# Supporting Information

# Emphasis on pharmaceutically acceptable solvates: Linking Solubility with Iso-structurality for Better Drug Design

Ramesh Reddy Mudda,[a] Ramesh Devarapalli,[a] Manjunath Bollineni,[a] Arijit Das,[a] Ramanaiah Chennuru.[a*]

[a]Centre of Excellence Polymorphism, Research and Development, Integrated Product Development (IPD), Cipla Ltd., Bangalore, India.

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*Corresponding authors

Dr. Ramanaiah Chennuru

Centre of Excellence Polymorphism, Research and Development, Integrated Product Development (IPD), Cipla Ltd., Virgonagar, Bangalore-560 049, Karnataka, India

Email: Ramanaiah.Chennuru@Cipla.com

Contact No: +91-80-46912332. Fax No: +91-80-28472795.

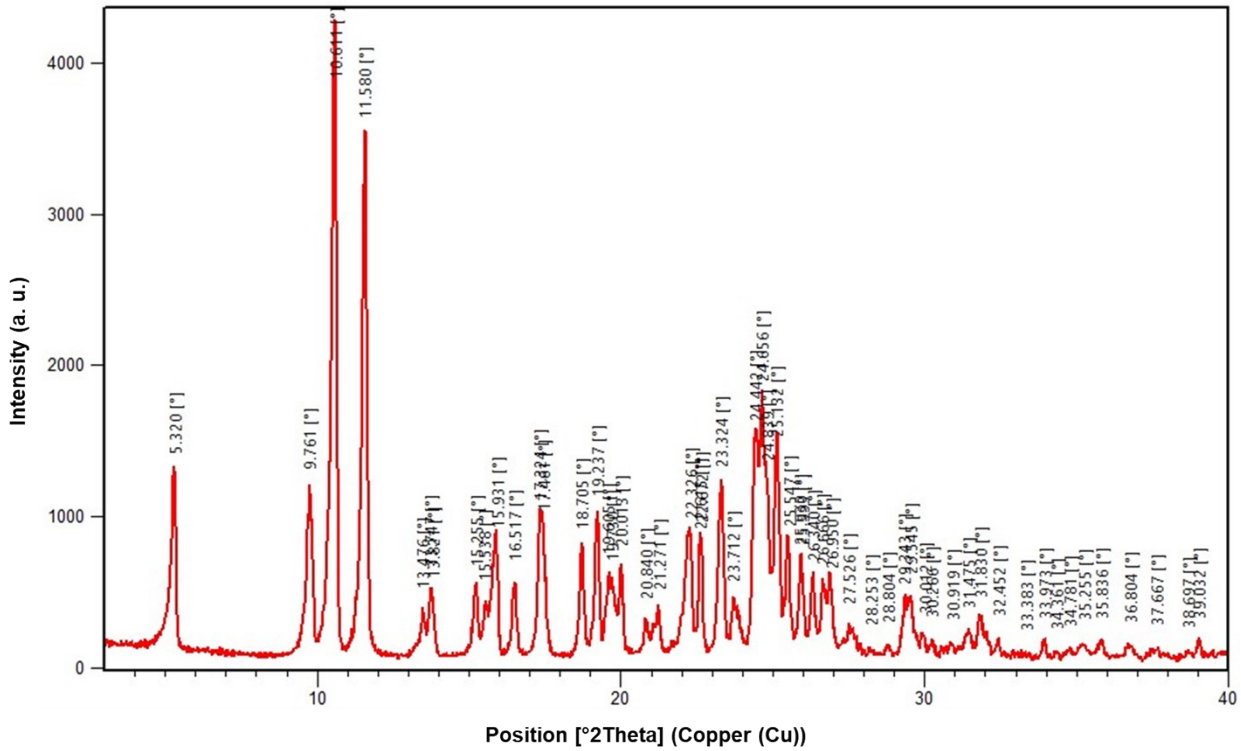


**Figure S1:** Powder X-ray Diffraction pattern of AM-I.

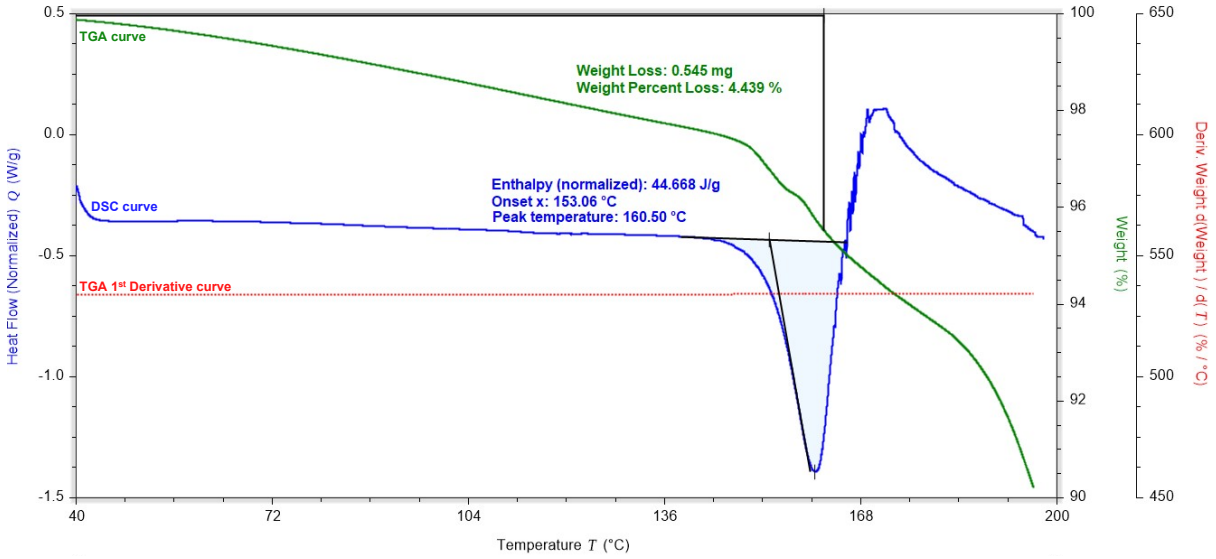


**Figure S2.** Overlay of DSC, TGA thermograms and TGA 1st derivative curve of AM-I.

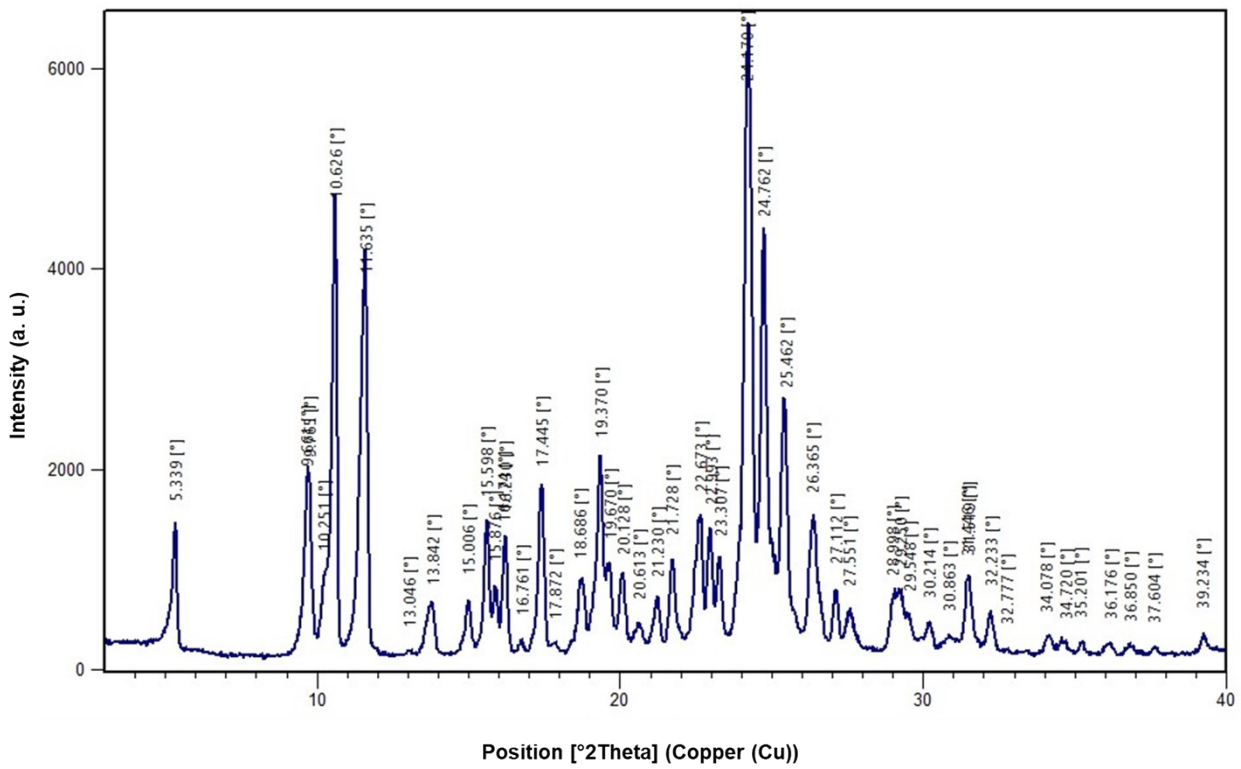


**Figure S3:** Powder X-ray Diffraction pattern of AM-II.

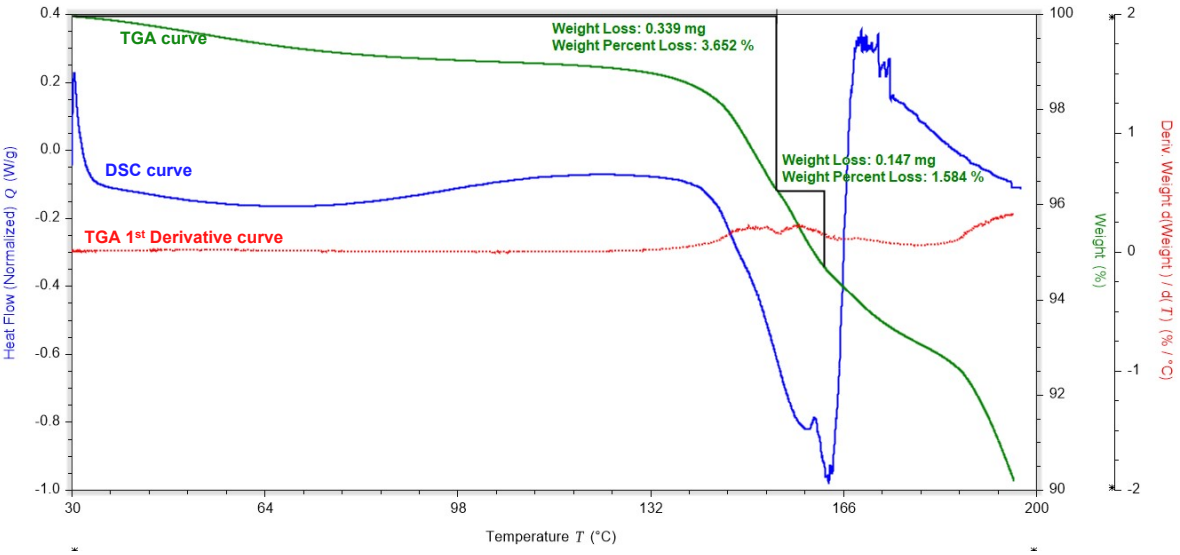


**Figure S4.** Overlay of DSC, TGA thermograms and TGA 1st derivative curve of AM-II.

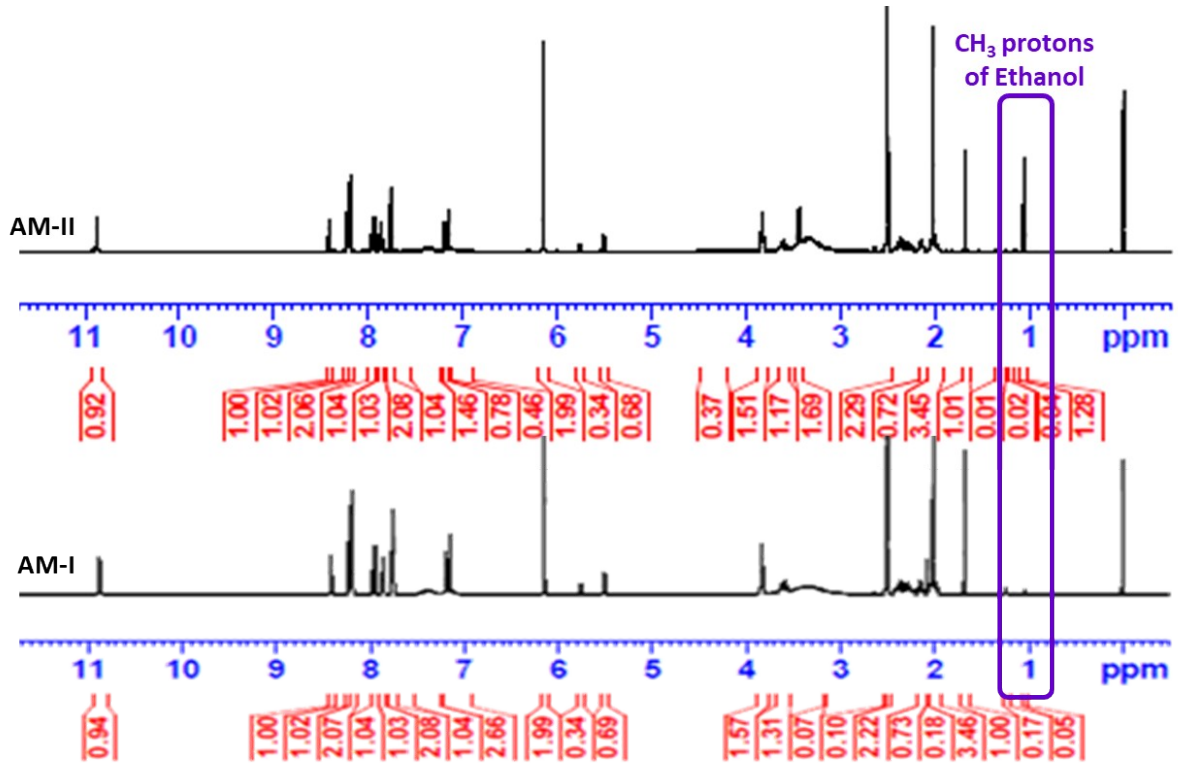


**Figure S5:** $^{1}$H NMR overlay of AM-I and AM-II.

**AM-I $^{1}$H-NMR** (500 MHz, *d6*-DMSO) δ: 1 .67 (s, 1 H), 1.95 - 2.06 (m, 3 H), 2.08 - 2.50 (m, 3 H), 3.55-3.63 (m, 1 H), 3.83 (t, J = 7 Hz, 1 H), 5.49 – 5.77 (m, 1 H), 6.14 (s, 2 H), 7.14 – 7.20 (m, 2 H), 7.37 (s, 1 H), 7.74 – 7.77 (m, 2 H), 7.87 (t, J = 7.5 Hz, 1 H), 7.93 – 7.97 (m, 1 H), 8.21 (d, J = 8 Hz, 2 H), 8.22 (d, J = 8.4 Hz, 1 H), 8.41 (d, J = 4.7 Hz, 1 H).

**AM-II $^{1}$H-NMR** (500 MHz, *d6*-DMSO) δ: 1.10 (t, J= 7 Hz, 1 H), 1 .67 (s, 1 H), 1.98-2.04 (m, 3 H), 2.12 - 2.50 (m, 3 H), 3.33 (q, J = 7 Hz, 2 H), 3.41-3.63 (m, 1 H), 3.83 (t, J = 7 Hz, 1 H), 5.49 – 5.77 (m, 1 H), 6.14 (s, 2 H), 7.14 – 7.20 (m, 2 H), 7.35 (s, 1 H), 7.74 – 7.77 (m, 2 H), 7.85 (t, J = 7.5 Hz, 1 H,), 7.93 – 7.97 (m, 1 H), 8.20 (d, J = 8 Hz, 2 H), 8.22 (d, J = 8.4 Hz, 1 H), 8.40 (d, J = 4.7 Hz, 1 H).

