Supporting Information

Benzothiazole Amides as TRPC3/6 Inhibitors for Gastric Cancer Treatment

Yingjie Wei[a,1], Mengxian Zhang[d,1], Zhenbin Lyu[b,1], Guolin Yang[c], Tian Tian[b,d], Mingmin Ding[d], Xiaodong Zeng[d,e], Fuchun Xu[b], Pengyu Wang[d], Fangfang Li[a], Yixuan Liu[b], Zhengyu Cao[c], Jing Lu[a,f,*],Xuechuan Hong[b,d,e,*], Hongbo Wang[a,*]

[a] School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education; Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Yantai, 264005, China

[b] State Key Laboratory of Virology, College of Science, Research Center for Ecology, Laboratory of Extreme Environmental Biological Resources and Adaptive Evolution, Innovation Center for Traditional Tibetan Medicine Modernization and Quality Control, Tibet University, Lhasa, 850000, China.

[c] State Key Laboratory of Natural Medicines, Jiangsu Provincial Key laboratory for TCM Evaluation and Translational Development, China Pharmaceutical University, Nanjing, Jiangsu Province 211198, China

[d] Key Laboratory of Combinatorial Biosynthesis and Drug Discovery (MOE) and Hubei Province Engineering and Technology Research Center for Fluorinated Pharmaceuticals, Wuhan University School of Pharmaceutical Sciences, Wuhan, 430071, China.

[e] Shenzhen Institute of Wuhan University, Shenzhen 518057, China

[f] State Key Laboratory of Long-acting Targeting Drug Delivery Technologies (Luye Pharma Group Ltd.), Yantai 264003, China

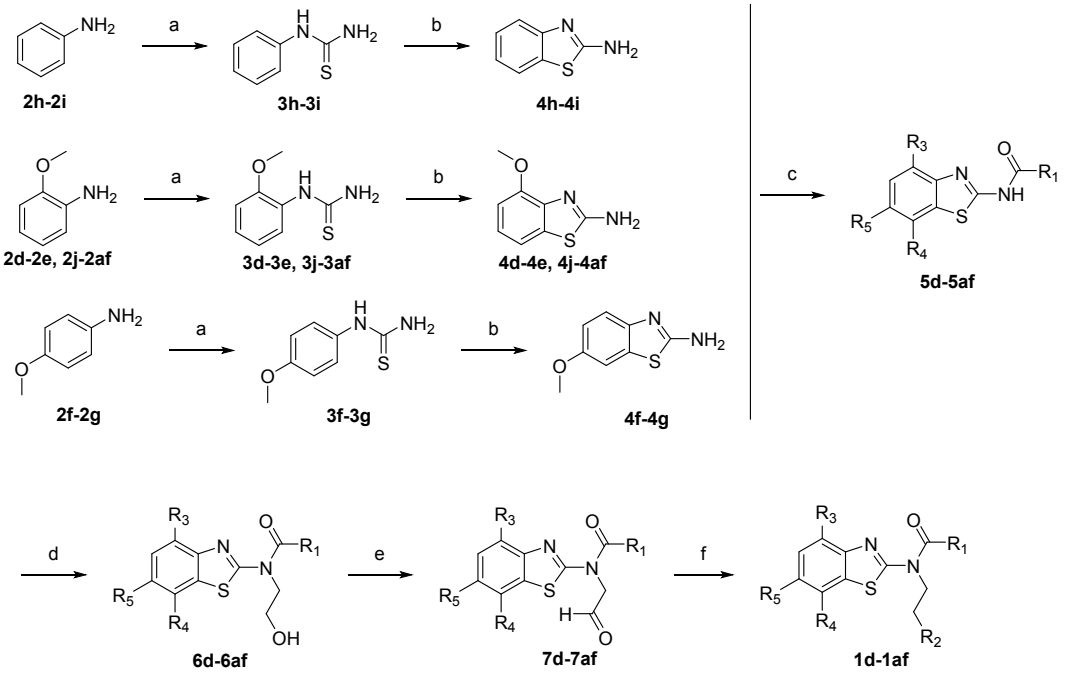
* Corresponding Author.

E-mail addresses: hongbowangyt@ytu.edu.cn (H. B. Wang, lead contact), xhy78@whu.edu.cn (X. C. Hong), lujing_ytu@126.com (J. Lu)

1. Experimental section

1.1 Chemistry

Benzothiazole amide analogs **1d-1af** were prepared via a synthetic route as depicted in Scheme S1. Starting from the commercially available aniline **2**, thiourea **3** was obtained after the reaction with potassium isothiocyanate under aqueous acidic conditions in high yields. The Hugerschoff reaction of arylthiourea **3** with Br_2 under oxidative conditions provided benzothiazol-2-ylamine **4** [1]. Amidation of compound **4** with appropriate carboxylic acids gave rise to benzothiazole amides 5 in 50-80% yields. Substitution of compound **5** with 2-iodoethanol, followed by IBX oxidation afforded aldehydes **7** in excellent yields. The desired benzothiazole amide analogs **1d-1af** were synthesized by reductive amination of **7** with commercially available secondary amines in high yields.



(a) KSCN, TFA, IPAc, 80 ^{o}C, overnight; (b) LiBr, Br_2, AcOH, 40 ^{o}C, overnight; (c) R_1CO_2H, HOBT, HBTU, DIPEA, DMF, r.t., 4 h; (d) 2-Iodoethanol, K_2CO_3, DMF, 50 ^{o}C, overnight; (e) IBX, DMSO, r.t., 4 h; (f) $R_2H.HCl$, $NaBH_3CN$, MeOH, r.t., 24 h

Scheme S1. Synthesis route of benzothiazole amides derivatives.

1.2 Synthesis

*1.2.1 General procedure for the synthesis of compounds **1d-1af***

To a solution of **7** (0.22 mmol) in methanol/dichloromethane (v/v=1:1, 4 mL) was added the

appropriate amine (3.22 mmol), and the mixture was stirred at room temperature for 30 min. Then sodium cyanoborohydride (0.66 mmol) was added and the mixture was stirred at room temperature for 24 h. Then the solvent was removed under reduced pressure, the crude was dissolved in dichloromethane and washed with water (5 mL × 3) and brine (3 mL). The organic layer was dried by $MgSO_4$ and concentrated under reduced pressure, followed by purification of flash column chromatography on silica gel to obtain the target compounds.

*N-(2-(dimethylamino)ethyl)-2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl) isonicotinamide (**1d**)*

White solid, yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.2 Hz, 1H), 8.45 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.30 – 7.23 (m, 2H), 6.94 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.06 – 4.90 (m, 2H), 4.01 (m, 3H), 3.99 (m, 3H), 2.87 – 2.69 (m, 2H), 2.42 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 167.2, 166.2, 149.9, 147.2, 139.6, 128.6, 126.1, 125.7, 124.5, 115.1, 110.2, 109.2, 57.7, 55.9, 53.9, 46.3, 45.9. HRMS (ESI) m/z: Calcd for $C_{19}H_{23}N_4O_3S^+$ $[M + H]^+$ 387.1485; found: 384.1487.

*N-(2-(diethylamino)ethyl)-2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)isonicotinamide (**1e**)*

White solid, yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.2 Hz, 1H), 8.47 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.29-7.23 (m, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.05 – 4.89 (m, 2H), 4.02 (m, 3H), 3.99 (m, 3H), 2.94 – 2.82 (m, 2H), 2.68 (q, *J* = 7.1 Hz, 4H), 1.06 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 167.2, 166.1, 149.9, 147.2, 139.6, 128.7, 126.2, 125.8, 124.4, 115.1, 110.1, 109.1, 55.9, 53.9, 51.0, 47.6, 46.5, 12.3. HRMS (ESI) m/z: Calcd for $C_{21}H_{27}N_4O_3S^+$ $[M + H]^+$ 415.1798; found: 415.1799.

*2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl) ethyl) isonicotinamide (**1f**)*

White solid, yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.3 Hz, 1H), 8.46 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.26 – 7.19 (m, 2H), 6.94 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.10 – 4.97 (m, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.00 – 2.88 (m, 2H), 2.75-2.69 (m, 4H), 1.95 – 1.73 (m, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 167.2, 166.2, 149.9 , 147.3, 139.6, 128.6, 126.2, 125.7, 124.4, 115.1, 110.2, 109.2, 55.9, 54.5, 53.9, 30.9, 23.6. HRMS (ESI) m/z: Calcd for $C_{21}H_{25}N_4O_3S^+$

$[M + H]^+$ 413.1642; found: 413.1635.

*2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl) ethyl) isonicotinamide (**1g**)*

White solid, yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.3 Hz, 1H), 8.45 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.28-7.19 (m, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 2.84 – 2.75 (m, 2H), 2.60 (t, *J* = 5.3 Hz, 4H), 1.63-1.56 (m, 4H), 1.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 167.3, 166.2, 149.9, 147.3, 139.6, 128.7, 126.2, 125.8, 124.4, 115.1, 110.2, 109.1, 57.4, 55.9, 54.9, 53.9, 25.9, 24.1. HRMS (ESI) m/z: Calcd for $C_{22}H_{27}N_4O_3S^+$ $[M + H]^+$ 427.1798; found: 428.1800.

*N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)cinnamamide (**1h**)*

White solid, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 15.9 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.44-7.35 (m, 3H), 7.32 – 7.24 (m, 2H), 6.96 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.89 (d, *J* = 15.9 Hz, 1H), 5.05 – 4.89 (m, 2H), 4.01 (s, 3H), 2.86 – 2.73 (m, 2H), 2.47 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 166.9, 147.2, 141.9, 135.6, 129.5, 128.8, 128.0, 126.7, 125.8, 124.3, 115.2, 109.1, 57.7, 55.9, 46.2, 45.9. HRMS (ESI) m/z: Calcd for $C_{21}H_{24}N_3O_2S^+$ $[M + H]^+$ 382.1584; found: 382.1586.

*N-(2-(diethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) cinnamamide (**1i**)*

White solid, yield 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 15.9 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.43 – 7.31 (m, 3H), 7.29 – 7.24 (m, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.85 (d, *J* = 15.9 Hz, 1H), 4.95 – 4.86 (m, 2H), 3.97 (s, 3H), 2.93 – 2.83 (m, 2H), 2.71 (q, *J* = 7.1 Hz, 4H), 1.14 (t, *J* = 7.1 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 166.9, 147.2, 141.8, 135.7, 129.5, 128.8, 128.0, 126.7, 125.9, 124.2, 115.1, 109.1, 55.9, 50.9, 47.9, 46.4, 12.4. HRMS (ESI) m/z: Calcd for $C_{23}H_{28}N_3O_2S^+$ $[M + H]^+$ 410.1897; found: 410.1901.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl) ethyl) cinnamamide (**1j**)*

White solid, yield 54%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (d, *J* = 15.9 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.41 (q, *J* = 5.6 Hz, 3H), 7.35 – 7.24 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.80

(d, *J* = 15.9 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.01 (s, 3H), 3.01 – 2.87 (m, 2H), 2.78 (s, 4H), 1.89 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 166.8, 147.2, 141.8, 135.7, 129.5, 128.8, 128.0, 126.8, 125.8, 124.2, 115.1, 109.1, 55.9, 54.6, 54.5, 47.2, 23.6. HRMS (ESI) m/z: Calcd for $C_{23}H_{26}N_3O_2S^+$ $[M + H]^+$ 408.1740; found: 408.1743.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)cinnamamide (**1k**)*

White solid, yield 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 15.9 Hz, 1H), 7.62-7.54 (m, 2H), 7.43 – 7.33 (m, 3H), 7.29 – 7.20 (m, 3H), 6.93 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.86 (d, *J* = 15.9 Hz, 1H), 5.03 – 4.93 (m, 2H), 3.98 (s, 3H), 2.83 – 2.74 (m, 2H), 2.72-2.51 (m, 4H), 1.68-1.56 (m, 4H), 1.51-1.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 166.9, 147.2, 141.8, 135.7, 129.5, 128.8, 128.0, 126.8, 124.2, 115.1, 109.1, 57.5, 55.9, 54.9, 45.8, 26.1, 24.3. HRMS (ESI) m/z: Calcd for $C_{24}H_{28}N_3O_2S^+$ $[M + H]^+$ 422.1897; found: 422.1898.

*N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide (**1l**)*

White solid, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.19 (m, 2H), 6.98 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.13 – 4.98 (m, 2H), 4.02 (s, 3H), 2.87 – 2.73 (m, 2H), 2.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 167.9, 147.4, 140.0, 129.7, 128.6, 125.7, 125.1, 124.7, 115.2, 109.3, 57.7, 55.9, 46.5, 45.9. HRMS (ESI) m/z: Calcd for $C_{20}H_{21}F_3N_3O_2S^+$ $[M + H]^+$ 424.1301; found: 424.1303.

*N-(2-(diethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide (**1m**)*

White solid, yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.15 (m, 2H), 6.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.08 – 4.93 (m, 2H), 4.01 (s, 3H), 2.99 – 2.86 (m, 2H), 2.72 (q, *J* = 7.1 Hz, 4H), 1.10 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 167.9, 147.4, 140.0, 129.7, 128.6, 125.8, 125.0, 124.6, 115.2, 109.2, 55.9, 51.0, 47.7, 46.8, 12.3. HRMS (ESI) m/z: Calcd for $C_{22}H_{25}F_3N_3O_2S^+$ $[M + H]^+$ 452.1614; found: 452.1613.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoromethyl) benzamide (**1n**)*

White solid, yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* =

8.2 Hz, 2H), 7.44 – 7.19 (m, 3H), 7.00 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.20 – 5.02 (m, 2H), 4.03 (s, 3H), 3.11 – 2.89 (m, 2H), 2.79-2.74 (m, 4H), 1.96-1.86 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 167.9, 147.4, 129.7, 125.1, 124.7, 115.2, 109.3, 56.0, 54.6, 47.5, 23.6. HRMS (ESI) m/z: Calcd for $C_{22}H_{23}F_3N_3O_2S^+$ $[M + H]^+$ 450.1458; found: 450.1450.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)-4-(trifluoromethyl) benzamide (**1o**)*

White solid, yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.22 (m, 2H), 6.96 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.11 – 5.01 (m, 2H), 4.00 (s, 3H), 2.88 – 2.77 (m, 2H), 2.66-2.59 (m, 4H), 1.65-1.58 (m, 4H), 1.50-1.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 167.9, 147.4, 140.0, 129.7, 128.6, 125.0, 124.6, 115.1, 109.2, 57.5, 55.9, 55.0, 46.0, 26.0, 24.2. HRMS (ESI) m/z: Calcd for $C_{23}H_{25}F_3N_3O_2S^+$ $[M + H]^+$ 464.1614; found: 464.1618.

*N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide (**1p**)*

Light yellow solid, yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.31 – 7.16 (m, 2H), 6.93 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 5.04 – 4.90 (m, 2H), 3.98 (s, 3H), 2.84 – 2.71 (m, 2H), 2.43 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 167.1, 150.7, 147.6, 147.1, 131.3, 128.6, 125.7, 125.0, 124.3, 115.1, 109.4, 109.2, 107.7, 101.5, 57.4, 55.9, 46.0, 45.6. HRMS (ESI) m/z: Calcd for $C_{20}H_{22}N_3O_4S^+$ $[M + H]^+$ 400.1326; found: 400.1328.

*N-(2-(diethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide (**1q**)*

Light yellow solid, yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.84 (d, *J* = 1.6 Hz, 1H), 7.28 – 7.19 (m, 2H), 6.93 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 5.02 – 4.89 (m, 2H), 3.98 (s, 3H), 2.95 – 2.82 (m, 2H), 2.70 (q, *J* = 7.1 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 167.2, 150.7, 147.5, 147.2, 131.4, 128.7, 125.9, 125.0, 124.2, 115.2, 109.5, 109.0, 107.7, 101.5, 55.9, 51.0, 47.7, 46.5, 12.3. HRMS (ESI) m/z: Calcd for $C_{22}H_{26}N_3O_4S^+$ $[M + H]^+$ 428.1639; found: 428.1641.

*N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide (**1r**)*

Light yellow solid, yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.01 – 7.95 (m, 1H), 7.92-7.86 (m, 2H), 7.56-7.51 (m, 2H), 7.31 – 7.28 (m, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.21 – 4.95 (m, 2H), 4.00 (s, 3H), 2.97 – 2.76 (m, 2H), 2.50 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 167.4, 147.2, 135.3, 134.2, 132.9, 130.5, 129.5, 128.8, 127.7, 127.5, 126.2, 125.9, 124.4, 115.3, 109.2, 57.7, 55.9, 46.3, 45.9. HRMS (ESI) m/z: Calcd for $C_{23}H_{24}N_3O_2S^+$ $[M + H]^+$ 406.1584; found: 406.1583.

*N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-5,6,7,8- tetrahydronaphthalene -2-carboxamide (**1s**)*

White solid, yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.11 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 9.4, 6.4 Hz, 2H), 3.97 (s, 3H), 2.82 – 2.76 (m, 6H), 2.43 (s, 6H), 1.82-1.79 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 167.4, 146.9, 141.5, 136.7, 133.4, 129.9, 129.0, 127.5, 126.3, 125.1, 124.7, 115.3, 110.4, 56.5, 55.7, 42.9, 29.0, 28.9, 22.7, 22.6. HRMS (ESI) m/z: Calcd for $C_{23}H_{28}N_3O_2S^+$ $[M + H]^+$ 410.1897; found: 410.1898.

*N-(2-(diethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide (**1t**)*

White solid, yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.45 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.98 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.93-7.89 (m, 2H), 7.59-7.52 (m, 2H), 7.35 – 7.28 (m, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.17 – 4.92 (m, 2H), 4.00 (s, 3H), 3.06 – 2.90 (m, 2H), 2.80 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 167.4, 147.2, 135.2, 134.2, 132.8, 130.5, 129.4, 128.8, 127.7, 127.1, 127.5, 126.2, 125.9, 124.7, 124.4, 115.2, 109.1, 55.9, 50.9, 47.7, 46.5, 12.3. HRMS (ESI) m/z: Calcd for $C_{25}H_{28}N_3O_2S^+$ $[M + H]^+$ 434.1897; found: 434.1898.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-2-naphthamide (**1u**)*

White solid, yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.47 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.00 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.95-7.90 (m, 2H), 7.60-7.53 (m, 2H), 7.35 – 7.22 (m, 2H), 6.97

(dd, *J* = 8.1, 1.1 Hz, 1H), 5.22 – 5.08 (m, 2H), 4.02 (s, 3H), 3.12 – 2.96 (m, 2H), 2.96 – 2.76 (m, 4H), 1.97-1.88 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 167.4, 147.3, 135.3, 134.2, 132.8, 130.5, 129.5, 128.8, 127.7, 127.2, 127.5, 126.2, 125.9, 125.3, 124.4, 115.2, 109.2, 55.9, 54.6, 47.3, 23.7. HRMS (ESI) m/z: Calcd for $C_{25}H_{26}N_3O_2S^+$ $[M + H]^+$ 432.1740; found: 432.1744.

N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)-2-naphthamide ***(1v)***

White solid, yield 39%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.46 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.04 – 7.96 (m, 1H), 7.94-7.90 (m, 2H), 7.60-7.52 (m, 2H), 7.35 – 7.28 (m, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.00 (s, 3H), 2.96 – 2.83 (m, 2H), 2.72 (t, *J* = 5.3 Hz, 4H), 1.73 – 1.61 (m, 4H), 1.54-1.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 167.5, 147.3, 135.3, 134.3, 132.9, 130.5, 129.4, 128.8, 127.7, 127.5, 126.2, 125.9, 124.3, 115.2, 109.1, 57.5, 55.9, 55.0, 45.8, 26.1, 24.2. HRMS (ESI) m/z: Calcd for $C_{26}H_{28}N_3O_2S^+$ $[M + H]^+$ 446.1897; found: 446.1899.

5-chloro-N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide ***(1w)***

White solid, yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 4.0 Hz, 1H), 7.27 – 7.20 (m, 2H), 6.98 – 6.92 (m, 2H), 4.98 – 4.89 (m, 2H), 3.99 (s, 3H), 2.83 – 2.71 (m, 2H), 2.44 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 166.8, 147.3, 141.1, 135.6, 130.7, 128.6, 127.5, 125.7, 124.6, 115.1, 109.3, 57.7, 55.9, 46.3, 45.9. HRMS (ESI) m/z: Calcd for $C_{17}H_{19}ClN_3O_2S_2^+$ $[M + H]^+$ 396.0602; found: 396.0595.

5-chloro-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thiophene-2-carboxamide ***(1x)***

White solid, yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 4.0 Hz, 1H), 7.32 – 7.22 (m, 2H), 6.99 – 6.90 (m, 2H), 5.03 – 4.91 (m, 2H), 3.99 (s, 3H), 2.98 – 2.85 (m, 2H), 2.82 – 2.66 (m, 4H), 1.86 (t, *J* = 4.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 166.8, 147.4, 141.2, 135.7, 130.7, 128.6, 127.5, 125.7, 124.9, 115.1, 109.3, 56.0, 54.6, 47.3, 23.6. HRMS (ESI) m/z: Calcd for $C_{19}H_{21}ClN_3O_2S_2^+$ $[M + H]^+$ 422.0758; found: 422.0752.

*5-chloro-N-(2-(dimethylamino)ethyl)-N-(6-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide **(1y)***

White solid, yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 3.9 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.94 (d, *J* = 3.9 Hz, 1H), 4.54 – 4.47 (m, 2H), 3.86 (s, 3H), 2.78 – 2.68 (m, 2H), 2.41 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.1, 156.8, 141.0, 135.7, 130.7, 130.5, 128.2, 127.5, 115.0, 112.2, 106.7, 56.2, 56.1, 45.9, 44.0. HRMS (ESI) m/z: Calcd for $C_{17}H_{19}ClN_3O_2S_2^+$ $[M + H]^+$ 396.0602; found: 396.0597.

*5-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thiophene-2-carboxamide **(1z)***

Light yellow solid, yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.94 (d, *J* = 4.0 Hz, 1H), 4.60 – 4.50 (m, 2H), 3.86 (s, 3H), 2.96 – 2.84 (m, 2H), 2.78 – 2.67 (m, 4H), 1.84 (p, *J* = 3.2 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.1, 156.9, 141.0, 135.7, 130.7, 130.5, 128.1, 127.5, 115.0, 112.3, 106.7, 56.0, 54.5, 52.8, 44.9, 23.6. HRMS (ESI) m/z: Calcd for $C_{19}H_{21}ClN_3O_2S_2^+$ $[M + H]^+$ 422.0758; found:422.0752.

*N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-(dimethylamino)ethyl)thiophene-2-carboxamide (**1aa**)*

Light yellow solid, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.44 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.28 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (d, *J* = 3.9 Hz, 1H), 4.57 – 4.47 (m, 2H), 2.78 – 2.69 (m, 2H), 2.40 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 166.7, 140.9, 136.5, 135.8, 130.9, 127.5, 127.1, 126.8, 124.0, 123.0, 111.5, 56.0, 45.9, 43.8. HRMS (ESI) m/z: Calcd for $C_{16}H_{17}ClN_3OS_2^+$ $[M + H]^+$ 366.0496; found: 366.0493.

*N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-(pyrrolidin-1-yl)ethyl)thiophene-2-carboxamide (**1ab**)*

White solid, yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.49 – 7.39 (m, 2H), 7.33 – 7.28 (m, 1H), 6.94 (d, *J* = 3.9 Hz, 1H), 4.63 – 4.54 (m, 2H), 2.97 – 2.86 (m, 2H), 2.72 (td, *J* = 5.4, 4.2, 2.7 Hz, 4H), 1.85 (p, *J* = 3.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 166.7,

140.9, 136.6, 135.9, 130.9, 127.6, 127.1, 126.8, 124.0, 123.0, 111.5, 54.5, 52.7, 44.8, 23.6. HRMS (ESI) m/z: Calcd for $C_{18}H_{19}ClN_3OS_2^+$ $[M + H]^+$ 392.0653; found:392.0645.

*5-bromo-N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**1ac**)*

White solid, yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 4.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.07 (d, *J* = 4.0 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.00 – 4.87 (m, 2H), 3.99 (s, 3H), 2.83 – 2.72 (m, 2H), 2.45 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 166.8, 147.3, 144.1, 131.4, 131.1, 128.6, 125.7, 124.6, 118.7, 115.1, 109.3, 57.6, 56.0, 46.2, 45.9. HRMS (ESI) m/z: Calcd for $C_{17}H_{19}BrN_3O_2S_2^+$ $[M + H]^+$ 440.0097; found: 440.0099.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thiophene-2-carboxamide (**1ad**)*

White solid, yield 62%. 1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 4.0 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.07 (d, *J* = 3.9 Hz, 1H), 6.93 (dd, *J* = 7.5, 1.8 Hz, 1H), 5.02 – 4.91 (m, 2H), 3.98 (s, 3H), 2.97 – 2.86 (m, 2H), 2.79 – 2.70 (m, 4H), 1.91-1.81 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 166.9, 147.4, 144.1, 131.4, 131.1, 128.6, 125.7, 124.6, 118.7, 115.1, 109.3, 56.0, 54.6, 47.2, 23.6. HRMS (ESI) m/z: Calcd for $C_{19}H_{21}BrN_3O_2S_2^+$ $[M + H]^+$ 466.0253; found: 466.0258.

*5-bromo-N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) furan-2-carboxamide (**1ae**)*

White solid, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 3H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.47 (d, *J* = 3.4 Hz, 1H), 5.00 – 4.91 (m, 2H), 4.00 (s, 3H), 2.83 – 2.72 (m, 2H), 2.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 165.3, 153.4, 147.3, 128.7, 126.2, 125.7, 124.6, 117.9, 115.1, 113.8, 109.3, 57.8, 56.0, 46.1, 45.8. HRMS (ESI) m/z: Calcd for $C_{17}H_{19}BrN_3O_3S^+$ $[M + H]^+$ 424.0325; found: 424.0328.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)furan-2-carboxamide (**1af**)*

White solid, yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 3H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.47 (d, *J* = 3.4 Hz, 1H), 5.04 – 4.93 (m, 2H), 4.00 (s, 3H), 2.97 – 2.87 (m, 2H), 2.82 – 2.70 (m, 4H), 1.93-1.82 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 165.3, 153.4, 147.3, 129.8, 128.6, 126.2, 125.7, 124.6, 118.0, 115.1, 113.79, 109.2, 56.0, 54.7, 54.5, 47.2, 23.6. HRMS (ESI) m/z: Calcd for $C_{19}H_{21}BrN_3O_3S^+$ $[M + H]^+$ 450.0482; found: 450.0488.

1.2.2 General pr℃edure for the synthesis of compounds ***3d-3af***

To a solution of **2** (15.98 mmol) with potassium thi℃yanate (29.36 mmol) in sec-Butyl acetate (50 mL) at 0 ℃ (precooled for 10 min), trifluoroacetic acid 3.74 mL (48.94 mmol) was added over 5 min. Then the mixture was stirred at r.t. for 5 min and heated to 80 ℃ overnight. After completion of the reaction checked by TLC, the reaction mixture was cooled to room temperature and 6 mL water was added. The mixture was stirring at 0 ℃ for 1 h, then the solution was filtrated. The precipitate was washed with water (10 mL × 3) and dried in a vacuum oven at 40 ℃ overnight to give the target compounds.

*1- (2-methoxyphenyl) thiourea (****3d-3e, 3j-3af****)*

White solid, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.64 (dd, *J* = 7.6, 2.3 Hz, 1H), 7.34-6.98 (m, 2H), 6.88 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.86 (s, 3H). ESI-MS (m/z): Calcd for $C_8H_{11}N_2OS^+$ $[M + H]^+$ 183.06; found: 183.20.

*1- (4-methoxyphenyl) thiourea (****3f-3g****)*

This compound is reported by the literature [2]. ESI-MS (m/z): Calcd for $C_8H_{11}N_2OS^+$ $[M + H]^+$ 183.06; found: 183.30.

*phenylthiourea (****3h-3i****)*

This compound is reported by the literature [3]. ESI-MS (m/z): Calcd for $C_7H_9N_2S^+$ $[M + H]^+$ 153.05; found: 153.10.

1.2.3 General pr℃edure for the synthesis of compounds ***4d-4af***

To a solution of **3** (13.08 mmol) with lithium bromide (19.61 mmol) in sec-Butyl acetate (50 mL) at 0 ℃ (precooled for 10 min), liquid bromine 1.34 mL (13.08 mmol) was added over 5 min. Then the mixture was stirred at r.t. for 5 min and heated to 40 ℃ overnight. After completion of the reaction checked by TLC, the reaction mixture was cooled to room temperature and filtrated. The filter cake was washed with acetic acid (20 mL × 3) and dried in a vacuum oven at 40 ℃ overnight to give the target compounds.

*4-methoxybenzo[d]thiazol-2-amine (**4d-4e, 4j-4af**)*

White solid, yield 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 2H), 7.58 (dd, J = 7.5, 1.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 3.88 (s, 3H). ESI-MS (m/z): Calcd for $C_8H_9N_2OS^+$ $[M + H]^+$ 181.04; found: 181.20.

*6-methoxybenzo[d]thiazol-2-amine (**4f-4g**)*

Light gray solid, yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 2H), 7.60 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.04 (ddd, J = 8.9, 2.7, 1.2 Hz, 1H), 3.77 (d, J = 1.3 Hz, 3H). ESI-MS (m/z): Calcd for $C_8H_9N_2OS^+$ $[M + H]^+$ 181.04; found: 181.10.

*benzo[d]thiazol-2-amine (**4h-4i**)*

White solid, yield 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 2H), 7.60 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 7.5, 1.5 Hz, 1H), 7.19 (td, J = 7.5, 1.5 Hz, 1H), 6.99 (td, J = 7.4, 1.6 Hz, 1H). ESI-MS (m/z): Calcd for $C_7H_7N_2S^+$ $[M + H]^+$ 151.03; found: 151.10.

*1.2.4 General pr℃edure for the synthesis of compounds **5d-5af***

Compound **4** (5.56 mmol) reacted with appropriate acid (6.10 mmol) for 4 h in the presence of HOBT/HBTU (16.18 mmol) and DIPEA (48.54 mmol) in dimethylformamide (50 mL). TLC indicated completion of the reaction. The solution was diluted with ethyl acetate (250 mL) and washed with water (40 mL × 5) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, followed by purification of flash column chromatography on silica gel to obtain the target compounds.

*5-chloro-N-(4-methoxybenzo[d]thiazol-2-yl) thiophene-2-carboxamide (**5d-5e**)*

White solid, yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 1H), 7.42 (dd, *J* = 6.1, 1.9 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.00 – 6.63 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 158.8, 151.4, 138.2, 137.3, 135.4, 133.1, 130.1, 127.5, 125.2, 113.5, 106.8, 55.3. ESI-MS (m/z): Calcd for $C_{13}H_{10}ClN_2O_2S_2^+$ $[M + H]^+$ 324.99; found: 325.00.

*5-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**5f-5g**)*

White solid, yield: 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.66 – 7.46 (m, 2H), 7.22 (dt, *J* = 7.0, 3.4 Hz, 1H), 6.97 (dq, *J* = 8.8, 2.3 Hz, 1H), 3.73 (d, *J* = 2.0 Hz, 3H). ESI-MS (m/z): Calcd for $C_{13}H_{10}ClN_2O_2S_2^+$ $[M + H]^+$ 324.99; found: 325.00.

*N-(benzo[d]thiazol-2-yl)-5-chlorothiophene-2-carboxamide (**5h-5i**)*

White solid, yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.54 – 7.41 (m, 1H), 7.41 – 7.26 (m, 2H). ESI-MS (m/z): Calcd for $C_{12}H_8ClN_2OS_2^+$ $[M + H]^+$ 294.98; found:295.10.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl) thiophene-2-carboxamide (**5j-5k**)*

White solid, yield 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.07 (d, *J* = 3.9 Hz, 1H), 7.49 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.37 (d, *J* = 4.1 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.1, 0.9 Hz, 1H), 3.87 (s, 3H). ESI-MS (m/z): Calcd for $C_{13}H_{10}BrN_2O_2S_2^+$ $[M + H]^+$ 368.94; found: 368.70.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl) furan-2-carboxamide (**5l-5m**)*

White solid, yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 4.1 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.88 – 6.80 (m, 2H), 3.76 (s, 3H). ESI-MS (m/z): Calcd for $C_{13}H_{10}BrN_2O_3S^+$ $[M + H]^+$ 352.96; found: 352.40.

*2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl) isonicotinamide (**5n-5q**)*

White solid, yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.10 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 3.99 (s, 3H), 3.82 (s, 3H). ESI-MS (m/z): Calcd for $C_{15}H_{14}N_3O_3S^+$ $[M + H]^+$ 316.08; found: 316.10.

*N-(4-methoxybenzo[d]thiazol-2-yl) cinnamamide (**5r-5u**)*

White solid, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.53 (s, 1H), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.45 – 7.26 (m, 6H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 3H). ESI-MS (m/z): Calcd for $C_{17}H_{15}N_2O_2S^+$ $[M + H]^+$ 311.09; found: 311.40.

*N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide (**5v-5y**)*

White solid, yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.3 Hz, 3H), 7.34 – 7.27 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.42 (s, 3H). ESI-MS (m/z): Calcd for $C_{16}H_{12}F_3N_2O_2S^+$ $[M + H]^+$ 353.06; found: 353.30.

*N-(4-methoxybenzo[d]thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide (**5z-5aa**)*

White solid, yield 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.81 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.17 (s, 2H), 3.93 (s, 3H). ESI-MS (m/z): Calcd for $C_{16}H_{13}N_2O_4S^+$ $[M + H]^+$ 329.06; found: 329.20.

