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MODIFICATION OF ALANTOLACTONES BY NATURAL ALKALOIDS

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Previously unknown compounds combining fragments of a sesquiterpene lactone and a natural alkaloid were synthesized. Derivatives of alantolactone were modified using a Michael reaction with alkaloids of various structural types.

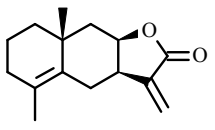
Keywords: sesquiterpene lactones, alkaloids, Michael reaction, adducts of alantolactones and alkaloids.

Natural products that are effective drugs have stimulated the interest of researchers for the whole history of the development of pharmaceuticals. The alkaloids of *Vinca* and taxol, which are widely employed in clinical practice, are prime examples. Furthermore, substances of plant origin are sources of an infinite variety of chemical compounds that are highly competitive even when compared with the modern methodology of combinatorial chemical synthesis [1].

A promising direction for using natural compounds is currently the structural modification of secondary plant metabolites that produce previously unknown derivatives. The goal of such modifications is to enhance the biological activity of the natural compounds or to impart to them new types of activity. We attempted to link in one molecule two native structural moieties, i.e., a sesquiterpene lactone and an alkaloid. These classes of compounds are widely distributed in plants and exhibit different types of biological activity [2].

One of the characteristic features of biologically active natural sesquiterpene lactones is the presence of an activated double bond in the lactone ring. Therefore, they react readily with nucleophiles including amines [3]. On the other hand, alkaloids that contain a nucleophilic N atom in a saturated heterocycle or primary amine are well known. Therefore, the reaction of the lactone with such alkaloids should occur rather readily and produce adducts with the two active moieties.

The available sesquiterpene lactones isoalantolactone (**1**) and alantolactone (**2**) that were isolated from roots of *Inula helenium* L. (Asteraceae) in addition to their derivatives **3**–**6** that were prepared by us previously [4] were selected for the modification. Compound **3** was formed via isomerization of **1** using acids; epoxide derivatives **4** and **5**, via epoxidation with peracetic acid of lactones **1** and **2**, respectively; sesquiterpene alcohol **6**, via opening of the epoxide ring in **5** in acidic medium. Only the substituents of the hydrogenated naphthalene ring of the sesquiterpene lactones were involved in all these transformations. Because the active lactone exomethylene group in **3**–**6** was preserved, it was interesting to study their behavior in reactions with *N*-nucleophiles.



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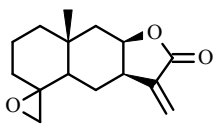

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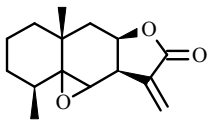

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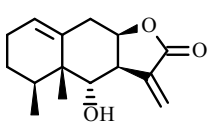

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We used several types of natural alkaloids as the nucleophiles. Derivatives of phenylethylamine [phenethylamine (**7**), tyramine methyl ether (**8**), ephedrine (**9**)] and indole [tryptamine (**10**), serotonin (**11**), and mexamine (**12**)] contained a primary or secondary amine in the side chain of the (hetero)aromatic ring. Derivatives of pyridine [anabasine (**13**)], isoquinoline [salsoline (**14**) and salsolidine (**15**)], and quinolizidine [cytisine (**16**)] had a secondary amine in the heterocycle.

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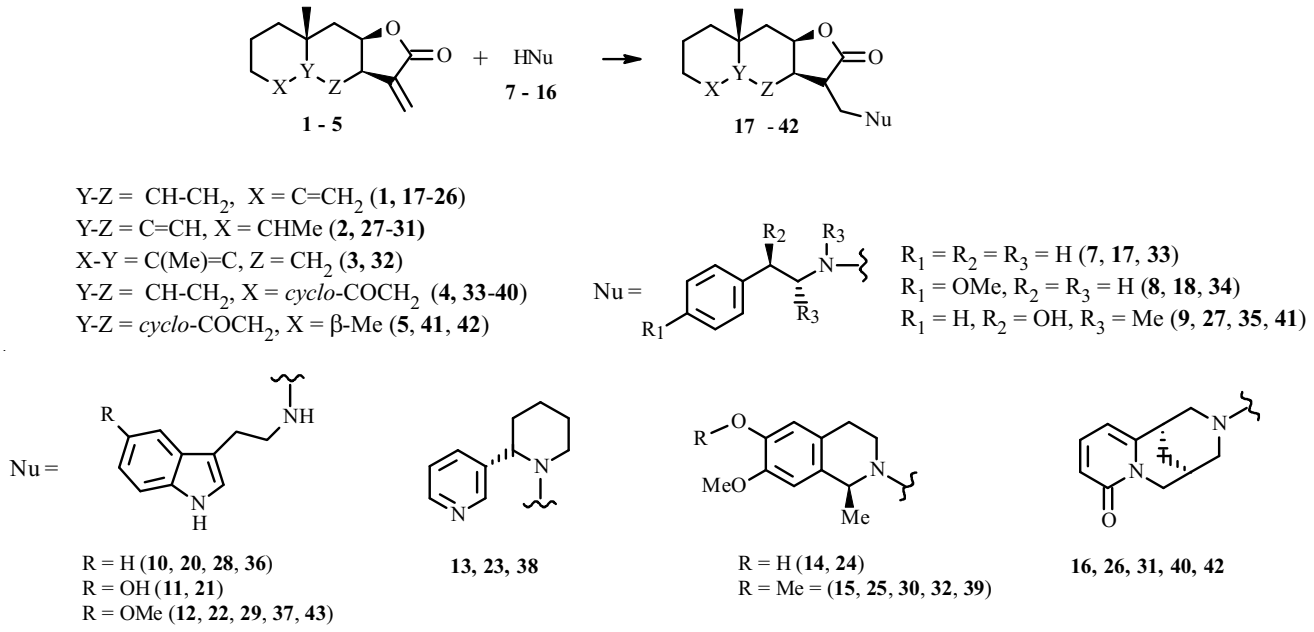
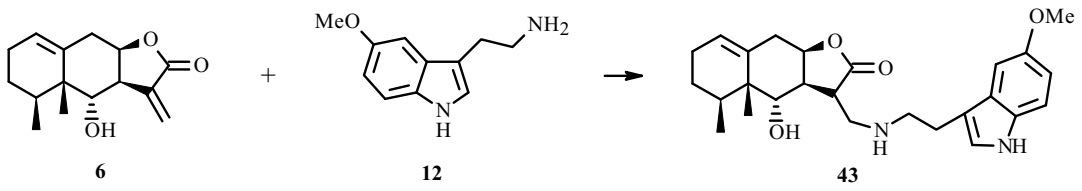
The lactones reacted with the amines under mild conditions, i.e., stirring the reagents (10% excess of amine) in MeOH at room temperature for 1–2 h to several days. All prepared compounds were crystalline with the exception of the adduct with serotonin, which was isolated and characterized as the hydrochloride. The reaction rates and product yields depended on the nature of the starting compounds. Secondary amines **13**–**16** were the most reactive. However, the yields of the salsoline (**14**) adducts were low. The compounds themselves were rather labile and difficult to purify using chromatography. Obviously this was a consequence of the presence of the phenol hydroxyl in the molecules. For this reason we could not prepare the tyramine derivative but had to use its *O*-methylated derivative. Reactions with primary amines required longer reaction times although the product yields were rather high. The electronic structure of the amine played a significant role. Thus, tryptamine (**10**) reacted with the lactones slower than serotonin (**11**) and mexamine (**12**), which contained electron-donating groups in the indole 5-position (Scheme 1).



