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Tricyclic Fused Pyrazoles with a 'Click' 1,2,3-Triazole Substituent in Position 3 Are Nanomolar CB_1 Receptor Ligands

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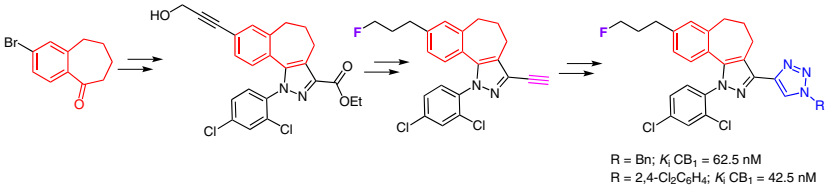

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Abstract Structural modification of the potent conformationally constrained tricyclic pyrazole CB_1 ligand NESS0327 was achieved by replacing: (1) the chlorine substituent on the tricycle with a 3-fluoropropyl chain, and (2) the pyrazole 3-[[(piperidino)amino]carbonyl] substituent with a 4-substituted 1,2,3-triazole group obtained by click chemistry from an alkynyl precursor. Among the resulting compounds, two are particularly promising candidates for [^{18}F]radiolabelling and PET imaging studies of the CB_1 receptor, as they displayed K_i CB_1 = 62.5 nM and 42.5 nM, respectively, in the same range as that displayed by rimonabant.

Key words cannabinoids, PET imaging, fluorine, Sonogashira reaction, click chemistry

Cannabinoid receptors belong to the family of G-protein coupled receptors (GPCRs).[1] Two subgroups of cannabinoid receptors have been discovered and extensively studied: CB_1 and CB_2.[2] Although CB_1 receptors are predominantly localised in the central nervous system (CNS)[2] while CB_2 receptors are mostly present in the peripheral nervous system (PNS),[3] some studies have shown the presence of CB_1 receptors in the PNS[4] and of CB_2 in the CNS, albeit in low density.[5] CB_1 receptors have a prominent role in drug discovery as they have been shown to play an important role in a number of disorders, including chronic pain,[6] depression,[7] anxiety,[8] stress,[9] schizophrenia,[10] and obesity.[11] Consequently, several cannabinoid ligands were developed as drug candidates, including rimonabant (SR141716A),[12] which is a pyrazole-core inverse agonist discovered by Sanofi-Synthelabo (now Sanofi-Aventis) in 1994. Rimonabant (Figure 1) was marketed in Europe as an anti-obesity drug, but it was subsequently withdrawn from the market owing to its side effects, which included severe depression and suicidal tendencies.[13] Since then, the pharmaceutical industry's interest in cannabinoid ligands has somewhat declined, whereas academic cannabinoid research has remained vibrant. In particular, the relationship between density, distribution, and functional modification of CB_1 receptors and the onset of a pathological state is still not well understood. For this reason the development of radio-ligands suitable for in vivo PET functional imaging of CB_1 receptors has emerged as an important area of research in medicine and drug development. A small number of PET radiotracers[14] based on the structure of rimonabant have been synthesised, radiolabelled, and tested in vivo, but the majority afforded unsatisfactory CNS-imaging capacity as a consequence of their poor brain uptake. A few radiolabelled CB_1 PET ligands[15] have also been tested in clinical trials on humans.[16] Recently, we described a new class of high-affinity CB_1 ligands **A** (Figure 1), bearing a 'click' *N*-(4-fluorobutyl)-1,2,3-triazolyl function in position 3 of the pyrazolyl ring, as candidate PET tracers.[17] In agreement with previously reported data on rimonabant analogues having nitrogen- and oxygen-containing aromatic rings replacing the rimonabant-type hydrazide moiety in position 3 of the pyrazole ring,[18] our results showed that the 1,2,3-triazole group is well tolerated by the CB_1 binding pocket, although the effect of varying the substituent in position 4 of the triazole ring was not investigated. Taking into account the high CB_1 affinity of NESS0327 (Figure 1), a conformationally constrained tricyclic pyrazole analogue of rimonabant, that was reported to have CB_1 affinity in the femtoMolar range,[19] we have now extended our investigation to the 1-(2,4-dichlorophenyl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide structural scaffold for the development of novel CB_1 PET tracer candidates **1** (Figure 1).