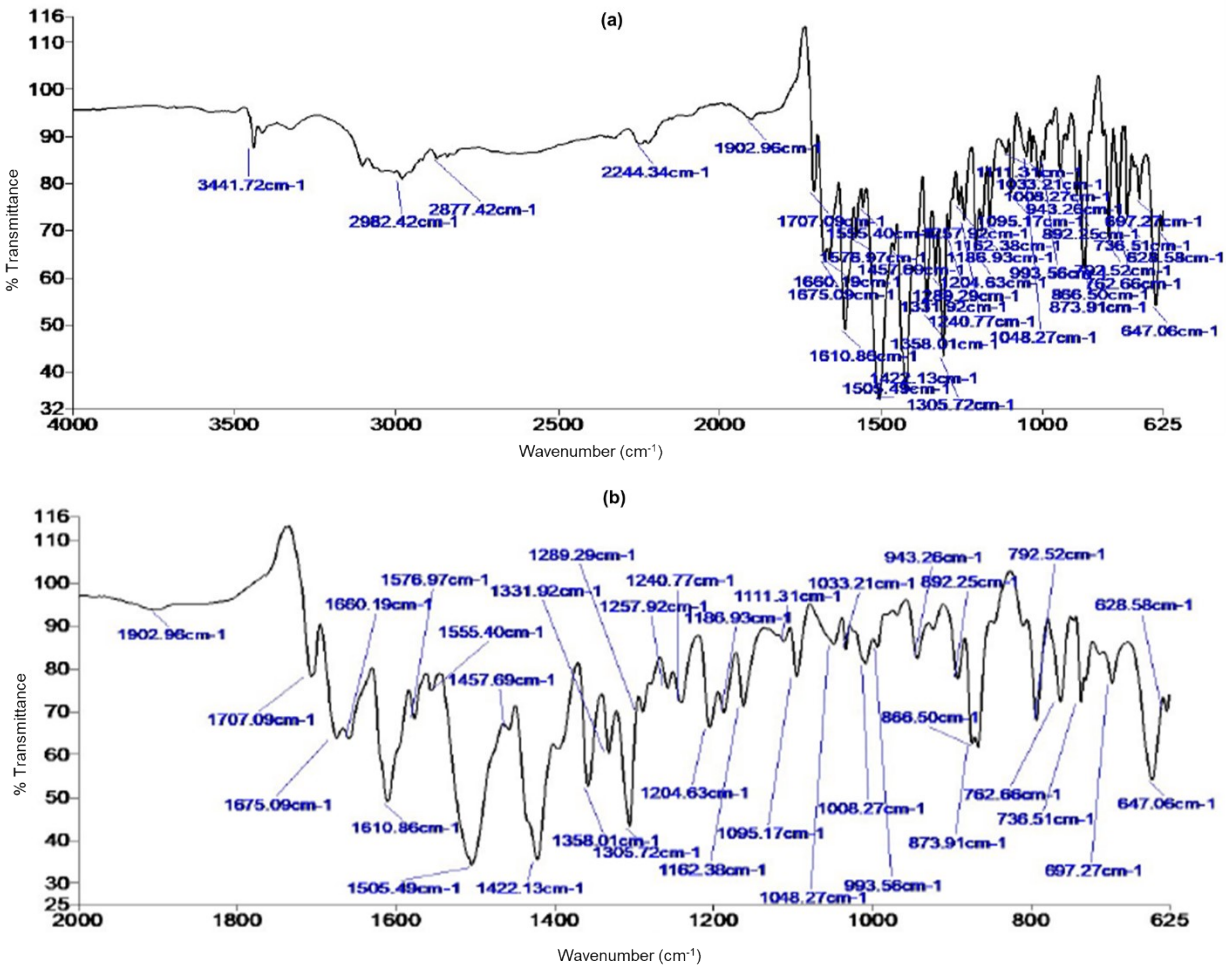


**Figure S6:** FTIR spectra of AM-I (a) 625 to 4000cm$^{-1}$ (b) 625 to 2000 cm$^{-1}$.

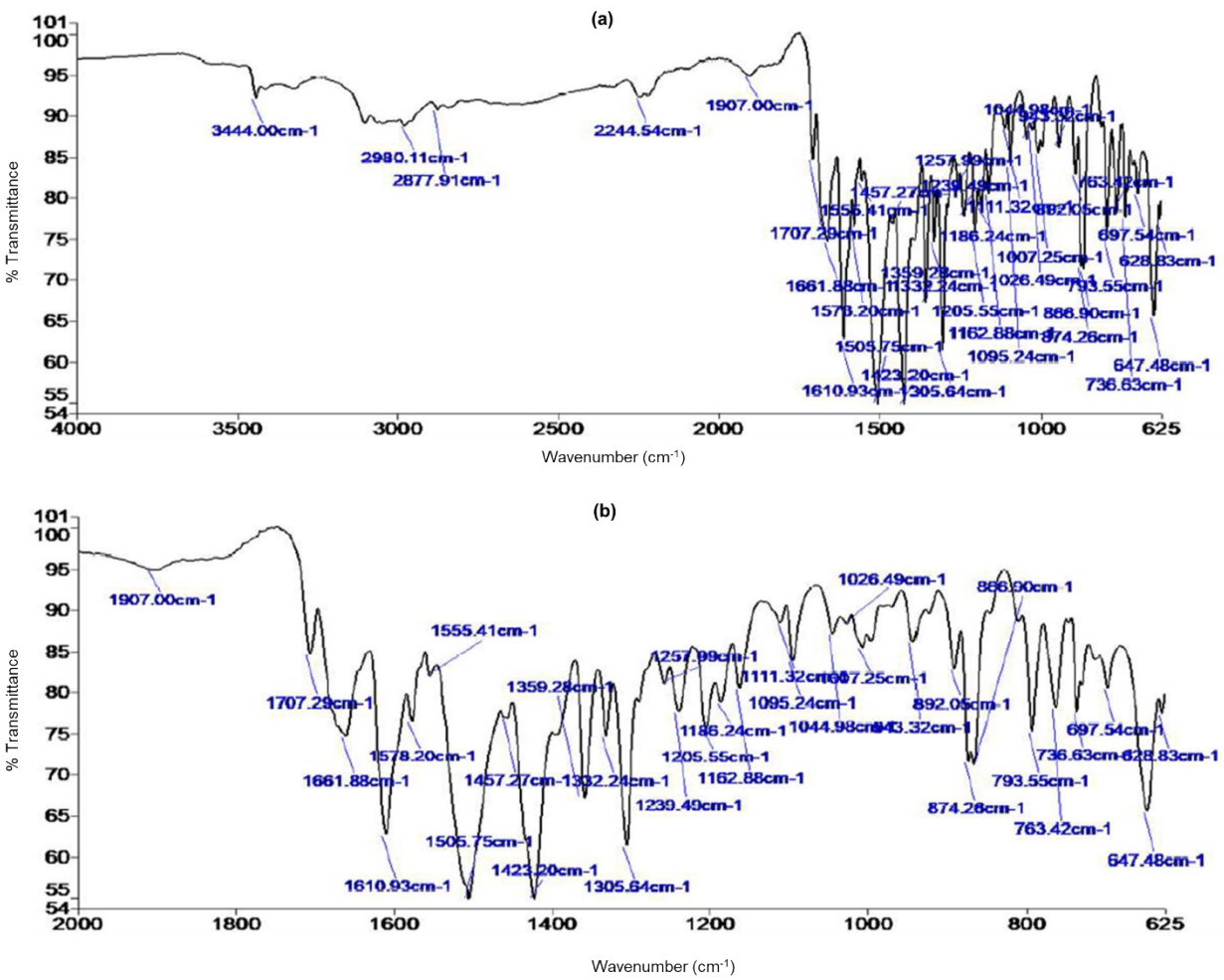


**Figure S7:** FTIR spectra of AM-II (a) 625 to 4000cm$^{-1}$ (b) 625 to 2000 cm$^{-1}$.

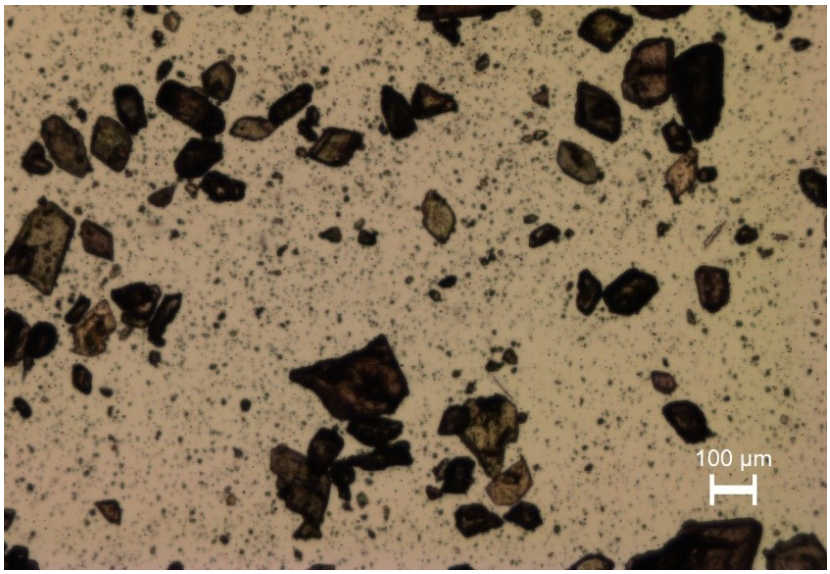


**Figure S8:** Microscopic image of AM-I single crystals.

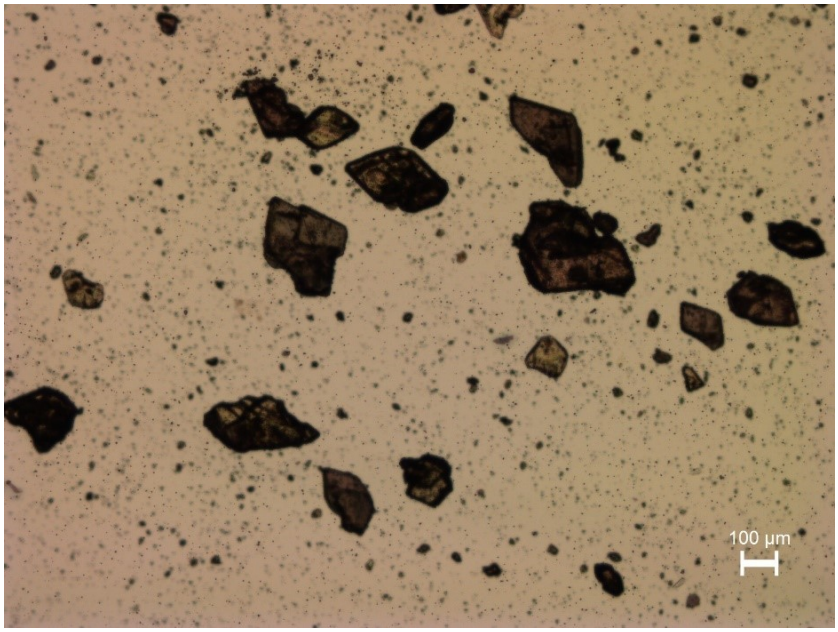


**Figure S9:** Microscopic image of AM-II single crystals.

**Table S1:** Experimental polymorph screening details of Acalabrutinib maleate.

| Slurry crystallization | | | | |
|---|---|---|---|---|
| **S. No.** | **Input form** | **Solvent** | **Temp. (°C)** | **XRD Result** |
| 1 | Amorphous | 2-Butanol | 25-30 | AM-I |
| 2 | Amorphous | Acetone | 25-30 | AM-I |
| 3 | Amorphous | Acetone + Water (1:1) | 25-30 | AM-I |
| 4 | Amorphous | Acetone + Water (9:1) | 25-30 | AM-I |
| 5 | Amorphous | Acetonitrile | 25-30 | AM-I |
| 6 | Amorphous | Acetonitrile | 45-50 | AM-I |
| 7 | Amorphous | Acetonitrile + Water (1:1) | 25-30 | AM-I |
| 8 | Amorphous | Acetonitrile + Water (9:1) | 25-30 | AM-I |
| 9 | Amorphous | Ethanol | 25-30 | AM-I and extra peaks observed |
| 10 | Amorphous | Ethanol | 0-5 | AM-I |
| 11 | Amorphous | Ethanol | 65-70 | AM-I and extra peaks observed |
| 12 | Amorphous | Ethanol + Isopropanol (1:1) | 0-5 | AM-I |
| 13 | Amorphous | Ethanol + Acetone (1:1) | 25-30 | AM-I |
| 14 | Amorphous | Ethanol + Water (1:1) | 25-30 | AM-I |
| 15 | Amorphous | Ethanol + Water (9:1) | 25-30 | AM-I |
| 16 | Amorphous | Ethyl acetate | 25-30 | AM-I |
| 17 | Amorphous | Isopropyl acetate | 25-30 | AM-I |
| 18 | Amorphous | n-Butyl acetate | 25-30 | AM-I |

| | | | | |
|---|---|---|---|---|
| 19 | Amorphous | Heptane | 25-30 | AM-I |
| 20 | Amorphous | Isopropanol | 25-30 | AM-I |
| 21 | Amorphous | Isopropanol + Water (1:1) | 25-30 | AM-I |
| 22 | Amorphous | Isopropanol + Water (9:1) | 25-30 | AM-I |
| 23 | Amorphous | Methanol | 50-55 | AM-I |
| 24 | Amorphous | Methanol + Water (1:1) | 25-30 | AM-I |
| 25 | Amorphous | Methanol + Water (9:1) | 25-30 | AM-I |
| 26 | Amorphous | Nitromethane + Water (1:1) | 25-30 | AM-I |
| 27 | Amorphous | Nitromethane + Water (9:1) | 25-30 | AM-I |
| 28 | Amorphous | Toluene | 25-30 | AM-I |
| 29 | Amorphous | Water | 25-30 | AM-I |
