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# Impurity Free and Scalable Process of Sorafenib Tosyalte: Hepatocellular Carcinoma

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An efficient, impurities free and scalable process of hepatocellular carcinoma and renal cell carcinoma of sorafenib tosylate with good quality and higher yield.

**Keywords: Scalable, Impurities free, Hepatocellular carcinoma, Sorafenib tosyalte.**

## INTRODUCTION

Sorafenib tosylate is well known drug used in treatment of certain types of hepatocellular carcinoma (a type of liver cancer), renal cell carcinoma (a type of kidney cancer) and thyroid cancer. Sorafenib tosylate blocks certain proteins, sorafenib tosyalte is an oral multikinase inhibitor cell surface tyrosinr kinase receptor [1-3] and has been used for advanced renal cell carcinoma, this is one type of kidney cancer, also used for liver cancer treatment [4]. Sorfenib mechanism involves by blocking the action of abnormal proteins, FDA approved this drug in carcinoma in year 2005 [5] and in hepatocellular carcinoma (HCC) in year 2007 [6]. Sorafenib tosylate therapy treats only a 3-month perfection in patients who have expected sorafenib tosylate as a drug compared to other drugs [7,8]. There are some patents, which report the synthesis of sorafenib tosylate, but in all the cases impurities have been observed [9-15].

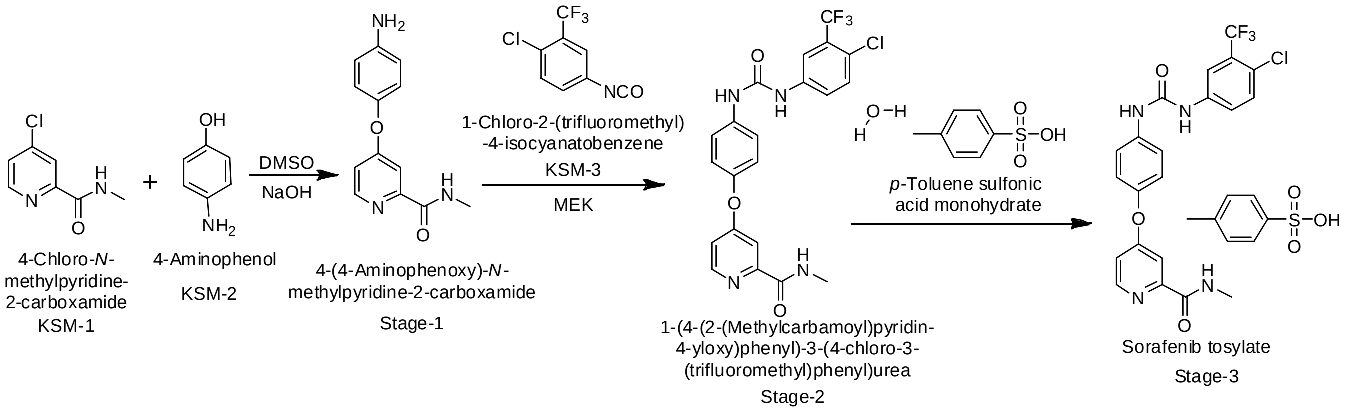
One of the typical literature reports that sorafenib tosylate can be synthesized by using 4-chloro-*N*-methyl-2-pyidine carboxamide (KSM-1, **Scheme-I**) as a starting material. Our main objective is to improve the yield, reduce the impurities and reduce the cost of the starting materials used for the synthesis of sorafenib tosylate. 4-Chloro-*N*-methyl-2-pyidine carboxamide (KSM-1) coupled with 4-aminophenol (KSM-2) by using NaOH in dimethyl sulfoxide (DMSO) to obtain stage-1 (71%). In the second step, stage-1 was coupled with 4-chloro-3-trifluoro methyl phenyl isocyanate (KSM-3) in the presence methyl ethyl ketone as solvent at 70-80 ºC to yield stage-2 (80%). In the third step, the reaction between stage-2 (sorafenib base) and *p*-toluene sulfonic acid monohydrate in methanol solvent at 40-50 ºC to stage-3 (sorafenib tosylate), yield (80%). (HPLC purity 99.9%).

