Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.


# Discovery of novel Bcr-Abl inhibitors with diacylated piperazine as flexible linker

*Xiaoyan Pan,[a] Jinyun Dong,[a] Yaling Shi,[a] Ruili Shao,[a] Fen Wei,[a] Jinfeng Wang,[a] and Jie Zhang[a]*

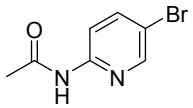
*[a]School of Pharmacy, Health Science Center, Xi'an Jiaotong University, No. 76, Yanta We st Road, Xi'an, Shaanxi Province, 710061, P.R. China.*

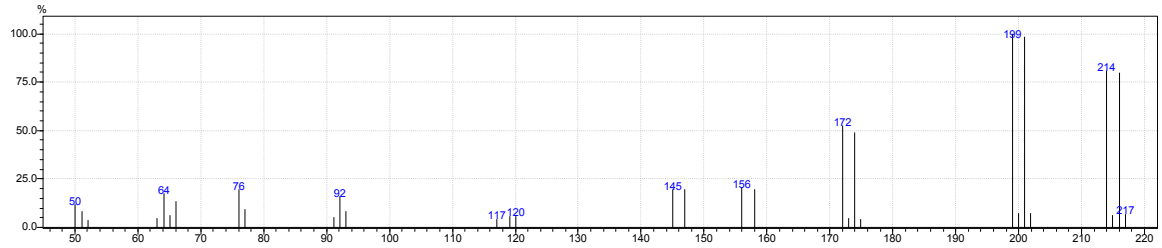
**Table of Contents**

**The Name, Structure, Melting point, Mass Spectrometry and $^{1}$H-NMR Spectrum of Key Intermediates and Title Compounds**

**The Name, Structure, $^{13}$C-NMR Spectrum and HRMS of Title Compounds**

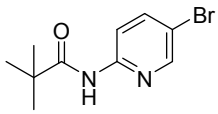
***N*-(5-bromopyridin-2-yl)acetamide (1a)**

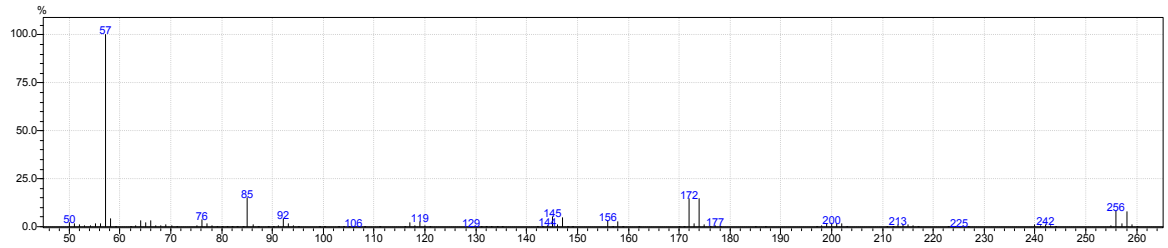



Mp 78-81 ºC; EI-MS (m/z) 214$[M]^+$.

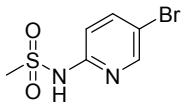
***N*-(5-bromopyridin-2-yl)-2,2-dimethylpropanamide (1b)**

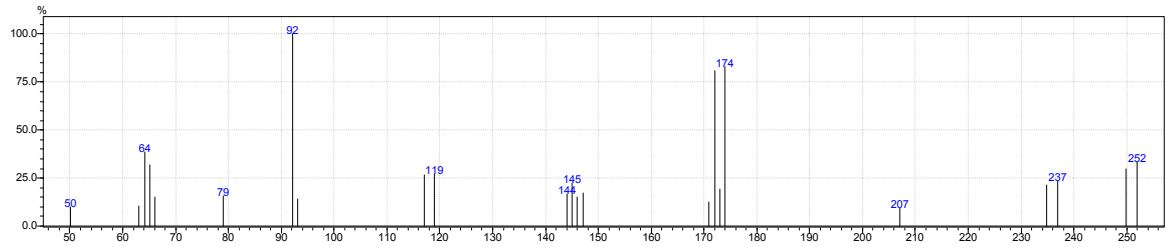



Mp 42-44 ºC; EI-MS (m/z) 256$[M]^+$.

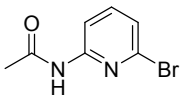
***N*-(5-bromopyridin-2-yl)methanesulfonamide (1c)**

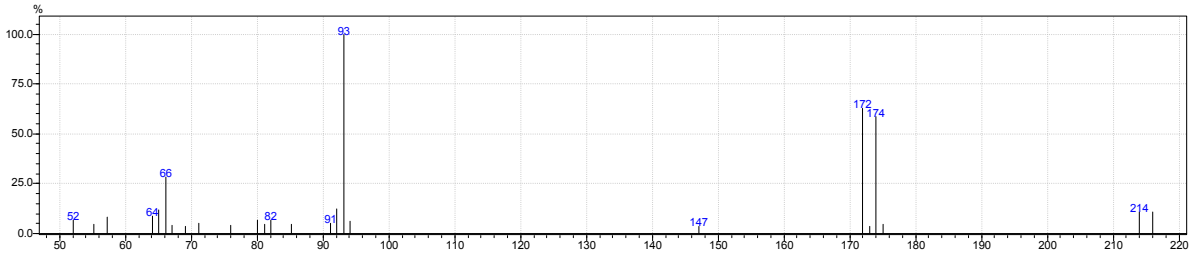



Mp 161-163 ºC; EI-MS (m/z) 250$[M]^+$.

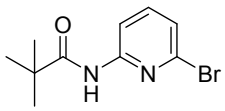
## *N*-(6-bromopyridin-2-yl)acetamide (2a)

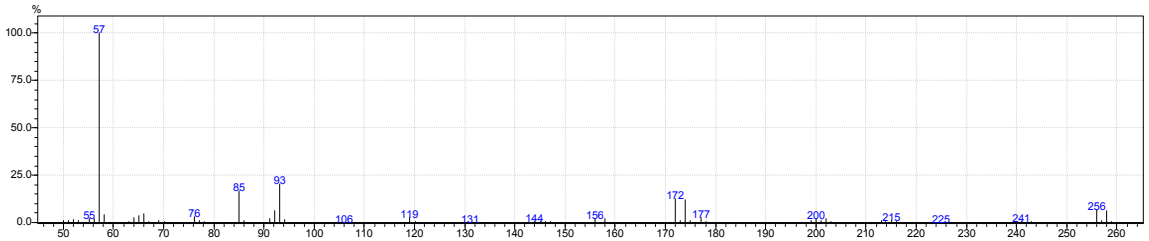





Mp 159-160 ºC; EI-MS (m/z) 214$[M]^+$.

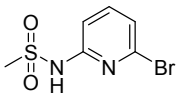
## *N*-(6-bromopyridin-2-yl)-2,2-dimethylpropanamide (2b)

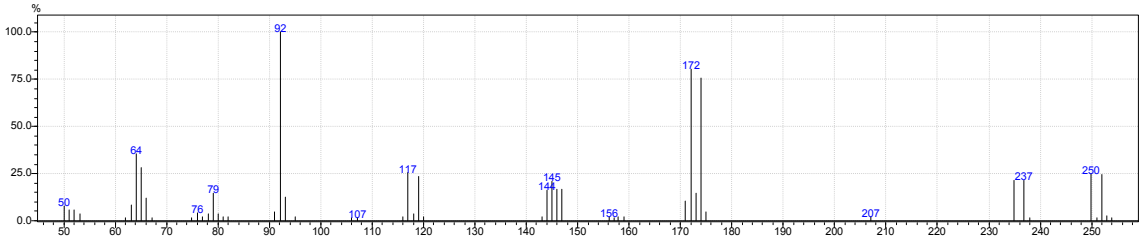





Mp 90-91 ºC; EI-MS (m/z) 256$[M]^+$.

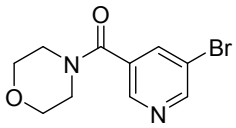
## *N*-(6-bromopyridin-2-yl)methanesulfonamide (2c)

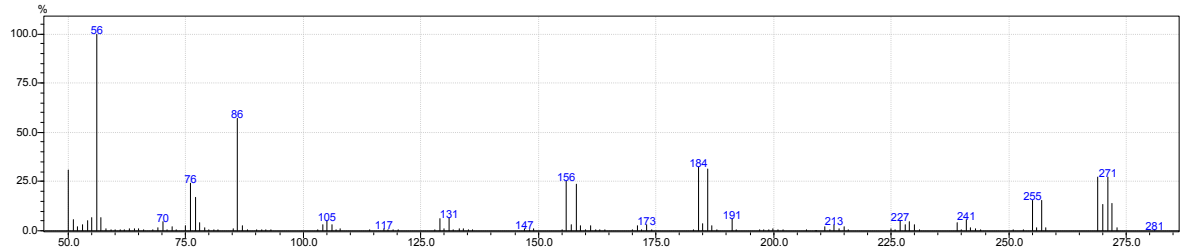





Mp 179-180 ºC; EI-MS (m/z) 250$[M]^+$.

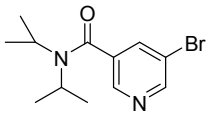
**4-[(5-bromopyridin-3-yl)carbonyl]morpholine(3a)**

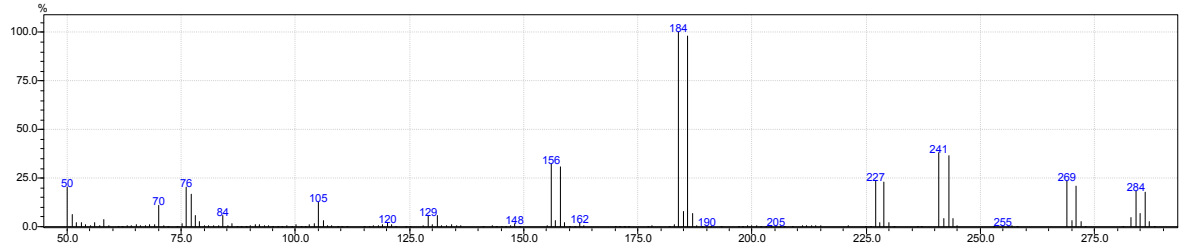





Mp 76-78 ºC; EI-MS (m/z) 271$[M]^+$.

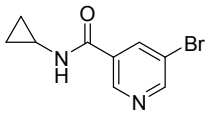
**5-bromo-*N*,*N*-diisopropylnicotinamide(3b)**

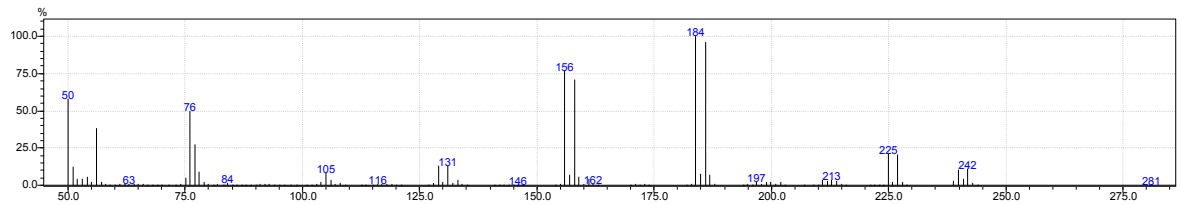





Mp 90-91 ºC; EI-MS (m/z) 284$[M]^+$.

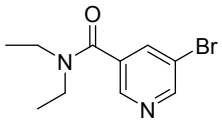
**5-bromo-*N*-cyclopropylnicotinamide(3c)**

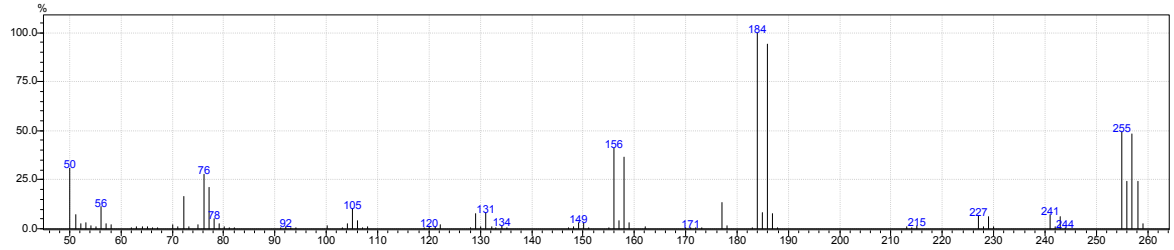





Mp 140-142 ºC; EI-MS (m/z) 240$[M]^+$.

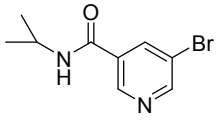
**5-bromo-*N*,*N*-diethylnicotinamide(3d)**

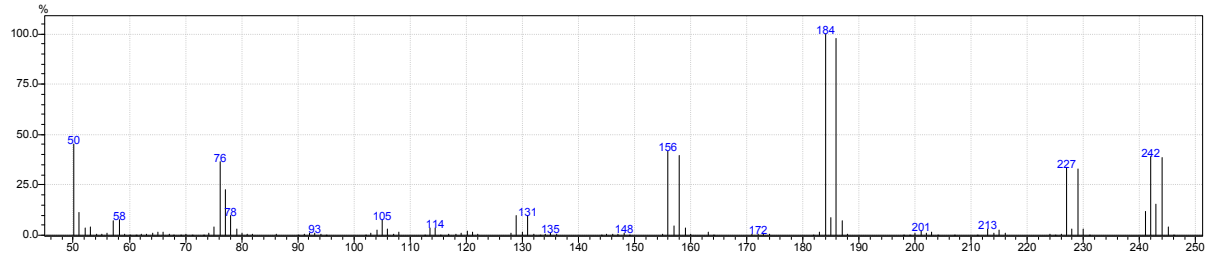



EI-MS (m/z) 256[M]$^+$.

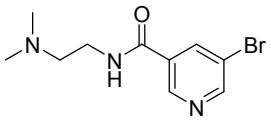
**5-bromo-*N*-isopropylnicotinamide(3e)**

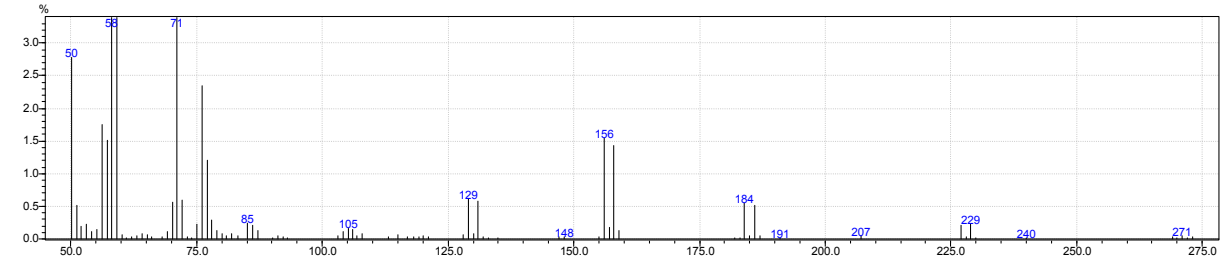



Mp 105-106 ºC; EI-MS (m/z) 242[M]$^+$.

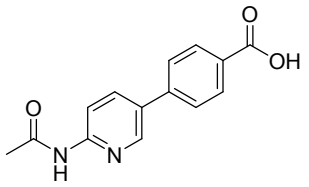
**5-bromo-*N*-[2-(dimethylamino)ethyl]nicotinamide(3f)**

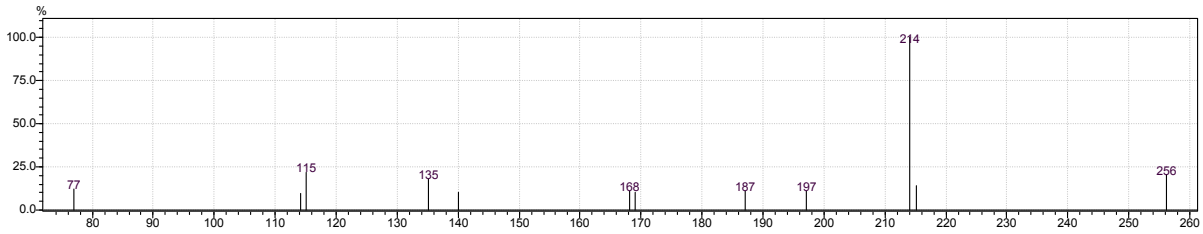


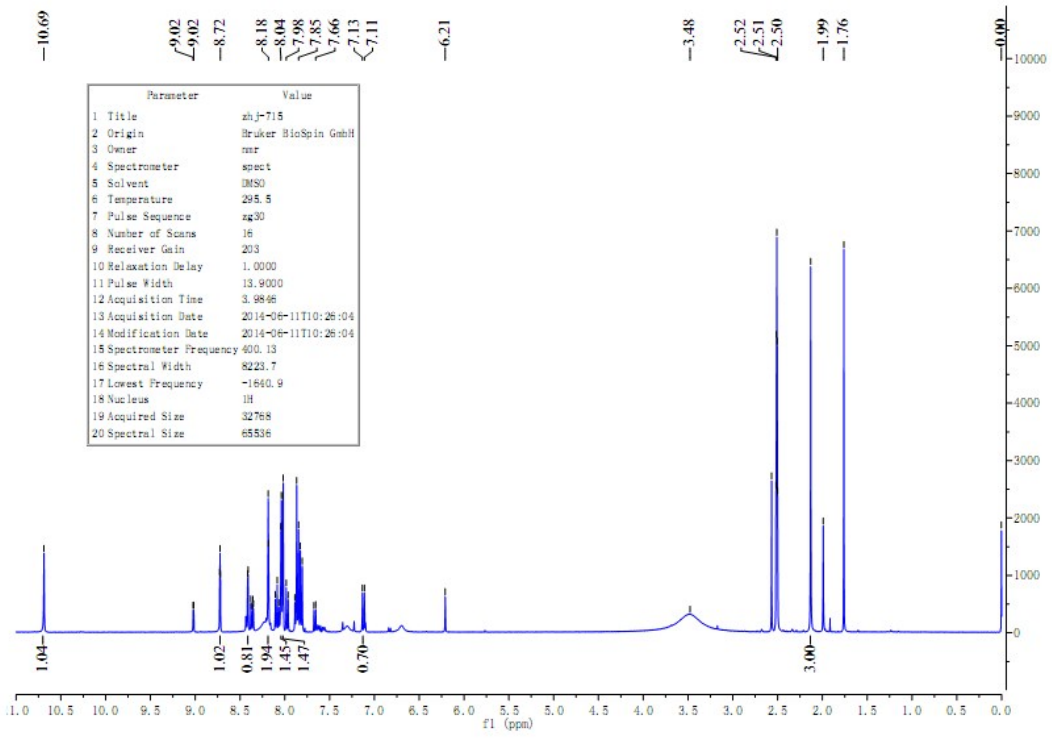




EI-MS (m/z) 271[M]$^+$.

**4-[6-(acetylamino)pyridin-3-yl]benzoic acid (4a)**

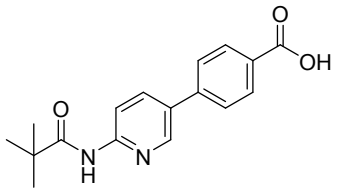


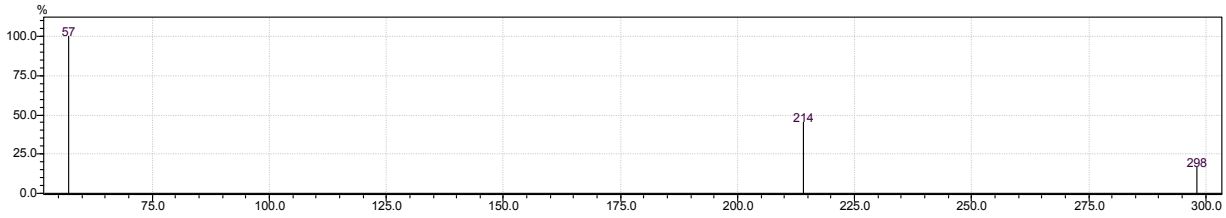



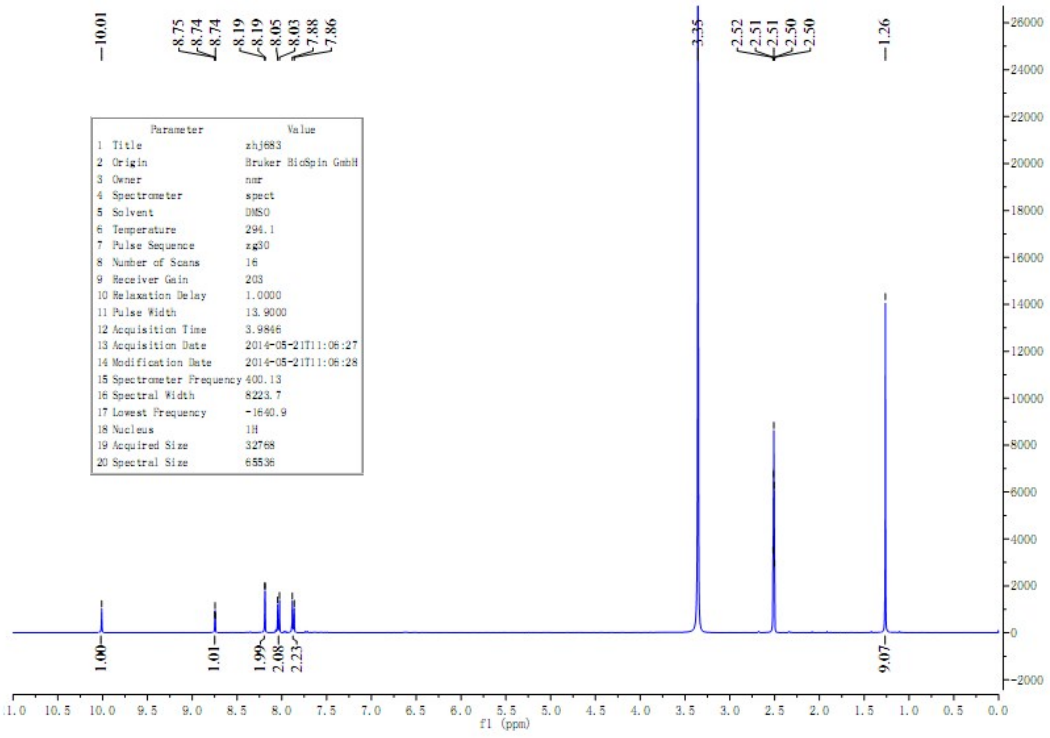




Mp 156-158 ºC; EI-MS (m/z) 256[M]$^{+}$; $^{1}$H NMR (400MHz, DMSO-$d_6$) δ 8.74–8.71 (m, 1H), 8.41 (d, *J*= 2.3 Hz, 1H), 8.18 (d, *J*= 1.9 Hz, 2H), 8.04 (d, *J*= 1.8 Hz, 1H), 8.02 (d, *J*= 1.7 Hz, 1H), 7.12 (d, *J*= 9.3 Hz, 1H), 2.13 (s, 3H).

**4-{6-[(2,2-dimethylpropanoyl)amino]pyridin-3-yl}benzoic acid (4b)**

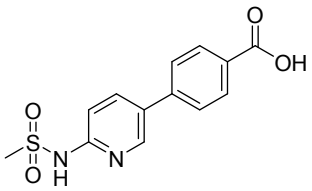


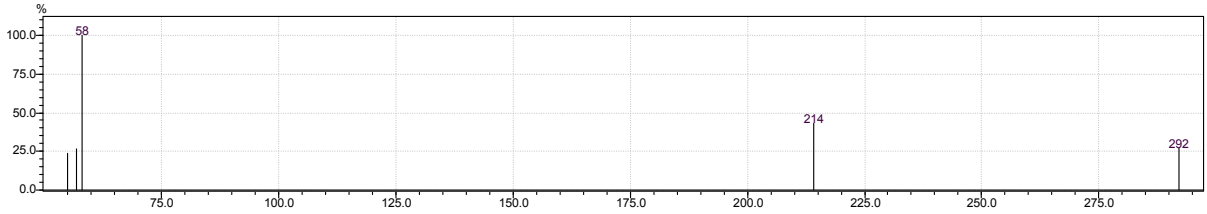



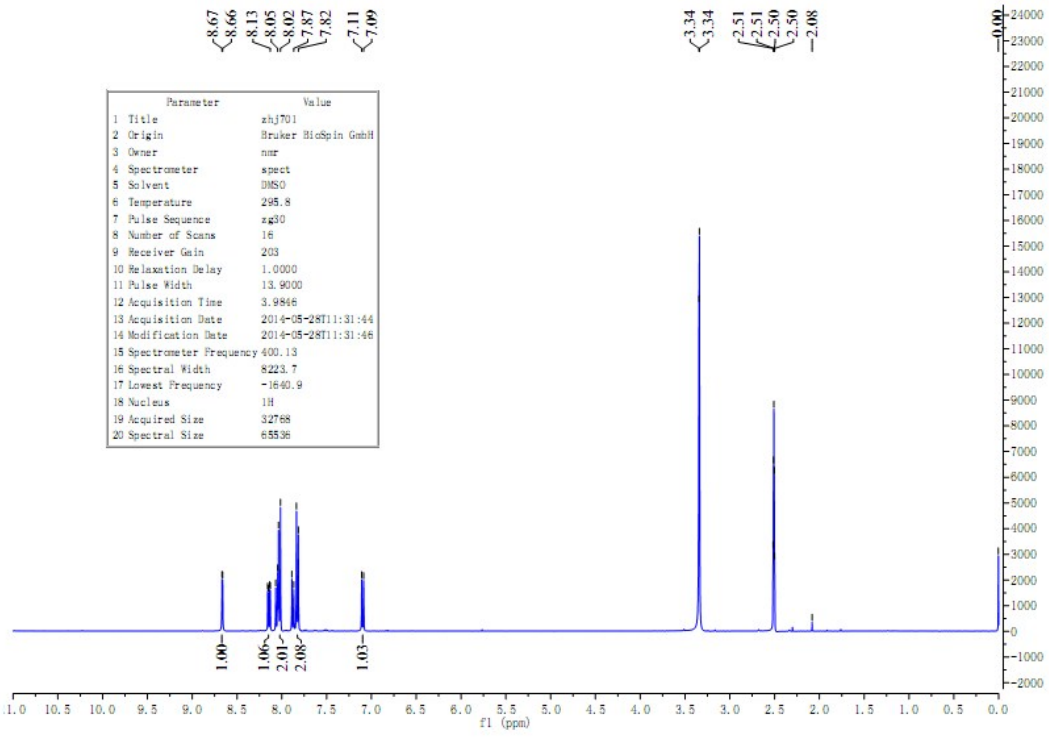




Mp 276-277 ºC; EI-MS (m/z) 298[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.74 (t, $J$= 1.6 Hz, 1H), 8.19 (d, $J$= 1.6 Hz, 2H), 8.04 (d, $J$= 8.5 Hz, 2H), 7.87 (d, $J$= 8.5 Hz, 2H), 1.26 (s, 9H).

**4-{6-[(methylsulfonyl)amino]pyridin-3-yl}benzoic acid (4c)**

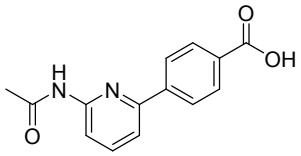


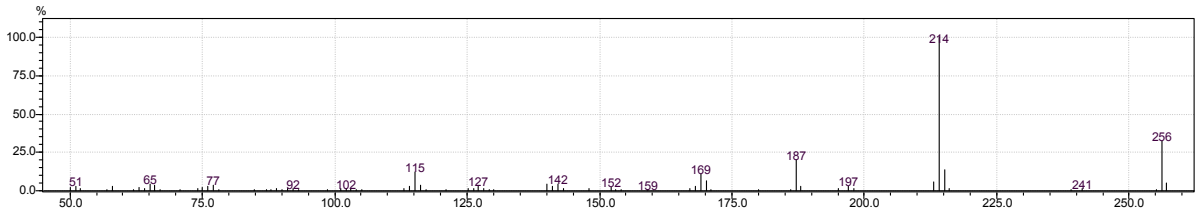



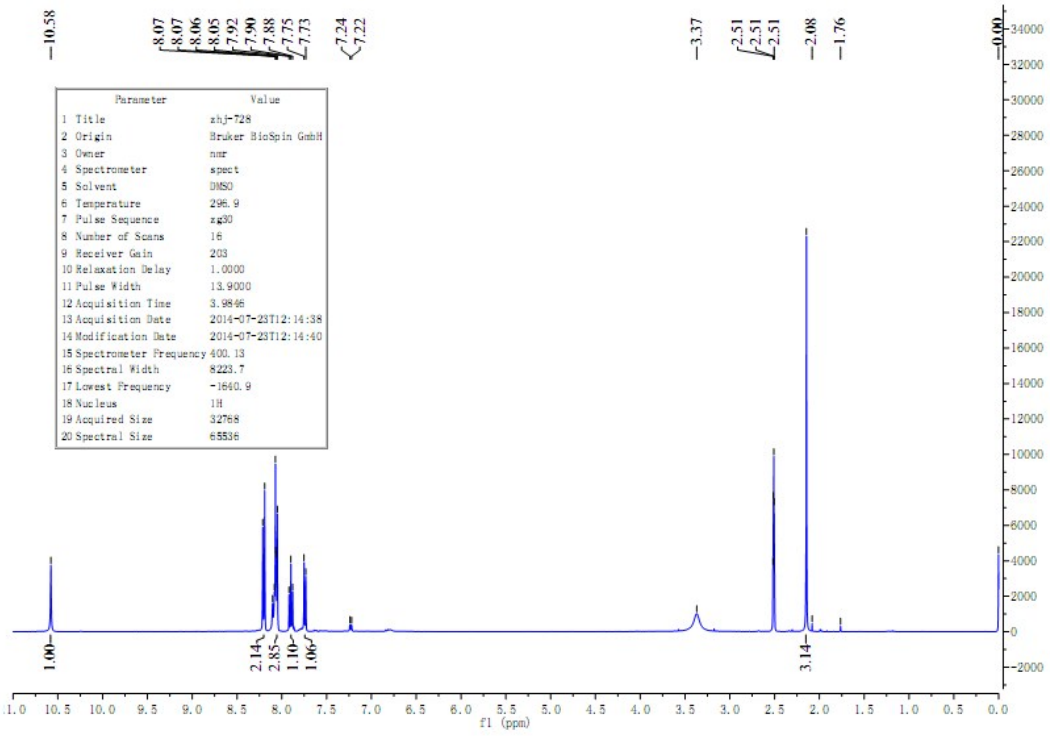




Mp 294-295 ºC; EI-MS (m/z) 292[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.66 (d, $J$ = 2.3 Hz, 1H), 8.14 (dd, $J$ = 8.7, 2.5 Hz, 1H), 8.06 (d, $J$ = 8.5 Hz, 1H), 8.03 (d, $J$ = 8.5 Hz, 1H), 7.88 (d, $J$ = 8.5 Hz, 1H), 7.83 (d, $J$ = 8.5 Hz, 1H), 7.10 (d, $J$ = 8.6 Hz, 1H), 3.34 (s, 3H).

**4-[6-(acetylamino)pyridin-2-yl]benzoic acid (5a)**

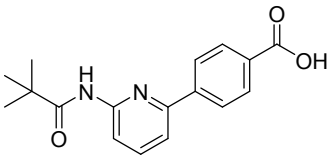


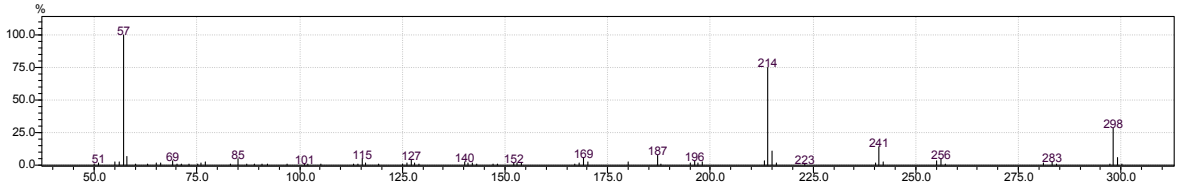



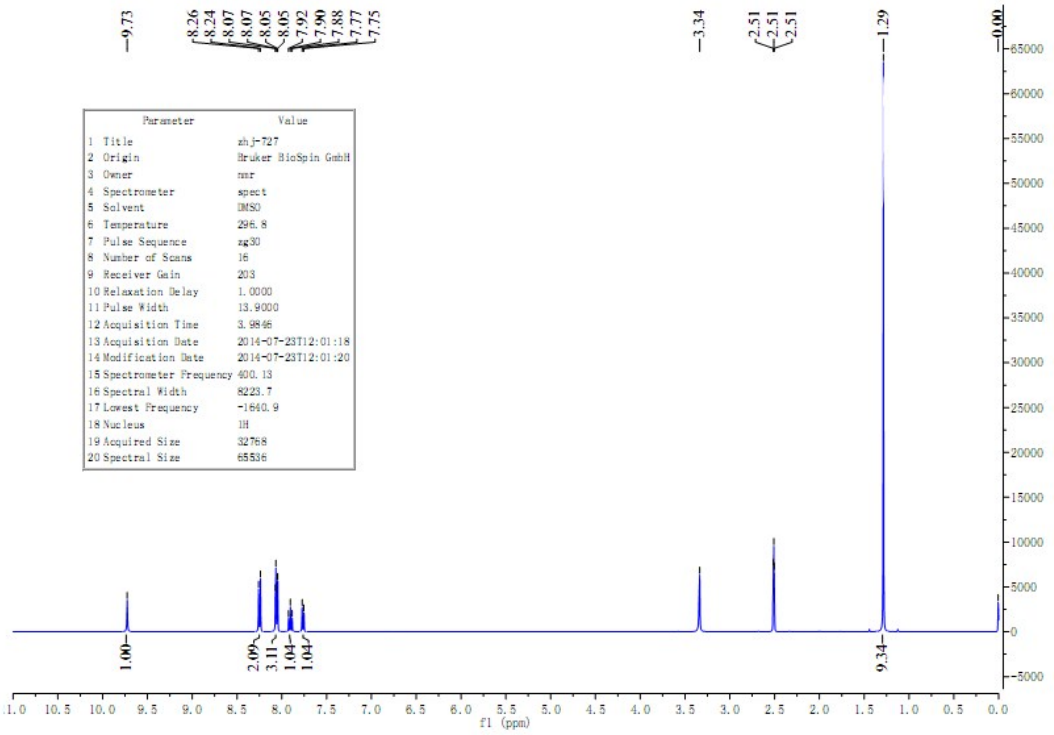




Mp 317-318 ºC; EI-MS (m/z) 256[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 10.58 (s, 1H), 8.20 (d, $J$ = 8.5 Hz, 2H), 8.06 (dd, $J$ = 4.8, 3.7 Hz, 3H), 7.90 (t, $J$ = 7.9 Hz, 1H), 7.74 (d, $J$ = 7.6 Hz, 1H), 2.15 (s, 3H).

**4-{6-[(2,2-dimethylpropanoyl)amino]pyridin-2-yl}benzoic acid (5b)**

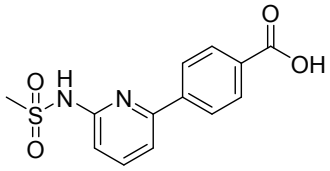


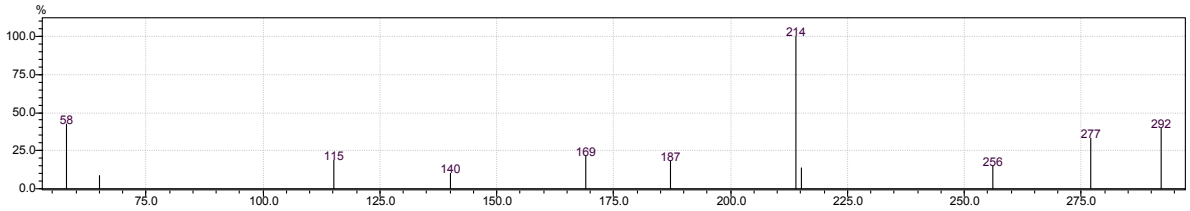



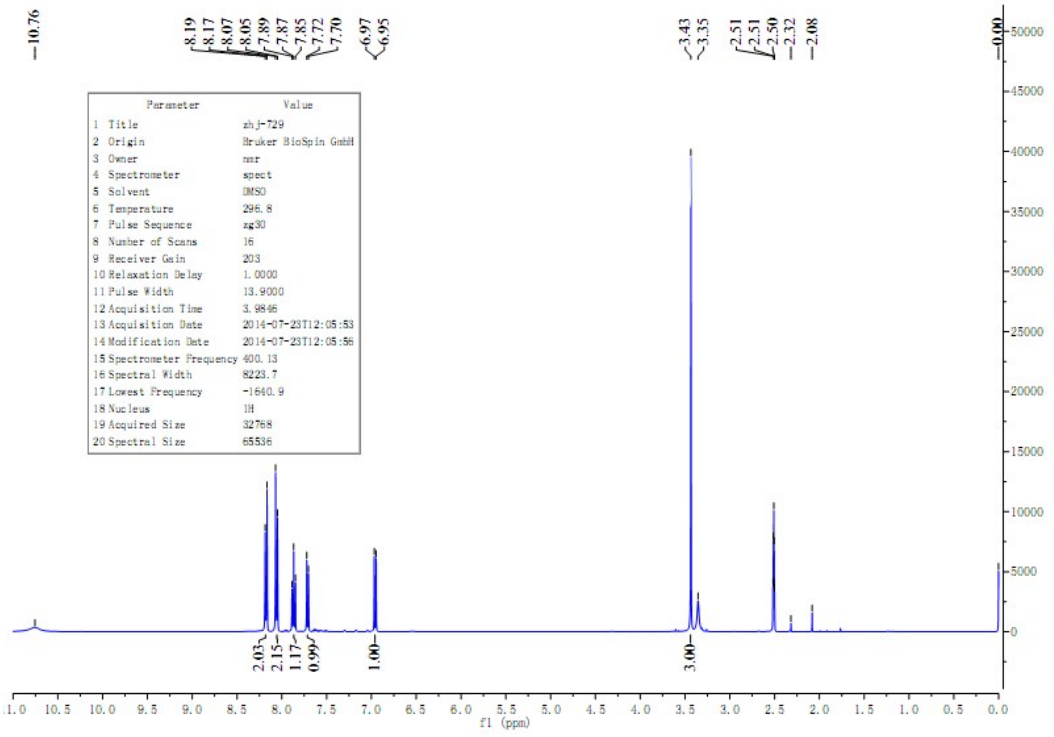




Mp 266-268 ºC; EI-MS (m/z) 298[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.73 (s, 1H), 8.25 (d, $J$ = 8.4 Hz, 2H), 8.06 (dd, $J$ = 8.3, 1.9 Hz, 3H), 7.90 (t, $J$ = 7.9 Hz, 1H), 7.76 (d, $J$ = 7.6 Hz, 1H), 1.29 (s, 9H).

**4-{6-[(methylsulfonyl)amino]pyridin-2-yl}benzoic acid (5c)**

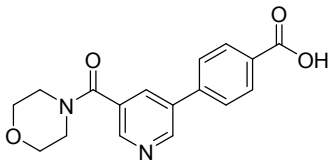


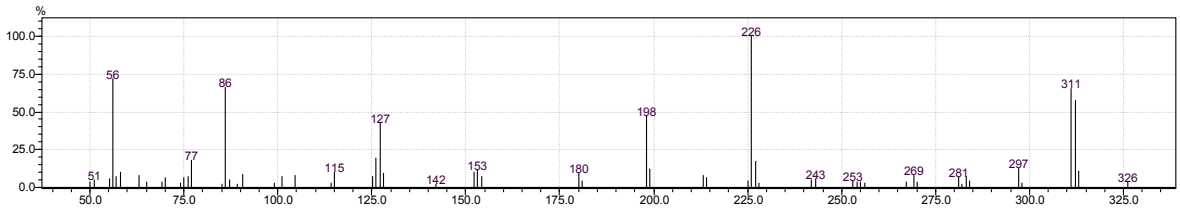


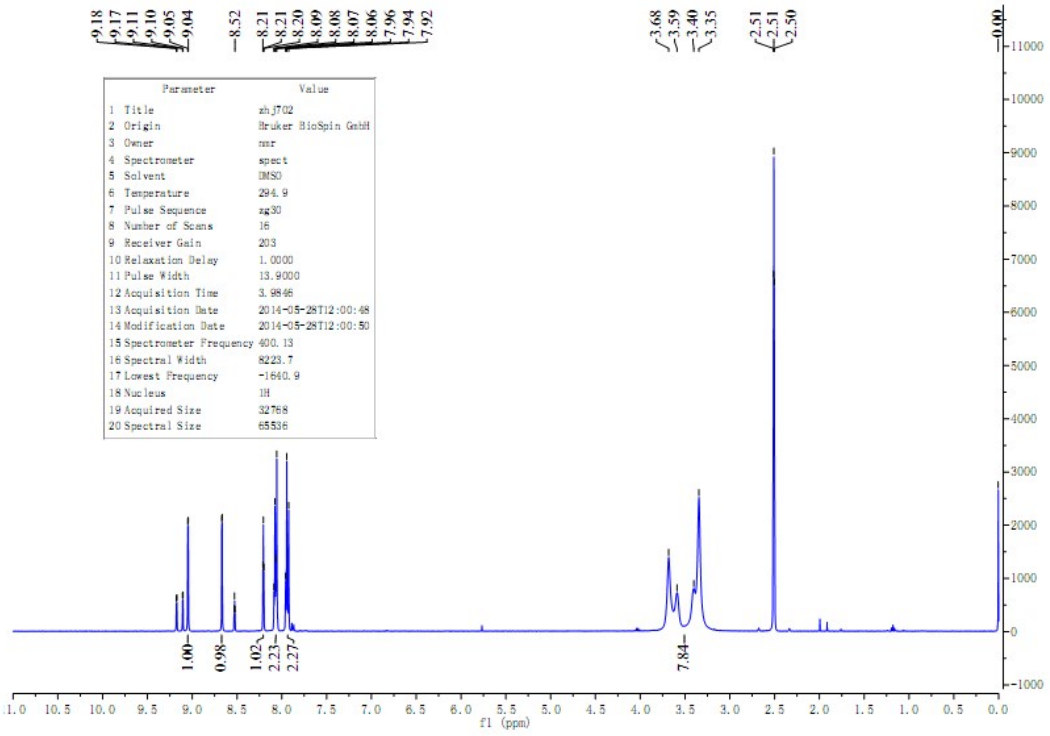




Mp 280-281 ºC; EI-MS (m/z) 292[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.18 (d, $J$ = 8.5 Hz, 2H), 8.06 (d, $J$ = 8.5 Hz, 2H), 7.87 (t, $J$ = 7.9 Hz, 1H), 7.71 (d, $J$ = 7.6 Hz, 1H), 6.96 (d, $J$ = 8.1 Hz, 1H), 3.43 (s, 3H).

**4-[5-(morpholin-4-ylcarbonyl)pyridin-3-yl]benzoic acid (6a)**

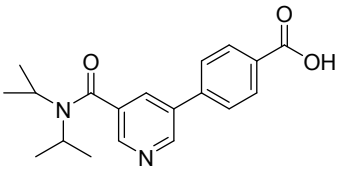


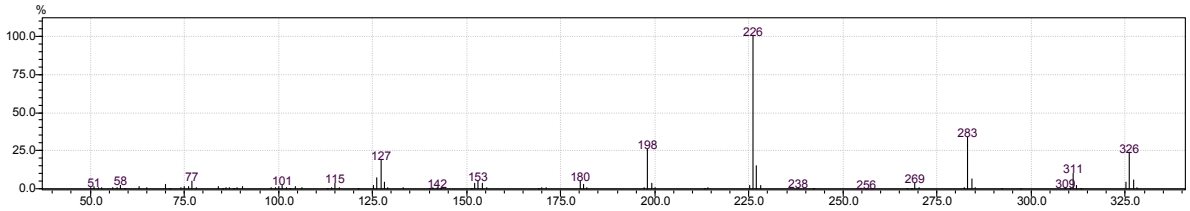



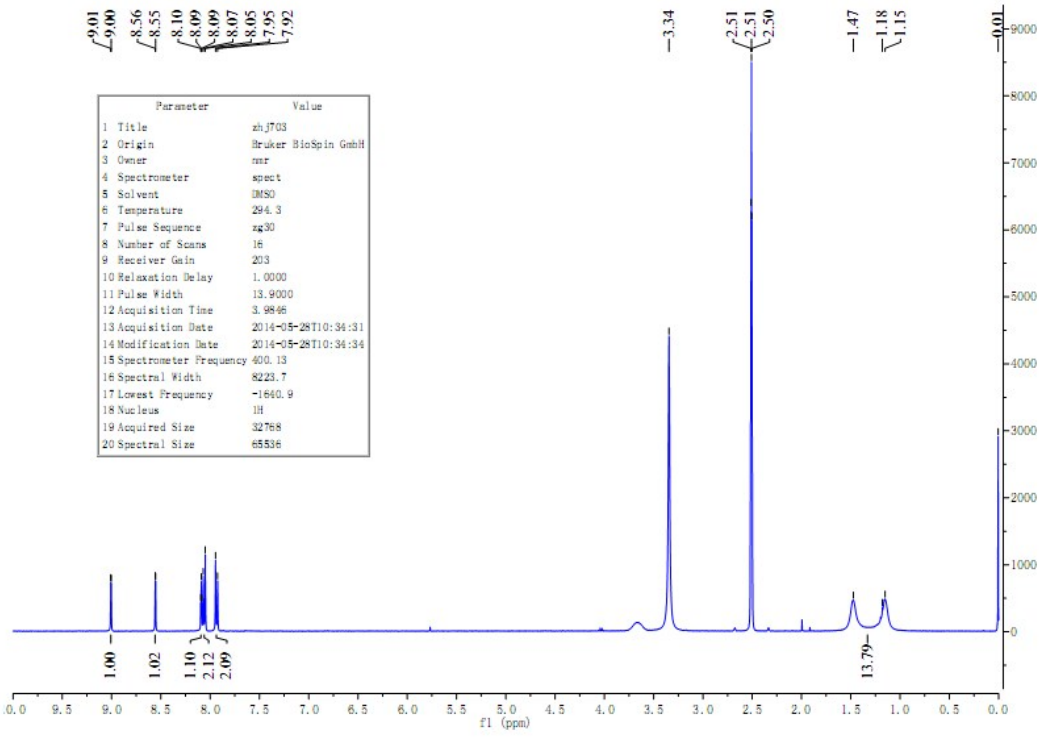




Mp 216-218 ºC; EI-MS (m/z) 312[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.05 (d, $J$ = 2.2 Hz, 1H), 8.67 (d, $J$ = 1.9 Hz, 1H), 8.21 (t, $J$ = 2.1 Hz, 1H), 8.07 (dd, $J$ = 8.4, 4.0 Hz, 2H), 7.94 (t, $J$ = 7.0 Hz, 2H), 3.78-3.38 (m, 8H).

**4-{5-[(diisopropylamino)carbonyl]pyridin-3-yl}benzoic acid (6b)**

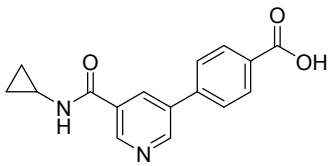


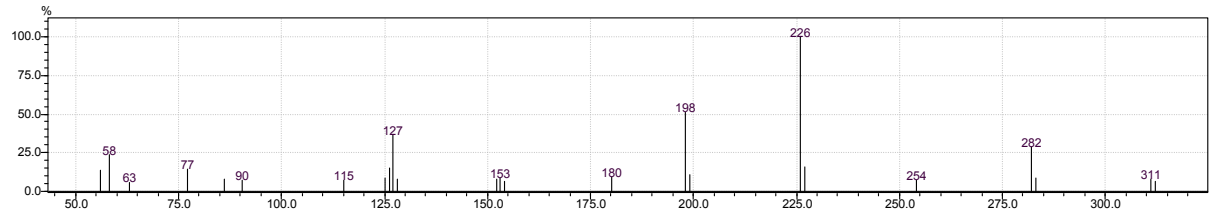



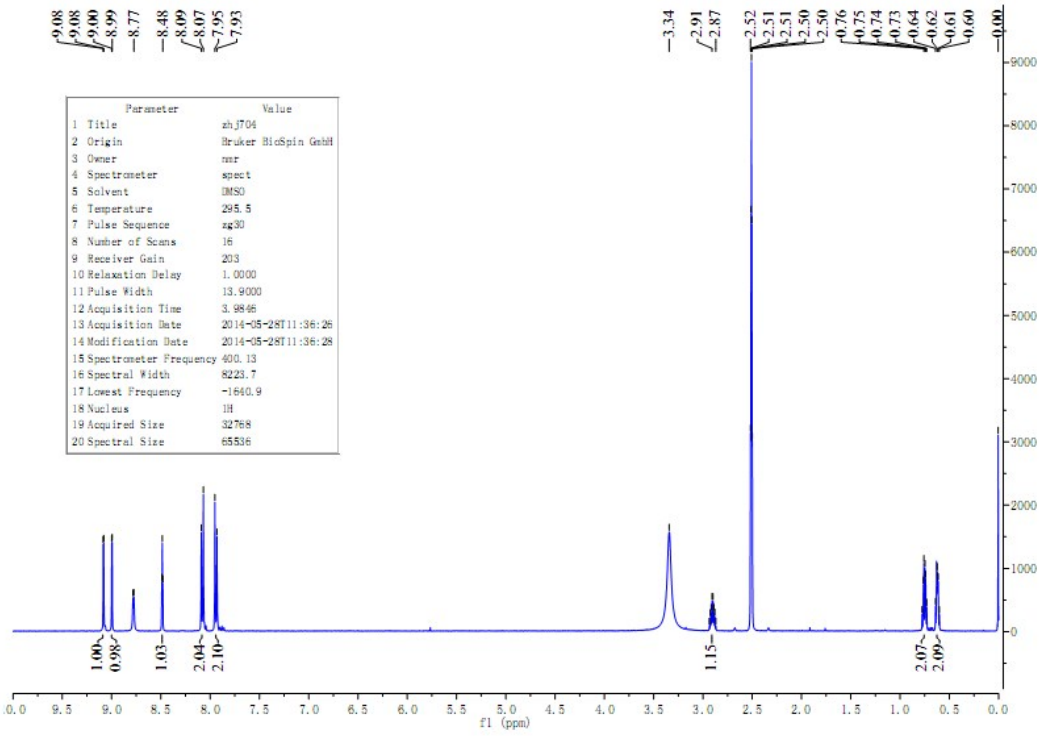




Mp 74-76 ºC; EI-MS (m/z) 326[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (d, $J$ = 2.2 Hz, 1H), 8.56 (d, $J$ = 1.9 Hz, 1H), 8.09 (t, $J$ = 2.1 Hz, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.93 (d, $J$ = 8.4 Hz, 2H), 1.63-1.03 (m, 14H).

