Supporting Information

Synthesis and Biological Assessment of Novel 4*H*-Chromene-3-Carbonitrile Derivatives as Tyrosinase Inhibitors

A) spectrums of compound 6a:

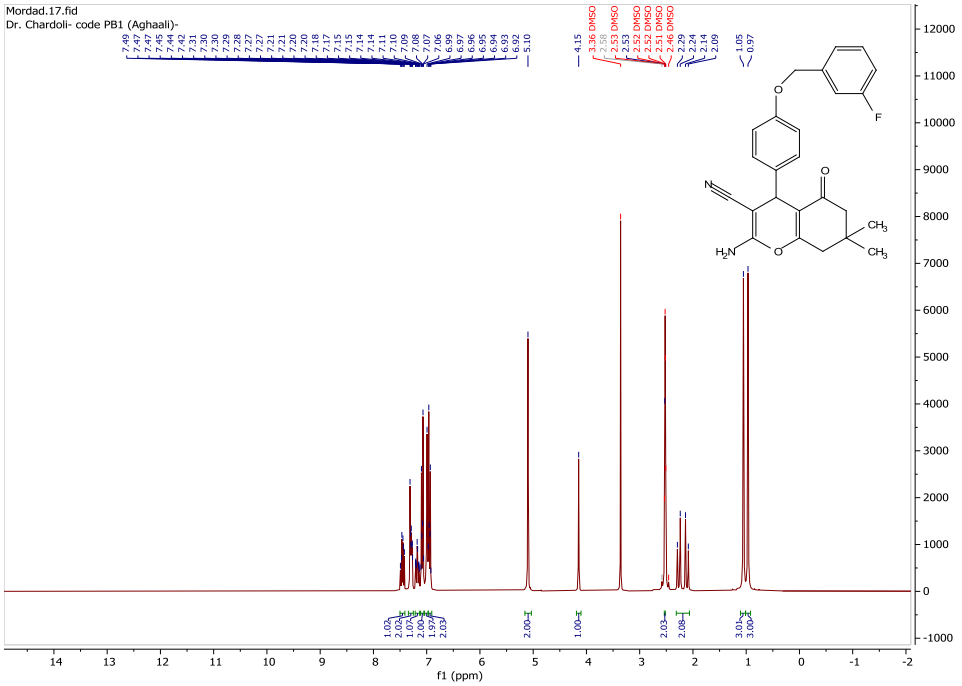


Figure S1. [1]H-NMR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6a)

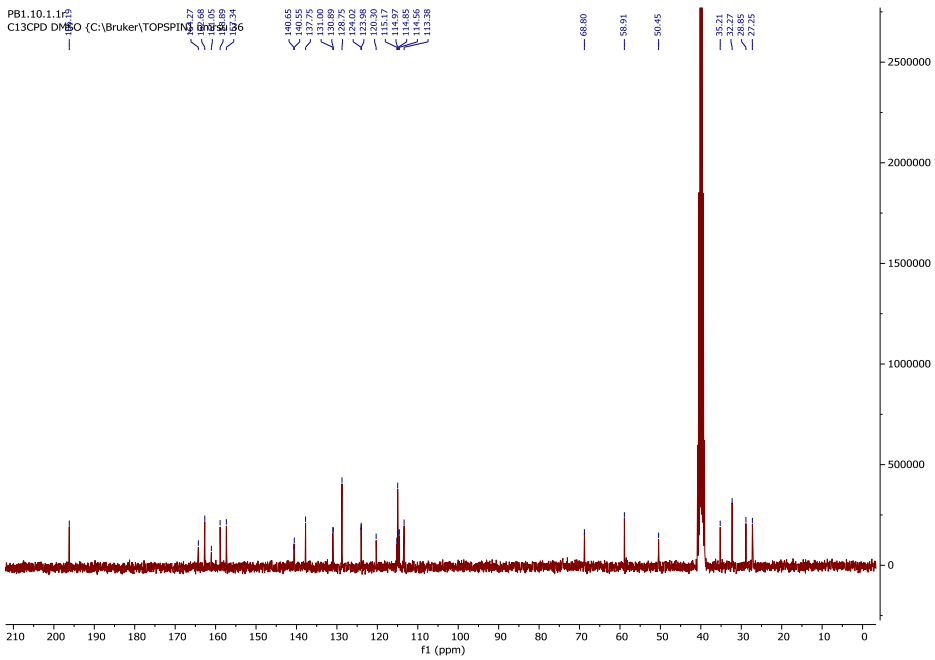


Figure S2. ^{13}C-NMR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6a)

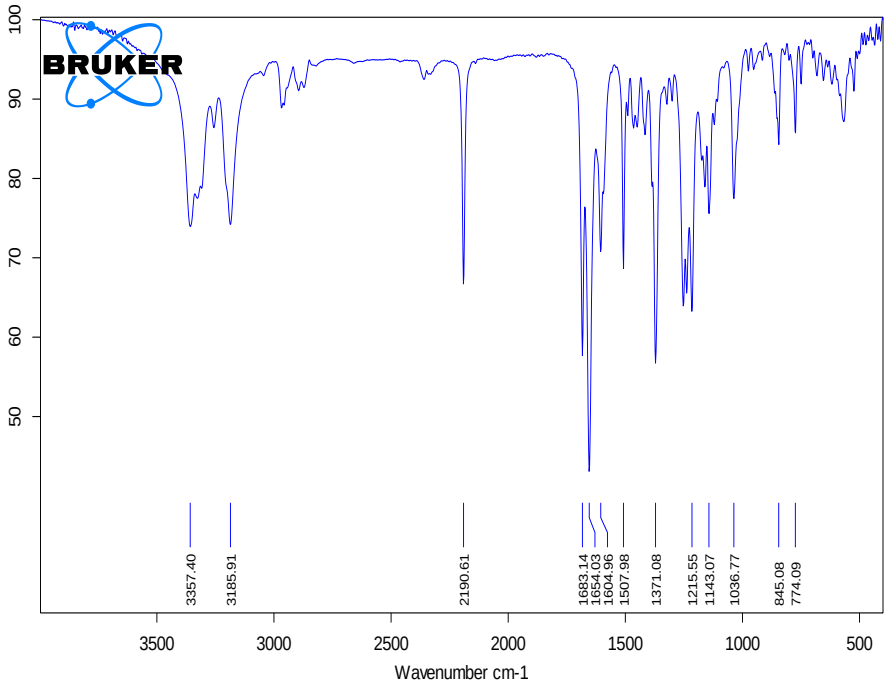


Figure S3. FT-IR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6a)

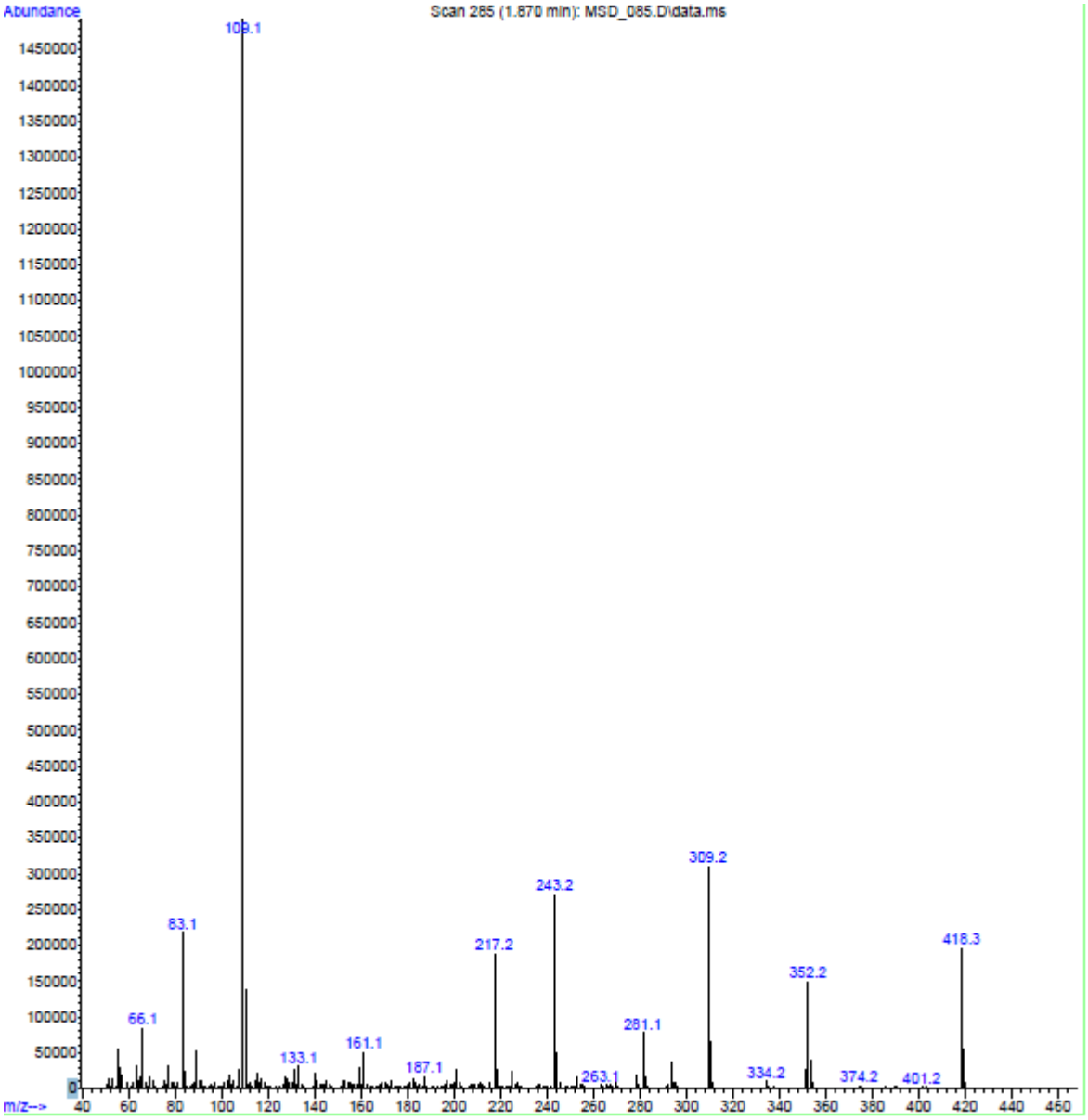


Figure S4. Mass spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6a)

B) spectrums of compound 6b:

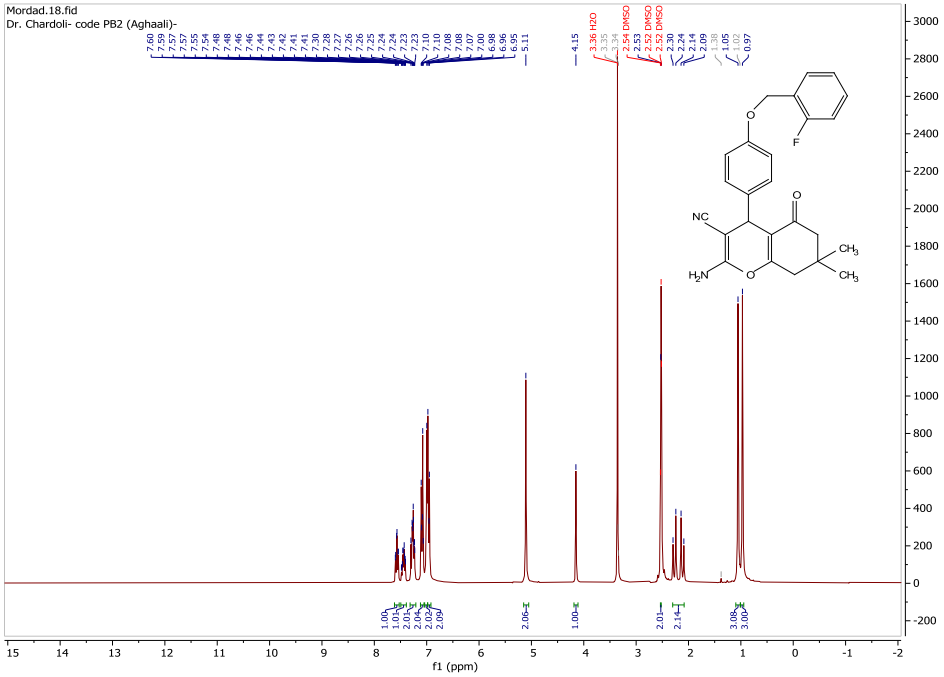


Figure S5. [1]H-NMR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6b)

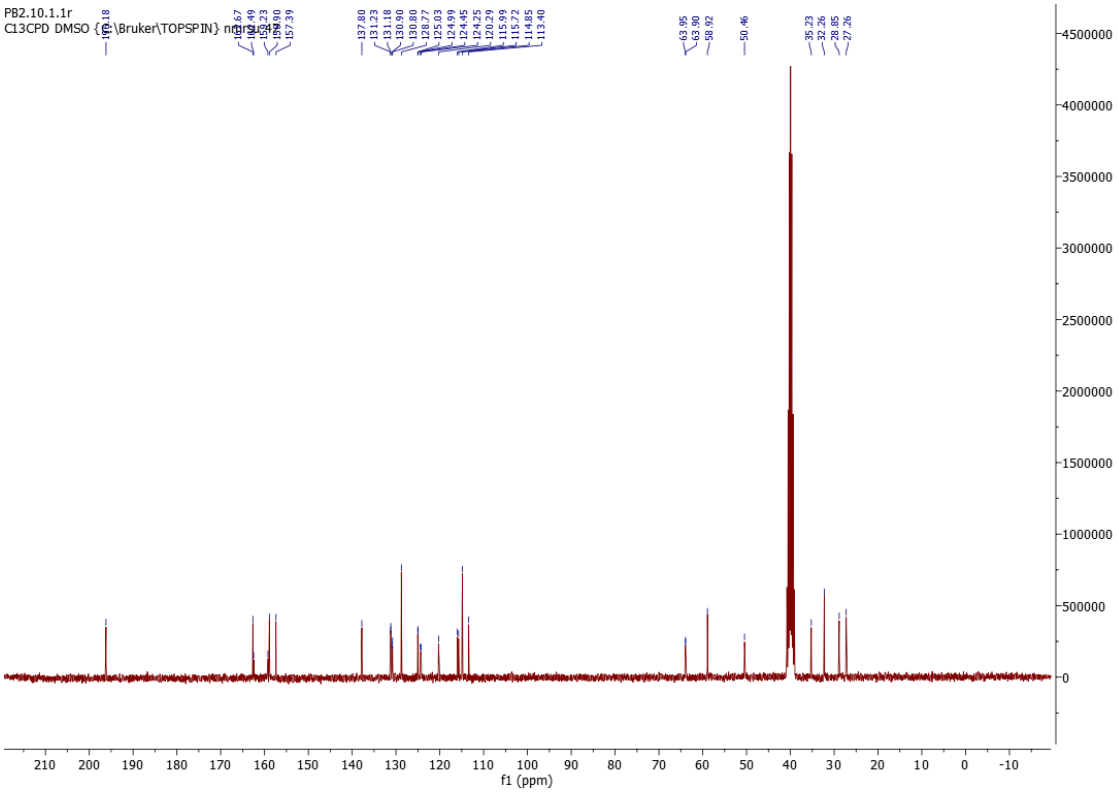


Figure S6. ^{13}C-NMR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6b)

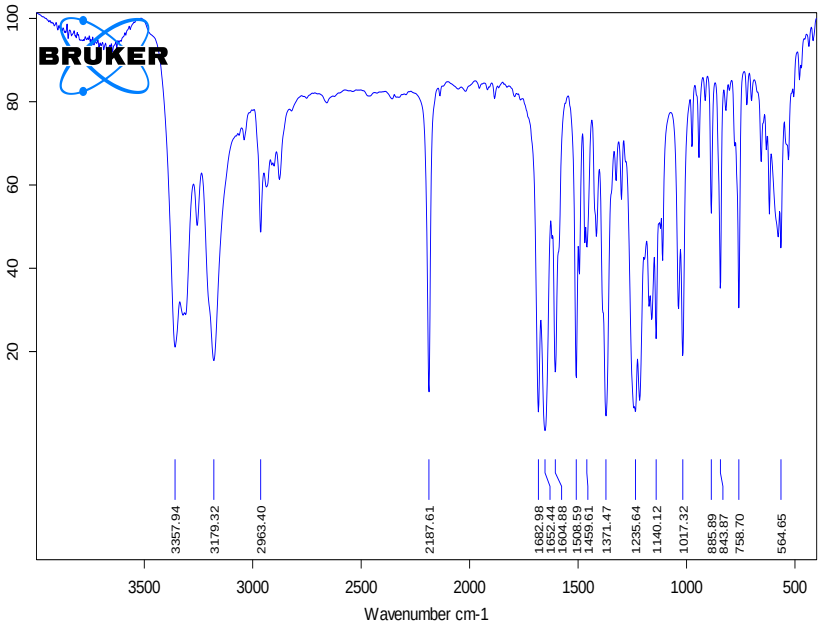


Figure S7. FT-IR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6b)

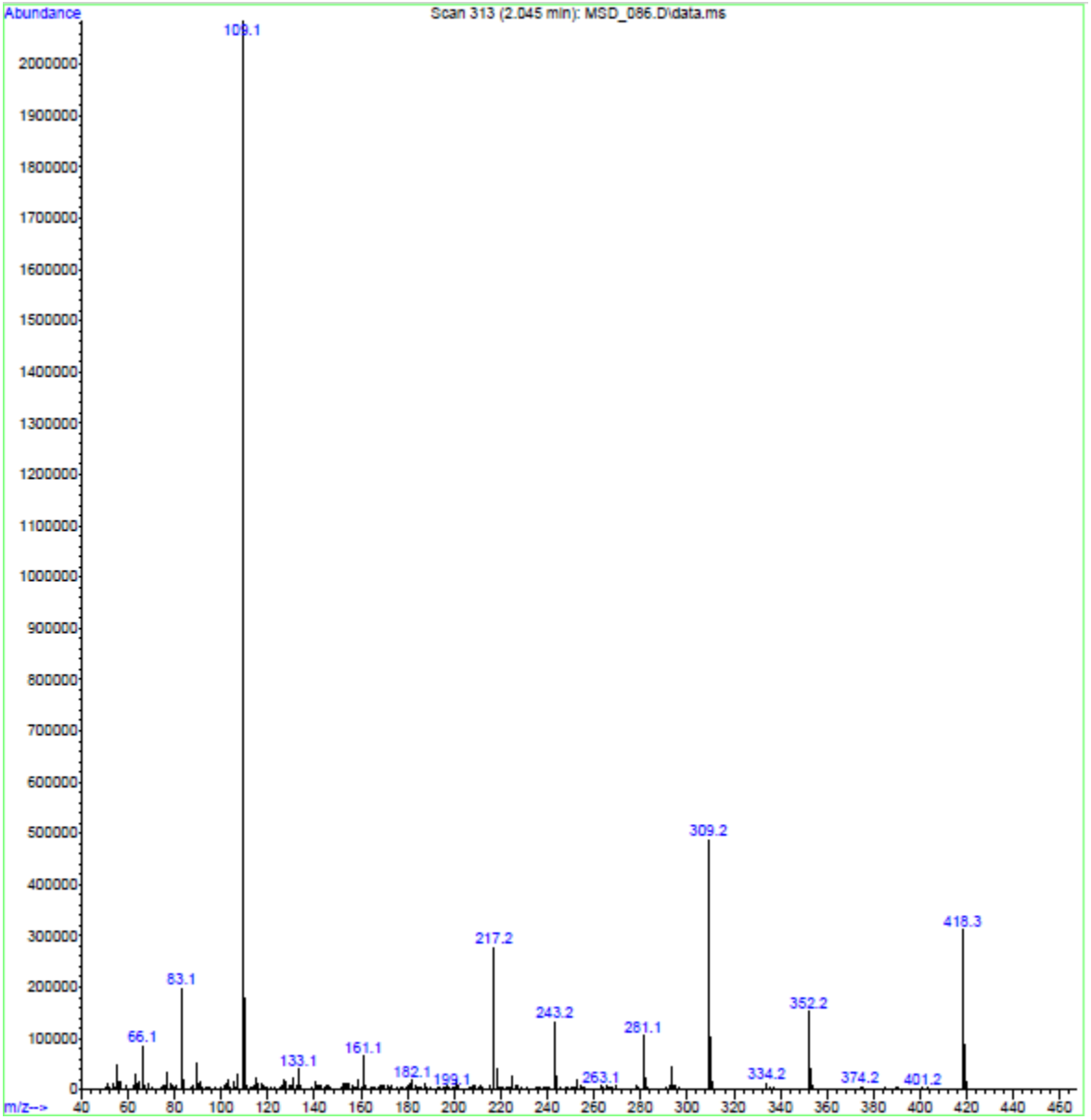


Figure S8. Mass spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6b)

C) spectrums of compound 6c:

