

Table S1. Structures of purpurealidin analogs (compounds **1–12**).

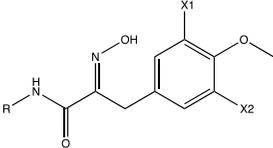
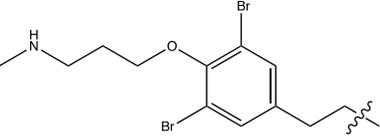
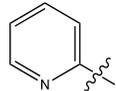
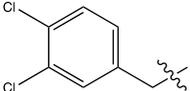
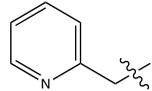
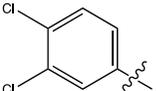
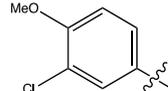
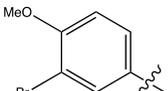
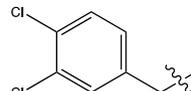
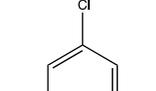
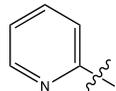
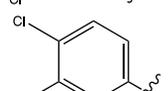
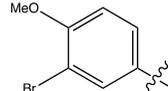
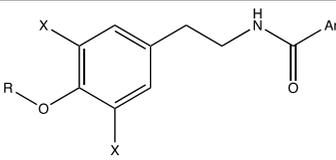
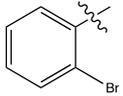
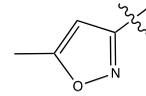
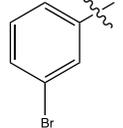
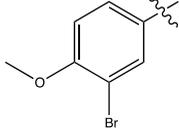
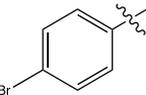
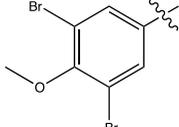
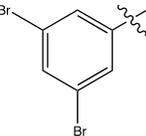
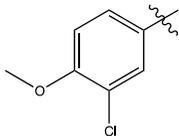
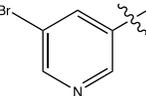
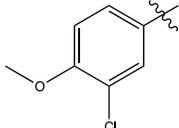
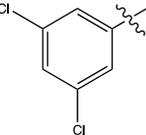
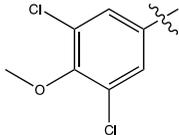
							
#	X1	X2	R	#	X1	X2	R
1	Br	Br		7	Br	Br	
2	Br	Br		8	Br	Br	
3	Br	Br		9	Br	Br	
4	Br	Br		10	H	H	
5	Br	Br		11	Br	H	
6	Br	Br		12	Br	H	

Table S2. Structures of purpurealidin analogs (compounds 13–40).

							
#	Ar	X	R	#	Ar	X	R
13		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	27		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$
14		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	28		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$
15		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	29		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$
16		Br	$(\text{CH}_2)_3\text{-CH}(\text{CH}_3)_2$	30		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$
17		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	31		Br	$(\text{CH}_2)_3\text{-NH-CH}_3$
18		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	32		Br	$(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$