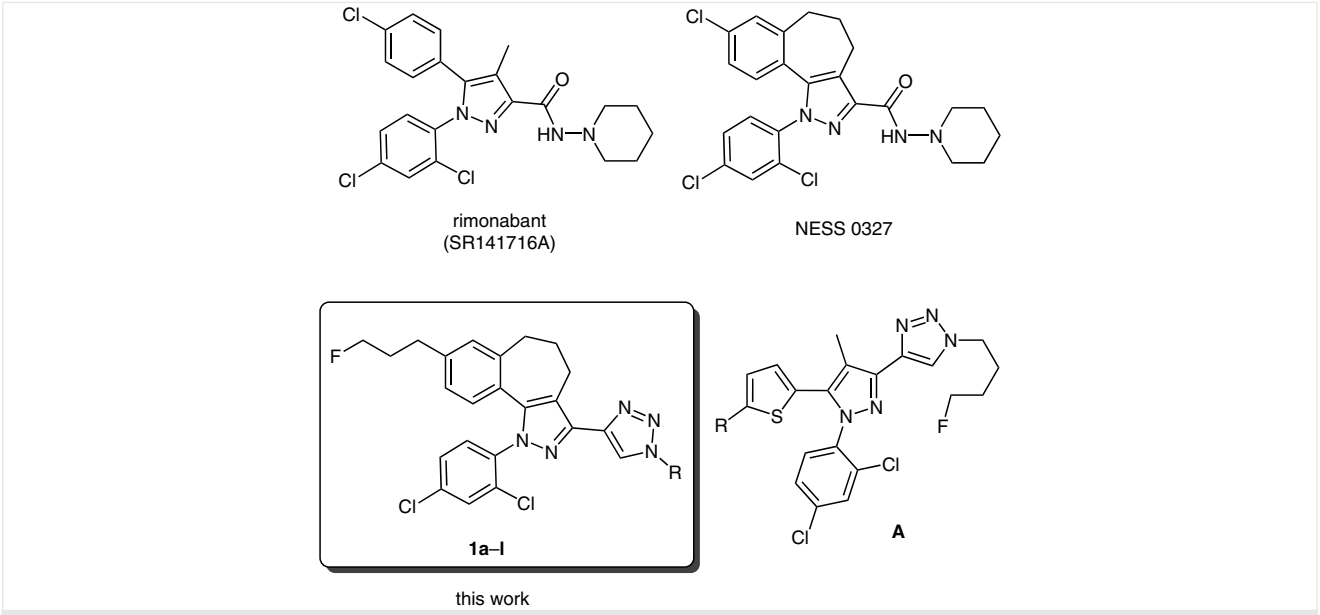


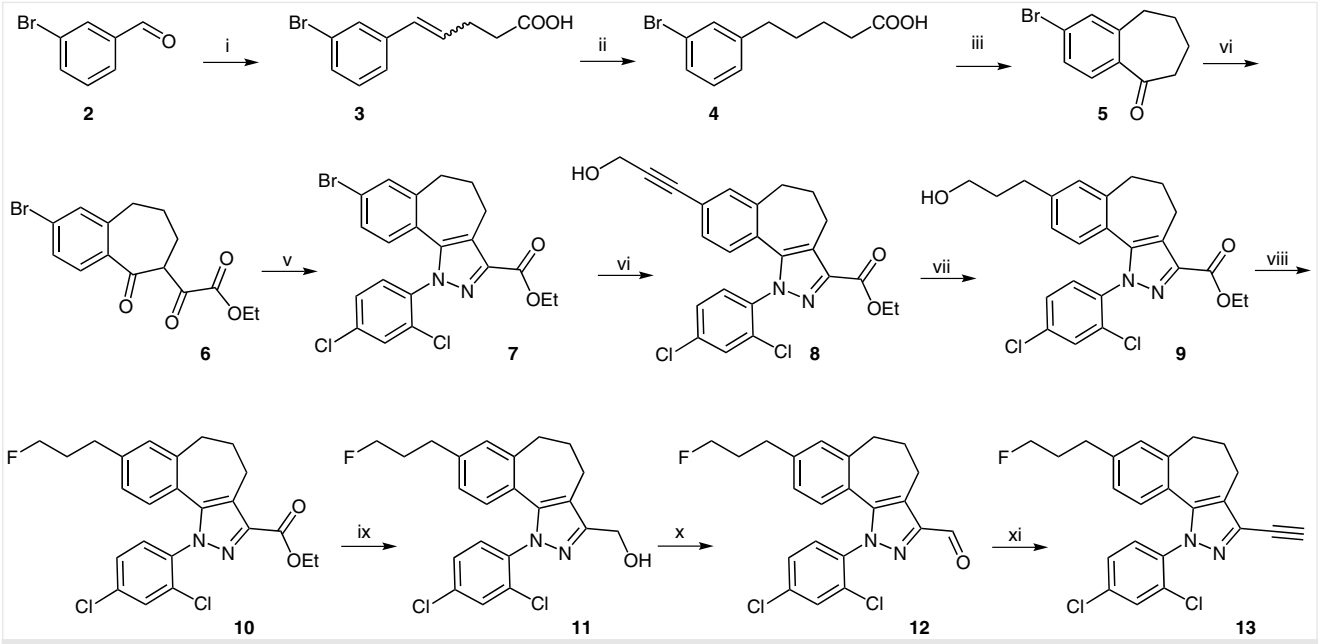
Figure 1 CB_1 receptor ligands relevant to this work

In this work we describe: (1) the synthesis of tricyclic fused pyrazoles **1** carrying a 3-fluoropropyl group as an aromatic substituent and differently 4-substituted 1,2,3-triazole groups in position 3 of the pyrazole ring; and (2) the assessment of the CB_1 and CB_2 affinity of these new ligands. Some of them, in particular **1g** and **1l**, showed excellent CB_1 affinity in line with rimonabant, although selectivity vs. CB_2 was quite modest, suggesting that these compounds may indeed have potential as PET tracers for imaging the cannabinoid system in vivo.

The synthesis of target compounds **1** started from 3-bromobenzaldehyde (**2**) (Scheme 1), which was submitted to a Wittig olefination with (3-carboxypropyl)triphenylphosphonium bromide affording the carboxylic acid **3** as a mixture of *E* and Z geometric isomers.[20] Catalytic hydrogenation of **3**, over palladium on carbon catalyst provided the saturated derivative **4**, which was first transformed into the corresponding acyl chloride and then submitted to an intramolecular Friedel–Crafts acylation promoted by aluminium trichloride to give the benzosuberone **5**.[21] The latter was subjected to Dieckmann reaction with diethyl oxalate in the presence of sodium ethoxide[20] to give the 1,3-diketo ester **6** as a tautomeric mixture, predominantly containing the alkenylidene structure. Next, the tricarbonyl compound **6** and 2,4-dichlorophenylhydrazine were heated in ethanol to afford the pyrazole **7**.[20] A solvent-free palladium-catalysed Sonogashira cross coupling[22] with prop-2-yn-1-ol afforded the alkyne **8**. A first attempt to hydrogenate the propargylic alcohol **8** by employing palladium on carbon in ethyl acetate under hydrogen (1 atm) resulted in a concomitant reductive de-chlorination of the benzene ring. A second attempt was carried out with the Wilkinson catalyst in benzene (1 atm of H_2) but, after 24 hours at 60 °C, only partial hydrogenation to the corresponding alkene was observed and the reaction did not proceed further. At this point we opted for Raney nickel as catalyst[23] under hydrogen (1 atm) and when ethanol was used as the solvent we still obtained a significant amount of de-chlorinated compounds, however, when tetrahydrofuran was used as the solvent we were able to obtain the desired saturated product **9** in quantitative yield. Next, the alcohol **9** was treated with the dehydroxy-fluorinating agent Deoxofluor[24] affording the fluoro ester **10** which was directly submitted to reduction with lithium aluminium hydride. The resulting alcohol **11** was oxidised with the Dess–Martin periodinane providing the corresponding aldehyde **12**. The latter was homologated under Bestmann–Ohira alkynylation conditions[25] leading to the key alkyne intermediate **13**.

The synthesis of the target compounds **1a**–**l** was completed by using a copper-catalysed azide-alkyne cycloaddition[26] between **13** and a series of azides (Scheme 2).

We next tested the CB_1 and CB_2 affinity of compounds **1a**–**l**. To that end, we performed [^{3}H]CP55940 displacement binding assays with membranes obtained from hCB_1 and hCB_2 CHO cells using methods we have described previously.[27] The results are summarised in Table 1 and affinity to CB_1 and CB_2 are expressed as K_i values. All the compounds, with the exception of **1b** that showed higher affinity for the CB_2 receptor, evidenced nanomolar affinity for the CB_1 receptor and moderate to low CB_1/CB_2 selectivity. Compounds **1g** and **1l** stand out for their high CB_1 affinity, which was comparable to that displayed by rimonabant. Moreover, K_i CB_1 values of both **1g** and **1l** were in line with the CB_1 affinity of NESS0327 as reported by Zhang et al.[28] It is worth

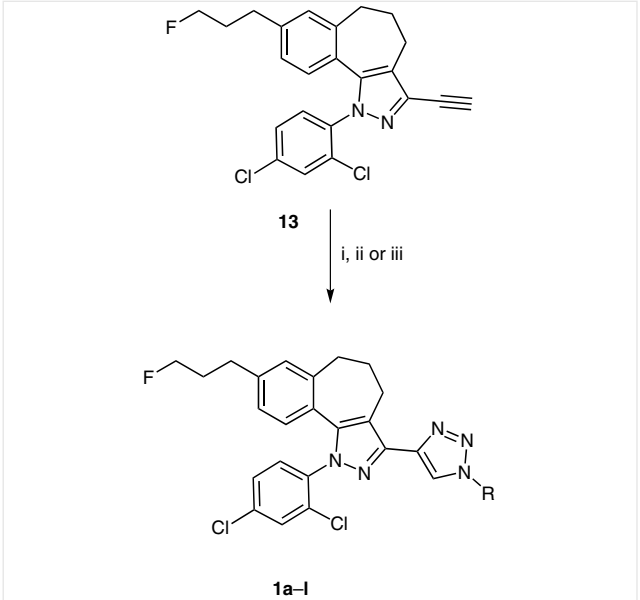


Scheme 1 Synthesis of alkyne **13**. *Reagents and conditions*: (i) $Ph_3P^+(CH_2)_3CO_2H{\cdot}Br^-$, *t*-BuOK, DMSO, r.t., overnight (80%); (ii) H_2, Pd/C, EtOAc, AcOH, r.t., overnight; (iii) 1. $(COCl)_2$, DMF, r.t., 1 h; 2. $AlCl_3$, CH_2Cl_2, r.t., overnight (80% over 3 steps); (vi) diethyl oxalate, NaOEt, EtOH, r.t., overnight; (v) 2,4-dichlorophenylhydrazine hydrochloride, EtOH, reflux, overnight (50% over 2 steps); (vi) prop-2-yn-1-ol, $PdCl_2(PPh_3)_2$, TBAF, 70 °C, 4 h (70%); (vii) H_2, Raney Ni, THF–H_2O, r.t., 3 h; (viii) Deoxofluor, THF, CH_2Cl_2, r.t., 2 h (80% over 2 steps); (ix) $LiAlH_4$, THF, r.t., 2 h (85%); (x) DMP, CH_2Cl_2, r.t., 3 h; (xi) dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, r.t., overnight (90% over 2 steps).

