Supporting Information

Synthesis of Imatinib by C–N Coupling Reaction of Primary Amide and Bromo-Substituted Pyrimidine Amine

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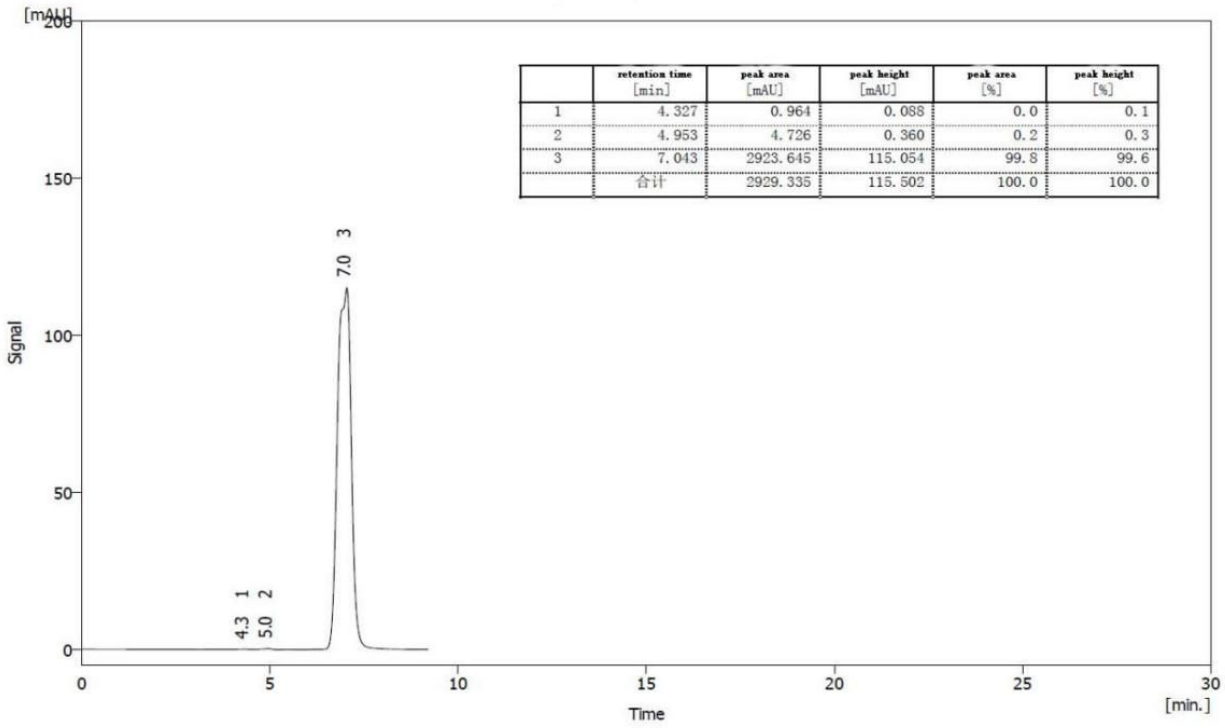
Table of Contents

1. General information

General. Melting points were determined on a WRS-1B digital melting-point apparatus (Shanghai YiCe Instrument Equipment Co., Ltd.), in open capillary tubes, and were uncorrected. Elemental analyses were performed by using an Elementar Vario EL III. IR spectra were recorded on a Bruker Equinox-55. ^{1}H NMR spectra were recorded on a Varian Inova 600 MHz instrument using DMSO-*d*6 as a solvent with chemical shifts that were reported relative to tetramethylsilane. The product purity was analyzed by using an Agilent 1100 HPLC with a DAD detector and a Zorbax SB-C_{18} column (250 mm × 4.6 mm, 5 μm), a column temperature of 30°C, a mobile phase of methanol (0.1% formic acid)–water (50:50), a flow rate of 0.6 $mL \cdot min^{-1}$, a detection wavelength of 254 nm, and an injection volume of 10 μL. Liquid chromatography (LC-MS) was performed by using an Agilent 1200 HPLC coupled to an Agilent 6520 Quadrupole time-of-flight mass spectrometer (EI). Flash-column chromatography was performed with silica gel (100–200 mesh). An imatinib standard sample was purchased from Sigma-Aldrich Life Science and High Technology Company. ZnO (15-25nm, 99.5% metals basis, Aladdin Reagent Co., Ltd.). All other reagents were used as purchased from commercial suppliers without further purification. All materials were weighed in air.

