Supplementary Material

Easy synthesis of new series of pteridine analogs: di- and tetra-hydropyrimido[4,5-*d*]pyrimidines via 5-pyrimidinecarbaldehydes

José M. de la Torre,[a] Manuel Nogueras,[a] Eduardo J. Borkowski,[b] Fernando D. Suvire,[b] Ricardo D. Enriz,[b] and Justo Cobo*[a]

[a] Depto Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Campus las Lagunillas, Universidad de Jaén, E-23071 Jaén, Spain
[b] Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, Chacabuco 915, 5700 San Luis, Argentina
E-mail: jcobo@ujaen.es

In Memoriam: Professor Alan R. Katritzky, for his dedication and contribution to the world of chemistry

Index

Page 2: Figure 1S,

Page 3: Figure 2S

Page 4: Figure 3S

Page 5: Table 1S and figure 4S

Pages 6-31: ^{1}H-NMR and ^{13}C-NMR spectra,

Pages 32-44: MS spectra.

 ©ARKAT-USA, Inc.

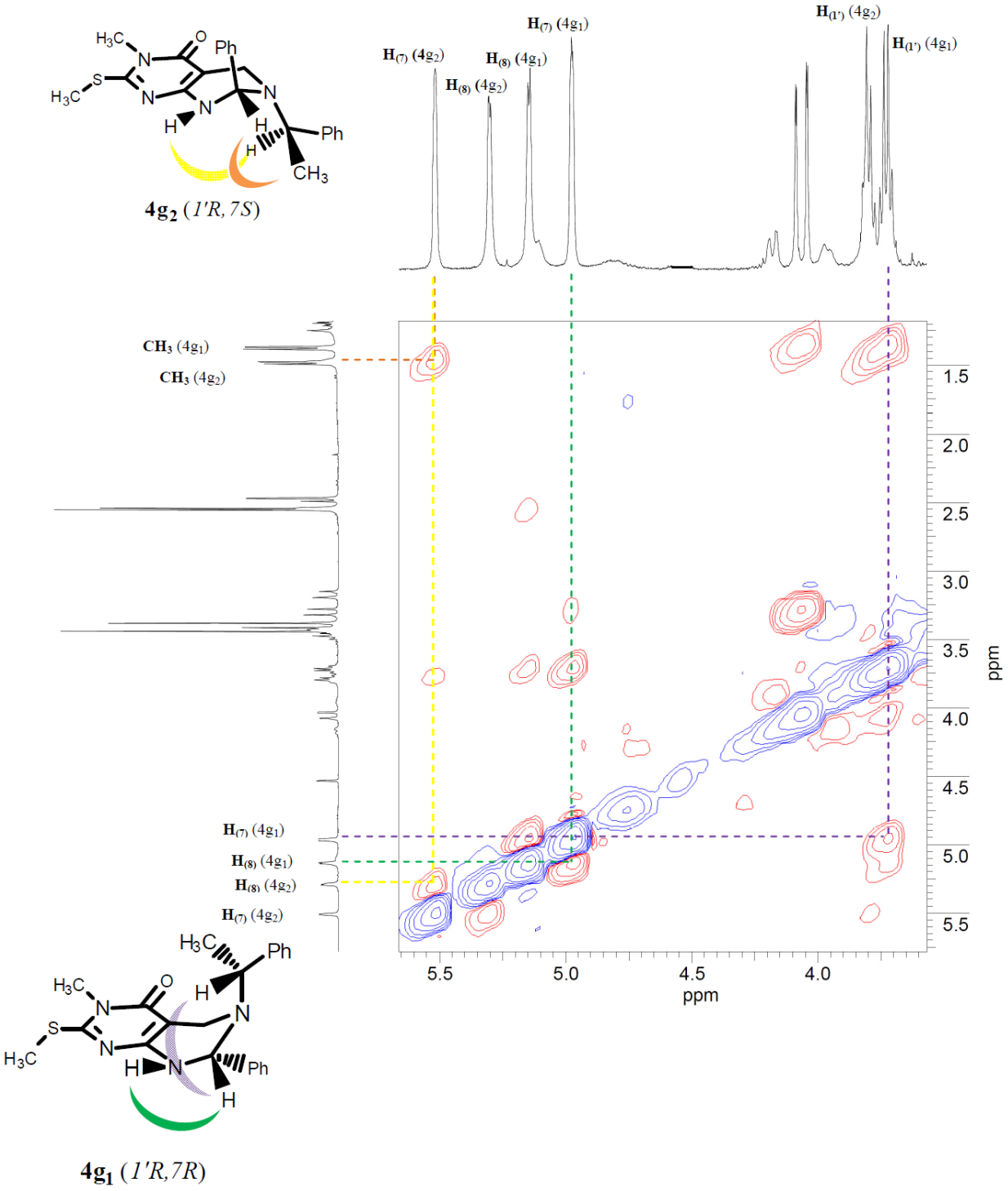
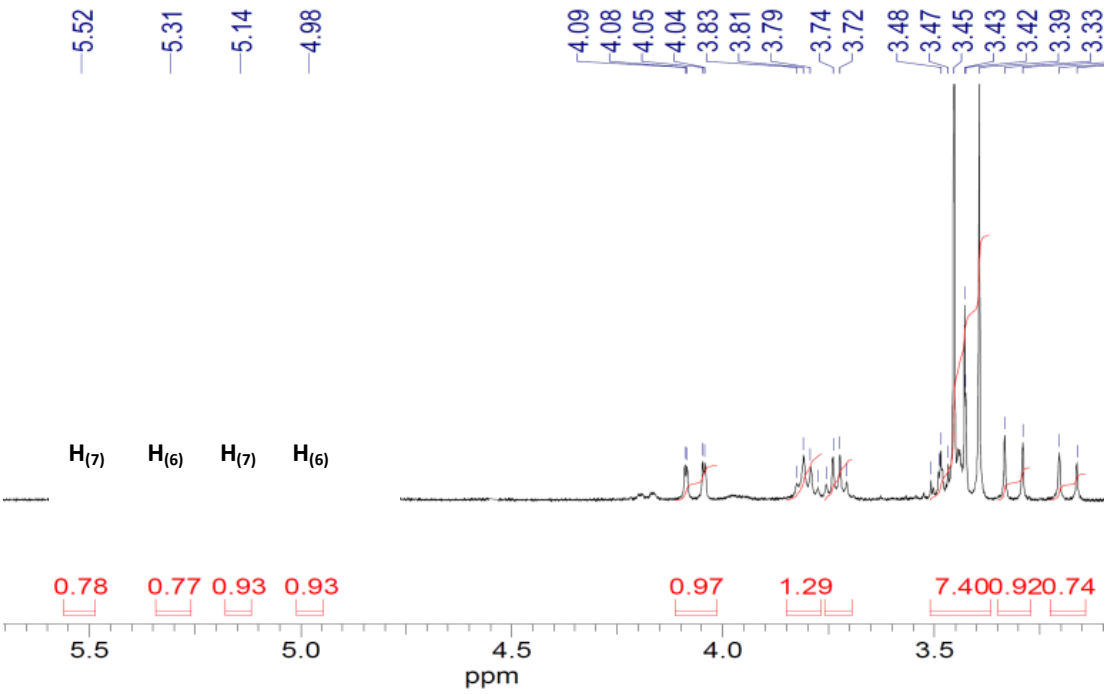


Figure 1S. Selected window to observe NOESY interaction of H-7 in the diasteromeric mixture corresponding with entry 1 Table 4

©ARKAT-USA, Inc.

a)



b)

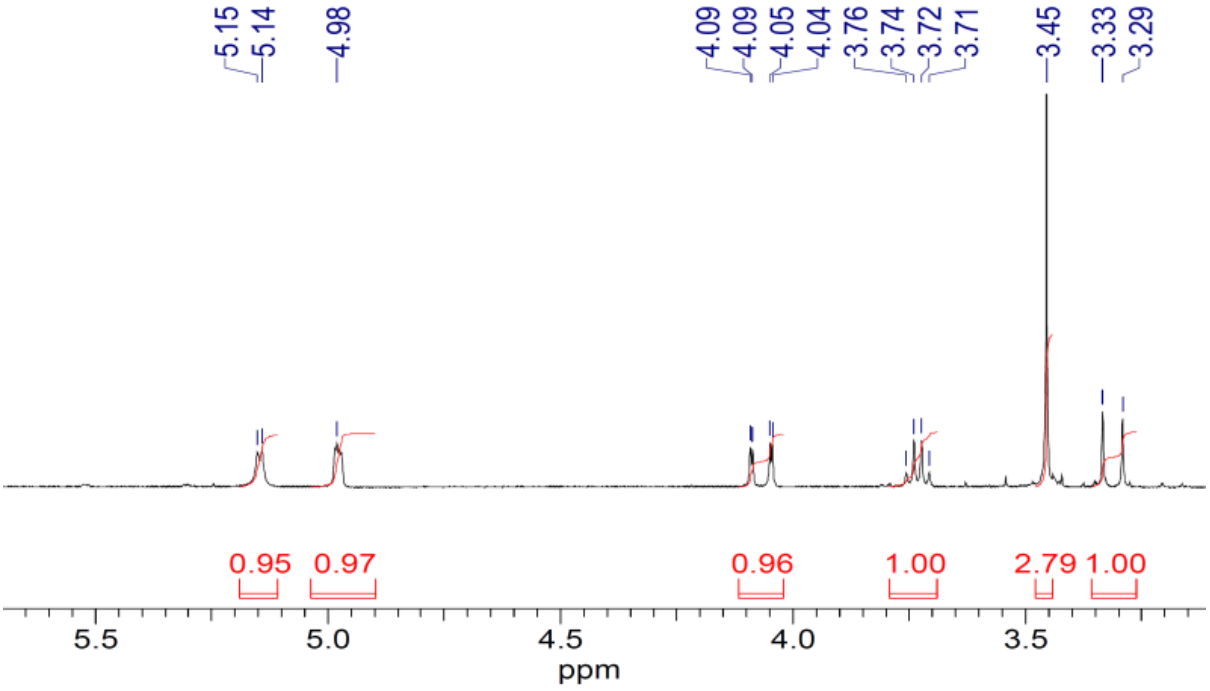


Figure 2S. [1]H-NMR spectra for reaction mixture corresponding with: a) no stereochemical induction, entry 1; b) with a diasteromeric induction of 88% de, entry 4

©ARKAT-USA, Inc.

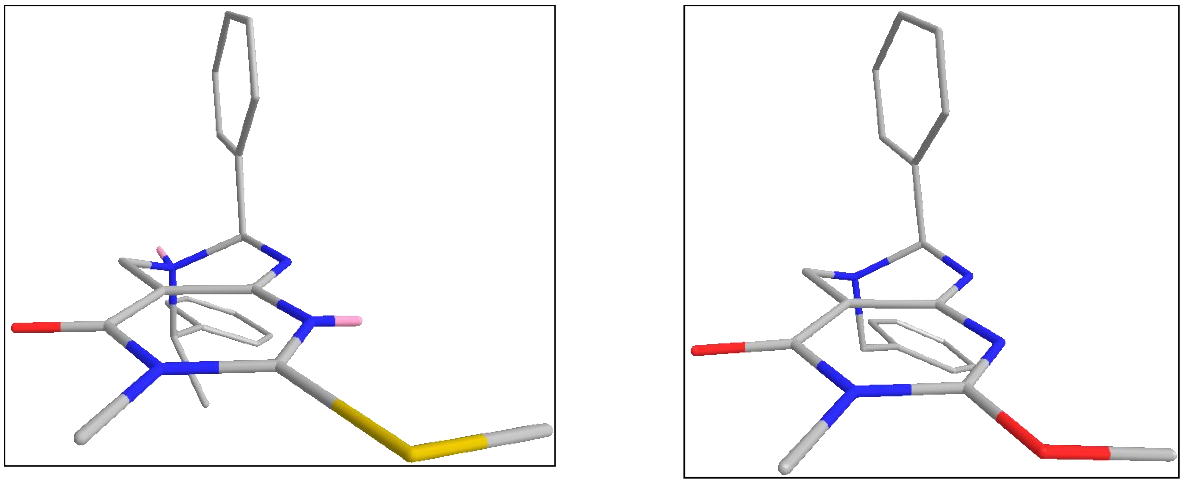


Figure 3S. Spatial view of the preferred conformations of compound **4g$_2$** obtained from DFT optimizations (left) and compound **4c** obtained from X-Ray diffraction (right)

©ARKAT-USA, Inc.

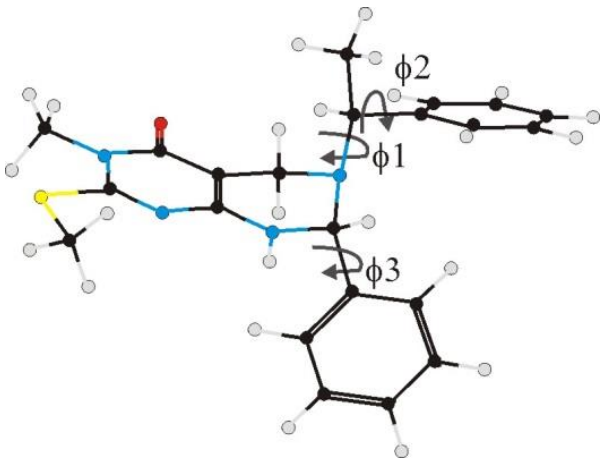


Figure 4S. Spatial view of the energetically preferred conformation obtained for compound **4g$_2$**. The most relevant torsional angles are also shown in this figure

Table 1S: Different conformations obtained for compounds **4g$_{1-4}$** from B3LYP/6-31G(d) optimizations

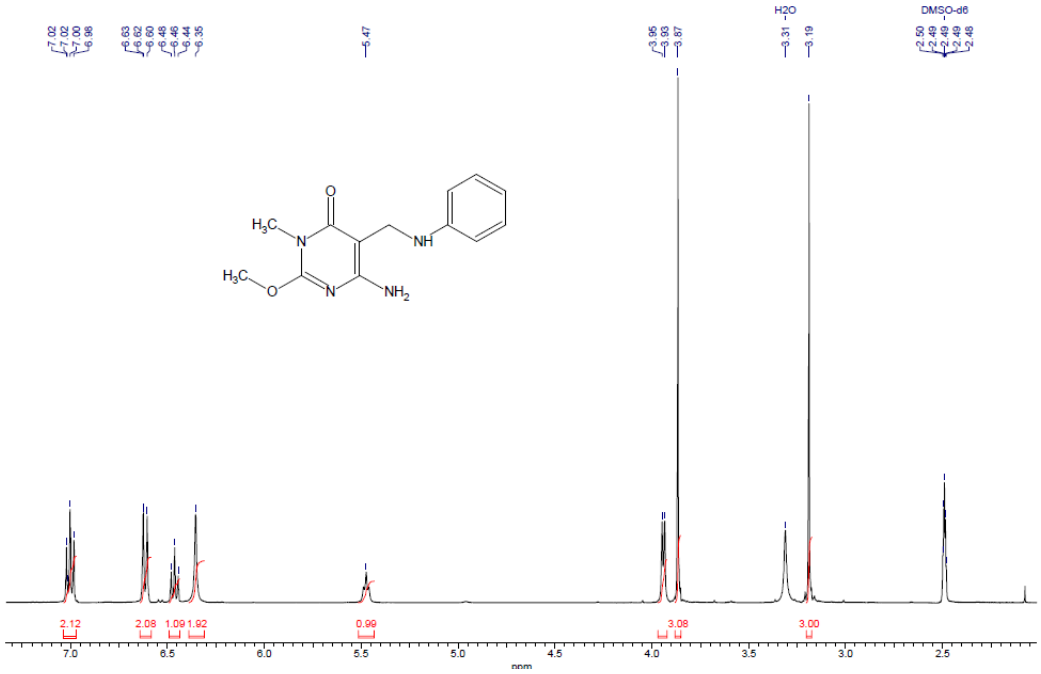
Diasteromer	Conformation	Torsional Angles			Energy Gap ΔE (Kcal.mol^{-1})
		Φ_1	Φ_2	Φ_3	
4g$_1$/4g$_4$	C1	-168.6	-125.2	-105.5	0.00
	C2	-68.2	104.7	123.1	2.73
	C3	-172.2	58.3	127.7	6.75
	C4	81,3	-86.2	131.2	6.06
4g$_2$/4g$_3$	C4	65.3	52.1	118.4	0.00
	C2	159.5	112.3	97.8	1.24
	C1	-66.6	80.8	50.1	1.51
	C3	64.7	56.6	46.1	4.80

©ARKAT-USA, Inc.

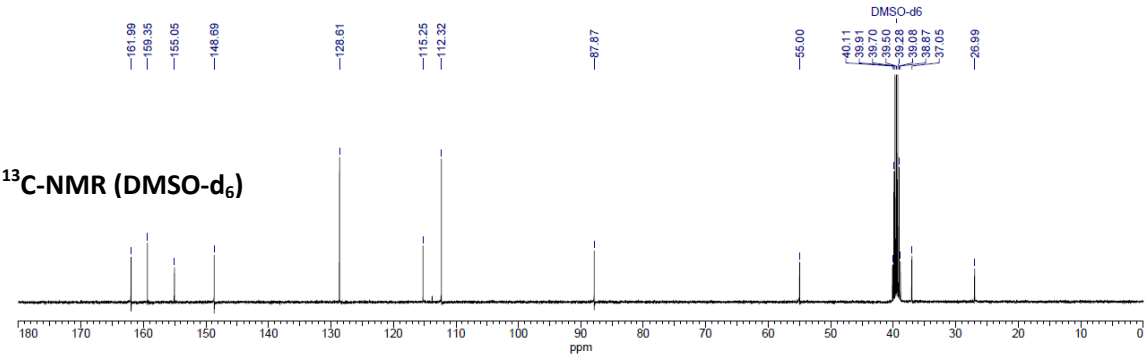
NMR SPECTRA

6-Amino-2-methoxy-3-methyl-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2a)**

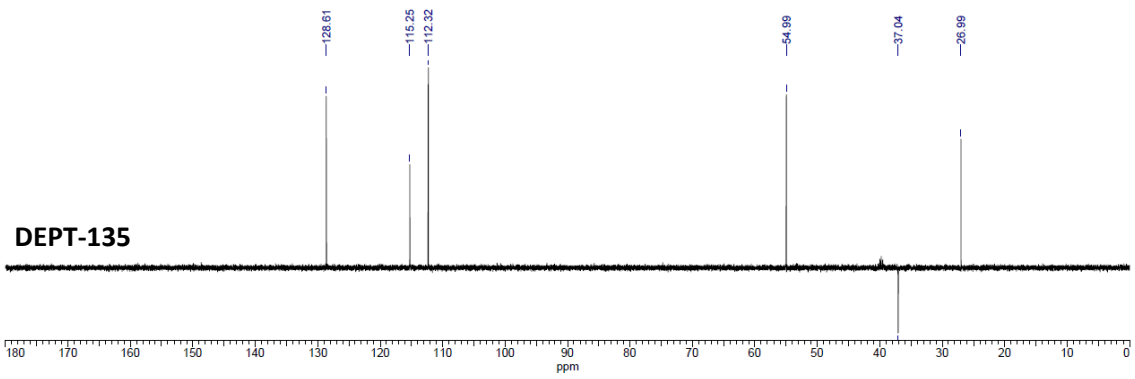
^{1}H-NMR (DMSO-d$_6$)



^{13}C-NMR (DMSO-d$_6$)



