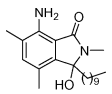
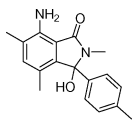
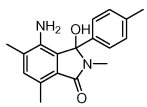
Entry	Structure	Yield (%)	*Bacillus subtilis* ATCC 6051	*Staphylococcus aureus* ATCC 6538	*Escherichia coli* ATCC 11229
1	 **1a**	62	r	10	r
2	 **1b**	11	r	10	r
3	 **3**	38	r	10	r
4	 **4**	35	r	r	r
5	 **5**	34	r	r	r
6	 **6**	45	r	r	r
7	 **7**	70	8	11	11
8	 **8a**	27	r	13	10
9	 **8b**	60	7	14	12
10	 **9a**	34	r	14	r
11	 **9b**	48	r	13	r
12	 **10**	44	12	8	r

Table 2 (*Contd.*)

Entry	Structure	Yield (%)	*Bacillus subtilis* ATCC 6051	*Staphylococcus aureus* ATCC 6538	*Escherichia coli* ATCC 11229
13	 **11a**  **11b**	60 (1 : 2)	8	r	12
14	 **12**	73	r	r	r
15	 **13**	73	r	r	r
16	 **14**	58	r	r	r
17	 **15**	20	r	r	r
18	 **16**	30	r	r	r
19	 **17**	11	r	r	r
20	 **18a**	29	r	r	r
21	 **18b**	22	r	r	r
	Ampicillin	—	17	15	n.t.
	Gentamicin	—	n.t.	n.t.	12

[a] Inhibition zones are stated in diameter (mm) without the diameter of the paper disc (6 mm); r = resistant; n.t. = not tested.

were prepared from the two-step MCR/oxidation sequence.[18] In the case of **9a**, **9b**, **10**, **11**, **12** the *N*-methylphthalimide precursors were synthesized from the corresponding phthalic acids,[22] which are commercially available from Aldrich. The precursors of **8a**, **8b** were synthesized by a Sandmeyer reaction from 4-aminophthalimide.[23]

Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Melting points were

recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra were recorded as KBr pellets on a Nicolet Magna 550. Mass spectra were obtained on AMD 402/3 of AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with QNP probe head (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C.

General procedure for the synthesis of the *N*-analogous corollosporines

N-Methylphthalimide (0.5 mmol) was dissolved under an Ar atmosphere in 10 mL absolute THF and cooled to 0 °C. In the case of 4-aminophthalimide derivatives a three-fold excess of 2 M hexylmagnesium bromide (1.5 mmol) was slowly added. The solution becomes deep red and was warmed up in 2–3 h to ambient temperature. During this time the color of the solution changed to green/yellow. In the case of halide-containing phthalimides an equimolar amount of Grignard solution was used. After adding 1 mL water the solution became colorless and the solvent was removed under high vacuum. Water was added to the residue and extracted three times with ethyl acetate. The organic phase was dried with Na_2SO_4. After removing the solvent the remaining solid was purified by chromatography with heptane–EtOAc and crystallized from toluene if necessary.

7-Amino-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (1a)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.11. Yield: 62%. Mp: 129 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.19 (dd, J = 7.2 and 7.9 Hz, 1H, *m*-C*H*-Ar), 6.61 (d, J = 7.1 Hz, 1H, C*H*-Ar), 6.57 (d, J = 8.1 Hz, 1H, C*H*-Ar), 6.03 (s, 1H, O*H*), 5.99 (s, 2H, NH_2), 2.72 (s, 3H, NCH_3), 1.88 (m, 2H, COHCH_2), 1.20–1.05 (m, 6H, (CH_2)$_3$CH$_2$Me), 0.78 (t, J = 6.8 Hz, 3H, (CH$_2$)$_5$*Me*), 0.84–0.73 (m, 1H, CH_2Me), 0.64–0.51 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.0 (*C*O); 148.6, 145.8 and 112.4 (3 *C*); 132.7, 114.2 and 108.7 (3 *C*H); 89.3 (*C*OH); 35.7, 31.0, 28.4, 23.0 and 21.9 (5 *C*H$_2$); 22.4 and 13.8 (2 *C*H$_3$). **IR** (KBr) cm^{-1}: $1/\lambda$ = 3470 (s), 3349 (s), 3255 (m), 2936 (s), 2856 (m), 1664 (s), 1621 (s), 1607 (m), 1596 (m), 1482 (s), 1467 (m), 1433 (m), 1395 (m), 1361 (m), 1327 (m), 1228 (w), 1203 (w), 1127 (w), 1085 (m), 1034 (m), 1016 (m), 959 (w), 807 (m), 773 (m), 705 (m), 584 (w), 542 (w). **MS** (EI, 70 eV): *m*/*z* (%) = 262 (9) [M]$^+$, 244 (38) [M − H_2O]$^+$, 187 (76), 177 (100), 162 (15), 118 (10), 91 (9), no other peaks >5%. **HR MS** (EI): calc. for $C_{15}H_{22}N_2O_2$: 262.16812; found: 262.16722 [M]$^+$.