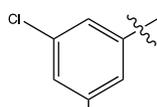
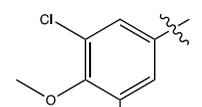
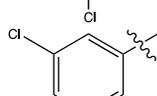
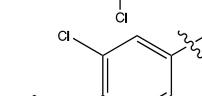
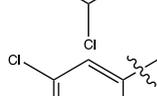
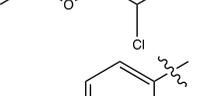
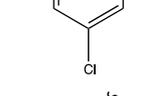
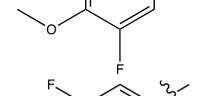
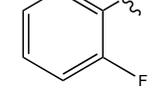
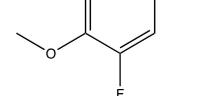
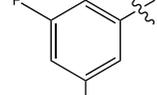
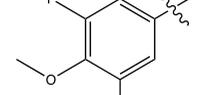
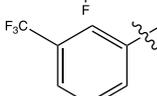
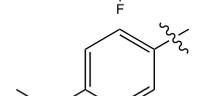
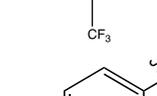
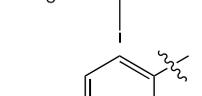
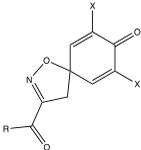
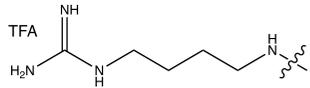
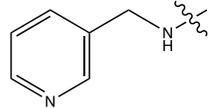
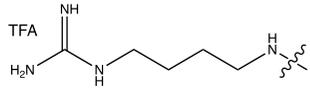
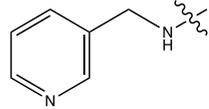
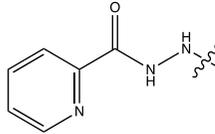
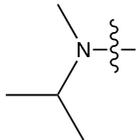
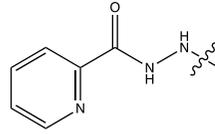
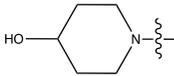
