Supporting Information
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SUPPORTING INFORMATION

Titanium(IV)isopropoxide as an efficient catalyst for direct amidation of non-activated carboxylic acids

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Table of contents

1. General experimental information ............................................. 3
2. Instrumentation ................................................................................... 3
3. Material .................................................................................................. 3
4. General experimental procedure for the titanium(IV)isopropoxide catalyzed amide formation ................................................ 3
5. Compound characterisation ............................................................... 4
6. $^1$H-NMR and $^{13}$C-NMR spectra ..................................................... 10
7. HPLC chromatograms ......................................................................... 39
1. General
Catalytic amide formation was performed in oven dried microwave tubes 2-5 ml from Biotage, with a Teflon-coated magnetic stirring bar. The tubes were fitted with a cap containing a septum and the reactions were run under nitrogen atmosphere. Plugs and flash chromatography were performed using silica gel (40 – 60 mesh) purchased from Acros Organics. All work up and purification were carried out with reagent grade solvent under ambient atmosphere.

2. Instrumentation
Characterizations were made by $^1$H and $^{13}$C NMR spectroscopy. NMR spectra were recorded at 400 MHz ($^1$H) and 100 MHz ($^{13}$C), and were referenced internally with CDCl$_3$ ($\delta$H 7.26, $\delta$C 77.16 ppm). HPLC was conducted on a chiral AD-column using a mixture of isohexane and 2-propanol as eluent.

3. Material
Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. THF was purchased from Fischer Scientific, and dispersed from a solvent drying system. Ti(OiPr)$_4$ was purchased from Aldrich and used as received. Molecular sieves 4Å were activated by flame drying under vacuum.

4. General procedure for the titanium(IV) isopropoxide catalyzed amide formation.
Dry THF (2.5 ml) was added to the carboxylic acid (1.2 mmol) and molecular sieves 4Å (0.5 g) under nitrogen atmosphere and the mixture was heated under stirring to 40 °C. The titanium(IV) isopropoxide (10 – 20 mol%) was added, the temperature was increased to 70 °C and the amine (1.0 mmol) was added dropwise. The reaction was stirred at the same temperature for 24 – 48 h and then cooled to r.t. The mixture was run through a plug of silica (4 x 4 cm) eluted with 80-100 ml EtOAc:Et$_3$N (200:1 ). The solvent was removed under reduced pressure affording analytically pure product unless otherwise noted. All amide products presented in Table 3 are previously known and reported compounds.
5. Compound characterisation

\textit{N-benzyl-2-phenylacetamide (3a)}
White solid, 91% yield. $^1$H-NMR (CDCl$_3$) δ 7.22-7.38 (m, 8 H), δ 7.15-7.20 (m, 2 H), δ 5.66 (bs, 1 H), δ 4.42 (d, $J$ = 5.85 Hz, 2 H), δ 3.64 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 170.99, 138.27, 134.92, 129.57, 129.18, 128.78, 127.61, 127.55, 127.52, 43.96, 43.71.

\textit{N-benzyl-2-(naphthalen-1-yl)acetamide (3b)}
White solid, 79% yield. $^1$H-NMR (CDCl$_3$) δ 7.99-8.04 (m, 1 H), δ 7.86-7.91 (m, 1 H), δ 7.79-7.84 (m, 1 H), δ 7.50-7.59 (m, 2 H), δ 7.38-7.47 (m, 2 H), δ 7.16-7.23 (m, 3 H), δ 6.98-7.06 (m, 2 H), δ 5.74 (bs, 1 H), δ 4.35 (d, $J$ = 5.92 Hz, 2 H), δ 4.08 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 170.93, 138.18, 134.08, 132.16, 131.13, 128.90, 128.62, 128.57, 128.46, 127.33, 126.88, 126.30, 125.72, 123.98, 43.45, 41.91.

