Table S1 Crystal data and structure refinement for mirabegron edisylate monohydrate form 1A

Empirical formula	$C_{23}H_{32}N_4O_9S_3$
Formula weight	604.70
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	14.8579(8)
b/Å	10.6858(5)
c/Å	18.1456(9)
α/°	90
β/°	111.810(6)
γ/°	90
Volume/Å^3	2674.7(3)
Z	4
ρ_{calc}g/cm^3	1.502
μ/mm^{-1}	3.055
F(000)	1272.0
Crystal size/mm^3	0.11 × 0.035 × 0.015
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.246 to 136.464
Index ranges	-17 ≤ h ≤ 16, -12 ≤ k ≤ 12, -20 ≤ l ≤ 21
Reflections collected	15978
Independent reflections	8292 [R_{int} = 0.0337, R_{sigma} = 0.0360]
Data/restraints/parameters	8292/1/717
Goodness-of-fit on F^2	1.024
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.0960
Final R indexes [all data]	R_1 = 0.0485, wR_2 = 0.1003
Largest diff. peak/hole / e Å^{-3}	0.54/-0.45
Flack parameter	0.051(14)

Crystal Data for $C_{23}H_{32}N_4O_9S_3$ (*M* =604.70 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 14.8579(8) Å, *b* = 10.6858(5) Å, *c* = 18.1456(9) Å, *β* = 111.810(6)°, *V* = 2674.7(3) Å^3, *Z* = 4, *T* = 100.01(10) K, μ(Cu Kα) = 3.055 mm^{-1}, *Dcalc* = 1.502 g/cm^3, 15978 reflections measured (5.246° ≤ 2Θ ≤ 136.464°), 8292 unique (R_{int} = 0.0337, R_{sigma} = 0.0360) which were used in all calculations. The final R_1 was 0.0410 (I > 2σ(I)) and wR_2 was 0.1003 (all data). CCDC: 2388447

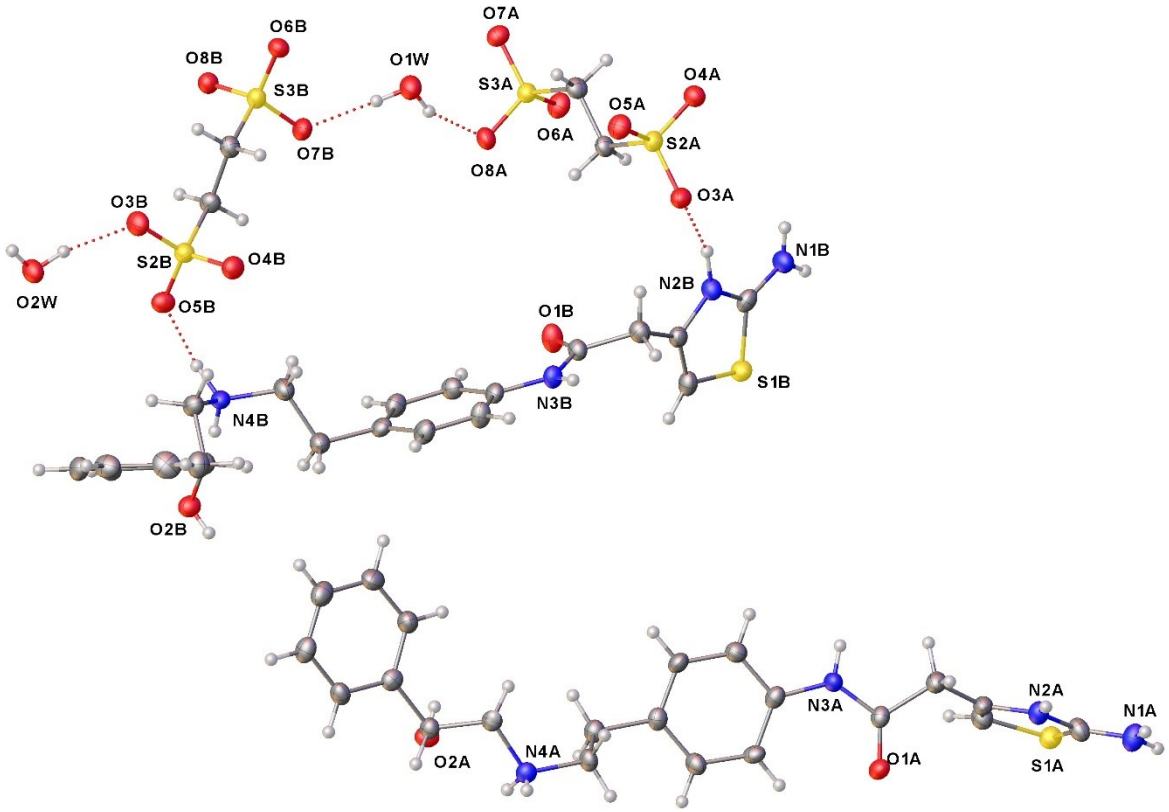

Figure S1 ORTEP representation of the mirabegron edisylate monohydrate form 1A

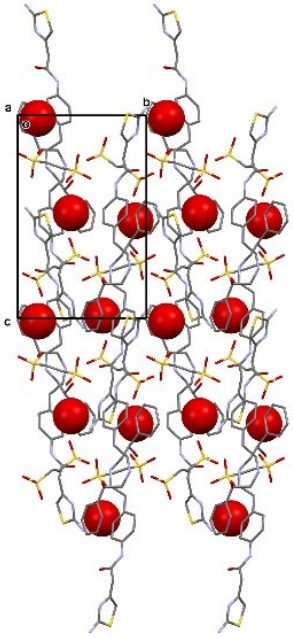

Figure S2 Crystal packing of mirabegron edisylate monohydrate form 1A viewed down the crystallographic a-axis showing positions of the water molecules

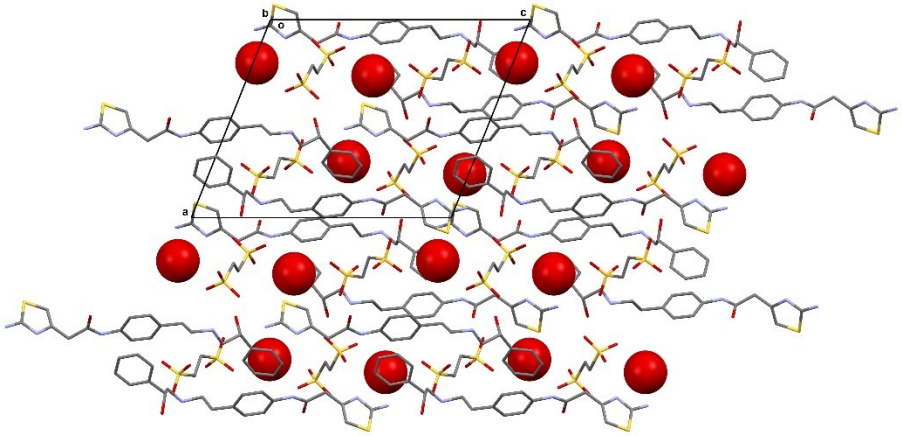

Figure S3 Crystal packing of mirabegron edisylate monohydrate form 1A viewed down the crystallographic b-axis showing positions of the water molecules

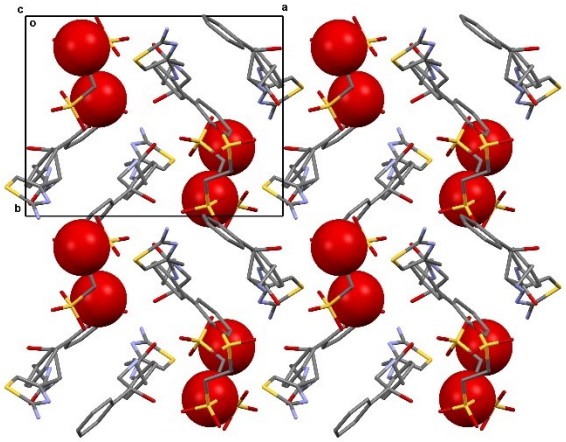

Figure S4 Crystal packing of mirabegron edisylate monohydrate form 1A viewed down the crystallographic c-axis showing positions of the water molecules

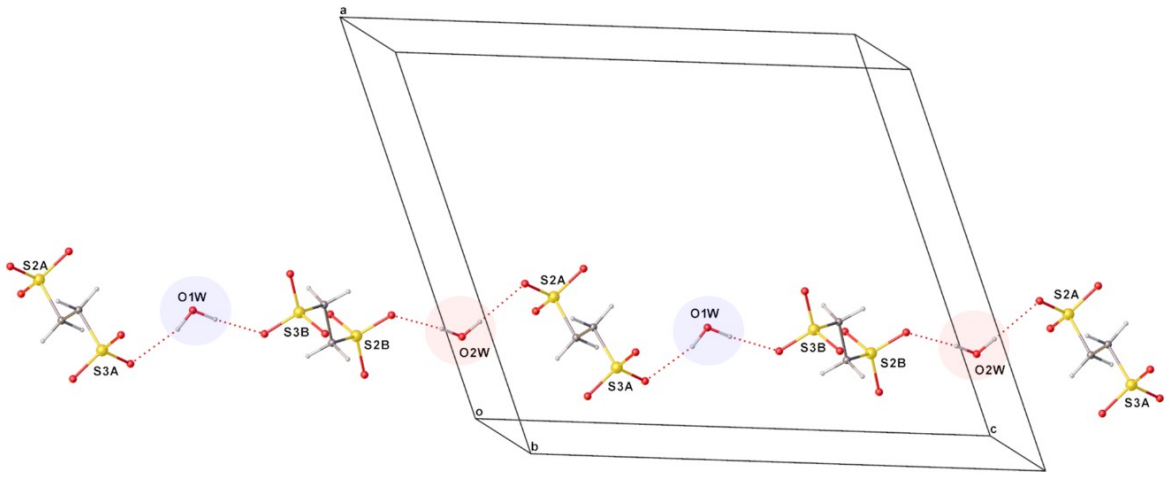

Figure S5 An infinite chain of alternating-EDS-water-EDS-water- in Mrbg EDS form 1A propagating along crystallographic c-axis

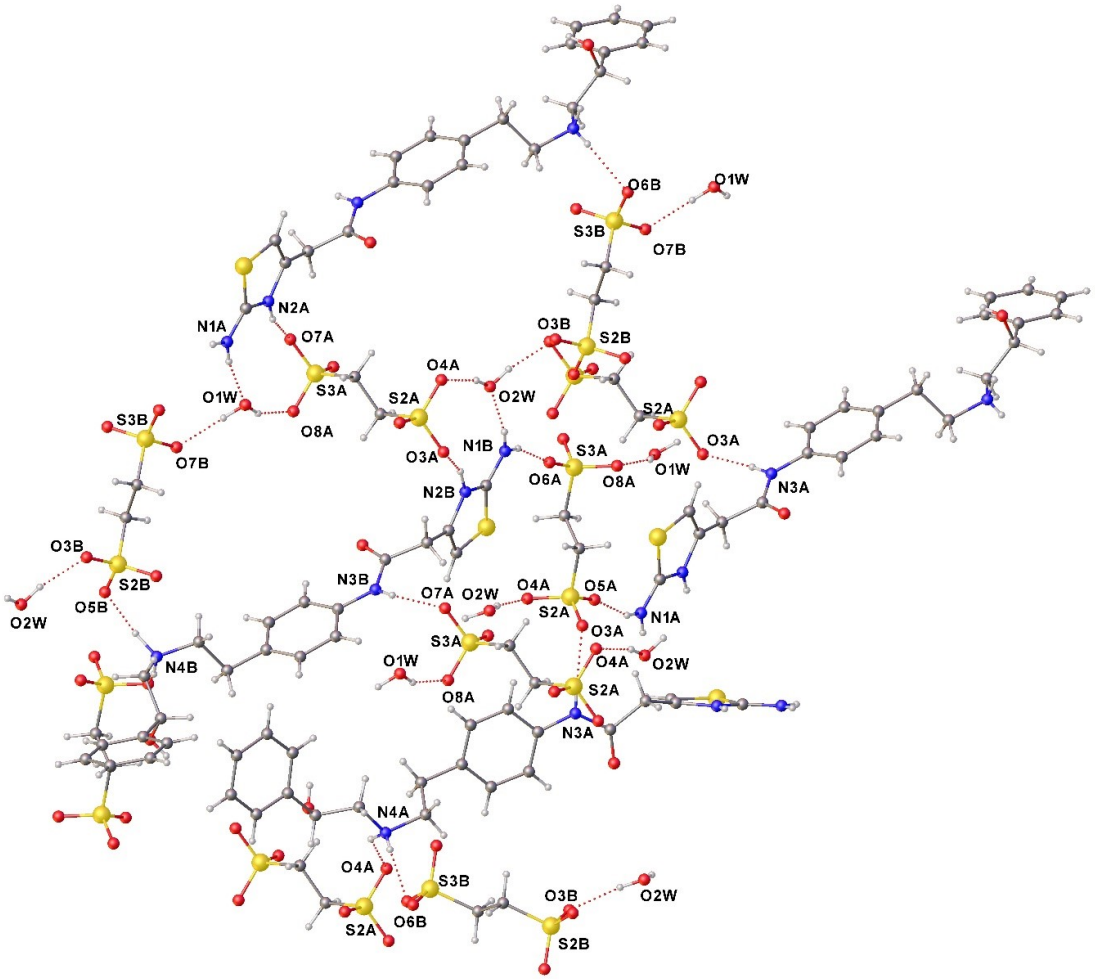

Figure S6 Hydrogen bond network in the mirabegron edisylate monohydrate form 1A structure. Hydrogen bonds are denoted as dashed lines

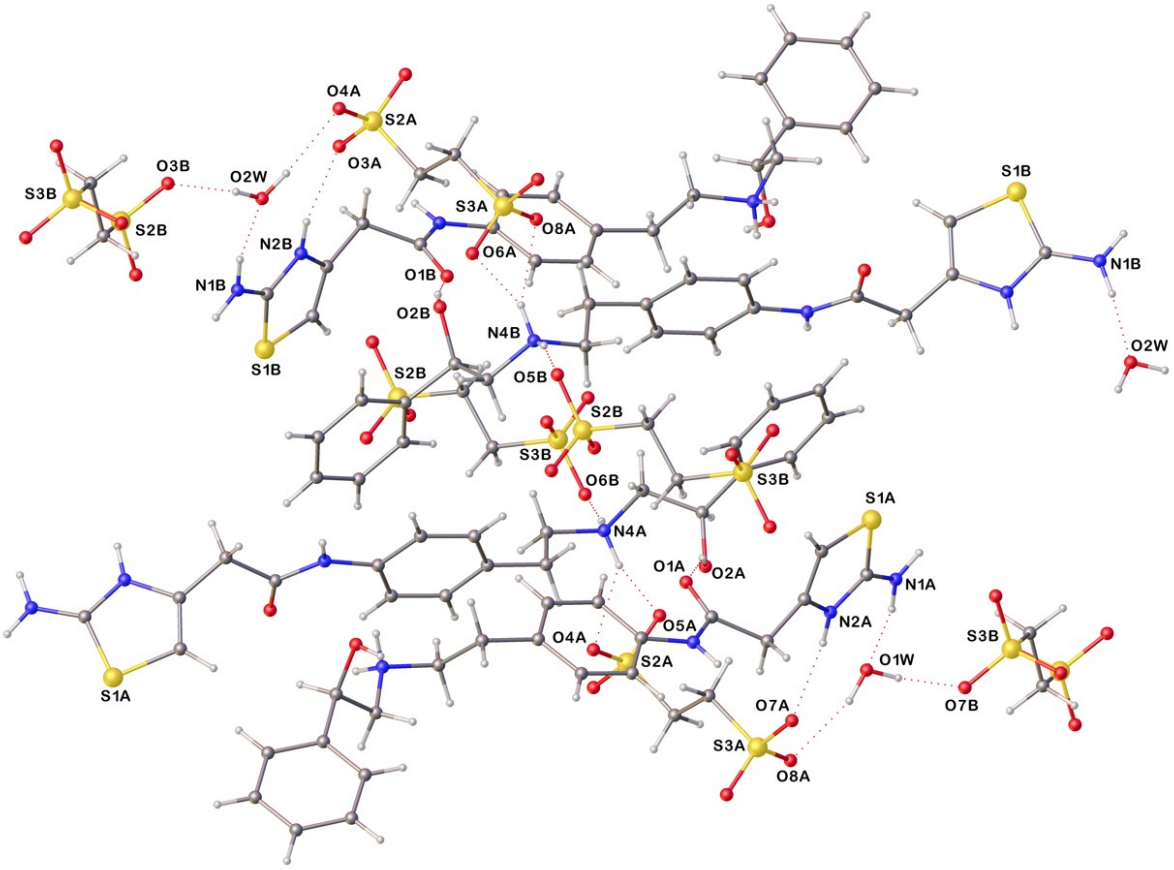

Figure S7 Hydrogen bond network in the mirabegron edisylate monohydrate form 1A structure showing functionality of the protonated amine atoms N4A and N4B. Hydrogen bonds are denoted as dashed lines

Table S2 Crystal data and structure refinement for mirabegron edisylate hemihydrate form 1B

Empirical formula	$C_{46}H_{62}N_8O_{17}S_6$
Formula weight	1191.39
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	14.91352(16)
b/Å	10.64981(10)
c/Å	18.2350(2)
α/°	90
β/°	112.7368(13)
γ/°	90
Volume/Å^3	2671.13(5)
Z	2
ρ_{calc}g/cm^3	1.481
μ/mm^{-1}	3.036
F(000)	1252.0
Crystal size/mm^3	0.23 × 0.04 × 0.01
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.254 to 136.488
Index ranges	-17 ≤ h ≤ 17, -11 ≤ k ≤ 12, -20 ≤ l ≤ 21
Reflections collected	47589
Independent reflections	9557 [R_{int} = 0.0574, R_{sigma} = 0.0387]
Data/restraints/parameters	9557/1/705
Goodness-of-fit on F^2	1.074
Final R indexes [I>=2σ (I)]	R_1 = 0.0441, wR_2 = 0.1110
Final R indexes [all data]	R_1 = 0.0462, wR_2 = 0.1121
Largest diff. peak/hole / e Å^{-3}	0.52/-0.49
Flack parameter	0.041(9)

Crystal Data for $C_{46}H_{62}N_8O_{17}S_6$ (*M* =1191.39 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 14.91352(16) Å, *b* = 10.64981(10) Å, *c* = 18.2350(2) Å, *β* = 112.7368(13)°, *V* = 2671.13(5) Å^3, *Z* = 2, *T* = 100.00(10) K, μ(Cu Kα) = 3.036 mm^{-1}, *Dcalc* = 1.481 g/cm^3, 47589 reflections measured (5.254° ≤ 2Θ ≤ 136.488°), 9557 unique (R_{int} = 0.0574, R_{sigma} = 0.0387) which were used in all calculations. The final R_1 was 0.0441 (I > 2σ(I)) and wR_2 was 0.1121 (all data). CCDC: 2388448

