SUPPORTING INFORMATION (SI)

Title of Manuscript: A New Positron Emission Tomography (PET) Radioligand for Imaging Sigma-1 Receptors in Living Subjects.

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Contents of SI: Synthesis of **c**ompounds **10** and **11**, table detailing affinities and selectivity ratios of some known sigma-1 receptor ligands, and a table showing *in vitro* binding affinities of compound **13**.

6-(3-chloropropanoyl)benzo[d]thiazol-2(3*H*)-one (10). DMF (8.6 mL, 111 mmol) was slowly added to aluminium chloride (53.3 g, 400 mmol) under vigorous stirring. After 15 min of stirring, 2-hydroxybenzothiazole (6.04 g, 40 mmol) was added, and the mixture was brought to 45 °C. After 15 min, 3-chloropropionyl chloride (5.8 mL, 60 mmol) was added and the reaction mixture was heated at 85 °C for 3 h. The hot mixture was carefully poured onto ice, and the crude product was collected by filtration. The solid was dissolved in ethyl acetate and water was added. The layers were then separated and, the organic layer was washed with brine and dried. The solvent was removed in vacuo, and the residue was recrystallized from toluene/dioxane to give 5.15 g (54%) of 6-(3-chloropropanoyl)benzo[d]thiazol-2(3*H*)-one as a orange solid. ^{1}H NMR (DMSO-d_6): δ 12.26 (br s, 1H), 8.24 (d, J = 1.4 Hz, 1H), 7.90 (dd, J = 8.4, 1.7 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 3.91 (t, J = 6.4 Hz, 2H), 3.50 (d, J = 6.3 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 195.07, 170.37, 140.49, 130.94, 126.89, 123.77, 123.25, 111.19, 40.38, 39.52. MS (EI) *m/z* 242 (M^{+}+1).

6-(3-chloropropyl)benzo[d]thiazol-2(3*H*)-one (11). Triethylsilane (4.2 mL, 26 mmol) was added to a stirred solution of **10** (2.73 g, 11.3 mmol) in trifluoroacetic acid (15 mL) and the reaction mixture was stirred for 4 h at room temperature. The solvent was removed in vacuo, and

the residue was purified by chromatography on a silica gel column using a gradient of petroleum ether/ether (7:3 to 5:5) as the eluent and recrystallized from toluene/hexanes to give 1.85 g (72%) of 6-(3-chloropropyl)benzo[d]thiazol-2(3*H*)-one as a white solid. ^{1}H NMR (DMSO-d_6): δ 11.76 (br s, 1H), 7.38 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.99 (quart, J = 7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 169.89, 135.12, 134.45, 126.53, 123.40, 122.13, 111.31, 44.52, 33.75, 31.79. MS (EI) *m/z* 226 (M^+-1)

Table 1. Affinities and selectivity ratios of sigma-1 receptor (S1R) ligands reported in literature.

Ligand Name	**K_i (nM)**		**Selectivity Ratio**	**Reference(s)**
	S1R	**S2R**	**K_i S2R/ K_i S1R**	
1 ((+)-Pentazocine)	**4.6**	**1052**	**229**	**49**
2 (Haloperidol)	**3.1**	**55**	**18**	**49**
3 (SA4503)	**4.4**	**242**	**55**	**41**
4 (FM SA4503)	**6.4**	**250**	**39**	**35**
5 (FPS)	**0.5**	**144**	**288**	**38**
6 (SFE)	**5.0**	**361**	**72**	**38**
7	**2.7**	**103**	**38**	**30**
8 (Fluspidine)	**1.4**	**>600**	**>429**	**28**
9 (SN56)	**0.56**	**>1000**	**>1000**	**33**

