Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting Information

Co-Crystals of Zwitterionic GABA API's Pregabalin and Phenibut: Properties and Application

Daniel Komisarek, Takin Haj Hassani Sohi, and Vera Vasylyeva

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1 Structural Details

All structures are deposited to CCDC. Deposition Number: 2170100-2170108. Bijvoet analysis was conducted on all received structures with PLATON software v. 1.19 to confirm molecular chirality, shown in **chapter 5**.[1]

1.1 Pregabalin (1)

Pure Pregabalin is examined as its (S)- and (R)-enantiomer in the context of this work. Single crystals of the enantiomerically pure forms were obtained by slow evaporation of solvent from aqueous solution. Block shaped diffraction quality crystals were obtained. The lattice and measurement parameters are shown in **Table S1**. Interaction distances and angles are shown in **Table S2**.

Table S1. *Lattice and measurement parameters of (R)- and (S)-Pregabalin.*

Parameters	**(R)-Pregabalin**	**(S)-Pregabalin**
Formula	C_8 H_{17} N O_2	C_8 H_{17} N O_2
M_r [g mol^{-1}]	159.22	159.22
Temperature [K]	100(2)	100(2)
System/space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
a (Å)	6.368(4)	6.344(4)
b (Å)	7.817(6)	7.809(4)
c (Å)	18.504(4)	18.493(3)
β (°)	90	90
V (Å^3)	921.25(5)	916.27(5)
Z/Z'	4/1	4/1
Density [g/cm^3]	1.148	1.154
μ [mm^{-1}]	0.656	0.660
T_{min}/T_{max}	0.514/1.000	0.622/1.000
F (000)	352	352
Crystal size [mm]	0.36 · 0.25 · 0.10	0.32 · 0.20 · 0.03
2θ range [°]	4.8 – 77.5	4.8 – 77.5
Completeness [%]	99.7	99.1
Recorded refl.	4569	6940
Independent refl.	1779	1757
Flack x	-0.04(19)	0.03(11)
Goodness-of-fit F^2	1.053	1.043
X-Ray Source	Cu Kα (λ = 1.54184)	Cu Kα (λ = 1.54184)
R_1 [%] /wR_2 [%] /S	4.05/ 9.95/ 1.053	3.01/ 7.86/ 1.043

Table S2. *Hydrogen bond distances and angles in (R)- as well as (S)-Pregabalin.*

	D - H [Å]	H…A [Å]	D…A [Å]	D - H…A [°]
(S)-Pregabalin				
N1-H6…O1	0.90(3)	1.86(3)	2.755(8)	171(2)
N1-H7…O1	0.94(2)	1.79(2)	2.728(0)	171(2)
N1-H8…O2	0.91(2)	1.87(2)	2.771(1)	172(2)
(R)-Pregabalin				
N1-H6…O1	0.91(3)	1.86(3)	2.757(2)	170(3)
N1-H7…O1	0.93(3)	1.80(3)	2.731(2)	174(2)
N1-H8…O2	0.92(3)	1.86(3)	2.767(2)	172(3)

A comparison of the asymmetric unit and lattice packing of both compounds is shown in **Figure S1**. Three distinct HB are formed in both systems. From each donor nitrogen N1 two interactions are formed with acceptor oxygen O1 with a length of 2.755(8) Å (S)/ 2.757(2) Å (R) and 2.728(0) Å (S)/ 2.731(2) Å (R) and one interaction with acceptor oxygen O2 at 2.771(1) Å (S)/ 2.767(2) Å (R). The donor/acceptor distance in each case is short enough to be considered a strong hydrogen bond and the D-H…A angle is around 172.[2] These values suggest that the ionicity on the ammonium and carboxylate groups may enforce the HB, leading to strong, charge assisted HB. To further elucidate on possible binding interactions, Hirshfeld- as well as electron density surface analysis was conducted with Crystal Explorer 21.5 (**Figure S2**).[3] In electron density surfaces, red spots suggest high electron density which indicates high probability for binding interactions while white spots suggest surface electron density as expected from not interacting atoms and blue spots indicate low surface electron density most. In Hirshfeld surfaces red spots indicate close contacts between surface atoms shorter than the sum of their respective van der Waals radii, white spots indicate surface atoms close contacts equal to the sum of their van der Waals radii and blue spots indicate that surface atoms are further away from other surface atoms than the sum of their van der Waals radii. Both surface analyses additionally confirm that bonding interactions take place via the ammonium- and carboxylate subunits and molecular vicinity as well as electron density is increased exactly around the HB interaction spots. In congruence with the packing motif depicted in **Figure S1** it can be concluded that rows of symmetrically equivalent Pregabalin molecules connect via charge assisted HB-interactions. As no conspicuous electron density features or close vicinity is present around the isobutyl group and furthermore no π-systems are present in Pregabalin, dispersive forces probably best explain the structural motif with regard to the alkylic residues.

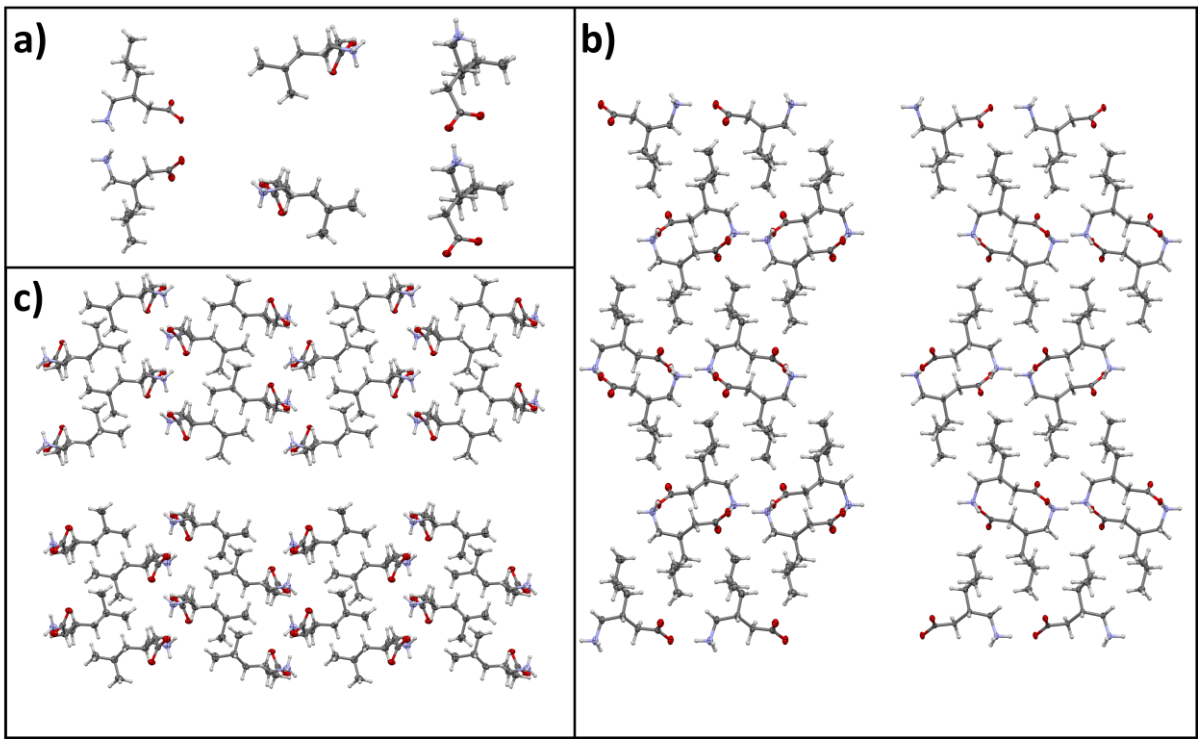

Figure S1. *The asymmetric unit of (S)-Pregabalin (**a)**, top) and (R)-Pregabalin (**a)**, bottom) is shown: from left to right a-axis, b-axis, c-axis. In **b)** the packing of a 2 · 2 · 2 unit cell from a-axis view is shown, (S)-Pregabalin top, (R)-Pregabalin bottom. In **c)** the packing of a 2 · 2 · 2 unit cell from b-axis view is shown, (S)-Pregabalin right, (R)-Pregabalin left. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

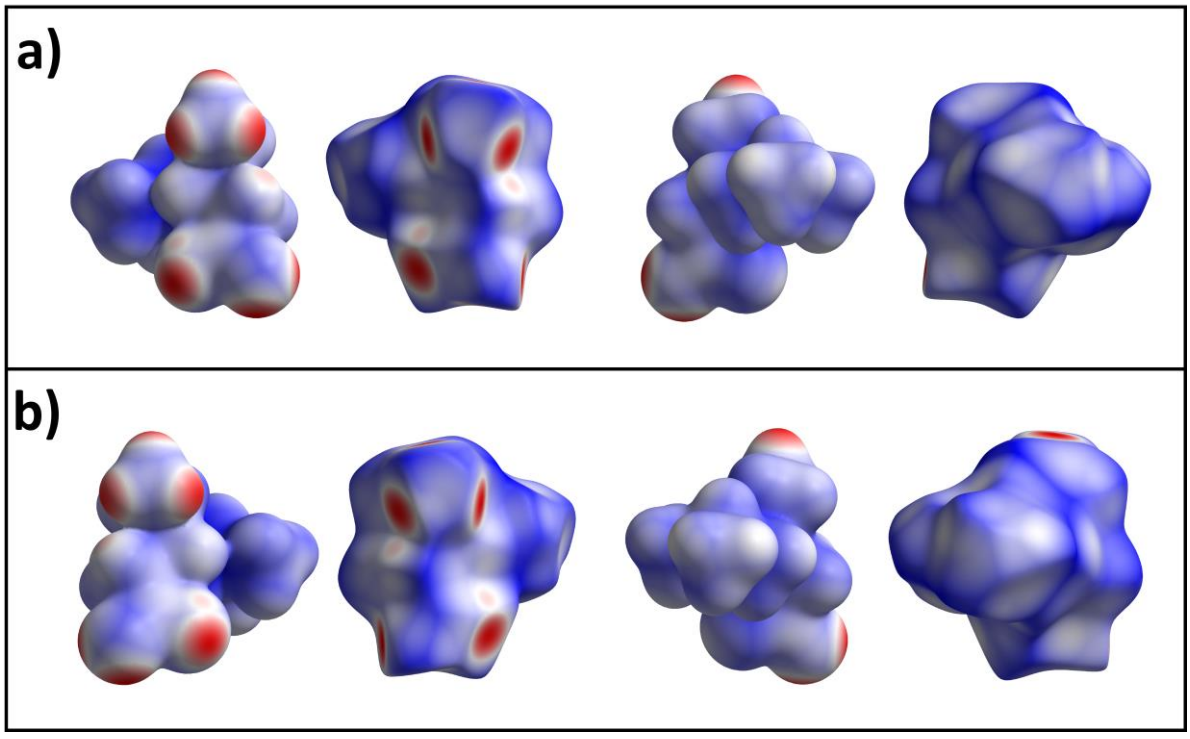

Figure S2. *Electron density and Hirshfeld surfaces of (S)- and (R)-Pregabalin. **a)** shows the electron density and Hirshfeld surface of the sole symmetrically inequivalent Pregabalin molecule in the (S)-Pregabalin lattice from two sides. **b)** shows the electron density and Hirshfeld surface of the sole symmetrically inequivalent Pregabalin molecule in the (R)-Pregabalin lattice from two sides.*

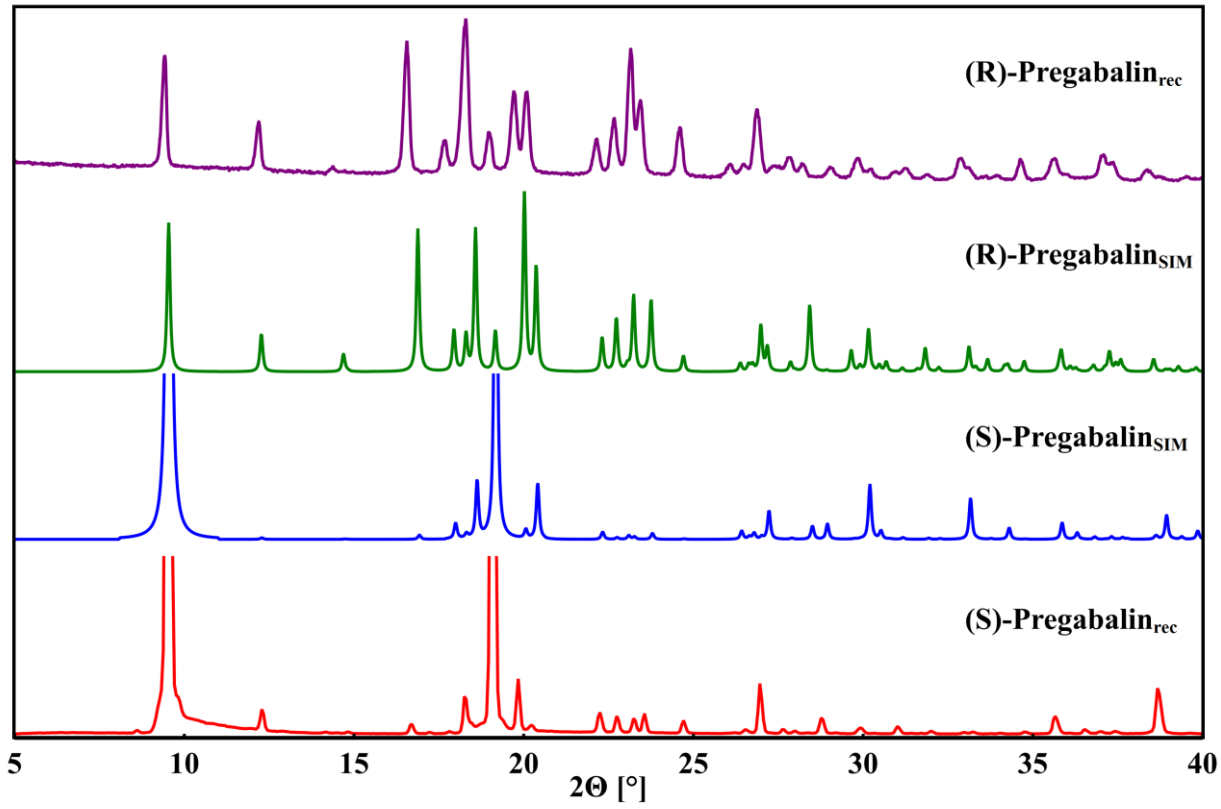

Figure S3. *Powder pattern of (S)-Pregabalin recorded (red) compared to a simulated pattern by single crystal data (blue) and powder pattern of (R)-Pregabalin (purple) compared to a simulated pattern by single crystal data (green) in a range of 5° – 40°. (S)-Pregabalin was recrystallized from water leading to preferential directions while (R)-Pregabalin was measured after stirring in acetone/water mixture for 40 h as by the racemic separation process described in this work leading to more uniform sized particles and distribution of signal intensities. The simulated pattern for (S)-Pregabalin was customized regarding hkl distribution to account for preferential directions (hkl = 4, 4, 0, March-Dollase parameter = 4).*

1.2 Phenibut (2)

The structural properties of (rac)-Phenibut are revaluated regarding the herein discussed items based on our published structure in ZAAC 2021.[4] Needle shaped single crystals were obtained from aqueous solution by slow evaporation of the solvent. The lattice and measurement parameters are shown in **Table S3**. Interaction distances and angles, including those for π-interactions, are shown in **Table S4**. The asymmetric unit consisting of a single Phenibut molecule as well as the crystal packing from axis *a* – *c* is shown in **Figure S4**. (rac)-Phenibut behaves very similar in terms of its packing compared to the Pregabalin enantiomers. Two axes, in the case of Phenibut the *a*- and *c*-axis, are relatively short at below 10 Å considering the large c-axis at 27.505(3) Å. While in Pregabalin the longest axis is 18.504(4) Å the difference is easily explained by the number of molecules in the unit cell, Z. Contrary to enantiomerically pure Pregabalin forms (rac)-Phenibut contains 8 molecules in its unit cell.

Table S3. *Lattice and measurement parameters of (rac)-Phenibut.*

Parameters	(rac)-Phenibut
Formula	C_{10} H_{13} N O_2
M_r [g mol^{-1}]	179.21
Temperature [K]	140(2)
System/space group	Orthorhombic, *Pbca*
a (Å)	9.384(7)
b (Å)	6.978(10)
c (Å)	27.505(3)
β (°)	90
V (Å^3)	1801.4(4)
Z/Z'	8/1
Density [g/cm^3]	1.322
μ [mm^{-1}]	0.092
T_{min}/T_{max}	0.7990/ 1.0000
F (000)	768
Crystal size [mm]	0.06 · 0.10 · 0.60
2θ range [°]	2.63 – 25.17
Completeness [%]	99.8
Recorded refl.	6997
Independent refl.	1609
Goodness-of-fit F^2	1.013
X-Ray Source	Mo Kα (λ = 0.71073)
R_1 [%] /wR_2 [%] /S	4.81/ 11.97/ 1.013

Table S4. *Hydrogen bond and edge-to-face interaction distances and angles in (rac)-Phenibut.*

	D - H (Å)	H…A [Å]	D…A [Å]	D - H…A [°]
HB				
N1-H6…O2	0.95(3)	1.84(3)	2.775(3)	172(3)
N1-H7…O1	1.13(3)	1.64(3)	2.732(3)	160(3)
N1-H8…O2	0.96(4)	1.84(4)	2.795(3)	173(2)
C-H…π		**H…Cg [Å]**	**C…Cg [Å]**	**C-H…Cg [°]**
C8-H11…Cg1		2.85(3)	3.845(3)	170(2)

Contrary to Pregabalin, Phenibut has a further phenyl residue as opposed to Pregabalins isobutyl chain. Therefore, next to the HB interactions, π-interactions can be performed possibly strengthening the overall molecular attractions. The HB-network in (rac)-Phenibut is very similar to that in the Pregabalin entities. Three distinct HB with the different ammonium subunit hydrogens towards the two carboxylate oxygens are formed. HB lengths are nearly non-distinguishable from those in Pregabalin at about 2.7 Å between nitrogen and oxygen atoms. The angles in Phenibut are also very close apart from N1-H7…O1 at 160° slightly further from the "ideal" 180° as compared to all other angles in Phenibut and Pregabalin at about 170°. The edge-to-face π-interaction between C8-H11…Cg1 is the distinctive feature of (rac)-Phenibut

interactions compared to Pregabalin. Electron density- and Hirshfeld surface confirm the discussed intermolecular bonding motif (**Figure S5**). Higher-than-average electron density and close atom proximity can be observed right around the relevant molecular subunits. The additional close range or high electron density spots indicate a closer packing as compared to the Pregabalin enantiomers. In the latter, some close ranges could be observed along the GABA chain that do not contribute to attractive interactions but none along the isobutyl subunit. In Phenibut however, more of these spots can be observed on both surface types which also indicates a closer packing as discussed in regard to the lattice properties.

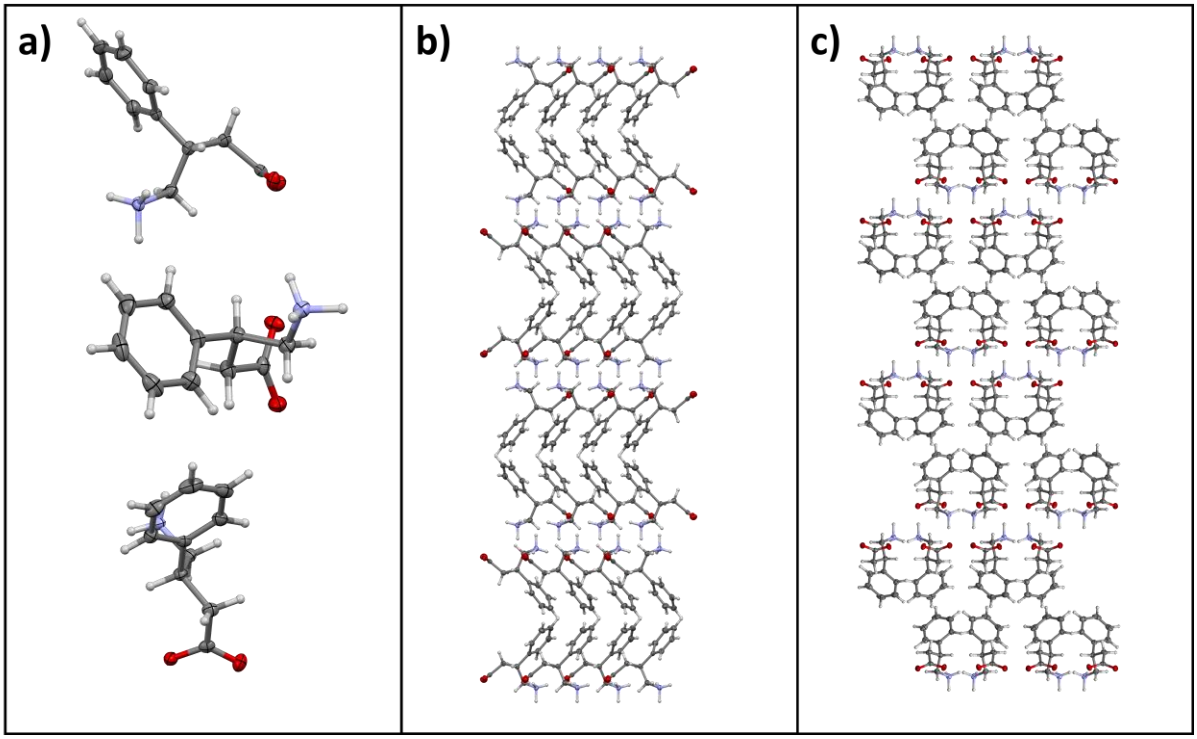

Figure S4. *The asymmetric unit of (rac)-Phenibut is shown in **a)**: from top to bottom a-axis, b-axis, c-axis. In **b)** the packing of a 2 · 2 · 2 unit cell from a-axis view is shown. In **c)** the packing of a 2 · 2 · 2 unit cell from b-axis view is shown. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

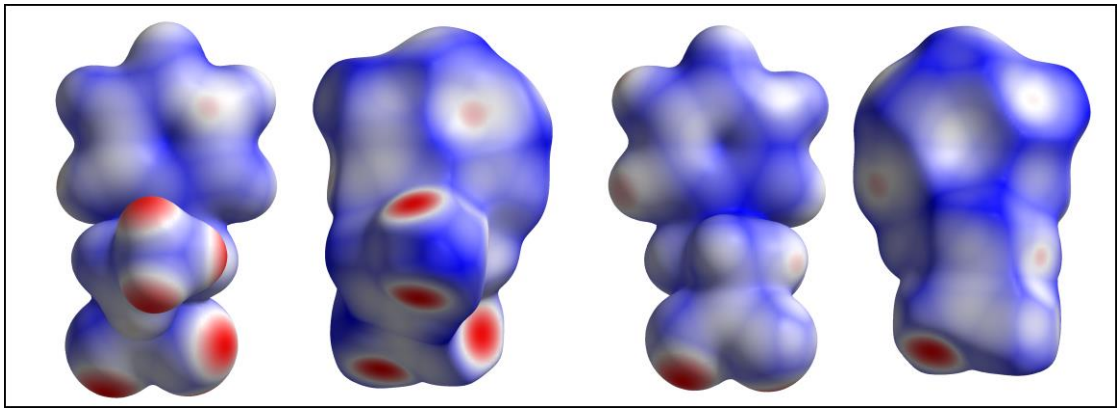

Figure S5. *Electron density and Hirshfeld surfaces of (rac)-Phenibut. **a)** shows the electron density surface of the sole symmetrically inequivalent Phenibut molecule in the (rac)-Phenibut lattice from two sides. **b)** shows the Hirshfeld surface of the same entity.*

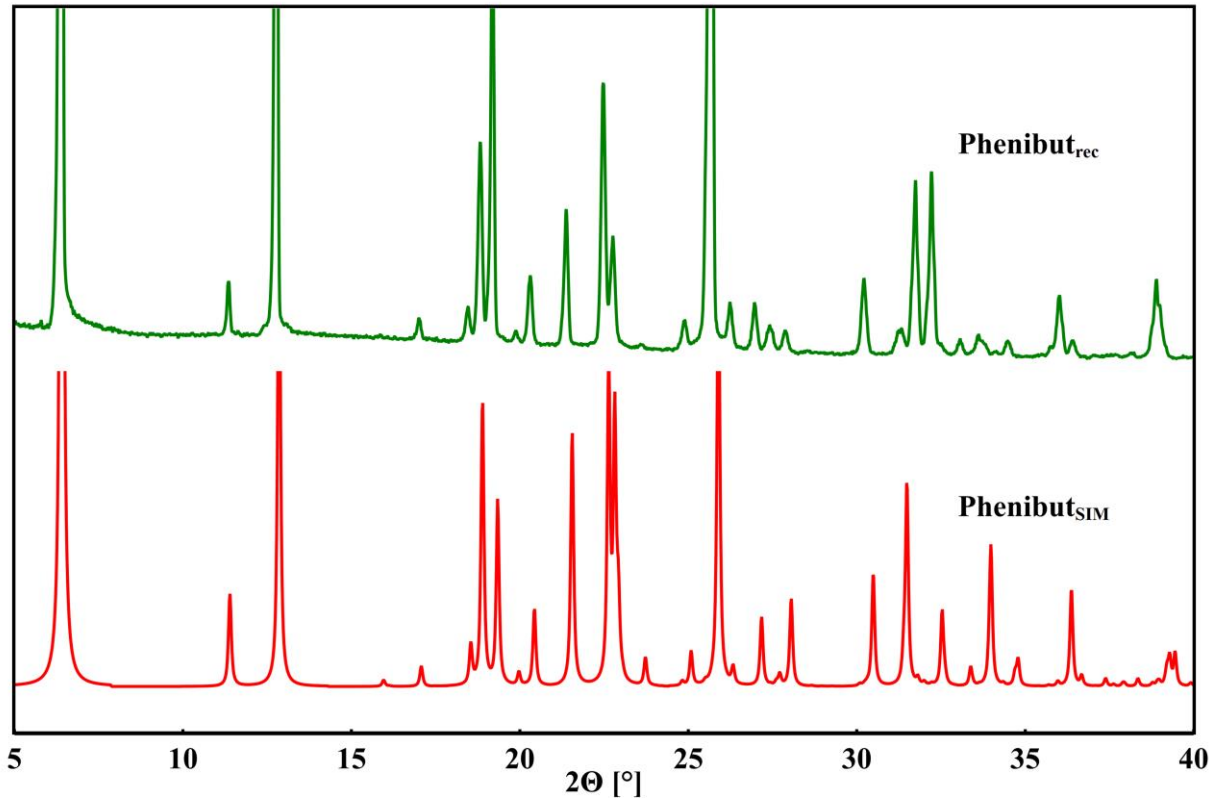

Figure S6. *Powder pattern of (rac)-Phenibut as recorded (red) compared to a simulated pattern by single crystal data (green) in a range of 5° – 40°.*

1.3 Homo- and heterochiral Pregabalin:mandelic acid (1:3), ratio (1:1)

Four Pregabalin:mandelic acid multicomponent systems were obtained. The homochiral (R, R) and (S, S) as well as the heterochiral (R, S) and (S, R) are isostructural. In each case single crystals were obtained by dissolving equimolar amounts of enantiomerically purified Pregabalin and mandelic acid in water and subsequent slow evaporation of the solvent. Thereby, colourless elongated plates were obtained. The lattice and measurement parameters for (R, R) and (S, S) are given in **Table S5** and intermolecular interactions for them are shown in **Table S6** while lattice and measurement parameters for (S, R) and (R, S) are presented in **Table S7** and their intermolecular interactions are depicted in **Table S8**.