**4-{5-[(cyclopropylamino)carbonyl]pyridin-3-yl}benzoic acid (6c)**

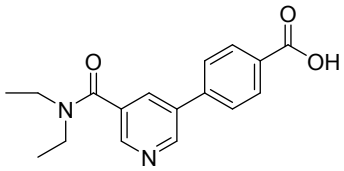


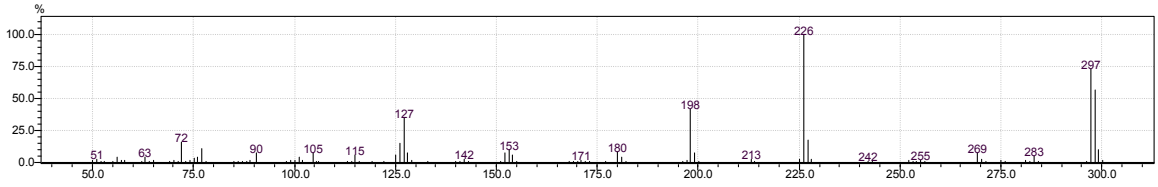



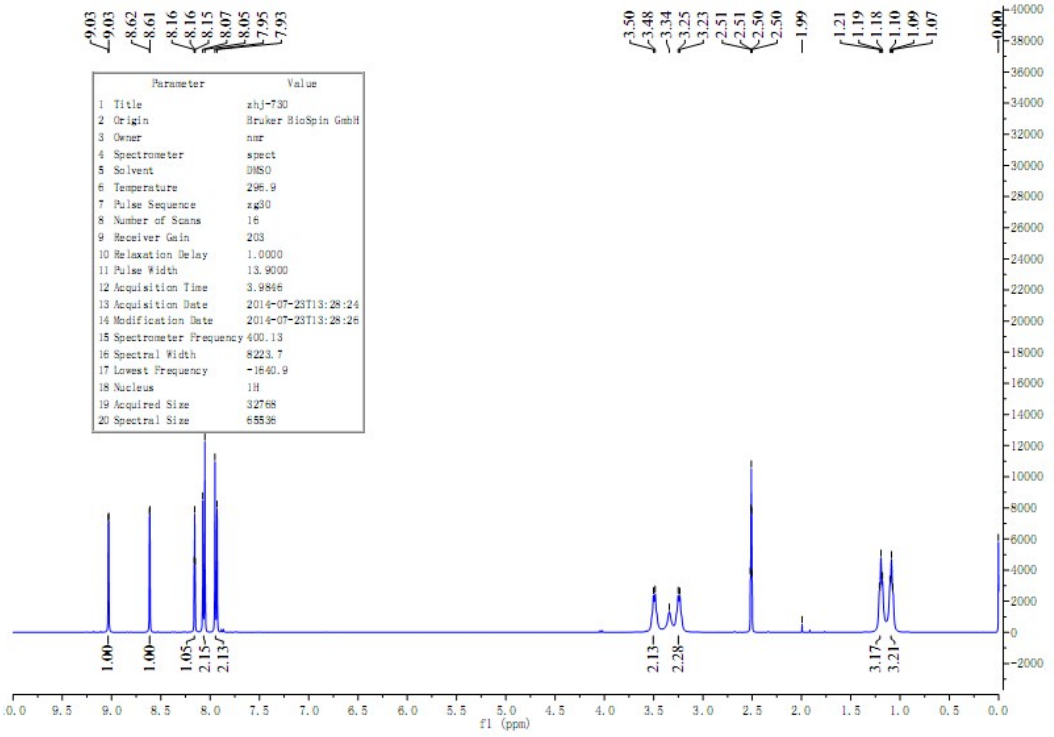




Mp 258-260 ºC; EI-MS (m/z) 282[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.08 (d, $J$ = 2.2 Hz, 1H), 9.00 (d, $J$ = 2.0 Hz, 1H), 8.49 (t, $J$ = 2.1 Hz, 1H), 8.08 (d, $J$ = 8.4 Hz, 2H), 7.94 (d, $J$ = 8.4 Hz, 2H), 2.97-2.85 (m, 1H), 0.73-0.78 (m, 2H), 0.67-0.58 (m, 2H).

**4-{5-[(diethylamino)carbonyl]pyridin-3-yl}benzoic acid (6d)**

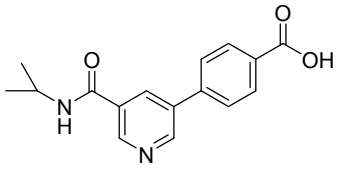


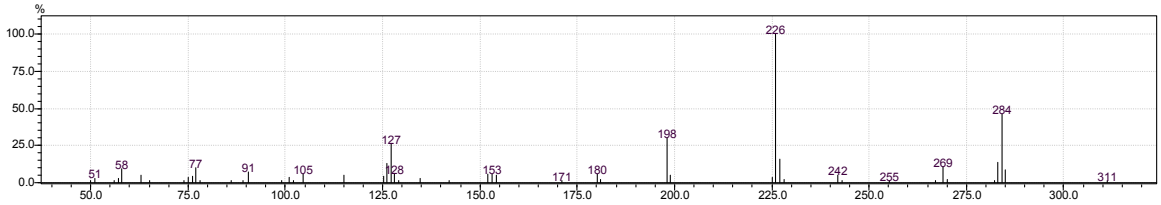



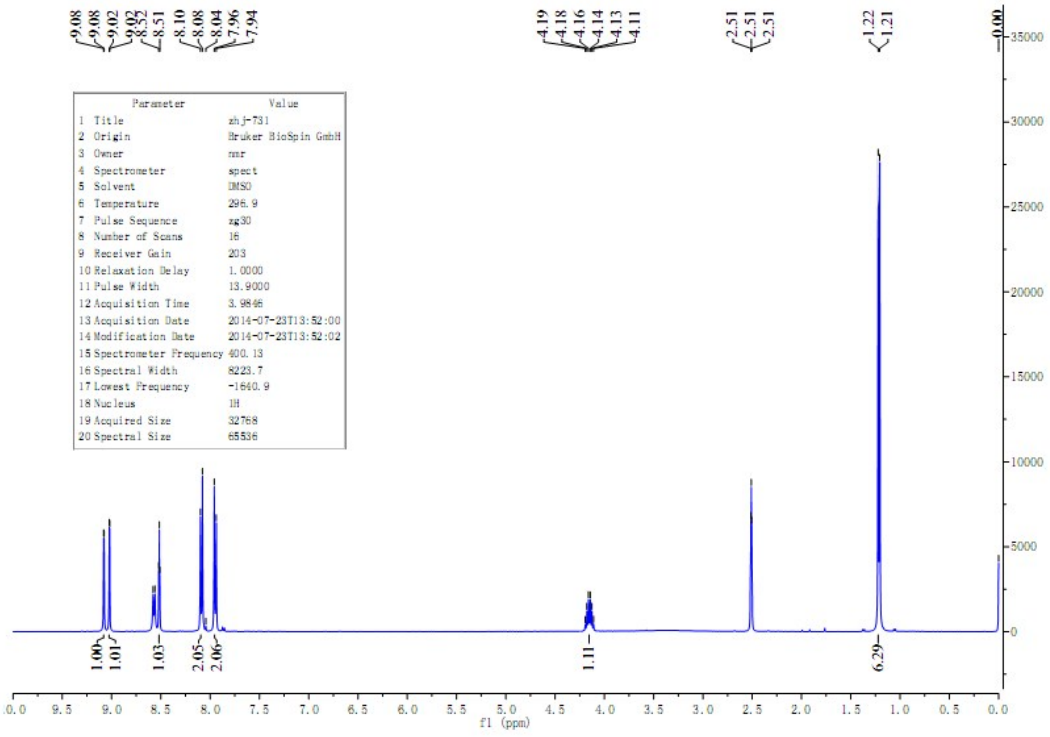




Mp 235-236 ºC; EI-MS (m/z) 298[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.03 (d, $J$ = 2.2 Hz, 1H), 8.61 (d, $J$ = 1.9 Hz, 1H), 8.16 (t, $J$ = 2.1 Hz, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.94 (d, $J$ = 8.4 Hz, 2H), 3.49 (q, $J$ = 6.6 Hz, 2H), 3.24 (q, $J$ = 6.5 Hz, 2H), 1.19 (t, $J$ = 6.1 Hz, 3H), 1.09 (t, $J$ = 6.0 Hz, 3H).

**4-{5-[(isopropylamino)carbonyl]pyridin-3-yl}benzoic acid (6e)**

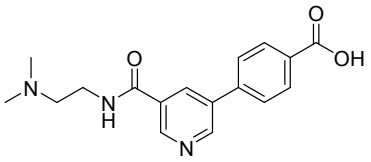


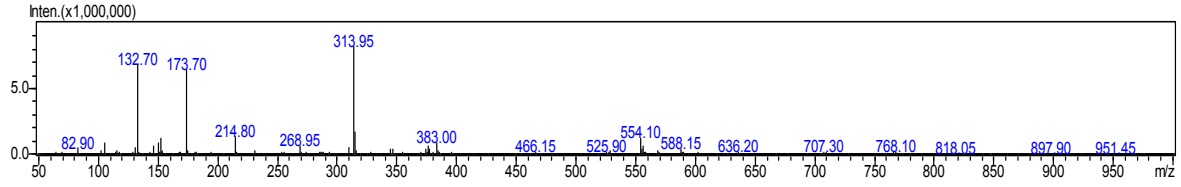



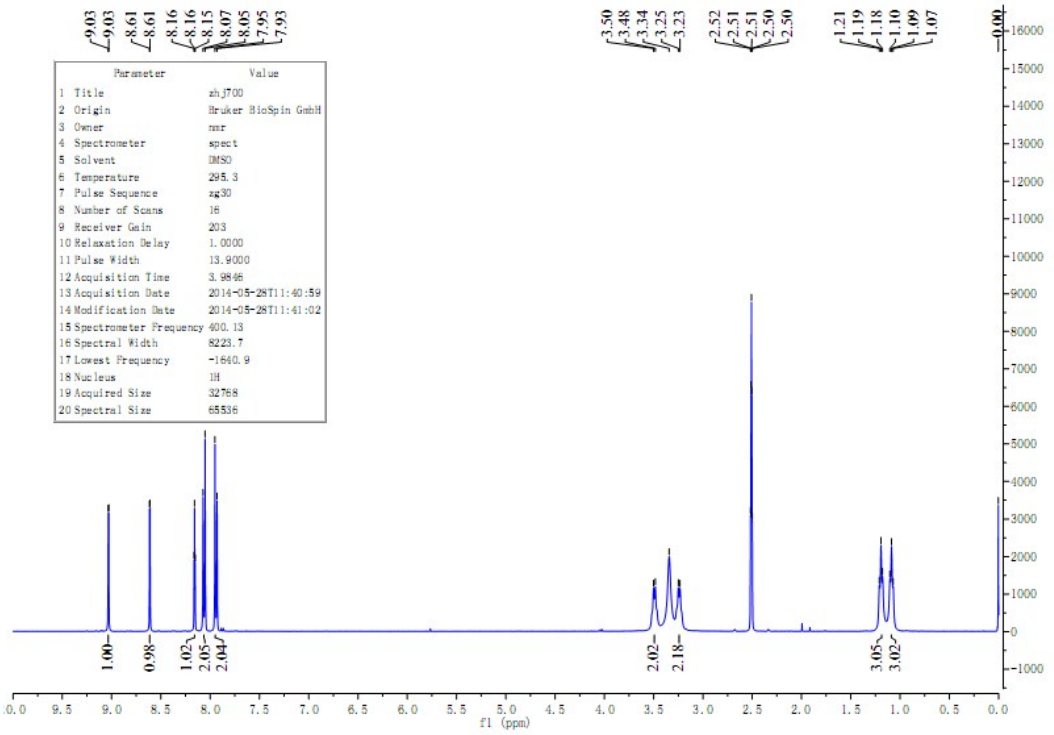




Mp 290-291 ºC; EI-MS (m/z) 284[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.08 (d, $J$ = 2.1 Hz, 1H), 9.02 (d, $J$ = 2.0 Hz, 1H), 8.52 (t, $J$ = 2.1 Hz, 1H), 8.09 (d, $J$ = 8.4 Hz, 2H), 7.95 (d, $J$ = 8.3 Hz, 2H), 4.11-4.19 (m, 1H), 1.21 (d, $J$ = 6.6 Hz, 6H).

**4-[5-({[2-(dimethylamino)ethyl]amino}carbonyl)pyridin-3-yl]benzoic acid (6f)**

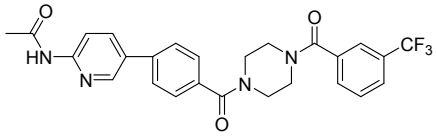


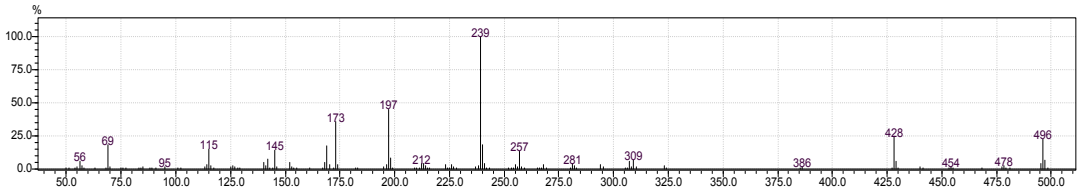



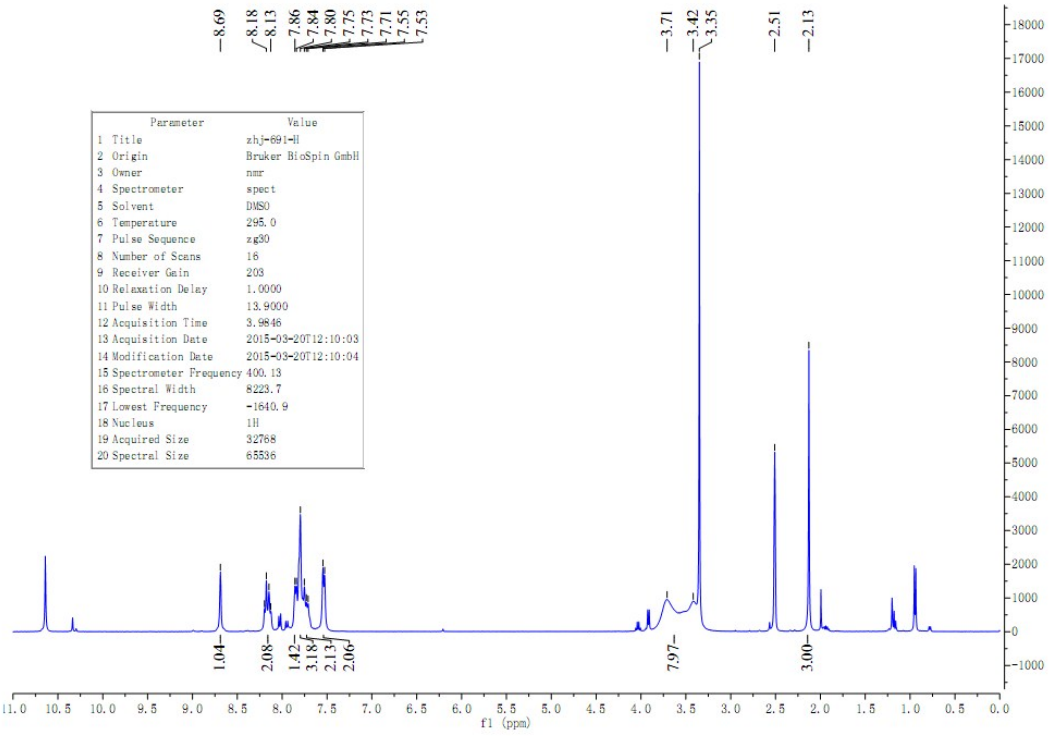




Mp 160-162 ºC; EI-MS (m/z) 313.95$[M+H]^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.03 (d, $J$ = 2.2 Hz, 1H), 8.61 (d, $J$ = 1.9 Hz, 1H), 8.16 (t, $J$ = 2.1 Hz, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.94 (d, $J$ = 8.5 Hz, 2H), 3.49 (d, $J$ = 6.9 Hz, 2H), 3.24 (d, $J$ = 6.9 Hz, 2H), 1.19 (t, $J$ = 6.2 Hz, 3H), 1.09 (t, $J$ = 6.5 Hz, 3H).

***N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (8a)**

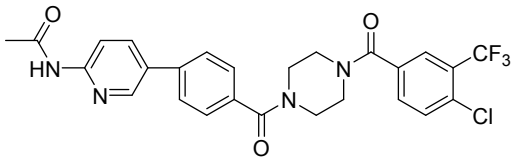


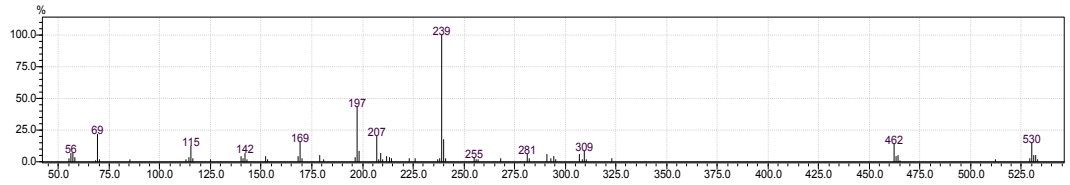


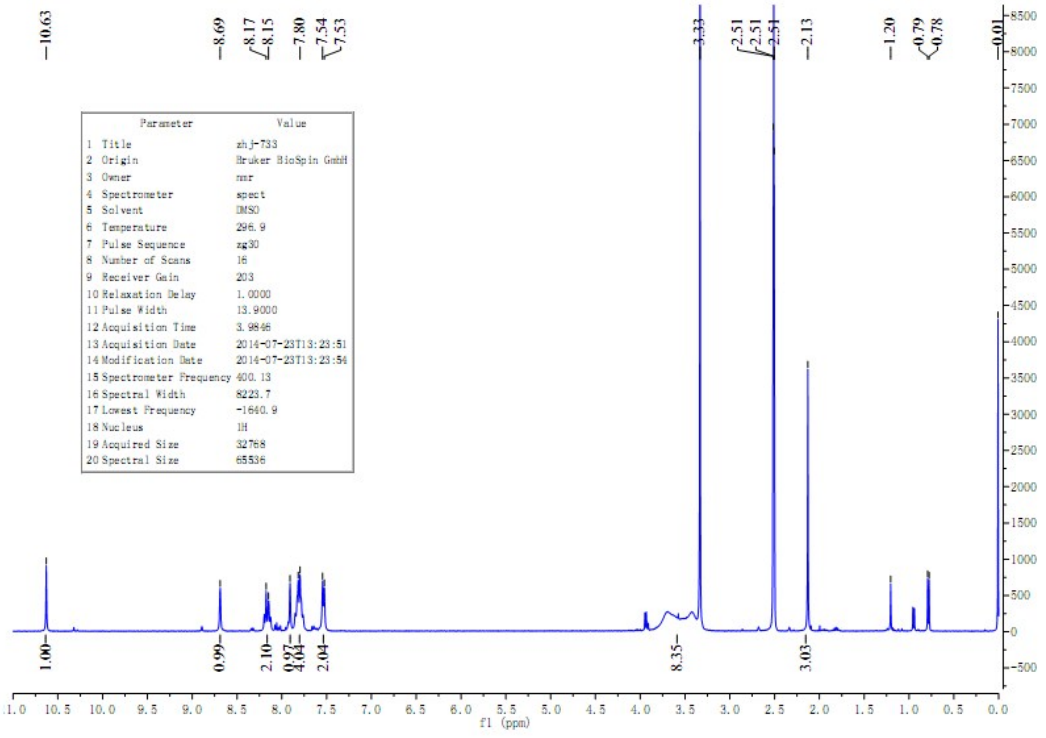



Mp 224-226ºC; EI-MS (m/z) 496[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.16 (d, $J$ = 11.7 Hz, 2H), 7.85 (d, $J$ = 6.7 Hz, 1H), 7.80 (s, 3H), 7.78 – 7.68 (m, 2H), 7.54 (d, $J$ = 7.4 Hz, 2H), 3.84-3.40 (m, 8H), 2.13 (s, 3H).

**_N_-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (8b)**

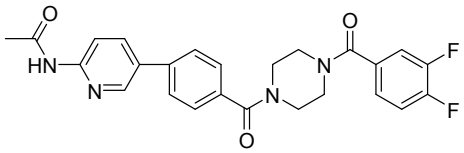


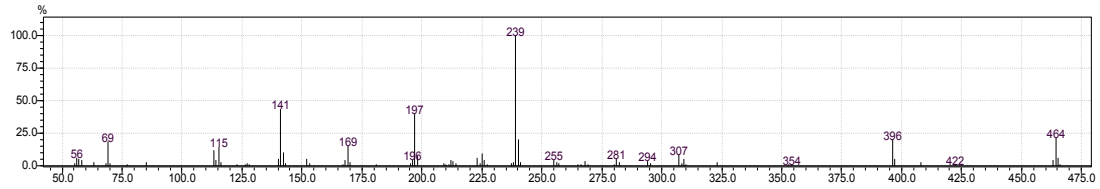



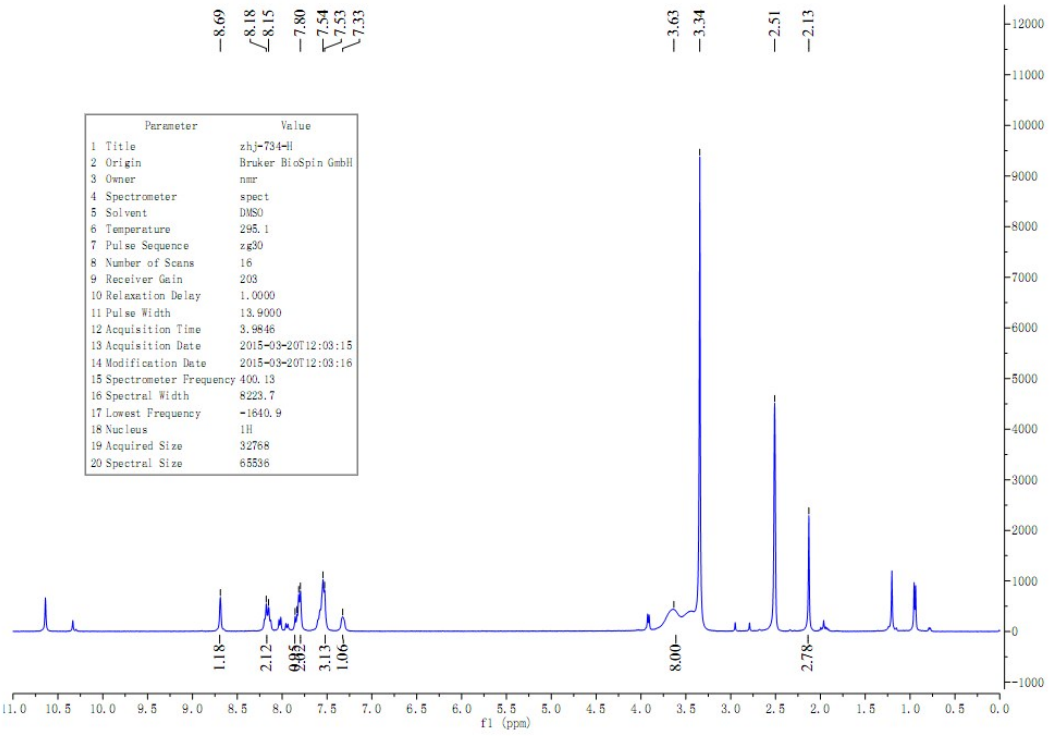




Mp 241-242ºC; EI-MS (m/z) 530[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.16 (d, $J$ = 10.7 Hz, 2H), 7.91 (s, 1H), 7.81 (d, $J$ = 8.0 Hz, 4H), 7.54 (d, $J$ = 7.7 Hz, 2H), 3.80-3.38 (m, 8H), 2.13 (s, 3H).

***N*-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (8c)**

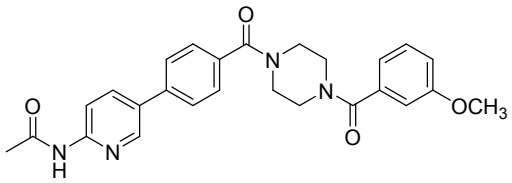


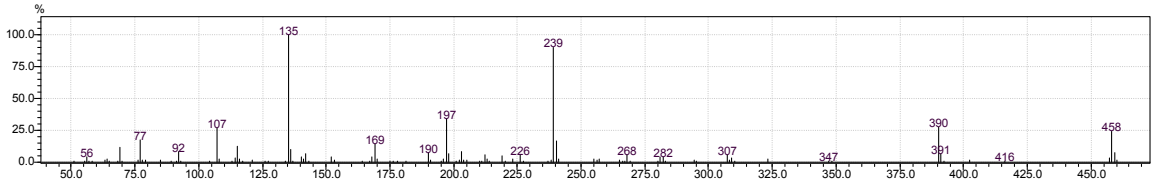


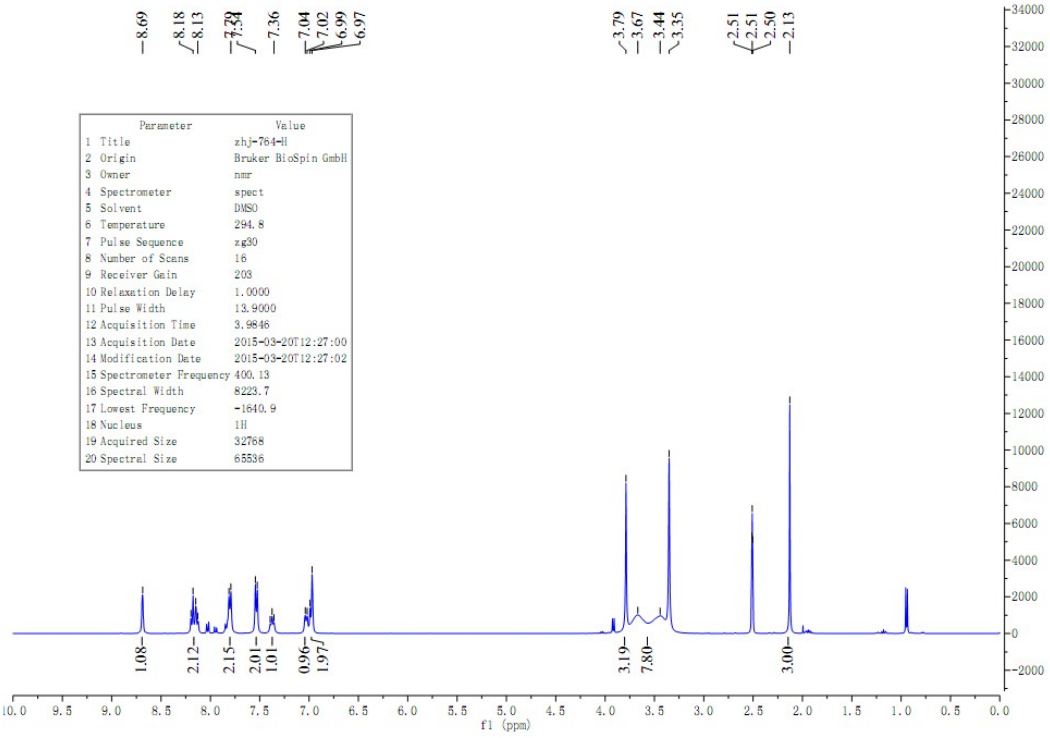



Mp 263-266ºC; EI-MS (m/z) 464[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.16 (d, $J$ = 10.1 Hz, 2H), 7.84 (d, $J$ = 8.5 Hz, 1H), 7.81 (d, $J$ = 7.7 Hz, 2H), 7.54 (d, $J$ = 7.1 Hz, 3H), 7.33 (s, 1H), 3.63 - 3.34 (m, 8H), 2.13 (s, 3H).

**N-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (8d)**

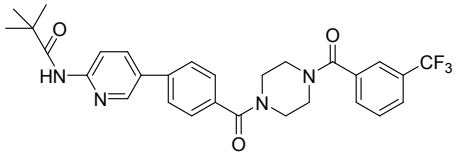


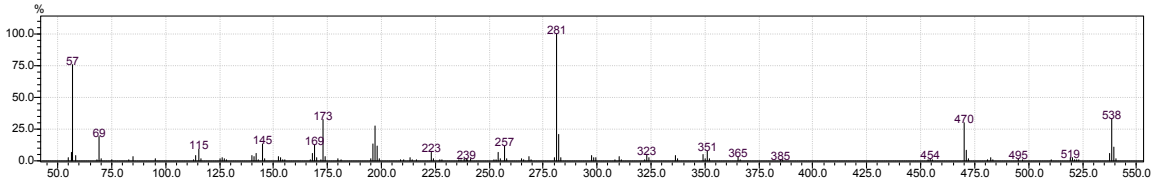


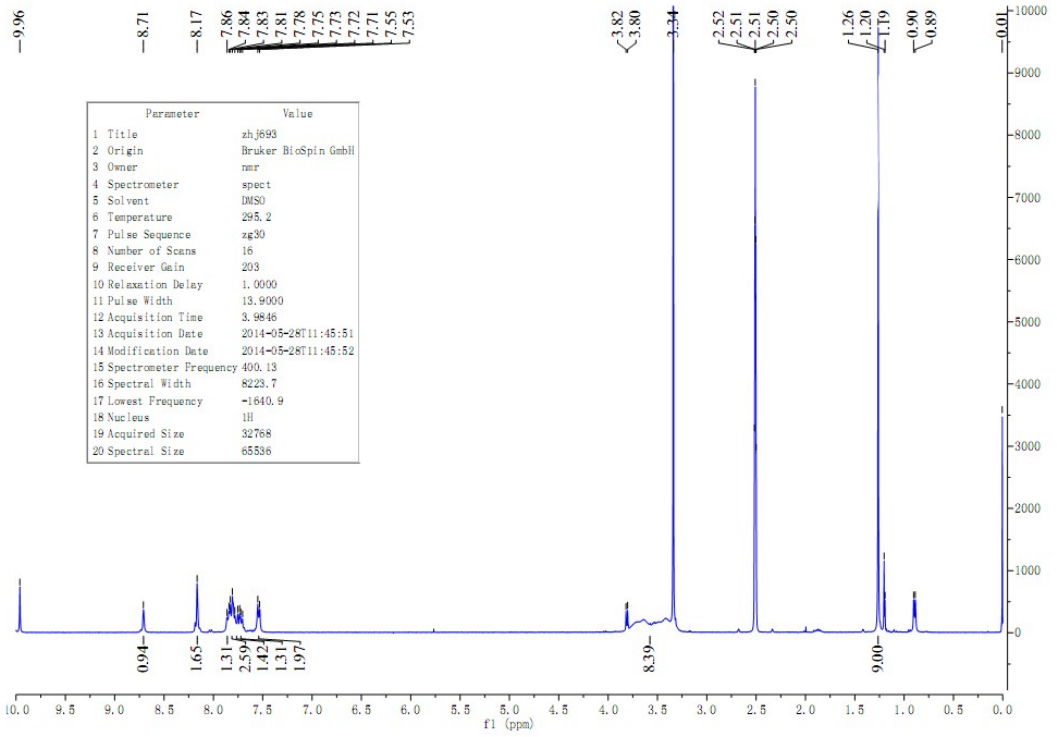



Mp 207-209ºC; EI-MS (m/z) 458[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.69 (s, 1H), 8.16 (d, $J$ = 10.8 Hz, 2H), 7.80 (d, $J$ = 7.8 Hz, 2H), 7.53 (d, $J$ = 7.9 Hz, 2H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.03 (d, $J$ = 7.7 Hz, 1H), 6.98 (d, $J$ = 7.9 Hz, 2H), 3.79 (s, 3H), 3.67 - 3.44 (m, 8H), 2.13 (s, 3H).

**2,2-dimethyl-*N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}propanamide (8e)**

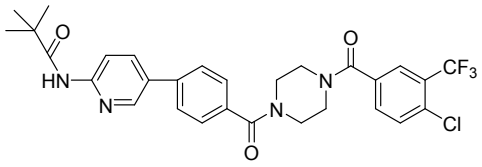


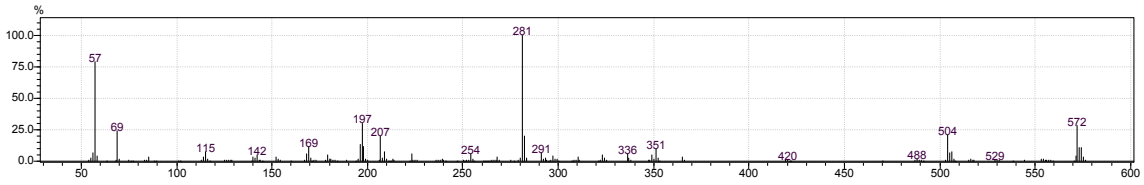



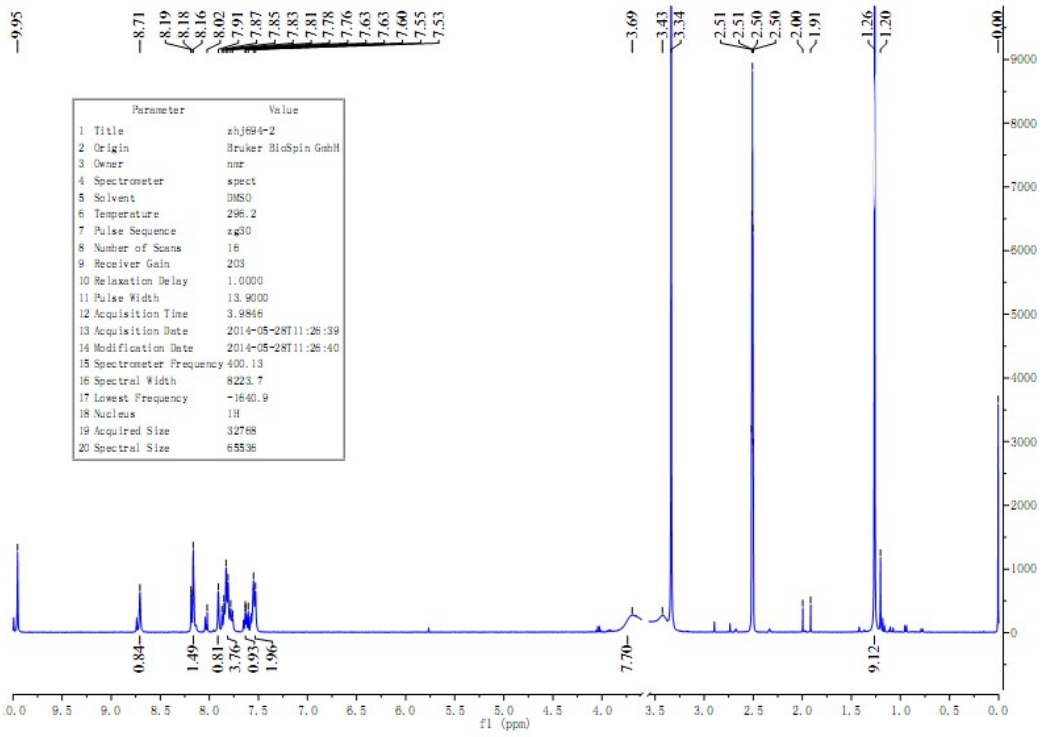




Mp 190-193ºC; EI-MS (m/z) 538[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.71 (s, 1H), 8.17 (s, 2H), 7.85 (d, $J$ = 7.7 Hz, 1H), 7.82 (d, $J$ = 8.4 Hz, 3H), 7.79-7.74 (m, 1H), 7.74-7.70 (m, 1H), 7.54 (d, $J$ = 6.8 Hz, 2H), 3.75-3.41 (m, 8H), 1.26 (s, 9H).

***N*-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}-2,2-dimethylpropanamide (8f)**

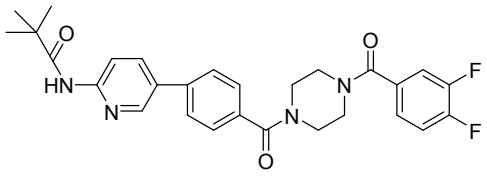


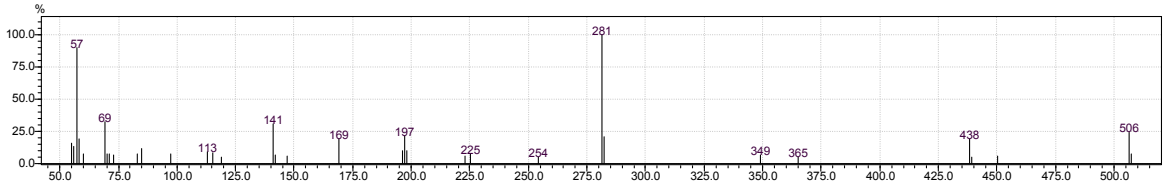


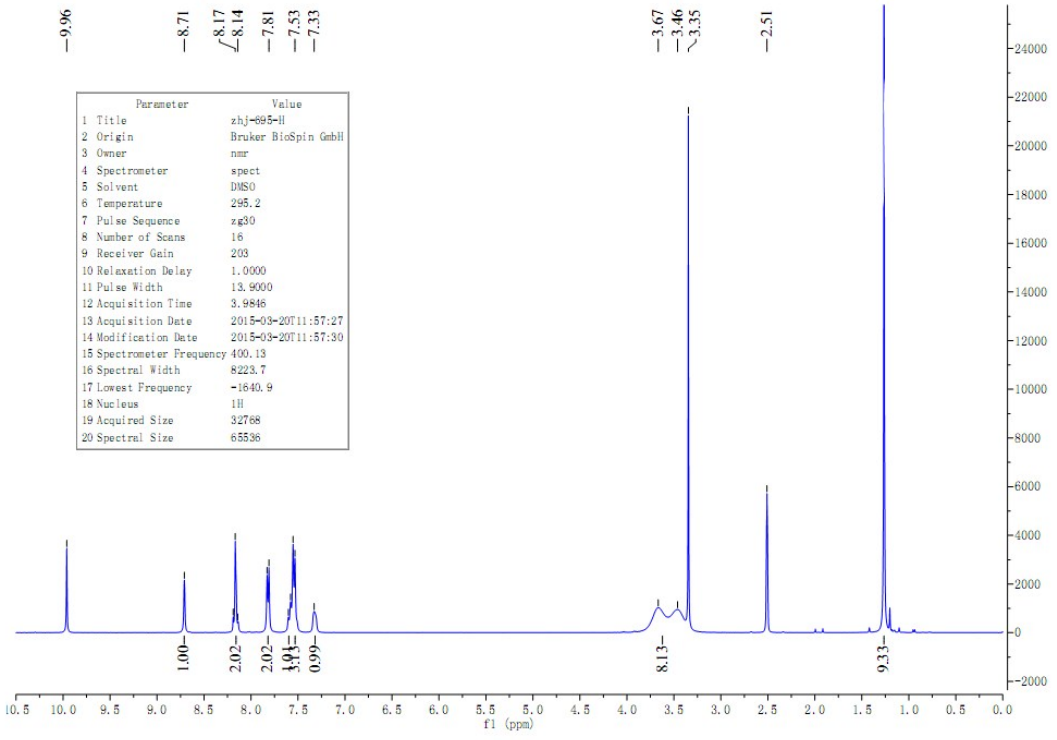



Mp 194-196ºC; EI-MS (m/z) 572[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.71 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.88-7.75 (m, 4H), 7.67-7.59 (m, 1H), 7.54 (d, $J$ = 7.9 Hz, 2H), 3.43-3.69 (m, 8H), 1.26 (s, 9H).

**_N_-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide(8g)**

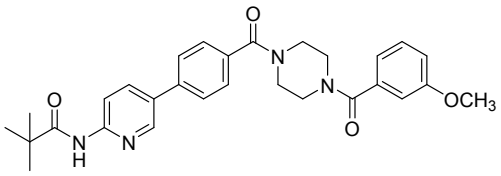


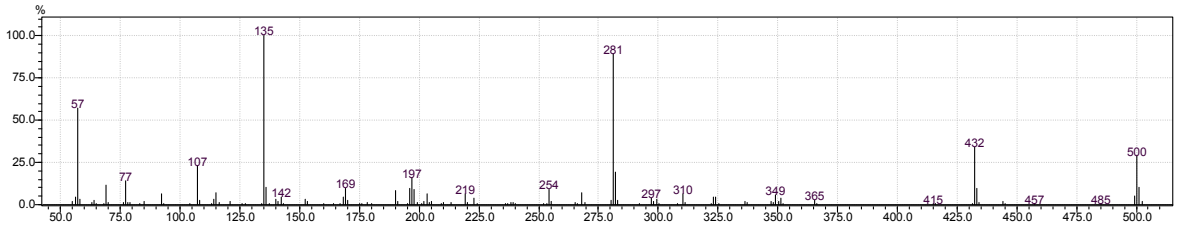



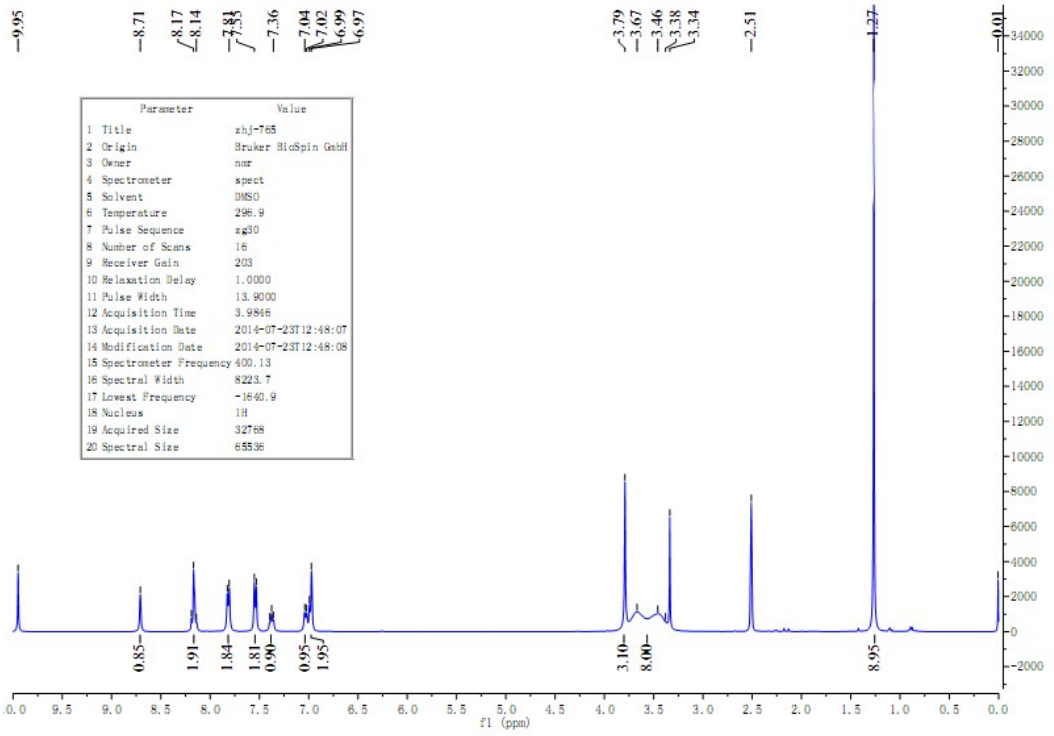




Mp 191-193ºC; EI-MS (m/z) 506[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.71 (s, 1H), 8.17 (s, 2H), 7.82 (d, $J$ = 7.9 Hz, 2H), 7.59 (d, $J$ = 9.5 Hz, 1H), 7.54 (d, $J$ = 8.0 Hz, 3H), 7.33 (s, 1H), 3.67- 3.46 (m, 8H), 1.26 (s, 9H).

***N*-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide (8h)**

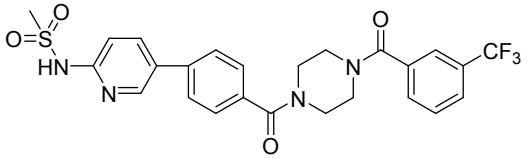


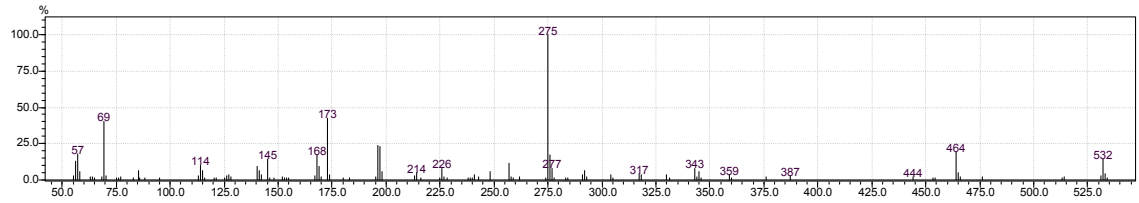


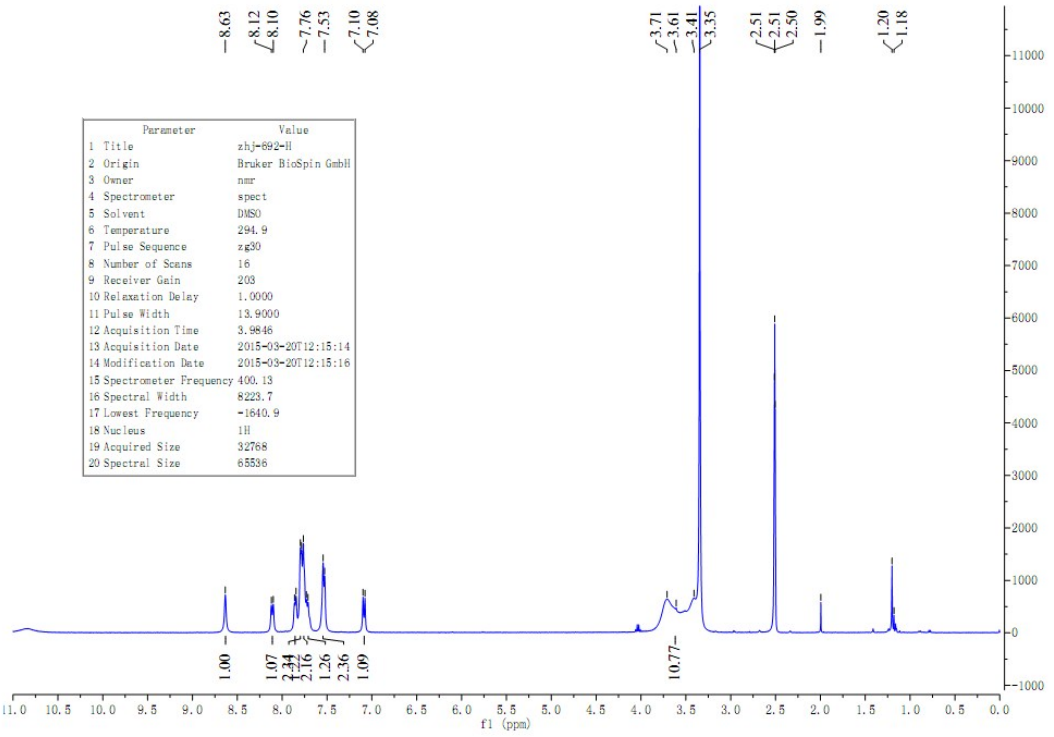




Mp 176-177ºC; EI-MS (m/z) 500[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.71 (s, 1H), 8.21-8.12 (m, 2H),, 7.82 (d, $J$ = 7.7 Hz, 2H), 7.54 (d, $J$ = 7.9 Hz, 2H), 7.38 (t, $J$ = 7.4 Hz, 1H), 7.03 (d, $J$ = 7.7 Hz, 1H), 6.98 (d, $J$ = 7.9 Hz, 2H), 3.79 (s, 3H), 3.77-3.36 (m, 8H), 1.27 (s, 9H).

