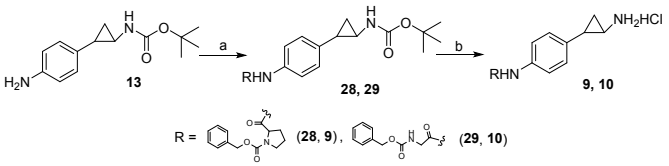
# Electronic Supplementary Information

## Experimental

**Chemistry**. Melting points were determined on a Buchi 530 melting point apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker AC 400 spectrometer; chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethylsilane ($Me_4Si$). EIMS spectra were recorded with a Fisons Trio 1000 spectrometer; only molecular ions ($M^+$) and base peaks are given. All compounds were routinely checked by TLC, $^1$H NMR and $^{13}$C NMR spectra. TLC was performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F254) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure of ca. 20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Elemental analysis has been used to determine purity of the described compounds, that is >95%. Analytical results are within ± 0.40% of the theoretical values. All chemicals were purchased from Aldrich Chimica, Milan (Italy), or from Alfa Aesar, Milan (Italy), and were of the highest purity.




**Scheme S1.** Synthesis of **9** and **10**. Reagents and conditions: (a) Z-Gly-OH or Z-Pro-OH, EDCI, TEA, HOBt, dry THF, overnight, r.t.; (e) 4N HCl dry 1,4-dioxane/ THF, overnight, r.t.

**General procedure for the synthesis of *trans tert*-butyl 2-[4-(*N*-carbobenzyloxyprolyl or glycyl)phenyl]cyclopropyl carbamates 28 and 29. Example: *trans* benzyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)cyclopropyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 28.** Triethylamine (0.9 mmol, 0.12 mL) and *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.9 mmol, 0.4 g) were added to a solution of *N*-carbobenzyloxy-L-proline (0.7 mmol, 0.2 g) and *N*-hydroxybenzotriazole (0.9 mmol, 0.12 g) in dry dichloromethane (5 mL), and the mixture was stirred over a period of 1 h. After this time **13** (0.8 mmol, 0.2 g) was added, and the stirring was continued for 1 h. The reaction was poured into water (50 mL) and extracted with dichloromethane (3 × 10 mL). The organic layers were washed with saturated sodium chloride solution (3 × 10 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by chromatographic column on silica gel eluting with ethyl acetate/*n*-hexane 1/2 to afford the pure **28** as a colorless solid. $^1$H-NMR ($CDCl_3$, 400MHz) δ 1.13-1.15 (m, 2H, C$H_2$ cyclopropane), 1.47 (s, 9H, Boc group), 1.75-1.92 (m, 3H, NCH$_2$C$H_2$C*H*HCHCO), 2.04-2.12 (m, 2H, NCH$_2$C$H_2$CH*H*CHCO and PhC*H*), 2.77-2.82 (m, 1H, C*H*NHBoc), 3.43-3.50 (m, 2H, NC$H_2$CH$_2$CH$_2$CHCO), 4.48-4.52 (m, 1H, NCH$_2$CH$_2$CH$_2$C*H*CO), 4.78-4.81 (br s, 1H, NHBoc), 5.14 (m, 2H, PhC$H_2$O), 7.12-7.17 (m, 3H, benzene protons), 7.20-7.27 (m, 2H, benzene protons), 7.30-7.37 (m, 2H, benzene protons), 7.51-7.57 (t, 2H, benzene protons), 9.68 (br s, 1H, CON*H*). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 18.48, 24.11, 26.87, 28.34 (3C), 30.54, 35.34, 47.10, 60.95, 66.01, 79.69, 121.43 (2C), 126.63 (2C), 127.97, 128.06 , 128.32 (2C), 136.17, 136.20 (2C), 139.71, 154.91, 158.72, 170.42. MS (EI) *m/z*: 479.24 $[M]^+$.

**General procedure for the synthesis of the ethyl $N_1$-substituted-1*H*-pyrrole-2-carboxylates 14a-c and the ethyl $N_1$-substituted-1*H*-indole-2-carboxylates 15a-c. Example: ethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (14a).** A solution of ethyl 1*H*-pyrrole-2-carboxylate (1.08 mmol, 0.15 g) and $K_2CO_3$ (1.61 mmol, 0.22 g) in dry acetonitrile (5 mL) was stirred at 85 ºC for 5 min. After this time, 2-bromo-1-phenylethanone (1.08 mmol, 0.21 g) was added, and the stirring was continued for 2 h. The solvent was evaporated, and the obtained residue was purified by column chromatography ($SiO_2$ eluting with ethyl acetate/*n*-hexane 1:8) to provide the pure **14a**. $^1$H NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 1.27-1.30 (t, 3H, COOCH$_2$C$H_3$), 4.18-4.23 (q, 2H, COOC$H_2$CH$_3$), 5.79 (s, 2H, C$H_2$), 6.28 (s, 1H, pyrrole proton), 6.86 (s, 1H, pyrrole proton), 7.08 (s, 1H, pyrrole proton), 7.51-7.55 (m, 2H, benzene protons), 7.62-7.66 (m, 1H, benzene proton), 8.02-8.04 (d, 2H, benzene protons); $^{13}$C NMR ($CDCl_3$, 100 MHz, δ; ppm) δ 14.40, 52.70, 60.1, 111.4, 117.1, 120.3, 127.0, 128.3 (2C), 132.6, 133.5 (2C), 134.9, 159.60, 190.5.MS (EI) *m/z*: 258.09 $[M]^+$.

