Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Preferred Formation of the Carboxylic Acid-Pyridine Heterosynthon in 2-Anilinonicotinic Acids

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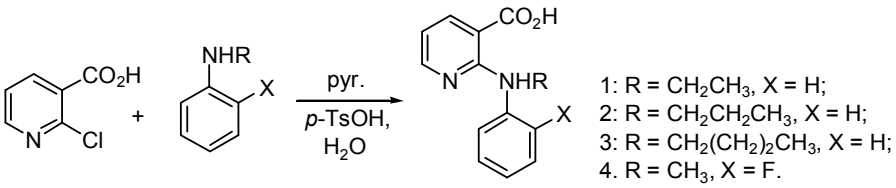
Synthesis

2-MPNA analogs were synthesized according to a literature method[1], shown as the following:



All starting materials and solvents were obtained from commercial sources and used as received.

1.1.1 Synthesis of 2-(Ethyl-phenyl-amino)-nicotinic acid (1)

2-Chloronicotinic acid (3.45 g, 21.9 mmol), *N*-ethylaniline (2.65 g, 21.9 mmol), pyridine (1.75 g, 22.7 mmol), *p*-toluenesulfonic acid (*p*-TsOH) (0.84 g, 4.9 mmol) were added to a round-bottom flask with 20 mL water. The mixture was refluxed overnight. When cooled down, solid precipitated and was recovered by filtration (4.13 g, 78 %).

^{1}H NMR (DMSO-*d6*, 400 MHz) δ 8.38 (dd, 1H), 7.79 (dd, 1H), 7.23 (m, 2H), 6.96 (m, 5H), 4.03 (q, 2H), 1.12 (t, 3H); ^{13}C NMR (DMSO-*d6*, 100 MHz) δ 167.4, 155.8, 150.0, 147.0, 139.2, 129.1, 122.8, 122.0, 118.5, 115.5, 45.9, 13.0; IR (KBr, cm^{-1}) 3060 (s), 3036 (s), 3000~2500 (s), 1919 (m), 1715(s), 1586 (s), 1565 (s), 1493 (m), 1435 (m), 1380 (m), 1344 (s), 763 (s), 699 (s); ESI-MS m/z 243.09 (M+1) ; mp: 118~120 °C.

1.1.2 Synthesis of 2-(Phenyl-propyl-amino)-nicotinic acid (2)

The procedure is similar to the preparation of 2-EPNA with 2-chloronicotinic acid (2.6 g, 16.8 mmol), *N*-propylaniline (2.3 g, 17.3 mmol), pyridine (1.3 g, 17.0 mmol), *p*-TsOH (0.5 g, 2.8 mmol), and water (30 mL) to yield colorless solid (2.7 g, 63%).

^{1}H NMR (DMSO-*d6*, 400 MHz) δ 12.38 (br, 1H), 8.38 (dd, 1H), 7.80 (m, 1H), 7.21 (m, 2H), 6.95 (m, 4H), 3.93 (t, 2H), 1.60 (m, 2H), 0.88 (t, 3H); ^{13}C NMR (DMSO-*d6*, 100 MHz) δ 167.5, 156.0, 150.1, 147.8, 139.2, 129.1, 122.6, 121.7, 118.8, 115.6, 52.9, 20.7, 11.3; IR (KBr, cm^{-1}) 3035(s), 2966 (s), 2942 (s), 2873 (s), 2000~1800 (w), 1703 (s), 1583 (s), 1566 (s), 1493 (m), 1454 (m), 1372 (m), 1302 (s), 766 (s), 698 (s); MS (EI) 256; mp: 121~123 °C.

1.1.3 Synthesis of 2-(Butyl-phenyl-amino)-nicotinic acid (3)

The procedure is similar to the preparation of 2-EPNA with 2-chloronicotinic acid (3.17 g, 20.0 mmol), *N*-butylaniline (3.10 g, 20.8 mmol), pyridine (1.62 g, 20.5 mmol), *p*-TsOH (0.63 g, 3.3 mmol), and water (25 mL) to yield colorless solid (3.54 g, 65 %).

^{1}H NMR (DMSO-*d6*, 400 MHz) δ 8.37 (dd, 1H), 7.81 (dd, 1H), 7.22 (m, 2H), 6.95 (m, 5H), 3.94 (t, 2H), 1.50 (m, 2H), 1.30 (m, 2H), 0.86 (t, 3H); ^{13}C NMR (DMSO-*d6*, 100 MHz) δ 167.5, 155.9, 150.2, 147.9, 139.1, 129.0, 122.5, 121.8, 118.9, 115.5, 53.0, 29.5, 20.7, 11.3; IR (KBr, cm^{-1}) 3062 (s), 3036 (s), 2957 (s), 2935 (s), 2873 (s), 3000~2500 (s), 1919 (s), 1716 (s), 1589 (s), 1564 (s), 1476 (s), 1432 (m), 1375 (m), 763 (s), 699 (s); ESI-MS m/z 271.12 (M+1) ; mp: 100~102 °C.