\textit{N-benzyl-2-(4-bromophenyl)acetamide (3c)}
White solid, 85% yield; $^1$H-NMR (CDCl$_3$) δ 7.43-7.49 (m, 2 H), δ 7.24-7.35 (m, 3 H), δ 7.12-7.22 (m, 4 H), δ 5.73 (bs, 1 H), δ 4.41 (d, $J$ = 5.84 Hz, 2 H), δ 3.55 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 170.23, 138.11, 133.88, 132.22, 131.22, 128.86, 127.76, 127.70, 121.54, 43.87, 43.23.

\textit{N-benzyl-2-phenoxyacetamide (3d)}
Purified by column chromatography (pentane:ethyl acetate, 2:1) to give 3d as a white solid in 99% yield. $^1$H-NMR (CDCl$_3$) δ 7.26-7.38 (m, 7 H), δ 7.03 (tt, $J$ = 7.26, 1.07 Hz), δ 6.86-6.98 (m, 3 H), δ 4.53-4.58 (m, 4 H). $^{13}$C-NMR (CDCl$_3$) δ 168.28, 157.25, 137.87, 129.90, 128.86, 127.81, 127.73, 122.26, 114.80, 67.46, 43.07.

\textit{N-benzyl-2-(naphthalen-2-yloxy)acetamide (3e)}
Offwhite crystalline solid, 99% yield. $^1$H-NMR (CDCl$_3$) δ 7.72-7.81 (m, 3 H), δ 7.45-7.51 (m, 1 H), δ 7.36-7.41 (m, 1 H), δ 7.26-7.35 (m, 5 H), δ 7.14-7.19 (m, 2 H), δ 6.93 (bs, 1 H), δ 4.69 (s, 2 H) δ 4.57 (d, $J$ = 5.92 Hz, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 168.17, 155.10, 137.86, 134.39, 130.05, 129.63, 128.88, 127.85, 127.79, 127.76, 127.12, 126.91, 124.53, 118.19, 107.80, 67.55, 43.14.
\textit{N}-benzyl-2-(phenylthio)acetamide (3f)

Purified by column chromatography (pentane:ethyl acetate, 1:2) to give 3f as a white crystalline solid in 94\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.19-7.32 (m, 8 H), $\delta$ 7.02-7.17 (m, 3 H), $\delta$ 4.43 (d, $J = 5.87$ Hz, 2 H), $\delta$ 3.68 (s, 2 H). $^{13}\text{C-NMR}$ (CDCl$_3$) $\delta$ 167.77, 137.79, 134.60, 129.41, 128.73, 128.31, 127.59, 127.56, 126.79, 43.83, 37.40.

\textit{N}-benzyl-2-(thiophen-3-yl)acetamide (3g)

Purified by column chromatography (pentane:ethyl acetate, 2:1) to give 3g as a white solid in 88\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.23-7.36 (m, 4 H), $\delta$ 7.17-7.22 (m, 2 H), $\delta$ 7.13-7.16 (m, 1 H), $\delta$ 7.01 (dd, $J = 4.90$, 1.10 Hz, 1 H), $\delta$ 5.81 (bs, 1 H), $\delta$ 4.42 (d, $J = 5.79$ Hz, 2 H), $\delta$ 3.65 (s, 2 H). $^{13}\text{C-NMR}$ (CDCl$_3$) $\delta$ 170.51, 138.25, 134.88, 128.82, 128.58, 127.64, 127.60, 126.94, 123.62, 43.72, 38.28.

\textit{N}-benzylfuran-2-carboxamide (3h)

Pale yellow solid, 72\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.39-7.41 (m, 1 H), $\delta$ 7.25-7.38 (m, 5 H), $\delta$ 7.13 (dd, $J = 3.47$, 0.87 Hz, 1 H), $\delta$ 6.78 (bs, 1 H), $\delta$ 6.48 (dd, $J = 3.57$, 1.83 Hz, 1 H), $\delta$ 4.60 (d, $J = 5.98$ Hz, 2 H). $^{13}\text{C-NMR}$ (CDCl$_3$) $\delta$ 158.37, 148.00, 143.98, 138.14, 128.81, 127.96, 127.66, 114.43, 112.22, 43.21.

