

Supporting Information

Synthesis of Diverse Substituted Pyrimidines through Cu Catalyst-Controlled Ts Group's Elimination and Reinsertion Pathway from 2*H*-Azirines with TosMICs

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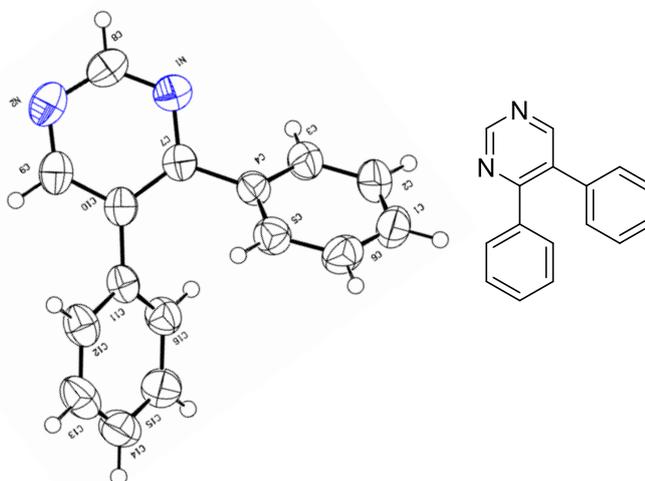
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Table of Contents

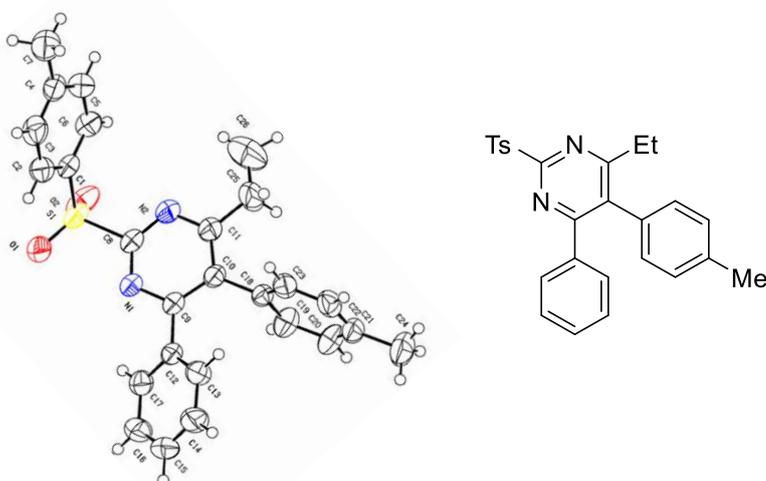
1. X-Ray Data	S3-S5
2. Experimental Section.....	S6-S10
3. ^1H NMR, ^{13}C $\{^1\text{H}\}$ NMR and ^{19}F NMR Spectra of the Products.....	S11-S70

1. X-Ray Data

Crystal structures of the compound **3a** and **4l**. Thermal ellipsoids are shown at 40% probability level. The crystal of **3a** and **4l** was achieved by volatilizing a dichloromethane solution of **3a** and **4l** in the air at room temperature.



3a (CCDC: 2366439)



4l (CCDC: 2469112)

Table 1. Crystal data and structure refinement for **3a**.

Identification code	0314-1
Empirical formula	C ₁₆ H ₁₂ N ₂
Formula weight	232.28
Temperature/K	293
Crystal system	monoclinic
Space group	P 2 ₁ /n
a/Å	11.7603(4)
b/Å	6.9704(2)
c/Å	14.8503(6)
α /°	90
β /°	91.506(3)
γ /°	90
Volume/Å ³	1216.92(7)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.268
μ/mm^{-1}	0.589
F (000)	488.0
Crystal size/mm ³	0.3 × 0.2 × 0.1
Radiation	Cu K α (λ = 1.54184)
2 Θ range for data collection/°	9.472 to 147.722
Index ranges	-14 ≤ h ≤ 14, -7 ≤ k ≤ 8, -17 ≤ l ≤ 18
Reflections collected	10672
Independent reflections	2413 [R_{int} = 0.0537, R_{sigma} = 0.0396]
Data/restraints/parameters	2413/0/164
Goodness-of-fit on F ²	1.047
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0435, wR_2 = 0.1239
Final R indexes [all data]	R_1 = 0.0468, wR_2 = 0.1283
Largest diff. peak/hole / e Å ⁻³	0.20/-0.18

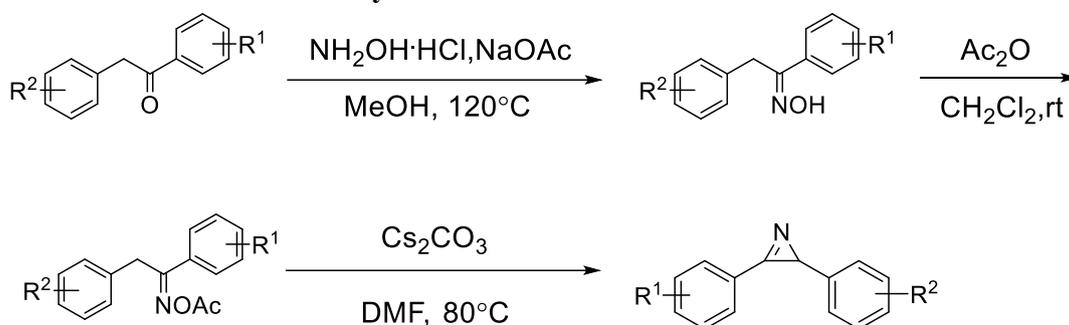
Table 2. Crystal data and structure refinement for **4I**.

Identification code	mo 20250311A 0m a
Empirical formula	C ₂₆ H ₂₄ N ₂ O ₂ S
Formula weight	428.53
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 ₁ /n
Unit cell dimensions	a = 11.2932(15) Å α = 90°. b = 14.2849(18) Å β = 93.613(5)°. c = 14.4944(16) Å γ = 90°.
Volume	2333.6(5) Å ³
Z	4
Density (calculated)	1.220 Mg/m ³
Absorption coefficient	0.163 mm ⁻¹
F(000)	904
Crystal size	0.220 x 0.200 x 0.180 mm ³
Theta range for data collection	2.004 to 25.598°.
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 17, -17 ≤ l ≤ 17
Reflections collected	76409
Independent reflections	4387 [R(int) = 0.0842]
Completeness to theta = 25.242°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4387 / 6 / 283
Goodness-of-fit on F ²	1.005
Final R indices [I > 2σ(I)]	R1 = 0.0452, wR2 = 0.1131
R indices (all data)	R1 = 0.0551, wR2 = 0.1218
Extinction coefficient	n/a
Largest diff. peak and hole	0.496 and -0.319 e.Å ⁻³

2. Experimental Section

General Information. All reagents including **2a**, **2f** and all solvents were purchased from commercial suppliers, and were used without further purification. The progress of reactions was monitored by TLC. All heating reactions were carried out in an oil bath. For chromatographic purifications, 200-300 mesh silica gel was used. ^1H (400 MHz) and ^{13}C $\{^1\text{H}\}$ (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded with tetramethylsilane as an internal standard. HRMS measurements were carried out using the ESI ionization technique with an ESI - FT analyzer. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. CCDC (for **3a** and **4l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

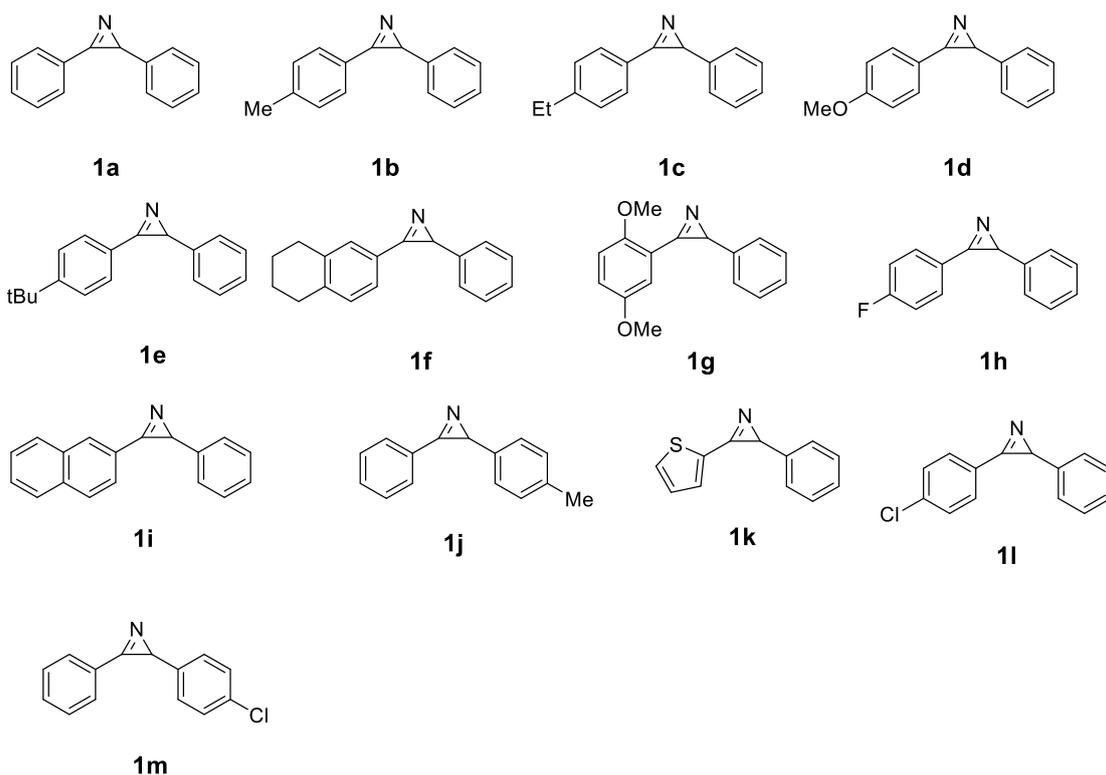
General Procedure for the Synthesis of 2*H*-Azirines **1**¹.



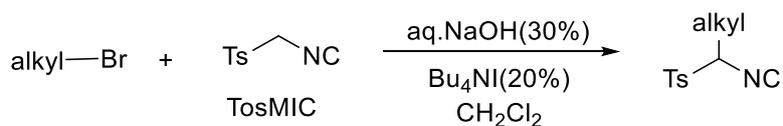
The mixture of ketone (5 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (6 mmol, 416.9 mg) and NaOAc (7.5 mmol, 615.0 mg) was stirred in MeOH (20 mL) at 120°C oil bath. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, diluted with EtOAc (25 mL \times 2) and washed with brine (20 mL). The organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford crude ketoximes. The desired ketoximes were obtained by recrystallization (hexanes).

Then, the mixture of ketoxime and acetic anhydride (2.0 equiv) was stirred overnight in dichloromethane at room temperature and monitored by TLC until reaction completion. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with H_2O (20 mL) and brine (10 mL). The organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by recrystallization (hexanes) to afford corresponding ketoxime acetates.

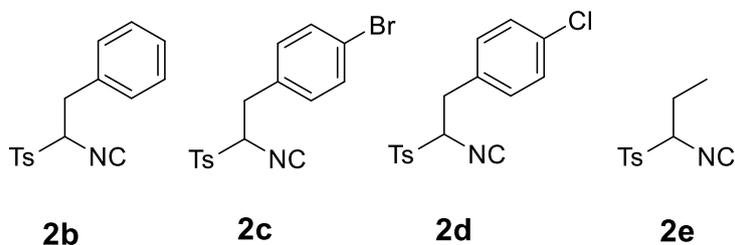
In a 50 mL round bottom flask, ketoxime acetate (5 mmol), Cs_2CO_3 (6 mmol, 1.95g) were stirred in *N,N*-dimethylformamide (DMF, 15 mL) at 80°C under Ar. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (v/v = 50:1) as the eluent to afford the corresponding 2*H*-azirines **1a-1m**.



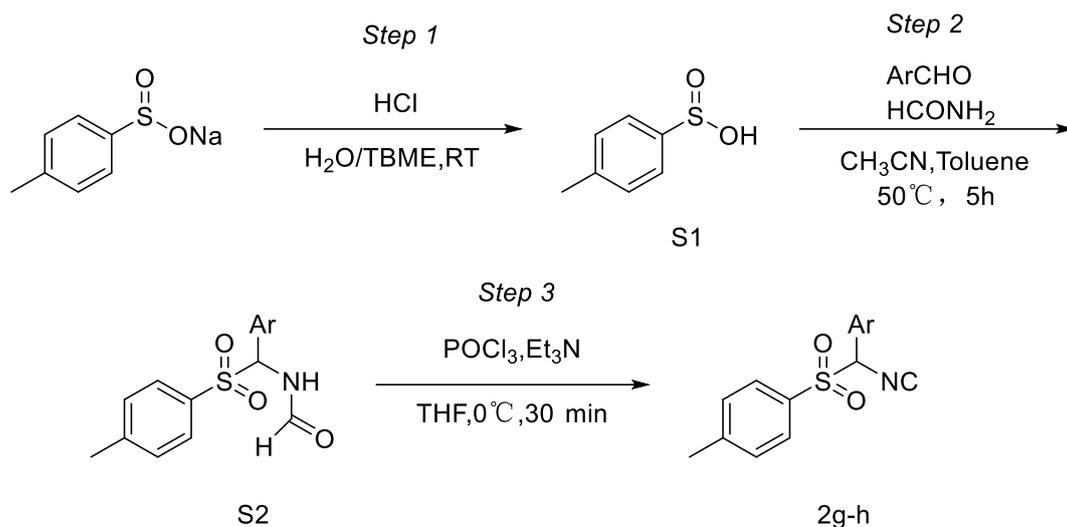
General Procedure for the Synthesis of α -alkyl TosMIC derivatives **2b-2e.²**



A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with TosMIC (**2a**) (1.95 g, 10.0 mmol), alkyl bromide (11.0 mmol, 1.10 equiv), and Bu_4NI (2.00 mmol), then CH_2Cl_2 (25 mL) and 30% NaOH aqueous solution (25 mL) were added under ice-water bath condition. After vigorous stirring for 3 h at room temperature, the mixture was poured into H_2O (20 mL), and was extracted with CH_2Cl_2 (3×15 mL), dried over MgSO_4 , and concentrated under reduced pressure with the aid of a rotary evaporator and the crude product was purified by chromatography on silica gel (PE-DCM, 2:1 to 1:1) to provide pure compounds **2b-2e** as pale-yellow solid.



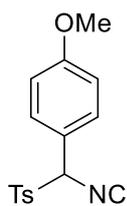
General Procedure for the Synthesis of α -phenyl TosMIC derivatives **2g, 2h³⁻⁵.**



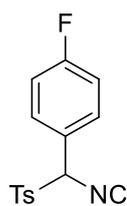
Step 1: Treat a solution of p-toluenesulfonic acid sodium salt, (6.0 g, 33.7 mmol) in water (20 mL) and tert-butyl methyl ether (10 mL) dropwise with concentrated HCl (3 mL) and stir for 10 minutes. Separate the solution in a separatory funnel and wash the organic layer with saturated aqueous sodium chloride. Dry the organic over Na₂SO₄, filter, and remove the solvent to afford 5.2 g (quantitative) of p-toluenesulfonic acid (S1) that is used in the next step⁴.

Step 2: Combine the acid with benzaldehyde (2.4 g, 22.5 mmol), formamide (3.8 g, 84.2 mmol), and trimethylsilyl chloride (4.0 g, 37.0 mmol) in 30 mL of a 1:1 solution of toluene/acetonitrile. Heat the reaction to 50°C and stir for 5 hours. Cool the reaction and dilute with water (100 mL) and tert-butyl methyl ether (30 mL). Cool the solution in an ice bath and filter to afford 4.5 g (70%) of desired product (S2) which is used in the next step without further purification. Dry the solid under vacuum overnight to remove any residual water⁴.

Step 3: A 100 mL, three-necked, round-bottomed flask fitted with an overhead stirrer, a 25 mL addition funnel and a temperature probe is charged with 20 mL of THF and S2 (2.76 g, 9.48 mmol). Phosphorus oxychloride (1.77 mL, 19.0 mmol) is added and the resulting solution is stirred for 5 min at 25°C. After cooling the solution to 0°C, Et₃N (7.93 mL, 56.9 mmol) is added slowly over 15-20 min while keeping the internal reaction temperature below 10°C. After the triethylamine addition is complete, the reaction is warmed to 5-10°C and held there for 30-45 min. EtOAc (14.0 mL) and H₂O (14.0 mL) are added sequentially to the reaction, the mixture is stirred for 5 min and, after transferring the mixture to a separatory funnel, the aqueous layer is removed. The organic layer is washed with H₂O (2 × 14.0 mL), saturated NaHCO₃ solution (14.0 mL) and brine (7.0 mL). The organic layer is transferred to a 250 mL, round bottomed flask and concentrated on a rotary evaporator. The residue is diluted with 14.0 mL of 1-propanol and this solution is concentrated on a rotary evaporator to half of its original volume. The residue is cooled to 5-10°C for 30 min and the beige solid that crystallizes is filtered through a Büchner funnel. The filter cake is rinsed twice with 7.5 mL of 1-propanol. The beige solid is dried under vacuum for 3-4 hr to give 1.81-1.97 g (70-76%) of **2g-2h**⁵.

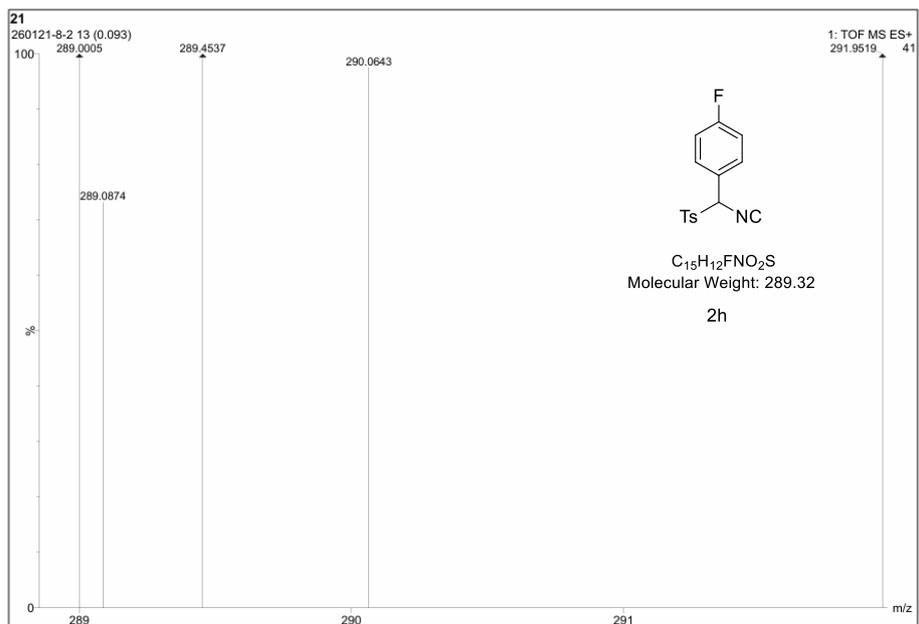
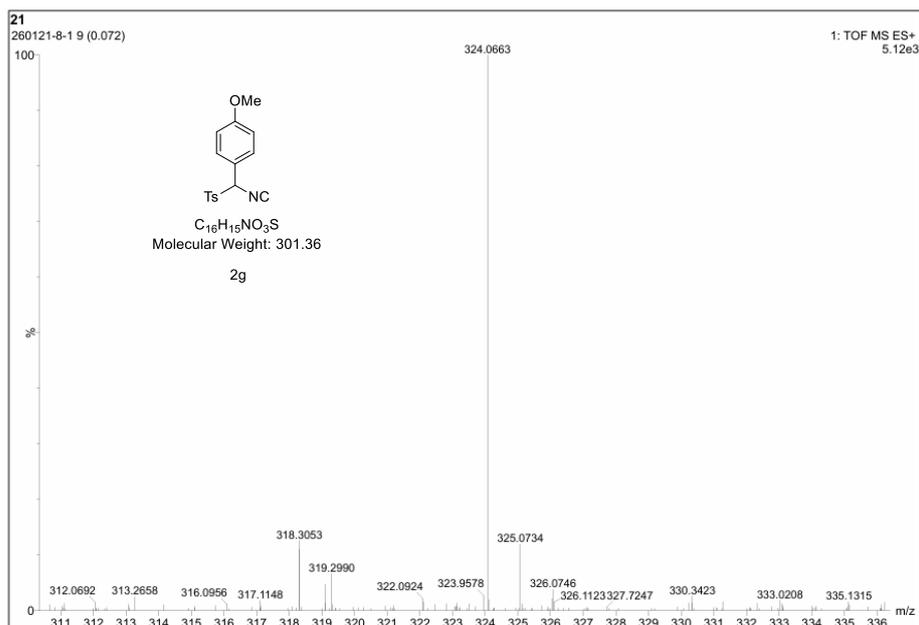


2g



2h

HRMS spectra of representative compounds in SI

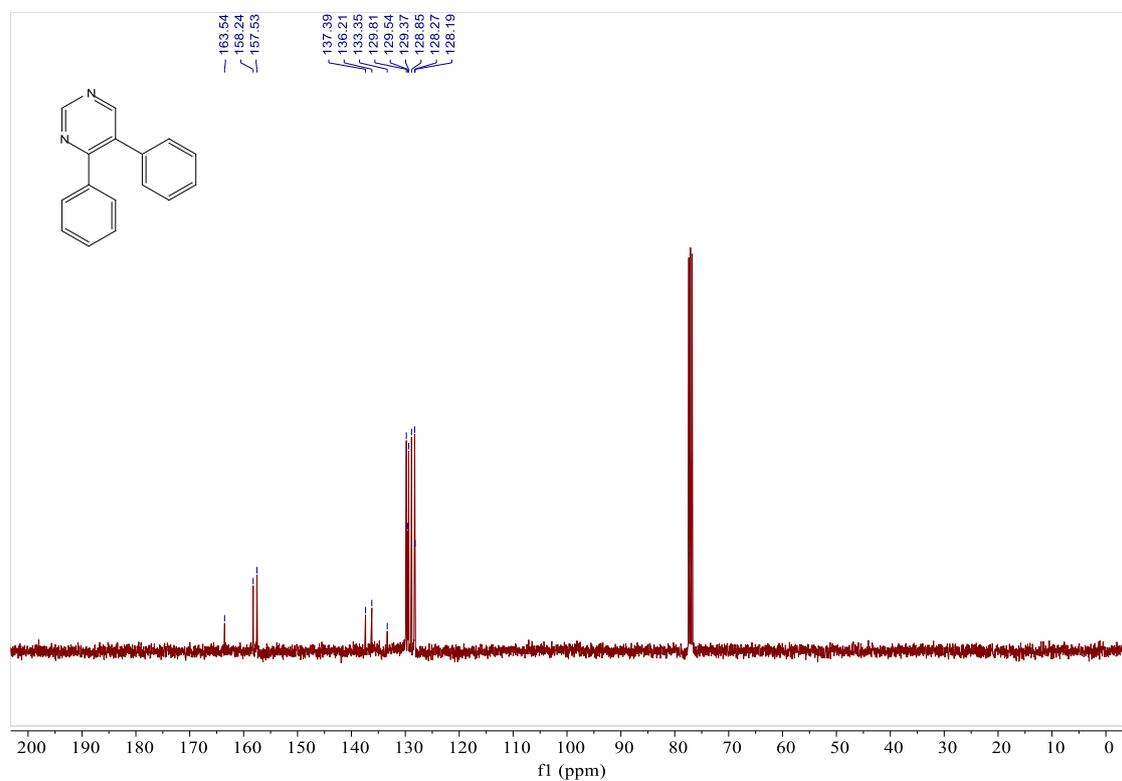
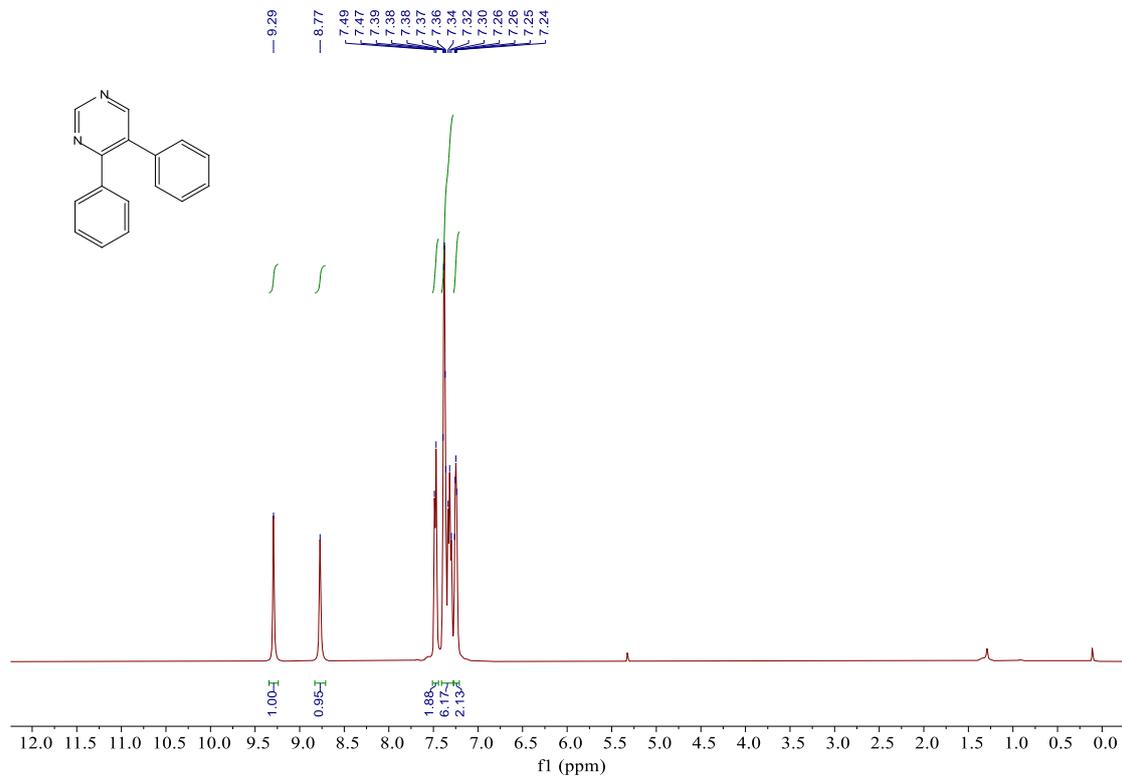


References

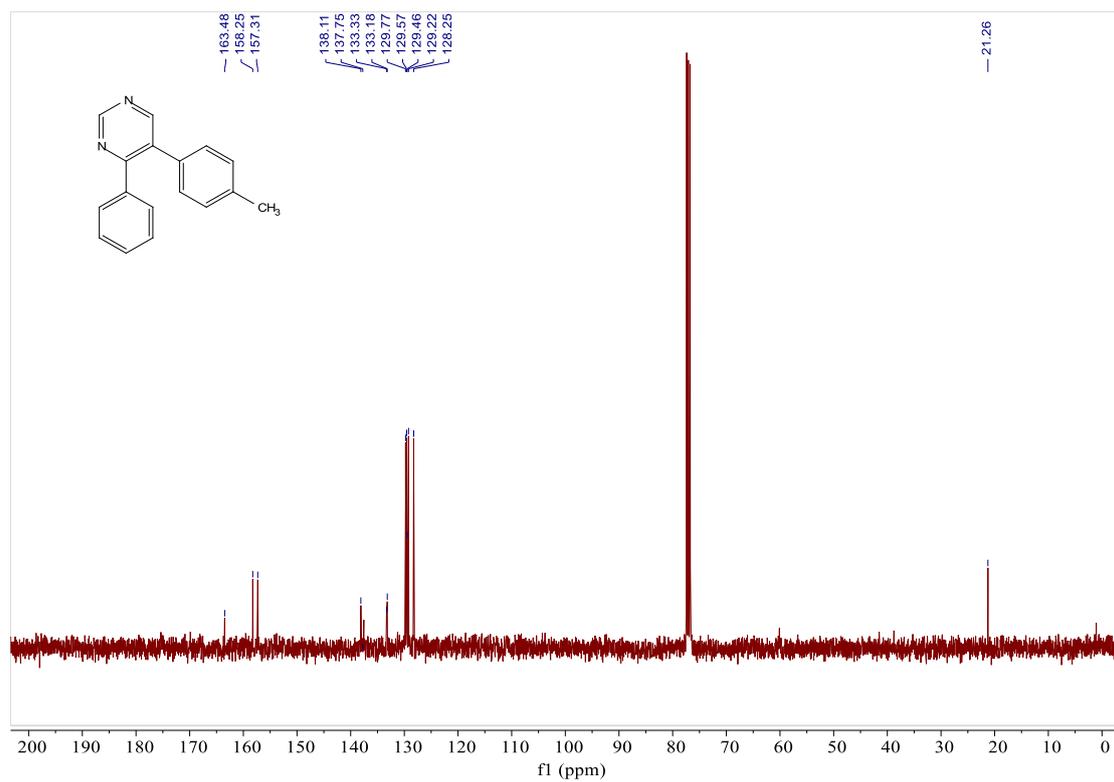
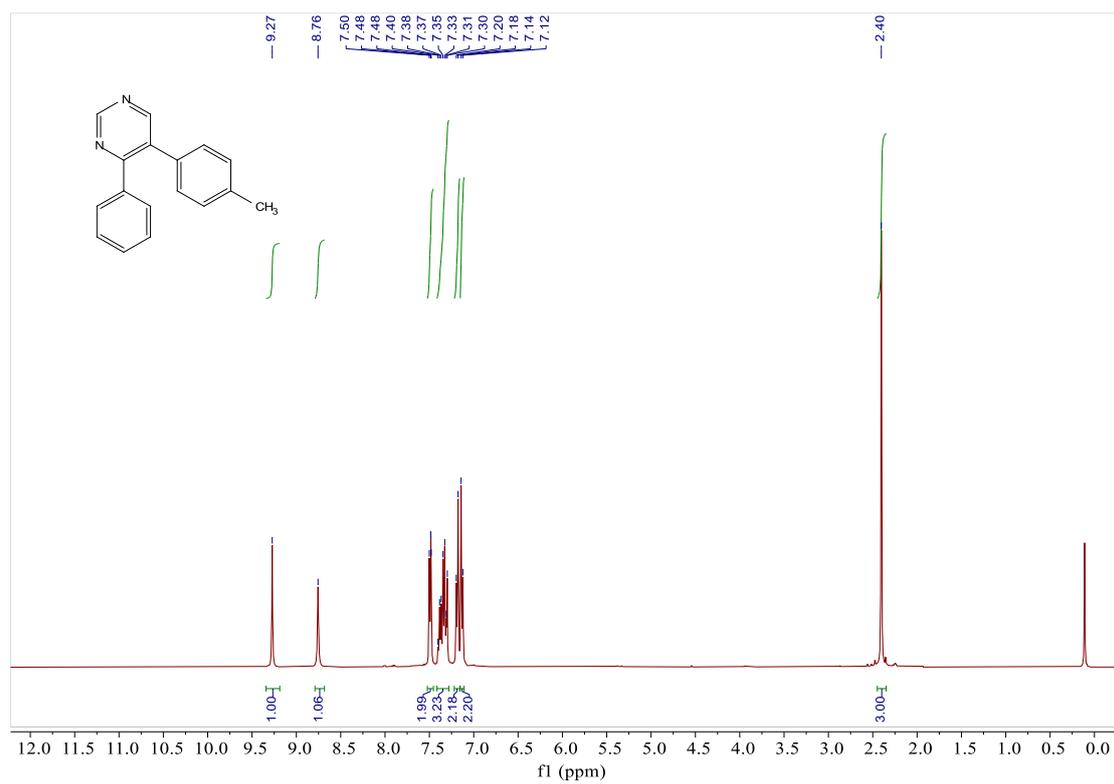
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- 3 K. Satyam, V. Muruges and S. Suresh, *Org. Biomol. Chem.*, 2019, **17**, 5234–5238.
- 4 R. Bonjouklian, R. D. Dally, D. A. De, P. C. M. F. Del, C. Dominguez-Fernandez, A. C. Jaramillo, D. U.-G. B Lopez, S. C. Montero and T. A. Shepherd, *World Intellectual Property Organization* WO2005080380, 2005-09-01.
- 5 J. Sisko, M. Mellinger, P. W. Sheldrake and N. H. Baine, *Org. Synth.*, 2000, **77**, 198–203.

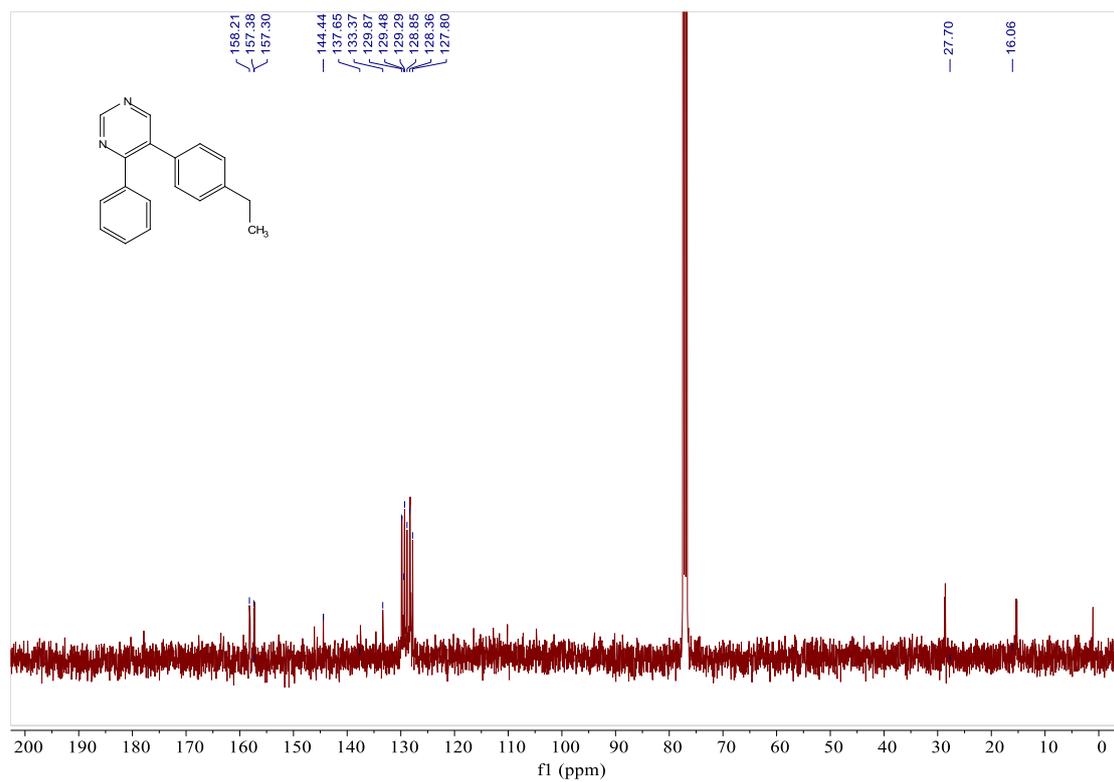
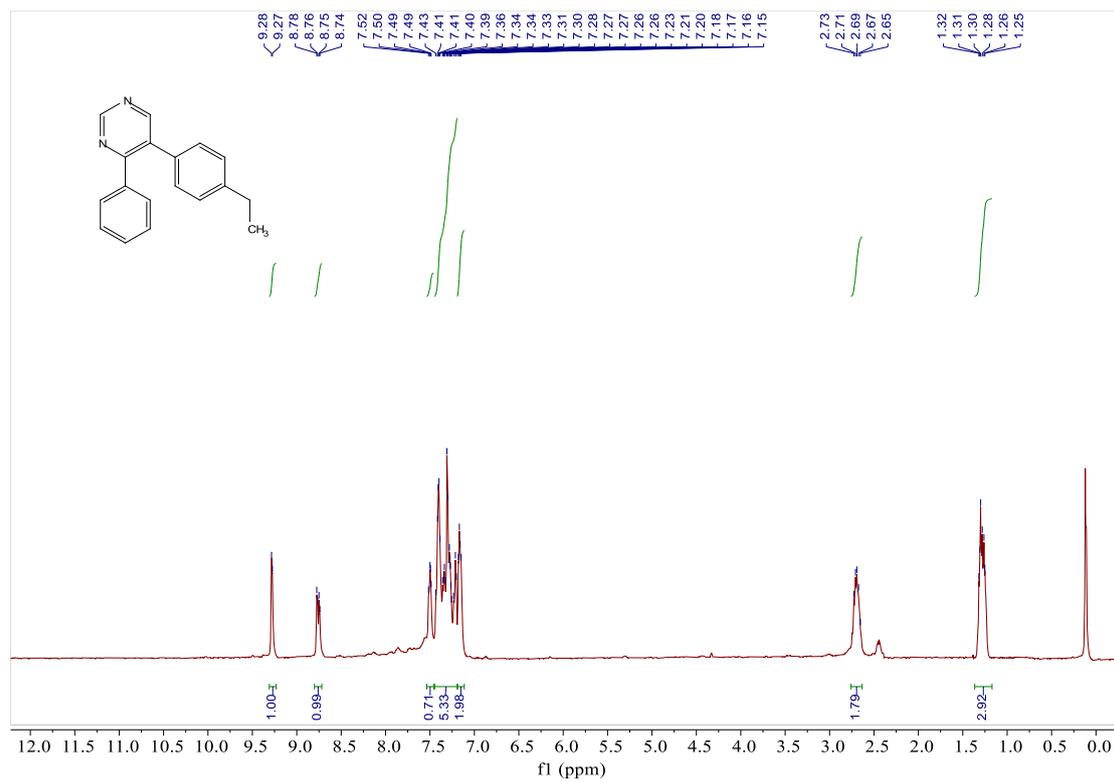
**3. ^1H (400 MHz, CDCl_3), $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3) and ^{19}F (376 MHz, CDCl_3)
NMR Spectra of the Products
*4,5-diphenylpyrimidine (3a)***



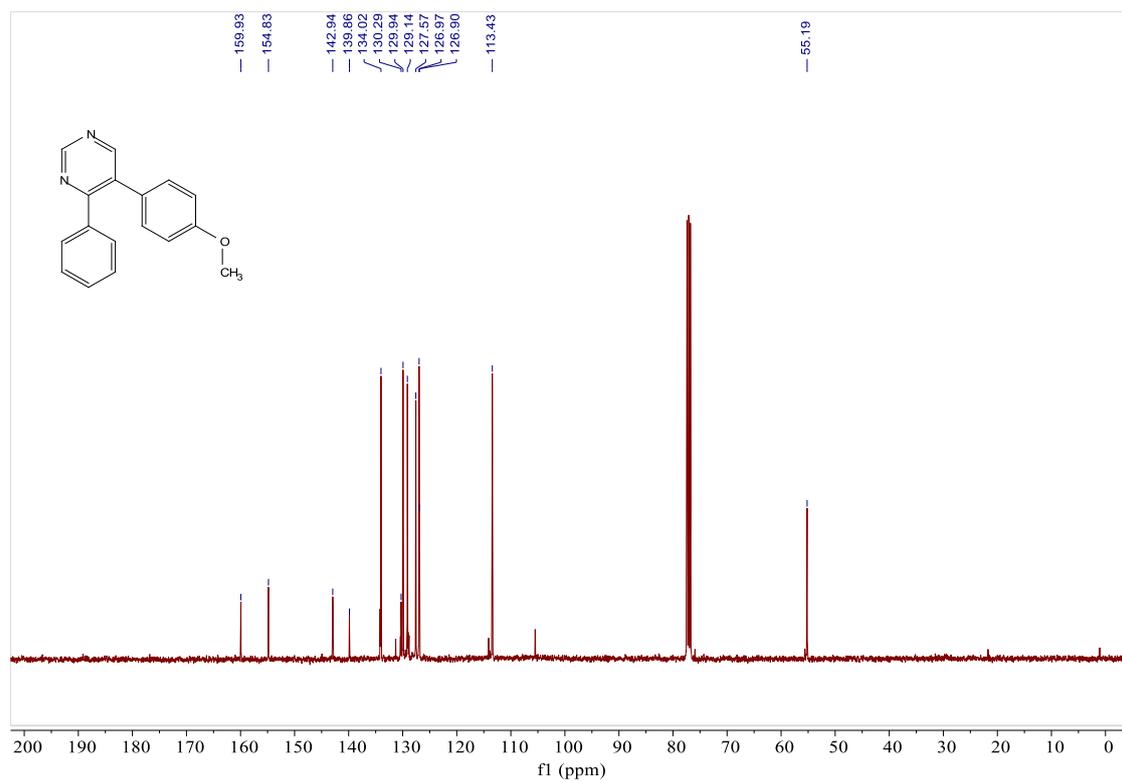
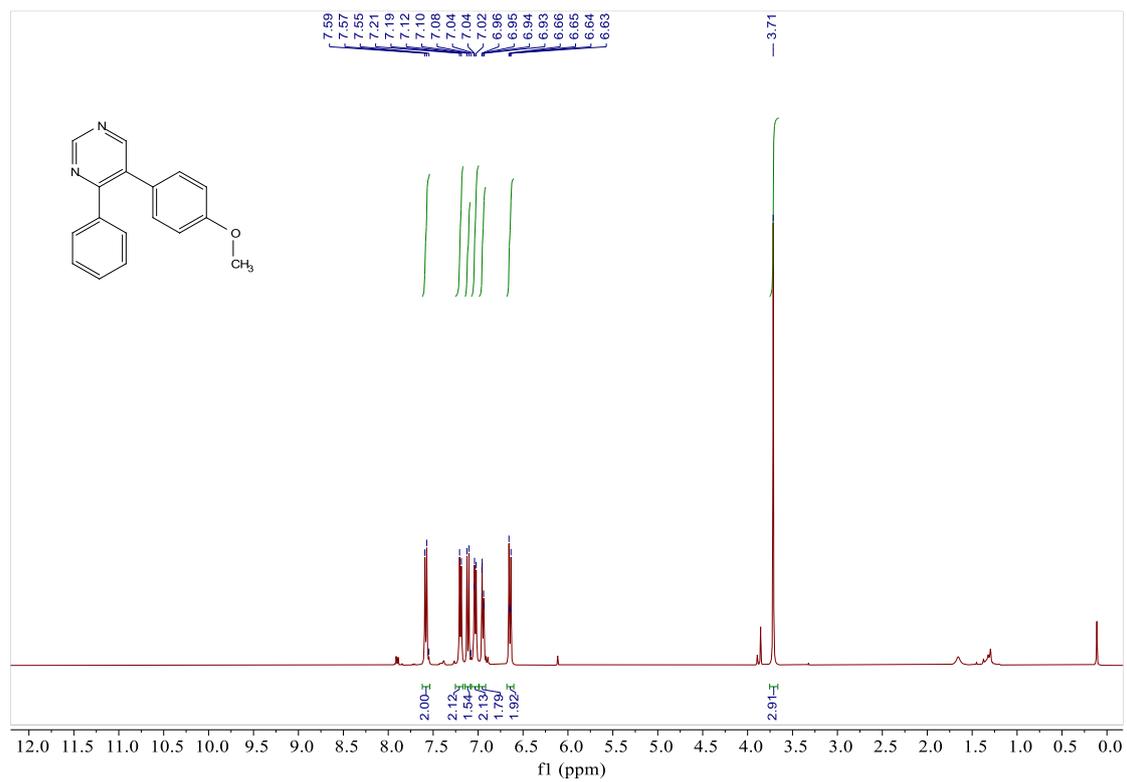
4-phenyl-5-(p-tolyl)pyrimidine (3b)



