

Supporting Information

Discovery of Picomolar ABL Kinase Inhibitors Equipotent for Wild Type and T315I Mutant via Structure-Based *de novo* Design

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I. General Methods and Materials. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F₂₅₄ plates and visualization on TLC was achieved by UV light (254 and 354nm). Flash column chromatography was undertaken on silica gel (400-630 mesh). ¹H NMR was recorded on 400 MHz or 300 MHz and chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. Coupling constants, *J*, were reported in hertz unit (Hz). ¹³C NMR was recorded on 100 MHz and was fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Mass spectral data were obtained by using EI method. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane was distilled from calcium hydride. THF was distilled from sodium.

II. Preparation of Compounds

General Procedure (GP I) for Suzuki Coupling. A solution of 4-bromo-1,2-diaminobenzene **2** (300 mg, 1.60 mmol), 3,4-dimethoxyboronic acid (321 mg, 1.76 mmol), K₂CO₃ (663 mg, 4.80 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (261 mg, 0.32 mmol) in 1,4-dioxane:H₂O = 3:1 (4 mL) was heated to 100 °C for 4 h. The resulting solution was concentrated *in vacuo* and filtrated on silica-celite using EtOAc and hexane. The filtrate was concentrated and purified with flash column chromatography (EtOAc:Hexane) to give the intermediate **3** (80 mg, 20%). ¹H NMR (300 MHz, CDCl₃) δ 2.15 (s, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 6.75 (m, 1H), 6.90 (m, 3H), 7.02 (m, 2H).

General Procedure (GP II) for introducing 2-Urea or Carbamate. *methyl 5-(3,4-dimethoxyphenyl)-1H-benzof[*d*]imidazol-2-ylcarbamate (8).* 3',4'-Dimethoxybiphenyl-3,4-diamine (30 mg, 0.12 mmol) and reagent A (30 mg, 0.14 mmol) was dissolved in 0.5 mL AcOH:H₂O = 3:10 and stirred for 5 h at 100 °C. The reaction mixture was cooled to room temperature, and then

neutralized using sat. NaHCO_3 . It was concentrated *in vacuo* and purified with flash column chromatography to give the product **8** as a white solid (20 mg, 50% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.74 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 7.01 (d, $J = 8.3$, 1H), 7.13 (dd, $J = 2.1$, 8.2 Hz, 1H), 7.17 (d, $J = 2.2$ Hz, 1H), 7.34 (dd, $J = 1.7$, 8.3 Hz, 1H), 7.41 (d, $J = 8.3$ Hz, 1H), 7.60 (s, 1H), 11.64 (s, 2H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 52.4, 55.5, 55.6, 110.6, 112.2, 118.7, 120.0, 133.6, 134.2, 147.8, 148.0, 148.9, 155.1. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$, 328.1297; found 328.1293.

1-Ethyl-3-(5-(thiophene-2-carbonyl)-1H-benzof[d]imidazol-2-yl)urea (7). The solution of 3,4-dinitrobenzoic acid (300mg, 1.414 mmol) in thionyl chloride (5 mL) was stirred for 5 h at 60 °C and cooled to room temperature. The mixture was concentrated and 3,4-dinitrobenzoyl chloride was obtained as yellow solid. The yellow solid (326 mg, 1.414 mmol), AlCl_3 (566 mg, 4.245 mmol) and thiophene (113 μL , 1.414 mmol) was dissolved in anhydrous CH_2Cl_2 and stirred 5 h at 60 °C. The reaction was quenched with H_2O at 0 °C and filtrated to remove solid. The filtrate was extracted 3 times with CH_2Cl_2 and dried over MgSO_4 . The organic layer was concentrated *in vacuo* and purified with flash column chromatography (Hexane: EtOAc = 5:1) to give intermediate 3,4-(dinitrophenyl)(thiophen-2-yl)methanone (59 mg, 15% yield).

The above 3,4-(dinitrophenyl)(thiophen-2-yl)methanone (42 mg, 0.151 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (206mg, 0.910 mmol) in $\text{EtOH}:\text{H}_2\text{O}=1:1$ was stirred for 12 h at 80 °C. After cooling to room temperature, sat. NaHCO_3 was added to the reaction mixture. The precipitate was removed by filtration and the filtrate was extracted 3 times with CH_2Cl_2 , dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified with flash column chromatography (Hexane:EtOAc = 1:2) to give (3,4-diaminophenyl)(thiophen-2-yl)methanone. (33 mg, 99.7% yield). Finally, **7** was prepared (15 mg, 32% yield) according to GP II from (3,4-diaminophenyl)(thiophen-2-yl)methanone (33 mg, 0.151 mmol). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.10 (t, $J = 7.2$ Hz, 3H), 2.95-4.06 (m, 2H), 7.11 (s, 1H), 7.20-7.35 (m, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.62 (d, $J = 8.3$ Hz, 1H), 7.73 (d, $J = 3.8$ Hz, 1H), 7.94 (s, 1H), 8.04 (d, $J = 5.0$ Hz, 1H), 10.17 (s, 1H), 11.82 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 15.2,

34.1, 114.6, 122.7, 128.4, 129.8, 134.3, 134.5, 143.5, 150.5, 153.9, 186.8. HRMS (EI+) m/z calcd. for $C_{15}H_{14}N_4O_2S$ $[M + H]^+$, 315.0916; found 315.0923.

1-(5-(3,4-Dimethoxyphenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (9). Compound **9** was prepared (6 mg, 31% yield) according to GP II from 3',4'-dimethoxybiphenyl-3,4-diamine (15 mg, 0.061 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 1.10 (t, $J = 7.1$ Hz, 3H), 3.18-3.28 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 7.00 (d, $J = 8.4$ Hz, 1H), 7.12 (dd, $J = 2.1, 8.3$ Hz, 1H), 7.17 (d, $J = 2.2$ Hz, 1H), 7.26-7.40 (m, 3H), 7.58 (s, 1H), 9.85 (s, 1H), 11.47 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.7, 34.5, 55.9, 56.0, 111.0, 112.7, 119.0, 119.9, 134.8, 148.2, 149.2, 149.4, 154.5. HRMS (EI+) m/z calcd. for $C_{18}H_{20}N_4O_3$ $[M + H]^+$, 341.1614; found 341.1595.

1-Ethyl-3-(6-phenyl-1H-benzo[d]imidazol-2-yl)urea (10). Compound **10** was prepared (18 mg, 78% yield) according to GP II from biphenyl-3,4-diamine (15 mg, 0.081 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, $J = 7.2$ Hz, 1H), 3.14-3.27 (m, 2H), 7.29-7.33 (m, 3H), 7.40-7.44 (m, 3H), 7.60-7.63 (m, 3H), 9.89 (s, 1H), 11.54 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 119.7, 126.4, 126.6, 128.8, 133.1, 141.5, 148.9, 154.1. HRMS (EI+) m/z calcd. for $C_{16}H_{16}N_4O$ $[M + H]^+$, 281.1402; found 281.1401.

1-Ethyl-3-(5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)urea (11). Compound **11** was prepared (9 mg, 30% yield) according to GP II from 4-(pyridin-4-yl)benzene-1,2-diamine (20 mg, 0.10 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, $J = 7.2$ Hz, 3H), 3.19-3.26 (m, 2H), 7.23 (s, 1H), 7.47 (s, 2H), 7.66 (d, $J = 6.1$ Hz, 2H), 7.78 (s, 1H), 8.53-8.60 (m, 2H), 9.98 (s, 1H), 11.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 119.6, 121.0, 129.6, 148.1, 149.4, 150.0, 154.0. HRMS (EI+) m/z calcd. for $C_{15}H_{15}N_5O$ $[M + H]^+$, 282.1355; found 282.1360.

1-Ethyl-3-(6-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)urea (12). Compound **12** was prepared (10 mg, 46% yield) according to GP II from 4-(pyridin-3-yl)benzene-1,2-diamine (15 mg, 0.081 mmol). 1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, $J = 7.2$ Hz, 3H), 3.17-3.26 (m, 2H), 7.26 (s, 1H), 7.36 (dd, $J = 1.8, 8.3$ Hz, 1H), 7.41-7.47 (m, 2H), 7.67 (d, $J = 1.7$ Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 8.50 (dd, $J =$

1.6, 4.7 Hz, 1H), 8.85 (d, J = 2.6 Hz, 1H), 9.92 (s, 1H), 11.62 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 119.8, 123.7, 129.8, 133.8, 136.8, 147.4, 147.6, 149.1, 154.0. HRMS (EI+) m/z calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}$ $[\text{M} + \text{H}]^+$, 282.1355; found 282.1343.

1-(6-(2-Chlorophenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (13). Compound **13** was prepared (5 mg, 38% yield) according to GP II from 2'-chlorobiphenyl-3,4-diamine (15 mg, 0.068 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, J = 7.2 Hz, 3H), 3.05-3.29 (m, 2H), 7.07 (dd, J = 1.9, 8.1 Hz, 1H), 7.25 (s, 1H), 7.31-7.45 (m, 5H), 7.53 (dd, J = 1.7, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 113.1, 114.1, 122.1, 127.3, 128.5, 129.7, 131.2, 131.5, 131.8, 136.7, 140.8, 148.9, 154.0. HRMS (EI+) m/z calcd. for $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}$ $[\text{M} + \text{H}]^+$, 315.1013; found 315.1001.

Ethyl-3-(5-(2-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (14). Compound **14** was prepared (31 mg, 71% yield) according to GP II from 2'-methoxybiphenyl-3,4-diamine (30 mg, 0.14 mmol). ^1H NMR (300 MHz, DMSO- d_6) δ 1.12 (t, J = 7.2 Hz, 3H), 3.19-3.25 (m, 2H), 3.75 (s, 3H), 7.01 (t, J = 7.3 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 7.12 (dd, J = 1.7, 8.1 Hz, 1H), 7.24-7.30 (m, 2H), 7.31-7.42 (m, 2H), 7.47 (d, J = 1.6 Hz, 1H), 9.86 (s, 1H), 11.51 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 55.4, 111.7, 120.6, 122.2, 127.9, 130.6, 131.0, 148.7, 154.1, 156.1. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 311.1508; found 311.1511.

1-(5-(2-Ethoxyphenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (15). Compound **15** was prepared (15 mg, 62% yield) according to GP II from 2'-ethoxybiphenyl-3,4-diamine (17 mg, 0.072 mmol). ^1H NMR (300 MHz, DMSO- d_6) δ 1.10 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H), 3.21 (p, J = 7.0 Hz, 2H), 4.02 (q, J = 6.8 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 8.2, 1.7 Hz, 1H), 7.23-7.35 (m, 4H), 7.49 (s, 1H), 9.82 (s, 1H), 11.50 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.1, 15.7, 34.5, 64.0, 113.4, 121.2, 122.6, 128.4, 131.1, 131.6, 149.1, 154.6, 155.8. HRMS (EI+) m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 325.1665; found 325.1653.

1-Ethyl-3-(5-(2-isopropoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (16). Compound **16** was prepared (10 mg, 55% yield) according to GP II from 2'-isopropoxybiphenyl-3,4-diamine (12 mg,

0.051 mmol). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.11 (t, $J = 7.2$ Hz, 3H), 1.18 (d, $J = 6.1$ Hz, 6H), 3.15-3.27 (m, 2H), 4.50 (p, $J = 6.0$ Hz, 1H), 6.98 (td, $J = 1.1, 7.4$ Hz, 1H), 7.06 (d, $J = 7.4$ Hz, 1H), 7.15 (dd, $J = 1.7, 8.3$ Hz, 1H), 7.20-7.30 (m, 3H), 7.33 (d, $J = 8.2$ Hz, 1H), 7.50 (s, 1H), 9.85 (s, 1H), 11.52 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 15.3, 21.8, 34.1, 69.8, 115.0, 120.8, 122.2, 127.7, 130.9, 132.1, 148.6, 153.9, 154.2. HRMS (EI+) m/z calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 339.1821; found 339.1798.

1-Ethyl-3-(5-(2-phenoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (17). Compound **17** was prepared (13 mg, 62% yield) according to GP II from 2'-phenoxybiphenyl-3,4-diamine (15 mg, 0.054 mmol). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.09 (t, $J = 7.2$ Hz, 3H), 3.18-3.22 (m, 2H), 6.87 (d, $J = 7.6$ Hz, 2H), 7.01 (t, $J = 7.2$ Hz, 2H), 7.18 (dd, $J = 1.7, 8.3$ Hz, 1H), 7.21-7.36 (m, 6H), 7.45-7.55 (m, 2H), 9.82 (s, 1H), 11.51 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 15.2, 34.0, 117.4, 120.4, 121.7, 122.5, 124.5, 128.3, 129.8, 131.4, 134.3, 148.8, 152.6, 154.0, 157.4. HRMS (EI+) m/z calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 373.1665; found 373.1646.

1-Ethyl-3-(5-o-tolyl-1H-benzo[d]imidazol-2-yl)urea (18). Compound **18** was prepared (10 mg, 34% yield) according to GP II from 2'-methylbiphenyl-3,4-diamine (20 mg, 0.10 mmol). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.10 (t, $J = 7.2$ Hz, 3H), 2.22 (s, 3H), 3.16-3.25 (m, 2H), 6.95 (dd, $J = 1.5, 8.1$ Hz, 1H), 7.20-7.27 (m, 6H), 7.37 (d, $J = 8.1$ Hz, 1H), 9.85 (s, 1H), 11.52 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 15.2, 20.3, 34.0, 121.7, 125.7, 126.6, 129.8, 130.1, 133.7, 134.8, 142.4, 148.7, 154.1. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$, 295.1559; found 295.1557.

1-Ethyl-3-(5-p-tolyl-1H-benzo[d]imidazol-2-yl)urea (19). Compound **19** was prepared (12 mg, 55% yield) according to GP II from 4'-methylbiphenyl-3,4-diamine (15 mg, 0.075 mmol). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.11 (t, $J = 7.1$ Hz, 3H), 2.32 (s, 3H), 3.16-3.28 (m, 2H), 7.23 (d, $J = 7.9$ Hz, 2H), 7.26-7.34 (m, 2H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.50 (d, $J = 7.8$ Hz, 2H), 7.56 (s, 1H), 9.89 (s, 1H), 11.47 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 15.2, 20.6, 34.1, 119.5, 126.4, 129.4, 133.0, 135.5, 138.6, 148.9, 154.1. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$, 295.1559; found 295.1537.

1-Ethyl-3-(6-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)urea (20). Compound **20** was prepared (4 mg, 19% yield) according to GP II from 3'-methylbiphenyl-3,4-diamine (15 mg, 0.075 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.11 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 3.18-3.25 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.28-7.32 (m, 3H), 7.33-7.48 (m, 3H), 7.59 (s, 1H), 9.98 (s, 1H), 11.54 (s, 1H). ¹³C NMR (100 MHz DMSO-*d*₆) δ 15.3, 21.2, 34.1, 113.1, 119.7, 123.8, 127.1, 127.4, 128.7, 133.2, 137.8, 141.5, 149.0, 154.1. HRMS (EI⁺) *m/z* calcd. for C₁₇H₁₈N₄O [M + H]⁺, 295.1559; found 295.1562.

1-(5-(2,6-Dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-3-ethylurea (21). Compound **21** was prepared (10 mg, 44% yield) according to GP II from 2',6'-dimethylbiphenyl-3,4-diamine (15 mg, 0.070 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.10 (t, *J* = 7.2 Hz, 3H), 1.95 (s, 6H), 3.18-3.23 (m, 2H), 6.73 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.03-7.15 (m, 4H), 7.32 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 9.85 (s, 1H), 11.52 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 15.3, 20.6, 34.0, 121.23, 126.5, 127.1, 132.6, 135.6, 142.4, 148.6, 154.1. HRMS (EI⁺) *m/z* calcd. for C₁₈H₂₀N₄O [M + H]⁺, 309.1715; found 309.1716.

