

Supporting Information

for

Ugi post-condensation copper-triggered oxidative cascade towards pyrazoles

Aurélie Dos Santos, Laurent El Kaim*, Laurence Grimaud* and Caroline Ronsseray

Address: Laboratoire Chimie et Procédés, Laboratoire Chimie et procédés, UMR 7652-DCSO-CNRS- ENSTA-École Polytechnique, École Nationale Supérieure de Techniques Avancées, 32 Bd Victor, Paris 75015, France

Email: Laurent El Kaim - laurent.elkaim@ensta.fr; Laurence Grimaud - laurence.grimaud@ensta.fr

* Corresponding author

Table of contents:

I. General procedures	S2
II. General Procedure for Syntheses	S3
III. Spectral data for products	S4–S20

I. General procedures

^1H NMR spectra were recorded on a Bruker Avance 400 spectrometer, using CDCl_3 solvent as reference and/or internal deuterium lock. ^{13}C NMR spectra were recorded on a Bruker Avance 400 (100.6 MHz) spectrometer. Two-dimensional NMR spectroscopy [^1H - ^1H COSY spectra, ^1H - ^{13}C COSY spectra (HSQC) and long-range ^1H - ^{13}C COSY spectra (HMBC)], were carried out to determine the correlation between ^1H and ^{13}C . The chemical shifts for all NMR spectra are expressed in parts per million up to the high frequency of the TMS reference. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.1 Hz.

The IR spectra were obtained on a Bruker IFS 66 or a Perkin-Elmer FT 1600 spectrometer. Low resolution mass spectral analysis (EI and CI) were recorded on a Hewlett-Packard HP5989 mass spectrometer by either direct injection or GC/MS coupling with a Hewlett-Packard HP5890 chromatograph. High resolution (HR) mass spectra were performed on a JEOL JMS-GCmate II, GC/MS system spectrometer. TLC was carried out on precoated plates of silica gel 60F₂₅₄.

II. General Procedure for Syntheses

General Procedure A: preparation of Ugi adducts:

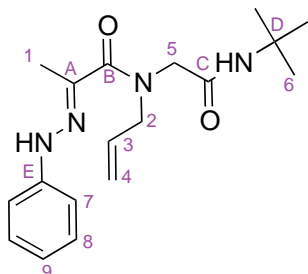
To a solution of aldehyde (1 equiv) in methanol (1 M) were added successively allylamine (1 equiv), hydrazono acetic acid (1 equiv) and isocyanide (1 equiv). The resulting mixture was stirred at 40 °C until completion of the reaction (TLC). The solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel (PE/Et₂O).

General Procedure B: preparation of pyrrazolidinone:

To a solution of hydrazone **1** (1 equiv) in a 10/70/20 DMF/CH₃COOH/H₂O mixture (0.06 M) was added Cu(OAc)₂ (20 mol %). The resulting mixture was heated at 80 °C under argon. The pH was adjusted to 6 with an aqueous sodium hydrogencarbonate solution, the aqueous phase was extracted with AcOEt. Then the organic layers were washed ten times with water, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The product was isolated by flash chromatography on silica gel (PE/Et₂O with 1 % of TEA).

III. Spectral data for products from Table 1

(*E*)-*N*-allyl-*N*-(2-(*tert*-butylamino)-2-oxoethyl)-2-(2-phenylhydrazono)propanamide (2a)



$C_{18}H_{26}N_4O_2$
Mol wt = 330.21 $g \cdot mol^{-1}$

Compound 2a was prepared following the general procedure A applied to 2-(2-phenylhydrazono)propanoic acid (500 mg, 2.8 mmol), formaldehyde (210 μ L, 2.8 mmol), *tert*-butylisocyanide (230 mg, 2.8 mmol).

Yield: 64% (600 mg)

R_f : 0.2 (3:7 P.E./Et₂O)

White solid.

Mp: 137–138 °C

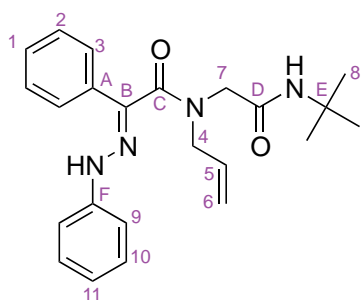
¹H NMR (CDCl₃, 400 MHz) δ 7.52 (br s, 1H, NH) 7.29 (dd, $J = 7.8, 7.3$ Hz, 2H, H₈), 7.09 (d, $J = 7.8$ Hz, 2H, H₇), 6.95 (t, $J = 7.3$ Hz, 1H, H₉), 6.16 (br s, 1H, NH), 5.96–5.88 (m, 1H, H₃), 5.28–5.23 (m, 2H, H₄), 4.34–4.00 (m, 4H, H₂, H₅), 2.14 (s, 3H, H₁), 1.35 (s, 9H, H₆).

¹³C NMR (CDCl₃, 100.6 MHz) δ 168.7 (C_C), 168.6 (C_B), 143.9 (C_E), 136.9 (C_A), 132.8 (C₃), 129.8 (C₈), 122.0 (C₉), 119.0 (C₄), 114.0 (C₇), 53.9 (C₂), 51.7 (C₅), 51.3 (C_D), 29.1 (C₆), 12.6 (C₁).

IR (v, cm⁻¹): 1684, 1653, 1558, 1541, 1508, 1457.

HRMS: calculated for C₁₈H₂₆N₄O₂ 330.2056, found 330.2064.

(E)-N-allyl-N-(2-(*tert*-butylamino)-2-oxoethyl)-2-phenyl-2-(2-phenylhydrazono)acetamide (2b)



$C_{23}H_{28}N_4O_2$
Mol wt = 392.49 g·mol⁻¹

Compound 2b was prepared following the general procedure A applied to 2-phenyl-2-(2-phenylhydrazono)acetic acid (500 mg, 2.1 mmol), formaldehyde (160 μ L, 2.1 mmol), *tert*-butylisocyanide (175 mg, 2.1 mmol).

