Structure of racemic duloxetine hydrochloride

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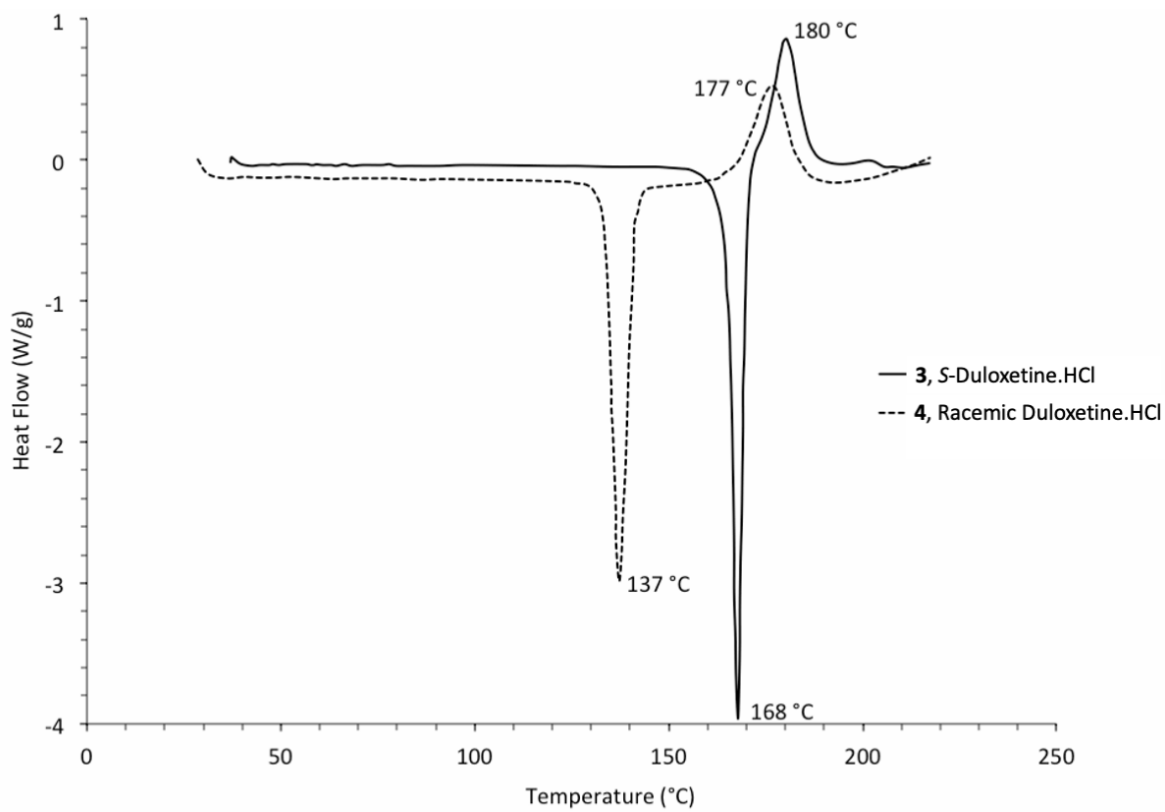
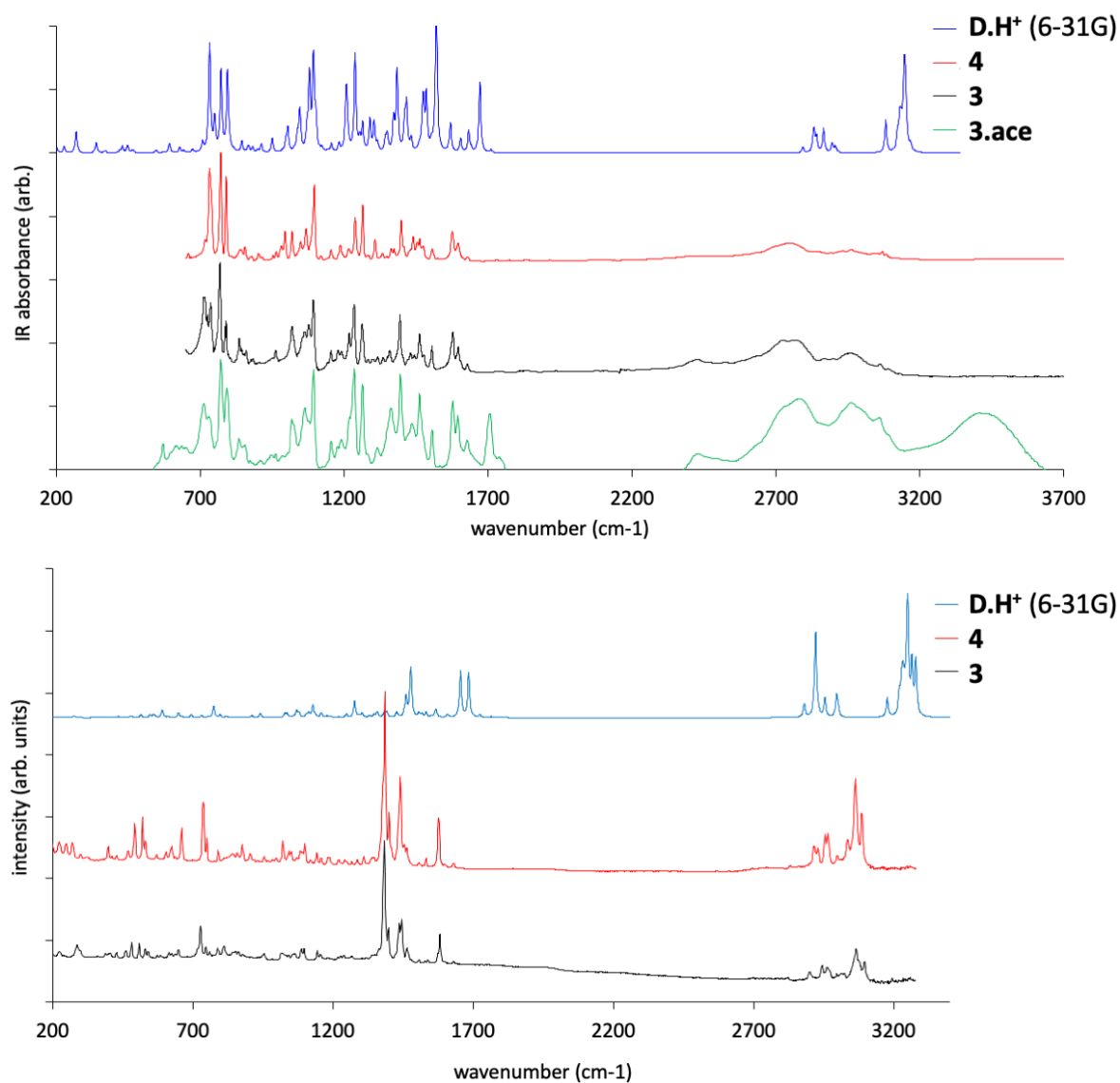Fig. S1: DSC runs of *S*-duloxetine, **3**, and duloxetine racemate, **4**.