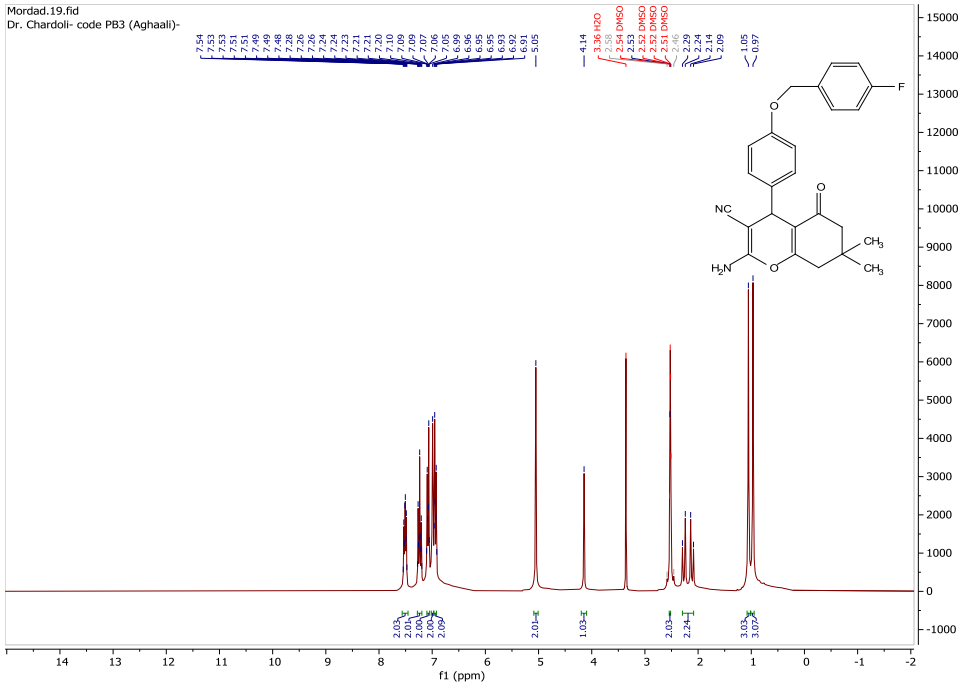


Figure S9. [1]H-NMR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6c)

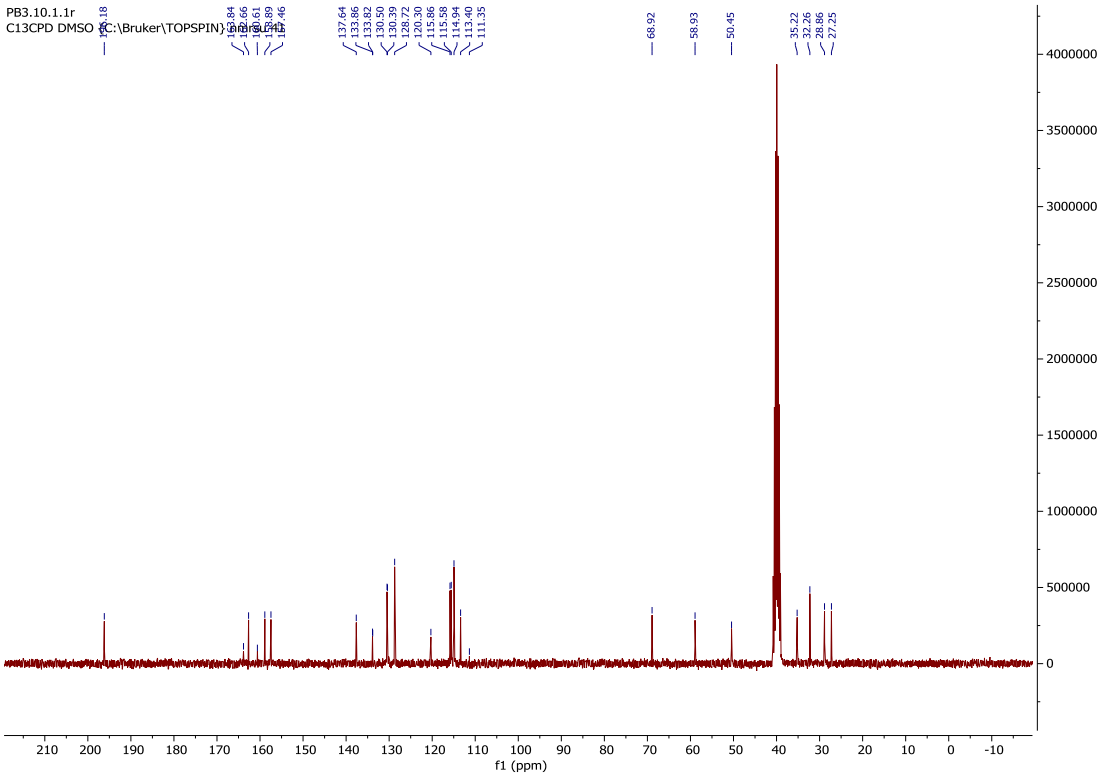


Figure S10. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6c)

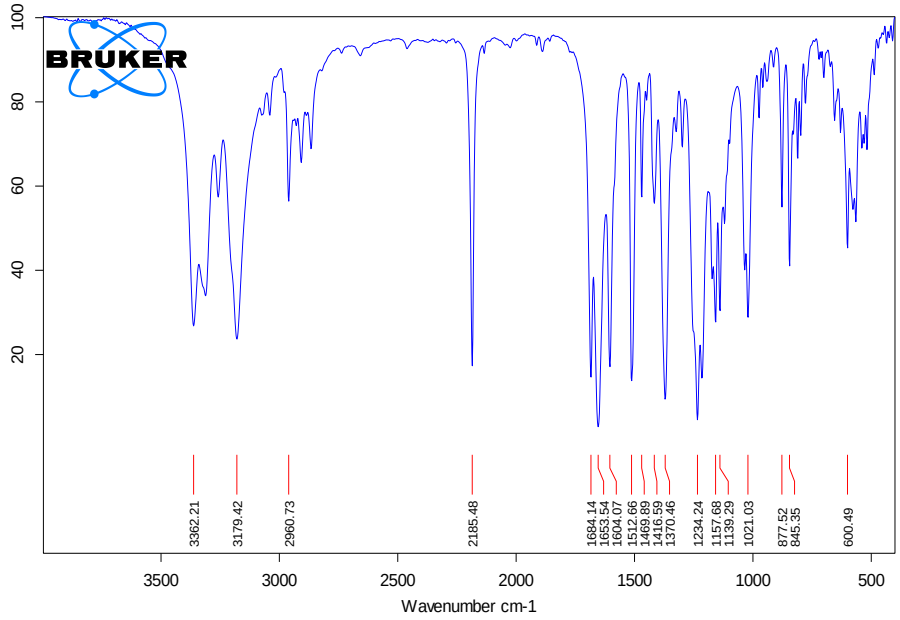


Figure S11. FT-IR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6c)

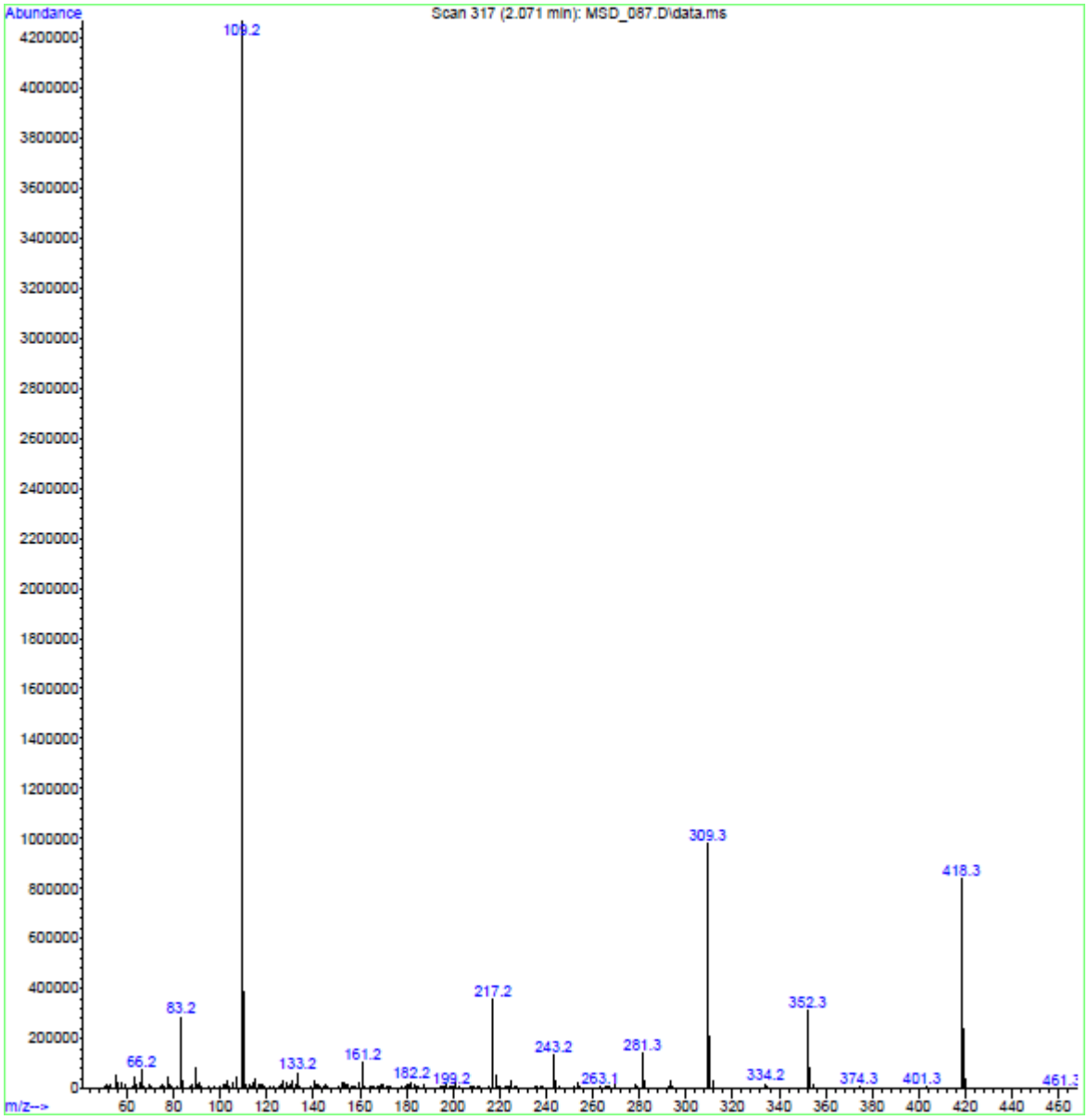


Figure S12. Mass spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6c)

D) spectrums of compound 6d:

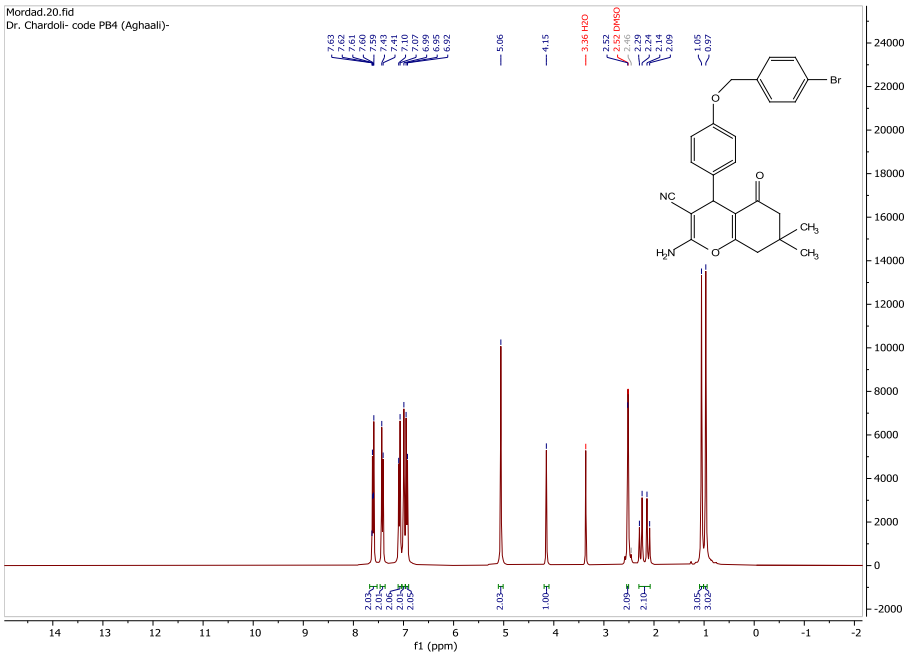


Figure S13. [1]H-NMR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6d)

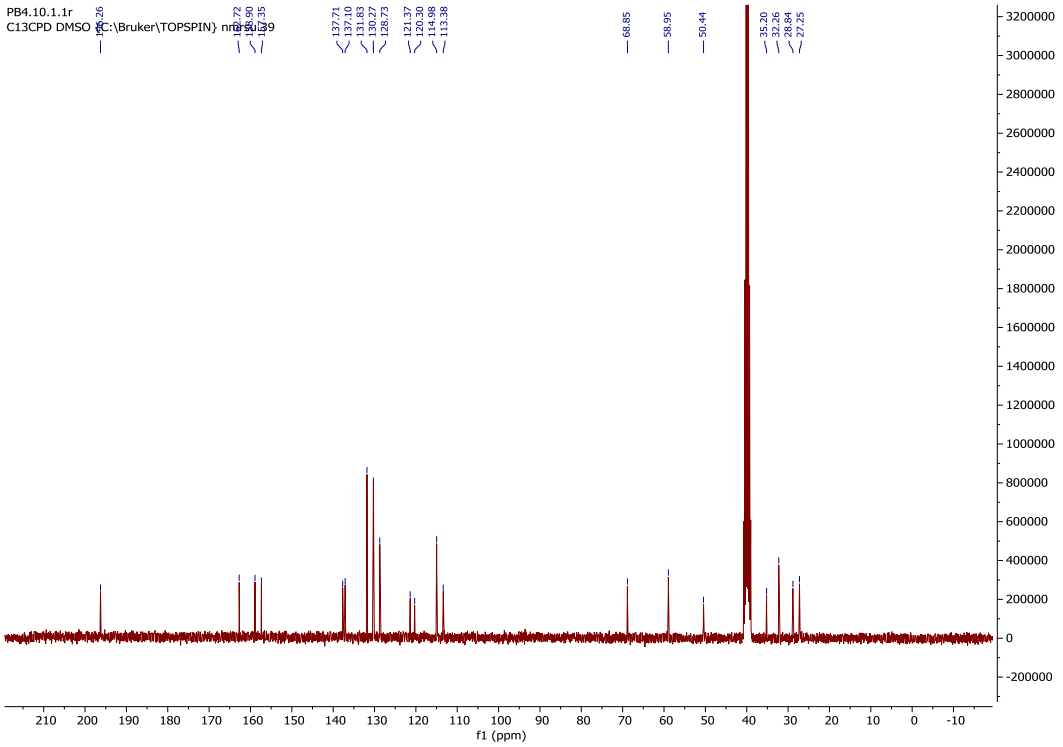


Figure S14. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6d)

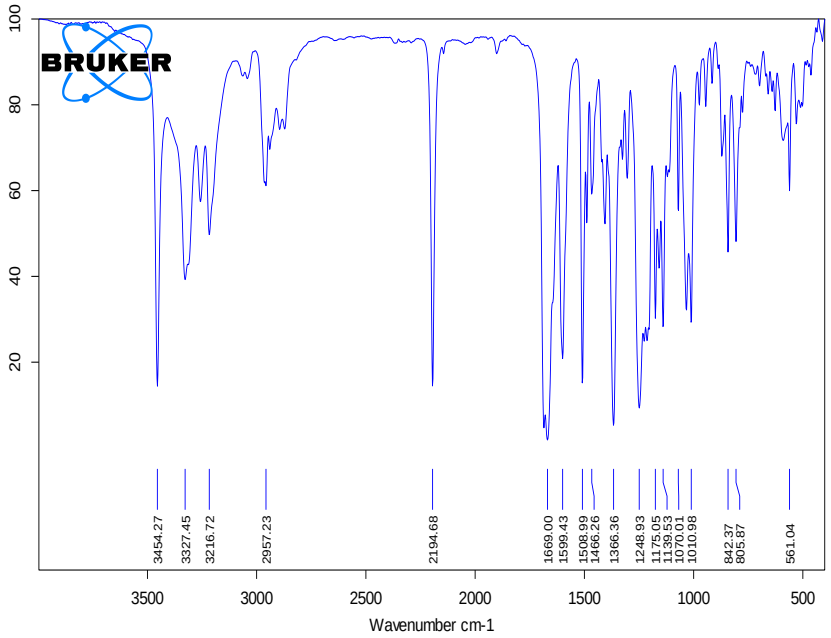


Figure S15. FT-IR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6d)

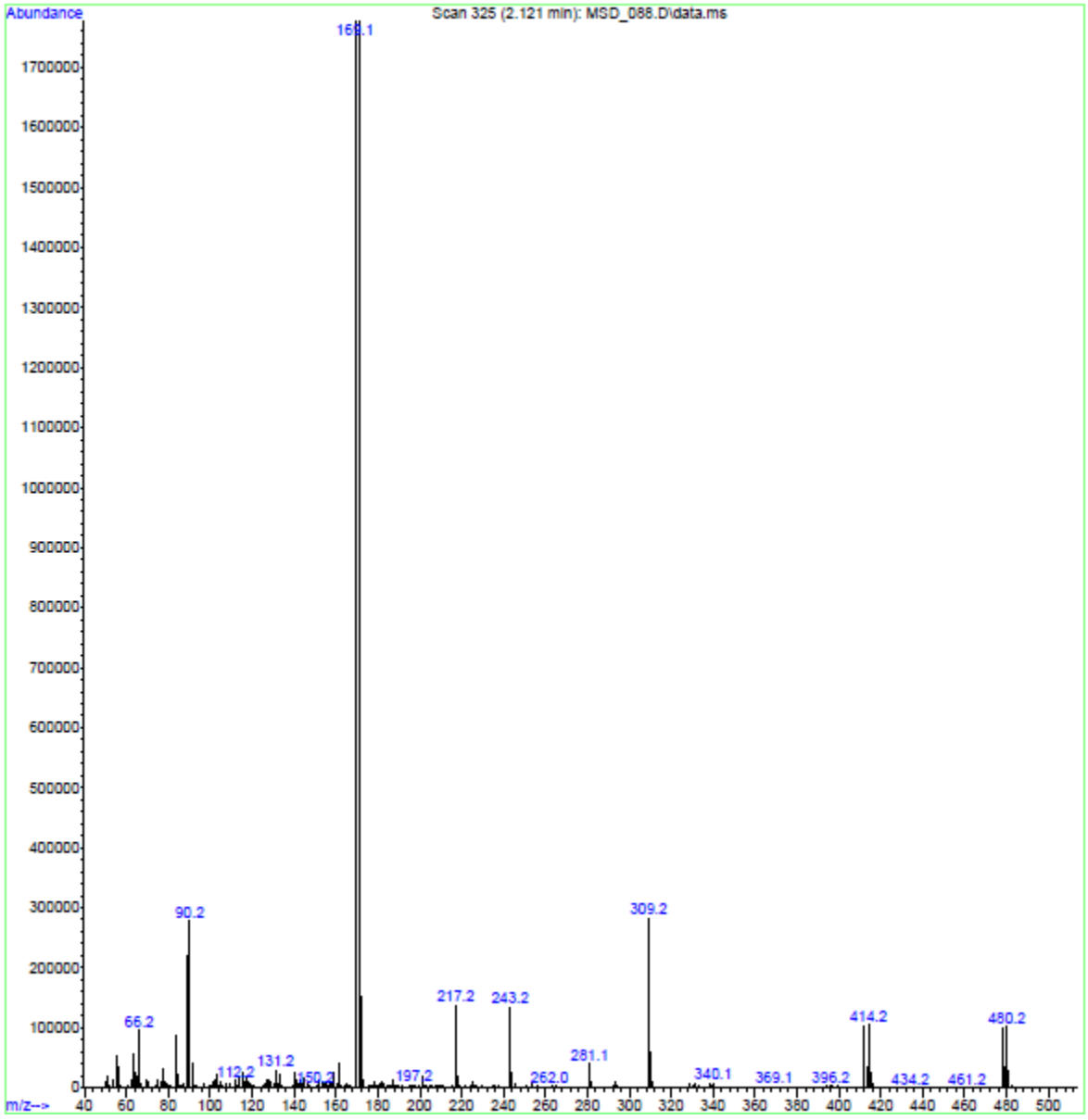


Figure S16. Mass spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6d)

E) spectrums of compound 6e:

