One pot Synthesis of Macrocycles by a Tandem three-component Reaction and Intramolecular [3 + 2] Cycloaddition

Tracey Pirali,[a] Gian Cesare Tron,[a] and Jieping Zhu[b]

a) Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche and Drug and Food Biotechnology Center, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy.

b) Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

Contents :

1. Experimental procedures and spectral data for all new compounds
2. ^{13}C NMR spectra for macrocycles

Commercially available reagents and solvents were used without further purification and were purchased from Sigma-Aldrich or Lancaster. CuI was purified[1] and stored under nitrogen. THF was distilled immediately before use from Na/benzophenone, CH_2Cl_2 was dried by distillation from P_2O_5 and stored on activated molecular sieves (4 Å), toluene was distilled from Na and stored on activated molecular sieves (4 Å). When needed the reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen .

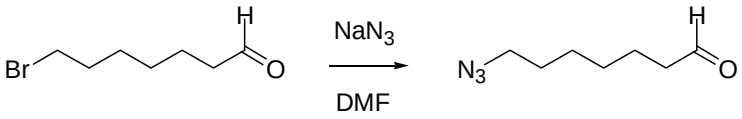
NMR spectra were recorded with a JEOL ECP 300 Mhz spectrometer and the δ values are in part per million. Mass spectra were recorded using a Thermo Finningan LCQ Deca XP-*plus* equipped with an ESI source and an ion trap detector. IR spectra were recorded using FT-IR THERMO-NICOLET AVATAR.

Column chromatography was performed on silica gel (Merck Kieselgel 70-230 mesh ASTM) using the indicated eluants. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$, Dragendorff reagent or silver nitrate.

Compounds **2a**, **2e**, **3b** were purchased from Sigma-Aldrich or Lancaster.

Compound **2d** was synthesized following the literature procedure.[2]

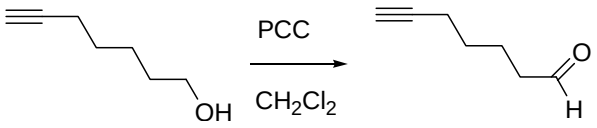
Aldehydes



7-azidoheptanal (2b)

7-bromoheptanal was synthesized following the literature procedure.[3]

To a solution of 7-bromoheptanal (700 mg, 3.63 mmol) in DMF (7 mL) sodium azide (471 mg, 7.26 mmol) was added. The resulting suspension was stirred at room temperature for 18 hours. The reaction was worked up by dilution with Et_2O and washing with water (x 3) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 8:2 to give **2b** as a colorless oil (397 mg, 70%). R_f = 0.13 (PE/EtOAc 95:5 x 2). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 9.74 (br s, 1H), 3.24 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 7.4 Hz, 2H), 1.56 (br s, 4H), 1.35 (br s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 202.0, 51.1, 43.5, 28.8 (2C), 25.9, 21.7; IR (liquid film) 2935, 2092, 1707, 1257, 729 cm^{-1}; MS (ESI) *m/z* 156 $(M+H)^+$.



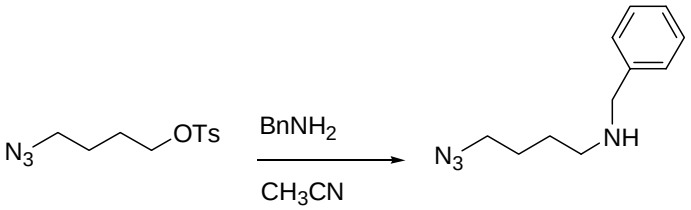
6-heptynale (2c)

Heptyn-1-ol was synthesized following the literature procedure.[4]

To a solution of heptyn-1-ol (688 mg, 5.63 mmol) in dry CH_2Cl_2 (20 mL) PCC (1.81 g, 8.45 mmol) was added. The resulting suspension was stirred at room temperature for 2 hours. The reaction was filtered and through a Celite pad, washed with CH_2Cl_2 and evaporated. The crude product was purified by column chromatography using as eluant PE/EtOAc 8:2 to give **2c** as a yellow oil (291 mg, 47%). R_f = 0.78 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 9.70 (br s, 1H), 2.40 (td, J = 7.1/1.6 Hz, 2H), 2.15 (td, J = 6.8/2.7 Hz, 2H), 1.90 (t, J = 2.7 Hz, 1H), 1.68 (m,

2H), 1.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 202.2, 83.0, 68.8, 43.3, 28.0, 21.1, 18.3; IR (liquid film) 3295, 2944, 1705, 1412, 1234, 634 cm^{-1}; MS (ESI) *m/z* 149 $(M+K)^+$

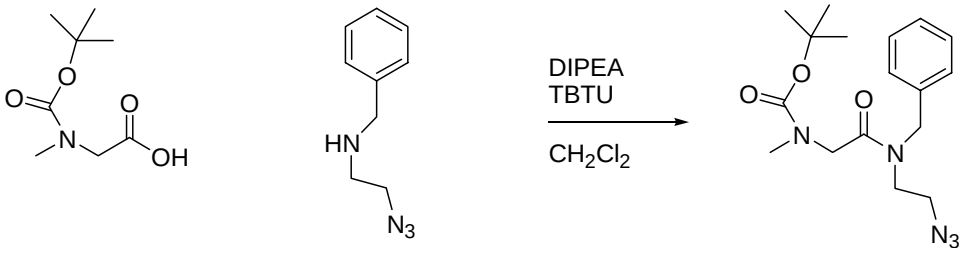
Amines



***N*-(4-azidobutyl)-*N*-benzylamine (3a)**

4-azidobutyl 4-methylbenzenesulfonate was synthesized following the literature procedure.[5]

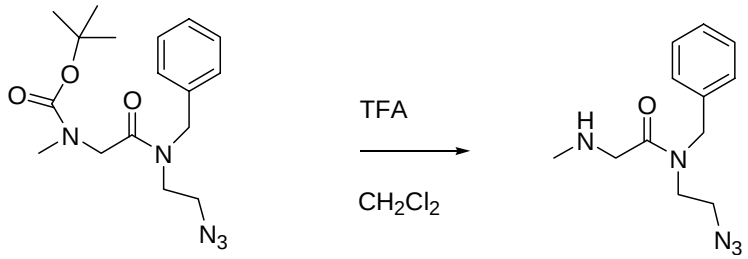
To a solution of toluene-4-sulfonic acid 4-azidobutylester (6.32 g, 23.5 mmol) in CH_3CN (60 mL) $BnNH_2$ (6.99 mL, 63.4 mmol) was added. The resulting mixture was heated at reflux for 22 hours. The reaction was worked up by evaporation of the solvent, dilution with Et_2O and washing with NaOH 2N (x 3) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 8:2 and PE/EtOAc 5:5 (+ TEA 1%) to give **3a** as a pale yellow oil (4.02 g, 84%). R_f = 0.16 (PE/EtOAc 5:5 + TEA 1%). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 3.78 (s, 2H), 3.26 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.6 Hz, 2H), 1.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.3, 128.5, 128.2, 127.1, 54.2, 51.4, 48.7, 27.2, 26.1; IR (liquid film) 2937, 2092, 1739, 1453, 1364, 1255 $cm^{-1;}$ MS (ESI) *m/z* 205 $(M+H)^+$



***tert*-butyl 2-[(2-azidoethyl)(benzyl)amino]-2-oxoethyl(methyl)carbamate**

2-[(*tert*-butoxycarbonyl)(methyl)amino]acetic acid[6] and *N*-(2-azidoethyl)-*N*-benzylamine[5] were synthesized following the literature procedure.

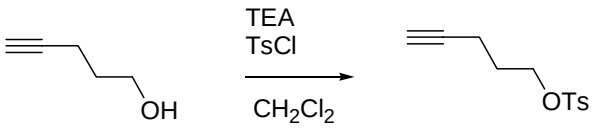
To a solution of *N*-(2-azidoethyl)-*N*-benzylamine (1.20g, 8.50 mmol) in dry CH_2Cl_2 (100 mL) (2-[(*tert*-butoxycarbonyl)(methyl)amino]acetic acid (3.20 g, 17.0 mmol), DIPEA (4.40 mL, 25.5 mmol) and TBTU (8.10 g, 25.8 mmol) were added. The resulting mixture was stirred at room temperature for 2 days. The reaction was worked up by dilution with CH_2Cl_2 and washing with HCl 2N (x 2), saturated aqueous Na_2CO_3 (x 1) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 8:2 and PE/EtOAc 7:3 to give a mixture of *tert*-butyl 2-[(2-azidoethyl)(benzyl)amino]-2-oxoethyl(methyl)carbamate and 1-hydroxybenzotriazole. The mixture was used in the next step without further purification.



***N*-(2-azidoethyl)-*N*-benzyl-2-(methylamino)acetamide (3c)**

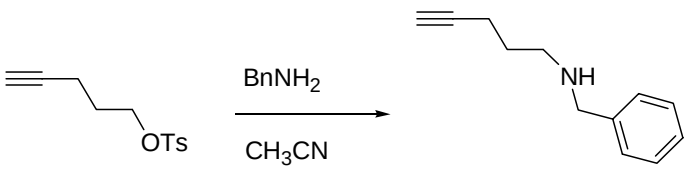
To a cooled (0°C) and stirred solution of *tert*-butyl 2-[(2-azidoethyl)(benzyl)amino]-2-oxoethyl(methyl)carbamate in dry CH_2Cl_2 (40 mL) TFA (12 mL) was added dropwise over a period of 30 minutes. The resulting mixture was stirred at this temperature for 1 hour. The reaction was worked up by dilution with CH_2Cl_2 and washing with water. The combined acqueous phases were treated with NaOH 2N until pH = 8 and then extracted with EtOAc (x 2). The resulting combined organic phase were washed with brine (x 1), dried over sodium sulphate and evaporated to give **3c** as a pale yellow solid (429 mg, 20% overall yield). R_f = 0.02 (EtOAc). M.p. = 64.9-65.3°C. Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 7.28-7.03 (m, 5H), 4.47 (s, 2H), 3.41-3.26 (m, 6H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred

to the main rotamer) δ 171.9, 136.3, 129.0, 127.8, 126.4, 52.4, 51.5, 49.4, 45.9, 36.3; IR (liquid film) 2092, 1636, 1419, 1217, 1085, 701 cm^{-1}; MS (ESI) *m/z* 248 $(M+H)^+$



