Electronic Supplementary Material (ESI) for Chemical Communications.

Amidation by Reactive Extrusion for the Synthesis of Active Pharmaceutical Ingredients Teriflunomide and Moclobemide

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General information:

All reagents were purchased from Sigma Aldrich, Iris Biotech GmbH, Fluorochem and Alfa Aesar and used without further purification. Reactive extrusion experiments were performed in a Xplore Pharma Melt parallel co-rotating twin screw extruder. The interchangeable barrel, including a recirculation channel, is made of stainless steel, with a volume of 2 mL. The extruder outlet can be set to continuous mode or batch mode. The screws are fully intermeshing, 10 cm long and made of stainless steel, with a conical shape.

η is defined as the ratio of added liquid volume to the total mass of reagents. It is expressed in mL/g.

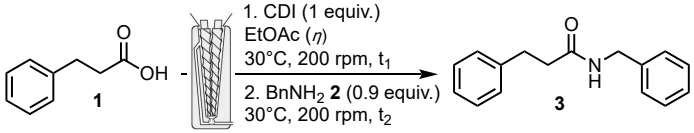
HPLC conversion was measured on an Agilent technologies 1220 Infinity LC using a Chromolith® high resolution RP-18^{e} 50-4.6 mm column and a linear gradient of 0 to 100% CH_3CN/0.1% TFA in H_2O/0.1% TFA over 3 min, detection at 214 nm. Flow rate : 3 mL/min. Conversion of the starting carboxylic acid to the expected amide was evaluated by measuring the surface areas of the peaks of both compounds and calculating the ratio area of the peak of amide/ total of areas.

NMR analyses were performed at the "Plateforme Technologique Laboratoire de Mesures Physiques" (IBMM, Université de Montpellier). ^{1}H NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm and DMSO-d_6 at 2.50 ppm). Data are reported as s = singlet, d = doublet, t = triplet, qd = quadruplet, qt = quintuplet, m = multiplet; coupling constant in Hz; integration. ^{13}C NMR spectra were recorded on a Bruker Avance III HD 101 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm and DMSO-d_6 at 39.52 ppm). Mass spectra were obtained by LC-MS with ESI using a Water Alliance 2695 as LC, coupled to a Waters ZQ spectrometer with electrospray source, a simple quadrupole analyzer and a UV Waters 2489 detector. HRMS analyses were performed on UPLC Acquity H-Class from Waters hyphenated to a Q-Tof mass spectrometer (Synapt G2-S from Waters) with a dual ESI source.

CDI stands for 1,1'-carbonyldiimidazole, EDC·HCl for *N*-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride, Oxyma for ethyl (hydroxyimino)cyanoacetate, COMU for 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholino)] uronium hexafluorophosphate, DIPEA for Diisopropyl ethylamine.

Procedures

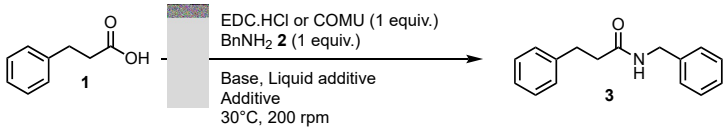
General procedure for the CDI-promoted amidation in the extruder



A mixture of phenyl-3-propionic acid (766 mg, 5.10 mmol, 1 equiv.), 1,1'-carbonyldiimidazole (827 mg, 5.10 mmol, 1 equiv.), EtOAc (quantities, see Table 1 main text) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After t_1 min of recirculation (see Table 1 main text), benzyl amine (492 mg, 4.59 mmol, 0.9 equiv.) was added and the recirculation was pursued for t_2 min (see Table 1 main text). Then the manual fold gate was turned to extrusion mode and a yellow gel was recovered and analyzed by HPLC. The paste was then dissolved in EtOAc (50 mL), washed with 1N HCl, 1N NaOH and brine. The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure to afford *N*-

Benzyl-3-phenylpropanamide **3** as a pale yellow solid (Table 1 main text, entry 6: m = 989 mg, 81% yield).

General procedure for the EDC.HCl or COMU-promoted amidation in the extruder



The loading of the reaction mixture was maintained to 2 g in each experiment. Quantities of starting material, reactants and additives (see Table 2 main text) were adjusted to reach this total masse of 2 g.