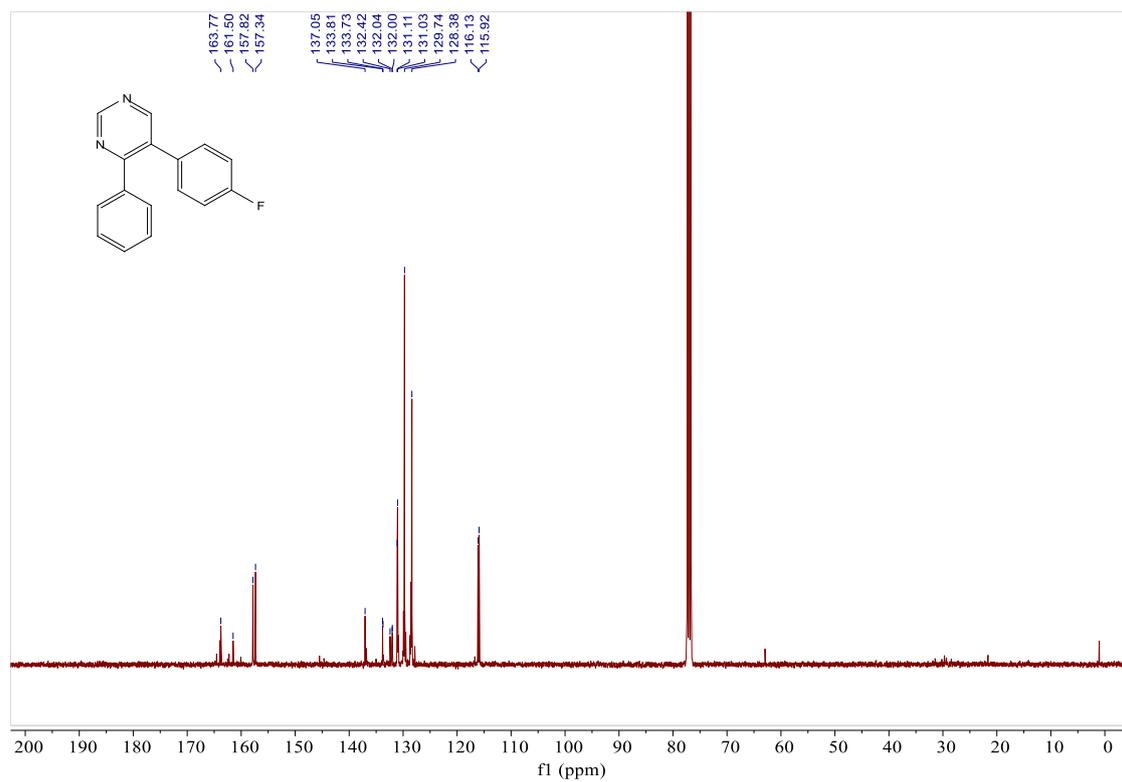
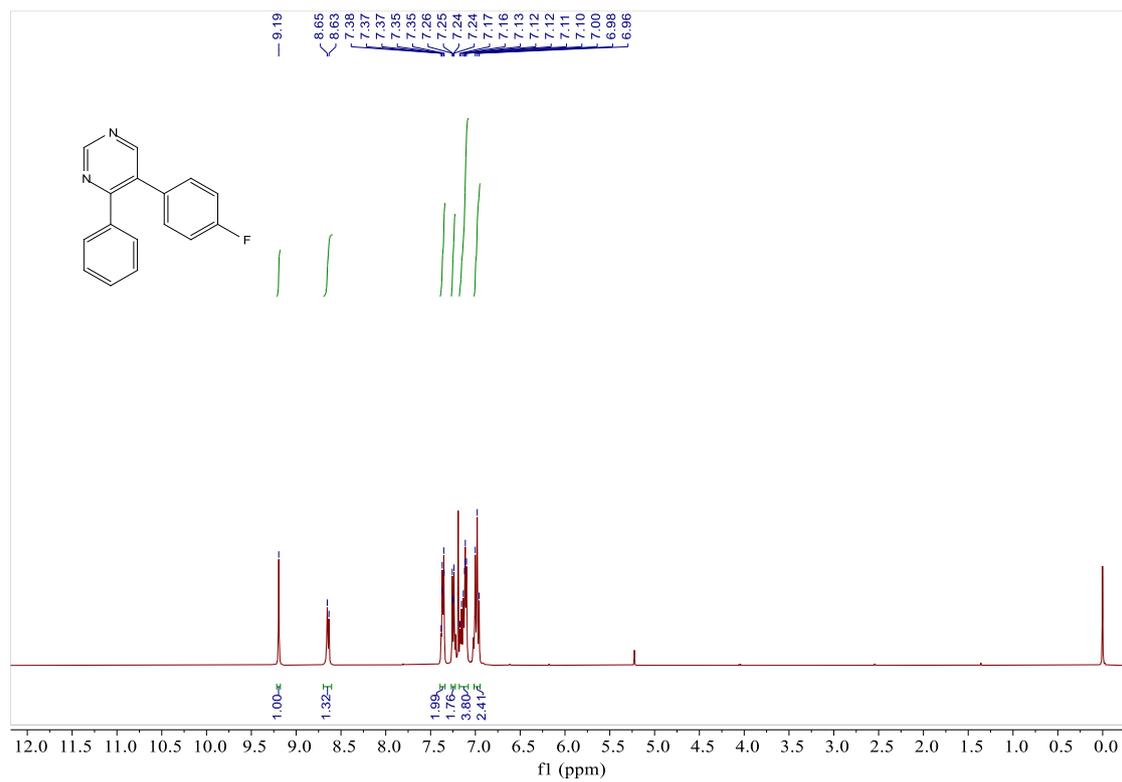
5-(4-ethylphenyl)-4-phenylpyrimidine(3c)

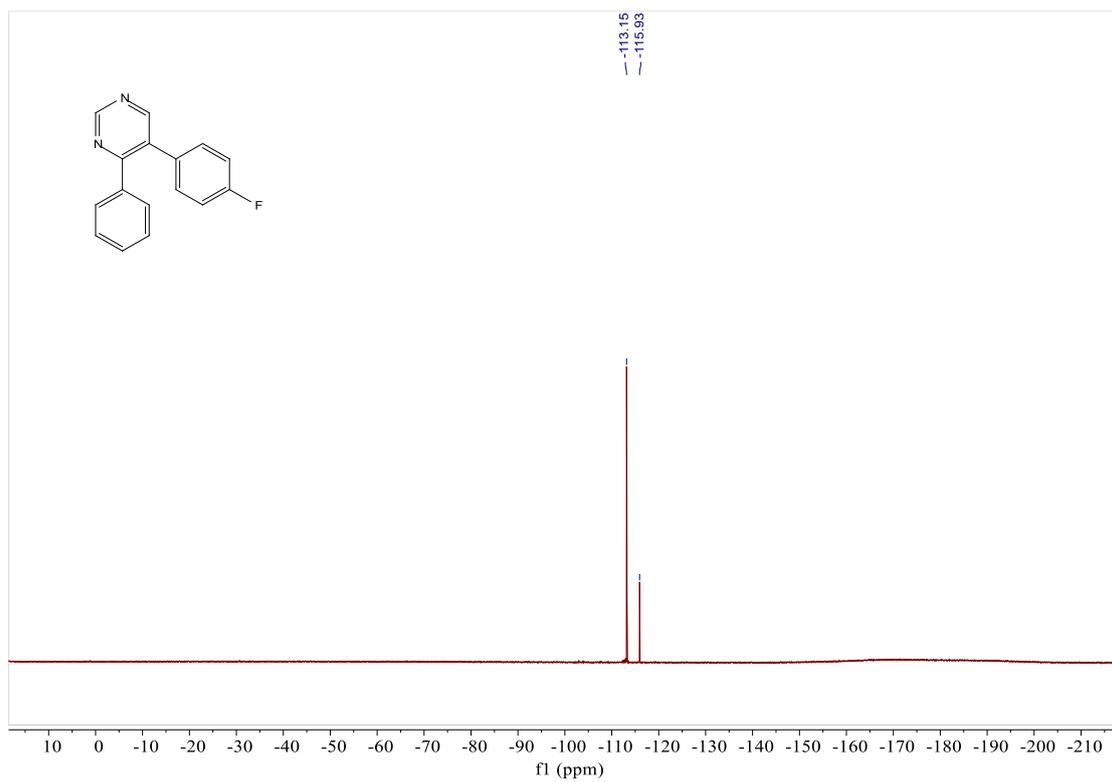


5-(4-methoxyphenyl)-4-phenylpyrimidine(3d)

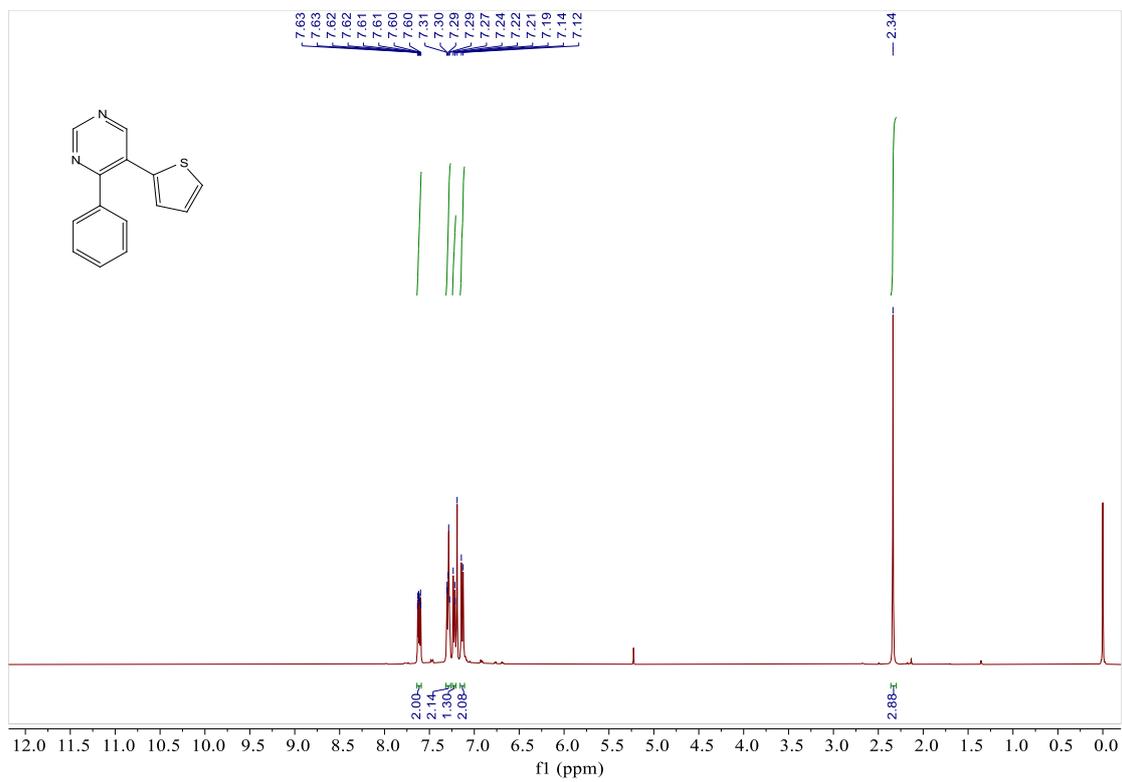


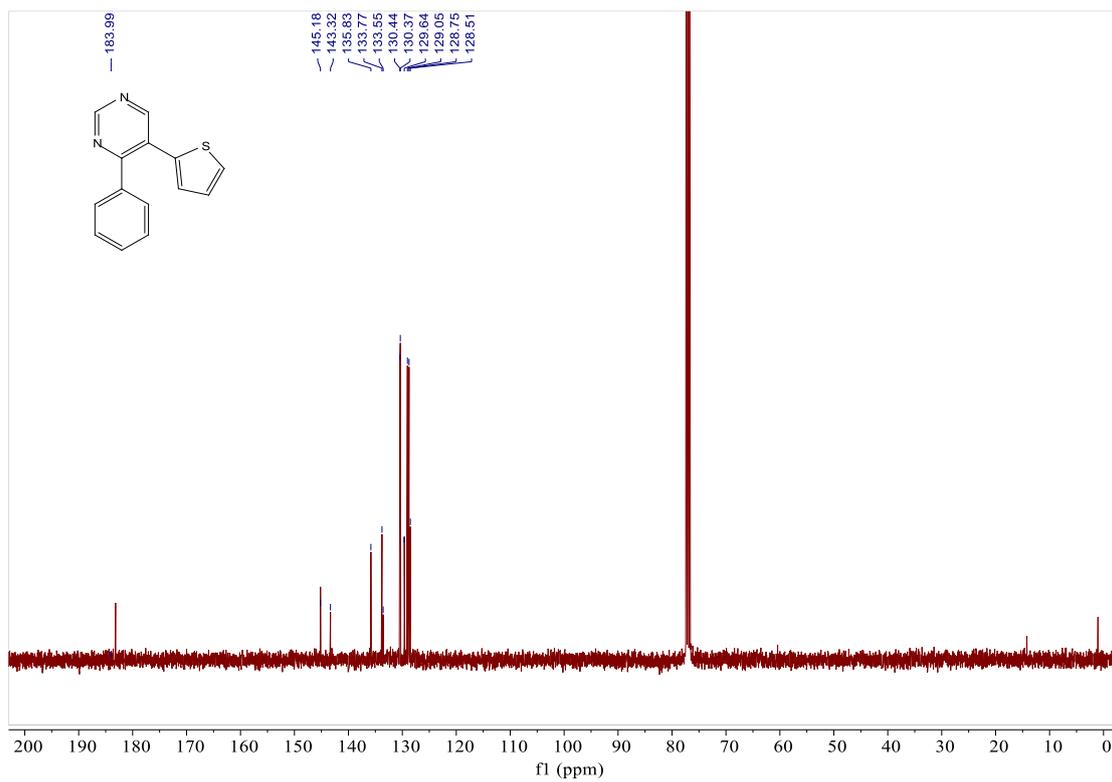
5-(4-fluorophenyl)-4-phenylpyrimidine(3e)



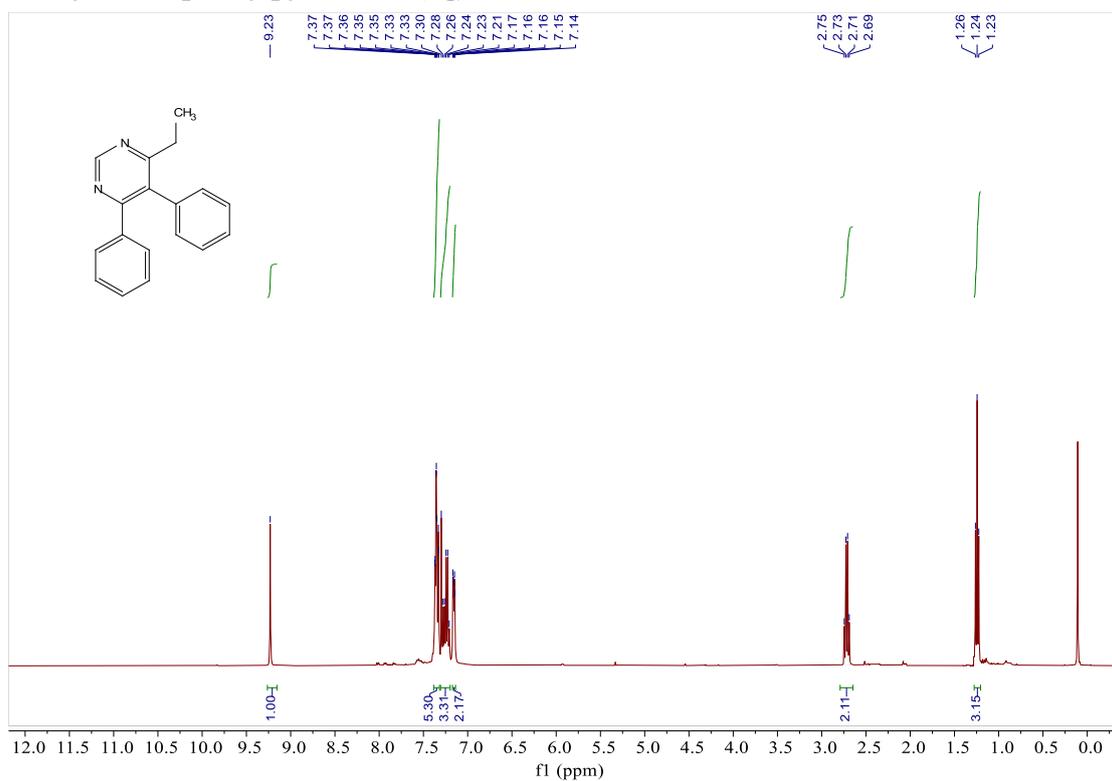


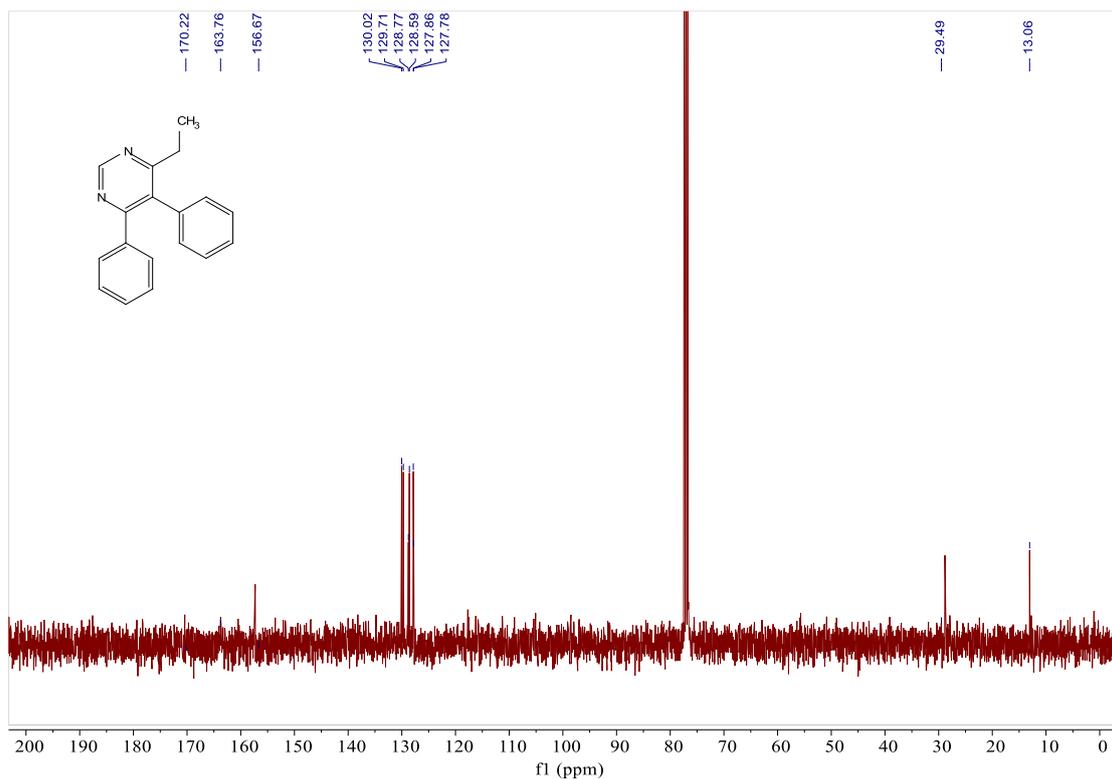
4-phenyl-5-(thiophen-2-yl)pyrimidine(3f)



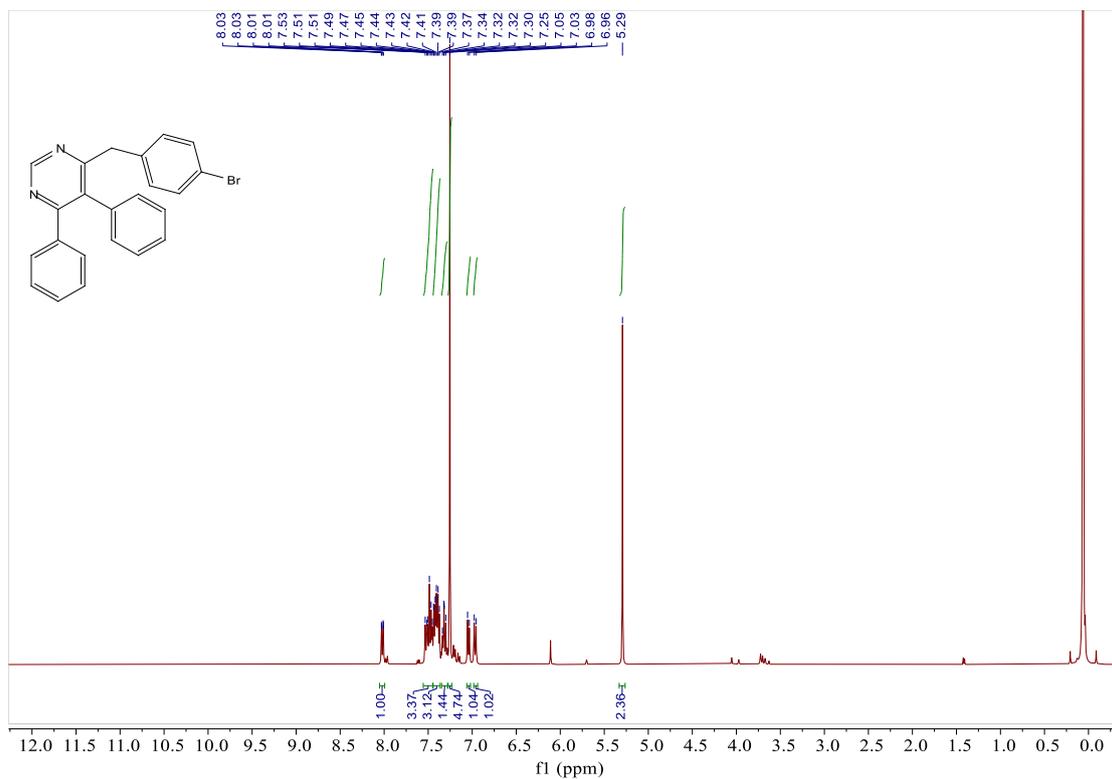


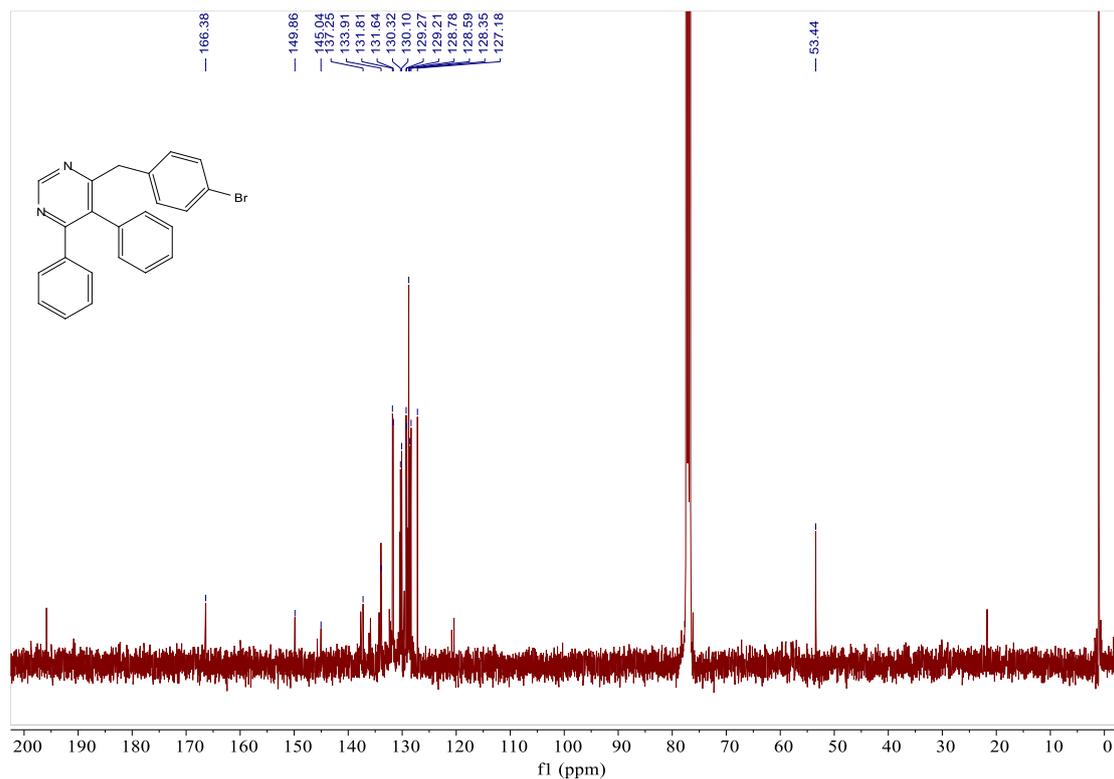
4-ethyl-5,6-diphenylpyrimidine(3g)



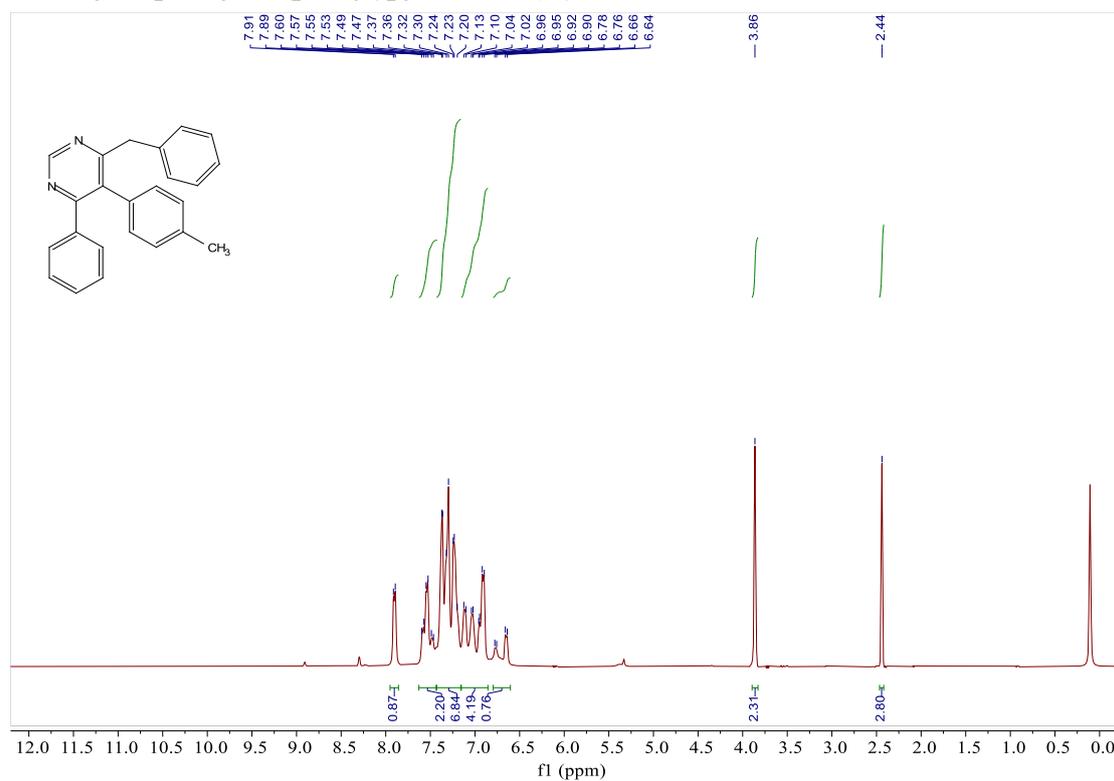


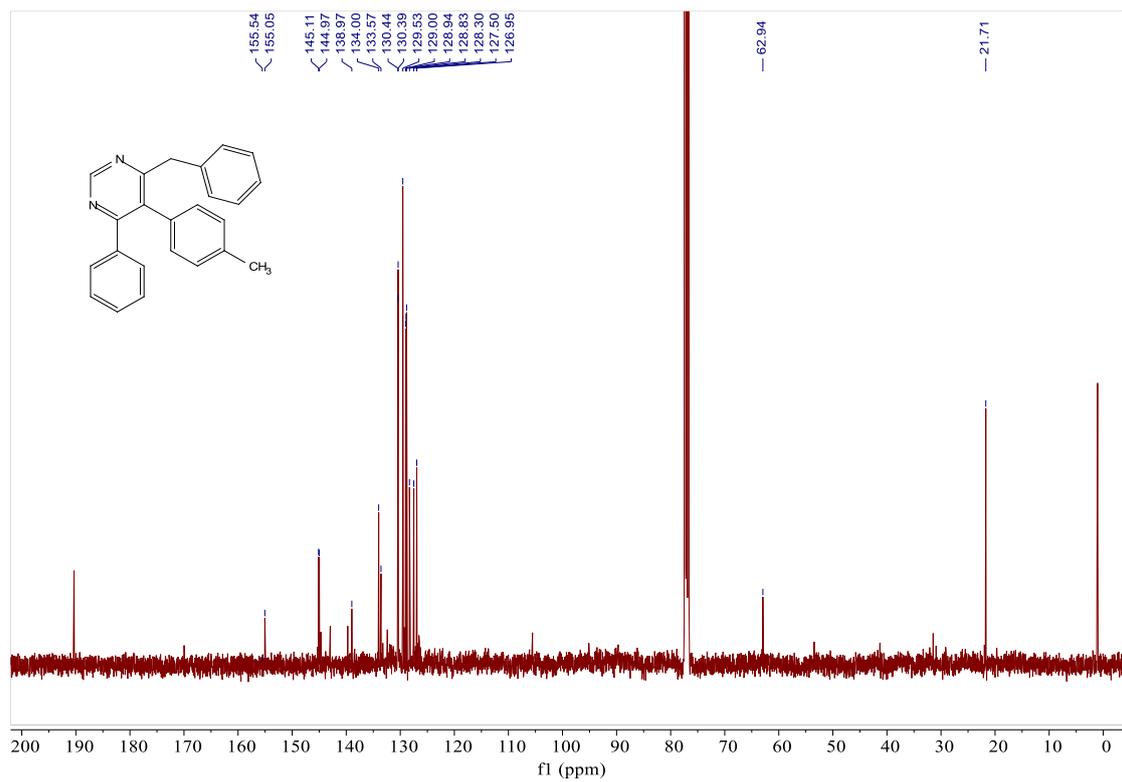
4-(4-bromobenzyl)-5,6-diphenylpyrimidine(3h)



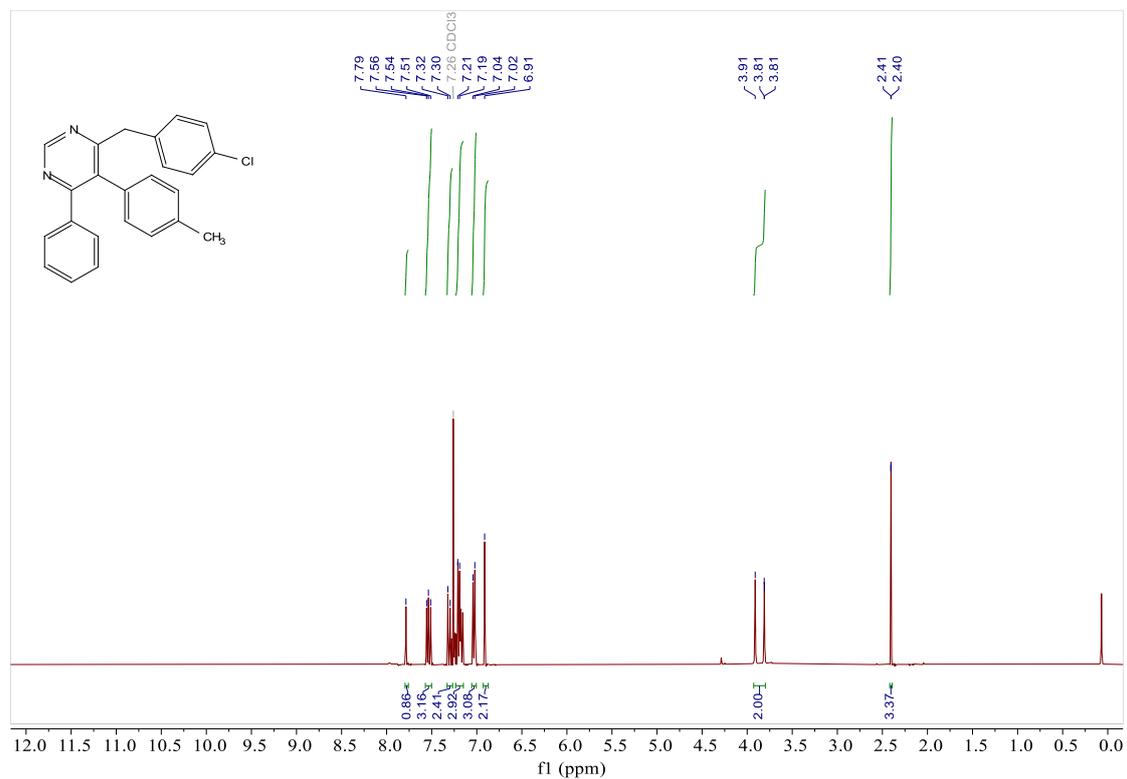


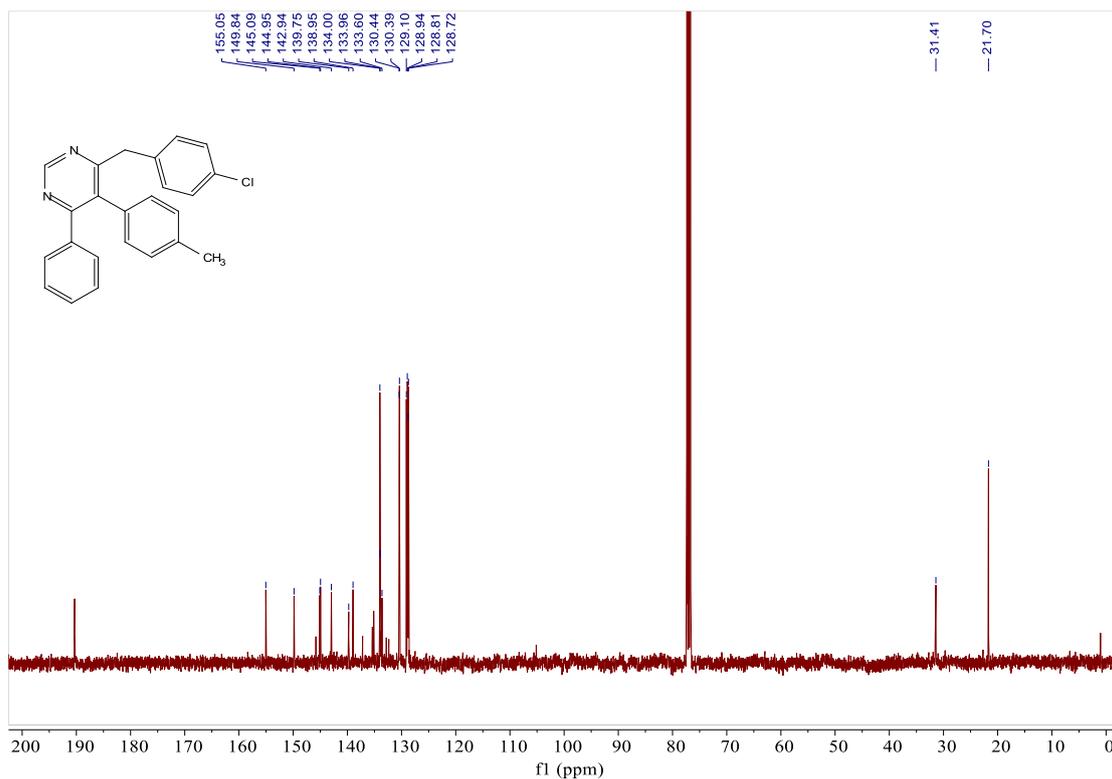
4-benzyl-6-phenyl-5-(p-tolyl)pyrimidine(3i)



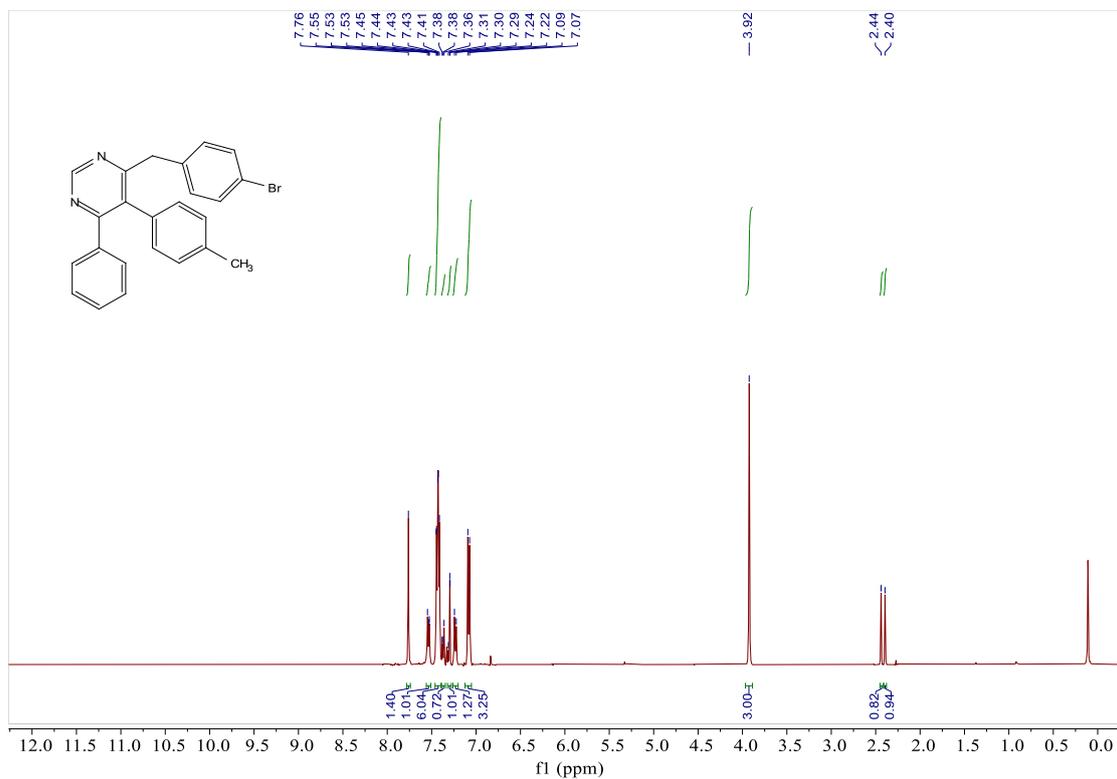


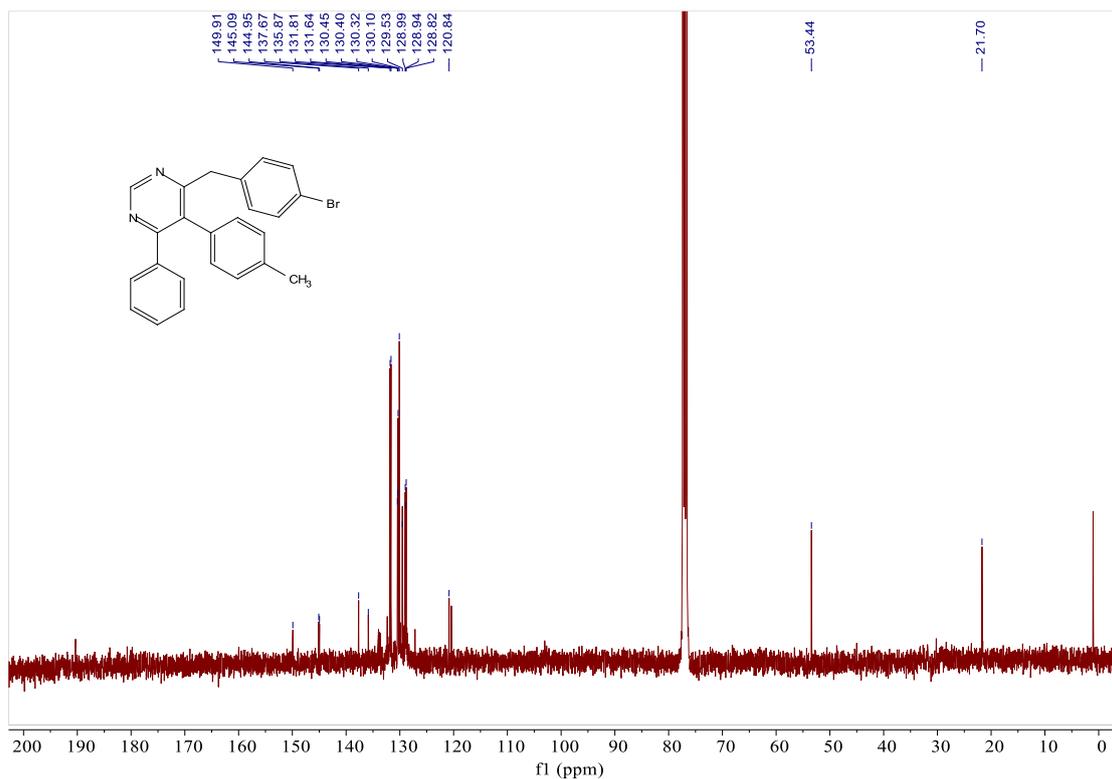
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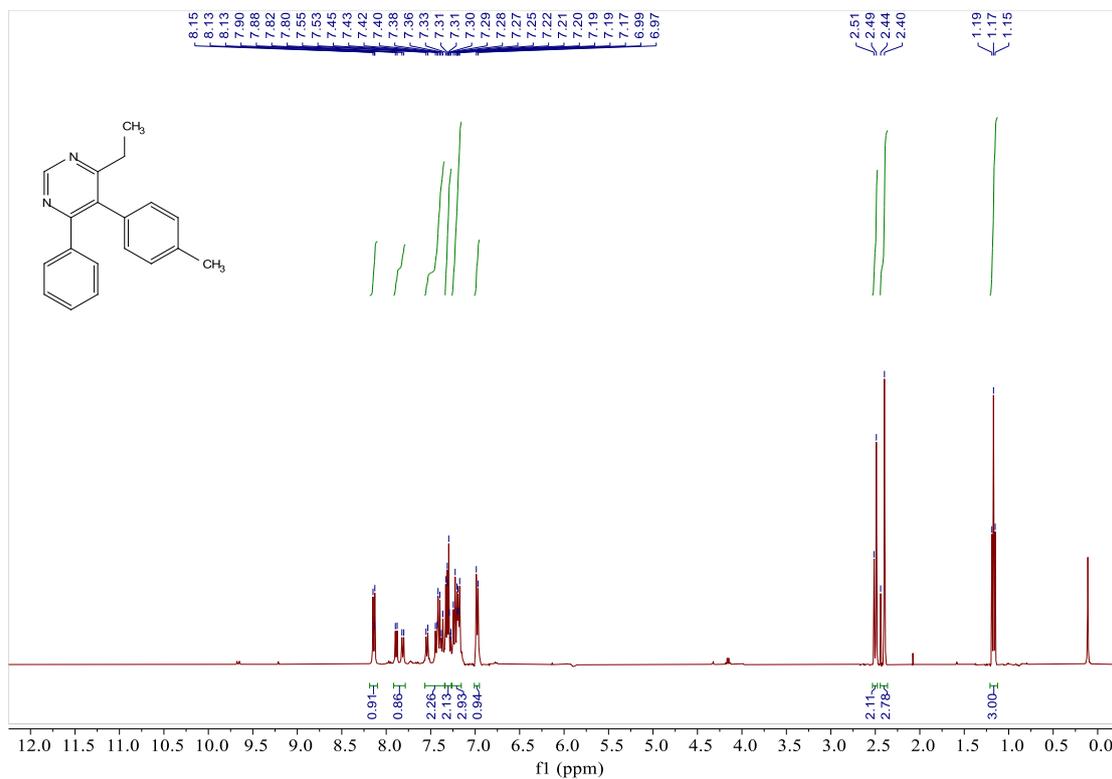