4-Amino-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (1b)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.08. Yield: 11%. Mp: 92–95 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.19 (dd, J = 7.7 and 7.5 Hz, 1H, *m*-C*H*-Ar), 6.80 (d, J = 7.5 Hz, 1H, C*H*-Ar), 6.77 (d, J = 7.7 Hz, 1H, C*H*-Ar), 6.13 (s, 1H, O*H*), 5.13 (s, 2H, NH_2), 2.75 (s, 3H, NCH_3), 2.32–2.21 (m, 1H, COHCH_2), 1.92–1.81 (m, 1H, COHCH_2), 1.19–0.96 (m, 6H, (CH_2)$_3$CH$_2$Me), 0.76 (t, J = 6.8 Hz, 3H, (CH$_2$)$_5$*C*H$_3$), 0.71–0.56 (m, 1H, CH_2CH$_3$), 0.51–0.36 (m, 1H, CH_2 CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 166.4 (*C*O); 143.2, 132.6 and 128.7 (3 *C*); 129.6, 117.8 and 109.7 (3 *C*H); 89.7 (*C*OH); 32.2, 31.0, 28.2, 23.2 and 21.9 (5 *C*H$_2$); 22.5 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): *m*/*z* (%) = 262 (9) [M]$^+$, 244 (38) [M − H_2O]$^+$, 187 (76), 177 (100), 162 (15), 118 (10), 91 (9) no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3450 (s), 3347 (s), 3228 (m), 2956 (m), 2924 (s), 2856 (m), 1664 (s), 1634 (m), 1609 (m), 1490 (s), 1469 (m), 1432 (s), 1398 (m), 1353 (s), 1313 (m), 1085 (m), 1044 (m), 968 (w), 863 (w), 816 (w), 762 (m), 697 (w), 584 (w), 535 (w). **HR MS** (EI): calc. for $C_{15}H_{22}N_2O_2$: 262.16812; found: 262.16722 [M]$^+$.

N-(2-Methyl-1,3-dioxoisoindolin-4-yl)acetamide (2)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.14. Yield: 86%. Mp: 149 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.64 (s, 1H, NH), 8.39 (d, J = 8.37 Hz, 1H, CH arom.), 7.72 (dd, J = 7.2 and 8.4 Hz, 1H, CH arom.), 7.50 (d, J = 7.2 Hz, 1H, CH arom.), 2.99 (s, 3H, NMe), 2.18 (s, 3H, Ac). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 169.1, 168.5 and 167.4 (3 *C*O); 136.0, 131.9 and 117.2 (3 *C*); 135.3, 125.3 and 117.7 (3 *C*H); 24.2 and 23.5 (2 *C*H$_3$). **MS** (EI, 70 eV): *m*/*z* (%) = 218 (18) [M]$^+$, 176 (100) [M − acetyl + 1] $^+$, 132 (11), 119 (10), 91 (7), 69 (7), no other peaks of >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3345 (m), 3084 (w), 2950 (w), 1761 (s), 1698 (s), 1621 (s), 1530 (s), 1478 (s), 1444 (s), 1419 (s), 1366 (m), 1294 (m), 1258 (m), 1238 (m), 1162 (w), 1036 (w), 1004 (m), 825 (m), 744 (s), 691 (m), 621 (w), 594 (w), 532 (m). **HR MS** (EI): calc. for $C_{11}H_{10}N_2O_3$: 218.0686; found: 218.0679 [M$^+$].

N-(3-Hexyl-3-hydroxy-2-methyl-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl)acetamide (2a)

R_f (SiO_2, *n*-heptane–EtOAc = 1 : 2): 0.13. Yield: 67%. Mp: 118–120 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.84 (s, 1H, N*H*), 7.88 (d, J = 7.5 Hz, 1H, C*H*-Ar), 7.49-7.37 (m, 2H, C*H*-Ar), 6.58 (s, 1H, O*H*), 2.80 (s, 3H, NCH_3), 2.13 (s, 3H, CH_3CO), 2.26–2.09 (m, 1H, COHCH_2), 2.03–1.92 (m, 1H, COHCH_2), 1.18–0.98 (m, 6H, (CH_2)$_3$CH$_2$Me), 0.75 (t, J = 6.9 Hz, 3H, (CH$_2$)$_5$CH_3), 0.71–0.58 (m, 1H, CH_2Me), 0.45–0.31 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.8 and 165.4 (2 *C*O); 135.3, 133.1 and 132.6 (3 *C*); 129.6, 127.0 and 118.3 (3 *C*H); 89.7 (*C*OH); 33.3, 30.9, 28.0, 23.0 and 21.8 (5 *C*H$_2$); 23.7, 22.7 and 13.8 (3 *C*H$_3$). **MS** (EI, 70 eV): *m*/*z* (%) = 304 (0.1) [M]$^+$, 219 (49) [M − hexyl]$^+$, 229 (1) [M − NHAc]$^+$, 219 (49), 187 (7), 187 (13), 177 (100) [M − hexyl − acetyl]$^+$, 43 (25), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3407 (m), 3259 (m), 2935 (m), 2855 (w), 1704 (s), 1686 (s), 1608 (s), 1526 (s), 1486 (s), 1420 (s), 1396 (m), 1365 (m), 1287 (s), 1236 (w), 1086 (w), 1043 (w), 760 (w), 635 (w), 577 (w), 541 (w), 479 (w). **HR MS** (EI): calc. for $C_{17}H_{24}N_2O_3$: 304.17868; found: 304.17455 [M]$^+$.

7-Amino-3-hexyl-3-hydroxy-2,4,6-trimethyl-2,3-dihydroisoindol-1-one (3)

R_f (SiO_2, *n*-heptane–EtOAc = 1 : 1): 0.17. Yield: 38%, crystallized from toluene. Mp: 101 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.88 (s, 1H, C*H*), 5.98 (s, 1H, O*H*), 5.68 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.23 (s, 3H, =CCH_3), 2.13–1.99 (m, 1H, CH_2COH), 2.05 (s, 3H, =CCH_3), 1.95–1.84 (m, 1H, CH_2COH), 1.13 (m, 6H, 3 CH_2), 0.77 (t, J = 6.9 Hz, 3H, CH$_2$CH_3), 0.73–0.60 (m, 1H, CH_2CH$_3$), 0.57–0.41 (m, 1H, CH_2CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 142.2, 142.1, 122.3, 119.0 and 112.8 (5 *C*); 135.6 (*C*H-Ar); 89.8 (*C*OH); 33.7, 31.0, 28.3, 23.1 and 21.9 (5 *C*H$_2$); 22.2 (N*C*H$_3$); 16.3 and 16.2 (2 =C*C*H$_3$); 13.8 (CH$_2$*C*H$_3$). **MS** (EI, 70 eV): *m*/*z* (%) = 290 (14) [M]$^+$, 172 (26)