As a typical example, reaction from Table 2 main text, entry 12 is described. A mixture of phenyl-3-propionic acid **1** (384 mg, 2.56 mmol, 1 equiv.), benzyl amine **2** (274 mg, 2.56 mmol, 1 equiv.) COMU (1.10 g, 2.56 mmol, 1 equiv.), DIPEA (331 mg, 2.56 mmol, 1 equiv.), CH_3CN (1.2 mL) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After a 10 min mixing, the manual fold gate was turned to extrusion mode and a red gel was recovered and analyzed by HPLC. The paste was then dissolved in EtOAc (50 mL), washed with 1N HCl, 1N KOH and brine. The organic phase was dried over MgSO4, filtered and concentrated under reduced pressure to afford the *N*-Benzyl-3-phenylpropanamide **3** as a pale yellow solid (m = 490 mg, 80% yield).

2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (teriflunomide):

CDI method: A mixture of 5-methylisoxazole-4-carboxylic acid (619 mg, 4.87 mmol, 1.1 equiv.), 1,1'-carbonyldiimidazole (753 mg, 4.65 mmol, 1.05 equiv.), CH_3CN (1.2 mL) was slowly poured into the extruder that was heated at 50°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After 10 min of recirculation, 4-(trifluoromethyl) aniline (713 mg, 4.42 mmol, 1 equiv.) was added and the recirculation was pursued for 20 min. Then the manual fold gate was turned to extrusion mode and a yellow gel with a solid suspension was recovered then transferred into a round bottom flask, pH was adjusted to 1 with concentrated hydrochloric acid, and stirred during 24 hours. The suspension was then filtered and dried under vacuum over P_2O_5 to obtain a white solid (915 mg, 77%).

EDC.HCl/Oxyma method: A mixture of 5-methylisoxazole-4-carboxylic acid (401 mg, 3.15 mmol, 1 equiv.), 4-(trifluoromethyl) aniline (508 mg, 3.15 mmol, 1 equiv.), EDC.HCl (605 mg, 3.15 mmol, 1 equiv.), Oxyma (448 mg, 3.15 mmol, 1 equiv.), DIPEA (122 mg, 0.947 mmol, 0.3 equiv.) and CH_3CN (1.2 mL) was slowly poured into the extruder that was heated at 50°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After 1 h of recirculation, the manual fold gate was turned to extrusion mode and a red gel was recovered then transferred into a round bottom flask, pH was adjusted to 1 with concentrated hydrochloric acid, and stirred during 24 hours. The suspension was then filtered, dissolved in a minimum amount of CH_3CN, precipitated in water, filtered and dried under vacuum over P_2O_5 to obtain a white solid (637 mg, 75 %).

COMU method: A mixture of 5-methylisoxazole-4-carboxylic acid (294 mg, 2.31 mmol, 1 equiv.), 4-(trifluoromethyl) aniline (373 mg, 2.31 mmol, 1 equiv.), COMU (1.09 g, 2.54 mmol, 1.1 equiv.), DIPEA (329 mg, 2.54 mmol, 1.1 equiv.) and CH_3CN (1.2 mL) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After 2 h of recirculation, the manual fold gate was turned to extrusion mode and a purple gel was recovered then transferred into a round bottom flask, pH was adjusted to 1 with concentrated hydrochloric acid, and stirred during 24 hours. The suspension was then filtered, dissolved in a minimum amount of CH_3CN, precipitated in water, filtered and dried under vacuum over P_2O_5 to obtain a white solid (497 mg, 80%).

4-Chloro-*N*-[2-(4-morpholinyl)ethyl]benzamide (moclobemide):

CDI method: A mixture of 4-chlorobenzoic acid (760 mg, 4.85 mmol, 1.1 equiv.), 1,1'-carbonyldiimidazole (751 mg, 4.63 mmol, 1.05 equiv.), EtOAc (1.2 mL) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After 10 min of recirculation, 4-aminoethyl morpholine (574 mg, 4.41 mmol, 1 equiv.) was added and the recirculation was pursued for 20 min. Then the manual fold gate was turned to extrusion mode and a yellow gel with a solid suspension was recovered, dissolved in water and the pH was adjusted to 10 with concentrated potassium hydroxide. The aqueous phase was extracted thrice with EtOAc. The collected organic phases were dried over $MgSO_4$, evaporated to the point of crystallization and filtered. The desired product was recovered (805mg, 68%) as colorless crystals by repeated crystallization from the mother liquor.

