Supporting Information

Discovery And Optimization of Novel SUCNR1 Inhibitors: Design of Zwitterionic Derivatives with Salt Bridge for Improvement of Oral Exposure

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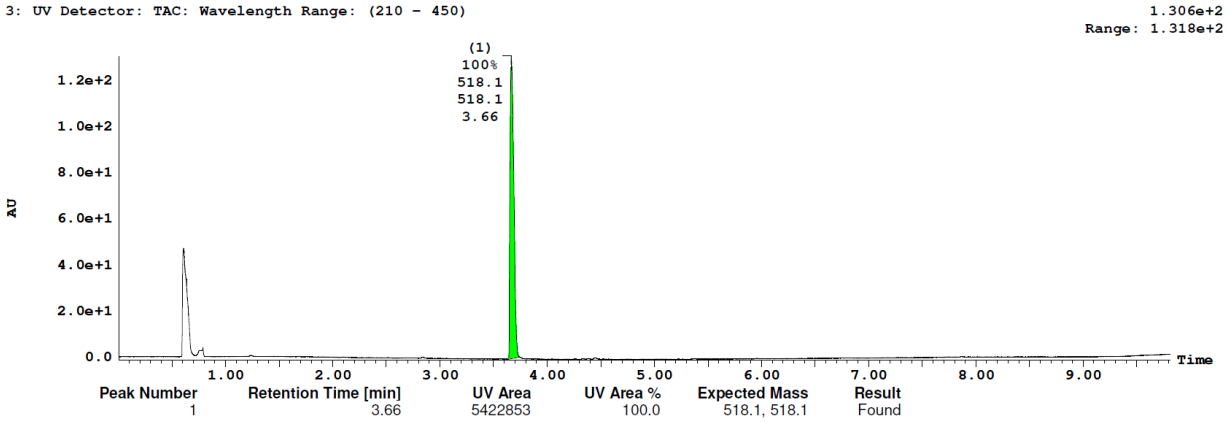
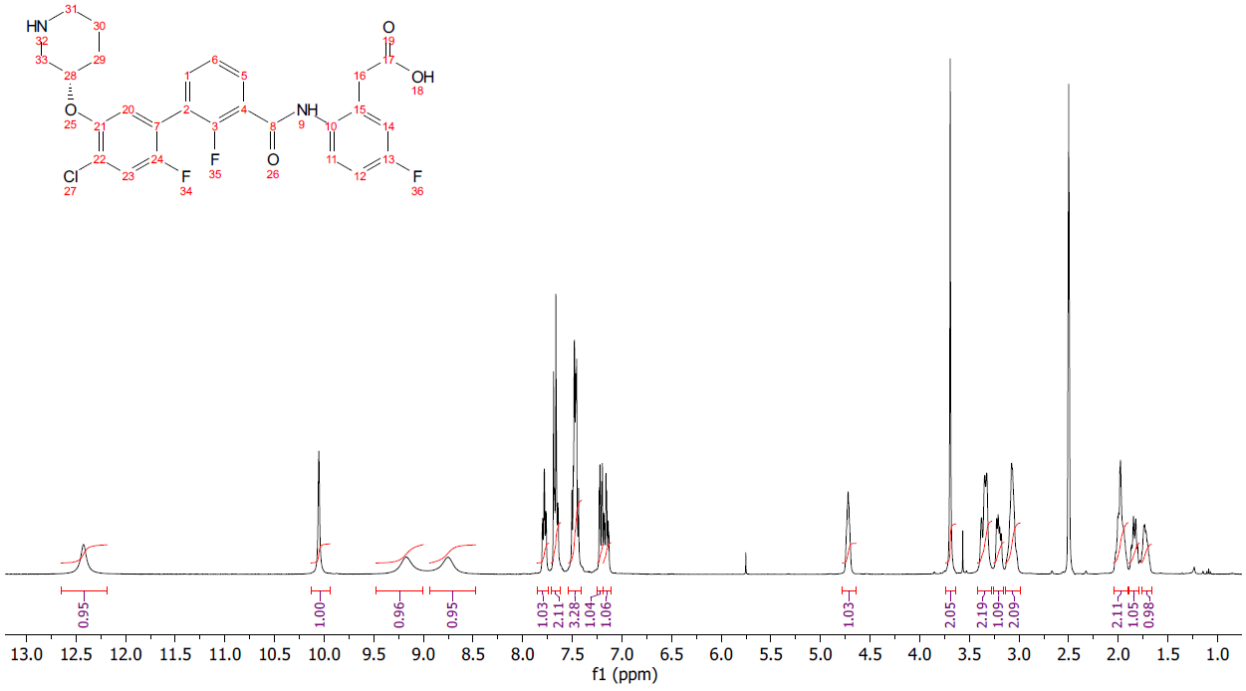
