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Annelation of Benzimidazoles with α,β-Acetylenic γ-Hydroxyacid Nitriles and Hydrolytic Rearrangement of the Cycloadducts on Alumina

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1-Substituted benzimidazoles are readily annelated regio- and stereoselectively with α,β-acetylenic γ-hydroxyacid nitriles under mild conditions (20–25 °C, no catalyst, no solvent) to form new polyfunctional condensed systems, 4-cyanomethylene-1,3-oxazolobenzimidazoles (30–88 % yield). Unexpectedly, the latter, when chromatographed on neutral Al_2O_3 at room temperature, undergo a complex multi-position hydrolytic rearrangement involving the cleavage of the imidazole ring to aminophenyl N-substituted formamides with an aminodihydrofuran moiety in the aminophenyl substituent, *N*-(2-{[5-amino-2,2-dialkyl-3(2*H*)-furanylidene]-amino}phenyl)-*N*-substituted formamides, a novel class of highly functionalized pharmacophoric compounds. The results contribute to the basic benzimidazole chemistry and provide for prospective families of drug candidates.

Introduction

The benzimidazole structure is found in molecules of many physiologically active compounds (vitamin B_{12},[1] omeprazole,[2] lansoprazole, (s)-rabeprazole,[3] etc.). Certain benzimidazole derivatives possess antithrombic[4] and antiproliferative[5] activity and they can act as hair growth stimulating agents.[6]

Among condensed benzimidazoles, in particular imidazobenzimidazoles, antioxidants, radioprotectors as well as compounds showing antiarrhythmic, spasmolytic and antisecretory properties can be found;[7] some of these compounds have also been shown to decrease the transport of calcium ions through the membranes and reduce blood pressure.[7]

Consequently, functionalization of benzimidazole, in particular to produce new condensed derivatives, remains an important task of organic synthesis. Of special interest are the practically unknown functionalized condensed derivatives of benzimidazole containing a 1,3-oxazolidine moiety.

This work is aimed at the development of a general methodology for the synthesis of functionalized benzimidazoles condensed with the 1,3-oxazolidine cycle. To reach this goal, we have studied the reaction of 1-substituted benzimidazoles with available α,β-acetylenic γ-hydroxyacid nitriles.[8,9] Such nitriles, as electron-deficient acetylenes, have been recently found to readily annelate with pyridines,[10] tris(pyridyl)ethylphosphane oxide,[11] quinoline and quinoxaline,[12] phenanthridines,[13] and natural alkaloids (such as anabazine[14]) to afford new condensed heterocyclic systems – 1,3-oxazoloazines. It might be expected, that a similar annelation will proceed with benzimidazole derivatives to result in 1,3-oxazolobenzimidazoles.

Results and Discussion

Experiments have shown that 1-substituted benzimidazoles **1**–**4** do react with α,β-acetylenic γ-hydroxyacid nitriles **5** and **6** under mild conditions (20–25 °C, 5–72 h, no catalyst, no solvent) to give the expected novel functionalized benzimidazole condensed systems, 1,3-oxazolobenzimidazoles, **7**–**12** (yield 30–98%, Scheme 1).

The maximum yield of 1,3-oxazolobenzimidazoles **7**–**12** (88 and 98%) is reached when 1-methyl(ethyl or allyl)benzimidazole (**1**, **2**, **4**) and acetylene **5** are used as the starting reagents, whereas in the case of acetylene **6**, the yield of cycloadduct **9** is 63% and is probably due to the negative steric effect of the cyclohexyl moiety. The electron-withdrawing vinyl substituent in benzimidazole **3** decreases its

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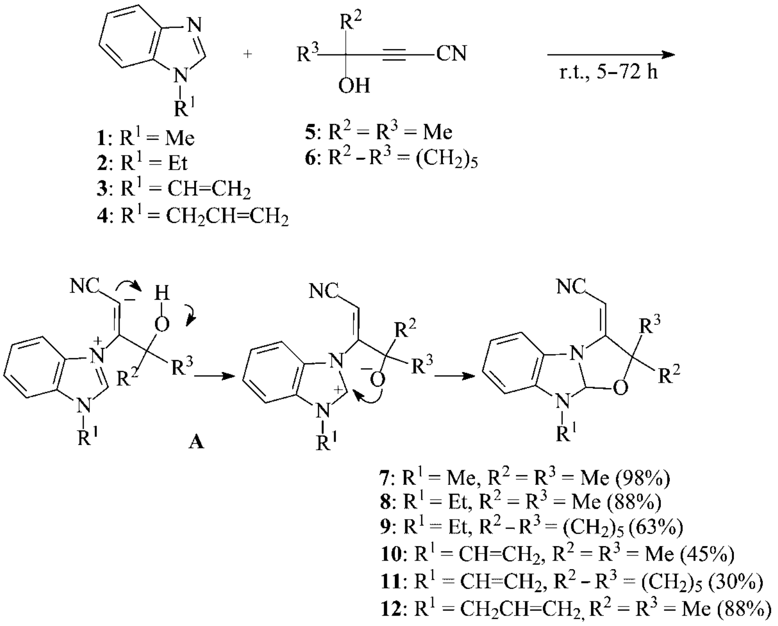


Scheme 1. Synthesis of annelated 1,3-oxazolobenzimidazoles **7**–**12**.

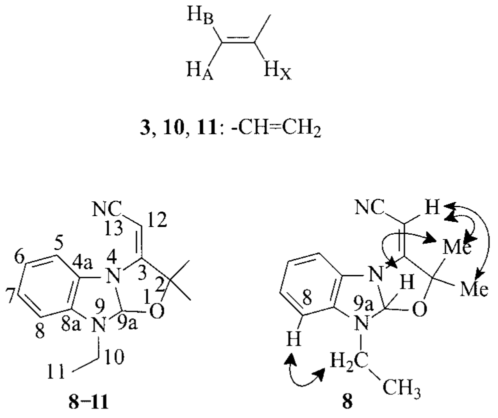


Figure 1. Labeling of hydrogen and carbon atoms in the compounds **3**, **8**–**11** and cross-peaks in the 2D NOESY spectrum of 1,3-oxazolobenzimidazole **8**.

reactivity towards acetylenes **5** and **6**: the yields of 1,3-oxazolobenzimidazoles **10** and **11** drop to 45 and 30%, respectively, and the reaction time increases to 72 h.

It is likely that the formation of oxazolobenzimidazoles **7**–**12** proceeds through zwitterion **A**, which further closes to the oxazolidine cycle (Scheme 1).

The structure of 1,3-oxazolobenzimidazoles **7**–**12** has been determined by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and 2D NOESY techniques.