*N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide (**5ab,5ad-5af**)*

White solid, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.42 (s, 1H), 8.06-8.02 (m, 1H), 7.93 – 7.82 (m, 2H), 7.64 – 7.44 (m, 4H), 7.23 (t, *J* = 8.0 Hz, 1H). 6.63 (d, *J* = 7.7 Hz, 1H), 3.54 (s, 3H). ESI-MS (m/z): Calcd for $C_{19}H_{15}N_2O_2S^+$ $[M + H]^+$ 335.09; found: 335.00.

*1.2.5 General pr℃edure for the synthesis of compounds **6d-6af***

To a solution of **5** (3.65 mmol) with potassium carbonate (10.95 mmol) in dimethylformamide (25 mL) was added 2-iodoethanol 1.34 mL (10.95 mmol). Then the mixture was heated to 50℃

overnight. The solution was diluted with ethyl acetate (120 mL) and washed with water (30 mL × 5) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, followed by purification of flash column chromatography on silica gel to obtain the target compounds.

*5-chloro-N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**6d-6e**)*

White solid, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 4.0, 0.8 Hz, 1H), 7.28 (ddd, *J* = 6.4, 3.9, 0.8 Hz, 2H), 6.98 (dd, *J* = 6.3, 2.8 Hz, 1H), 6.94 (dd, *J* = 4.0, 0.8 Hz, 1H), 5.05 (t, *J* = 5.0 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 4.07 – 3.90 (m, 3H), 3.55 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 168.4, 147.4, 140.4, 136.1, 130.9, 128.6, 127.6, 125.8, 125.0, 115.3, 109.6, 63.1, 56.2, 51.2.ESI-MS (m/z): Calcd for $C_{15}H_{14}ClN_2O_3S_2^+$ $[M + H]^+$ 369.01; found: 369.40.

*5-chloro-N-(2-hydroxyethyl)-N-(6-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**6f-6g**)*

White solid, yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 3.9 Hz, 1H), 7.28 (dd, *J* = 5.8, 3.2 Hz, 2H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.98 (dd, *J* = 6.5, 2.6 Hz, 1H), 5.06 (t, *J* = 5.1 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 4.00 (s, 3H), 3.51 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 165.9, 156.8, 141.6, 134.2, 131.6, 131.3, 128.9, 127.3, 115.3, 114.6, 107.0, 58.7, 56.2, 48.8. ESI-MS (m/z): Calcd for $C_{15}H_{14}ClN_2O_3S_2^+$ $[M + H]^+$ 369.01; found: 369.10.

*N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-hydroxyethyl)thiophene-2-carboxamide (**6h-6i**)*

White solid, yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.87 (m, 1H), 7.72 (dt, *J* = 14.4, 4.4 Hz, 2H), 7.52 (td, *J* = 7.7, 2.8 Hz, 1H), 7.35 (td, *J* = 7.6, 3.3 Hz, 1H), 7.22 (dd, *J* = 6.8, 3.9 Hz, 1H), 4.99 (t, *J* = 5.7 Hz, 1H), 4.52 (t, *J* = 3.0 Hz, 1H), 3.88 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.8, 166.6, 141.5, 137.8, 134.5, 131.5, 128.9, 127.5, 126.0, 124.4, 123.3, 113.8, 58.6, 48.7. ESI-MS (m/z): Calcd for $C_{14}H_{12}ClN_2O_2S_2^+$ $[M + H]^+$ 339.00; found: 339.30.

*5-bromo-N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)thiophene-2-carboxamide (**6j-6k**)*

White solid, yield: 61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 3.9 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.16 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.92 (t, *J* = 5.8 Hz, 1H),

4.83 (t, *J* = 6.4 Hz, 2H), 3.96 (s, 3H), 3.78 (d, *J* = 6.1 Hz, 2H). ESI-MS (m/z): Calcd for $C_{15}H_{14}BrN_2O_3S_2^+$ $[M + H]^+$ 412.96; found: 413.00.

*5-bromo-N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)furan-2-carboxamide (**6l-6m**)*

White solid, yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 1H), 7.27 (s, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 6.97 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.46 (d, *J* = 3.5 Hz, 1H), 5.24 – 4.91 (m, 2H), 4.19 – 4.12 (m, 2H), 3.98 (s, 3H). ESI-MS (m/z): Calcd for $C_{15}H_{14}BrN_2O_4S^+$ $[M + H]^+$ 396.99; found: 396.60.

*N- (2-hydroxyethyl) -2-methoxy-N- (4-methoxybenzo[d]thiazol-2-yl) isonicotinamide (**6n-6q**)*

White solid, yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 2.3 Hz, 1H), 8.39 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.33 – 7.24 (m, 2H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.10 (t, *J* = 5.2 Hz, 2H), 4.17 (q, *J* = 4.6 Hz, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.62 (d, *J* = 4.8 Hz, 1H). ESI-MS (m/z): Calcd for $C_{17}H_{18}N_3O_4S^+$ $[M + H]^+$ 360.10; found: 360.40.

*N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) cinnamamide (**6r-6u**)*

White solid, yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.40 – 7.33 (m, 3H), 7.28 – 7.21 (m, 2H), 6.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.82 (d, *J* = 15.9 Hz, 1H), 5.08 – 5.00 (m, 2H), 4.35 (s, 1H), 4.14 (t, *J* = 4.9 Hz, 2H), 3.94 (s, 3H). ESI-MS (m/z): Calcd for $C_{19}H_{19}N_2O_3S^+$ $[M + H]^+$ 355.11; found: 355.30.

*N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifluoromethyl) benzamide (**6v-6y**)*

White solid, yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.20 (m, 2H), 6.97 (dd, *J* = 7.3, 1.8 Hz, 1H), 5.13 (t, *J* = 5.1 Hz, 2H), 4.18 (t, *J* = 5.0 Hz, 2H), 3.99 (s, 3H), 3.62 (s, 1H). ESI-MS (m/z): Calcd for $C_{18}H_{16}F_3N_2O_3S^+$ $[M + H]^+$ 397.08; found: 397.10.

*N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide(**6z-6aa**)*

White solid, yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.31 – 7.19 (m, 2H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.05 (s, 2H), 5.10 (t, *J* = 5.0 Hz, 2H), 4.18 (d, *J* = 4.9 Hz, 2H), 3.98 (s, 3H), 3.91 (s, 1H). ESI-MS (m/z): Calcd for $C_{18}H_{17}N_2O_5S^+$ $[M + H]^+$ 373.09; found: 373.00.

*N-(2-hydroxyethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide (**6ab**,**6ad-6af**)*

White solid, yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.37 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 8.5 Hz, 2H), 7.68 – 7.46 (m, 2H), 7.37 – 7.15 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.25 – 5.09 (m, 2H), 4.24 (t, *J* = 5.0 Hz, 2H), 3.99 (s, 3H). ESI-MS (m/z): Calcd for $C_{21}H_{19}N_2O_3S^+$ $[M + H]^+$ 379.11; found: 379.30.

*1.2.6 General pr℃edure for the synthesis of compounds **7d-7af***

To a solution of **6** (1.61 mmol) in dimethyl sulfoxide (15 mL) was added 2-iodoxybenzoic acid (3.22 mmol), and the mixture was stirred at room temperature for 4 h. The solution was diluted with ethyl acetate (60 mL) and washed with sat. sodium thiosulfate solution (5 mL × 3), water (10 mL × 5) and brine (10 mL). The organic layer was dried by $MgSO_4$ and concentrated under reduced pressure, followed by purification of flash column chromatography on silica gel to obtain the target compounds.

*5-chloro-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl)thiophene-2-carboxamide (**7d-7e**)*

White solid, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.65 (d, *J* = 4.0 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.95 – 6.89 (m, 2H), 5.58 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 168.5, 167.4, 146.9, 140.4, 136.2, 131.1, 128.0, 127.5, 125.1, 115.3, 109.4, 57.0, 56.1. ESI-MS (m/z): Calcd for $C_{15}H_{12}ClN_2O_3S_2^+$ $[M + H]^+$ 367.00; found: 367.30.

*5-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl)thiophene-2-carboxamide (**7f-7g**)*

White solid, yield: 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.68 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.20 (dd, *J* = 4.1, 2.9 Hz, 1H), 7.10 (dt, *J* = 9.1, 2.4 Hz, 1H), 5.45 (d, *J* = 2.0 Hz, 2H), 3.81 (d, *J* = 1.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.0, 167.1, 166.0,

156.6, 140.7, 134.1, 131.2, 130.2, 128.4, 126.6, 115.0, 113.4, 107.0, 55.8, 54.6. ESI-MS (m/z): Calcd for $C_{15}H_{12}ClN_2O_3S_2^+$ $[M + H]^+$ 367.00; found: 367.50.

*N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-oxoethyl)thiophene-2-carboxamide (**7h-7i**)*

White solid, yield: 89%. ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 0.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.67 (d, *J* = 4.0 Hz, 1H), 7.47 (ddd, *J* = 8.4, 7.5, 1.3 Hz, 1H), 7.36 (td, *J* = 7.6, 1.0 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 4.0 Hz, 1H), 5.17 (d, *J* = 0.8 Hz, 2H). ESI-MS (m/z): Calcd for $C_{14}H_{10}ClN_2O_2S_2^+$ $[M + H]^+$ 336.99; found: 337.10.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl) thiophene-2-carboxamide (**7j-7k**)*

White solid, yield 84 %. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.59 (s, 2H), 3.90 (s, 3H). ESI-MS (m/z): Calcd for $C_{15}H_{12}BrN_2O_3S_2^+$ $[M + H]^+$ 410.95; found:411.20.

*5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl) furan-2-carboxamide (**7l-7m**)*

White solid, yield 56%. ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.38 – 7.21 (m, 2H), 7.16 (d, *J* = 3.4 Hz, 1H), 6.93 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 5.60 (s, 2H), 3.90 (s, 3H).ESI-MS (m/z): Calcd for $C_{15}H_{12}BrN_2O_4S^+$ $[M + H]^+$ 394.97; found: 395.10.

*2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl) isonicotinamide (**7n-7q**)*

White solid, yield 87%. ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.3 Hz, 1H), 9.12 (t, *J* = 1.8 Hz, 1H), 8.39-8.36 (m, 1H), 7.35 – 7.25 (m, 2H), 6.94 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.67 (d, *J* = 1.4 Hz, 2H), 4.03 (s, 3H), 3.93 (s, 3H). ESI-MS (m/z): Calcd for $C_{17}H_{16}N_3O_4S^+$ $[M + H]^+$ 358.09; found: 358.20.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl) cinnamamide (**7r-7u**)*

White solid, yield 66 %. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.81 (d, *J* = 15.9 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.41 – 7.34 (m, 3H), 7.32 – 7.25 (m, 2H), 6.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 (d, *J* = 15.9 Hz, 1H), 5.61 (s, 2H), 3.89 (s, 3H). ESI-MS (m/z): Calcd for $C_{19}H_{17}N_2O_3S^+$ $[M + H]^+$

353.10; found: 353.40.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl)-4-(trifluoromethyl) benzamide (**7v-7y**)*

White foam, yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.38 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.37 – 7.26 (m, 2H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.68 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 173.5, 168.6, 147.0, 139.3, 129.7, 128.1, 126.6, 124.5, 115.5, 109.5, 57.2, 56.1. ESI-MS (m/z): Calcd for $C_{18}H_{14}F_3N_2O_3S^+$ $[M + H]^+$ 395.07; found: 395.10.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl)benzo[d][1,3]dioxole-5-carboxamide (**7z-7aa**)*

Light yellow foam, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.92 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.27-7.23 (m, 1H), 6.93 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 2H), 5.64 (s, 2H), 3.91 (s, 3H). ESI-MS (m/z): Calcd for $C_{18}H_{15}N_2O_5S^+$ $[M + H]^+$ 371.07; found: 371.30.

*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-oxoethyl)-2-naphthamide (**7ab,7ad-7af**)*

Yellow solid, yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.83 (s, 1H), 8.33 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.04 – 7.96 (m, 1H), 7.90-7.87 (m, 2H), 7.58-7.51 (m, 2H), 7.35-7.32 (m, 1H), 7.29-7.23 (m, 1H), 6.94 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.72 (s, 2H), 3.92 (s, 3H). ESI-MS (m/z): Calcd for $C_{21}H_{17}N_2O_3S^+$ $[M + H]^+$ 377.10; found: 377.30.

2. Results

2.1 Docking modes of the compounds interacted with the antagonist-bound conformation of TRPC6.

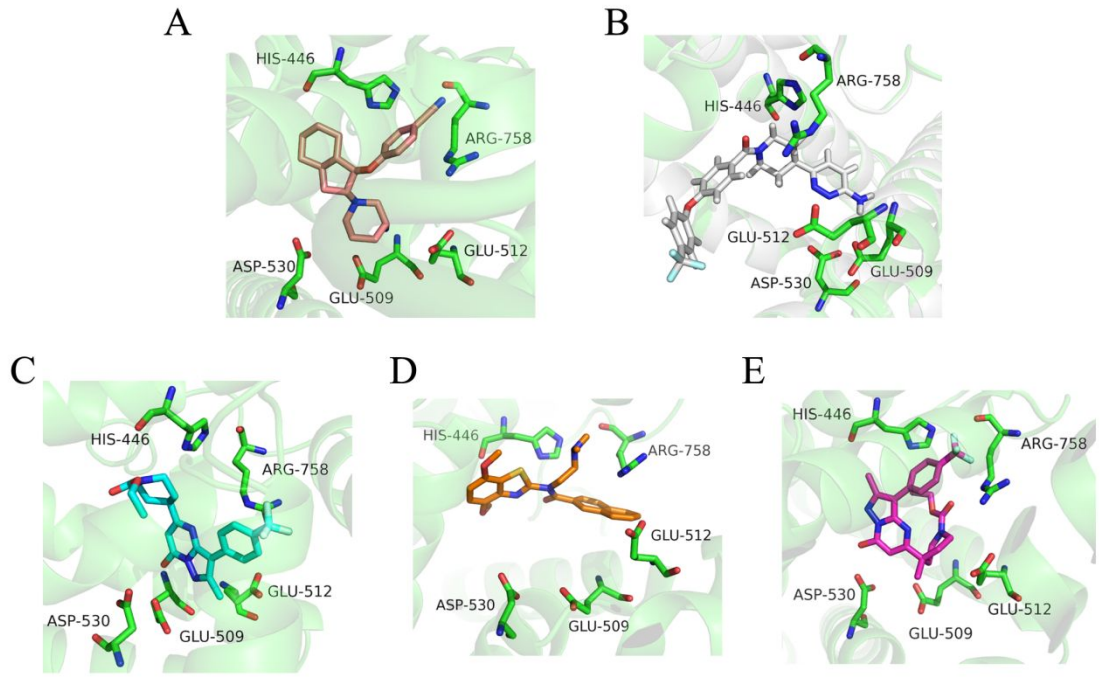
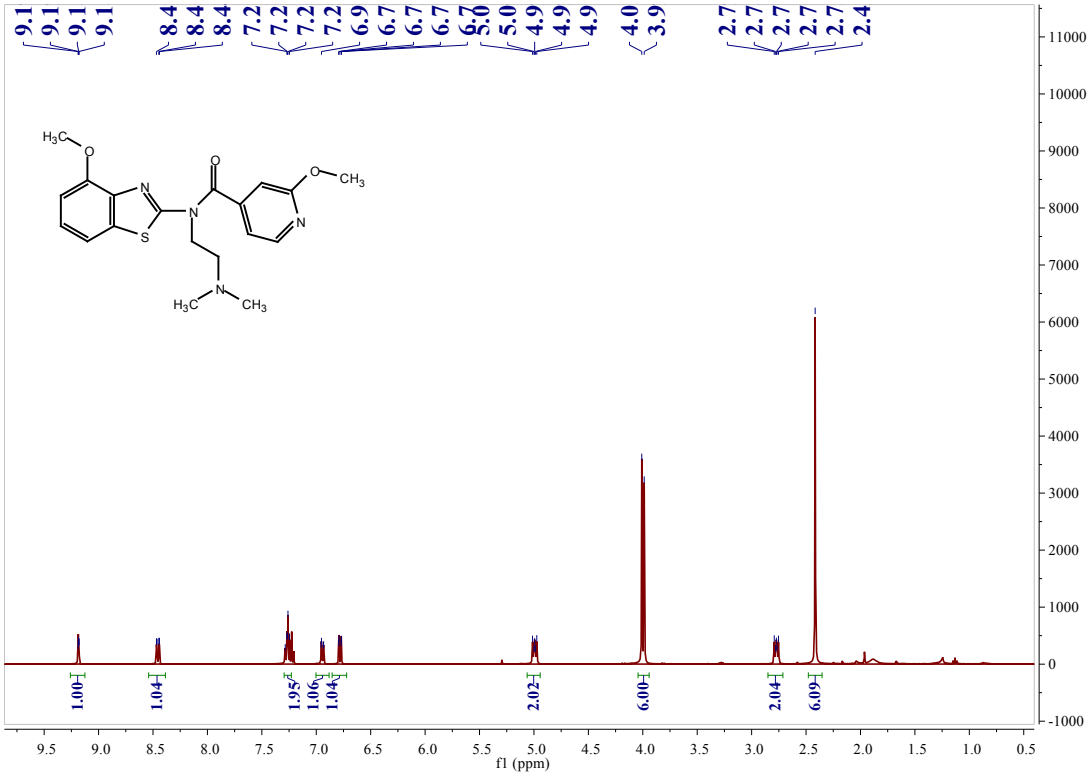
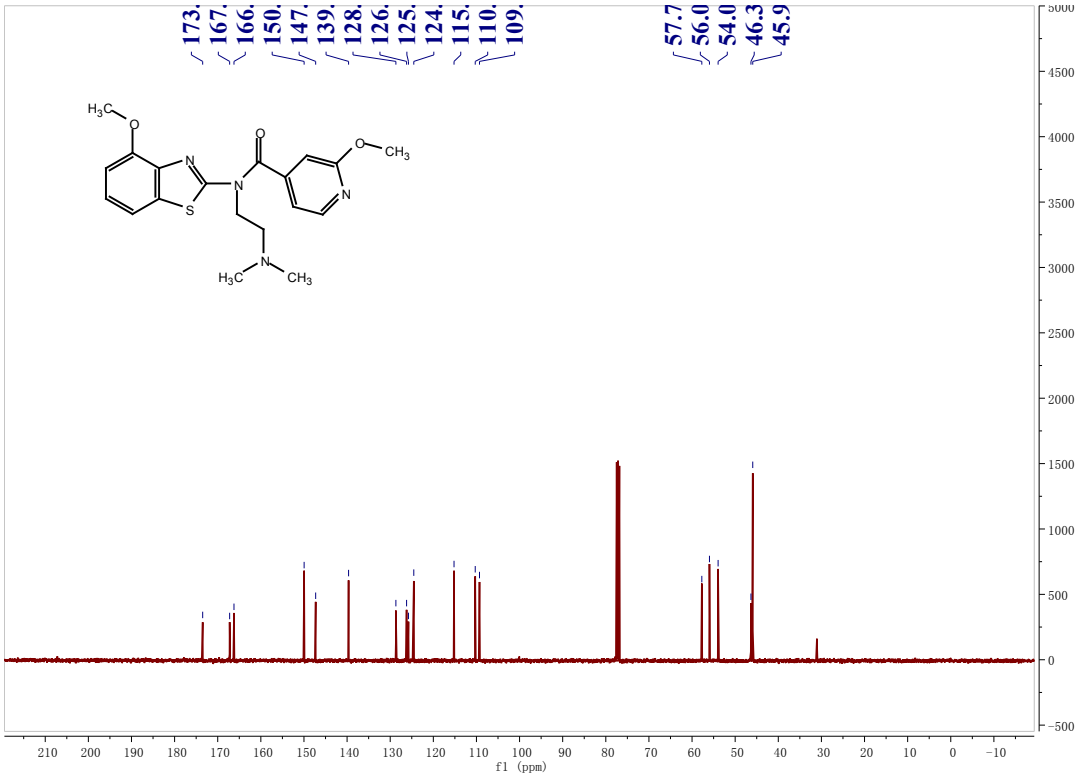


Figure S1. The 3D modes of **SAR-7334** (A), **BI 749327** (B), **HDM** (C), **1a** (D) and **HQR** (E) interacted with the antagonist-bound conformation of TRPC6 (PDB ID: 6uza). In the 3D binding modes, **SAR-7334**, **BI 749327**, **HDM**, **1a** and **HQR** are displayed in pink, white, cyan, orange and magenta sticks, respectively, and the key residues of TRPC6 are shown in green sticks.

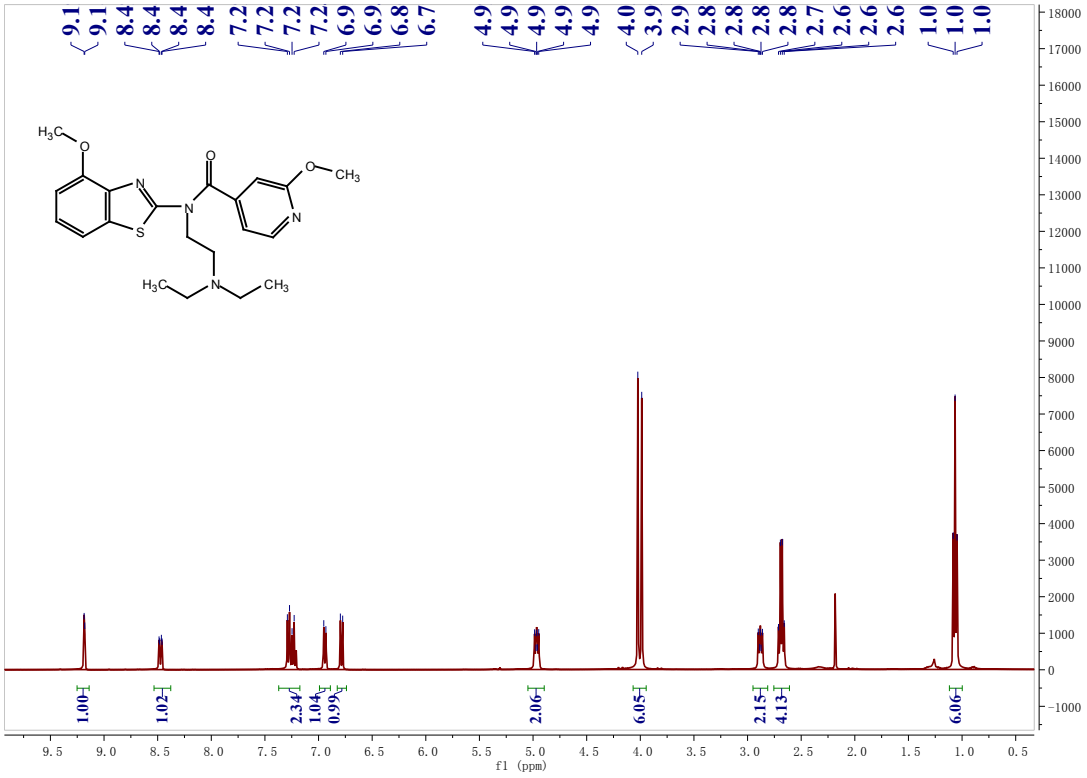
3 ^{1}H and ^{13}C NMR of 1d-1af

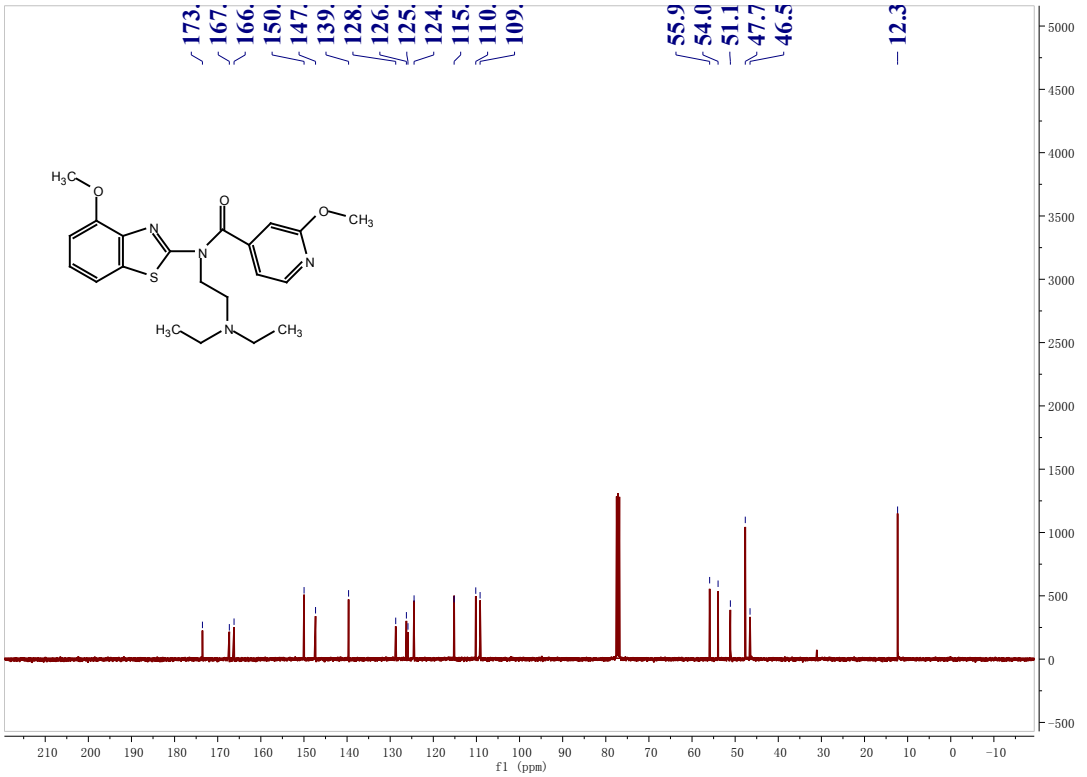
^{1}H and ^{13}C NMR of*N-(2-(dimethylamino)ethyl)-2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)iso-nicotinamide (**1d**)*



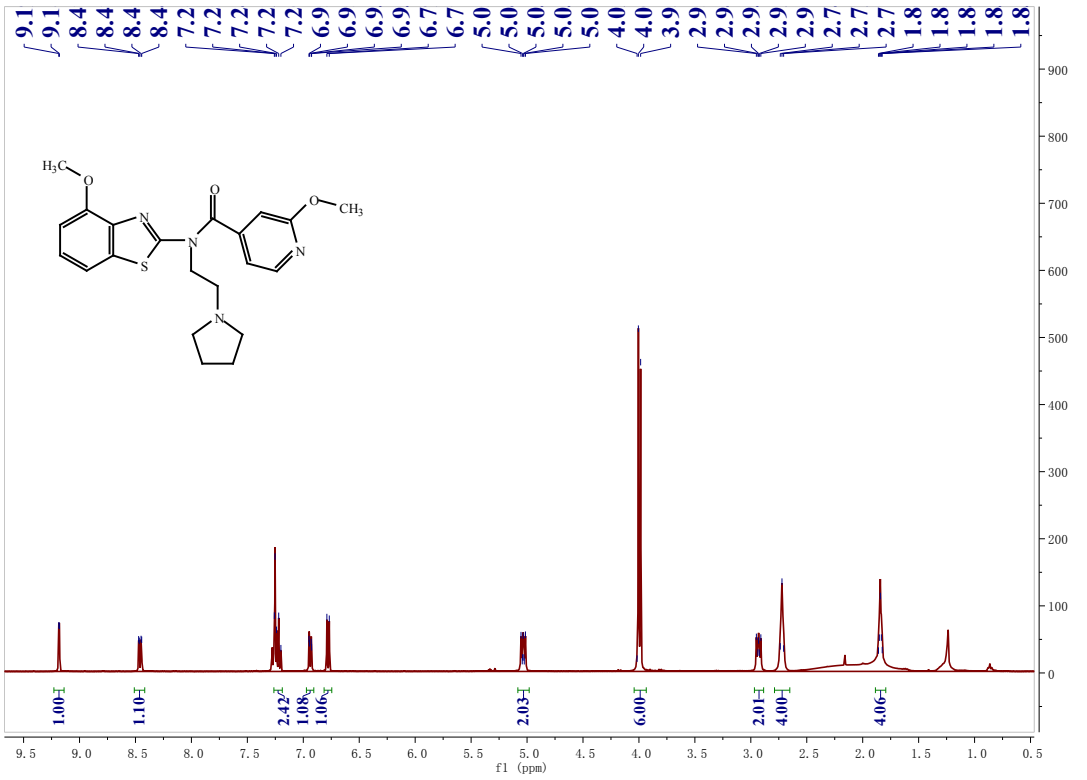


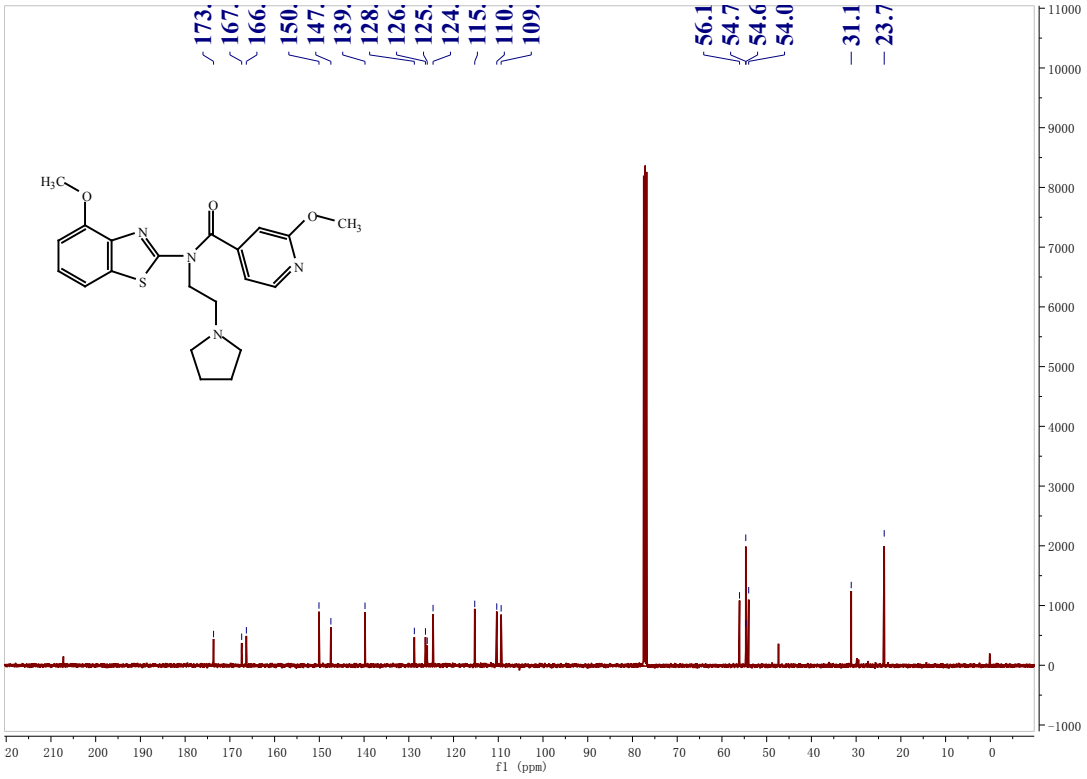
^{1}H and ^{13}C NMR of *N-(2-(diethylamino)ethyl)-2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)iso-nicotinamide* ***(1e)***



