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An efficient approach to isoindolo[2,1-*b*][2]benzazepines via intramolecular [4+2] cycloaddition of maleic anhydride to 4-α-furyl-4-*N*-benzylaminobut-1-enes

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Abstract—Acylation of 4-α-furyl-4-*N*-benzylaminobut-1-enes with maleic anhydride gave 4-oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid via amide formation followed by intramolecular Diels–Alder reaction of furan (IMDAF). The cycloaddition proceeded under mild reaction conditions (25 °C) and provided only the *exo*-adduct in quantitative yield. Treatment of this compound with PPA gave isoindolo[2,1-*b*][2]benzazepine derivatives via ring opening, aromatization and intramolecular electrophilic alkylation. In order to extend the scope of the reaction sequence, 7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids were further transformed into useful synthetic intermediates.

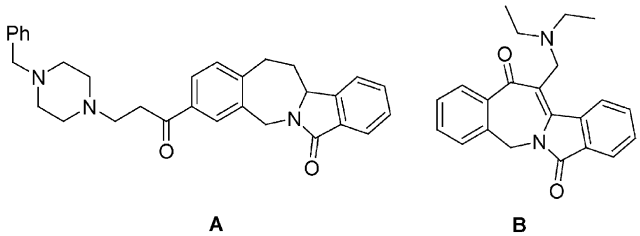
1. Introduction

Compounds with the isoindolo[2,1-*b*][2]benzazepine core are known to have important biological activities.[1,2] For example, 5,11b,12,13-tetrahydro-3-[1-oxo-3[1-(phenylmethyl)-4-piperidinyl]propyl]-7*H*-isoindolo[2,1-*b*][2]benzazepine-7-one (**A**) and 12-diethylaminomethyl-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**B**) are known to have AChE-inhibiting activity[1a] and a protective effect against nitrogen-induced hypoxia[2] respectively (Scheme 1).

Although compounds with the isoindolo[2,1-*b*][2]benzazepine moiety show interesting biological properties, to the best of our knowledge, only two synthetic routes to isoindolo[2,1-*b*][2]benzazepines have been reported in the literature. The first route is based on the intramolecular Friedel–Crafts acylation of 2,3-dihydro-3-oxo-2-(phenylmethyl)-1*H*-isoindol-1-acetic acids[2] whereas the second one utilized the π-cyclization of *N*-acyliminium ions generated from *N*-alkenyl-3-hydroxyisoindolin-1-ones.[3] Both approaches involve many steps and yielded the desired products in moderate yields. Recently,[4] we reported a synthetic approach to substituted oxoisoindolo[2,1-*a*]quinolines from 4-α-furyl-4-*N*-arylaminobut-1-ens (homoallylamines) using an intramolecular Diels–Alder reaction of furan as the key transformation. As part of our continuing effort to investigate the reactivity of homoallylfuryl amines,[5] we extended this approach to prepare various polycyclic nitrogen heterocycles. In this paper we describe a three-step protocol for the synthesis of 7-oxotetrahydroisoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids **5a-e** from readily available 4-α-furyl-4-*N*-benzylaminobut-1-enes **3a-e** (Scheme 2).

2. Results and discussion

The starting 4-*N*-benzylaminobut-1-enes **3a-e** were readily obtained by a two-step one-pot procedure.[5c] Condensation of benzylamines **1** with furaldehydes **2** gave the intermediate imines, which were immediately treated with



Scheme 1.

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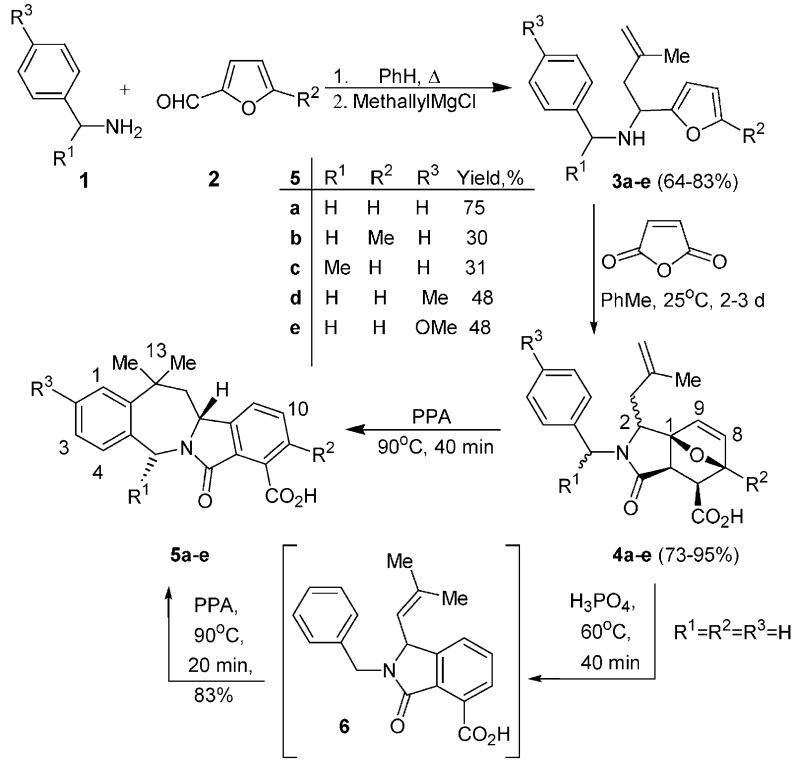


5	R^1	R^2	R^3	Yield,%
a	H	H	H	75
b	H	Me	H	30
c	Me	H	H	31
d	H	H	Me	48
e	H	H	OMe	48

Scheme 2.

methallylmagnesium chloride to provide the desired amines **3a**-**e** in good overall yields (Scheme 2). It is noteworthy that the α-methylbenzylamine derivative **3c** was isolated as a 1:1.1 mixture of diastereoisomers with (R^*,R^*)- and (R^*,S^*)-oriented methallyl and CH_3 (R^1) groups.

The reaction of homoallylamines **3a**-**e** with maleic anhydride[6] proceeded smoothly (toluene, rt, 2–3 days) to give the corresponding 3-benzyl-2-methallyl-3-aza-10-oxatricyclo [5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids **4a**-**e** as a ~1:1 mixture of isomers at C-2. The products are formed via an initial *N*-acylation followed by the IMDA cycloaddition reaction sequence. The IMDA cycloaddition reaction was highly stereoselective and furnished only the *exo*-cycloadducts **4a**-**e**. Under the acylation reaction conditions, amine **3c** with two stereogenic centers gave a 1:5:10 mixture of *exo*-isomers, determined from the ^{1}H NMR spectrum of the crude product. No additional experiment was carried out to establish the relative stereochemistry of compound **4c**. The *exo*-configuration of Diels–Alder adducts **4a**,**c**-**e** (R^2=H) was confirmed by comparing the $^3J_{6\text{-H},7\text{-H}}$ value of compounds **4a**,**c**-**e** with the analogous bridged systems reported in the literature.[7] The reported $^3J_{6\text{-H},7\text{-H}}$ value for 6-H in molecules with an *endo*-orientation is <1 Hz whereas, the $^3J_{6\text{-H},7\text{-H}}$ value for 6-H in molecules with an *exo*-orientation is around 3 Hz. So the observed coupling constants for compounds **4a**,**c**-**e** ($^3J_{6\text{-H},7\text{-H}}$=0–0.8 Hz) unambiguously proves the *endo*-orientation of 6-H (and 5-H correspondingly). The stereochemistry of adducts **4b** (R^2=Me) can be surmised by analogy with compounds **4a**,**c**-**e**. We were unable to separate the isomer mixtures due to the insoluble nature of compound **4** in commonly used solvents.