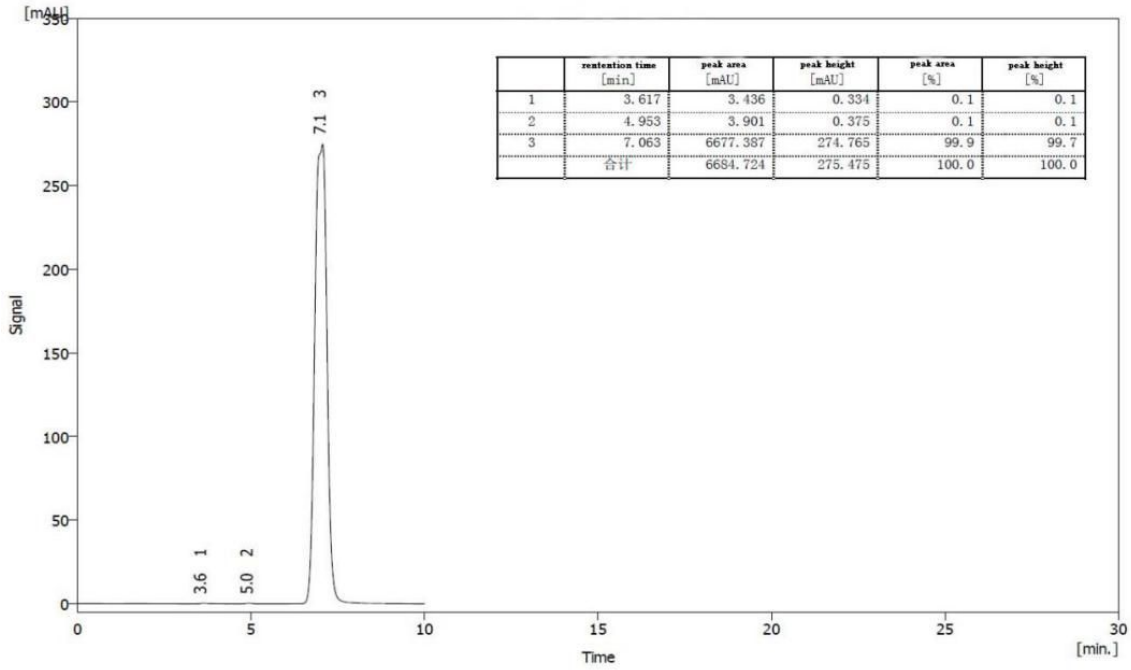
2. Content analysis and genetoxic impurities

High-performance liquid chromatography (HPLC) was used to analyze the content and the genetoxic impurities: N-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyridineamine (**5**) and 4-chloromethyl-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl-amino)-phenyl]benzamide (**10**) of standard samples from Sigma-Aldrich Company (**Figure S1**) and our synthetic imatinib (**Figure S2**). Imatinib prepared by our new method (Scheme **4**, see text) did not detect genetic impurities.



	retention time [min]	peak area [mAU]	peak height [mAU]	peak area [%]	peak height [%]
1	4.327	0.964	0.088	0.0	0.1
2	4.953	4.726	0.360	0.2	0.3
3	7.043	2923.645	115.054	99.8	99.6
	合计	2929.335	115.502	100.0	100.0

Figure S1. Imatinib standard content analysis.



	retention time [min]	peak area [mAU]	peak height [mAU]	peak area [%]	peak height [%]
1	3.617	3.436	0.334	0.1	0.1
2	4.953	3.901	0.375	0.1	0.1
3	7.063	6677.387	274.765	99.9	99.7
	合计	6684.724	275.475	100.0	100.0

Figure S2. Content of imatinib sample prepared by Scheme **4**.

The results show that the content of imatinib standard from Sigma-Aldrich Company was 99.8%, and the content of imatinib obtained by our synthetic method was 99.9%.

Imatinib that was synthesized by the two methods (**Schemes 2** Method **B** and **Schemes 4**) was subjected to HPLC-mass spectrometry (MS). The results are shown in **Figures** S**3** and **4**. The HPLC-MS spectrum of the imatinib that was synthesized by Method **B** in the **Scheme 2** route is shown in **Figure S3**, and the HPLC-MS spectrum of imatinib that was synthesized by the **Scheme 4** route is shown in **Figure S4**. The liquid chromatogram of **Figure S3** shows that two impurity peaks exist on the left side of the imatinib peak, and the retention times are 2.791 and 2.934, respectively. In the total-ion chromatogram, the mass-spectrum ion peak of the impurity with time = 3.007 is 278.2, which is the M+H peak of the genotoxic impurity, and indicates that

this impurity is the genotoxic substance N-(5-amino-2-methyl-phenyl)-4-(3-pyridyl) -2-pyrimidinamine (**5**). **Figure S4** shows that the purity of the imatinib that was synthesized by the **Scheme 4** route is significantly higher than that of the former, the chromatogram is a single peak, and no other impurity exists in front of the imatinib peak, the molecular ion peak that was obtained by time = 3.587 in the mass spectrum is 494.3, which is the M+H peak of the imatinib. The peak at m/z = 247.6 is the peak of the imatinib molecular cleavage product, which is a positive carbon ion (**25**), and its structure (**Figure S5**) is as follows.

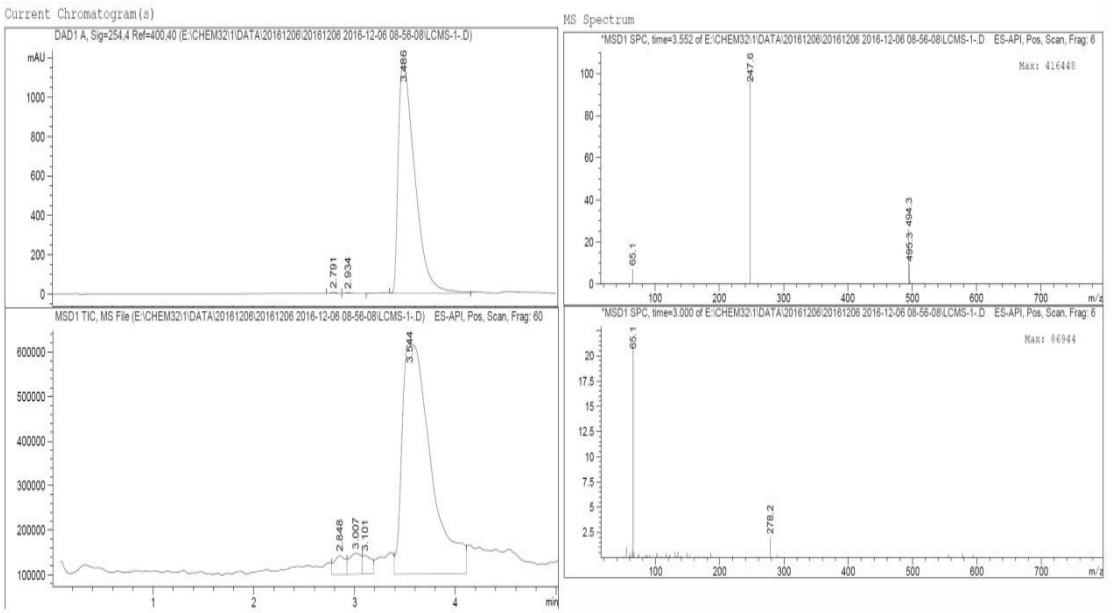


Figure S3. HPLC-MS spectrum of imatinib synthesized by Method **B** in **Scheme 2**.