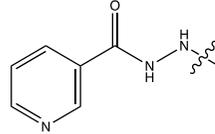
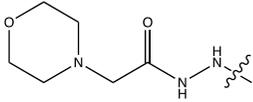
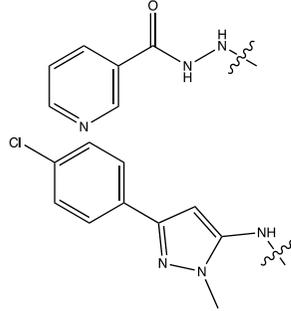
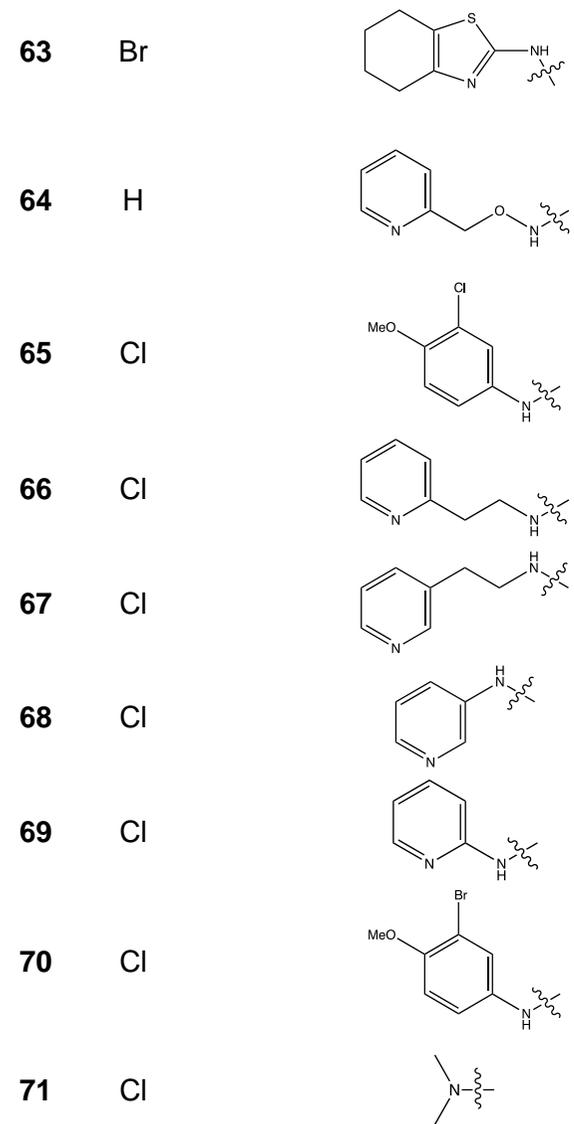
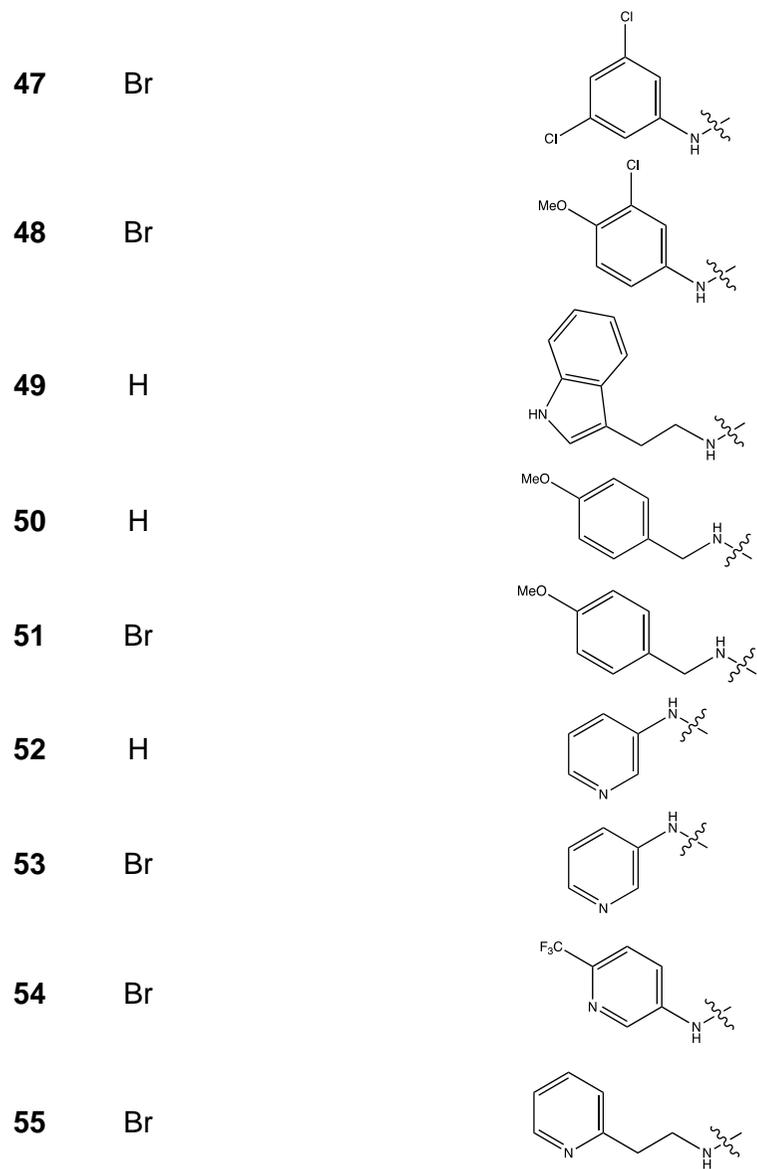
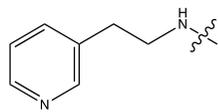
19		Br	$(\text{CH}_2)_3\text{-CH-(CH}_3)_2$	33		Br	$(\text{CH}_2)_3\text{-NH-CH}_3$
20		H	$(\text{CH}_2)_3\text{-N(CH}_3)_2$	34		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$
21		H	H	35		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$
22		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$	36		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$
23		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$	37		Br	$(\text{CH}_2)_3\text{-NH-CH}_3$
24		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$	38		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$
25		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$	39		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$
26		Br	$(\text{CH}_2)_3\text{-NH-CH}_3$	40		Br	$(\text{CH}_2)_3\text{-N(CH}_3)_2$