Yield: 79% (868 mg)

R_f : 0.5 (3:7 PE/Et₂O)

White solid.

Mp: 169–170 °C

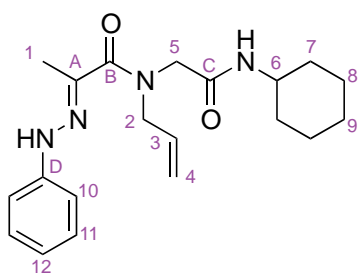
¹H NMR (CDCl₃, 400 MHz) δ 10.29 (br s, 1H, NH), 7.73 (d, J = 7.3 Hz, 2H, H₃), 7.41–7.37 (m, 4H, H₂, H₉), 7.33–7.29 (m, 3H, H₁, H₁₀), 6.90 (t, J = 7.1 Hz, 1H, H₁₁), 5.68–5.58 (m, 1H, H₅), 5.48 (br s, 1H, NH), 5.16–5.13 (m, 2H, H₆), 4.14 (m, 2H, H₇), 3.94 (d, J = 6.1 Hz, 2H, H₄), 1.44 (s, 9H, H₈).

¹³C NMR (CDCl₃, 100.6 MHz) δ 167.6 (C_D), 167.5 (C_C), 145.5 (C_F), 136.7 (C_B), 134.7 (C_A), 132.9 (C₅), 129.5 (C₁₀), 129.0 (C₂), 128.5 (C₁), 125.5 (C₃), 120.5 (C₁₁), 119.7 (C₆), 113.5 (C₉), 52.7 (C_E), 52.1 (C₄), 47.6 (C₇), 29.3 (C₈).

IR (ν , cm⁻¹): 1653, 1558, 1541, 1508, 1457.

HRMS: calculated for C₂₃H₂₈N₄O₂ 392.2212, found 392.2217.

(E)-N-allyl-N-(2-(cyclohexylamino)-2-oxoethyl)-2-(2-phenylhydrazono)propanamide (2c)



$C_{20}H_{28}N_4O_2$
Mol wt = 356.46 g·mol⁻¹

Compound **2c** was prepared following the general procedure A applied to 2-(2-phenylhydrazono)propanoic acid (500 mg, 2.8 mmol), formaldehyde (210 μ L, 2.8 mmol), cyclo-hexylisocyanide (403 μ L, 2.8 mmol).

Yield: 78% (780 mg)

R_f : 0.1 (3:7 PE/Et₂O)

Brown solid.

Mp: 95–96 °C

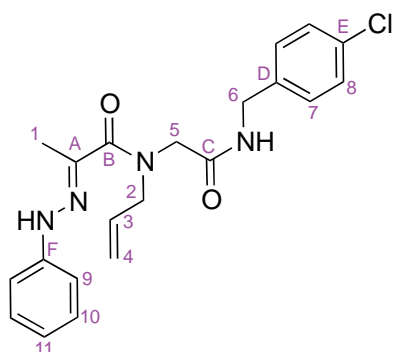
¹H NMR (CDCl₃, 400 MHz) δ 7.43 (br s, 1H, NH), 7.29–7.25 (m, 2H, H₁₁), 7.05 (d, J = 7.3 Hz, 2H, H₁₀), 6.94 (t, J = 8.5 Hz, 1H, H₁₂), 6.31–6.11 (m, 1H, NH), 5.92–5.85 (m, 1H, H₃), 5.27–5.21 (m, 2H, H₄), 4.36–4.18 (m, 2H, H₅), 4.15–4.03 (m, 2H, H₂), 3.85–3.76 (m, 1H, H₆), 2.13 (s, 3H, H₁), 1.89–1.86 (m, 2H, H₇), 1.68–1.63 (m, 2H, H₈), 1.61–1.56 (m, 2H, H₉), 1.36–1.30 (m, 2H, H₈), 1.19–1.10 (m, 2H, H₇).

¹³C NMR (CDCl₃, 100.6 MHz) δ 168.1 (C_B, C_C), 143.5 (C_D), 136.2 (C_A), 131.7 (C₃), 129.2 (C₁₁), 121.5 (C₁₂), 118.7 (C₄), 113.6 (C₁₀), 53.3 (C₂), 50.7 (C₅), 48.3 (C₆), 32.8 (C₇), 25.4 (C₉), 24.6 (C₈), 12.1 (C₁).

IR (v, cm⁻¹): 1653, 1597, 1541, 1496, 1454, 1424, 1244.

HRMS: calculated for C₂₀H₂₈N₄O₂ 356.2212, found 356.2215

(E)-N-allyl-N-(2-(4-chlorobenzylamino)-2-oxoethyl)-2-(2-phenylhydrazono)propanamide (2d)



$C_{21}H_{23}ClN_4O_2$
Mol wt = 398.89 g·mol⁻¹

Compound **2d** was prepared following the general procedure A applied to 2-(2-phenylhydrazono)propanoic acid (500 mg, 2.8 mmol), formaldehyde (210 μL, 2.8 mmol), *p*-chlorobenzylisocyanide (420 mg, 2.8 mmol).

Yield: 71% (800 mg)

R_f : 0.1 (3:7 PE/Et₂O)

Yellow solid.

Mp: 96–97 °C

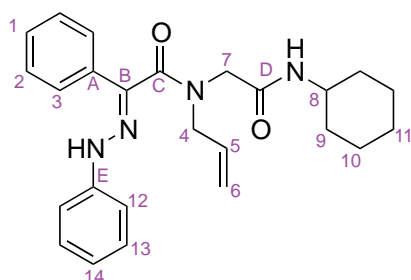
¹H NMR (CDCl₃, 400 MHz) δ 7.51 (br s, 1H, NH) 7.29–7.24 (m, 4H, H₈, H₁₀), 7.19–7.17 (m, 2H, H₇), 7.03 (d, J = 7.3 Hz, 2H, H₉), 6.96 (t, J = 7.3 Hz, 1H, H₁₁), 6.91 (br s, 1H, NH), 5.94–5.87 (m, 1H, H₃), 5.32–5.25 (m, 2H, H₄), 4.43 (d, J = 6.0 Hz, 2H, H₆), 4.28–4.16 (m, 4H, H₂, H₅), 2.09 (s, 3H, H₁).

