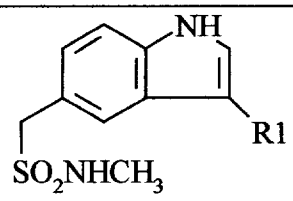
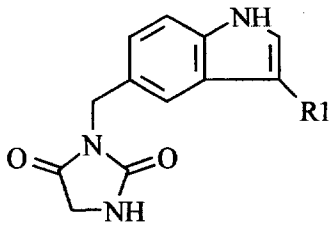
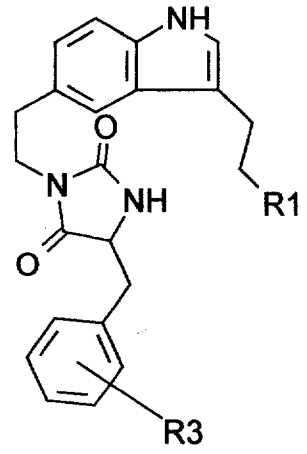
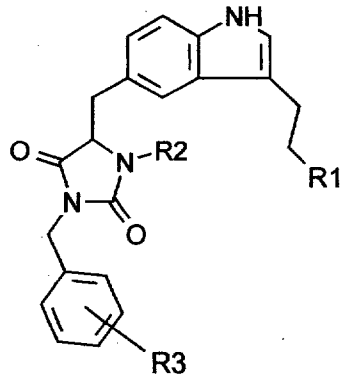
Pharmacokinetic model: data

Compounds were prepared as detailed in reference e, unless indicated otherwise

Table 1. Structures of tryptamine 5-HT agonists

Structure	No	R1	R2	R3	REF
	39	$(CH_2)_2NH_2$	-	-	
				-	
	40	$(CH_2)_2NH_2$	-		
	41	$(CH_2)_2N(CH_3)_2$			
			-		
	42	NH_2	-	4-$SO_2N(CH_3)_2$	
	43	$N(CH_3)_2$	-	4-$SO_2N(CH_3)_2$	
	44	NH_2	-	3-$NHCOCH_3$	
	45	$NHCH_3$	-	3-$NHCOCH_3$	
	46	$N(CH_3)_2$	-	3-$NHCOCH_3$	
	47	NH_2	-	4-$CONH_2$	
	48	$N(CH_3)_2$	-	4-$CONH_2$	
	49	NH_2	-	3-$CONH_2$	
	50	NH_2	methyl	-	
	51	$N(CH_3)_2$	methyl	-	
	52	NH_2	H	3-O-phenyl	
	53	$N(CH_3)_2$	H	3-O-phenyl	
	54	NH_2	H	3-$NHSO_2CH_3$	
	55	$N(CH_3)_2$	H	3-$NHSO_2CH_3$	
	56	NH_2	H	3-$CONHCH_3$	
	57	$NHCH_3$	H	3-$CONHCH_3$	
	58	$N(CH_3)_2$	H	3-$CONHCH_3$	
	59	$N(CH_3)_2$	H	3-CONH-	
	60	NH_2	benzyl	phenyl	
				-	

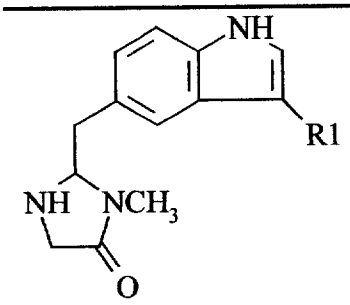
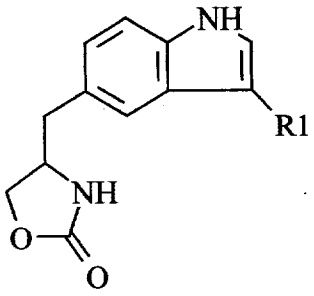
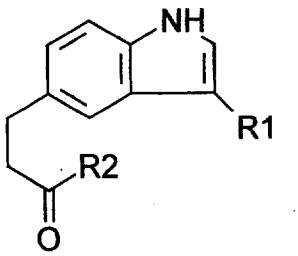
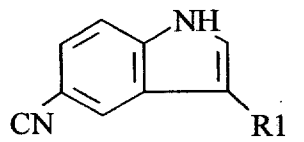
	61	$(CH_2)_2NH_2$	-	
	62	$(CH2)_2N(CH_3)_2$	-	
	63	$(CH_2)_2NH_2$	-	
	64	$(CH_2)_2NHCH_3$	-	
	65	N-methylpiperidine		c
	66	N-methylpiperidine	NH_2	c
	67	N-methylpiperidine	$NHCH_3$	c
	68	N-methylpiperidine	$N(CH_3)_2$	c
	69	N-methylpiperidine	-	b

