Supporting Information

Synthesis of Imatinib in Greener Solvent: A Sustainable Approach

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1. Experimental Section

1.1 Material and methods

All the commercial chemicals and reagents were purchased from Aldrich, BLD, TCI and used as such without further purification. 1H (400 MHz, 300 MHz) and 13C (100 MHz, 75 MHz) spectra were recorded on Bruker Avance 400 or 300 spectrometers. The chemical shifts (ppm) and coupling constants (Hz) are reported in the standard fashion with reference to internal tetramethylsilane or residual chloroform or DMSO. LCMS analysis were carried out using Agilent Technologies 1200 series instrument using direct inlet mode. Analytical thin-layer chromatography (TLC) were performed on pre-coated 0.2 mm thick Merck 60 F245 silica plates and various combinations of ethyl acetate, CH_2Cl_2, MeOH and hexanes were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour. All compounds provide spectroscopic data consistent with being ≥ 95 % the assigned structure.

2. NMR and LCMS spectra of synthesized intermediates (22, 23) and Imatinib

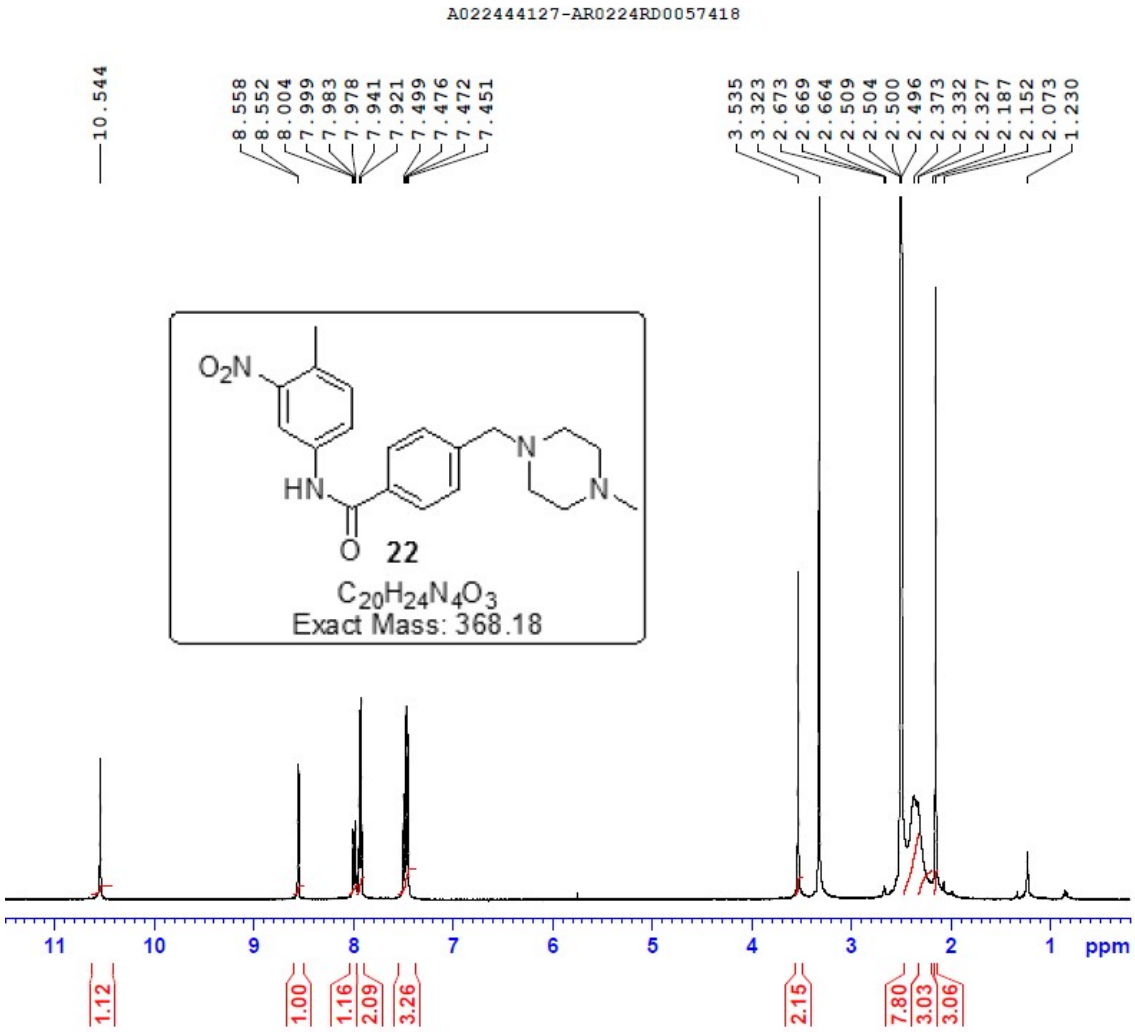

Figure S1: ^{1}H-NMR of Intermediate-22 (DMSO-d_6)

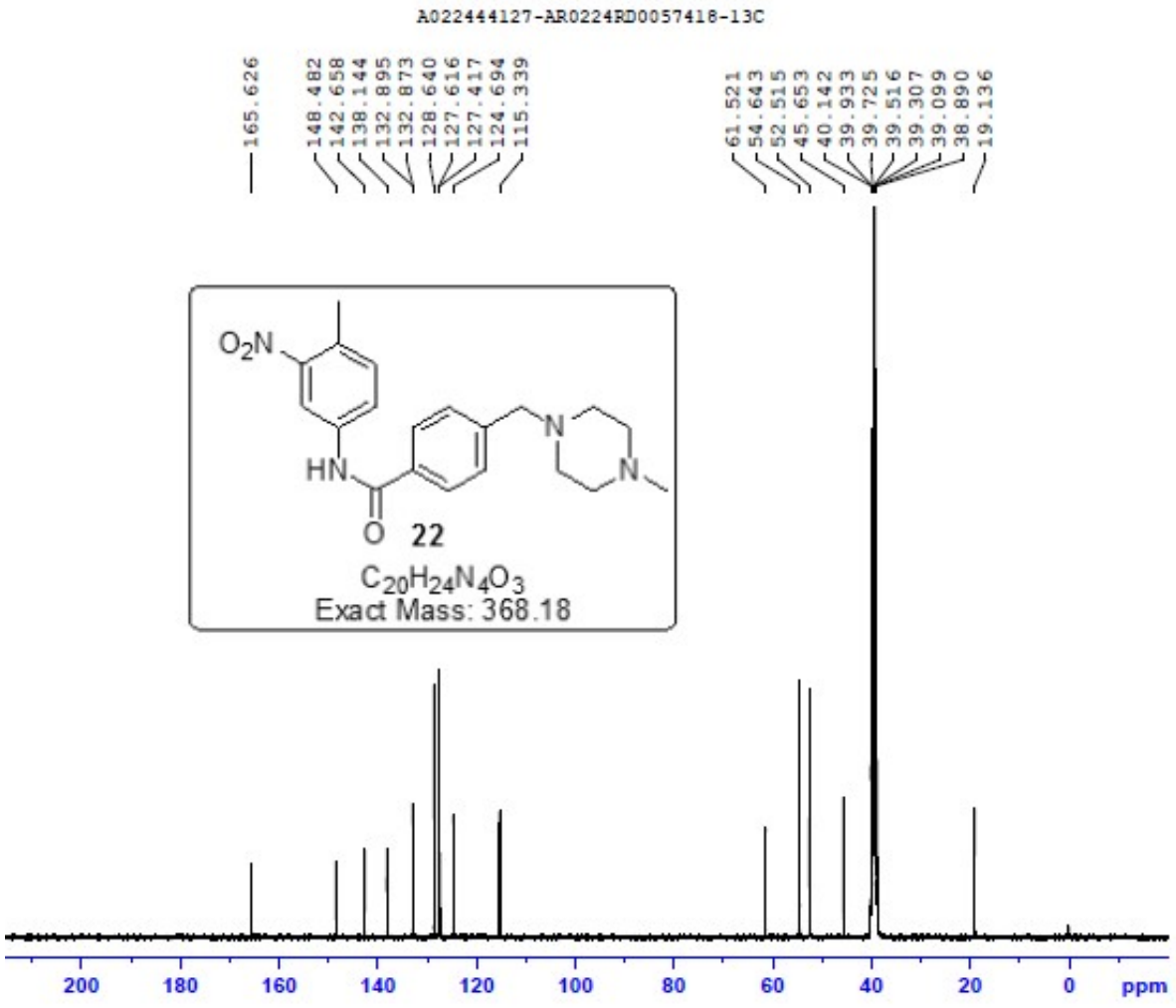

Figure S2: ^{13}C-NMR of Intermediate-22 (DMSO-d_6)

