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# Development of an efficient chemo-enzymatic process for the synthesis of Nilotinib

Sagar Narayan Tarate[1,2,3†], Saurav Subhash Gite[1†], Ravinder Reddy Patlolla[1,2], Kethavath Anjali Priya Naik[1,2], Kethavath Santhosh Nayak[1,2], KRS Sambasiva Rao[4] & Linga Banoth[1,2]*

[1]Department of Energy & Environmental Engg. Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, Telangana, India

[2]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201 002, Uttar Pradesh, India

[3]API- R&D, Cipla Ltd., Mumbai-400 013, Maharashtra, India

[4]School of Pharmacy, Dr. RVR NRI Institute of Technology Deemed to be University, Pothavarappadu (V), Agiripalli (M), Vijayawada Rural-521 212, Andhra Pradesh, India

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Nilotinib is one of the important second-generation tyrosine kinase inhibitors used in the treatment of chronic myeloid leukemia. The synthesis of Nilotinib involves expensive intermediates like carboxylic acids. Traditional methods of such intermediates involve chemical hydrolysis using acids or bases, leading to the formation of toxic compounds and high consumption of energy. This study focused on the development of a green and economical chemo-enzymatic approach to nilotinib synthesis by making use of a nitrilase biocatalyst. In this study, thirteen nitrilases were screened for their ability to produce carboxylic acid from nitrile, an intermediate of nilotinib under mildly buffered aqueous medium, and NIT-EW 101 was found to be the best enzyme. Time course study of this enzyme showed that 99.37% of the reaction was complete after 48 h. The isolated acid intermediate was then used to synthesize nilotinib by using the Curtius rearrangement and amide coupling. This route offers a sustainable and industry-feasible alternative to the conventional synthesis of Nilotinib.

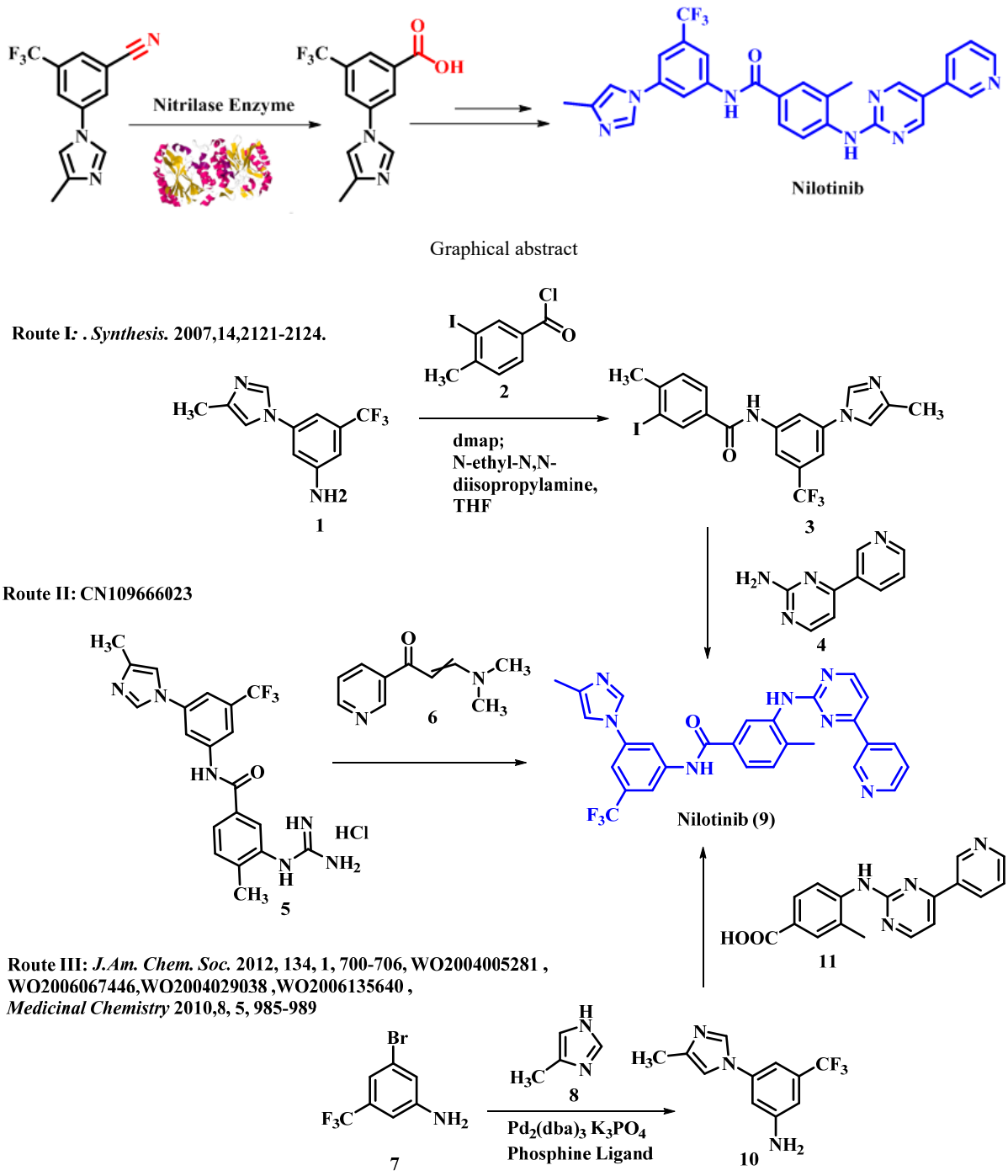
**Keywords**: Biocatalysis, Green Chemistry, Nilotinib, Nitrilase, Sustainable manufacturing

