

Original Research Article

Novel salts of Sunitinib an anticancer drug with improved solubility

ABSTRACT

Polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly water solubility in the present case. Co-crystal formation was evaluated with urea and nicotinamide. These cofomers do not have any ionic groups that favors the formation of salts. Sunitinib malate salt is being currently sold in the market. It is poorly soluble in water. Salt screening experiments were conducted with adipic acid, glutaric acid, nicotinic acid, 4-hydroxy benzoic acid and saccharin. The salts with 1:1 ratios were obtained with these acids, except for adipic acid, which yielded a 2:1 solid form. The solubility of these salts in DI water was found to be 6 to 10 times greater than that of the marketed salt (sunitinib malate).

Reversible Z-E isomerization was also well thought-out especially in presence of light and the isomerization was checked by HPLC. Formation of undesired E-isomer was additionally confirmed by ¹H NMR. This observation has implications in the solubility study of sunitinib salt samples using HPLC method.

Keywords :Sunitinib, Photosensitive, Novel salts, Malate, Solubility and HPLC.

1 Introduction

An important goal of solid-state pharmaceutical development is to increase drug solubility while maintaining a stable form. This objective is critical because solubility and permeability are the major factors used to describe oral absorption according to the biopharmaceutics classification system (BCS). The use of salts in the pharmaceutical industry is a well-known fact. Salts modify properties of the solid forms such as melting temperature, solubility, stability, dissolution rate and bioavailability without altering the desired effect of drug.^[1] Salt formation is essentially a three component system involving an acid (A), a base (B) and one or more solvents. A salt is formed by the transfer of a proton (H⁺) from an acid (A) to a base (B): A-H + B → (A⁻) (B⁺-H). In order to assist salt selection a number of empirical rules have been proposed, such as the 'rule of three'. This states that salt formation generally requires a difference of at least three pK_a units between the conjugate base and the conjugate acid, pK_a (Base) - pK_a (Acid) ≥ 3, where pK_a is the ability of an ionisable group to donate a proton (H⁺) in an aqueous medium and is often referred to as the dissociation constant. When the difference is ≤ 3, the product can be either salt or co-crystal.

API co-crystals, like API salts, have demonstrated the ability to modify physicochemical properties of the APIs.^[2a-f] Cocrystals can be made for nonionizable drugs, which are restricted from salt formation. Also, for ionizable drugs, the number of suitable cocrystal ligands (i.e. cofomers) can exceed the number of suitable counter ions. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent.^[3] If the incorporated solvent is water, the solvate is commonly known as a hydrate. Different polymorphs of a given crystalline compound (salt or co-crystal) can have different physicochemical properties.^[4] Systematic screening for polymorphs has therefore become an essential step in drug development to select a factual form in order to avoid problems caused by polymorphic transitions during processing.^[5] The crystallization of polymorphs can be affected by numerous factors, which include, the nature of solvents^[6a-d] and the presence of polymers^[7] or other additives.^[8] The relationships among various solid forms are shown in Figures 1 and 2.

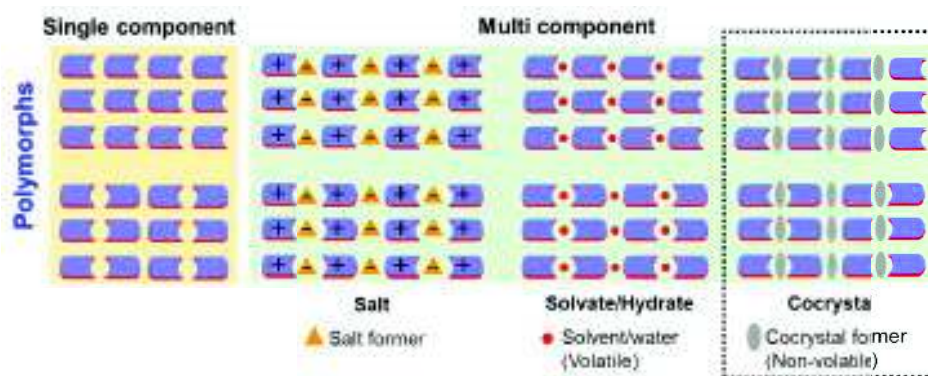


Figure 1. Graphical depiction of various solid forms possible for a given API

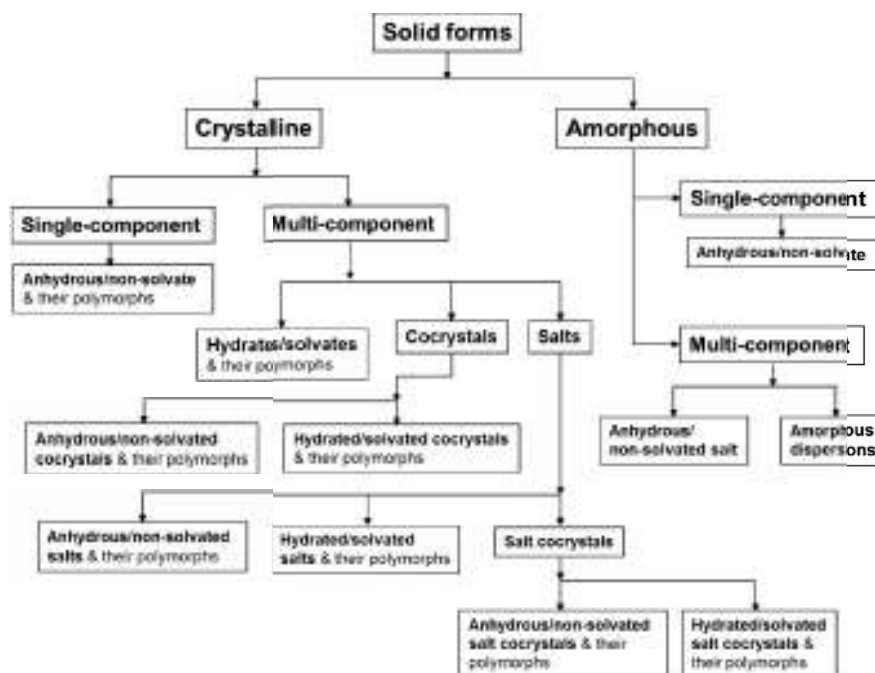


Figure 2. Graphical representation of various solid forms possible for a given API

Sunitinib is a new vascular endothelial growth factor receptor inhibitor, has demonstrated high activity in renal cell carcinoma (RCC) and is now extensively used for patients with metastatic disease. Although generally well tolerated and associated with a low incidence of common toxicity criteria grade 3 or 4 toxicities.^[9-10] It is sold as malate salt by Pfizer under the brand name Sutent. Sunitinib is a yellow to orange powder with solubility of 25mg/ml in acidic solutions (pH 1.2 - 6.8).^[11] The solubility of sunitinib rapidly decreases at pH greater than 6.8. Hence the sunitinib is classified as a low solubility compound according to the biopharmaceutical classification. Consequently there is a need to obtain new salts of sunitinib with improved water solubility. Hence, exploring its solid form landscape (screening for polymorphs, salts and co-crystals) expands the scope for the identification of novel solid forms. Several salts have already been identified for this API.^[12-13]

Sunitinib molecule has an exocyclic double bond at the 3-position of the oxindole ring and consequently it can exhibit Z-E isomerism. Anand and Narmada have revealed that SU5416, closely related to sunitinib, undergoes photo induced conversion into the less stable E isomer in solution.^[14] The present study deals with the synthesis of sunitinib, Z-E isomerization and identification of novel salts with improved water solubility.

2 Materials and methods

All the key intermediates for synthesis of sunitinib were procured from Shanghai Parling pharma co. ltd. China. Solvents and reagents were used by way of obtained from Rankem, Qualigens and Ranbaxy Labs. Ltd., India. Waters HPLC 2695 alliance separation module (with customized syringe and loop volume of 2.5 mL) with PDA 2998 detector was used for investigation. Perkin Elmer CHNS/O analyzer 2400 was used for CHN analysis. Melting point was recorded on Buchi b 545. IR spectra were recorded on Perkin-Elmer Spectrum One FT-IR spectrometer. ¹H NMR spectra was recorded in DMSO-d₆ at 400 MHz using TMS as an internal standard. Mass/Ms-Ms data was generated by using QTRAP LC/MS/MS system (Applied Biosystems). The XRPD of the samples were determined by using Instrument: PANalytical; Model X'pert PRO; Detector: X'celerator; Scan Range: 3-40; Step size: 0.02; Range: 3-40 degree 2 theta; CuKα radiation at 45kV and 40 mA. DSC of the samples was determined by using Mettler-Toledo 821e. Data collection parameters: Scanning rate: 10°C/min; Temperature: 30°C to 300°C. TGA of the samples were determined by using TA Q500 between 30°C to 300°C at 10°C/min scan rate. In the Z-E isomerization studies, the solutions (in 100 ml volumetric flasks) - prepared by means of dissolving 25 mg of sunitinib in 100 ml of each solvent - were either directly exposed to halogen lamp (150 W) or sunlight.

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3 Experimental

3.1 Z-E isomerization

Photo induced Z-E isomerization study in sunitinib molecule was carried out by HPLC method using Kromasil C₈ (250 × 4.6 mm; 5 μm particle size) (procured from Akzonobel) stationary phase. The gradient elution consisted of potassium dihydrogen orthophosphate buffer (pH 4.5) and acetonitrile (1:1 v/v) with an injection volume and flow rate of 5 μl and 1 ml/min, respectively with detection wavelength 210 nm. This transformation of desired Z-isomer into unstable E-isomer was moreover proved by ¹H NMR of compound in DMSO-d₆ after going on exposure to light. Pure Z-Isomer ¹H NMR (400 MHz, DMSO): δ 0.98 (6 H, t, C27, 29-H_a), 2.43 (3H, s, C21-H_a), 2.45 (3H, s, C18-H_a), 2.47-2.57 (*6H, m, C28, 26, 24-H_a), 3.27-3.34 (2H, m, C23-H_a), 6.83-6.86 (1H, m, Ar-H_a), 6.90-6.95 (1H, m, Ar-H), 7.43 (1H, t, N22-H_a), 7.71 (1H, s, C11a-H_{aa}), 7.75 (1H, d, Ar-H), 10.89 (1H, s, N-H), 13.68 (1H, s, N-H).

When Z-Isomer exposed to sunlight for 4 hours (E-Isomer) ¹H NMR (400 MHz, DMSO): δ 1.00 (6 H, t, C27, 29-H_b), 2.21 (3H, s, C21-H_b), 2.43-2.45 (3H, s, C18-H_b), 2.51-2.55 (*6H, m, C28, 26, 24-H_b), 3.27-3.30 (2H, m, C23-H_b), 6.81-6.86 (1H, m, Ar-H_b), 6.99-7.04 (1H, m, Ar-H_b), 7.34 (1H, d, Ar-H_b), 7.37-7.43

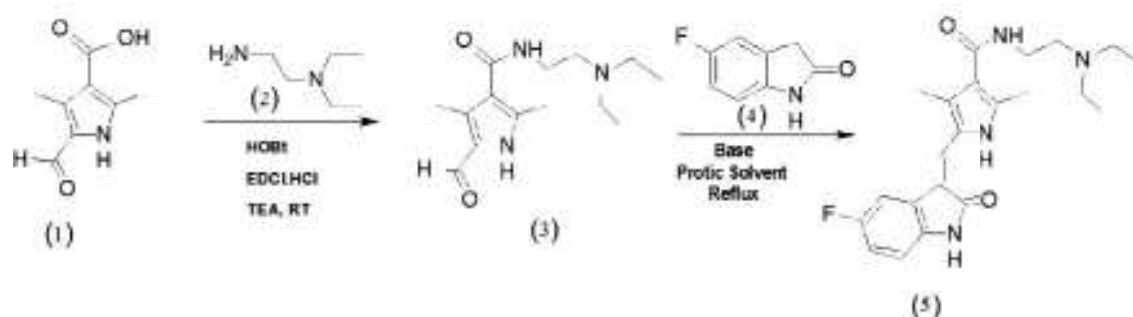
3.2 Solubility data

The equilibrium solubility study of sunitinib salts in DI (Deionized water) water was carried out by using gradient elution HPLC method consisted of potassium dihydrogen orthophosphate buffer (pH 6.5) and acetonitrile-MeOH mixture (1:1 v/v) with an injection volume and flow rate of 10 μl and 0.75 ml/min on Kromasil C₈ column (250 × 4.6 mm; 5 μm particle size), respectively through detection at 270 nm.

3.3 Sunitinib synthesis

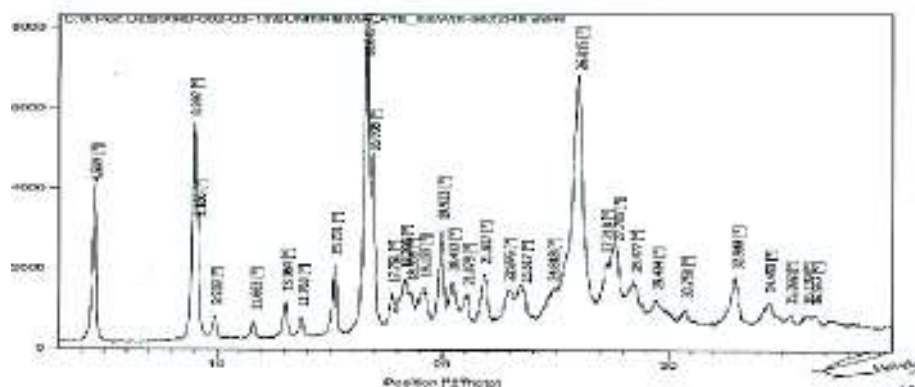
Sunitinib was prepared in two steps from imidazole derivative (**1**) as per the reported procedure (Scheme 1).^[15] Amidation of **1** with diethylethylenediamine (**2**) in presence of EDCI.HCl (N-Ethyl-N'-(3-dimethylaminopropyl) carbodiimidehydrochloride), HOBt (Hydroxybenzotriazole) and TEA (triethylamine) at RT yielded imidazole-amide derivative (**3**). Intermediate **3** was then and there condensed with oxindole derivative (**4**) in presence of base in protic solvent to give crude sunitinib (**5**) in quantitative yields. The crude sunitinib (**5**) was then purified via acid-base treatment as reported earlier.^[16]

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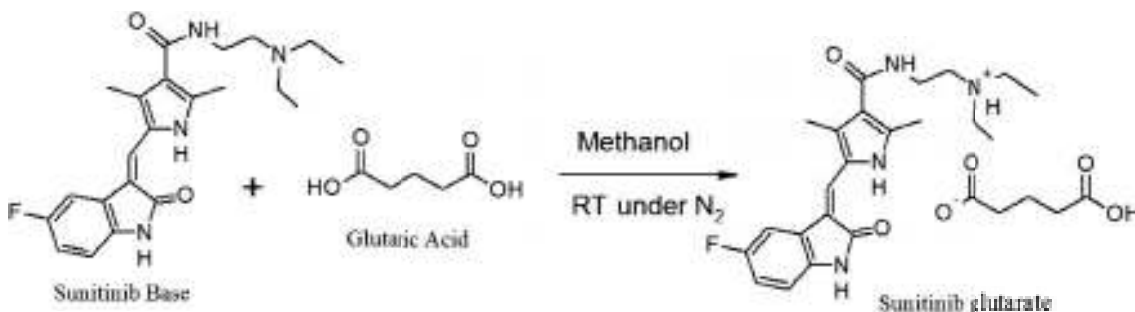
Scheme 1: Scheme for the synthesis of sunitinib

M. P.: 216.6 °C, IR (KBr) V_{max} (in cm^{-1}): 3424, 3339, 3042, 2955, 2470, 1968, 1870, 1675, 1637, 1563, 1194, 1520, 1476, 1463, 1440, 1377, 1322, 1286, 1253, 1193, 1151, 1096, 1071, 1047, 800, 666 and 586. ^1H NMR (400 MHz, DMSO): δ 1.00 (6 H, t, C27, 29-H, $J = 7.1$ Hz), 2.43 (3H, s, C21-H), 2.45 (3H, s, C18-H), 2.55-2.62 (6H, m, C28, 26, 24-H), 3.29-3.34 (2H, m, C23-H), 6.83-6.86 (1H, m, Ar-H), 6.90-6.95 (1H, m, Ar-H), 7.47 (1H, t, N22-H), 7.72 (1H, s, C11a-H), 7.76 (1H, d, Ar-H, $J = 9.4$ Hz), 10.90 (1H, s, N-H), 13.69 (1H, s, N-H), ^{13}C NMR (100.6 MHz, CDCl_3): 15.82, 17.06, 18.56, 42.17, 51.74, 56.87, 111.12, 115.20, 117.56, 119.82, 125.93, 130.07, 131.02, 132.38, 135.36, 139.73, 141.79, 162.29, 169.73 (CO), 174.79 (CO). Mass: 398.4 $[\text{M} + \text{H}]^+$, 399.3; MS/MS: 326.1, 283.1, CHN: C-65.90, H-7.12, N-13.94. Theoretical CHN: C (66.31%), H (6.83), F (4.77%), N (14.06%), O (8.03%), DSC: Single endotherm at 234.37 °C, TGA: No significant weight loss and X-ray powder diffraction (XRPD) peak pattern is depicted in Figure 3 indicates the obtained sunitinib base is a crystalline solid.