*N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (**8i**)

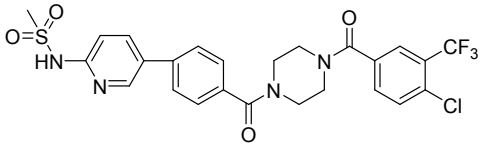


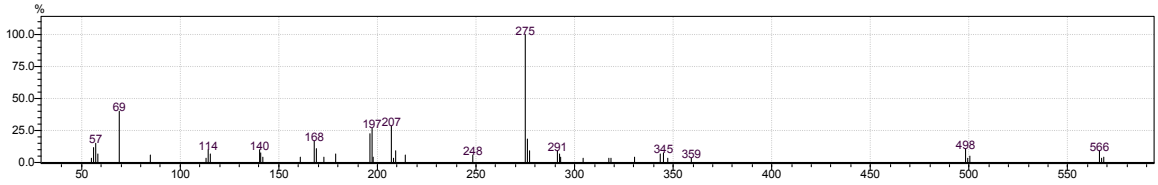


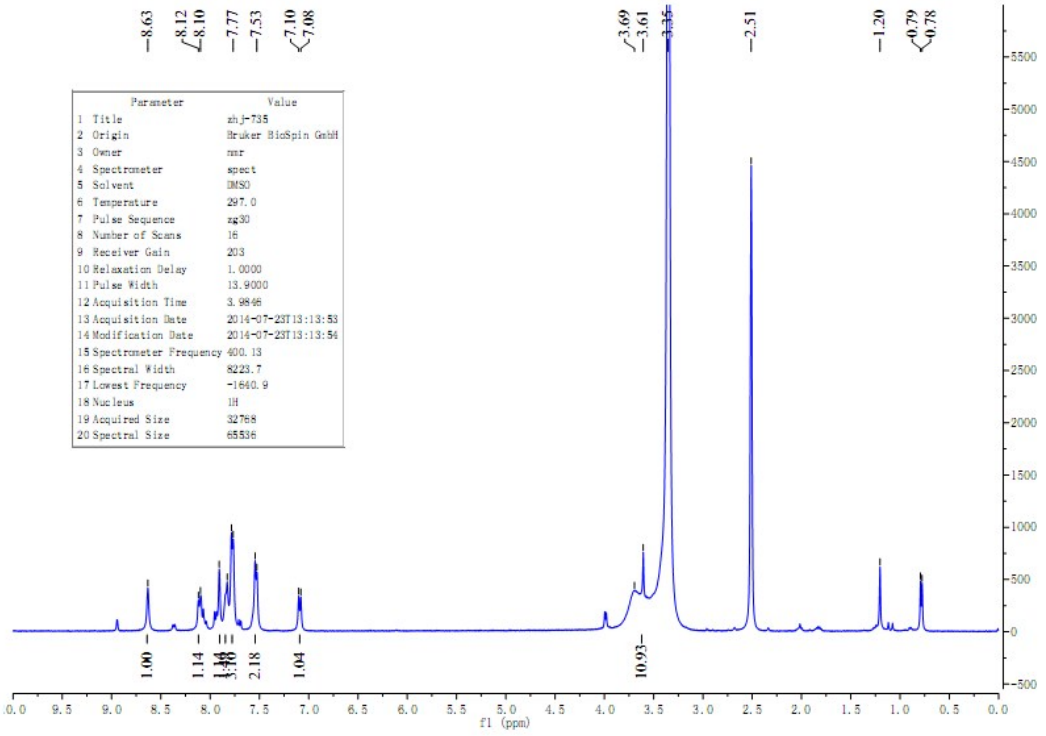



Mp 261-263ºC; EI-MS (m/z) 532[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.11 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 6.7 Hz, 1H), 7.79 (d, $J$ = 4.9 Hz, 2H), 7.76 (s, 2H), 7.72 (d, $J$ = 7.4 Hz, 1H), 7.54 (d, $J$ = 7.1 Hz, 2H), 7.09 (d, $J$ = 8.7 Hz, 1H), 3.86 – 3.37 (m, 11H).

***N*-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (8j)**

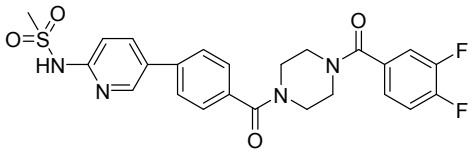


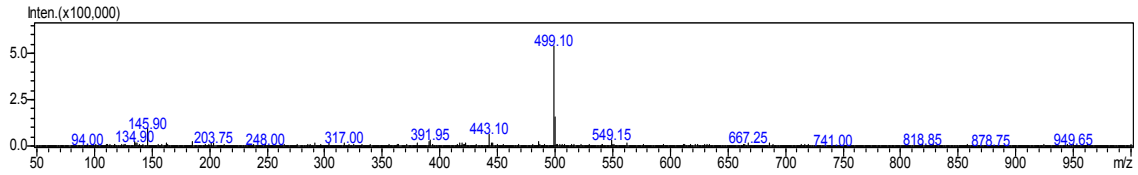


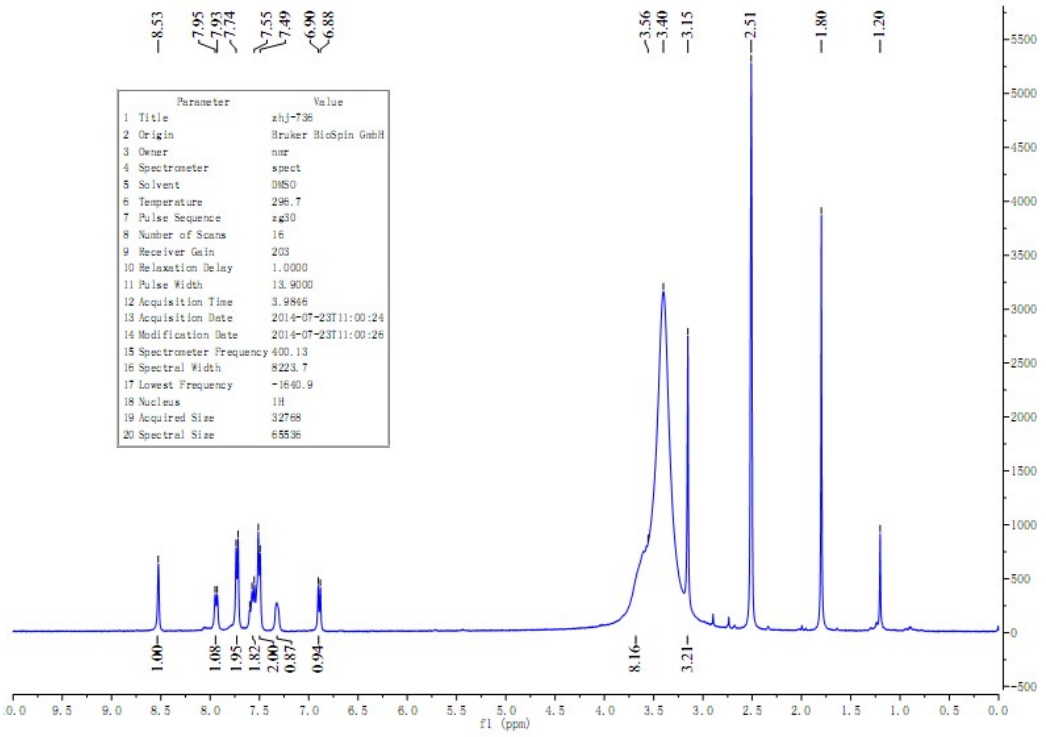




Mp 247-250ºC; EI-MS (m/z) 566[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.11 (d, $J$ = 8.4 Hz, 1H), 7.91 (s, 1H), 7.83 (s, 1H), 7.77 (d, $J$ = 6.9 Hz, 3H), 7.53 (d, $J$ = 7.2 Hz, 2H), 7.09 (d, $J$ = 8.6 Hz, 1H), 3.61 (s, 3H), 3.36-3.69 (m, 8H).

***N*-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide (8k)**

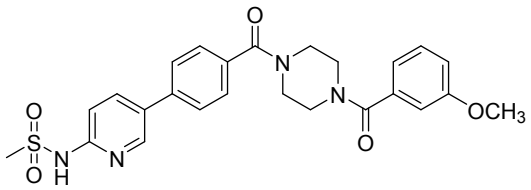


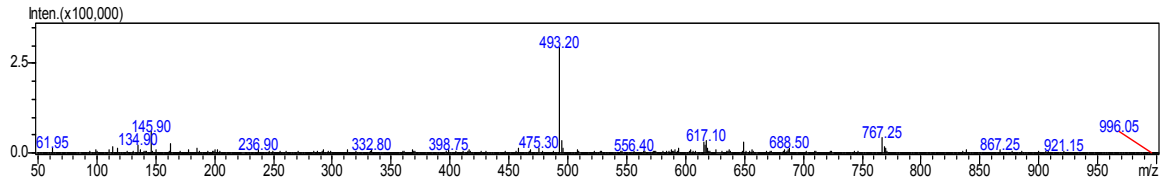


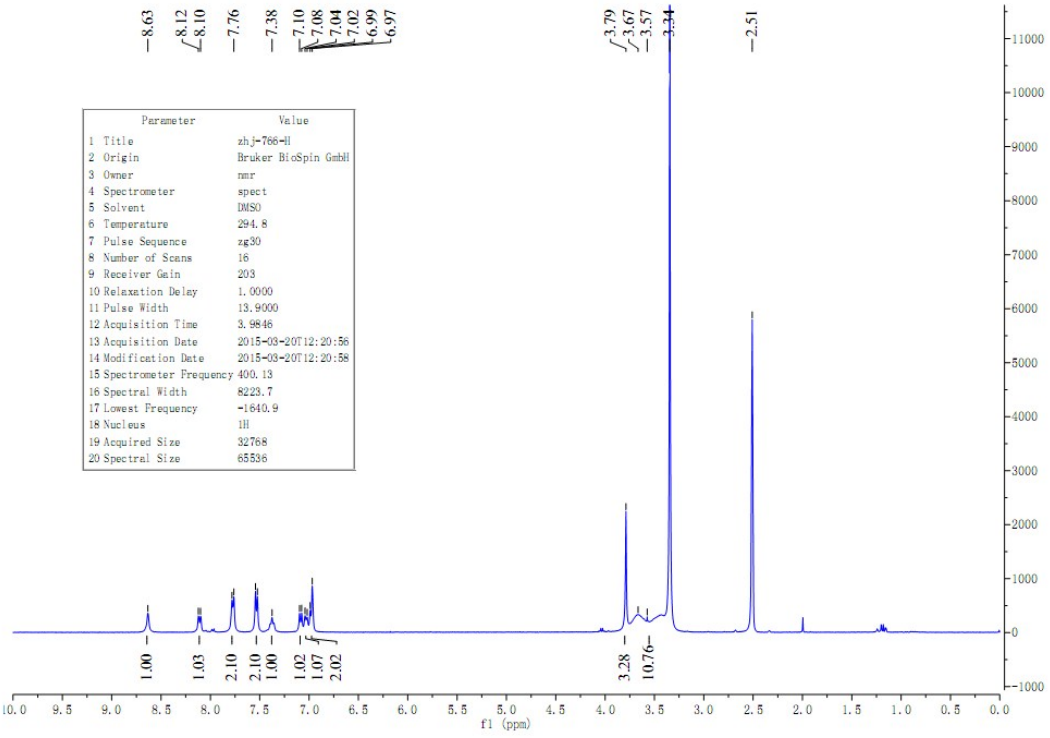




Mp 270-272ºC; EI-MS (m/z) 499.10[M-1]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.53 (s, 1H), 7.94 (d, $J$ = 8.4 Hz, 1H), 7.73 (d, $J$ = 7.8 Hz, 2H), 7.61-7.52 (m, 2H), 7.50 (d, $J$ = 7.6 Hz, 2H), 7.36-7.28 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 3.40-3.78 (m, 8H), 3.15 (s, 3H).

**_N_-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide (8l)**

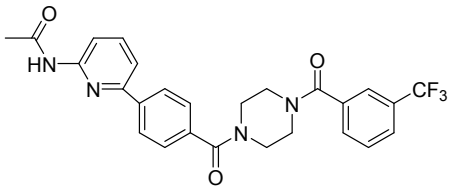


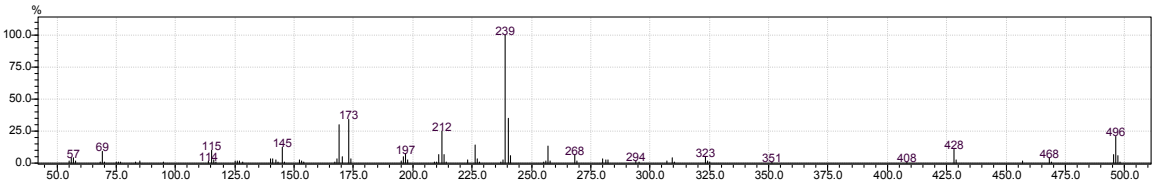


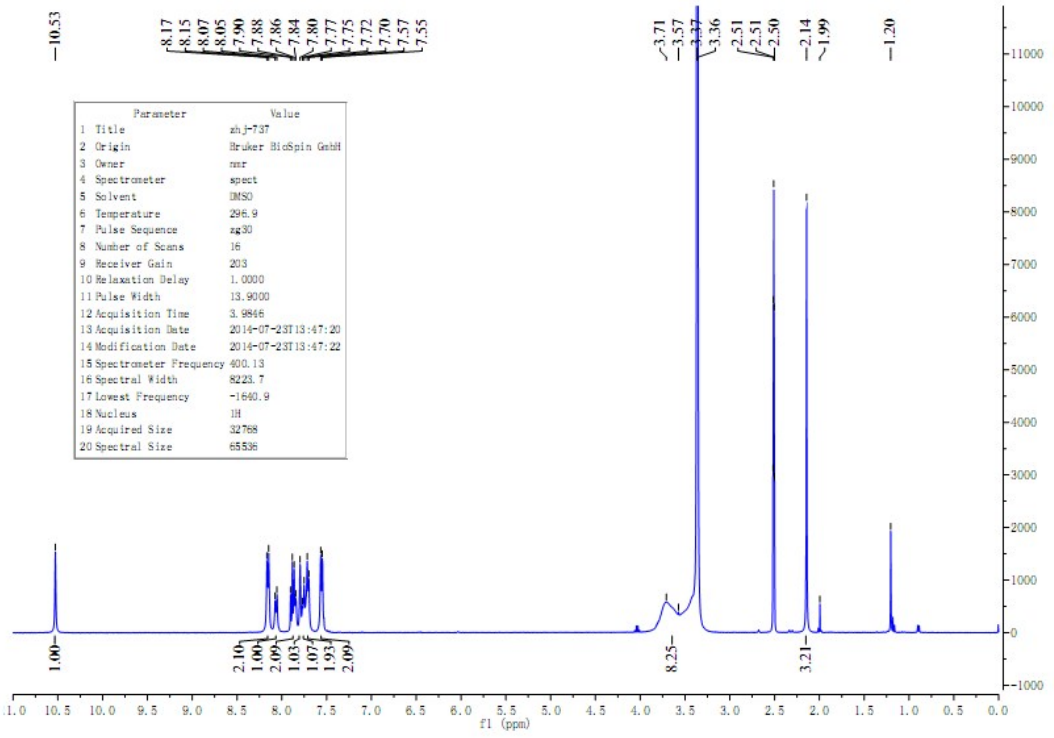




Mp 270-272ºC; EI-MS (m/z) 493.20[M-1]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.11 (d, $J$ = 8.8 Hz, 1H), 7.77 (d, $J$ = 7.7 Hz, 2H), 7.53 (d, $J$ = 7.8 Hz, 2H), 7.38 (s, 1H), 7.09 (d, $J$ = 8.7 Hz, 1H), 7.03 (d, $J$ = 8.5 Hz, 1H), 6.98 (d, $J$ = 8.2 Hz, 2H), 3.79 (s, 3H), 3.67 - 3.43 (m, 11H).

**_N_-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (9a)**

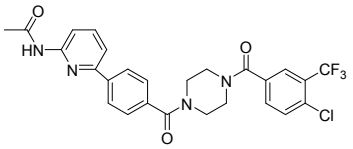


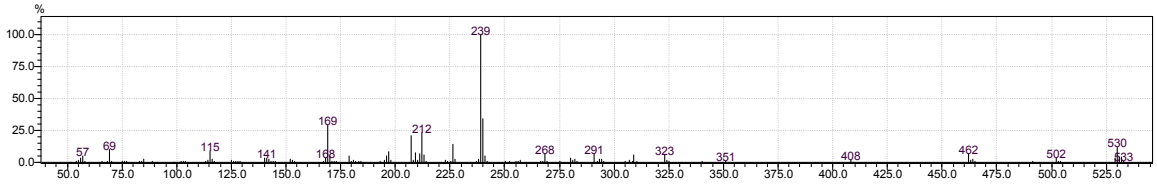



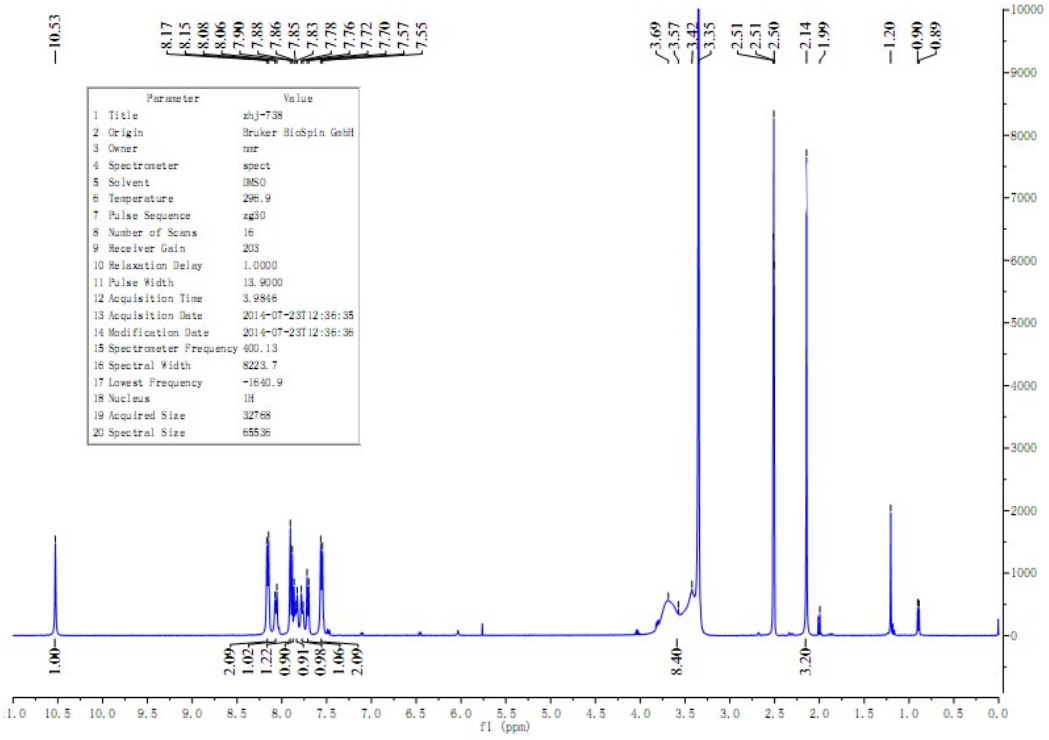




Mp 214-216ºC; EI-MS (m/z) 496 $[M]^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.16 (d, $J$ = 8.1 Hz, 2H), 8.06 (d, $J$ = 8.1 Hz, 1H), 7.87 (dd, $J$ = 15.7, 7.6 Hz, 2H), 7.80 (s, 1H), 7.76 (d, $J$ = 7.4 Hz, 1H), 7.71 (d, $J$ = 7.3 Hz, 2H), 7.56 (d, $J$ = 7.1 Hz, 2H), 3.37-3.71 (m, 8H), 2.14 (s, 3H).

**_N_-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (9b)**

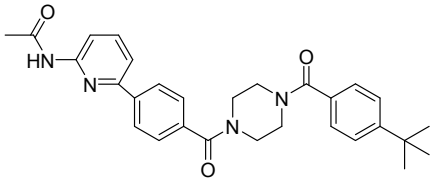


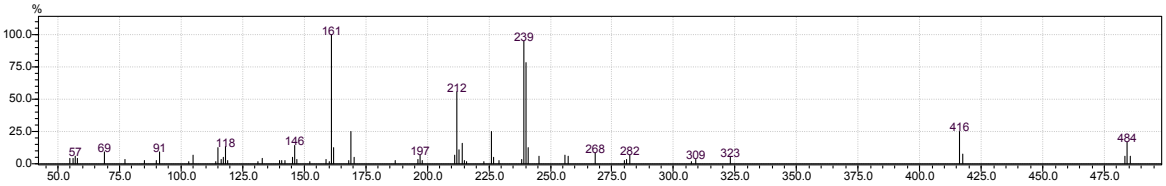


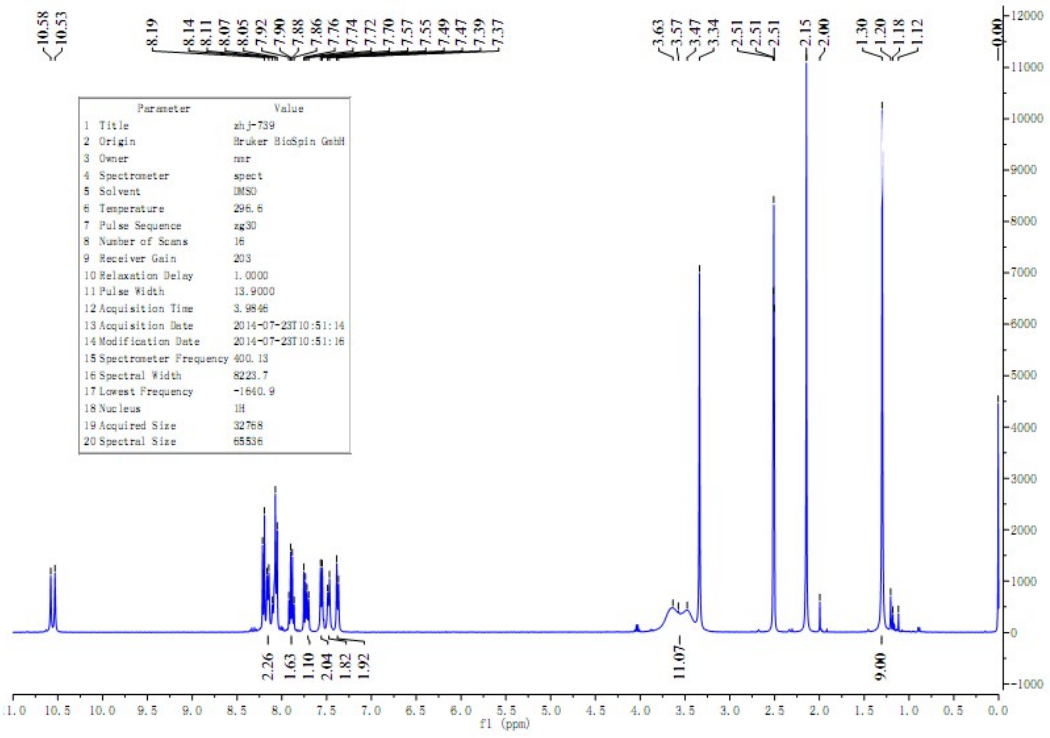


Mp 226-228ºC; EI-MS (m/z) 530[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.16 (d, $J$ = 8.1 Hz, 2H), 8.07 (d, $J$ = 8.0 Hz, 1H), 7.90 (s, 1H), 7.87 (d, $J$ = 8.1 Hz, 1H), 7.84 (d, $J$ = 7.9 Hz, 1H), 7.77 (d, $J$ = 8.1 Hz, 1H), 7.71 (d, $J$ = 7.6 Hz, 1H), 7.56 (d, $J$ = 7.9 Hz, 2H), 3.78-3.40 (m, 8H), 2.14 (s, 3H).

**_N_-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (9c)**

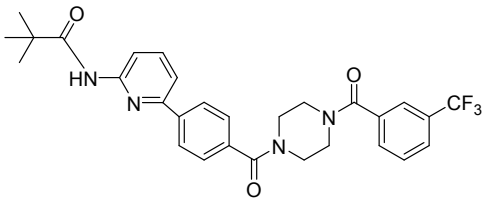


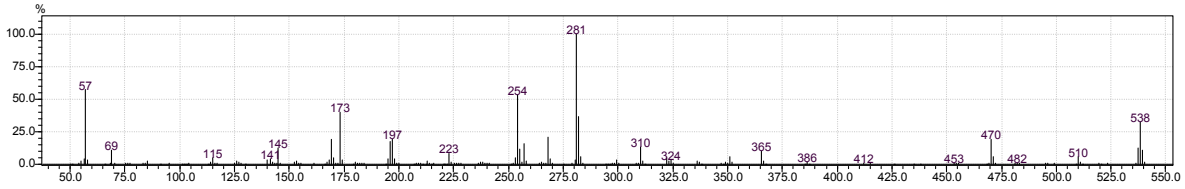


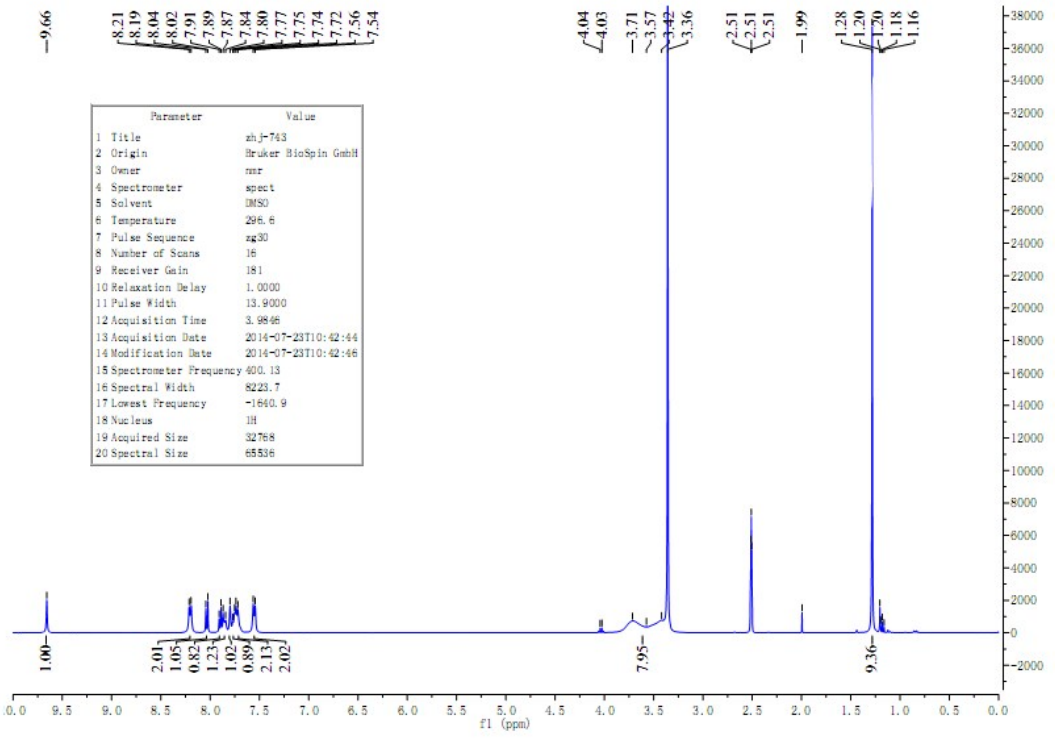




Mp 217-220ºC; EI-MS (m/z) 484[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.15 (d, $J$ = 8.0 Hz, 2H), 7.89 (d, $J$ = 7.8 Hz, 2H), 7.71 (d, $J$ = 7.7 Hz, 1H), 7.56 (d, $J$ = 8.0 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 2H), 7.38 (d, $J$ = 8.1 Hz, 2H), 3.47-3.63 (m, 8H), 3.34 (s, 3H), 1.30 (s, 9H).

**2,2-dimethyl-*N*-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}propanamide (9d)**



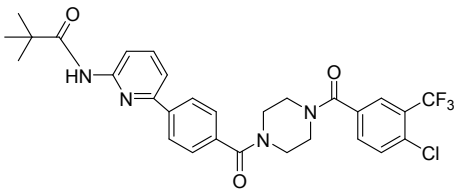


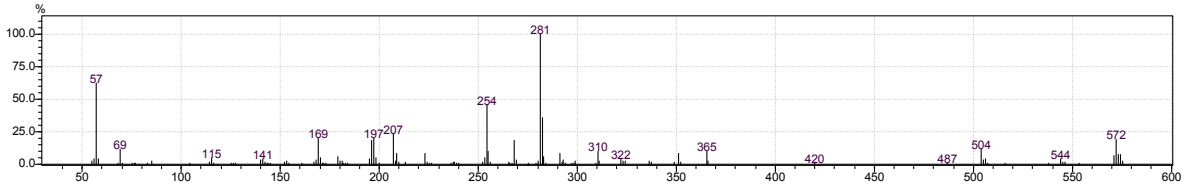


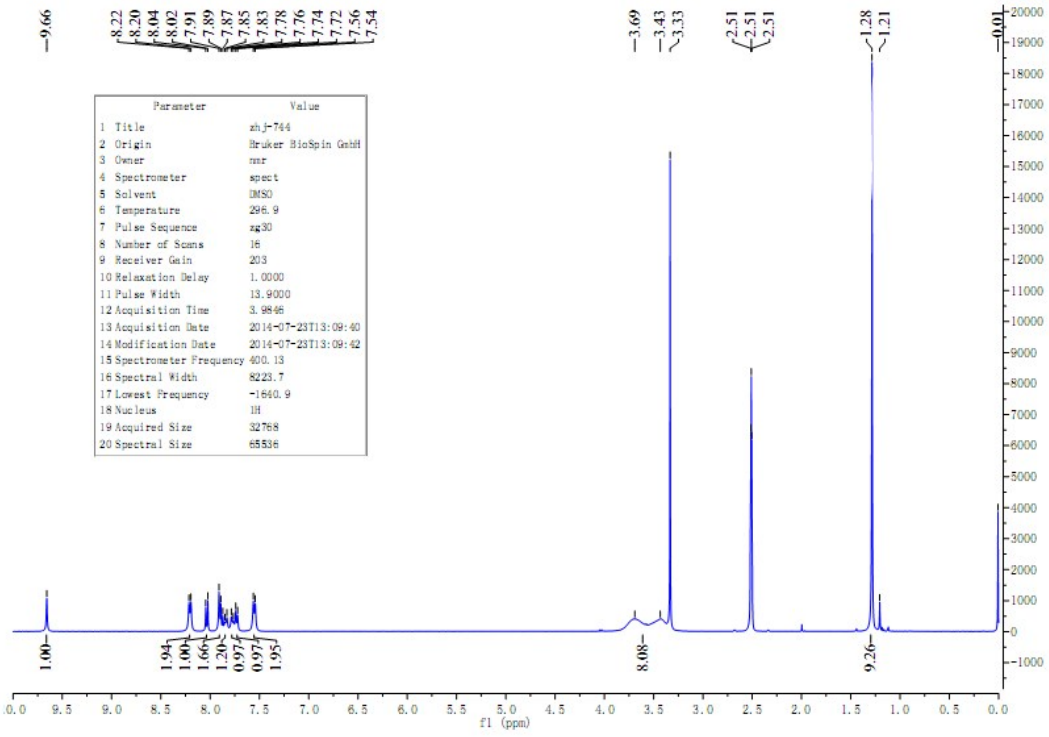
| Parameter | Value |
|---|---|
| 1 Title | zhj-743 |
| 2 Origin | Bruker BioSpin GmbH |
| 3 Owner | nmr |
| 4 Spectrometer | spect |
| 5 Solvent | DMSO |
| 6 Temperature | 296.6 |
| 7 Pulse Sequence | zg30 |
| 8 Number of Scans | 16 |
| 9 Receiver Gain | 181 |
| 10 Relaxation Delay | 1.0000 |
| 11 Pulse Width | 13.9000 |
| 12 Acquisition Time | 3.9846 |
| 13 Acquisition Date | 2014-07-23T10:42:44 |
| 14 Modification Date | 2014-07-23T10:42:46 |
| 15 Spectrometer Frequency | 400.13 |
| 16 Spectral Width | 8223.7 |
| 17 Lowest Frequency | -1640.9 |
| 18 Nucleus | 1H |
| 19 Acquired Size | 32768 |
| 20 Spectral Size | 65536 |

Mp 171-174ºC; EI-MS (m/z) 538[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.20 (d, $J$ = 8.0 Hz, 2H), 8.03 (d, $J$ = 8.2 Hz, 1H), 7.90 (d, $J$ = 7.8 Hz, 1H), 7.86 (d, $J$ = 9.9 Hz, 1H), 7.80 (s, 1H), 7.76 (d, $J$ = 7.5 Hz, 1H), 7.73 (d, $J$ = 7.5 Hz, 2H), 7.55 (d, $J$ = 7.5 Hz, 2H), 3.83-3.39 (m, 8H), 1.28 (s, 9H).

***N*-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}-2,2-dimethylpropanamide (9e)**

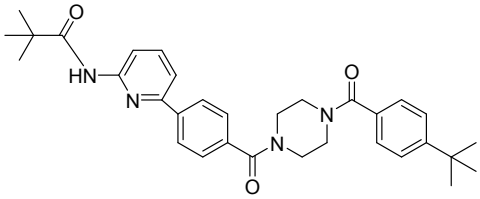


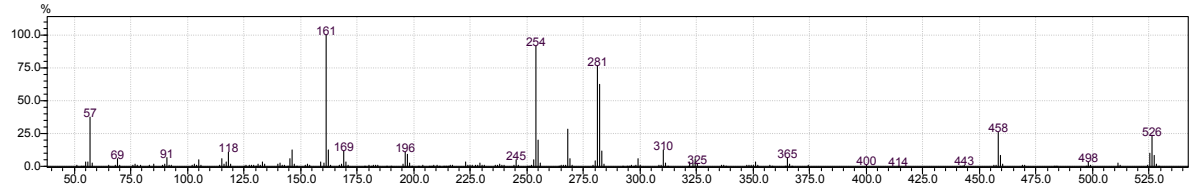



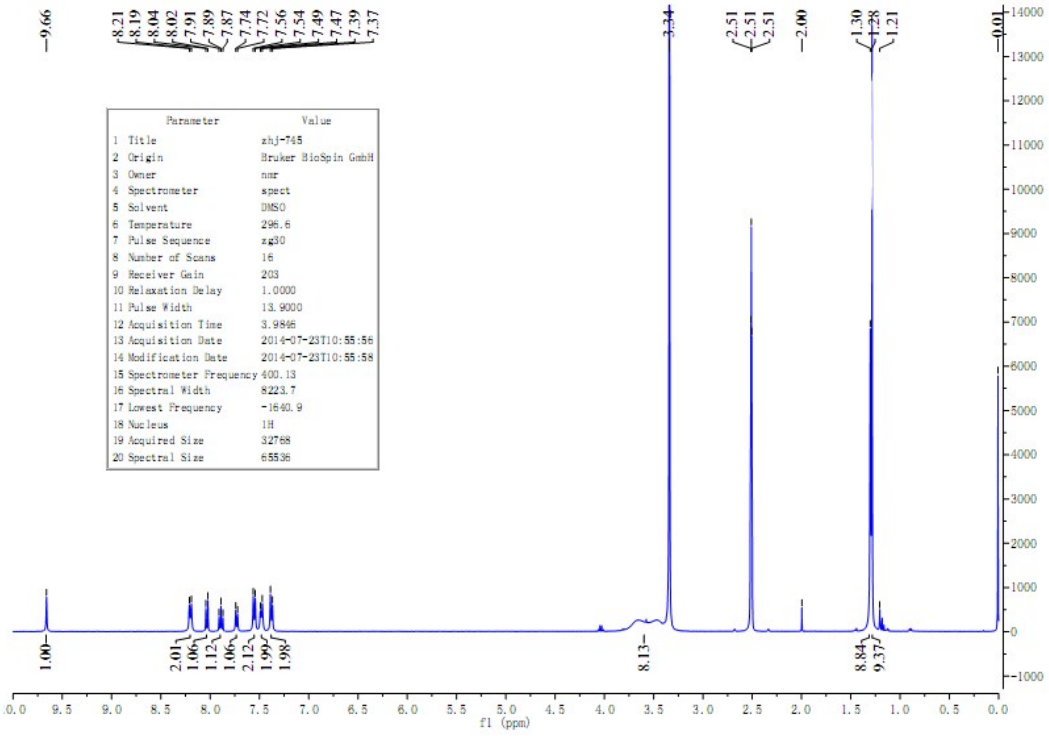




Mp 187-190ºC; EI-MS (m/z) 572[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.21 (d, $J$ = 7.9 Hz, 2H), 8.03 (d, $J$ = 8.2 Hz, 1H), 7.90 (d, $J$ = 7.7 Hz, 2H), 7.88-7.81 (m, 1H), 7.77 (d, $J$ = 7.8 Hz, 1H), 7.73 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 7.8 Hz, 2H), 3.43-3.69 (m, 8H), 1.28 (s, 9H).

***N*-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide (9f)**

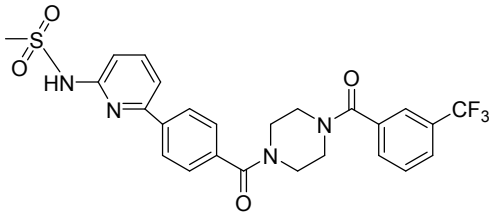


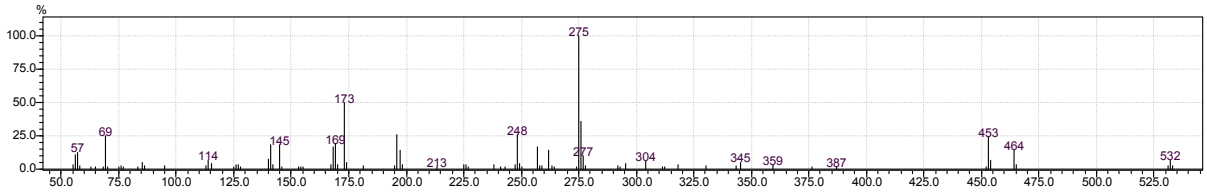


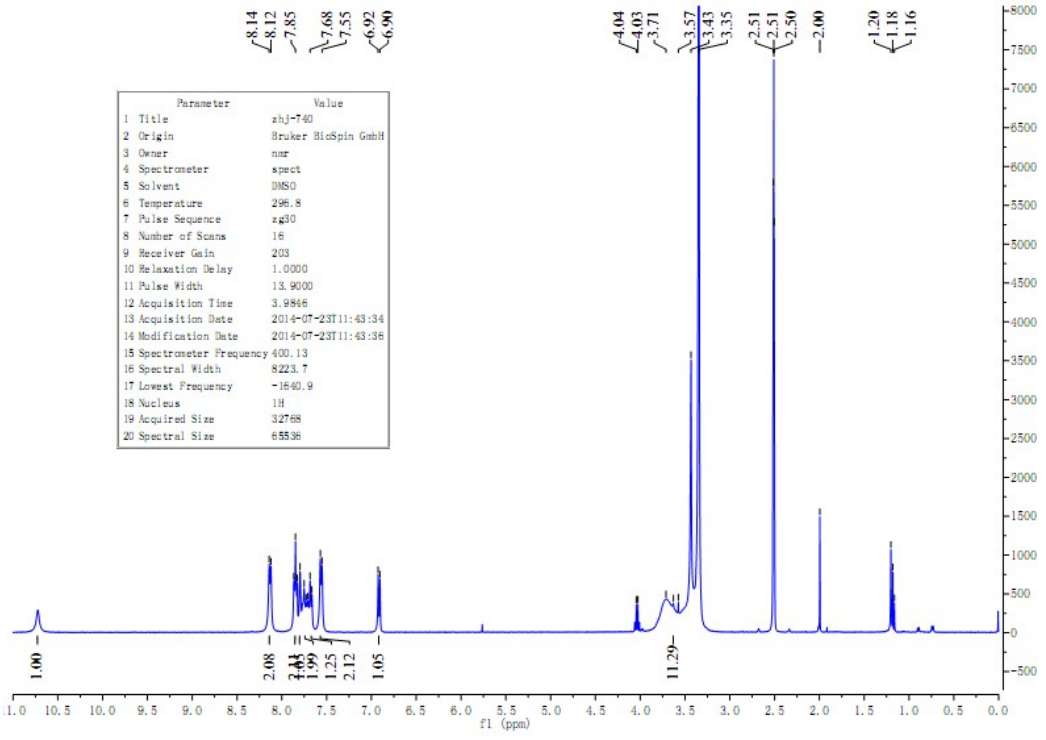



Mp 237-240ºC; EI-MS (m/z) 526[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.20 (d, $J$ = 7.9 Hz, 2H), 8.03 (d, $J$ = 8.2 Hz, 1H), 7.89 (t, $J$ = 8.0 Hz, 1H), 7.73 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 8.1 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 3.78-3.42 (m, 8H), 1.30 (s, 9H), 1.28 (s, 9H).

***N*-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (9g)**



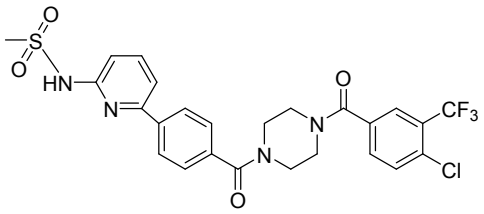


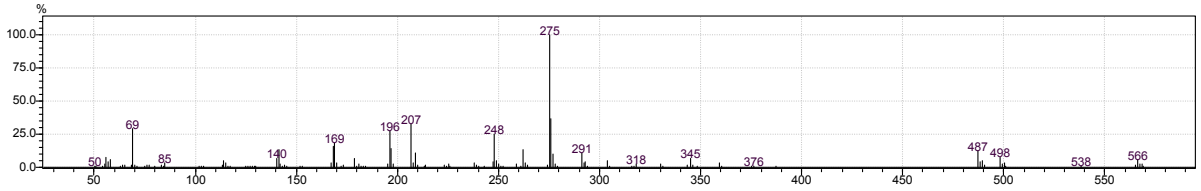


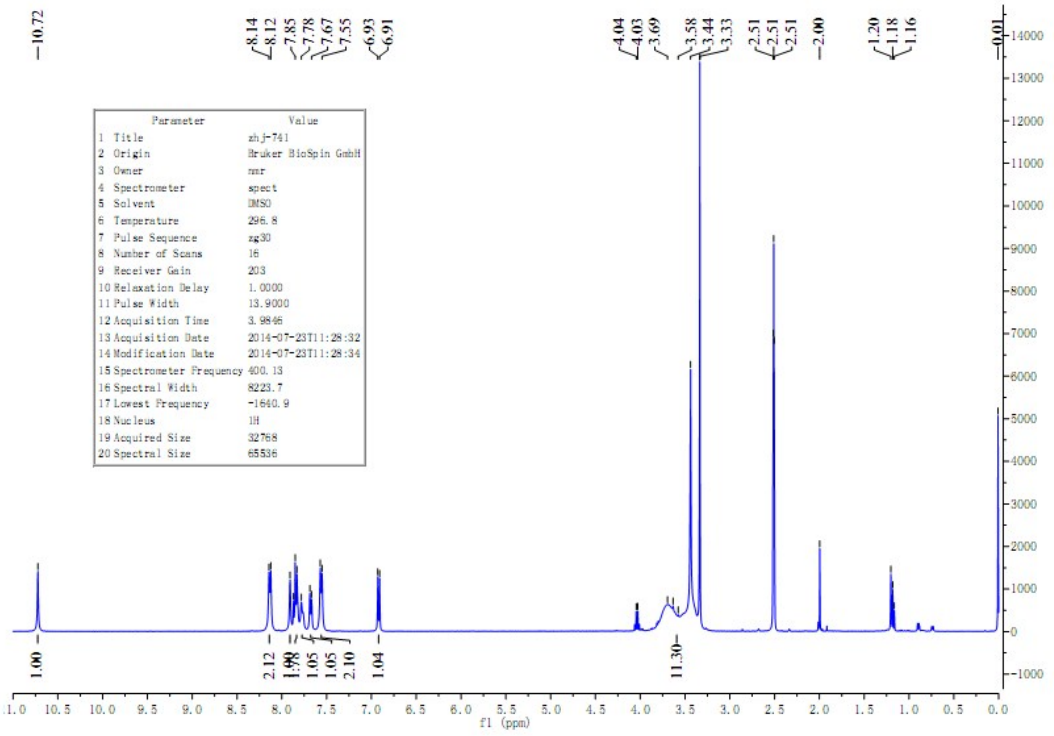
| Parameter | Value |
|---|---|
| 1 Title | zhj-740 |
| 2 Origin | Bruker BioSpin GmbH |
| 3 Owner | nmr |
| 4 Spectrometer | spect |
| 5 Solvent | DMSO |
| 6 Temperature | 296.8 |
| 7 Pulse Sequence | zg30 |
| 8 Number of Scans | 16 |
| 9 Receiver Gain | 203 |
| 10 Relaxation Delay | 1.0000 |
| 11 Pulse Width | 13.9000 |
| 12 Acquisition Time | 3.9846 |
| 13 Acquisition Date | 2014-07-23T11:43:34 |
| 14 Modification Date | 2014-07-23T11:43:36 |
| 15 Spectrometer Frequency | 400.13 |
| 16 Spectral Width | 8223.7 |
| 17 Lowest Frequency | -1640.9 |
| 18 Nucleus | 1H |
| 19 Acquired Size | 32768 |
| 20 Spectral Size | 65536 |

Mp 243-244ºC; EI-MS (m/z) 532[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.13 (d, $J$ = 8.1 Hz, 2H), 7.85 (t, $J$ = 7.8 Hz, 2H), 7.80 (s, 1H), 7.79-7.70 (m, 2H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.56 (d, $J$ = 7.1 Hz, 2H), 6.91 (d, $J$ = 8.1 Hz, 1H), 3.43 (s, 3H), 3.44-3.71(m, 8H).

***N*-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (9h)**

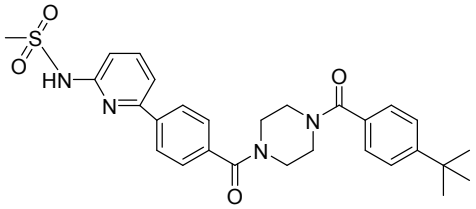


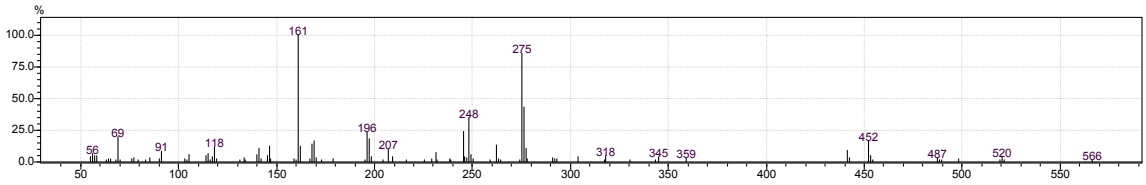


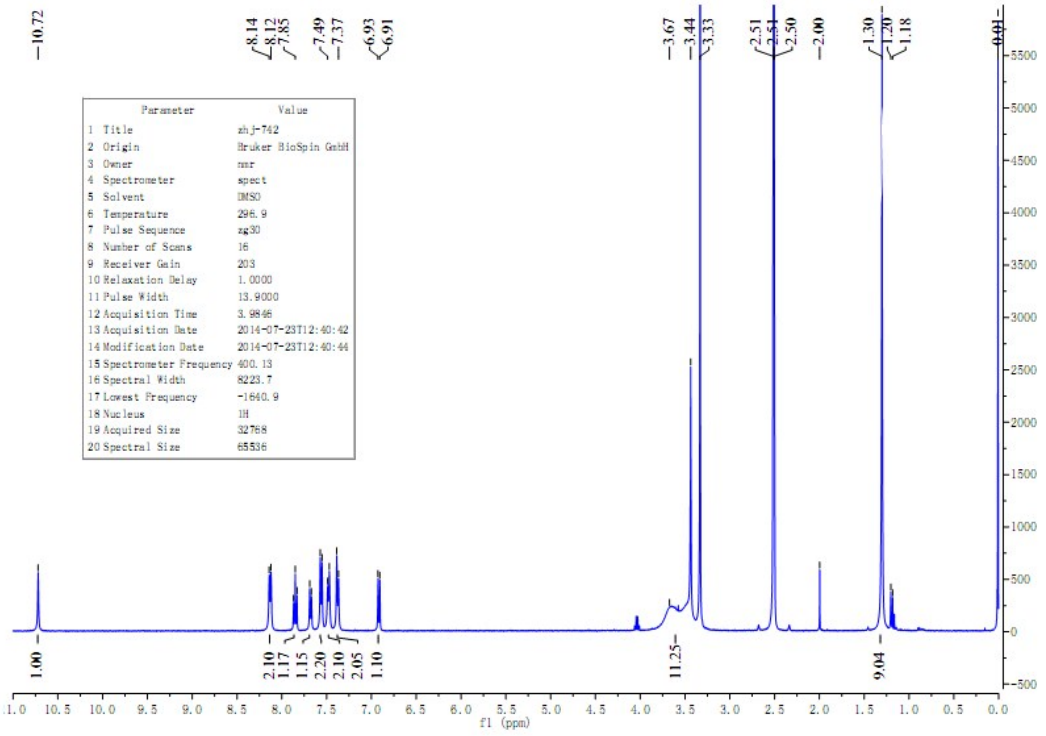


Mp 120-122ºC; EI-MS (m/z) 566[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.13 (d, $J$ = 8.0 Hz, 2H), 7.91 (s, 1H), 7.84 (d, $J$ = 7.9 Hz, 2H), 7.78 (s, 1H), 7.68 (d, $J$ = 7.6 Hz, 1H), 7.56 (d, $J$ = 7.6 Hz, 2H), 6.92 (d, $J$ = 8.1 Hz, 1H), 3.44 (s, 3H), 3.79-3.39 (m, 8H).

