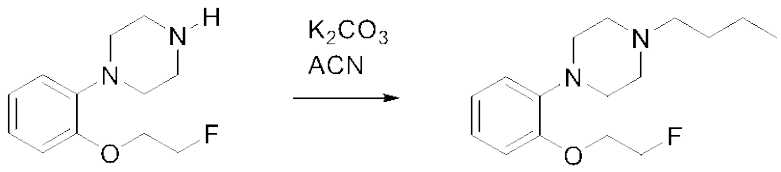
Supplementary Materials

Supporting Figures

Supplementry Materials

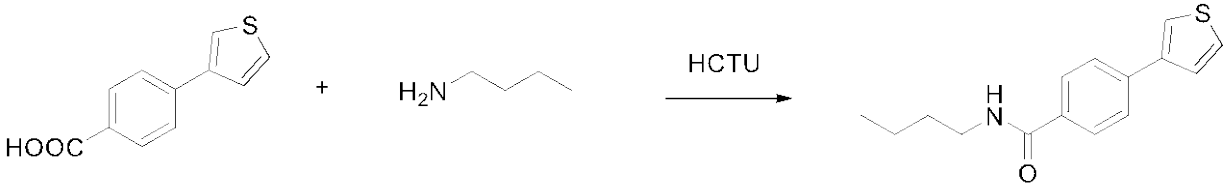
Synthesis and Characterization of Compounds



KX-02-063 Compound 2

1-Butyl-4-(2-(2-fluoroethoxy)phenyl)piperazine (Compound 2)

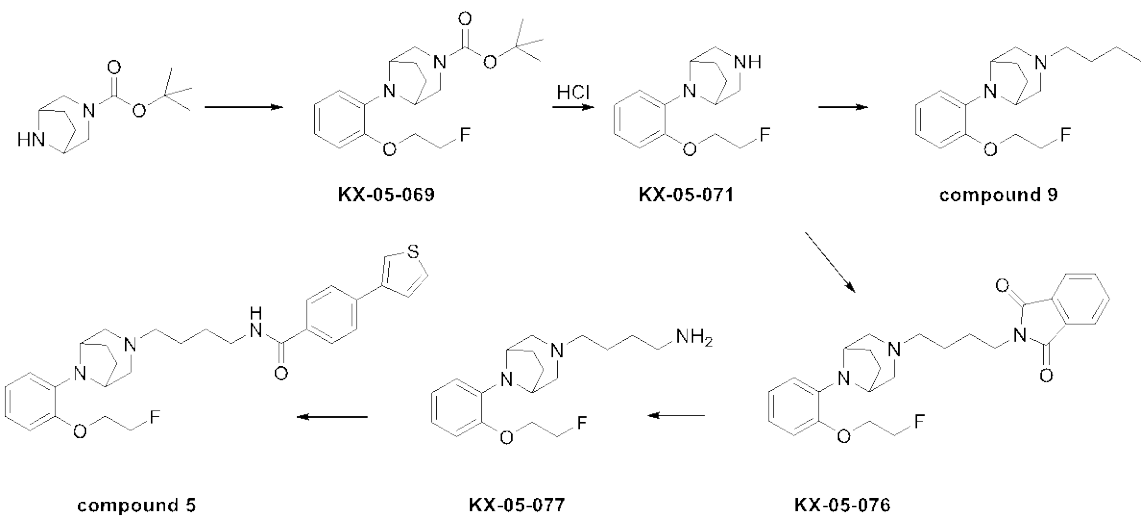
Compound 2 was obtained (112 mg, 0.5 mmol) from KX-02-063via General Procedure A as a colorless oil (85 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.35 (m, 2H), 1.54 (m, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 2.68 (s, 4H), 3.16 (s, 4H), 4.25 (dt, *J* = 29.0, 4.0 Hz, 2H), 4.77 (dt, *J* = 47.5, 4.0 Hz), 6.85 (m, 1H), 6.95-6.97 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.99, 20.75, 28.61, 50.33, 53.46, 58.52, 67.48, 67.64, 81.29, 82.56, 113.76, 118.43, 122.14, 122.61, 141.99, 150.93. HRMS m/z (ESI): calculated for $C_{16}H_{26}FN_2O^+$ ($[M + H]^+$) 281.2024, found 281.2019.



Compound 3

N-Butyl-4-(thiophen-3-yl)benzamide (Compound 3)

Using General Procedure B, Compound 3 was obtained from n-butylamine (146 mg, 2 mmol) as colorless solid (120 mg, 46%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.38-1.48 (m, 2H), 1.58-1.66 (m, 2H), 3.44-3.50 (m, 2H), 6.20 (br s, 1H), 7.40 (s, 1H), 7.41 (s, 1H), 7.52 (t, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.77, 20.16, 31.76, 39.83, 121.42, 126.14, 126.37, 126.59, 127.45, 133.22, 138.61, 141.22, 167.12. HRMS m/z (ESI): calcd for $C_{15}H_{18}NOS^+$ ($[M + H]^+$)260.1104, found 260.1120.