Nilotinib is an oral synthetic aminopyridine drug that acts as a specific second-generation tyrosine kinase inhibitor (TKI)[1]. It is mainly prescribed for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) at chronic and accelerated stages of the disease among people resistant or intolerant to other treatments, like imatinib[2]. While its primary role is in oncology, recent systematic reviews have explored nilotinib as a potential treatment for Parkinson's disease due to its ability to inhibit the cellular Abelson tyrosine kinase (c-Abl), a protein implicated in neurodegenerative progression[3,4]. The synthesis of nilotinib is critical because it offers a significantly improved therapeutic profile over first-generation drugs like imatinib, with inhibitory potency 20 to 50 times higher against sensitive CML cell lines[2].

There are three previously reported approaches for the synthesis of Nilotinib (Scheme 1). In the first route, synthesis begins with the acylation of the amino-substituted heteroaromatic precursor 1 with acid chloride 2 in THF, using DMAP and N-ethyl-N, N-diisopropylamine, affording the corresponding amide intermediate 3. This activated amide then undergoes nucleophilic substitution with heterocyclic amine 4, forming the corresponding Nilotinib core structure[5] (Route 1). In the second route, intermediate 5 reacts with the activated enone reagent 6 under standard condensation conditions as described in CN109666023. Subsequent cyclisation and coupling steps lead to the yield of Nilotinib[6] (Route 2). In the third route, the synthesis of Nilotinib is completed by coupling intermediate 10, obtained from the Pd-catalyzed C–N/C–C bond formation between aryl bromide 7 and imidazole 8. The carboxylic acid 11 is activated under standard amide-bond-forming conditions and reacts with the amino functionality of intermediate 10 to give the final Nilotinib 9[7-12] (Route 3).