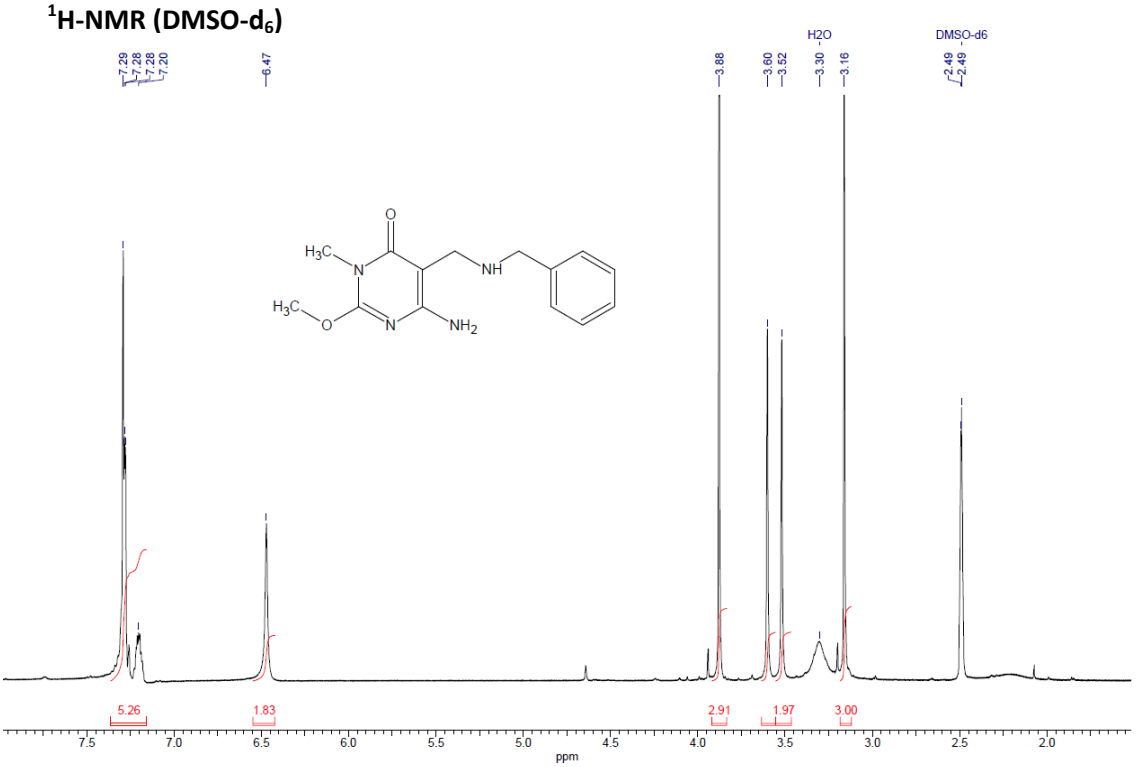
DEPT-135



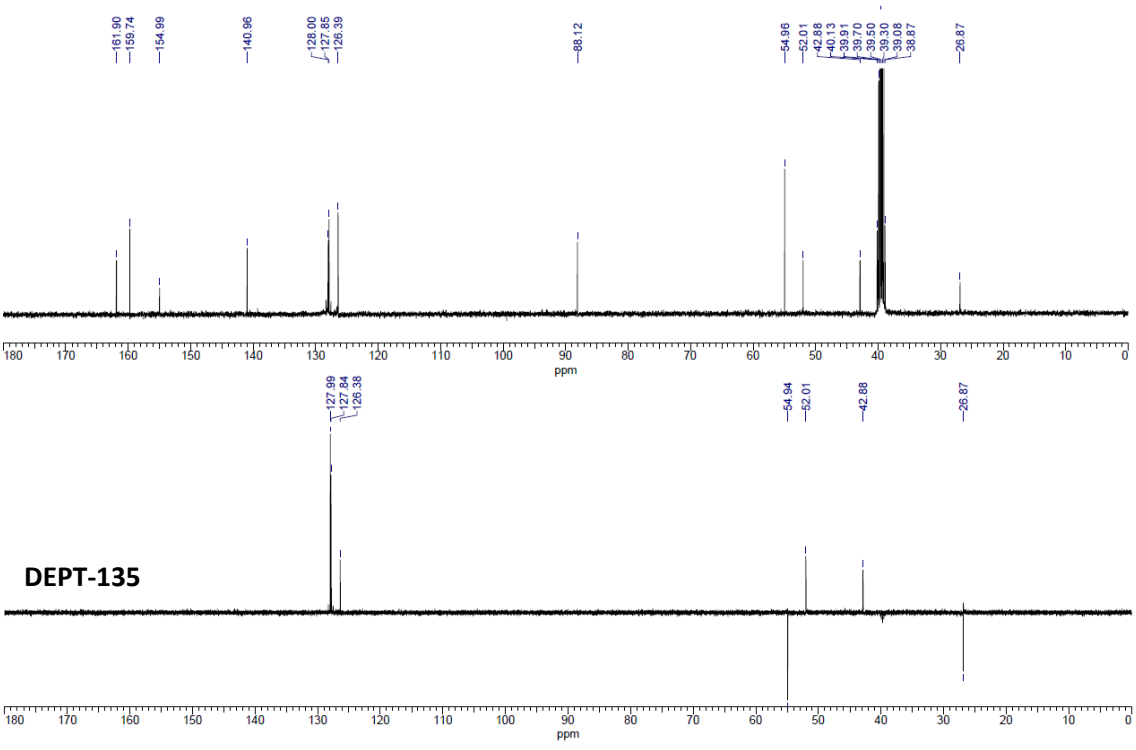
©ARKAT-USA, Inc.

6-Amino-3-methyl-2-(methylthio)-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2b)**

^{1}H-NMR (DMSO-d$_6$)



^{13}C-NMR (DMSO-d$_6$)

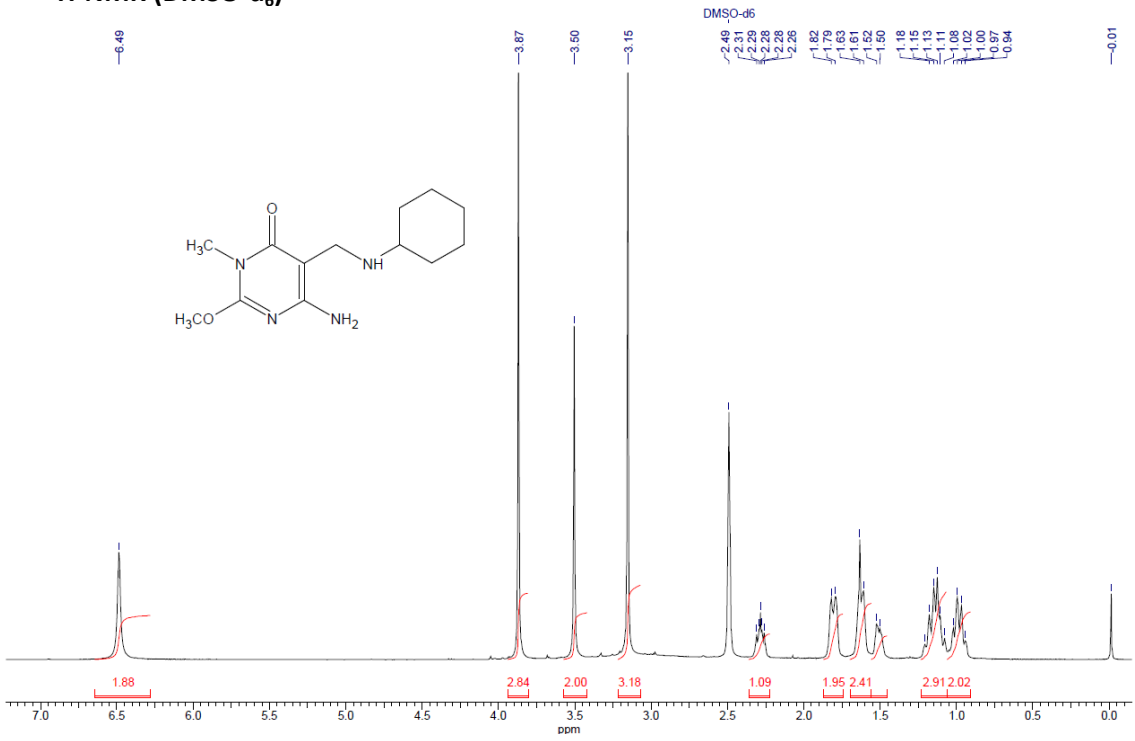


DEPT-135

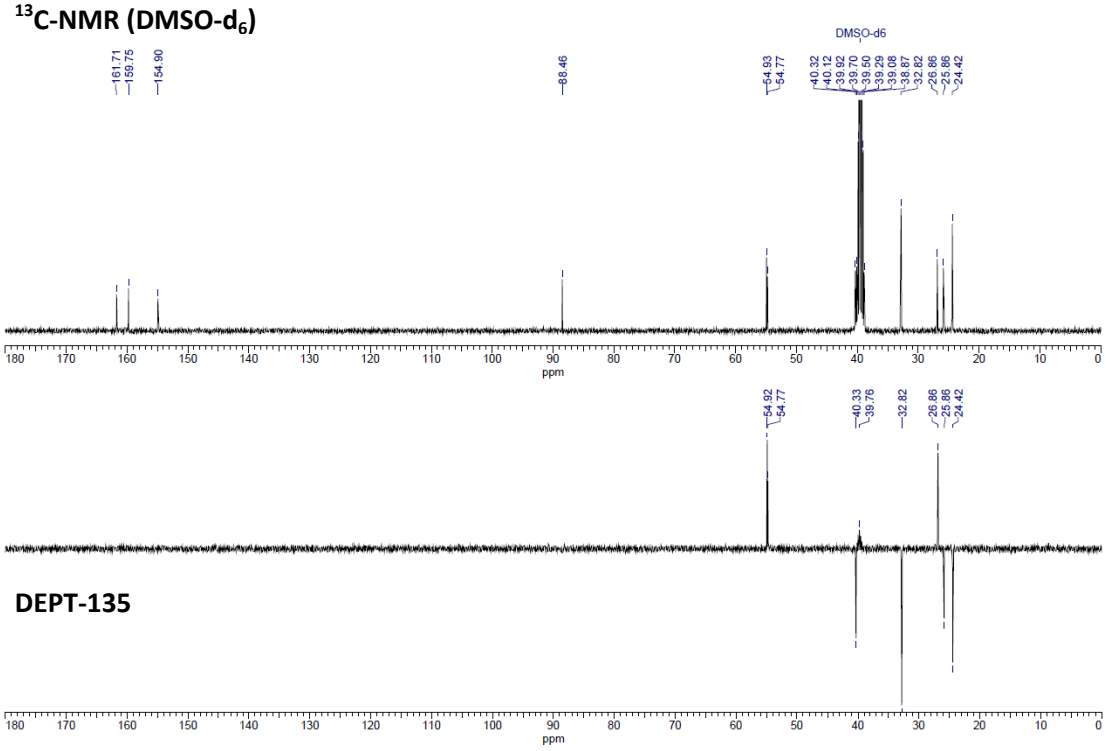
©ARKAT-USA, Inc.

6-Amino-5-((cyclohexylamino)methyl)-2-methoxy-3-methylpyrimidin-4(3H)-one **(2c)**

^{1}H-NMR (DMSO-d$_6$)



^{13}C-NMR (DMSO-d$_6$)

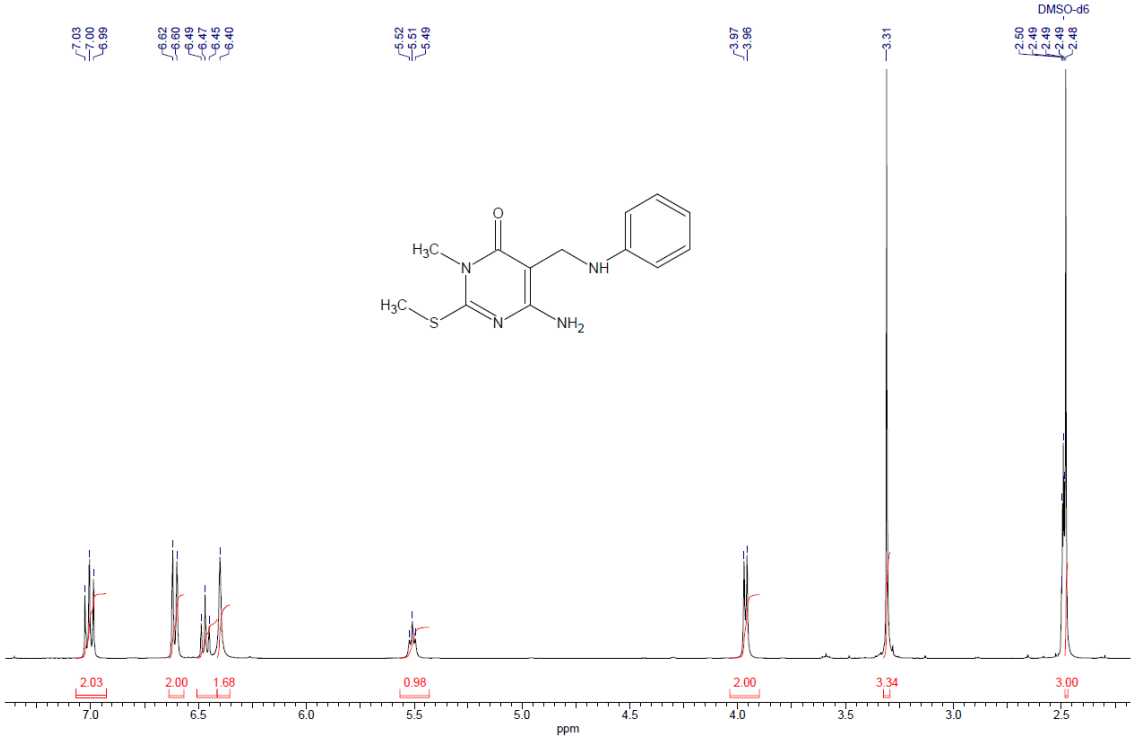


DEPT-135

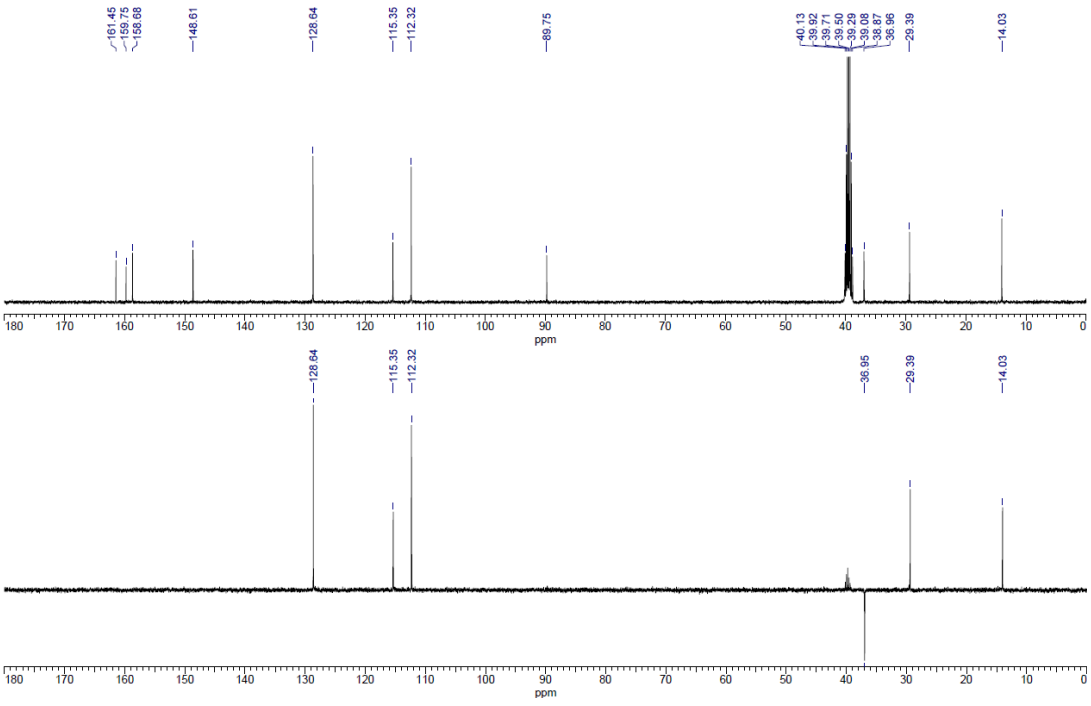
©ARKAT-USA, Inc.

6-Amino-3-methyl-2-(methylthio)-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2d)**

^{1}H-NMR (DMSO-d$_6$)



^{13}C-NMR (DMSO-d$_6$)

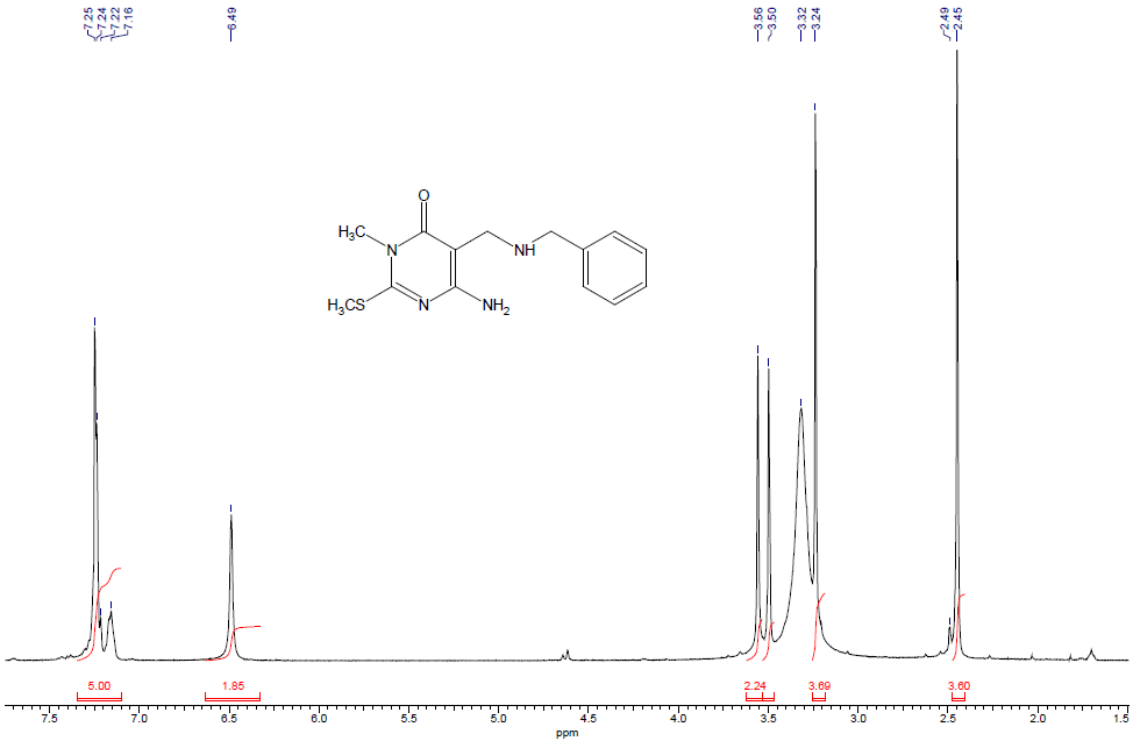


DEPT-135

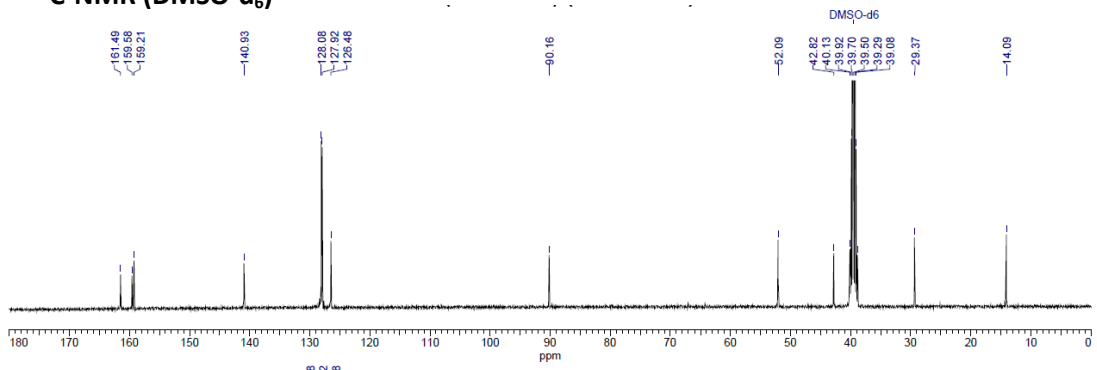
 ©ARKAT-USA, Inc.

