Supporting information

Synthesis and biological evaluation of new quinoxaline derivatives of ICF01012 as melanoma-targeting probes

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Materials for Chemical Syntheses

Unless otherwise mentioned, all manipulations were performed under argon; all reagents were purchased from the following commercial suppliers: Sigma-Aldrich, Acros Organics, Carlo Erba, TCI Europa.. Anhydrous DMF, anhydrous triethylamine were purchased from Acros Organics. THF was distilled over benzophenone and sodium. Dichloromethane was distilled over hydride calcium. Nuclear magnetic resonance (NMR) spectra were acquired on Bruker AC-200 operating at 200 and 50 MHz for ^{1}H NMR and ^{13}C NMR, respectively. All ^{1}H NMR spectra are reported in δ units, parts per million (ppm) and the coupling constants are indicated in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, m =multiplet, and br = broad. Electrospray ionization mass spectra (ESI-MS) were recorded on Esquire-LC 000800 (Bruker Daltonics, Wissenbourg, France) spectrometer. TLC was performed on glass backed silica gel sheets (60F254 plates) and visualized under UV light (254 nm). Column chromatography was performed using silica gel normal phase (35-70 μm). Uncorrected melting points (Mp) were recorded on a Wagner & Munz Heizbank-Koffler apparatus. Infrared spectra (IR) were recorded on a Bruker FT Vector 22.

Materials for Radiolabeling with iodine-125

[^{125}I]NaI (3.7 GBq/mL, 643.8 MBq/mg) was purchased from Perkin Elmer Life and Analytical Sciences (331 Treble Cove Road, Billerica, MA 01862, USA) as a no-carrier-added solution in reductant free 1.0 x 10^{-5} M aqueous sodium hydroxide solution (pH 8-11). Extrelut and citrate buffer solution (pH = 4) were purchased from Merck (Darmstadt, Germany). The radio TLC strips (Merck neutral aluminum oxide $60F_{254}$ plates) were developed with CH_2Cl_2/MeOH (80/20 or 75/25, v/v) and measured on an AMBIS 400 (Scanalytics, CSPI, San Diego, CA, USA).

The semi-preparative and analytical RP-HPLC purifications of radiotracers was performed on a Perkin Elmer system consisting of a Flexar LC autosampler and PDA detector, a Series 200 pump, a Peltier column oven and vacuum degasser and a GabiStar Raytest detector. . The separation was carried out on a C_{18} column (Waters, SymmetryPep^{TM} C18, 7.8 ×300 mm, 7 μM) using the following conditions : gradient time = 20 min, flow rate = 2.5 mL/min, eluent

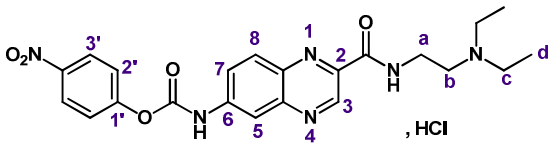
A (H_2O/0.2% NH_4OH), eluent B (MeOH 0.2 % NH_4OH); gradient: 15/85 (A/B, v/v) from 0 to 15 min, 0/100 (A/B, v/v) from 15 to 20 min, λ = 254 nm.

Analytical RP-HPLC measurements were performed on the same Perkin Elmer system. The separation was carried out on a C_{18} column (Agilent Zorbax, 80 Å, 4.6 mm × 150 mm, 5 μM) using the following conditions: gradient time = 20 min, flow rate = 0.5 mL/min, eluent A (H_2O/0,2 % NH_4OH), eluent B (MeOH 0.2 % NH_4OH); gradient: 25/75 (A/B, v/v) for 0 to 15 min, 0/100 (A/B, v/v) for 15 to 20 min, λ = 254 nm.

All radiolabeled compounds were compared by TLC or analytical HPLC to the authentic nonradioactive material and to be free of significant chemical and radiochemical impurities.

Access to compound (11)

4-Nitrophenyl (2-((2-(*N*,*N*-diethylamino)ethyl)carbomoyl)quinoxalin-6-yl)carbamate hydrochloride (11)[1]

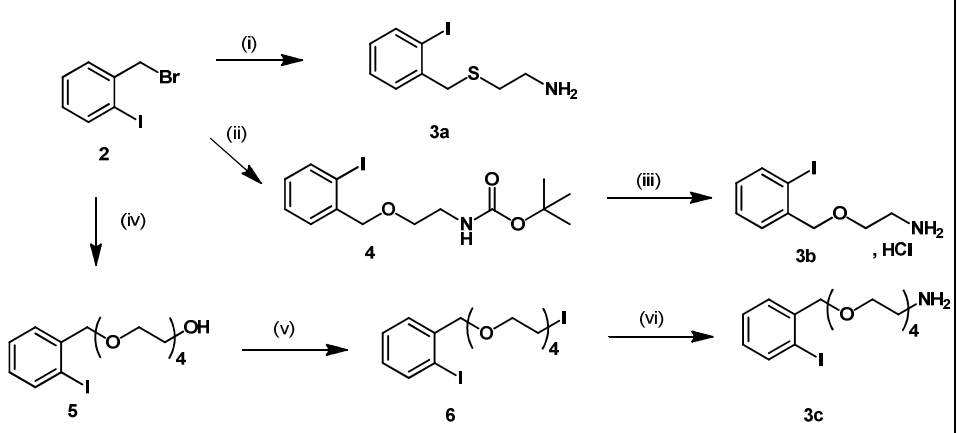


To a solution of compound **(10)**[1] (1 g, 3.48 mmol, 1 eq.) dissolved in 30 mL of anhydrous DCM were added anhydrous pyridine (1.0 mL, 12.42 mmol, 3.6 eq.) and 4-nitrophenylchloroformiate (772.0 mg, 3.83 mmol, 1.1 eq.). The resulting mixture was stirred at room temperature for 30 min, then the reaction solvent was evaporated under reduced pressure. The crude product was triturated with anhydrous ethyl ether (10 mL). The precipitate was filtered off, washed with anhydrous ethyl ether (15 mL) and dried under reduced pressure (1.54 g). The orange precipitate **(10)** was used without further purification for the next step. Yield: 91%; Mp: 173 ± 1 °C; IR (KBr) ν (cm^{-1}) 3248, 2638, 1753 (C=O), 1664 (C=O), 1579, 1528, 1490; ^{1}H NMR (200 MHz, MeOD) δ 9.46 (s, 1H, H-3), 8.35 (m, 2H, H-3'), 8.19 (d, ^{3}J = 9.2 Hz, 1H, H-8), 8.07 (dd, ^{3}J = 9.2 Hz, ^{4}J = 2.3 Hz, 1H, H-7), 8.02 (d, ^{4}J = 2.3 Hz, 1H, H-5), 7.59 (m, 2H, H-2'), 3.88 (t, ^{3}J = 6.1 Hz, 2H, H-a), 3.39 (m, 6H, H-b, H-c), 1.36 (t, ^{3}J = 7.3 Hz, 6H, H-d); ^{13}C NMR (50 MHz, DMSO) δ 164.8 (C=O), 164.0 (C=O), 152.9 (C-1'), 146.2 (C-4'), 144.8 (C-4a), 144.2 (C-3), 138.5 (C-2), 136.5 (C-8a), 134.3 (C-6), 130.7 (C-7), 126.6 (C-3'), 124.3 (C-5), 116.2 (C-2'), 104.6 (C-8), 49.8 (C-b), 47.1 (C-c), 35.3 (C-a), 8.8 (C-d); ESI-SM m/z 453.21 $[M+H^{+}]^{+}$.

[1] J. Morlieras; J-M. Chezal; E. Miot-Noirault; A. Roux; L. Heinrich-Balard; R. Cohen, S. Tarrit, C. Truillet; A. Mignot; R. Hachani; D. Kryza; R. Antoine; P. Dugourd; P. Perriat; M. Janier; L. Sancey; F. Lux; O. Tillemint. Development of gadolinium based nanoparticles having an affinity towards melanin**.** *Nanoscale* 2013, 5, 1603-1615.

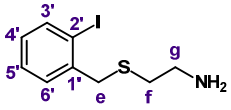
Access to compounds 3a-c

Scheme 2



[a] **Reactants and conditions:** (i) 2-aminoethanethiol hydrochloride, LiOH monohydrate, H_2O/EtOH (1/3, v/v), 35°C; (ii) *tert*-butyl (2-hydroxyethyl)carbamate, KOH, dry dichloromethane, rt; (iii) TFA, dry dichloromethane, rt; (iv) NaH, dry THF, rt; (v) imidazole, PPh_3, I_2, dry dichloromethane, rt; (vi) (a) potassium phtalimide, dry DMF, 30°C; (b) hydrazine monohydrate, ethanol, 30°C.

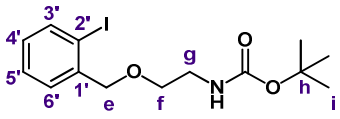
2-((2-Iodobenzyl)thio)ethanamine (3a)



To a solution of monohydrate lithium hydroxide (301.4 mg, 7.18 mmol, 2.04 eq.) dissolved in 12 mL of water/ethanol (1/3, v/v) were added 2-aminoethanethiol hydrochloride (400 mg, 3.52 mmol, 1 eq.) and 2-iodobenzyl bromide **(2)**[2] (1.04 mg, 3.52 mmol, 1 eq.). The reaction mixture was heated at 35 °C for 2 h 30 min, then was evaporated under reduced pressure. The crude product was dissolved with a saturated solution of $NaHCO_3$ (10 mL) and extracted with dichloromethane (2×15 mL). The pooled organic layer were washed with brine (30 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with dichloromethane/methanol (90/10, v/v) to afford **(3a)** (820 mg). Yield: 80%; IR (KBr) ν (cm^{-1}) 2918, 1576, 1562; ^{1}H NMR (200 MHz, MeOD) δ 7.88 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1H, H-3'), 7.39 (m, 1H, H-6'), 7.35 (m, 1H, H-5'), 6.99 (m, 1H, H-4'), 3.86 (s, 2H, H-e), 2.82 (m, 2H, H-g), 2.63 (m, 2H, H-f); ^{13}C NMR (50 MHz, MeOD) δ 141.0 (C-1'), 139.6 (C-3'), 129.9 (C-6'), 128.5 (C-4'), 128.1 (C-5'), 99.8 (C-2'), 40.5 (C-e), 40.1 (C-g), 34.2 (C-f); ESI-SM m/z 293.97 $[M+H^+]^+$.

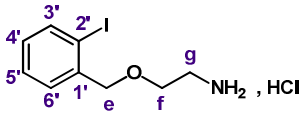
Synthesis of compound (3b)

***tert*-Butyl *N*-(2-((2-iodobenzyl)oxy)ethyl)carbamate (4)[3]**



To a solution of *tert*-butyl *N*-(2-hydroxyethyl)carbamate[2] (1.36 g, 8.40 mmol, 1 eq.) and 2-iodobenzyl bromide **(2)**[3] (3.0 g, 10.10 mmol, 1.2 eq.) dissolved in 20 mL of dry dichloromethane, potassium hydroxide (566.7 mg, 10.10 mmol, 1.2 eq.) was added at 0 °C. After 18 h at room temperature, water (40 mL) was added. The solution was decanted and the organic layer was washed with brine (20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with DCM to afford 1.79 g of **6**. Yield: 57% ; IR (KBr) ν (cm^{-1}) 3358, 2976, 2930, 1712 (C=O), 1507; ^{1}H NMR (200 MHz, MeOD) δ 7.82 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.1 Hz, 1H, H-3'), 7.45 (m, 1H, H-6'), 7.36 (m, 1H, H-5'), 7.01 (m, 1H, H-4'), 4.49 (s, 2H, H-e), 3.58 (t, ^{3}J = 5.6 Hz, 2H, H-f), 3.30 (m, 2H, H-g), 1.44 (s, 9H, H-i); ^{13}C NMR (50 MHz, MeOD) δ 156.1 (C=O), 139.5 (C-1'), 138.1 (C-3'), 128.1 (C-4'), 127.8 (C-6'), 127.1 (C-5'), 96.2 (C-2'), 77.8 (C-h), 75.4 (C-e), 68.5 (C-f), 30.0 (C-g), 26.5 (C-i); IE-SM m/z 217 $[M\text{-}C_7H_{16}NO_3]^+$, 90 $[M\text{-}C_7H_{16}NO_3\text{-}I]^+$.