Conventional industrial chemical routes for converting nitrile intermediates into high-value acids

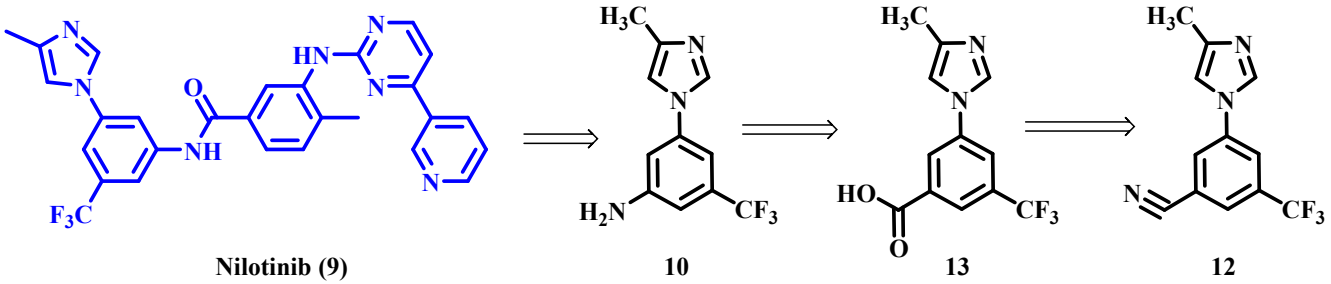
†Equal Contribution
*Correspondence:
E-mail: linga@csiriict.in




Graphical abstract

Scheme 1 — Various synthetic approaches to Nilotinib

typically require strongly acidic or basic media, entail high energy expenditure, and often generate toxic by-products. Developing new chemo-enzymatic pathways is crucial for overcoming the inherent disadvantages of traditional chemical synthesis, as they utilize enzymes that operate under mild reaction conditions and are environmentally sustainable. Enzymes are highly specific biological catalysts and are valuable tools in modern synthetic chemistry and pharmaceutical manufacturing. Advances in protein engineering and enzyme discovery have significantly expanded their industrial applications[13-15].




Scheme 2 — Proposed method for synthesis of Nilotinib

Among industrial enzymes, hydrolases such as lipases, proteases, epoxide hydrolases, and nitrilases are particularly important because they catalyse hydrolytic reactions without requiring expensive cofactors[16-18]. Nitrilases (EC 3.5.5.1) catalyse the direct conversion of nitriles into carboxylic acids and ammonia in a single step, providing an efficient and environmentally friendly alternative to conventional chemical hydrolysis[19]. In addition, nitrilase-mediated biotransformation supports green chemistry principles due to their biodegradability and operation in aqueous media under sustainable reaction conditions[20-22].

In this study, we report a sustainable and cost-effective synthetic route for the industrial production of nilotinib 9. The synthesis initiates with the nitrilase-mediated enzymatic hydrolysis of the nitrile intermediate 12 to selectively transform the –CN group into the corresponding carboxylic acid 13. Subsequent Curtius rearrangement of 13 yields the aniline derivative 10, which undergoes amide bond formation with 3-methyl-4-((5-(pyridine-3-yl)pyrimidin-2-yl)amino)benzoic acid 11 to form the target molecule, nilotinib (Scheme 2).

## Materials and Methods

### Reagents

3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) benzoic acid and 3-methyl-4-((5-(pyridine-3-yl) pyrimidin-2-yl) amino) benzoic acid was used as the primary starting materials in both synthetic steps. Diphenyl phosphoryl azide (DPPA) and thionyl chloride served as the acyl azide transfer reagent and acid-activating agent, respectively. Triethylamine (TEA) and aqueous ammonia solution were employed as base reagents for proton neutralization and pH adjustment at different stages of the synthesis. tert-Butanol and N-methylpyrrolidone (NMP) functioned as the principal reaction solvents in the Curtius rearrangement and amide coupling steps, respectively. Ethyl acetate, methanol, acetone, and methyl tert-butyl ether (MTBE) were used as auxiliary solvents for extraction, washing, precipitation, and purification purposes. Purified water was used for all aqueous workup procedures.