*Figure S2: Upper stack plot, FTIR spectra between 650-3700 cm^{-1} calculated for gas state of **duloxetine.H$^+$** (DFT 6-31G basis set), and measured for **4**, **3** and **3.ace**; Lower stack plot, Raman spectra between (200-3250 cm^{-1}) of gas state of **duloxetine.H$^+$** (DFT 6-31G basis set), and measured spectra of **4** and **3**.*
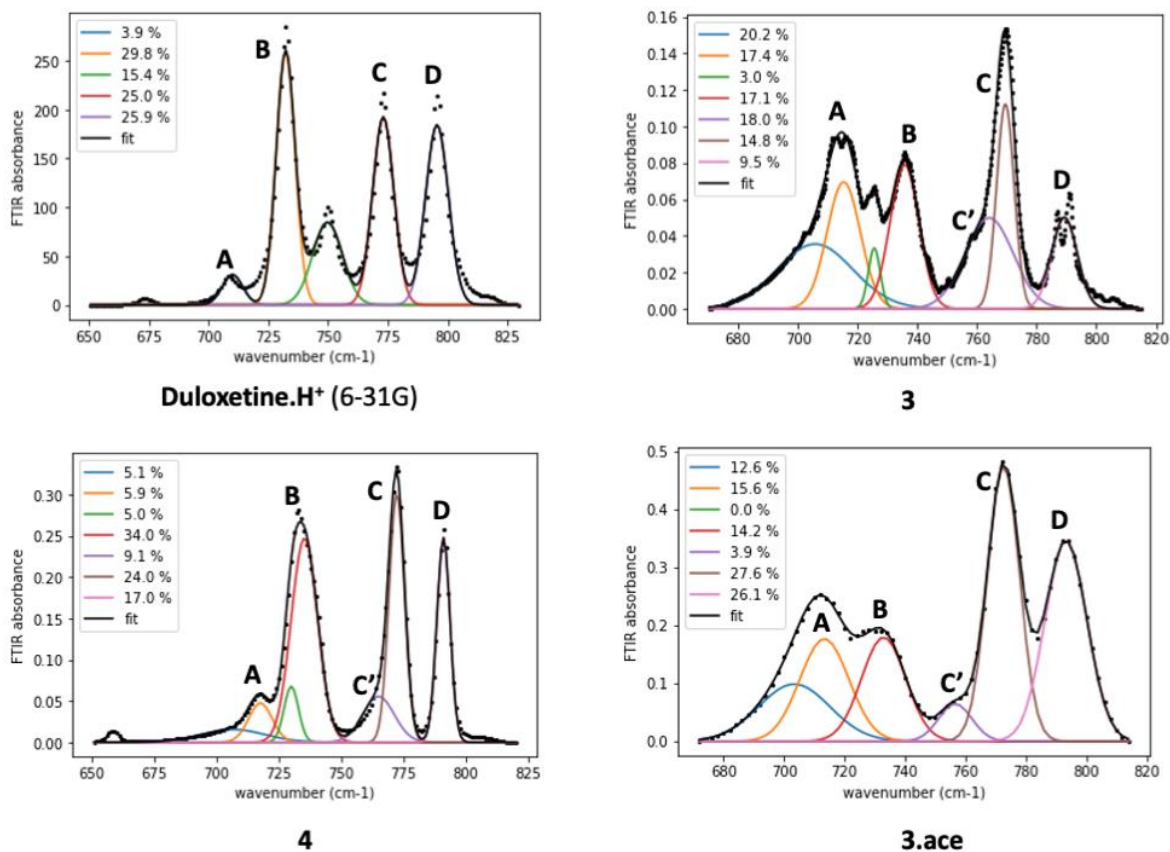
*Figure S3: Gaussian fits to FTIR spectra from 670-810 cm^{-1} for gas state **duloxetine.H$^+$ (6-31G)**, **3**, **4** and **3.ace**. Peak area ratios were calculated from the area under peak A (orange) and the combination of peaks C' and C (purple and brown).*