EDC.HCl/Oxyma method: A mixture of 4-chlorobenzoic acid (1.48 g, 9.45 mmol, 1 equiv.), 4-aminoethyl morpholine (1.23 g, 9.45 mmol, 1 equiv.), EDC.HCl (1.81 g, 9.45 mmol, 1 equiv.), Oxyma (1.34 g, 9.45 mmol, 1 equiv.), K_2CO_3 (392 mg, 2.83 mmol, 0.3 equiv.) and CH_3CN (3.6 mL) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the extrusion mode. A purple gel with white solid suspension, recovered over the course of 1 min, was then transferred into a round bottom flask. Residual CH_3CN was evaporated, pH was adjusted to 4 with 1N hydrochloric acid, then to 10 with 1N potassium hydroxide. The aqueous phase was extracted thrice with EtOAc. The collected organic phases were dried over $MgSO_4$. The desired product was recovered (2.2 g, 87%) as colorless crystals by repeated crystallization from the mother liquor.
The same procedure performed on 4-chlorobenzoic acid (7.4 g, 47.25 mmol, 1 equiv.), 4-aminoethyl morpholine (6.15 g, 47.25 mmol, 1 equiv.), afforded 11 g (87%) of the expected product.

COMU method: A mixture of 4-chlorobenzoic acid (363 mg, 2.32 mmol, 1 equiv.), 4-aminoethyl morpholine (302 mg, 2.32 mmol, 1 equiv.), COMU (1.09 g, 2.55 mmol, 1 equiv.), DIPEA (329 mg, 2.55 mmol, 0.3 equiv.) and CH_3CN (1.2 mL) was slowly poured into the extruder that was heated at 30°C, the screw rotation speed being set at 200 rpm and the manual fold gate turned towards the recirculation pipe. After 10 min of recirculation, the manual fold gate was turned to extrusion mode and a purple gel was recovered then transferred into a round bottom flask. Residual CH_3CN was evaporated, pH was adjusted to 10 with 1N potassium hydroxide. The aqueous phase was extracted thrice with EtOAc. The

collected organic phases were dried over $MgSO_4$. The desired product was recovered (587 mg, 95%) as colorless crystals by repeated crystallization from the mother liquor.

Analytical data

N-Benzyl-3-phenylpropanamide[1] [10264-10-5]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47–7.07 (m, 10H), 5.60 (br s, 1H), 4.40 (br d, *J* = 2.0 Hz, 2H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.52 (t, J = 6.7 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 140.8, 138.1, 128.7, 128.6, 128.4, 127.8, 127.5, 126.3, 43.7, 38.6, 31.8.
HRMS calculated for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1383; found: 240.1387.

2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (teriflunomide)[2] [163451-81-8]

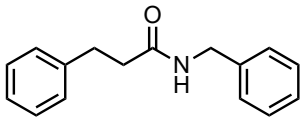
^{1}H NMR (400 MHz, DMSO): δ 10.98 (br s, 1H), 7.0-8.15 (br s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 2.24 (s, 3H).
^{13}C NMR (101 MHz, DMSO): δ 187.6, 166.9, 142.4, 126.34 $J(^{19}F,^{13}C)$ = 3 Hz, 124.9 $J(^{19}F,^{13}C)$ = 270 Hz, 123.9 $J(^{19}F,^{13}C)$ = 32 Hz, 121.1, 119.6, 80.8 ,24.2.
^{19}F NMR (376 MHz, DMSO): δ 60.33
HRMS calculated for $C_{12}H_{10}F_3N_2O_2$ $[M+H]^+$: 271.0689; found: 271.0690.

4-Chloro-*N*-[2-(4-morpholinyl)ethyl]benzamide (moclobemide) [71320-77-9]