1.1.4 Synthesis of 2-[(2-Fluoro-phenyl)-methyl-amino]-nicotinic acid (4)

The procedure is similar to the preparation of 2-EPNA with 2-chloronicotinic acid (2.3 g, 14.6 mmol), (2-fluoro-phenyl)-methyl-amine (1.83 g, 14.6 mmol), pyridine (1.20 g, 15.2 mmol), *p*-TsOH (0.40 g, 2.1 mmol), and water (15 mL) to yield colorless solid (1.25 g, 35 %).

^{1}HNMR ($CDCl_3$, 300 MHz) δ 11.55 (br, 1H), 8.39 (d, 1H), 8.01 (d, 1H), 7.06 (d, 2H), 7.02 (d, 2H), 6.95 (t, 1H), 3.4 (s, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 170.05, 158.48, 157.88, 156.00, 151.06, 140.61, 136.21, 126.57, 125.36, 124.70, 116.84, 116.10, 115.55, 40.07; IR (KBr, cm^{-1}) 3066 (s), 3022 (s), 3000~2500 (s), 2000~1800 (m), 1713 (s), 1589 (s), 1507 (s), 1480 (s), 1450 (m), 1412 (s), 1365 (m), 761(s); MS (EI): 246; mp: 139~141 °C.

Crystal Growth

Crystal growth was carried out for each compound in organic/aqueous solvents. Typically, a compound was dissolved in a given solvent to make a saturated solution at room temperature. Then the solution was set for slow evaporation until single crystals were harvested with solvent remaining or totally evaporated. All crystallization experiments were conducted in an unmodified atmosphere. An example is given as the following: 50 mg compound **1** was dissolved in 10 mL HPLC grade methanol

in a glass vial at room temperature. The vial was sealed with perforated parafilm. Crystals were obtained as aggregated plates in about a week. Preliminary polymorph screening was performed for each compound. For compound **1**, three forms were produced. **1-I** was from ethyl acetate, *iso*-propanol, methanol, acetone, ethanol, dimethylformamide, chloroform, dichloromethane, acetonitrile, hexane, toluene, and tetrahydrofuran, **1-II** was from ether, benzene, water and acetic acid, and **1-III** was from ethyl acetate. For compound **2**, two polymorphs were harvested. **2-I** was from ethyl acetate, methanol, acetone, ethanol, *iso*-propanol, water, toluene, benzene, chloroform, dichloroform, acetic acid, acetonitrile, ethyl ether, dimethylformamide, and pet ether; **2-II** was from hexane and dimethyl sulfoxide. Two crystal forms were prepared for compound **3** in the solvents tested (methanol, acetone, acetonitrile, ethyl acetate, *iso*-propanol, dimethylformamide, ethanol, hexane, pet ether, benzene, acetic acid, dichloroform, and chloroform for **3-I,** and toluene for **3-II**). Only one crystal form was obtained for compound **4** in the solvents tested (methanol, ethanol, acetone, ethyl acetate, ether, acetonitrile, and dimethylsulfoxide).