Table 2. Relationship between CMR, calculated $logD_{pH7.4}$ and average plasma concentrations (at 0.5 and 2h) after oral administration (10mg/kg) to rats. for a range of 5-HT_1 agonists and other tryptamine analogues.

Compound	Amine substitution	Molecular weight	CMR	Calculated $logD_{pH7.4}$	Average Concentration (μg/mL)
39	Primary	267	7.27	-2.21	0.04
63	Primary	259	7.34	-1.93	0.05
64	Secondary	273	7.80	-2.00	0.07
61	Primary	272	8.02	-1.83	0.04
40	Primary	286	8.05	-2.23	ND
62	Tertiary	300	8.95	-0.88	0.10
41	Tertiary	314	8.98	-1.28	0.08
50	Primary	362	10.99	0.36	0.02
47	Primary	419	11.90	-1.78	0.05
49	Primary	419	11.90	-1.78	ND
56	Primary	419	11.90	-1.75	ND
51	Tertiary	390	11.92	1.32	0.03
54	Primary	455	12.27	-1.66	0.04
44	Primary	433	12.36	-1.27	0.02
57	Secondary	427	12.36	-1.90	ND
48	Tertiary	447	12.82	-0.83	0.02
45	Secondary	447	12.82	-1.43	ND
58	Tertiary	447	12.82	-0.80	ND
55	Tertiary	483	13.20	-0.71	ND
42	Primary	483	13.20	-1.10	ND
52	Primary	454	13.23	1.63	ND
46	Tertiary	461	13.29	-0.32	0.01
60	Primary	452	13.54	2.17	0.02
43	Tertiary	511	14.12	-0.14	ND
53	Tertiary	482	14.16	2.58	0.11
58	Tertiary	509	14.87	0.96	ND
69	N-Methyl piperidine	239	7.26	0.45	0.30
66	N-Methyl piperidine	285	8.58	-0.68	0.15
67	N-Methyl piperidine	299	9.04	-0.52	0.12
68	N-Methyl piperidine	313	9.50	-0.25	0.26
65	N-Methyl piperidine	313	9.02	-0.21	0.05
almotriptan	tertiary	335	9.41	-0.41	
eletriptan	tertiary	382	11.9	1.17 (-0.5)	
frovatriptan	secondary	243	7.18	-1.48 (-1.0)	
rizatriptan	tertiary	269	8.01	-0.76 (-0.7)	
naratriptan	tertiary	335	9.41	-0.5 (-0.2)	
zolmitriptan	Tertiary	287	8.27	-0.91 (-1.0)	0.22
sumatriptan	Tertiary	295	8.19	-1.46 (-1.5)	0.20
1	Tertiary		9.02	-0.29	0.2

ND Not detected (detection limits ranged from 0.01 to 0.05μg/mL with the exception of **25** for which the minimum detectable concentration was 0.1μg/mL)

log D's were calculated using the formula log D = clog P – log(1 + $10^{(pKa-pH)}$) from ref d. cLog P's calculated using the Pomona Medchem software. cLogP's for triptans were calculated using the latest version and may differ slightly from the other values. Values in brackets refer to reported values in ref f.