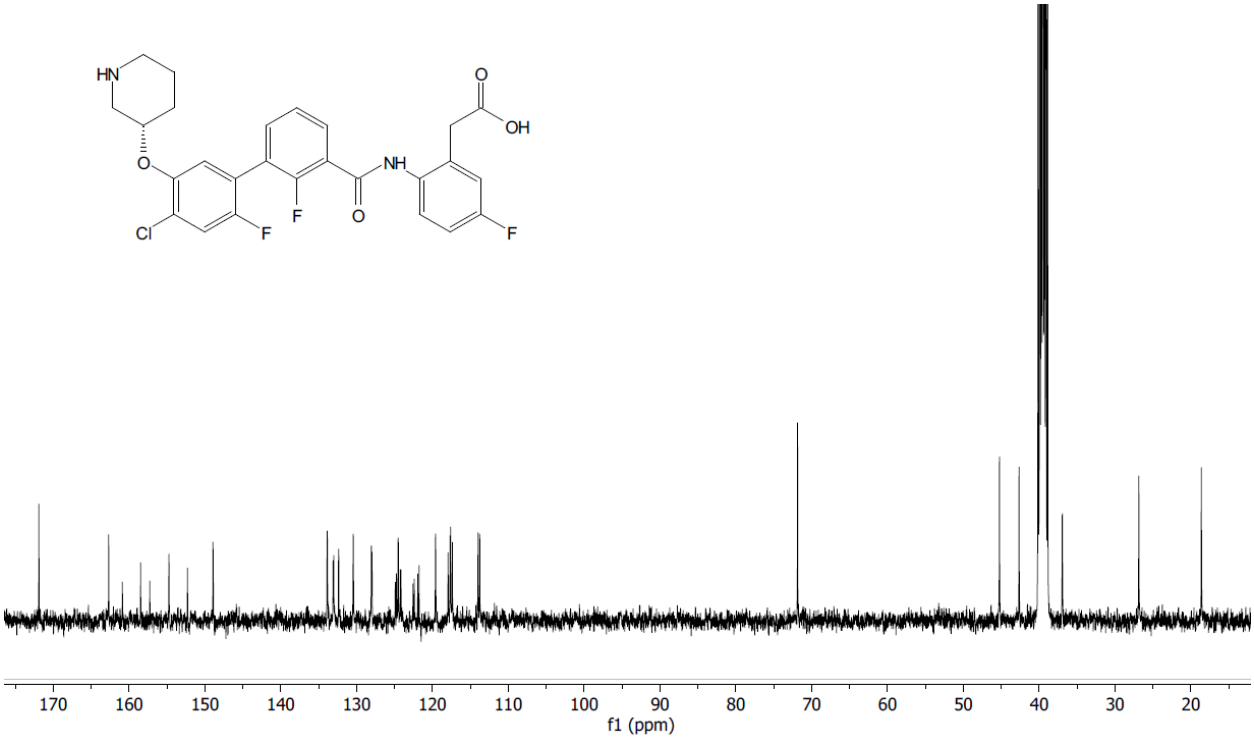
HPLC AND NMR CHARTS FOR COMPOUND 20 (HCl salt)






HN
O
Cl
F
F
O
NH
O
OH
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

EXTENDED DATA TABLE S1

Data collection and refinement statistics for the humanized ratSUCNR1-Nanobody6-**20** complex.

