

Discovery of 5-trifluoromethyl-2-aminopyrimidine derivatives as potent dual inhibitors of FLT3 and CHK1

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^g National Key Laboratory of Advanced Drug Delivery and Release Systems, Zhejiang University, Hangzhou 310058, P.R. China

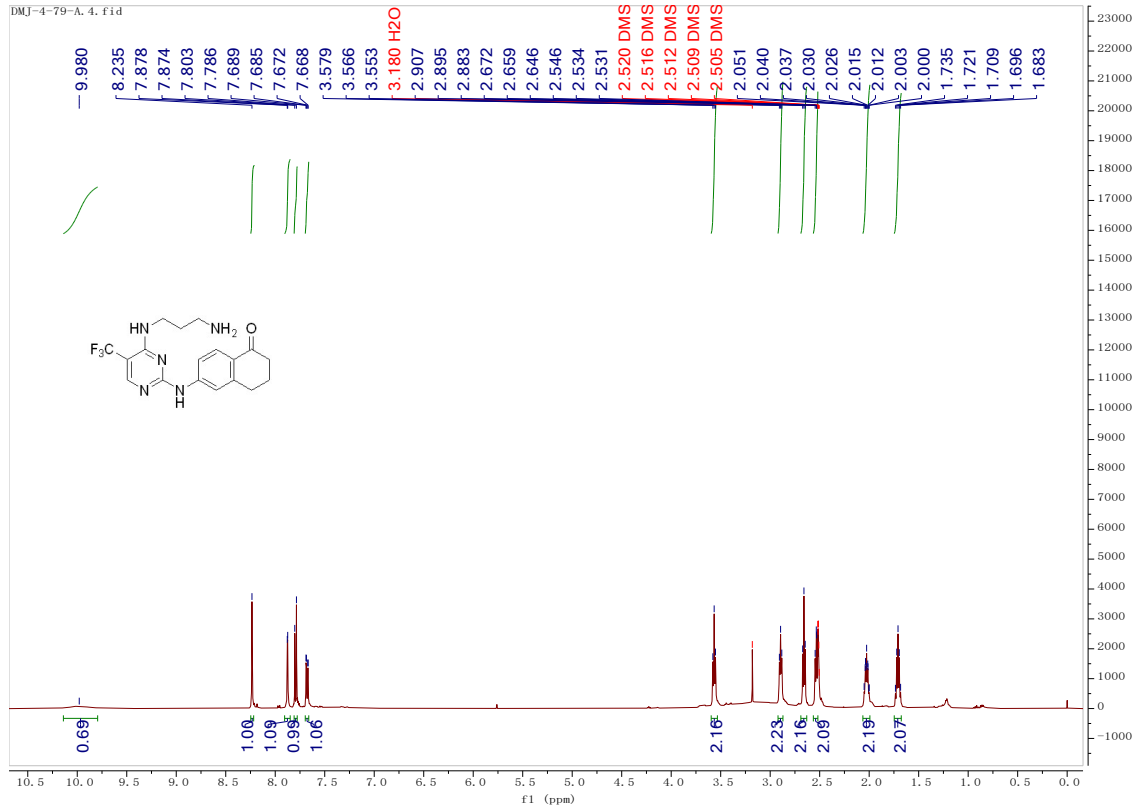
E-mail: ybzhou@simm.ac.cn, lt601@zju.edu.cn

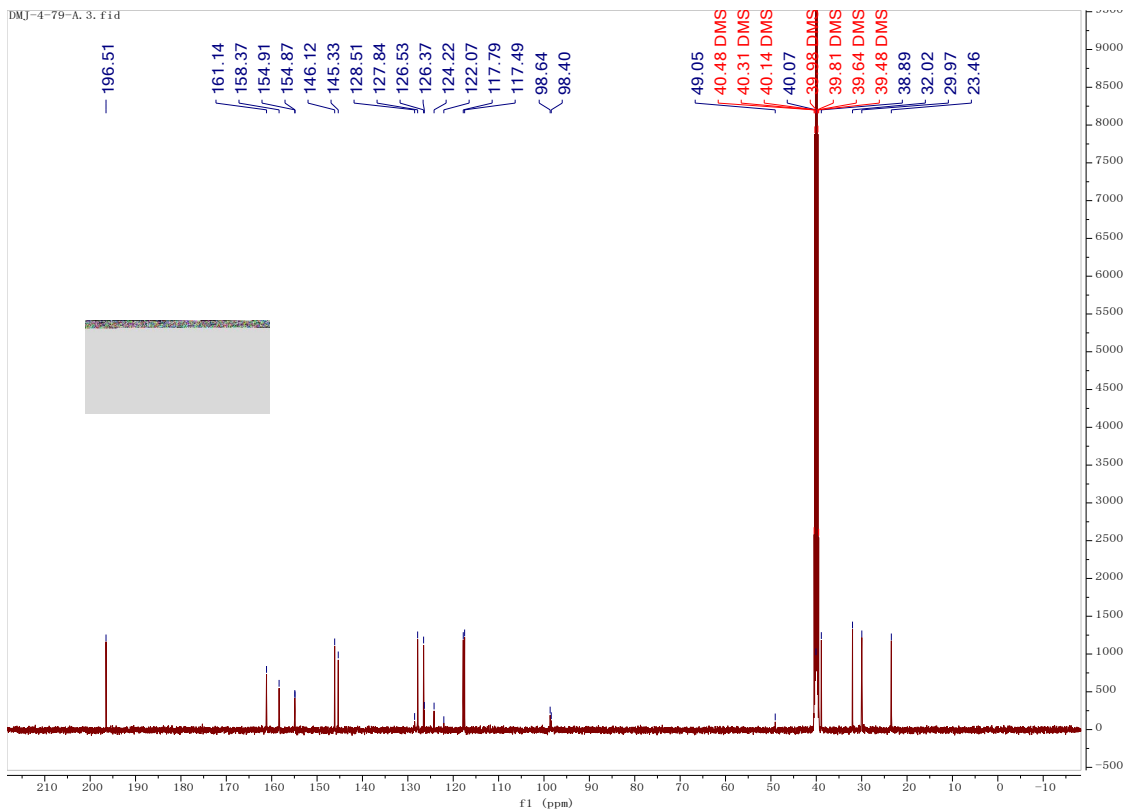
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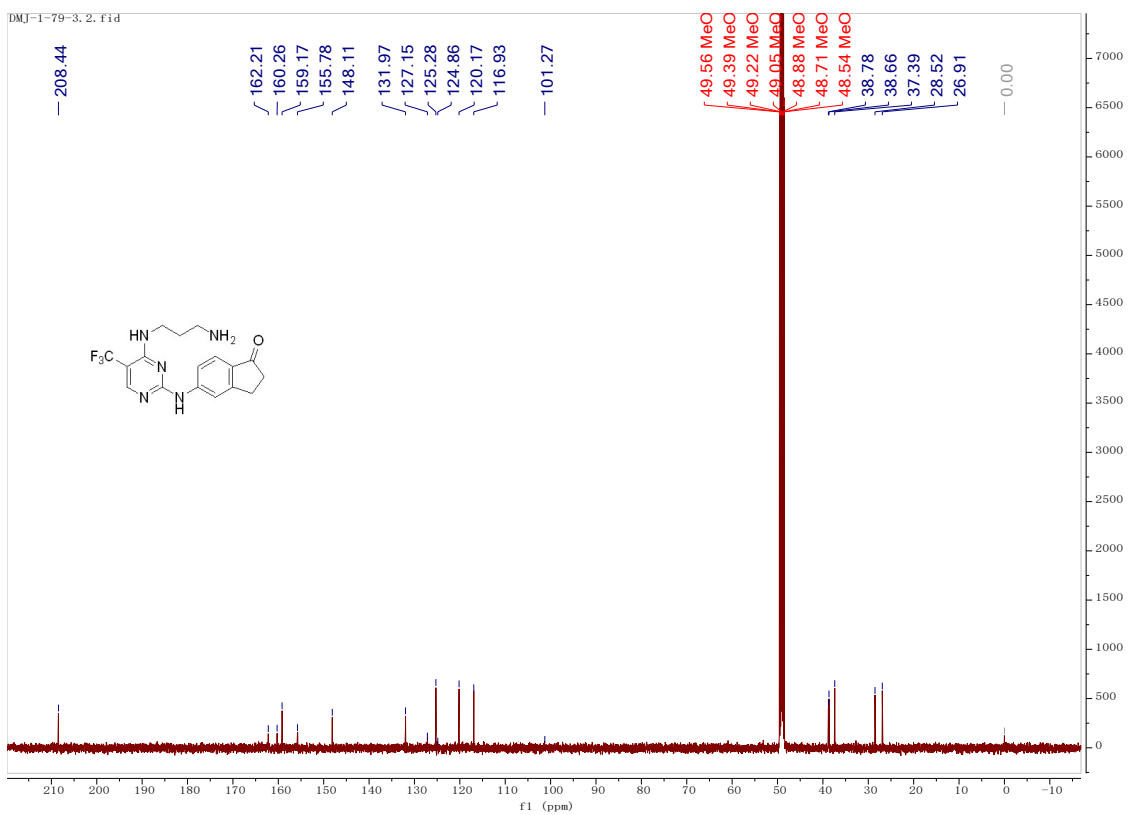
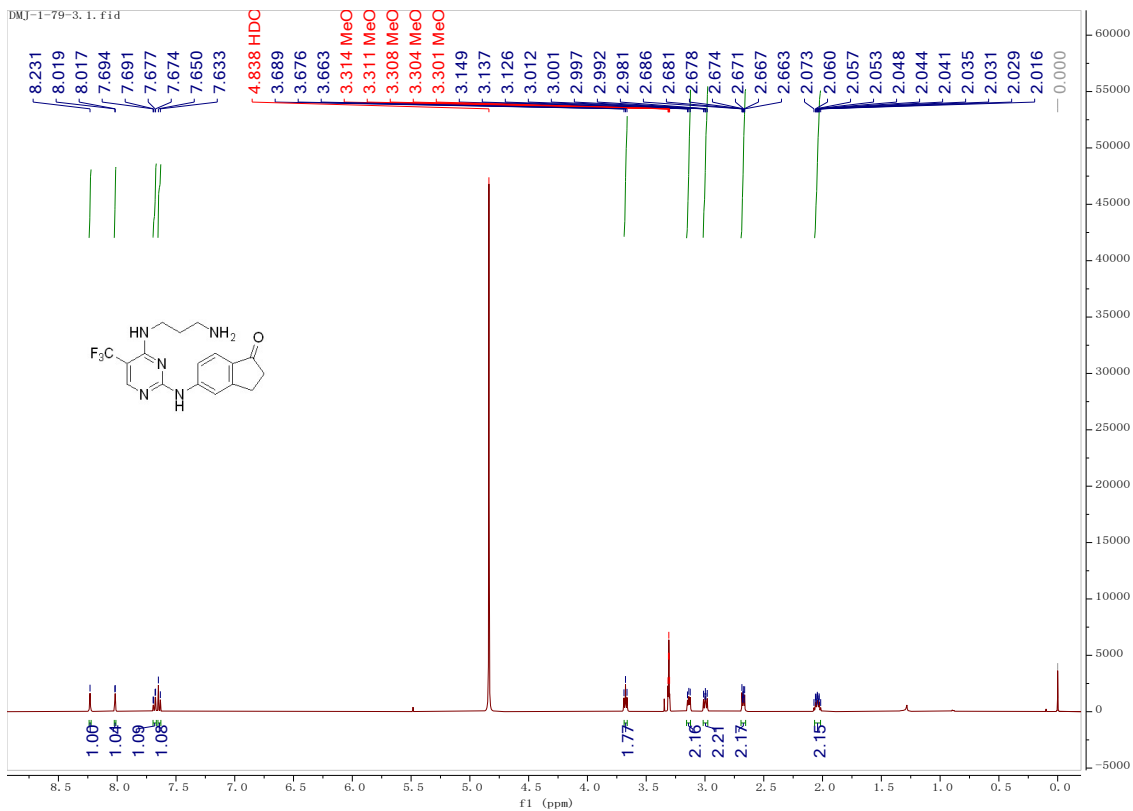
NMR spectra of target compounds

6-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-3,4-dihydronaphthalen-1(2H)-one

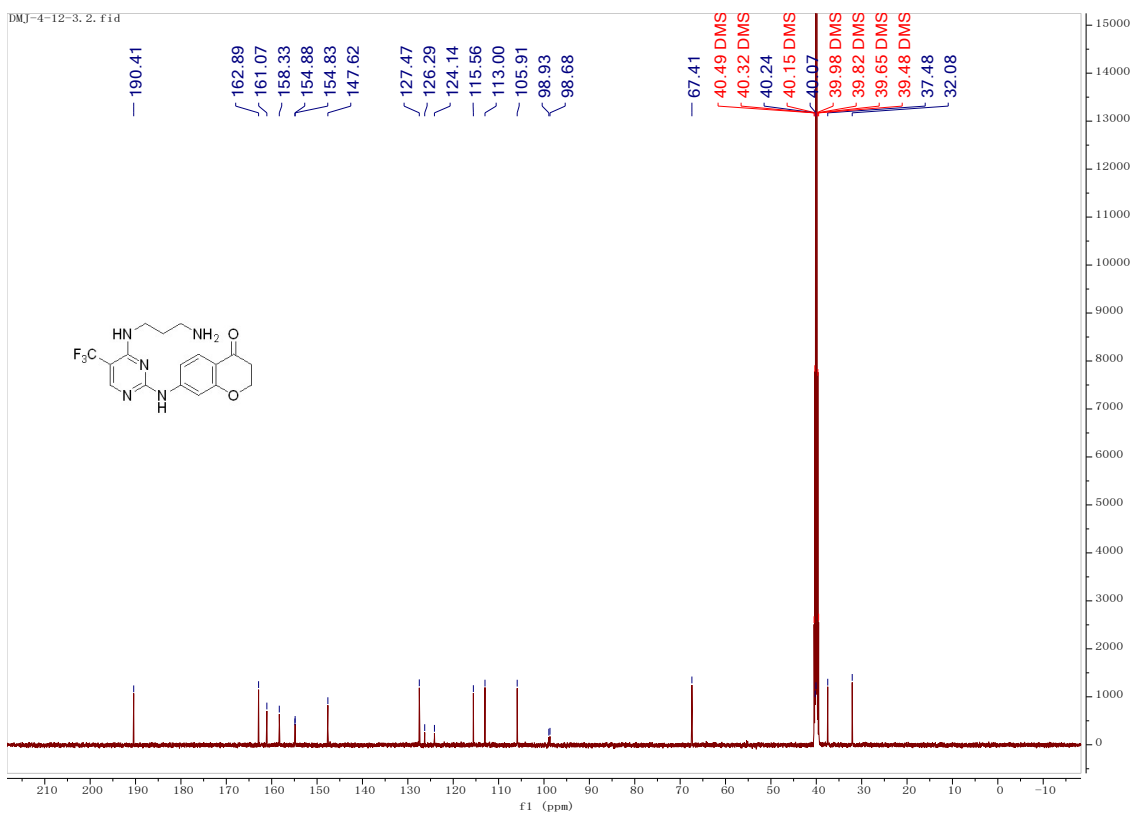
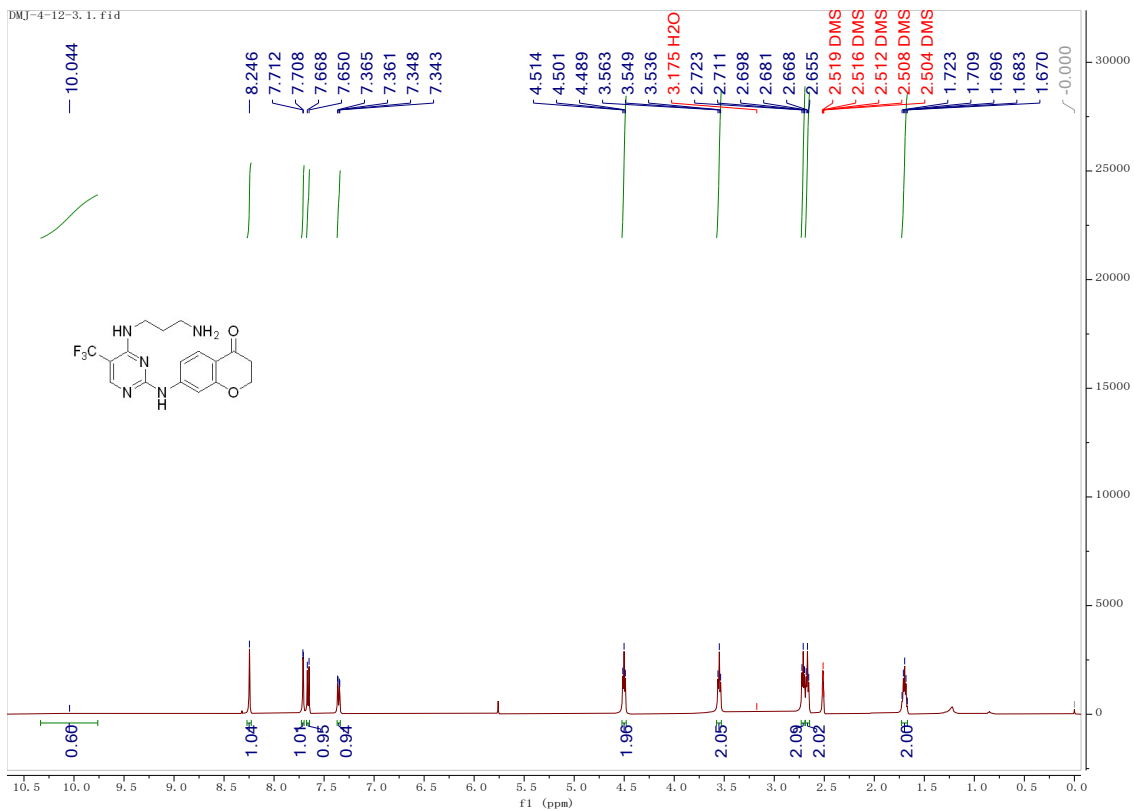




5-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2,3-dihydro-1H-inden-1-one

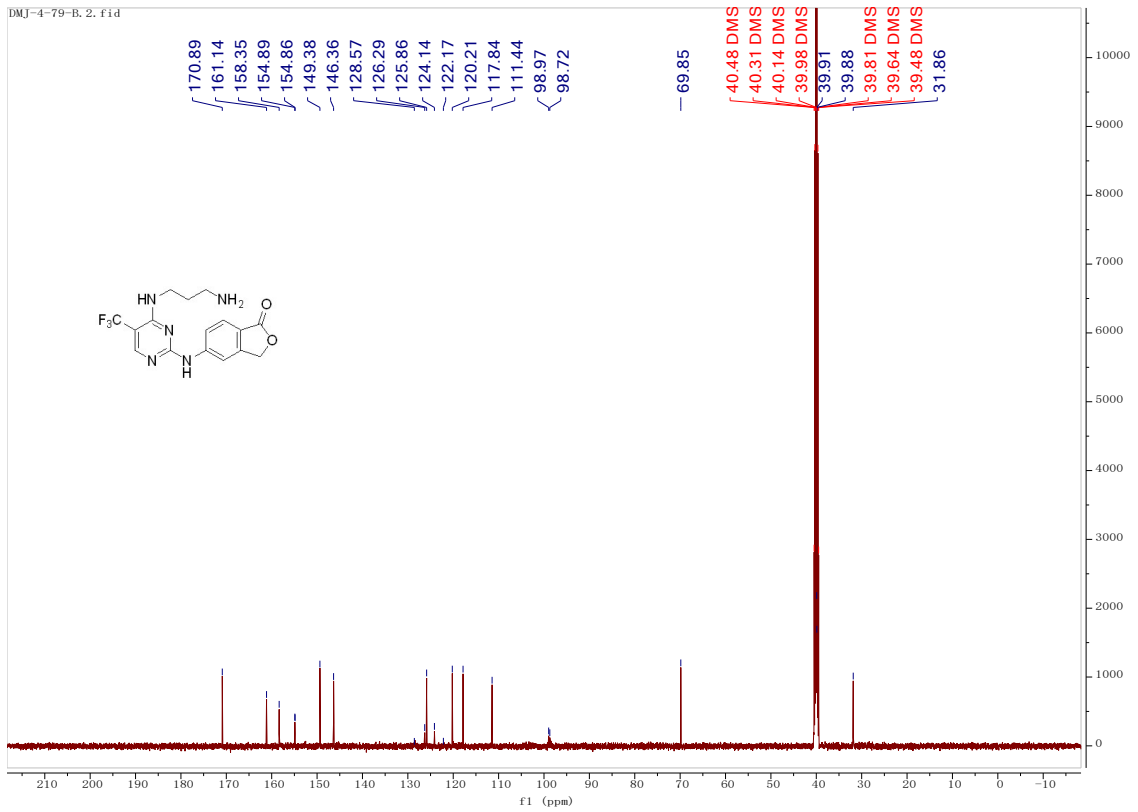
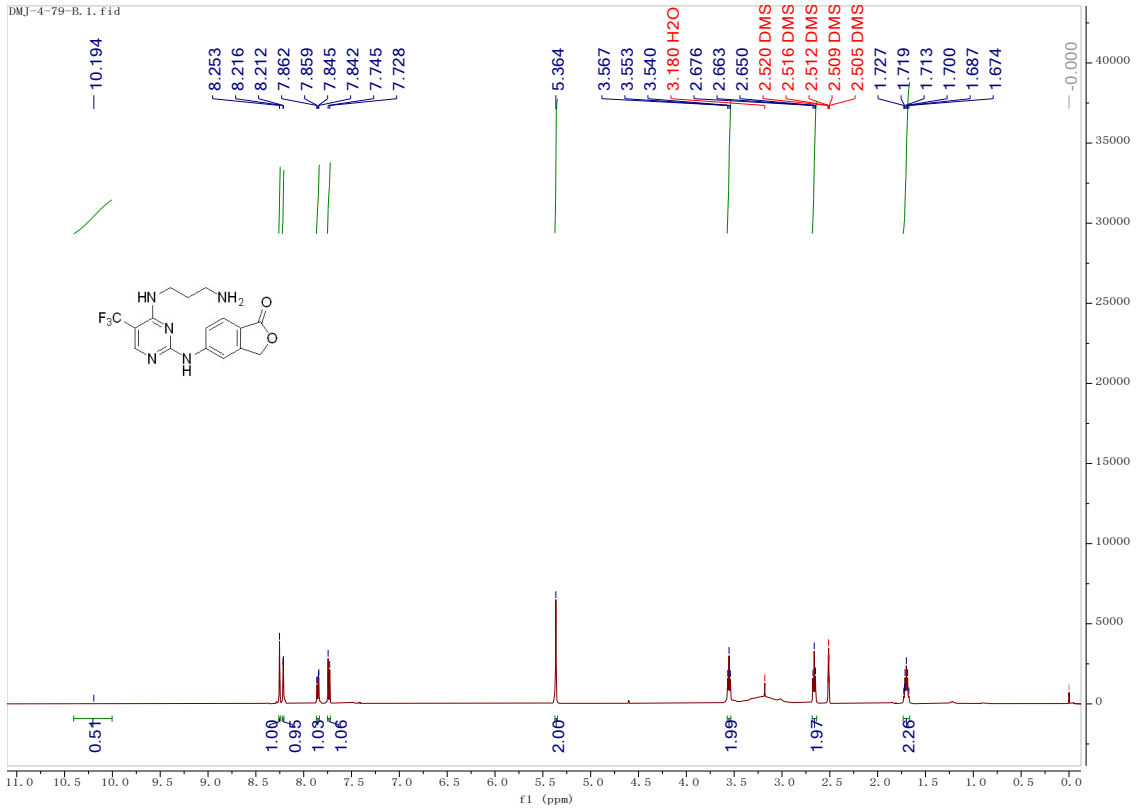


