

Supporting information

S_NAr reaction in aqueous medium in presence of mixed organic and inorganic bases

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- 1. General procedure for protocol 1: Synthesis of 2,4-diaminoquinazoline:** In a round bottom flask add 3 ml N,N-dimethylacetamide (DMA), 0.001 mole of 2-fluorobenzonitrile, 0.001 mole of guanidine carbonate, 0.001 mole of N,N-diisopropylethylamine (DIPEA) and 0.001 mole of Na₂CO₃. Reaction was carried out at 125⁰C in an oil bath. After 3 hours, reaction was stopped by cooling the reaction mixture. The product was precipitated out by adding 1 ml dicloromethane followed by excess hexane on an ice bath. Precipitates were separated, washed with 3 ml water and recrystallized from methanol to achieve the pure product.
- 2. General procedure for protocol 2: Synthesis of 2-piperidinylbenzonitrile:** In a round bottom flask add 3 ml water, 0.001 mole of 2-fluorobenzonitrile, 0.001 mole of piperidine, 0.001 mole of N,N-diisopropylethylamine (DIPEA), 0.0001 mol of tert-butylammoniumbromide (TBAB) and 0.001 mole of Na₂CO₃. Reaction was carried out at reflux for 3 hours. Then reaction mixture was cooled and extracted with ethyl acetate. The productes were purified by flash chromatography on silica by using hexane-ethylacetate mobile phase.

Table S1: Spectroscopic data (Table 3)

Compounds	MS (MH ⁺)		NMR	Reference
	Calculated	Observed		
Table 3 (entry a)	161.0749	161.0314	(DMSO- <i>d</i> ₆ , δ): 5.957 (2H, s), 6.995 (1H, m), 7.194 (1H, m), 7.246 (2H, s), 7.465 (1H, m), 7.933 (1H, m).	12
Table 3 (entry b)	179.0655	178.9325	(MeOD, δ): 6.806 (1H, m), 7.098 (1H, m), 7.499 (1H, m).	12
Table 3 (entry c)	179.0655	178.9757	(DMSO- <i>d</i> ₆ , δ): 5.798 (2H, s), 7.054 (1H, m), 7.197 (2H, s), 7.363 (1H, m), 7.820 (1H, m).	
Table 3 (entry d)	179.0655	178.9613	(DMSO- <i>d</i> ₆ , δ): 6.102 (2H, s), 6.684 (2H, m), 7.304 (2H, s), 8.021 (1H, m).	
Table 3 (entry e)	197.0561	197.1419	(DMSO- <i>d</i> ₆ , δ): 5.911 (4H, s), 6.854 (1H, m), 7.559 (1H, m).	
Table 3 (entry f)	191.0855	191.0940	(CDCl ₃ , δ): 3.950 (3H, s), 4.793 (2H, s), 5.611 (2H, s), 6.521 (1H, m), 7.023 (1H, m), 7.451 (1H, m).	12

Table 3 (entry a)

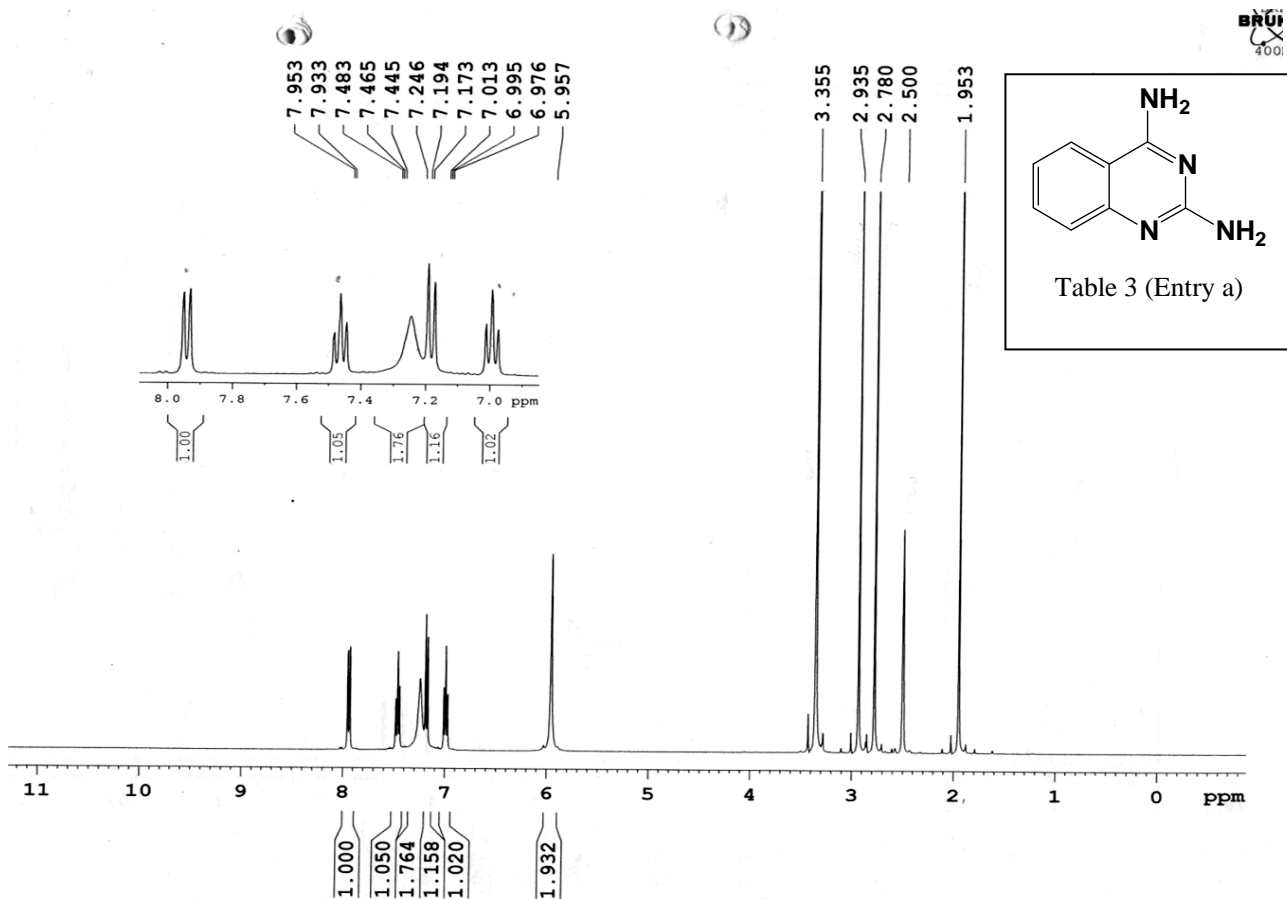
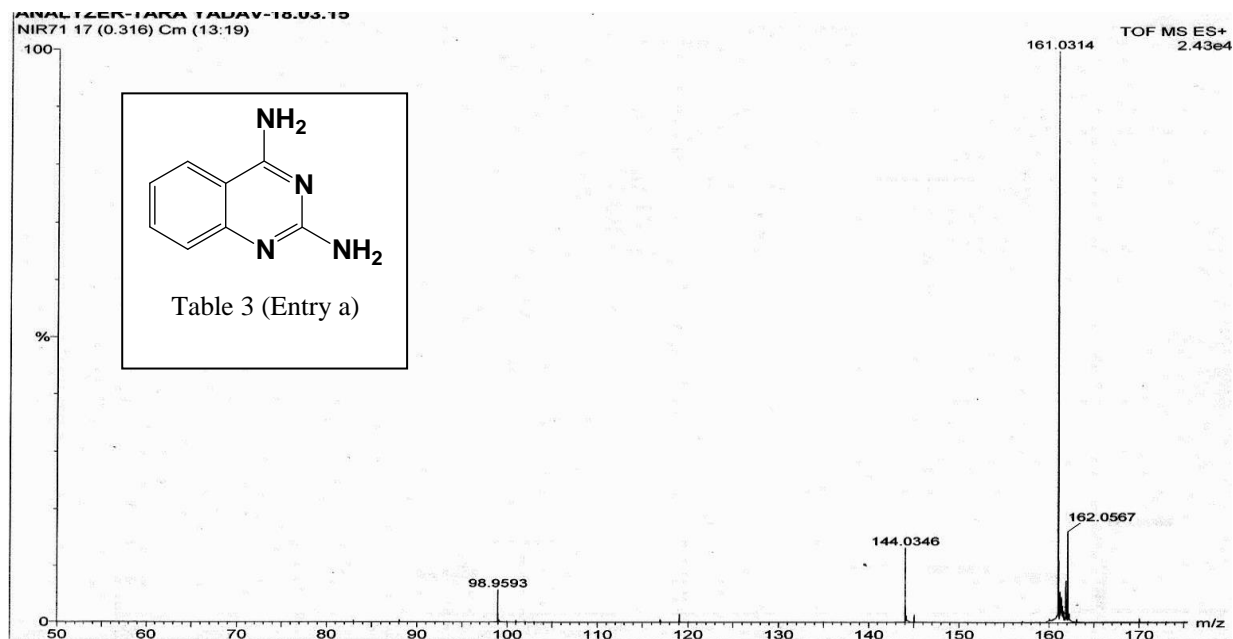
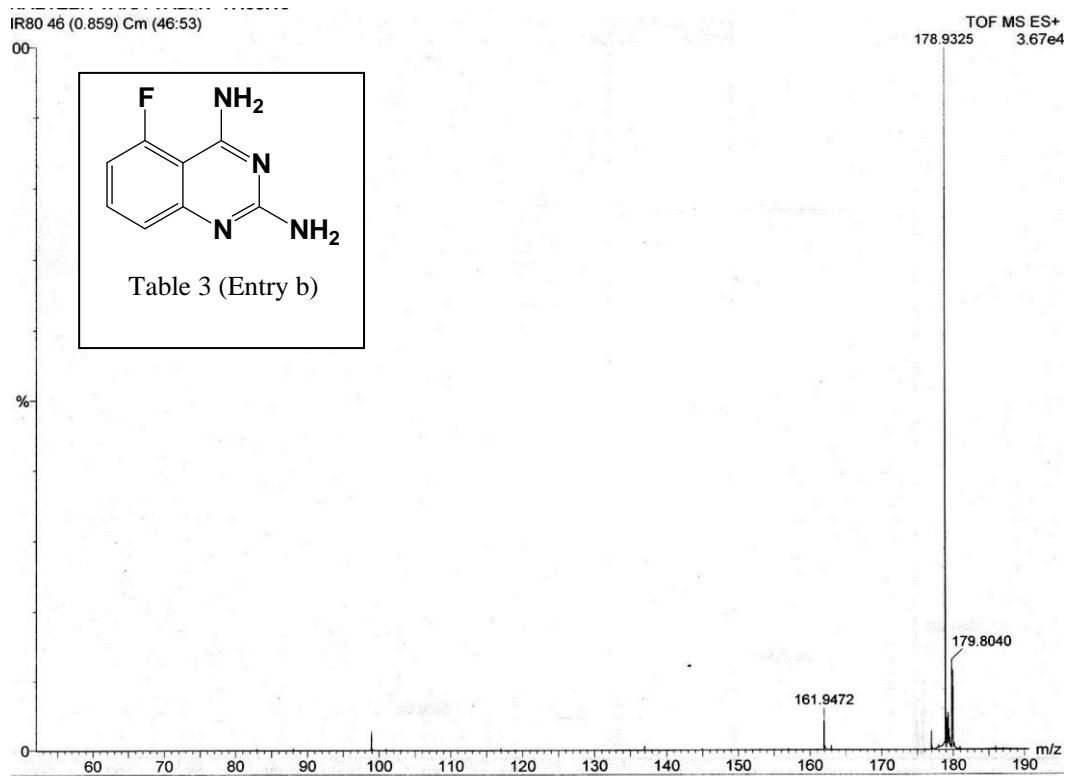
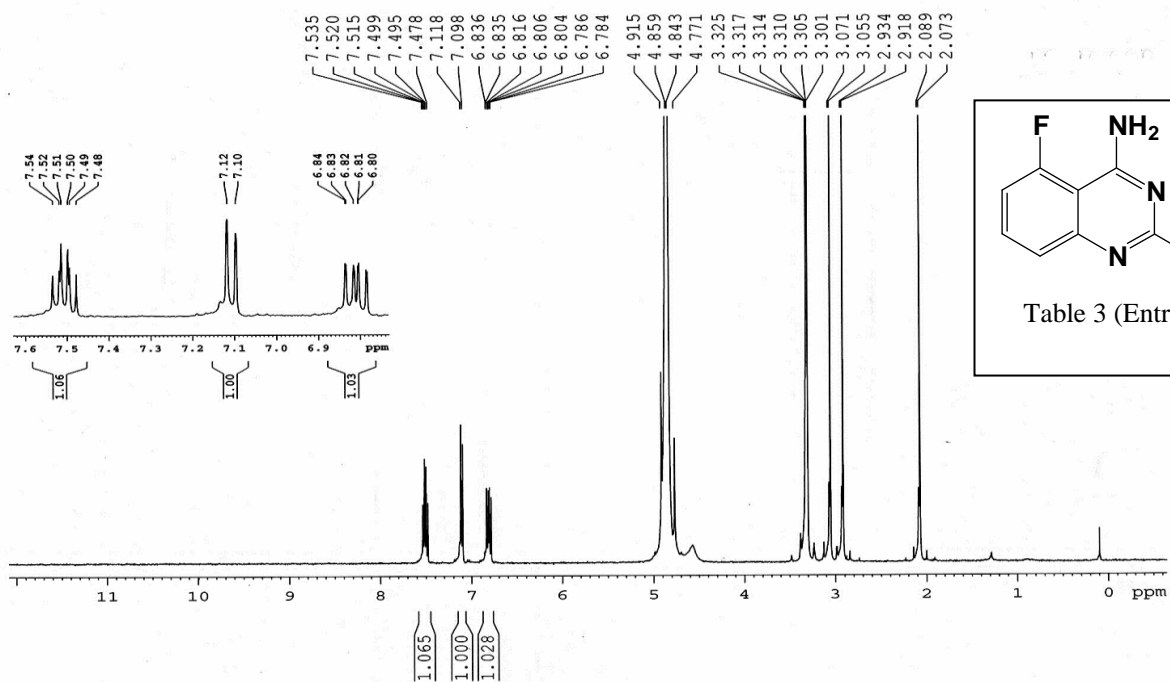