	Humanized ratSUCNR1-Nanobody6-**20**[#]
Data collection	
Space group	C2
Cell dimensions	
a, *b*, *c* (Å)	76.84, 151.0, 68.21
α, β, γ (°)	90, 112.29, 90
Wavelength (Å)	0.999
Wilson B-factor (Å^2)	52.1
Reflections	139197 (7966)
Resolution (Å)[a]	63.12-2.27 (2.44-2.27)
R_{pim}	0.089 (1.184)
$I/\sigma(I)$	5.6 (0.6)
$CC_{1/2}$	0.995 (0.214)
Completeness (%)	

spherical	77.3 (19.5)
ellipsoidal	90.6 (45.2)
Redundancy	5.4 (6.2)
Refinement	
Resolution (Å)	63.12-2.27
No. reflections	25647
R_{work} / R_{free}	20.38 / 22.26
No. atoms	
Protein	3268
Ligands	255
Water	154
B factors	
Protein	59.20
Ligand/ion	79.13
Water	63.96
r.m.s deviations	

Bond lengths (Å)	0.008
Bond angles (°)	0.95
Ramachandran (%)	
favored	98.76
allowed	1.24
outliers	0

[#] Data obtained from a single crystal

[a] Values in parentheses are for highest-resolution shell.

COORDINATION DATA FOR CRYSTAL STRUCTURES OF 9, 10 AND 20

Compound **9** was crystallized as a hydrochloride from methanol by slow evaporation of the solvent, compound **10** was crystallized as a hydrochloride from acetonitrile / hydrochloric acid, compound **20** was crystallized as hydrochloride from a mixture of ethanol and isobutylmethylketone. Intensity data were collected at 100 K on a Bruker AXS three-circle diffractometer with monochromated Cu(K_α)-radiation (multilayer mirrors), microfocus rotating anode generator, and a Smart 6000 CCD detector using the SMART software. Several ω-scans at different Φ-positions were performed to ensure appropriate data redundancy. Data processing and global cell refinement were performed with Saint V7.36A. A semi-empirical absorption correction was applied, based on the intensities of symmetry-

related reflections measured at different angular settings (SADBS V2008/1). The structures were solved by dual space-recycling methods and subsequent DF syntheses and refined based on full-matrix least-squares on F2 using the SHELXTL program suite. Anisotropic displacement parameters were used for all non-hydrogen atoms. Hydrogen atoms were located in DF maps and refined in idealized positions using a riding model. For **10**, an isolated residual electron density peak was refined as partially occupied water molecule without hydrogen atoms. Crystal data, data collection parameters, and convergence results are listed in Table **S2** Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2009710 (**9**), CCDC 2009711 (**10**) and CCDC 2009712 (**20**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax (+44) 1223 336033, email: deposit@ccdc.cam.ac.uk]. This material is available free of charge via the internet at http://pubs.acs.org.

Extended Data Table S2

Identification code	**9**	**10**	**20**
Empirical formula	C22 H22 Cl N O3	C22 H20 Cl2 N2 O4	C32 H35 Cl2 F3 N2 O5
Formula weight	383.86	447.30	655.52
Temperature		100(2) K	
Wavelength		1.54178 Å	
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	P21/n	P212121	P212121
Unit cell dimensions	*a* = 19.865(2) Å	a = 4.989(3) Å	a = 7.396(3) Å
	b = 4.453(5) Å	b = 14.365(7) Å	b = 13.040(6) Å
	c = 21.536(2) Å	c = 28.185(14) Å	c = 32.182(15) Å
	β = 99.147(5) °		
Volume	1881(2) $Å^3$	2019.9(19) $Å^3$	3104(2) $Å^3$
Z	4	4	4
Density (calculated)	1.356 g/cm^3	1.471 g/cm^3	1.403 g/cm^3
Absorption coefficient	1.982 mm^{-1}	3.175 mm^{-1}	2.415 mm^{-1}
F(000)	808	928	1368
Crystal size [mm3]	0.28x0.03x0.02	0.30x0.02x0.01	0.19x0.11x0.02
Theta range	2.81 to 68.22°	3.14 to 68.31°	2.75 to 68.52°
Index ranges	-23,23; -4,5; -25,25	-5,5; -17,17; -33,33	-8,8; -15,15; -38,38
Reflections collected	37330	41796	61328
Independent reflections	3410, R(int) = 0.0721	3661, R(int) = 0.0576	5683, R(int) = 0.1207