\textit{N}-benzylbenzamide (3i)

White solid, 82\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.80-7.78 (m, 2 H), $\delta$ 7.51-7.29 (m, 8 H), $\delta$ 6.48 (bs, 1 H), $\delta$ 4.65 (d, $J = 5.68$ Hz, 2 H). $^{13}\text{C-NMR}$ (CDCl$_3$) $\delta$ 167.52, 138.31, 134.53, 131.70, 128.94, 128.74, 128.07, 127.78, 127.10, 44.31.

\textit{N}-benzylpentanamide (3j)

Purified by silica gel plug (pentane:ethyl acetate, 1:2) to give 3j as a pale yellow crystalline solid in 81\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.22-7.36 (m, 5 H), $\delta$ 5.97 (bs, 1 H), $\delta$ 4.41 (d, $J = 5.77$ Hz, 2 H), $\delta$ 2.20 (t, $J = 7.52$ Hz, 2 H), $\delta$ 1.62 (m, 2 H), $\delta$ 1.34 (m, 2 H), $\delta$ 0.91 (t, $J = 7.26$ Hz, 3 H). $^{13}\text{C-NMR}$ (CDCl$_3$) $\delta$ 173.17, 138.58, 128.76, 127.86, 127.52, 43.62, 36.57, 27.94, 22.52, 13.88.

\textit{N}-benzylcyclohexanecarboxamide (3k)

Beige solid, 80\% yield. $^1\text{H-NMR}$ (CDCl$_3$) $\delta$ 7.36-7.30 (m, 2 H), $\delta$ 7.30-7.24 (m, 3 H), $\delta$ 5.69 (bs, 1 H), $\delta$ 4.44 (d, $J = 5.56$ Hz, 2 H), $\delta$ 2.11 (tt, $J = 3.49$, 11.75 Hz, 1 H), $\delta$ 1.93-1.86 (m, 2
H), δ 1.83-1.76 (m, 2 H), δ 1.70-1.64 (m, 1 H), δ 1.52-1.41 (m, 1 H), δ 1.33-1.87 (m, 3 H).

13C-NMR (CDCl3) δ 176.02, 138.70, 128.84, 127.87, 127.59, 45.73, 43.53, 29.88, 25.88.

**N-benzyl-1-ademantanecarboxamide (3l)**

General purification method was followed by extraction with Na2CO3(aq) and 2 x EtOAC/2 x DCM. White solid, 65% yield. 1H-NMR (CDCl3) δ 7.36-7.30 (m, 2 H), δ 7.30-7.23 (m, 2 H), δ 7.16-7.10 (m, 4 H), δ 5.85 (bs, 1 H) δ 4.44 (d, J = 5.55 Hz, 2 H) δ 2.05 (m, 3 H), δ 1.89 (m, 6 H), δ 1.80-1.66 (m, 6 H). 13C-NMR (CDCl3) δ 177.93, 138.85, 128.85, 127.81, 127.55, 43.50, 40.82, 39.48, 36.67, 28.92.

**N-benzylcinnamamide (3m)**

Purified by column chromatography (pentane:ethyl acetate, 1:2) to give 3m as a white solid in 61% yield. 1H-NMR (CDCl3) δ 7.25-7.20 (m, 2 H), δ 7.19-7.13 (m, 2 H), δ 6.73 (bs, 1 H) δ 4.52 (d, J = 5.79 Hz, 2 H), δ 4.50 (d, J = 5.75 Hz, 2 H). 13C-NMR (CDCl3) δ 165.88, 141.59, 138.34, 134.93, 129.87, 129.97, 128.91, 128.09, 127.95, 127.75, 120.56, 44.04.

**N-benzyl-2,2-dichloroacetamide (3n)**

White solid, 75% yield; 1H-NMR (CDCl3) δ 7.21-7.13 (m, 5 H), δ 6.46 (bs, 1 H) δ 5.97 (bs, 1 H), δ 5.79 (bs, 1 H). 13C-NMR (CDCl3) δ 164.22, 136.32, 129.15, 128.12, 127.82, 66.52, 44.37.