2-((2-Iodobenzyl)oxy)ethanamine hydrochloride salt (3b)



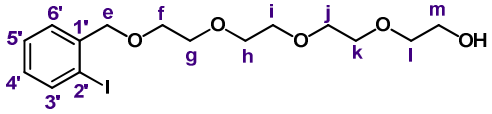
To a solution of *tert*-butyl *N*-(2-((2-iodobenzyl)oxy)ethyl)carbamate **(4)**[3] (1.2 g, 3.18 mmol, 1 eq.) dissolved in dry dichloromethane (20 mL), at 0 °C, TFA (292 µL, 3.82 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. Excess of TFA was co-evaporated with toluene (2×30 mL), ethanol (20 mL) then DCM (15 mL). The crude product was dissolved in DCM (50 mL) and cooled at 0 °C. The precipitate was filtered off, washed with ether petroleum (20 mL) and dried under reduced pressure to afford **(3b)**

[2] R. Varala; S. Nuvula; S. R. Adapa. Molecular Iodine-Catalyzed Facile Procedure for *N*-Boc Protection of Amines. *J. Org. Chem*., **2006**, 71(21), 8283-8286.

(977.3 mg). Yield: 98%; Mp: 78 ± 1 °C; IR (KBr) ν (cm^{-1}) 3351, 2490, 2243, 2220, 2071, 1676; ^{1}H NMR (200 MHz, MeOD) δ 7.77 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.0 Hz, 1H, H-3'), 7.43 (m, 1H, H-6'), 7.31 (m, 1H, H-5'), 6.96 (m, 1H, H-4'), 4.53 (s, 2H, H-e), 3.70 (t, ^{3}J = 4.9 Hz, 2H, H-f), 3.12 (t, ^{3}J = 4.9 Hz, 2H, H-g); ^{13}C NMR (50 MHz, MeOD) δ 139.9 (C-1'), 139.2 (C-3'), 129.4 (C-4'), 129.1 (C-6'), 128.2 (C-5'), 97.5 (C-2'), 76.7 (C-e), 66.2 (C-f), 39.4 (C-g); ESI-SM m/z 278.00 $[M+H^{+}]^{+}$.

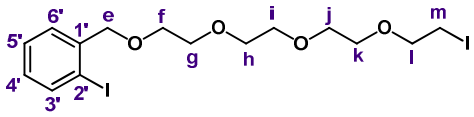
Synthesis of compound (3c)

1-(2-Iodophenyl)-2,5,8,11-tetraoxatridecan-13-ol (5)



To a solution of tetraethylene glycol (611.8 mg, 3.15 mmol, 1 eq.) dissolved in dry THF (15 mL), cooled at 0 °C, were added sodium hydride (176.4 mg, 4.63 mmol, 1.46 eq.) and 2-iodobenzyl bromide **(2)**[2] (1.5 g, 5.05 mmol, 1.6 eq.). The resulting mixture was stirred at room temperature for 20 h. Then, methanol (5 mL) was added and the reaction mixture was evaporated under reduced pressure. The crude product was dissolved in ethyl acetate (40 mL), washed with water (15 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure to afford **6** (750 mg). Yield: 58%; IR (KBr) ν (cm^{-1}) 3409, 2870, 1636, 1564; ^{1}H NMR (200 MHz, MeOD) δ 7.83 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.0 Hz, 1H, H-3'), 7.46 (m, 1H, H-6'), 7.38 (m, 1H, H-5'), 7.02 (m, 1H, H-4'), 4.53 (s, 2H, H-e), 3.36 (m, 14H, H-f, H-g, H-h, H-i, H-j, H-k, H-l), 3.63 (m, 2H, H-m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5 (C-1'), 139.1 (C-3'), 129.3 (C-4'), 128.9 (C-6'), 128.3 (C-5'), 97.8 (C-2'), 77.0 (C-e), 72.7 – 70.7 – 70.6 – 70.3 – 70.1 (C-f, C-g, C-h, C-i, C-j, C-k, C-l), 61.1 (C-m); IE-SM m/z 217 $[M-C_8H_{17}O_5]^{+}$, 90 $[M-C_8H_{17}O_5-I]^{+}$.

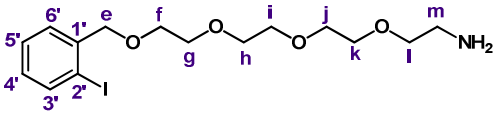
13-Iodo-1-(2-iodophenyl)-2,5,8,11-tetraoxatridecane (6)



To a solution of 1-(2-iodophenyl)-2,5,8,11-tetraoxatridecan-13-ol **(5)** (700.0 mg, 1.7 mmol, 1 eq.) dissolved in dichloromethane (15 mL), cooled at 0 °C, were added successively

imidazole (151.1 mg, 2.22 mmol, 1.3 eq.), triphenylphosphine (582.3 mg, 2.22 mmol, 1.3 eq.) and diiode (563.5 mg, 2.22 mmol, 1.3 eq.). The resulting mixture was stirred at room temperature for 18 h. Then, a solution of sodium bisulfite (10%) was added and the aqueous layer was extracted with dichloromethane (20 mL). The pooled organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was dissolved in pentane (30 mL) and stirred for 30 min. The precipitate was filtered off. The filtrate was dried under reduced pressure and purified on silica gel eluted with dichloromethane/ethanol (99/1, v/v) to afford **3c** (490 mg). Yield: 55%; IR (KBr) ν (cm^{-1}) 2867, 1564; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.1 Hz, 1H, H-3'), 7.45 (m, 1H, H-6'), 7.32 (m, 1H, H-5'), 6.96 (m, 1H, H-4'), 4.52 (s, 2H, H-e), 3.67 (m, 14H, H-f, H-g, H-h, H-i, H-j, H-k, H-l), 3.23 (m, 2H, H-m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6 (C-1'), 138.2 (C-3'), 128.3 (C-4'), 128.1 (C-6'), 127.9 (C-5'), 96.8 (C-2'), 76.0 (C-e), 71.0 – 69.8 – 69.7 – 69.3 – 69.2 (C-f, C-g, C-h, C-i, C-j, C-k, C-l), 2.2 (C-m); IE-SM m/z 217 $[M-C_8H_{16}O_4I]^+$, 90 $[M-C_8H_{16}O_4I-I]^+$.

1-(2-Iodophenyl)-2,5,8,11-tetraoxatridecan-13-amine (3c)

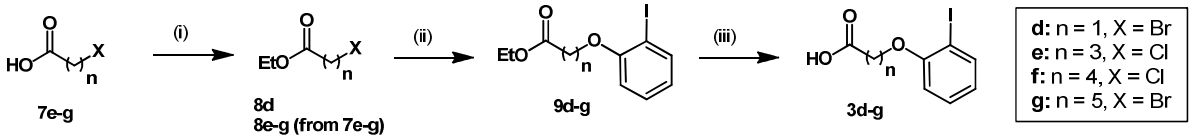


To a solution of 13-iodo-1-(2-iodophenyl)-2,5,8,11-tetraoxatridecane **(6)** (640.0 mg, 1.23 mmol, 1 eq.) in dimethylformamide (20 mL) was added potassium phtalimide (455.6 mg, 2.46 mmol, 2.2 eq.). The resulting mixture was heated at 30 °C for 18 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3×40 mL). The pooled organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was dissolved in absolute ethanol (15 mL), before adding of hydrazine (540.5 µL, 11.14 mmol, 6 eq.). The reaction mixture was heated at 30 °C for 18 h. After cooling to room temperature, the precipitate was filtered off and the filtrate was dried under reduced pressure. The crude product was purified on silica gel eluted with dichloromethane/methanol/ammonium hydroxide (90/10/1, v/v/v) to afford **(3c)** (190 mg). Yield: 38%; IR (KBr) ν (cm^{-1}) 3371, 2869, 1564; ^{1}H NMR (200 MHz, MeOD) δ 7.84 (dd, ^{3}J = 7.8 Hz, ^{4}J = 0.9 Hz, 1H, H-3'), 7.49 (m, 1H, H-6'), 7.38 (m, 1H, H-5'), 7.03 (m, 1H, H-4'), 4.55 (s, 2H, H-e), 3.62 (m, 14H, H-f, H-g, H-h, H-i, H-j, H-k, H-l), 3.51 (t, ^{3}J = 5.2 Hz, 2H, NH_2), 2.77 (t, ^{3}J = 5.2 Hz, 2H, H-m); ^{13}C NMR (50 MHz, MeOD) δ 140.5 (C-1'), 139.0 (C-

3'), 129.0 (C-4'), 128.7 (C-6'), 128.0 (C-5'), 97.1 (C-2'), 76.5 (C-e), 71.7 - 70.2 - 69.9 - 69.8 (C-f, C-g, C-h, C-i, C-j, C-k, C-l), 40.6 (C-m); ESI-SM m/z 410.12 $[M+H^+]^+$.

Access to compounds 3d-g

Scheme 2[a]

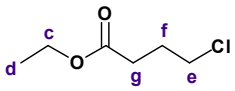


[a] **Reactants and conditions:** (i) Acetyl chloride, dry ethanol, rt; (ii) 2-iodophenol, dry DMF, 80°C; (iii) (a) LiOH monohydrate, THF/H_2O/MeOH (3/1/1, v/v/v), rt; (b) HCl (1N).

General method for synthesis of 8e-g

To a solution of the appropriated acid derivatives **(7e-g)** (1 eq.) dissolved in anhydrous ethanol (20 mL) was added dropwise acetyl chloride (2.1 eq.). The resulting mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The obtained product was used without further purification for the next step.

Ethyl 4-chloro-butanoic acid (8e)[3]

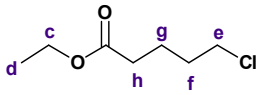


Ethyl 4-chloro-butanoic acid **(8e)** was synthesized from 4-chlorobutanoic acid (0.5 g, 4.08 mmol). Yield: 73%; IR (KBr) ν (cm^{-1}) 2984, 1732 (C=O), 1647, 1445, 1375, 1301, 1211, 1146, 1026; ^1H NMR (200 MHz, $CDCl_3$) δ 4.15 (q, ^3J = 7.1 Hz, 2H, H-c), 3.60 (t, ^3J = 6.3 Hz, 2H, H-e), 2.49 (t, ^3J = 7.2 Hz, 2H, H-g), 2.09 (m, 2H, H-f), 1.26 (t, ^3J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6 (C=O), 60.5 (C-c), 44.0 (C-e), 31.1 (C-g), 27.6 (C-f), 14.1 (C-d).

Ethyl 5-chloro-pentanoic acid (8f)[4]

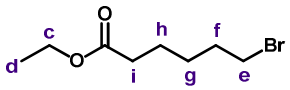
[3] This product is commercially available under CAS 3153-36-4

[4] This product is commercially available under CAS 2323-81-1 and described by P. M. Henrichs; P. E. Peterson. Proton and carbon-13 nuclear magnetic resonance spectra of equilibrating organic cations. Evidence for a six-membered-ring halonium ion in equilibrium with a tertiary carbonium ion *J. Org. Chem*. **1976**, 41, 362–367.



Ethyl 5-chloro-pentanoic acid **(8f)** was synthesized from 5-chloropentanoic acid (4.0 g, 29.29 mmol). Yield: 95%; IR (KBr) ν (cm^{-1}) 2982, 1734 (C=O), 1635, 1447, 1374, 1278, 1184, 1030; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (q, ^{3}J = 7.1 Hz, 2H, H-c), 3.54 (m, 2H, H-e), 2.33 (m, 2H, H-h), 1.80 (m, 4H, H-g, H-f), 1.25 (t, ^{3}J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2 (C=O), 60.4 (C-c), 44.5 (C-e), 33.5 (C-h), 31.9 (C-g), 22.3 (C-f), 14.2 (C-d).