Table S3. Structures of purpurealidin analogs (compounds 41–72).

					
#	X	R	#	X	R
41	H		57	H	
42	Br		58	Br	
43	Br		59	H	
44	Br		60	Br	
45	H		61	Br	
46	H		62	Br	



56 Br



72 Cl

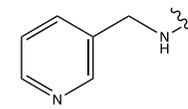
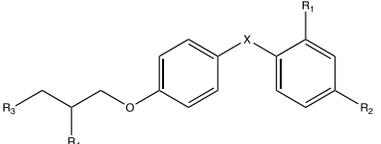
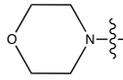
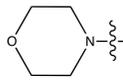
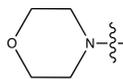
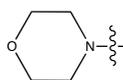
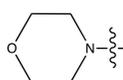
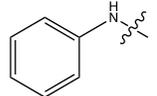
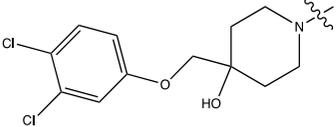


Table S4. Structures of purpurealidin analogs (compounds 73–103).

											
#	X	R1	R2	R3	R4	#	X	R1	R2	R3	R4
73	NH	NO ₂	H		H	89	NH	NO ₂	CF ₃		OH
74	NH	NO ₂	CF ₃		H	90	NH	COOMe	H		OH
75	NH	NO ₂	H		OH	91	NH	COOMe	CF ₃		OH
76	NH	NO ₂	CF ₃		OH	92	NH	COOH	H		OH
77	NH	NH ₂	CF ₃		OH	93	NH	NO ₂	NO ₂		OH
78	NH	H	H		OH	94	NH	NO ₂	CF ₃		OH
79	NH	H	CF ₃		OH	95	NH	NO ₂	CF ₃		OH

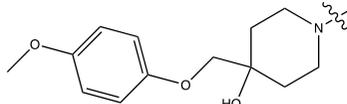
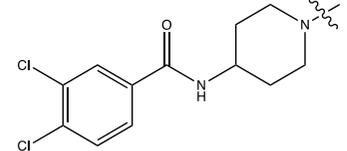
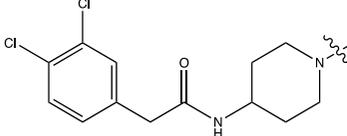
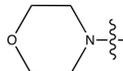
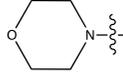
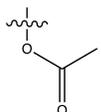
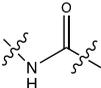
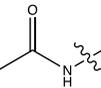
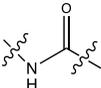
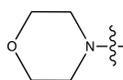
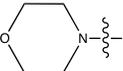
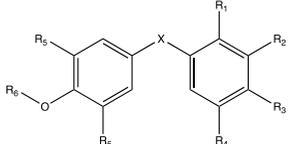
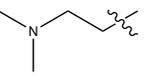
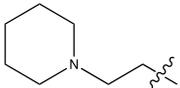
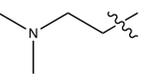
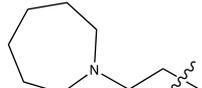
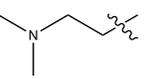
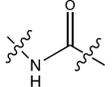
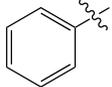
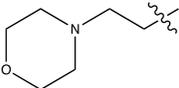
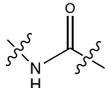
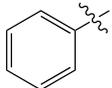
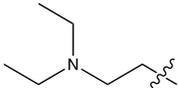
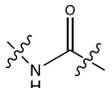
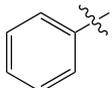
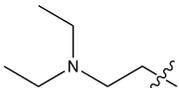
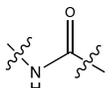
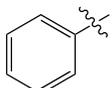
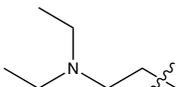
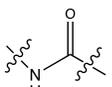
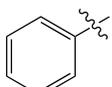
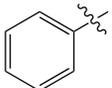
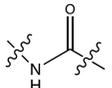
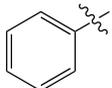
80	NH	COOMe	H		OH	96	NH	NO ₂	CF ₃		OH
81	NH	COOMe	CF ₃		OH	97	NH	NO ₂	CF ₃		OH
82	NH	COOH	H		OH	98	NH	NO ₂	CF ₃		OH
83	NH	COOH	CF ₃		OH	99	O	NO ₂	CF ₃		OH
84	NH	NO ₂	NO ₂		OH	100	O	NO ₂	CF ₃		OH
85	NH	NO ₂	CF ₃		OH	101	O	COOMe	H		OH
86	NH	NO ₂	CF ₃			102		NO ₂	CF ₃		OH
87	NH	NO ₂	CF ₃		OH	103		NO ₂	CF ₃		OH
88	NH	NO ₂	H		OH						

Table S5. Structures of purpurealidin analogs (compounds **104–120**).