4-pentynyl 4-methylbenzenesulfonate

To a cooled (0°C) solution of 4-pentyn-1-ol (5.00 g, 59.0 mmol) in dry CH_2Cl_2 (50 mL) TEA (12.6 mL, 88.5 mmol) and tosyl chloride (10.48 g, 88.5 mmol) were added. The resulting mixture was heated at 50°C for 24 hours. The reaction was worked up by dilution with CH_2Cl_2 and washing with HCl 2N (x 2) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 95:5 to give 4-pentynyl 4-methylbenzenesulfonate as a yellow oil (7.20 g, 51%). R_f = 0.50 (PE/EtOAc 8:2). Spectral data: ^1H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.72 (d, J = 7.7 Hz, 2H), 7.28 (d, J = 7.7 Hz, 2H), 4.07 (t, J = 5.2 Hz, 2H), 2.38 (s, 3H), 2.18 (m, 2H), 1.84 (t, J = 2.7 Hz, 1H), 1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 144.9, 132.9, 129.9, 127.9, 82.1, 69.5, 68.8, 27.7, 21.6, 14.7; IR (liquid film) 3321, 1357, 1173, 920, 662 cm^{-1}; MS (ESI) *m/z* 261 $(M+Na)^+$

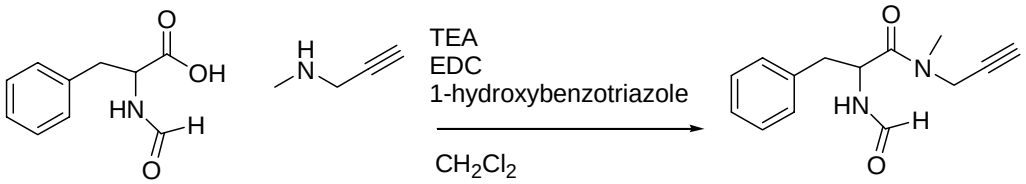


***N*-(4-methylbenzyl)-4-pentyn-1-amine (3d)**

To a cooled (0°C) solution of 4-pentynyl 4-methylbenzenesulfonate (4.75 g, 19.0 mmol) in CH_3CN (50 mL) $BnNH_2$ (5.94 mL, 53.0 mmol) was added. The resulting mixture was heated at reflux for 24 hours. The reaction was worked up by dilution with EtOAc and washing with saturated acqueous

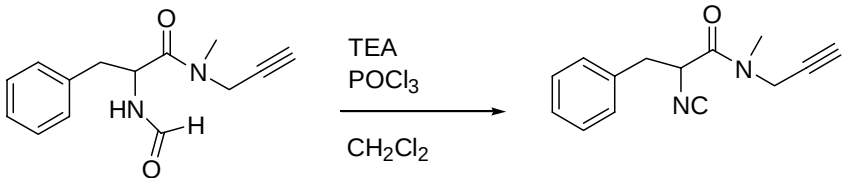
$NaHCO_3$ (x 1) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 7:3 and PE/EtOAc 4:6 to give **3d** as a dark brown oil (1.40 g, 30%). R_f = 0.28 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.31 (m, 5H), 3.78 (s, 2H), 2.73 (t, J = 7.1 Hz, 2H), 2.25 (tt, J = 6.8/2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.72 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 140.4, 128.5, 128.2, 127.0, 84.2, 68.7, 54.0, 48.2, 28.7, 16.4; IR (liquid film) 3296, 2939, 1494, 1452, 1118, 698 cm^{-1}; MS (ESI) *m/z* 174 $(M+H)^+$

α-isocyanoacetamides



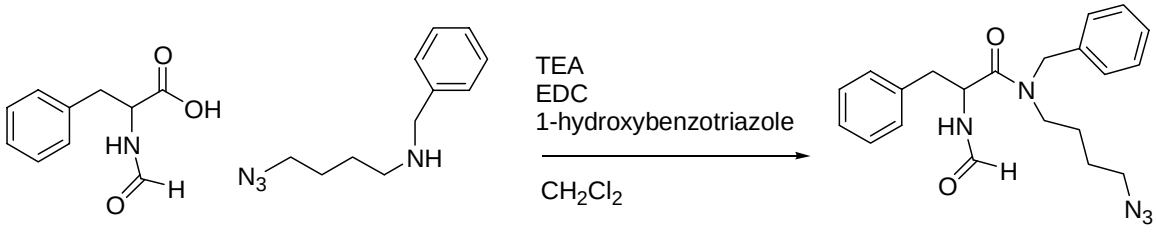
2-(formylamino)-*N*-methyl-3-phenyl-*N*-(2-propynyl)propanamide

To a suspension of *N*-formylphenylalanine[7] (6.79 g, 35.2 mmol) in dry CH_2Cl_2 (20 mL) *N*-methylpropargilamine (2.92 g, 42.2 mmol), TEA (3.05 mL, 42.2 mmol), EDC (8.10 g, 42.2 mmol) and 1-hydroxybenzotriazole (5.70 g, 42.2 mmol) were added. The resulting mixture was stirred at room temperature for 8 hours. The reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous NH_4Cl (x 2), saturated aqueous $NaHCO_3$ (x 1) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 5:5 and EtOAc to give 2-(formylamino)-*N*-methyl-3-phenyl-*N*-(2-propynyl)propanamide as a pale yellow oil (7.95 g, 92%). R_f = 0.15 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C, referred to the main rotamer) δ 8.33 (br s, 1), 7.31-7.18 (m, 5H), 5.21 (m, 1H), 4.16 (dd AB, J = 17.3/2.5 Hz, 1H), 3.84 (dd AB, J = 17.3/2.5 Hz, 1H), 3.01 (br d, J = 6.9 Hz, 2H), 2.74 (s, 3H), 2.21 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C, referred to the main rotamer) δ 171.0, 161.0, 135.8, 129.6, 128.6, 127.2, 73.8, 72.6, 49.0, 39.3, 36.8, 34.3; IR (KBr) 3290, 1640, 1492, 1258, 701 cm^{-1}; MS (ESI) *m/z* 267 $(M+Na)^+$



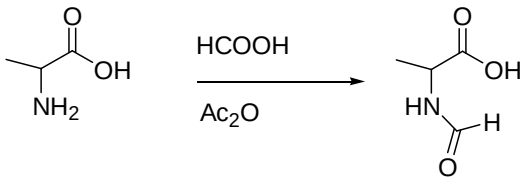
2-isocyano-*N*-methyl-3-phenyl-*N*-(prop-2-ynyl)propanamide (4a)

To a solution of 2-(formylamino)-*N*-methyl-3-phenyl-*N*-(2-propynyl)propanamide (1.00 g, 3.84 mmol) in CH_2Cl_2 (10 mL) TEA (2.67 mL, 19.2 mmol) was added. The resulting mixture was cooled at -30°C and a solution of $POCl_3$ (536 μL, 5.76 mmol) in CH_2Cl_2 (15 mL) was added dropwise over a period of 30 minutes. The reaction mixture became rapidly dark. After 2 hours at -30°C the reaction was quenched with saturated aqueous $NaHCO_3$ and it is left to reach the room temperature. Then the reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous $NaHCO_3$ (x 2) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 6:4 to give **4a** as a pale yellow solid (785 mg, 90%). R_f = 0.50 (PE/EtOAc 5:5). M.p. = 79.5-79.8°C. Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C, referred to the main rotamer) δ 7.40-7.21 (m, 5H), 4.53 (t, J = 7.4 Hz, 1H), 4.29 (dd AB, J = 17.3/2.5 Hz, 1H), 4.12 (dd AB, J = 17.3/2.5 Hz, 1H), 3.19 (d, J = 8.2 Hz, 1H), 3.13 (d, J = 8.2 Hz, 1H), 2.98 (s, 3H), 2.25 (t, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C, referred to the main rotamer) δ 164.7, 159.8, 135.1, 129.5, 128.9, 127.8, 74.3, 73.0, 55.8, 39.0 37.4, 34.6; IR (liquid film) 3270, 2153, 1653, 1354, 1027, 703 cm^{-1}; MS (ESI) *m/z* 227 $(M+H)^+$



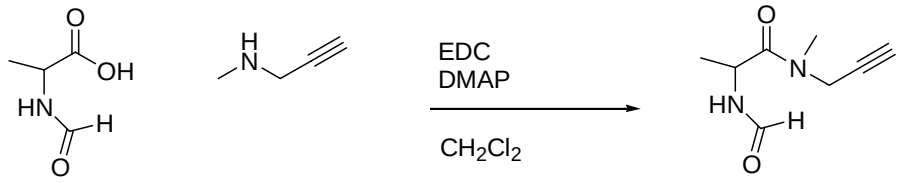
***N*-(4-azidobutyl)-*N*-benzyl-2-(formylamino)-3-phenylpropanamide**

To a solution of **6** (2.50 g, 12.2 mmol) in dry CH_2Cl_2 (25 mL) *N*-formylphenylalanine[7] (2.35 g, 12.2 mmol), TEA (2.02 mL, 14.6 mmol), EDC (2.79 g, 14.6 mmol) and 1-hydroxybenzotriazole (1.97 g, 14.6 mmol) were added. The resulting mixture was heated at 40°C for 28 hours. The reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous HCl (x 2), saturated aqueous $NaHCO_3$ (x 1) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 6:4 and PE/EtOAc 5:5 to give *N*-(4-azidobutyl)-*N*-benzyl-2-(formylamino)-3-phenylpropanamide as a pale yellow oil (2.20 g, 50%). R_f = 0.30 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 8.10 (d, J = 9.8 Hz, 1H), 7.26-7.00 (m, 10H), 5.24 (m, 1H), 4.67 (d, J = 14.7, 1H), 4.32 (d, J = 14.7, 1H), 3.22-2.95 (m, 6H), 1.54-1.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 171.7, 160.4, 136.8, 136.2, 129.5, 128.9, 128.6, 128.0, 127.1, 126.8, 52.1, 49.1, 48.9, 46.6, 39.9, 26.0, 24.0; IR (liquid film) 2095, 1628, 1495, 1451, 1258, 699 cm^{-1}; MS (ESI) *m/z* 402 $(M+Na)^+$