### Analysis

Bruker spectrometers (400 or 500 MHz) used for $^{1}H$ and $^{13}C$ NMR. Samples (≈5 mg) were dissolved in $CDCl_3$ (550 µL), and spectra were acquired at 25 °C. The progress of the reaction was monitored using thin-layer chromatography (TLC) on precoated silica gel plates (Merck), and the product was purified by column chromatography using 100-200 mesh silica gel (SRL). A rotary evaporator was used to remove solvents under vacuum. To confirm the product's identity, high-resolution mass spectra were collected on an Orbitrap or a Q-STAR XL mass spectrometer (Thermo Scientific Exactive™). The enzymatic reaction conversion was measured using an HPLC system with a C18 column (150 × 4.6 mm, 5 µm) at a flow rate of 0.8 mL $min^{-1}$. For this analysis, a gradient system was used. Mobile phase-A was a 95:5 volume ratio of 20 mM potassium dihydrogen phosphate buffer (pH 3.5) and acetonitrile, and mobile phase-B was an 80:20 volume ratio of acetonitrile and water.

### Preparation of 3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) benzoic acid (13)

0.1 M potassium phosphate buffer (500mL, pH 8.0) was mixed with 5 g each of EDTA and DTT, and the solution was stirred for 30 minutes. Next, 15 g of nitrilase enzyme was added, and the mixture was stirred for another 30 minutes. A solution containing 100 g of nitrile 12 dissolved in 200 mL of DMSO was then introduced, and the entire mixture was shaken at 25-30 °C and 250 rpm for 24 h while progress was monitored using TLC. Once the reaction was complete, the mixture was filtered, and the resulting liquid was acidified with dilute HCl to precipitate the product. Finally, the suspended

mixture was cooled, stirred for 2 hours, filtered, and the remaining solid was dried under vacuum to give the final product in a 90% yield (96.83 g). $^{1}$H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 8.53 (d, *J* = 25.8 Hz, 2H), 8.25 (d, *J* = 36.9 Hz, 2H), 2.36 (s, 3H).$^{13}$C NMR (101 MHz, DMSO) δ 165.4, 136.8, 135.1, 134.5, 131.6, 131.3, 126.8, 126.3, 124.8, 123.6, 117.9, 10.3. HRMS (m/z): [M]+calcd for $C_{12}H_{10}F_3N_2O_2$, 271.0694; found, 271.0705.

**Synthesis of 3-(4-methyl-1h-imidazol-1-yl)-5-(trifluoromethyl) aniline (10)**

The target compound 3-(4-methyl-1h-imidazol-1-yl)-5-(trifluoromethyl) aniline was synthesized from 3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) benzoic acid using a Curtius rearrangement. Under a nitrogen atmosphere at 25-35 °C, a round-bottom flask was filled with 5 mL of tert-butanol, followed by the sequential addition of the starting compound benzoic acid (1.0 g, 3.71 mmol), diphenyl phosphoryl azide (1.3 g, 4.72 mmol), and triethylamine (0.9 mL, 6.42 mmol). The mixture was heated and stirred at 80-85 °C for 2 hours, with reaction progress monitored by TLC until the starting material was completely consumed. After cooling the mixture back to 25-35 °C, it was filtered, and the collected solid was washed with 5 mL of ethyl acetate. The combined liquid portion was concentrated under vacuum below 45 °C and then cooled to 30-35 °C. This residue was dissolved in 20 mL of water and 15 mL of ethyl acetate, and the aqueous layer was then extracted with ethyl acetate (20 mL × 3). Then the combined organic layers were concentrated under vacuum. The crystals were generated by stirring the crude product in 5 mL of MTBE at room temperature (RT). The resulting white solid was collected by filtration, washed with 2 mL of MTBE, and dried under vacuum at 35-40 °C to give a final mass of 0.6 g. $^{1}$H NMR (400 MHz, DMSO) δ 9.58 (s, 1H), 7.97 – 7.94 (m, 1H), 7.22 – 7.13 (m, 1H), 7.06 – 7.01 (m, 2H), 2.35 (s, 3H).$^{13}$C NMR (101 MHz, DMSO) δ 136.9, 134.2, 131.9, 131.6, 130.8, 130.2, 120.41 (d, *J* = 5.0 Hz), 117.9, 10.1. HRMS (*m/z*): [M]+ Calculated for $C_{11}H_{11}F_3N_3$, 242.0905; found 242.0910.