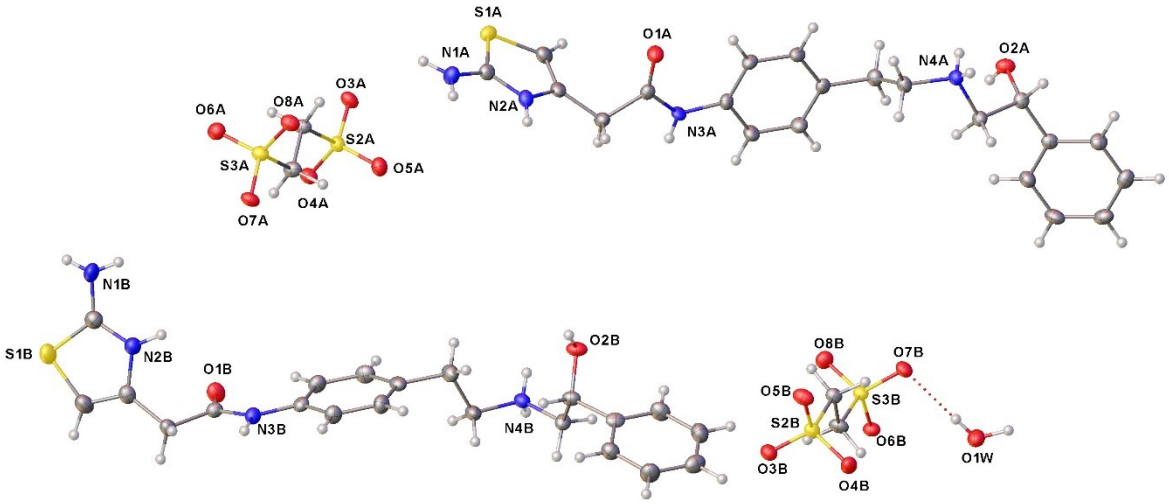

Figure S8 ORTEP representation of the mirabegron edisylate hemihydrate form 1B

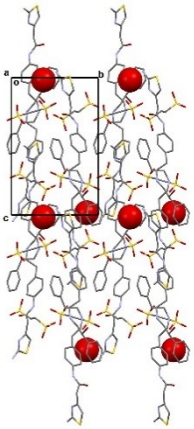

Figure S9 Crystal packing of mirabegron edisylate hemihydrate form 1B viewed down the crystallographic a-axis showing positions of the water molecules

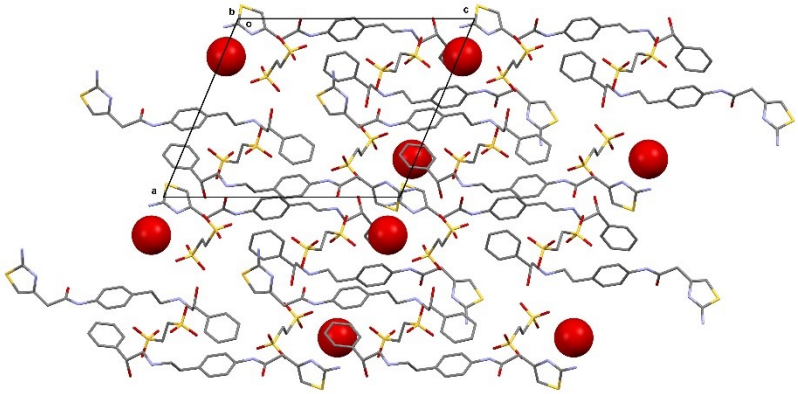

Figure S10 Crystal packing of mirabegron edisylate hemihydrate form 1B viewed down the crystallographic b-axis showing positions of the water molecules

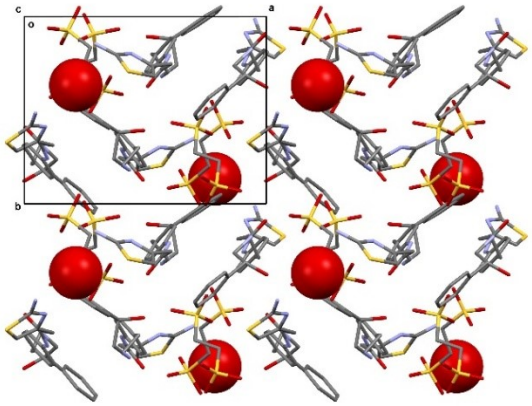

Figure S11 Crystal packing of mirabegron edisylate hemihydrate form 1B viewed down the crystallographic c-axis showing positions of the water molecules

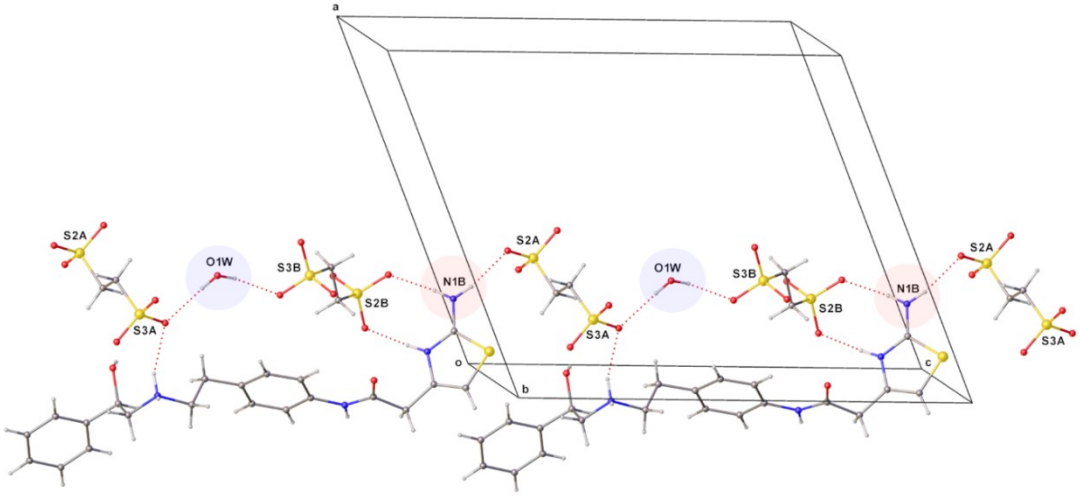

Figure S12 An infinite chain of alternating –EDS–water–EDS–NH_2– EDS–water– in Mrbg EDS form 1B propagating along crystallographic c-axis

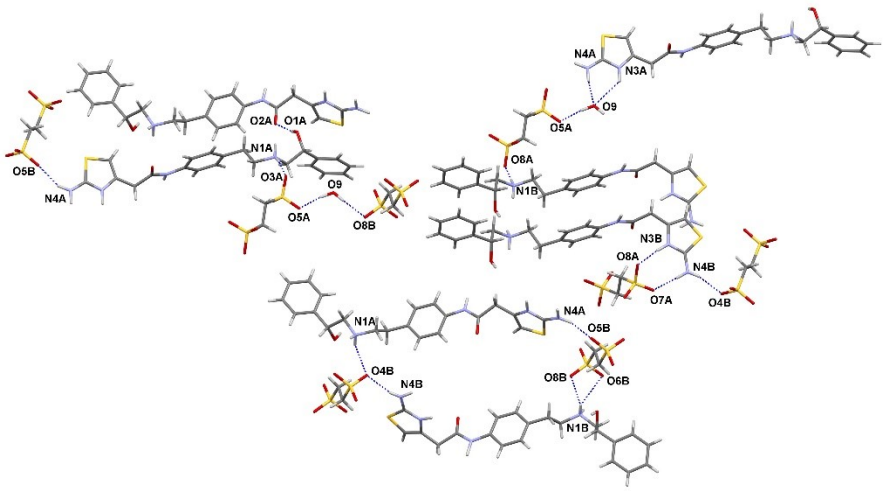

Figure S13 Hydrogen bond network in the mirabegron edisylate hemihydrate form 1B structure. Hydrogen bonds are denoted as dashed lines

Table S3 Crystal data and structure refinement for anhydrous mirabegron edisylate form 1C

Empirical formula	$C_{23}H_{30}N_4O_8S_3$
Formula weight	586.69
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	14.9020(2)
b/Å	10.51080(12)
c/Å	18.3869(2)
α/°	90
β/°	112.8704(15)
γ/°	90
Volume/Å^3	2653.57(6)
Z	4
ρ_{calc}g/cm^3	1.469
μ/mm^{-1}	3.033
F(000)	1232.0
Crystal size/mm^3	0.14 × 0.07 × 0.04
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.216 to 140.104
Index ranges	-18 ≤ h ≤ 18, -12 ≤ k ≤ 12, -19 ≤ l ≤ 22
Reflections collected	48813
Independent reflections	10000 [R_{int} = 0.0322, R_{sigma} = 0.0227]]
Data/restraints/parameters	10000/1/693
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.0240, wR_2 = 0.0633
Final R indexes [all data]	R_1 = 0.0249, wR_2 = 0.0637
Largest diff. peak/hole / e Å^{-3}	0.24/-0.28
Flack parameter	0.009(4)

Crystal Data for $C_{23}H_{30}N_4O_8S_3$ (*M* =586.69 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 14.9020(2) Å, *b* = 10.51080(12) Å, *c* = 18.3869(2) Å, *β* = 112.8704(15)°, *V* = 2653.57(6) Å^3, *Z* = 4, *T* = 100.00(10) K, μ(Cu Kα) = 3.033 mm^{-1}, *Dcalc* = 1.469 g/cm^3, 48813 reflections measured (5.216° ≤ 2Θ ≤ 140.104°), 10000 unique (R_{int} = 0.0322, R_{sigma} = 0.0227) which were used in all calculations. The final R_1 was 0.0240 (I > 2σ(I)) and wR_2 was 0.0637 (all data). CCDC: 2388449

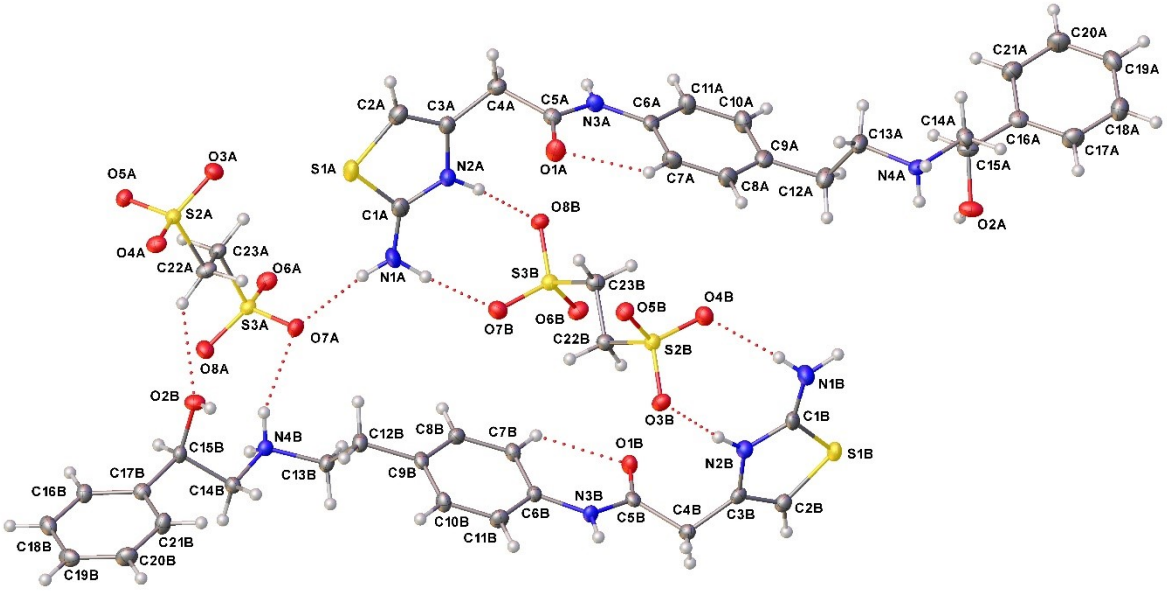

Figure S14 ORTEP representation of the anhydrous mirabegron edisylate form 1C.

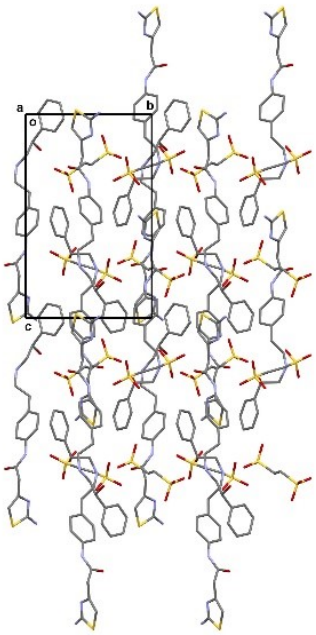

Figure S15 Crystal packing of anhydrous mirabegron edisylate form 1C viewed down the crystallographic a-axis

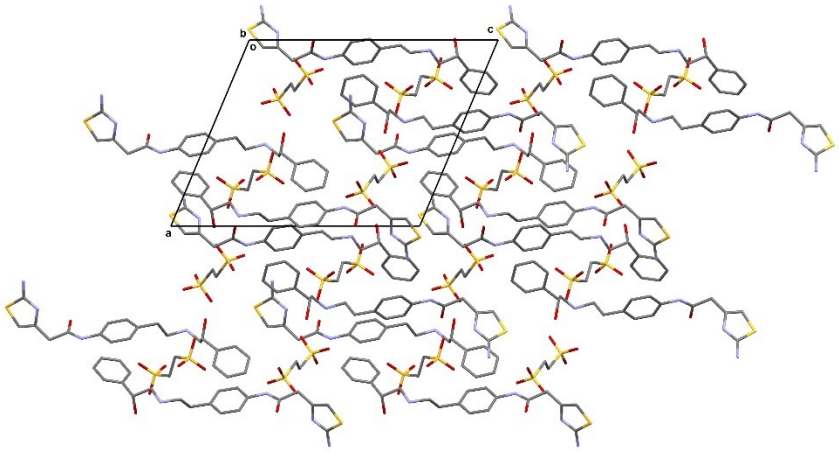

Figure S16 Crystal packing of anhydrous mirabegron edisylate form 1C viewed down the crystallographic b-axis

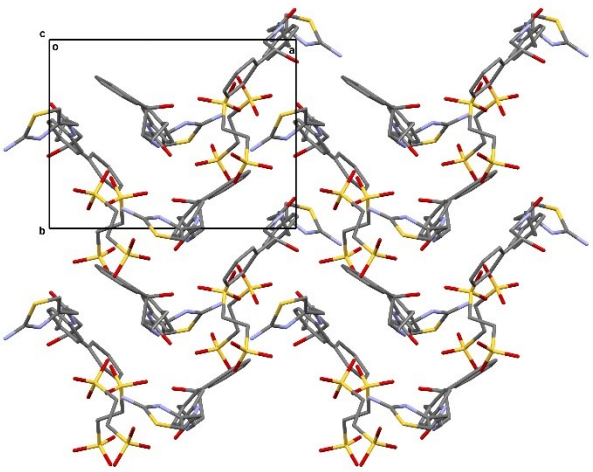

Figure S17 Crystal packing of anhydrous mirabegron edisylate form 1C viewed down the crystallographic c-axis

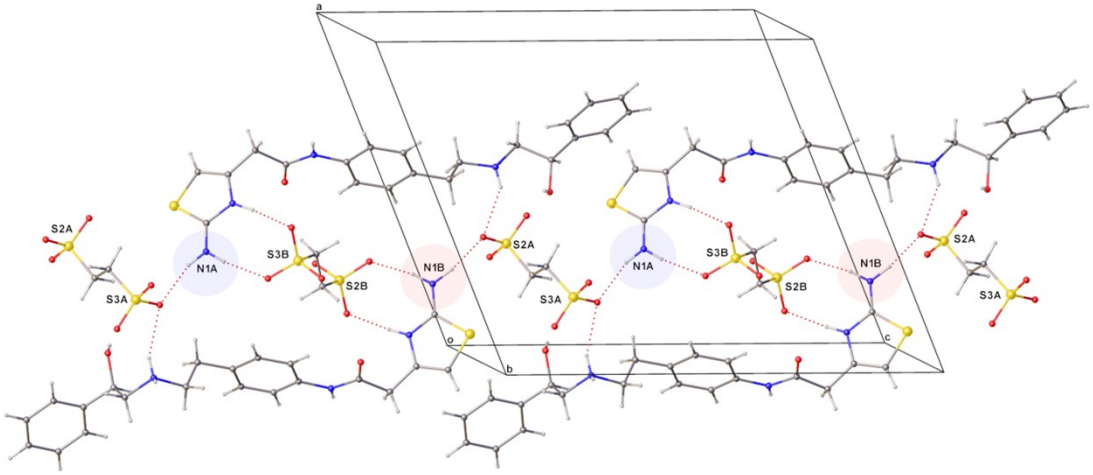

Figure S18 An infinite chain of alternating –EDS–NH_2–EDS–NH_2– in Mrbg EDS form 1C propagating along crystallographic c-axis

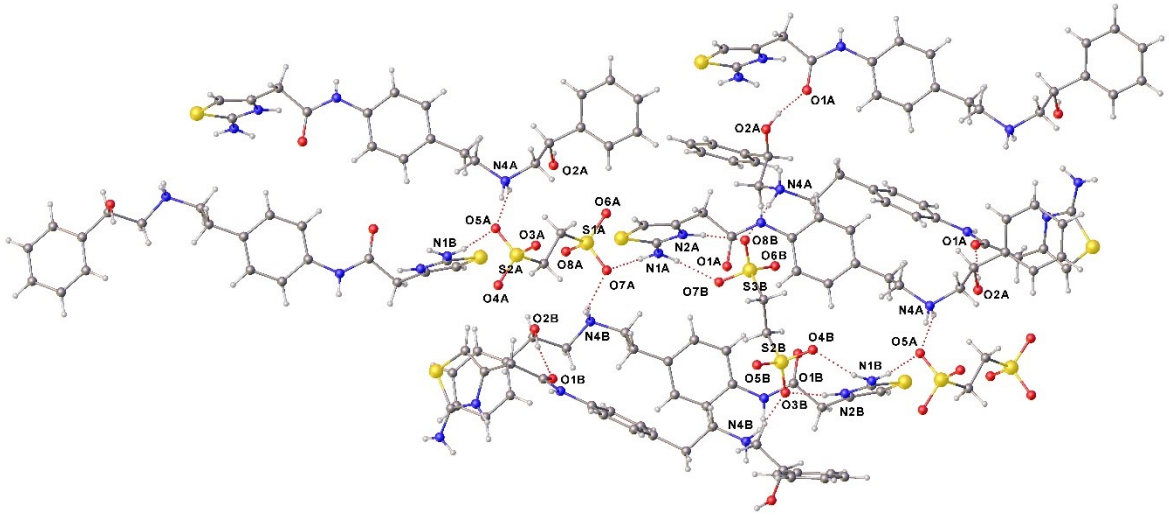

Figure S19 Hydrogen bond network in the anhydrous mirabegron edisylate form 1C structure. Hydrogen bonds are denoted as dashed lines

For the structure presented in Figure S11, with the stereocentre C15 A/B in the *R* configuration, the Flack[i] parameter for this structure is 0.008(4). Determination of the absolute structure using Bayesian statistics on Bijvoet differences[ii] reveals that the probability of the absolute structure as presented being correct is 1.000, while the probabilities of the absolute structure being a racemic twin or false are both 0.000 (Figure S19). The Flack equivalent (Hooft parameter) and its uncertainty are calculated through this program to be 0.012(2). The calculation was based on 4669 Bijvoet pairs with a coverage of 98 %.