Ethyl 6-bromo-hexanoic acid (8g)[5]



Ethyl 6-bromo-hexanoic acid (**8g**) was synthesized from 6-bromohexanoic acid (3.76 g, 16.85 mmol). Yield: 66%; IR (KBr) ν (cm-1) 2939, 2866, 1734, 1462, 1373, 1350, 1254, 1190, 1124, 1030; ^{1}H NMR (200 MHz, CDCl3) δ 4.11 (q, ^{3}J = 7.1 Hz, 2H, H-c), 3.40 (t, ^{3}J = 6.7 Hz, 2H, H-e), 2.30 (t, ^{3}J = 7.1 Hz, 2H, H-i), 1.83 (m, 2H, H-f), 1.61 (m, 2H, H-h), 1.44 (m, 2H, H-g), 1.24 (t, ^{3}J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, CDCl3) δ 173.7 (C=O), 60.3 (C-c), 34.1 (C-i), 33.5 (C-e), 32.4 (C-f), 27.6 (C-g), 24.1 (C-h), 14.2 (C-d).

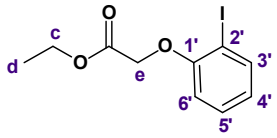
General method for synthesis of 9d-g

To a solution of the appropriate ester derivatives (8d-g) (1.1 eq.) dissolved in anhydrous DMF (20 mL), were successively added potassium carbonate (2.5 eq.) and 2-iodophenol[6] (1.0 eq.). The resulting mixture was heated at 80 °C for 3 days. After cooling to room temperature, a saturated solution of sodium carbonate (30 mL) was added and the solution was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with hydrochloric acid 1N (20 mL), water (20 mL), brine (20 mL), dried over magnesium sulfate,

[5] This product is commercially available under CAS 10140-96-2 and described by E. Arstad; A. G. M. Barrett; B. T. Hopkins; J. Kobberling. ROMPgel-Supported Triphenylphosphine with Potential Application in Parallel Synthesis. *Org. Lett.*, **2002**, 4, 11, 1975-1977.

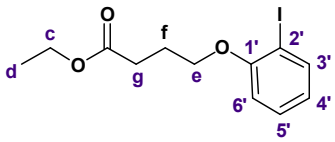
[6] P. L. Zabel; Y. Zea-Ponce; G. W. Brown; G. Morrissey; D. H. Hunter; A. A. Driedger; M. J. Chamberlain; Preparation and evaluation of radioiodinated (iodophenyl)cholines and their morpholinium and piperidinium analogues as myocardial perfusion imaging agents. *J. Med. Chem.*, **1986**, 29(5), 757-64.

filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with ethyl acetate/cyclohexane (8/2, v/v).**Ethyl 2-(2-iodophenoxy)acetic acid (9d)**[7]



Ethyl 2-(2-iodophenoxy)acetic acid **(9d)** was synthesized from ethyl 2-bromo-acetic acid **(8d)** (1.51 g, 9.04 mmol). Yield: 48%; IR (KBr) ν (cm^{-1}) 2981, 1758 (C=O), 1733 (C=O), 1582, 1472; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (dd, ^{3}J = 7.6 Hz, ^{4}J = 1.6 Hz, 1H, H-3'), 7.27 (m, 1H, H-5'), 6.74 (m, 2H, H-4', H-6'), 4.67 (s, 2H, H-e), 4.26 (q, ^{3}J = 7.1 Hz, 2H, H-c), 1.29 (t, ^{3}J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4 (C=O), 156.7 (C-1'), 139.9 (C-3'), 129.4 (C-5'), 123.6 (C-4'), 112.4 (C-6'), 86.5 (C-2'), 66.4 (C-e), 61.5 (C-c), 14.2 (C-d).

Ethyl 4-(2-iodophenoxy)butanoic acid (9e)[8]

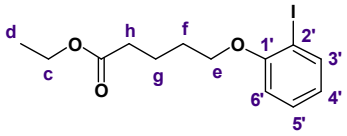


Ethyl 4-(2-iodophenoxy)butanoic acid **(9e)** was synthesized from ethyl 4-chloro-butanoic acid **(8e)** (0.75 g, 4.98 mmol). Yield: 74%; IR (KBr) ν (cm^{-1}) 2979, 1732 (C=O), 1582, 1466, 1440; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, H-3'), 7.28 (m, 1H, H-5'), 6.74 (m, 2H, H-4', H-6'), 4.15 (q, ^{3}J = 7.1 Hz, 2H, H-c), 4.07 (t, ^{3}J = 6.0 Hz, 2H, H-e), 2.62 (t, ^{3}J = 7.3 Hz, 2H, H-g), 2.17 (m, 2H, H-f), 1.26 (t, ^{3}J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3 (C=O), 157.5 (C-1'), 139.4 (C-3'), 129.5 (C-5'), 122.6 (C-4'), 112.1 (C-6'), 86.7 (C-2'), 67.9 (C-e), 60.5 (C-c), 30.8 (C-g), 24.5 (C-f), 14.3 (C-d).

[7] This product is commercially available under CAS 90794-32-4 and described by C-F. Wu; X. Zhao; W-X. Lan; C. Cao; J-T Liu; X-K. Jiang; Z-T. Li. A 1,4-Diphenyl-1,2,3-Triazole-Based β-Turn Mimic Constructed by Click Chemistry. *J. Org. Chem*., **2012**, 77, 4261-4270.

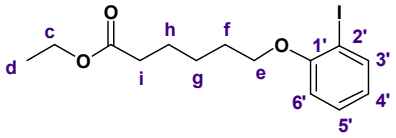
[8] This product is commercially available under CAS 132902-23-9 and described by R. R. Karimov; Z-G. M. Kazhkenov; M. J. Modjewski; E. M. Peterson; V. V. Zhdankin. Preparation and Reactivity of Polymer-Supported 2-Iodylphenol Ethers, an Efficient Recyclable Oxidizing System. *J. Org. Chem*. **2007**, 72, 8149-8151.

Ethyl 5-(2-iodophenoxy)pentanoic acid (9f)[9]



Ethyl 5-(2-iodophenoxy)pentanoic acid **(9f)** was synthesized from ethyl 5-chloro-pentanoic acid **(8f)** (4.63 g, 28.12 mmol). Yield: 65%; IR (KBr) ν (cm^{-1}) 2940, 1733 (C=O), 1582, 1466, 1439; NMR ^{1}H (200 MHz, $CDCl_3$) δ 7.74 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, H-3'), 7.26 (m, 1H, H-5'), 6.69 (m, 2H, H-4', H-6'), 4.11 (q, ^{3}J = 7.1 Hz, 2H, H-c), 3.98 (m, 2H, H-e), 2.40 (m, 2H, H-h), 1.87 (m, 4H, H-f, H-g), 1.25 (t, ^{3}J = 7.1Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5 (C=O), 157.4 (C-1'), 139.6 (C-3'), 129.6 (C-5'), 122.6 (C-4'), 112.1 (C-6'), 86.7 (C-2'), 68.6 (C-e), 60.3 (C-c), 33.9 (C-h), 28.5 (C-f), 21.7 (C-g), 14.3 (C-d).

Ethyl 6-(2-iodophenoxy)hexanoic acid (9g)[10]



6-(2-iodophenoxy)hexanoic acid ethyl ester **(9g)** was synthesized from ethyl 6-bromo-hexanoic acid **(8g)** (5.82 g, 26.08 mmol). Yield: 30%; IR (KBr) ν (cm^{-1}) 2941, 1733 (C=O), 1582, 1466, 1439; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, H-3'), 7.26 (m, 1H, H-5'), 6.67 (m, 2H, H-4', H-6'), 4.10 (q, ^{3}J = 7.1 Hz, 2H, H-c), 3.98 (t, ^{3}J = 6.2 Hz, 2H, H-e), 2.34 (t, ^{3}J = 7.1 Hz, 2H, H-i), 1.84 (m, 2H, H-f), 1.74 (m, 2H, H-h), 1.57 (m, 2H, H-g), 1.24 (t, ^{3}J = 7.1 Hz, 3H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7 (C=O), 157.5 (C-1'), 139.4 (C-3'), 129.8 (C-5'), 122.4 (C-4'), 112.0 (C-6'), 86.7 (C-2'), 68.8 (C-e), 60.3 (C-c), 34.3 (C-i), 28.8 (C-f), 25.7 (C-g), 24.7 (C-h), 14.3 (C-d).

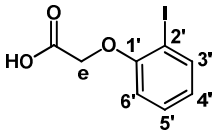
General method for synthesis of 3d-g

To a solution of the appropriate ester derivatives **(9d-g)** (1 eq.) dissolved in THF/methanol (3/1, v/v), was added a solution of lithium hydroxide monohydrate (2 eq.) in water (1/v). The resulting mixture was stirred at room temperature for 18 h. After cooling to room temperature, the reaction solvents were evaporated under reduced pressure. The crude product was

[9] This product is commercially available under CAS 132902-33-1.
[10] This product is commercially available under CAS 1410578-64-1.

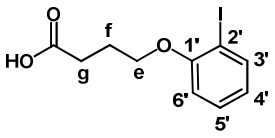
dissolved with water (40 mL) and was acidified to pH = 1 with a solution of hydrochloric acid 1 N. The aqueous solution was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The obtained product was used without further purification for the next step.

2-(2-Iodophenoxy)acetic acid (3d)[11]



2-(2-iodophenoxy)acetic acid **(3d)** was synthesized from 2-(2-iodophenoxy)acetic acid ethyl ester **(9d)**. (1.34 g, 4.37 mmol). Yield: 97%; Mp: 125 ± 1 °C; IR (KBr) ν (cm^{-1}) 2919, 2361, 1745 (C=O), 1707 (C=O), 1579, 1478, 1439, 1425; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.30 (m, 1H, H-5'), 6.81 (m, 2H, H-4', H-6'), 4.72 (s, 2H, H-e) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6 (C=O), 156.2 (C-1'), 140.0 (C-3'), 129.7 (C-5'), 124.2 (C-4'), 112.6 (C-6'), 86.5 (C-2'), 65.9 (C-e).

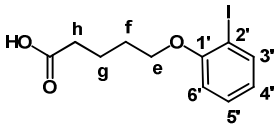
4-(2-Iodophenoxy)butanoic acid (3e)[12]



4-(2-iodophenoxy)butanoic acid **(3e)** was synthesized from 4-(2-iodophenoxy)butanoic acid ethyl ester **(9e)** (1.05 g, 3.14 mmol). Yield: 53%; Mp: 67.9 ± 1 °C; IR (KBr) ν (cm^{-1}) 2925, 2361, 1702 (C=O), 1582, 1480, 1463, 1438; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.20 (br, 1H, H-acide), 7.82 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.35 (m, 1H, H-5'), 6.81 (m, 2H, H-4',H-6'), 4.13 (t, ^{3}J = 5.8 Hz, 2H, H-e), 2.77 (t, ^{3}J = 7.2 Hz, 2H, H-g), 2.25 (m, 2H, H-f); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.7 (C=O), 157.1 (C-1'), 139.4 (C-3'), 129.4 (C-5'), 122.6 (C-4'), 112.0 (C-6'), 86.5 (C-2'), 67.5 (C-e), 30.6 (C-g), 24.2 (C-f).

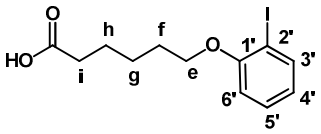
[11] This product is commercially available under CAS 1878-92-8.
[12] This product is commercially available under CAS 957040-08-3 and described by R. R. Karimov; Z-G. M. Kazhkenov; M. J. Modjewski; E. M. Peterson; V. V. Zhdankin. Preparation and Reactivity of Polymer-Supported 2-Iodylphenol Ethers, an Efficient Recyclable Oxidizing System. *J. Org. Chem*. **2007**, 72, 8149-8151.