Table 3 (entry b)



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400MHz



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Table 3 (entry c)

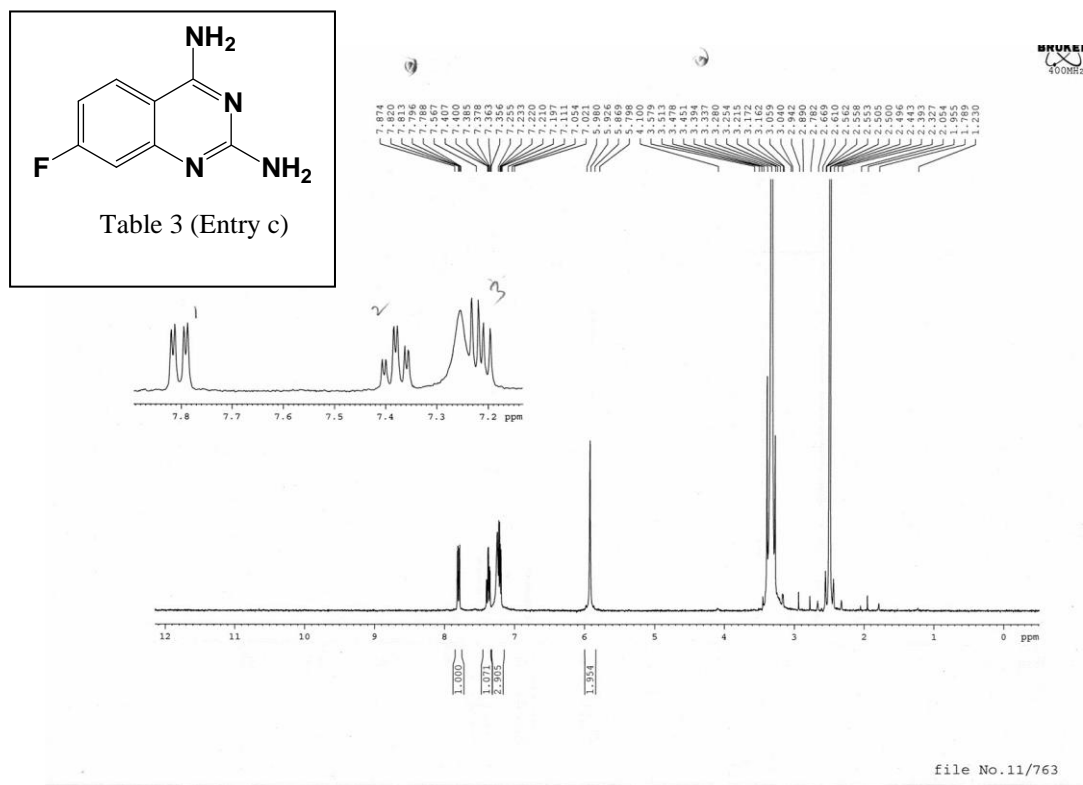
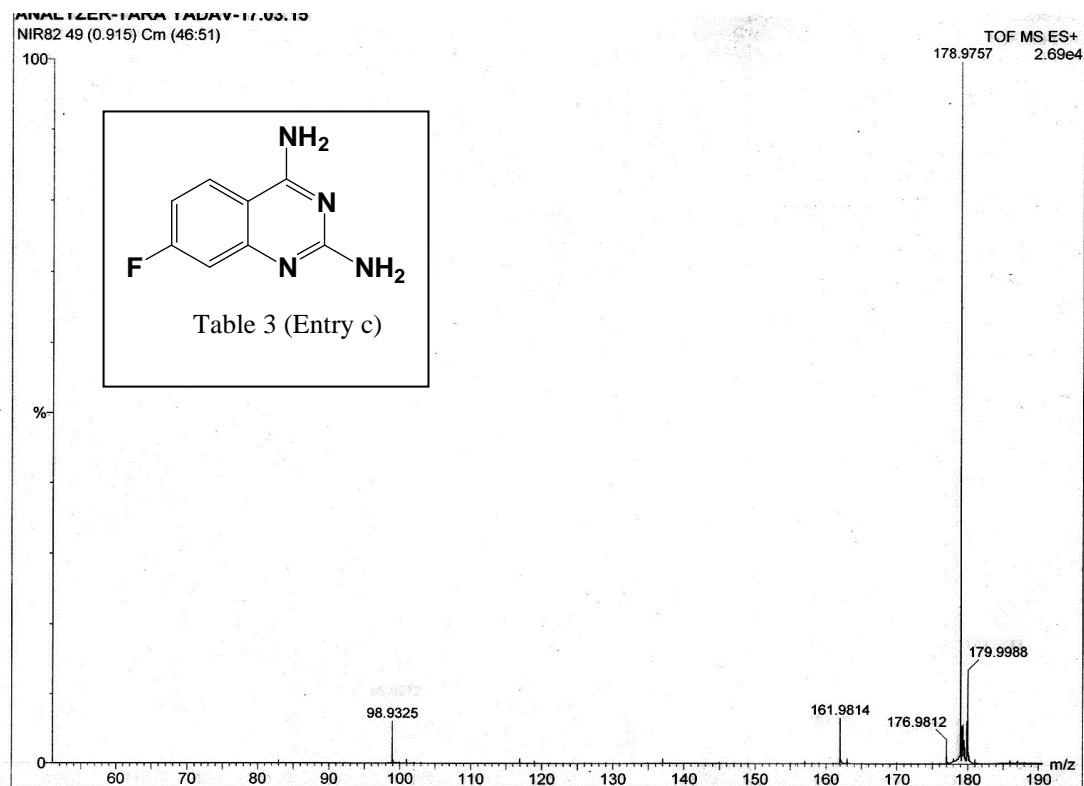
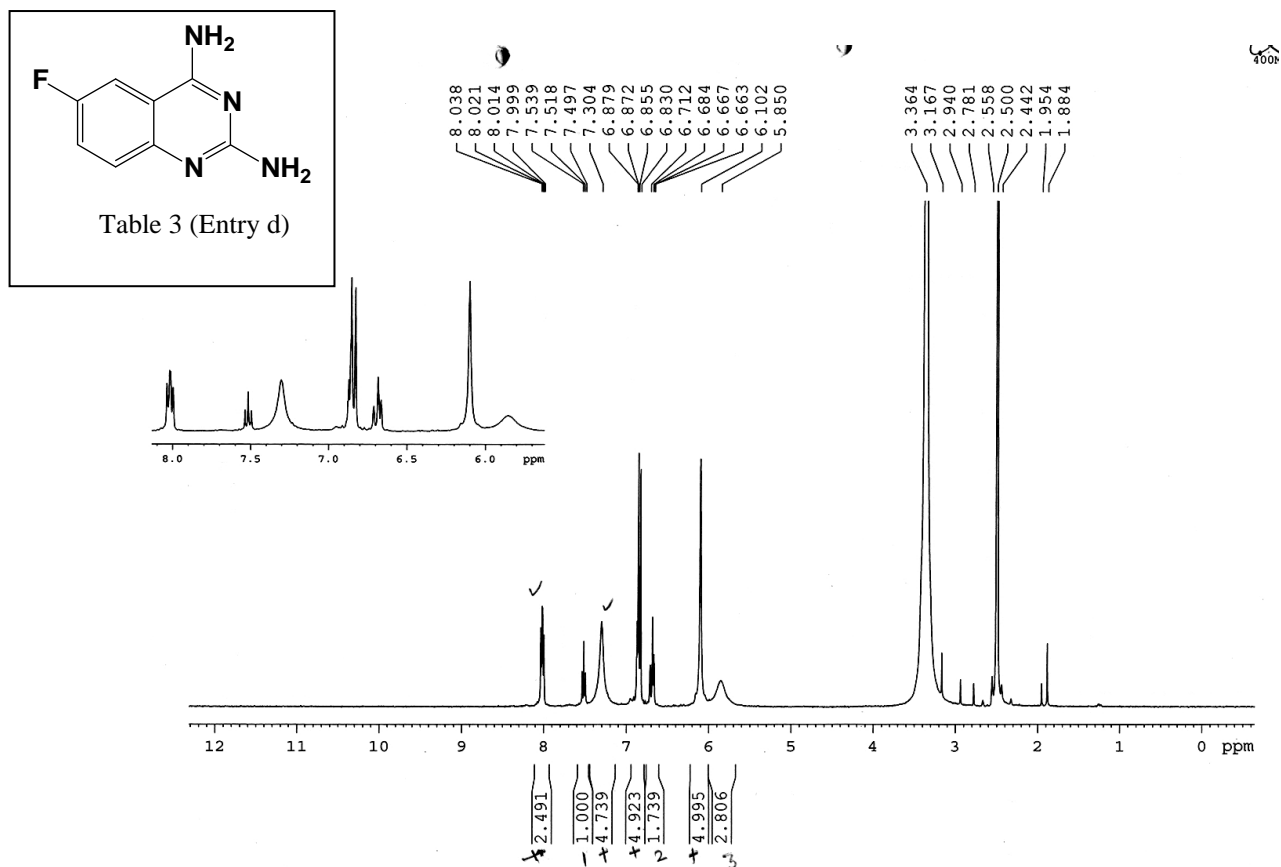
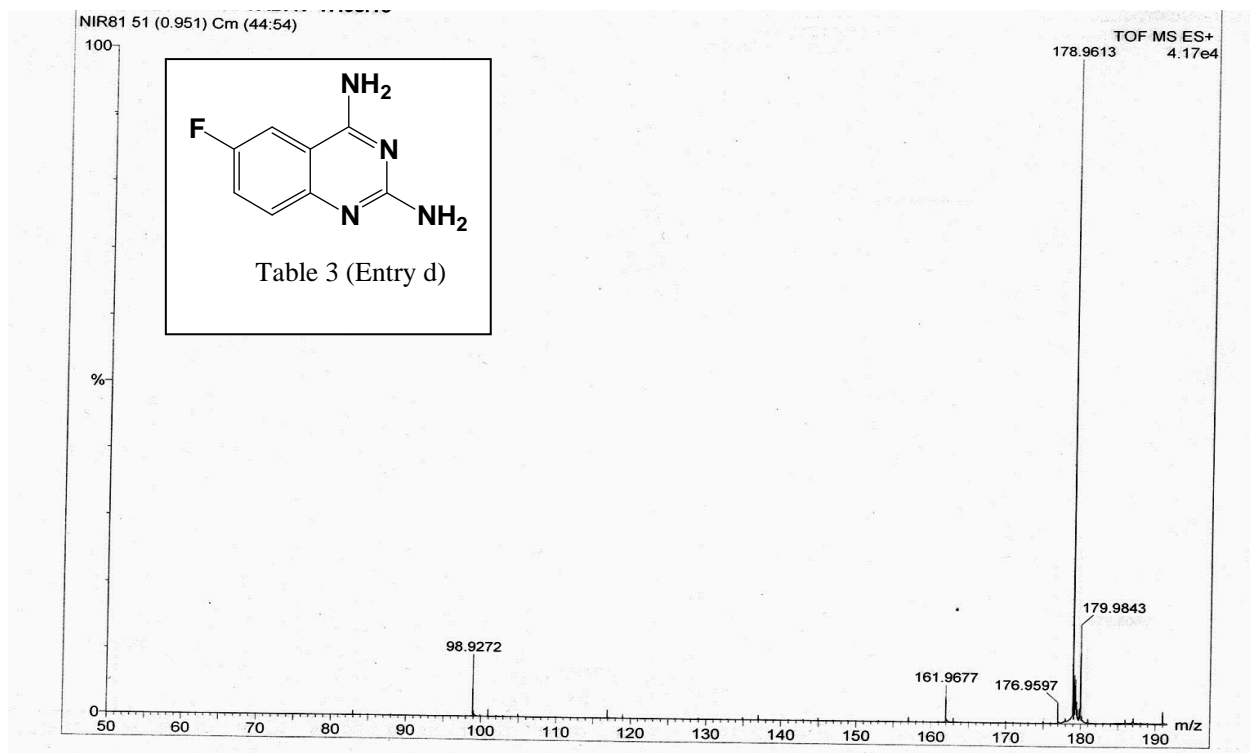
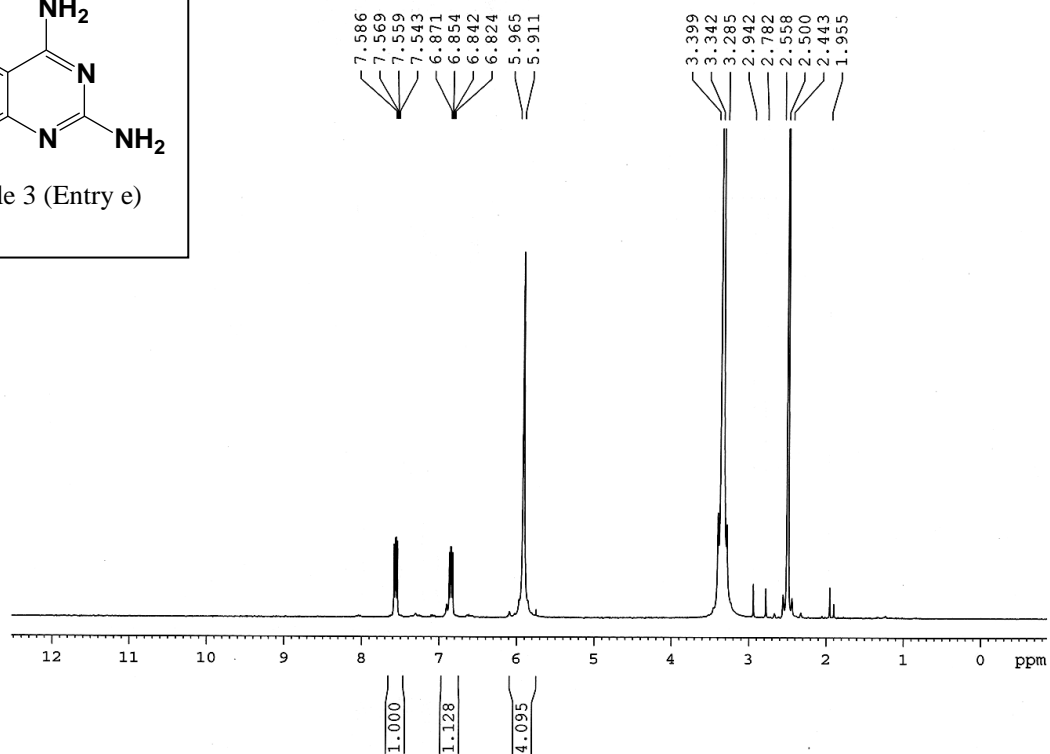
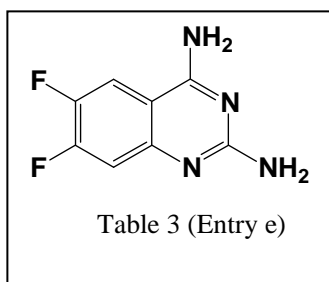