Scheme 1

The most reactive lactones were **1** and its epoxide **4**. The others had comparable reactivities. Alloalantolactone (**3**) polymerized if stored in MeOH solution. Therefore, we used it only in the reaction with the most reactive amine (**15**). Epoxyalantolactone (**5**) underwent opening of the lactone ring if stored for a long time with the amines. This was detected using the resonance of the aldehyde in PMR spectra. Lactone **6** turned out to be labile in reactions with the most basic secondary amines. Therefore, only one derivative of this lactone (**43**) was synthesized as an example (Scheme 2).



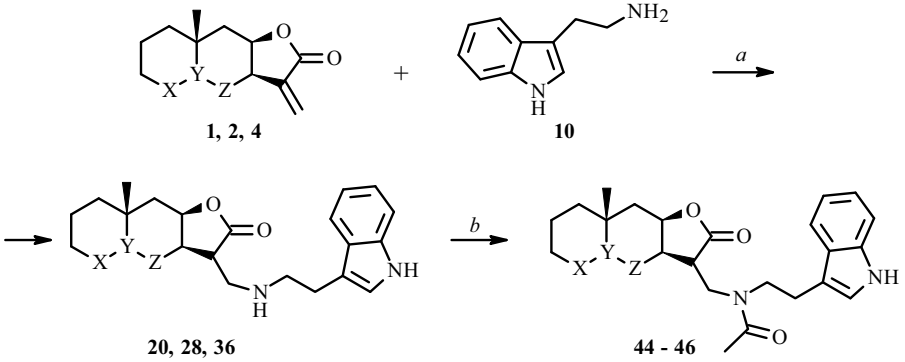
Scheme 2

Acylation of tryptamine adducts **20**, **28**, and **36** at the amine N atom was used as an example to show that preparation of **44**–**46** was possible. These products combined the sesquiterpene lactone and melatonin in their structures. The acylation occurred under phase-transfer conditions with cooling for 1 h. The products were formed in quantitative yields. The acylating agent was acetylchloride with K_2CO_3 as the base (Scheme 3).

TABLE 1. Yields and Constants of **17**–**43** (See Schemes 1 and 2)

Starting compounds		Product	Yield, %	Mp, °C	$[\alpha]_D^{30}$ (*c* 0.1; MeOH)
lactone	HNu				
1	**7**	**17**	64	96–97	+70
	8	**18**	70	78–80	+75
	9	**19**	86	165–166	+125
	10	**20**	90	169–170	+42
	11	**21**[a]	68	190–192	+42
	12	**22**	93	146–148	+75
	13	**23**	85	88–90	+92
	14	**24**	74	115–117	+16
	15	**25**	89	137–139	+85
	16	**26**	91	196–197	–50
2	**9**	**27**	79	166–167	+115
	10	**28**	83	184–185	+53
	12	**29**	86	160–163	+54
	15	**30**	78	122–124	+35
	16	**31**	75	132–134	–40
3	**15**	**32**	75	163–164	+36
4	**7**	**33**	87	140–141	+5
	8	**34**	77	122–124	+12
	9	**35**	89	202–203	+46
	10	**36**	92	106–108	+20
	12	**37**	90	92–93 (dec.)	+23
	13	**38**	84	158–160	–51
	15	**39**	89	193–195	+35
	16	**40**	85	250	–87
5	**9**	**41**	79	144–145	+74
	16	**42**	77	219–221	–70
6	**12**	**43**	69	93–96 (dec.)	–33

[a]Isolated as the hydrochloride.



Y-Z = CH-CH_2, X = C=CH_2 (**1, 20, 44**)
cyclo-$COCH_2$ (**4, 36, 46**)
Y-Z = C=CH, X = CHMe (**2, 28, 45**)

a. MeOH, 20°C; *b*. AcCl, K_2CO_3, CH_2Cl_2, H_2O, 0°C

Scheme 3

Table 1 presents the yields and constants of prepared adducts **17**–**43**. Acetylated derivatives **44**–**46** are described in the Experimental part. The amination of sesquiterpene lactones **1**–**6** was stereospecific, i.e., one geometric isomer was formed. Preparative HPLC was used to isolate the pure products. The structures of the prepared compounds were proved using a

combination of physicochemical methods such as UV and IR spectroscopy, NMR data, and mass spectrometry (see Experimental part). Because all derivatives **17**–**46** contained a (hetero)aromatic ring or conjugated system of multiple bonds, they typically had strong absorption in the UV spectral region in the range 200–220 nm. IR spectra exhibited vibrations for amine (for adducts of primary amines) at 3300 cm^{-1} and lactone carbonyl around 1760 cm^{-1}. PMR spectra of amine derivatives **17**–**46** lacked resonances for the exocyclic $=CH_2$ group (doublets near 6.18 and 5.54 ppm) and showed resonances for amine protons and C-13 protons in the range 2.8–3.0 ppm. Resonances of other protons agreed with the proposed structure. High-resolution mass spectra confirmed the empirical formulas of the compounds and had distinct and rather strong peaks for the molecular ions.

The synthesized compounds were interesting with respect to studying their biological activity because they contained two known pharmacophores. This could cause synergy between the known properties of these moieties and the manifestation of new types of activity.

EXPERIMENTAL

UV spectra were recorded on a Lambda 35 instrument (Perkin–Elmer); IR spectra, in KBr pellets on a ZFS-113 instrument (Bruker). Mass spectra were recorded on an LXQ chromatograph–mass spectrometer (Finnigan) in positive-ion mode using a Kromasil C18 column (2 × 50 mm, 3 μm) and gradient elution (eluent A, 0.1% trifluoroacetic acid, pH 2.0; eluent B, CH_3CN). The flow rate was 0.3 mL·min^{-1}. High-resolution mass spectra were taken in a QStar mass spectrometer (Sciex) with orthogonal ion injection and on an Exactive mass spectrometer (Thermo Fisher) with an electrospray ionization source and Orbitrap mass analyzer. Solutions of starting compounds in CH_3CN of concentration ~10^{-5} M were used for the ionization. The following atomic masses were used to calculate the molecular weights: H, 1.007825; O, 15.994915; C, 12.000000; N, 14.003074. PMR spectra were obtained on a DPX 200 instrument (Bruker) at operating frequency 200 MHz. Specific rotation was measured on a Model 341 polarimeter (Perkin–Elmer).

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using C_6H_6:EtOAc (3:2) and by GC (Chrom5 chromatograph, 3.6 m × 3 mm column packed with Inerton Super, 0.125–0.160 mm with 5% XE-60; flame-ionization detector; detector and vaporizer temperature 250°C; thermostat from 75 to 225°C). Pure components were isolated by semi-preparative HPLC (Turbo LC 200 chromatograph, Perkin–Elmer) with UV detection at 254 nm using an analytical column (4 × 100 mm, Kromasil C18, 5 μm; preparative column 10 × 250 mm, Kromasil C18, 5 μm) and gradient elution [eluent A, 1% TFA in distilled H_2O (pH 2.0); eluent B, CH_3CN] at flow rate 1 mL·min^{-1} for the analytical column and 4 mL·min^{-1} for the preparative column. Fractions were collected using an FC-204 programmed fraction collector (Gilson). Elemental analyses of all newly prepared compounds agreed with those calculated.