***N*-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide(9i)**

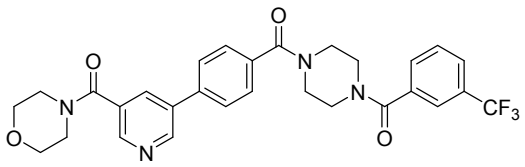


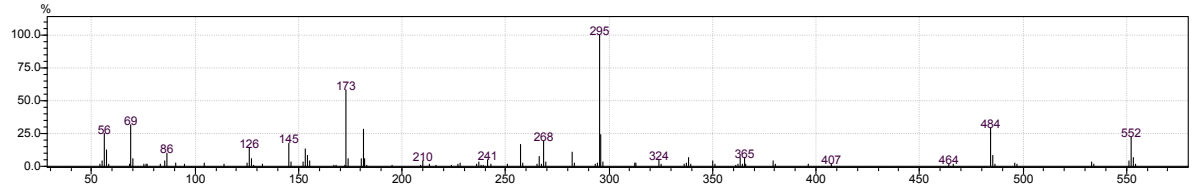


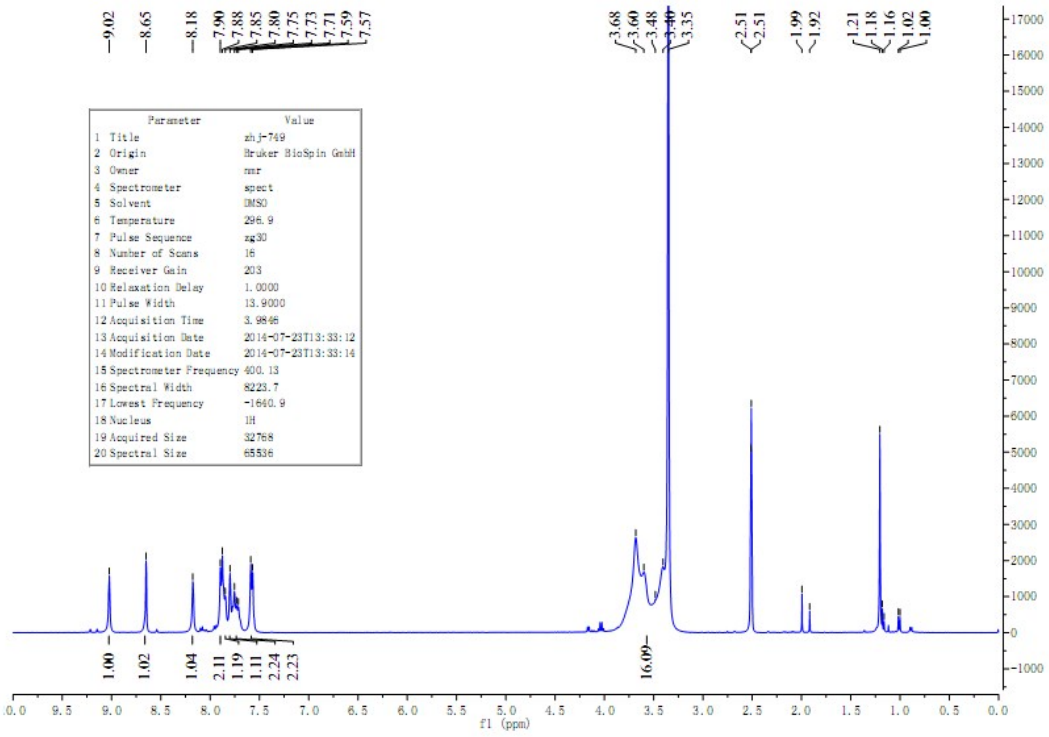




Mp 225-228ºC; EI-MS (m/z) 520[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.13 (d, $J$ = 8.0 Hz, 2H), 7.85 (t, $J$ = 7.9 Hz, 1H), 7.68 (d, $J$ = 7.7 Hz, 1H), 7.56 (d, $J$ = 8.1 Hz, 2H), 7.48 (d, $J$ = 7.9 Hz, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 6.92 (d, $J$ = 8.1 Hz, 1H), 3.44 (s, 3H), 3.33-3.67 (m, 8H), 1.30 (s, 9H).

**4-({5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-3-yl}carbonyl)morpholine (10a)**

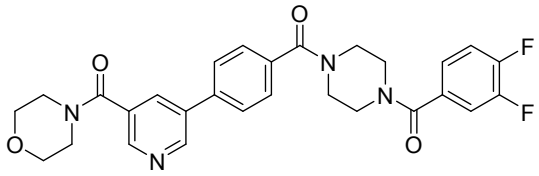


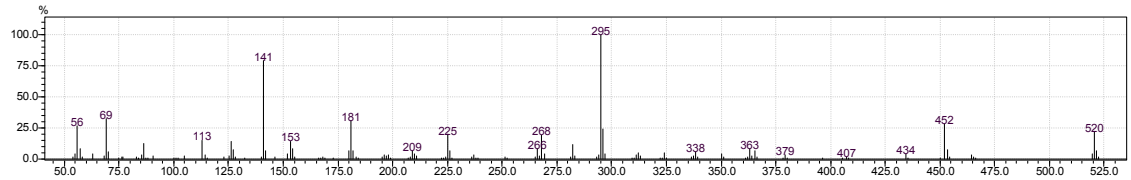



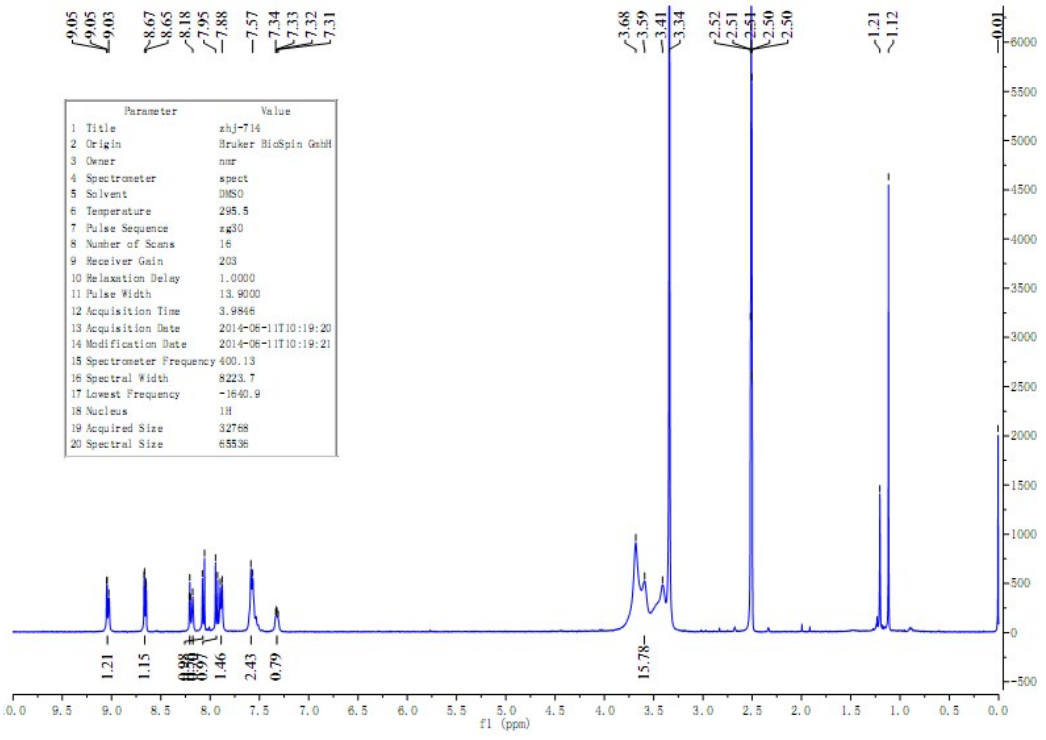




Mp 179-181ºC; EI-MS (m/z) 552[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.02 (s, 1H), 8.65 (s, 1H), 8.18 (s, 1H), 7.89 (d, $J$ = 8.1 Hz, 2H), 7.85 (s, 1H), 7.80 (s, 1H), 7.79-7.68 (m, 2H), 7.58 (d, $J$ = 6.8 Hz, 2H), 3.54 (m, 16H).

**4-{[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-3-yl]carbonyl}morpholine (10b)**

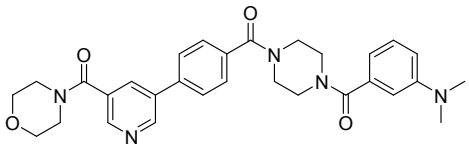


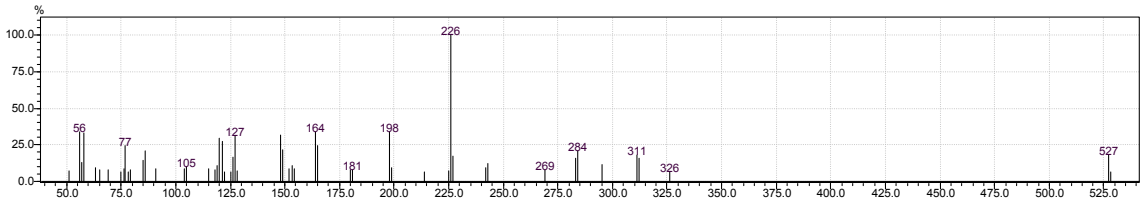


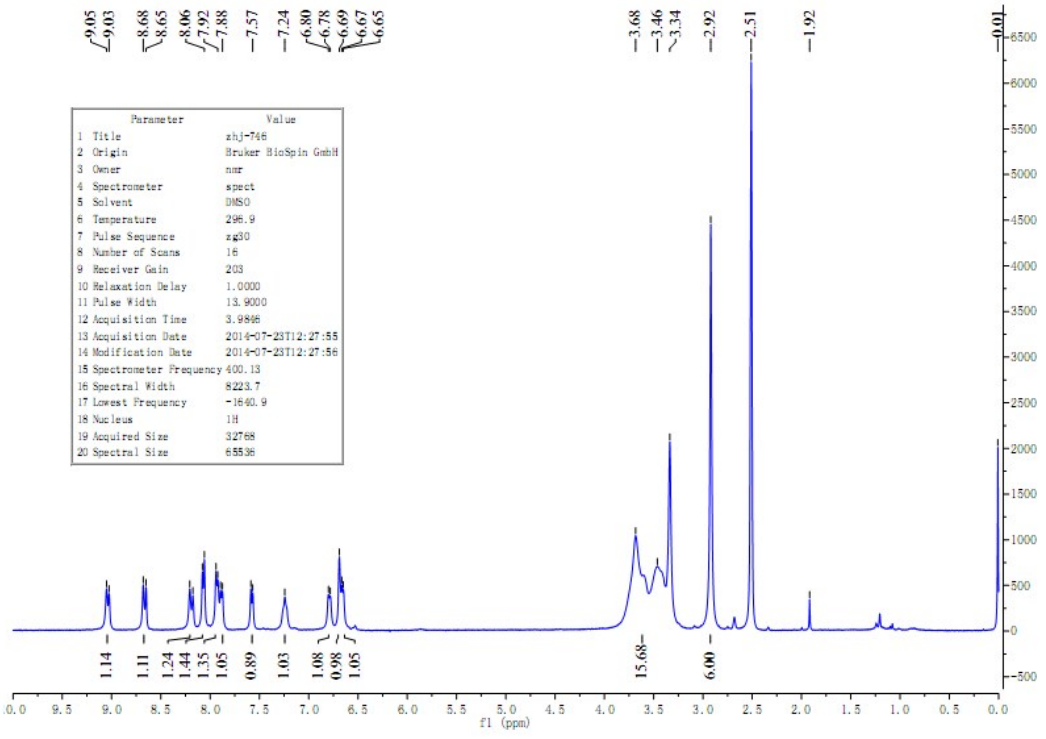




Mp 212-213ºC; EI-MS (m/z) 520[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.04 (dd, $J$= 8.5, 1.8 Hz, 1H), 8.66 (dd, $J$ = 7.2, 1.8 Hz, 1H), 8.21 (t, $J$ = 2.1 Hz, 1H), 8.18 (s, 1H), 8.07 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.5 Hz, 1H), 7.89 (d, $J$ = 7.7 Hz, 1H), 7.58 (d, $J$ = 7.3 Hz, 2H), 3.81-3.38 (m, 16H).

**Dimethyl{3-[(4-{4-[5-(morpholin-4-ylcarbonyl)pyridin-3-yl]benzoyl}piperazin-1-yl)carbonyl]phenyl}amine (10c)**

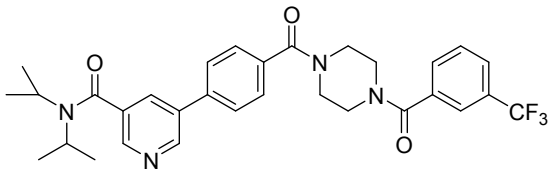


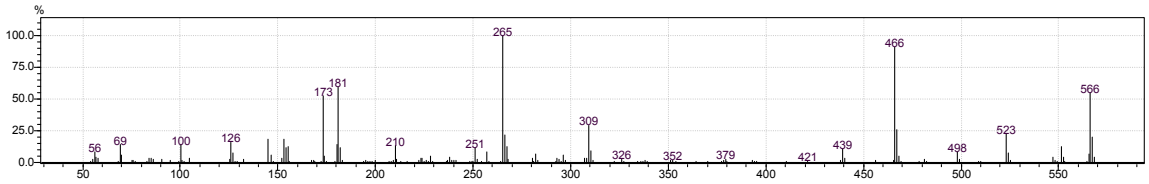


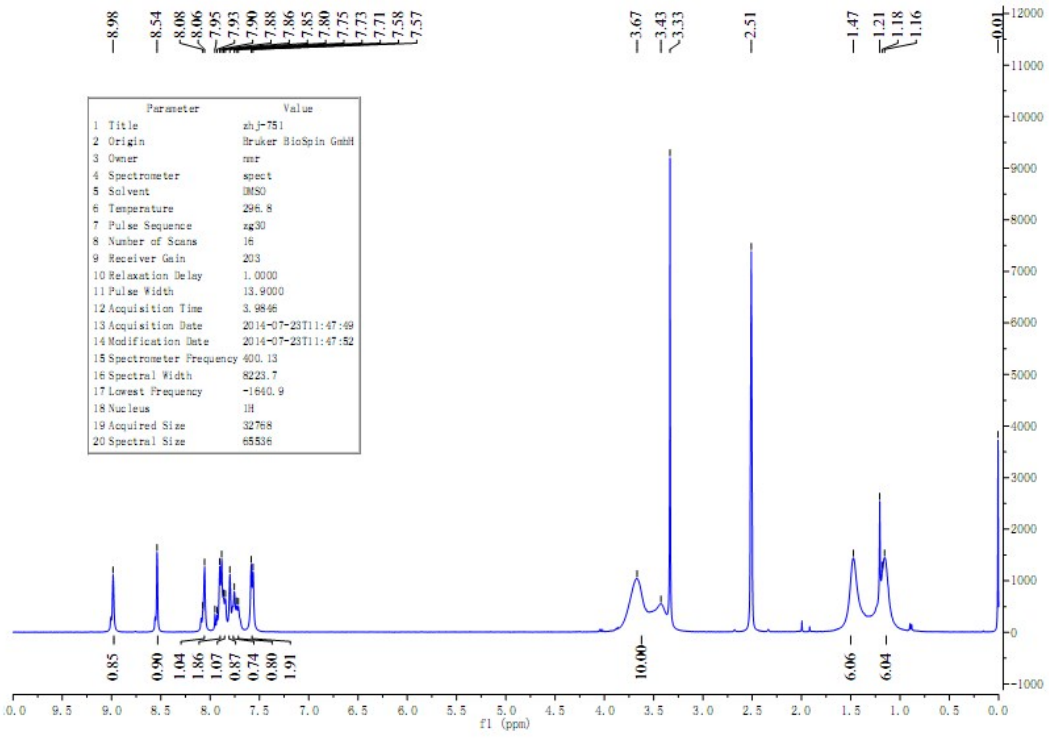




Mp 185-187ºC; EI-MS (m/z) 527[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.04 (d, $J$ = 9.9 Hz, 1H), 8.66 (d, $J$ = 11.3 Hz, 1H), 8.19 (d, $J$ = 12.8 Hz, 1H), 8.07 (d, $J$ = 7.8 Hz, 1H), 7.93 (d, $J$ = 7.3 Hz, 1H), 7.89 (d, $J$ = 7.7 Hz, 1H), 7.58 (d, $J$ = 7.4 Hz, 1H), 7.24 (s, 1H), 6.79 (d, $J$ = 7.0 Hz, 1H), 6.69 (s, 1H), 6.66 (d, $J$ = 6.5 Hz, 1H), 3.90-3.33 (m, 16H), 2.92 (s, 6H).

**_N,N_-diisopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10d)**

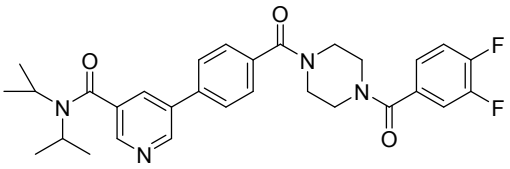


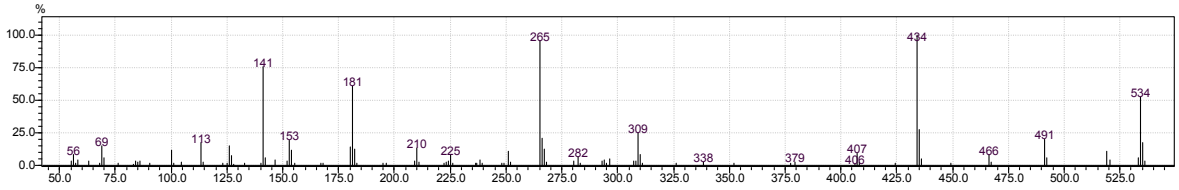



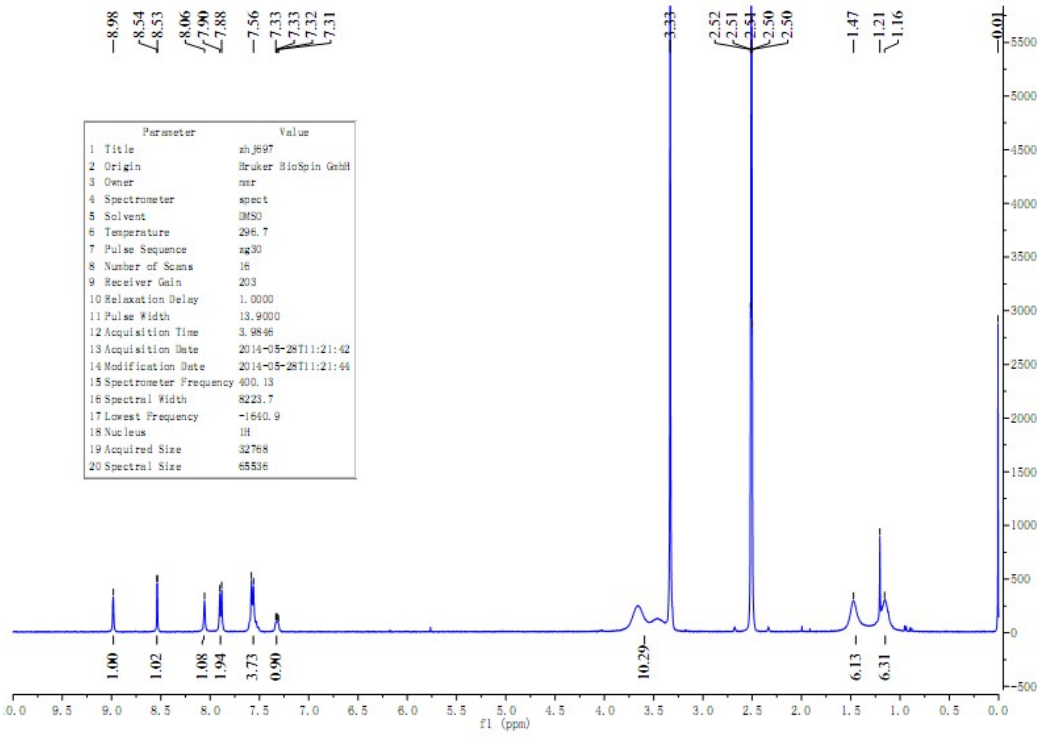




Mp 161-163ºC; EI-MS (m/z) 566[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.98 (s, 1H), 8.54 (s, 1H), 8.07 (s, 1H), 7.89 (d, $J$ = 7.9 Hz, 2H), 7.85 (d, $J$ = 4.0Hz, 1H), 7.80 (s, 1H), 7.75 (s, 1H), 7.72 (d, $J$ = 7.9 Hz, 1H), 7.57 (d, $J$ = 7.1 Hz, 2H), 3.43-3.67 (m, 10H), 1.47 (s, 6H), 1.16 (s, 6H).

**5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*,*N*-diisopropylnicotinamide (10e)**

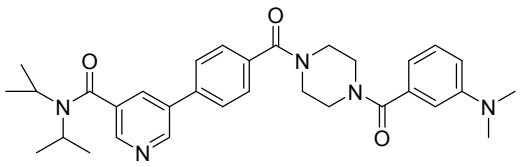


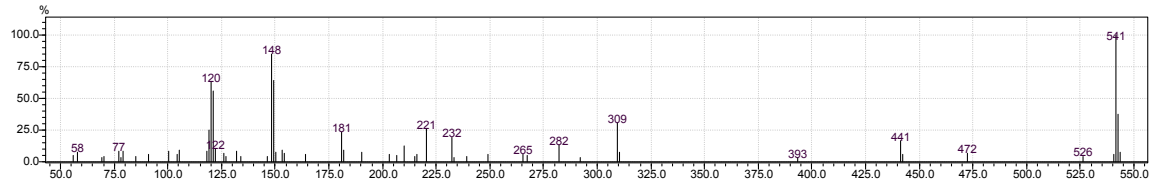


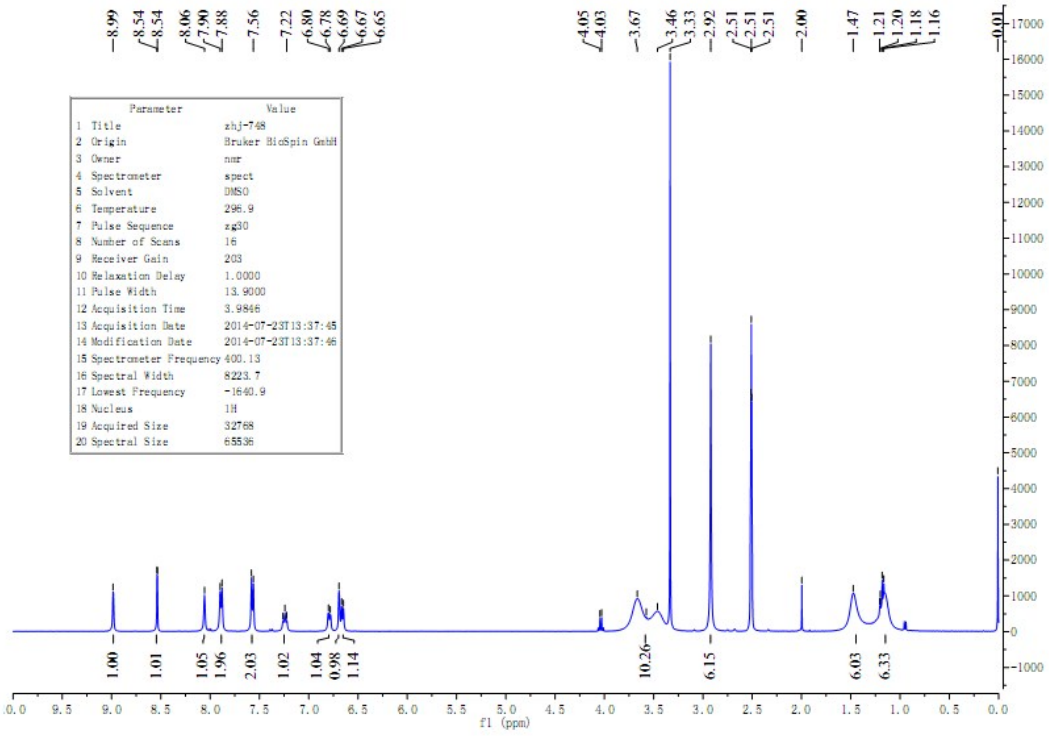


Mp 194-197ºC; EI-MS (m/z) 534[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.98 (s, 1H), 8.54 (d, *J*= 1.8 Hz, 1H), 8.06 (s, 1H), 7.89 (d, *J*= 7.8 Hz, 2H), 7.57 (d, *J*= 8.1 Hz, 4H), 7.31-7.33 (m, 1H), 3.46-3.68 (m, 8H), 1.48 (s, 6H), 1.16 (s, 6H).

**5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diisopropylnicotinamide (10f)**

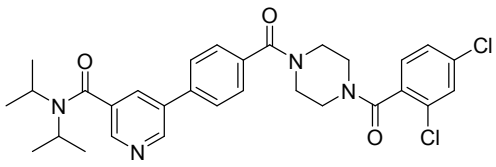


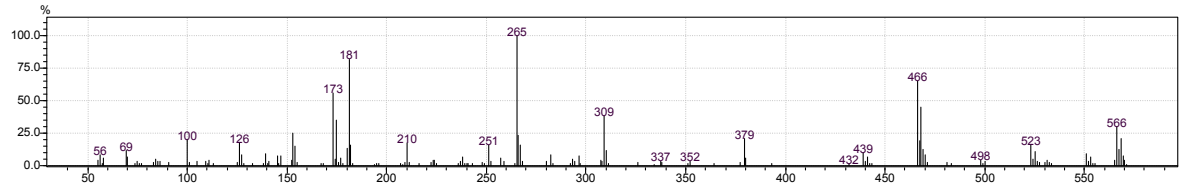


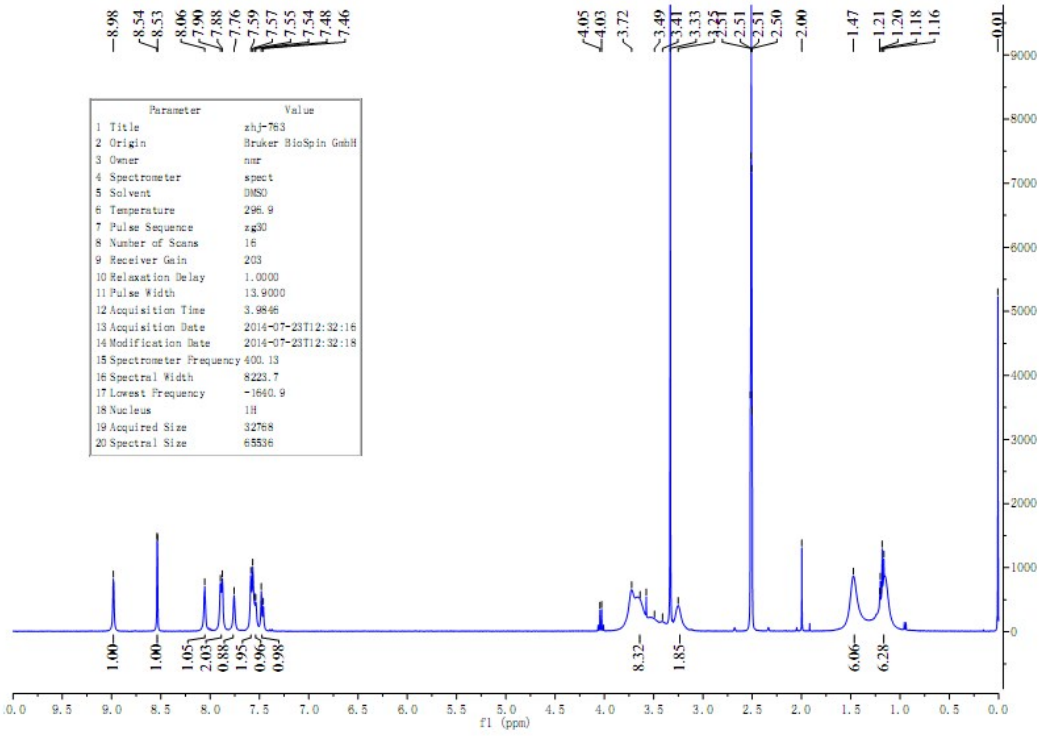




Mp 197-199ºC; EI-MS (m/z) 541[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.99 (s, 1H), 8.54 (d, $J$ = 1.7 Hz, 1H), 8.06 (s, 1H), 7.89 (d, $J$ = 7.8 Hz, 2H), 7.57 (d, $J$ = 8.0 Hz, 2H), 7.24 (t, $J$ = 7.7 Hz, 1H), 6.79 (d, $J$ = 7.6 Hz, 1H), 6.69 (s, 1H), 6.66 (d, $J$ = 7.3 Hz, 1H), 3.79-3.37 (m, 10H), 2.92 (s, 6H), 1.47 (s, 6H), 1.16 (s, 6H).

**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*,*N*-diisopropylnicotinamide (10g)**

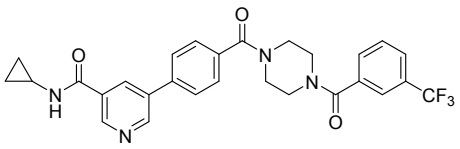


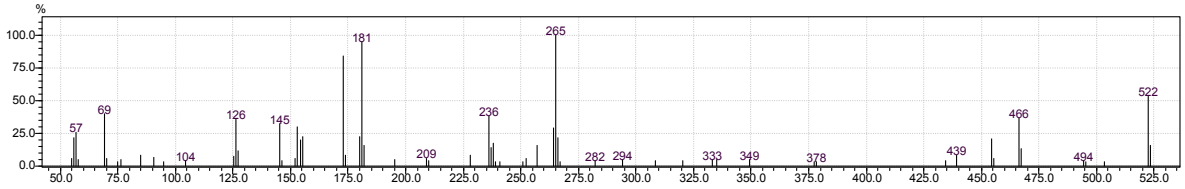



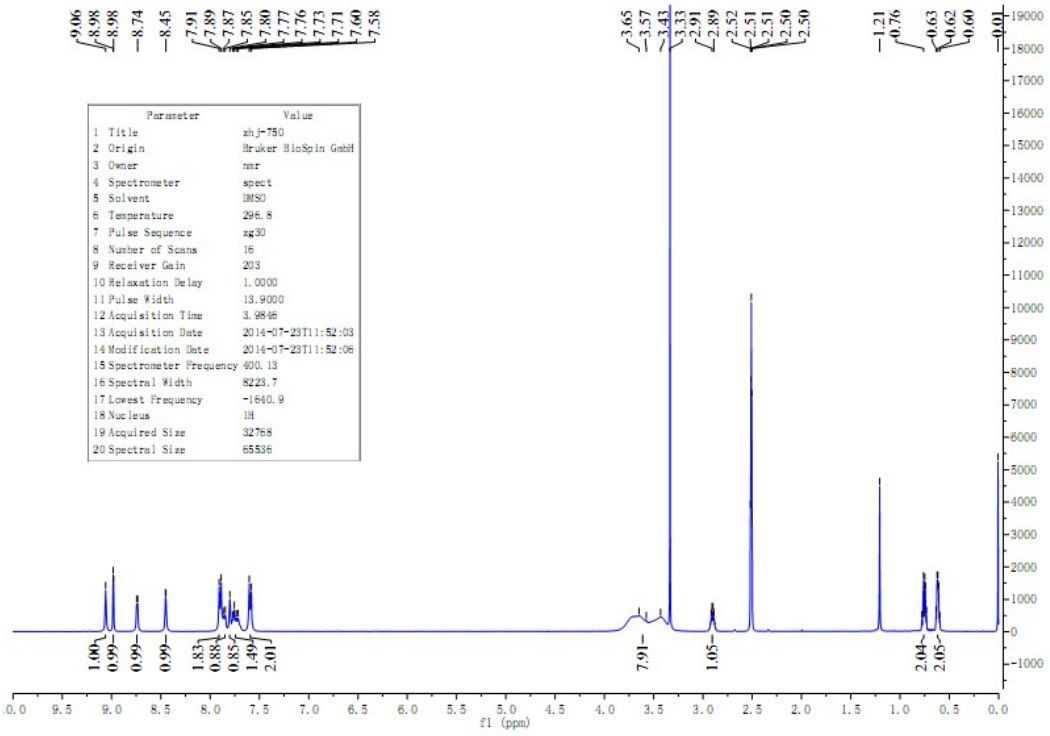




Mp 214-215ºC; EI-MS (m/z) 566[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.98 (s, 1H), 8.54 (d, $J$ = 1.8 Hz, 1H), 8.06 (s, 1H), 7.89 (d, $J$ = 7.5 Hz, 2H), 7.76 (s, 1H), 7.58 (d, $J$ = 7.6 Hz, 2H), 7.54 (d, $J$ = 3.7 Hz, 1H), 7.47 (d, $J$ = 8.2 Hz, 1H), 3.83-3.40 (m, 8H), 3.25 (s, 2H), 1.47 (s, 6H), 1.19 (s, 6H).

**_N_-cyclopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10h)**

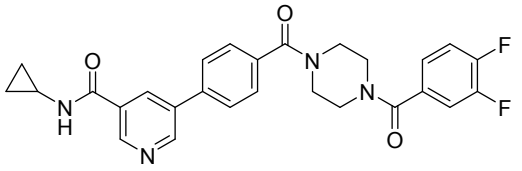


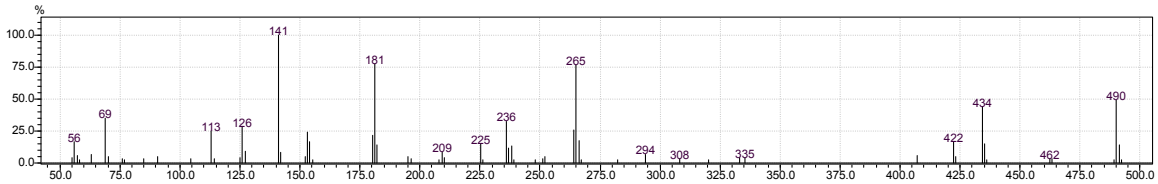


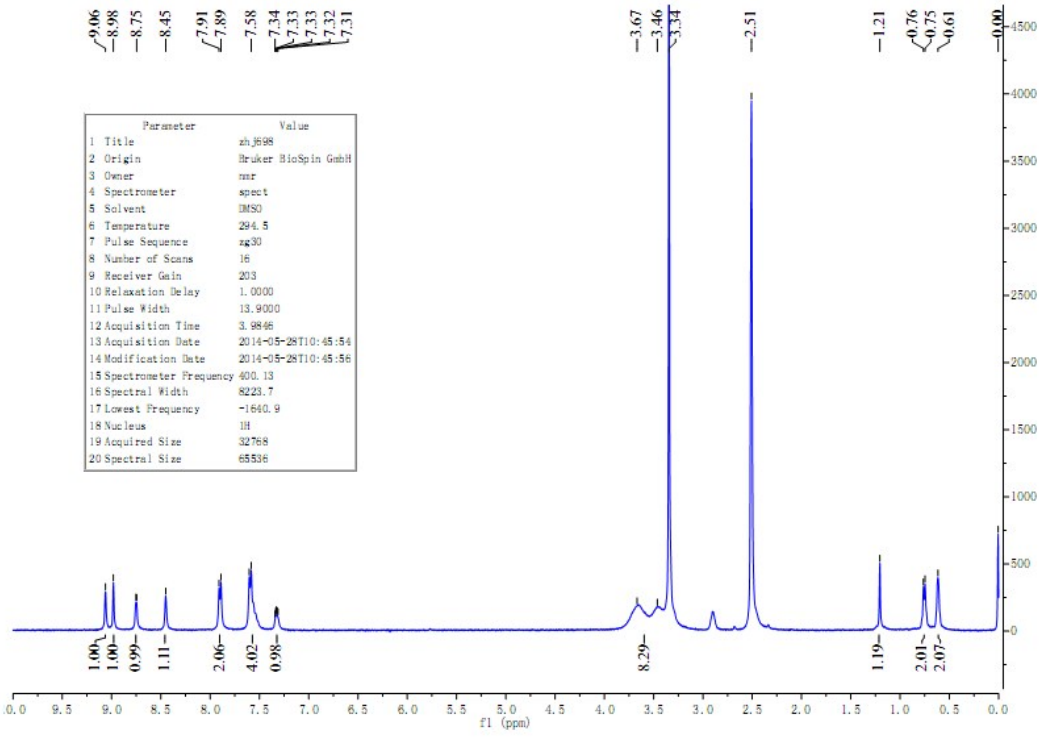


Mp 180-182ºC; EI-MS (m/z) 522[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.06 (s, 1H), 8.98 (d, $J$ = 1.5 Hz, 1H), 8.74 (d, $J$ = 3.8 Hz, 1H), 8.45 (d, $J$ = 2.0 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 2H), 7.86 (d, $J$ = 7.6 Hz, 1H), 7.80 (s, 1H), 7.74 (dd, $J$ = 15.9, 7.1 Hz, 1H), 7.59 (d, $J$ = 8.1 Hz, 2H), 3.84-3.38 (m, 8H), 2.90 (dd, $J$ = 7.3, 3.4 Hz, 1H), 0.80-0.72 (m, 2H), 0.66-0.58 (m, 2H).

**_N_-cyclopropyl-5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)nicotinamide (10i)**

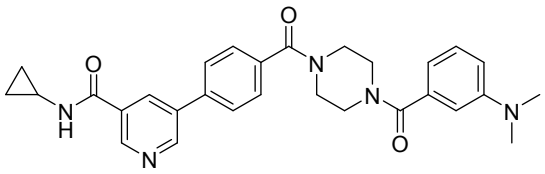


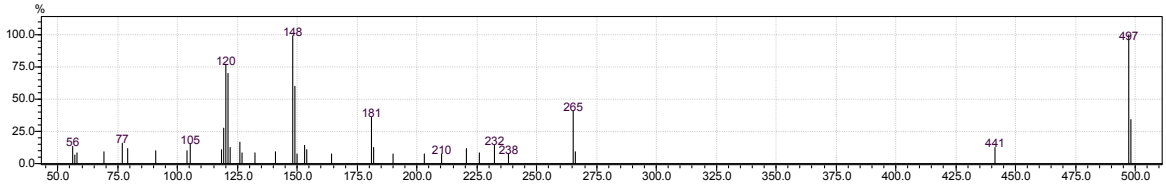


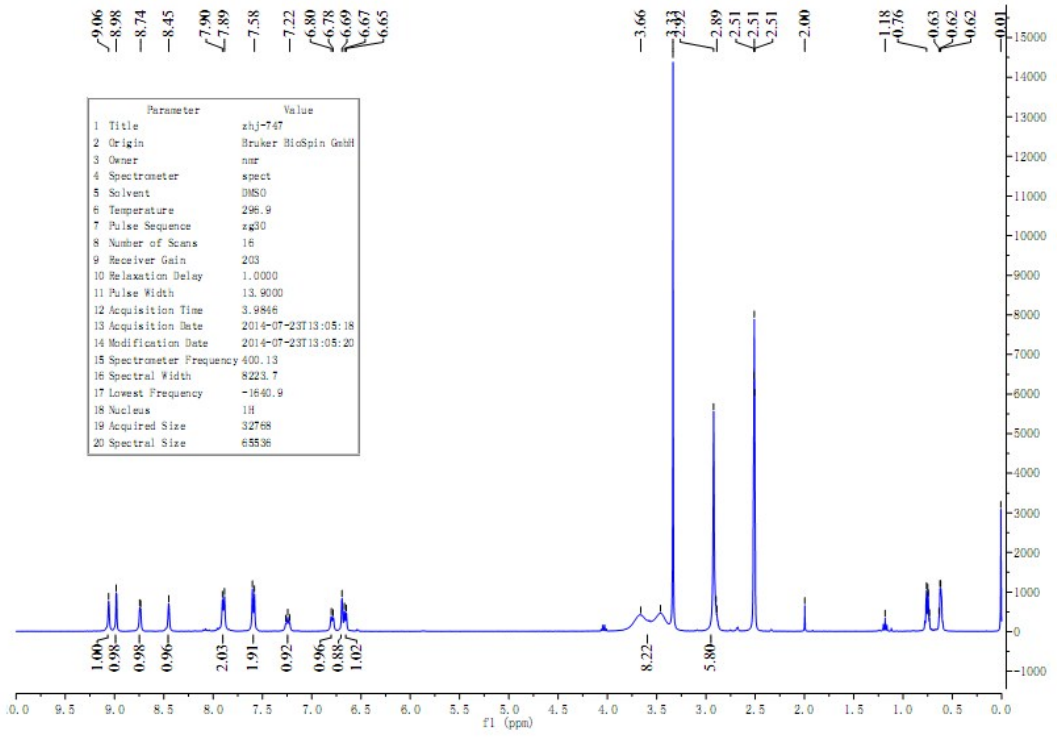




Mp 221-222ºC; EI-MS (m/z) 490[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.98 (s, 1H), 8.75 (d, $J$ = 3.1 Hz, 1H), 8.45 (s, 1H), 7.90 (d, $J$ = 7.7 Hz, 2H), 7.59 (d, $J$ = 7.6 Hz, 4H), 7.39-7.28 (m, 1H), 3.44 -3.66 (m, 8H), 1.21 (s, 1H), 0.75 (d, $J$ = 6.3 Hz, 2H), 0.61 (d, $J$ = 4.0 Hz, 2H).

**_N_-cyclopropyl-5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10j)**

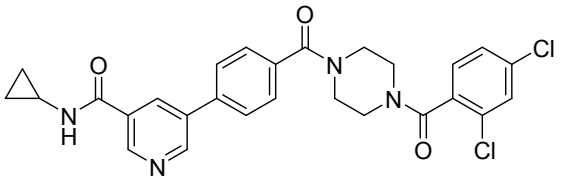


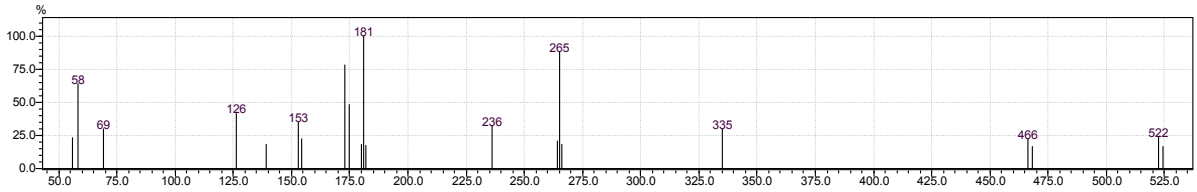


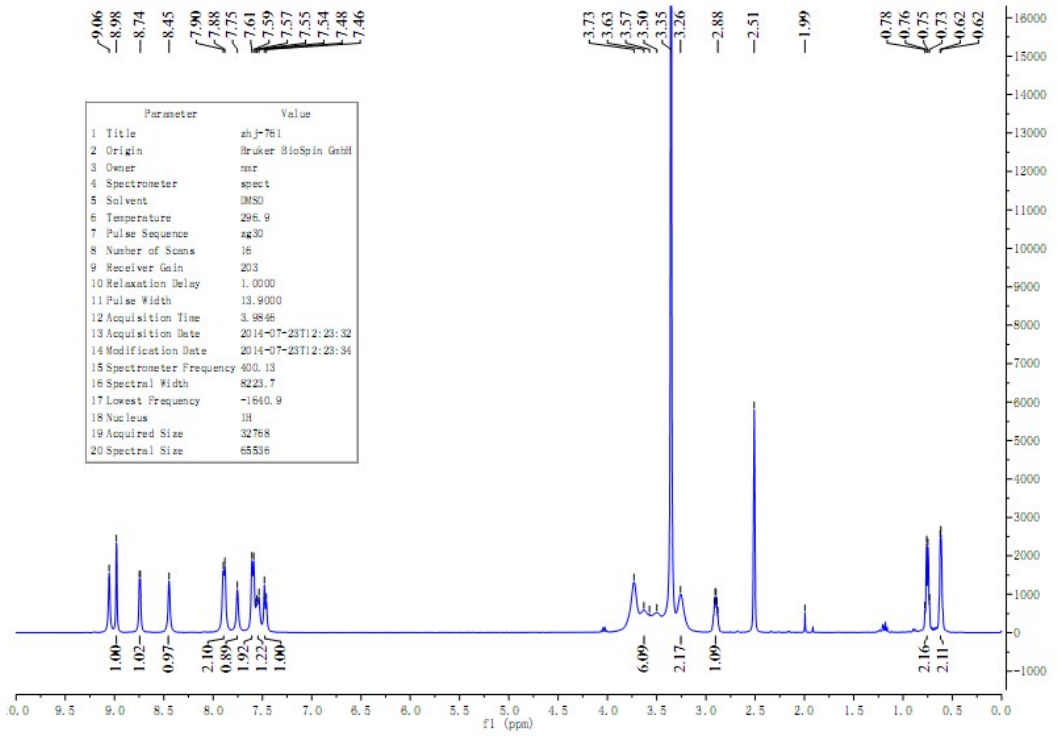




Mp 184-186ºC; EI-MS (m/z) 497[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.06 (s, 1H), 8.98 (s, 1H), 8.74 (d, $J$ = 3.8 Hz, 1H), 8.45 (s, 1H), 7.90 (d, $J$ = 7.6 Hz, 2H), 7.59 (d, $J$ = 8.0 Hz, 2H), 7.24 (t, $J$ = 7.8 Hz, 1H), 6.79 (d, $J$ = 7.4 Hz, 1H), 6.69 (s, 1H), 6.66 (d, $J$ = 7.3 Hz, 1H), 3.46-3.66 (m, 8H), 2.92 (s, 6H).

**_N_-cyclopropyl-5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)nicotinamide (10k)**

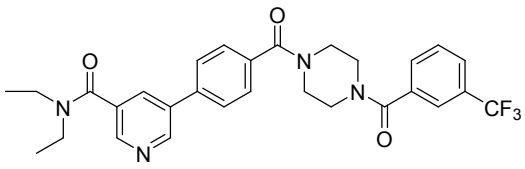


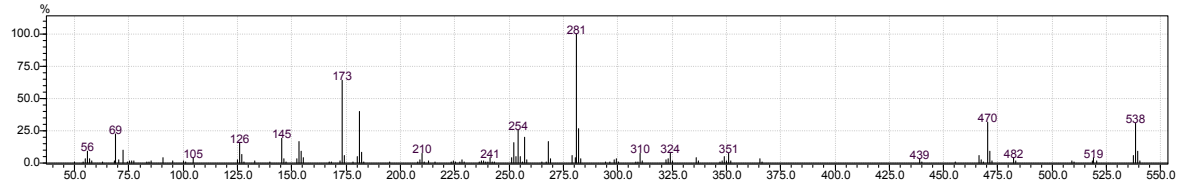


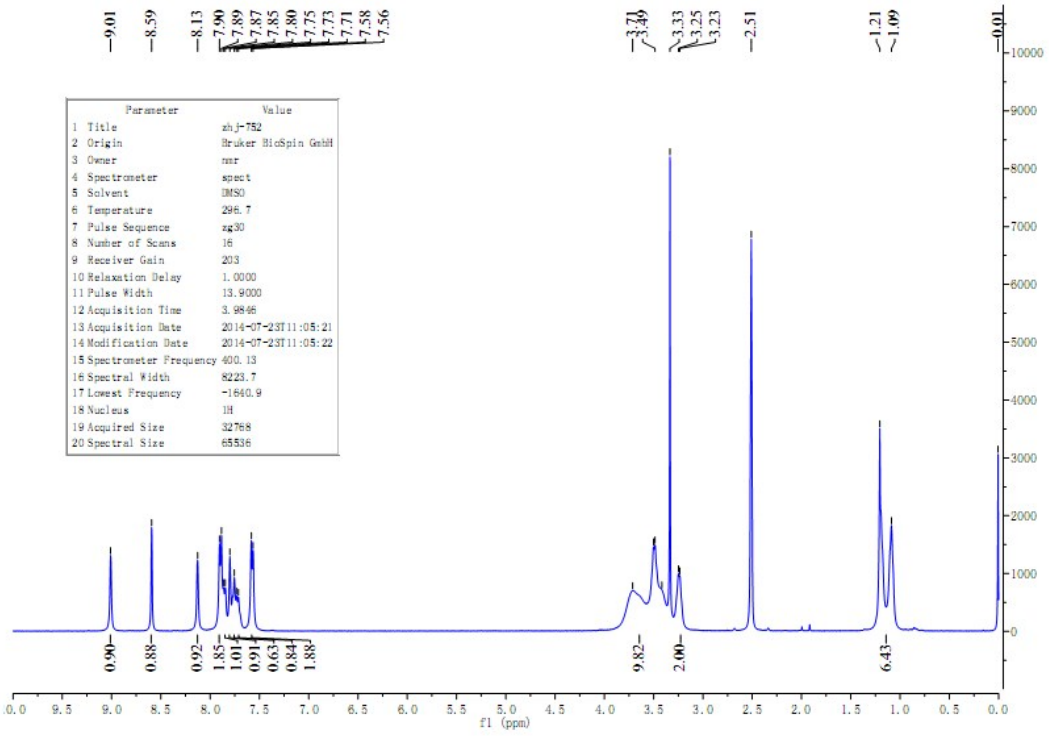




Mp 183-185ºC; EI-MS (m/z) 522[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 8.98 (s, 1H), 8.74 (d, $J$ = 3.5 Hz, 1H), 8.45 (s, 1H), 7.89 (d, $J$ = 6.3 Hz, 2H), 7.75 (s, 1H), 7.60 (d, $J$ = 7.5 Hz, 2H), 7.58–7.51 (m, 1H), 7.47 (d, $J$ = 8.0 Hz, 1H), 3.26-3.73 (m, 8H), 2.96-2.85 (m, 1H), 0.75 (q, $J$ = 6.6 Hz, 2H), 0.62 (d, $J$ = 2.4 Hz, 2H).