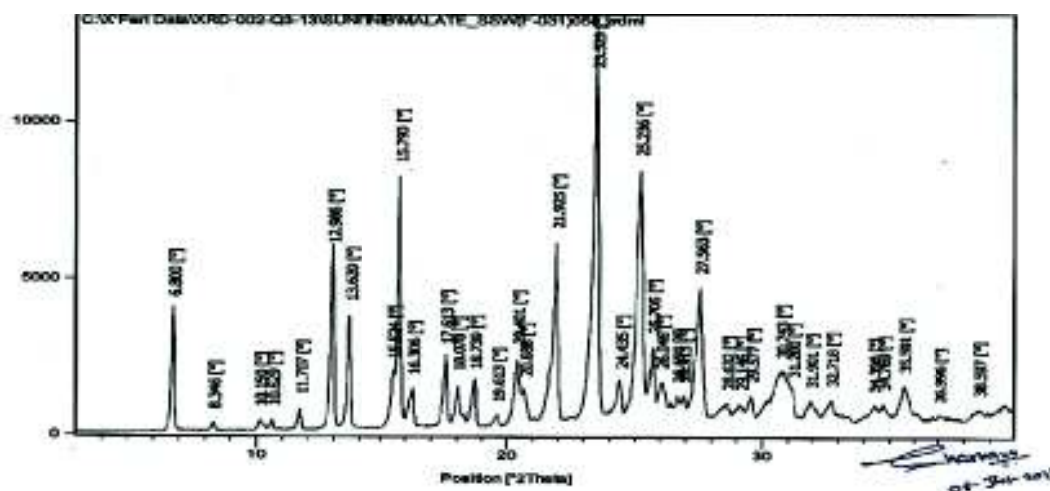


3.4.1 Sunitinibglutarate

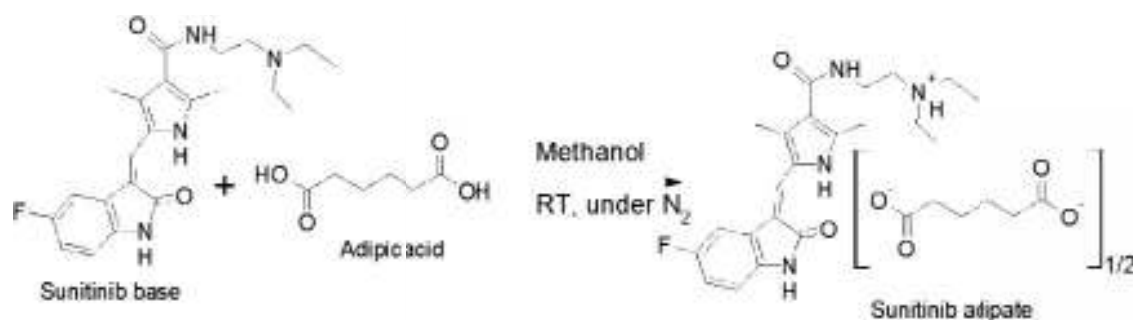
5.0 g of Sunitinib base was suspended in 75 ml of methanol at RT under N₂. 1.82 g of glutaric acid (1.1 meq) was added to the mixture at RT. The mixture was stirred at RT for about 16 hours and then cooled down to 0-5 °C and stirred at this temperature for 1 hour. Red colored solids were collected by vacuum filtration and washed the material with 25 ml of methanol. Dried the product under vacuum at 50 °C temperature for 12 to 14 h. The crystalline Form I of a glutarate salt of sunitinib (scheme 2) was obtained and characterized by X-ray powder diffraction (XRPD) peaks pattern substantially as depicted in Figure 4.



Scheme 2: Scheme for the synthesis of Sunitinibglutarate.



°C for 12 to 14 h. The crystalline Form I of an adipate salt of sunitinib (scheme 3) was characterized by XRPD peak pattern substantially as shown in Figure 5.



Scheme 3: Scheme for the synthesis of Sunitinib adipate.

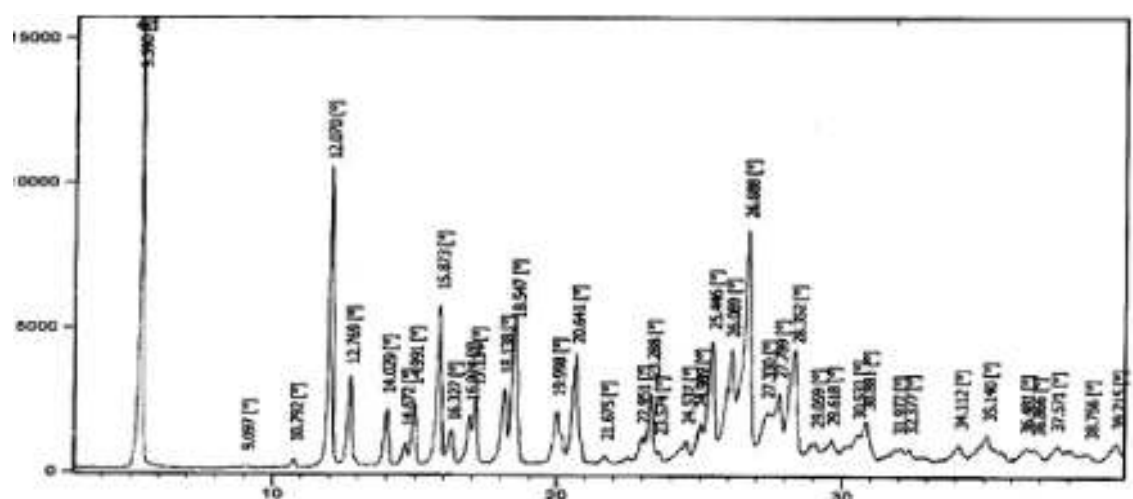
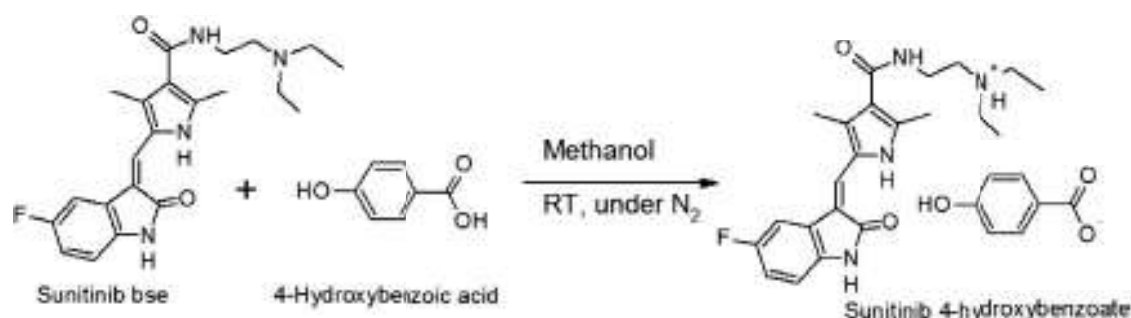


Figure 5: XRD spectrum of sunitinib adipate

% Yield = 70.3, M. P. = 200.0 °C, IR (KBr) V_{max} (in cm^{-1}): 3230, 2952, 1680, 1627, 1588, 1527, 1479, 1328, 1147, 667 and 588. ^1H NMR (400 MHz, CDCl_3): δ 0.98 (6H, t, C27, 29-H, J = 7.08, 7.12 Hz), 1.50 (2H, m, C34, 35-H), 2.20 (2H, m, C33, 36-H), 2.42-2.56 (12 H, m, C18, 21, C24, 26, 28-H), 3.26-3.31 (2H, m, C23-H), 6.84 (1H, d, Ar-H, J = 8.4 Hz), 6.90-6.95 (1H, m, Ar-H), 7.43 (1H, t, N-H), 7.71 (1H, s, C11-H), 7.76 (1H, d, Ar-H, J = 9.4 Hz), 10.88 (1H, s, N-H), 13.68 (1H, s, N-H) DSC: Endotherms at 184.3 and 207.4 °C, TGA: No significant weight loss.

3.4.3 Sunitinib 4-hydroxy benzoate

5.0 g of Sunitinib base and 1.90 g of 4-hydroxybenzoic acid (1 meq) were suspended in 75 ml of methanol under N_2 and stirred at RT for 16 hours. Cooled the mixture to about 10 °C and stirred at this temperature for 1 hour. Orange colored material was collected by filtration and washed with 25.0 ml of MeOH (methanol). Dried the product under vacuum at 50 °C for 12 to 14 h. The crystalline Form I of a 4-hydroxybenzoate salt of sunitinib (scheme 4) is characterized by XRPD peak pattern substantially as depicted in Figure 6.



Scheme 4: Scheme for the synthesis of Sunitinib4-hydroxybenzoate.

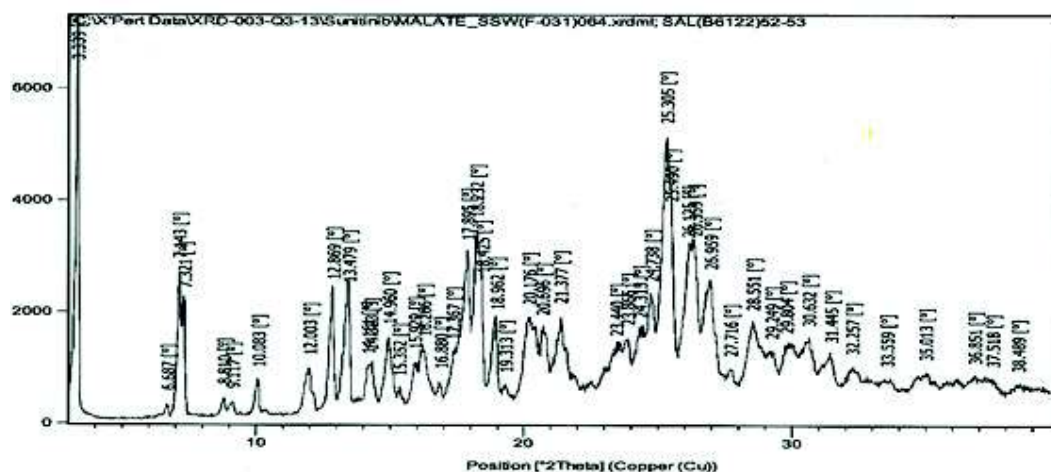
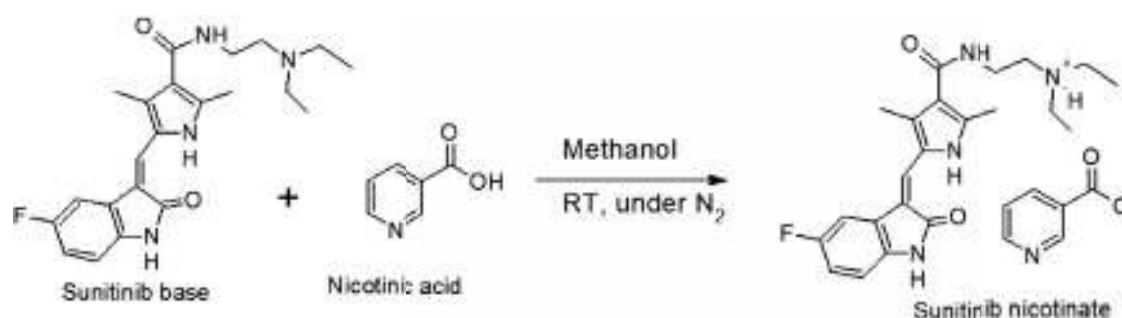


Figure 6: XRD spectrum of sunitinib4-hydroxy benzoate

% Yield = 72.8, M. P. = 195.3 °C, IR (KBr) V_{max} (in cm^{-1}): 3427, 3190, 3047, 2988, 2207, 1679, 1629, 1572, 1526, 1474, 1441, 1369, 1326, 1280, 1258, 1222, 1195, 1179, 1144, 697, 666 and 589. ^1H NMR (400 MHz, CDCl_3): δ 0.98 (6H, t, C29, 27-H, J = 7.08, 7.12 Hz), 2.43 (6H, d, C18, 21-H, J = 7.64 Hz), 2.49-2.59 (6H, m, C24, 26, 28-H), 3.27-3.32 (2H, m, C23-H), 6.80-6.86 (3H, m, Ar-H), 6.90-6.95 (1H, m, Ar-H), 7.45 (1H, t, Ar-H, J = 5.48, 5.6 Hz), 7.71-7.79 (4H, m, Ar, 11a, N13-H), 10.8 (1H, s, N22-H), 13.68 (1H, s, N1-H). DSC: Endotherms at 188.22 and 195.25 °C. TGA: No significant weight loss was observed.

3.4.4 Sunitinibnicotinate

5.0 g of Sunitinib base and 1.69 g of nicotinic acid (1.1 meq) were suspended in 50 ml of methanol at room temperature under N_2 and stirred the resulting mixture at RT for 16 hours. Cooled down the solution to 10 °C and stirred the reaction mixture for 1 hour at equal temperature. The orange solids were filtered, washed with 25 ml of methanol and dried 50 °C for 12 to 14 h under vacuum. The crystalline Form I of a nicotinate salt of sunitinib(scheme 5) is characterized by XRPD peak pattern significantly as depicted in Figure 7.



Scheme 5: Scheme for the synthesis of Sunitinibnicotinate.