**N-benzyl-2,2,2-trifluoroacetamide (3o)**

White solid, 64% yield. 1H-NMR (CDCl3) δ 7.21-7.13 (m, 5 H), δ 6.67 (bs, J = 14.96 Hz, 1 H) δ 4.55 (d, J = 5.80 Hz, 2 H). 13C-NMR (CDCl3) δ 157.3 (q, J = 37.08 Hz), 135.97, 129.19, 128.47, 128.11, 116.02 (q, J = 287.08 Hz), 44.07.

tert-Butyl 2-(benzylamino)-2-oxoethylcarbamate (3p)

White crystalline solid, 93% yield. 1H-NMR (DMSO-d6) δ 8.26 (bs, 1 H), δ 7.18-7.36 (m, 5 H), δ 6.97 (bs, 1 H), δ 4.29 (d, J = 6.01 Hz, 2 H), δ 3.58 (d, J = 6.20 Hz, 2 H), δ 1.39 (s, 9 H). 13C-NMR (DMSO-d6) δ 169.40, 155.83, 139.42, 128.18, 127.15, 126.70, 78.04, 43.39, 41.99, 28.19.

(S)-N-benzyl-2-(4-isobutylphenyl)propanamide (3q)


Pale yellow solid, 80% yield. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.34-7.16 (m, 5 H), \(\delta\) 7.16-7.04 (m, 4 H), \(\delta\) 5.65 (bs, 1 H), \(\delta\) 4.39 (d, \(J = 5.60\) Hz, 2 H) \(\delta\) 3.58 (q, \(J = 7.12\) Hz, 1 H), \(\delta\) 2.46 (d, \(J = 7.12\) Hz, 2 H) \(\delta\) 1.85 (h, \(J = 6.61\) Hz, 1 H) \(\delta\) 1.60-1.48 (m, 3 H), \(\delta\) 0.90 (d, \(J = 6.61\) Hz, 6 H). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 174.95, 140.95, 138.60, 138.51, 129.81, 129.52, 128.72, 127.51, 127.45, 46.96, 45.14, 43.66, 30.31, 22.50, 18.56. Chiral HPLC IA column, 90:10 isohexane:2-PrOH, flow 0.5 ml/min, 30 °C, retention time 15.272 min (Retention times for racemate = 15.247 and 22.527 min)

((S)-\textit{tert}-Butyl 2-(benzylcarbamoyl)pyrrolidine-1-carboxylate (3r))

Purified by column chromatography (1:1 ethyl acetate:methanol) to yield the product as a white solid in 78% yield. \(^1\)H NMR (d-4 MeOD) \(\delta\) 8.45-8.36 (m, 1 H), \(\delta\) 7.30-7.23 (m, 5 H), \(\delta\) 4.46-4.42 (m, 1 H), \(\delta\) 4.34-4.16 (m, 2 H), \(\delta\) 3.54-3.49 (m, 1 H), \(\delta\) 4.43-3.37 (m, 1 H), \(\delta\) 2.23-2.21 (m, 1 H), \(\delta\) 1.97-1.83 (m, 3 H), \(\delta\) 1.33 (s, 9 H). \(^{13}\)C-NMR (d-4 MeOD) \(\delta\) 175.57, 156.05, 140.07, 129.49, 128.88, 128.27, 81.45, 61.99, 47.90, 44.05, 32.54 28.56, 24.62. Chiral HPLC AD column, 90:10 isohexane:2-PrOH, flow 0.5 ml/min, 30 °C, retention time 30.702 min (Retention times for racemate = 21.549 and 30.288 min)

((S)-\textit{tert}-Butyl 1-(benzylamino)-1-oxopropan-2-ylcarbamate (3s))