a Preparation of 3-(4-piperidinyl)- and 3-(1,2,3,6-tetrahydro-4-pyridinyl)indoles as antimigraine agents. Oxford, A. W.; Coates, I. H.; Butina, D.; EP303506, **1989.**

b Preparation of [(aminoalkyl)indolyl]thiazoles as 5-HT1 receptor agonists. Nowakowski, J. T.;, WO9213856, **1992**

c Robertson, A. D.; Hill, A. P.; Glen, R. C.; Martin, G. R.; Preparation of (oxazolidinonylalkyl)indolyl]ethylamines and related compounds as serotonin agonists., WO9118897, **1991.**

d Hersey, A.; Hill, A. P.; Hyde, R. M.; Livingstone, D. J.Principles of method selection in partition studies. *Quant. Struct.-Act. Relat.* **1989**, *8*, 288-96.

e Glen, R. C.; Martin, G. R.; Hill, A. P.; Hyde, R. M.; Woollard, P. M.; Salmon, J. A.; Buckingham, J.; Robertson, A. D. Computer-aided design and synthesis of 5-substituted tryptamines and their pharmacology at the 5-HT1D receptor: discovery of compounds with potential anti-migraine properties. *J. Med. Chem.* **1995**, *38*, 3566-80.

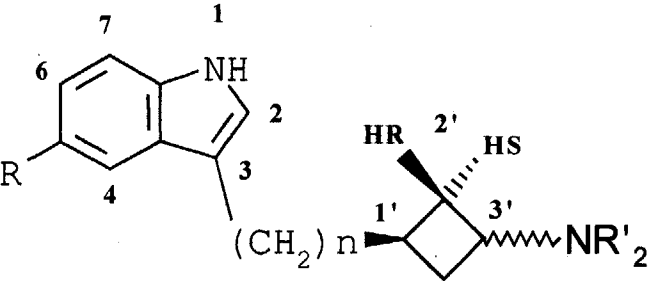
f Fox, A. W. Comparitive tolerablility of oral 5-$HT_{1B/1D}$ agonists. *Headache* **2000**, *40*, 521-527.