Completeness	98.6 %	99.6 %	99.9 %
Absorption correction	Semi-empirical from equivalents		
Max/min. transmission	0.9614 and 0.6069	0.9689 and 0.4493	0.9533 and 0.6569
Refinement method	Full-matrix least-squares on F^2		
Data/restraints/param.	3410 / 0 / 246	3661 / 0 / 269	5683 / 0 / 401
Goodness-of-fit on F^2	1.040	1.036	1.137
Final R [I>2s(I)]	R1 = 0.0363	R1 = 0.0312	R1 = 0.0669
	wR2 = 0.0871	wR2 = 0.0754	wR2 = 0.1616
R indices (all data)	R1 = 0.0471	R1 = 0.0347	R1 = 0.0725
	wR2 = 0.0934	wR2 = 0.0772	wR2 = 0.1643
Abs. structure parameter	n.a.	0.451(13)	0.08(3)
Largest diff. peak hole	0.31 / -0.24 e·Å^{-3}	0.20 / -0.15 e·Å^{-3}	0.70 / -0.43 e·Å^{-3}

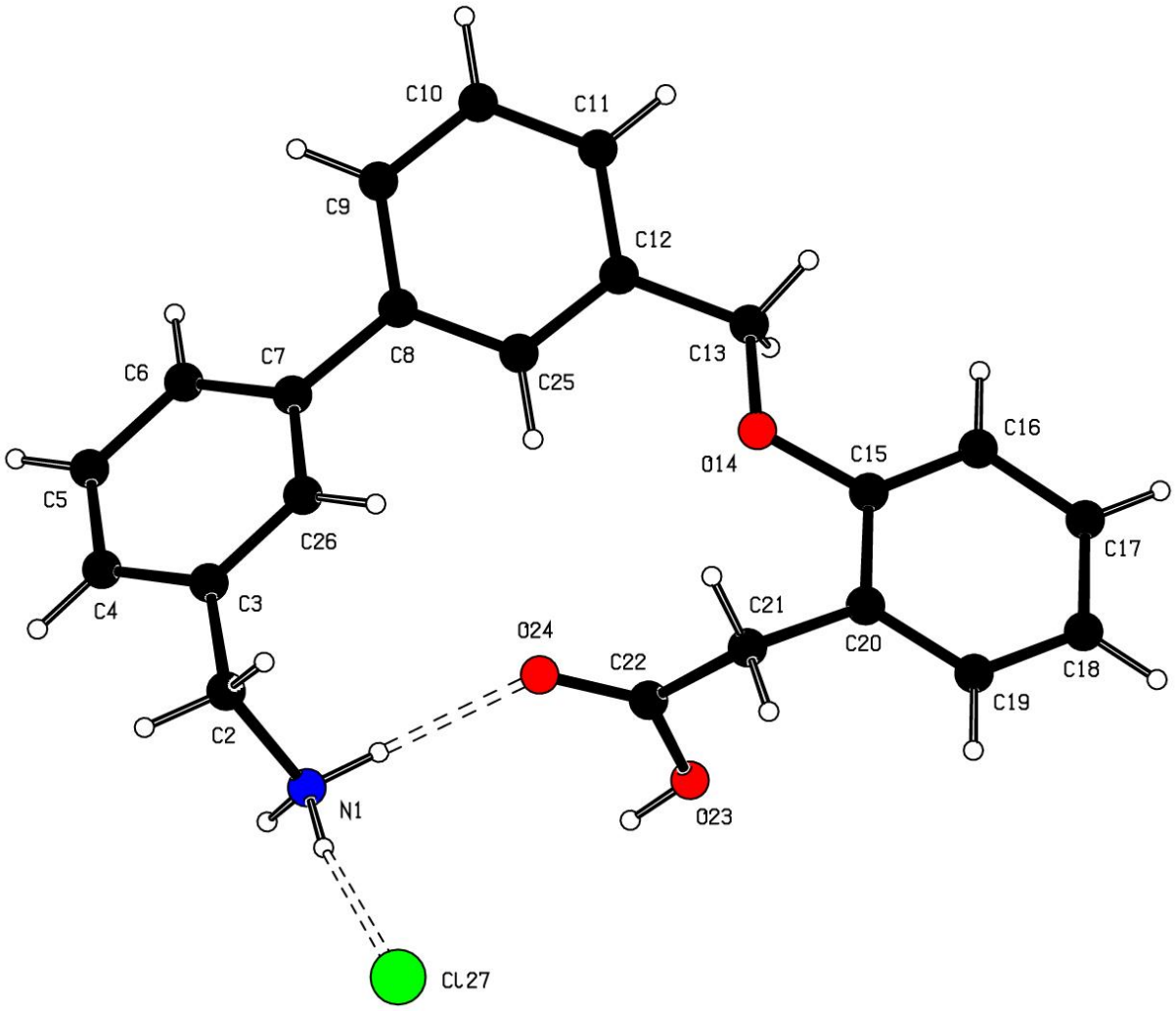


Figure S1: Structure of **9** in the crystal along with numbering scheme. Hydrogen bonds shown as dotted lines.