**Synthesis of 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) phenyl)-3-((4-(pyridin-3-yl) pyrimidin-2-yl) amino) benzamide (9)**

In order to synthesise 9, compound 11 (0.8 g, 2.61 mmol) was added in 10 mL of N-Methylpyrrolidine in an RB flask under an inert $N_2$ environment. The mixture was then cooled to 5 °C, and $SOCl_2$ (0.7 g, 5.88 mmol) was added dropwise to the corresponding acid of 11 to form the acyl chloride intermediate. Then the mixture was slowly warmed to RT and stirred for 2 h to check the complete activation. Further, a separate solution of compound 10 (600 mg, 2.50 mmol) in 2 mL of N-methylpyrrolidine was added slowly under a nitrogen atmosphere, and the mixture was stirred at RT for 3 h. Completion of the reaction was checked by TLC. After completion, 10 mL of acetone was added, and the mixture was stirred for another 3 h to precipitate the product. The resulting cream-coloured crude solid (1.2 g) was filtered, washed with 5 mL of acetone, and dried under vacuum. To convert the compound into its free base form, the 1.2 g of solid was mixed in 12 mL of methanol, and aqueous ammonia was added slowly until the pH reached 8. The compound mixture was stirred for 1 h to get complete neutralisation, and then the resulting solid was filtered, washed with 4 mL of methanol, and dried under vacuum to get nilotinib (0.9 g). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 9.34 (d, *J* = 1.6 Hz, 1H), 8.89 (d, *J* = 1.6 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.57 (d, *J* = 5.2 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.28 (d, *J* = 16.5 Hz, 2H), 7.88 (d, *J* = 1.3 Hz, 1H), 7.76 (s, 1H), 7.62 – 7.56 (m, 1H), 7.46 – 7.34 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 2H), 2.47 (s, 3H), 2.31 (s, 3H).$^{13}$C NMR (126 MHz, DMSO) δ 173.6, 166.1, 162.1, 161.5, 160.0, 151.9, 148.6, 141.8, 139.2, 138.7, 138.5, 137.3, 135.4, 134.7, 132.5, 132.2, 131.5 – 130.4, 131.5 – 130.7, 131.7 – 130.7, 124.7, 124.1, 115.4, 114.7, 112.0, 108.4, 72.6, 18.7, 13.9.HRMS (m/z): [M]+calcd for $C_{28}H_{23}F_3N_7O$, 530.1916; found, 530.1937.

## Results and Discussion

**Enzyme screening**

The biocatalytic hydrolysis of 12 to the corresponding carboxylic acid 13 was investigated using a panel of thirteen commercially available nitrilases (NIT-EW101 to NIT-EW113). Initial screening experiments were performed under standardized conditions to evaluate enzyme efficiency and selectivity.

The reactions were carried out in potassium phosphate buffer (0.1 M, pH 8.0) supplemented with Ethylenediaminetetraacetic acid (EDTA) (as a protease inhibitor) and Dithiothreitol (DTT), which served as both an antioxidant and a stabilising agent for sulfhydryl-containing enzymes. The addition of DTT was found to be important for preserving enzyme activity, possibly by preventing oxidative

deactivation of active-site cysteine residues. The substrate was introduced as a DMSO solution in a dropwise method to decrease potential enzyme inhibition due to high local substrate concentration or solvent effects.

Depending on the experimental conditions (concentration of substrate: 0.2 mM, temperature: ambient, reaction time: 24 h), various conversion levels were observed among the enzyme samples, suggesting differences in substrate affinity and efficiency among the nitrilase enzymes. From the screened enzymes, NIT-EW101 proved to be a better enzyme, achieving the maximum conversion (66.11%) to carboxylic acid 13.