| 30 | Amorphous | Water | 70-75 | AM-I |
| 31 | AM-I | Dimethyl acetamide | 25-30 | AM-I |
| 32 | AM-I | Dimethyl acetamide | 70-75 | AM-I |
| 33 | AM-I | Dimethyl formamide | 25-30 | AM-I |
| 34 | AM-I | Dimethyl formamide | 70-75 | AM-I |
| 35 | AM-I | Dimethyl sulfoxide | 25-30 | AM-I |
| 36 | AM-I | Dimethyl sulfoxide | 70-75 | AM-I |
| 37 | AM-I | Ethanol + Water (9.5:0.5) | 55-60 | AM-II |
| 38 | AM-I | Methanol + Water (9.5:0.5) | -5 - -10 | AM-I |
| 39 | AM-I | Toluene | 50-55 | AM-I |
| 40 | AM-I | Toluene | 95-100 | AM-I |
| 41 | AM-I | Xylene | 50-55 | AM-I |
| 42 | AM-I | Water | 50-55 | AM-I |
| 43 | AM-I | Heptane | 50-55 | AM-I |
| 44 | AM-I | Methyl tertiary butyl ether | 40-45 | AM-I |
| 45 | AM-I | Methyl isobutyl ketone | 25-30 | AM-I |
| 46 | AM-I | Methyl isobutyl ketone | 50-55 | AM-I |
| 47 | AM-I | Di isopropyl ether | 25-30 | AM-I |
| 48 | AM-I | Di isopropyl ether | 45-50 | AM-I |
| 49 | AM-I | 2-Methyl tetrahydrofuran | 55-60 | AM-I |
| 50 | AM-I | Methyl isopropyl ketone | 45-50 | AM-I |
| 51 | AM-I | Dimethyl carbonate | 45-50 | AM-I |
| 52 | AM-I | Dimethyl carbonate | 80-85 | AM-I |

**Recrystallization**

| S. No. | Input Form | Solvent | Temp. (°C) | XRD Result |
|---|---|---|---|---|
| 1 | Amorphous | Benzyl alcohol | 0-5 | AM-I |
| 2 | AM-I | Trifluoro ethanol | -10 - -15 | AM-I |
| 3 | AM-I | Acetic acid | 25-30 | AM-I |
| 4 | Amorphous | Acetonitrile | -10 - -15 | AM-I |

| | | | | |
|---|---|---|---|---|
| 5 | AM-I | Aniline | 25-30 | AM-I |
| 6 | AM-I | Benzyl alcohol/Methanol | 25-30 | AM-I |
| 7 | Amorphous | Chloroform | -10 - -15 | AM-I |
| 8 | Amorphous | Dichloromethane | -10 - -15 | AM-I |
| 9 | Amorphous | Dichloromethane/Acetone | -10 - -15 | AM-I |
| 10 | AM-I | N, N-Dimethylacetamide | 0-5 | AM-I |
| 11 | AM-I | Dimethyl sulfoxide | 25-30 | AM-I |
| 12 | Amorphous | 1,4-Dioxane | 25-30 | AM-I |
| 13 | Amorphous | 2-Ethoxyethanol | -10 - -15 | AM-I |
| 14 | Amorphous | Methanol | -10 - -15 | AM-I |
| 15 | Amorphous | Methanol/Water | -10 - -15 | AM-I |
| 16 | AM-I | N-Methylpyrrolidone | 25-30 | AM-I |
| 17 | Amorphous | Propylene glycol | -10 - -15 | AM-I |
| 18 | Amorphous | Tetrahydrofuran/Methanol | -10 - -15 | AM-I |
| 19 | Amorphous | Tetrahydrofuran/Acetone | -10 - -15 | AM-I |
| 20 | Amorphous | Tetrahydrofuran | -10 - -15 | AM-I |