Summing up, an improved bulk level synthesis of sorafenib tosylate with very good yield and excellent purity is attempted. Present method involves the use of easily handle reaction conversion of sorafenib tosylate in each and every step. This lowers costs and avoids the need to remove API impurities from the final product.

## EXPERIMENTAL

AR grade reagents and solvents were used without further purification. All the reactions were carried out in oven-dried flasks. IR spectra were recorded on Perkin-Elmer 1000 instrument (Sigma-Aldrich, India) in the KBr phase. Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz (Varian) spectrometer in suitable solvents using tetramethylsilane (TMS) as the internal standard or the solvent signals as secondary standards. The compound was also checked by high performance liquid chromatography (HPLC) for purity.

**Synthesis:** An initial convergent synthesis of sorfenib tosylate (**Scheme-I**) began with the commercially available 4-chloro-*N*-methyl-2-pyridine carboxamide (KSM-01), synthesis of 4-(4-aminophenoxy)-*N*-methylpyridine-2-carboxamide (stage-1) involves coupling with 4-aminophenol in presence of KOH in DMF solvent medium. However, this method compromise the product quality, therefore different solvents like



**Scheme-I:** Synthetic route

DMAC, DMSO, toluene, methanol (Table-1, entries 1-4) and base like NaOH, $K_2CO_3$ and DIPEA (Table-1, entries 11-13) were tried, based on the experimental data DMSO and NaOH taken in to for further studies, next we focused on dimer control like 4-aminophenol mol ratio 0.293, 0.366, 0.439, 0.527, 0.586 when 0.293 and 0.366 (Table-1, entries 6-10) mol ratio of 4-aminophenol were used, the yields were 61 and 65%, but the HPLC purity 98.10 and 98.57%.

However, 0.439, 0.527 and 0.586 mol ratio of 4-aminophenol gave yields almost similar 71.0, 70.5 and 71.5% with HPLC purity were 99.83, 99.80, 99.78% respectively. Based on the above experimental data, 0.439 mol equivalent of 4-aminophenol was taken for further studies. Next, we focused on different reaction temperature like 25-35, 40-50, 50-60, 60-70, 70-80, 80-90 and 90-100 ºC and different interval period of time like 1-2, 2-3, 3-4 and 5-6 and 24 h (Table-1, entries 17-20). Based on the results, it was observed that at 70-80 ºC for 2-3 h gave 71% yield and 99.83% purity of 4-(4-aminophenoxy)-*N*-methylpyridine-2-carboxamide (stage-1) and above time and temperature the yield and purity were almost similar. Therefore, we fixed to 80-85 ºC for 3-4 h during the reaction for desired yield and purity achieved. We include the workup process like toluene and 10% NaOH, water and DCM:hexane to increase the colour of the product and quality.

Conversation of 4-(4-aminophenoxy)-*N*-methylpyridine-2-carboxamide (stage-2) to 1-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea in the presence of methyl ethyl ketone using 4-chloro-3-trifluoro methyl phenyl isocyanate (KSM-3). Initially, we screened the effect of solvents like toluene, methyl ethyl ketone, dichloromethane (Table-2, entries 1-4). The methanol reaction conversion monitor by TLC based on TLC methyl ethyl ketone as a solvents provided more efficient and clean reaction. We also performed the experiments by different mole equivalents of KSM-3 (1.0, 1.2, 1.5 1.7 and 1.9). The results showed the yields 70.5 and 75.4% and HPLC purities 90.7 and 96.5% with 1.0