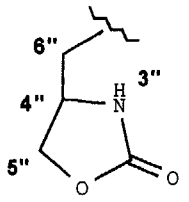
Combustion analyses

	Formula	CHN calc or accurate mass	CHN found
7	$C_{14}H_{17}NO_3$	C 68.02, H 6.88, N 5.67	C 67.92, H 6.90, N 5.63
23	$C_{16}H_{19}N_3O_2$. 1.26 H_2O, 0.23 C_2H_6O	62.04; 7.24; 13.19	62.35; 6.95; 12.88
24	$C_{16}H_{19}N_3O_2$	285.1488	285.1477
1	$C_{18}H_{23}N_3O_2$	68.98; 7.40; 13.41.	69.12; 7.52; 13.30.
26	$C_{21}H_{28}N_4O_2$, 0.2 $CHCl_3$	368.22123	368.22119
25	$C_{19}H_{24}N_4O_2$. 0.22 H_2O	66.26; 7.15; 16.27.	66.49; 7.16; 15.98
27	$C_{19}H_{24}N_4O_2$. 0.09 $CHCl_3$	65.29; 6.91; 15.95	65.10; 7.21; 15.81.
28	$C_{24}H_{25}N_3O_2$. 0.4 H_2O, 0.3$CHCl_3$	67.80; 6.11; 9.76.	67.71; 6.05; 9.67.
29	$C_{16}H_{22}N_3O_2S$. 0.089$CHCl_3$	58.17; 7.00; 12.64.	58.35; 7.00; 12.51.
31	$C_{18}H_{23}N_3O_2$. 0.66H_2O, 0.33 $C_4H_8O_2$	65.46; 7.68; 11.85	65.62; 7.26; 11.84
30	$C_{19}H_{25}N_3O_2$. 0.13 $CHCl_3$	67.00; 7.39; 12.25.	66.92; 7.64; 12.41
32	$C_{20}H_{26}N_4O_2$, 0.1 H_2O,0.2$CHCl_3$	63.83; 7.00; 14.74	63.70; 7.06; 14.91
33	$C_{18}H_{22}N_2O_2$	326.17428	326.17371
12	$C_{19}H_{25}N_3O_2$. 0.42 H_2O	68.12; 7.77; 12.54.	68.08; 7.82; 12.53.
13	$C_{17}H_{21}N_3O_2$. 1.0 H_2O	64.33; 7.30; 13.24.	64.62; 7.06; 12.95
34	$C_{19}H_{25}N_3O_2$. O.75H_2O	66.96; 7.84; 12.33.	67.03; 7.87; 12.20.
22	$C_{16}H_{21}N_3O$	271.16846	271.16713
14	$C_{15}H_{19}N_3O$. 0.34 H_2O, 0.1AcOEt	68.11; 7.57; 15.47.	68.17; 7.87; 15.43
35	$C_{18}H_{23}N_3O_2$.	313.17903	313.17683
36	$C_{18}H_{18}N_2O$. $C_6H_6O_4$	66.67; 6.11; 7.07.	66.41; 6.16; 6.92.
37	$C_{20}H_{22}N_2O$.HBr, 0.1C_3H_8O, 0.1H_2O	61.70; 6.13; 7.09;	61.4; 5.97; 7.02
21	$C_{23}H_{27}N_3O$	361.21541	361.2154
15	$C_{22}H_{25}N_3O$. 0.71H_2O	73.35; 7.39; 11.66	73.60; 7.61; 11.38
38	$C_{18}H_{22}N_4O$		
20	$C_{18}H_{23}N_5$ 1.0 H_2O	66.03; 7.70; 21.39	59.73; 7.85; 21.02

19	$C_{17}H_{20}N_40.\ 0.57\ H_2O,0.04C_4H_8O_2$	66.22;7.00; 17.39	66.17; 6.69; 17.62

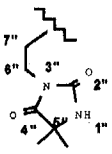
NMR asignments

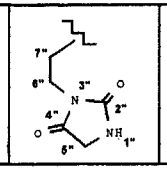


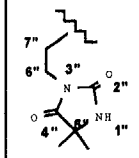
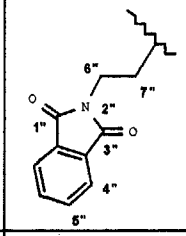
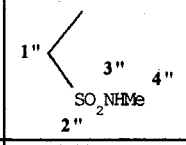


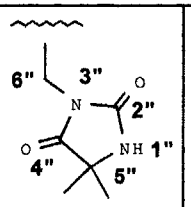
= ox

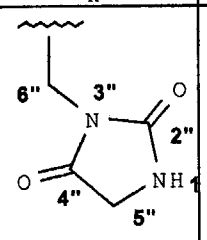
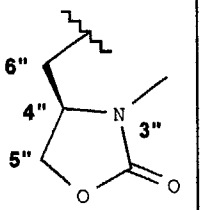
s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, b = broad, c = complex, m = multiplet, o = obscured, * = not distinguished