The IR spectra show absorption bands in the region of 2190–2210 cm^{-1}, assignable to the cyano group at the double bond, as well as bands in the region of 1020–1150 cm^{-1}, which are typical for the C–O–C bonds.

In the ^{1}H NMR spectra of 1,3-oxazolobenzimidazoles **7**–**12**, there is an olefin proton signal at 4.40–4.59 ppm that is indicative of the formation of only one isomer. The (*Z*) configuration of the isomers followed from the fact that in the 2D NOESY spectrum of 1,3-oxazolobenzimidazole **8**, a cross-peak between signals of the olefin proton and methyl group protons is observed. The spectrum also contains cross-peaks between the 9a-H proton and the protons of a methyl group as well as between the 8-H proton and protons of the CH_2 of the ethyl substituent (Figure 1).

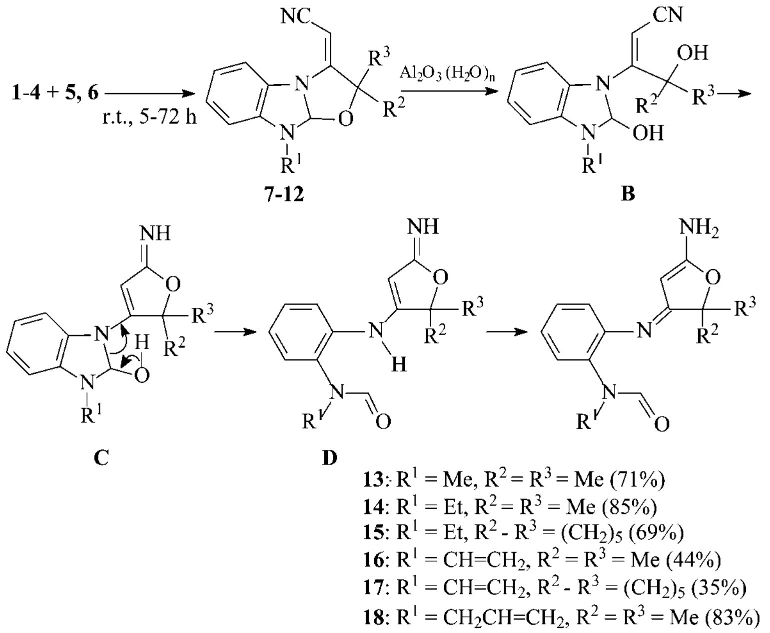
Cycloadducts **8**–**11** are powders of flesh color, stable at room temperature, soluble in chloroform, ethanol, and DMSO, but insoluble in diethyl ether. Therefore, they are isolated from the reaction mixture by their careful washing with several small portions of Et_2O, thus extracting unreacted starting materials and side products. Compounds **7** and **12** are oils, soluble in diethyl ether, chloroform, ethanol, and DMSO.

An unsubstituted benzimidazole (R^1 = H) with acetylenes (**5**, **6**) is known to yield the expected addition products across the triple bond, no annelation being absorb,[15] whereas the simple substituted imidazoles under the same conditions and with the same acetylenes undergo another reaction, which will be reported elsewhere.

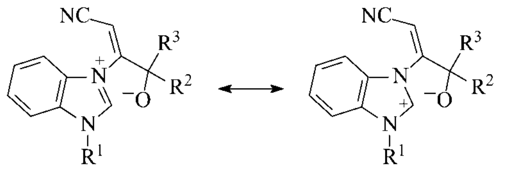
An attempt to purify cycloadducts **8**–**12** by column chromatography on neutral Al_2O_3 unexpectedly led to aminophenylformamides **13**–**18** (Scheme 2). Thus, passage of the reaction mixture through the neutral Al_2O_3 column (chloroform/benzene/ethanol, 20:4:1) resulted in the isolation of formamides **13**–**18** in 35–85% yield (Scheme 2).

The rearrangement is assumed to start with the hydrolytic cleavage of the 1,3-oxazolidine entity by water present in Al_2O_3 to give intermediate diol **B** (Scheme 2). The insertion of a water molecule should be easy because of the zwitterionic character of the 1,3-oxazolidine fragment (Scheme 3).

Diol **B** further undergoes ring-closure to form the iminodihydrofuran ring and this is followed by configurational change in the NCCH=C moiety to afford intermediate **C**,



Scheme 2. Rearrangement of oxazolidines **7**–**12** to aminophenyl *N*-substituted formamides **13**–**18**.



Scheme 3. The zwitterionic character of the 1,3-oxazolidine fragment in compounds **7**–**12**.

which then rearranges to intermediate **D** with imidazoline ring cleavage. A prototropic shift completes the formation of formamides **13**–**18**.

Noteworthy is that similar cycloadducts of **5** and **6** with diverse azines (1,3-oxazoloazines) in no case were observed to be prone to any rearrangement under the same conditions.[10–14] Therefore, the unusually complex multi-position rearrangement of 1,3-oxazolobenzimidazoles **7**–**12** with the cleavage of the imidazole fragment to absolutely unexpected species **13**–**18** is unique and unveils a novel facet of basic benzimidazole chemistry.

The annelation (Scheme 1) and rearrangement (Scheme 2) can be realized as a one-pot procedure to directly yield formamides **13**–**18** simply by subjecting the equimolar mixture of benzimidazoles **1**–**4** with acetylenes **5** and **6**, that was kept at room temperature for 5–72 h, to chromatography on alumina.

The structure of rearrangement products **13**–**18** was established by X-ray analysis (**14**, **16**) and confirmed by IR, ^{1}H NMR, ^{13}C NMR, and 2D NOESY spectroscopy.

Their IR spectra show the absorption bands in the regions of 1050–1170 cm^{-1} (C–O–C), 1660–1670 cm^{-1} (C=O, in KBr), and 3412, 3520 cm^{-1} (NH_2, in $CHCl_3$).

According to the NMR spectra ($CDCl_3$), formamides **13**–**18** are mixtures of *syn*- and *anti*-rotamers due to the hindered rotation of the formyl moiety (see Experimental Section).[16,17] The *syn*- (s-*cis*; R^1, C=O) conformation of formamides **13**–**18** is populated to a significantly greater extent than the *anti*- (s-*trans*) conformation (with a *syn*/*anti* ratio of ca. 4:1, Figure 2).

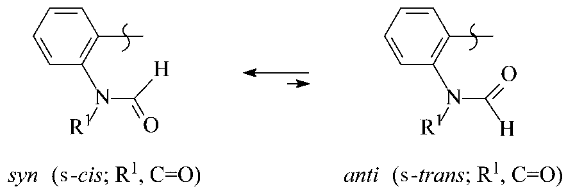


Figure 2. *Syn* and *anti* conformation of formamides **13**–**18**.