5-(2-Iodophenoxy)pentanoic acid (3f)[13]



5-(2-iodophenoxy)pentanoic acid **(3f)** was synthesized from 5-(2-iodophenoxy)pentanoic acid ethyl ester **(9f)** (5.0 g, 14.36 mmol). Yield: 90%; Mp: 63.2 ± 1 °C; IR (KBr) ν (cm^{-1}) 2935, 1711 (C=O), 1582, 1567, 1479, 1463, 1437; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.15 (br, 1H, H-acide), 7.76 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.28 (m, 1H, H-5'), 6.74 (m, 2H, H-4',H-6'), 4.02 (t, ^{3}J = 5.3 Hz, 2H, H-e), 2.49 (m, 2H, H-h), 1.91 (m, 4H, H-f, H-g); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.8 (C=O), 156.9 (C-1'), 139.0 (C-3'), 129.1 (C-5'), 122.1 (C-4'), 111.7 (C-6'), 86.3 (C-2'), 68.1 (C-e), 33.3 (C-h), 28.0 (C-f), 21.1 (C-g).

6-(2-Iodophenoxy)hexanoic acid (3g)[14]



6-(2-iodophenoxy)hexanoic acid **(3g)** was synthesized from 6-(2-iodophenoxy)hexanoic acid ethyl ester **(9g)** (2.5 g, 6.90 mmol). Yield: quant.; Mp: 59.1 ± 1 °C; IR (KBr) ν (cm^{-1}) 2950, 1712 (C=O), 1580, 1483, 1466, 1441; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.26 (m, 1H, H-5'), 6.70 (m, 2H, H-4',H-6'), 4.02 (t, ^{3}J = 6.1 Hz, 2H, H-e), 2.43 (t, ^{3}J = 7.4 Hz, 2H, H-i), 1.88 (m, 2H, H-f), 1.73 (m, 2H, H-h), 1.66 (m, 2H, H-g); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.0 (C=O), 157.0 (C-1'), 138.9 (C-3'), 129.1 (C-5'), 122.0 (C-4'), 111.7 (C-6'), 86.3 (C-2'), 68.3 (C-e), 33.6 (C-i), 28.3 (C-f), 25.2 (C-g), 23.9 (C-h).

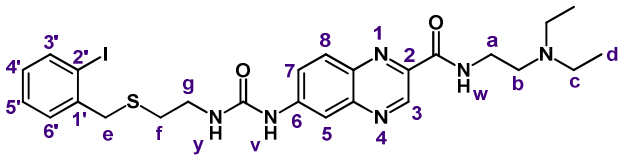
General Method for synthesis of quinoxaline derivatives (1a-c)

To a solution of 4-nitrophenyl (2-((2-(*N*,*N*-diethylamino)ethyl)carbomoyl)quinoxalin-6-yl)carbamate **(11)** (1.1 eq.) dissolved in dry THF (20 mL), DMAP was added (1.65 eq.) and the resulting mixture was stirred at room temperature for 30 min. Then, the appropriate amine derivative **(3a-c)** (1 eq.) dissolved in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at room temperature until disappearance of starting material as monitored

[13] This product is commercially available under CAS 1155918-73-2.
[14] This product is commercially available under CAS 1236230-64-0.

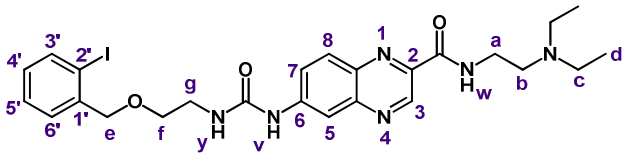
by TLC. The reaction mixture was evaporated under reduced pressure. The crude product was dissolved with a saturated solution of $NaHCO_3$ (20 mL) and extracted with dichloromethane (3×40 mL). The pooled organic layers were washed with a saturated solution of $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure.

_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(_N_-(2-((2-iodobenzyl)thio)ethyl)ureido)quinoxaline-2-carboxamide (1a)



_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(_N_-(2-((2-iodobenzyl)thio)ethyl)ureido)quinoxaline-2-carboxamide **(1a)** was synthesized from **(11)** and 2-((2-iodobenzyl)thio)ethanamine **(3a)** (660 mg, 2.25 mmol). After 2 h 30 and work-up, the crude product was triturated with DCM. The precipitate was filtered off (810 mg). Yield: 60%; Mp 188 ± 1 °C; IR (KBr) ν (cm^{-1}) 3346, 2964, 2932, 1695 (C=O), 1656 (C=O), 1556, 1522; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.41 (br, 1H, NH-v), 9.34 (s, 1H, H-3), 8.78 (t, ^3J = 5.5 Hz, 1H, NH-w), 8.34 (d, ^4J = 2.1 Hz, 1H, H-5), 8.02 (d, ^3J = 9.2 Hz, 1H, H-8), 7.86 (m, 1H, H-7, H-3'), 7.47 (m, 1H, H-6'), 7.36 (m, 1H, H-4'), 7.01 (m, 1H, H-5'), 6.63 (t, ^3J = 5.7 Hz, 1H, NH-y), 3.86 (s, 2H, H-e), 3.36 (m, 2H, H-a), 2.57 (m, 10H, H-b, H-c, H-f, H-g), 0.99 (t, ^3J = 7.0 Hz, 6H, H-d). ^{13}C NMR (50 MHz, DMSO-d_6) δ 163.5 (C=O), 155.2 (C=O), 144.8 (C-4a), 144.1 (C-3), 143.9 (C-6), 142.0 (C-2), 141.2 (C-1'), 139.9 (C-3'), 136.0 (C-8a), 130.7 (C-6'), 130.2 (C-8), 129.4 (C-4'), 128.8 (C-5'), 124.8 (C-7), 112.6 (C-5), 101.4 (C-2'), 51.7 (C-b), 47.1 (C-c), 40.6 (C-e), 39.3 (C-g), 37.5 (C-a), 31.6 (C-f), 12.4 (C-d); ESI-SM m/z 607.12 $[M+H^+]^+$.

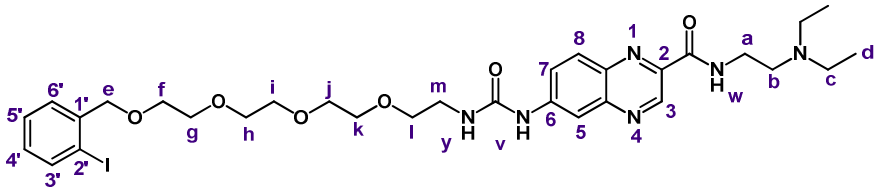
_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(3-(2-((2-iodobenzyl)oxy)ethyl)ureido)quinoxaline-2-carboxamide (1b)



_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(3-(2-((2-iodobenzyl)oxy)ethyl)ureido)quinoxaline-2-

carboxamide **(1b)** was synthesized from **(11)** and 2-((2-iodobenzyl)oxy)ethanamine hydrochloride **(3b)** (940.8 mg, 3.0 mmol). After 16 h and work-up, the crude product was purified on silica gel eluted with dichloromethane/methanol (80/20, v/v) to afford (770 mg, 1.3 mmol) of **(1b)**. Yield: 44%; IR (KBr) ν (cm^{-1}) 3352, 2966, 1655 (C=O), 1652 (C=O), 1523; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.43 (s, 1H, H-3), 8.91 (br, 1H, N-v), 8.40 (t, ^{3}J = 5.5 Hz, 1H, NH-w), 8.04 (d, ^{4}J = 1.8 Hz, 1H, H-5), 7.91 (m, 1H, H-7), 7.79 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.66 (m, 1H, H-3'), 7.28 (m, 1H, H-6'), 7.17 (m, 1H, H-5'), 6.85 (m, 1H, H-4'), 6.43 (m, 1H, NH-y), 4.40 (s, 2H, H-e), 3.60 (m, 6H, H-a, H-f, H-g), 2.72 (t, ^{3}J = 6.1 Hz, 2H, H-b), 2.62 (q, ^{3}J = 7.0 Hz, 4H, H-c), 1.07 (t, ^{3}J = 7.0 Hz, 6H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.0 (C=O), 155.9 (C=O), 144.9 (C-4a), 143.7 (C-3), 143.1 (C-6), 141.2 (C-2), 139.9 (C-1'), 139.1 (C-3'), 136.6 (C-8a), 130.2 (C-8), 129.3 (C-4'), 128.9 (C-6'), 128.2 (C-5'), 124.6 (C-7), 113.9 (C-5), 98.1 (C-2'), 76.8 (C-e), 70.1 (C-f), 51.6 (C-b), 47.1 (C-c), 40.3 (C-g), 37.3 (C-a), 11.9 (C-d); ESI-SM m/z 591.20 $[M+H^{+}]^{+}$.

_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(3-(1-(2-iodophenyl)-2.5.8.11-tetraoxatridecan-13-yl)ureido)quinoxaline-2-carboxamide (1c)



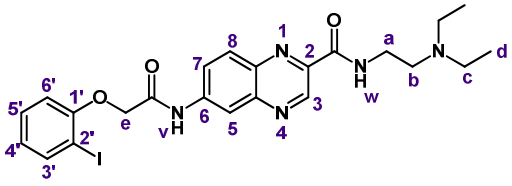
N-(2-(*N,N*-Diethylamino)ethyl)-6-(3-(1-(2-iodophenyl)-2,5,8,11-tetraoxatridecan-13-yl)ureido)quinoxaline-2-carboxamide **(1c)** was synthesized from **(11)** and 1-(2-iodophenyl)-2.5.8.11-tetraoxatridecan-13-amine **(3c)** (300 mg, 0.73 mmol). After 4 h and work-up, the crude product was purified on silica gel eluted with dichloromethane/methanol/ammonium hydroxide (90/10/1, v/v/v) to afford **(1c)** (350 mg). Yield: 66%; IR (KBr) ν (cm^{-1}) 1703 (C=O), 1667 (C=O), 1527, 1485, 1343, 1242, 1132, 1108; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.51 (s, 1H, H-3), 8.44 (br, 1H, NH-v), 8.37 (t, ^{3}J = 5.5 Hz, 1H, NH-w), 8.20 (dd, ^{3}J = 9.2 Hz, ^{4}J = 2.3 Hz, 1H, H-7), 7.91 (d, ^{4}J = 2.3 Hz, 1H, H-5), 7.86 (d, ^{3}J = 9.2 Hz, 1H, H-8), 7.64 (dd, ^{3}J = 7.9 Hz, ^{4}J = 1.0 Hz, 1H, H-3'), 7.27 (m, 1H, H-6'), 7.12 (m, 1H, H-5'), 6.81 (m, 1H, H-4'), 6.21 (t, ^{3}J = 4.8 Hz, 1H, NH-y), 4.46 (s, 2H, H-e), 3.80 (m, 16H, H-a, H-f, H-g, H-h, H-i, H-j, H-k, H-l), 3.44 (m, 2H, H-m), 2.75 (t, ^{3}J = 6.3 Hz, 2H, H-b), 2.65 (q, ^{3}J = 7.0 Hz, 4H, H-c), 1.11 (t, ^{3}J = 7.0 Hz, 6H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.9 (C=O), 155.3 (C=O), 144.9 (C-4a), 143.9 (C-3), 143.6 (C-6), 141.3 (C-2), 139.1 (C-1'), 136.5 (C-3'), 136.5 (C-8a),

130.0 (C-8), 129.3 (C-4'), 129.1 (C-6'), 128.1 (C-5'), 124.3 (C-7), 113.3 (C-5), 98.2 (C-2'), 77.0 (C-e), 70.6 – 70.5 – 70.0 – 69.9 – 69.8 (C-f, C-g, C-h, C-i, C-j, C-k, C-l), 51.7 (C-b), 47.2 (C-c), 40.1 (C-m), 37.3 (C-a), 12.0 (C-d); ESI-SM m/z 723.35 $[M+H^+]^+$.