Crystal Structure Determination

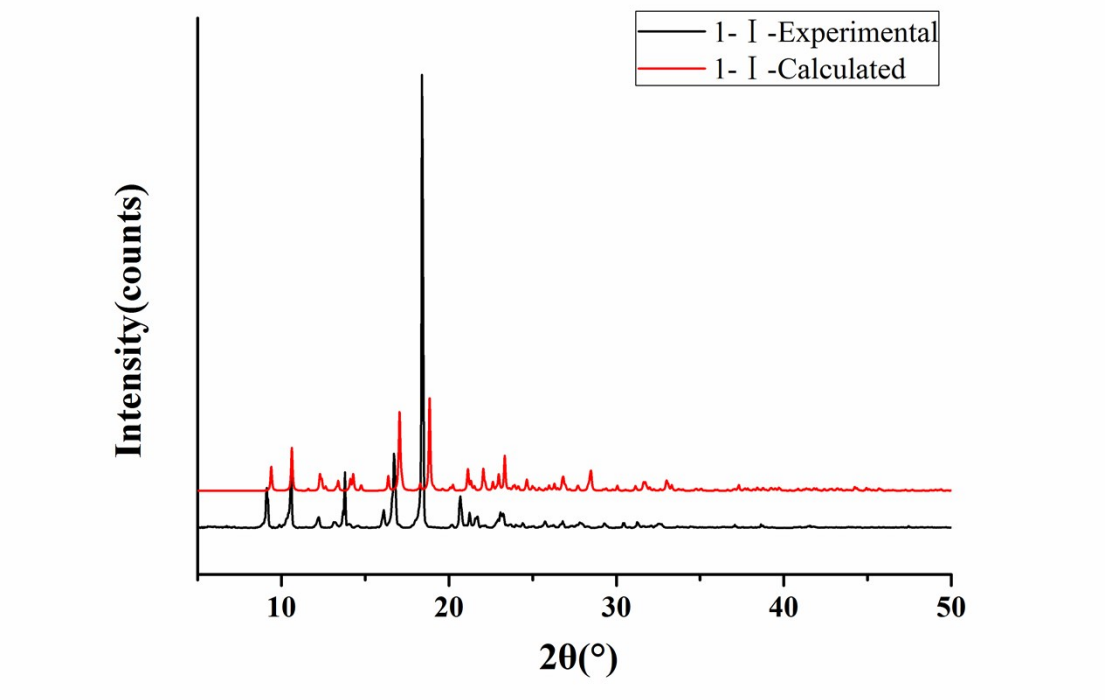
Crystal structures of all the compounds were determined by single-crystal X-ray diffraction. Data collection for the crystals were carried out at 90K on a Nonius kappaCCD diffractometer with MoKα radiation (λ = 0.71073 Å).[2] Cell refinement and data reduction were done using SCALEPACK and DENZO-SMN.[3] Structure solution and refinement were carried out using the SHELXS97 and SHELXL97 program, respectively.[4, 5]

Powder X-ray Diffraction (PXRD)

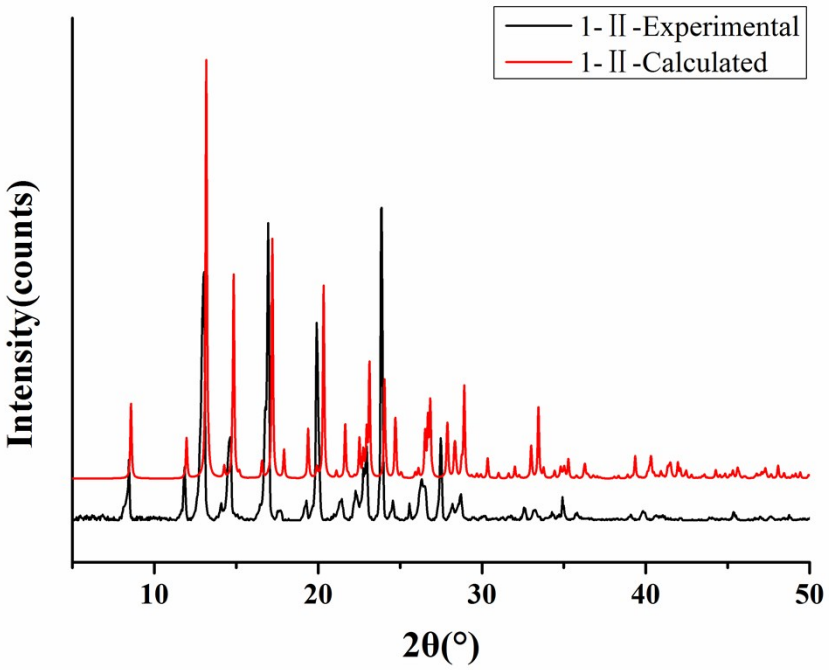
PXRD analysis was performed with a Bruker D8 ADVANCE X-ray diffractometer (Bruker, Germany) with Ni-filtered Cu Kα radiation (40 kV, 30 mA). The data were collected over a 2θ range of 5.0º to 50.0º at a scan rate of 1.0º/min.

Based on the mapping of the experimental and the calculated PXRD patterns, bulk 1-I and 1-II seem to be relatively pure and 1-III actually is a mixture of 1-I and 1–III; bulk 2-I and 2-II are pure as well; bulk 3-I is also pure, but 3-S loses the solvent readily to become 3-I; and bulk 4 shows one extra peak in the PXRD pattern, other than that, the match between the experimental and calculated PXRD patterns is almost perfect.