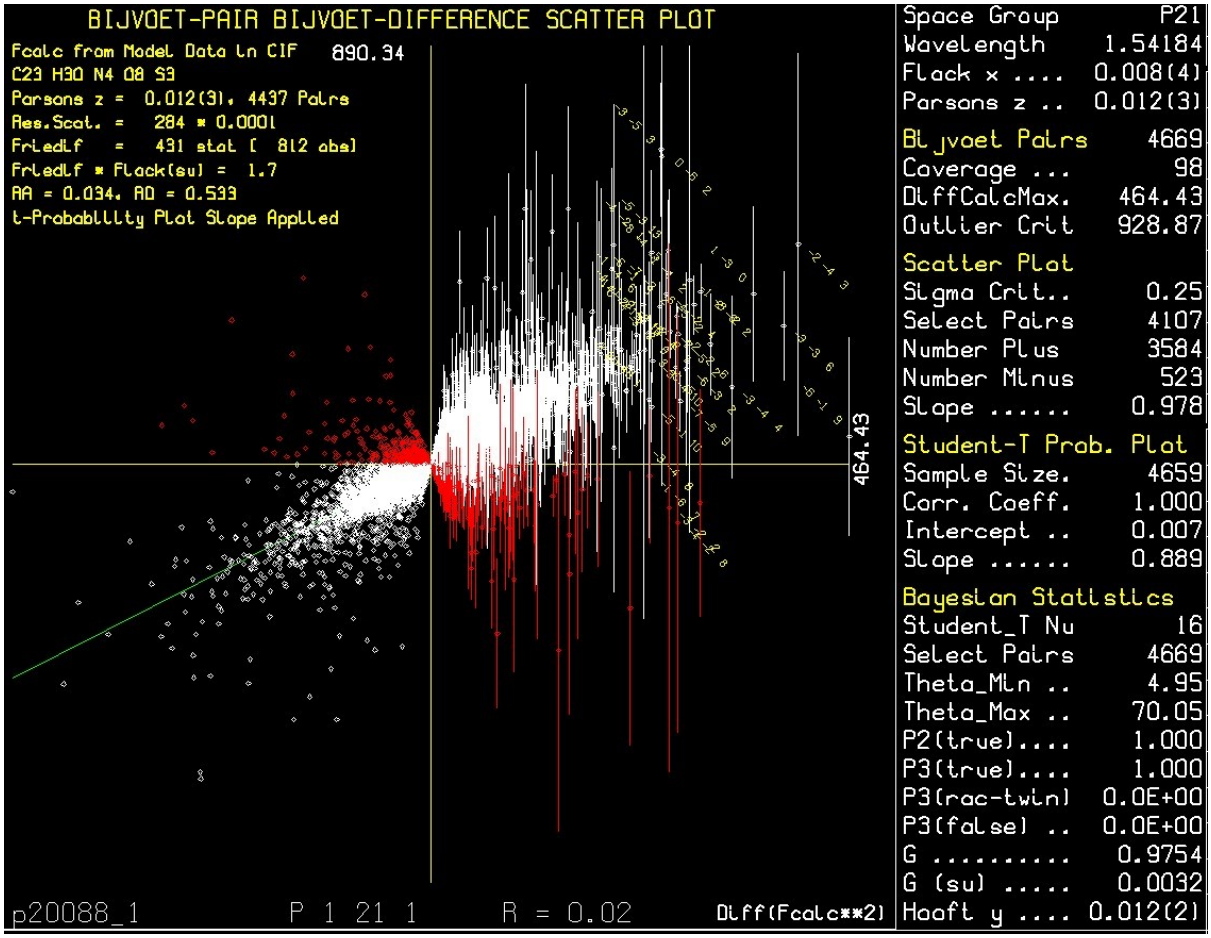

Figure S20 Determination of the absolute structure of anhydrous mirabegron edisylate form 1C using Bayesian probability statistics on Bijvoet differences

Table S4 Crystal data and structure refinement for mirabegron edisylate 1,4-dioxane partial solvate

Empirical formula	$C_{50}H_{69.3}N_8O_{18.65}S_6$
Formula weight	1273.19
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P1
a/Å	9.7367(2)
b/Å	11.3761(2)
c/Å	14.6395(3)
α/°	85.1410(10)
β/°	72.053(2)
γ/°	71.7410(10)
Volume/Å^3	1464.85(5)
Z	1
ρ_{calc}g/cm^3	1.443
μ/mm^{-1}	2.827
F(000)	670.0
Crystal size/mm^3	0.30 × 0.22 × 0.02
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.184 to 136.46
Index ranges	-10 ≤ h ≤ 11, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17
Reflections collected	53310
Independent reflections	10194 [R_{int} = 0.0392, R_{sigma} = 0.0221]
Data/restraints/parameters	10194/381/827
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0398, wR_2 = 0.1118
Final R indexes [all data]	R_1 = 0.0407, wR_2 = 0.1128
Largest diff. peak/hole / e Å^{-3}	0.50/-0.44
Flack parameter	-0.001(8)

Crystal Data for $C_{50}H_{69.3}N_8O_{18.65}S_6$ (*M* =1273.19 g/mol): triclinic, space group P1 (no. 1), *a* = 9.7367(2) Å, *b* = 11.3761(2) Å, *c* = 14.6395(3) Å, *α* = 85.1410(10)°, *β* = 72.053(2)°, *γ* = 71.7410(10)°, *V* = 1464.85(5) Å^3, *Z* = 1, *T* = 100.00(10) K, μ(Cu Kα) = 2.827 mm^{-1}, *Dcalc* = 1.443 g/cm^3, 53310 reflections measured (8.184° ≤ 2Θ ≤ 136.46°), 10194 unique (R_{int} = 0.0392, R_{sigma} = 0.0221) which were used in all calculations. The final R_1 was 0.0398 (I > 2σ(I)) and wR_2 was 0.1128 (all data). CCDC: 2493741

In the structure, N4b and C13b atoms of the Mrbg molecule B are positionally disordered and modelled over two sites with an occupancy ratio of approximately 95:5. The 1,4-dioxane molecule also exhibits positional disorder and has been modelled over two sites with occupancies of 80% and 20%, respectively. The water oxygen atom (O1W) is partially occupied, with a refined site occupancy factor (SoF) of 0.6628, and was fixed at 65% during refinement.

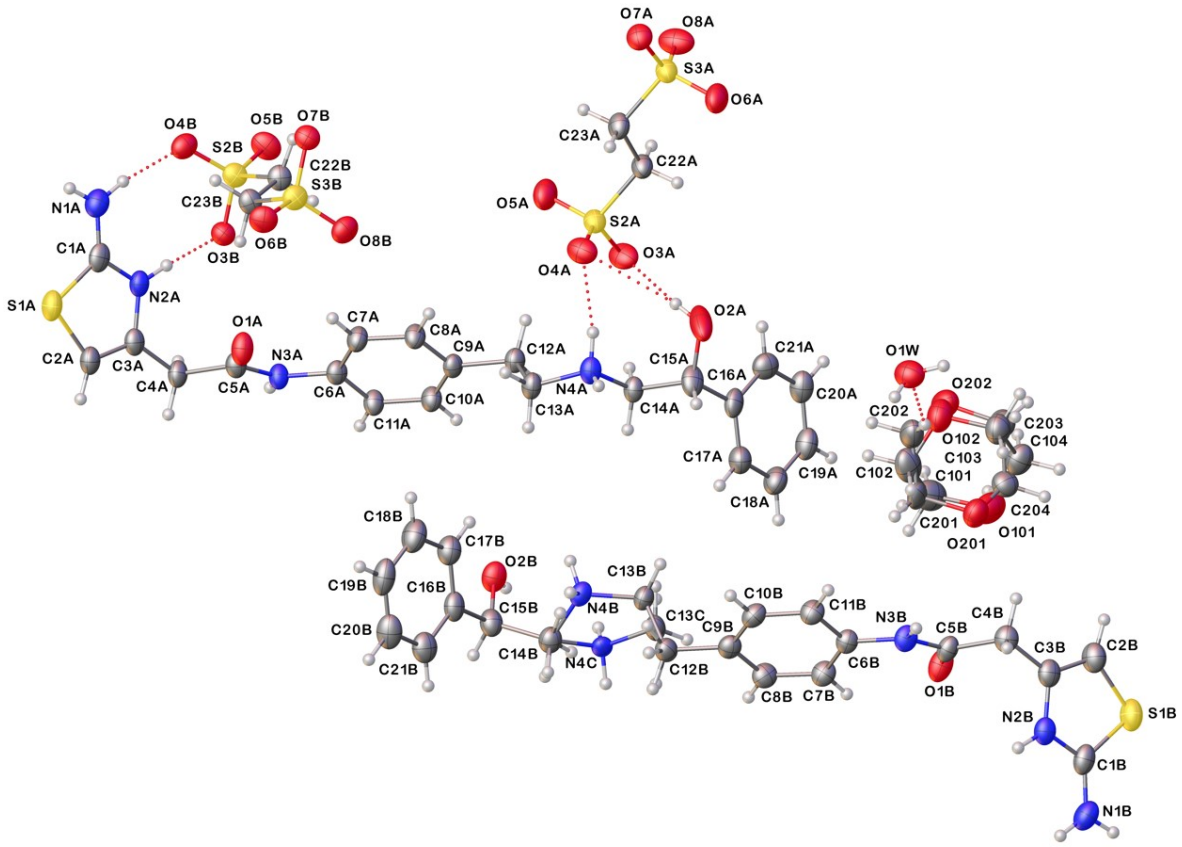

Figure S21 ORTEP representation of the mirabegron edisylate 1,4-dioxane partial solvate

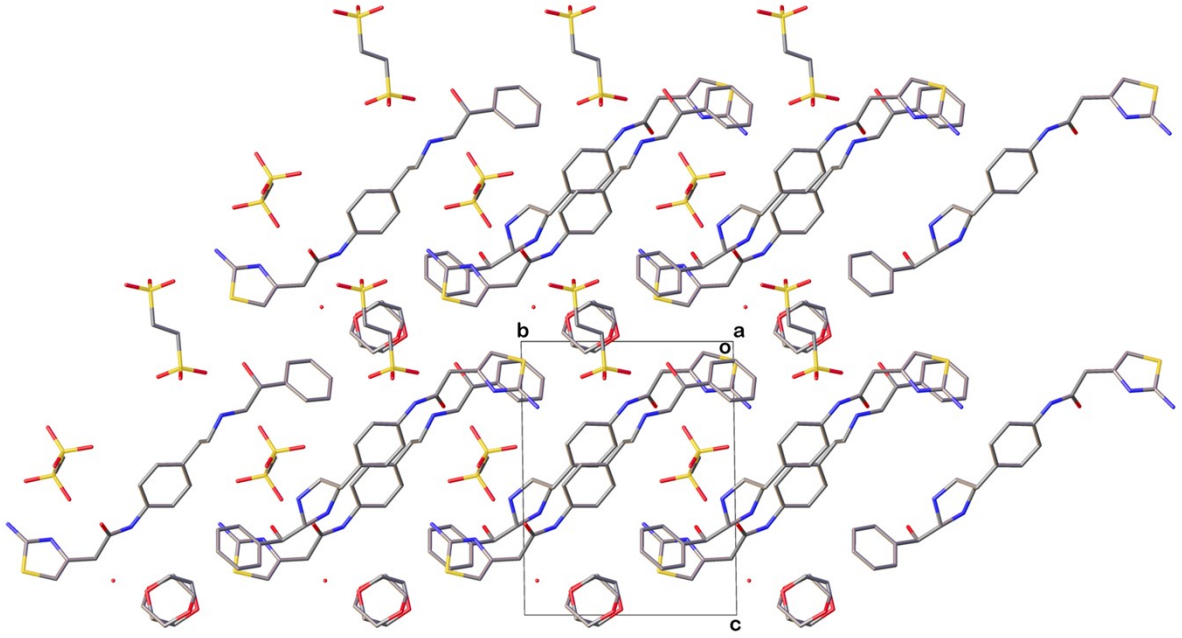

Figure S22 Crystal packing of mirabegron mirabegron edisylate 1,4-dioxane partial solvate viewed down the crystallographic a-axis

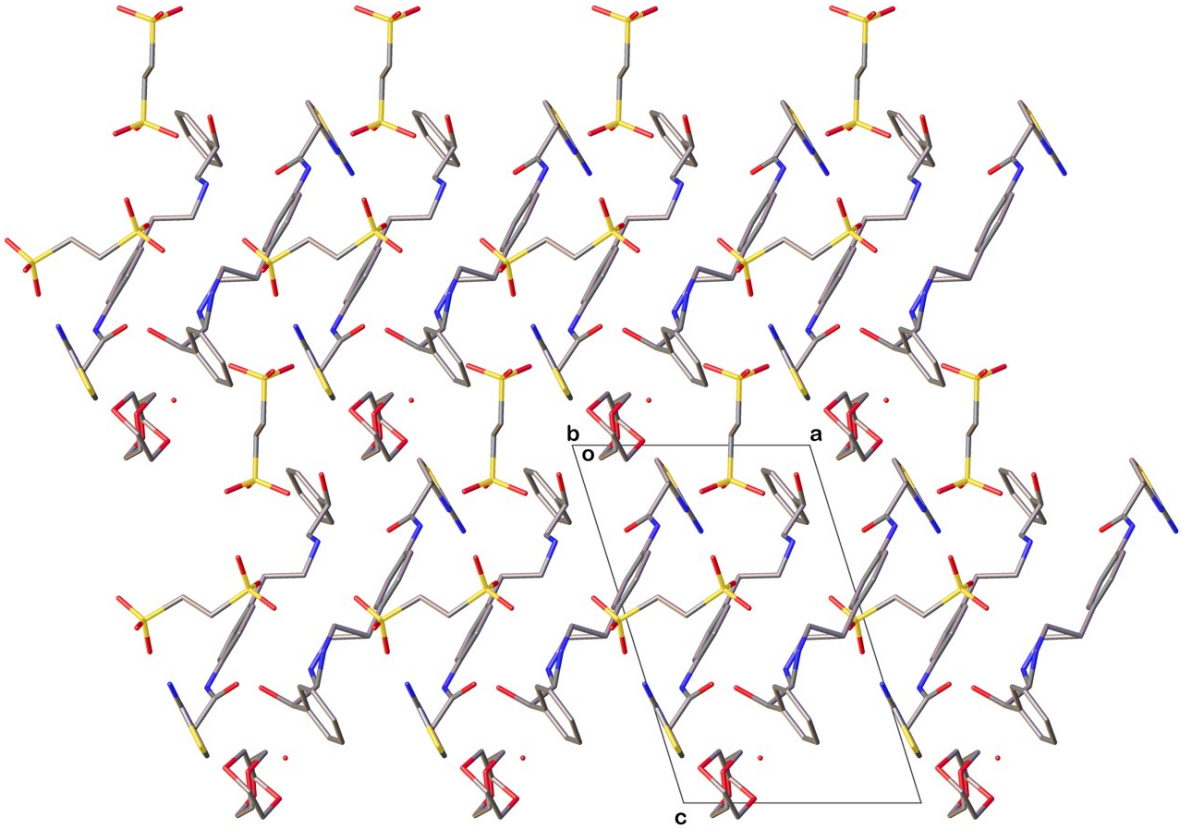

Figure S23 Crystal packing of mirabegron mirabegron edisylate 1,4-dioxane partial solvate viewed down the crystallographic b-axis

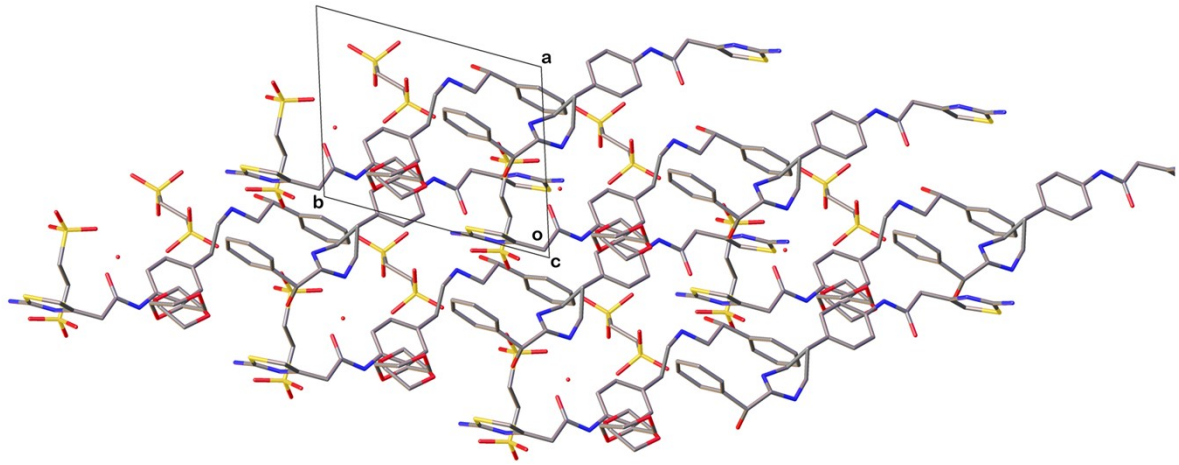

Figure S24 Crystal packing of mirabegron mirabegron edisylate 1,4-dioxane partial solvate viewed down the crystallographic c-axis

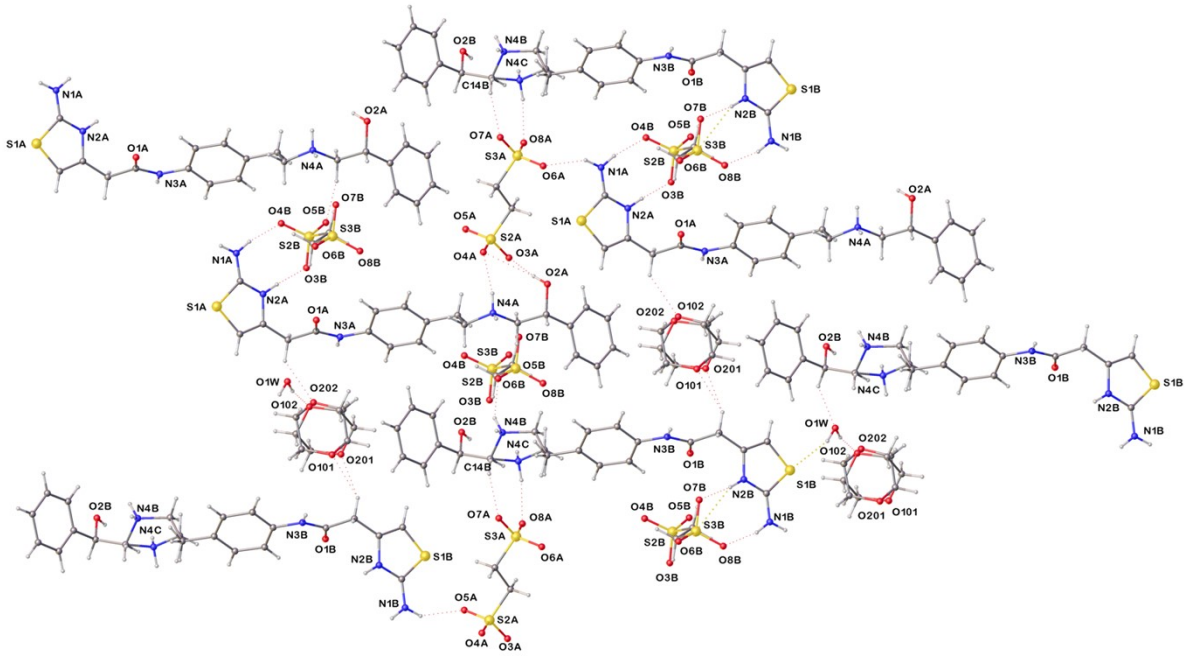

Figure S25 Hydrogen bond network in the mirabegron edisylate 1,4-dioxane partial solvate (Form 2A) structure. Hydrogen bonds are denoted as dashed lines