General Method for synthesis of quinoxaline derivatives (1d-g)

To a solution of the appropriate ω-(2-iodophenoxy)alkoxy acid derivative **(3d-g)** (3.13 mmol, 6 eq.) dissolved in anhydrous DCM (20 mL) cooled to 0 °C, was added thionyl chloride (227 µL, 3.13 mmol, 6 eq.). The resulting mixture was heated at reflux for 5 h. After cooling to room temperature, excess of solvent was co-evaporated under reduced pressure with anhydrous toluene (3×10 mL). The residue was dissolved in anhydrous DCM (20 mL). Then, 4-dimethylaminopyridine (76.5 mg, 0.63 mmol, 1.2 eq.) and 6-amino-*N*-(2-(*N,N*-diethylamino)ethyl)quinoxaline-2-carboxamide **(10)** (0.15 g, 0.52 mmol, 1 eq.) were added. The resulting mixture was heated at 45 °C for 18 h. After cooling to room temperature, a saturated solution of sodium carbonate (20 mL) was added. The aqueous solution was extracted with DCM (3×20 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with DCM/methanol (95/5, v/v).

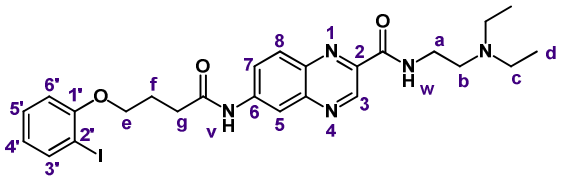
***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(2-(2-iodophenoxy)acetamido)quinoxaline-2-carboxamide (1d)**



N-(2-(*N,N*-Diethylamino)ethyl)-6-(2-(2-iodophenoxy)acetamido)quinoxaline-2-carboxamide **(1d)** (0.23 g, 0.42 mmol) was synthesized from 6-amino-*N*-(2-(*N,N*-diethylamino)ethyl)quinoxaline-2-carboxamide **(10)** and 2-(2-iodophenoxy)acetic acid **(3d)** (0.87 g). Yield: 81%; Mp: 163 ± 1 °C; IR (KBr) ν (cm^{-1}) 3348, 2968, 2804, 1702 (C=O), 1679 (C=O), 1618, 1540, 1494, 1471, 1431; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.63 (s, 1H, H-3), 9.31 (br, 1H, NH-v), 8.47 (d, ^4J = 2.1 Hz, 1H, H-5), 8.41 (t, ^3J = 5.6 Hz, 1H, NH-w), 8.25 (dd, ^3J = 9.1 Hz, ^4J = 2.1 Hz, 1H, H-7), 8.10 (d, ^3J = 9.1 Hz, 1H, H-8), 7.83 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, H-3'), 7.39 (m, 1H, H-5'), 6.87 (m, 2H, H-4',H-6'), 4.71 (s, 2H, H-e), 3.62 (q, ^3J =

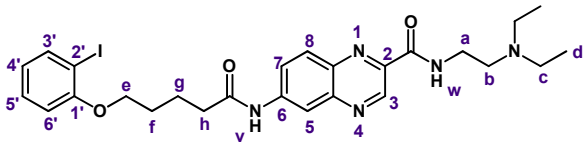
5.8 Hz, 2H, H-a), 2.75 (t, ^{3}J = 6.1 Hz, 2H, H-b), 2.65 (q, ^{3}J = 7.1 Hz, 4H, H-c), 1.10 (t, ^{3}J = 7.1 Hz, 6H, H-d) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7 (C=O), 163.4 (C=O), 155.2 (C-1'), 144.6 (C-4a), 144.5 (C-3), 142.9 (C-2), 139.8 (C-6), 139.5 (C-3'), 137.8 (C-8a), 130.8 (C-8), 130.1 (C-5'), 124.3 (C-7, C-4'), 116.9 (C-5), 112.6 (C-6'), 86.6 (C-2'), 68.0 (C-e), 51.7 (C-b), 47.2 (C-c), 37.3 (C-a), 12.0 (C-d); ESI-SM m/z 548,14 $[M+H^{+}]^{+}$.

_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(4-(2-iodophenoxy)butanamido)quinoxaline-2-carboxamide (1e)



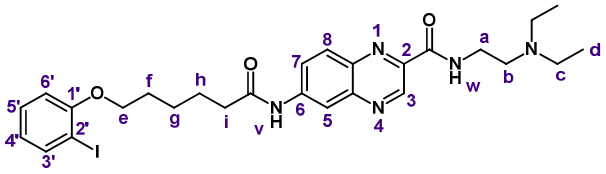
N-(2-(*N,N*-Diethylamino)ethyl)-6-(4-(2-iodophenoxy)butanamido)quinoxaline-2-carboxamide **(1e)** (0.20 g, 0.35 mmol) was synthesized from 6-amino-*N*-(2-(*N,N*-diethylamino)ethyl)quinoxaline-2-carboxamide **(10)** and 4-(2-iodophenoxy)butanoic acid **(3e)** (0.96g). Yield: 67%; Mp: 147 ± 1 °C; IR (KBr) ν (cm^{-1}) 3312, 2967, 2804, 1715 (C=O), 1655 (C=O), 1625, 1575, 1523, 1476; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.56 (s, 1H, H-3), 8.54 (br, 1H, NH-v), 8.44 (t, ^{3}J = 4.6 Hz, 1H, NH-w), 8.34 (d, ^{3}J = 2.1 Hz, 1H, H-5), 8.08 (dd, ^{3}J = 9.1 Hz, ^{4}J = 2.1 Hz, 1H, H-7), 7.98 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.71 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.4 Hz, 1H, H-3'), 7.26 (m, 1H, H-5'), 6.72 (m, 2H, H-4',H-6'), 4.10 (t, ^{3}J = 5.5 Hz, 2H, H-e), 3.61 (q, ^{3}J = 5.8 Hz, 2H, H-a), 2.82 (t, ^{3}J = 6.8 Hz, 2H, H-g), 2.74 (t, ^{3}J = 6.6 Hz, 2H, H-b), 2.64 (q, ^{3}J = 7.1 Hz, 4H, H-c), 2.29 (m, 2H, H-f), 1.09 (t, ^{3}J = 7.1 Hz, 6H, H-d) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5 (C=O), 163.6 (C=O), 156.9 (C-1'), 144.5 (C-4a), 144.3 (C-3), 142.4 (C-2), 141.0 (C-6), 139.4 (C-3'), 137.4 (C-8a), 130.4 (C-8), 129.7 (C-5'), 124.6 (C-7), 122.9 (C-4'), 116.4 (C-5), 112.3 (C-6'), 86.6 (C-2'), 67.5 (C-e), 51.6 (C-b), 47.2 (C-c), 37.2 (C-a), 34.0 (C-g), 24.8 (C-f), 11.8 (C-d); ESI-SM m/z 576.15 $[M+H^{+}]^{+}$.

_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(5-(2-iodophenoxy)pentanamido)quinoxaline-2-carboxamide (1f)



N-(2-(*N,N*-Diethylamino)ethyl)-6-(5-(2-iodophenoxy)pentanamido)quinoxaline-2-carboxamide **(1f)** (0.30 g, 0.51 mmol) was synthesized from 6-amino-*N*-(2-(*N,N*-diethylamino)ethyl)quinoxaline-2-carboxamide **(10)** and 5-(2-iodophenoxy)pentanoic acid **(3f)** (1.00 g). Yield: 98%; Mp: 142.7 ± 1 °C; IR (KBr) ν (cm^{-1}) 3294, 2966, 2804, 1692 (C=O), 1658 (C=O), 1625, 1577, 1523, 1465; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.59 (s, 1H, H-3), 8.43 (br, 1H, NH-v), 8.30 (d, ^{3}J = 1.6 Hz, 1H, H-5), 8.14 (m, 2H, H-7, NH-w), 8.02 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.75 (dd, ^{3}J = 7.1 Hz, ^{4}J = 1.2 Hz, 1H, H-3'), 7.27 (m, 1H, H-5'), 6.72 (m, 2H, H-4',H-6'), 4.07 (t, ^{3}J = 5.5 Hz, 2H, H-e), 3.60 (q, ^{3}J = 5.6 Hz, 2H, H-a), 2.68 (m, 8H, H-b, H-h, H-c), 2.00 (m, 2H, H-f, H-g), 1.11 (t, ^{3}J = 7.1 Hz, 6H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8 (C=O), 163.5 (C=O), 157.3 (C-1'), 144.6 (C-4a), 144.3 (C-3), 142.5 (C-2), 140.9 (C-6), 139.4 (C-3'), 137.4 (C-8a), 130.5 (C-8), 129.6 (C-5'), 124.6 (C-7), 122.6 (C-4'), 116.4 (C-5), 112.1 (C-6'), 86.6 (C-2'), 68.9 (C-e), 51.6 (C-b), 47.2 (C-c), 37.4 and 37.2 (C-a, C-h), 28.2 (C-f), 22.6 (C-g), 11.9 (C-d); ESI-SM m/z 590.20 $[M+H^{+}]^{+}$.

_N_-(2-(_N,N_-Diethylamino)ethyl)-6-(6-(2-iodophenoxy)hexanamido)quinoxaline-2-carboxamide (1g)



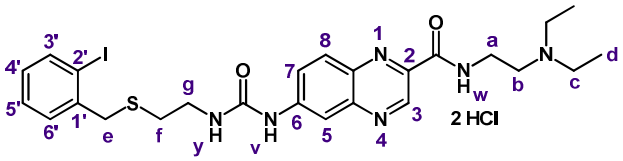
N-(2-(*N,N*-Diethylamino)ethyl)-6-(6-(2-iodophenoxy)hexanamido)quinoxaline-2-carboxamide **(1g)** (91.1 mg, 0.15 mmol) was synthesized from 6-amino-*N*-(2-(*N,N*-diethylamino)ethyl)quinoxaline-2-carboxamide **(10)** and 6-(2-iodophenoxy)hexanoic acid **(3g)** (1.05 g). Yield: 29%; Mp: 101.2 ± 1 °C; IR (KBr) ν (cm^{-1}) 3317, 2950, 1715 (C=O), 1660 (C=O), 1625, 1578, 1520, 1463, 1437, 1417; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.53 (s, 1H, H-3), 8.42 (t, ^{3}J = 4.8 Hz, 1H, NH-v), 8.27 (d, ^{4}J = 2.1 Hz, 1H, H-5), 8.22 (br, 1H, NH-w), 8.06 (dd, ^{3}J = 9.1 Hz, ^{4}J = 2.1 Hz, 1H, H-7), 7.96 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.69 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.22 (m, 1H, H-5'), 6.67 (m, 2H, H-4',H-6'), 3.96 (t, ^{3}J = 5.8 Hz, 2H, H-e), 3.58 (q, ^{3}J = 5.8 Hz, 2H, H-a), 2.75 (t, ^{3}J = 5.8 Hz, 2H, H-b), 2.65 (q, ^{3}J = 7.1 Hz,

4H, H-c), 2.50 (t, ^{3}J = 7.2 Hz, 2H, H-i), 1.84 (m, 4H, H-f, H-h), 1.65 (m, 2H, H-g), 1.07 (t, ^{3}J = 7.1 Hz, 6H, H-d) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.43 (C=O), 165.1 (C=O), 158.9 (C-1'), 146.0 (C-4a), 145.7 (C-3), 143.9 (C-2), 142.6 (C-6), 140.9 (C-3'), 138.9 (C-8a), 132.0 (C-8), 131.0 (C-5'), 126.2 (C-7), 123.9 (C-4'), 117.8 (C-5), 113.6 (C-6'), 88.6 (C-2'), 70.3 (C-e), 53.1 (C-b), 48.7 (C-c), 39.3 (C-i); 38.6 (C-a); 30.3 (C-f), 27.4 (C-g), 26.6 (C-h), 13.2 (C-d). ESI-SM m/z 604.23 $[M+H^{+}]^{+}$.

General Method for synthesis of dihydrochloride salt derivatives (12a-g)

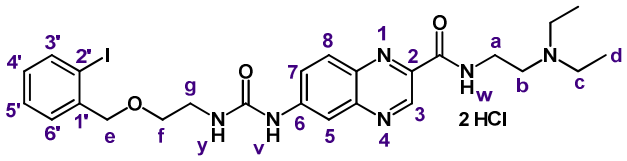
To a stirred solution of the appropriate **(1a-g)** derivatives dissolved in anhydrous dichloromethane (1.5 mL) was added a solution of 1 N hydrochloric acid in ethyl ether (1.5 mL). After stirring at room temperature for 15 min, 2 mL of ethyl ether were added. The resulting mixture was stirred at room temperature overnight. The precipitate was filtered off and dried under reduced pressure.