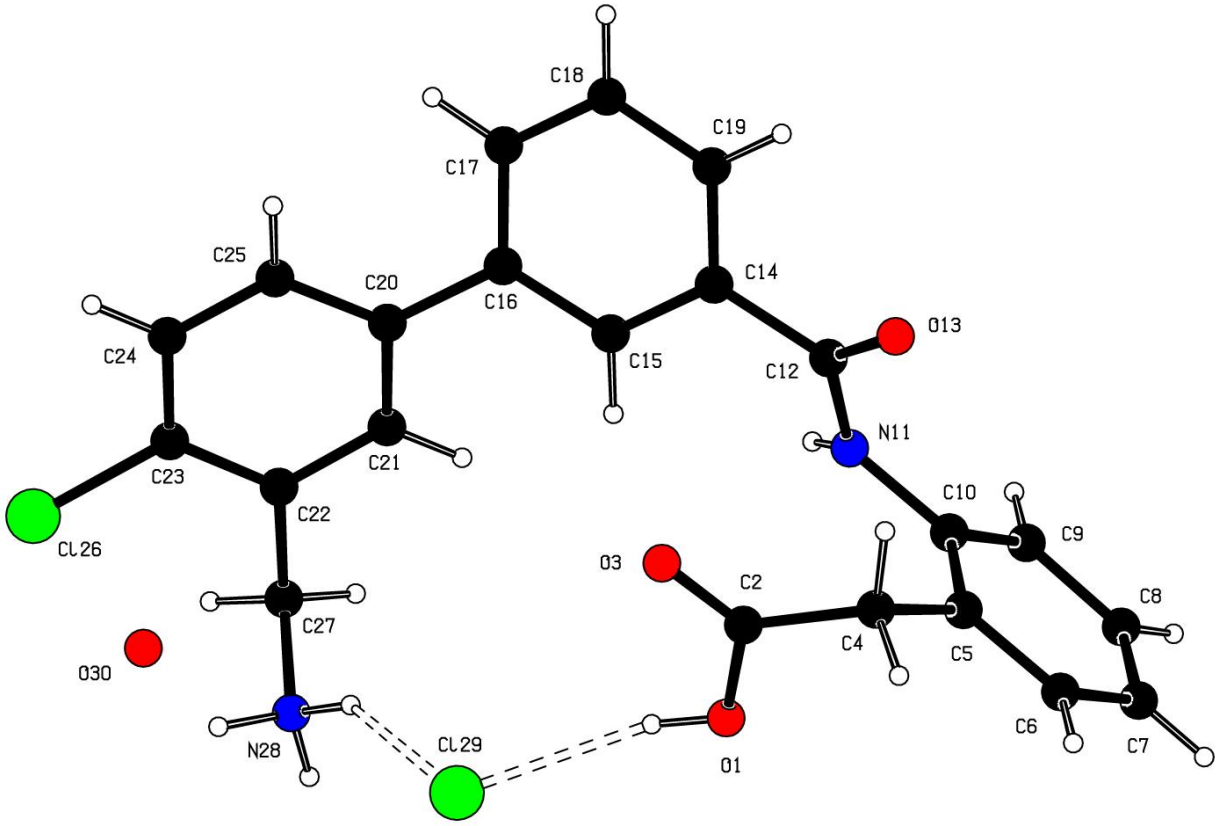


Figure S2: Structure of **10** in the crystal along with numbering scheme. Hydrogen bonds shown as dotted lines.