Table 2. In vitro binding affinities of compound 13

	Radioligand	Nonspecific binding	Tissue	K_i (nM)
Sigma receptors:				
S1R	5 nM [^{3}H](+)-pentazocine	10 mM haloperidol	Rat brain	0.0025 $\pm$ 0.0009
S2R	3 nM [^{3}H]di-o-tolylguanidine	10 mM haloperidol	Rat brain	364 $\pm$ 63
S1R	5 nM [^{3}H](+)-pentazocine	10 mM haloperidol	Rat liver	0.96 ± 0.21
S2R	3 nM [^{3}H]di-o-tolylguanidine	10 mM haloperidol	Rat liver	467 ± 60
Monoamine transporters:				
Dopamine	0.5 nM [^{3}H]WIN 35,428	50 mM cocaine	Rat striatum	3586 $\pm$ 286
Serotonin	0.2 nM [^{3}H]paroxetine	1.5 mM imipramine	Rat brainstem	>10,000
Norepinephrine	0.5 nM [^{3}H]nisoxetine	4 mM desipramine	Rat cerebral cortex	68 $\pm$ 5
Other neurotransmitter receptors:				
Adenosine	4.0 nM [^{3}H]NECA	1 mM NECA	Bovine striatum	>10,000 [a]
Adrenergic, alpha$_1$	0.3 nM [^{3}H]7-MeOxy-prazosin	1 mM phentolamine	Rat forebrain	>10,000 [a]
Adrenergic, beta$_1$ neuroepithelioma	0.04 nM [^{125}I](-)iodocyanopindolol	3 mM alprenolol	Human	>10,000 [a]
Cannabinoid, CB$_1$ HEK293 cells	0.5 nM [^{3}H]CP 55940	1 mHU-210	Human recombinant	>10,000 [a]
Cannabinoid, CB$_2$ CHO cells	0.5 nM [^{3}H]CP 55940	1 mM HU-210	Human recombinant	>10,000 [a]
Dopamine, non-selective	0.3 nM [^{3}H]spiperone	1 mM spiperone	Bovine striatum	>10,000 [b]
Dopamine D$_2$	5 nM [^{3}H](-)-sulpiride	1 mM haloperidol	Rat brain	>10,000
GABA A, agonist site	5 nM [^{3}H]GABA	1 mM GABA	Bovine cerebellum	>10,000 [a]
GABA A, BDZ alpha 1	1 nM [^{3}H]flunitrazepam	0.5 mM flumazenil	Bovine cortex	>10,000 [a]
GABA-B	1 nM [^{3}H]CGP 54626A	100 mM baclofen	Rat cerebral cortex	>10,000 [a]
Glutamate, AMPA	5 nM [^{3}H]AMPA	100 mM AMPA	Rat forebrain	>10,000 [a]
Glutamate, kainate	10 nM [^{3}H]kainic acid	10 mM kainic acid	Rat forebrain	>10,000 [a]
Glutamate, NMDA agonist	2 nM [^{3}H]CGP 39653	300 mM NMDA	Rat forebrain	>10,000 [a]

Glutamate, NMDA glycine	4 nM [^{3}H]MDL-105,519	3 mM MDL-105,519	Rat cortex/hippoc	>10,000 [a]
Glutamate, NMDA/PCP	10 nM [^{3}H]TCP	100 mM (+)-MK801	Rat forebrain	>10,000 [a]
5 nM [^{3}H]TCP	10 mM cyclazocine		Rat brain	>10,000
Glutamate, mGluR1	20 nM [^{3}H]quisqualic acid	1 mM L-glutamate	Rat cerebellum	>10,000 [a]
Glutamate, mGluR5	10 nM [^{3}H]MPEP	10 mM MPEP	Rat brain	>10,000 [a]
Glycine,strychnine	16 nM [^{3}H]strychnine	100 mM strychnine nitrate	Rat spinal cord	>10,000 [a]
Histamine H_1	2 nM [^{3}H]pyrilamine	10 mM triprolidine	Bovine cerebellum	>10,000 [a]
Histamine H_3	0.2 nM [^{3}H]N-a-methylhistamine	0.1 nM R(-)-a-methylhistamine	Rat forebrain	>10,000 [a]
Muscarinic, central	0.15 nM [^{3}H]QNB	0.1 mM atropine	Rat cerebral cortex	>10,000 [a]
Muscarinic M_1	0.5 nM [^{3}H]N-methyl scopolamine	1 mM (-)scopolamine	Human recombinant	>10,000 [a]
CHO cells				
Nicotinic, muscle	1 nM [^{125}I]a-bungarotoxin	10 mM nicotine	Human TE671 cells	>10,000 [a]
Opioid, non-selective	0.5 nM [^{3}H]bremazocine	10 mM levallorphan	Rat brain	1318 $\pm$ 19
Hormones, peptides, steroids:				
Angiotensin II, AT_1	0.06 nM [^{125}I](Sar^1-Ile^8)angiotensin	1 mM angiotensin II	Human KAN-TS cells	>10,000 [a]
Angiotensin II, AT_2	0.1 nM [^{125}I]Tyr^4-angiotensin II	0.05 mM angiotensin II	Bovine cerebellum	>10,000 [a]
Bradykinin, BK_2	0.2 nM [^{3}H]bradykinin	100 nM bradykinin TFA	Guinea pig ileum	>10,000 [a]
Cholecystokinin, CCK_A	0.02 nM [^{125}I]CCK-8	1 mM CCK-8	Mouse pancreas	>10,000 [a]
Cholecystokinin, CCK_B	0.02 nM [^{125}I]CCK-8	1 mM CCK-8	Mouse forebrain	>10,000 [a]
CRF, non-selective	0.1 nM [^{125}I]Tyr^0-oCRF	1 mM Tyr^0-oCRF	Rat cerebral cortex	>10,000 [a]
Endothelin, ET_A	0.033 nM [^{125}I]endothelin-1	0.1 mM endothelin-1	Human neuroblastoma	>10,000 [a]
Endothelin, ET_B	0.025 nM [^{125}I]endothelin-1	0.1 mM endothelin-1	Human astrocytoma	>10,000 [a]
Estrogen	0.1 nM [^{125}I]3,7b-estradiol	10 nM 17b-estadiol	Human breast cancer	>10,000 [a]
Galanin, non-selective	0.07 nM [^{125}I]galanin	100 nM galanin (porcine)	Rat brain	>10,000 [a]
Glucocorticoid	1 nM [^{3}H]dexamethasone	10 mM triamcinolone	Human recombinant	>10,000 [a]
Neurokinin, NK_1	1.4 nM [^{3}H]substance P	1 mM substance P	Rat submaxillary gland	>10,000 [a]
Neurokinin, NK_2	0.1 nM [^{125}I]neurokinin A	1 mM neurokinin A	Human recombinant	
Platelet activating factor	1.7 nM [^{3}H]hexadecyl-acetyl-PAF	1 mM C_{16}-PAF	Rabbit platelets	>10,000 [a]
CHO cells				
Neurokinin, NK_3 (NKB)	0.1 nM [^{125}I]eledoisin	1 mM eledoisin	Rat cerebral cortex	>10,000 [a]
Oxytocin	1 nM [^{3}H]oxytocin	1 mM oxytocin	Rat uterus	>10,000 [a]
Platelet activating factor	1.7 nM [^{3}H]hexadecyl-acetyl-PAF	1 mM C_{16}-PAF	Rabbit platelets	>10,000 [a]