Having successfully isolated compounds **4a**-**e** in high yields, we then proceeded to study the acid promoted ring opening/ ring forming sequence. Treatment of epoxyisoindolines **4a**-**e** with excess polyphosphoric acid (PPA) at 90 °C for 40 min smoothly promoted a 1,7-oxygen bridge opening/ aromatization/ intramolecular electrophilic cyclization sequence to give the isoindolobenzazepine carboxylic acids **5a**-**e** in 30–75% yields (Scheme 2). Treatment of compound **4a** with H_3PO_4 at 60 °C gave a mixture of the cyclized compound **5a** and the uncyclized double bond migration product **6** (~1:2). Isolation of intermediate **6** shows that the reaction sequence involves an initial cleavage of the 1,7-oxygen bridge followed by aromatization to give **6**. Electrophilic cyclization of pure isoindolone **6** under the action of PPA at 90 °C proceeds via formation of the thermodynamically stable tertiary carbocation and yields isoindolobenzazepine **5a** in 83% yield.

Compounds **5a**,**b**,**d**,**e** exist in the form of one conformer with the pseudo-axial orientation of 11b-H, as evidenced by ^{1}H NMR spectroscopic data. In particular, the vicinal coupling constant values $J_{11b,12A(ax)}$=12.0–14.0 Hz and $J_{11b,12B(eq)}$=2.5–2.9 Hz unambiguously prove the pseudo-axial orientation of 11b-H. Although heating isomeric mixtures of compound **4c** (R^1=Me) with PPA could lead to a mixture of two stereoisomers of compound **5c** (*cis*- and *trans*-configurations of the methyl group at C-5 and the proton at C-11b), to our surprise, acid **5c** was isolated as a single *cis*-isomer with the pseudo-equatorial orientation of the 5-CH_3 group and the pseudo-axial of the 11b proton.

The *cis*-structure of compound **5c** was confirmed by NOE. The NOE values (η) indicated an increase of H_i signal

intensity when H_j signal was saturated ($\eta_{Hi}\{H_j\}$, %). The values of $\eta_{11b\text{-}H}\{5\text{-}H\}=9.5\%$, on one hand, and $\eta_{5\text{-}H}\{11b\text{-}H\}=5\%$, on the other hand, proved that 11b-H and 5-H were situated on the one side of the benz-2-azepine ring plane.

The carboxylic acids **5a**-**e** are crystalline with high melting points and insoluble in most of the commonly used organic solvents. The low (~30%) yield of cyclization products **5b** and **5c** is explained by considerable resinification of reaction mixtures and losses during recrystallization from the *i*-PrOH–DMF mixture. Probably, the second (minor) *trans*-isomer of **5c** could be lost at the purification stage of the reaction mixture.

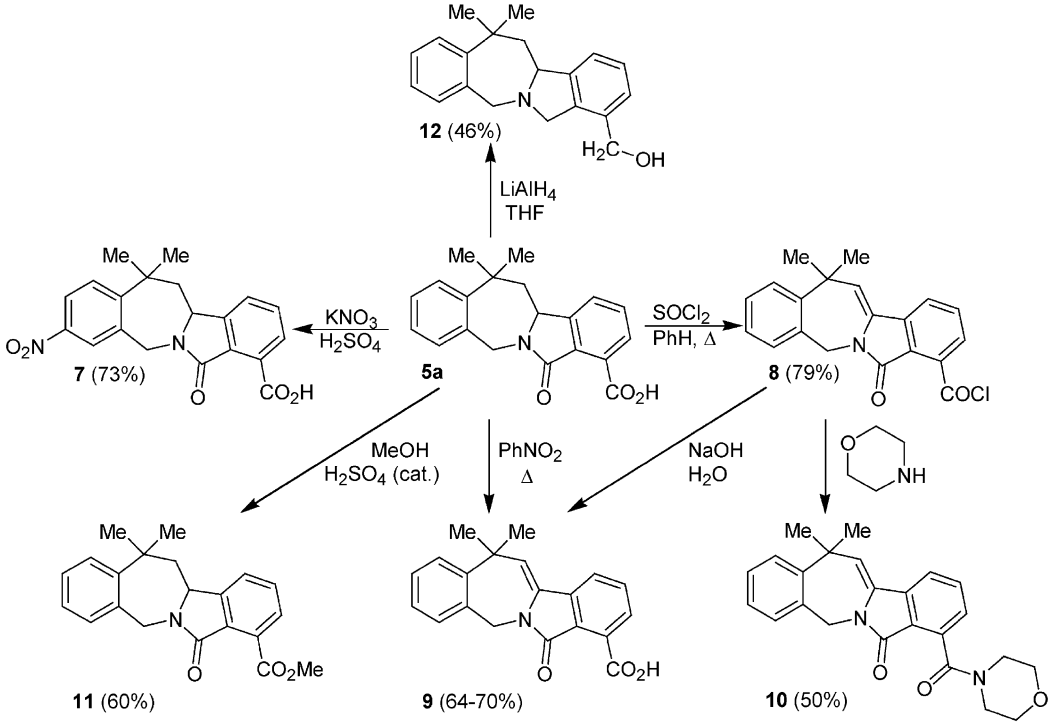
Having developed an efficient simple synthetic route for the isoindolo[2,1-*b*][2]benzazepine system, we turned our attention to further functionalize the system to make the reaction sequence synthetically useful. Accordingly, compound **5a** was chosen as the test substrate and subjected to various reaction conditions and the results are shown in Scheme 3.

As far as we know there is only one example of the aromatic electrophilic substitution of 7-oxoisoindolo[2,1-*b*][2]benzazepines.[8] The authors regioselectively acylated isoindolobenzazepines at the C-3 position with AcCl/$AlCl_3$ in boiling dichloroethane. Unfortunately, our attempts to acylate the isoindolobenzazepine carboxylic acid **5a** with excess Ac_2O/$AlCl_3$ in dichloromethane (or AcCl/$AlCl_3$ in dichloroethane or nitrobenzene) using the published procedure[8] met with failure.

Treatment of **5a** with potassium nitrate and concentrated sulfuric acid afforded the 3-nitro substituted azepine **7** as a single compound in 73% yield. The structure of compound **7** was confirmed by ^{1}H NMR spectroscopy, based on the multiplicities of proton signals of the nitro substituted benzene ring, and NOE values for the same protons. High NOE values were measured for the doublet signal δ 7.69 ($J_{ortho}=8.9$ Hz, NOE=13%) with 13-CH_3 saturation (δ 1.50), and for the doublet signal δ 8.30 ($J_{meta}=2.7$ Hz, NOE=18%) with 5-H_A saturation (δ 5.37) thus proving 1 and 4 position of the above mentioned aromatic protons, and 3 nitro substituent position.[9]

Heating acid **5a** in $PhNO_2$ smoothly oxidized the ring to give compound **9**. Heating compound **5a** with thionyl chloride in benzene gave the unexpected ring oxidized acid chloride **8**. We suppose, that the dehydrogenation occurs due to an oxidative action of $SOCl_2$ itself or products of its decomposition (SO_2, Cl_2). Several examples of similar dehydrogenation exist in the literature,[10] but in all cases the oxidation was carried out under basic conditions (pyridine, picoline). The structure of the acid chloride **8** was confirmed by ^{1}H and ^{13}C NMR spectra and by conversion into compound **9** by hydrolysis of acid chloride **8** with NaOH. The amide **10** and ester **11** were prepared from the acid chloride **8** and acid **5a**, respectively, in moderate yields. The reduction of **5a** with 8 mol equiv. lithium aluminum hydride in boiling THF gave alcohol **12** (Scheme 3).