$[M - H_2O]^+$, 215 (74), 205 (100), 189 (11), 146 (8), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3469$ (m), 3363 (s), 3294 (m), 2925 (m), 2859 (m), 1658 (s), 1596 (m), 1498 (m), 1434 (m), 1356 (w), 1309 (w), 1267 (w), 1078 (m), 1038 (w), 901 (w), 804 (w), 729 (w), 558 (w). **HR MS** (EI): calc. for $C_{17}H_{26}N_2O_2$: 290.19918; found: 290.19943 $[M]^+$.

7-Amino-4,6-diethyl-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (4)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.20. Yield: 35%, crystallized from toluene. Mp: 154 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.94 (s, 1H, C*H*), 6.01 (s, 1H, O*H*), 5.78 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.68–2.57 (m, 2H, =CCH_2), 2.53–2.40 (m, 2H, =CCH_2), 2.00–1.90 (m, 2H, COHCH_2), 1.20–1.02 (m, 12H, 2 =CH$_2$CH_3 and (CH_2)$_3$CH$_2$Me), 0.77 (t, J = 6.7 Hz, 3H, (CH$_2$)$_5$CH_3), 0.73–0.61 (m, 1H, (CH$_2$)$_4$CH_2Me), 0.56–0.43 (m, 1H, (CH$_2$)$_4$CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 141.7, 141.6, 128.4, 125.8 and 112.6 (5 *C*); 132.2 (*C*H-Ar); 89.8 (*C*OH); 34.9 (COH*C*H$_2$); 31.0, 28.3 and 21.9 ((*C*H$_2$)$_3$Me), 23.2 ((CH$_2$)$_4$*C*H$_2$Me); 22.7 and 22.5 (2 =C*C*H$_2$Me); 22.1 (N*C*H$_3$); 15.9 and 13.4 (2 =CH$_2$*C*H$_3$); 13.8 ((CH$_2$)$_5$*C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 318 (12) $[M]^+$, 300 (3) $[M - H_2O]^+$, 243 (6), 233 (100), 217 (6), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3467$ (s), 3364 (s), 3265 (s), 2964 (s), 2931 (s), 2870 (m), 1658 (s), 1628 (m), 1594 (s), 1490 (m), 1438 (s), 1417 (m), 1398 (m), 1367 (m), 1308 (m), 1264 (w), 1228 (w), 1082 (m), 1055 (m), 1031 (w), 897 (w), 844 (w), 808 (w), 686 (w). **Anal. Calc.** for $C_{19}H_{30}N_2O_2$: C 71.66, H 9.50, N 8.80; found: C 72.50, H 9.50, N 8.92%.

7-Amino-3-hexyl-3-hydroxy-2-methyl-4,6-diisopropyl-2,3-dihydroisoindol-1-one (5)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.11. Yield 34%, crystallized from toluene. Mp: 159–162 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.11 (s, 1H, C*H*), 6.04 (s, 1H, O*H*), 5.86 (s, 2H, NH_2), 3.41–3.28 (m, 1H, C*H*Me$_2$), 3.05–2.95 (m, 1H, C*H*Me$_2$), 2.71 (s, 3H, NCH_3), 2.01–2.00 (m, 2H, COHCH_2), 1.22–1.03 (m, 18H, 2 CH(CH_3)$_2$ and (CH_2)$_3$CH$_2$Me), 0.77 (t, J = 6.8 Hz, 3H, (CH$_2$)$_5$CH_3), 0.73–0.62 (m, 1H, CH_2Me), 0.56–0.43 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 141.2, 140.5, 128.4, 133.1 and 131.1 (5 *C*); 125.7 (*C*H-Ar); 89.7 (*C*OH); 35.4 (COH*C*H$_2$); 31.0, 28.3 and 22.0 ((*C*H$_2$)$_3$CH$_2$Me); 23.2 ((CH$_2$)$_3$*C*H$_2$Me); 26.8 and 25.9 (*C*HMe$_2$); 24.1 and 22.7 (2 CH(*C*H$_3$)$_2$); 22.2 (N*C*H$_3$); 13.8 ((*C*H$_2$)$_5$*C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 346 (30) $[M]^+$, 328 (6) $[M - H_2O]^+$, 271 (8), 261 (100) $[M -$ hexyl$]^+$, 245 (14), 231 (11), 43 (12), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3471$ (s), 3371 (s), 3288 (m), 2962 (s), 2932 (m), 2870 (m), 1655 (s), 1629 (w), 1593 (m), 1489 (m), 1439 (m), 1415 (w), 1400 (w), 1363 (w), 1352 (w), 1248 (m), 1080 (m), 1037 (w), 1009 (w), 900 (w), 810 (w), 793 (w), 636 (w), 577 (w), 519 (w). **HR MS** (EI): calc. for $C_{21}H_{34}N_2O_2$: 346.26202; found: 346.26089 $[M]^+$.