**_N,N_-diethyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10l)**

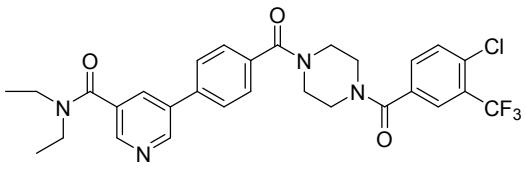


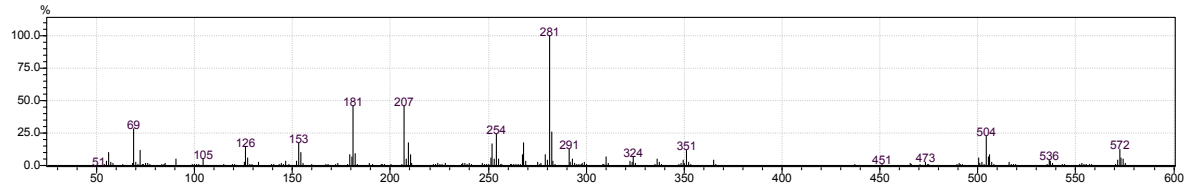



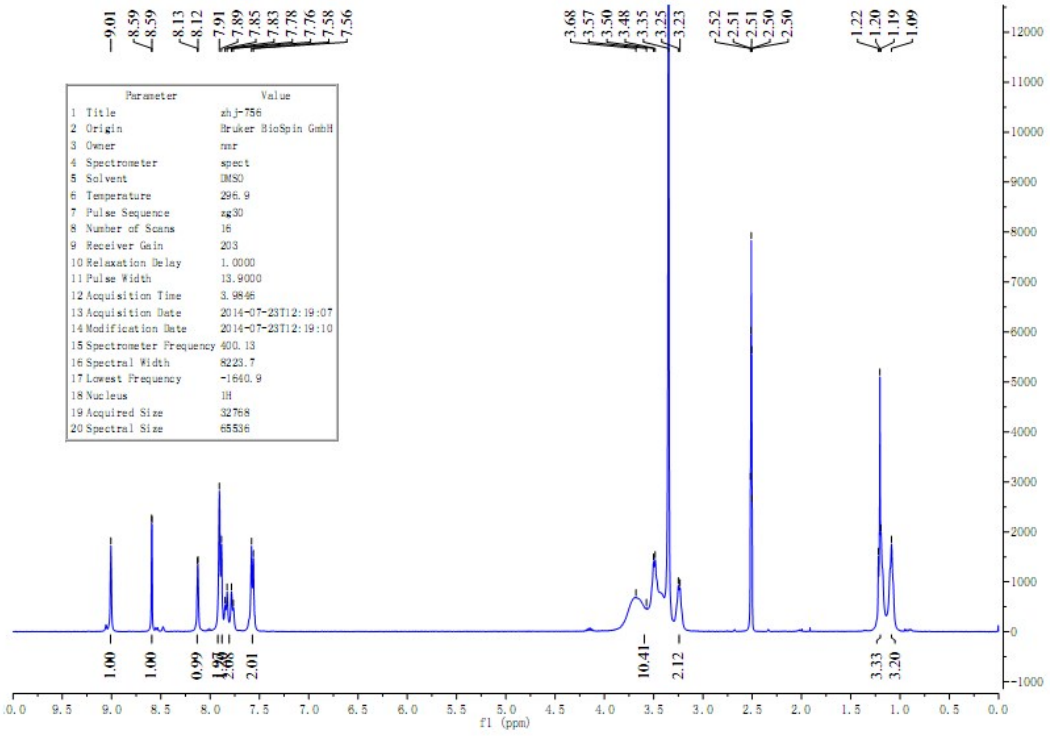




Mp 125-127ºC; EI-MS (m/z) 538[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (s, 1H), 8.59 (s, 1H), 8.13 (s, 1H), 7.90 (d, $J$ = 7.7 Hz, 2H), 7.86 (d, $J$ = 7.8 Hz, 1H), 7.80 (s, 1H), 7.75 (s, 1H), 7.72 (d, $J$ = 7.8 Hz, 1H), 7.57 (d, $J$ = 7.1 Hz, 2H), 3.42-3.71 (m, 8H), 3.49 (d, $J$= 4.0Hz, 2H), 3.24 (d, $J$= 8.0Hz, 2H), 1.15 (d, $J$ = 47.4 Hz, 6H).

**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diethylnicotinamide (10m)**

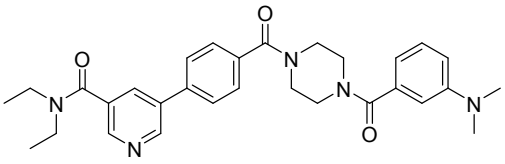


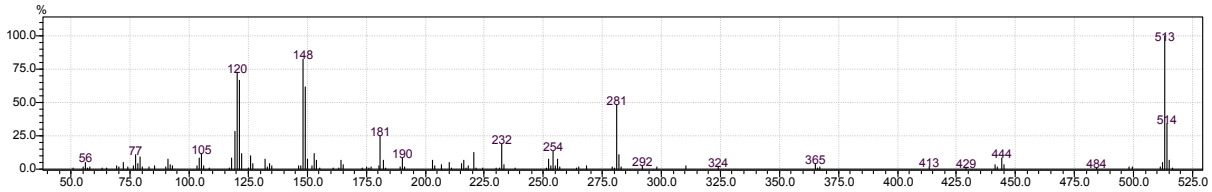


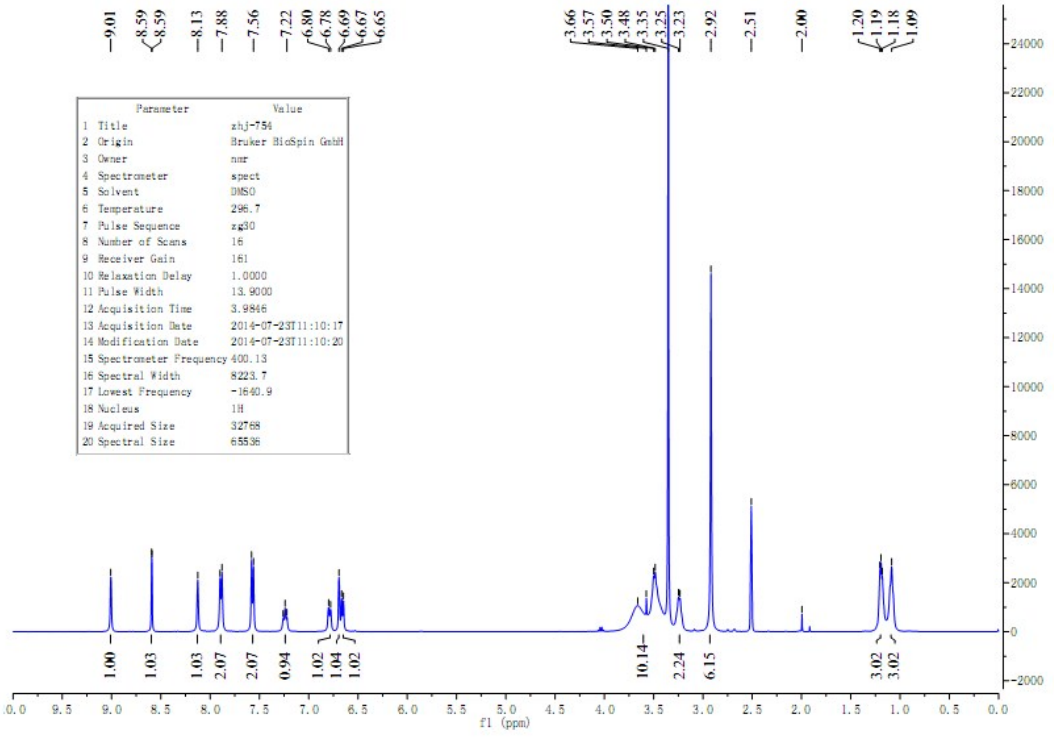


Mp 149-151ºC; EI-MS (m/z) 572[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (s, 1H), 8.59 (d, $J$ = 1.8 Hz, 1H), 8.13 (d, $J$ = 1.6 Hz, 1H), 7.91 (s, 2H), 7.89 (s, 1H), 7.81 (dd, $J$ = 25.5, 7.8 Hz, 2H), 7.57 (d, $J$ = 7.9 Hz, 2H), 3.43 - 3.68 (m, 8H), 3.49 (d, $J$ = 6.5 Hz, 2H), 3.24 (d, $J$ = 6.5 Hz, 2H), 1.19 (s, 3H), 1.09 (s, 3H).

**5-[4-({4-[4-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diethylnicotinamide (10n)**

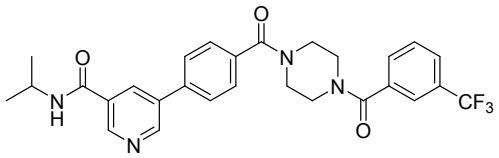


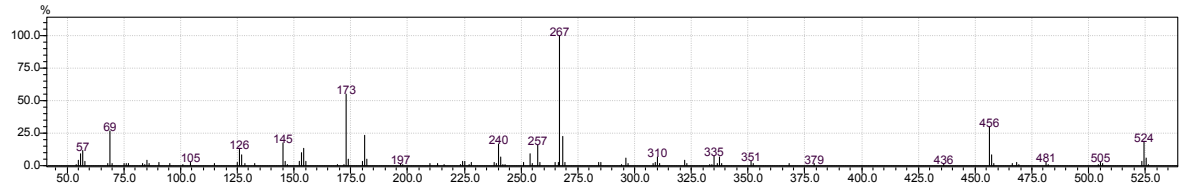


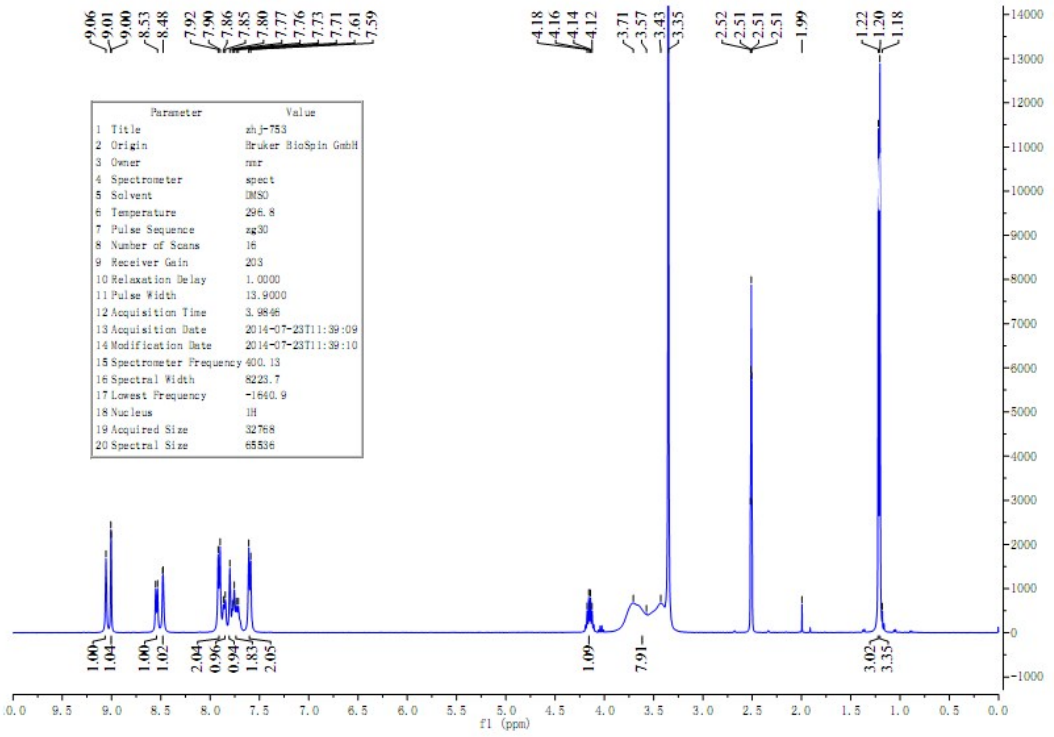




Mp 157-158ºC; EI-MS (m/z) 513[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (s, 1H), 8.59 (d, $J$ = 1.4 Hz, 1H), 8.13 (s, 1H), 7.89 (d, $J$ = 7.7 Hz, 2H), 7.57 (d, $J$ = 7.9 Hz, 2H), 7.24 (t, $J$ = 7.5 Hz, 1H), 6.79 (d, $J$ = 8.0 Hz, 1H), 6.69 (s, 1H), 6.66 (d, $J$ = 7.3 Hz, 1H), 3.36-3.66 (m, 8H), 3.49 (d, $J$ = 5.9 Hz, 2H), 3.24 (d, $J$ = 5.9 Hz, 2H), 2.92 (s, 6H), 1.19(t, $J$ = 4.0Hz, 3H), 1.09 (s, 3H).

**_N_-isopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10o)**

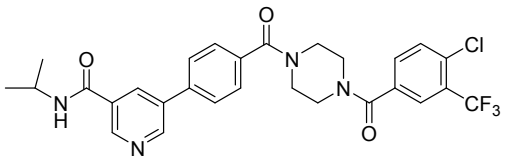


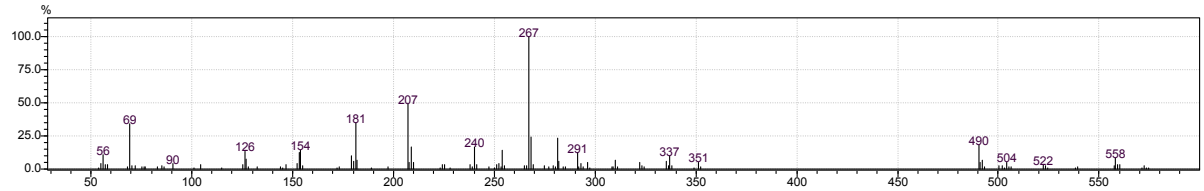


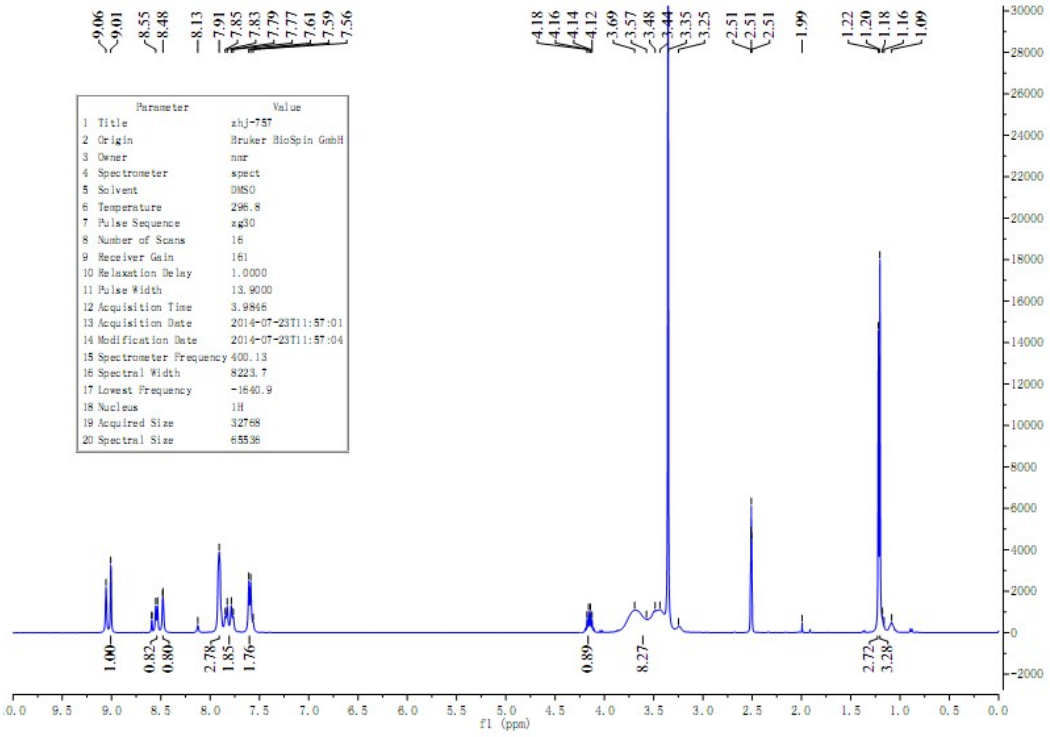


Mp 225-227ºC; EI-MS (m/z) 524[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.06 (s, 1H), 9.01 (d, $J$ = 1.6 Hz, 1H), 8.54 (d, $J$ = 7.6 Hz, 1H), 8.48 (d, $J$ = 2.0 Hz, 1H), 7.91 (d, $J$ = 8.1 Hz, 2H), 7.86 (d, $J$ = 7.0 Hz, 1H), 7.80 (s, 1H), 7.74 (dd, $J$ = 16.3, 7.3 Hz, 2H), 7.60 (d, $J$ = 7.9 Hz, 2H), 4.15 (dd, $J$ = 13.7, 6.8 Hz, 1H), 3.84-3.39 (m, 8H), 1.22 (s, 3H), 1.20 (s, 3H).

**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-isopropylnicotinamide (10p)**

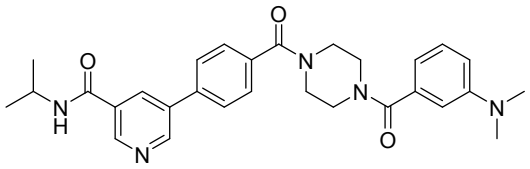


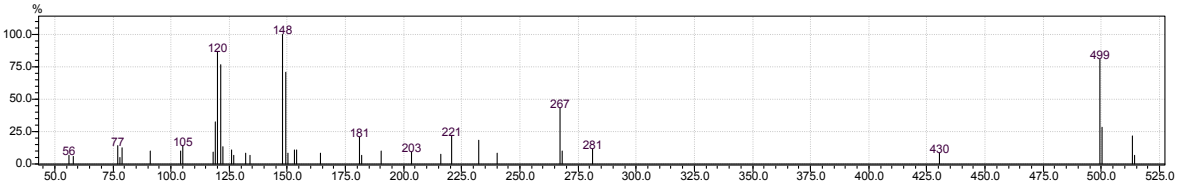



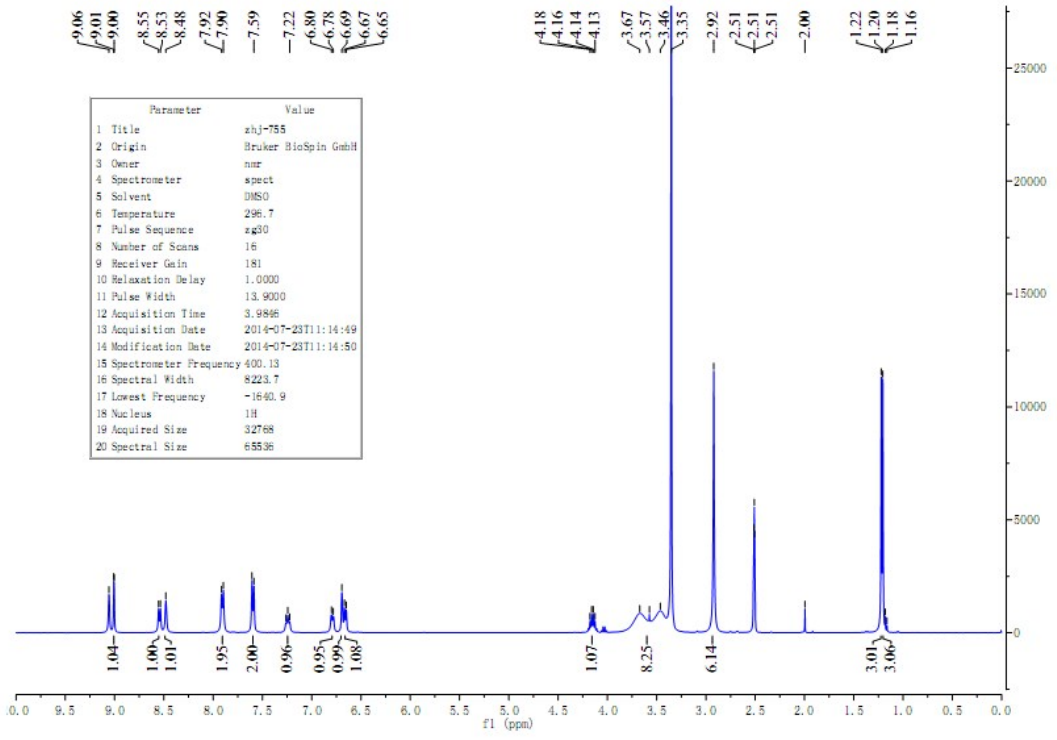




Mp 162-164ºC; EI-MS (m/z) 558[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (s, 1H), 8.54 (d, $J$ = 7.5 Hz, 1H), 8.48 (d, $J$ = 1.8 Hz, 1H), 7.91 (s, 3H), 7.81 (dd, $J$ = 24.7, 7.7 Hz, 2H), 7.60 (d, $J$ = 8.0 Hz, 2H), 4.15 (dd, $J$ = 13.7, 6.8 Hz, 1H), 3.44-3.69 (m, 8H), 1.22 (s, 3H), 1.20 (s, 3H).

**5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-isopropylnicotinamide (10q)**

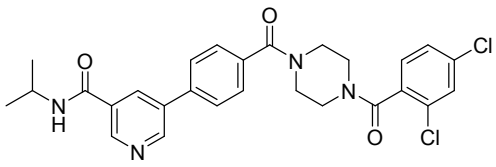


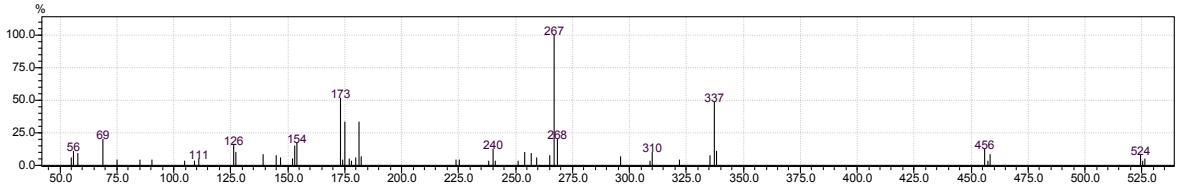


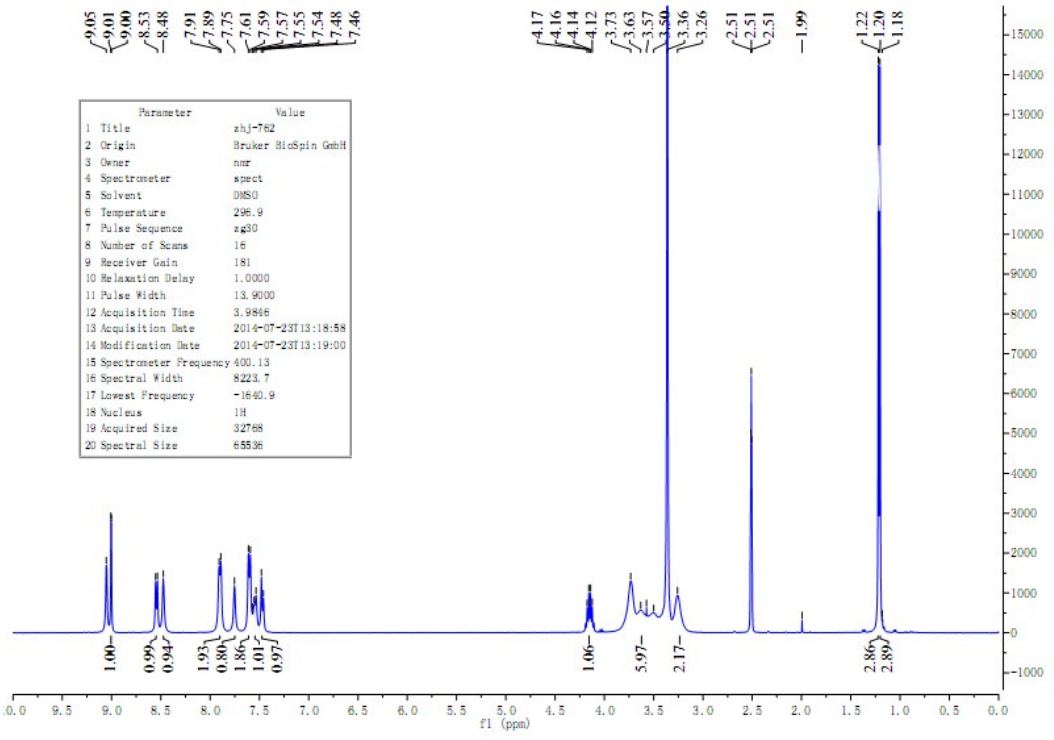




Mp 216-218ºC; EI-MS (m/z) 499[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (d, $J$ = 1.7 Hz, 1H), 8.54 (d, $J$ = 7.6 Hz, 1H), 8.48 (s, 1H), 7.91 (d, $J$ = 7.7 Hz, 2H), 7.60 (d, $J$ = 8.0 Hz, 2H), 7.24 (t, $J$ = 7.5 Hz, 1H), 6.79 (d, $J$ = 7.7 Hz, 1H), 6.69 (s, 1H), 6.66 (d, $J$ = 7.4 Hz, 1H), 4.15 (dd, $J$ = 13.6, 6.8 Hz, 1H), 3.79-3.40 (m, 8H), 2.92 (s, 6H), 1.22 (s, 3H), 1.20 (s, 3H).

**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*-isopropylnicotinamide (10r)**

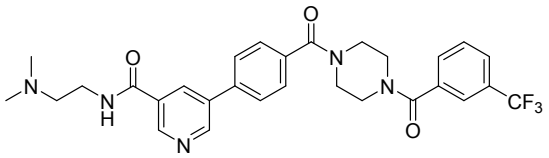


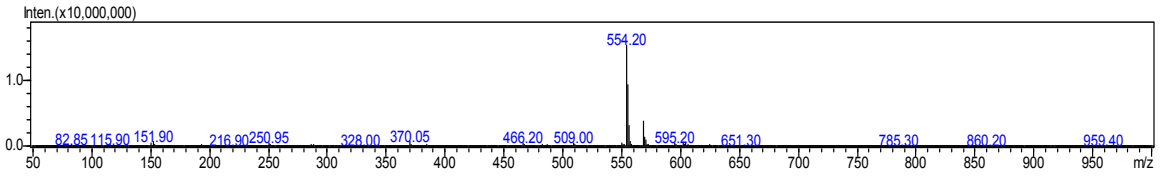


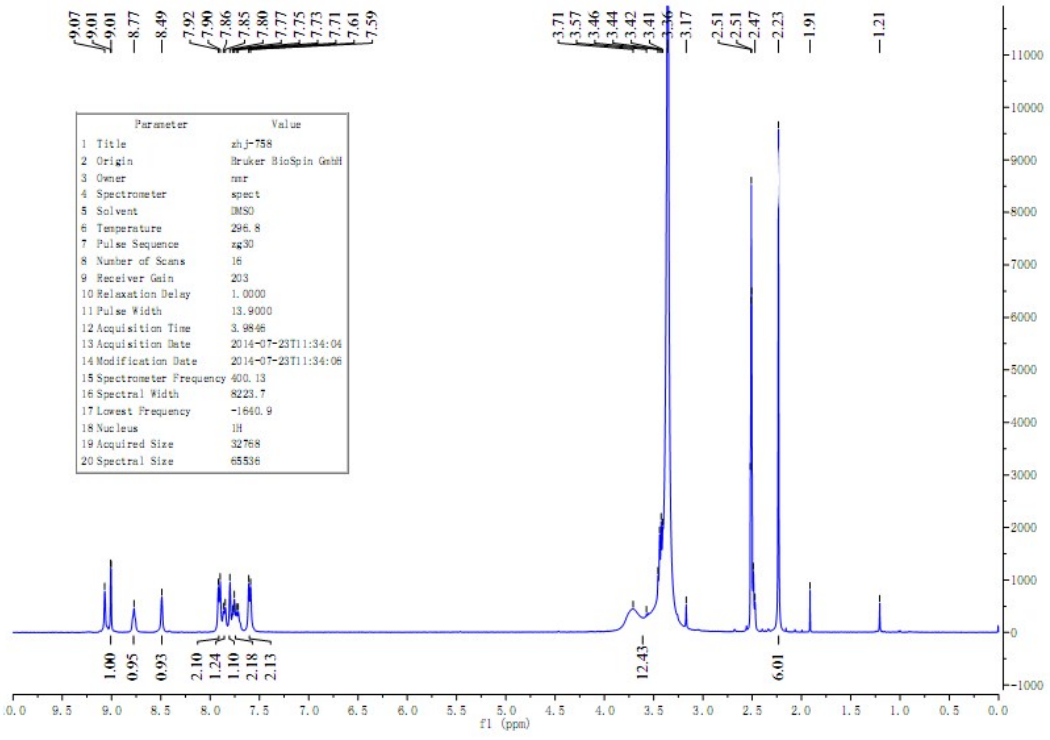


Mp 225-227ºC; EI-MS (m/z) 524[M]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.00 (d, $J$ = 1.7 Hz, 1H), 8.54 (d, $J$ = 7.6 Hz, 1H), 8.48 (s, 1H), 7.90 (d, $J$ = 6.4 Hz, 2H), 7.75 (s, 1H), 7.60 (d, $J$ = 7.7 Hz, 2H), 7.58-7.51 (m, 1H), 7.47 (d, $J$ = 8.0 Hz, 1H), 4.15 (dd, $J$ = 13.6, 6.8 Hz, 1H), 3.26-3.73 (m, 8H), 1.22 (s, 3H), 1.20 (s, 3H).

**_N_-[2-(dimethylamino)ethyl]-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10s)**

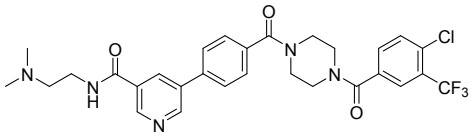


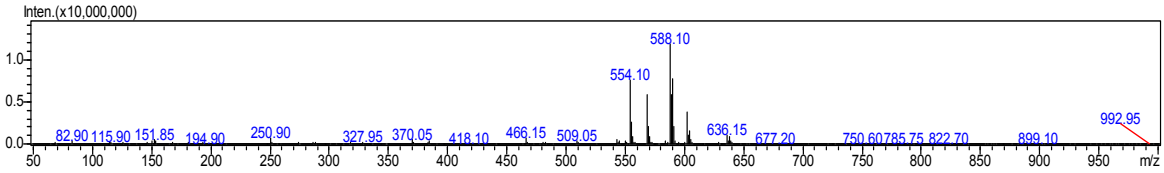


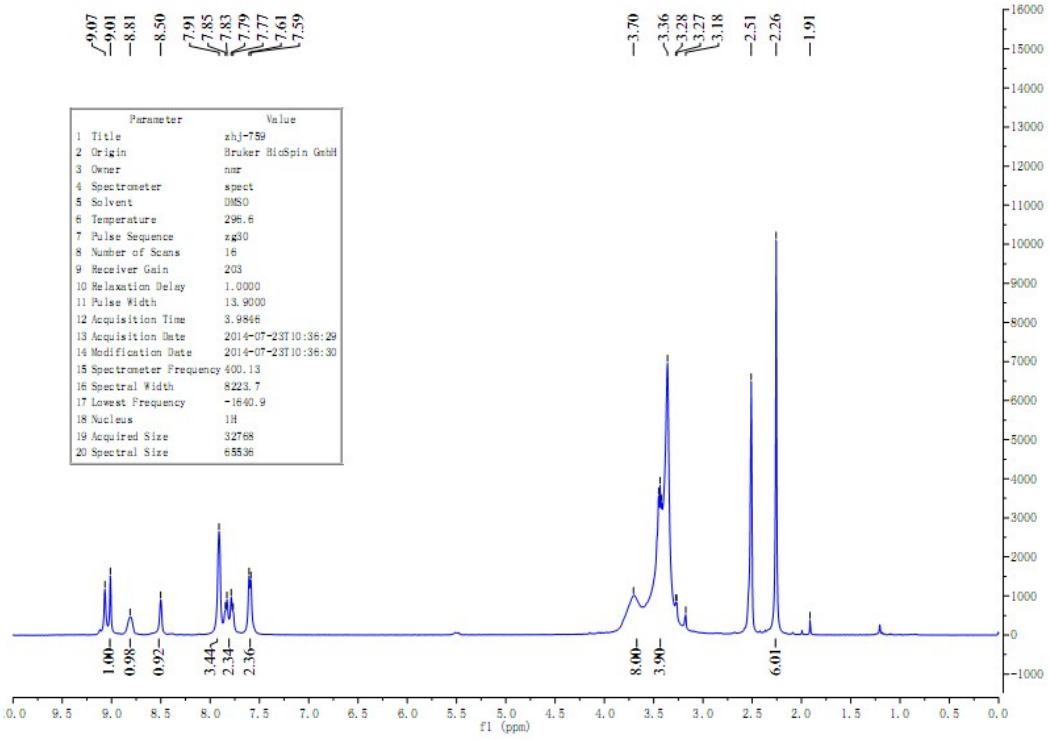




Mp 109-111ºC; EI-MS (m/z) 554.20[M+1]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (d, $J$ = 1.8 Hz, 1H), 8.77 (s, 1H), 8.49 (s, 1H), 7.91 (d, $J$ = 7.8 Hz, 2H), 7.86 (d, $J$ = 7.3 Hz, 1H), 7.80 (s, 1H), 7.74 (dd, $J$ = 16.0, 7.3 Hz, 2H), 7.60 (d, $J$ = 7.5 Hz, 2H), 3.80-3.42 (m, 12H), 2.23 (s, 6H).

**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-[2-(dimethylamino)ethyl]nicotinamide (10t)**

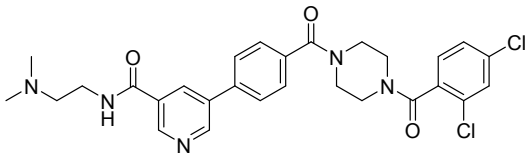


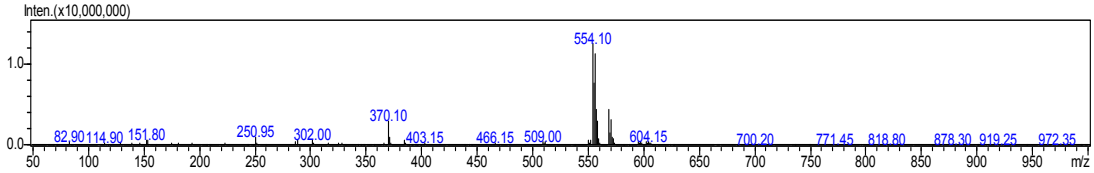


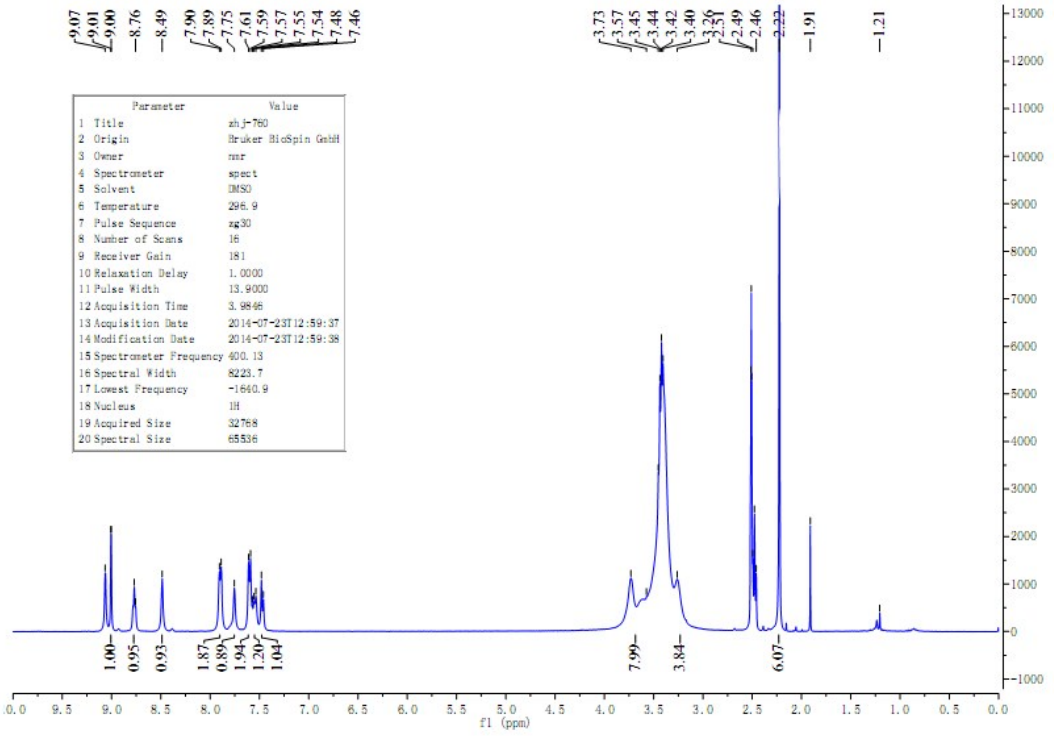




Mp 133-135ºC; EI-MS (m/z) 588.10[M+1]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (s, 1H), 8.81 (s, 1H), 8.50 (s, 1H), 7.91 (s, 3H), 7.81 (dd, $J$ = 24.5, 7.0 Hz, 2H), 7.60 (d, $J$ = 7.3 Hz, 2H), 3.44-3.70 (m, 8H), 3.44 (t, $J$ = 6.0 Hz, 4H), 2.26 (s, 6H).

**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*-[2-(dimethylamino)ethyl]nicotinamide (10u)**

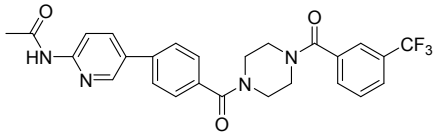


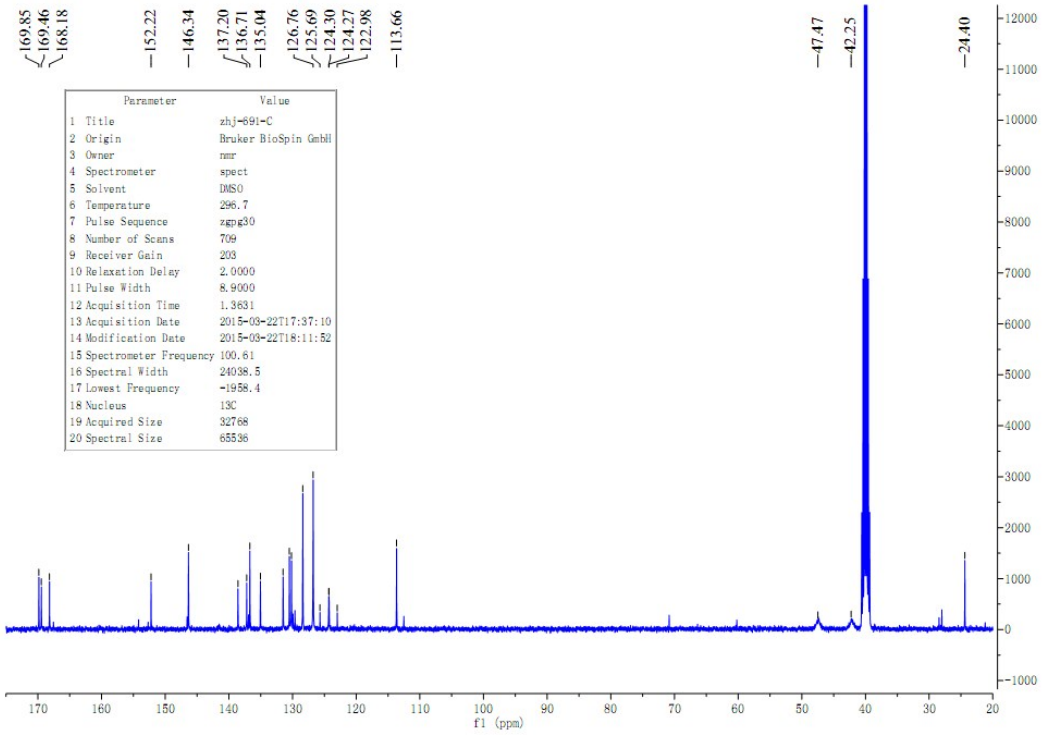



Mp 114-116ºC; EI-MS (m/z) 554.10[M+1]$^+$; $^1$H NMR (400MHz, DMSO-$d_6$) δ 9.01 (d, $J$ = 1.6 Hz, 1H), 8.76 (d, $J$ = 5.1 Hz, 1H), 8.49 (s, 1H), 7.90 (d, $J$ = 6.3 Hz, 2H), 7.75 (s, 1H), 7.60 (d, $J$ = 7.7 Hz, 2H), 7.58-7.52 (m, 1H), 7.47 (d, $J$ = 8.1 Hz, 1H), 3.57-3.73 (m, 8H), 3.26 (s, 4H), 2.22 (s, 6H).

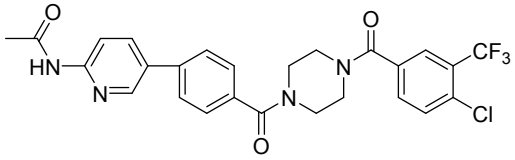
***N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (8a)**

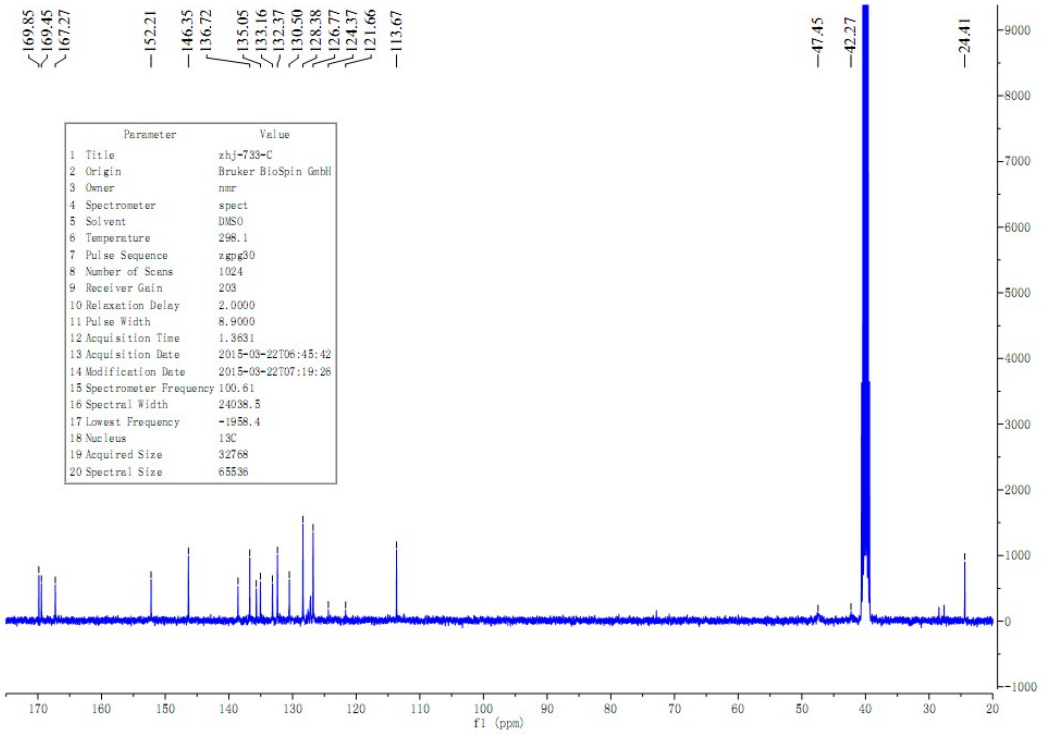



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.85, 169.46, 168.18, 152.22, 146.34, 138.57, 137.20, 136.71, 135.04, 131.48, 130.50, 130.16, 128.39, 126.76, 125.69, 124.30, 124.27, 122.98, 113.66, 47.47, 42.25, 24.40.

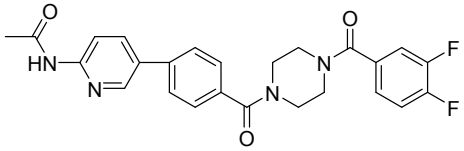
***N*-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (8b)**

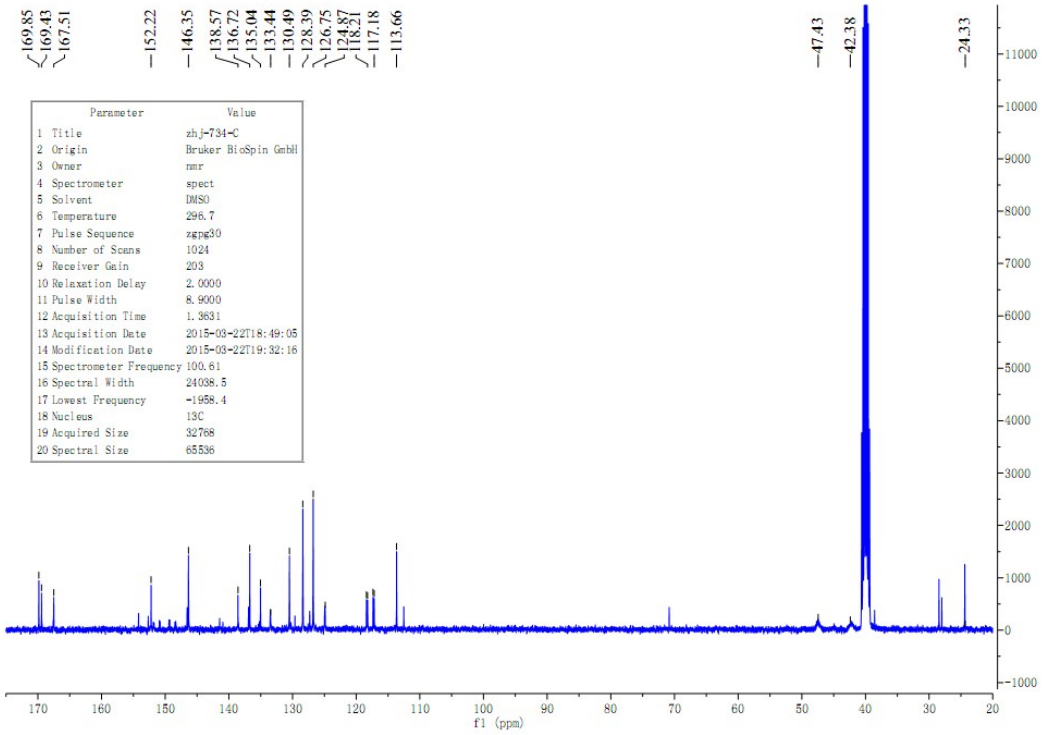



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.85, 169.45, 167.27, 152.21, 146.35, 138.57, 136.72, 135.69, 135.05, 133.16, 132.37, 130.50, 128.38, 126.77, 124.37, 121.66, 113.67, 47.45, 42.27, 24.41.