Table 3 (Entry d)



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Table 3(entry e)



file No.11/764

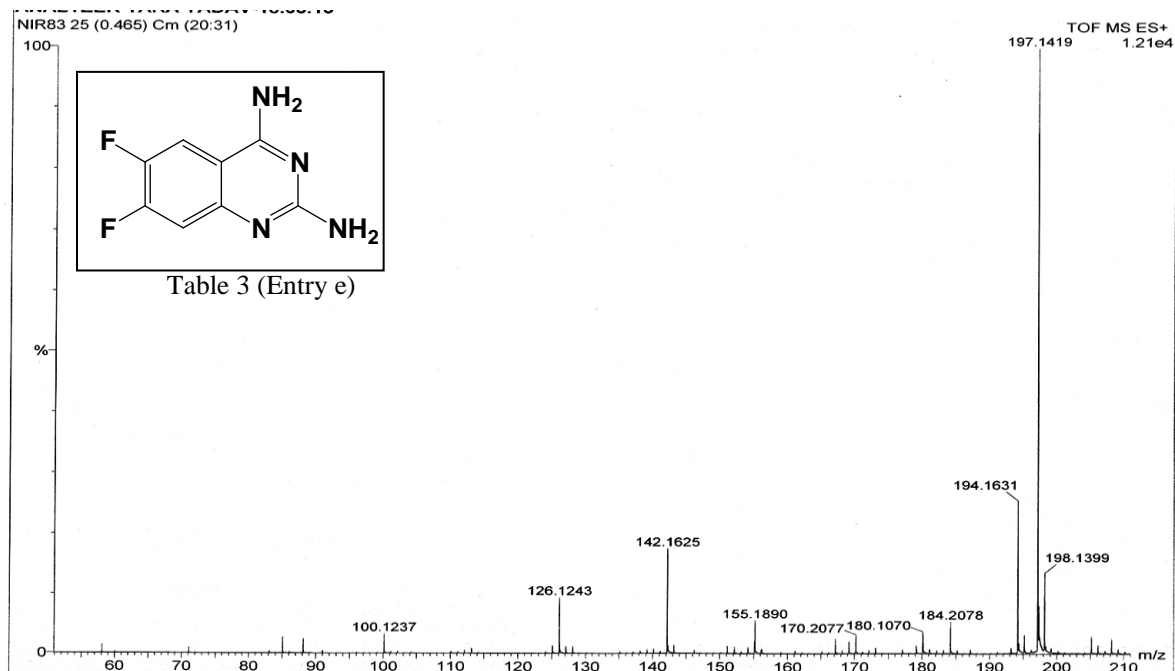
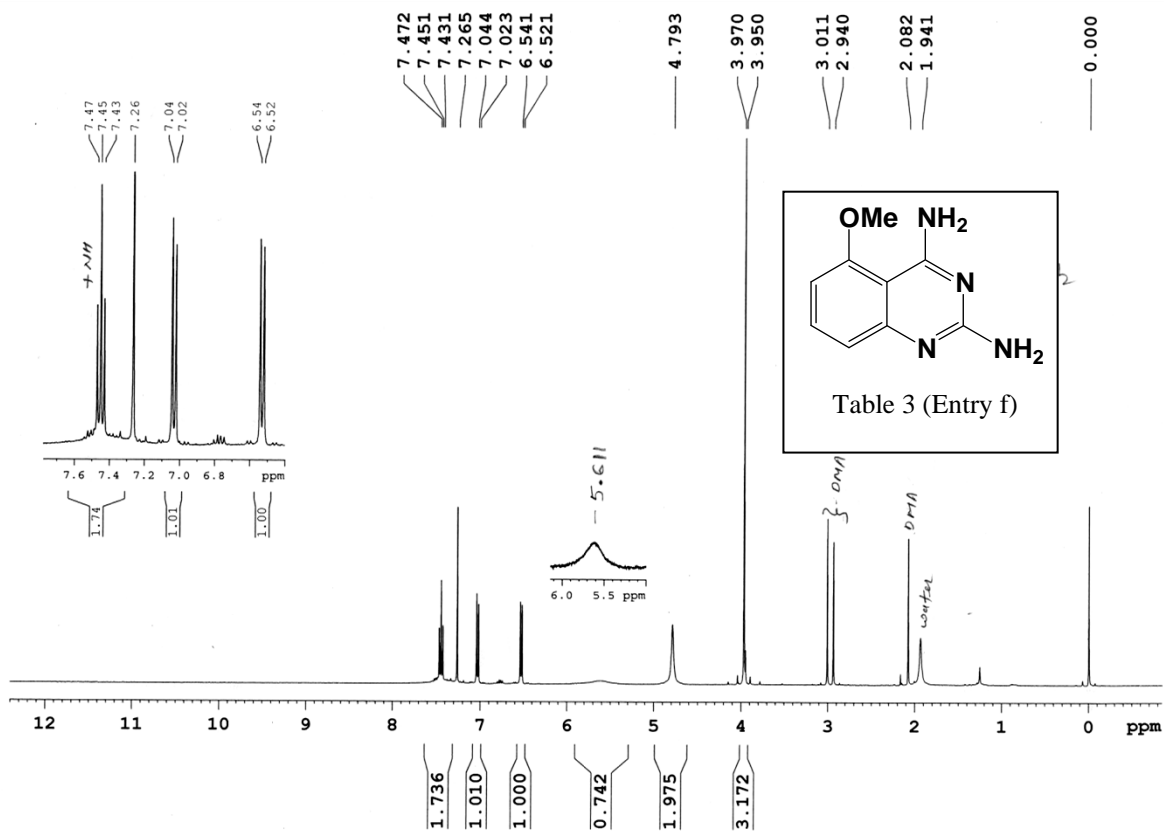
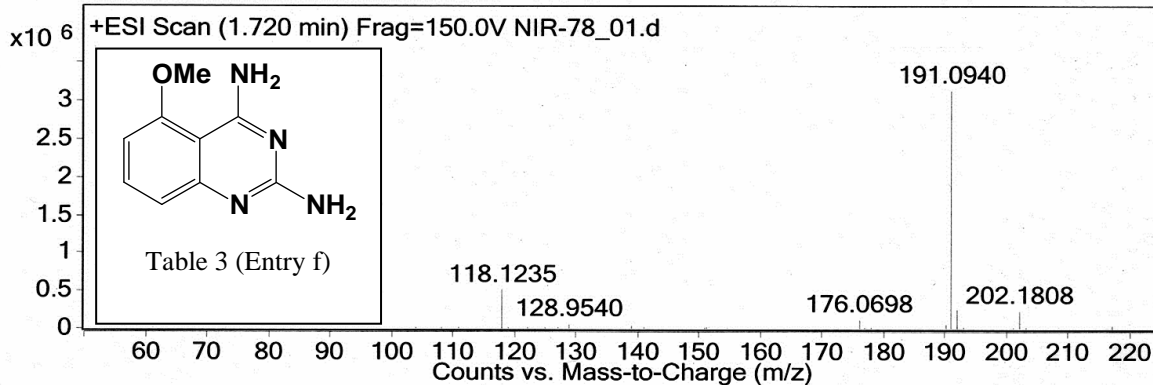


Table 3 (entry f)

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Table S2: Spectroscopic data (Table 4)