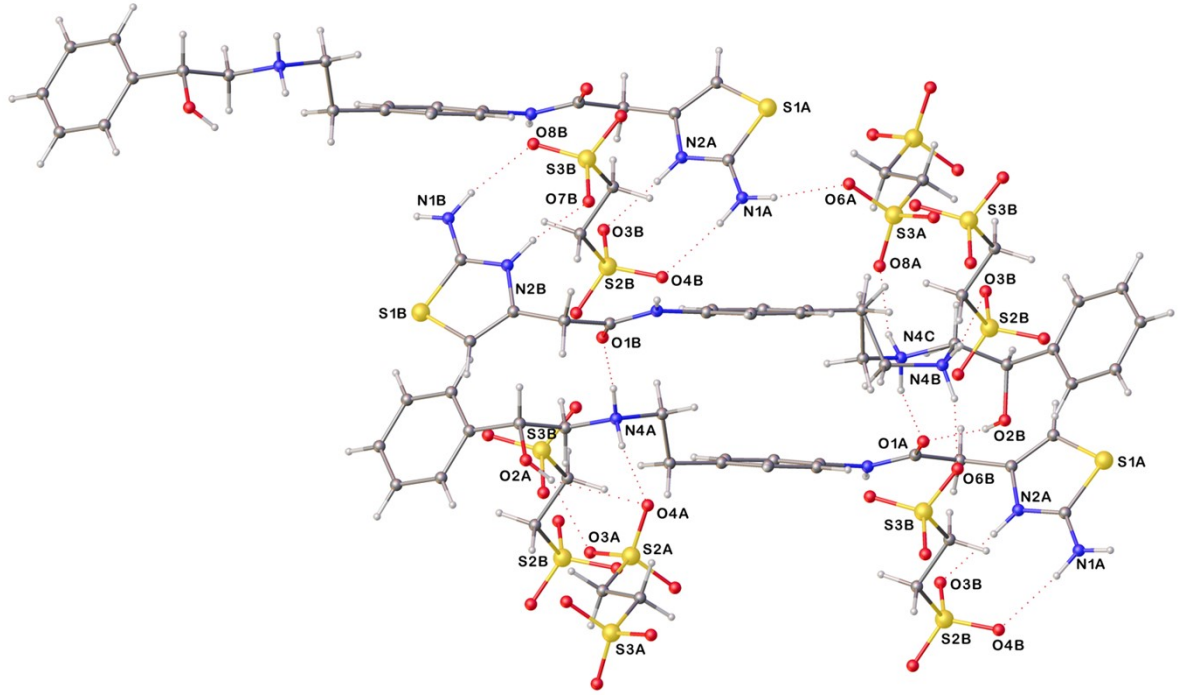

Figure S26 Hydrogen bond network in the mirabegron edisylate 1,4-dioxane partial solvate (Form 2A) structure. Hydrogen bonds are denoted as dashed lines

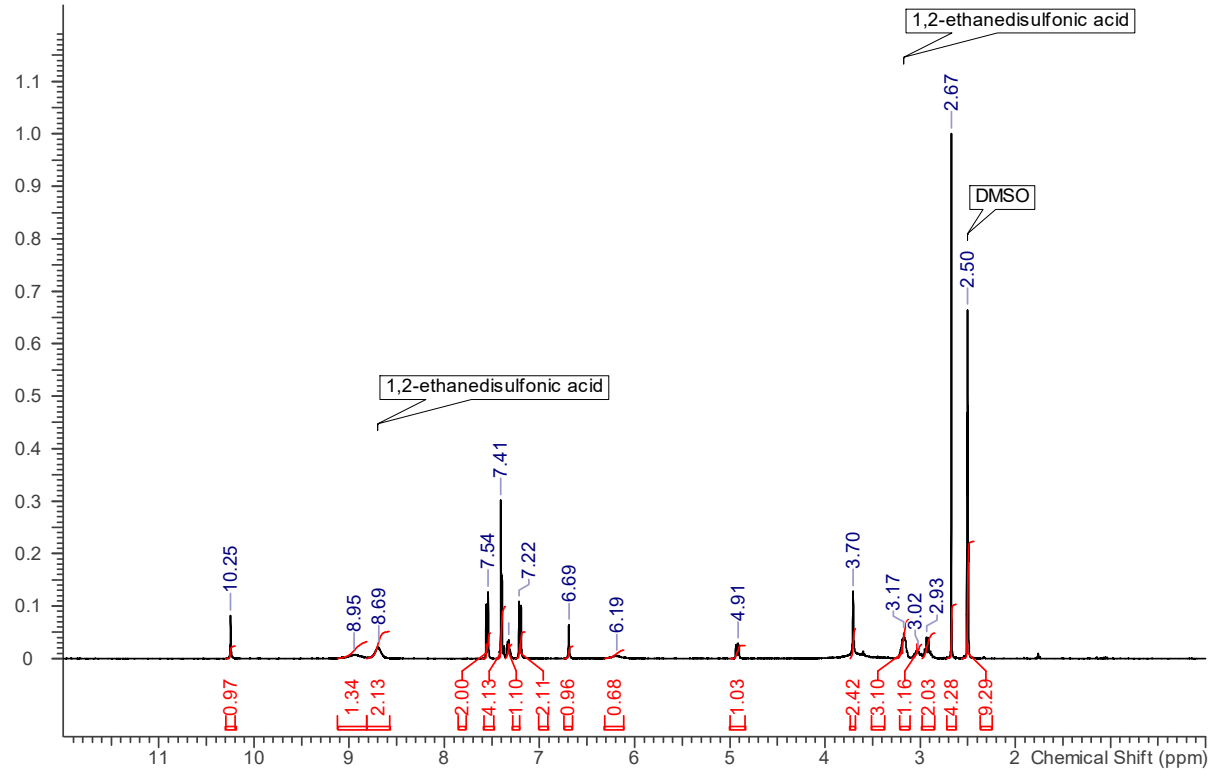

Figure S27. [1]H-NMR mirabegron edisylate form 1A as obtained

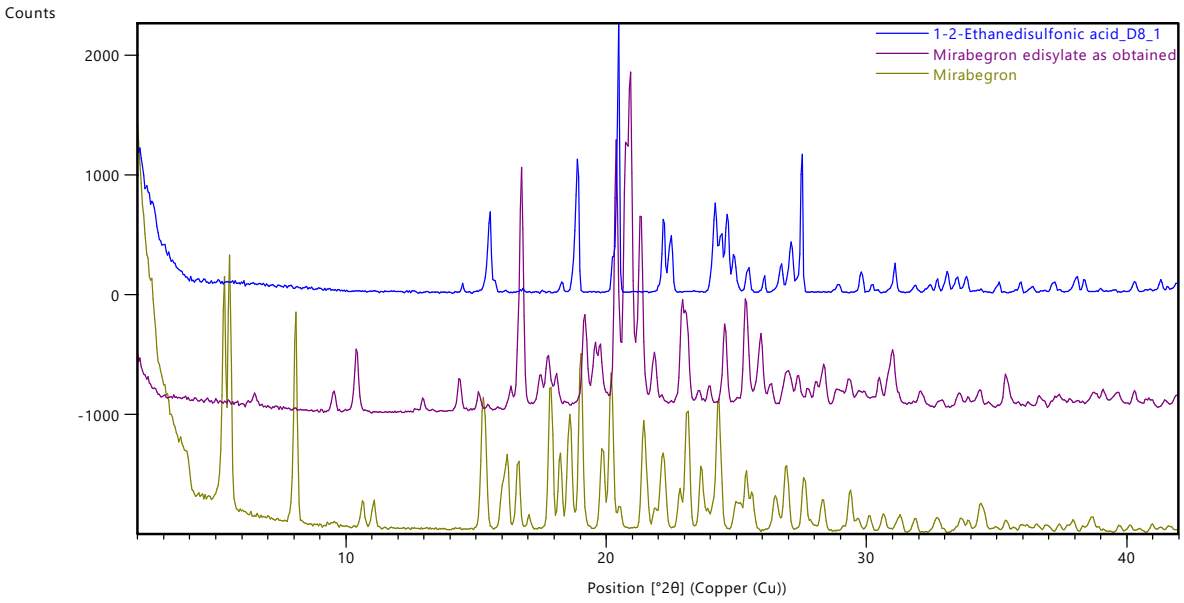

Figure S28. XPRD overlay of mirabegron, 1,2-ethanedisulfonic acid and mirabegron edisylate form 1A

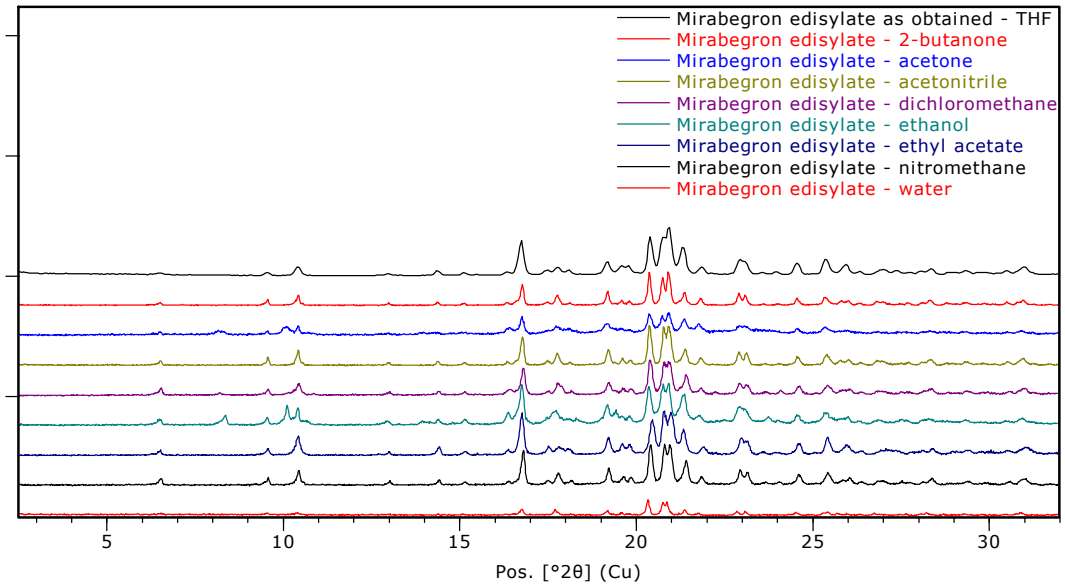

Figure S29 XPRD overlay of mirabegron edisylate forms 1A obtained from different solvents

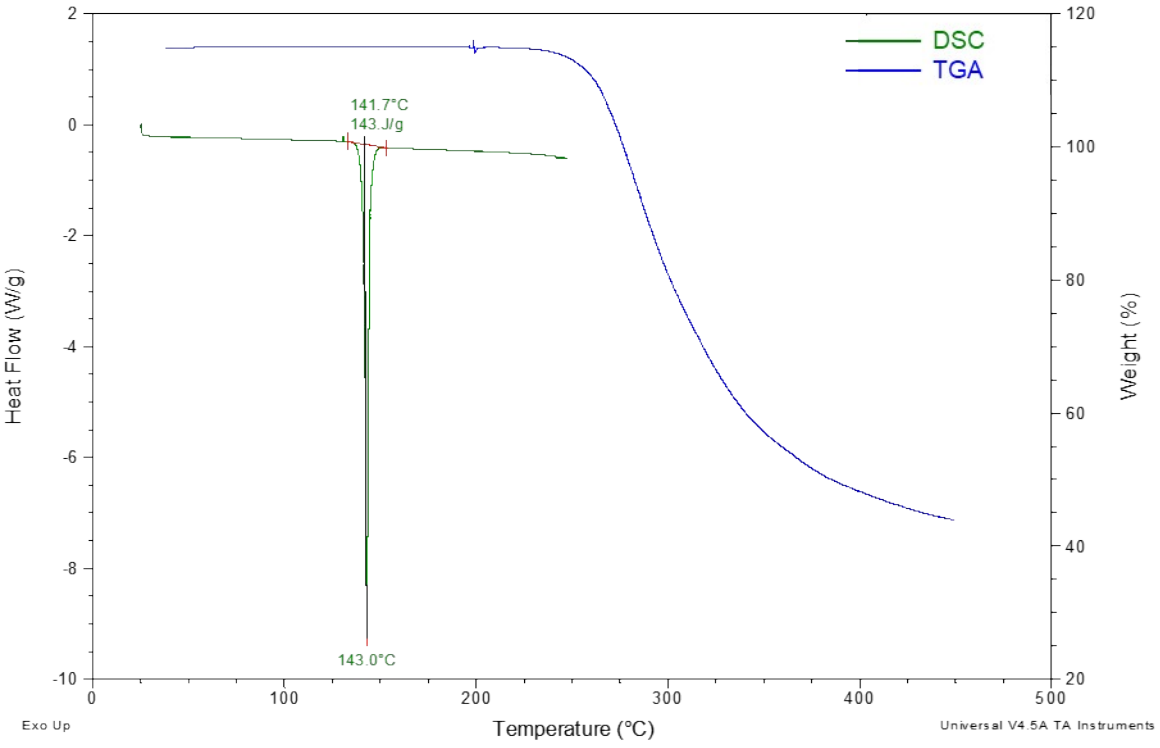

Figure S30 DSC and TGA analysis of mirabegron free form

Preparation of Mirabegron HCl

Mirabegron (100 mg) was dispersed in 4 ml HPLC vials and dissolved in ethanol (2 ml), after stirring for 5 min at 35 °C. Hydrochloric acid was added in a stoichiometric amount (2eq. 1M aqueous solution). The solution was stirred for another hour at 50 °C and cooled to 5 °C at 0.1 °C/min overnight. The resulting solid was isolated by filtration.

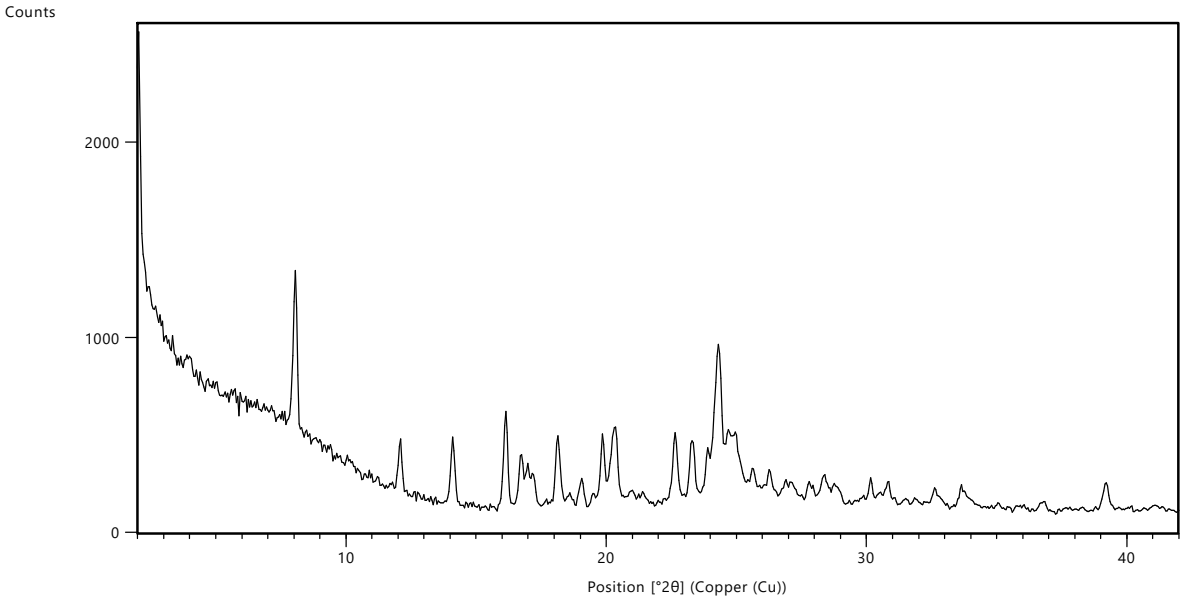

Figure S31 PXRD diffractogram of mirabegron dihydrochloride salt used as reference

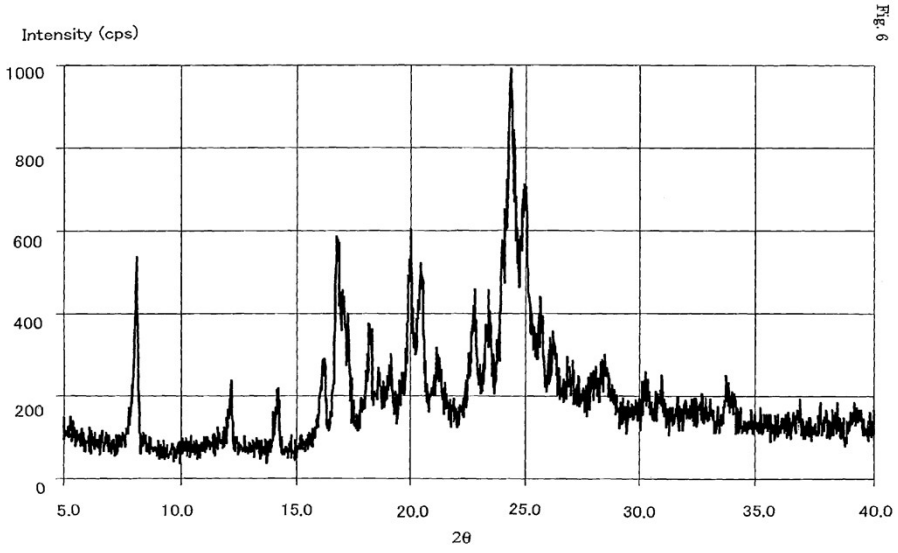

Figure S32 Reference for mirabegron dihydrochloride salt, from US7342117 B2 patent