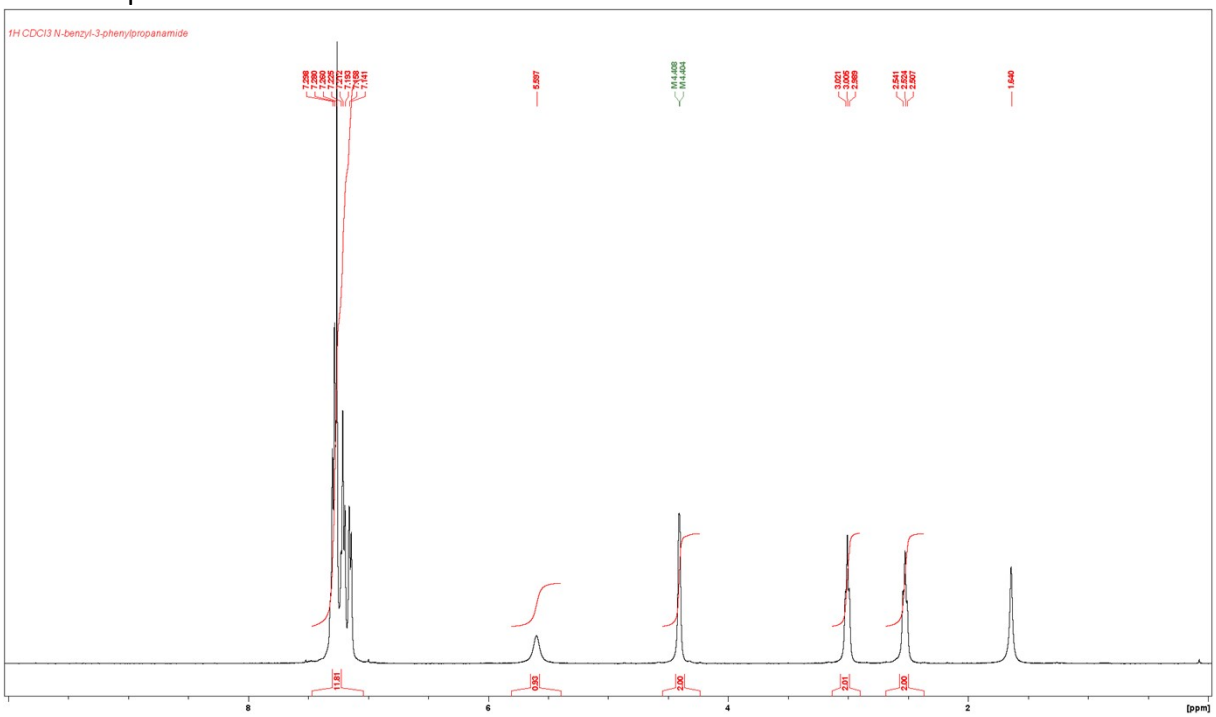
^{1}H NMR (400 MHz, DMSO) δ (ppm): 8.49 (br t, J = 5.4 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7, 2H), 3.56 (t, *J* = 4.6 Hz, 4H), 3.37 (q, *J* = 6.1 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 4.3 Hz, 4H).
^{13}C NMR (101 MHz, DMSO) δ (ppm): 165.0, 135.9, 133.2, 129.0, 128.3, 66.1, 57.3, 53.3, 36.6.
HRMS calculated for $C_{13}H_{18}ClN_2O_2$ $[M+H]^+$: 269.1051; found: 269.1061.