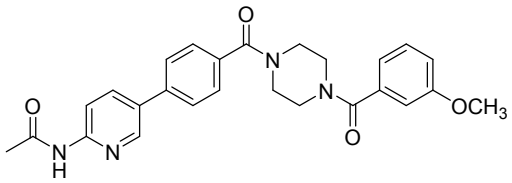
***N*-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (8c)**

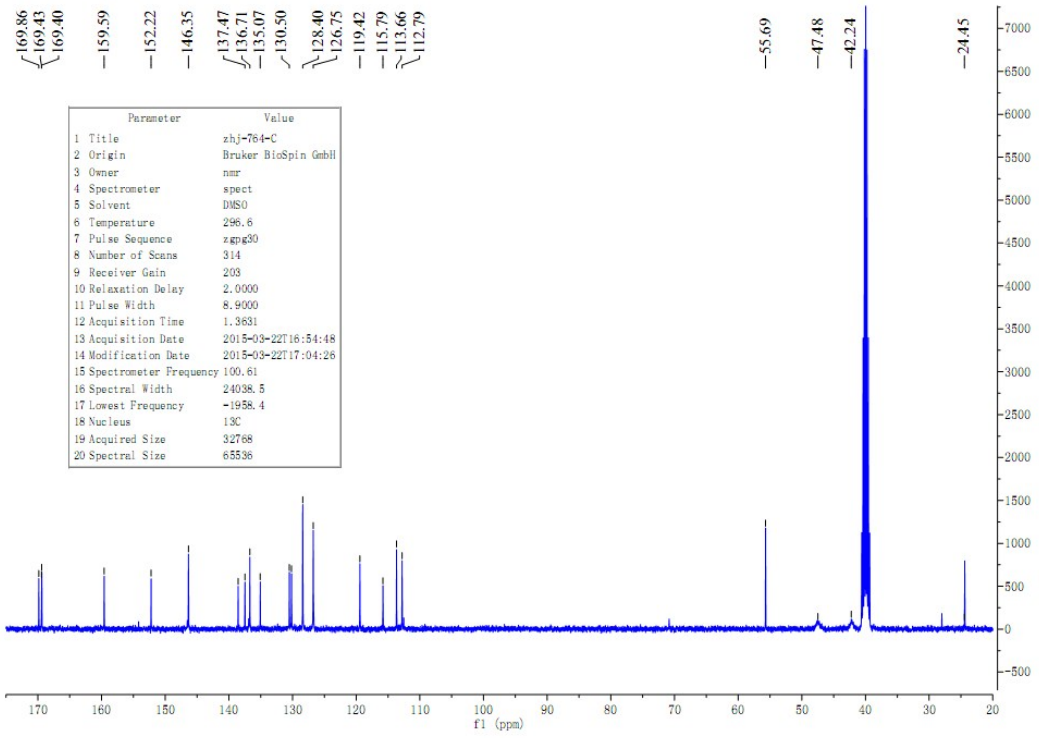


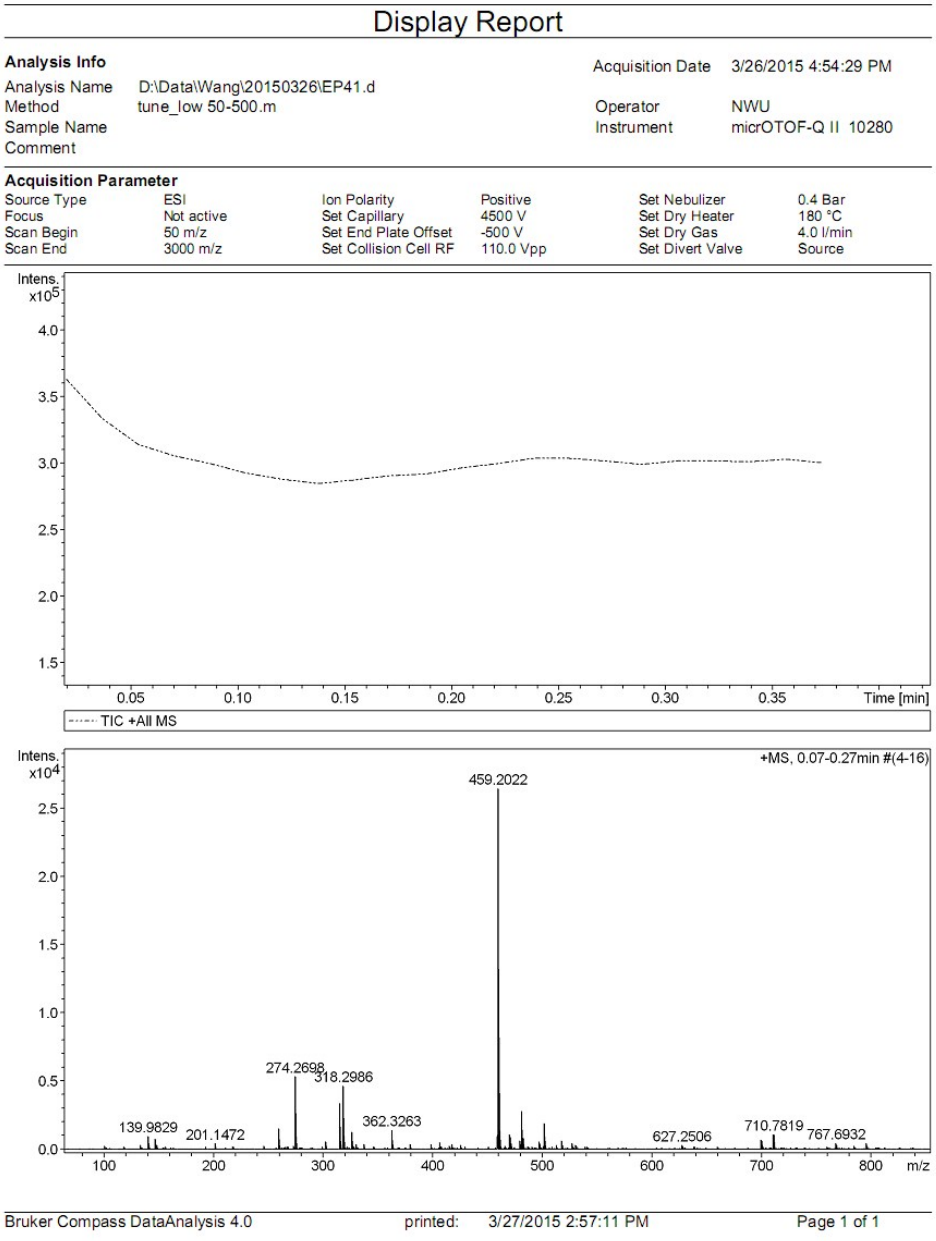

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.85, 169.43, 167.51, 152.22, 146.35, 138.57, 136.72, 135.04, 133.44, 130.49, 128.39, 126.75, 124.87, 118.39, 118.21, 117.36, 117.18, 113.66, 47.43, 42.38, 24.33.

**N-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (8d)**



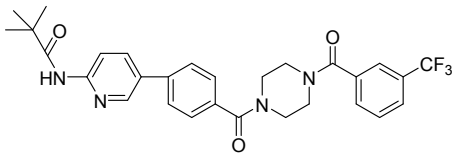


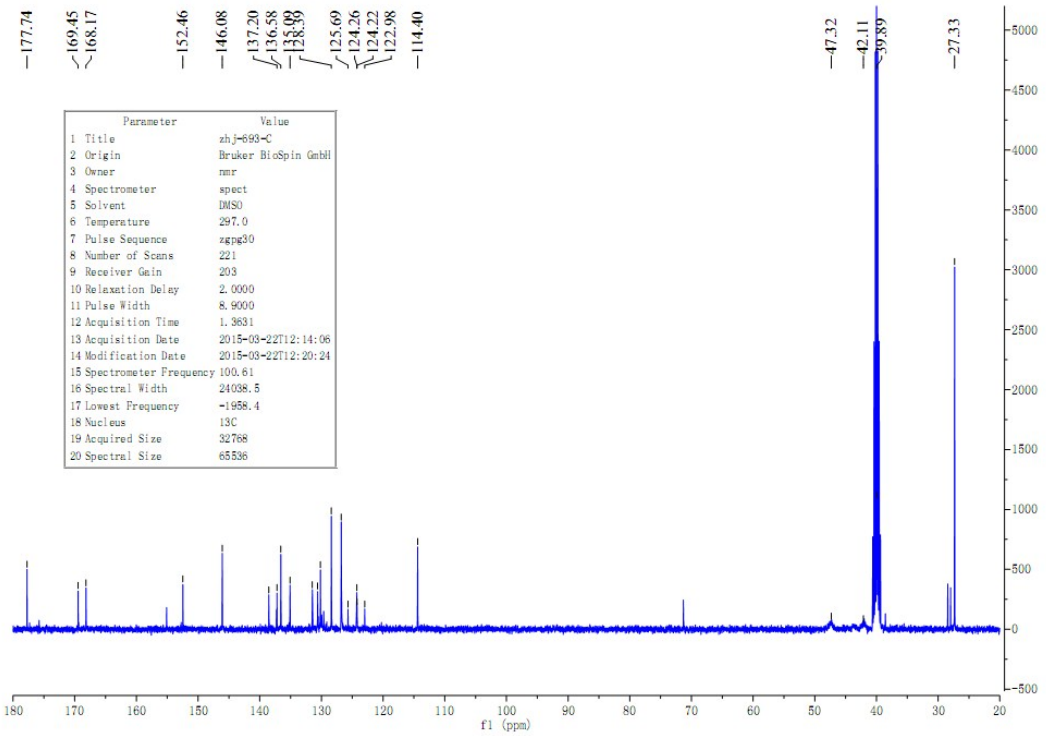

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.86, 169.43, 169.40, 159.59, 152.22, 146.35, 138.55, 137.47, 136.71, 135.07, 130.50, 130.16, 128.40, 126.75, 119.42, 115.79, 113.66, 112.79, 55.69, 47.48, 42.24, 24.45.




HRMS (ESI): Calcd. for $[M+H]^+$ $C_{26}H_{27}N_4O_4$: 459.2032, found 459.2022.

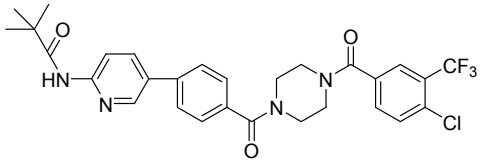
**2,2-dimethyl-*N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}propanamide (8e)**

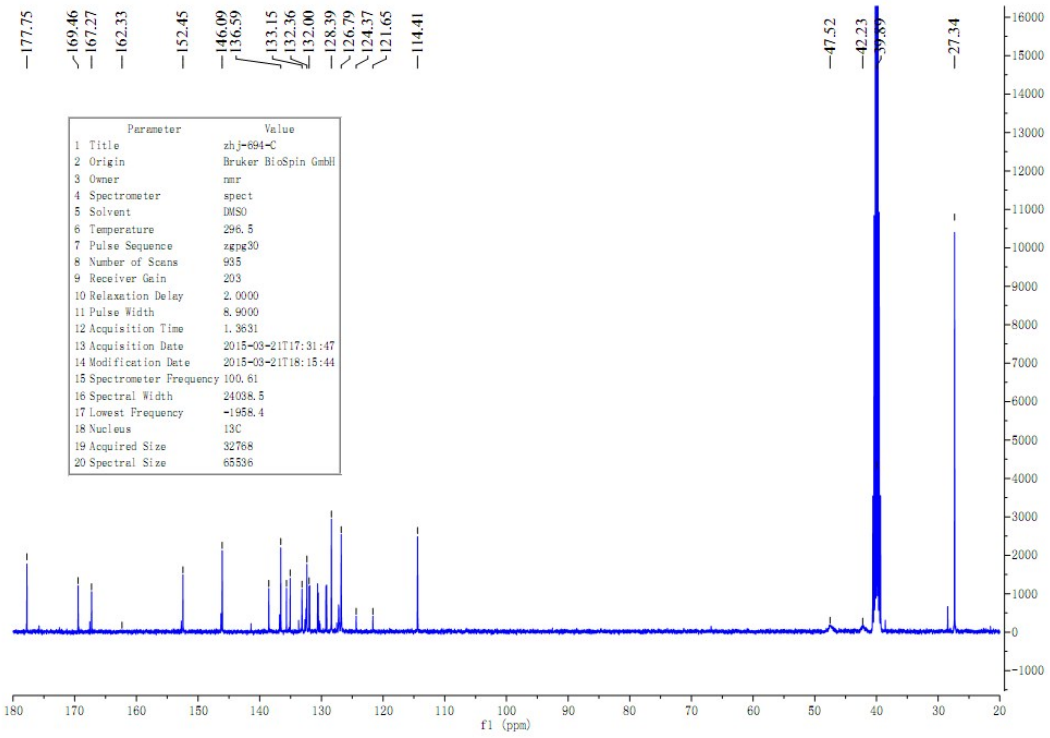



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.74, 169.45, 168.17, 152.46, 146.08, 138.53, 137.20, 136.58, 135.09, 131.48, 130.62, 130.16, 128.39, 126.78, 125.69, 124.26, 124.22, 122.98, 114.40, 47.32, 42.11, 39.89, 27.33.

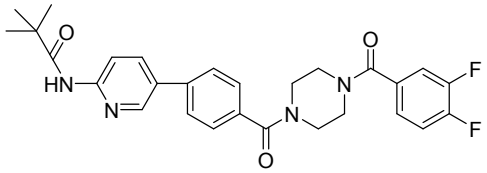
***N*-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}-2,2-dimethylpropanamide (8f)**

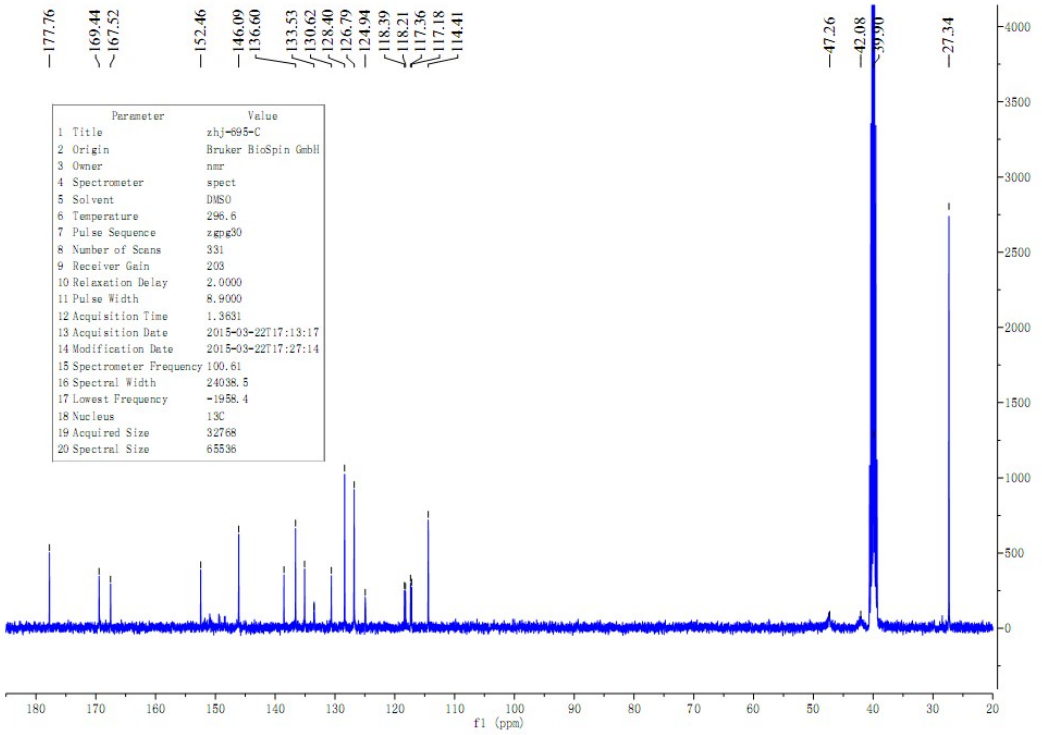



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.75, 169.46, 167.27, 152.45, 146.09, 138.53, 136.59, 135.67, 135.07, 133.15, 132.36, 132.00, 128.39, 126.79, 124.37, 121.65, 114.41, 47.52, 42.23, 39.89, 27.34.

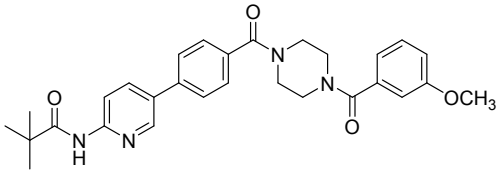
***N*-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide(8g)**

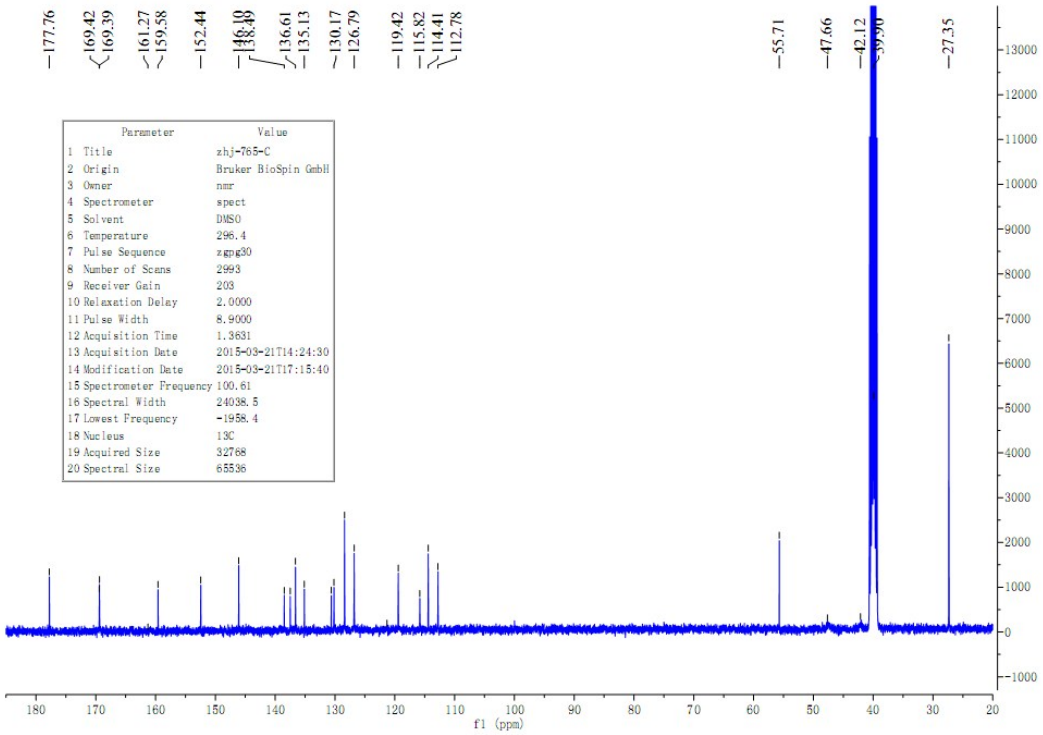


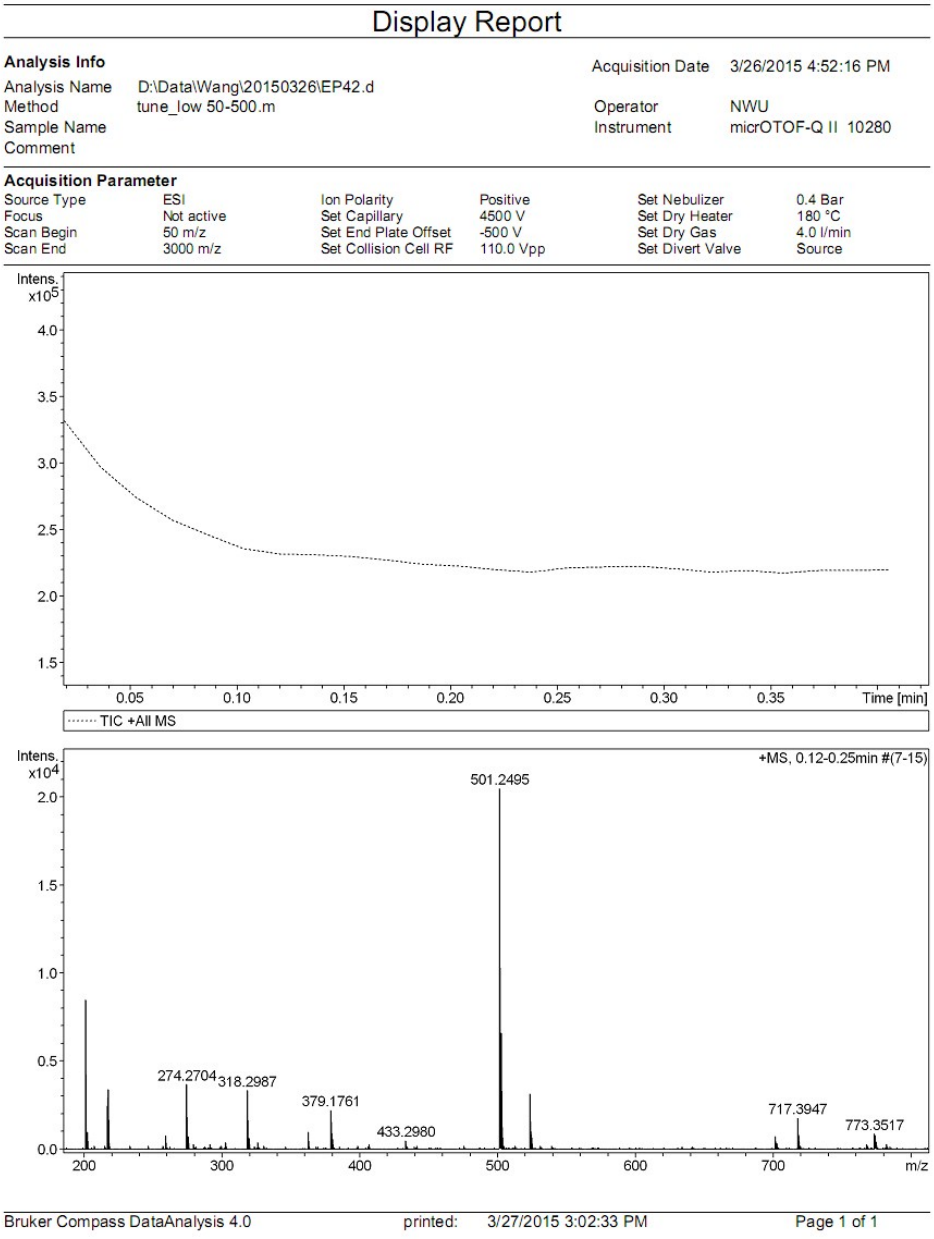

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.76, 169.44, 167.52, 152.46, 146.09, 138.53, 136.60, 135.08, 133.53, 130.62, 128.40, 126.79, 124.94, 118.39, 118.21, 117.36, 117.18, 114.41, 47.26, 42.08, 39.90, 27.34.

***N*-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide (8h)**



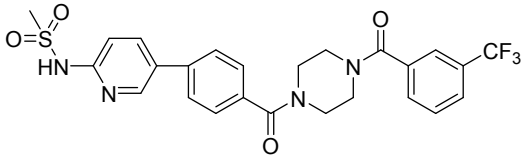



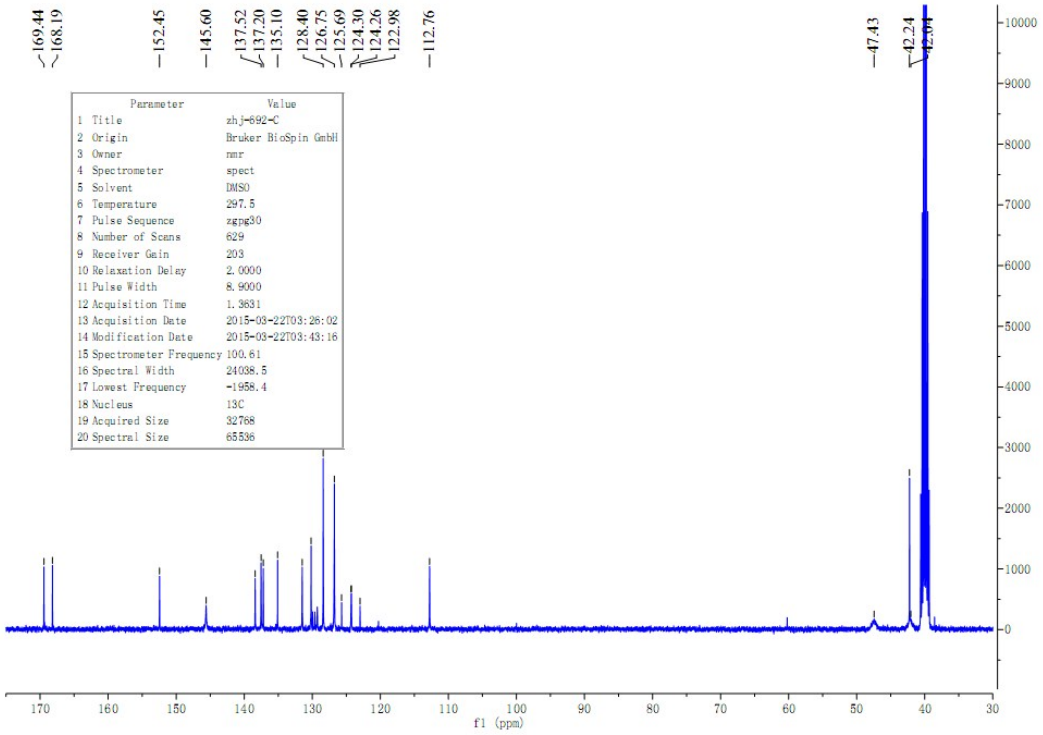

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.76, 169.42, 169.39, 161.27, 159.58, 152.44, 146.10, 138.49, 137.48, 136.61, 135.13, 130.62, 130.17, 128.40, 126.79, 119.42, 115.82, 114.41, 112.78, 55.71, 47.66, 42.12, 39.90, 27.35.




HRMS (ESI): Calcd. for $[M+H]^+$ $C_{29}H_{33}N_4O_4$: 501.2502, found 501.2495.

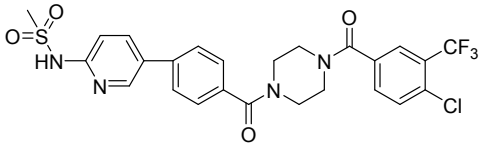
*N*-{5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (**8i**)

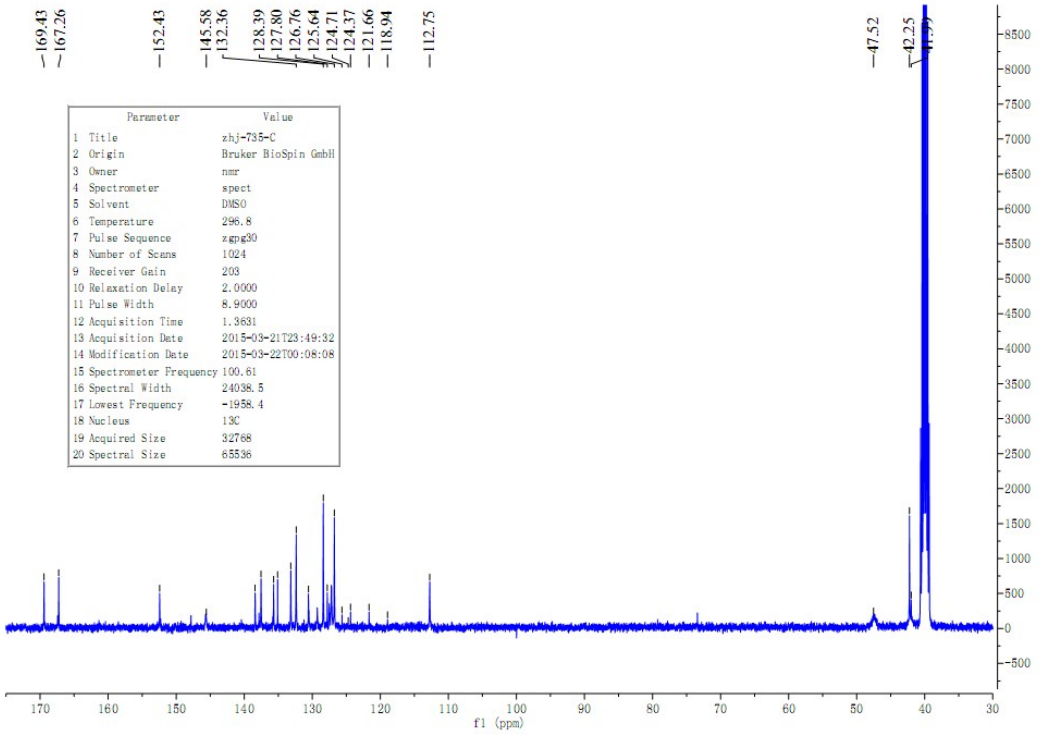





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.44, 168.19, 152.45, 145.60, 138.40, 137.52, 137.20, 135.10, 131.48, 130.17, 128.40, 126.75, 125.69, 124.30, 124.26, 122.98, 112.76, 47.43, 42.24, 42.04.

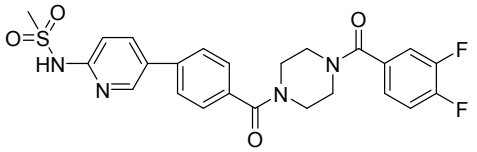
***N*-{5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (8j)**

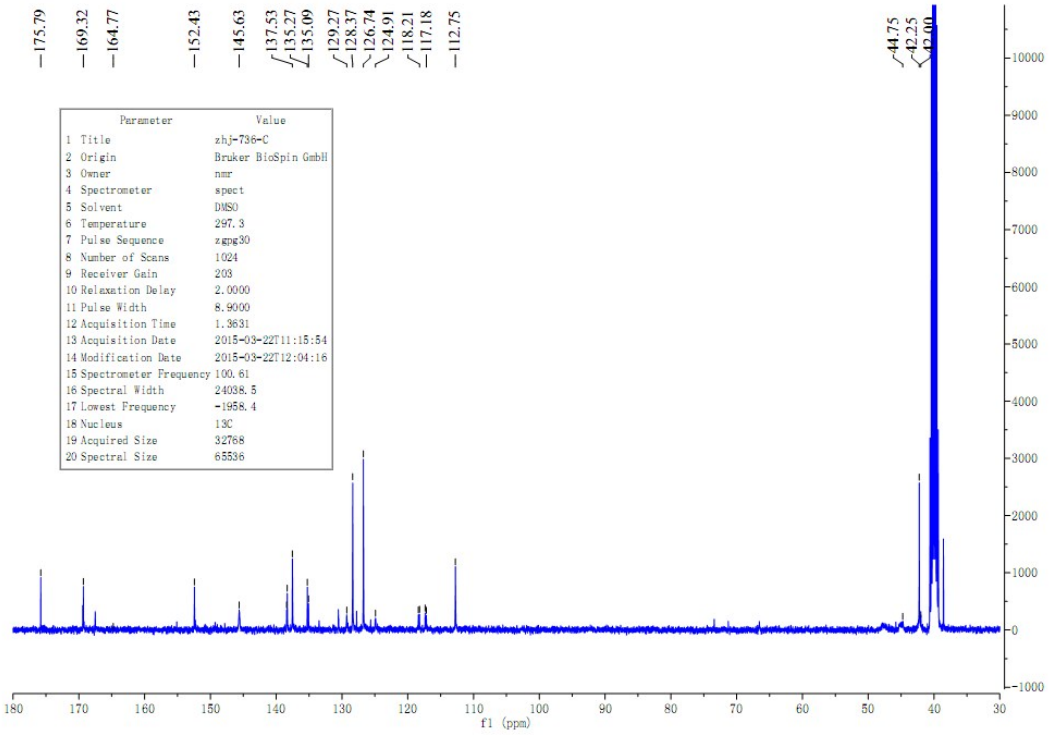





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.43, 167.26, 152.43, 145.58, 138.41, 137.53, 135.68, 135.09, 133.15, 132.36, 130.57, 128.39, 127.80, 126.76, 125.64, 124.37, 121.66, 118.94, 112.75, 47.52, 42.25, 41.99.

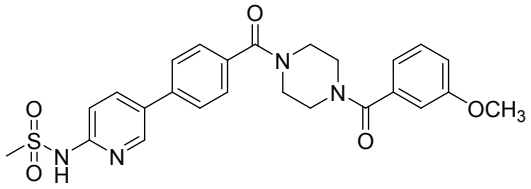
***N*-[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide (8k)**

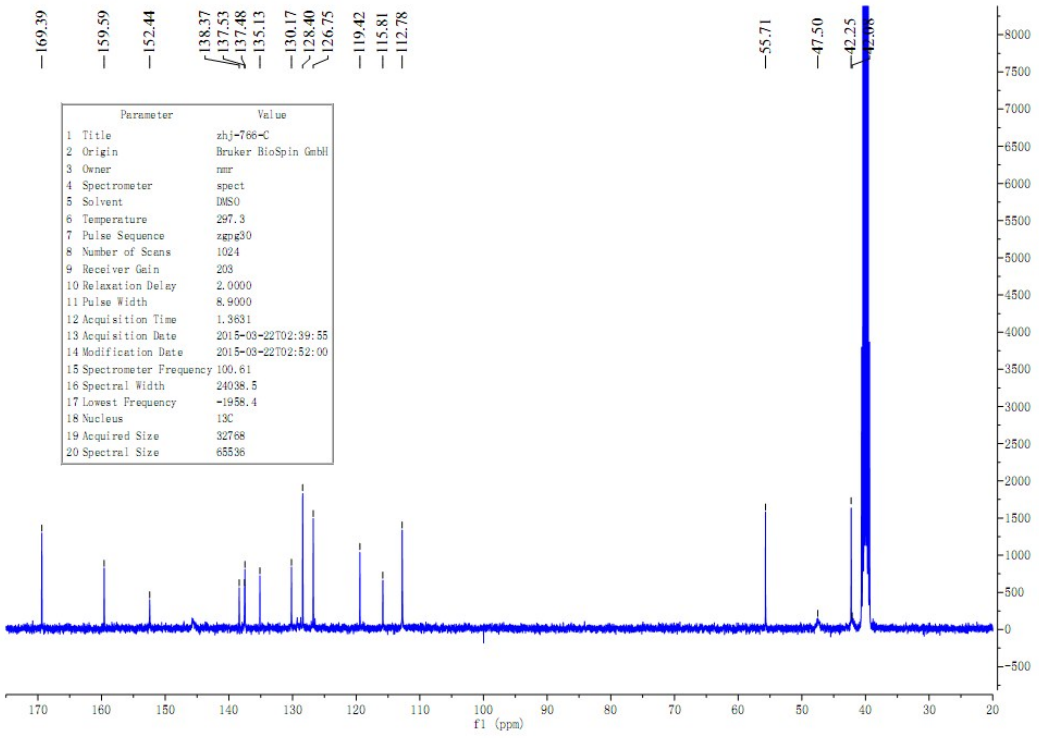




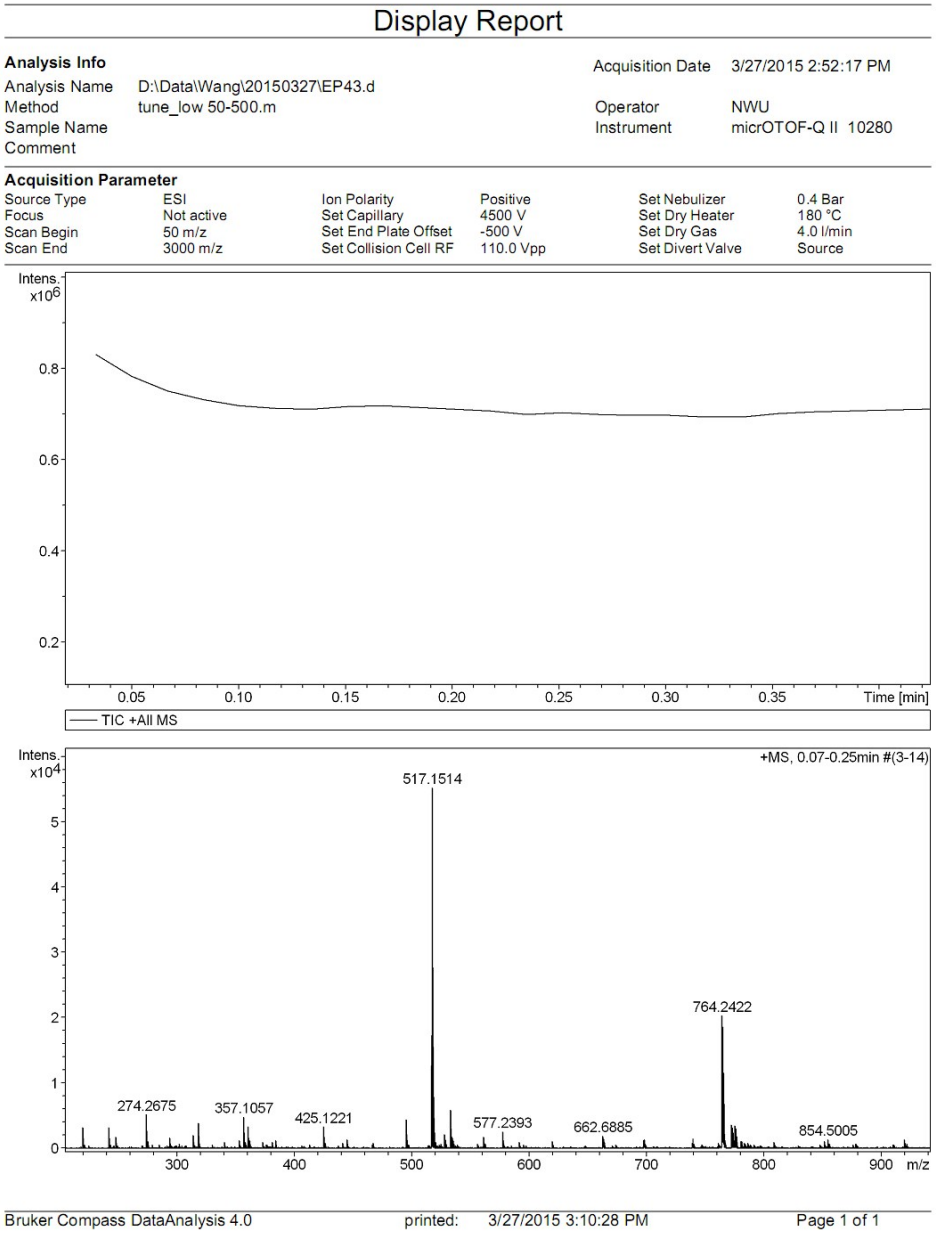

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.79, 169.32, 152.43, 145.63, 138.41, 138.32, 137.53, 135.27, 135.09, 129.27, 128.37, 126.74, 124.91, 118.38, 118.21, 117.36, 117.18, 112.75, 44.75, 42.25, 42.00.

***N*-[5-(4-{[4-(3-methoxybenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide (8l)**



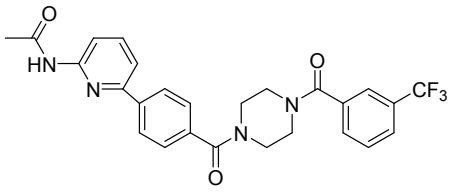


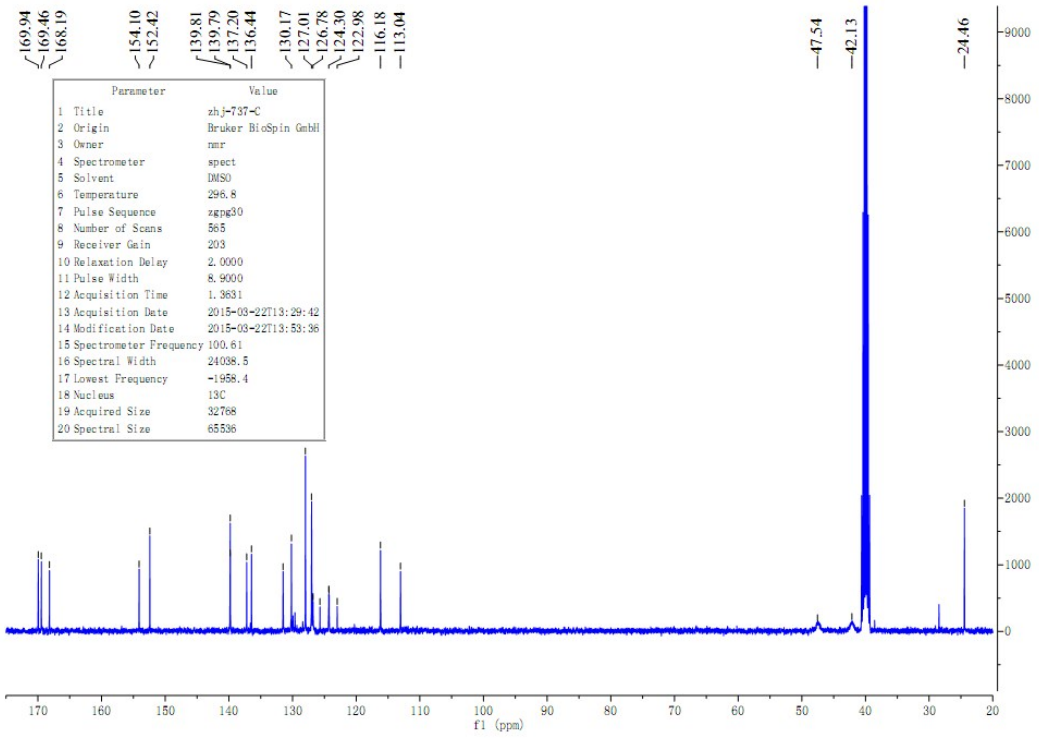

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.39, 159.59, 152.44, 138.37, 137.53, 137.48, 135.13, 130.17, 128.40, 126.75, 119.42, 115.81, 112.78, 55.71, 47.50, 42.25, 42.08.




HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{25}H_{26}N_4O_5SNa$: 517.1522, found 517.1514.

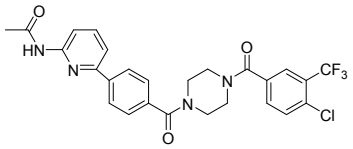
***N*-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (9a)**

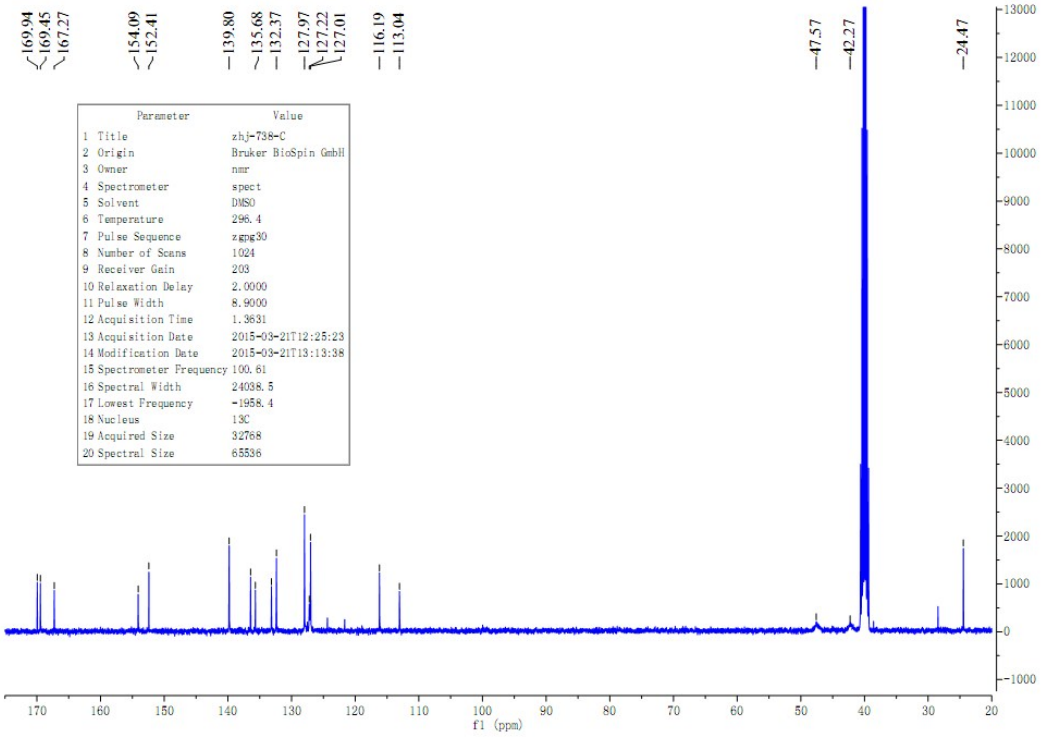



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.94, 169.46, 168.19, 154.10, 152.42, 139.81, 139.79, 137.20, 136.44, 131.49, 130.17, 127.97, 127.01, 126.82, 126.78, 125.69, 124.30, 124.26, 122.98, 116.18, 113.04, 47.54, 42.13, 24.46.

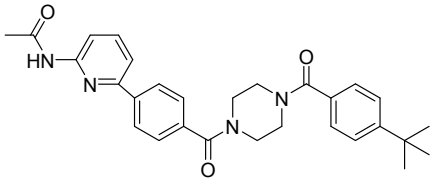
***N*-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}acetamide (9b)**

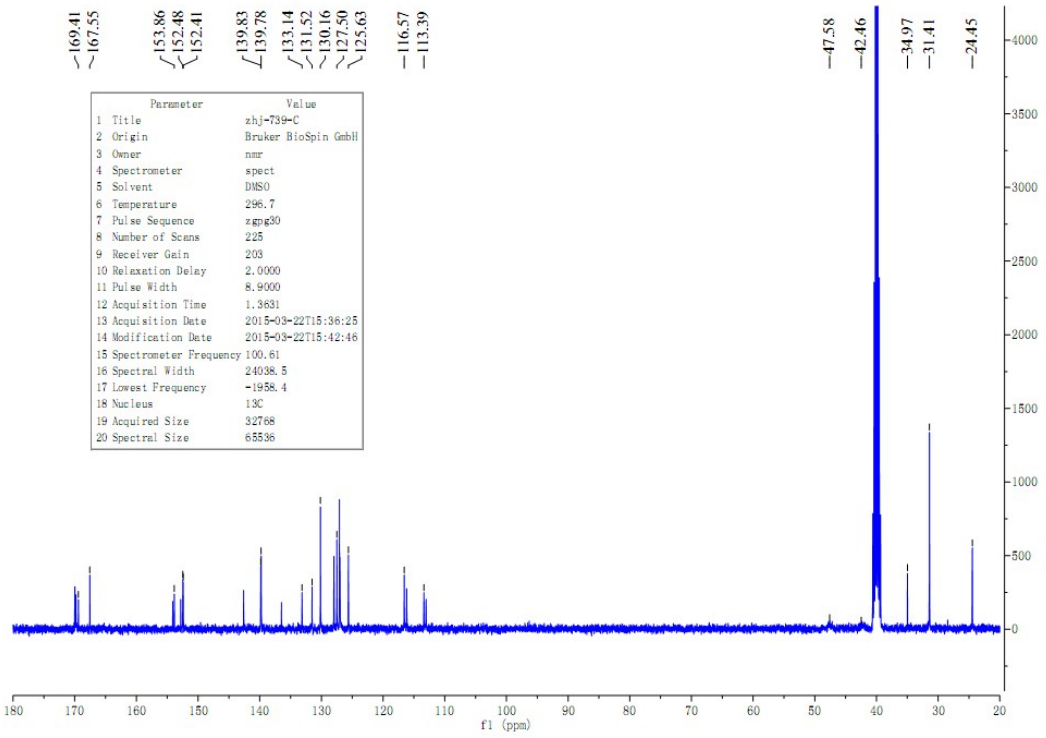





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.94, 169.45, 167.27, 154.09, 152.41, 139.80, 136.43, 135.68, 133.16, 132.37, 127.97, 127.22, 127.01, 116.19, 113.04, 47.57, 42.27, 24.47.

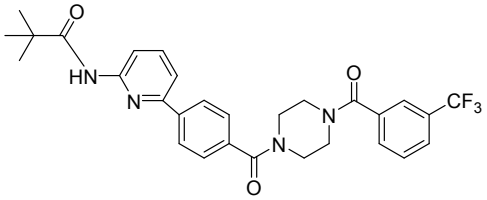
***N*-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]acetamide (9c)**

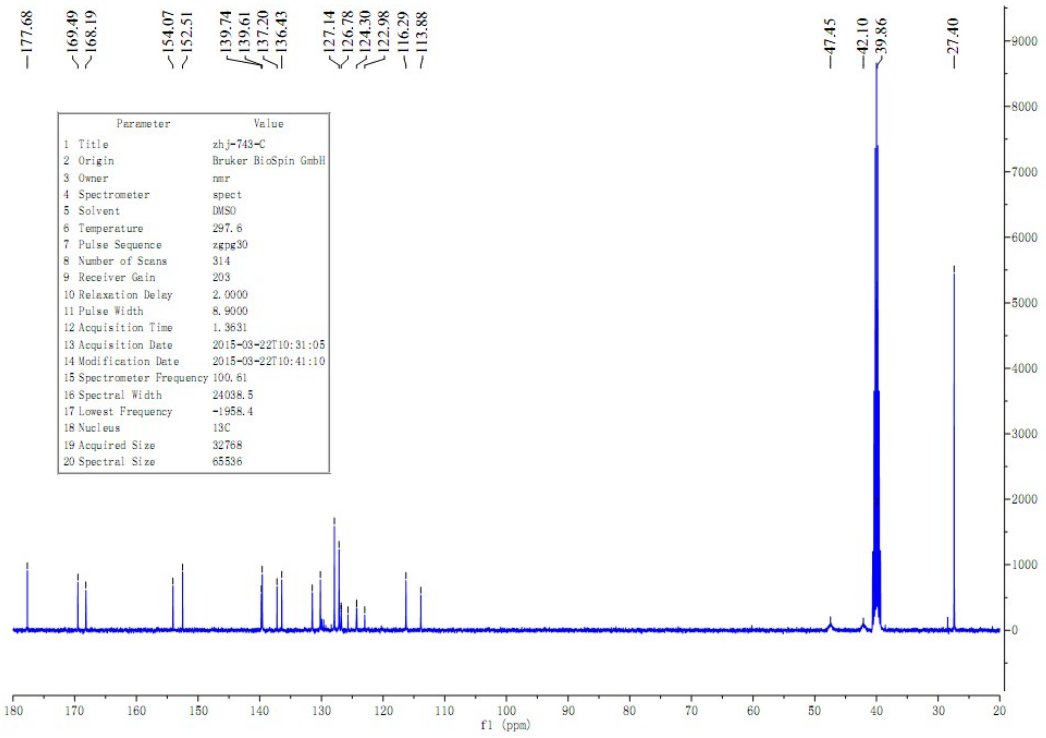





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.41, 167.55, 153.86, 152.48, 152.41, 139.83, 139.78, 133.14, 131.52, 130.16, 127.50, 125.63, 116.57, 113.39, 47.58, 42.46, 34.97, 31.41, 24.45.