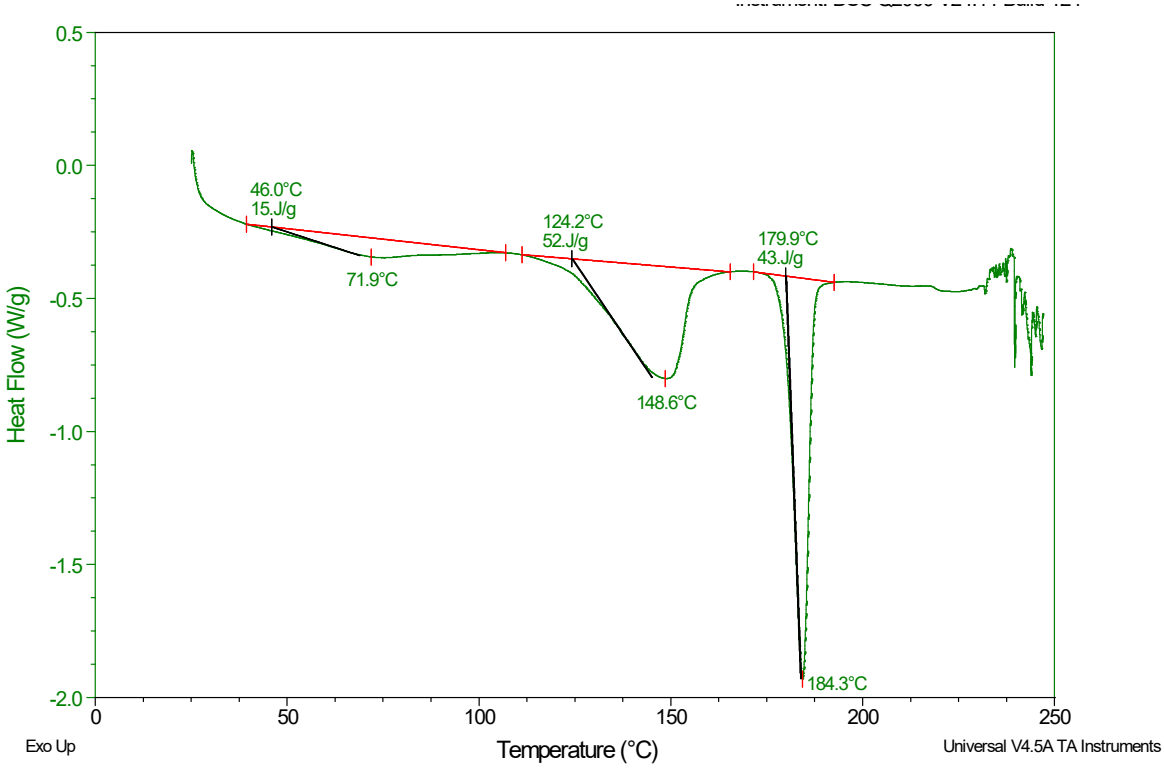

Figure S33 DSC analysis of mirabegron dihydrochloride salt

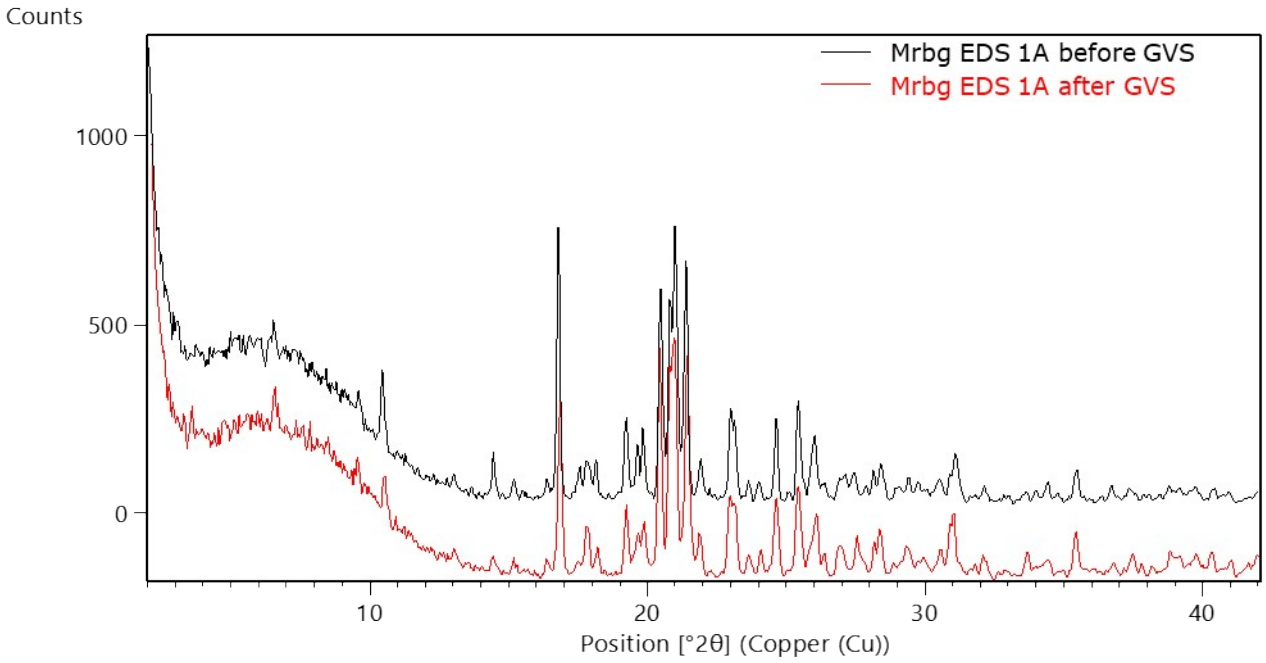

Figure S34 PXRD overlay of mirabegron edisylate form 1A before and after GVS

VH-PXRD conditions:

Started at 40%RH – t0; ramped to 70%RH and held for 10h; ramped to 85%RH (duration ramp was 10 min) and held for 10h; humidity was reduced to 40%RH (over 10 min) and held at 40%RH for 10h; humidity further reduced to 25%RH (over 10 min) and held for 10h; humidity reduced to 5%RH (over 5 min) and held for 10 h; humidity increase back to 40%RH (over 5 min) and one PXRD recorded.

During the 10h holds, an PXRD was recorded every 1h.

Solvates and form 1D characterisation

2A

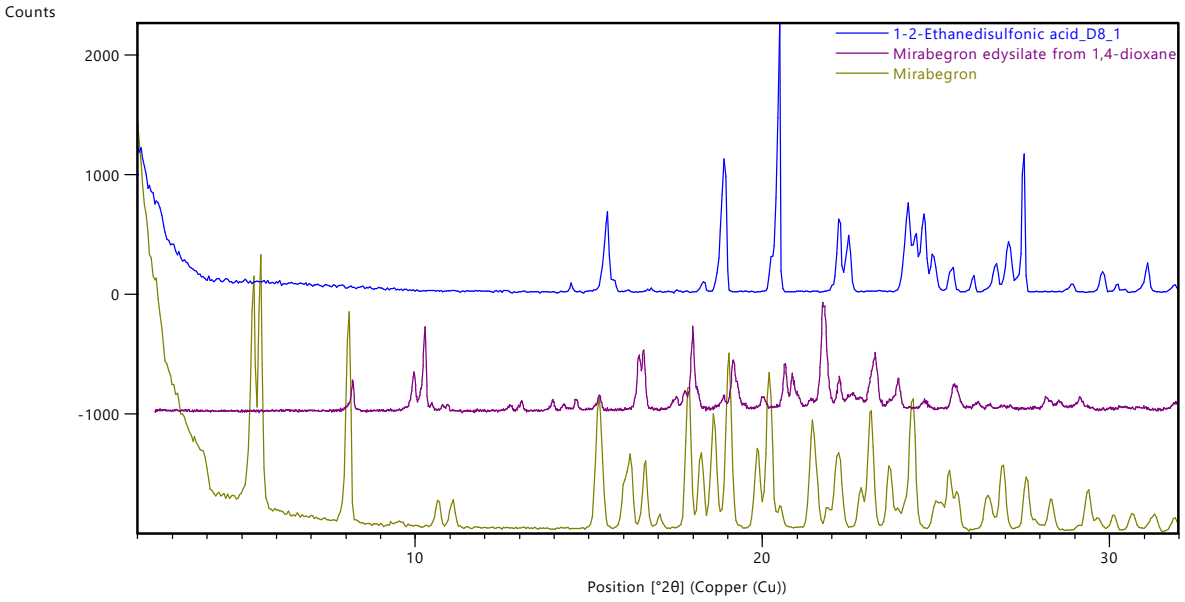

Figure S35 XPRD overlay of mirabegron, 1,2-ethanedisulfonic acid and mirabegron edisylate form 2A from 1,4-dioxane

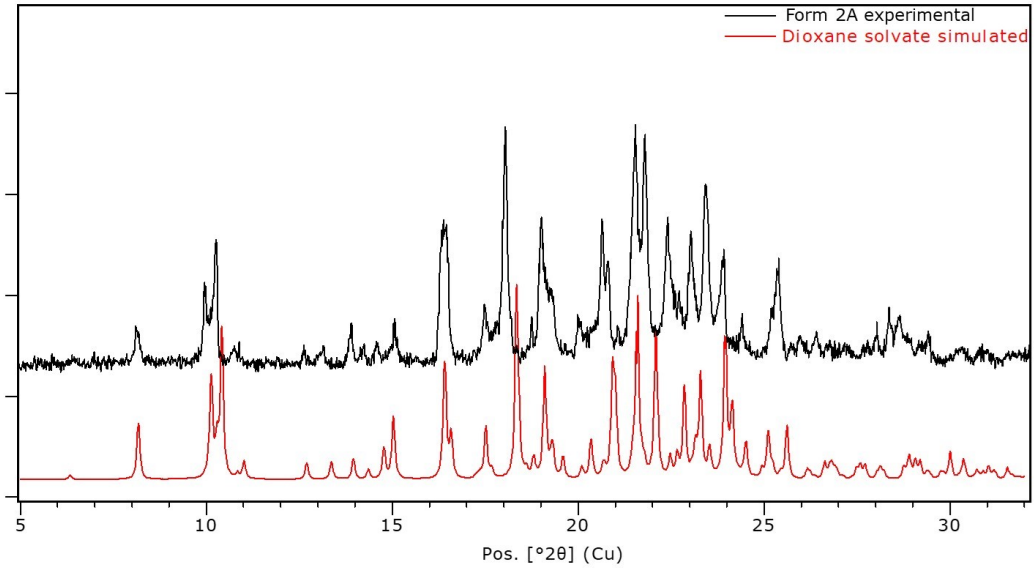

Figure S36 XPRD overlay of mirabegron edisylate form 2A from 1,4-dioxane with simulated data from single crystal X-ray

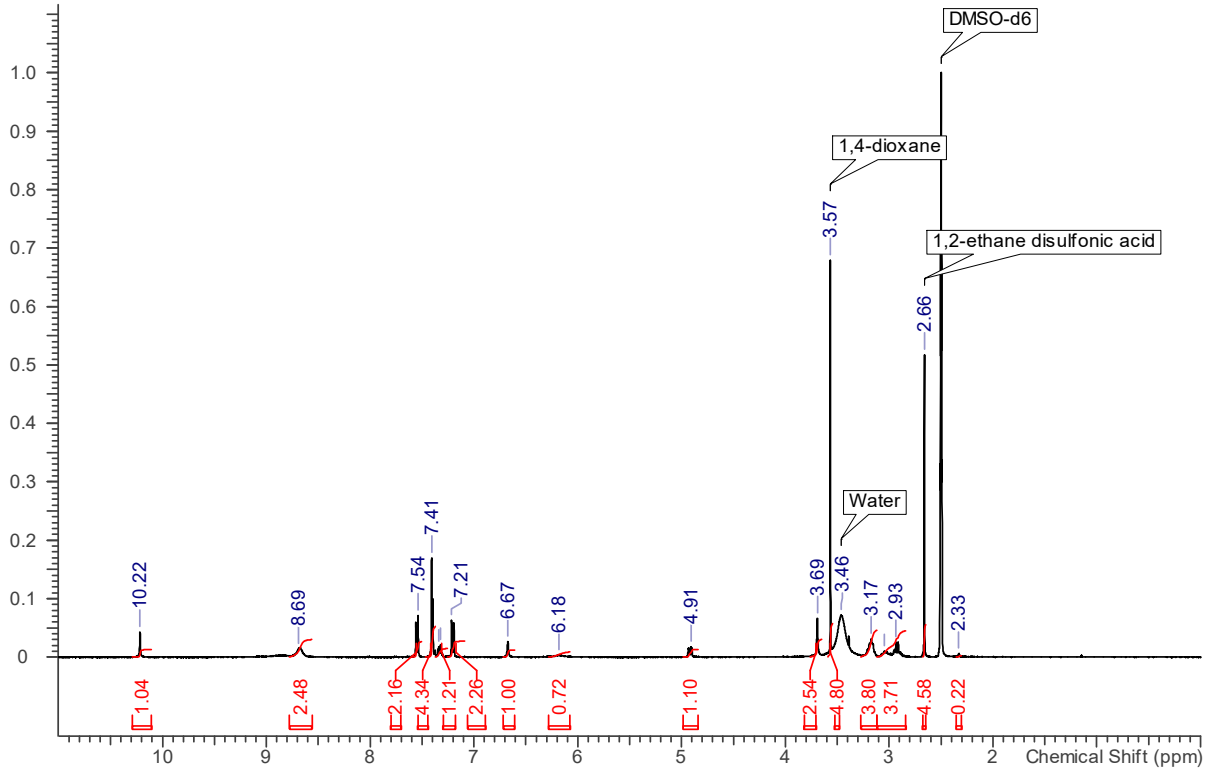

Figure S37 ^{1}H-NMR of mirabegron edisylate form 2A from 1,4-dioxane after isolation and vacuum drying at RT overnight

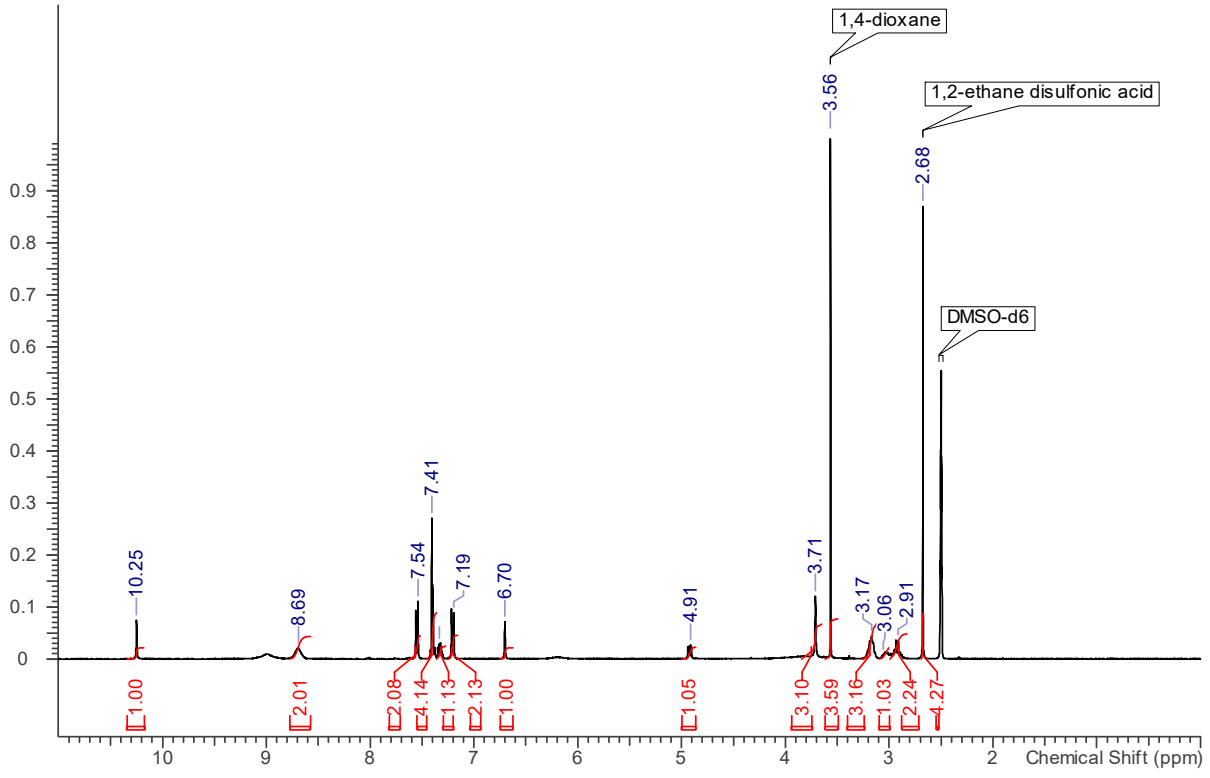

Figure S38 [1]H-NMR of mirabegron edisylate form 2A from 1,4-dioxane after vacuum drying at 40 °C over weekend

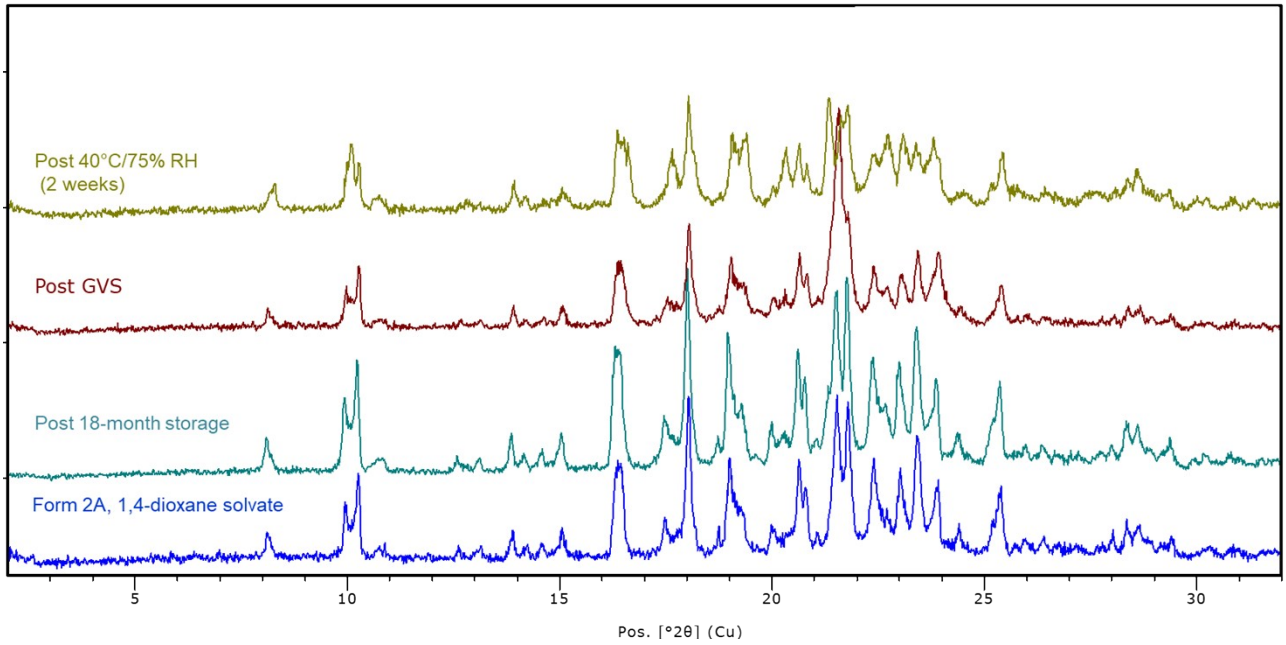

Figure S39 XPRD overlay of mirabegron edisylate form 2A from 1,4-dioxane before and after storage and post GVS