In conclusion, this paper describes a simple and efficient synthetic approach to isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids. The synthetic route involves intramolecular Diels–Alder cycloaddition of 4-α-furyl-4-*N*-benzylaminobut-1-enes with maleic anhydride followed by PPA acid-promoted intramolecular seven-membered ring formation sequence. This two-step synthetic sequence is very efficient and yielded the tetracyclic compounds in high



Scheme 3.

yields. Further functionalization of the acid was also examined. Considering the mild reaction conditions, and stereochemical control associated with the IMDA cycloaddition/ acid promoted cyclization reaction sequence, we believe that this methodology could be of use in organic synthesis for the preparation of polycyclic drug- and natural product-like molecules.

3. Experimental

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a UR-20 spectrometer in KBr pellets for solid or in thin film for oils. ^{1}H NMR spectra were recorded on a Bruker WP-200 or WH-400 spectrometers for solutions (2%) in deuteriochloroform or DMSO-D_6 at 30 °C and using TMS as internal standard. Chemical shifts are reported in ppm units, and coupling constants (J) are quoted in Hz. Abbreviations of coupling patterns: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), ddd (doublet doublet of doublets), ddt (doublet doublet of triplets), m (multiplet). Mass spectra were obtained by electron impact at 70 eV on a Varian MAT-112 spectrometer or Finnegan MAT95XL chromatomass spectrometer. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC silufol UV_{254} plates.

3.1. 4-(2-Furyl)-4-*N*-benzylaminobut-1-enes 3. Typical procedure

The freshly obtained[5c,9] aldimine (0.30 mol) was added slowly drop-wise at reflux to a stirred solution of methallylmagnesium chloride, prepared from methallyl chloride (41 mL, 0.45 mol) and magnesium turnings (22.0 g, 0.90 mol) in mixture THF–ether (1:1, 300 mL). After the addition of the Schiff base the reaction mixture was stirred for one hour at room temperature. The cooled reaction mixture was taken up in saturated aqueous NH_4Cl solution (300 mL) under ice cooling and extracted with ether (3×100 mL). The organic layer was dried $MgSO_4$ and concentrated. The residue was distilled in vacuo to give the products **3** as colourless oils.

3.1.1. 2-Methyl-4-(2-furyl)-4-*N*-benzylaminobut-1-ene (3a). Yield 83%; bp 158–160 °C/7 mm Hg; n_D^{20} 1.5350; IR 3320 (NH), and 1640 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 241 (1), 186 (50), 91 (100), 77 (32), 55 (9), 51 (16), 39 (22); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H, Me-2), 1.72 (brs, 1H, NH), 2.35–2.60 (m, 2H, H-3), 3.56 (d, 1H, NCH_AH$_B$, J=13.4 Hz), 3.77 (d, 1H, NCH$_A$$H_B$, J=13.4 Hz), 3.85 (dd, 1H, H-4, J=8.2, 6.4 Hz), 4.73 (brs, 1H, H-1), 4.79 (brs, 1H, H-1), 6.18 (dd, 1H, H-3′, J=3.1, 0.9 Hz), 6.31 (dd, 1H, H-4′, J=3.1, 1.8), 7.15–7.35 (m, 5H, Ph-H), 7.36 (dd, 1H, H-5′, J=1.8, 0.9). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.4 (C-2′), 142.2 (C$_{qu.}$-Ph), 141.4 (C-5′), 140.2 (C-2), 128.23 (2C, *orto*-Ph), 128.10 (2C, *meta*-Ph), 126.8 (*para*-Ph), 113.29 (C-1), 109.8 (C-3′), 106.4 (C-4′), 53.0 (C-4), 51.1 (CH_2N), 43.5 (C-3), 21.8 (Me-2). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.69; H, 7.86; N, 5.81.

3.1.2. 2-Methyl-4-(2-(5-methylfuryl))-4-*N*-benzylaminobut-1-ene (3b). Yield 34%; bp 158–159 °C/3 mm Hg; IR 3310 (NH), and 1640 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (57), 91 (100), 77 (8), 65 (15), 51 (10), 39 (20); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H, Me-2), 1.73 (brs, 1H, NH), 2.29 (brs, 3H, Me-5′), 2.41 (dd, 1H, H-3B, J=5.5, 13.8 Hz), 2.51 (dd, 1H, H-3A, J=8.9, 13.8 Hz), 3.57 (d, 1H, NCH_AH$_B$, J=13.4 Hz), 3.77 (dd, 1H, H-4, J=8.9, 5.5 Hz), 3.80 (d, 1H, NCH$_A$$H_B$, J=13.4 Hz), 4.76 (brs, 1H, H-1), 4.80 (brs, 1H, H-1), 5.89 (dq, 1H, H-4′, J=3.0, 1.0 Hz), 6.06 (d, 1H, H-3′, J=3.0 Hz), 7.17–7.37 (m, 5H, Ph–H). Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.00; H, 8.22; N, 5.47.

3.1.3. 2-Methyl-4-*N*-(α-methylbenzyl)-4-(2-furyl)aminobut-1-ene (3c). Mixture of two diastereoisomers in the ratio ~1:1.1, yield 79%; bp 150–155 °C/7 mm Hg; n_D^{20} 1.5274; IR 3305 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (51), 105 (100), 96 (90), 79 (28), 77 (33), 55 (15), 41 (14), 39 (21); ^{1}H NMR ($CDCl_3$, 200 MHz) maj isomer δ 1.33 (d, 3H, *Me*CHN, J=6.5 Hz), 1.62 (s, 3H, Me-2), 1.68 (brs, 1H, NH), 2.43 (dd, 1H, H-3B, J=13.7, 7.1 Hz), 2.52 (dd, 1H, H-3A, J=13.7, 7.1 Hz), 3.74 (q, 1H, MeC*H*N, J=6.5 Hz), 3.90 (t, 1H, H-4, J=7.1 Hz), 4.68 (m, 1H, H-1), 4.75 (m, 1H, H-1), 6.06 (brd, 1H, H-3′, J=3.0, 0.8 Hz), 6.22 (dd, 1H, H-4′, J=3.0, 1.8 Hz), 7.29 (dd, 1H, H-5′, J=1.8, 0.8 Hz), 7.16–7.31 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.61 (C-2′), 145.74 (C$_{qu.}$-Ph), 142.2 (C-5′), 140.9 (C-2), 126.40 (2C, *ortho*-Ph), 128.10 (2C, *meta*-Ph), 126.58 (*para*-Ph), 113.0 (C-1), 109.7 (C-3′), 105.9 (C-4′), 55.1 (*C*HMe), 52.2 (C-4), 43.0 (C-3), 22.8 (CH*Me*), 22.1 (Me-2); min isomer δ 1.29 (d, 3H, *Me*CHNH, J=6.7 Hz), 1.45 (s, 3H, Me-2), 1.68 (brs, 1H, NH), 2.31 (dd, 1H, H-3B, J=13.5, 5.4 Hz), 2.45 (dd, 1H, H-3A, J=13.5, 9.1 Hz), 3.52 (dd, 1H, H-4, J=9.1, 5.4 Hz), 3.59 (q, 1H, MeC*H*N, J=6.7 Hz), 4.72 (m, 1H, H-1), 4.78 (m, 1H, H-1), 6.06 (brd, 1H, H-3′, J=3.0, 0.7 Hz), 6.29 (dd, 1H, H-4′, J=3.0, 1.7 Hz), 7.36 (dd, 1H, H-5′, J=1.7, 0.7 Hz), 7.16–7.31 (m, 5H, Ph-H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.56 (C-2′), 145.23 (C$_{qu.}$-Ph), 142.1 (C-5′), 141.2 (C-2), 126.48 (2C, *ortho*-Ph), 128.18 (2C, *meta*-Ph), 126.7 (*para*-Ph), 113.2 (C-1), 109.6 (C-3′), 106.2 (C-4′), 55.0 (*C*HMe), 51.0 (C-4), 43.9 (C-3), 24.5 (CH*Me*), 21.6 (Me-2); Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.02; H, 8.25; N, 5.50.