***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(*N*-(2-((2-iodobenzyl)thio)ethyl)ureido)quinoxaline-2-carboxamide, dihydrochloride salt (12a)**



Compound **(12a)** (18.9 mg, 27.8 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(*N*-(2-((2-iodobenzyl)thio)ethyl)ureido)quinoxaline-2-carboxamide (33.0 µmol) **(1a)**. Yield: 84%; Mp: 184 ± 1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (br, 2H, NH-v, HCl), 9.33 (s, 1H, H-3), 9.19 (t, ^{3}J = 5.9 Hz, 1H, NH-w), 8.33 (d, ^{4}J = 2.5 Hz, 1H, H-5), 8.01 (d, ^{3}J = 9.2 Hz, 1H, H-8), 7.88 (dd, ^{3}J = 9.2 Hz, ^{4}J = 2.5 Hz, 1H, H-7), 7.83 (dd, ^{3}J = 7.6 Hz, ^{4}J = 0.8 Hz, 1H, H-3'), 7.44 (dd, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz, 1H, H-6'), 7.34 (m, 1H, H-5'), 6.98 (td, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz, 1H, H-4'), 6.75 (t, ^{3}J = 5.4 Hz, 1H, NH-y), 3.80 (s, 2H, H-e), 3.69 (q, ^{3}J = 6.4 Hz, 2H, H-a), 3.35 (q, ^{3}J = 6.4 Hz, 2H, H-b), 3.27 (m, 2H, H-g), 3.18 (m, 4H, H-c), 2.55 (t, ^{3}J = 6.9 Hz, 2H, H-f), 1.20 (t, ^{3}J = 5.2 Hz, 6H, H-d); For $C_{25}H_{33}Cl_2IN_6O_2S$: calc: C, 44.19, H, 4.90, N, 12.37, found: C, 44.34, H, 5.10, N, 12.50.

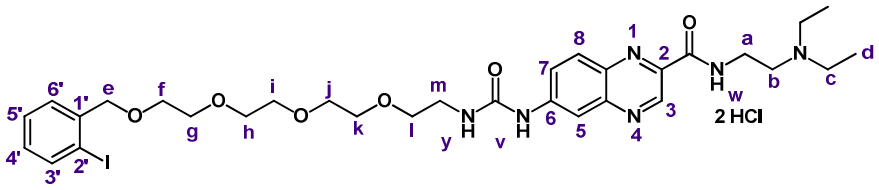
***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(3-(2-((2-iodobenzyl)oxy)ethyl)ureido)quinoxaline-2-carboxamide, dihydrochloride salt (12b)**



Compound **(12b)** (16.5 mg, 24.9 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(3-(2-((2-iodobenzyl)oxy)ethyl)ureido)quinoxaline-2-carboxamide (33.9 µmol) **(1b)**. Yield: 73%; Mp: 139 ± 1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.61 (br, 2H, NH-v, HCl), 9.33 (s, 1H, H-3), 9.18 (t, ^{3}J = 6.0 Hz, 1H, NH-w), 8.32 (d, ^{4}J = 2.4 Hz, 1H, H-5), 8.01 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.86 (dd, ^{3}J = 9.1 Hz, ^{4}J = 2.4 Hz, 1H, H-7), 7.83 (dd, ^{3}J = 7.6 Hz, ^{4}J = 0.9 Hz, 1H, H-3'), 7.49 (dd, ^{3}J = 7.6 Hz, ^{4}J = 1.4 Hz, 1H, H-6'), 7.37 (m, 1H, H-5'), 7.04 (td, ^{3}J = 7.6 Hz, ^{4}J = 1.4 Hz, 1H, H-4'), 6.65 (t, ^{3}J = 5.5 Hz, 1H, NH-y), 4.46 (s, 2H, H-e), 3.68 (q, ^{3}J = 6.3 Hz, 2H, H-a), 3.59 (t, ^{3}J = 5.5 Hz, 2H, H-f), 3.37 (q, ^{3}J = 5.5 Hz, 2H, H-b), 3.27 (q, ^{3}J = 5.5 Hz, 2H, H-g), 3.19 (m, 4H, H-c), 1.20 (t, ^{3}J = 7.2 Hz, 6H, H-d) ; For $C_{25}H_{33}Cl_2IN_6O_3$: calc.: C, 45.26, H, 5.01, N, 12.67, found: C, 45.35, H, 5.12, N, 12.53.

.

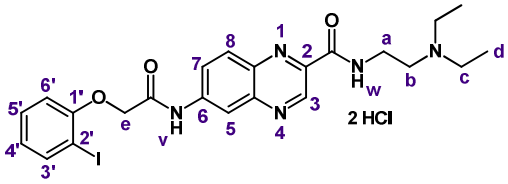
***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(3-(1-(2-iodophenyl)-2.5.8.11-tetraoxatridecan-13-yl)ureido)quinoxaline-2-carboxamide, dihydrochloride salt (12c)**



Compound **(12c)** (15.9 mg, 20.0 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(3-(1-(2-iodophenyl)-2.5.8.11-tetraoxatridecan-13-yl)ureido)quinoxaline-2-carboxamide (27.7 µmol) **(1c)**. Yield: 72%; Mp: 50 ± 1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (br, 1H, NH-v), 9.71 (s, 1H, HCl), 9.33 (s, 1H, H-3), 9.19 (t, ^{3}J = 5.9 Hz, 1H, NH-w), 8.32 (d, ^{4}J = 1.8 Hz, 1H, H-5), 8.00 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.86 (dd, ^{3}J = 9.1 Hz, ^{4}J = 1.8 Hz, 1H, H-7), 7.80 (m, 1H, H-3'), 7.38 (m, 2H, H-6', H-5'), 7.02 (m, 1H, H-4'), (6.61 br, 1H, NH-y), 4.40 (s, 2H, H-e), 3.70 (q, ^{3}J = 6.0 Hz, 2H, H-a), 3.47 (m, 10H, H-b, H-f, H-g, H-h, H-i, H-j, H-k ou H-l), 3.45 (t, ^{3}J = 5.4 Hz, 2H, H-m), 3.26 (m, 6H, H-b, H-f, H-g, H-h, H-i, H-j, H-k ou H-l), 3.17

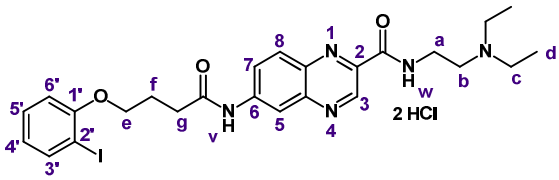
(m, 4H, H-c), 1.20 (t, ^{3}J = 7.2 Hz, 6H, H-d).For $C_{31}H_{45}Cl_2IN_6O_6$: calc.: C, 46.80, H, 5.70, N, 10.56, found: C, 46.78, H, 5.79, N, 10.64

***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(2-(2-iodophenoxy)acetamido)quinoxaline-2-carboxamide, dihydrochloride salt (12d)**



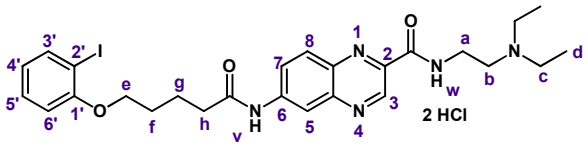
Compound (**12d)** (18.9 mg, 30.5 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(2-(2-iodophenoxy)acetamido)quinoxaline-2-carboxamide (36.5 µmol) **(1d)**. Yield: 84%; Mp: 193 ± 1 °C; ^{1}H NMR (200 MHz, DMSO-d_6) (200 MHz) δ 11.08 (s, 1H, HCl), 10.07 (br, 1H, NH-v), 9.41 (s, 1H, H-3), 9.30 (t, ^{3}J = 5.7 Hz, 1H, NH-w), 8.62 (s, 1H, H-5), 8.15 (s, 2H, H-7, H-8), 7.81 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.5 Hz, 1H, H-3'), 7.35 (m, 1H, H-5'), 7.01 (m, 1H, H-6'), 6.78 (m, 1H, H-4'), 4.97 (s, 2H, H-e), 3.71 (m, 2H, H-a), 3.26 (m, 2H, H-b), 3.16 (m, 4H, H-c), 1.23 (t, ^{3}J = 7.0 Hz, 6H, H-d); For $C_{23}H_{28}Cl_2IN_5O_3$: calc.: C, 44.53, H, 4.55, N, 11.29, found: C, 44.47, H, 4.62, N, 11.18.

***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(4-(2-iodophenoxy)butamido)quinoxaline-2-carboxamide, dihydrochloride salt (12e)**



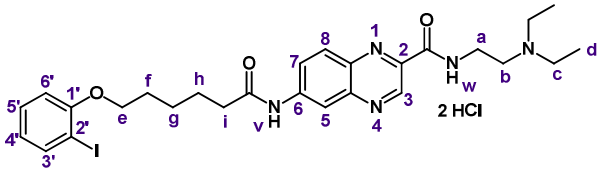
Compound **(12e)** (17.5 mg, 27.0 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(4-(2-iodophenoxy)butanamido)quinoxaline-2-carboxamide (34.8 µmol) **(1e)**. Yield: 78%; Mp: 158 ± 1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H, HCl), 9.67 (br, 1H, NH-v), 9.38 (s, 1H, H-3), 9.24 (m, 1H, NH-w), 8.60 (s, 1H, H-5), 8.08 (m, 2H, H-7, H-8) , 7.73 (d, ^{3}J = 7.7 Hz, 1H, H-3'), 7.33 (m, 1H, H-5'), 7.01 (m, 1H ,H-6'), 6.72 (m, 1H ,H-4'), 4.10 (t, ^{3}J = 5.7 Hz, 2H, H-e), 3.72 (m, 2H, H-a), 3.28 (m, 2H, H-b), 3.19 (m, 2H, H-c), 2.69 (t, ^{3}J = 6.8 Hz, 2H, H-g), 2.09 (t, ^{3}J = 6.8 Hz, H-f), 1.20 (t, ^{3}J = 6.9 Hz, 6H, H-d); For $C_{25}H_{32}Cl_2IN_5O_3$: calc.: C, 46.31, H, 4.97, N, 10.80, found: C, 46.42, H, 5.03, N, 10.89.

***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(5-(2-iodophenoxy)pentamido)quinoxaline-2-carboxamide, dihydrochloride salt (12f)**



Compound **(12f)** (18.7 mg, 28.2 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(5-(2-iodophenoxy)pentanamido)quinoxaline-2-carboxamide (33.9 µmol) **(1f)**. Yield: 83%; Mp: 158 ± 1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H, HCl), 9.87 (br, 1H, NH-v), 9.38 (s, 1H, H-3), 9.24 (t, ^{3}J = 5.7 Hz, 1H, NH-w), 8.60 (s, 1H, H-5), 8.08 (m, 2H, H-7, H-8), 7.73 (d, ^{3}J = 7.8 Hz, 1H, H-3'), 7.31 (m, 1H, H-5'), 7.01 (d, ^{3}J = 8.3 Hz, 1H, H-6'), 6.70 (m, 1H , H-4'), 4.04 (t, ^{3}J = 5.6 Hz, 2H, H-e), 3.70 (q, ^{3}J = 6.2 Hz, 2H, H-a), 3.27 (m, 2H, H-b), 3.17 (m, 4H, H-c), 2.54 (m, 2H, H-h), 1.84 (m, 4H, H-f, H-g), 1.22 (t, ^{3}J = 7.2 Hz, 6H, H-d); For $C_{26}H_{34}Cl_2IN_5O_3$: calc.: C, 47.14, H, 5.17, N, 10.57, found: C, 47.21, H, 5.22, N, 10.63.