¹³C NMR (CDCl₃, 100.6 MHz) δ 169.6 (C_C), 168.7 (C_B), 143.8 (C_F), 136.9 (C_D), 136.8 (C_A), 133.6 (C_E), 132.9 (C₃), 129.8 (C₈), 129.4 (C₁₀), 129.2 (C₇), 122.1 (C₁₁), 119.2 (C₄), 114.4 (C₉), 53.7 (C₂), 50.9 (C₅), 43.1 (C₆), 12.5 (C₁).

IR (ν, cm⁻¹): 1601, 1541, 1492, 1458, 1242.

HRMS: calculated for C₂₁H₂₃ClN₄O₂ 398.1510, found 398.1516.

(E)-N-allyl-N-(2-(cyclohexylamino)-2-oxoethyl)-2-phenyl-2-(2-phenylhydrazono)acetamide (2e)



$C_{25}H_{30}N_4O_2$
Mol wt = 418.53 g·mol⁻¹

Compound **2e** was prepared following the general procedure A applied to 2-phenyl-2-(2-phenylhydrazono)acetic acid (673 mg, 2.8 mmol), formaldehyde (210 μ L, 2.8 mmol), cyclohexylisocyanide (403 μ L, 2.8 mmol).

Yield: 94% (1.1 g)

R_f : 0.3 (3:7 PE/Et₂O)

White solid.

Mp: 184–185 °C

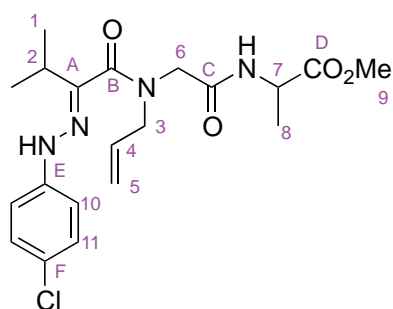
¹H NMR (CDCl₃, 400 MHz) δ 9.99 (br s, 1H, NH), 7.63 (d, J = 7.6 Hz, 2H, H₃), 7.31–7.27 (m, 3H, H₁, H₁₂), 7.24–7.19 (m, 4H, H₂, H₁₃), 6.81 (t, J = 7.3 Hz, 1H, H₁₄), 5.64 (br s, 1H, NH), 5.59–5.49 (m, 1H, H₅), 5.07–5.03 (m, 2H, H₆), 4.10 (s, 2H, H₇), 3.86 (d, J = 5.8 Hz, 2H, H₄), 3.85–3.76 (m, 1H, H₈), 1.91–1.87 (m, 2H, H₉), 1.65–1.62 (m, 2H, H₁₀), 1.57–1.52 (m, 2H, H₁₁), 1.33–1.27 (m, 2H, H₁₀), 1.13–1.06 (m, 2H, H₉).

¹³C NMR (CDCl₃, 100.6 MHz) δ 167.5 (C_D), 167.3 (C_C), 145.3 (C_E), 136.7 (C_B), 134.7 (C_A), 132.9 (C₅), 129.5 (C₂), 129.0 (C₁₃), 128.6 (C₁), 125.5 (C₃), 120.6 (C₁₄), 119.9 (C₆), 113.6 (C₁₂), 52.2 (C₄), 49.4 (C₈), 47.2 (C₇), 33.4 (C₉), 26.0 (C₁₁), 25.3 (C₁₀).

IR (v, cm⁻¹): 1653, 1624, 1558, 1541, 1507, 1457.

HRMS: calculated for C₂₅H₃₀N₄O₂ 418.2369, found 418.2375.

(E)-methyl 2-(2-(N-allyl-2-(2-(4-chlorophenyl)hydrazono)-3-methylbutanamido)acetamido)propanoate (2f)



$C_{20}H_{27}ClN_4O_4$
Mol wt = 422.91 g·mol⁻¹

Compound **2f** was prepared following the general procedure A applied to 2-(2-(4-chlorophenyl)hydrazono)-3-methylbutanoic acid (78 mg, 0.32 mmol), formaldehyde (25 μ L, 0.32 mmol), methyl 2-isocyanopropanoate (37 mg, 0.32 mmol).

Yield: 37% (50 mg)

R_f : 0.3 (100% Et₂O)

Yellow oil.

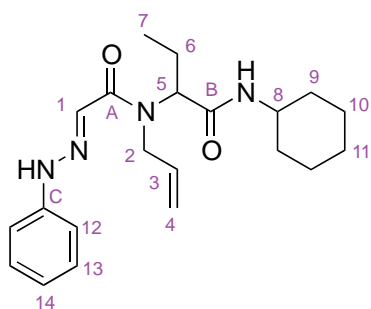
¹H NMR (CDCl₃, 400 MHz) δ 7.55 (br s, 1H, NH), 7.15 (d, J = 8.6 Hz, 2H, H₁₁), 7.09 (d, J = 8.6 Hz, 2H, H₁₀), 6.57 (br s, 1H, NH), 5.70 (ddt, J = 16.9, 10.8, 5.6 Hz, 1H, H₄), 5.23 (d, J = 10.8 Hz, 1H, H₅), 5.18 (d, J = 16.9 Hz, 1H, H₅), 4.67 (quint, J = 7.3 Hz, 1H, H₇), 4.20 (d, J = 15.9 Hz, 1H, H₆), 4.10 (d, J = 15.9 Hz, 1H, H₆), 3.87 (ddt, J = 16.9, 10.8, 5.6 Hz, 2H, H₃), 3.77 (s, 3H, H₉), 2.83 (sept, J = 7.1 Hz, 1H, H₂), 1.45 (d, J = 7.3 Hz, 3H, H₈), 1.21 (d, J = 7.1 Hz, 3H, H₁), 1.19 (d, J = 7.1 Hz, 3H, H₁).