TABLE-1
OPTIMIZATION CONDITIONS FOR THE SYNTHESIS OF STAGE-1

| Entry[a] | Solvent | KSM-2 mole ratio | Different base | Base mole ratio | Temp. (°C)/ Time (h) | Yield[b] (%) | Purity (%) |
|---|---|---|---|---|---|---|---|
| 1 | DMF | 0.439 | NaOH | 0.58 | 70-80/2-3 | 60.0 | 97.7% |
| 2 | DMAC | 0.439 | NaOH | 0.58 | 70-80/2-3 | 63.0 | 95.0 |
| 3 | Toluene | 0.439 | NaOH | 0.58 | 70-80/2-3 | 72.0 | 50.0 |
| 4 | Methanol | 0.439 | NaOH | 0.58 | 70-80/2-3 | 50.0 | 30.0 |
| 5 | DMSO | 0.439 | NaOH | 0.58 | 70-80/2-3 | 71.0 | 99.83 |
| 6 | DMSO | 0.293 | NaOH | 0.58 | 70-80/2-3 | 61.0 | 98.10 |
| 7 | DMSO | 0.366 | NaOH | 0.58 | 70-80/2-3 | 65.0 | 98.5 |
| 8 | DMSO | 0.439 | NaOH | 0.58 | 70-80/2-3 | 71.0 | 99.83 |
| 9 | DMSO | 0.527 | NaOH | 0.58 | 70-80/2-3 | 70.5 | 99.80 |
| 10 | DMSO | 0.586 | NaOH | 0.58 | 70-80/2-3 | 71.5 | 99.78 |
| 11 | DMSO | 0.439 | KOH | 0.43 | 70-80/2-3 | 62.0 | 98.2 |
| 12 | DMSO | 0.439 | $K_2CO_3$ | 0.43 | 70-80/2-3 | 70.0 | 42.3 |
| 13 | DMSO | 0.439 | DIPEA | 0.43 | 70-80/2-3 | 72.0 | 25.7 |
| 14 | DMSO | 0.439 | NaOH | 0.43 | 70-80/2-3 | 71.2 | 99.80 |
| 15 | DMSO | 0.439 | NaOH | 0.29 | 70-80/2-3 | 65.0 | 95.20 |
| 16 | DMSO | 0.439 | NaOH | 0.11 | 70-80/2-3 | 70.5 | 99.83 |
| 17 | DMSO | 0.439 | NaOH | 0.58 | 60-70/2-3 | 68.3 | 99.28 |
| 18 | DMSO | 0.439 | NaOH | 0.58 | 80-90/2-3 | 71.0 | 99.80 |
| 19 | DMSO | 0.439 | NaOH | 0.58 | 70-80/3-4 | 71.5 | 99.82 |
| 20 | DMSO | 0.439 | NaOH | 0.58 | 70-80/1-2 | 65.5 | 75.0 |

[a]Reaction conditions: 4-Chloro-*N*-methyl-2-pyidine carboxamide (KSM-01), 4-aminophenol (KSM-2), sodium hydroxide (NaOH) and DMSO solvent. [b]Yields of isolated products.

TABLE-2
OPTIMIZATION CONDITIONS FOR
THE SYNTHESIS OF STAGE-2

| Entry[a] | Solvent | KSM-3 mole equivalent | Temp. (°C)/ Time (h) | Yield[b] (%) | Purity (%) |
|---|---|---|---|---|---|
| 1 | Toluene | 1.5 | 70-80/5-6 | 70.0 | 85.17% |
| 2 | MEK | 1.5 | 70-80/5-6 | 80.0 | 99.89 |
| 3 | DCM | 1.5 | 70-80/5-6 | 73.0 | 97.5 |
| 4 | Methanol | 1.5 | 70-80/5-6 | 50.0 | 70.80 |
| 5 | MEK | 1.0 | 70-80/5-6 | 70.5 | 90.71 |
| 6 | MEK | 1.2 | 70-80/5-6 | 75.4 | 96.5 |
| 7 | MEK | 1.5 | 70-80/5-6 | 78.0 | 99.95 |
| 8 | MEK | 1.7 | 70-80/5-6 | 80.0 | 99.80 |
| 9 | MEK | 1.9 | 70-80/5-6 | 80.5 | 99.91 |
| 10 | MEK | 1.5 | 70-80/2-3 | 71.5 | 99.28 |
| 11 | MEK | 1.5 | 70-80/3-4 | 62.0 | 98.2 |
| 12 | MEK | 1.5 | 70-80/5-6 | 80.10 | 99.90 |
| 13 | MEK | 1.5 | 70-80/6-8 | 80.0 | 99.85 |
| 14 | MEK | 1.5 | 70-80/9-10 | 80.2 | 99.93 |
| 15 | MEK | 1.5 | 25-35/6-8 | 80.0 | 90.20 |
| 16 | MEK | 1.5 | 60-70/6-8 | 80.0 | 97.10 |
| 17 | MEK | 1.5 | 70-80/6-8 | 80.5 | 99.05 |
| 18 | MEK | 1.5 | 80-90/6-8 | 81.0 | 99.10 |