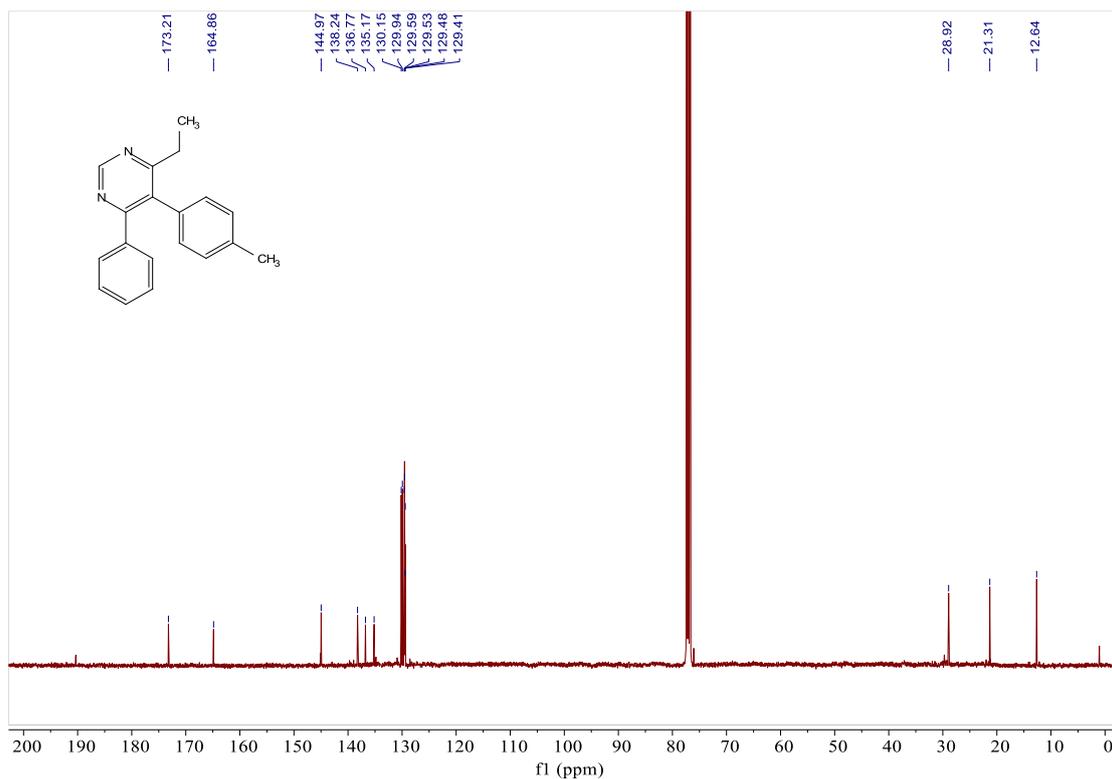
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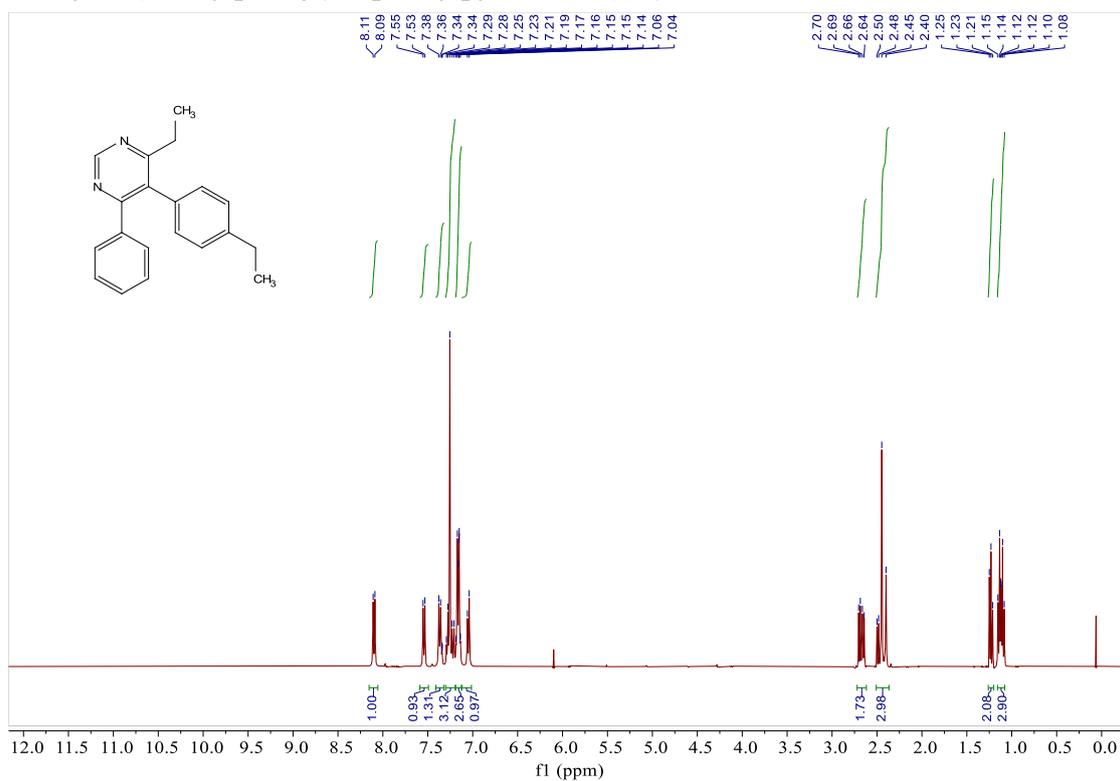


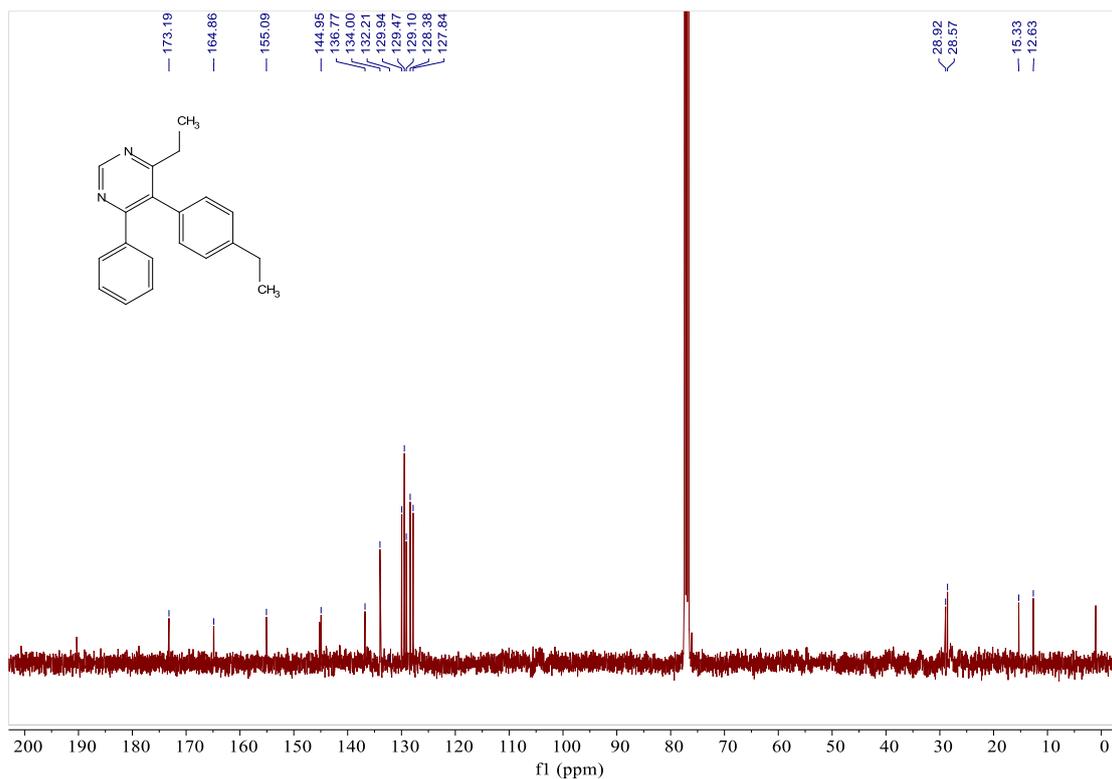
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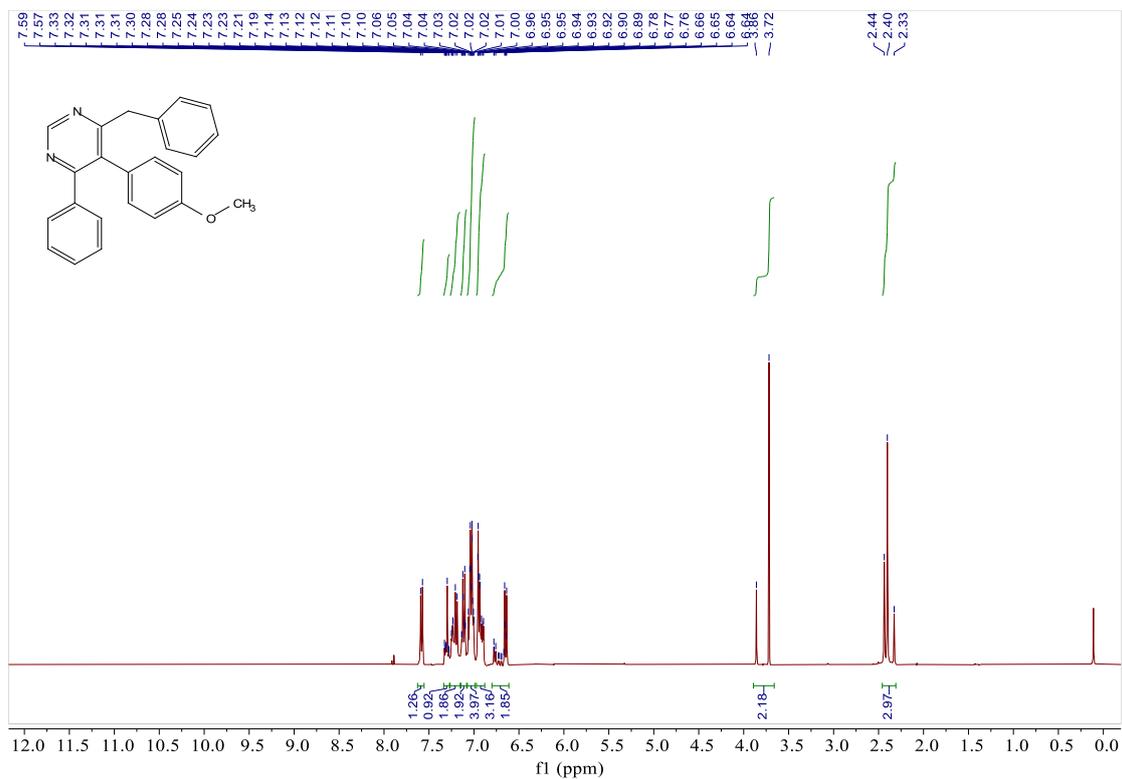


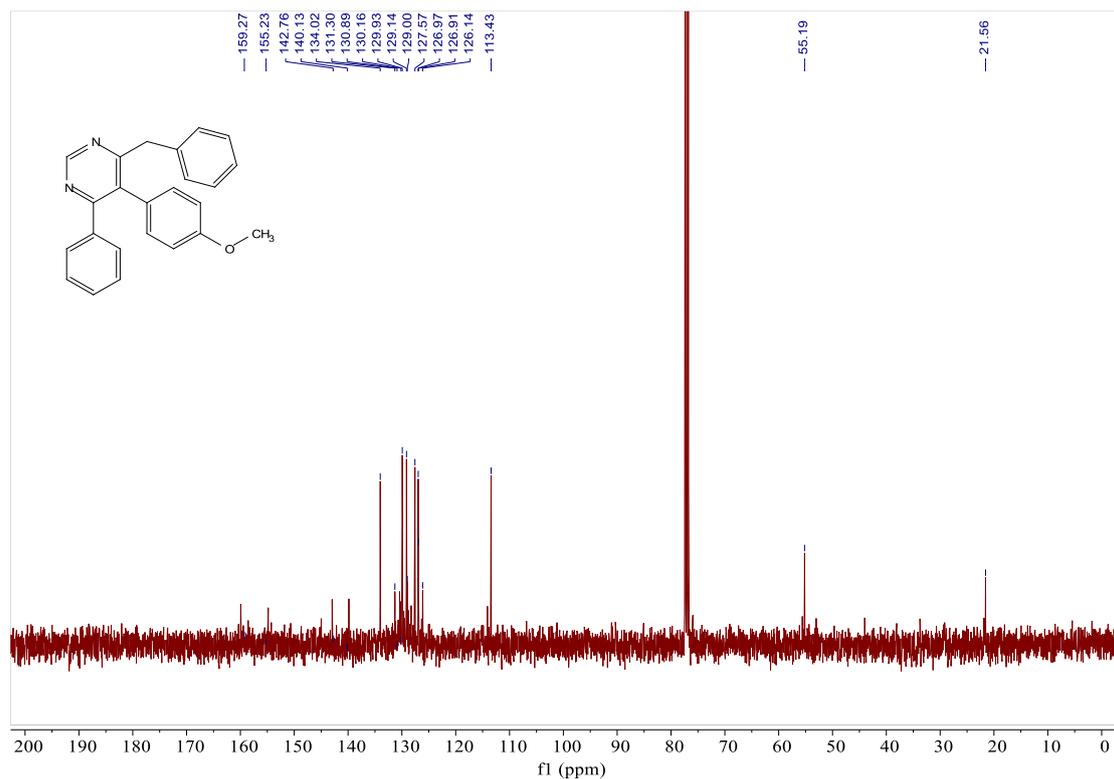
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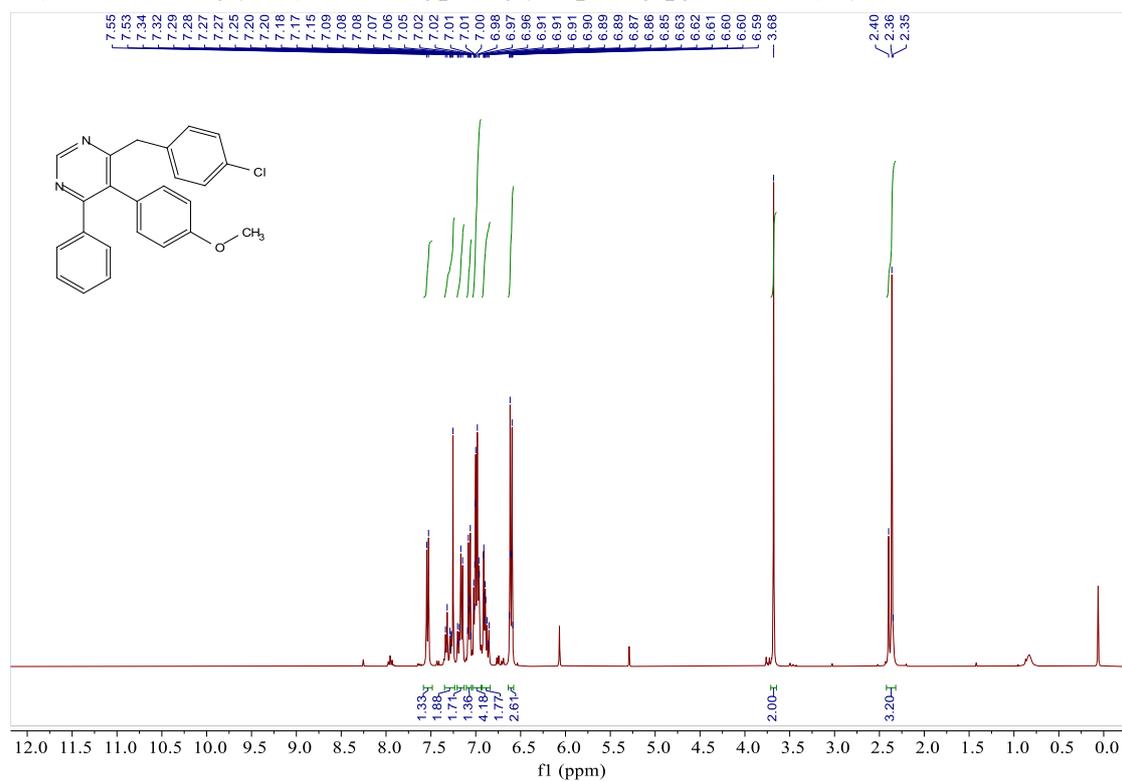


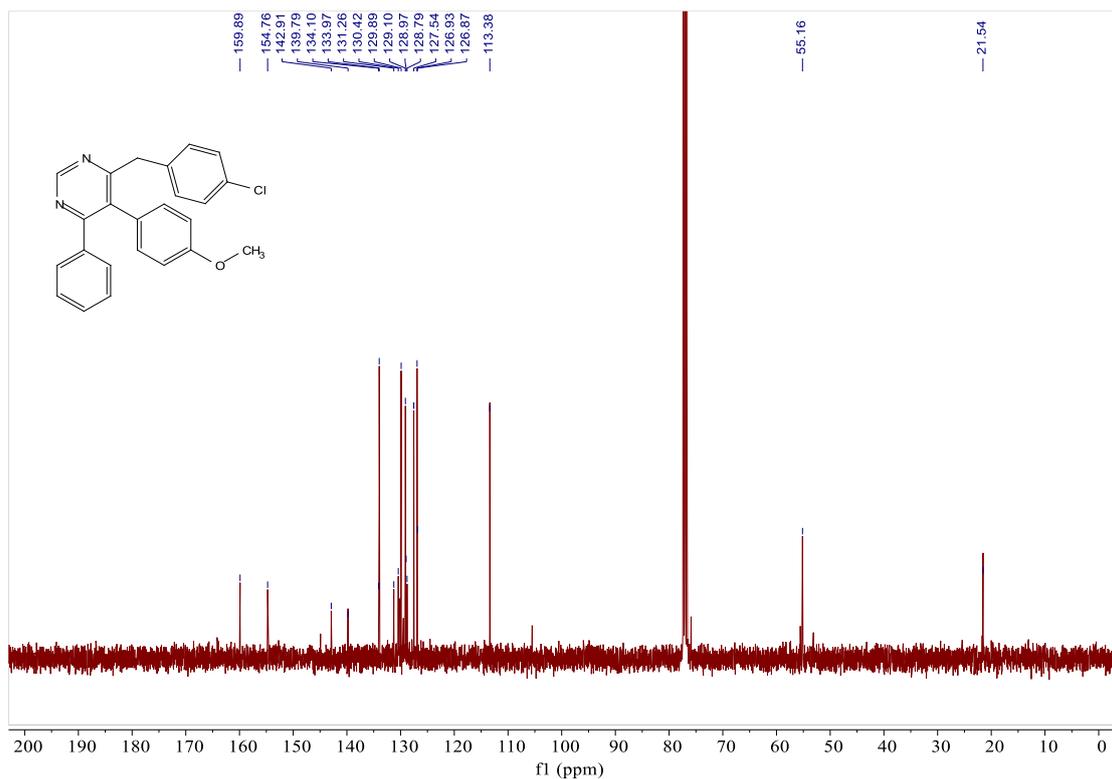
4-benzyl-5-(4-methoxyphenyl)-6-phenylpyrimidine(3n)



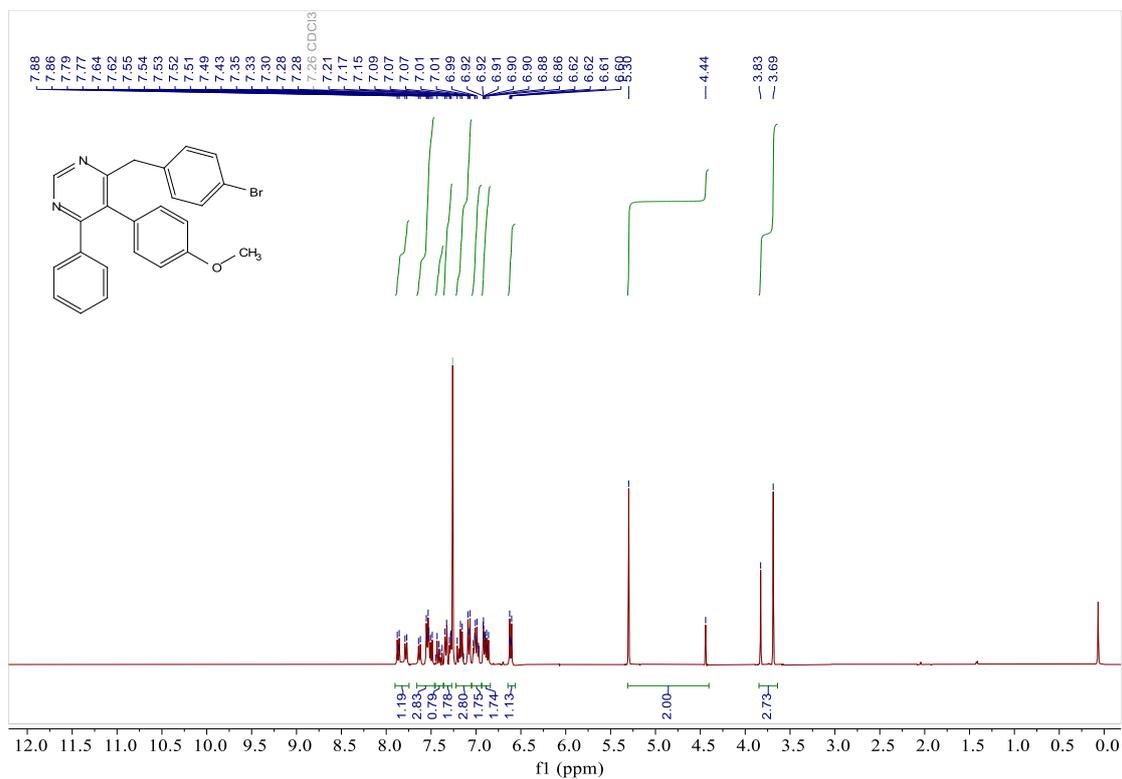


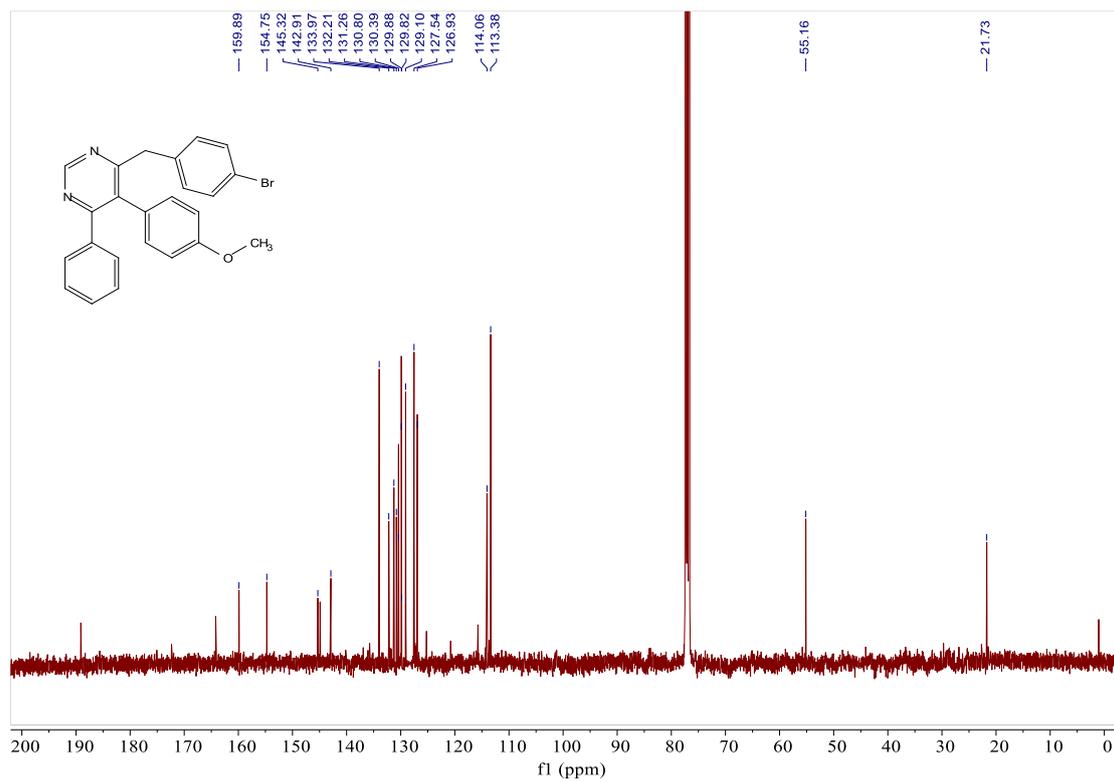
4-(4-chlorobenzyl)-5-(4-methoxyphenyl)-6-phenylpyrimidine(3o)



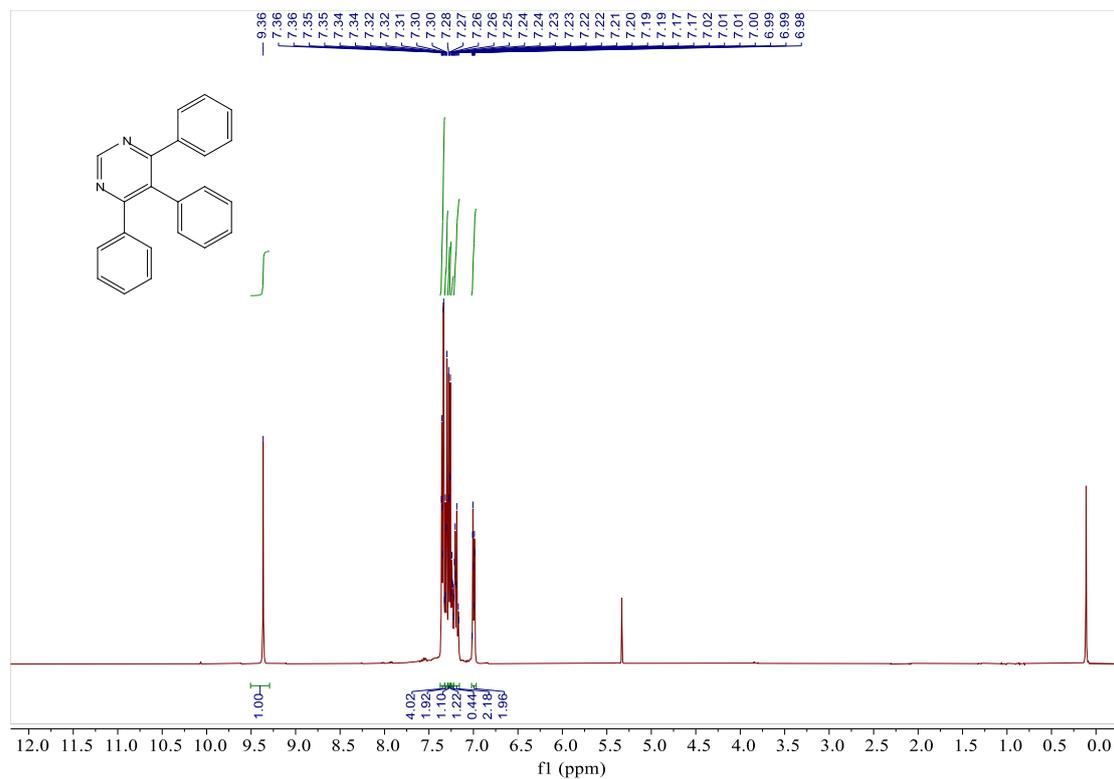


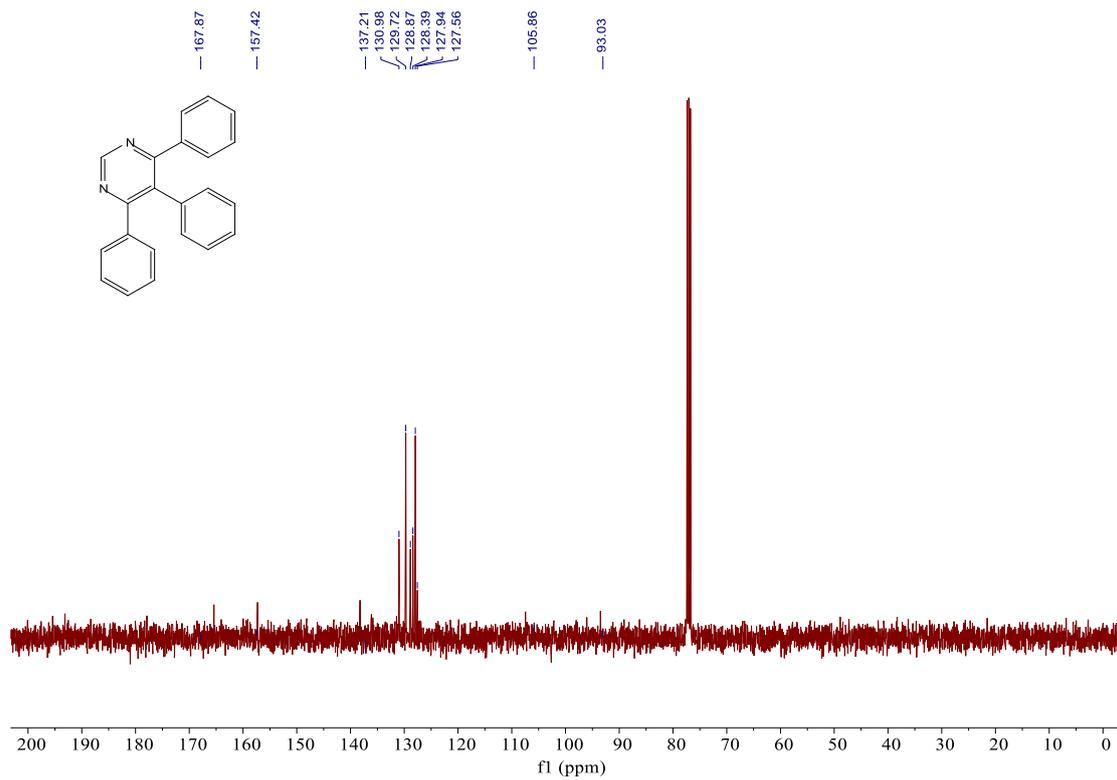
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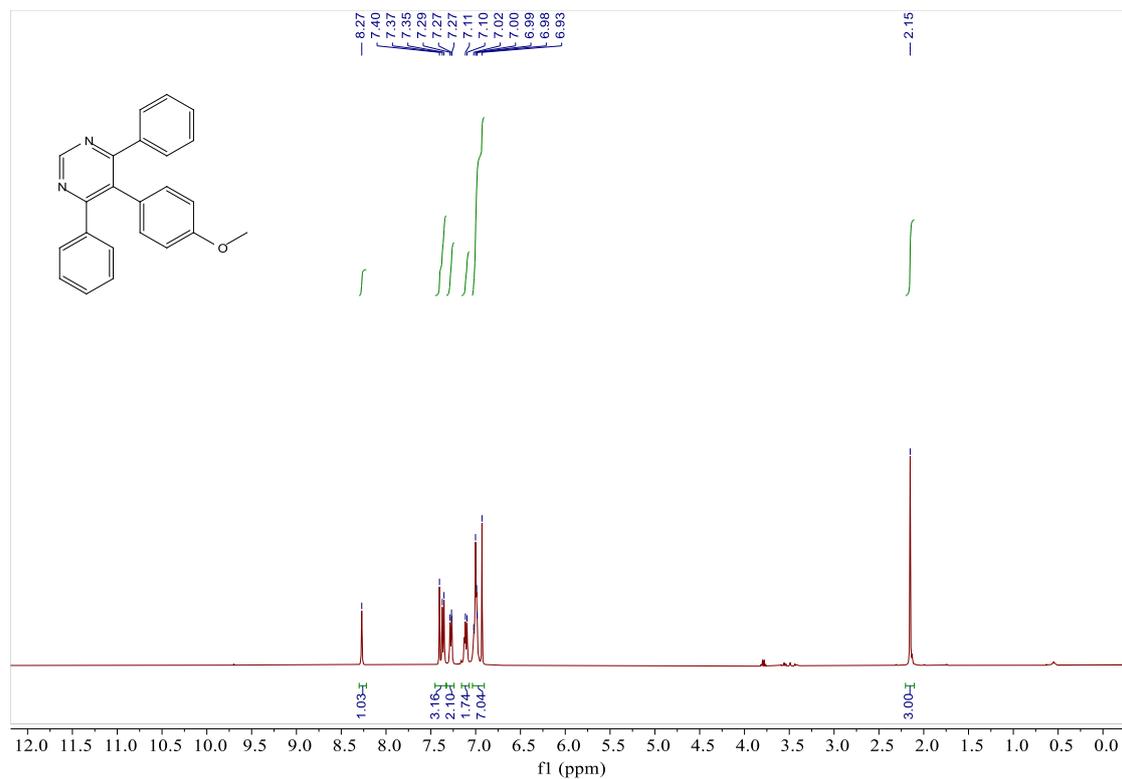


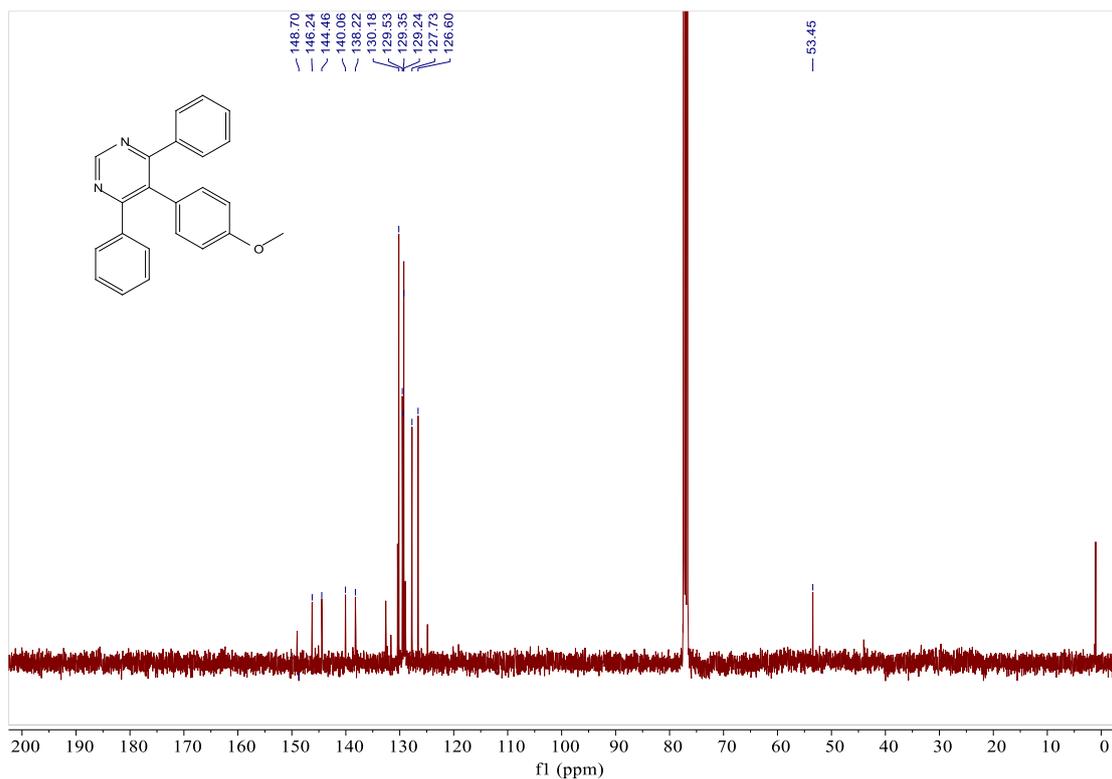
4,5,6-triphenylpyrimidine(3q)



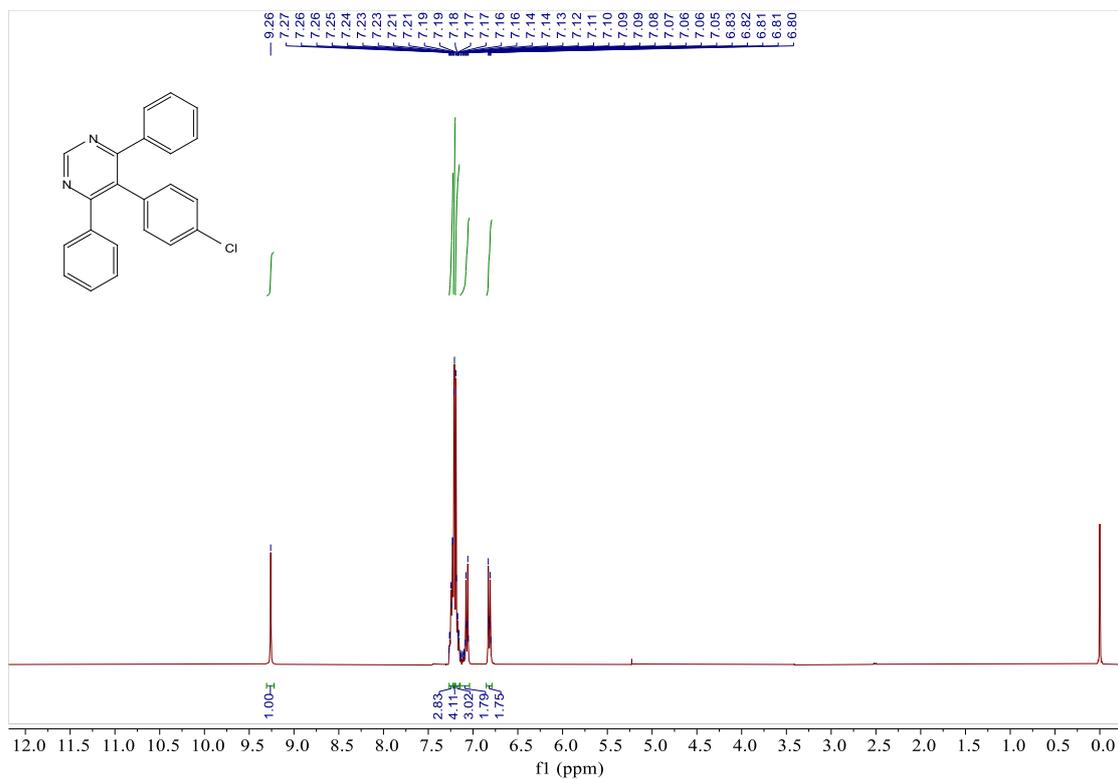


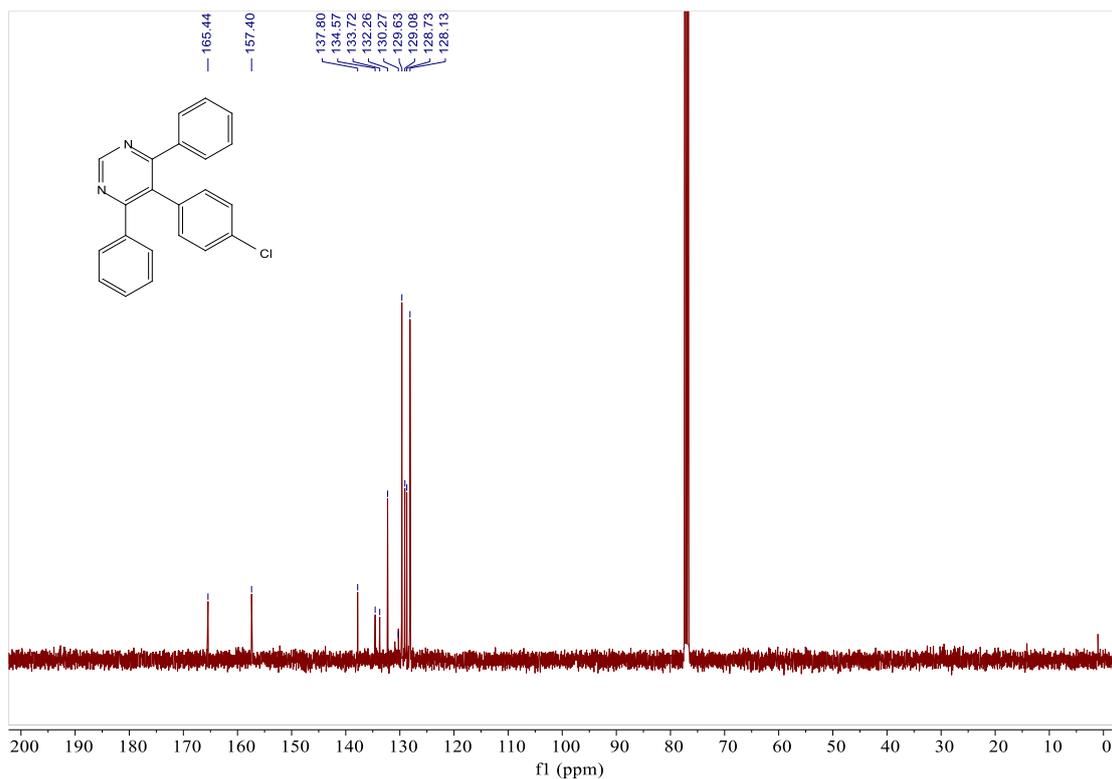
5-(4-methoxyphenyl)-4,6-diphenylpyrimidine(3r)