***tert*-Butyl 8-(2-(2-fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (KX-05-069)**

KX-05-069 was generated via general procedure C with 3,8-diazabicyclo[3,2,1]octane-3-carboxylic acid *tert*-butyl ester (106 mg, 0.5 mmol) as slightly brown oil (145 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.75 (m, 2H), 1.92 (m, 2H), 3.26 (dd, *J* = 35.6, 12.1 Hz, 2H), 3.79 (dd, *J* = 69.0, 12.1 Hz, 2H), 4.13 (m, 2H), 4.23 (dt, *J* = 27.9, 4.1 Hz, 2H), 4.76 (dt, *J* = 47.6, 4.1 Hz, 2H), 6.81-6.91 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.41, 26.54, 28.43 49.25, 50.43, 57.21, 57.27, 67.57 (d, J_{F-C} = 20.3 Hz), 79.44, 81.98 (d, J_{F-C} = 171.1 Hz), 113.84, 117.03, 121.33, 121.98, 139.14, 149.93, 156.08. ESI-MS (m/z): 351.22 [M+H].

8-(2-(2-Fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octane (KX-05-071)

KX-05-069 (200 mg, 0.57 mmol) was carried on with general procedure F, yielding KX-05-071 as slightly yellow oil (150 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11-2.14 (m, 2H), 2.26-2.29 (m, 2H), 3.23 (dd, *J* = 12.1, 1.6 Hz, 2H), 3.40-3.43 (m, 3H), 4.15-4.23 (m, 4H), 4.74 (dt, *J* = 47.6, 4.1 Hz, 2H), 6.74 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.83 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.86-6.91 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.99, 48.48, 55.92, 67.61 (d, J_{F-C} = 18.9 Hz), 81.79 (d, J_{F-C} = 172.8 Hz), 113.66, 116.54, 121.97, 122.26, 137.49, 149.75. ESI-MS (m/z): 251.20 [M+H].

2-(4-(8-(2-(2-Fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)butyl)isoindoline-1,3-dione (KX-05-076)

KX-05-076 was obtained from KX-05-071 (100 mg, 0.4 mmol) via general procedure D as colorless oil (110, 61%). ESI-MS (m/z): 452.24 [M+H].

4-(8-(2-(2-Fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)butan-1-amine (KX-05-077)

KX-05-077 was obtained (50 mg, 0.11 mmol) from KX-05-076 (50 mg, 0.11 mmol) with general procedure E as colorless oil (30 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48-1.50 (m, 4H), 1.86-1.91 (m, 4H), 2.26 (br s, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 2.45 (d, *J* = 10.3 Hz, 2H), 2.69-2.72 (m, 4H), 4.10 (s, 2H), 4.21 (dt, *J* = 28.2, 4.1 Hz, 2H), 4.76 (dt, *J* = 47.5, 4.1 Hz), 6.81-6.87 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.15, 27.39, 31.08, 41.85, 57.35, 57.89, 58.51, 67.42 (d, J_{F-C} = 20.6 Hz), 82.04 (d, J_{F-C} = 171.0 Hz), 113.81, 117.09, 120.65, 121.91, 139.42, 149.75. ESI-MS (m/z): 322.22 [M+H].

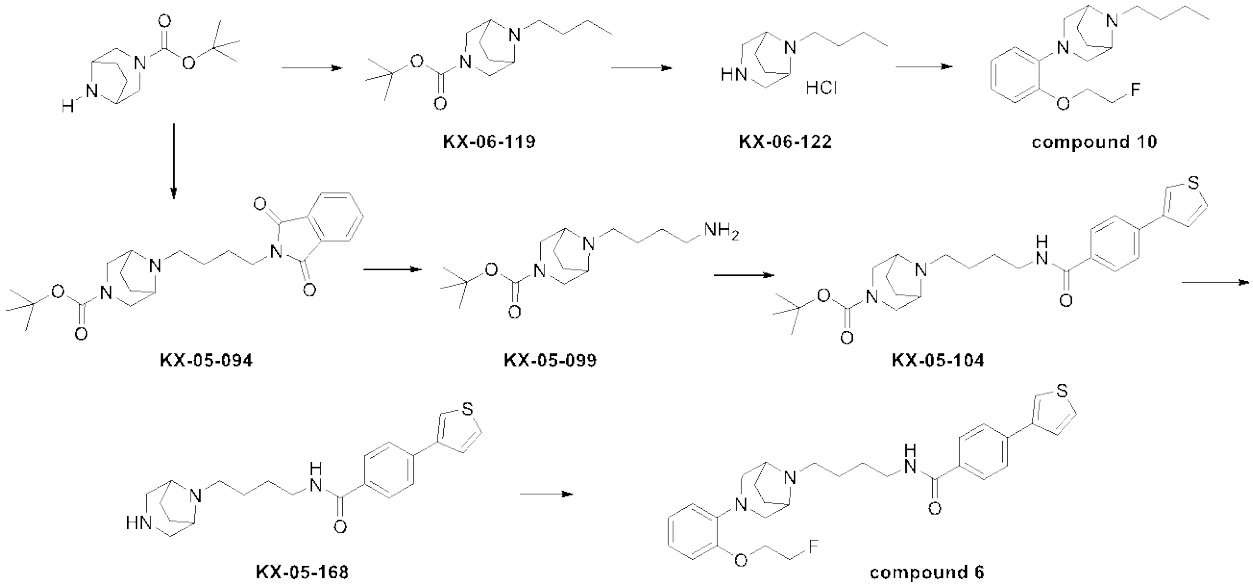
N-(4-(8-(2-(2-Fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)butyl)-4-(thiophen-3-yl)benzamide (Compound 5).