7-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)chroman-4-one

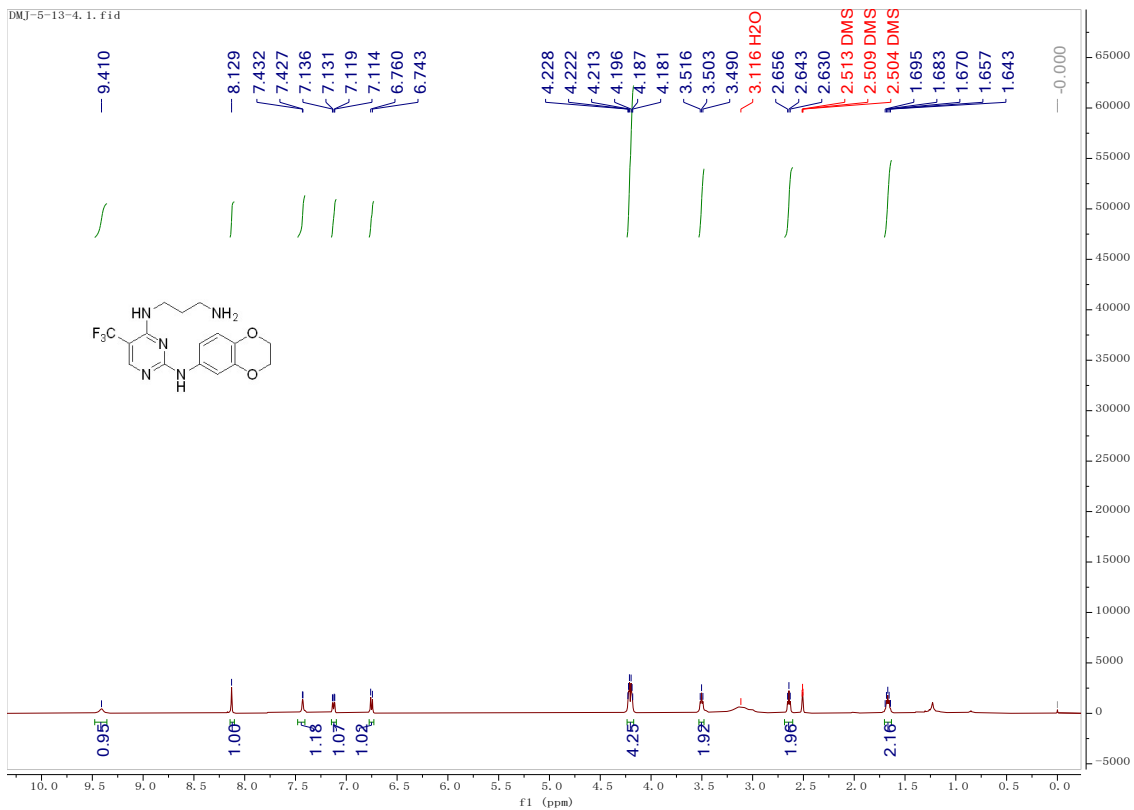


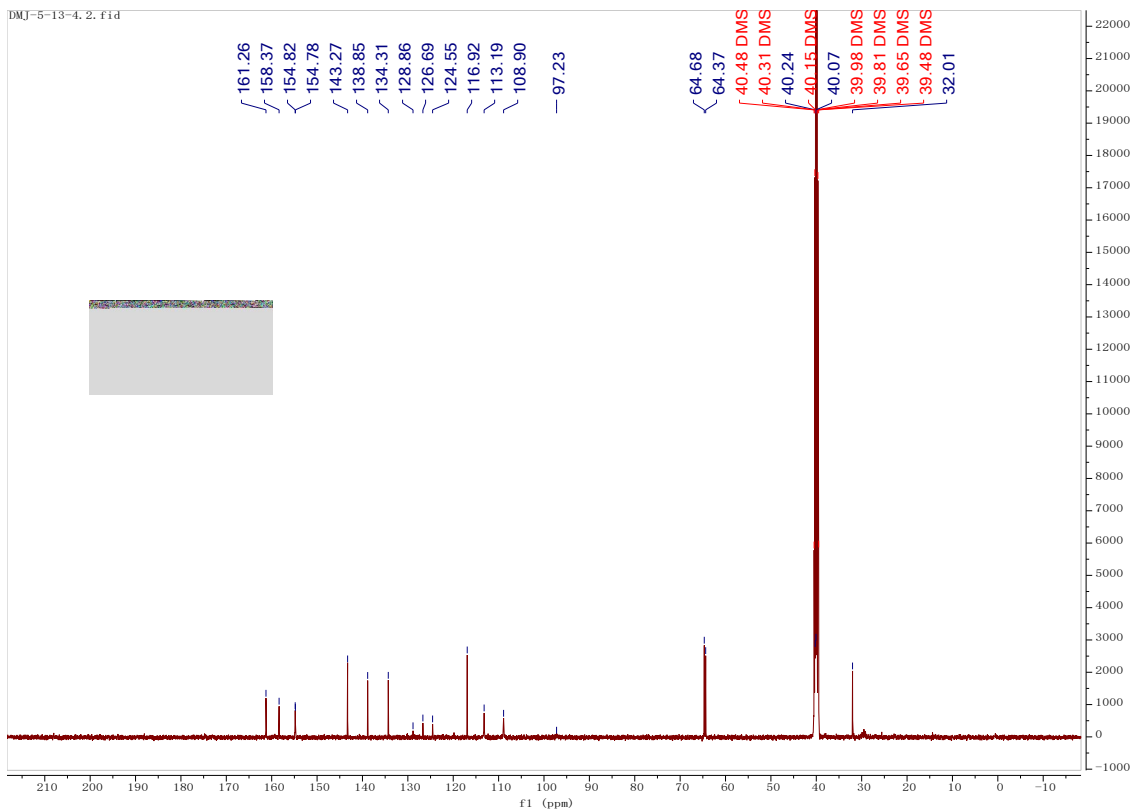
5-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)isobenzofuran-

1(3H)-one

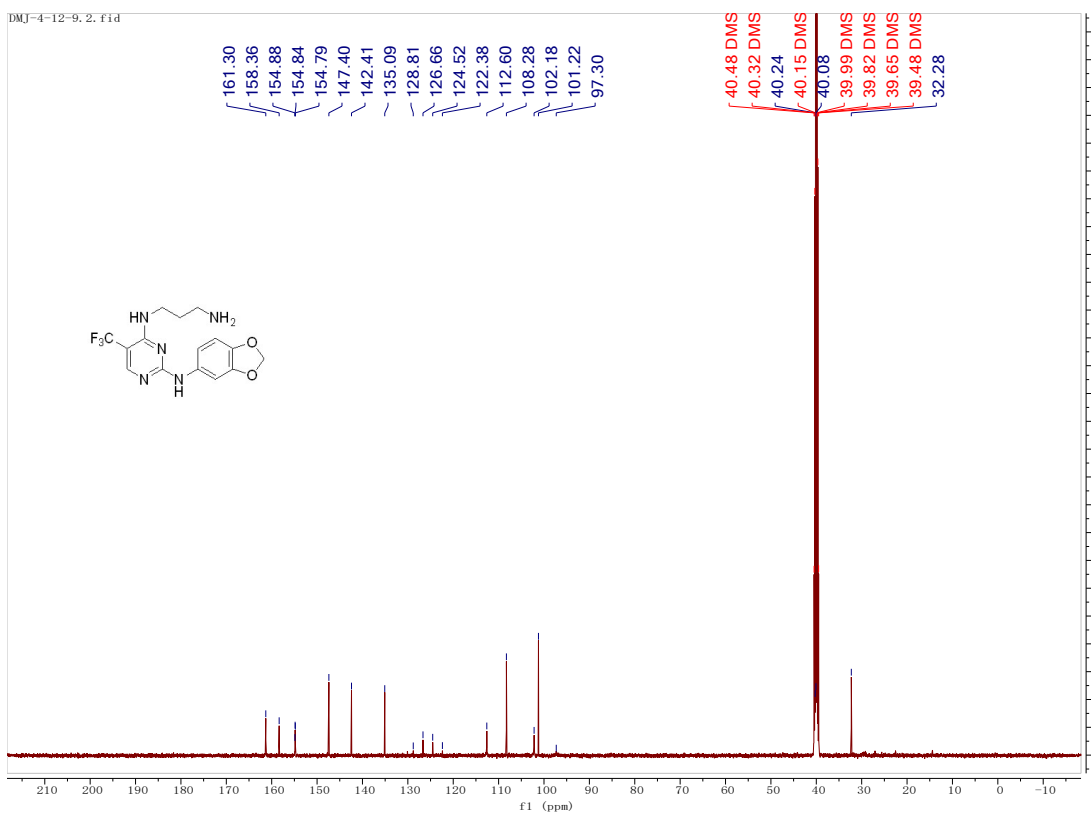
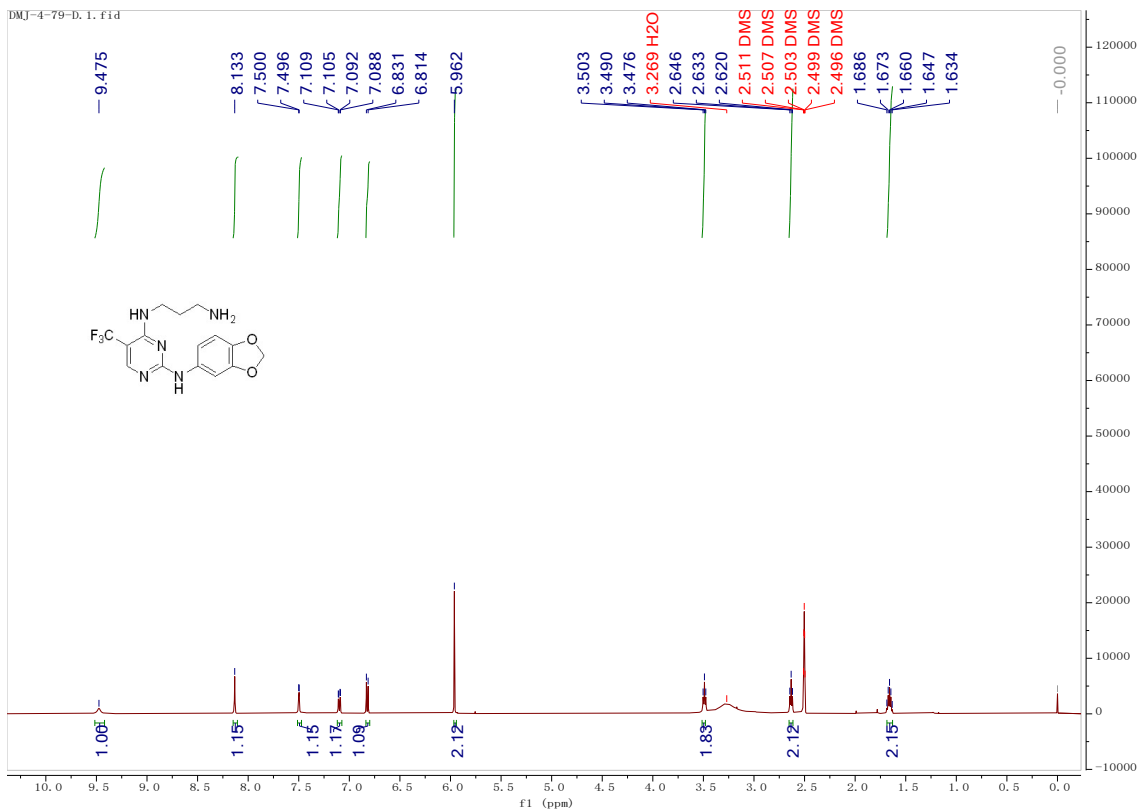


*N*⁴-(3-aminopropyl)-*N*²-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



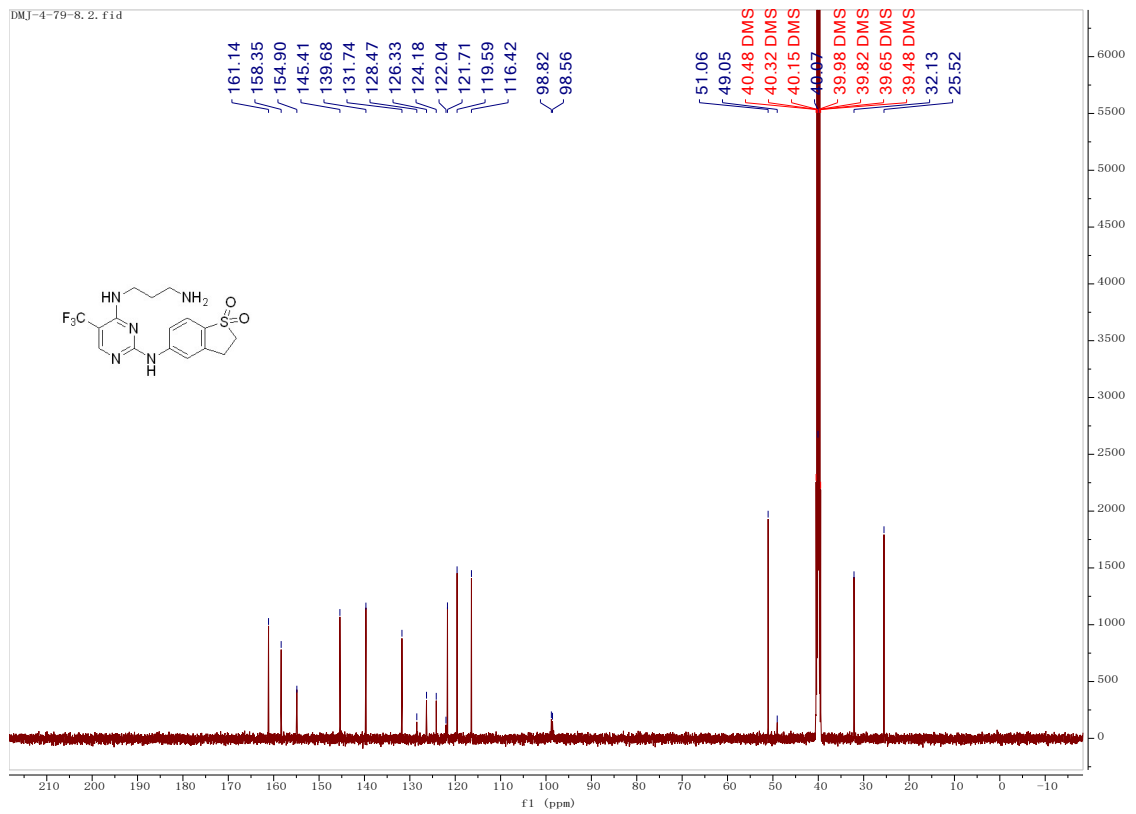
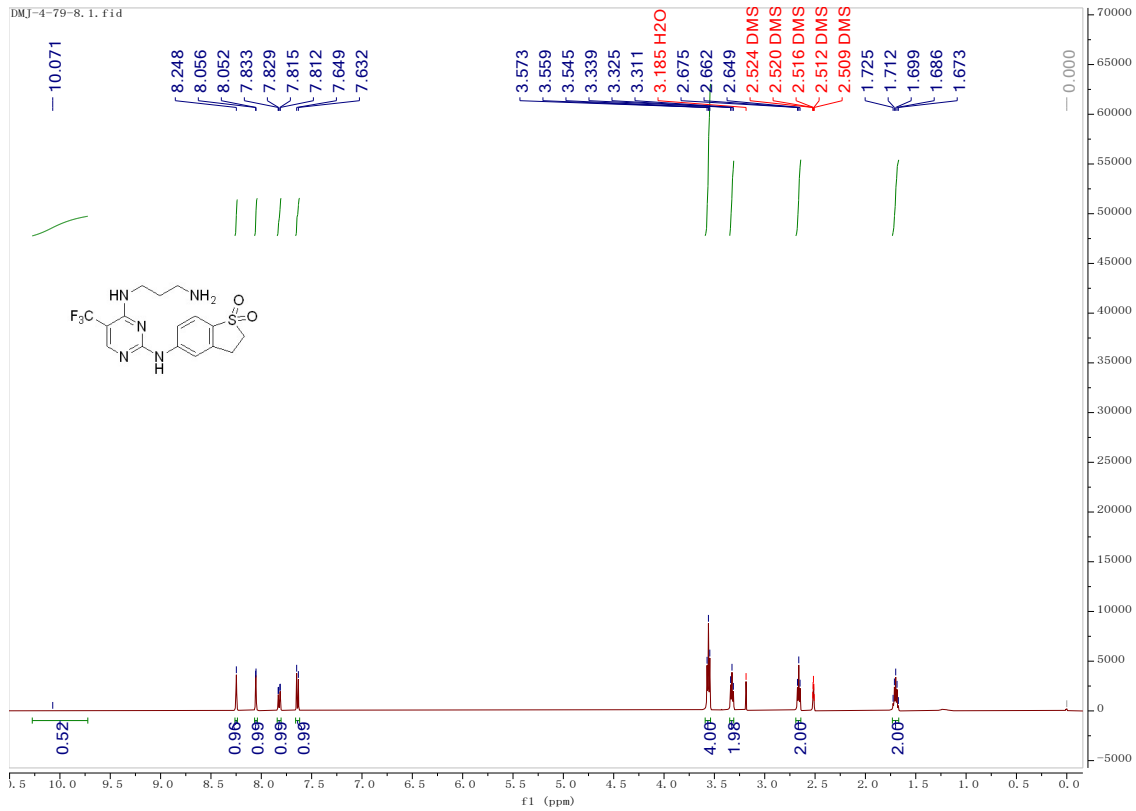