															
#	X	R1	R2	R3	R4	R5	R6	#	X	R1	R2	R3	R4	R5	R6
104	NH	NO ₂	H	CF ₃	H	H		113	NH	NO ₂	H	CF ₃	H	H	
105	NH	NO ₂	H	CF ₃	H	Br		114	NH	NO ₂	H	CF ₃	H	H	
106	NH	NO ₂	H	CF ₃	H	Cl		115		NO ₂	H	H	H	H	
107	NH	NO ₂	H	CF ₃	H	H		116		H	NO ₂	H	H	H	
108	NH	NO ₂	H	CF ₃	H	H		117		NO ₂	H	NO ₂	H	H	
109	NH	NO ₂	H	CF ₃	H	Br		118		H	NO ₂	NO ₂	H	H	
110	NH	NO ₂	H	CF ₃	H	Cl		119		H	NO ₂	H	NO ₂	H	
111	NH	NO ₂	H	CF ₃	H	H		120		H	NO ₂	Cl	H	H	

112

NH

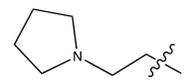
NO₂

H

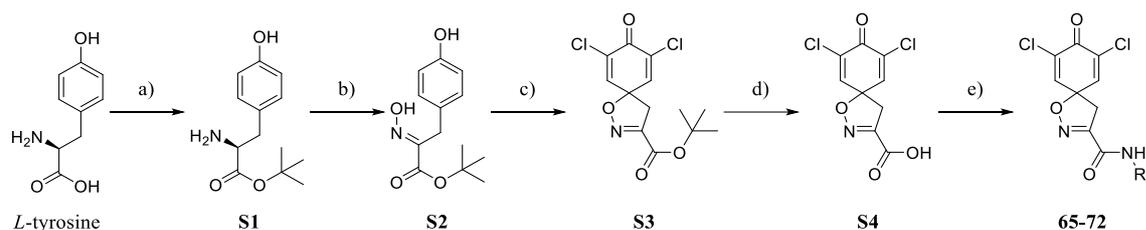
CF₃

H

H



Chemistry: Compounds 65-72



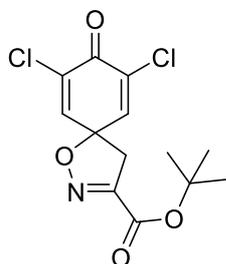
Scheme S1. General scheme for synthesis of chlorinated spirocycles **65–72**. Reagents and conditions: a) *tert*-butyl acetate, 20–25 °C, 18 h; b) Na₂WO₄·2H₂O, H₂O₂, EtOH, 20–25 °C, 7 h; c) NCS, DMF, 20–25 °C, 4 h; d) TFA, DCM, 20–25 °C, 6 h; e) amine, EDC·HCl, HOBt, DCM, 20–25 °C, 5–15 h. The R substituents are given in Table 3.

Synthesis of S1 and S2 as previously described in Patel, P.A., *et al.* [23]

General

All reactions were carried out using commercially available starting materials unless otherwise stated. ¹H NMR and ¹³C NMR spectra in CDCl₃, *d*₆-acetone or CD₃CN at ambient temperature were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to the NMR reference solvent signals (CDCl₃: 7.26 ppm, 77.16 ppm; *d*₆-acetone: 2.05 ppm, 29.84 ppm, CD₃CN: 1.94 ppm, 118.26 ppm). Multiplicities are indicated by s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), and m (multiplet). The coupling constants *J* are quoted in hertz (Hz). LC-MS and HRMS-spectra were recorded using Waters Acquity UPLC®-system including PDA (with Acquity UPLC® BEH C18 column, 1.7 μm, 50 mm × 2.1 mm, Waters) with Waters Synapt G2 HDMS with the ESI (+), high resolution mode. The mobile phase consisted of H₂O (A) and acetonitrile (B) both containing 0.1% HCOOH. Microwave syntheses were performed in sealed tubes using Biotage Initiator+ instrument equipped with an external IR sensor. The flash chromatography was performed with Biotage Isolera One flash chromatography purification system with 200-800 nm UV-VIS detector using SNAP KP-Sil 10 g, or 25 g cartridges. The TLC plates were provided by Merck (Silica gel 60-F254) and visualization of the amine compounds was done using ninhydrin (a 0.2% w/v solution in a 3% solution of acetic acid in 1-butanol) staining.