Isolation and Synthesis of Starting Sesquiterpene Lactones. Isoalantolactone (1) and alantolactone (2) were isolated from roots of *Inula helenium* L. (Asteraceae). The separation was carried out over a column impregnated with silver nitrate as described before [4].

Alloalantolactone (3). A solution of **1** (1.16 g, 5 mmol) in $CHCl_3$ (20 mL) was stirred, treated with trifluoroacetic acid (TFA, 4.5 mL), and left at room temperature. After the starting lactone disappeared (course of the reaction monitored using PMR spectroscopy), the mixture was poured into H_2O, neutralized with saturated Na_2CO_3 solution, and extracted with $CHCl_3$ (3 × 20 mL). The extracts were washed and dried. The solid formed after evaporating the solvent was passed over a layer of silica gel (elution by benzene) to afford a yellowish oil (0.94, g, 81%). The spectral characteristics of the product agreed with those published [5].

Epoxidation of Alanto- and Isoalantolactones. Lactones **1** and **2** were epoxidized at the non-conjugated double bonds. The starting lactone was treated with peracetic acid solution at room temperature for 1–7 d, diluted with a large amount of H_2O, and worked up with $NaHCO_3$ solution. The corresponding epoxy derivatives were obtained in quantitative yield by extraction with $CHCl_3$. This method was used to synthesize epoxyisoalantolactone (**4**) (mp 137–138°C, lit. [6] mp 136–138°C) and epoxyalantolactone (**5**) (mp 168–169°C, lit. [6] mp 169–171°C).

4-Hydroxy-4a,5-dimethyl-3-methylene-3a,4,4a,5,6,7,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (6). Epoxyalantolactone **5** (2.48 g, 10 mmol) was refluxed in an aqueous solution of oxalic acid (5 g acid, 50 mL H_2O) for 5 h, cooled, neutralized with $NaHCO_3$ solution (5%), and extracted with $CHCl_3$ (3 × 30 mL). The solvent was evaporated to form a yellow oil that crystallized from benzene:hexane (3:1) to afford **6** (1.2 g, 48%). The mother liquor was evaporated and

passed through a column of silica gel (Silpearl) with elution by EtOAc (5%) to isolate another portion of **6** (0.28 g), mp 101–102°C. Total yield 61%, mp 111–112°C, lit. [7] mp 110–110.5°C.

Reaction of Sesquiterpene Lactones with Alkaloids (General Method). A mixture of lactone (1 mmol) and the appropriate alkaloid (1.1 mmol) were dissolved with stirring in MeOH and left at room temperature. After the reaction was finished (TLC monitoring), the mixture was evaporated in a rotary evaporator. The solid was dissolved in CH_3CN and purified by reversed-phase HPLC. This method produced the following derivatives (Table 1 presents the constants and yields).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-5-methylidene-3-(phenethylaminomethyl)decahydronaphtho[2,3-*b*]furan-2-one (17). Found: *m*/*z* 353.2417 $[M]^+$, $C_{23}H_{31}NO_2$; calcd: M = 353.2355. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.44). IR spectrum (KBr, ν, cm^{-1}): 704m, 883m, 1168m, 1744s (C=O), 2931m, 3344br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, s, H-15); 1.08–1.28 (2H, m, H-2); 1.37–1.80 (7H, m, H-1, H-3, H-6, H-9a); 1.89–2.05 (1H, m, H-5); 2.14 (1H, dd, J_1 = 1.76, J_2 = 15.45, H-9b); 2.27–2.50 (1H, m, H-7); 2.72–2.94 [6H, m, $(C\underline{H}_2)_2$Ph, H-13]; 3.04 (1H, m, H-11); 4.76 (1H, d, J = 1.17, H-14a); 4.43 (1H, d, J = 1.37, H-14b); 4.46 (1H, m, H-8); 7.17–7.29 (5H, m, H_{arom}); 7.31 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-5-methylidene-3-{[2-(4-methoxyphenyl)ethylamino]methyl}decahydronaphtho[2,3-*b*]furan-2-one (18). Found: *m*/*z* 383.2534 $[M]^+$, $C_{24}H_{33}NO_3$; calcd: M = 383.2460. UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.44), 224 (4.21), 278 (3.43). IR spectrum (KBr, ν, cm^{-1}): 982m, 1155m, 1245s, 1512s, 1753s (C=O), 2834m, 3332br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, s, H-15); 1.08–1.28 (2H, m, H-2); 1.37–1.82 (7H, m, H-1, H-3, H-6, H-9a); 1.89–2.05 (1H, m, H-5); 2.14 (1H, dd, J_1 = 1.56, J_2 = 15.26, H-9b); 2.26–2.48 (1H, m, H-7); 2.68–2.95 [6H, m, $C\underline{H}_2)_2$Ph, H-13]; 2.99–3.09 (1H, m, H-11); 3.77 (3H, s, OMe); 4.42 (1H, d, J = 1.51, H-14a); 4.76 (1H, d, J = 1.17, H-14b); 4.45 (1H, m, H-8); 6.8 and 7.11 (4H, two d, J_1 = 8.61, J_2 = 8.22, *m*- and *o*-H_{arom}); 7.24 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-3-{[(1*R*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)methylamino]methyl}-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one (19). Found: *m*/*z* 397.2625 $[M]^+$, $C_{25}H_{35}NO_3$; calcd: M = 397.2617. UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.46). IR spectrum (KBr, ν, cm^{-1}): 984m, 1164m, 1202m, 1760s (C=O), 2912m, 2933m, 3444br.s (NH) and 3481br.s (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, d, J = 6.65, CH<u>Me</u>); 0.81 (3H, s, H-15); 1.19–1.31 (2H, m, H-2); 1.44–1.88 (7H, m, H-1, H-3, H-6, H-9a); 1.84–2.06 (1H, m, H-5); 2.18 (1H, dd, J_1 = 1.57, J_2 = 15.46, H-9b); 2.33 (3H, s, NMe), 2.56–2.75 (3H, m, H-7, H-13); 2.90–3.01 (2H, m, H-11, C<u>H</u>Me); 4.23 (1H, d, J = 9.5, C<u>H</u>OH); 4.47 (1H, d, J = 1.17, H-14a); 4.77 (1H, d, J = 1.35, H-14b); 4.53 (1H, m, H-8); 7.32 (5H, s, H_{arom}).