NMR spectra

N-Benzyl-3-phenylpropanamide



^{1}H NMR spectrum



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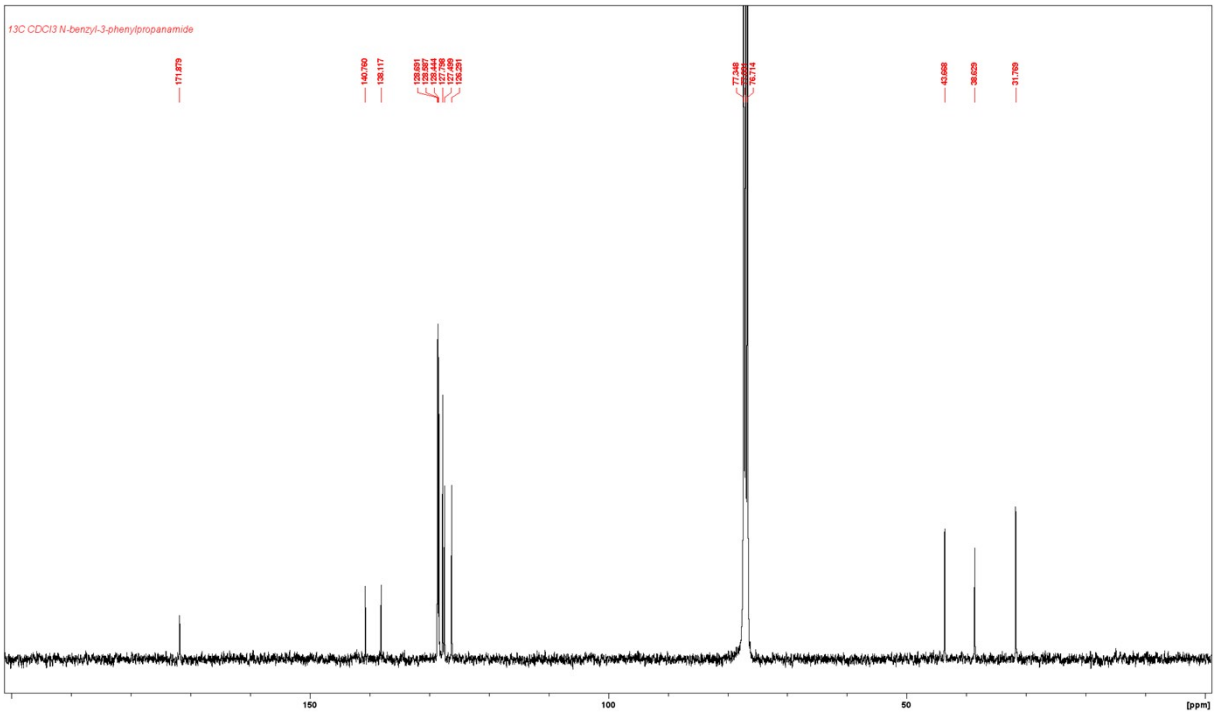
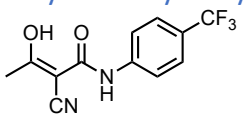
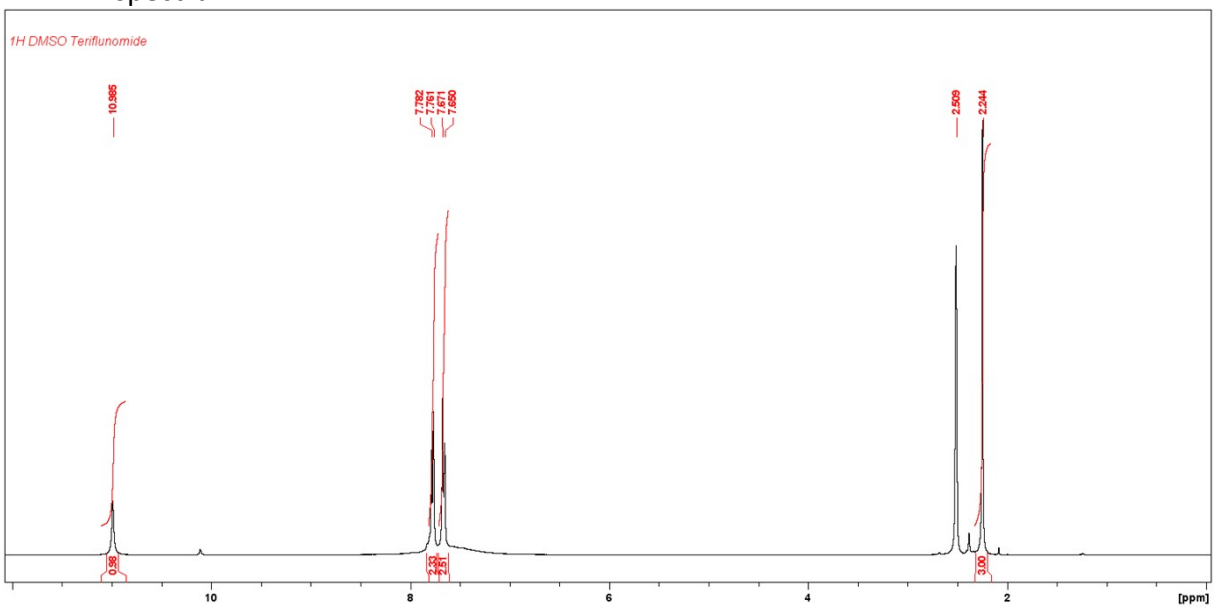


2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (teriflunomide):