6-Amino-5-((benzylamino)methyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one **(2e)**

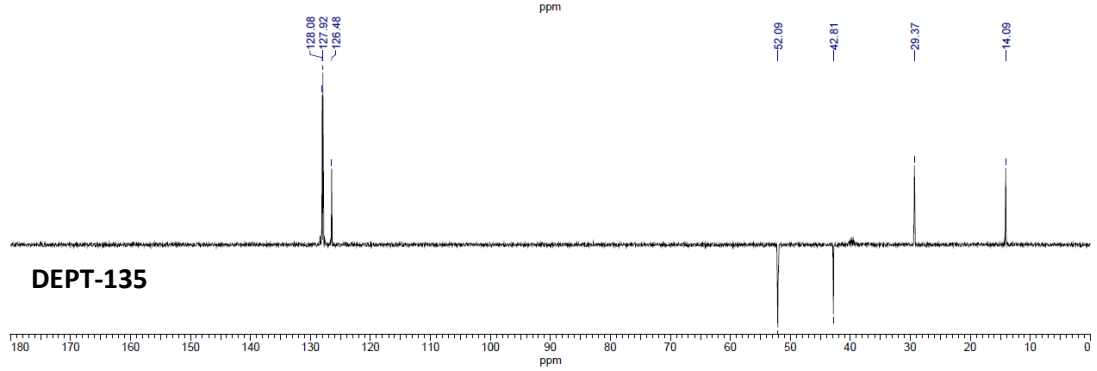
^{1}H-NMR (DMSO-d$_6$)



^{13}C-NMR (DMSO-d$_6$)



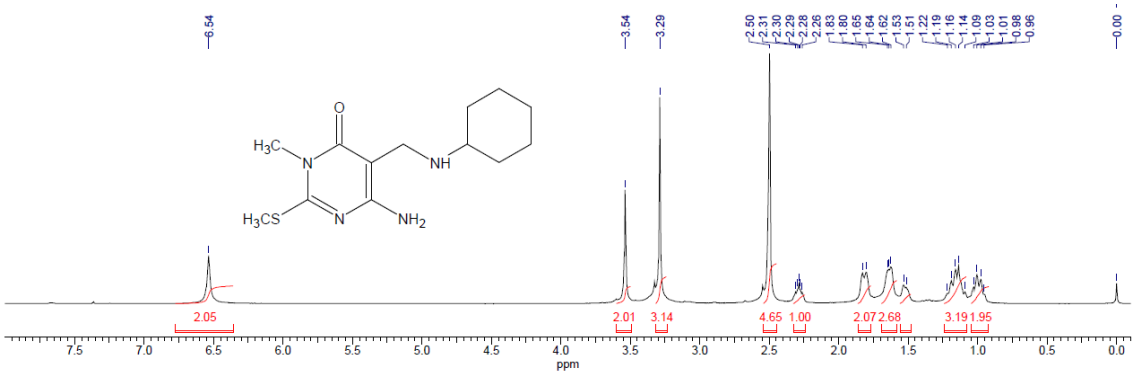
DEPT-135



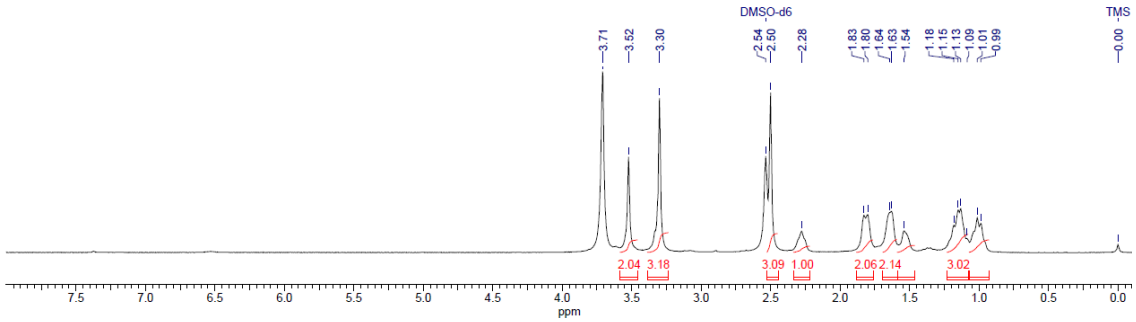
 ©ARKAT-USA, Inc.

6-Amino-5-((cyclohexylamino)methyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one **(2f)**

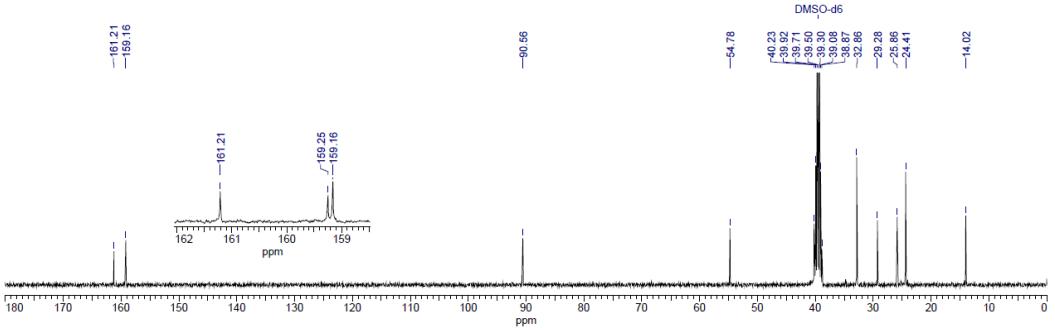
^{1}H-NMR (DMSO-d$_6$)

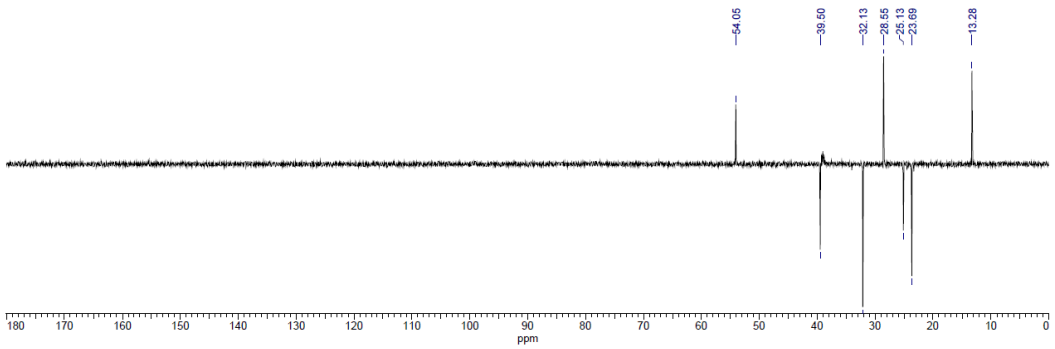


(1H + D2O)



^{13}C-NMR (DMSO-d$_6$)



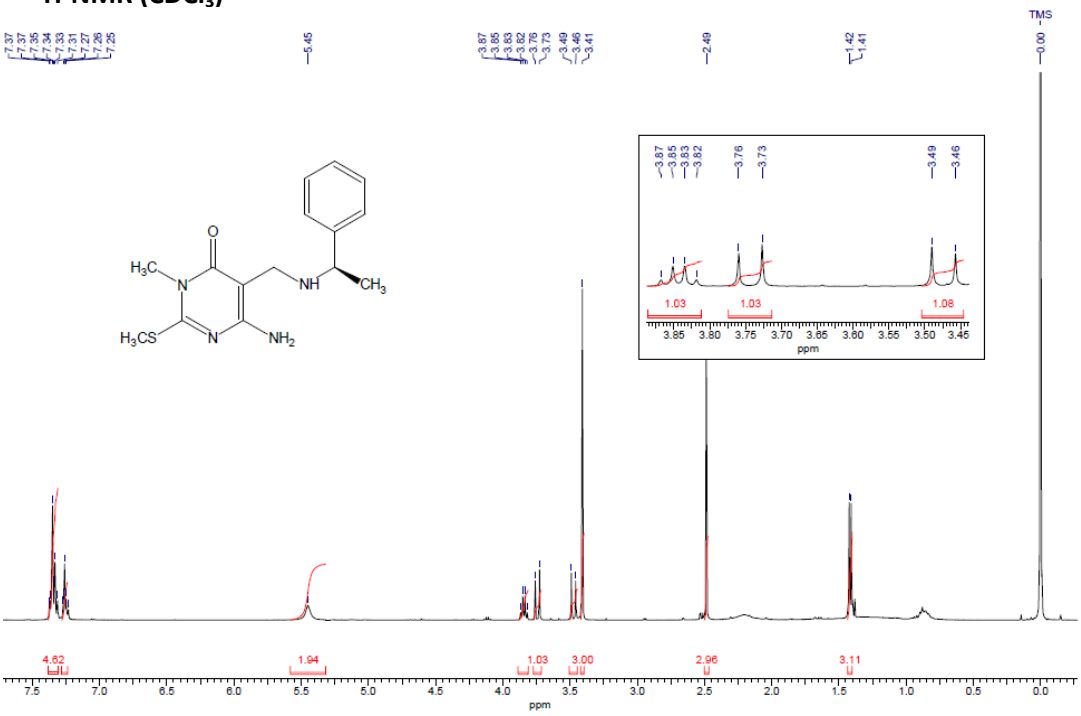


DEPT-135

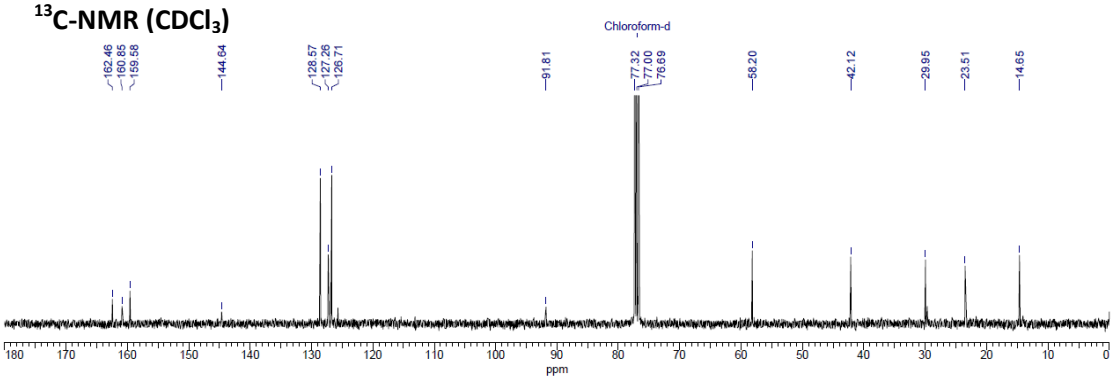
©ARKAT-USA, Inc.

(R)-6-Amino-3-methyl-2-methylthio-5-(((1-phenylethyl)amino)methyl)pyrimidin-4(3*H*)-one **(2g)**

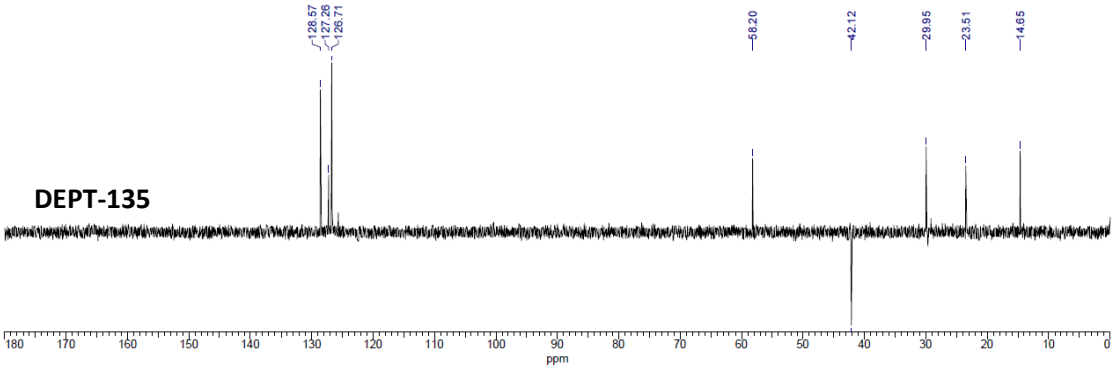
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)



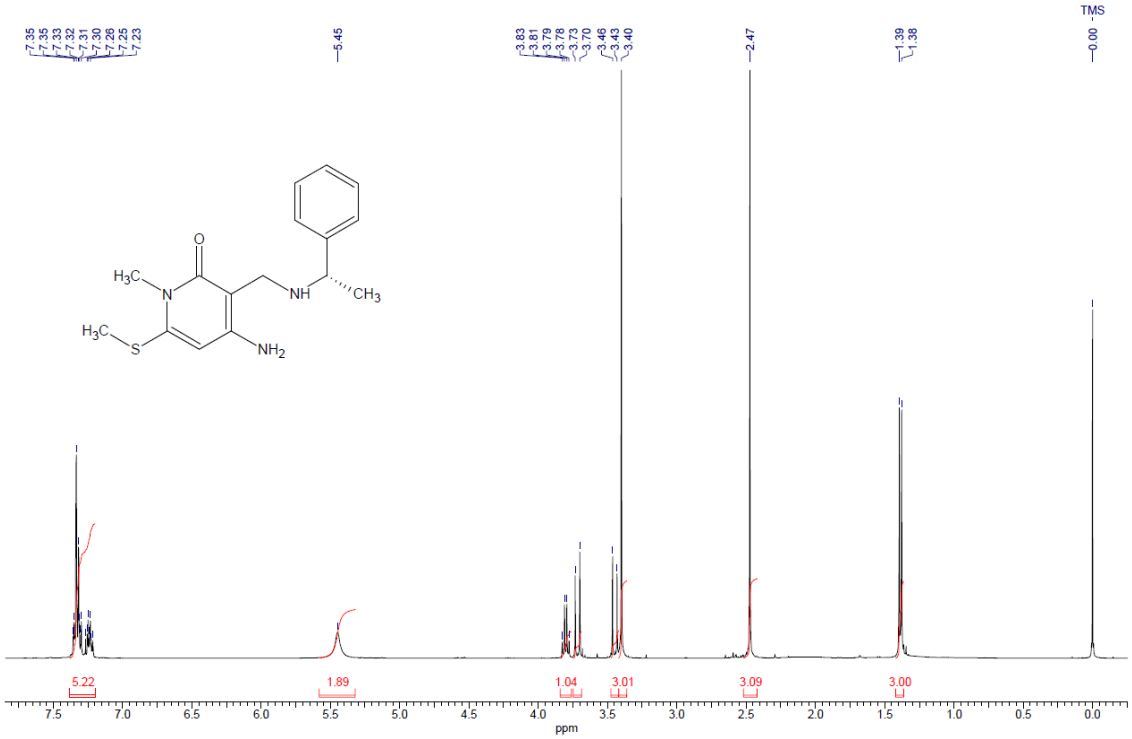
DEPT-135



©ARKAT-USA, Inc.

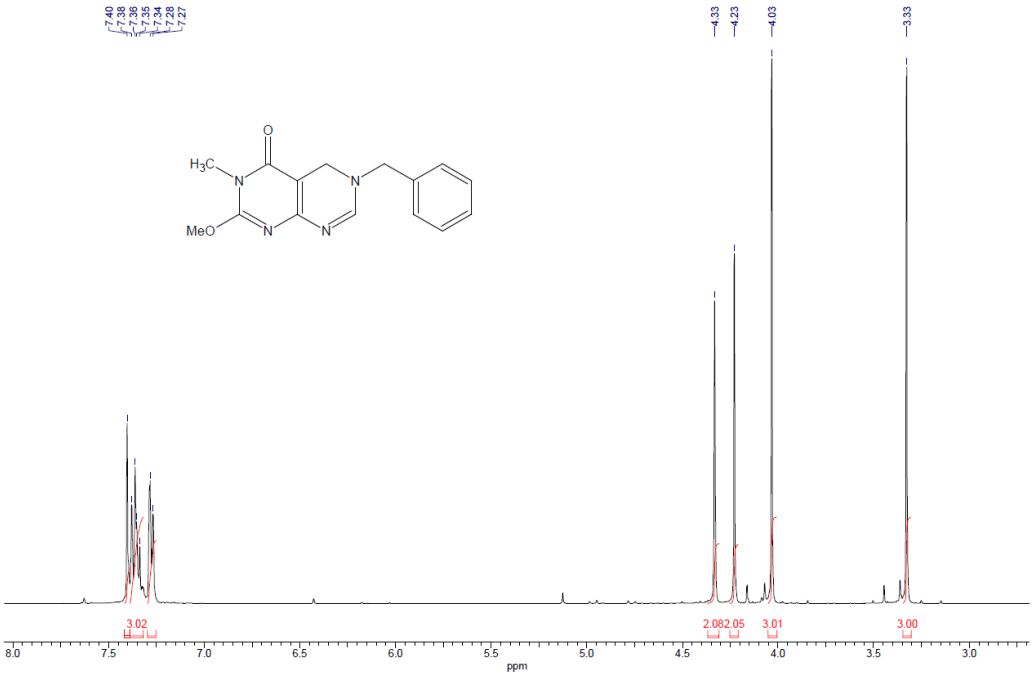
(*S*)-6-Amino-3-methyl-2-methylthio-5-(((1-phenylethyl)amino)methyl)pyrimidin-4(3*H*)-one **(2g')**

^{1}H-NMR ($CDCl_3$)