Purified by column chromatography (1:1 ethyl acetate:methanol) to yield the product as a white solid in 78% yield. Spectra obtained as a mixture of rotamers with major rotamer reported as: \(^1\)H NMR (d-4 MeOD) \(\delta\) 7.32-7.22 (m, 5 H), \(\delta\) 4.43 (d, \(J = 15.00\) Hz, 1 H) \(\delta\) 4.33 (d, \(J = 15.00\) Hz, 1 H), \(\delta\) 4.08 (m, 1 H), \(\delta\) 1.43 (bs, 9 H), \(\delta\) 1.31 (d, \(J = 7.20\) Hz, 3 H). \(^{13}\)C-NMR (d-4 MeOD) \(\delta\) 175.94, 157.59, 139.86, 129.47, 128.34, 128.13, 80.59, 51.83, 43.92, 28.69, 18.42. Chiral HPLC AD column, 90:10 isohexane:2-PrOH, flow 0.5 ml/min, 30 °C, retention time 19.882 min (Retention times for racemate = 19.889 and 23.475 min)

((R)-2-Phenyl-N-(1-phenylethyl)acetamide (3t))

Beige solid, 81% yield. \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 7.13-7.4 (m, 10 H), \(\delta\) 5.59 (bs, 1 H), \(\delta\) 5.12 (quin, \(J = 7.21\) Hz, 1 H), \(\delta\) 3.58 (s, 2 H), \(\delta\) 1.40 (d, \(J = 6.89\) Hz, 3 H). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 170.11, 143.21, 135.06, 129.49, 129.13, 128.74, 127.45, 127.39, 126.07, 48.85, 44.01, 21.91. Chiral HPLC AD column, 90:10 isohexane:2-PrOH, flow 1.5 ml/min, 30 °C, retention time 9.319 min (Retention times for racemate = 9.322 and 11.895 min)
2-Phenyl-N-(thiophen-2-ylmethyl)acetamide (3u)
White solid, 97% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.24-7.38 (m, 5 H), $\delta$ 7.19 (dd, $J = 5.12$, 1.25 Hz, 1 H) $\delta$ 6.85-6.94 (m, 2 H), $\delta$ 5.74 (bs, 1 H), $\delta$ 4.58 (d, $J = 5.69$, 2 H), 3.61 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 170.75, 141.05, 134.76, 129.56, 129.13, 127.49, 126.93, 125.80, 125.16, 43.76, 38.55.

N-(Furan-2-ylmethyl)-2-phenylacetamide (3v)
White solid, 96% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.28-7.22 (m, 6 H), $\delta$ 6.26 (dd, $J = 1.89$ Hz, $J = 3.23$ Hz, 1 H) $\delta$ 6.11 (dd, $J = 0.85$ Hz, $J = 3.23$ Hz, 1 H), $\delta$ 5.72 (bs, 1 H), $\delta$ 4.37 (d, $J = 5.64$, 2 H), 3.57 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 170.84, 151.32, 142.23, 134.80, 129.53, 129.11, 127.47, 110.49, 107.34, 43.75, 36.74.

N-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-phenylacetamide (3w)
White solid, 91% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.37-7.25 (m, 5 H), $\delta$ 6.71 (d, $J = 7.92$ Hz, 1 H) $\delta$ 6.68 (d, $J = 1.52$ Hz, 1 H), $\delta$ 6.63 (dd, $J = 1.52$ Hz, $J = 7.92$ Hz, 1 H), $\delta$ 5.93 (s, 2 H), 5.61 (bs, 1 H), $\delta$ 4.31 (d, $J = 5.84$ Hz, 1 H), $\delta$ 3.61 (s, 2 H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 170.90, 148.02, 147.05, 134.90, 132.15, 129.57, 129.19, 127.54, 120.94, 108.38, 108.29, 101.17, 43.96, 43.57.

N-Isobutyl-2-phenylacetamide (3x)
White solid, 88% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.36-7.24 (m, 5 H), $\delta$ 5.57 (bs, 1 H), $\delta$ 3.56 (s, 2 H), $\delta$ 3.01 (t, $J = 6.44$ Hz, 2 H), $\delta$ 1.67 (septet, $J = 6.74$ Hz, 1 H), 0.80 (d, $J = 6.72$ Hz, 6 H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 171.02, 135.25, 129.48, 129.06, 127.37, 46.96, 43.98, 28.44, 20.01.