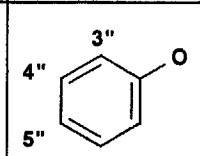
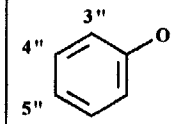
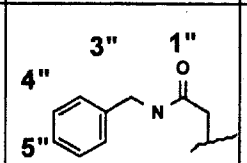
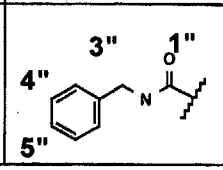
						{----------Indol------}						{------Cyclobutyl-------}					{----------R--*e.g.* Oxazolidine----------}						
	R	R'	n	Isomer	Parameter	1NH	2	4	6	7	n	1'	$2'_R$	$2'_S$	3'	R'	1"	NH"	4"	5"b	5"a	6"b	6"a	7"
23	(S) ox	H	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d6	10.71 bs	7.16 dd 0.5 1.2	7.27 s	6.93 dd 1.2 8.2	7.25 d 8.2	-	~3.8 o	2.24 bm	2.40 bm	~3.7 o	-	-	7.72 bs	4.04 m	4.22 tm	4.00 m	2.88 dd 4.6 -13.5	2.77 dd 6.9 -13.5	-
24	(S) ox	H	0	cis	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d6	10.70 bs	7.08 dd 0.7 1.5	7.41 s	6.92 dd 1.5 8.2	7.24 d 8.2	-	3.19 bm	1.97 bm	2.61 bm	~4.05 o	-	-	7.79 bs	4.04 m	4.23 tm	4.00 m	2.89 dd 4.5 -13.5	2.78 dd 6.8 -13.5	-
1	(S) ox	Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d6	10.69 bs	7.17 dd 0.8 2.1	7.27 o	6.93 dd 1.4 8.3	7.25 d 8.2	-	3.51 m	2.29 m	2.19 m	2.78 m	2.06 s	-	7.73 bs	4.04 m	4.22 tm	3.99 m	2.88 dd	2.76 dd	-
26		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	7.89 bs	7.03 dd 1.3 1.7	7.35 s	7.09 dd 1.7 8.3	7.32 d 8.3	-	3.62 ttt 1.0 4.3 9.1	*2.31 m	*2.46 m	2.90 q 7.6	2.20 s	-	5.13 bs	-	1.32 s	1.32 s	3.62 ct 7.6	3.62 ct 7.6	3.78 ct 7.6

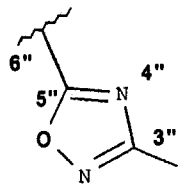
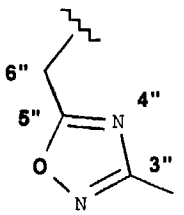
25		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	7.96 bs	7.04 dd 1.2 2.2	7.37 dt 0.6 1.5	7.10 dd 1.6 8.5	7.29 dd 0.6 8.3	-	3.62 ttt 1.2 4.0 9.2	*2.30 m	*2.44 qm	2.89 pd 1.1 7.2	2.18 s	-	5.51 bs	-	3.92 d -17.7	3.85 d -17.7	3.02 ct 6.1 8.2	3.02 ct 6.1 8.2	3.79 ct 6.0 8.0

	R	R'	n	Isomer	Parameter	1NH	2	4	6	7	n	1'	$2'_R$	$2'_S$	3'	R'	1"	NH"	4"	5"b	5"a	6"b	6"a	7"
27		H	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.63 bs	7.12 dd 1.0 2.2	7.14 m	6.87 dd 1.6 8.4	7.22 dd 0.7 8.2	-	~3.5 om	*2.10 m	*2.31 m	~2.9 om	-	-	8.11 bs	-	1.16 s	1.16 s	2.88 ct 7.5	2.88 ct 7.5	3.57 ct 7.5
28		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	7.87 bs	7.01 dd 1.3 2.1	7.34 dt 0.5 1.5	7.13 dd 1.5 8.3	7.29 dd 0.5 8.3	-	3.56 ttt 1.2 4.6 9.1	*2.22 m	*2.39 qm	2.86 pd 0.9 7.2	2.17 s	-	-	7.82 m $AA'B$ B	7.68 m $AA'BB'$	7.68 m $AA'BB'$	3.08 ct 5.9 7.9	3.08 ct 5.9 7.9	3.96 ct 5.8 7.7
29		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.82 bs	7.22 dd 0.9 1.9	7.44 m	7.08 dd 1.5 8.2	7.31 d 8.1	-	3.51 ttt 1.0 4.5 9.0	*2.21 m	*2.30 m	2.81 pd 0.6 6.8	2.06 s	4.32 s	6.73 q 4.9	2.53 d 4.9	-	-	-	-	-
30	N-methyl (S) ox	Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	8.06 bs	7.08 dd 1.2 2.3	7.40 m	6.97 dd 1.5 7.2	7.32 dd 0.7 7.2	-	3.64 ttt 1.0 4.1 9.2	*2.30 m	*2.47 m	2.91 pdo 1.1 7.5	2.19s	-	3" Me 2.92 s	3.94 m	4.17 t 8.1	4.05 dm	3.24 dd 4.6 -13.6	2.77 dd 8.6 -13.6	-
31	N-methyl (R) ox	Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.69 bs	7.17 dd 0.6 1.6	7.27 om	6.93 dd 1.2 8.3	7.25 d 8.2	-	3.51 ttt 1.0 4.4 9.2	*2.19 m	*2.31 m	2.78 om	2.06 s	-	7.72 bs	3.99 m	4.22 ct	4.03 m	2.88 dd	2.75 om	-