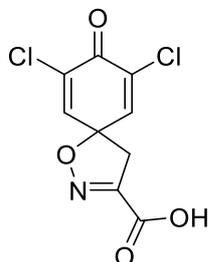
tert-Butyl 7,9-dichloro-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxylate (S3)



To a solution of *tert*-butyl (*E*)-2-(hydroxyimino)-3-(4-hydroxyphenyl)propanoate P8 (4.0 g, 0.016 mol) in anhydrous DMF (10 mL), *N*-chlorosuccinimide (7.0 g, 0.053 mol, 3.3 equiv) in anhydrous DMF (27 mL) was added dropwise (15 min). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with Et₂O (60 mL), and washed with H₂O (3 × 30 mL) and a 10% solution of Na₂S₂O₃ in H₂O (2 × 40 mL). The aqueous phase was back-extracted with Et₂O (4 × 120 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified with automated flash chromatography (*n*-heptane/EtOAc

gradient: 5→20%) to give the compound **S1** as a yellow solid (2.34 g, 46%). ¹H NMR (400 MHz, CDCl₃) δ 7.05 (s, 2H), 3.43 (s, 2H), 1.57 (s, 9H).

7,9-Dichloro-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxylic acid (**S4**)



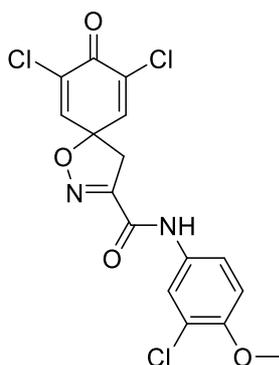
To a solution of *tert*-butyl 7,9-dichloro-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxylate **S1** (0.074 g, 0.2 mmol) in anhydrous DCM (5.0 mL), trifluoroacetic acid (2.5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 19 h, after which the solvent was removed *in vacuo* to give the compound **S2** as a white solid (0.061 g, quant.). ¹H NMR (400 MHz, *d*₆-acetone) δ 7.49 (s, 2H), 3.70 (s, 2H).

Amidation

General procedure for EDC-mediated coupling (A). Carboxylic acid **S2** (0.30 mmol), amine (0.45 mmol, 1.5 equiv), HOBT hydrate (0.45 mmol, 1.5 equiv), and EDC·HCl (0.45 mmol, 1.5 equiv) were dissolved in anhydrous DCM (3 mL). The mixture was irradiated under microwave irradiation at 60 °C for 2 h, after which it was diluted with DCM (10 mL). The solution was washed with a saturated solution of NH₄Cl in H₂O, water, and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified with automated flash column chromatography (*n*-heptane/EtOAc-EtOH 3:1 (12→100%)) to give the pure product.

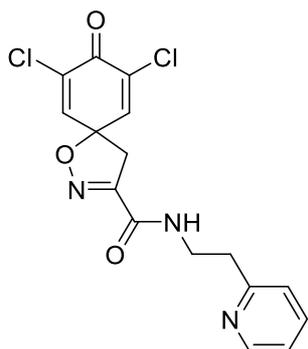
General procedure for EDC-mediated coupling (B). Carboxylic acid **S2** (0.3 mmol) was dissolved in anhydrous DCM and anhydrous THF at 0 °C. HOBT (0.1 equiv), and EDC·HCl (1.1 equiv) were added and the mixture was stirred at 0 °C for 15 min. After this, the amine (1.2 equiv) was added, and the reaction mixture was stirred at room temperature for 19 h. The solvent was removed *in vacuo* (compounds **66–67**, **70–71**) or diluted with DCM (10 mL), washed with saturated solution of NaHCO₃ in H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered before removal of solvent *in vacuo* (compounds **68–69**). The crude product was purified with automated flash column chromatography (*n*-heptane/EtOAc gradient 0→100%) to give the pure product. Procedure B for compounds **66–71**.

7,9-Dichloro-*N*-(3-chloro-4-methoxyphenyl)-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (**65**)



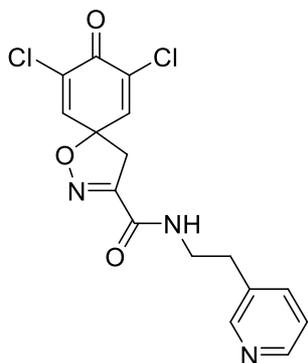
General procedure A was followed to give the compound **65** as light yellow solid (0.022 g, 16%). ¹H NMR (400 MHz, *d*₆-acetone) δ 9.52 (br s, 1H), 7.97 (d, *J* = 2.6 Hz, 1H), 7.72 (ddd, *J* = 9.0, 2.6, 1.9 Hz, 1H), 7.52 (d, *J* = 0.8 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 2H). ¹³C NMR (101 MHz, *d*₆-acetone) δ 172.6, 157.6, 156.1, 152.9, 142.5, 132.6, 122.9, 122.5, 120.8, 113.5, 85.5, 68.1, 56.7, 44.1. HRMS (ESI⁺): calculated 399.9784 (C₁₆H₁₁Cl₃N₂O₄), found 399.9786. LC-MS: [M + H]⁺ *m/z* 402 (*t*_r = 4.80 min), >95%.