3.1.4. 2-Methyl-4-*N*-(4-methylbenzyl)-4-(2-furyl)aminobut-1-ene (3d). Yield 75%; bp 147–148 °C/2 mm Hg; n_D^{22} 1.5315; IR 3320 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (31), 105 (100), 95 (18), 94 (13), 91 (22), 79 (21), 77 (26), 65 (11), 39 (35); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 3H, Me-2), 1.78 (brs, 1H, NH), 2.34 (s, 3H, *Me*-Ar), 2.43 (dd, 1H, H-3B, J=13.7, 5.7 Hz), 2.53 (ddd, 1H, H-3A, J=13.7, 8.7, 0.7 Hz), 3.52 (d, 1H, NCH_AH$_B$, J=13.0 Hz), 3.76 (d, 1H, NCH$_A$$H_B$, J=13.0 Hz), 3.85 (dd, 1H, H-4, J=8.7, 5.7 Hz), 4.75 (d, 1H, H-1, J=0.7 Hz), 4.80 (brs, 1H, H-1), 6.20 (brd, 1H, H-3′, J=3.0 Hz), 6.34 (dd, 1H, H-4′, J=3.0, 1.7 Hz), 7.13 (BB′, 2H, H-Ar), 7.16 (AA′, 2H, H-Ar), 7.39 (dd, 1H, H-5′, J=1.7, 0.7 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.3 (C-2′), 142.0 (C$_{qu.}$–C_6H_4Me), 141.2 (C-5′), 137.0 (C$_{qu.}$–C_6H_4Me), 136.1 (C-2), 128.8 (2C,

ortho-C_6H_4Me), 127.9 (2C, *meta*-C_6H_4Me), 113.1 (C-1), 109.7 (C-3′), 102.2 (C-4′), 50.7 (CH_2N), 52.8 (C-4), 43.3 (C-3), 20.9 ($C_6H_4\mathit{Me}$), 22.7 (Me-2); Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.00; H, 8.28; N, 5.52.

3.1.5. 2-Methyl-4-*N*-(4-methoxybenzyl)-4-(2-furyl)aminobut-1-ene (3e). Yield 71%; bp 162 °C/2 mm Hg; n_D^{22} 1.5381; IR 3310 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): $[M-55\ (-CH_2C(Me)=CH_2)]^+$ 216 (28), 121 (100), 91 (11), 77 (18), 65 (8), 55 (7), 39 (12); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (brs, 3H, Me-2), 1.81 (brs, 1H, NH), 2.43 (brdd, 1H, H-3B, $J=13.7$, 5.9 Hz), 2.52 (dd, 1H, H-3A, $J=13.7$, 8.7 Hz), 3.50 (d, 1H, NCH_AH_B, $J=13.1$ Hz), 3.73 (d, 1H, NCH_AH_B, $J=13.1$ Hz), 3.79 (s, 3H, OMe), 3.84 (dd, 1H, H-4, $J=8.7$, 5.9 Hz), 4.74 (m, 1H, H-1), 4.80 (m, 1H, H-1), 6.20 (dd, 1H, H-3′, $J=3.2$, 0.8 Hz), 6.33 (dd, 1H, H-4′, $J=3.2$, 1.8 Hz), 6.85 (BB′, 2H, H-Ar), 7.18 (AA′, 2H, H-Ar), 7.39 (dd, 1H, H-5′, $J=1.8$, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 158.5 ($C_{qu.}$–C_6H_4OMe), 156.4 (C-2′), 142.1 ($C_{qu.}$–C_6H_4OMe), 141.3 (C-5′), 132.2 (C-2), 129.2 (2C, *ortho*-C_6H_4OMe), 113.6 (2C, *meta*-C_6H_4OMe), 113.2 (C-1), 109.7 (C-3′), 106.3 (C-4′), 55.0 (MeO), 50.5 (CH_2N), 52.8 (C-4), 43.4 (C-3), 21.8 (Me-2); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.49. Found: C, 75.29; H, 7.72; N, 5.19.

3.2. 4-Oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids (4). Typical procedure

Corresponding amine **3** (0.1 mol) was dissolved in 150 mL of toluene and an equimolar amount of maleic anhydride (0.1 mol, 9.8 g) was added in one portion. Reaction mixture was stirred for 30–60 h at room temperature and then crystalline product was filtered off, washed with toluene (2×100 mL), ether (2×80 mL) and dried at 100 °C to give desired products **4** as white solids.

3.2.1. 3-Benzyl-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4a). Ratio of isomers **A/B** ~1:1.6; yield 95%; mp 169–170 °C; IR 1710 (COOH), and 1640 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 339 (2), 284 (10), 204 (8), 194 (7), 120 (6), 99 (12), 91 (100), 78 (16), 65 (16), 51 (8), 39 (10); ^1H NMR ($CDCl_3$, 200 MHz) isomer **A** δ 1.71 (s, 3H, Me-2′), 2.40–2.55 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 3.04 (d, 1H, H-5, $J=9.2$ Hz), 3.95 (dd, 1H, H-2, $J=8.2$, 5.5 Hz), 4.08 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 4.82 (brs, 1H, H-1′), 4.92 (brs, 1H, H-1′), 5.09 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 5.25 (d, 1H, H-7, $J=1.5$ Hz), 6.35 (dd, 1H, H-8, $J=5.8$, 1.5 Hz), 6.48 (d, 1H, H-9, $J=5.8$ Hz), 7.15–7.45 (m, 5H, H-Ph), 11.03 (brs, 1H, COOH); isomer **B** δ 1.71 (s, 3H, Me-2′), 2.40–2.55 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 2.89 (d, 1H, H-7, $J=9.2$ Hz), 4.10 (dd, 1H, H-3, $J=8.1$, 6.6 Hz), 4.19 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 4.71 (brs, 1H, H-1′), 4.82 (brs, 1H, H-1′), 4.95 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 5.29 (s, 1H, H-7), 6.28 (s, 2H, H-8 and H-9), 7.15–7.45 (m, 5?, H-Ph), and 11.03 (brs, 1H, COOH). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 74.80; H, 6.20; N, 4.13. Found: C, 74.80; H, 6.21; N, 4.10.