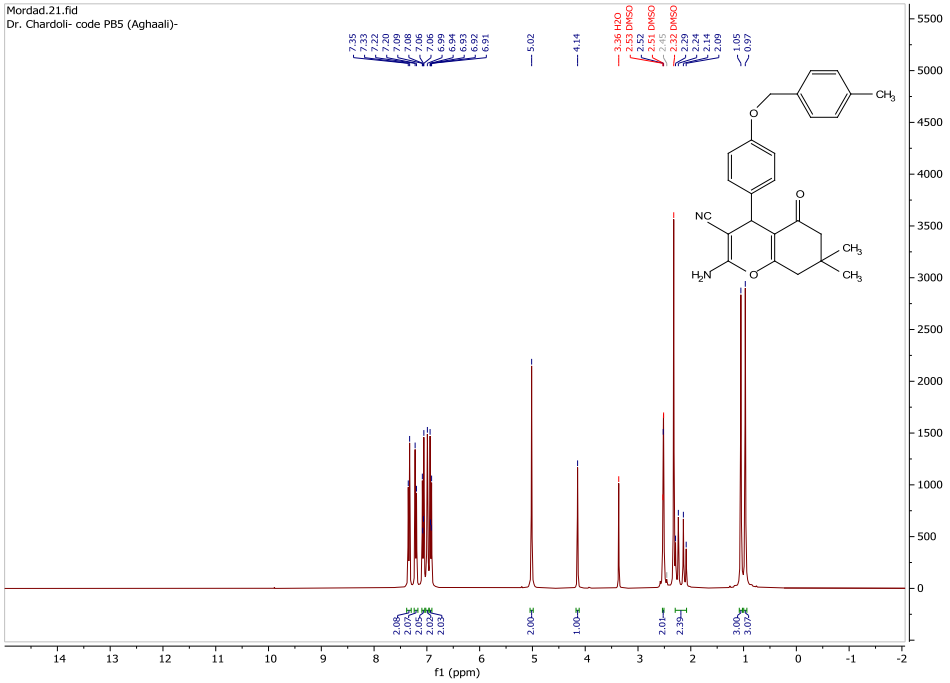


Figure S17. [1]H-NMR spectrum of 2-amino-7,7-dimethyl-4-(4-((4-methylbenzyl)oxy)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6e)

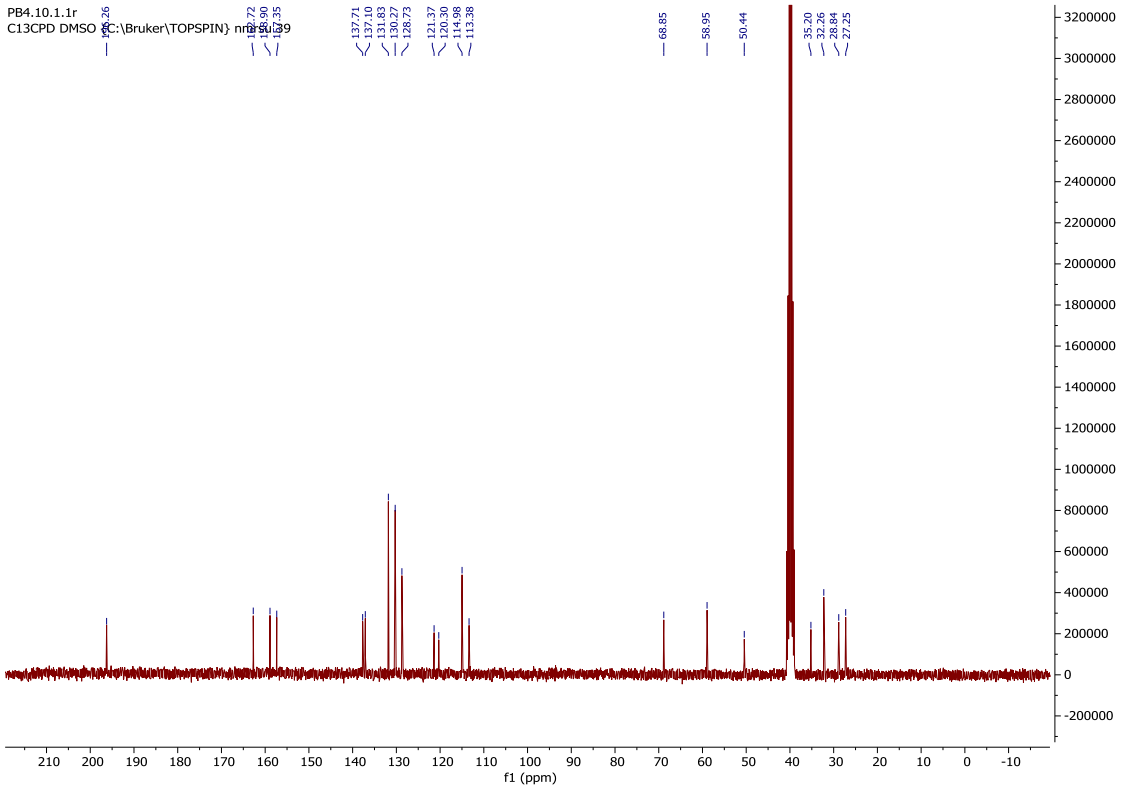


Figure S18. ^{13}C-NMR spectrum of 2-amino-7,7-dimethyl-4-(4-((4-methylbenzyl)oxy)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6e)

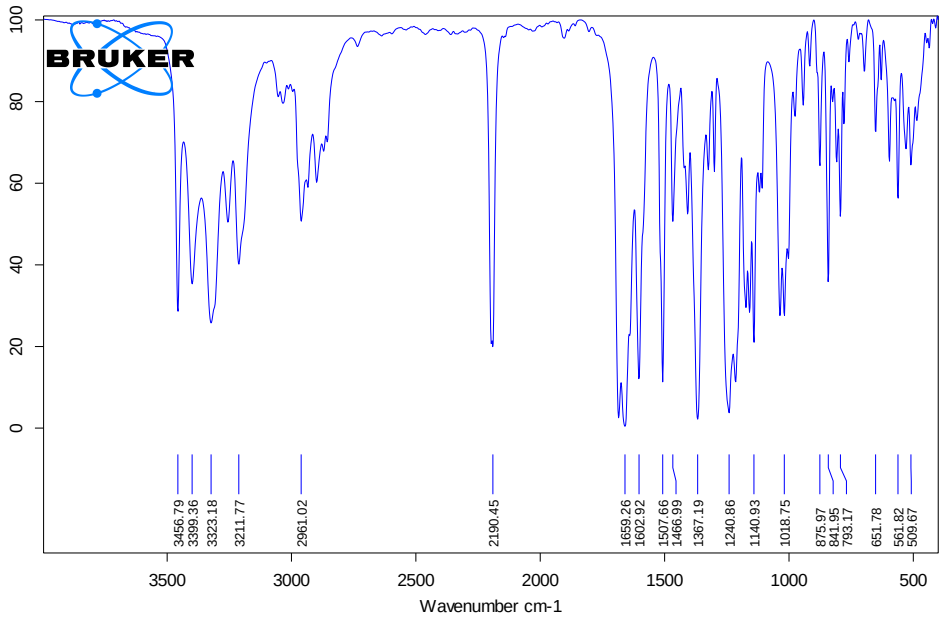


Figure S19. FT-IR spectrum of 2-amino-7,7-dimethyl-4-(4-((4-methylbenzyl)oxy)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6e)

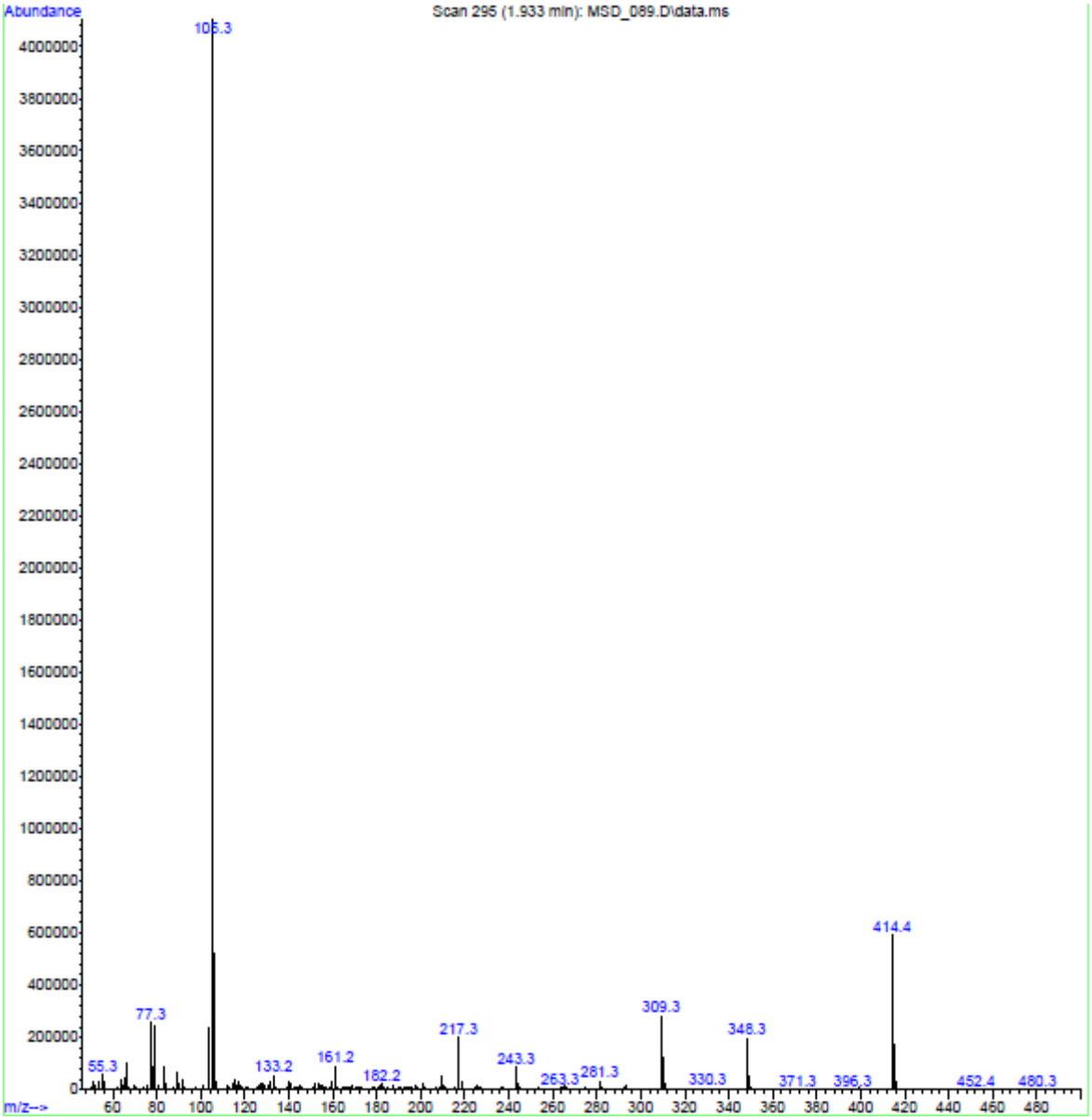


Figure S20. Mass spectrum of 2-amino-7,7-dimethyl-4-(4-((4-methylbenzyl)oxy)phenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6e)

F) spectrums of compound 6f:

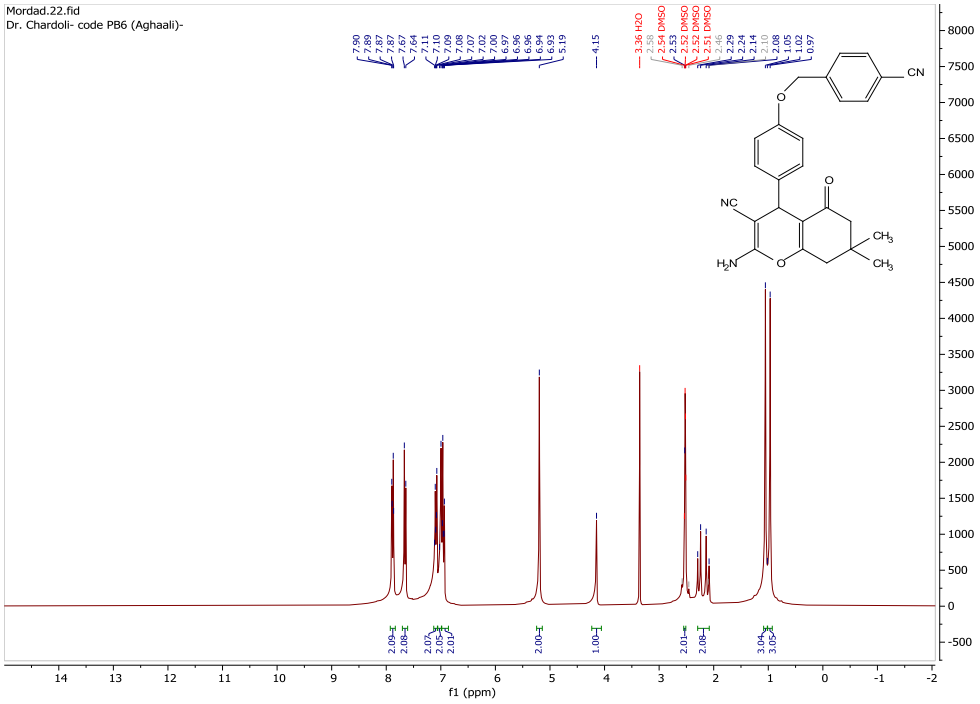


Figure S21. [1]H-NMR spectrum of 2-amino-4-(4-((4-cyanobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6f)

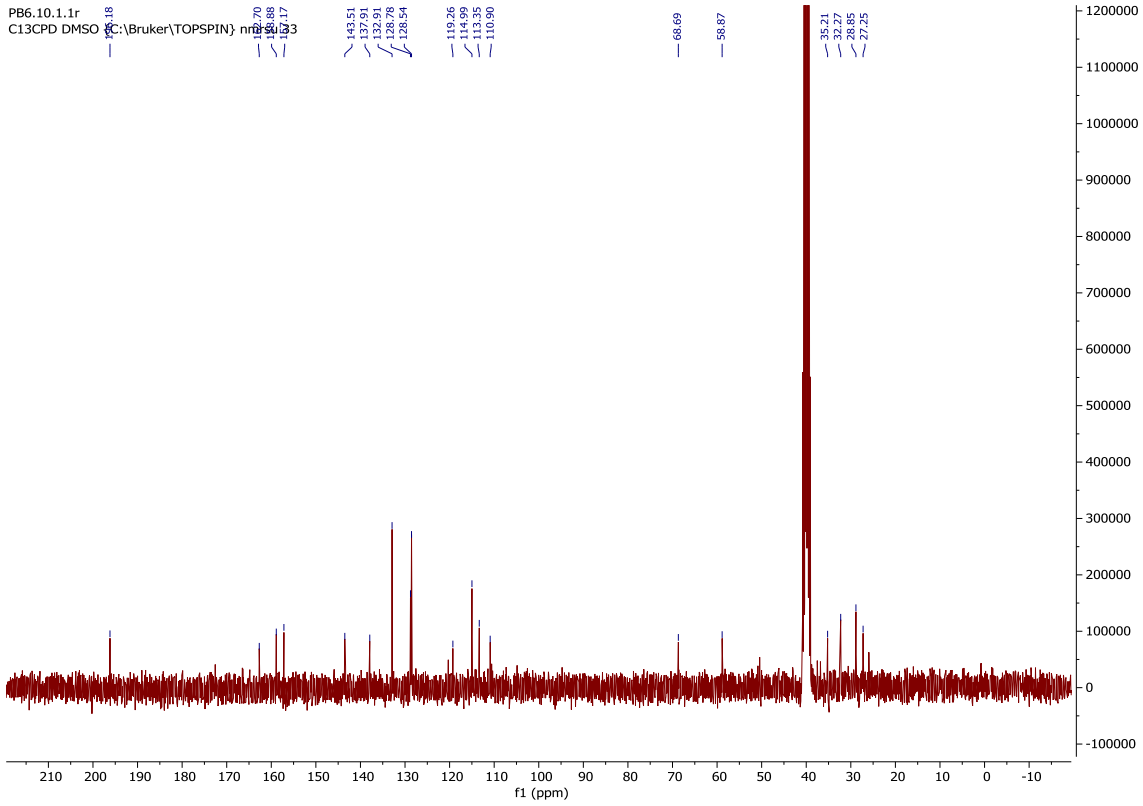


Figure S22. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-cyanobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6f)

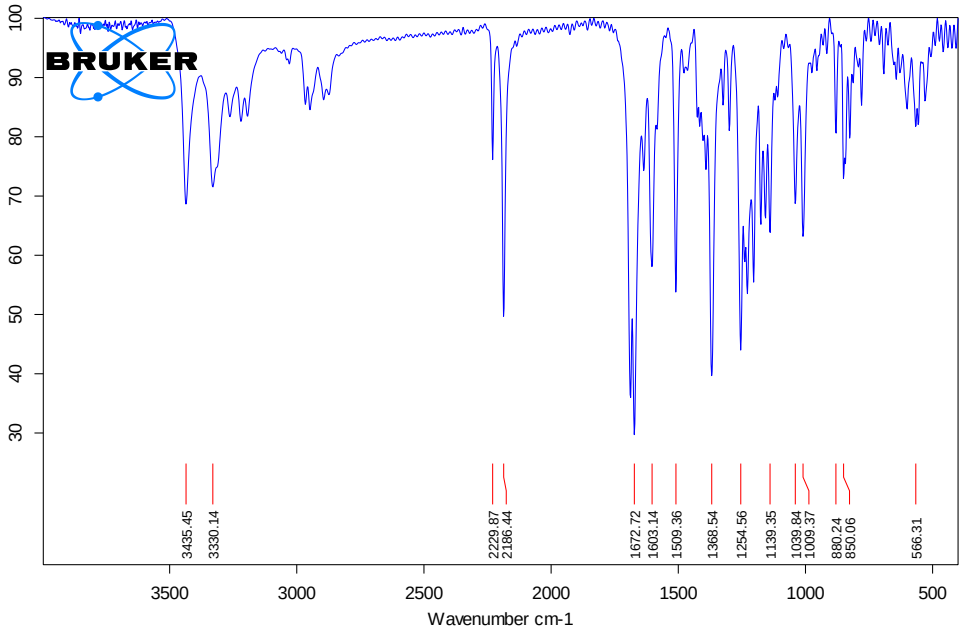


Figure S23. FT-IR spectrum of 2-amino-4-(4-((4-cyanobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6f)

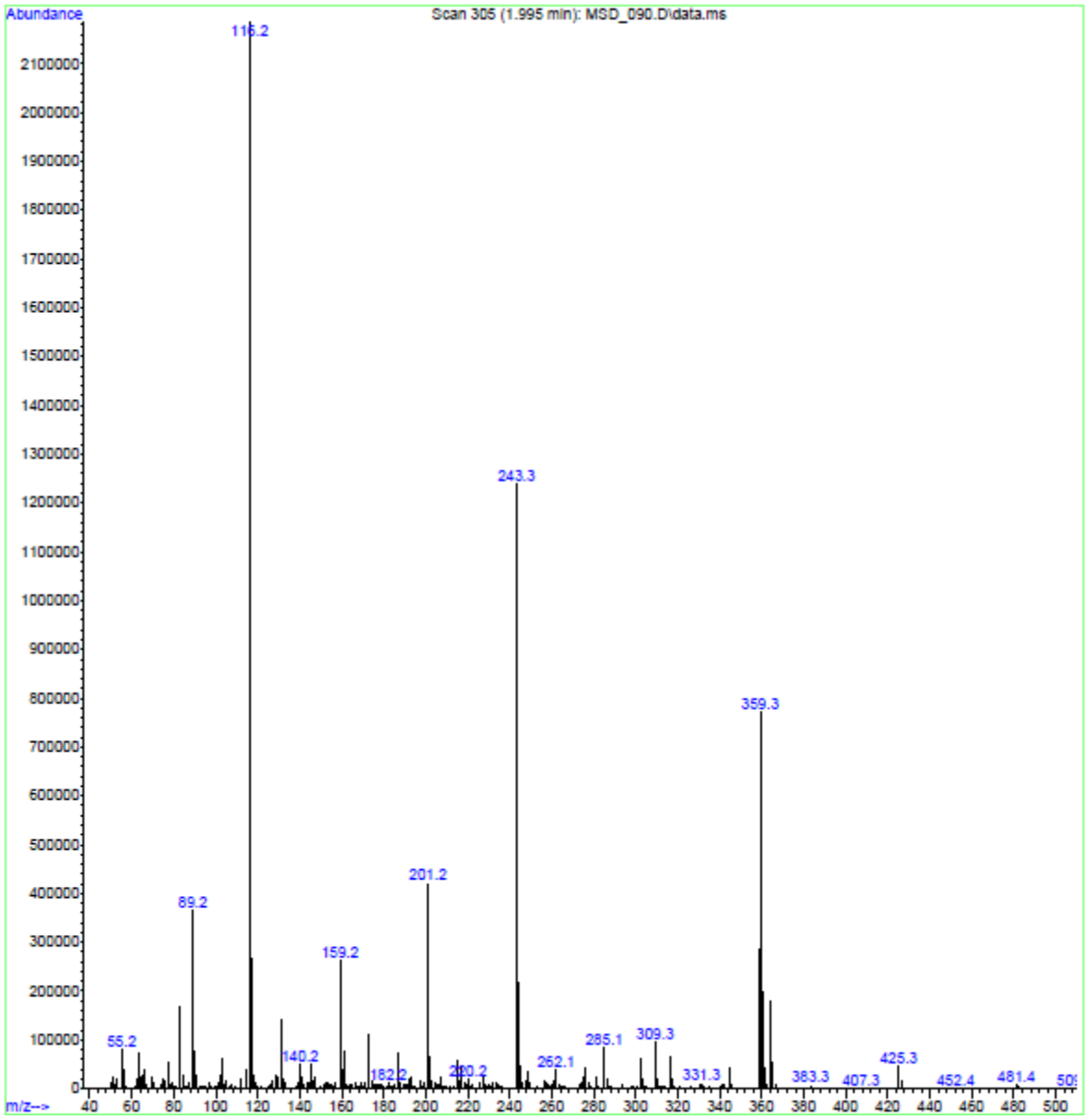


Figure S24. Mass spectrum of 2-amino-4-(4-((4-cyanobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6f)