(3a*R*,8a*R*,9a*R*)-3-{[2-(1*H*-Indol-3-yl)ethylamino]methyl}-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one (20). $C_{25}H_{32}N_2O_2$. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 391 (2.2) $[M - 1]^+$, 216 (9), 191 (14), 169 (50), 145 (61), 130 (100), 115 (43), 105 (47), 95 (35), 79 (47). UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.61), 221 (4.7), 282 (3.32). IR spectrum (KBr, ν, cm^{-1}): 892m, 1158m, 1438m, 1762s (C=O), 2920m, 3296br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, s, H-15); 1.13–1.28 (2H, m, H-2); 1.39–1.86 (7H, m, H-1, H-3, H-6, H-9a); 1.91–2.07 (1H, m, H-5); 2.16 (1H, dd, J_1 = 1.7, J_2 = 15.45, H-9b); 2.29–2.45 (2H, m, $C\underline{H}_2$Ind); 2.76–3.14 (6H, m, $NC\underline{H}_2$, H-7, H-11, H-13); 4.35 (1H, m, H-8); 4.43 (1H, d, J = 1.17, H-14a); 4.78 (1H, d, J = 1.56, H-14b); 7.03–7.20 (3H, m, H-2′, H-5′, H-6′); 7.34 (1H, d, J = 7.95, H-7′); 7.60 (1H, d, J = 7.53, H-4′); 8.07 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-3-{[2-(5-Hydroxy-1*H*-indol-3-yl)ethylamino]methyl}-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one hydrochloride (21) was prepared by reaction of the base with methanolic HCl. $C_{25}H_{33}N_2O_3Cl$. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 262 (18), 203 (22), 190(100), 185 (13), 179 (12), 163 (30), 158 (13), 148 (50), 143 (47), 131 (65). UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.43), 276 (3.35). IR spectrum (KBr, ν, cm^{-1}): 934m, 1222m, 1456m, 1486m, 1759s (C=O), 2950m, 3300br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.74 (3H, s, H-15); 0.69–0.76 (2H, m, H-2); 1.00–1.70 (7H, m, H-1, H-3, H-6, H-9a); 1.85–1.99 (1H, m, H-5); 2.06 (1H, d, J = 15.66, H-9b); 2.29–2.35 (2H, m, $C\underline{H}_2$Ind); 2.72–3.07 (6H, m, $NC\underline{H}_2$, H-7, H-11, H-13); 4.27 (1H, br.s, OH); 4.31 (1H, m, H-8); 4.46 (1H, d, J = 1.37, H-14a); 4.73 (1H, d, J = 1.36, H-14b); 6.72 (1H, dd, J_1 = 1.76, J_2 = 8.82, H-6′); 6.92 (1H, d, J = 8.82, H-7′); 7.13 (1H, d, J = 8.61, H-2′); 7.31 (1H, br.s, H-4′); 8.13 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-3-{[2-(5-Methoxy-1*H*-indol-3-yl)ethylamino]methyl}-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one (22). $C_{26}H_{34}N_2O_4$. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 262 (35), 214 (7), 203 (8), 190 (100), 174 (26), 164 (41), 158 (33), 148 (13) 143 (31), 133 (60). UV spectrum (EtOH, λ_{max}, log ε): 203 (4.46), 223 (4.39), 278 (3.78). IR spectrum (KBr, ν, cm^{-1}): 801m, 1155m, 1213m, 1482m, 1747s (C=O), 2830m, 2935m, 3406br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, s, H-15); 1.13–1.26 (2H, m, H-2); 1.36–1.73 (7H, m, H-1, H-3, H-6, H-9a); 1.91–2.04 (1H, m, H-5); 2.13 (1H, dd, J_1 = 1.88, J_2 = 15.20, H-9b); 2.26–2.43 (2H, m, C$\underline{H}_2$Ind); 2.73–3.11 (6H, m, NC$\underline{H}_2$, H-7, H-11, H-13); 3.85 (3H, s, OMe); 4.40 (1H, d, J = 1.17, H-14a); 4.73 (1H, d, J = 1.56, H-14b); 4.43 (1H, m, H-8); 6.84 (1H, dd, J_1 = 2.56, J_2 = 8.54, H-6′); 7.01 (1H, d, J = 2.56, H-4′); 7.02 (1H, s, H-2′); 7.22 (1H, dd, J_1 = 3.32, J_2 = 8.54, H-7′); 8.00 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-5-methylidene-3-(3,4,5,6-tetrahydro-2*H*-[2,3′]bipyridin-1-ylmethyl)decahydronaphtho[2,3-*b*]furan-2-one (23). Found: *m/z* 394.2715 $[M]^+$, $C_{25}H_{34}N_2O_2$; calcd: M = 394.2620. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.59), 2.86 (3.63). IR spectrum (KBr, ν, cm^{-1}): 962m, 1137m, 1263m, 1440m, 1511m, 1758s (C=O), 2928m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.69 (3H, s, H-15); 0.79–0.97 (2H, m, H-2); 1.15–1.89 (13H, m, aliphatic protons); 2.08 (1H, dd, J_1 = 2.08, J_2 = 15.35, H-9b); 2.22–2.48 (3H, m, H-5, H-7, H-6′a); 2.90 (1H, dd, J_1 = 3.02, J_2 = 13.49, H-6′b); 3.05 (1H, m, H-2′); 3.17 (1H, dd, J_1 = 3.02, J_2 = 10.24, H-13b); 4.30 (1H, d, J = 1.39, H-14a); 4.71 (1H, d, J = 1.62, H-14b); 4.31 (1H, m, H-8); 7.20-7.27 (1H, m, H-5″); 7.70 (1H, dt, J_1 = 1.86, J_2 = 2.33, J_3 = 7.91, H-4″); 8.47 (1H, dd, J_1 = 1.86, J_2 = 4.88, H-6″); 8.52 (1H, dd, J_1 = 0.69, J_2 = 2.09, H-2″).

(3a*R*,8a*R*,9a*R*)-3-((*R*)-6-Hydroxy-7-methoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-ylmethyl)-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one (24). Found: *m/z* 425.2511 $[M]^+$, $C_{26}H_{35}NO_4$; calcd: M = 425.2566. UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.46), 234 (4.05), 310 (3.60). IR spectrum (KBr, ν, cm^{-1}): 883m, 1082m, 1154m, 1761s (C=O), 2807m, 2926m, 2938m, 3502br.s (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.79 (3H, s, H-15); 1.12–1.45 (3H, m, H-2, H-9a); 1.30 (3H, d, J = 6.97, Me-1′); 1.48–1.80 (6H, m, H-1, H-3, H-6); 1.90–2.04 (1H, m, H-7); 2.11–2.37 (2H, m, H-9b, H-5); 2.50–2.65 (2H, m, H-4′), 2.76 (1H, dd, J_1 = 1.86, J_2 = 5.82, H-13a); 2.85 (1H, dd, J_1 = 1.86, J_2 = 6.84, H-13b); 2.94–3.10 (3H, m, H-3′, H-11); 3.75 (1H, q, J = 6.28, H-1′); 3.83 (3H, s, OMe); 4.44 (1H, d, J = 0.72, H-14a); 4.75 (1H, d, J = 0.72, H-14b); 4.48 (1H, m, H-8); 6.52 (1H, d, J = 5.1, H-8′); 6.63 (1H, s, H-5′).

(3a*R*,8a*R*,9a*R*)-3-((*R*)-6,7-Dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-ylmethyl)-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]furan-2-one (25). Found: *m/z* 439.2250 $[M]^+$, $C_{27}H_{37}NO_4$; calcd: M = 439.2723. UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.60), 284 (3.50). IR spectrum (KBr, ν, cm^{-1}): 854m, 1116m, 1172s, 1222m, 1513m, 1762s (C=O), 2905m, 2931m, 2938m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.79 (3H, s, H-15); 1.13–1.41 (3H, m, H-2, H-9a); 1.35 (3H, d, J = 6.46, Me-1′), 1.48–1.61 (4H, m, H-1, H-3); 1.74–1.83 (2H, m, H-6); 1.97 (1H, m, H-7); 2.16 (1H, dd, J_1 = 1.95, J_2 = 15.65, H-9b); 2.31 (1H, dt, J = 12.91, H-5); 2.48–2.71 (2H, m, H-4′), 2.75–2.91 (2H, m, H-13); 2.95–3.18 (3H, m, H-3′, H-11), 3.70 (1H, q, J = 6.50, H-1′); 3.82 (6H, s, OMe); 4.43 (1H, d, J = 1.36, H-14a); 4.74 (1H, d, J = 1.36, H-14b); 4.48 (1H, m, H-8); 6.53 (2H, s, H-5′, H-8′).