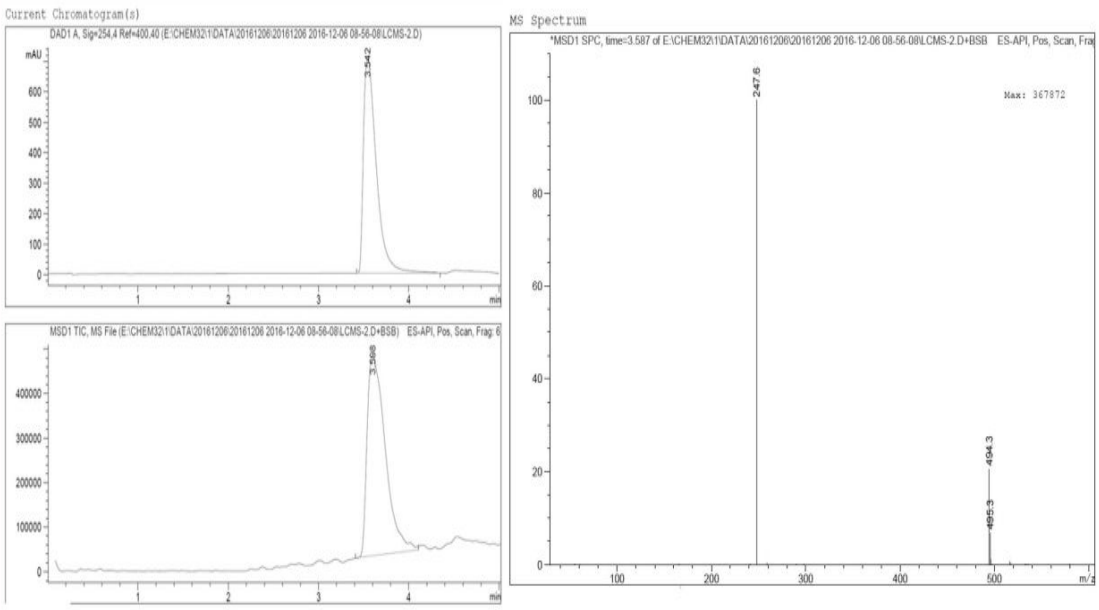
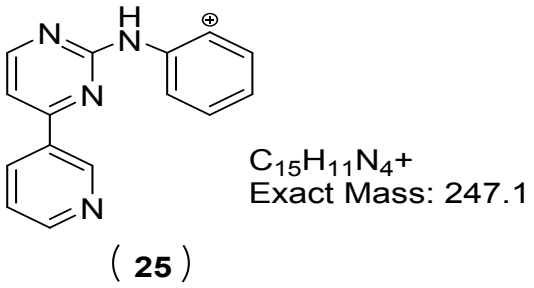


Figure S4. HPLC-MS spectrum of imatinib synthesized by **Scheme 4**.



（**25**）

Figure S5. Structure of positive carbon ion **25**

Therefore, genetoxic impurities (compound **5** and **10**) that are restricted by the FDA were not detected in imatinib (**1**) that was prepared via the new synthetic route of **Scheme 4**.