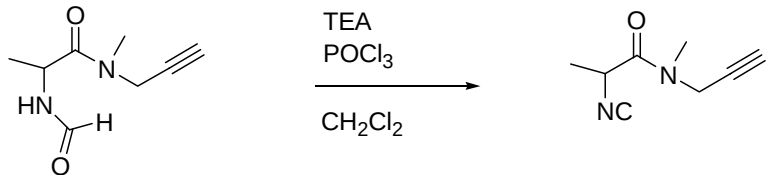
***N*-formylalanine**

To a cooled (5°C) solution of L-alanine (10.0 g, 112 mmol) in formic acid (100 mL) acetic anhydride (84.6 mL, 896 mmol) was added. The reaction mixture was let to reach the room temperature. After 3 hours H_2O was added (40 mL) and the solvent was evaporated. The white solid obtained was used in the next step without further purification (11.8 g, 90%). M.p. = 127.8-128.3. Spectral data: ^{1}H NMR (DMSO-d_6, 300 MHz, 50°C, referred to the main rotamer) δ 8.94 (s, 1H), 4.85 (q, J = 7.1, 1H), 1.26 (d, J = 7.1, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz, 50°C, referred to the main rotamer) δ 174.1, 161.4, 46.8, 18.0; IR (liquid film) 3375, 2425, 1923, 1602, 1343, 1207, 639; MS (ESI) *m/z* 116 $(M+H)^+$



2-(formylamino)-*N*-methyl-*N*-(2-propynyl)propanamide

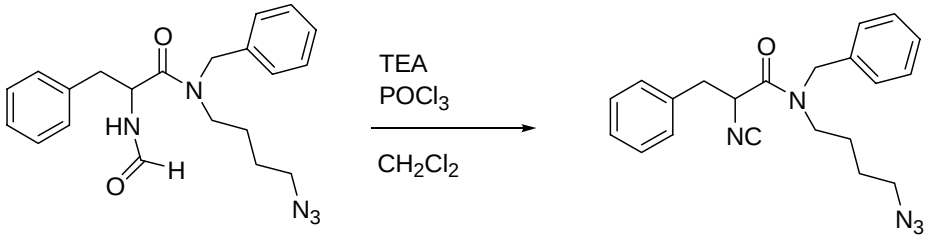
To a suspension of *N*-formylalanine (100 mg, 0.855 mmol) in dry CH_2Cl_2 (1 mL) *N*-methylpropargilamine (107 µL, 1.28 mmol), EDC (245 mg, 1.28 mmol) and DMAP (156 mg, 1.28 mmol) were added. The resulting mixture was stirred at room temperature for 3 hours. The reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous HCl (x 2) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 5:5 and PE/EtOAc 2:8 to give 2-(formylamino)-*N*-methyl-*N*-(2-propynyl)propanamide as a white solid (33.0 mg, 23%). R_f = 0.25 (EtOAc). M.p. = 73.3-73.9°C. Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 8.12 (s, 1H), 6.81 (br s, 1H), 4.96 (m, 1H), 4.24 (m, 2H), 3.12 (s, 3H), 2.22 (br s, 1H), 1.35 (br d, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 171.9, 160.4, 73.5, 72.5, 43.9, 36.8, 34.2, 18.3; IR (liquid film) 3221, 1632, 1541, 1396, 1252, 694 cm^{-1}; MS (ESI) *m/z* 191 $(M+Na)^+$



2-isocyano-N-methyl-N-prop-2-ynln-propionamide (4b)

To a solution of 2-(formylamino)-*N*-methyl-*N*-(2-propynyl)propanamide (2.80 g, 16.7 mmol) in dry CH_2Cl_2 (20 mL) TEA (1.16 ml, 83.7 mmol) was added. The resulting mixture was cooled at -30°C and a solution of $POCl_3$ (2.33 mL, 25.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise over a period of 30 minutes. The reaction mixture became rapidly dark. After 1 hour and 30 minutes at -30°C the reaction was quenched with saturated aqueous $NaHCO_3$ and left to reach the room

temperature. Then the reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous $NaHCO_3$ (x 2) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 6:4 to give **4b** as a yellow oil (2.28 g, 90%). R_f = 0.26 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 4.50 (q, J = 6.9 Hz, 1H), 4.23 (dd, J = 17.3/2.51 Hz, 1H), 4.09 (dd, J = 17.3/2.5 Hz, 1H), 3.11 (s, 3H), 2.24 (t, J = 2.5, 1H), 1.53 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 165.3, 159.4, 74.0, 72.8, 49.7, 37.4, 34.5, 18.6; IR (KBr) 3288, 2144, 1668, 1486, 1408, 1091 cm^{-1}; MS (ESI) *m/z* 173 $(M+Na)^+$



***N*-(4-azidobutyl)-*N*-benzyl-2-isocyano-3-phenylpropanamide (4c)**

To a solution of *N*-(4-azidobutyl)-*N*-benzyl-2-(formylamino)-3-phenylpropanamide (2.30 g, 6.10 mmol) in dry CH_2Cl_2 (25 mL) TEA (4.18 mL, 30.0 mmol) was added. The resulting mixture was cooled at -30°C and a solution of $POCl_3$ (848 μL, 9.10 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over a period of 45 minutes. The reaction mixture became rapidly dark. After 1 hour and 30 minutes at -30°C the reaction was quenched with saturated aqueous $NaHCO_3$ and left to reach the room temperature. Then the reaction was worked up by dilution with CH_2Cl_2 and washing with saturated aqueous $NaHCO_3$ (x 2) and brine (x 1). After drying over sodium sulphate and evaporation of the solvent, the crude product was purified by column chromatography using as eluant PE/EtOAc 7:3 to give **4c** as a dark yellow oil (1.55 g, 71%). R_f = 0.56 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 7.30-6.94 (m, 10H), 4.65-4.44 (m, 1H), 4.34 (m, 2H), 3.40-3.00 (m, 6H), 1.61-1.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 75

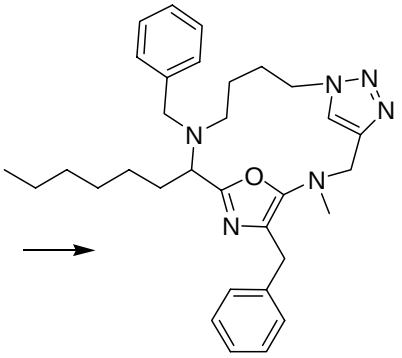
MHz, 50°C, referred to the main rotamer) δ 165.6, 165.0, 135.8, 135.2, 129.5, 129.2, 128.7 (2C), 127.6, 126.0, 55.1, 50.8, 49.3, 46.8, 39.6, 25.9, 24.5; IR (KBr) 3028, 2939, 2195, 1643, 1453, 1124 cm^{-1}; MS (ESI) *m/z* 384 $(M+Na)^+$

Macrocycles

General procedure for the tandem synthesis of the macrocycles (1a) (1b) (1c) (1d) (1e) (1f) (1g) (1h) (1i) (1j)

To a solution of the aldehyde (1 eq) in dry toluene (0.5 M) the amine (1 eq) was added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 30 minutes. Then the isocyanide (1 eq) and NH_4Cl (1.5 eq) were added. The reaction mixture was heated at 80°C until the TLC revealed the disappearance of the three components. NH_4Cl was filtred off and the reaction mixture was diluted with dry THF (0.001 M). DIPEA (20 eq) and CuI (2 eq) were added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 21 hours. CuI was filtered off and the solvent was evaporated. The crude product was purified by column chromatography.

2a, 3a, 4a →



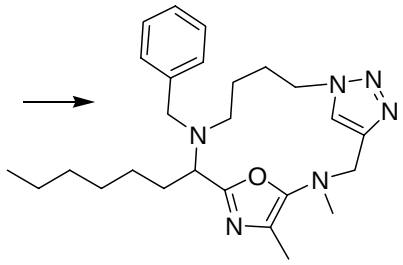
1a

12,16-dibenzyl-13-hexyl-2-methyl-17-oxa-2,5,6,7,12,15-hexaazatricyclo[12.2.1.1^{4,7}]octadeca-1(16),4(18),5,14-tetraene (1a)

The crude product was purified by column chromatography using as eluant PE/EtOAc 8:2 and PE/EtOAc 6:4 to give **1a** as a yellow amorphous solid (76%). R_f = 0.51 (EtOAc). Spectral data: ^1H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.39-7.10 (m, 10H), 6.57 (br s, 1H), 4.21 (m, 1H), 4.07–4.01 (m, 3H), 3.87 (m, 3H), 3.55 (br t, 2H), 2.90 (s, 3H), 2.25 (m, 1H), 1.90 (m, 1H), 1.76 (br s, 4H), 1.52 (br

s, 2H), 1.31–1.02 (br s, 8H), 0.82 (br t, J = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 159.6, 150.5, 143.3, 140.3, 139.9, 128.8, 128.7, 128.4, 128.3, 126.8, 126.6, 126.3, 123.6, 58.4, 54.3, 50.9, 50.1, 49.7, 40.8, 31.7, 30.0, 28.9, 27.1, 26.4, 22.6, 20.0, 14.1; IR (liquid film) 3027, 2928, 1641, 1453, 1217, 698 cm^{-1}; MS (ESI) *m/z* 397 $(M+Na)^+$

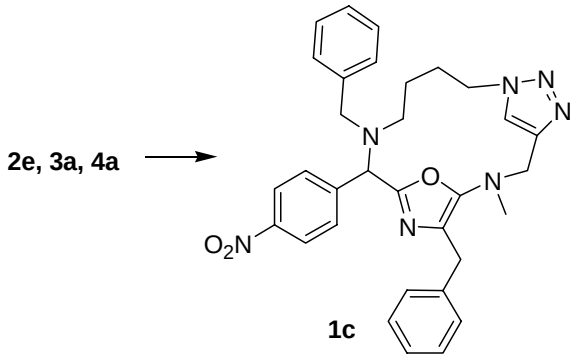
2a, 3a, 4b →



1b

12-benzyl-13-hexyl-2,16-dimethyl-17-oxa-2,5,6,7,12,15-hexaazatricyclo[12.2.1.1^{4,7}]octadeca-1(16),4(18),5,14-tetraene (1b)