2-Phenyl-N-((tetrahydrofuran-2-yl)methyl)acetamide (3y)
White solid, 71% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.35-7.24 (m, 5 H), $\delta$ 5.78 (bs, 1 H), $\delta$ 3.93-3.86 (m, 1 H), $\delta$ 3.69-3.65 (m, 2 H), $\delta$ 3.56 (s, 2 H), 3.47 (ddd, $J = 3.45$ Hz, $J = 6.02$ Hz, $J = 13.87$ Hz, 1 H), 3.17 (dt, $J = 6.19$ Hz, $J = 13.71$ Hz, 1 H), 1.94-1.71 (m, 3 H), 1.50-1.41 (m, 1 H). $^{13}$C-NMR (CDCl$_3$) $\delta$ 171.17, 135.10, 129.47, 129.05, 127.37, 77.69, 68.23, 43.96, 43.21, 28.53, 25.98.

N-Dodecyl-2-phenylacetamide (3z)
White solid, 79% yield. $^1$H-NMR (CDCl$_3$) $\delta$ 7.37-7.24 (m, 5 H), $\delta$ 5.36 (bs, 1 H), $\delta$ 3.56 (s, 2 H), $\delta$ 3.19 (q, $J = 6.72$ Hz, 2 H), $\delta$ 1.40 (quint., $J = 6.96$ Hz, 2 H), 1.32-1.18 (m, 18 H), 0.88 (t,
$J = 6.53 \text{ Hz, 3 H}$. $^{13}$C-NMR (CDCl$_3$) δ 171.06, 135.19, 129.55, 129.10, 127.41, 43.98, 39.81, 32.02, 29.73, 29.64, 29.60, 29.53, 29.45, 29.31, 26.88, 22.79, 14.21.

2-phenyl-1-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)ethanone (3aa)
74% yield. $^1$H-NMR (CDCl$_3$) δ 7.34-7.27 (m, 2 H), δ 7.26-7.20 (m, 3 H), δ 3.97-3.89 (m, 4 H), δ 3.76 (s, 2 H), δ 3.74-3.69 (m, 2 H), δ 3.52-3.47 (m, 2 H), δ 1.68-1.62 (m, 2 H), δ 1.47-1.41 (m, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 169.45, 135.27, 128.92, 128.61, 126.95, 107.00, 64.57, 44.33, 41.38, 40.09, 35.38, 34.76.

2-phenyl-1-(piperidin-1-yl)ethanone (3ab)
69% yield. $^1$H-NMR (CDCl$_3$) δ 7.35-7.28 (m, 2 H), δ 7.27-7.20 (m, 3 H), δ 3.73 (s, 2 H), δ 3.57 (m, 2 H), δ 3.37 (m, 2 H), δ 1.62-1.48 (m, 4 H), δ 1.38-1.30 (m, 2 H). $^{13}$C-NMR (CDCl$_3$) δ 169.36, 135.59, 128.78, 128.72, 126.76, 47.39, 43.01, 41.33, 26.32, 25.62, 24.57.

1-morpholino-2-phenylethanone (3ac)
76% yield. $^1$H-NMR (CDCl$_3$) δ 7.36-7.29 (m, 2 H), δ 7.28-7.20 (m, 3 H), δ 3.73 (s, 2 H), δ 3.64 (s, 4 H), δ 3.50-3.40 (m, 4 H). $^{13}$C-NMR (CDCl$_3$) δ 169.75, 134.92, 128.94, 128.65, 127.03, 66.92, 66.58, 46.65, 42.27, 40.98.
6. $^1$H-NMR and $^{13}$C-NMR spectra

![Chemical Structure]

![NMR Spectra]
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\begin{align*}
&\text{F} \quad \text{O} \\
&\text{F} \quad \text{F} \\
&\text{N} \\
&\text{C}_6\text{H}_5
\end{align*}
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7. HPLC chromatograms