Bioinformatic study on Some Phenyl piperidine derivatives as novel serotonin transporter (SERT) inhibitors for antipsychotic agents targeting Depression

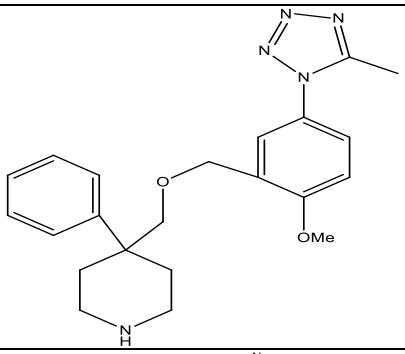
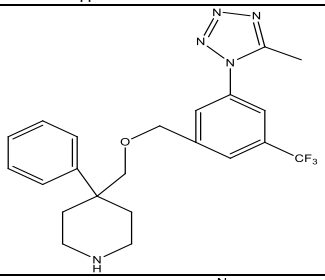
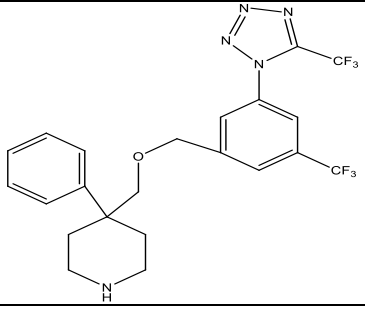
Sabitu Babatunde Olasupo[1*]
Adamu Uzairu[2]
Gideon Adamu Shallangwa[2]
Sani Uba[2]
[1]National Agency for Food and Drug Administration and Control (NAFDAC)
[2]Department of Chemistry, Ahmadu Bello University Zaria, Nigeria

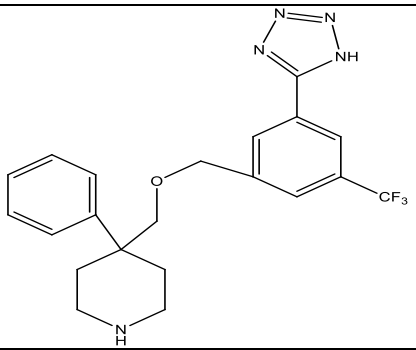
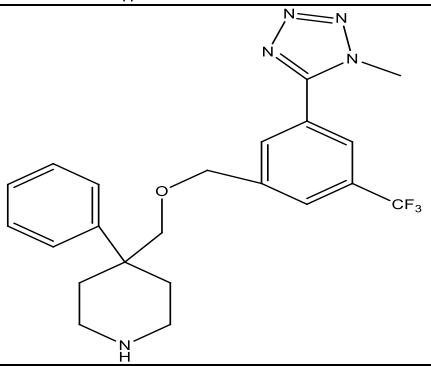
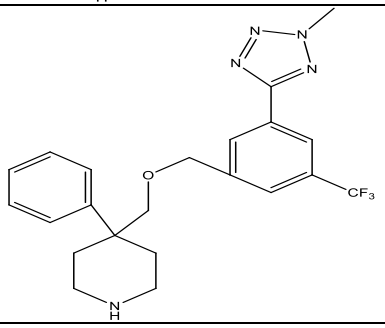
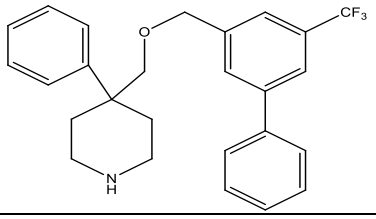
Doi: 10.21608/ajsr.2020.177501