3. IR, ^{1}H NMR and MS data

5.1
N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (1):

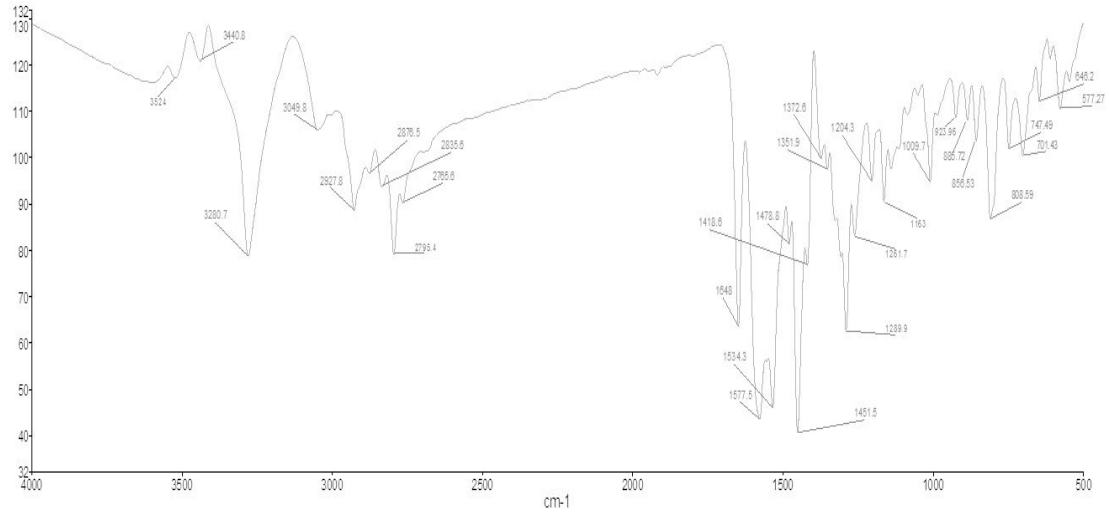


Figure S6. IR spectrum of compound **1**

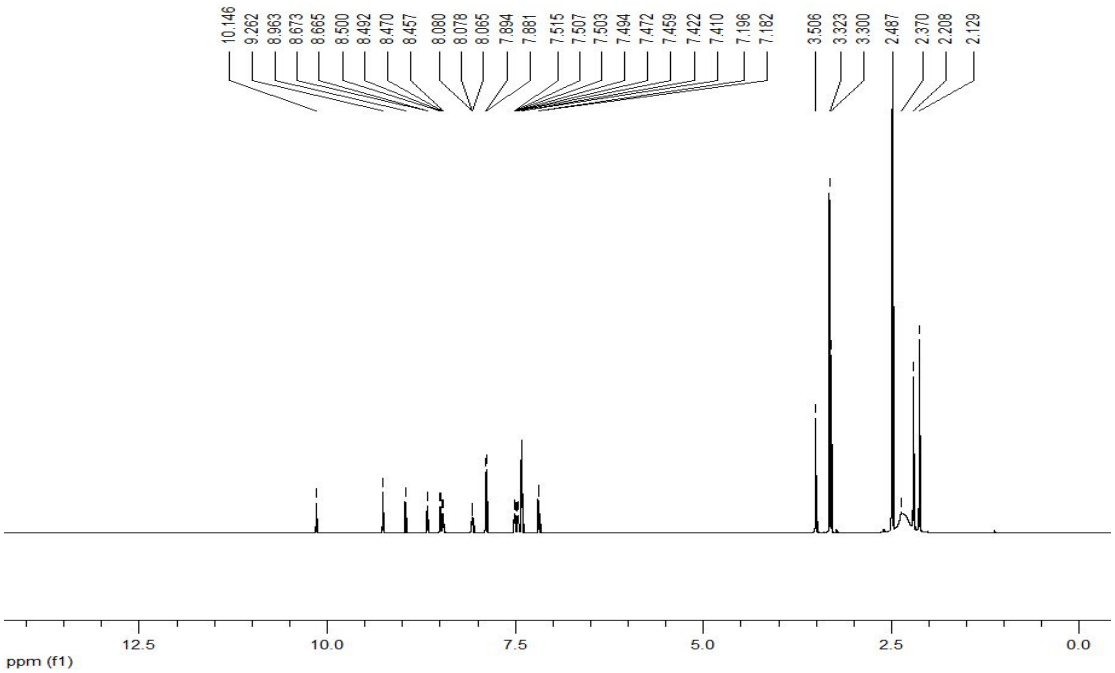


Figure S7. ^{1}H-NMR spectrum of compound **1**

MS: 494.3 (M+H).

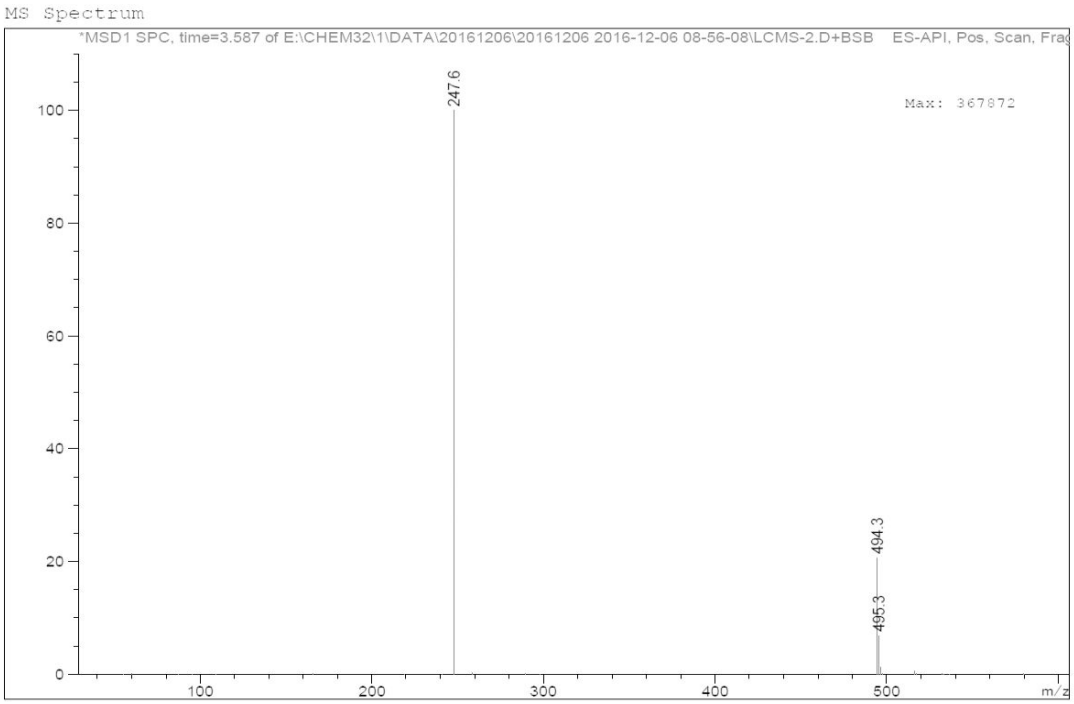


Figure S8. MS of compound **1**

5.2
4-(4-Methylpiperazin-1-ylmethyl)-benzonitrile (20):