1-Ethyl-3-(5-(3-methoxyphenoxy)-1*H*-benzo[d]imidazol-2-yl)urea (22). 3-Methoxyphenol (67 μL, 0.61 mmol) and 60% NaH (26 mg, 0.64 mmol) in anhydrous DMF was stirred for 10 min at 90 °C and 5-chloro-2-nitroaniline (100 mg, 0.58 mmol) was added to reaction mixture. It was additionally stirred for 24 h and cooled to room temperature. To a reaction mixture was added sat. NH₄Cl, and the generated precipitate was filtrated. The solid was purified with flash column chromatography to give 4-(-3-methoxyphenoxy)-2-nitroaniline (44 mg, 30% yield). 4-(-3-methoxyphenoxy)-2-nitroaniline (44 mg, 0.17 mmol) and SnCl₂·2H₂O (191 mg, 0.85 mmol) in EtOH:H₂O = 4:1 was stirred for 12 h at 80 °C. After cooling to room temperature, sat. NaHCO₃ was added to the reaction mixture. The precipitate was removed by filtration and the filtrate was extracted 3 times with CH₂Cl₂, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified with flash column chromatography (Hexane:EtOAc) to give 4-(3-methoxyphenoxy)-benzene-1,2-diamine (27.7 mg, 71% yield). Compound **23** was prepared (17.0 mg, 43% yield) according to GP II from 4-(3-methoxyphenoxy)-benzene-1,2-diamine (27.7 mg, 0.120 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.09 (t, *J* = 7.2 Hz,

3H), 3.19 (qd, $J = 5.4, 7.1$ Hz, 2H), 3.69 (s, 3H), 6.44 (ddd, $J = 0.9, 2.4, 8.2$ Hz, 1H), 6.48 (t, $J = 2.3$ Hz, 1H), 6.55-6.66 (m, 1H), 6.75 (dd, $J = 2.3, 8.5$ Hz, 1H), 7.02 (s, 1H), 7.20 (t, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 8.5$ Hz, 1H), 9.87 (s, 1H), 11.52 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 55.1, 103.3, 107.8, 109.2, 113.0, 130.2, 149.0, 150.0, 154.0, 159.8, 160.6. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_3$ $[\text{M} + \text{H}]^+$, 327.1457; found 327.1453.

1-(5-(2-Chlorophenoxy)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (23). 2-Chlorophenol (125 μL , 1.23 mmol) and 60% NaH (70 mg, 1.75 mmol) in anhydrous DMF was stirred for 10 min at 90 $^\circ\text{C}$ and 5-chloro-2-nitroaniline (200 mg, 1.16 mmol) was added to reaction mixture. It was additionally stirred for 24 h and cooled to room temperature. To a reaction mixture was added sat. NH_4Cl , and the generated precipitate was filtrated. The solid was purified with flash column chromatography to give nitroaniline (31.2 mg, 11% yield).

The above product (31.2 mg, 0.12 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (133 mg, 0.59 mmol) in $\text{EtOH}:\text{H}_2\text{O} = 4:1$ was stirred for 12 h at 80 $^\circ\text{C}$. After cooling to room temperature, sat. NaHCO_3 was added to the reaction mixture. The precipitate was removed by filtration and the filtrate was extracted 3 times with CH_2Cl_2 , dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified with flash column chromatography (Hexane:EtOAc) to give 4-(2-chlorophenoxy)-benzene-1,2-diamine (13.8 mg, 48% yield). Compound **23** was prepared (10.1 mg, 52 % yield) according to GP II from 4-(2-chlorophenoxy)-benzene-1,2-diamine (13.8 mg, 0.058 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 1.09 (t, $J = 7.2$ Hz, 3H), 3.19 (qd, $J = 5.5, 7.2$ Hz, 2H), 6.73 (dd, $J = 2.4, 8.5$ Hz, 1H), 6.89 (dd, $J = 1.5, 8.2$ Hz, 1H), 6.97 (s, 1H), 7.10 (td, $J = 1.5, 7.7$ Hz, 1H), 7.21 (s, 1H), 7.27 (ddd, $J = 1.6, 7.4, 8.2$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.54 (dd, $J = 1.6, 8.0$ Hz, 1H), 9.90 (s, 1H), 11.52 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.3, 34.1, 112.1, 119.1, 123.3, 124.0, 128.5, 130.5, 149.2, 150.3, 153.5, 154.0. HRMS (EI+) m/z calcd. for $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}_2$ $[\text{M} + \text{H}]^+$, 331.0962; found 331.0952.

1-(5-(3-Cyanophenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (24). Compound **24** was prepared (10 mg, 47% yield) according to GP II from 3',4'-diaminobiphenyl-3-carbonitrile (15 mg, 0.071 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, $J = 7.2$ Hz, 3H), 3.14-3.27 (m, 2H), 7.27 (s, 1H), 7.39 (dd, J

= 1.8, 8.2 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.69 (d J = 1.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 9.95 (s, 1H), 11.64 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 111.9, 118.9, 119.8, 130.0, 130.8, 131.4, 142.6, 149.2, 154.0. HRMS (EI+) m/z calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}$ $[\text{M} + \text{H}]^+$, 306.1355; found 306.1351.

1-(5-(2,6-Dichlorophenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (25). Compound **25** was prepared (9 mg, 45% yield) according to GP II from 2',6'-dichlorobiphenyl-3,4-diamine (15 mg, 0.059 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, J = 7.2 Hz, 3H), 3.15-3.26 (m, 2H), 6.85 (dd, J = 1.6, 8.1 Hz, 1H), 7.19 (s, 1H), 7.24 (s, 1H), 7.36-7.43 (m, 2H), 7.55 (d, J = 8.0 Hz, 2H), 9.91 (s, 1H), 11.64 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 121.8, 128.2, 129.6, 134.5, 139.8, 149.0, 154.0. HRMS (EI+) m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$, 349.0623; found 349.0607.

1-Ethyl-3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-2-yl)urea (26). Compound **26** was prepared (7 mg, 22% yield) according to GP II from 3'-fluorobiphenyl-3,4-diamine (20 mg, 0.098 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 1.11 (t, J = 7.2 Hz, 3H), 2.91-3.73 (m, 2H), 7.10 (td, J = 6.6, 2.9 Hz, 1H), 7.27 (s, 1H), 7.35 (dd, J = 8.3, 1.8 Hz, 1H), 7.39-7.50 (m, 4H), 7.66 (s, 1H), 9.98 (s, 1H), 11.51 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.2, 34.1, 112.8, 113.0, 113.0, 113.2, 119.7, 122.5, 122.6, 130.5, 130.6, 131.6, 144.0, 144.0, 149.1, 154.0, 161.4, 163.9. HRMS (EI+) m/z calcd. for $\text{C}_{16}\text{H}_{15}\text{FN}_4\text{O}$ $[\text{M} + \text{H}]^+$, 299.1308; found 299.1317.

General Procedure (GP III) for preparation of 6-aryl 2-aminobenzothiazole.

A solution of 2-amino-6-bromobenzothiazole (300 mg, 1.31 mmol), 3,4-dimethoxyboronic acid (357 mg, 1.96 mmol), K_2CO_3 (543 mg, 3.93 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (214 mg, 0.26 mmol) in 1,4-dioxane: H_2O = 3:1 (4 mL) was heated to 120 $^\circ\text{C}$ for 6 h. The resulting solution was concentrated *in vacuo* and filtrated on silica-celite using EtOAc and hexane. The filtrate was concentrated and purified with flash column chromatography (EtOAc:Hexane) to give the 6-(3,4-dimethoxyphenyl)benzo[d]thiazol-2-amine (230 mg, 41%). ^1H NMR (300 MHz, DMSO- d_6) δ 3.78 (s,

3H), 3.84 (s, 3H), 7.00 (d, $J = 8.4$, 1H), 7.17 (dd, $J = 8.3$, 2.1, 1H), 7.21 (d, $J = 2.1$, 1H), 7.35 (d, $J = 8.4$, 1H), 7.49 (m, 3H), 7.96 (d, $J = 1.8$, 1H).

General Procedure (GP IV) for introducing 2-Urea.

1-(6-(3,4-Dimethoxyphenyl)benzo[d]thiazol-2-yl)-3-ethylurea (27). To a solution of 6-(3,4-dimethoxyphenyl)benzo[d]thiazol-2-amine (16 mg, 0.056 mmol) in 1, 4-dioxane was added ethyl isocyanate (110 μ L, 0.28 mmol) and stirred for 15 h at 90 °C. After reaction finished, the resulting solution was concentrated *in vacuo* and then, H₂O was added. It was heated to 100 °C for 3 h. The resulting solid was filtrated and washed with H₂O and additionally purified with flash column chromatography to give compound **27** (9.7 mg, 46% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.09 (t, $J = 7.1$ Hz, 3H), 3.17-3.23 (m, 2H), 3.77 (s, 3H), 3.85 (s, 3H), 6.75 (s, 1H), 6.94-7.07 (m, 1H), 7.16-7.23 (m, 1H), 7.26 (s, 1H), 7.62 (s, 2H), 8.16 (s, 1H), 10.70 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 15.2, 34.3, 55.5, 55.6, 110.5, 112.2, 118.7, 118.9, 119.6, 124.5, 132.3, 132.8, 134.9, 148.1, 148.2, 149.1, 153.7, 160.0. HRMS (EI+) m/z calcd. for C₁₈H₁₉N₃O₃S [M + H]⁺, 358.1225; found 358.1220.

1-Ethyl-3-(6-(pyridin-4-yl)benzo[d]thiazol-2-yl)urea (28). Compound **28** was prepared (10 mg, 25% yield) according to GP IV from 6-(pyridin-4-yl)benzo[d]thiazol-2-amine (41.2 mg, 0.137 mmol). ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, $J = 7.2$ Hz, 3H), 3.43 (qd, $J = 5.4$, 7.2 Hz, 2H), 7.41-7.56 (m, 2H), 7.62 (dd, $J = 1.8$, 8.5 Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.94 (d, $J = 1.8$ Hz, 1H), 8.47-8.80 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 15.1, 35.2, 104.1, 119.7, 120.4, 121.5, 125.2, 132.1, 133.3, 147.9, 150.1, 154.5, 162.6. HRMS (EI+) m/z calcd. for C₁₅H₁₄N₄OS [M + H]⁺, 299.0967; found 299.0960.

1-Ethyl-3-(6-(2-methoxyphenyl)benzo[d]thiazol-2-yl)urea (29). Compound **29** was prepared (18 mg 54% yield) according to GP IV from 6-(2-methoxyphenyl)benzo[d]thiazol-2-amine (26.1 mg, 0.101 mmol). ¹H NMR (300 MHz, CDCl₃) δ 1.25 (t, $J = 7.2$ Hz, 3H), 3.37-3.46 (m, 2H), 3.81 (s, 3H), 6.75-7.12 (m, 2H), 7.29-7.35 (m, 2H), 7.56 (dd, $J = 1.8$, 8.4 Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 1.7$ Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 15.1, 35.1, 55.5, 111.2, 119.1, 120.9, 122.0, 127.9, 128.6,

130.0, 130.9, 130.9, 133.9, 148.0, 154.7, 156.4, 161.9. HRMS (EI+) m/z calcd. for C₁₇H₁₇N₃O₂S [M + H]⁺, 328.1120; found 328.1117.

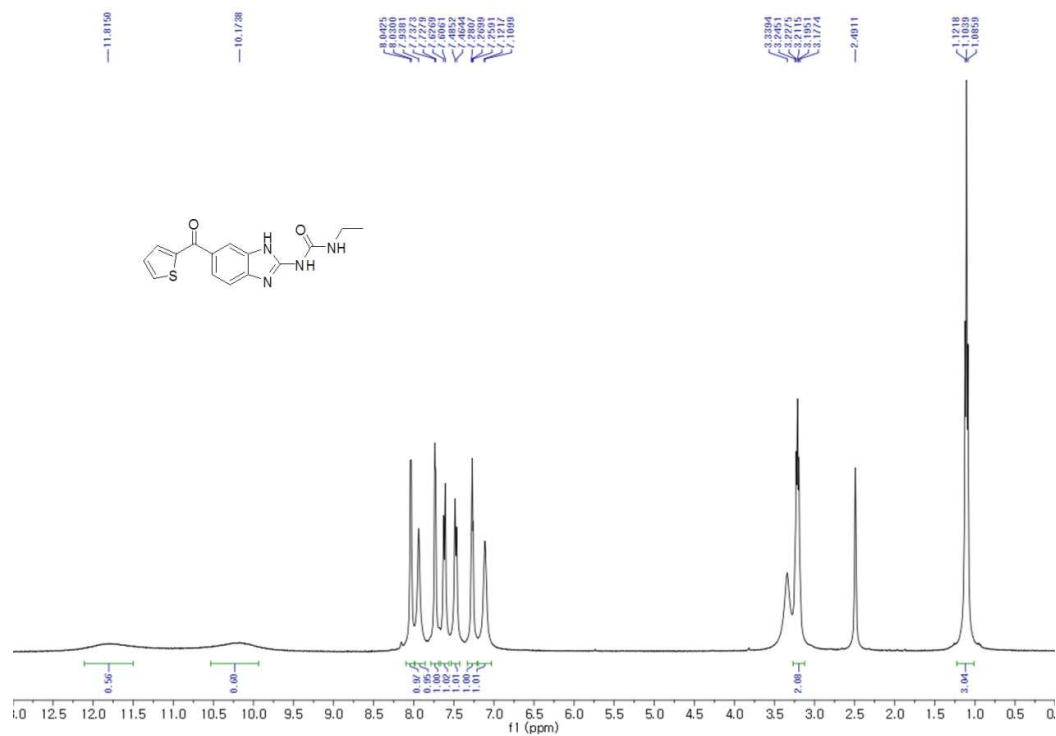
Kinase Assay. The effects of compounds on the kinase activity of ABL1 and ABL1^{T315I} were analyzed the Reaction Biology Corp. (Malvern, PA, USA) using radiometric kinase assays ([γ -³³P]-ATP). Briefly, reactions contained Abltide (EAIYAAPFAKKK) in freshly prepared Base Reaction Buffer (20 mM HEPES (pH 7.5), 10 mM MgCl₂, 1 mM EGTA, 0.02% BRIJ-35, 0.02 mg/ml BSA, 0.1 mM Na₃VO₄, 2 mM DTT, 1% DMSO). ABL1 (NP_005148.2) or ABL1^{T315I} (NP_005148.2) were delivered into the substrate solution and gently mixed. The compounds in DMSO with indicated concentrations were then delivered to the reaction. Then, ³³P-ATP (specific activity 10 Ci/μl) was added to initiate the reaction, and the mixture was further incubated for 2 h at room temperature. Reactions are spotted onto P81 ion exchange paper (Whatman # 3698-915). The filters were washed extensively in 0.75% phosphoric acid. Compounds were tested in a 10-dose IC₅₀ mode with 3-fold serial dilutions starting at 1 μM.

Appendix I

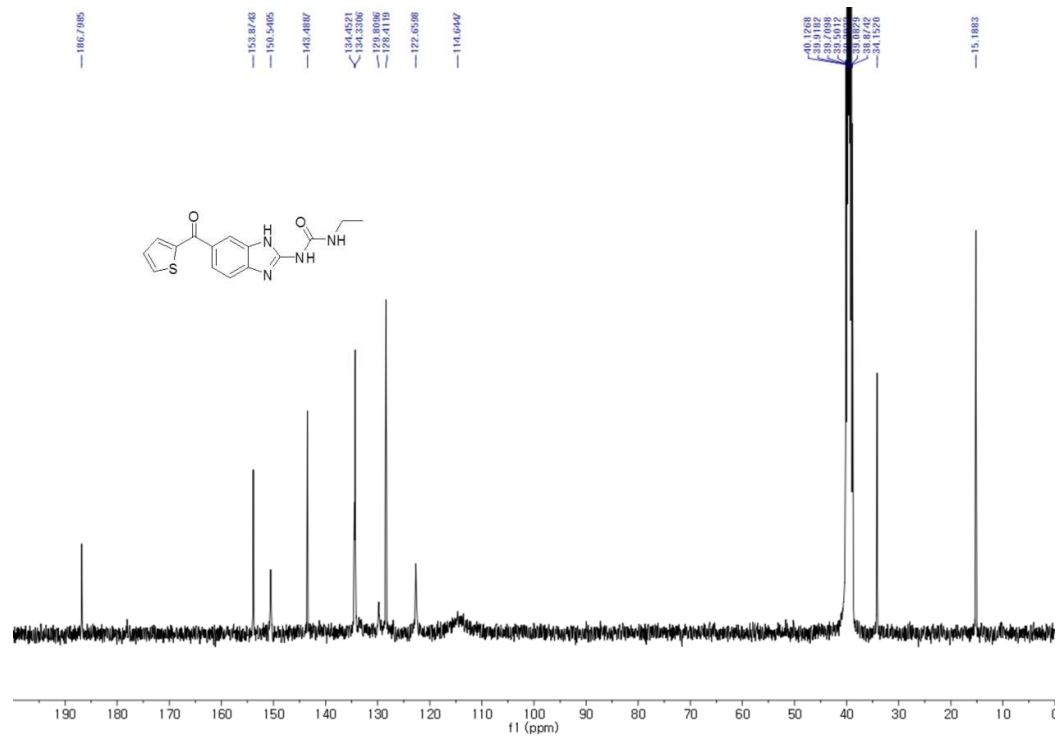
Spectral Copies of ^1H and ^{13}C NMR Data