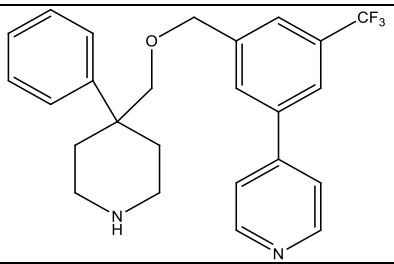
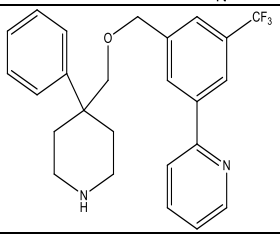
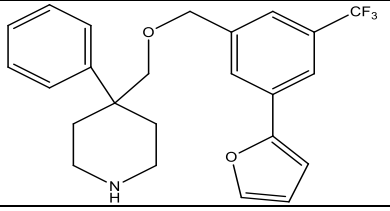
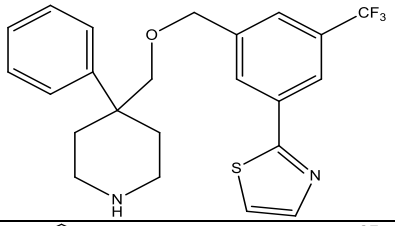
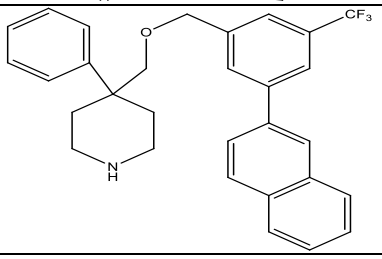
Olasupo , Sabitu Babatunde & Uzairu, Adamu & Gideon Adamu Shallangwa, Uba ,Sani (2020). Bioinformatic study on Some Phenyl piperidine derivatives as novel serotonin transporter (SERT) inhibitors for antipsychotic agents targeting Depression. ***The Arab Journal of Scientific Research***, AIESA, Vol. 4 Issue 4.

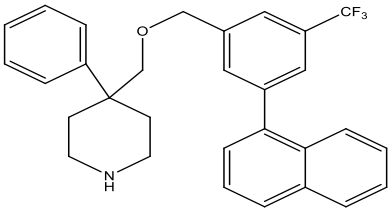
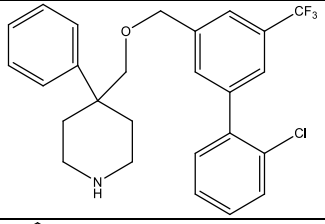
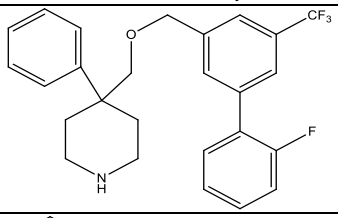
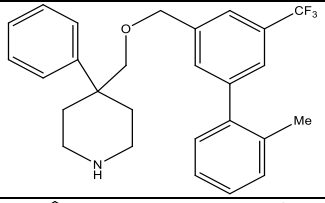
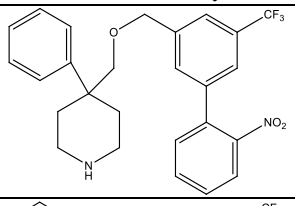
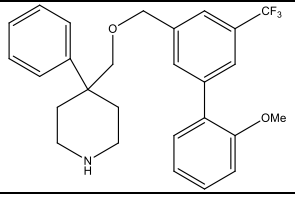
Supplementary Tables

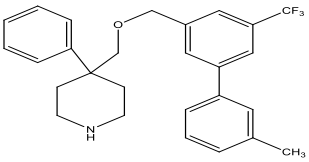
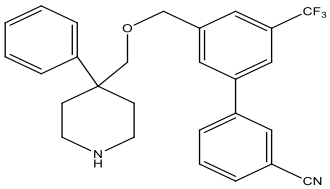
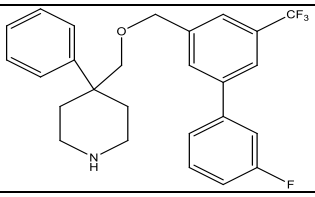
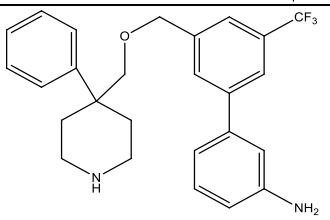
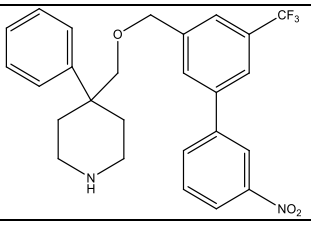
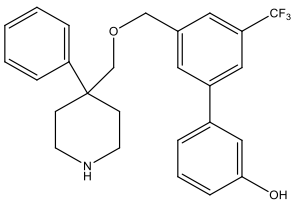
Supplementary Table S1: Chemical Names, Chemical Structures and Experimental pIC_{50} values of Phenyl piperidine (Data set)