32		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	7.94 bs	7.05 dd 1.2 2.4	7.55 dt 0.8 1.5	7.24 dd 1.5 8.3	7.29 dd 0.8 8.3	-	3.63 ttt 1.2 4.5 9.4	*2.30 m	*2.44 qm 1.8 -9.6	2.90 pd 1.0 7.4	2.18 s	-	5.2 bs	-	1.41 s	1.41 s	4.75 s	4.75 s	-

	R	R'	n	Isomer	Parameter	NH	2	4	6	7	n	1'	$2'_R$	$2'_S$	3'	R'	1"	NH"	4"	5"b	5"a	6"b	6"a	7"
33		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.76 bs	7.20 dd 1.1 2.2	7.37 dt 0.6 1.6	7.02 dd 1.6 8.2	7.27 dd 0.6 8.3	-	3.49 ttt 1.1 4.4 9.5	*2.17 m	*2.29 m	2.80 pd 1.0 7.1	2.06 s	-	8.02 bs	-	3.93 s	3.93 s	4.56 s	4.56 s	-
12	(S) ox	Me	1		δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.66 bs	7.05 d 2.3	7.34 dt 0.7 1.6	6.92 dd 1.5 8.3	7.24 dd 0.5 8.3	2.80 d 8.0	2.42 m	*1.91 m	*1.78 m	2.75 om	2.00 s	-	7.73 bs	4.04 om	4.22 ct	4.00 oct	2.89 dd 4.5 -13.7	2.77 dd 6.8 -13.7	-
13	(S) ox	Me,H	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	8.11 bs	7.07 dd 1.0 2.0	7.32 dt 0.7 1.5	6.98 dd 1.6 8.3	7.31 dd 0.6 8.3	-	3.73 ttt 1.2 4.0 9.0	*2.28 m	*2.43 om	3.42 pm 1.1 6.6	Me 2.40 s NH 3.48 s	-	5.16 bs	4.12 td 5.6 8.0	4.47 t 8.0	4.19 dd 5.6 -8.0	2.98 dd	2.91 dd	-
34		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.72 bs	7.18 dd 1.0 2.3	7.29 om	6.94 dd 1.6 8.2	7.27 dd 0.5 8.2	-	3.51 ttt 1.1 4.4 9.0	*2.18 m	*2.30 m	2.77 pm 6.5	2.06 s	-	3"Me 2.80 s	4.00 om	4.14 cm	3.96 ct	3.17 dd 3.7 -13.5	3.05 dd 3.7	-
22	CH2CONH2 1" 2" 3"	Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.76 bs	7.17 dd 1.2 2.5	7.30 dt 0.9 1.5	6.98 dd 1.6 8.3	7.24 dd 0.5 8.1	-	3.50 ttt 1.1 4.4 8.8	*2.19 m	*2.30 m	2.81 pd 0.8 7.0	2.07 s	3.39 s	6.74 7.29 bs	-	-	-	-	-	-