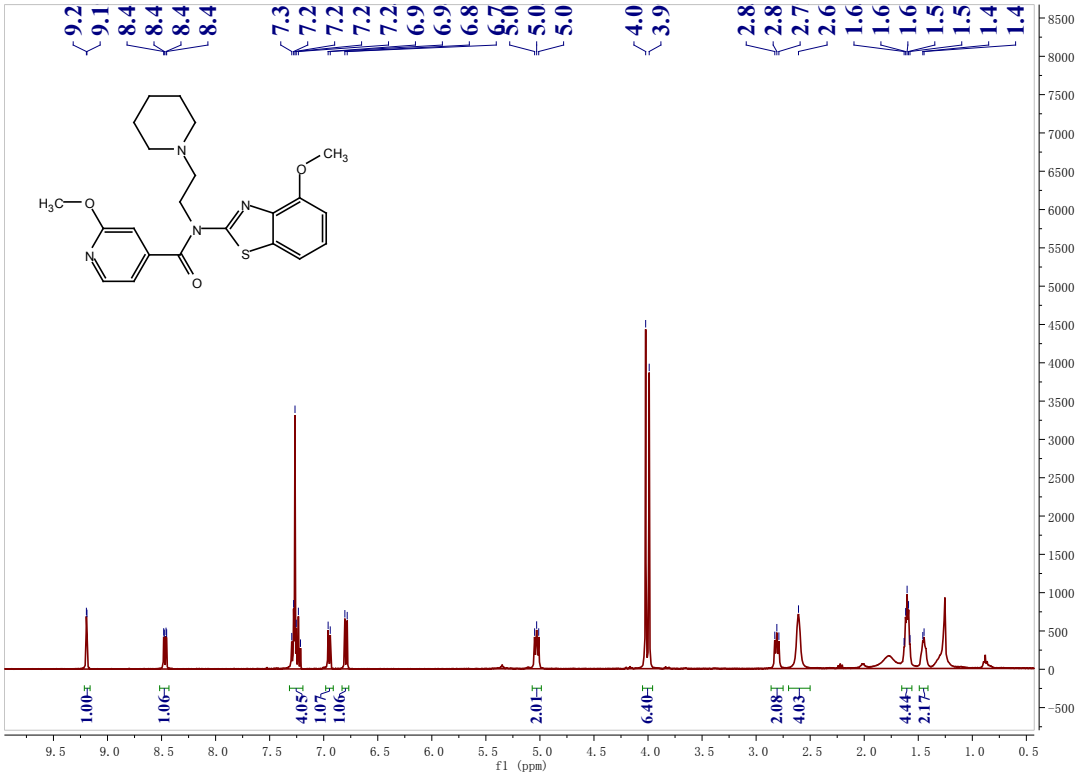


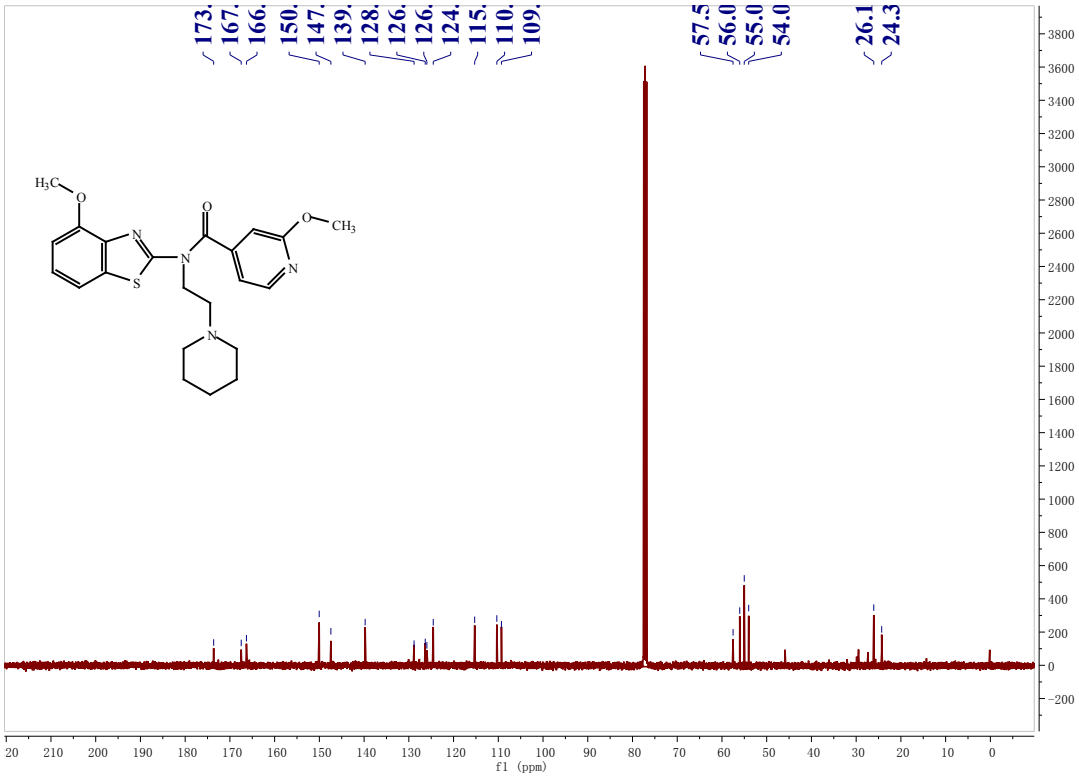
^{1}H and ^{13}C NMR of *2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)iso-nicotinamide* ***(1f)***



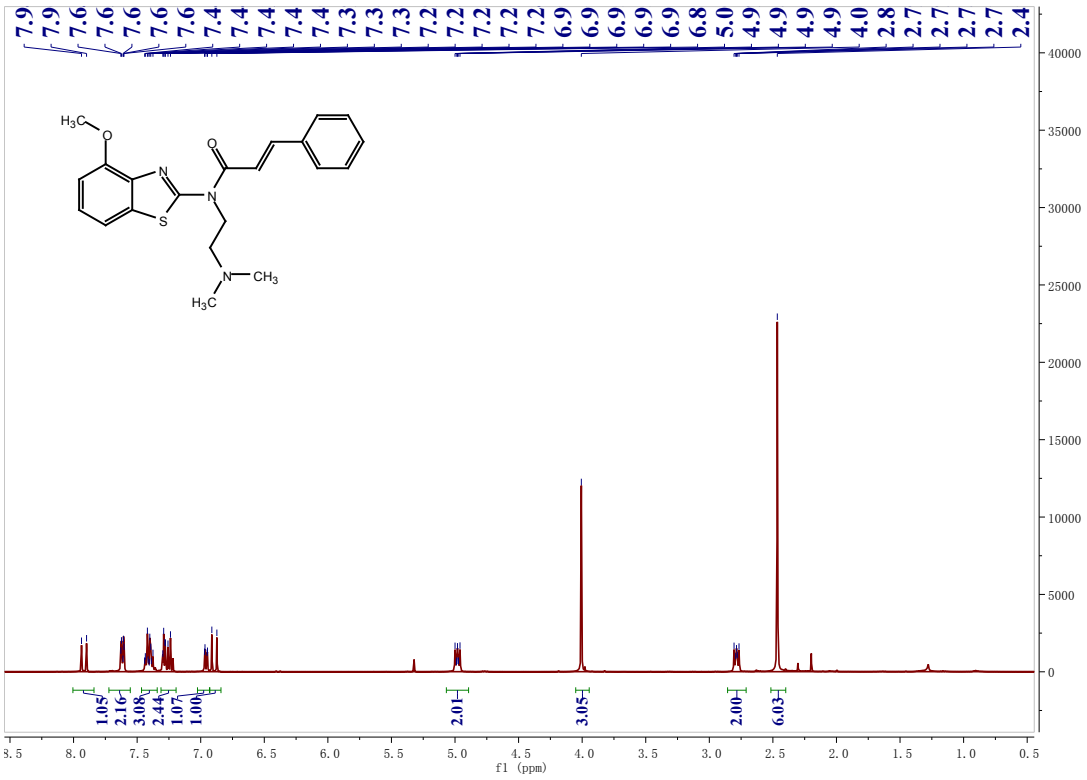


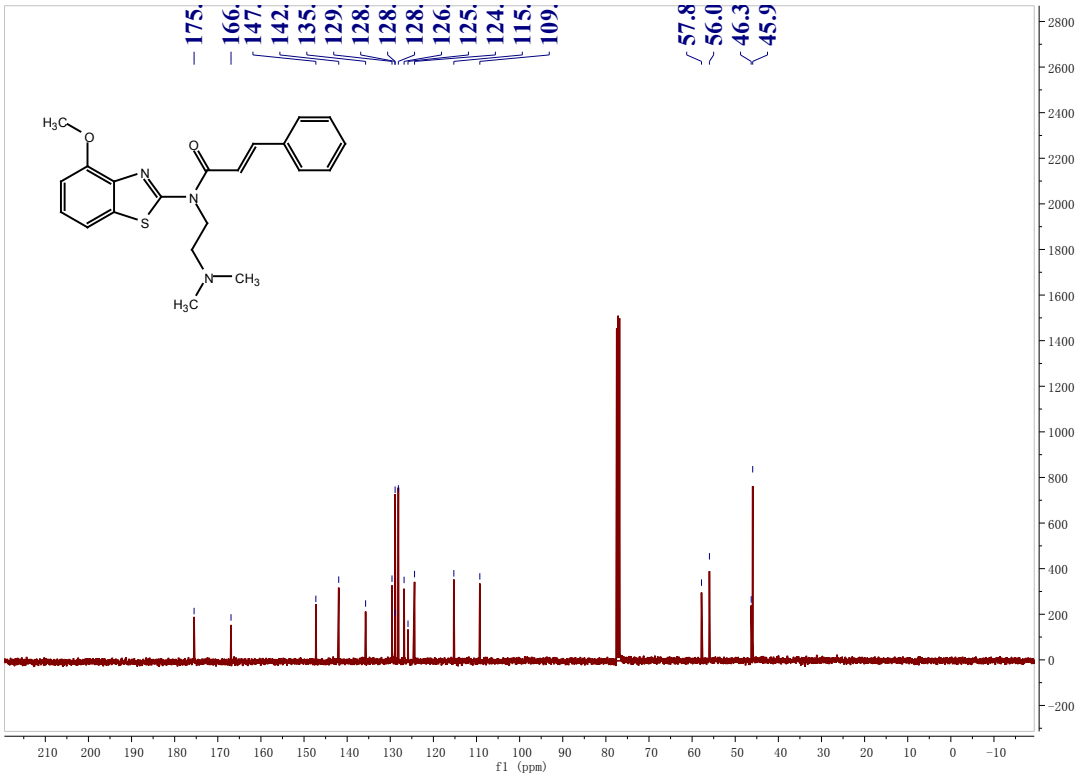
^{1}H and ^{13}C NMR of *2-methoxy-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)isonicotinamide (**1g**)*



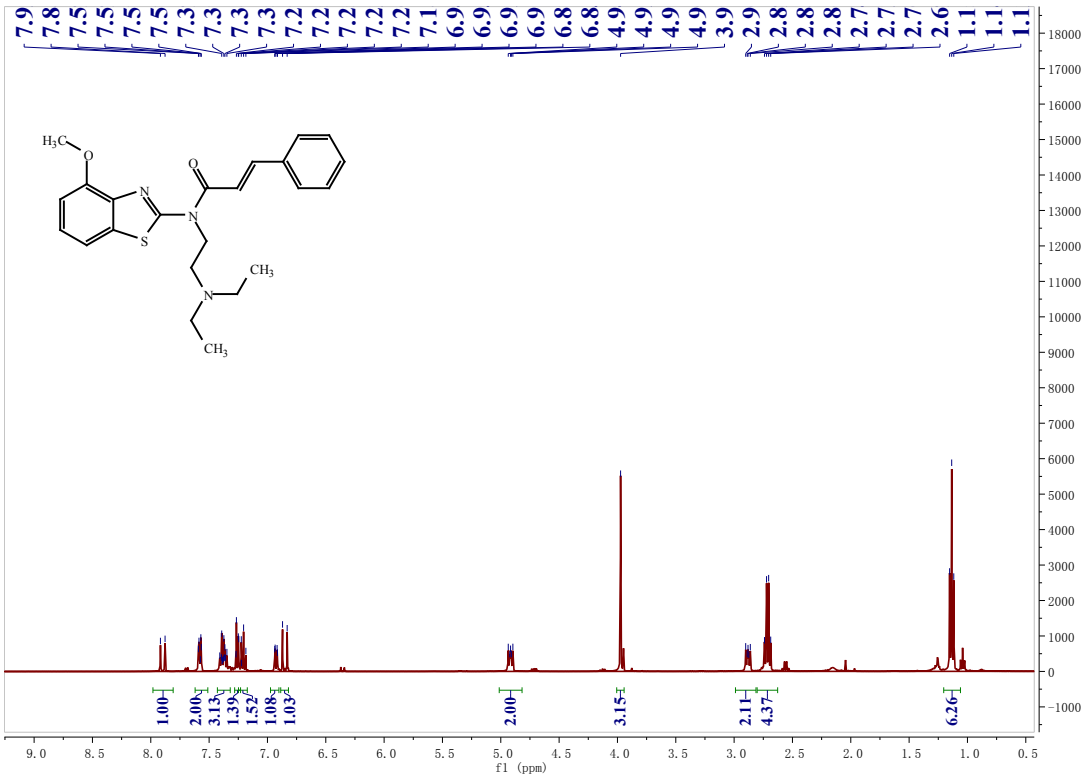


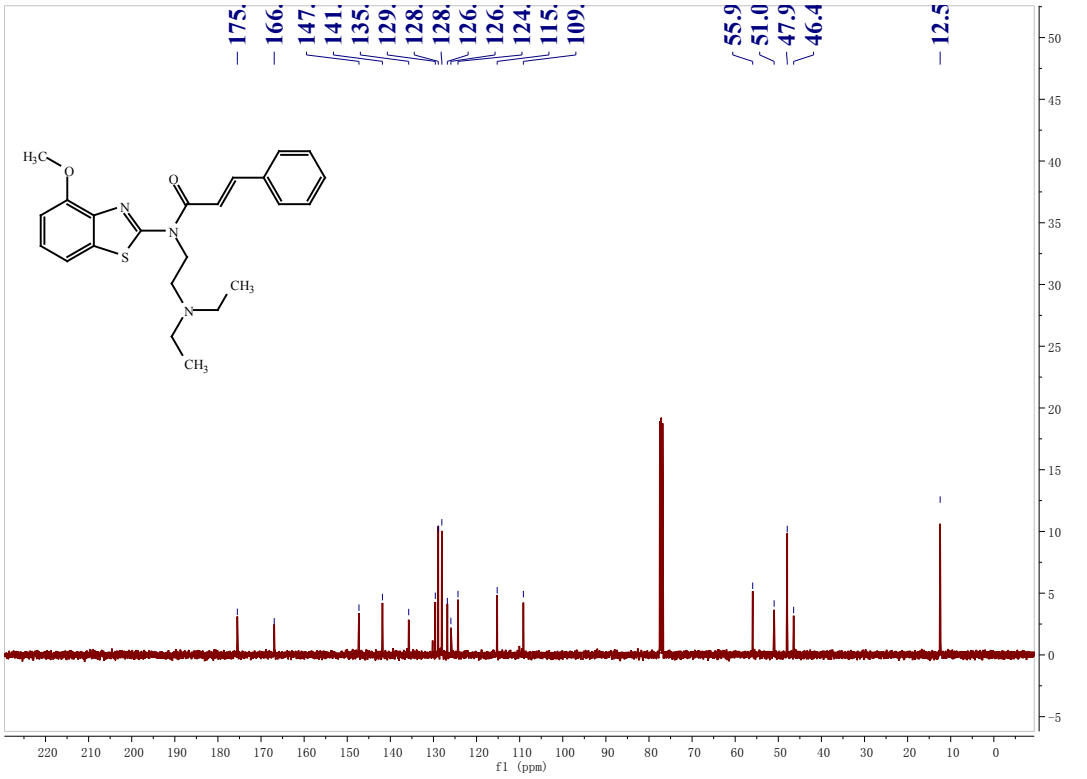
^{1}H and ^{13}C NMR of *N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)cinnamamide(**1h**)*



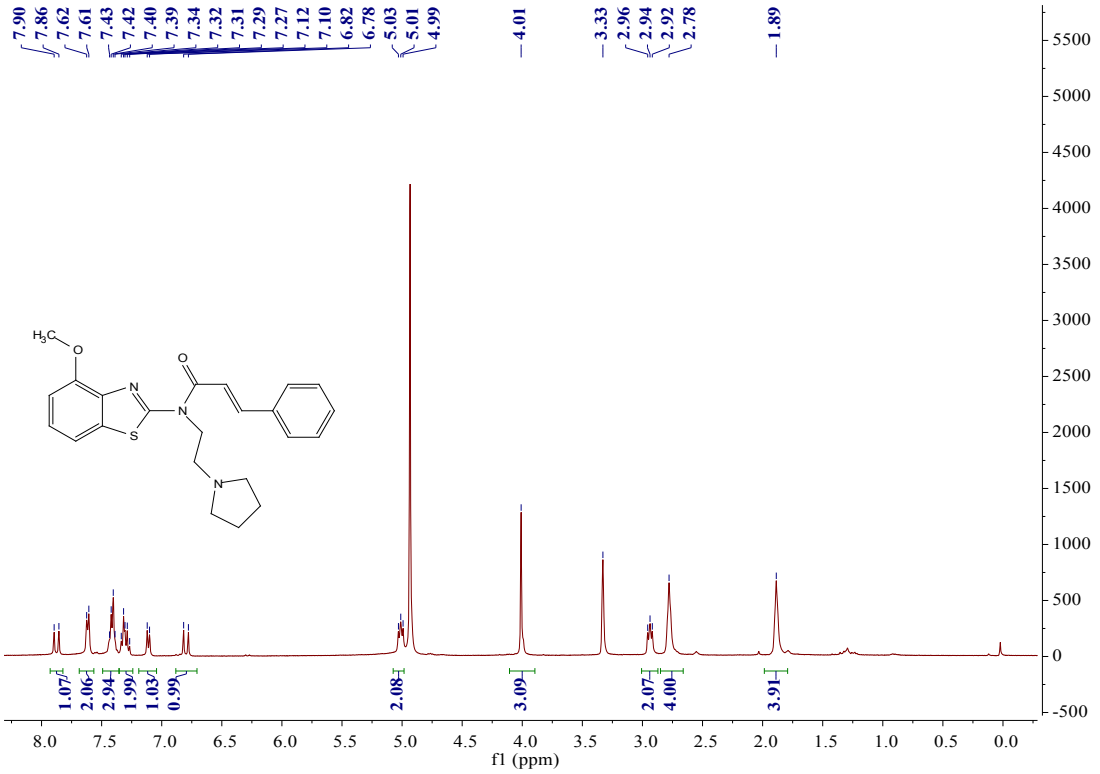


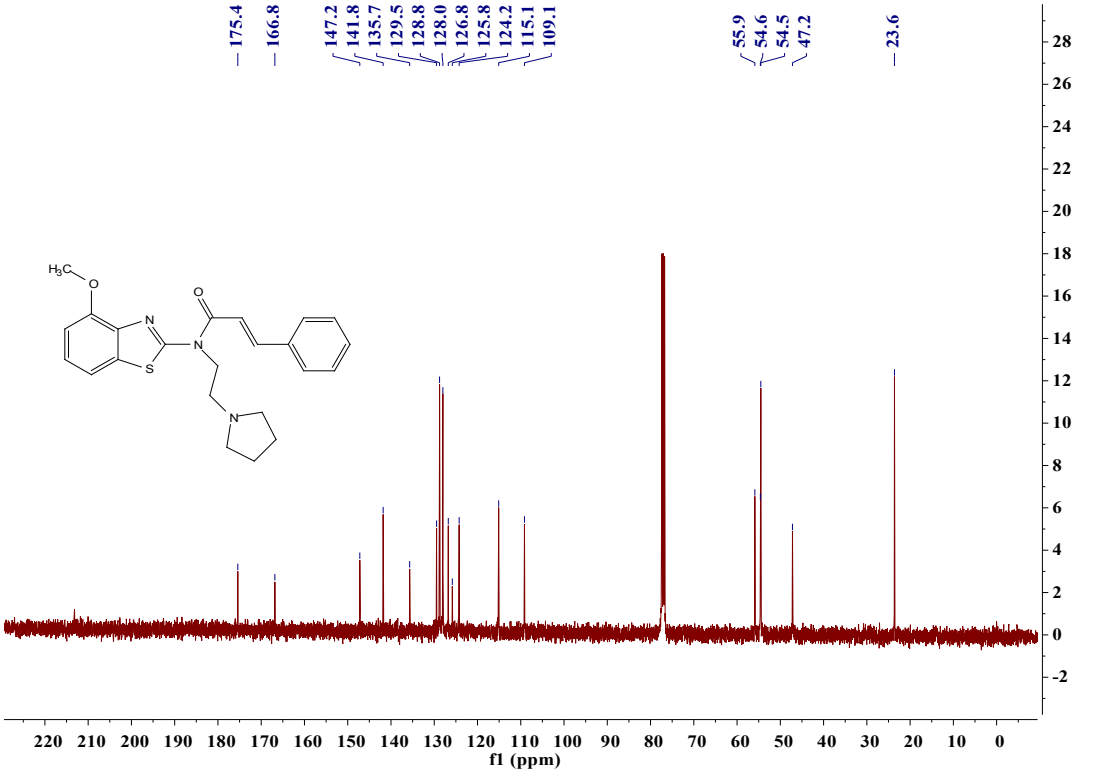
^{1}H and ^{13}C NMR of *N-(2-(diethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) cinnamamide* ***(1i)***



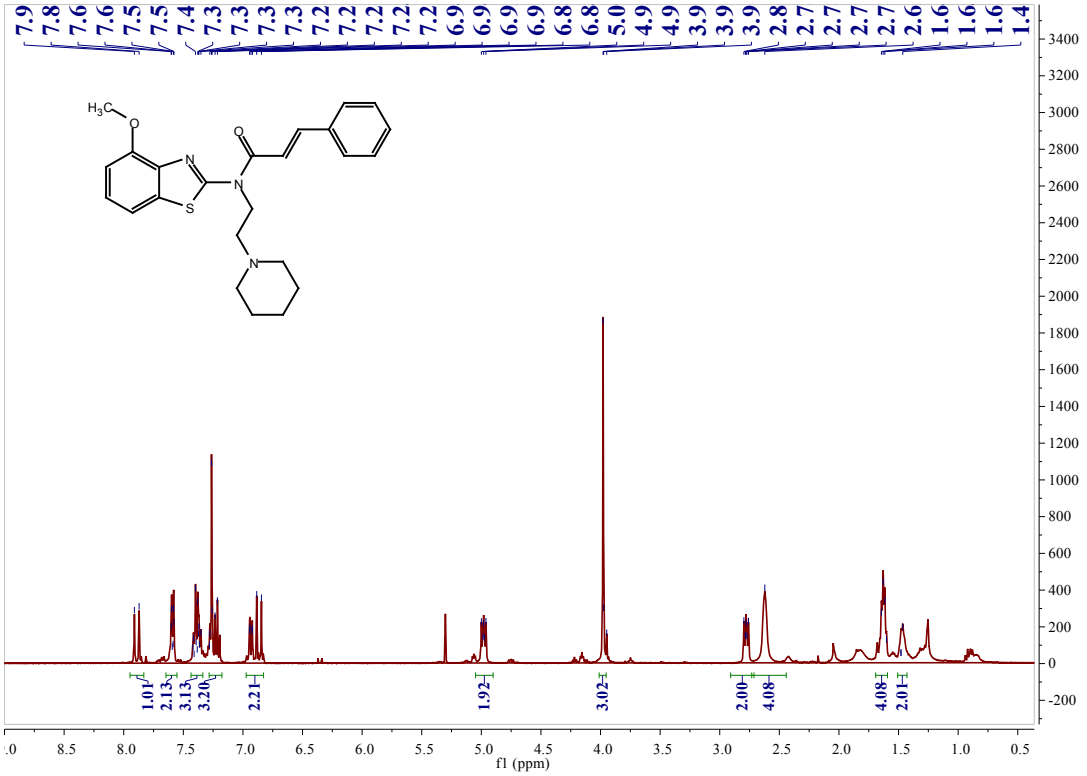


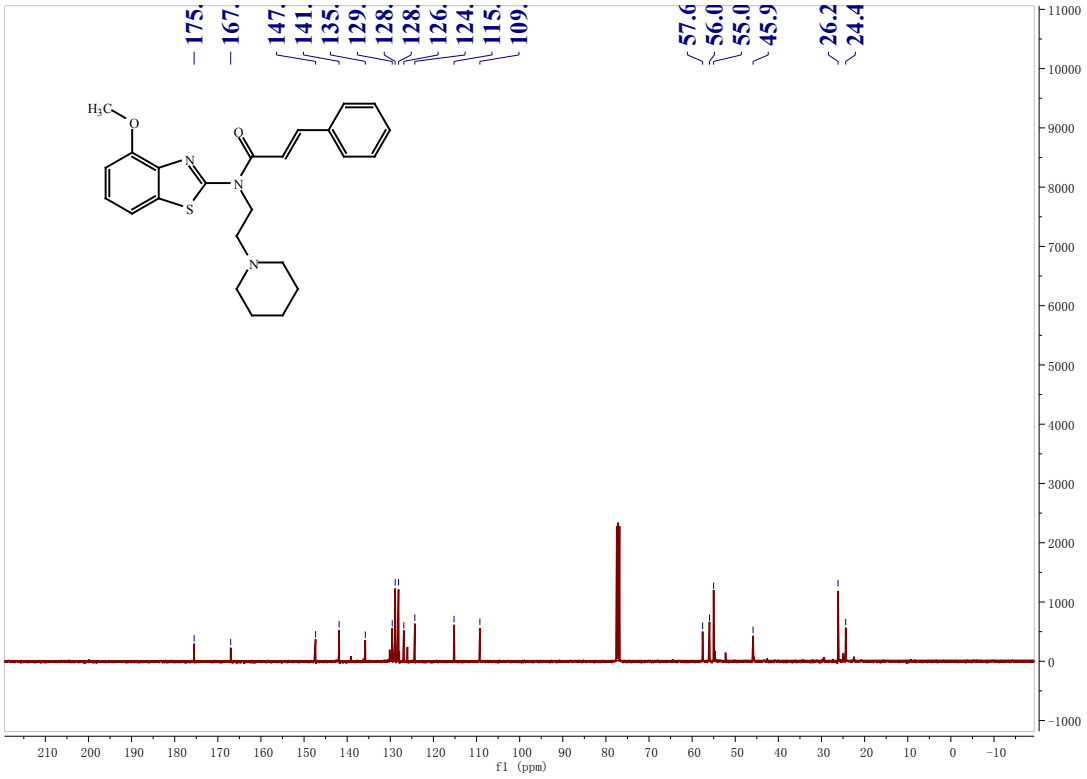
^{1}H and ^{13}C NMR of *N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl) ethyl) cinnamamide* ***(1j)***



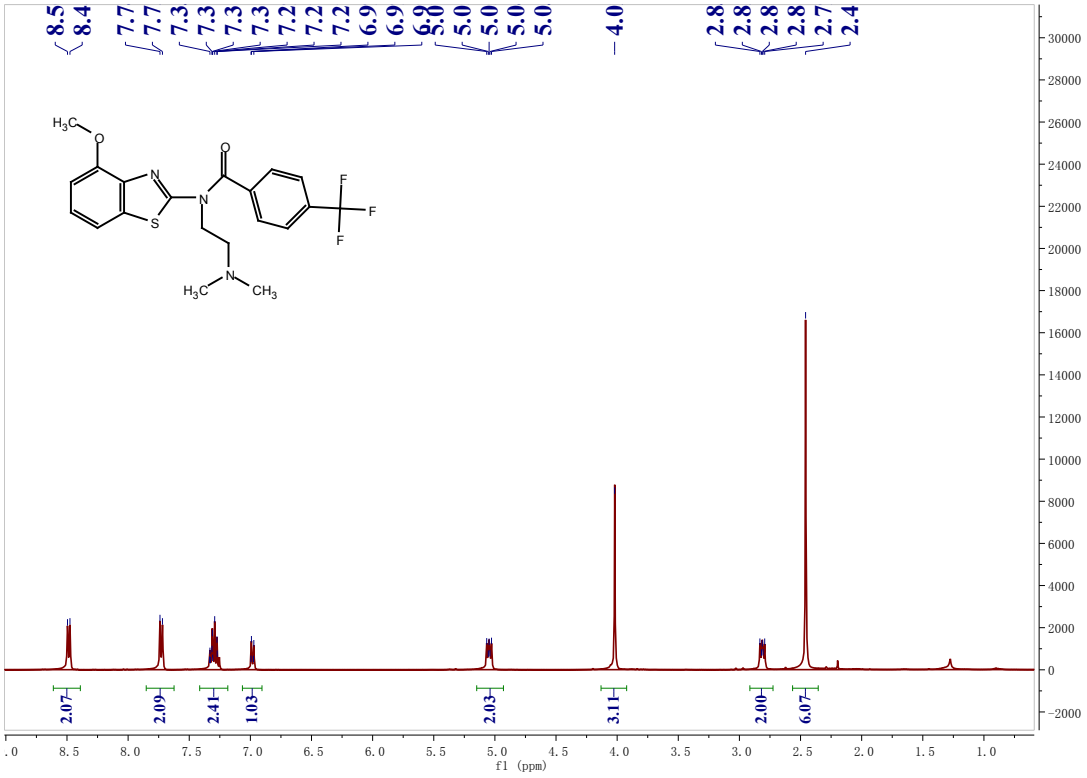


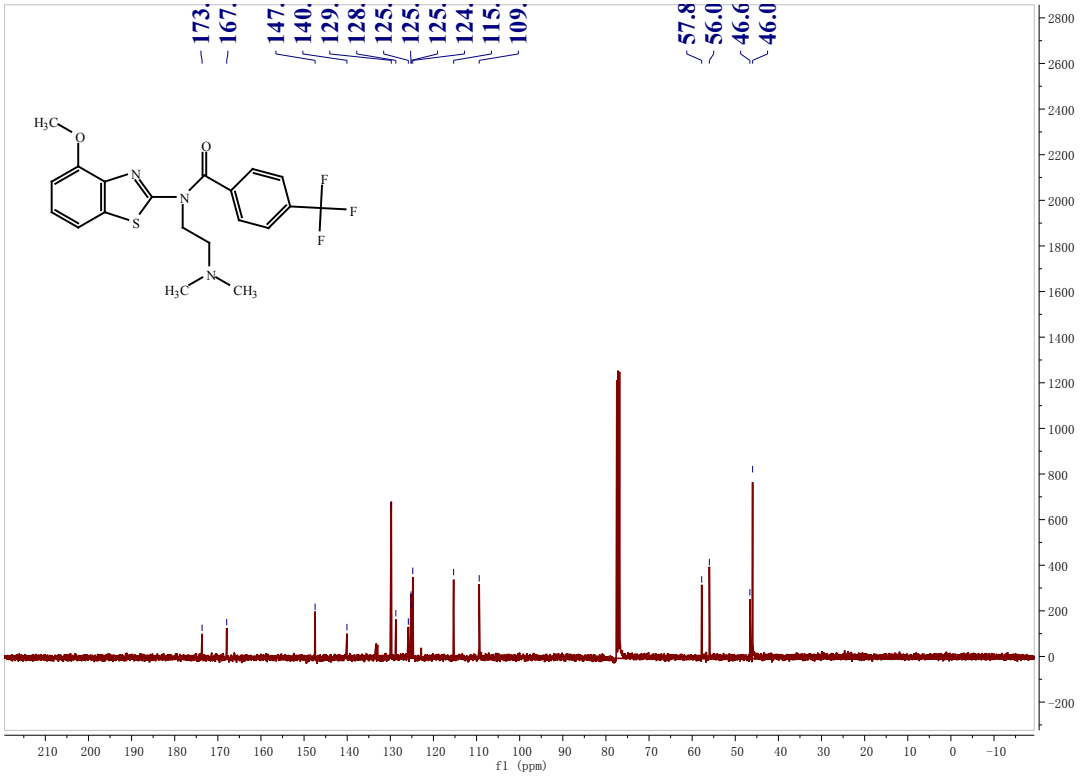
^{1}H and ^{13}C NMR of*N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)cinnamamide* ***(1k)***



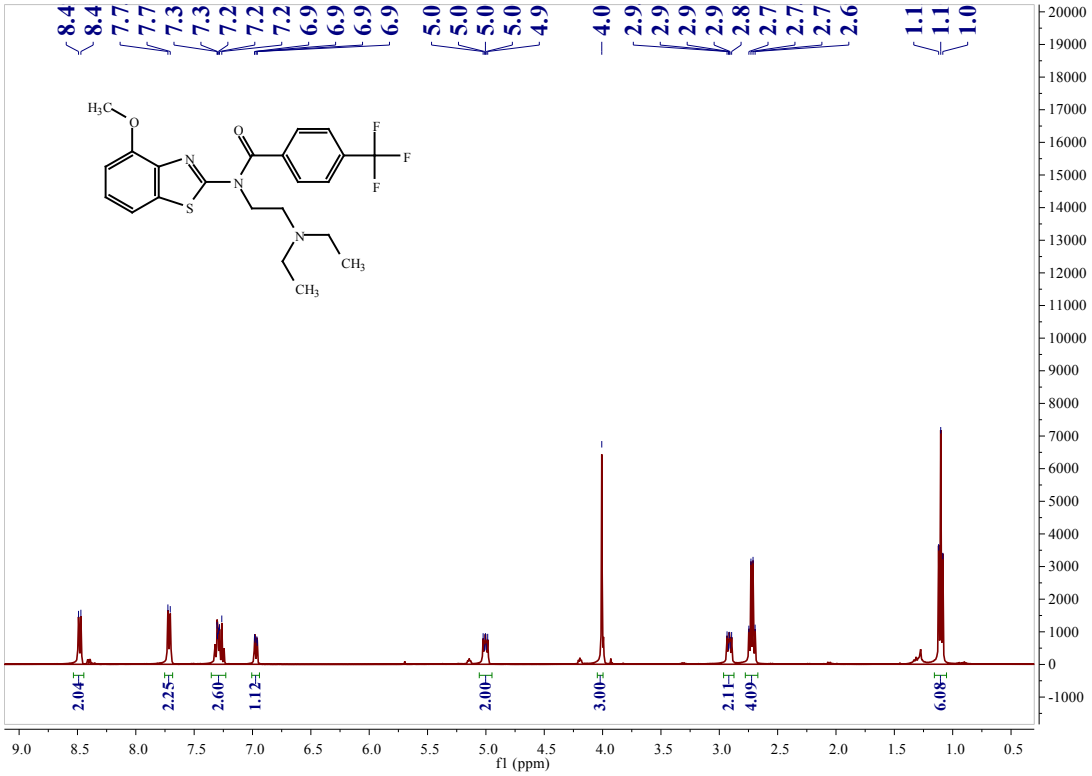


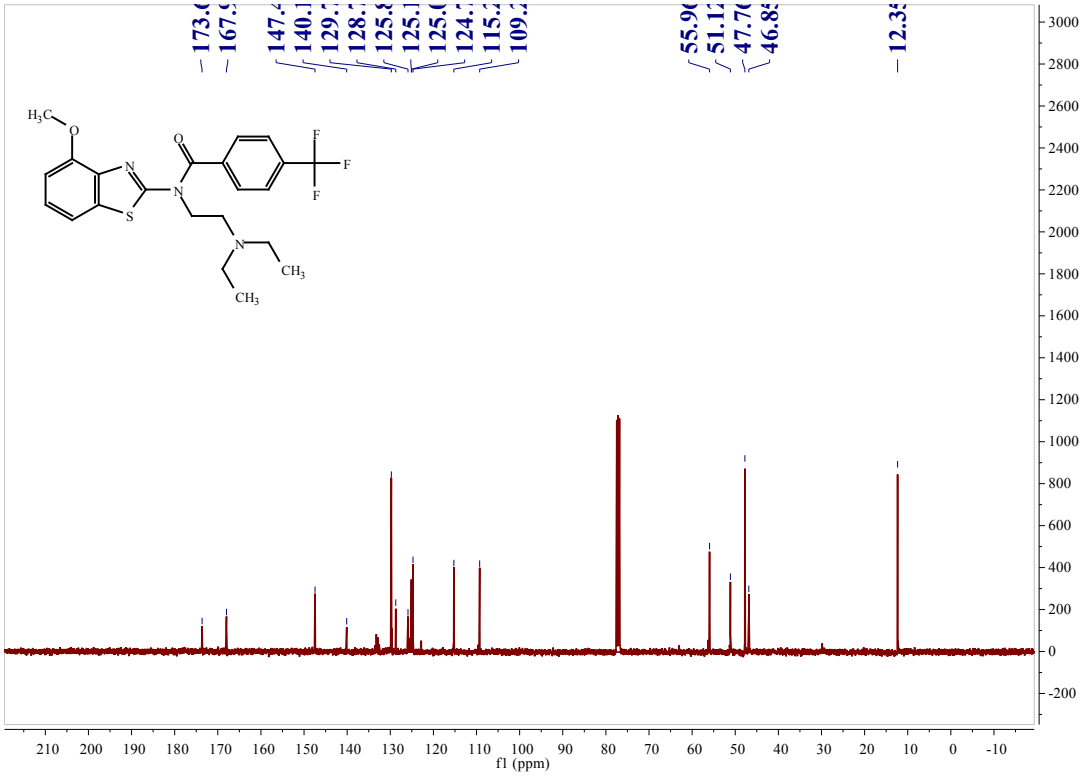
^{1}H and ^{13}C NMR of *N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifleoro-methyl) benzamide* ***(1l)***