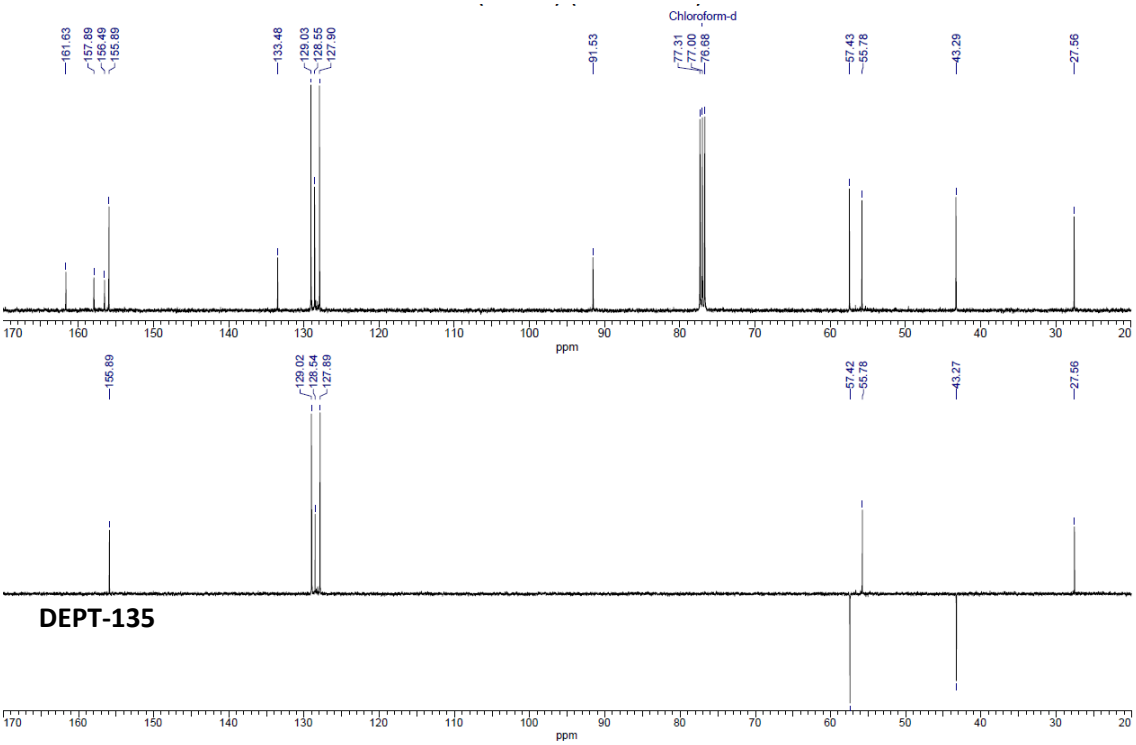
6-Benzyl-2-methoxy-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3a)**

^{1}H-NMR ($CDCl_3$)



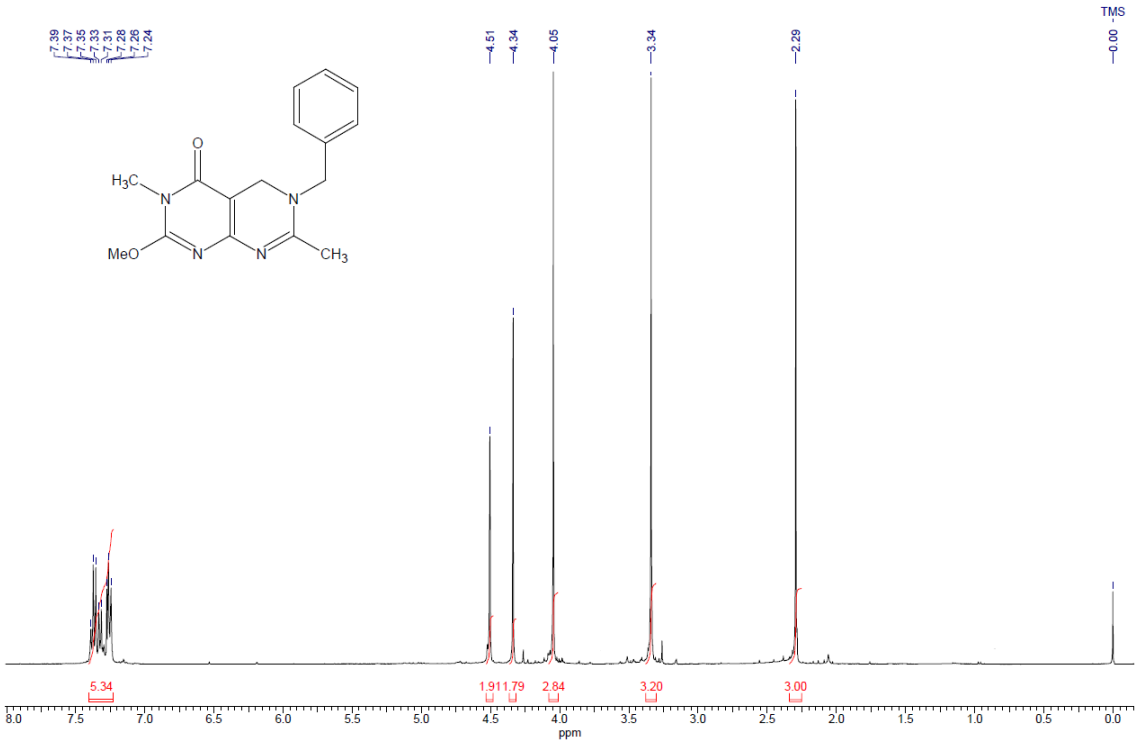
©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



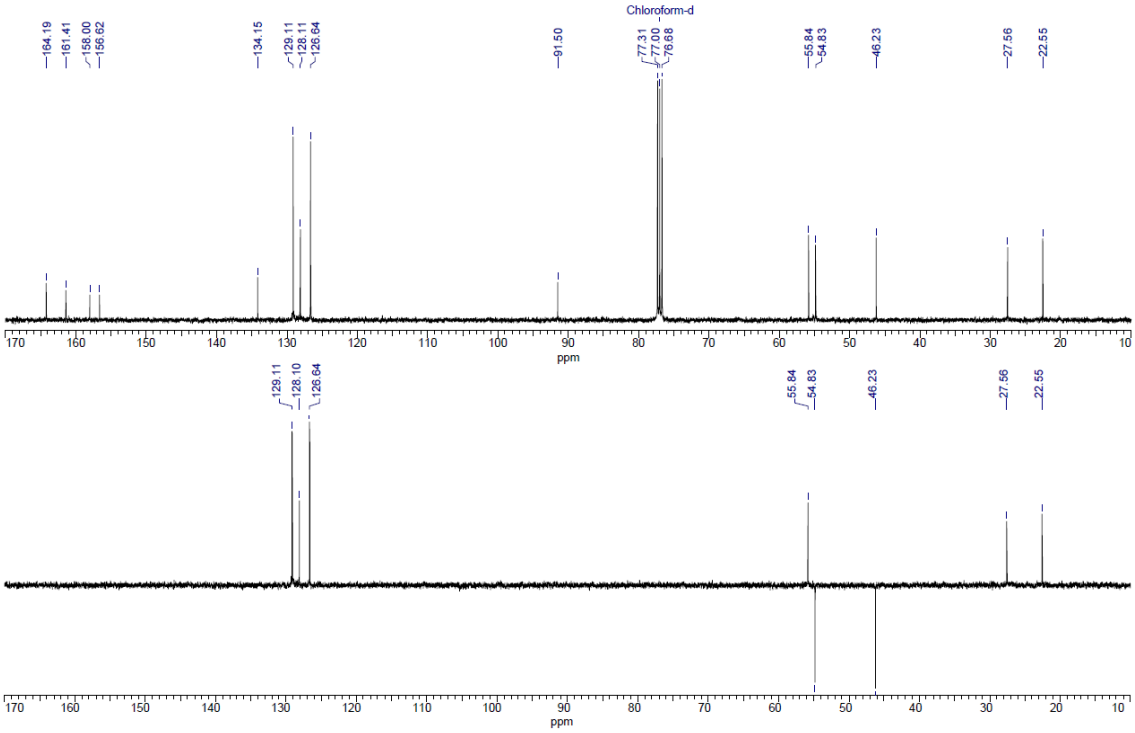
6-Benzyl-2-methoxy-3,7-dimethyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3b)**

^{1}H-NMR ($CDCl_3$)



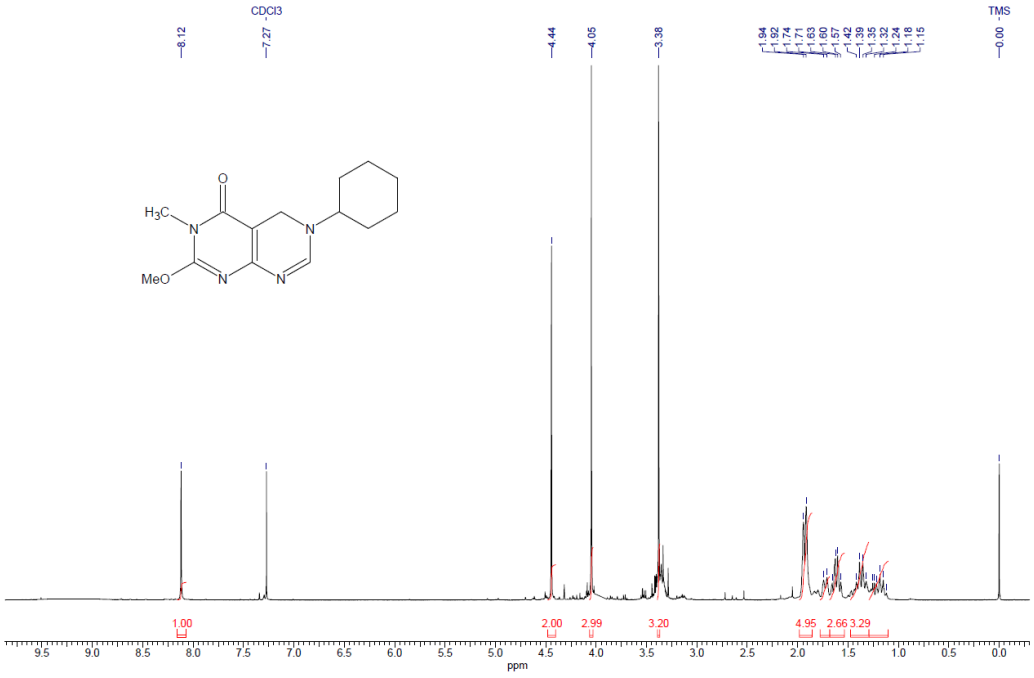
 ©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



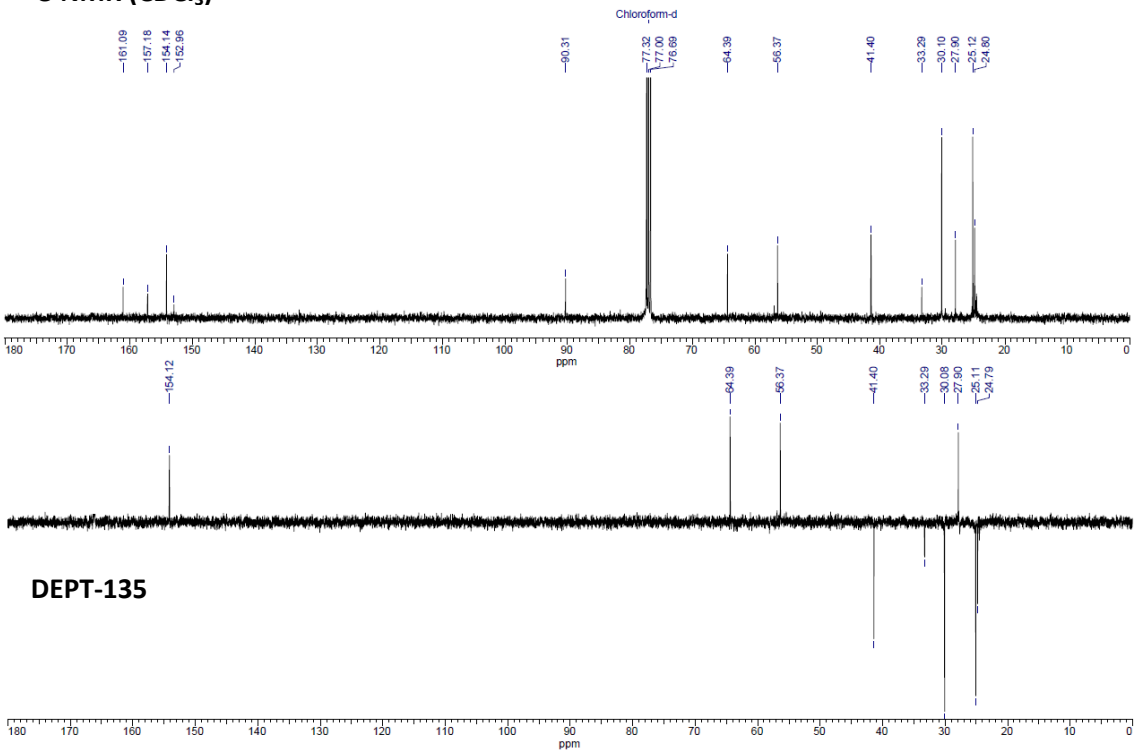
6-Cyclohexyl-2-methoxy-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3c)**

^{1}H-NMR ($CDCl_3$)



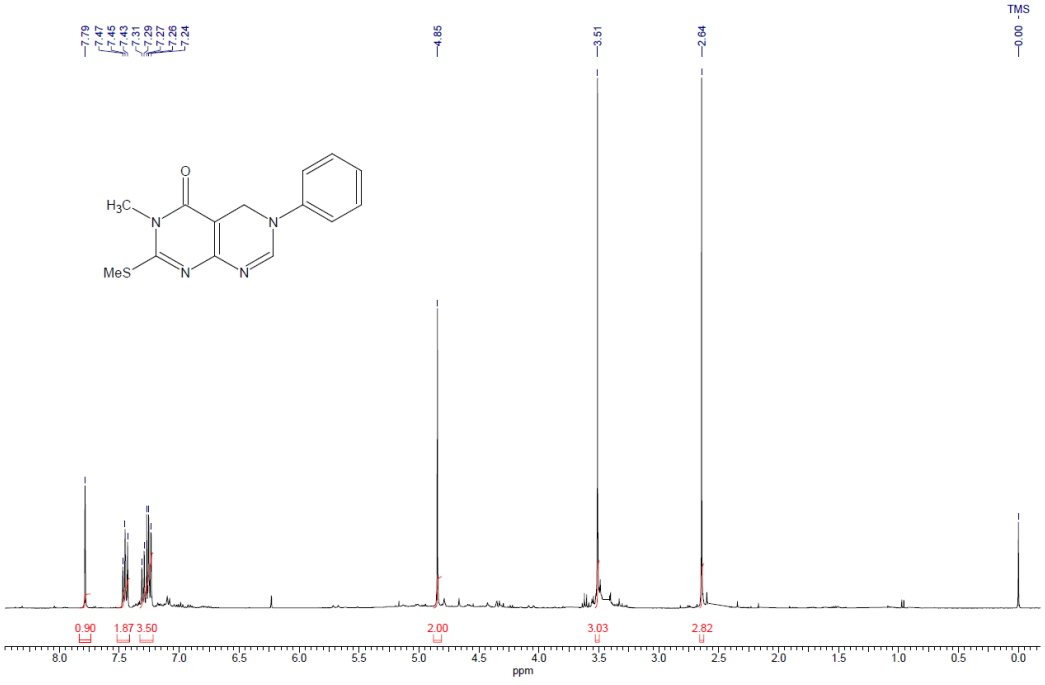
©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



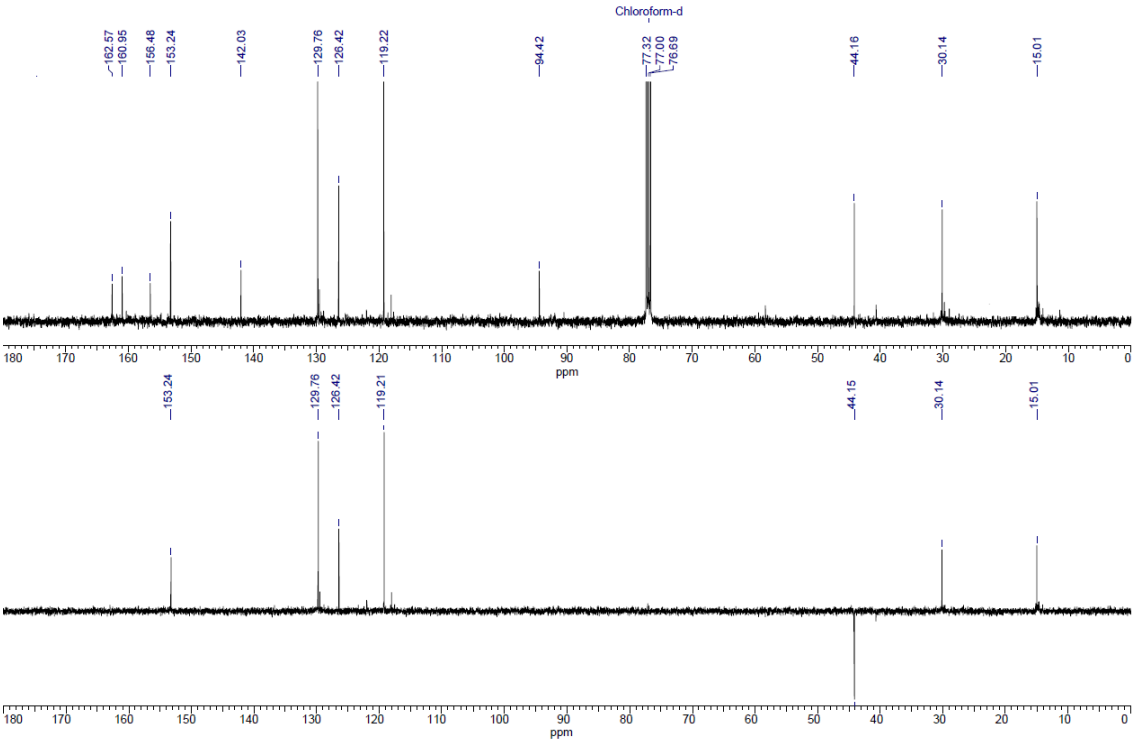
3-Methyl-2-(methylthio)-6-phenyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3d)**

^{1}H-NMR ($CDCl_3$)



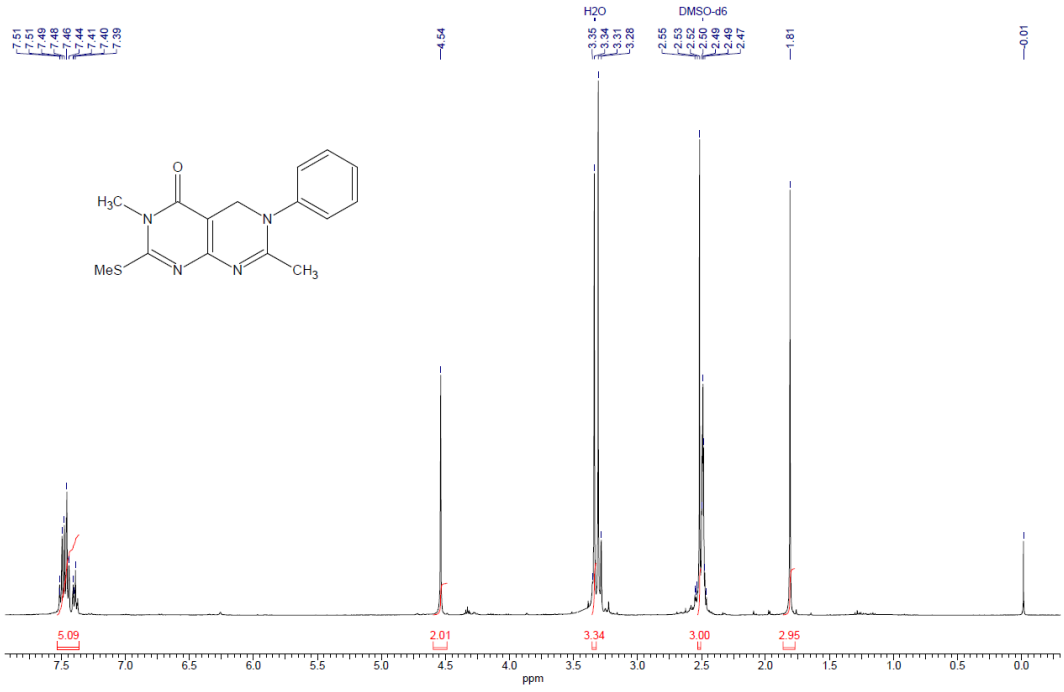
©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