Table S4: Proposed peak assignments in Raman spectra of **3** and **4** based on major peaks found in calculated spectrum of **duloxetine.H**[+] (DFT 6-31G) with frequencies scaled by 0.97.

Description	duloxetine.H+		
	calc.	**3**	**4**
aromatic CH stretching range	3167-3130	3106-3030	3106-3018
thiophene symmetric CH stretch	3180	3096	3086
CH_3 asymmetric stretch	2905	2974	2966
CH_2 asymmetric stretch	2865	2964	2956
CH_2, CH_3 symmetric stretch	2833	2944	2930
CH stretch	2794	2902	2918
thiophene ring deformation	1633	1632	1632
naphthalene ring deformation	1605	1582	1576
	1434	1446	1440
naphthalene ring deformation CH_2 wag	1417	1434	1434
C-O stretch naphthalene CH in-plane wag	1239	1240	1244
thiophene CH in-plane wag CH_2 rock	1123	1146	1144
C-O stretch naphthalene ring deformation	1039	1024	1022
naphthalene CH out-of-plane wag	1004	956	956
C-C str, naphthalene ring deformation	913		908
naphthalene CH out-of-plane wag C-C-C bend	750	746	750
naphthalene ring deformation	708	726	738
thiophene ring deformation	629	626	626
CH_2 rock	572	574	572
	499	508	520

Table S5: Proposed peak assignments in FTIR spectra of **3** , **3.ace** and **4** based on major peaks found in calculated spectrum of **duloxetine.H$^+$** (DFT 6-31G) with frequencies scaled by 0.97.