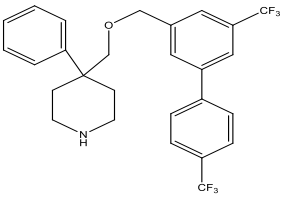
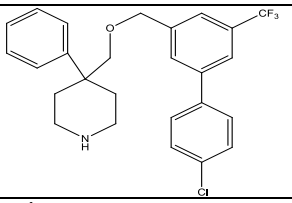
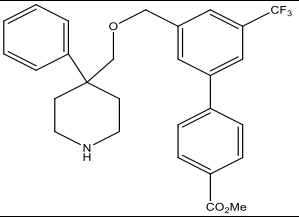
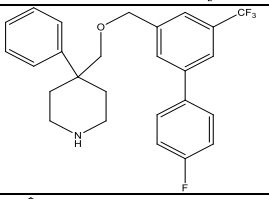
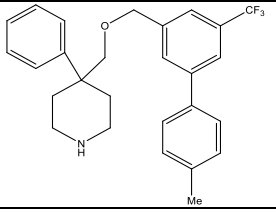
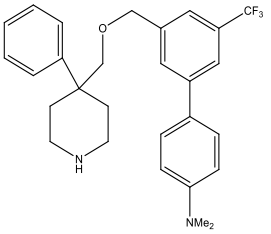
S/N	Chemical Name	Chemical Structure	Experimental pIC_{50}
1.	4-(((2-methoxy-5-(5-methyl-1H-tetrazol-1-yl)benzyl)oxy)methyl)-4-phenylpiperidine		7.432
2.	4-(((3-(5-methyl-1H-tetrazol-1-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		7.155
3.	4-phenyl-4-(((3-(trifluoromethyl)-5-(5-(trifluoromethyl)-1H-tetrazol-1-yl)benzyl)oxy)methyl)piperidine		7.244

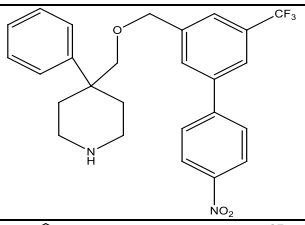
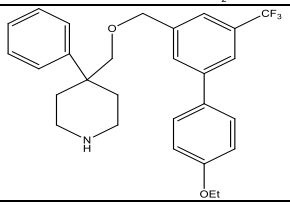
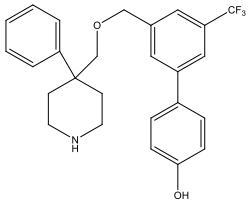
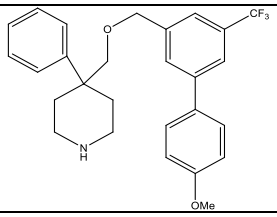
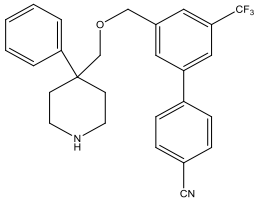
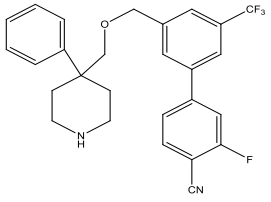
4.	4-(((3-(1H-tetrazol-5-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		8.066
5.	4-(((3-(1-methyl-1H-tetrazol-5-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		7.301
6.	4-(((3-(2-methyl-2H-tetrazol-5-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		8.018
7.	4-phenyl-4-(((5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)piperidine		8.432