Compounds	MS (MH ⁺)		NMR
	Calculated	Observed	
Table 4 (entry a)	187.1157	187.1159	(CDCl ₃ , δ): 1.601 (2H, m), 1.763 (4H, m), 3.158 (4H, m), 6.977 (2H, m), 7.446 (1H, m), 7.541 (1H, m).
Table 4 (entry b)	205.1063	205.1146	(CDCl ₃ , δ): 1.666 (6H, m), 3.345 (4H, m), 6.505 (1H, m), 6.595 (1H, m), 7.352 (1H, m).
Table 4 (entry c)	205.1063	205.1152	(CDCl ₃ , δ): 1.616 (2H, m), 1.751 (4H, m), 3.216 (4H, m), 6.666 (1H, m), 6.718 (1H, m), 7.373 (1H, m).
Table 4 (entry d)	221.0767	221.1961	(CDCl ₃ , δ): 1.664 (6H, s), 3.334 (4H, s), 6.717 (1H, m), 6.834 (1H, s), 7.397 (1H, m).
Table 4 (entry e)	239.1160	239.1003	(CDCl ₃ , δ): 1.604 (2H, m), 1.742 (4H, m), 3.159 (4H, m), 3.891 (3H, s), 6.503 (1H, m), 6.572 (1H, m), 7.351 (1H, m).
Table 4 (entry f)	252.0906	252.0992	(CDCl ₃ , δ): 1.604 (2H, m), 1.742 (4H, m), 3.159 (4H, m), 3.891 (3H, s), 6.503 (1H, m), 6.572 (1H, m), 7.351 (1H, m).
Table 4 (entry g)	205.1063	205.0961	(CDCl ₃ , δ): 1.755 (6H, m), 3.261 (4H, m), 7.128 (1H, m), 8.201 (1H, m), 8.645 (1H, m).
Table 4 (entry h)	189.0950	189.1897	(CDCl ₃ , δ): 3.210 (4H, m), 3.905 (4H, m), 7.040 (2H, m), 7.490 (1H, m), 7.591 (1H, m).
Table 4 (entry i)	227.0906	227.0937	(CDCl ₃ , δ): 3.210 (4H, m), 3.905 (4H, m), 7.040 (2H, m), 7.490 (1H, m), 7.591 (1H, m).
Table 4 (entry j)	234.1328	234.1206	(CDCl ₃ , δ): 4.434 (2H, m), 5.118 (1H, s), 6.427 (2H, m), 7.308 (6H, m).

Table 4 (Entry a)

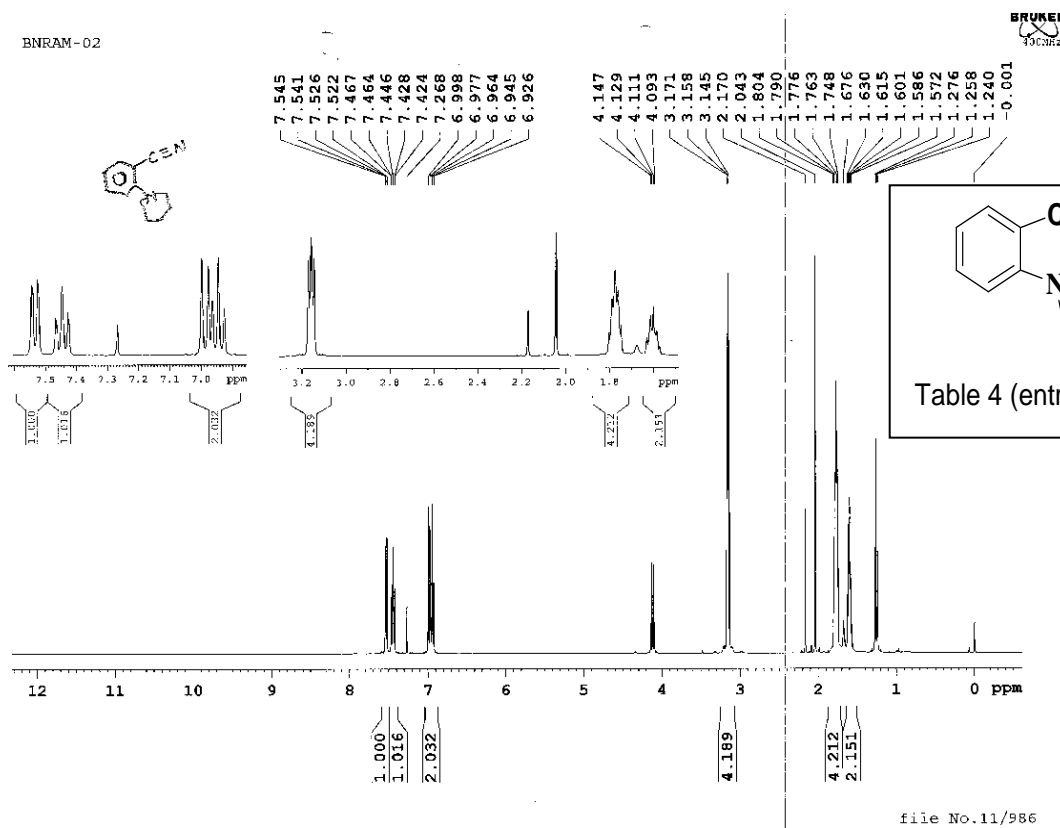
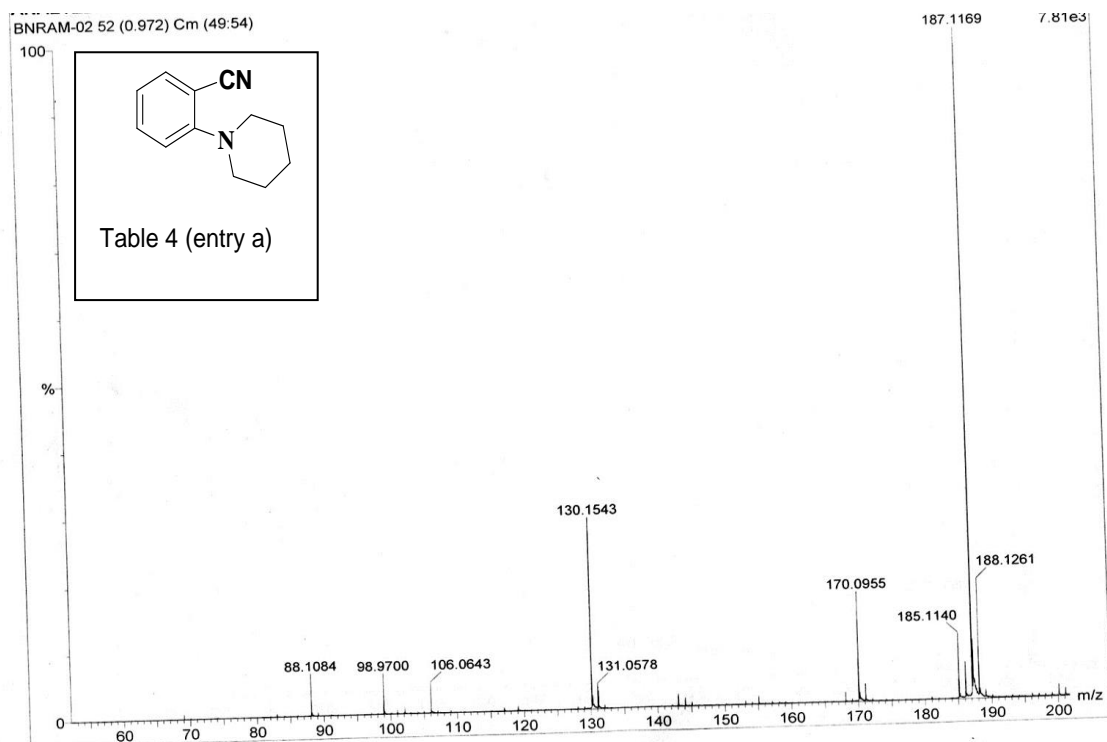


Table 4 (entry b)

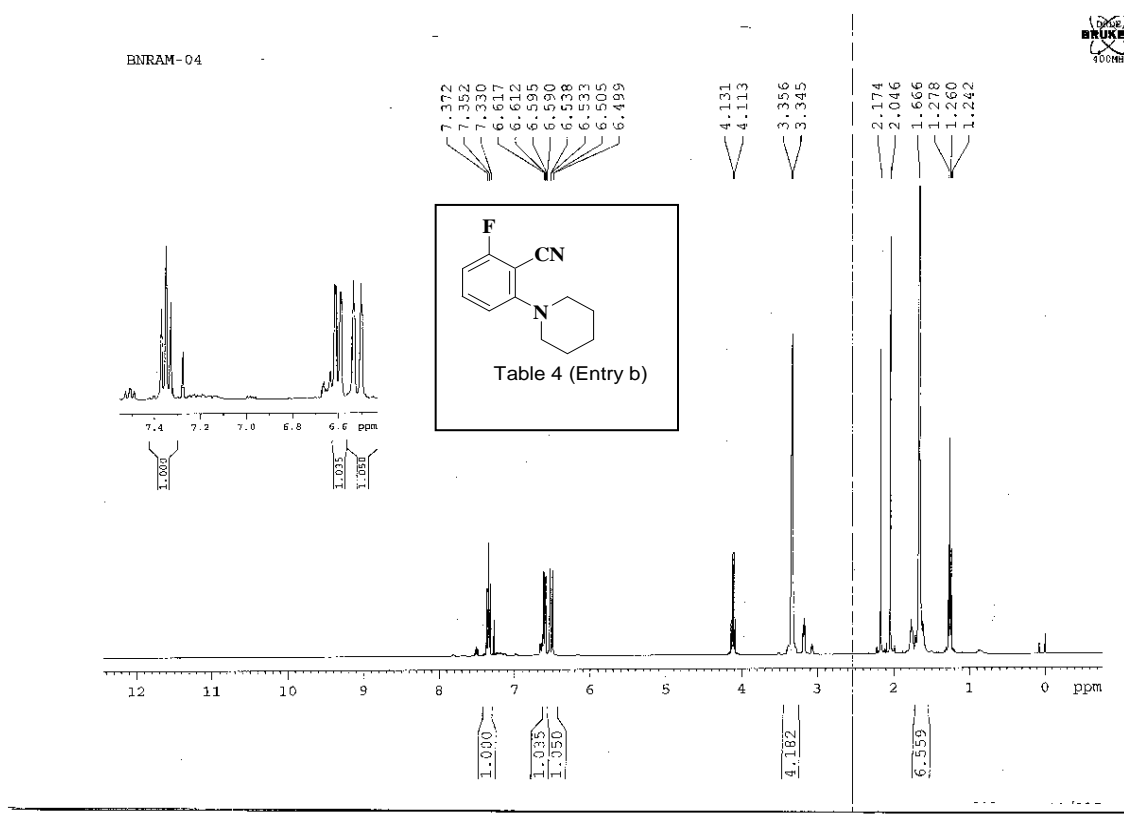
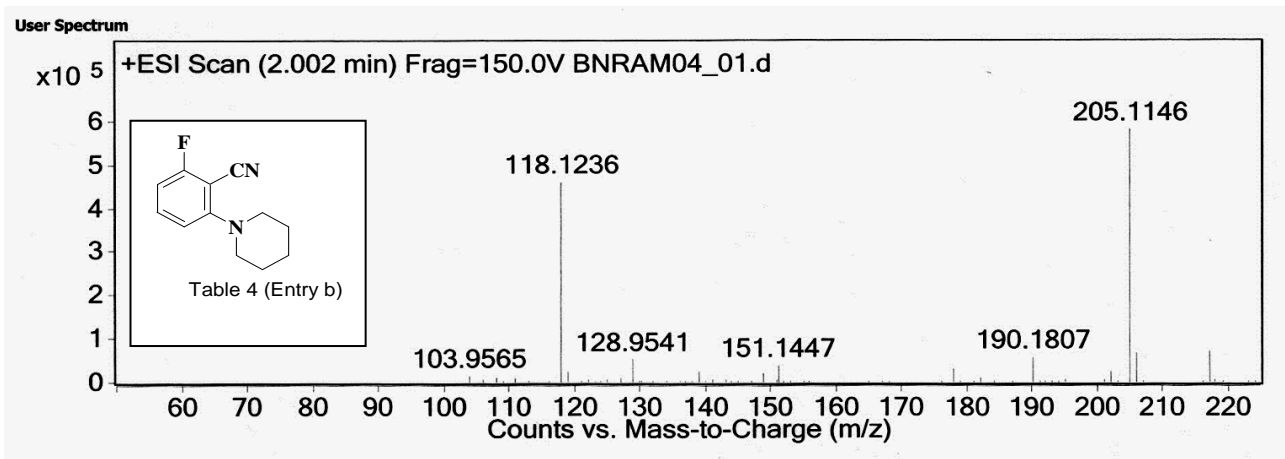
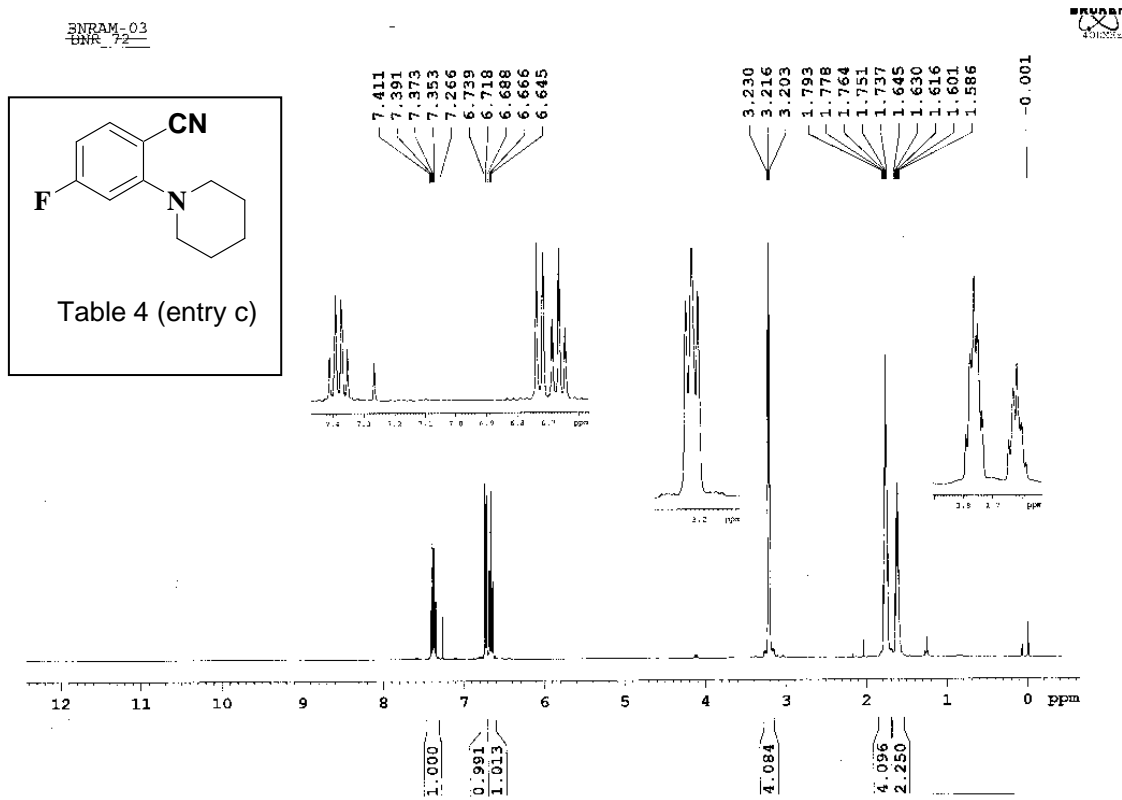
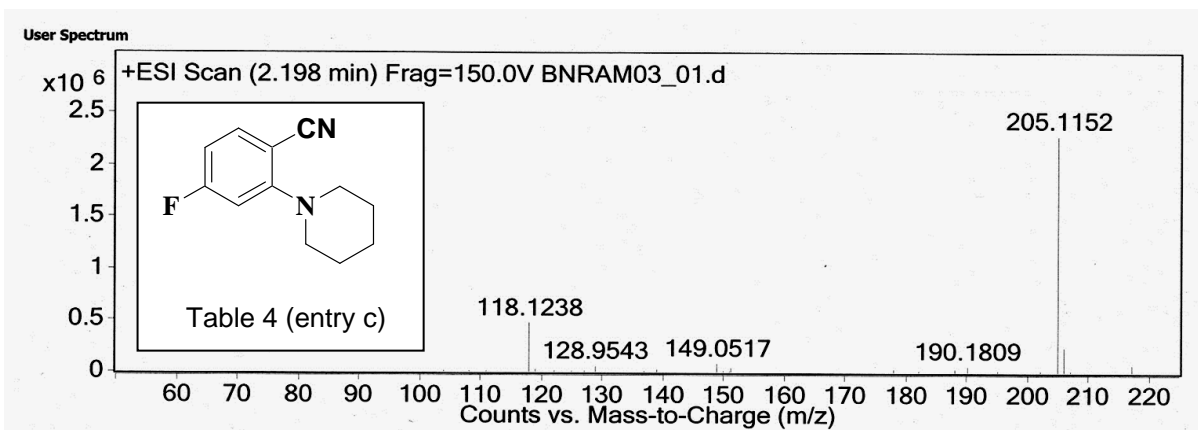