Special attention to the fact that in the ^{1}H NMR spectra of formamides **16**–**17** the signal of the vinyl proton H_X in the *syn* conformation is shifted downfield (7.34, 7.35 ppm) compared with that of the *anti* conformation (6.73, 6.74 ppm, $\Delta = 0.61$ ppm). This results from the intramolecular hydrogen bond between the proton H_X and the formyl oxygen ($H_X \cdots O$).[17] At the same time, the signal of the formyl proton in the *syn* conformation is shifted upfield (8.01–8.02 ppm) relative to that of the *anti* conformation ($\delta = 8.48$ ppm, $\Delta = 0.26$–0.51 ppm).[17]

In the crystal state, formamides **14** and **16** exist in the *syn* conformation, which follows from the X-ray analysis data (Figure 3).

Formamides **14** and **16** are isostructural. Their crystalline structures are formed by one crystallographic independent molecule, which takes general position in the unit cell. The dihydrofuran and phenyl cycles of the molecules are practically planar. Maximum deviations of the C(2) and C(7) carbon atoms for formamide **14** are 0.03 Å and 0.005 Å, respectively. The dihedral angle formed by the planes of

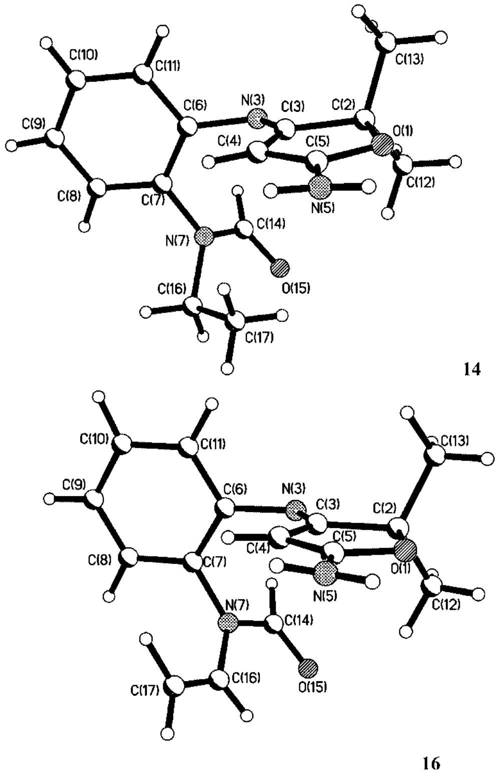


Figure 3. Molecular structures of formamides **14** and **16**.

these cycles is 86.3°. The nitrogen N(3) atom is out of the planes of the dihydrofuran and phenyl moieties by 0.10 Å and 0.11 Å, respectively. Thus, the N(5) and N(7) atoms are in the planes of dihydrofuran and phenyl ring. Torsion angles of C(7)–N(7)–C(14)–O(15) and C(7)–N(7)–C(16)–C(17) are 178.3(1)° and 94.0(3)°, respectively. In the crystals of formamide **16**, all of the molecules are bound by hydrogen bonds into a supramolecular polymer structure (Figure 4).

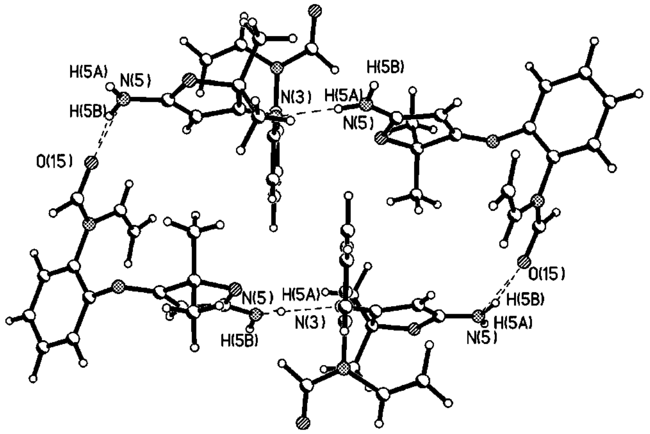


Figure 4. Fragment of the supramolecular network of formamide **16**.

All the X-ray analysis data related to formamide **16** are similar to those of amide **14**. The compounds differ only in the substituent R^1 rotation angle with respect to the N(7)–C(16) bond: torsion angle C(7)–N(7)–C(16)–C(17) in compound **14** differs from the angle in compound **16** by 173.5° (the angles are 178.3 and 4.8°, respectively).

Disorder of two positions is observed for the ethyl substituent in formamide **14** with occupancies of 0.63 and 0.37. For disordered atoms of the ethyl substituent, the hydrogen atoms were partially determined experimentally and refined isotropically, and partially calculated.

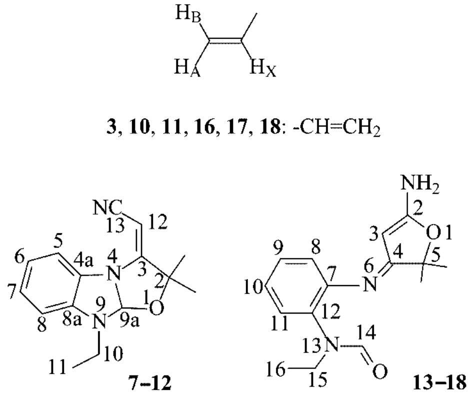
Conclusions

1-Substituted benzimidazoles are annelated regio- and stereoselectively with α,β-acetylenic γ-hydroxyacid nitriles under mild conditions to furnish new functional condensed systems – 1,3-oxazolobenzimidazoles, which unexpectedly and readily rearrange on neutral Al_2O_3 to form a novel family of aminophenylformamides that contain an iminoaminodihydrofuran moiety. These functionalized dihydrofurans are promising candidates for drug design because the dihydrofuran structure is intrinsic for a number of natural (ascorbic and penicillin acids, derivatives of tetronic acid), and biologically active products (azadirachtin, clerodin, austocystin A, etc.),[18,19] some of which show antibacterial, antifungicidal,[20] antiviral,[21] and antiAIDS properties.[21,22]

Thus, the results contribute both to basic benzimidazole chemistry and provide a new prospective family of drug candidates.