7-Amino-4,6-dibenzyl-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (6)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.11. Yield: 45%, crystallized from toluene. Mp: 131–134 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.35–7.04 (m, 10H, 2 Ph), 6.87 (s, 1H, C*H*-Ar), 6.17 (s, 1H, O*H*), 5.91 (s, 2H, NH_2), 4.12 (d, J = 15.9 Hz, 1H, PhCH_2), 3.94 (d, J = 15.9 Hz, 1H, PhCH_2), 3.90–3.76 (m, 2H PhCH_2), 2.70 (s, 3H, NCH_3), 1.92–1.68 (m, 2H, COHCH_2), 1.12–0.98 (m, 2H, (CH_2)$_4$Me), 1.12–0.98 (m, 2H (CH_2)$_4$Me), 0.98 (t, J = 7.2 Hz, 3H, (CH$_2$)$_5$CH_3), 0.66–0.50 (m, 2H, (CH_2)$_4$Me), 0.39–0.22 (m, 2H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.0 (*C*O); 143.2, 142.4, 141.4, 140.0, 125.7, 121.8 and 113.1 (7 *C*); 136.3 (*C*H-Ar); 128.6 (2 *C*H-Ar); 128.4 (4 *C*H-Ar); 128.1 (2 *C*H-Ar); 125.9 and 125.6 (2 *C*H-Ar); 89.8 (*C*OH); 35.2, 35.0, 35.0, 31.0, 28.0, 23.2 and 22.0 (7 *C*H$_2$); 22.2 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 442 (36) $[M]^+$, 424 (57) $[M - H_2O]^+$, 367 (33), 357 (61), 353 (23), 341 (13), 297 (100), 261(5), 91 (19), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3456$ (s), 3362 (s), 3257 (m), 3062 (w), 3028 (w), 2948 (m), 2923 (s), 2857 (m), 1664 (s), 1629 (m), 1594 (s), 1493 (s), 1433 (s), 1394 (m), 1358 (m), 1261 (w), 1128 (w), 1107 (w), 1081 (m), 1045 (m), 1017 (m), 948 (w), 929 (w), 891 (w), 863 (w), 814 (w), 729 (m), 698 (s), 644 (w), 602 (w). **HR MS** (EI): calc. for $C_{29}H_{34}N_2O_2$: 442.2615; found: 442.26062 $[M]^+$.

3-Hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (7)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.08. Yield: 70%. Mp: 80 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.66–7.53 (m, 3H, C*H*-Ar), 7.51–7.44 (m, 1H, C*H*-Ar), 6.24 (s, 1H, O*H*), 2.80 (s, 3H, NCH_3), 2.08–1.88 (m, 2H, COHCH_2), 1.20–0.99 (m, 6H, CH$_2$(CH_2)$_3$Me), 0.76 (t, J = 6.9 Hz, 3H, CH$_2$CH_3), 0.82–0.70 (m, 1H, CH_2Me), 0.53–0.41 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 165.8 (*C*O); 147.5 and 131.6 (2 *C*); 131.9, 129.0, 122.0 and 122.0 (4 *C*H); 89.7 (*C*OH); 35.4, 31.0, 28.3, 23.0 and 21.9 (5 *C*H$_2$); 22.8 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 247 (0.1) $[M]^+$, 229 (3) $[M - H_2O]^+$, 172 (19), 162 (100) $[M - H_2O]^+$, 133 (21), 105 (10), 91 (5), 77 (18), 41 (11), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3282$ (vs), 3058 (m), 2929 (s), 2867 (s), 1687 (s), 1617 (m), 1480 (m), 1569 (s), 1429 (s), 1397 (s), 1337 (w), 1284 (m), 1242 (w), 1196 (w), 1121 (m), 1090 (s), 1059 (s), 1025 (m), 1013 (m), 987 (w), 954 (w), 925 (w), 834 (w), 770 (s), 702 (s), 671 (m), 622 (m), 551 (m), 499 (w), 470 (w). **HR MS** (ESI): calc. for $C_{15}H_{22}NO_2$: 248.16505; found: 248.16497 $[M + 1]^+$.

7-Chloro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (8a)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.25. Yield: 27%, oily product. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.59 (t, J = 7.7 Hz, 1H, 5-C*H*-Ar), 7.54 (dd, J = 7.53 and 1.1 Hz, 1H, C*H*-Ar), 7.47 (dd, J = 7.7 and 1.1 Hz, 1H, C*H*-Ar), 6.30 (s, 1H, O*H*), 2.79 (s, 3H, NCH_3), 2.08–1.91 (m, 2H, COHCH_2), 1.20–1.01 (m, 6H, (CH_2)$_3$CH$_2$Me), 0.76 (t, J = 6.8 Hz, 3H, (CH$_2$)$_5$CH_3), 0.83–0.69 (m, 1H, CH_2Me), 0.56–0.41 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 163.5 (*C*O); 150.3, 128.7 and 127.1 (3 *C*); 133.4, 130.4 and 121.0 (3 *C*H); 88.6 (*C*OH); 35.2, 30.9, 28.2, 22.9 and 21.9 (5 *C*H$_2$); 23.0 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 263 (1) $[M - H_2O]^+$, 206 (6), 198 (34), 196 (100) $[M -$ hexyl$]^+$, 167 (5), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda = 3359$ (s), 2978 (s), 2859 (s), 1700 (s), 1606 (m), 1457 (s), 1420 (s), 1395 (s), 1250 (w), 1196 (w), 1172 (w), 1147 (w), 1091 (m), 1058 (m), 1021 (s), 943 (w), 833 (m), 806 (s), 781 (m), 699 (m), 675 (w), 639 (w), 608 (w), 566 (m), 497 (w). **HR MS** (ESI): calc. for $C_{15}H_{21}ClNO_2$: 282.12607; found: 282.12497 $[M + 1]^+$.