Table 4 (entry c)



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Table 4 (entry d)

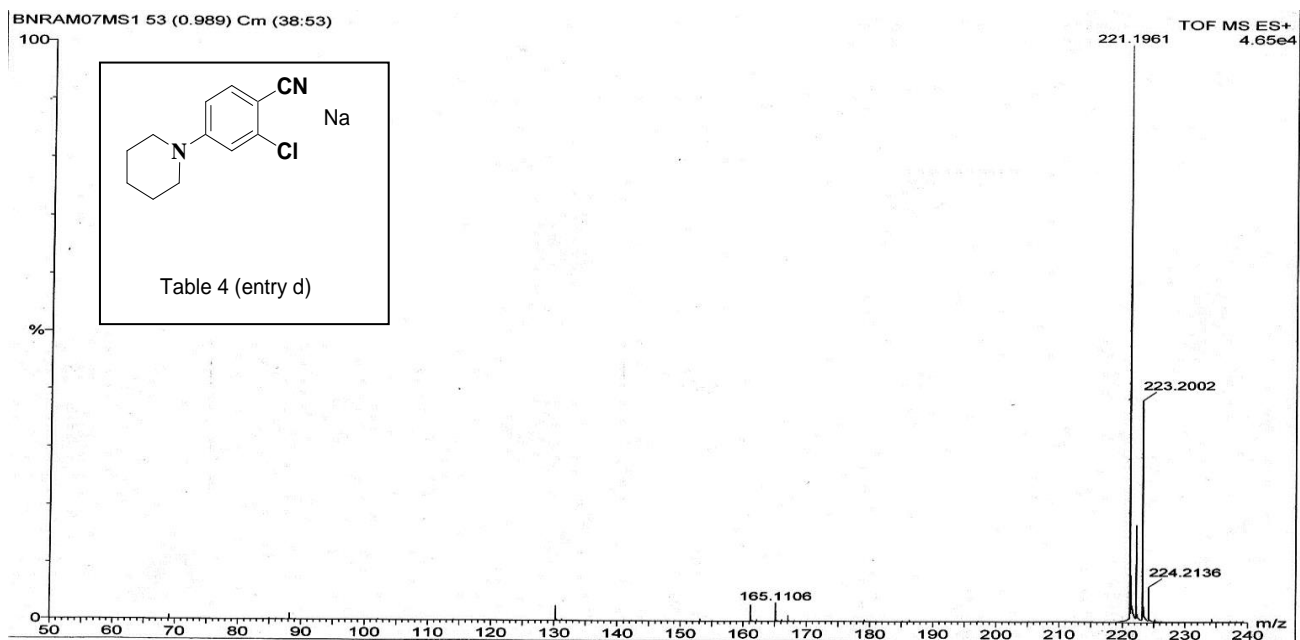
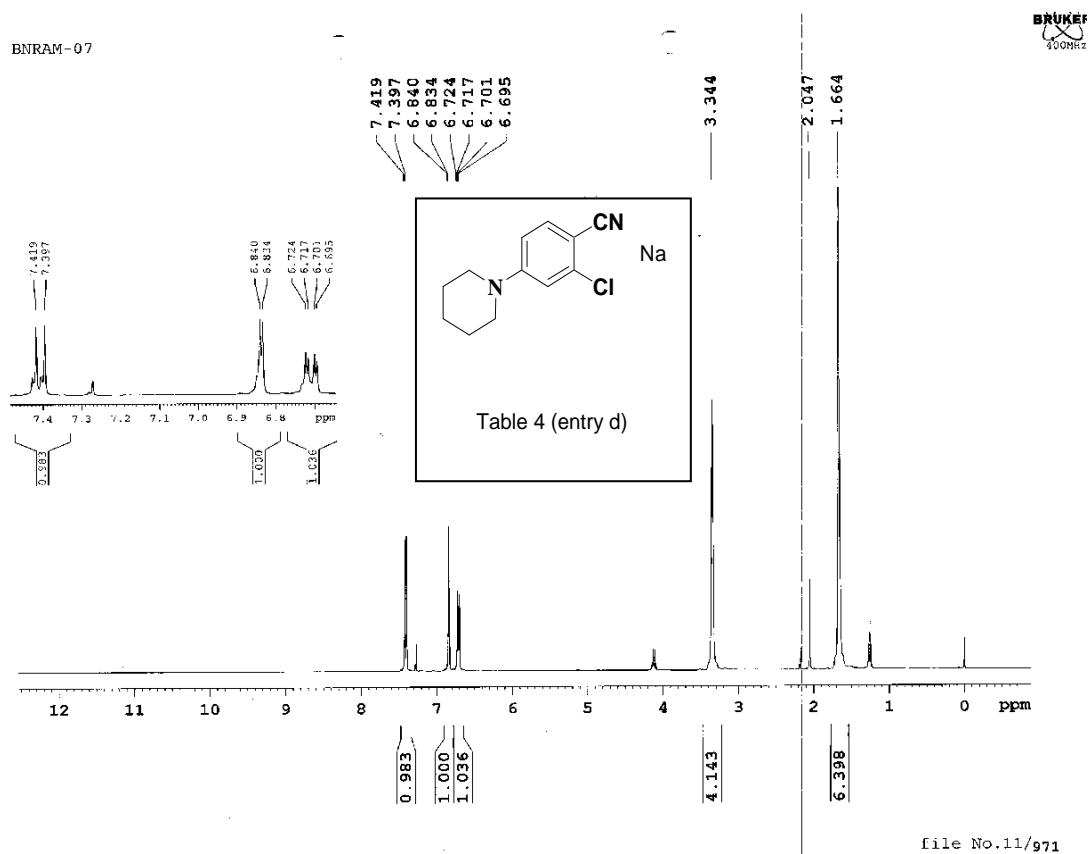
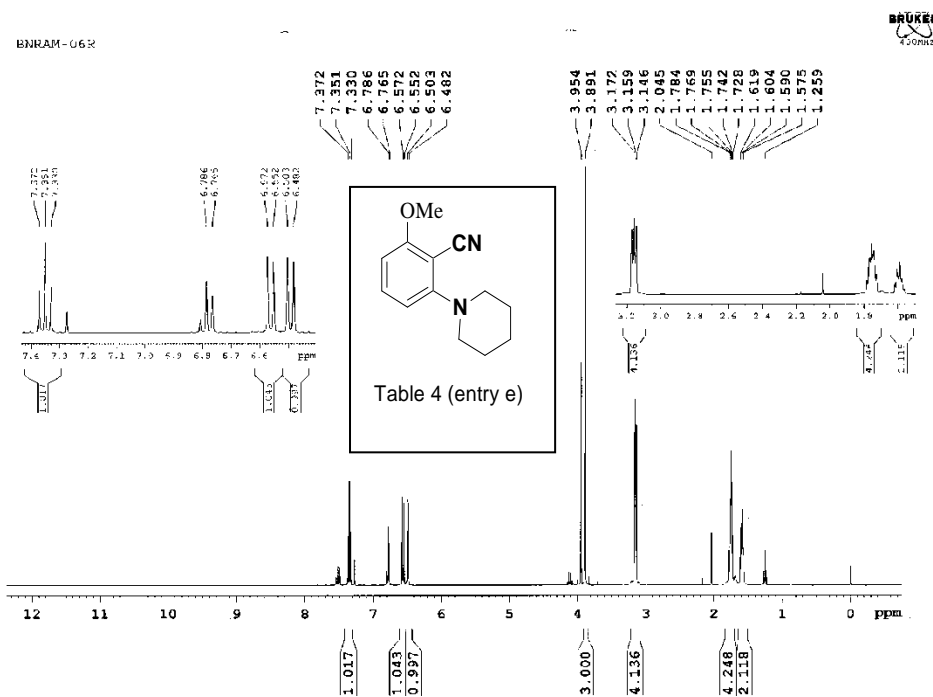
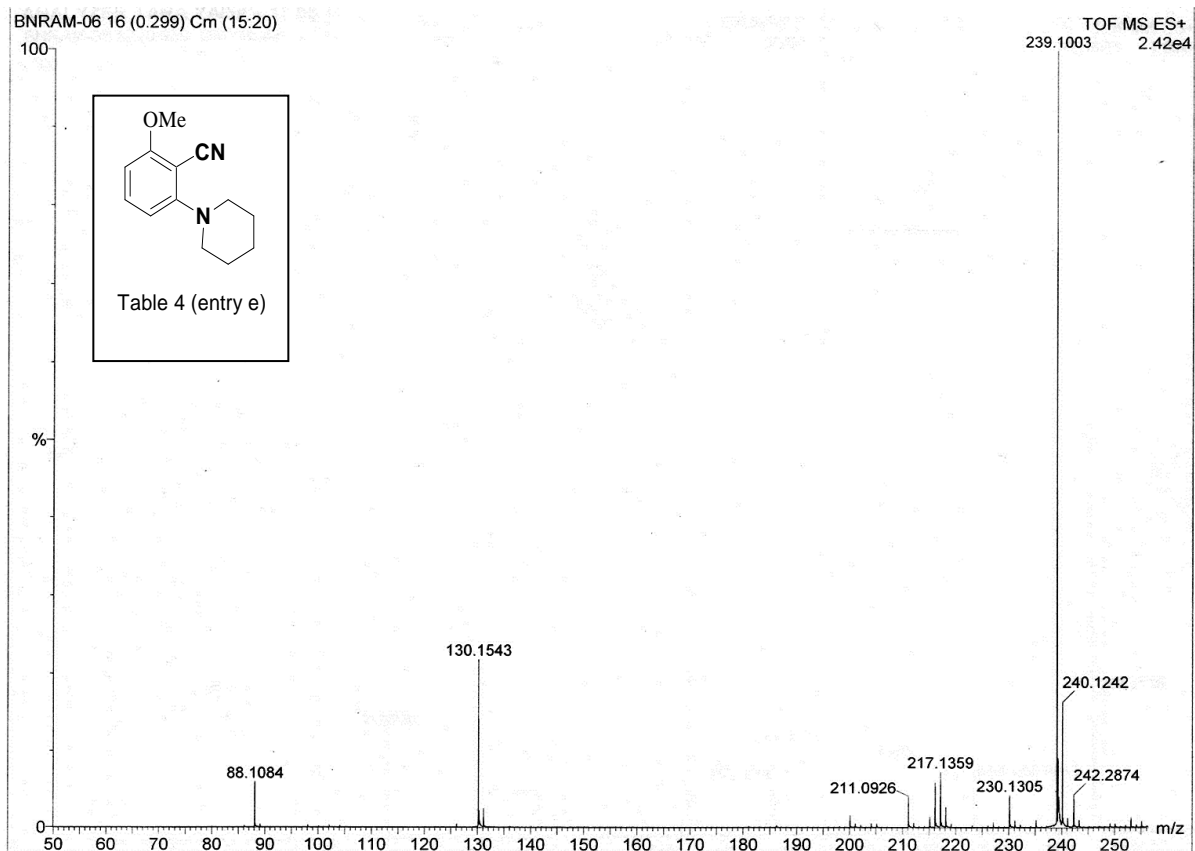