Compound 5 was obtained from KX-05-077 (25 mg, 0.078 mmol) via general procedure B as colorless solid (20 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54-1.59 (m, 2H), 1.65-1.69 (m, 2H), 1.84-1.90 (m, 4H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.48 (d, *J* = 10.2 Hz, 2H), 2.73 (dd, *J* = 10.4, 2.4 Hz, 2H), 3.46-3.50 (m, 2H), 4.10 (s, 2H), 4.22 (dt, *J* = 28.3, 4.1 Hz, 2H), 4.75 (dt, *J* = 47.6, 4.1 Hz), 6.80-6.90 (m, 4H), 4.39 (s, 1H), 4.40 (s, 1H), 7.51 (t, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.10, 27.33, 38.53, 39.87, 56.99, 57.82, 58.45, 67.43 (d, J_{F-C} = 20.0 Hz), 82.03 (d, J_{F-C} = 170.4 Hz), 113.82, 117.06, 120.72, 121.35, 121.91, 126.09, 126.28, 126.54, 127.47, 133.20, 138.51, 139.33, 141.16, 149.74, 167.14. HRMS m/z (ESI): calcd for $C_{29}H_{35}FN_3O_2S^+$ ($[M + H]^+$) 508.2429, found 508.2435.

3-Butyl-8-(2-(2-fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octane (KX-06-112)

Compound 9 was obtained from KX-05-071 (50 mg, 0.2 mmol) via general procedure A as colorless oil (25 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31-1.36 (m, 2H), 1.41-1.46 (m, 2H), 1.84-1.87 (m, 2H), 1.90-1.93 (m, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.45

(d, J = 10.2 Hz, 2H), 2.71 (d, J = 10.4 Hz, 2H), 4.12 (s, 2H), 4.23 (dt, J = 28.1, 4.2 Hz, 2H), 4.77 (dt, J = 47.4, 4.2 Hz), 6.82-6.88 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.02, 20.54, 27.43, 29.03, 57.39, 58.00, 58.57, 67.41 (d, J_{F-C} = 20.2 Hz), 82.09 (d, J_{F-C} = 170.1 Hz), 113.91, 117.16, 120.29, 121.96, 139.62, 149.80. HRMS m/z (ESI): calcd for $C_{18}H_{28}FN_2O^+$ ([M + H]$^+$) 307.2180, found 307.2179.



tert-Butyl 8-(4-(1,3-dioxoisoindolin-2-yl)butyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (KX-05-094)

The title compound was obtained from 3,8-diazabicyclo[3,2,1]octane-3-carboxylic acid *tert*-butyl-ester (106 mg, 0.5 mmol) via gernal procedure D as colorless oil (190 mg, 92%). 1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.45-1.51 (m, 2H), 1.53-1.59 (m, 2H), 1.68-1.74 (m, 2H), 1.82 (s, 2H), 2.31 (t, J = 7.5 Hz, 2H), 2.97 (dd, J = 43.8, 12.1 Hz, 2H), 3.10 (d, J = 29.1 Hz, 2H), 3.60 (dd, J = 65.6, 12.0 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.67-7.69 (m, 2H), 7.78-7.82 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.92, 25.07, 25.74, 26.38, 28.35, 37.72, 49.24, 50.41, 52.10, 58.52, 58.62, 79.23, 123.08, 132.05, 133.80, 155.93, 168.34. ESI-MS (m/z): 414.24 [M+H].

***tert*-Butyl 8-(4-aminobutyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (KX-05-099)**

KX-05-099 was obtained from KX-05-094 (190 mg, 0.46 mmol) via general procedure E as colorless oil (105 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.44-1.47 (m, 2H),

1.52-1.57(m, 2H), 1.90-1.91 (m, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 2.97 (dd, *J* = 12.4, 41.8 Hz, 2H), 3.10 (d, *J* = 32.6 Hz, 2H), 3.59 (dd, *J* = 12.4, 64.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.73, 25.87, 28.32, 31.39, 41.89, 52.41, 58.44, 79.32, 155.98. ESI-MS (m/z): 284.24 [M+H].

***tert*-Butyl 8-(4-(4-(thiophen-3-yl)benzamido)butyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (KX-05-104)**

KX-05-104 was yielded from KX-05-099 (90 mg, 0.32 mmol) via general procedure B as colorless solid (88 mg, 59%). ESI-MS (m/z): 470.28 [M+H].