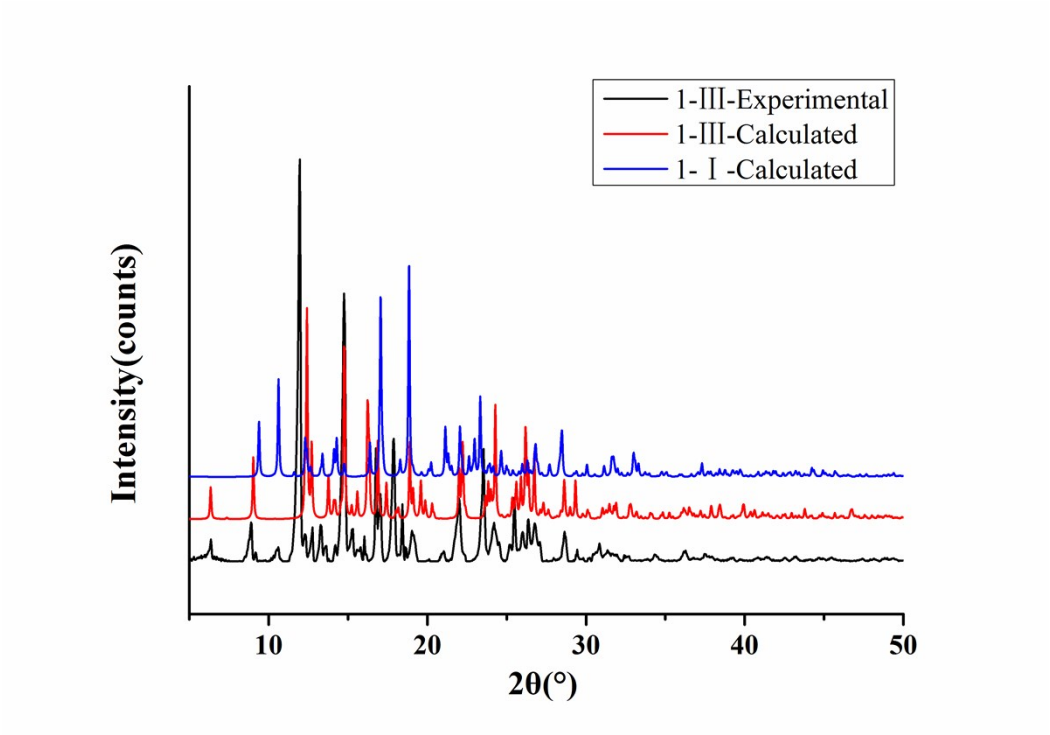
S1. Experimental and Calculated PXRD of 1-I



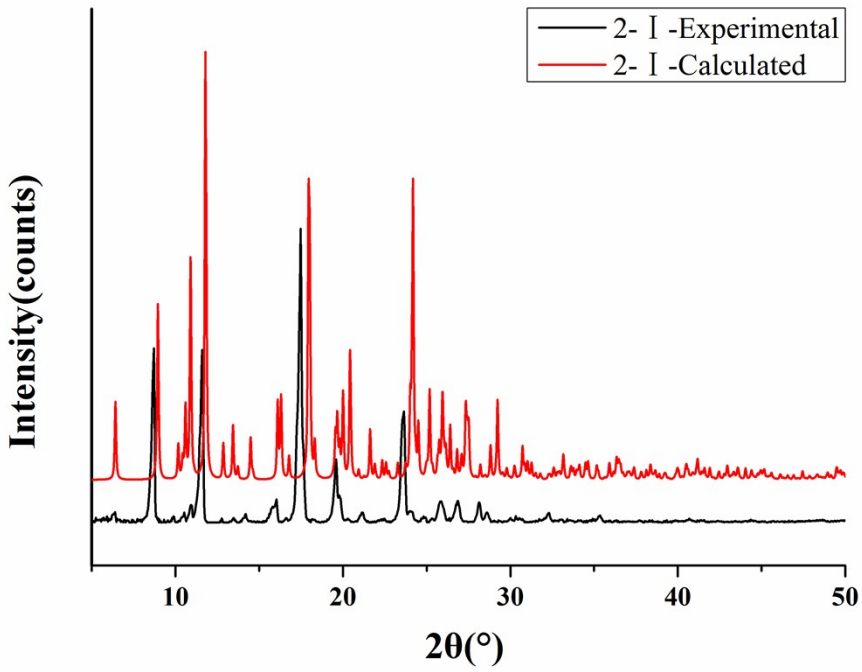
S2. Experimental and Calculated PXRD of 1-II