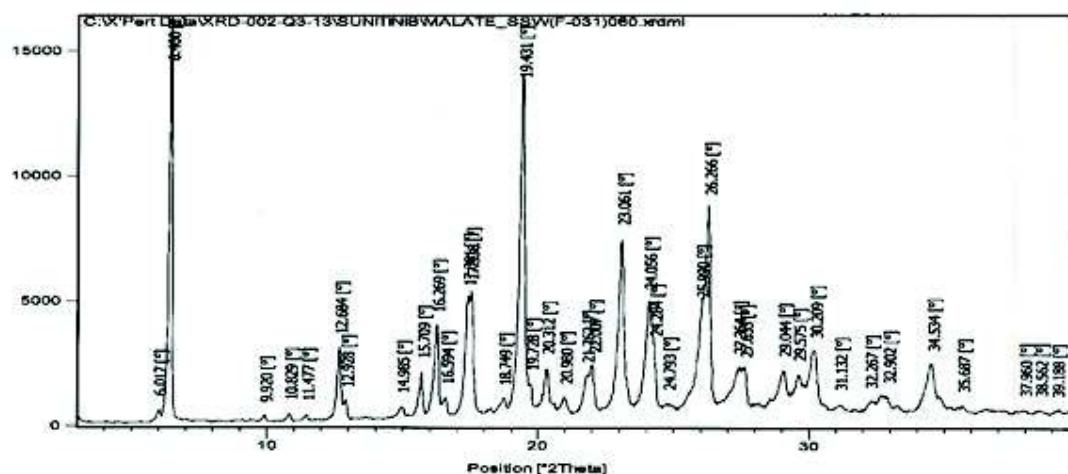
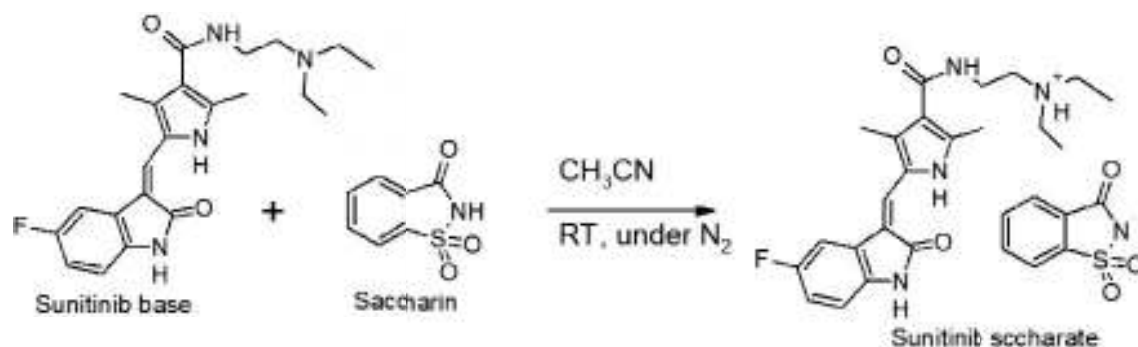


Figure 7: XRD spectrum of sunitinibNicotinate

% Yield = 60.8, M. P. = 203.3 °C, IR (KBr) V_{max} (in cm^{-1}): 3427, 3190, 3047, 2988, 2204, 1679, 1629, 1573, 1526, 1474, 1326, 1195, 1179, 666 and 589. ^1H NMR (400 MHz, CDCl_3): δ 1.03 (6H, t, C29, 27-H, J = 7.12, 7.12 Hz), 2.43 (6H, d, C18, 21-H, J = 7.72 Hz), 2.68 (6H, t, C24, 26, 28-H, J = 7.24, 7.64 Hz), 3.35 (2H, d, C23, J = 6.2 Hz), 6.84 (1H, d, Ar-H, J = 8.44 Hz), 6.92 (1H, t, Ar-H, J = 8.52, 9.48 Hz), 7.48 (1H, dd, Ar-H, J = 4.84, 5.04 Hz), 7.56 (1H, s, Ar-H), 7.75 (1H, d, Ar-H, J = 9.4 Hz), 8.21-8.24 (1H, m, Ar-H), 8.72 (1H, dd, Ar-H, J = 1.64, 1.64), 9.04 (1H, t, N22-H, J = 0.76, 1.32 Hz), 10.9 (1H, s, N13-H), 13.68 (1H, s, N1-H), DSC: Single endotherm at 205.25°C. TGA: No Significant weight loss.

3.4.5 Sunitinibsaccharate

5.0 g of Sunitinib base was suspended in 75 ml of acetonitrile at room temperature under N_2 . Charged 2.52 g of Saccharin (1 meq) at RT. After 5 to 10 minutes the mixture became dense paste. Additional 20 ml acetonitrile was added to it and stirred at RT for 16 h. The orange solids were filtered, washed with 25 ml of acetonitrile and dried the product under vacuum at 50 °C for 12 to 14 h. The crystalline Form I of a saccharate salt of sunitinib(scheme 6) is characterized by XRPD peak pattern substantially as represented in Figure 8.



Scheme 6: Scheme for the synthesis of Sunitinib saccharate.

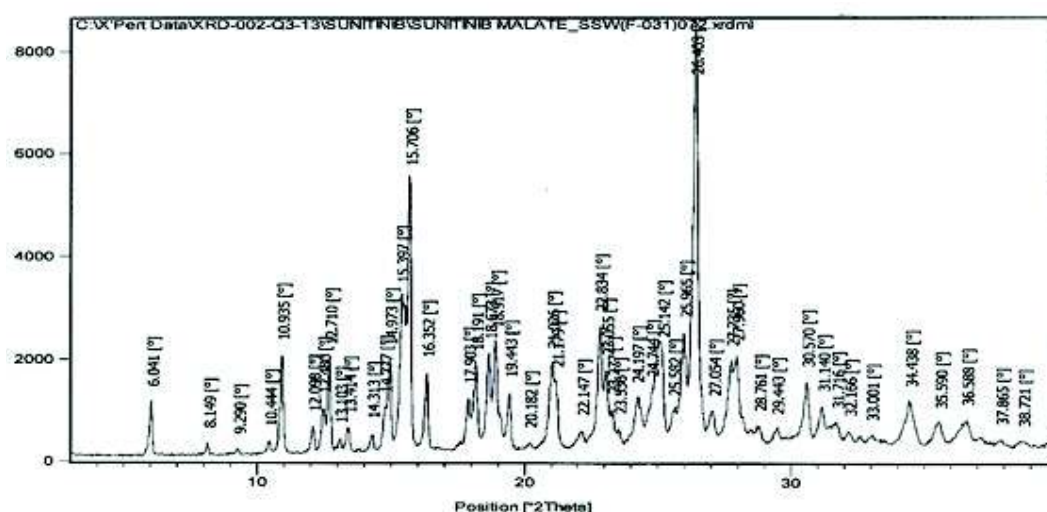


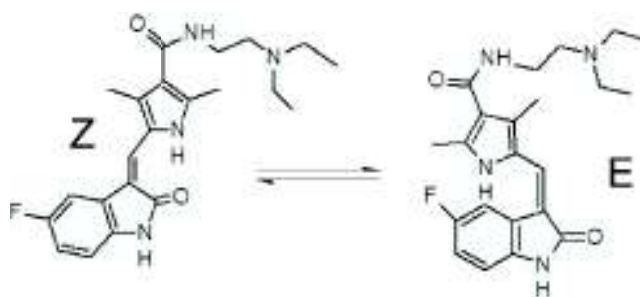
Figure 8: XRD spectrum of sunitinib saccharate

% Yield = 92.0, M. P. = 202-207 °C, IR (KBr) V_{max} (in cm^{-1}): 3429, 3303, 3226, 2969, 2929, 2814, 1824, 1677, 1589, 1542, 1480, 1467, 1333, 1192, 668 and 585. ^1H NMR (400 MHz, CDCl_3): δ 1.24 (6H, t, C39, 41-H, $J = 7.24$, 13.04 Hz), 2.46 (6H, dd, C33, 30-H, $J = 11.16$, 18.72 Hz), 3.21-3.22 (6H, m, C36, 38, 40-H), 3.58 (2H, t, C35, $J = 6.0$, 6.04 Hz), 6.86 (1H, dd, Ar-H, $J = 4.56$, 4.56 Hz), 6.94 (1H, t, Ar-H, $J = 8.76$, 9.2), 7.56-7.62 (3H, m, Ar, N1-H), 7.64-7.67 (1H, m, C23-H), 7.74-7.80 (3H, m, Ar-H), 9.23 (1H, s, N-H), 10.93 (1H, s, N-H), 13.76 (1H, s, N-H), DSC: Single endotherm at 233.07 °C. TGA: No significant weight loss.

4 Results and Discussion

4.1 Z-E Isomerism

HPLC analysis of the lab batches of sunitinib exhibited large variation of the undesired E-isomer content that varied from 0.1% to 8% (Scheme 7). This prompted us to study the probability of the conversion of the sunitinib into the undesired E-isomer in presence of heat and light. This is further confirmed when the solutions, prepared in 1:1 mixture of acetonitrile and water, were exposed to both halogen lamp (20 hours exposure) and sunlight (6 hours) at 10-15 °C (during winter). The conversions were found to be about 3% and 28% in halogen lamp and sunlight, respectively (Figure 9&10). This conversion and characterization of E-isomer was additionally supported by ^1H NMR spectroscopy. (Conversion Z-isomer 66% and E-Isomer 34%)



Scheme 7. E-Z Isomerization in sunitinib in presence of light

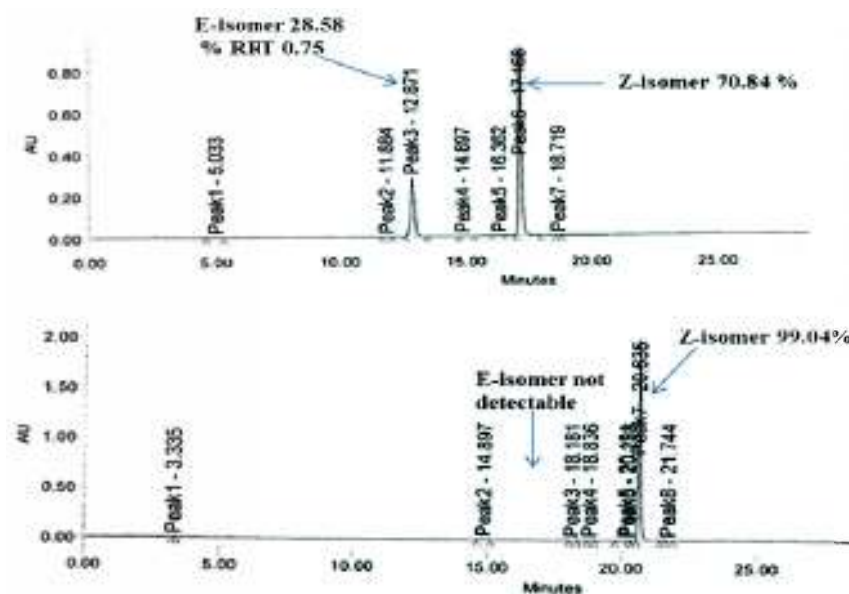


Figure 9. HPLC chromatogram of the samples exposed to sunlight (above) and then kept in dark (below).

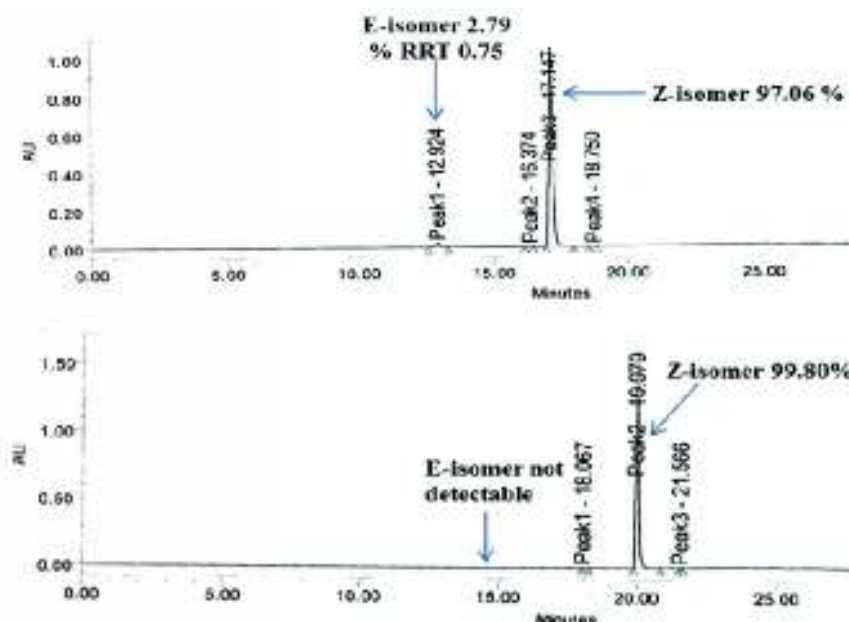


Figure 10. HPLC chromatogram of the samples exposed to halogen lamp (above) and then kept in dark (below).

When the samples were kept in dark for about 40 hours, the E-isomer could not be detected in the resulting solutions confirming that the Z-E isomerization in sunitinib is reversible.

4.2 Solid form screening

Polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly, water solubility in the present case.

4.3 Polymorph screening

Three polymorphs of sunitinibmalate are reported in the literature.^[17-19] Both reactive crystallization and solvent mediated transformation methods were explored in as many as twenty solvents which included EtOH, 1-butanol, IPA, ethyl acetate, dichloromethane, DMSO, THF, methyl isobutyl ketone, toluene, heptane, water, 2-methyl THF, acetone, DMF, acetonitrile, cyclohexane and methyl tertiary butyl ether. Only the reported form was obtained in the screening experiments.

4.4 Co-crystal screening

Co-crystal screening experiments were carried out with two coformers, namely, urea and nicotinamide using solvent mediated conversion method in acetonitrile and MeOH. Both these coformers do not have any acidic groups that favor salt formation with sunitinib. The screening results by XRPD revealed that only the physical mixture of components (starting materials) were obtained.

4.5 Salt screening

Several salts are reported in the patent literature.^[12-13] Malate salt is being currently sold in the market. Its solubility in water is about 25 mg/ml in acidic conditions (pH 1.2 - 6.8),^[11] which rapidly decreases at pH > 6.8. Hence the sunitinib is classified as a low solubility compound. Salt screening experiments were conducted with adipic acid, glutaric acid, nicotinic acid, 4-hydroxy benzoic acid and saccharin as their corresponding salts (Figure 11) were not covered in the patent literature, and all of them are also well thought-out pharmaceutically acceptable salt formers. The desired salts with 1:1 ratios were obtained when sunitinib was treated with these acids, except for adipic acid, which yielded a 2:1 [sunitinib][adipic acid] salt.