N-(4-(3,8-Diazabicyclo[3.2.1]octan-8-yl)butyl)-4-(thiophen-3-yl)benzamide (KX-05-168)

KX-05-168 was yielded from KX-05-104 (88 mg, 0.19 mmol) via general procedure F as slightly yellow solid (65 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59-1.69 (m, 4H), 1.80-1.84 (m, 2H), 1.95-1.98 (m, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.69 (dd, *J* = 2.1, 12.5 Hz, 2H), 3.10 (d, *J* = 12.1 Hz, 2H), 3.24 (s, 2H), 3.44-3.48 (m, 2H), 4.62 (s, 2H), 6.97 (t, *J* = 5.4 Hz, 1H), 7.38-7.39 (m, 2H), 7.50 (t, *J* = 2.1 Hz,1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.59, 24.70, 27.00, 39.40, 50.31, 52.13, 59.94, 121.35, 126.08, 126.24, 126.55, 127.58, 133.08, 138.50, 141.16, 167.30. ESI-MS (m/z): 370.20 [M+H].

N-(4-(3-(2-(2-Fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)butyl)-4-(thiophen-3-yl)benzamide (compound 6)

Compound 6 was obtained from KX-05-168 (50 mg, 0.13 mmol) via general procedure C as colorless solid (25 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74-1.78 (m, *J* = 7.3 Hz, 3H), 2.00-2.04 (m, 2H), 2.13 (br s, 2H), 2.39 (d, *J* = 8.2 Hz, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 3.32-3.35 (m, 2H), 3.56-3.60 (m, 2H), 3.65-3.69 (m, 2H), 3.85 (s, 1H), 4.23 (dt, *J* = 28.3, 4.0 Hz, 2H), 4.77 (dt, *J* = 47.4, 4.0 Hz), 6.82 (d, *J* = 7.9 Hz, 1H), 6.92-6.95 (m, 2H), 6.99-7.01 (m, 1H),7.37-7.41 (m, 2H), 7.49 (dd, *J* = 2.4, 1.7 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.84 (br s, 1H), 8.04 (d, *J* = 8.3 Hz, 2H). HRMS m/z (ESI): calcd for $C_{29}H_{34}FN_3O_2S^+$ ($[M + H]^+$) 508.2429, found 508.2435.

***tert*-Butyl 8-butyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (KX-06-119)**

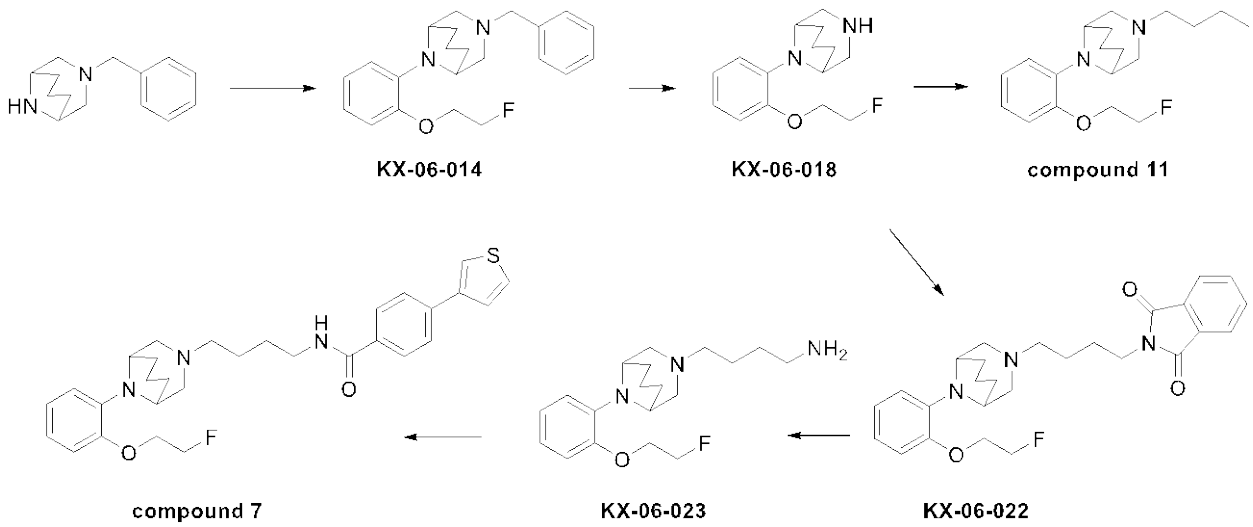
The title compound was obtained from 3,8-diazabicyclo[3,2,1]octane-3-carboxylic acid *tert*-butyl-ester (106 mg, 0.5 mmol) via general procedure A as slightly brown solid (90 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.26-1.34 (m, 2H), 1.39-1.45 (m, 11H), 1.53-1.59 (m, 2H), 1.80-1.87 (m, 2H), 2.27 (t, *J* = 7.7 Hz, 2H), 2.99 (dd, *J* = 12.1, 40.8 Hz, 2H), 3.12 (d, *J* = 34.3 Hz, 1H), 3.60 (dd, *J* = 12.1, 68.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.97, 20.61, 24.99, 25.17, 28.38, 30.73, 49.17, 50.33, 52.36, 58.45, 79.22, 155.99. ESI-MS (m/z): 268.24 [M+H].