Experimental Section

IR spectra were measured with Specord IR 75 and IFS 25 instruments. ^{1}H-, ^{13}C-NMR- and 2D NOESY spectra were recorded with an AV-400 Bruker BioSpin spectrometer with HMDS as an internal standard. Labeling of carbon and hydrogen atoms in compounds **3**, **7**–**18** are given in Figure 5. Column and thin-layer chromatography was carried out on neutral Al_2O_3 with chloroform/benzene/ethanol (20:4:1) mixture as the eluent. 1-Methylbenzimidazole (**1**) and 1-allylbenzimidazole (**4**) were prepared according to known procedures,[23] 1-ethylbenzimidazole (**2**) and 1-vinylbenzimidazole (**3**) by the procedure outlined in ref.,[24] and α,β-acetylenic γ-hydroxyacid nitriles **5** and **6** by the procedure outlined in ref.[25] X-ray diffraction studies of compounds **14** and **16** were carried out



3, **10**, **11**, **16**, **17**, **18**: -CH=CH$_2$

Figure 5. Labeling of hydrogen and carbon atoms in compounds **3**, **7**–**18** used for NMR assignments.

with Enraf–Nonius CAD-4 and KM-4 KUMA DIFFRACTION diffractometers at room temperature ($\omega/2\theta$-scanning, Mo-K_α radiation, graphite monochromator). Crystalline structures were solved by direct methods followed with Fourier synthesis by using SHELXS-97.[26] All non-hydrogen atoms were refined by using anisotropic full-matrix approximation with the use of SHELXL-97.[27]

3-Cyanomethylene-2,3,9,9a-tetrahydro-9-methyl-2,2-dimethyl-1,3-oxazolo[3,2-*a*]benzimidazole (7): A mixture of 1-methylbenzimidazole (**1**) (0.26 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) were stirred at 20–25 °C for 5 h to afford 1,3-oxazolobenzimidazole **7** (0.48 g, 98% purity according to ^{1}H NMR spectroscopic data) as a yellow oil. IR (microlayer): $\tilde{\nu}$ = 3060, 2980, 2920, 2860, 2210, 1640, 1590, 1480, 1450, 1430, 1390, 1370, 1360, 1320, 1270, 1240, 1170, 1120, 1060, 1010, 980, 970, 940, 900, 830, 770, 730, 690, 650, 550, 530, 510, 470 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (m, 1 H, 5-H), 6.99 (m, 1 H, 7-H), 6.78 (m, 1 H, 6-H), 6.51 (m, 1 H, 8-H), 6.28 (s, 1 H, 9a-H), 4.40 (s, 1 H, 12-H, =C*H*-CN), 2.89 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.42 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.51 (C-3), 142.67 (C-8a), 134.23 (C-4a), 125.08 (C-7), 119.31 (C-6), 118.83 (C-12, CN), 116.13 (C-5), 108.97 (C-9a), 107.04 (C-8), 84.41 (C-2), 67.92 (C-11, =*C*H-CN), 32.21 (Me), 28.31 (Me), 26.86 (Me) ppm. $C_{14}H_{15}N_3O$ (241.29): calcd. C 69.69, H 6.27, N 17.41; found C 69.20, H 6.18, N 17.65.

3-Cyanomethylene-9-ethyl-2,3,9,9a-tetrahydro-2,2-dimethyl-1,3-oxazolo[3,2-*a*]benzimidazole (8): A mixture of 1-ethylbenzimidazole (**2**) (0.29 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) were stirred at 20–25 °C for 5 h. The reaction mixture was washed with diethyl ether (5 mL, 1 × 5 mL). The residue, insoluble in diethyl ether, was dried in vacuo to give 1,3-oxazolobenzimidazole **8** (0.37 g, 88%, based on consumed benzimidazole **2**; 0.05 g of the latter being recovered by column chromatography from the ether solution). Flesh colored powder. M.p. 108–110 °C. IR (KBr): $\tilde{\nu}$ = 3070, 2970, 2930, 2860, 2200, 1640, 1590, 1480, 1460, 1410, 1390, 1370, 1340, 1320, 1290, 1260, 1220, 1150, 1120, 1060, 1030, 990, 970, 950, 910, 840, 790, 750, 740, 730, 680, 670, 600, 560, 540, 520, 470 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.71 (m, 1 H, 5-H), 6.93 (m, 1 H, 7-H), 6.75 (m, 1 H, 6-H), 6.47 (m, 1 H, 8-H), 6.37 (s, 1 H, 9a-H), 4.40 (s, 1 H, 12-H, =C*H*-CN), 3.39, 3.24 (2 m, 2 H, 10-H, C*H*$_2$ from Et), 1.48 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.26 (t, 3 H, Me from Et) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.77 (C-3), 141.58 (C-8a), 134.75 (C-4a), 124.88 (C-7), 119.29 (C-6), 119.07 (C-13, CN), 115.82 (C-5), 107.42 (C-9a), 107.29 (C-8), 83.82 (C-2), 68.47 (C-12, =*C*H-CN), 40.82 (C-10, *C*H$_2$ from Et), 28.30 (Me), 26.83 (Me), 12.98 (C-11, Me from Et) ppm. $C_{15}H_{17}N_3O$ (255.32): calcd. C 70.56, H 6.71, N 16.46; found C 70.25, H 6.52, N 16.75.

Spiro-1,3-oxazolobenzimidazole 9: Analogously, from 1-ethylbenzimidazole (**2**) (0.29 g, 2 mmol) and acetylene **6** (0.30 g, 2 mmol) (20–25 °C, 5 h) was obtained 1,3-oxazolobenzimidazole **9** (0.19 g, 63%, based on consumed **2**, 0.14 g of the latter being recovered). Flesh colored powder. M.p. 118–121 °C. IR (KBr): $\tilde{\nu}$ = 3060, 3010, 2960, 2920, 2850, 2190, 1630, 1580, 1470, 1450, 1440, 1410, 1370, 1350, 1310, 1260, 1230, 1180, 1130, 1070, 1060, 1040, 1020, 990, 970, 950, 930, 910, 890, 850, 830, 790, 740, 730, 680, 640, 590, 570, 550, 520, 510 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.73 (m, 1 H, 5-H), 6.96 (m, 1 H, 7-H), 6.76 (m, 1 H, 6-H), 6.51 (m, 1 H, 8-H), 6.39 (s, 1 H, 9a-H), 4.44 (s, 1 H, 12-H, =C*H*-CN), 3.42, 3.27 (2 m, 2 H, 10-H, C*H*$_2$ from Et), 1.70–1.39 (m, 10 H, cyclohexyl), 1.26 (t, 3 H, Me from Et) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.14 (C-3), 141.66 (C-8a), 135.10 (C-4a), 124.85 (C-7), 119.26 (C-6), 119.26 (C-13, CN), 115.91 (C-5), 107.70 (C-9a), 107.31 (C-8), 85.61 (C-2), 69.28 (C-12, =*C*H-CN), 40.86 (C-10, *C*H$_2$ from Et), 36.81–21.99 (5 C, cyclohexyl), 13.16 (C-11, Me from Et) ppm. $C_{18}H_{21}N_3O$ (295.38): calcd. C 73.19, H 7.17, N 14.23; found C 72.75, H 7.48, N 14.21.