**General procedure for the synthesis of the $N_1$-substituted-1*H*-pyrrole-2-carboxylic acids 16a-c and the $N_1$-substituted-1*H*-indole-2-carboxylic acids 17a-c. Example: 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylic acid (16a).** A mixture of ethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (**14a**) (0.2 mmol, 0.05 g) and 2N LiOH (0.8 mmol, 0.03 g) in tetrahydrofuran (2 mL) was stirred at room temperature for 3 h. The solvent was evaporated, and 2N HCl was slowly added until pH was 5. The precipitate was filtered, washed with water (3 × 5 mL) and recrystallized from methanol to obtain the pure **16a**. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 5.87 (s, 2H, C$H_2$), 6.16 (s, 1H, pyrrole proton), 6.86 (bs, 1H, benzene proton), 7.09 (s, 1H, benzene proton), 7.57-7.61 (t, 2H, benzene protons), 7.70-7.73 (t, 1H, pyrrole proton), 8.02-8.03 (d, 2H, benzene protons), 12.09 (bs, 1H, COO*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 58.4, 111.0, 117.4, 123.0, 128.2, 128.9 (2C) ,133.4, 133.5 (2C), 134.4, 162.5, 190.0 ppm; MS (EI) *m/z*: 229.07 $[M]^+$.

**General procedure for the synthesis of the *trans tert*-butyl (2-(4-($N_1$-substituted-1*H*-pyrrole- and -indole-2- and -3-carboxamido)phenyl)cyclopropyl)carbamates 18a-d, 19a-d, 26a,b and 27a,b. Example: *trans tert*-butyl (2-(4-(1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxamido)phenyl)cyclopropyl)carbamate (18b).** Triethylamine (0.84 mmol, 0.12 mL) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBop) (0.25 mmol, 0.14 g) were added to a solution of 1-(2-oxo-2-phenylethyl)-1*H*-indole-2-carboxylic acid (**16a**) (0.22 mmol, 0.05 g) in anhydrous *N,N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred for 45 min at room temperature followed by the addition of trans *tert*-butyl (2-(4-aminophenyl)cyclopropyl)carbamate **13**[1] (0.22 mmol, 0.055 g) under a nitrogen atmosphere, and the reaction was stirred overnight. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with saturated sodium chloride solution (2 × 15 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by chromatographic column on silica gel eluting with ethyl acetate/*n*-hexane 1:2 to afford the pure **18b**. $^1$H NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 1.15-1.18 (m, 2H, C*H*H cyclopropane), 1.48 (m, 9H, (C$H_3$)$_3$), 2.03-2.06 (m, 1H, C*H*NH$_2$), 2.72 (m, 1H, PhC*H*), 5.79 (s, 2H, C$H_2$), 6.28 (s, 1H, pyrrole proton), 6.86 (s, 1H, pyrrole proton), 7.08 (s, 1H, pyrrole proton), 7.26-7.29 (m, 2H, benzene protons), 7.51-7.55 (m, 2H, benzene protons), 7.62-7.66 (m, 1H, benzene proton), 7.70-7.72 (m, 2H, benzene protons), 8.02-8.04 (d, 2H, benzene protons), 8.24 (bs, 1H, CON*H*), 9.08 (bs, 1H, CON*H*) ppm; $^{13}$C NMR ($CDCl_3$, 100 MHz, δ; ppm) δ 15.0, 22.6, 28.3 (3C), 32.3,

58.4, 79.8, 111.0, 113.2, 121.9 (2C), 125.1 (2C), 126.6, 128.7 (2C), 131.3, 133.1, 133.9 (2C), 134.0, 134.6, 137.6, 155.3, 162.9, 190.7 ppm; MS (EI) *m/z*: 459.22 $[M]^+$.

**General procedure for the synthesis of the *trans* benzyl 2-((4-((2-aminocyclopropyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 9, the benzyl (2-((4-(2-aminocyclopropyl)phenyl)amino)-2-oxoethyl)carbamate 10, and the *trans* *N*-(4-(2-aminocyclopropyl)phenyl)-$N_1$-substituted-1*H*-pyrrole and -1*H*-indole-2- and -3-carboxamides hydrochlorides 11a-f and 12a-f. Example: *trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1*H*-pyrrole-2-carboxamide hydrochloride (11a).** A solution of *trans tert*-butyl (2-(4-(1*H*-pyrrole-2-carboxamido)phenyl)cyclopropyl)carbamate **18a** (0.15 mmol, 0.05 g) in dry THF (5 mL) was treated with 4N HCl in dioxane (4.38 mmol, 1.1 mL) at 0 ºC, and the resulting reaction mixture was left under stirring at room temperature for 24 h. After the end of the reaction, the resulting precipitate was isolated by filtration, and washed with diethyl ether to give **11a**. Mp, >300 °C (methanol); yield, 63%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.15-1.18 (m, 2H, C$H_2$ cyclopropane), 2.03-2.06 (m, 1H, C*H*$NH_2$HCl), 2.72 (m, 1H, PhC*H*), 6.31 (s, 1H, pyrrole proton), 7.0 (s, 1H, pyrrole proton), 7.15-7.14 (d, 3H, benzene and pyrrole protons), 7.70-7.73 (d, 2H, benzene protons), 8.47 (bs, 3H, N$H_3^+$), 9.48 (bs, 1H, CON*H*), 11.5 (bs, 1H, N*H* pyrrole) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 109.3, 110.4, 121.4 (2C), 121.9, 125.2 (2C), 126.9, 134.1, 137.6, 162.7 ppm; MS (EI) *m/z*: 241.12 $[M]^+$.