Description	duloxetine.H+ calc.	4	3	3.ace
aromatic CH stretching range	3167-3130	3120-3040	3120-3040	3120-3040
aliphatic CH stretching range	2905-2794	2990-2900	2990-2900	2990-2900
C=O stretch, acetone guest	-	-	-	1710
thiophene ring deformation	1633	1634	1634	1632
naphthalene ring deformation	1570	1579	1580	1580
CH$_2$, CH$_3$ scissor	1521	1510	1507	1508
CH$_2$ scissor	1486	1478	1482	1480
CH$_2$ scissor	1475	1464	1464	1464
CH$_2$ rock naphthalene ring deformation	1417	1442	1436	1442
C-O stretch CH wag	1384	1400	1398	1398
CH$_2$ twist CH wag	1306	1310	1320	1320
naphthalene ring deformation	1290 1265	- -	- -	- -
C-O stretch naphthalene ring deformation	1239	1266	1264	1266
CH, CH$_2$, CH$_3$ rock	1207	1240	1236	1236
C-C, C-N stretch	1103	-	-	-
C-O stretch naphthalene ring deformation	1093	1098	1096	1096
CH$_2$, CH$_3$ twist naphthalene ring deformation thiophene ring deformation	1081	1070	1080	1082
C-O, C-C stretch naphthalene ring deformation thiophene ring deformation.	1047	1052	1066	1066
naphthalene CH deformation	1004	1021	1021	1022

CH$_2$, CH$_3$ twist				
naphthalene CH deformation	795	791	792	794
thiophene ring deformation	774	773	770	772
naphthalene ring deformation thiophene ring deformation C-C-C and C-C-C bend	757	-	-	-
thiophene CH deformation	732	733	736	734
thiophene CH deformation naphthalene ring deformation CH$_2$ rock	708	720	718	714
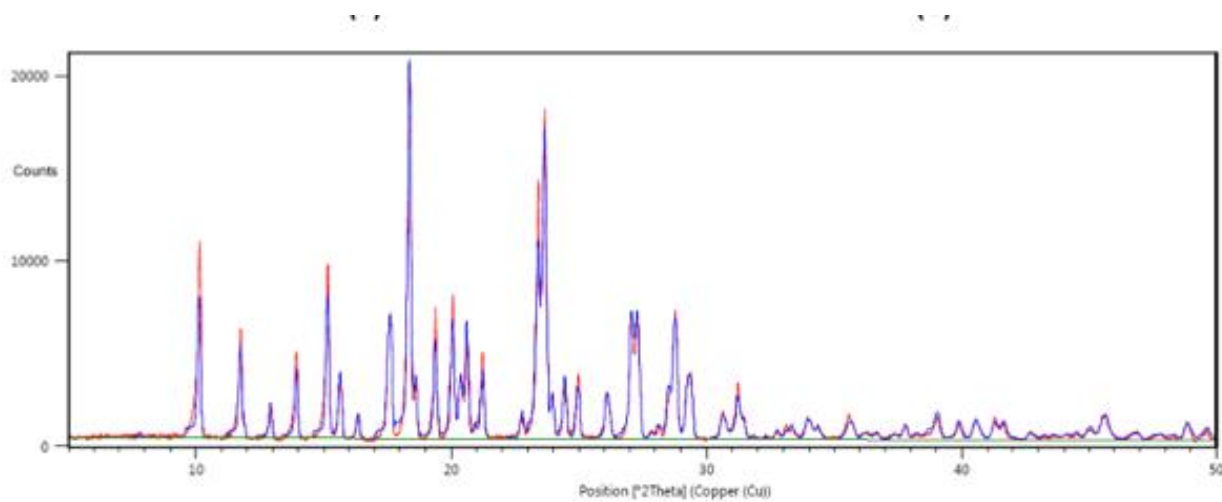
*Fig. S6: Cu K$_\alpha$ X-ray powder diffraction data of **4** (red) and corresponding Rietveld refinement (blue) using the synchrotron single-crystal data of **4**.*

Table S7: Subset of refined parameters from Rietveld analysis (High Score Plus, Panalytical, Netherlands) of powder XRD for **4** using the synchrotron single crystal data.