3-Cyanomethylene-2,2-dimethyl-2,3,9,9a-tetrahydro-9-vinyl-1,3-oxazolo[3,2-*a*]benzimidazole (10): Analogously, from 1-vinylbenzimidazole (**3**) (0.29 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) (20–25 °C, 20 h) was prepared 1,3-oxazolobenzimidazole **10** (0.10 g, 45%, based on consumed benzimidazole **3**, 0.17 g of the latter being recovered). Flesh colored powder. M.p. 109–111 °C. IR (KBr): $\tilde{\nu}$ = 3050, 3020, 2970, 2930, 2860, 2210, 1640, 1620, 1590, 1490, 1460, 1400, 1370, 1360, 1340, 1310, 1270, 1250, 1210, 1160, 1130, 1110, 1070, 1030, 1010, 960, 910, 900, 830, 780, 760, 730, 690, 670, 630, 550 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (m, 1 H, 5-H), 6.88 (m, 1 H, 7-H), 6. 27 (m, 1 H, 6-H), 6.70 (m, 1 H, 8-H), 6.65 (dd, $^3J_{AX}$ = 8.8 Hz, $^3J_{BX}$ = 16.1 Hz, 1 H, H$_X$), 6.51 (s, 1 H, 9a-H), 4.60 (dd, $^3J_{AB}$ = 1.0 Hz, $^3J_{BX}$ = 16.1 Hz, 1 H, H$_B$), 4.57 (s, 1 H, 12-H, =C*H*-CN), 4.35 (dd, $^3J_{AB}$ = 1.0 Hz, $^3J_{AX}$ = 8.8 Hz, 1 H, H$_A$), 1.52 (s, 3 H, Me), 1.37 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.63 (C-3), 136.92 (C-8a), 134.77 (C-4a), 130.29 (C-10), 124.63 (C-7), 120.93 (C-6), 118.56 (C-13, CN), 115.59 (C-5), 106.90 (C-8), 103.45 (C-9a), 91.44 (C-11), 83.75 (C-2), 70.92 (C-12, =*C*H-CN), 28.05 (Me), 26.67 (Me) ppm. $C_{15}H_{15}N_3O$ (253.30): calcd. C 71.13, H 5.97, N 16.59; found C 71.40, H 5.80, N 16.85.

Spiro-1,3-oxazolobenzimidazole 11: Analogously, from 1-vinylbenzimidazole (**3**) (0.29 g, 2 mmol) and acetylene **6** (0.30 g, 2 mmol) (20–25 °C, 72 h) was prepared 1,3-oxazolobenzimidazole **11** (0.06 g, 30%, based on consumed benzimidazole **3**, 0.19 g of the latter being recovered). Flesh colored powder. M.p. 170–173 °C. IR (KBr): $\tilde{\nu}$ = 3050, 3020, 2960, 2920, 2850, 2210, 1640, 1610, 1580, 1490, 1450, 1410, 1380, 1360, 1340, 1320, 1280, 1260, 1210, 1150, 1120, 1100, 1080, 1020, 960, 920, 910, 840, 780, 760, 740, 690, 670, 620, 550 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.55 (m, 1 H, 5-H), 7.15 (dd, $^3J_{AX}$ = 8.7 Hz, $^3J_{BX}$ = 16.2 Hz, 1 H, H$_X$), 7.05 (m, 1 H, 7-H), 6.92 (m, 1 H, 6-H), 6.55 (m, 1 H, 8-H), 6.23 (s, 1 H, 9a-H), 4.70 (dd, $^3J_{AB}$ = 1.1 Hz, $^3J_{BX}$ = 16.2 Hz, 1 H, H$_B$), 4.59 (s, 1 H, 12-H, =C*H*-CN), 4.40 (dd, $^3J_{AB}$ = 1.1 Hz, $^3J_{AX}$ = 8.7 Hz, 1 H, H$_A$), 1.70–1.40 (m, 10 H, cyclohexyl) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.98 (C-3), 141.90 (C-8a), 130.46 (C-4a), 128.20 (C-10), 124.67 (C-7), 120.67 (C-13, CN), 120.58 (C-6), 115.83 (C-5), 110.52 (C-9a), 103.72 (C-8), 91.50 (C-11), 85.09 (C-2), 65.99 (C-12, =*C*H-CN), 38.94–24.88 (5 C, cyclohexyl) ppm. $C_{18}H_{19}N_3O$ (293.37): calcd. C 73.70, H 6.53, N 14.32; found C 73.40, H 6.32, N 14.55.

9-Allyl-3-cyanomethylene-2,3,9,9a-tetrahydro-2,2-dimethyl-1,3-oxazolo[3,2-*a*]benzimidazole (12): A mixture of 1-allylbenzimidazole (**4**) (0.32 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) were stirred at 20–25 °C for 9 h to give 1,3-oxazolobenzimidazole **12** (0.54 g, 88% purity, according to ^{1}H NMR spectroscopic data) as a yellow oil. IR (microlayer): $\tilde{\nu}$ = 3060, 2970, 2930, 2860, 2210, 1660, 1640, 1590, 1480, 1460, 1430, 1410, 1380, 1350, 1320, 1270, 1250, 1240, 1200, 1170, 1150, 1120, 1100, 1060, 1010, 980, 970, 940, 920, 840, 810, 770, 730, 690, 650, 620, 590, 560, 540, 510, 490 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.77 (m, 1 H, 5-H), 6.98 (m, 1 H, 7-H), 6.81 (m, 1 H, 6-H), 6.57 (m, 1 H, 8-H), 6.43 (s, 1 H, 9a-H), 5.88 (m, 1 H, 11-H, H$_X$ from allyl), 5.30 (m, 2 H,12-H, =C*H*$_2$ from allyl), 4.49 (s, 1 H, 13-H, =C*H*-CN), 3.92 (m, 2 H, 10-H, -C*H*$_2$ from allyl), 1.50 (s, 3 H, Me), 1.43 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.13 (C-3), 141.59 (C-8a), 135.02 (C-4a), 133.41 (C-11, *C*-H$_X$ from allyl), 125.26 (C-7), 120.44 (C-6), 118.94 (C-14, CN), 118.00 (C-12, =*C*H$_2$ from allyl), 116.00 (C-5), 107.65 (C-9a), 107.29 (C-8), 83.74 (C-2), 69.75 (C-13, =*C*H-CN), 48.93 (C-10, -*C*H$_2$ from allyl), 28.59 (Me), 27.07 (Me) ppm.

$C_{16}H_{17}N_3O$ (267.33): calcd. C 71.89, H 6.41, N 15.72; found C 72.05, H 6.20, N 15.40.