***trans* benzyl 2-((4-((2-aminocyclopropyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate (9).** Mp. 194-195 °C (acetonitrile), yield, 94%. $^1$H-NMR (DMSO) δ 1.13-1.18 (m, 1H, CHH cyclopropane), 1.30-1.33 (m, 1H, CHH cyclopropane), 1.81-1.96 (m, 3H, $NCH_2CH_2CHHCHCO$), 2.24-2.26 (m, 2H, $NCH_2CH_2CHHCHCO$ and PhCH), 2.75-2.76 (m, 1H, $CHNH_2HCl$), 3.43-3.51 (m, 2H, $NCH_2CH_2CH_2CHCO$), 4.31-4.38 (m, 1H, $NCH_2CH_2CH_2CHCO$), 5.03-5.06 (m, 2H, $PhCH_2O$), 7.09-7.15 (d, 3H, benzene protons), 7.18-7.25 (m, 2H, benzene protons), 7.31-7.38 (m, 2H, benzene protons), 7.49-7.55 (t, 2H, benzene protons), 8.14-8.30 (bs, 3H, $NH_2$·HCl), 10.03-10.05 (d, 1H, CONH) ppm. $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 17.35, 23.95, 25.96, 30.46, 33.89, 47.03, 60.82, 66.01, 122.20 (2C), 126.10 (2C), 127.97, 128.06 (2C), 128.32 (2C), 136.02, 136.20, 139.75, 154.91, 170.42. MS (EI) *m/z*: 379.19 $[M]^+$.

***trans* benzyl (2-((4-(2-aminocyclopropyl)phenyl)amino)-2-oxoethyl)carbamate (10).** Mp. 185-186 °C (acetonitrile), yield 92%. $^1$H-NMR (DMSO) δ 1.14-1.19 (m, 1H, C*H*H cyclopropane), 1.34-1.41 (m, 1H, CH*H* cyclopropane), 2.25-2.30 (m, 1H, PhC*H*), 2.74-2.78 (m, 1H, C*H*$NH_2$HCl), 3.79 (d, 2H, NHC$H_2$CONH), 5.05 (s, 2H, $PhCH_2O$), 7.09 (d, 2H, benzene protons), 7.26-7.40 (m, 5H, benzene protons), 7.52 (d, 2H, benzene protons), 7.55 (m, 1H, OCON*H*$CH_2$), 8.42 (bs, 3H, $NH_2$·*H*Cl), 10.01 (s, 1H, CON*H*) ppm. $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 17.35, 25.96, 33.89, 45.22, 66.17, 121.73 (2C), 126.16 (2C), 127.97, 128.06 (2C), 128.32 (2C), 136.60 (2C), 139.23, 156.48, 167.58. MS (EI) *m/z*: 339.16 $[M]^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxamide hydrochloride (11b).** Mp, >300 °C (methanol), yield, 67%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.15-1.16 (m, 2H, C$H_2$ cyclopropane), 2.04-2.06 (m, 1H, C*H*$NH_2$HCl), 2.72 (m, 1H, PhC*H*), 6.16 (s, 2H, C$H_2$), 6.30-6.32 (s, 1H, pyrrole proton), 7.0 (s, 1H, pyrrole proton), 7.15-7.14 (d, 1H, pyrrole proton), 7.27-7.31 (m, 2H, benzene protons), 7.44-7.46 (d, 2H, benzene protons), 7.52-7.56 (m, 1H, benzene proton), 7.61-7.62 (d, 2H, benzene protons), 7.77-7.83 (d, 2H, benzene and pyrrole protons), 8.37 (bs, 3H, N$H_3^+$), 10.34 (bs, 1H, CON*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 58.4, 110.8, 113.2, 121.0 (2C), 125.2 (2C), 125.9, 128.1 (2C), 131.1, 133.3, 133.8 (2C), 134.9 (2C), 137.4, 162.1, 190.6 ppm; MS (EI) *m/z*: 359.16 $[M]^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-oxo-2-(phenylamino)ethyl)-1*H*-pyrrole-2-carboxamide hydrochloride (11c).** Mp, 243-245 °C (methanol); yield, 68%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.17-1.18 (m, 2H, C$H_2$ cyclopropane), 2.03-2.05 (m, 1H, C*H*$NH_2$HCl), 2.70 (m, 1H, PhC*H*), 5.14 (s, 2H, C$H_2$), 6.13-6.15 (m, 1H, pyrrole proton), 6.80-6.82 (m, 1H, benzene proton), 7.04-7.08 (m, 2H, benzene and pyrrole protons), 7.29-7.32 (m, 2H, pyrrole protons), 7.56-7.58 (d, 2H, benzene protons), 7.44-7.46 (d, 2H, benzene protons), 7.61-7.62 (d, 2H, benzene protons), 8.37 (bs, 3H, N$H_3^+$), 10.30 (bs, 1H, CON*H*), 10.62 (bs, 1H, CON*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 37.3, 111.4, 113.8, 121.0 (2C), 121.4 (2C), 125.3 (2C), 126.1, 127.9, 128.7 (2C), 131.6, 134.1, 137.5, 138.1, 162.6, 168.3 ppm; MS (EI) *m/z*: 374.17 $[M]^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-(benzylamino)-2-oxoethyl)-1*H*-pyrrole-2-carboxamide hydrochloride (11d).** Mp, 154-156 °C (acetonitrile); yield, 69%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.15-1.18 (m, 2H, C$H_2$ cyclopropane), 2.04-2.05 (m, 1H, C*H*$NH_2$HCl), 2.70 (m, 1H, PhC*H*), 4.37 (s, 2H, C$H_2$), 5.04 (s, 2H, C$H_2$), 6.06 (s, 1H, pyrrole proton), 6.89 (s, 1H, pyrrole proton), 6.95 (s, 1H, pyrrole proton), 7.28-7.32 (m, 5H, benzene protons), 7.62-7.60 (d, 2H, benzene protons), 7.72-7.74 (d, 1H, benzene proton), 8.07-8.05 (d, 1H, benzene proton), 8.37 (bs, 3H, N$H_3^+$), 8.57 (bs, 1H, CON*H*), 10.34 (bs, 1H, CON*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 38.3, 43.4, 111.8, 113.3, 121.0 (2C), 125.2 (2C), 126.0, 126.7, 126.9 (2C), 128.5 (2C), 131.6, 134.3, 137.3, 137.9, 162.6, 166.8 ppm; MS (EI) *m/z*: 388.19 $[M]^+$.