noting that the originally reported femtoMolar CB_1 affinity of NESS0327[20] was not confirmed in literature by other authors who determined for the same compound K_i CB_1 values in the range 18.4–126 nM.[29] Relative to rimonabant, both **1g** and **1l** showed lower CB_1/CB_2 selectivity (K_i CB_2/K_i CB_1 <10).

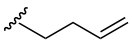
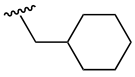
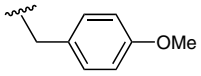
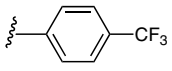
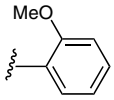
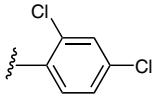
In the light of their high CB_1 affinities **1g**,**l** are therefore the most promising candidates for further development, including their possible use as a PET tracer for imaging the CB_1 receptor in vivo.

In conclusion, we have described the structural modification of the potent conformationally constrained tricyclic pyrazole CB_1 ligand NESS0327, which was achieved by replacing: (1) the chlorine substituent in the tricycle with a 3-fluoropropyl chain, which is amenable to radiofluorination, and (2) the pyrazole 3-{[(piperidino)amino]carbonyl} substituent with a 4-substituted 1,2,3-triazole group obtained by click chemistry from the alkynyl precursor **13**. Compounds **1g** and **1l** are particularly promising candidates for [^{18}F]radiolabelling and PET imaging studies of the CB_1 receptor, as they displayed K_i CB_1 = 62.5 nM and 42.5 nM, respectively, in the same range as that displayed by rimonabant, although CB_1/CB_2 selectivity was fairly low for both the novel derivatives. Moreover, K_i CB_1 values of **1g** and **1l** are in line with that of the reference analogue NESS0327,



Scheme 2 Synthesis of CB_1 ligands **1a–l**. *Reagents and conditions*: (i) $TMSN_3$, $CuSO_4$, sodium ascorbate, DMF–H_2O, microwaves, 120 °C, 30 min (45% **1a**); (ii) NaN_3, $CuSO_4$, sodium ascorbate, DMF–H_2O, MeI, 120 °C, overnight (48% **1b**); (iii) RN_3, $CuSO_4$, sodium ascorbate, *t*-BuOH–H_2O, r.t., overnight (60–82% **1c–l**).

Table 1 CB_1 and CB_2 Affinities of Compounds **1a–l**

Compound	R	Receptor affinity			
		K_i CB_1 (nM)[a] (95% CL)[b]	Max. disp. (95% CL)[b]	K_i CB_2 (nM)[a] (95% CL)[b]	Max. Disp. (95% CL)[b]
1a	H	393.6 (217.4–712.6)	79.7 (67.7–91.7)	2212 (829.2–5903)	84.8 (57.0–112.5)
1b	Me	2260.0 (361.6–14120)	87.8 (38.7–136.9)	1271 (998.8–1617)	99.6 (92.5–106.6)
1c	Pr	226.6 (141.2–363.8)c	71.3 (64.7–77.8)	1446 (1093–1912)	71.8 (65.8–77.8)
1d	$(CH_2)_4Me$	250.6 (144.1–435.6)	78.9 (69.5–88.3)	883.1 (544.4–1433)	78.8 (68.2–89.4
1e		458.0 (94.4–2221)	70.6 (44.4–96.8	935.0 (690.1–1267)	784.2 (476.1–92.3
1f		116.3 (70.4–192.3)	62.8 (57.6–67.9)	685.3 (302.9–1550)	45.7 (36.8–54.6)
1g	Bn	62.5 (28.1–139.1)	60.2 (50.2–70.2)	358.4 (243.2–528.0)	60.8 (55.7–65.9)
1h		–[d]	–[d]	415.0 (287.9–598.4)	49.5 (44.7–54.4)
1i	Ph	338.1 (69.8–1637)	26.9 (11.4–42.5)	648.4 (218.4–1925)	30.4 (19.0–41.7)
1j		112.7 (20.7–613.3)	27.9 (14.6–41.1)	1023 (122.1–8570)	25.5 (4.6–46.4)
1k		91.9 (41.3–204.7)	47.8 (41.3–54.2)	508.6 (159.7–1620)	32.3 (24.2–40.4)
1l		42.5 (24.4–74.1)	40.9 (36.6–45.2)	195.4 (126.0–303.0)	30.1 (26.6–33.7)
rimonabant (SR141716A)[18]		31.7 (22.4–45.0)[e]	87.8 (83.1–92.4)	1400 (500–3700)	92.4 (70.4–114)

[a] n = 4, unless otherwise indicated.
[b] CL = confidence limits.
[c] n = 12.
[d] Plateau could not be reached, n = 2.
[e] n = 24.

which some authors reported to be in the nM range[29] whereas the original study had measured for the same compound a K_i CB_1 = 0.00035 nM.[20]

^1H (400.13 MHz), ^{13}C (100.58 MHz), and ^{19}F (376.45 MHz) NMR spectra were recorded on a Bruker Avance III spectrometer. ^1H NMR chemical shifts are reported relative to the solvent resonance ($CDCl_3$, δ = 7.26). ^{13}C NMR spectra were recorded with complete proton decoupling, and the chemical shifts are reported relative to the solvent resonance ($CDCl_3$, δ = 77.0). MS experiments were performed on an Agilent Technologies 1200 Series HPLC system equipped with a DAD and a 6120 MS detector composed by a ESI ionisation source and a Single Quadrupole mass selective detector. A CEM Discover® System was used to perform reaction with microwaves. Melting points were recorded using a Griffin melting point apparatus. All reactions were carried out in oven- or flame-dried glassware under a N_2 atmosphere, unless stated otherwise. All commercially available reagents were used as received. Reactions were magnetically stirred and monitored by TLC on silica gel (60 F254 pre-coated glass plates, 0.25-mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate or $KMnO_4$ solution. Flash chromatography was performed on silica gel (60 Å, particle size 0.040–0.062 mm). Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

5-(3-Bromophenyl)pent-4-enoic Acid (3)[30]

To a suspension of (3-carboxypropyl)triphenylphosphonium bromide (30.0 g, 69.9 mmol, 1.2 equiv) in anhyd DMSO (20 mL), *t*-BuOK (17.3 g, 153.7 mmol, 2.2 equiv) was added. The mixture was stirred for 1 h

at r.t., then a solution of 3-bromobenzaldehyde (**2**, 6.8 mL, 58.3 mmol, 1.0 equiv) in DMSO (30 mL) was added dropwise. The resulting mixture was stirred overnight, poured into H_2O (150 mL), and extracted with $CHCl_3$ (2 × 200 mL). The aqueous layer was acidified with concd HCl and extracted with $CHCl_3$ (2 × 200 mL). The combined organic layers were washed with H_2O (2 × 200 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 7:3) to give **3** (11.85 g, 80%) as a yellow oil as an *E*/*Z* diastereomeric mixture; R_f = 0.25 (hexane–EtOAc, 6:4).