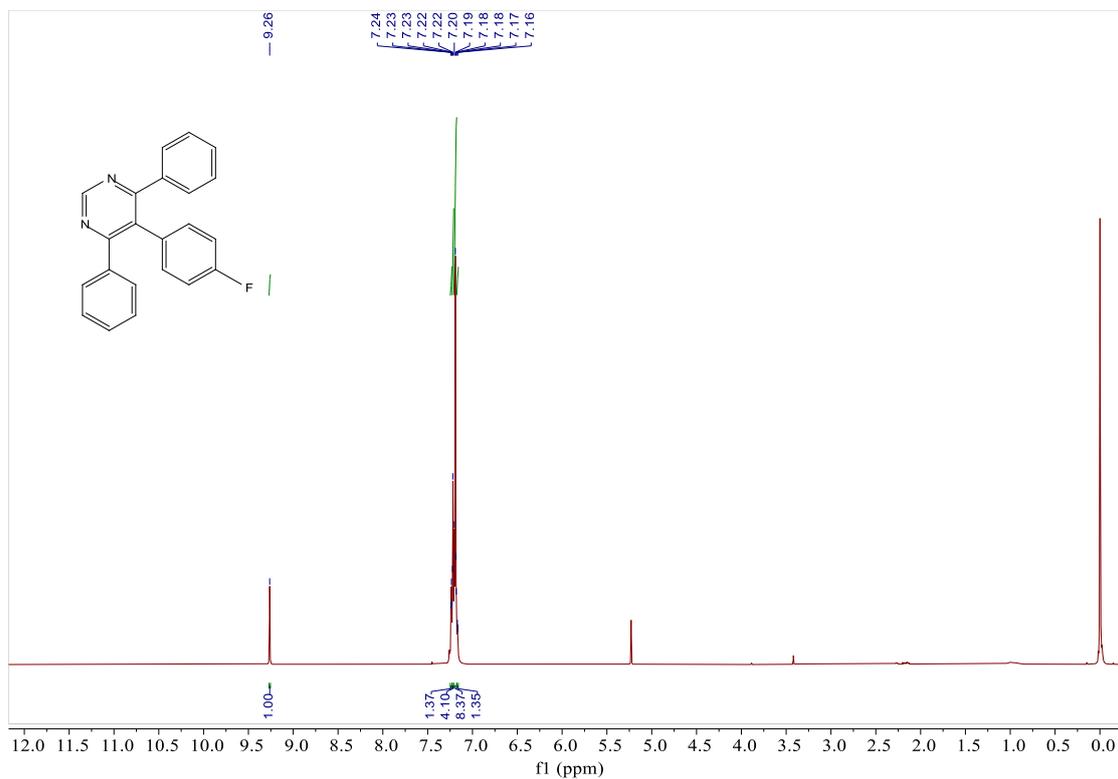


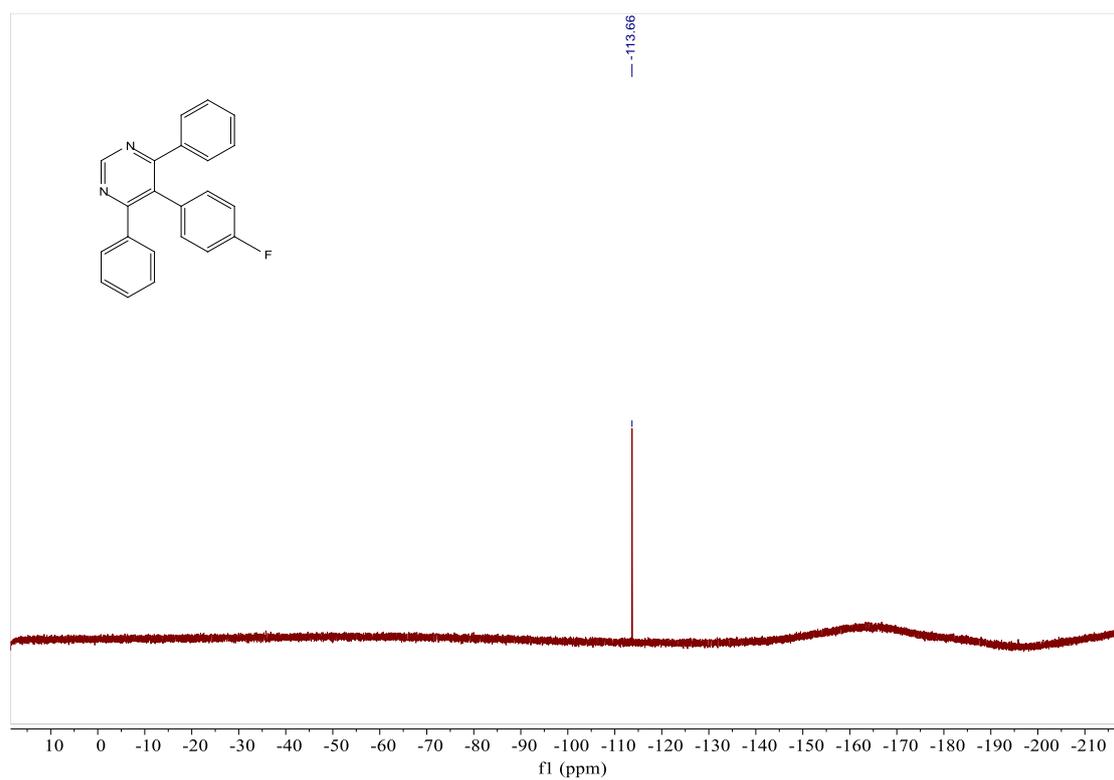
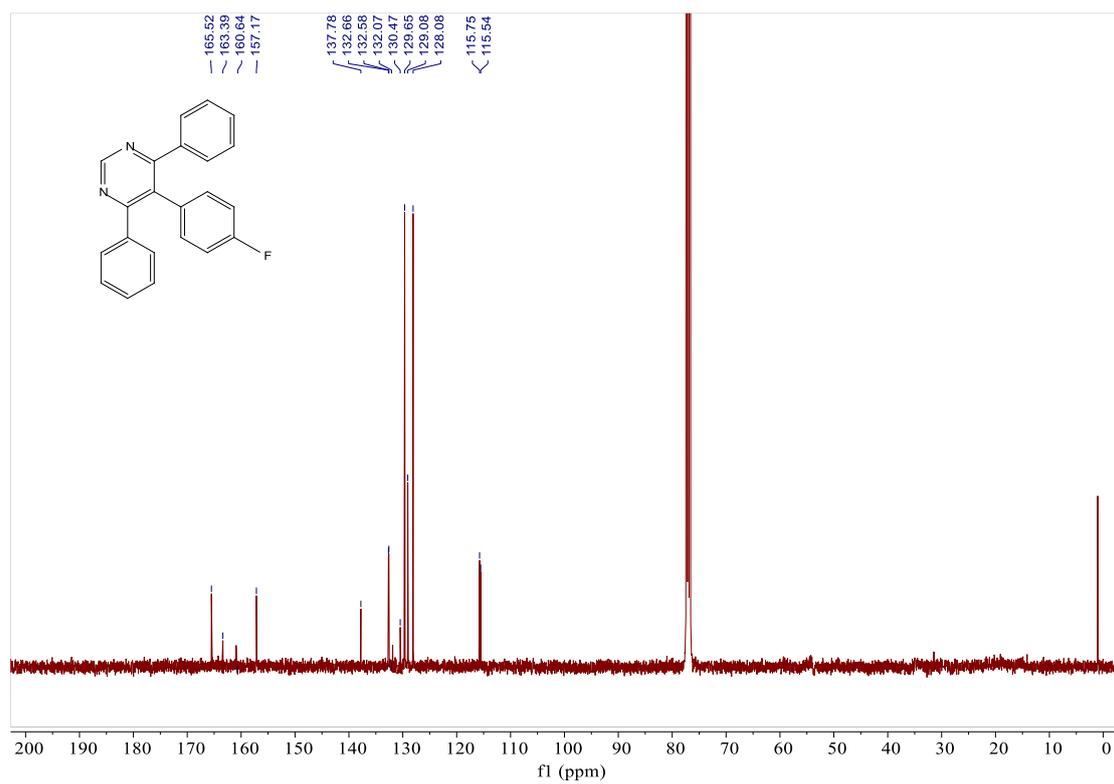
5-(4-chlorophenyl)-4,6-diphenylpyrimidine(3s)



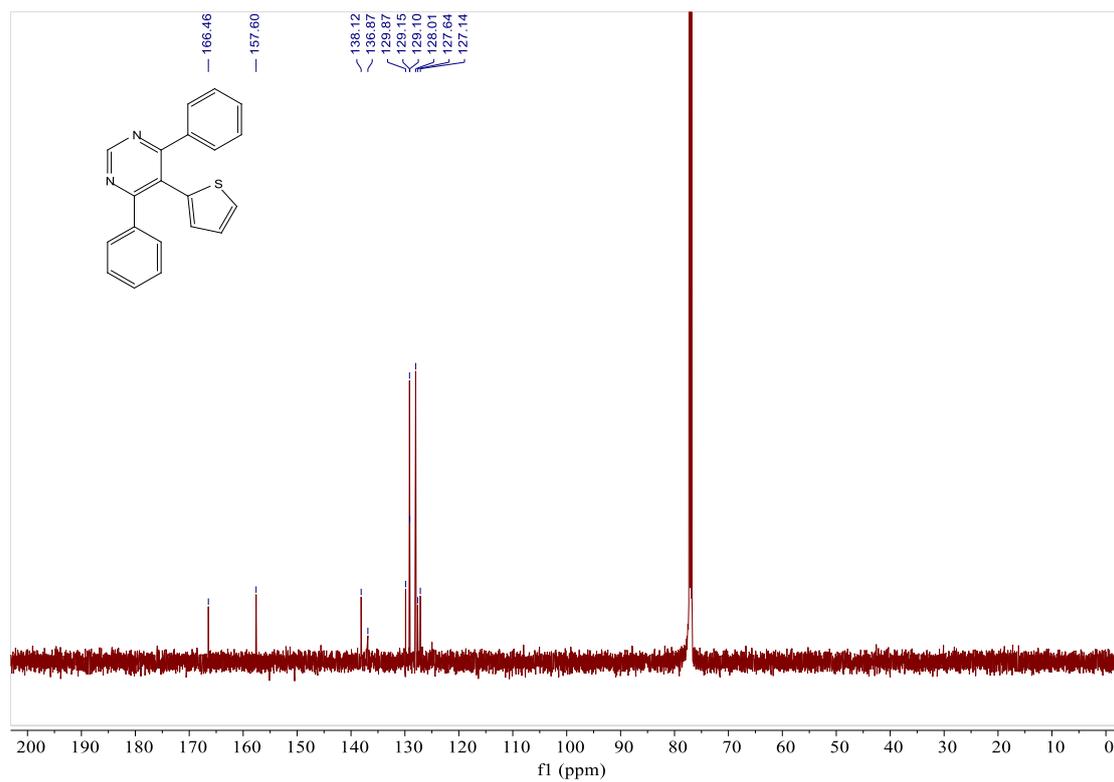
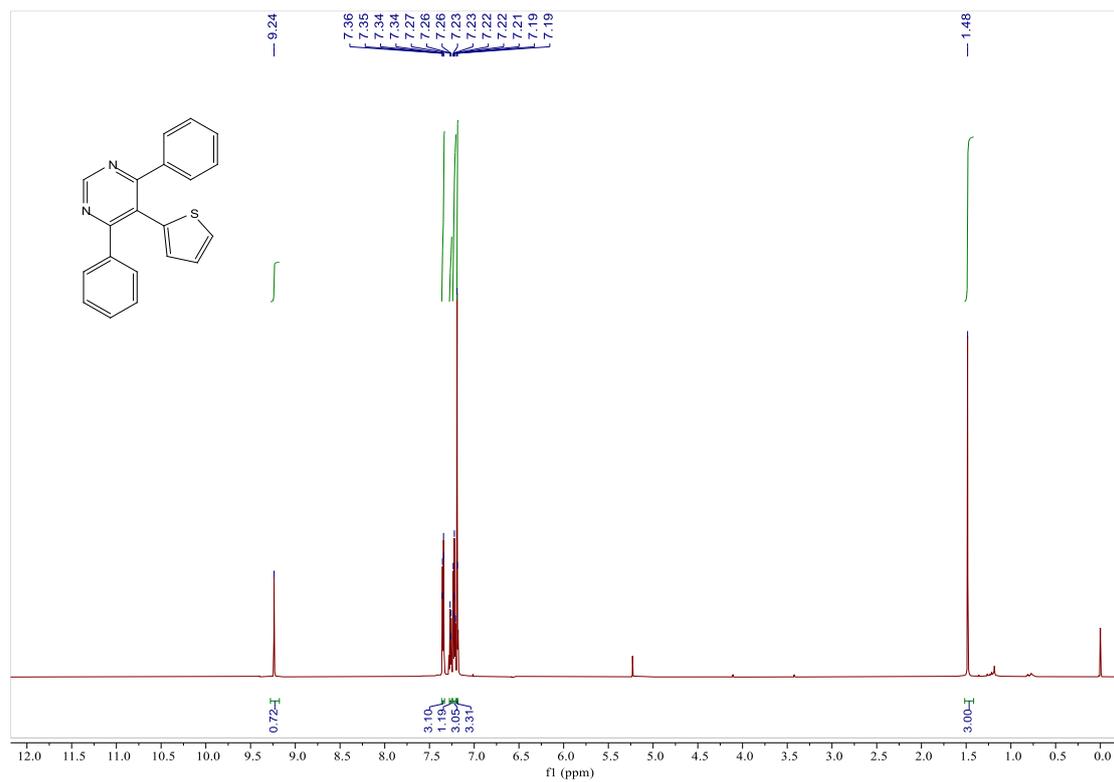


5-(4-fluorophenyl)-4,6-diphenylpyrimidine(3t)

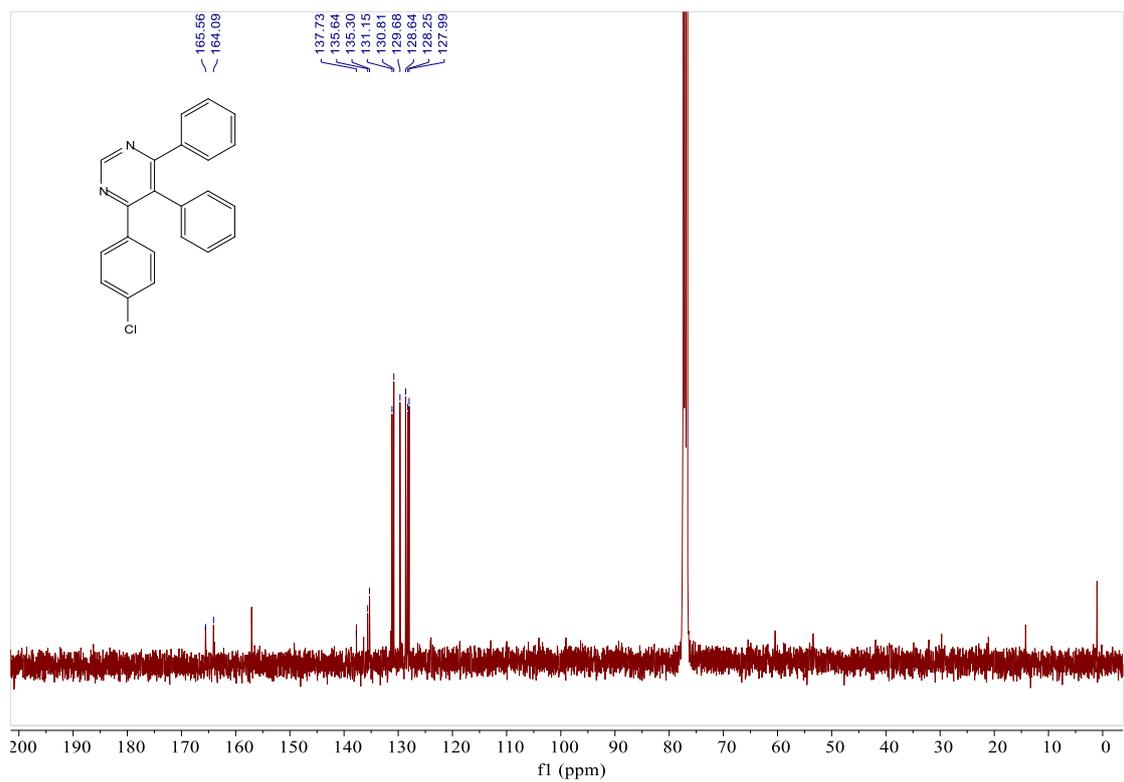
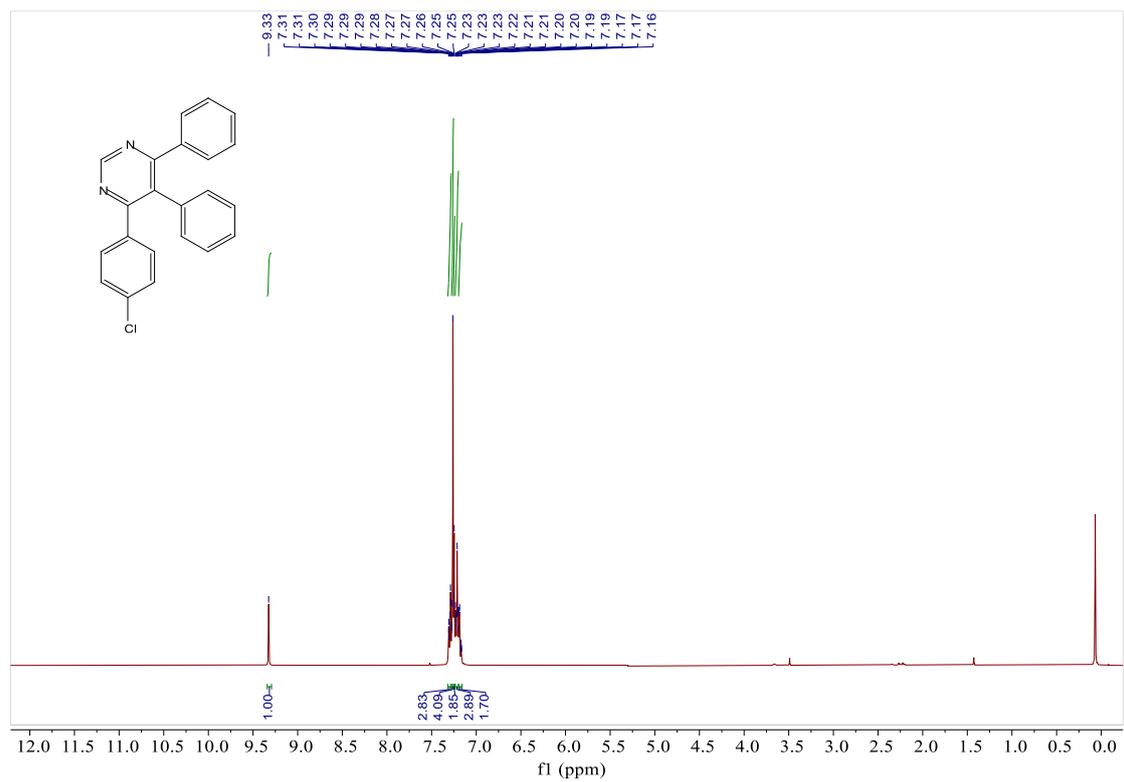




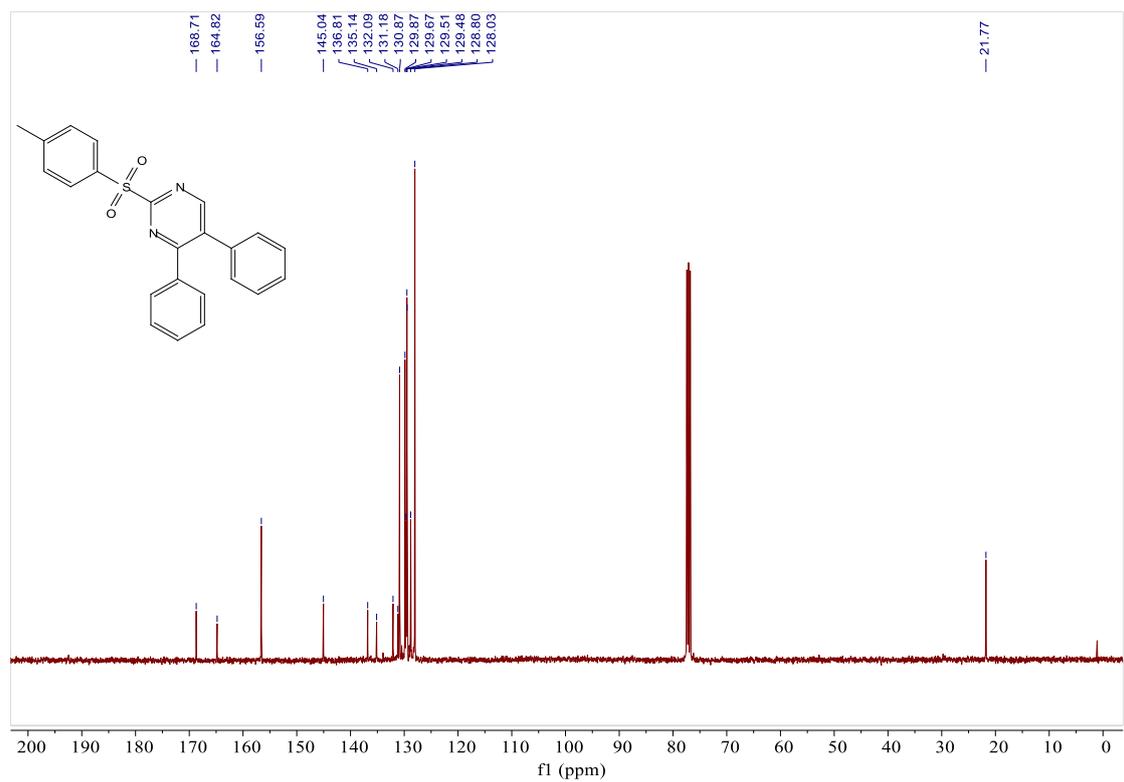
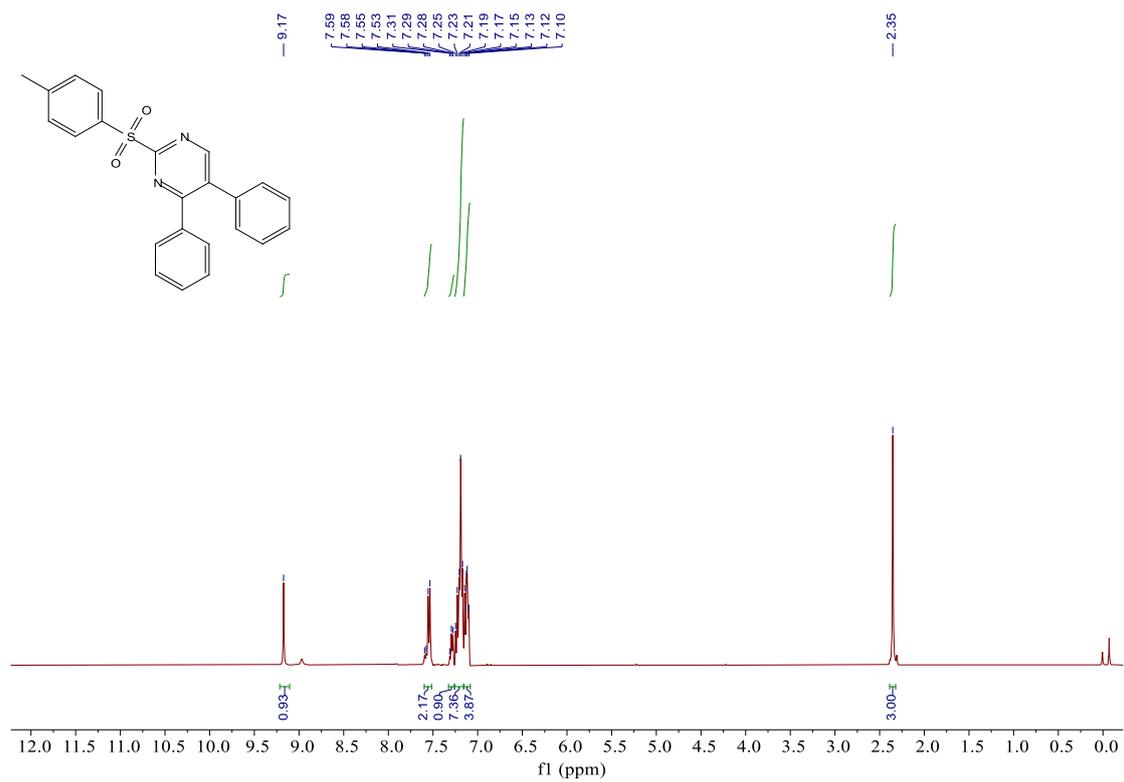
4,6-diphenyl-5-(thiophen-2-yl)pyrimidine(3u)



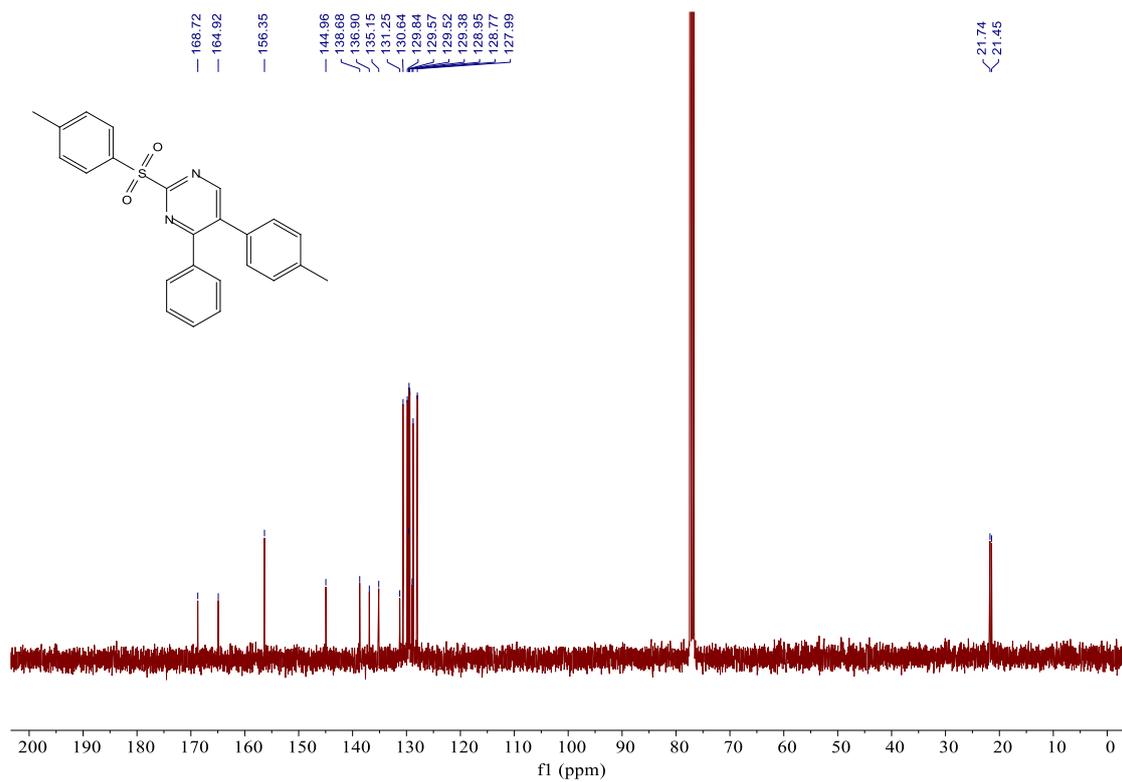
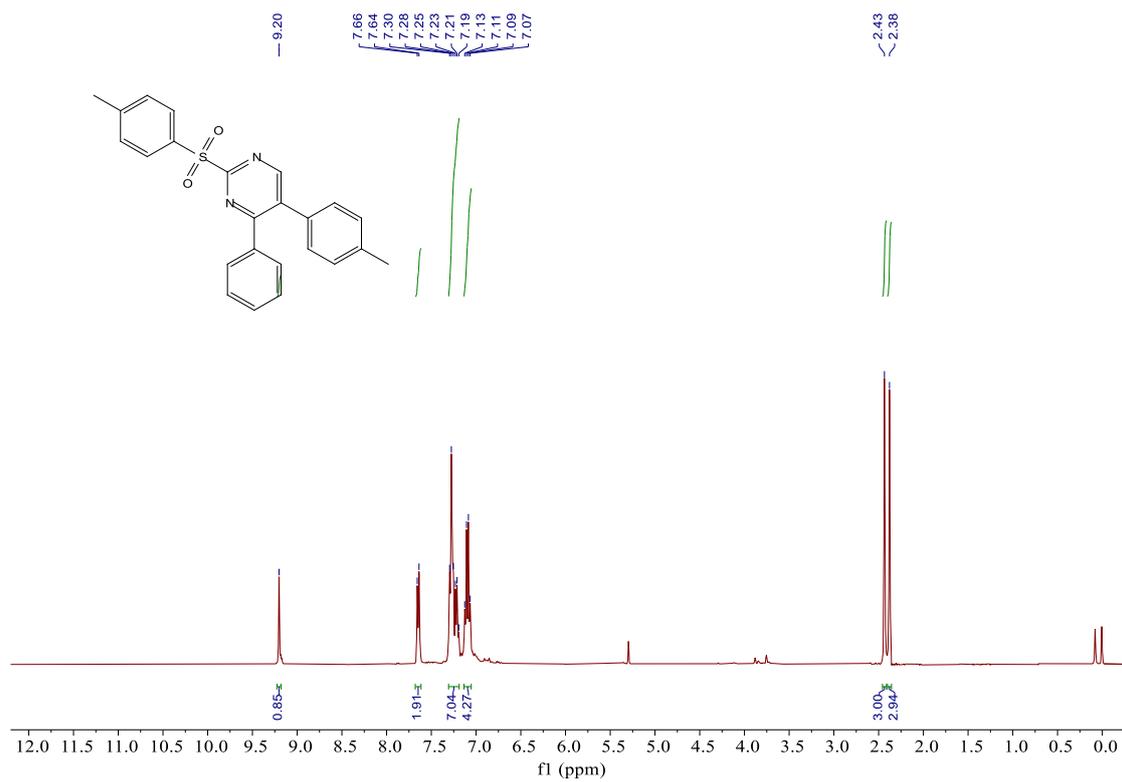
4-(4-chlorophenyl)-5,6-diphenylpyrimidine(3v)



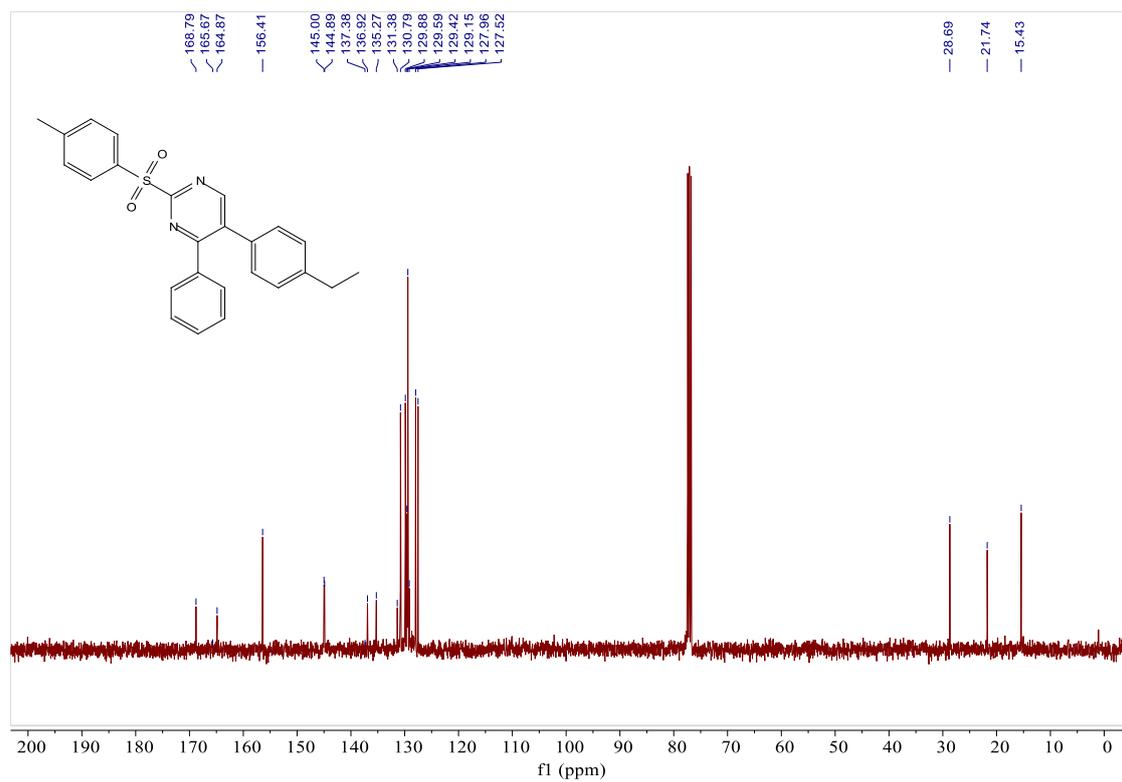
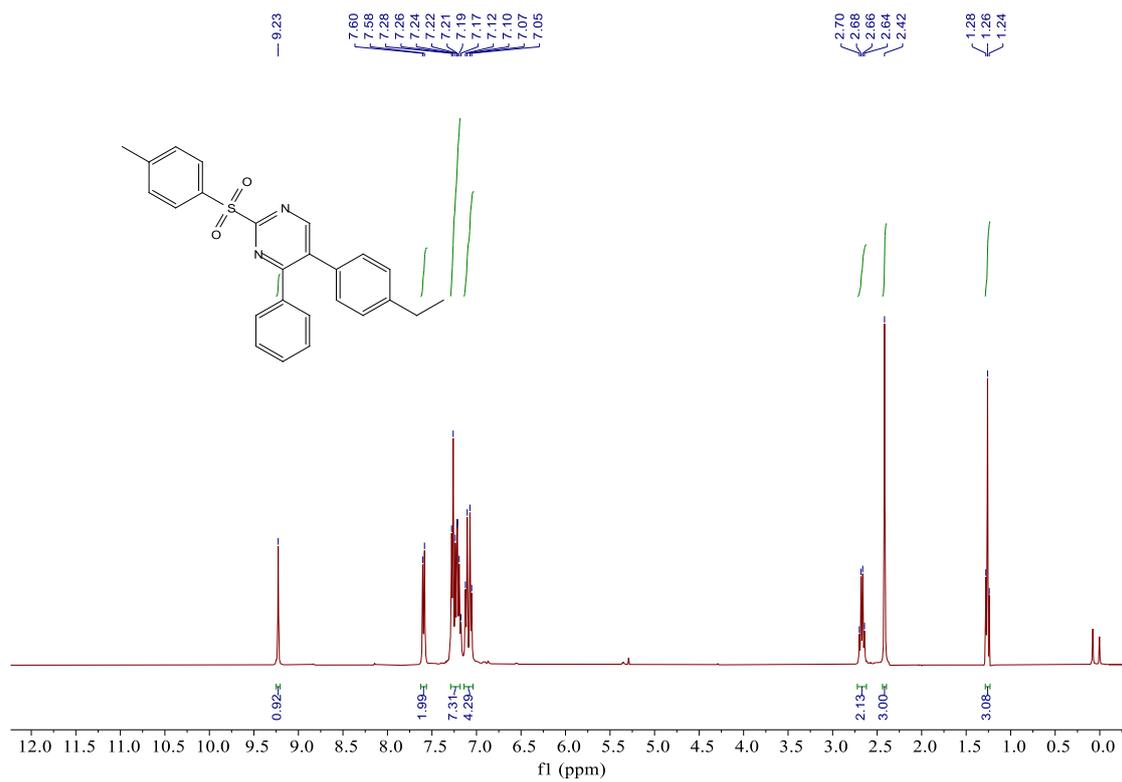
4,5-diphenyl-2-tosylpyrimidine(4a)



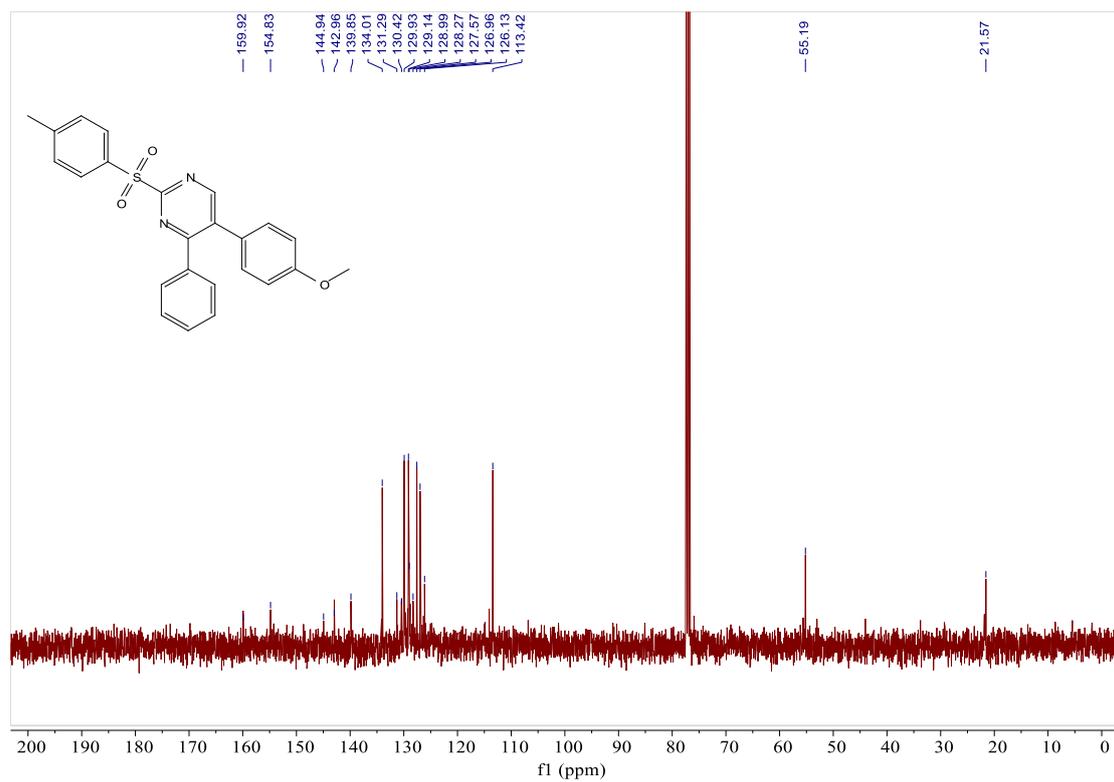
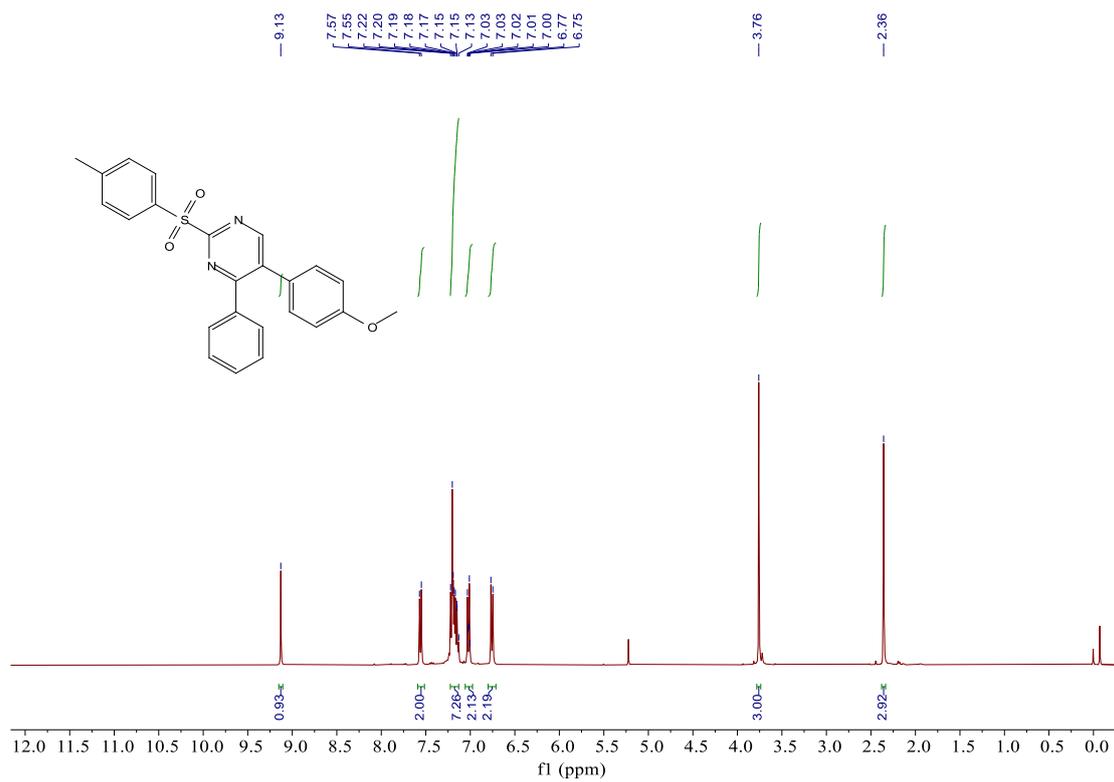
4-phenyl-5-(p-tolyl)-2-tosylpyrimidine(4b)