4-Chloro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (8b)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.15. Yield: 60%. Mp: 76–77 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.76 (dd, J = 7.7 and 0.9 Hz, 1H, C*H*-Ar), 7.60 (dd, J = 7.5 and 0.89 Hz, 1H, C*H*-Ar), 7.51 (t, J = 7.5 Hz, 1H, 6-C*H*-Ar), 6.43 (s, 1H, O*H*), 2.81 (s, 3H, NCH_3), 2.48–2.34 (m, 1H, COHCH_2), 2.03–1.88 (m, 1H, COHCH_2), 1.20–0.97 (m, 6H, (CH_2)$_3$CH_2Me), 0.76 (t, J = 6.5 Hz, 3H, (CH_2)$_5$CH_3), 0.79–0.62 (m, 1H, CH_2Me), 0.51–0.32 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 164.4 (*C*O); 142.6, 134.4 and 128.3 (3 *C*); 132.8, 131.1 and 121.1 (3 *C*H); 90.4 (*C*OH); 32.5, 30.8, 28.1, 22.8 and 21.8 (5 *C*H$_2$); 22.8 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 264 (0.2) [M − H_2O]$^+$, 206 (1), 198 (37), 196 (100) [M − hexyl]$^+$, 162 (10), 103 (7), 75 (5), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3279 (s), 2952 (s), 2930 (m), 2860 (s), 1691 (s), 1609 (w), 1585 (m), 1479 (m), 1466 (s), 1421 (s), 1397 (s), 1337 (w), 1312 (w), 1229 (w), 1151 (w), 1092 (s), 1032 (s), 1018 (m), 896 (w), 874 (w), 818 (w), 792 (m), 764 (m), 720 (w), 694 (w), 627 (w), 600 (w), 567 (w). **HR MS** (ESI): calc. for $C_{15}H_{21}ClNO_2$: 282.12607; found: 282.12524 [M + 1]$^+$.

6-Chloro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (9a)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.15. Yield: 34%. Mp: 127 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.66 (dd, J = 7.9 and 2.2 Hz, 1H, C*H*-Ar), 7.63–7.59 (m, 2H, C*H*-Ar), 6.35 (s, 1H, O*H*), 2.81 (s, 3H, NCH_3), 2.10–1.88 (m, 2H, COHCH_2), 1.20–1.02 (m, 6H, (CH_2)$_3$CH_2Me), 0.76 (t, J = 6.9 Hz, 3H, (CH_2)$_5$CH_3), 0.84–0.68 (m, 1H, CH_2Me), 0.56–0.41 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 164.4 (*C*O); 146.1, 133.8 and 133.6 (3 *C*); 131.8, 124.0 and 121.9 (3 *C*H); 89.6 (*C*OH); 35.2, 30.9, 28.2, 22.9 and 21.9 (5 *C*H$_2$); 23.0 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 280 (0.2) [M]$^+$, 263 (0.6) [M − H_2O]$^+$, 230 (7), 206 (4), 198 (34), 196 (100) [M − hexyl]$^+$, 167 (6), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3303 (s), 2925 (s), 2860 (m), 1680 (s), 1612 (w), 1454 (m), 1441 (m), 1411 (m), 1392 (m), 1286 (w), 1230 (w), 1194 (w), 1091 (m), 1069 (m), 1057 (w), 1024 (m), 995 (w), 931 (w), 890 (w), 837 (m), 787 (w), 714 (m), 696 (w), 669 (w), 636 (w), 587 (w). **HR MS** (ESI): calc. for $C_{15}H_{21}ClNO_2$: 282.12607; found: 282.12497 [M + 1]$^+$.

5-Chloro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (9b)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.13. Yield: 48%. Mp: 133–135 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.68 (dd, J = 1.6 Hz, 1H, C*H*-Ar), 7.62 (d, J = 8.1 Hz, 1H, C*H*-Ar), 7.54 (dd, J = 8.1 and 1.6 Hz, 1H, C*H*-Ar), 6.39 (s, 1H, O*H*), 2.80 (s, 3H, NCH_3), 2.11–1.90 (m, 2H, COHCH_2), 1.19–1.03 (m, 6H, (CH_2)$_3$CH_2Me), 0.77 (t, J = 6.8 Hz, 3H, (CH_2)$_5$CH_3), 0.80–0.67 (m, 1H, CH_2Me), 0.55–0.39 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 164.8 (*C*O); 149.5, 136.8 and 130.4 (3 *C*); 129.3, 123.9 and 122.4 (3 *C*H); 89.5 (*C*OH); 35.0, 30.9, 28.2, 22.9 and 21.9 (5 *C*H$_2$); 23.0 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 263 (1) [M − H_2O]$^+$, 230 (4), 206 (3), 198 (32), 196 (100) [M − hexyl]$^+$, 167 (7), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3274 (s), 2922 (s), 2856 (s), 1685 (s), 1613 (m), 1481 (m), 1461 (m), 1429 (s), 1396 (s), 1287 (s), 1262 (s), 1231 (s), 1217 (s), 1196 (s), 1127 (s), 1094 (s), 1078 (s), 1046 (w), 1020 (m), 933 (s), 879 (m), 843 (m), 790 (m), 700 (m), 597 (w), 526 (w). **HR MS** (ESI): calc. for $C_{15}H_{21}ClNO_2$: 282.12607; found: 282.12525 [M + 1]$^+$.