Obtained in this Study

1-Ethyl-3-(5-(thiophene-2-carbonyl)-1H-benzo[d]imidazol-2-yl)urea (7)

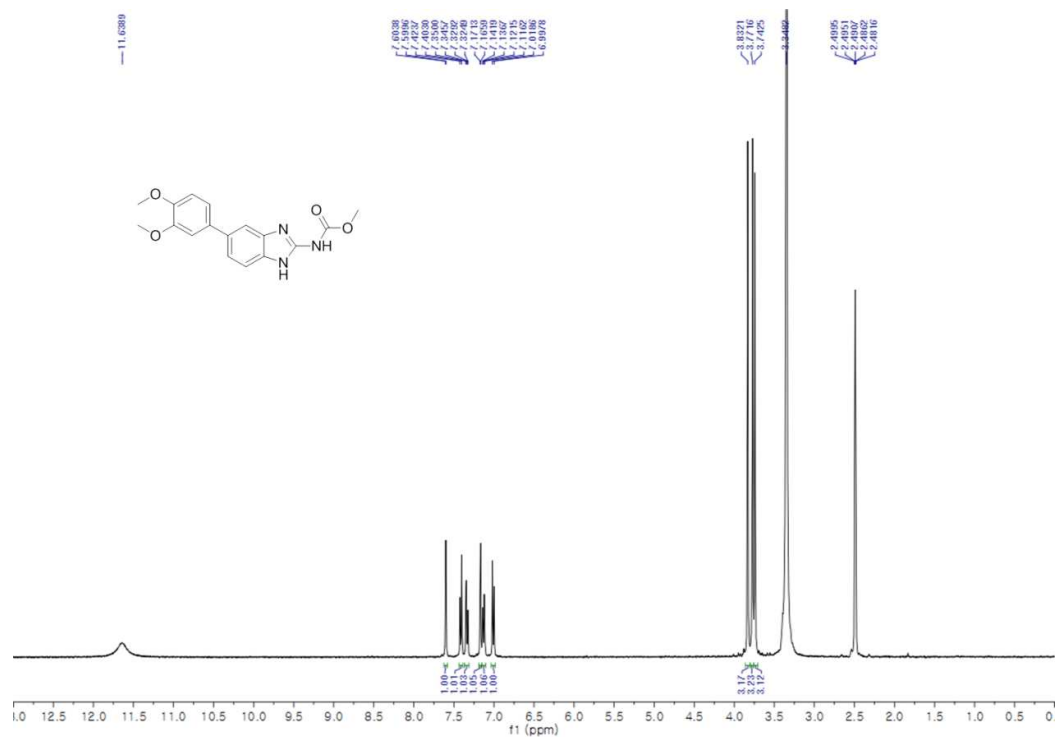


400 MHz, ¹H NMR in DMSO-*d*₆

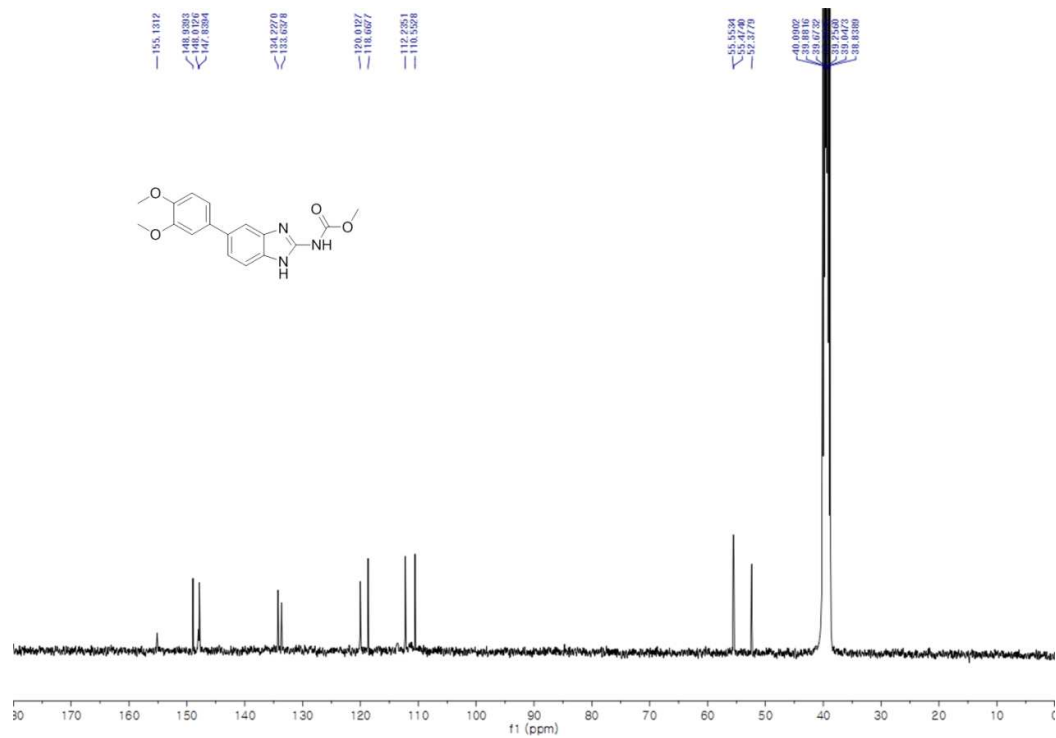


100 MHz, ¹³C NMR in DMSO-*d*₆

Methyl 5-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazol-2-ylcarbamate (8)

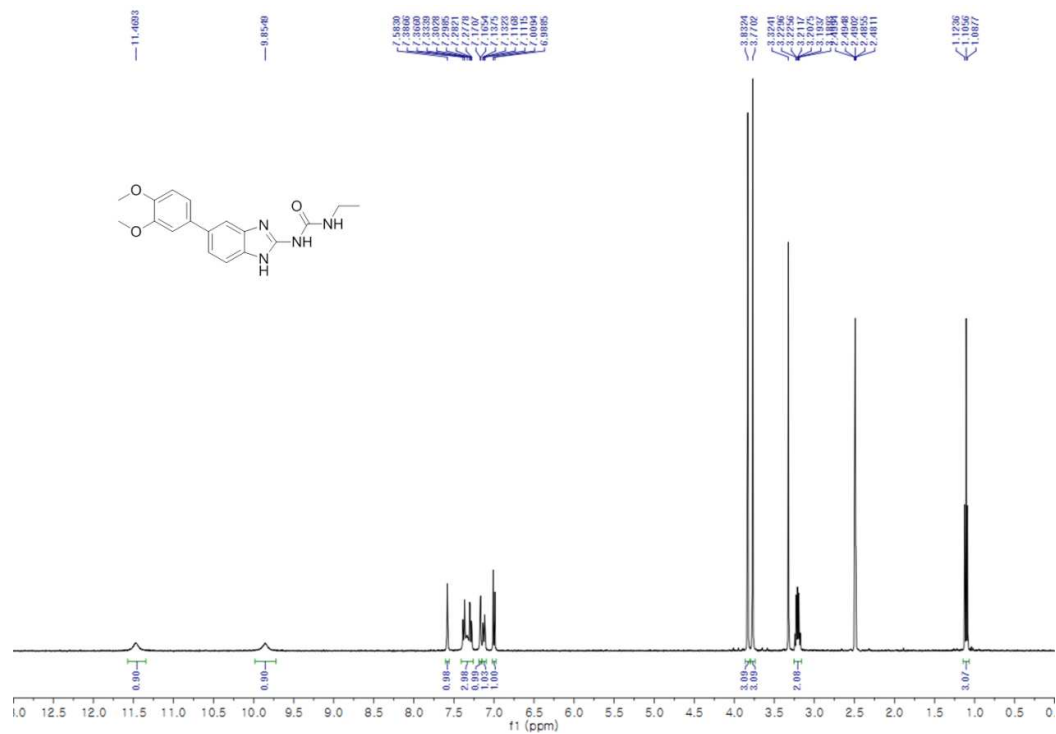


400 MHz, ¹H NMR in DMSO-*d*₆

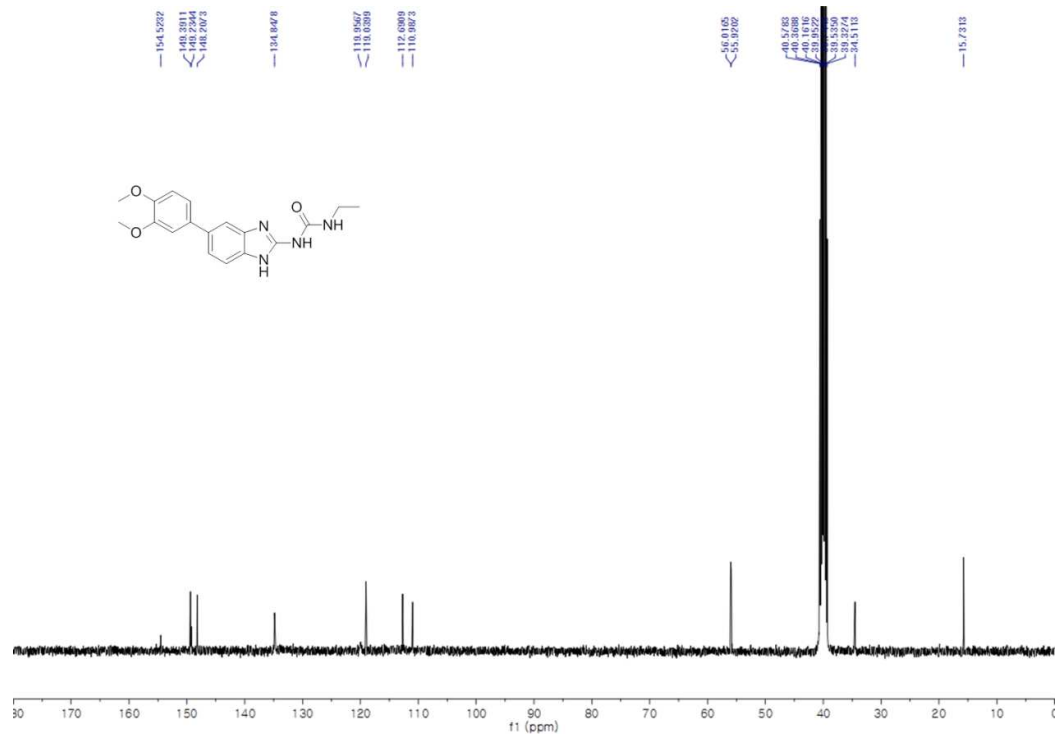


100 MHz, ¹³C NMR in DMSO-*d*₆

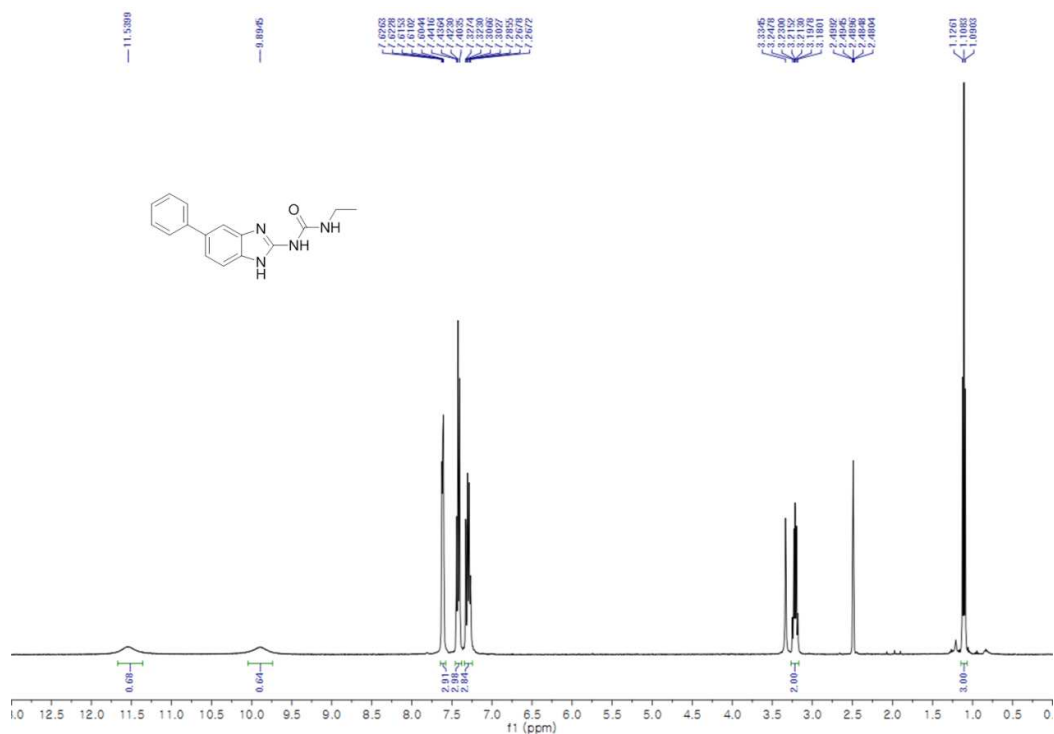
1-(5-(3,4-Dimethoxyphenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (9)



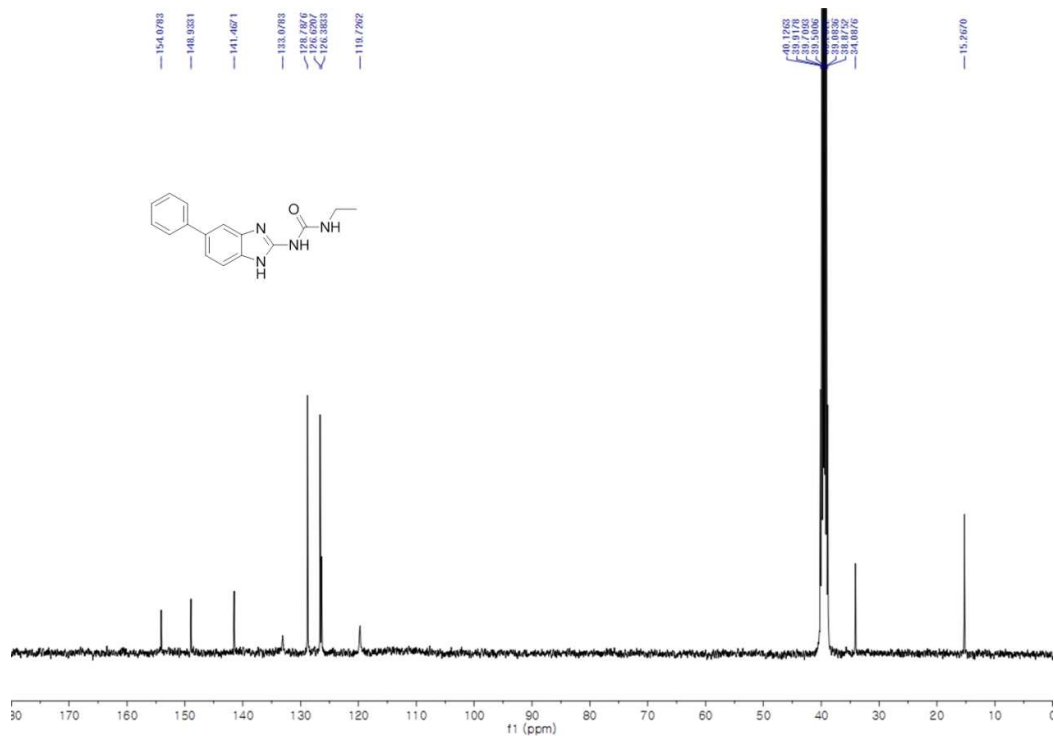
400 MHz, ¹H NMR in DMSO-*d*₆



1-Ethyl-3-(6-phenyl-1H-benzo[d]imidazol-2-yl)urea (10)