The asymmetric unit and packing of homochiral compound **(S, S)-1:3** is shown in **Figure S7**, heterochiral compound **(R, S)-1:3** is depicted in **Figure S8**. The homochiral systems crystallize in the same space group with the same unit cell parameters, as do the heterochiral forms respectively. In homochiral forms, Pregabalin and mandelic acid keep their default protonation status, while in heterochiral forms both molecules become formally charged. Notable is the occurrence of an uncommon packing phenomenon in Z' = 2. Z' is defined as the number of formula units in the unit cell divided by the number of independent general positions and a

value larger than 1 could indicate a non-optimal structure in terms of stability or symmetry, as defined by Steed and Desiraju respectively.[5, 6]

Table S5. *Lattice and measurement parameters of (R, R)- and (S, S)-Pregabalin:mandelic acid systems.*

Parameters	**(R, R)-1:3**	**(S, S)-1:3**
Formula	$C_8\ H_{17}\ N\ O_2$, $C_8\ H_8\ O_3$	$C_8\ H_{17}\ N\ O_2$, $C_8\ H_8\ O_3$
M_r [g mol^{-1}]	311.37	311.37
Temperature [K]	100(2)	100(2)
System/space group	Monoclinic, $P2_1$	Monoclinic, $P2_1$
a (Å)	6.252(7)	6.245(5)
b (Å)	27.384(8)	27.388(0)
c (Å)	9.960(3)	9.962(4)
β (°)	90.483(0)	90.462(2)
V (Å^3)	1705.43(4)	1704.03(5)
Z/Z'	4/2	4/2
Density [g/cm^3]	1.221	1.214
μ [mm^{-1}]	0.738	0.739
T_{min}/T_{max}	0.458/1.000	0.560/1.000
F (000)	672	672
Crystal size [mm]	0.40 · 0.11 · 0.09	0.59 · 0.22 · 0.07
2θ range [°]	3.2 – 77.7	3.2 – 77.8
Completeness [%]	99.9	99.9
Recorded refl.	47481	19149
Independent refl.	6627	6561
Flack x	-0.02(5)	0.15(11)
Goodness-of-fit F^2	1.035	1.084
X-Ray Source	Cu Kα (λ = 1.54184)	Cu Kα (λ = 1.54184)
R_1 [%] /wR_2 [%] /S	2.78/ 6.89/ 1.035	4.58/ 11.86/ 1.084

There are two symmetrically distinct Pregabalin and mandelic acid molecules. HB are the dominating intermolecular attraction force. Twelve distinct HB interactions occur in the (S, S) variant and fourteen in the (R, R) system. The discrepancy in the number of interactions between (S, S)- and (R, R)-Pregabalin:mandelic acid might have two reasons. In (R, R) an additional interaction is added for N1A-H6A…O3C and N1B-H8B…O3D. Both interaction distances are larger than 3 Å in (R, R) and thus may not have been recognized as interactions by PLATON in (S, S). Mercury however, measures distances of 3.003 Å and 3.033 Å for the former and the latter interaction. It should further be noted that the melting points of both systems differ, which could be accounted to by these differences. It is notable that the shortest interactions occur from the non-ionic mandelic acid oxygens O1C and O3D and to Pregabalin carboxylate Oxygen O1A or B. The distances range from 2.487(3) Å - 2.690(3) Å in (S, S) and from 2.489(7) Å - 2.695(2) Å in (R, R). When these distance values are compared to HB formed between two oppositely charged molecular fragments like N1A-H7A…O2B at 2.770(4) Å in (S, S) or the corresponding N1A-H7A…O2B at 2.767(2) Å in (R, R) it is highlighted that assumed charge assistance between two charged sub molecular entities does not result in the

shortest interaction distances in both systems. In the heterochiral (S, R) and (R, S)-forms HB are also the main occurring bonding interaction and the same 14 types are observable in both compounds.

Table S6. *Hydrogen bond distances and angles in (S, S) as well as (R, R) Pregabalin:mandelic acid cosystems. Bold written entities are charged at their oxygen or nitrogen atoms. A and B indices mark the different Pregabalin molecules, C and D the different mandelic acid molecules.*

	D - H [Å]	H…A [Å]	D…A [Å]	D - H…A [°]
(S, S)-1:3				
N1A-H6A…O2C	0.87(4)	1.93(4)	2.787(4)	165(3)
N1A-H7A…**O2B**	0.88(5)	1.89(5)	2.770(4)	175(4)
N1A-H8A…**O1B**	0.88(4)	2.24(4)	3.036(4)	151(4)
N1A-H8A…**O2A**	0.88(4)	2.40(4)	2.940(4)	120(3)
N1B-H6B…**O2A**	1.07(6)	1.72(6)	2.780(4)	171(5)
N1B-H7B…**O1A**	0.90(5)	2.26(4)	3.033(4)	144(4)
N1B-H7B…**O2B**	0.90(5)	2.30(5)	2.906(4)	125(4)
N1B-H8B…O2D	0.86(4)	1.96(4)	2.802(4)	168(4)
O1C-H1C…**O1A**	0.97(8)	1.52(8)	2.487(3)	174(2)
O3C-H2C…**O1B**	0.92(6)	1.80(6)	2.690(3)	161(6)
O1D-H1D…**O1B**	0.93(6)	1.56(6)	2.492(3)	178(9)
O3D-H2D…**O1A**	0.87(6)	1.82(6)	2.682(4)	169(5)
(R, R)-1:3				
N1A-H6A…O2C	0.91(3)	1.88(3)	2.786(2)	171(3)
N1A-H6A…O3C	0.91(3)	2.55(3)	3.006(2)	111(2)
N1A-H7A…**O2B**	0.98(3)	1.79(3)	2.767(2)	171(3)
N1A-H8A…**O1B**	0.87(3)	2.26(3)	3.038(2)	148(3)
N1A-H8A…**O2A**	0.87(3)	2.37(3)	2.934(2)	123(2)
N1B-H6B…**O2A**	0.96(3)	1.83(3)	2.783(2)	176(2)
N1B-H7B…**O1A**	0.91(3)	2.23(3)	3.035(2)	148(3)
N1B-H7B…**O2B**	0.91(3)	2.33(3)	2.906(2)	121(2)
N1B-H8B…O2D	0.88(3)	192(3)	2.798(2)	172(3)
N1B-H8B…O3D	0.88(3)	2.56(3)	3.031(2)	114(2)
O1C-H1C…**O1A**	0.97(4)	1.53(4)	2.489(7)	172(4)
O3C-H3C…**O1B**	0.84(3)	1.88(3)	2.695(2)	166(3)
O1D-H1D…**O1B**	0.92(3)	1.58(3)	2.497(9)	177(3)
O3D-H2D…**O1A**	0.89(4)	1.81(4)	2.682(2)	166(4)

Table S7. *Lattice and measurement parameters of (S, R) and (R, S) Pregabalin:mandelic acid cosystems.*

Parameters	**(S, R)-1:3**	**(R, S)-1:3**
Formula	$C_8\ H_{18}\ N\ O_2$, $C_8\ H_7\ O_3$	$C_8\ H_{18}\ N\ O_2$, $C_8\ H_7\ O_3$
M_r [g mol^{-1}]	311.37	311.37
Temperature [K]	100(2)	100(2)
System/space group	Monoclinic, $P2_1$	Monoclinic, $P2_1$
a (Å)	6.077(1)	6.051(7)
b (Å)	29.926(5)	29.898(9)
c (Å)	9.306(6)	9.306(9)
β (°)	92.662(0)	92.641(0)
V (Å^3)	1690.73(4)	1682.19(4)
Z/Z'	4/2	4/2
Density [g/cm^3]	1.223	1.229
μ [mm^{-1}]	0.745	0.748
T_{min}/T_{max}	0.351/1.000	0.580/ 1.000
F (000)	672	672
Crystal size [mm]	0.54 · 0.38 · 0.15	0.31 · 0.12 · 0.09
2θ range [°]	3.0 – 77.8	3.0 – 77.1
Completeness [%]	100	99.8
Recorded refl.	21324	25468
Independent refl.	6745	6336
Flack x	-0.05(12)	-0.15(7)
Goodness-of-fit F^2	1.050	1.048
X-Ray Source	Cu Kα (λ = 1.54184)	Cu Kα (λ = 1.54184)
R_1 [%] /wR_2 [%] /S	4.97/ 12.05/ 1.05	3.00/ 7.33/ 1.05

Consideration of HB interaction distances shows no especially noticeable deviations from (S, S) and (R, R) systems HB network. The shortest distances occur between carboxyl Pregabalin donors and carboxylate mandelic acid acceptor oxygens at 2.570(3) Å for O1B-H1B…O1D (S, R) and (R, S). This highlights that the shortest contacts occur between a charged and a neutral subunit as is the case in the (S, S) and (R, R) systems. Interactions where both subunits are charged like N1A-H7A…O1D, N1A-H9A…O2D, N1B-H7B…O2C and N1B-H8B…O1C with values around 2.7 – 2.8 Å lie in a median range compared to all shown interactions in **Tables S2**, **S4**, **S6** and **S8**. To further elucidate on the binding interactions, Hirshfeld surfaces and electron density surfaces of homo- and heterochiral systems were calculated (**Figures S9 & S10**). Again, the closest interactions as derived from the Hirshfeld surface occur around the HB interactions sites, where the highest electron density can also be located. In homochiral forms, neither close distances nor electron density accumulations can be observed around the mandelic acid phenyl subunits. However, C7D-H7D in (S, S) and (R, R) mandelic acid phenyl rings are directed towards the phenyl ring centre of gravity of their respective symmetry unrelated mandelic acid molecule C. While this possible interaction is not recognized by PLATON analysis, Mercury measures a distance C7D-H7D…Cg_C of 3.672 Å or

C7D…Cg_C of 4.664 Å for (S, S) and 3.707 Å as well as 4.658 Å in (R, R). This could suggest possible weak edge-to-face C-H…π influences in both systems.

Table S8. *Hydrogen bond distances and angles in (S, R) as well as (R, S) Pregabalin:mandelic acid cosystems. Bold written entities are charged at their oxygen or nitrogen atoms. A and B indices mark the different Pregabalin molecules, C and D the different mandelic acid molecules.*

	D - H [Å]	H…A [Å]	D…A [Å]	D - H…A [°]
(S, R)-1:3				
N1A-H7A…**O1D**	0.85(4)	1.91(4)	2.736(3)	163(4)
N1A-H8A…O1B	0.84(4)	2.45(3)	2.916(3)	116(3)
N1A-H8A…O2A	0.84(4)	2.19(4)	2.876(3)	139(3)
N1A-H9A…**O2D**	0.92(4)	1.92(5)	2.786(3)	158(4)
N1B-H7B…**O2C**	0.94(4)	1.82(4)	2.757(3)	173(4)
N1B-H8B…**O1C**	0.96(6)	1.87(5)	2.812(3)	167(5)
N1B-H9B…O2A	0.91(4)	2.35(4)	3.004(3)	129(3)
N1B-H9B…O3D	0.91(4)	2.44(4)	3.012(3)	121(3)
O1A-H1A…**O1C**	0.89(6)	1.72(6)	2.578(3)	161(5)
O1B-H1B…**O1D**	0.97(5)	1.60(5)	2.570(3)	179(6)
O3C-H2C…O2B	0.77(4)	2.23(4)	2.880(3)	143(4)
O3C-H2C…**O2C**	0.77(4)	2.19(4)	2.645(3)	118(4)
O3D-H2D…O1A	0.84(4)	2.19(4)	2.963(3)	152(4)
O3D-H2D…**O2D**	0.84(4)	2.19(4)	2.645(3)	114(3)
(R, S)-1:3				
N1A-H7A…**O1D**	0.93(3)	1.83(3)	2.734(2)	163(3)
N1A-H8A…O1B	0.87(3)	2.44(2)	2.905(3)	115(2)
N1A-H8A…O2A	0.87(3)	2.19(3)	2.881(2)	136(2)
N1A-H9A…**O2D**	0.94(3)	1.92(3)	2.782(2)	153(3)
N1B-H7B…**O2C**	0.95(3)	1.81(3)	2.758(2)	169(3)
N1B-H8B…**O1C**	0.98(4)	1.84(4)	2.807(2)	166(3)
N1B-H9B…O2A	0.92(3)	2.35(3)	2.993(2)	127(2)
N1B-H9B…O3D	0.92(3)	2.34(3)	3.006(2)	129(2)
O1A-H1A…**O1C**	0.92(4)	1.70(4)	2.588(2)	163(3)
O1B-H1B…**O1D**	0.92(4)	1.66(4)	2.570(2)	174(4)
O3C-H2C…O2B	0.87(4)	2.18(3)	2.881(3)	138(2)
O3C-H2C…**O2C**	0.87(4)	2.10(3)	2.642(2)	120(3)
O3D-H2D…O1A	0.86(3)	2.17(3)	2.958(2)	152(3)
O3D-H2D…**O2D**	0.86(3)	2.16(3)	2.648(2)	115(2)

The heterochiral systems contrast the (S, S) and (R, R) forms, the phenyl subunits are not tilted in a favourable angle to engage into C-H…π interactions with each other. As again no such interaction is identified by PLATON analysis, the measured distances between C_{phenyl}-H and close C_{phenyl} atoms lie between 3.060 Å and 3.204 Å with Mercury software calculations. Centroid distances are not taken into consideration this time as the angles between possible C_{phenyl}-H and close centroids are too unfavourable. While the distances of these possible edge-to-edge interactions seem reasonably short the charge distribution, which is alike on all phenyl rings, makes them unlikely.[7]

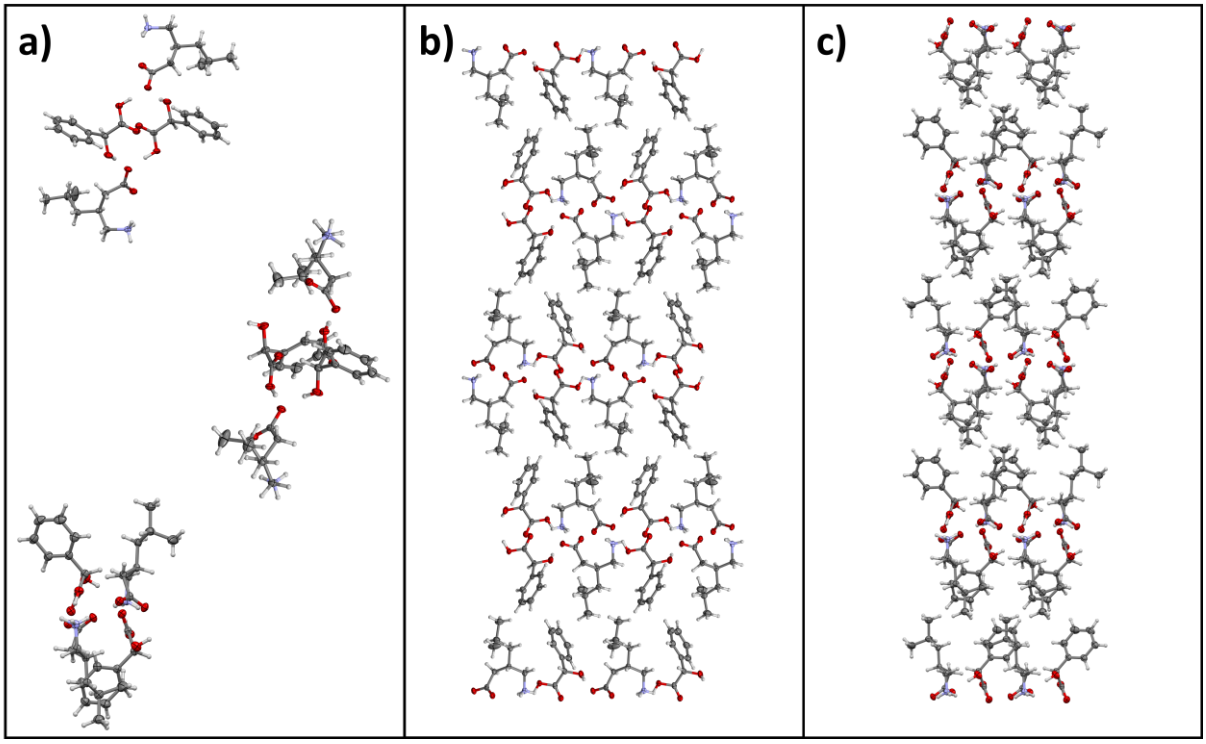

Figure S7. *The asymmetric unit of (S, S)-Pregabalin:mandelic acid species is shown in a): from top to bottom a-axis, b-axis, c-axis. In **b)** the packing of a 2 · 2 · 2 unit cell from a-axis view is shown. In **c)** the packing of a 2 · 2 · 2 unit cell from c-axis view is shown. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

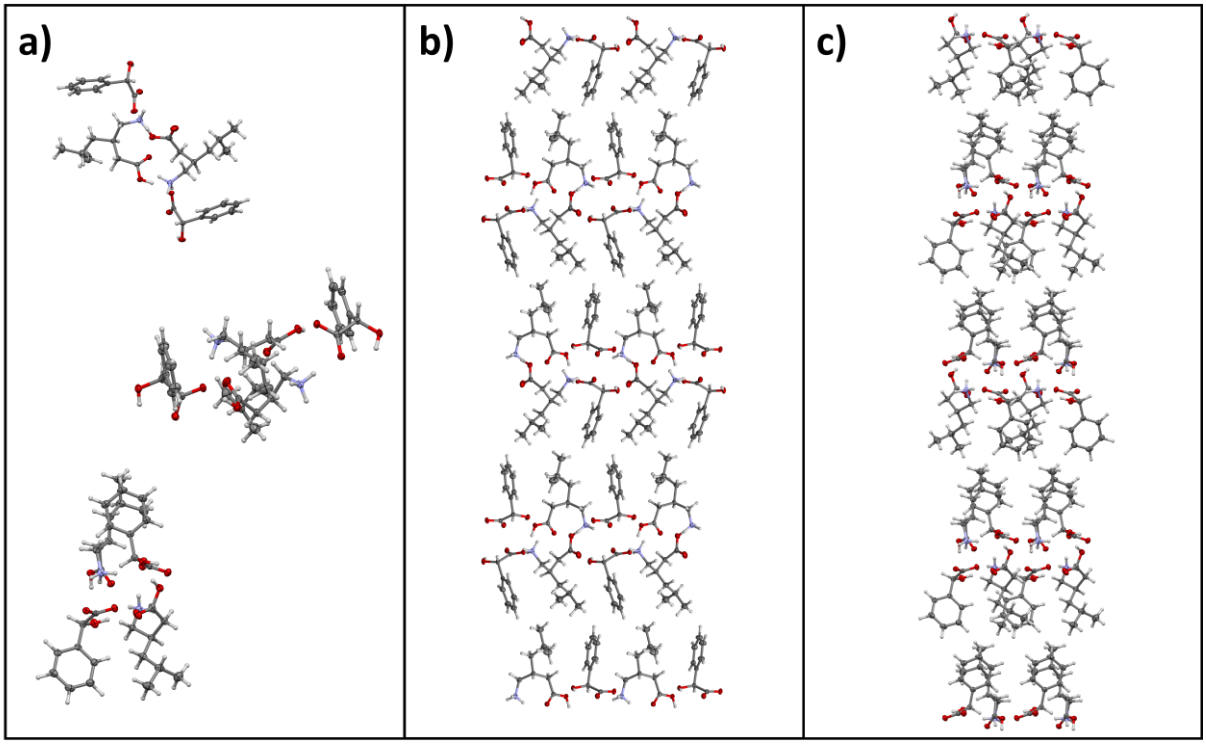

Figure S8. *The asymmetric unit of (R, S)-Pregabalin:mandelic acid species is shown: from top to bottom a-axis, b-axis, c-axis. In **b)** the packing of a 2 · 2 · 2 unit cell from a-axis view is shown. In **c)** the packing of a 2 · 2 · 2 unit cell from c-axis view is shown. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

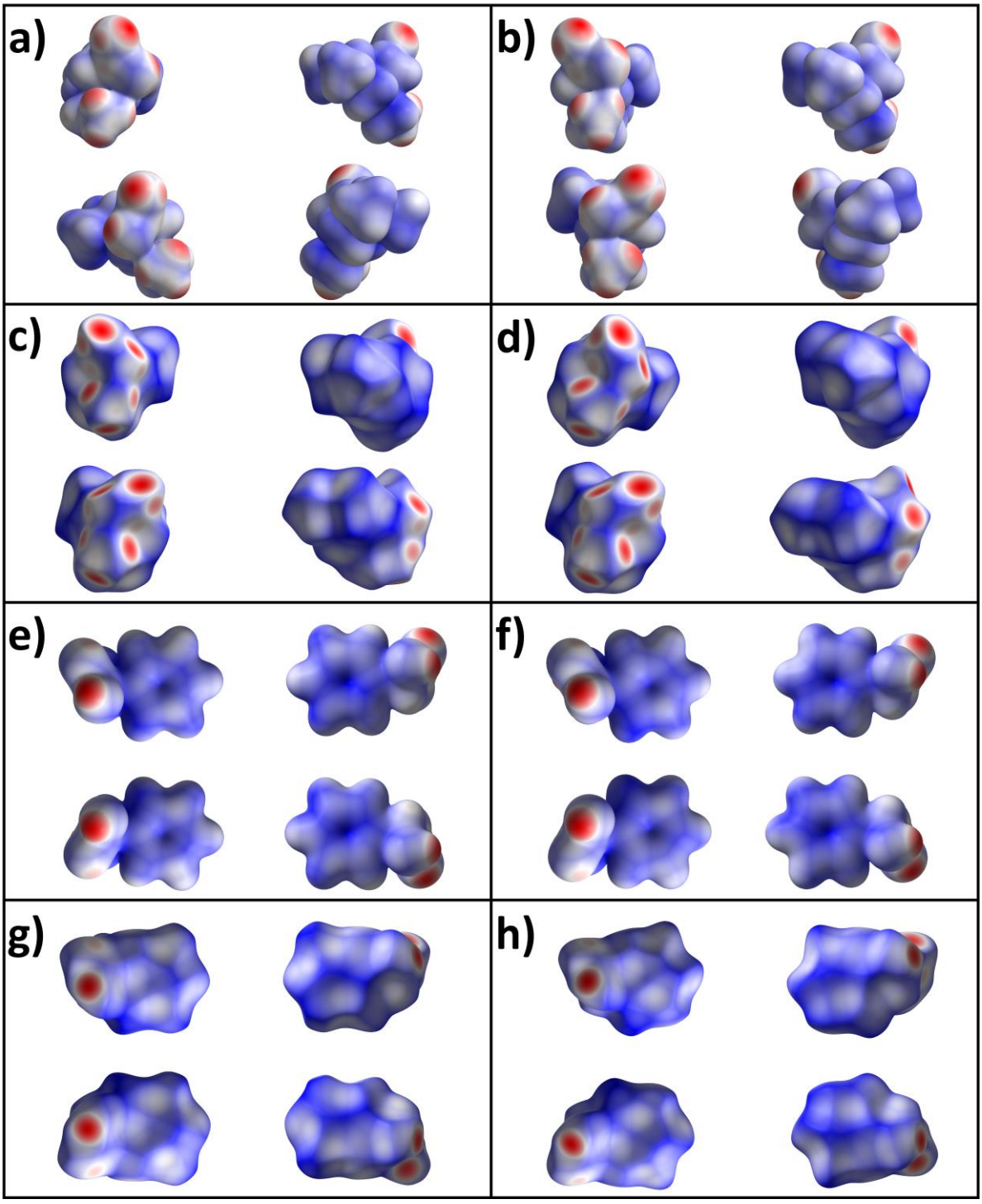

Figure S9. *Electron density and Hirshfeld surfaces of (S, S)- and (R, R) Pregabalin:mandelic acid species.* ***a)*** *and* ***b)*** *show the electron density surface of the two symmetrically inequivalent Pregabalin molecules in the (S, S) and (R, R) lattice respectively, from two sides.* ***c)*** *and* ***d)*** *show the corresponding Hirshfeld surfaces.* ***e)*** *and* ***f)*** *show the electron density surface of the two symmetrically inequivalent mandelic acid molecules in the (S, S) and (R, R) lattice respectively, from two sides.* ***g)*** *and* ***h)*** *show the corresponding Hirshfeld surfaces.*

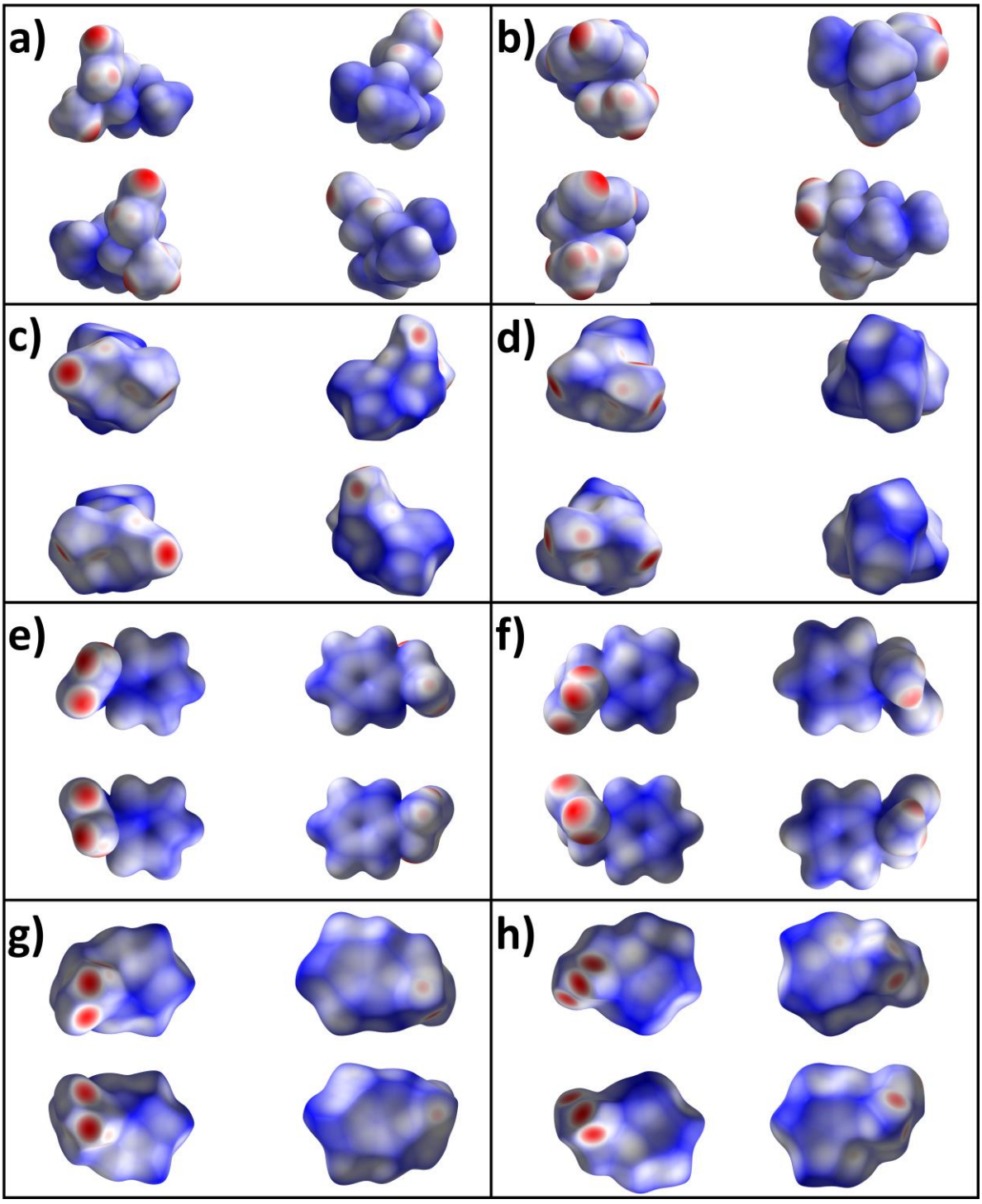

Figure S10. *Electron density and Hirshfeld surfaces of (S, R)- and (R, S) Pregabalin:mandelic acid species.* ***a)*** *and* ***b)*** *show the electron density surface of the two symmetrically inequivalent Pregabalin molecules in the (S, R) and (R, S) lattice respectively, from two sides.* ***c)*** *and* ***d)*** *show the corresponding Hirshfeld surfaces.* ***e)*** *and* ***f)*** *show the electron density surface of the two symmetrically inequivalent mandelic acid molecules in the (S, R) and (R, S) lattice respectively, from two sides.* ***g)*** *and* ***h)*** *show the corresponding Hirshfeld surfaces.*