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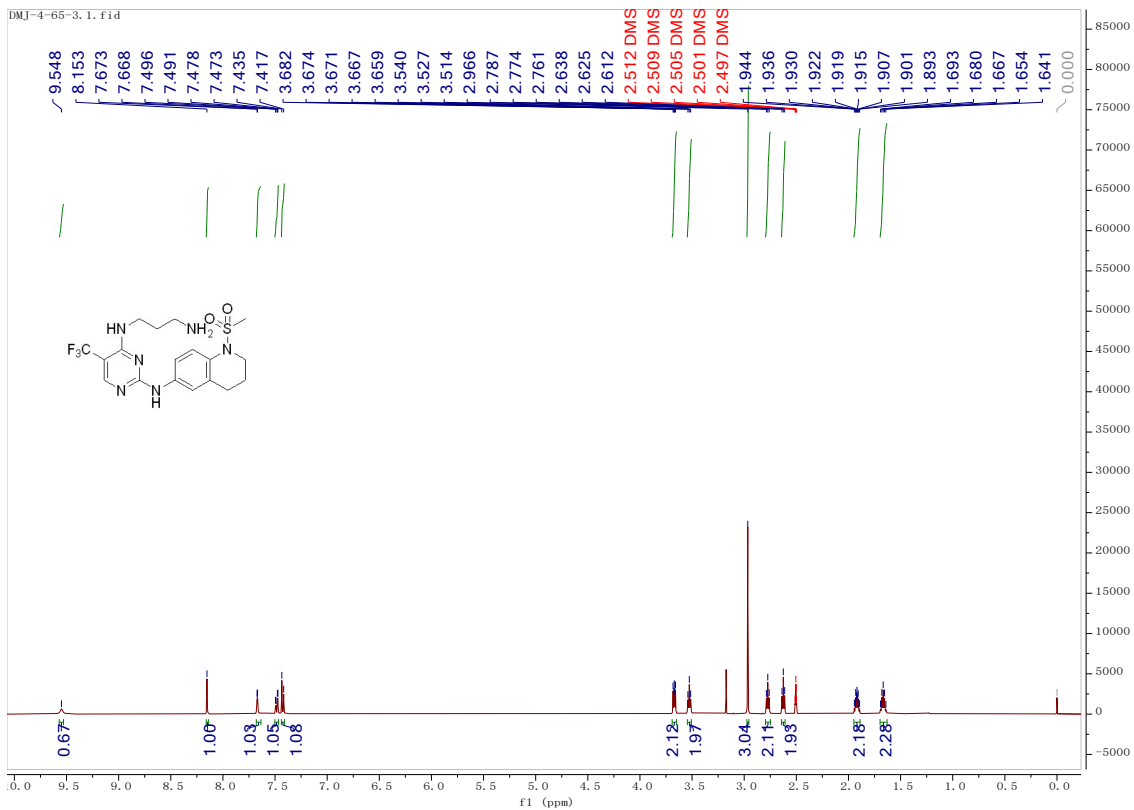


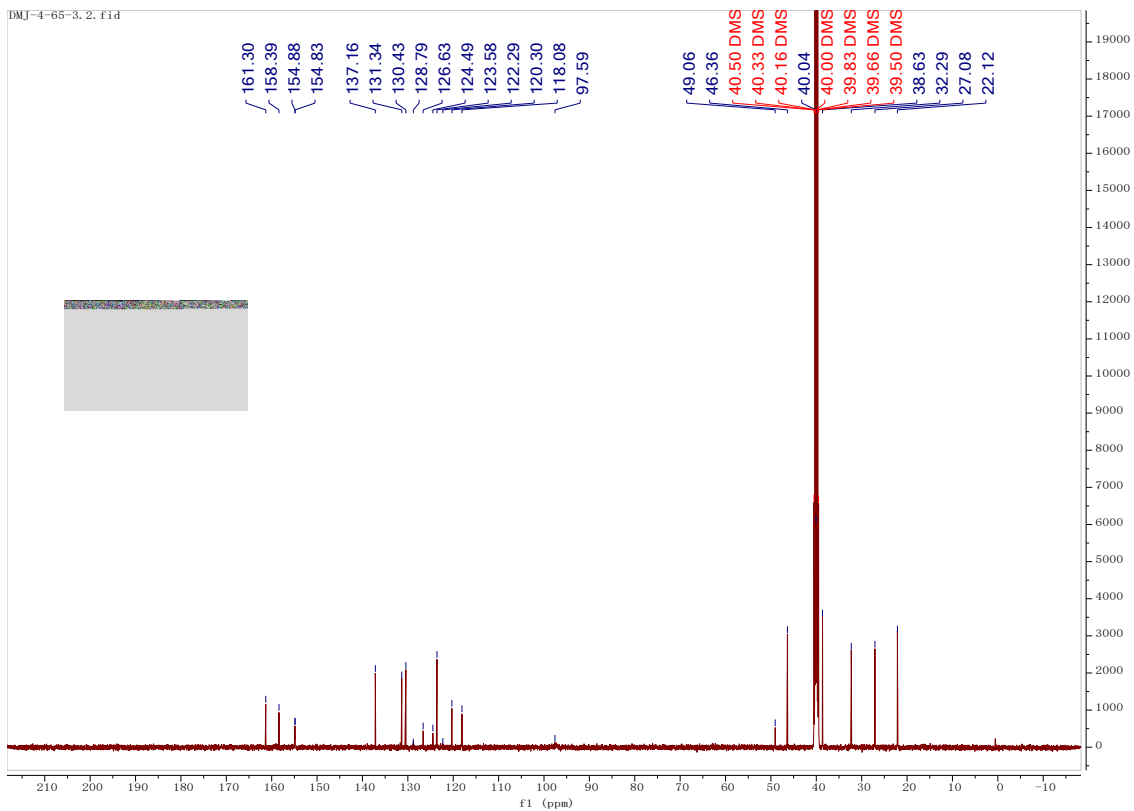
5-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2,3-

dihydrobenzo[*b*]thiophene 1,1-dioxide

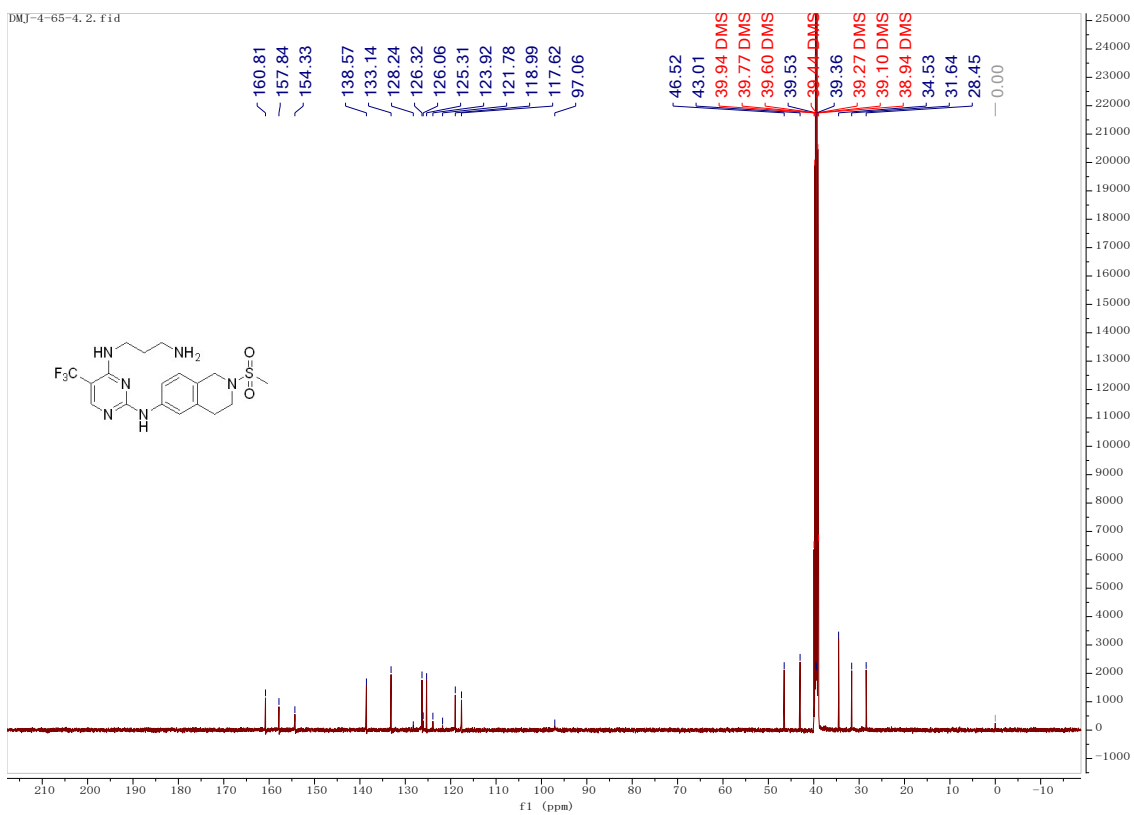
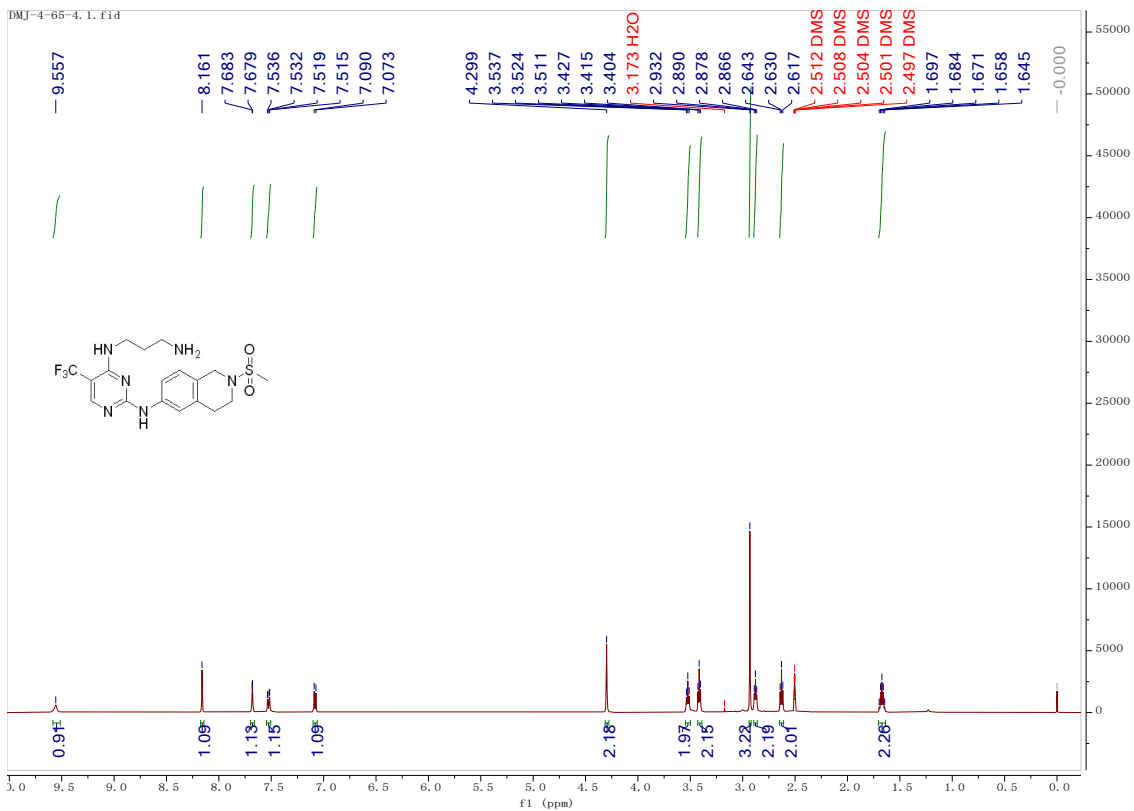


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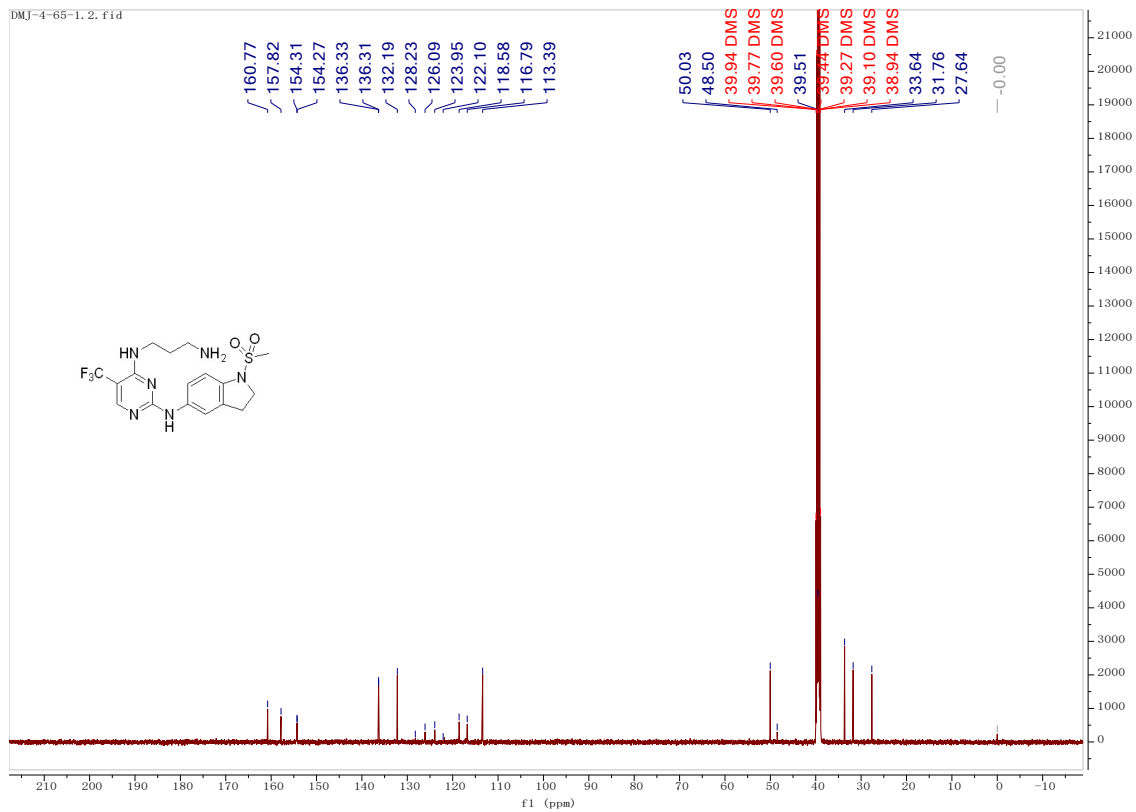
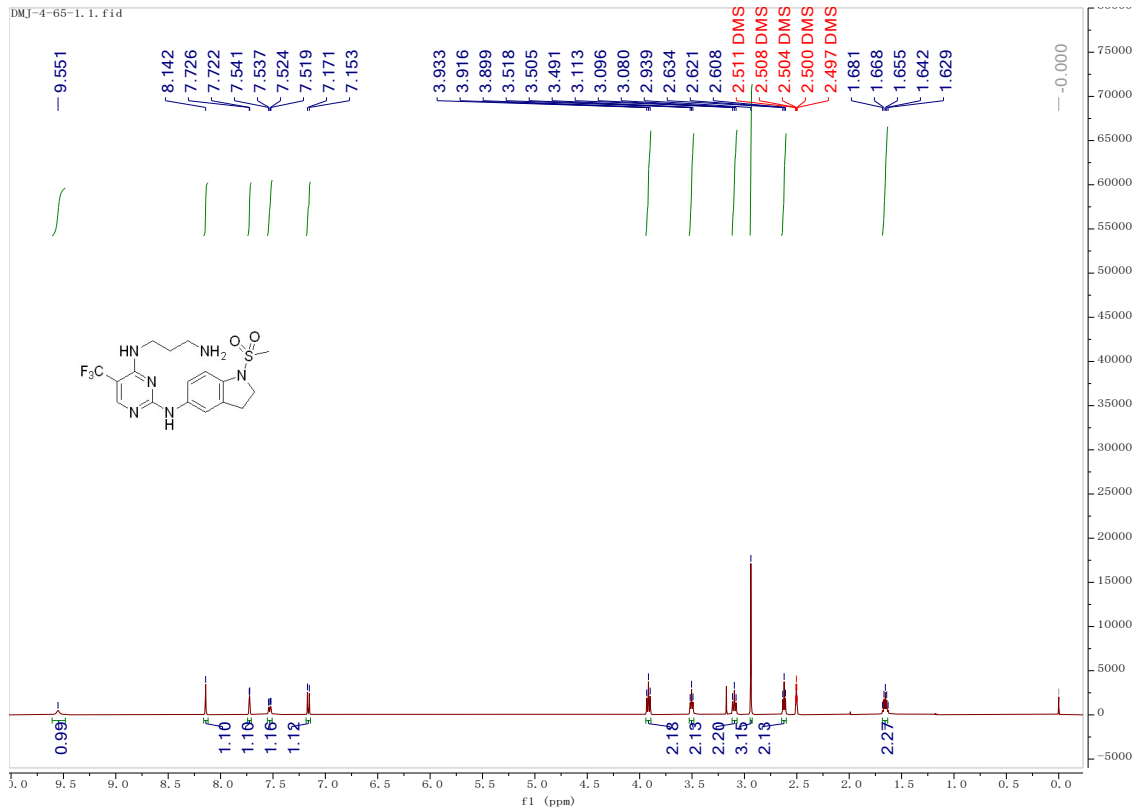


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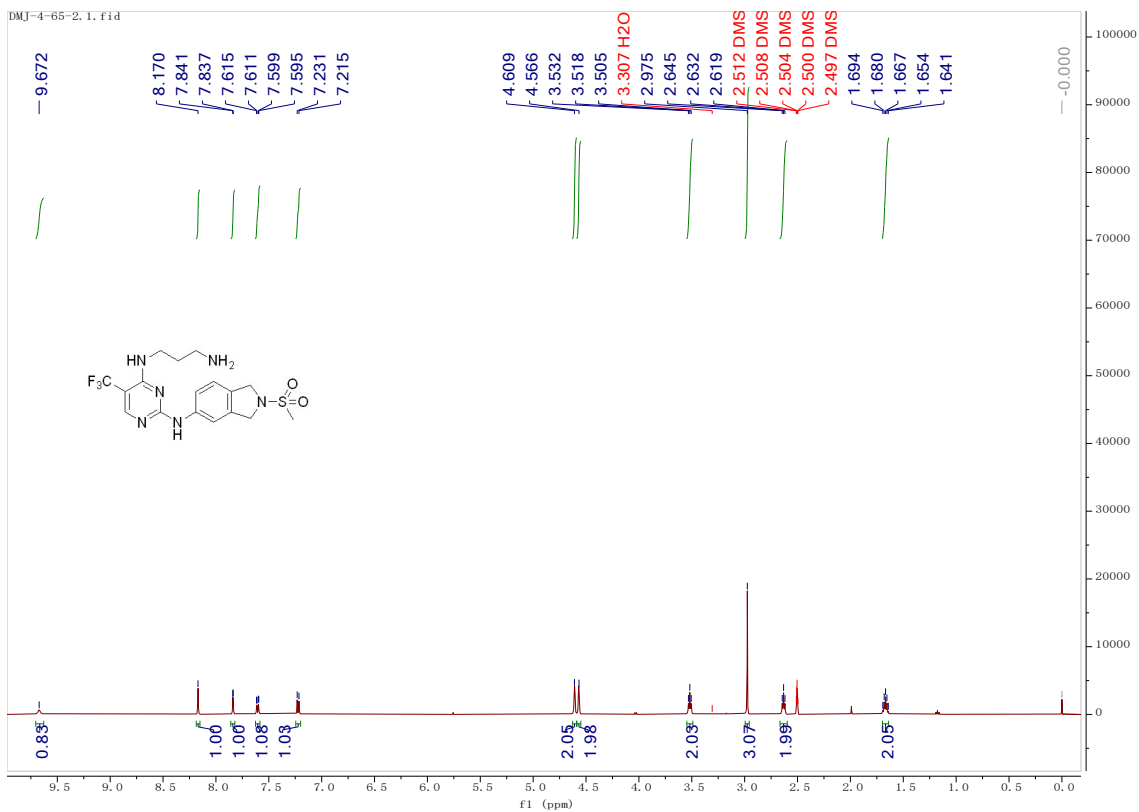