7,9-Dichloro-8-oxo-*N*-[2-(pyridin-2-yl)ethyl]-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide
(**66**)



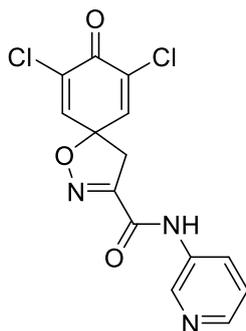
General procedure B was followed to give the compound **66** as white solid (0.076 g, 55%). ¹H NMR (400 MHz, CD₃CN) δ 8.51 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.69 (td, *J* = 7.7, 1.9 Hz, 1H), 7.59 (br s, 1H), 7.27-7.18 (m, 4H), 3.65 (td, *J* = 6.8, 5.9 Hz, 2H), 3.47 (s, 2H), 3.00 (t, *J* = 6.8 Hz, 2H). ¹³C NMR (101 MHz, CD₃CN) δ 173.2, 160.2, 159.2, 155.8, 150.0, 142.5, 137.7, 132.7, 124.4, 122.7, 85.0, 44.2, 39.6, 37.5. HRMS (ESI⁺): calculated 366.0412 (C₁₆H₁₄Cl₂N₃O₃), found 366.0415. LC-MS: [M + H]⁺ *m/z* 366 (*t*_r = 1.88 min), >95%.

7,9-Dichloro-8-oxo-*N*-[2-(pyridin-3-yl)ethyl]-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide
(**67**)



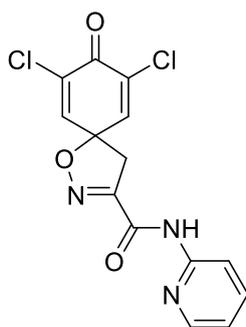
General procedure B was followed to give the compound **67** as white solid (0.070 g, 63%). ¹H NMR (400 MHz, CD₃CN) δ 8.46 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.62 (m, 1H), 7.28 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.23 (s, 2H), 7.22 (br s, 1H), 3.53 (td, *J* = 7.0, 6.2 Hz, 2H), 3.45 (s, 2H), 2.86 (t, *J* = 7.1 Hz, 2H). ¹³C NMR (101 MHz, CD₃CN) δ 173.2, 159.4, 155.7, 151.2, 148.7, 142.5, 137.2, 135.6, 132.7, 124.3, 85.0, 44.1, 41.0, 33.2. HRMS (ESI⁺): calculated 366.0412 (C₁₆H₁₄Cl₂N₃O₃), found 366.0415. LC-MS: [M + H]⁺ *m/z* 366 (*t*_r = 1.85 min), >99%.

7,9-Dichloro-8-oxo-N-(pyridin-3-yl)-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (68)



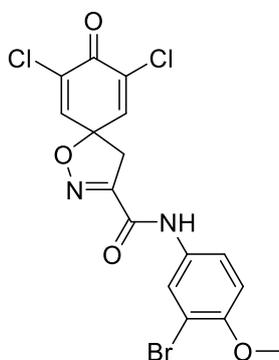
General procedure B was followed to give the compound **68** as yellow solid (0.032 g, 35%). ¹H NMR (400 MHz, CD₃CN) δ 8.98 (s, 1H), 8.81 (dd, *J* = 2.7, 0.8 Hz, 1H), 8.37 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.09 (ddd, *J* = 8.3, 2.6, 1.5 Hz, 1H), 7.36 (m, 1H), 7.28 (s, 2H), 3.57 (s, 2H). ¹³C NMR (101 MHz, CD₃CN) δ 173.2, 158.3, 155.9, 146.8, 143.1, 142.2, 135.2, 133.0, 128.5, 124.6, 85.7, 43.8. HRMS (ESI⁺): calculated 338.0099 (C₁₄H₁₀Cl₂N₃O₃), found 338.0102. LC-MS: [M + H]⁺ *m/z* 338 (*t_r* = 2.20 min), >96%.