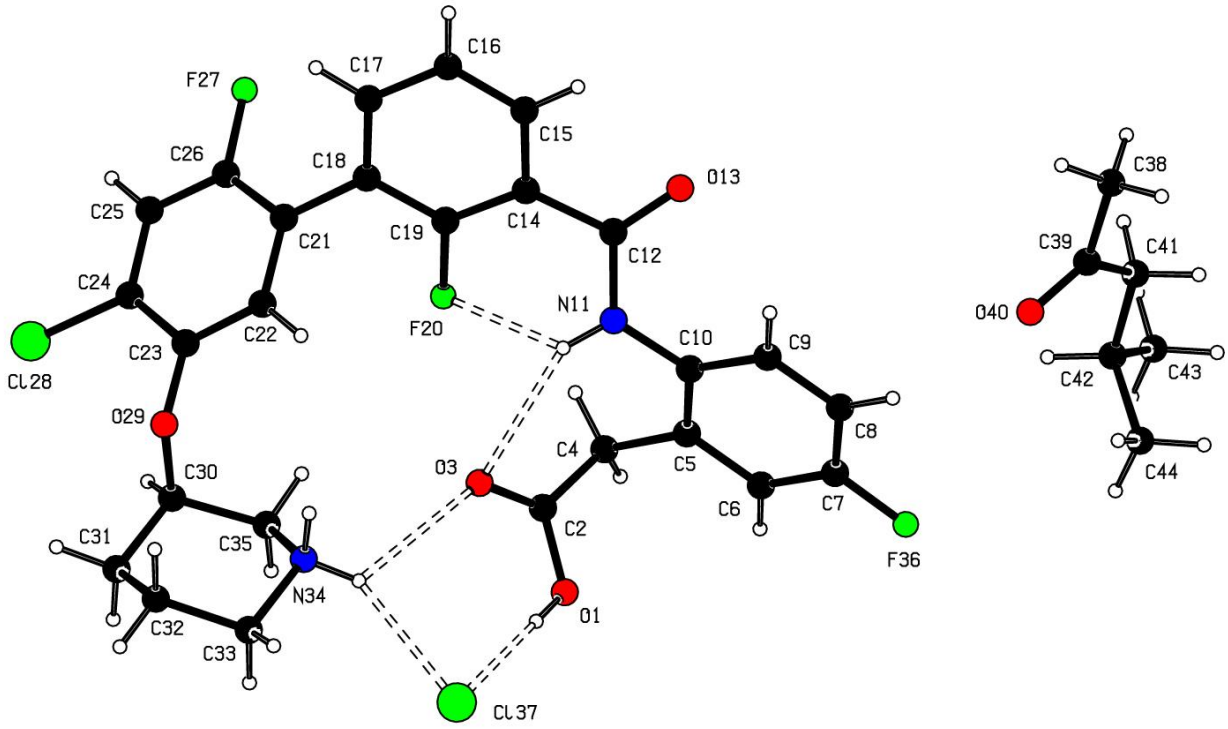


Figure S3: Structure of **20** in the crystal along with numbering scheme. Hydrogen bonds shown as dotted lines.