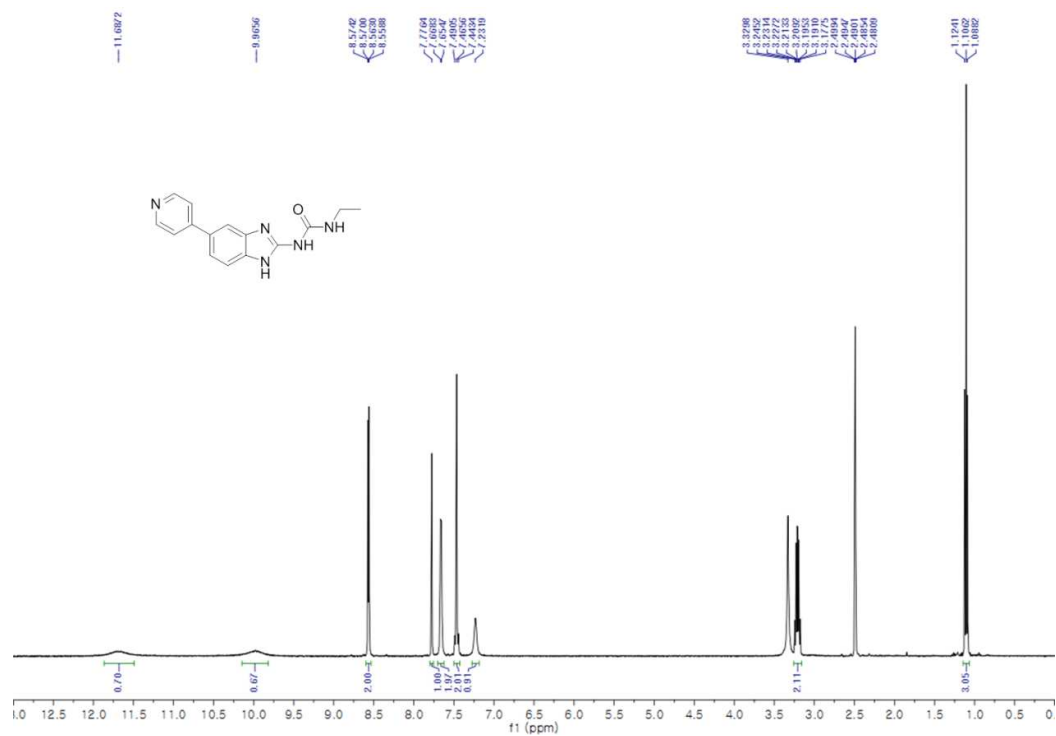


400 MHz, ¹H NMR in DMSO-*d*₆

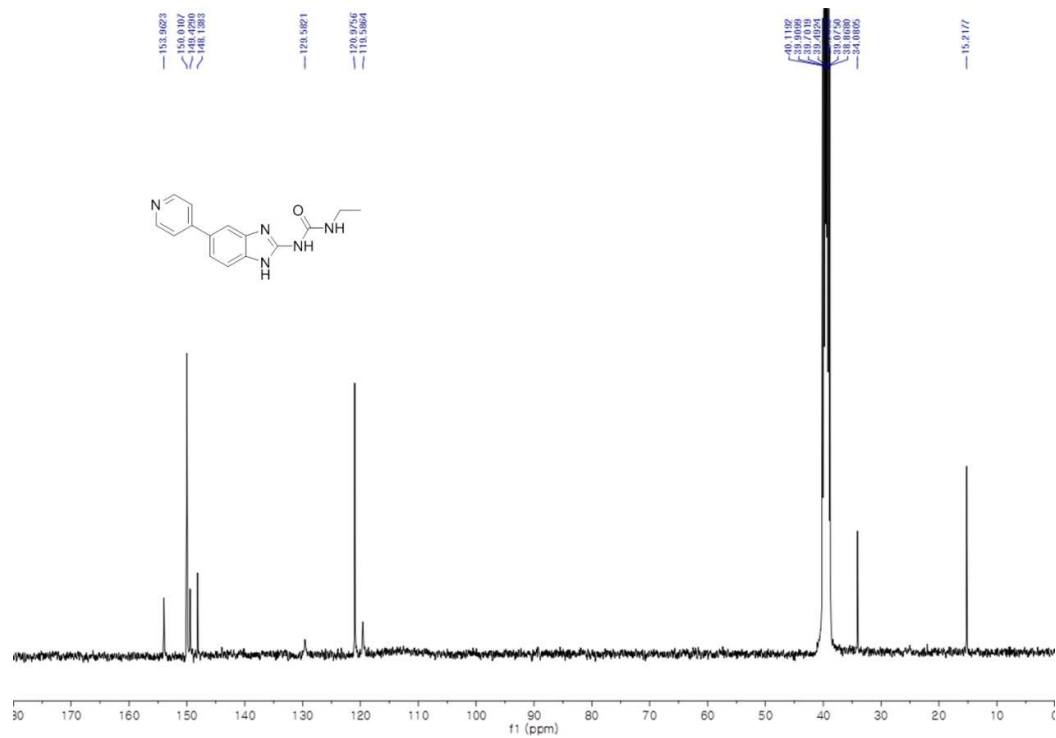


100 MHz, ¹³C NMR in DMSO-*d*₆

1-Ethyl-3-(5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)urea (11)

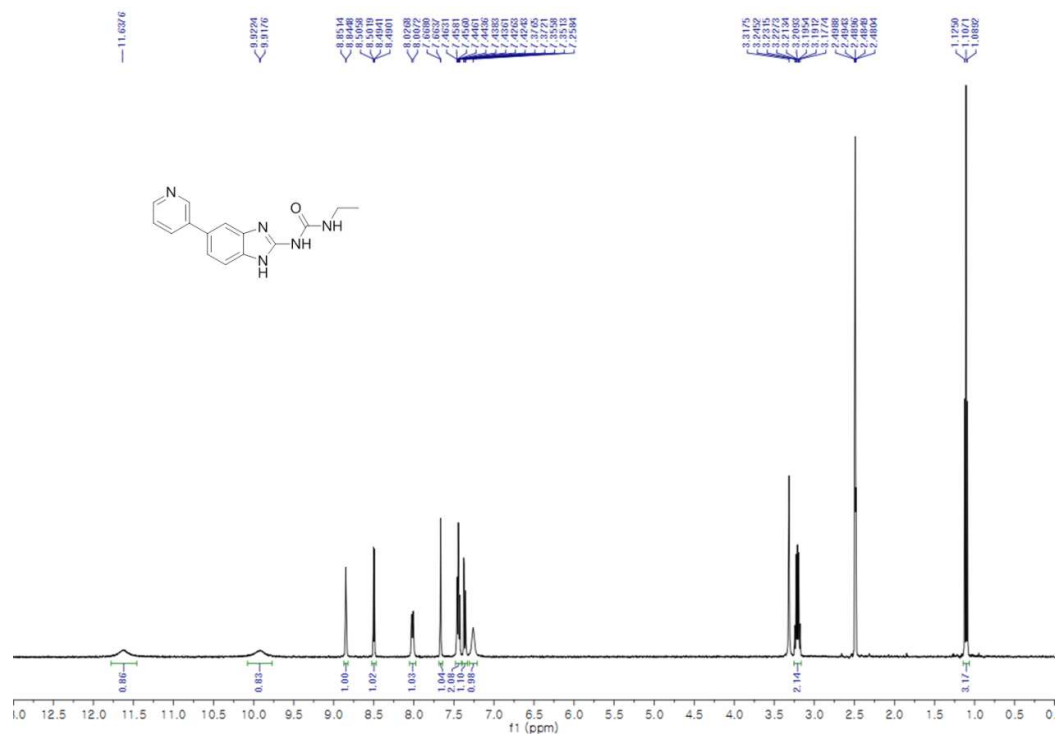


400 MHz, ¹H NMR in DMSO-*d*₆



100 MHz, ¹³C NMR in DMSO-*d*₆

1-Ethyl-3-(6-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)urea (12)



Chemical structure: CCNC(=O)Nc1nc2ccccc2c(c1)C3=CC=CC=C3Cl

¹H NMR spectrum (CDCl₃) showing peaks at 7.5460, 7.5384, 7.5300, 7.5226, 7.5178, 7.4880, 7.4146, 7.4079, 7.3958, 7.3872, 7.3825, 7.3781, 7.3527, 7.3500, 7.3420, 7.3342, 7.3203, 7.2966, 7.2824, 7.2524, 7.0783, 7.0581, 7.0525, 3.32603, 3.29605, 3.27755, 3.2725, 3.2720, 3.2581, 3.2581, 3.1954, 3.1906, 2.45411, 2.4505, 2.4501, 1.1542, 1.1485, 1.0885. Integration values are shown below the peaks: 1.01, 1.00, 1.00, 2.31, 3.03.

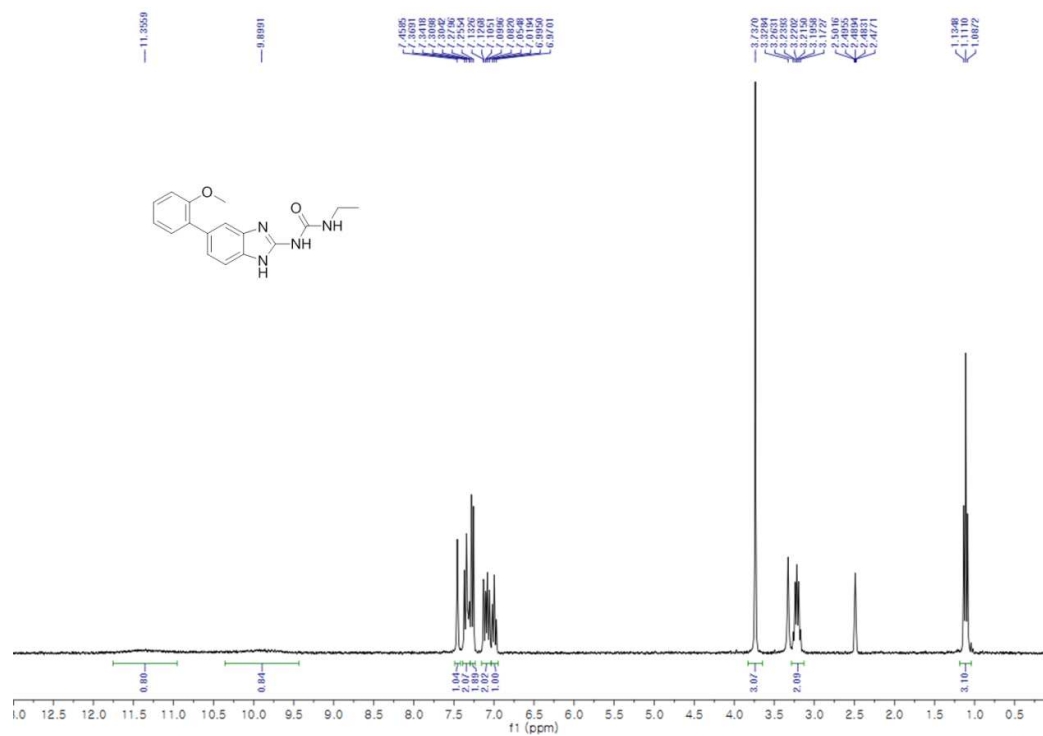
Chemical structure: CCNC(=O)Nc1nc2ccc(cc2c1-c1ccccc1Cl)O

¹³C NMR spectrum (ppm):

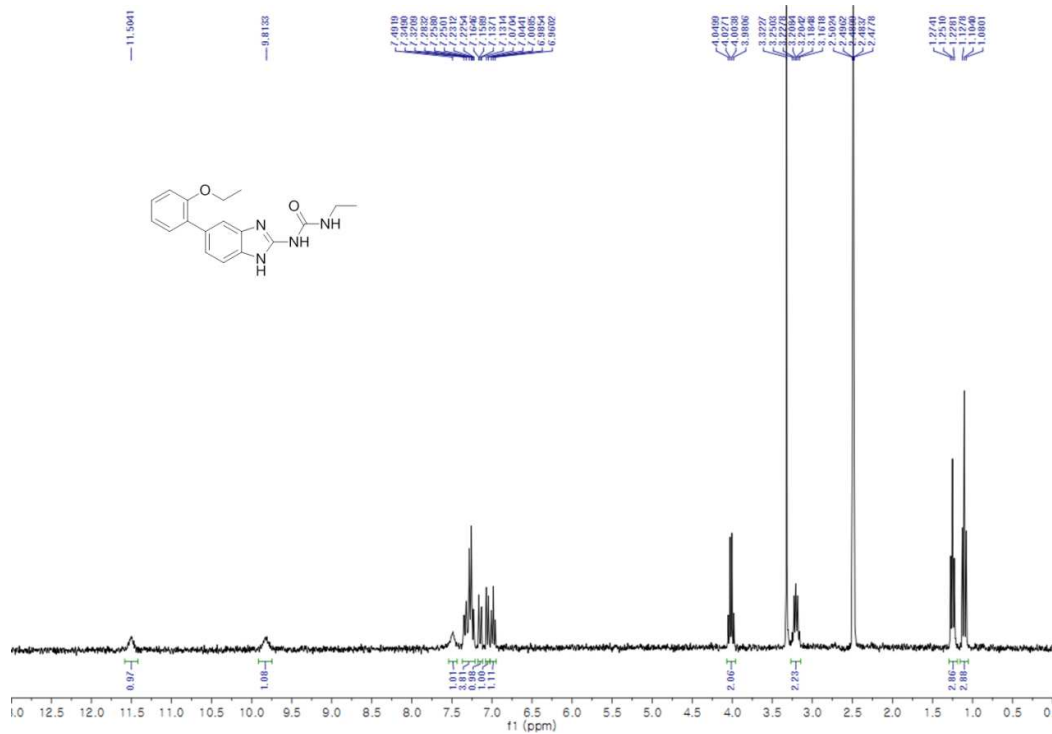
- 153.942
- 148.886
- 140.832
- 136.407
- 131.818
- 131.526
- 129.721
- 129.594
- 127.294
- 122.824
- 114.652
- 113.885
- 39.154
- 38.916
- 38.701
- 38.283
- 38.114
- 37.944
- 15.2709

100 MHz, ^{13}C NMR in DMSO- d_6

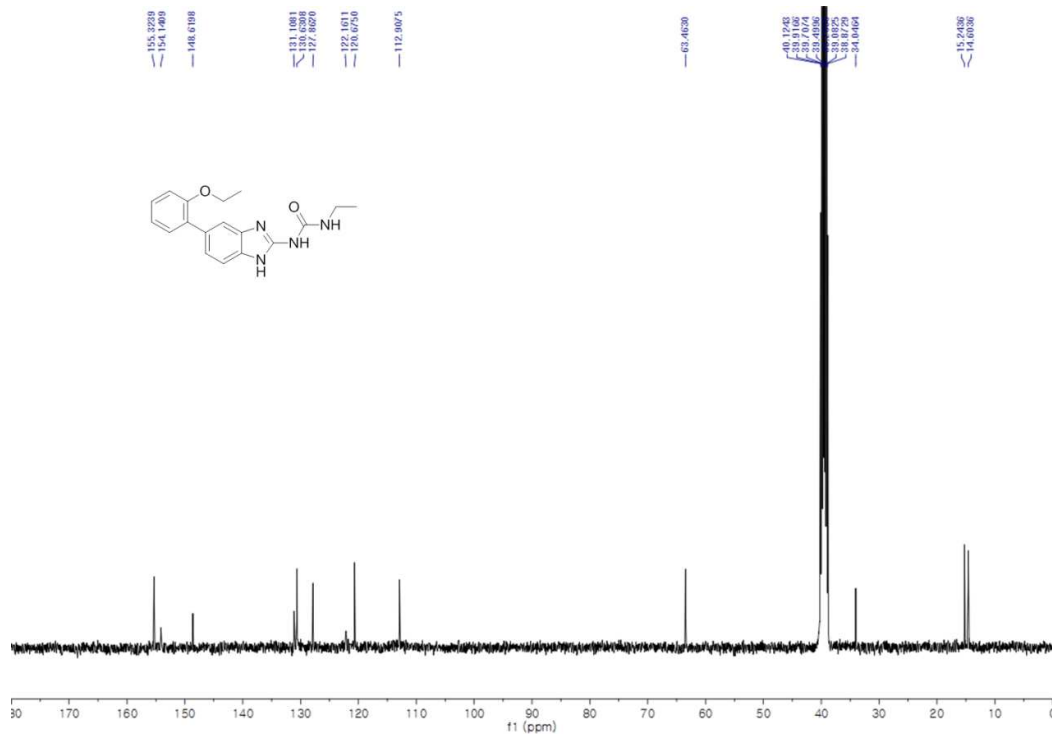
Ethyl-3-(5-(2-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (14)



1-(5-(2-Ethoxyphenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (15)