3-((3a*R*,8a*R*,9a*R*)-8a-Methyl-5-methylidene-2-oxodecahydronaphtho[2,3-*b*]furan-3-ylmethyl)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (26). Found: *m/z* 422.2272 $[M]^+$, $C_{26}H_{34}N_2O_3$; calcd: M = 422.2569. UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.34), 235 (3.95), 310 (4.02). IR spectrum (KBr, ν, cm^{-1}): 960m, 1164m, 1552m, 1583m, 1651s and 1757s (C=O), 2906m, 2917m, 2937m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.71 (3H, s, H-15); 0.96–2.96 (23H, aliphatic protons); 3.77 (1H, dd, J_1 = 5.95, J_2 = 15.65, H-6′a); 3.94 (1H, d, J = 15.65, H-6′b); 4.30 (1H, m, H-8); 4.35 (1H, d, J = 1.10, H-14a); 4.75 (1H, d, J = 1.10, H-14b); 5.92 (1H, dd, J_1 = 1.32, J_2 = 9.04, H-11′); 6.36 (1H, dd, J_1 = 1.32, J_2 = 6.84, H-9′); 7.22 (1H, dd, J_1 = 6.84, J_2 = 9.05, H-10′).

(3aR,5S,8a*R*,9a*R*)-3-{[((1*R*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)methylamino]methyl}-5,8a-dimethyl-3a,5,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (27). Found: *m/z* 397.2532 $[M]^+$, $C_{25}H_{35}NO_3$; calcd: M = 397.2617. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.56). IR spectrum (KBr, ν, cm^{-1}): 984m, 1038m, 1164m, 1760s (C=O), 2933m, 3508 and 3527br.s (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, d, J = 6.75, NCH$\underline{Me}$); 1.18 (3H, d, J = 7.67, H-14); 1.27 (3H, s, H-15); 1.39–1.92 (7H, m, H-1, H-2, H-3, H-9a); 2.10 (1H, dd, J_1 = 3.27, J_2 = 14.89, H-9b); 2.37 (3H, s, NMe), 2.47–2.56 (1H, m, H-4); 2.60–2.74 (2H, m, NC$\underline{H}$Me, H-11); 2.89–3.10 (2H, m, H-13); 3.28 (1H, m, H-7); 4.29 (1H, d, J = 9.77, C$\underline{H}$OH); 4.81 (1H, m, H-8); 5.35 (1H, d, J = 2.79, H-6); 7.32 (5H, s, H_{arom}).

(3a*R*,5*S*,8a*R*,9a*R*)-3-{[2-(1*H*-Indol-3-yl)ethylamino]methyl}-5,8a-dimethyl-3a,5,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (28). $C_{25}H_{32}N_2O_2$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 392 (0.4) $[M]^+$, 217 (20), 176 (46), 171 (81), 160 (71), 145 (61), 130 (100), 115 (77), 105 (81), 95 (80), 80 (76). UV spectrum (EtOH, λ_{max}, nm, log ε): 201

(4.30), 222 (4.34), 282 (3.90). IR spectrum (KBr, ν, cm^{-1}): 1108m, 1170m, 1178m, 1757s (C=O), 2850m, 2924m, 3296br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.08 (3H, d, J = 7.70, H-14); 1.20 (3H, s, H-15); 1.30–1.87 (7H, m, H-1, H-2, H-3, H-9a); 2.08 (1H, dd, J_1 = 1.43, J_2 = 14.70, H-9b); 2.36 (1H, m, H-4); 2.70–3.10 [8H, m, $N(C\underline{H}_2)_2$, H-7, H-11, H-13]; 4.70 (1H, m, H-8); 5.03 (1H, d, J = 2.40, H-6); 7.05–7.25 (3H, m, H-2′, H-5′, H-6′); 7.35 (1H, d, J = 7.71, H-7′); 7.62 (1H, d, J = 7.49, H-4′); 8.03 (1H, br.s, NH).

(3a*R*,5*S*,8a*R*,9a*R*)-3-{[2-(5-Methoxy-1*H*-indol-3-yl)ethylamino]methyl}-5,8a-dimethyl-3a,5,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (29). Found: *m/z* 423.2765 $[M]^+$, $C_{26}H_{34}N_2O_4$; calcd: M = 423.2640. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.70), 276 (3.90). IR spectrum (KBr, ν, cm^{-1}): 1217m, 1488m, 1754s (C=O), 2927m, 2994m, 3326br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.08 (3H, d, J = 7.55, H-14); 1.19 (3H, s, H-15); 1.35–1.87 (6H, m, H-1, H-2, H-3); 2.07 (2H, dd, J_1 = 3.43, J_2 = 14.71, H-9); 2.35 (1H, m, H-4); 2.76–3.07 [8H, m, $N(C\underline{H}_2)_2$, H-7, H-11, H-13]; 3.85 (3H, s, OMe); 4.68 (1H, m, H-8); 5.01 (1H, d, J = 2.44, H-6); 6.29 (1H, d, J_1 = 2.33, J_2 = 8.84, H-6′); 6.57 (1H, dd, J_1 = 2.33, J_2 = 9.54, H-7′); 6.65 (1H, d, J = 7.66, H-4′); 6.76 (1H, d, J = 5.41, H-2′); 8.28 (1H, br.s, NH).

(3a*R*,5*S*,8a*R*,9a*R*)-3-((*S*)-6,7-Dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-ylmethyl)-5,8a-dimethyl-3a,5,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (30). Found: *m/z* 439.2838 $[M]^+$, $C_{27}H_{37}NO_4$; calcd: M = 439.2723. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.70), 284 (3.75). IR spectrum (KBr, ν, cm^{-1}): 1110m, 1224m, 1464m, 1744s (C=O), 2923m, 2955m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.12 (3H, d, J = 7.83, H-14); 1.22 (3H, s, H-15); 1.35 (3H, d, J = 6.45, Me-1′); 1.43–1.89 (7H, m, H-1, H-2, H-3, H-9a); 2.09 (1H, dd, J_1 = 3.13, J_2 = 14.67, H-9b); 2.30–2.94 (5H, m, H-7, H-4, H-11, H-13); 2.99–3.20 (4H, m, H-3′, H-4′); 3.79 (1H, q, J = 6.50, H-1′); 3.83 (6H, s, OMe); 4.73 (1H, br.s, H-8); 5.44 (1H, br.s, H-6); 6.54 (2H, s, H-5′, H-8′).