Background	
Method	Polynomial
Use Extended Background Terms	False
Flat Background	313.8689
Coefficient 1	1.672172
Coefficient 2	178.684
Agreement Indices	

Last Marquard Value	0
Condition Number	558416800
R expected	5.6136
R profile	12.60323
Weighted R profile	14.6943
D-statistics	0.10903
Weighted D-statistics	0.12988
Goodness of Fit	6.85195
General Properties	
Sample Geometry	Flat Plate Geometry
Automatic Cell Constraints	True
Automatic Anisotropic Displacement Constraints	True
Specimen Displacement [mm]	0.00042
Zero Shift [2Theta]	-0.03918
Polarisation Correction Coefficient	1
Linear Absorption Coefficient [1/cm]	0
Use Brindley Micro absorption Correction	False
Refinement	
Weighting Scheme	Against Iobs
Use summed March/Dollase Function	False
Recycle HKL's (Le-Bail Fit only)	True
Profile Function	Pseudo Voigt
Profile Base Width	4
Intensity Limit	0
Max. No. of Least-Squares Cycles	20
EPS (stop if all shifts < EPS*esd)	0.5
Job Type	X-rays
Least-Squares Type	Newton-Raphson
Marquardt Start Value	0
Max. Angle for Rietveld Asymmetry correction	60
Relaxation Factors	
Coordinates, isotropic Displacement and sof	0.8
Anisotropic Displacement	0.8
Scale, Zero, Background, Cell, Pref.Ori. and Bov.	0.8

FWHM, Asymmetry and Shape	0.8
Profile Fit Settings	
Max. No of Profile Fit Cycles	20
Profile Fit Peak Base Width	20
Use Caglioti Function	False
Use Shape Function	False
Calculate Errors	True
Asymmetry Type	Split Shape

Table S8: Torsion angle tables for molecules having alkyl chains like (a) Imipramine (b) Citalopram and (c) Fluoxetine.
Angles ~180 ° indicate extended conformation, deviation from 180 ° indicate the extent of folding (highlighted in yellow).

(a)

No.	NAME	TOR1	TOR2	TOR3	TOR4
1	CAPTAZ	-128.708	-151.861	-126.744	146.303
2	COSFOF	110.302	-176.708	169.988	-176.933
3	DOHFOV	-102.561	163.679	-169.788	167.977
4	DUKTOS	134.937	179.551	166.595	162.177
4	DUKTOS	144.984	-171.483	-164.903	170.729
5	IMIPRB	137.194	-179.441	174.083	170.795
5	IMIPRB	-161.154	161.742	59.196	-171.568
6	IMIPRC	137.145	-179.655	173.5	169.388
6	IMIPRC	-159.667	160.477	60.901	-172.332
7	PROMZC01	142.876	-166.268	-151.934	163.419
8	TFPROM10	-148.476	141.643	57.789	-170.253
8	TFPROM10	138.693	-178.15	179.369	172.491
9	ROJJEG	-105.812	-178.281	176.848	-174.364
10	ROJJIK	106.113	-176.73	-170.956	166.413
11	CEJLAE	89.311	166.819	-174.716	160.263
12	IPRINC	84.293	177.003	-167.469	177.254
13	MAPTML10	80.255	-175.54	170.306	-173.482
14	CMPBIM	-96.599	173.915	164.079	-178.182
15	COSFUL	88.912	-173.476	177.647	-171.939
16	ZUWHOO	-86.28	-167.95	179.9	-168.14
17	SITYEC	-63.393	173.529	178.862	64.939
18	VICXAH	81.148	-173.25	-170.692	176.255
19	CIMPRA	-142.454	71.159	167.628	-169.961
20	GIKJOC	169.242	-59.395	-178.351	169.669
21	HAWZAG	140.319	-58.632	166.74	-178.496
22	MUWSIJ	104.408	-57.763	174.096	177.211
23	REZBII	143.414	-72.291	161.371	174.575
24	VICXAH	124.505	-60.805	-147.797	175.083
25	BOLTAX	-91.401	159.666	61.419	-169.523
26	MIGQID	-160.551	53.771	57.777	176.022
27	DUNGAV	165.178	-53.28	-59.806	-177.968
27	DUNGAV	-160.592	63.985	-168.792	-178.292
28	SINTAM10	-71.989	-179.386	-58.88	-175.396

(b)