3.2.2. 3-Benzyl-7-methyl-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4b). Ratio of isomers **A/B** ~1:2; yield 89%; mp 174.5–175 °C; IR 1730 (COOH), and 1650 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (10), 309 (3), 298 (53), 262 (23), 254 (6), 208 (10), 149 (15), 131 (5), 106 (10), 99 (20), 91 (100), 65 (18), 55 (13); ^1H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.69 (s, 6H, Me-2′ and Me-7), 2.31 (dd, 1H, H-3′A, $J=15.3$, 8.7 Hz), 2.50 (dd, 1H, H-3′B, $J=15.3$, 5.2 Hz), 2.83 (d, 1H, H-6, $J=8.7$ Hz), 3.09 (d, 1H, H-5, $J=8.7$ Hz), 3.96 (dd, 1H, H-2, $J=8.7$, 5.2 Hz), 4.11 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 4.82 (brs, 1H, H-1′), 4.91 (brs, 1H, H-1′), 5.10 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 6.12 (d, 1H, H-8, $J=5.7$ Hz), 6.54 (d, 1H, H-9, $J=5.7$ Hz), 7.20–7.35 (m, 5H, H-Ph), 9.38 (brs, 1H, COOH); isomer **B** δ 1.69 (s, 6H, Me-2′ and Me-7), 2.50 (m, 2H, H-3′), 2.82 (d, 1H, H-6, $J=8.6$), 2.93 (d, 1H, H-5, $J=8.6$ Hz), 3.98 (m, 1H, H-3), 4.15 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 4.71 (brs, 1H, H-1′), 4.80 (brs, 1H, H-1′), 5.01 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 6.06 (d, 1H, H-8, $J=5.6$ Hz), 6.33 (d, 1H, H-9, $J=5.6$ Hz), 7.20–7.35 (m, 5H, H-Ph), 9.38 (brs, 1H, COOH). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.39; H, 6.51; N, 3.98.

3.2.3. 2-Methallyl-4-oxo-3-(α-phenylethyl)-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4c). Ratio of isomers **A/B/C** ~10:5:1; yield 73%; mp 212–215 °C; IR 1730 (COOH), and 1660 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (2), 298 (6), 186 (10), 120 (14), 105 (100), 96 (28), 91 (36), 77 (18), 65 (12), 51 (6), 39 (10); ^1H NMR ($CDCl_3$, 200 MHz) isomer **A** (maj) δ 1.58 (brs, 3H, Me-2′), 1.63 (d, 3H, MeCH, $J=7.3$ Hz), 1.90–2.15 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 2.99 (d, 1H, H-5, $J=9.2$ Hz), 4.19 (dd, 1H, H-2, $J=10.1$, 4.0 Hz), 4.70 (brs, 1H, H-1′), 4.84 (brs, 1H, H-1′), 5.28 (d, 1H, H-7, $J=1.5$ Hz), 5.35 (q, 1H, C*H*Me, $J=7.3$ Hz), 6.37 (dd, 1H, H-8, $J=5.8$, 1.5 Hz), 6.46 (d, 1H, H-9, $J=5.8$v), 7.15–7.50 (m, 5H, H-Ph). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.41; H, 6.48; N, 3.97.

3.2.4. 3-(4-Methylbenzyl)-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4d). Ratio of isomers **A/B** ~ 1:1.2; yield 92%; mp 109.5–111 °C; IR 1720 (COOH), and 1665 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (9), 218 (36), 194 (17), 120 (33), 105 (100), 99 (15), 91 (10), 77 (16), 65 (7), 55 (9), 39 (9); ^1H NMR (DMSO-D_6, 400 MHz) isomer **A** δ 1.56 (s, 3H, Me-2′), 2.26 (s, 3H, Me-Ar), 2.36–2.52 (m, 2H, H-3′), 2.49 (d, 1H, H-6, $J=9.1$ Hz), 2.99 (d, 1H, H-5, $J=9.1$ Hz), 4.16 (dd, 1H, H-2, $J=10.1$, 4.5 Hz), 4.59 (d, 1H, CH_AH_BN, $J=15.3$ Hz), 4.63 (m, 1H, H-1′), 4.71 (m, 1H, H-1′), 4.80 (d, 1H, CH_AH_BN, $J=15.3$ Hz), 5.01 (d, 1H, H-7, $J=1.7$ Hz), 6.29 (dd, 1H, H-8, $J=5.8$, 1.7 Hz), 6.43 (d, 1H, H-9, $J=5.8$ Hz), 7.07–7.15 (m, 4H, H-Ar); isomer **B** δ 1.67 (s, 3H, Me-2′), 2.14 (dd, 1H, H-3′A, $J=13.9$, 9.0 Hz), 2.25 (s, 3H, Me-Ar), 2.40 (m, 1H, H-3′B), 2.49 (d, 1H, H-6, $J=9.1$ Hz), 2.82 (d, 1H, H-5, $J=9.1$ Hz), 3.68 (dd, 1H, H-2, $J=9.0$, 5.5 Hz), 3.99 (d, 1H, CH_AH_BN, $J=15.4$ Hz), 4.19 (d, 1H, CH_AH_BN, $J=15.4$ Hz), 4.77 (m, 1H, H-1′), 4.85 (m, 1H, H-1′), 4.97 (d, 1H, H-7, $J=1.7$ Hz), 6.39 (dd, 1H, H-8, $J=5.8$, 1.7 Hz), 6.54 (d, 1H, H-9, $J=5.8$ Hz), 7.07–7.15 (m, 4H, H-Ar). ^{13}C NMR (DMSO-D_6, 65 °C, 100.6 MHz) isomer **A** δ 173.5, 172.5, 140.5, 135.6, 132.2, 127.0, 56.1, 44.3, 38.1, 22.5, 158.9, 133.7, 128.8, 92.1, 90.6, 81.5, 81.4, 55.1, 50.7, 49.3, 45.9. Isomer **B** δ 173.6, 173.1, 139.8, 136.4,

127.8, 114.4, 56.3, 43.7, 34.5, 22.8, 158.9, 133.7, 128.8, 92.1, 90.6, 81.5, 81.4, 55.1, 50.7, 49.3, 45.9. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.41; H, 6.49; N, 3.95.

3.2.5. 3-(4-Methoxybenzyl)-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4e). Ratio of isomers **A/B** ~1:3.1; yield 74%; mp 136.5–139 °C; IR 1715 (COOH), and 1695 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 369 (4), 314 (3), 248 (11), 234 (38), 216 (20), 175 (10), 150 (8), 136 (29), 121 (100), 91 (4), 77 (4); ^{1}H NMR (DMSO-D_6, 400 MHz) isomer **A** δ 1.57 (s, 3H, Me-2′), 2.15 (dd, 1H, H-3′A, J=13.1, 10.5 Hz), 2.39–2.56 (m, 1H, H-3′B), 2.47 (d, 1H, H-6, J=9.3 Hz), 2.81 (d, 1H, H-5, J=9.3 Hz), 3.72 (s, 3H, OMe), 4.15 (dd, 1H, H-2, J=10.5, 4.1 Hz), 4.16 (d, 1H, CH_AH$_B$N, J=15.5 Hz), 4.58 (d, 1H, CH$_A$$H_B$N, J=15.5 Hz), 4.64 (brs, 1H, H-1′), 4.72 (brs, 1H, H-1′), 5.01 (d, 1H, H-7, J=1.6 Hz), 6.29 (dd, 1H, H-8, J=5.8, 1.6 Hz), 6.43 (d, 1H, H-9, J=5.8 Hz), 6.86 (AB, 2H, H-Ar), 7.17 (AB, 2H, H-Ar); isomer **B** δ 1.67 (s, 3H, Me-2′), 2.39–2.56 (m, 2H, H-3′), 2.47 (d, 1H, H-6, J=9.3 Hz), 2.99 (d, 1H, H-5, J=9.3 Hz), 3.68 (dd, 1H, H-2, J=8.5, 5.5 Hz), 3.71 (s, 3H, OMe), 3.98 (d, 1H, CH_AH$_B$N, J=15.5 Hz), 4.79 (d, 1H, CH$_A$$H_B$N, J=15.5 Hz), 4.78 (brs, 1H, H-1′), 4.97 (d, 1H, H-7, J=1.5 Hz), 6.86 (brs, 1H, H-1′), 6.39 (dd, 1H, H-8, J=5.8, 1.5 Hz), 6.54 (d, 1H, H-9, J=5.8 Hz), 6.83 (AB, 2H, H-Ar), 7.17 (AB, 2H, H-Ar). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.31; H, 6.24; N, 3.82.