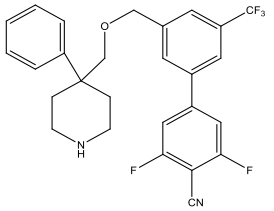
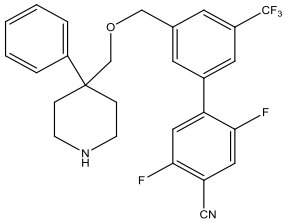
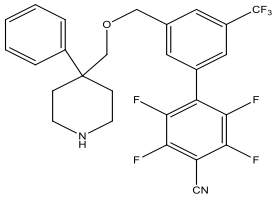
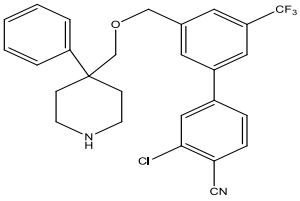
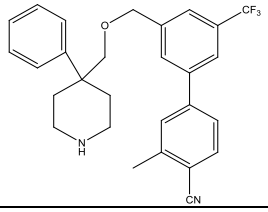
8.	4-(3-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5-(trifluoromethyl)phenyl)pyridine		7.796
9.	2-(3-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5-(trifluoromethyl)phenyl)pyridine		8.131
10.	4-(((3-(furan-2-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		7.745
11.	2-(3-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5-(trifluoromethyl)phenyl)thiazole		8.387
12.	4-(((3-(naphthalen-2-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		6.959

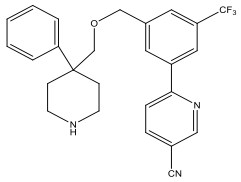
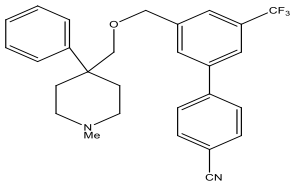
13.	4-(((3-(naphthalen-1-yl)-5-(trifluoromethyl)benzyl)oxy)methyl)-4-phenylpiperidine		6.921
14.	4-(((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.194
15.	4-(((2'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.119
16.	4-(((2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		7.886
17.	4-(((2'-nitro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.456
18.	4-(((2'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.377

19.	4-(((3'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		7.854
20.	3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile		8.000
21.	4-(((3'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.201
22.	3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-3-amine		7.523
23.	4-(((3'-nitro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.377
24.	3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-3-ol		7.569

25.	4-(((4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		7.444
26.	4-(((4'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.745
27.	methyl 3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate		7.602
28.	4-(((4'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.824
29.	4-(((4'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.194
30.	N,N-dimethyl-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine		8.456

31.	4-(((4'-nitro-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		8.137
32.	4-(((4'-ethoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		7.854
33.	3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-ol		7.569
34.	4-(((4'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)methyl)-4-phenylpiperidine		7.824
35.	3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.398
36.	3-fluoro-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.051

37.	3,5-difluoro-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.155
38.	2,5-difluoro-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.432
39.	2,3,5,6-tetrafluoro-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		7.328
40.	3-chloro-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.509
41.	3-methyl-3'-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.569

42.	6-(3-(((4-phenylpiperidin-4-yl)methoxy)methyl)-5-(trifluoromethyl)phenyl)nicotinonitrile		8.398
43.	3'-(((1-methyl-4-phenylpiperidin-4-yl)methoxy)methyl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile		8.022

Supplementary Table S2a: Euclidean Based Applicability Domain (**Training set**)

S/N	Distance Score	Mean Distance	Normalized Mean Distance
1	**24.903**	**0.830**	**0.837**
2	**17.964**	**0.599**	**0.388**
3	**12.911**	**0.430**	**0.060**
4	**15.360**	**0.512**	**0.219**
5	**16.729**	**0.558**	**0.308**
6	**13.763**	**0.459**	**0.115**
7	**12.584**	**0.419**	**0.039**
8	**13.140**	**0.438**	**0.075**
9	**12.444**	**0.415**	**0.030**
10	**15.145**	**0.505**	**0.205**
12	**25.389**	**0.846**	**0.869**
14	**11.985**	**0.400**	**0.000**
15	**12.257**	**0.409**	**0.018**
16	**19.772**	**0.659**	**0.505**
19	**19.186**	**0.640**	**0.467**
20	**27.411**	**0.914**	**1.000**