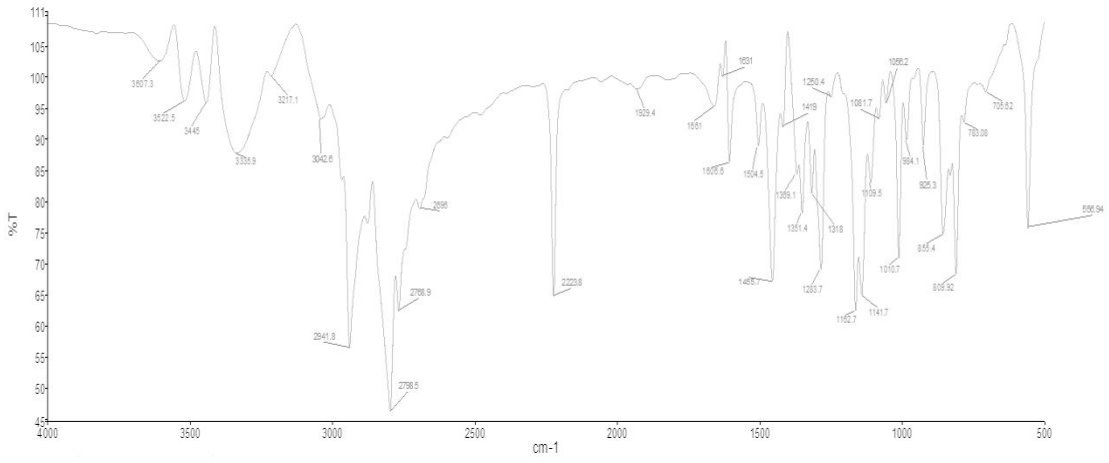


Figure S9. IR of compound **20**

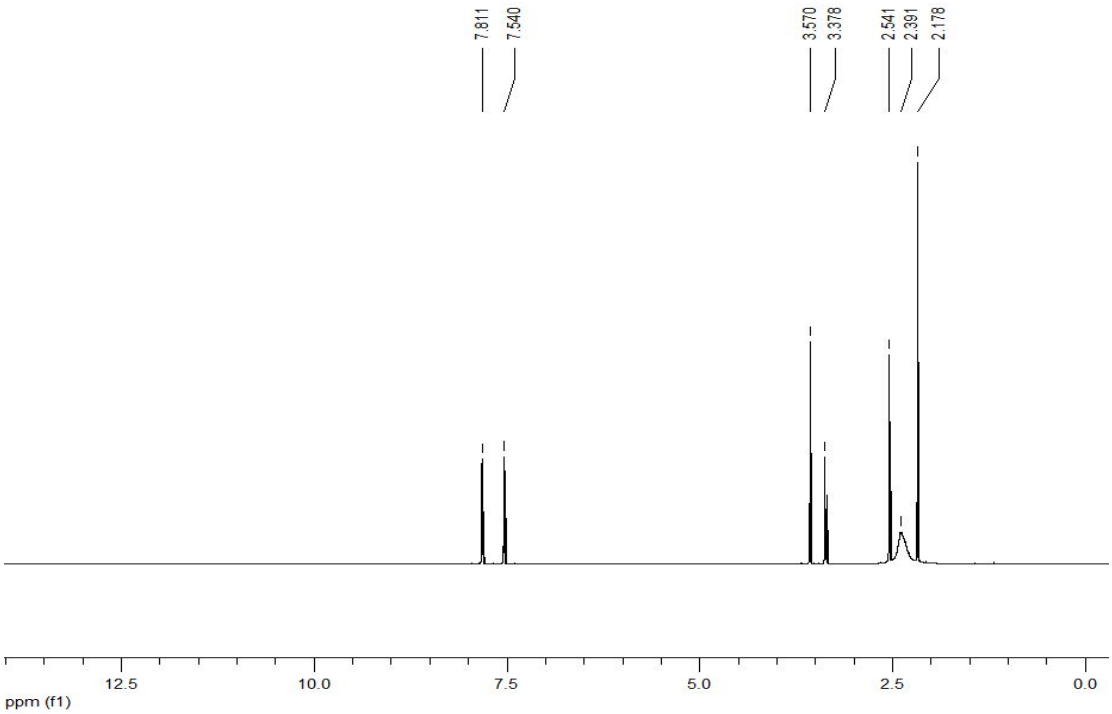


Figure S10. ^{1}H-NMR of compound **20**

5.3

4-(4-Methylpiperazin-1-ylmethyl)-benzamide (18)