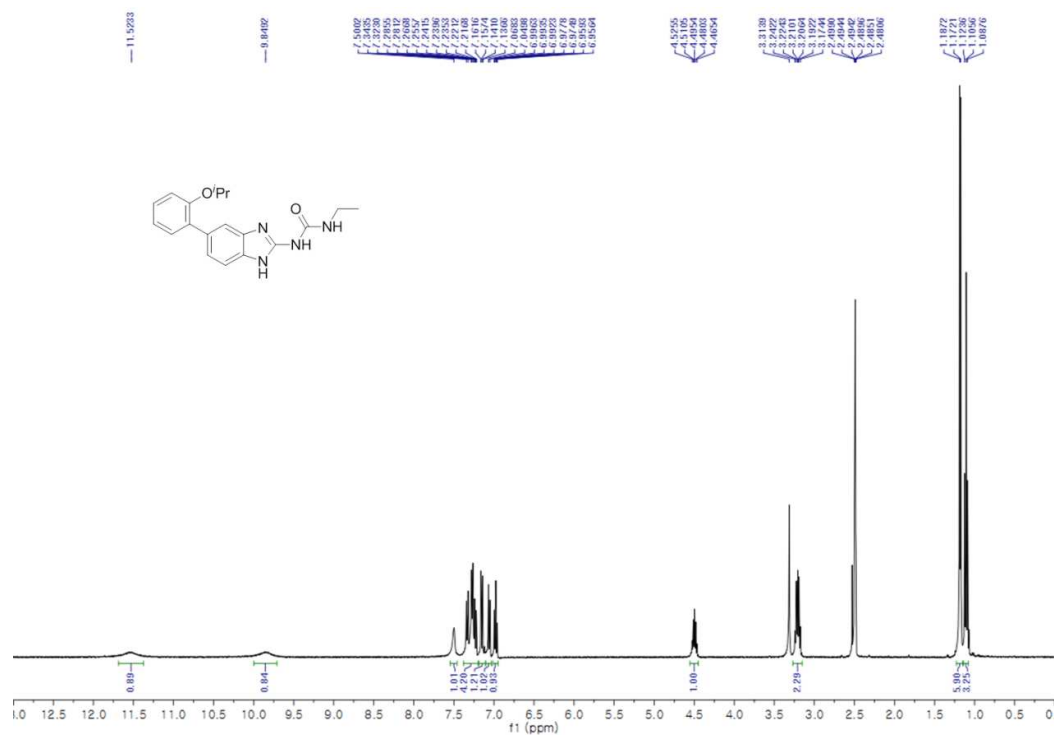


300 MHz, ^1H NMR in DMSO- d_6

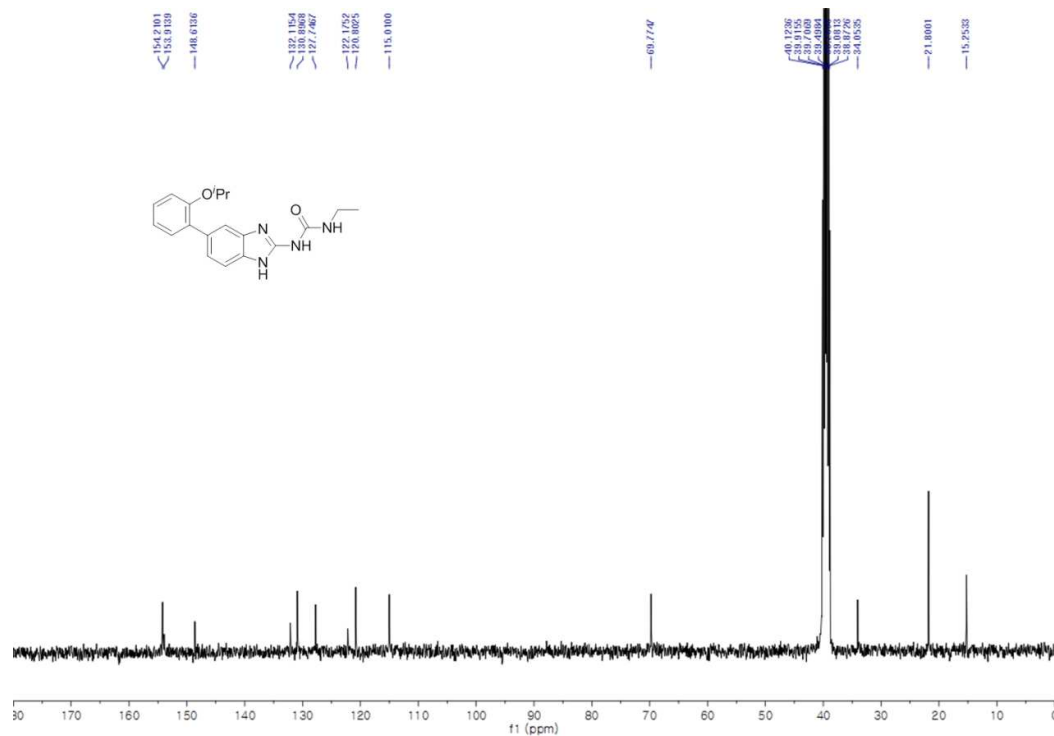


100 MHz, ^{13}C NMR in DMSO- d_6

1-Ethyl-3-(5-(2-isopropoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (16)

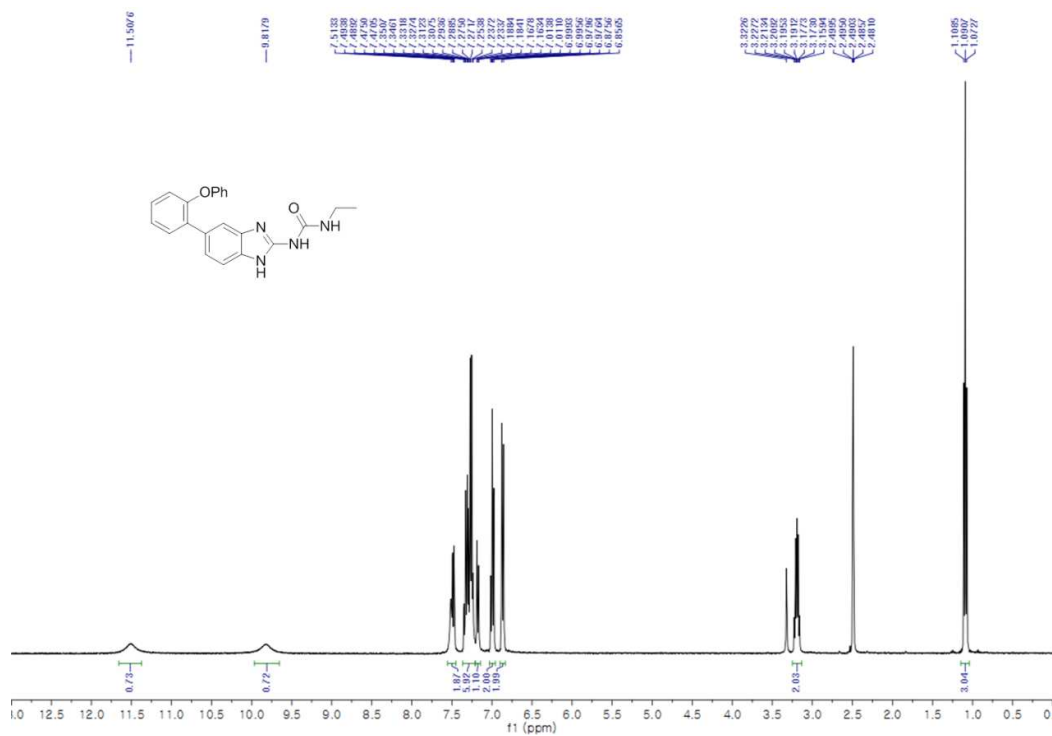


400 MHz, ¹H NMR in DMSO-*d*₆

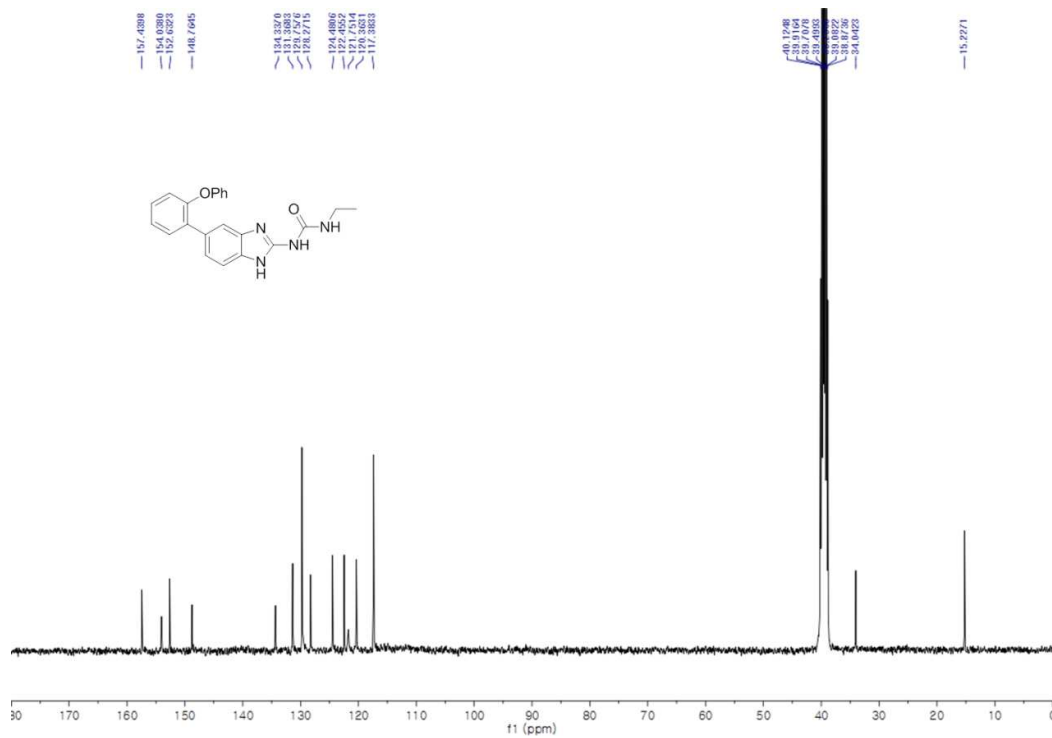


100 MHz, ¹³C NMR in DMSO-*d*₆

1-Ethyl-3-(5-(2-phenoxyphenyl)-1H-benzo[d]imidazol-2-yl)urea (17)

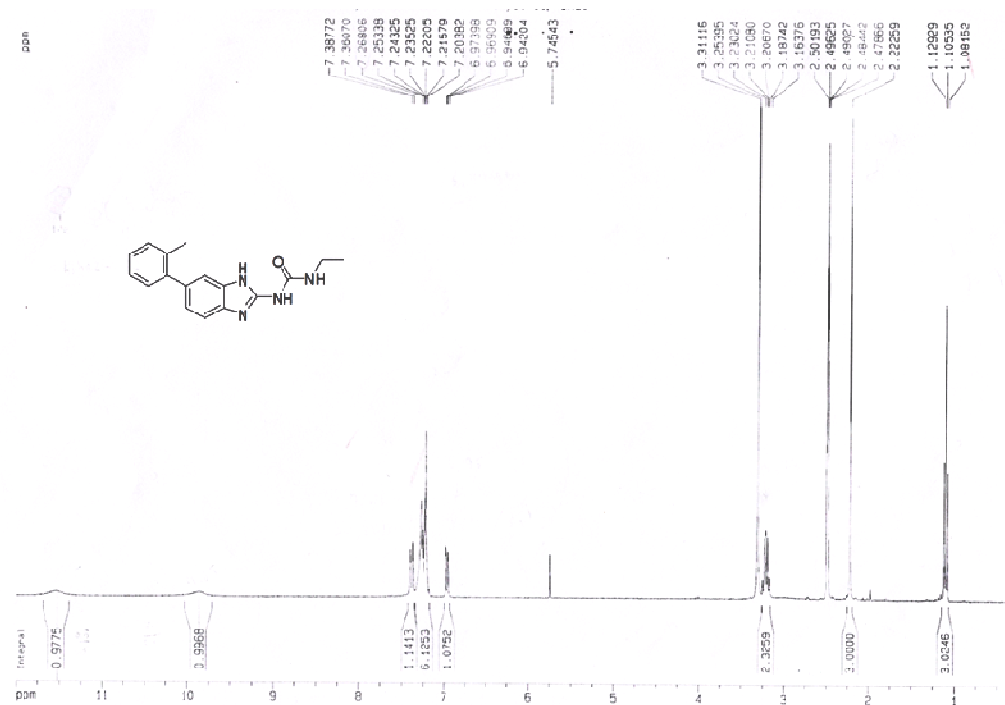


400 MHz, ^1H NMR in DMSO- d_6

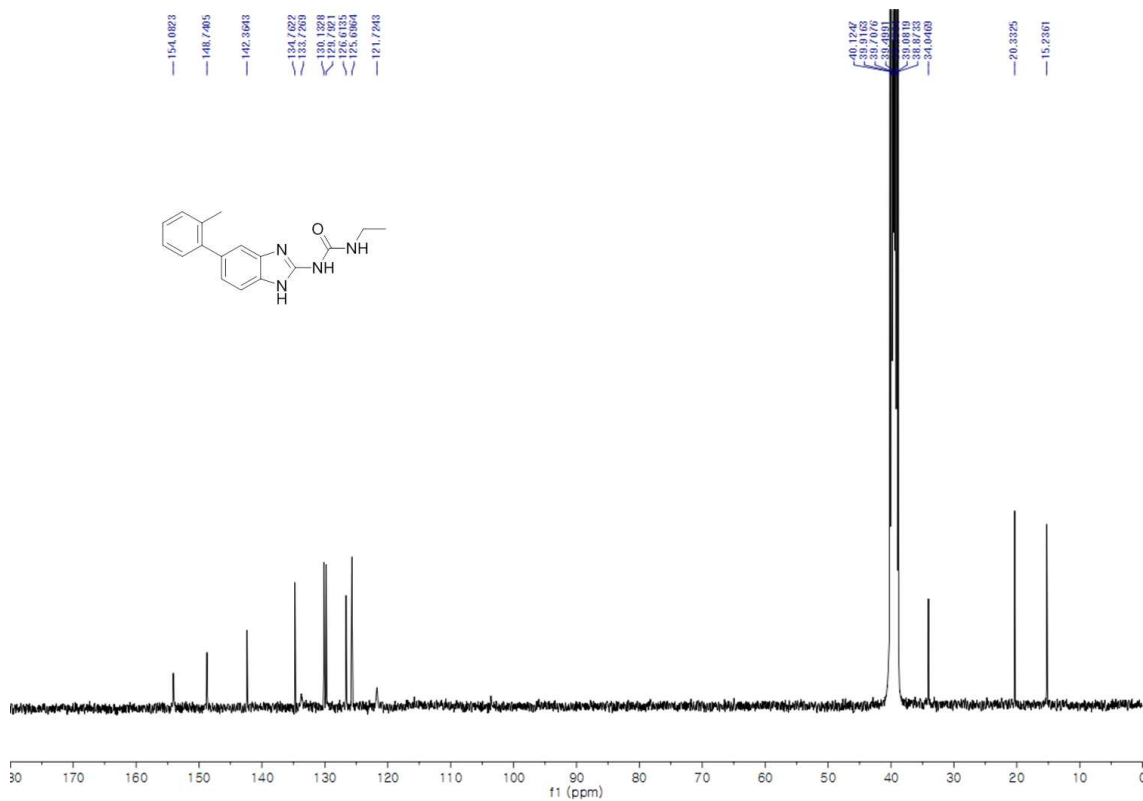


100 MHz, ^{13}C NMR in DMSO- d_6

1-Ethyl-3-(5-o-tolyl-1H-benzo[d]imidazol-2-yl)urea (18)