(1*S*,5*S*)-3-((3a*R*,5*S*,8a*R*,9a*R*)-5,8a-Dimethyl-2-oxo-2,3,3a,5,6,7,8,8a,9,9a-decahydronaphtho[2,3-*b*]furan-3-ylmethyl)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (31). Found: *m/z* 422.2780 $[M]^+$, $C_{26}H_{34}N_2O_3$; calcd: M = 422.2569. UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.70), 234 (4.30), 310 (4.37). IR spectrum (KBr, ν, cm^{-1}): 960m, 1164m, 1139m, 1544m, 1648s and 1755s (C=O), 2923m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, d, J = 7.60, H-14); 1.04 (3H, s, H-15); 1.23–2.92 (21H, aliphatic protons); 3.80 (1H, dd, J_1 = 6.26, J_2 = 15.46, H-6′a); 4.00 (1H, d, J = 15.46, H-6′b); 4.48 (1H, unresolved t, J = 2.34, H-8); 4.85 (1H, d, J = 2.74, H-6); 5.86 (1H, d, J = 6.85, H-11′); 6.29 (1H, d, J = 9.22, H-9′); 7.18 (1H, dd, J_1 = 7.15, J_2 = 9.22, H-4′).

(3a*R*,8a*R*,9a*R*)-3-((*S*)-6,7-Dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-ylmethyl)-5,8a-dimethyl-3a,4,6,7,8,8a,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (32). Found: *m/z* 439.2082 $[M]^+$, $C_{27}H_{37}NO_4$; calcd: M = 439.2723. UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.64). IR spectrum (KBr, ν, cm^{-1}): 1089m, 1160m, 1248m, 1464m, 1514m, 1745s (C=O), 2922m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.10 (3H, s, H-15); 1.36 (3H, d, J = 6.65, Me-1′); 1.59 (3H, s, H-14); 1.44–1.76 (7H, m, H-1, H-2, H-6, H-9a); 1.85–1.95 (2H, m, H-3); 2.14 (1H, dd, J_1 = 1.96, J_2 = 15.46, H-9b); 2.34–3.19 (8H, m, H-7, H-11, H-13, H-3′, H-4′); 3.73 (1H, q, J = 6.85, H-1′); 3.83 (6H, s, OMe); 4.47 (1H, m, H-8); 6.53 and 6.54 (2H, both s, H-5′, H-8′).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-3-(phenethylaminomethyl)decahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (33). Found: *m/z* 369.2417 $[M]^+$, $C_{23}H_{31}NO_3$; calcd: M = 369.2304. UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.20), 284 (3.64). IR spectrum (KBr, ν, cm^{-1}): 957m, 1128m, 1756s (C=O), 2942m, 3300br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.72 (1H, q, J = 12.90, H-6a); 0.93 (3H, s, H-15); 1.08–1.94 (9H, m, aliphatic protons); 2.16 (1H, dd, J_1 = 1.76, J_2 = 15.65, H-9b); 2.38 (1H, m, H-7); 2.54 (1H, d, J = 4.50, H-14a); 2.63–2.99 [7H, m, $(C\underline{H}_2)_2Ph$, H-13, H-14b); 3.04 (1H, m, H-11); 4.43 (1H, dt, J_1 = 1.70, J_2 = J_3 = 3.90, H-8); 7.15–7.34 (5H, m, H_{arom}).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-3-{[2-(4-methoxyphenyl)ethylamino]methyl}decahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (34). Found: *m/z* 383.2534 $[M]^+$, $C_{24}H_{33}NO_4$; calcd: M = 383.2460. UV spectrum (EtOH, λ_{max}, nm, log ε): 201 (4.35), 224 (4.23), 284 (3.32). IR spectrum (KBr, ν, cm^{-1}): 985m, 1157m, 1243m, 1512m, 1751s (C=O), 2933m, 3332br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.71 (1H, q, J = 12.72, H-6a); 0.93 (3H, s, H-15); 1.07–1.93 (9H, m, aliphatic protons); 2.13 (1H, dd, J_1 = 1.96, J_2 = 15.26, H-9b); 2.34 (1H, m, H-7); 2.54 (1H, d, J = 4.30, H-14a); 2.60–2.98 [8H, m, $(C\underline{H}_2)_2$, H-11, H-13, H-14b); 3.76 (3H, s, OMe); 4.43 (1H, m, H-8); 6.82 (2H, d, J = 8.60, *o*-H); 7.10 (2H, d, J = 8.60, *m*-H).

(3a*R*,8a*R*,9a*R*)-3-{[((1*R*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)methylamino]methyl}-8a-methyldecahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (35). Found: *m/z* 413.2688 $[M]^+$, $C_{25}H_{35}NO_4$; calcd: M = 413.2566. UV spectrum (EtOH, λ_{max}, nm, log ε): 206 (4.42). IR spectrum (KBr, ν, cm^{-1}): 947m, 1144m, 1163m, 1759s (C=O), 2934m, 3412br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.70 (1H, q, J = 13.11, H-6a); 0.74 (3H, d, J = 6.65, CHMe), 0.95 (3H, s, H-15); 1.10–1.71 (8H, m, H-1, H-2, H-3, H-9a, H-6b); 1.77–1.90 (1H, m, H-7); 2.16 (1H, dd, J_1 = 1.56, J_2 = 15.46, H-9b); 2.28 (3H, s, NMe); 2.47–2.71 (5H, m, H-5, H-13, H-14); 2.86–2.98 (2H, m, CHMe, H-11); 4.09 (1H, d, J = 9.78, CHOH); 4.38 (1H, m, H-8); 7.19 (5H, m, H_{arom}).

(3a*R*,8a*R*,9a*R*)-3-{[2-(1*H*-Indol-3-yl)ethylamino[methyl}-8a-methyldecahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (36). $C_{25}H_{32}N_2O_3$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 408 (1.4) $[M]^+$, 276 (4), 201 (4), 188 (4), 160 (13), 155 (8), 145 (22), 130 (100), 115 (25), 105 (48). UV spectrum (EtOH, λ_{max}, nm, log ε): 221 (4.67), 282 (3.95). IR spectrum (KBr, ν, cm^{-1}): 742m, 1158m, 1456m, 1756s (C=O), 2938m, 3400br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.70 (1H, q, J = 12.56, H-6a); 0.92 (3H, s, H-15); 1.07–1.23 (2H, m, H-2); 1.30–2.00 (7H, m, H-1, H-3, H-5, H-6b, H-9a); 2.12 (1H, dd, J_1 = 1.86, J_2 = 15.35, H-9b); 2.25 (1H, m, H-7); 2.54–3.03 [9H, m, $N(CH_2)_2$, H-11, H-13, H-14]; 4.39 (1H, br.s, H-8); 7.03–7.25 (3H, m, H-2′, H-5′, H-6′); 7.36 (1H, d, J = 7.67, H-7′); 7.60 (1H, dd, J_1 = 1.44, J_2 = 7.67, H-4′); 8.15 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-3-{[2-(5-Methoxy-1*H*-indol-3-yl)ethylamino[methyl}-8a-methyldecahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (37). $C_{26}H_{34}N_2O_4$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 437 (4.2) $[M - 1]^+$, 278 (76), 187 (56), 162 (59), 157 (48), 147 (83), 137 (49), 117 (100), 107 (70), 91 (78). UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.60), 277 (3.94). IR spectrum (KBr, ν, cm^{-1}): 958m, 1027m, 1485m, 1757s (C=O), 2936m, 3390br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.70 (1H, q, J = 12.79, H-6a); 0.92 (3H, s, H-15); 1.11–1.93 (9H, m, aliphatic protons); 2.12 (1H, dd, J_1 = 1.76, J_2 = 15.40, H-9b); 2.18 (1H, m, H-7); 2.53–2.75 (2H, m, H-11, H-14a); 2.80–3.03 [7H, m, $N(CH_2)_2$, H-13, H-14b]; 3.85 (3H, s, OMe); 4.39 (1H, m, H-8); 6.84 (1H, dd, J_1 = 2.40, J_2 = 8.82, H-6′); 7.02 (1H, dd, J_1 = 2.40, J_2 = 4.00, H-7′); 7.24 (1H, d, J = 8.82, H-2′); 7.25 (1H, s, H-4′); 8.05 (1H, br.s, NH).