**Anti-solvent addition crystallization**

| S. No. | Input Form | Solvent | Antisolvent | Temp. (°C) | XRD Result |
|---|---|---|---|---|---|
| 1 | Amorphous | Trifluoro ethanol | Isopropyl acetate | 25-30 | AM-I |
| 2 | AM-I | Acetic acid | Methyl tertiary butyl ether | 0-5 | AM-I |
| 3 | AM-I | Acetic acid | Heptane | 0-5 | AM-I |
| 4 | AM-I | Acetic acid | Acetone | 25-30 | AM-I |
| 5 | AM-I | Acetic acid | Methyl isobutyl ketone | 25 | AM-I |
| 6 | Amorphous | Acetonitrile | Methyl tertiary butyl ether | 25-30 | AM-I |
| 7 | Amorphous | Acetonitrile | Isopropyl acetate | 0-5 | AM-I |
| 8 | Amorphous | Acetonitrile | Heptane | 25-30 | AM-I |
| 9 | AM-I | Aniline | Di isopropyl ether | 0-5 | AM-I |
| 10 | AM-I | Aniline | Heptane | 0-5 | AM-I |
| 11 | Amorphous | Benzyl alcohol | Isopropyl acetate | 25-30 | AM-I |
| 12 | AM-I | Benzyl alcohol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 13 | AM-I | Benzyl alcohol | Ethyl acetate | 0-5 | AM-I |
| 14 | AM-I | Benzyl alcohol | Heptane | 0-5 | AM-I |
| 15 | Amorphous | Chloroform | Methyl tertiary butyl ether | 0-5 | AM-I |
| 16 | Amorphous | Chloroform | Toluene | 25-30 | AM-I |
| 17 | Amorphous | Chloroform | Heptane | 0-5 | AM-I |
| 18 | Amorphous | Dichloromethane | Di isopropyl ether | 0-5 | AM-I |
| 19 | AM-I | Dichloromethane | Methyl isobutyl ketone | 23-75 | Solid not isolated |
| 20 | Amorphous | Dichloromethane | Heptane | 25-30 | AM-I |
| 21 | AM-I | N, N-Dimethylacetamide | Methyl tertiary butyl ether | 0-5 | AM-I |

| | | | | | |
|---|---|---|---|---|---|
| 22 | AM-I | N, N-Dimethylacetamide | Heptane | 25-30 | AM-I |
| 23 | AM-I | N, N-Dimethylformamide | Methyl tertiary butyl ether | 25-30 | AM-I |
| 24 | AM-I | N, N-Dimethyl formamide | Heptane | 0-5 | AM-I |
| 25 | AM-I | Dimethyl sulfoxide | Di isopropyl ether | 0-5 | AM-I |
| 26 | AM-I | Dimethyl sulfoxide | n-propyl acetate | 25-30 | AM-I |
| 27 | AM-I | Dimethyl sulfoxide | Hexane | 0-5 | AM-I |
| 28 | Amorphous | 1,4-Dioxane | Methyl tertiary butyl ether | 0-5 | AM-I |
| 29 | Amorphous | 1,4-Dioxane | Heptane | 25-30 | AM-I |
| 30 | Amorphous | 2-Ethoxyethanol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 31 | Amorphous | 2-Ethoxyethanol | Pentane | 0-5 | AM-I |
| 32 | AM-I | Formic acid | Methyl isobutyl ketone | 70-75 | AM-I and extra peak |
| 33 | AM-I | Formic acid | Acetone + Methyl isobutyl ketone | 50-55 | AM-I |
| 34 | Amorphous | Methanol | Methyl tertiary butyl ether | 0-5 | AM-I |
| 35 | Amorphous | Methanol | 2-Butanol + Water | 0-5 | AM-I |
| 36 | Amorphous | Methanol | Water | 25-30 | AM-I |
| 37 | Amorphous | Methanol | Ethyl acetate | 0-5 | AM-I |
| 38 | Amorphous | Methanol | Xylene | 0-5 | AM-I |
| 39 | AM-I | 2-Methoxyethanol | Acetone | 75°C | AM-I |
| 40 | AM-I | N-Methyl pyrrolidine | Water | 75°C | AM-I |
| 41 | AM-I | N-Methyl pyrrolidine | Ethyl acetate | 75°C | AM-I |
| 42 | AM-I | N-Methylpyrrolidone | Methyl tertiary butyl ether | 0-5 | AM-I |
| 43 | AM-I | N-Methylpyrrolidone | Heptane | 0-5 | AM-I |
| 44 | AM-I | Propylene glycol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 45 | AM-I | Propylene glycol | Ethyl acetate | 0-5 | AM-I |
| 46 | AM-I | Propylene glycol | Heptane | 0-5 | AM-I |
| 47 | Amorphous | Tetrahydrofuran | Methyl tertiary butyl ether | 0-5 | AM-I |
| 48 | Amorphous | Tetrahydrofuran | Water | 25-30 | AM-I |
| 49 | Amorphous | Tetrahydrofuran | Xylene | 0-5 | AM-I |
| 50 | Amorphous | Tetrahydrofuran | Heptane | 25-30 | AM-I |

**Reactive crystallization**

In the following mentioned experiments, Different polymorphs of Acalabrutinib base were used. Maleic acid was calculated (~1 to 1.1 mole equivalents) according to the input base quantity.

| S. No. | Solvent | Antisolvent | Temperature (°C) | XRD Result |
|---|---|---|---|---|
| 1 | Water | NA | 25-30 | AM-I |
| 2 | Water | NA | 70-75 | AM-I |

| | | | | |
|---|---|---|---|---|
| 3 | 1,4-Dioxane + Ethanol (9.5:0.5) | NA | 0-5 | AM-I |
| 4 | 1,4-Dioxane + Water (9.5:0.5) | NA | 25-30 | AM-I |
| 5 | 1-Butanol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 6 | 2-Butanol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 7 | 2-Ethoxy ethanol | Methyl tertiary butyl ether + Heptane (1:1) | -5 - -10 | AM-I |
| 8 | 2-Methyl tetrahydrofuran | NA | 25-30 | AM-I |
| 9 | 2-Pentanol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 10 | Acetic acid | Water | 0-5 | Solid not isolated |
| 11 | Acetone | Heptane | 45-50 | AM-I |
| 12 | Acetone | Heptane | 0-5 | AM-I |
| 13 | Acetone | Water | 35-40 | AM-I |
| 14 | Acetone | Water | 25-30 | AM-I |
| 15 | Acetone | Water | 0-5 | AM-I |
| 16 | Acetonitrile | Methyl tertiary butyl ether | 45-50 | AM-I |
| 17 | Acetonitrile | DIPE | -5 - -10 | AM-I |
| 18 | Acetonitrile | DIPE | 45-50 | AM-I |
| 19 | Anisole | NA | 25-30 | AM-I |
| 20 | Cyclopentyl methyl ether | NA | 25-30 | AM-I |
| 21 | Cyclopentyl methyl ether + Ethanol (1:1) | NA | 25-30 | AM-I |
| 22 | Cyclopentyl methyl ether + Ethanol (1:1) | NA | 60-65 | AM-I |
| 23 | Dichloromethane | NA | 0-5 | AM-I |
| 24 | Dichloromethane | NA | 25-30 | AM-I |
| 25 | Diethyl carbonate | NA | 25-30 | AM-I |
| 26 | Diethyl carbonate | NA | 55-60 | AM-I |
| 27 | Dimethoxy methane | NA | 25-30 | AM-I |
| 28 | Di isopropyl ether | NA | 25-30 | AM-I |
| 29 | Dimethyl formamide + Water (9:1) | Methyl tertiary butyl ether | 0-5 | AM-I |
| 30 | Dimethyl formamide + Water (9:1) | Methyl tertiary butyl ether | 50-55 | AM-I |

| | | | | |
|---|---|---|---|---|
| 31 | Dimethyl sulfoxide | Ethyl acetate + Methyl tertiary butyl ether (1:1) | 0-5 | AM-I |
| 32 | Dimethyl sulfoxide + Water (9:1) | NA | 25-30 | AM-I |
| 33 | **Ethanol** | **NA** | **50-55** | **AM-II** |
| 34 | **Ethanol + Water (9:1)** | **NA** | **0-5** | **AM-II** |
| 35 | **Ethanol + Water (9:1)** | **NA** | **50-55** | **AM-II** |
| 36 | Ethyl acetate | Heptane | 25-50 | AM-I |
| 37 | Formic acid | Water | 0-5 | Solid not isolated |
| 38 | Formic acid | Water | 25-45 | AM-I |
| 39 | Heptane | NA | 25-50 | Acalabrutinib Base |
| 40 | Isopropanol | NA | 0-5 | AM-I |
| 41 | Isopropanol | NA | 50-55 | AM-I |
| 42 | Isopropanol | Heptane | 35-40 | AM-I |
| 43 | Isopropanol | Hexane | 35-40 | AM-I |
| 44 | Isopropyl acetate + Isopropanol (1:1) | NA | 25-30 | AM-I |
| 45 | Isobutyl acetate + Isopropanol (1:2) | NA | 25-30 | AM-I |
| 46 | Isopropyl acetate | NA | 25-30 | AM-I |
| 47 | Dichloromethane | Heptane | 0-5 | Amorphous |
| 48 | Dichloromethane | Heptane | 25-30 | AM-I |
| 49 | Dichloromethane | Tetrahydrofuran | 25-30 | AM-I |
| 50 | Methanol | NA | 0-5 | AM-I |
| 51 | Methanol | NA | 45-50 | AM-I |
| 52 | Methanol + Water (9:1) | NA | 0-5 | AM-I |
| 53 | Methanol + Water (9:1) | NA | 50-55 | AM-I |
| 54 | Methyl isobutyl ketone | Heptane | 25-30 | AM-I |
| 55 | Methyl isobutyl ketone | Heptane | 40-45 | AM-I |
| 56 | Methyl tertiary butyl ether | NA | 25-30 | AM-I |
| 57 | Methyl tertiary butyl ether | NA | 50-55 | AM-I |
| 59 | Water | NA | 70-75 | AM-I |
| 60 | Water | NA | 25-30 | AM-I |

| | | | | |
|---|---|---|---|---|
| 61 | Nitromethane | NA | 55-60 | AM-I |
| 62 | Nitromethane | NA | 25-30 | AM-I |
| 63 | Propionitrile | NA | 25-30 | AM-I |
| 64 | Tertiary butyl alcohol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 65 | Tetrahydrofuran | Heptane | 0-5 | Amorphous |
| 66 | Tetrahydrofuran | Heptane | 40-45 | Amorphous |
| 67 | Tetrahydrofuran | Water | 25-30 | AM-I |
| 68 | Tetrahydrofuran | Water | 45-50 | AM-I |
| 69 | Trifluoroethanol | Methyl tertiary butyl ether | 0-5 | AM-I |
| 70 | Trifluoroethanol | Methyl tertiary butyl ether | 25-30 | AM-I |
| 71 | Vinyl acetate + Ethanol (1:2) | NA | 0-5 | AM-I |
| 72 | Vinyl acetate + Ethanol (1:2) | NA | 60-65 | AM-I |