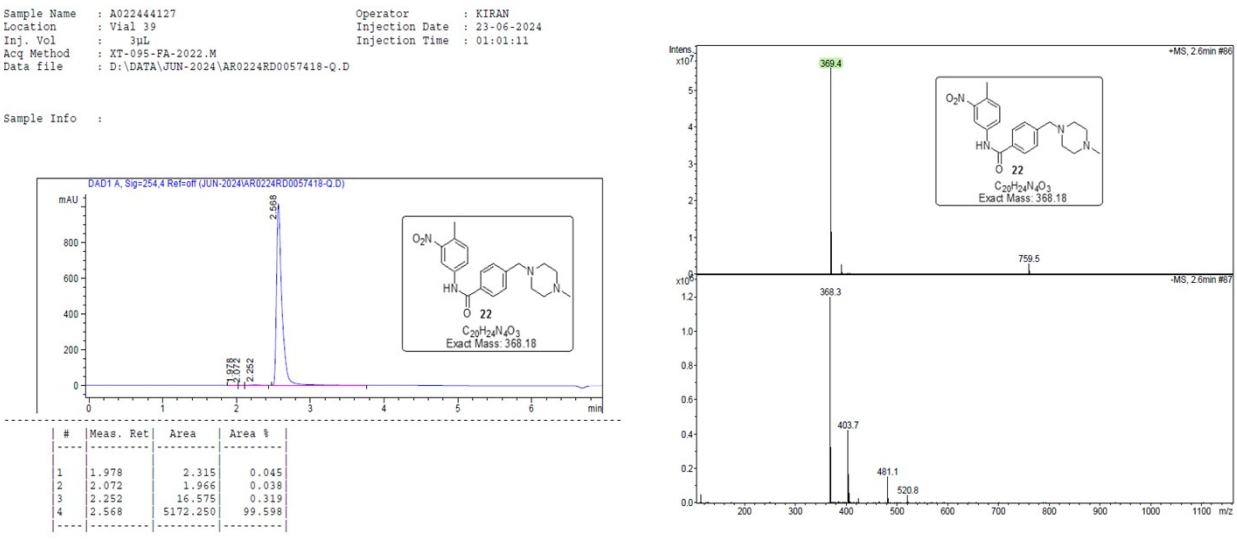

Figure S3: LCMS of Intermediate-22