[a]Reaction conditions: 4-(4-Aminophenoxy)-*N*-methyl picolinamide (stage-1), 4-chloro-3-trifluoro methyl phenyl isocyanate (KSM-3) in methyl ethyl ketone (MEK) solvent. [b]Yields of isolated products.

and 1.2 mol equivalents of 4-chloro-3-trifluoro methyl phenyl isocyanate. Moreover, we also tried with 1.5, 1.7 and 1.9 equivalents of KSM-3, the result indicated 78, 80, 80.5 of yields with purity wise all most similar like 99.95, 99.80, 99.91% (Table-2, entries 5-9), based the above result 1.5 mol equivalent of KSM-3 was taken for further studies.

Further, the effect of reaction temperature (25-35, 60-70, 70-80 and 80-90 ºC) (Table-2, entries 15-18) on product yield was evaluated and found that 70-80 ºC led to better yield and purity. Further, the effect of time like 2-3, 3-4, 5-6, 6-8 and 9-10 h (Table-2, entries 10-14) on the course of the reaction, 6-8 h time gave highest yield and purity.

After the successful formation of stage-2, next stage is tosylated salt formation, after optimization of this stage, it was observed that no critical on this stage, mainly equivalence *p*-toluene sulfonic acid (PTSA), suitable solvent and temperature and time play a major role in the formation of sorafenib tosylate. During the study, it was found that PTSA mol equivalence like 1.0, 1.1 and 1.2, it is observed that 1.1 mol equivalence of PTSA get better salt formation. Consequently, different solvents were tested the preparation of salt formation like methanol, DCM, isopropyl alcohol and acetone, it is observed that gave better yield and quality in methanol solvents, In this stage, HPLC not critical only tosylated salt formation only main aim because sorafenib base meet the purity in specification.