8-Butyl-3,8-diazabicyclo[3.2.1]octane (KX-06-122)

The title compound was obtained from **KX-06-119** via general procedure F. The solid formed was used for next step without purification. ESI-MS (m/z): 169.19 [M+H].

8-Butyl-3-(2-(2-fluoroethoxy)phenyl)-3,8-diazabicyclo[3.2.1]octane (KX-06-123)

Compound 10 was yielded from **KX-06-122** (70 mg, 0.42 mmol) via general procedure C as colorless oil (50 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.33-1.39 (m, 2H), 1.68-1.73 (m, 2H), 1.99-2.03 (m, 2H), 2.17 (d, *J* = 7.6 Hz, 2H), 2.64 (dd, *J* = 8.0, 8.6 Hz, 2H), 3.27 (dd, *J* = 2.8, 12.0 Hz, 2H), 3.40 (d, *J* = 11.3 Hz, 2H), 3.57 (s, 2H), 4.21 (dt, *J* = 28.3, 4.1 Hz, 2H), 4.76 (dt, *J* = 47.5, 4.1 Hz), 6.81 (d, *J* = Hz, 7.5 Hz, 1H), 6.91-6.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.49, 20.47, 24.94, 28.43, 51.91, 53.92, 60.50, 67.39 (d, J_{F-C} = 19.7 Hz), 82.35 (d, J_{F-C} = 171.3 Hz), 112.78, 119.40, 121.92, 122.71, 140.57, 151.02. HRMS m/z (ESI): calcd for $C_{18}H_{27}FN_2O^+$ ($[M + H]^+$) 307.2180, found 307.2189.



3-Benzyl-9-(2-(2-fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonane (KX-06-014)

The title compound was obtained from 3-benzyl-3,9-diazabicyclo[3.3.1]nonane dihydrochloride (290 mg, 1.0 mmol) via general procedure C as a slightly brown solid (200 mg, 56%). ESI-MS (m/z): 169.19 [M+H]. ESI-MS (m/z): 355.21 [M+H].

9-(2-(2-Fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonane (KX-06-018)

KX-06-014 (200 mg, 0.56 mmmol) was dissolved in methanol (3 ml), 4N HCl (1 ml) was added followed by the addition of Pd/C (20 mg). The mixture was kept stirring under a H_2 atmosphere overnight. Then the resulted reaction mixture was neutralized with 7N methanolic ammonia and condensed. The residue was applied to FC (dichloromethane/7N methanolic ammonia 0-15%) yielding KX-060-018 as slightly brown oil (80 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78-1.84 (m, 3H), 2.09-2.17 (m, 2H), 2.41-2.49 (m, 1H), 3.35 (d, J = 12.7 Hz, 2H), 3.49 (dd, J = 4.0, 12.6 Hz, 2H), 3.97 (s, 2H), 4.17 (dt, J = 28.2, 4.0 Hz, 2H), 4.73 (dt, J = 47.4, 4.0 Hz), 6.80 (d, J = 7.5 Hz, 1H), 6.85-6.91 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.52, 26.57, 45.73, 48.06, 67.49 (d, J_{F-C} = 19.9 Hz), 81.82 (d, J_{F-C} = 170.9 Hz), 113.43, 118.07, 121.51, 122.00, 138.50, 149.97. ESI-MS (m/z): 265.18 [M+H].

2-(4-(9-(2-(2-Fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonan-3-yl)butyl)isoindoline-1,3-dione (KX-06-022)

KX-06-022 was obtained from KX-06-018 (30 mg, 0.11 mmol) via general procedure D as slightly yellow oil (40 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49-1.55 (m, 3H), 1.64-1.67

(m, 2H), 1.72-1.79 (m, 2H), 2.01-2.08 (m, 2H), 2.23 (t, *J* = 6.9 Hz, 2H), 2.48 (d, *J* = 10.8 Hz, 2H), 2.70-2.77(m, 1H), 2.80 (d, *J* = 10.7 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 3.84 (s, 2H), 4.18 (dt, *J* = 28.2, 4.1 Hz, 2H), 4.73 (dt, *J* = 47.5, 4.1 Hz), 6.75-6.80 (m, 2H), 6.88-6.94 (m, 2H), 7.68-7.72 (m, 2H), 7.82-7.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.51, 23.97, 26.32, 28.89, 37.92, 51.38, 57.31, 58.13, 67.57 (d, J_{F-C} = 20.2 Hz), 82.10 (d, J_{F-C} = 171.0 Hz), 114.31, 118.17, 119.47, 122.08, 123.12, 132.11, 133.81, 140.39, 149.73, 168.43. ESI-MS (m/z): 466.14 [M+H].