5,6-Dichloro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (10)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.16. Yield: 44%. Mp: 102–104 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.93 (s, 1H, C*H*-Ar), 7.83 (s, 1H, C*H*), 6.46 (s, 1H, O*H*), 2.81 (s, 3H, NCH_3), 2.08 (m, 1H, COHCH_2), 1.94 (m, 1H, COHCH_2), 1.19–1.00 (m, 6H, (CH_2)$_3$CH_2Me), 0.76 (t, J = 6.7 Hz, 3H, (CH_2)$_5$CH_3), 0.80–0.68 (m, 1H, CH_2CH$_3$), 0.58–0.44 (m, 1H, CH_2CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 163.7 (*C*O); 147.4, 134.8, 132.2 and 131.9 (4 *C*); 124.7 and 124.1 (2 *C*H); 89.5 (*C*OH); 34.9, 30.9, 28.3, 23.1 and 21.9 (5 *C*H$_2$); 22.9 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 315 (1) [M]$^+$, 234 (44), 233 (25), 232 (83), 231 (42), 230 (100) [M − hexyl]$^+$, 219 (6), 217 (13), 214 (18), 203 (15), 201 (19), 198 (6), 195 (6), 173 (6), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3322 (m), 3059 (m), 2923 (s), 2858 (m), 1673 (s), 1469 (m), 1435 (s), 1404 (s), 1299 (m), 1109 (m), 1088 (m), 1066 (m), 1025 (m), 1000 (w), 932 (m), 874 (m), 790 (w), 702 (m), 659 (w), 610 (m). **HR MS** (ESI): calc. for $C_{15}H_{20}Cl_2NO_2$: 316.0866; found: 316.0869 [M + 1]$^+$.

4-Fluoro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindole-1-one (11a) and (11b)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.08. Yield: 60%. Mp: 89–90 °C. **MS** (EI, 70 eV): m/z (%) = 266 (1) [M + 1]$^+$, 180 (100) [M − hexyl]$^+$, 151 (19), 148 (8), 123 (6), 103 (22), 95 (12), 75 (11), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3315 (s), 2957 (m), 2929 (s), 2859 (m), 1690 (s), 1627 (w), 1604 (m), 1484 (s), 1425 (s), 1391 (m), 1253 (m), 1085 (m), 1056 (w), 1025 (w), 995 (w), 969 (w), 928 (w), 859 (w), 811 (w), 770 (m), 702 (m), 677 (w), 582 (w). **HR MS** (ESI): calc. for $C_{15}H_{21}FNO_2$: 266.15508, found: 266.15540 [M + 1]$^+$. A 1 : 2 mixture of isomers was obtained.

4,5,6,7-Tetrafluoro-3-hexyl-3-hydroxy-2-methyl-2,3-dihydroisoindol-1-one (12)

R_f (SiO_2, *n*-heptane–EtOAc = 5 : 1): 0.11. Yield: 73%. Mp: 116–118 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.83 (s, 1H, O*H*), 2.79 (s, 3H, NCH_3), 2.07 (m, 2H, COHCH_2), 1.25–1.04 (m, 6H, (CH_2)$_3$CH_2Me), 0.78 (t, J = 6.8 Hz, 3H, (CH_2)$_5$CH_3), 0.87–0.73 (m, 1H, CH_2Me), 0.71–0.60 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 160.5 (*C*O); 142.8 (J = 257 Hz, *C*F); 142.7 (J = 261 Hz, *C*F); 141.8 (J = 250 Hz, *C*F); 141.0 (J = 252 Hz, *C*F); 128.9 (d, J = 13 Hz, *C*); 114.8 (d, J = 9 Hz, *C*); 89.3 (*C*OH); 34.2, 30.9, 28.2, 22.8 and 21.9 (5 *C*H$_2$); 23.0 and 13.8 (2 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 319 (1) [M]$^+$, 300 (7) [M − F]$^+$, 234 (100) [M − hexyl]$^+$, 205 (11), 202 (12), 177 (9), 149 (5), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3347 (s), 2956 (s), 2931 (s), 2869 (m), 1681 (s), 1649 (m), 1511 (s), 1429 (s), 1397 (s), 1307 (w), 1143 (w), 1090 (m), 1023 (m), 1006 (m), 969 (w), 912 (m), 883 (w), 804 (m), 791 (w), 778 (w), 725 (w), 675 (w). **HR MS** (EI): calc. for $C_{15}H_{17}F_4NO_2$: 319.1190; found: 319.11828 [M]$^+$.

7-Amino-3-ethyl-3-hydroxy-2,4,6-trimethyl-2,3-dihydroisoindol-1-one (13)

R_f (SiO_2, *n*-heptane–EtOAc = 1 : 1): 0.10. Yield: 73%, crystallized from toluene. Mp: 156–158 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.89 (s, 1H, C*H*), 6.00 (s, 1H, O*H*), 5.68 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.23 (s, 3H, =CCH_3), 2.06 (m, 1H, CH_2), 2.05 (s, 3H, =CCH_3), 1.92 (m, 1H, CH_2), 0.30 (t, J = 7.4 Hz, 3H, CH_2CH_3). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.3 (*C*O); 142.1, 141.7, 122.3, 119.0 and 113.1 (5 *C*); 135.6 (*C*H-Ar); 90.4 (*C*OH); 26.7 (*C*H_2); 22.1 (N*C*H_3); 16.3 and 16.2 (2 =C*C*H_3), 7.7 (CH_2CH_3). **MS** (EI, 70 eV): m/z (%) = 234 (44) $[M]^+$, 216 (17) $[M - H_2O]^+$, 205 (100) $[M -$ ethyl$]^+$, 161 (16), 146 (23), 131 (5), 119 (9), 102 (10), 91 (10), 79 (9), 65 (5), 42 (5), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3469 (s), 3364 (s), 3266 (m), 2970 (m), 2938 (s), 1662 (s), 1632 (m), 1596 (s), 1496 (m), 1461 (m), 1433 (m), 1397 (m), 1377 (w), 1355 (w), 1322 (w), 1304 (w), 1276 (w), 1262 (w), 1119 (w), 1090 (m), 1062 (w), 1027 (m), 961 (w), 872 (w), 804 (w), 685 (w), 561 (w), 542 (w), 510 (w), 483 (w). **HR MS** (EI): calc. for $C_{13}H_{18}N_2O_2$: 234.13683; found: 234.13662 $[M]^+$.