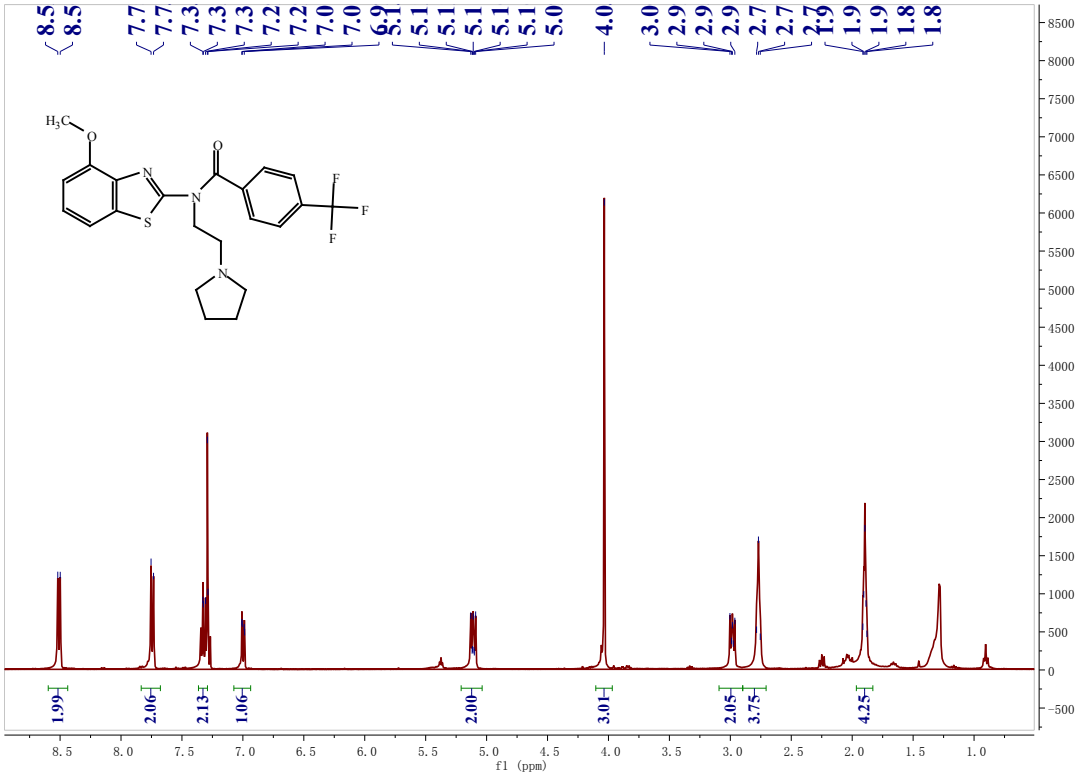


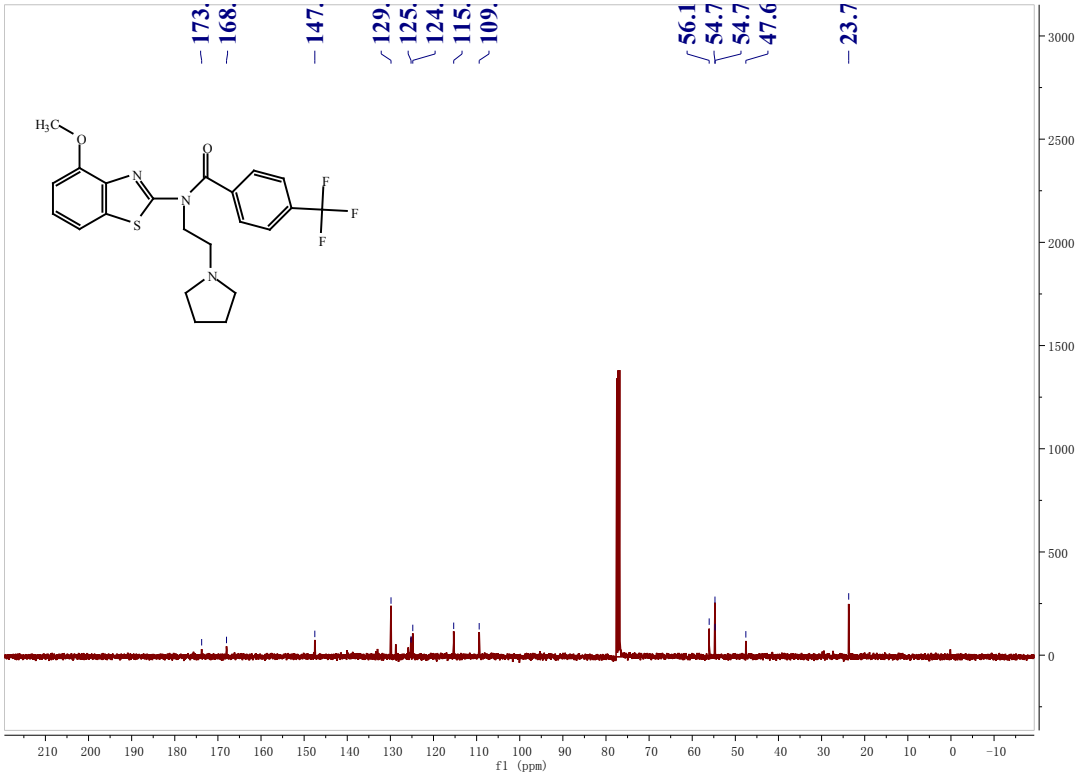
^{1}H and ^{13}C NMR of *N-(2-(diethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-4-(trifluoro-methyl) benzamide (**1m**)*



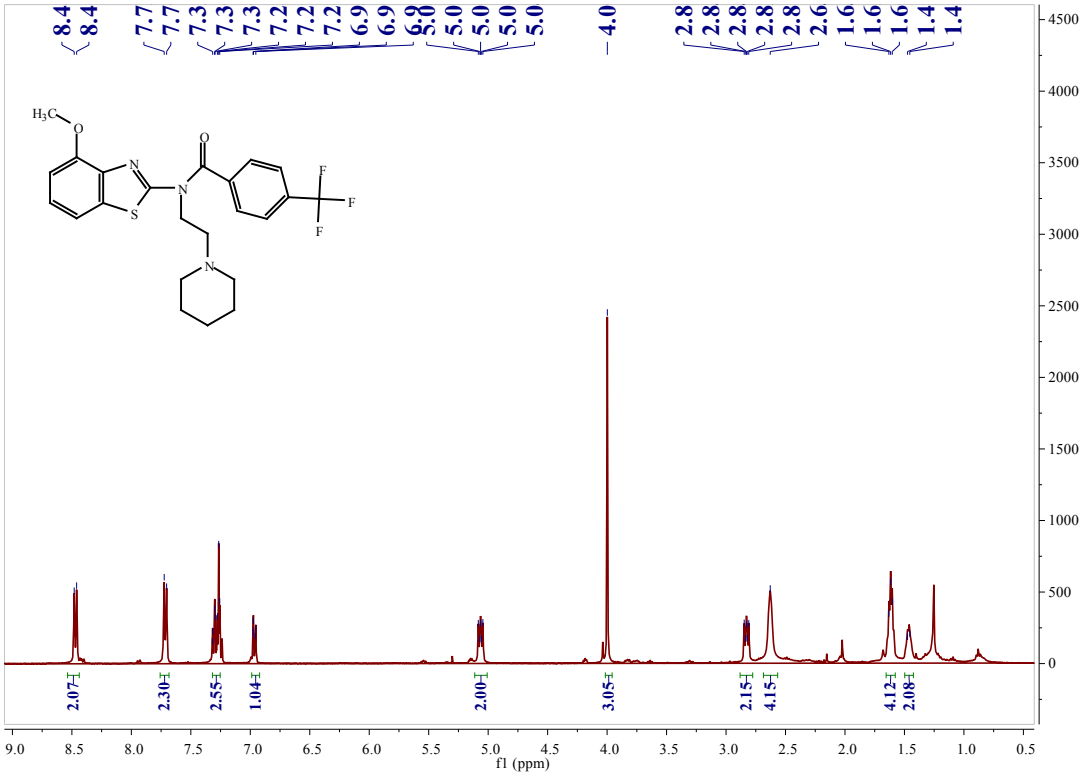


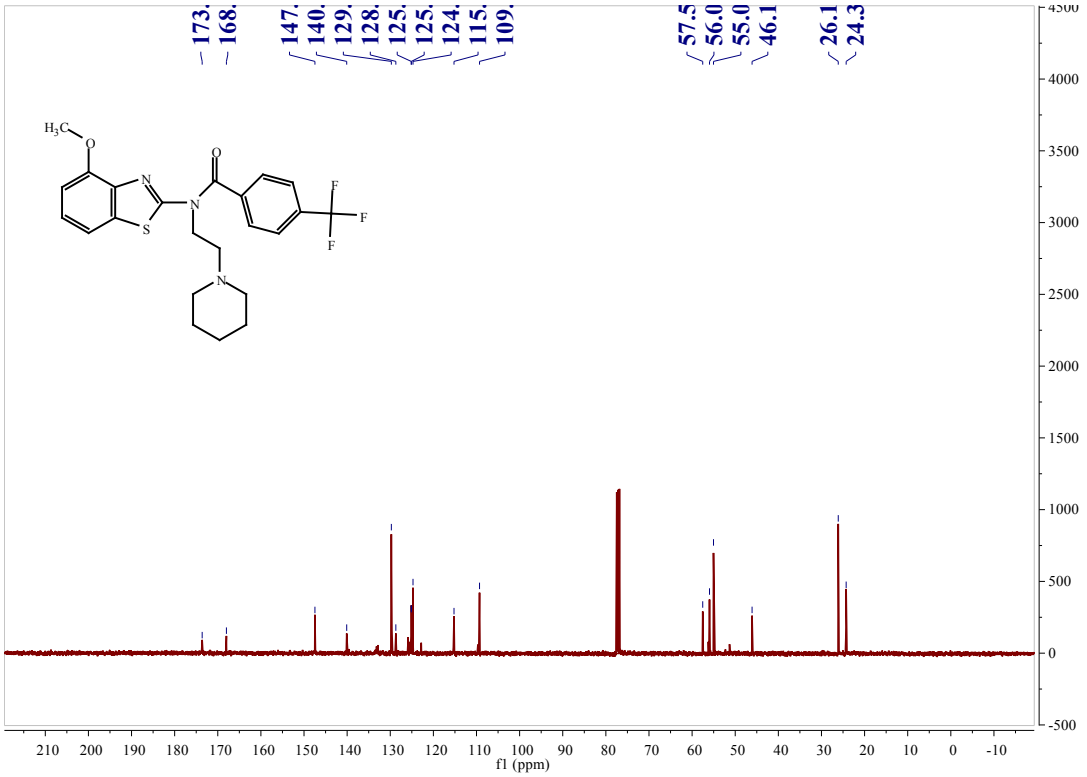
^{1}H and ^{13}C NMR of *N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-4-(trifluoro-methyl)benzamide* (***1n***)



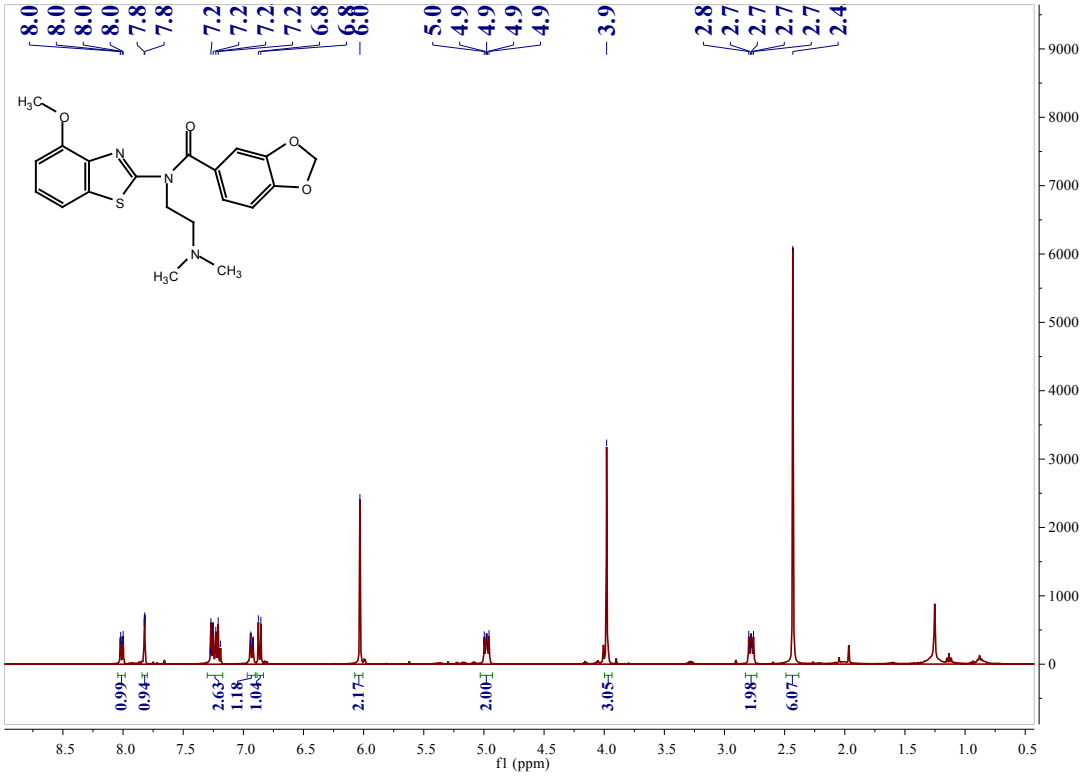


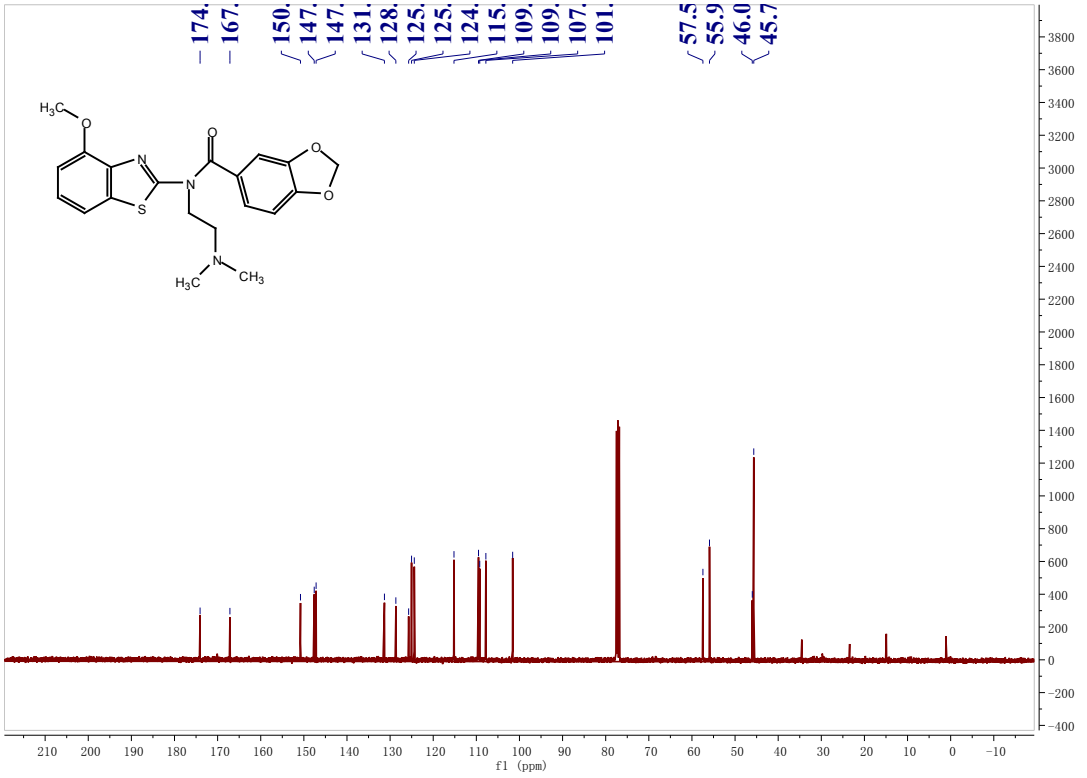
^{1}H and ^{13}C NMR of *N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)-4-(trifluoro-methyl) benzamide (**1o**)*



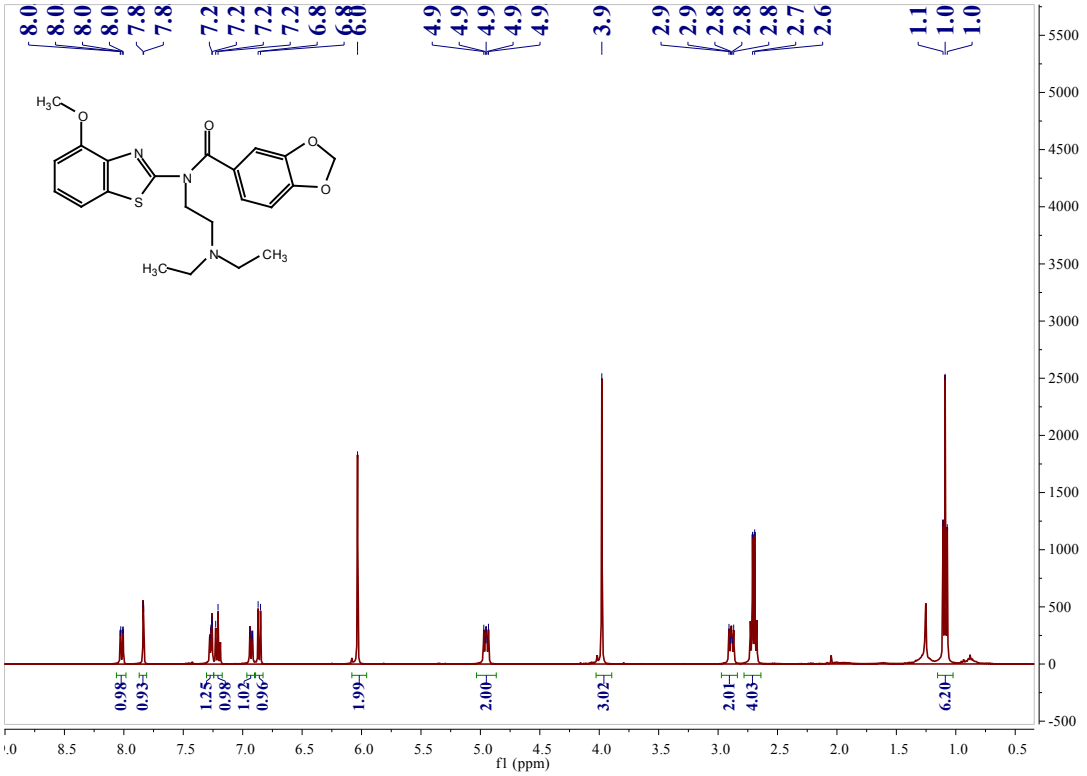


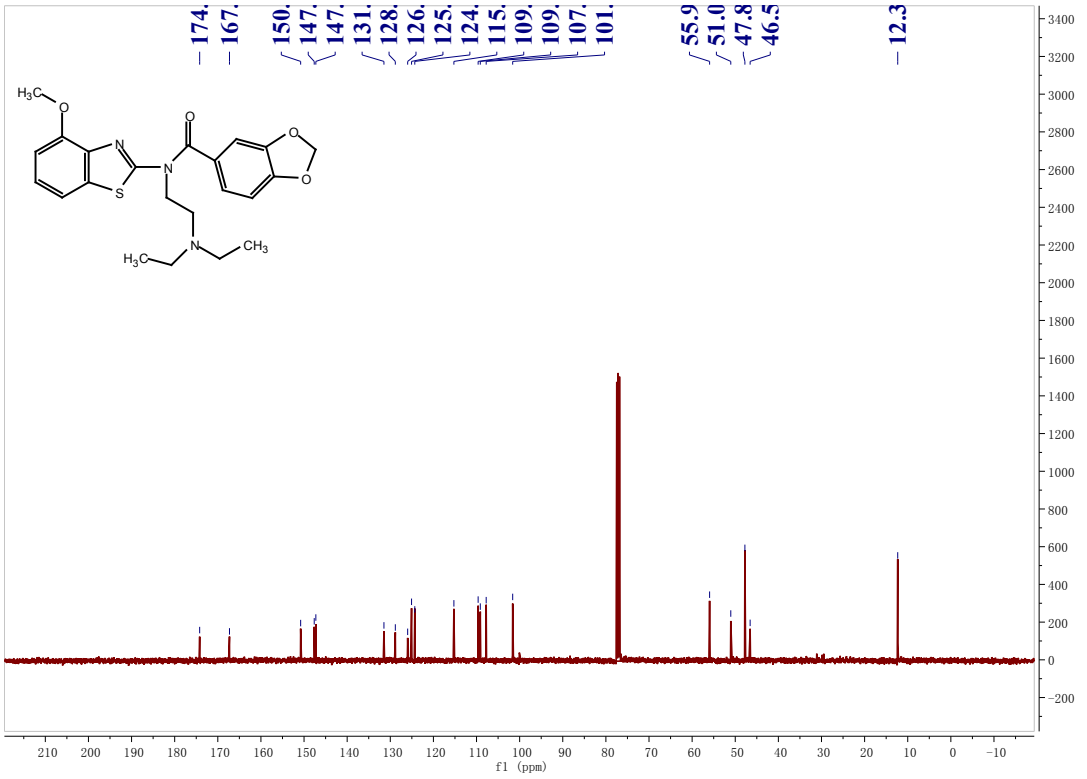
^{1}H and ^{13}C NMR of *N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) benzo[d][1,3] dioxole-5-carboxamide (**1p**)*



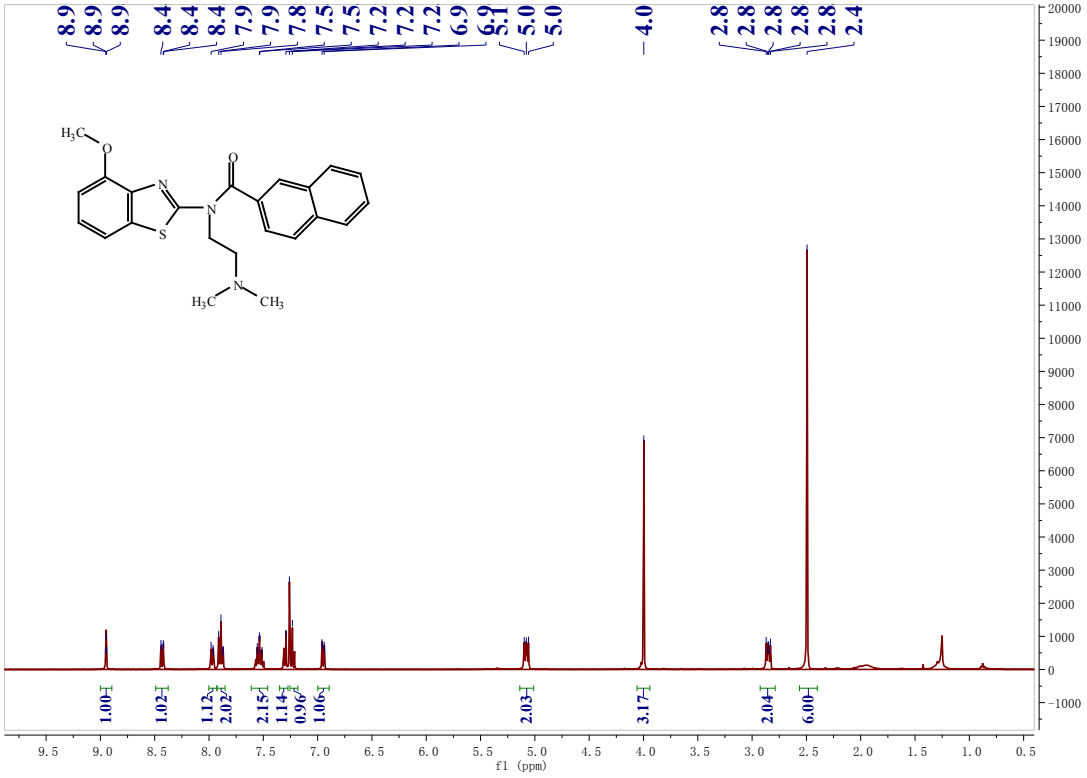


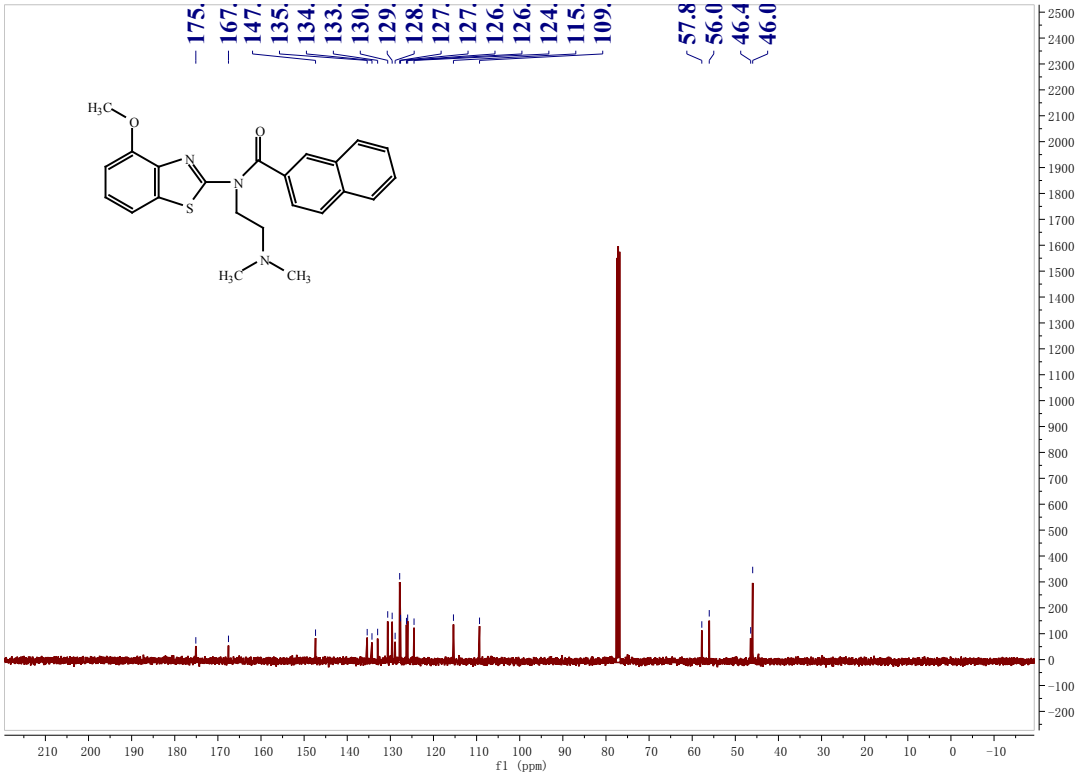
^{1}H and ^{13}C NMR of *N-(2-(diethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)benzo[d][1,3]-dioxole-5-carboxamide* (***1q***)



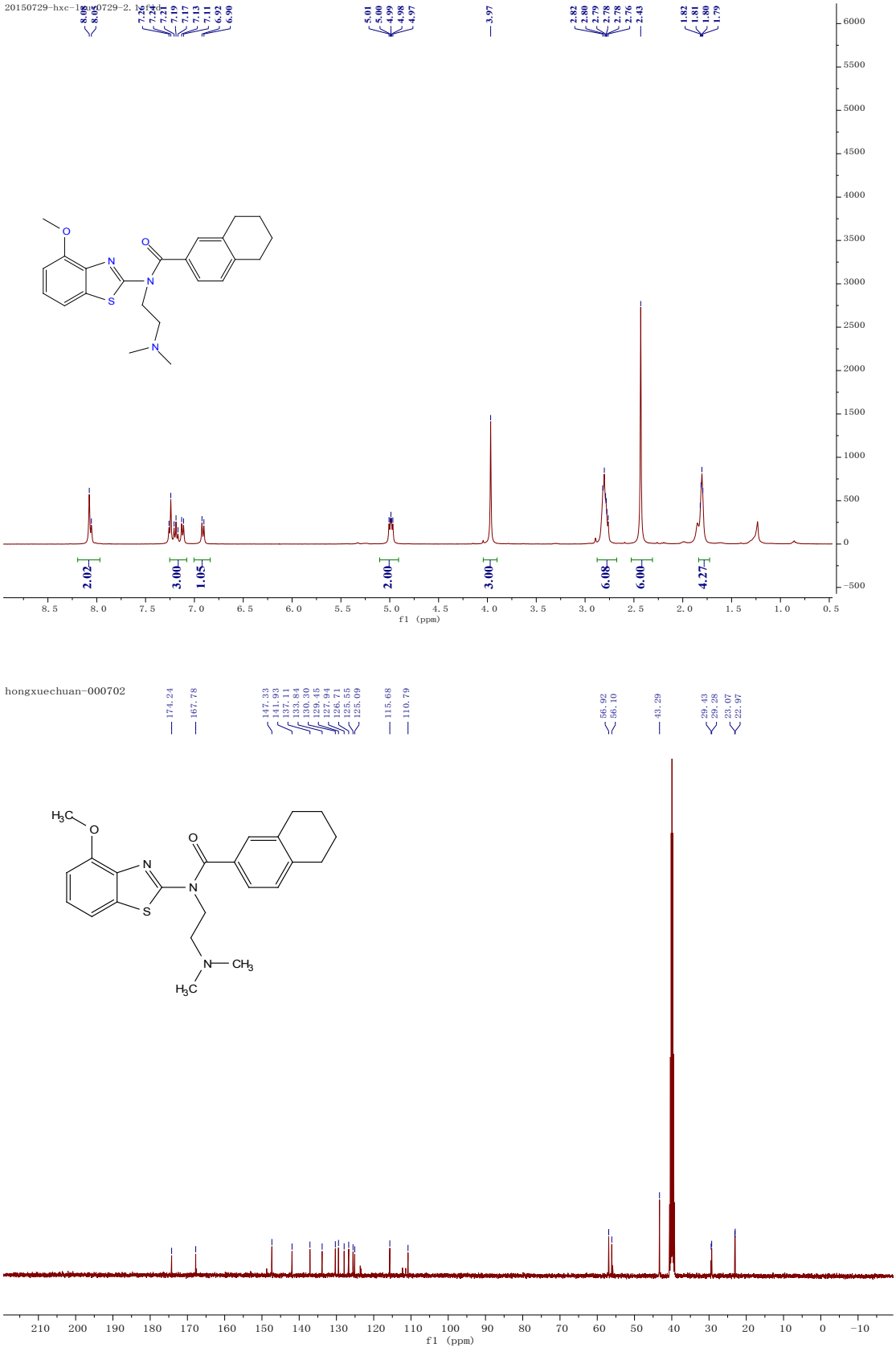


^{1}H and ^{13}C NMR of *N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide (**1r**)*