22	**12.925**	**0.431**	**0.061**
23	**17.117**	**0.571**	**0.333**
24	**13.272**	**0.442**	**0.083**
25	**17.966**	**0.599**	**0.388**
27	**15.197**	**0.507**	**0.208**
28	**12.424**	**0.414**	**0.028**
30	**14.508**	**0.484**	**0.164**
32	**19.409**	**0.647**	**0.481**
33	**13.905**	**0.463**	**0.124**
35	**13.061**	**0.435**	**0.070**
37	**17.410**	**0.580**	**0.352**
39	**20.524**	**0.684**	**0.554**
42	**12.452**	**0.415**	**0.030**
43	**13.524**	**0.451**	**0.100**

Supplementary Table S2b: Euclidean Based Applicability Domain (**Test set**)

S/N	Distance Score	Mean Distance	Normalized Mean Distance
11	14.002	0.467	0.131
13	20.054	0.668	0.523
17	17.336	0.578	0.347
18	13.011	0.434	0.067
21	11.931	0.398	-0.003
26	13.148	0.438	0.075
29	13.032	0.434	0.068
31	16.526	0.551	0.294
34	12.606	0.420	0.040
36	16.275	0.542	0.278
38	15.764	0.525	0.245
40	17.426	0.581	0.353
41	14.406	0.480	0.157

Table S3 : Pharmacokinetic/ ADMET properties of the studied compounds with a Standard Drug (Brexpiprazole) as a control

Compds S/N	MW	ADMET_Risk	S+logP	S+logD	LogBB	Pgp_Inh	S+CL_Renal	RO5	RO5_Code	hERG_pIC50	TOX_Risk	%Fa_hum-100.0	%Fb_hum-100.0
1	393.49	2.74	3.50	1.11	-0.30	Yes (48%)	No (99%)	0		4.85	1.25	81.37	52.78
2	431.46	5.85	4.57	2.19	0.47	Yes (61%)	No (99%)	1	LP	5.14	2.29	93.86	59.37
3	485.44	7.92	5.89	3.55	0.92	Yes (61%)	No (82%)	1	LP	5.17	2.69	97.21	55.60
4	417.44	6.24	3.43	3.43	-0.18	No (96%)	Yes (61%)	0		4.51	2.00	19.58	17.64
5	431.46	5.80	4.52	2.14	0.54	Yes (70%)	No (99%)	1	LP	5.17	2.40	94.84	58.34
6	431.46	5.32	4.69	2.32	0.62	Yes (97%)	No (99%)	1	LP	5.12	1.86	97.55	66.86
7	425.50	8.71	5.80	3.47	1.06	Yes (51%)	No (99%)	1	LP	6.45	1.00	100.00	35.64
8	426.49	6.43	5.10	2.77	0.95	Yes (59%)	No (99%)	0		6.24	1.62	99.94	44.55
9	426.49	6.29	5.26	2.92	1.05	Yes (51%)	No (99%)	1	LP	6.40	1.00	99.97	47.85
10	415.46	8.57	5.33	2.98	0.84	Yes (97%)	No (99%)	1	LP	6.06	2.30	99.97	38.93
11	432.51	8.98	5.26	2.92	1.02	Yes (97%)	No (99%)	0		6.10	4.00	99.95	49.72
12	475.56	10.25	6.74	4.46	1.14	Yes (97%)	No (99%)	1	LP	6.86	2.41	91.74	25.92
13	475.56	9.46	6.60	4.33	1.14	Yes (97%)	No (95%)	1	LP	6.73	1.73	83.08	22.14
14	459.94	9.94	6.20	3.97	1.18	Yes (97%)	No (99%)	1	LP	6.61	1.85	99.99	28.92
15	443.49	8.88	6.07	3.74	1.20	Yes (97%)	No (99%)	1	LP	6.46	1.78	99.99	29.13