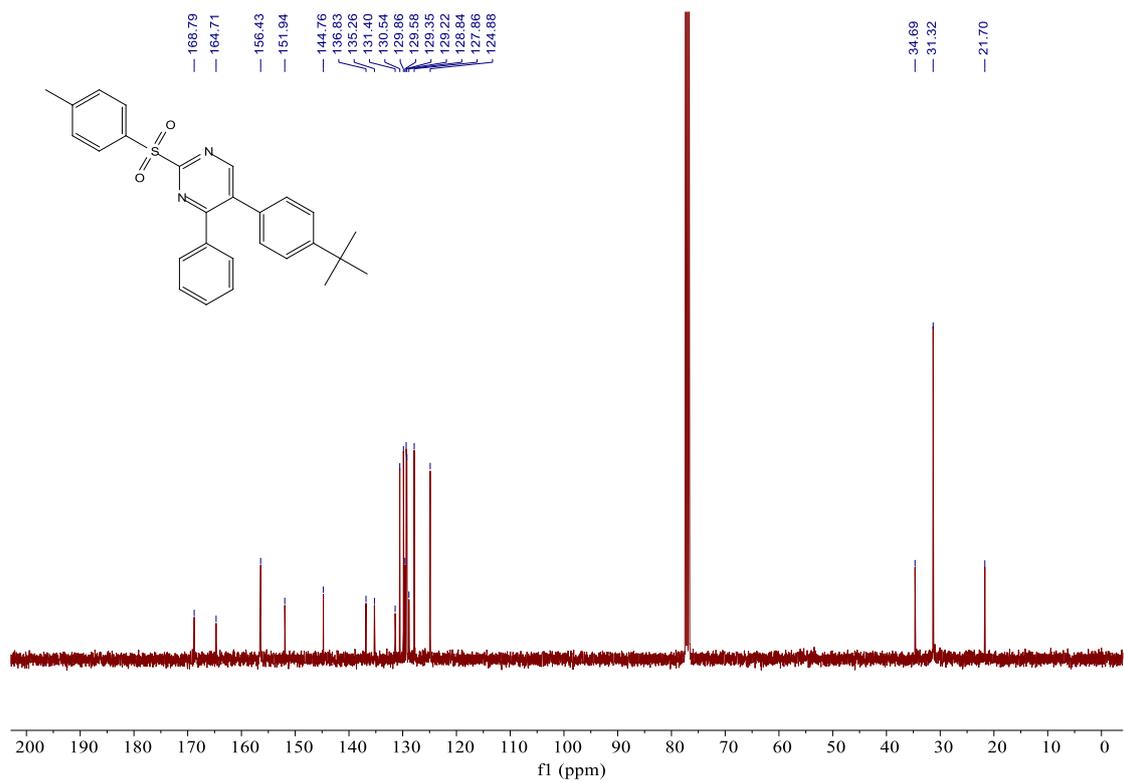
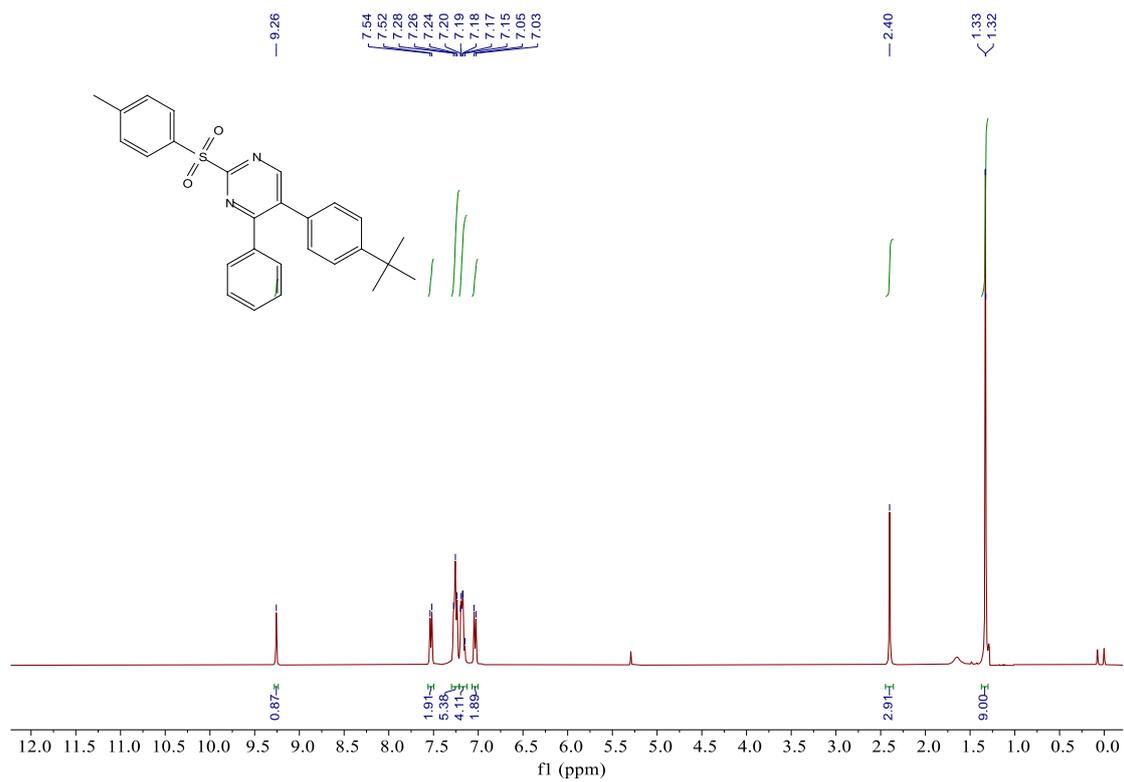
5-(4-ethylphenyl)-4-phenyl-2-tosylpyrimidine(4c)



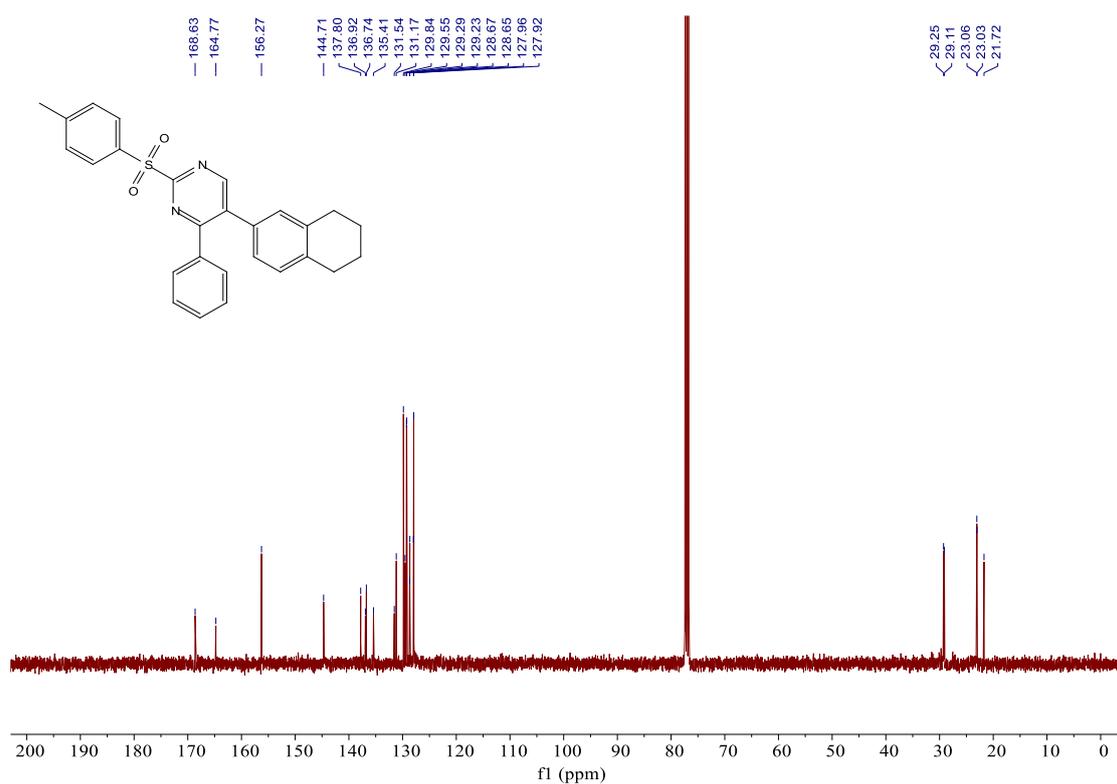
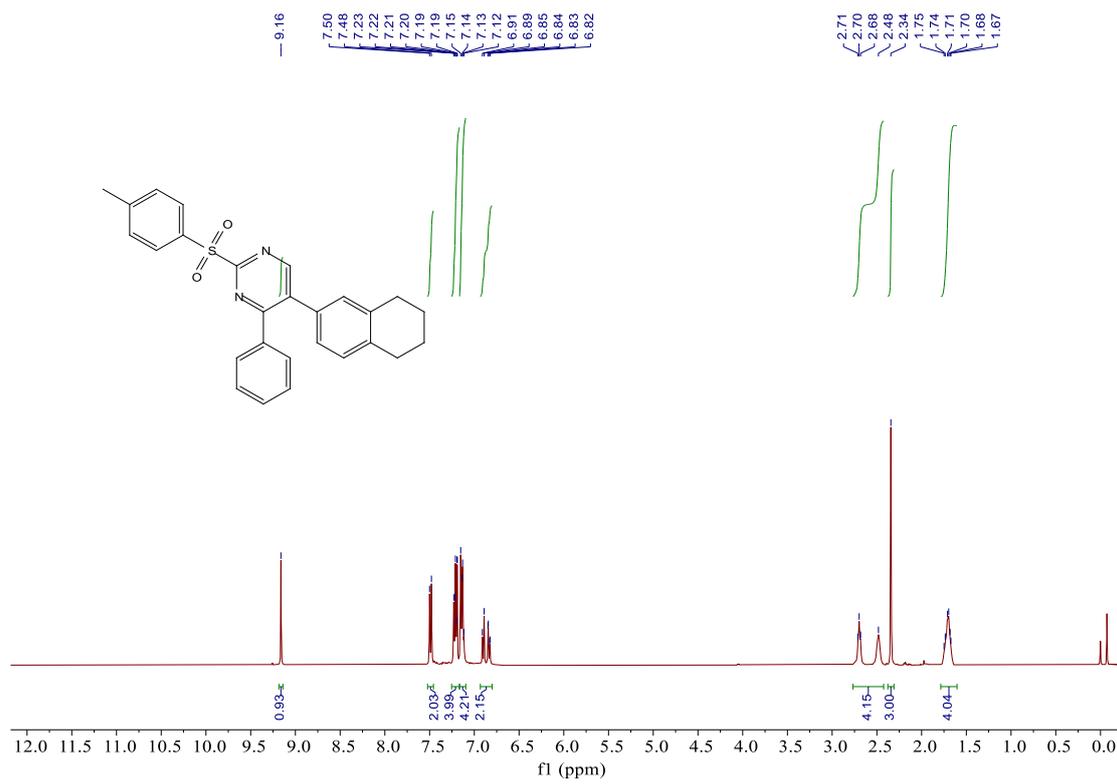
5-(4-methoxyphenyl)-4-phenyl-2-tosylpyrimidine(4d)



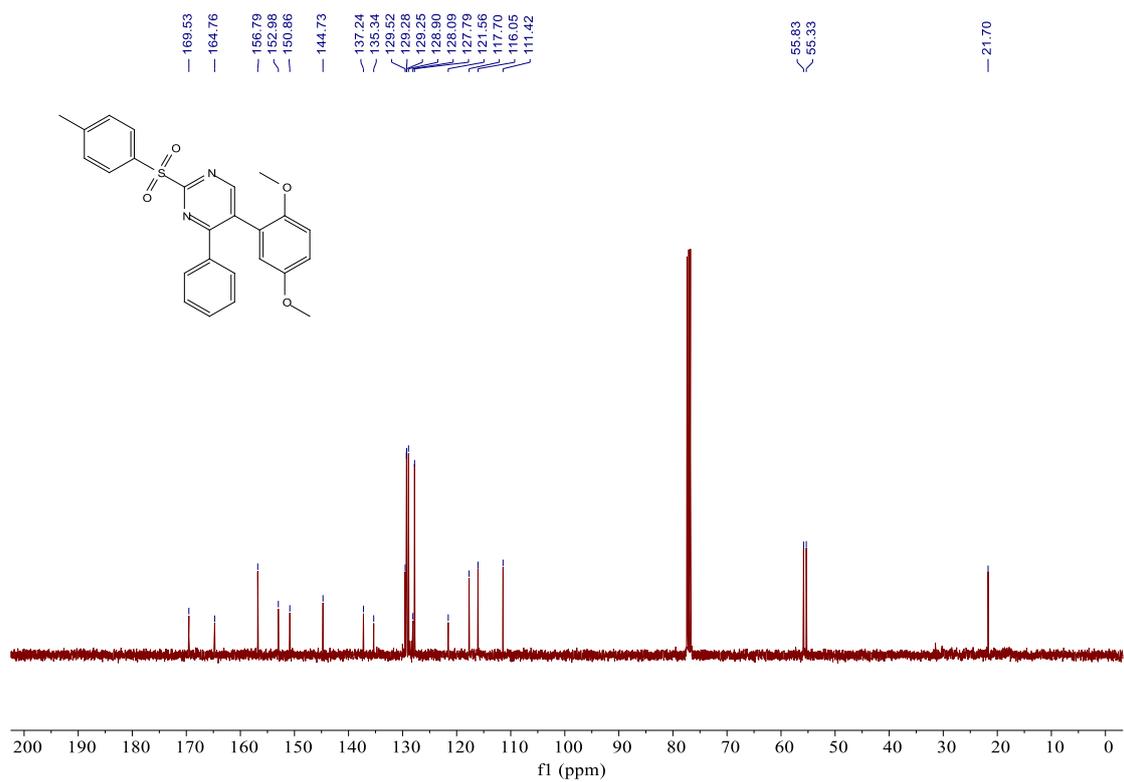
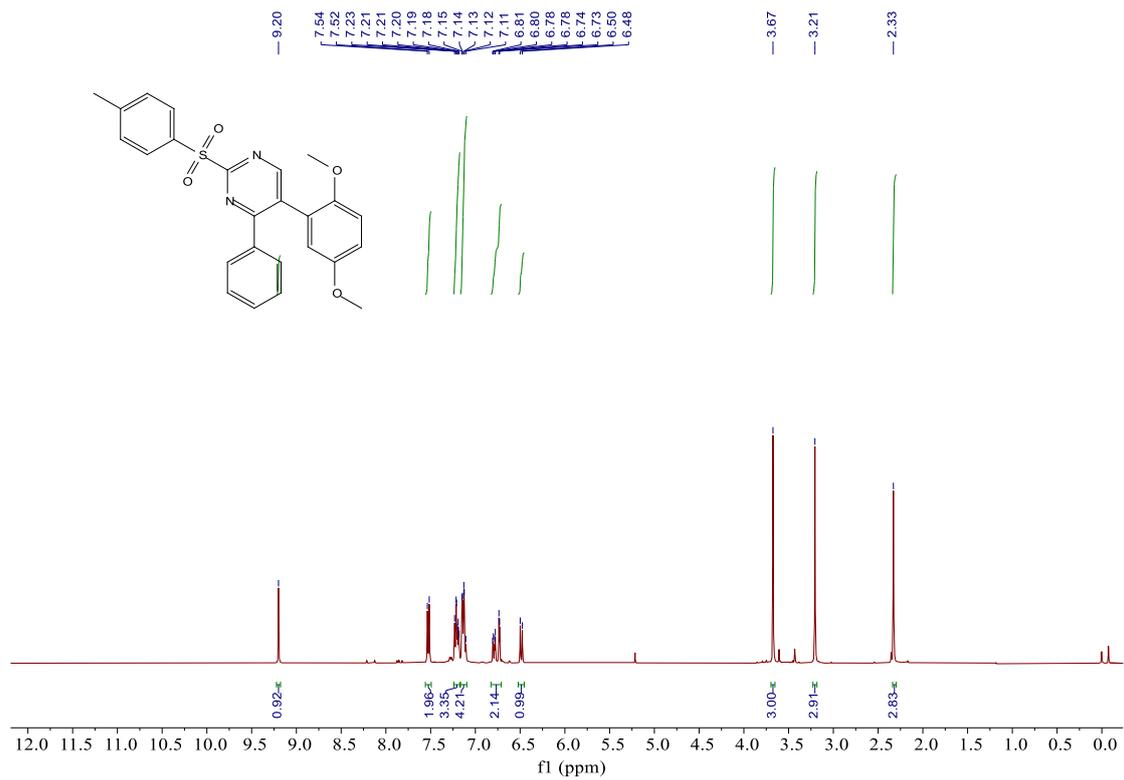
5-(4-(tert-butyl)phenyl)-4-phenyl-2-tosylpyrimidine(4e)



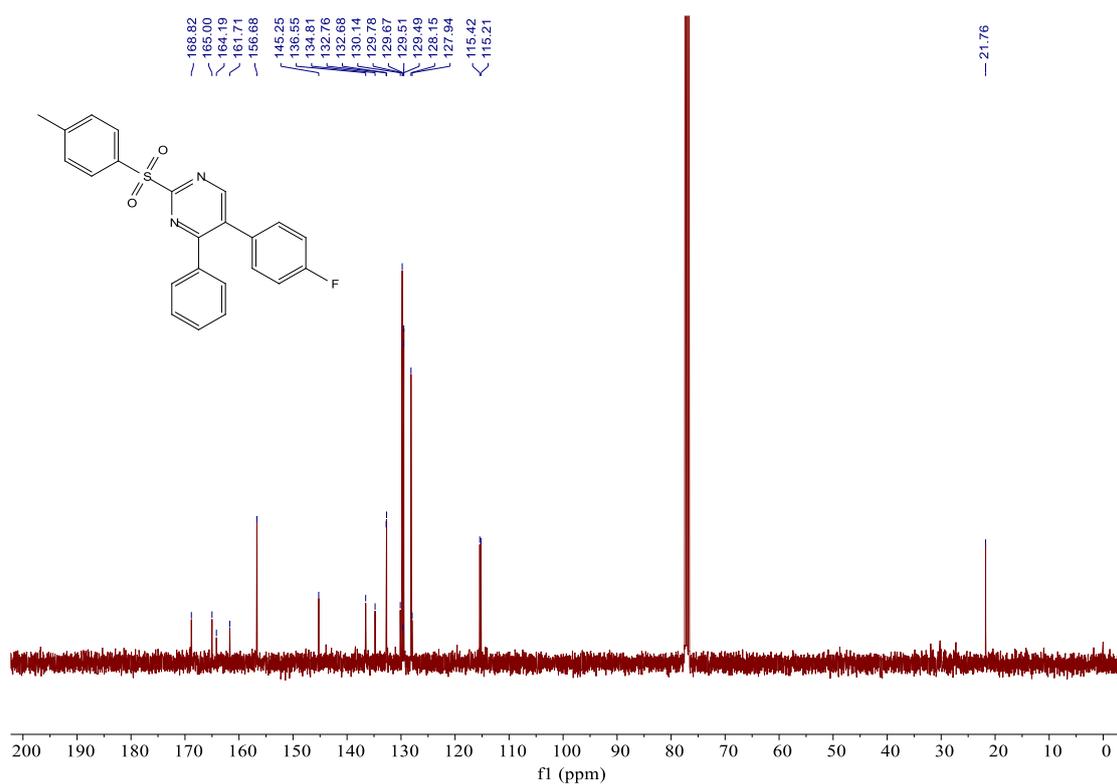
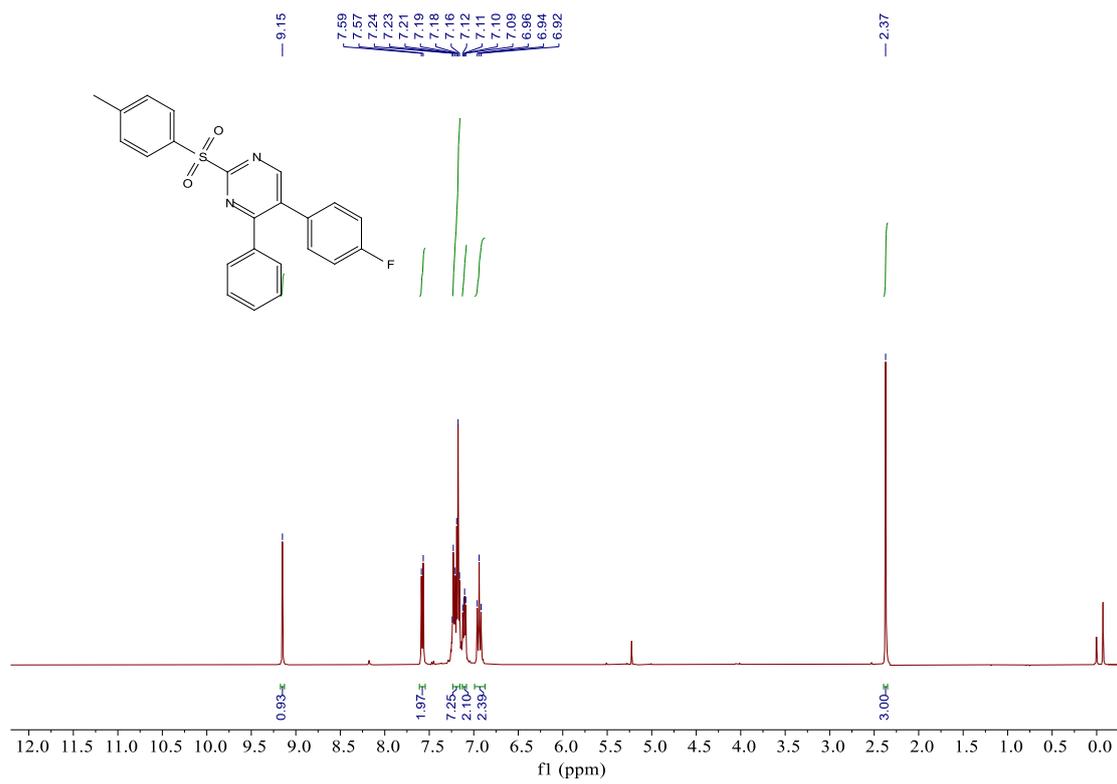
4-phenyl-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-tosylpyrimidine(4f)

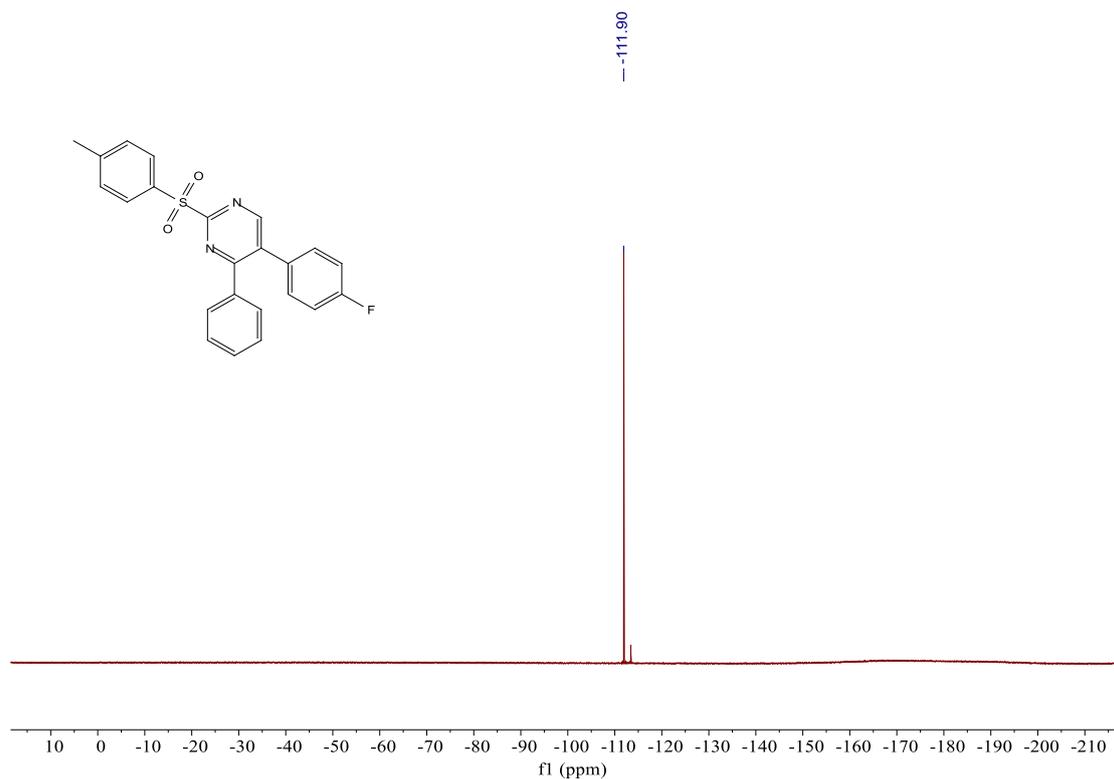


5-(2,5-dimethoxyphenyl)-4-phenyl-2-tosylpyrimidine(4g)

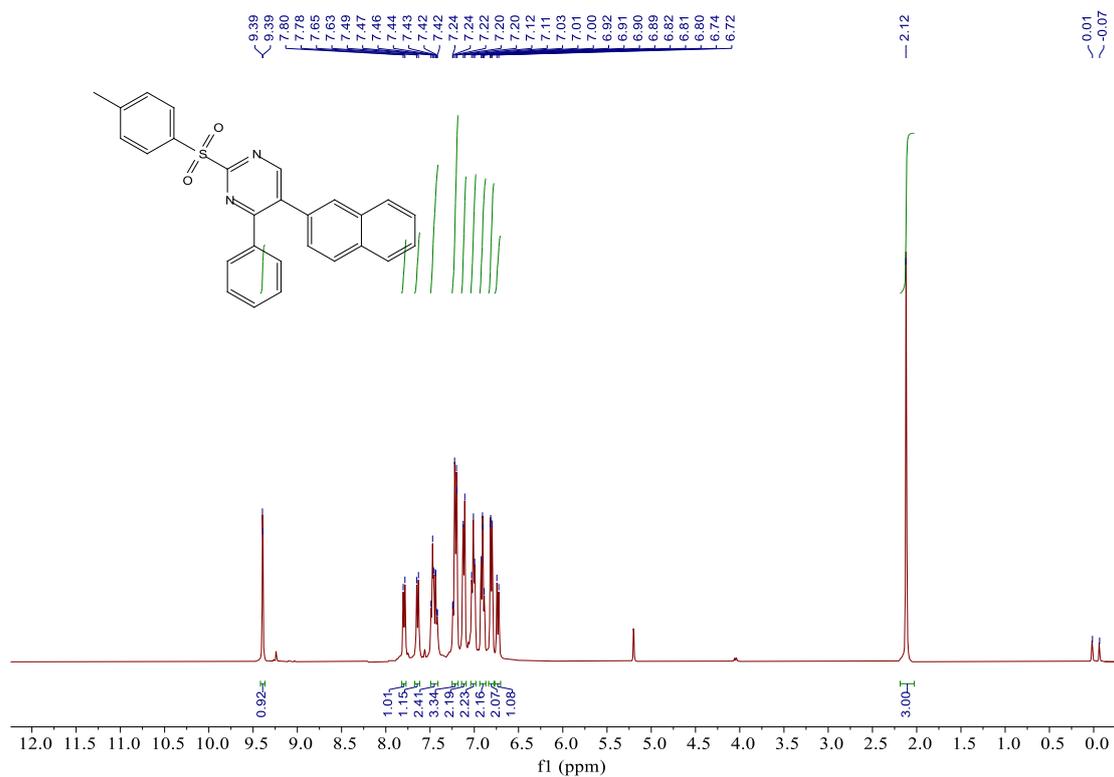


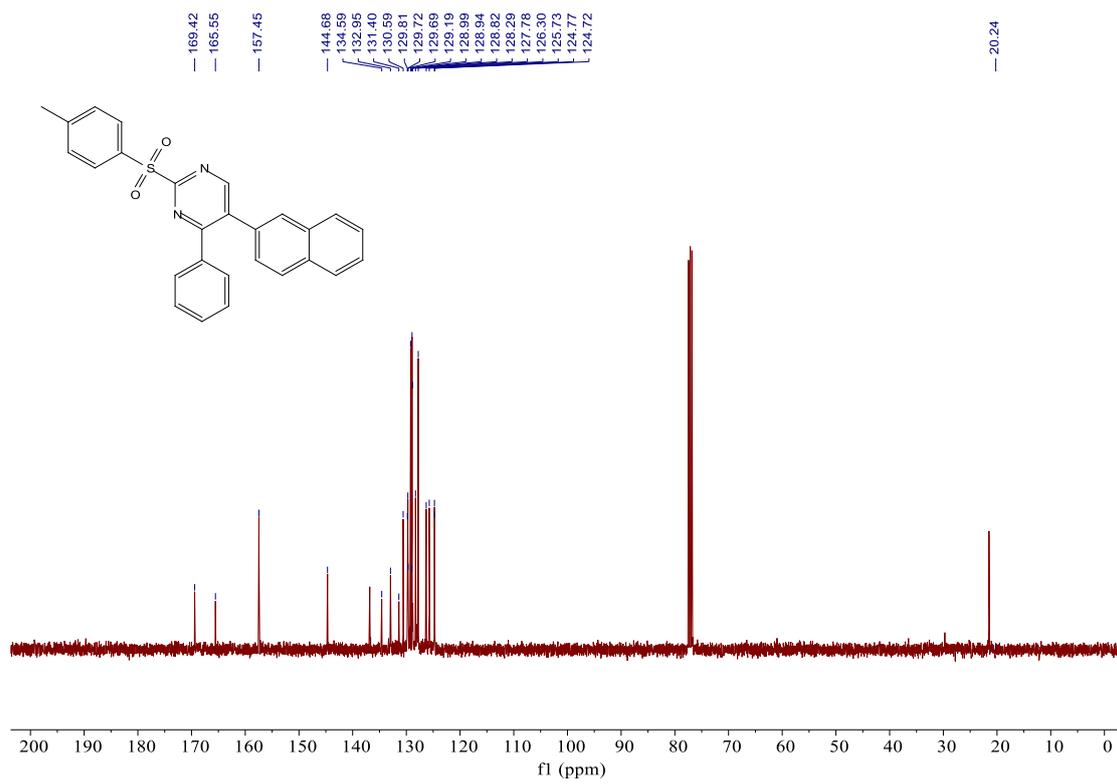
5-(4-fluorophenyl)-4-phenyl-2-tosylpyrimidine(4h)



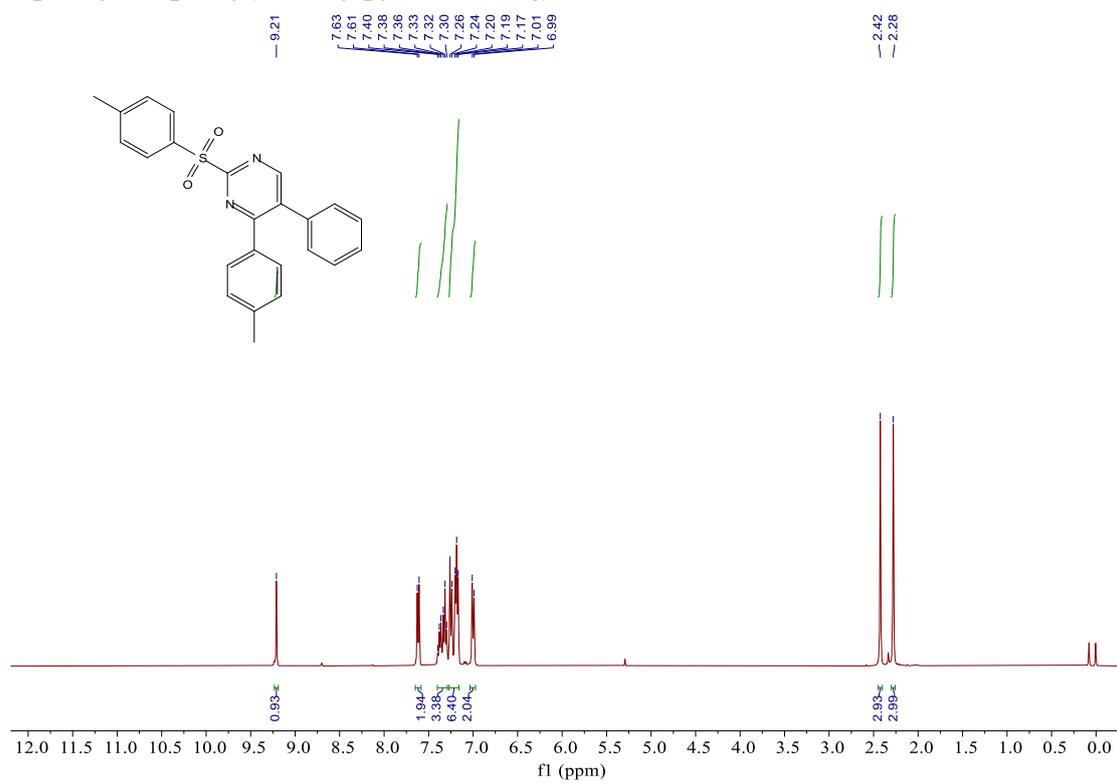


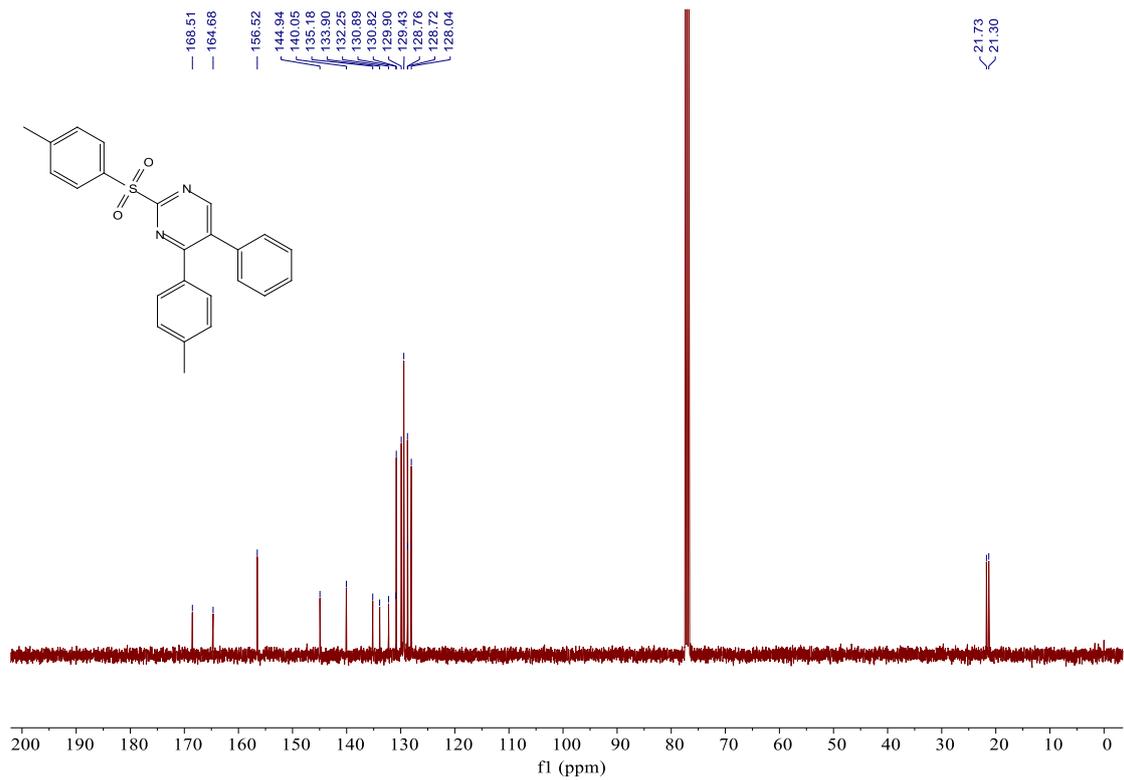
5-(naphthalen-2-yl)-4-phenyl-2-tosylpyrimidine(4i)



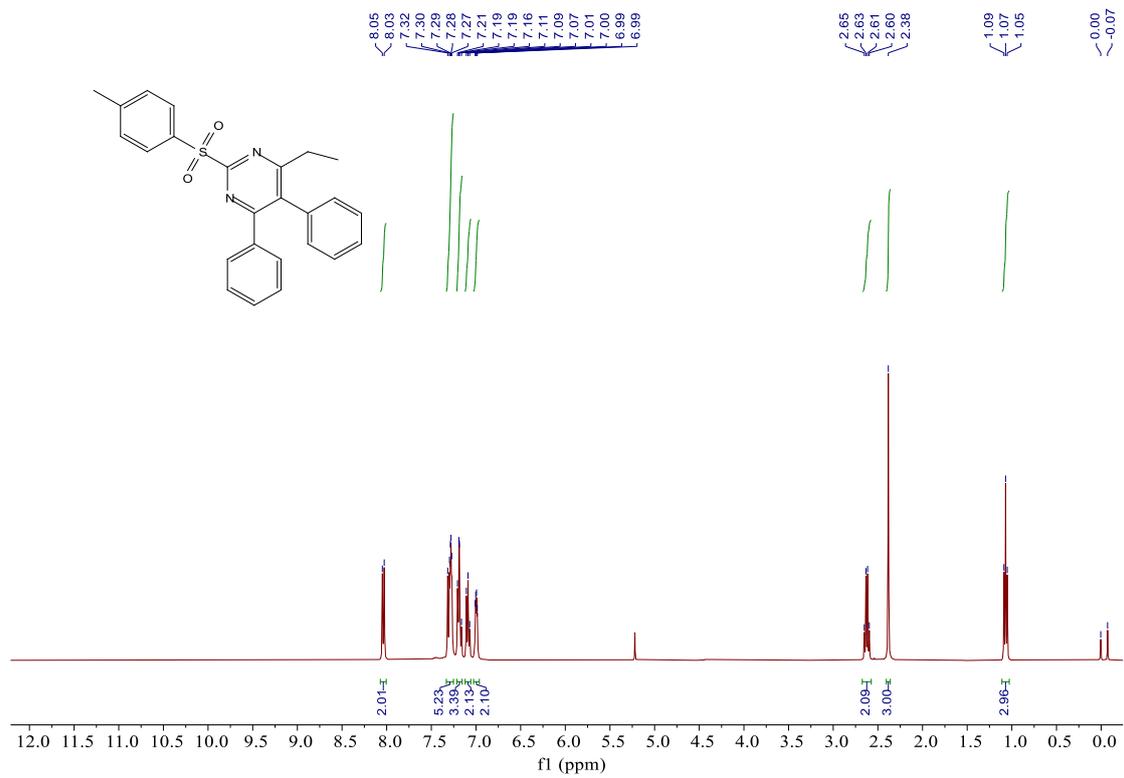


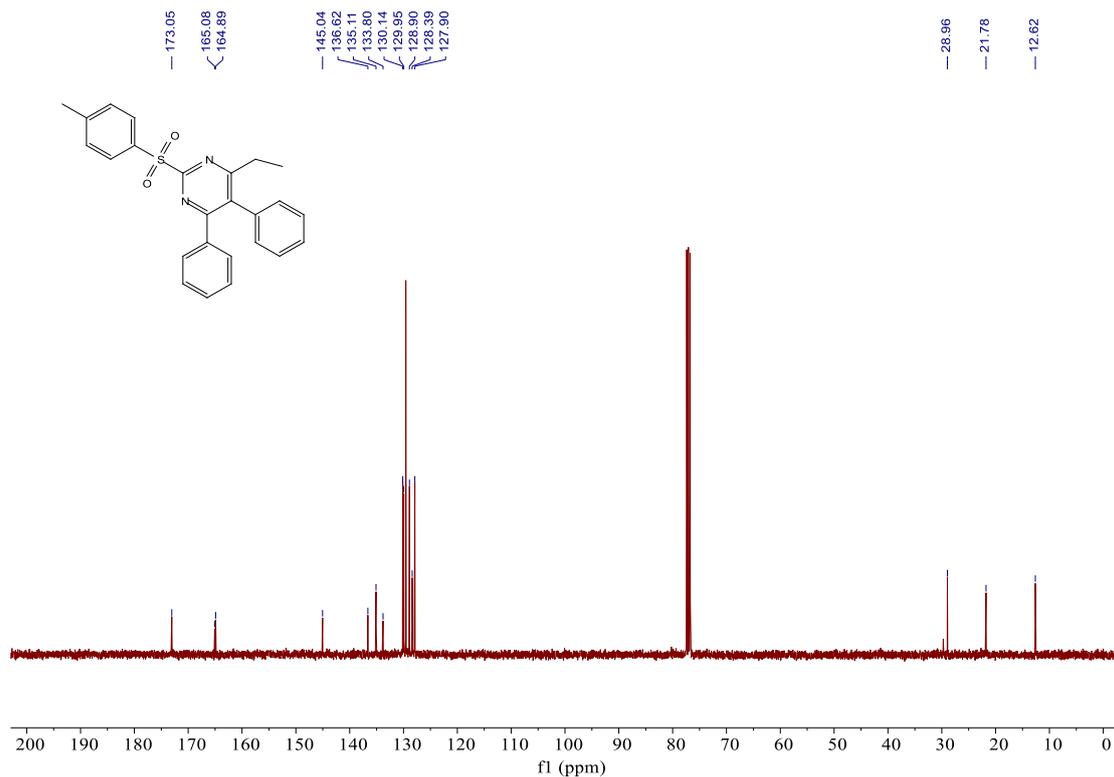
5-phenyl-4-(p-tolyl)-2-tosylpyrimidine(4j)