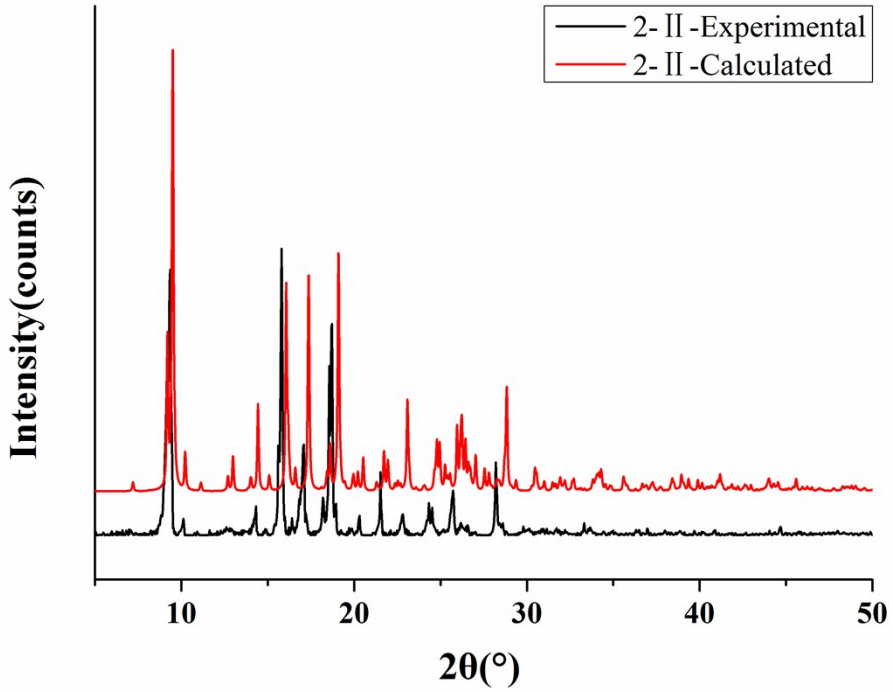
S3. Experimental and Calculated PXRD of 1-III



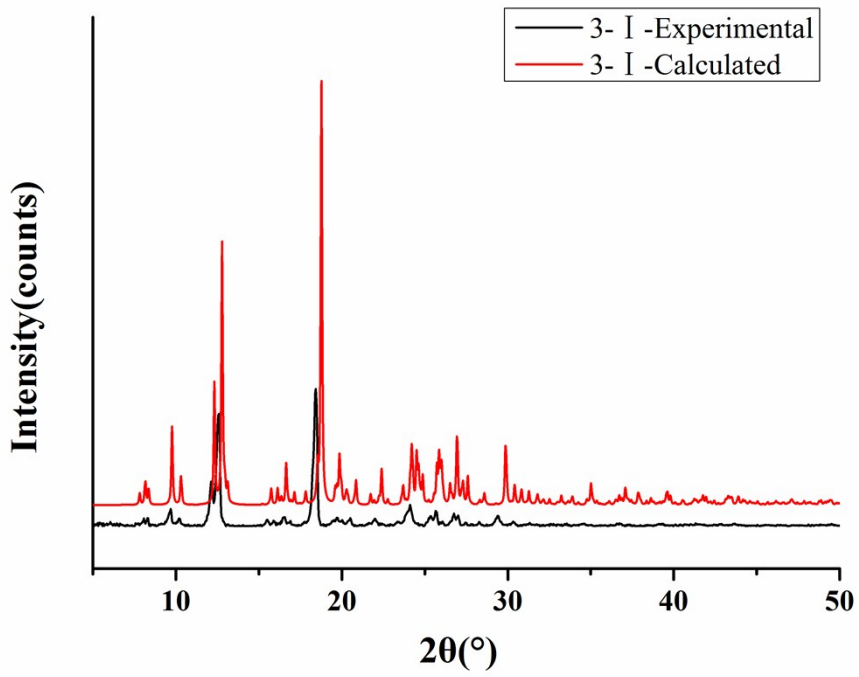
S4. Experimental and Calculated PXRD of 2-I



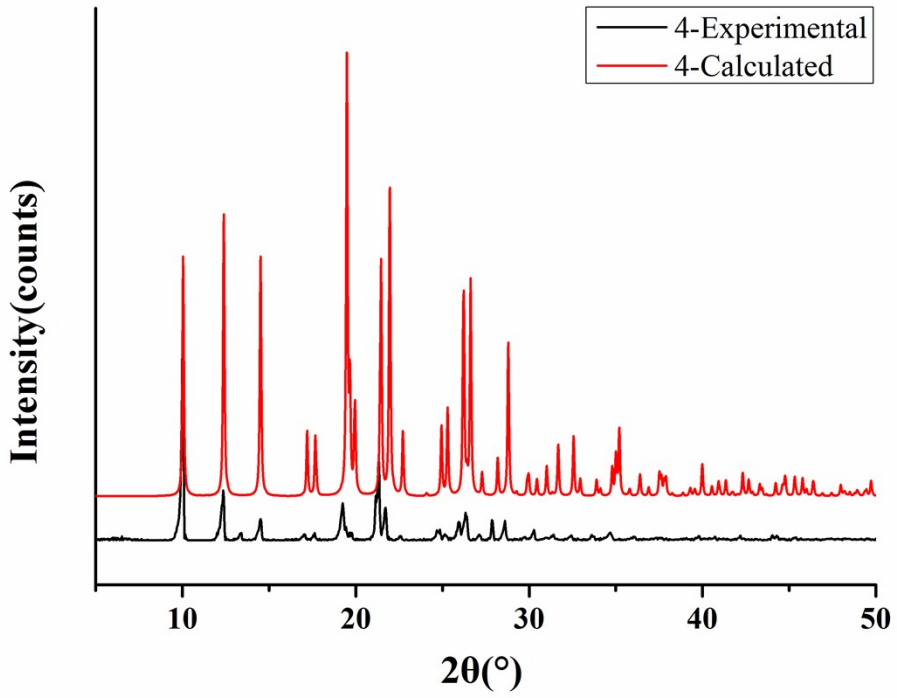
S5. Experimental and Calculated PXRD of 2-II