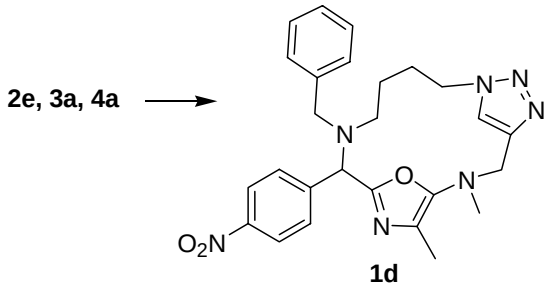
The crude product was purified by column chromatography using as eluant PE/EtOAc 7:3 and PE/EtOAc 4:6 to give **1b** as a yellow oil (32%). R_f = 0.24 (PE/EtOAc 4:6). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.35–7.15 (m, 5H), 7.12 (s, 1H), 4.32 (m, 1H), 4.18 (m, 1H), 4.15 (s, 2H), 3.86 (d, J = 14.2 Hz, 1H), 3.54 (m, 3H), 2.90 (s, 3H), 2.22 (m, 1H), 2.14 (s, 3H), 2.11(m, 1H), 1.87 (m, 2H), 1.74 (m, 2H), 1.55 (m, 2H), 1.30-1.04 (m, 8H), 0.82 (br t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 159.3, 150.1, 143.5, 140.3, 128.7, 128.2, 126.8, 123.7, 123.5, 58.3, 54.3, 50.9, 50.1, 49.8, 40.8, 31.7, 30.2, 28.9, 27.2, 26.4, 23.9, 22.6, 14.1, 11.3; IR (KBr) 1646.3, 1457,8, 1218, 733.8 cm^{-1}; MS (ESI) *m/z* 451 $(M+H)^+$



1c

12,16-dibenzyl-2-methyl-13-(4-nitrophenyl)-17-oxa-2,5,6,7,12,15-hexaazatricyclo[12.2.1.1^{4,7}]octadeca-1(16),4(18),5,14-tetraene (1c)

The crude product was purified by column chromatography using as eluant PE/EtOAc 5:5 and PE/EtOAc 4:6 to give **1c** as a yellow amorphous solid (24%). R_f = 0.39 (PE/EtOAc 4:6). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C) δ 8.11 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.50–7.10 (m, 6H), 6.55 (s, 1H), 4.87 (s, 1H), 4.23 (m, 2H), 4.12 (m, 2H), 3.88 (br s, 2H), 3.57 (br s, 2H), 2.89 (s, 3H), 2.31 (m, 2H), 1.61 (m, 2H), 1.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 155.6, 151.5, 147.5, 146.0, 143.3, 139.5, 138.7, 129.4, 128.8, 128.6 (2C), 128.5, 127.2, 126.8, 26.5, 123.6, 123.2, 63.1, 54.7, 50.8, 50.7, 49.5, 40.6, 31.8, 27.1, 23.2; IR (KBr) 2938, 1640, 1514, 1452, 1346, 729 cm^{-1}; MS (ESI) *m/z* 564 $(M+H)^+$

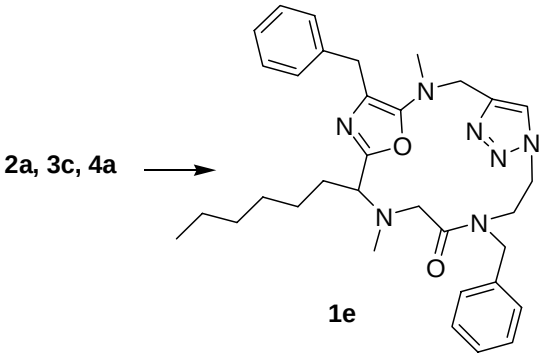


1d

12-benzyl-2,16-dimethyl-13-(4-nitrophenyl)-17-oxa-2,5,6,7,12,15-hexaazatricyclo[12.2.1.1^{4,7}]octadeca-1(16),4(18),5,14-tetraene (1d)

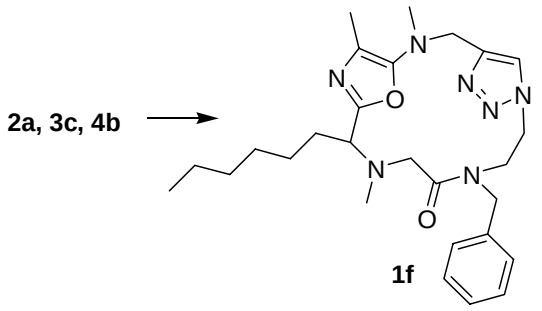
The crude product was purified by column chromatography using as eluant EtOAc to give **(1d)** as a orange oil (24%). R_f = 0.08 (EtOAc). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C) δ 8.10 (d, J = 8.5 Hz, 2H), 7.56 (d, J =8.5 Hz, 2H), 7.20 (m, 5-H), 7.13 (s, 1H), 4.85 (s, 1H), 4.39-4.21 (m, 2H),

4.18 (br d, 2H), 3.54 (s, 2H), 2.89 (s, 3H), 2.29-2.22 (m, 2H), 2.16 (s, 3H), 1.92-1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C) δ 155.4, 151.3, 147.6, 145.9, 143.6, 138.7, 129.3, 128.5, 128.3, 127.1, 123.8, 123.4, 123.1, 63.4, 54.8, 50.0, 50.7, 49.7, 40.6, 27.1, 23.6, 11.2; IR (liquid film) 2948, 1648, 1519, 1345, 729, 699 cm^{-1}; MS (ESI) *m/z* 516 $(M+Na)^+$



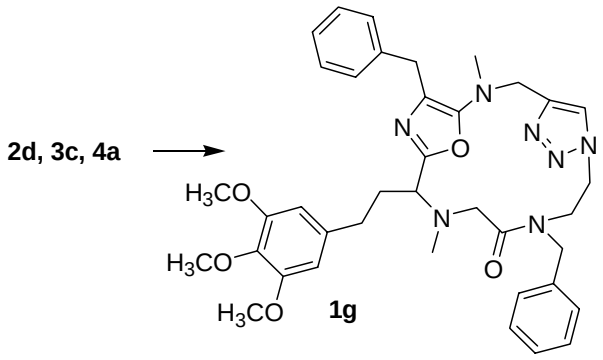
10,17-dibenzyl-14-hexyl-2,13-dimethyl-18-oxa-2,5,6,7,10,13,16-heptaazatricyclo[13.2.1.1^{4,7}]nonadeca-1(17),4(19),5,15-tetraen-11-one (1e)

The crude product was purified by column chromatography using as eluant PE/EtOAc 5:5 and EtOAc to give **1e** as a yellow amorphous solid (44%). R_f = 0.22 (EtOAc). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 7.35–7.10 (m, 10H), 6.93 (s, 1H), 4.63-4.50 (m, 2H), 4.28-4.07 (m, 4H), 3.85-3.62 (m, 5H), 3.33 (d, J = 14.0 Hz, 1H), 3.12 (d, J = 14.0 Hz, 1H), 2.81 (s, 3H), 2.43 (s, 3H), 1.92-1.77 (m, 2H), 1.25 (br s, 8H, 0.85 (br s, 3H)**;** ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 171.7, 158.5, 152.1, 143.0, 139.7, 136.7, 129.0, 128.5, 128.4, 127.7, 126.2, 126.1 (2C), 124.6, 63.3, 56.3, 52.4, 50.7, 47.8, 47.4, 40.7, 38.2, 31.7, 31.6, 29.2, 26.8, 26.5, 22.5, 13.9; IR (KBr) 2929, 1647, 1452, 1047, 698 cm$^-$1; MS (ESI) *m/z* 570 $(M+K)^+$



10-benzyl-14-hexyl-2,13,17-trimethyl-18-oxa-2,5,6,7,10,13,16-heptaazatricyclo[13.2.1.1^{4,7}]nonadeca-1(17),4(19),5,15-tetraen-11-one (1f)

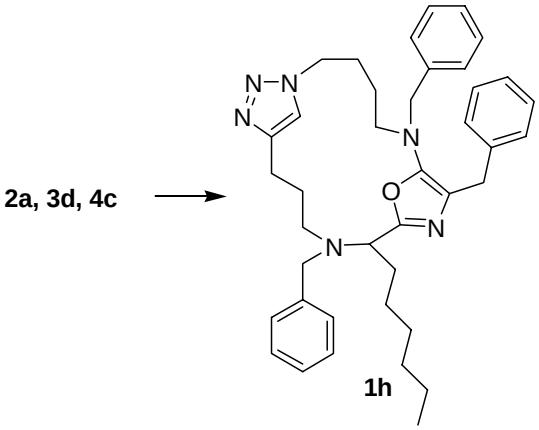
The crude product was purified by column chromatography using as eluant EtOAc to give **1f** as a yellow oil (45%). R_f = 0.08 (EtOAc). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 7.35–7.10 (m, 5H), 6.93 (s, 1H), 4.70-4.44 (m, 2H), 4.33 (d, J = 15.1 Hz, 1H), 4.14 (d, J = 15.1 Hz, 1H), 3.83-3.57 (m, 5H), 3.34 (d, J = 13.5 Hz, 1H), 3.09 (d, J = 13.5 Hz, 1H), 2.84 (s, 3H), 2.45 (s, 3H), 2.05 (s, 3H), 1.90–1.55 (m, 2H), 1.24 (br s, 8H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 171.7, 158.2, 151.6, 143.5, 136.7, 129.0, 127.7, 126.2, 121.2, 63.2, 56.0, 52.5, 50.4, 47.9, 47.5, 40.6, 38.4, 31.6, 29.2, 26.9, 26.1, 22.5, 13.9, 11.1 ; IR (liquid film) 2928, 1641, 1453, 1228, 730 cm^{-1}; MS (ESI) *m/z* 516 $(M+Na)^+$



10,17-dibenzyl-2,13-dimethyl-14-(3,4,5-trimethoxyphenethyl)-18-oxa-2,5,6,7,10,13,16-heptaazatricyclo[13.2.1.1^{4,7}]nonadeca-1(17),4(19),5,15-tetraen-11-one (1g)

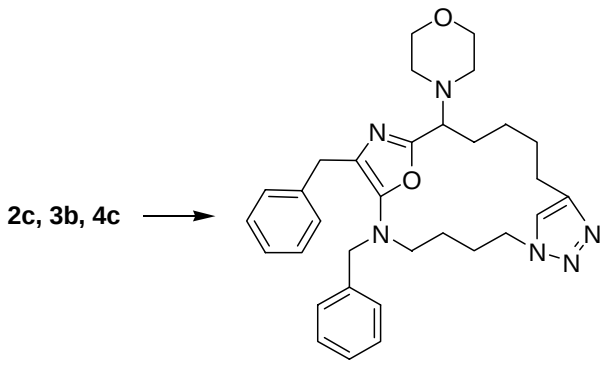
The crude product was purified by column chromatography using as eluant PE/EtOAc 5:5 and EtOAc/MeOH 9:1 to give **1g** as a yellow amorphous solid (47%). R_f = 0.13 (EtOAc). Spectral

data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C, referred to the main rotamer) δ 7.40–7.14 (m, 10H), 6.90 (s, 1H), 6.30 (s, 2H), 4.50 (m, 2H), 4.31–4.12 (m, 4H), 3.77 (br s, 14H), 3.31 (d, J = 14.0 Hz, 1H), 3.09 (d, J = 14.0 Hz, 1H), 2.83 (s, 3H), 2.62 (m, 2H), 2.46 (s, 3H), 2.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C, referred to the main rotamer) δ 171.5, 157.9, 153.3, 152.2, 143.2, 139.7, 136.9, 136.7, 136.6, 129.0, 128.5, 128.4 (2C), 127.7, 126.2, 124.6, 126.1, 105.9, 61.7, 60.8, 56.2, 52.3, 50.5, 47.8, 47.4, 40.8, 38.3, 33.1, 31.8, 29.7; IR (KBr) 2961, 1653, 1453, 1123, 728 cm^{-1}; MS (ESI) *m/z* 702 $(M+Na)^+$