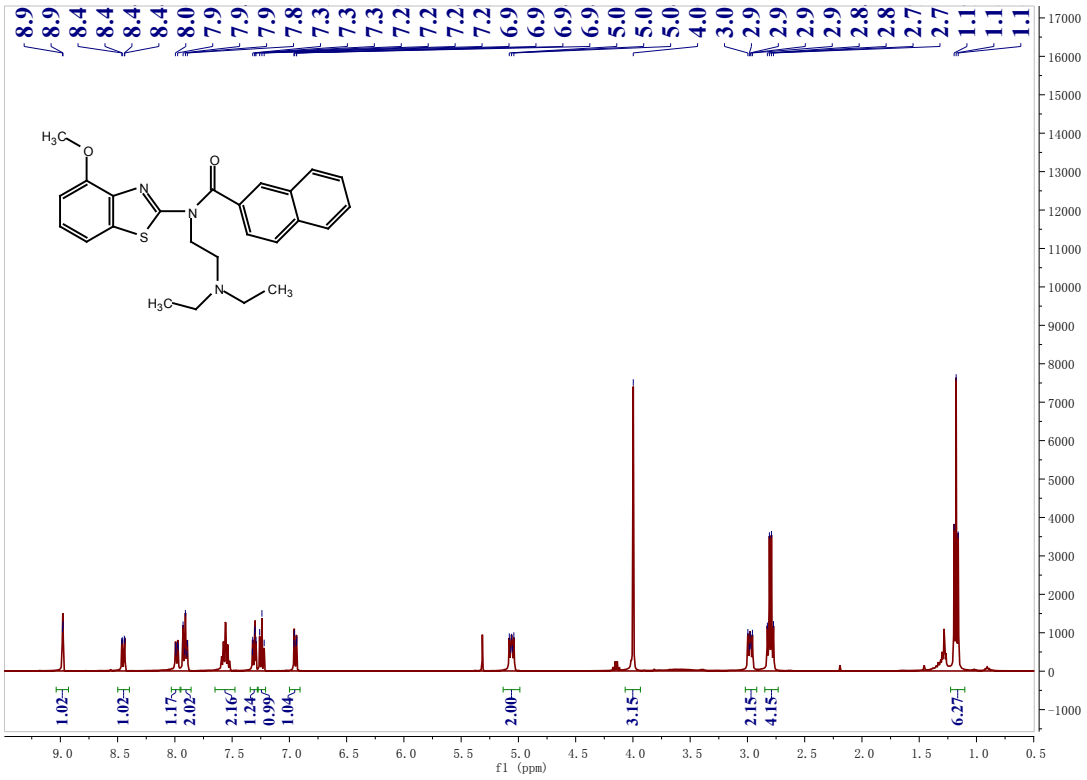


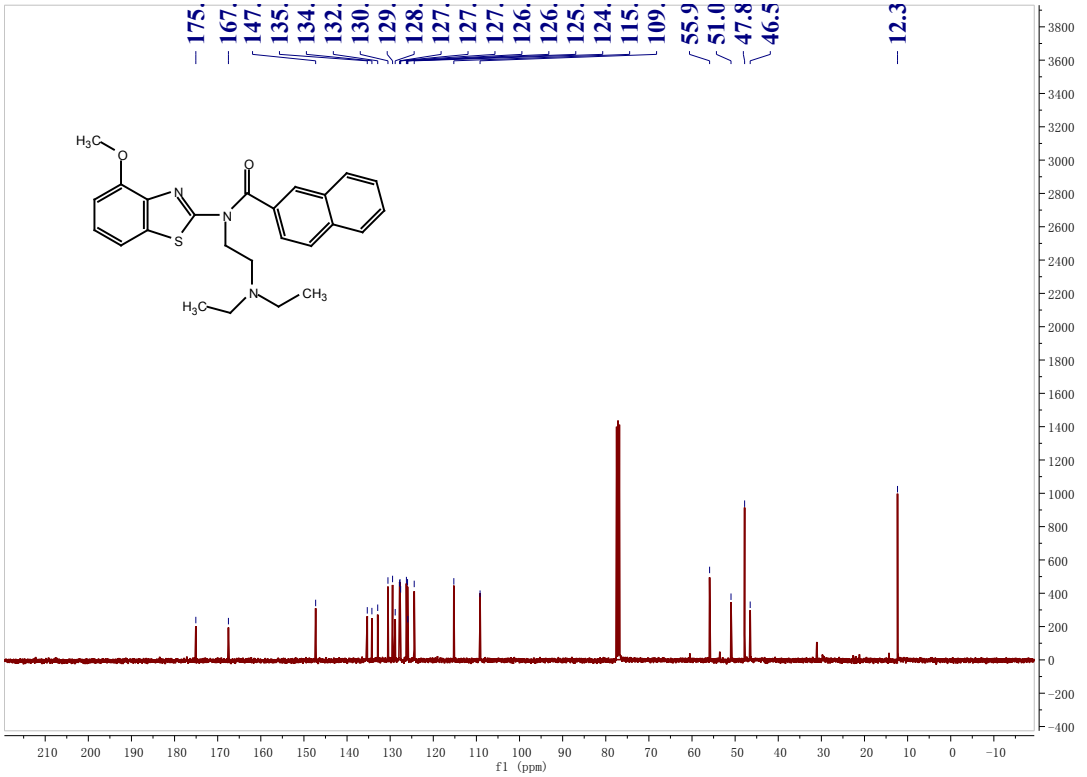
^{1}H and ^{13}C NMR of *N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (**1s**)*



^{1}H and ^{13}C NMR of *N-(2-(diethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)-2-naphthamide*

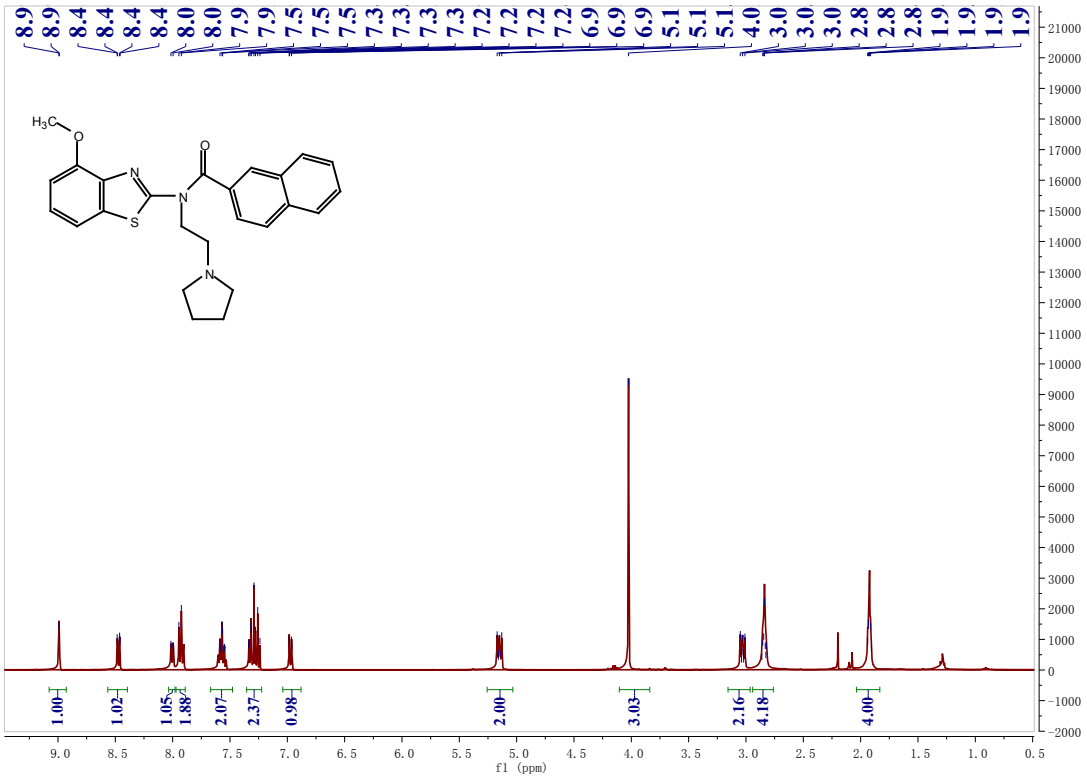
(1t)

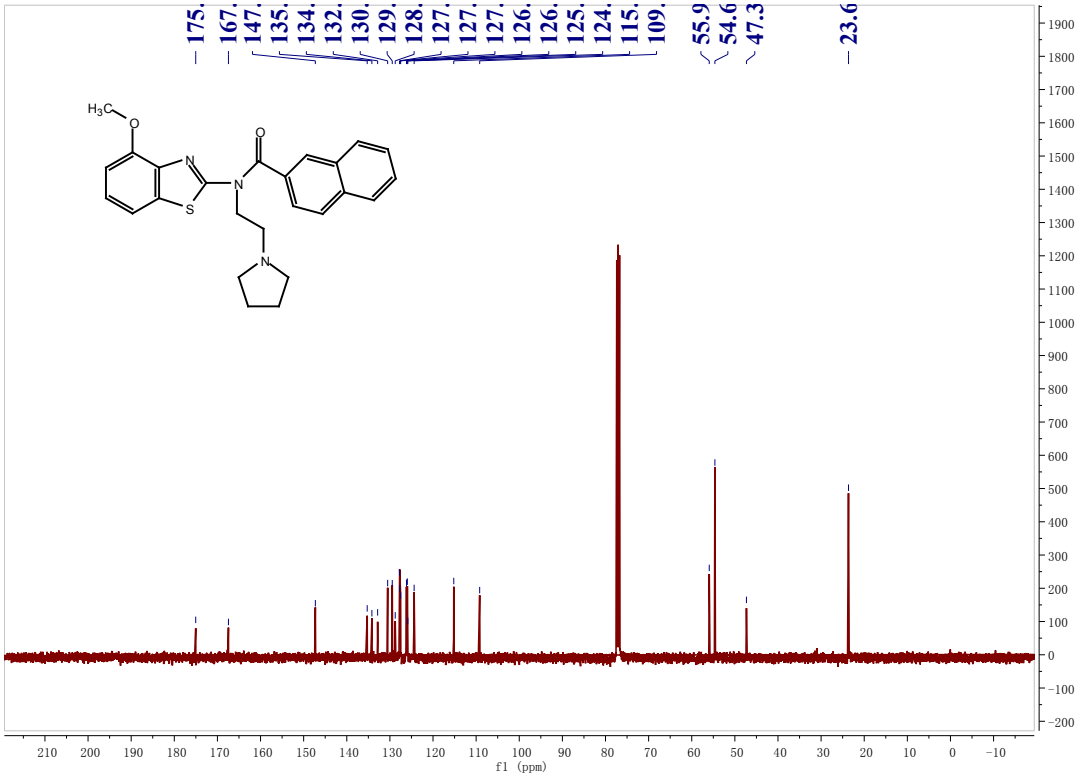




^{1}H and ^{13}C NMR of *N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-2-naphtha-*

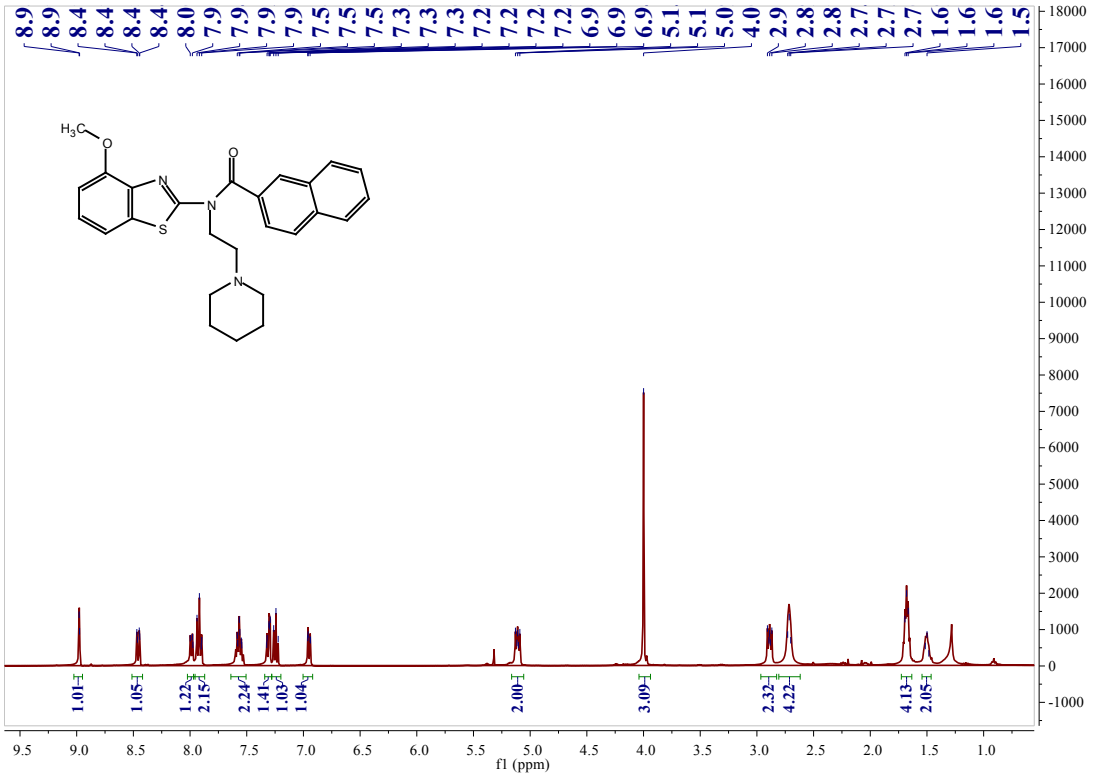
*mide (**1u**)*

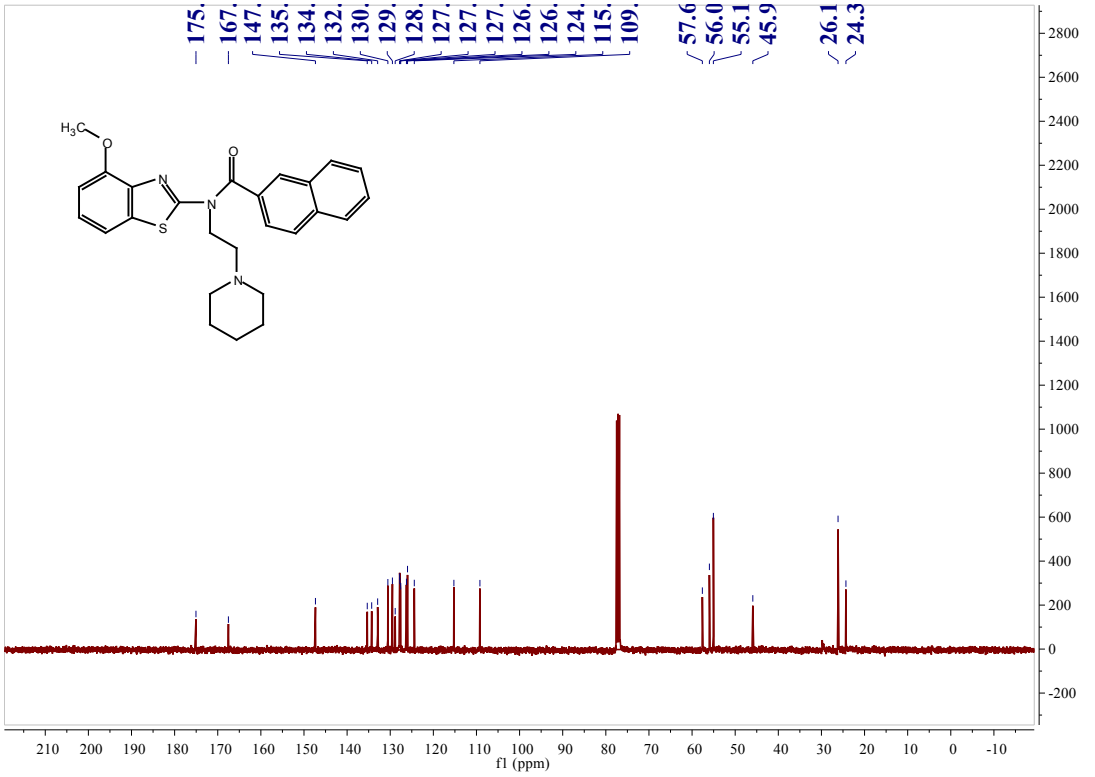




^{1}H and ^{13}C NMR of *N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(piperidin-1-yl)ethyl)-2-naphthamide*

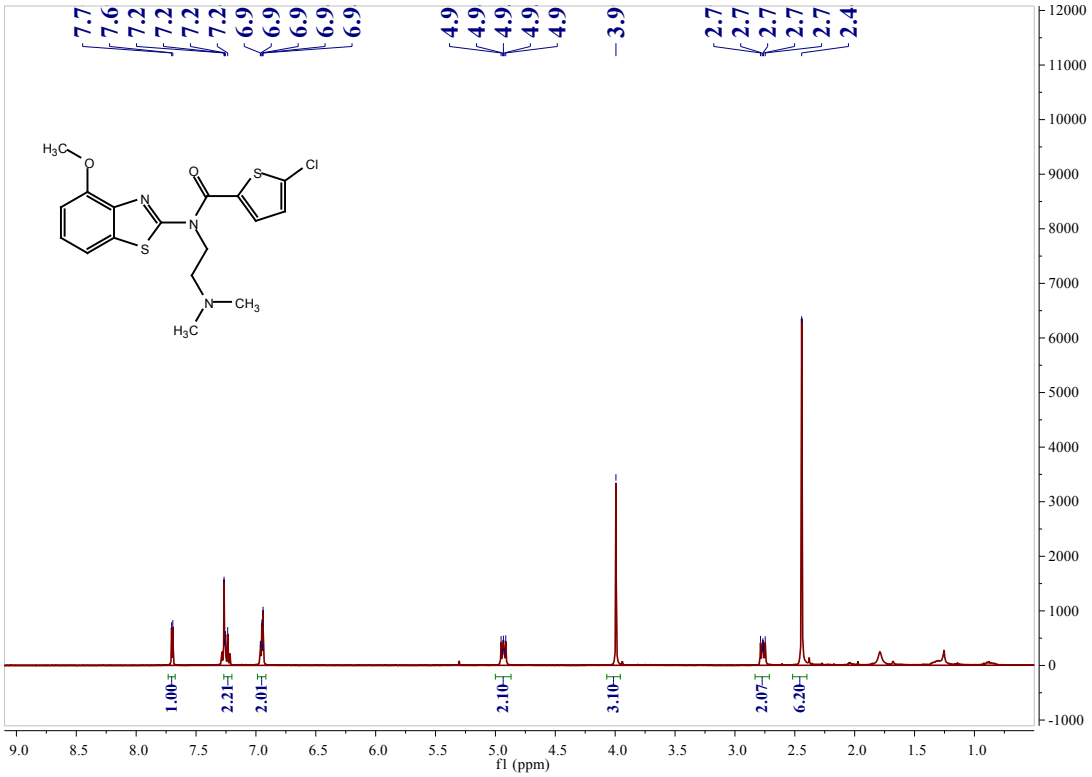
(1v)

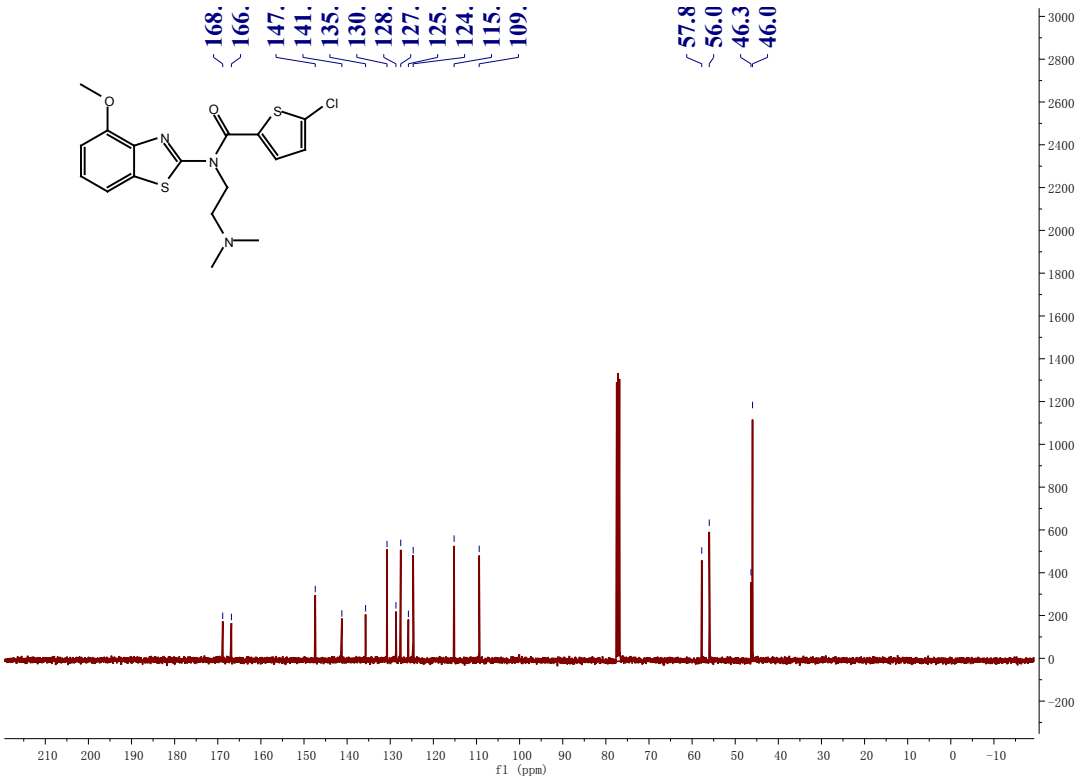




^{1}H and ^{13}C NMR of *5-chloro-N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2yl)thio-*

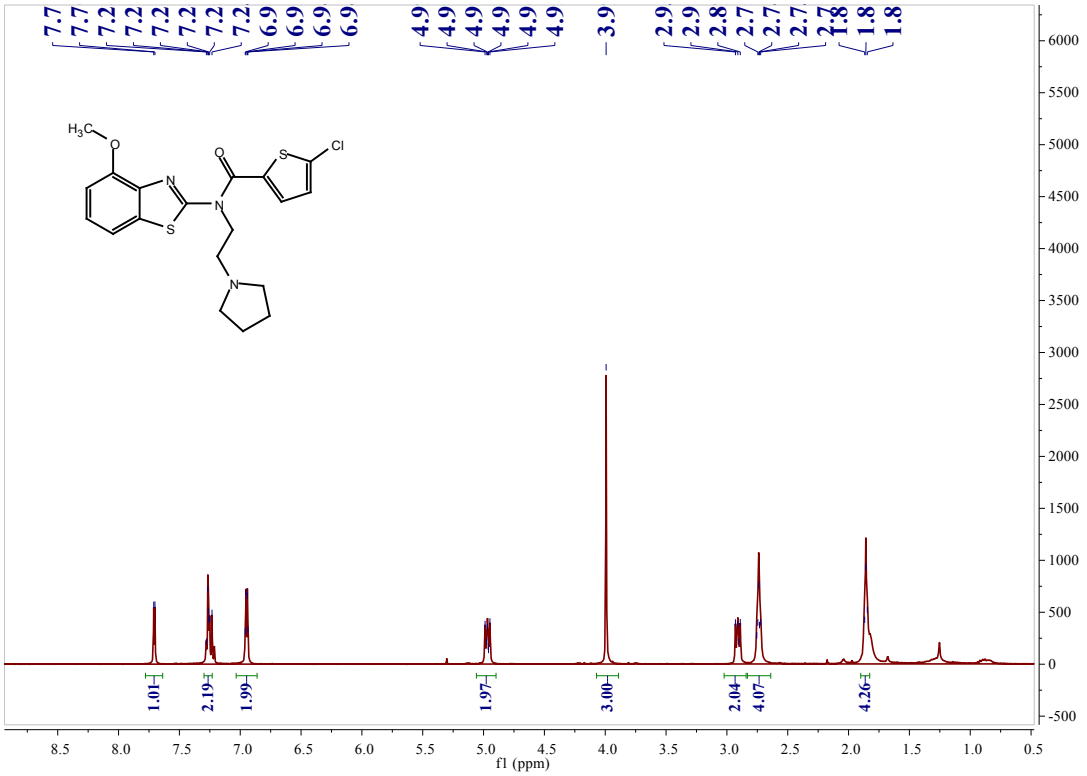
*phene-2-carboxamide (**1w**)*

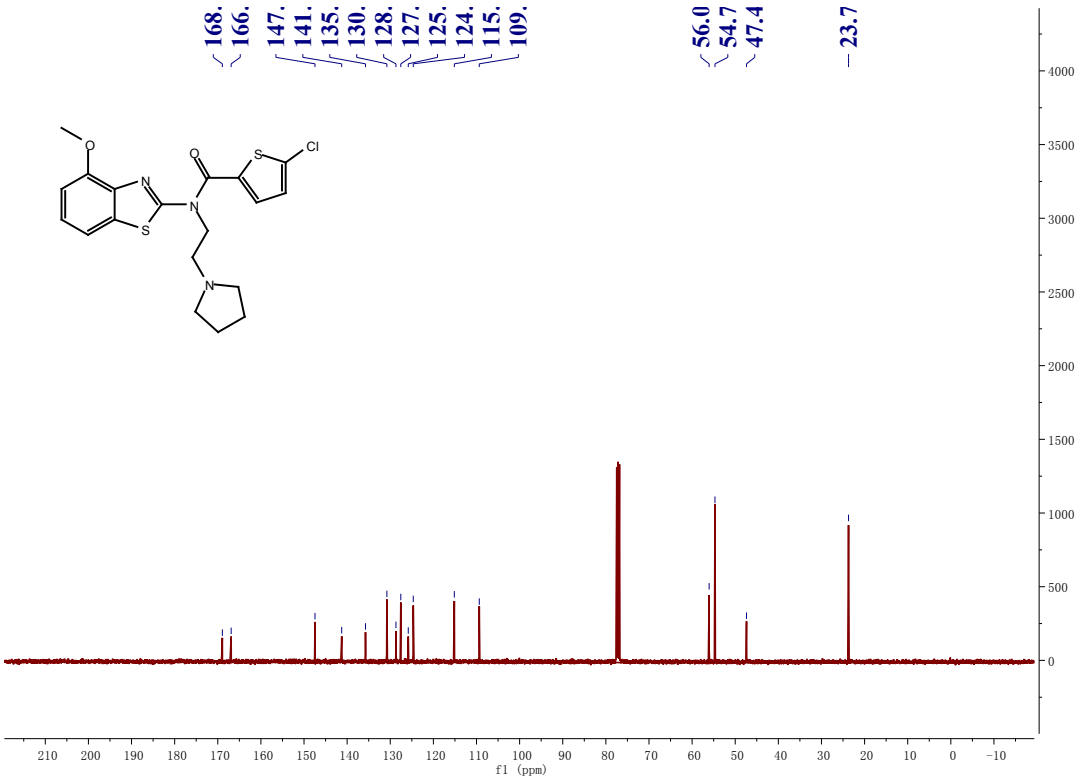




^{1}H and ^{13}C NMR of *5-chloro-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thio-*

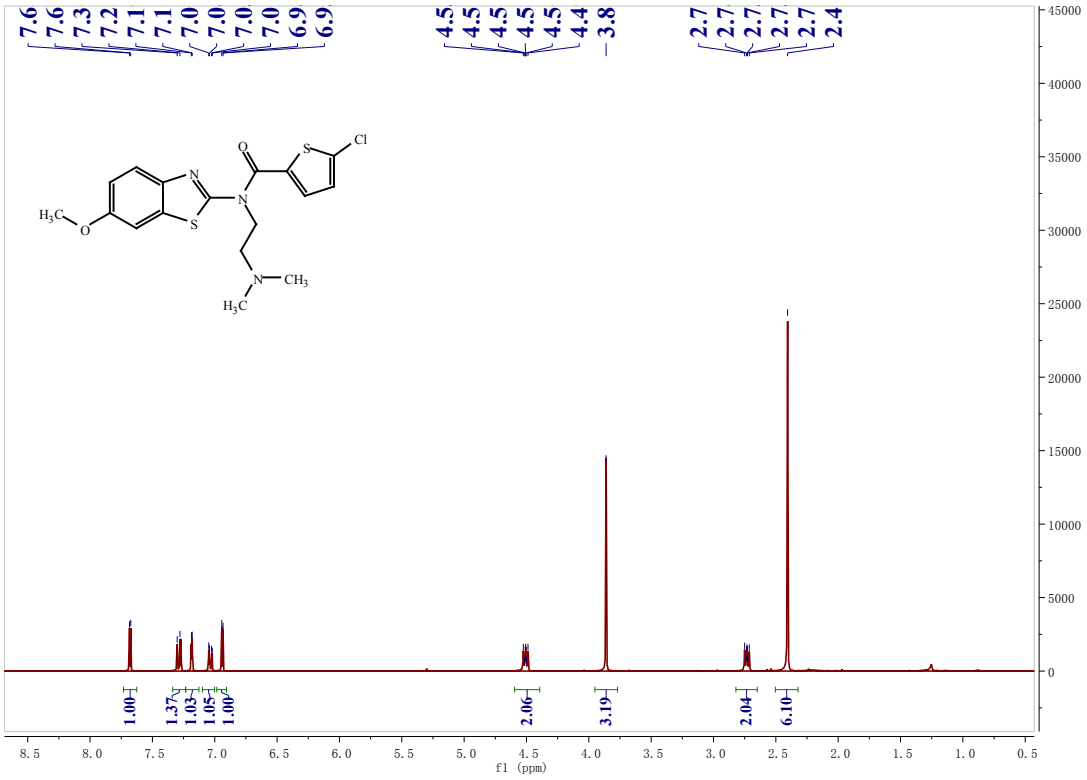
*phene-2-carboxamide (**1x**)*

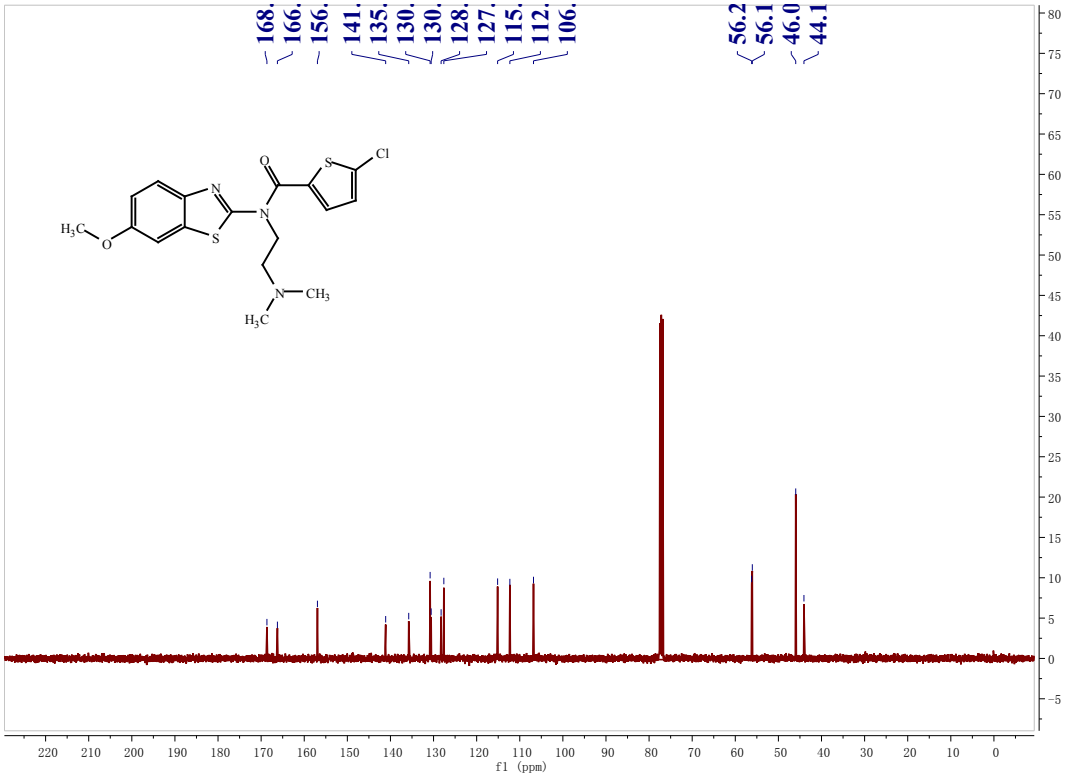




^{1}H and ^{13}C NMR of *5-chloro-N-(2-(dimethylamino)ethyl)-N-(6-methoxybenzo[d]thiazol-2-yl)thio-*