^{1}H NMR spectrum



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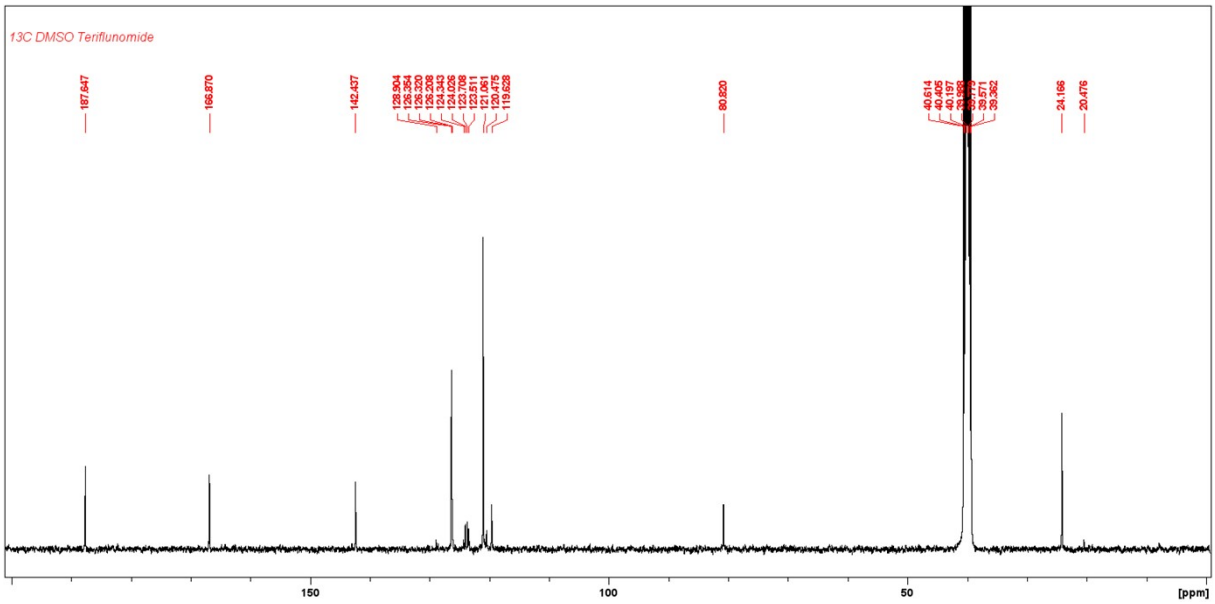
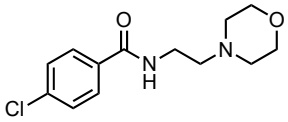
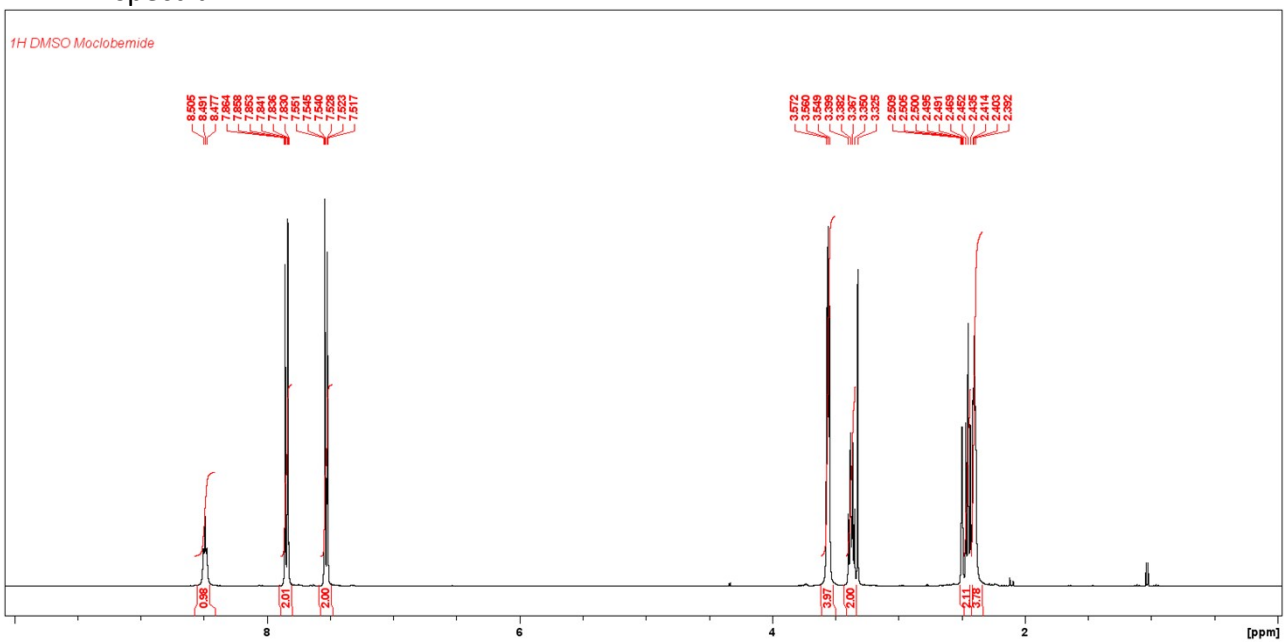