6,8,12-tribenzyl-11-hexyl-20-oxa-1,6,9,12,17,18-hexaazatricyclo[14.2.1.1^{7,10}]icosa-7,9,16(19),17-tetraene (1h)

The crude product was purified by column chromatography using as eluant PE/EtOAc 6:4 and PE/EtOAc 5:5 to give **1h** as a yellow amorphous solid (29%). R_f = 0.19 (PE/EtOAc 5:5). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C) δ 7.40–7.10 (m, 15H), 6.84 (br s, 1H), 4.18 (m, 1H), 4.02 (s, 2H), 3.83 (d, J = 14.3 Hz, 1H), 3.73 (br t, 2H), 3.65 (br s, 2H), 3.35 (d, J = 14.3 Hz, 1H), 2.83 (t, J = 7.7 Hz, 2H), 2.55 (m, 2H), 2.35 (m, 2H), 1.9-1.6 (m, 8H), 1.35–1.0 (br s, 8-H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C) δ 160.5, 150.0, 146.8, 140.3, 139.9, 137.7, 129.0, 128.7 (3C), 128.5, 128.3, 128.2, 127.6, 126.8, 126.2, 122.0, 59.2, 57.9, 55.3, 52.3, 49.8, 49.4, 31.9, 31.4, 30.6, 29.1, 27.6, 27.5, 26.3, 24.2, 23.4, 22.7, 14.2; IR (liquid film) 2929, 1652, 1455,1028, 731 cm^{-1}; MS (ESI) *m/z* 631 $(M+H)^+$



1j

6,8-dibenzyl-11-(4-morpholinyl)-20-oxa-1,6,9,17,18-pentaazatricyclo[14.2.1.1^{7,10}]icosa-7,9,16(19),17-tetraene (1j)

The crude product was purified by column chromatography using as eluant PE/EtOAc 2:8 and EtOAc/MeOH 95:5 to give **1j** as a yellow amorphous solid (40%). R_f = 0.07 (EtOAc x 2). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.40–7.00 (m, 10H), 4.18 (m, 2H), 3.63 (br s, 5H), 3.40 (m, 1H), 2.95 (m, 2H), 2.70 (m, 2H), 2.43 (br s, 2H), 2.30 (br s, 2H), 1.90-1.58 (br s, 8H), 0.92 (q, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 159.0, 150.3, 147.1,139.3, 137.4, 129.5, 129.1, 128.8, 128.4 (2C), 127.6, 126.2, 121.4, 67.0, 64.4, 59.3, 52.7, 50.7, 49.4, 31.4, 30.3, 28.7, 27.4, 24.7, 24.4, 24.3; IR (liquid film) 2944, 1737, 1453, 1260, 1115, 699 cm^{-1}; MS (ESI) *m/z* 563 $(M+Na)^+$

General procedure for the two steps synthesis of the macrocycles (1i) (1h)

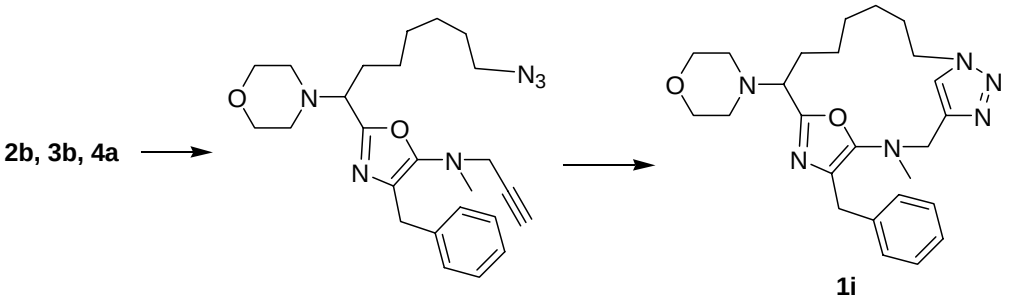
-three component reaction:

To a solution of the aldehyde (1 eq) in dry toluene (0.5 M) the amine (1 eq) was added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 30 minutes. Then the isocyanide (1 eq) and NH_4Cl (1.5 eq) were added. The reaction mixture was heated at 80°C until

the TLC revealed the almost complete disappearance of the three components. The reaction mixture was diluted with aqueous saturated $NaHCO_3$ and extracted with EtOAc (x 2). The combined organic layers were washed with brine, dried over sodium sulphate and evaporated. The crude product was purified by column chromatography.

-intramolecular [3 + 2] cycloaddition:

To a solution of the 5-aminooxazole intermediate (1 eq) in dry THF (0.001 M), DIPEA (20 eq) and CuI (2 eq) were added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 21 hours. CuI was filtered off and the solvent was evaporated. The crude product was purified by column chromatography.

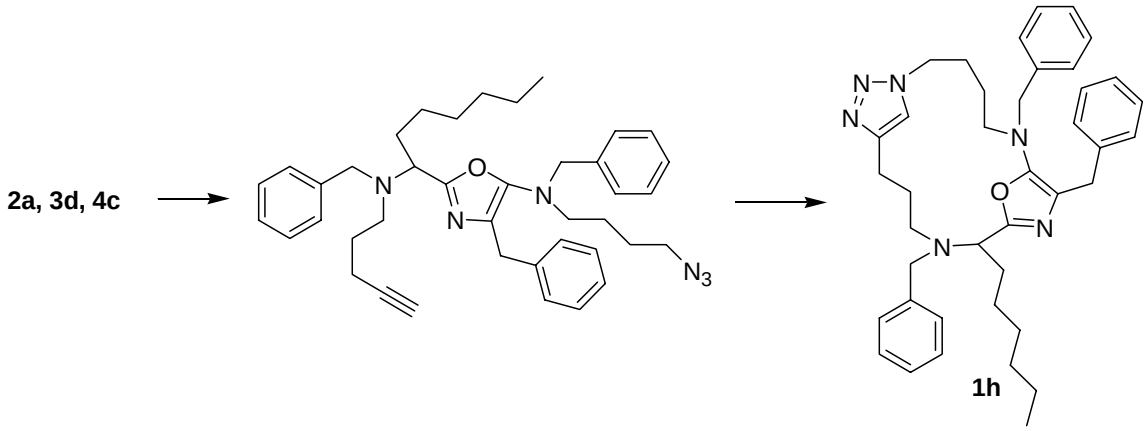


2-[7-azido-1-(4-morpholinyl)heptyl]-4-benzyl-*N*-methyl-*N*-(2-propynyl)-1,3-oxazol-5-amine

The crude product was purified by column chromatography using as eluant PE/EtOAc 9:1 and PE/EtOAc 7:3 to give 2-[7-azido-1-(4-morpholinyl)heptyl]-4-benzyl-*N*-methyl-*N*-(2-propynyl)-1,3-oxazol-5-amine as a pale yellow oil (68%). R_f = 0.22 (PE/EtOAc 7:3). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.27–7.12 (m, 5H), 3.84 (s, 2H), 3.66 (br s, 7H), 3.23 (t, J = 6.6 Hz, 2H), 2.79 (s, 3H), 2.56 (br s, 2H), 2.49 (br s, 2H), 2.23 (br t, 1H), 1.87 (br s, 2H), 1.53 (br s, 2H), 1.33–1.21 (br s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 157.9, 151.7, 139.7, 128.4, 126.1, 124.5, 77.5, 73.3, 70.9, 67.4, 63.2, 51.5, 50.2, 45.1, 40.0, 31.6, 29.8, 28.9, 26.6, 26.2; IR (liquid film) 2936, 2095, 1739, 1364, 1217, 1115, 669 cm^{-1}; MS (ESI) *m/z* 473 $(M+Na)^+$

18-benzyl-2-methyl-15-(4-morpholinyl)-19-oxa-2,6,7,8,17-pentaazatricyclo[14.2.1.0^{4,8}]nonadeca-1(18),4,6,16-tetraene (1i)

The crude product was purified by column chromatography using as eluant PE/EtOAc 7:3 and EtOAc to give **1i** as a yellow amorphous solid (35%). R_f = 0.27 (EtOAc). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C) δ 7.35–7.10 (m, 5H), 6.40 (s, 1H), 4.24 (m, 2H), 4.09 (m, 1H), 3.88 (d, J = 15.4 Hz, 1H), 3.80 (d, J = 15.4 Hz, 1H), 3.67 (br s, 4H), 3.38 (m, 2H), 2.95 (s, 3H), 2.48 (br s, 4H), 1.70–1.18 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ 151.5, 144.4, 139.7, 128.7, 128.4, 126.4, 123.9, 121.2, 67.0, 64.1, 50.5, 49.9, 41.1, 31.7, 30.2, 28.5, 26.9, 26.0, 25.7; IR (KBr) 2933, 1641, 1453, 1115, 730 cm^{-1}; MS (ESI) *m/z* 473 $(M+Na)^+$



***N*-(4-azidobutyl)-*N*,4-dibenzyl-2-{1-[benzyl(4-pentynyl)amino]heptyl}-1,3-oxazol-5-amine**

The crude product was purified by column chromatography using as eluant PE/EtOAc 95:5 to give *N*-(4-azidobutyl)-*N*,4-dibenzyl-2-{1-[benzyl(4-pentynyl)amino]heptyl}-1,3-oxazol-5-amine as a colourless oil (90%). R_f = 0.81 (PE/EtOAc 8:2). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz, 50°C) δ 7.35-7.10 (m, 5H), 4.08 (s, 2H), 3.83 (d, J = 14.0 Hz, 1H), 3.71 (br s, 3H), 3.32 (d, J = 14.0 Hz, 1H), 3.09 (t, J = 6.3 Hz, 2H), 2.97 (t, J = 6.0 Hz, 2H), 2.73 (m, 1H), 2.35 (m, 1H), 2.15 (m, 2H), 1.86 (br s, 3H), 1.65 (m, 2H), 1.47 (m, 4H), 1.21 (br s, 8H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 50°C) δ 159.8, 150.5, 140.3, 139.7, 137.9, 128.8-126.0, 127.6, 85.0, 68.2, 58.9, 58.1, 55.5, 52.7, 51.2, 49.6, 31.8, 31.5, 30.5, 29.1, 27.4, 26.5, 26.4, 25.3, 22.6, 16.2, 14.0; IR (liquid film) 2930, 2096, 1734, 1455, 1364, 698 cm^{-1}; MS (ESI) *m/z* 653 $(M+Na)^+$