3.3. 13,13-Dimethyl-7-oxoisoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5). Typical procedure

A mixture of fine powdered adduct **4** (0.01 mol) and 40 mL of PPA (prepared from 30 g of P_2O_5 and 30 mL of 85% H_3PO_4) was stirred at 90 °C for 40 min (TLC control). Then the reaction mixture was cooled and poured into 100 mL of water. The obtained precipitate was filtered off washed with cold water (5×80 mL), isopropanol (2×30 mL) and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) in case of **5a**,**c**-**e** or on Al_2O_3 (1.5×3 cm, chloroform) in case of **5b** to give desired isoindolobenzazepines **5** as colorless crystals.

3.3.1. 13,13-Dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5a). Yield 75%; mp 255–257 °C; IR 1700 (COOH), and 1680 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 321 (27), 306 (2), 278 (13), 277 (52), 276 (20), 275 (100), 131 (14), 115 (8), 103 (3), 91 (14), 77 (3); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.42 (dd, 1H, H-12A(ax), J=11.9, 14.0 Hz), 1.47 (s, 3H, Me-13), 1.57 (s, 3H, Me-13), 2.55 (dd, 1H, H-12B(eq), J=3.4, 14.0 Hz), 4.97 (d, 1H, H-5A, J=15.5 Hz), 5.13 (d, 1H, H-5B, J=15.5 Hz), 5.30 (dd, 1H, H-11b, J=3.4, 11.9 Hz), 7.21 (dd, 1H, H-1, J=1.6, 7.5 Hz), 7.37 (dt, 1H, H-2, J=1.1, 7.5 Hz), 7.37 (dt, 1H, H-3, J=1.6, 7.5 Hz), 7.41 (dd, 1H, H-4, J=1.1, 7.5 Hz), 7.82 (t, 1H, H-10, J=7.7), 7.99 (brd, 1H, H-11, J=7.7 Hz), 8.12 (dd, 1H, H-9, J=7.7, 0.7 Hz), 9.03 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 167.1 and 169.1 (s, C=O), 147.8, 147.2, 134.9, 128.1, 128.6 (s, C-Ar), 132.6, 131.9, 130.9, 128.3, 127.0, 126.62, 126.56 (d, C-Ar), 60.6 (d, C-11b), 46.8 (t, C-5), 45.6 (t, C-12), 37.5 (s, C-13), 32.3, 25.5 (q, Me-13). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.78; H, 5.90; N, 4.37.

3.3.2. 9,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5b). Yield 30%; mp 133.5–135 °C; IR 1710 (COOH), and 1660 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (1), 291 (100), 276 (25), 262 (5), 248 (25), 235 (5), 172 (113), 160 (13), 146 (34), 131 (30), 115 (40), 91 (63), 77 (16), 65 (13), 39 (13); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 3H, Me-13), 1.60 (dd, 1H, H-12A(ax), J=14.0, 12.2 Hz), 1.61 (s, 3H, Me-13), 2.25 (dd, 1H, H-12B(eq), J=14.0, 3.0 Hz), 2.42 (s, 3H, Me-9), 4.69 (d, 1H, H-5A, J=15.6 Hz), 4.86 (dd, 1H, H-11b(ax), J=3.0, 12.2 Hz), 5.31 (d, 1H, H-5B, J=15.6 Hz), 7.16–7.42 (m, 6H, H-Ar), 7.63 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 166.0 (2C, COOH and C-7), 147.8, 144.1, 138.0, 137.2, 132.8, 132.0, 131.0, 128.2, 126.9, 126.7, 123.4, 122.6 (C-Ar), 59.2 (d, C-11b), 47.2 (t, C-5), 46.5 (t, C-12), 38.1 (s, C-13), 32.9 (q, C-9), 21.3, 26.1 (q, Me-13). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.14; H, 6.25; N, 4.17.

3.3.3. 5,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5c). Yield 31%; mp 209.5–211.5 °C; IR 1710 (COOH), and 1680 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (8), 320 (100), 289 (17), 276 (23), 138 (6), 129 (10), 115 (7), 103 (4), 91 (7), 81 (4), 44 (36), 28 (22); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (brs, 3H, Me-13), 1.55 (s, 3H, Me-13), 1.81 (d, 3H, Me-5, J=7.4 Hz), 2.17 (dd, 1H, H-12A, J=14.7, 6.0 Hz), 2.70 (dd, 1H, H-12B, J=14.7, 6.0 Hz), 5.16 (t, 1H, H-11b, J=6.0 Hz), 5.94 (q, 1H, H-5, J=7.4 Hz), 7.21–7.45 (m, 4H, H-Ar), 7.73–7.79 (m, 2H, H-Ar), 8.43 (dd, 1H, H-9, J=7.4, 1.7 Hz), 15.80 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 50.3 MHz) δ 168.2 and 165.3 (C=O), 147.4, 145.6, 138.8, 129.5, 129.0 (s, C-Ar), 133.4, 132.4, 130.5, 128.3, 127.5, 127.0, 126.0 (d, C-Ar), 57.2 (d, C-11b), 53.3 (d, C-5), 44.5 (s, C-13), 39.2 (t, C-12), 32.8, 31.9, 23.5 (q, Me-13 and Me-5). Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.11; H, 6.28; N, 4.20.

3.3.4. 2,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5d). Yield 48%; mp 219–221 °C; IR 1705 (COOH), and 1695 (N-C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (23), 291 (22), 289 (100), 207 (1), 159 (3), 144 (5), 129 (7), 115 (5), 91 (3), 77 (2); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.37 (dd, 1H, H-12A(ax), J=13.5, 11.7 Hz), 1.46 (s, 3H, Me-13), 1.55 (s, 3H, Me-13), 2.26 (s, 3H, Me-2), 2.53 (dd, 1H, H-12B(eq), J=2.6, 13.5 Hz), 4.91 (d, 1H, H-5A, J=15.4 Hz), 5.08 (d, 1H, H-5B, J=15.4 Hz), 5.28 (dd, 1H, H-11b(ax), J=2.6, 11.7 Hz), 7.00 (brd, 1H, H-3, J=7.4 Hz), 7.19 (brs, 1H, H-1), 7.24 (d, 1H, H-4, J=7.4 Hz), 7.81 (t, 1H, H-10, J=7.6 Hz), 7.99 (d, 1?, H-11, J=7.6 Hz), 8.12 (d, 1?, H-9, J=7.6 Hz). ^{13}C NMR (DMSO-D_6, 50.3 MHz) δ 167.6 and 165.5 (C=O), 148.4, 147.6, 137.9, 133.9, 132.9, 132.5, 132.1, 129.1, 128.7, 128.4, 127.2, 126.6, 60.3, 48.6, 47.3, 38.0, 32.8, 26.0, 21.7. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.12; H, 6.29; N, 4.18.