7,9-Dichloro-8-oxo-N-(pyridin-2-yl)-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (69)



General procedure B was followed to give the compound **69** as white solid (0.022 g, 21%). ¹H NMR (400 MHz, CD₃CN) δ 8.94 (s, 1H), 8.35 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.11 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.82 (ddd, *J* = 8.3, 7.4, 1.9 Hz, 1H), 7.28 (s, 2H), 7.17 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 3.57 (s, 2H). ¹³C NMR (101 MHz, CD₃CN) δ 173.2, 158.0, 156.0, 151.4, 149.5, 142.1, 139.6, 133.0, 121.6, 114.9, 86.0, 43.5. HRMS (ESI⁺): calculated 338.0099 (C₁₄H₁₀Cl₂N₃O₃), found 338.0098. LC-MS: [M + H]⁺ *m/z* 338 (*t_r* = 3.69 min), >96%.

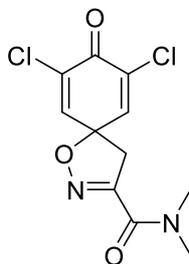
N-(3-Bromo-4-methoxyphenyl)-7,9-dichloro-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (70)



General procedure B was followed to give the compound **70** as yellow solid (0.083 g, 49%). ¹H NMR (400 MHz, *d₆*-DMSO) δ 10.61 (s, 1H), 8.05 (d, *J* = 2.5 Hz, 1H), 7.73 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.64 (s, 2H, H), 7.13 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 2H). ¹³C NMR (101 MHz, *d₆*-DMSO) δ 171.9, 156.8, 155.4,

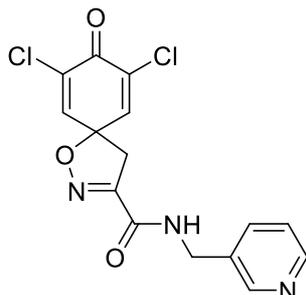
152.1, 142.2, 132.0, 130.8, 124.8, 120.9, 112.6, 110.0, 84.1, 56.3, 43.4. HRMS (ESI+): calculated 446.9355(C₁₆H₁₂BrCl₂N₂O₄), found 446.9318. LC-MS: [M + H]⁺ *m/z* 447 (*t_r* = 4.92 min), >96%.

7,9-Dichloro-*N,N*-dimethyl-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (71)



General procedure B was followed to give the compound **71** as white solid (0.041 g, 34%). ¹H NMR (400 MHz, CDCl₃) δ 7.05 (s, 2H), 3.56 (s, 2H), 3.32 (s, 3H), 3.09 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.0, 159.2, 153.7, 140.5, 133.2, 82.4, 46.2, 38.8, 36.4. HRMS (ESI+): calculated 289.0147 (C₁₁H₁₁Cl₂N₂O₃), found 289.0150. LC-MS: [M + H]⁺ *m/z* 289 (*t_r* = 3.10 min), >99%.

7,9-Dichloro-8-oxo-*N*-(pyridin-3-ylmethyl)-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxamide (72)



General procedure A was followed to give the compound **72** as white solid (0.010 g, 13%). ¹H NMR (400 MHz, *d*₆-acetone) δ 8.62–8.56 (m, 1H), 8.48 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.37 (s, 1H), 7.75 (ddd, *J* = 7.8, 2.3, 1.7 Hz, 1H), 7.49 (s, 2H), 7.32 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 2H), 3.69 (s, 2H). ¹³C NMR (101 MHz, *d*₆-acetone) δ 172.6, 159.5, 155.7, 150.3, 149.4, 142.7, 136.2, 135.3, 132.5, 124.2, 85.1, 44.3, 41.3. HRMS (ESI+): calculated 352.0256 (C₁₅H₁₂Cl₂N₃O₃), found 352.0258. LC-MS: [M + H]⁺ *m/z* 352 (*t_r* = 1.84 min), >98%.

Figure S1. Reversibility of binding of compounds 74, 76, 79

Normalized Cav3.2 channel current during wash-in and wash-out of compound 74, 76 and 79 over time.