No.		NAME	TOR1	TOR2	TOR3	TOR4
	1	APFMHA	-169.176	172.211	-169.711	178.452
	1	APFMHA	162.694	-172.032	170.562	-174.796
	2	AZOWUI	178.378	-164.675	178.819	-65.774
	3	EZIQEL	166.647	-176.338	-165.426	176.694
	3	EZIQEL	170.903	176.919	171.855	122.628
	4	IJUGOK	-175.27	-174.238	-163.743	-147.892
	5	IQIRUX	174.202	160.44	164.692	130.87
	6	SETVUJ	179.989	-174.336	-174.605	65.102
	6	SETVUJ	179.989	-174.336	-174.605	-171.508
	7	WASGAA	-179.403	-175.383	-175.394	-171.874
	7	WASGAA	174.594	-178.973	179.51	173.61
	8	WASGEE	-177.218	177.123	175.568	173.088

(c)

No.	NAME	TOR1	TOR2	TOR3
1	BPAMAL	167.078	-171.669	170.043
2	CPHMAL10	173.331	-161.183	176.873
3	DUFTOO	159.92	175.624	154.169
4	EJUKEZ	-168.786	-164.144	177.986
5	FUQTUI	-179.272	-172.62	-172.452
6	HEVDUI	-173.673	-159.098	-160.699
7	JEGWUN	168.419	-171.006	170.159
8	LUDYIV	-178.241	-168.955	171.828
9	ZITZAD	-175.682	-168.302	179.288
10	YIGNEI02	176.72	177.05	-172.94
11	ZUHFIR	-175.748	-82.045	-58.725
11	ZUHFIR	170.242	-174.634	65.094
12	FUDCOW	-175.71	-179.96	77.93
13	RAJFEO	-176.8	70.69	173.31
14	DETGIV	179.63	-157.53	-176.06
14	DETGIV	-176.84	-176.93	-61.51
15	EMIQOI	160.07	-74.97	-174.57
16	EMIQOI01	-160.03	73.27	173.88
16	EMIQOI01	166.54	-71.2	-170.44
17	EMIQOI04	159.36	-75.04	-174.97
18	RAJFAK	-169.59	69.19	174.2
18	RAJFAK	-168.17	73.62	176.1
19	S-Duloxetine	168.04	-127.34	172.84
20	S-duloxetine.ac	164.59	-78.19	178.02
21	Rac-Duloxetine	64.44	70.09	165.96