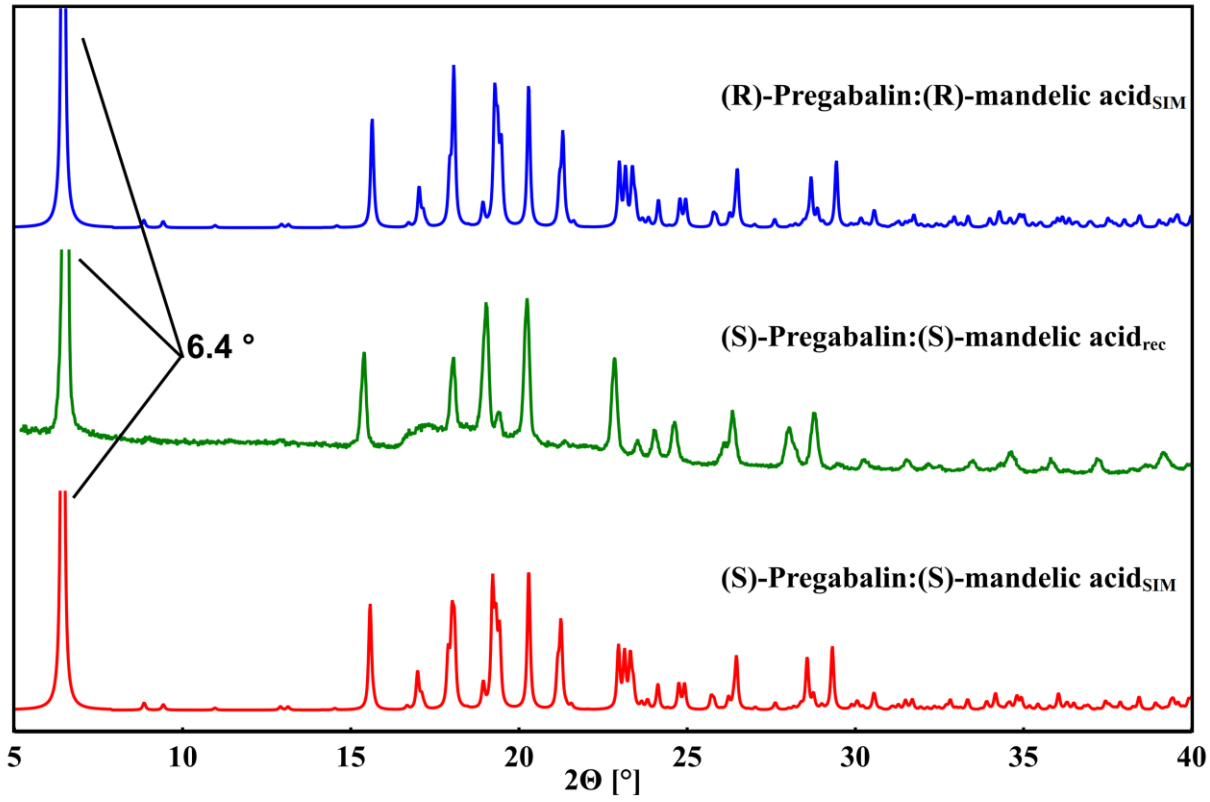

Figure S11. *Powder pattern of (S, S) Pregabalin:mandelic acid as recorded (green) compared to simulated patterns of (S, S) (red) and (R, R) (blue) systems single crystal data in a range of 5° – 40°. Only (S, S)$_{rec}$ is shown for clarity.*

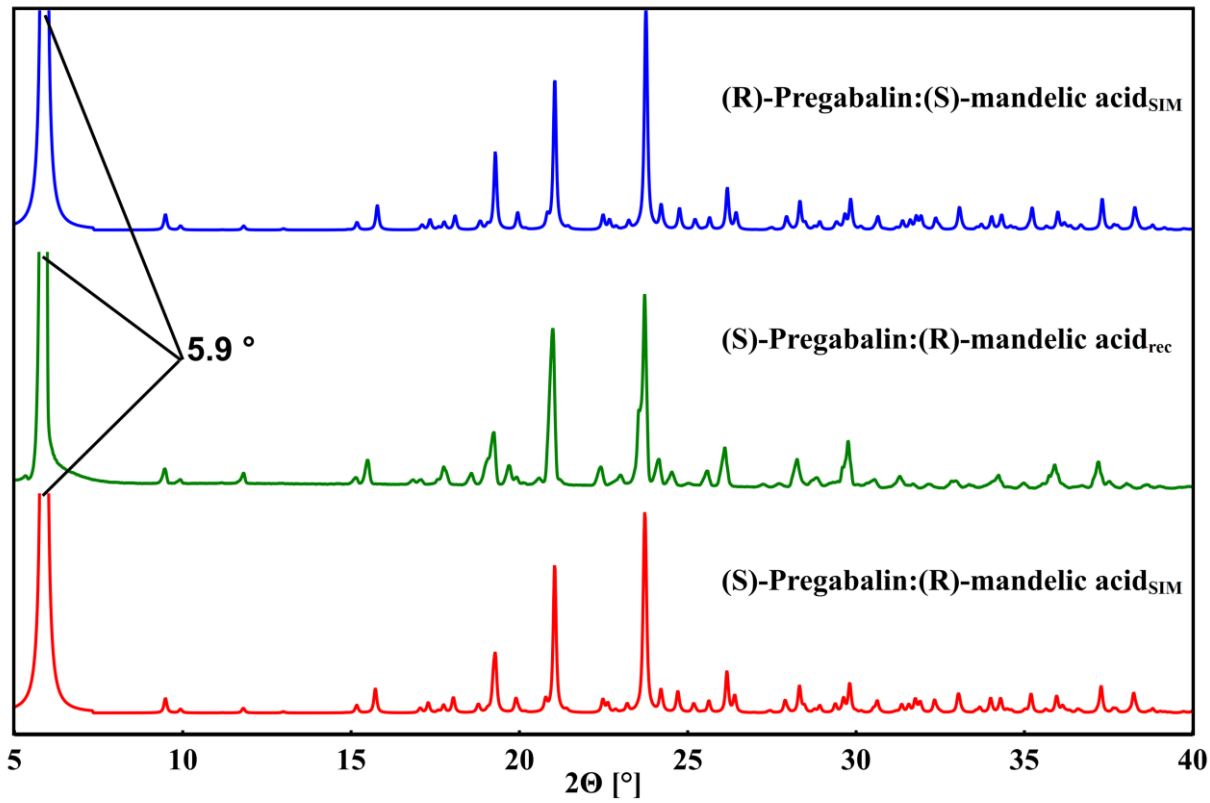

Figure S12. *Powder pattern of (S, R) Pregabalin:mandelic acid as recorded (green) compared to simulated patterns of (S, R) (red) and (R, S) (blue) systems single crystal data in a range of 5° – 40°. Only (S, R)$_{rec}$ is shown for clarity.*

1.4 Phenibut:mandelic acid (2:3), ratio (1:1)

A single crystal of (R)-Phenibut:(S)-mandelic acid was obtained by dissolving equimolar amounts of (rac)-Phenibut and (S)-mandelic acid in aqueous solution. Elongated, diffraction quality crystalline plates were obtained by slow evaporation of the solvent. **Table S9** shows lattice and measurement parameters. Supramolecular interactions involving HB- and π-interactions are shown in **Table S10**.

Table S9. *Lattice and measurement parameters of (R)-Phenibut:(S)-mandelic acid.*

Parameters	**(R, S)-2:3**
Formula	C_{10} H_{13} N O_2, C_8 H_8 O_3
M_r [g mol^{-1}]	331.36
Temperature [K]	100(2)
System/space group	Monoclinic, $P2_1$
a (Å)	10.130(7)
b (Å)	6.353(9)
c (Å)	13.063(3)
β (°)	95.469(2)
V (Å^3)	837.06(2)
Z/Z'	2/1
Density [g/cm^3]	1.315
μ [mm^{-1}]	0.794
T_{min}/T_{max}	0.239/ 1.000
F (000)	352
Crystal size [mm]	0.52 · 0.37 · 0.12
2θ range [°]	3.4 – 77.9
Completeness [%]	99.9
Recorded refl.	19556
Independent refl.	3246
Flack x	0.00(10)
Goodness-of-fit F^2	1.068
X-Ray Source	Cu Kα (λ = 1.54184)
R_1 [%] /wR_2 [%] /S	3.15/ 8.24/ 1.070

Table S10. *Hydrogen bond and edge-to-face interaction distances and angles in (R)-Phenibut:(S)-mandelic acid. Bold written entities are charged at their oxygen or nitrogen atoms. A indices mark Phenibut molecules, B mandelic acid molecules.*

	D - H (Å)	H…A [Å]	D…A [Å]	D - H…A [°]
HB				
N1A-H6A…**O2A**	0.90(3)	2.36(3)	2.929(2)	121(2)
N1A-H6A…**O1A**	0.90(3)	2.21(3)	2.998(3)	146(3)
N1A-H7A…O2B	0.91(3)	1.92(3)	2.808(2)	163(3)
N1A-H7A…O3B	0.91(3)	2.50(3)	3.020(2)	117(2)
N1A-H8A…**O2A**	0.97(3)	1.83(3)	2.801(3)	177(3)
O1B-H1B…**O1A**	0.99(4)	1.52(4)	2.504(2)	175(4)
O3B-H3B…**O1A**	0.95(4)	1.77(3)	2.689(2)	163(3)
C-H…π		**H…Cg [Å]**	**C…Cg [Å]**	**C-H…Cg [°]**
C5B-H5B…Cg1*		2.57(3)	3.354(2)	136(2)
C7A-H10A…Cg2*		2.88(3)	3.582(2)	133(2)
C9A-H12A…Cg1*		2.98(3)	3.657(2)	129(2)

Asymmetric unit and packing are shown in **Figure S13**. The protonation status of Phenibut and mandelic acid stays in its default state, zwitterionic and neutral respectively. However, contrary to **1**:**3** species, a heterochiral species with these characteristics is received. The Phenibut:mandelic acid system could not be accessed as readily as its Pregabalin analogues. PXRD data shows that disregarding the mandelic acid chirality in the crystallization attempt if a multicomponent structure is formed at all, all possible chiral permutations lead to an isostructural form (**Figure S15**). The number of HB with 7 distinct types is halved compared to Pregabalin:mandelic acid systems. The shortest interaction distance derives from the carboxyl mandelic acid donor to the carboxylate Phenibut acceptor in the O1B-H1B…O1A interaction with 2.504(2) Å. In this case the corresponding angle at 175(4)° is also close to 180°. It can be noted that this HB is not between two subunits of opposing charges but rather between a charged and a neutral subunit. Interactions formed with the positively charged ammonium subunit lead to median ranged distances of about 2.8 Å – 3 Å which includes charged-charged HB. Furthermore, the angles exhibited for HB in this structure show a distribution of values close to 180°. In contrast to other multicomponent species, strong evidence for π-interactions is shown in the lattice. While each Phenibut phenyl Cg1 is in interaction twice being connected to another Phenibut phenyl and additionally a mandelic acid phenyl Cg2, the latter solely interacts once with Phenibut. The C5B-H5B…Cg1 edge-to-face interaction is also the shortest in H…Cg as well as C…Cg distance at 2.57(3) Å and 3.354(2) Å respectively, between all described compounds. Clear evidence for edge-to-face interactions is visible upon examination of Hirshfeld and electron density surface (**Figure S14**). In the former, close contacts occur around Phenibut and Mandelic Acid phenyl subunits and in the latter, higher electron density can be observed on the same spots.

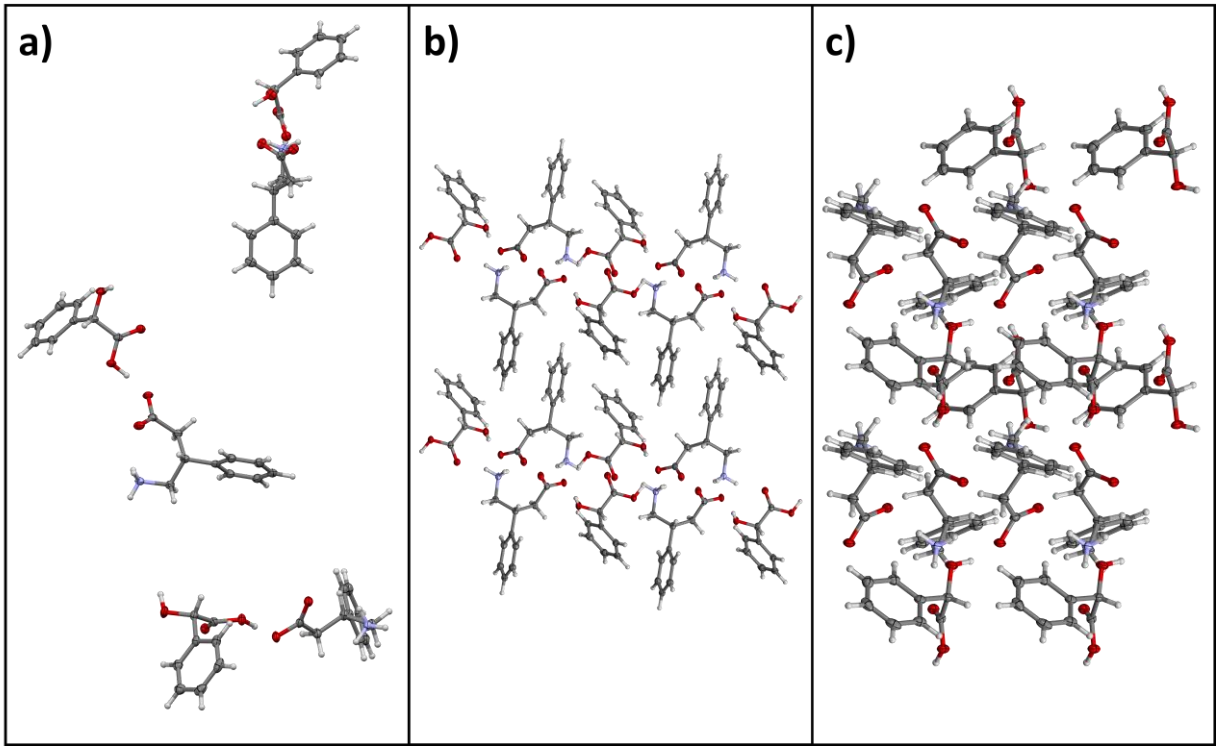

Figure S13. *The asymmetric unit of (R)-Phenibut:(S)-mandelic acid is shown in **a)**: from top to bottom a-axis, b-axis, c-axis. In **b)** the packing of a 2 · 2 · 2 unit cell from b-axis view is shown. In **c)** the packing of a 2 · 2 · 2 unit cell from c-axis view is shown. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

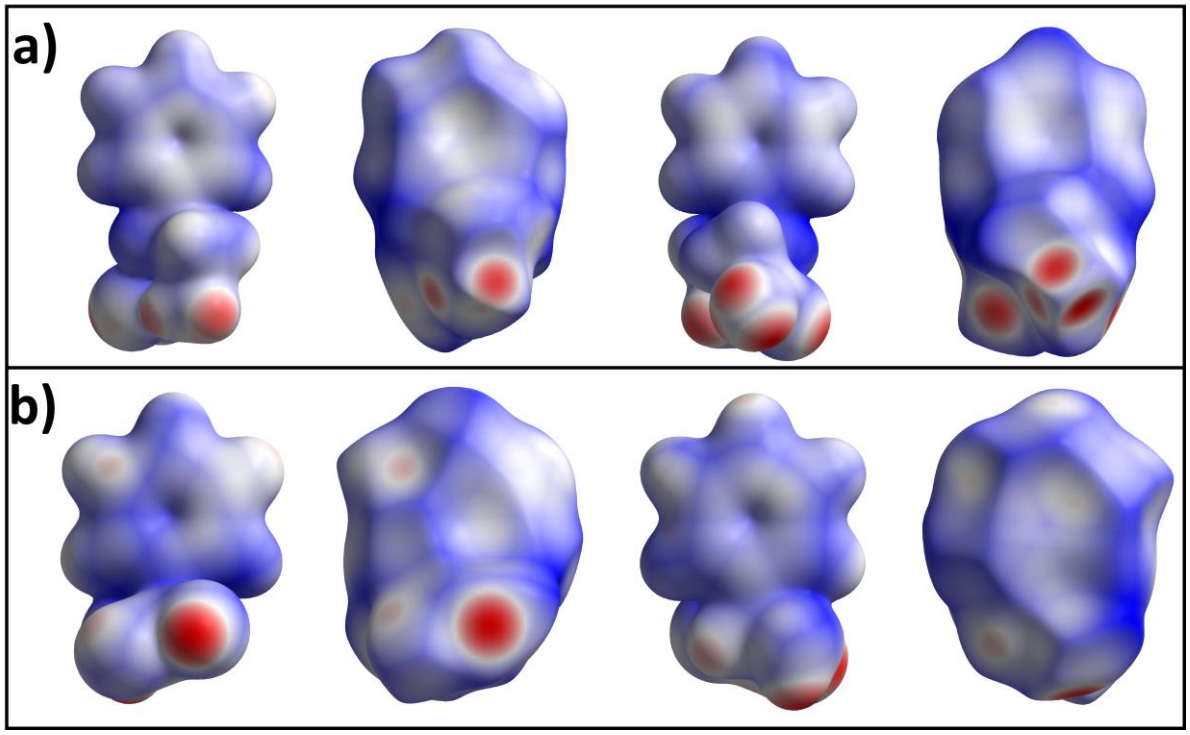

Figure S14. *Electron density and Hirshfeld surfaces of (R)-Phenibut:(S)-mandelic acid. **a)** shows the electron density and Hirshfeld surface of the sole symmetrically inequivalent Phenibut molecule in the lattice from two sides. **b)** shows the electron density and Hirshfeld surface of the sole symmetrically inequivalent mandelic acid molecule in the lattice from two sides.*

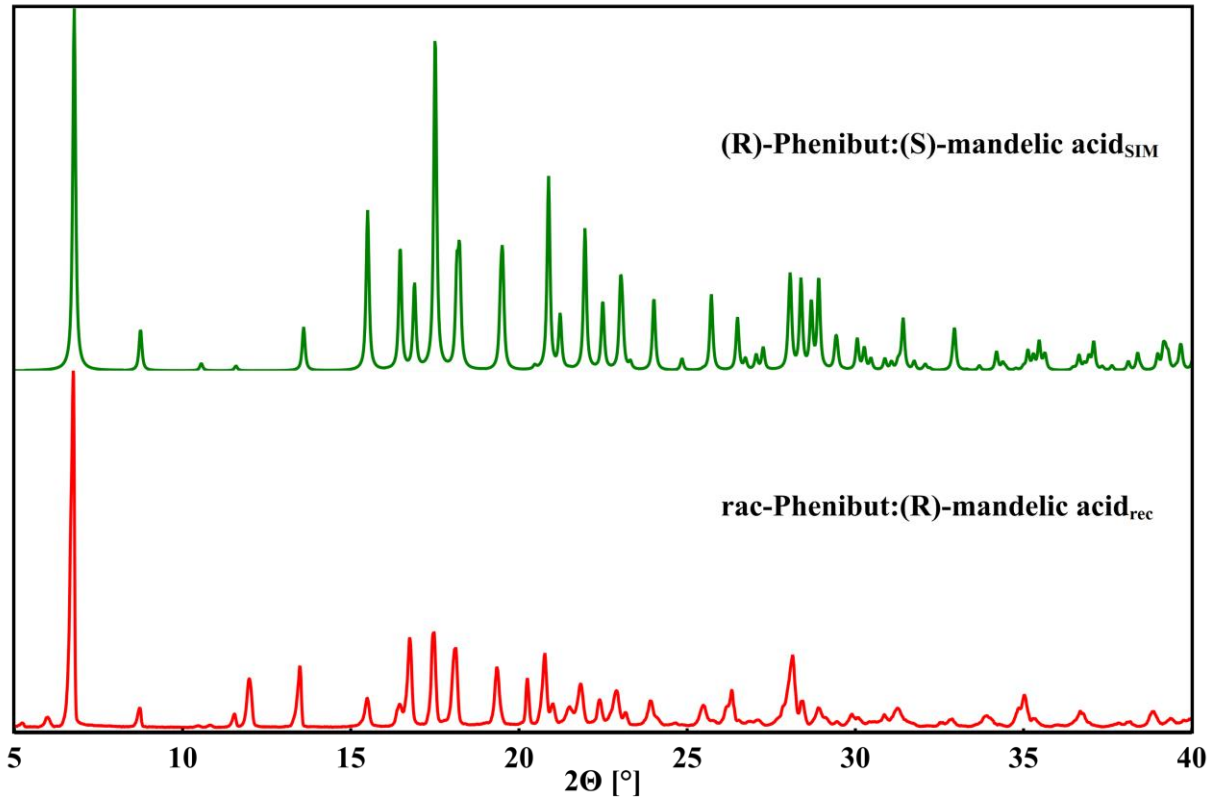

Figure S15. *Powder pattern of (R)-Phenibut:(S)-mandelic acid simulated from single crystal data (green) compared to a recorded pattern of a (rac)-Phenibut:(R)-mandelic acid co-crystallization attempt (red) in a range of 5° – 40°. The comparison to a pattern received by an attempted crystallization with (R)-mandelic acid to the simulated pattern with (S)-mandelic acid while (rac)-Phenibut was used in both cases highlights isostructural crystallization. The presence of less intense Phenibut and mandelic acid signals at low angles shows the problematic crystallization of the multicomponent system. The multicomponent system seems to be not favourable and cannot always be obtained.*

1.5 Homo- and heterochiral Pregabalin:malic acid (1:4), ratio (1:1)

Single crystals of (S)-Pregabalin and (R)- as well as (S)-malic acid were grown from aqueous solution. Diffraction quality, plate shaped crystals were obtained by slow evaporation of the solvent. During the conducted experiments the Pregabalin:malic acid entities exhibited a similarly problematic crystallization behaviour as the Phenibut:mandelic acid system. While the latter could sometimes not be obtained and always showed impurities of its precursors in the powder pattern, the former can take weeks or even months to crystallize. Lattice and measurement parameters for (S, S) and (S, R)-Pregabalin:malic acid systems are shown in **Table S11**, HB properties are shown in **Table S12**.

The asymmetric unit shows one symmetry independent and charged Pregabalin and malic acid molecule in both homo- and heterochiral **1**:**4** (**Figure S16**). Pregabalin units are intertwined with malic acid in closely HB-connected rows, with the alkylic residues of Pregabalin being shifted towards each other and away from the HB interacting subunits. There are 8 distinct HB present in each compound. The shortest interaction in the presented

structures is between two malic acid molecules, connected via carboxyl donor to a carboxylate of an identical molecule via O1B-H1B…O5B in (S, S) and O1B-H1B…O4B in (S, R) at 2.446(4) Å and 2.475(2) Å respectively. Furthermore, as is the case in heterochiral Pregabalin:mandelic acid, uncharged HB interactions are present in both discussed entities even though all participating molecules are formally charged. The comparison between (S, S) and (S, R) reveals differences in the interaction motif that are larger than those present in homochiral Pregabalin:mandelic acid forms and more akin to differences between homo- and heterochiral Pregabalin:mandelic acid.

Table S11. *Lattice and measurement parameters of (S, S) and (S, R) Pregabalin:malic acid co-systems.*

Parameters	**(S, S)-1:4**	**(S, R)-1:4**
Formula	$C_8\ H_{18}\ N\ O_2$, $C_4\ H_5\ O_5$	$C_8\ H_{18}\ N\ O_2$, $C_4\ H_5\ O_5$
M_r [g mol^{-1}]	293.31	293.31
Temperature [K]	100(2)	100(2)
System/space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$
a (Å)	7.500(9)	7.440(4)
b (Å)	7.558(1)	7.703(9)
c (Å)	26.180(5)	25.956(6)
β (°)	90	90
V (Å^3)	1484.24(3)	1487.83(3)
Z/Z'	4/1	4/1
Density [g/cm^3]	1.313	1.309
μ [mm^{-1}]	0.915	0.913
T_{min}/T_{max}	0.535/1.000	0.500/1.000
F (000)	632	632
Crystal size [mm]	0.26 · 0.22 · 0.05	0.36 · 0.16 · 0.08
2θ range [°]	3.4 – 77.7	6.0 – 77.8
Completeness [%]	99.4	99.6
Recorded refl.	8059	22743
Independent refl.	2826	3009
Flack x	0.01(6)	0.01(5)
Goodness-of-fit F^2	1.053	1.109
X-Ray Source	Cu Kα (λ = 1.54184)	Cu Kα (λ = 1.54184)
R_1 [%] /wR_2 [%] /S	2.49/ 5.94/ 1.05	3.01/ 7.78/ 1.11

Table S12. *Hydrogen bond distances and angles in (S, S) and (S, R) Pregabalin:malic acid cosystems. Bold written entities are charged at their oxygen or nitrogen atoms. A indices mark Pregabalin molecules, B malic acid molecules.*

	D - H (Å)	H…A [Å]	D…A [Å]	D - H…A [°]
(S, S)-1:4				
N1A-H7A…O3B	0.90(2)	2.46(3)	3.065(2)	125(2)
N1A-H7A…**O4B**	0.90(2)	1.94(2)	2.792(6)	157(2)
N1A-H8A…O3B	0.93(2)	2.11(2)	2.976(1)	155(2)
N1A-H9A…**O4B**	0.93(2)	1.87(2)	2.761(0)	161(2)
O1A-H1A…O2B	0.90(4)	1.85(4)	2.733(4)	168(3)
O1B-H1B…**O5B**	1.07(4)	1.39(4)	2.446(4)	172(3)
O1B-H1B…**O4B**	1.07(4)	2.59(3)	3.154(3)	112(2)
O3B-H5B…O2A	0.81(3)	1.88(3)	2.688(9)	175(3)
(S, R)-1:4				
N1A-H7A…O2B	0.86(3)	2.15(3)	2.880(2)	142(3)
N1A-H7A…O3B	0.86(3)	2.52(3)	3.103(2)	127(3)
N1A-H8A…O3B	0.93(3)	1.94(3)	2.850(2)	166(3)
N1A-H9A…**O4B**	0.87(3)	2.09(3)	2.920(2)	161(3)
N1A-H9A…**O4B**	0.87(3)	2.33(3)	2.854(2)	119(2)
O1A-H1A…**O5B**	0.97(4)	1.64(4)	2.609(2)	174(4)
O1B-H1B…**O4B**	0.90(4)	1.58(4)	2.475(2)	175(3)
O3B-H5B…O2A	0.85(4)	1.86(4)	2.693(2)	166(4)

A Hirshfeld and electron density surface analysis was conducted (**Figure S17**). Close contacts and electron density maxima occur around the HB interaction sites. The close packing of the Pregabalin:malic acid systems leads to closer contacts around alkylic Pregabalin residues, which can be derived from both surface types. However, actual binding interactions with C_{alkyl}-H are highly unlikely. The high connectivity stemming from the large sum of possible HB donors and acceptors leads to close distances for large parts of both molecules which results in these short contacts.