G) spectrums of compound 6g:

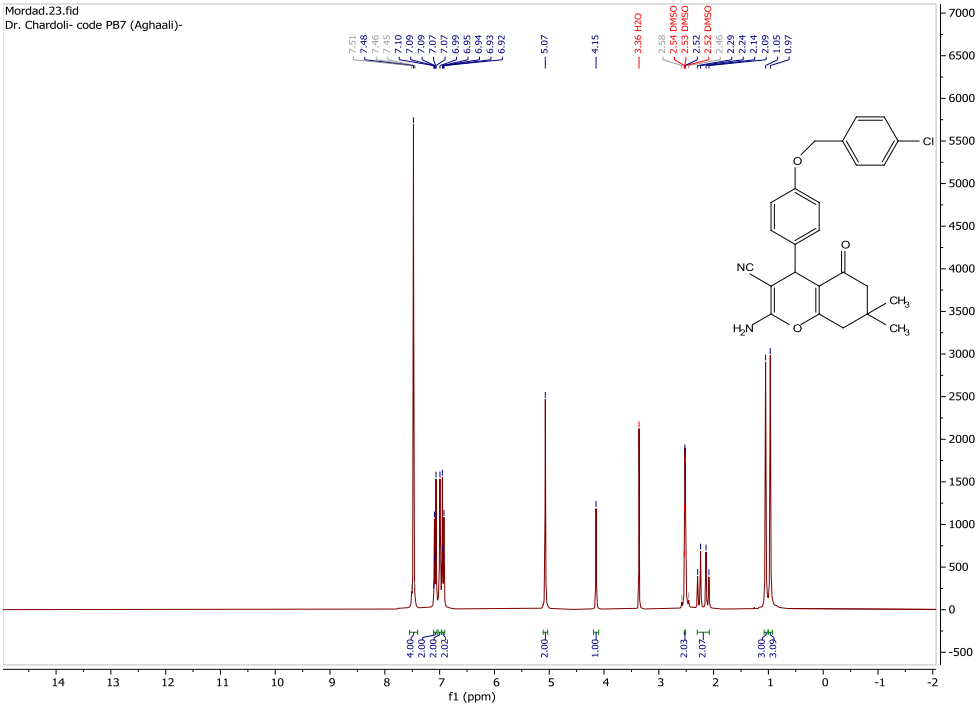


Figure S25. [1]H-NMR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6g)

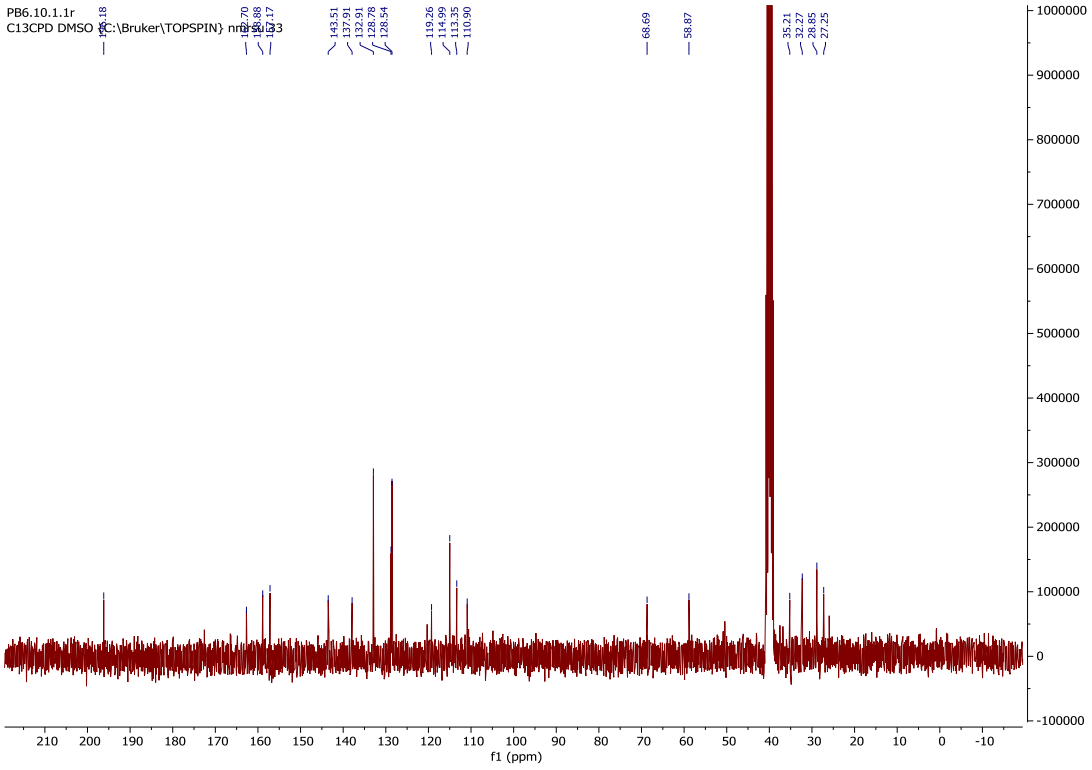


Figure S26. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6g)

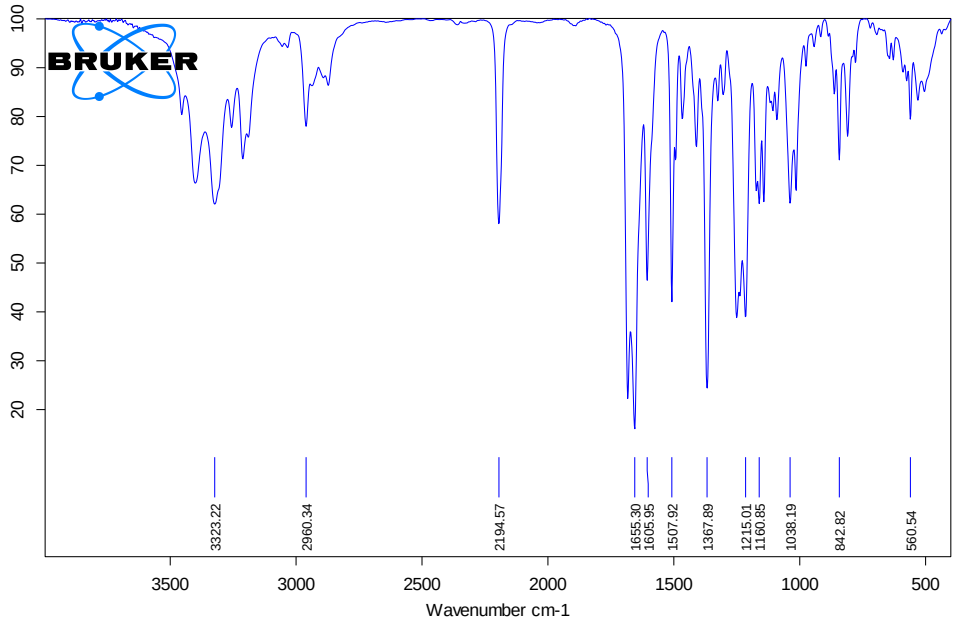


Figure S27. FT-IR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6g)

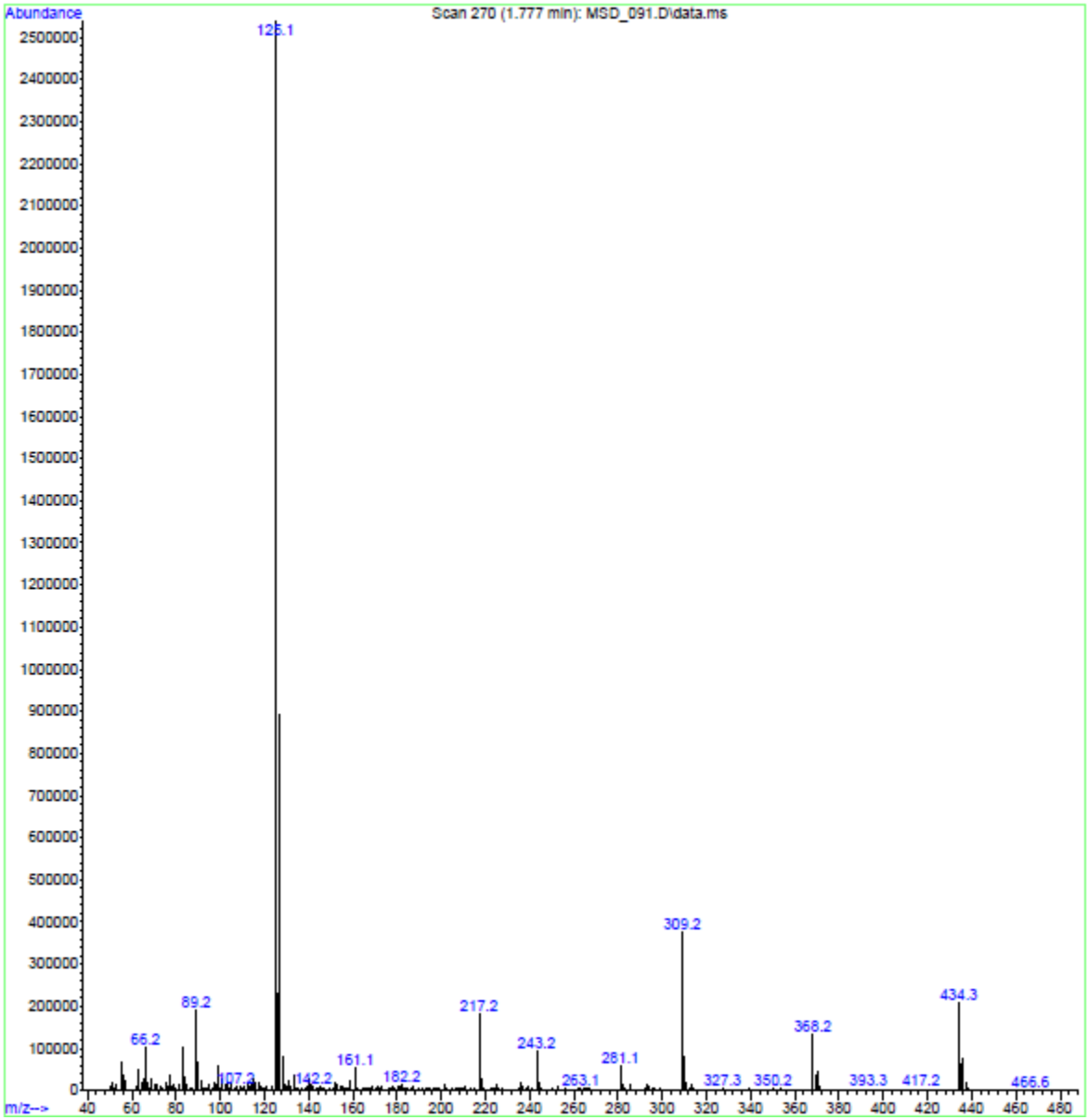


Figure S28. Mass spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6g)

H) spectrums of compound 6h:

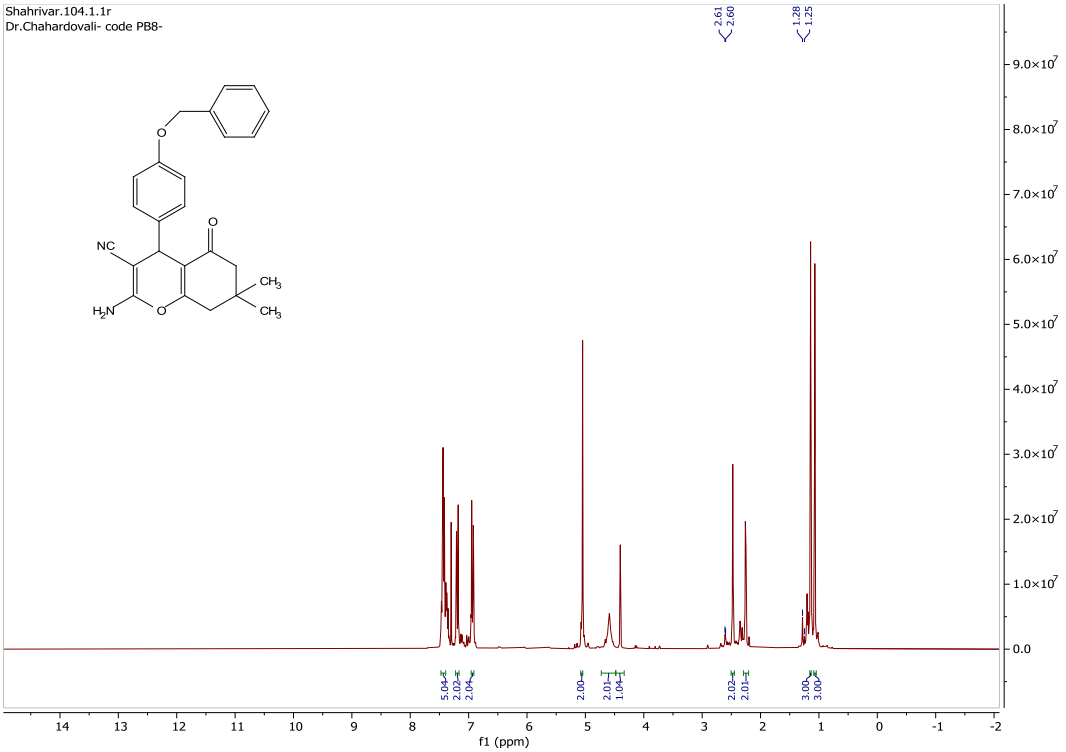


Figure S29. [1]H-NMR spectrum of 2-amino-4-(4-(benzyloxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6h)

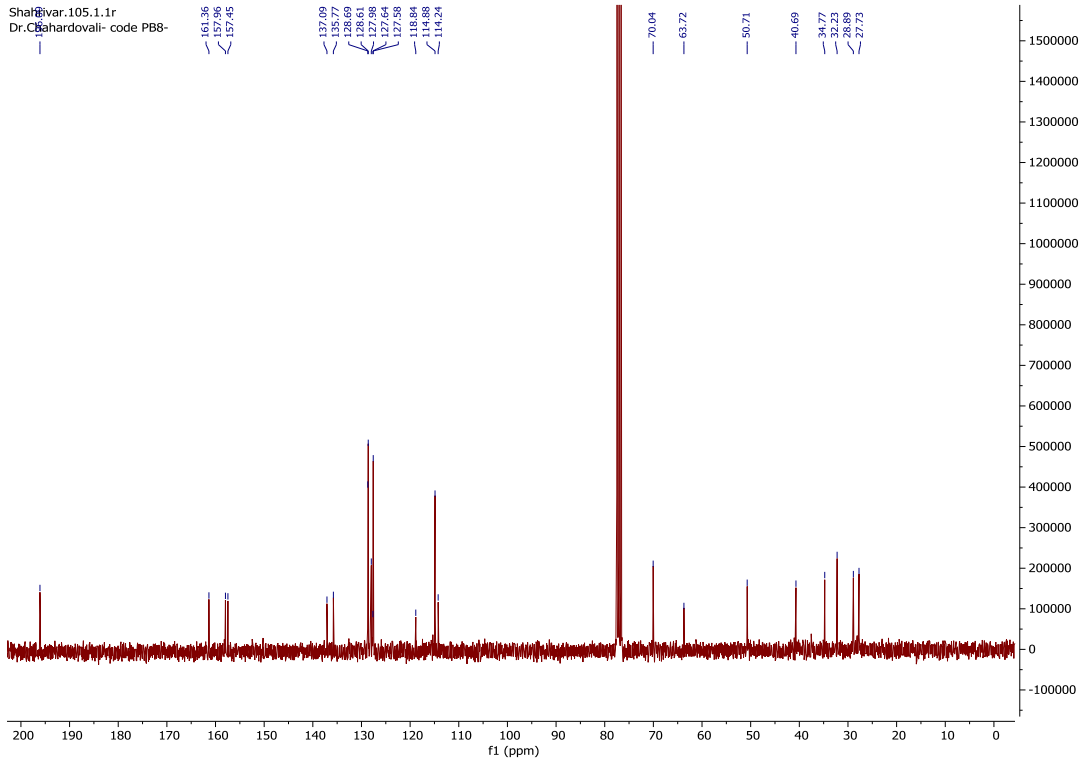


Figure S30. ^{13}C-NMR spectrum of 2-amino-4-(4-(benzyloxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6h)

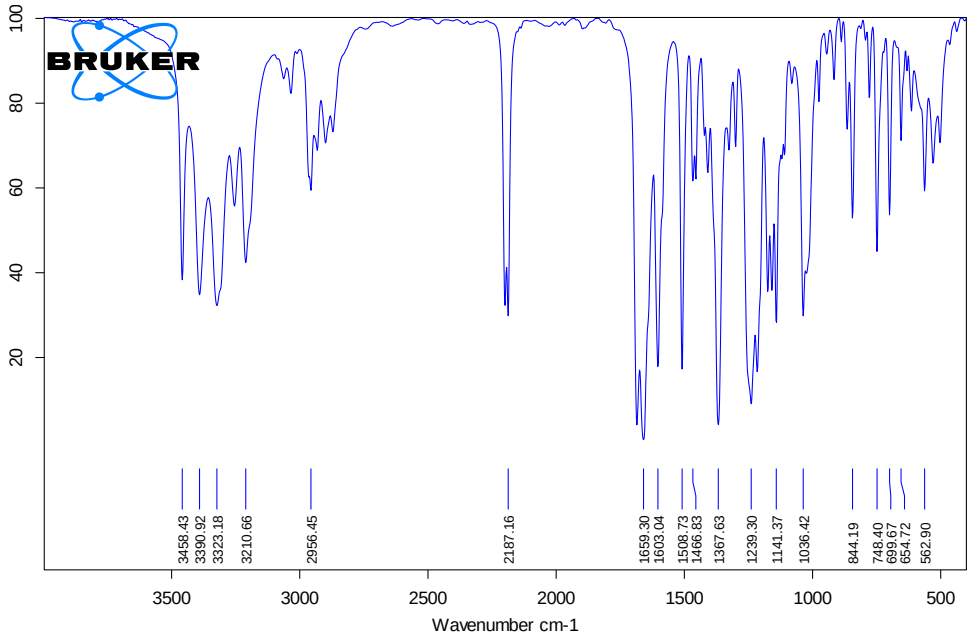


Figure S31. FT-IR spectrum of 2-amino-4-(4-(benzyloxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6h)