***trans* benzyl 2-((4-(2-aminocyclopropyl)phenyl)carbamoyl)-1*H*-pyrrole-1-carboxylate hydrochloride (11e).** Mp, 192-194 °C (methanol); yield, 61%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.33-1.35 (m, 2H, C$H_2$ cyclopropane), 2.28 (m, 1H, C*H*$NH_2$HCl), 2.76-2.78 (m, 1H, PhC*H*), 5.57 (s, 2H, C$H_2$), 6.79 (s, 1H, pyrrole proton), 6.91 (s, 1H, pyrrole proton), 7.11-7.13 (d, 2H benzene protons), 7.39-7.43 (m, 4H, benzene and pyrrole protons), 7.52-7.54 (d, 2H, benzene protons), 7.64-7.66 (d, 2H, benzene protons), 8.31 (bs, 3H, N$H_3^+$), 10.01 (bs, 1H, CON*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 66.1, 109.0, 110.8, 121.0 (2C), 124.0, 124.7, 125.2 (2C) 127.1 (2C), 127.7, 128.6 (2C), 134.5, 136.1, 137.6, 150.3, 162.7 ppm; MS (EI) *m/z*: 375.18 $[M]^+$.

***trans* benzyl 3-((4-(2-aminocyclopropyl)phenyl)carbamoyl)-1*H*-pyrrole-1-carboxylate hydrochloride (11f).** Mp, 177-179 °C (acetonitrile/methanol); yield, 62%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.33-1.35 (m, 2H, C$H_2$ cyclopropane), 2.27 (m, 1H, C*H*$NH_2$HCl), 2.77-2.78 (m, 1H, PhC*H*), 5.46 (s, 2H, C$H_2$), 6.79 (s, 1H, pyrrole proton), 7.11-7.13 (d, 2H benzene protons), 7.41-7.47 (m, 4H, benzene and pyrrole protons), 7.52-7.54 (d, 2H, benzene protons), 7.64-7.66 (d, 2H, benzene protons), 8.33 (bs, 3H, N$H_3^+$), 9.91 (bs, 1H, CON*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 66.3, 102.4, 109.8, 115.0, 118.9, 121.0 (2C), 125.2 (2C), 127.0 (2C), 127.8, 128.7 (2C), 134.6, 136.4, 137.9, 150.1, 164.9 ppm; MS (EI) *m/z*: 375.16 $[M]^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1*H*-indole-2-carboxamide hydrochloride (12a).** Mp, >300 °C (methanol); yield,