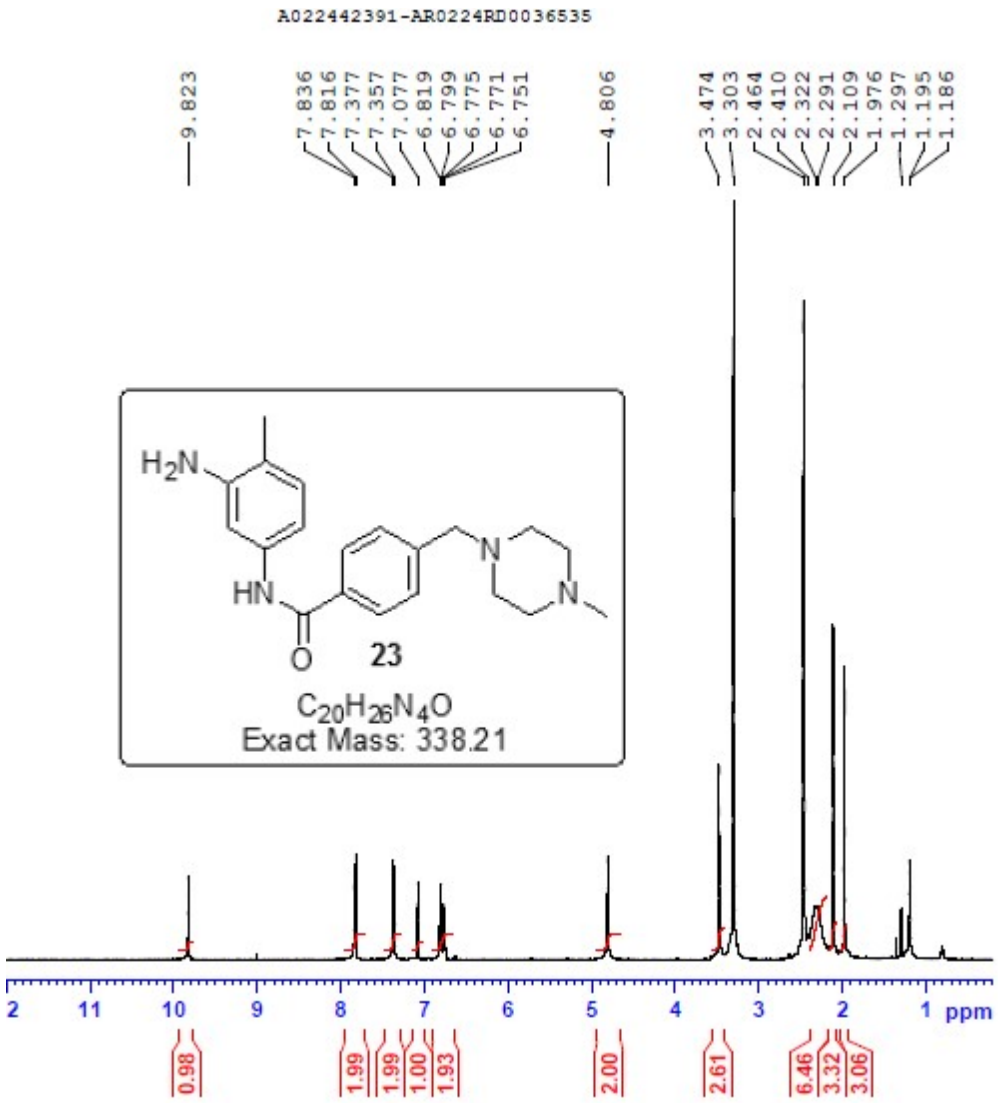

Figure S4: ^{1}H-NMR of Intermediate-23 (DMSO-d_6)