4-(9-(2-(2-Fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonan-3-yl)butan-1-amine (KX-06-023)

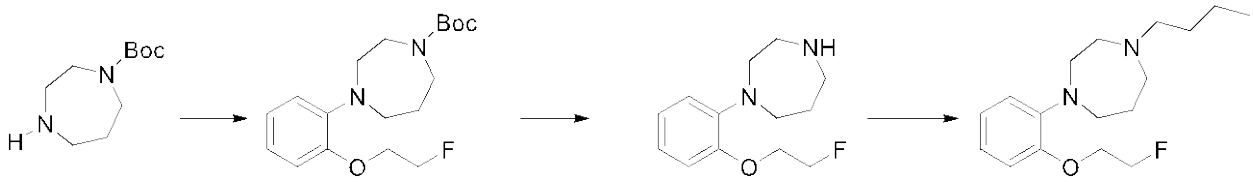
KX-06-023 was yielded from KX-06-022 (40 mg, 0.08 mmol) via general procedure E as colorless oil (22 mg, 76%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50-1.54 (m, 5H), 1.65-1.71 (m, 2H), 1.98 (s, 2H), 2.00-2.10 (m, 2H), 2.20-2.24 (m, 2H), 2.50 (d, *J* = 11.2 Hz, 2H), 2.71-2.84 (m, 5H), 3.86 (s, 2H), 4.19 (dt, *J* = 28.1, 4.3 Hz, 2H), 4.74 (dt, *J* = 47.5, 4.1 Hz), 6.77-6.82 (m, 2H), 6.88-6.92 (m, 2H), ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.54, 24.14, 28.99, 31.21, 42.01, 51.46, 57.40, 57.40, 58.71, 67.71 (d, J_{F-C} = 19.8 Hz), 82.13 (d, J_{F-C} = 171.1 Hz), 114.53, 118.22, 119.50, 122.16, 140.53, 149.80. ESI-MS (m/z): 336.25 [M+H].

N-(4-(9-(2-(2-Fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonan-3-yl)butyl)-4-(thiophen-3-yl)benzamide (KX-06-026)

Compound 7 was obtained from KX-06-023 (22 mg, 0.06 mmol) via general procedure B as slightly brown solid (18 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58-1.64 (m, 4H), 1.65-1.71 (m, 4H), 2.02-2.10 (m, 2H), 2.33 (s, 2H), 2.58 (m, 2H), 2.88 (d, *J* = 9.8 Hz, 2H), 3.48-3.52 (m, 2H), 3.88 (s, 2H), 4.19 (dt, *J* = 28.4, 4.1 Hz, 2H), 4.77 (dt, *J* = 47.5, 4.1 Hz), 6.39 (s, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 6.88-6.95 (m, 2H) 7.40 (d, *J* = 2.2 Hz, 2H), 7.52 (t, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.35, 23.91, 27.21, 28.65, 39.86, 51.13, 57.25, 58.44, 67.58 (d, J_{F-C} = 20.2 Hz), 82.10 (d, J_{F-C} = 170.6 Hz), 118.20, 119.78, 121.41, 122.08, 126.10, 126.32, 126.59, 127.46, 127.82, 139.79, 133.05, 138.56, 141.13, 149.75, 167.23. HRMS m/z (ESI): calcd for $C_{33}H_{37}FN_3O_2S^+$ ($[M + H]^+$) 522.2585, found 522.2580.

3-Butyl-9-(2-(2-fluoroethoxy)phenyl)-3,9-diazabicyclo[3.3.1]nonane (compound 11)

Compound 11 was obtained from KX-06-018 (20 mg, 0.07 mmol) via general procedure A as a slightly brown oil (15 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.34-1.40 (m, 2H), 1.42-1.49 (m, 2H), 1.54-1.58 (m, 2H), 1.69 (dd, *J* = 5.7, 13.1 Hz, 2H), 2.02-2.10 (m, 2H), 2.20 (t, *J* = 7.0 Hz, 2H), 2.49 (d, *J* = 10.8 Hz, 2H), 2.78-2.84 (m, 2H), 3.86 (s, 2H), 4.20 (dt, *J* = 28.2, 4.1 Hz, 2H), 4.74 (dt, *J* = 47.5, 4.1 Hz), 6.76-6.82 (m, 2H), 6.89-6.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.05, 20.53, 29.03, 51.51, 57.42, 58.70, 67.68 (d, J_{F-C} = 20.1 Hz), 82.16 (d, J_{F-C} = 170.8 Hz), 114.50, 118.25, 119.48, 122.16, 140.56, 149.79. HRMS m/z (ESI): calcd for $C_{19}H_{30}FN_2O^+$ ([M + H]$^+$) 321.2337, found 321.2341.