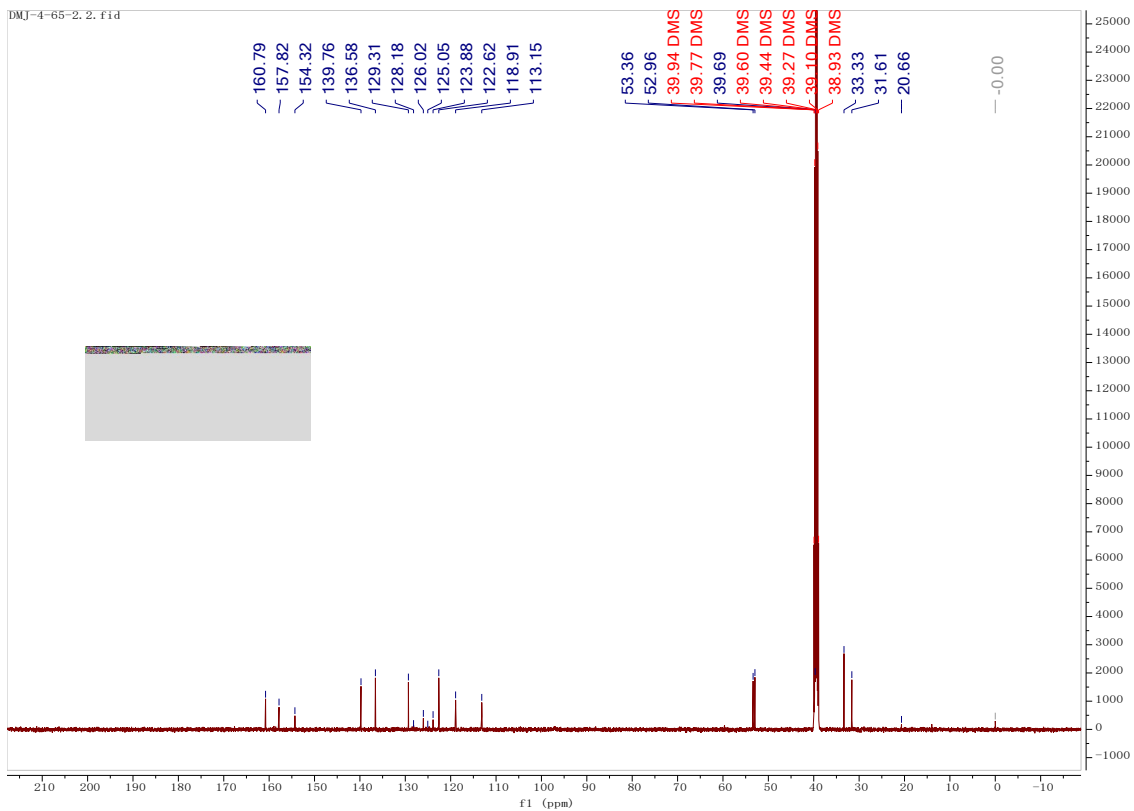
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2,4-diamine

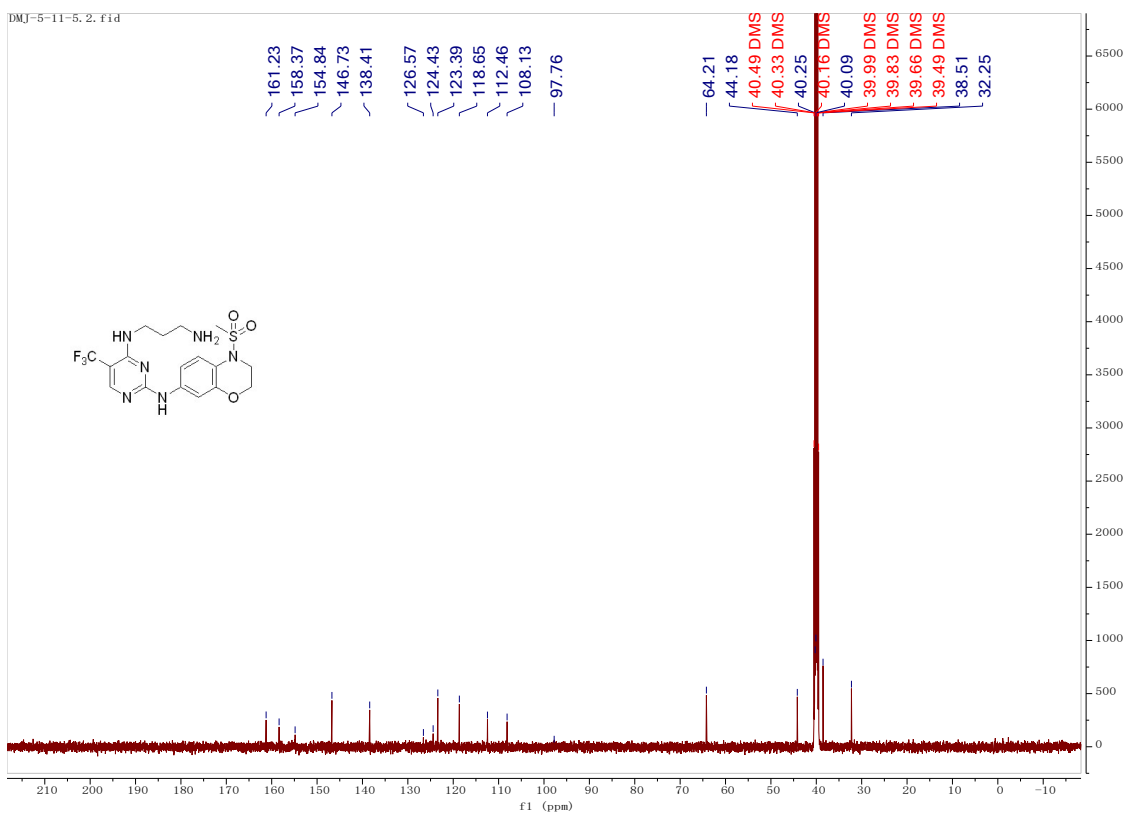
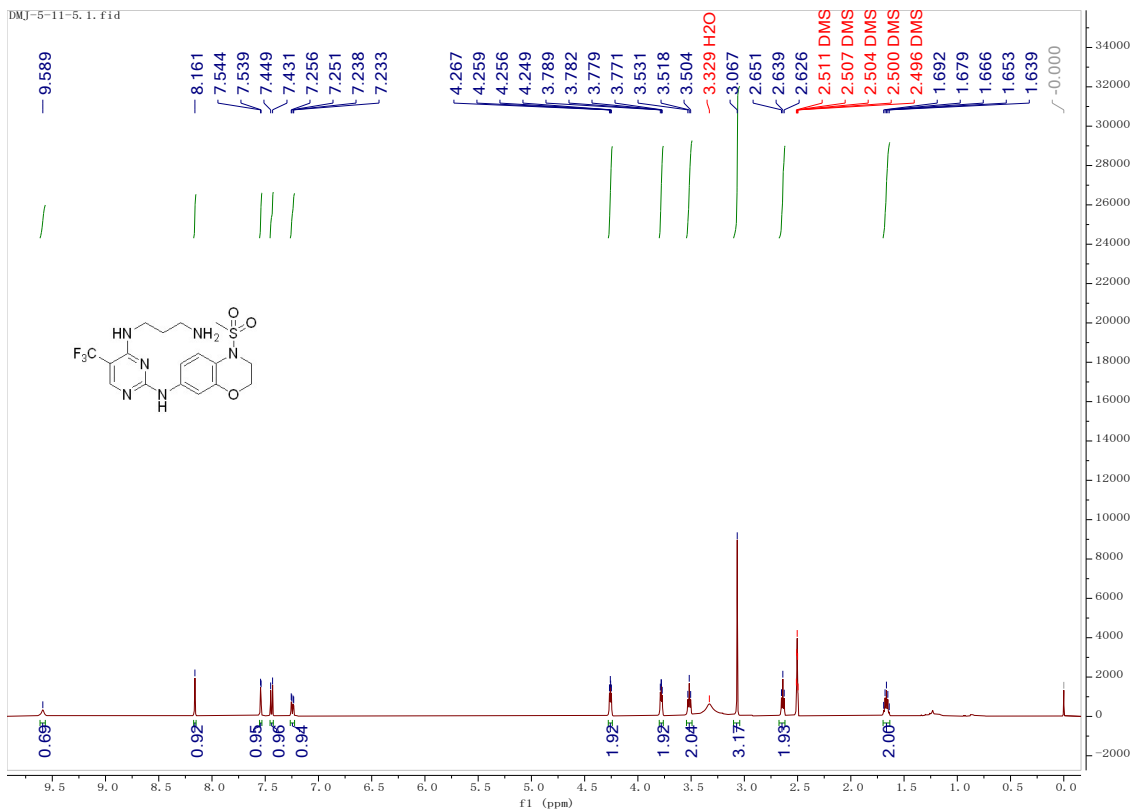


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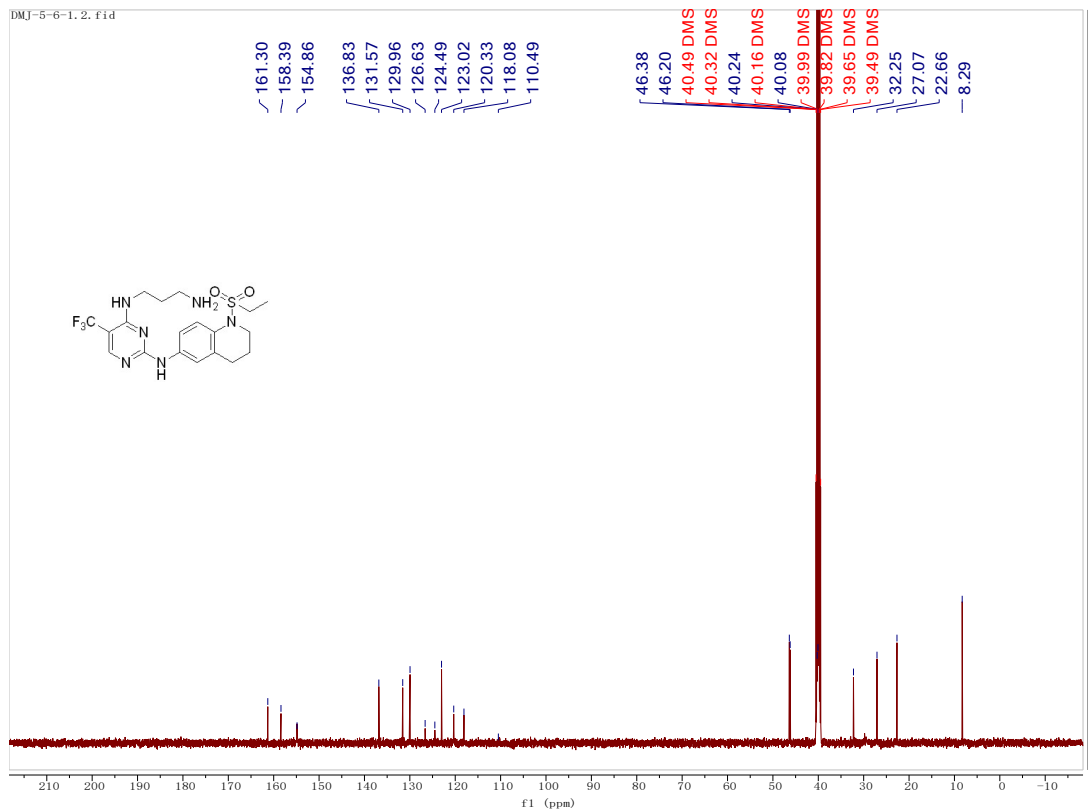
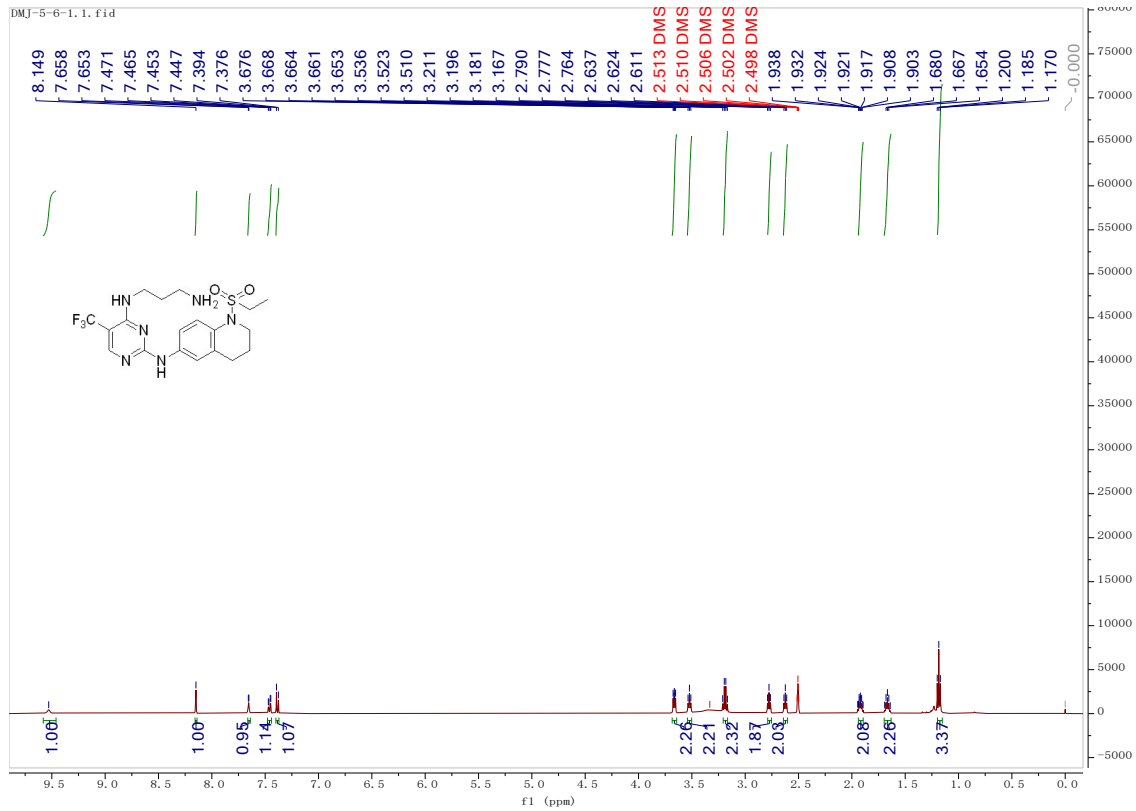


N^4 -(3-aminopropyl)- N^2 -(4-(methylsulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-7-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine

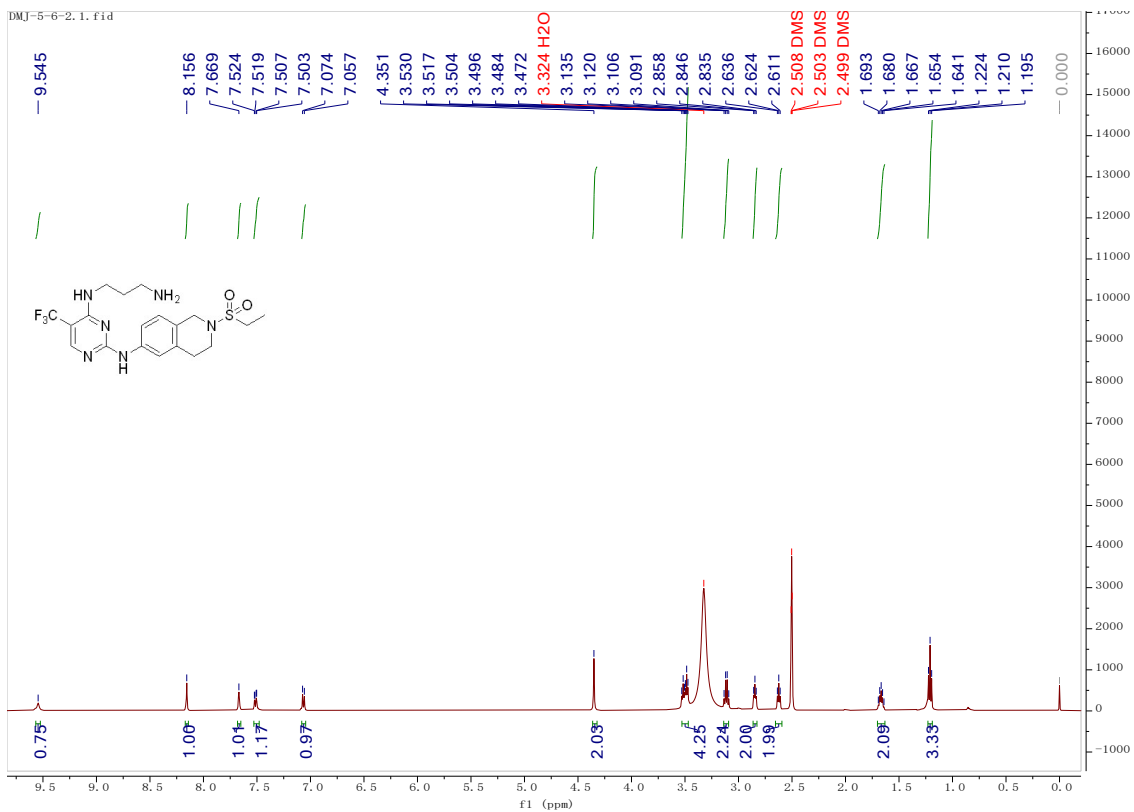


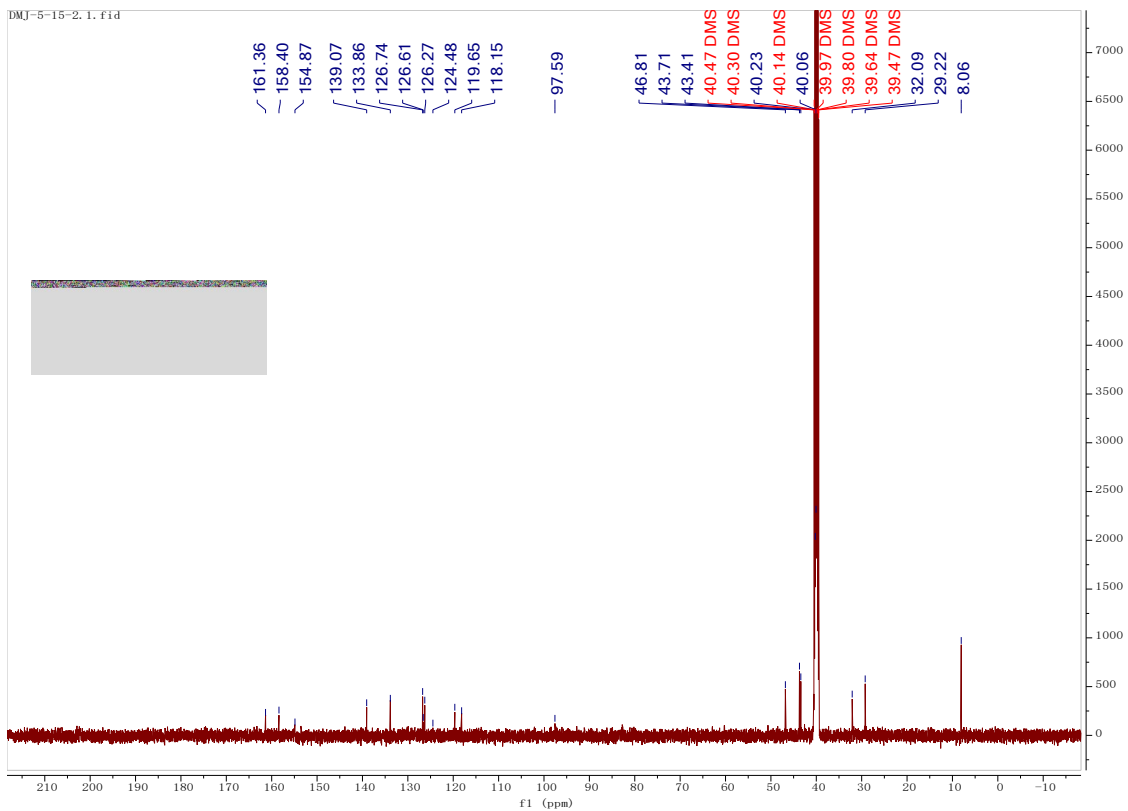
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(trifluoromethyl)pyrimidine-2,4-diamine