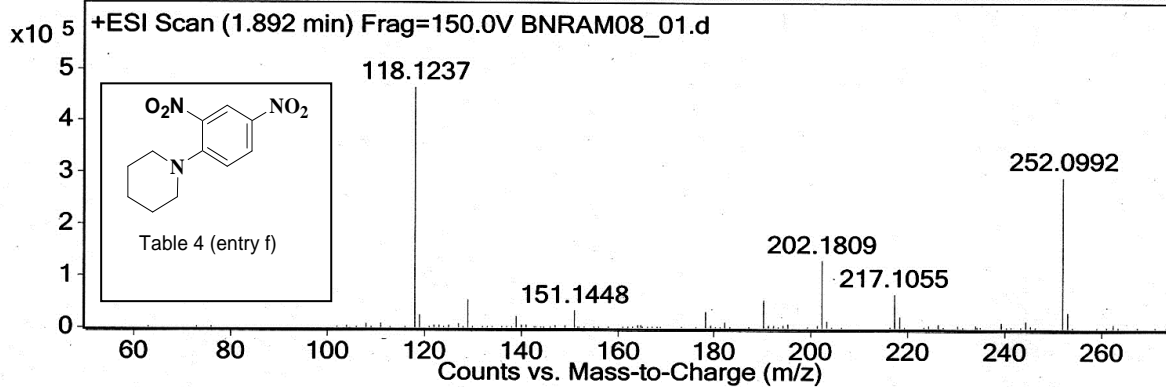
Table 4 (entry e)



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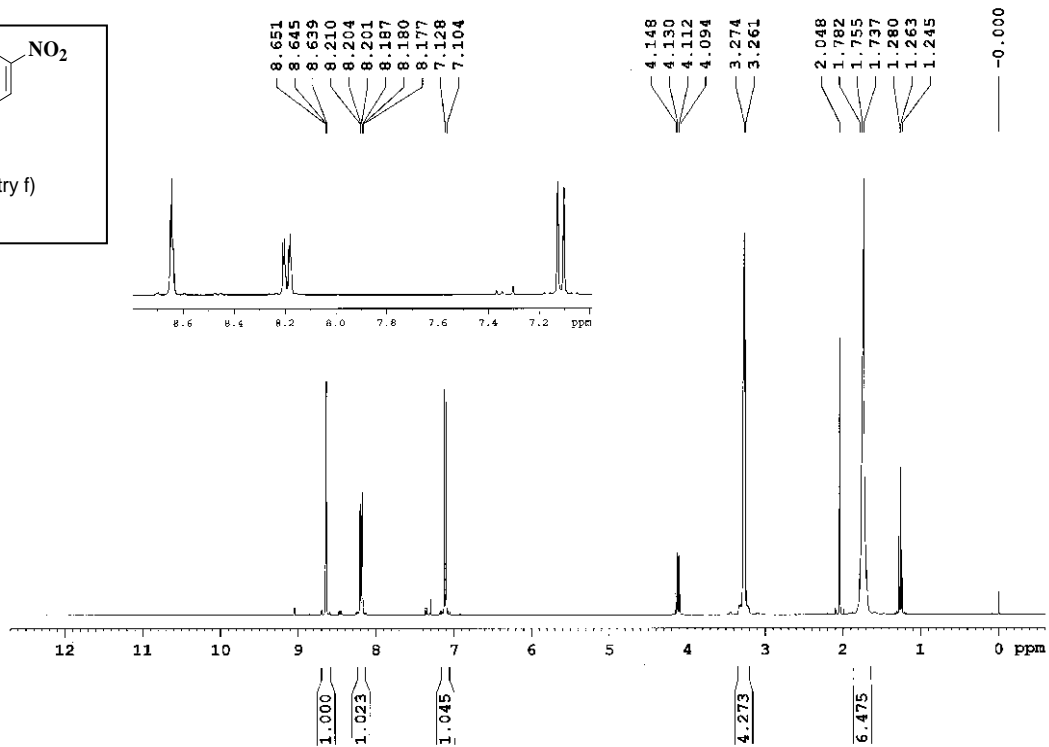
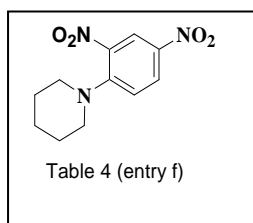
Table 4 (entry f)

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Table 4 (entry g)

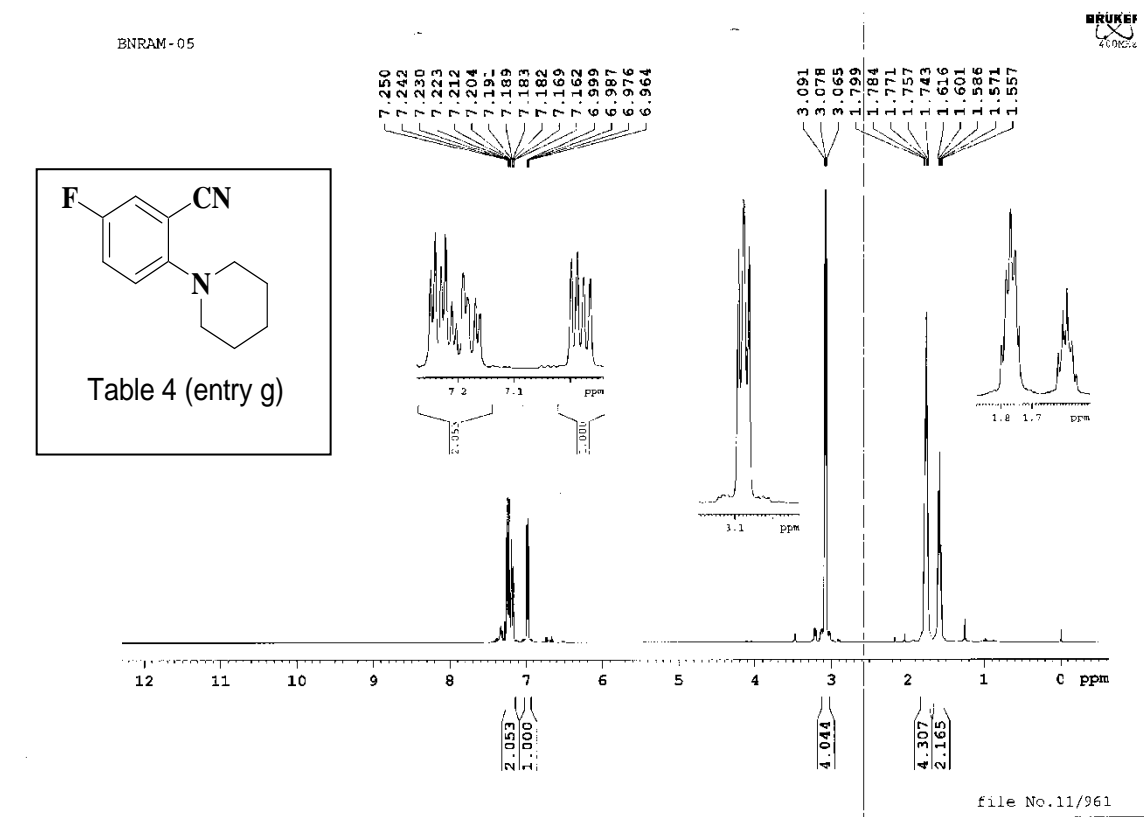
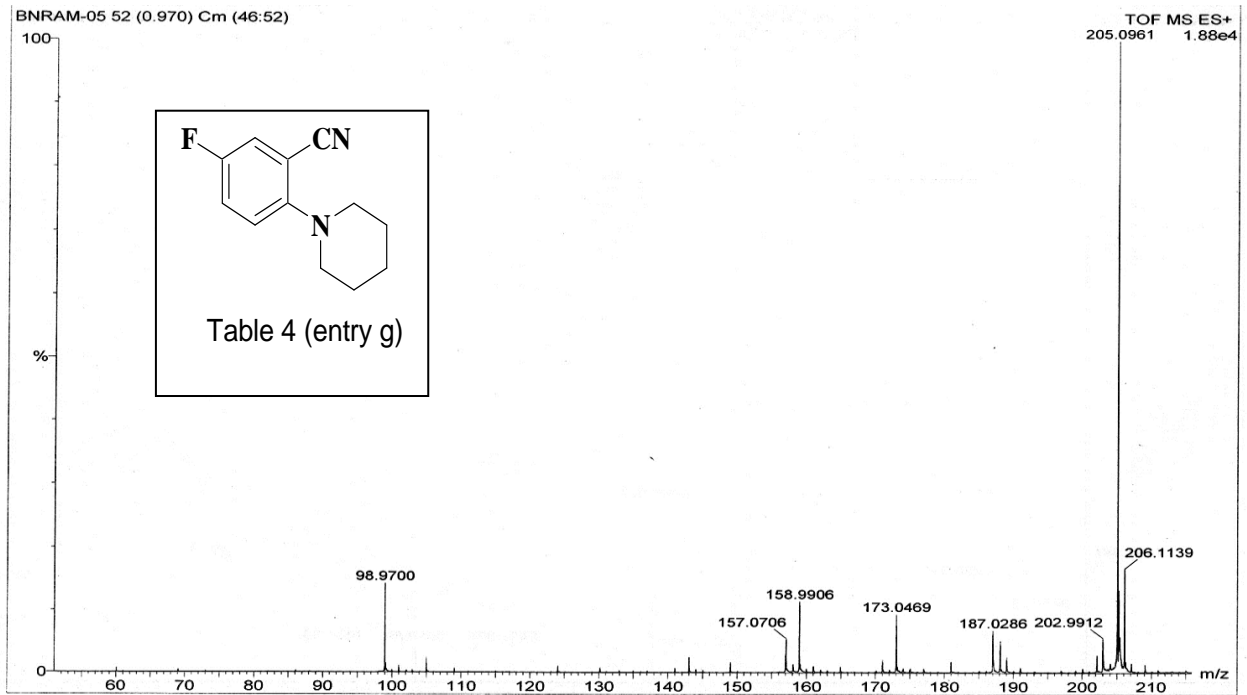
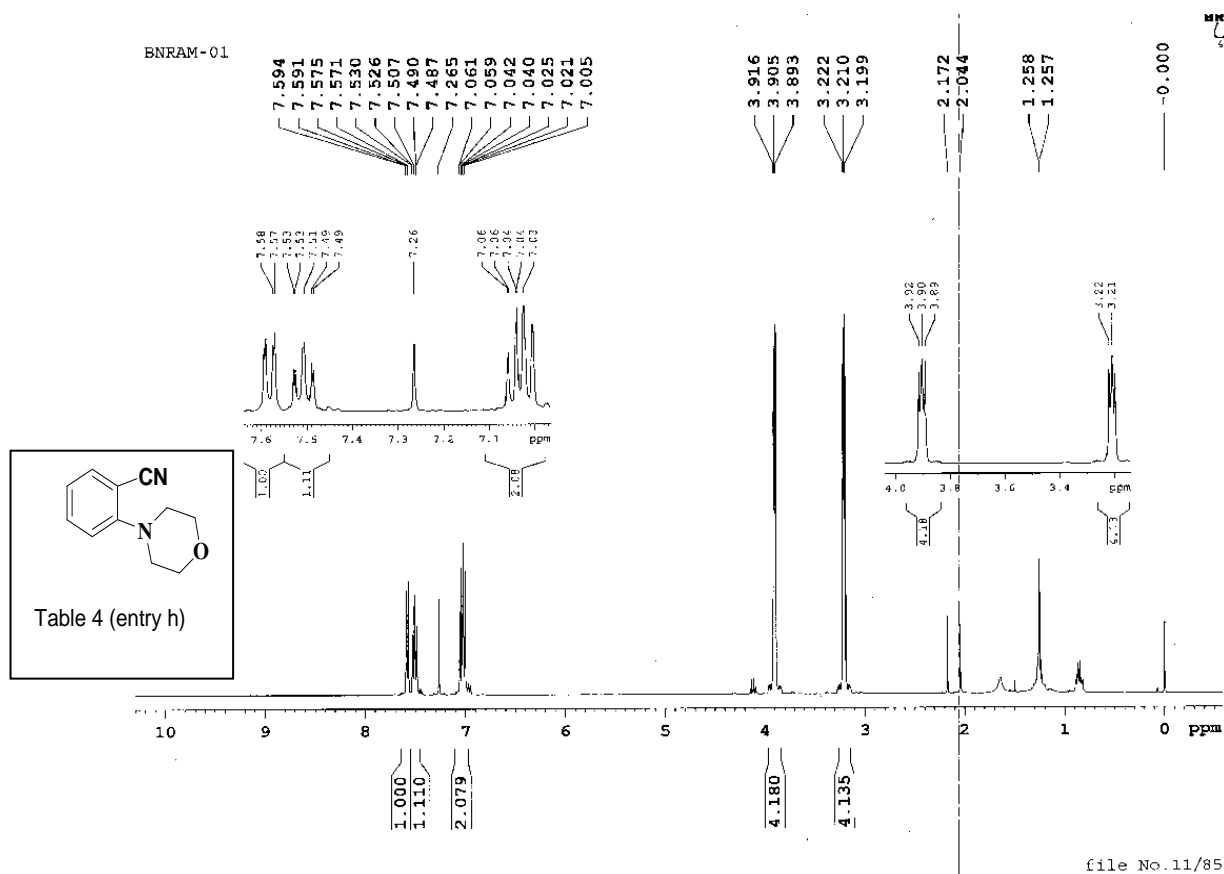