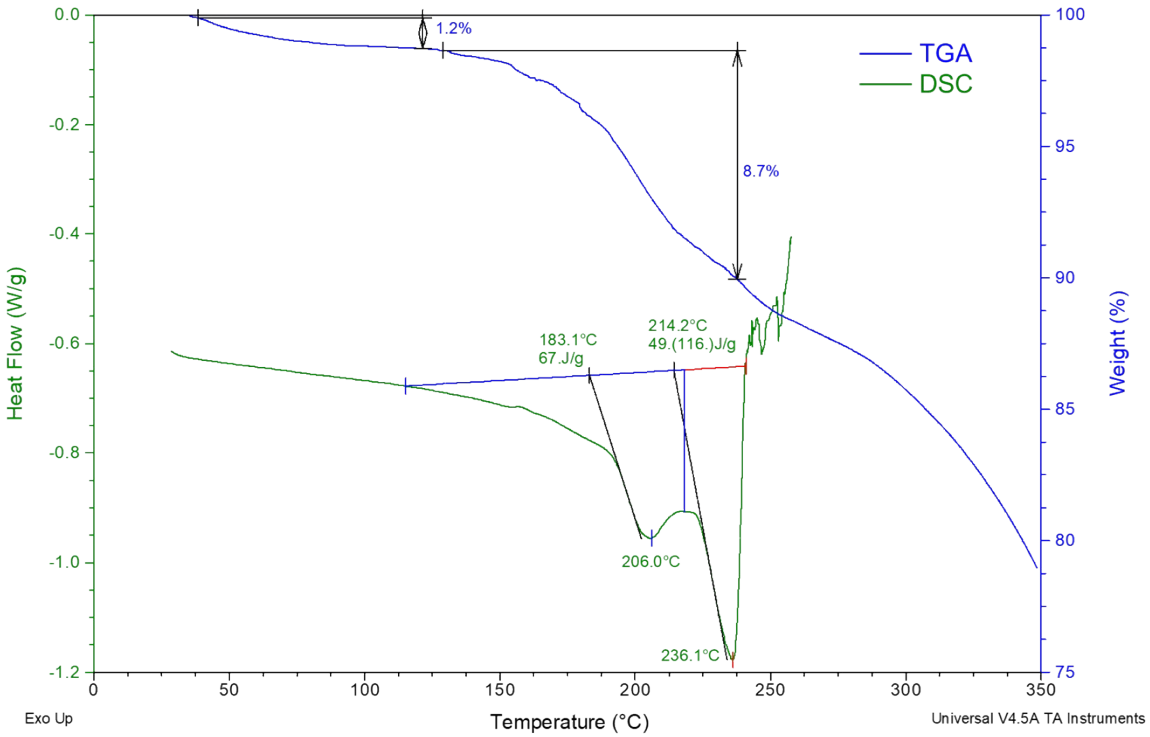

Figure S40 TGA and DSC overlay of form 2A

2B

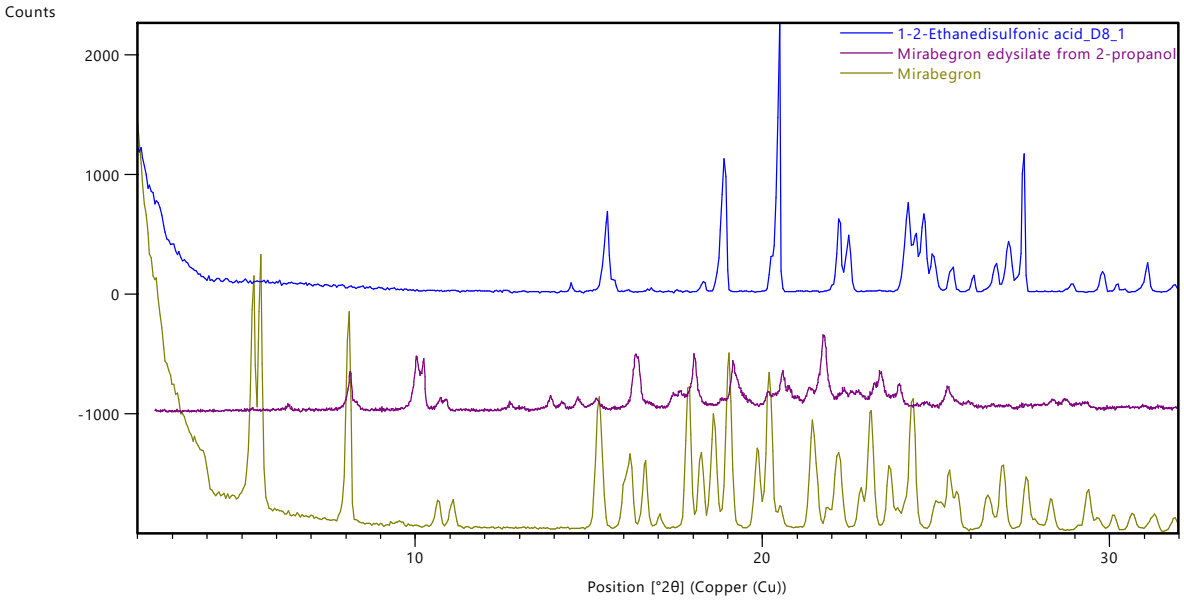

Figure S41 XPRD overlay of mirabegron, 1,2-ethanedisulfonic acid and mirabegron edisylate form 2B from 2-propanol

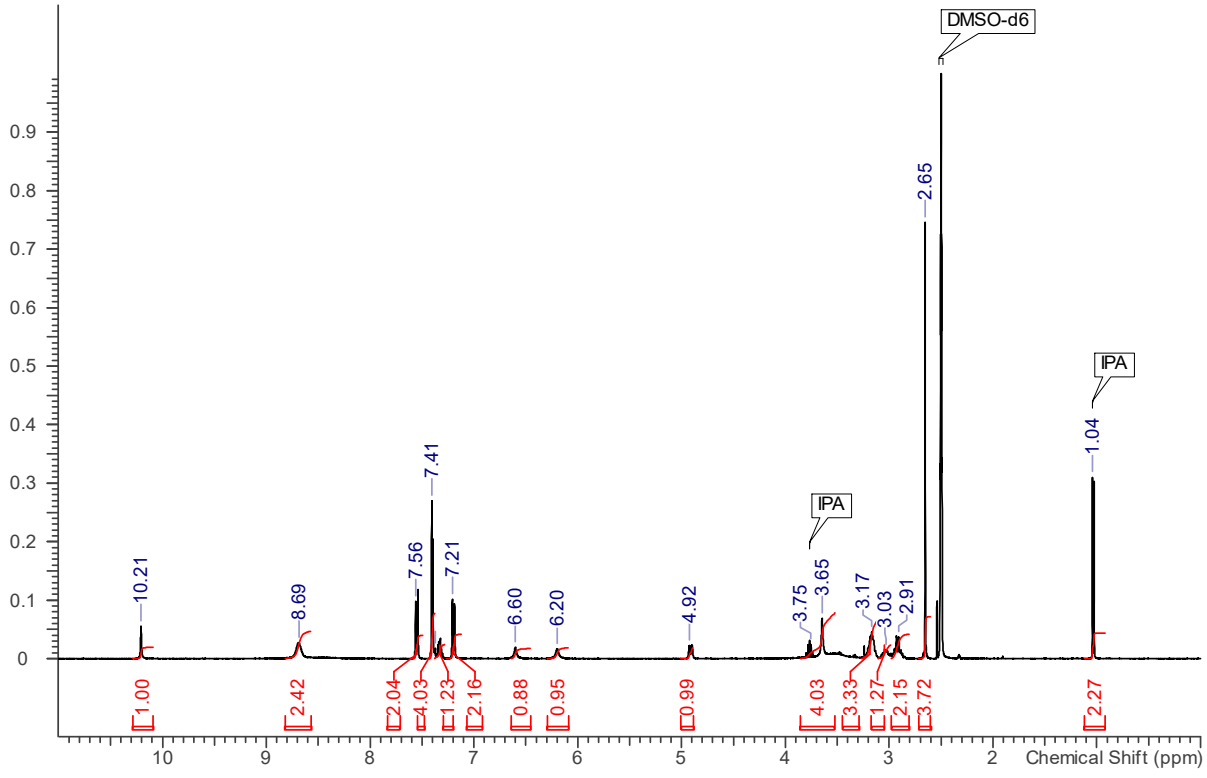

Figure S42 [1]H-NMR overlay of mirabegron edisylate form 2B from 2-propanol after vacuum drying at 40 °C overnight

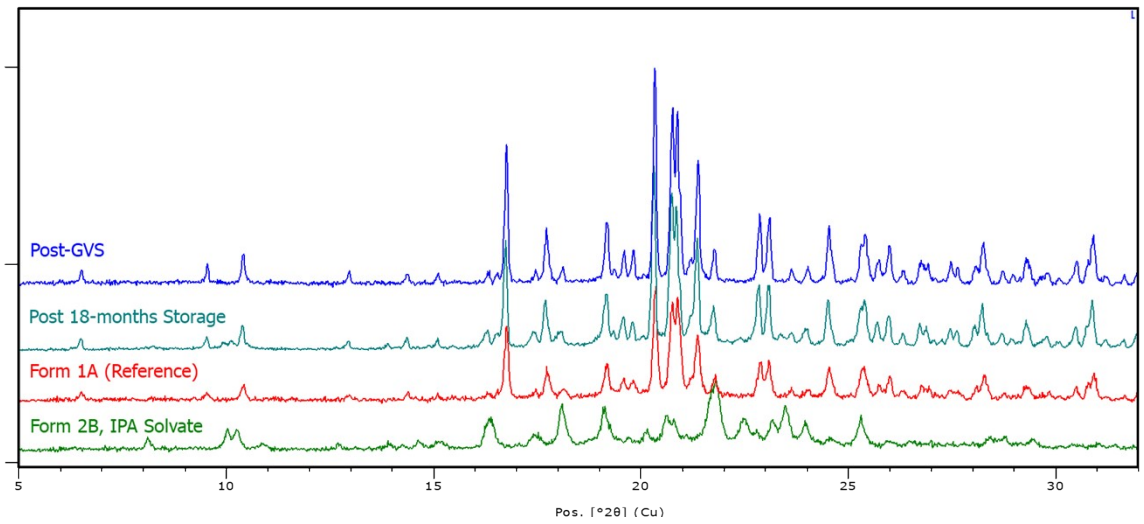

Figure S43 XPRD overlay of mirabegron edisylate form 2B from 2-propanol before and after storage and post GVS

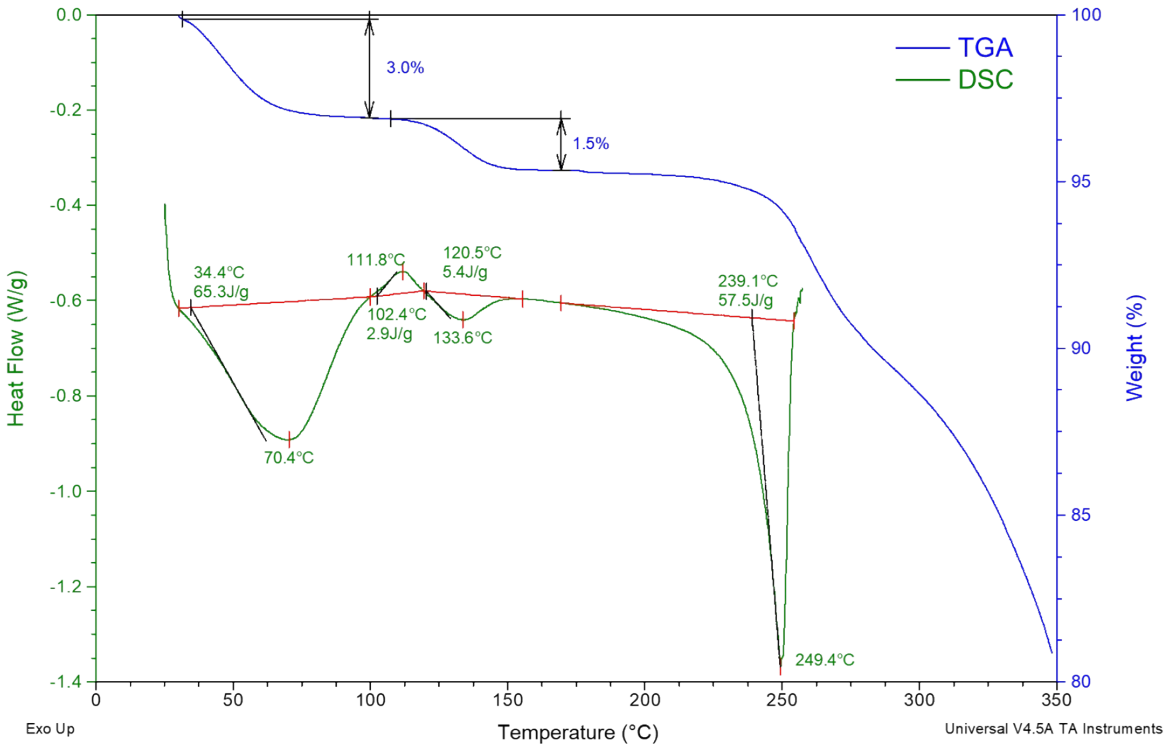

Figure S44 TGA and DSC overlay of form 2B

2C

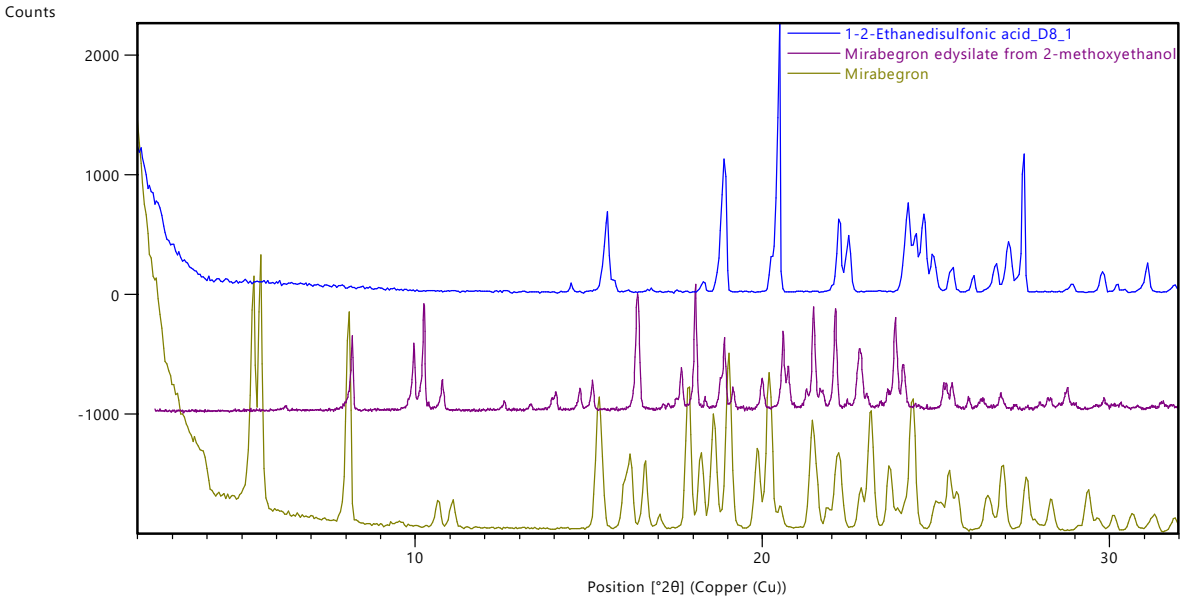

Figure S45 XPRD overlay of mirabegron, 1,2-ethanedisulfonic acid and mirabegron edisylate form 2C from 2-methoxyethanol

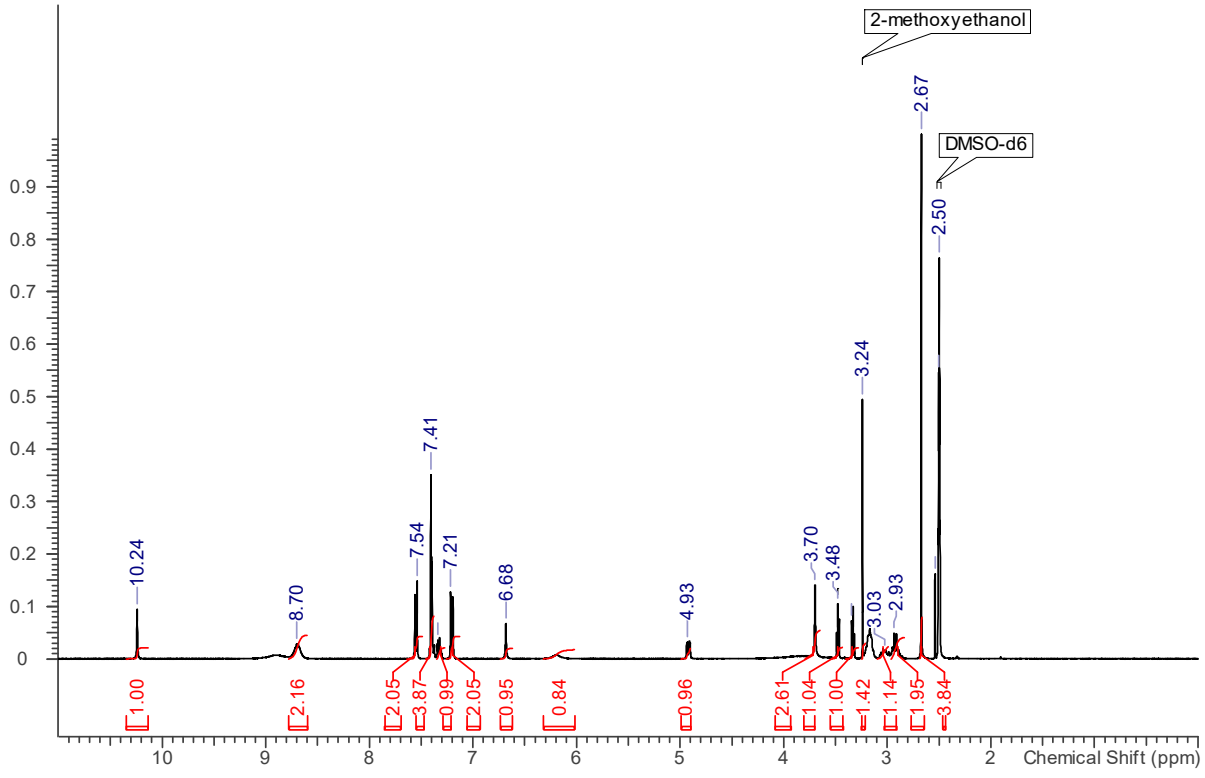

Figure S46 ^{1}H-NMR overlay of mirabegron edisylate form 2C from 2-methoxyethanol after vacuum drying at 40 °C overnight