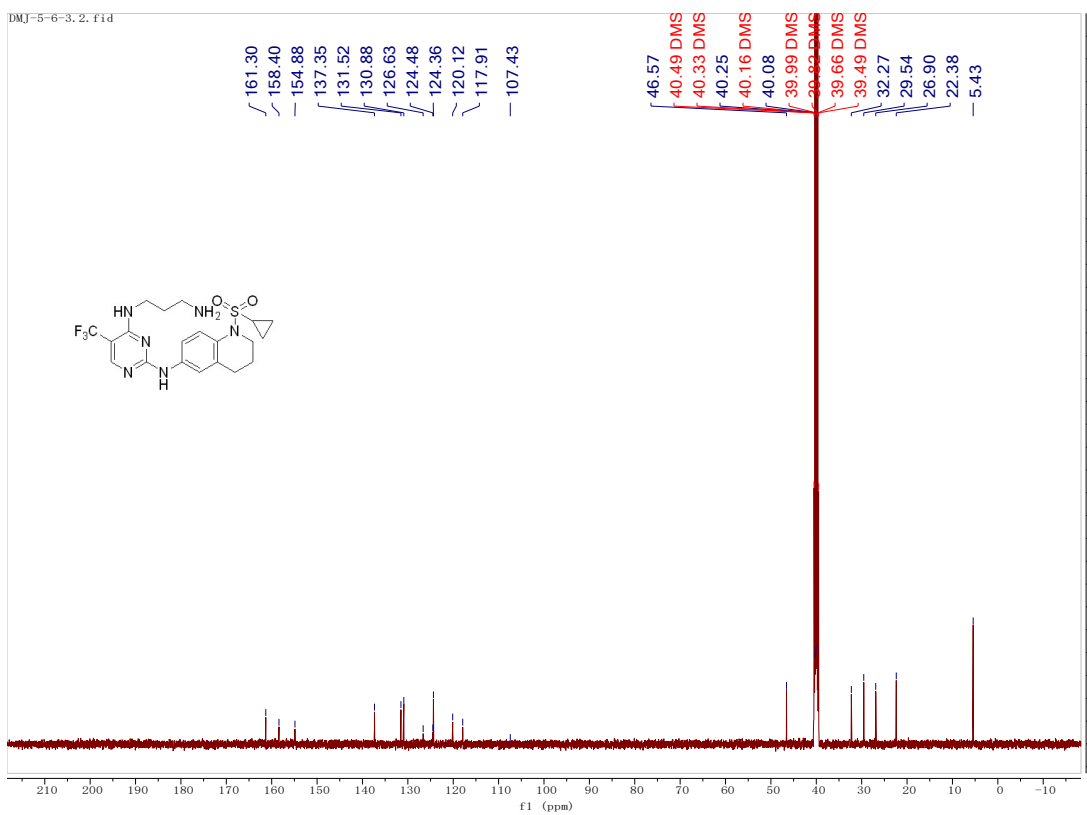
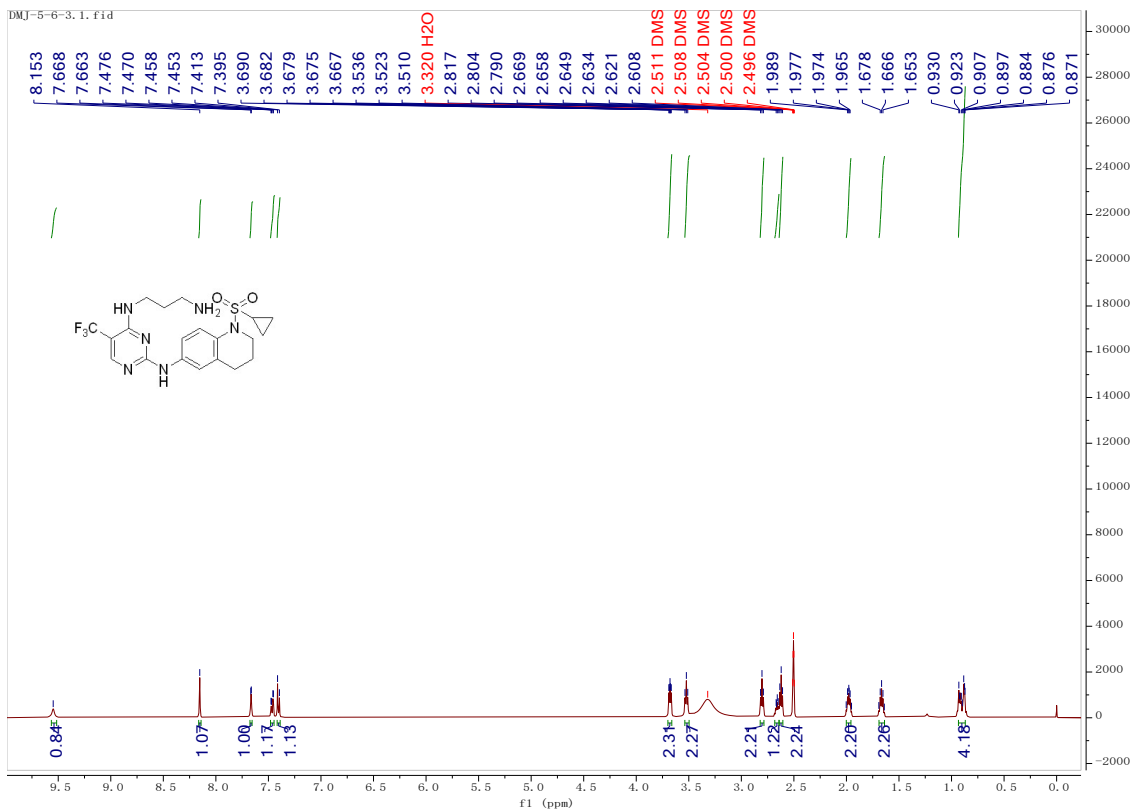


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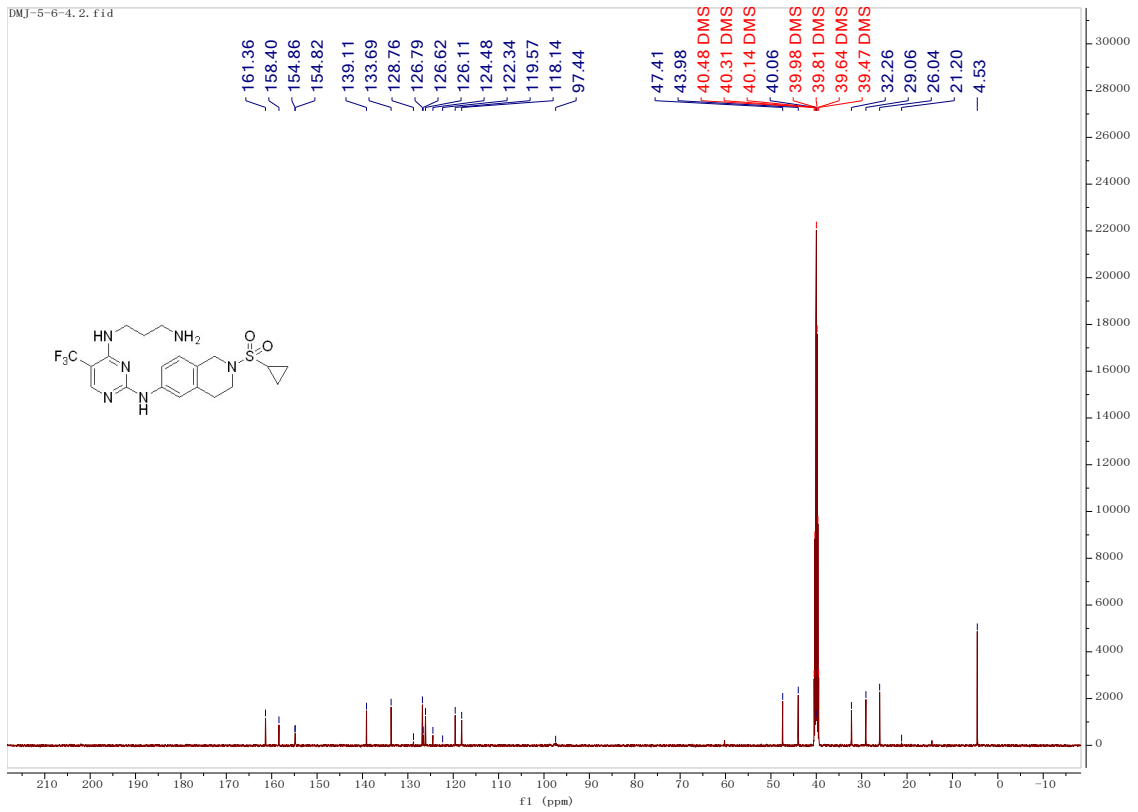
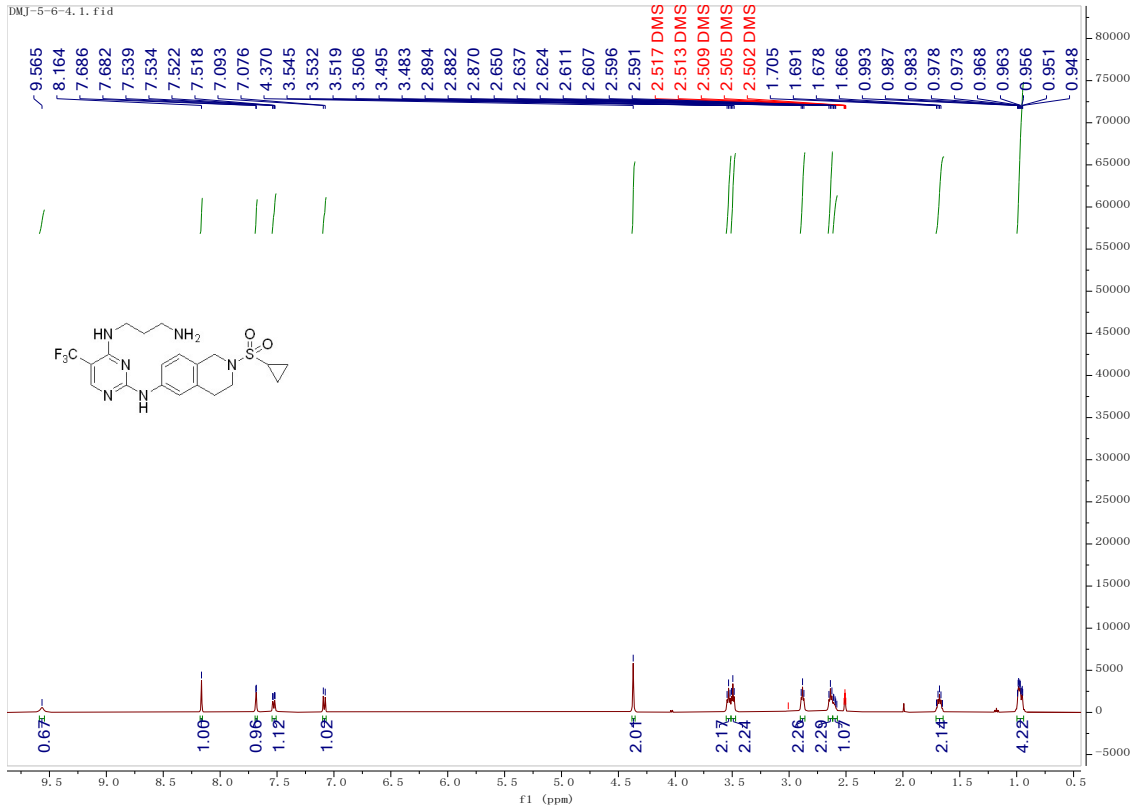


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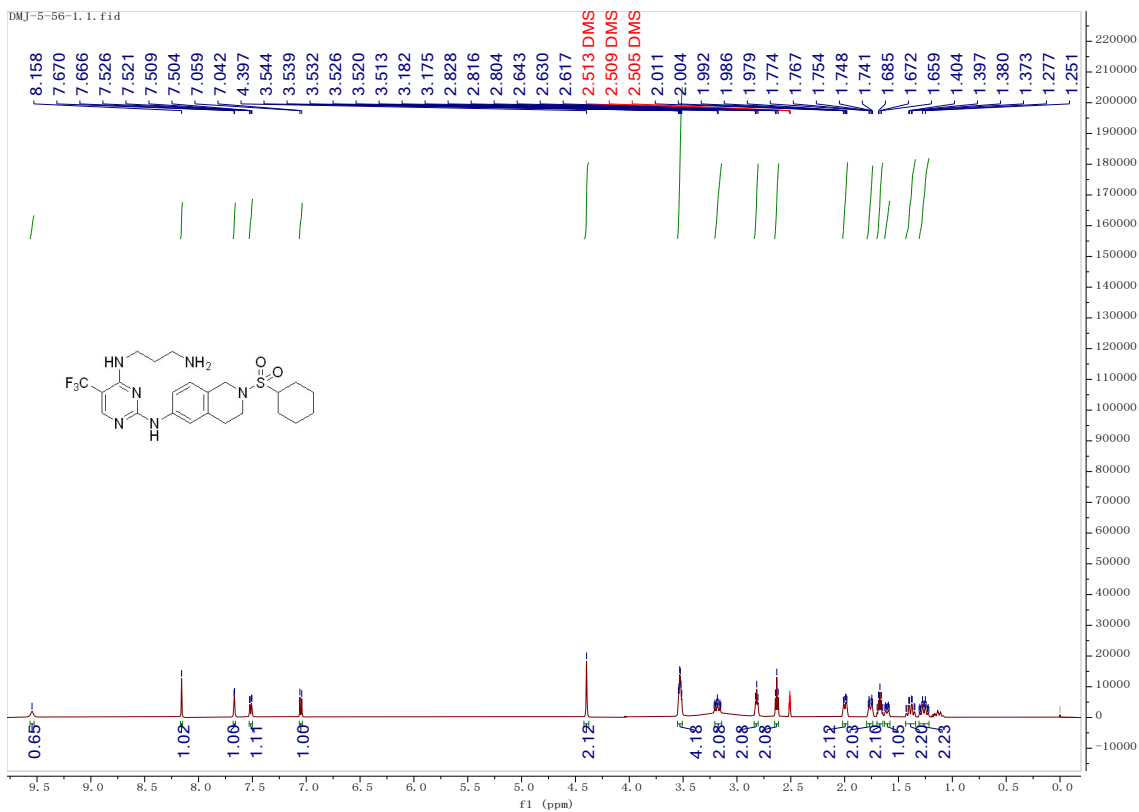


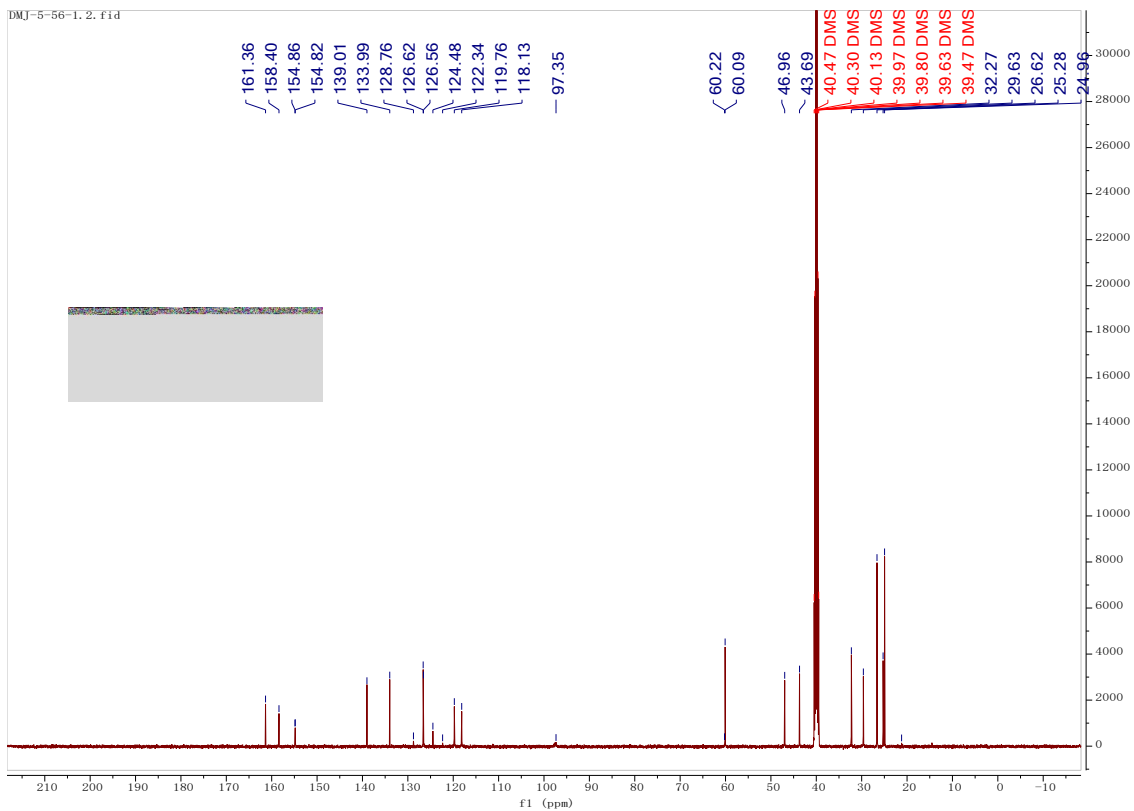
*N*⁴-(3-aminopropyl)-*N*²-(2-(cyclopropylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-

(trifluoromethyl)pyrimidine-2,4-diamine

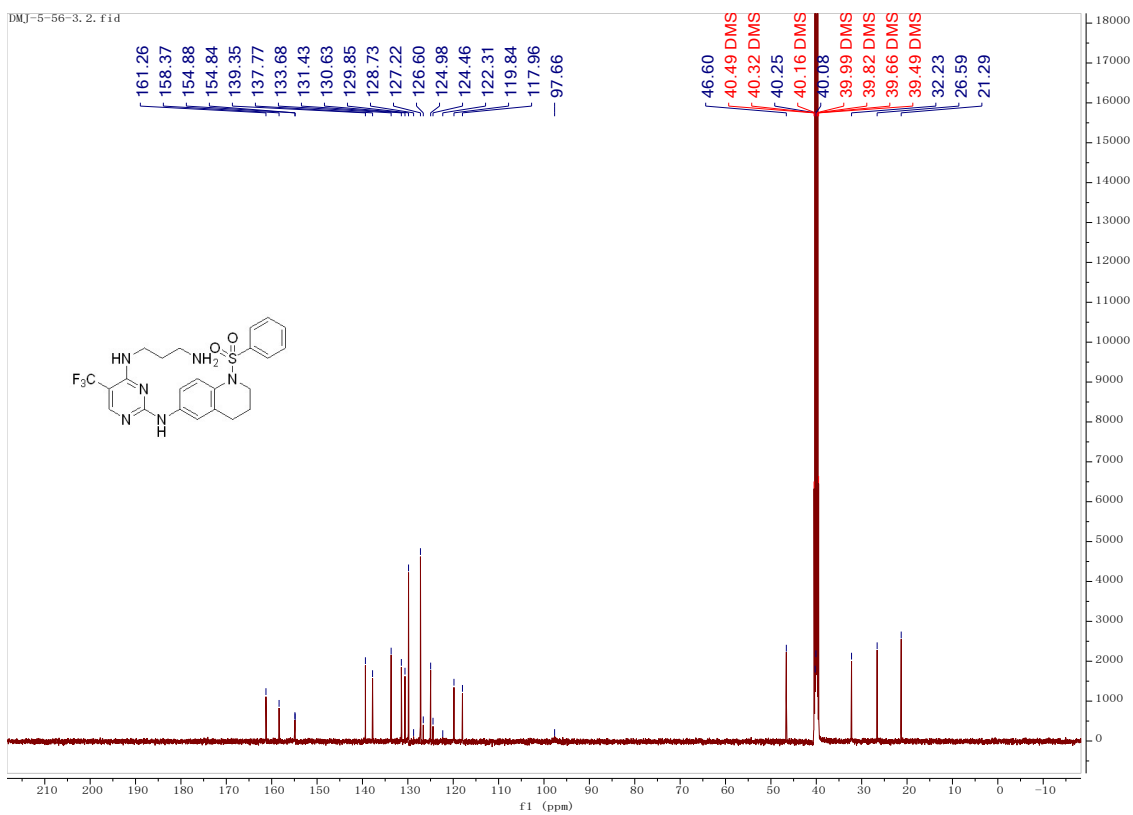
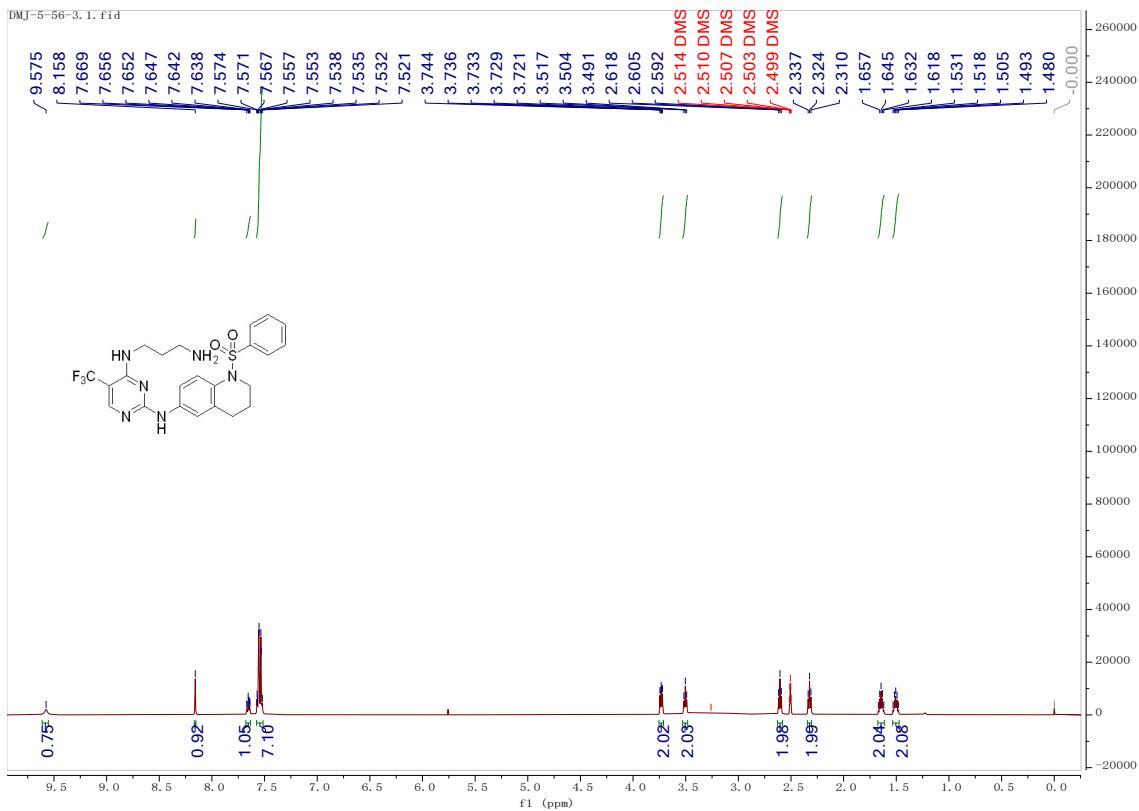