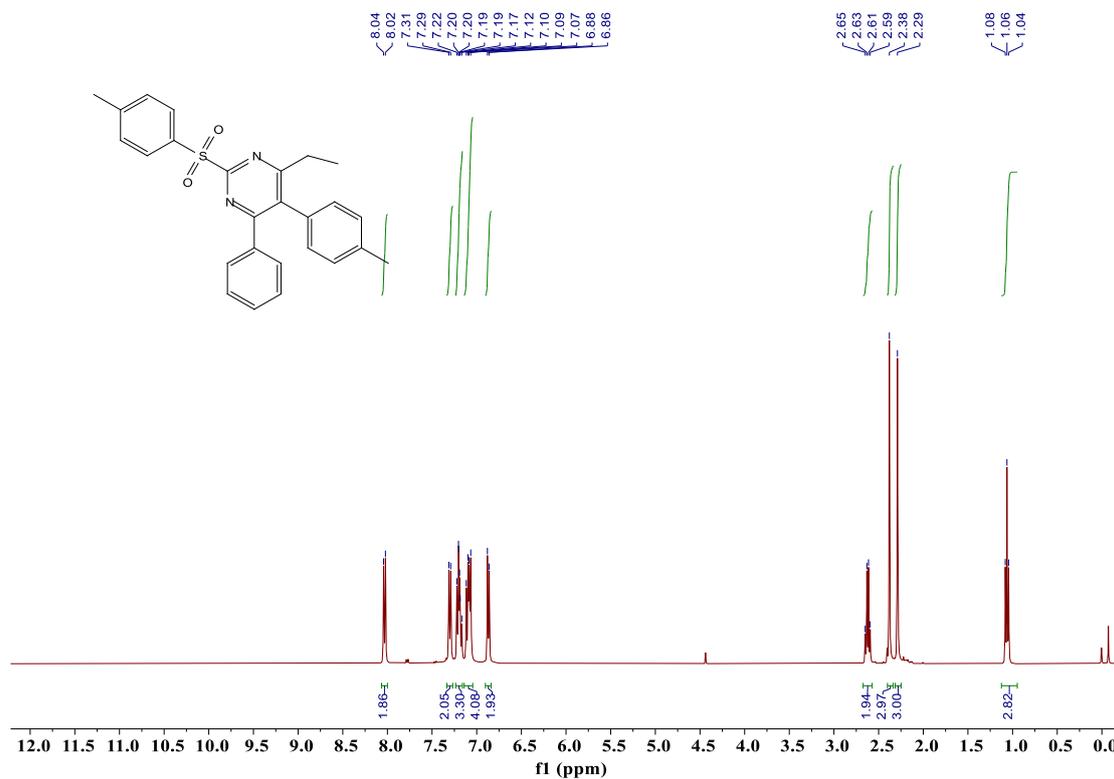


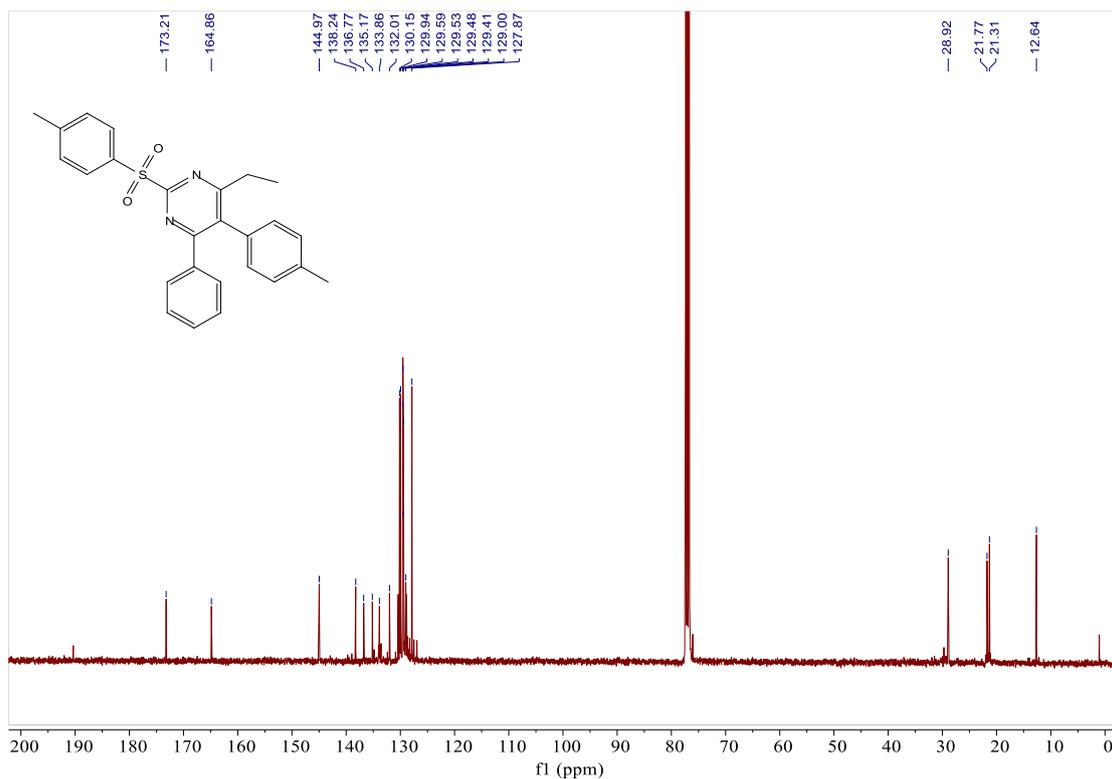
4-ethyl-5,6-diphenyl-2-tosylpyrimidine(4k)



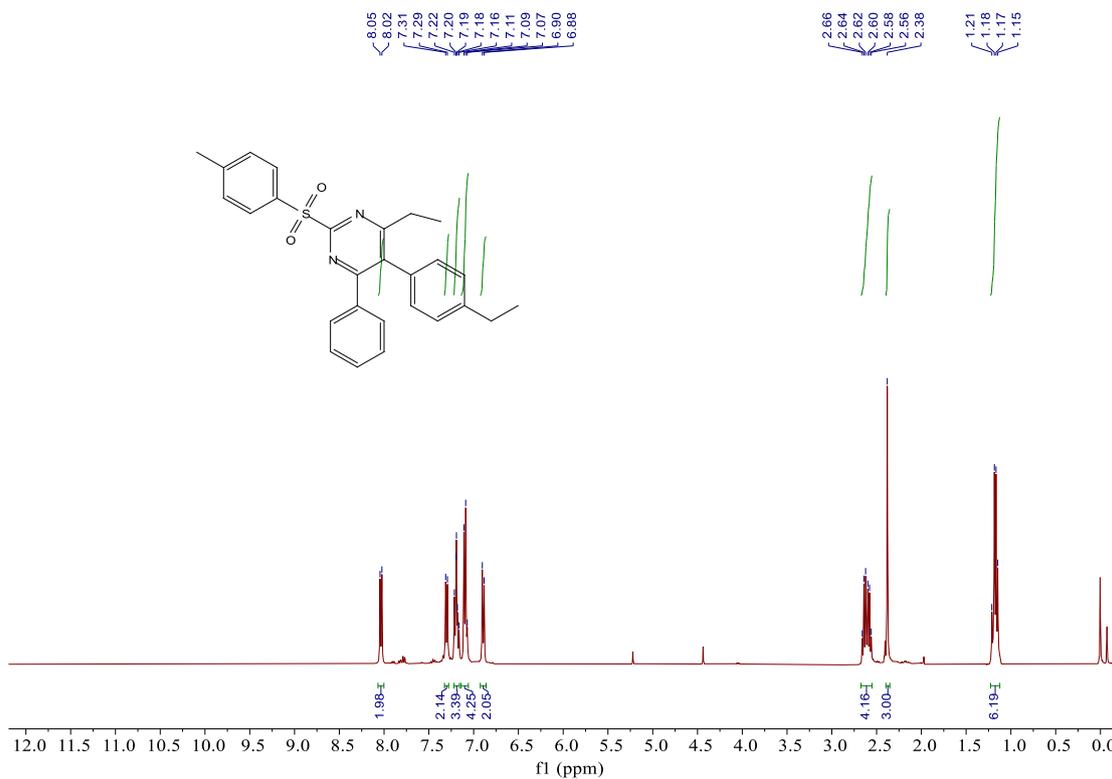


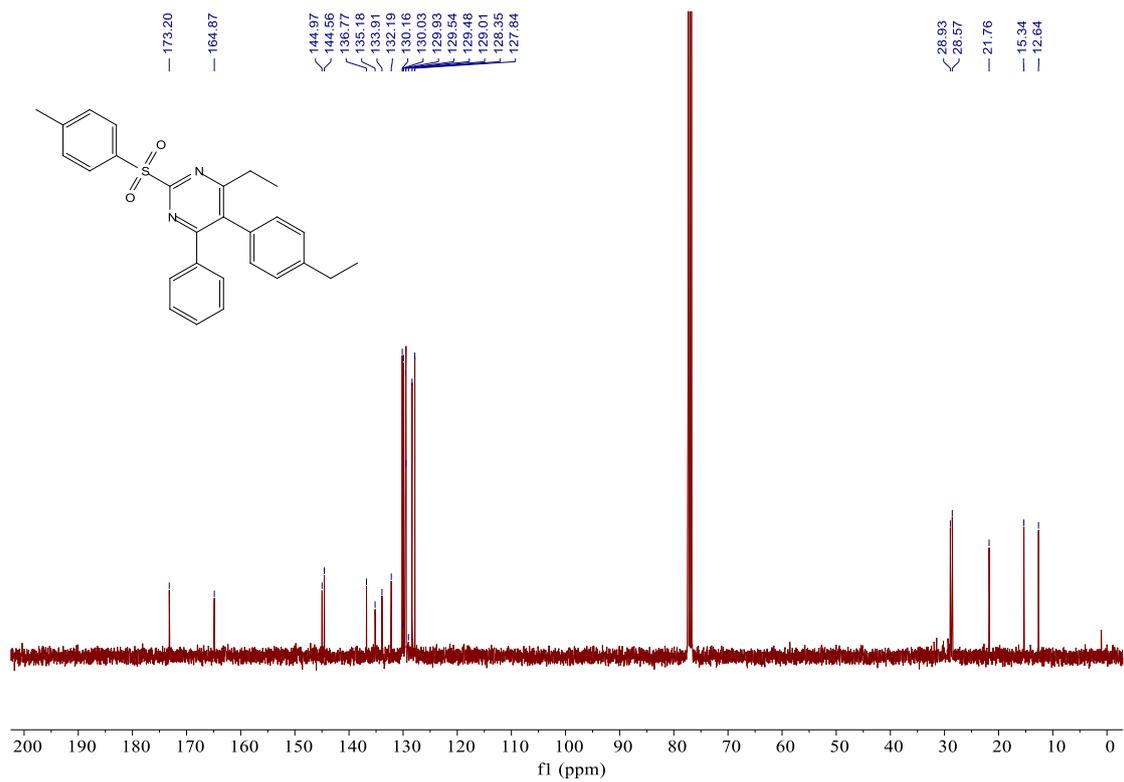
4-ethyl-6-phenyl-5-(p-tolyl)-2-tosylpyrimidine (4l)



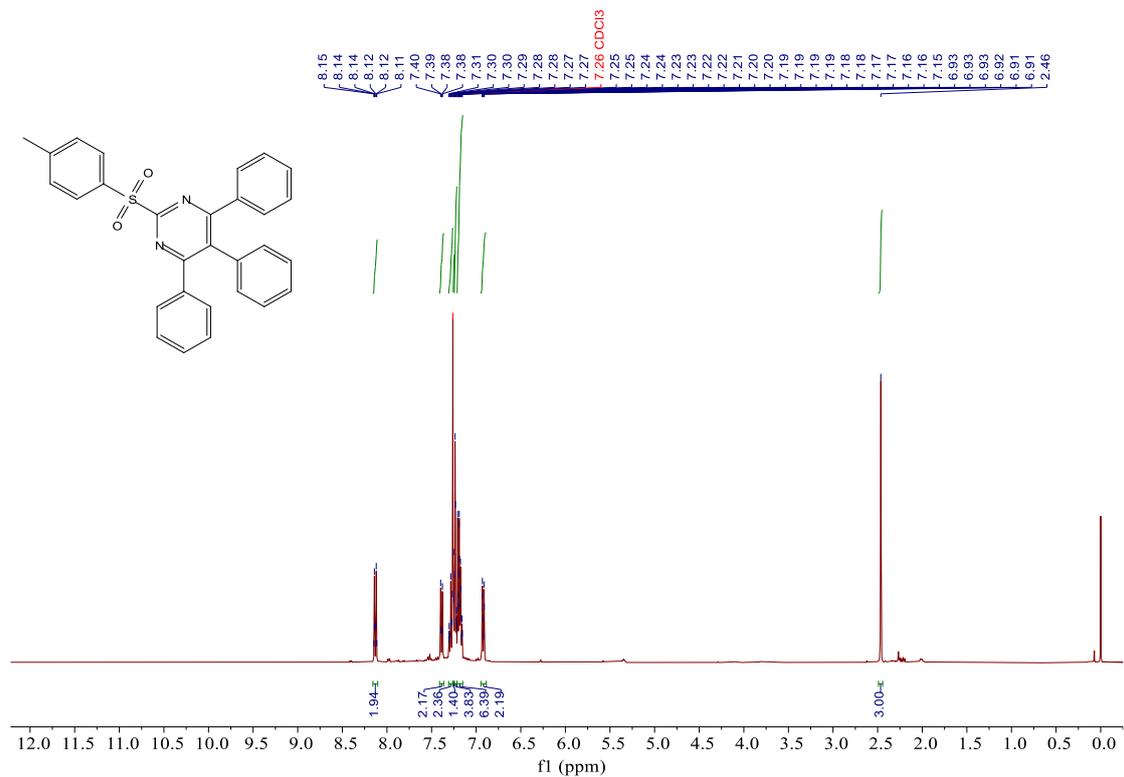


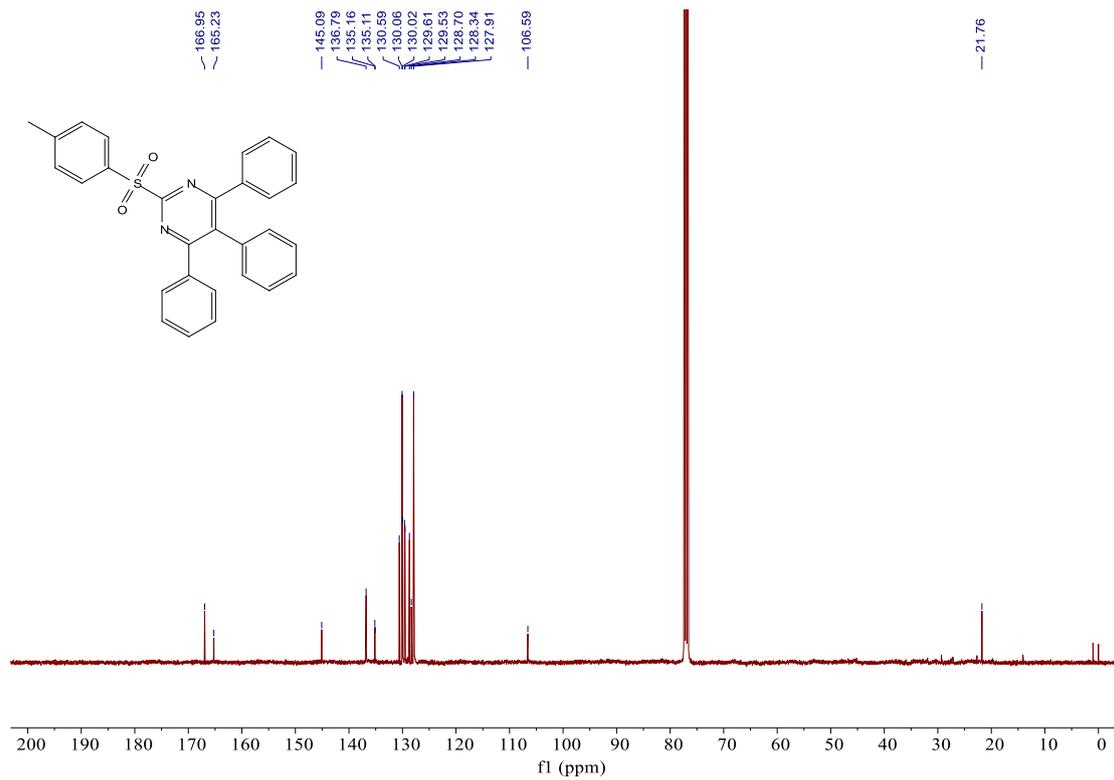
4-ethyl-5-(4-ethylphenyl)-6-phenyl-2-tosylpyrimidine(4m)



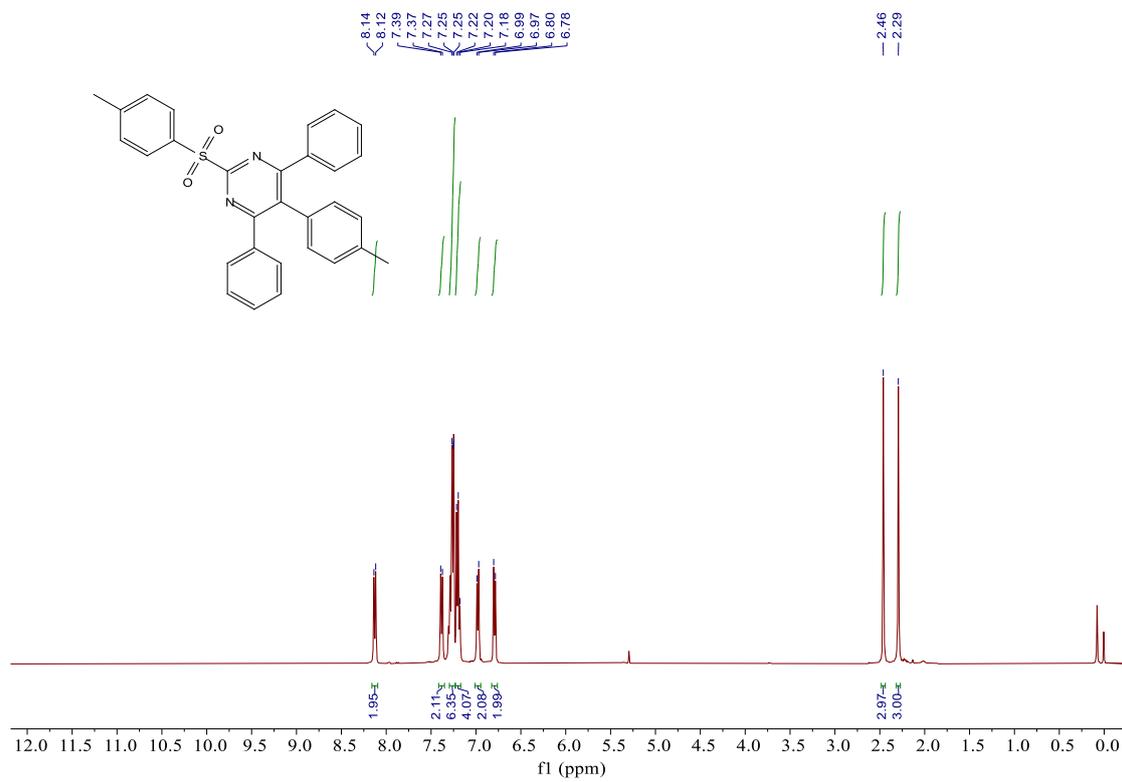


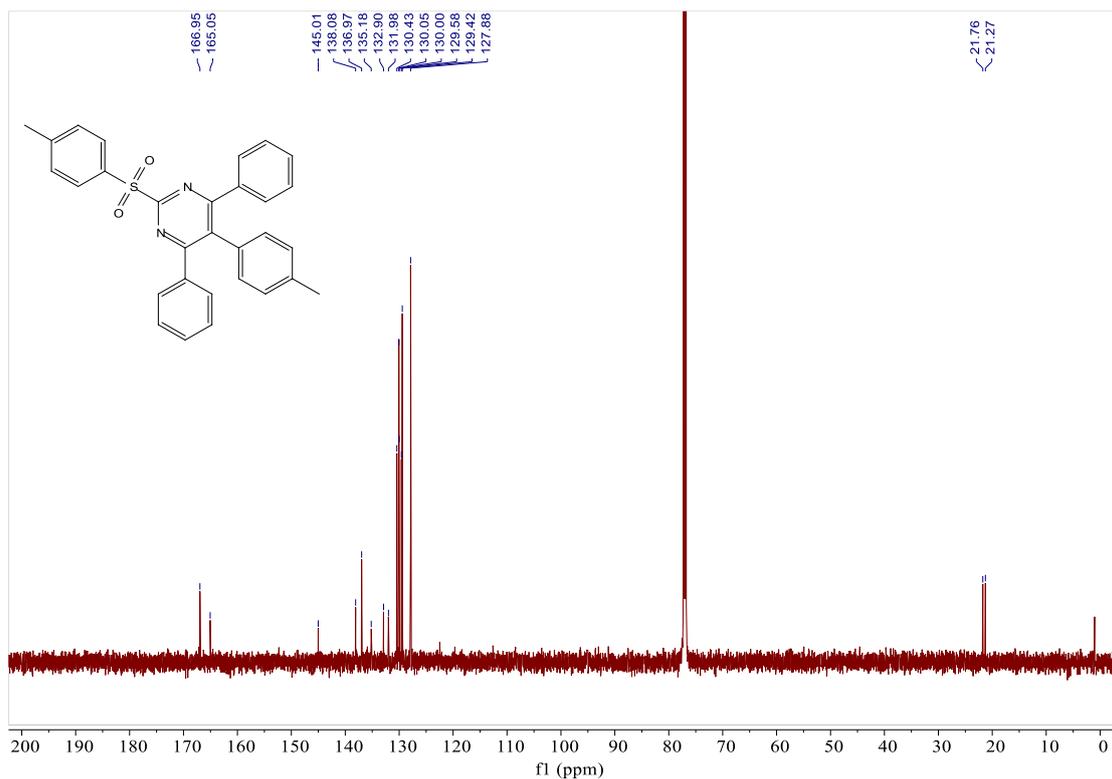
4,5,6-triphenyl-2-tosylpyrimidine(4n)



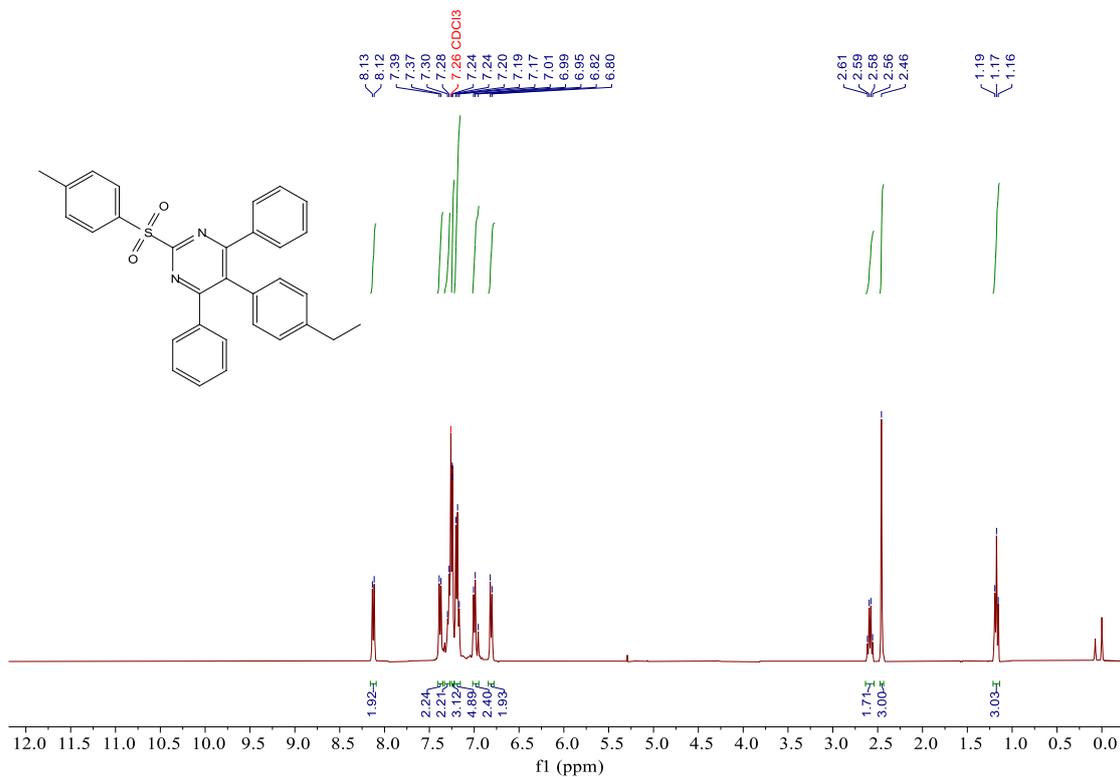


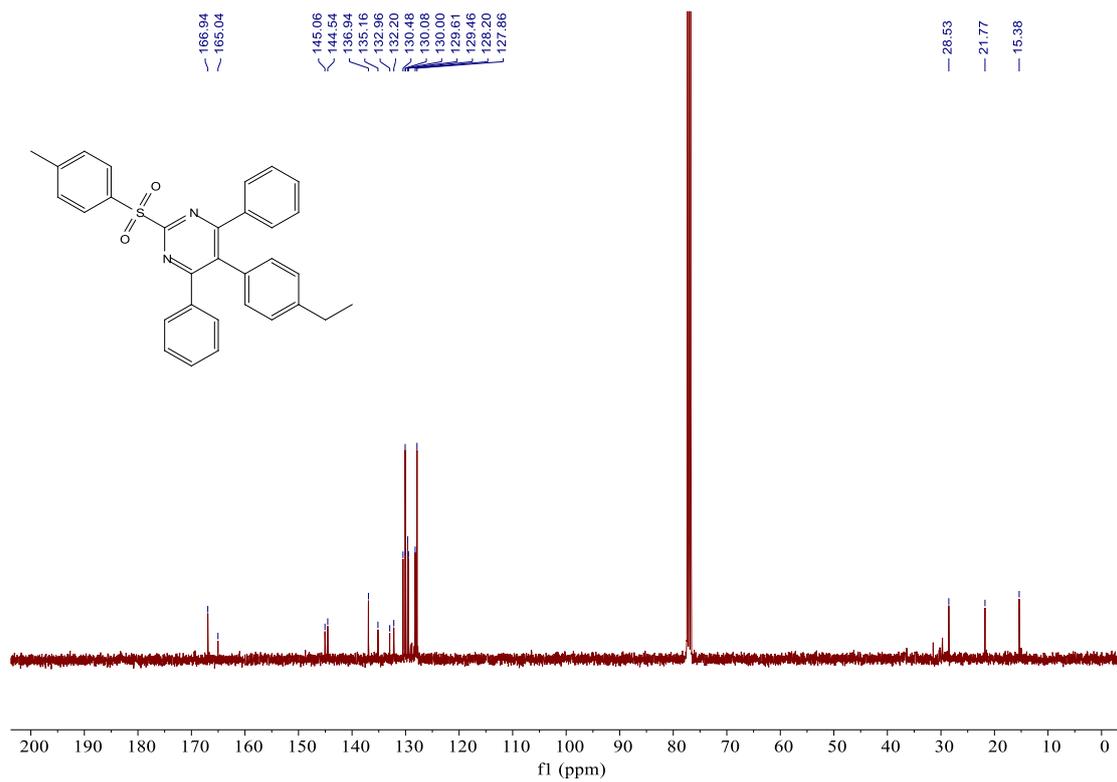
4,6-diphenyl-5-(p-tolyl)-2-tosylpyrimidine(4o)



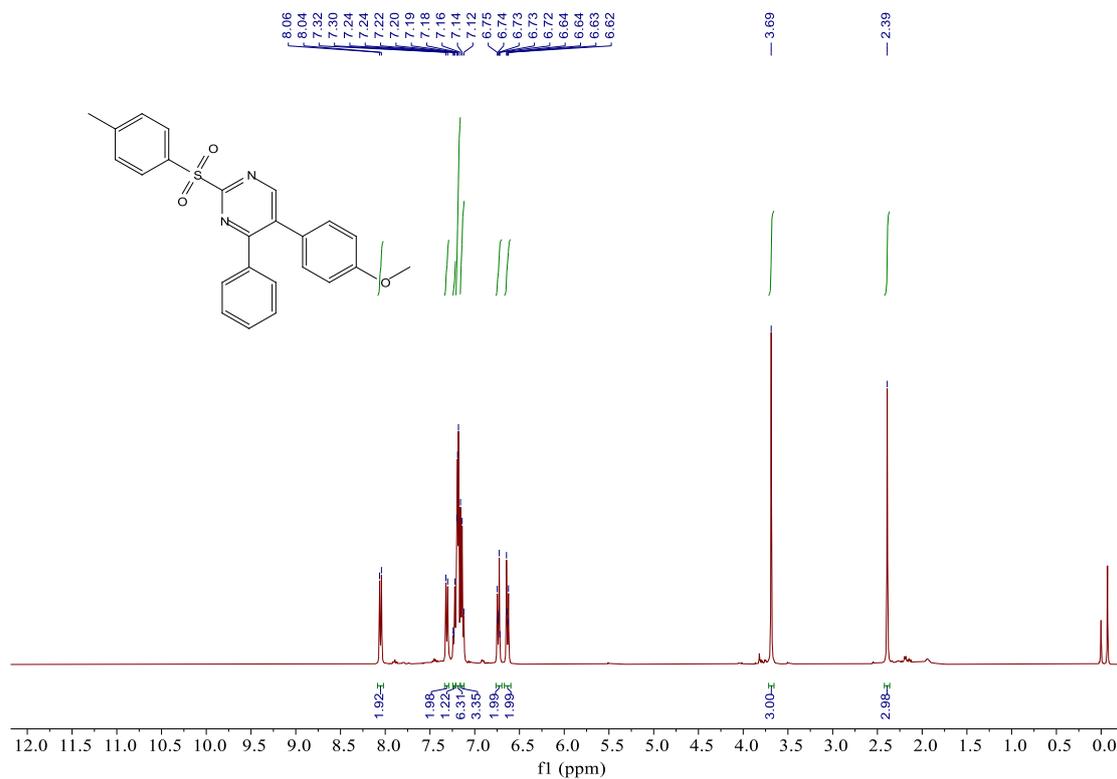


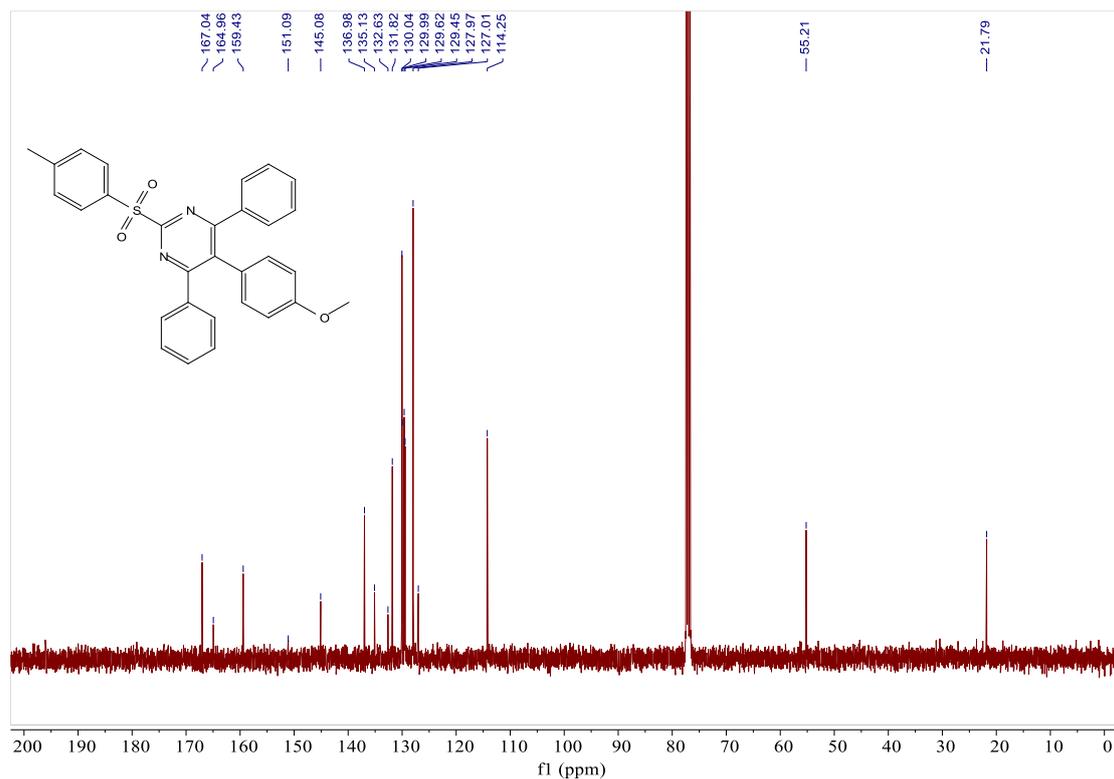
5-(4-ethylphenyl)-4,6-diphenyl-2-tosylpyrimidine(4p)



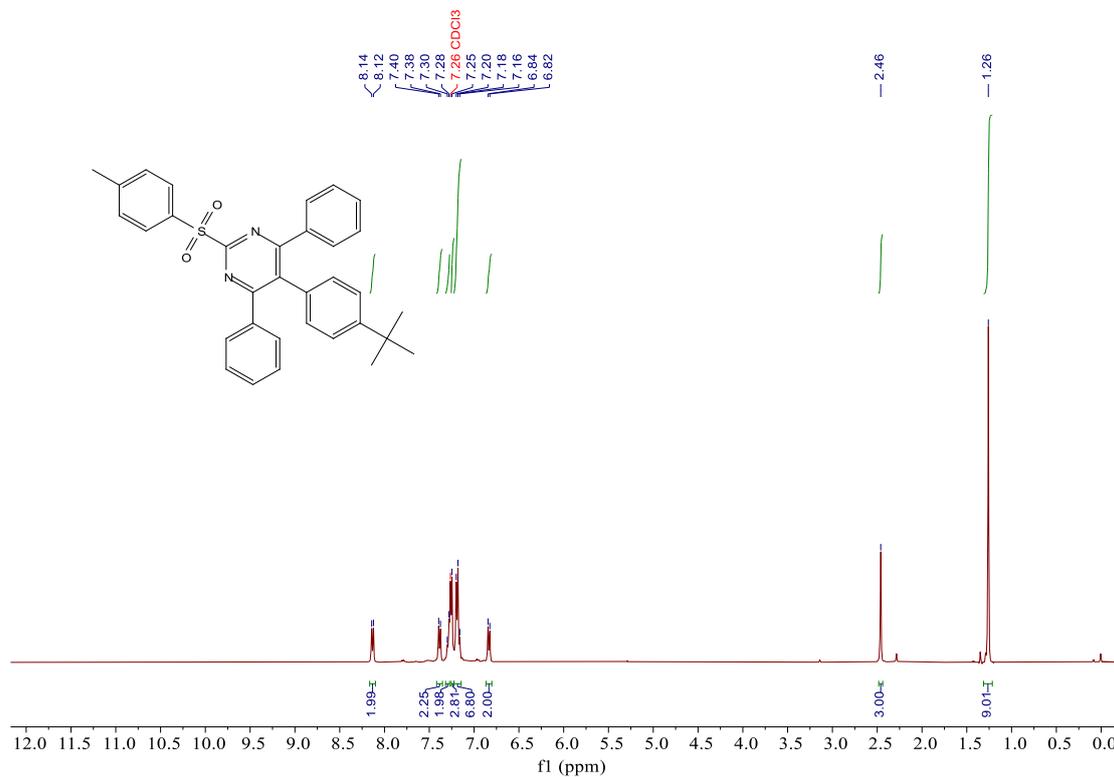


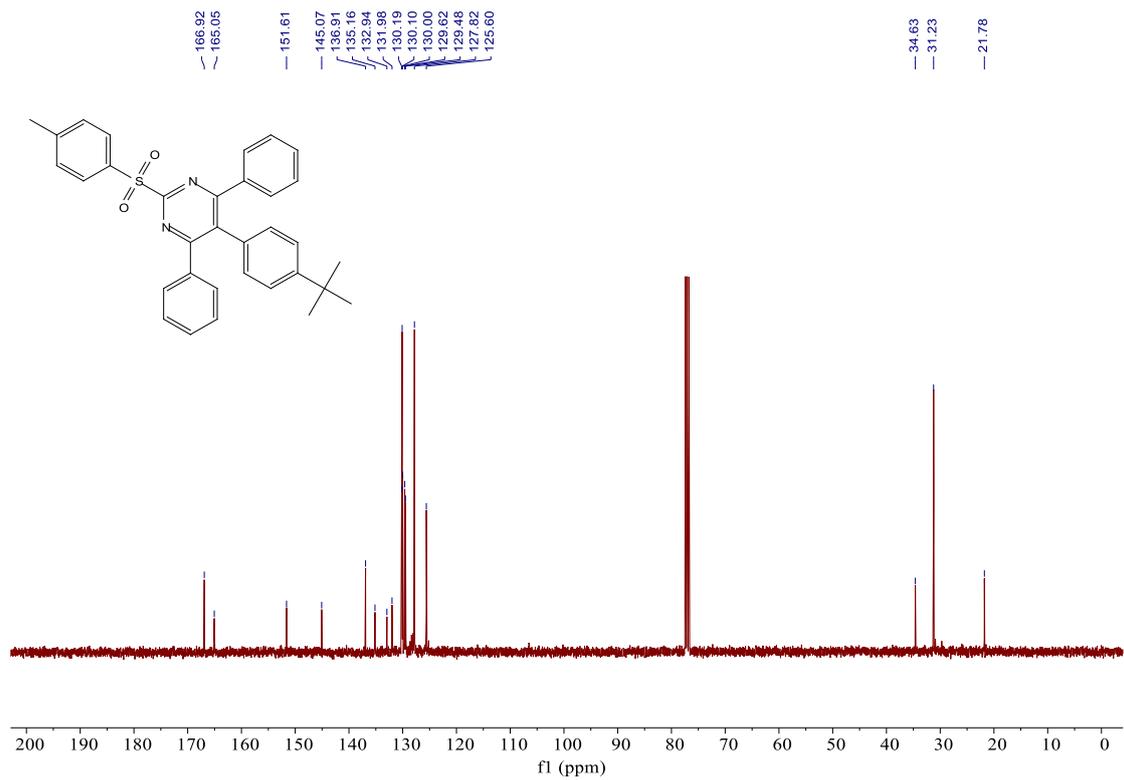
5-(4-methoxyphenyl)-4,6-diphenyl-2-tosylpyrimidine(4q)



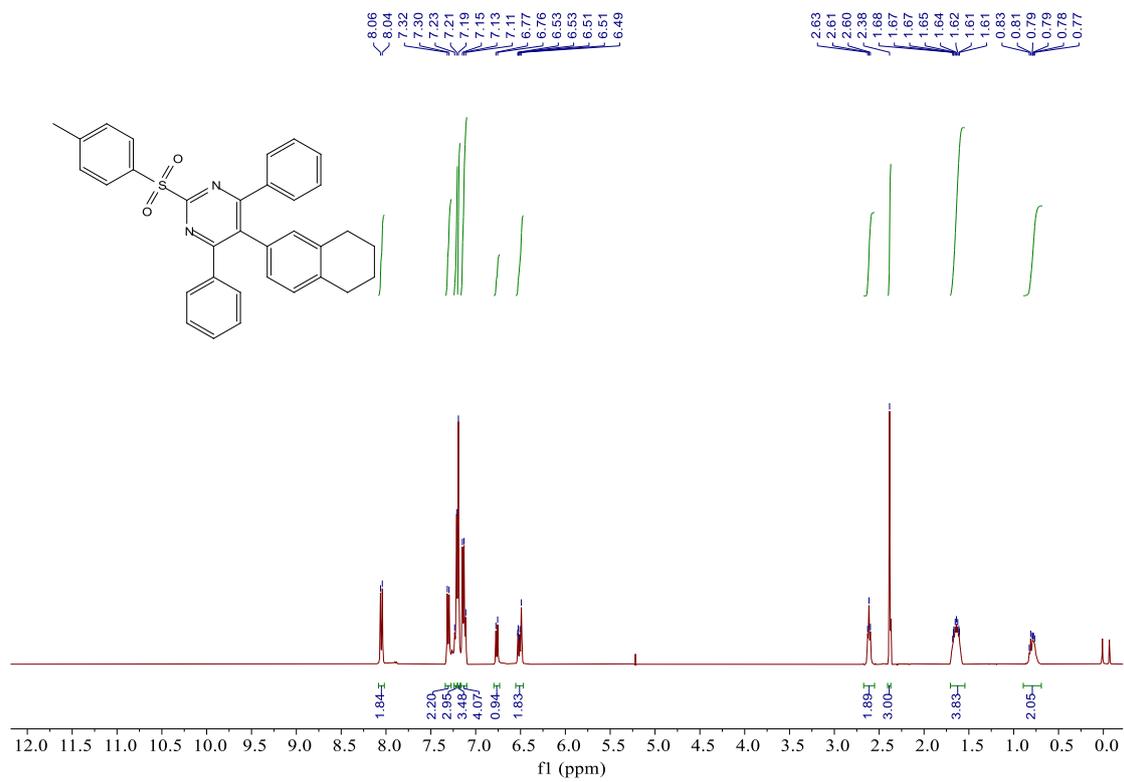


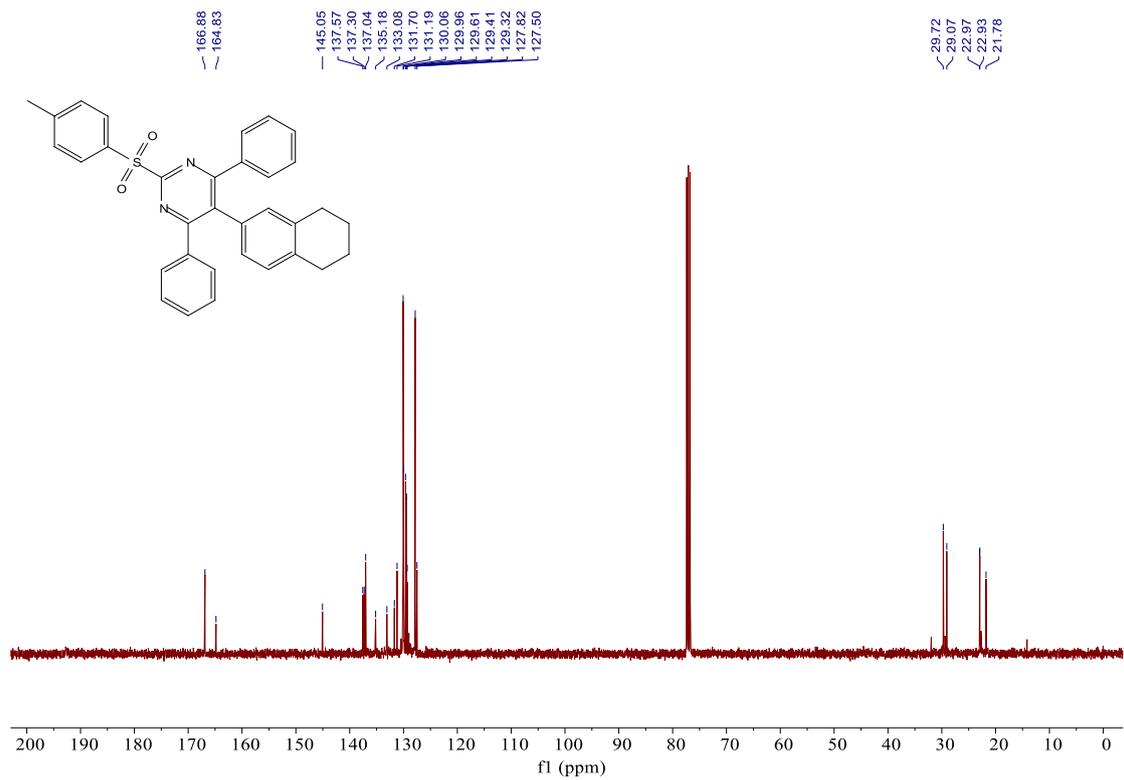
5-(4-(tert-butyl)phenyl)-4,6-diphenyl-2-tosylpyrimidine(4r)