	R	R'	n	Isomer	Parameter	1NH	2	4	6	7	n	1'	$2'_R$	$2'_S$	3'	R'	1"	NH"	4"	5"b	5"a	6"b	6"a	7"
14	CONH2	Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	11.00 bs	7.28 dd 1.1 2.2	8.07 dt 0.6 1.6	7.65 dd 1.6 8.5	7.33 dd 0.6 8.6	-	3.57 ttt 1.1 4.4 9.0	*2.21 m	*2.35 m	2.81 pd 0.7 7.0	2.07 s	-	7.02 7.80 bs	-	-	-	-	-	-
35	(S) ox	Me	0	cis	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	8.27 bs	7.03 dd 0.7 2.4	7.44 dt 0.7 1.7	6.95 dd 1.6 8.3	7.29 dd 0.6 8.3	-	3.31 tdd 1.0 7.5 10.2	*2.62 m	*2.13 m	2.75 m	2.25 s	-	5.28 bs	4.14 om	4.47 ct 7.8	4.18 ct	3.00 dd 5.7 -13.5	2.90 dd 7.8 -13.5	-
35		H	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.90 bs	7.09 d 2.3	7.30 om	6.83 dd 2.3 8.6	7.38 dd 0.4 8.6	-	3.74 om	2.42 t 7.1	2.42 t 7.1	3.74 om	-	3" 6.90 cd 1.0 8.7	-	4" 7.31 ct 8.3	5" 7.02 tt 1.0 7.3	-	-	-	-
36		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	11.06 d 1.6	7.13 d 2.2	7.41 dd 0.6 2.5	6.85 dd 2.2 8.6	7.41 dd 0.4 8.6	-	3.59 m	*2.40 ctdd	*2.67 oqd	3.86 pd 1.0 8.0	2.69 s	3" 6.89 cd 1.1 8.7	-	4" 7.31 cdd 7.1 8.5	5" 7.02 tt 1.1 7.3	-	-	-	-
21		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	8.08 bs	7.06 om	7.40 dt 0.6 1.5	7.07 odd 1.8 8.1	7.32 dd 0.5 8.3	-	3.63 ttt 1.1 4.0 9.2	*2.28 m	*2.44 m	2.92 pd 1.1 7.3	2.19 s	4.39 d 5.8	5.79 bt 5.6	3" 7.15 dm	4" 7.22 dd	5" 7.25 om	4.32 s	-	-
15		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.96 bs	7.28 dd 1.0 2.2	8.09 m	7.67 dd 1.7 8.5	7.35 dd	-	3.58 ttt 1.0 4.5 9.3	*2.20 m	*2.34 m	2.84 pd 1.0 7.3	2.08 s	4.5 d 6.0	8.78 t 6.0	3" 7.32 m	4" 7.32 m	5" 7.22 tt 3.2 6.2	-	-	-

19		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	11.26 bs	7.39 dd 1.2 2.2	8.20 d 0.5 1.5	7.79 dd 1.6 8.4	7.53 dd 0.5 8.5	-	3.61 ttt 0.9 4.3 9.3	*2.22 m	*2.38 om	2.87 pd 0.9 8.0	2.10 s	-	-	-	5Me 2.39 s	-	-	-	-
38		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) $CDCl_3$	7.97 bs	7.03 dd 1.1 2.2	7.42 dt 0.7 1.6	7.11 dd 1.7 8.3	7.28 dd 0.7 8.3	-	3.63 ttt 1.2 4.0 9.3	*2.29 m	*2.44 qm	2.89 pd 1.2 7.3	2.17 s	-	NMe 3.68 s	-	-	-	3.71 s	3.71 s	-
20		Me	0	trans	δ (ppm) multiplicity Coupling constants J (Hz) DMSO-d_6	10.59 bs	7.15 dd 0.7 2.0	7.31 m	6.96 dd 1.6 8.2	7.23 dd 05 7.9	-	3.49 ttt 1.0 4.6 9.0	*2.17 m	*2.30 qm	2.82 pd 1.0 7.2	2.07 s	-	-	-	13.12 bs	-	3.97 m	3.97 m	