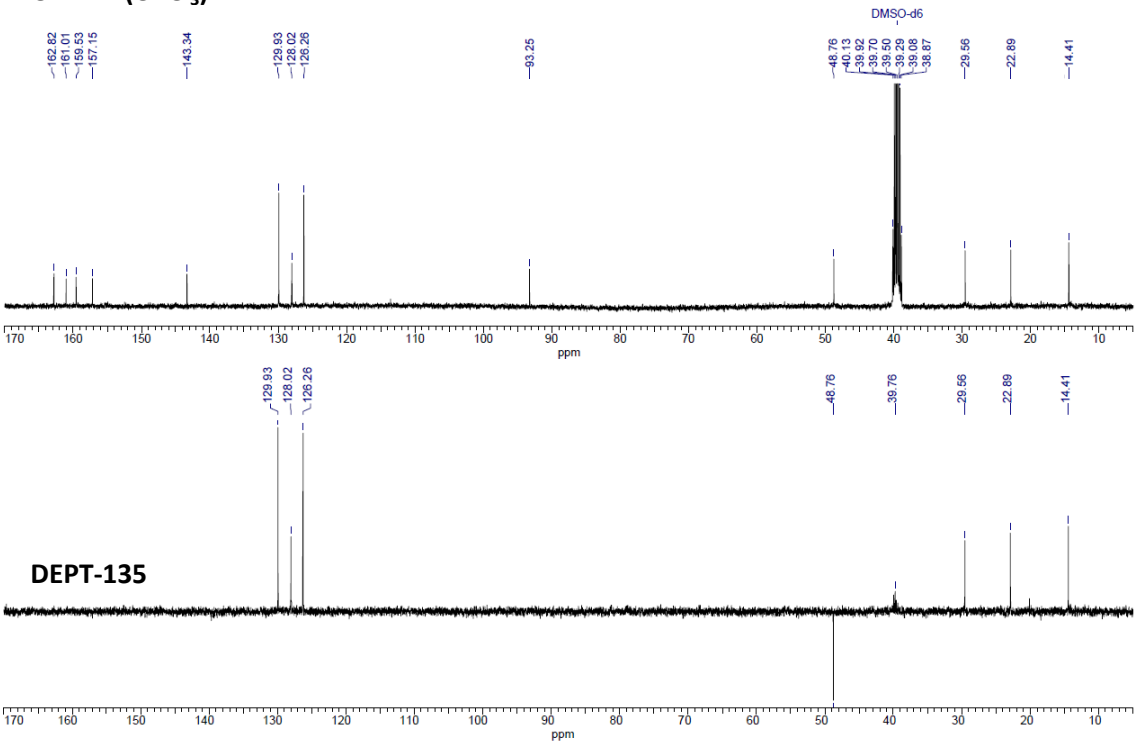
3,7-Dimethyl-2-(methylthio)-6-phenyl-5,6-dihydropyrimido-[4,5-d]pyrimidin-4(3H)-one **(3e)**

^{1}H-NMR ($CDCl_3$)



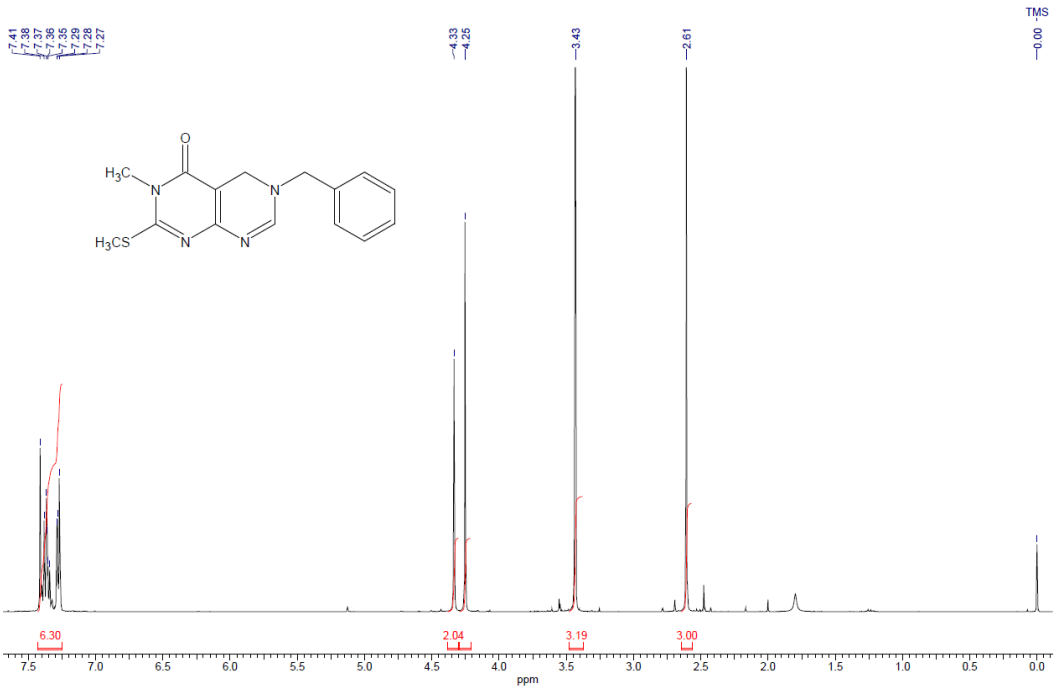
 ©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



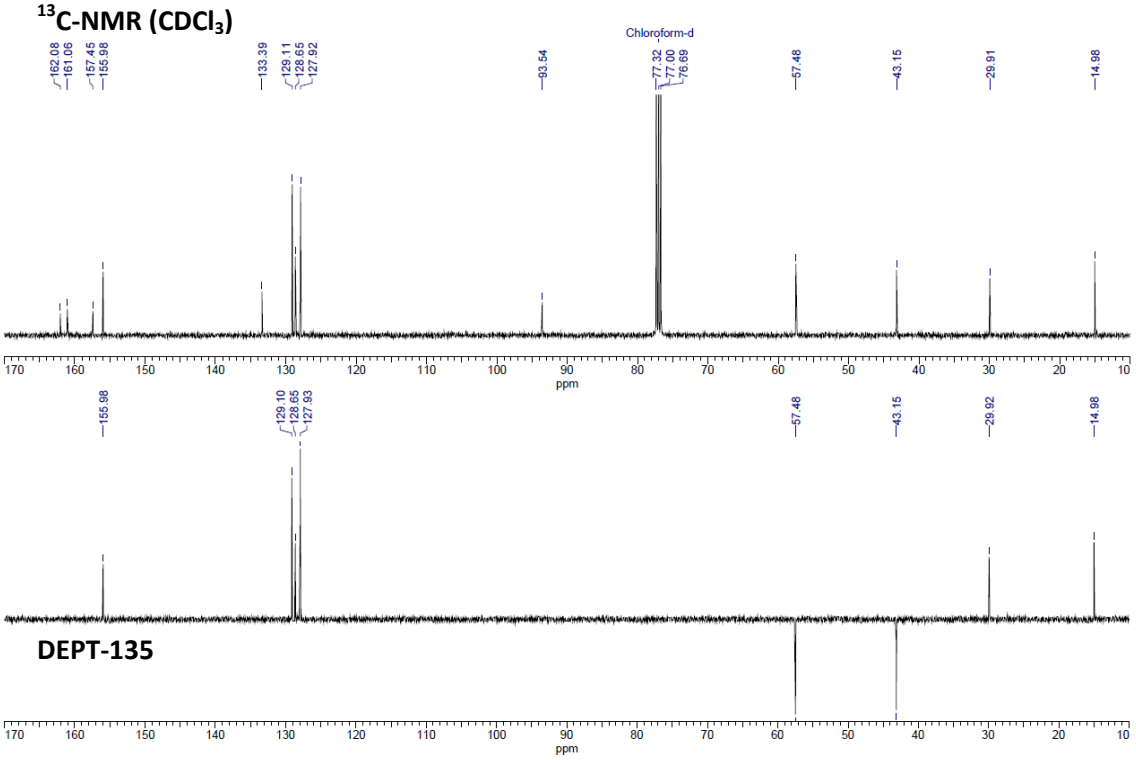
6-Benzyl-3-methyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3f)**

^{1}H-NMR ($CDCl_3$)



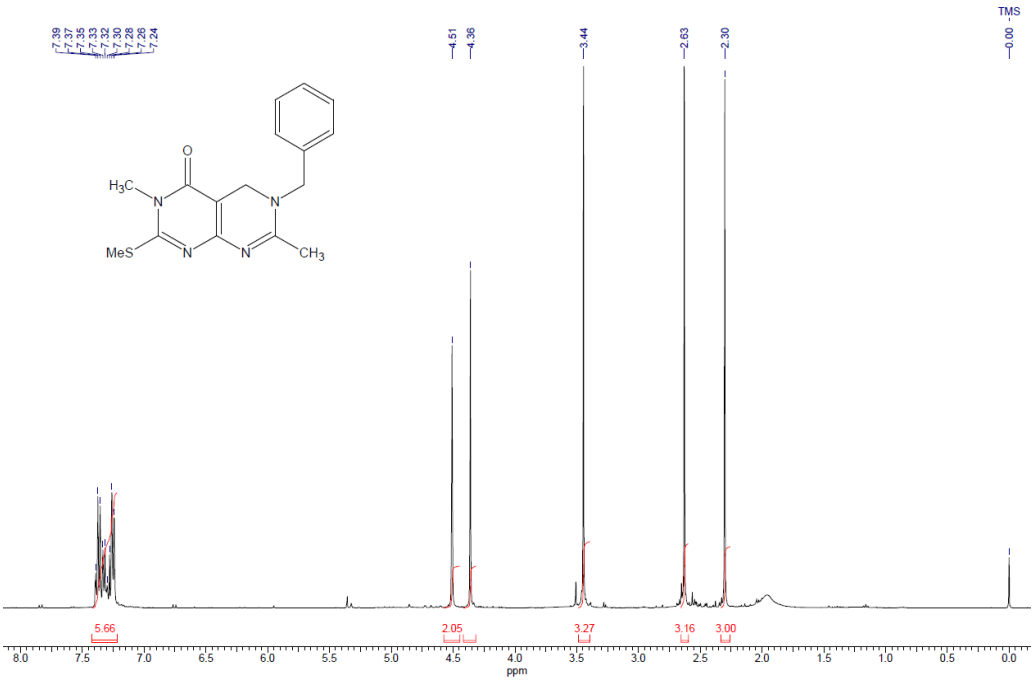
 ©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



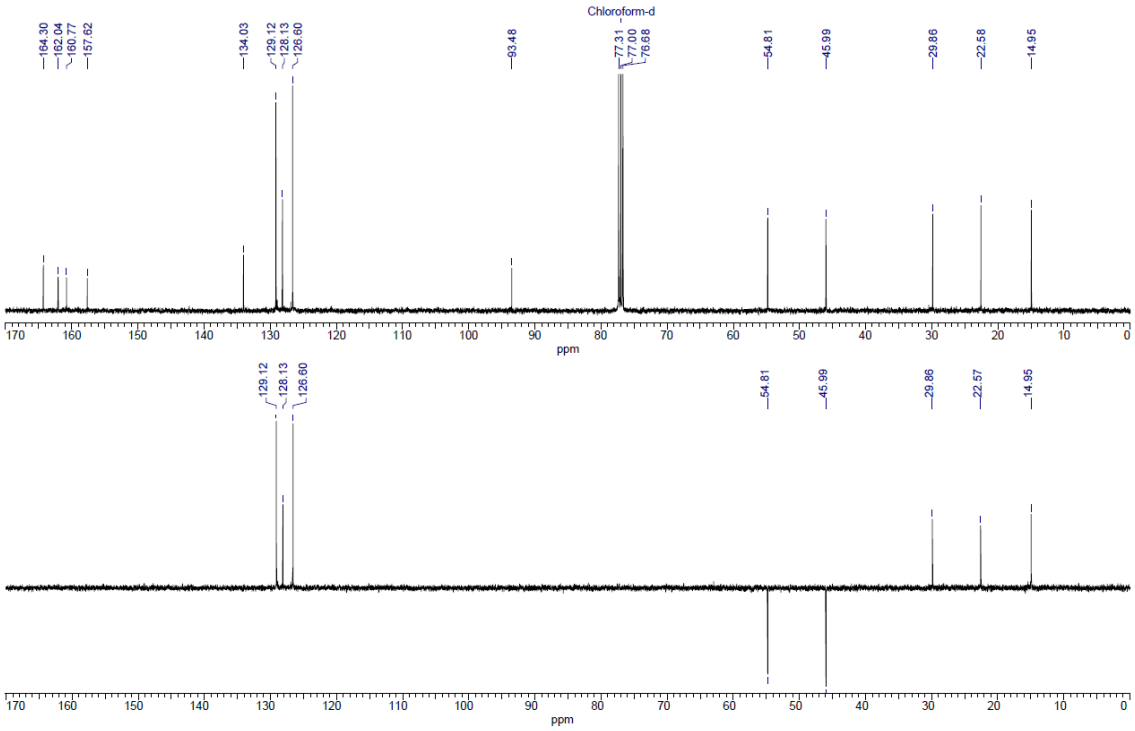
6-Benzyl-3,7-dimethyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3g)**

^{1}H-NMR ($CDCl_3$)



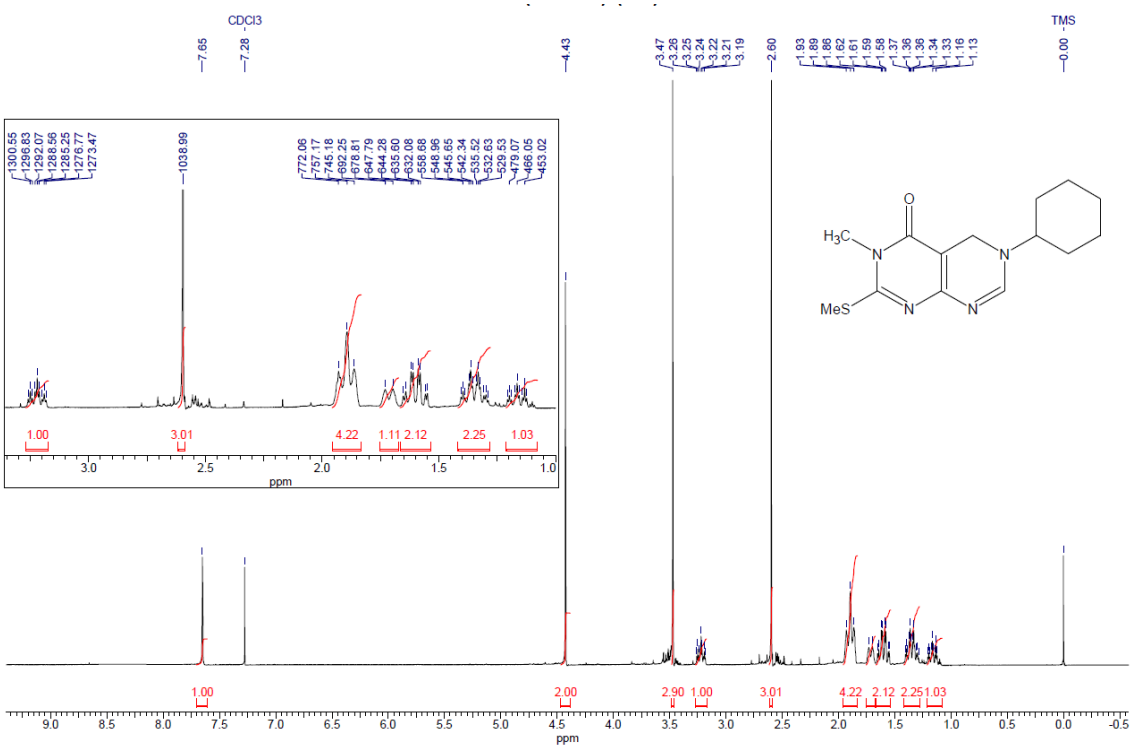
©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



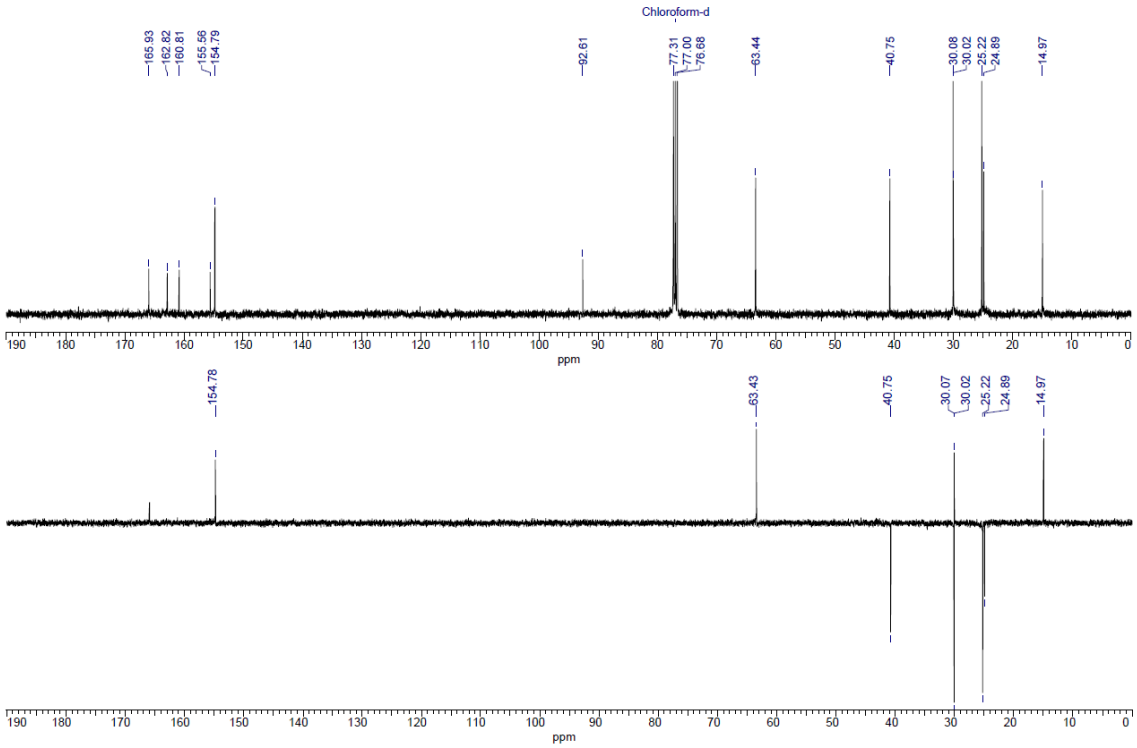
6-Cyclohexyl-3-methyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3h)**

^{1}H-NMR ($CDCl_3$)



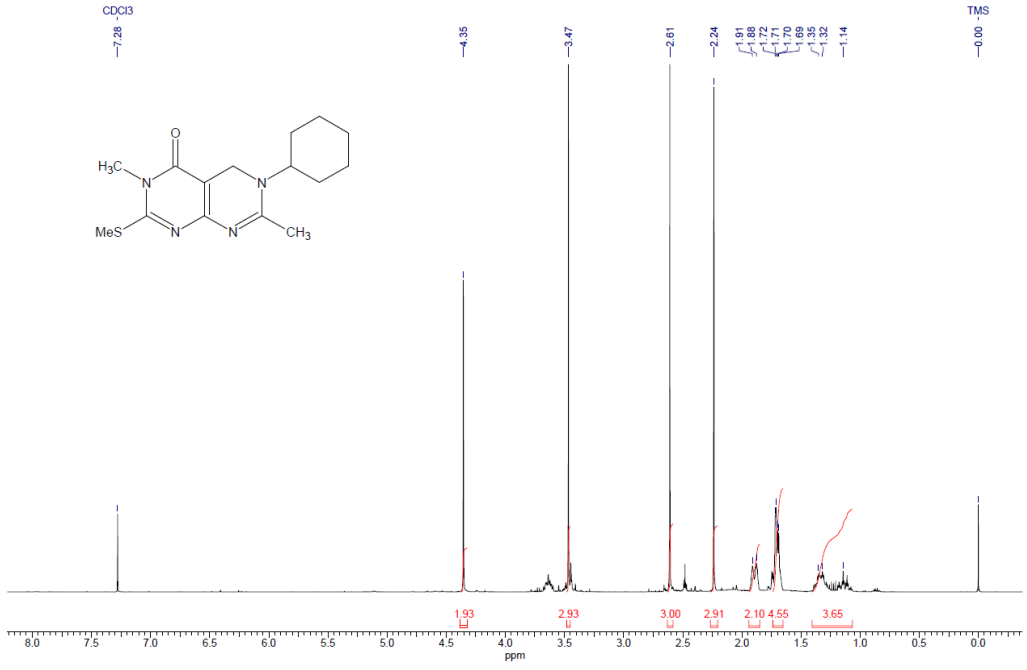
 ©ARKAT-USA, Inc.