4-Chloro-*N*-[2-(4-morpholinyl)ethyl]benzamide (moclobemide):



^{1}H NMR spectrum



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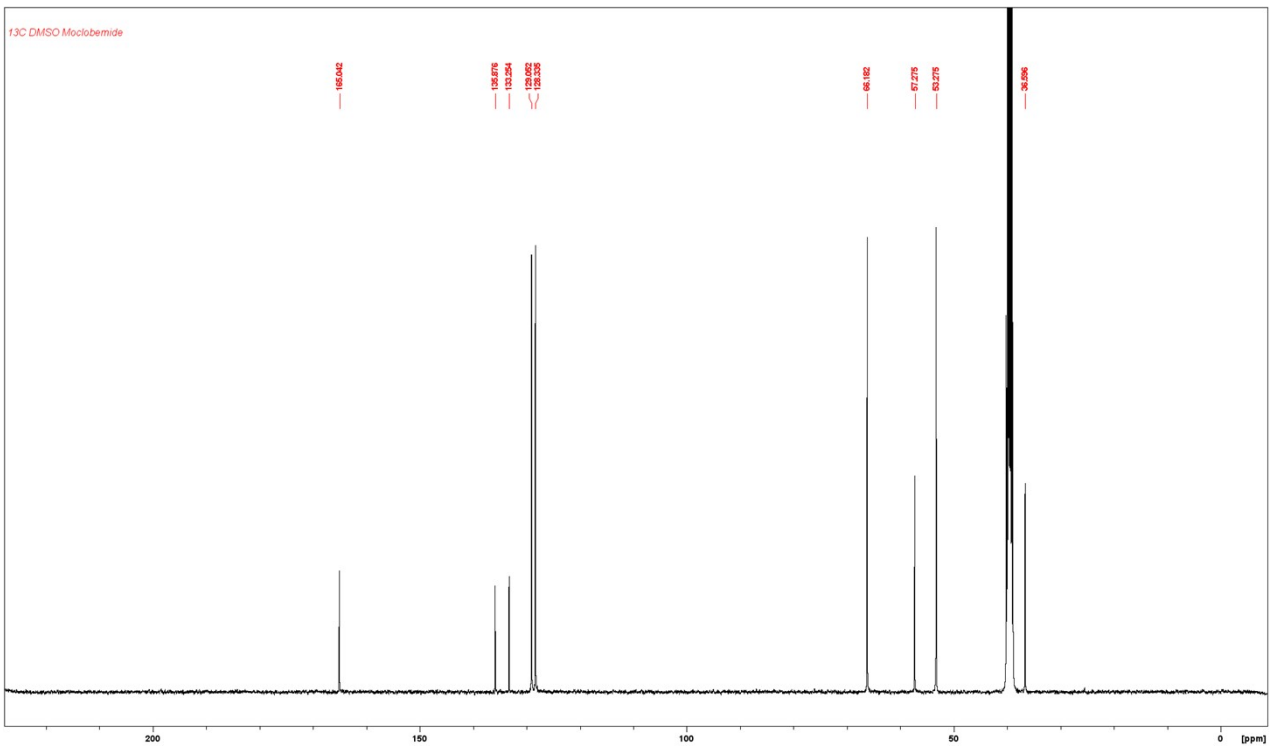

References :

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2. M. Kurz, D. Gretzke, R. Hoerlein, S. Turpault, J. Atzrodt, V. Derdaur *Journal of Labelled Compounds and Radiopharmaceuticals* **2021**, *64*, 82-88