KX-06-110 KX-06-113 compound 8

***tert*-Butyl 4-(2-(2-fluoroethoxy)phenyl)-1,4-diazepane-1-carboxylate (KX-06-110)**

The title compound was achieved using 1-boc-hexahydro-1,4-diaepine (100 mg, 0.5 mmol) via general procedure C as slightly yellow oil (110 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 1.45, 1.47 (2 s, 9H), 1.94-2.04 (m, 2H), 3.50-3.65 (m, 2H), 4.22 (dt, *J* = 28.3, 4.1 Hz, 2H), 4.78 (dt, *J* = 47.7, 4.0 Hz), 6.81-6.83 (m, 1H), 6.89-6.91 (m, 2H), 6.94-6.96 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) (mixture of rotamers) δ 28.44, 28.58, 44.86, 45.94, 47.90, 48.18, 53.15, 53.34, 53.91, 67.58 (d, J_{F-C} = 20.2 Hz), 79.18, 81.85 (d, J_{F-C} = 171.2 Hz), 113.26, 118.95, 119.05, 121.52, 121.58, 121.74, 142.81, 142.90, 150.58, 155.45, 155.51. ESI-MS (m/z): 339.20 [M+H].

***tert*-Butyl 4-(2-(2-fluoroethoxy)phenyl)-1,4-diazepane-1-carboxylate (KX-06-113)**

Compound **KX-06-113** HCl salt was obtained from **KX-06-110** (110 mg 0.32 mmol) via general procedure F as a slightly brown solid (75 mg, 97%). ESI-MS (m/z): 239.18 [M+H].

1-Butyl-4-(2-(2-fluoroethoxy)phenyl)-1,4-diazepane (KX-06-116) Compound 8.

Compound 8 was yielded from **KX-06-113** (40mg, 0.17 mmol) via general procedure A as a slight brown oil (16 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.35-1.42 (m, 2H), 1.81-1.87 (m, 2H), 2.51 (s, 2H), 2.97-3.00 (m, 2H), 3.29 (t, *J*

= 6.7 Hz, 2H), 3.37 (t, J = 5.0 Hz, 2H), 3.45 (t, J = 4.3 Hz, 2H), 3.51 (t, J = 4.3 Hz, 2H), 4.23 (dt, J = 28.8, 4.0 Hz, 2H), 4.77 (dt, J = 47.7, 4.0 Hz), 6.82-6.85 (m, 1H), 6.91-6.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) (mixture of rotamers) δ 13.54, 20.25, 24.21, 26.01, 48.89, 49.15, 52.26, 56.64, 57.61, 67.23 (d, J_{F-C} = 19.1 Hz), 81.77 (d, J_{F-C} = 171.2 Hz),112.31, 118.05, 121.76, 121.91, 141.61, 150.08. HRMS m/z (ESI): calcd for $C_{17}H_{28}FN_2O^+$ ($[M + H]^+$) 295.2180, found 295.2176.

Supporting Figures

SUPPORTING FIGURE 1.