**Table S2.** Crystallographic parameters of AM-I and AM-II.

| **Crystallographic parameters** | **Acalabrutinib maleate sesquihydrate (AM-I)** | **Acalabrutinib maleate hemiethanol hemihydrate (AM-II)** |
|---|---|---|
| Chemical formula | $C_{60}H_{60}N_{14}O_{15}$ | $C_{62}H_{62}N_{14}O_{14}$ |
| Asymmetric unit | $2(C_{26}H_{24}N_7O_2)$, $2(C_4H_3O_4)$, $3(H_2O)$ | $2(C_{26}H_{24}N_7O_2)$, $2(C_4H_3O_4)$, $(C_2H_6O)$, $(H_2O)$ |
| Formula weight | 1217.22 | 1227.26 |
| Crystal system | Triclinic | Triclinic |
| Space group | *P*1 | *P*1 |
| *T* [K] | 100.01(10) | 100.00(10) |
| *a* [Å] | 9.5583(5) | 9.49588(14) |
| *b* [Å] | 9.5900(5) | 9.79722(17) |
| *c* [Å] | 17.1147(5) | 17.0733(2) |
| *α* [°] | 78.722(3) | 78.0108(13) |
| *β* [°] | 79.352(3) | 81.7049(12) |
| *γ* [°] | 69.659(5) | 70.9622(14) |
| *Z* | 1 | 1 |
| *Z*' | 1 | 1 |
| *V*[Å$^3$] | 1430.89 (11) | 1463.72 (4) |

| | | |
|---|---|---|
| $\rho_{calc}$ [g/cm$^3$] | 1.413 | 1.392 |
| Radiation | CuKα (λ = 1.54184) | CuKα (λ = 1.54184) |
| Absorption correction | multiscan | multiscan |
| Index ranges | -11 ≤ h ≤ 11<br>-11 ≤ k ≤ 11<br>-19 ≤ l ≤ 20 | -10 ≤ h ≤ 11<br>-11 ≤ k ≤ 11<br>-20 ≤ l ≤ 20 |
| Reflections collected | 12710 | 25082 |
| Independent reflns. | 6679 | 8266 |
| Data/restraints/parameters | 6679/3/836 | 8266/3/821 |
| $R_1$ [I>=2σ (I)] | 0.0504 | 0.0429 |
| w$R_2$ (all) | 0.1330 | 0.1151 |
| Δρmax (e/Å$^3$) | 0.26 | 0.31 |
| Δρmin (e/Å$^3$) | -0.41 | -0.29 |
| Goodness-of-fit on F$^2$ | 1.049 | 1.053 |
| Instrument | XtaLAB Synergy, Dualflex, HyPix3000 | XtaLAB Synergy, Dualflex, HyPix3000 |
| CCDC No. | 2274946 | 2274947 |

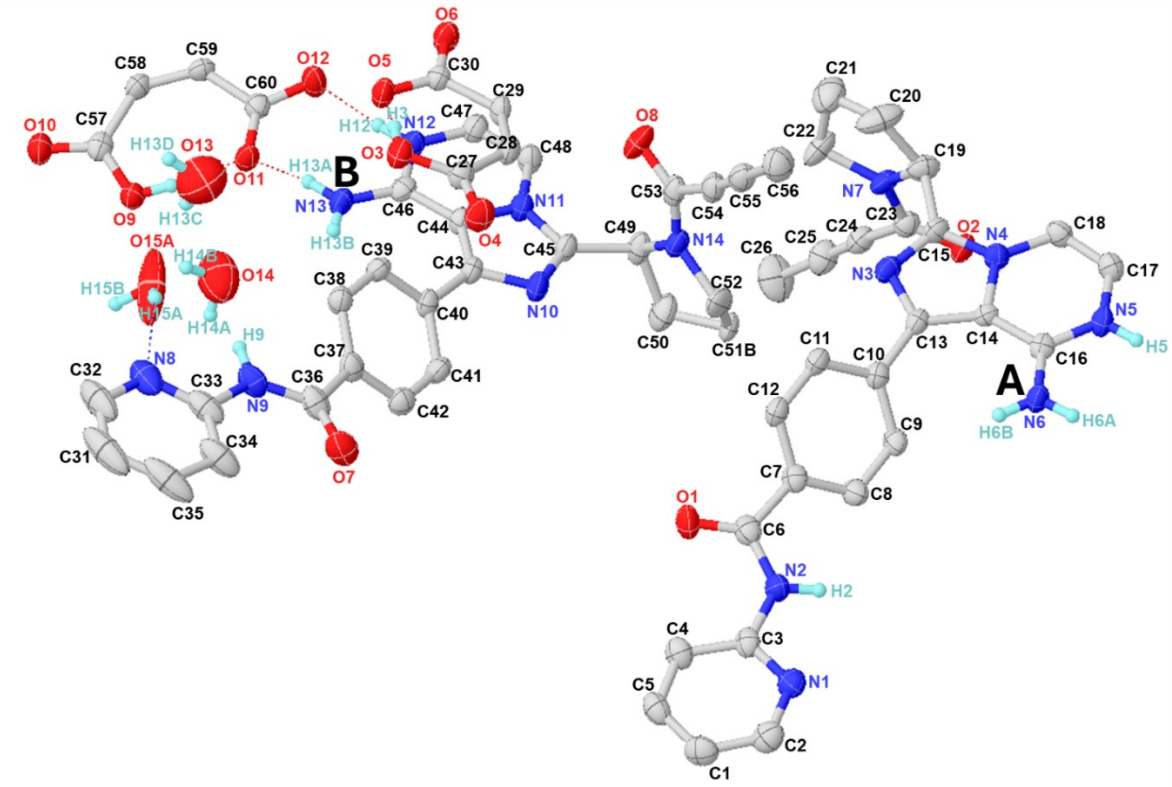


**Figure S10:** View of asymmetric unit of AM-I showing the atomic numbering and 50% probability displacement ellipsoids. C - bound H atoms omitted for clarity. For the disordered atoms O15 and C51, only major components are shown. The big letters A and B near the corresponding Acalabrutinib cations represent the molecule A and molecule B in the manuscript.

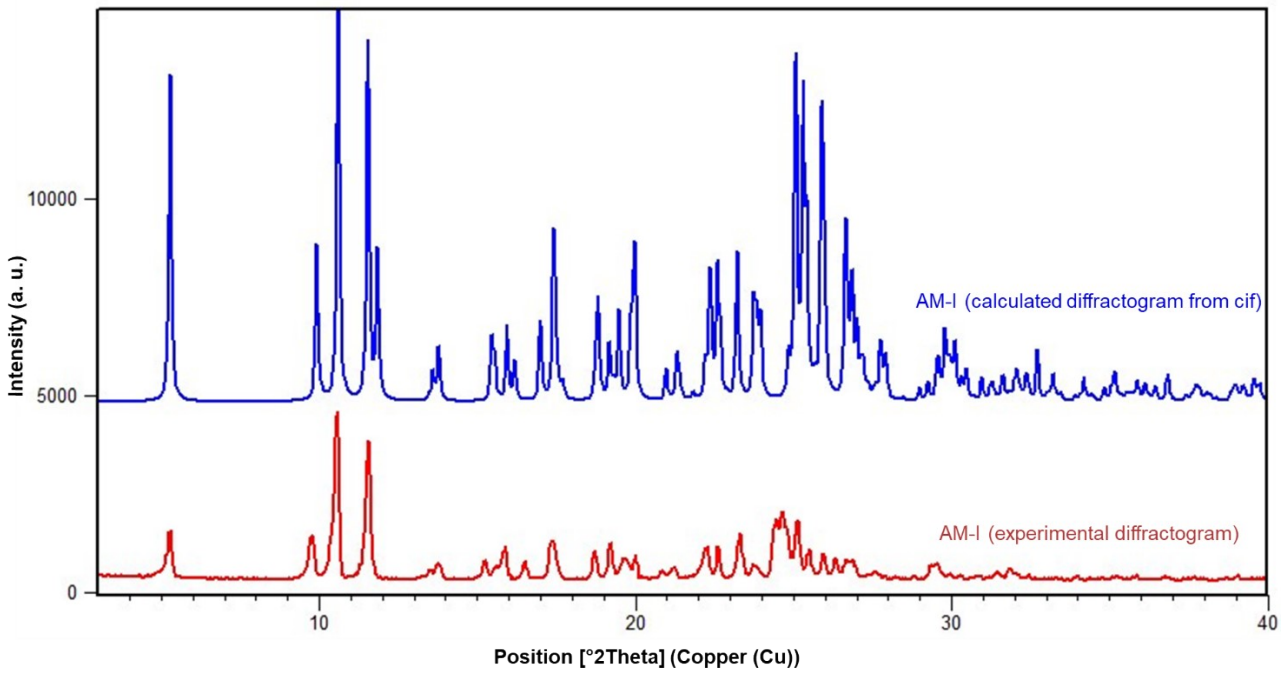


**Figure S11:** Comparision of experimental and calculated PXRD plots of AM-I.

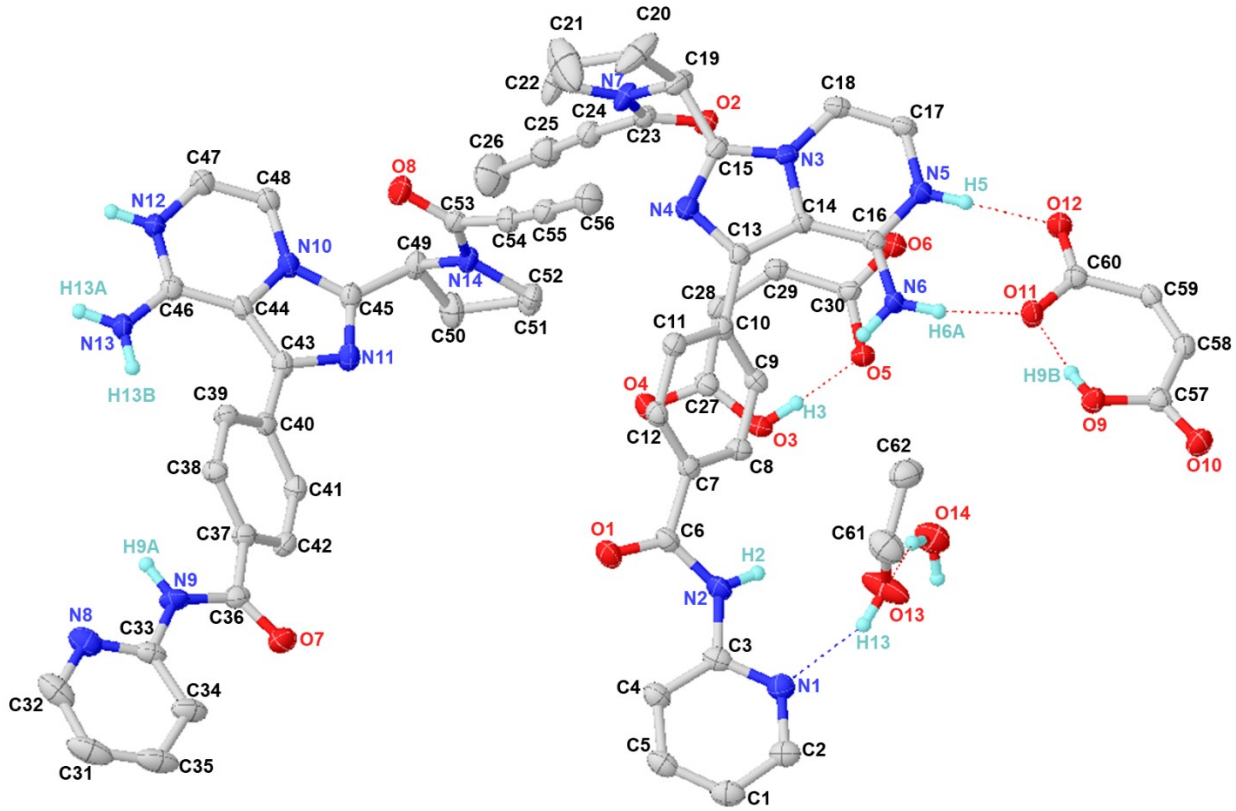


**Figure S12:** View of asymmetric unit of AM-II showing the atomic numbering and 50% probability displacement ellipsoids. C - bound H atoms omitted for clarity.