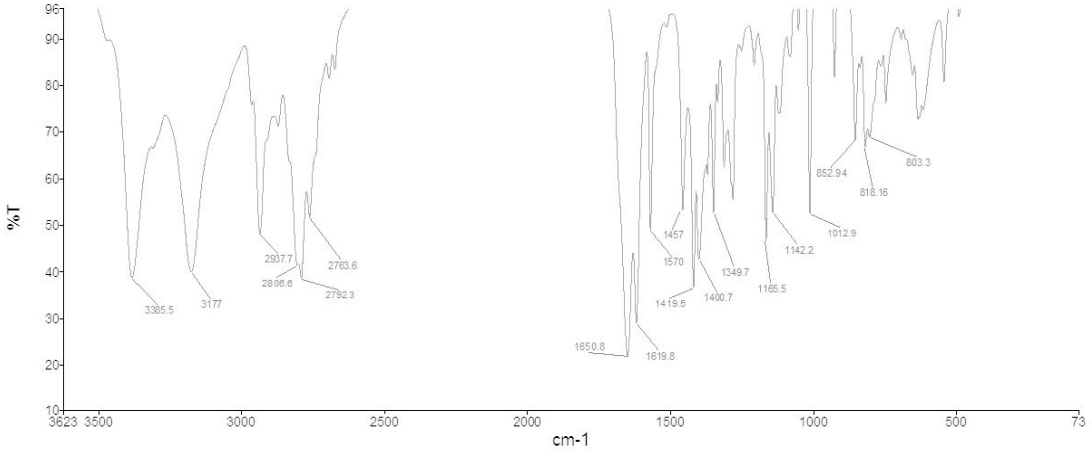


Figure S11. IR of compound **18**

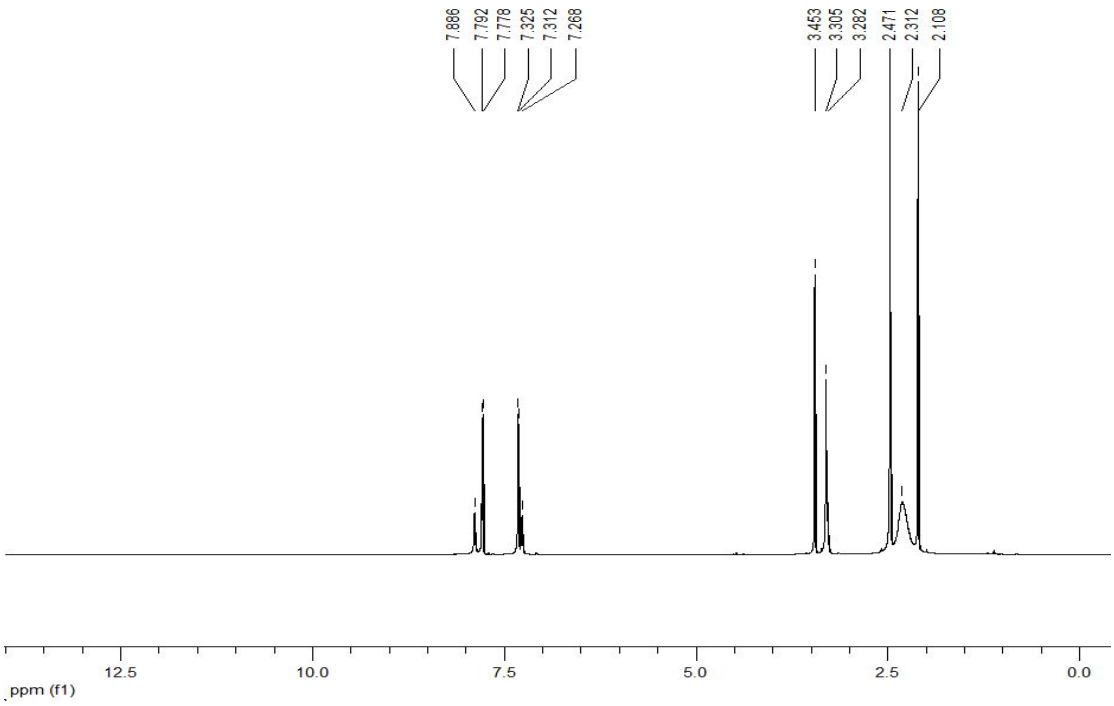


Figure S12. ^{1}H-NMR of compound **18**

MS: 234.16 (M+H).

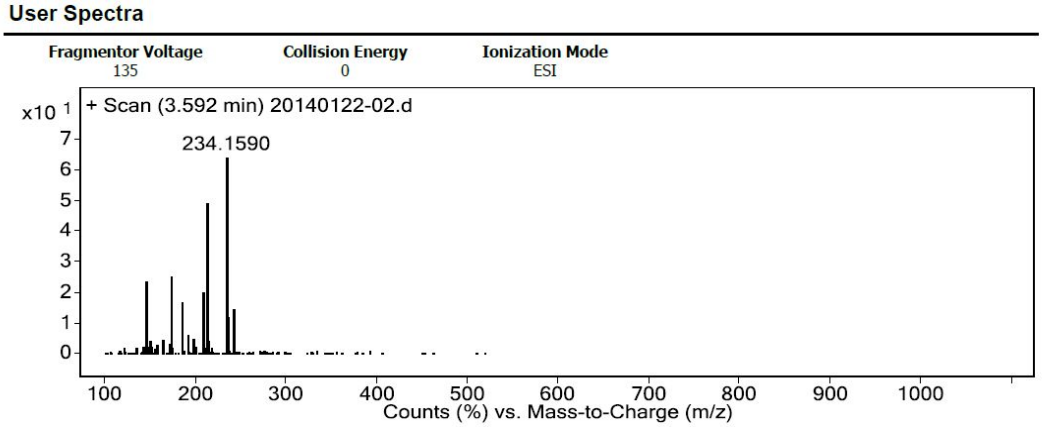


Figure S13. MS of compound **18**

5.4

N-(5-bromo-2-methylphenyl)-4-(pyridin-3-yl)-pyrimidin-2-ylamine (17):