3.3.5. 2-Methoxy-13,13-trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5e). Yield 48%; mp 197–198?; IR 1705 (COOH), and 1695 (N-C=O) cm^{-1}; EI-MS (70 eV) m/z (rel. intensity): M^+ 351 (15), 334 (4), 305 (100), 290 (2), 175 (4), 160 (5), 145 (4), 131 (3), 115 (3), 91 (4), 44 (7), 28 (5); 1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (dd, ^{1}H, H-12A(*ax*), J=14.3, 12.2), 1.55 (s, 3H, Me-13), 1.64 (s, 3H, Me-13), 2.32 (dd, 1H, H-12B(*eq*), J=14.3, 3.3), 3.79 (s, 3H, OMe), 4.78 (d, 1H, H-5A, J=15.4), 5.06 (dd, 1H, H-11b(*ax*), J=12.2, 3.3), 5.24 (d, 1H, H-5B, J=15.4), 6.72 (dd, 1H, H-3, J=8.3, 2.6), 6.79 (d, 1H, H-1, J=2.6), 7.31 (d, 1H, H-4, J=8.3), 7.65 (dd, 1H, H-11, J=7.6, 1.1), 7.70 (t, 1?, H-10, J=7.6), 8.35 (dd, 1H, H-9, J=7.6, 1.1). ^{13}C NMR (DMSO-D6−CDCl3, 75.4 MHz) δ 172.4 and 170.1 (s, C=O), 164.3 (C-2), 153.8 (s), 152.8 (s), 137.7 (d), 137.6 (d), 137.3 (d), 133.9 (s), 133.6 (s), 132.20 (d), 132.16 (s), 119.2 (d), 115.1 (d), 65.9 (OMe), 60.2 (d, C-11b), 51.5 (t), 51.1 (t), 44.9 (s), 37.5 (q), 30.5 (q). Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.99. Found: C, 71.81; H, 5.99; N, 4.01.

3.3.6. 1-Oxo-2-benzyl-3-(2′-methylpropenyl)-1,2-dihydro-3*H*-isoindole-7-carboxylic acid (6). A mixture of fine powdered adduct **4a** (1.69 g, 5.0 mmol) and 25 mL of H_3PO_4 (85%) was stirred at 60 °C for 40–60 min (TLC control—before a disappearance of the initial compound spot). Then the reaction mixture was cooled and poured into 100 mL of water. The obtained precipitate was filtered off washed with cold water (5×80 mL) and dried. Then the crude product was washed with isopropanol (6×30 mL) and the solid fraction was discarded. The isopropanol solution was concentrated in vacuo and the formed precipitate was filtered off. The double recrystallization (heptane–ethyl acetate) gave desired isoquinoline **6** as colorless crystals, yield 13%; mp 149.5–150 °C; IR 1705 (COOH), and 1695 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 321 (43), 277 (100), 260 (4), 234 (4), 212 (6), 199 (14), 183 (4), 170 (9), 157 (4), 128 (8), 106 (7), 91 (49), 65 (5), 28 (8); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (d, 3H, Me-1′, J=1.3 Hz), 1.86 (d, 3H, Me-2′, J=1.3 Hz), 4.18 (d, 1H, CH_AH_BN, J=14.7 Hz), 4.80 (dt, 1H, H-3′, J=10.0, 1.3 Hz), 5.18 (d, 1H, H-3, J=10.0 Hz), 5.29 (d, 1H, CH_AH_BN, J=14.7 Hz), 7.25–7.35 (m, 5H, H-Ph), 7.46 (dd, 1H, H-4, J=7.7, 0.8 Hz), 7.67 (t, 1H, H-5, J=7.7 Hz), 8.36 (dd, 1H, H-6, J=7.7, 0.8 Hz). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.80; H, 5.94; N, 4.35.

3.3.7. 3-Nitro-13,13-dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (7). Potassium nitrate (0.66 g, 6.5 mmol) was added in portion to a stirred solution of **5a** (2.00 g, 6.23 mmol) in 15 mL of sulfuric acid. Then the reaction mixture was stirred at 40 °C for 30 min and poured into 50 mL of water. The obtained precipitate was filtered off, washed with water to pH ~7 and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) to give the desired nitroderivative **7** as white crystals. Yield 73%; mp 240–242 °C; IR 1720 (COOH), 1690 (N–C=O), 1560 (NO_2 s), and 1380 (NO_2 as) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 366 (3), 322 (100), 204 (20), 190 (5), 176 (5), 144 (8), 129 (28), 115 (33), 109 (68), 103 (15), 91 (18), 77 (18), 73 (41), 63 (10), 51 (9), 44 (83), 33 (18); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.51 (s, 3H, Me-13), 1.52 (dd, 1H, H-12A(ax), J=14.3, 11.0 Hz), 1.62 (s, 3H, Me-13), 2.62 (dd, 1H, H-12B(eq), J=14.3, 3.5 Hz), 5.05 (d, 1H, H-5A, J=15.9 Hz), 5.34 (dd, 1H, H-11b(ax), J=11.0, 3.5 Hz), 5.37 (d, 1H, H-5B, J=15.9 Hz), 7.69 (d, 1H, H-1, J=8.9 Hz), 7.83 (t, 1H, H-10, J=7.6 Hz), 8.00 (d, 1H, H-11, J=7.6), 8.12 (d, 1H, H-9, J=7.6 Hz), 8.13 (dd, 1H, H-2, J=2.7, 8.9 Hz), 8.30 (d, 1H, H-4, J=2.7 Hz). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 25.1, 32.3 (q, Me-13), 38.5 (s, C-13), 46.1 (t, C-5), 44.8 (t, C-12), 60.4 (d, C-11b), 123.0 (d, C-2), 125.1 (d, C-4), 127.0 (d, C-11), 128.7 (d, C-1), 131.9 (d, C-9), 132.8 (d, C-10), 128.0, 128.8, 137.0, 145.6, 147.7, 155.3 (all s, 6C-Aryl), 165.0 (COOH), 167.4 (C-7). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.92; N, 7.65. Found: C, 65.59; H, 4.92; N, 7.67.

3.3.8. Chloroanhydride of 5,13-dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (8). Four molar equivalents of thionylchloride (1.79 mL, 25 mmol) were added to a suspension of acid **5a** (2.0 g, 6.23 mmol) in 50 mL of benzene. Then the reaction mixture was refluxed for 6 h. The precipitate formed on cooling of the reaction mixture was filtered off. The mother liquor was concentrated in vacuo and the formed precipitate was filtered off. The crystalline fractions were combined, washed with ether and recrystallized from chloroform–DMF to give the desired product **8** as yellow crystals. Yield 79%; mp 203–204 °C; IR 1700 (COCl), and 1668 (N–C=O and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 339 (6), 337 (18), 322 (100), 294 (25), 286 (8), 259 (23), 230 (15), 192 (13), 164 (6), 151 (6), 143 (35), 129 (20), 115 (46), 101 (15), 83 (5), 78 (25), 63 (10), 51 (13), 36 (30); ^{1}H NMR (DMSO-D_6, 200 MHz) δ 1.73 (s, 6H, Me-13), 5.26 (s, 2H, H-5), 6.43 (s, 1H, H-12), 7.20–7.50 (m, 4H, H-1,2,3,4), 7.80 (t, 1H, H-10, J=7.4 Hz), 8.01 (dd, 1H, H-11, J=7.4, 0.8 Hz), 8.20 (dd, 1H, H-9, J=7.4, 0.8 Hz). Anal. Calcd for $C_{20}H_{16}NO_2Cl$: C, 71.11; H, 4.75; N, 4.15. Found: C, 71.15; H, 4.74; N, 4.14.

3.3.9. 5,13-Dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (9). *Procedure A*. A mixture of chloroanhydride **8** (2.0 g, 5.93 mmol) and 10% solution of NaOH (30 mL) was stirred at 80 °C for 30 min. Then the reaction mixture was poured into 30 mL of water and acidified with 16% HCl to pH ~7. The obtained precipitate was filtered off, washed with water (3×100 mL) and dried in air. Recrystallization from *i*-PrOH–DMF gave the desired acid **9** as white crystals. Yield 70%.