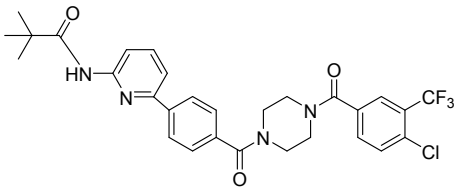
**2,2-dimethyl-*N*-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}propanamide (9d)**

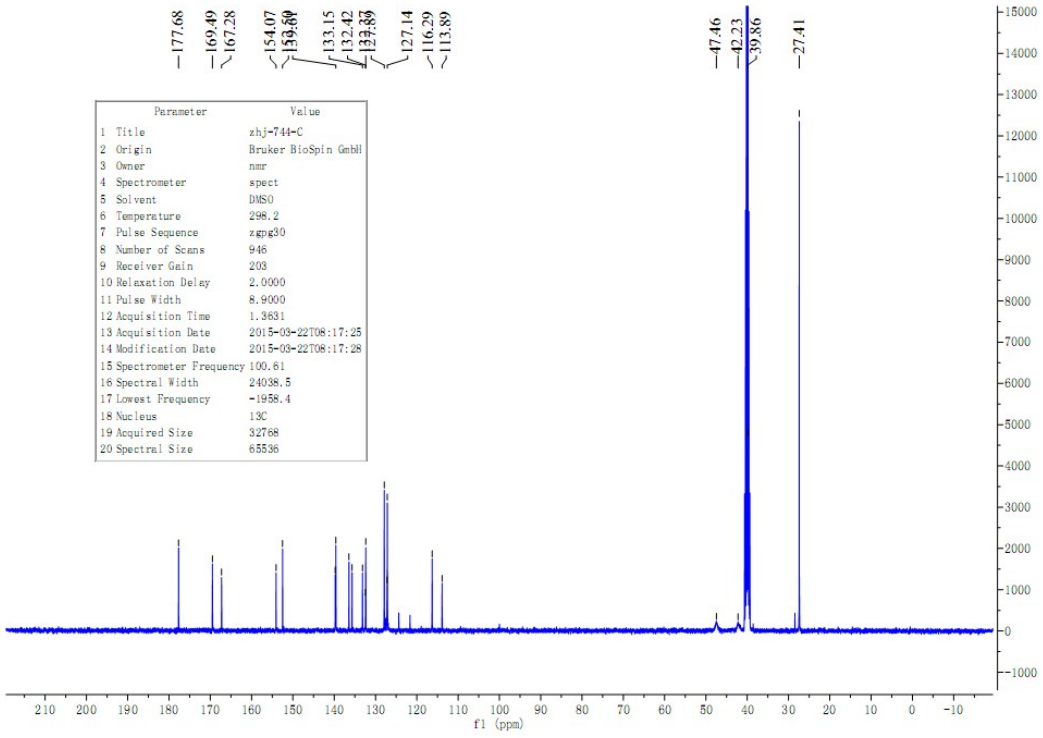


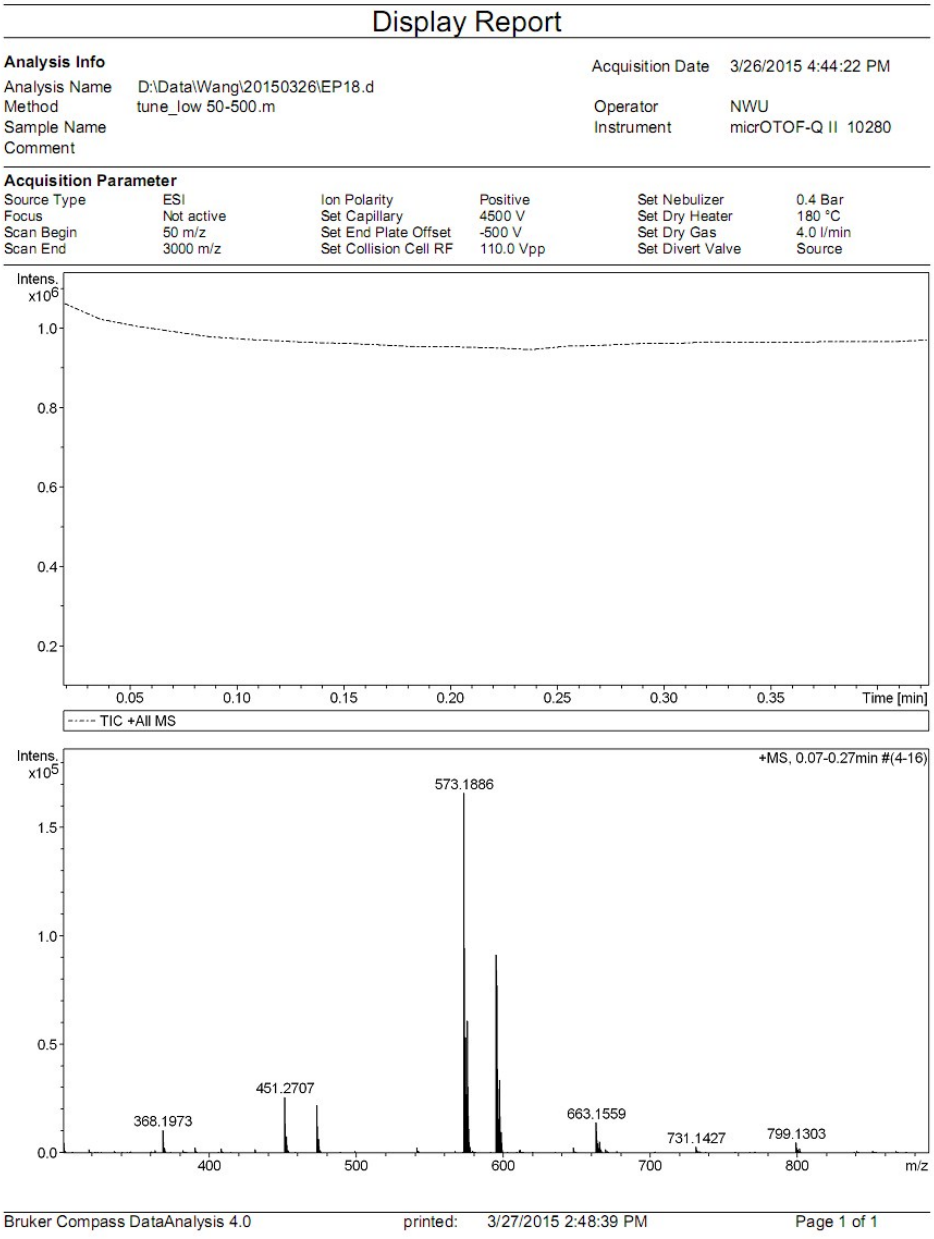

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.68, 169.49, 168.19, 154.07, 152.51, 139.74, 139.61, 137.20, 136.43, 131.48, 130.17, 127.90, 127.14, 126.82, 126.78, 125.69, 124.30, 124.27, 122.98, 116.29, 113.88, 47.45, 42.10, 39.86, 27.40.

***N*-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}-2,2-dimethylpropanamide (9e)**



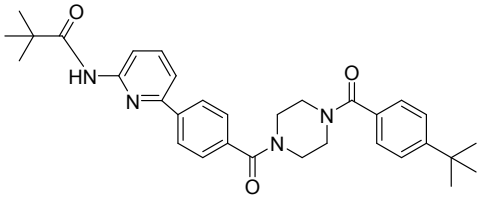



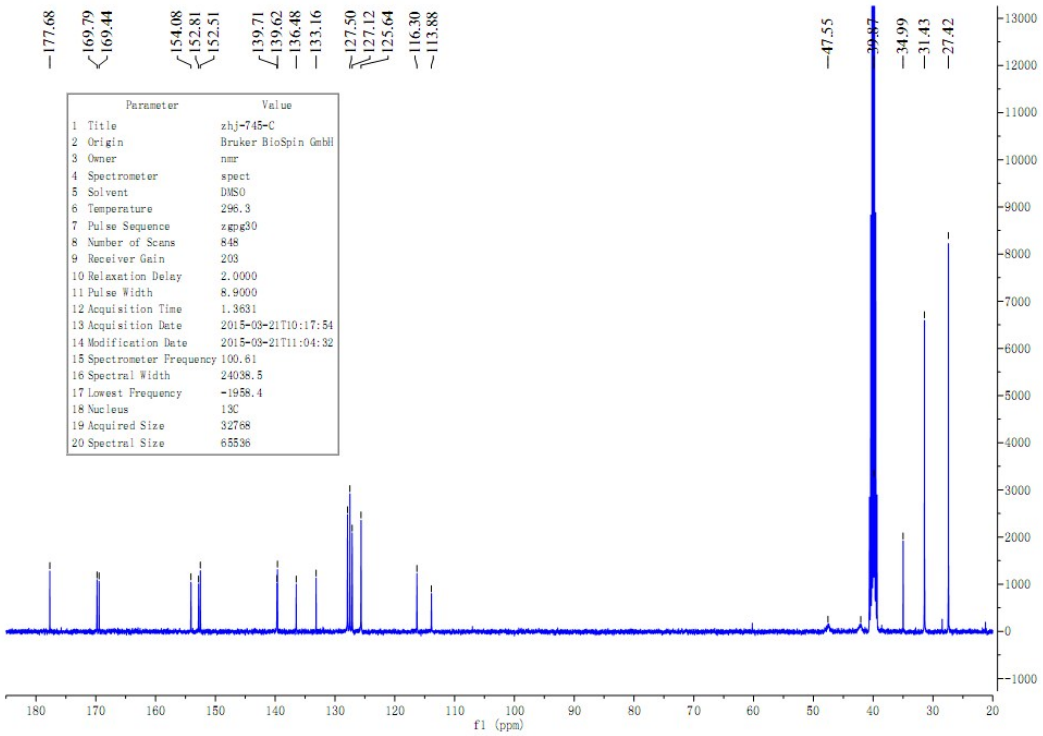

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.68, 169.49, 167.28, 154.07, 152.50, 139.75, 139.61, 136.43, 135.68, 133.15, 132.42, 132.37, 127.89, 127.22, 127.14, 116.29, 113.89, 47.46, 42.23, 39.86, 27.41.




HRMS (ESI): Calcd. for $[M+H]^+$ $C_{29}H_{29}ClF_3N_4O_3$: 573.1880, found 573.1886.

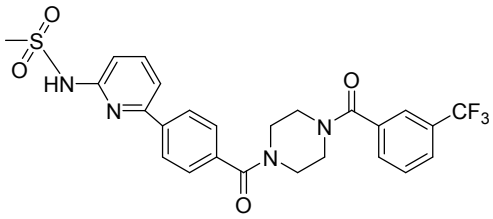
***N*-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]-2,2-dimethylpropanamide (9f)**

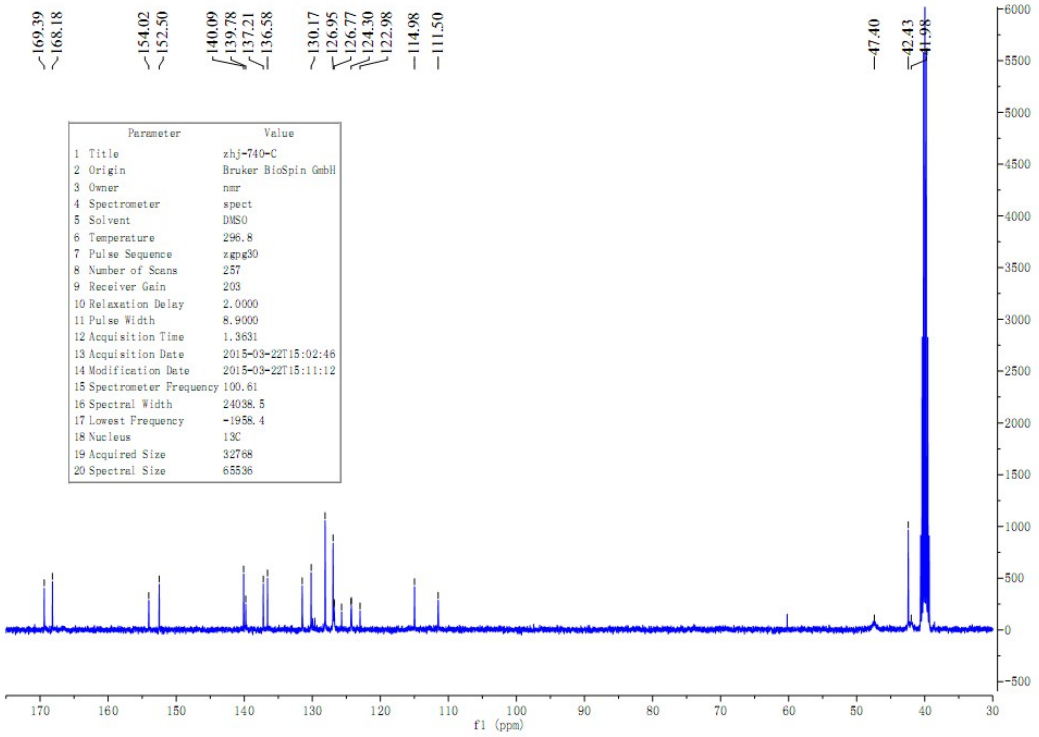





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 177.68, 169.79, 169.44, 154.08, 152.81, 152.51, 139.71, 139.62, 136.48, 133.16, 127.90, 127.50, 127.12, 125.64, 116.30, 113.88, 47.55, 42.07, 39.87, 34.99, 31.43, 27.42.

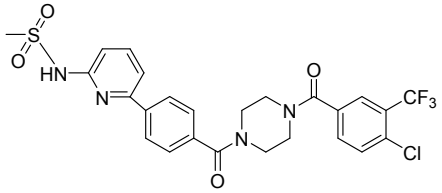
***N*-{6-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (9g)**

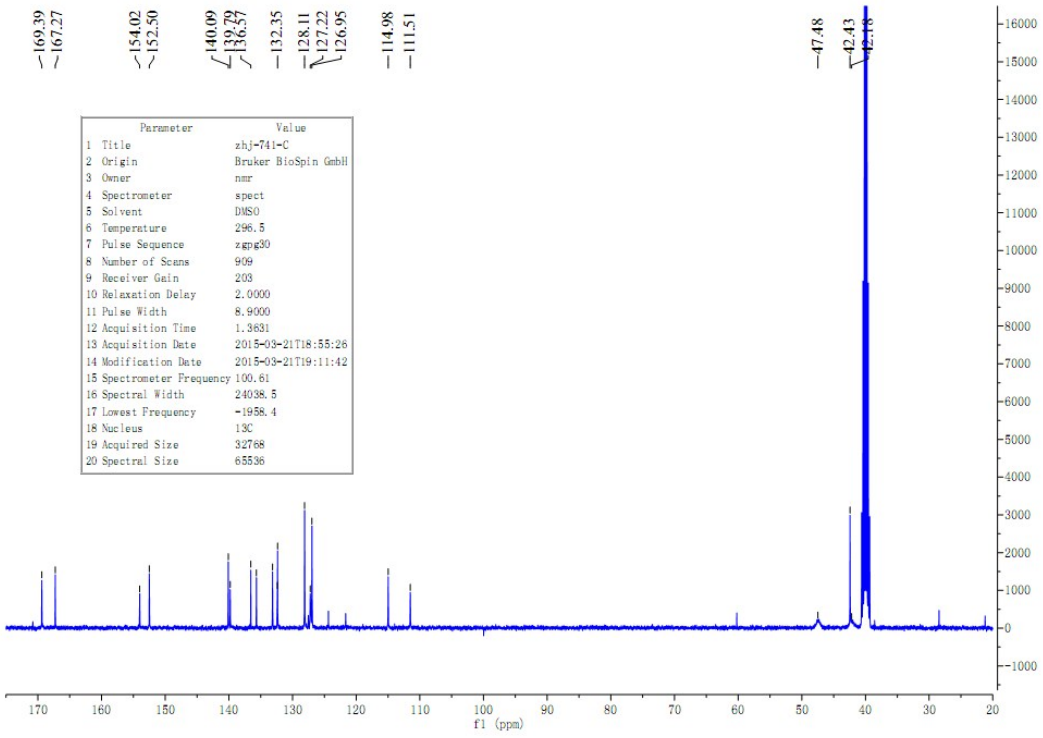




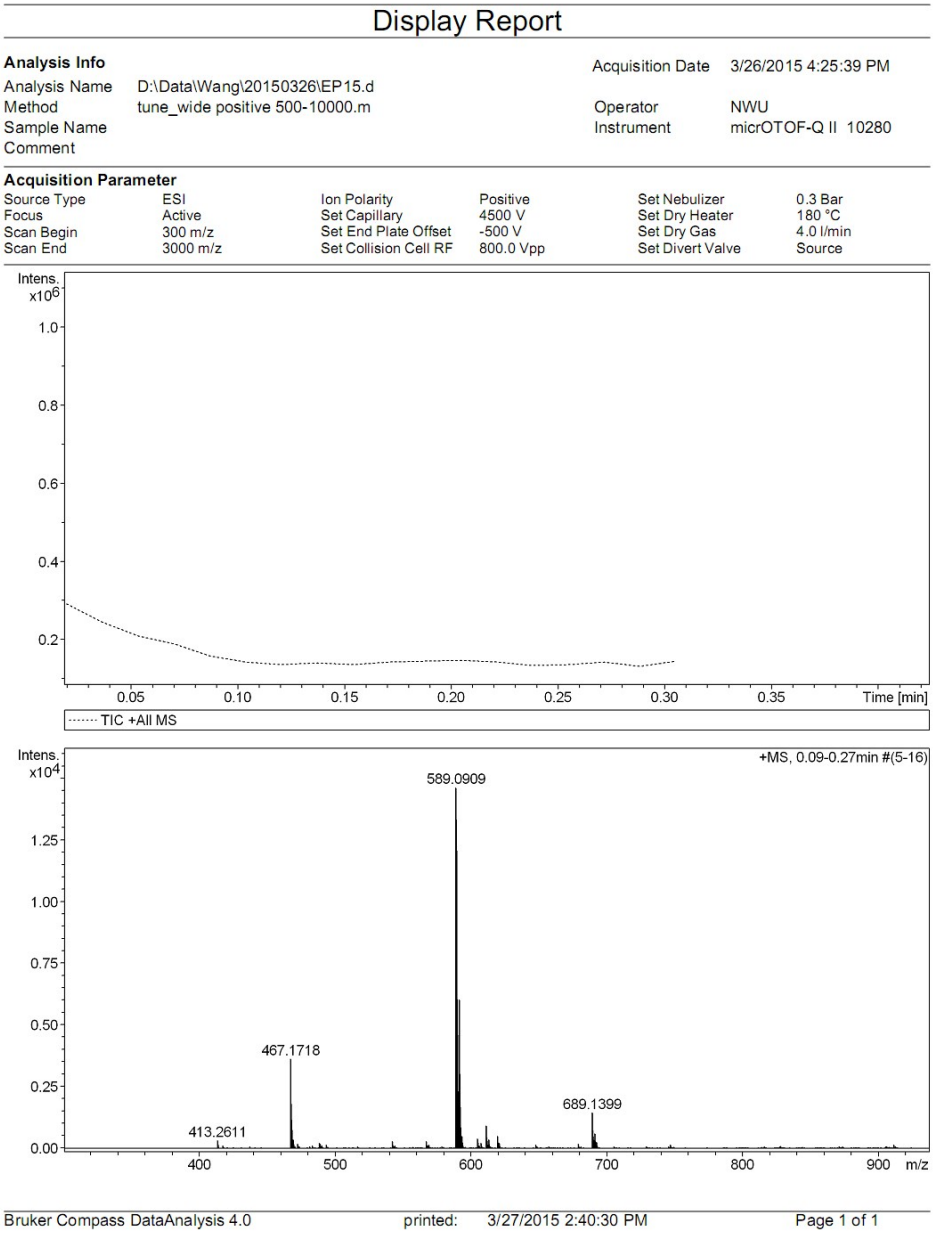

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.39, 168.18, 154.02, 152.50, 140.09, 139.78, 137.21, 136.58, 131.48, 130.17, 128.11, 126.95, 126.81, 126.77, 125.69, 124.30, 124.26, 122.98, 114.98, 111.50, 47.40, 42.43, 41.98.

***N*-{6-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-2-yl}methanesulfonamide (9h)**



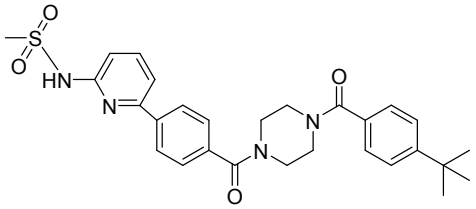


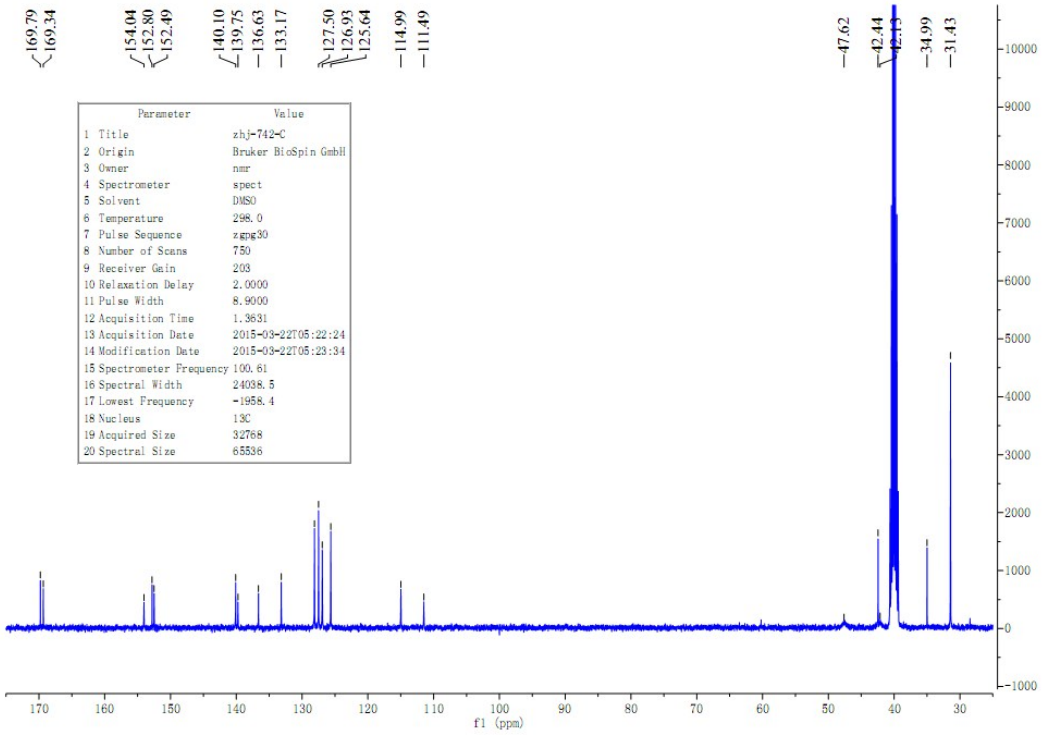

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.39, 167.27, 154.02, 152.50, 140.09, 139.79, 136.57, 135.68, 133.14, 132.39, 132.35, 128.11, 127.22, 126.95, 114.98, 111.51, 47.48, 42.43, 42.18.




HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{25}H_{22}ClF_3N_4O_4SNa$: 589.0900, found 589.0909.

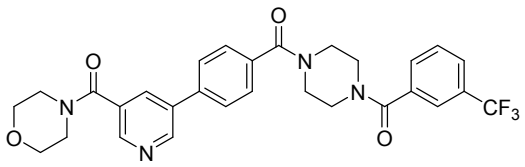
***N*-[6-(4-{[4-(4-tert-butylbenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-2-yl]methanesulfonamide(9i)**

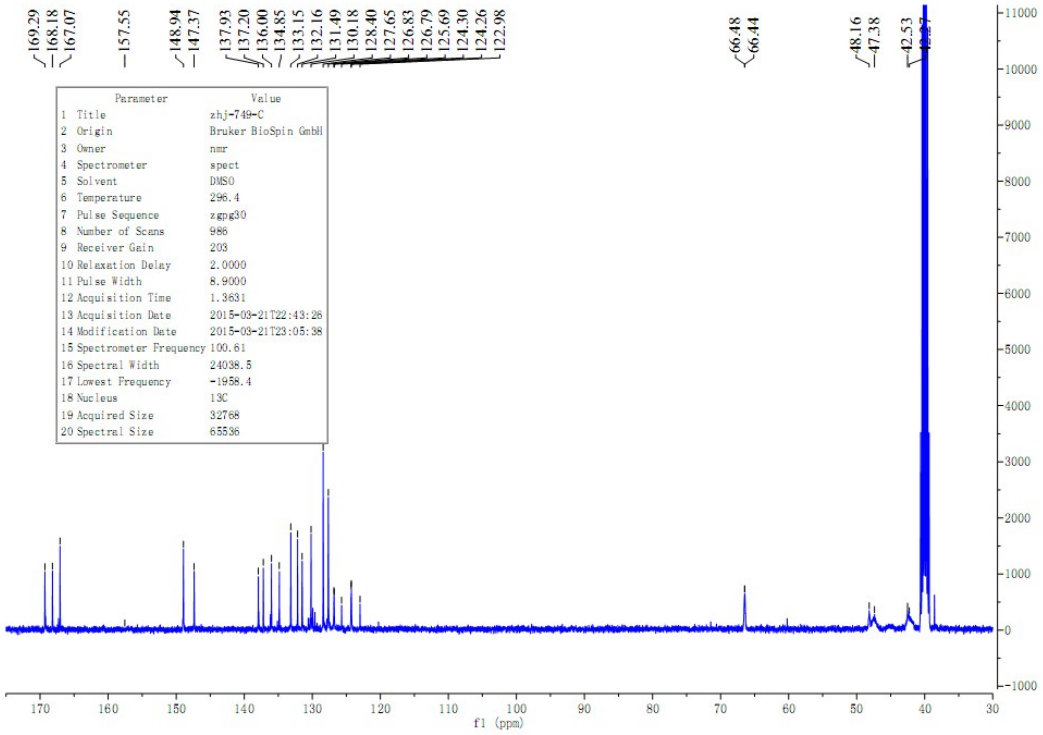





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.79, 169.34, 154.04, 152.80, 152.49, 140.10, 139.75, 136.63, 133.17, 128.12, 127.50, 126.93, 125.64, 114.99, 111.49, 47.62, 42.44, 42.13, 34.99, 31.43.

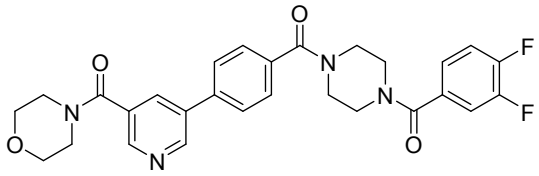
**4-({5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]pyridin-3-yl}carbonyl)morpholine (10a)**

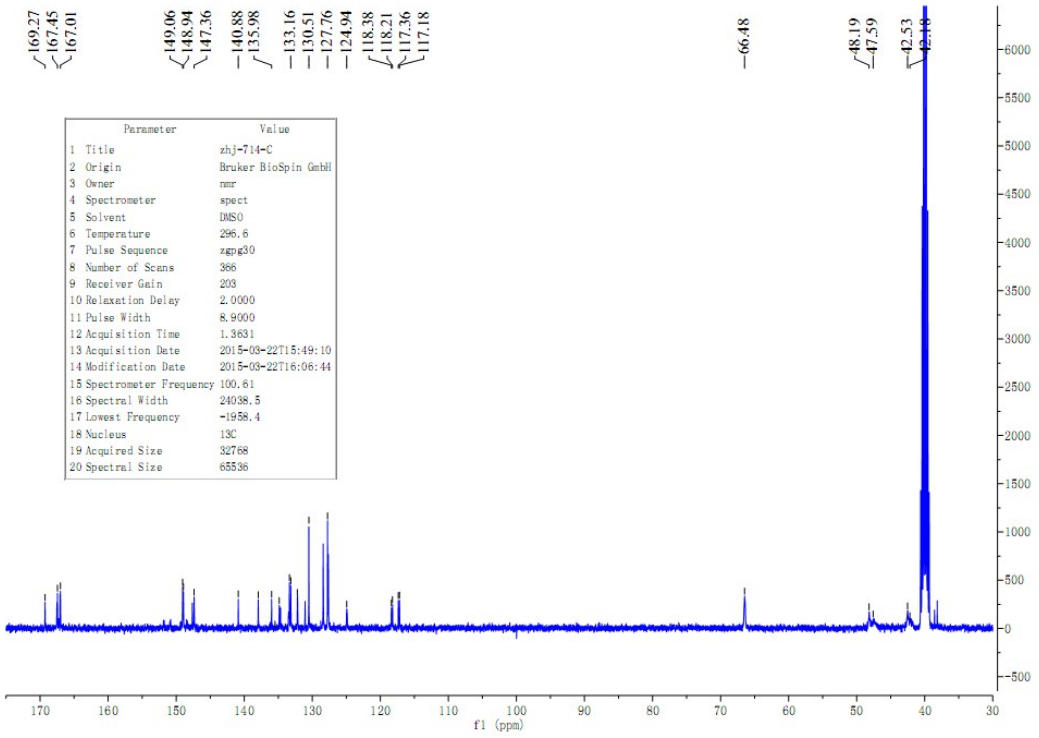



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.29, 168.18, 167.07, 148.94, 147.37, 137.93, 137.20, 136.00, 134.85, 133.15, 132.16, 131.49, 130.18, 128.40, 127.65, 126.83, 126.79, 125.69, 124.30, 124.26, 122.98, 66.48, 66.44, 48.16, 47.38, 42.53, 42.27.

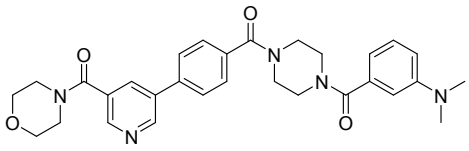
**4-{[5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)pyridin-3-yl]carbonyl}morpholine (10b)**

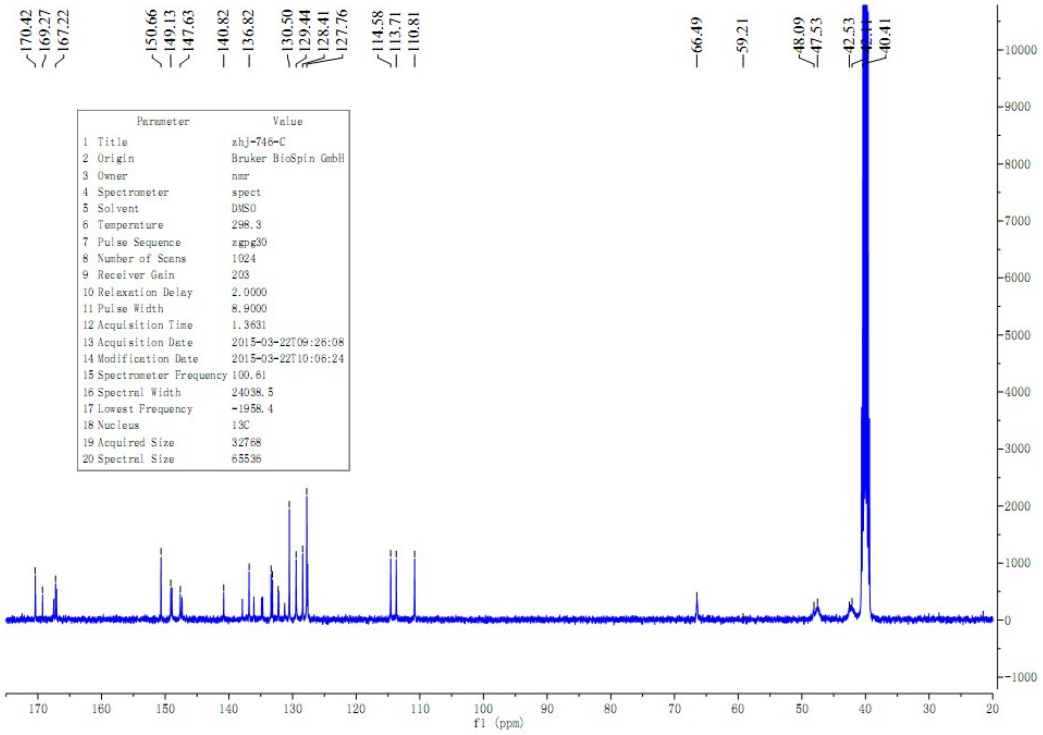





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.27, 167.45, 167.01, 149.06, 148.94, 147.36, 140.88, 137.94, 135.98, 134.85, 133.36, 133.16, 132.19, 130.51, 127.76, 124.94, 118.38, 118.21, 117.36, 117.18, 66.48, 48.19, 47.59, 42.53, 42.18.

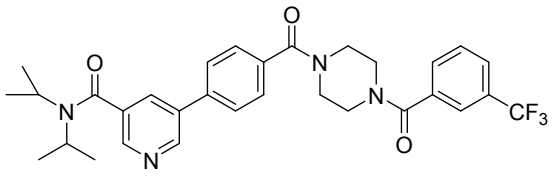
**Dimethyl{3-[(4-{4-[5-(morpholin-4-ylcarbonyl)pyridin-3-yl]benzoyl}piperazin-1-yl)carbonyl]phenyl}amine (10c)**

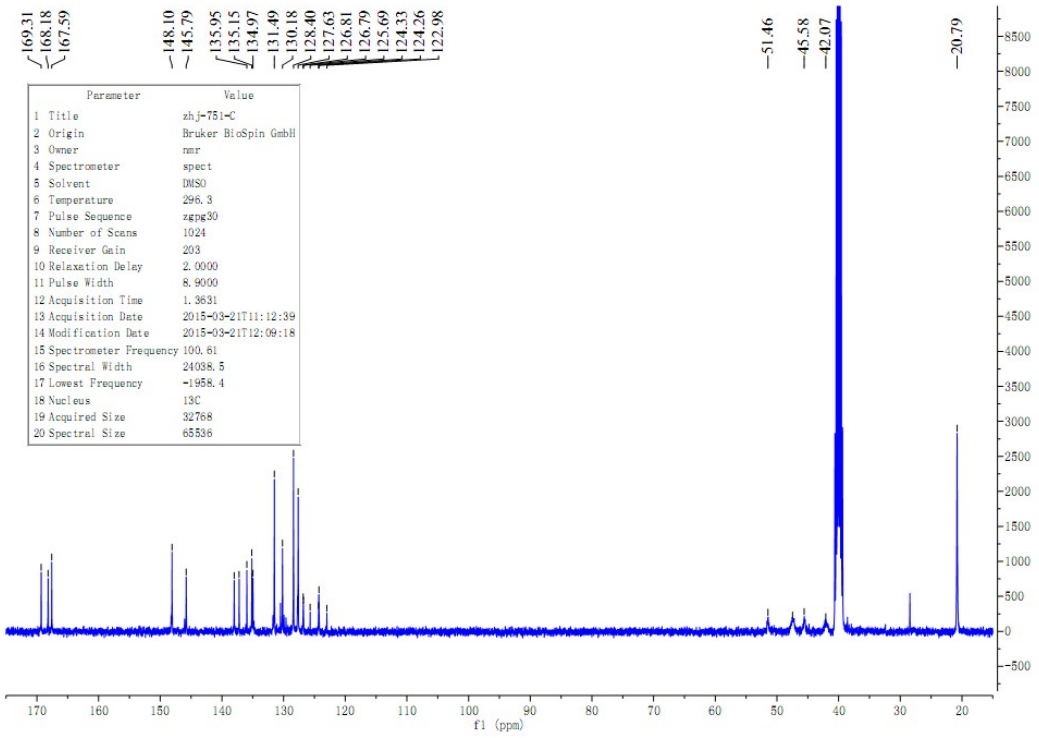





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.42, 169.27, 167.22, 150.66, 149.13, 147.63, 140.82, 136.82, 133.37, 133.15, 132.25, 130.50, 129.44, 128.41, 127.76, 114.58, 113.71, 110.81, 66.49, 48.09, 47.53, 42.53, 42.11, 40.41.

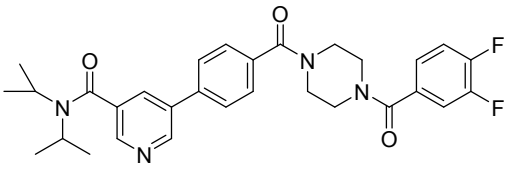
**_N,N_-diisopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10d)**

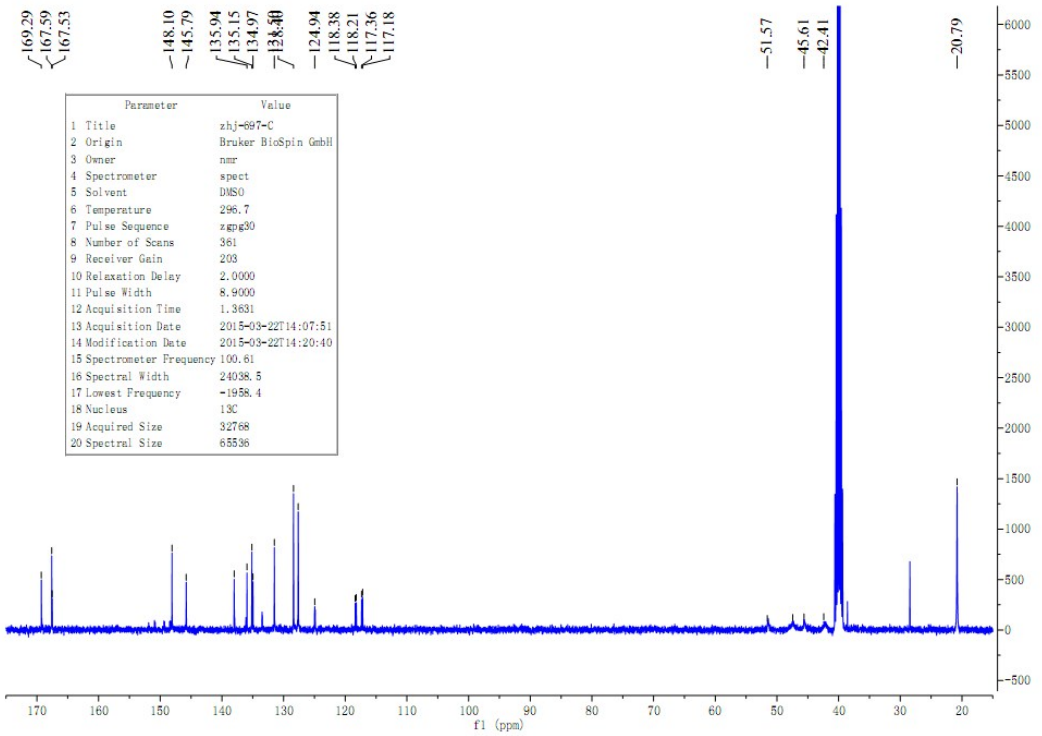



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.31, 168.18, 167.59, 148.10, 145.79, 138.00, 137.20, 135.95, 135.15, 134.97, 131.49, 130.18, 128.40, 127.63, 126.81, 126.79, 125.69, 124.33, 124.26, 122.98, 51.46, 47.47, 45.58, 42.07, 20.79.

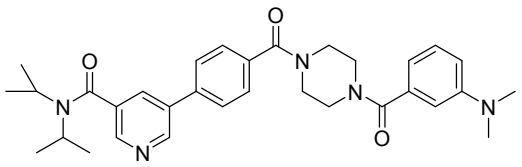
**5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*,*N*-diisopropylnicotinamide (10e)**

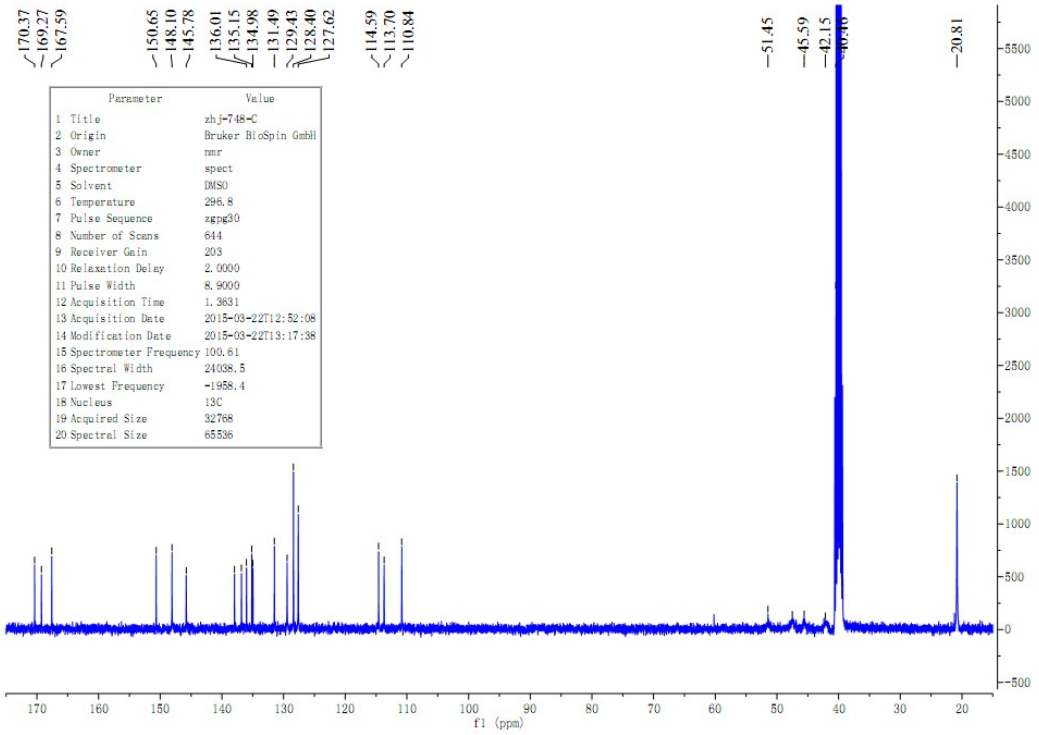





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.29, 167.59, 167.53, 148.10, 145.79, 138.01, 135.94, 135.15, 134.97, 131.50, 128.40, 127.63, 124.94, 118.38, 118.21, 117.36, 117.18, 51.57, 47.45, 45.61, 42.41, 20.79.

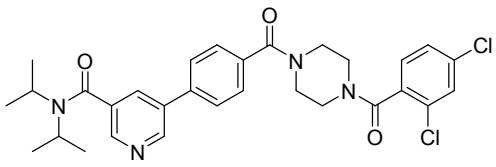
**5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diisopropylnicotinamide (10f)**

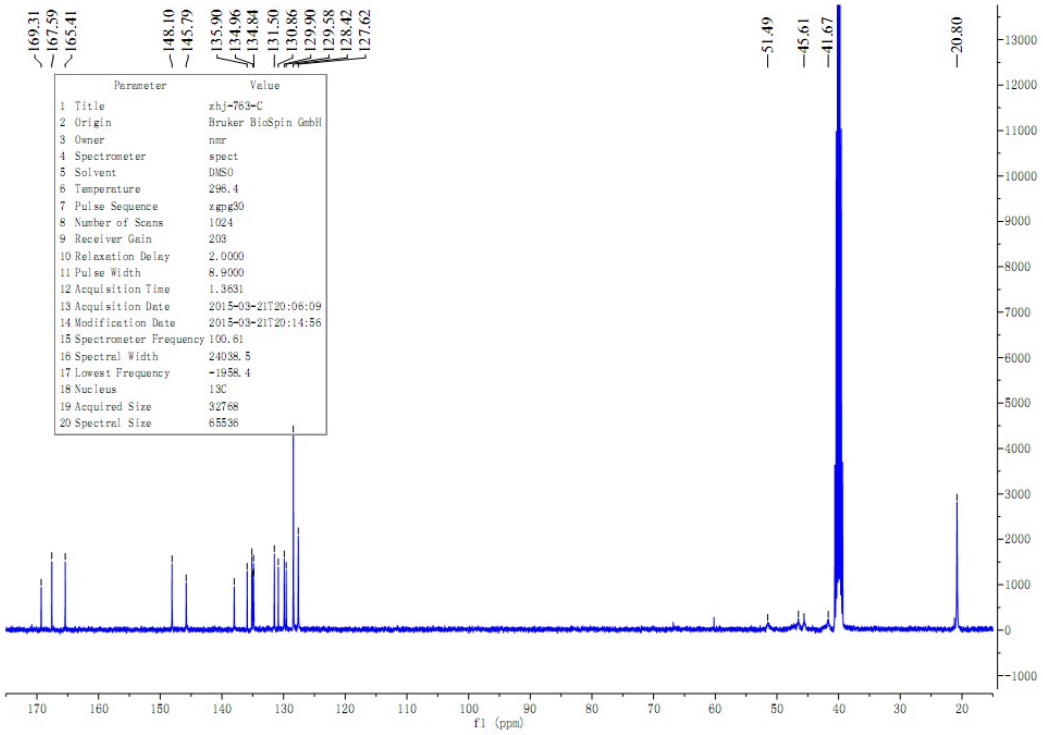





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.37, 169.27, 167.59, 150.65, 148.10, 145.78, 137.96, 136.83, 136.01, 135.15, 134.98, 131.49, 129.43, 128.40, 127.62, 114.59, 113.70, 110.84, 51.45, 47.51, 45.59, 42.15, 40.46, 20.81.

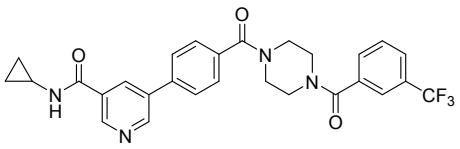
**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*,*N*-diisopropylnicotinamide (10g)**

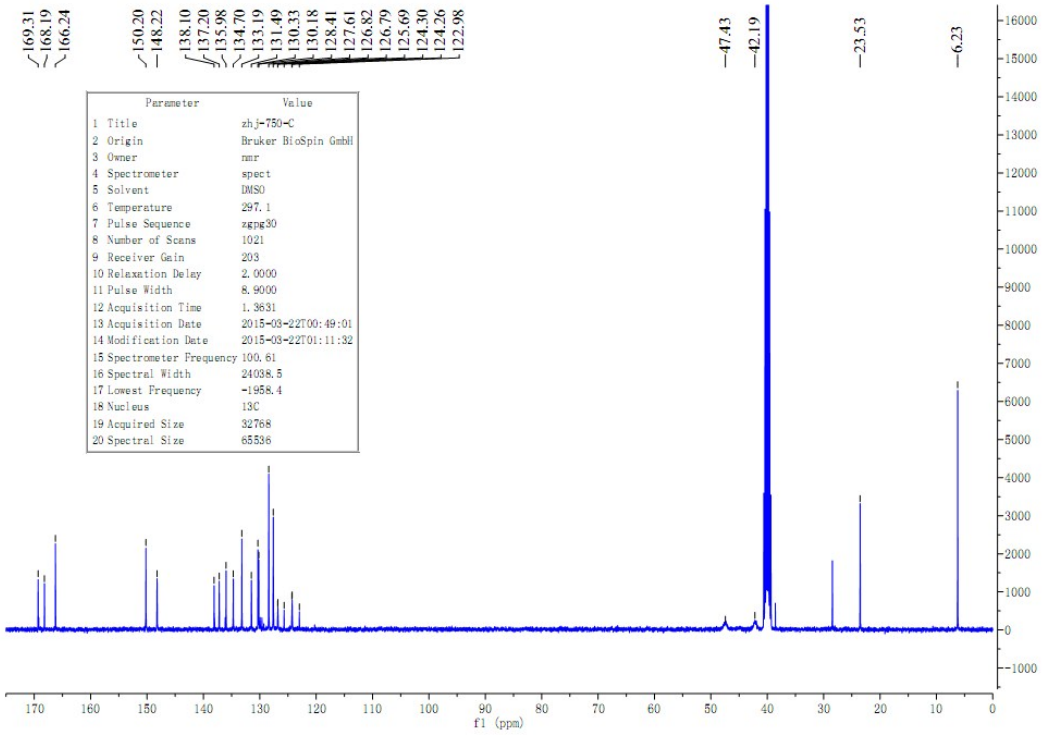



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.31, 167.59, 165.41, 148.10, 145.79, 138.00, 135.90, 135.15, 134.96, 134.88, 134.84, 131.50, 130.86, 129.90, 129.58, 128.42, 127.62, 51.49, 46.51, 45.61, 41.67, 20.80.