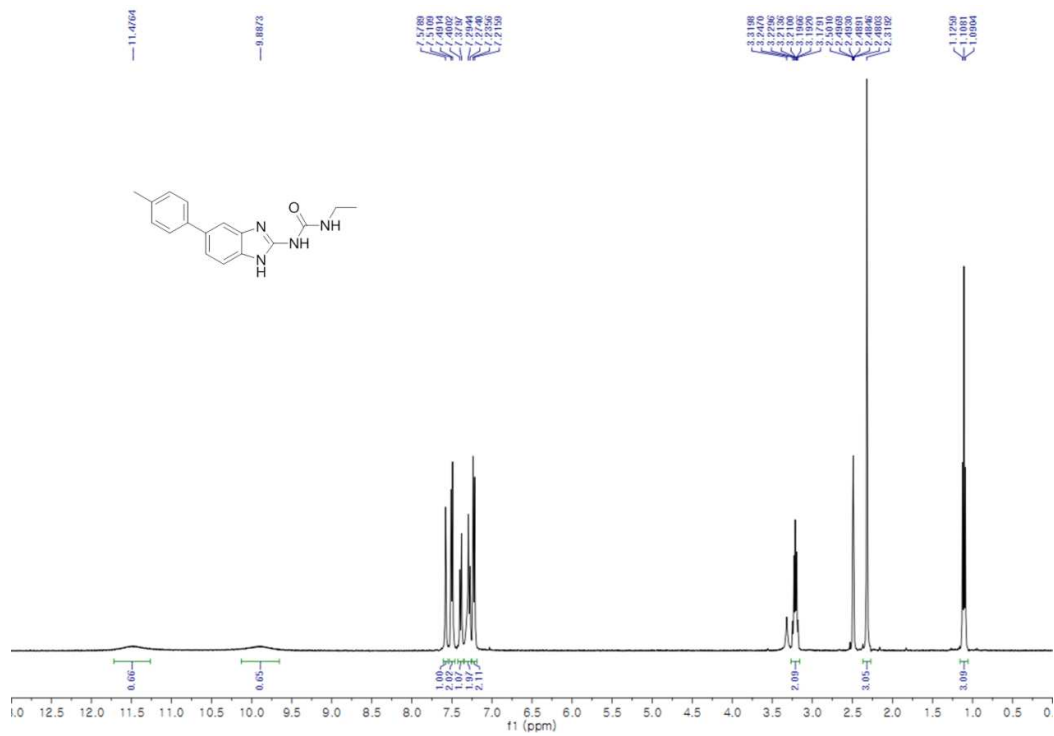


300 MHz, ¹H NMR in DMSO-*d*₆

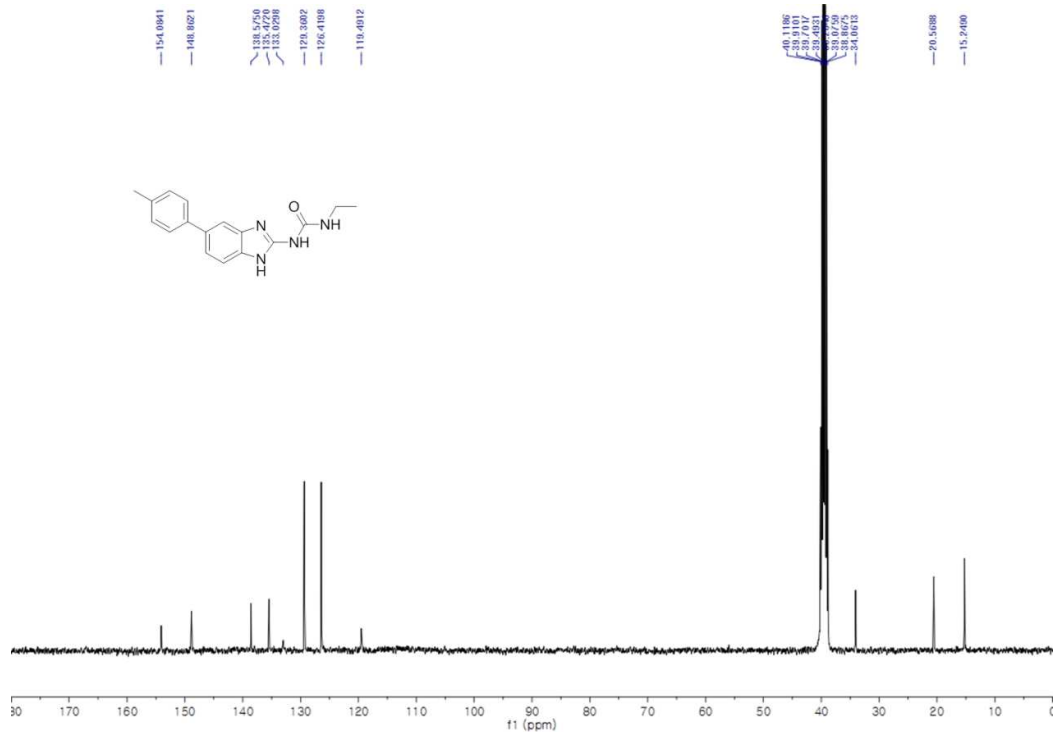


100 MHz, ¹³C NMR in DMSO-*d*₆

1-Ethyl-3-(5-p-tolyl-1H-benzo[d]imidazol-2-yl)urea (19)

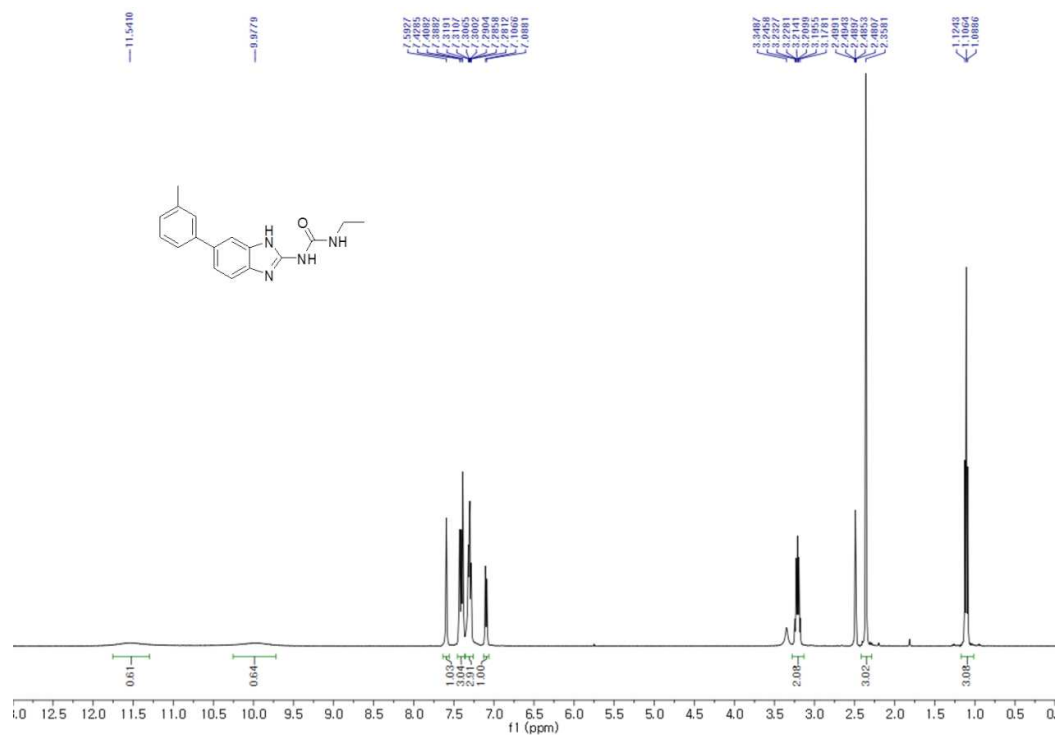


400 MHz, ¹H NMR in DMSO-*d*₆

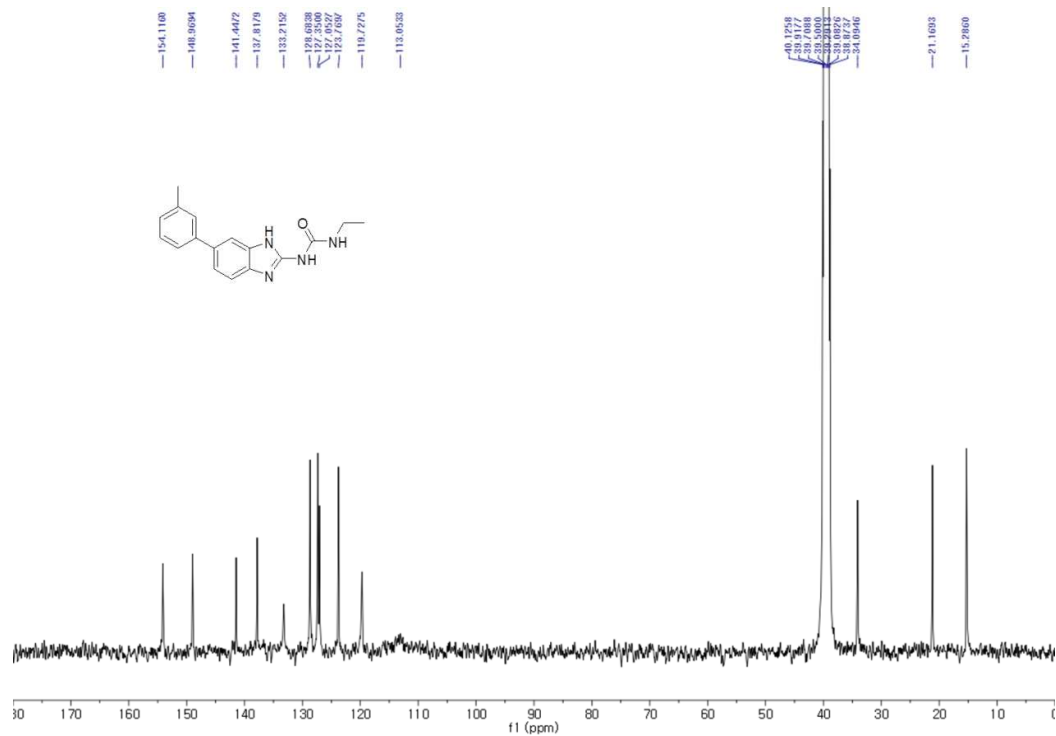


100 MHz, ^{13}C NMR in DMSO- d_6

1-Ethyl-3-(6-m-tolyl-1H-benzo[d]imidazol-2-yl)urea (20)

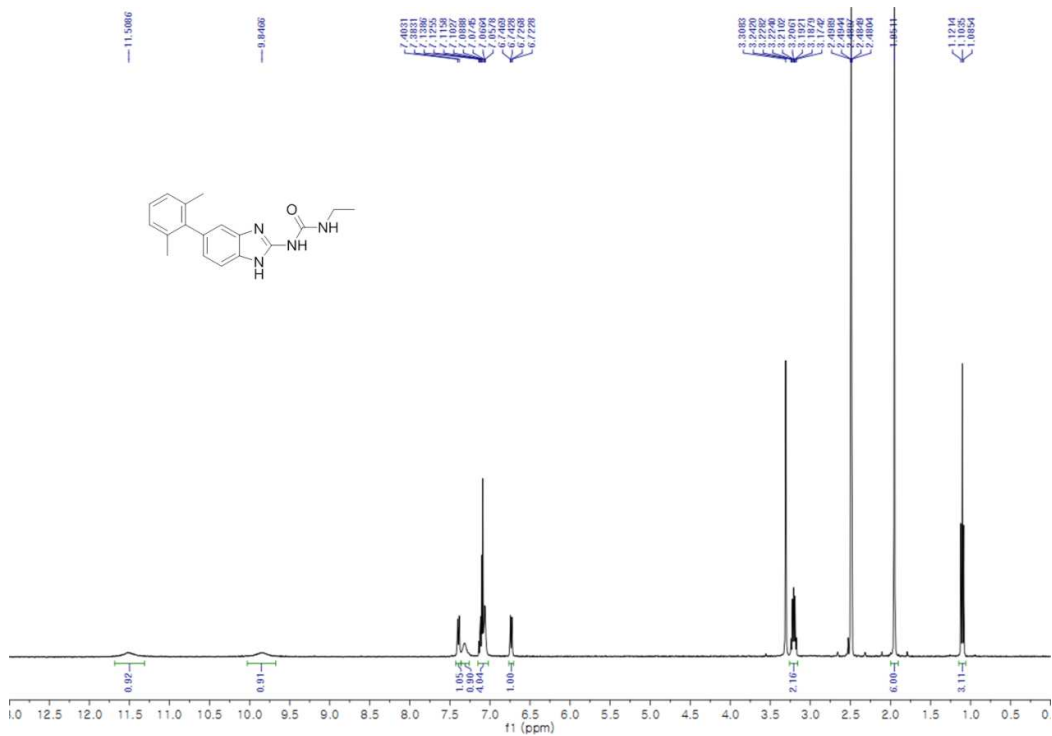


400 MHz, ¹H NMR in DMSO-*d*₆

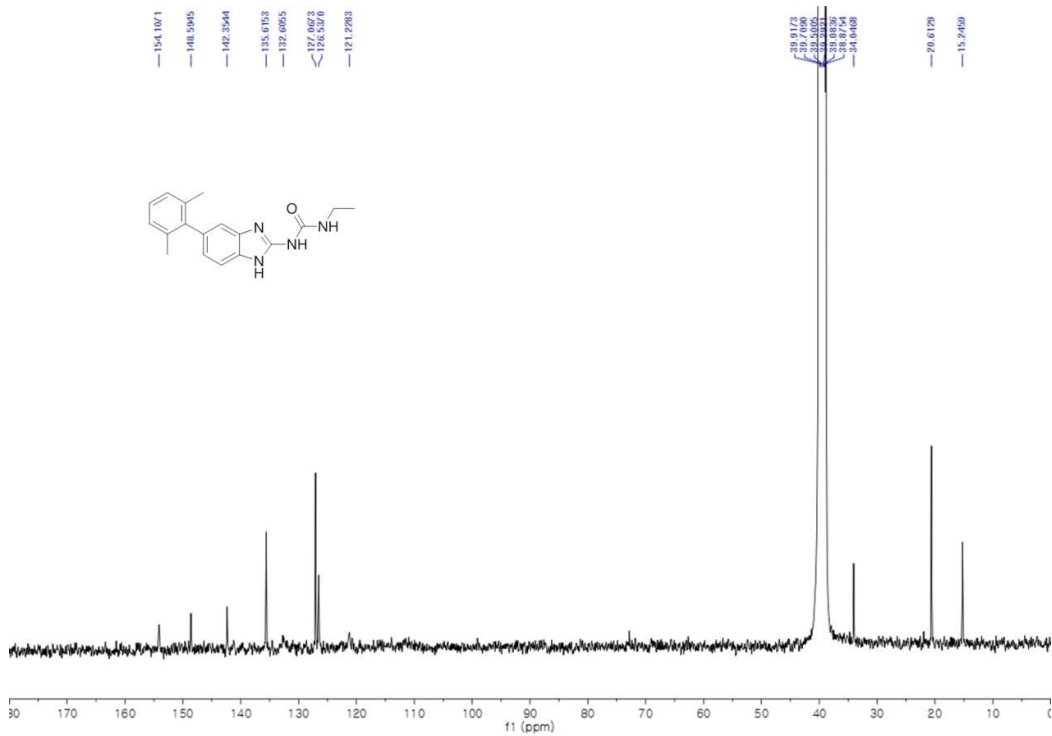


100 MHz, ¹³C NMR in DMSO-*d*₆

1-(5-(2,6-Dimethylphenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (21)



400 MHz, ^1H NMR in DMSO- d_6



100 MHz, ^{13}C NMR in DMSO- d_6

Chemical structure: CCNC(=O)Nc1ccc(Oc2ccc(OC)cc2)cc1

¹H NMR spectrum (ppm):

- 7.3518, 7.3318, 7.2178, 7.1712, 7.167, 7.0909, 6.7552, 6.7240, 6.6261, 6.6188, 6.6015, 6.5991, 6.4815, 6.477, 6.4531, 6.4317, 6.4452, 6.4329, 6.4271, 6.4248
- 3.8540, 3.8341, 3.7275, 2.2699, 1.9357, 1.9101, 1.8984, 1.8720

Integration values:

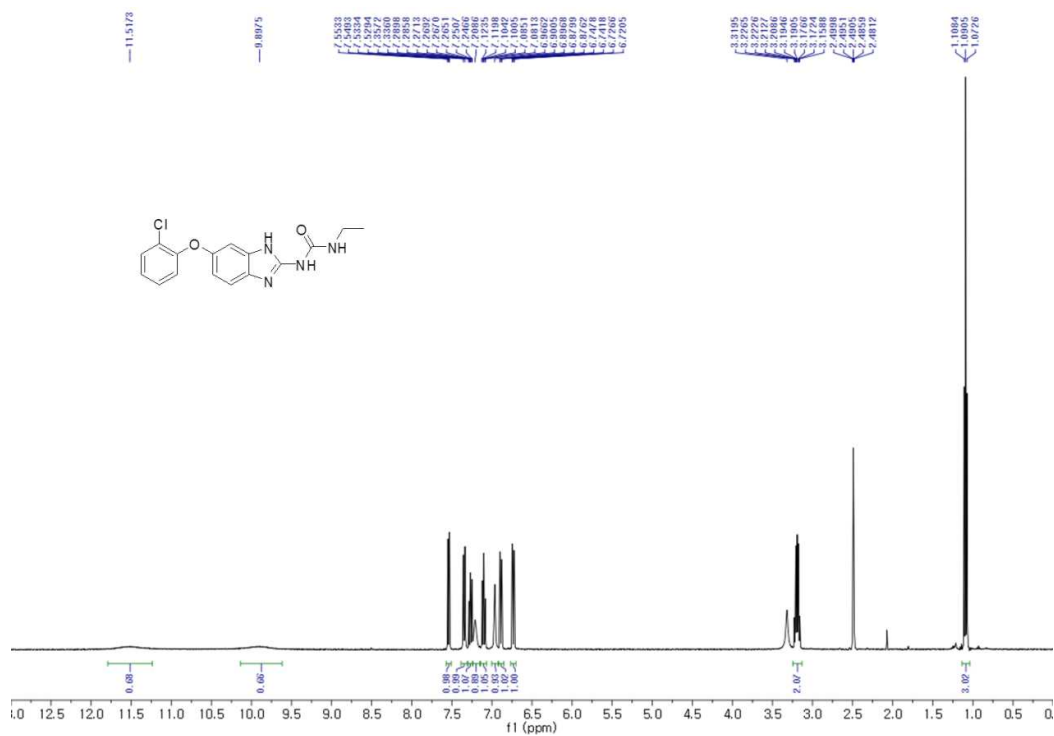
- 0.70 (aromatic, 11.5 ppm)
- 0.71 (aromatic, 10.0 ppm)
- 1.00, 0.93, 0.93, 1.00, 0.99, 1.02 (aromatic, 6.5-7.5 ppm)
- 3.67 (methoxy, 3.8 ppm)
- 2.10 (solvent, 3.3 ppm)
- 3.12 (ethyl, 1.0-1.2 ppm)