There were no by-products generated due to the formation of amides in the reaction process, implying that the nitrilases used for this process do not produce amides but rather prefer nitrile hydrolysis directly to acids. The general mechanism of nitrilases usually requires the involvement of a catalytic triad (Cys-Glu-Lys), where the nucleophilic cysteine acts on the carbon atom of the nitrile compound to produce a thioimidate complex, which is further hydrated twice to release ammonia and finally produce the acid[23,24].

The reaction under an inert $N_2$ environment further improved the enzyme stability by minimising oxidative degradation. Low levels of organic solvents, particularly DMSO, were compatible with the biocatalysts and provided termination of the poorly water-soluble substrate while maintaining high catalytic efficiency. These results highlight the effectiveness of the enzymatic system for transforming the nitrile substrate into its corresponding carboxylic acid. Among all the tested enzymes, NIT-101 exhibited excellent performance and signifies a robust candidate for subsequent process development and scale-up studies (Table 1).

**Effect of reaction time**

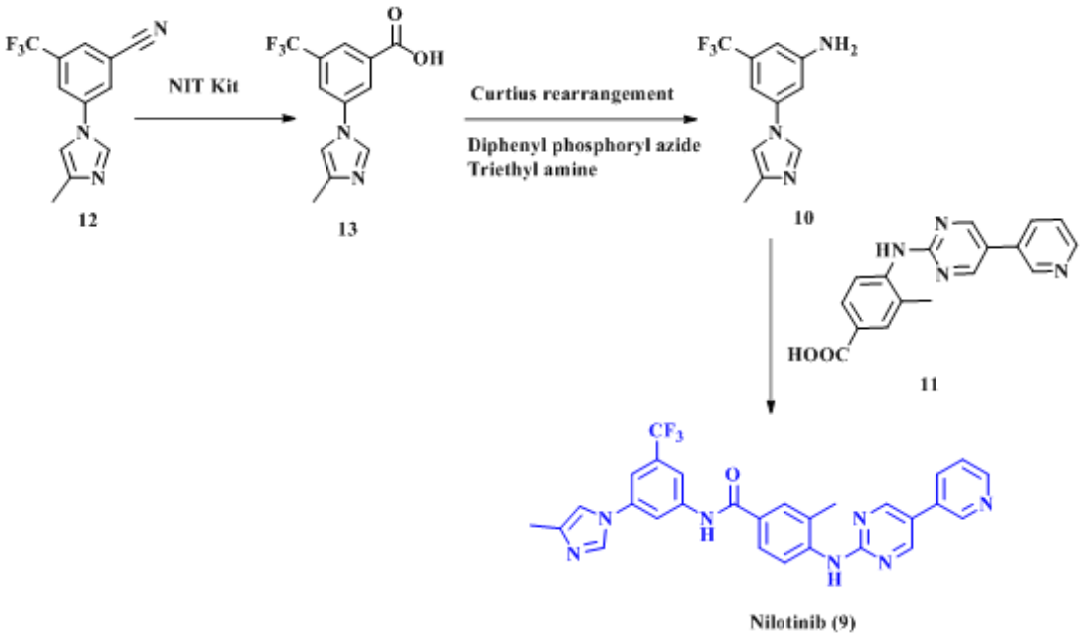
Upon initial enzyme screening, NIT-EW 101 was recognized as the most suitable enzyme, giving the highest conversion (66.11%) under well-optimized conditions (15% enzyme loading and 24 h). To confirm its performance and determine the optimal reaction duration, a comprehensive time-course study was conducted using NIT-EW 101 while keeping all other reaction conditions unchanged. The conversion was increased steadily from 15.71% after 6 h to 99.37% after 48 h, demonstrating efficient catalytic activity throughout the reaction period (see SI section 2). Maximum conversion was observed at 48 h, and extending the reaction did not show much improvement (Table 2). This finding clearly demonstrates that a reaction time of 48 h provides the best enzymatic efficiency and stability and was therefore selected for subsequent studies.