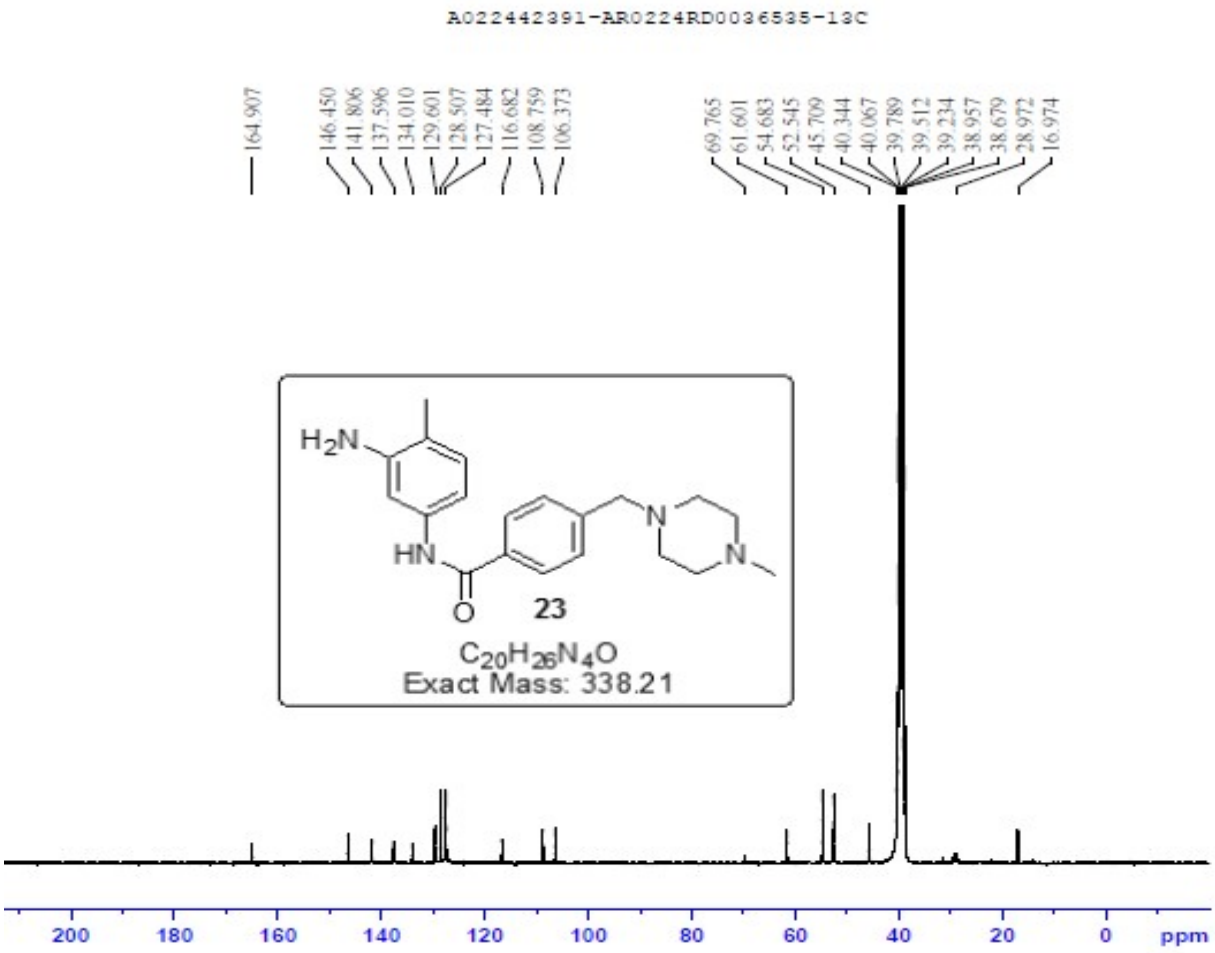

Figure S5: ^{13}C-NMR of Intermediate-23 (DMSO-d_6)