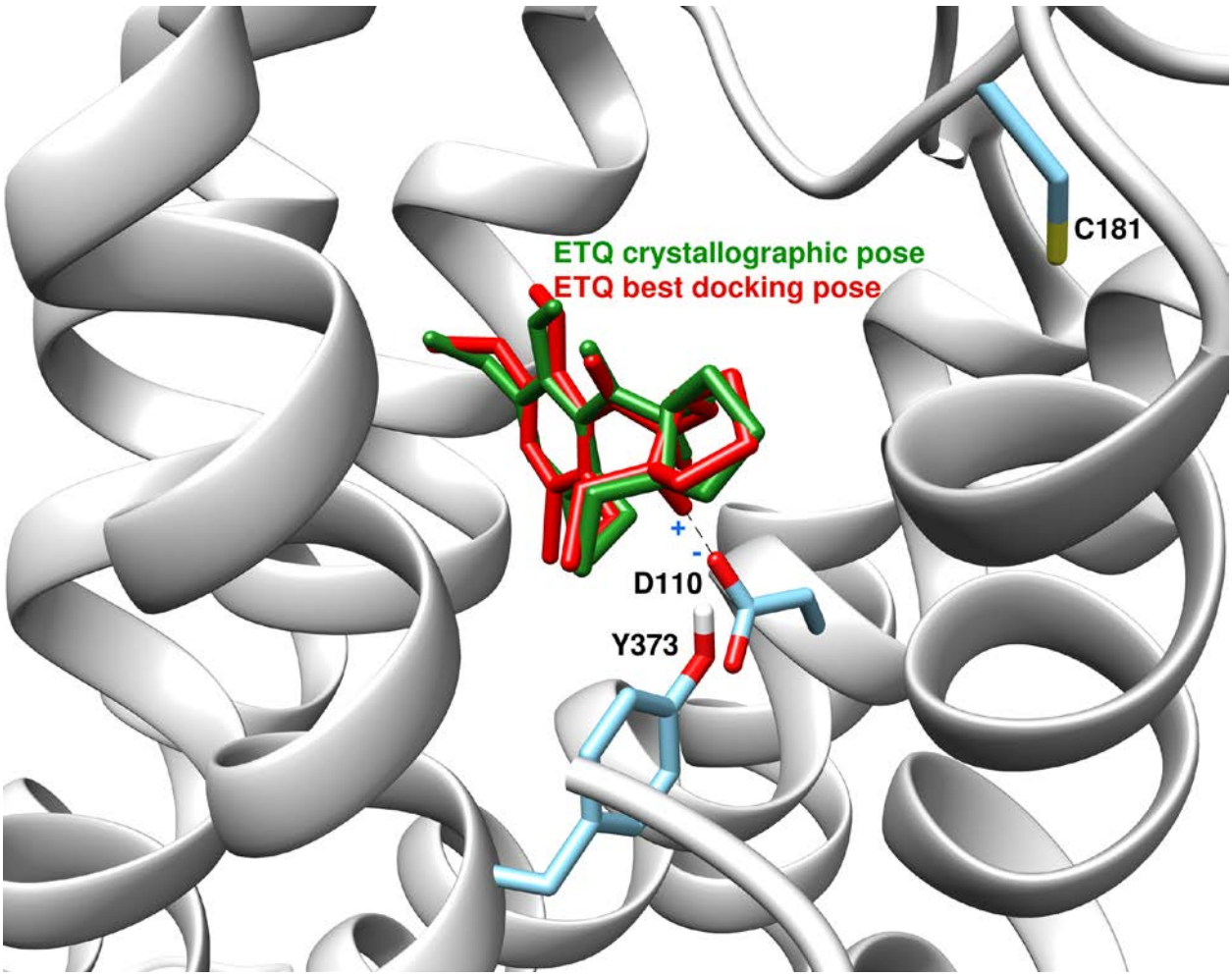
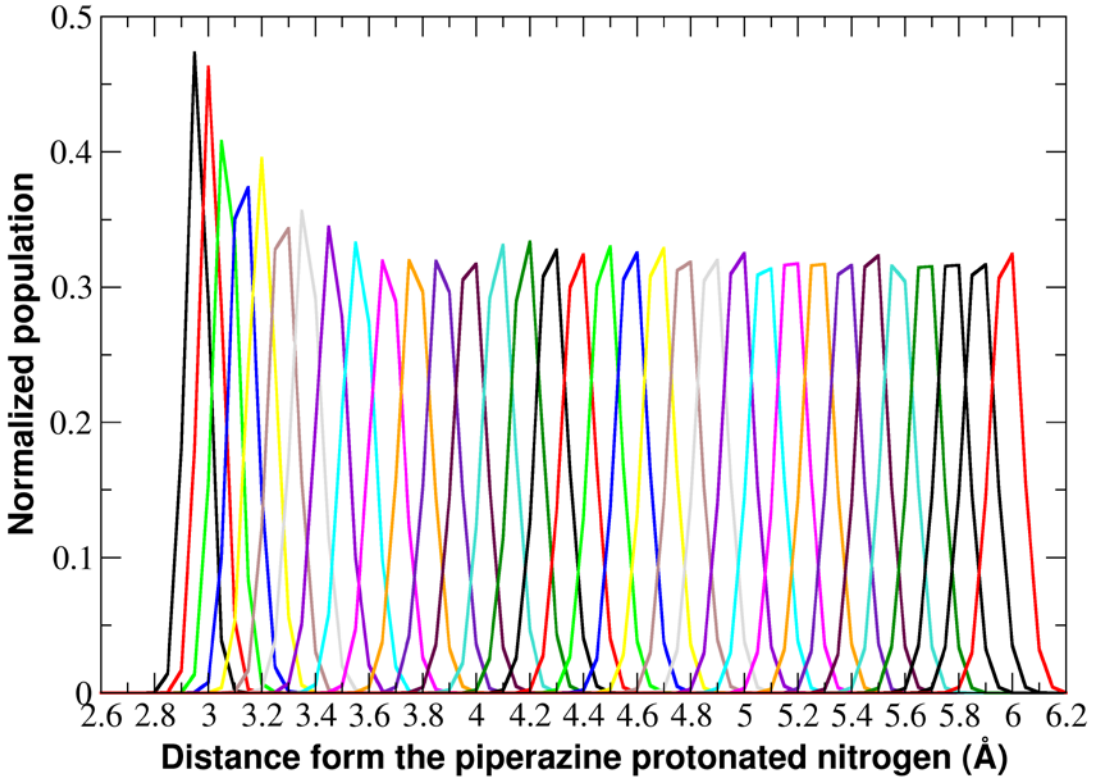


Figure 1. The crystallographic vs. docked poses of 3-chloro-5-ethyl-N-{[(2S)-1-ethylpyrrolidin-2-yl]methyl}-6-hydroxy-2-methoxybenzamide (ETQ) on according to the crystal structure 3PBL and our docking result with Autodock vina.

SUPPORTING FIGURE 2.



Supporting Figure 2. The histograms of normalized populations of sampled reaction coordinates at umbrella sampling windows. Each plot represents a window starting from 2.8 Å and ending to 6.0 Å. The plot shows that the neighboring windows sample overlapped regions of the reaction coordinate, which is a crucial criterion for validity of PMF calculations based on umbrella sampling simulations.