(3a*R*,8a*R*,9a*R*)-8a-Methyl-3-(3,4,5,6-tetrahydro-2*H*-[2,3′]bipyridin-1-ylmethyl)decahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (38). Found: *m/z* 410.2739 $[M]^+$, $C_{25}H_{34}N_2O_3$; calcd: M = 410.2569. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.32), 262 (3.56). IR spectrum (KBr, ν, cm^{-1}); 809m, 957m, 1154m, 1759s (C=O), 2967m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.41 (1H, q, J = 12.70, H-6a); 0.82 (3H, s, H-15); 1.03–1.85 (15H, m, aliphatic protons); 2.00–2.34 (4H, m, H-14a, H-7, H-9b); 2.45–2.55 (3H, m, H-6′a, H-14b, H-13a); 2.86 (1H, dd, J_1 = 3.72, J_2 = 13.69, H-6′b); 3.05 (1H, m, H-2′); 3.06 (1H, dd, J_1 = 2.94, J_2 = 10.36, H-13b); 4.28 (1H, m, H-8); 7.25 (1H, m, H-5″); 7.65 (1H, d, J_1 = J_2 = 1.95, J_3 = 7.83, H-4″); 8.43 (1H, dd, J_1 = 1.56, J_2 = 4.69, H-6″); 8.50 (1H, d, J = 1.95, H-2″).

(3a*R*,8a*R*,9a*R*)-3-((*R*)-6,7-Dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-ylmethyl)-8a-methyldecahydrospiro[naphtho[2,3-*b*]furan-2-on-5,2′-oxirane] (39). Found: *m/z* 455.2118 $[M]^+$, $C_{27}H_{37}NO_5$; calcd: M = 455.2671. UV spectrum (EtOH, λ_{max}, nm, log ε): 206 (4.66), 284 (3.58). IR spectrum (KBr, ν, cm^{-1}): 1124m, 1172m, 1222m, 1259m, 1513m, 1761s (C=O), 2945m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.67 (1H, q, J = 12.50, H-6a); 0.92 (3H, s, H-15); 1.09–1.75 (8H, m, H-1, H-3, H-2, H-9a, H-6b); 1.31 (3H, d, J = 6.45, Me-1′), 1.78–1.92 (1H, m, H-7); 2.15 (1H, dd, J_1 = 1.95, J_2 = 15.80, H-9b); 2.37–2.71 (5H, m, H-5, H-3′, H-4′); 2.75–3.15 (3H, m, H-11, H-13), 3.72 (1H, q, J = 6.65, H-1′); 3.82 (6H, s, OMe); 4.43 and 4.74 (2H, two unresolved d, H-14); 4.45 (1H, m, H-8); 6.51 and 6.53 (2H, two s, H-5′, H-8′).

3-((3a*R*,8a*R*,9a*R*)-8a-Methyl-2-oxodecahydrospiro[naphtho[2,3-*b*]furan-5,2′-oxiran]-3-ylmethyl)-1,2,3,4,5,6,-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (40). Found: *m/z* 438.2472 $[M]^+$, $C_{26}H_{34}N_2O_4$; calcd: M = 438.2519. UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.50), 234 (4.30), 310 (4.32). IR spectrum (KBr, ν, cm^{-1}); 961m, 1128m, 1158m, 1208m, 1545m, 1576m, 1653s and 1751s (C=O), 2913m, 2932m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.51 (1H, q, J = 12.57, H-6a); 0.87 (3H, s, H-15); 1.95–2.10 (14H, aliphatic protons); 2.34–2.67 (7H, m, H-7, H-13, H-2′, H-4′); 2.90–2.93 (3H, m, H-11, H-14); 3.85 (1H, dd, J_1 = 6.17, J_2 = 15.66, H-6′a); 4.02 (1H, d, J = 15.66, H-6′b); 4.31 (1H, m, H-8); 5.94 (1H, dd, J_1 = 1.32, J_2 = 6.84, H-11′); 6.42 (1H, dd, J_1 = 1.54, J_2 = 9.04, H-9′); 7.25 (1H, dd, J_1 = 6.84, J_2 = 9.04, H-10′).

(3a*S*,4*R*,5*S*,8a*R*,9a*R*)-3-{[((1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)methylamino]methyl}-5,8a-dimethyl-4,4a-epoxydecahydronaphtho[2,3-*b*]furan-2-one (41). Found: *m/z* 413.2066 $[M]^+$, $C_{25}H_{35}NO_4$; calcd: M = 413.2566. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.44). IR spectrum (KBr, ν, cm^{-1}): 1046m, 1199m, 1452w, 1758s (C=O), 2914m, 2934m, 3474br.s (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, d, J = 6.39, CHMe), 1.14 (3H, d, J = 7.72 , H-14); 1.20 (3H, s, H-15); 1.05–1.95 (8H, m, aliphatic protons); 2.34 (3H, s, NMe), 2.47–2.56 (1H, m, H-4); 2.64–2.84 (4H, m, NCHMe, H-11, H-13); 2.96–3.20 (2H, m, H-6, H-7); 4.30 (1H, d, J = 9.92, CHOH); 4.57–4.75 (1H, m, H-8); 7.33 (5H, s, H_{arom}).

3-((3a*R*,4a*R*,5*S*,8a*R*,9a*R*)-5,8a-Dimethyl-2-oxo-4,4a-epoxydecahydronaphtho[2,3-*b*]furan-3-ylmethyl)-1,2,3,4,5,6,-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (42). Found: *m/z* 438.2222 $[M]^+$, $C_{26}H_{34}N_2O_4$; calcd: M = 438.2519. UV spectrum (EtOH, λ_{max}, nm, log ε): 201 (4.22), 234 (3.97), 309 (4.02). IR spectrum (KBr, ν, cm^{-1}); 970m, 1130m, 1336m, 1473m, 1583m, 1653s and 1752s (C=O), 2913m.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.05 (3H, d, J = 7.28, H-14); 1.09 (3H, s, H-15); 1.23–2.98 and 2.31–3.04 (11H each, two m, aliphatic protons); 3.79–3.84 (1H, dd, J_1 = 4.95, J_2 = 15.66, H-6′a); 3.98 (1H, d, J = 15.66, H-6′b); 4.45 (1H, m, H-8); 5.97 (1H, dd, J_1 = 1.32, J_2 = 6.84, H-11′); 6.47 (1H, d, J_1 = 1.32, J_2 = 9.26, H-9′); 7.28 (1H, dd, J_1 = 6.84, J_2 = 9.26, H-10′).