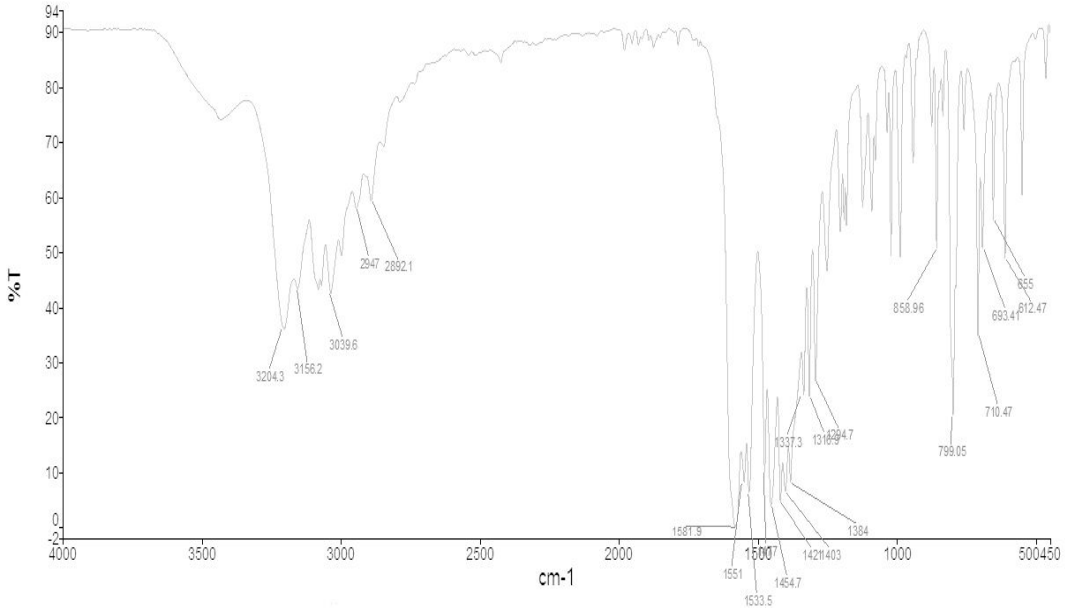


Figure S14. IR of compound **17**

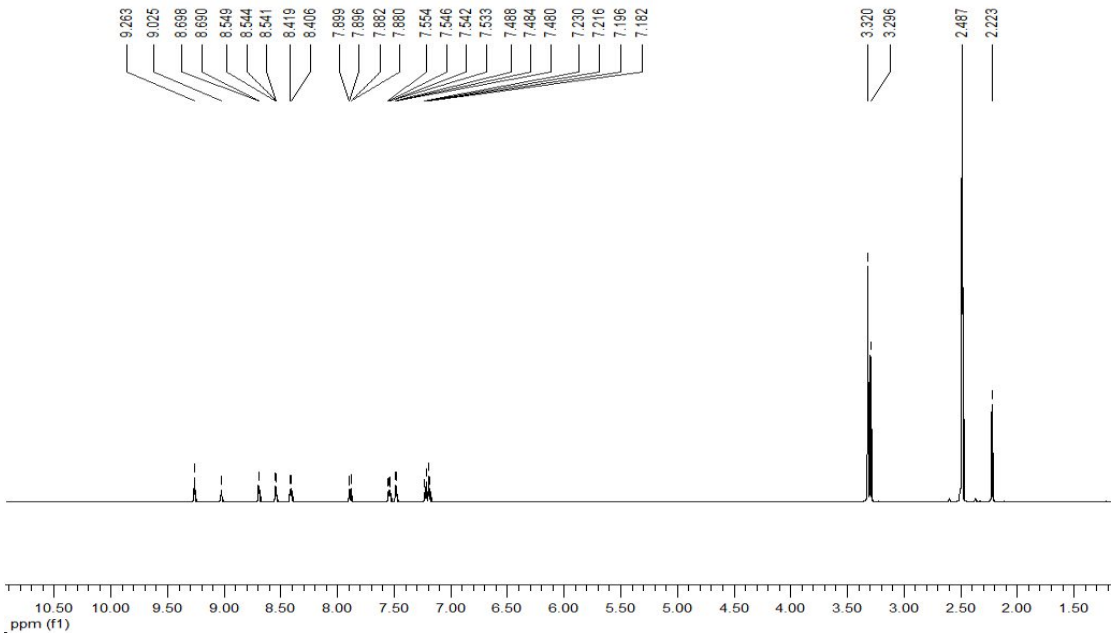


Figure S15. [1]H-NMR of compound **17**

MS: 341.0 (M+H), 343.0 (bromine isotope peak), 363.0 (M+Na).

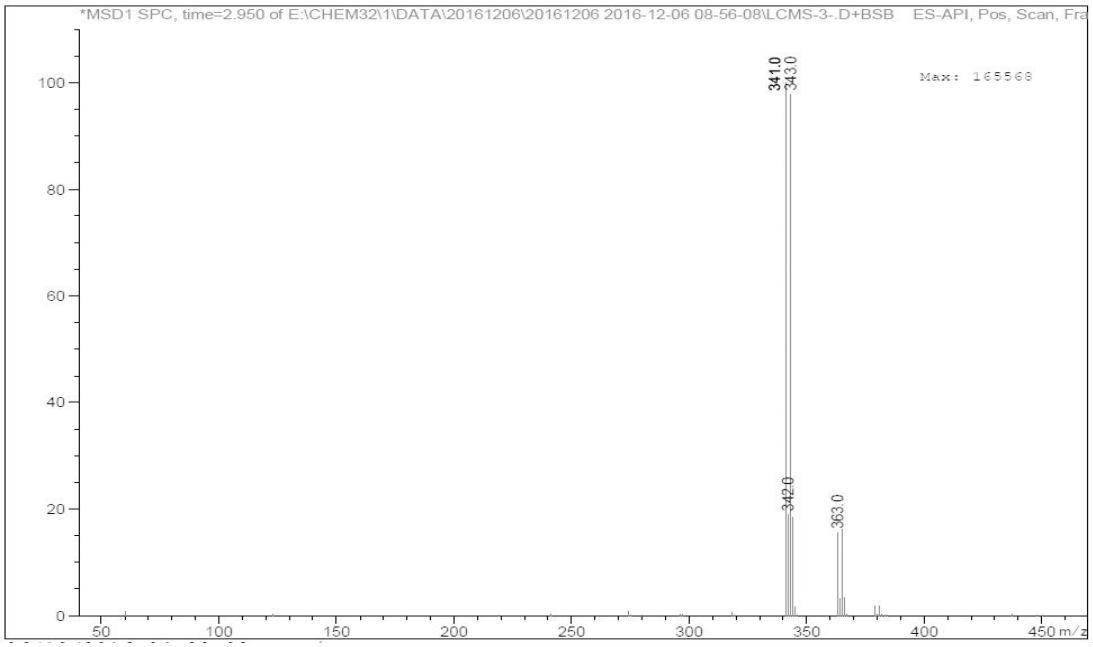


Figure S16. MS of compound **17**

5.5

5-Bromo-2-methylphenylguanidine nitrate (22):