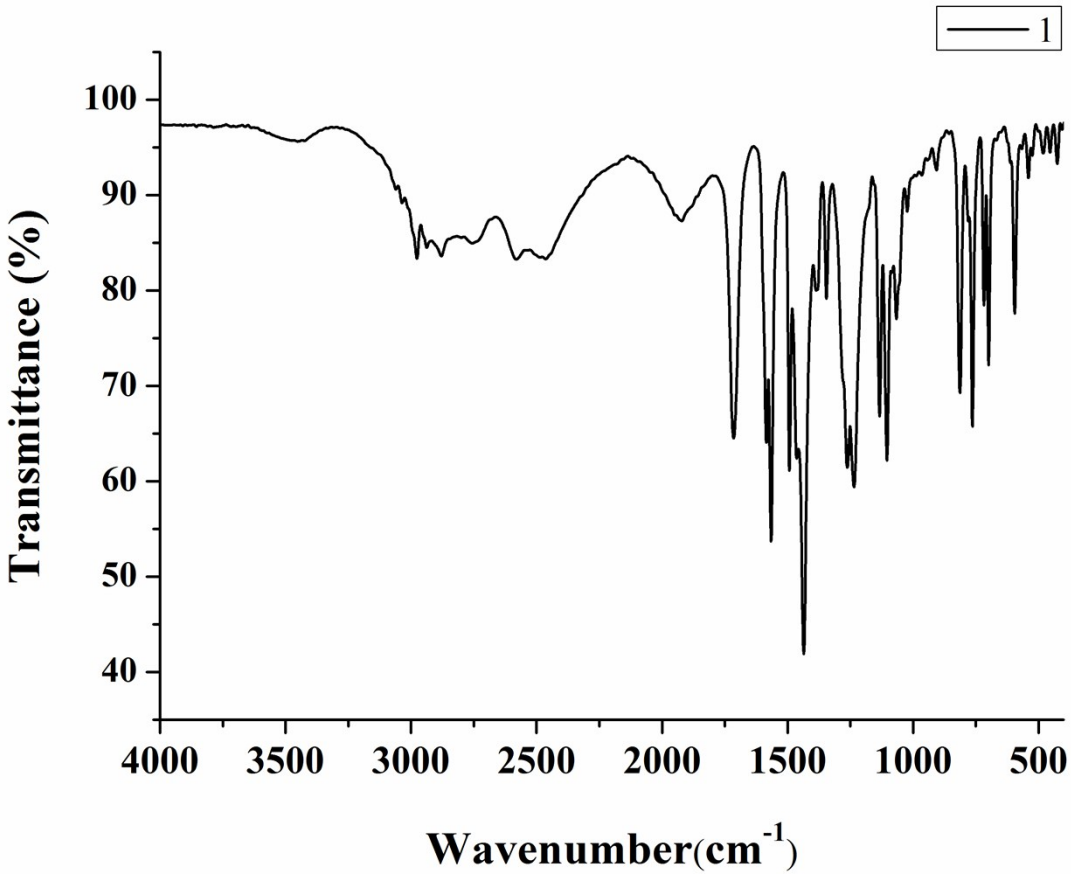
S6. Experimental and Calculated PXRD of 3-I