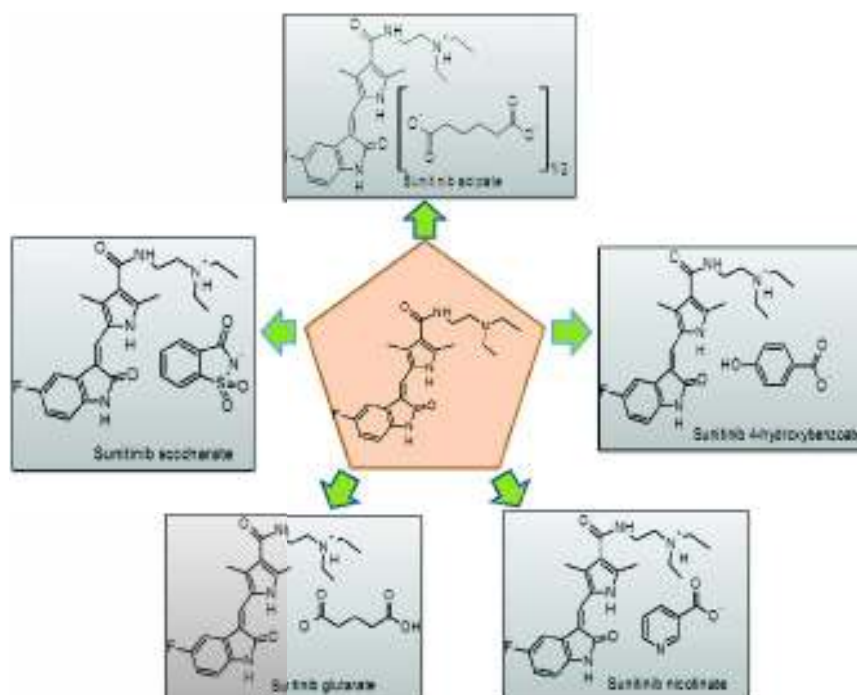


Figure 11. Adipate, saccharate, 4-hydroxybenzoate, glutarate and nicotinate salts of sunitinib

The solid form characterization data is shown in Table 1. Glutarate and nicotinate salts show a single endotherm in DSC. TGA data reveals that these salts are neither hydrates nor solvates. The melting points of nicotinate, 4-hydroxy benzoate and saccharate salts are lower than those of the corresponding components (both salt-former and sunitinib), while that of adipate and glutarate salts lie between the melting points the corresponding salt former and sunitinib. Sunitinib base melts at 216.6 °C with an endotherm in the DSC at 234.4 °C.

Table 1. Thermal characterization of various salts identified in the present study

Sunitinib salts	Stoichiometry (base:acid)	Melting point*	DSC*	TGA of salts	Melting point of the salt former
Adipatesalt	1:0.5	200 °C	184.3, 207.4	No significant weight loss	149-153°C
Glutarate salt	1:1	204.2 °C	202.4	No significant weight loss	94-97 °C
Nicotinate salt	1:1	203.3 °C	205.2	No significant weight loss	234-237 °C
4-Hydroxy benzoate salt	1:1	195.3 °C	188.2, 195.2	No significant weight loss	214-215 °C
Saccharate salt	1:1	202-207 °C	233.1, 222.6	No significant weight loss	225-227 °C

*Sunitinib base: melting point: 216.6 °C; DSC: endotherm at 234.4 °C

The equilibrium solubility of these solid forms was evaluated by HPLC method. Solubility data revealed that these salts exhibit variable water (DI water) solubility (Table 2). Nicotinate and adipate salts exhibited excellent water solubility, particularly at a higher pH (of about pH 7.0). The solubility of these salts in DI water was found to be 6 to 10 times greater than that of the marketed form (malate salt). Solubility of adipate, glutarate and 4-hydroxy benzoate salts are less soluble in water than the marketed malate salt.

Table 2. Equilibrium solubility of sunitinib solid forms in DI water at room temperature

Solid form	malate salt	Sunitinib	Adipate salt	Glutarate salt	Nicotinate salt	4-Hydroxy benzoate salt	Saccharate salt
Solubility (mg/ml)	~25 (reported)	~0.048	272	6.2	162	3.42	2

Another interesting point that is worth noting here is the stoichiometry of the adipate salt. It is likely that both acidic protons of adipic acid are engaged in the protonating sunitinib leading to a 2:1 (sunitinib: adipic acid) salt. Alternatively, the same stoichiometry can be resulted if there one neutral sunitinib, one protonated sunitinib and one singly deprotonated adipic acid species as shown in Figure 12. If this is indeed the case, then we are in the salt co-crystal region. In other words, the adipate salt referred herein can also be a salt co-crystal. However, this needs to be confirmed by single crystal X-ray diffraction studies.

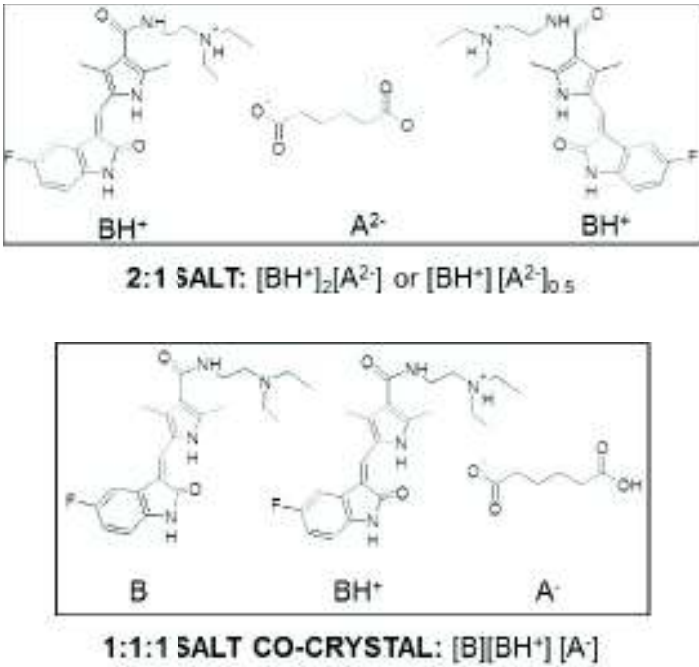


Figure 12. Two possible solid forms of sunitib with adipic acid for a 2:1 sunitinb: adipic acid stoichiometry: salt (above) / salt co-crystal (below)

318 5 Conclusion

319 HPLC analysis of the lab batches of sunitinib showed large variation of the undesired E-isomer
 320 content that varied from 0.1% to 8%. Further investigations revealed that the variation observed was
 321 due to the occurrence of Z-E isomerization in sunitinib when exposed to light and heat was likewise
 322 additionally confirmed by ¹H-NMR. Importantly, these results suggest that care should be taken while
 323 handling the analytical solutions of sunitinib - particularly protection from light and heat during
 324 preparation and storage - in the standard HPLC testing procedures for obtaining consistent and
 325 accurate data. Polymorph, co-crystals and salt screening experiments of sunitinib were carried out to
 326 identify novel solid forms with the improved solubility. Only the thermodynamically stable form of
 327 malate salt was obtained in the polymorph screening experiments, in co-crystals screening
 328 experiments the physical mixture of starting components was seen in XRPD spectrum, whereas five
 329 novel (adipate, glutarate, nicotinate, 4-hydroxybenzoate and saccharate) salts were identified in the
 330 salt screening experiments. Nicotinate and Adipate salts exhibited excellent water solubility,
 331 particularly at a higher pH (of about pH 7.0). The solubility of these salts in DI water was found to be 6
 332 to 10 times greater than that of the marketed form (malate salt).

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Supporting Information for synthesized salts

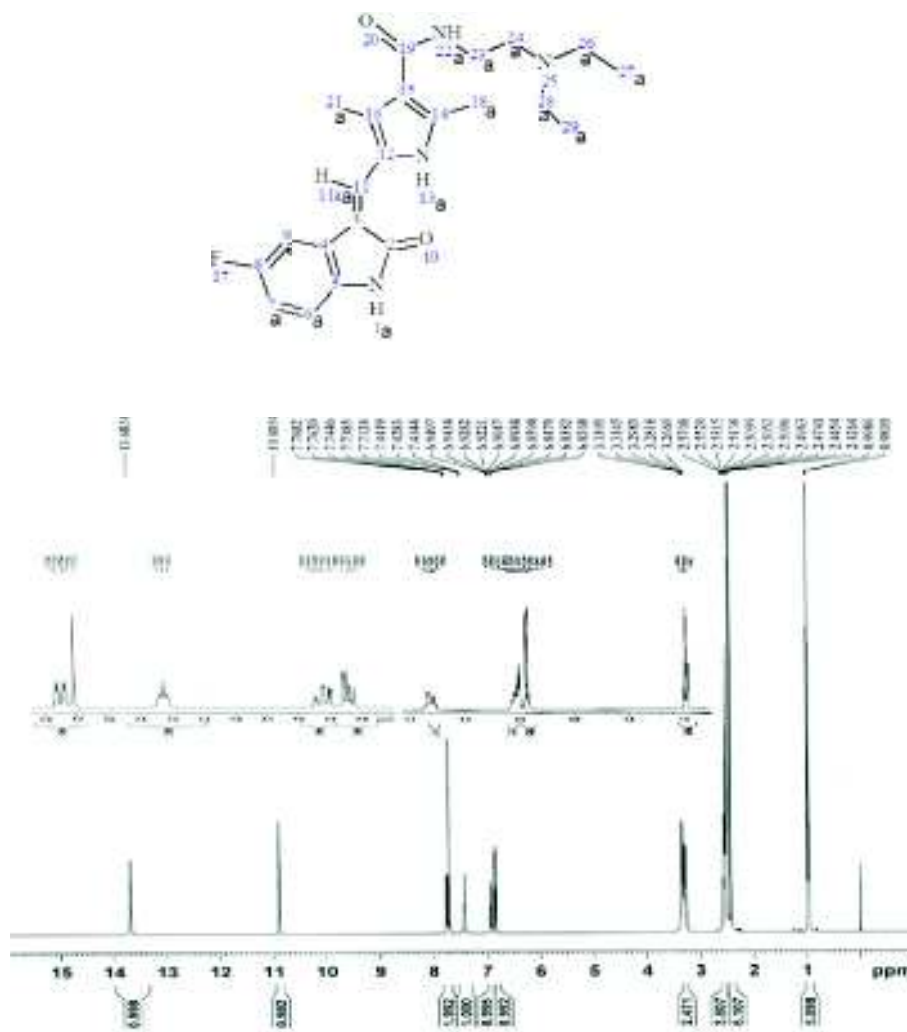


Figure S1: ^1H NMR spectrum of sunitinib (Z-isomer) in DMSO-d_6 . The expansion of the region 1.0-3.5 and 6.8-7.8 ppm is inserted for clarity

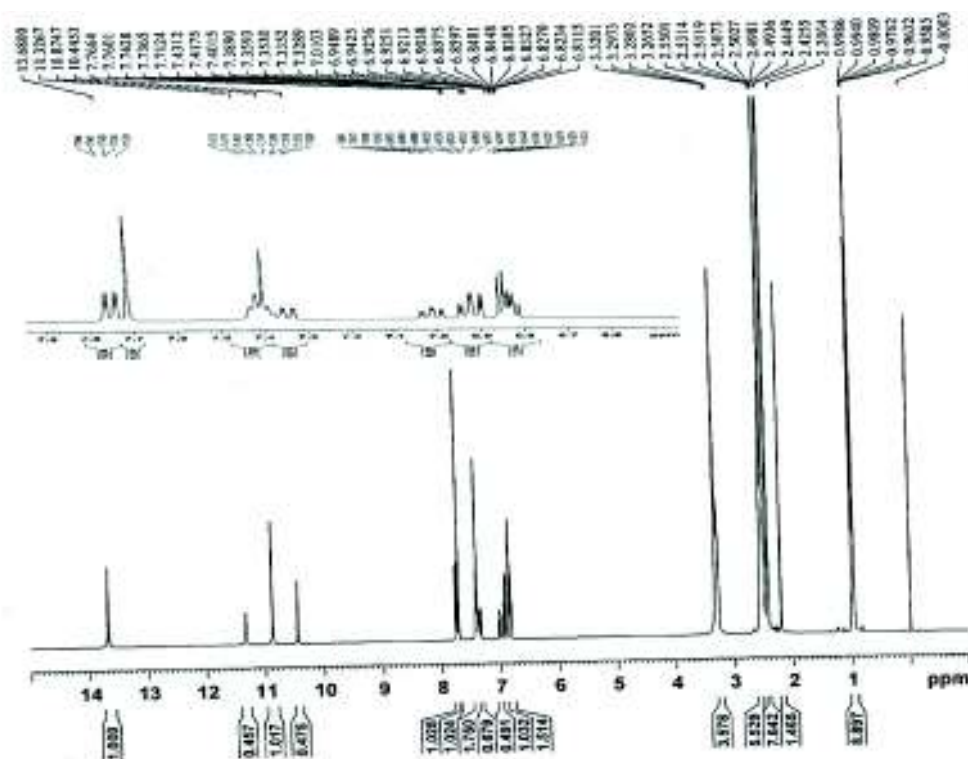
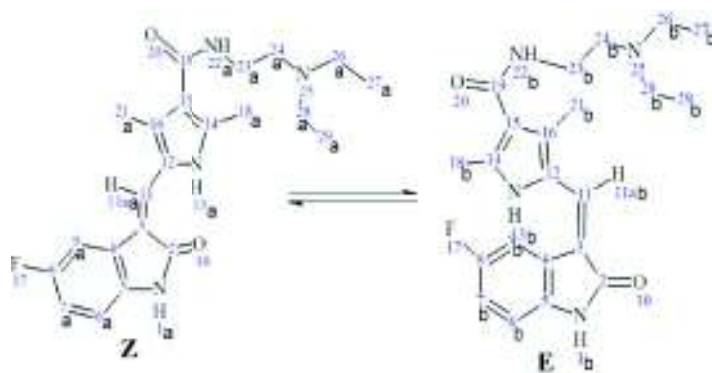


Figure S2: ^1H NMR spectrum of sunitinib (a solution of DMSO-d_6 exposed to sunlight for 4 hours). The expansion of the region 6.8-7.8 ppm is also inserted for clarity

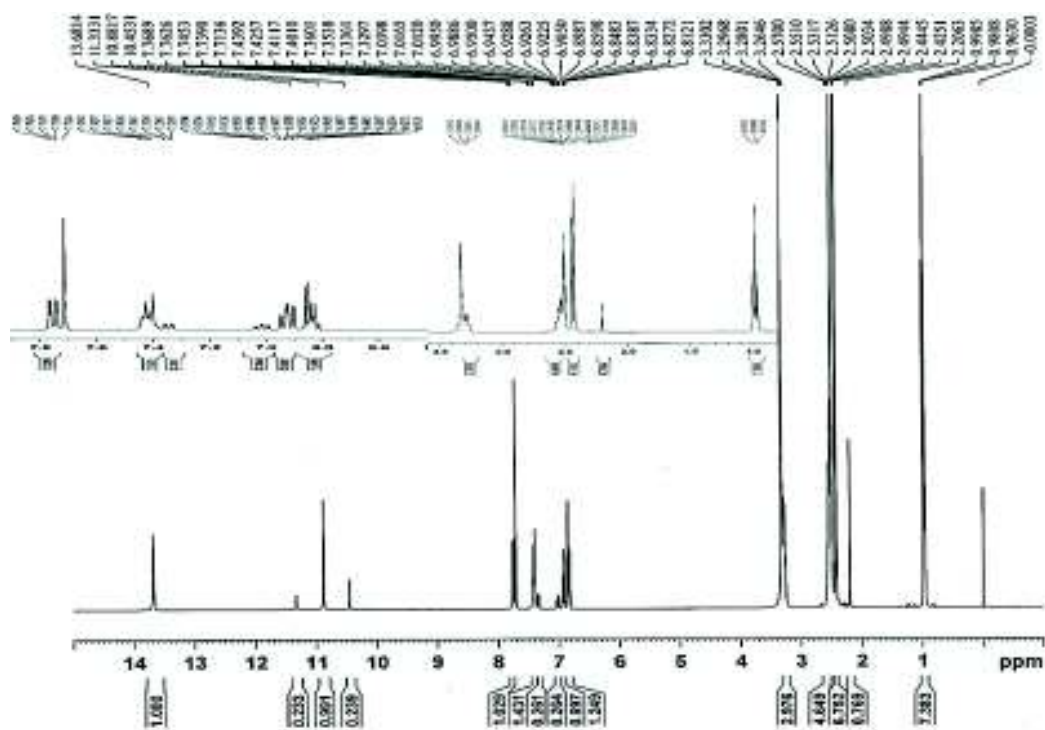


Figure S3: ^1H NMR spectrum of sunitinib (the solution of DMSO-d_6 that was exposed to sunlight for 4 hours and then kept in dark for 60 hours). The expansion of the region 1.0-3.5 and 6.8-7.8 ppm is inserted for clarity