^{13}C-NMR ($CDCl_3$)



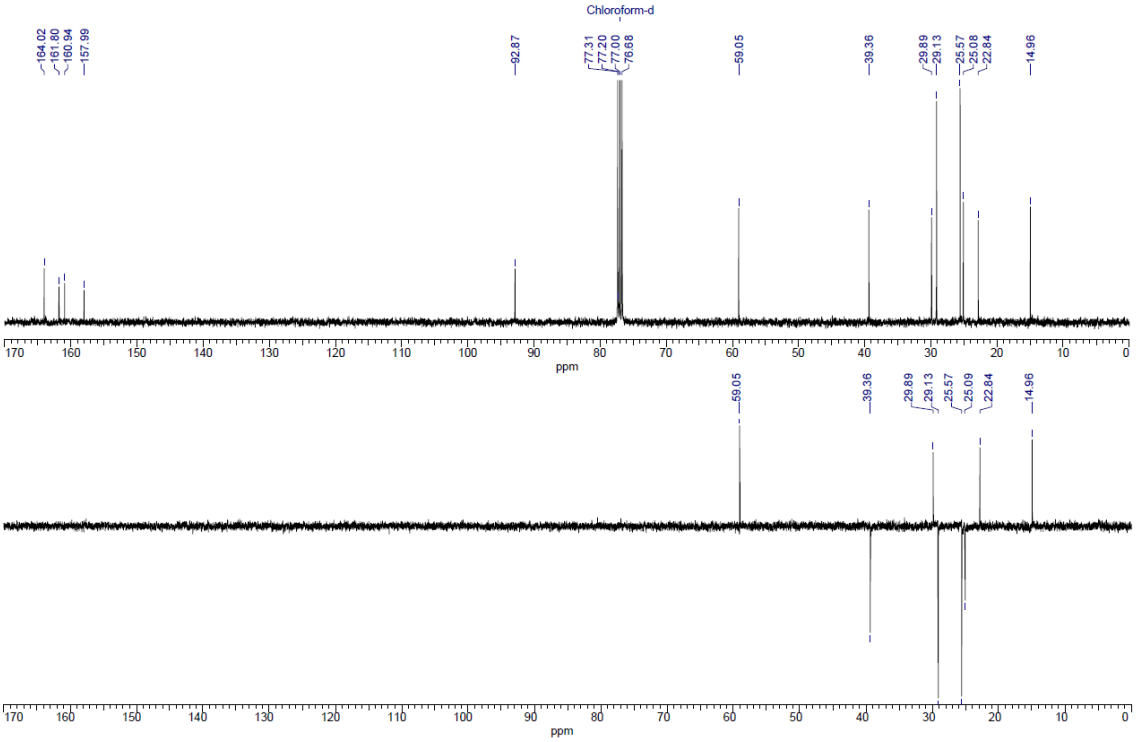
6-Cyclohexyl-3,7-dimethyl-2-(methylthio)-5,6-dihydropyrimido-[4,5-d]pyrimidin-4(3H)-one **(3i)**

^{1}H-NMR ($CDCl_3$)



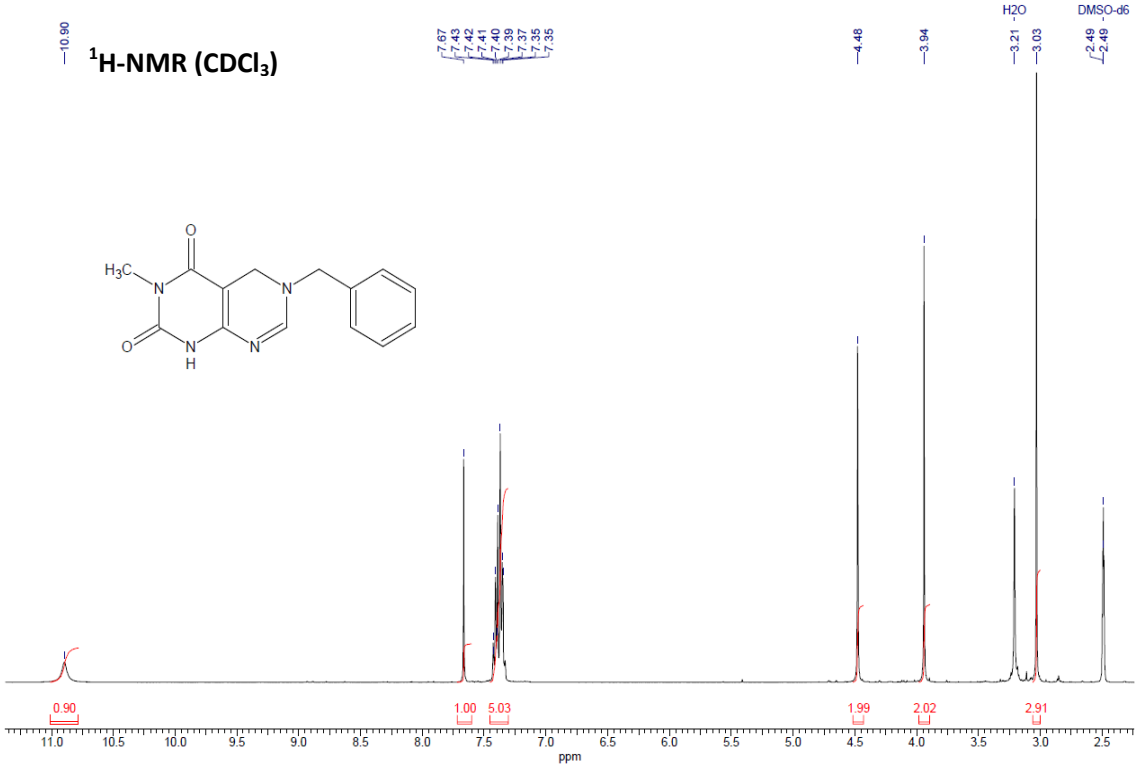
 ©ARKAT-USA, Inc.

^{13}C-NMR (CD_3Cl)



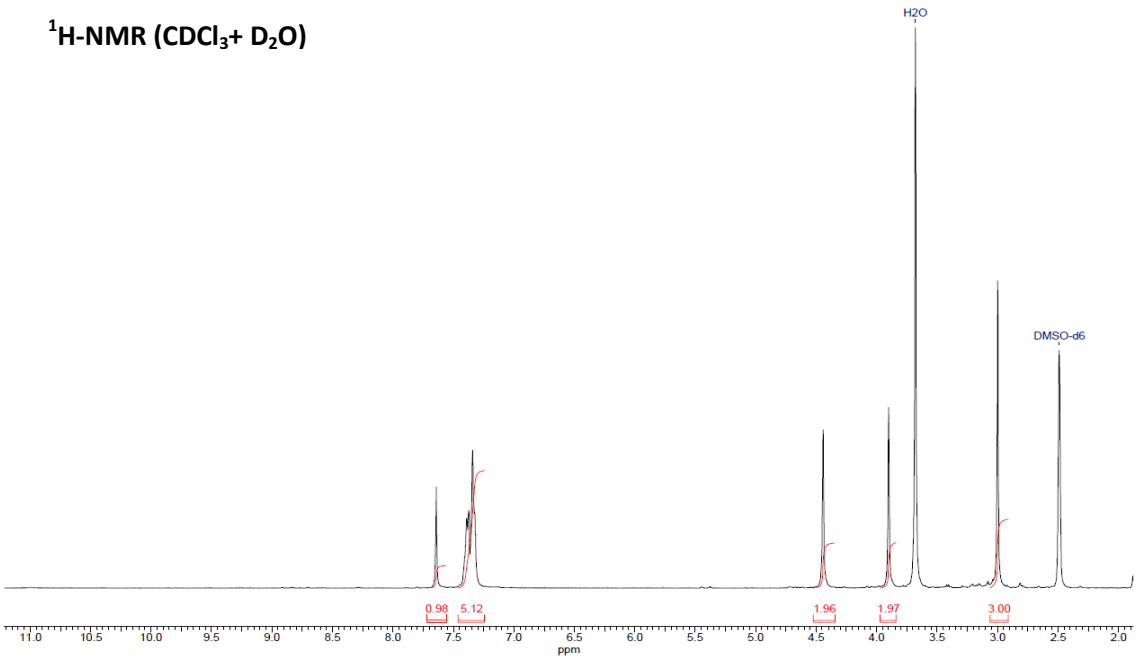
6-Benzyl-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione **(3j)**

^{1}H-NMR ($CDCl_3$)



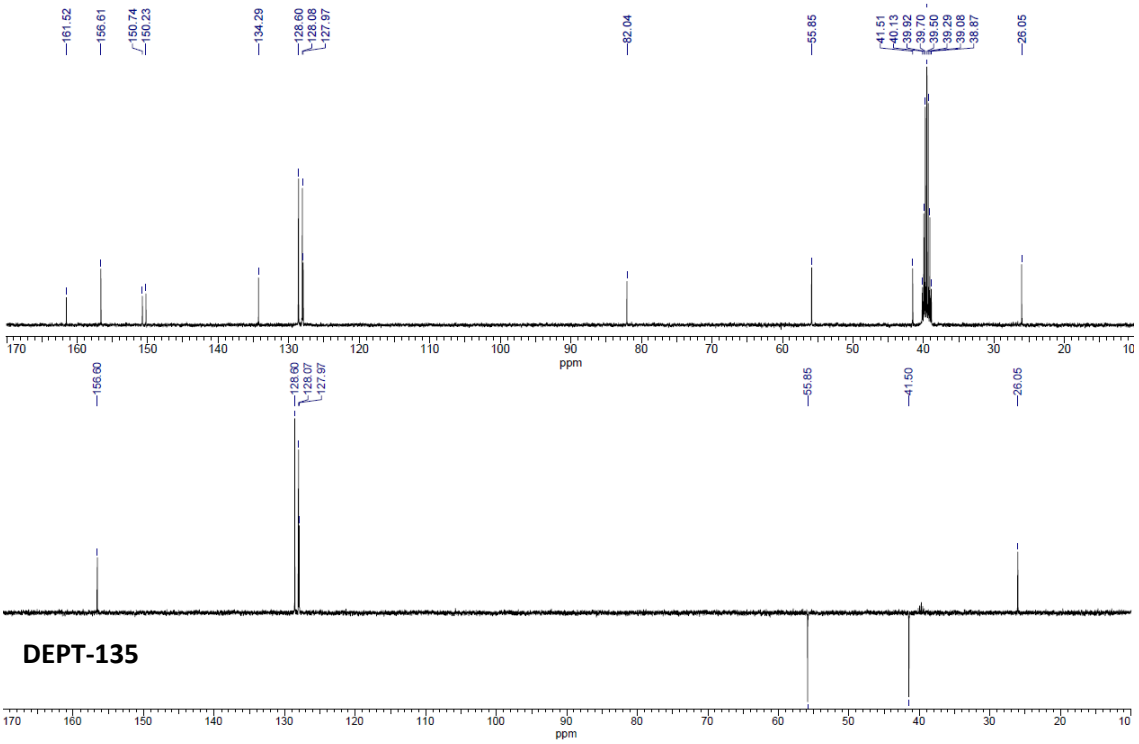
©ARKAT-USA, Inc.

^{1}H-NMR ($CDCl_3$+ D_2O)



6-Benzyl-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione **(3j)**

^{13}C-NMR ($CDCl_3$)

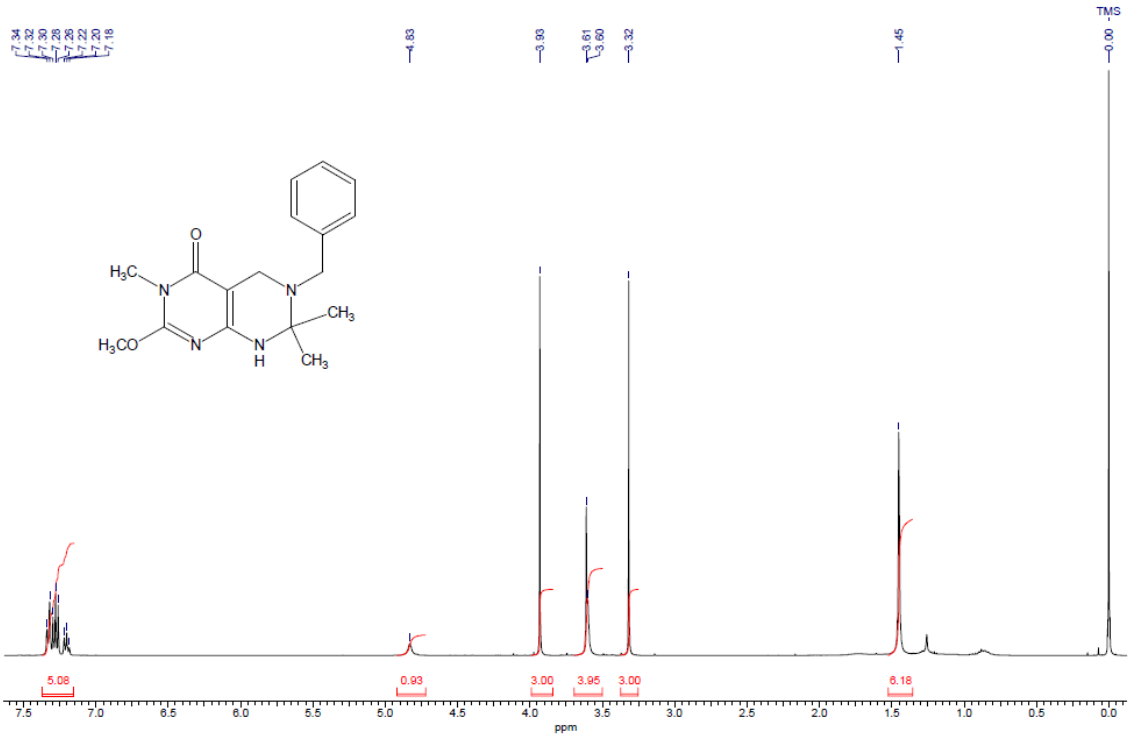


DEPT-135

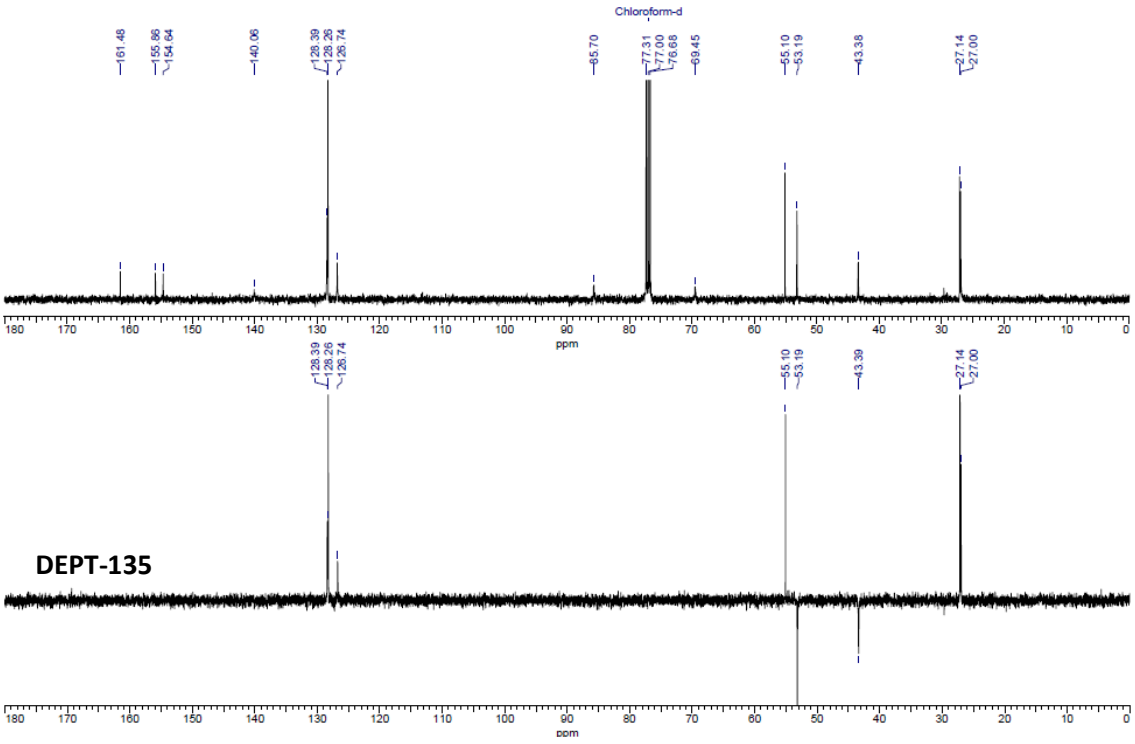
 ©ARKAT-USA, Inc.