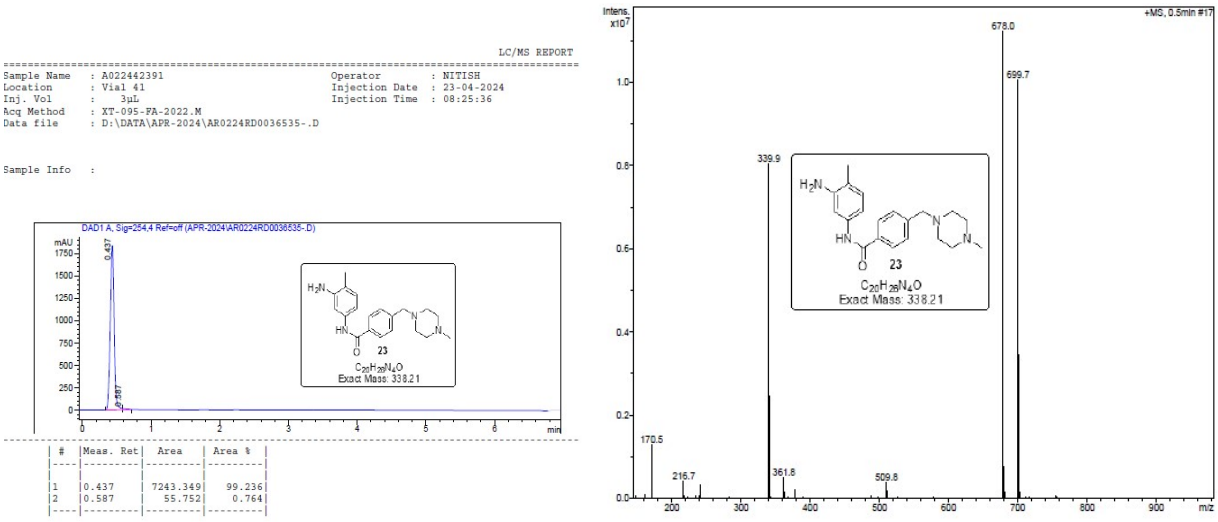

Figure S6: LCMS of Intermediate-23

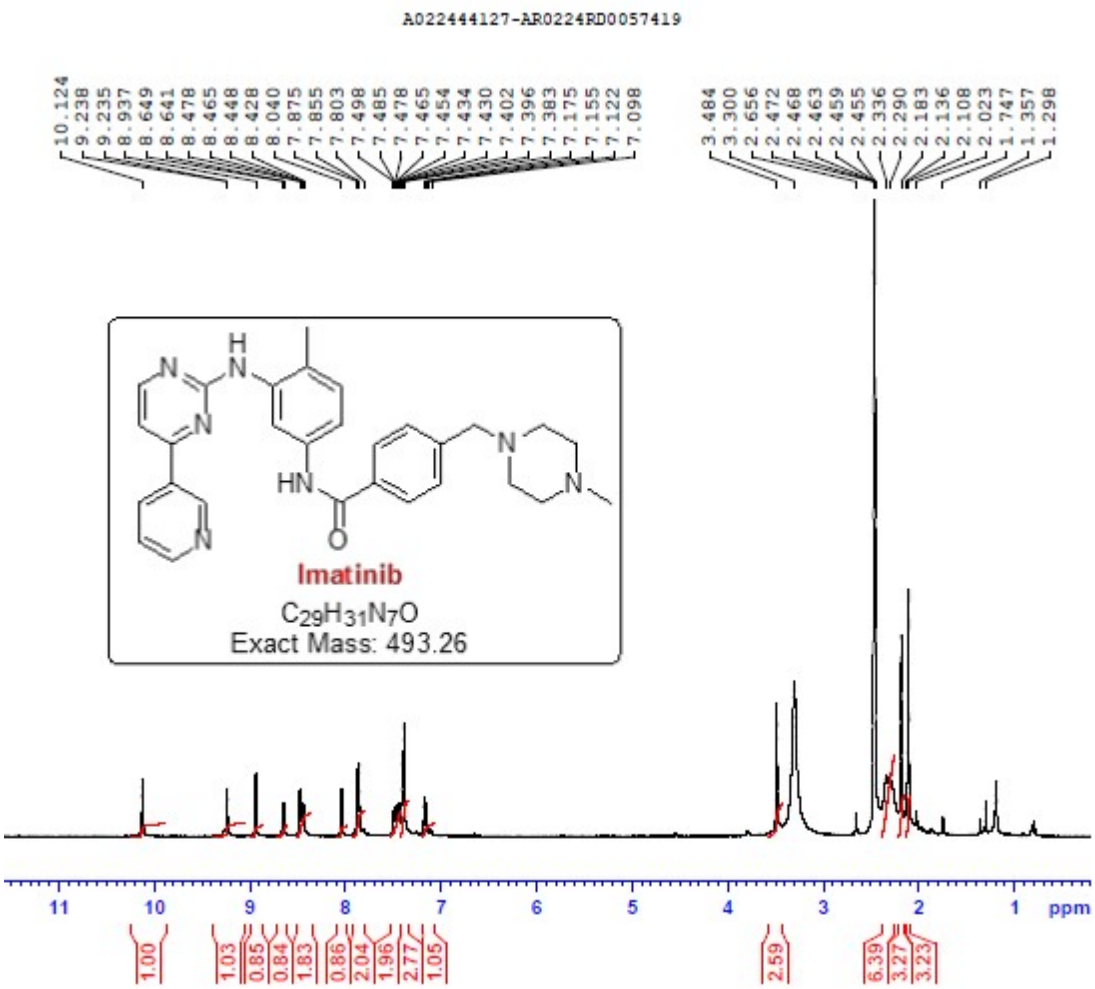

Figure S7: ^{1}H-NMR of Imatinib (DMSO-d_6)