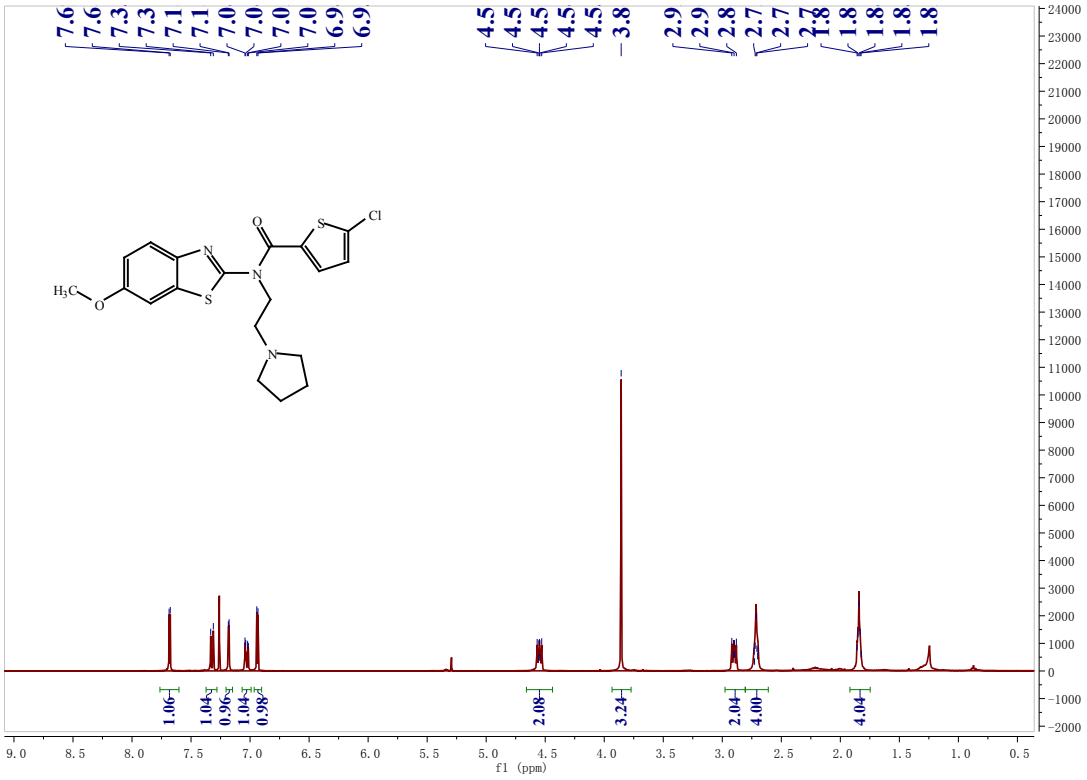
*phene-2-carboxamide (**1y**)*

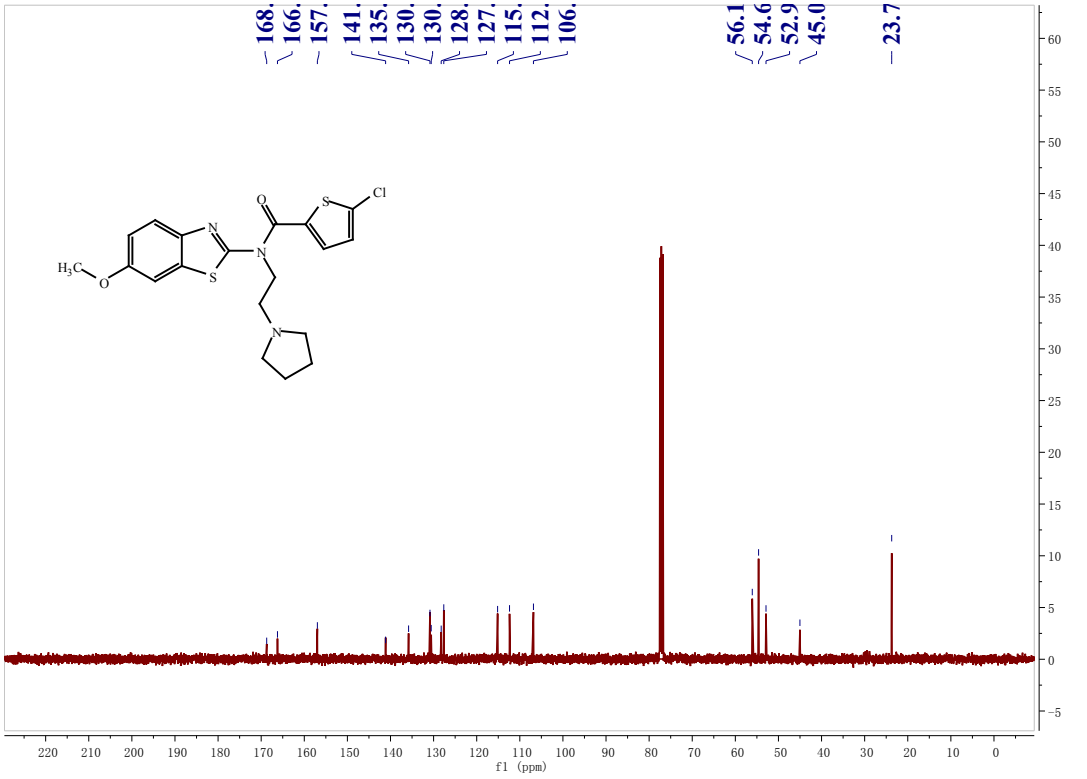




^{1}H and ^{13}C NMR of*5-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thiop-*

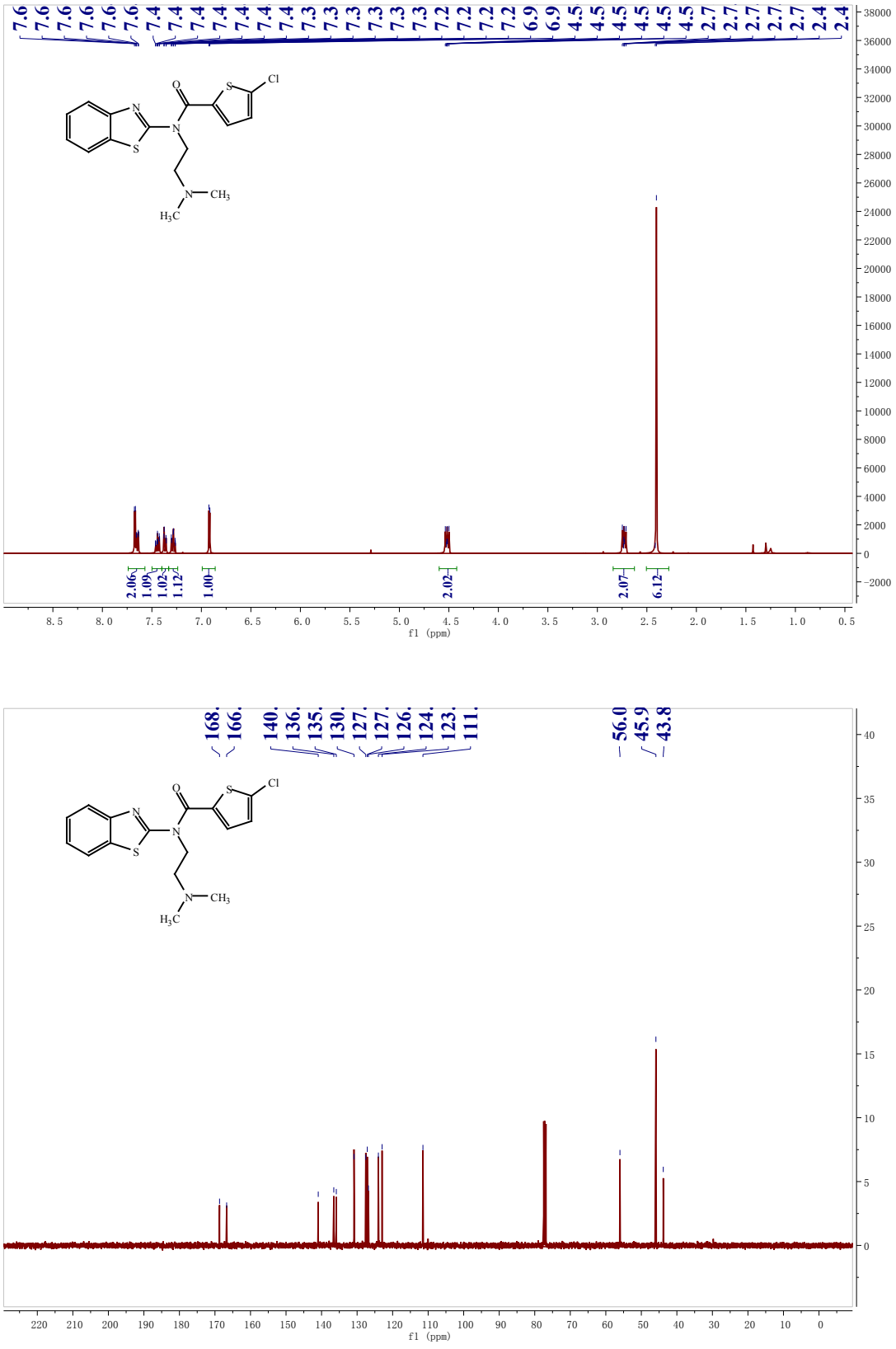
*hene-2-carboxamide (**1z**)*





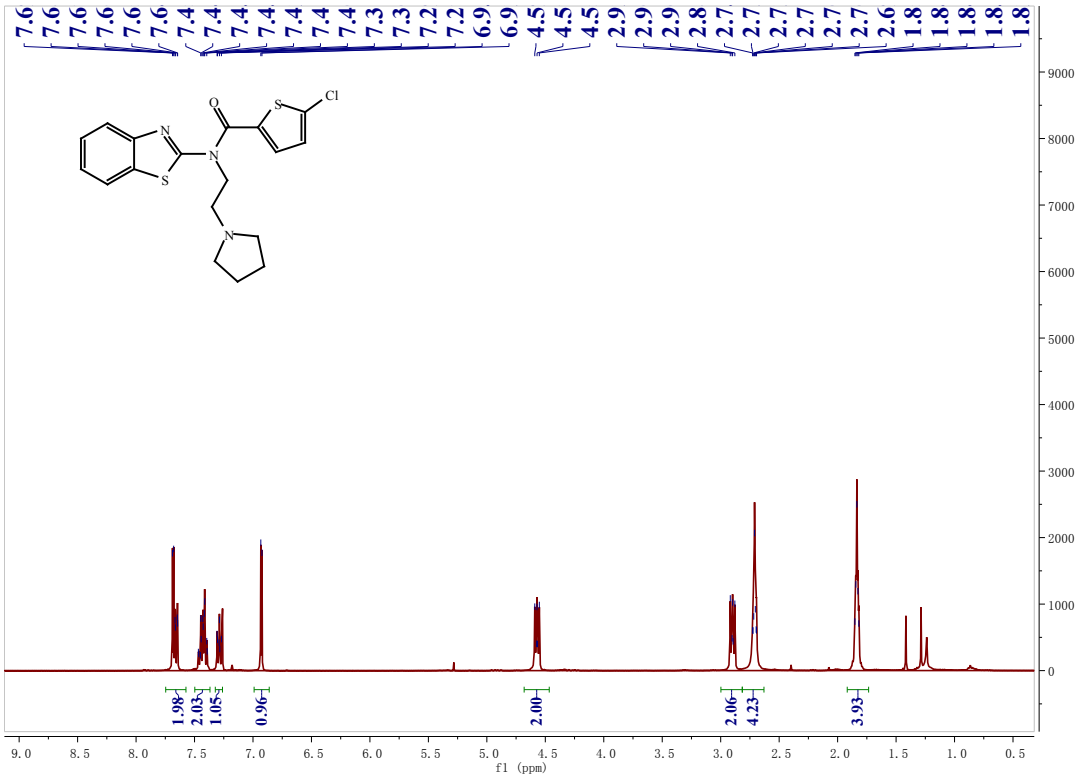
^{1}H and ^{13}C NMR of*N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-(dimethylamino)ethyl)thiophene-2-car-*

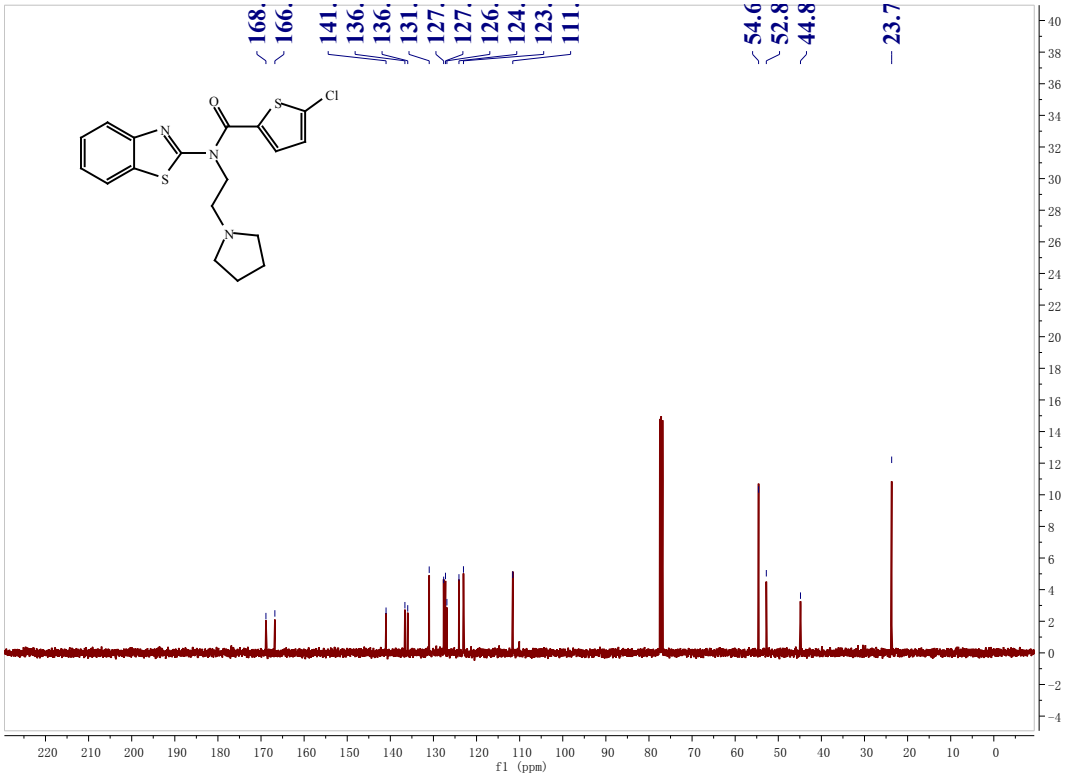
*boxamide (**1aa**)*



^{1}H and ^{13}C NMR of *N-(benzo[d]thiazol-2-yl)-5-chloro-N-(2-(pyrrolidin-1-yl)ethyl)thiophene-2-*

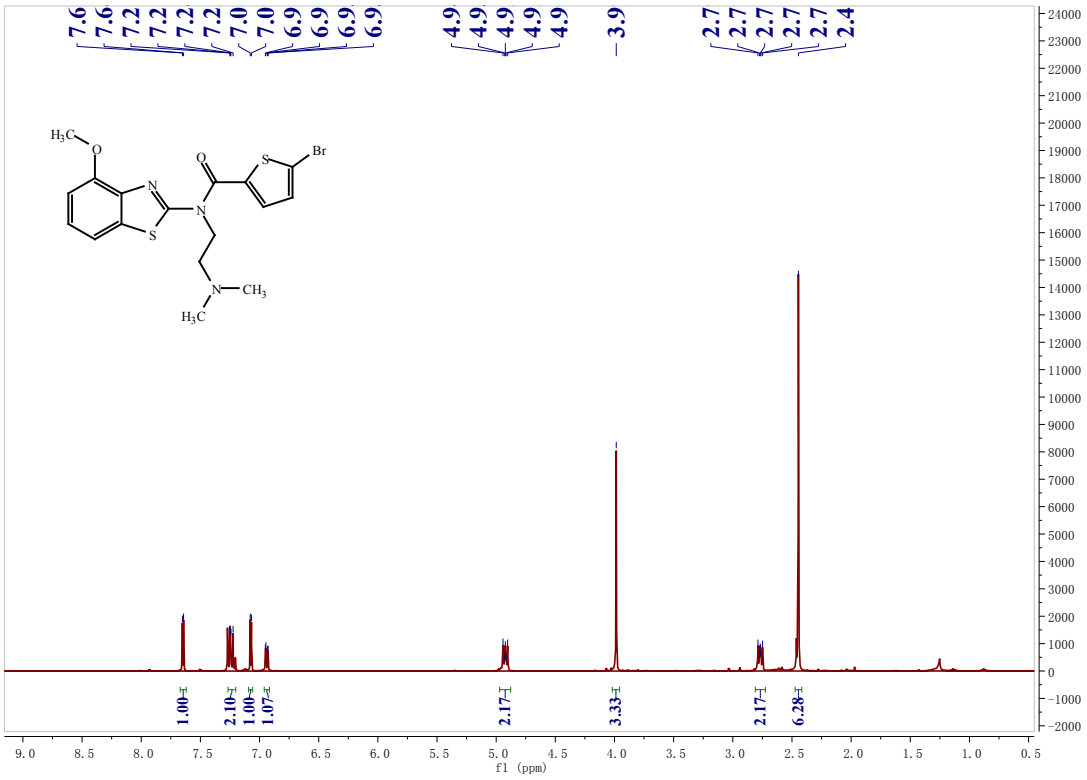
*carboxamide (**1ab**)*

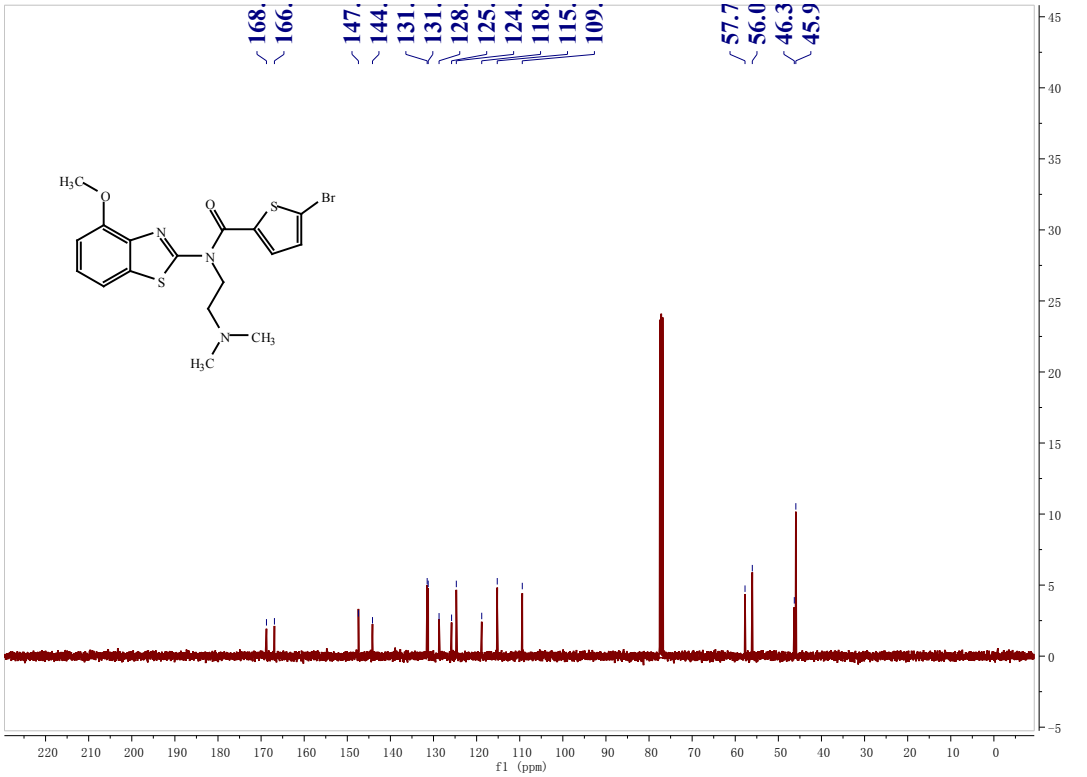




^{1}H and ^{13}C NMR of *5-bromo-N-(2-(dimethylamino) ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl) thio-*

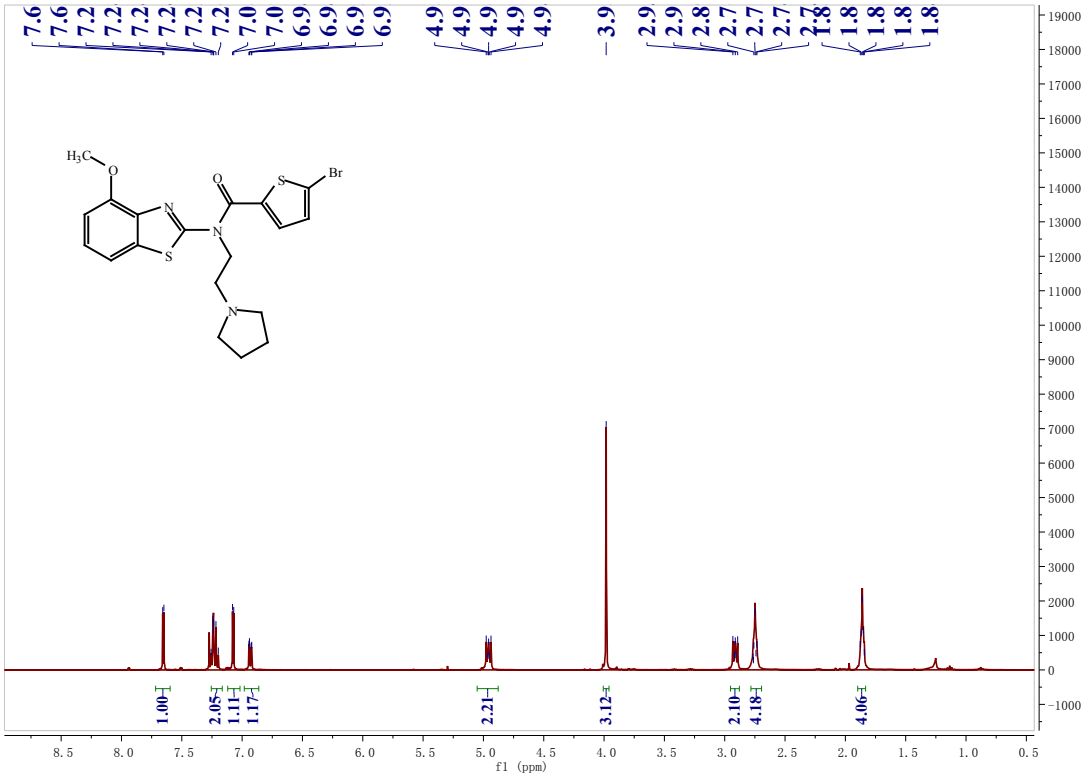
*phene-2-carboxamide (**1ac**)*

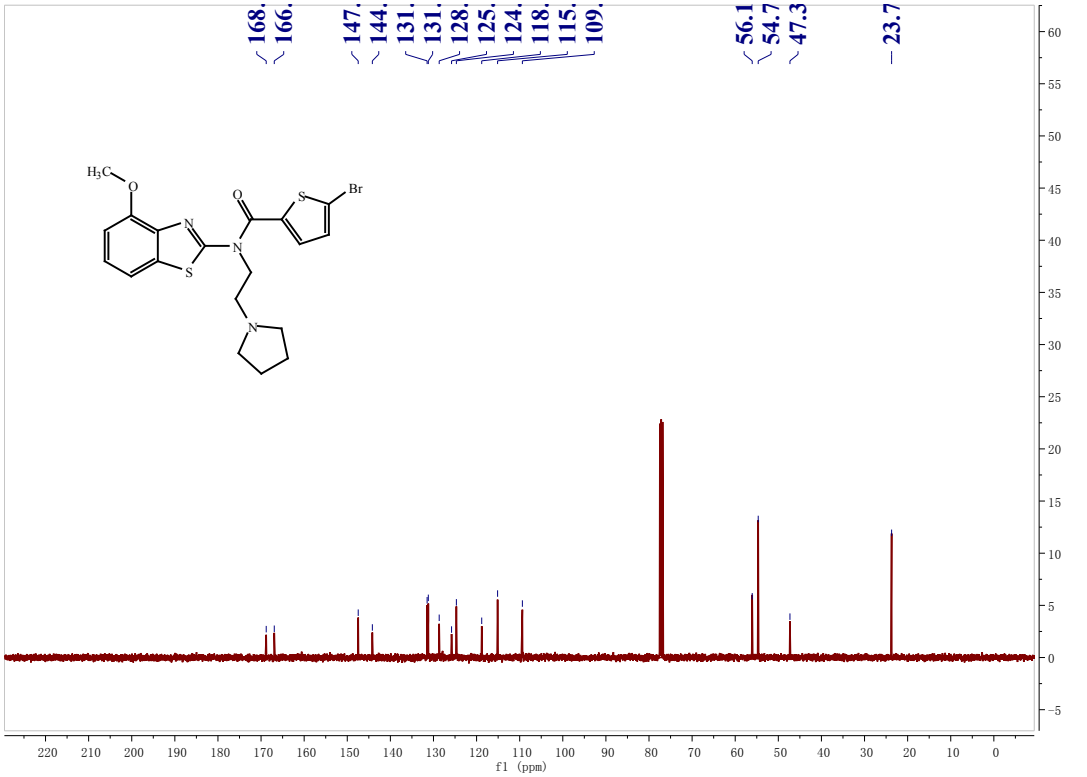




^{1}H and ^{13}C NMR of *5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-yl)ethyl)thio-*

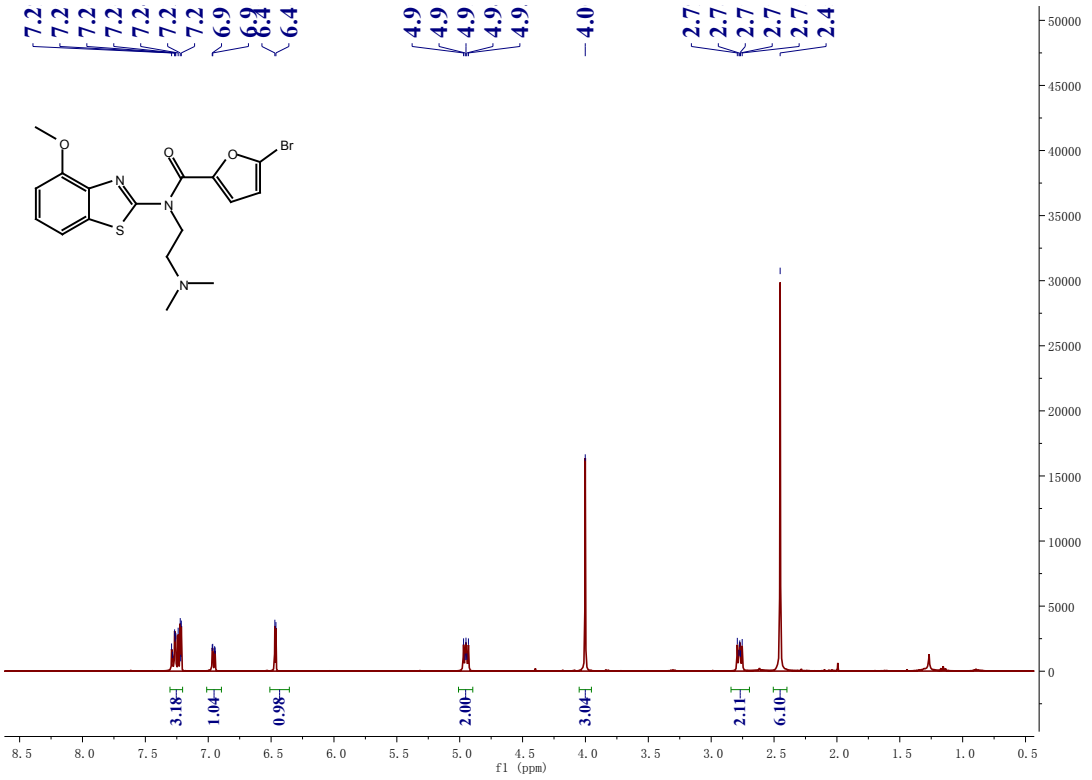
*phene-2-carboxamide (**1ad**)*

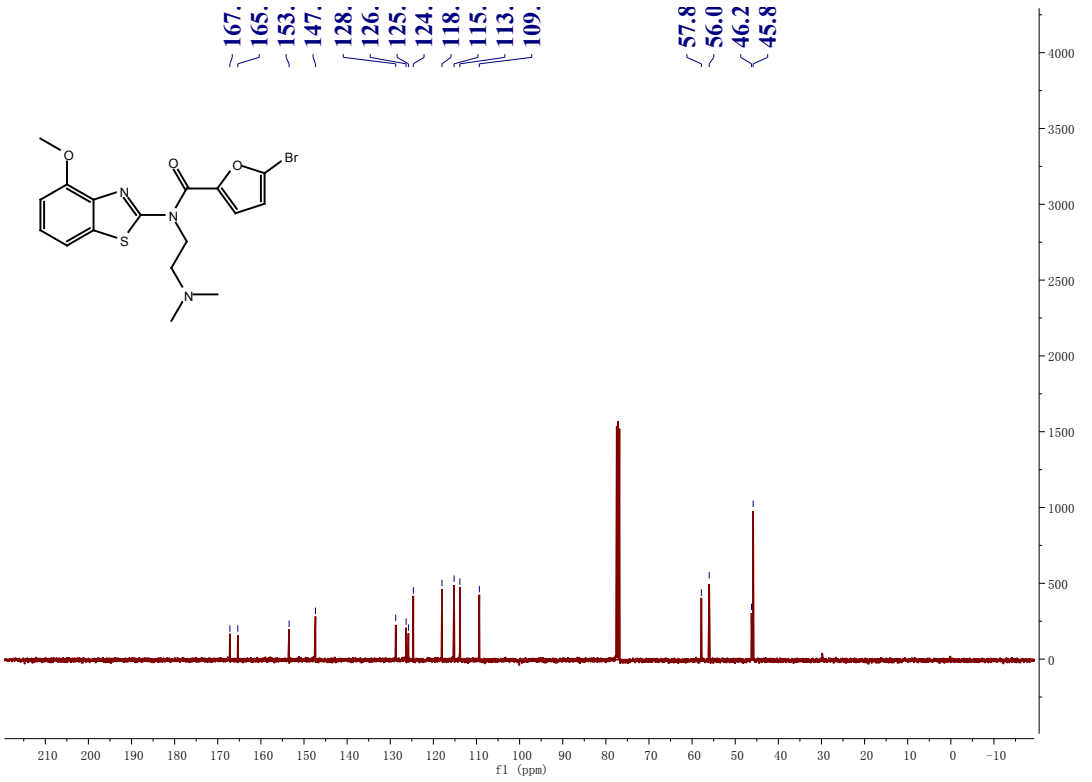




^{1}H and ^{13}C NMR of *5-bromo-N-(2-(dimethylamino)ethyl)-N-(4-methoxybenzo[d]thiazol-2-yl)fur-*

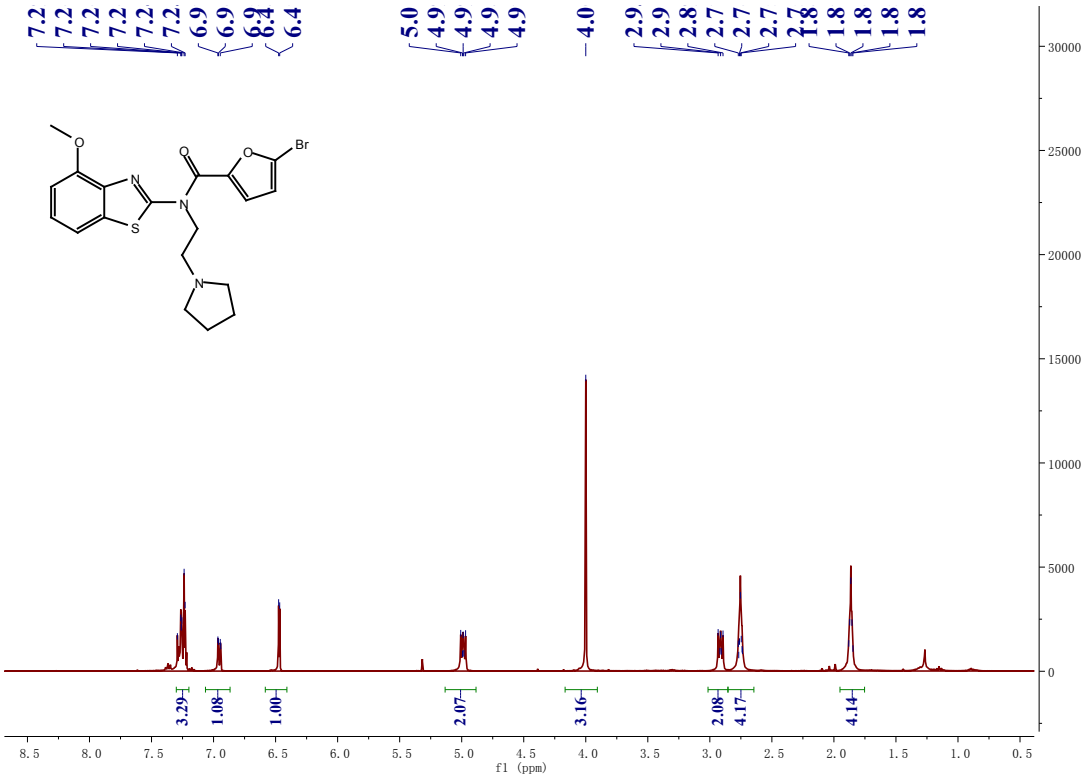
*an-2-carboxamide (**1ae**)*

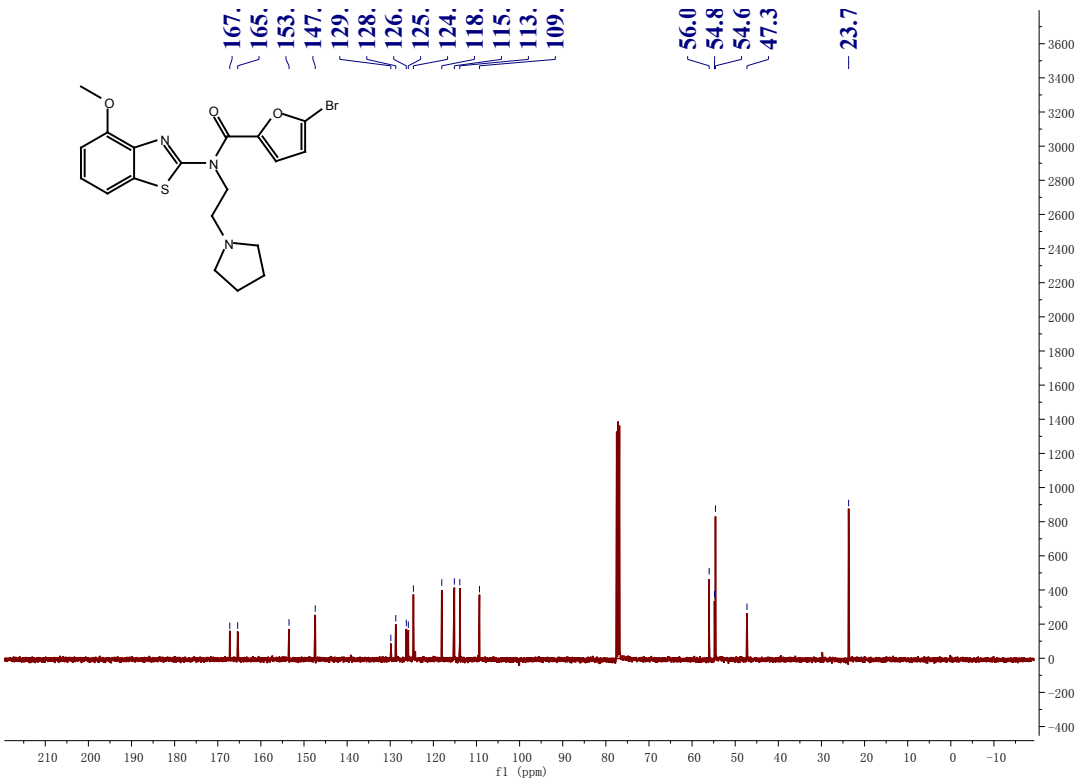




^{1}H and ^{13}C NMR of *5-bromo-N-(4-methoxybenzo[d]thiazol-2-yl)-N-(2-(pyrrolidin-1-*