¹³C NMR (CDCl₃, 100.6 MHz) δ 173.2 (C_D), 167.9 (C_B), 167.8 (C_C), 144.1 (C_E), 143.9 (C_A), 132.3 (C₄), 128.8 (C₁₁), 123.7 (C_F), 119.4 (C₅), 113.6 (C₁₀), 52.6 (C₉), 51.1 (C₃), 48.5 (C₇), 46.2 (C₆), 32.3 (C₂), 20.2 (C₁), 19.9 (C₁), 18.4 (C₈).

IR (v, cm⁻¹): 2926, 2361, 1744, 1688, 1626, 1602, 1542, 1492, 1454, 1255, 1209.

HRMS: calculated for C₂₀H₂₇ClN₄O₄ 422.1721, found 422.1722.

(E)-2-(N-allyl-2-(2-phenylhydrazono)acetamido)-N-cyclohexylbutanamide (3g)



$C_{21}H_{30}N_4O_2$
Mol wt = 370.48 g·mol⁻¹

Compound **3g** was prepared following the general procedure A applied to 2-(2-phenylhydrazono)acetic acid (500 mg, 3.05 mmol), propionaldehyde (220 μ L, 3.05 mmol), cyclo-hexylisocyanide (380 μ L, 3.05 mmol).

Yield: 58% (653 mg)

R_f : 0.25 (100% Et₂O)

Red solid.

Mp: 95–96 °C

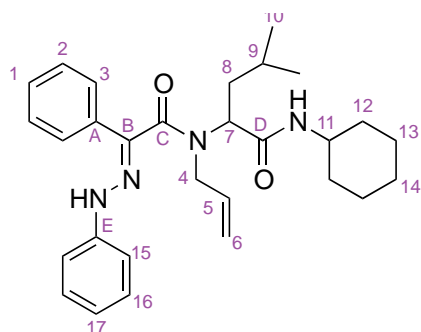
¹H NMR (CDCl₃, 400 MHz) δ 8.26 (br s, 1H, NH), 7.34 (s, 1H, H₁), 7.32–7.30 (m, 2H, H₁₃), 7.07 (d, J = 7.1 Hz, 2H, H₁₂), 7.00–6.97 (m, 1H, H₁₄), 6.40–6.38 (m, 1H, NH), 5.95–5.89 (m, 1H, H₃), 5.23 (d, J = 16.9 Hz, 1H, H₄), 5.18 (d, J = 10.1 Hz, 1H, H₄), 4.83 (t, J = 6.8 Hz, 1H, H₅), 4.34–4.16 (m, 2H, H₂), 3.75–3.76 (m, 1H, H₈), 2.08–2.01 (m, 1H, H₆), 1.91–1.82 (m, 2H, H₉), 1.70–1.67 (m, 3H, H₆, H₁₀), 1.62–1.58 (m, 1H, H₁₁), 1.38–1.31 (m, 2H, H₁₀), 1.17–1.12 (m, 3H, H₉, H₁₁), 0.96 (t, J = 6.8 Hz, 3H, H₇).

¹³C NMR (CDCl₃, 100.6 MHz) δ 170.1 (C_B), 166.3 (C_A), 143.6 (C_C), 135.3 (C₃), 129.7 (C₁₃), 128.0 (C₁), 122.1 (C₁₄), 117.5 (C₄), 114.0 (C₁₂), 60.2 (C₅), 48.6 (C₈), 47.9 (C₂), 33.3 (C₉), 33.1 (C₉), 25.8 (C₁₁), 25.2 (C₁₀), 22.0 (C₆), 11.2 (C₇).

IR (v, cm⁻¹): 2931, 2361, 1648, 1538, 1453, 1250.

HRMS: calculated for C₂₁H₃₀N₄O₂ 370.2369, found 370.2369

(E)-2-(N-allyl-2-phenyl-2-(2-phenylhydrazono)acetamido)-N-cyclohexyl-4-methylpentanamide (3h)



$C_{29}H_{38}N_4O_2$
Mol wt = 474.64 g·mol⁻¹

Compound **3h** was prepared following the general procedure A applied to 2-phenyl-2-(2-phenylhydrazono)acetic acid (673 mg, 2.8 mmol), isovaleraldehyde (300 μL, 2.8 mmol), cyclohexylisocyanide (403 μL, 2.8 mmol).

Yield: 52% (660 mg)

R_f : 0.6 (5:5 PE/Et₂O)

Yellow solid

Mp: 67–68 °C

Obtained as a mixture of two rotamers A:B in a 1.2:0.8 ratio

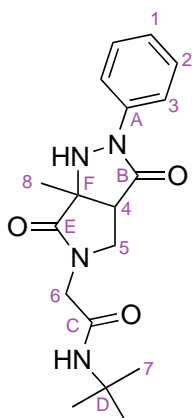
¹H NMR (CDCl₃, 400 MHz) δ 9.15 (br s, 0.6 H_A, NH), 8.13 (br s, 0.4 H_B, NH), 7.70 (d, $J = 7.8$ Hz, 0.8H_B, H₃), 7.65 (d, $J = 7.8$ Hz, 1.2H_A, H₃), 7.44–7.35 (m, 2H, H₂), 7.32–7.24 (m, 3H, 1.2H_A, H₁, H₁₅, H₁₆), 7.16 (d, $J = 8.3$ Hz, 0.8H_B, H₁₅), 6.94 (t, $J = 7.8$ Hz, 0.4H_B, H₁₇), 6.90 (t, $J = 7.8$ Hz, 0.6H_A, H₁₇), 6.05–5.96 (m, 0.4H_B, H₅), 5.96 (br s, 1H, NH), 5.63 (ddt, $J = 16.7, 10.3, 6.5$ Hz, 0.6H_A, H₅), 5.37 (d, $J = 16.7$ Hz, 0.4H_B, H₆), 5.25 (d, $J = 10.3$ Hz, 0.4H_B, H₆), 5.02 (d, $J = 16.7$ Hz, 0.6H_A, H₆), 4.98 (d, $J = 10.3$ Hz, 0.6H_A, H₆), 4.93–4.90 (m, 1H, H₇), 4.31 (dd, $J = 14.4, 6.5$ Hz, 0.4H_B, H₄), 4.04 (dd, $J = 14.4, 6.5$ Hz, 0.4H_B, H₄), 3.98–3.91 (m, 1H, H₁₁), 3.89–3.77 (m, 1.2H_A, H₄), 2.03–1.94 (m, 2H, H₁₂), 1.74–1.61 (m, 6H, H₈, H₁₃), 1.41–1.36 (m, 2H, H₁₄), 1.25–1.17 (m, 3H, H₉, H₁₂), 1.06 (d, $J = 6.0$ Hz, 1.8H_A, H₁₀), 1.02 (d, $J = 6.0$ Hz, 1.8H_A, H₁₀), 0.62 (d, $J = 6.0$ Hz, 1.2H_B, H₁₀), 0.46 (d, $J = 6.0$ Hz, 1.2H_B, H₁₀).