Rearrangement of 3-Cyanomethylene-9-ethyl-2,3,9,9a-tetrahydro-2,2-dimethyl-1,3-oxazolo[3,2-*a*]benzimidazole (8) to *N*-(2-{[5-Amino-2,2-dimethyl-3(2*H*)-furanylidene]amino}phenyl)-*N*-ethylformamide (14): 1,3-Oxazolobenzimidazole **8** (0.26 g, 2 mmol) was dissolved in a mixture of chloroform/benzene/ethanol (20:4:1, 5 mL). Column chromatography on Al_2O_3 was employed to afford formamide **14** (0.27 g, 97%). Light yellowish powder. M.p. 191–193 °C. IR (KBr): $\tilde{\nu}$ = 3350, 3250, 2940, 2970, 2930, 2860, 2790, 2730, 1640, 1620, 1590, 1550, 1540, 1470, 1450, 1410, 1360, 1310, 1290, 1280, 1250, 1190, 1170, 1120, 1090, 1070, 990, 980, 940, 930, 870, 810, 800, 760, 740, 690, 660, 640, 610, 590, 540, 520, 470 cm^{-1}. *syn*-**14**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H, 14-H, *H*C=O), 7.23 (m, 1 H, 10-H), 7.10 (m, 1 H, 8-H), 7.02 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.56 (s, 2 H, NH_2), 4.38 (s, 1 H, 3-H), 3.69 (q, $^3J_{CH_2CH_3}$ = 7.1 Hz, 2 H, 15-H, C*H₂* from Et), 1.52 (s, 6 H, 2 Me), 1.07 (t, $^3J_{CH_2CH_3}$ = 7.1 Hz, 3 H, 16-H, Me from Et) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.86 (C-4), 173.26 (C-2), 162.24 (C-14, H*C*=O), 150.70 (C-7), 132.47 (C-12), 127.81 (C-11), 127.69 (C-9), 122.03 (C-8), 121.68 (C-10), 88.27 (C-5), 69.46 (C-3), 39.29 (C-15, *C*H_2 from Et), 25.15 (2 C, 2 Me), 12.40 (C-16, Me from Et) ppm. *anti*-**14**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, 14-H, *H*C=O); 7.34 (m, 1 H, 10-H), 7.10 (m, 1 H, 8-H), 7.02 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.88 (s, 1 H, 3-H), 4.56 (s, 2 H, NH_2), 3.73 (q, $^3J_{CH_2CH_3}$ = 7.1 Hz, 2 H, 15-H, C*H₂* from Et), 1.52 (s, 6 H, 2 Me), 1.06 (t, $^3J_{CH_2CH_3}$ = 7.1 Hz, 3 H, 16-H, Me from Et) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 175.84 (C-4), 172.87 (C-2), 161.68 (C-14, H*C*=O), 149.56 (C-7), 130.43 (C-12), 129.67 (C-11), 127.45 (C-9), 122.03 (C-8), 121.16 (C-10), 87.93 (C-5), 70.18 (C-3), 42.57 (C-15, *C*H_2 from Et), 25.15 (2 C, 2 Me), 14.49 (C-16, Me from Et) ppm (*syn*/*anti* ratio 80:20). $C_{15}H_{19}N_3O_2$ (273.33): calcd. C 65.91, H 7.01, N 15.37; found C 65.58, H 6.84, N 14.95.

Synthesis of Aminophenyl-*N*-alkylformamides 13–18 Directly from Benzimidazoles 1–4 and Acetylenes 5 and 6 (Typical Procedure): A mixture of benzimidazole **2** (0.29 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) was stirred at 20–25 °C for 5 h. Column chromatography on Al_2O_3 was employed to afford formamide **14** (0.46 g, 85%).

***N*-{2-(2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene)aminophenyl}-*N*-methylformamide (13):** A mixture of 1-methylbenzimidazole (**1**) (0.26 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) was stirred at 20–25 °C for 5 h. Column chromatography on Al_2O_3 was employed to afford formamide **13** (0.36 g, 71%). Flesh colored powder. M.p. 179–180 °C. IR (KBr): $\tilde{\nu}$ = 3350, 3300, 3110, 2970, 2930, 2870, 2800, 2730, 1660, 1650, 1620, 1540, 1530, 1480, 1440, 1420, 1360, 1350, 1320, 1290, 1280, 1200, 1170, 1120, 1080, 1070, 990, 970, 950, 930, 880, 840, 810, 800, 760, 740, 710, 660, 640, 620, 590, 550, 480 cm^{-1}. *syn*-**13**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, 14-H, *H*C=O), 7.21 (m, 1 H, 10-H), 7.10 (m, 1 H, 8-H), 7.00 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.59 (s, 2 H, NH_2), 4.32 (s, 1 H, 3-H), 3.14 (s, 3 H, 15-H, Me), 1.51 (s, 6 H, 2 Me) ppm.^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.13 (C-4), 173.31 (C-2), 162.77 (C-14, H*C*=O), 149.95 (C-7), 134.12 (C-12), 127.68 (C-11), 126.74 (C-9), 122. 53 (C-8), 121.99 (C-10), 88.27 (C-5), 69.45 (C-3), 32.08 (C-15, Me), 25.35 (2 C, 2 Me) ppm. *anti*-**13**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H, 14-H, *H*C=O); 7.30 (m, 1 H, 10-H), 7.10 (m, 1 H, 8-H), 7.00 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.59 (s, 2 H, NH_2), 4.32 (s, 1 H, 3-H), 3.33 (s, 3 H, 15-H, Me); 1.50 (s, 6 H, 2 Me) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.13 (C-4), 172.96 (C-2), 162.10 (C-14, H*C*=O), 149.95 (C-7), 132.42 (C-12), 128.45 (C-11), 126.74 (C-9), 122.35 (C-8), 121.99 (C-10), 88.11 (C-5), 69.45 (C-3), 35.69 (C-15, Me), 25.35 (2 C, 2 Me) ppm. (*syn*/*anti* ratio 90:10). $C_{14}H_{17}N_3O_2$ (259.31): calcd. C 64.85, H 6.61, N 16.20; found C 64.50, H 6.72, N 15.95.