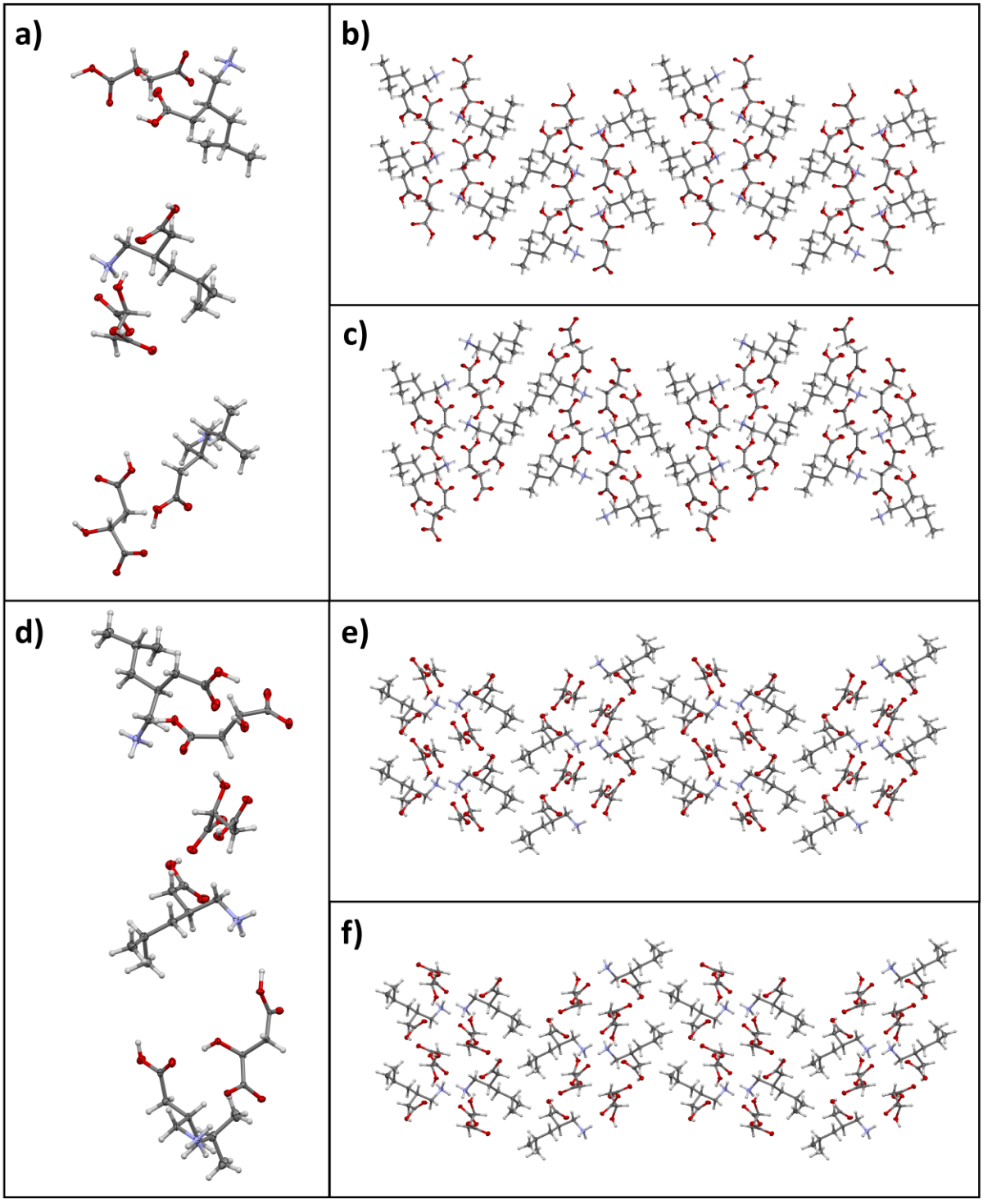

Figure S16. *The asymmetric unit of (S, S)-Pregabalin:malic acid is shown in **a)**: top to bottom a-axis, b-axis, c-axis. In e) the same for (S, R)-Pregabalin:malic acid is presented. In **b)** and **e)** the packing of a 2 · 2 · 2 unit cell from a-axis view is shown, for (S, S) and (S, R) respectively. In **c)** and f) the packing of a 2 · 2 · 2 unit cell from b-axis view is shown, for (S, S) and (S, R) respectively. Carbon atoms are depicted in grey, hydrogen atoms in white, nitrogen atoms in blue and oxygen atoms in red.*

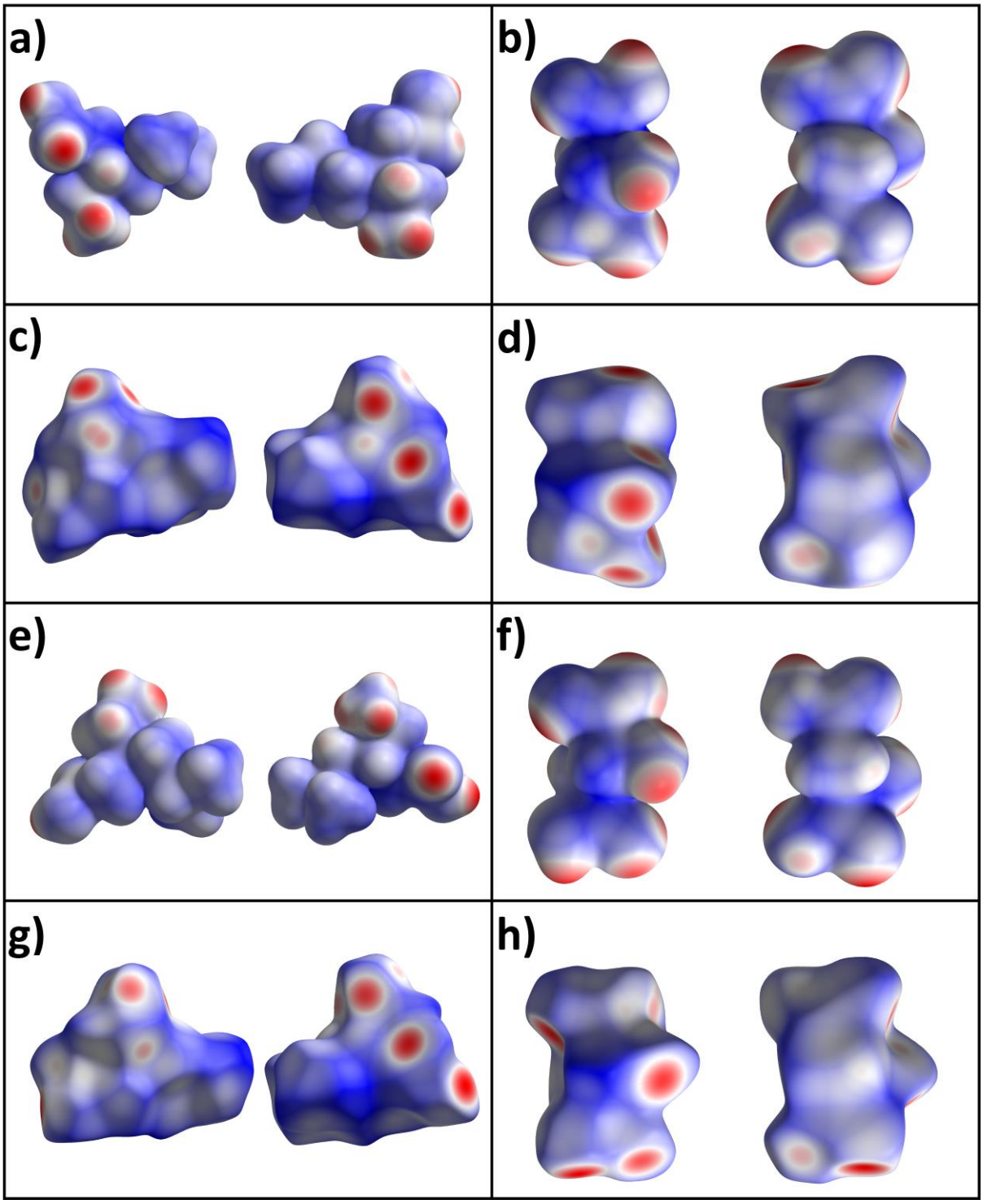

Figure S17. *Electron density and Hirshfeld surfaces of (S, S)- and (S, R) Pregabalin:malic acid species.* ***a)*** *and* ***b)*** *show the electron density surface of the Pregabalin and malic acid molecules in (S, S) from two sides.* ***c)*** *and* ***d)*** *show the corresponding Hirshfeld surfaces.* ***e)*** *and* ***f)*** *show the electron density surface of Pregabalin and malic acid molecules in the (S, R) from two sides.* ***g)*** *and* ***h)*** *show the corresponding Hirshfeld surfaces.*

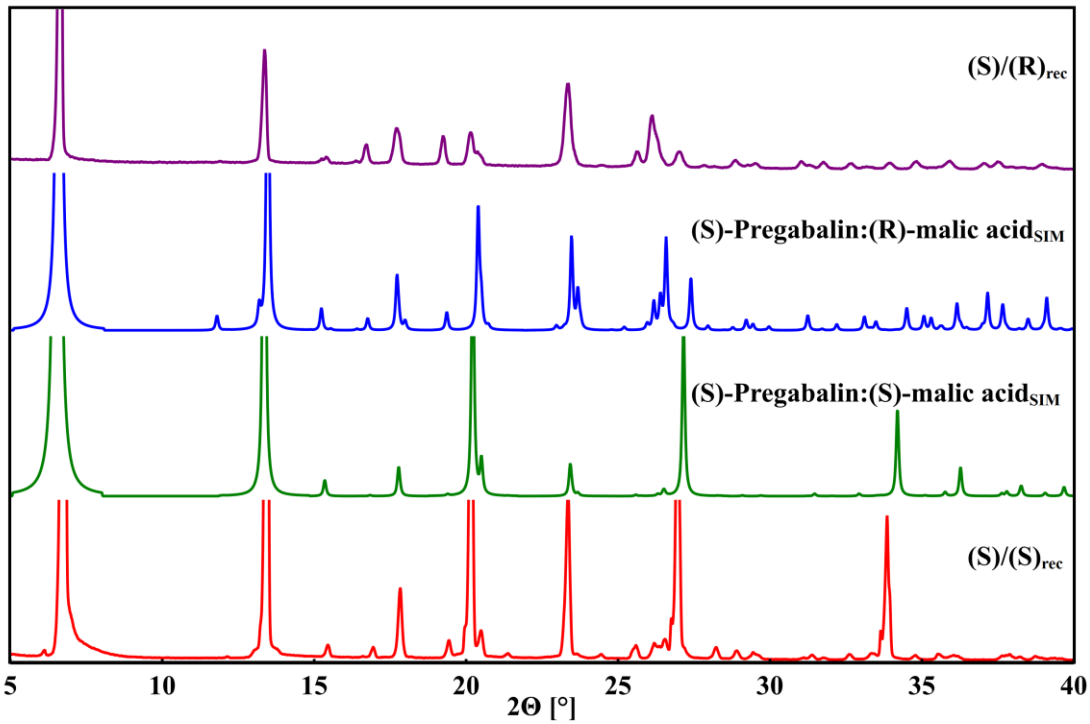

Figure S18. *Powder pattern of (S)-Pregabalin:(S)-malic acid (red) and (S)-Pregabalin:(R)-malic acid (purple) as recorded compared simulated from single crystal data of (S)-Pregabalin:(S)-malic acid (green) and (S)-Pregabalin:(R)-malic acid (blue) in a range of 5° – 40°.*

2 Physical properties

2.1 Determination of melting points with differential scanning calorimetry

Table S13 shows all melting points that could be determined via DSC.

Table S13. *Melting points of all examined substances as determined by DSC.*

Substance name	Melting point [°C]
(S)-Pregabalin	185
(R)-Pregabalin	187
(rac)-Phenibut*	-
(S)-mandelic acid	133
(R)-mandelic acid	133
(S)-malic acid	106
(R)-malic acid	106
(S)-Pregabalin:(S)-mandelic acid	138
(R)-Pregabalin:(R)-mandelic acid	132
(S)-Pregabalin:(R)-mandelic acid	111
(R)-Pregabalin:(S)-mandelic acid	105
(S)-Pregabalin:(S)-malic acid	85
(S)-Pregabalin:(R)-malic acid	95
(R)-Phenibut:(S)-mandelic acid	150

** = (rac)-Phenibut decomposes prior to melting at about 200 °C, as such no melting point could be determined.*

Corresponding DSC-curves are shown in **Figures S19** – **S21**.

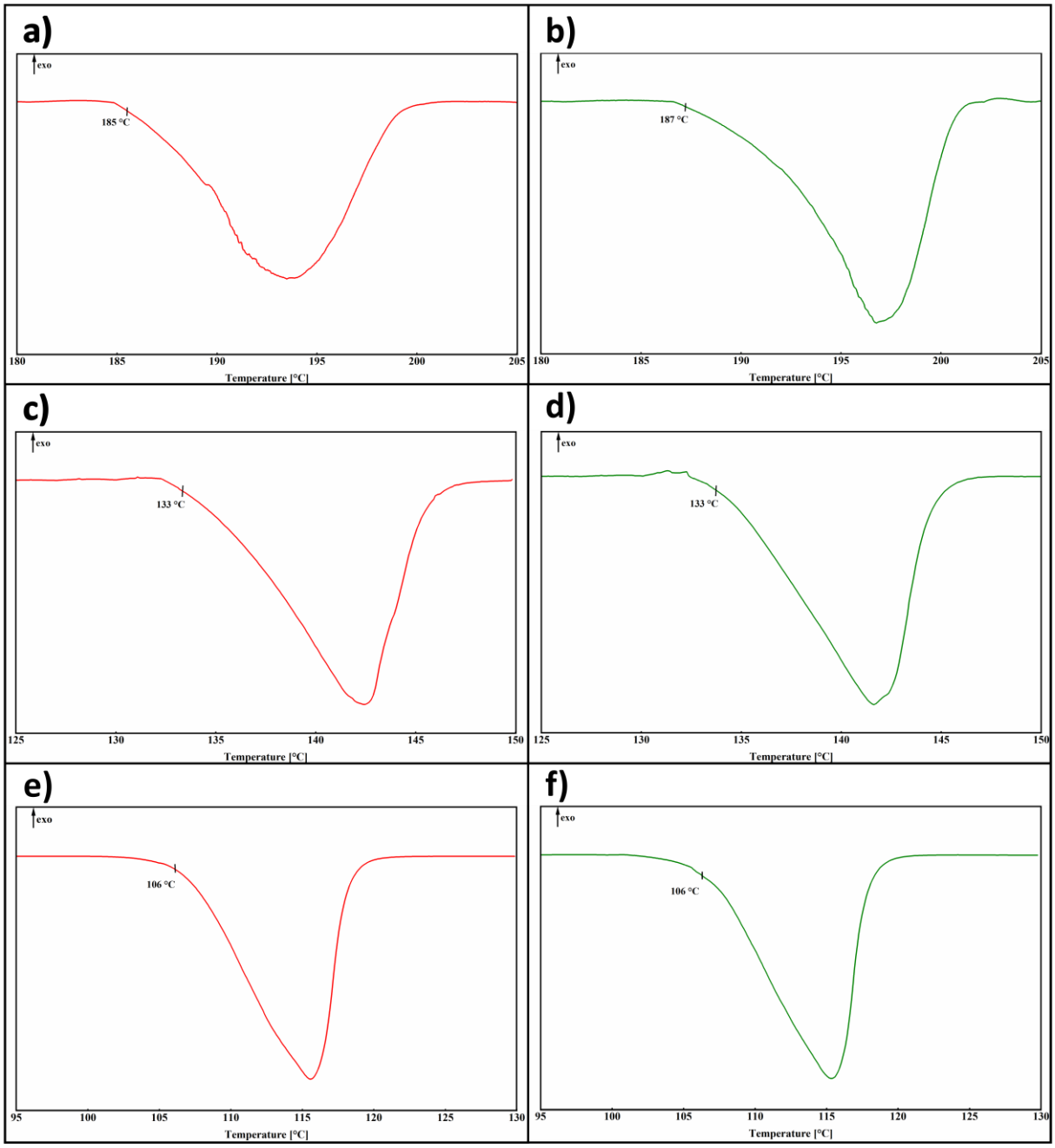

Figure S19. *Differential Scanning Calorimetry of* ***a)*** *(S)-Pregabalin* ***b)*** *(R)-Pregabalin* ***c)*** *(S)-mandelic acid,* ***d)*** *(R)-mandelic acid,* ***e)*** *(S)-malic acid and* ***f)*** *(R)-malic acid. The samples were heated with 5 °C/min, specific ranges including the measured melting signal are depicted. Background has been subtracted.*

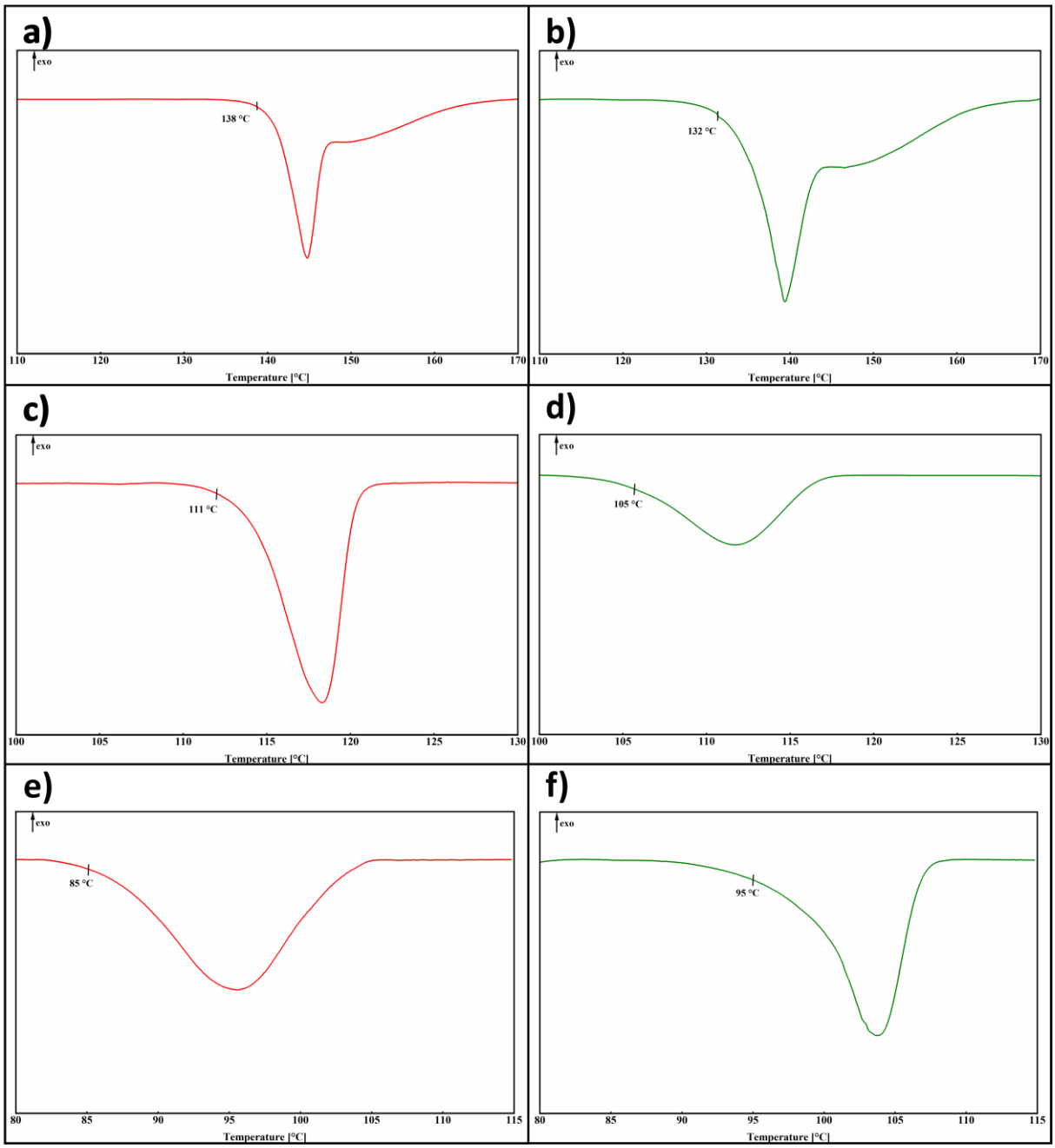

Figure S20. *Differential Scanning Calorimetry of **a)** (S, S)-Pregabalin:mandelic acid **b)** (R, R)-Pregabalin:mandelic acid **c)** (S, R)-Pregabalin:mandelic acid, **d)** (R, S)-Pregabalin:mandelic acid, **e)** (S, S)-Pregabalin:malic acid and **f)** (S, R)-Pregabalin:malic acid. The samples were heated with 5 °C/min, specific ranges including the measured melting signal are depicted. Background has been subtracted.*

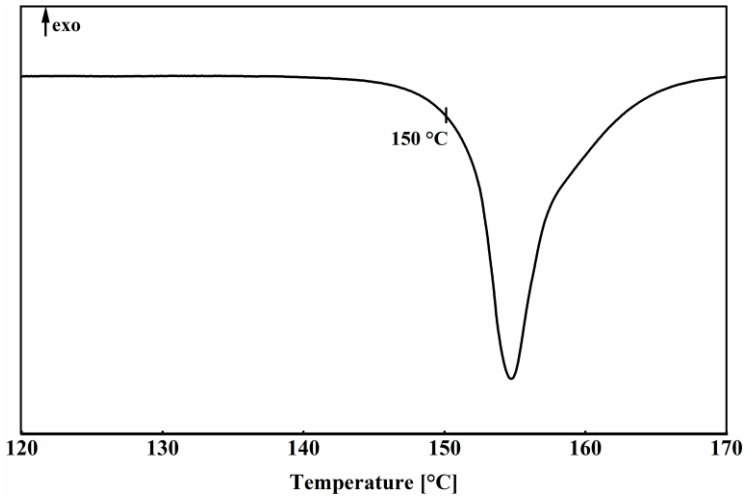

Figure S21. *Differential Scanning Calorimetry of (R)-Phenibut:(S)-mandelic acid. The sample was heated with 5 °C/min, the range from 120 °C – 170 °C is depicted. Melting starts at 150 °C. Background has been subtracted.*

2.2 Determination of solubility with ^{1}H-NMR-spectroscopy

Solubilities of the discussed compounds were determined by ^{1}H-NMR. Powdery samples of each system were layered with phosphate buffer at pH 6.8 in such a way that the solid did not dissolve completely after multiple days. The dispersion was left in an incubator at 37 °C and shaken at 60 min^{-1}. After 1, 2 and in some cases 3 and 4 days 50 µL of solution were taken from the sample and added to 450 µL of D_2O. ^{1}H-NMR was measured from these samples. The processes were repeated twice for each system. Solubility was determined by comparing the integrals of water to that of the investigated substance. For this, a prevalent signal was integrated and the corresponding value of the water signal was taken from the spectrum. The following **Equation 1** was used to determine the solubility in gL^{-1}.

$$S_p = \left(\frac{M_p}{\frac{I_w}{2} M_w} \rho_w \right) \qquad (1)$$

Where S_p is the products solubility in the buffer at pH 6.8 and 37 °C in gL^{-1}, M_p is the molar mass of the investigated substance in gmol^{-1}, I_w is the value of the water integral taken from the ^{1}H-NMR spectrum, M_w the molar mass of water and ρ_w the density of water at 37 °C of 993.33 gL^{-1}. The used model does not consider trace impurities of water in the D_2O as well as the error of the micropipette. For each system 4 values were calculated based on 2 spectra recorded after 1 and 2 days or 3 and 4 days, based on when stability of the received values was reached. The average of these values is given as the final solubility. A standard deviation on these 4 values was calculated by **Equation 2**.

$$V = \sqrt{\frac{\sum(x - \bar{x})^2}{(n-1)}} \qquad (2)$$

With V as the standard deviation, x the average of the 4 values, $\bar{x}$ the singular values and n the number of all values, four. **Table S14** shows solubilities and their standard deviations as well as the borders set for the integral of the Pregabalin or Phenibut signal. The water signal was always integrated between 4.830 and 4.750 ppm. A ^{1}H-NMR spectrum for each compound is shown in **Chapter 5**.

Table S14. *Solubilities and their standard deviations for the examined compounds and integral borders set for the ^{1}H-NMR signal integrals of the investigated substance in the spectra.*

Substance name	Solubility/Standard deviation [gL^{-1}]	Integral borders [ppm]
(S)-1	35 ±0.4	0.865/0.870 – 0.910
(R)-1	33 ±0.3	0.865 – 0.915
(rac)-2*[1]	18 ±1	2.520 – 2.665
(S)/(R)-3	203 ±3	7.370 – 7.500
(S)/(R)-4	2061 ±76	2.760 – 2.900
(S, S)-1:3	37 ±1	0.865/0.870 – 0.910/0.915
(R, R)-1:3	40 ±4	0.865 – 0.915
(S, R)-1:3	316 ±18	0.850/0.860/0.890 – 0.910/0.920/0.950
(R, S)-1:3	307 ±6	0.855/0.860 – 0.905/0.910
(S, S)-1:4*[2]	>800	0.825/0.845 – 0.890/0.910
(S, R)-1:4*[2]	>800	0.835/0.845/0.850 – 0.900/0.910/0.915
(R, S)-2:3	71 ±3	2.650 – 2.800

[1]= solubility equilibrium was reached after 3 and 4 days respectively. [2] = a maximum solubility could not be determined. Complete dissolution of the substance always occurred. At higher concentrations a highly viscous substance was received with which reliable measurement was impossible.

3 Lattice energies

3.1 Model description and verification

To calculate lattice energies, an adapted method based on Marchese Robinson et al.[8] and Voronin et al.[9] was used. Step by step, the following actions were performed:

- Recording of crystal structure in .cif format and subsequent conversion to QE readable .qein input format.
- Self-consistent field (SCF) calculations were performed on the files for (S)-Pregabalin, (rac)-Phenibut, (R, R)/(R, S)-Pregabalin:mandelic acid, (S, S)-Pregabalin:malic acid and (R, S)-Phenibut:mandelic acid to determine a uniform energy convergence threshold (*ecutrho*) and force convergence threshold (*ecutwfc*) (**Table S15**).
- K-points were set to form a grid of about 20 - 25 Å^{3} around the first Brillouin zone for each compound, see **Table S15**.
- Geometric optimization using the '*variable cell relax*' (*vc-relax*) command in QE of the examined structures as well as some literature known validation examples was

performed with the determined threshold and K-point grids to receive the ideal static solid energy E_{iss}.

- Geometry parameters for each singular geometrically independent molecule in each structure were gathered from the previously received outputs. For each of these molecules, a further optimization was performed in a fixed 20 $Å^3$ otherwise empty cell with the '*relax*' command in QE to calculate the energy of the ideal static gas for this molecule, E_{isg}.
- **Equation 3**, **5** or **6** were then used to calculate the lattice energy E_{lat} from the received values. These equations shall be explained in detail in the upcoming remarks.

SCF calculations were performed on the described systems with an energy convergence threshold starting at 30 Ry and a force convergence threshold starting at 3 Ry subsequently adding 10 Ry or 1 Ry up until 100 Ry and 10 Ry were reached. Based on the received energy values for these calculations it was determined that 60 Ry and 6 Ry were acceptable values to reach convergence for all examined systems.

Table S15. *Variables ecutrho, ecutwfc and chosen K-point grid for each calculated sample. All values were used in SCF calculations and geometry optimizations. For the simulated gas phase calculations K-points were neglected.*

Sample	ecutroh [Ry]	ecutwfc [Ry]	K-point grid
Aspirin[10]	60	6	2 · 4 · 2
Glycine-α[11]			5 · 2 · 5
Glycine-β[12]			5 · 4 · 5
Glycine-γ[13]			4 · 4 · 4
Benzoic acid[14]			4 · 5 · 1
Naphthalene[15]			3 · 4 · 3
Carbendazim Maleate[9]			3 · 3 · 1
Fenamic acid[16]			3 · 3 · 2
(S)-Pregabalin/(1)			4 · 3 · 2
(R)-Pregabalin/(1)			4 · 3 · 2
(rac)-Phenibut/(2)			3 · 4 · 1
(S, S)-Pregabalin:malic acid/(1:4)			3 · 3 · 1
(S, R)-Pregabalin:malic acid/(1:4)			3 · 3 · 1
(S, S)-Pregabalin:mandelic acid/(1:3)			4 · 1 · 3
(R, R)-Pregabalin:mandelic acid/(1:3)			4 · 1 · 3
(S, R)-Pregabalin:mandelic acid/(1:3)			4 · 1 · 3
(R, S)-Pregabalin:mandelic acid/(1:3)			4 · 1 · 3
(R, S)-Phenibut:mandelic acid/(2:3)			3 · 4 · 2

Naphthalene, aspirin and benzoic acid were chosen as model compounds that are commonly used to verify energy models, they show similar capabilities for intermolecular interactions as the investigated compounds. Glycine polymorphs were chosen because they are well investigated amino acids that exhibit zwitterionicity and as polymorphs should be energetically close regarding each other. Carbendazim maleate was examined by Voronin et al. and serves

to verify that the model works for multicomponent entities. Fenamic acid exhibits Z' = 2 and was energetically investigated by Yang et al. in the past,[17] thus enabling its use as a model compound for systems with this characteristic. The necessary crystallographic information files (.cif) for these compounds were gathered from the crystal structure database via Mercury 2020.2.0.[9 - 16] A geometric optimization and subsequent simulated gas phase of the geometrically optimized singular molecules was performed using the determined parameters to receive values for E_{iss} and E_{isg}, sufficient to calculate E_{lat} as shown in **Equation 3** for naphthalene**,** aspirin, benzoic acid and the glycine polymorphs.

$$E_{lat} = \frac{E_{iss}}{Z} - E_{isg} \tag{3}$$

Where Z is the crystallographic Z, describing the formular units in the unit cell. For further validation purposes, it was assumed that systems that are highly comparable by means of the participating molecules could be used to obtain ΔE_{lat} values without the need to calculate E_{isg} by variation of **Equation 3** under the assumptions that E_{isg} values for the same molecules would be negligible as shown in **Equation 4**.

$$\Delta E_{lat} = E_{lat1} - E_{lat2}$$

$$\Delta E_{lat} = (\frac{E_{iss1}}{Z_1} - E_{isg}) - (\frac{E_{iss2}}{Z_2} - E_{isg})$$

$$\Delta E_{lat} = \frac{E_{iss1}}{Z_1} - \frac{E_{iss2}}{Z_2} \tag{4}$$

These values could then be used to verify lattice energy differences calculated by E_{lat} values obtained via **Equation 3**. It was further attempted to consider the influence of Z'. In systems where Z' > 1 E_{iss} has to be adjusted by Z' via division to obtain correct values for E_{lat} in the presented model (**Equation 5**).

$$E_{lat} = \frac{E_{iss}}{Z} - \frac{E_{isg}}{Z'} \tag{5}$$

Finally, for multicomponent species each crystallographcally distinct molecule has to be considered by their E_{isg} values to obtain E_{lat}, which can be achieved by summation of the different contributions. **Equation 6** considers all discussed influences.

$$E_{lat} = \frac{E_{iss}}{Z} - \frac{\sum E_{isgn}}{Z'} \tag{6}$$

Tables S16 shows E_{iss} and Eisg values on the model compounds obtained by the described model, **Table S17** shows corresponding lattice energies.