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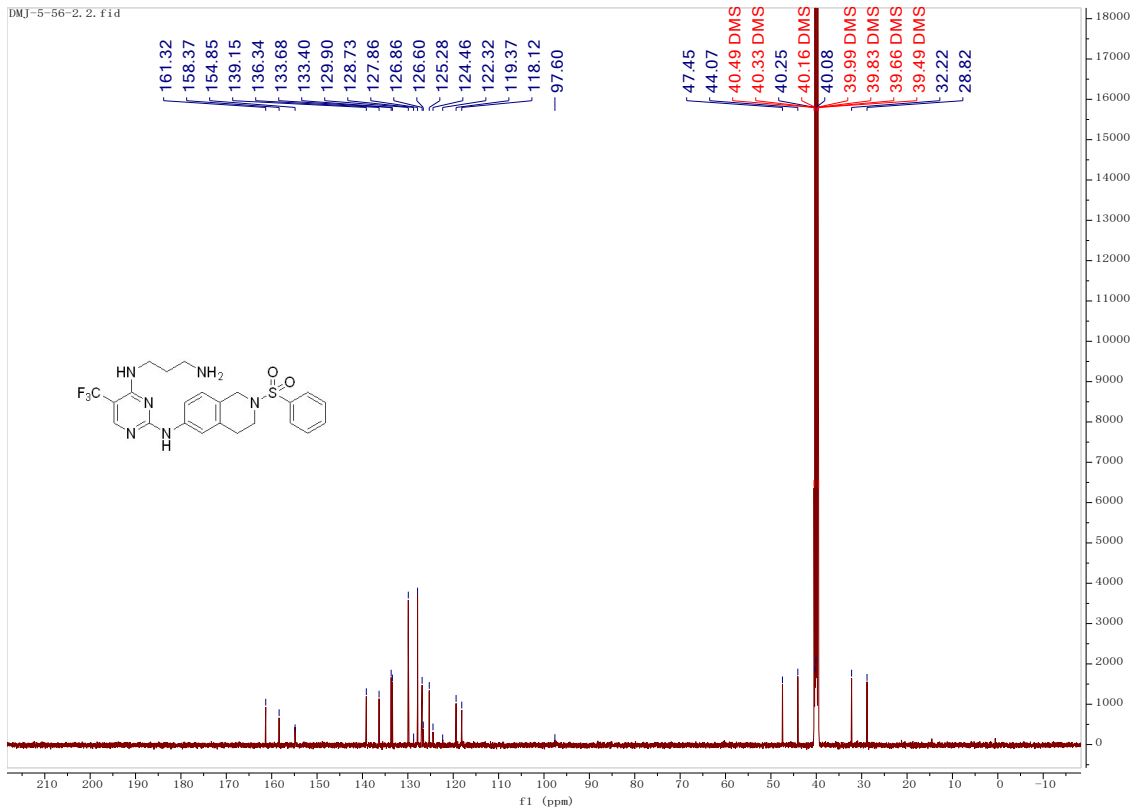
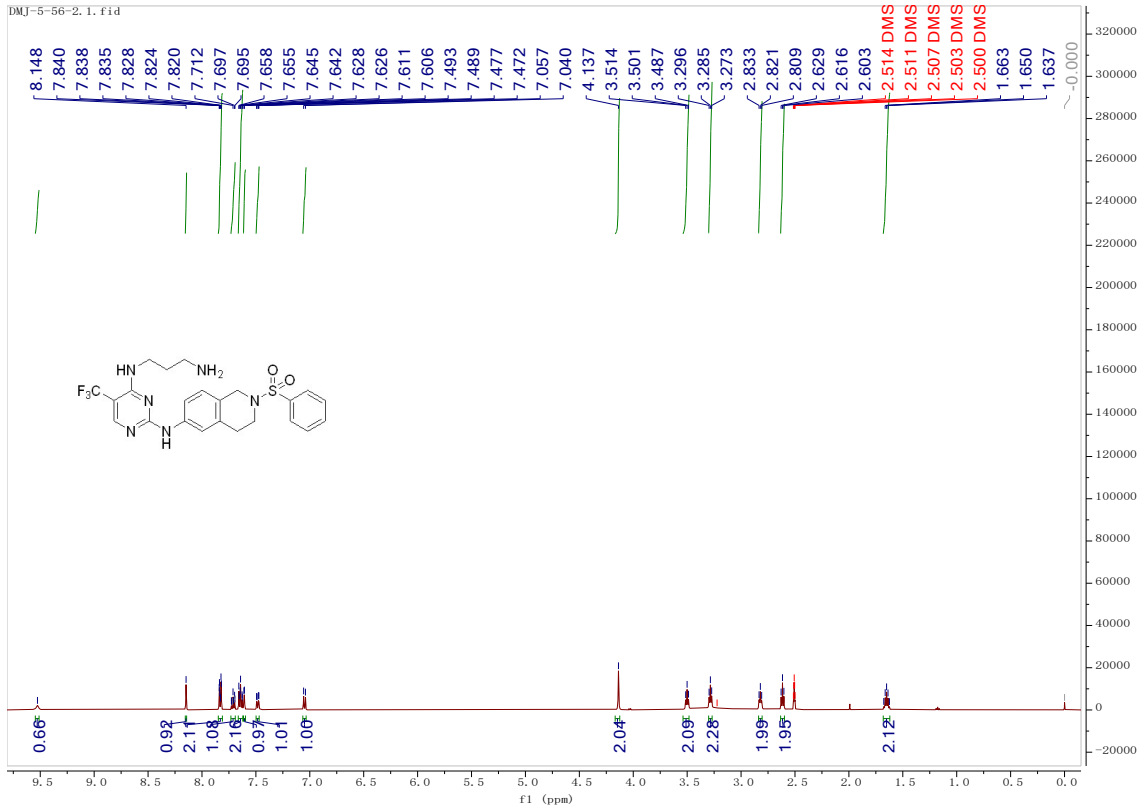


N^4 -(3-aminopropyl)- N^2 -(1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



*N*⁴-(3-aminopropyl)-*N*²-(2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-

(trifluoromethyl)pyrimidine-2,4-diamine



HPLC methods and spectra

System: Agilent 1260 Series

Column: Cosmosil 5C18-AR-II column (4.6 mm × 250 mm)

Flow rate: 1.0 mL/min

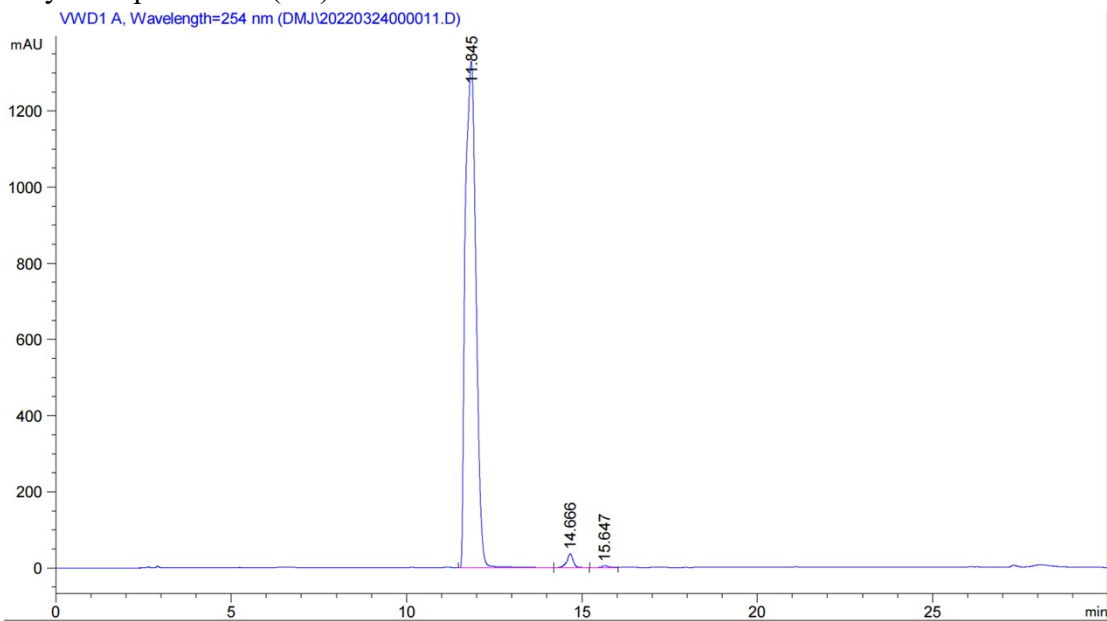
Method A

t (min)	mobile phase A (% CH ₃ COONH ₄ + 0.01% CF ₃ COOH)	mobile phase B (% CH ₃ OH)
0	70	30
5	60	40
10	30	70
15	15	85
20	5	95
25	60	40
30	70	30

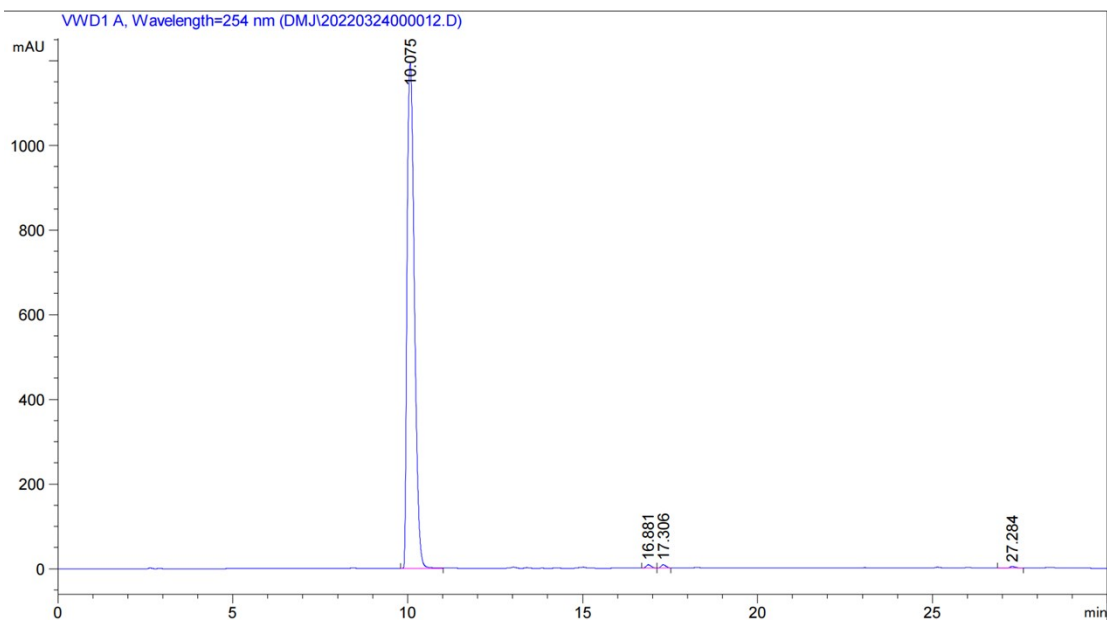
Method B

t (min)	mobile phase A (% CF ₃ COOH)	mobile phase B (% CH ₃ OH)
0	90	10
5	80	20
10	75	25
15	60	40
20	40	60
25	50	50
30	90	10

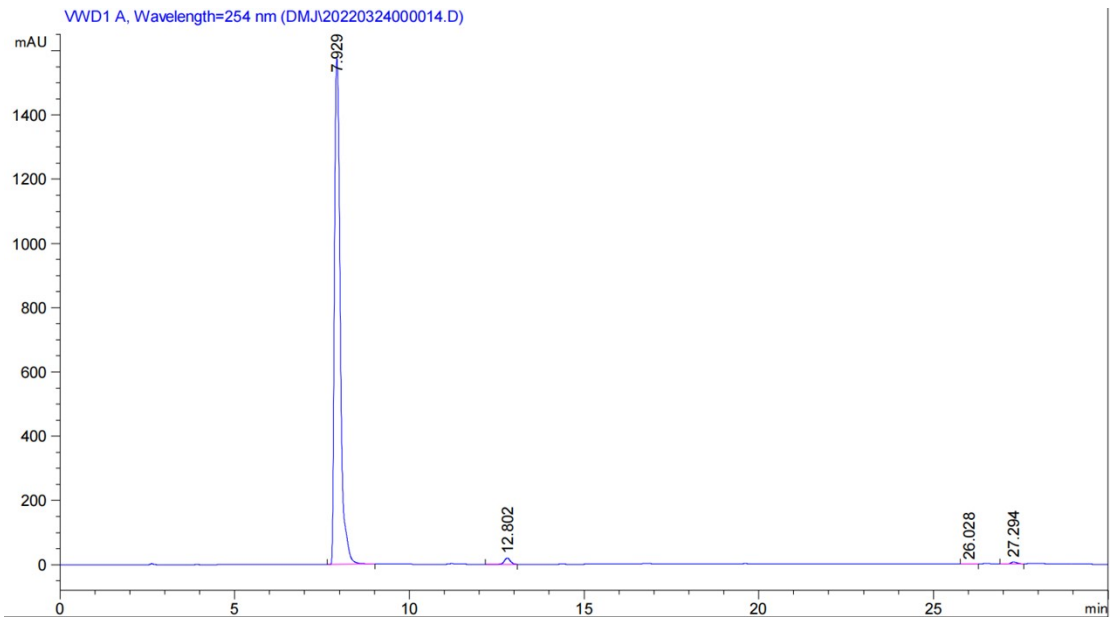
6-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-3,4-dihydronaphthalen-1(2H)-one



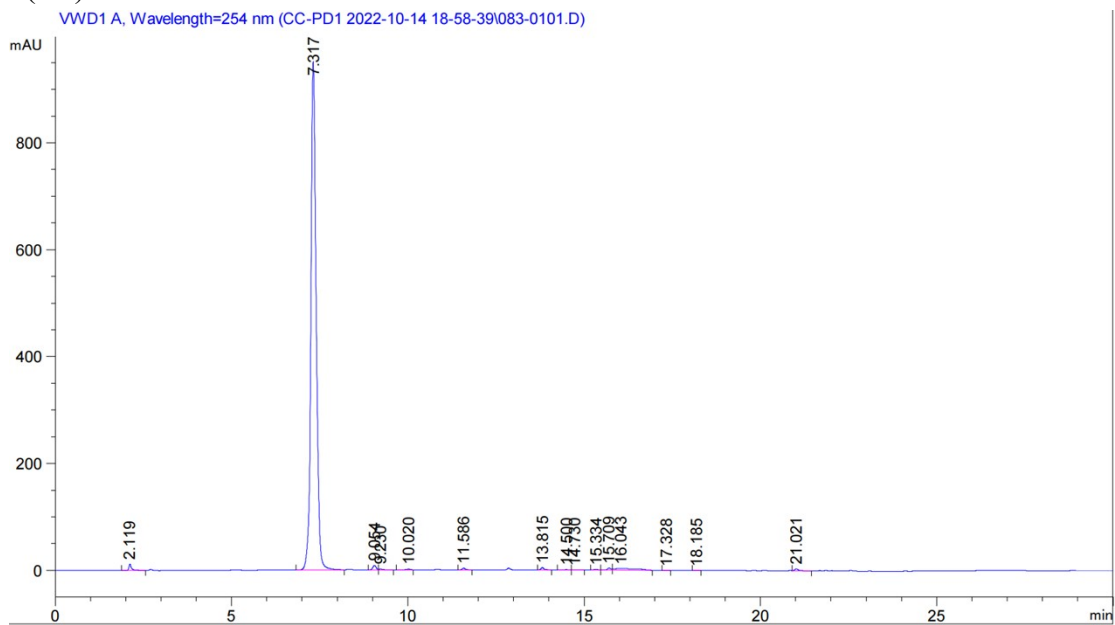
5-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2,3-dihydro-1H-inden-1-one



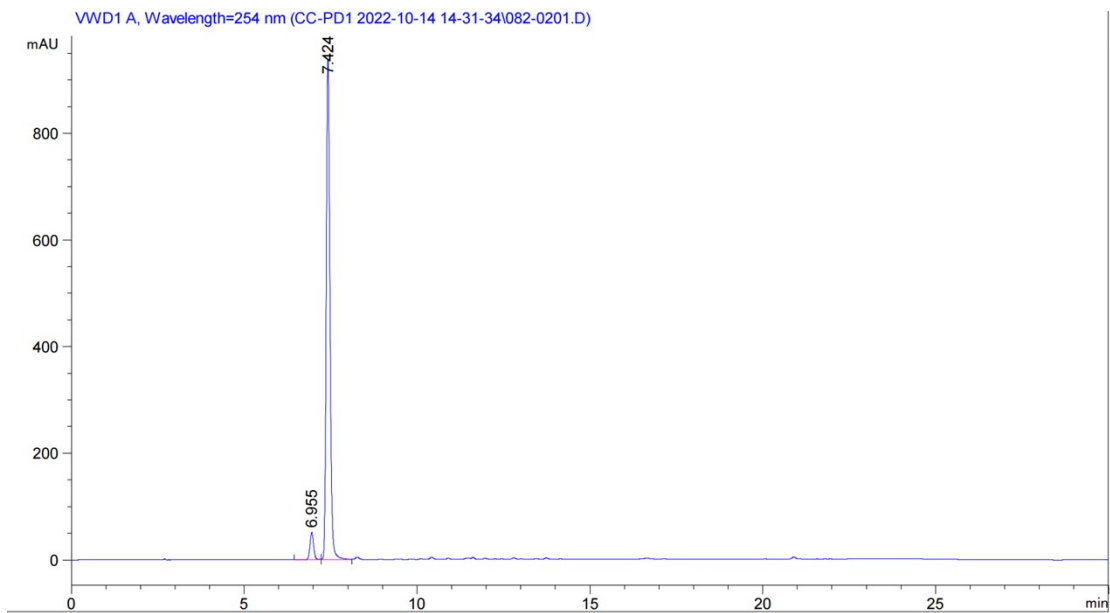
7-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)chroman-4-one



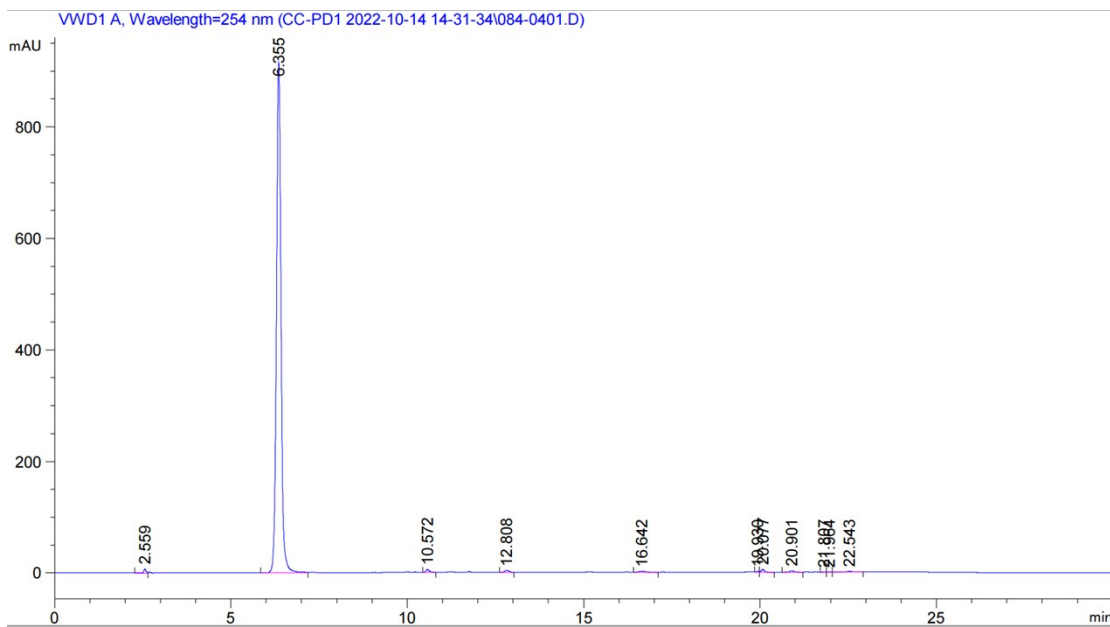
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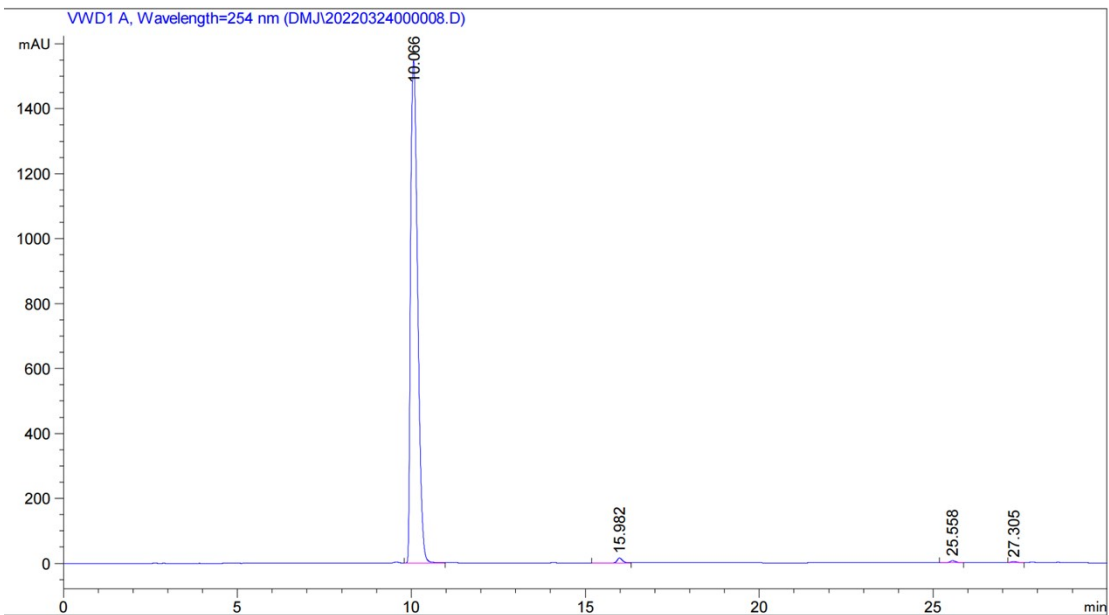
*N*⁴-(3-aminopropyl)-*N*²-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