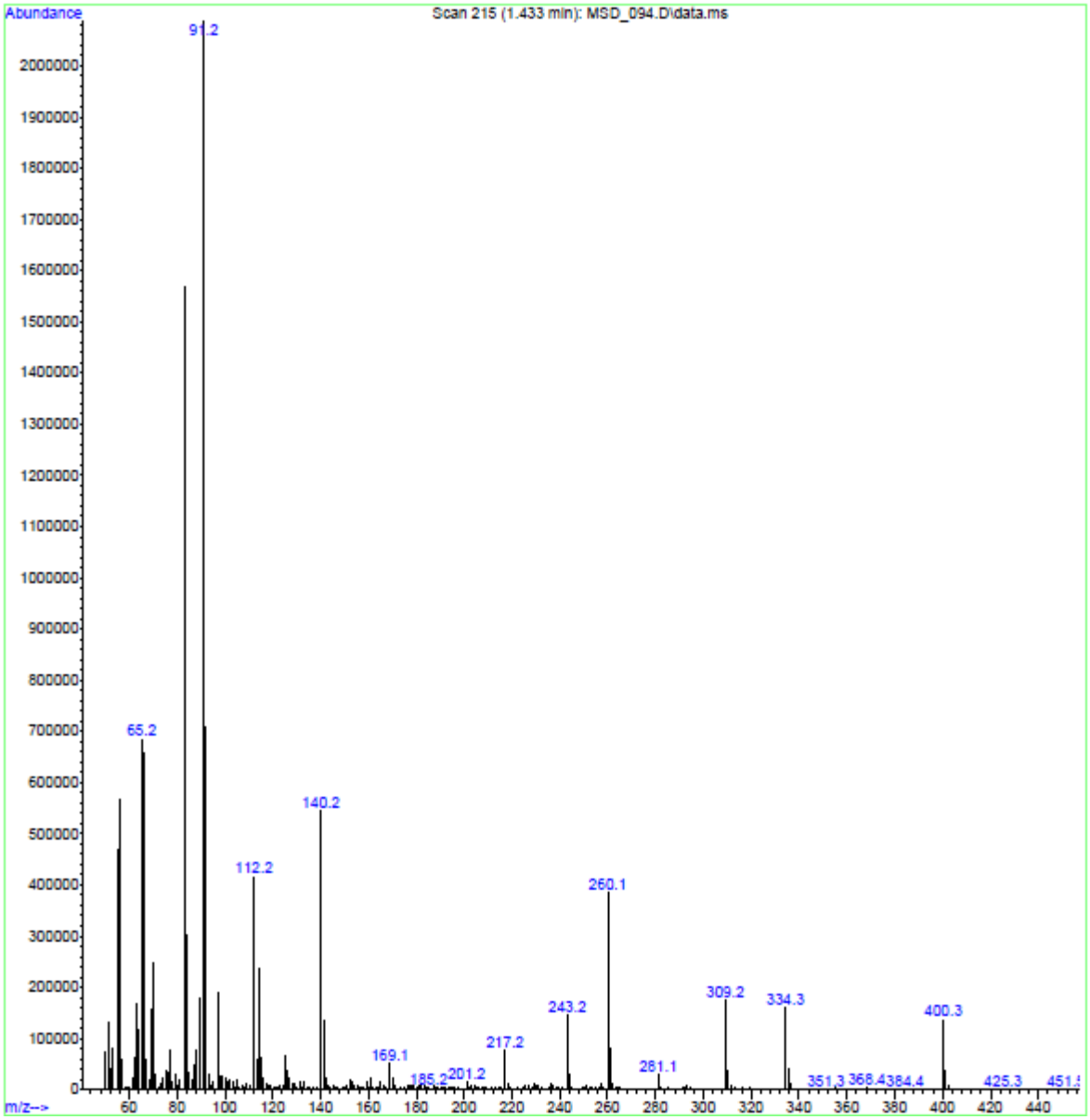


Figure S32. Mass spectrum of 2-amino-4-(4-(benzyloxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6h)

I) spectrums of compound 6i:

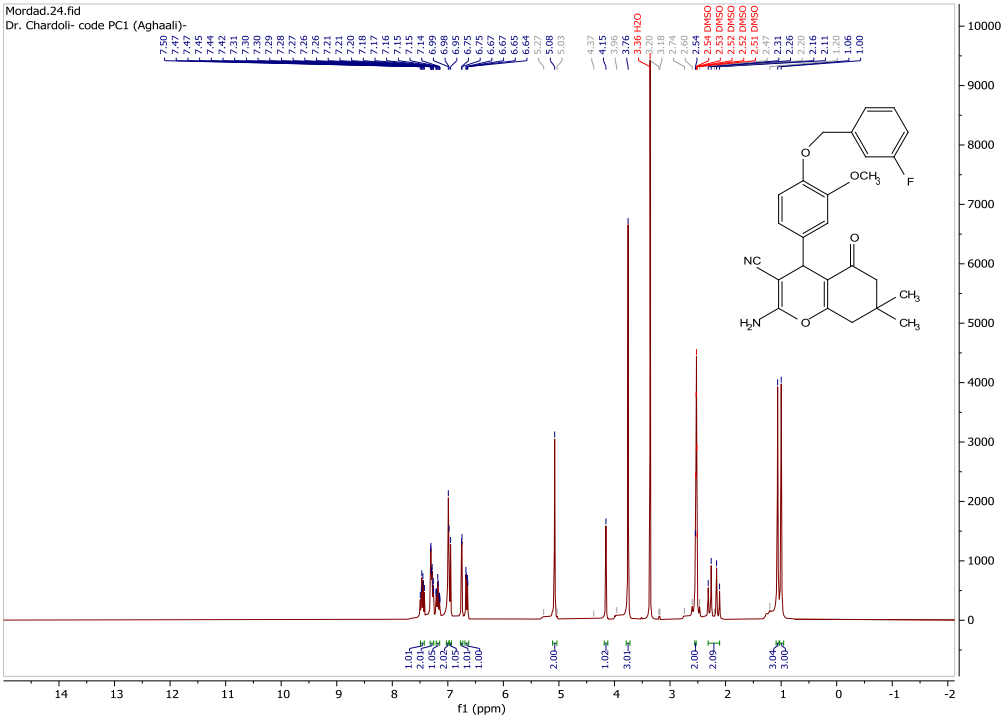


Figure S33. [1]H-NMR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6i)

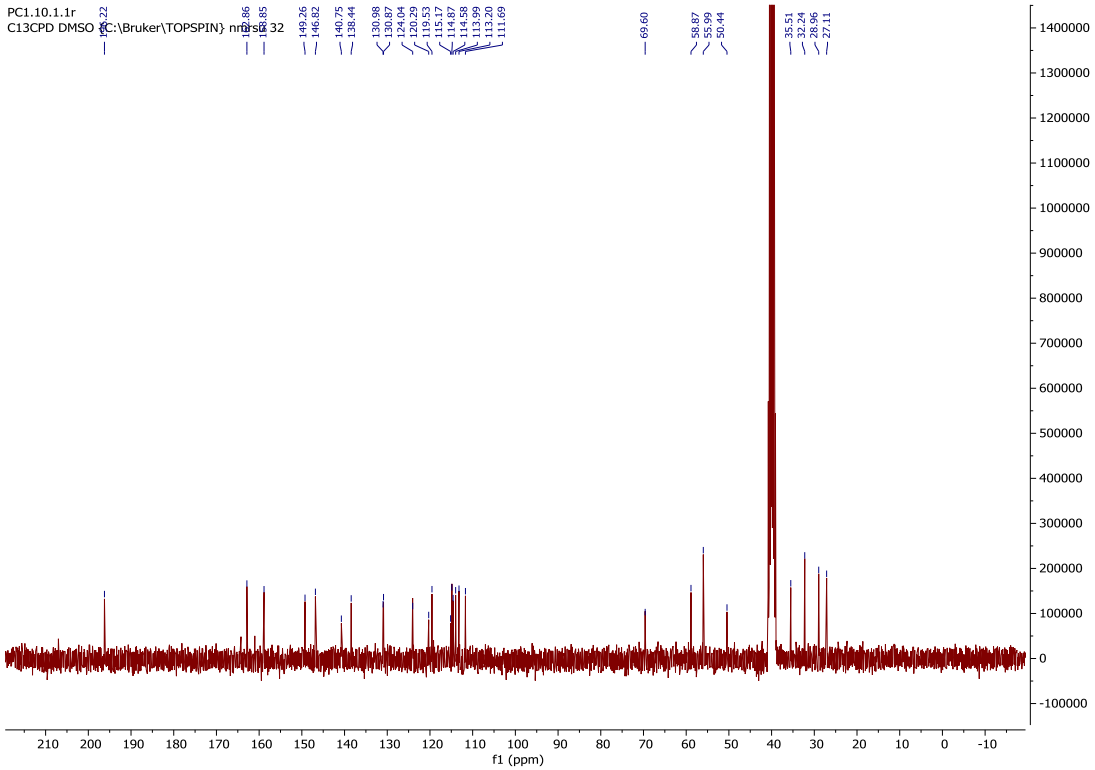


Figure S34. ^{13}C-NMR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6i)

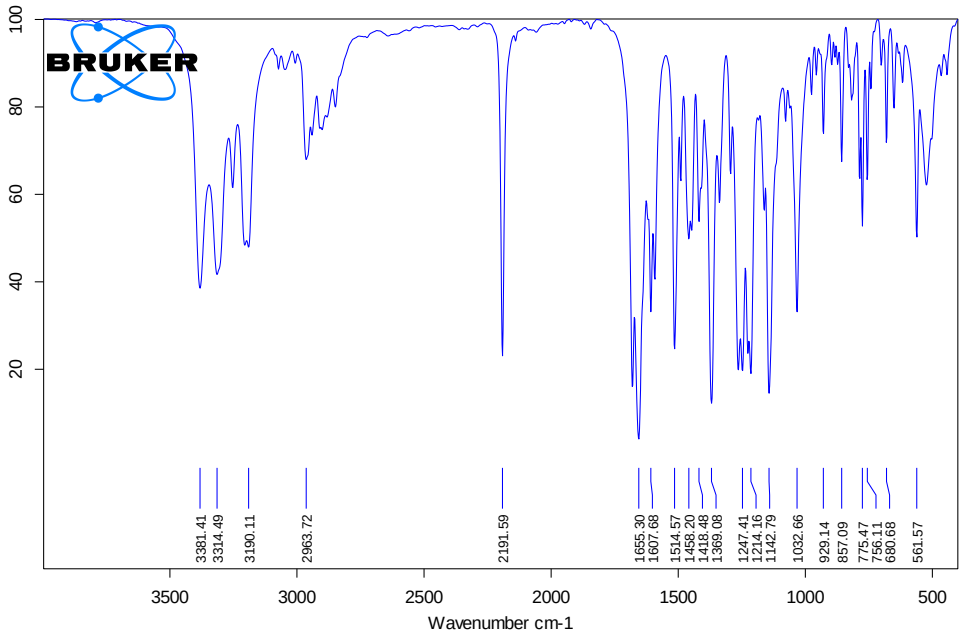


Figure S35. FT-IR spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6i)

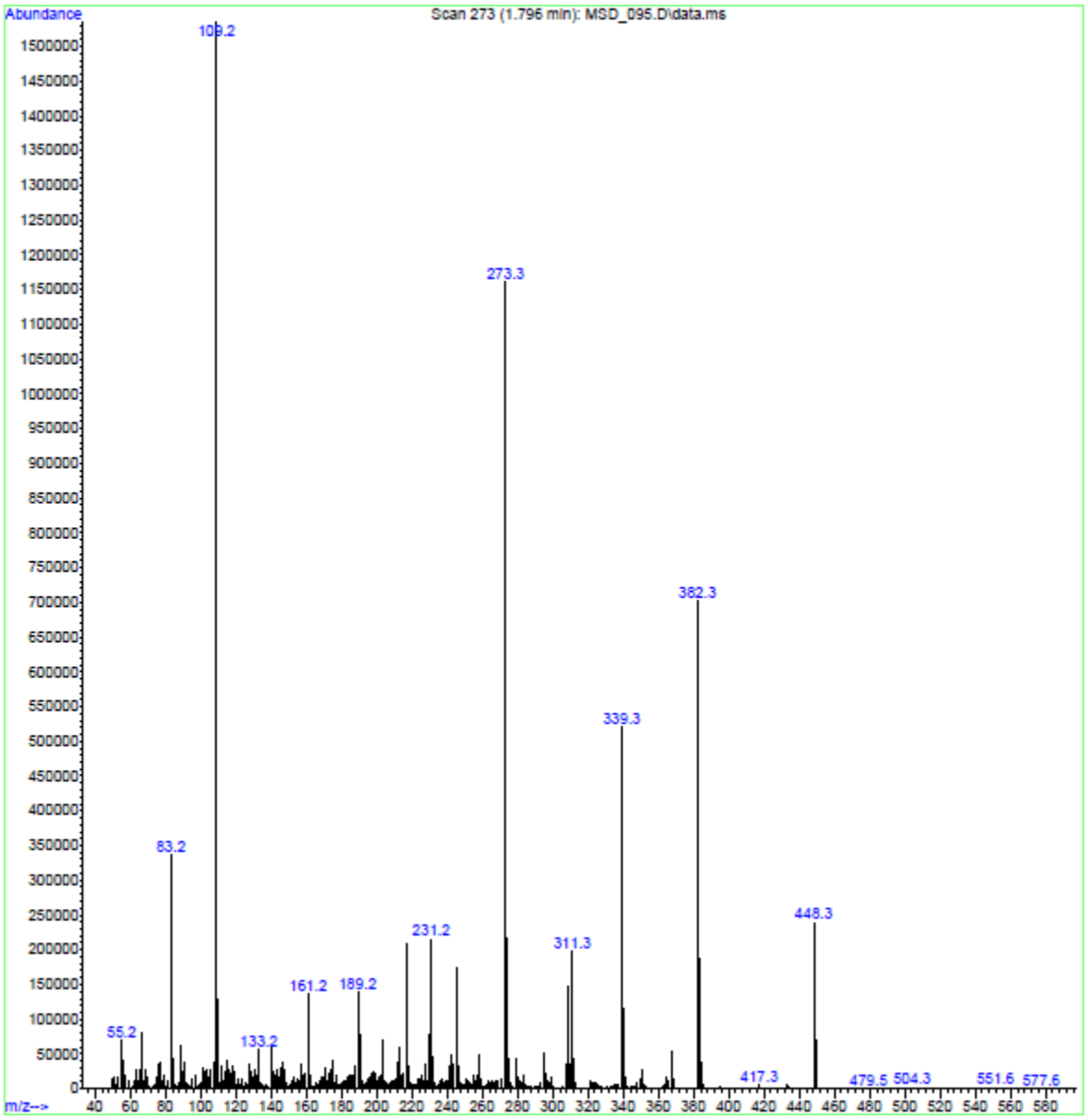


Figure S36. Mass spectrum of 2-amino-4-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6i)

J) spectrums of compound 6j:

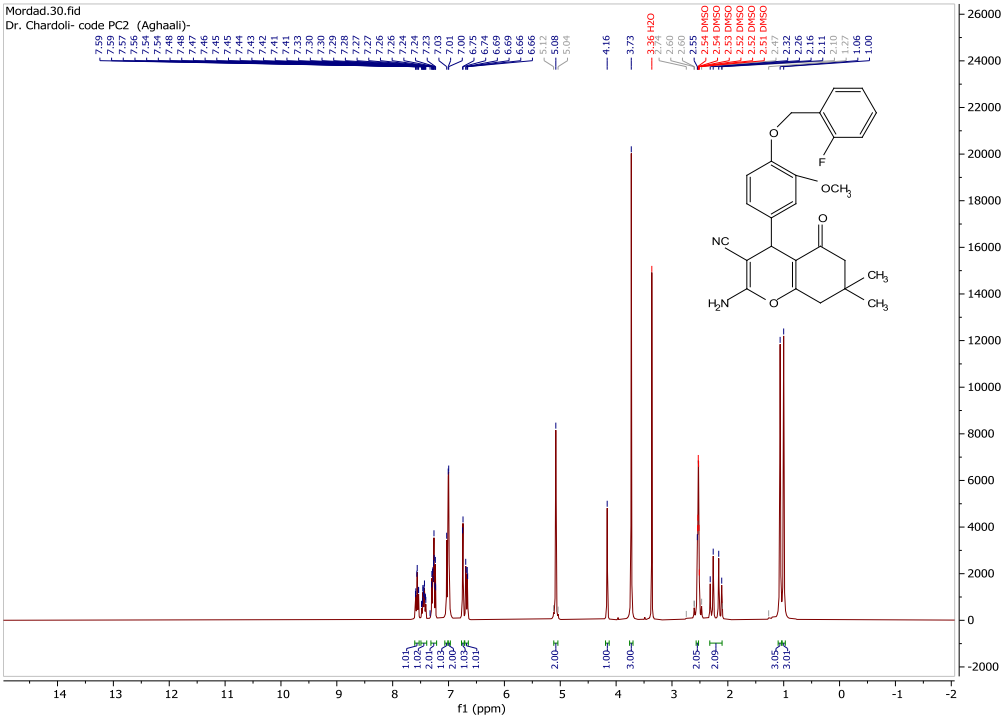


Figure S37. [1]H-NMR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6j)

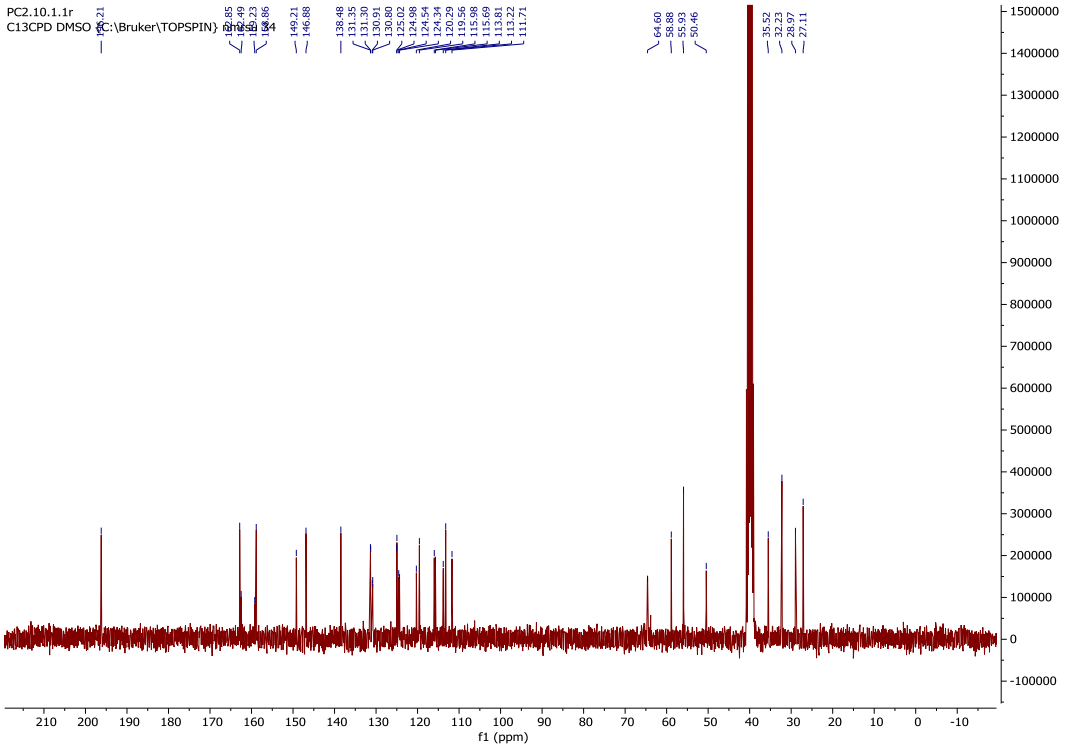


Figure S38. ^{13}C-NMR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6j)

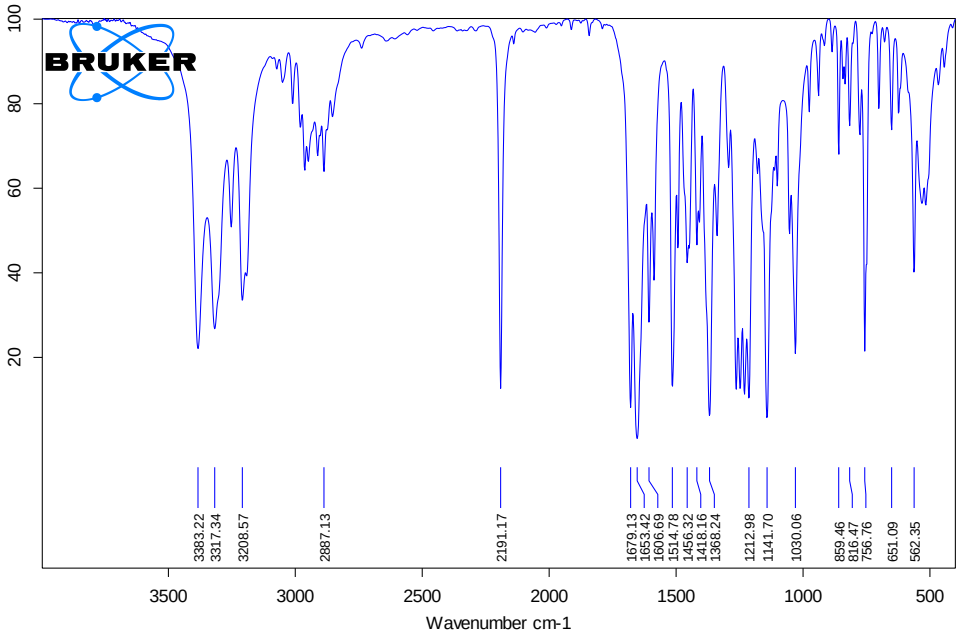


Figure S39. FT-IR spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6j)