Table S16. *Resulting values of E_{iss} and E_{isg} for the validation compounds. In carbendazim maleate, carbendazim entities are marked with 'C' and maleate entities are marked with 'M'. In fenamic acid, the crystallographically independent molecules are marked as A and B.*

Sample	Z	E_{iss} [Ry]	E_{isg} (neutral) [Ry]	E_{isg} (zwitt./charge) [Ry]
Aspirin	4	-1348.01234	-336.89571	-
Benzoic acid	4	-864.49243	-216.03921	-
Naphthalene	2	-380.81223	-190.34592	-
Carbendazim maleate	4	-2238.98103	-317.81712^{C} -241.69462^{M}	-318.65171^{C} -240.74749^{M}
Fenamic acid	4	-1405.17232	-351.18464^{A} -351.18407^{B}	- -
Glycine-α	4	-580.77370	-145.06565	-145.06563
Glycine-β	2	-290.38351	-145.06570	-145.06570
Glycine-γ	3	-435.58159	-145.05057	-145.06558

Table S17. *Resulting values of E_{lat} for the validation compounds. Literature values were obtained from the cited sources.*

Sample	E_{lat} (neutral) [Ry]	E_{lat} (zwitt./ charge) [Ry]	E_{lat} (neutral) [kJmol^{-1}]	E_{lat} (zwitt./ charge) [kJmol^{-1}]	E_{lat} (lit.) [kJmol^{-1}]
Aspirin	-0.10737	-	-140.96	-	-131.27[18]*
Benzoic acid	-0.08389	-	-110.14	-	-96.0[19]
Naphthalene	-0.06020	-	-79.03	-	-79.4[19]
Carbendazim maleate	-0.23351	-0.34606	-306.54	-454.29	-278.3[9]* -625.0[9]*
Fenamic acid	-0.10873	-	-142.73	-	-136.5[17]
Glycine-α	-0.12777	-0.12779	-167.73	-167.76	-144.93[20]
Glycine-β	-0.12606	-0.12605	-165.48	-165.48	-143.13[20]
Glycine-γ	-0.14329	-0.12829	-188.11	-168.41	-144.12[20]

** = the cited sources give a plethora of values obtained through differing models and equations. The closest one to the calculated results was picked for this presentation. For Carbendazim maleate the lattice energy values based on neutral molecules and charged molecules are given.*

The model's accuracy for polymorphic substances was tested on glycine polymorphs assuming zwitterionic conditions for E_{isg} using **Equations 3 & 4** (**Table S18**).

Table S18. *ΔElat as calculated by Equation 3 & Equation 4 for permutations of the Glycine polymorphs, the zwitterionic state energy values were used.*

Sample	ΔE_{lat} (Eq. 3) [kJmol^{-1}]	ΔE_{lat} (Eq. 4) [kJmol^{-1}]	Deviation [kJmol^{-1}]
Glycine-α - Glycine-β	-2.28	-2.19	0.09
Glycine-α - Glycine-γ	0.58	0.65	0.17
Glycine-β - Glycine-γ	2.93	2.77	0.16

3.2 Compound categorization and model application

After verification of the used model its principles were applied to the central Pregabalin and Phenibut based compounds. First, the compounds were categorized based on some of their properties which could influence the calculation results. **Category A** contains (S)-Pregabalin, (R)-Pregabalin and (rac)-Phenibut. These are the simplest examined compounds as they exhibit only one type of molecule in the unit cell, Z' = 1 and each molecule is in its default zwitterionic state. In **Category B** only (R, S)-Phenibut:mandelic acid is placed. Here, two different kinds of molecules occur in the unit cell but Z' remains 1 and each molecule keeps its default state with zwitterionic Phenibut and neutral mandelic acid. (S, S)- and (S, R)-Pregabalin:malic acid are placed in **Category C**. Here, two types of molecules occur in the cell, Z' = 1 but each species contains a formal charge. **Category D** is composed of (S, S)- and (R, R)-Pregabalin:mandelic acid. These systems are formed from two different molecular species and four crystallographically inequivalent molecules but Z' = 2 and default charge status on the molecules is retained. Lastly, **Category E** consists of (S, R)- and (R, S)-Pregabalin:mandelic acid. All previously established complications are applied to this category, as there are two different kinds of molecules and four crystallographically inequivalent ones, Z' = 2 and formal charges are present on each molecule. A comprehensive overview on the categories, the involved samples and properties is shown in **Table S19**.

Table S19. *Characteristics of the determined categories: contained samples, number of different molecular species, Z' value as determined by PLATON software and information on whether the molecular species are charged (neither zwitterionic nor neutral).*

	Samples	Molecule types	Z'	Charge
Category A	(S)-, (R)-Pregabalin, (rac)-Phenibut	1	1	No
Category B	(R)-Phenibut:(S)-mandelic acid	2	1	No
Category C	(S, S)-, (S, R)-Pregabalin:malic acid	2	1	Yes
Category D	(S, S)-, (R, R)-Pregabalin:mandelic acid	2	2	No
Category E	(S, R)-, (R, S)-Pregabalin:mandelic acid	2	2	Yes

It was determined that **Category A** would not require any additional effort to apply the used model on, as its characteristics are the same as those of the model compounds. For **Category B – E** it was assumed that E_{isg} would be determined by summation of $E_{isgA} + E_{isgB} + \ldots + E_{isgn}$ for all geometrically independent molecules. For each category it was furthermore examined whether neutral, zwitterionic or, if applicable, charged states on isolated molecules would lead to the most consistent results. Additionally, for **Category D** and **E** it was attempted to consider the influence of Z'.

Category A

Table S20. *Resulting values of E_{iss} and E_{isg} for the **Category A** compounds.*

Sample	Z	E_{iss} [Ry]	E_{isg} (neutral) [Ry]	E_{isg} (zwitt.) [Ry]
(S)-Pregabalin (1)	4	-1071.82432	-267.79802	-267.80748
(R)-Pregabalin (1)	4	-1071.82525	-267.79161	-267.80764
(rac)-Phenibut (2)	8	-2396.20653	-299.23844	-299.12074

Table S21. *Resulting values of E_{lat} as calculated by **Equation 6** for the **Category A** compounds.*

Sample	E_{lat} (neutral) [Ry]	E_{lat} (zwitt.) [Ry]	E_{lat} (neutral) [kJmol^{-1}]	E_{lat} (zwitt.) [kJmol^{-1}]
(S)-Pregabalin (1)	-0.15806	-0.14860	-207.50	-195.08
(R)-Pregabalin (1)	-0.16470	-0.14867	-216.21	-195.17
(rac)-Phenibut (2)	-0.16238	-0.28008	-213.16	-367.68

Table S22. *Comparison of ΔE_{lat} values obtained by **Equation 6** and **Equation 4** for **Category A** compounds (S)- and (R)-Pregabalin.*

	ΔE_{lat} (Eq. 3) [kJmol^{-1}]	ΔE_{lat} (Eq. 4) [kJmol^{-1}]	Deviation [kJmol^{-1}]
(S)-1 – (R)-1 (neutral)	-8.71	-0.31	8.40
(S)-1 – (R)-1 (zwitt.)	-0.09		0.22

Category B & C

Table S23. *Resulting values of E_{iss} and E_{isg} for the **Category B** & **C** compounds crystallographically independent occurring molecular species.*

Sample	E_{iss} [Ry]	E_{isg} (neutral) [Ry]	E_{isg} (zwitt.) [Ry]	E_{isg} (charged) [Ry]
(S, S)-1:4 (Z = 4)				
(S)-Pregabalin	-2213.33805	-267.79195	-267.80910	-268.61130
(S)-malic acid		-285.25372	-	-284.27132
(S, R)-1:4 (Z = 4)				
(S)-Pregabalin	-2213.34508	-267.79369	-267.80880	-268.61136
(R)-malic acid		-285.25091	-	-284.22893
(R, S)-2:3 (Z = 2)				
(R)-Phenibut	-1154.28106	-299.24119	-299.24904	-
(S)-mandelic acid		-277.63003	-	-

Table S24. *Resulting values of E_{lat} as calculated by **Equation 6** for the **Category B** & **C** compounds using the E_{isg} values of singular molecules depicted in **Table S23**.*

Sample	E_{lat} (neutral) [Ry]	E_{lat} (zwitt.) [Ry]	E_{lat} (charged) [Ry]
(S, S)-1:4	-0.28884	-0.27169	-0.45190
(S, R)-1:4	-0.29166	-0.27656	-0.49598
(R, S)-2:3	-0.26931	-0.26146	-
	E_{lat} (neutral) [kJmol^{-1}]	**E_{lat} (zwitt.) [kJmol^{-1}]**	**E_{lat} (charged) [kJmol^{-1}]**
(S, S)-1:4	-379.17	-356.66	-593.23
(S, R)-1:4	-382.88	-363.05	-651.10
(R, S)-2:3	-353.54	-343.23	-

Table S25. *Comparison of ΔE_{lat} values received by **Equation 6** and **Equation 4** for **Category C** compounds (S, S)- and (S, R)-Pregabalin:malic acid.*

Sample	ΔE_{lat} (Eq. 3) [kJmol^{-1}]	ΔE_{lat} (Eq. 4) [kJmol^{-1}]	Deviation [kJmol^{-1}]
(S, S)-1:4 – (S, R)-1:4 (neutral)	3.71		1.40
(S, S)-1:4 – (S, R)-1:4 (zwitt.)	6.39	2.31	4.08
(S, S)-1:4 – (S, R)-1:4 (charged)	57.87		55.66

Category D & E

Table S26. *Resulting values of E_{iss} and E_{isg} for the **Category D** & **E** compounds crystallographically independent occurring molecular species.*

Sample	E_{iss} [Ry]	E_{isg} (neutral) [Ry]	E_{isg} (zwitt.) [Ry]	E_{isg} (charged) [Ry]
(S, S)-1:3 (Z = 4)				
(S)-Pregabalin 1	-2182.72832	-267.79208	-267.80897	-
(S)-Pregabalin 2		-267.79387	-267.80898	-
(S)-mandelic acid 1		-277.62920	-	-
(S)-mandelic acid 2		-277.62893	-	-
(R, R)-1:3 (Z = 4)				
(R)-Pregabalin 1	-2182.73030	-267.79375	-267.80898	-
(R)-Pregabalin 2		-267.79208	-267.80900	-
(R)-mandelic acid 1		-277.62918	-	-
(R)-mandelic acid 2		-277.82695	-	-
(S, R)-1:3 (Z = 4)				
(S)-Pregabalin 1	-2182.68327	-267.79976	-267.80809	-268.64999
(S)-Pregabalin 2		-267.81182	-267.80928	-268.59870
(R)-mandelic acid 1		-277.62918	-	-276.65999
(R)-mandelic acid 2		-277.63009	-	-276.63286
(R, S)-1:3 (Z = 4)				
(R)-Pregabalin 1	-2182.68421	-267.79397	-267.80932	-268.59859
(R)-Pregabalin 2		-267.79977	-267.80897	-268.65003
(S)-mandelic acid 1		-277.62918	-	-276.64477
(S)-mandelic acid 2		-277.62575	-	-276.63280

Table S27. *Resulting values of E_{lat} as calculated by **Equation 6** for the **Category D** & **E** compounds using the E_{isg} values of singular molecules depicted in **Table S26**.*

Sample	E_{lat} (neutral) [Ry]	E_{lat} (zwitt.) [Ry]	E_{lat} (charged) [Ry]
(S, S)-1:3	-0.26004	-0.24404	-
(R, R)-1:3	-0.26095	-0.24452	-
(S, R)-1:3	-0.23540	-0.23208	-0.40005
(R, S)-1:3	-0.24672	-0.23445	-0.40796
	E_{lat} (neutral) [kJmol^{-1}]	E_{lat} (zwitt.) [kJmol^{-1}]	E_{lat} (charged) [kJmol^{-1}]
(S, S)-1:3	-341.37	-320.36	-
(R, R)-1:3	-342.09	-320.99	-
(S, R)-1:3	-309.02	-305.66	-525.17
(R, S)-1:3	-323.88	-307.77	-535.55

Table S28. *Comparison of ΔE_{lat} values received by **Equation 6** and **Equation 4** for **Category D** & **E** compounds inside the respective categories and between both categories in varying permutations.*

Sample	ΔE_{lat} (Eq. 5) [kJmol^{-1}]	ΔE_{lat} (Eq. 4) [kJmol^{-1}]	Deviation [kJmol^{-1}]
(S, S)-1:3 - (R, R)-1:3 (neutral)	0.72	0.65	0.07
(S, S)-1:3 - (R, R)-1:3 (zwitt.)	0.63		0.02
(S, R)-1:3 - (R, S)-1:3 (neutral)	14.86		14.55
(S, R)-1:3 - (R, S)-1:3 (zwitt.)	2.11	0.31	1.80
(S, R)-1:3 - (R, S)-1:3 (charged)	10.38		10.07
(S, S)-1:3 - (S, R)-1:3 (neutral)	-32.35	-14.79	17.56
(S, S)-1:3 - (S, R)-1:3 (zwitt.)	-15.71		0.92
(S, S)-1:3 - (R, S)-1:3 (neutral)	-17.49	-14.48	3.01
(S, S)-1:3 - (R, S)-1:3 (zwitt.)	-12.59		1.89
(R, R)-1:3 - (S, R)-1:3 (neutral)	-33.07	-15.44	17.63
(R, R)-1:3 - (S, R)-1:3 (zwitt.)	-16.33		0.89
(R, R)-1:3 - (R, S)-1:3 (neutral)	-18.21	-15.13	3.08
(R, R)-1:3 - (R, S)-1:3 (zwitt.)	-13.22		1.91

It was determined that the most overall consistent results can be obtained by application of zwitterionicity on Pregablin/Phenibut molecules and neutral charge status on mandelic- or malic acid.

4 Applications: enantiopurification of (rac)-Pregabalin hydrate

Detailed PXRD pattern comparisons of products received during enantiopurification steps **I** – **III** are presented in **Figures S22** – **S24**.

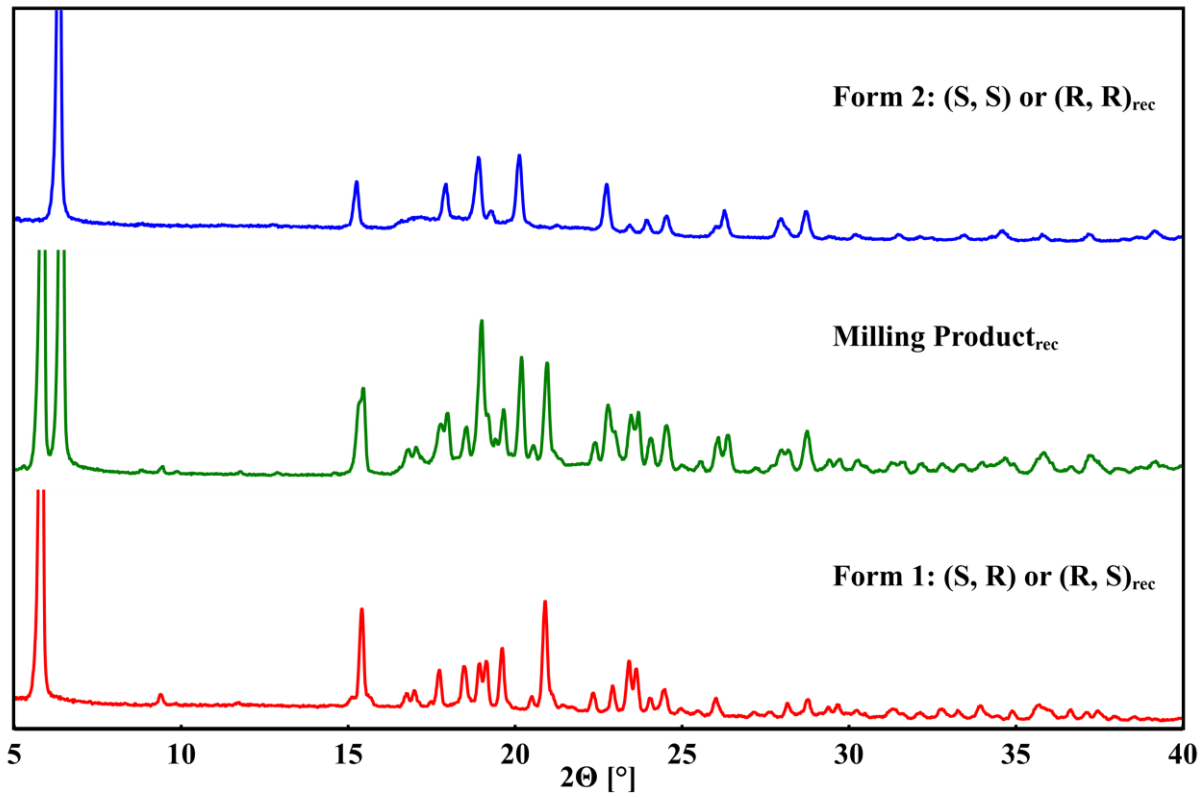

Figure S22. *Powder pattern of the milling product of racemic Pregabalin hydrate and (S)-mandelic acid (green). A comparison to the two co-crystalline compounds is shown for (S, R)-Pregabalin:mandelic acid (red) as well as (S, S)-Pregabalin:mandelic acid (blue). Thus, the milling product is identified as a mixture. The depicted angle range is 5° – 40°.*

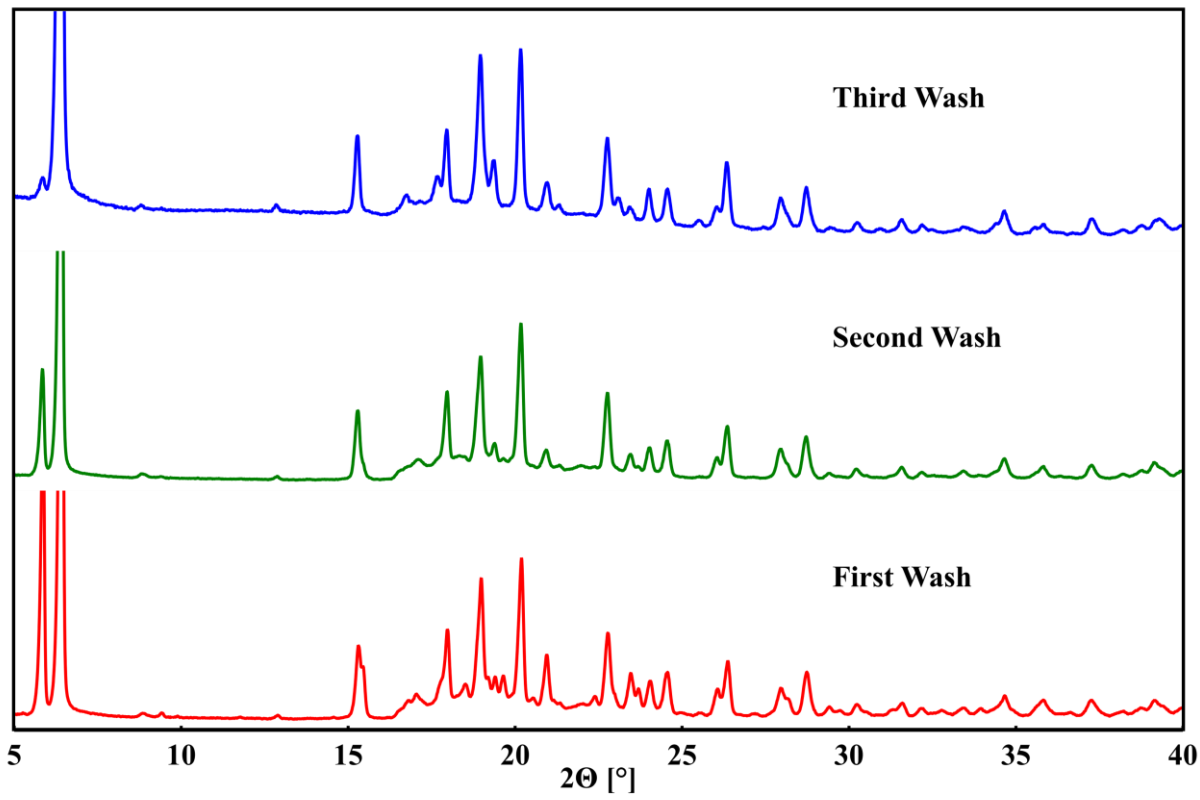

Figure S23. *Powder pattern of the milling product of racemic Pregabalin hydrate and (R)-mandelic acid after subsequent washing and drying procedure from 5° – 40°. The signals of the more soluble heterochiral co-crystalline entity vanish from red – blue pattern, easily visible in the lowest ° signal.*

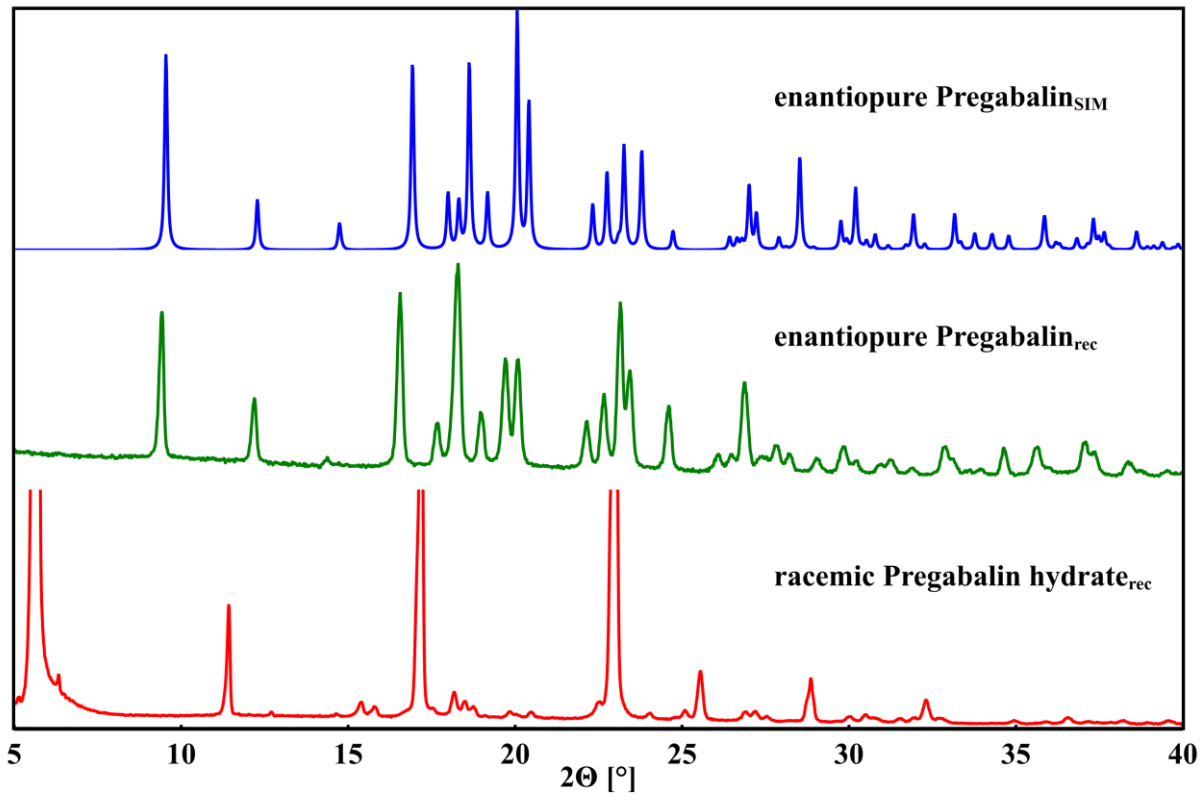

Figure S24. *Powder pattern of the final (R)-Pregabalin (green) after removal of (R)-mandelic acid) compared to a simulated pattern from single crystal data (blue) and the recorded pattern of the racemic Pregabalin hydrate (red) in a range of 5° – 40°.*

5 Addendum

Table S29. *Bijvoet-analysis for confirmation of chiral purity conducted with PLATON software.*

	(S)-1	(R)-1	(S, S)-1:3	(R, R)-1:3	(S, R)-1:3	(R, S)-1:3	(S, S)-1:4	(S, R)-1:4	(R, S)-2:3
Flack x	0.03(11)	-0.04(19)	0.15(11)	-0.02(5)	-0.05(12)	-0.15(7)	0.01(6)	0.01(5)	0.00(10)
Parsons z	0.06(11)	0.00(18)	0.14(9)	-0.04(5)	0.05(8)	-0.17(6)	-0.01(6)	-0.01(4)	-0.01(8)
Bijvoet Pairs	663	696	3038	3150	3209	2991	1133	1210	1412
Coverage	84	88	86	89	91	85	86	91	87
DiffCalcMax.	6.47	6.58	18.43	18.07	28.52	30.71	38.34	39.17	10.17
Outlier Crit.	12.94	13.16	36.85	36.14	57.03	61.43	76.67	78.33	20.34
Sigma Crit.	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Select Pairs	84	27	86	528	99	322	280	464	167
Number Plus	55	18	55	352	58	208	179	313	106
Number Minus	29	9	31	176	41	114	101	151	61
Slope	0.908	1.525	0.709	1.024	1.175	1.358	0.949	0.951	1.091
Sample Size	653	686	3028	3140	3199	2981	1123	1200	1402
Corr. Coeff.	0.997	0.999	0.999	1.000	0.999	1.000	0.999	0.998	0.997
Intercept	0.018	-0.065	0.014	-0.034	-0.004	-0.065	-0.076	0.033	-0.151
Slope	0.854	0.840	0.911	0.947	1.009	1.034	0.870	0.944	0.985
Student_T Nu	100	32	9	32	7	32	100	99	19
Select Pairs	663	696	3038	3150	3209	2991	1133	1210	1412
Theta_min	9.32	9.30	5.49	3.23	2.95	2.96	8.50	8.46	7.76
Theta_Max	76.05	76.13	77.15	76.90	77.53	75.38	76.51	77.79	76.14
P2 (true)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
P3 (true)	1.000	0.995	1.000	1.000	1.000	1.000	1.000	1.000	1.000
P3 (rac-twin)	0.3E-04	0.005	0.3E-03	0.1E-32	0.9E-06	0.1E-21	0.2E-17	0.9E-30	0.8E-08
P3 (false)	0.2E-20	0.3E-09	0.3E-21	0.1E-121	0.22E-23	0.4E-70	0.3E-70	0.2E-120	0.2E-31
G	0.8773	0.9606	0.7438	1.0754	1.0198	1.3180	1.0004	0.9897	1.0117
G (su)	0.1916	0.2946	0.1728	0.0871	0.1929	0.1270	0.1107	0.0840	0.1652
Hooft y	0.06(10)	0.02(15)	0.13(9)	-0.04(4)	-0.01(10)	-0.16(6)	0.00(6)	0.01(4)	-0.01(8)