***N*-{2-(2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene)aminophenyl}-*N*-ethylformamide (15):** From 1-ethylbenzimidazole (**2**) (0.29 g, 2 mmol) and acetylene **6** (0.30 g, 2 mmol) (20–25 °C, 7 h) was prepared formamide **15** (0.43 g, 69%). Light yellowish powder. M.p. 183–186 °C. IR (KBr): $\tilde{\nu}$ = 3380, 3280, 3050, 2960, 2930, 2850, 2750, 2710, 1640, 1610, 1550, 1540, 1530, 1470, 1430, 1420, 1370, 1360, 1280, 1260, 1240, 1230, 1180, 1120, 1080, 1070, 1050, 980, 940, 920, 870, 820, 800, 790, 750, 740, 690, 650, 570, 540, 520, 490, 440 cm^{-1}. *syn*-**15**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, 14-H, *H*C=O), 7.22 (m, 1 H, 10-H), 7.08 (m, 1 H, 8-H), 7.00 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.61 (s, 2 H, NH_2), 4.33 (s, 1 H, 3-H), 3.68 (q, $^3J_{CH_2CH_3}$ = 7.1 Hz, 2 H, 15-H, C*H₂* from Et), 1.77–1.32 (m, 10 H, cyclohexyl), 1.06 (t, $^3J_{CH_2CH_3}$ = 7.1 Hz, 3 H, 16-H, Me from Et) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.01 (C-4), 173.60 (C-2), 162.47 (C-14, H*C*=O), 151.04 (C-7), 132.45 (C-12), 128.12 (C-11), 128.01 (C-9), 122.37 (C-8), 121.89 (C-10), 89.83 (C-5), 69.89 (C-3), 39.51 (C-15, *C*H_2 from Et), 33.82–21.73 (5 C, cyclohexyl), 12.72 (C-16, Me from Et) ppm. *anti*-**15**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, 14-H, *H*C=O), 7.32 (m, 1 H, 10-H), 7.08 (m, 1 H, 8-H), 7.00 (m, 1 H, 9-H), 6.95 (m, 1 H, 11-H), 4.84 (s, 1 H, 3-H), 4.61 (s, 2 H, NH_2), 3.71 (q, $^3J_{CH_2CH_3}$ = 7.1 Hz, 2 H, 15-H, C*H₂* from Et), 1.77–1.32 (m, 10 H, cyclohexyl); 1.05 (t, $^3J_{CH_2CH_3}$ = 7.1 Hz, 3 H, 16-H, Me from Et) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.11 (C-4), 173.44 (C-2), 162.07 (C-14, H*C*=O), 149.07 (C-7), 130.52 (C-12), 128.38 (C-11), 127.79 (C-9), 122.73 (C-8), 121.80 (C-10), 89.75 (C-5), 70.95 (C-3), 42.72 (C-15, *C*H_2 from Et), 33.82–21.73 (5 C, cyclohexyl), 14.81 (C-16, Me from Et) ppm (*syn*/*anti* ratio 80:20). $C_{18}H_{23}N_3O_2$ (313.40): calcd. C 68.98, H 7.40, N 13.41; found C 68.57, H 7.14, N 13.70.

***N*-(2-{[5-Amino-2,2-dimethyl-3(2*H*)-furanylidene]amino}phenyl)-*N*-vinylformamide (16):** From 1-vinylbenzimidazole (**3**) (0.29 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) (20–25 °C, 30 h) was prepared formamide **16** (0.24 g, 44%). Light yellowish powder. M.p. 185–187 °C. IR (KBr): $\tilde{\nu}$ = 3340, 3300, 2960, 2910, 2850, 2780, 2760, 2730, 1660, 1610, 1540, 1520, 1460, 1430, 1410, 1380, 1360, 1340, 1300, 1280, 1260, 1230, 1180, 1160, 1130, 1110, 1060, 1050, 1010, 980, 950, 930, 870, 840, 810, 790, 740, 730, 680, 660, 590, 570, 550, 520, 480, 420 cm^{-1}. *syn*-**16**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, 14-H, *H*C=O), 7.35 (dd, $^3J_{AX}$ = 8.8 Hz, $^3J_{BX}$ = 15.9 Hz, 1 H, H_X), 7.32 (m, 1 H, 10-H), 7.18 (m, 1 H, 8-H), 7.06 (m, 1 H, 9-H), 7.06 (m, 1 H, 11-H), 4.73 (s, 1 H, 3-H), 4.43 (d, $^3J_{AX}$ = 8.8 Hz, 1 H, H_A), 4.40 (s, 2 H, NH_2), 4.28 (d, $^3J_{BX}$ = 15.9 Hz, 1 H, H_B), 1.46 (s, 6 H, 2 Me) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.38 (C-4), 173.42 (C-2), 161.68 (C-14, H*C*=O), 151.42 (C-7), 130.05 (C-15), 129.22 (C-12), 129.14 (C-8), 129.08 (C-10), 122.59 (C-11), 121.87 (C-9), 95.83 (C-16), 88.53 (C-5), 69.30 (C-3), 25.38 (2 C, 2 Me) ppm. *anti*-**16**: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H, 14-H, *H*C=O), 7.32 (m, 1 H, 10-H); 7.18 (m, 1 H, 8-H), 7.18 (m, 1 H, 11-H), 7.14 (m, 1 H, 9-H), 6.73 (dd, $^3J_{AX}$ = 8.8 Hz, $^3J_{BX}$ = 15.2 Hz, 1 H, H_X); 4.73 (s, 1 H, 3-H), 4.43 (d, $^3J_{AX}$ = 8.8 Hz, 1 H, H_A), 4.40 (s, 2 H, NH_2), 4.32 (d, $^3J_{BX}$ = 15.2 Hz, 1 H, H_B), 1.46 (s, 6 H, 2 Me) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.38 (C-4), 172.96 (C-2), 162.55 (C-14, H*C*=O), 151.42 (C-7), 135.01 (C-15), 129.07 (C-12), 128.80 (C-8), 127.89 (C-10), 122.43 (C-11), 121.95 (C-9), 93.51 (C-16), 88.19 (C-5), 69.30 (C-3), 25.38 (2 C, 2 Me) ppm (*syn*/*anti* ratio 85:15). $C_{15}H_{17}N_3O_2$ (271.32): calcd. C 66.40, H 6.32, N 15.49; found C 66.46, H 6.40, N 15.75.