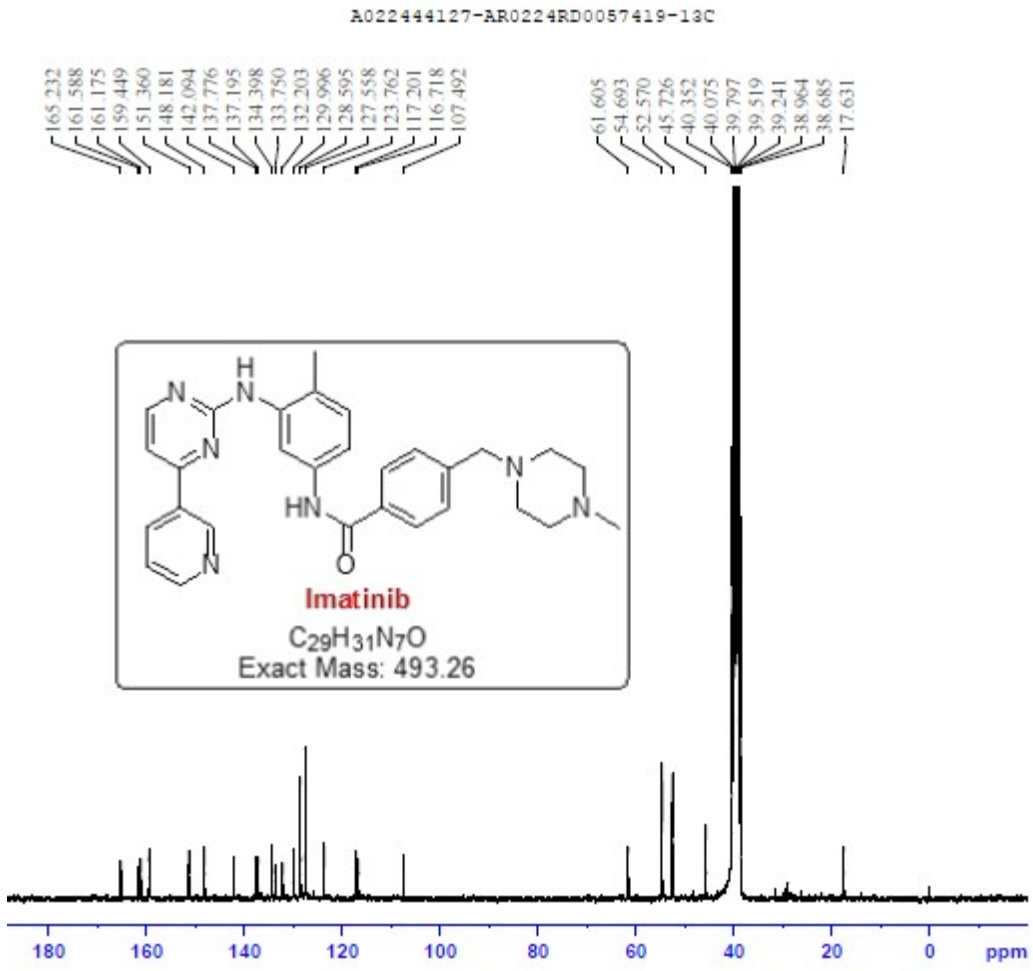

Figure S8: ^{13}C-NMR of Imatinib (DMSO-d_6)

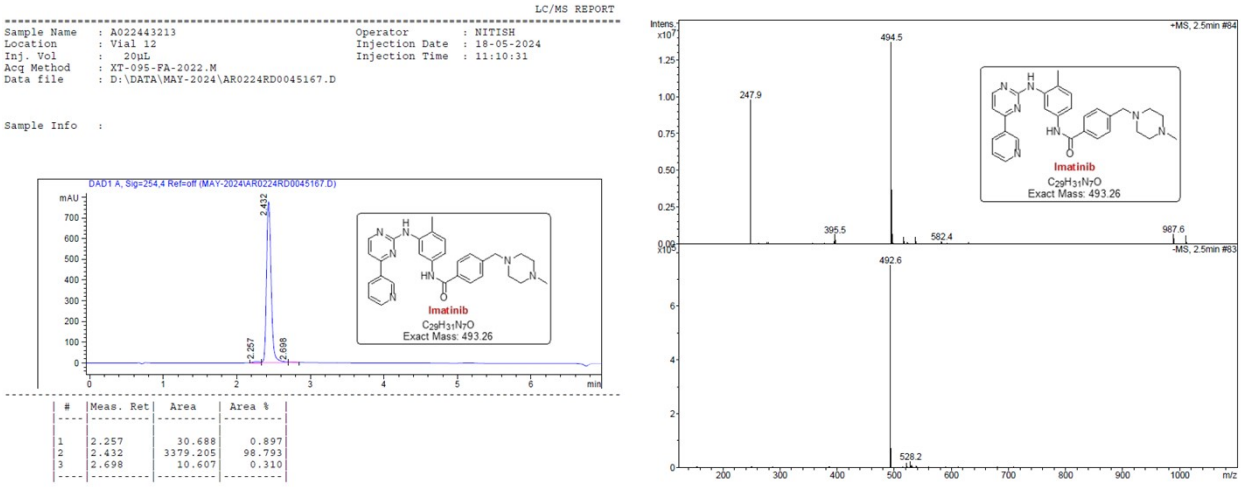

Figure S9: LCMS of Imatinib

EcoScale calculation for synthesis of N-(4-Methyl-3-nitro-phenyl)-4-(4-methyl-piperazin-1-ylmethyl) benzamide (22): -