Testosterone, cytosolic	0.5 nM [^{3}H]methyltrienolone	0.7 mM methyltrienolone	Human LnCAP cells	>10,000 [a]
TRH	2 nM [^{3}H](3MeHis^{2})TRH	10 mM TRH	Rat forebrain	>10,000 [a]
VIP, non-selective	0.05 nM [^{125}I]VIP	1 mM VIP	Rat forebrain	>10,000 [a]
Vasopressin 1	0.5 nM [^{3}H]phenylalanyl- 3,4,5-v	1 mM Arg^{8}-vasopressin	Rat liver	>10,000 [a]
Ion channels:				
Calcium, type L (DHP)	0.2 nM [^{3}H]nitrendipine	1 mM nifedipine	Rat cerebral cortex	>10,000 [a]
Calcium, type N	0.01 nM [^{125}I]w-conotoxin GVIA	0.1 mM w-conotoxin GVIA	Rat cerebral cortex	>10,000 [a]
Potassium, ATP-sensitive	0.2 nM [^{3}H]glibenclamide	0.1 mM glibenclamide	Rat cerebral cortex	>10,000 [a]
Potassium, Ca^{2+} act VI	0.05 nM [^{125}I]apamin	100 nM apamin	Rat forebrain	>10,000 [a]
Enzymes and other miscellaneous:				
Choline acetyltransferase	0.2 nM [^{14}C]acetyl coenzyme	0.1 mM Ro 41-1049	Rat cerebral cortex	>10,000 [a]
Glutamic acid decarboxylase	4 mM [^{14}C]L-glutamic acid	100 mM aminooxy acetic acid	Rat striatum	>10,000 [a]
Leukotriene, LTB_4 (BLT)	0.48 nM [^{3}H]leukotriene B_4	500 nM leukotriene B_4	Guinea pig spleen	>10,000 [a]
Leukotriene, LTD_4 (CysLT1)	0.2 nM [^{3}H]leukotriene D_4	1 mM leukotriene D_4	Guinea pig lung	>10,000 [a]
MAO-A oxidase, peripheral	50 mM [^{14}C]5-HT	1 mM Ro 41-1049	Rat liver mitochondria	>10,000 [a]
MAO-B oxidase, peripheral	10 mM [^{14}C]phenylethylamine	10 mM Ro 16-6491	Rat liver mitochondria	>10,000 [a]
Nitric oxide, NOS	5 nM [^{3}H]NOARG	100 mM NOARG	Rat brain	>10,000 [a]
Thromboxane, TXA_2	2 nM [^{3}H]SQ 29,548	10 mM pinane-thromboxane	Human platelets	>10,000 [a]

Affinities (K_i in nM) were determined in tissue or cell homogenates. The values in this table represent the mean $\pm$ SEM from replicate assays. Values of >10,000 signify that there was less than 50% displacement of the radioligand at that concentration. [a]These values were determined by NovaScreen. All other values were determined in-house using the assay conditions described in the Experimental Section of this manuscript. BTZ = benzothiazepine; CRF = corticotrophin releasing factor; DHA = dihydroalprenolol; DHP = dihydropyridine; GABA = γ-aminobutyric acid; LSD = lysergic acid diethylamide; MAO = monoamine oxidase; MPEP = 2-methyl-6-(phenylethynyl)pyridine; NECA = 5'-N-ethylcarboxamidoadenosine; NOARG = L-N^{G}-nitro-arginine; PAF = platelet activating factor; QNB = quinuclidinyl benzilate; S1R = sigma-1 receptor; S2R = sigma-2 receptor; TBOB = t-butylbicycloorthobenzoate; TBPS = t-butylbicyclophosphorothionate; TCP = 1-[1-)2-thienyl)cyclohexyl]piperidine; TRH = thyrotropin releasing hormone; VIP = vasoactive intestinal peptide.