Procedure B. A mixture of **5a** (2.0 g, 6.23 mmol) and nitrobenzene (20 mL) was refluxed for 4 h. After that the reaction mixture was concentrated in vacuo to half of its volume and the formed crystals were filtered off, washed with ether and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) to give desired dehydroderivative **9** as white crystals. Yield 64%; mp 285.5–287 °C; IR 1720 (COOH), and 1645 (N–C=O and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 319 (18), 304 (100), 276 (30), 260 (5), 245 (5), 230 (8), 217 (10), 204 (8), 189 (5), 174 (8), 143 (5), 130 (20), 115 (50), 109 (20), 102 (50), 91 (13), 77 (13), 63 (15), 51 (9), 39 (15); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.69 (s, 6H, Me-13), 5.21 (s,

2H, H-5), 6.39 (s, 1H, H-12), 7.27 (dt, 1H, H-2, J=1.2, 7.4 Hz), 7.35 (dt, 1H, H-3, J=1.2, 7.4 Hz), 7.44 (dd, 1H, H-1, J=1.2, 7.4 Hz), 7.46 (dd, 1H, H-4, J=1.2, 7.4 Hz), 7.78 (t, 1H, H-10, J=7.7 Hz), 7.98 (dd, 1H, H-11, J=0.8, 7.7 Hz), 8.20 (dd, 1H, H-9, J=0.8, 7.7 Hz). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.24; H, 5.33; N, 4.39. Found: C, 75.24; H, 5.36; N, 4.41.

3.3.10. Morpholine amide of 5,13-dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (10). A mixture of chloroanhydride **8** (0.75 g, 2.23 mmol) and 10 mL of morpholine was refluxed for 4 h. Then the reaction mixture was cooling, poured into 30 mL of water and acidified with 15% hydrochloric acid. The formed precipitate was filtered off, washed with water (5×20 mL) and dried in air. The crude product was recrystallized (*i*-PrOH–DMF) to give the desired amide **10** as slightly-yellow crystals. Yield 50%; mp 223–224 °C; IR 1700 and 1638 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 388 (55), 373 (100), 345 (30), 302 (15), 288 (20), 275 (28), 259 (48), 245 (15), 230 (20), 216 (20), 202 (15), 189 (9), 172 (11), 158 (13), 143 (45), 136 (8), 130 (29), 115 (35), 102 (15), 91 (15), 86 (35), 73 (21), 56 (19), 44 (28); ^{1}H NMR (DMSO-D_6, 200 MHz) δ 1.74 (s, 3H, Me-13), 1.76 (s, 3H, Me-13), 3.05–4.05 (m, 8H, H-morpholine), 5.16 (d, 1H, H-5A, J=15.3 Hz), 5.26 (d, 1H, H-5B, J=15.3 Hz), 5.86 (s, 1H, H-12), 7.15–7.70 (m, 7H, H-Ar). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 166.7 and 164.4 (s, C=O), 147.5, 137.3, 134.3, 134.0, 133.3 (all s, C-Ar), 132.9, 131.6, 129.2, 127.7, 127.3, 126.1 (all d, C-Ar), 123.7 (s, C-11b), 120.7 (d), 118.0 (d, C-12), 66.4 (t, 2C), 47.4, 45.4, 42.3, 38.8 (s, C-13), 32.6 (q, 2C, Me-13). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.23; H, 6.19; N, 7.22. Found: C, 74.24; H, 6.20; N, 7.25.

3.3.11. Methyl ether of 13,13-dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (11). A mixture of acid **5a** (2.00 g, 6.23 mmol), 30 mL of dry methanol and 0.05 mL of 96% sulfuric acid was refluxed for 6 h. After the reaction mixture was cooled, poured into water (80 mL) and extracted with ethyl acetate (3×30 mL). The organic phase was dried with $MgSO_4$ and concentrated. The crude product was recrystallized (hexane–ethyl acetate) to give the desired ester **11** as white crystals. Yield 60%; mp 167–169 °C; IR 1720 (O–C=O), and 1690 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 335 (35), 304 (6), 292 (5), 275 (100), 158 (11), 145 (6), 129 (15), 115 (18), 91 (28), 77 (8), 51 (2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 3H, Me-13), 1.60 (s, 3H, Me-13), 1.60 (dd, 1H, H-12A(ax), J=14.1, 12.0 Hz), 2.25 (dd, 1H, H-12B(eq), J=3.0, 14.1 Hz), 3.98 (s, 3H, COOMe), 4.68 (d, 1H, H-5A, J=15.5 Hz), 4.90 (dd, 1H, H-11b(ax), J=3.0, 12.0 Hz), 5.28 (d, 1H, H-5B, J=15.5 Hz), 7.14–7.55 (m, 7H). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 169.1 and 165.1 (s, C=O), 148.1 (2C, s), 136.9, 130.6, 128.6 (s, C-Ar), 132.8, 131.6, 129.1, 127.8, 127.49, 127.55, 125.7 (d, C-Ar), 60.1 (d, C-11b), 53.6 (q, OMe), 47.3 (t, C-5), 46.9 (s, C-13), 38.5 (t, C-12), 33.2, 26.3 (q, Me-13). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.11; H, 6.28; N, 4.20.

3.3.12. 5,11b,12,13-Tetrahydro-13,13-dimethyl-8-hydroxymethyl-7*H*-isoindolo[2,1-*b*][2] benzazepine (12). Eight molar equivalents of lithium aluminum hydride (0.90 g, 24.9 mmol) were added to a suspension of the acid **5a** (1.0 g, 3.10 mmol) in 40 mL of THF. The resulting reaction mixture was refluxed for 2 h. Then the excess $LiAlH_4$ was decomposed with water (50 mL). The obtained product was extracted with chloroform (4×50 mL). The organic extract was dried with $MgSO_4$ and concentrated. The crude product was recrystallized from hexane–ethyl acetate mixture to give the desired benzylic alcohol **12** as colorless crystals. Yield 46%; mp 146.5–148.5 °C; IR 3150 (OH) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 293 (100), 278 (20), 250 (33), 237 (12), 218 (9), 202 (4), 174 (6), 161 (12), 146 (18), 131 (72), 91 (84), 77 (13), 55 (11), 39 (12); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 3H, Me-13A), 1.50 (s, 3H, Me-13B), 1.96–2.06 (m, CH_2−12), 3.72 (brd, 1H, H-5B, J=12.9 Hz), 3.92 (brd, 1H, H-5A, J=12.9 Hz), 3.96 (d, 1H, H-7B, J=14.0 Hz), 4.26 (m, CH_2OH), 4.26 (d, 1H, H-7A, J=14.0 Hz), 4.26 (m, 1H, H-11b), 7.05 (brd, 1H, J=7.2 Hz), 7.16–7.28 (m, 5H-Ar), 7.44 (brd, 1H, J=7.7 Hz). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 147.7, 145.1, 138.6, 137.4, 136.3 (s, C-Ar), 131.0, 127.3, 126.74, 126.68, 126.0, 125.1, 119.7 (d, C-Ar), 65.8 (d, C-11b), 61.3 (t), 58.4 (t), 57.0 (t), 44.9 (q, C-13), 38.5 (C-12), 33.0, 28.2 (q, Me-13). Calcd for $C_{20}H_{23}NO$: C, 81.91; H, 7.85; N, 4.78. Found: C, 81.93; H, 7.86; N, 4.80.

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