References

(1) Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory chemicals* - 4th Edition – Butterworth - Heinemann

(2) Rosowsky, A.; Chen H.; Fu H.; Queener, S. F. *Bioorg. Med. Chem.* **2003**, *11* , 59

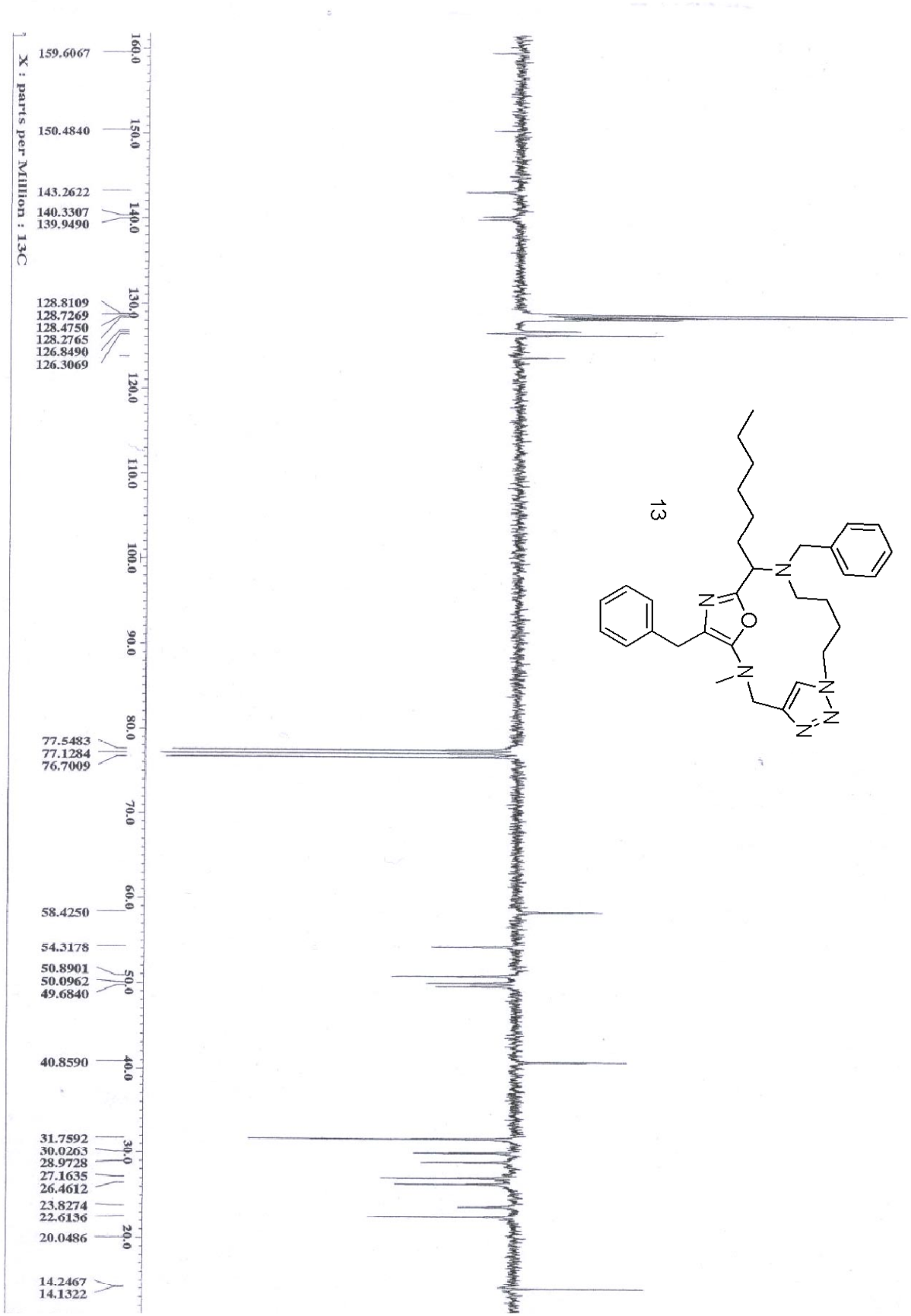
(3) Ballini, R.; Bosica, G.; Rafaiani, G. *Helv. Chim. Acta* **1995**, *78*, 879

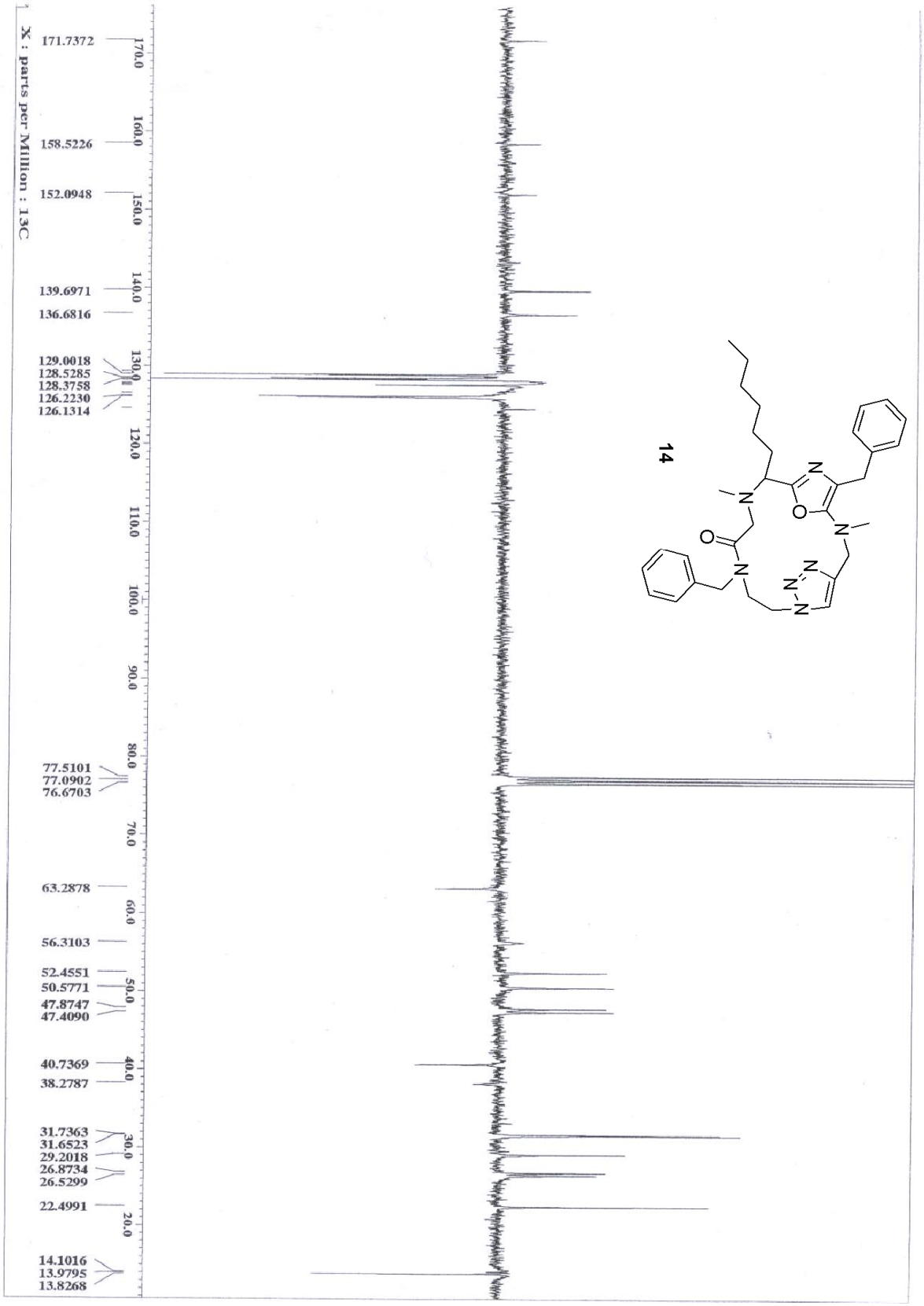
(4) Petri, A. F.; Kuhnert S. M.; Scheufler, F.; Maier, M. E. *Synthesis* **2003**, 940