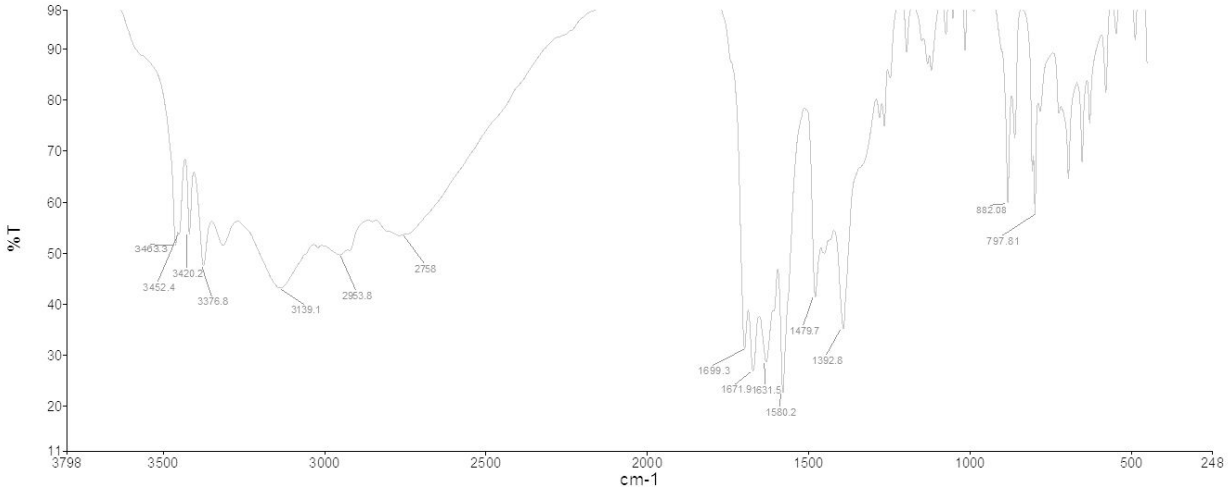


Figure S17. IR of compound **22**

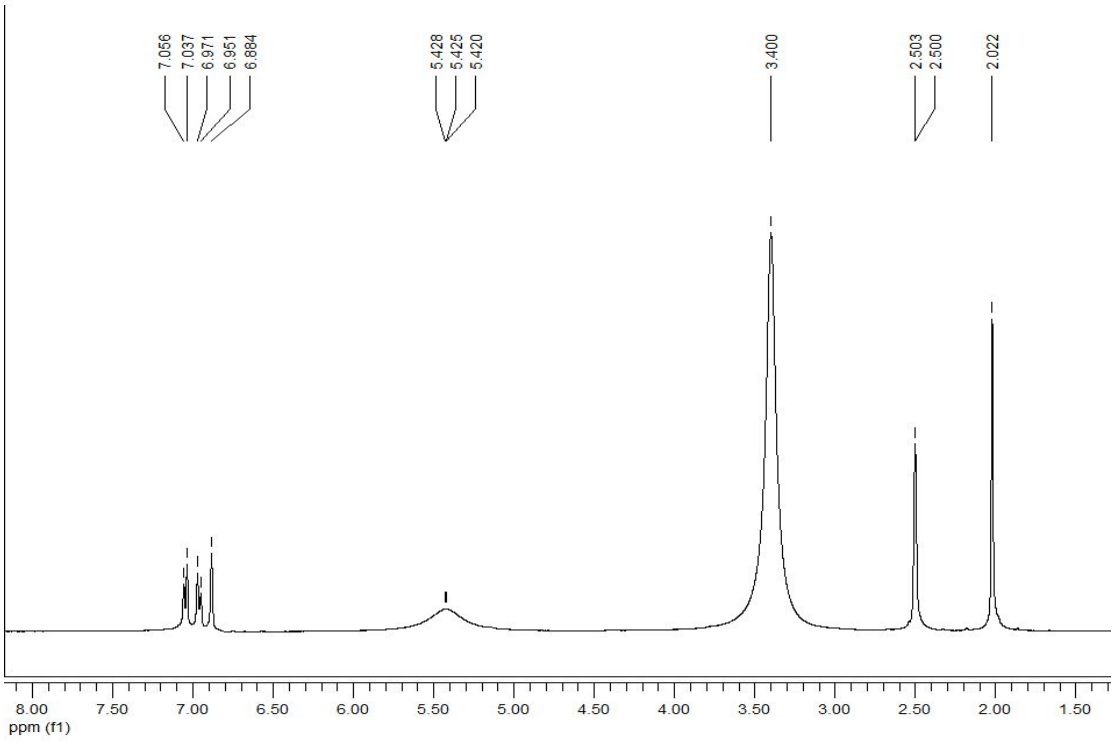


Figure S18. ^{1}H-NMR of compound **22**