Table 4 (entry h)



3NRAM01MIX1 14 (0.260) Cm (13:19)

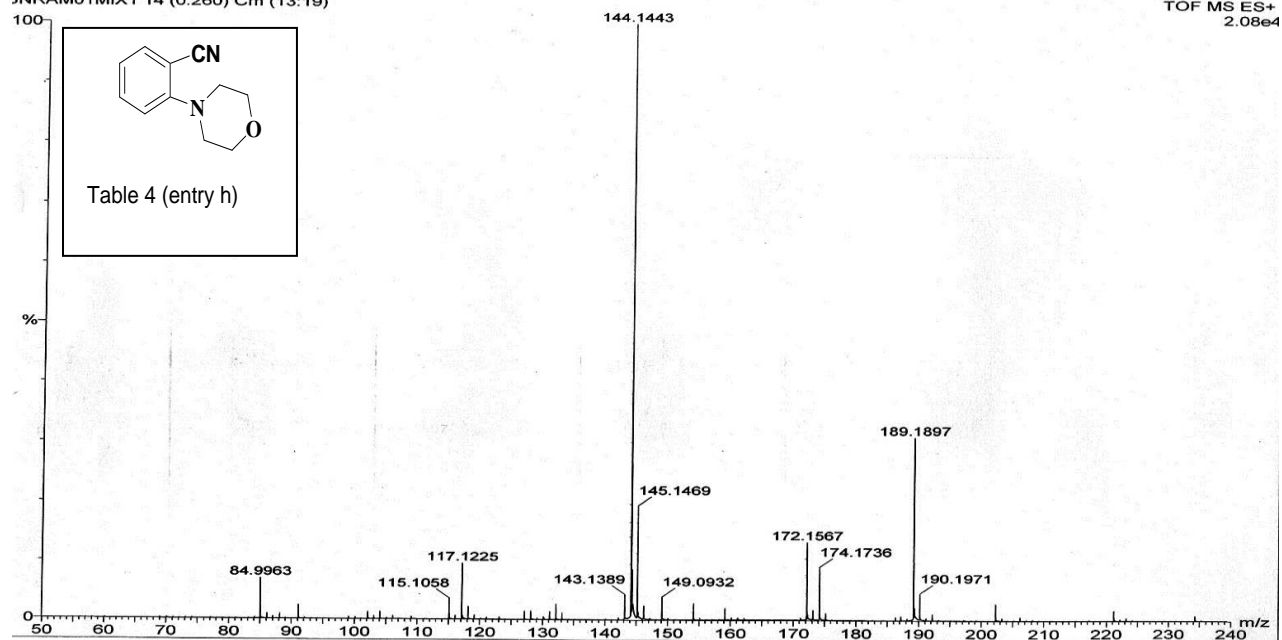


Table 4(entry i)