7-Amino-3-hydroxy-2,4,6-trimethyl-3-pentyl-2,3-dihydroisoindol-1-one (14)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.08. Yield: 58%, crystallized from toluene. Mp: 132–133 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.88 (s, 1H, C*H*-Ar), 5.98 (s, 1H, OH), 5.67 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.23 (s, 3H, =CCH_3), 2.12–2.00 (m, 1H, CH_2COH), 2.05 (s, 3H, =CCH_3), 1.94–1.85 (m, 1H, CH_2COH), 1.17–1.03 (m, 4H, 2 CH_2), 0.74 (m, 3H, CH_2CH_3), 0.72–0.61 (m, 1H, CH_2Me), 0.54–0.43 (m, 1H, CH_2Me). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.3 (*C*O); 142.2, 142.2, 122.3, 119.0 and 112.9 (5 *C*); 135.6 (*C*H-Ar); 89.8 (*C*OH); 33.7, 30.9, 22.8 and 21.9 (4 *C*H_2); 22.2 (N*C*H_3); 16.3 and 16.2 (2 =C*C*H_3); 13.8 (CH_2CH_3). **MS** (EI, 70 eV): m/z (%) = 276 (13) $[M]^+$, 158 (5) $[M - H_2O]^+$, 215 (15), 205 (100), 146 (6), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3463 (s), 3374 (s), 3297 (s), 2947 (s), 2924 (s), 2861 (m), 1662 (s), 1632 (s), 1598 (m), 1498 (s), 1432 (s), 1397 (m), 1354 (w), 1298 (m), 1269 (w), 1240 (w), 1124 (w), 1078 (m), 1036 (w), 1016 (w), 875 (w), 743 (w), 592 (w), 567 (w). **HR MS** (EI): calc. for $C_{16}H_{24}N_2O_2$: 276.18378; found: 276.18335 [M$^+$].

7-Amino-3-heptyl-3-hydroxy-2,4,6-trimethyl-2,3-dihydroisoindol-1-one (15)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.05. Yield: 20%, crystallized from toluene. Mp: 119 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.88 (s, 1H, C*H*), 5.98 (s, 1H,O*H*), 5.67 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.23 (s, 3H, =CCH_3), 2.11–2.00 (m, 1H, CH_2COH), 2.05 (s, 3H, =CCH_3), 1.93–1.85 (m, 1H, CH_2COH), 1.25–1.03 (m, 8H, 4 CH_2), 0.79 (t, J = 7.0 Hz, 3H, CH_2CH_3), 0.73–0.61 (m, 1H, CH_2CH$_3$), 0.54–0.42 (m, 1H, CH_2CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 142.2, 142.3, 122.3, 119.0 and 112.9 (5 *C*); 135.6 (*C*H-Ar); 89.8 (*C*OH); 33.7, 31.1, 28.6, 28.4, 23.1 and 22.0 (6 *C*H_2); 22.2 (N*C*H_3); 16.3 and 16.2 (2 =C*C*H_3); 13.9 (CH_2CH_3). **MS** (EI, 70 eV): m/z (%) = 304 (13) $[M]^+$, 286 (4) $[M - H_2O]^+$, 215 (14), 205 (100), 190 (6), 146 (6), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3473 (s), 3369 (s), 3298 (s), 2954 (s), 2931 (s), 2867 (s), 1659 (s), 1629 (m), 1593 (s), 1497 (m), 1459 (m), 1433 (s), 1397 (m), 1355 (m), 1307 (m), 1267 (m), 1077 (m), 1022 (m), 896 (w), 866 (m), 803 (w), 725 (w), 663 (w), 641 (w), 615 (w), 557 (w). **HR MS** (EI): calc. for $C_{18}H_{28}N_2O_2$: 304.21509; found: 304.21488 $[M]^+$.

7-Amino-3-hydroxy-2,4,6-trimethyl-3-octyl-2,3-dihydroisoindol-1-one (16)

R_f (SiO_2, *n*-heptane–EtOAc = 3 : 1): 0.08. Yield: 30%, crystallized from toluene. Mp: 118 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.88 (s, 1H, C*H*), 5.98 (s, 1H, O*H*), 5.67 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.22 (s, 3H, =CCH_3), 2.09–2.00 (m, 1H, CH_2COH), 2.05 (s, 3H, =CCH_3), 1.94–1.84 (m, 1H, CH_2COH), 1.25–1.04 (m, 10H, 5 CH_2), 0.80 (t, J = 7.1 Hz, 3H, CH_2CH_3), 0.72–0.62 (m, 1H, CH_2CH$_3$), 0.54–0.43 (m, 1H, CH_2CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 142.2, 142.1, 122.3, 119.0 and 112.9 (5 *C*); 135.6 (*C*H-Ar); 89.8 (*C*OH); 33.7, 31.1, 28.7, 28.6, 28.5, 23.1 and 22.0 (7 *C*H_2); 22.2 (N*C*H_3); 16.3 and 16.2 (2 =C*C*H_3); 13.9 (CH_2CH_3). **MS** (EI, 70 eV): m/z (%) = 318 (10) $[M]^+$, 300 (6) $[M - H_2O]^+$, 215 (20), 205 (100), 189 (6), 146 (5), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3467 (s), 3361 (s), 3288 (s), 2951 (s), 2928 (s), 2857 (s), 1660 (s), 1630 (m), 1597 (s), 1498 (m), 1459 (m), 1433 (s), 1396 (m), 1356 (m), 1309 (w), 1267 (w), 1081 (m), 1028 (m), 902 (w), 867 (w), 803 (w), 669 (w), 557 (w). **HR MS** (EI): calc. for $C_{19}H_{30}N_2O_2$: 318.23074; found: 318.22980 $[M]^+$.