5-(3-Bromophenyl)pentanoic Acid (4)[30]

To a solution of pentenoic acid **3** (7.30 g, 28.7 mmol, 1.0 equiv) in EtOAc (150 mL) and a catalytic amount of AcOH (0.5 mL), Pd/C (365.0 mg, 5% w/w) was added. The mixture was stirred under H_2 (1 atm) overnight and then filtered on a short pad of Celite; the solvent was evaporated under reduced pressure. Compound **4** was obtained as yellow oil in a quantitative yield and was used without further purification; R_f = 0.25 (hexane–EtOAc, 6:4).

2-Bromo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (5)[30]

To an ice-cooled solution of carboxylic acid **4** (7.35 g, 28.7 mmol, 1.0 equiv), oxalyl chloride (2.46 mL, 28.7 mmol, 1.0 equiv) and a catalytic amount of DMF (1.0 mL) were added, and then the mixture was stirred for 1 h at r.t. The excess oxalyl chloride was removed under reduced pressure and CH_2Cl_2 (5.0 mL) was added to the residue and evaporated. This washing procedure was repeated (3 ×) then the crude product was diluted with CH_2Cl_2 (5.0 mL) and added to a suspension of $AlCl_3$ (4.21 g, 31.0 mmol, 1.1 equiv) in CH_2Cl_2 (5.0 mL). The mixture was stirred overnight at r.t., poured into ice, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 5% aq $NaHCO_3$ (200 mL) and H_2O (2 × 200 mL), dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1) to give **5** (5.46 g, 80%) as a yellow oil; R_f = 0.52 (hexane–EtOAc, 9:1).

Ethyl 2-{2-Bromo-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl}-2-oxoacetate (6)[30]

Na metal (874 mg, 38.0 mmol, 2.0 equiv) was added in one small portion to dry EtOH (100 mL) and the mixture was stirred until all the Na had reacted. Ethyl oxalate (1.97 mL, 19.0 mmol, 1.0 equiv) was added, followed by a solution of bromo-benzosuberone **5** (4.57 g, 19.0 mmol, 1.0 equiv) in dry EtOH (5.0 mL). The solution was stirred at r.t. overnight then the mixture was slowly poured into ice, and 2 M aq HCl (10 mL) was added. The resulting mixture was extracted with $CHCl_3$ (2 × 100 mL), dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. Compound **6** was obtained as yellow oil in a quantitative yield and was used without further purification; R_f = 0.45 (hexane–EtOAc, 9:1).

Ethyl 12-Bromo-3-(2,4-dichlorophenyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene-5-carboxylate (7)[30]

A stirred mixture of diketo ester **6** (4.57 g, 19.0 mmol, 1.0 equiv) and 2,4-dichlorophenylhydrazine hydrochloride (4.06 g, 19.0 mmol, 1.0 equiv) in EtOH (130 mL) was heated at 80 °C overnight. The mixture was allowed to cool to r.t. and the solvent was removed under reduced pressure to give a red-orange solid that was purified by flash chromatography (hexane–EtOAc, 9:1) to afford **7** (4.56 g, 50%) as a pale orange solid; mp 90–92 °C; R_f = 0.60 (hexane–EtOAc, 9:1).

Ethyl 3-(2,4-Dichlorophenyl)-12-(3-hydroxyprop-1-ynyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene-5-carboxylate (8)

A mixture of bromide **7** (3.0 g, 6.24 mmol, 1.0 equiv), prop-2-yn-1-ol (0.36 mL, 6.24 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.19 mmol, 131.4 mg, 0.03 equiv), and 1 M TBAF (18.7 mL, 18.7 mmol, 3.0 equiv) was stirred at 70 °C for 4 h. Then the mixture was diluted with water (20 mL), extracted with EtOAc (2 × 50 mL), dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH, 95:5) to give **8** (2.0 g, 70%) as a white solid; mp 110–112 °C; R_f = 0.23 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.1 Hz, 3 H), 1.97 (br s, OH), 2.25 (br s, 2 H), 2.65 (br s, 1 H), 2.67 (t, *J* = 6.5 Hz, 2 H), 3.24 (br s, 1 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 4.49 (s, 2 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 7.10 (dd, *J* = 1.4, 8.0 Hz, 1 H), 7.35–7.44 (m, 3 H), 7.55 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 20.7, 31.4, 32.4, 51.6, 61.1, 85.1, 88.4, 122.7, 123.7, 126.9, 128.1, 129.2, 129.3, 130.3, 130.6, 132.5, 132.9, 135.9, 136.0, 141.8, 142.0, 142.5, 162.8.

MS (ESI): *m*/*z* calcd $C_{24}H_{20}{}^{35}Cl_2N_2O_3$: 455.1 [M + H]$^+$, 457.1 [M + 2 + H]$^+$, 477.1 [M + Na]$^+$, 479.1 [M + 2 + Na]$^+$; found: 455.1 [M + H]$^+$ (100), 457.1 [M + 2 + H]$^+$ (70), 477.1 [M + Na]$^+$ (20), 479.1 [M + 2 + Na]$^+$ (15).

Ethyl 3-(2,4-Dichlorophenyl)-12-(3-hydroxypropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene-5-carboxylate (9)

Raney Ni was washed with H_2O until the washings were pH neutral and transferred into a round-bottom flask. A solution of alkyne **8** (1.65 g, 3.60 mmol, 1.0 equiv) in THF (240 mL) was added, and the mixture was degassed and then purged with H_2 (3 ×). After stirring for 3 h at r.t. the mixture was filtered through a short pad of Celite and the solvent was evaporated under reduced pressure. Compound **9** was obtained as a white solid in a quantitative yield and was used without further purification. R_f = 0.23 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.1 Hz, 3 H), 1.65 (br s, OH), 1.90 (tt, *J* = 6.4, 13.0 Hz, 2 H), 2.27 (br s, 2 H), 2.61–2.79 (m, 5 H), 3.19 (br s, 1 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 6.61 (d, *J* = 7.9 Hz, 1 H), 6.88 (dd, *J* = 1.6, 7.9 Hz, 1 H), 7.15 (d, *J* = 1.6 Hz, 1 H), 7.39 (dd, *J* = 2.3, 8.4 Hz, 1 H), 7.42 (d, *J* = 2.3 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 20.7, 31.8, 31.9, 32.5, 33.8, 61.0, 62.3, 123.2, 126.1, 126.6, 127.0, 128.0, 129.9, 130.2, 130.7, 132.8, 135.7, 136.4, 141.8, 141.9, 142.4, 143.2, 163.0.

MS (ESI): *m*/*z* calcd $C_{24}H_{24}{}^{35}Cl_2N_2O_3$: 459.1 [M + H]$^+$, 461.1 [M + 2 + H]$^+$, 481.1 [M + Na]$^+$, 483.1 [M + 2 + Na]$^+$; found: 459.1 [M + H]$^+$ (100), 461.1 [M + 2 + H]$^+$ (70), 481.1 [M + Na]$^+$ (40), 483.1 [M + 2 + Na]$^+$ (30).