EcoScale = 100 - sum of individual penalties

#	Parameters	Penalty points	Value
1.	Yield	(100 – %yield)/2=100-75/2	12.5
2.	Price of reaction components	Expensive (> $10 and < $50)	03
3.	Safety	N (dangerous for environment)	05
4.	Technical setup	Common setup	00
5.	Temperature/time	Heating, > 1 h	03
6.	Workup and purification	Cooling to room temperature, Adding solvent(Water), Simple filtration, Removal of solvent with bp < 150°C	01
		Total penalty points	24.5
		EcoScale = 100 - sum of individual penalties	100-24.5=**75.5**

E factor calculation for synthesis of N-(4-Methyl-3-nitro-phenyl)-4-(4-methyl-piperazin-1-ylmethyl) benzamide (22): -

E factor = Raw materials- Final product/Final product

#	Reagents	Quantity
1.	1-(4-Bromo-benzyl)-4-methyl-piperazine	5.0 g
2.	4-Methyl-3-nitro-phenylamine	3.39 g
3.	N-tetrabutylamine hydrobromide	0.5 g
4.	2,6 Lutidine	3.22 g
5.	Tungsten hexacarbonyl	6.53 g
6.	TPGS-750M	1.0 g
7.	[Bis(di-tert-butyl(4-dimethylaminophenyl) phosphine)dichloropalladium(II)]	0.13 g
	Total	**19.7 g**
E factor = Raw materials- Final product/Final product = 19.7 g - 5.13 g/5.13 g		**2.84**

EcoScale calculation Synthesis of N-(3-Amino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (23): -

EcoScale = 100 - sum of individual penalties

#	Parameters	Penalty points	Value
1.	Yield	(100 – %yield)/2=100-90/2	5
2.	Price of reaction components	Expensive (> $10 and < $50)	03
3.	Safety	N (dangerous for environment)	05
4.	Technical setup	Common setup	00
5.	Temperature/time	Heating, > 1 h	01
6.	Workup and purification	Cooling to room temperature, Adding solvent(Water), Simple filtration, Removal of solvent with bp < 150°C	01
		Total penalty points	14
		EcoScale = 100 - sum of individual penalties	100-14=**86**

E factor calculation Synthesis of N-(3-Amino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (23): -

E factor = Raw materials- Final product/Final product

#	Reagents	Quantity
1.	N-(4-Methyl-3-nitro-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide	1.0 g
2.	Zinc dust	0.88 g
3.	Ammonium chloride	0.18 g
4.	TPGS-750M	0.2 g
	Total	**2.1 g**
E factor = Raw materials- Final product/Final product = 2.1 g - 0.83 g/0.83 g		**1.5**

EcoScale calculation Synthesis of N-(3-Amino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide: -

EcoScale = 100 - sum of individual penalties

#	Parameters	Penalty points	Value
1.	Yield	(100 – %yield)/2=100-67/2	16.5
2.	Price of reaction components	Expensive (> $10 and < $50)	03
3.	Safety	N (dangerous for environment)	05
4.	Technical setup	Common setup	00
5.	Temperature/time	Heating, > 1 h	03
6.	Workup and purification	Cooling to room temperature, Adding solvent(Water), Simple filtration, Removal of solvent with bp < 150°C	01
		Total penalty points	28.5
		EcoScale = 100 - sum of individual penalties	100-28.5=**71.5**

E factor calculation Synthesis of N-(3-Amino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide: -

E factor = Raw materials- Final product/Final product

#	Reagents	Quantity
1.	N-(4-Methyl-3-nitro-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide	0.8 g
2.	2-Chloro-4-pyridin-3-yl-pyrimidine	0.45 g
3.	Acetic Acid	5.0 g
	Total	**6.25 g**
E factor = Raw materials- Final product/Final product = 6.25 g - 0.78 g/0.78 g		**7.0**