7-Amino-3-decyl-3-hydroxy-2,4,6-trimethyl-2,3-dihydroisoindol-1-one (17)

R_f (SiO_2, *n*-heptane–EtOAc = 1 : 1): 0.11. Yield: 11%, crystallized from toluene. Mp: 99–102 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 6.87 (s, 1H, C*H*), 5.98 (s, 1H, O*H*), 5.67 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.23 (s, 3H, =CCH_3), 2.05 (s, 3H, =CCH_3), 2.10–2.00 (m, 1H, CH_2COH), 1.94–1.83 (m, 1H, CH_2COH), 1.28–1.04 (m, 14H, (CH_2)$_7$Me), 0.82 (t, J = 7.1 Hz, 3H, CH_2CH_3), 0.73–0.60 (m, 1H, CH_2CH$_3$), 0.54–0.41 (m, 1H, CH_2CH$_3$). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.2 (*C*O); 142.2, 142.1, 122.3, 118.9 and 112.8 (5 *C*); 135.5 (*C*H-Ar); 89.8 (*C*OH); 33.6, 31.2, 28.8, 28.8, 28.7, 28.6, 28.5, 23.1 and 22.1 (9 *C*H_2); 22.1 (N*C*H_3); 16.3 and 16.2 (2 =C*C*H_3); 13.9 (CH_2CH_3). **MS** (EI, 70 eV): m/z (%) = 346 (10) $[M]^+$, 328 (5) $[M - H_2O]^+$, 215 (15), 205 (100) $[M -$ decyl$]^+$, no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3466 (s), 3361 (s), 3291 (m), 2953 (m), 2924 (s), 2853 (s), 1657 (s), 1630 (m), 1598 (s), 1499 (m), 1434 (m), 1411 (m), 1396 (m), 1357 (m), 1309 (m), 1263 (m), 1085 (m), 1030 (m), 908 (w), 878 (w), 803 (w), 716 (w), 666 (w), 557 (w), 491 (w), 433 (w). **HR MS** (EI): calc. for $C_{21}H_{34}N_2O_2$: 346.26202; found: 346.25677 $[M]^+$.

7-Amino-3-hydroxy-2,4,6-trimethyl-3-*p*-tolyl-2,3-dihydroisoindol-1-one (18a)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.14. Yield: 29%, crystallized from toluene. Mp: 218–219 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.10 (s, 4H, C*H*-tolyl), 6.80 (s, 1H, C*H*-phenyl), 6.58 (s, 1H, O*H*), 5.75 (s, 2H, NH_2), 2.46 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.77 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 168.4 (*C*O); 144.6, 142.3, 136.7, 136.4, 122.7, 119.2 and 111.9 (7 *C*); 135.7 (*C*H-phenyl); 128.7 and 125.9 (2 *C*H-phenyl); 89.2 (*C*OH); 22.7, 20.6, 16.4 and 15.8 (4 *C*H_3). **MS** (EI, 70 eV): m/z (%) = 296 (72) $[M]^+$, 279 (78) $[M - OH]^+$, 264 (8), 250 (8),

205 (100) [M − tolyl]$^+$, 161 (6), 146 (13), 132 (9), 119 (13), 91 (26), 77 (8), 65 (14), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3481 (s), 3367 (m), 3210 (m), 2920 (w), 1668 (s), 1588 (s), 1497 (m), 1440 (m), 1397 (m), 1378 (m), 1354 (w), 1301 (w), 1272 (w), 1198 (w), 1175 (m), 1081 (w), 1033 (m), 969 (w), 920 (w), 885 (w), 845 (w), 816 (m), 800 (w), 790 (w), 766 (w), 609 (w), 552 (w), 518 (w). **HR MS** (EI): calc. for $C_{18}H_{20}N_2O_2$: 296.15247; found: 296.15255 [M]$^+$.

4-Amino-3-hydroxy-2,5,7-trimethyl-3-(4-tolyl)-2,3-dihydroisoindol-1-one (18b)

R_f (SiO_2, *n*-heptane–EtOAc = 2 : 1): 0.19. Yield: 22%, crystallized from toluene. Mp: 130–133 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.12 (m, 4H, C*H*-tolyl), 6.85 (s, 1H, C*H*-phenyl), 6.68 (s, 1H, O*H*), 4.25 (s, 2H, NH_2), 2.46 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.00 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** (100.6 MHz, DMSO-d_6): δ 167.4 (*C*O); 138.4, 137.0, 135.9, 131.6, 126.3, 125.9 and 122.6 (7 *C*); 133.0, 129.0 and 125.9 (3 *C*H-Ar); 88.2 (*C*OH); 22.9, 20.6, 17.1 and 15.9 (4 *C*H$_3$). **MS** (EI, 70 eV): m/z (%) = 296 (27) [M]$^+$, 279 (37) [M − OH]$^+$, 278 (23) [M − H_2O]$^+$, 277 (100), 263 (21), 250 (5), 205 (22) [M − tolyl]$^+$, 132 (6), 119 (9), 91 (33), 65 (11), no other peaks >5%. **IR** (KBr) cm^{-1}: $1/\lambda$ = 3475 (s), 3382 (s), 3265 (s), 3028 (w), 2921 (w), 1662 (s), 1636 (s), 1499 (s), 1439 (s), 1396 (m), 1301 (m), 1242 (w), 1196 (w), 1176 (m), 1125 (m), 1098 (m), 1020 (m), 963 (m), 874 (w), 852 (w), 825 (m), 787 (w), 766 (m), 735 (m), 697 (w), 591 (w), 572 (w), 525 (w), 466 (w). **HR MS** (EI): calc. for $C_{18}H_{20}N_2O_2$: 296.15247; found: 296.15234 [M]$^+$.

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