59%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.13-1.15 (m, 2H, C$H_2$ cyclopropane), 2.00-2.03 (m, 1H, C$H$NH$_2$HCl), 2.70 (m, 1H, PhC$H$), 7.13-7.15 (m, 2H, indole protons), 7.33 (m, 1H, indole proton), 7.44.7.46 (d, 2H, benzene protons), 7.49-7.50 (m, 2H, indole protons), 7.52-7.56 (t, 2H, benzene protons), 8.47 (bs, 3H, N$H_3^+$), 9.34 (bs, 1H, CON$H$), 11.97 (bs, 1H, N$H$ indole) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 111.1, 114.8, 119.8, 120.7, 121.0 (2C), 121.7, 125.2 (2C), 131.3, 134.4, 137.4, 138.5, 139.8, 162.6 ppm; MS (EI) *m*/*z*: 291.14 [*M*]$^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-oxo-2-phenylethyl)-1*H*-indole-2-carboxamide hydrochloride (12b).** Mp, >300 °C (methanol); yield, 68%. $^1$H NMR (DMSO-d$_6$, 400 MHz, δ; ppm) δ 1.13-1.16 (m, 2H, C$H_2$ cyclopropane), 2.03-2.06 (m, 1H, C$H$NH$_2$HCl), 2.71 (m, 1H, PhC$H$), 6.18 (s, 2H, C$H_2$), 7.14-7.16 (m, 3H, indole protons), 7.26-7.37 (m, 4H, indole and benzene protons), 7.40-7.46 (m, 3H, indole and benzene protons), 7.62-7.60 (d, 2H, benzene protons) 7.72-7.74 (d, 1H, benzene proton), 8.07-8.05 (d, 1H, benzene proton), 8.37 (bs, 3H, N$H_3^+$), 10.63 (bs, 1H, CON$H$) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 59.8, 109.6, 115.2, 119.8, 120.7, 121.0 (2C), 121.7, 125.2 (2C), 126.7, 128.6 (2C), 133.9, 133.9 (2C), 134.3, 134.4, 137.3, 142.1, 145.3, 162.6, 190.9 ppm; MS (EI) *m*/*z*: 409.18 [*M*]$^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-oxo-2-(phenylamino)ethyl)-1*H*-indole-2-carboxamide hydrochloride (12c).** Mp, 255-258 °C (methanol); yield, 65%. $^1$H NMR (DMSO-d$_6$, 400 MHz, δ; ppm) δ 1.15-1.17 (m, 2H, C$H_2$ cyclopropane), 2.03-2.06 (m, 1H, C$H$NH$_2$HCl), 2.72 (m, 1H, PhC$H$), 5.44 (s, 2H, C$H_2$), 7.14-7.16 (m, 3H, indole protons), 7.26-7.37 (m, 4H, indole and benzene protons), 7.40-7.46 (m, 3H, indole and benzene protons), 7.62-7.60 (d, 2H, benzene protons) 7.72-7.74 (d, 1H, benzene proton), 8.07-8.05 (d, 1H, benzene proton), 8.37 (bs, 3H, N$H_3^+$), 10.38 (bs, 1H, CON$H$), 10.63 (bs, 1H, CON$H$) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 40.3, 109.4, 115.2, 119.8, 120.7, 121.1 (2C), 121.7 (2C), 121.9, 125.2 (2C), 126.7, 128.2, 128.9 (2C), 134.4, 137.3, 138.6, 142.1, 145.3, 162.7, 168.3 ppm; MS (EI) *m*/*z*: 424.18 [*M*]$^+$.

***trans* *N*-(4-(2-aminocyclopropyl)phenyl)-1-(2-(benzylamino)-2-oxoethyl)-1*H*-indole-2-carboxamide hydrochloride (12d).** Mp, 166-168 °C (acetonitrile); yield, 58%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.15-1.17 (m, 2H, C$H_2$ cyclopropane), 2.03-2.06 (m, 1H, C$H$NH$_2$HCl), 2.75 (m, 1H, PhC$H$), 4.47 (s, 2H, C$H_2$), 5.34 (s, 2H, C$H_2$), 7.12-7.13 (m, 2H, indole protons), 7.27-7.33 (m, 6H, indole and benzene protons), 7.53-7.56 (d, 1H, benzene proton), 7.60-7.62 (d, 2H, benzene protons), 7.65-7.67 (d, 1H, benzene proton), 7.72-7.74 (d, 1H, benzene proton), 8.07-8.05 (d, 1H, benzene proton), 8.37 (bs, 3H, N$H_3^+$), 9.09 (bs, 1H, CON$H$), 10.34 (bs, 1H, CON$H$) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 40.6, 43.3, 109.8, 115.2, 119.8, 120.7, 121.0 (2C), 121.9, 125.2 (2C), 126.7 (2C), 126.9 (2C), 128.6 (2C), 134.3, 137.3, 137.9, 142.1, 145.3, 162.6, 166.8 ppm; MS (EI) *m*/*z*: 438.21 [*M*]$^+$.

***trans* benzyl 2-((4-(2-aminocyclopropyl)phenyl)carbamoyl)-1*H*-indole-1-carboxylate hydrochloride (12e).** Mp, 202-204 °C (methanol); yield, 63%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.31-1.33 (m, 2H, C$H_2$ cyclopropane), 2.26 (m, 1H, C$H$NH$_2$HCl), 2.74-2.75 (m, 1H, PhC$H$), 5.44 (s, 2H, C$H_2$), 7.28-7.31 (m, 2H, benzene and indole protons), 7.31-7.43 (m, 4H benzene and indole protons), 7.47-7.52 (d, 2H, benzene protons), 7.59-7.61 (d, 2H, benzene protons), 7.69-7.71 (d, 2H, benzene protons), 7.94-7.96 (d, 1H, benzene proton), 8.14 (s, 1H, indole proton), 8.30 (bs, 3H, N$H_3^+$), 9.99 (bs, 1H, CON$H$) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 66.3, 114.4, 115.8, 119.9, 121.2 (2C), 123.9, 124.1, 125.6 (2C), 127.0 (2C), 127.5, 127.9, 128.9 (2C), 134.1, 136.0, 136.9, 137.9, 144.1, 150.0, 162.3 ppm; MS (EI) *m*/*z*: 425.17 [*M*]$^+$.