CCNC(=O)Nc1nc2cc(OC3=CC=C(OC)C=C3)ccc2[nH]1

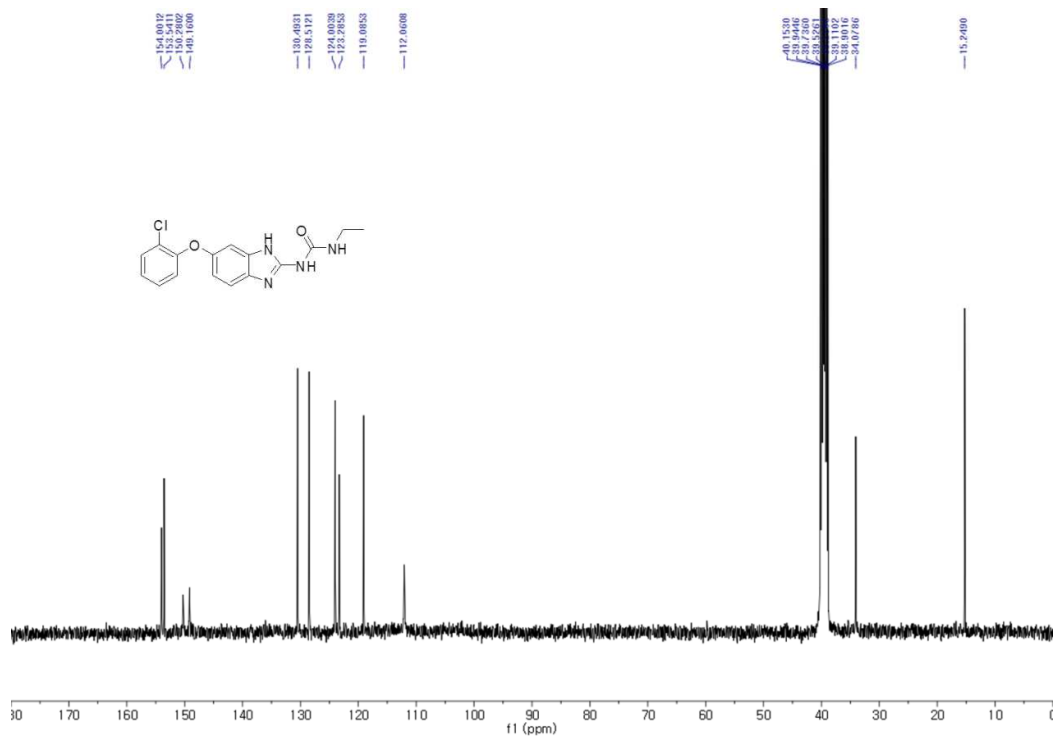
160.5467
 159.7900
 155.3987
 150.0260
 149.0304
 130.1929
 113.0113
 109.1744
 107.5222
 103.3072
 55.1395
 40.1356
 39.1359
 38.7687
 38.4829
 38.0810
 37.4871
 34.6001
 15.2789

100 MHz, ^{13}C NMR in DMSO- d_6

1-(5-(2-Chlorophenoxy)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (23)

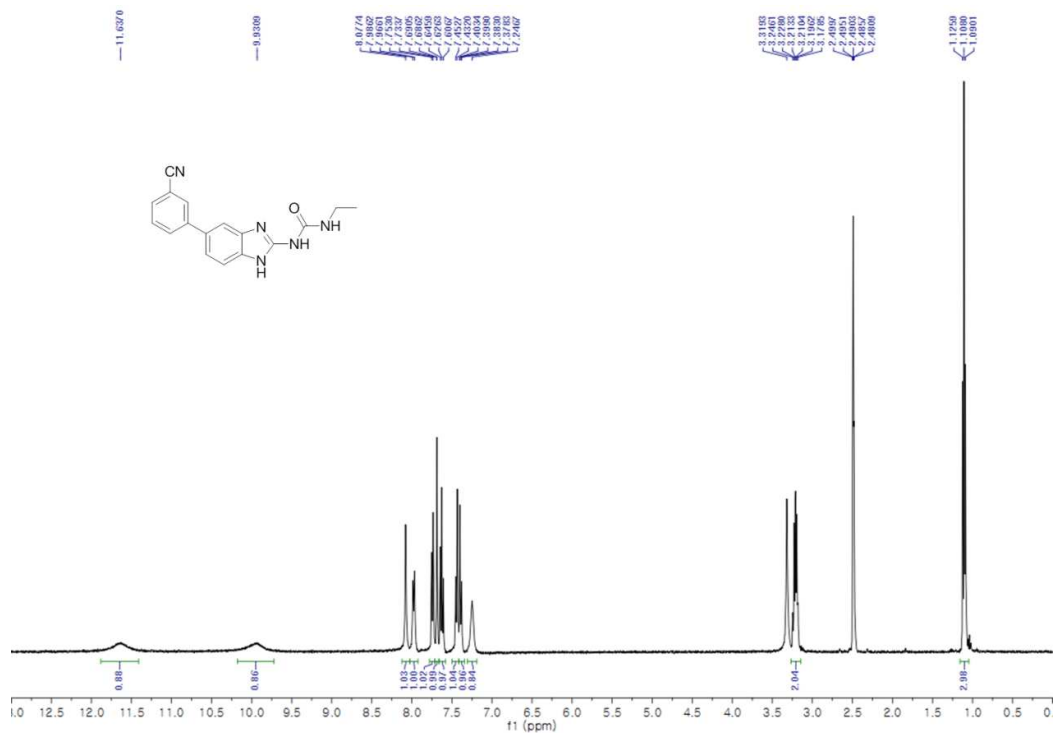


400 MHz, ^1H NMR in DMSO- d_6

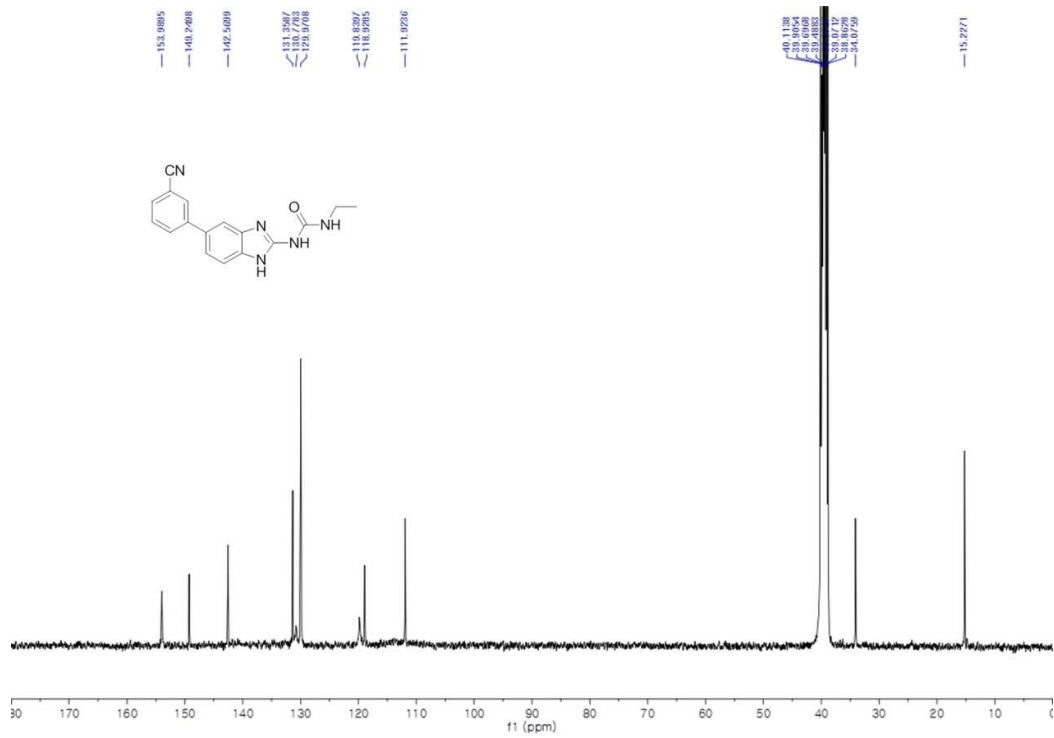


400 MHz, ^1H NMR in DMSO- d_6

1-(5-(3-Cyanophenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (24)

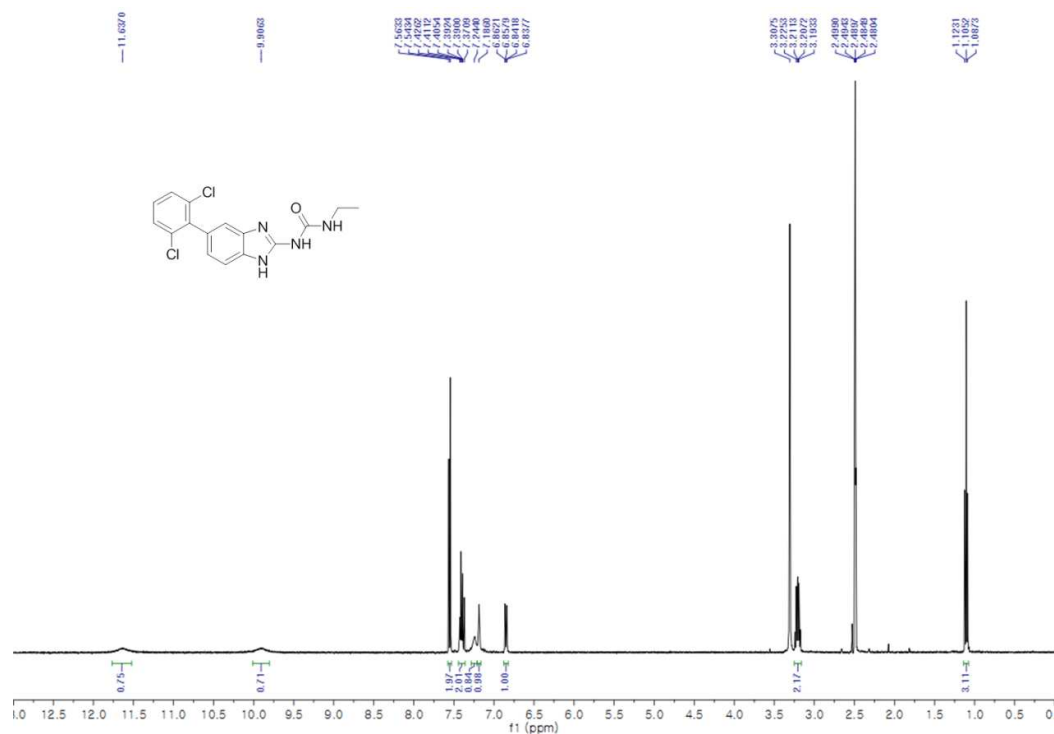


400 MHz, ^1H NMR in DMSO- d_6

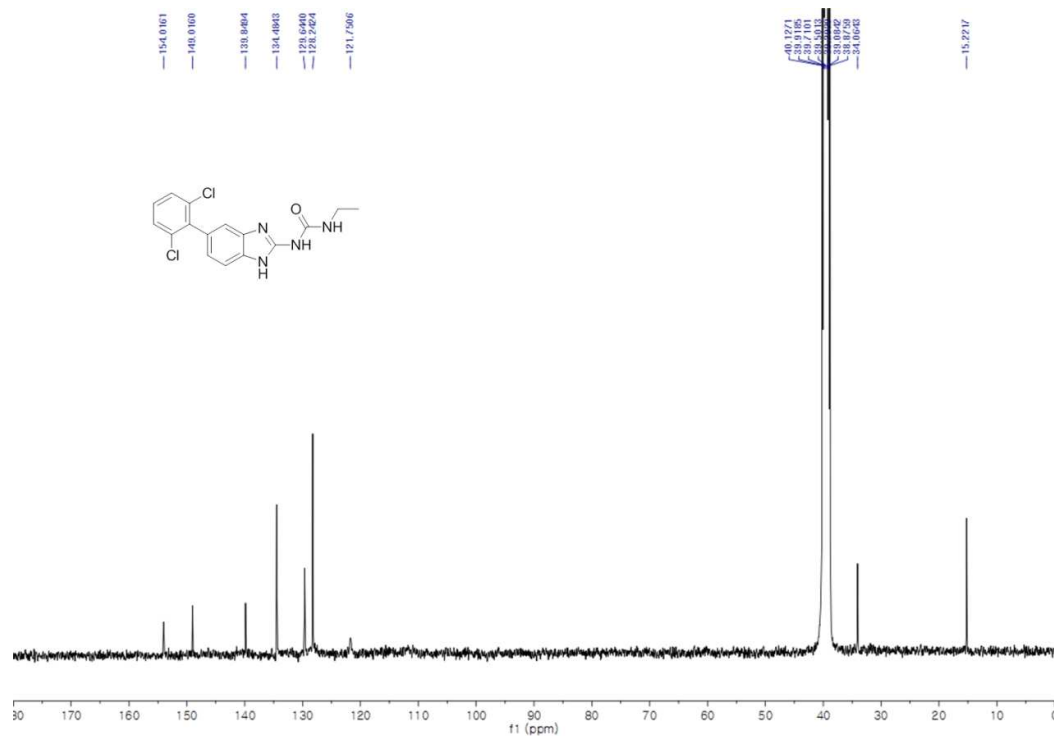


100 MHz, ^{13}C NMR in DMSO- d_6

1-(5-(2,6-Dichlorophenyl)-1H-benzo[d]imidazol-2-yl)-3-ethylurea (25)