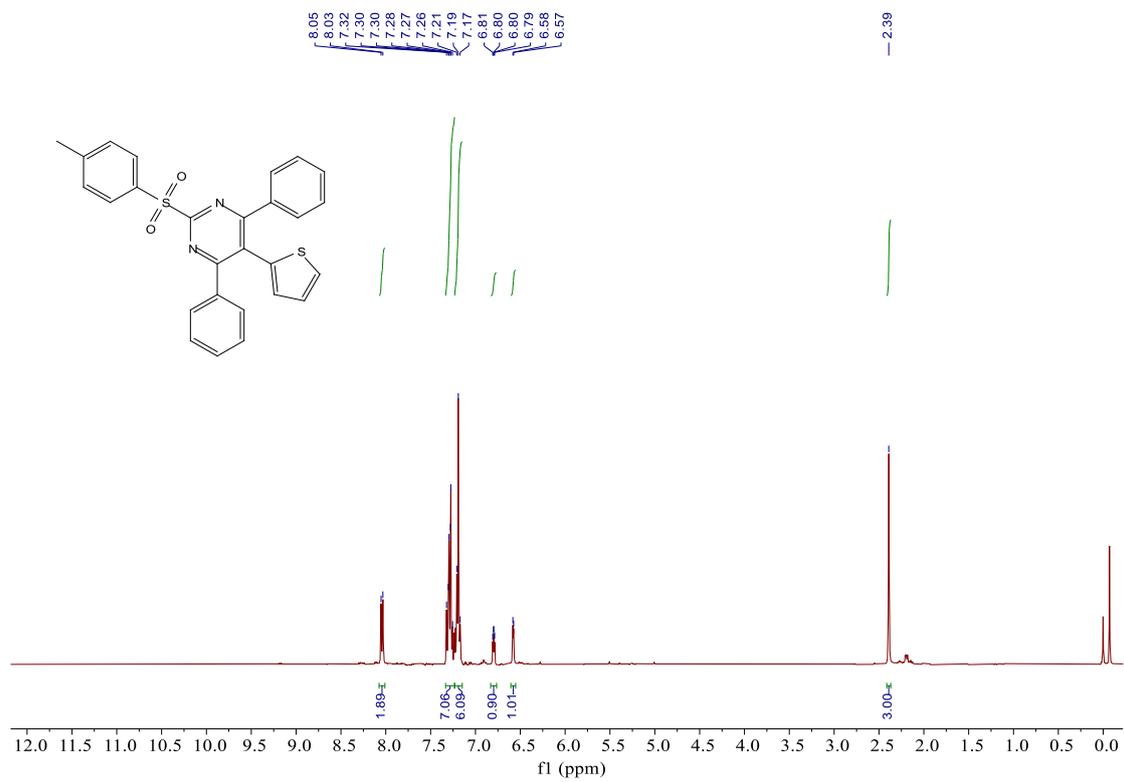


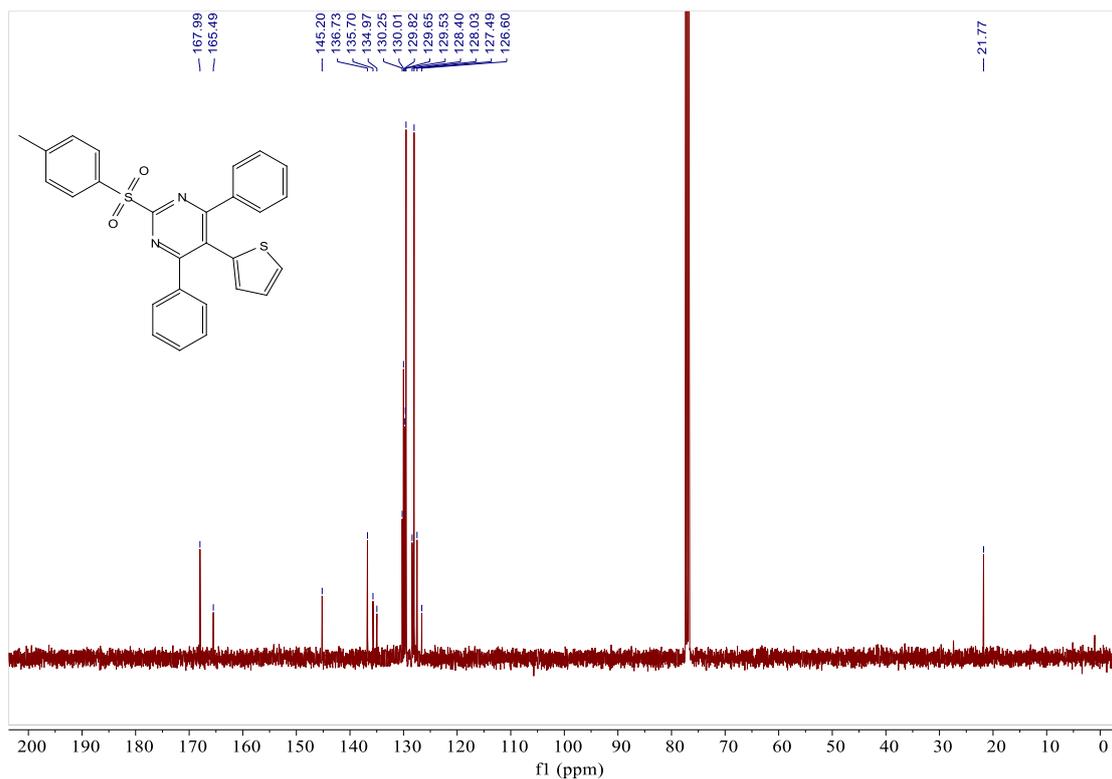
4,6-diphenyl-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-tosylpyrimidine(4s)



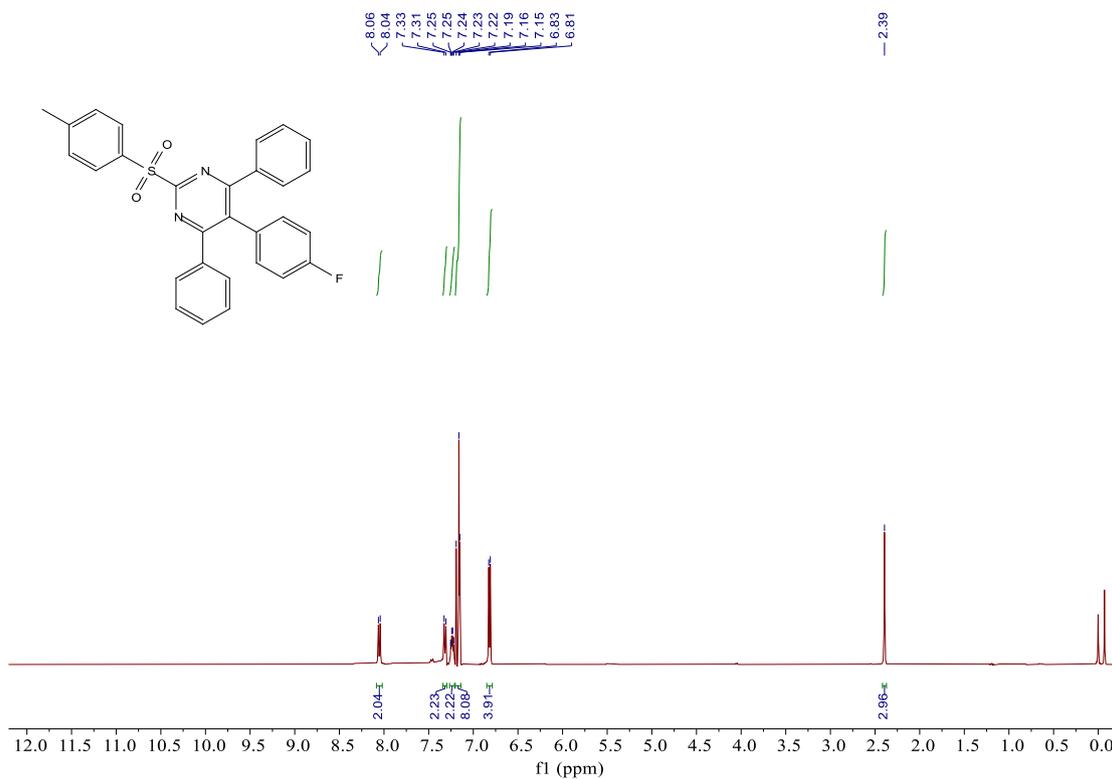


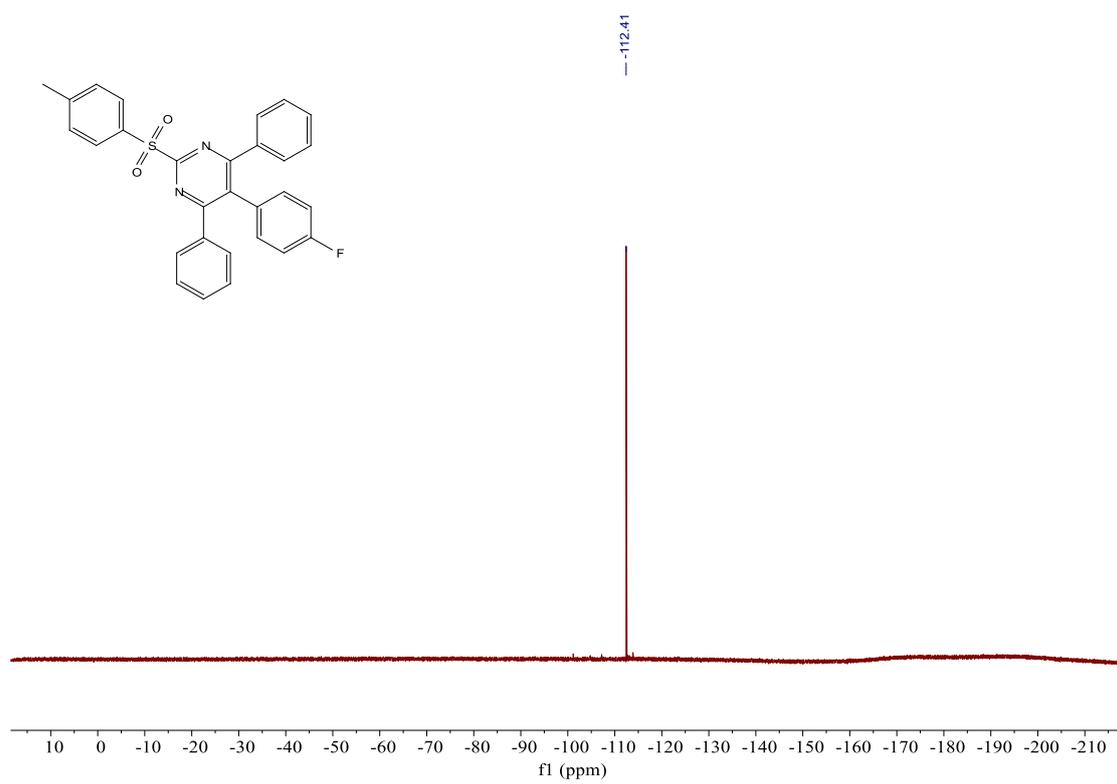
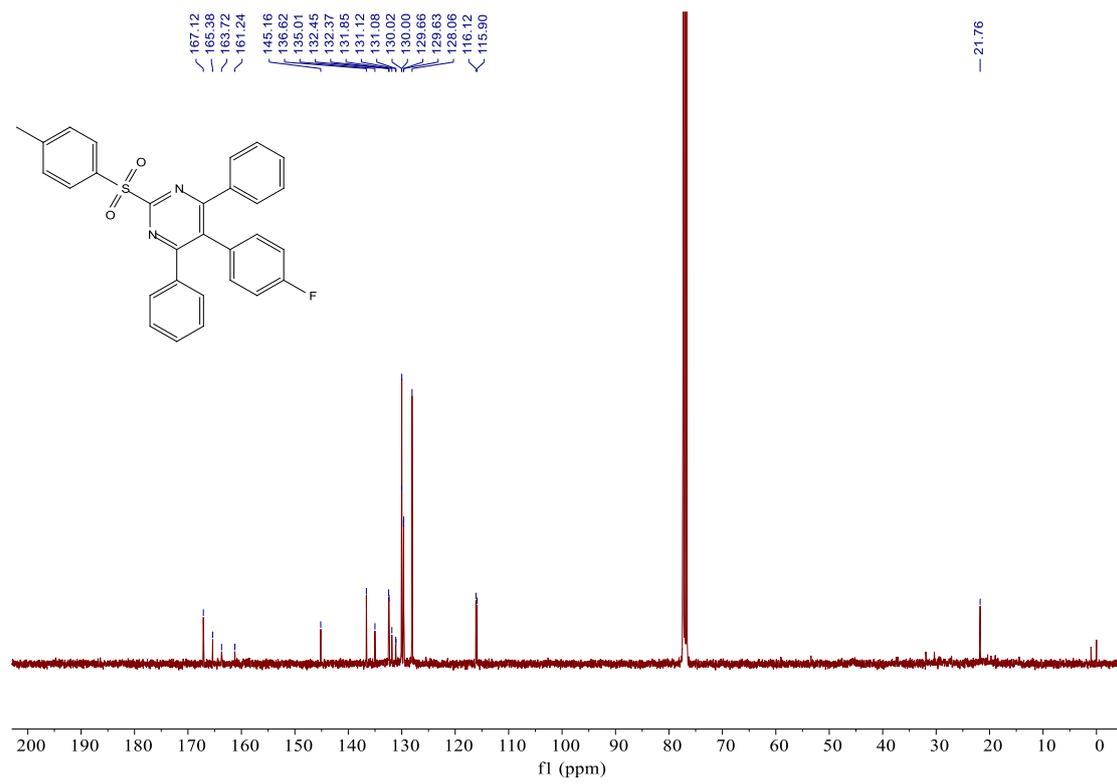
4,6-diphenyl-5-(thiophen-2-yl)-2-tosylpyrimidine(4t)



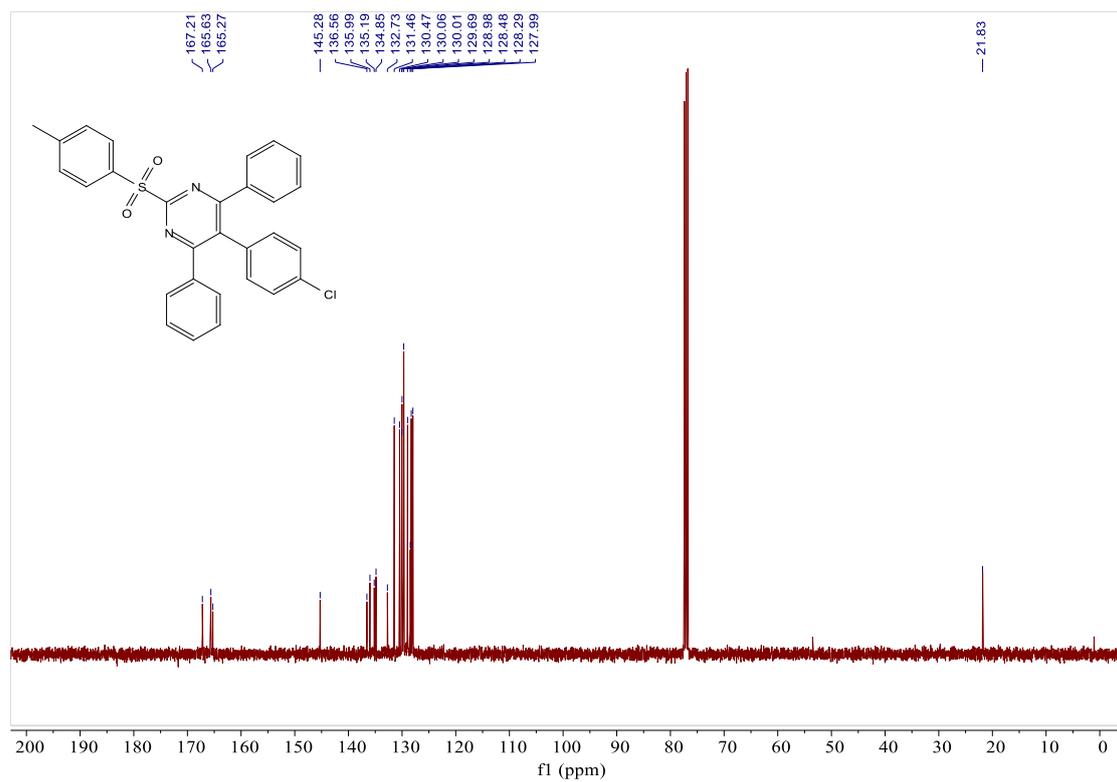
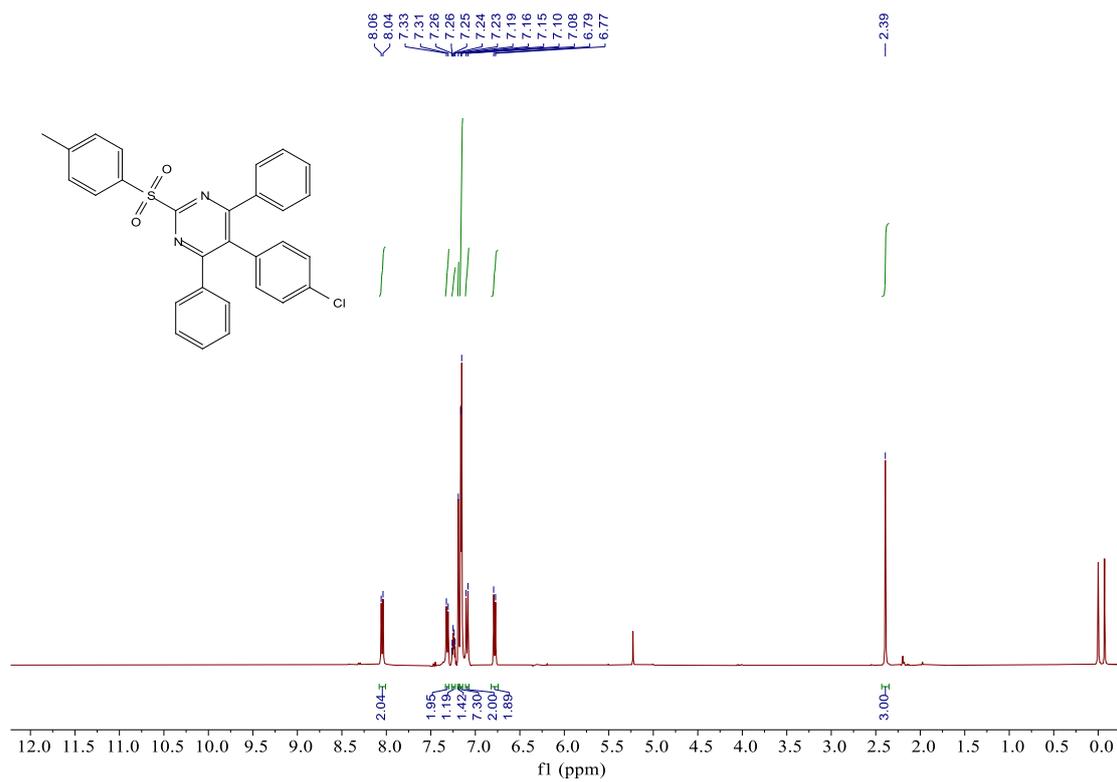


5-(4-fluorophenyl)-4,6-diphenyl-2-tosylpyrimidine(4u)

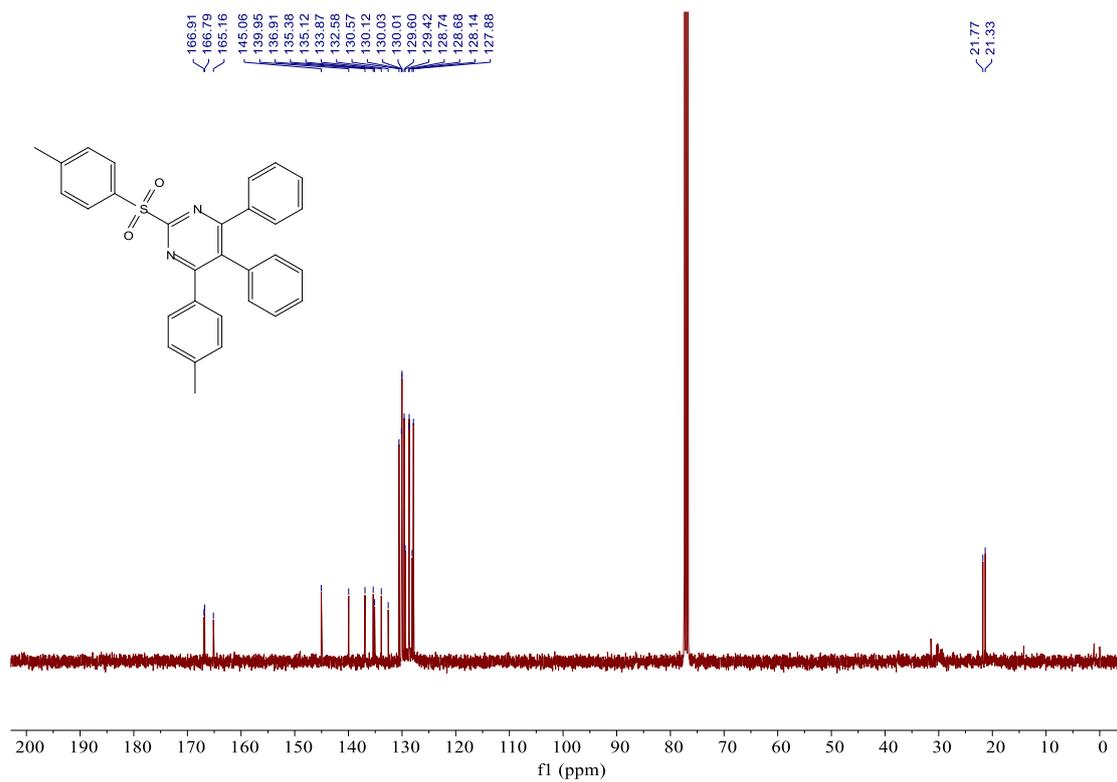
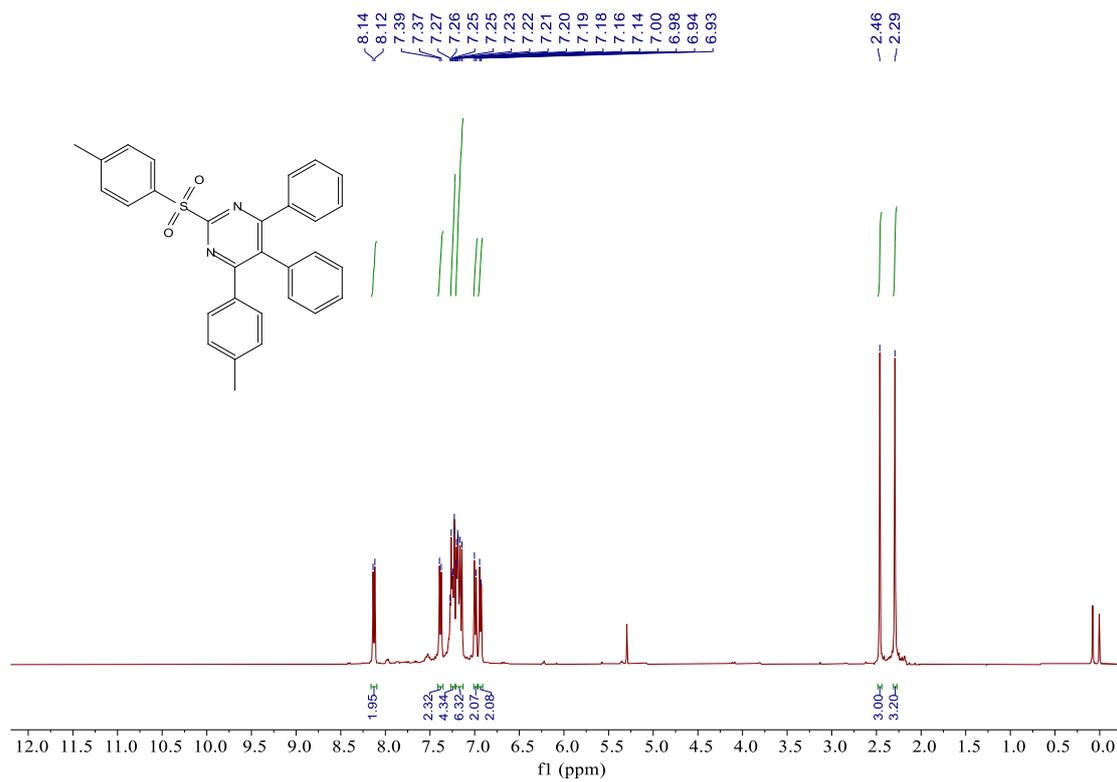




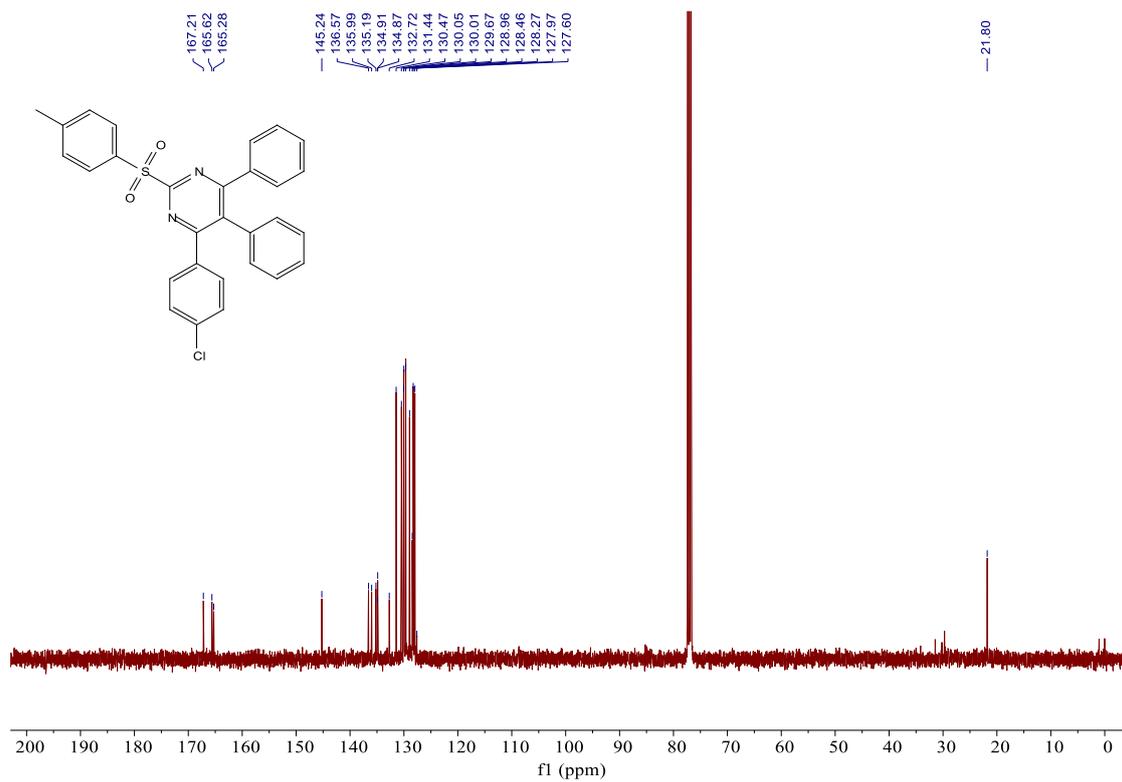
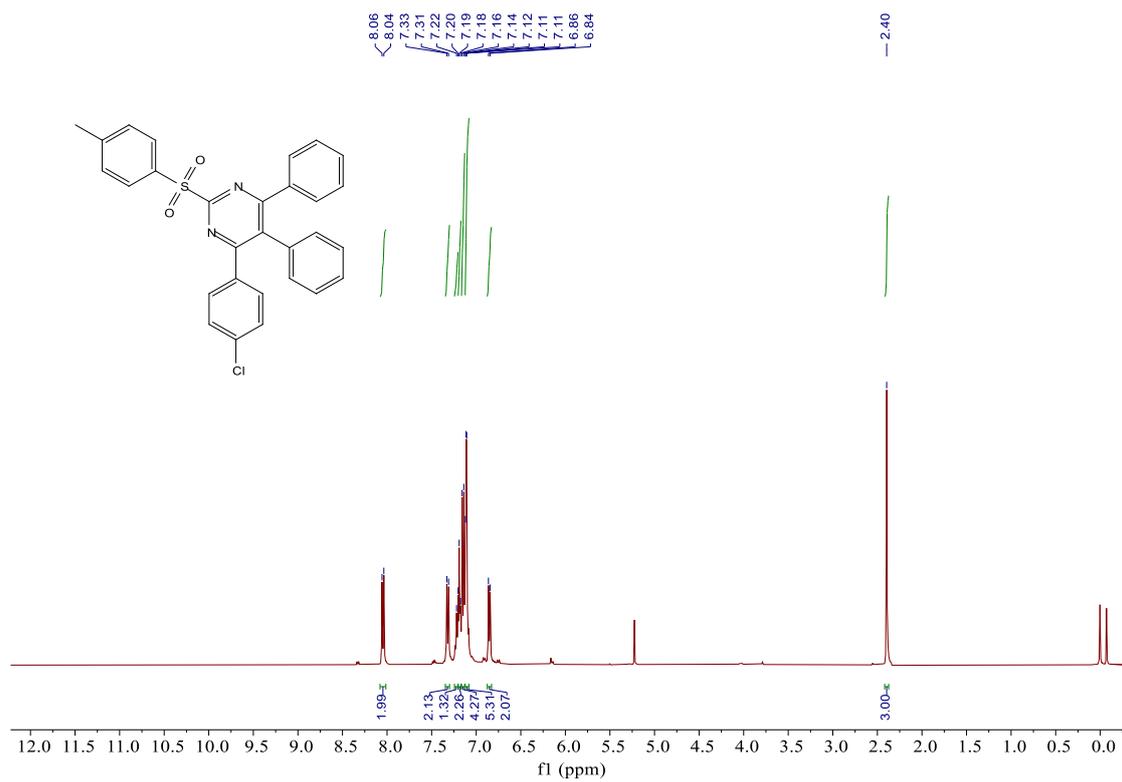
5-(4-chlorophenyl)-4,6-diphenyl-2-tosylpyrimidine(4v)



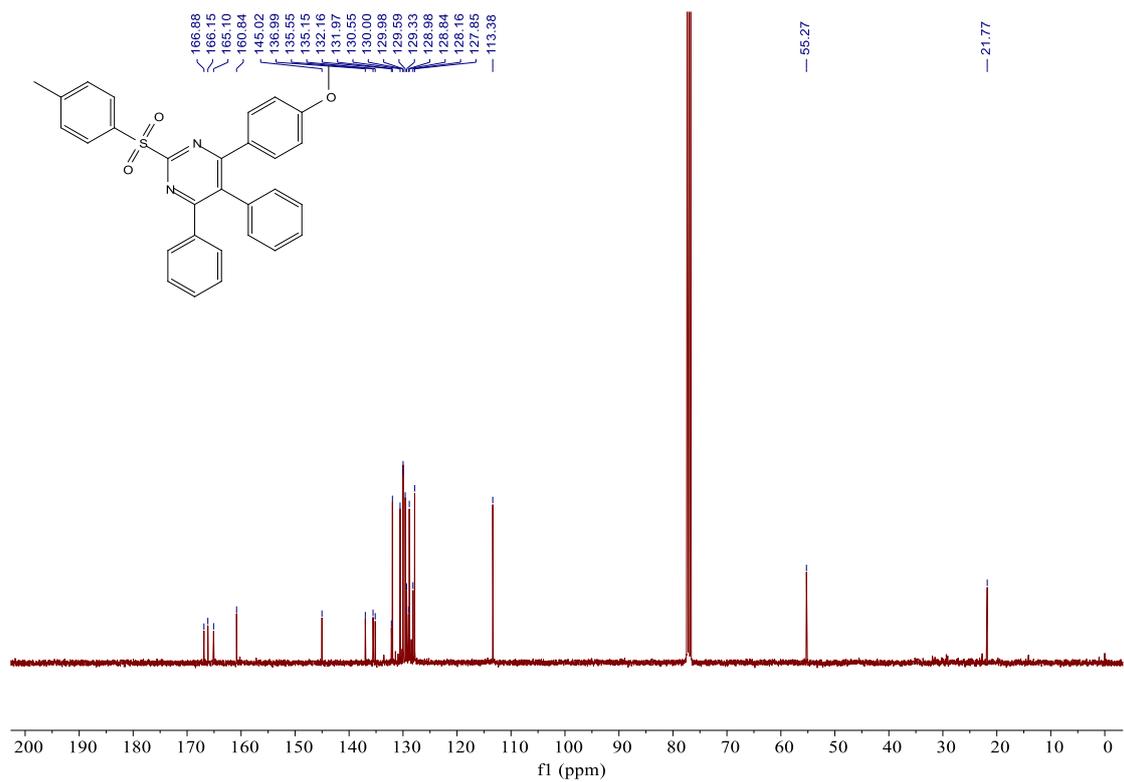
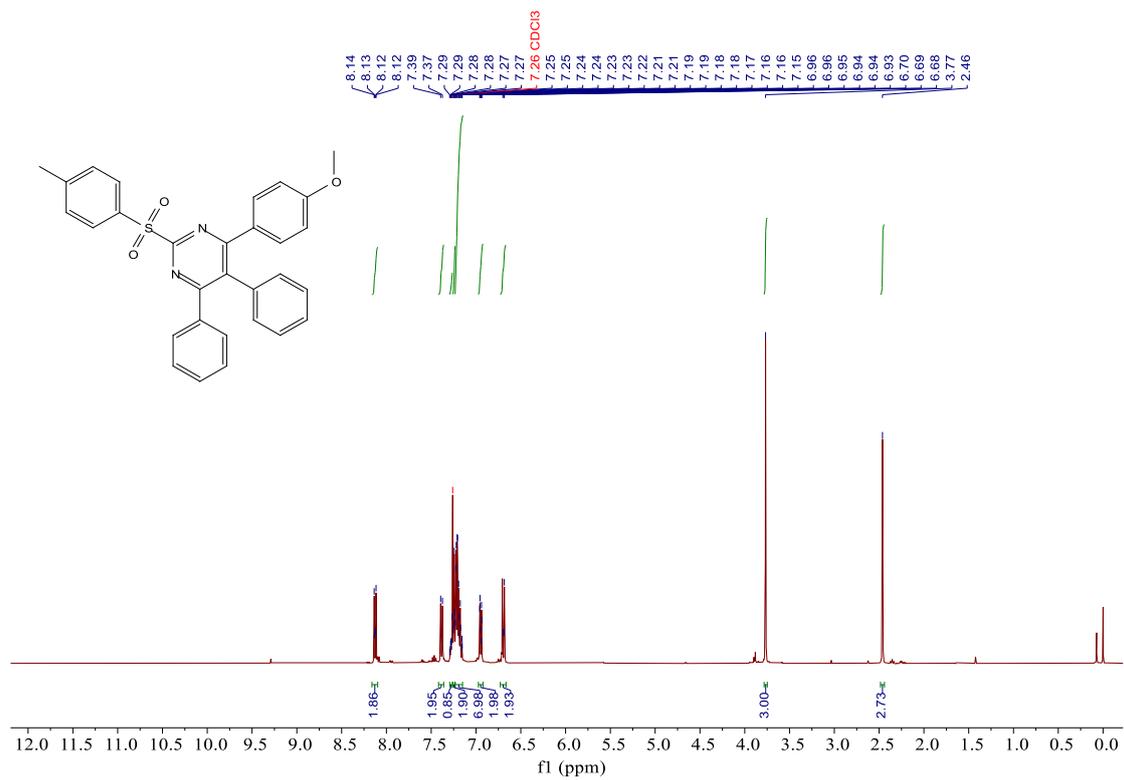
4,5-diphenyl-6-(p-tolyl)-2-tosylpyrimidine(4w)



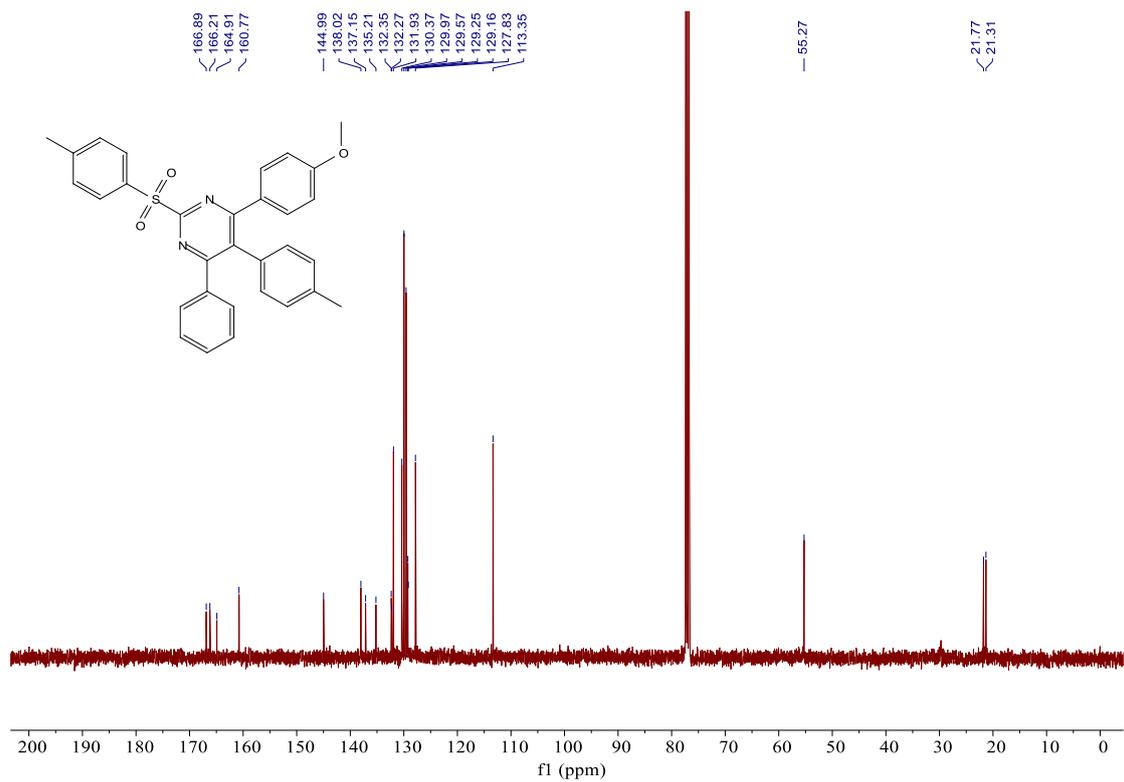
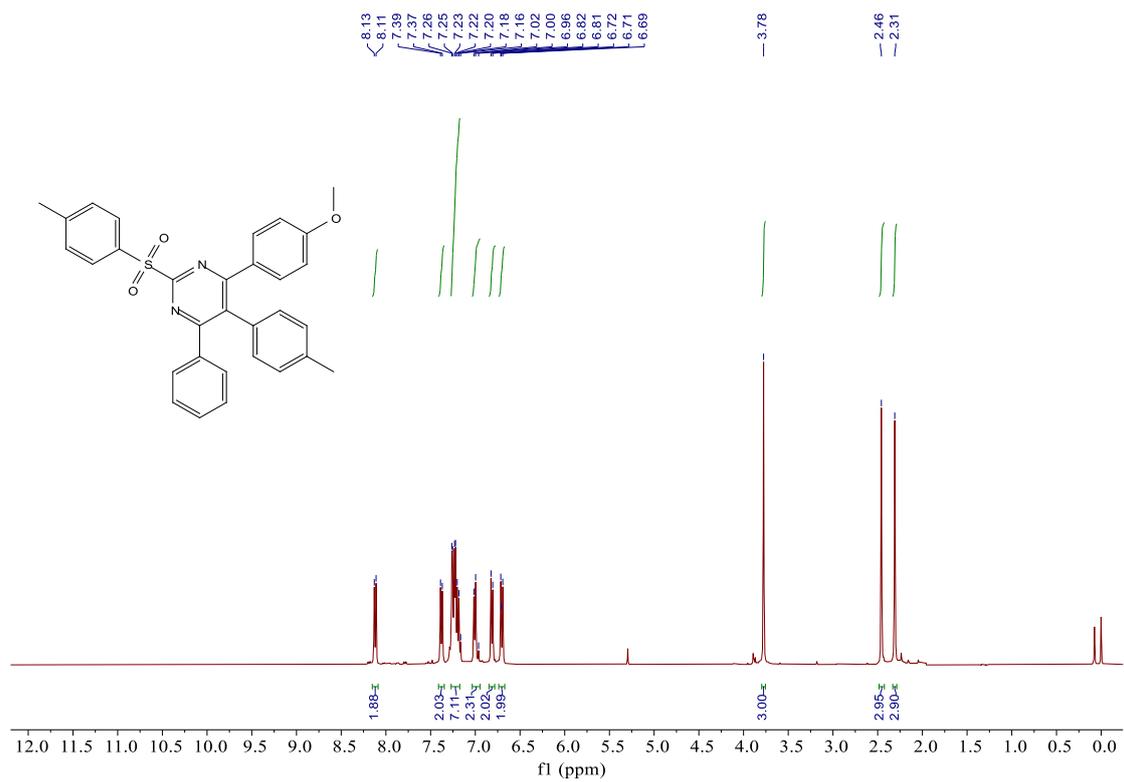
4-(4-chlorophenyl)-5,6-diphenyl-2-tosylpyrimidine(4x)