Table 1 — Enzyme screening for the hydrolysis of the nitrile intermediate

| S. No | Enzyme | Enzyme Conc. | Time | Conversion (%) |
|---|---|---|---|---|
| 1. | NIT-EW 101 | 15% | 24 h | 66.11 |
| 2. | NIT-EW 102 | 15% | 24 h | 54.59 |
| 3. | NIT-EW 103 | 15% | 24 h | 48.43 |
| 4. | NIT-EW 104 | 15% | 24 h | 43.96 |
| 5. | NIT-EW 105 | 15% | 24 h | NA |
| 6. | NIT-EW 106 | 15% | 24 h | NA |
| 7. | NIT-EW 107 | 15% | 24 h | NA |
| 8. | NIT-EW 108 | 15% | 24 h | NA |
| 9. | NIT-EW 109 | 15% | 24 h | NA |
| 10. | NIT-EW 110 | 15% | 24 h | NA |
| 11. | NIT-EW 111 | 15% | 24 h | NA |
| 12. | NIT-EW 112 | 15% | 24 h | NA |
| 13. | NIT-EW 113 | 15% | 24 h | NA |

Table 2 — Time-course study for the enzymatic conversion of nitrile using NIT-EW 101

| S. No. | Time (h) | Enzyme (NIT-EW 101) | Enzyme Conc. | Conversion (%) |
|---|---|---|---|---|
| 1. | 6 h | NIT-EW 101 | 15% | 15.71% |
| 2. | 12 h | NIT-EW 101 | 15% | 29.67% |
| 3. | 24 h | NIT-EW 101 | 15% | 66.11% |
| 4. | 48 h | NIT-EW 101 | 15% | 99.37 % |




Scheme 3 — Synthesis of Nilotinib

**Synthesis of Nilotinib**

The synthesis of nilotinib begins with 3-(3-methyl-1H-pyrrol-1-yl)-5-(trifluoromethyl) benzoic acid (13), which was prepared via nitrilase catalysed hydrolysis of the corresponding nitrile with simple isolation by acid precipitation (Scheme 3). The characteristic $^{1}H$ NMR and $^{13}C$ NMR spectra confirmed the successful formation of the acid (see SI). Subsequently, 3-(3-methyl-1H-pyrrol-1-yl)-5-(trifluoromethyl) benzoic acid was converted into the corresponding aniline derivative 10 through a Curtius rearrangement using diphenyl phosphoryl azide and triethylamine in *tert*-butanol under a nitrogen atmosphere.

The rearrangement proceeded smoothly at elevated temperature, enabling efficient decarboxylative amination while retaining the sensitive heteroaryl and trifluoromethyl substituents. Finally, the target molecule nilotinib 9 was synthesized by amide bond formation between 3-methyl-4-((5-(pyridine-3-yl) pyrimidin-2-yl) amino) benzoic acid 11 and 3-(4-methyl-1h-imidazol-1-yl)-5-(trifluoromethyl) aniline 10 via an in situ-generated acyl chloride using thionyl chloride in N-methylpyrrolidone. The coupling reaction proceeded cleanly under controlled-temperature conditions, and subsequent free-base conversion with aqueous ammonia afforded nilotinib in good yield. Spectral analyses of the final product showed characteristic aromatic and heteroaromatic proton resonances in the NMR spectroscopy.

## Conclusion

A chemo-enzymatic synthesis of nilotinib was established by selective hydrolysis of a sterically hindered nitrile intermediate using NIT-EW 101. This process is well established over traditional chemical routes by operating under mild conditions and neutral pH; time-interval studies show the best results at 48 h (yielding 99.37%), indicating this as the best reaction condition. Further successful coupling to the final drug molecule, this enzymatic process represents a scalable and green alternative for the commercial synthesis of high-value pharmaceutical intermediates.

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## Conflict of interest

All authors declare no conflict of interest.

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