***trans* benzyl 3-((4-(2-aminocyclopropyl)phenyl)carbamoyl)-1*H*-indole-1-carboxylate (12f).** Mp, 225-228 °C (methanol); yield, 70%. $^1$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 1.15-1.18 (m, 2H, C$H_2$ cyclopropane), 2.23-2.28 (m, 1H, C$H$NH$_2$HCl), 2.78 (m, 1H, PhC$H$), 5.56 (s, 2H, C$H_2$), 7.14-712 (d, 2H, benzene protons), 7.38-7.48 (m, 5H benzene and indole protons), 7.59-7.61 (d, 2H, benzene protons), 7.69-7.71 (d, 2H, benzene protons), 8.15-8.17 (d, 1H, indole proton), 8.27-8.29 (d, 1H, indole proton), 8.34 (bs, 3H, N$H_3^+$), 8.86 (s, 1H, indole proton), 10.24 (bs, 1H, CON$H$) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 17.2, 25.6, 34.3, 66.3, 112.4, 115.8, 119.0, 121.2 (2C), 121.9, 124.1 (2C), 125.6 (2C), 126.7, 127.0 (2C), 127.9, 128.9 (2C), 134.1, 135.6, 136.3, 137.9, 150.6, 164.0 ppm; MS (EI) *m*/*z*: 425.17 [*M*]$^+$.

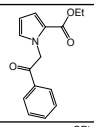
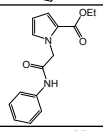
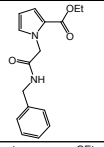
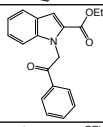
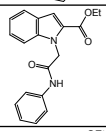
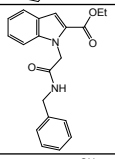
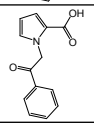
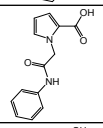
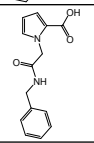
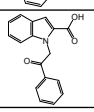
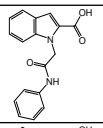
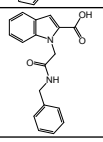
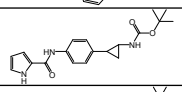
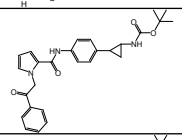
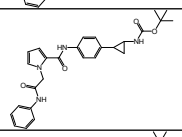
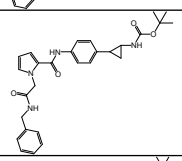
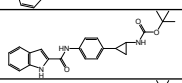
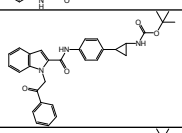
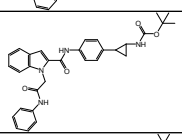
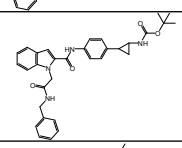
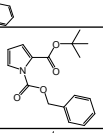
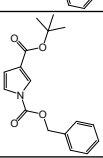
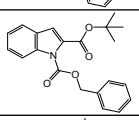
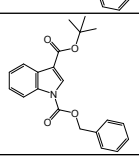
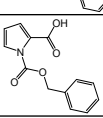
**General procedure for the synthesis of the *tert*-butyl 1*H*-pyrrole- and -1*H*-indole–2- and -3-carboxylates 20a,b and 21a,b. Example: *tert*-butyl 1*H*-pyrrole-3-carboxylate (20b).** A mixture of 1*H*-pyrrole-3-carboxylic acid (1.0 mmol, 0.11 g) and *N*,*N*-dimethylformamide di-*tert*-butyl acetal (3.96 mmol, 0.80 g, 0.95 mL) in anhydrous benzene (15 mL) was stirred at 80 ºC for 1 h. Afterwards, the solvent was evaporated and the residue obtained was purified by column chromatography ($SiO_2$ eluting with ethyl acetate/petroleum ether 1:9) to provide the pure **20b**. $^1$H NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 1.63 (s, 9H, ($CH_3$)$_3$), 6.78 (s, 1H, pyrrole proton), 7.12 (s, 1H, pyrrole proton), 7.46 (s, 1H, pyrrole proton), 11.3 (bs, 1H, N$H$ pyrrole) ppm; $^{13}$C NMR ($CDCl_3$, 100 MHz, δ; ppm) δ 28.4, 81.7, 108.1, 118.8, 119.3, 122.0, 164.3. MS (EI) *m*/*z*: 167.09 [M]$^+$.