Ethyl 3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene-5-carboxylate (10)

To an ice-cooled solution of alcohol **9** (1.4 g, 3.2 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL), 50% Deoxofluor in THF (2.0 mL, 4.8 mmol, 1.5 equiv) was added. The mixture was stirred at r.t. for 2 h, then sat. aq $NaHCO_3$ (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL), dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 7:3) to give fluorinated compound **10** (1.18 g, 80%) as white solid; mp 100–102 °C; R_f = 0.50 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.1 Hz, 3 H), 1.95–2.09 (m, 2 H), 2.27 (br s, 2 H), 2.67–2.75 (m, 5 H), 3.20 (br s, 1 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 6.63 (d, *J* = 7.9 Hz, 1 H), 6.88 (dd, *J* = 1.7, 7.9 Hz, 1 H), 7.15 (d, *J* = 1.7 Hz, 1 H), 7.39 (dd, *J* = 2.2, 8.4 Hz, 1 H), 7.42 (d, *J* = 2.2 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 31.1 (d, J_{C-F} = 5.3 Hz), 31.7 (d, J_{C-F} = 20.2 Hz), 31.8, 61.0, 82.5, 83.1 (d, J_{C-F} = 165.1 Hz), 123.3, 126.2, 126.8, 127.1, 128.0, 130.0, 130.2, 130.7, 132.8, 135.8, 136.3, 141.7, 141.9 (2 C), 143.2, 163.0.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –220.0 (tt, *J* = 25.3, 47.1 Hz, 1 F).

MS (ESI): *m*/*z* calcd for $C_{24}H_{23}{}^{35}Cl_2FN_2O_2$: 461.1 [M + H]$^+$, 463.1 [M + 2 + H]$^+$, 483.1 [M + Na]$^+$, 485.1 [M + 2 + Na]$^+$; found: 461.1 [M + H]$^+$ (100), 463.1 [M + 2 + H]$^+$ (65). 483.1 [M + Na]$^+$ (100), 485.1 [M + 2 + Na]$^+$ (65).

[3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaen-5-yl]methanol (11)

A solution of ester **10** (2.47 g, 5.36 mmol, 1.0 equiv) in THF (53.0 mL) was added to a suspension of $LiAlH_4$ (223.8 mg, 5.90 mmol, 1.1 equiv) in THF (53.0 mL) at 0 °C. The mixture was warmed to r.t. and stirred for 2 h. The solution was cooled to 0 °C and quenched with H_2O (5.4 mL), 15% aq NaOH (11 mL), and H_2O (5.4 mL). After vigorously stirring for 1 h, the mixture was filtered on a short pad of silica, dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 1:1) to give fluorinated alcohol **11** (1.92 g, 85%) as white solid; mp 104–106 °C; R_f = 0.25 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.08 (m, 2 H), 2.19–2.26 (m, 2 H), 2.39 (t, *J* = 7.6 Hz, OH), 2.62 (br s, 4 H), 2.72 (t, *J* = 7.6 Hz, 2 H), 4.47 (dt, J_{H-H} = 5.8 Hz, J_{H-F} = 47.2 Hz, 2 H), 4.79 (d, *J* = 5.8 Hz, 2 H), 6.62 (d, *J* = 7.9 Hz, 1 H), 6.87 (dd, *J* = 1.7, 7.9 Hz, 1 H), 7.13 (d, *J* = 1.7 Hz, 1 H), 7.35 (dd, *J* = 2.2, 8.5 Hz, 1 H), 7.43 (d, *J* = 2.0 Hz, 1 H), 7.44 (d, *J* = 4.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 31.1 (d, J_{C-F} = 5.4 Hz), 31.2, 31.7 (d, J_{C-F} = 19.8 Hz), 32.8, 57.7, 83.1 (d, J_{C-F} = 165.0 Hz), 118.2, 126.1, 127.0, 127.4, 128.0, 129.9, 130.3, 130.5, 132.7, 135.0, 136.8, 141.1, 141.7, 142.1, 151.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, *J* = 25.2, 47.1 Hz, 1 F).

MS (ESI): *m*/*z* calcd for $C_{22}H_{21}{}^{35}Cl_2FN_2O$: 419.1 [M + H]$^+$, 421.1 [M + 2 + H]$^+$; found: 419.1 [M + H]$^+$ (100), 421.1 [M + 2 + H]$^+$ (70).

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene-5-carbaldehyde (12)

To a solution of alcohol **11** (1.91 g, 4.58 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL), Dess–Martin periodinane (DMP, 2.33 g, 5.50 mmol, 1.2 equiv) was added at 0 °C The mixture was warmed to r.t. and stirred for 3 h. Then sat. aq $NaHCO_3$ (93 mL) and $Na_2S_2O_3$ (5.2 g, 33.4 mmol, 7.3 equiv) were added. After stirring for 1 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Aldehyde **12** was obtained as a white solid in a quantitative yield and was used without further purification; R_f = 0.70 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.10 (m, 2 H), 2.19–2.34 (m, 2 H), 2.65–2.80 (m, 4 H), 3.14 (br s, 2 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.63 (d, *J* = 7.9 Hz, 1 H), 6.89 (dd, *J* = 1.7, 7.9 Hz, 1 H), 7.16 (d, *J* = 1.5 Hz, 1 H), 7.43 (dd, *J* = 2.3, 8.4 Hz, 1 H), 7.49 (d, *J* = 1.3 Hz, 1 H), 7.50 (d, *J* = 8.5 Hz, 1 H), 10.2 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 31.1 (d, J_{C-F} = 5.3 Hz), 31.2, 31.6 (d, J_{C-F} = 19.8 Hz), 32.7, 83.1 (d, J_{C-F} = 165.1 Hz), 121.7, 126.2, 126.3, 127.2, 128.2, 130.0, 130.2, 130.5, 132.6, 136.0, 136.3, 141.9, 142.1, 143.6, 148.9, 188.2.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –220.0 (tt, *J* = 25.4, 47.2 Hz, 1 F).

MS (ESI): *m*/*z* calcd for $C_{22}H_{19}{}^{35}Cl_2FN_2O$: 417.1 [M + H]$^+$, 419.1 [M + 2 + H]$^+$; found: 417.1 [M + H]$^+$ (100), 419.1 [M + 2 + H]$^+$ (70).

3-(2,4-Dichlorophenyl)-5-ethynyl-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (13)

K_2CO_3 (2.1 g, 15.1 mmol, 3.3 equiv) and dimethyl 1-diazo-2-oxopropylphosphonate (1.37 mL, 9.16 mmol, 2.0 equiv) were added to an ice-cold solution of aldehyde **12** (1.90 g, 4.58 mmol, 1.0 equiv) in MeOH (50 mL). After 5 min the ice bath was removed, the mixture was allowed to warm to r.t. and stirred for an additional 12 h. 5% aq $NaHCO_3$ solution (10 mL) was added and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 7:3) to give alkyne **13** (1.7 g, 90%) as a white solid; mp 112–114 °C; R_f = 0.72 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.08 (m, 2 H), 2.25 (br s, 2 H), 2.49–2.82 (m, 6 H), 3.28 (s, 1 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.61 (d, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 6.6 Hz, 1 H), 7.14 (s, 1 H), 7.38 (dd, *J* = 2.2, 8.5 Hz, 1 H), 7.43 (d, *J* = 2.1 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 31.0, 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.8 Hz), 32.7, 80.1, 83.1 (d, J_{C-F} = 165.0 Hz), 123.5, 126.2, 126.8, 126.9, 128.0, 130.0, 130.3, 130.4, 130.6, 132.6, 135.0, 135.4, 136.5, 141.2, 141.5, 141.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –220.0 (tt, *J* = 25.3, 47.2 Hz, 1 F).