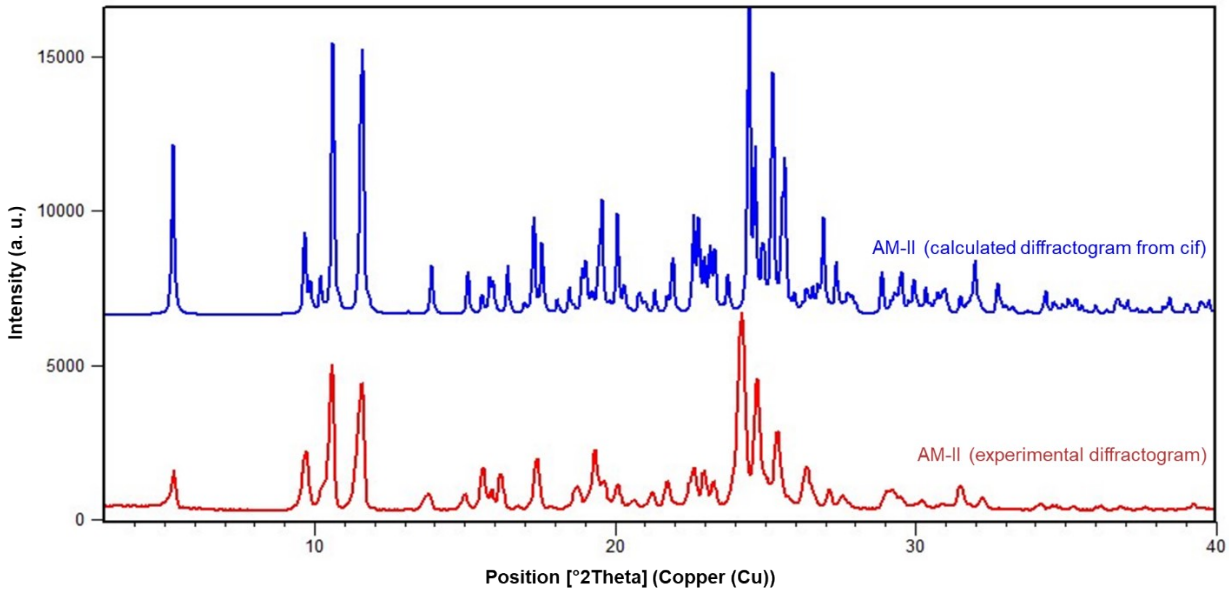


**Figure S13:** Comparision of experimental and calculated PXRD plots of AM-II.

**Table S3:** Torsion angles (°) that are majorly deviated in AM-I and AM-II.

| Considered consecutive atoms | AM-I | | AM-II | |
|---|---|---|---|---|
| | Molecule A | Molecule B | Molecule A | Molecule B |
| C6-N2-C3-N1 | -167.1(4) | -174.5(4) | -160.9(2) | -175.5(3) |
| C3-N2-C6-C7 | 172.9(4) | 176.5(4) | 170.0(2) | 175.6(2) |
| N3-C15-C19-N7 | 120.3(5) | 128.6(5) | 125.8(3) | 119.7(3) |
| N4-C15-C19-N7 | -58.0(6) | -49.5(6) | -53.4(3) | -54.6(4) |
| C9-C10-C13-N4 | 137.1(4) | 139.9(4) | 131.7(2) | 136.1(3) |

**Table S4:** Hydrogen bond parameters of AM-I and AM-II

| Interaction | D–H/Å | H···A/Å | D···A/Å | ∠D–H···A/° | Symmetry code |
|---|---|---|---|---|---|
| **AM-I** | | | | | |
| N5–H5···O6 | 0.86 | 1.88 | 2.733(4) | 173 | x, y, -1+z |
| O3–H3···O5 | 0.82 | 1.67 | 2.471(4) | 164 | x, y, z |
| N6–H6A···O5 | 0.86 | 1.97 | 2.794(4) | 160 | x, y, -1+z |
| N9–H9···O15A | 0.86 | 2.33 | 3.090(9) | 147 | x, y, z |
| O9–H9B···O11 | 0.82 | 1.65 | 2.472(4) | 174 | x, y, z |
| N12–H12···O12 | 0.86 | 1.86 | 2.711(5) | 170 | x, y, z |
| N13–H13A···O11 | 0.86 | 2 | 2.808(4) | 156 | x, y, z |
| O13–H13D···O14 | 0.85 | 2.27 | 2.991(9) | 142 | x, y, z |
| O14–H14A···O6 | 0.85 | 2.43 | 3.163(7) | 145 | x, y, z |
| O15A–H15A···N8 | 0.85 | 2.09 | 2.804(10) | 142 | x, y, z |
| O15A–H15B···N1 | 0.85 | 2.11 | 2.930(12) | 161 | x, 1+y, z |
| C1–H1···O12 | 0.93 | 2.5 | 3.398(6) | 162 | x, y, -1+z |
| C5–H5A···O2 | 0.93 | 2.45 | 3.339(6) | 161 | x, y, -1+z |
| C26–H26B···N11 | 0.96 | 2.61 | 3.466(7) | 148 | x, 1+y, z |
| C29–H29···O8 | 0.93 | 2.35 | 3.164(5) | 146 | x, y, z |
| C31–H31···O6 | 0.93 | 2.45 | 3.378(7) | 179 | x, 1+y, z |
| C35–H35···O8 | 0.93 | 2.33 | 3.245(8) | 169 | x, 1+y, z |
| C48–H48···O4 | 0.93 | 2.47 | 3.392(6) | 170 | x, -1+y, z |
| C49–H49···O4 | 0.98 | 2.56 | 3.503(6) | 162 | x, -1+y, z |
| C52–H52B···N4 | 0.97 | 2.61 | 3.531(6) | 158 | x, y, z |
| C59–H59···O2 | 0.93 | 2.36 | 3.208(5) | 151 | x, 1+y, z |
| **AM-II** | | | | | |
| O3–H3···O5 | 0.84 | 1.61 | 2.453(3) | 175 | x, y, z |
| N5–H5···O12 | 0.88 | 1.87 | 2.747(3) | 172 | x, y, z |
| N6–H6A···O11 | 0.88 | 1.92 | 2.775(3) | 163 | x, y, z |
| O9–H9B···O11 | 0.84 | 1.63 | 2.466(3) | 175 | x, y, z |
| N12–H12A···O6 | 0.88 | 1.85 | 2.717(3) | 168 | x, y, 1+z |
| O13–H13···N1 | 0.84 | 2.02 | 2.817(3) | 158 | x, y, z |
| N13–H13A···O5 | 0.88 | 2.04 | 2.819(3) | 146 | x, y, 1+z |
| O14–H14A···O13 | 0.87 | 1.94 | 2.766(3) | 158 | x, y, z |
| O14–H14B···O12 | 0.87 | 2.16 | 2.989(3) | 158 | -1+x, y, z |
| C1–H1···O6 | 0.95 | 2.59 | 3.513(4) | 164 | x, -1+y, z |

| | | | | | |
|---|---|---|---|---|---|
| C5–H5A···O2 | 0.95 | 2.37 | 3.302(3) | 167 | x, y, -1+z |
| C9–H9···O5 | 0.95 | 2.59 | 3.517(3) | 166 | x, y, z |
| C18–H18···O4 | 0.95 | 2.57 | 3.505(4) | 169 | x, y, -1+z |
| C19–H19···O4 | 1 | 2.45 | 3.432(4) | 168 | x, y, -1+z |
| C29–H29···O2 | 0.95 | 2.32 | 3.165(3) | 148 | x, y, z |
| C35–H35···O8 | 0.95 | 2.32 | 3.251(4) | 168 | x, 1+y, 1+z |
| C48–H48···O10 | 0.95 | 2.43 | 3.370(3) | 169 | -1+x, -1+y, z |
| C49–H49···O10 | 1 | 2.48 | 3.460(3) | 167 | -1+x, -1+y, z |
| C52–H52B···N4 | 0.99 | 2.51 | 3.464(3) | 162 | x, y, z |
| C59–H59···O8 | 0.95 | 2.39 | 3.238(3) | 148 | x, y, -1+z |

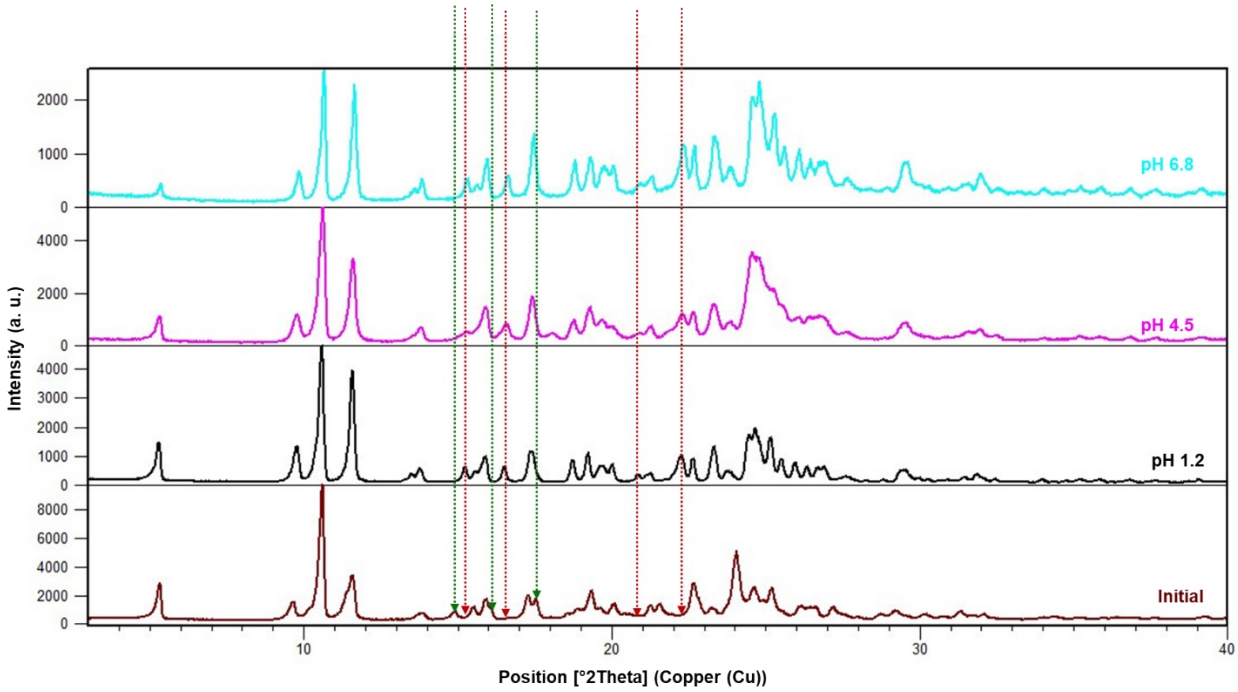


**Figure S14**: PXRD pattern overlay of solubility study residues in comparison with initial AM-II. In all the three pH conditions, AM-II has converted to AM-I. The characteristic peaks of AM-II are shown with dotted lines (green: novel peaks of AM-II; Red: Absent peaks of Am-I in AM-II) to clearly identify the transformation.