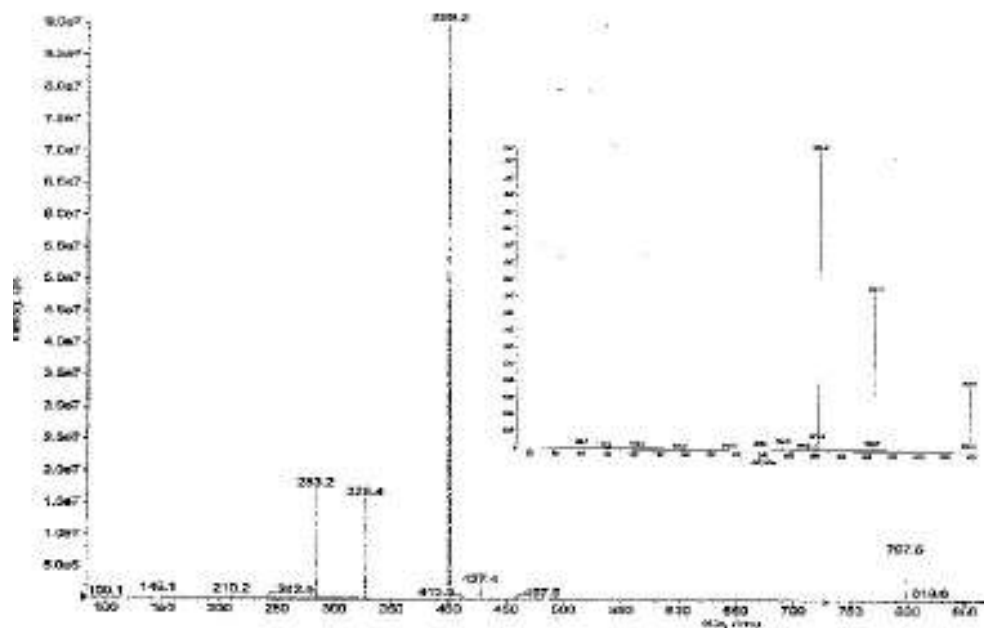
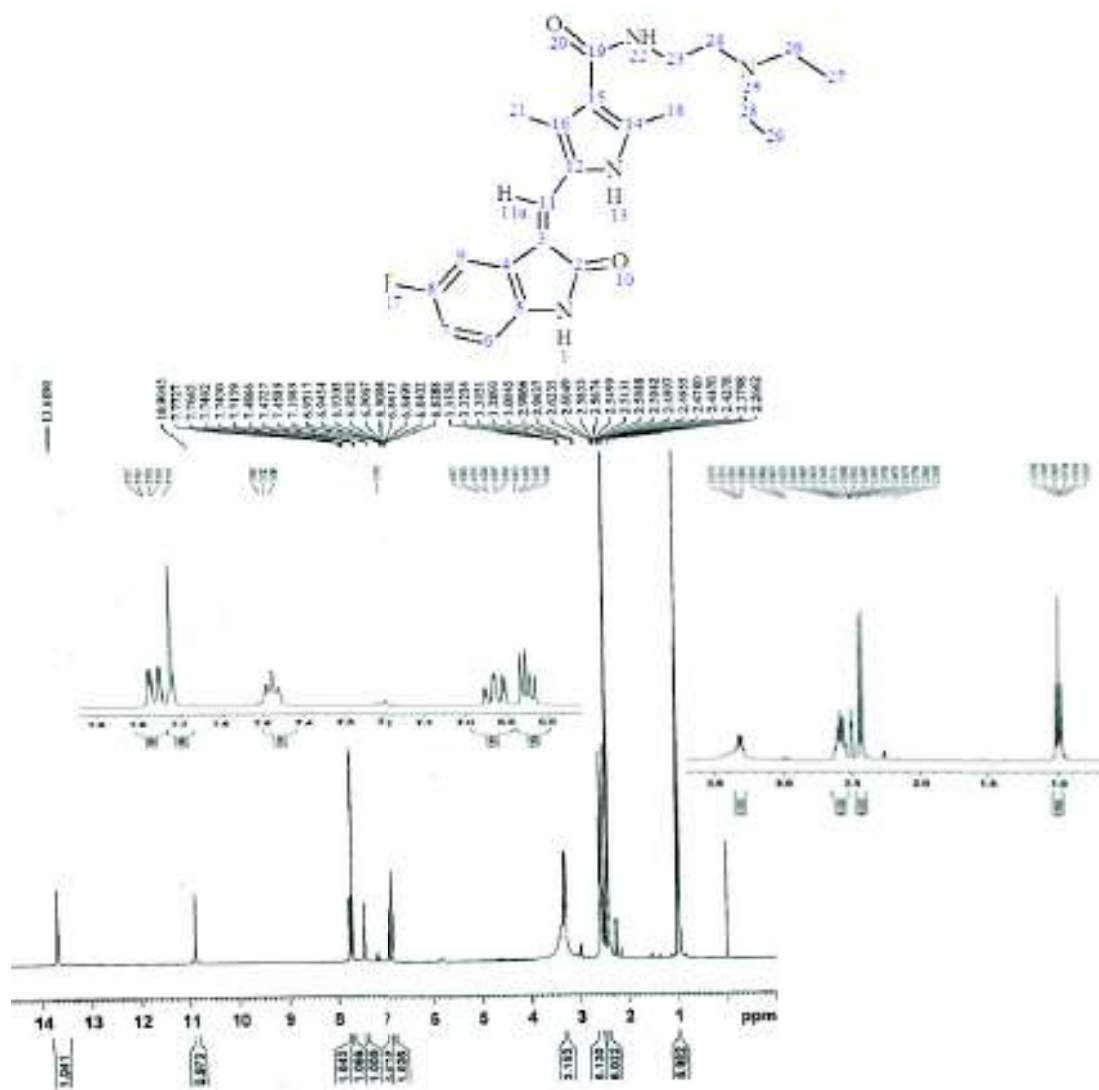


Figure S4: Mass and MS-MS (insert) spectrum of sunitinib.

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403 **Figure S5:** ¹H NMR spectrum of sunitinib. The expansion of the region 1.0-3.6 and 6.0-7.8 ppm
404 is inserted for clarity

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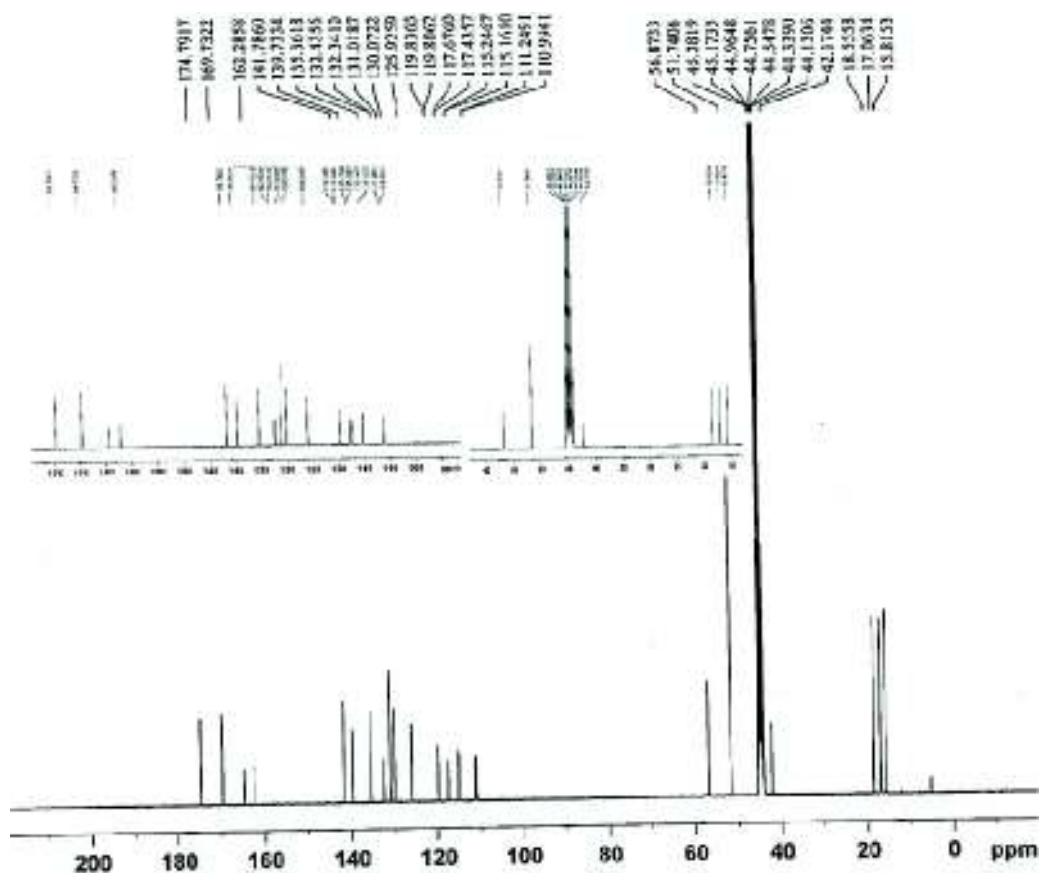


Figure S6: ^{13}C NMR spectrum of sunitinib. The expansion of the region between 15-60 and 110-176 ppm is inserted