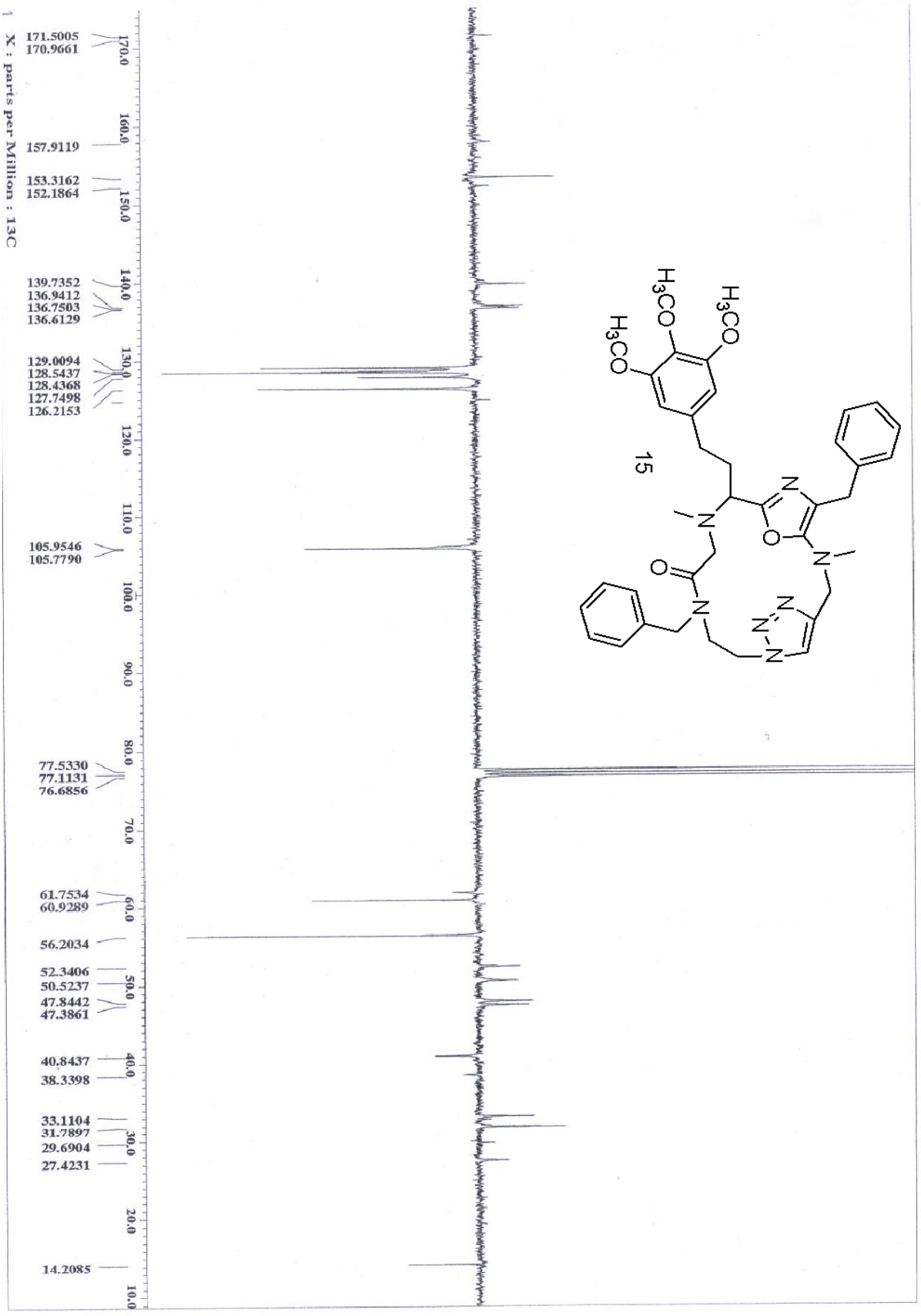
(5) Zachary P. D.; Sharpless, K.B. *Org. Lett.* **2001**, *3*, 4091

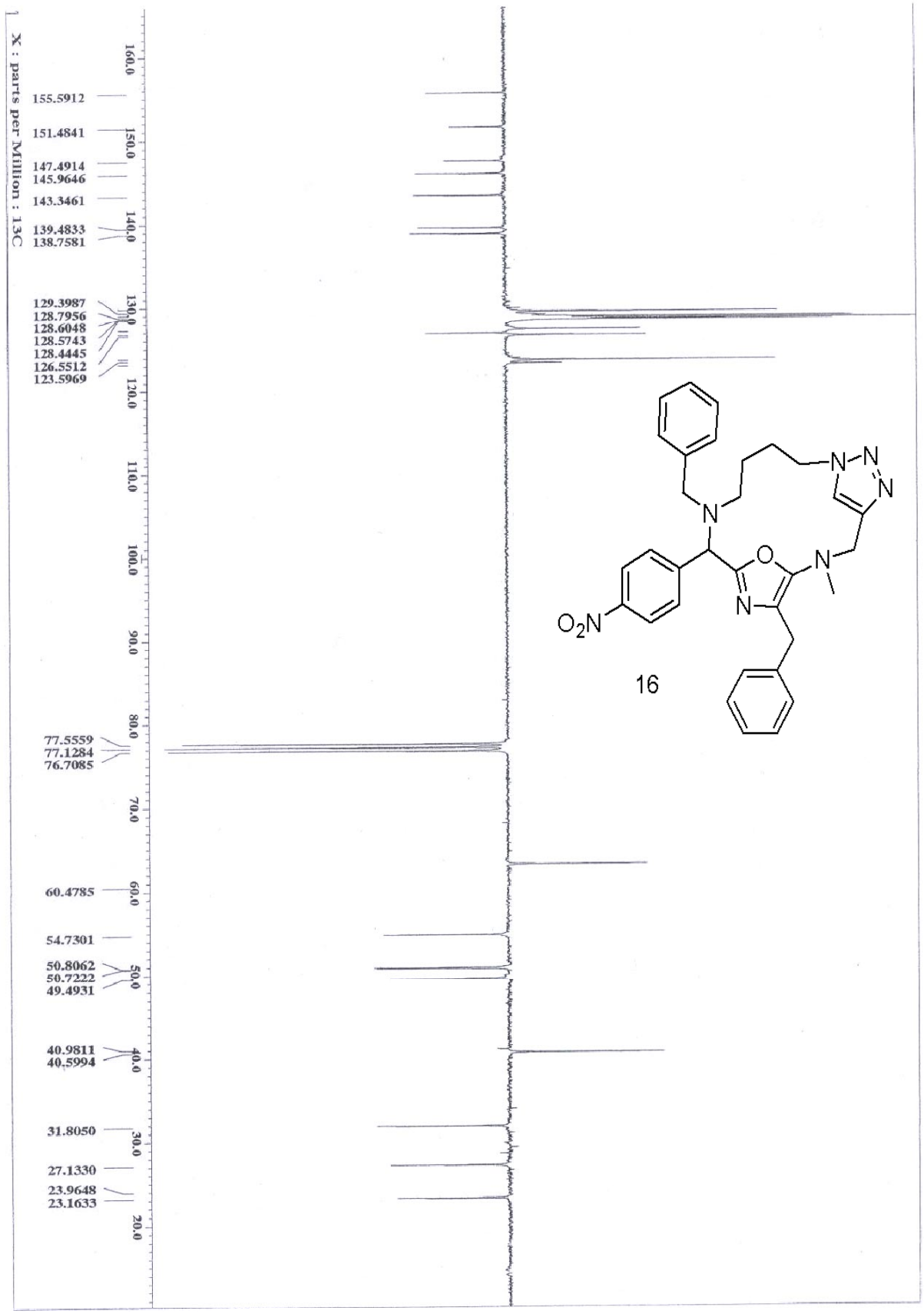
(6) Scapecchi, S.; Martini E.; Manetti D.; Ghelardini C.; Martelli C.; Dei, S.; Galeotti, N.; Guandalini, L.; Romanelli, M. N.; Teodori, E. *Bioorg. Med. Chem.* **2004**, *12*, 71

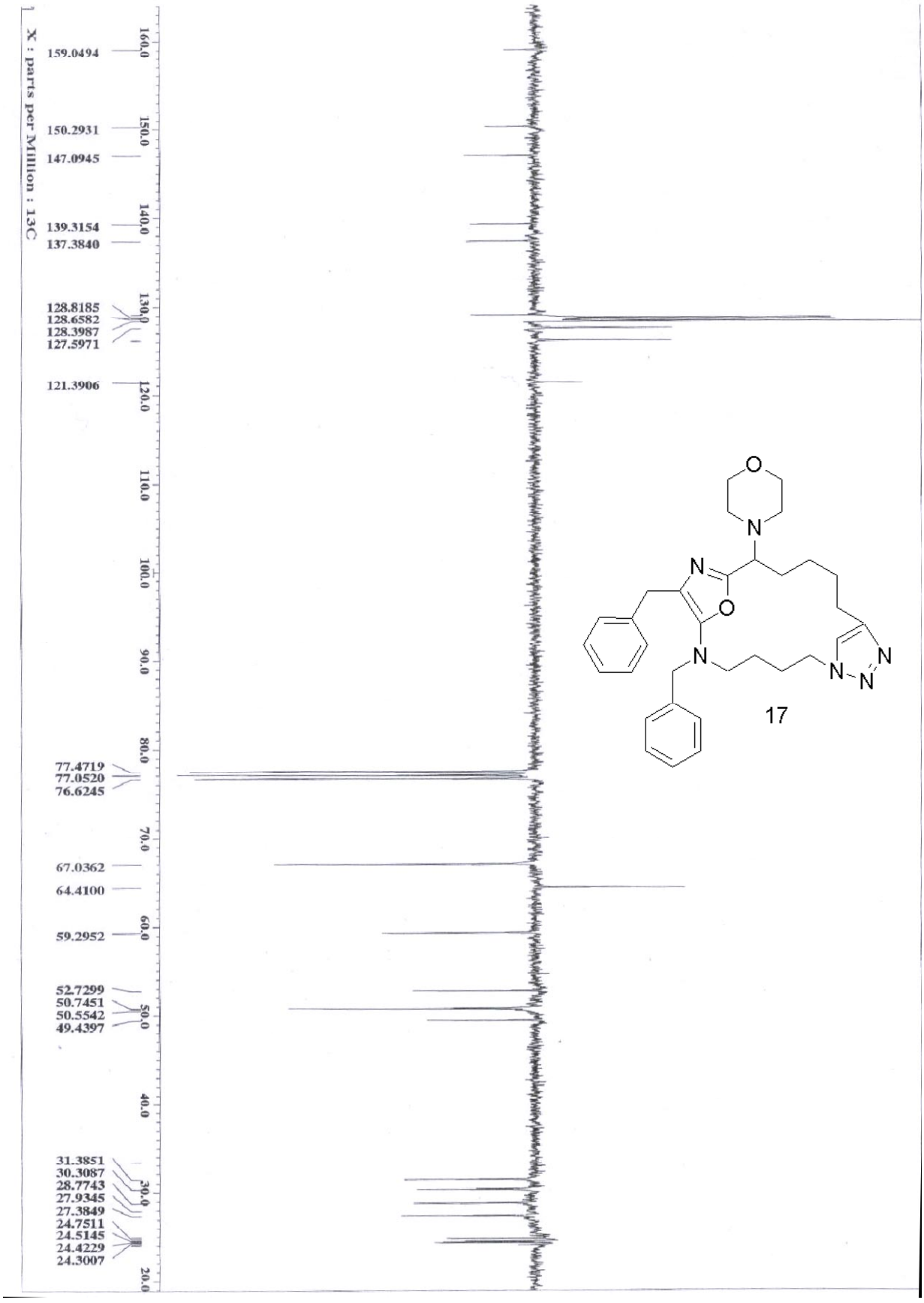
(7) Fayol U.; Housseman C.; Sun X.; Janvier P.; Bienayme H. ; Zhu, J. *Synthesis* **2005**, 161