6-Benzyl-3,7,7-trimethyl-2-methoxy-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4a)**

^{1}H-NMR ($CDCl_3$)



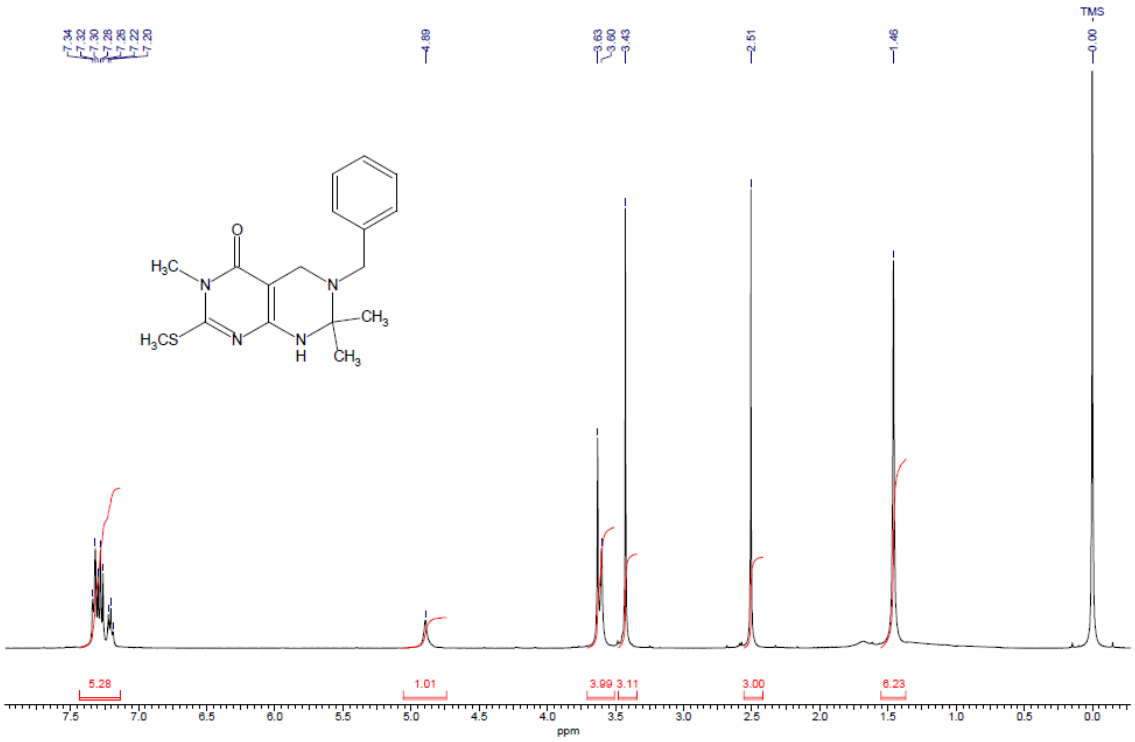
^{13}C-NMR ($CDCl_3$)



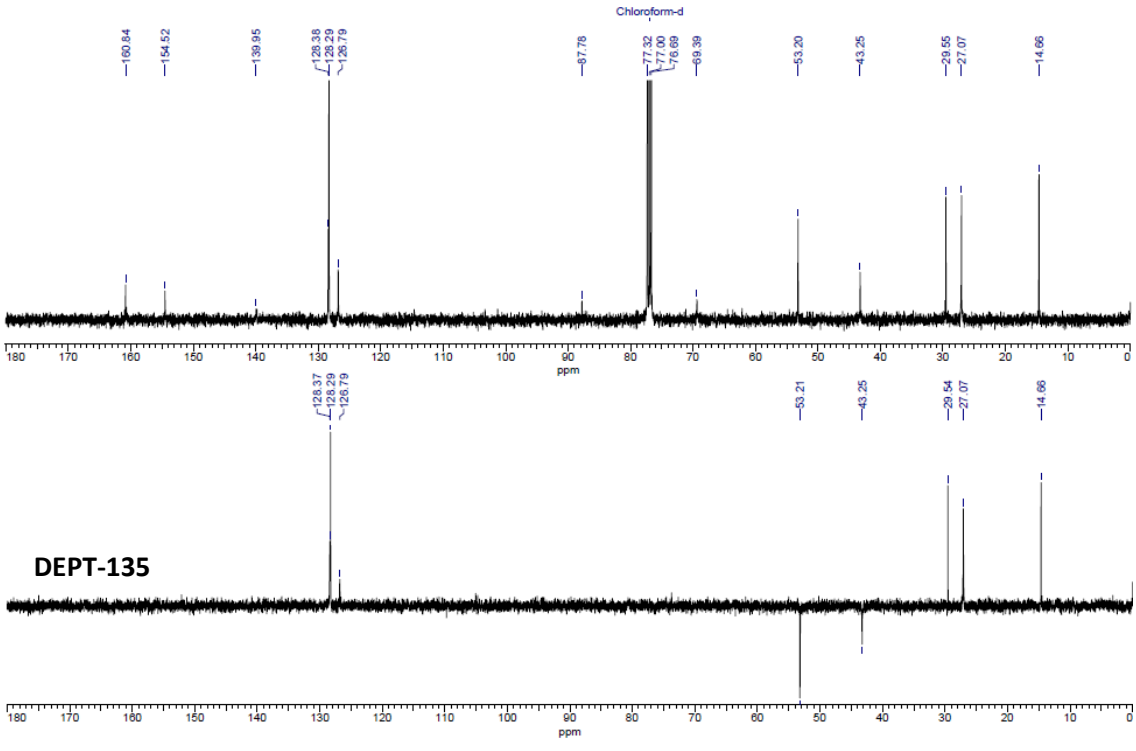
 ©ARKAT-USA, Inc.

6-Benzyl-3,7,7-trimethyl-2-(methylthio)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4b)**

^{1}H-NMR ($CDCl_3$)



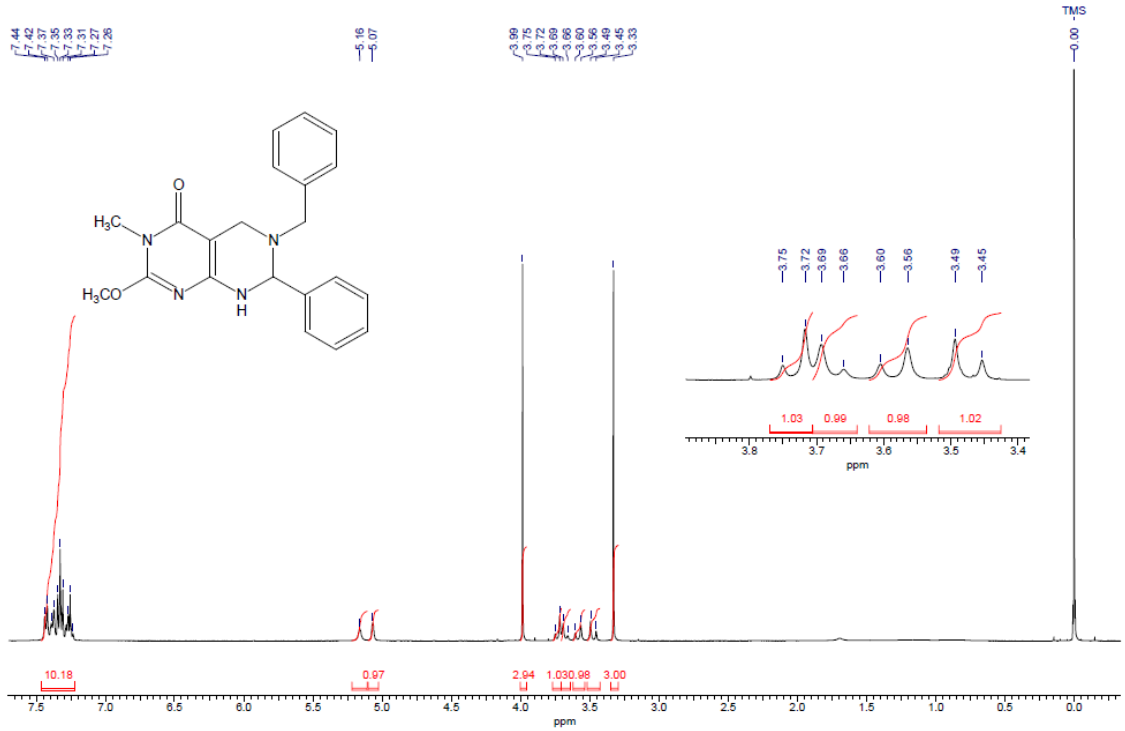
^{13}C-NMR ($CDCl_3$)



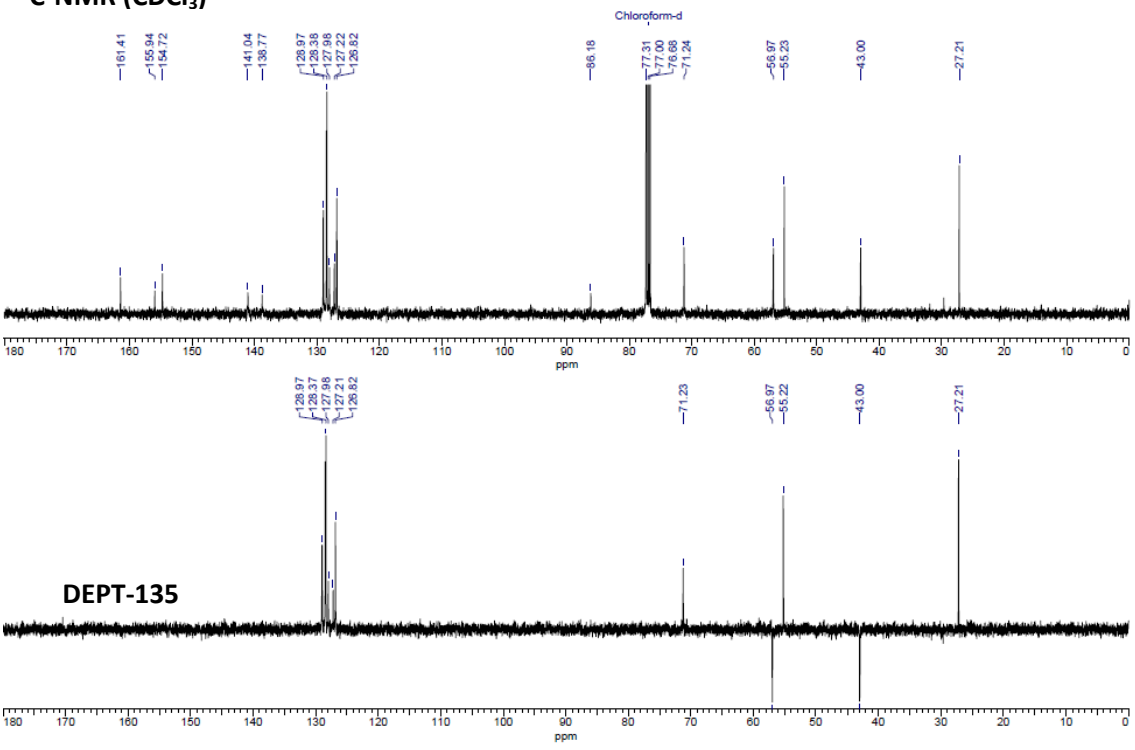
©ARKAT-USA, Inc.

6-Benzyl-3-methyl-2-methoxy-7-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4c)**

^{1}H-NMR ($CDCl_3$)



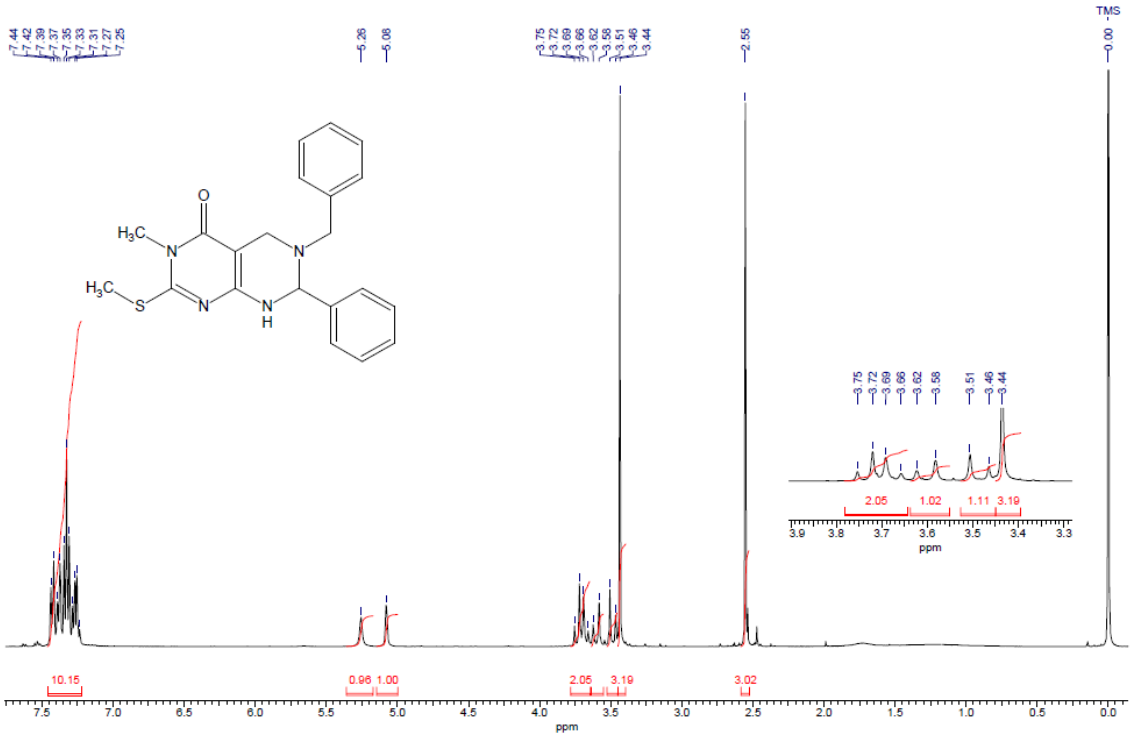
^{13}C-NMR ($CDCl_3$)



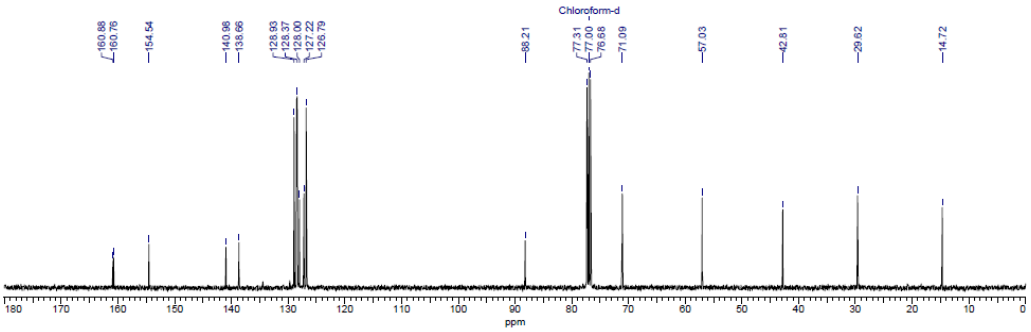
©ARKAT-USA, Inc.

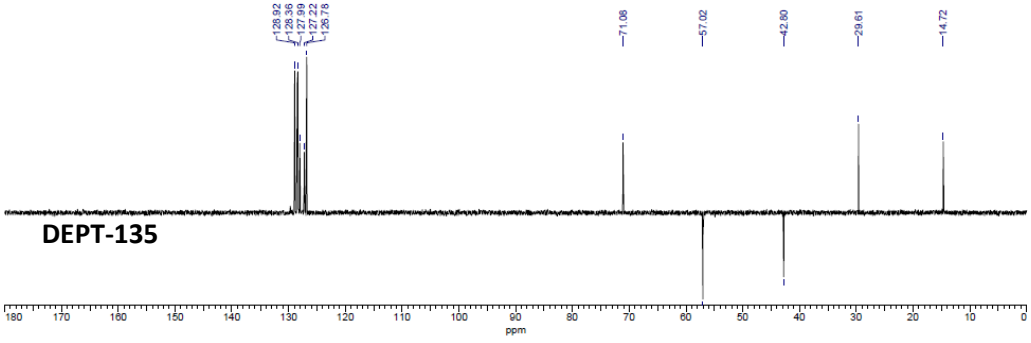
6-Benzyl-3-methyl-2-(methylthio)-7-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4d)**

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

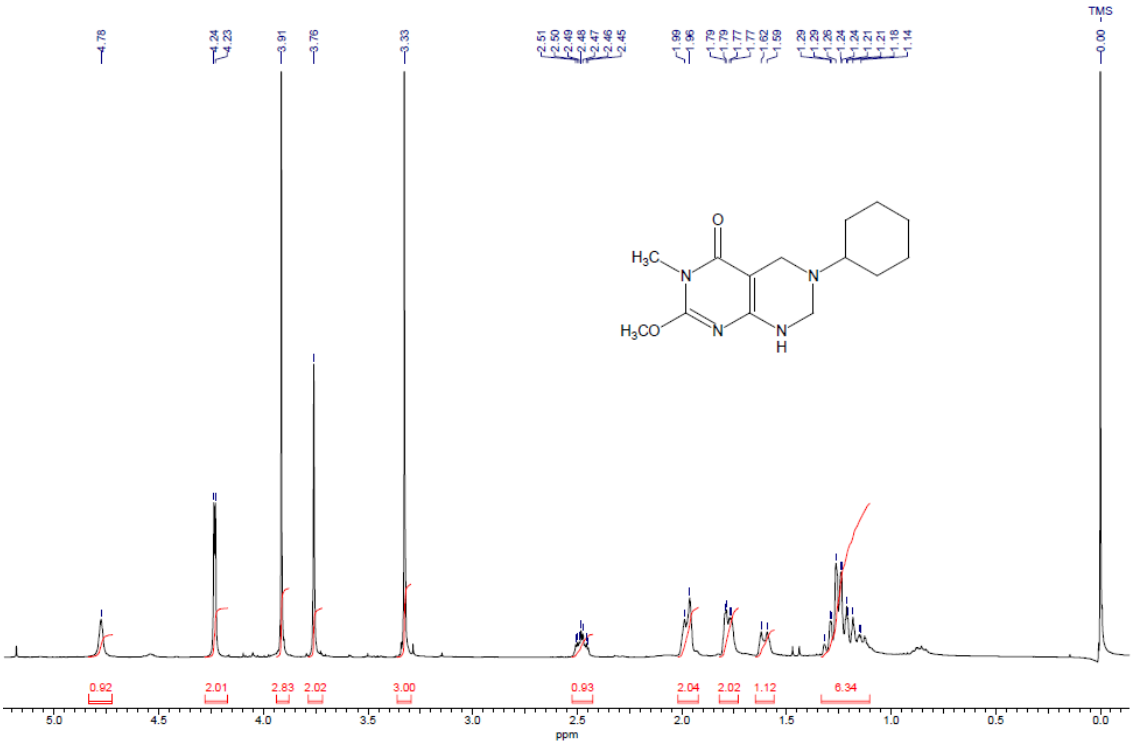




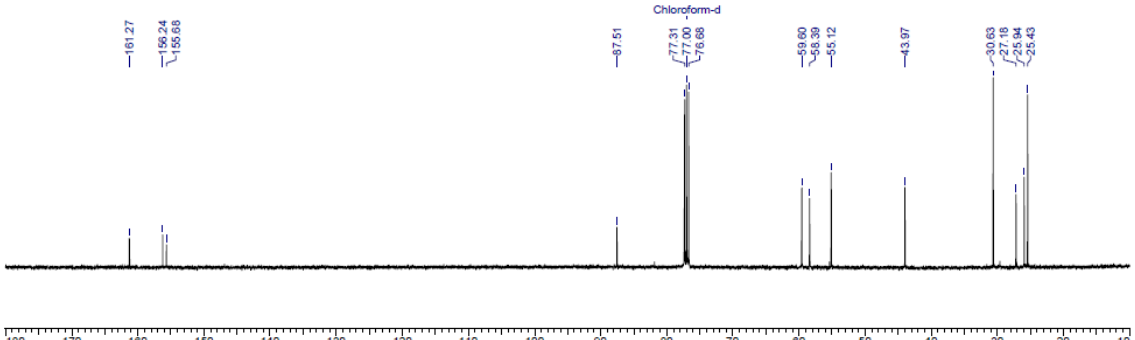
©ARKAT-USA, Inc.