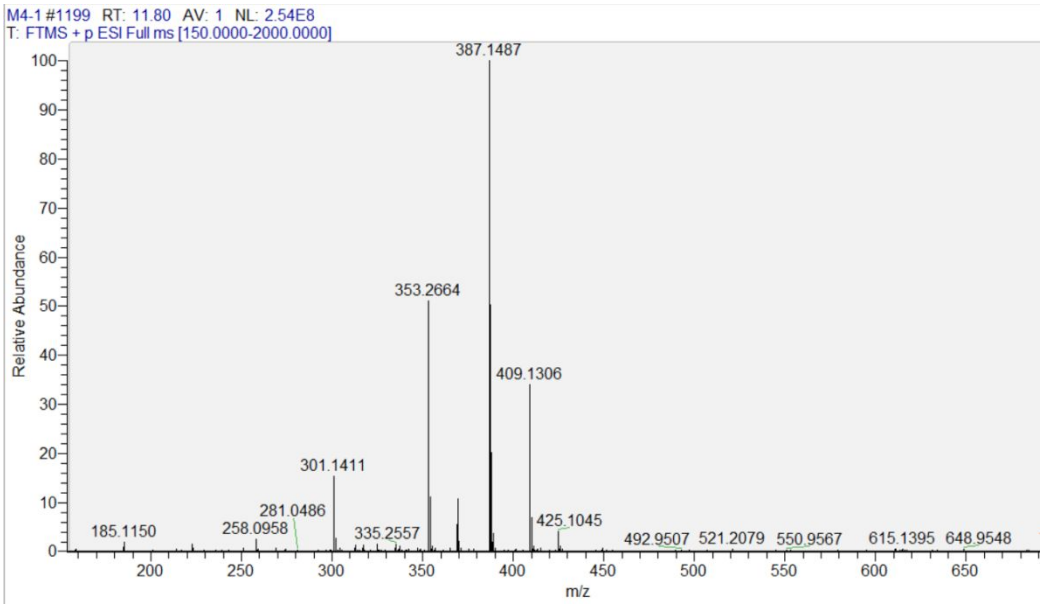
*yl)ethyl)furan-2-carboxamide (**1af**)*



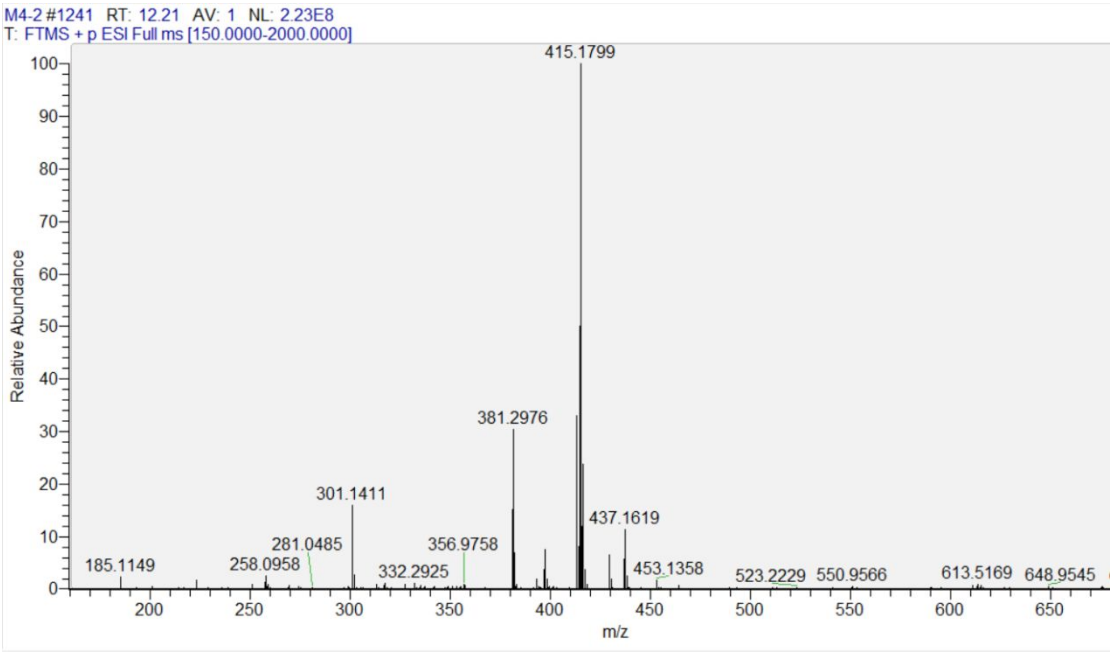


4 HRMS of **1d-1af**

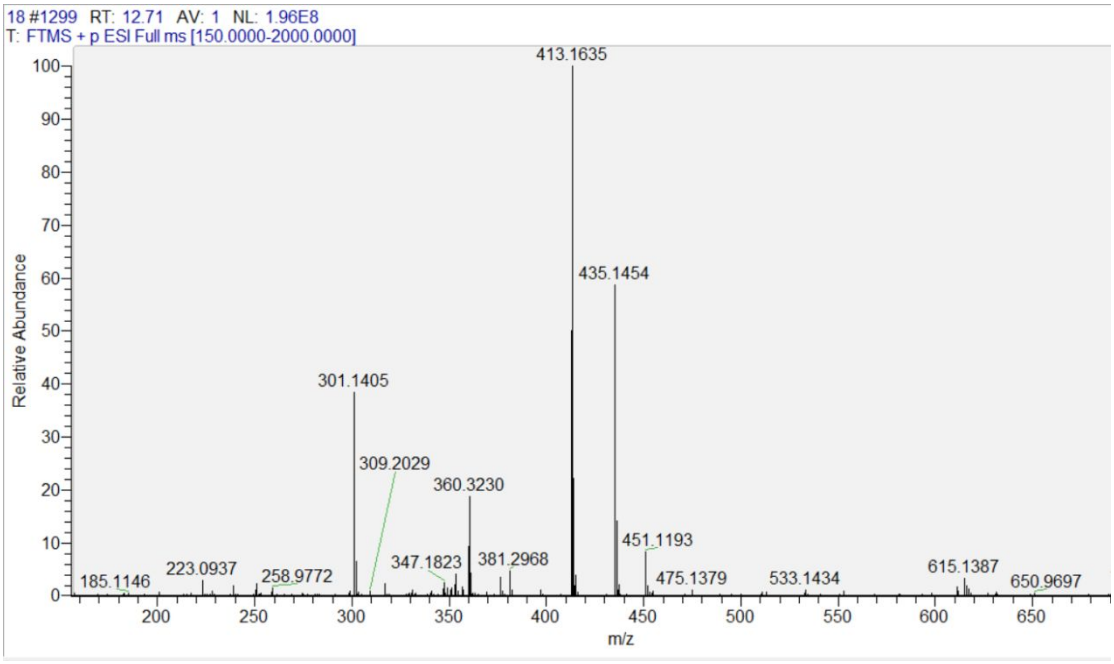
1d (387.1485)



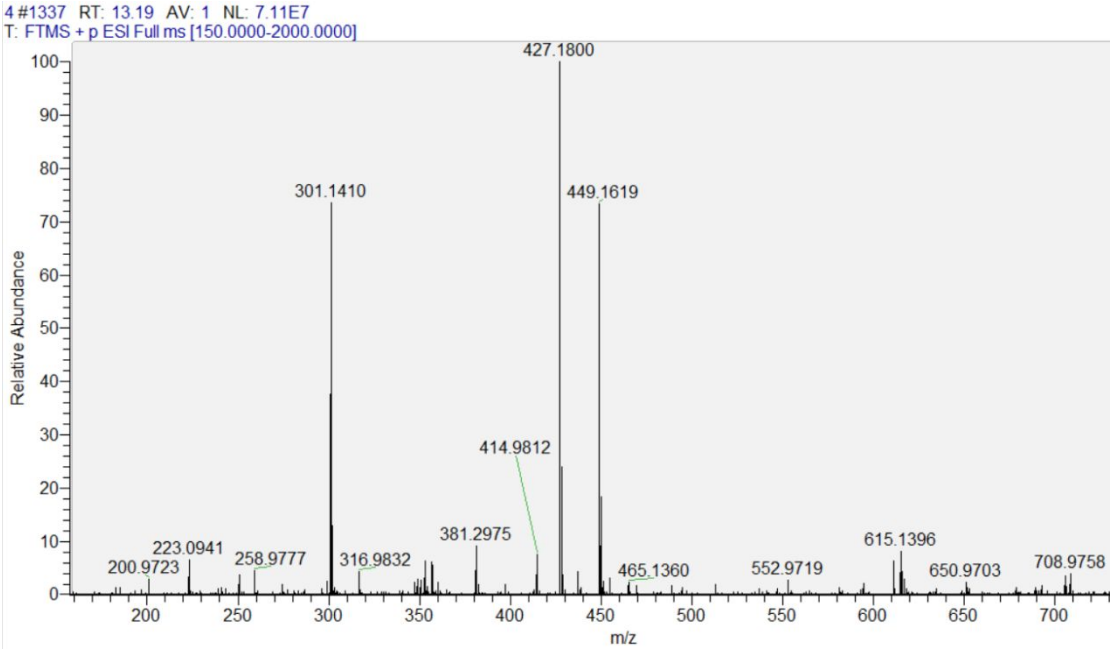
1e (415.1798)



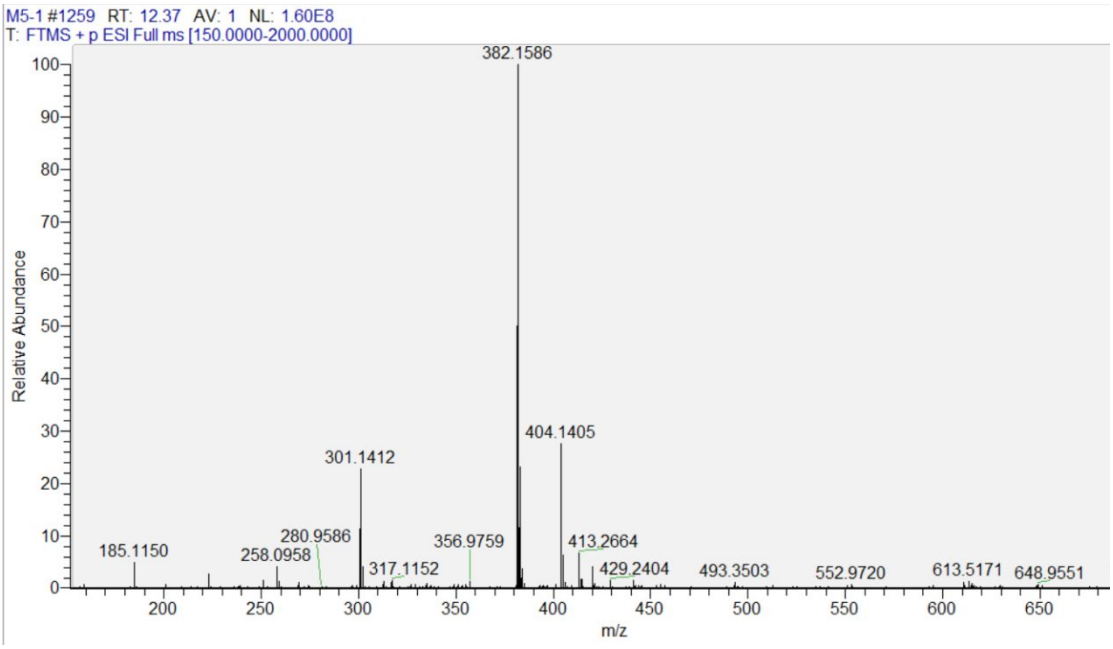
1f (413.1642)



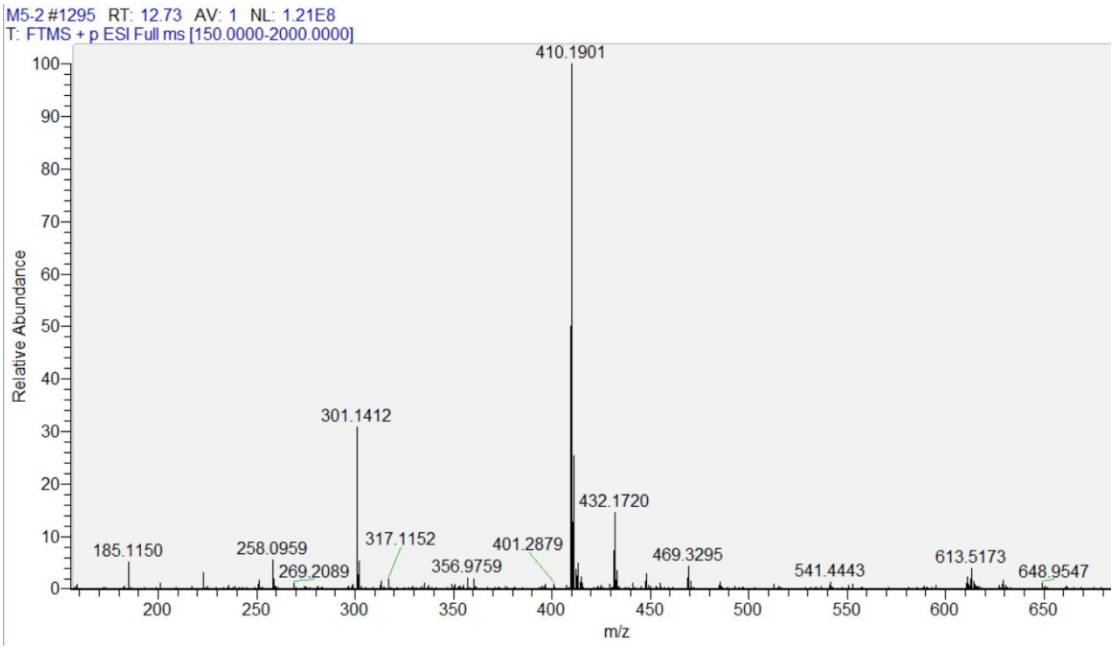
1g (427.1798)



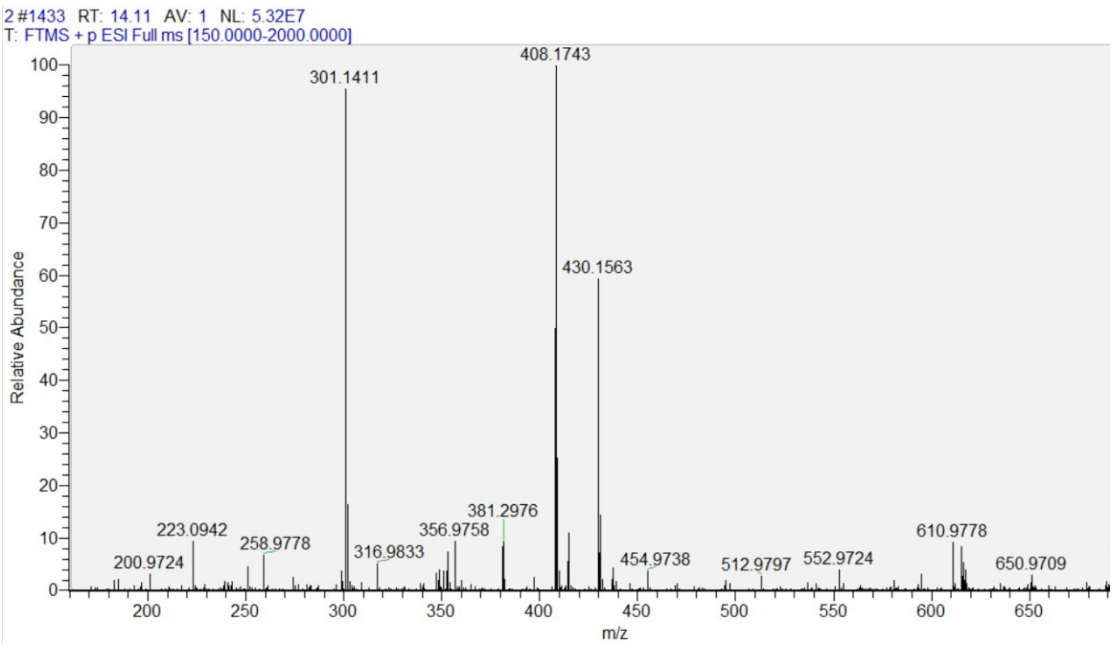
1h (382.1584)



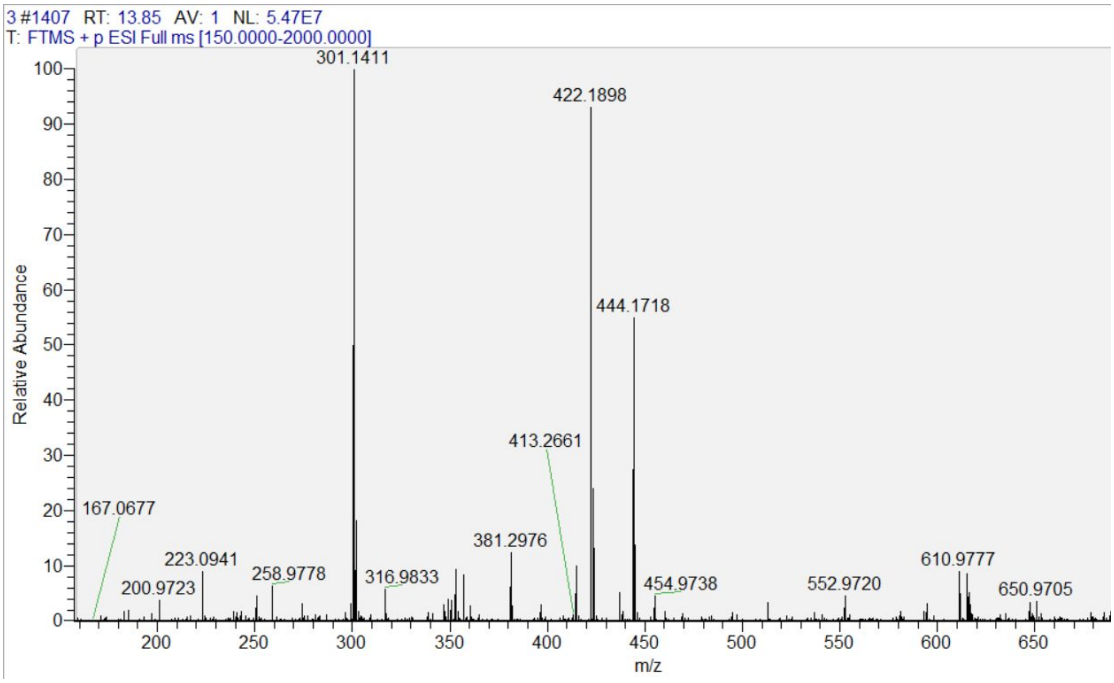
1i (410.1897)



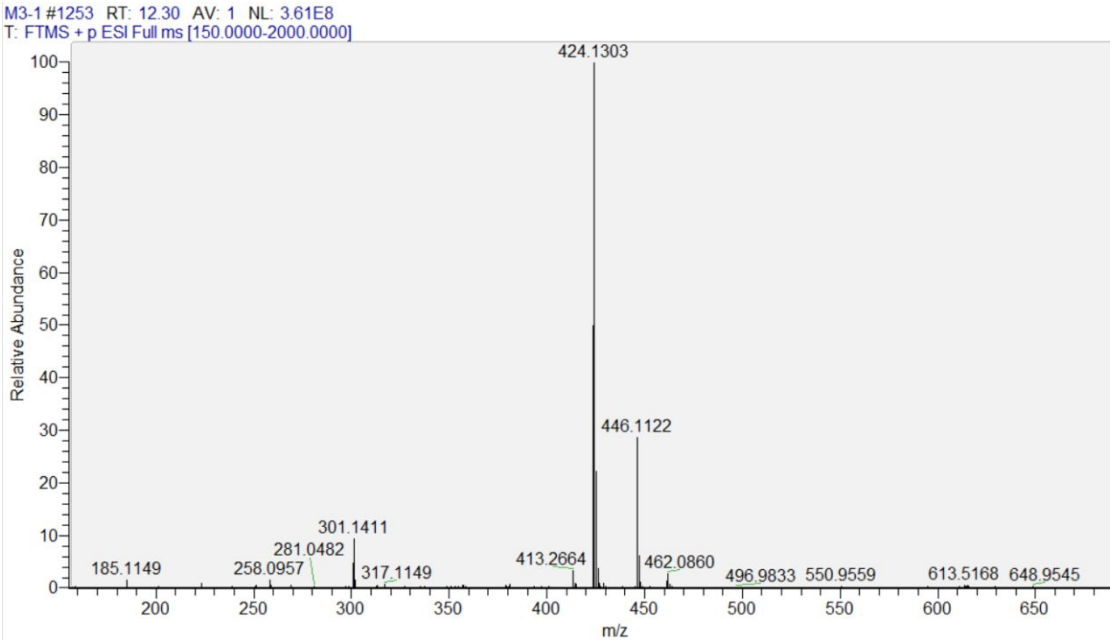
1j (408.1740)



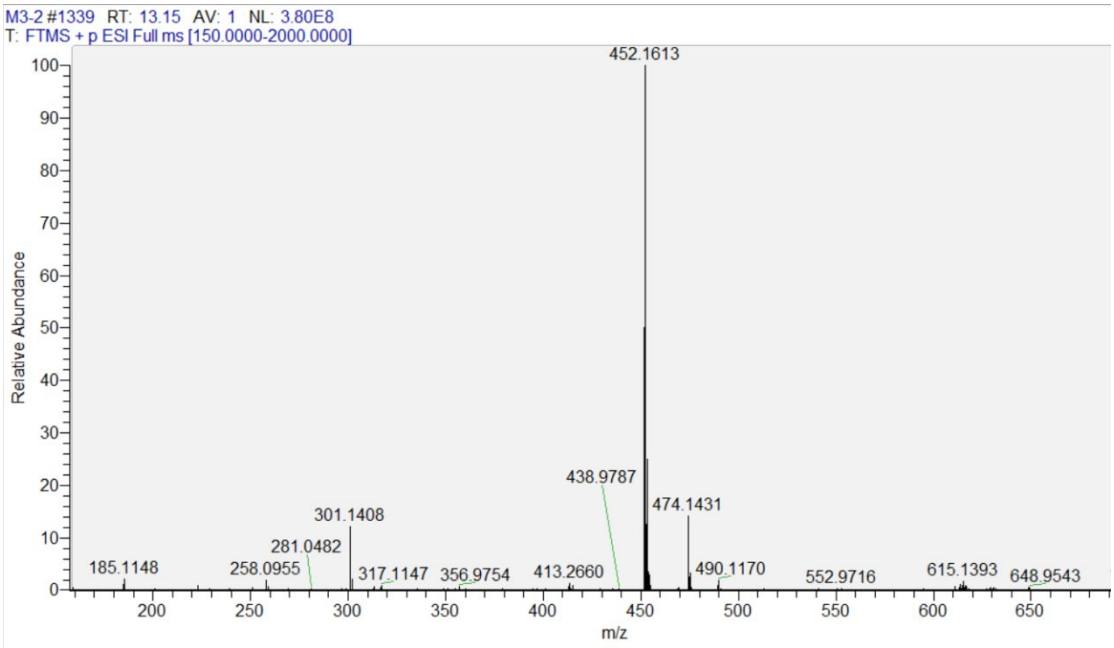
1k (422.1897)



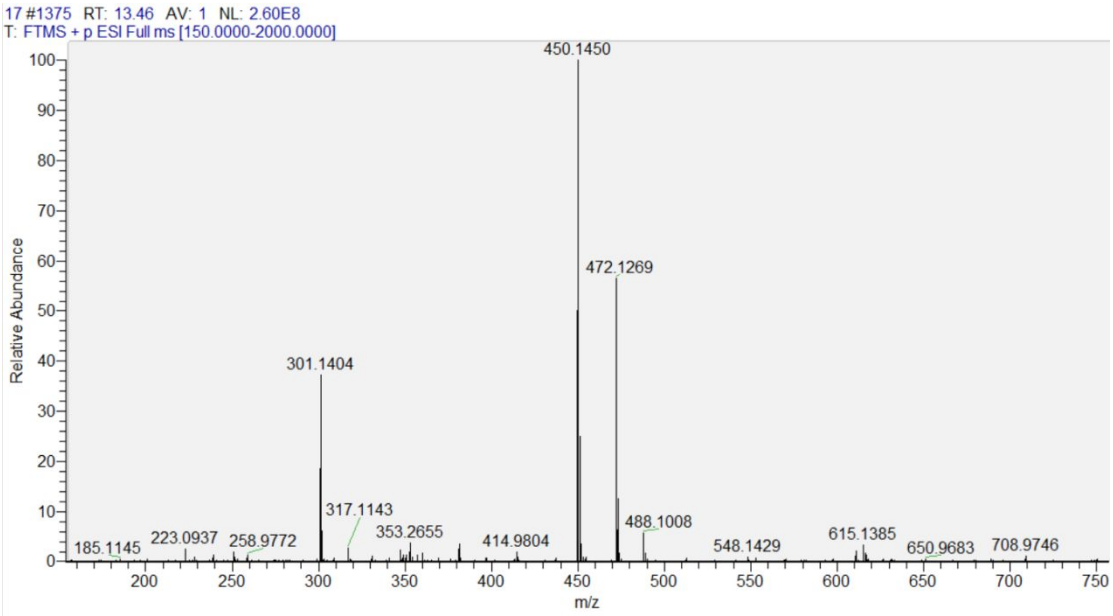
1l (424.1301)



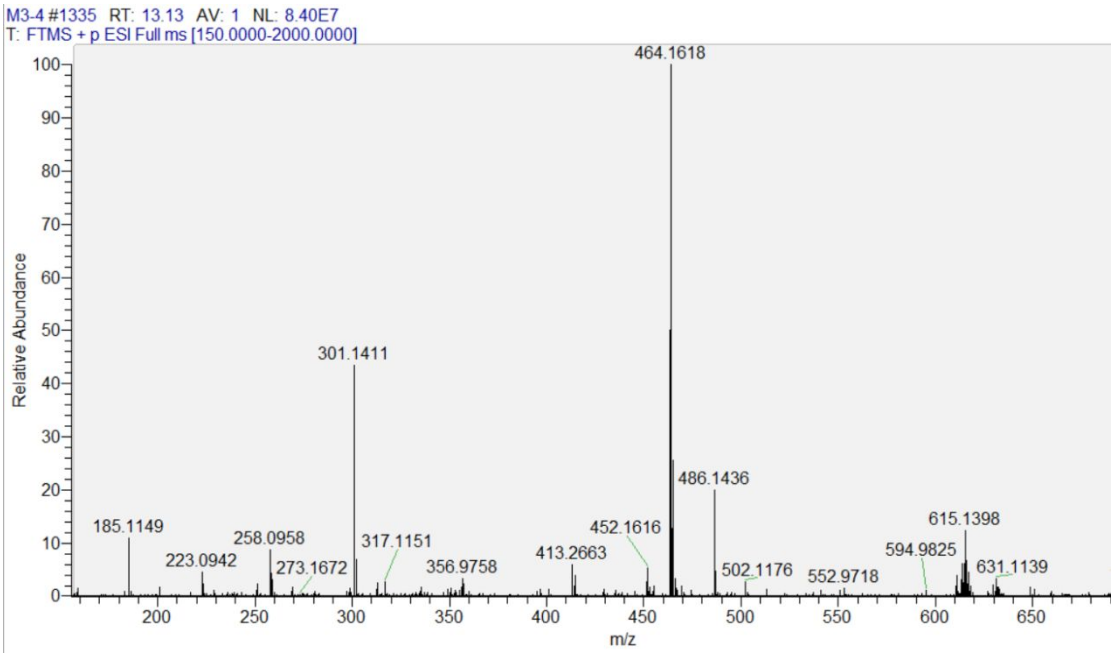
1m （452.1614）



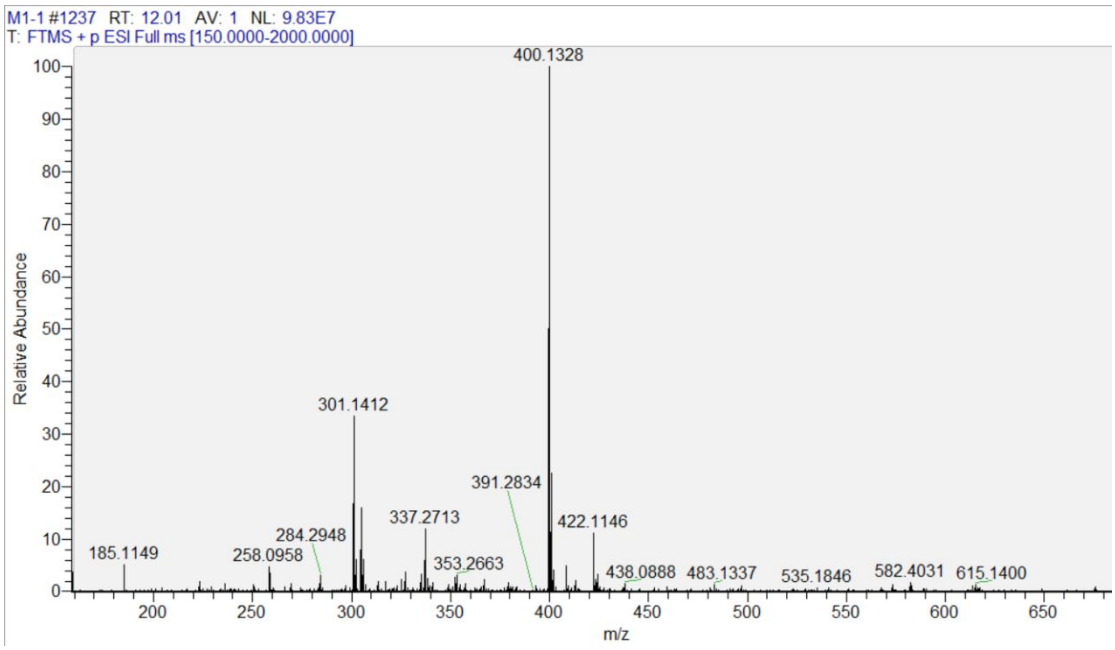
1n (450.1458)