(3a*S*,4*S*,4a*R*,5*S*,9a*R*)-4-Hydroxy-3-{[2-(5-methoxy-1*H*-indol-3-yl)ethylamino]methyl}-4a,5-dimethyl-3a,4,4a,5,6,7,9,9a-octahydro-3*H*-naphtho[2,3-*b*]furan-2-one (43). Found: *m/z* 439.2739 $[M]^+$, $C_{26}H_{34}N_2O_4$; calcd: M = 439.2590. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.68), 277 (3.96). IR spectrum (KBr, ν, cm^{-1}): 921m, 1171m, 1213m, 1485m, 1756s (C=O), 2930m, 2954m, 3432br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (3H, s, H-15); 0.98 (3H, d, J = 6.81, H-14); 1.21–1.51 (5H, m, H-3, H-2, H-4, H-9a); 2.34 (1H, dd, J_1 = 1.67, J_2 = 15.24, H-9b); 2.36–2.53 (2H, m, CH_2Ind); 2.73–3.11 (6H, m, NCH_2, H-7, H-11, H-13); 3.74 (3H, s, OMe); 4.18 (1H, dd, J_1 = 2.86, J_2 = 11.74, H-6); 4.56 (1H, dt, J_1 = 7.21, J_2 = 8.02, J_3 = 7.64, H-8); 5.33 (1H, m, OH); 5.48 (1H, m, H-1); 6.75 (1H, dd, J_1 = 2.86, J_2 = 8.54, H-6′); 6.92 (1H, br.s, H-2′); 7.16 (1H, dd, J_1 = 0.81, J_2 = 2.86, H-4′); 7.26 (1H, dd, J_1 = 1.10, J_2 = 8.54, H-7′); 7.95 (1H, br.s, NH).

Acylation of Tryptamine Derivatives 20, 28, and 36 (General Method). The tryptamine derivative of the lactone (**20**, **28**, or **36**, 0.12 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with K_2CO_3 (100 mg) in H_2O (1 mL). Acetylchloride (30 mg, 0.36 mmol, 0.03 mL) was added dropwise with stirring and cooling in ice. The cooling was removed after 0.5 h. The mixture was stirred at room temperature for 1 h. The aqueous layer was separated. The organic layer was washed with citric acid solution and H_2O (2×) and dried over anhydrous Na_2SO_4. The solvent was evaporated. The solid was recrystallized from MeOH. This method was used to prepare the following compounds.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-*N*-((3a*R*, 8a*R*,9a*R*)-8a-methyl-5-methylidene-2-oxodecahydronaphtho[2,3-*b*]furan-3-ylmethyl)acetamide (44)** was prepared from **20**. Yield 85%, mp 193–194°C, $[\alpha]_D^{30}$ +75° (*c* 0.1, MeOH). $C_{27}H_{34}N_2O_3$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 433 (1.2) $[M - 1]^+$, 264 (5), 218 (6), 204 (9), 199 (14), 191 (15), 164 (8), 159 (27), 130 (100), 129 (24). UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.60), 222 (4.69), 282 (3.28). IR spectrum (KBr, ν, cm^{-1}): 969m, 1146m, 1455m, 1612s and 1761s (C=O), 2933m, 3300br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, s, H-15); 0.99–1.20 (2H, m, H-2); 1.35–1.77 (7H, m, H-1, H-3, H-6, H-9a); 1.88 (3H, s, NAc); 2.1 (1H, dd, J_1 = 1.62, J_2 = 15.58, H-9b); 2.31 (1H, dd, J_1 = 1.62, J_2 = 13.72, H-5); 2.49 (1H, m, H-7); 2.94–3.14 (3H, m, CH_2Ind, H-13a); 3.22 (1H, dd, J_1 = 6.28, J_2 = 13.72, H-13b); 3.62–3.96 (3H, m, NCH_2, H-11); 4.40 (1H, m, H-8); 4.43 (1H, d, J = 1.16, H-14a); 4.75 (1H, d, J = 1.16, H-14b); 6.97 (1H, d, J = 2.09, H-2′); 7.15 (2H, dt, J_1 = 1.39, J_2 = 6.97, J_3 = 7.44, H-5′, H-6′); 7.36 (1H, dd, J_1 = 1.39, J_2 = 6.97, H-7′); 7.58 (1H, dd, J_1 = 1.39, J_2 = 7.44, H-4′); 8.32 (1H, br.s, NH).

***N*-((3a*R*,5*S*,8a*R*,9a*R*)-5,8a-Dimethyl-2-oxo-2,3,3a,5,6,7,8,8a,9,9a-decahydronaphtho[2,3-*b*]furan-3-ylmethyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (45)** was prepared from **28.** Yield 79%, mp 189–191°C, $[\alpha]_D^{30}$ +75° (*c* 0.1, MeOH). $C_{27}H_{34}N_2O_3$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 435 (1.2) $[M + 1]^+$, 263 (17), 246 (6), 215 (15), 199 (9), 176 (69), 171 (76), 160 (16), 155 (10), 145 (42), 130 (100). UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.4), 222 (4.44), 282 (3.66). IR spectrum (KBr, ν, cm^{-1}): 993m, 1188m, 1433m, 1643s and 1759s (C=O), 2924m, 3398br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.10 (3H, d, J = 7.49, H-14); 1.23 (3H, s, H-15); 1.43–1.66 (7H, m, H-1, H-2, H-3, H-9a); 1.90 (3H, s, NAc); 2.07 (1H, dd, J_1 = 2.64, J_2 = 14.91, H-9b); 2.46 (1H, m, H-4); 2.90–3.27 [6H, m, $N(CH_2)_2$, H-13]; 3.78 (1H, m, H-11); 3.98 (1H, m, H-7); 4.66 (1H, m, H-8); 5.27 (1H, d, J = 2.40, H-6); 6.99 (1H, unresolved d, H-2′); 7.15 (2H, t, J = 7.93, H-5′, H-6′); 7.36 (1H, d, J = 7.93, H-7′); 7.57 (1H, d, J = 7.71, H-4′); 8.95 (1H, br.s, NH).

***N*-[2-(1*H*-Indol-3-yl)ethyl]-*N*-((3a*R*,8a*R*,9a*R*)-8a-methyl-2-oxodecahydrospironaphtho[2,3-*b*]furan-5,2′-oxiran)-3-ylmethyl)acetamide (46)** was prepared from **36**. Yield 83%, mp 248–250°C, $[\alpha]_D^{30}$ +20° (*c* 0.1, MeOH). $C_{27}H_{34}N_2O_4$. Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 278 (15), 261 (2), 248 (2), 204 (5), 199 (6), 188 (6), 183 (7), 176 (9), 171 (60), 161

(30), 146 (23), 131 (100). UV spectrum (EtOH, λ_{max}, nm, log ε): 202 (4.42), 222 (4.29), 282 (3.64). IR spectrum (KBr, ν, cm^{-1}): 959m, 1117m, 1213m, 1455m, 1624s and 1750s (C=O), 2931m, 2957m, 3214br.s (NH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.61 (1H, q, J = 12.64, H-6a); 0.93 (3H, s, H-15); 1.09–2.21 (10H, m, aliphatic protons); 1.84 (3H, s, NAc); 2.44 (1H, m, H-5); 2.53 (1H, d, J = 4.62, H-14a); 2.62 (1H, d, J = 4.62, H-14b); 2.93–3.11 (4H, m, CH_2Ind, H-13); 3.55–3.97 (3H, m, NC$\underline{H}_2$, H-11); 4.38 (1H, m, H-8); 6.96 (1H, d, J = 2.09, H-2′); 7.15 (2H, dt, J_1 = 1.36, J_2 = 7.24, J_3 = 7.44, H-5′, H-6′), 7.36 (1H, d, J = 7.24, H-7′); 7.56 (1H, dd, J_1 = 1.40, J_2 = 7.44, H-4′); 8.20 (1H, br.s, NH).

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