MS (ESI): *m*/*z* calcd for $C_{23}H_{19}{}^{35}Cl_2FN_2$: 413.1 [M + H]$^+$, 415.1 [M + 2 + H]$^+$; found: 413.1 [M + H]$^+$ (100), 415.1 [M + 2 + H]$^+$ (70).

Synthesis of Benzylic and Aliphatic Azides;[31] General Procedure

NaN_3 (2.0 equiv) in H_2O (0.1 mL/mmol) was added to a stirred solution of the benzylic/aliphatic bromide (1.0 equiv) in THF (2.5 mL/mmol). The resulting suspension was stirred at 80 °C for 3 h. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The azide was obtained in quantitative yield and was used without further purification and isolation.

Synthesis of Aromatic Azides;[31] General Procedure

A solution of aromatic amine (1.0 equiv) in MeCN (2 mL/mmol) was cooled to 0 °C and *t*-BuONO (1.5 equiv) followed by $TMSN_3$ (1.5 equiv) were added dropwise. The resulting solution was stirred at r.t. for 1 h. The mixture was concd under vacuum, diluted with hexane, and filtered on a short pad of silica gel. The azide was obtained in quantitative yield and was used without further purification and isolation.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-(1*H*-1,2,3-triazol-4-yl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1a)

To solution of alkyne **13** (70 mg, 0.17 mmol, 1.0 equiv) and $TMSN_3$ (0.02 mL, 0.2 mmol, 1.2 equiv) in DMF–H_2O (4:1, 2.0 mL), $CuSO_4$ (1.4 mg, 0.008 mmol, 0.05 equiv) and sodium ascorbate (14.0 mg, 0.07 mmol, 0.4 equiv) were added. The mixture was placed in a microwave reactor and irradiated for 30 min at 120 °C. The solution was cooled, ice was added, and it was extracted with EtOAc (3 × 5 mL). The organic layers were washed with H_2O, brine, dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1a** (34.8 mg, 45%) as a white solid; mp 94–96 °C; R_f = 0.20 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.10 (m, 2 H), 2.30 (br s, 2 H), 2.69–2.86 (m, 4 H), 2.88 (br s, 2 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.90 (d, J = 7.5 Hz, 1 H), 7.17 (s, 1 H), 7.39 (dd, J = 1.8, 8.3 Hz, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.57 (d, J = 8.4 Hz, 1 H), 8.19 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 31.1 (d, J_{C-F} = 5.3 Hz), 31.5, 31.7 (d, J_{C-F} = 19.5 Hz), 32.7, 83.1 (d, J_{C-F} = 165.0 Hz), 118.8, 126.2, 127.1, 127.2, 128.1, 130.0, 130.4, 130.7, 132.8, 135.5, 136.5, 141.5 (2 C), 141.9, 142.0 (2 C), 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{23}H_{20}{}^{35}Cl_2FN_5$: 456.1 [M + H]$^+$, 458.1 [M + 2 + H]$^+$; found: 456.1 [M + H]$^+$ (100), 458.1 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{23}H_{21}Cl_2FN_5$: 456.1153; found: 456.1149.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1b)

A solution of NaN_3 (102 mg, 1.5 mmol, 6.0 equiv), $CuSO_4$ (8.0 mg, 0.05 mmol, 0.2 equiv), and sodium ascorbate (24.8 mg, 0.125 mmol, 0.5 equiv) in DMF–H_2O (1:1, 8.0 mL) was stirred for 5 min at r.t. Then a solution of alkyne **13** (103 mg, 0.25 mmol, 1.0 equiv) in DMF (1 mL) and MeI (0.1 mL, 0.58 mmol, 1.6 equiv) were added and the resulting mixture was stirred overnight at 120 °C. The solution was cooled and extracted with EtOAc (3 × 20 mL). The organic layers were washed with H_2O, brine, dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1b** (56.2 mg, 48%) as a white solid; mp 88–90 °C; R_f = 0.25 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96–2.09 (m, 2 H), 2.23–2.37 (m, 2 H), 2.69–2.83 (m, 4 H), 2.30 (br s, 2 H), 4.17 (s, 3 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.66 (d, J = 7.8 Hz, 1 H), 6.88 (dd, J = 1.7, 7.9 Hz, 1 H), 7.16 (d, J = 1.3 Hz, 1 H), 7.38 (dd, J = 2.3, 8.5 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.96 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.9 Hz), 31.8, 32.8, 36.7, 83.1 (d, J_{C-F} = 165.0 Hz), 118.9, 122.2, 126.1, 127.1, 127.4, 128.0, 129.9, 130.3, 130.7, 132.8, 135.2, 136.8, 141.2, 142.0, 142.6, 142.7, 142.8.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{24}H_{22}{}^{35}Cl_2FN_5$: 470.1 [M + H]$^+$, 472.1 [M + 2 + H]$^+$; found: 470.1 [M + H]$^+$ (100), 472.1 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{24}H_{23}Cl_2FN_5$: 470.1309; found: 470.1305.

Compounds 1c–l; General Synthetic Procedure

Sodium ascorbate (0.2 equiv) and $CuSO_4$ (0.04 equiv) were added to a solution of alkyne **13** (1.0 equiv) and the appropriate azide (1.0 equiv) in *t*-BuOH–H_2O (2:1, 12 mL per mmol). The mixture was stirred at r.t. for 24 h. Sat. aq NH_4Cl (10 mL/mmol) was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and filtered and the solvent was evaporated under reduced pressure.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-(1-propyl-1*H*-1,2,3-triazol-4-yl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1c)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1c** (40 mg, 65%) as a white solid; mp 122–124 °C; R_f = 0.40 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.4 Hz, 3 H), 1.97–2.11 (m, 2 H), 2.01 (dd, J = 7.2, 14.4 Hz, 2 H), 2.27–2.39 (m, 2 H), 2.70–2.82 (m, 4 H), 2.99 (br s, 2 H), 4.41 (t, J = 7.1 Hz, 2 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.66 (d, J = 7.8 Hz, 1 H), 6.89 (dd, J = 1.7, 7.9 Hz, 1 H), 7.17 (d, J = 1.5 Hz, 1 H), 7.39 (dd, J = 2.3, 8.4 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 20.9, 23.7, 31.1 (d, J_{C-F} = 5.5 Hz), 31.7 (d, J_{C-F} = 19.8 Hz), 31.8, 32.8, 52.0, 83.1 (d, J_{C-F} = 162.0 Hz), 118.9, 121.0, 126.0, 127.1, 127.3, 127.4, 129.9, 130.3, 130.7, 132.8, 135.2, 136.8, 141.2, 142.0, 142.5, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.1 Hz, 1 F).