[1]H-NMR spectroscopy

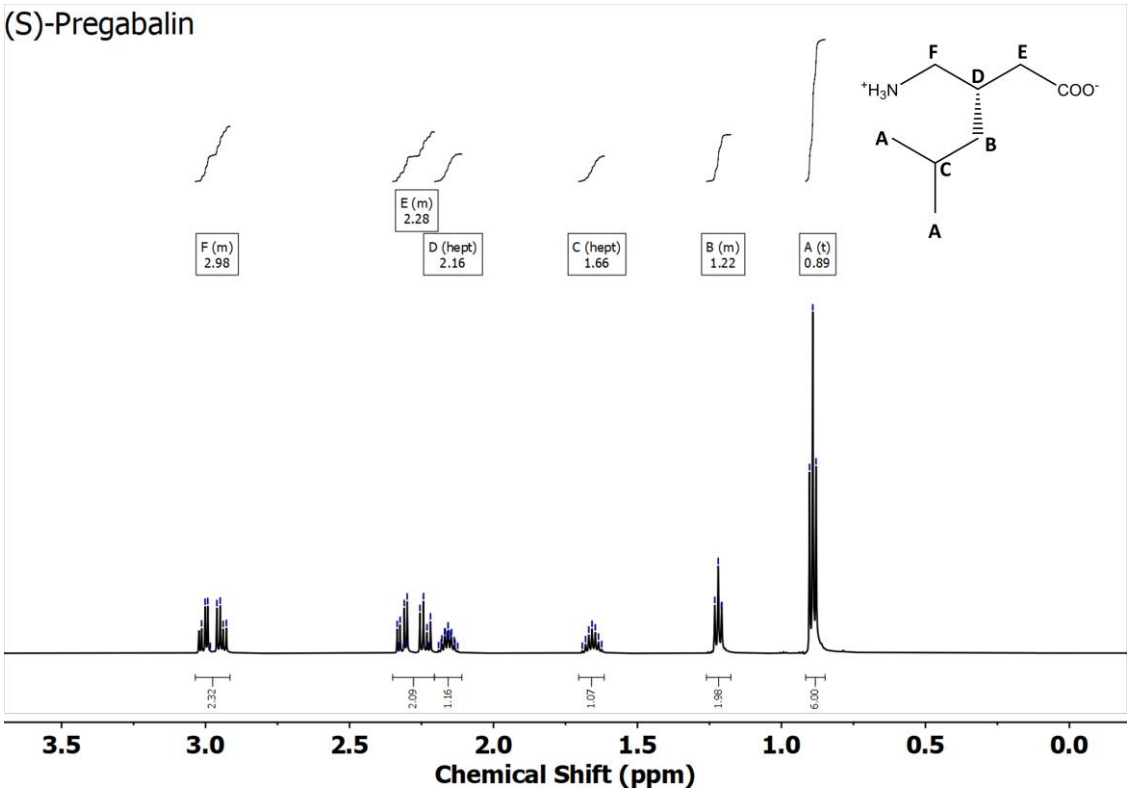

Figure S25. *[1]H-NMR spectrum of (S)-Pregabalin recorded in D_2O. The range between 0.25 ppm and 3.75 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

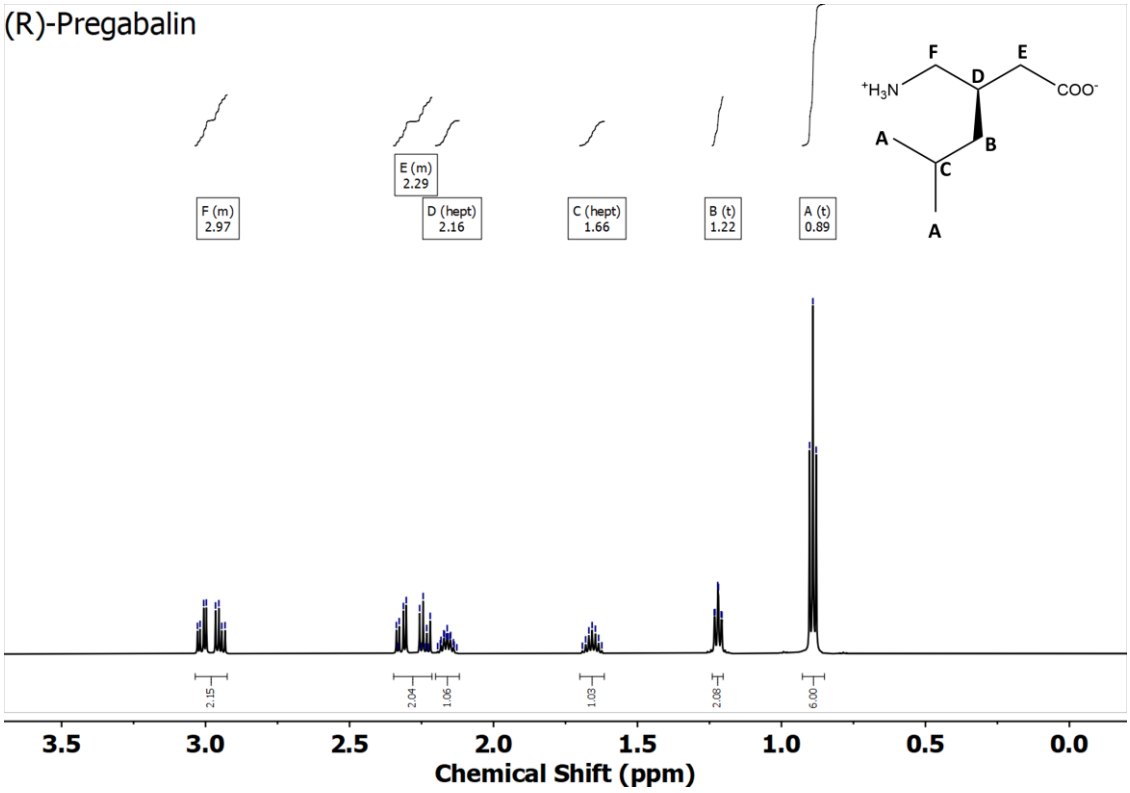

Figure S26. *[1]H-NMR spectrum of (R)-Pregabalin recorded in D_2O. The range between 0.25 ppm and 3.75 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

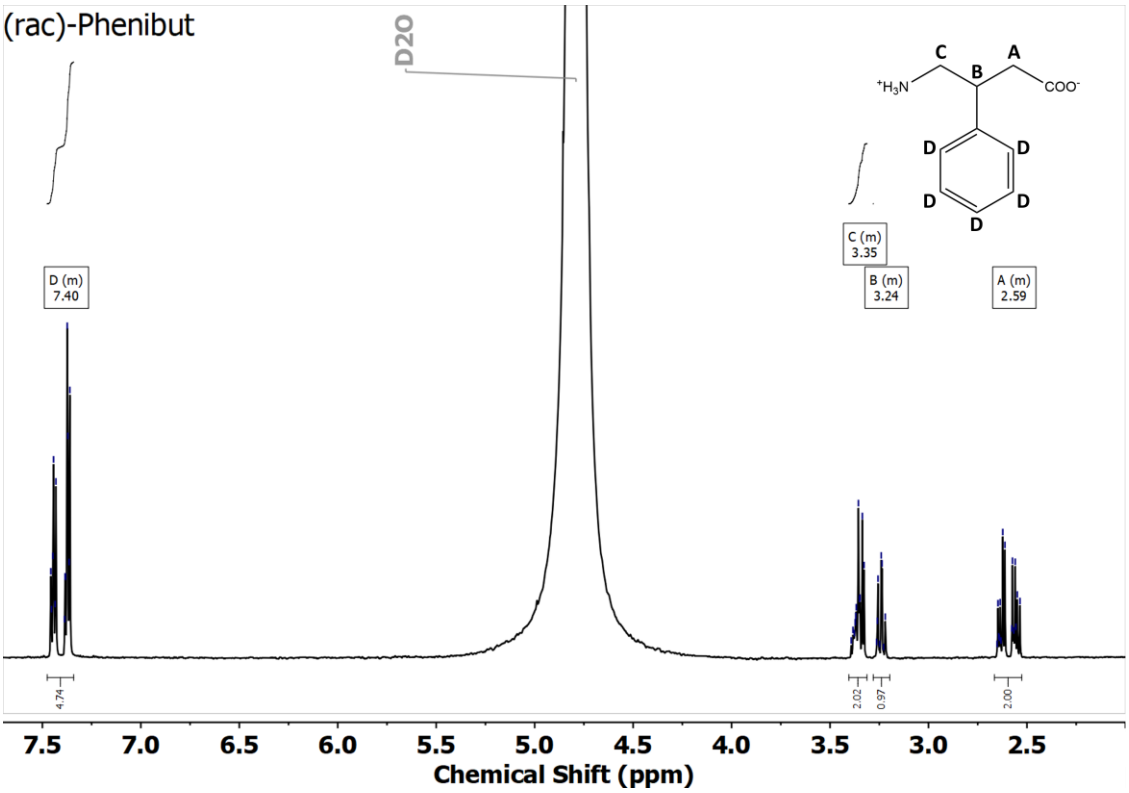

Figure S27. *^{1}H-NMR spectrum of (rac)-Phenibut recorded in D_2O. The range between 2.00 ppm and 7.75 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

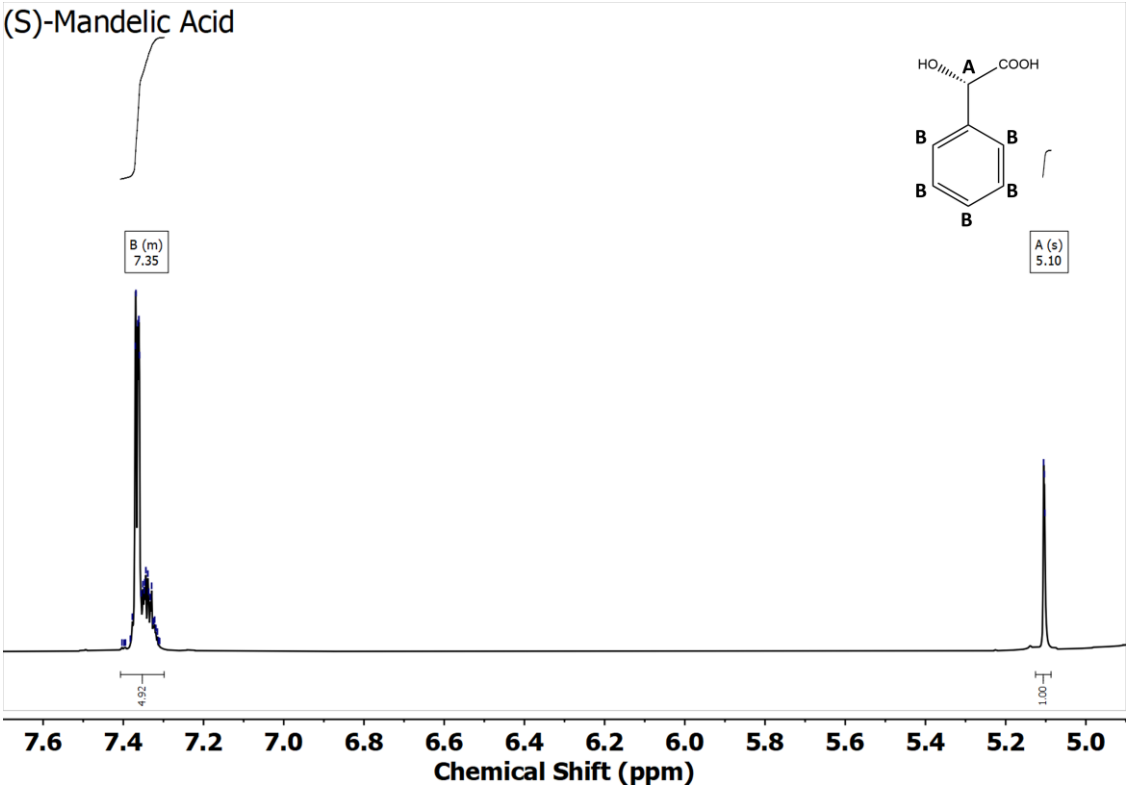

Figure S28. *^{1}H-NMR spectrum of (S)-mandelic acid recorded in D_2O. The range between 4.8 ppm and 7.8 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

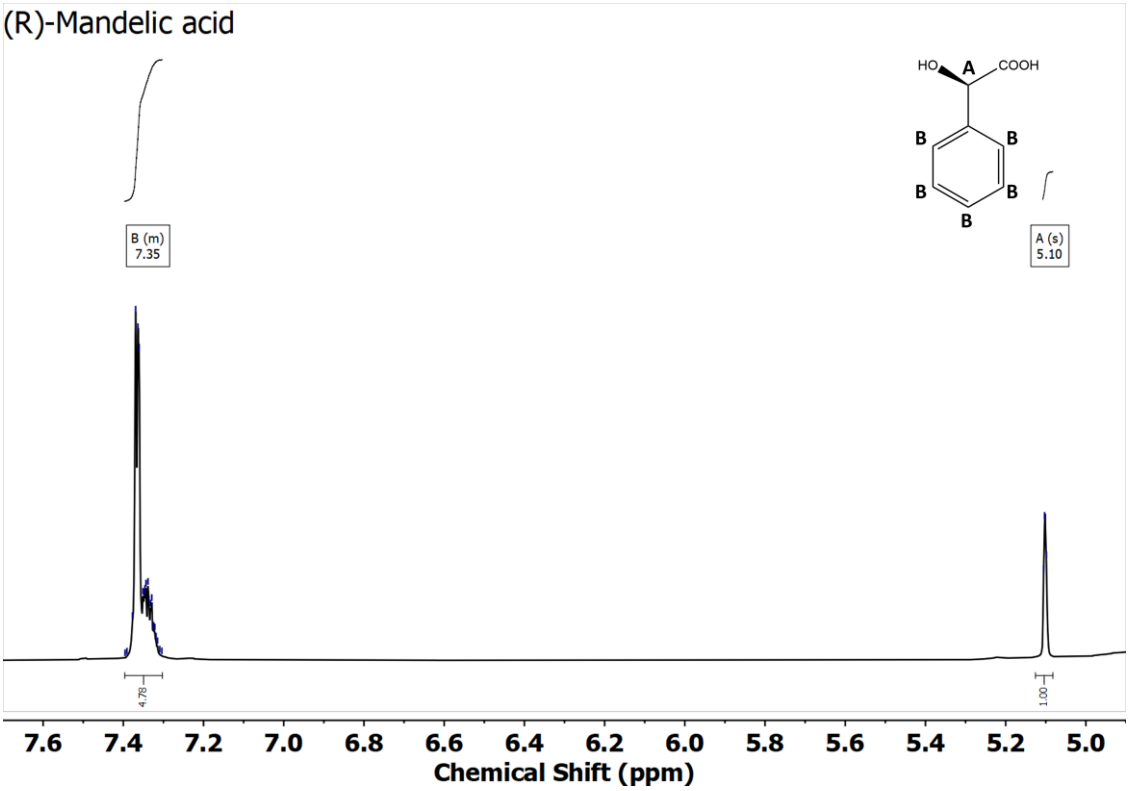

Figure S29. *^{1}H-NMR spectrum of (R)-mandelic acid recorded in D_2O. The range between 4.8 ppm and 7.8 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

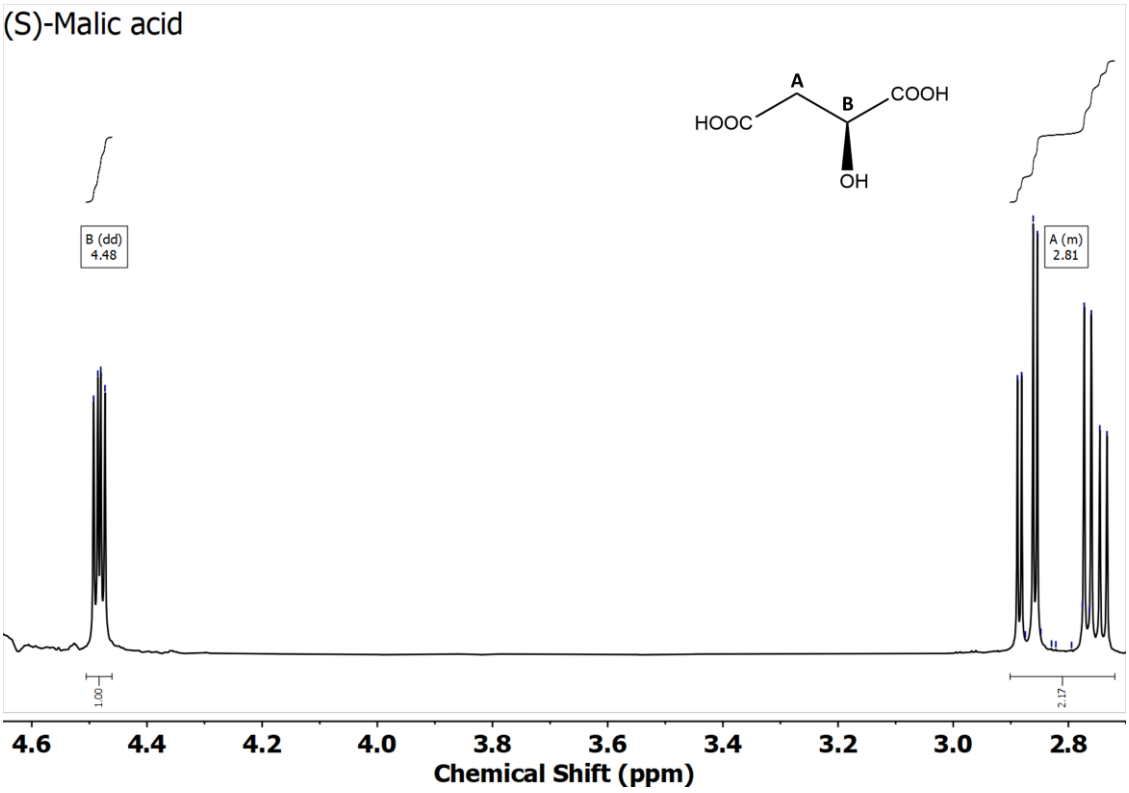

Figure S30. *^{1}H-NMR spectrum of (S)-Malic acid recorded in D_2O. The range between 2.6 ppm and 4.7 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

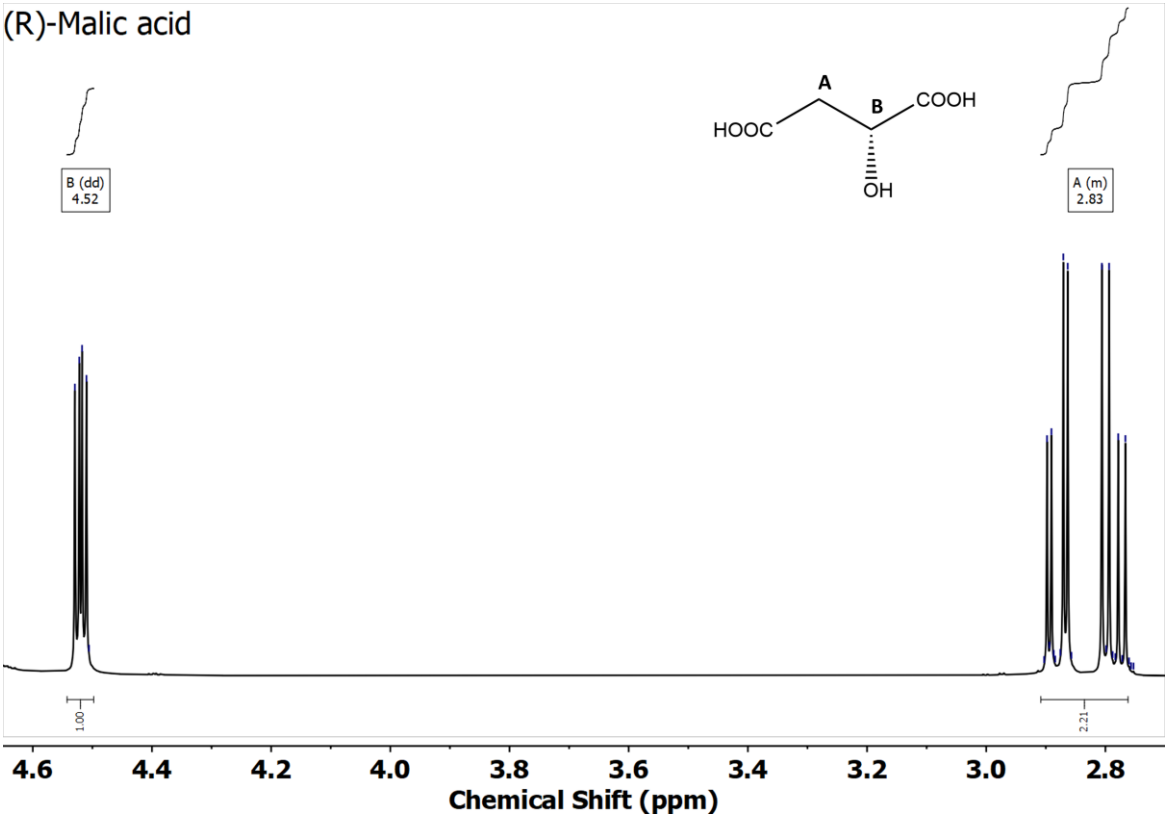

Figure S31. *^{1}H-NMR spectrum of (R)-Malic acid recorded in D_2O. The range between 2.6 ppm and 4.7 ppm is depicted, the signals are marked by letters according to the position on the molecule.*

IR-Spectroscopy

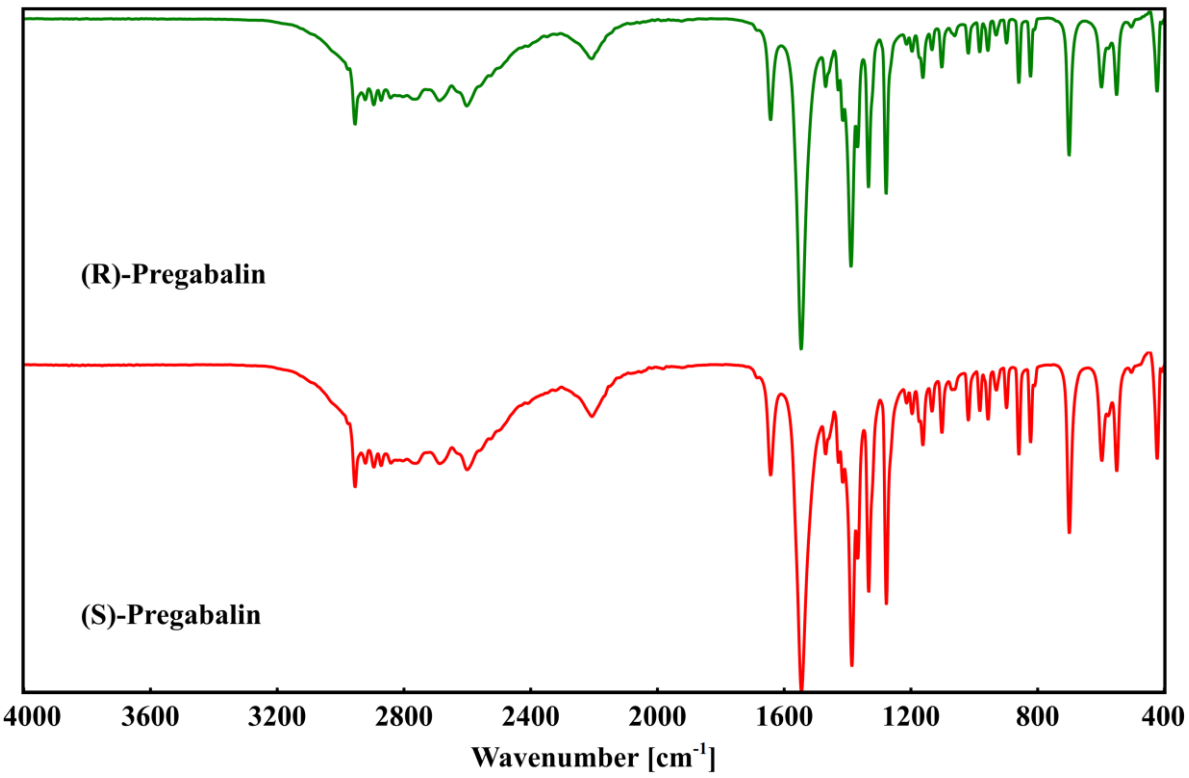

Figure S32. *IR-spectra of (S)-Pregabalin (red) and (R)-Pregabalin (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted.*

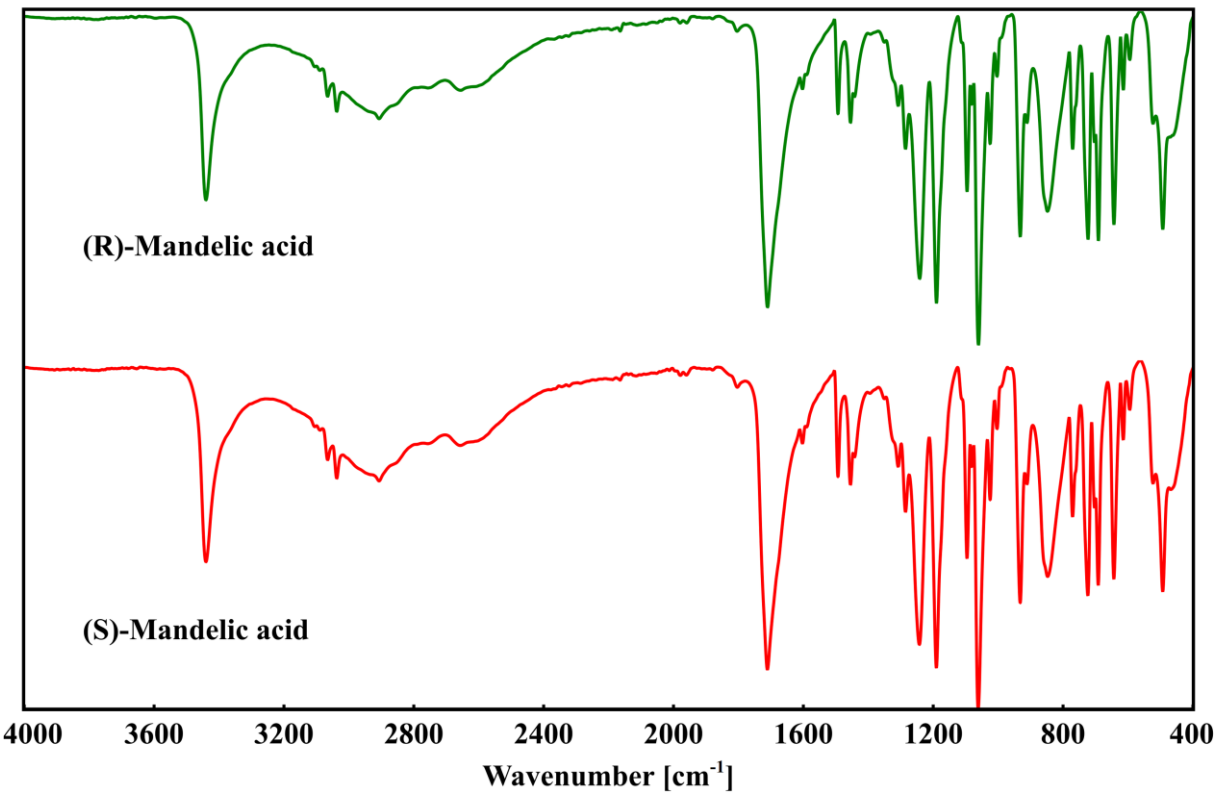

Figure S33. *IR-spectra of (S)-mandelic (red) and (R)-mandelic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted.*