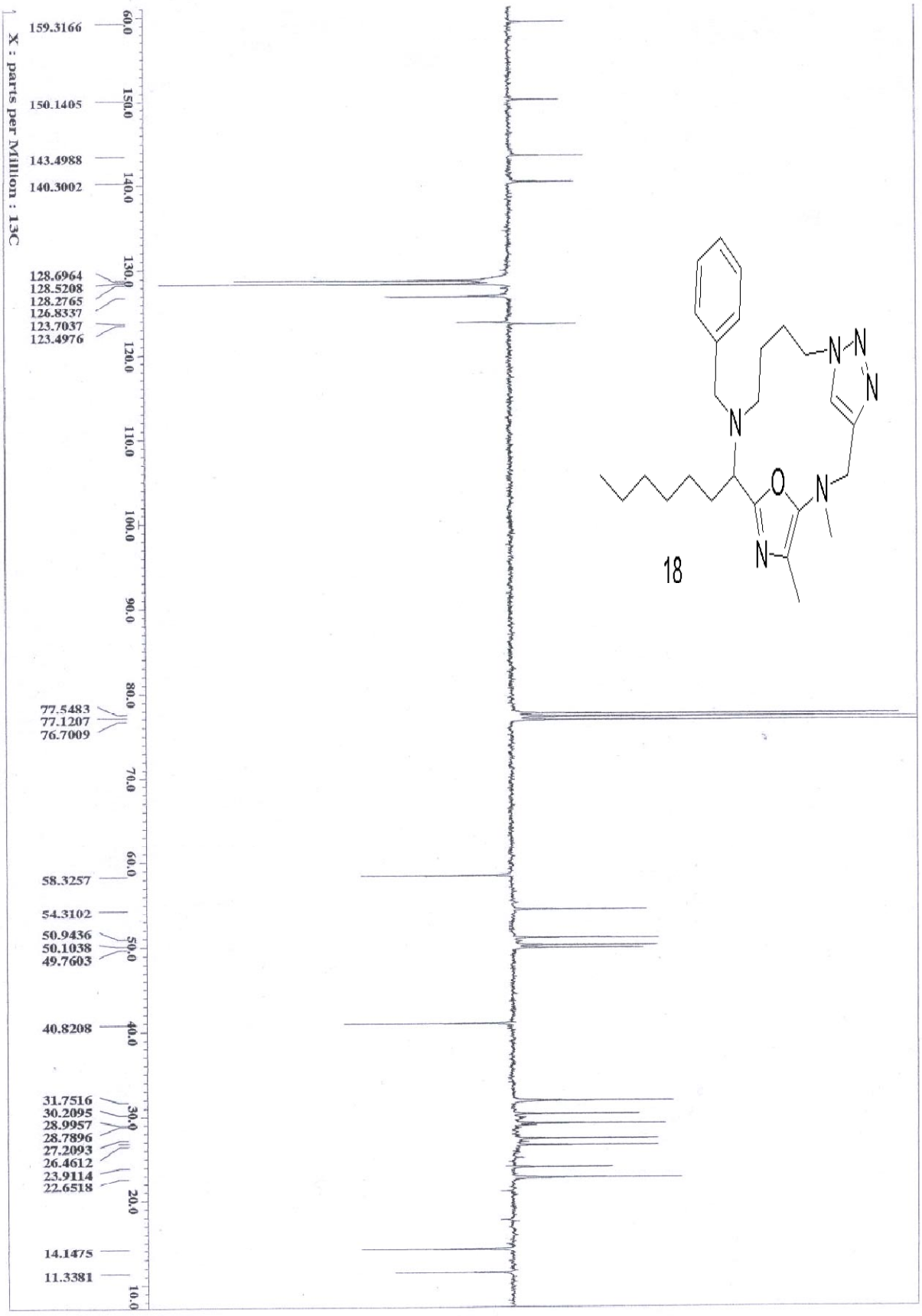

X : parts per Million : 13C
159.6067
150.4840
143.2622
140.3307
139.9490
128.8109
128.7269
128.4750
128.2765
126.8490
126.3069
77.5483
77.1284
76.7009
58.4250
54.3178
50.8901
50.0962
49.6840
40.8590
31.7592
30.0263
28.9728
27.1635
26.4612
23.8274
22.6136
20.0486
14.2467
14.1322
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
13

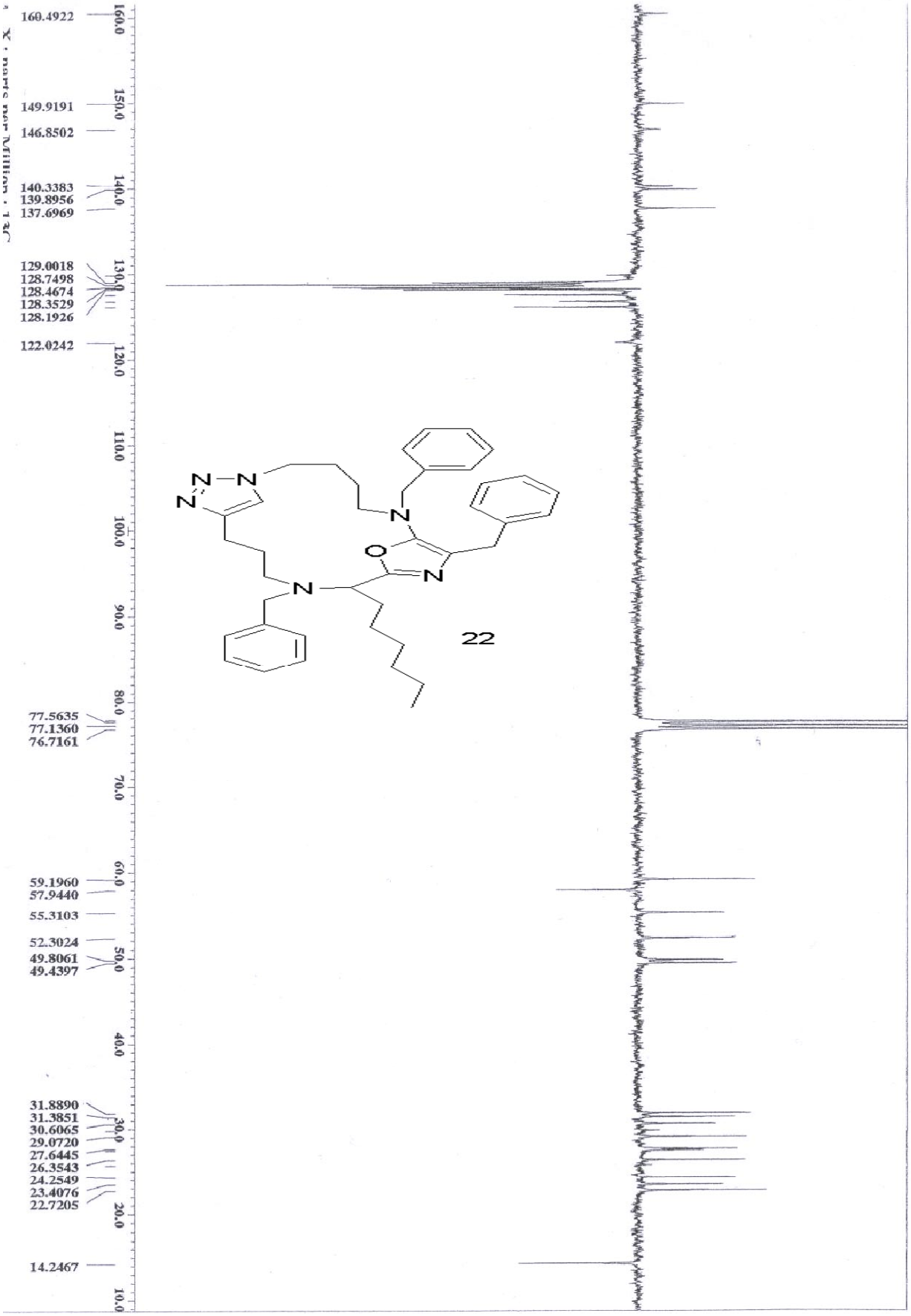

X : parts per Million : 13C
171.7372
158.5226
152.0948
139.6971
136.6816
129.0018
128.5285
128.3758
126.2230
126.1314
77.5101
77.0902
76.6703
63.2878
56.3103
52.4551
50.5771
47.8747
47.4090
40.7369
38.2787
31.7363
31.6523
29.2018
26.8734
26.5299
22.4991
14.1016
13.9795
13.8268
14


X : parts per Million : 13C
171.5005
170.9661
157.9119
153.3162
152.1864
139.7352
136.9412
136.7503
136.6129
129.0094
128.5437
128.4368
127.7498
126.2153
105.9546
105.7790
77.5330
77.1131
76.6856
61.7534
60.9289
56.2034
52.3406
50.5237
47.8442
47.3861
40.8437
38.3398
33.1104
31.7897
29.6904
27.4231
14.2085
H3CO
H3CO
H3CO
15


X : parts per Million : 13C
155.5912
151.4841
147.4914
145.9646
143.3461
139.4833
138.7581
129.3987
128.7956
128.6048
128.5743
128.4445
126.5512
123.5969
77.5559
77.1284
76.7085
60.4785
54.7301
50.8062
50.7222
49.4931
40.9811
40.5994
31.8050
27.1330
23.9648
23.1633
O2N
16


X : parts per Million : 13C
159.0494
150.2931
147.0945
139.3154
137.3840
128.8185
128.6582
128.3987
127.5971
121.3906
77.4719
77.0520
76.6245
67.0362
64.4100
59.2952
52.7299
50.7451
50.5542
49.4397
31.3851
30.3087
28.7743
27.9345
27.3849
24.7511
24.5145
24.4229
24.3007
17


X : parts per Million : 13C
159.3166
150.1405
143.4988
140.3002
128.6964
128.5208
128.2765
126.8337
123.7037
123.4976
77.5483
77.1207
76.7009
58.3257
54.3102
50.9436
50.1038
49.7603
40.8208
31.7516
30.2095
28.9957
28.7896
27.2093
26.4612
23.9114
22.6518
14.1475
11.3381
18


160.4922
149.9191
146.8502
140.3383
139.8956
137.6969
129.0018
128.7498
128.4674
128.3529
128.1926
122.0242
77.5635
77.1360
76.7161
59.1960
57.9440
55.3103
52.3024
49.8061
49.4397
31.8890
31.3851
30.6065
29.0720
27.6445
26.3543
24.2549
23.4076
22.7205
14.2467
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
N
N
N
N
O
N
N
22