¹³C NMR (CDCl₃, 100.6 MHz) δ 169.9 (C_D), 167.9 (A, C_C), 167.7 (B, C_C), 144.7 (A, C_E), 144.3 (B, C_E), 138.1 (A, C_B), 138.1 (B, C_B), 134.3 (A, C_A), 134.0 (B, C_A), 133.5 (A, C₅), 133.2 (B, C₅), 129.6 (B, C₁), 129.4 (B, C₁₆), 129.2 (A, C₁₆), 129.1 (B, C₂), 128.7 (B, C₂), 128.5 (A, C₁), 125.6 (B, C₃), 125.1 (A, C₃), 121.5 (B, C₁₇), 120.5 (A, C₁₇), 119.1 (A, C₆), 118.6 (B, C₆), 113.8 (B, C₁₅), 113.3 (A, C₁₅), 60.2 (B, C₇), 56.6 (A, C₇), 50.2 (C₄), 48.8 (A, C₁₁), 48.6 (B, C₁₁), 37.4 (A, C₈), 37.3 (B, C₈), 33.1 (A, C₁₂), 33.0 (B, C₁₂), 25.5 (B, C₁₄), 25.3 (A, C₁₄), 25.3 (C₉), 24.9 (A, C₁₃), 24.8 (B, C₁₃), 23.2 (A, C₁₀), 22.6 (B, C₁₀), 21.9 (A, C₁₀), 21.4 (B, C₁₀).

IR (ν, cm⁻¹): 2932, 2361, 1621, 1540, 1263.

HRMS: calculated for C₂₉H₃₈N₄O₂ 474.2994, found 474.2983.

***N*-tert-butyl-2-(6a-methyl-3,6-dioxo-2-phenyl-hexahydropyrrolo[3,4-c]pyrazol-5(1*H*)-yl)acetamide (3a)**



$C_{18}H_{24}N_4O_3$
Mol wt = 344.41 g·mol⁻¹

Compound **3a** was prepared following the general procedure B applied to hydrazone **2a** (100 mg, 0.3 mmol).

Yield: 84% (87 mg)

*R*_f: 0.3 (AcOEt 100%)

Yellow solid.

Mp: 200 °C (degradation)

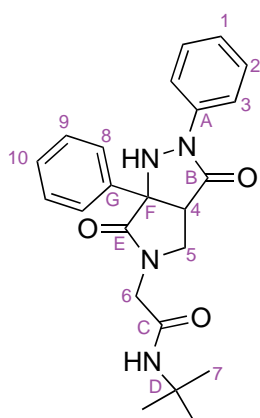
¹H NMR (CDCl₃, 400 MHz) δ 7.83 (d, *J* = 8.3 Hz, 2H, H₃), 7.37 (dd, *J* = 8.3, 7.3 Hz, 2H, H₂), 7.17 (t, *J* = 7.3 Hz, 1H, H₁), 5.52 (br s, 1H, NH *t*Bu), 4.89 (br s, 1H, NH), 3.93 (d, *J* = 16.2 Hz, 1H, H₆), 3.85 (dd, *J* = 10.3, 6.3 Hz, 1H, H₅), 3.80 (d, *J* = 16.2 Hz, 1H, H₆), 3.76 (d, *J* = 10.3 Hz, 1H, H₅), 3.22 (d, *J* = 6.3 Hz, 1H, H₄), 1.63 (s, 3H, H₈), 1.25 (s, 9H, H₇).

¹³C NMR (CDCl₃, 100.6 MHz) δ 174.6 (C_E), 169.8 (C_B), 166.3 (C_C), 138.1 (C_A), 129.2 (C₂), 125.8 (C₁), 119.5 (C₃), 63.7 (C_F), 52.0 (C_D), 48.0 (C₄, C₆), 47.6 (C₅), 29.0 (C₇), 18.9 (C₈).

IR (ν, cm⁻¹): 1684, 1541, 1497, 1363.

HRMS: calculated for C₁₈H₂₄N₄O₃ 344.1848, found 344.1855.

***N*-tert-butyl-2-(3,6-dioxo-2,6a-diphenyl-hexahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)acetamide (3b)**



$C_{23}H_{26}N_4O_3$
Mol wt = 406.48 g·mol⁻¹

Compound **3b** was prepared following the general procedure B applied to hydrazone **2b** (100 mg, 0.25 mmol).

Yield: 68% (60 mg)

R_f : 0.7 (AcOEt 100%)

Yellow solid.

Mp: 105–106 °C.

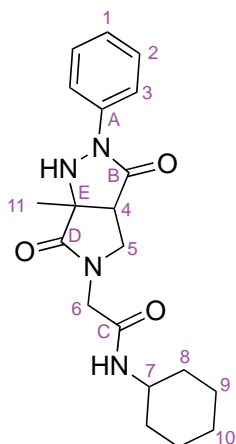
¹H NMR (CDCl₃, 400 MHz) δ 7.91 (d, J = 8.1 Hz, 2H, H₃), 7.66 (d, J = 7.6 Hz, 2H, H₈), 7.51–7.45 (m, 3H, H₉, H₁₀), 7.40 (dd, J = 8.1, 7.6 Hz, 2H, H₂), 7.20 (t, J = 7.6 Hz, 1H, H₁), 5.53 (br s, 1H, NH *t*-Bu), 5.23 (br s, 1H, NH), 3.97–3.84 (m, 4H, H₅, H₆), 3.74–3.72 (m, 1H, H₄), 1.18 (s, 9H, H₇).