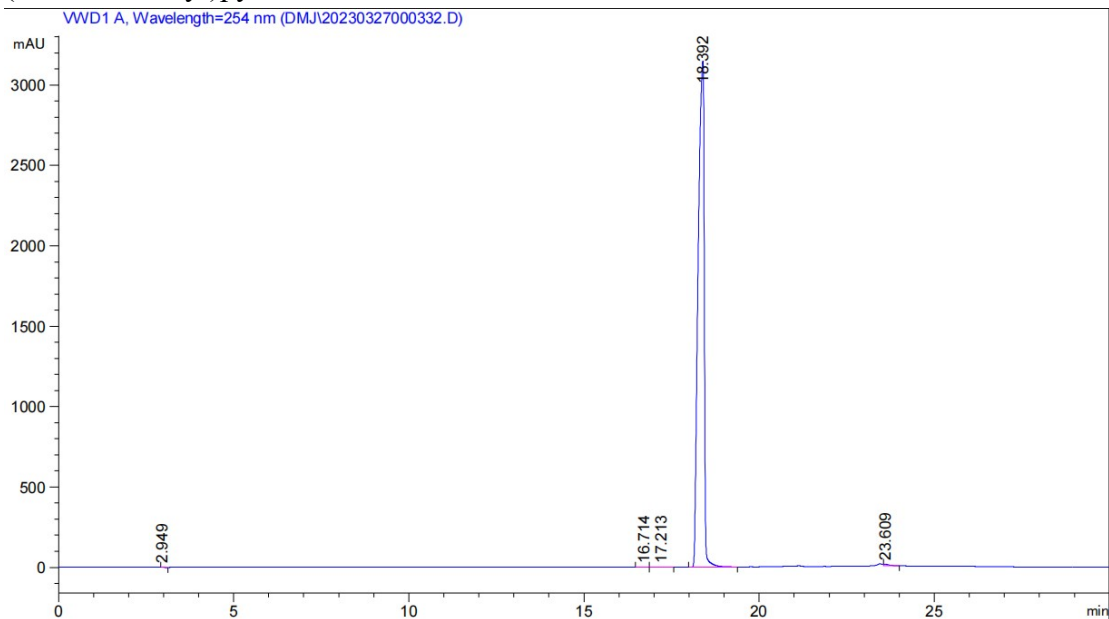
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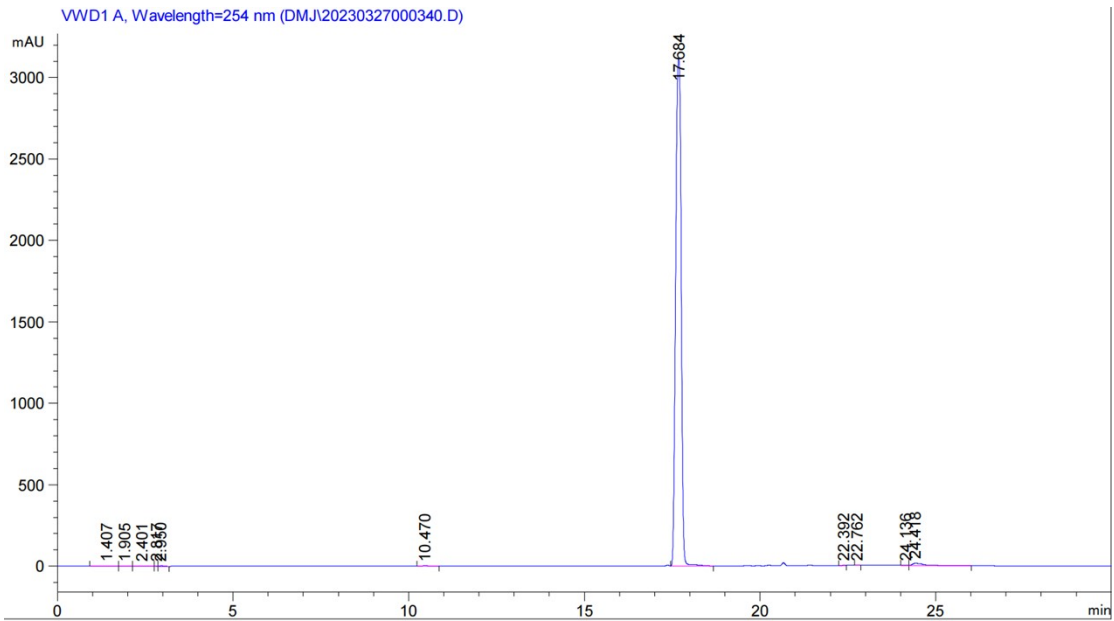
5-((4-((3-aminopropyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide



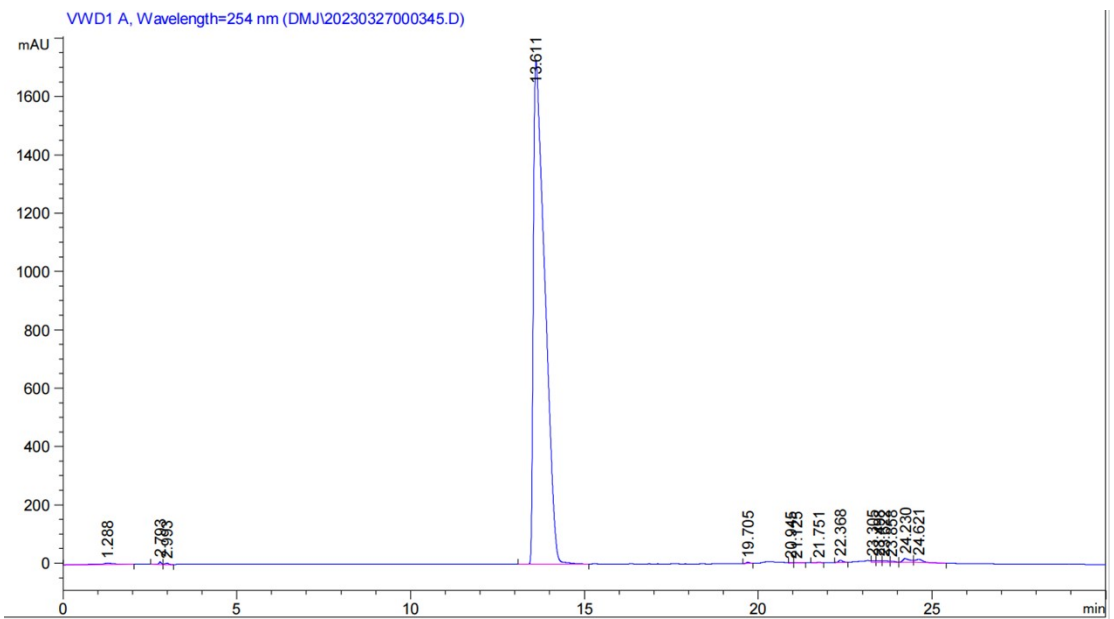
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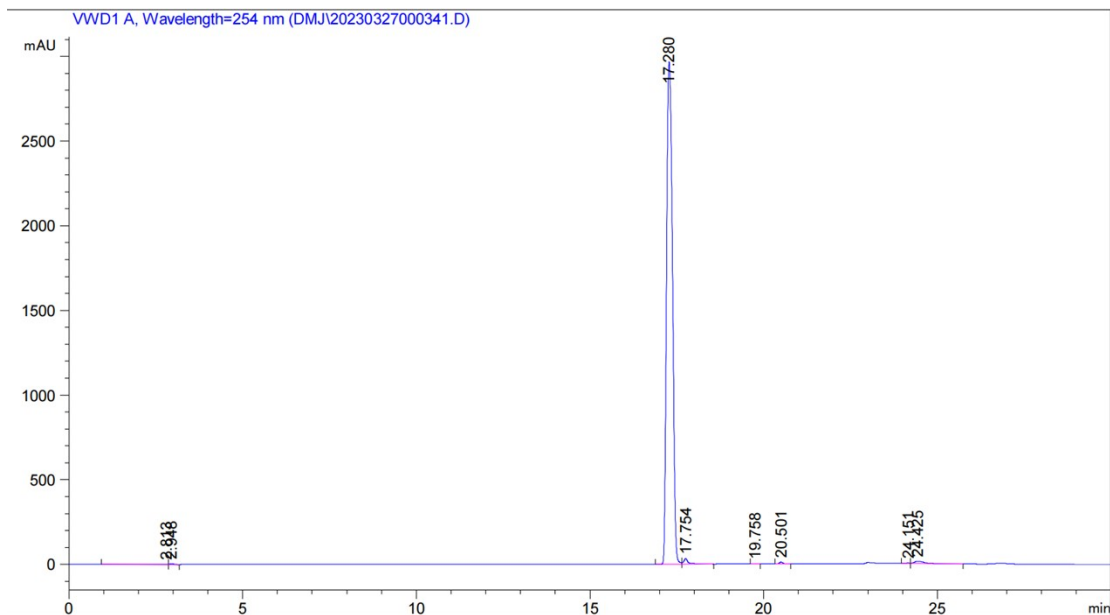
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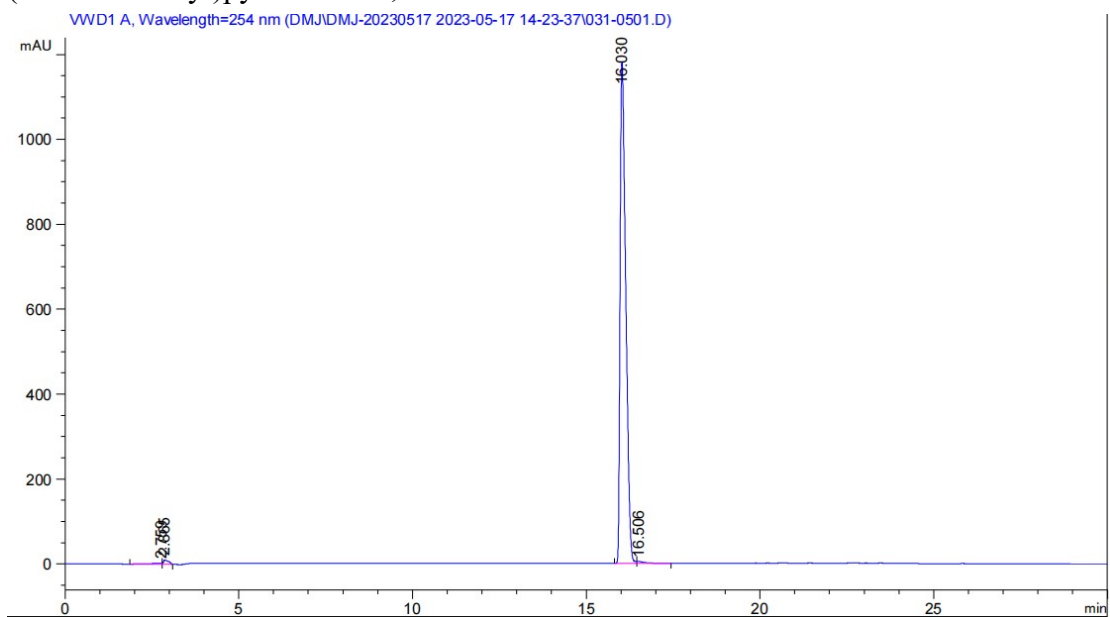
*N*⁴-(3-aminopropyl)-*N*²-(1-(methylsulfonyl)indolin-5-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



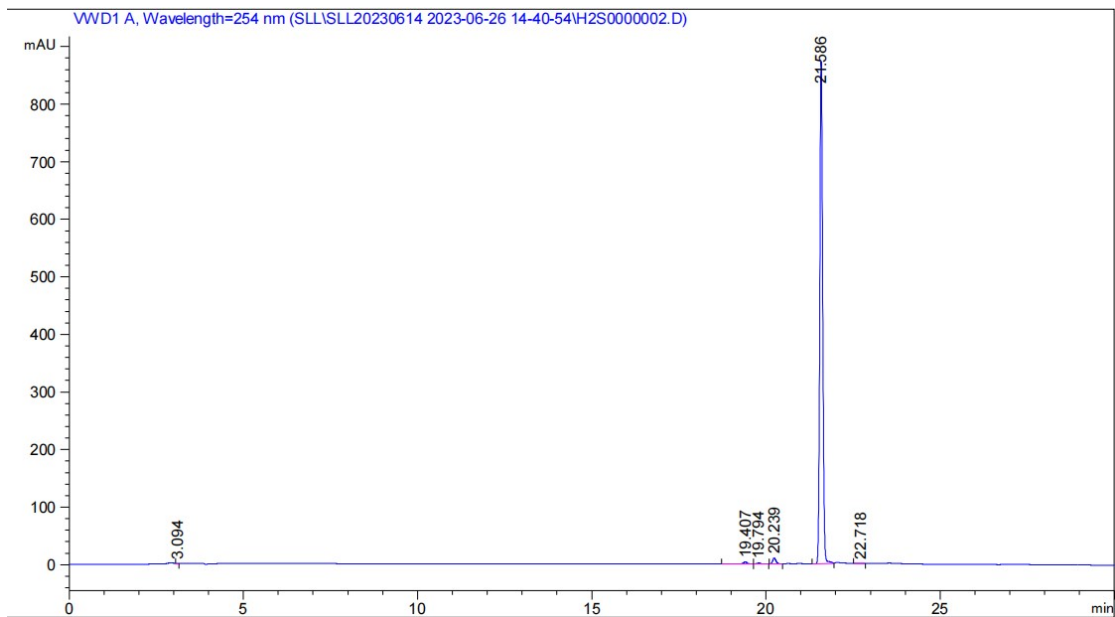
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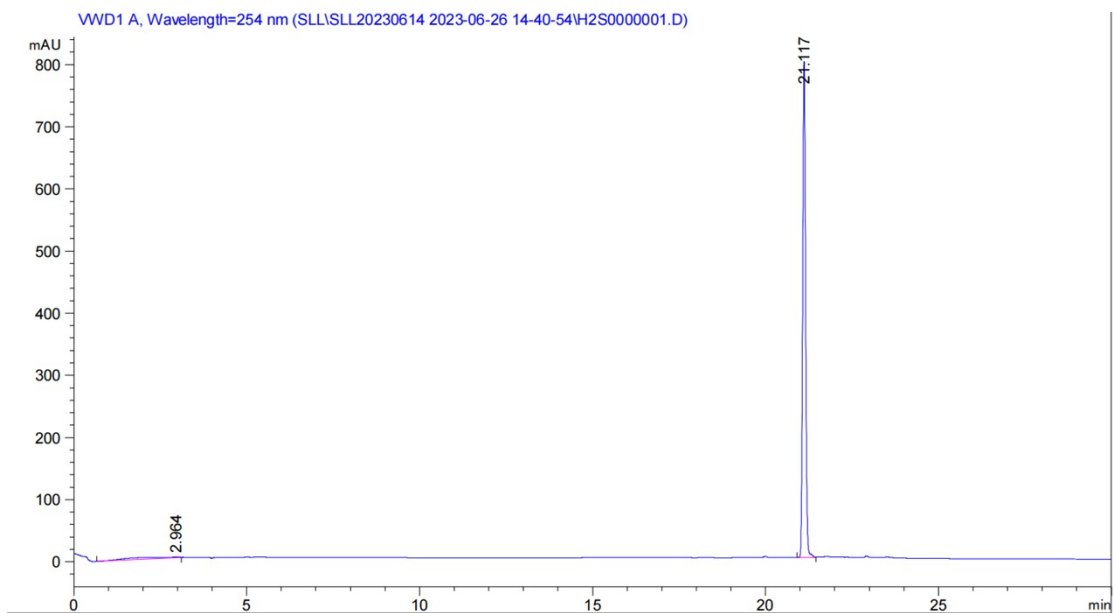
*N*⁴-(3-aminopropyl)-*N*²-(4-(methylsulfonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



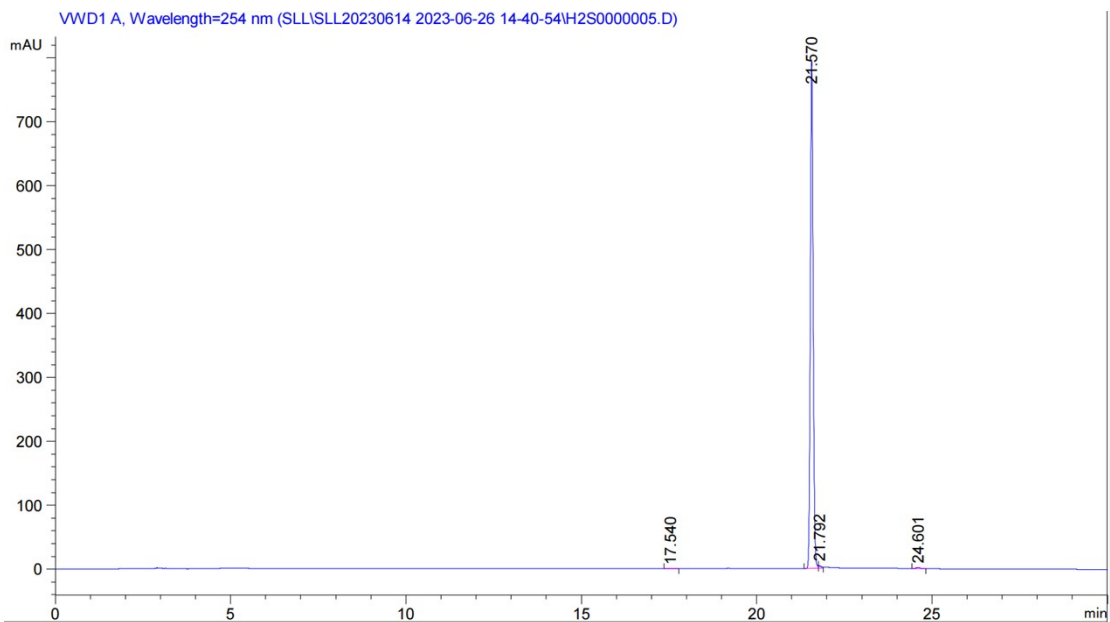
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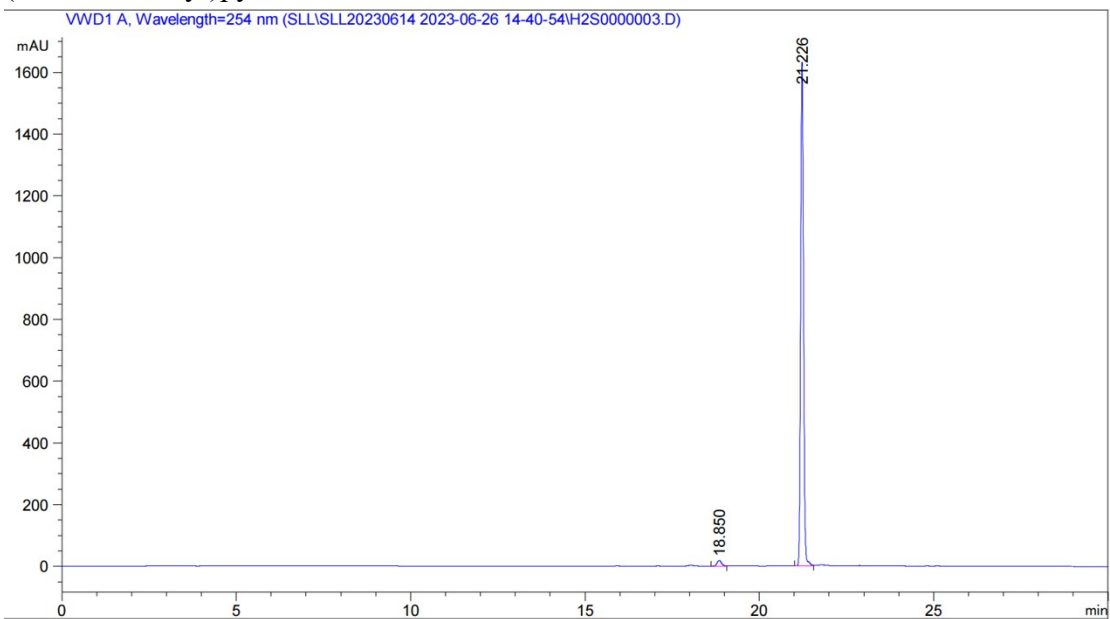
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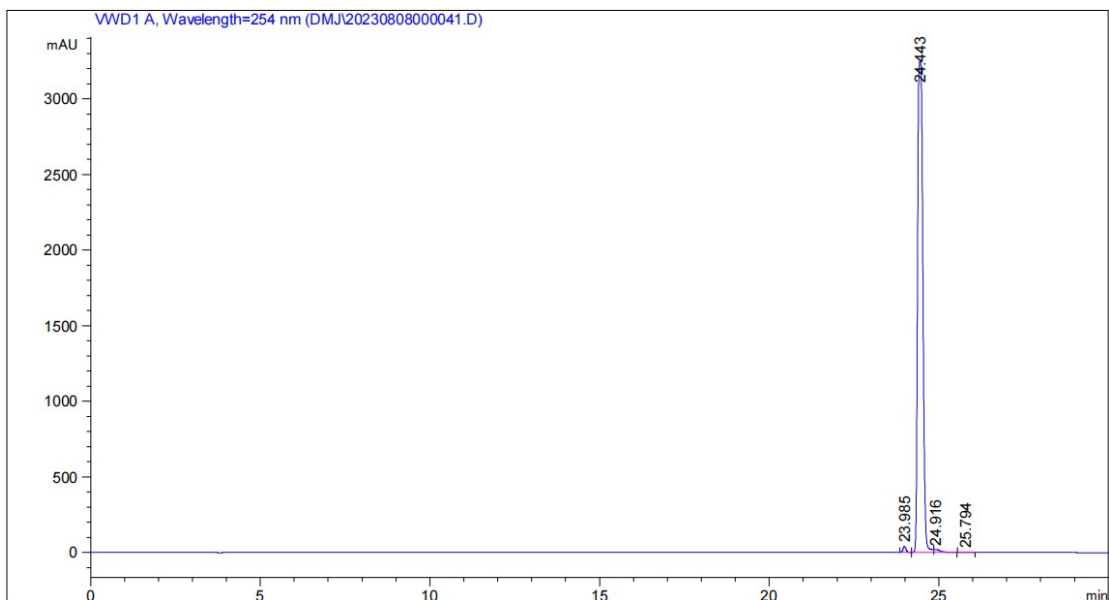
*N*⁴-(3-aminopropyl)-*N*²-(1-(cyclopropylsulfonyl)-1,2,3,4-tetrahydroquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