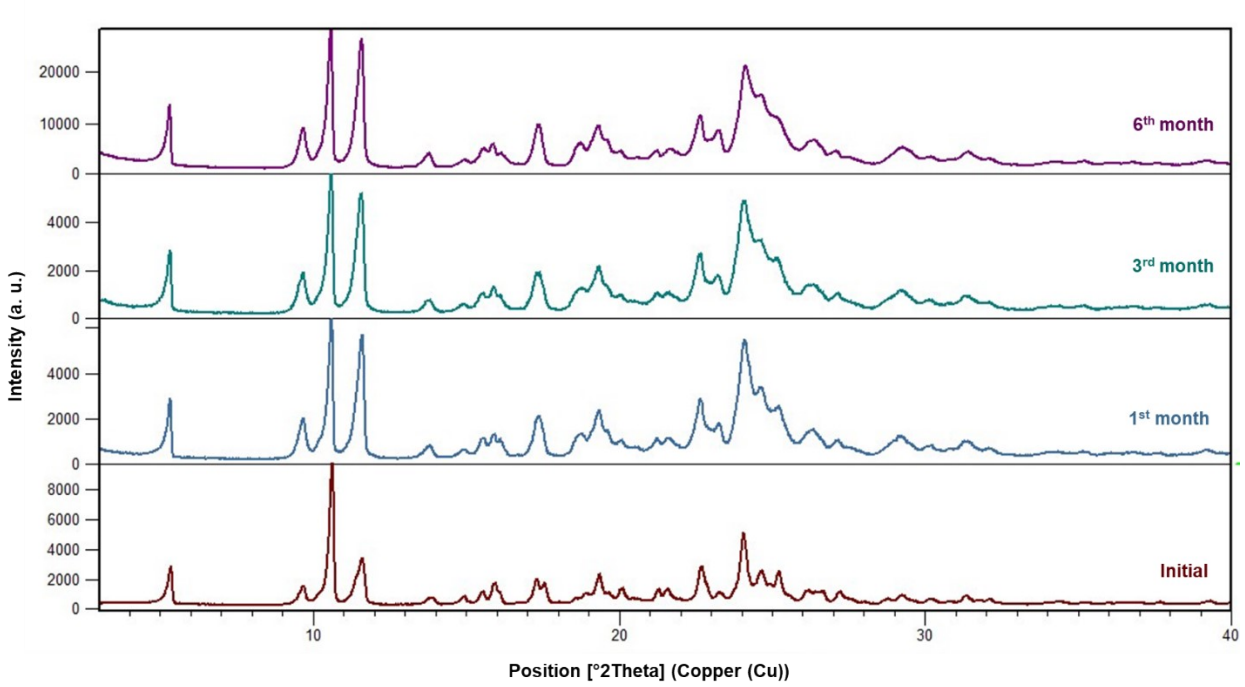


**Figure S15:** X-ray powder diffraction pattern overlay of initial, 1st, 3rd, and 6th month stability at 40°C/75%RH.

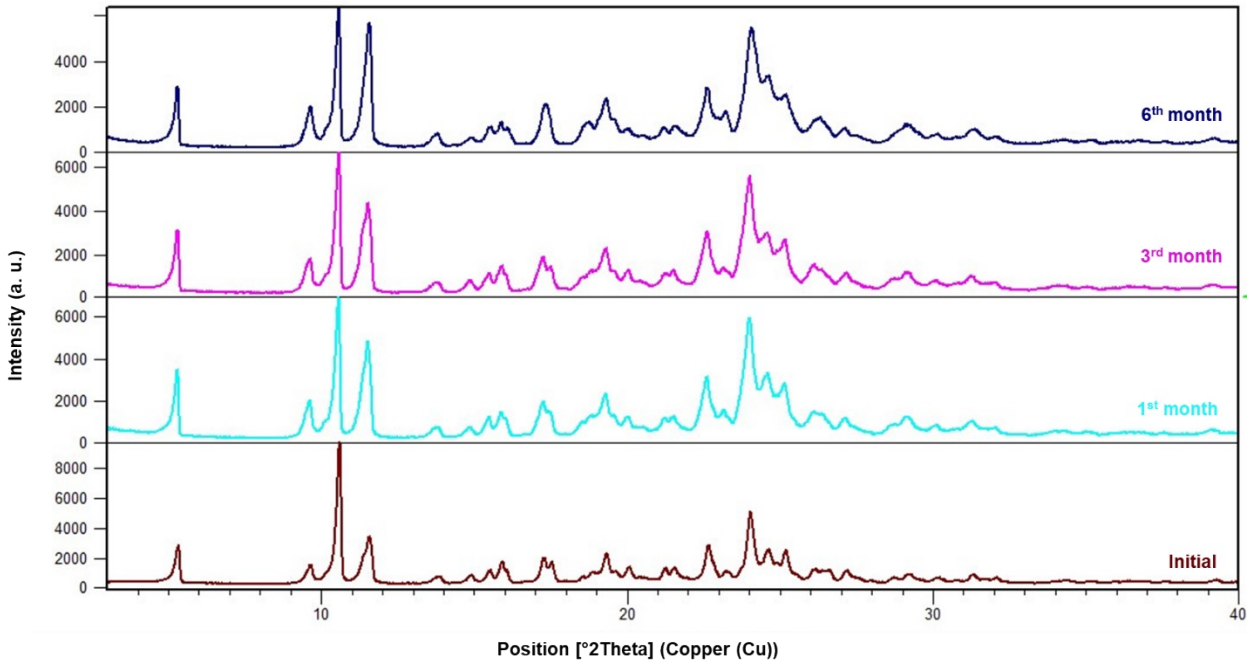


**Figure S16:** X-ray powder diffraction pattern overlay of initial, 1st, 3rd, and 6th month stability at 25°C/60%RH.

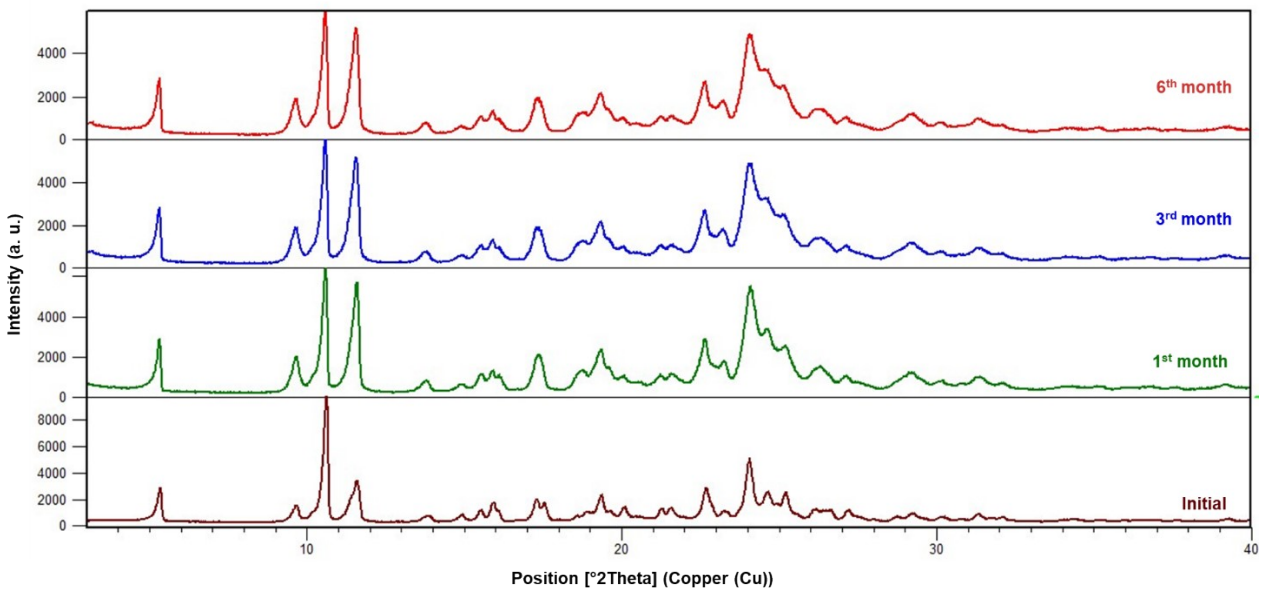


**Figure S17:** X-ray powder diffraction pattern overlay of initial, 1st, 3rd, and 6th month stability at 2-8 °C.

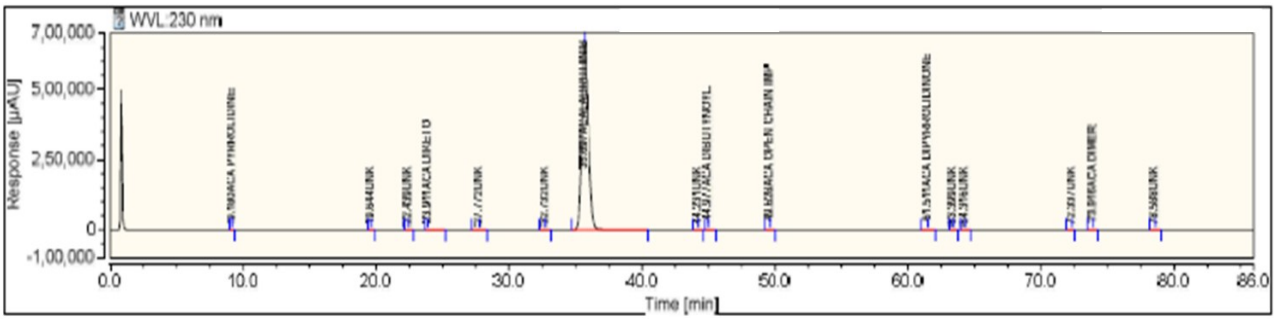


**Figure S18:** HPLC chromatogram of AM-II: Input material's HPLC chromatogram.

**Table S5:** Impurity details of AM-II: Input material used for stability study.

| Peak No. | Ret. Time (min) | Peak Name | Area (%) | RRT |
|---|---|---|---|---|
| 1 | 9.180 | ACA PYRROLIDINE | 0.003 | 0.257 |
| 2 | 19.644 | UNKNOWN | 0.006 | 0.550 |
| 3 | 22.439 | UNKNOWN | 0.031 | 0.629 |
| 4 | 23.911 | ACA DIKETO | 0.008 | 0.670 |
| 5 | 27.772 | UNKNOWN | 0.004 | 0.778 |
| 6 | 32.732 | UNKNOWN | 0.004 | 0.917 |
| 7 | 35.697 | ACALABRUTINIB | 99.872 | N.A. |
| 8 | 44.231 | UNKNOWN | 0.015 | 1.239 |
| 9 | 44.977 | ACA DIBUTYNOYL | 0.004 | 1.260 |
| 10 | 49.628 | ACA OPEN CHAIN IMP | 0.004 | 1.390 |
| 11 | 61.511 | ACA DIPYRROLIDINONE | 0.031 | 1.723 |

| | | | | |
|---|---|---|---|---|
| 12 | 63.399 | UNKNOWN | 0.003 | 1.776 |
| 13 | 64.316 | UNKNOWN | 0.003 | 1.802 |
| 14 | 72.337 | UNKNOWN | 0.002 | 2.026 |
| 15 | 73.916 | ACA DIMER | 0.006 | 2.071 |
| 16 | 78.588 | UNKNOWN | 0.004 | 2.202 |
| **Total:** | | | 100 | |

| **Summary** | |
|---|---|
| Total Known Imp | 0.060 % |
| Total Unknown Imp | 0.075 % |
| Total Imp | 0.135 % |