¹³C NMR (CDCl₃, 100.6 MHz) δ 173.2 (C_E), 169.0 (C_B), 166.3 (C_C), 138.0 (C_A), 134.9 (C_G), 130.0 (C₁₀), 129.8 (C₉), 129.3 (C₂), 126.4 (C₈), 126.0 (C₁), 119.7 (C₃), 68.9 (C_F), 51.9 (C_D), 48.9 (C₆), 48.2 (C₅), 48.0 (C₄), 28.8 (C₇).

IR (ν, cm⁻¹): 1684, 1558, 1541, 1508, 1457.

HRMS: calculated for C₂₃H₂₆N₄O₃ 406.2005, found 406.2004.

***N*-cyclohexyl-2-(6a-methyl-3,6-dioxo-2-phenyl-hexahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)acetamide (**3c**)**



$C_{20}H_{26}N_4O_3$
Mol wt = 370.45 g·mol⁻¹

Compound **3c** was prepared following the general procedure B applied to hydrazone **2c** (100 mg, 0.28 mmol).

Yield: 76% (83 mg)

R_f : 0.2 (AcOEt 100%)

White solid.

Mp: 197–198 °C (degradation)

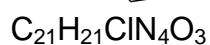
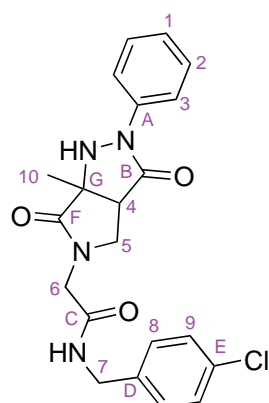
¹H NMR (CDCl₃, 400 MHz) δ 7.82 (d, J = 8.1 Hz, 2H, H₃), 7.35 (dd, J = 8.1, 7.5 Hz, 2H, H₂), 7.15 (t, J = 7.5 Hz, 1H, H₁), 5.60 (br s, 1H, NH Cy), 4.88 (br s, 1H, NH), 3.98 (d, J = 15.4 Hz, 1H, H₆), 3.86–3.82 (m, 2H, H₅, H₆), 3.75 (d, J = 10.1 Hz, 1H, H₅), 3.70–3.61 (m, 1H, H₇), 3.22 (d, J = 6.5 Hz, 1H, H₄), 1.79–1.75 (m, 2H, H₈), 1.62 (s, 3H, H₁₁), 1.60–1.49 (m, 4H, H₉, H₁₀), 1.28–1.21 (m, 2H, H₉), 1.02–0.92 (m, 2H, H₈).

¹³C NMR (CDCl₃, 100.6 MHz) δ 174.7 (C_D), 169.9 (C_B), 166.2 (C_C), 138.1 (C_A), 129.3 (C₂), 125.8 (C₁), 119.5 (C₃), 63.8 (C_E), 48.8 (C₄), 48.1 (C₇), 47.7 (C₆), 47.5 (C₅), 33.2 (C₈), 33.1 (C₈), 25.7 (C₁₀), 25.1 (C₉), 18.8 (C₁₁).

IR (ν, cm⁻¹): 1698, 1595, 1541, 1497, 1457, 1362.

HRMS: calculated for C₂₀H₂₆N₄O₃ 370.2005, found 370.2002.

N-(4-chlorobenzyl)-2-(6a-methyl-3,6-dioxo-2-phenyl-hexahydropyrrolo[3,4-c]pyrazol-5(1H)-yl)acetamide (3d)



Mol wt = 412.87 g·mol⁻¹

Compound **3d** was prepared following the general procedure B applied to hydrazone **2d** (100 mg, 0.25 mmol).

Yield: 90% (95 mg)

*R*_f: 0.2 (AcOEt 100%)

White solid.

Mp: 175–176°C (degradation)

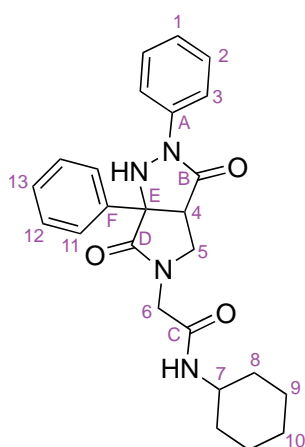
¹H NMR (CDCl₃, 400 MHz) δ 7.78 (d, *J* = 8.3 Hz, 2H, H₃), 7.37 (dd, *J* = 8.3, 7.0 Hz, 2H, H₂), 7.24 (d, *J* = 7.8 Hz, 2H, H₉), 7.19 (t, *J* = 7.0 Hz, 1H, H₁), 7.13 (d, *J* = 7.8 Hz, 2H, H₈), 6.10 (br s, 1H, NH Bn), 4.81 (br s, 1H, NH), 4.41–4.31 (m, 2H, H₇), 4.12 (d, *J* = 15.9 Hz, 1H, H₆), 3.89 (d, *J* = 15.9 Hz, 1H, H₆), 3.89–3.81 (m, 2H, H₅), 3.25 (d, *J* = 5.8 Hz, 1H, H₄), 1.61 (s, 3H, H₁₀).

¹³C NMR (CDCl₃, 100.6 MHz) δ 174.8 (C_F), 169.6 (C_B), 167.2 (C_C), 137.9 (C_A), 136.3 (C_D), 133.7 (C_E), 129.4 (C₈), 129.2 (C₂, C₉), 125.8 (C₁), 119.4 (C₃), 63.6 (C_G), 48.0 (C₄), 47.8 (C₆), 47.3 (C₅), 43.3 (C₇), 18.8 (C₁₀).