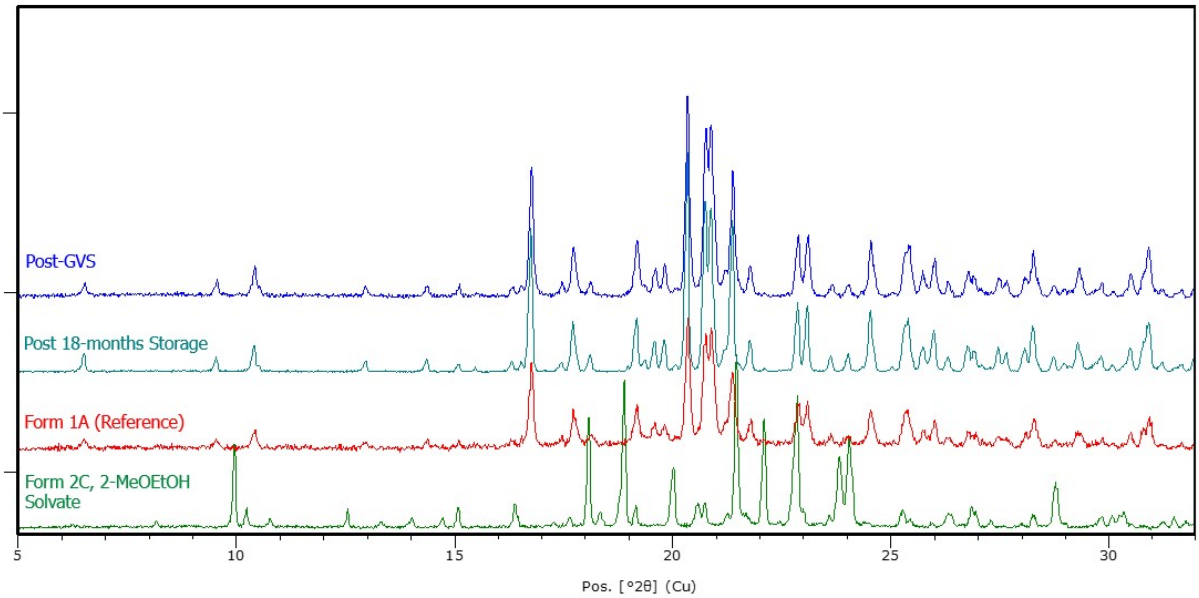

Figure S47 XPRD overlay of mirabegron edisylate form 2C from 2-methoxyethanol before and after storage and post GVS

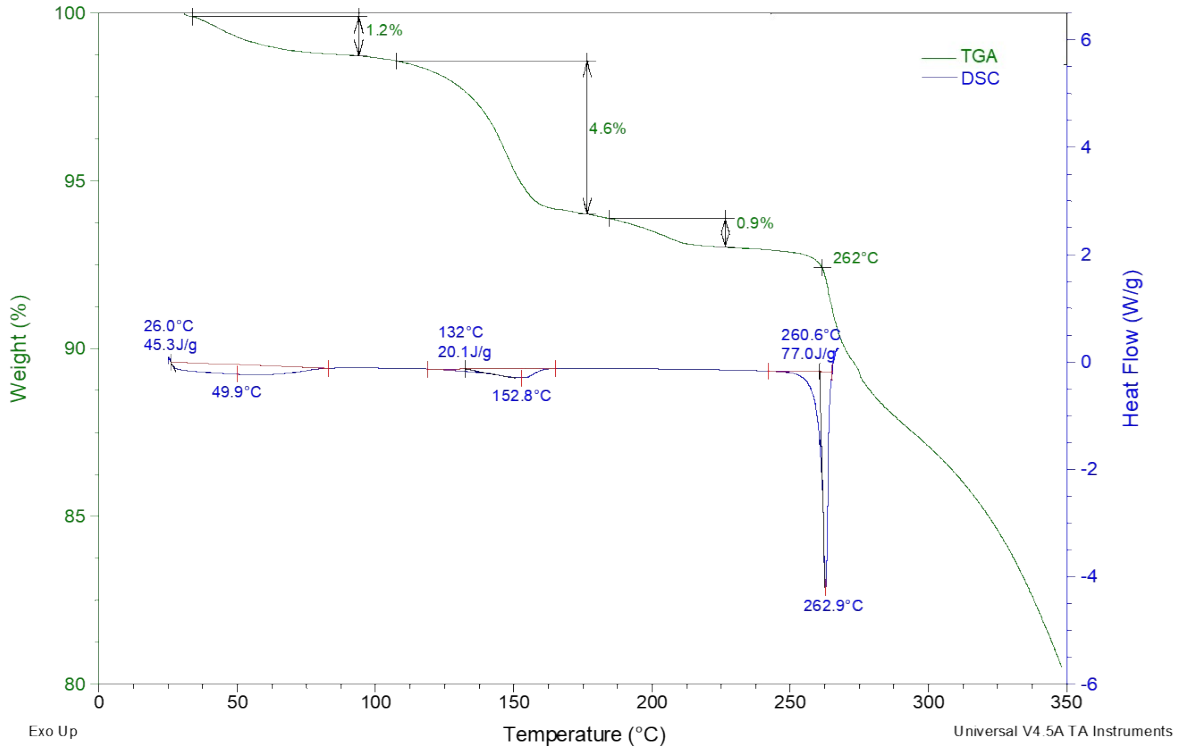

Figure S48 TGA and DSC overlay of form 2C

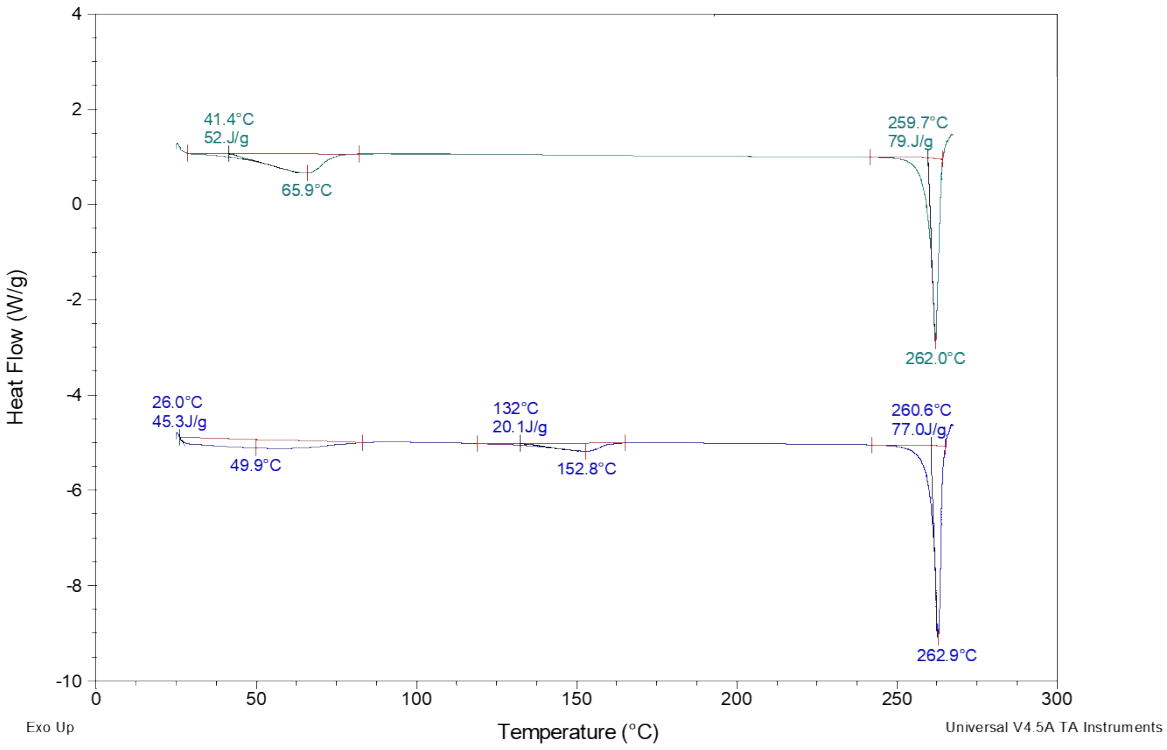

Figure S49 DSC overlay of form 2C (bottom) and form 1D (top, form 1D was obtained after vac. drying at 200 ℃ of form 2C)

2D

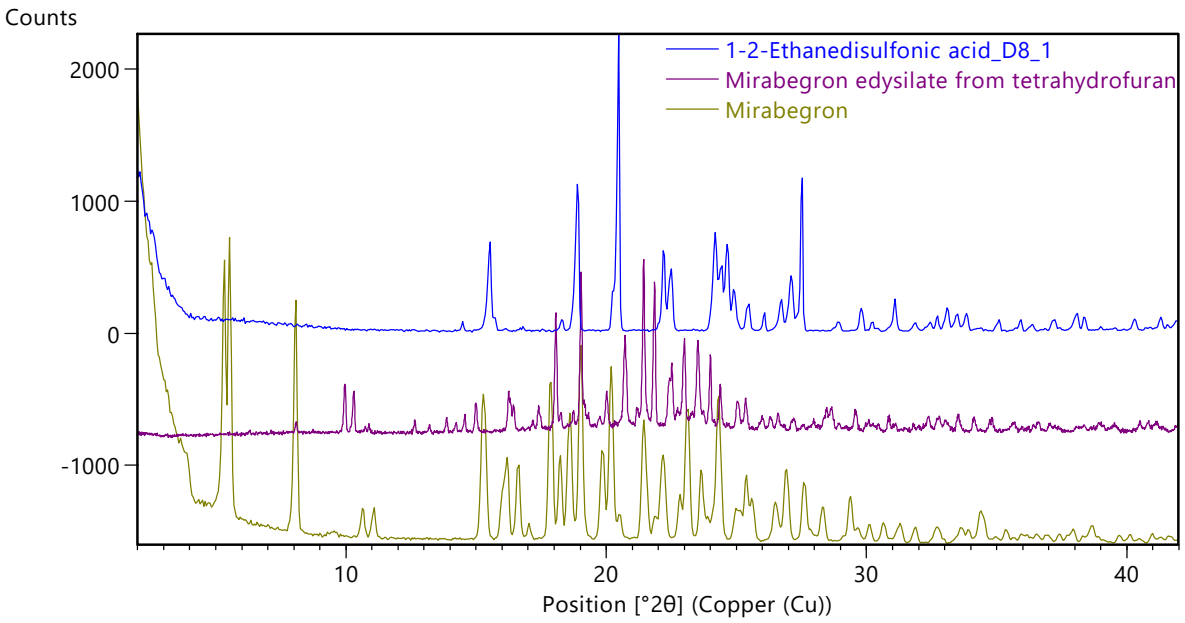

Figure S50 XPRD overlay of mirabegron, 1,2-ethanedisulfonic acid and mirabegron edisylate form 2D tetrahydrofuran

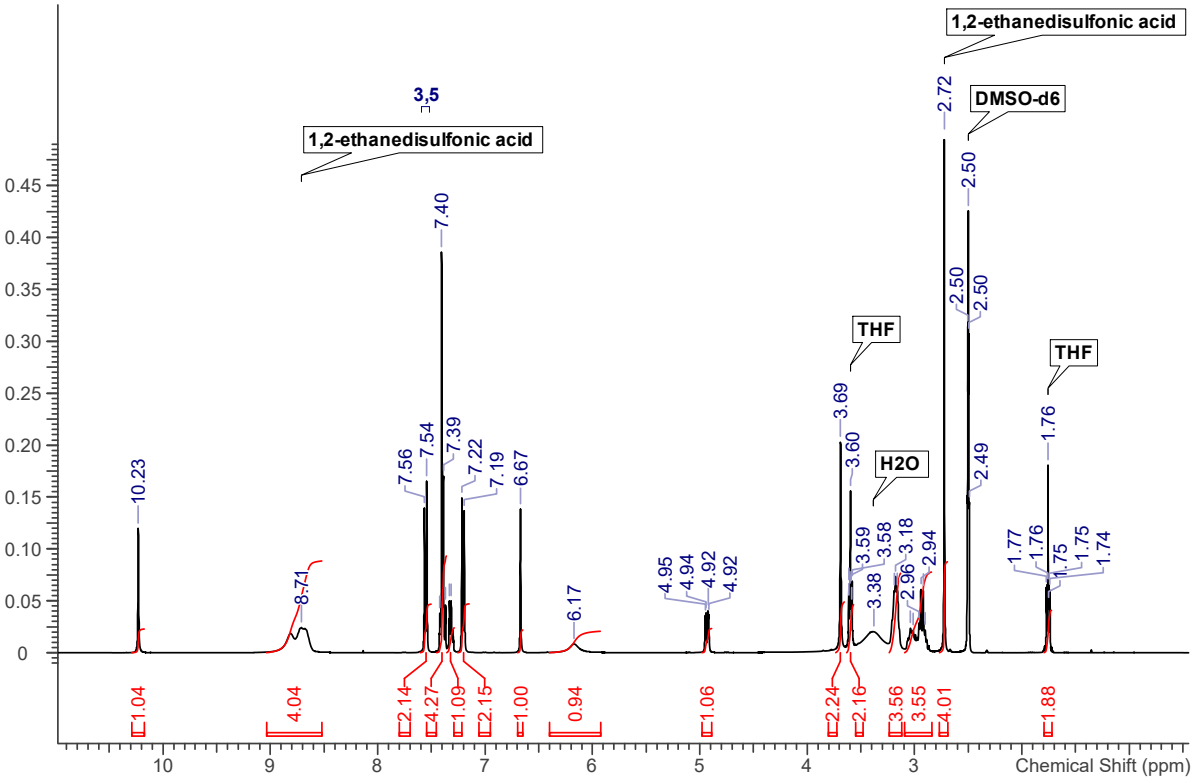

Figure S51 ^{1}H-NMR overlay of mirabegron edisylate form 2D from tetrahydrofuran

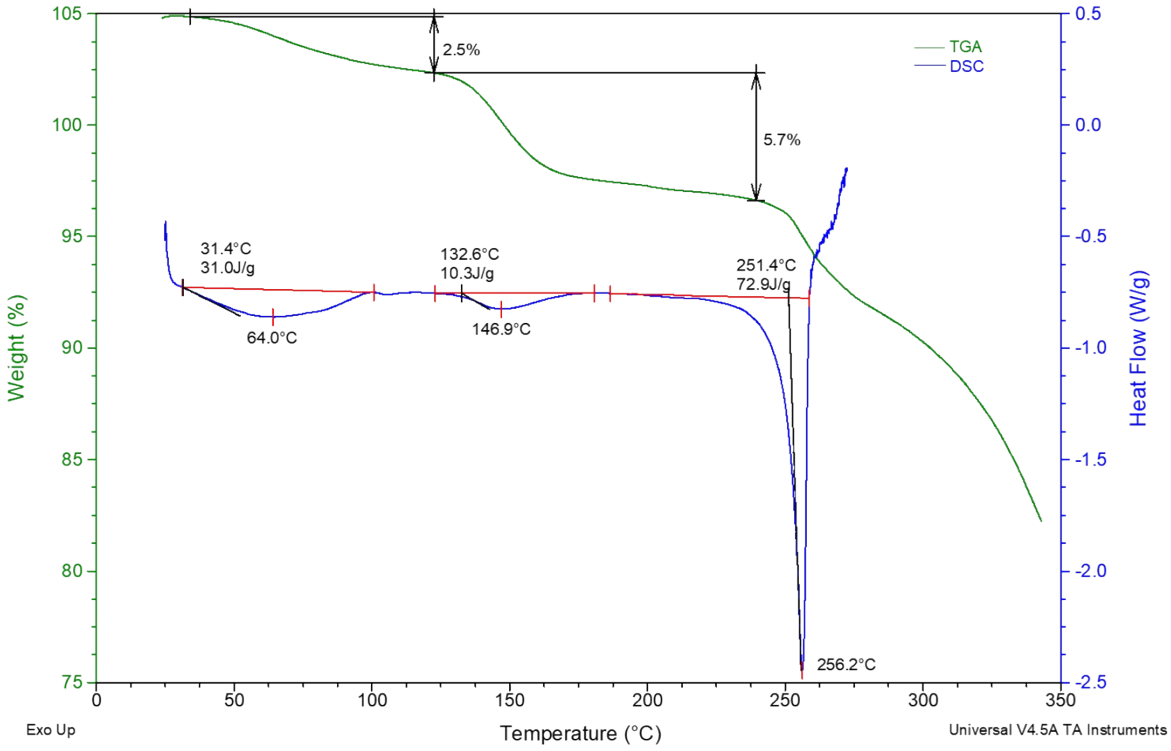

Figure S52 TGA and DSC overlay of form 2D from tetrahydrofuran

1D

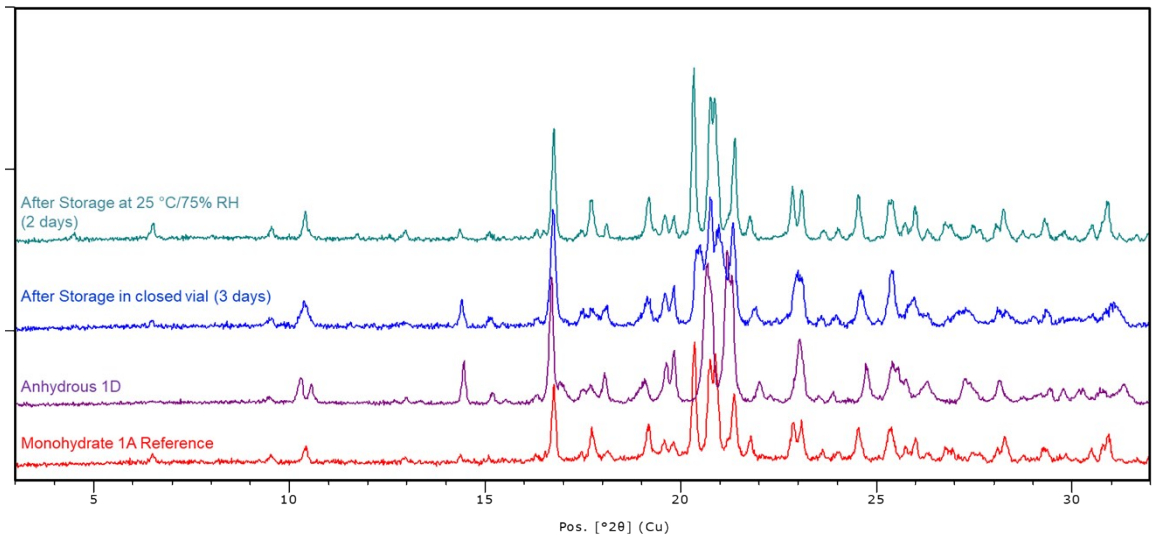

Figure S53 XPRD overlay of mirabegron edisylate form 1D before and after storage

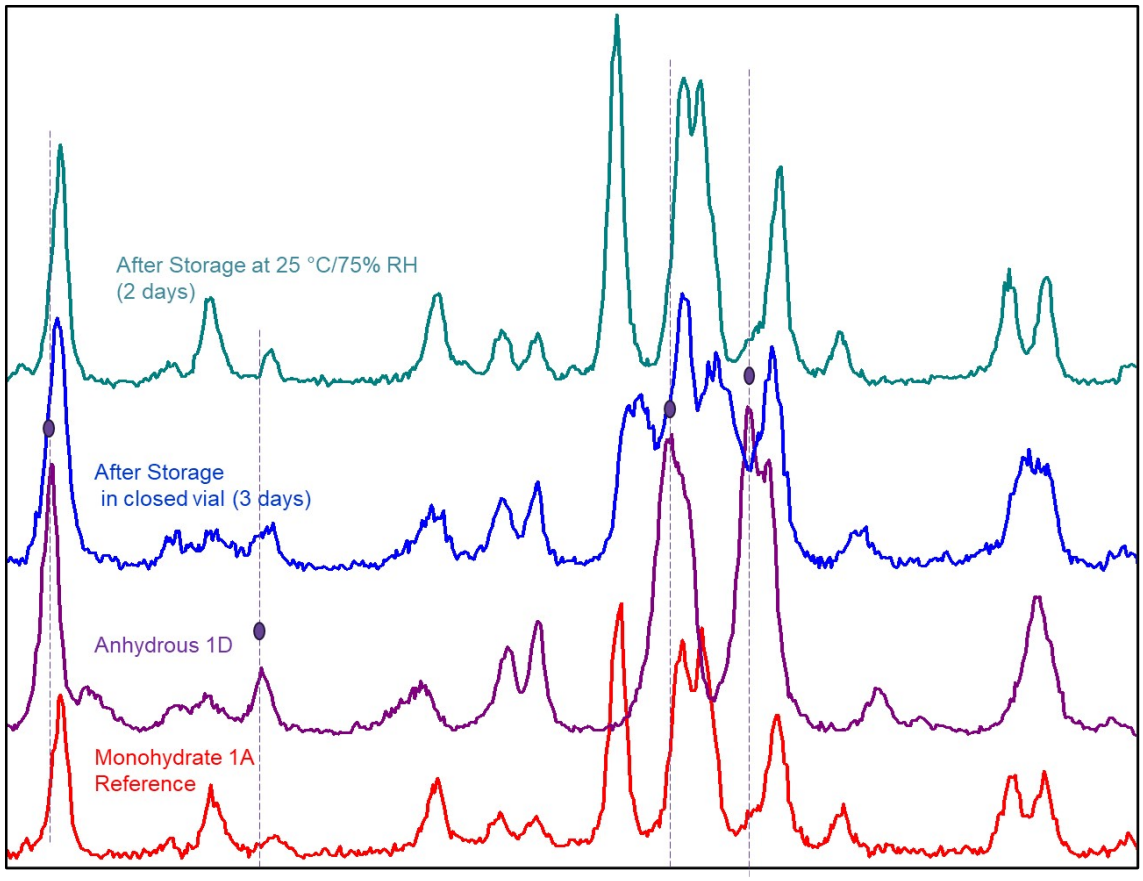

Figure S54 XPRD overlay of mirabegron edisylate form 1D before and after storage (zoom in between 16 and 24 2Θ) – Dots highlighting characteristic peaks of form 1D

Solvent mediated conversions

Conversion study form 2A to form 1 family are listed in Table S5:

Mirabegron edysilate form 2A (20 mg) was dispensed into HPLC vials with stirrer bars. 0.5 ml of solvent was added as described in the table below. The vials were stirred at 50 °C for 1h then cooled down to 5 °C overnight. If a suspension formed, it was filtered and the solid was analysed by PXRD.