**Stage-1: (4-(4-Aminophenoxy)-*N*-methylpyridine-2-carboxamide):** A NaOH (23.0 g, 0.58 mol) was placed in (250 mL, 5 vol.), DMSO was added at 25-30 ºC. Stirred for 10-20 min under nitrogen and 4-aminophenol (47.91 g, 0.439 mol) was added at 25-30 ºC and maintained for 10-20 min, 4-chloro-*N*-methyl-2-pyidine carboxamide (50.0 g, 0.293 mol) was added and heated to 80-85 ºC for 3-4 h. After completion of the reaction, cooled to 20-35 ºC, to this water (750 mL, 15 vol.) was added slowly and the reaction mixture was stirred at room temperature for 30-60 min. Charge toluene lot-1 (1000 mL, 10 vol.) at 25-35 ºC, heated the mass to 60-65 ºC then stirred for 20 min, separate the layers at 50-60 ºC. Organic layer kept aside at 50-60 ºC, taken aq. layer & toluene lot-2 (500 mL, 5 vol.) at 25-35 ºC, heated the mass to 60-65 ºC then stirred for 20 min, separate the layers at 60-65 ºC. Combined total organic layers, organic layer and distilled water lot-2 (500 mL) at 60-65 ºC, stirred for 10-20 min at 60-65 ºC, separate the layers at 60-65 ºC, charge carbon to the organic layer at 60-65 ºC, stirred the mass for 10-15 min at 60-65 ºC then filtered the mass through high-flown bed and washed the bed with hot toluene lot-3. Distilled off the toluene under vacuum at 60-65 ºC up to 2-5 volumes remains in reactor and cooled the mass to 25-35 ºC, charge hexane lot-1 (500 mL) to the reaction mass at 25-35 ºC and stirred the mass for 30-40 min at 25-35 ºC, filtered the mass and wash with hexane lot-2 (100 mL) under vacuum, taken wet material and DCM lot-1 (1000 mL, 10 vol.) and stirred the mass for 10-15 min at 25-35 ºC, charge 10% aq. NaOH (500 mL, 5 vol.) solution lot-1 at 25-35 ºC, stirred the mass for 20 min at 25-35 ºC. Separated the organic layers, charged organic layer and water lot-4 (500 mL, 5 vol.) at 25-35 ºC, stirred the mass for 15-20 min at 25-35 ºC then separated the organic layers dry with sodium sulphate, distilled off DCM under vacuum at 40 ºC up to 5 V remains in the round bottom flask then cooled the mass to 25-35 ºC, charged hexane lot-3 (500 mL, 5 vol.) to the mass at 25-35 ºC, stirred the mass for 60-90 min at 25-35 min then filtered the mass and wash with hexane lot-4 (100 mL, 2 vol.), dry the material at 50-60 ºC for 10-12 h to give (50.0 g) of stage-1. The yield was 71.0 with 99.0% purity. Description: off white colour powder, HPLC: 99.83 Mass: (*m/z*): 244.17(M+H peak). IR (KBr, $cm^{-1}$): 3339.05, 3015.11, 1658.97, 1241.66, 1151.16, $^1$H NMR (400 MHz, DMSO) δ: 8.715-8.749 (q, 1H), 8.440-8.454 (d, 1H), 7.332-7.339 (d, 1H), 7.054-7.075 (q, 1H), 6.849-6.871 (m, 2H), 6.632-6.654 (m, 2H), 5.174 (s, 2H), 2.771-2.783 (d, 3H). $^{13}$C NMR (100 MHz, DMSO) δ: 166.78, 163.91, 152.27, 150.10, 146.85, 142.85, 121.57, 114.89, 113.64, 108.35, 108.35.

**Stage-2: 1-(4-(2-(Methylcarbamoyl)pyridin-4-yloxy)-phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea:** Methyl ethyl ketone (150 mL, 15 vol.) and 4-(4-aminophenoxy)-*N*-methyl picolinamide (stage-1, 30 g, 0.123 mol) were placed in a suitable round bottomed flask, stirred the mass for up to formation of clear solution at 25-35 ºC, slowly added 4-chloro-3-trifluoromethyl phenyl isocyanate (KSM-3) (40.92 g, 0.185 mol) for about 10-20 min at 25-35 ºC. The reaction mixture was heated to 70-80 ºC and maintained for 6-8 h. After completion of the reaction by confirmation of TLC the mixture was cooled to 25-35 ºC and stirred for 30-60 min filtered the mass washed with toluene (150 mL, 15 vol.) at 25-35 ºC. Taken methyl ethyl ketone (1500 mL 15 volumes) and crude material heated the reaction mass to 50-55 ºC. Stirred the reaction mass for 30 min at 50-55 ºC. Charge activated carbon (5.0 g) at 50-55 ºC and stirred it for 10-15 min at 60-65 ºC. Filtered the reaction mass through high flow bed. Washed with hot methyl ethyl ketone (60 mL, 2 vol.), distilled off solvent under vacuum at