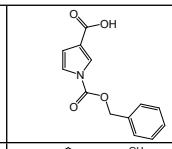
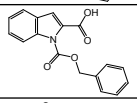
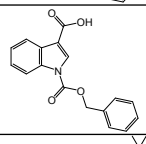
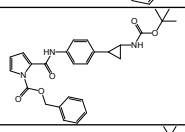
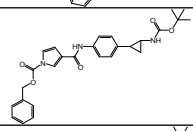
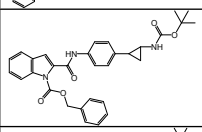
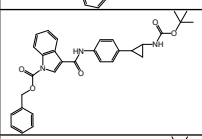
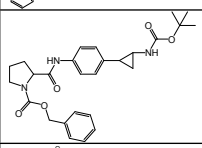
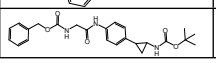
**General procedure for the synthesis of the 1-benzyl 2- and 3-*tert*-butyl 1*H*-pyrrole- and 1*H*-indole-1,2- and -1,3-dicarboxylates 22a,b and 23a,b. Example: 1-benzyl 3-*tert*-butyl 1*H*-pyrrole-1,3-dicarboxylate (22b).** *Tert*-butyl 1*H*-pyrrole-3-carboxylate **20b** (0.63 mmol, 0.14 g) in dry THF (2 mL) was added to a solution of NaH (0.94 mmol, 0.04 g) in dry THF (3 mL) at 0 ºC, and the mixture was stirred at room temperature for 30 min, followed by the addition of benzyl chloroformate (0.94 mmol, 0.13 mL), and the reaction was stirred for 1 h further. The reaction was then quenched with water (20 mL) and extracted with chloroform (3 × 30 mL). The organic layers were washed with saturated sodium chloride solution (2 × 15 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by chromatographic column on silica gel eluting with ethyl acetate/*n*-hexane 1:10 to afford the pure **22b**. $^1$H NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 1.63 (s, 9H, ($CH_3$)$_3$), 5.27 (s, 2H, C$H_2$), 6.48 (s, 1H, pyrrole proton), 7.02 (s, 1H, pyrrole proton), 7.33-7.36 (m, 3H, benzene protons), 7.54-7.56 (m, 2H, benzene protons), 8.03 (s, 1H, pyrrole proton) ppm; $^{13}$C NMR ($CDCl_3$, 100 MHz, δ; ppm) δ 28.2 (3C), 66.6, 81.3, 102.3, 109.4, 115.8, 118.0, 127.0 (2C), 127.8, 128.9 (2C), 136.1, 150.6, 164.6 ppm. MS (EI) *m*/*z*: 401.13 [*M*]$^+$.

**General procedure for the synthesis of the 1-(benzyloxycarbonyl)-1*H*-pyrrole- and -1*H*-indole-2- and -3-carboxylic acids 24a,b and 25a,b. Example: 1-(benzyloxycarbonyl)-1*H*-pyrrole-3-carboxylic acid (24b).** 1-Benzyl 3-*tert*-butyl 1*H*-pyrrole-1,3-dicarboxylate **22b** (0.64 mmol, 0.22 g) was added to a solution of trifluoroacetic acid (0.77 mmol, 0.05 mL) in dry dichloromethane (3 mL). The resulting mixture was stirred for 5 h at room temperature. The reaction was then quenched with water (30 mL) and extracted with ethyl acetate (3 × 30 mL).

The organic layers were washed with saturated sodium chloride solution (2 × 15 mL), dried with anhydrous sodium sulfate and concentrated in vacuo. The precipitated colorless solid was filtered, washed with petroleum ether and dried to afford the pure **24b**. $^{1}$H NMR (DMSO-$d_6$, 400 MHz, δ; ppm) δ 5.45 (s, 2H, C$H_2$), 6.78 (s, 1H, pyrrole proton), 7.12 (s, 1H, pyrrole proton), 7.43.7.46 (m, 3H, benzene protons), 7.64-7.66 (m, 2H, benzene protons), 8.33 (s, 1H, pyrrole proton), 12.09 (bs, 1H, COO*H*) ppm; $^{13}$C NMR (DMSO-$d_6$, 100 MHz, δ; ppm) δ 66.2, 103.6, 109.3, 115.3, 119.4, 126.8 (2C), 127.5, 128.0 (2C), 136.1, 150.6, 163.7 ppm; MS (EI) *m*/*z*: 245.07 $[M]^{+}$.

**Table S1.** Chemical and physical data for the intermediate compounds **14-19**, **22-29**.

| cpd | Structure | Mp., °C | Recryst. solvent[a] | yield, % |
|---|---|---|---|---|
| 14a |  | 92-94 | A | 72 |
| 14b |  | 130-132 | B | 67 |
| 14c |  | 128-130 | B | 64 |
| 15a |  | 122-124 | B | 71 |
| 15b |  | 213-215 | C | 65 |
| 15c |  | 155-157 | D | 62 |
| 16a |  | 196-198 | C | 86 |
| 16b |  | 171-173 | C | 82 |
| 16c |  | 124-126 | D | 85 |
| 17a |  | 235-237 | E | 83 |
| 17b |  | >250 | E | 74 |
| 17c |  | 190-192 | C | 78 |
| 18a |  | 50-52 | A | 67 |
| 18b |  | 93-95 | A | 58 |
| 18c |  | 97-99 | A | 63 |
| 18d |  | 118-120 | B | 60 |
| 19a |  | 123-125 | B | 69 |
| 19b |  | 127-129 | B | 63 |
| 19c |  | 132-134 | B | 57 |
| 19d |  | 165-167 | D | 62 |
| 22a |  | oil | - | 77 |
| 22b |  | oil | - | 69 |
| 23a |  | oil | - | 73 |
| 23b |  | oil | - | 70 |
| 24a |  | oil | - | 87 |

| | | | | |
|---|---|---|---|---|
| 24b |  | 135-137 | D | 90 |
| 25a |  | 38-40 | A | 85 |
| 25b |  | 170-172 | C | 88 |
| 26a |  | 184-186 | C | 65 |
| 26b |  | 223-225 | E | 68 |
| 27a |  | 201-203 | C | 55 |
| 27b |  | >250 | E | 72 |
| 28 |  | 100-102 | D | 70 |
| 29 |  | 143-145 | C | 63 |

[a]A: cyclohexane; B: cyclohexane/toluene; C: acetonitrile; D: toluene; E: acetonitrile/methanol.