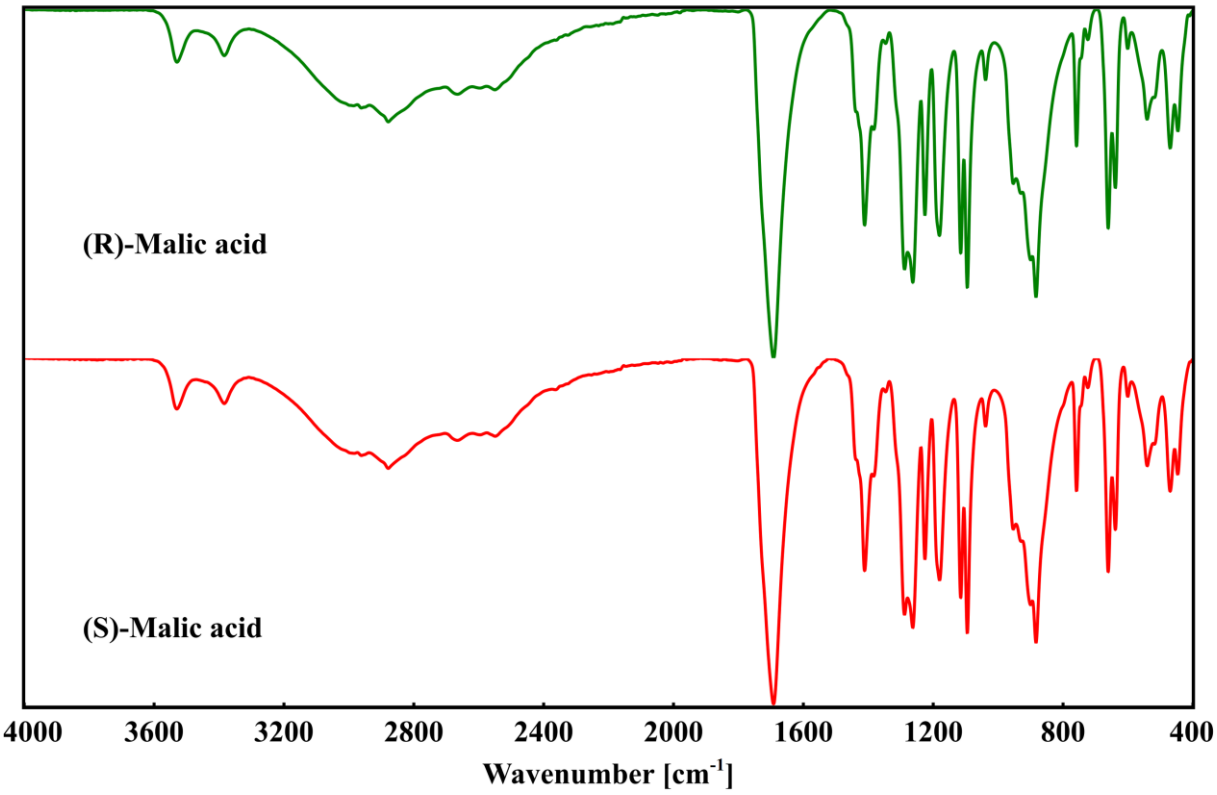

Figure S34. *IR-spectra of (S)-malic (red) and (R)-malic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted.*

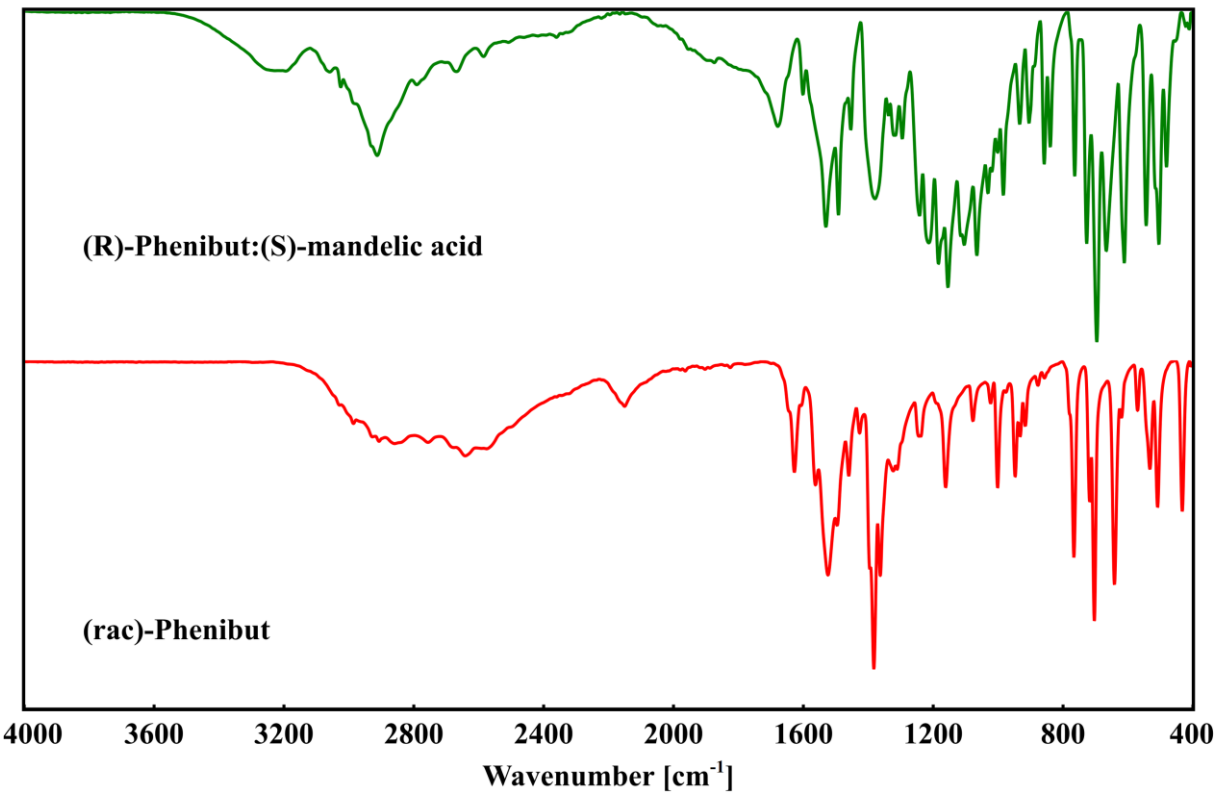

Figure S35. *IR-spectra of (rac)-Phenibut (red) and (R, S)-Phenibut:mandelic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted,*

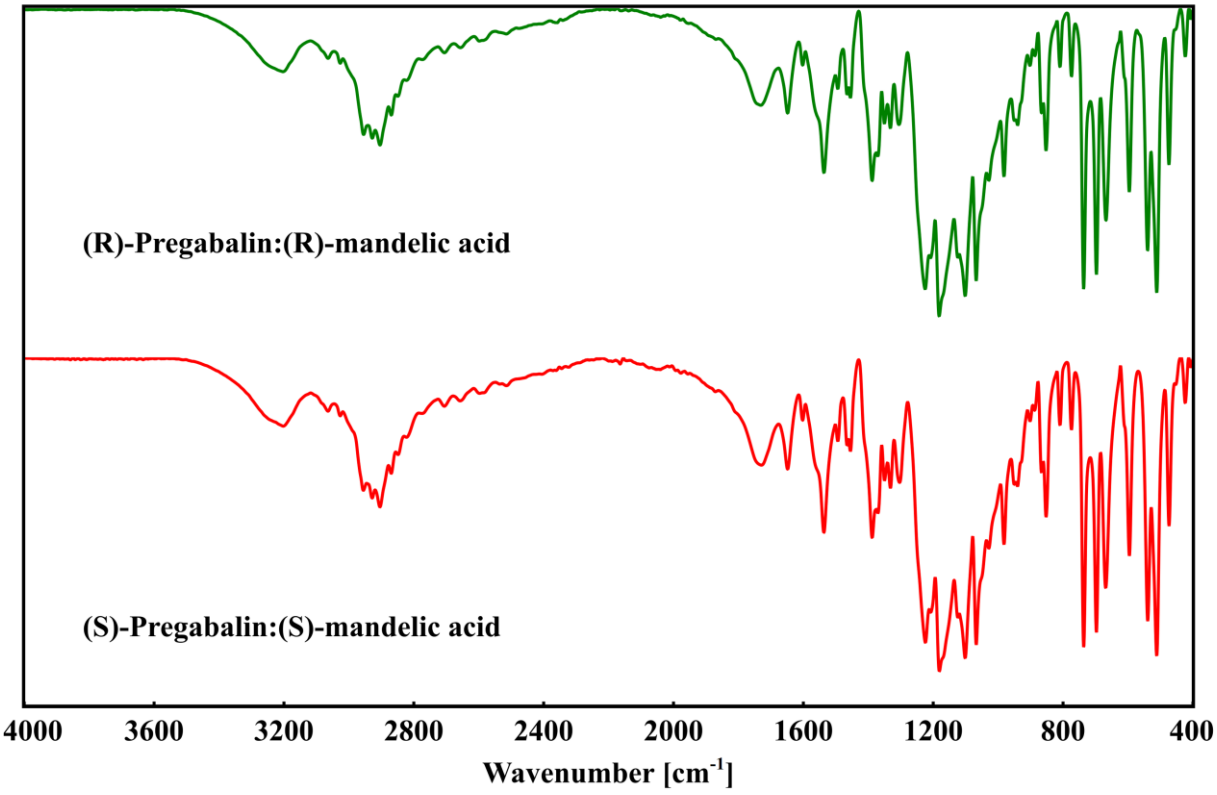

Figure S36. *IR-spectra of (S, S)-Pregabalin:mandelic acid (red) and (R, R)-Pregabalin:mandelic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted.*

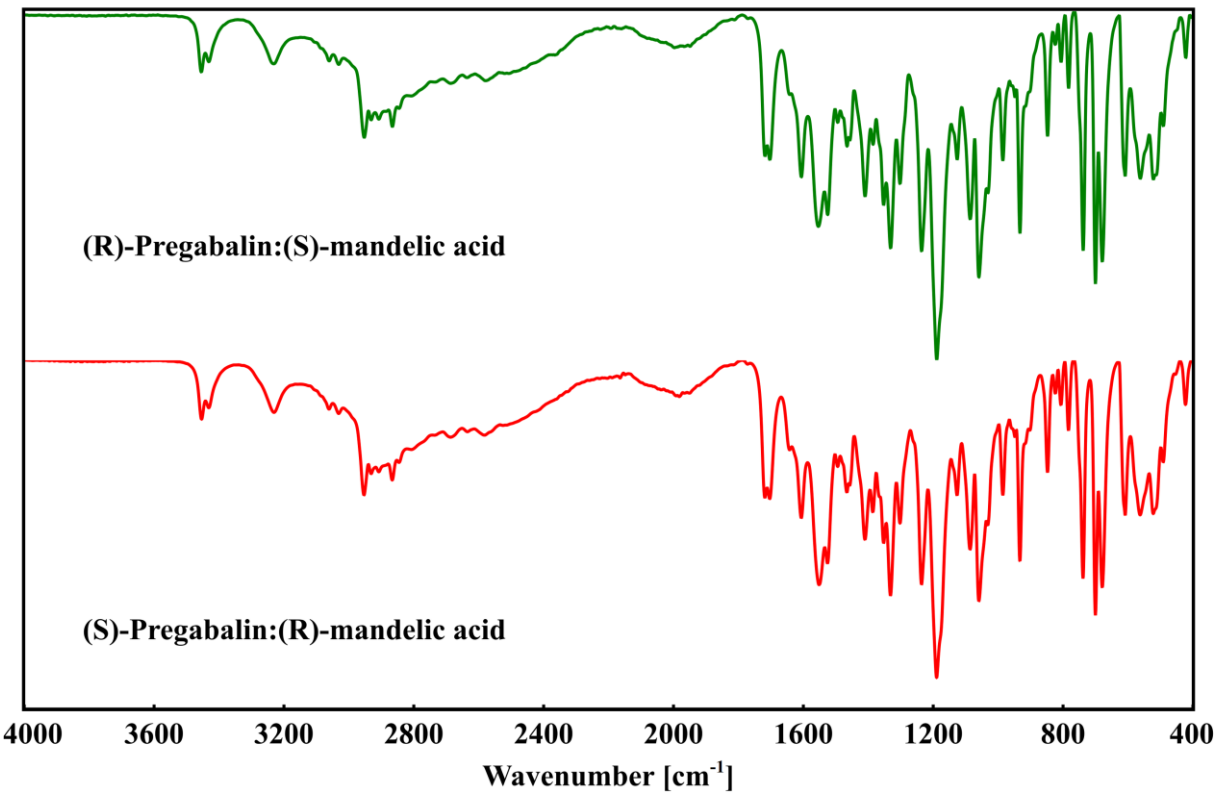

Figure S37. *IR-spectra of (S, R)-Pregabalin:mandelic acid (red) and (R, S)-Pregabalin:mandelic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted.*

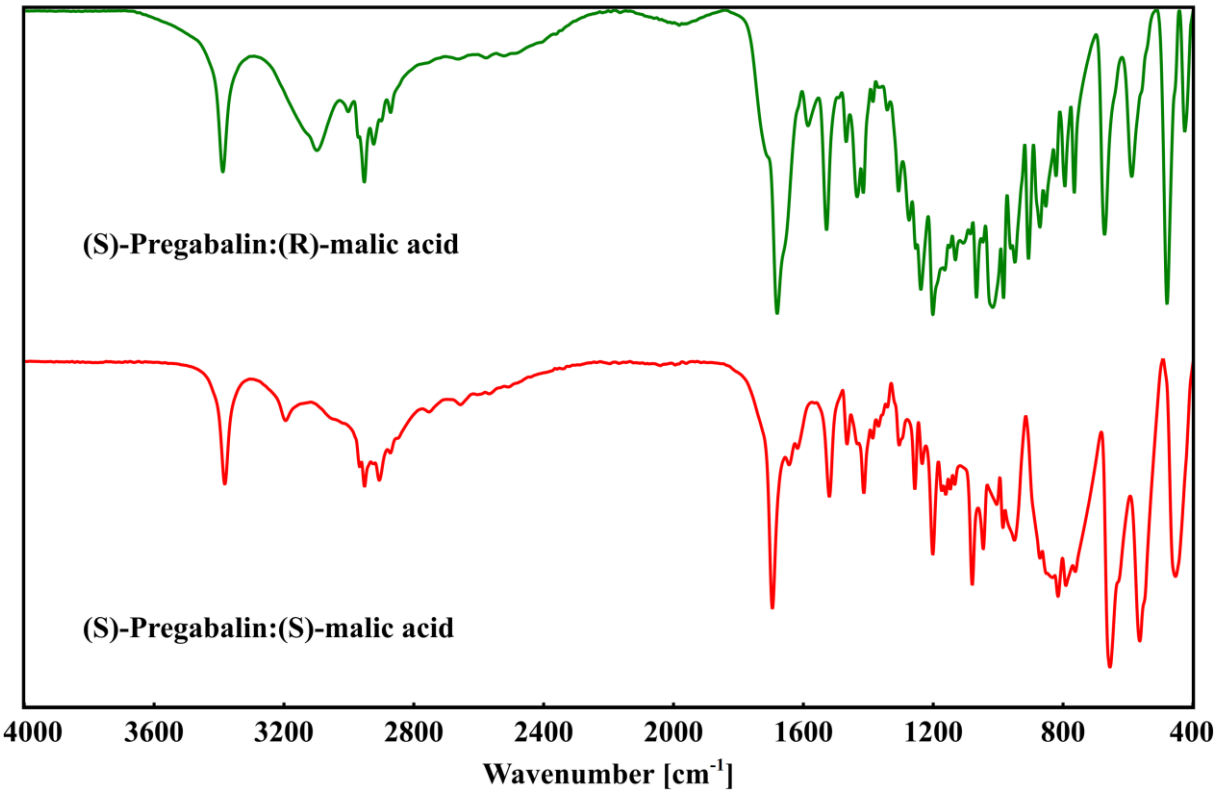

Figure S38. *IR-spectra of (S, S)-Pregabalin:malic acid (red) and (S, R)-Pregabalin:malic acid (green). The range from 400cm^{-1} to 4000 cm^{-1} is depicted*

Table S30. *E_{iss} in aspirin, benzoic acid, naphthalene, carbendazim and fenamic acid.*

	Aspirin	Benzoic acid	Naphthalene	Carbendazim Maleate	Fenamic acid
Total energy	-336.89571169 Ry	-864.48414572 Ry	-380.80902318 Ry	-2238.93849076 Ry	-1405.14750341 Ry
Estimated scf accuracy	9.5E-10 Ry	6.3E-09 Ry	4.0E-09 Ry	3.6E-09 Ry	2.5E-09 Ry
One-electron contribution	-1312.88831935 Ry	-431.66148218 Ry	-151.00679470 Ry	-1356.79696542 Ry	-729.97165977 Ry
Hartree contribution	666.38808897 Ry	288.25452830 Ry	111.67278034 Ry	865.02235307 Ry	491.21003984 Ry
Xc contribution	-75.71501968 Ry	-202.93841066 Ry	-102.34427854 Ry	-522.41418926 Ry	-350.97309805 Ry
Ewald contribution	474.77906097 Ry	-280.15301891 Ry	-121.17790015 Ry	-699.48265014 Ry	-435.89581744 Ry
DFT-D3 Dispersion	-0.01546025 Ry	-0.19853529 Ry	-0.12203006 Ry	-0.46184980 Ry	-0.36727809 Ry
One-center paw contribution	-89.44406235 Ry	-237.78722698 Ry	-117.83080007 Ry	-524.80518921 Ry	-379.14968990 Ry
PAW Hartree energy AE	27.95344349 Ry	112.86367996 Ry	46.89218991 Ry	140.64296658 Ry	84.07972051 Ry
PAW Hartree energy PS	-27.92749991 Ry	-112.54564220 Ry	-46.84845552 Ry	-140.30422592 Ry	-84.00187446 Ry
PAW xc energy AE	-30.96576143 Ry	-95.09279017 Ry	-51.68945232 Ry	-126.04609233 Ry	-92.95386241 Ry
PAW xc energy PS	13.26792153 Ry	41.22003547 Ry	22.18801792 Ry	54.48770059 Ry	39.85979623 Ry
Total E_H with PAW	666.41403255 Ry	288.57256606 Ry	111.71651473 Ry	865.36109373 Ry	491.28788589 Ry
Total E_XC with PAW	-93.41285959 Ry	-256.81116536 Ry	-131.84571294 Ry	-593.97258100 Ry	-404.06716423 Ry

Table S31. *E_{iss} in glycine polymorphs α – γ.*

	Glycine α	Glycine β	Glycine γ
Total energy	-580.75928600 Ry	-290.37728560 Ry	-435.57100873 Ry
Estimated scf accuracy	2.5E-09 Ry	1.4E-09 Ry	6.9E-10 Ry
One-electron contribution	-214.06562382 Ry	-110.70421627 Ry	-173.43139417 Ry
Hartree contribution	161.38931511 Ry	82.32377227 Ry	126.72740778 Ry
Xc contribution	-133.72136785 Ry	-66.86096752 Ry	-100.28869051 Ry
Ewald contribution	-274.25350224 Ry	-135.08390726 Ry	-198.50249159 Ry
DFT-D3 Dispersion	-0.15132600 Ry	-0.07472014 Ry	-0.11108147 Ry
One-center paw contribution	-119.95678120 Ry	59.97724668 Ry	-89.96475877 Ry
PAW Hartree energy AE	18.36286775 Ry	18.33019638 Ry	65.24929324 Ry
PAW Hartree energy PS	-18.34599330 Ry	-18.31334187 Ry	-64.97916769 Ry
PAW xc energy AE	-20.57600967 Ry	-20.56792933 Ry	-43.28660728 Ry
PAW xc energy PS	8.78096894 Ry	8.77300925 Ry	18.91587444 Ry
Total E_H with PAW	161.40618955 Ry	82.34062678 Ry	126.99753334 Ry
Total E_XC with PAW	-145.51640859 Ry	-78.65588760 Ry	-124.65942334 Ry

Table S32. *E_{iss} in (S)- and (R)-Pregabalin and (rac)-Phenibut*

	(S)-**1**	(R)-**1**	(rac)-**2**
Total energy	-1071.80165524 Ry	-1071.80170922 Ry	-2395.20650159 Ry
Estimated scf accuracy	5.1E-09 Ry	5.5E-09 Ry	0.00000016 Ry
One-electron contribution	-577.36224332 Ry	-577.93818768 Ry	-1174.63541450 Ry
Hartree contribution	387.44493557 Ry	387.65747211 Ry	811.05092165 Ry
Xc contribution	-277.66481361 Ry	-277.65938926 Ry	-604.74515244 Ry
Ewald contribution	-342.65463124 Ry	-342.29766682 Ry	-809.28613616 Ry
DFT-D3 Dispersion	-0.32003300 Ry	-0.31943849 Ry	-0.68856853 Ry
One-center paw contribution	-261.24486964 Ry	-261.24449907 Ry	-616.90215161 Ry
PAW Hartree energy AE	129.27305249 Ry	129.26729739 Ry	148.84527047 Ry
PAW Hartree energy PS	-128.94468573 Ry	-128.93889306 Ry	-148.49765287 Ry
PAW xc energy AE	-115.21439958 Ry	-115.21241556 Ry	-136.12237355 Ry
PAW xc energy PS	49.57481541 Ry	49.57288647 Ry	58.66198700 Ry
Total E_H with PAW	387.77330234 Ry	387.98587643 Ry	811.39853925 Ry
Total E_XC with PAW	-343.30439778 Ry	-343.29891835 Ry	-682.20553899 Ry

Table S33. *E_{iss} in (S, S)-, (R, R)-, (S, R)- and (R, S)-Pregabalin:mandelic acid.*

	(S, S)-**1**:**3**	(R, R)-**1**:**3**	(S, R)-**1**:**3**	(R, S)-**1**:**3**
Total energy	-2182.72816251 Ry	-2182.72828907 Ry	-2182.68324007 Ry	-2182.68437385 Ry
Estimated scf accuracy	1.3E-09 Ry	1.8E-09 Ry	9.5E-09 Ry	8.0E-09 Ry
One-electron contribution	-1533.51665515 Ry	-1549.49021097 Ry	-1814.50402550 Ry	-1813.82535919 Ry
Hartree contribution	956.64051386 Ry	964.50310881 Ry	1097.70041506 Ry	1097.23254769 Ry
Xc contribution	-534.05440736 Ry	-534.04862113 Ry	-534.00508650 Ry	-533.99359867 Ry
Ewald contribution	-512.26754807 Ry	-504.16306644 Ry	-372.32105602 Ry	-372.54636041 Ry
DFT-D3 Dispersion	-0.55923671 Ry	-0.55880178 Ry	-0.56773385 Ry	-0.56710848 Ry
One-center paw contribution	-558.97082908 Ry	-558.97069756 Ry	-558.98575325 Ry	-558.98449480 Ry
PAW Hartree energy AE	262.04303170 Ry	129.73847311 Ry	270.35132574 Ry	242.94333815 Ry
PAW Hartree energy PS	-261.15762810 Ry	-129.40728577 Ry	-269.46383582 Ry	-242.18723498 Ry
PAW xc energy AE	-202.21748403 Ry	-115.29581401 Ry	-212.40131788 Ry	-196.00997753 Ry
PAW xc energy PS	87.81410231 Ry	49.65568953 Ry	92.09786596 Ry	84.94470266 Ry
Total E_H with PAW	957.52591746 Ry	964.83429615 Ry	1098.58790498 Ry	1097.98865086 Ry
Total E_XC with PAW	-648.45778908 Ry	-599.68874561 Ry	-654.30853843 Ry	-645.05887354 Ry

Table S34. *E_{iss} in (S, S)- and (S, R)-Pregabalin:malic acid and (R, S)-Phenibut:mandelic acid.*

	(S, S)-**1**:**4**	(S, R)-**1**:**4**	(R, S)-**2**:**3**
Total energy	-2213.33656663 Ry	-2213.34434886 Ry	-1154.26774184 Ry
Estimated scf accuracy	1.3E-09 Ry	1.0E-08 Ry	1.6E-09 Ry
One-electron contribution	-1432.30160955 Ry	-1411.01995314 Ry	-662.88344334 Ry
Hartree contribution	901.97731634 Ry	891.31218524 Ry	431.46603161 Ry
Xc contribution	-514.37445599 Ry	-514.40952926 Ry	-279.31815141 Ry
Ewald contribution	-630.60581621 Ry	-641.20468387 Ry	-340.16377027 Ry
DFT-D3 Dispersion	-0.51310661 Ry	-0.51584702 Ry	-0.28393580 Ry
One-center paw contribution	-537.51889461 Ry	-537.50652081 Ry	-303.08447264 Ry
PAW Hartree energy AE	280.18921538 Ry	280.30096324 Ry	159.32291534 Ry
PAW Hartree energy PS	-279.18535867 Ry	-279.29446844 Ry	-158.85326536 Ry
PAW xc energy AE	-208.23496725 Ry	-208.24379479 Ry	-132.16104066 Ry
PAW xc energy PS	90.51428806 Ry	90.52373303 Ry	57.25806117 Ry
Total E_H with PAW	902.98117305 Ry	892.31868004 Ry	431.93568158 Ry
Total E_XC with PAW	-632.09513518 Ry	-632.12959102 Ry	-354.22113089 Ry

Table S35. *E_{isg} in aspirin, benzoic acid and naphthalene.*

	Aspirin	Benzoic acid	Naphthalene
Total energy	-336.89571169 Ry	-216.03921007 Ry	-190.34591573 Ry
Estimated scf accuracy	9.5E-10 Ry	4.8E-09 Ry	1.2E-09 Ry
One-electron contribution	-1312.88831935 Ry	-739.41836998 Ry	-736.59527298 Ry
Hartree contribution	666.38808897 Ry	376.18668573 Ry	374.44538692 Ry
Xc contribution	-75.71501968 Ry	-50.59087816 Ry	-51.06730146 Ry
Ewald contribution	474.77906097 Ry	257.24406025 Ry	281.79361367 Ry
DFT-D3 Dispersion	-0.01546025 Ry	-0.00788014 Ry	-0.00959746 Ry
One-center paw contribution	-89.44406235 Ry	-59.45282779 Ry	-58.91274441 Ry
PAW Hartree energy AE	27.95344349 Ry	56.37489016 Ry	28.13589881 Ry
PAW Hartree energy PS	-27.92749991 Ry	-56.11525462 Ry	-28.10975625 Ry
PAW xc energy AE	-30.96576143 Ry	-33.04993323 Ry	-31.01244409 Ry
PAW xc energy PS	13.26792153 Ry	14.57723675 Ry	13.31273914 Ry
Total E_H with PAW	666.41403255 Ry	376.44632128 Ry	374.47152947 Ry
Total E_XC with PAW	-93.41285959 Ry	-69.06357463 Ry	-68.76700641 Ry

Table S36. *E_{isg} in Carbendazim maleate, Carbendazim charged, Carbendazim neutral, maleic acid charged and maleic acid neutral.*

	Carbendazim (neutral)	Carbendazim (charge)	Maleic acid (neutral)	Maleic acid (charge)
Total energy	-317.81712031 Ry	-318.65170796 Ry	-241.69462491 Ry	-240.74748977 Ry
Estimated scf accuracy	5.4E-09 Ry	1.4E-09 Ry	8.6E-09 Ry	2.6E-09 Ry
One-electron contribution	-1331.80840675 Ry	-1349.82911878 Ry	-750.38874570 Ry	-741.67106561 Ry
Hartree contribution	675.48840558 Ry	677.97198443 Ry	381.58547061 Ry	383.02285946 Ry
Xc contribution	-80.09207190 Ry	-80.33880782 Ry	-50.11394916 Ry	-49.86629580 Ry
Ewald contribution	489.82645736 Ry	504.77755561 Ry	237.21931250 Ry	227.76142495 Ry
DFT-D3 Dispersion	-0.01432587 Ry	-0.01529829 Ry	-0.00631915 Ry	-0.00561997 Ry
One-center paw contribution	-71.21717873 Ry	-71.21802311 Ry	-59.99039401 Ry	-59.98879279 Ry
PAW Hartree energy AE	0.00000000 Ry	0.00000000 Ry	56.55146170 Ry	55.97546094 Ry
PAW Hartree energy PS	0.00000000 Ry	0.00000000 Ry	-56.29063300 Ry	-55.71544737 Ry
PAW xc energy AE	0.00000000 Ry	0.00000000 Ry	-33.07681606 Ry	-32.98567477 Ry
PAW xc energy PS	0.00000000 Ry	0.00000000 Ry	14.60409227 Ry	14.51384719 Ry
Total E_H with PAW	675.48840558 Ry	677.97198443 Ry	381.84629932 Ry	383.28287303 Ry
Total E_XC with PAW	-80.09207190 Ry	-80.33880782 Ry	-68.58667296 Ry	-68.33812339 Ry

Table S37. *E_{isg} in fenamic acid, molecule A and molecule B as well as Glycine α, neutral and zwitterionic.*

	Fenamic acid A	Fenamic acid B	Glycine α (neutral)	Glycine α (zwitt.)
Total energy	-351.18463954 Ry	-351.18406565 Ry	-145.06565496 Ry	-145.06563313 Ry
Estimated scf accuracy	6.6E-09 Ry	8.5E-10 Ry	2.0E-09 Ry	5.3E-09 Ry
One-electron contribution	-1464.34559523 Ry	-1464.03566170 Ry	-444.69888481 Ry	-444.67960905 Ry
Hartree contribution	743.17809909 Ry	743.04041847 Ry	226.93765648 Ry	226.92649777 Ry
Xc contribution	-87.54431237 Ry	-87.54001696 Ry	-33.25141345 Ry	-33.25068021 Ry
Ewald contribution	552.33753090 Ry	552.16178021 Ry	135.94233456 Ry	135.93350594 Ry
DFT-D3 Dispersion	-0.01986038 Ry	-0.01987773 Ry	-0.00368100 Ry	-0.00368579 Ry
One-center paw contribution	-94.79050154 Ry	-94.79070794 Ry	-29.99166675 Ry	-29.99166178 Ry
PAW Hartree energy AE	37.19247007 Ry	27.85123707 Ry	18.22767627 Ry	18.22421611 Ry
PAW Hartree energy PS	-37.15820627 Ry	-27.82543755 Ry	-18.21084902 Ry	-18.20739007 Ry
PAW xc energy AE	-41.26733921 Ry	-30.94234266 Ry	-20.54299767 Ry	-20.54215868 Ry
PAW xc energy PS	17.67303721 Ry	13.24517069 Ry	8.74823976 Ry	8.74740701 Ry
Total E_H with PAW	743.21236288 Ry	743.06621799 Ry	226.95448372 Ry	226.94332381 Ry
Total E_XC with PAW	-111.13861438 Ry	-105.23718894 Ry	-45.04617137 Ry	-45.04543188 Ry