***N*-{2-(2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene)aminophenyl}-*N*-vinylformamide (17):** From 1-vinylbenzimidazole (**3**) (0.29 g, 2 mmol) and acetylene **6** (0.30 g, 2 mmol) (20–25 °C, 72 h) was prepared formamide **17** (0.06 g, 35%, based on consumed benzimidazole **3**, 0.21 g of the latter being recovered). Light yellowish powder. M.p. 161–163 °C. IR (KBr): $\tilde{\nu}$ = 3330, 3270, 3160, 2940, 2930, 2850, 2780, 2700, 1670, 1640, 1610, 1570, 1560, 1540, 1480, 1440, 1400, 1330, 1300, 1270, 1200, 1130, 1090, 1050, 990, 980, 950, 930, 860, 830, 800, 790, 760, 750, 740, 690, 630, 570, 540, 510, 440 cm^{-1}. *syn*-**17**: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.01 (s, 1 H, 14-H, *H*C=O), 7.34 (dd, $^3J_{AX}$ = 8.6 Hz, $^3J_{BX}$ = 15.9 Hz, 1 H, H$_X$), 7.31 (m, 1 H, 10-H), 7.17 (m, 1 H, 8-H), 7.06 (m, 1 H, 9-H), 7.06 (m, 1 H, 11-H), 4.73 (s, 1 H, 3-H), 4.56 (s, 2 H, NH$_2$), 4.43 (d, $^3J_{AX}$ = 8.6 Hz, 1 H, H$_A$), 4.27 (d, $^3J_{BX}$ = 15.9 Hz, 1 H, H$_B$), 1.71–1.27 (m, 10 H, cyclohexyl) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.34 (C-4), 173.66 (C-2), 161.65 (C-14, H*C*=O), 151.41 (C-7), 130.03 (C-15), 129.25 (C-12), 129.18 (C-8), 129.05 (C-10), 122.82 (C-11), 121.99 (C-9), 95.96 (C-16), 89.91 (C-5), 69.99 (C-3), 33.79–21.68 (5 C, cyclohexyl) ppm. *anti*-**17**: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.48 (s, 1 H, 14-H, *H*C=O); 7.31 (m, 1 H, 10-H), 7.17 (m, 1 H, 8-H), 7.14 (m, 1 H, 9-H), 7.14 (m, 1 H, 11-H), 6.74 (dd, $^3J_{AX}$ = 9.1 Hz, $^3J_{BX}$ = 15.7 Hz, 1 H, H$_X$), 4.73 (s, 1 H, 3-H), 4.56 (s, 2 H, NH$_2$), 4.43 (d, $^3J_{AX}$ = 9.1 Hz, 1 H, H$_A$), 4.31 (d, $^3J_{BX}$ = 15.7 Hz, 1 H, H$_B$), 1.71–1.27 (m, 10 H, cyclohexyl) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 176.18 (C-4), 173.30 (C-2), 162.58 (C-14, H*C*=O), 151.41 (C-7), 134.96 (C-15), 129.25 (C-12), 128.83 (C-8), 127.94 (C-10), 122.73 (C-11), 121.99 (C-9), 93.67 (C-16), 89.68 (C-5), 69.99 (C-3), 33.79–21.68 (5 C, cyclohexyl) ppm (*syn*/*anti* ratio 85:15). $C_{18}H_{21}N_3O_2$ (311.38): calcd. C 69.43, H 6.80, N 13.49; found C 69.88, H 7.04, N 13.70.

***N*-{2-(2-Amino-1-oxaspiro[4.5]dec-2-en-4-ylidene)aminophenyl}-*N*-allylformamide (18):** A mixture of 1-allylbenzimidazole **4** (0.32 g, 2 mmol) and acetylene **5** (0.22 g, 2 mmol) was stirred at 20–25 °C for 9 h. Column chromatography on Al$_2$O$_3$ was employed to afford formamide **18** (0.48 g, 83%). Flesh colored powder. M.p. 176–177 °C. IR (KBr): $\tilde{\nu}$ = 3350, 3260, 3100, 2970, 2930, 2880, 2800, 2740, 1660, 1640, 1630, 1540, 1530, 1480, 1450, 1430, 1360, 1340, 1320, 1280, 1230, 1200, 1180, 1140, 1080, 1080, 1000, 980, 950, 930, 880, 840, 820, 760, 720, 670, 640, 600, 590, 540, 450 cm^{-1}. *syn*-**18**: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.07 (s, 1 H, 14-H, *H*C=O), 7.21 (m, 1 H, 10-H), 7.09 (m, 1 H, 8-H), 6.98 (m, 1 H, 9-H), 6.90 (m, 1 H, 11-H), 5.78 (m, 1 H, H$_X$ from allyl), 5.14 (d, $^3J_{BX}$ = 17.2 Hz, 1 H, H$_B$ from allyl), 5.05 (d, $^3J_{AX}$ = 10.2 Hz, 1 H, H$_A$ from allyl), 4.60 (s, 2 H, NH$_2$), 4.32 (s, 1 H, 3-H), 4.24 (d, $^3J_{CH_2CH_x}$ = 6.2 Hz, 2 H, 15-H, C*H$_2$* from allyl), 1.51 (s, 6 H, 2 Me) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.12 (C-4), 173.43 (C-2), 162.73 (C-14, H*C*=O), 150.22 (C-7), 133.52 (C-16, *C*-H$_X$ from allyl), 132.68 (C-12), 127.75 (C-11), 127.46 (C-9), 122.20 (C-8), 121.82 (C-10), 116.65 (C-17, =*C*H$_2$ from allyl), 88.52 (C-5), 69.38 (C-3), 46.78 (C-15, *C*H$_2$ from allyl), 25.40 (2 C, 2 Me) ppm. *anti*-**18**: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.28 (s, 1 H, 14-H, *H*C=O), 7.21 (m, 1 H, 10-H), 7.09 (m, 1 H, 8-H), 6.98 (m, 1 H, 9-H), 6.90 (m, 1 H, 11-H), 5.68 (m, 1 H, H$_X$ from allyl), 5.14 (d, $^3J_{BX}$ = 17.2 Hz, 1 H, H$_B$ from allyl), 5.05 (d, $^3J_{AX}$ = 10.2 Hz, 1 H, H$_A$ from allyl), 4.60 (s, 2 H, NH$_2$), 4.32 (s, 1 H, 3-H), 4.24 (d, $^3J_{CH_2CH_x}$ = 6.2 Hz, 2 H, 15-H, C*H$_2$* from allyl), 1.50 (s, 6 H, 2 Me) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 176.27 (C-4), 173.02 (C-2), 162.39 (C-14, H*C*=O), 150.22 (C-7), 135.01 (C-16, *C*-H$_X$ from allyl), 130.66 (C-12), 128.30 (C-11), 127.62 (C-9), 122.20 (C-8), 121.13 (C-10), 117.19 (C-17, =*C*H$_2$ from allyl), 88.19 (C-5), 69.38 (C-3), 50.63 (C-15, *C*H$_2$ from allyl), 25.40 (2 C, 2 Me) ppm. (*syn*/*anti* ratio 85:15). $C_{16}H_{19}N_3O_2$ (285.35): calcd. C 65.35, H 6.71, N 14.73; found C 65.00, H 6.80, N 14.70.

Supporting Information (see footnote on the first page of this article): Figure S1–S3 (and Tables) for compounds **14** and **16**.

CCDC-626380 and -626379 (for **14** and **16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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