**LSD1 enzyme inhibition assay**. The complex of human recombinant LSD1/CoREST protein was produced in *E. coli* as separate proteins and co-purified following previously reported procedures.[2,3] The experiments were performed in 96 well half area white plates (cat. 3693, Corning, Corning, NY) using a mono-methylated H3-K4 peptide containing 21 amino acids (custom synthesis done by Thermo Scientific) as substrate in 40 µL volume of 50 mM TRIS-HCl, pH 8.0 and 0.05 mg/ml BSA buffer. The peptide purity was >95% as checked by analytical high-pressure liquid chromatography and mass spectrometry. The demethylase activity was estimated under aerobic conditions and at room temperature by measuring the release of $H_2O_2$ produced during the catalytic process by the Amplex UltraRed detection system coupled with horseradish peroxidase (HRP). Briefly, 20 nM of LSD1/CoREST complex was incubated at room temperature for 15 min in the absence and/or the presence of various concentrations of the inhibitors, 50 µM Amplex UltraRed (Life Technologies) and 0.023 µM HRP (Sigma) in 50 mM Tris-HCl pH 8.0 and 0.05 mg/ml BSA. The inhibitors were tested twice in duplicates at each concentration. Tranylcypromine (Sigma) was used as control. After preincubation of the enzyme with the inhibitor, the reaction was initiated by addition of 4.5 µM of mono-methylated H3-K4 peptide. The conversion of the Amplex Ultra Red reagent to Amplex UltroxRed was monitored by fluorescence (excitation at 510 nm, emission at 595 nm) for 12 min and by using a microplate reader (Infinite 200, Tecan Group, Switzerland). Arbitrary units were used to measure the level of $H_2O_2$ produced in the absence and/or in the presence of inhibition. The maximum demethylase activity of LSD1/CoREST was obtained in the absence of inhibitors and corrected for background fluorescence in the absence of the substrate. The $IC_{50}$ values were calculated using GraphPad Prism version 4.0 (GraphPad Software, San Diego, CA).

**Crystallographic analysis**. The structure of the complex between LSD1/CoREST and **9** was obtained following the same protocols used for the structural analysis of the complex with **8**.[1] Crystallographic parameters (high resolution shell in brackets): resolution 2.9 Å; number of unique reflections 56002; completeness 99.9 % (99.7%); Rmerge 10.6% (85.5%); Rfactor 22.4% (23.9%).

**Anti-MAO assays.** Human recombinant MAO A and MAO B were expressed in *Pichia pastoris* and purified as published.[4] $IC_{50}$ values were measured by the horseradish peroxidase coupled-assay using a Cary-Eclipse spectrofluorimeter. Assays were performed using kynuramine (MAO A) and benzylamine (MAO B) as substrates in 50 mM Hepes/NaOH pH 7.5, 0.5% (v/v) reduced Triton X-100 after 15-minute incubation of the enzyme with the inhibitor.

**Gene modulation assays.** Human APL NB4 cells were grown in RPMI supplemented with 10% fetal bovine serum, 2 mM L-glutamine, and antibiotics and maintained in a humidified tissue culture incubator at 37 °C in 5% $CO_2$. Cells were treated at the biochemical $IC_{50}$ or with vehicle (DMSO). After 24 h the cells were collected for RNA analysis. Total RNA was purified using RNeasy Mini Kit (Qiagen, Valencia, CA), quantified and reverse transcribed. mRNA levels were measured by quantitative RT-PCR (Fast SYBR Green Master mix, Applied Biosystems Foster City, CA) using specific primers and normalized against TBP mRNA. Results are presented as fold induction relative to vehicle treated cells (DMSO). Primers used in this study were:
GFI-1b TCTGGCCTCATGCCCTTA - TCTGGCCTCATGCCCTTA;
ITGAM, AACCCCTGGTTCACCTCCT - CATGACATAAGGTCAAGGCTGT;
TBP, GCTGGCCCATAGTGATCTTT – CTTCACACGCCAAGAAACAGT

**Cell growth assays.** The antiproliferative effects of **8**, **11e,f** and **12e,f** on cell proliferation were evaluated against the AML MV4-11 and the APL NB4 cell lines using the CellTiter-Fluor Cell Viability Assay (Promega, Madison, WI, USA) according to the manufacturer's instructions. The cells were incubated for 48 hours with various inhibitor concentrations. An equivalent of the CellTiter-Fluor reagent was then added, the content was mixed and incubates for at least 90 min at 37 °C degree to obtain a stable signal. The fluorescence was recorded using an excitation wavelength of 360 nm and an emission at 535 nm $IC_{50}$ values were calculated using GraphPad software.

**References**

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