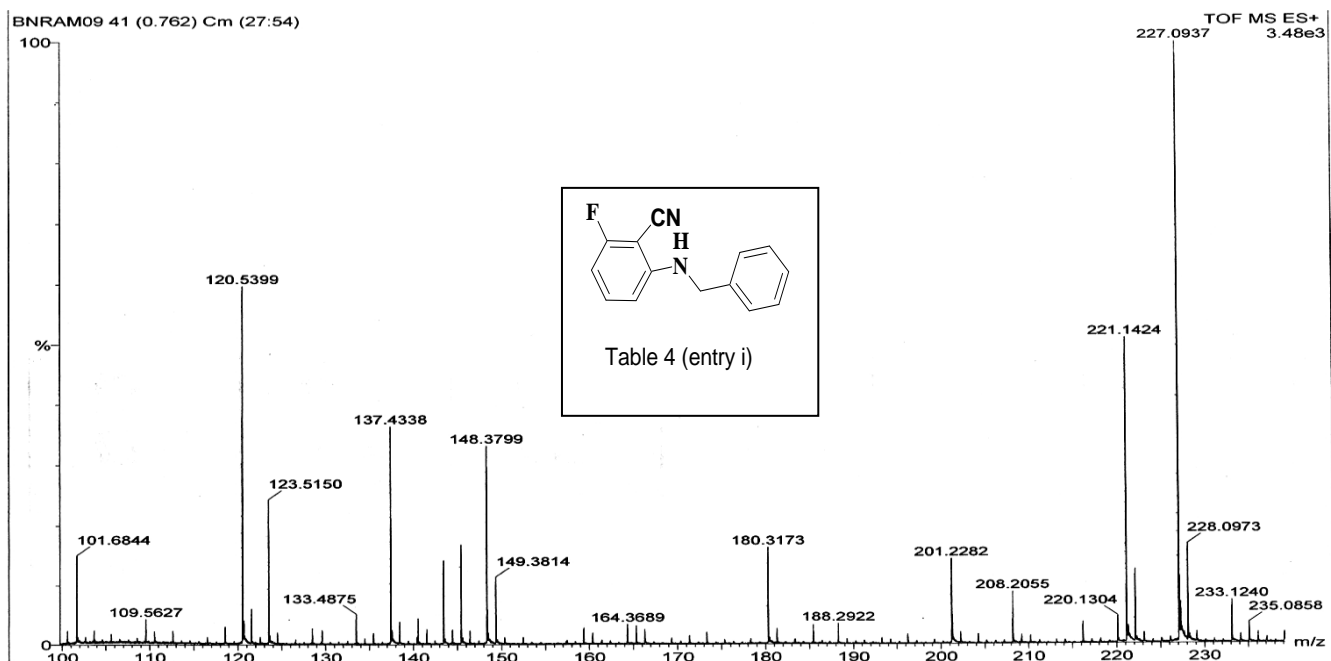
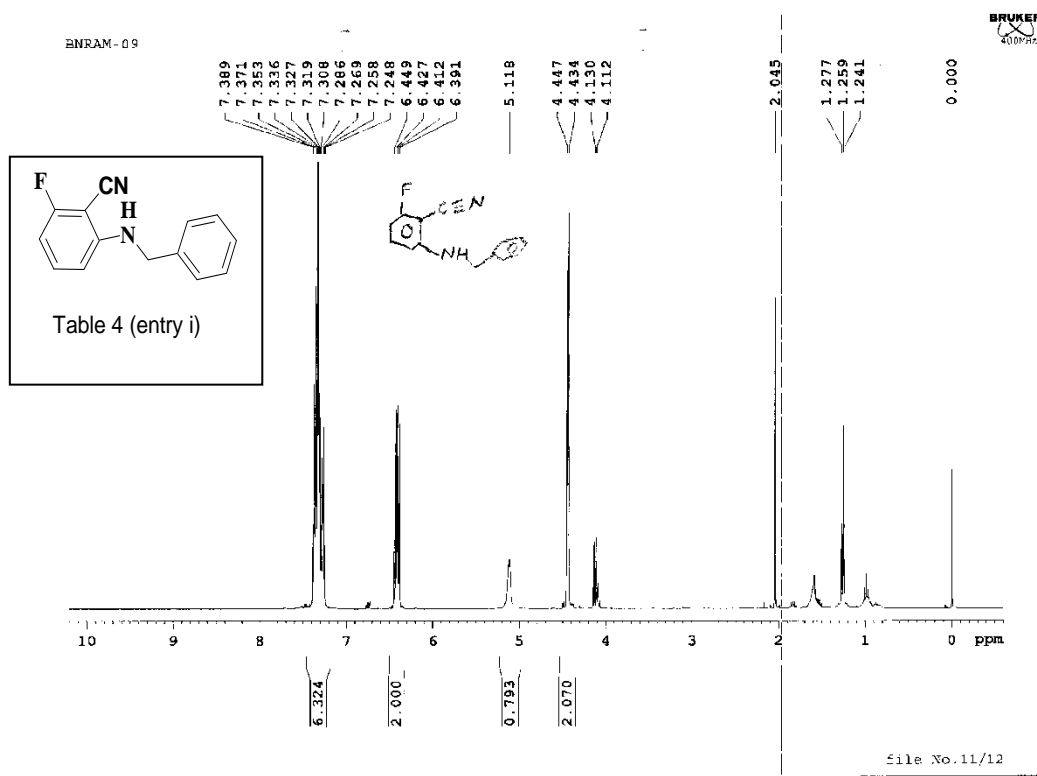
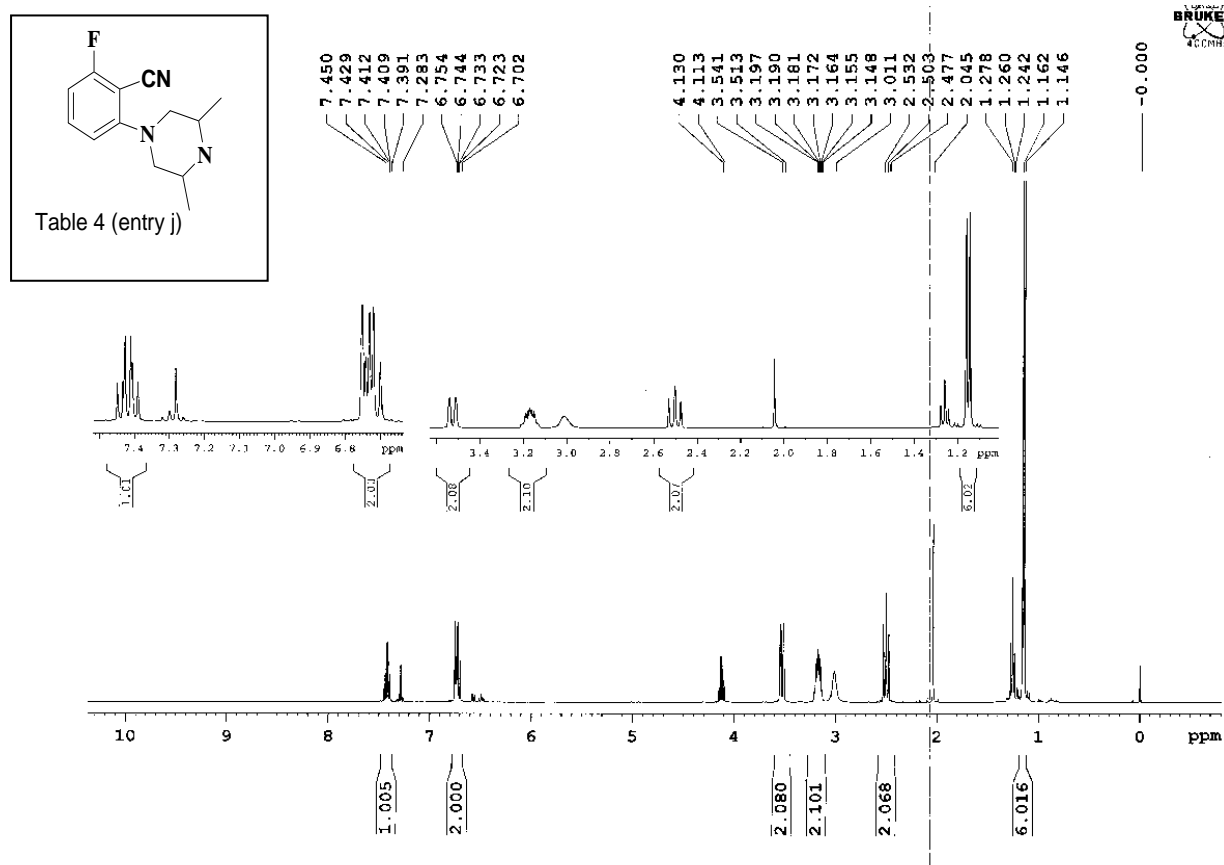
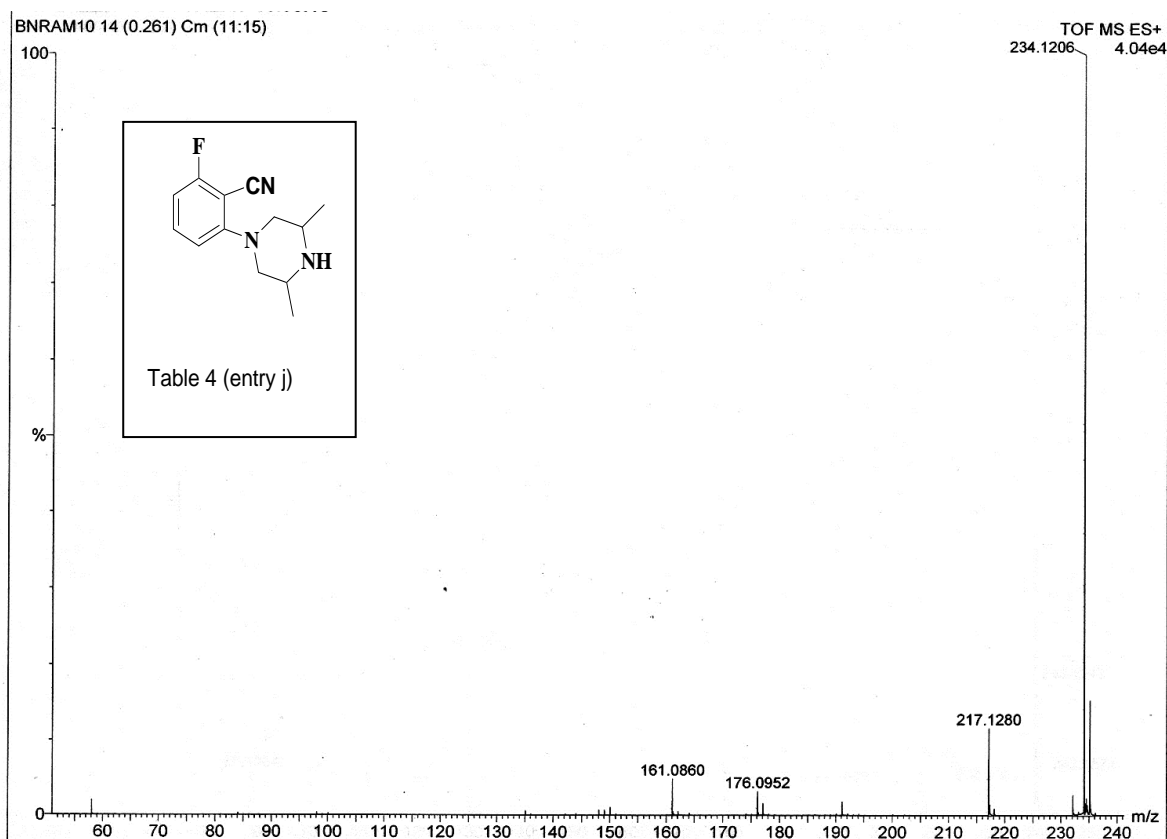


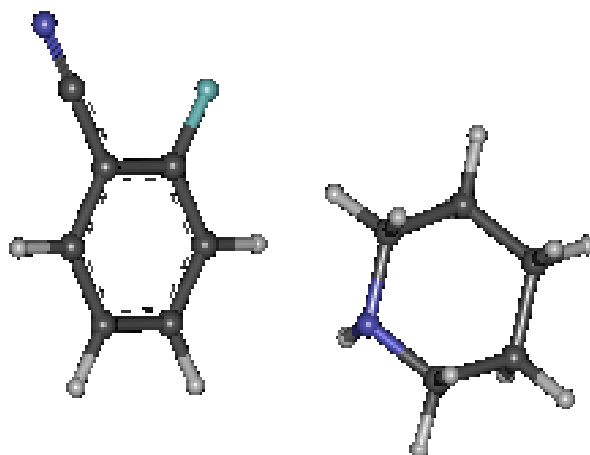
Table 4(entry i)



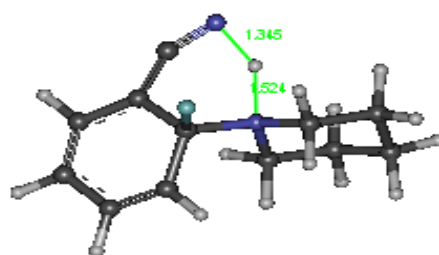
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AM1 Calculation:

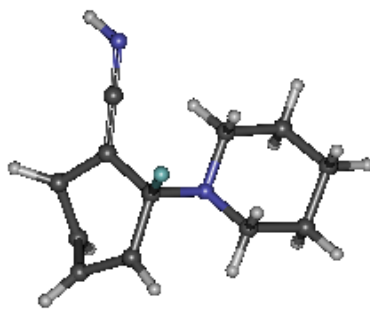
Structures, energies, and frequency calculations of 2-fluorobenzonitrile, piperidine, transition state 1 and 2, intermediate and product were calculated using semiempirical method AM1. Intermediate reaction coordinates (IRC) calculations were carried out in both forward and reverse directions. All the calculations were carried out by Gaussian 09.



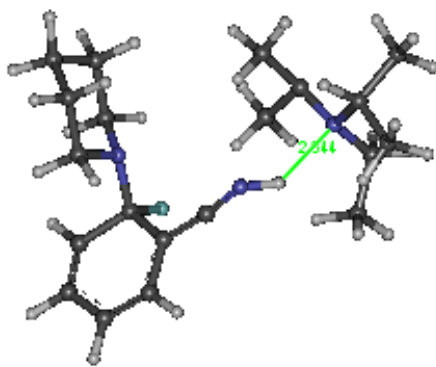
2-fluorobenzonitrile and piperidine: combined energy -12.75 Kcal/mol



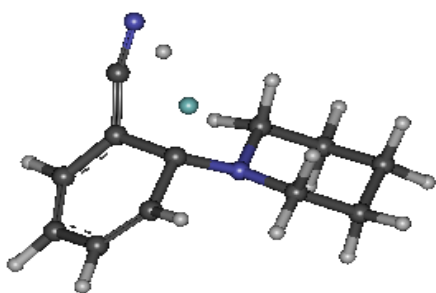
TS1 energy +88.38 Kcal/mol



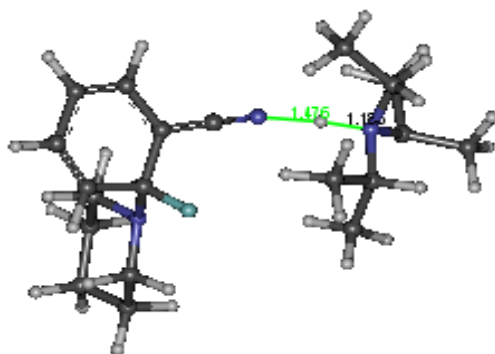
Intermediate energy +34.97 Kcal/mol



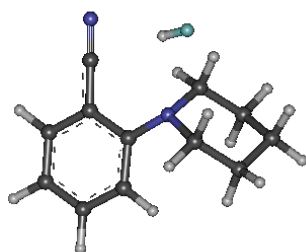
Intermediate + DIPEA , energy +10.28 Kcal/mol



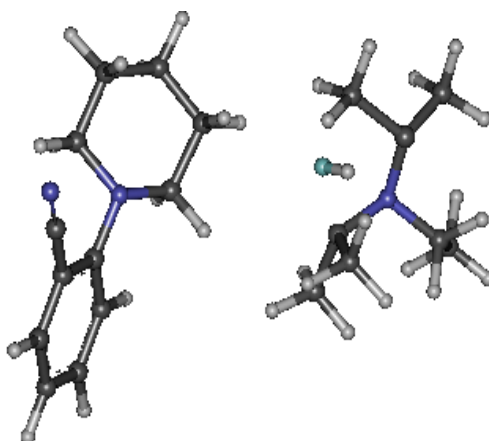
TS2 in absence of DIPEA, energy +106.48 Kcal/mol



TS2 in presence of DIPEA, energy +30.1 Kcal/mol



Product in absence of DIPEA, -28.25 Kcal/mol



Product in presence of DIPEA, -50.77 Kcal/mol

Table S1: Energy of various species

	energy In presence of DIPEA	Relative energy In presence of DIPEA	energy In absence of DIPEA	Relative energy In absence of DIPEA
2-FB-PIP	-12.79	37.98	-12.79	37.98
TS1	88.38	139.16	88.38	139.16
IM1-DIPEA	10.28	61.06	34.97	85.75
TS2	30.1	80.87	106.48	157.26
Product complex	-50.77	0	-28.25	22.52