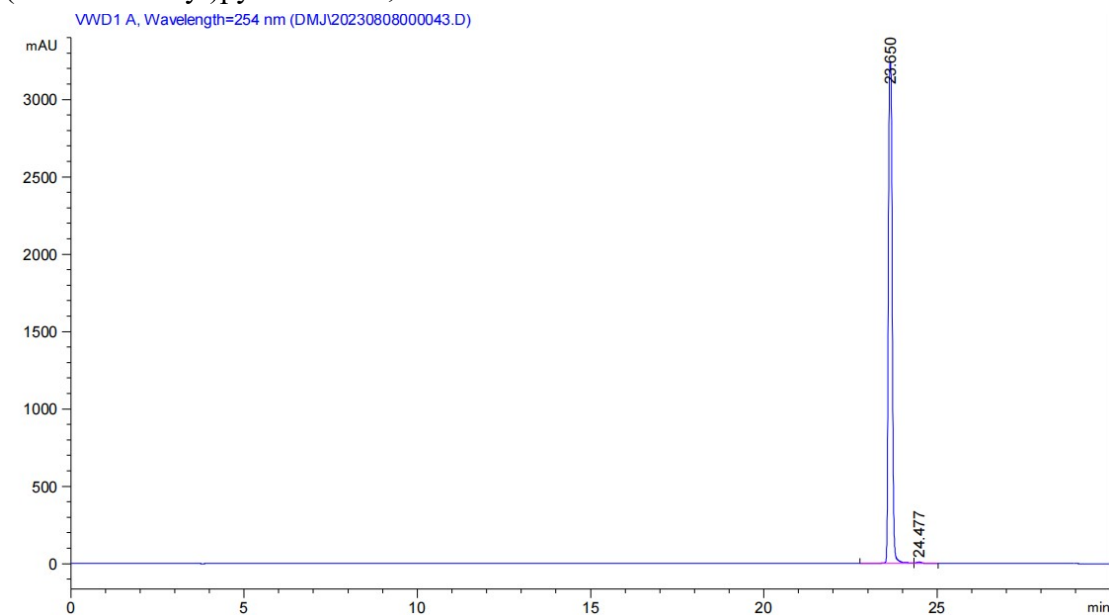
*N*⁴-(3-aminopropyl)-*N*²-(2-(cyclopropylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



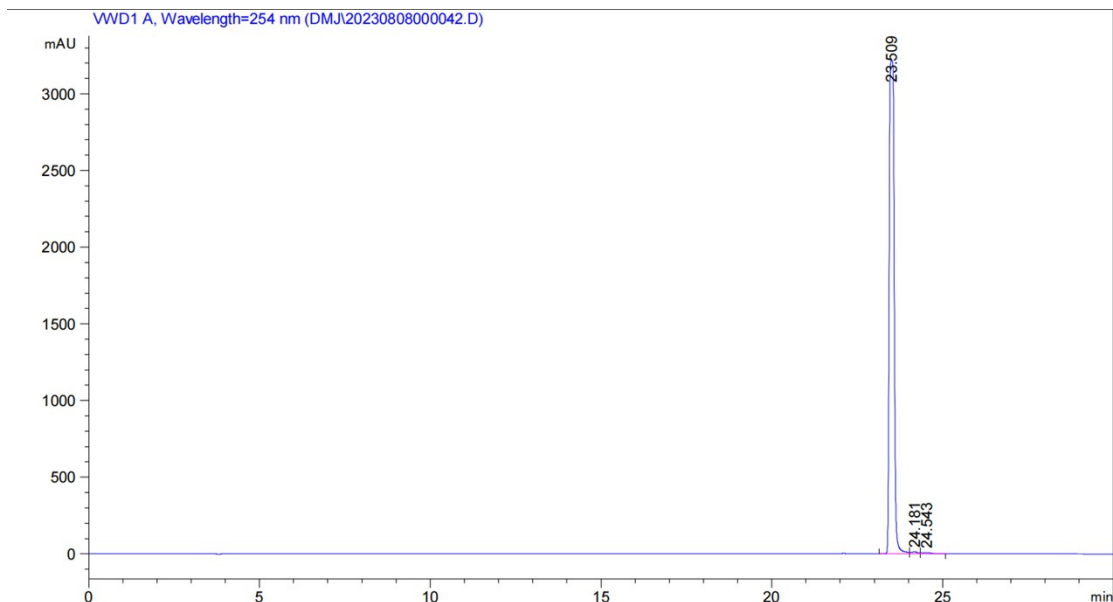
*N*⁴-(3-aminopropyl)-*N*²-(2-(cyclohexylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



*N*⁴-(3-aminopropyl)-*N*²-(1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine

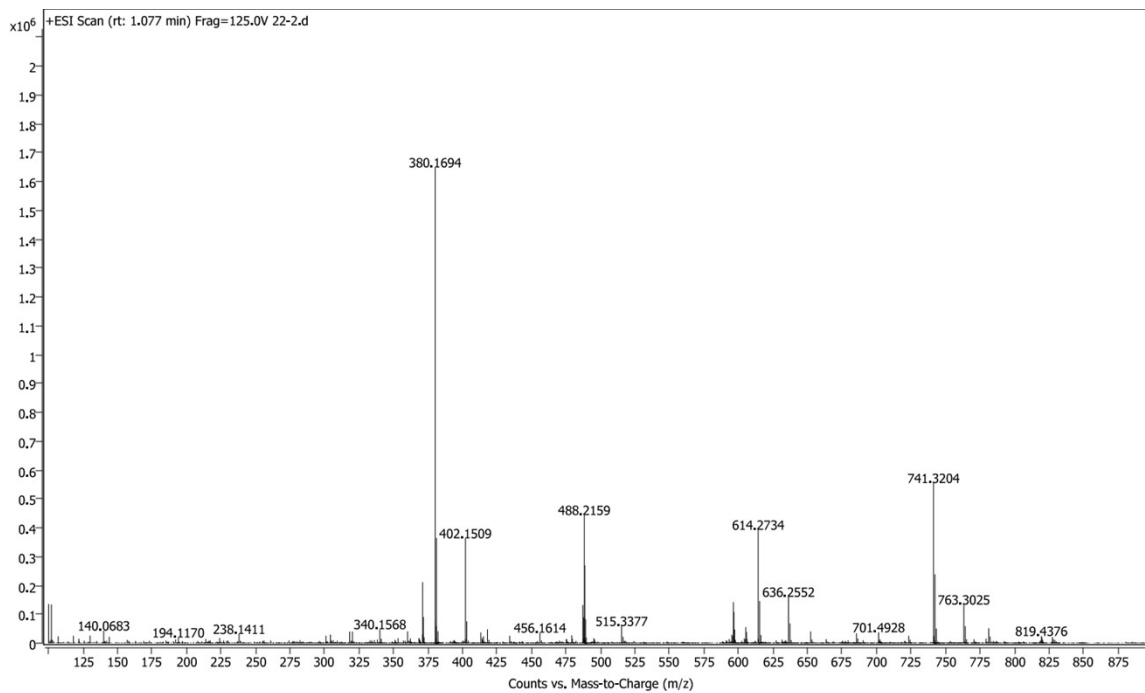


*N*⁴-(3-aminopropyl)-*N*²-(2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine

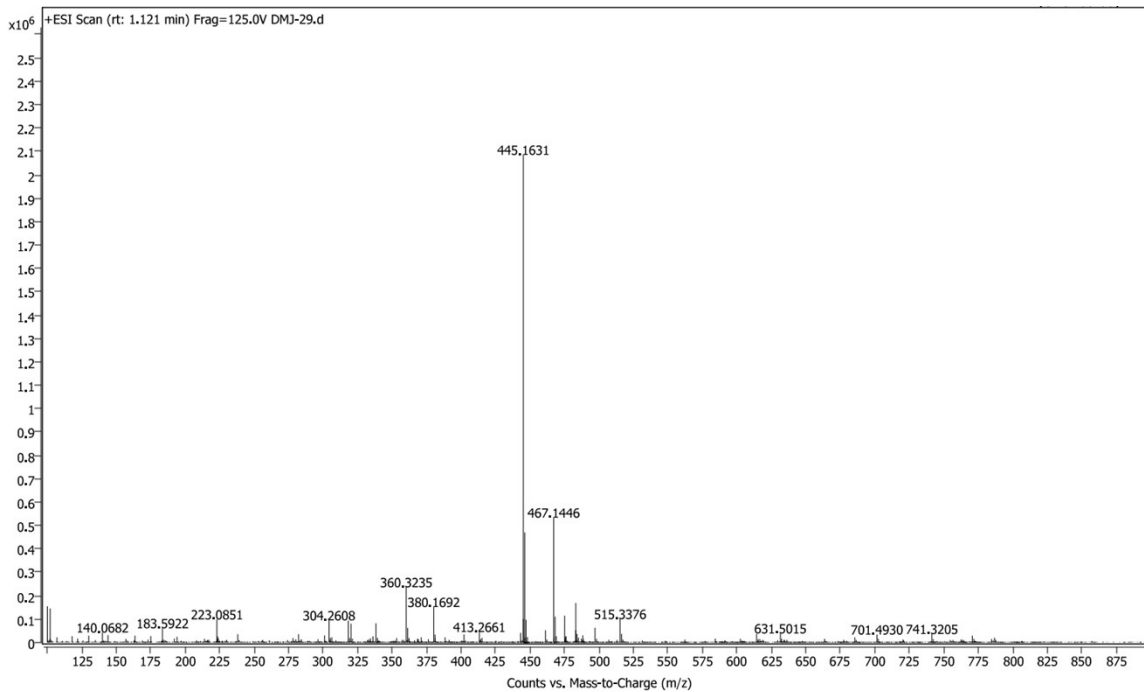


HRMS spectra of representative compounds

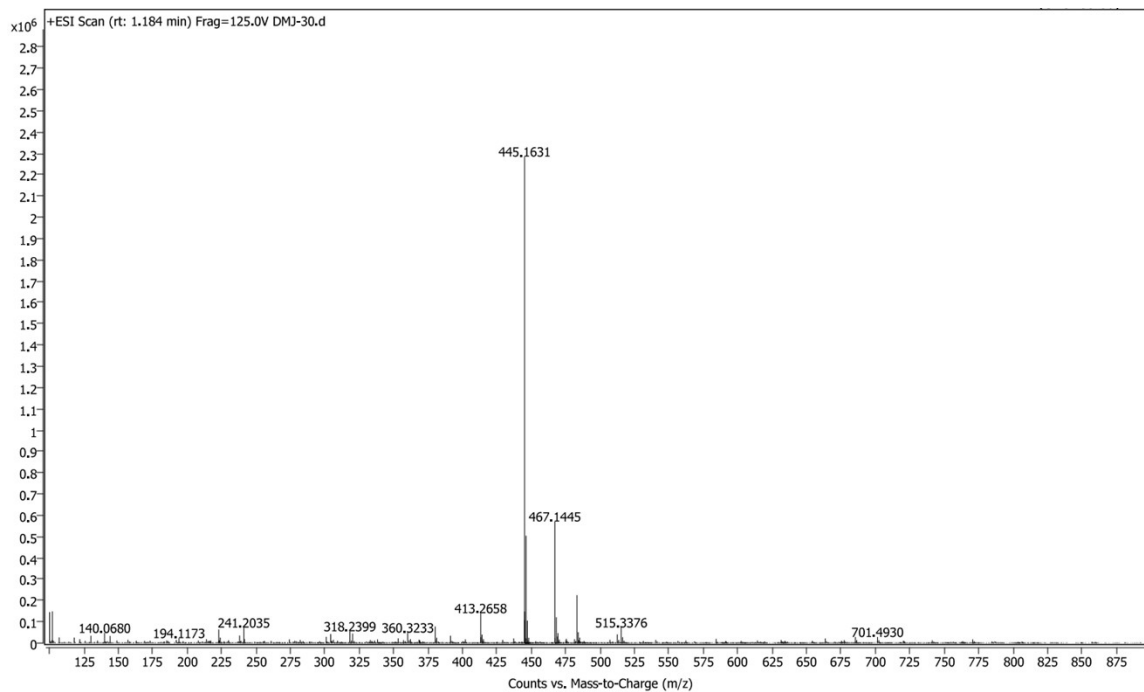
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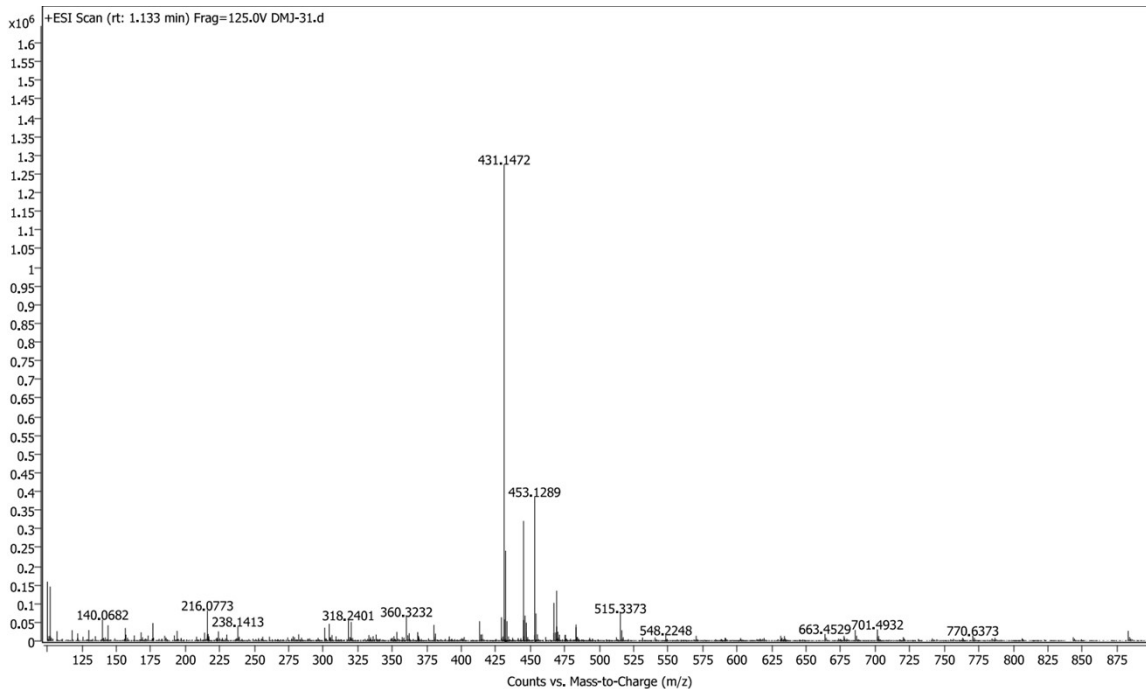
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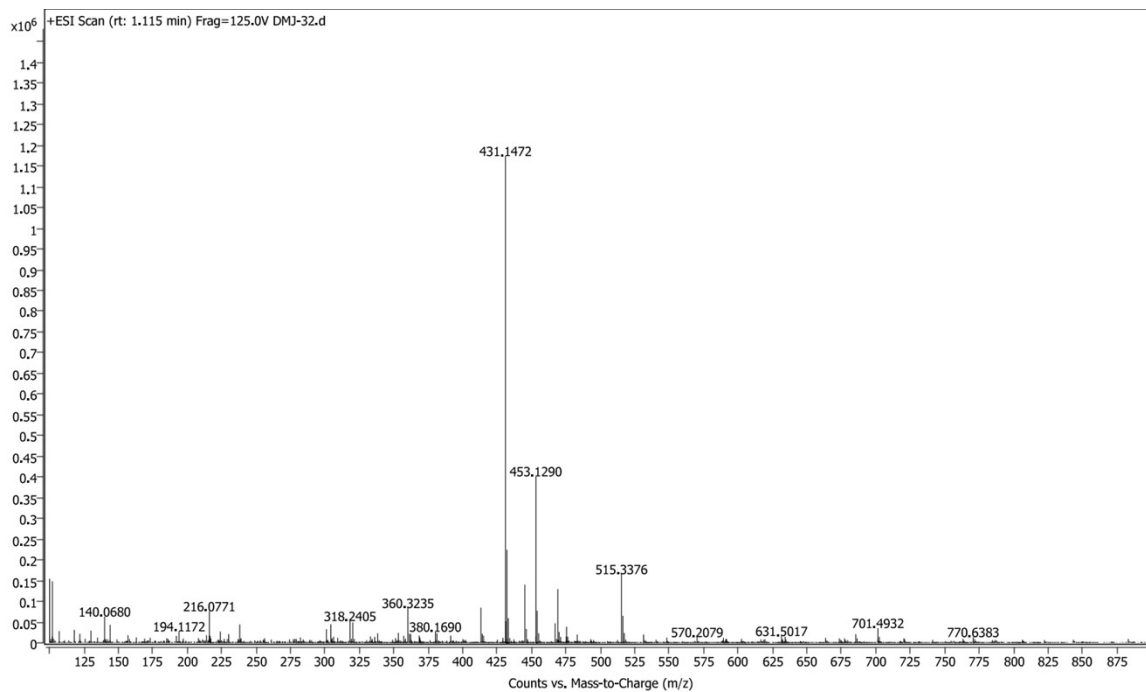
*N*⁴-(3-aminopropyl)-*N*²-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



*N*⁴-(3-aminopropyl)-*N*²-(1-(methylsulfonyl)indolin-5-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



*N*⁴-(3-aminopropyl)-*N*²-(2-(methylsulfonyl)isoindolin-5-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine



List of abbreviations

hERG: human ether-a-go-go related gene

TEA: triethylamine

DCM: dichloromethane

m-CPBA: 3-chloroperbenzoic acid

ACN: acetonitrile

Pd₂(dba)₃: bis(dibenzylideneacetone)palladium

TFA: trifluoroacetic acid