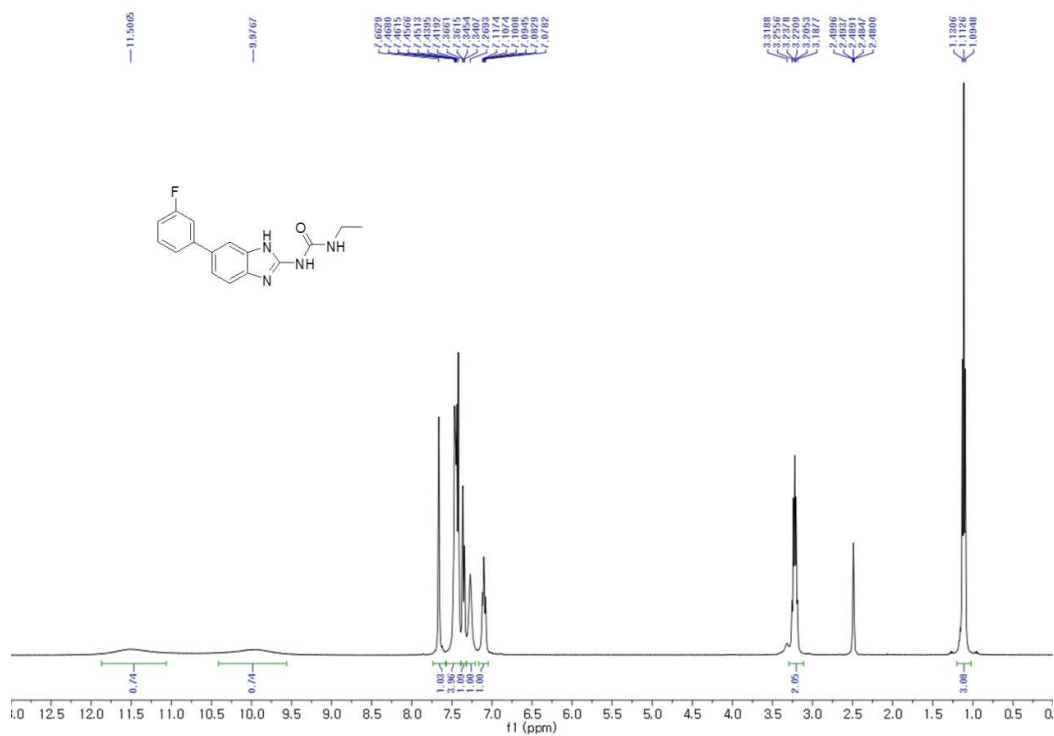


400 MHz, ¹H NMR in DMSO-*d*₆

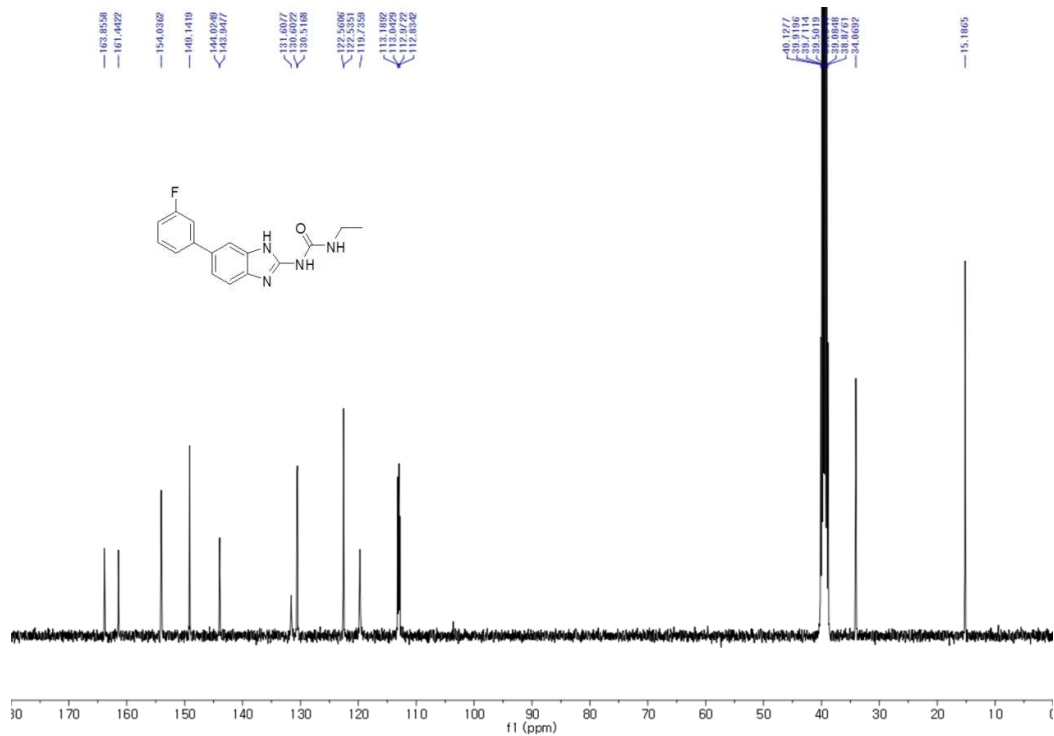


100 MHz, ¹³C NMR in DMSO-*d*₆

1-Ethyl-3-(6-(3-fluorophenyl)-1H-benzo[d]imidazol-2-yl)urea (26).

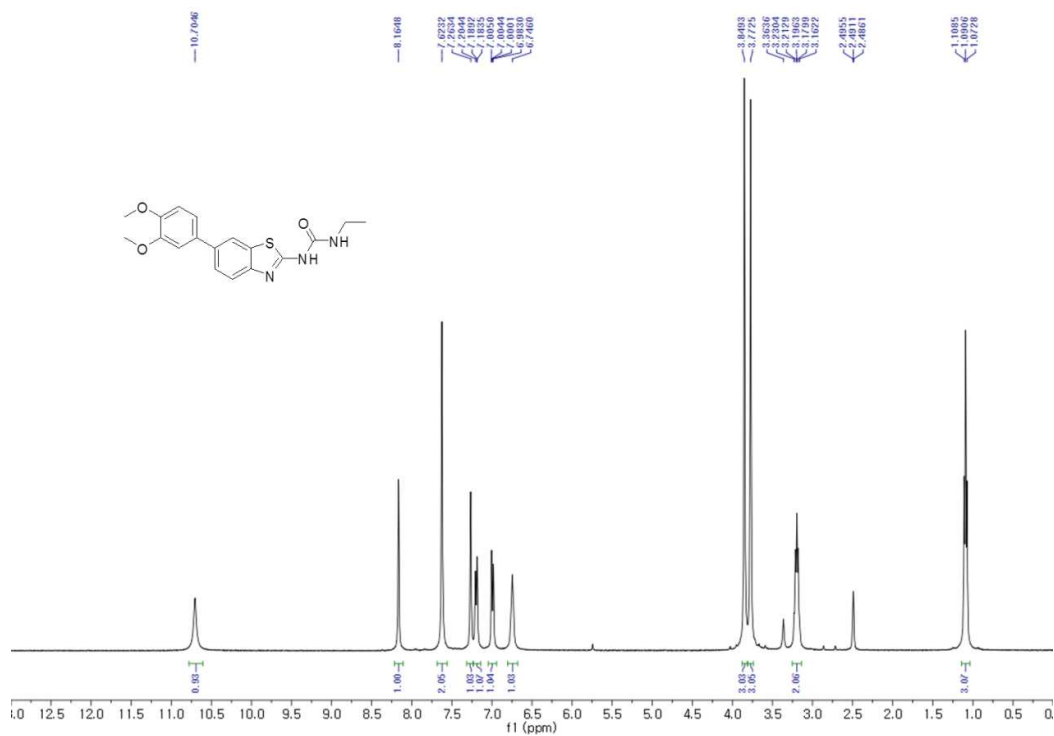


400 MHz, ^1H NMR in DMSO- d_6

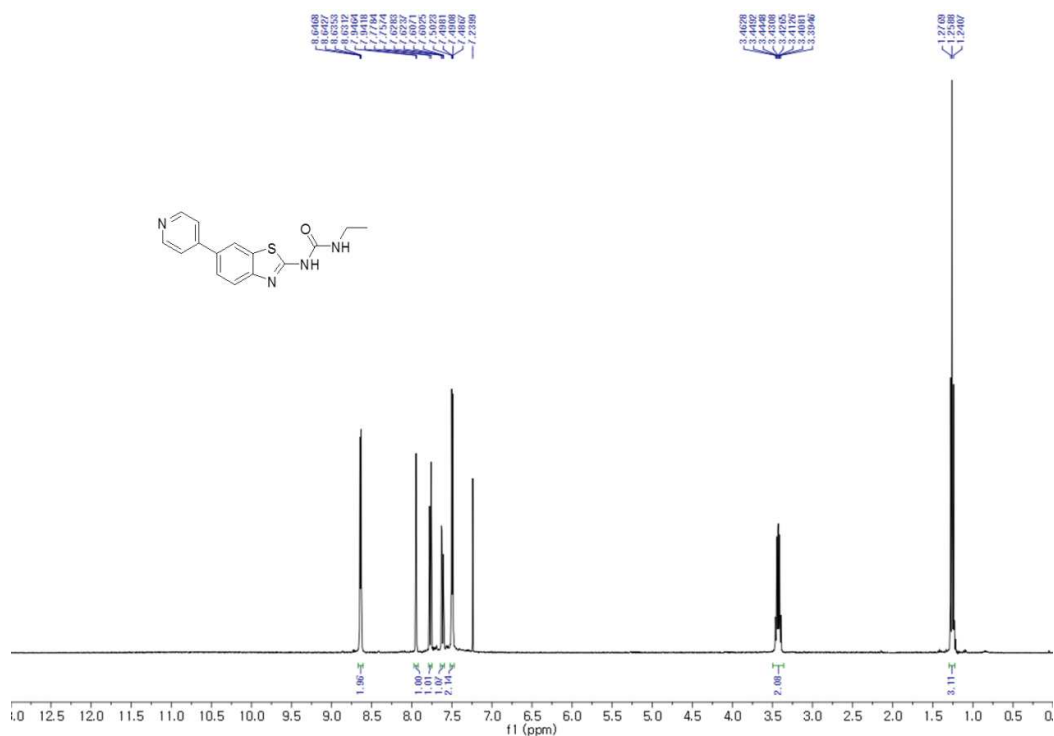


100 MHz, ^{13}C NMR in DMSO- d_6

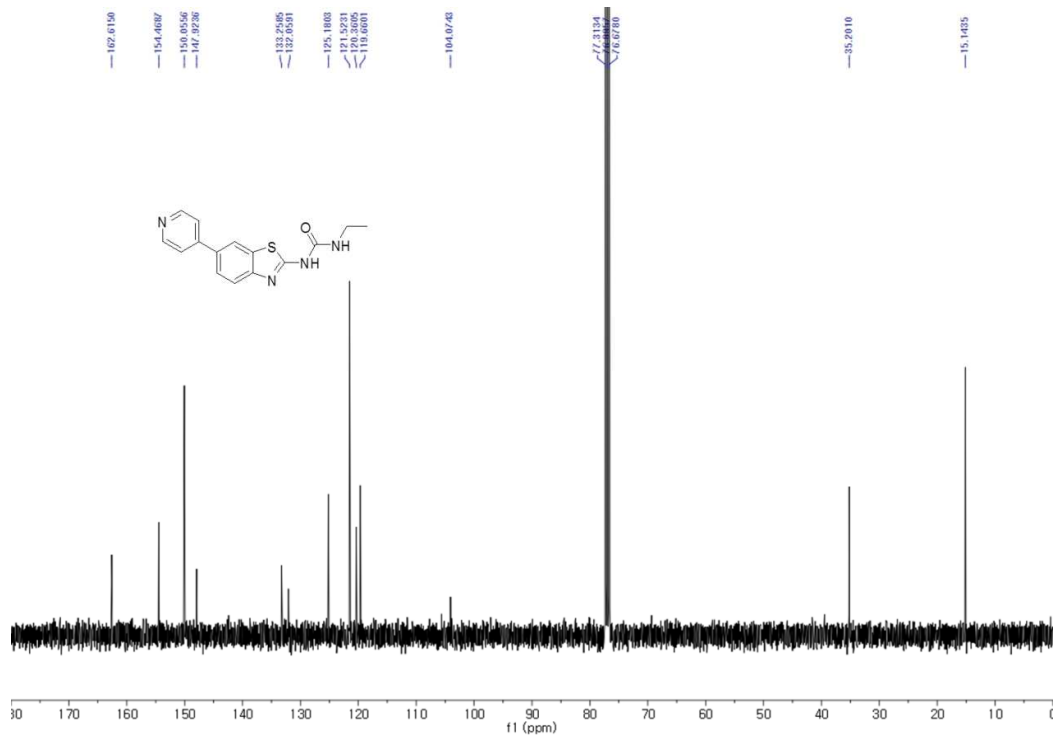
1-(6-(3,4-Dimethoxyphenyl)benzo[d]thiazol-2-yl)-3-ethylurea (27)



1-Ethyl-3-(6-(pyridin-4-yl)benzo[d]thiazol-2-yl)urea (28)

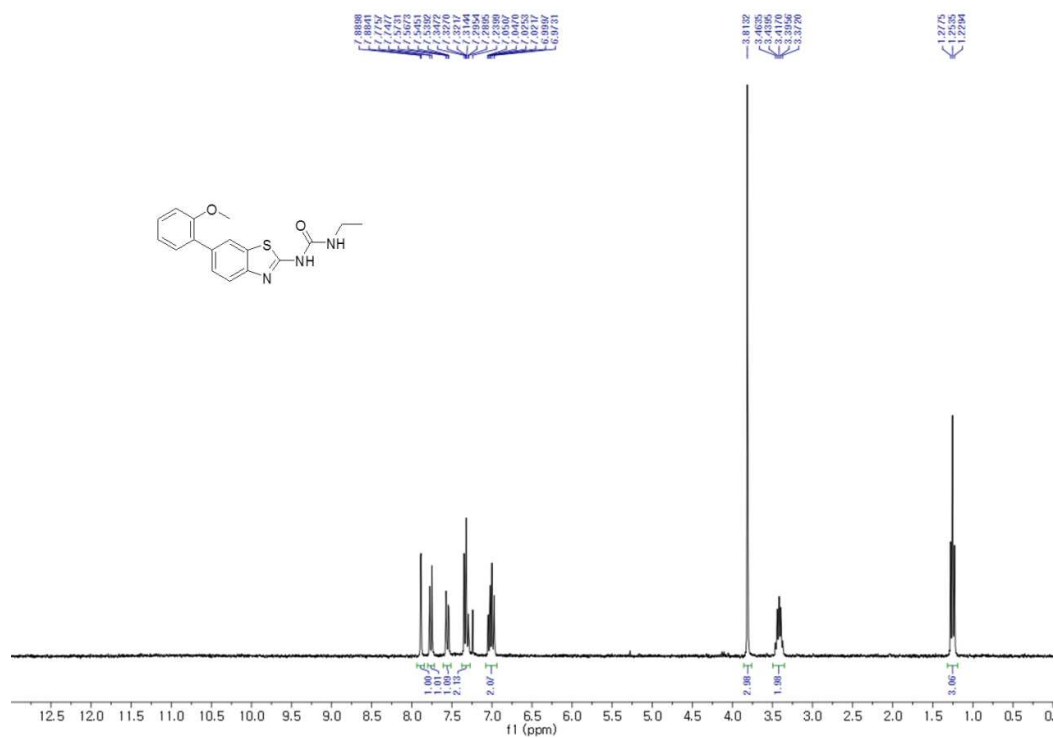


400 MHz, ^1H NMR in CDCl_3

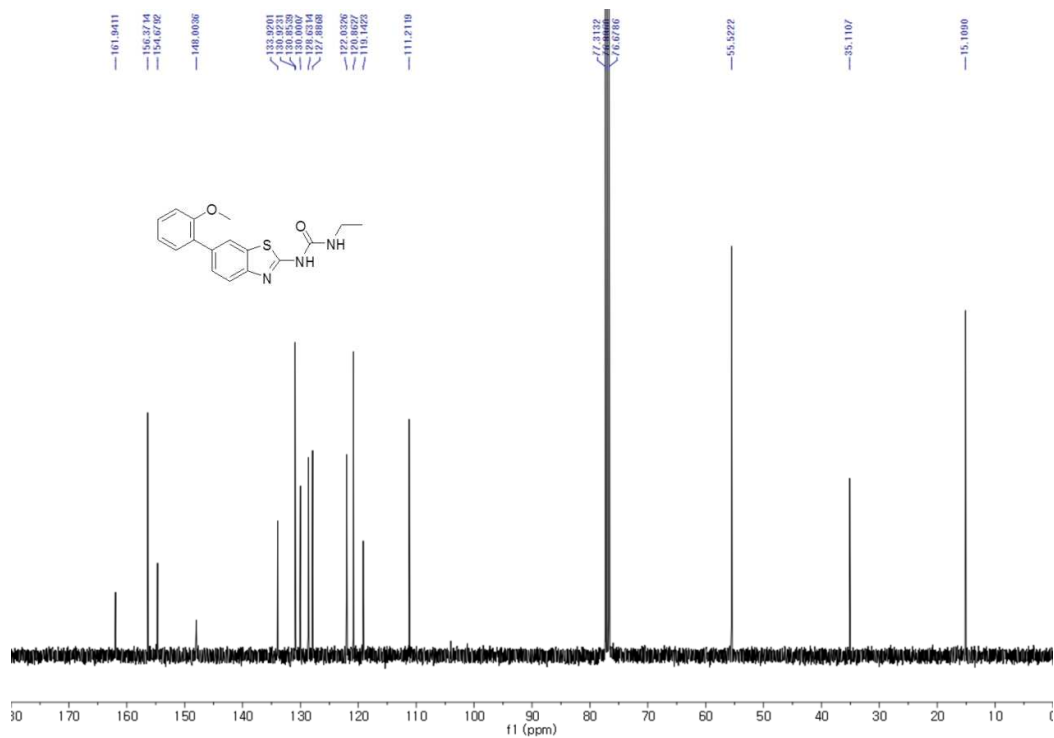


100 MHz, ^{13}C NMR in CDCl_3

1-Ethyl-3-(6-(2-methoxyphenyl)benzo[d]thiazol-2-yl)urea (29)



300 MHz, ¹H NMR in CDCl₃



100 MHz, ¹³C NMR in CDCl₃