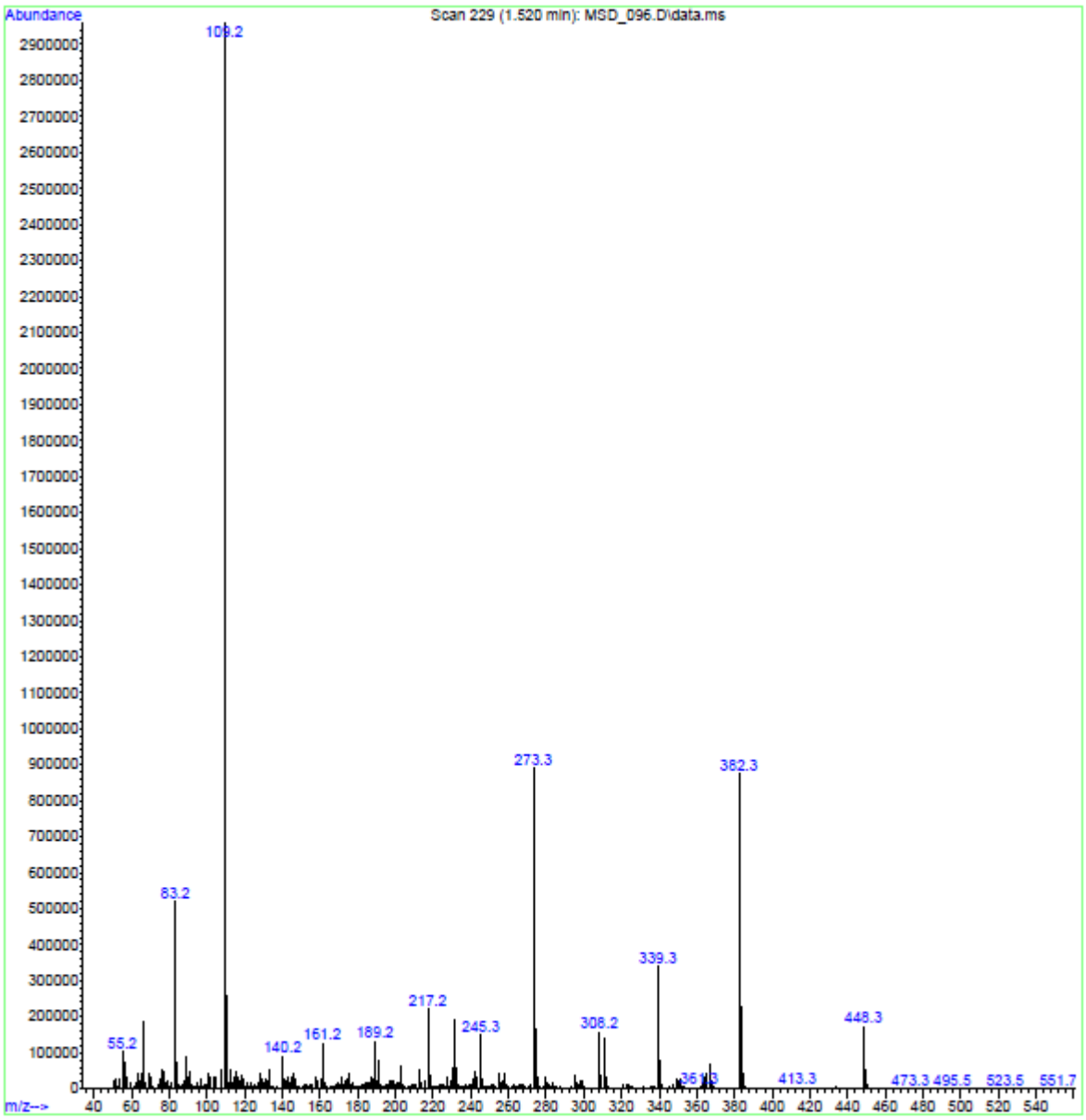


Figure S40. Mass spectrum of 2-amino-4-(4-((2-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6j)

K) spectrums of compound 6k:

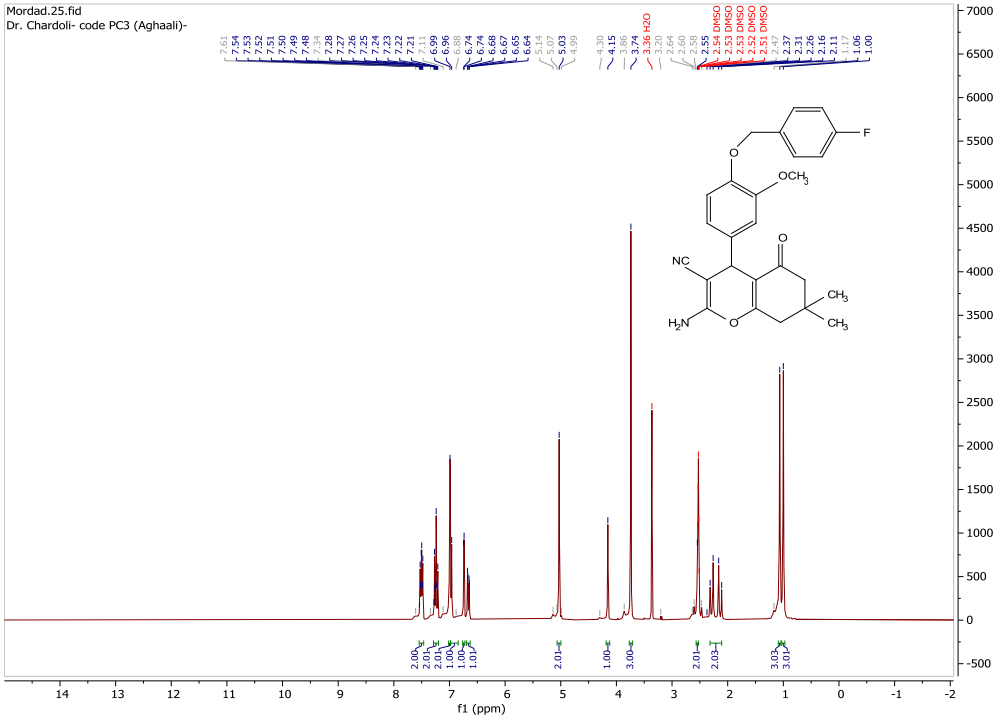


Figure S41. [1]H-NMR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6k)

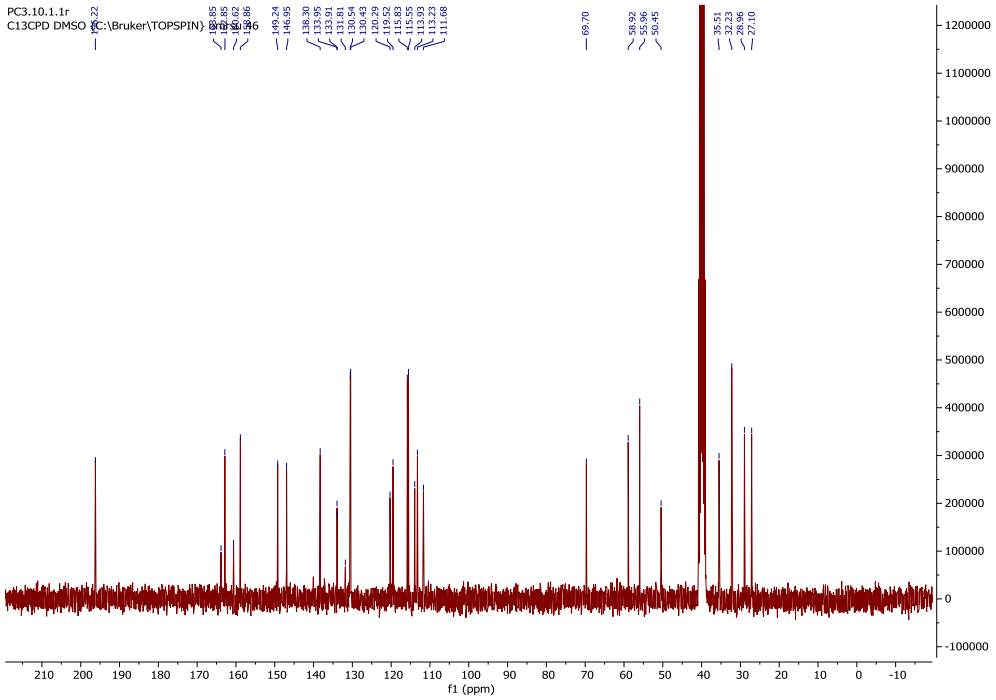


Figure S42. [13]C-NMR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6k)

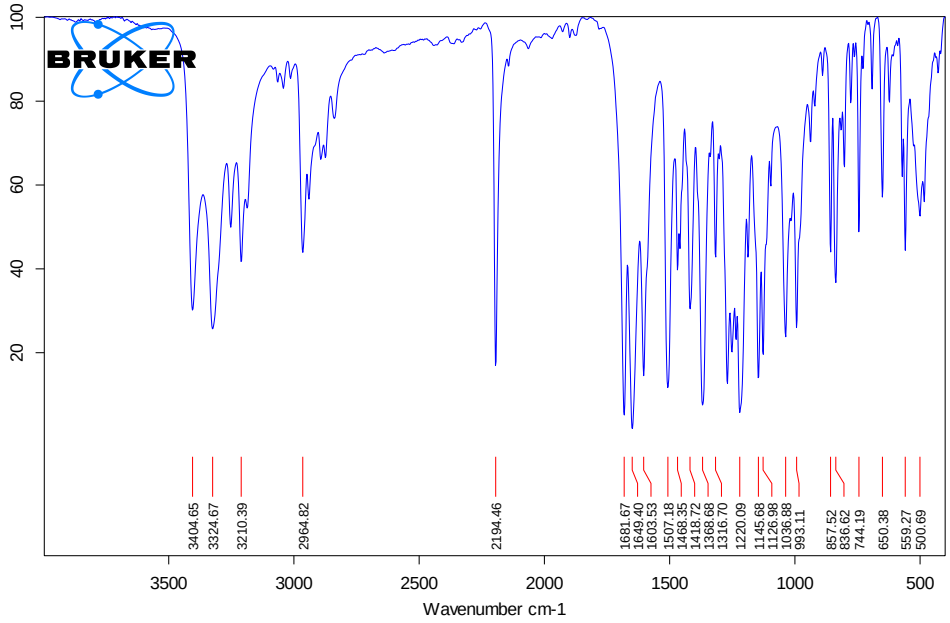


Figure S43. FT-IR spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6k)

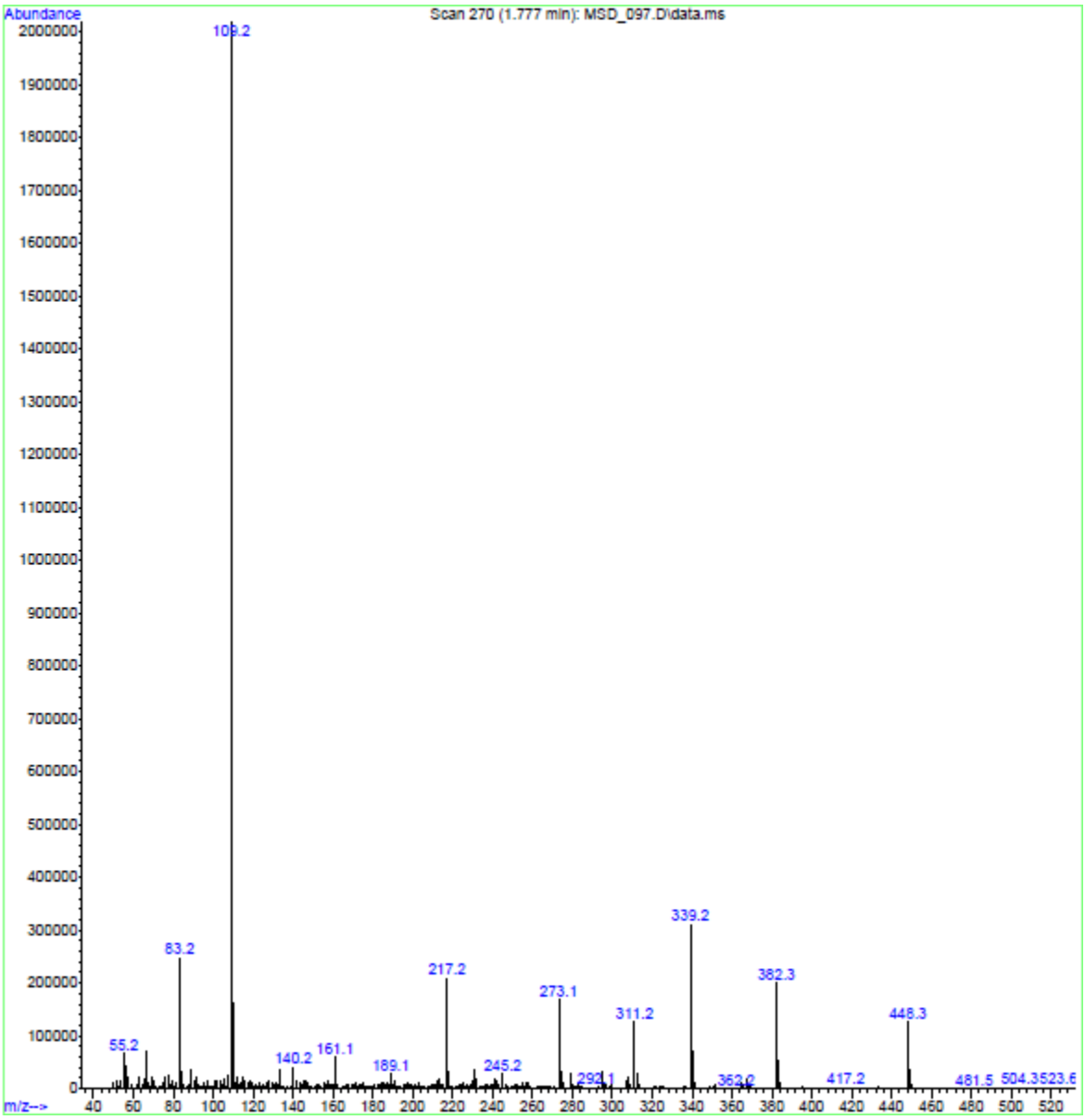


Figure S44. Mass spectrum of 2-amino-4-(4-((4-fluorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6k)

L) spectrums of compound 6l:

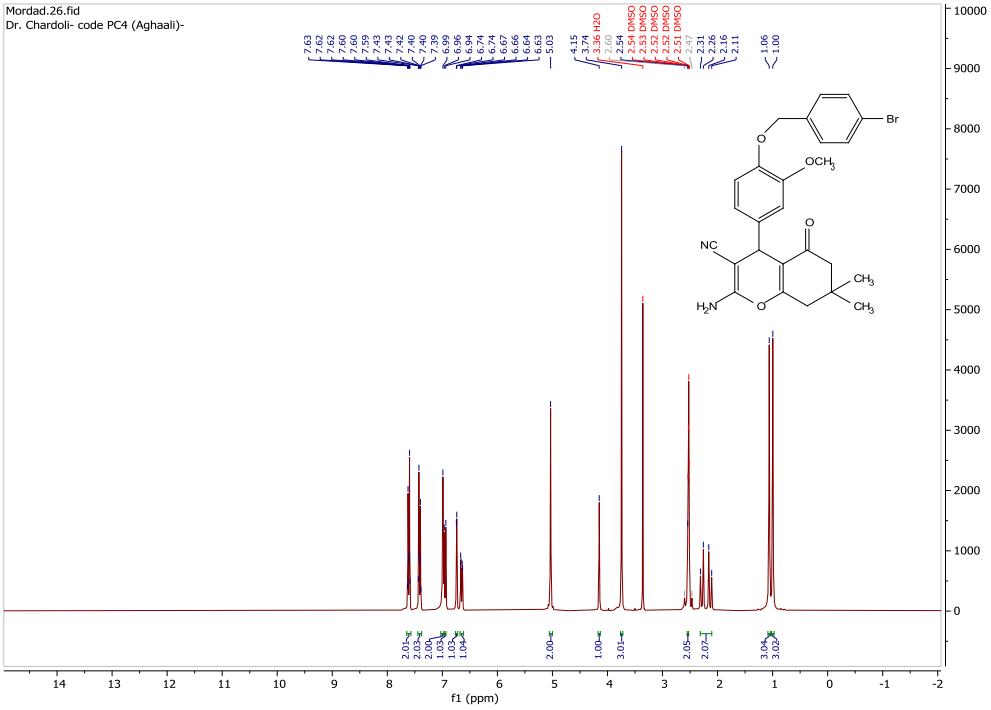


Figure S45. [1]H-NMR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6l)

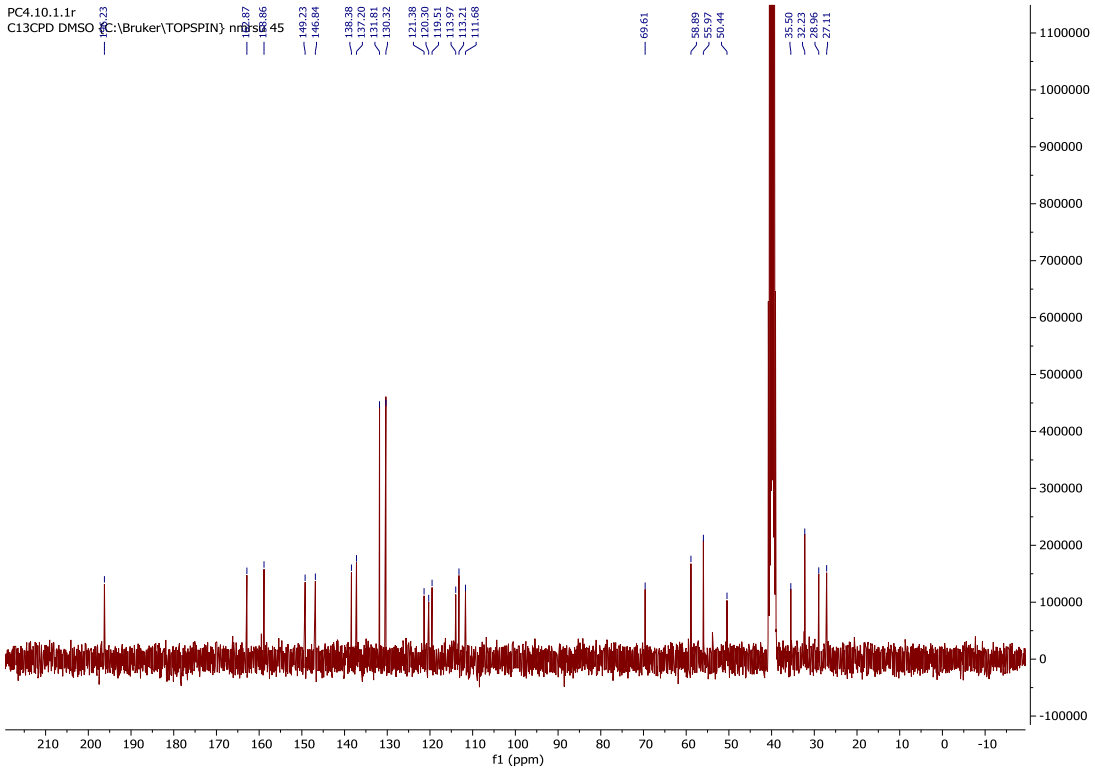


Figure S46. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6l)

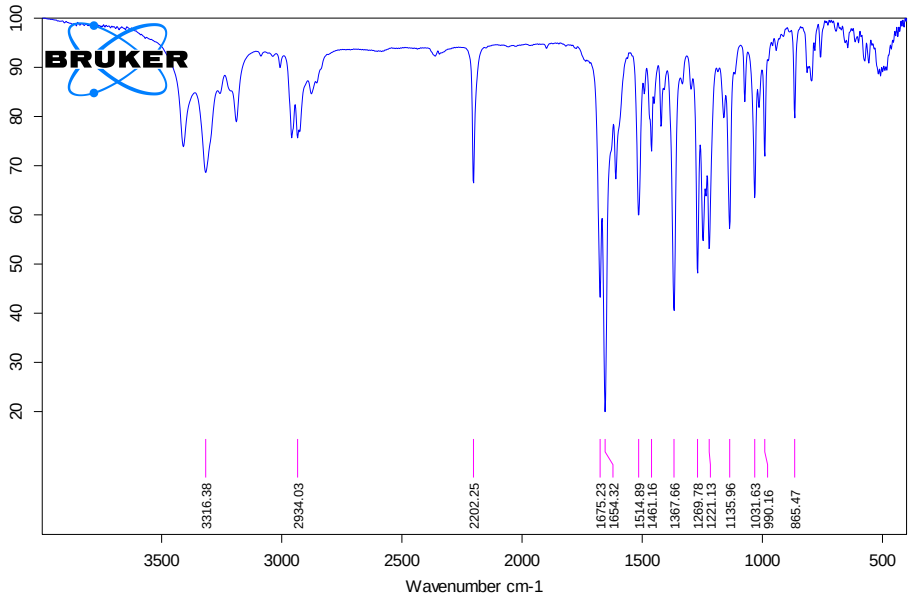


Figure S47. FT-IR spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6l)