MS (ESI): m/z calcd for $C_{26}H_{26}{}^{35}Cl_2FN_5$: 498.1 [M + H]$^+$, 500.1 [M + 2 + H]$^+$; found: 498.1 [M + H]$^+$ (100), 500.1 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{26}H_{27}Cl_2FN_5$: 498.1622; found: 498.1611.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-(1-pentyl-1*H*-1,2,3-triazol-4-yl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1d)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1d** (35 mg, 60%) as a white solid; mp 133–135 °C; R_f = 0.65 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.1 Hz, 3 H), 1.22–1.47 (m, 4 H), 1.86–2.13 (m, 4 H), 2.25–2.40 (m, 2 H), 2.64–2.85 (m, 4 H), 3.03 (br s, 2 H), 4.43 (t, J = 7.1 Hz, 2 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.66 (d, J = 7.8 Hz, 1 H), 6.89 (dd, J = 1.6, 7.8 Hz, 1 H), 7.16 (d, J = 1.3 Hz, 1 H), 7.38 (dd, J = 2.3, 8.4 Hz, 1 H), 7.45 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.98 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.9, 22.1, 28.6, 30.0, 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.8 Hz), 31.8, 32.8, 50.4, 83.1 (d, J_{C-F} = 165.0 Hz), 119.0, 121.0, 126.0, 127.1, 127.4, 128.0, 130.0, 130.3, 130.7, 132.8, 135.2, 136.8, 141.2, 142.0, 142.5, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{28}H_{30}{}^{35}Cl_2FN_5$: 526.2 [M + H]$^+$, 528.2 [M + 2 + H]$^+$; found: 526.2 [M + H]$^+$ (100), 528.2 [M + 2 + H]$^+$ (65).

HRMS: m/z [M + H]$^+$ calcd for $C_{28}H_{31}Cl_2FN_5$: 526.1935; found: 526.1924.

5-[1-(But-3-enyl)-1*H*-1,2,3-triazol-4-yl]-3-(2,4-dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1e)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1e** (25 mg, 60%) as a white solid; mp 138–140 °C; R_f = 0.80 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.12 (m, 2 H), 2.22–2.41 (m, 2 H), 2.61–2.82 (m, 6 H), 3.03 (br s, 2 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 4.50 (t, J = 7.1 Hz, 2 H), 5.09–5.21 (m, 2 H), 5.81 (ddt, J = 6.8, 10.2, 17.0 Hz, 1 H), 6.65 (d, J = 7.8 Hz, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 7.16 (s, 1 H), 7.38 (dd, J = 2.0, 8.5 Hz, 1 H), 7.44 (d, J = 2.1 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.8 Hz), 31.8, 32.8, 34.4, 49.7, 83.1 (d, J_{C-F} = 164.9 Hz), 118.5, 119.0, 121.1, 126.1, 127.1, 127.4, 128.0, 129.9, 130.3, 130.7, 132.8, 133.2, 135.2, 136.8, 141.2, 142.0, 142.5, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –220.0 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{27}H_{26}{}^{35}Cl_2FN_5$: 510.1 [M + H]$^+$, 512.1 [M + 2 + H]$^+$, 532.1 [M + Na]$^+$, 534.1 [M + 2 + Na]$^+$; found: 510.1 [M + H]$^+$ (100), 512.2 [M + 2 + H]$^+$ (70) 532.1 [M + Na]$^+$ (45), 534.1 [M + 2 + Na]$^+$ (30).

HRMS: m/z [M + H]$^+$ calcd for $C_{27}H_{27}Cl_2FN_5$: 510.1622; found: 510.1613.

5-[1-(Cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl]-3-(2,4-dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1f)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1f** (62 mg, 76%) as a white solid; mp 174–176 °C; R_f = 0.68 (hexane–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.13 (m, 2 H), 1.16–1.35 (m, 4 H), 1.63–1.82 (m, 4 H), 1.88–2.13 (m, 3 H), 2.27–2.42 (m, 2 H), 2.62–2.83 (m, 4 H), 3.03 (br s, 2 H), 4.25 (d, J = 7.2 Hz, 2 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.66 (d, J = 7.8 Hz, 1 H), 6.88 (dd, J = 1.4, 7.8 Hz, 1 H), 7.16 (d, J = 0.9 Hz, 1 H), 7.38 (dd, J = 2.2, 8.4 Hz, 1 H), 7.44 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.95 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.5 (2 C), 26.1, 30.5 (2 C), 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.7 Hz), 31.8, 32.8, 38.8, 56.5, 83.1 (d, J_{C-F} = 165.0 Hz), 110.0, 121.5, 126.0, 127.1, 127.5, 128.0, 129.9, 130.3, 130.7, 132.8, 135.2, 136.8, 141.1, 142.0, 141.4, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{30}H_{32}{}^{35}Cl_2FN_5$: 552.2 [M + H]$^+$, 554.2 [M + 2 + H]$^+$; found: 552.2 [M + H]$^+$ (100), 554.2 [M + 2 + H]$^+$ (65).

HRMS: m/z [M + H]$^+$ calcd for $C_{30}H_{33}Cl_2FN_5$: 552.2092; found: 552.2098.

5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-(2,4-dichlorophenyl)-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1g)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1g** (47 mg, 82%) as a white solid; mp 75–77 °C; R_f = 0.50 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96–2.11 (m, 2 H), 2.24–2.40 (m, 2 H), 2.68–2.80 (m, 4 H), 3.09 (br s, 2 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 5.60 (s, 2 H), 6.65 (d, J = 7.8 Hz, 1 H), 6.88 (dd, J = 1.8, 7.9 Hz, 1 H), 7.16 (d, J = 1.5 Hz, 1 H), 7.33–7.41 (m, 6 H), 7.43 (d, J = 2.2 Hz, 1 H), 7.48 (d, J = 8.5 Hz, 1 H), 7.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.3 Hz), 31.7 (d, J_{C-F} = 19.7 Hz), 31.8, 32.8, 54.3, 83.1 (d, J_{C-F} = 165.0 Hz), 118.0, 190.0, 126.1, 127.1, 127.3, 128.0, 128.4 (2 C), 128.8, 129.1 (2 C), 130.0, 130.3, 130.7, 132.8, 134.5, 135.3, 136.6, 136.7, 141.3, 142.0, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –220.0 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{30}H_{26}{}^{35}Cl_2FN_5$: 546.2 [M + H]$^+$, 548.2 [M + 2 + H]$^+$; found: 546.2 [M + H]$^+$ (100), 548.2 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{30}H_{27}Cl_2FN_5$: 546.1628; found: 546.1613.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-{1-[(4-methoxyphenyl)methyl]-1*H*-1,2,3-triazol-4-yl}-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1h)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1h** (50 mg, 78%) as a white solid; mp 70–72 °C; R_f = 0.60 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.11 (m, 2 H), 2.24–2.40 (m, 2 H), 2.66–2.80 (m, 4 H), 3.08 (br s, 2 H), 3.82 (s, 3 H), 4.47 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 5.53 (s, 2 H), 6.64 (d, J = 7.9 Hz, 1 H), 6.88 (d, J = 9.5 Hz, 1 H), 6.91 (d, J = 8.6 Hz, 2 H), 7.16 (s, 1 H), 7.30 (d, J = 9.5 Hz, 2 H), 7.36 (dd, J = 2.0, 8.5 Hz, 1 H), 7.43 (d, J = 2.2 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.85 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 29.7, 31.1 (d, J_{C-F} = 5.4 Hz), 31.7 (d, J_{C-F} = 19.7 Hz), 31.8, 32.8, 53.8, 55.4, 83.1 (d, J_{C-F} = 165.0 Hz), 114.5 (2 C), 119.0, 120.8, 126.0, 126.5, 127.0, 127.4, 128.0, 129.9, 130.0 (2 C), 130.3, 130.7, 132.8, 135.2, 136.8, 141.2, 142.0, 142.7, 142.8, 160.0.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{31}H_{28}{}^{35}Cl_2FN_5O$: 576.2 [M + H]$^+$, 578.2 [M + 2 + H]$^+$; found: 576.2 [M + H]$^+$ (100), 578.2 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{31}H_{29}Cl_2FN_5O$: 576.1728; found: 576.1720.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1i)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1i** (64 mg, 65%) as a white solid; mp 90–92 °C; R_f = 0.65 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.12 (m, 2 H), 2.26–2.44 (m, 2 H), 2.65–2.84 (m, 4 H), 3.10 (br s, 2 H), 4.48 (dt, J_{H-H} = 5.8 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.69 (d, J = 7.8 Hz, 1 H), 6.90 (dd, J = 1.4, 7.8 Hz, 1 H), 7.18 (s, 1 H), 7.40 (dd, J = 2.2, 8.4 Hz, 1 H), 7.45–7.49 (m, 2 H), 7.54 (d, J = 8.4 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 8.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.3 Hz), 31.7 (d, J_{C-F} = 18.0 Hz), 31.8, 32.8, 83.1 (d, J_{C-F} = 165.0 Hz), 119.1, 119.2, 120.4 (2 C), 126.1, 127.1, 127.3, 128.0, 128.7, 129.8 (2 C), 130.0, 130.4, 130.7, 132.9, 135.3, 136.8, 137.1, 141.3, 142.0, 142.5, 142.9, 143.3.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{29}H_{24}{}^{35}Cl_2FN_5$: 532.1 [M + H]$^+$, 534.1 [M + 2 + H]$^+$; found: 532.1 [M + H]$^+$ (100), 534.1 [M + 2 + H]$^+$ (70).