***N*-(2-(*N,N*-Diethylamino)ethyl)-6-(6-(2-iodophenoxy)hexamido)quinoxaline-2-carboxamide, dihydrochloride salt (12g)**



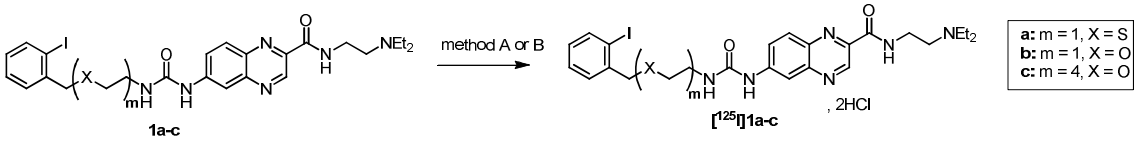
Compound **(12g)** (19.3 mg, 28.5 µmol) was synthesized from *N*-(2-(*N,N*-diethylamino)ethyl)-6-(6-(2-iodophenoxy)hexanamido)quinoxaline-2-carboxamide (33.1 µmol) **(1g)**. Yield: 86%; Mp:119 ± 1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H, HCl), 9.42 (br, 1H, NH-v), 9.38 (s, 1H, H-3), 9.22 (t, ^{3}J = 5.9 Hz, 1H, NH-w), 8.59 (s, 1H, H-5), 8.08 (m, 2H, H-7, H-8), 7.71 (d, ^{3}J = 7.5 Hz, 1H, H-3'), 7.31 (m, 1H, H-5'), 6.97 (d, ^{3}J = 8.0 Hz, 1H, H-6'), 6.69 (m, 1H , H-4'), 4.19 (t, ^{3}J = 6.5 Hz, 2H, H-e), 3.69 (q, ^{3}J = 6.1 Hz, 2H, H-a), 3.28 (m, 2H, H-b), 3.19 (m, 4H, H-c), 2.51 (m, 2H, H-i), 1.75 (m, 2H, H-f), 1.61 (m, 2H, H-h), 1.53 (m, 2H, H-g), 1.19 (t, ^{3}J = 7.2 Hz, 6H, H-d); For $C_{27}H_{36}Cl_2IN_5O_3$. calc.: C, 47.94, H, 5.36, N, 10.35, found: C, 49.89, H, 5.41, N, 10.43.

Preparation of Radioiodinated Compounds [^{125}I]1a-g

To a solution of the appropriate compound **1a-g** (1 mg) dissolved in 600 µL of acetic acid (method A) or 500 µL of citrate buffer (pH 4) (method B), were added 100 µL of a solution of copper sulfate in acetic acid (1 g/L) (method A) or an aqueous solution of copper buffer (5 g/L) (method B) and [^{125}I]NaI (1-2 µL, 1,9-3,7 MBq). The vial was sealed and the reaction mixture was heated at 130 °C for 15, 30 ou 45 min. After cooling to room temperature, water (500 µL) and an aqueous hydroxide solution 1 N (100 µL) were added. The vial cap and septum were removed. The resulting suspension was run through an Extrelut® column (the vial was washed with twice with absolute ethanol (150 µL). After ten minutes, the column was eluted with dichloromethane (25 mL). The eluting solution was concentrated under reduced pressure, diluted with methanol (200 µL) and filtered off. The semi-preparative RP-HPLC purifications of radiotracers was performed on the Perkin Elmer system mentioned above. The separation was carried out on a C_{18} column (Waters, SymmetryPep^{TM} C18, 7.8 ×300 mm, 7 µM) using the following conditions : gradient time = 20 min, flow rate = 2.5 mL/min, eluent A (H_2O/0.2 % NH_4OH), eluent B (MeOH 0.2 % NH_4OH); gradient: 15/85 (A/B, v/v) from 0 to 15 min, 0/100 (A/B, v/v) from 15 to 20 min, λ = 254 nm. The radioiodinated compound was collected and evaporated under reduced pressure. The crude product was diluted with dichloromethane (2 mL), and treated with 2N anhydrous hydrochloric acid in ether (2 mL). The resulting hydrochloride solution was evaporated under reduced pressure. The obtained product was co-injected with the appropriate hydrochloride derivatives **12a-g** and controlled by analytical RP-HPLC. Analytical RP-HPLC measurements were performed on the same Perkin Elmer system. The separation was carried out on a C_{18} column (Agilent Zorbax, 80 Å, 4.6 mm × 150 mm, 5 µM) using the following conditions: gradient time = 20 min, flow rate = 0.5 mL/min, eluent A (H_2O/0,2 % NH_4OH), eluent B (MeOH 0.2 % NH_4OH); gradient: 25/75 (A/B, v/v) for 0 to 15 min, 0/100 (A/B, v/v) for 15 to 20 min, λ = 254 nm. All radiolabeled compounds were compared by TLC or analytical HPLC to the authentic nonradioactive material and to be free of significant chemical and radiochemical impurities. All radiotracers were shown by radio-TLC and radio-RPHPLC to be identical to the authentic non-radioactive material and to be free of significant chemical and radiochemical impurities. Radiochemical yields based on TLC of exchange reaction mixture and radiochemical purities are given in tables S1 and S2.

Starting material	Product	Reaction time (min)	Radio-exchange yield[a](%)	Radiochemical yield[b](%)	Radiochemical purity (%)	HPLC Retention time (min)
1a	[^{125}I]**1a**	30	79	46	98.0	8.72
1b	[^{125}I]**1b**	30	75	52	99.8	8.68
1c	[^{125}I]**1c**	15	90	51	99.9	8.26
1d	[^{125}I]**1d**	30	91	56	99.9	8.76
1e	[^{125}I]**1e**	45	96	48	99.9	9.09
1f	[^{125}I]**1f**	45	84	43	98.6	9.53
1g	[^{125}I]**1g**	45	95	30	99.9	9.85

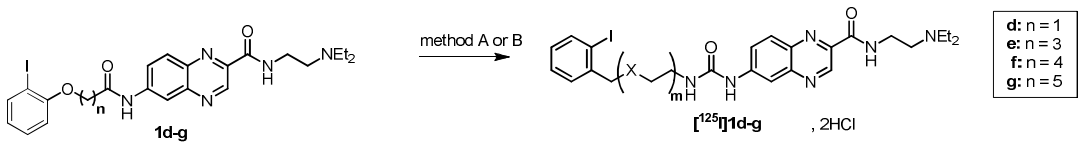
Table S1. Radiochemical data for [^{125}I]**1a-g** derivatives obtained with method A. [a]Radio-exchange yields were calculated by dividing the radioactivity in the radioiodinated product spot by the total amount of radioactivity displayed on radio-TLC plate and measured on Ambis. [b]Radiochemical yields were calculated by dividing the radioactivity in the final product (hydrochloride salt) by the initial amount of radioactive sodium iodide.



1a-c [^{125}I]**1a-c**

Starting material	Method	Reaction time (min)	Radio-exchange yield[a] (%)
1a	A	15	40
1a	A	**30**	**79**
1a	A	45	70
1a	B	15	24
1a	B	30	44
1a	B	45	49
1b	A	15	39
1b	A	**30**	**75**
1b	A	45	67
1c	A	**15**	**90**
1c	A	30	82
1c	A	45	68
1c	B	15	23
1c	B	30	39
1c	B	45	88

Table S2. Radiochemical data for [^{125}I]**1a-c** derivatives; [a]Radio-exchange yields were calculated by dividing the radioactivity in the radioiodinated product spot by the total amount of radioactivity displayed on radio-TLC plate and measured on Ambis. [b]Radiochemical yields were calculated by dividing the radioactivity in the final product (hydrochloride salt) by the initial amount of radioactive sodium iodide.



Starting material	Method	Reaction time (min)	Radio-exchange yield[a] (%)
1e	A	15	84
1e	A	30	92
1e	A	**45**	**96**
1f	A	15	65
1f	A	30	83
1f	A	**45**	**84**
1f	B	15	0
1f	B	30	27
1f	B	45	33
1g	A	15	64
1g	A	30	82
1g	A	**45**	**95**

Table S3. Radiochemical data for **[^{125}I]1e-g** derivatives; [a]Radio-exchange yields were calculated by dividing the radioactivity in the radioiodinated product spot by the total amount of radioactivity displayed on radio-TLC plate and measured on Ambis. [b]Radiochemical yields were calculated by dividing the radioactivity in the final product (hydrochloride salt) by the initial amount of radioactive sodium iodide.

Partition Coefficient Measurements

For each compound, the partition coefficient between *n*-octanol and phosphate buffer was determined. The measurement was performed by shaking 2 mL of **[^{125}I]1a-g** (7.4 MBq/20 mL) solution (50 μM in phosphate buffer solution, PBS, pH 7.4) with 2 mL of *n*-octanol. The activity of each phase was counted in the γ counter (Perkin Elmer, Wizard 3", 1480 automatic Gamma Counter). *P* was calculated as the ratio of activities (*n*-octanol/buffer), and its logarithm was determined to express lipophilicity.

$$\mathrm{Log}P = \frac{n-octanol\ radioactivity}{PBS\ (pH\ 7.4)\ radioactivity}$$

In Vitro Binding to Melanin.

An in vitro experiment was performed to evaluate the binding affinity of new compounds to melanin using synthetic melanin (Sigma Aldrich) suspended in two different media: water and PBS. The general procedure used was as follows: **[^{125}I]1a-g** (27.8 kBq/50 µL) was added to a melanin suspension (0.5 mg/10 mL of water or PBS). The suspension was incubated at room temperature for 22 h with stirring. After incubation, the tubes were centrifuged at 35000 *g* for 20 min, and aliquots of the supernatants were counted.

$$\%\ Melanin\ binding = 100 - \frac{Not\ binding\ radioactivity}{Total\ Radioactivity} \times 100$$

Cell culture

B16F0 melanoma cell cultures (from ATCC reference no. CRL-6322) were maintained as monolayers in Dulbecco's Modified Eagle's Medium (DMEM)/Glutamax (Invitrogen, Cergy Pontoise, France) supplemented with 10% fetal calf serum (Sigma, Saint-Quentin Fallavier, France). The cells were grown at 37 °C in a humidified incubator containing 5% CO_2.

Biodistribution in B16F0 melanoma bearing mice

Animals were handled and cared in accordance with the guidelines for the Care and Use of Laboratory Animals (National Research Council, 1996) and European Directive 2010/63/UE. Mice were maintained at 21 °C with a 12 h/12 h light/dark cycle. They were fed with a breeding diet (diet A04 from Safe, Villemoisson, France) and received water ad libitum. Protocols were performed under the authorization of the French Direction des Services Vétérinaires (authorization no. CE 18-09) and conducted under the supervision of authorized

investigators in accordance with the institution's recommendations for the use of laboratory animals.

C57Bl/6J male mice (6-8 weeks old) were obtained from Charles River (l'Arbresle, France). Cells in exponential growth phase were trypsinized, washed with phosphate buffer saline (PBS), and resuspended in PBS. Mice anesthetized by isoflurane (2%) inhalation were subcutaneously inoculated with 3×10^5 melanoma B16F0 cells in PBS (0.1 mL) by subcutaneous injection on the right shoulder. Ten days later, the tumors became palpable with a percentage of tumor take of 98-100% (Tumour volume of 450 ± 210 mm^3).

Scintigraphic imaging

Experiments were undertaken at days 12, 13 and 15 after cells inoculation (n = 4 animals/compound). Whole-body scintigraphic imaging scans were acquired 1 h after intravenous injection of **[^{125}I]1a-g** (3,7 MBq/0.2 mL of NaCl 0.9 %) via the tail vein and were anesthetized by intraperitoneal administration (200 µL/20 g-mouse) of a mixture of ketamine (Imalgene 500, Rhône Mérieux, Lyon, France) and xylazine (Rompun, Bayer, France) in saline, 4:1 ratio. Biodistribition of radiolabeled molecules was assessed by both planar in vivo Scintigraphic imaging (10 min-duration) and organ counting. Scintigraphic imaging was performed using a gamma camera dedicated for small animal imaging (γIMAGER, Biospace Mesures, Paris, France). This camera consists of a R 3292 Hamamatsu position-sensitive photomultiplier having a continuous 4 mm thick x120 mm diameter CsI(Na) crystal leading to a 10 cm field of view. For [^{125}I] imaging, the camera was equipped with parallel-hole collimator 1.8/0.2/20 (hole diameter/septum thickness/height in mm). All the acquisitions were performed with a 15% window centered on the 35 keV peak of ^{125}I.