50-55 ºC up to 2-4 volumes remains in flask then reaction mass cooled to 25-35 ºC. Charge toluene (150 mL) at 25-35 ºC. Stirred for 30 min at 25-35 ºC. Filtered the product and washed with toluene (60 mL). Dried the product under vacuum at 50-55 ºC for 10-15 h to give (46 g) stage-2. The yield was 80.0% with 99.0% purity. Description: white colour powder, HPLC: 99.95; IR (KBr, cm$^{-1}$): 3338.07, 3078.89, 1645.88, 1258.99, 1151.16; $^1$H NMR (400 MHz, DMSO): δ 2.778-2.790 (d, 3H); 7.140-7.186 (q, 1H), 7.170-7.188 (d, 2H); 7.375-7.381 (d, 2H); 7.581-7.630 (m, 2H), 8.118-8.123 (d, 1H); 8.497-8.511 (d, 1H); 8.750-8.785 (q, 1H), 8.994 (s, 1H), 9.211 (s, 1H,). $^{13}$C NMR (100 MHz, DMSO): δ 165.96, 163.79, 152.46, 152.49, 150.32, 147.83, 139.32, 137.06, 131.95, 127.189-126.27, 124.17, 123.06, 122.35 121.44, 120.49, 116.902-116.73, 113.98, 108.67, 25.98. Mass: (*m/z*) 465.31 (M+H peak).

**Stage-3: Sorafenib tosylate:** Stage-2 compound (10.0 g, 0.0215 mol) was dissolved in methanol (100.0 mL) at 25-35 ºC and stirred for 15-30 min, added PTSA into the reaction mass and heated to 40-50 ºC, stirred the mass for 5-6 h. Filtered and washed with methanol (20 mL). Dried the material at 50-55 ºC for 10-12 h to give 11.0 g of sorafenib tosylate. The yield was 80% with 99.90% purity. Description: white colour powder, HPLC: 99.80. IR (KBr, cm$^{-1}$): 3388.62, 3289.49, 3256.86, 3080.41, 2936.59, 1723.69, 1689.31, 1505.96, 1418.73, 1256.45, 637.18 (M), $^1$H NMR (400 MHz, DMSO): δ 2.288 (s, 3H), 2.821 (d, 3H), 10.740 (bs, 1H,) 7.142-7.217 (d, 2H,), 7.191-7.208 (d, 2H), 7.222-7.237 (d, 1H), 7.662-7.669 (d, 2H), 7.539-7.559 (d, 1H), 7.631-7.654 (d, 3H), 8.139-8.133 (d, 1H), 8.591-8.576 (d, 1H); 9.071-9.059 (d, 1H), 9.467 (s, 1H), 9.289 (s, 1H). $^{13}$C NMR (100 MHz, DMSO): δ 168.17, 161.68, 152.46, 149.37, 148.18, 147.29, 144.65, 139.47, 138.38, 137.73, 132.02, 128.35, 127.17-126.26, 125.49, 124.20, 122.99, 122.31, 121.37, 120.38, 116.79-116.63, 114.478, 110.048, 26.252, 20.80. Mass: (*m/z*) 637.18 (M+H peak).

## RESULTS AND DISCUSSION

Each and every stage of compounds in synthetic sequence of the synthesis of sorafenib tosylate was confirmed and characterized by spectral studies. The IR spectrum shows characteristics peaks at the range of above 3000 cm$^{-1}$ (3388.62, 3289.49, 3256.86, 3080.41 cm$^{-1}$), which responsible for the functional groups of sulfate –OH and secondary –NH groups of sorafenib tosylate. Amide (C=O) shows characteristic peak at 1689 cm$^{-1}$ and sulfone (S=O) shows at 1418 and 1505 cm$^{-1}$. $^1$H NMR spectrum of sorafenib tosylate shows singlet at δ 2.28 ppm represent aromatic attached (benzyl) -$CH_3$ protons and doublet at δ 2.81 ppm which response to –NH– attached –$CH_3$ protons, remaining all $sp^2$ protons appeared at the range of δ 7.1-9.4 ppm. $^{13}$C NMR spectrum of sorafenib tosylate shows benzyl carbon at δ 20.80 ppm and –NH- attached carbon appeared at δ 26.25 ppm, $sp^2$ carbons appeared in between the range of δ 110-149 ppm. Mass spectrum also shows *m/z* peak at 637.18 (M+H).

## Conclusion

In conclusion, an efficient, impurity free and scalable (bulk) process for the synthesis of sorafenib tosylate with good yield (80%) and excellent purity (99.90%). The main features and advantages of the present method is easily handle reaction conversion of sorafenib tosylate in each and every step.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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