Table S5 Conversion studies of form 2A to form 1A

Solvent	Observation after 15 min at 50 °C	PXRD aliq. after 2 days	PXRD aliq. after 5 days
THF	Suspension	Form 2A	Form 2A
Acetone	Suspension	Form 2A	Form 2A
Acetone/water (9:1)v/v	Suspension	Form 2A + peak Form 1A	Form 1A
Methanol	Suspension	Form 2A + peak shifts	Form 2A + peak shifts, similarities to Form 1A
Ethanol	Suspension	Form 2A	Form 2A
Dichloromethane	Suspension	Form 2A	Form 2A
Acetonitrile (ACN)	Suspension	Form 2A	Form 2A
ACN:water (1:1)v/v	Clear solution	Clear solution – N/P	Clear solution – N/P
IPA:water (9:1)v/v	Suspension	Form 2A	Form 2A
MEK	Suspension	Form 2A	Form 2A
1-BuOH	Suspension	Form 2A	Form 2A
THF:water (9:1)v/v	Suspension	Form 2A	Form 2A
Water	Clear solution	Clear solution – N/P	Clear solution – N/P

Extra Data

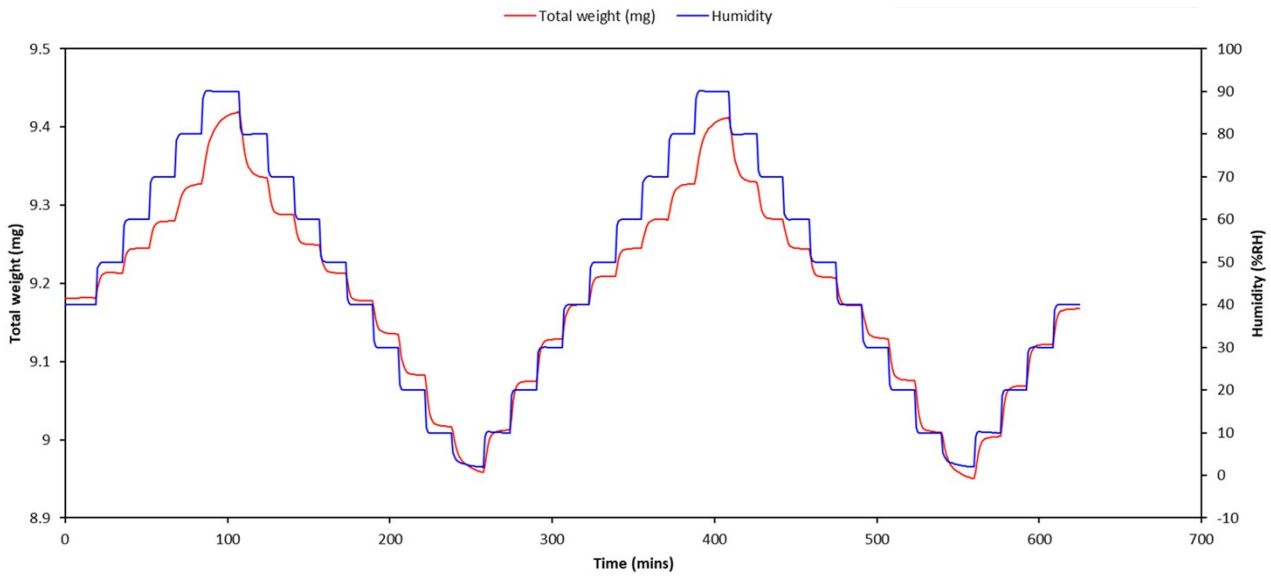

Figure S55 DVS kinetic plot for mirabegron edisylate form 1A

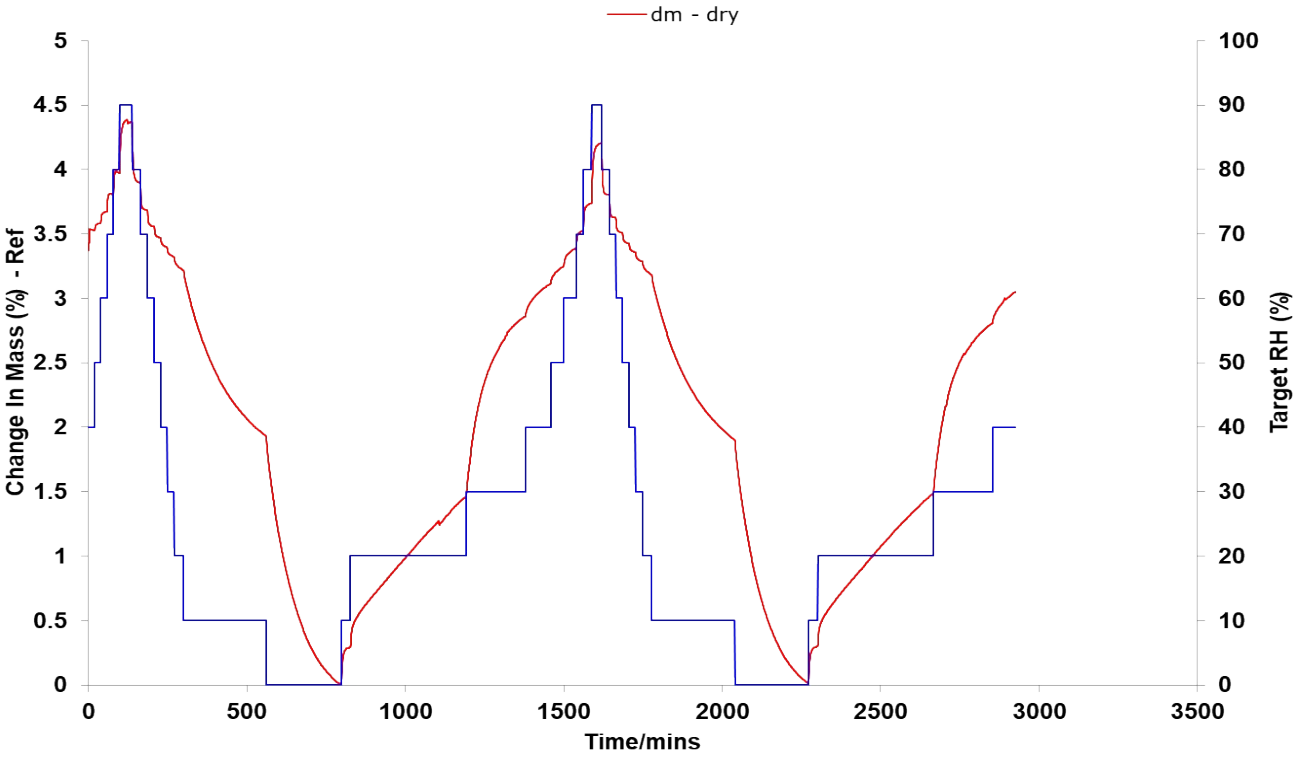

Figure S56. DVS kinetic plot for mirabegron edisylate form 2A

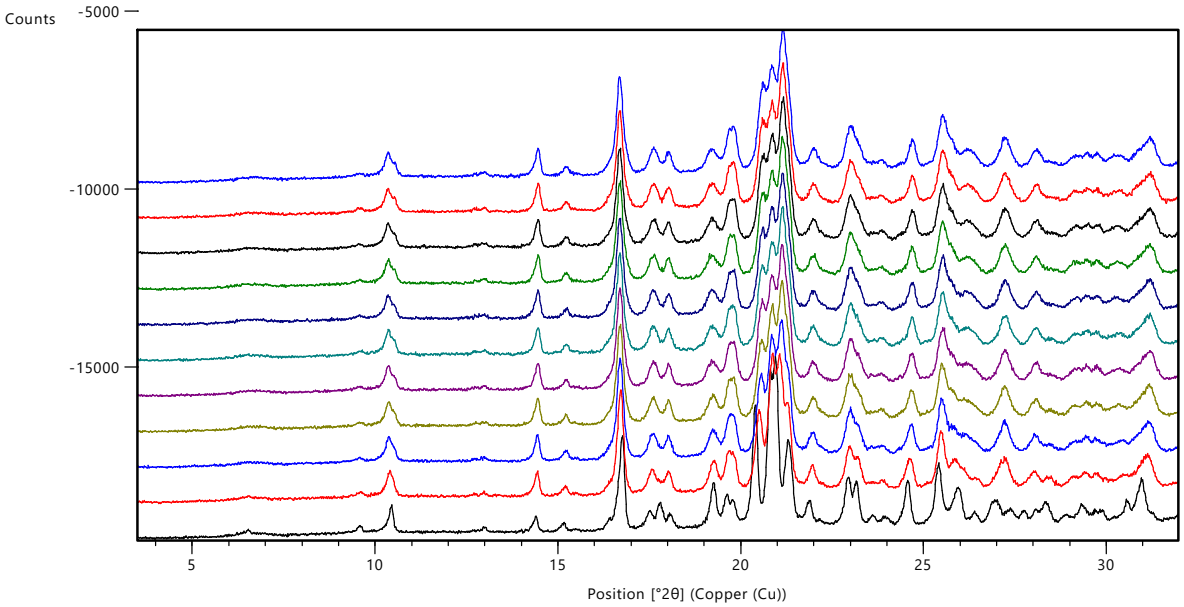

Figure S57.From bottom to top, t0 at 5%RH up to t10 at 5%RH

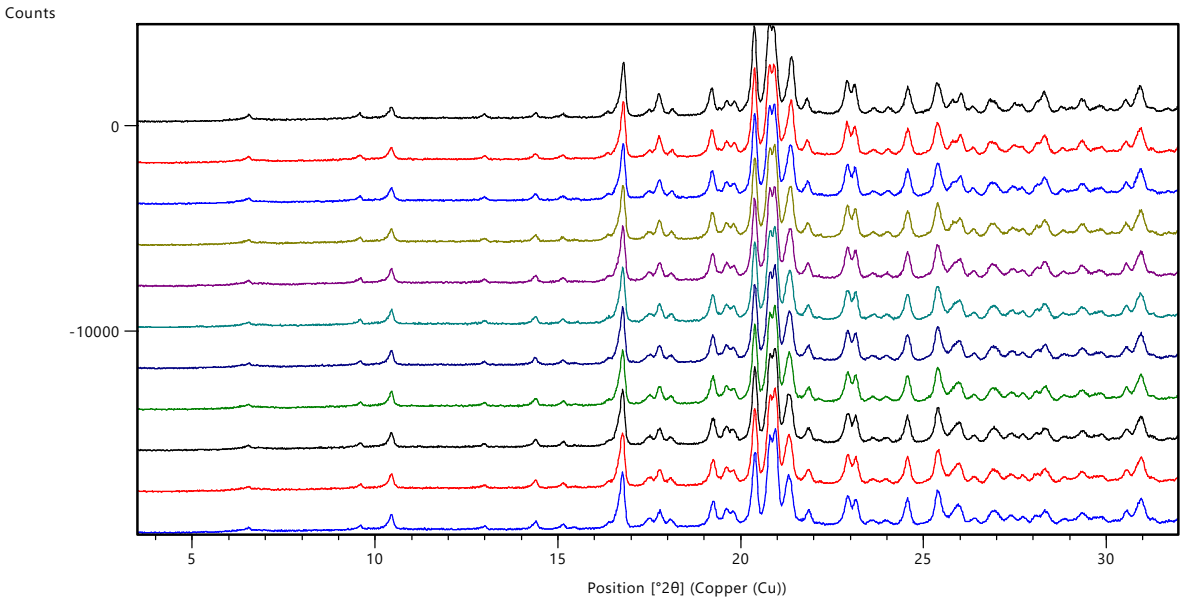

Figure S58 From bottom to top, t0 at 5%RH up to t10 at 5%RH

Drying of solvates: A small amount of material (*ca*. 30 mg) was vacuum dried overnight at 40 °C.

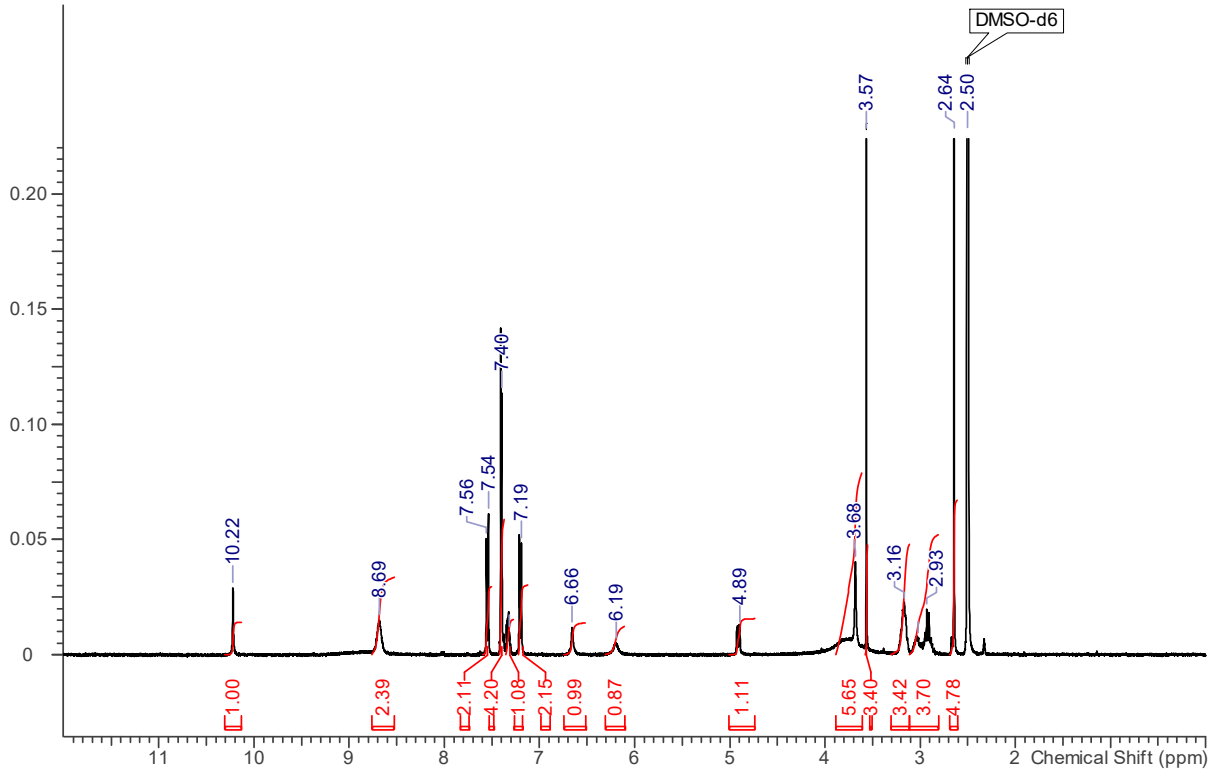

Figure S59 ^{1}H-NMR of mirabegron edisylate form 2A after drying

Table S6 Characterisation summary of mirabegron, mirabegron dihydrocholoride and mirabegron edisylate

Analysis	Mirabegron	Mirabegron 2HCl	Mirabegron edisylate
PXRD	Crystalline	Mrbg 2HCl form 1	Mrbg EDS form 1A
NMR	Consistent with structure	Consistent with structure, peak at 5.23ppm missing	Consistent with structure (peaks shifted), 1 eq 1,2-ethane disulfonic acid, THF traces, extra peaks
TGA	No weight loss before degradation starting ca. 250 °C	Not run	3.3 % weight loss between 40 – 100 °C (1 equivalent water)
DSC	Sharp endotherm with onset at 141.7 °C (143 J/g)	Wide endotherm with onset at 46.0 °C (15 J/g) Endotherm with onset at 124.2 °C (52 J/g) Sharp endotherm with onset at 179.9 °C (43 J/g)	Wide endotherm with onset at 59.6 °C (99 J/g), endotherm with onset at 229.3 °C (partially resolved)
GVS	Up to 0.18 % water uptake, reversible cycles with an initial 0.1 % water	Not run	Start at 3.5 % followed by a water uptake to 4.4 %, reversible cycles between 0 – 4.4 % with end at 3.5 %. Dehydratation under 3.5 % occurs under 20 % RH
Storage 25°C /97 % RH (10d)	Mirabegron form 1	Deliquesced	Mrbg EDS form 1A
Storage 40°C/75%RH (10d)	Mirabegron form 1	Mrbg 2HCl form 1	Mrbg EDS form 1A

[i]Parson, H. D. Flack and T. Wagner, *Acta Cryst.,* 2013. **B69**, 249-259
[ii] Rob W. W. Hooft,Leo H. Straver and Anthony L. Spek, *J. Appl. Cryst.,*2008, **41**, 96-103