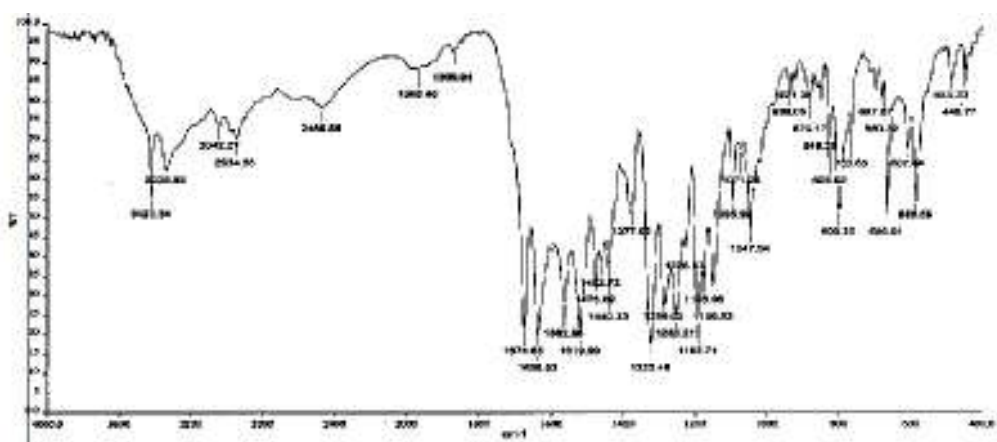


Figure S7: IR spectrum of sunitinib

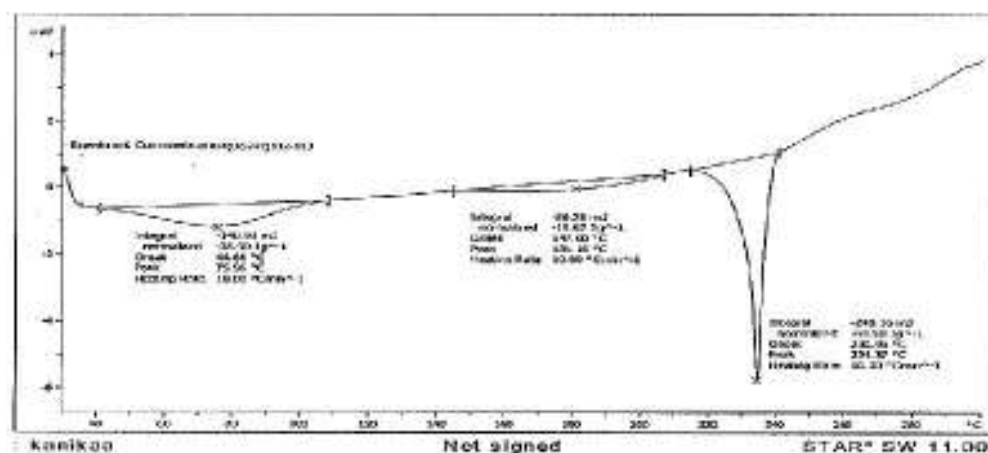


Figure S8: DSC thermogram of sunitinib base

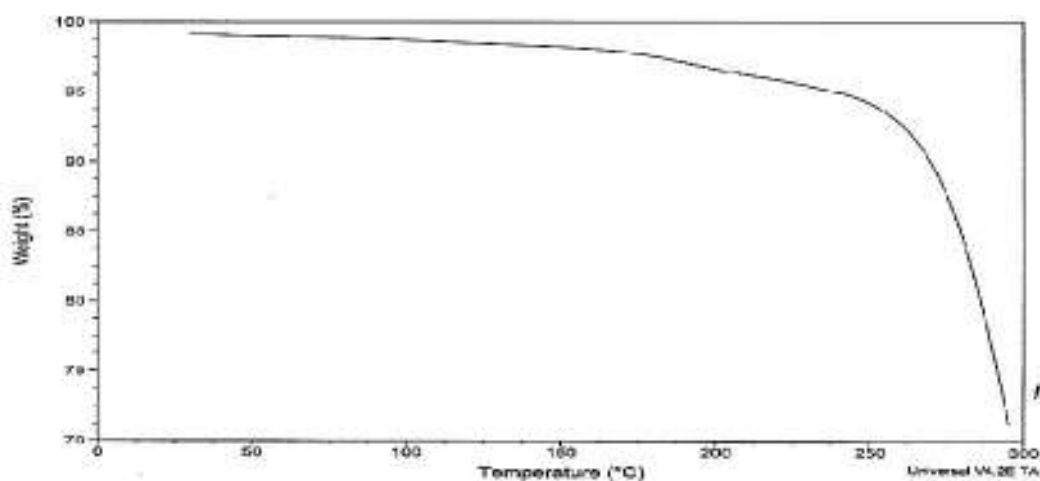


Figure S9: TGA thermogram of sunitinib base

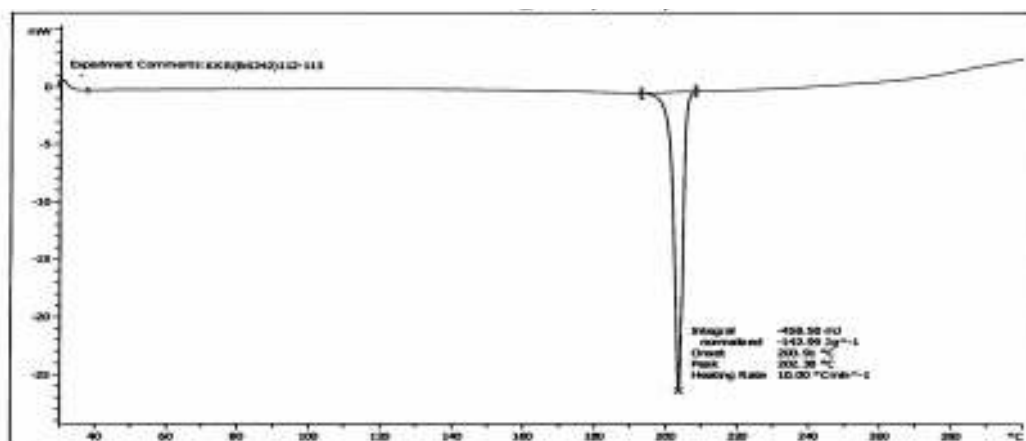
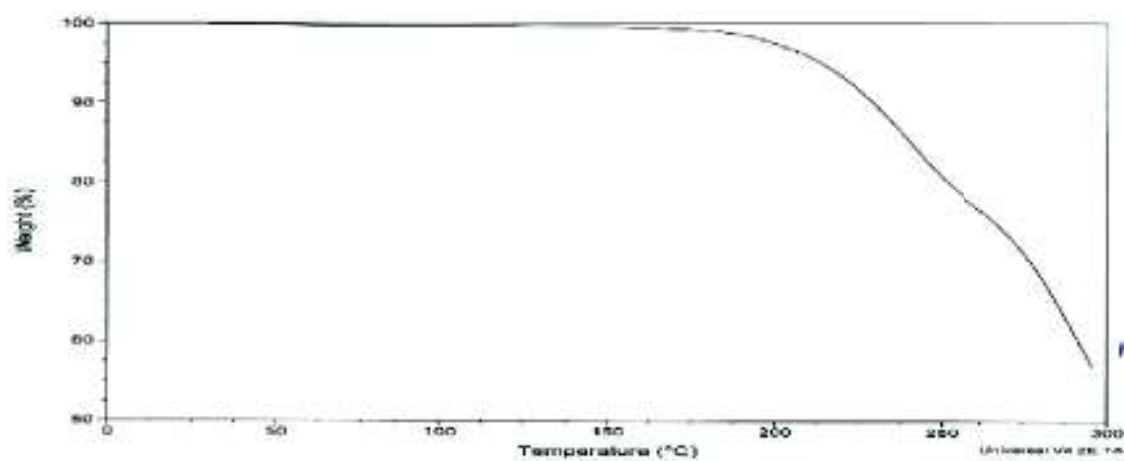


Figure S10: DSC thermogram of sunitinibglutarate

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Figure S11: TGA thermogram of sunitinibglutarate

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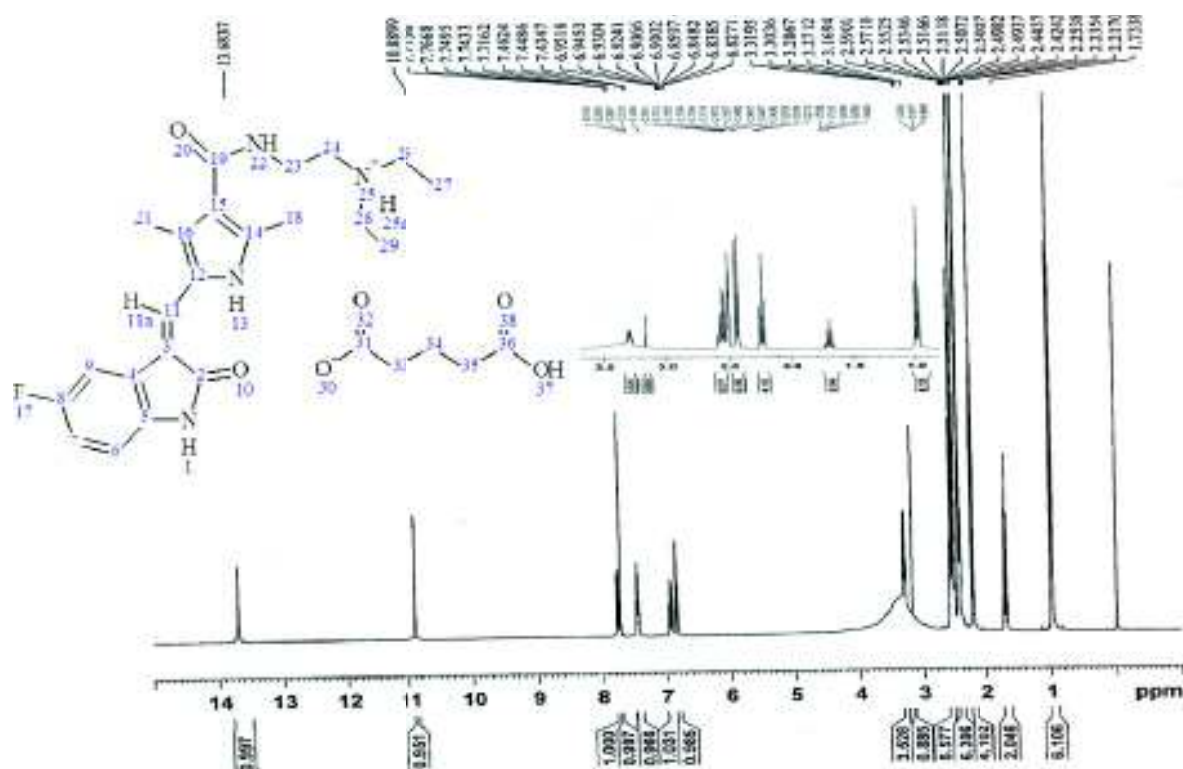


Figure S12: ¹H NMR spectrum of sunitinibglutarate. The expansion of the region 0.9-3.32 is inserted for clarity



Figure S13: IR spectrum of sunitinibglutarate salt

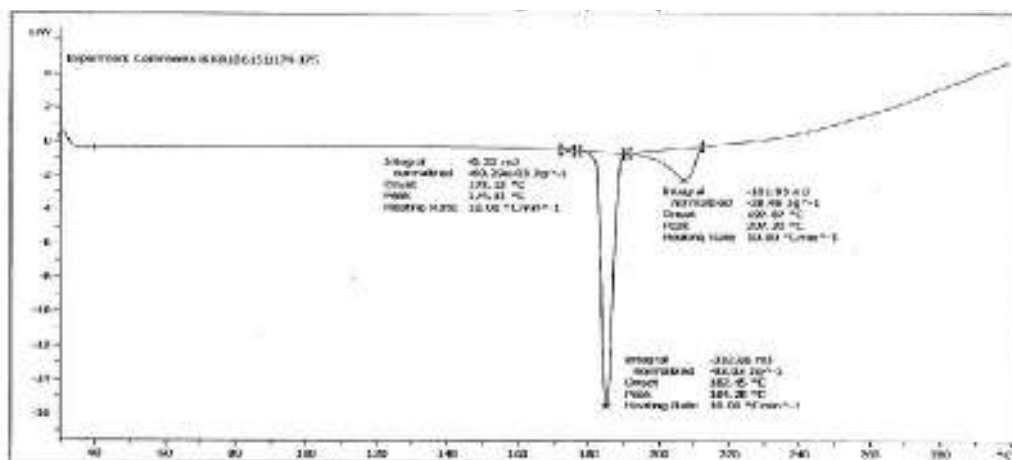
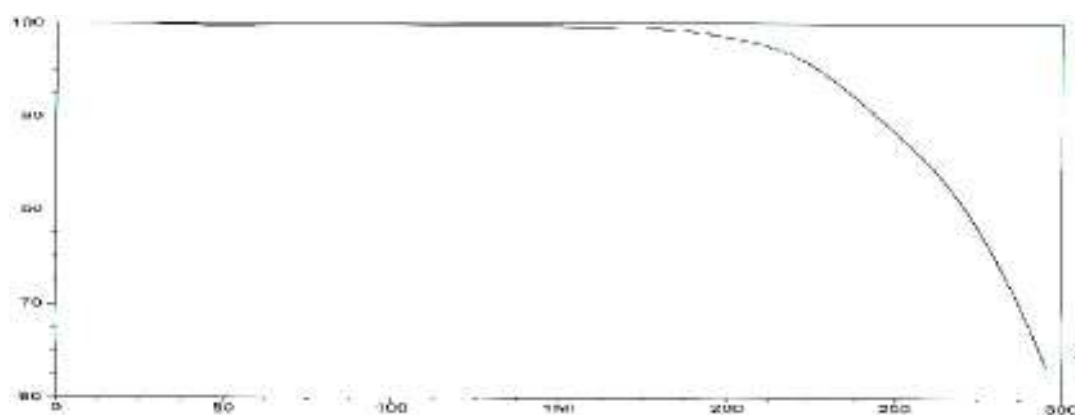


Figure S14: DSC thermogram of sunitinibadipate salt

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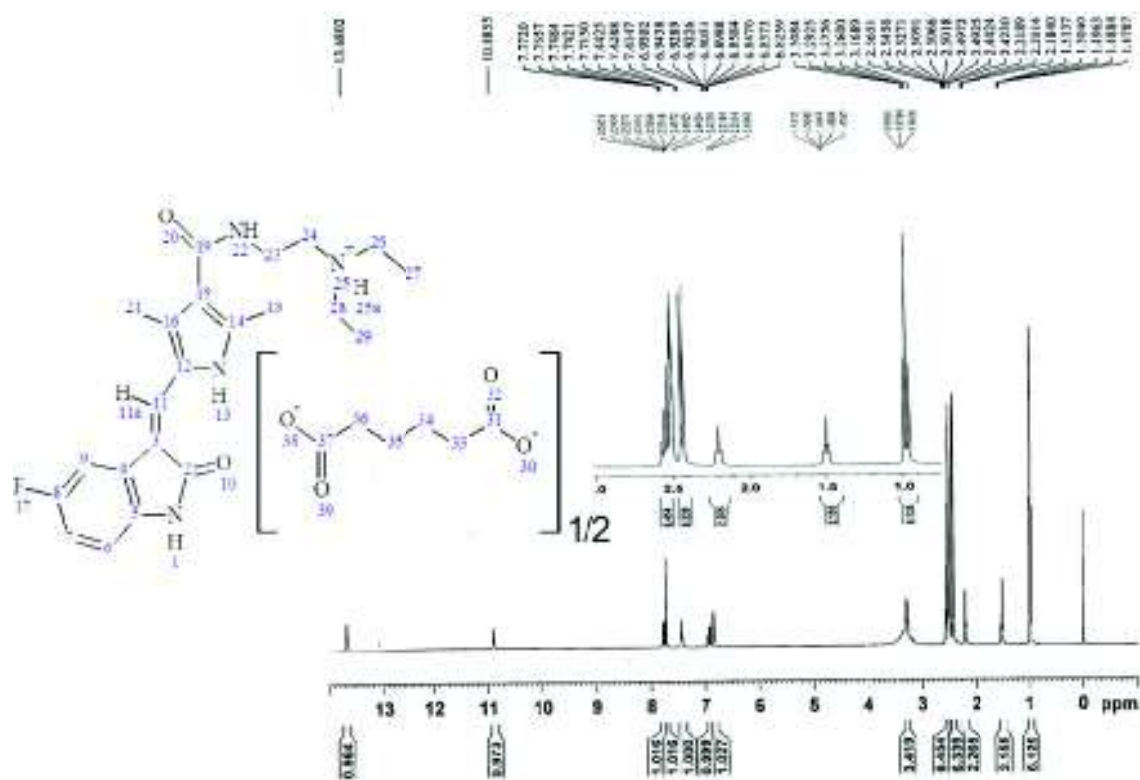


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Figure S15: TGA thermogram of sunitinibadipate

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Figure S16: ¹H NMR spectrum of sunitinibadipate. The expansion of the region 0.9 – 2.5 ppm is inserted for clarity

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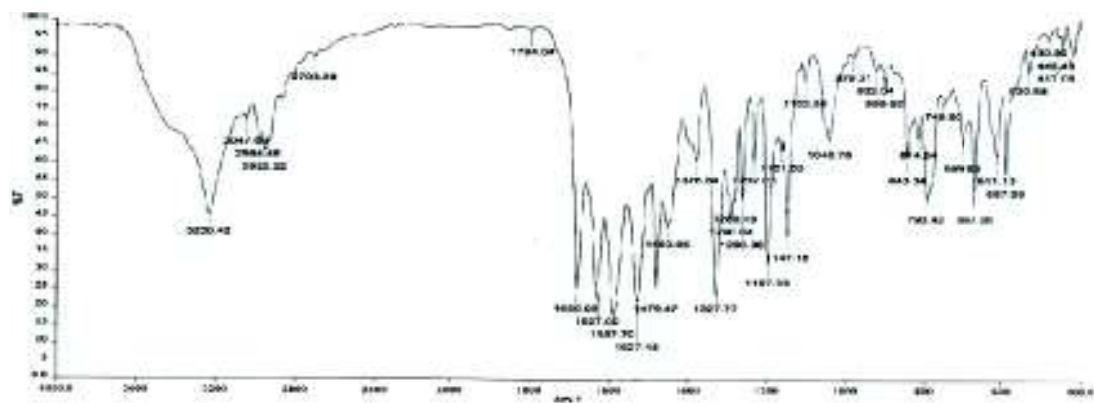


Figure S17: IR spectrum of sunitinibadipate salt

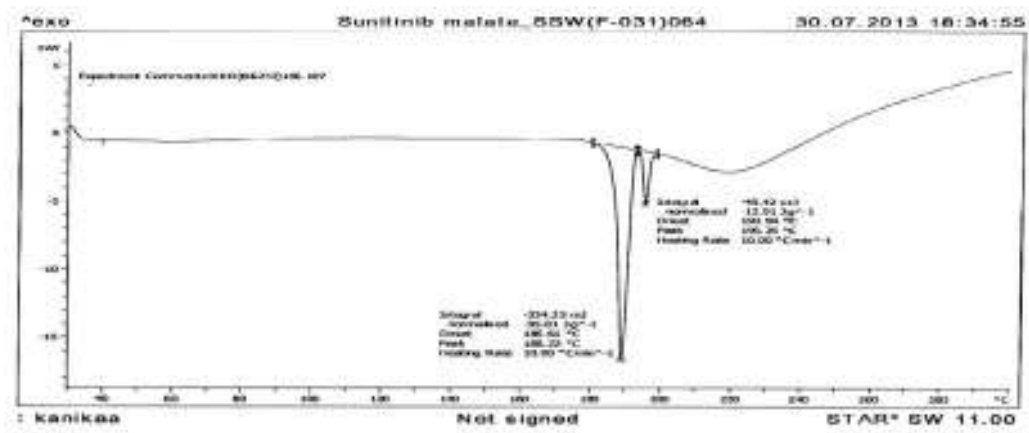
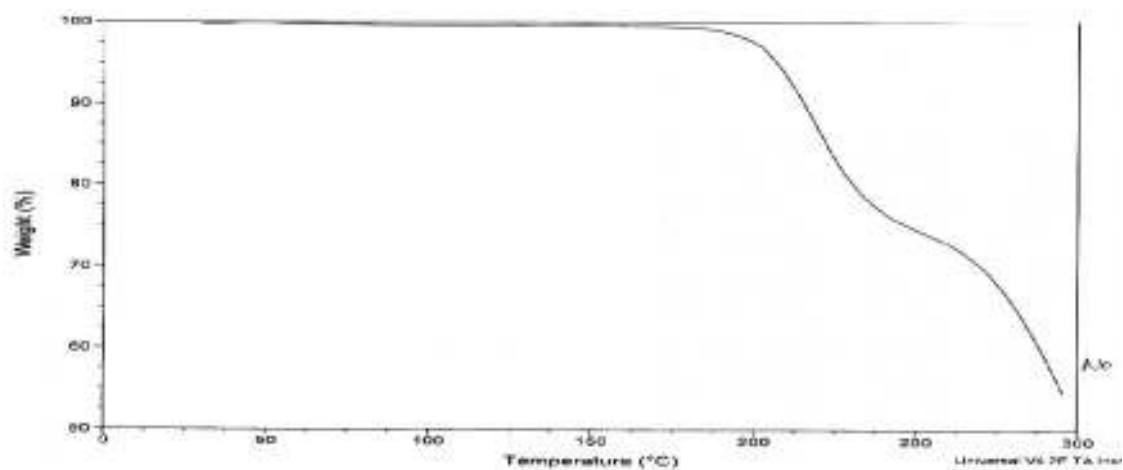