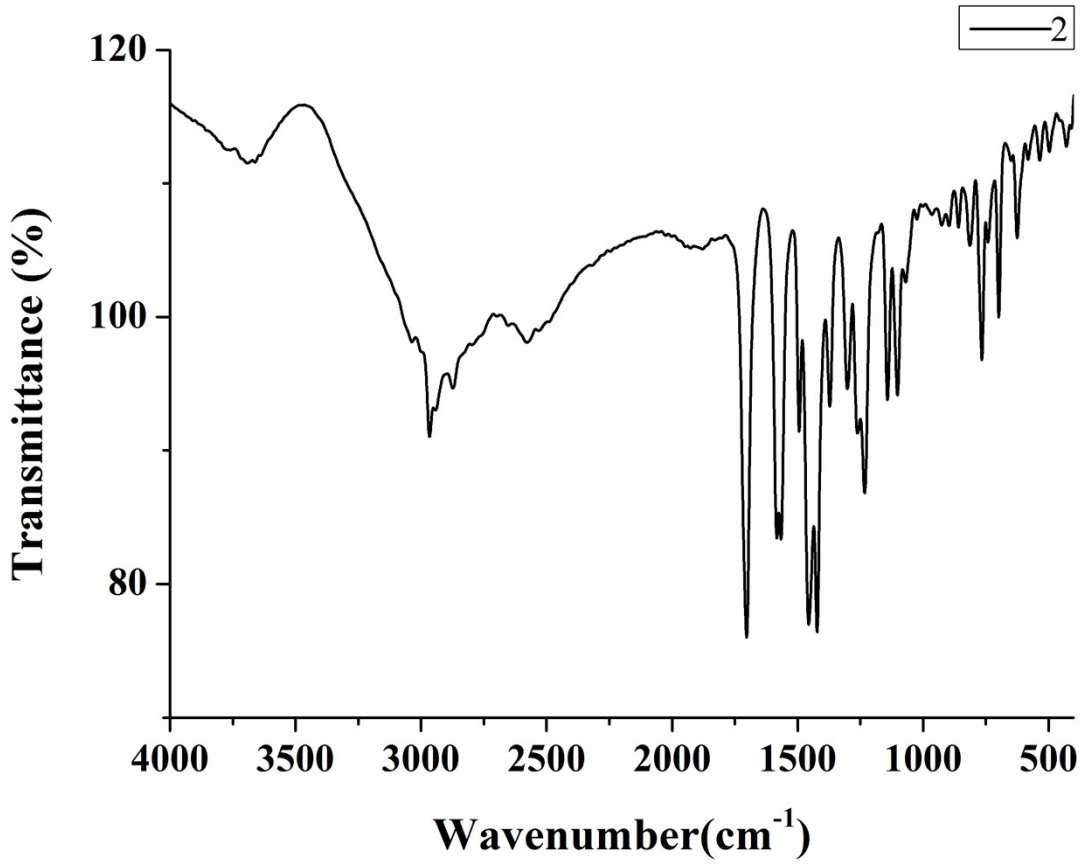
S7. Experimental and Calculated PXRD of 4