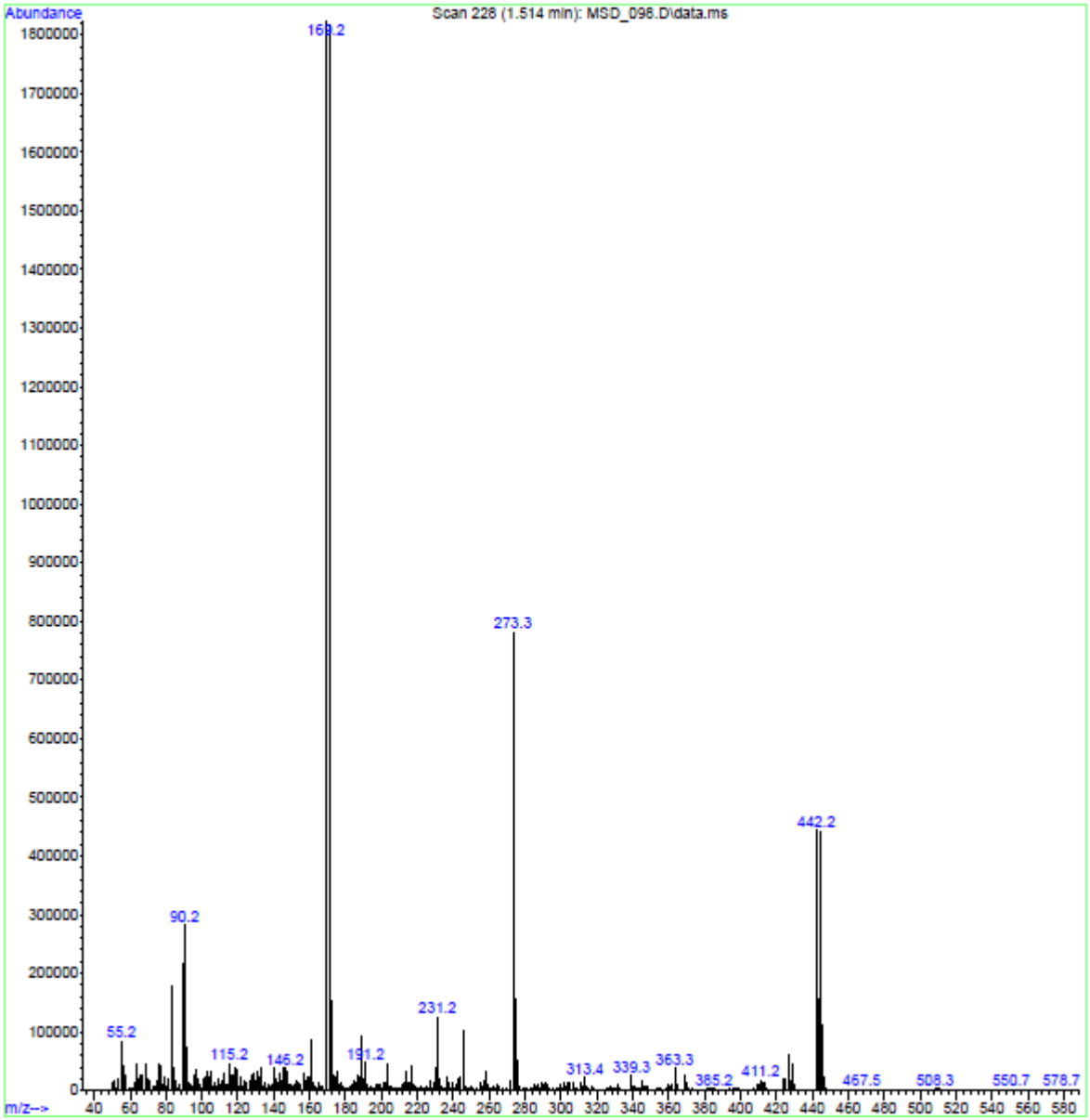


Figure S48. Mass spectrum of 2-amino-4-(4-((4-bromobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6l)

M) spectrums of compound 6m:

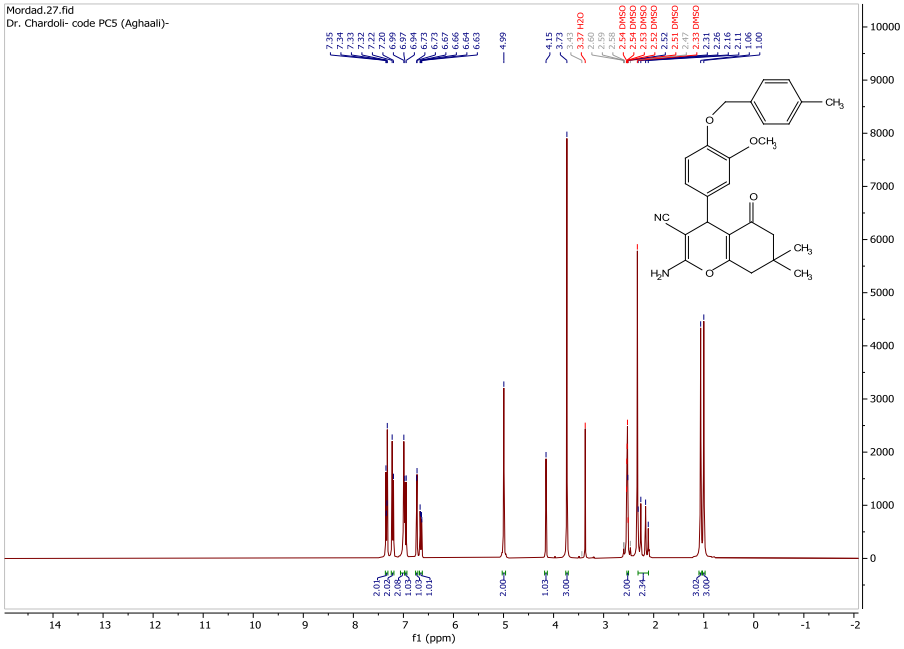


Figure S49. [1]H-NMR spectrum of 2-amino-4-(3-methoxy-4-((4-methylbenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6m)

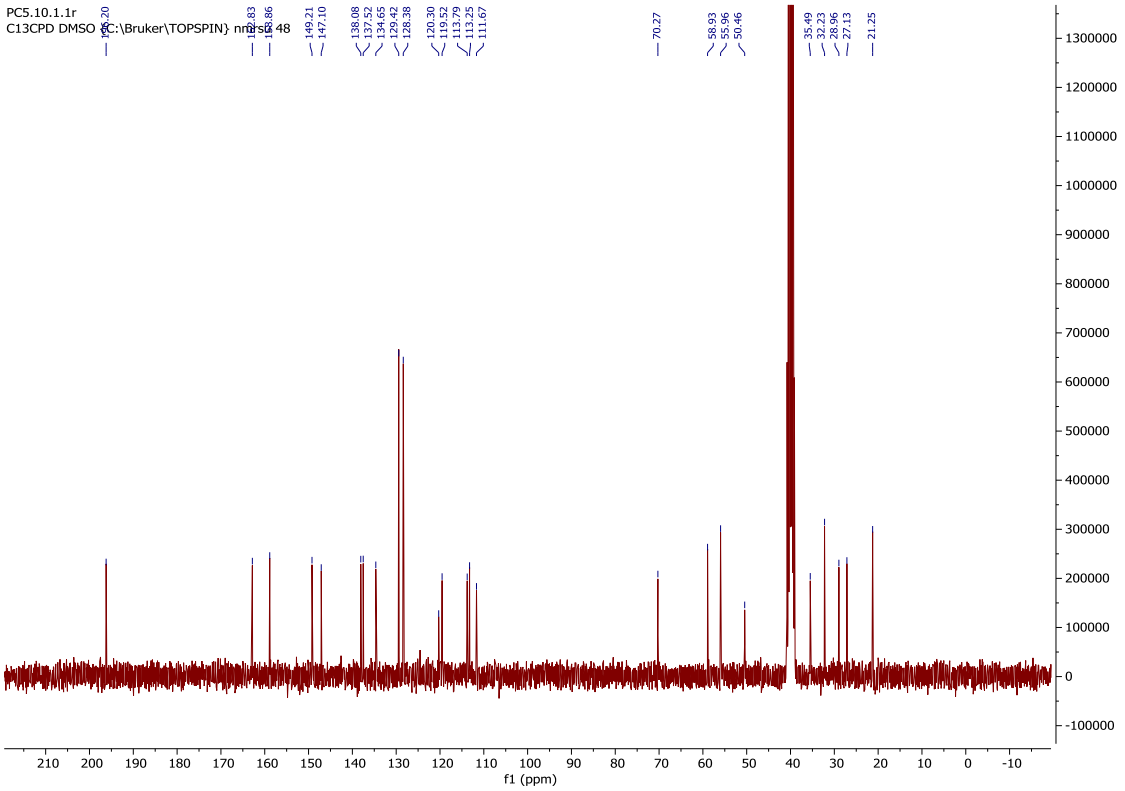


Figure S50. ^{13}C-NMR spectrum of 2-amino-4-(3-methoxy-4-((4-methylbenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6m)

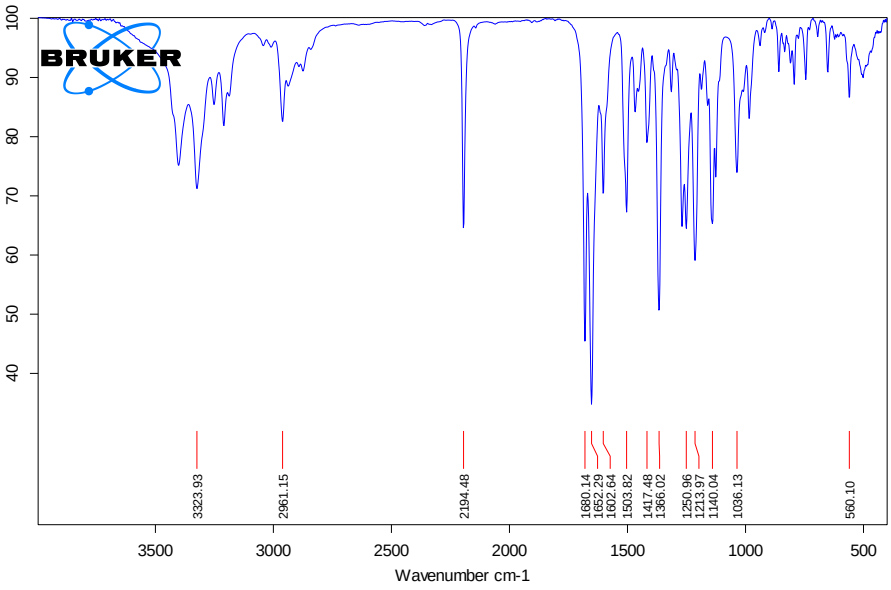


Figure S51. FT-IR spectrum of 2-amino-4-(3-methoxy-4-((4-methylbenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6m)

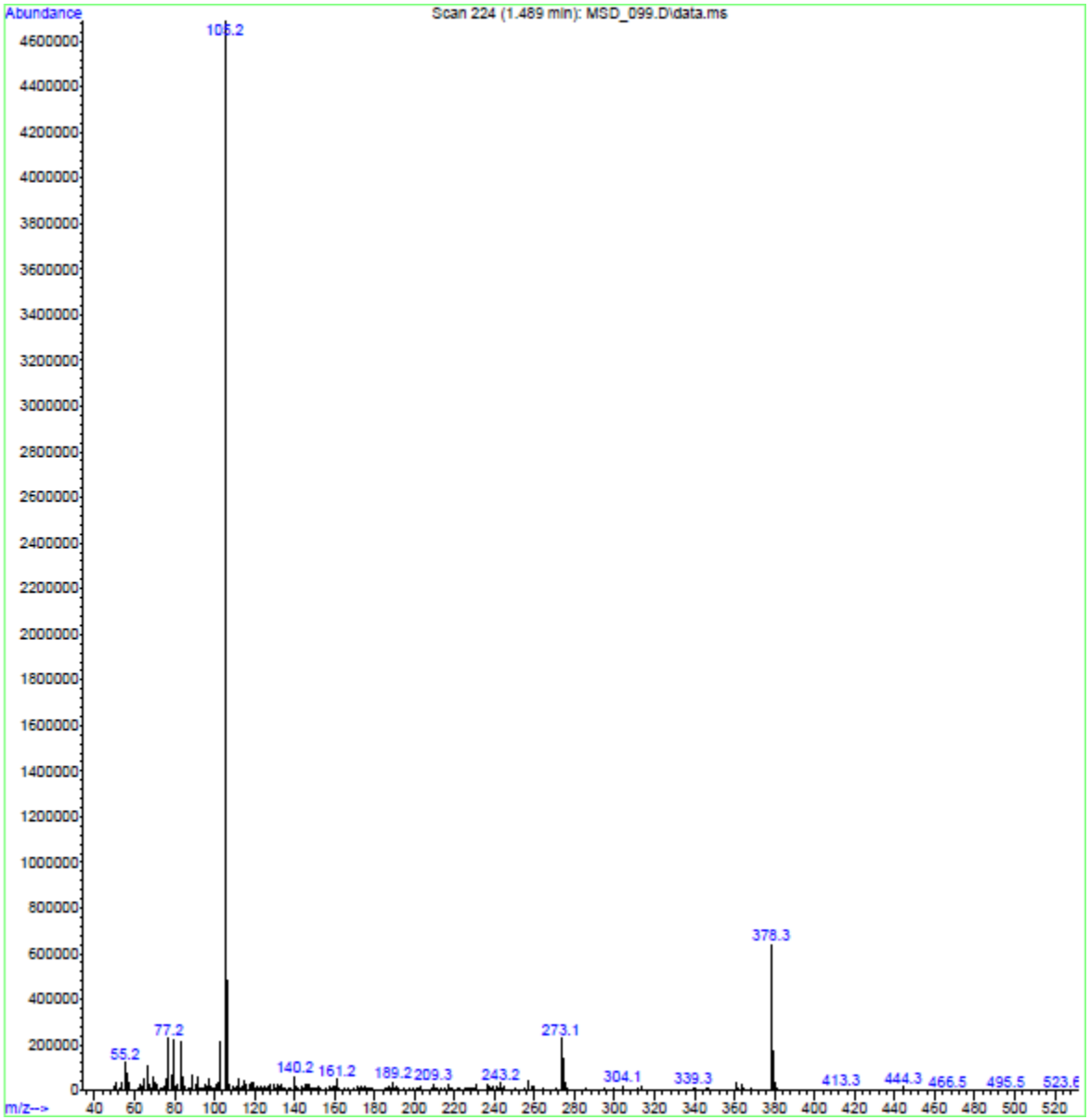


Figure S52. Mass spectrum of 2-amino-4-(3-methoxy-4-((4-methylbenzyl)oxy)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6m)

N) spectrums of compound 6n:

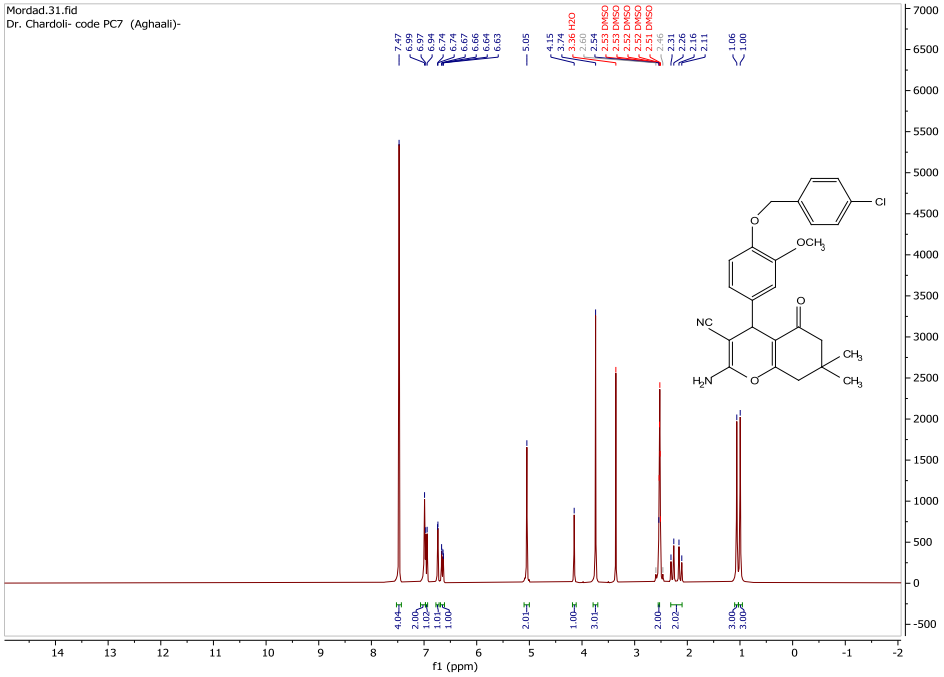


Figure S53. [1]H-NMR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6n)

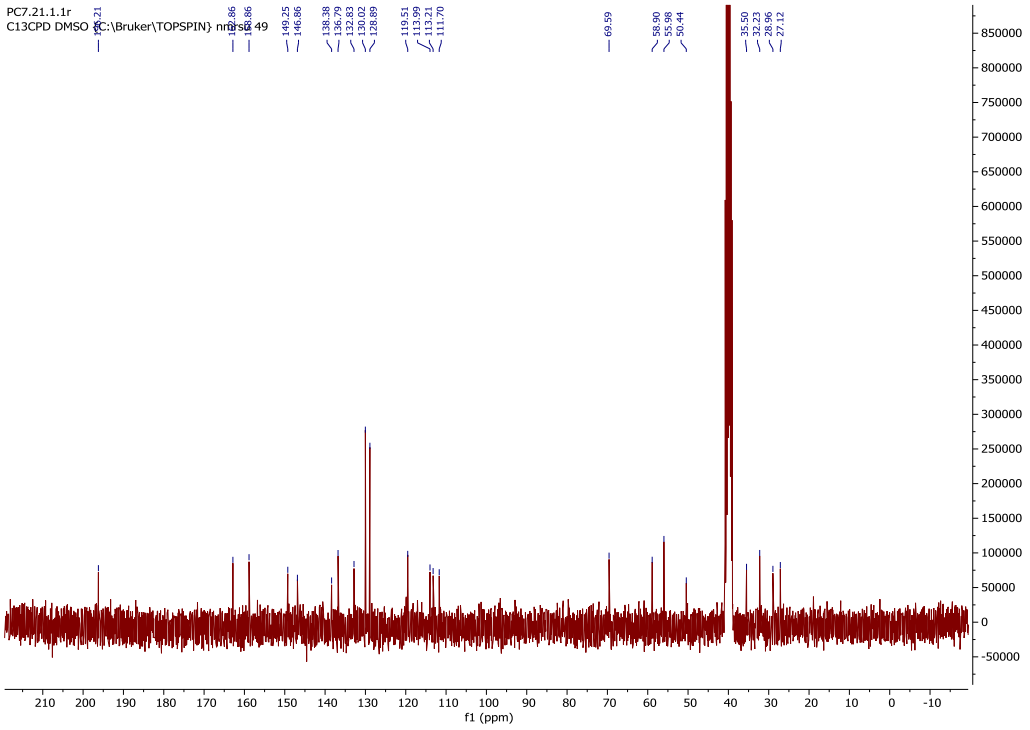


Figure S54. ^{13}C-NMR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6n)

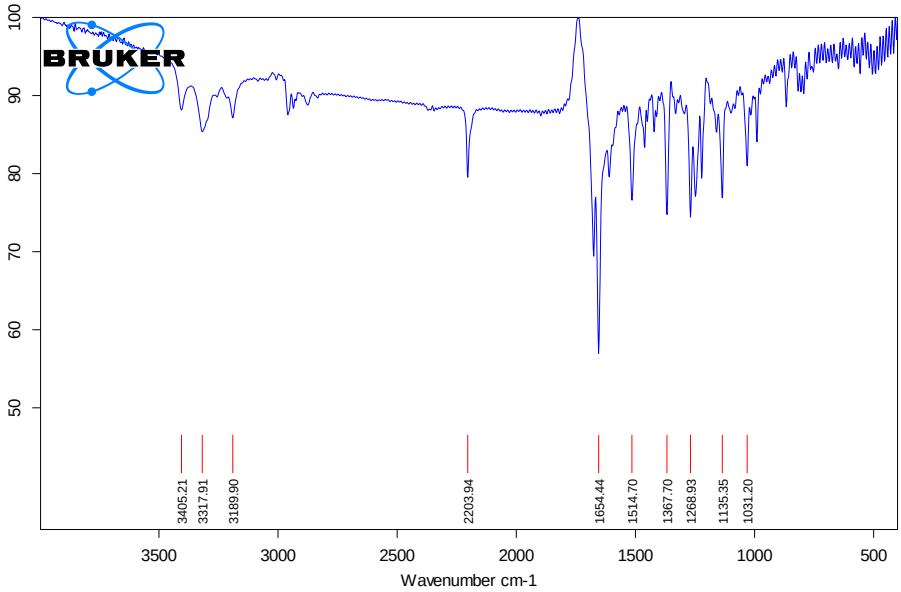


Figure S55. FT-IR spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6n)