IR (ν, cm⁻¹): 1684, 1541, 1276, 1261.

HRMS: calculated for C₂₁H₂₁ClN₄O₃ 412.1302, found 412.1290.

***N*-cyclohexyl-2-(3,6-dioxo-2,6a-diphenyl-hexahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl)acetamide (**3e**)**



$C_{25}H_{28}N_4O_3$
Mol wt = 432.51 g·mol⁻¹

Compound **3e** was prepared following the general procedure B applied to hydrazone **2e** (100 mg, 0.24 mmol).

Yield: 72% (75 mg)

*R*_f: 0.7 (AcOEt 100%)

Yellow oil

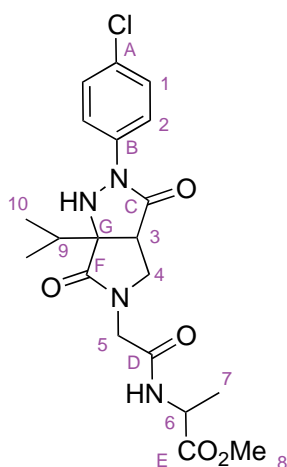
¹H NMR (CDCl₃, 400 MHz) δ 7.89 (d, *J* = 8.6 Hz, 2H, H₃), 7.65 (d, *J* = 8.1 Hz, 2H, H₁₁), 7.48–7.42 (m, 3H, H₁₂, H₁₃), 7.39 (dd, *J* = 8.6, 7.8 Hz, 2H, H₂), 7.18 (t, *J* = 7.8 Hz, 1H, H₁), 5.60 (br s, 1H, NH Cy), 5.21 (br s, 1H, NH cycle), 4.01–3.96 (m, 2H, H₆), 3.91–3.87 (m, 2H, H₅), 3.74–3.70 (m, 1H, H₇), 3.66–3.57 (m, 1H, H₄), 1.79–1.48 (m, 4H, H₈, H₉), 1.31–1.16 (m, 2H, H₁₀), 1.00–0.75 (m, 4H, H₈, H₉).

¹³C NMR (CDCl₃, 100.6 MHz) δ 173.3 (C_D), 169.0 (C_B), 166.1 (C_C), 138.0 (C_A), 134.7 (C_F), 129.9 (C₁₃), 129.7 (C₁₂), 129.3 (C₂), 126.4 (C₁₁), 125.9 (C₁), 119.7 (C₃), 68.9 (C_E), 48.6 (C₄), 48.3 (C₅), 47.9 (C₇), 33.0 (C₈), 32.9 (C₈), 25.6 (C₁₀), 24.9 (C₉).

IR (ν, cm⁻¹): 1697, 1596, 1542, 1496, 1448, 1363.

HRMS: calculated for C₂₅H₂₈N₄O₃ 432.2161, found 432.2169.

Methyl 2-(2-(2-(4-chlorophenyl)-6a-isopropyl-3,6-dioxohexahydropyrrolo[3,4-c]pyrazol-5(1H)-yl)acetamido)propanoate (3f)



$C_{20}H_{25}ClN_4O_5$
Mol wt = 436.88 g·mol⁻¹

Compound **3f** was prepared following the general procedure B applied to hydrazone **2f** (20 mg, 0.047 mmol).

Yield: 49% (10 mg)

R_f : 0.3 (AcOEt 100%)

Orange oil

Obtained as a mixture of two diastereomers A:B in a 1.1:0.9 ratio :

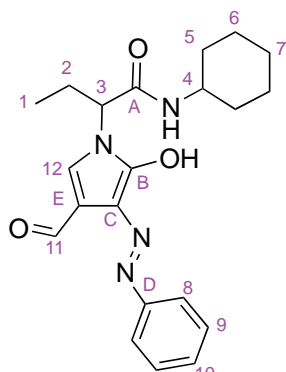
¹H NMR (CDCl₃, 400 MHz) δ 7.78 (d, J = 8.8 Hz, 1.1H_A, H₂), 7.77 (d, J = 8.8 Hz, 0.9H_B, H₂), 7.31 (d, J = 8.8 Hz, 2H, H₁), 6.42 (d, J = 7.5 Hz, 0.45H_B, NH), 6.41 (d, J = 7.5 Hz, 0.55H_A, NH), 5.00 (br s, 0.45H_B, NH), 4.98 (br s, 0.55H_A, NH), 4.54 (q, J = 6.8 Hz, 0.55H_A, H₆), 4.52 (q, J = 6.8 Hz, 0.45H_B, H₆), 4.28 (d, J = 16.4 Hz, 0.45H_B, H₅), 4.23 (d, J = 16.4 Hz, 0.55H_A, H₅), 3.89–3.85 (m, 1H, H₄), 3.80–3.72 (m, 2H, H₄, H₅), 3.71 (s, 1.65H_A, H₈), 3.71 (s, 1.35H_B, H₈), 3.28 (d, J = 7.5 Hz, 1H, H₃), 2.28 (sept, J = 6.5 Hz, 1H, H₉), 1.36 (d, J = 6.8 Hz, 1.35H_B, H₇), 1.35 (d, J = 6.8 Hz, 1.65H_A, H₇), 1.15–1.09 (m, 6H, H₁₀).

¹³C NMR (CDCl₃, 100.6 MHz) δ 174.2 (C_F), 173.0 (A, C_E), 172.8 (B, C_E), 168.7 (C_C), 166.4 (B, C_D), 166.3 (A, C_D), 136.3 (B, C_A), 136.1 (A, C_A), 130.4 (B, C_B), 130.3 (A, C_B), 128.8 (B, C₁), 128.8 (A, C₁), 120.2 (C₂), 69.0 (B, C_G), 69.0 (A, C_G), 52.6 (C₈), 49.2 (B, C₄), 49.2 (A, C₄), 48.1 (B, C₆), 48.0 (A, C₆), 46.6 (B, C₅), 46.5 (A, C₅), 44.0 (B, C₃), 43.8 (A, C₃), 32.0 (B, C₉), 31.9 (A, C₉), 18.3 (B, C₇), 18.1 (A, C₇), 17.3 (B, C₁₀), 17.2 (A, C₁₀).