16	439.52	8.24	6.04	3.70	1.00	Yes (64 %)	No (89 %)	1	LP	6.38	1.36	100.00	26.90
17	470.50	9.07	5.62	3.34	1.06	Yes (97 %)	No (99 %)	1	LP	7.06	3.00	99.94	80.33
18	455.52	7.84	5.77	3.41	1.02	Yes (97 %)	No (99 %)	1	LP	6.37	1.48	99.99	33.63
19	439.52	8.35	6.19	3.85	1.06	Yes (59 %)	No (95 %)	1	LP	6.43	1.11	100.00	26.55
20	450.51	7.76	5.46	3.19	0.73	Yes (97 %)	No (92 %)	1	LP	6.52	1.59	80.18	24.06
21	443.49	9.11	6.16	3.83	1.21	Yes (97 %)	No (99 %)	1	LP	6.55	1.84	100.00	29.98
22	440.51	8.69	5.56	3.24	0.81	Yes (97 %)	No (92 %)	1	LP	6.40	2.49	99.89	55.03
23	470.50	9.14	5.86	3.56	1.06	Yes (97 %)	No (99 %)	1	LP	7.17	2.85	99.88	79.98
24	441.50	6.63	5.36	3.29	0.88	No (69 %)	No (99 %)	1	LP	6.57	1.69	99.76	73.11
25	493.50	9.69	6.57	4.25	1.26	Yes (64 %)	No (89 %)	1	LP	6.67	2.83	97.69	19.15
26	459.94	9.43	6.42	4.19	1.23	Yes (97 %)	No (99 %)	1	LP	6.70	1.34	100.00	27.46
27	483.53	8.95	5.87	3.59	1.05	Yes (97 %)	No (99 %)	1	LP	6.32	1.51	99.97	57.05
28	443.49	9.03	6.22	3.88	1.21	Yes (97 %)	No (99 %)	1	LP	6.56	1.72	100.00	28.42
29	439.52	9.33	6.27	3.93	1.07	Yes (73 %)	No (95 %)	1	LP	6.43	1.10	100.00	26.91
30	468.57	9.87	6.52	4.11	1.18	Yes (97 %)	No (99 %)	1	LP	6.70	2.36	100.00	23.60
31	470.50	9.63	5.94	3.64	1.09	Yes (97 %)	No (99 %)	1	LP	7.14	2.99	98.42	76.14
32	469.55	10.62	6.31	3.93	1.09	Yes (97 %)	No (99 %)	1	LP	6.60	1.30	100.00	25.14
33	441.50	6.18	5.37	3.27	0.87	No (66	No (99	1	LP	6.51	1.18	99.76	70.61

						%)	%)						
34	455.52	9.36	5.97	3.61	1.08	Yes (97 %)	No (99 %)	1	LP	6.48	1.32	99.99	30.86
35	450.51	7.63	5.56	3.29	0.75	Yes (97 %)	No (92 %)	1	LP	6.54	1.22	77.69	23.37
36	468.50	8.75	5.92	3.64	1.01	Yes (97 %)	No (92 %)	1	LP	6.59	1.69	29.74	6.70
37	486.49	8.63	6.24	3.95	1.22	Yes (97 %)	No (92 %)	1	LP	6.62	2.00	11.15	1.71
38	486.49	9.09	6.16	3.88	1.17	Yes (97 %)	No (86 %)	1	LP	6.53	2.00	19.87	3.08
39	522.47	9.48	6.51	4.23	1.41	Yes (97 %)	No (82 %)	2	Mw; LP	6.33	2.00	5.08	0.28
40	484.95	10.06	6.19	4.00	0.99	Yes (97 %)	No (99 %)	1	LP	6.76	1.72	16.05	3.71
41	464.53	8.59	5.84	3.55	0.71	Yes (97 %)	No (92 %)	1	LP	6.52	1.51	45.29	10.54
42	451.50	6.73	5.03	2.73	0.72	Yes (97 %)	No (95 %)	0		6.42	1.00	99.83	31.55
43	464.53	8.72	5.81	4.48	0.81	Yes (97 %)	No (95 %)	1	LP	6.70	1.00	55.96	14.40
Brexpiprazole	433.57	6.583	4.725	4.396	0.22	Yes (78 %)	No (99 %)	0		6.82	2		

Brexpiprazole (Standard Drug) as a control