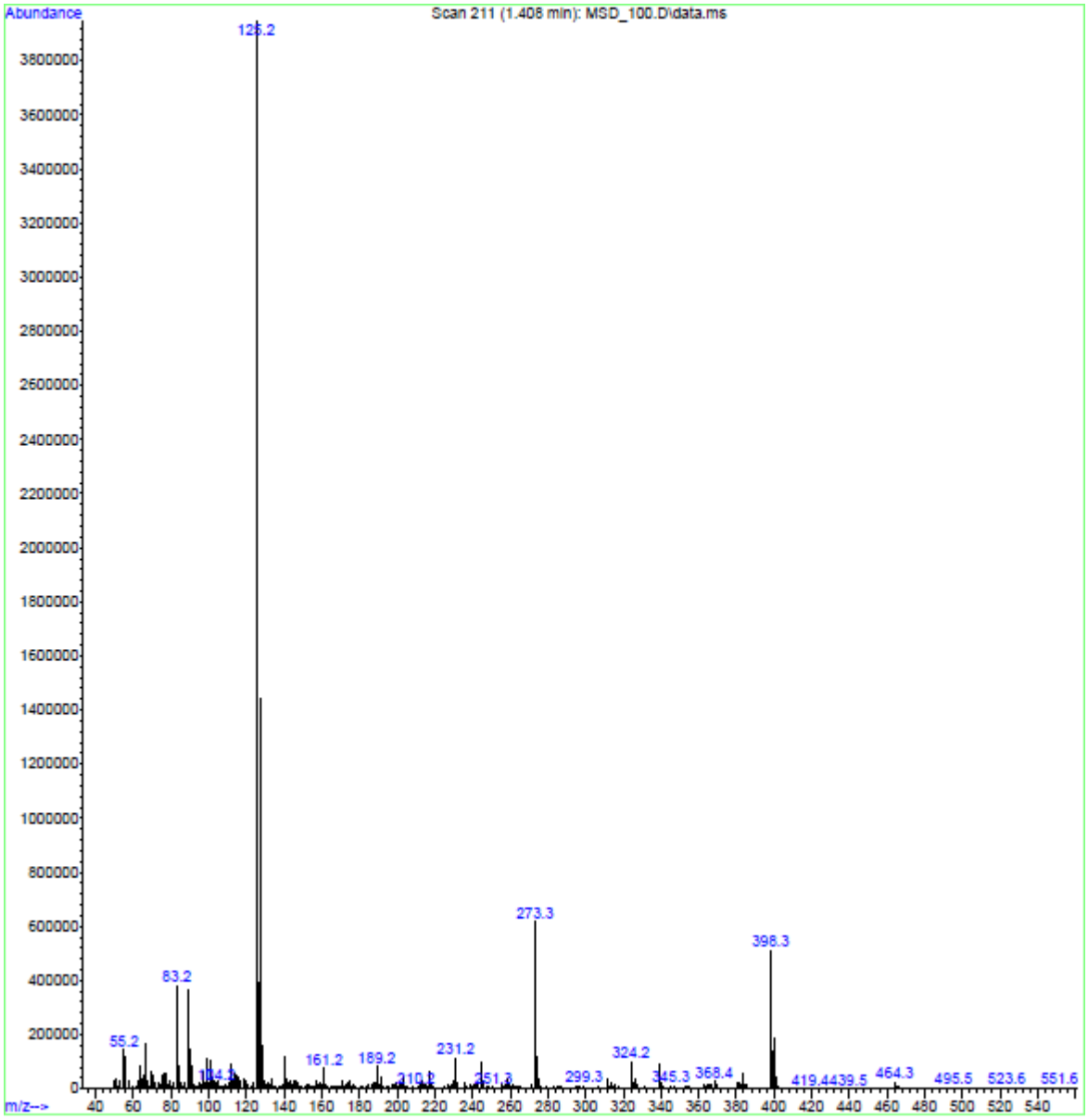


Figure S56. Mass spectrum of 2-amino-4-(4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6n)

O) spectrums of compound 6o:

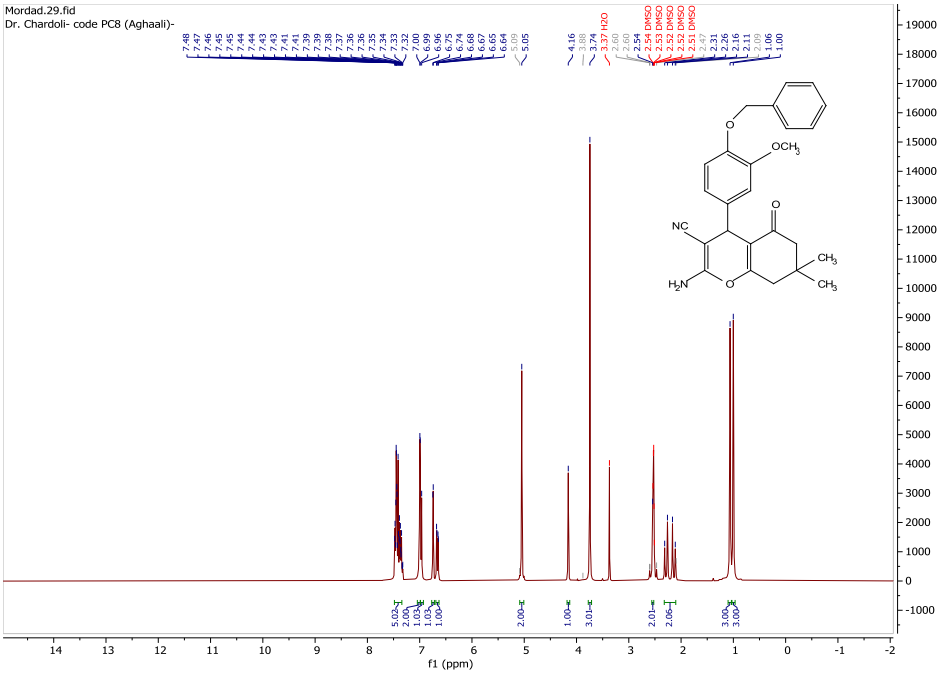


Figure S57. [1]H-NMR spectrum of 2-amino-4-(4-(benzyloxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6o)

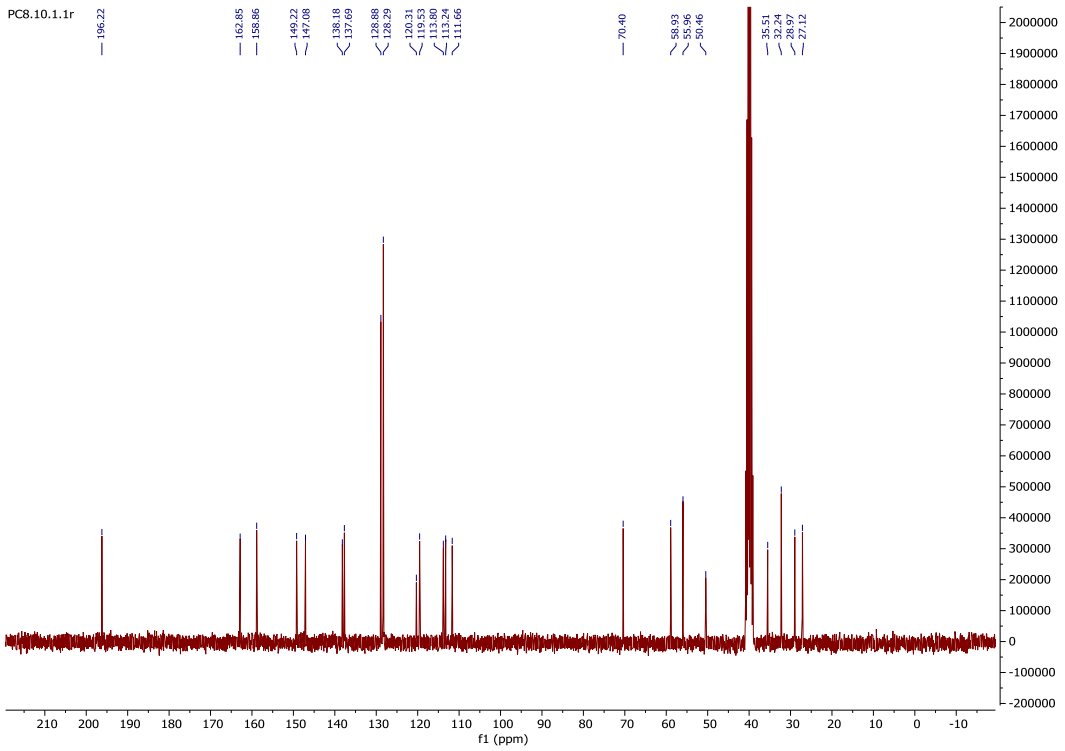


Figure S58. ^{13}C-NMR spectrum of 2-amino-4-(4-(benzyloxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6o)

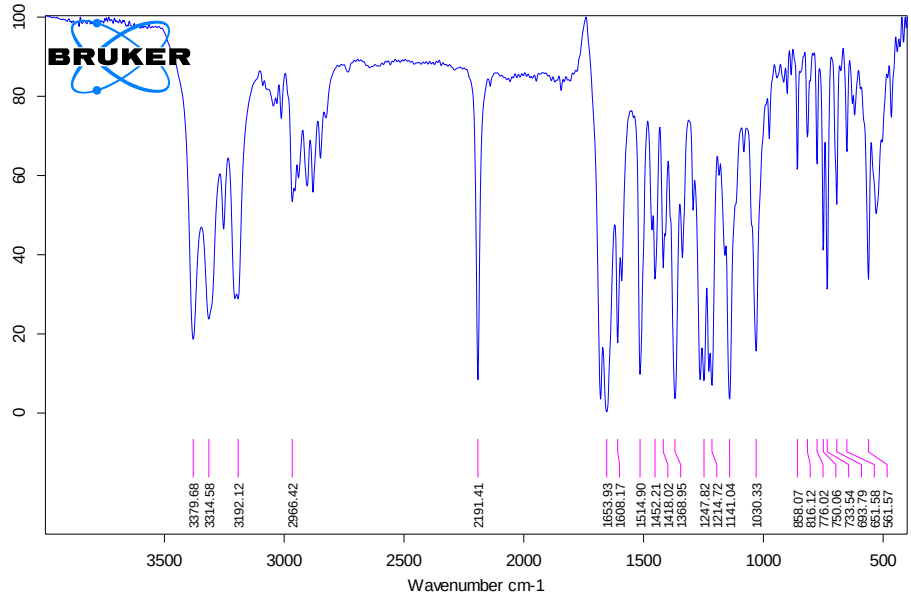


Figure S59. FT-IR spectrum of 2-amino-4-(4-(benzyloxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6o)

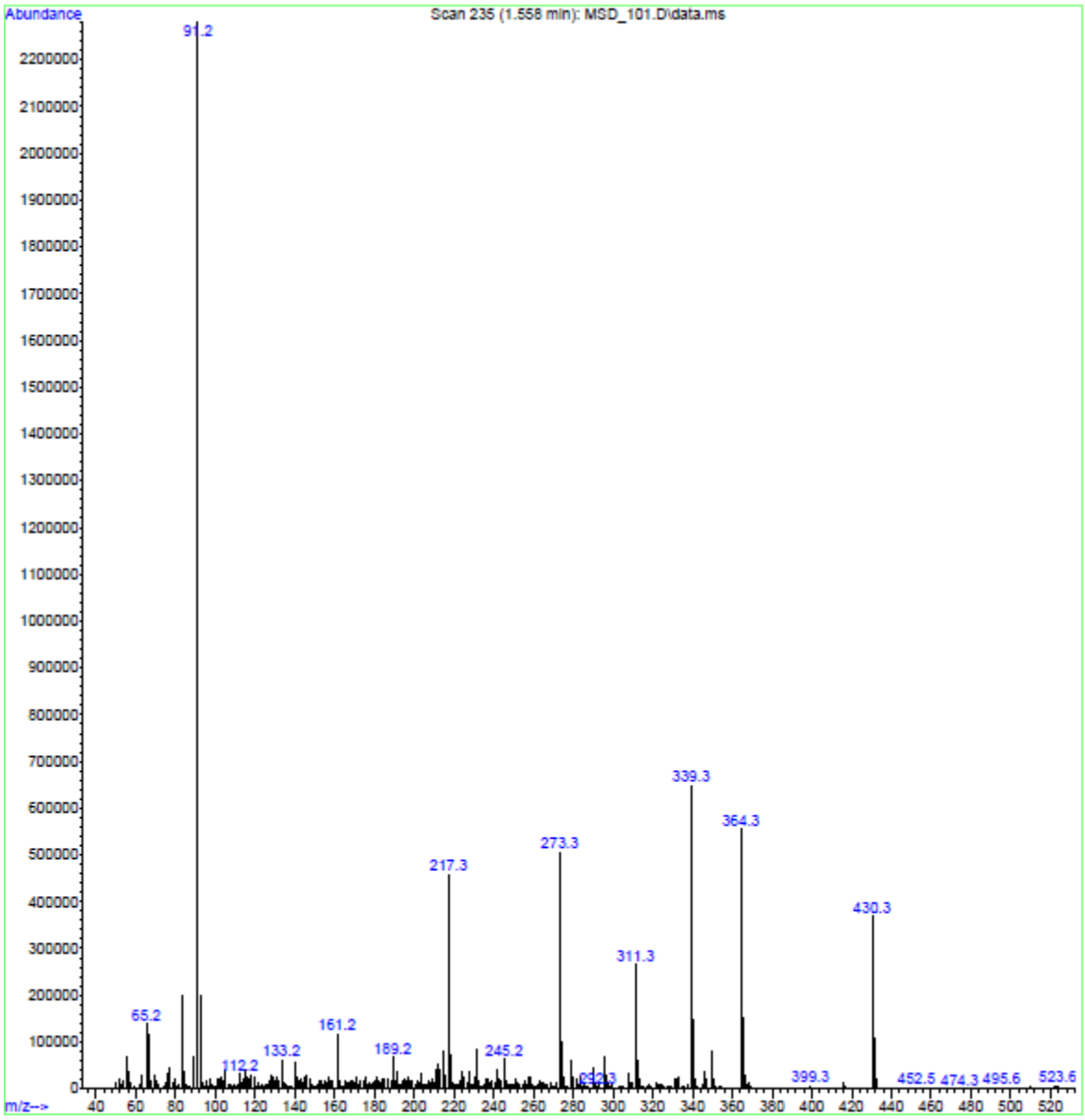
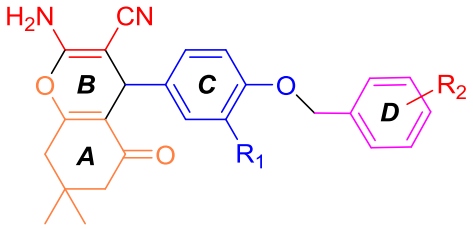


Figure S60. Mass spectrum of 2-amino-4-(4-(benzyloxy)-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6o)

Table S1. *Molecular docking results of* ***6a-o*** *in the active site of tyrosinase*



Entry	***compounds***	***R1***	***R2***	***Estimated free energy of binding***	***Protein-Ligand Contacts***		
					Ligand moiety	***Enzyme residues***	***Type of interaction***
1	***R-6a***	*H*	*3-F*	*-4.681*	*Fluorine*	*GLY281, SER282 and MET280*	*halogen-type interaction*
					Ring D	*His263*	*Pi-Pi stacked*
					Ring C	*His85*	*Pi-Pi stacked*
					Ring C and Ring D	*Val283*	*Pi-Alkyl*
2	***R-6b***	*H*	*2-F*	*-4.771*	*Fluorine*	*His85*	*halogen-type interaction*
					Amine	*Glu322*	*Hydrogen bond*
					Ring D	*His263 and Ser282*	*Pi-Pi stacked*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
3	***R-6c***	*H*	*4-F*	*-4.893*	*Fluorine*	*His61*	*halogen-type interaction*
					Fluorine	*Cu*	*Metal-Acceptor*
					Ring D	*His263*	*Pi-Pi stacked*
					Ring C	*His85*	*Pi-Pi stacked*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*Ala286*	*Pi-Alkyl*
4	***R-6d***	*H*	*4-Br*	*-5.001*	*Bromine*	*Cu*	*Metal-Acceptor*
					Bromine	*His61, His259, His296 and His263*	*Pi-Alkyl*
					Ring D	*His263 and SER282*	*Pi-Pi stacked*
					Ring D	*Ala286*	*Pi-Alkyl*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					cyanide	*His85*	*Hydrogen bond*
					Ring A	*Val248*	*Pi-Alkyl*
5	***R-6e***	*H*	*4-CH3*	*-7.306*	*cyanide*	*His85*	*Hydrogen bond*
					carbonyl	*Asn260*	*Hydrogen bond*
					Ring A	*Val248*	*Pi-Alkyl*
					Ring C	*His85*	*Pi-Pi stacked*

					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*His263*	*Pi-Pi stacked*
					Ring D	*Ala286*	*Pi-Alkyl*
					Methyl bonded to ring D	*Phe264*	*Pi-Alkyl*
6	***R-6f***	*H*	*4-CN*	*-5.44*	*Ring A*	*Val248 and His244*	*Pi-Alkyl*
					Methyl groups bonded to ring A	*His244*	*Pi-Alkyl*
					Cyanide bonded to ring B	*Arg268*	*Hydrogen bond*
					Ring C	*Arg268*	*Pi-cation*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*Ala286 and Val283*	*Pi-Alkyl*
					Ring D	*His263*	*Pi-Pi stacked*
7	***R-6g***	*H*	*4-Cl*	*-4.858*	*Amine*	*Glu322*	*Hydrogen bond*
					Ring D	*His259 and His85*	*Pi-Pi stacked*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					chlorine	*Phe292, His296, His263 and His 85*	*Pi-Alkyl*
8	***R-6h***	*H*	*H*	*-4.921*	*Carbonyl*	*His85*	*Hydrogen bond*
					Ring C	*His85*	*Pi-Pi stacked*
					Oxygen bonded to ring C	*Asn260*	*Unfavorable Acceptor-Acceptor*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*His263*	*Pi-Pi stacked*
					Ring D	*Ala286*	*Pi-Alkyl*
9	***R-6i***	*OCH_3*	*3-F*	*-4.744*	*Carbonyl*	*Arg268*	*Hydrogen bond*
					Methyl group bonded to ring A	*Phe192*	*Pi-Alkyl*
					Ring A	*Pro284*	*Pi-Alkyl*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*Ser282 and His263*	*Pi-Pi stacked*
					Ring D	*Ala286*	*Pi-Alkyl*
					Fluorine	*Asn260*	*halogen-type interaction*

10	***R-6j***	*OCH_3*	*2-F*	*-4.915*	*Methoxy, oxygen bonded to ring C and Fluorine*	*Asn260*	*Hydrogen bond*
					Ring D	*Phe264*	*Pi-Pi stacked*
					Ring D	*Val283*	*Pi-Alkyl*
11	***R-6k***	*OCH_3*	*4-F*	*-5.403*	*Carbonyl*	*His85 and Asn81*	*Hydrogen bond*
					Ring A	*Arg321*	*Pi-Alkyl*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*His263*	*Pi-Pi stacked*
					Fluorine	*Met280*	*halogen-type interaction*
12	***R-6l***	*OCH_3*	*4-Br*	*-5.136*	*Amine*	*Ala246*	*Hydrogen bond*
					cyanide	*Val248*	*Hydrogen bond*
					Ring C	*Val248*	*Pi-Alkyl*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*His259 and His85*	*Pi-Pi stacked*
					Bromine	*His263, Ala286 and His259*	*Pi-Alkyl*
13	***R-6m***	*OCH_3*	*4-CH_3*	*-6.042*	*Carbonyl*	*Asn81 and His85*	*Hydrogen bond*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Methyl group bonded to D	*Phe264*	*Pi-Alkyl*
14	***R-6n***	*OCH_3*	*4-Cl*	*-5.337*	*Amine*	*Glu322*	*Hydrogen bond*
					Ring A and Chlorine	*His85*	*Pi-Alkyl*
					Ring C and ring D	*Val283*	*Pi-Alkyl*
					Ring D	*His259 and His263*	*Pi-Pi stacked*
					Chlorine	*His259, His263 and His296*	*Pi-Alkyl*
					Chlorine	*Cu*	*Metal-acceptor*
15	***R-6o***	*OCH_3*	*H*	*-5.184*	*Ring A*	*Val248*	*Pi-Alkyl*
					Methyl groups bonded to ring A	*Phe264*	*Pi-Alkyl*
					Cyanide	*His85*	*Hydrogen bond*
					Ring C	*His85*	*Pi-Pi stacked*
					Ring D	*His263 and Phe264*	*Pi-Pi stacked*
					Hydrogen at the para position of ring D	*Phe264*	*Pi-sigma*