Table S38. *E_{isg} in Glycine β, neutral and zwitterionic as well as Glycine γ, neutral and zwitterionic.*

	Glycine β (neutral)	Glycine β (zwitt.)	Glycine γ (neutral)	Glycine γ (zwitt.)
Total energy	-145.06569801 Ry	-145.06570159 Ry	-145.05056883 Ry	-145.06557827 Ry
Estimated scf accuracy	6.9E-09 Ry	1.8E-09 Ry	4.9E-09 Ry	6.8E-09 Ry
One-electron contribution	-444.75995154 Ry	-444.62073980 Ry	-441.73616736 Ry	-444.81722053 Ry
Hartree contribution	226.97201711 Ry	226.90162080 Ry	225.42566450 Ry	226.99643361 Ry
Xc contribution	-33.25476841 Ry	-33.25109138 Ry	-33.22831266 Ry	-33.25077079 Ry
Ewald contribution	135.97232156 Ry	135.89987598 Ry	134.48347770 Ry	136.00136033 Ry
DFT-D3 Dispersion	-0.00367606 Ry	-0.00367672 Ry	-0.00395088 Ry	-0.00368777 Ry
One-center paw contribution	-29.99164066 Ry	-29.99169048 Ry	-29.99128013 Ry	-29.99169313 Ry
PAW Hartree energy AE	18.23912880 Ry	18.22323513 Ry	56.42606530 Ry	56.36291519 Ry
PAW Hartree energy PS	-18.22229626 Ry	-18.20640903 Ry	-56.16667109 Ry	-56.10418032 Ry
PAW xc energy AE	-20.54581868 Ry	-20.54192591 Ry	-33.05806132 Ry	-33.04778665 Ry
PAW xc energy PS	8.75102687 Ry	8.74717092 Ry	14.58523343 Ry	14.57528354 Ry
Total E_H with PAW	226.98884964 Ry	226.91844690 Ry	225.68505871 Ry	227.25516848 Ry
Total E_XC with PAW	-45.04956022 Ry	-45.04584637 Ry	-51.70114056 Ry	-51.72327390 Ry

Table S39. *E_{isg} in (S)-Pregabalin, neutral and zwitterionic, (R)-Pregabalin, neutral and zwitterionic as well as (rac)-Phenibut, neutral and zwitterionic.*

	(S)-**1** (neutral)	(S)-**1** (zwitt.)	(R)-**1** (neutral)	(R)-**1** (zwitt.)	(rac)-**2** (neutral)	(rac)-**2** (zwitt.)
Total energy	-267.79801705 Ry	-267.80747791 Ry	-267.79160852 Ry	-267.80763781 Ry	-299.23843736 Ry	-299.12073572 Ry
Estimated scf accuracy	1.0E-09 Ry	8.1E-09 Ry	1.6E-09 Ry	1.1E-09 Ry	3.8E-09 Ry	2.5E-09 Ry
One-electron contribution	-1132.97801838 Ry	-1137.10596586 Ry	-1139.37899930 Ry	-1137.15690002 Ry	-1233.30321001 Ry	-1243.07956735 Ry
Hartree contribution	576.18367680 Ry	577.94914245 Ry	579.17479627 Ry	577.96962803 Ry	626.59819637 Ry	631.59450463 Ry
Xc contribution	-69.16008416 Ry	-69.18545259 Ry	-69.15366478 Ry	-69.18727646 Ry	-75.30456653 Ry	-75.28054105 Ry
Ewald contribution	423.49226678 Ry	425.86835966 Ry	426.90277629 Ry	425.90049677 Ry	459.90584669 Ry	464.78434800 Ry
DFT-D3 Dispersion	-0.02235537 Ry	-0.02261513 Ry	-0.02260823 Ry	-0.02262865 Ry	-0.02054518 Ry	-0.02103308 Ry
One-center paw contribution	-65.31350272 Ry	-65.31094644 Ry	-65.31390877 Ry	-65.31095748 Ry	-77.11415871 Ry	-77.11844687 Ry
PAW Hartree energy AE	65.42093235 Ry	65.47325474 Ry	65.40966588 Ry	65.46862311 Ry	37.40491936 Ry	36.88010451 Ry
PAW Hartree energy PS	-65.15326146 Ry	-65.20405897 Ry	-65.14206060 Ry	-65.19944719 Ry	-37.26504078 Ry	-36.74389647 Ry
PAW xc energy AE	-43.30887949 Ry	-43.31644828 Ry	-43.30718024 Ry	-43.31556576 Ry	-26.80943871 Ry	-26.72862750 Ry
PAW xc energy PS	18.93592371 Ry	18.94489265 Ry	18.93411522 Ry	18.94402132 Ry	11.67352971 Ry	11.59424725 Ry
Total E_H with PAW	576.45134769 Ry	578.21833823 Ry	579.44240155 Ry	578.23880394 Ry	626.73807495 Ry	631.73071267 Ry
Total E_XC with PAW	-93.53303994 Ry	-93.55700822 Ry	-93.52672979 Ry	-93.55882090 Ry	-90.44047553 Ry	-90.41492130 Ry

Table S40. *E_{isg} in (S, S)-Pregabalin:mandelic acid, Pregabalin molecule A neutral and zwitterionic, Pregabalin molecule B neutral and zwitterionic, mandelic acid molecule A and mandelic acid molecule B.*

	(S)-**1_A** (neutral)	(S)-**1_A** (zwitt.)	(S)-**1_B** (neutral)	(S)-**1_B** (zwitt.)	(S)-**3_A** (neutral)	(S)-**3_B** (neutral)
Total energy	-267.79207687 Ry	-267.80896808 Ry	-267.79386670 Ry	-267.80897994 Ry	-277.62920472 Ry	-277.62892955 Ry
Estimated scf accuracy	8.4E-09 Ry	9.6E-09 Ry	1.4E-09 Ry	7.2E-09 Ry	8.4E-09 Ry	8.2E-09 Ry
One-electron contribution	-1146.57467144 Ry	-1149.12964591 Ry	-1150.27288277 Ry	-1149.76744088 Ry	-1029.52101511 Ry	-1029.30778810 Ry
Hartree contribution	582.84266957 Ry	584.04851409 Ry	584.64607854 Ry	584.36864185 Ry	523.17133645 Ry	523.06281742 Ry
Xc contribution	-69.15187735 Ry	-69.18326169 Ry	-69.16093982 Ry	-69.18745151 Ry	-63.90041076 Ry	-63.89877731 Ry
Ewald contribution	430.42887044 Ry	431.78954630 Ry	432.33012274 Ry	432.11151848 Ry	367.07359829 Ry	366.96757988 Ry
DFT-D3 Dispersion	-0.02309849 Ry	-0.02287750 Ry	-0.02321006 Ry	-0.02290010 Ry	-0.01230029 Ry	-0.01227256 Ry
One-center paw contribution	-65.31396958 Ry	-65.31124336 Ry	-65.31303533 Ry	-65.31134778 Ry	-74.44041329 Ry	-74.44048887 Ry
PAW Hartree energy AE	65.39274545 Ry	65.45833287 Ry	65.43766939 Ry	65.46017095 Ry	84.58268227 Ry	84.58009975 Ry
PAW Hartree energy PS	-65.12532377 Ry	-65.18933924 Ry	-65.16942296 Ry	-65.19119186 Ry	-84.19016010 Ry	-84.18763805 Ry
PAW xc energy AE	-43.30298523 Ry	-43.31464608 Ry	-43.30937372 Ry	-43.31535966 Ry	-49.57454296 Ry	-49.57420263 Ry
PAW xc energy PS	18.93003382 Ry	18.94297919 Ry	18.93652996 Ry	18.94368674 Ry	21.86736942 Ry	21.86699399 Ry
Total E_H with PAW	583.11009124 Ry	584.31750773 Ry	584.91432497 Ry	584.63762094 Ry	523.56385862 Ry	523.45527912 Ry
Total E_XC with PAW	-93.52482877 Ry	-93.55492858 Ry	-93.53378358 Ry	-93.55912444 Ry	-91.60758429 Ry	-91.60598595 Ry

Table S41. *E_{isg} in (R, R)-Pregabalin:mandelic acid, Pregabalin molecule A neutral and zwitterionic, Pregabalin molecule B neutral and zwitterionic, mandelic acid molecule A and mandelic acid molecule B.*

	(R)-**1_A** (neutral)	(R)-**1_A** (zwitt.)	(R)-**1_B** (neutral)	(R)-**1_B** (zwitt.)	(R)-**3_A** (neutral)	(R)-**3_B** (neutral)
Total energy	-267.79375084 Ry	-267.80898302 Ry	-267.79208315 Ry	-267.80900234 Ry	-277.62918420 Ry	-277.62894959 Ry
Estimated scf accuracy	4.5E-09 Ry	1.2E-09 Ry	8.4E-09 Ry	1.7E-09 Ry	4.2E-09 Ry	2.3E-09 Ry
One-electron contribution	-1150.18357840 Ry	-1149.37655749 Ry	-1146.61835649 Ry	-1149.27662069 Ry	-1029.64141539 Ry	-1029.31076807 Ry
Hartree contribution	584.60436837 Ry	584.17203235 Ry	582.86745891 Ry	584.12180134 Ry	523.23017098 Ry	523.06429268 Ry
Xc contribution	-69.16129377 Ry	-69.18656757 Ry	-69.15378472 Ry	-69.18739558 Ry	-63.90315362 Ry	-63.89762768 Ry
Ewald contribution	432.28297207 Ry	431.91632775 Ry	430.44963452 Ry	431.86736104 Ry	367.13794787 Ry	366.96786671 Ry
DFT-D3 Dispersion	-0.02319512 Ry	-0.02287986 Ry	-0.02309843 Ry	-0.02287231 Ry	-0.01230760 Ry	-0.01227643 Ry
One-center paw contribution	-65.31302397 Ry	-65.31133819 Ry	-65.31393693 Ry	-65.31127615 Ry	-74.44042645 Ry	-74.44043679 Ry
PAW Hartree energy AE	65.43436647 Ry	65.45507206 Ry	65.39334619 Ry	65.46939876 Ry	84.59206754 Ry	84.57999025 Ry
PAW Hartree energy PS	-65.16609918 Ry	-65.18611142 Ry	-65.12588796 Ry	-65.20034783 Ry	-84.19946124 Ry	-84.18751782 Ry
PAW xc energy AE	-43.30861886 Ry	-43.31433639 Ry	-43.30285552 Ry	-43.31665117 Ry	-49.57601963 Ry	-49.57417644 Ry
PAW xc energy PS	18.93578963 Ry	18.94268044 Ry	18.92991494 Ry	18.94496975 Ry	21.86883673 Ry	21.86697238 Ry
Total E_H with PAW	584.87263565 Ry	584.44099299 Ry	583.13491713 Ry	584.39085227 Ry	523.62277728 Ry	523.45676512 Ry
Total E_XC with PAW	-93.53412301 Ry	-93.55822352 Ry	-93.52672531 Ry	-93.55907699 Ry	-91.61033652 Ry	-91.60483174 Ry

Table S42. *E_{isg} in (S, R)-Pregabalin:mandelic acid, Pregabalin molecule A neutral, zwitterionic and charged as well as Pregabalin molecule B neutral, zwitterionic and charged.*

	(S)-**1_A** (neutral)	(S)-**1_A** (zwitt.)	(S)-**1_A** (charge)	(S)-**1_B** (neutral)	(S)-**1_B** (zwitt.)	(S)-**1_B** (charge)
Total energy	-267.79975583 Ry	-267.80894456 Ry	-268.64998668 Ry	-267.79703425 Ry	-267.80927522 Ry	-268.59869837 Ry
Estimated scf accuracy	2.6E-09 Ry	3.7E-09 Ry	4.5E-09 Ry	6.3E-09 Ry	1.2E-09 Ry	1.4E-09 Ry
One-electron contribution	-1150.32791801 Ry	-1144.52122571 Ry	-1157.74153844 Ry	-1061.81071755 Ry	-1170.79281370 Ry	-1175.44653807 Ry
Hartree contribution	584.88706105 Ry	581.71822027 Ry	582.42093762 Ry	540.85882190 Ry	594.89073189 Ry	591.44772100 Ry
Xc contribution	-69.16647533 Ry	-69.18155183 Ry	-69.41358892 Ry	-69.16717044 Ry	-69.19667954 Ry	-69.36887551 Ry
Ewald contribution	432.14302255 Ry	429.50919174 Ry	441.41688917 Ry	387.65948308 Ry	442.62496333 Ry	450.10991996 Ry
DFT-D3 Dispersion	-0.02306737 Ry	-0.02269933 Ry	-0.02362598 Ry	-0.02360571 Ry	-0.02410924 Ry	-0.02498421 Ry
One-center paw contribution	-65.31237873 Ry	-65.31087970 Ry	-65.30906012 Ry	-65.31384553 Ry	-65.31136797 Ry	-65.31594154 Ry
PAW Hartree energy AE	65.49651598 Ry	65.35817895 Ry	65.73962312 Ry	65.38430547 Ry	65.41420775 Ry	65.45657948 Ry
PAW Hartree energy PS	-65.22864191 Ry	-65.08926967 Ry	-65.46853461 Ry	-65.11687067 Ry	-65.14561066 Ry	-65.18980703 Ry
PAW xc energy AE	-43.31230587 Ry	-43.27938939 Ry	-43.33943230 Ry	-43.30085731 Ry	-43.30791188 Ry	-43.31980347 Ry
PAW xc energy PS	18.94509686 Ry	18.91257740 Ry	18.97314775 Ry	18.92766341 Ry	18.93618130 Ry	18.94662604 Ry
Total E_H with PAW	585.15493511 Ry	581.98712956 Ry	582.69202613 Ry	541.12625670 Ry	595.15932898 Ry	591.71449345 Ry
Total E_XC with PAW	-93.53368433 Ry	-93.54836382 Ry	-93.77987347 Ry	-93.54036434 Ry	-93.56841013 Ry	-93.74205294 Ry

Table S43. *E_{isg} in (S, R)-Pregabalin:mandelic acid, mandelic acid molecule A. neutral and charged, as well as mandelic acid molecule B, neutral and charged.*

	(R)-**3_A** (neutral)	(R)-**3_A** (charge)	(R)-**3_B** (neutral)	(R)-**3_B** (charge)
Total energy	-277.62952062 Ry	-276.65200500 Ry	-277.63008521 Ry	-276.63285774 Ry
Estimated scf accuracy	9.8E-09 Ry	1.8E-09 Ry	5.7E-09 Ry	0.00000095 Ry
One-electron contribution	-984.02556825 Ry	-836.65595354 Ry	-1033.27892563 Ry	-1015.73101764 Ry
Hartree contribution	500.53925577 Ry	431.98760346 Ry	525.05776382 Ry	522.32497785 Ry
Xc contribution	-63.91233143 Ry	-63.65826059 Ry	-63.91244102 Ry	-63.62993845 Ry
Ewald contribution	344.22059760 Ry	266.12644157 Ry	368.95578786 Ry	354.85796838 Ry
DFT-D3 Dispersion	-0.01254664 Ry	-0.01182641 Ry	-0.01256058 Ry	-0.01144589 Ry
One-center paw contribution	-74.43892767 Ry	-74.44000949 Ry	-74.43970966 Ry	-74.44340199 Ry
PAW Hartree energy AE	84.68111468 Ry	83.61206042 Ry	84.64220632 Ry	83.33311012 Ry
PAW Hartree energy PS	-84.28761471 Ry	-83.22235287 Ry	-84.24910181 Ry	-82.94553301 Ry
PAW xc energy AE	-49.58968685 Ry	-49.41921197 Ry	-49.58361938 Ry	-49.37621997 Ry
PAW xc energy PS	21.88259150 Ry	21.71404709 Ry	21.87654439 Ry	21.67079171 Ry
Total E_H with PAW	500.93275574 Ry	432.37731101 Ry	525.45086832 Ry	522.71255496 Ry
Total E_XC with PAW	-91.61942678 Ry	-91.36342547 Ry	-91.61951601 Ry	-91.33536671 Ry

Table S44. *E_{isg} in (R, S)-Pregabalin:mandelic acid, Pregabalin molecule A neutral, zwitterionic and charged as well as Pregabalin molecule B neutral, zwitterionic and charged.*

	(R)-**1**_**A** (neutral)	(R)-**1**_**A** (zwitt.)	(R)-**1**_**A** (charge)	(R)-**1**_**B** (neutral)	(R)-**1**_**B** (zwitt.)	(R)-**1**_**B** (charge)
Total energy	-267.79396641 Ry	-267.80931677 Ry	-268.59858887 Ry	-267.79977164 Ry	-267.80896960 Ry	-268.65003203 Ry
Estimated scf accuracy	4.0E-09 Ry	7.7E-10 Ry	8.0E-09 Ry	6.1E-09 Ry	2.4E-09 Ry	1.4E-09 Ry
One-electron contribution	-1153.10618141 Ry	-1170.83568908 Ry	-1175.35713834 Ry	-1151.10825527 Ry	-1144.69063057 Ry	-1158.22261487 Ry
Hartree contribution	586.31973900 Ry	594.91086176 Ry	591.41405146 Ry	585.27837240 Ry	581.80257085 Ry	582.65951124 Ry
Xc contribution	-69.15451484 Ry	-69.19512398 Ry	-69.36695264 Ry	-69.16943185 Ry	-69.18286439 Ry	-69.41795409 Ry
Ewald contribution	433.48355758 Ry	442.64608092 Ry	450.05223978 Ry	432.53498839 Ry	429.59556094 Ry	441.66382314 Ry
DFT-D3 Dispersion	-0.02323917 Ry	-0.02411122 Ry	-0.02498764 Ry	-0.02309794 Ry	-0.02270447 Ry	-0.02364287 Ry
One-center paw contribution	-65.31332757 Ry	-65.31133516 Ry	-65.31580150 Ry	-65.31234738 Ry	-65.31090194 Ry	-65.30915459 Ry
PAW Hartree energy AE	65.38648975 Ry	65.42178049 Ry	65.46347958 Ry	65.42252282 Ry	65.47250700 Ry	65.75107390 Ry
PAW Hartree energy PS	-65.11894629 Ry	-65.15316949 Ry	-65.19662209 Ry	-65.15426466 Ry	-65.20327838 Ry	-65.47967284 Ry
PAW xc energy AE	-43.30046858 Ry	-43.30947470 Ry	-43.32057164 Ry	-43.30306322 Ry	-43.31621869 Ry	-43.35300760 Ry
PAW xc energy PS	18.92728254 Ry	18.93772130 Ry	18.94743884 Ry	18.93057606 Ry	18.94465890 Ry	18.98099465 Ry
Total E_H with PAW	586.58728247 Ry	595.17947276 Ry	591.68090895 Ry	585.54663056 Ry	582.07179947 Ry	582.93091231 Ry
Total E_XC with PAW	-93.52770087 Ry	-93.56687738 Ry	-93.74008544 Ry	-93.54191901 Ry	-93.55442418 Ry	-93.78996704 Ry

Table S45. *E_{isg} in (R, S)-Pregabalin:mandelic acid, mandelic acid molecule A. neutral and charged, as well as mandelic acid molecule B, neutral and charged.*

	(S)-**3**_**A** (neutral)	(S)-**3**_**A** (charge)	(S)-**3**_**B** (neutral)	(S)-**3**_**B** (charge)
Total energy	-277.62917802 Ry	-276.64477180 Ry	-277.62574657 Ry	-276.63279628 Ry
Estimated scf accuracy	1.8E-09 Ry	2.3E-09 Ry	1.2E-09 Ry	8.7E-09 Ry
One-electron contribution	-1032.66358245 Ry	-1015.49434460 Ry	-1029.31666511 Ry	-1015.84614954 Ry
Hartree contribution	524.74114097 Ry	522.28819002 Ry	523.03937919 Ry	522.38115878 Ry
Xc contribution	-63.90590518 Ry	-63.64845335 Ry	-63.90083528 Ry	-63.62862274 Ry
Ewald contribution	368.65199764 Ry	354.66134689 Ry	367.00633024 Ry	354.91564817 Ry
DFT-D3 Dispersion	-0.01242153 Ry	-0.01169329 Ry	-0.01226152 Ry	-0.01145176 Ry
One-center paw contribution	-74.44040748 Ry	-74.43981747 Ry	-74.44169408 Ry	-74.44337920 Ry
PAW Hartree energy AE	84.60083134 Ry	83.58818023 Ry	84.51268735 Ry	83.32830041 Ry
PAW Hartree energy PS	-84.20818012 Ry	-83.19857792 Ry	-84.12089990 Ry	-82.94079809 Ry
PAW xc energy AE	-49.57735772 Ry	-49.41527993 Ry	-49.56417359 Ry	-49.37532787 Ry
PAW xc energy PS	21.87018418 Ry	21.71022287 Ry	21.85672289 Ry	21.66997428 Ry
Total E_H with PAW	525.13379219 Ry	522.67779234 Ry	523.43116664 Ry	522.76866110 Ry
Total E_XC with PAW	-91.61307873 Ry	-91.35351042 Ry	-91.60828599 Ry	-91.33397632 Ry

Table S46. *E_{isg} in (S, S)-Pregabalin:malic acid, Pregabalin neutral, zwitterionic and charged, as well as malic acid neutral and charged.*

	(S)-**1** (neutral)	(S)-**1** (zwitt.)	(S)-**1** (charge)	(S)-**4** (neutral)	(S)-**4** (charge)
Total energy	-267.79195190 Ry	-267.80910065 Ry	-268.61129733 Ry	-285.25372379 Ry	-284.27132001 Ry
Estimated scf accuracy	6.9E-10 Ry	8.4E-09 Ry	5.7E-09 Ry	1.7E-09 Ry	4.4E-09 Ry
One-electron contribution	-1136.31452856 Ry	-1145.23419082 Ry	-1149.91381033 Ry	-950.21680717 Ry	-935.83302748 Ry
Hartree contribution	577.57489783 Ry	582.07656352 Ry	578.72969549 Ry	483.26247560 Ry	482.11646018 Ry
Xc contribution	-69.15816236 Ry	-69.18910101 Ry	-69.37979494 Ry	-58.94285641 Ry	-58.66689854 Ry
Ewald contribution	425.44242786 Ry	429.87147012 Ry	437.28987967 Ry	309.73863934 Ry	297.20839694 Ry
DFT-D3 Dispersion	-0.02283875 Ry	-0.02270041 Ry	-0.02381648 Ry	-0.00965105 Ry	-0.00883028 Ry
One-center paw contribution	-65.31374792 Ry	-65.31114206 Ry	-65.31345074 Ry	-69.08552410 Ry	-69.08742084 Ry
PAW Hartree energy AE	65.41975252 Ry	65.47797193 Ry	65.59295620 Ry	56.20194601 Ry	56.03295602 Ry
PAW Hartree energy PS	-65.15208371 Ry	-65.20880712 Ry	-65.32452334 Ry	-55.94103201 Ry	-55.77213855 Ry
PAW xc energy AE	-43.30944981 Ry	-43.31787678 Ry	-43.33918912 Ry	-33.02222717 Ry	-32.99354773 Ry
PAW xc energy PS	18.93635720 Ry	18.94625060 Ry	18.96680997 Ry	14.55058100 Ry	14.52276720 Ry
Total E_H with PAW	577.84256664 Ry	582.34572833 Ry	578.99812834 Ry	483.52338960 Ry	482.37727766 Ry
Total E_XC with PAW	-93.53125497 Ry	-93.56072719 Ry	-93.75217409 Ry	-77.41450259 Ry	-77.13767908 Ry

Table S47. *E_{isg} in (S, R)-Pregabalin:malic acid, Pregabalin neutral, zwitterionic and charged, as well as malic acid neutral and charged.*

	(S)-**1** (neutral)	(S)-**1** (zwitt.)	(S)-**1** (charge)	(R)-**4** (neutral)	(R)-**4** (charge)
Total energy	-267.79369461 Ry	-267.80879947 Ry	-268.61135562 Ry	-285.25091193 Ry	-284.22893057 Ry
Estimated scf accuracy	1.6E-09 Ry	3.6E-09 Ry	1.0E-09 Ry	1.9E-09 Ry	9.8E-10 Ry
One-electron contribution	-1131.28671043 Ry	-1143.86090533 Ry	-1149.82367760 Ry	-952.95477737 Ry	-939.85881162 Ry
Hartree contribution	575.19633096 Ry	581.38466378 Ry	578.68652083 Ry	484.68449087 Ry	484.06054389 Ry
Xc contribution	-69.15608675 Ry	-69.18925831 Ry	-69.37972215 Ry	-58.94229589 Ry	-58.63695052 Ry
Ewald contribution	422.78905988 Ry	429.19015031 Ry	437.24272236 Ry	311.05700150 Ry	299.30453850 Ry
DFT-D3 Dispersion	-0.02257561 Ry	-0.02266884 Ry	-0.02379310 Ry	-0.00974501 Ry	-0.00955013 Ry
One-center paw contribution	-65.31371266 Ry	-65.31078108 Ry	-65.31340595 Ry	-69.08558604 Ry	-69.08870068 Ry
PAW Hartree energy AE	65.43919007 Ry	65.48267393 Ry	65.59452810 Ry	56.82543535 Ry	56.02910396 Ry
PAW Hartree energy PS	-65.17159110 Ry	-65.21334090 Ry	-65.32605466 Ry	-56.56252940 Ry	-55.77055731 Ry
PAW xc energy AE	-43.31264115 Ry	-43.31764738 Ry	-43.33959060 Ry	-33.11632309 Ry	-32.99343133 Ry
PAW xc energy PS	18.93954975 Ry	18.94609891 Ry	18.96723529 Ry	14.64453392 Ry	14.52167757 Ry
Total E_H with PAW	575.46392994 Ry	581.65399680 Ry	578.95499427 Ry	484.94739682 Ry	484.31909053 Ry
Total E_XC with PAW	-93.52917815 Ry	-93.56080677 Ry	-93.75207746 Ry	-77.41408506 Ry	-77.10870427 Ry

Table S48. *E_{isg} in (R, S)-Phenibut:mandelic acid, Phenibut neutral and zwitterionic as well as mandelic acid neutral.*

	(R)-**2** (neutral)	(R)-**2** (zwitt.)	(S)-**3** (neutral)
Total energy	-299.24118523 Ry	-299.24903734 Ry	-277.63003077 Ry
Estimated scf accuracy	2.0E-09 Ry	5.2E-09 Ry	4.4E-09 Ry
One-electron contribution	-1241.39331178 Ry	-1237.67805463 Ry	-1030.68394340 Ry
Hartree contribution	630.84461220 Ry	628.70733242 Ry	523.76518044 Ry
Xc contribution	-75.31692750 Ry	-75.33402510 Ry	-63.90941862 Ry
Ewald contribution	463.75757796 Ry	462.18718074 Ry	367.65037561 Ry
DFT-D3 Dispersion	-0.02048529 Ry	-0.02027812 Ry	-0.01241815 Ry
One-center paw contribution	-77.11265082 Ry	-77.11119265 Ry	-74.43980665 Ry
PAW Hartree energy AE	65.42696385 Ry	65.47298401 Ry	84.63610579 Ry
PAW Hartree energy PS	-65.15878090 Ry	-65.20386654 Ry	-84.24306855 Ry
PAW xc energy AE	-43.30416156 Ry	-43.31677390 Ry	-49.58274610 Ry
PAW xc energy PS	18.93168269 Ry	18.94518322 Ry	21.87563244 Ry
Total E_H with PAW	631.11279515 Ry	628.97644989 Ry	524.15821768 Ry
Total E_XC with PAW	-99.68940637 Ry	-99.70561579 Ry	-91.61653228 Ry

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