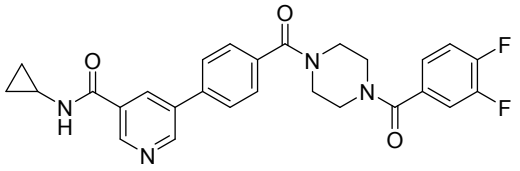
**_N_-cyclopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10h)**

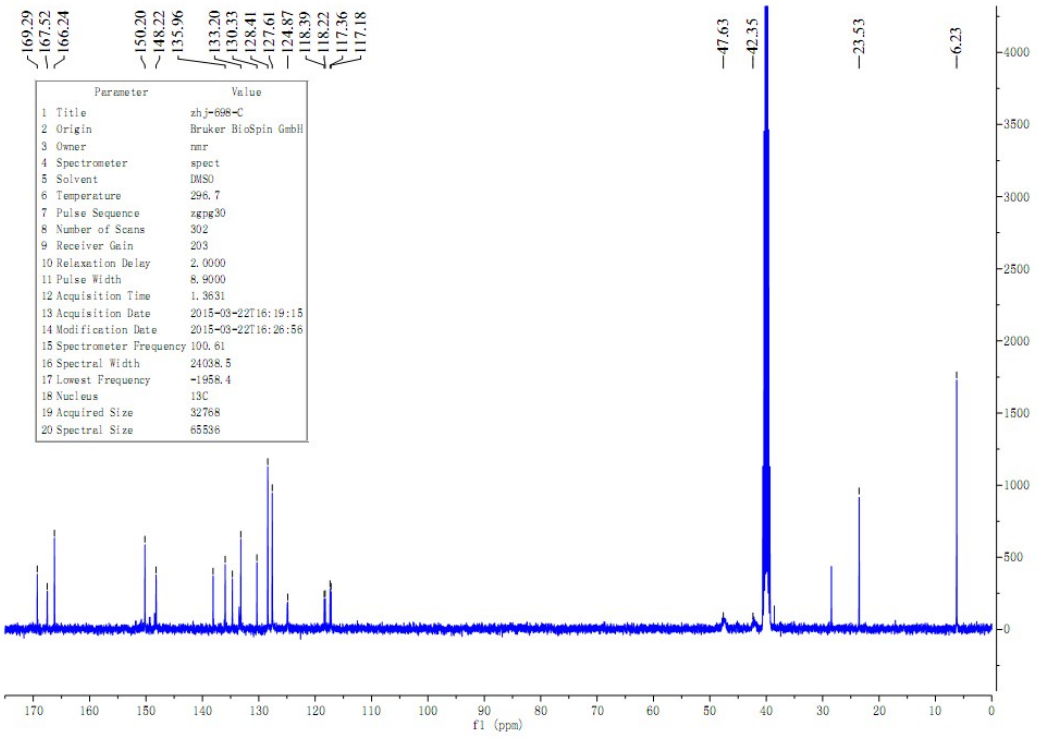





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.31, 168.19, 166.24, 150.20, 148.22, 138.10, 137.20, 135.98, 134.70, 133.19, 131.49, 130.33, 130.18, 128.41, 127.61, 126.82, 126.79, 125.69, 124.30, 124.26, 122.98, 47.43, 42.19, 23.53, 6.23.

**_N_-cyclopropyl-5-(4-{[4-(3,4-difluorobenzoyl)piperazin-1-yl]carbonyl}phenyl)nicotinamide (10i)**

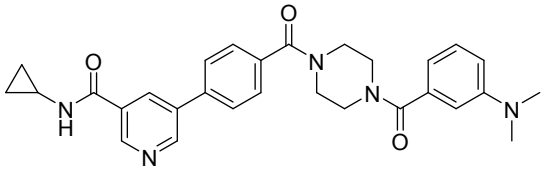


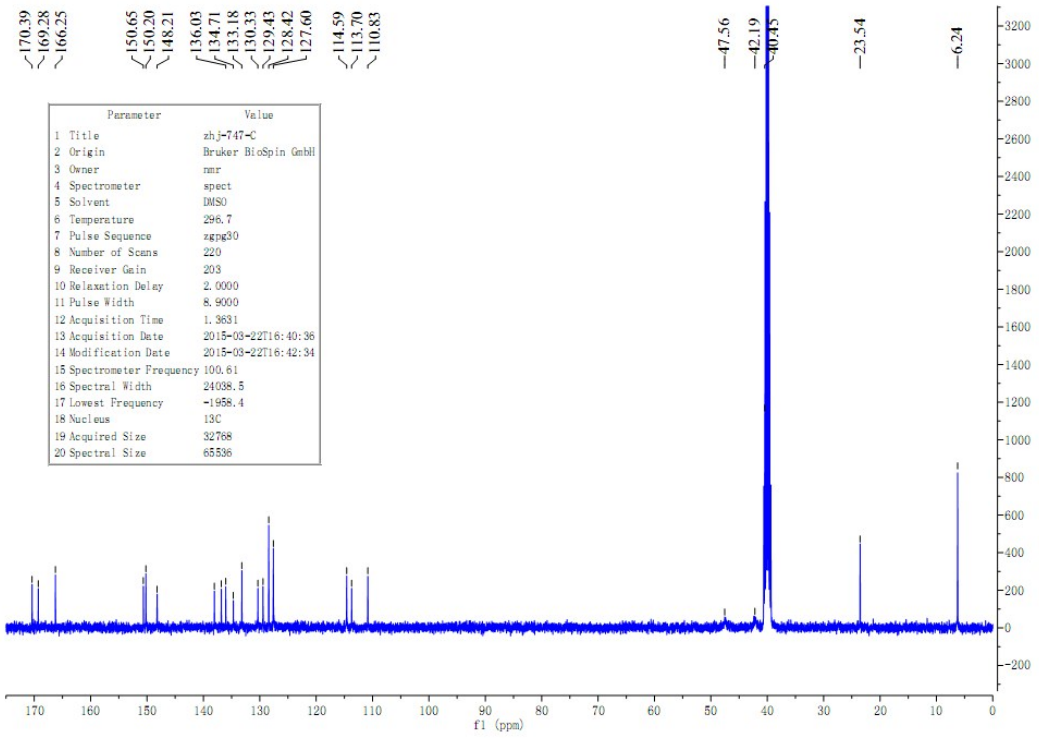



| Parameter | Value |
|---|---|
| 1 Title | zhj-698-C |
| 2 Origin | Bruker BioSpin GmbH |
| 3 Owner | nmr |
| 4 Spectrometer | spect |
| 5 Solvent | DMSO |
| 6 Temperature | 296.7 |
| 7 Pulse Sequence | zgpg30 |
| 8 Number of Scans | 302 |
| 9 Receiver Gain | 203 |
| 10 Relaxation Delay | 2.0000 |
| 11 Pulse Width | 8.9000 |
| 12 Acquisition Time | 1.3631 |
| 13 Acquisition Date | 2015-03-22T16:19:15 |
| 14 Modification Date | 2015-03-22T16:26:56 |
| 15 Spectrometer Frequency | 100.61 |
| 16 Spectral Width | 24038.5 |
| 17 Lowest Frequency | -1958.4 |
| 18 Nucleus | 13C |
| 19 Acquired Size | 32768 |
| 20 Spectral Size | 65536 |

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.29, 167.52, 166.24, 150.20, 148.22, 138.11, 135.96, 134.69, 133.20, 130.33, 128.41, 127.61, 124.87, 118.39, 118.22, 117.36, 117.18, 47.63, 42.35, 23.53, 6.23.

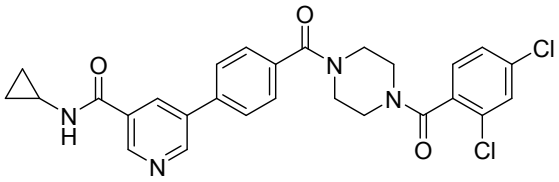
***N*-cyclopropyl-5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10j)**

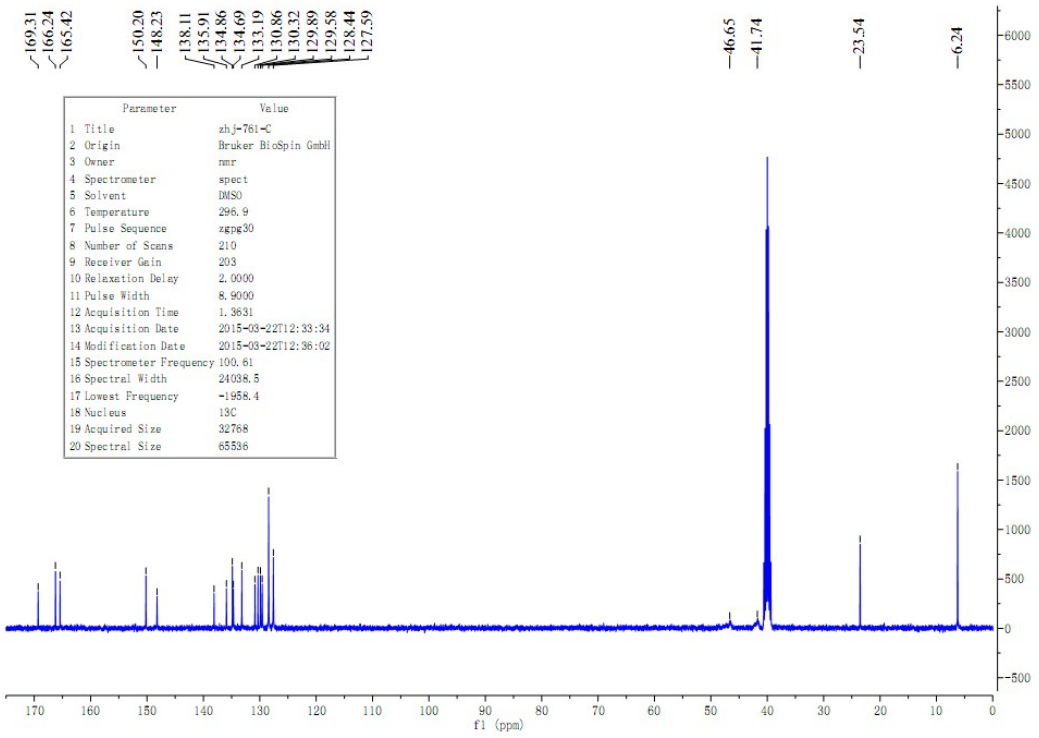





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.39, 169.28, 166.25, 150.65, 150.20, 148.21, 138.05, 136.82, 136.03, 134.71, 133.18, 130.33, 129.43, 128.42, 127.60, 114.59, 113.70, 110.83, 47.56, 42.19, 40.45, 23.54, 6.24.

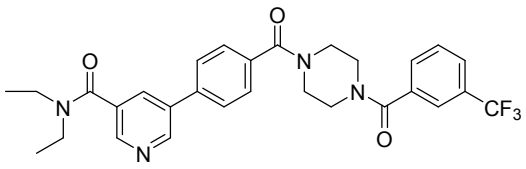
***N*-cyclopropyl-5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)nicotinamide (10k)**

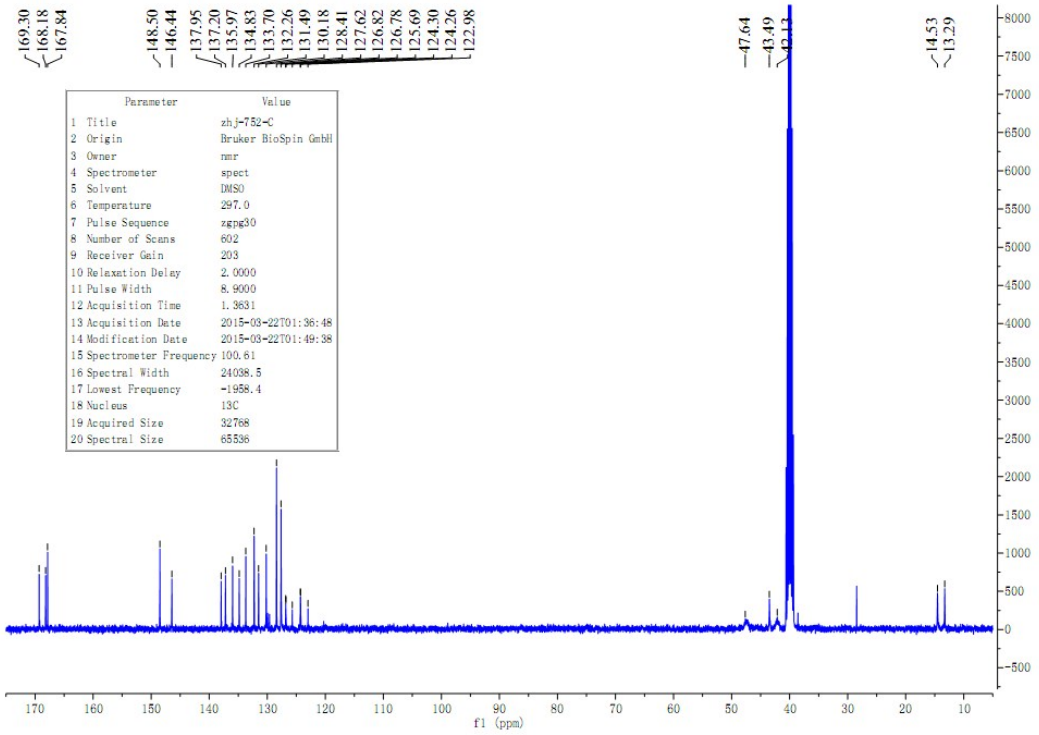



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.31, 166.24, 165.42, 150.20, 148.23, 138.11, 135.91, 134.86, 134.69, 133.19, 130.86, 130.32, 129.89, 129.58, 128.44, 127.59, 46.65, 41.74, 23.54, 6.24.

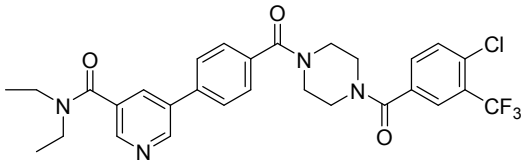
***N*,*N*-diethyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10l)**

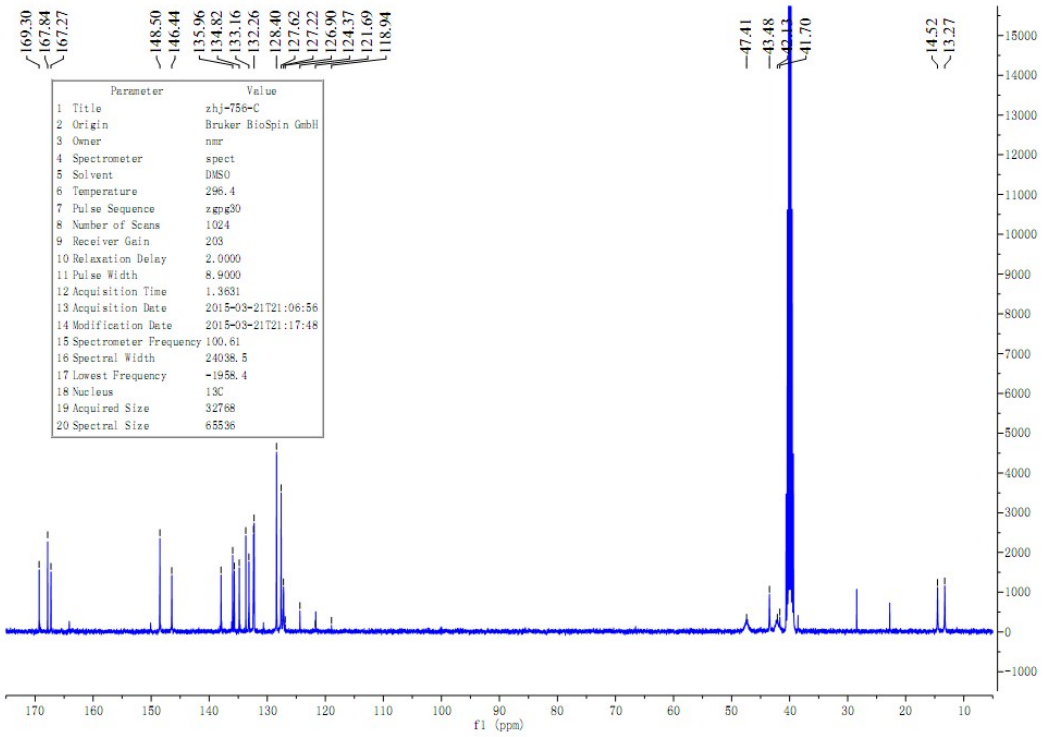




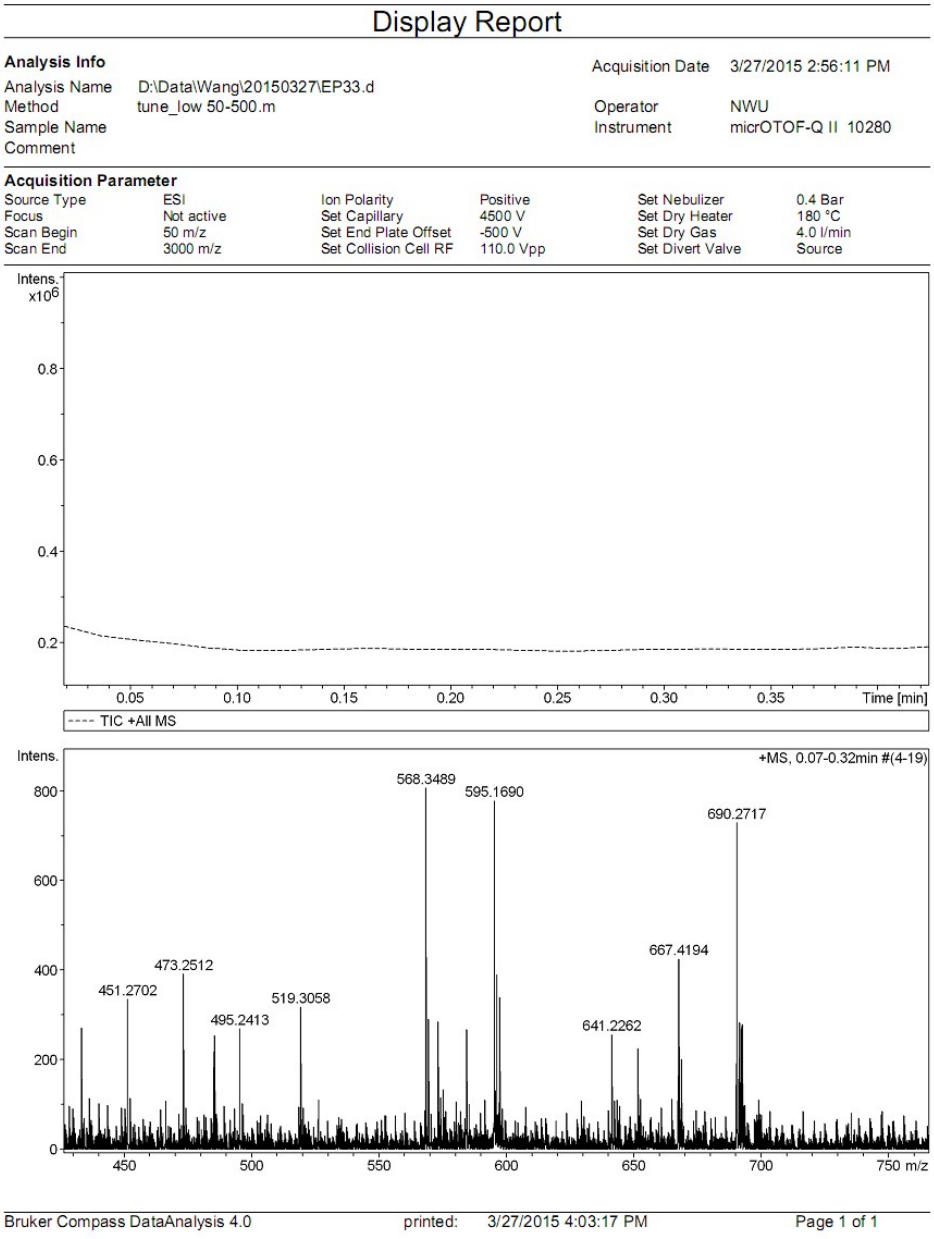

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.30, 168.18, 167.84, 148.50, 146.44, 137.95, 137.20, 135.97, 134.83, 133.70, 132.26, 131.49, 130.18, 128.41, 127.62, 126.82, 126.78, 125.69, 124.30, 124.26, 122.98, 47.64, 43.49, 42.13, 14.53, 13.29.

**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diethylnicotinamide (10m)**



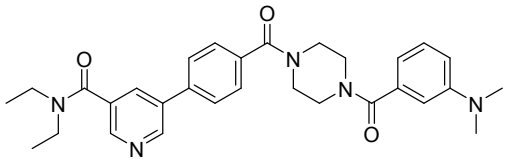



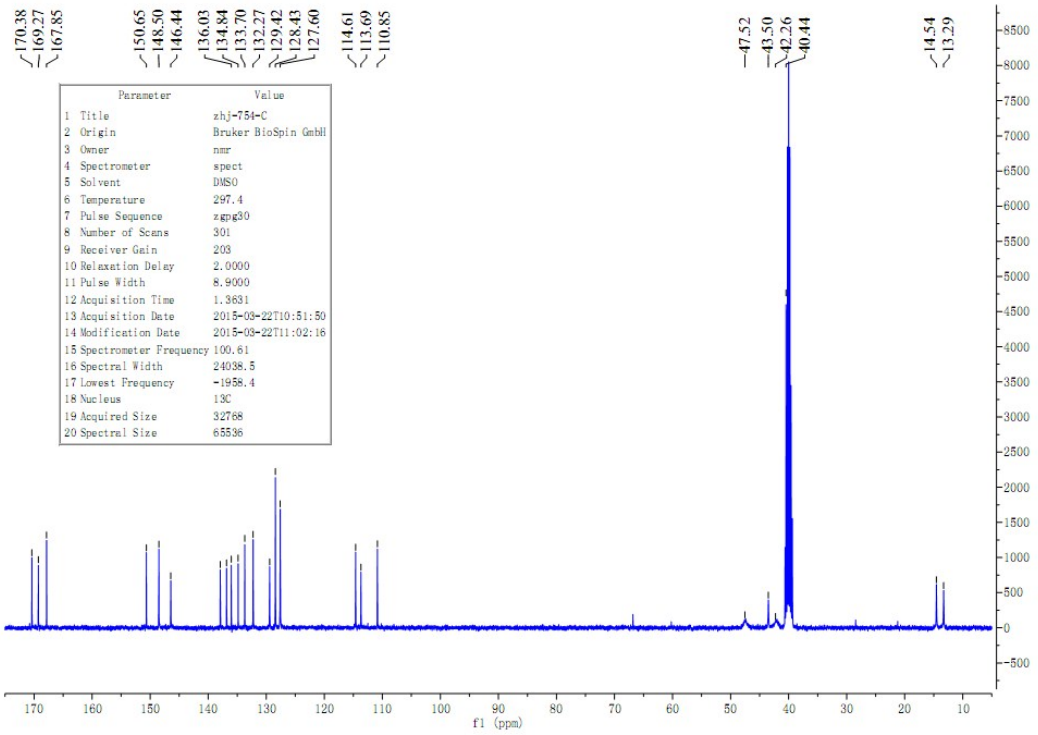

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.30, 167.84, 167.27, 148.50, 146.44, 137.96, 135.96, 135.67, 134.82, 133.70, 133.16, 132.36, 132.26, 128.40, 127.62, 127.22, 126.90, 124.37, 121.69, 118.94, 47.41, 43.48, 42.13, 41.70, 14.52, 13.27.




HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{29}H_{28}ClF_3N_4O_3Na$: 595.1700, found 595.1690.

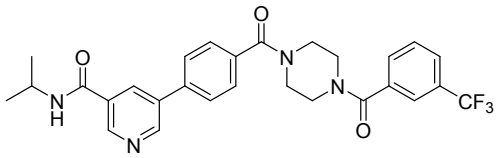
**5-[4-({4-[4-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*,*N*-diethylnicotinamide (10n)**

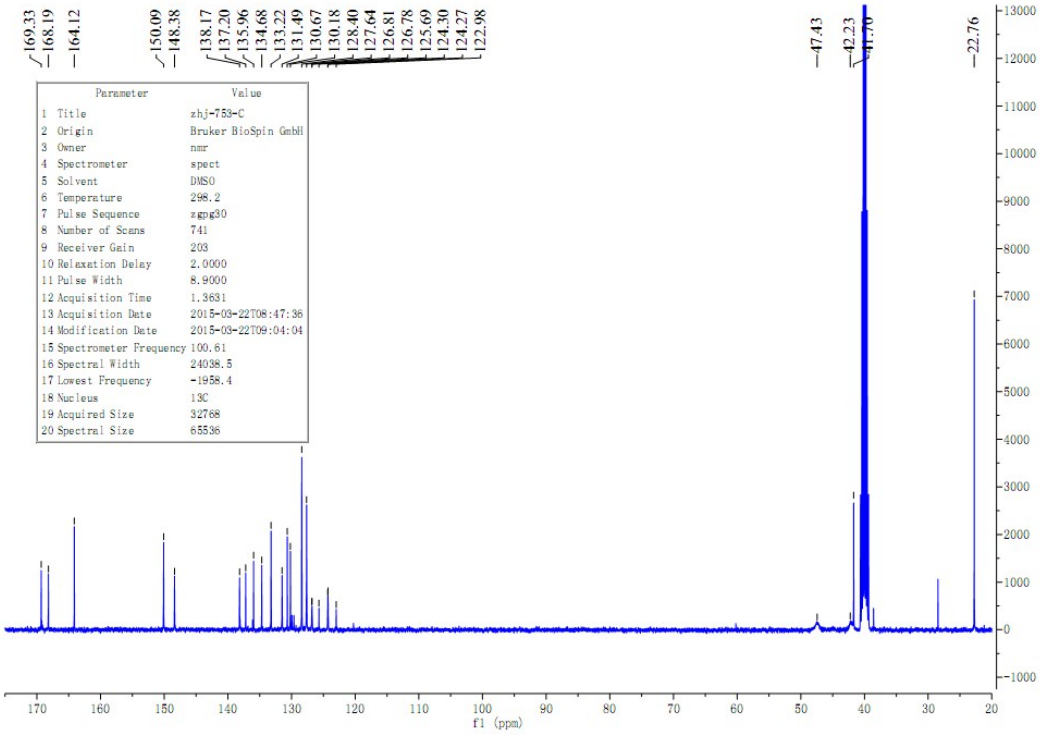





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.38, 169.27, 167.85, 150.65, 148.50, 146.44, 137.92, 136.84, 136.03, 134.84, 133.70, 132.27, 129.42, 128.43, 127.60, 114.61, 113.69, 110.85, 47.52, 43.50, 42.26, 40.44, 14.54, 13.29.

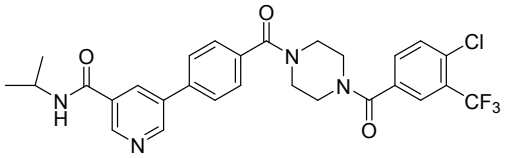
***N*-isopropyl-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10o)**

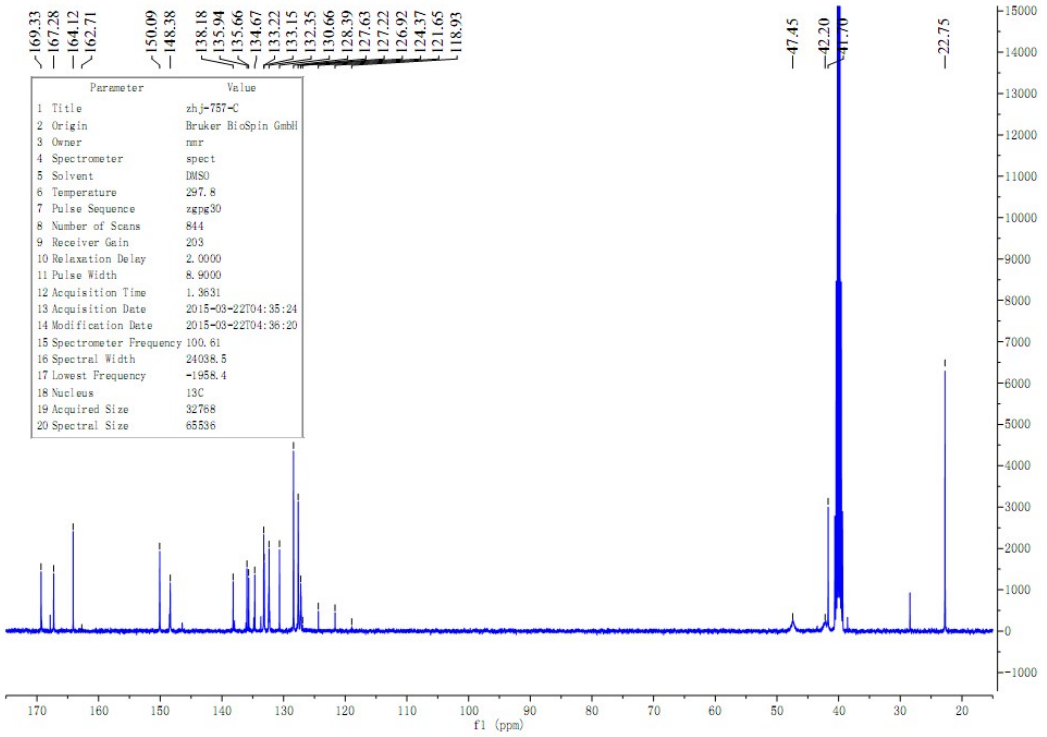




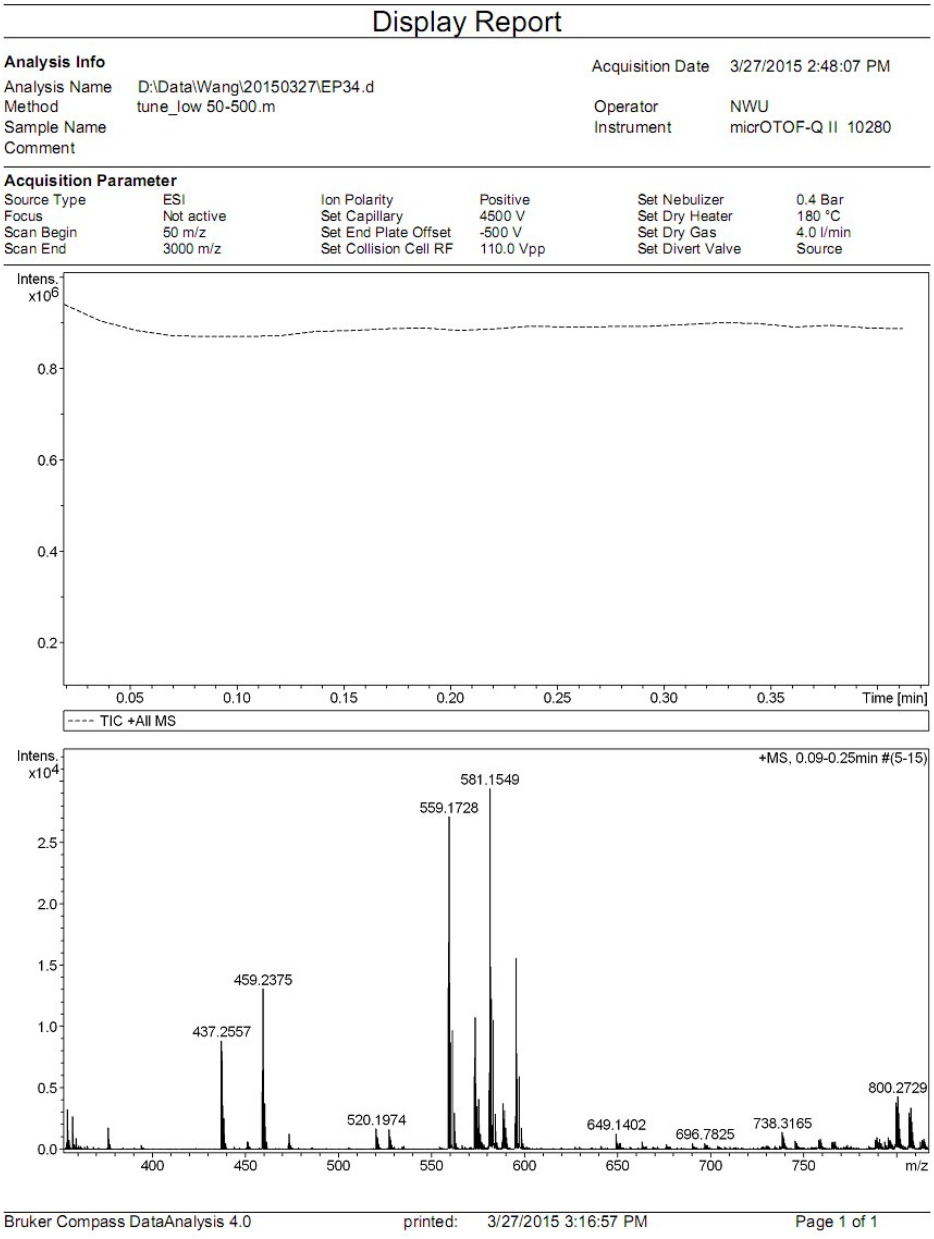

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.33, 168.19, 164.12, 150.09, 148.38, 138.17, 137.20, 135.96, 134.68, 133.22, 131.49, 130.67, 130.18, 128.40, 127.64, 126.81, 126.78, 125.69, 124.30, 124.27, 122.98, 47.43, 42.23, 41.70, 22.76.

**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-isopropylnicotinamide (10p)**



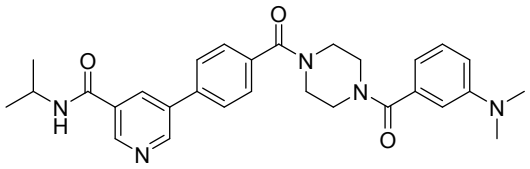



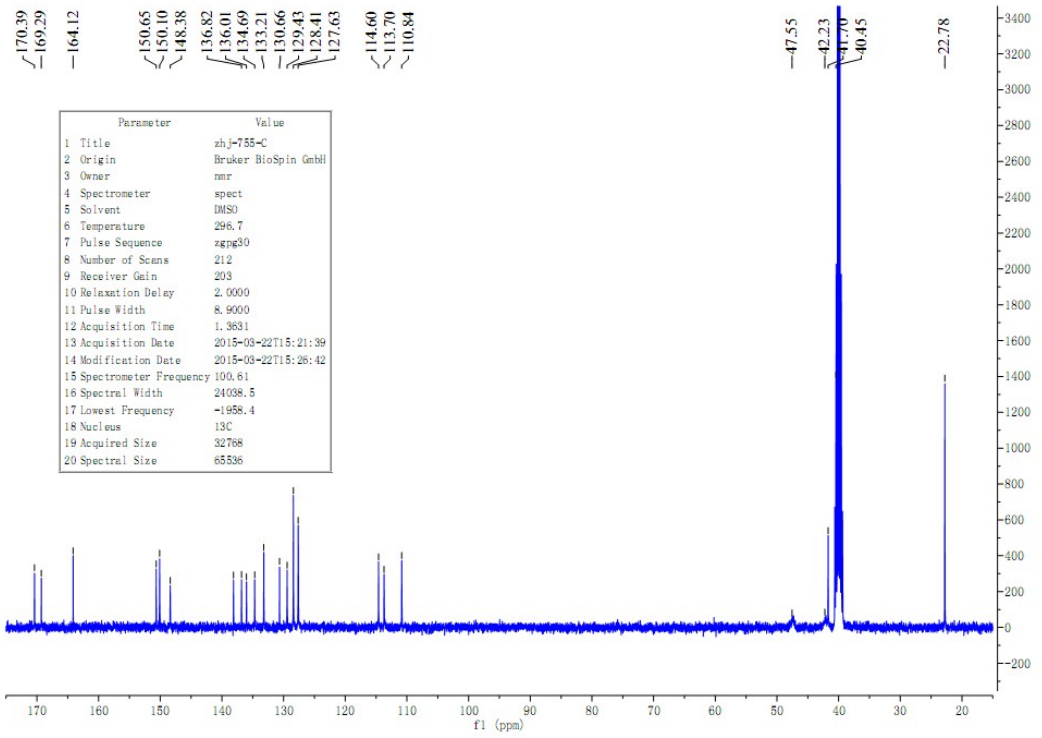

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.33, 167.28, 164.12, 150.09, 148.38, 138.18, 135.94, 135.66, 134.67, 133.22, 133.15, 132.35, 130.66, 128.39, 127.63, 127.22, 126.92, 124.37, 121.65, 118.93, 47.45, 42.20, 41.70, 22.75.




HRMS (ESI): Calcd. for $[M+H]^+$ $C_{28}H_{27}ClF_3N_4O_3$: 559.1724, found 559.1728.
HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{28}H_{26}ClF_3N_4O_3Na$: 581.1543, found 581.1549.

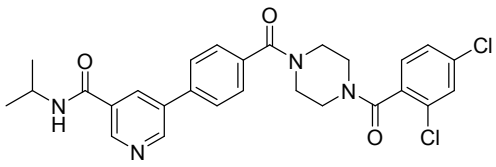
**5-[4-({4-[3-(dimethylamino)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-isopropylnicotinamide (10q)**

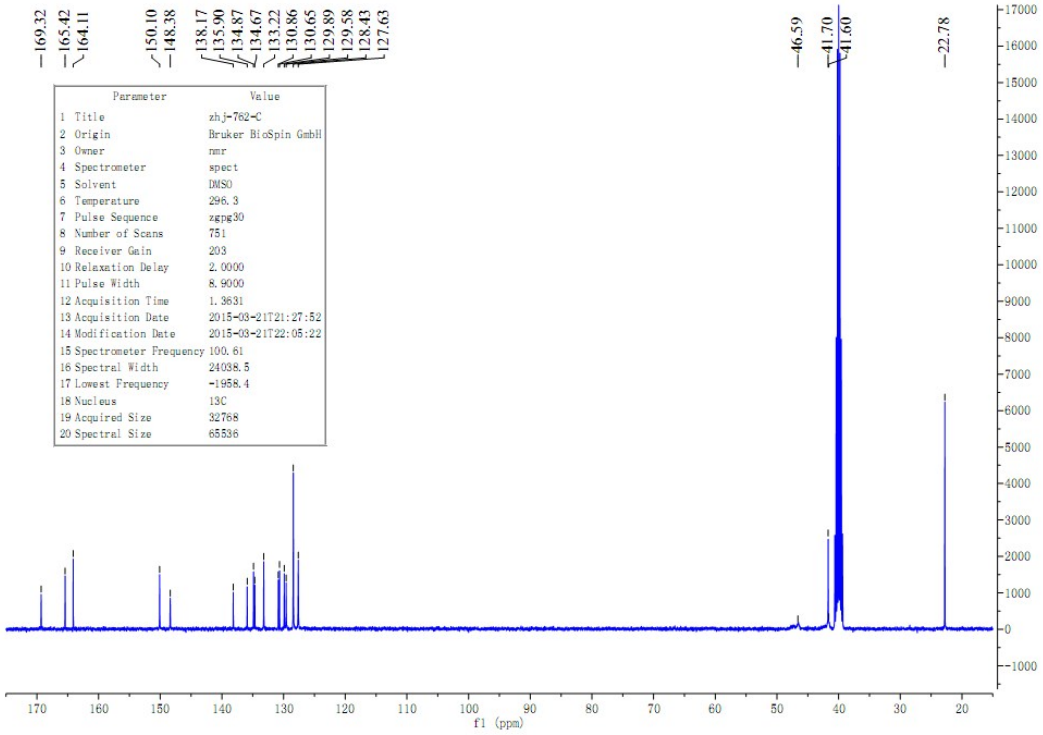





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.39, 169.29, 164.12, 150.65, 150.10, 148.38, 138.12, 136.82, 136.01, 134.69, 133.21, 130.66, 129.43, 128.41, 127.63, 114.60, 113.70, 110.84, 47.55, 42.23, 41.70, 40.45, 22.78.

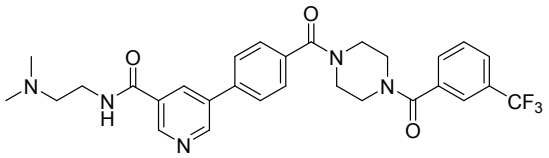
**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*-isopropylnicotinamide (10r)**

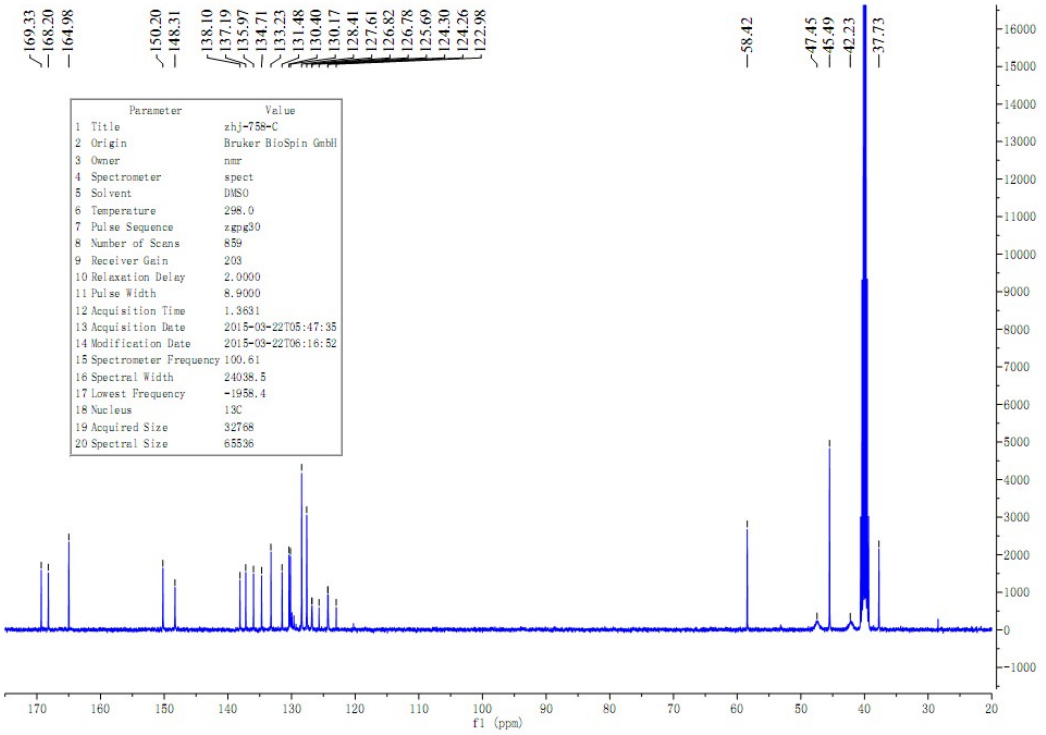



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.32, 165.42, 164.11, 150.10, 148.38, 138.17, 135.90, 134.87, 134.67, 133.22, 130.86, 130.65, 129.89, 129.58, 128.43, 127.63, 46.59, 41.70, 41.60, 22.78.

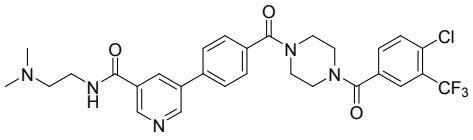
***N*-[2-(dimethylamino)ethyl]-5-[4-({4-[3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]nicotinamide (10s)**

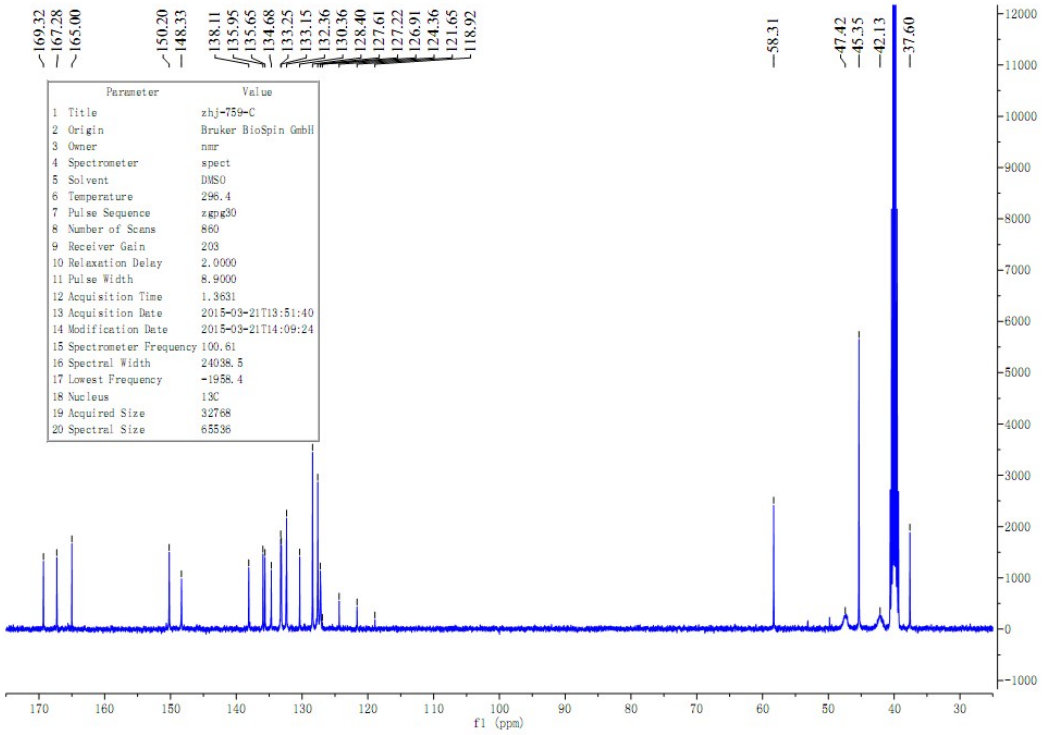





$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.33, 168.20, 164.98, 150.20, 148.31, 138.10, 137.19, 135.97, 134.71, 133.23, 131.48, 130.40, 130.17, 128.41, 127.61, 126.82, 126.78, 125.69, 124.30, 124.26, 122.98, 58.42, 47.45, 45.49, 42.23, 37.73.

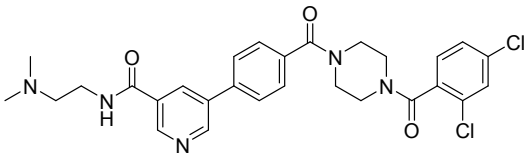
**5-[4-({4-[4-chloro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}carbonyl)phenyl]-*N*-[2-(dimethylamino)ethyl]nicotinamide (10t)**

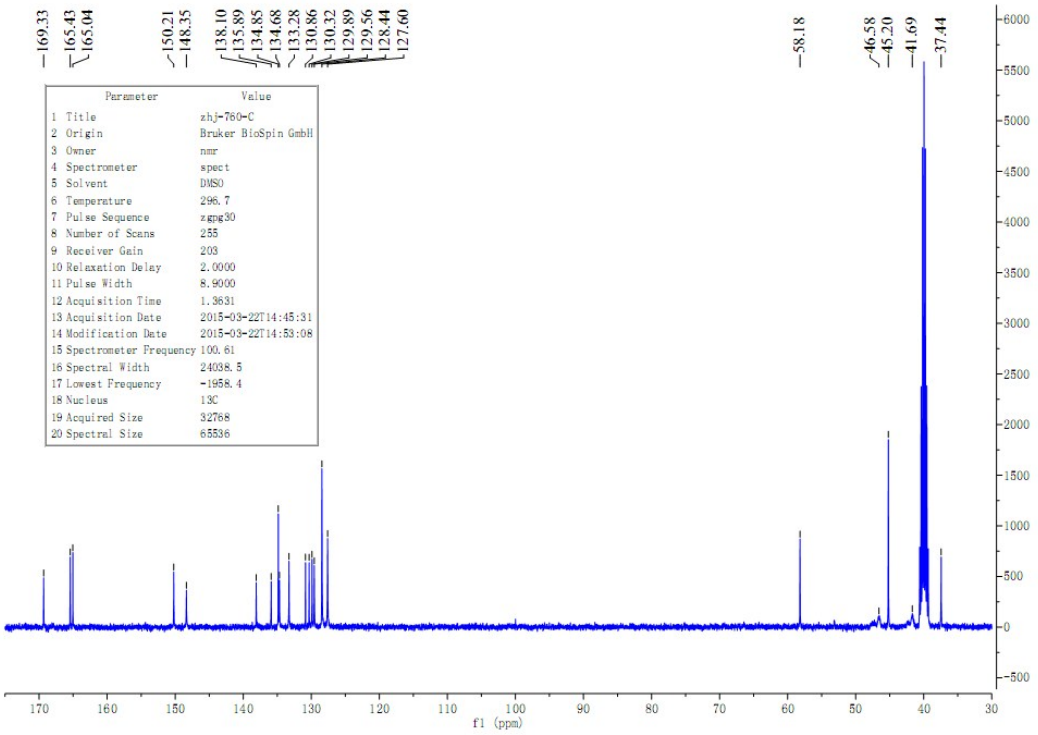



$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.32, 167.28, 165.00, 150.20, 148.33, 138.11, 135.95, 135.65, 134.68, 133.25, 133.15, 132.36, 130.36, 128.40, 127.61, 127.22, 126.91, 124.36, 121.65, 118.92, 58.31, 47.42, 45.35, 42.13, 37.60.

**5-(4-{[4-(2,4-dichlorobenzoyl)piperazin-1-yl]carbonyl}phenyl)-*N*-[2-(dimethylamino)ethyl]nicotinamide (10u)**






$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.33, 165.43, 165.04, 150.21, 148.35, 138.10, 135.89, 134.85, 134.68, 133.28, 130.86, 130.32, 129.89, 129.56, 128.44, 127.60, 58.18, 46.58, 45.20, 41.69, 37.44.