HRMS: m/z [M + H]$^+$ calcd for $C_{29}H_{25}Cl_2FN_5$: 532.1466; found: 532.1458.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-{1-[4-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1j)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1j** (39 mg, 75%) as a white solid; mp 88–90 °C; R_f = 0.68 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.13 (m, 2 H), 2.29–2.44 (m, 2 H), 2.65–2.83 (m, 4 H), 3.12 (br s, 2 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.91 (dd, J = 1.6, 7.9 Hz, 1 H), 7.18 (d, J = 1.3 Hz, 1 H), 7.41 (dd, J = 2.3, 8.4 Hz, 1 H), 7.48 (d, J = 2.2 Hz, 1 H), 7.53 (d, J = 8.5 Hz, 1 H), 7.67–7.83 (m, 2 H), 8.03–8.18 (m, 2 H), 8.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.3 Hz), 31.7 (d, J_{C-F} = 19.8 Hz), 31.8, 32.8, 83.1 (d, J_{C-F} = 165.0 Hz), 117.3 (q, J_{C-F} = 4.0 Hz), 118.9, 119.3, 123.3 (q, J_{C-F} = 272.9 Hz), 123.4, 125.9 (q, J_{C-F} = 3.4 Hz), 126.1, 127.1, 127.2, 128.1, 130.0, 130.4, 130.6 (2 C), 132.5 (q, J_{C-F} = 33.2 Hz), 132.8, 135.4, 136.7, 137.4, 141.4, 142.0, 142.1, 143.0, 143.8.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F), 62.9 (s, 3 F).

MS (ESI): m/z calcd for $C_{30}H_{23}{}^{35}Cl_2F_4N_5$: 600.1 [M + H]$^+$, 602.1 [M + 2 + H]$^+$; found: 600.1 [M + H]$^+$ (100), 602.1 [M + 2 + H]$^+$ (65).

HRMS: m/z [M + H]$^+$ calcd for $C_{30}H_{24}Cl_2F_4N_5$: 600.1339; found: 600.1347.

3-(2,4-Dichlorophenyl)-12-(3-fluoropropyl)-5-[1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1k)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1k** (38 mg, 60%) as a white solid; mp 128–130 °C; R_f = 0.62 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96–2.13 (m, 2 H), 2.26–2.45 (m, 2 H), 2.64–2.87 (m, 4 H), 3.10 (br s, 2 H), 3.93 (s, 3 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.90 (dd, J = 7.7 Hz, 1 H), 7.06–7.22 (m, 3 H), 7.34–7.51 (m, 3 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.87 (d, J = 1.4, 7.9 Hz, 1 H), 8.58 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.5 Hz), 31.7 (d, J_{C-F} = 20.0 Hz), 31.8, 32.8, 56.0, 83.1 (d, J_{C-F} = 164.9 Hz), 112.3, 119.1, 121.2, 123.3, 125.5, 126.1, 126.4, 127.1, 127.5, 128.0, 129.9, 130.1, 130.3, 130.8, 132.9, 135.2, 136.9, 141.3, 142.0, 142.7, 142.8, 124.9, 151.2.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.2, 47.1 Hz, 1 F).

MS (ESI): m/z calcd for $C_{30}H_{26}{}^{35}Cl_2FN_5O$: 562.2 [M + H]$^+$, 564.2 [M + 2 + H]$^+$; found: 562.2 [M + H]$^+$ (100), 564.2 [M + 2 + H]$^+$ (65).

HRMS: m/z [M + H]$^+$ calcd for $C_{30}H_{27}Cl_2FN_5O$: 562.157; found: 562.1564.

3-(2,4-Dichlorophenyl)-5-[1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl]-12-(3-fluoropropyl)-3,4-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2(6),4,10,12-pentaene (1l)

The crude product was purified by flash chromatography (hexane–EtOAc, 6:4) to give triazole **1l** (41 mg, 75%) as a white solid; mp 76–78 °C; R_f = 0.60 (hexane–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.14 (m, 2 H), 2.28–2.46 (m, 2 H), 2.68–2.84 (m, 4 H), 3.08 (br s, 2 H), 4.48 (dt, J_{H-H} = 5.9 Hz, J_{H-F} = 47.2 Hz, 2 H), 6.68 (d, J = 7.8 Hz, 1 H), 6.90 (dd, J = 1.6, 7.9 Hz, 1 H), 7.18 (d, J = 1.3 Hz, 1 H), 7.40 (dd, J = 2.3, 8.5 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.49 (d, J = 2.2 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 7.64 (d, J = 2.6 Hz, 1 H), 7.65 (d, J = 3.7 Hz, 1 H), 8.42 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.1 (d, J_{C-F} = 5.3 Hz), 31.7 (d, J_{C-F} = 19.3 Hz), 31.8, 32.8, 83.1 (d, J_{C-F} = 165.0 Hz), 119.2, 123.0, 126.1, 127.1, 127.3, 128.0, 128.3, 128.5, 129.5, 130.0, 130.4, 130.7 (2 C), 132.8, 133.6, 135.3, 136.3, 136.7, 141.4, 142.0, 142.2, 142.7, 142.9.

^{19}F NMR (376.45 MHz, $CDCl_3$): δ = –219.9 (tt, J = 25.3, 47.2 Hz, 1 F).

MS (ESI): m/z calcd for $C_{29}H_{22}{}^{35}Cl_4FN_5$: 600.1 [M + H]$^+$, 602.1 [M + 2 + H] + , 603.1 [M + 3 + H]$^+$, 604.1 [M + 4 + H]$^+$; found: 600.1 [M + H] + (100), 602.2 [M + 2 + H]$^+$ (80), 603.1[M + 3 + H]$^+$, 604.1 [M + 4 + H]$^+$.

HRMS: m/z [M + H]$^+$ calcd for $C_{29}H_{23}Cl_4FN_5$: 600.0686; found: 600.0692.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379887.

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