IR (ν, cm⁻¹): 2925, 2361, 1681, 1492, 1460, 1360, 1211.

HRMS: calculated for C₂₀H₂₅ClN₄O₅ 436,1513, found 436.1515.

(E)-N-cyclohexyl-2-(4-formyl-2-hydroxy-3-(phenyldiazenyl)-1H-pyrrol-1-yl)butanamide (4g)



$C_{21}H_{26}N_4O_3$
Mol wt = 382.45 $g \cdot mol^{-1}$

To a solution of hydrazone **3g** (400 mg, 1.08 mmol) in a 20/80 H_2O/CH_3CO_2H mixture (0.06 M) was added $Cu(OAc)_2$ (215 mg, 1.08 mmol, 1 equiv). The resulting mixture was heated at 80 °C under argon for 3 h. The pH was adjusted to 6 with an aqueous sodium hydrogenocarbonate solution, and the aqueous phase was extracted with AcOEt. Then the organic layers were washed ten times with water (1 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The product was isolated by flash chromatography on silica gel (PE/ Et_2O).

Yield: 14% (12 mg)

R_f : 0.4 (Et_2O 100%)

Yellow oil

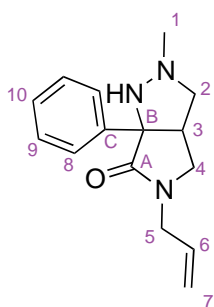
1H NMR ($CDCl_3$, 400 MHz) δ 9.26 (s, 1H, H_{11}), 8.27 (s, 1H, H_{12}), 7.48 (d, $J = 7.8$ Hz, 2H, H_8), 7.38 (dd, $J = 7.8, 7.3$ Hz, 2H, H_9), 7.13 (t, $J = 7.3$ Hz, 1H, H_{10}), 4.80 (t, $J = 7.8$ Hz, 1H, H_3), 3.79–3.70 (m, 1H, H_4), 2.15–2.08 (m, 1H, H_2), 1.96–1.82 (m, 3H, H_2, H_5), 1.74–1.66 (m, 3H, H_6, H_7), 1.60–1.50 (m, 1H, H_7), 1.38–1.29 (m, 2H, H_6), 1.20–1.11 (m, 2H, H_5), 0.98 (t, $J = 7.3$ Hz, 3H, H_1).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.1 (C_{11}), 168.3 (C_B), 164.6 (C_A), 148.2 (C_{12}), 142.5 (C_D), 129.8 (C_9), 126.3 (C_E), 124.8 (C_{10}), 116.8 (C_8), 114.4 (C_C), 56.8 (C_3), 49.3 (C_4), 33.3 (C_5), 33.1 (C_5), 26.2 (C_2), 25.7 (C_7), 25.2 (C_6), 25.1 (C_6), 10.8 (C_1).

IR (ν , cm^{-1}): 1733, 1717, 1698, 1653, 1558, 1541, 1521, 1508, 1473, 1419, 1276.

HRMS: calculated for $C_{21}H_{26}N_4O_3$ 382.2005, found 382.2008.

5-allyl-2-methyl-6a-phenyl-hexahydropyrrolo[3,4-c]pyrazol-6(6aH)-one (6)



$C_{15}H_{19}N_3O$
Mol wt = 257.33 g·mol⁻¹

A solution of 2-oxo-2-phenylacetic acid (150 mg, 1 mmol), in DCM (0.5 M, 2 mL), with oxalyl chloride (94 μ L, 1.1 mmol), with one drop of DMF was stirred for 2 h at room temperature. Then a solution of diallyamine (136 μ L, 1.1 mmol) in DCM (1 M, 1.1 mL) and TEA (153 μ L, 1.1 mmol) was added dropwise. The solution was filtered and washed with citric acid in water. The aqueous phase was extracted with DCM twice and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product, used without further purification, was diluted in methanol (1 M, 1 mL) with methylhydrazine (80 μ L, 1.5 mmol) and acetic acid (86 μ L, 1.5 mmol). The mixture was heated under microwave irradiation at 120 $^{\circ}C$ (200 W, 13 bar) for 30 min. The mixture was then washed with water and the aqueous phase was extracted with DCM. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo.

Yield: 62% (160 mg)

R_f : 0.1 (AcOEt 100%)

Orange oil

1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, $J = 7.1$ Hz, 2H, H_8), 7.27 (dd, $J = 7.8, 7.1$ Hz, 2H, H_9), 7.20 (t, $J = 7.8$ Hz, 1H, H_{10}), 5.71–5.61 (m, 1H, H_6), 5.18 (dd, $J = 15.4, 1.2$ Hz, 1H, H_7), 5.14 (dd, $J = 8.5, 1.2$ Hz, 1H, H_7), 4.00 (dd, $J = 15.4, 6.1$ Hz, 1H, H_5), 3.81 (dd, $J = 15.4, 6.1$ Hz, 1H, H_5), 3.67 (dd, $J = 10.6, 7.8$ Hz, 1H, H_4), 3.16 (dd, $J = 10.6, 1.5$ Hz, 1H, H_4), 3.04 (dddd, $J = 8.1, 7.8, 3.6, 1.5$ Hz, 1H, H_3), 2.90 (dd, $J = 10.1, 3.6$ Hz, 1H, H_2), 2.73 (dd, $J = 10.1, 8.1$ Hz, 1H, H_2), 2.46 (s, 3H, H_1).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 174.2 (C_A), 139.9 (C_C), 131.1 (C_6), 128.7 (C_9), 127.9 (C_{10}), 125.6 (C_8), 118.5 (C_7), 75.7 (C_B), 50.2 (C_4), 45.9 (C_5), 45.9 (C_2), 44.7 (C_3), 44.5 (C_1).

IR (ν , cm^{-1}): 1683, 1491, 1445, 1275.

HRMS: calculated for $C_{15}H_{19}N_3O$ 257.1528, found 257.1531.