Figure S18: DSC thermogram of sunitinib 4-hydroxy benzoate



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Figure S19: TGA thermogram of sunitinib 4-hydroxy benzoate

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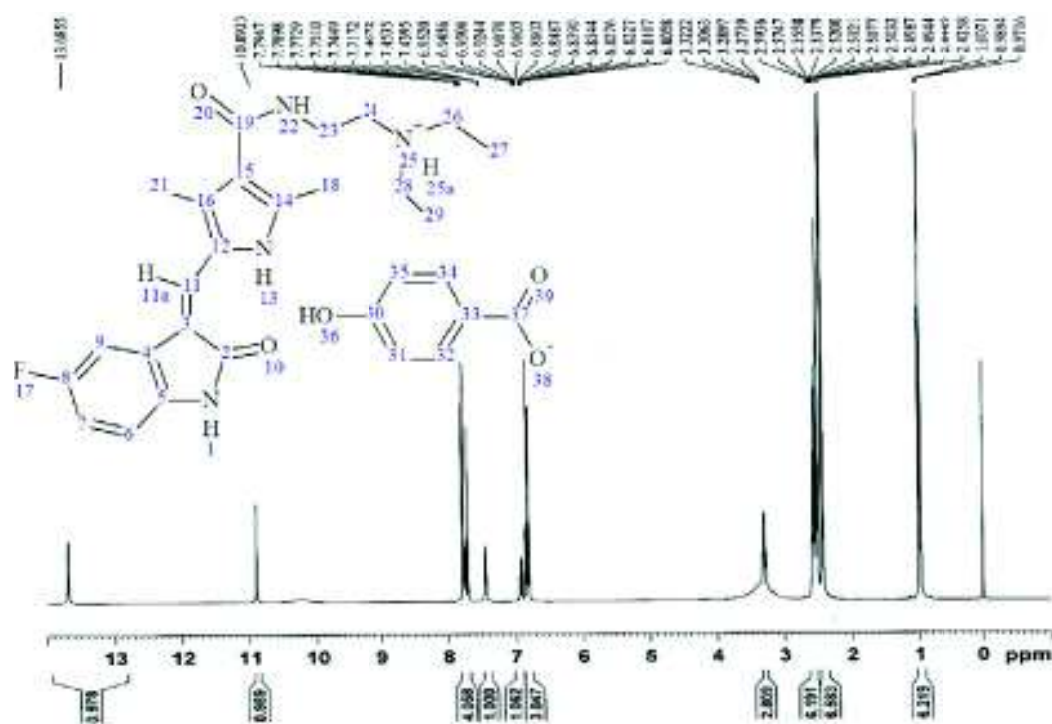


Figure S20: ^1H NMR spectrum of sunitinib 4-hydroxy benzoate

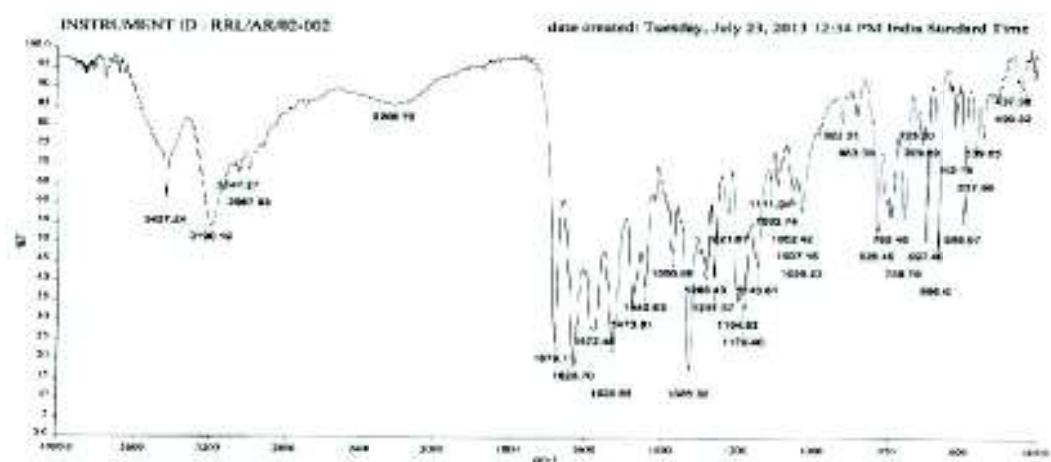


Figure S21: IR spectrum of sunitinib 4-hydroxy benzoate

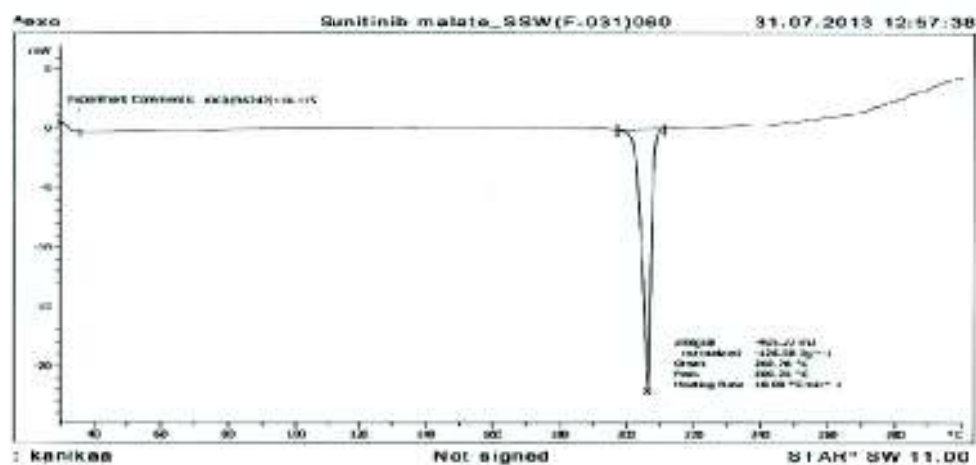
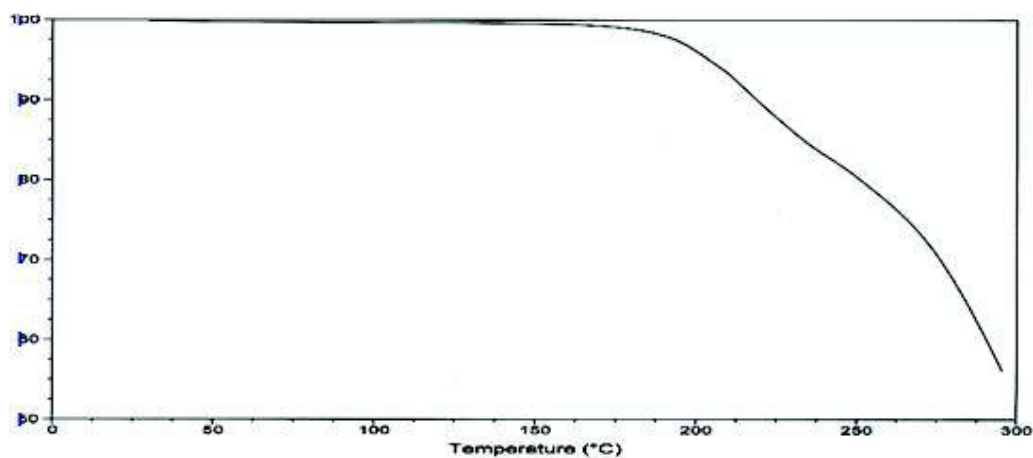