***Ex vivo* biodistribution studies**

Experiments were undertaken at days 12, 13 and 15 after cells inoculation (n = 2 animals/group). Animals were sacrificed by CO_2 asphyxiation 1 h, 3 h, 24 h and 72 after i.v. injection of **[^{125}I]1a-g** (3,7 MBq/0.2 mL of NaCl 0.9 %). Tumors, major organs (eyes, thyroid and submaxillary glands, liver, spleen, kidneys) and tissues were promptly excised, harvested, weighted and their radioactivity counted. After radioactive decay correction, results were expressed as % ID/g.

Compound	Time (h)	B16 Melanoma[a]	Liver[a]	Kidney[a]	Blood[a]	Muscle[a]	Eyes[a]	Spleen[a]	Thyroid and SG[a,b]
	1	1.05 ± 0.15	8.61 ± 0.44	9.34 ± 2.07	0.49 ± 0.02	0.61 ± 0.04	1.58 ± 0.07	2.08 ± 0.49	3.87 ± 0.17
[^{125}I]1a	3	1.15 ± 0.32	1.73 ± 0.70	6.01 ± 0.25	0.19 ± 0.02	0.32 ± 0.05	1.62 ± 0.18	0.75 ± 0.08	3.18 ± 0.61
	24	0.83 ± 0.26		0.28 ± 0.11			1.67 ± 0.38		1.54 ± 0.67
	72	0.37 ± 0.14					1.36 ± 0.56		0.99 ± 0.34
	1	1.92 ± 1.02	6.45 ± 0.38	11.48 ± 4.49	0.58 ± 0.04	0.72 ± 0.37	2.21 ± 0.11	2.38 ± 0.64	3.93 ± 1.24
[^{125}I]1b	3	2.03 ± 0.09	1.61 ± 0.29	3.48 ± 0.62	0.20 ± 0.06	0.34 ± 0.06	3.22 ± 0.11	0.61 ± 0.05	2.01 ± 0.01
	24	1.27 ± 0.70	0.22 ± 0.10	0.33 ± 0.09			2.50 ± 1.16	0.14 ± 0.01	0.74 ± 0.21
	72	0.87 ± 0.50	0.14 ± 0.12				2.91 ± 0.57		1.69 ± 1.19
	1	2.22 ± 0.05	2.03 ± 0.34	5.15 ± 1.80	0.68 ± 0.15	0.26 ± 0.01	1.97 ± 0.41	0.71 ± 0.19	1.99 ± 0.13
[^{125}I]1c	3	3.18 ± 0.72	1.13 ± 0.31	5.40 ± 5.24	0.49 ± 0.21	0.13 ± 0.08	2.39 ± 0.59	0.42 ± 0.05	1.35 ± 0.83
	24	0.71 ± 0.01					1.32 ± 0.09		0.66 ± 0.03
	72	0.61 ± 0.26					1.41 ± 0.28		1.37 ± 0.49
[^{125}I]1d	1	5.68 ± 1.16	6.21 ± 4.01	19.90 ± 10.27	1.67 ± 1.75	0.86 ± 0.31	5.67 ± 0.30	3.74 ± 0.82	4.12 ± 0.86
	3	5.60 ± 1.56	1.53 ± 0.85	7.74 ± 4.76	1.14 ± 1.03	0.27 ± 0.16	6.46 ± 0.18	1.44 ± 0.36	1.16 ± 0.20
	24	3.30 ± 0.75		0.11 ± 0.01			4.88 ± 1.98	0.59 ± 0.79	0.33 ± 0.04
	72	2.40 ± 0.30					7.04 ± 2.35		0.43 ± 0.12
[^{125}I]1e	1	2.43 ± 0.39	5.18 ± 0.48	6.62 ± 0.91	0.59 ± 0.12	0.71 ± 0.04	2.66 ± 0.83	2.37 ± 0.38	2.19 ± 0.33
	3	1.86 ± 0.50	0.83 ± 0.05	1.28 ± 0.35	0.20 ± 0.04	0.12 ± 0.01	1.89 ± 0.64	0.38 ± 0.09	0.49 ± 0.03
	24	1.67 ± 0.10					2.05 ± 0.15		0.72 ± 0.31
	72	0.75 ± 0.29					2.28 ± 0.61		0.73 ± 0.51
[^{125}I]1f	1	5.74[d]	15.81[d]	18.81[d]	1.15[d]	1.54[d]	4.96[d]	5,40d	5,87d
	3	4.55 ± 1.15	7.49 ± 0.14	9.17 ± 3.23	1.07 ± 0.07	0.96 ± 0.04	4.40 ± 0.19	3.90 ± 1.48	3.63 ± 0.05
	24	5.60 ± 2.10		0.12 ± 0.01			6.93 ± 2.88	0.32 ± 0.39	1.01 ± 0.07
	72	2.72 ± 1.76					7.15 ± 1.76		0.70 ± 0.20
[^{125}I]1g	1	3.62 ± 0.09	17.58 ± 1.12	20.22 ± 3.66	1.50 ± 0.11	2.05 ± 0.19	3.90 ± 0.16	10.93 ± 2.68	6.08 ± 0.41
	3	5.82 ± 1.26	6.85 ± 0.02	9.29 ± 0.44	0.66 ± 0.06	0.92 ± 0.07	5.54 ± 0.27	4.74 ± 0.58	3.75 ± 0.12
	24	2.99 ± 0.57	0.14 ± 0.03	0.18 ± 0.09			4.64 ± 0.91	0,89 ± 1.18	0.89 ± 0.01
	72	2.64 ± 0.37					7.30 ± 0.42		1.14 ± 0.32
ICF01012[e]	1	17.0 ± 11.1	13.78 ± 1.32	16.46 ± 2.98	3.45 ± 0.44	2.04 ± 0.37	33.82 ± 3.47	14.21 ± 14.32	
	3	27.7 ± 7.0	8.87 ± 1.11	9.30 ± 3.31	2.91 ± 0.33	0.86 ± 0.22	24.79 ± 6.78	4.69	39.76 ± 23.47
	24	21.7 ± 10.8	1.49 ± 0.18	7.69 ± 0.80	3.09 ± 0.52	0.87 ± 0.23	32.30 ± 6.52		94.22 ± 27.48
	72	12.45 ± 1.6					25.26 ± 8.38		

Table S4. Biodistribution of **[^{125}I]1a-g** compared to ICF01012 at various times after iv administration in B16F0 melanoma-bearing mice [a]Radioactive concentration values are expressed as means of %ID/g to ± SD (two mice, n determinations for each compound at each time point). [b]SG: submaxilary glands. [c]no value: no radioactive signal detected in the tissue. [d]No standard deviation when only one determination was made per organ. [e]ICF01012 values were obtained from previous work[3]

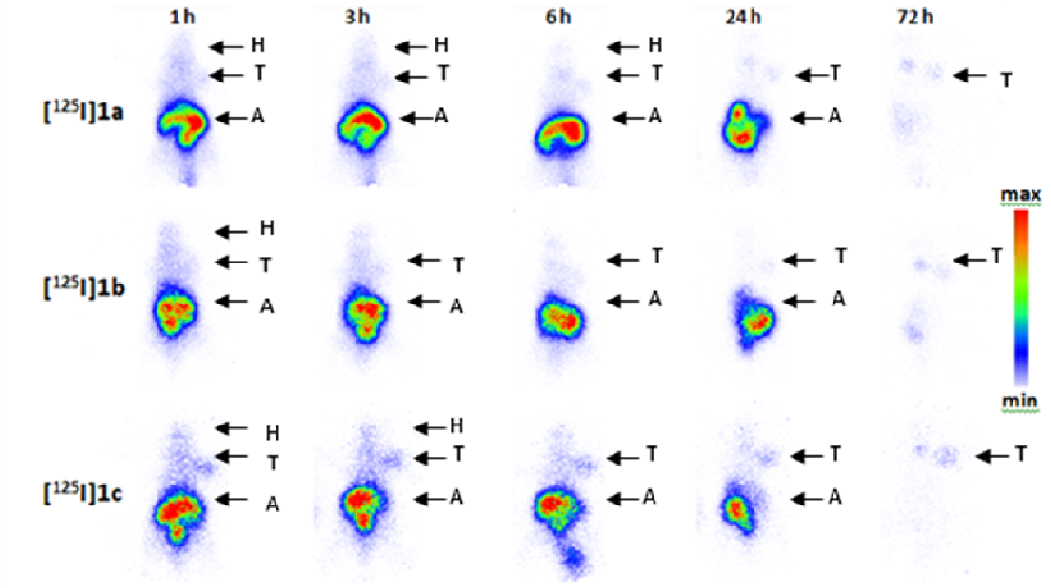


Figure S1. *In vivo* kinetic of compound **[^{125}I]1a-c** in a B16F0 melanoma-bearing C57Bl/6J mouse illustrated by serial planer scintigraphic images using a dedicated γ imager for small animal) after a 3.7 MBq iv injection dose (acquisition time : 10 min). H: Head; T: Tumour; A: Abdomen.

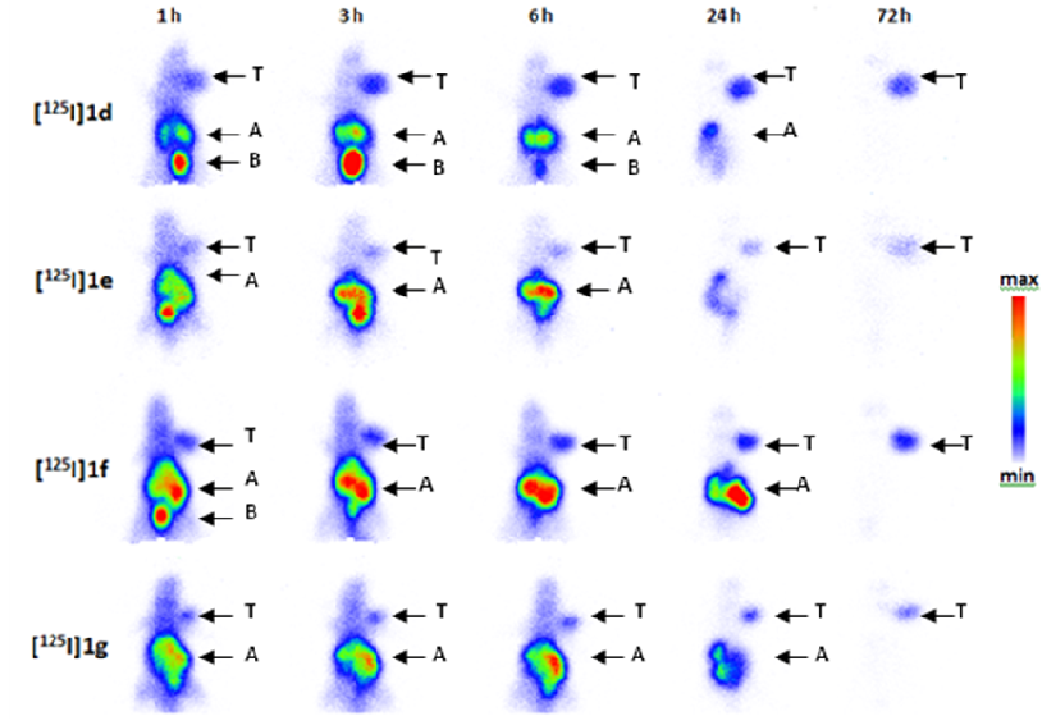


Figure S2. *In vivo* kinetic of compound **[^{125}I]1d-g** in a B16F0 melanoma-bearing C57Bl/6J mouse illustrated by serial planer scintigraphic images using a dedicated γ imager for small animal) after a 3.7 MBq iv injection dose (acquisition time : 10 min). T: Tumour; A: Abdomen; B: Bladder.