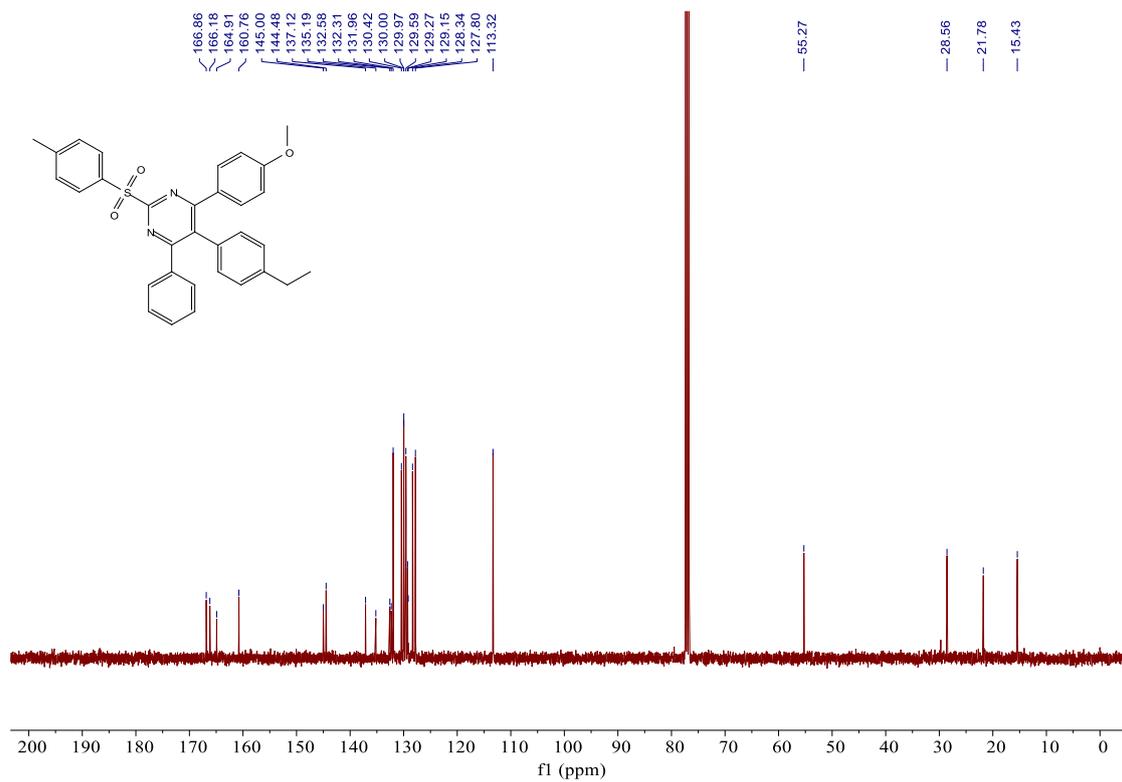
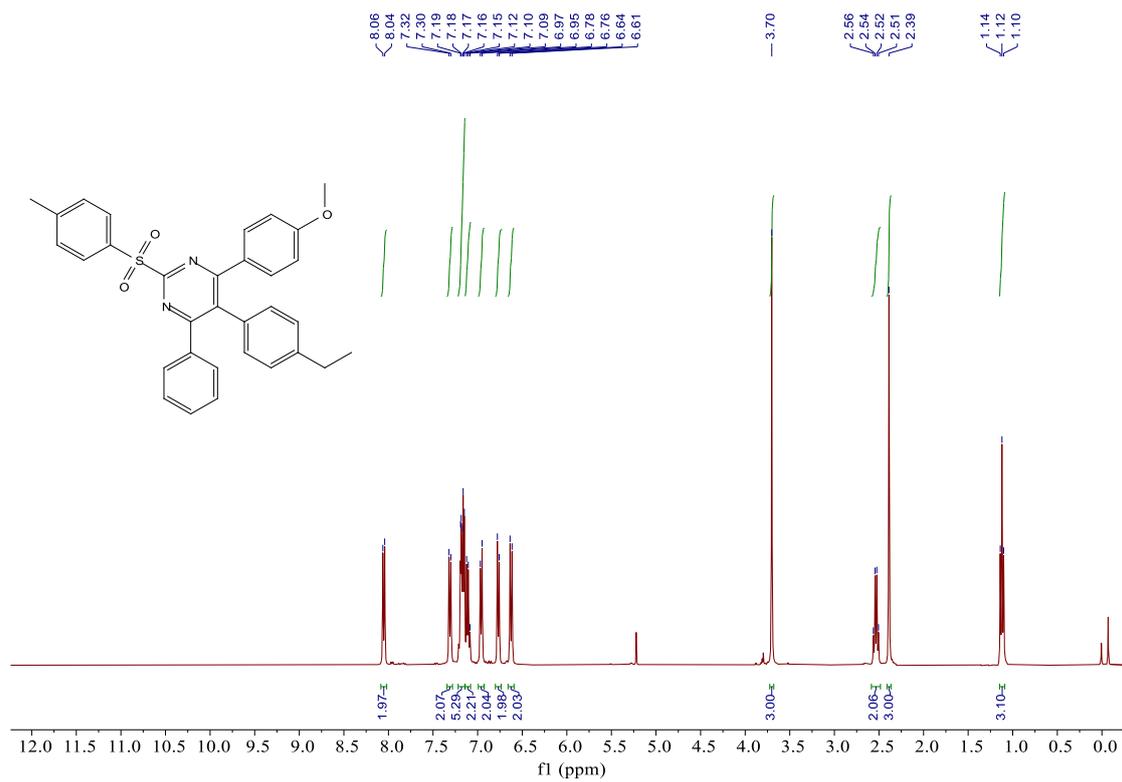
4-(4-methoxyphenyl)-5,6-diphenyl-2-tosylpyrimidine(4y)



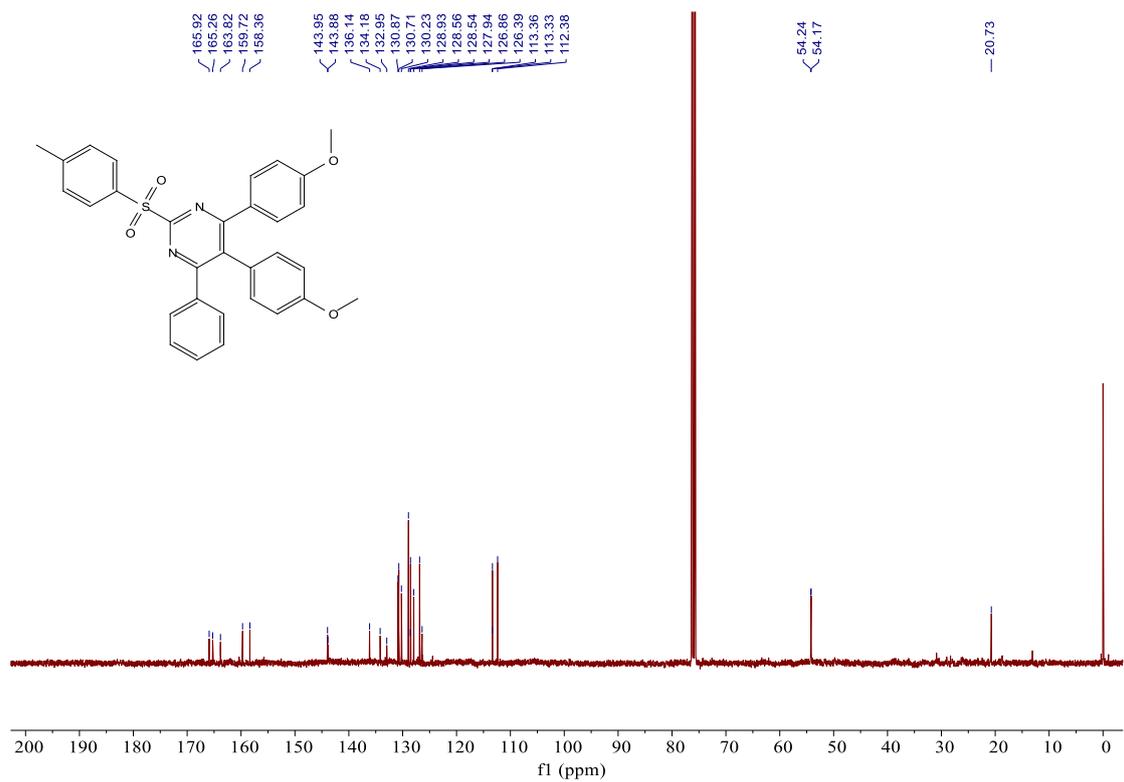
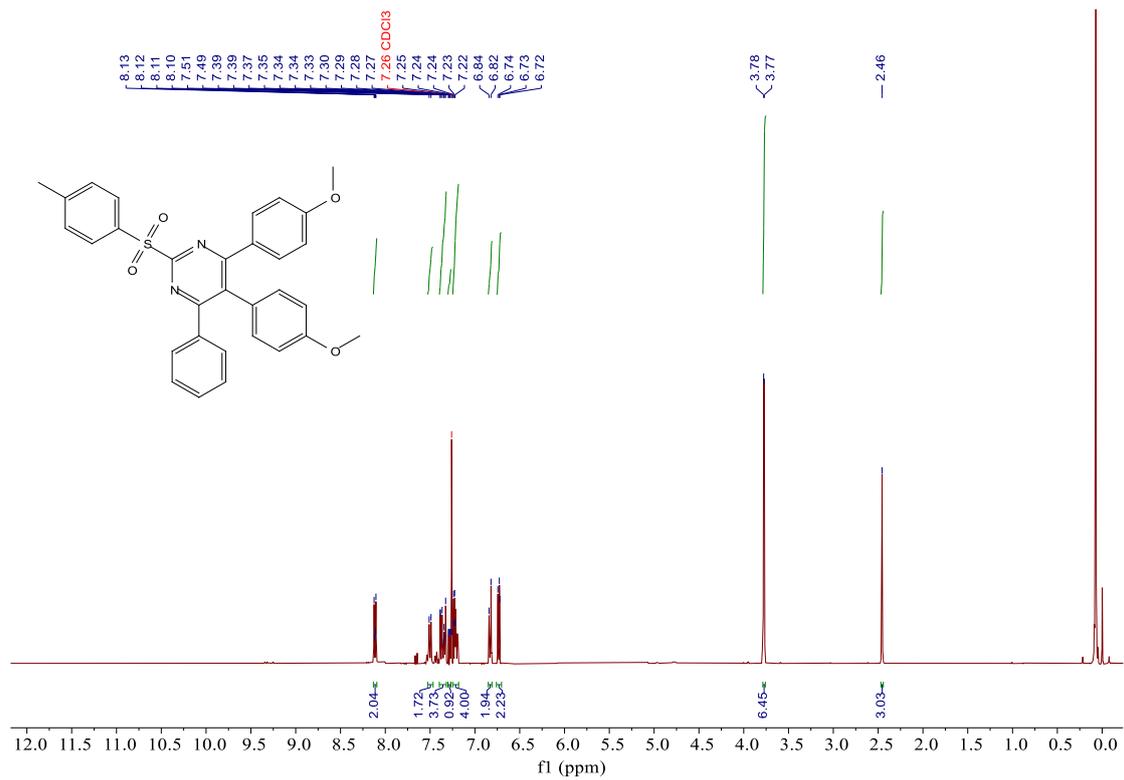
4-(4-methoxyphenyl)-5,6-diphenyl-2-tosylpyrimidine (4z)



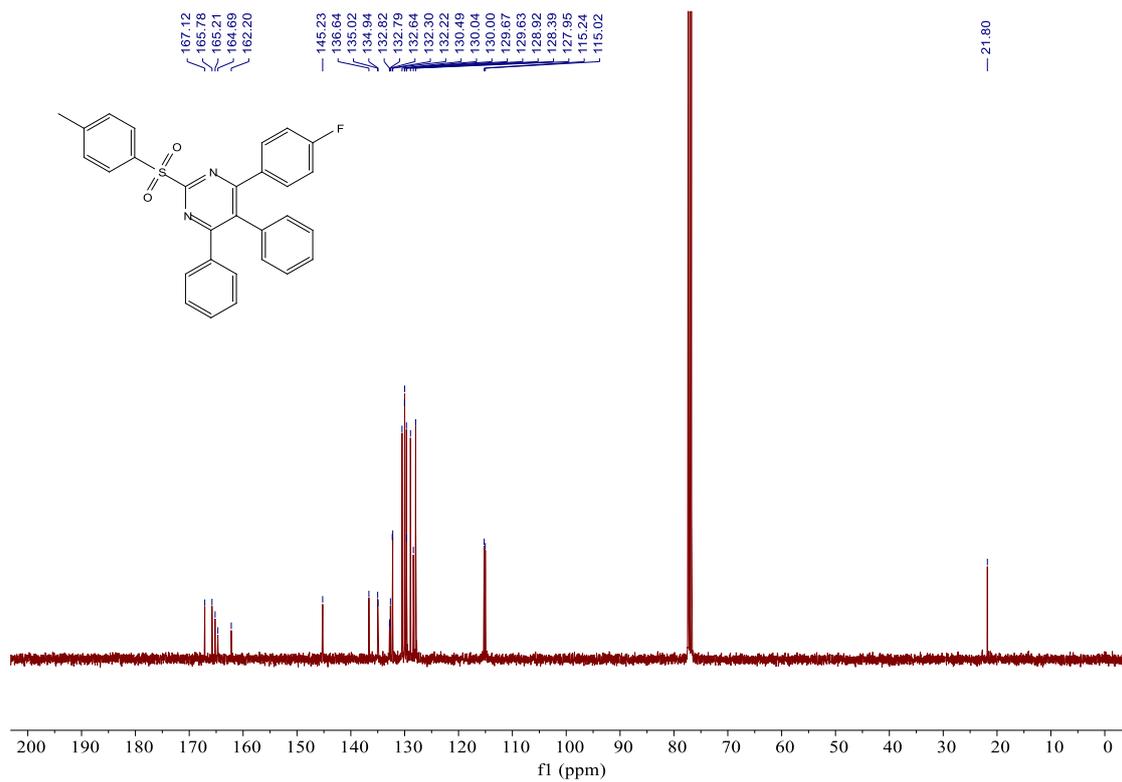
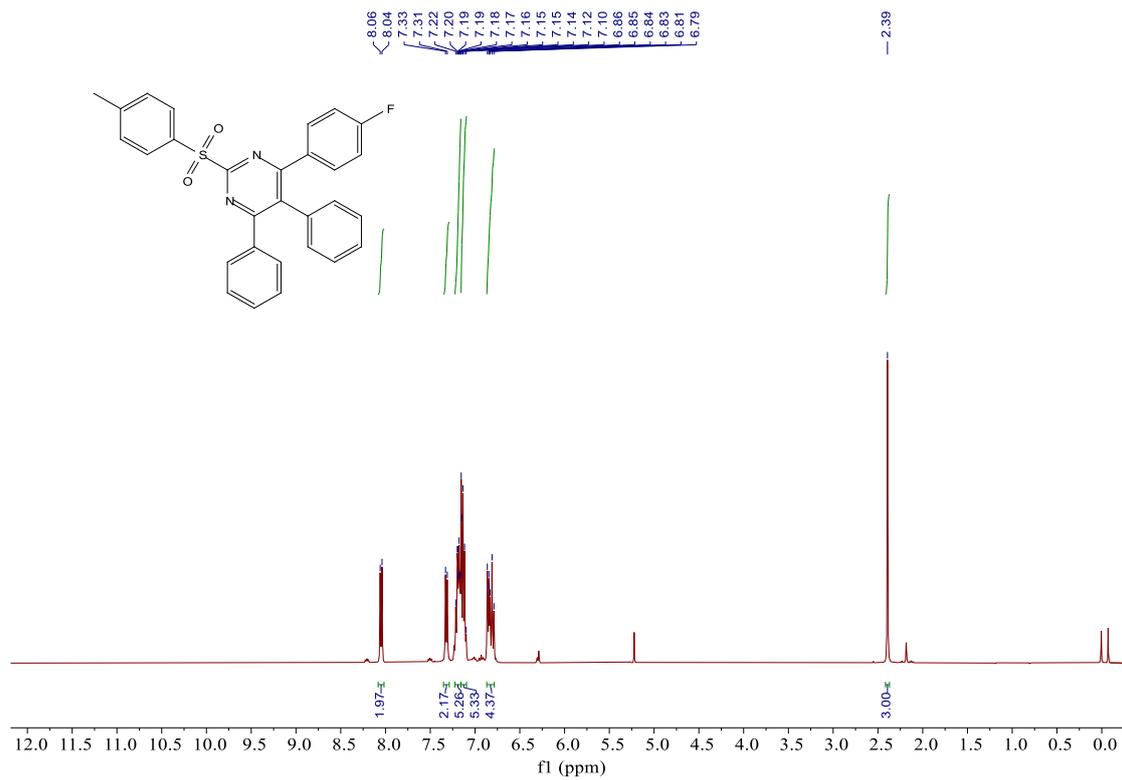
5-(4-ethylphenyl)-4-(4-methoxyphenyl)-6-phenyl-2-tosylpyrimidine(4ab)

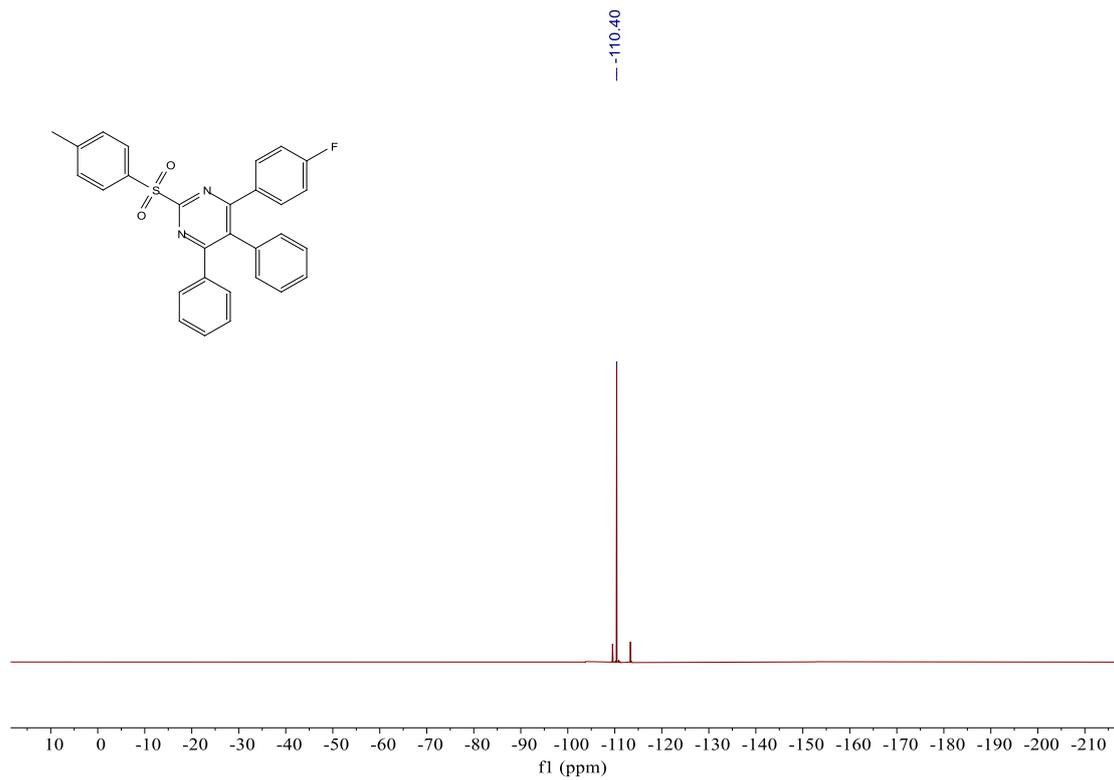


4,5-bis(4-methoxyphenyl)-6-phenyl-2-tosylpyrimidine(4ac)

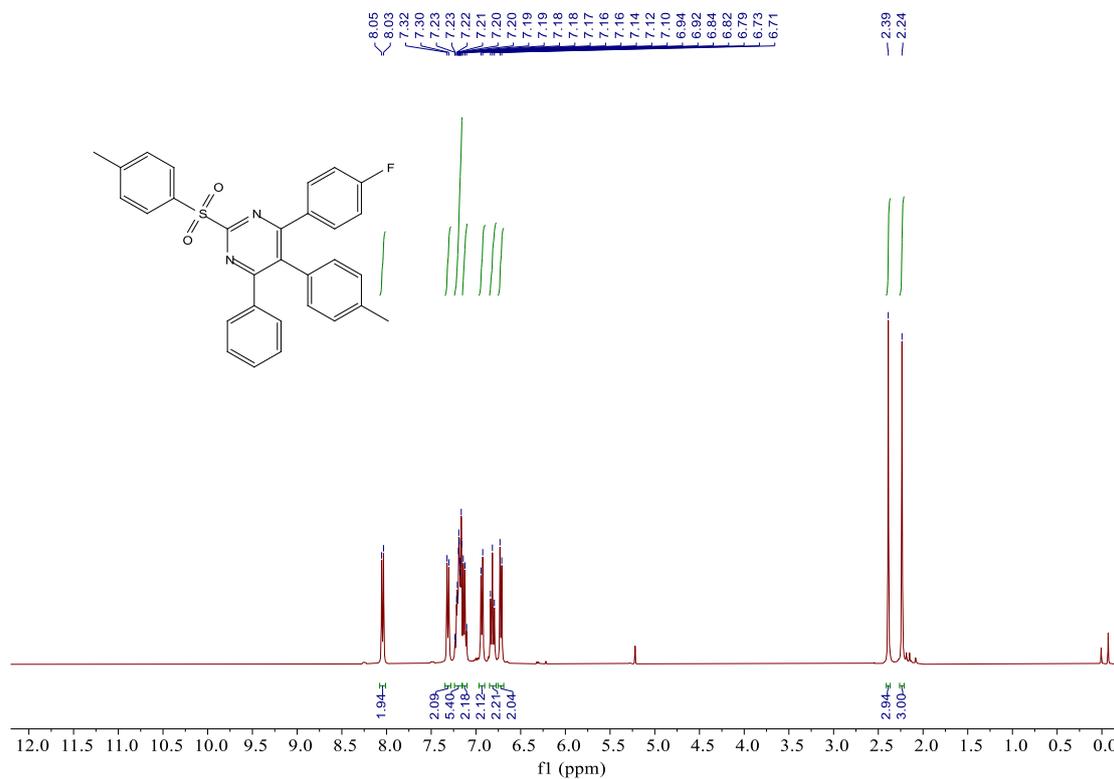


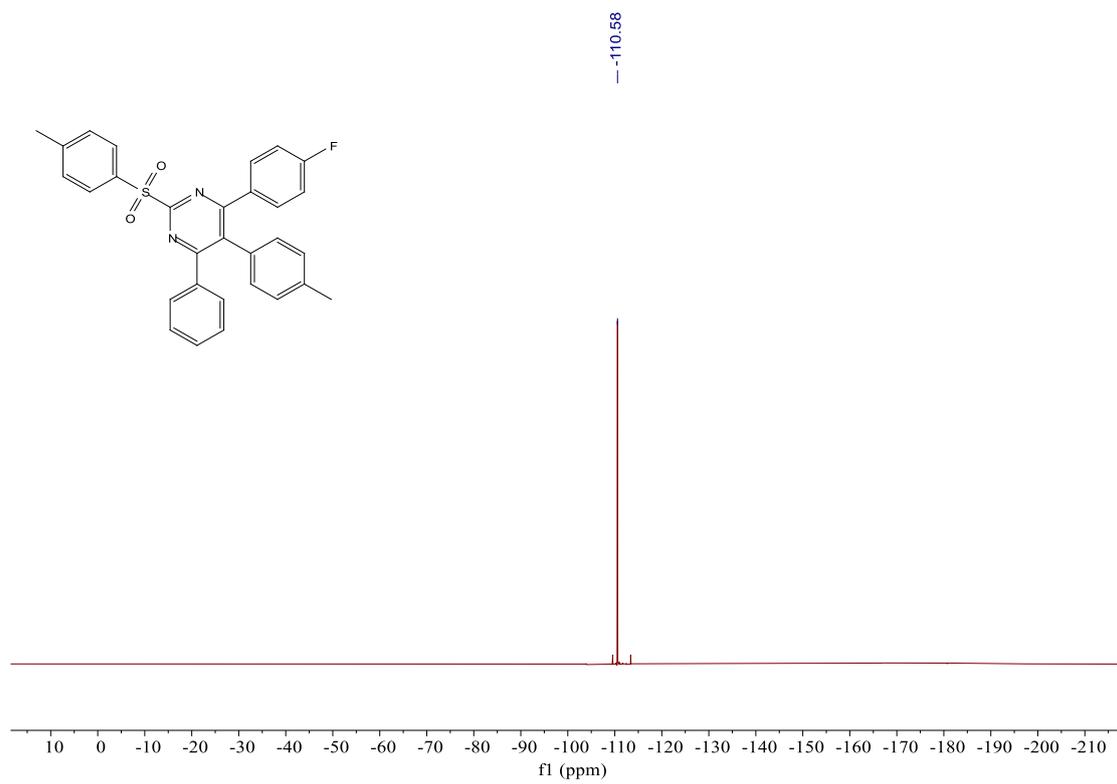
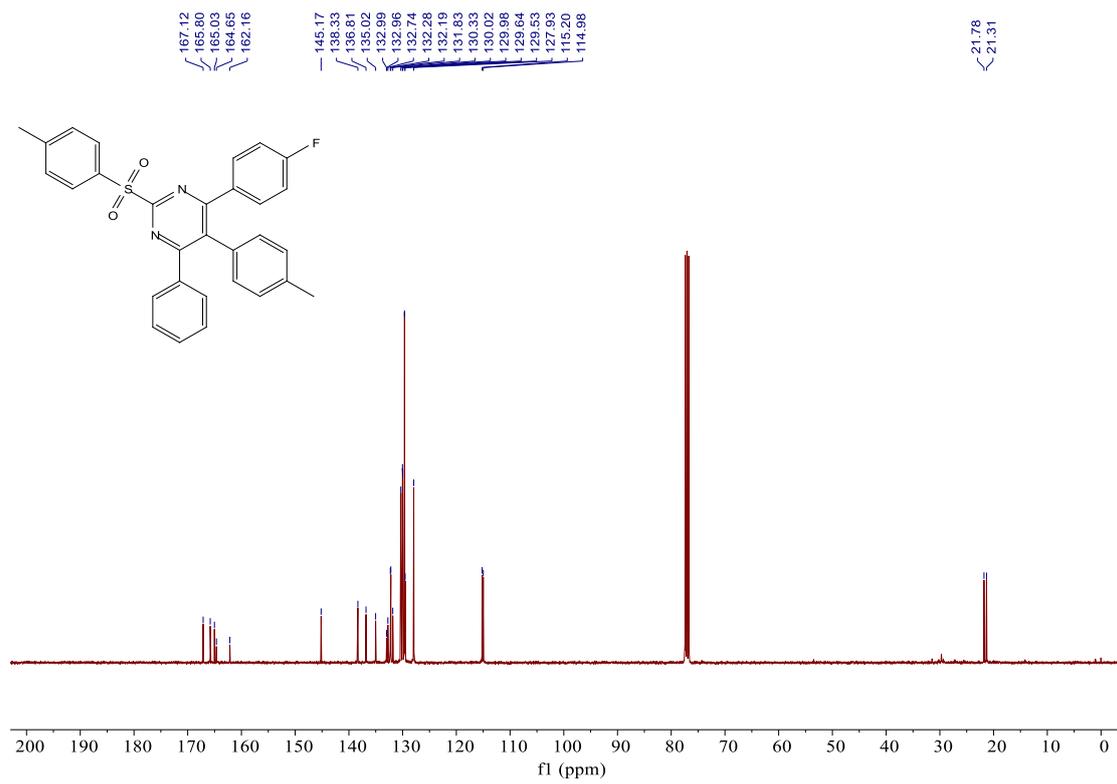
4-(4-fluorophenyl)-5,6-diphenyl-2-tosylpyrimidine(4ad)



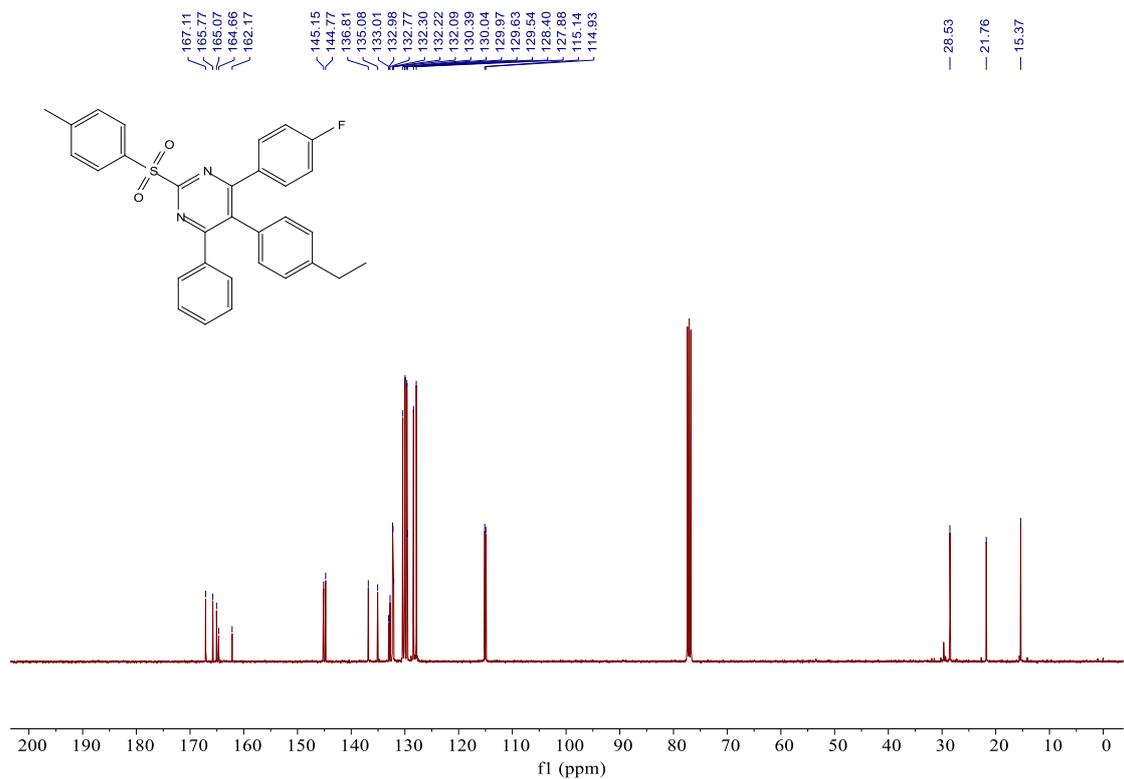
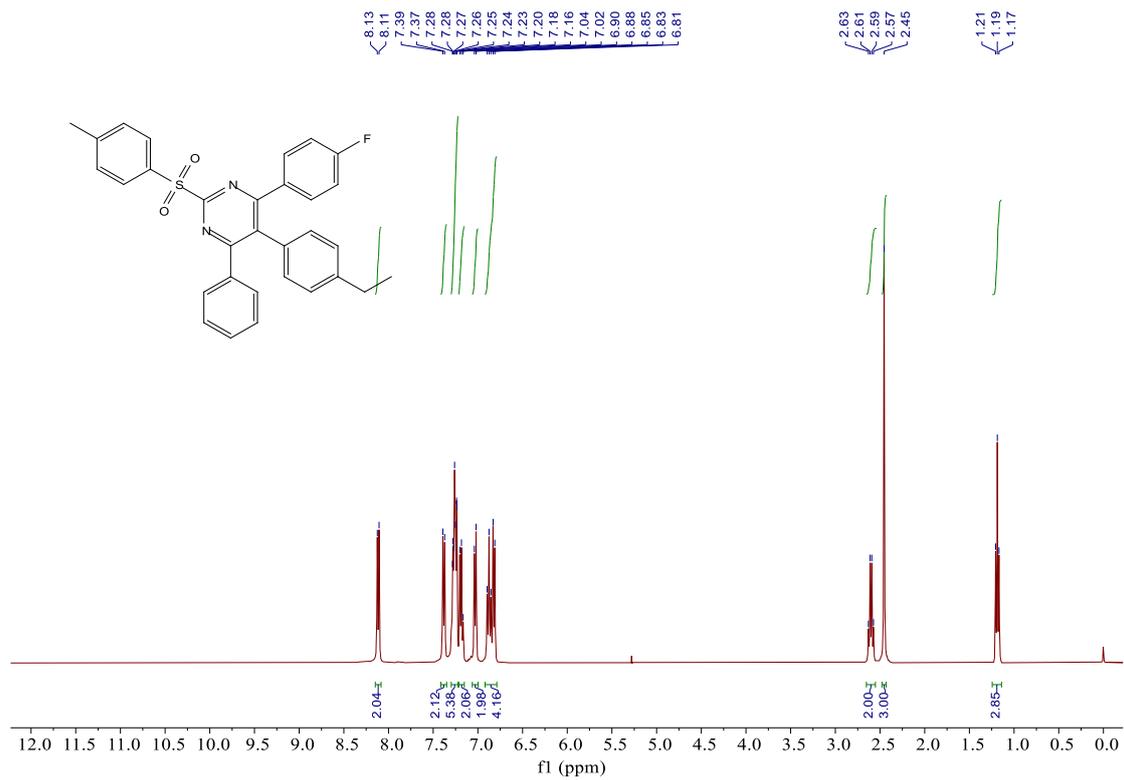


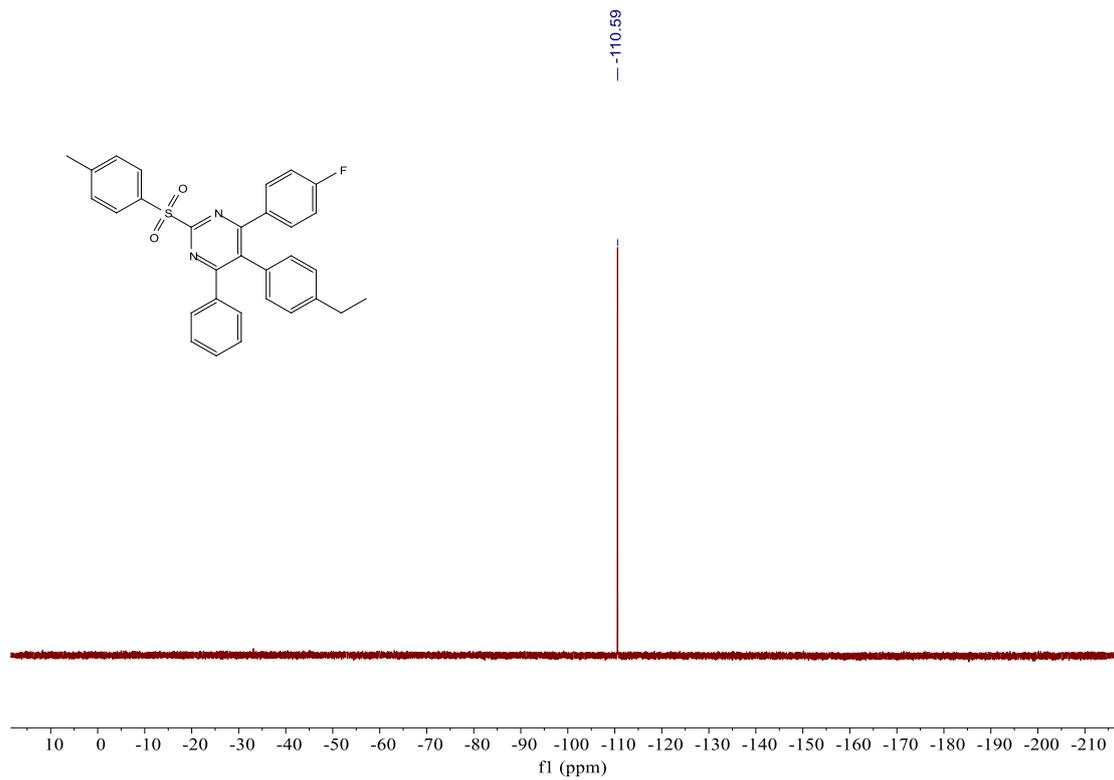
4-(4-fluorophenyl)-6-phenyl-5-(p-tolyl)-2-tosylpyrimidine(4ae)



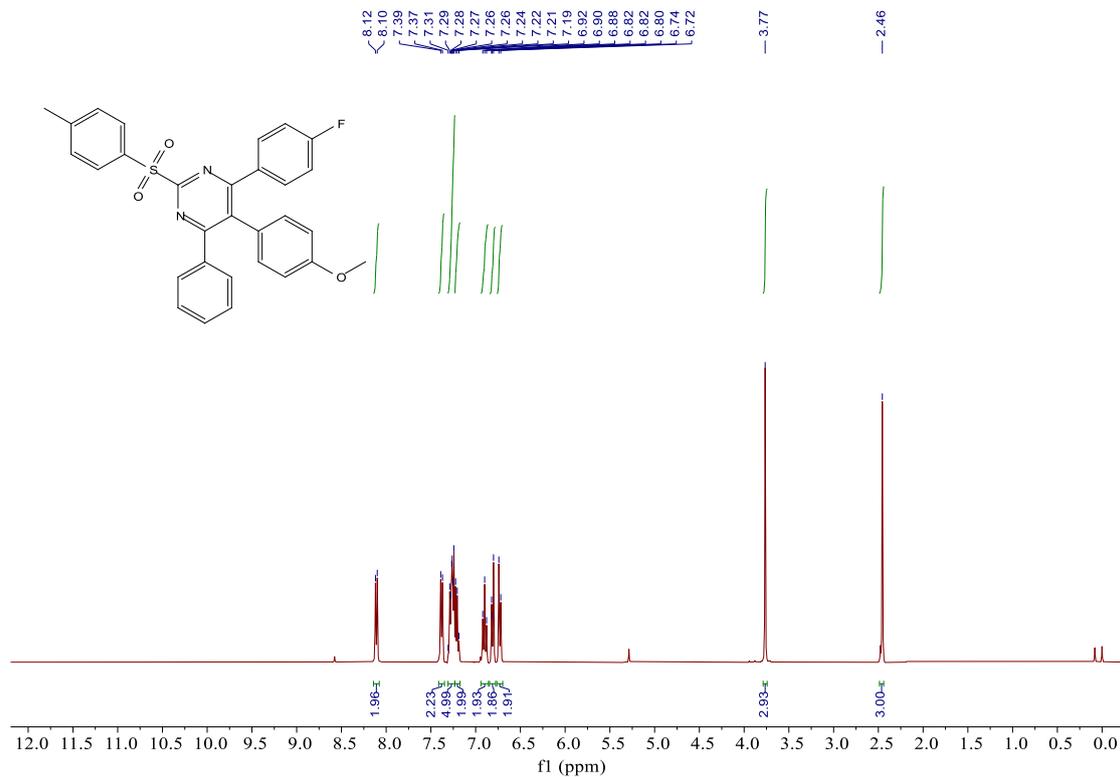


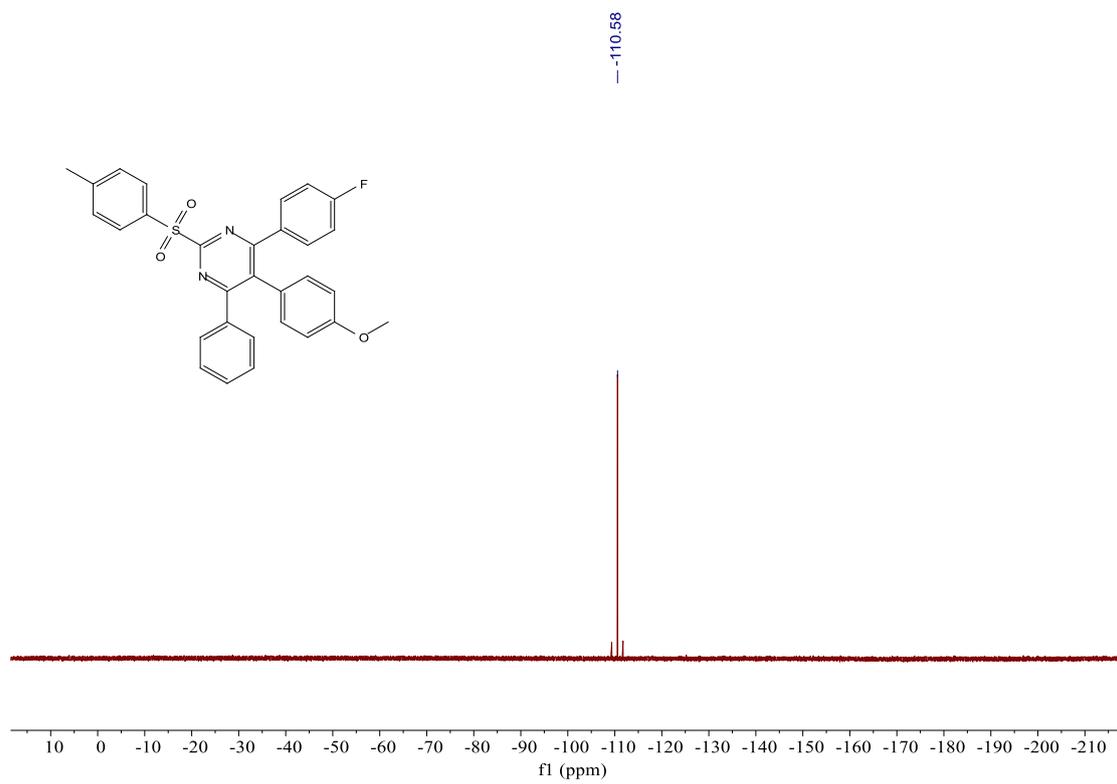
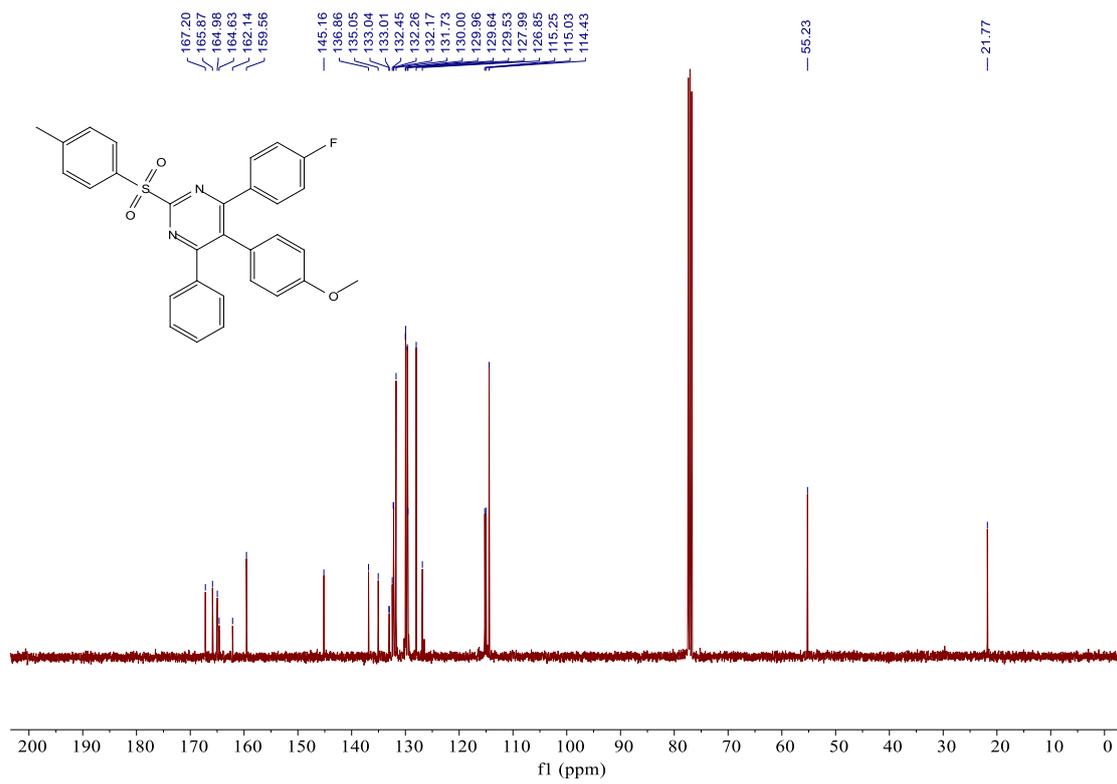
5-(4-ethylphenyl)-4-(4-fluorophenyl)-6-phenyl-2-tosylpyrimidine(4af)





4-(4-fluorophenyl)-5-(4-methoxyphenyl)-6-phenyl-2-tosylpyrimidine(4ag)





5-(4-(tert-butyl)phenyl)-4-(4-fluorophenyl)-6-phenyl-2-tosylpyrimidine(4ah)