Figure S22: DSC thermogram of sunitinibnicotinate



S23: TGA thermogram of sunitinibnicotinate

Figure

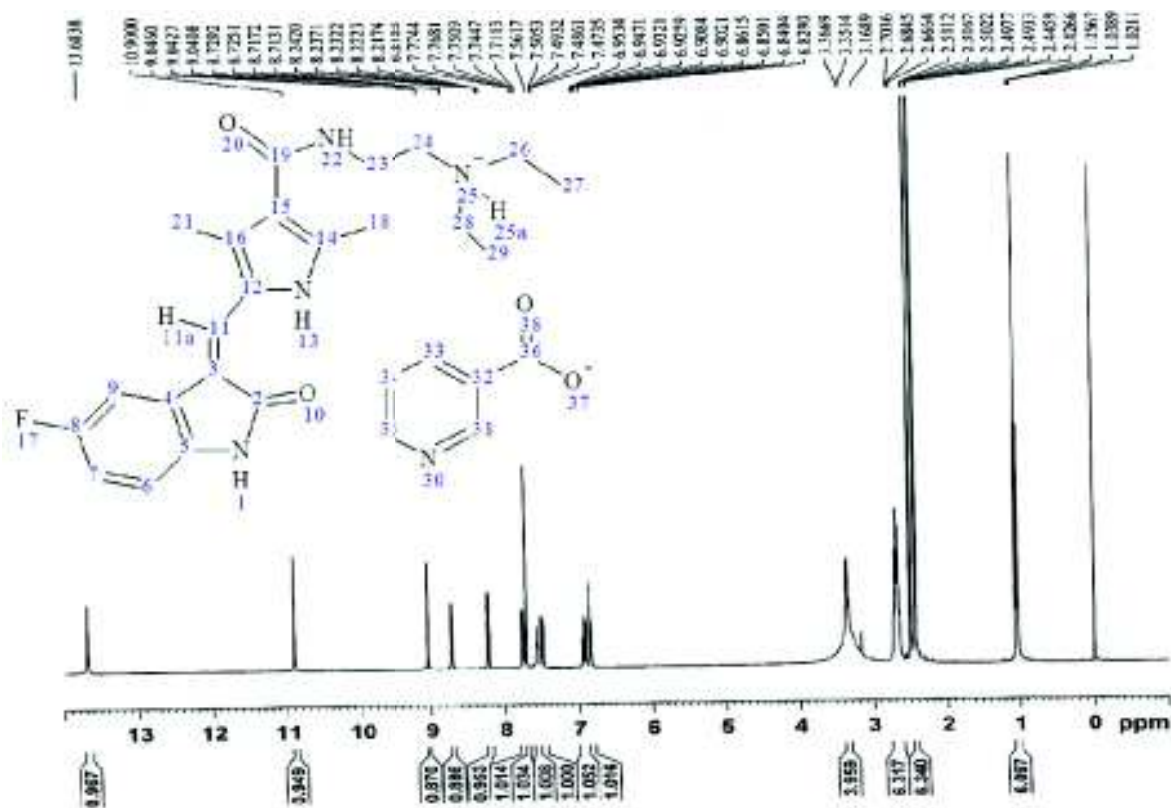


Figure S24: ^1H NMR spectrum of sunitinibnicotinate

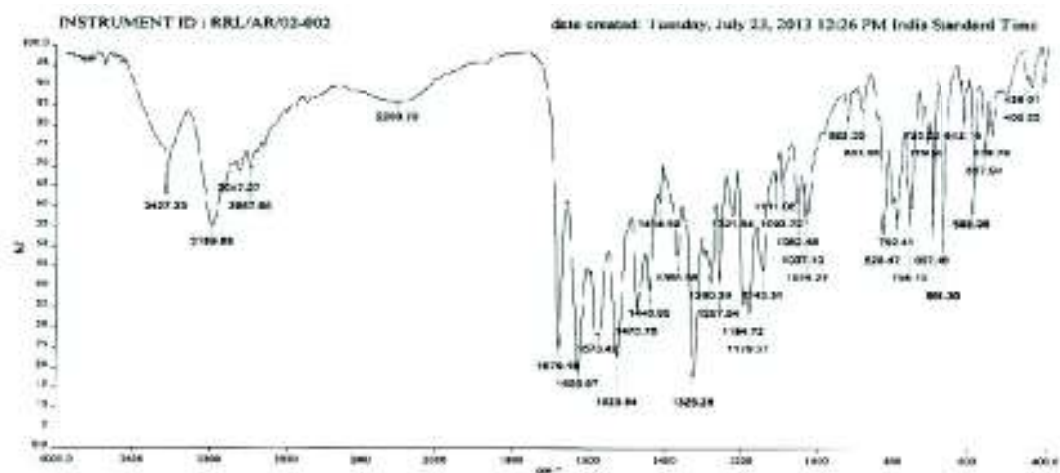


Figure S25: IR spectrum of sunitinibnicotinate

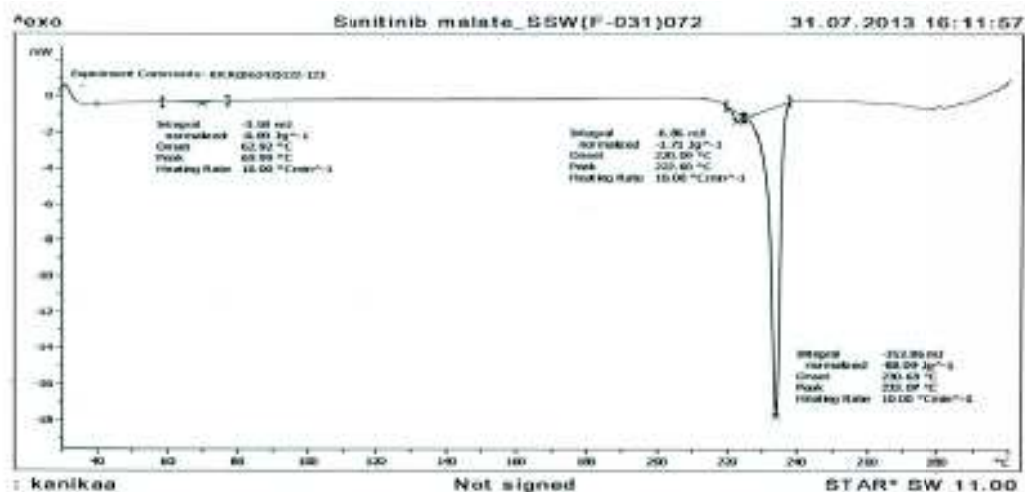


Figure S26: DSC endotherm of sunitinib saccharate

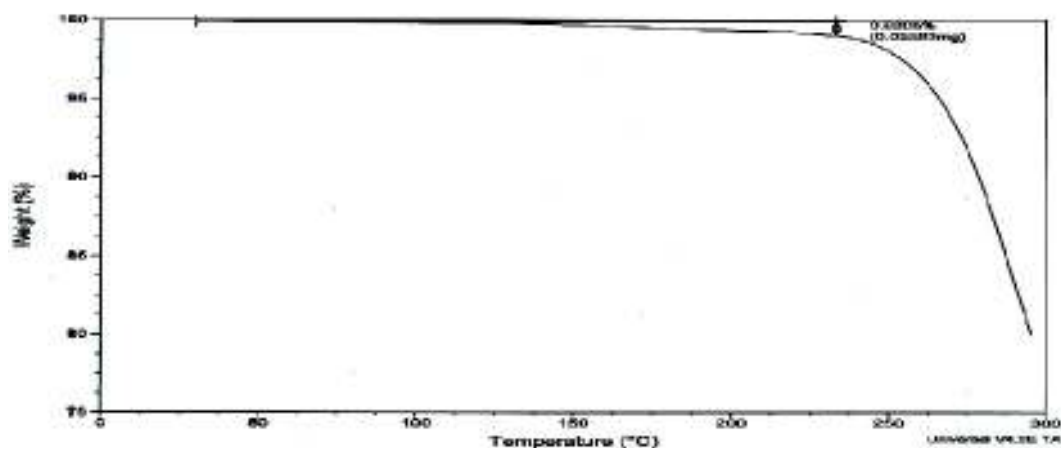


Figure S27: TGA endotherm of sunitinib saccharate

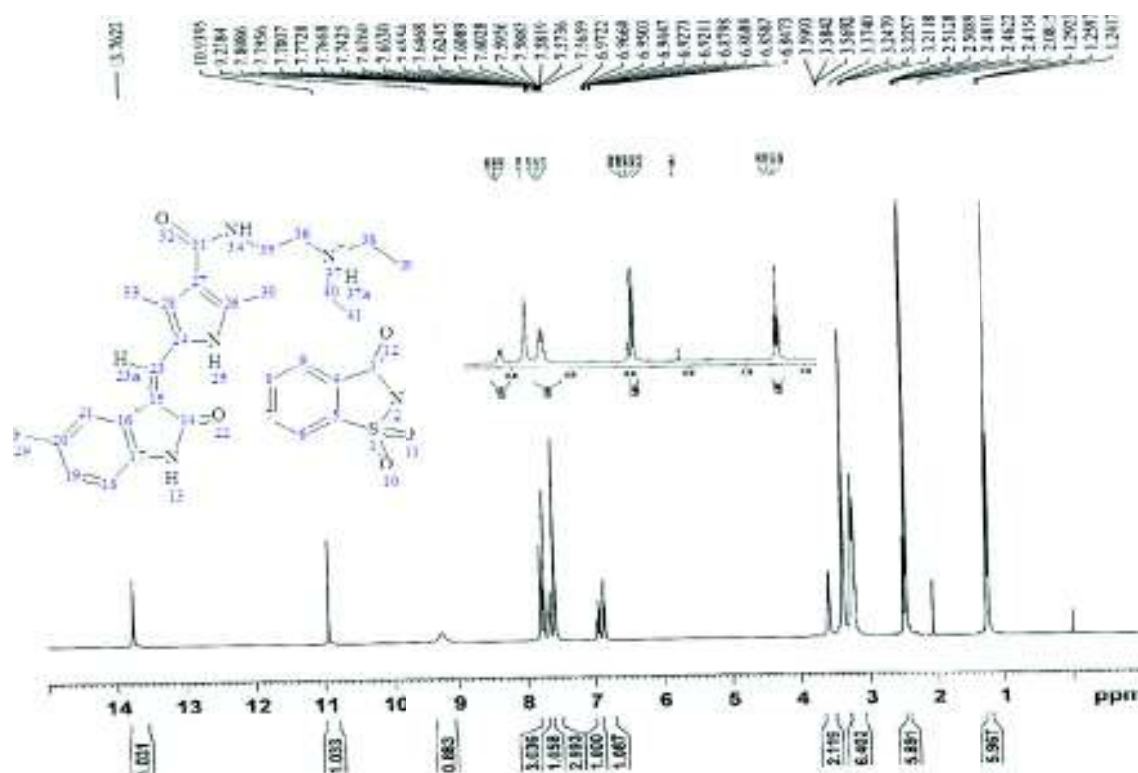


Figure S28: ^1H NMR spectrum of sunitinibsaccharate. The expansion of the region 1.21-4.0 is inserted for clarity

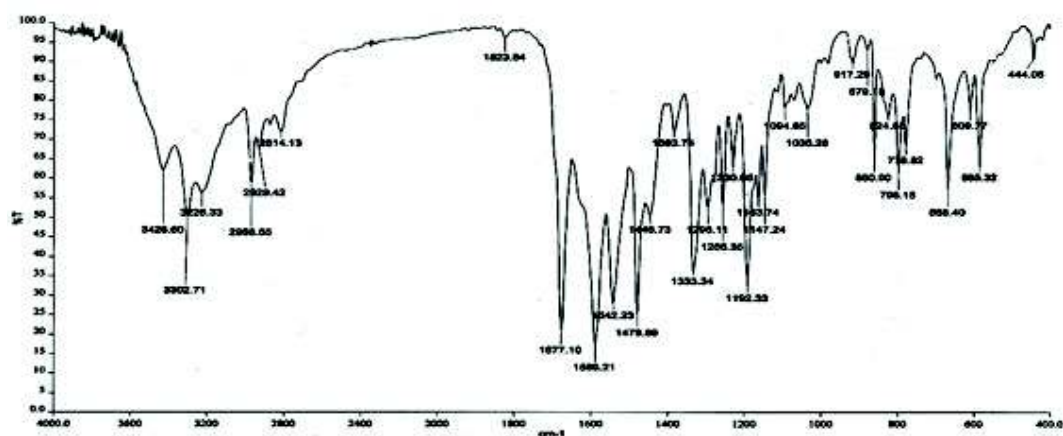
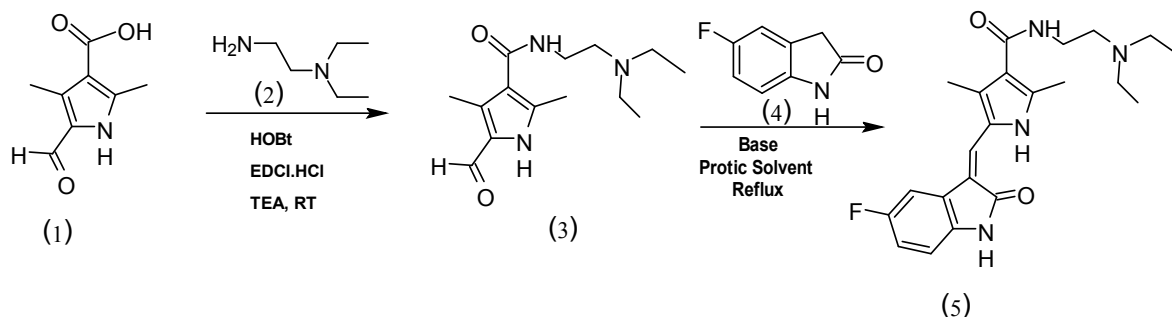
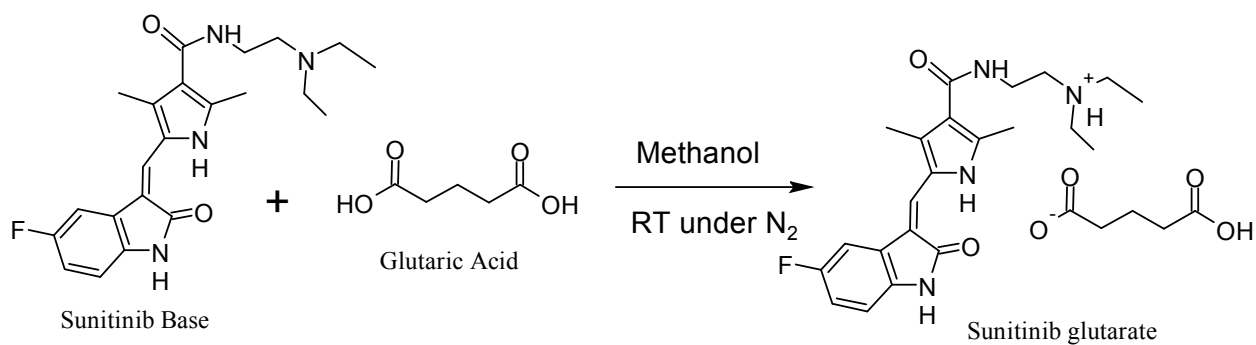


Figure S29: IR spectrum of sunitinibsaccharate

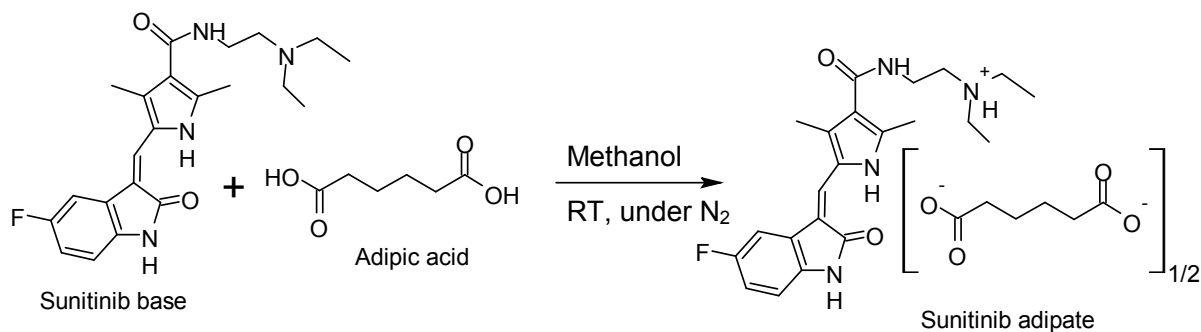
Sunitinibmanuscript original chem. draw file (Mole Files)



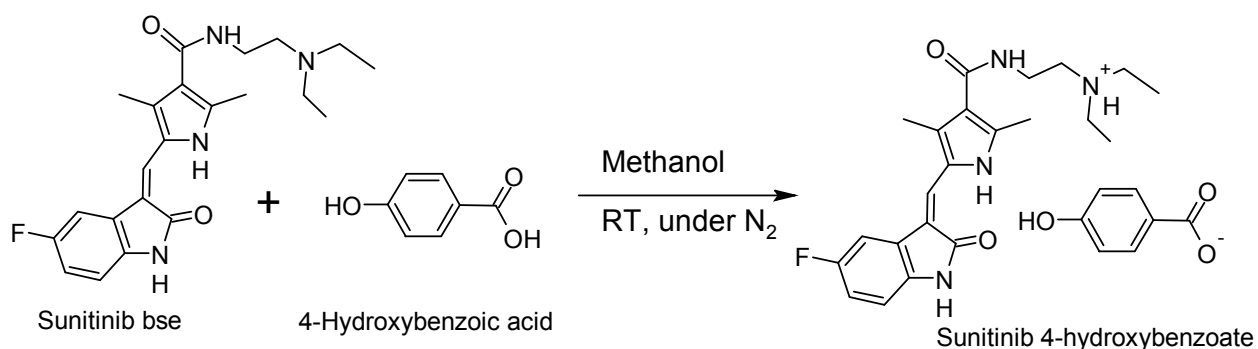
Sunitinibbase Synthetic Scheme



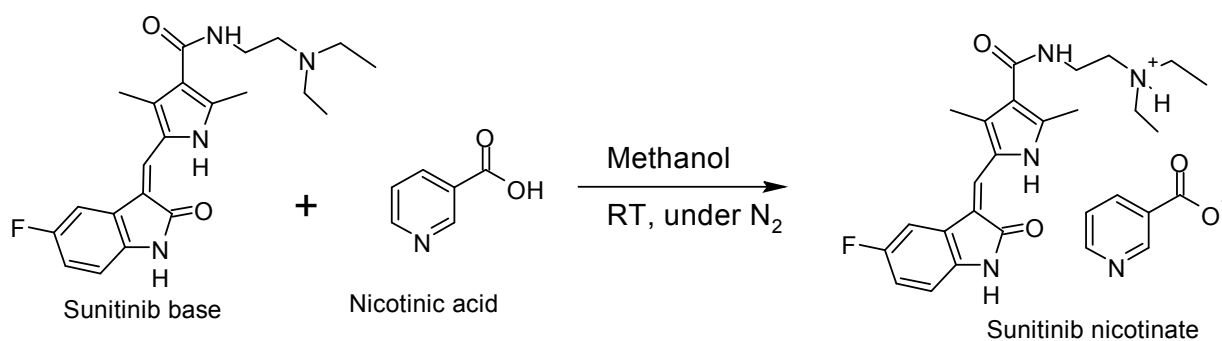
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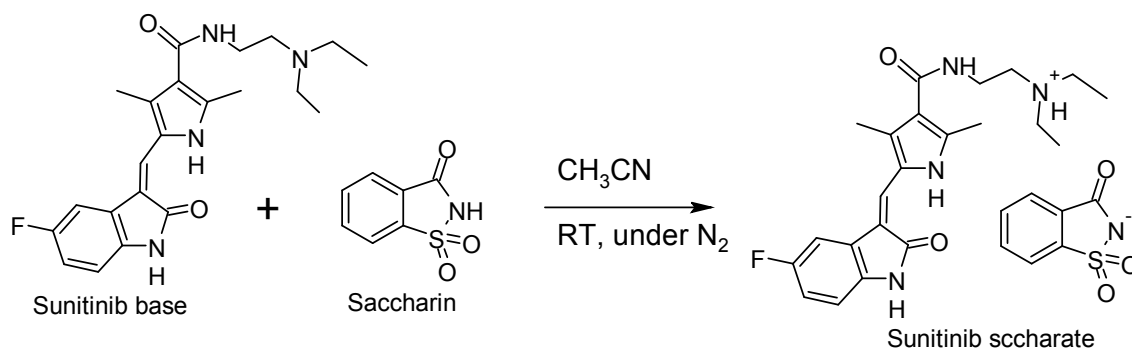
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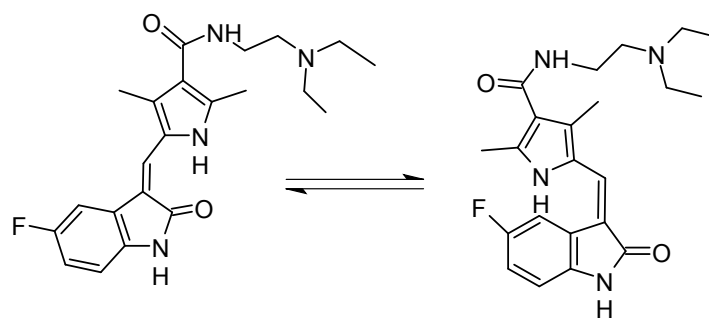
Sunitinib4-hydroxybenzoate Synthetic Scheme



SunitinibnicotinateSynthetic Scheme



SunitinibsaccharateSynthetic Scheme



Z-Isomer

E-Isomer

Z-E Isomerism in Sunitinib