Fig. S9: Selected examples of molecular packing with molecules having an Imipramine-like side chain with (a) all four torsion angles close to 180 °, (b) either tor1 or tor2 deviating from 180 ° and (c) tor3 deviating from 180 °.
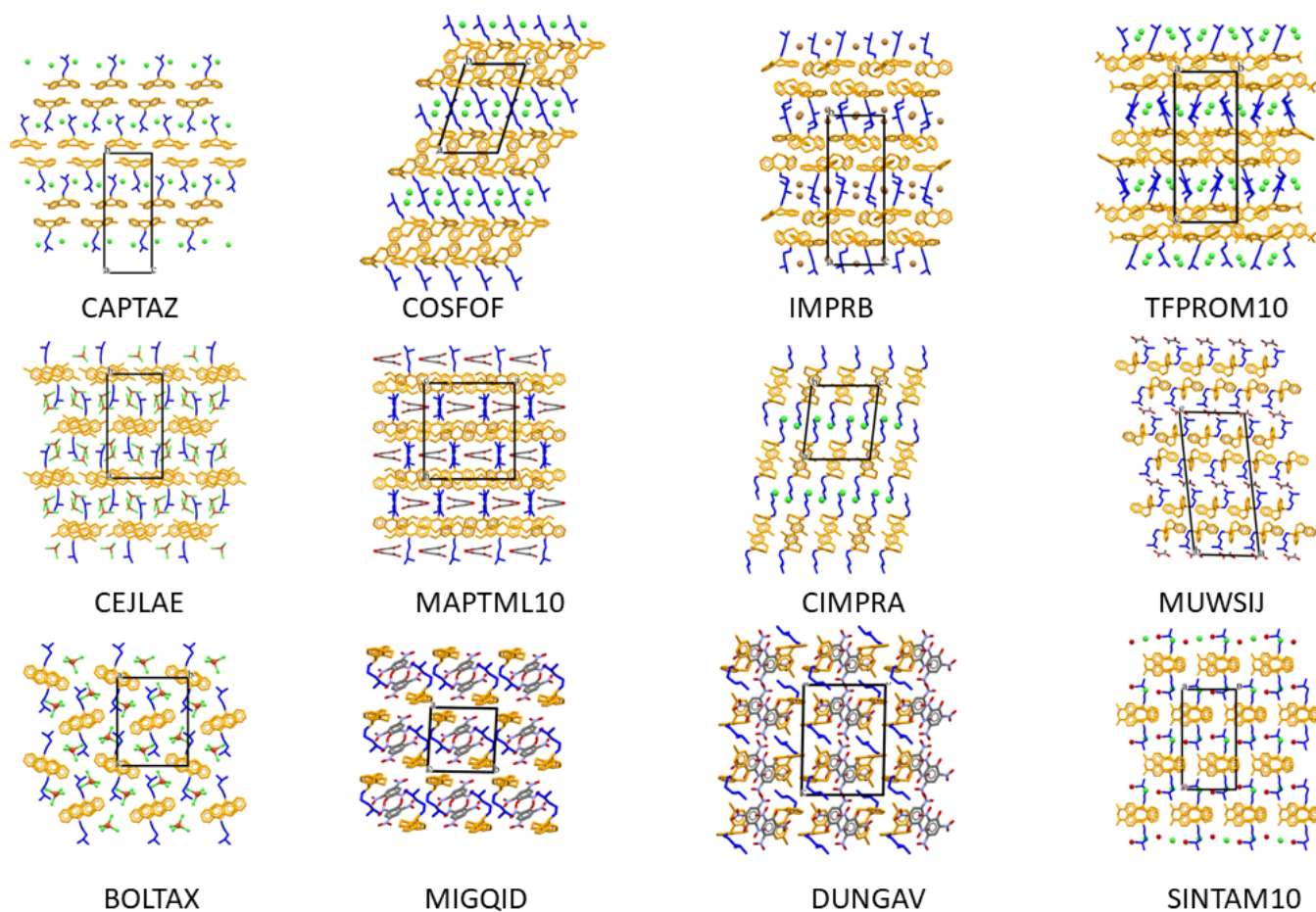

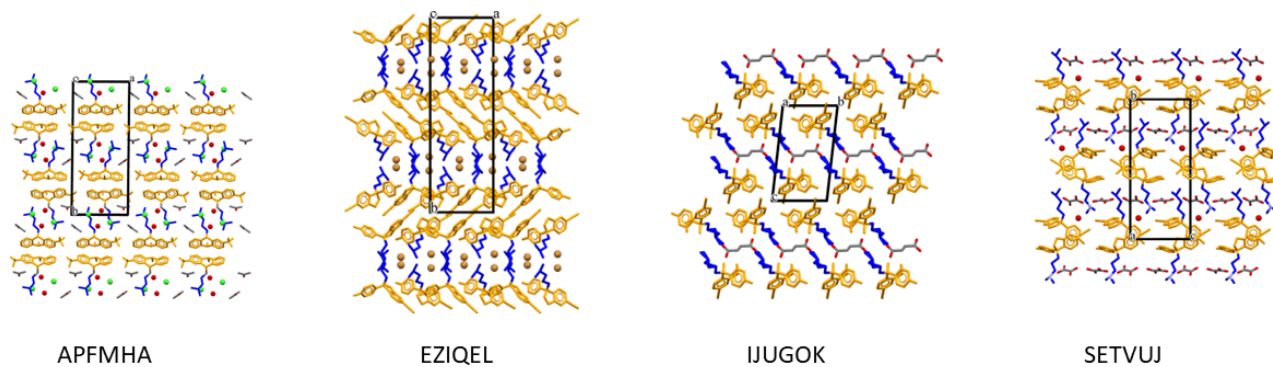Fig S10: Examples of molecular packing in the Citalopram-like class showing all torsion angles ~180 °.

Fig. S11: Selective examples of molecules with shorter side chain similar to Fluoxetine; packing of molecules with all the three torsion angles ~180 ° (a) either Tor2 or Tor3 deviating from 180 °.

BPAMAL   FUQTUI   HEVDUI   ZITZAD

ZUHFIR   FUDCOW   EMIQOI04   EMIQOI01