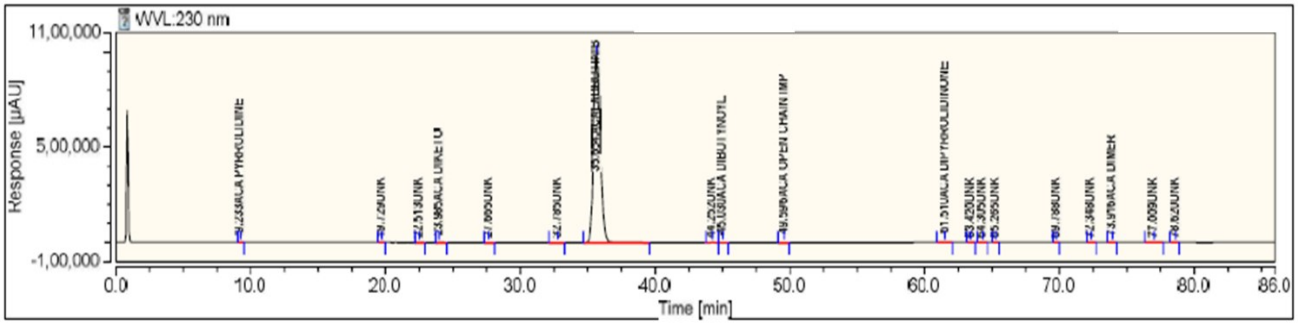


**Figure S19:** HPLC chromatogram of AM-II: Stability interval - 6 months at 40 °C/75%RH.

**Table S6:** Impurity details of AM-II: Stability interval - 6 months at 40 °C/75%RH.

| Peak No. | Ret. Time (min) | Peak Name | Area (%) | RRT |
|---|---|---|---|---|
| 1 | 9.233 | ACA PYRROLIDINE | 0.003 | 0.259 |
| 2 | 19.729 | UNKNOWN | 0.007 | 0.553 |
| 3 | 22.513 | UNKNOWN | 0.030 | 0.631 |
| 4 | 23.985 | ACA DIKETO | 0.005 | 0.673 |
| 5 | 27.665 | UNKNOWN | 0.002 | 0.776 |
| 6 | 32.785 | UNKNOWN | 0.005 | 0.920 |
| 7 | 35.654 | ACALABRUTINIB | 99.856 | N.A. |
| 8 | 44.252 | UNKNOWN | 0.015 | 1.241 |
| 9 | 45.030 | ACA DIBUTYNOYL | 0.004 | 1.263 |
| 10 | 49.596 | ACA OPEN CHAIN IMP | 0.003 | 1.391 |
| 11 | 61.510 | ACA DIPYRROLIDINONE | 0.030 | 1.725 |
| 12 | 63.420 | UNKNOWN | 0.003 | 1.779 |
| 13 | 64.305 | UNKNOWN | 0.003 | 1.804 |
| 14 | 65.265 | UNKNOWN | 0.001 | 1.830 |
| 15 | 69.788 | UNKNOWN | 0.001 | 1.957 |
| 16 | 72.348 | UNKNOWN | 0.003 | 2.029 |
| 17 | 73.916 | ACA DIMER | 0.006 | 2.073 |
| 18 | 77.009 | UNKNOWN | 0.020 | 2.160 |

| | | | | |
|---|---|---|---|---|
| 19 | 78.620 | UNKNOWN | 0.003 | 2.204 |
| **Total:** | | | 100 | |

| Summary | |
|---|---|
| Total Known Imp | 0.060 % |
| Total Unknown Imp | 0.092 % |
| Total Imp | 0.152 % |

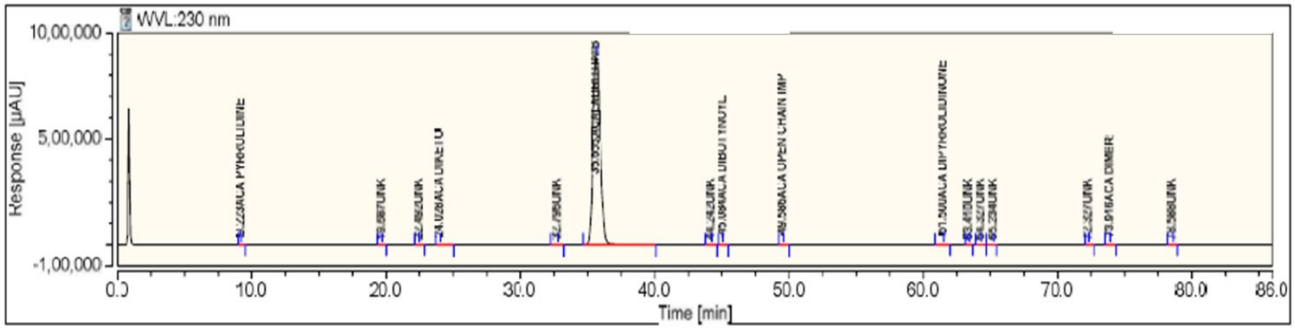


**Figure S20:** HPLC chromatogram of AM-II: Stability interval - 6 months at 25 °C/60%RH.

**Table S7:** Impurity details of AM-II: Stability interval - 6 months at 25 °C/60%RH.

| Peak No. | Ret. Time (min) | Peak Name | Area (%) | RRT |
|---|---|---|---|---|
| 1 | 9.223 | ACA PYRROLIDINE | 0.003 | 0.259 |
| 2 | 19.687 | UNKNOWN | 0.007 | 0.552 |
| 3 | 22.492 | UNKNOWN | 0.030 | 0.631 |
| 4 | 24.028 | ACA DIKETO | 0.008 | 0.674 |
| 5 | 32.796 | UNKNOWN | 0.006 | 0.920 |
| 6 | 35.655 | ACALABRUTINIB | 99.874 | N.A. |
| 7 | 44.242 | UNKNOWN | 0.015 | 1.241 |
| 8 | 45.084 | ACA DIBUTYNOYL | 0.004 | 1.264 |
| 9 | 49.586 | ACA OPEN CHAIN IMP | 0.004 | 1.391 |
| 10 | 61.500 | ACA DIPYRROLIDINONE | 0.029 | 1.725 |
| 11 | 63.410 | UNKNOWN | 0.002 | 1.778 |
| 12 | 64.327 | UNKNOWN | 0.003 | 1.804 |
| 13 | 65.234 | UNKNOWN | 0.002 | 1.830 |
| 14 | 72.327 | UNKNOWN | 0.002 | 2.029 |
| 15 | 73.916 | ACA DIMER | 0.006 | 2.073 |
| 16 | 78.588 | UNKNOWN | 0.003 | 2.204 |
| **Total:** | | | 100 | |

| Summary | |
|---|---|
| Total Known Imp | 0.065 % |
| Total Unknown Imp | 0.070 % |

| | |
|---|---|
| Total Imp | 0.135 % |

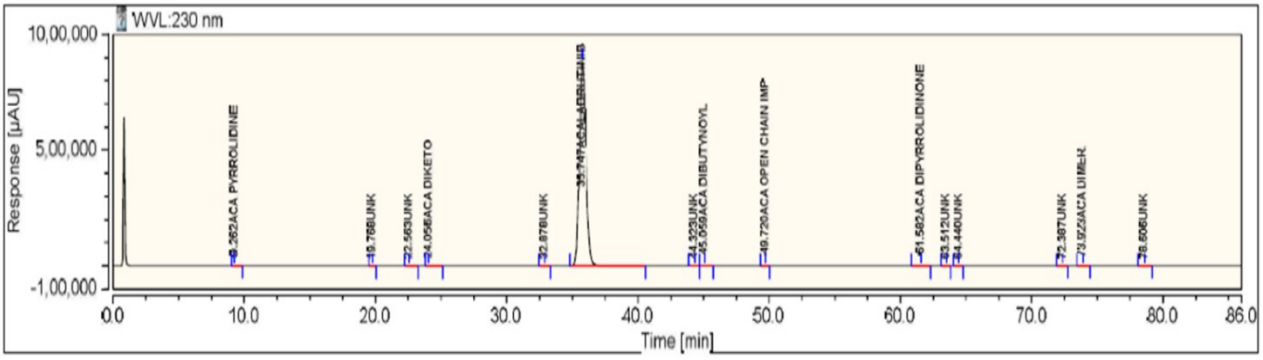


**Figure S21:** HPLC chromatogram of AM-II: Stability interval - 6 months at 2-8 °C.

**Table S8:** Impurity details of AM-II: Stability interval - 6 months at 2-8 °C.

| Peak No. | Ret. Time (min) | Peak Name | Area (%) | RRT |
|---|---|---|---|---|
| 1 | 9.262 | ACA PYRROLIDINE | 0.004 | 0.259 |
| 2 | 19.768 | UNKNOWN | 0.006 | 0.553 |
| 3 | 22.563 | UNKNOWN | 0.031 | 0.631 |
| 4 | 24.056 | ACA DIKETO | 0.008 | 0.673 |
| 5 | 32.878 | UNKNOWN | 0.005 | 0.920 |
| 6 | 35.747 | ACALABRUTINIB | 99.866 | N.A. |
| 7 | 44.323 | UNKNOWN | 0.017 | 1.240 |
| 8 | 45.059 | ACA DIBUTYNOYL | 0.007 | 1.260 |
| 9 | 49.720 | ACA OPEN CHAIN IMP | 0.003 | 1.391 |
| 10 | 61.582 | ACA DIPYRROLIDINONE | 0.032 | 1.723 |
| 11 | 63.512 | UNKNOWN | 0.003 | 1.777 |
| 12 | 64.440 | UNKNOWN | 0.003 | 1.803 |
| 13 | 72.387 | UNKNOWN | 0.003 | 2.025 |
| 14 | 73.923 | ACA DIMER | 0.007 | 2.068 |
| 15 | 78.606 | UNKNOWN | 0.005 | 2.199 |
| **Total:** | | | 100 | |

| **Summary** | |
|---|---|
| Total Known Imp | 0.070 % |
| Total Unknown Imp | 0.073 % |
| Total Imp | 0.143 % |