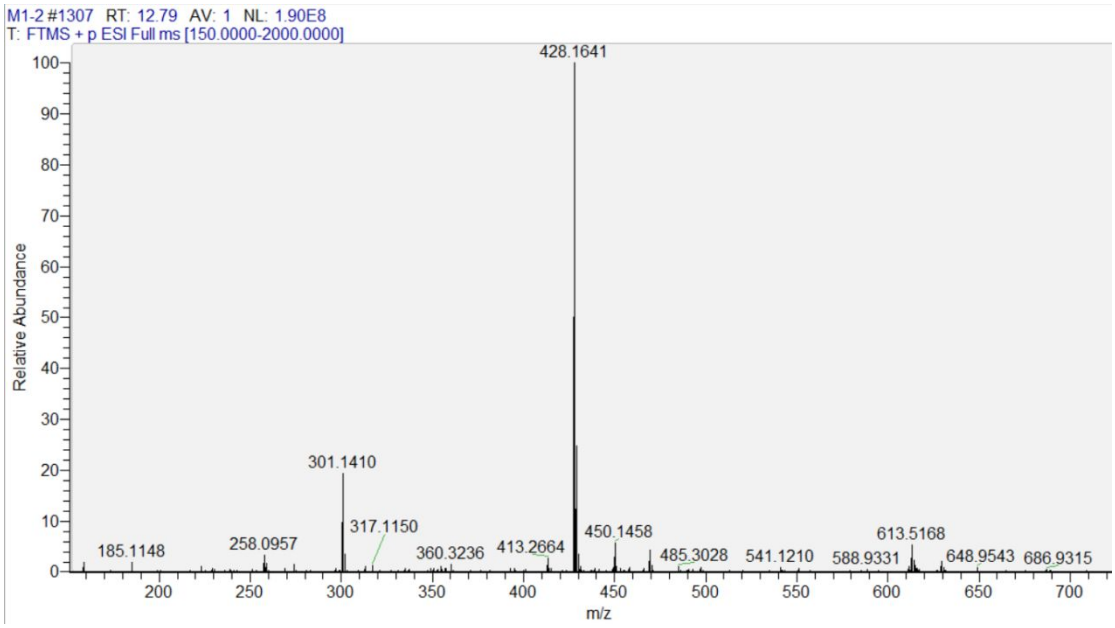
1o （464.1614）



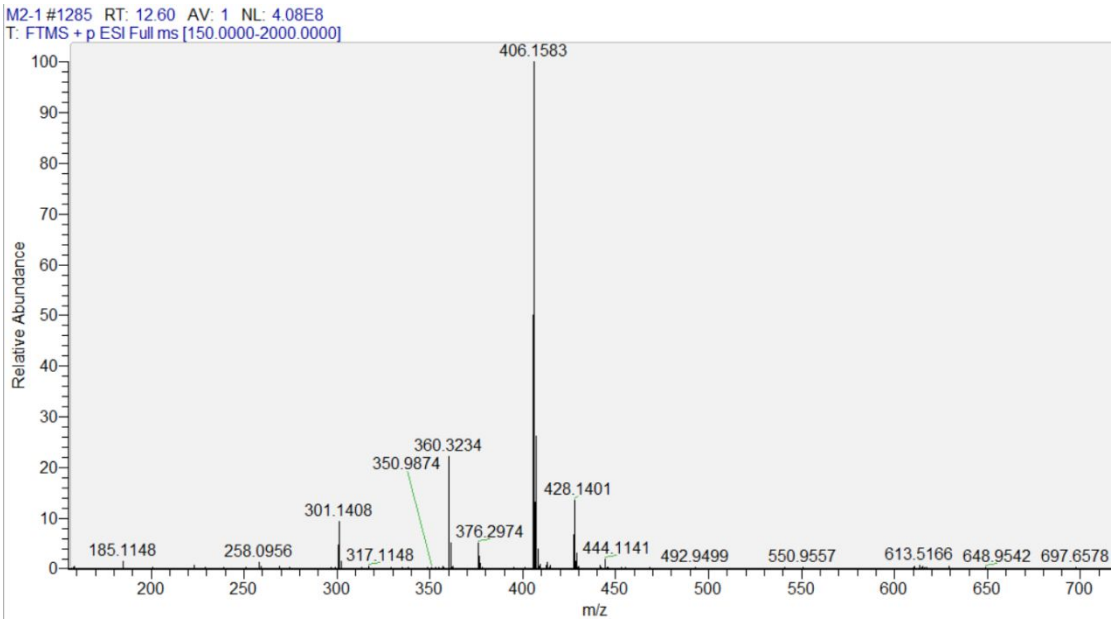
1p （400.1326）



1q （428.1639）



1r （406.1584）



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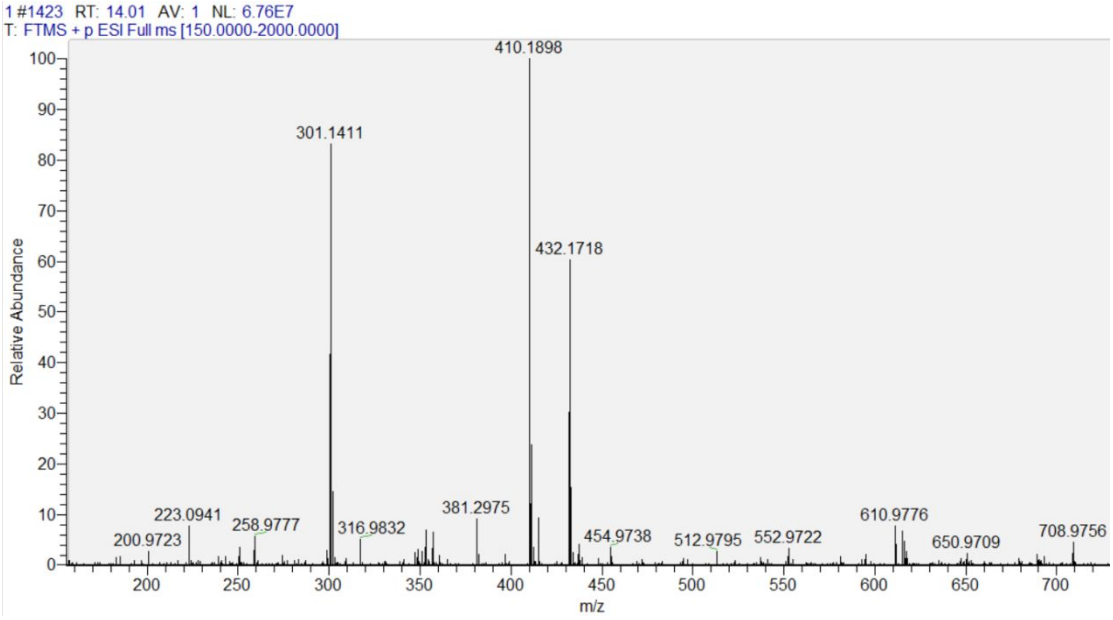
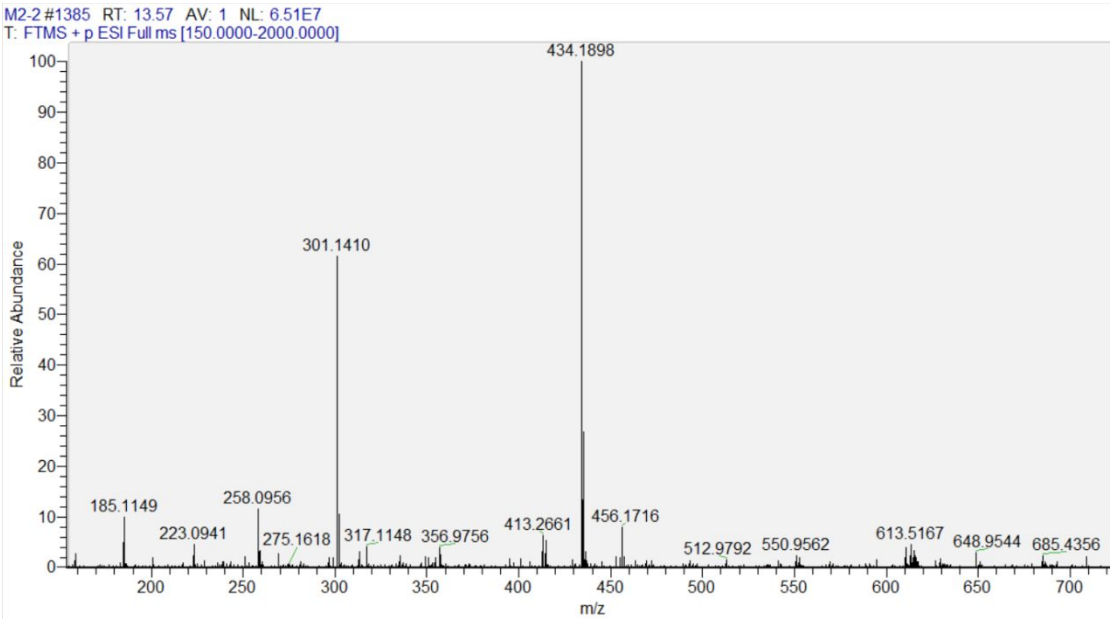
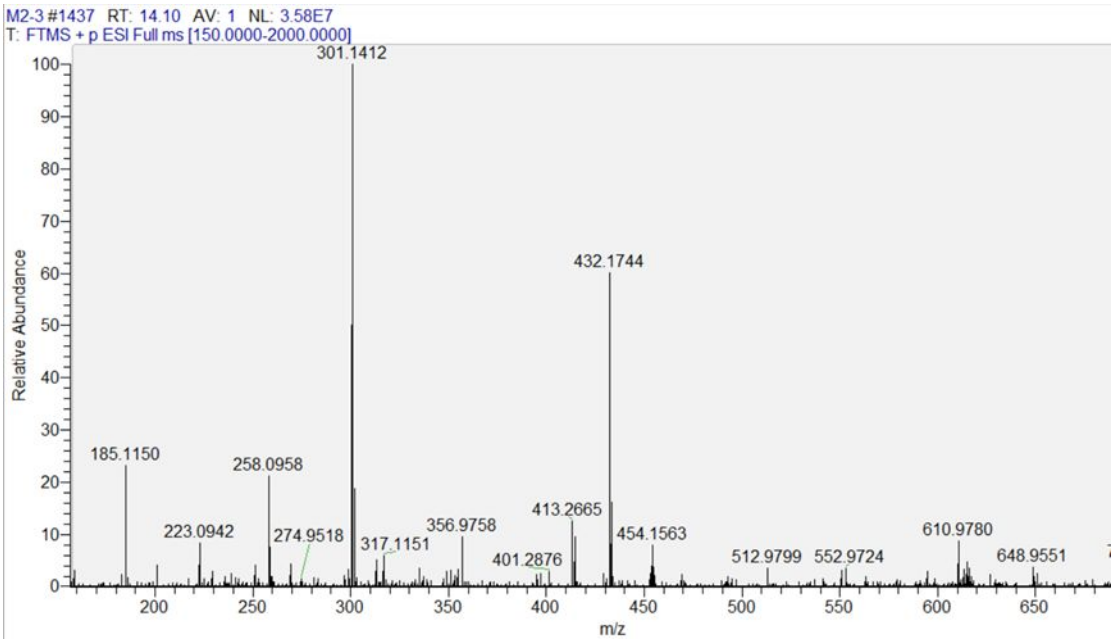


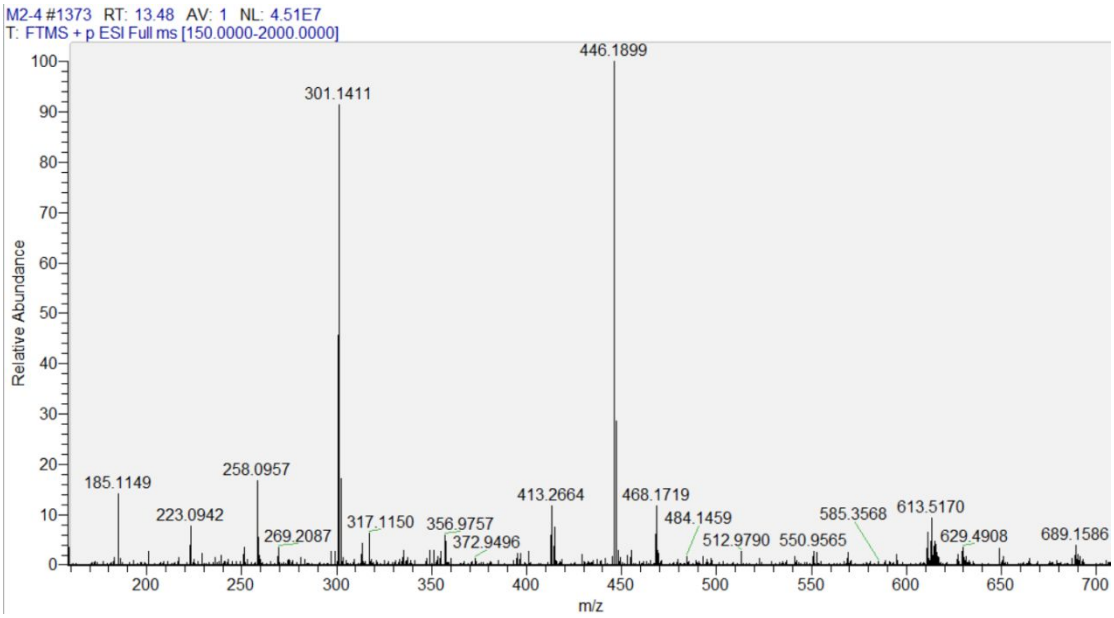
1t (434.1897)



1u (432.1740)



1v (446.1897)



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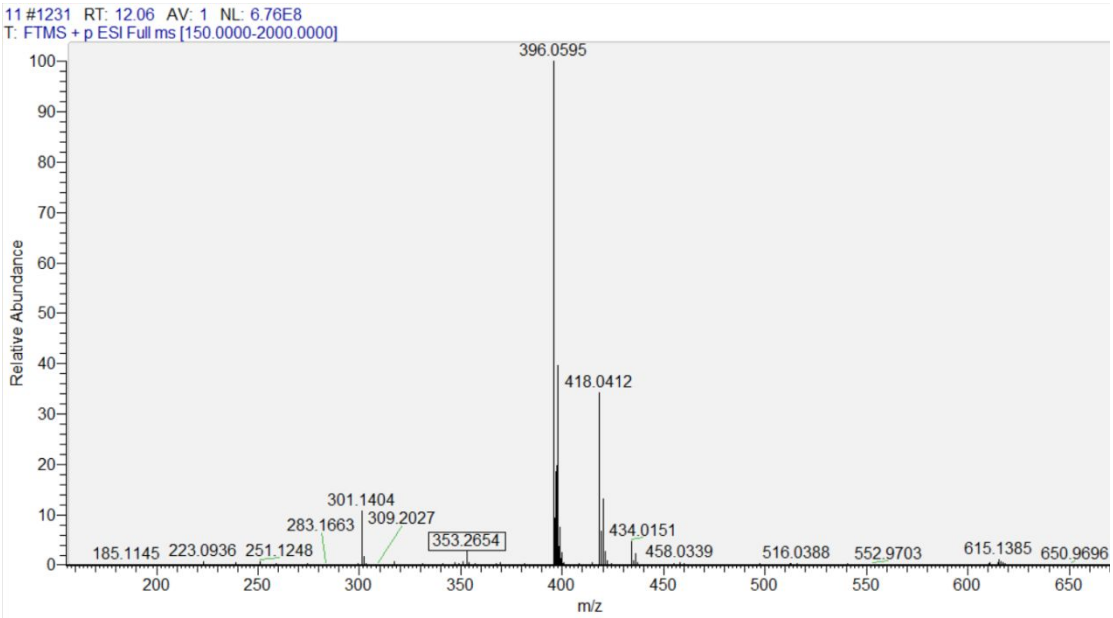
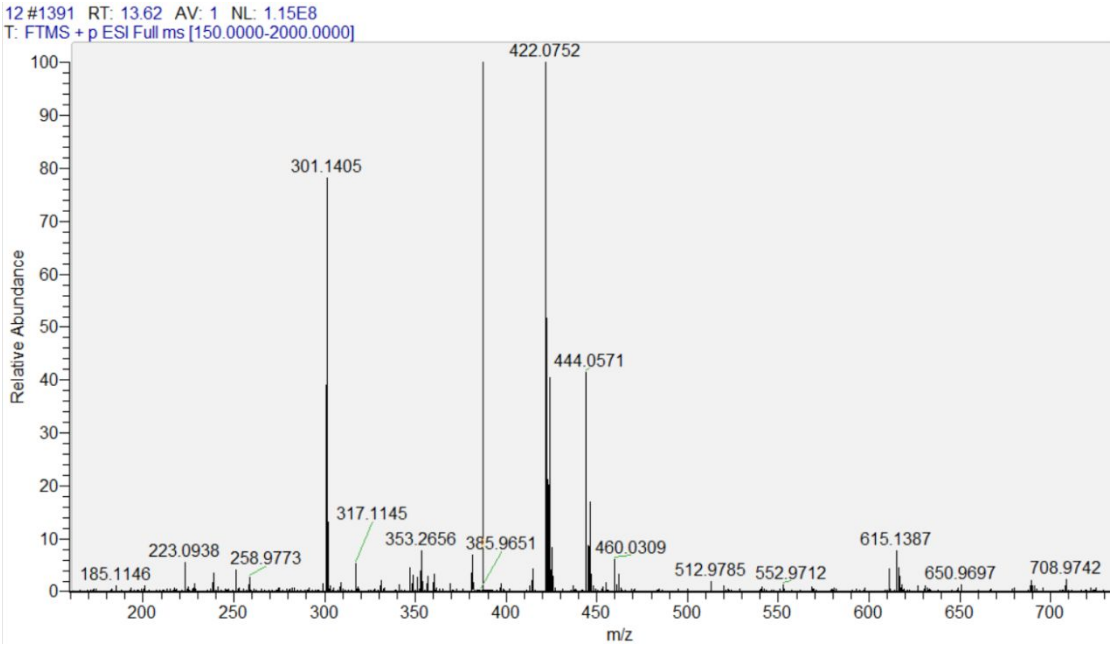


1x (422.0758)



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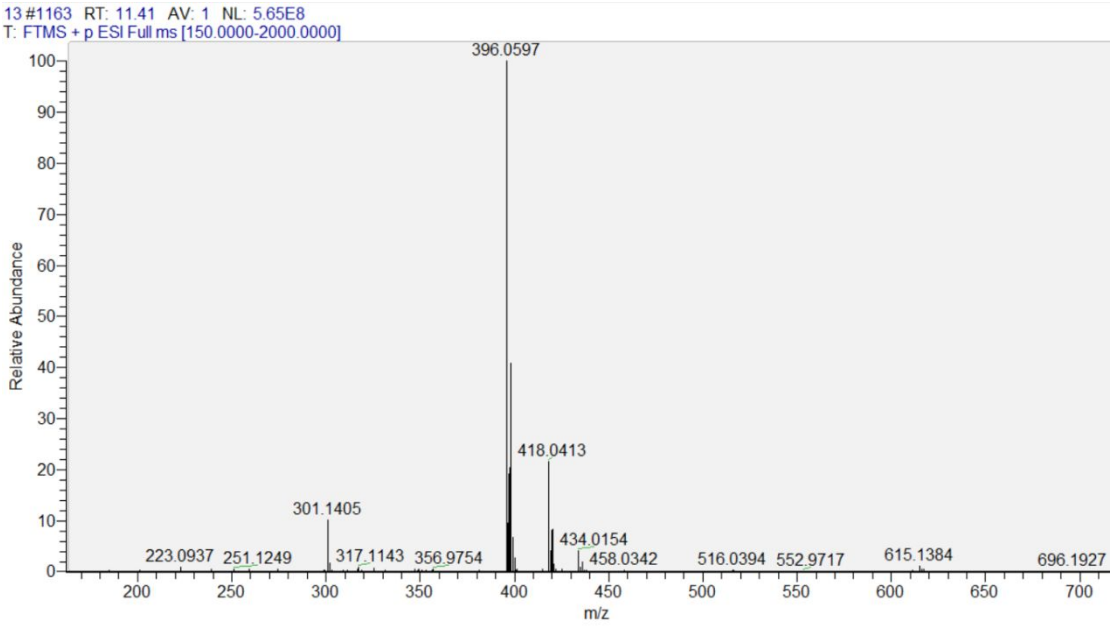

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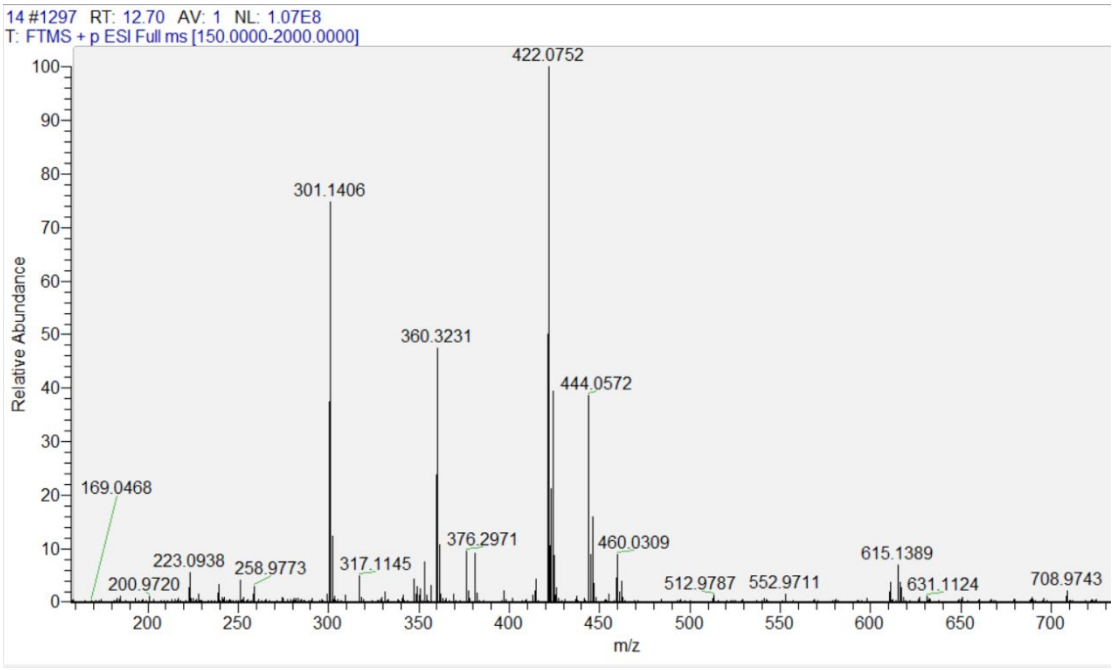

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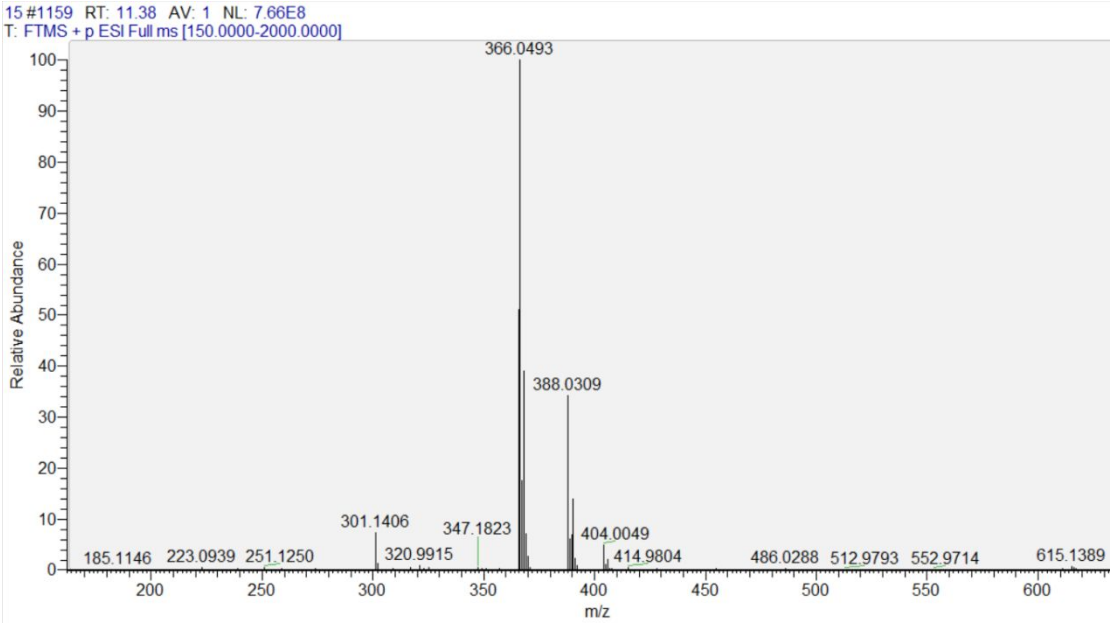

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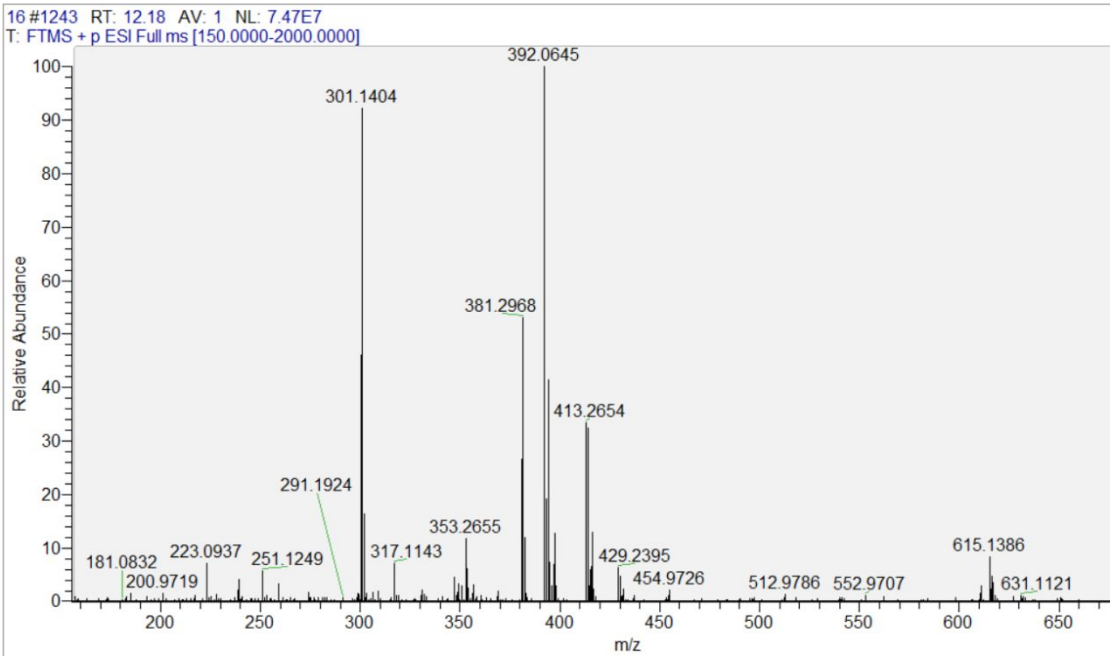

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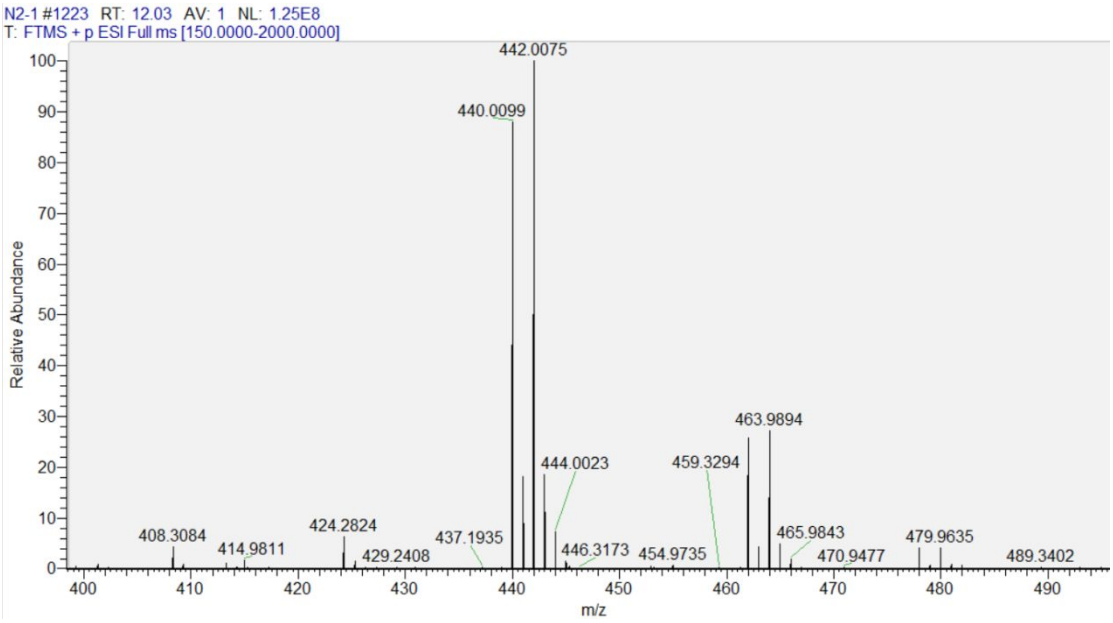

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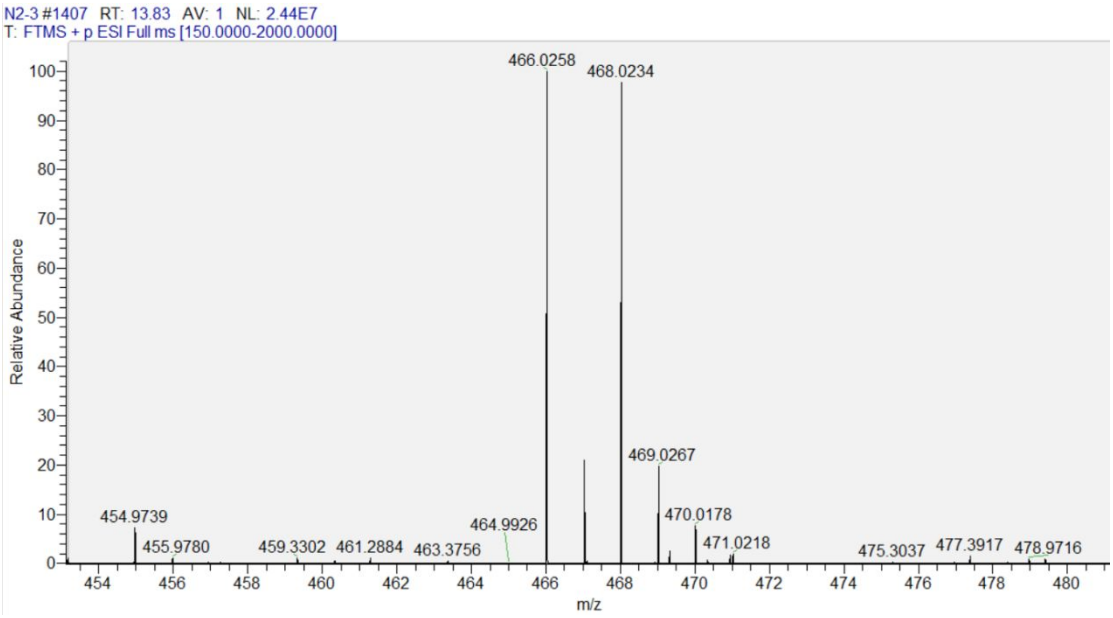

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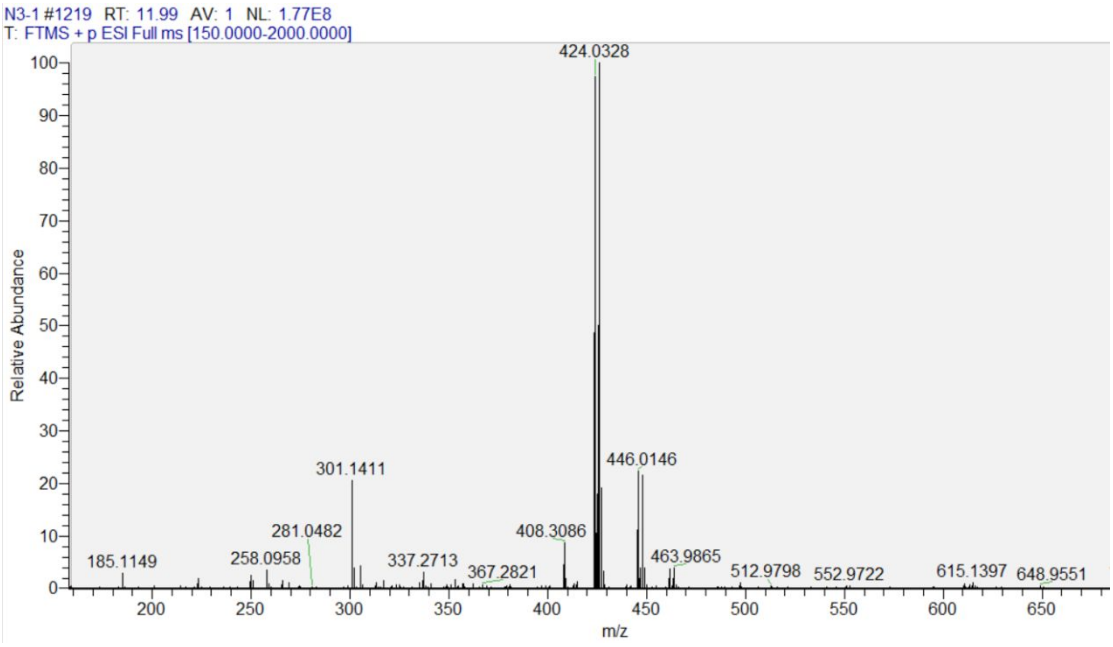

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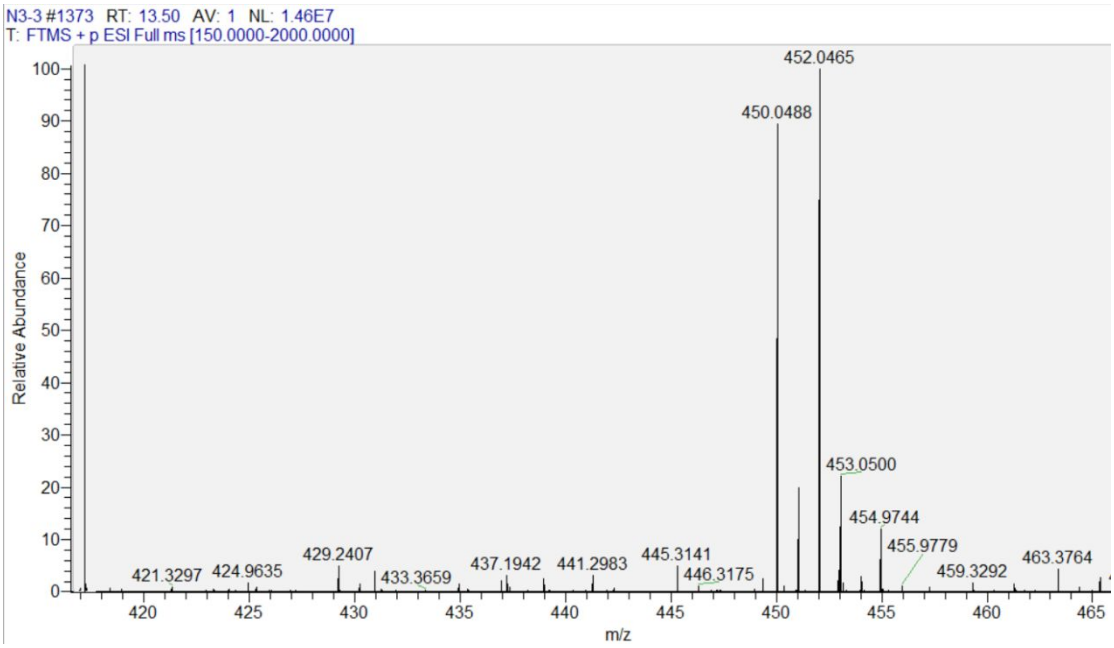

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S2. Dud, M.; Magdysyuk, O. V.; Margetic, D.; Strukil, V., Synthesis of monosubstituted thioureas by vapour digestion and mechanochemical amination of thiocarbamoyl benzotriazoles. *Green Chem.* **2016,** *18* (9), 2666-2674.

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