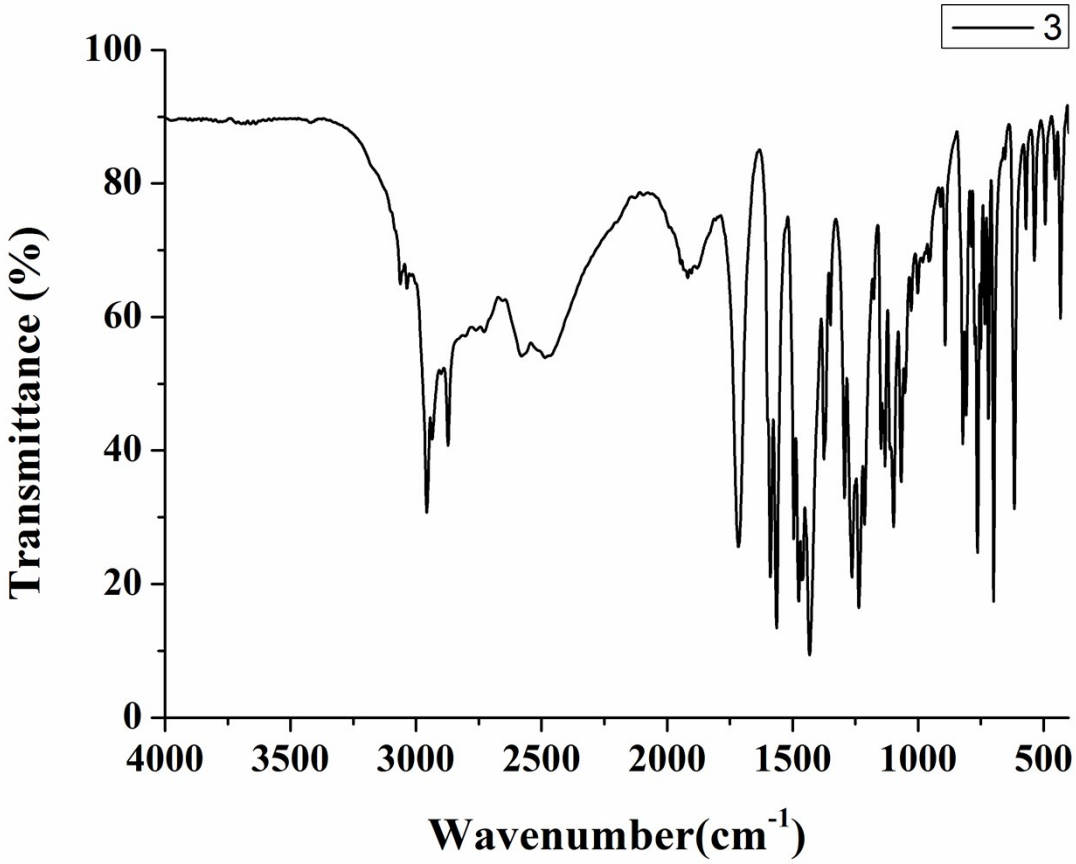
S8 IR spectrum of 1



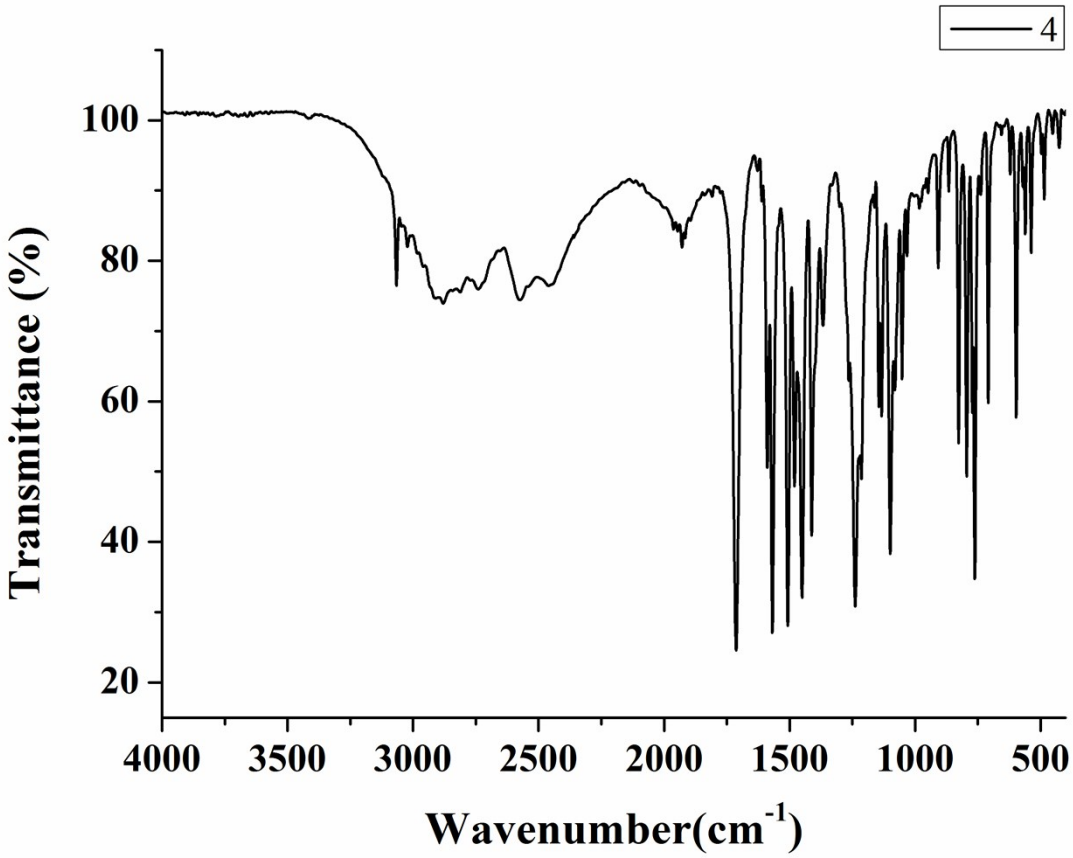
S9 IR spectrum of 2



S10 IR spectrum of 3



S11 IR spectrum of 4



1 Ting, P. C.; Kaminsky, J. J.; Sherlokc, M. H.; Tom, W. C.; Lee, J. F.; Bryant, R. W.; Watnick, A. S.; McPhail, A. T. J. Med. Chem. 1990, 33, 2697-2706.

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3 Otwinowski, Z.; Minor, W. In Methods in Enzymology: Macromolecular Crystallography, Part A; Cater, Jr., C. W., Sweet, R. M., Eds.; Academic Press: New York, 1997; Vol. 276, pp 307-326.

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