6-Cyclohexyl-3-methyl-2-methoxy-5,6,7,8-tetrahydropyrimido[4,5-d]pyr-imidine-4(3H)-one **(4e)**

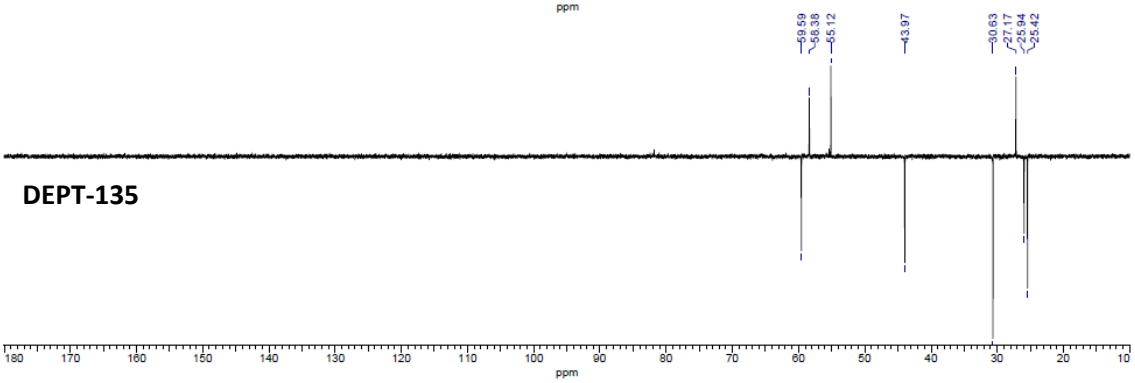
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)



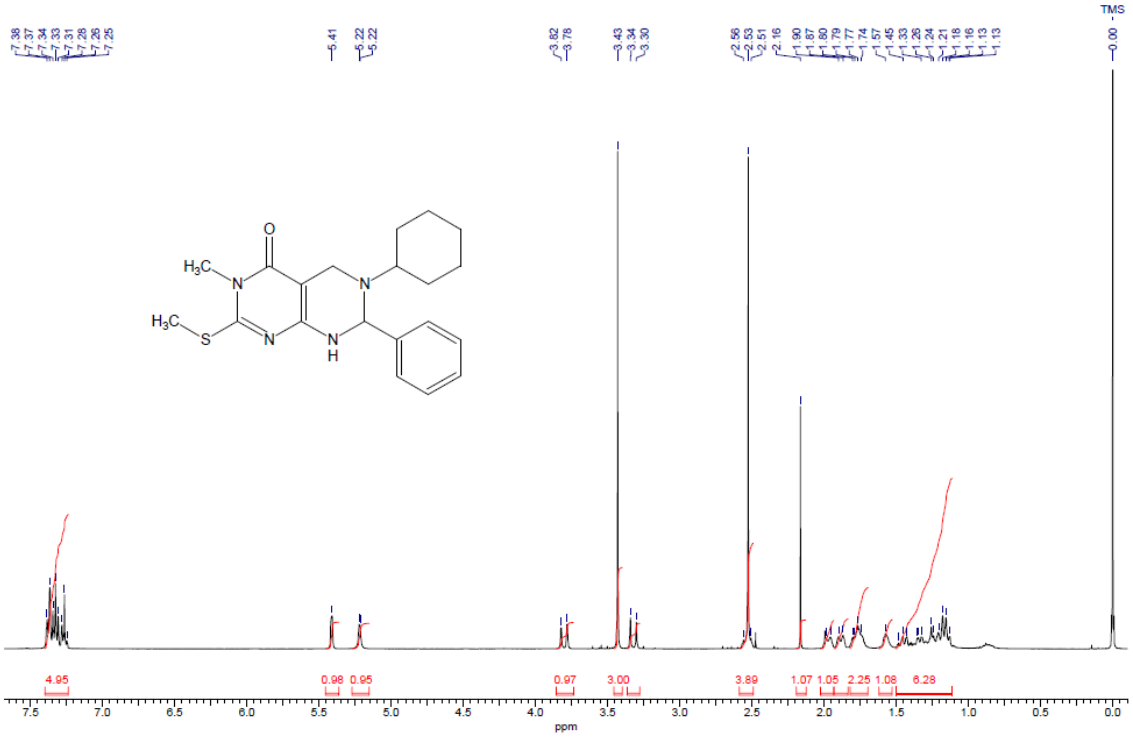
DEPT-135



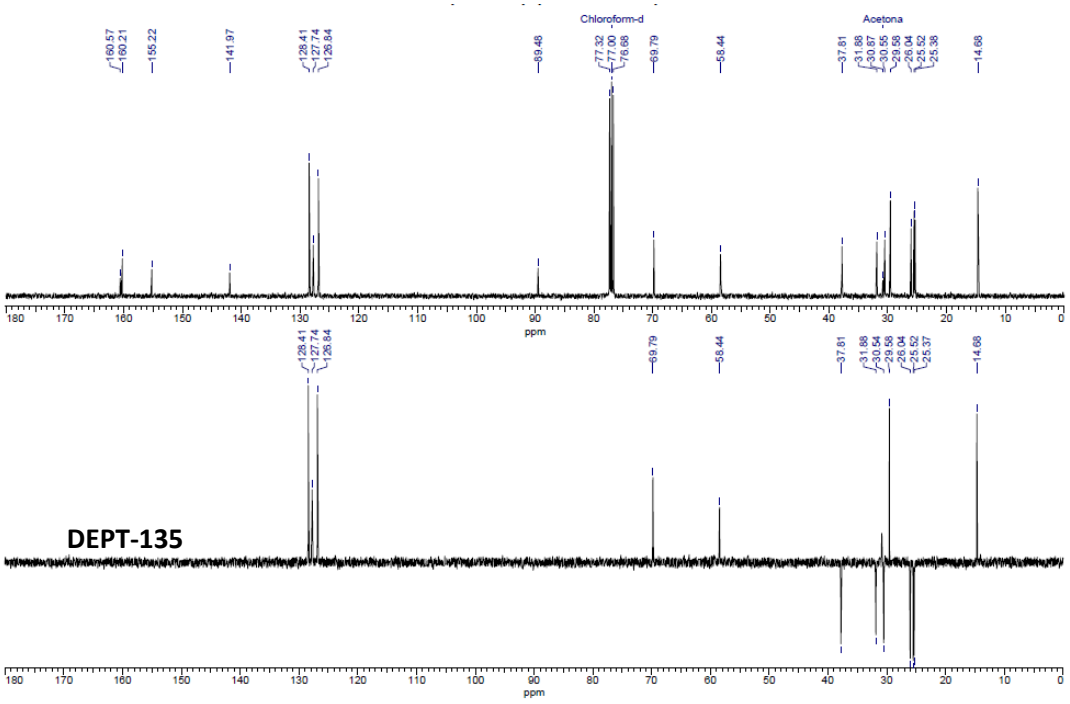
 ©ARKAT-USA, Inc.

6-Cyclohexyl-3-methyl-2-(methylthio)-7-phenyl-5,6,7,8-tetrahydropyrimido [4,5-d]pyrimidine-4(3H)-one **(4f)**

^{1}H-NMR ($CDCl_3$)



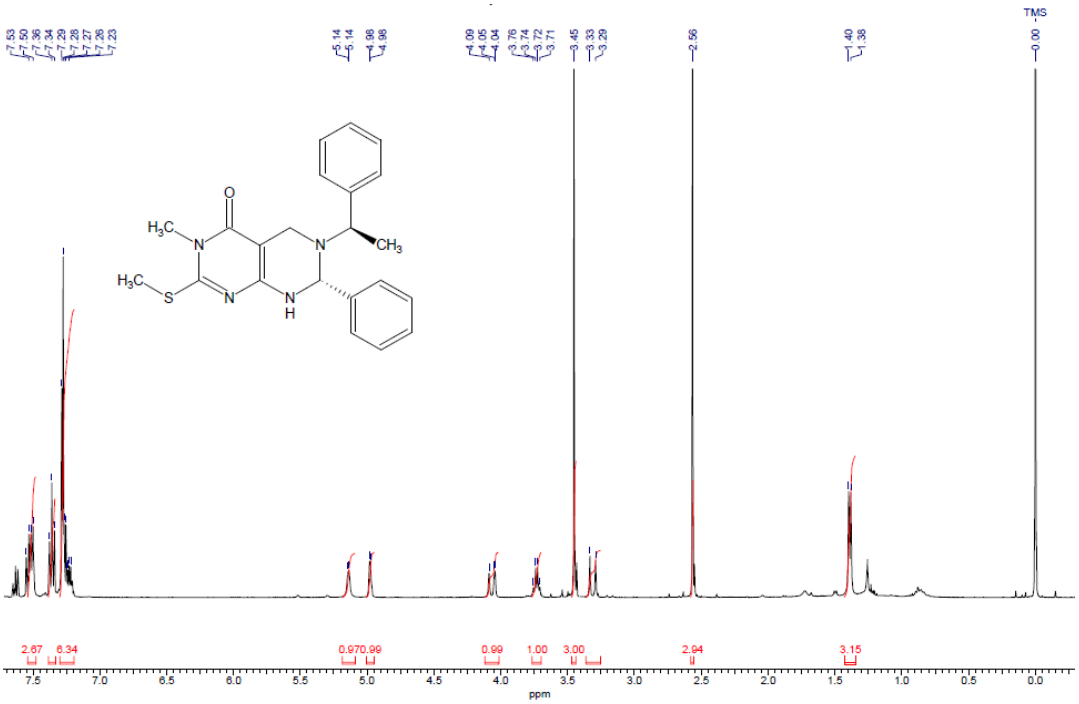
^{13}C-NMR ($CDCl_3$)



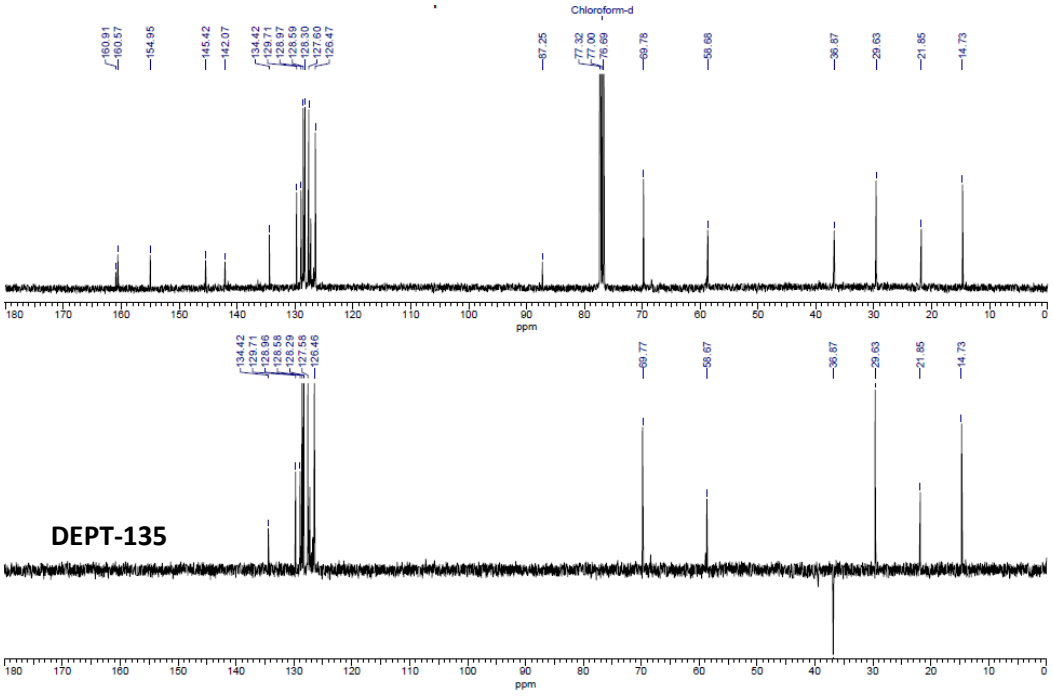
©ARKAT-USA, Inc.

3-Methyl-2-(methylthio)-7(R)-phenyl-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4g$_1$)** / *3-Methyl-2-(methylthio)-7(S)-phenyl-6-[(S)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one* **(4g$_4$)**

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

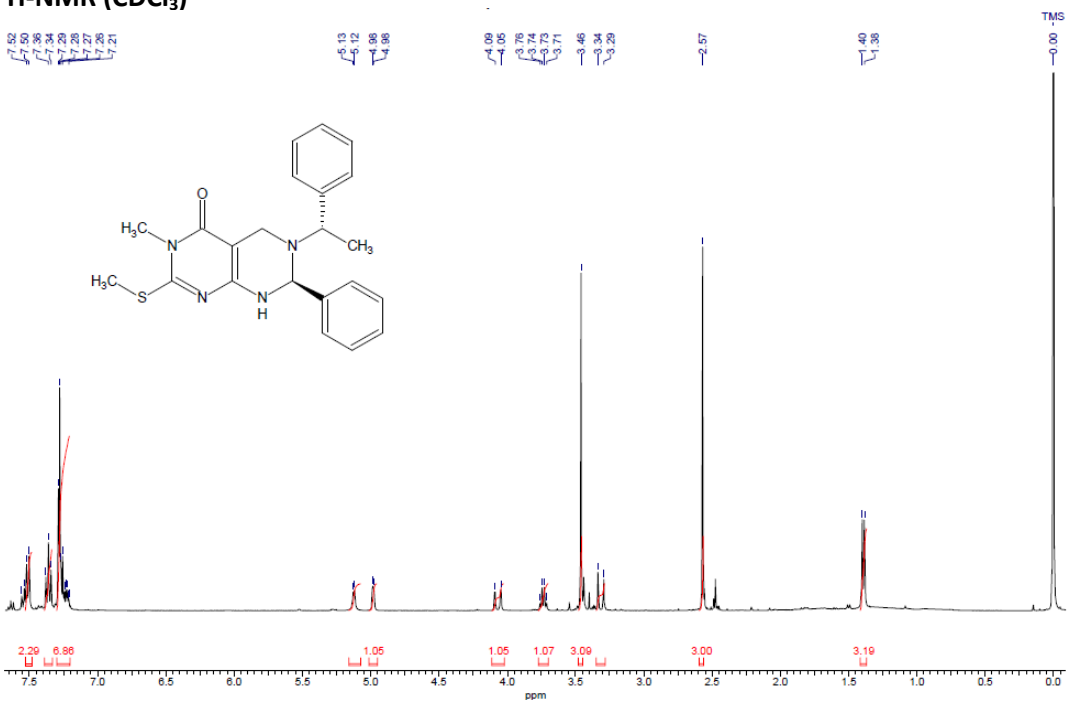


DEPT-135

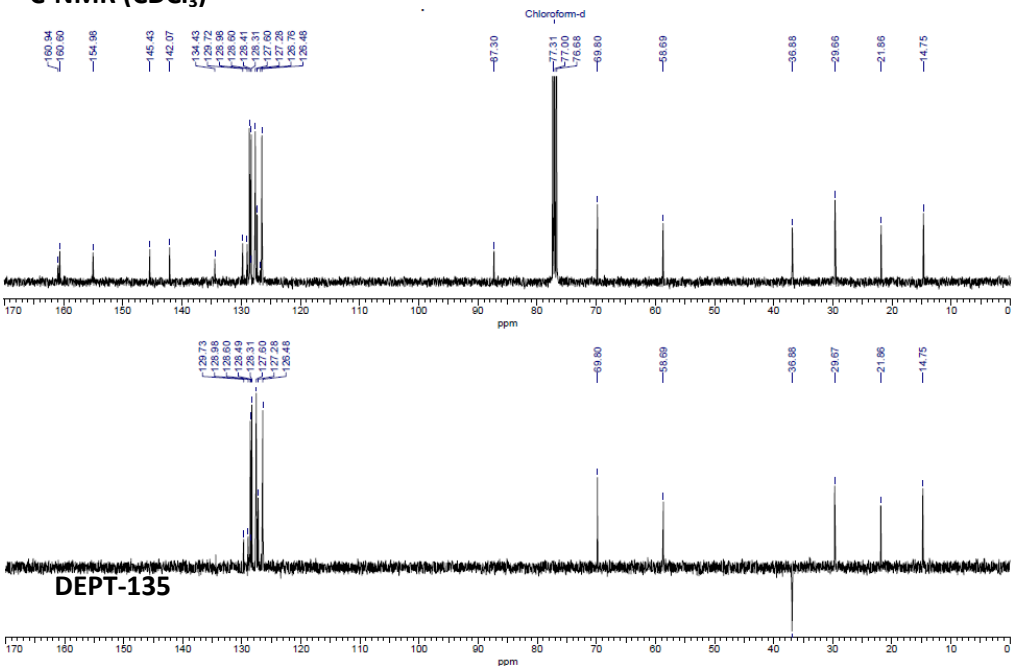
©ARKAT-USA, Inc.

3-Methyl-2-(methylthio)-7(S)-phenyl-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4g$_2$)**/*3-methyl-2-(methylthio)-7(R)-phenyl-6-[(S)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one* **(4g$_3$)**

^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

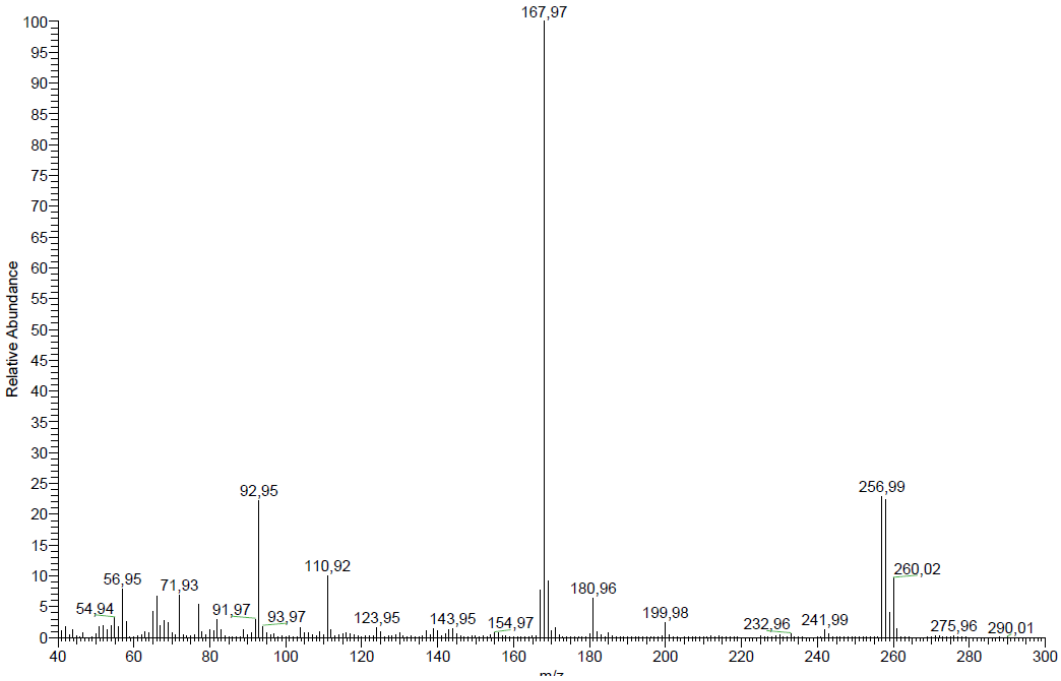


DEPT-135

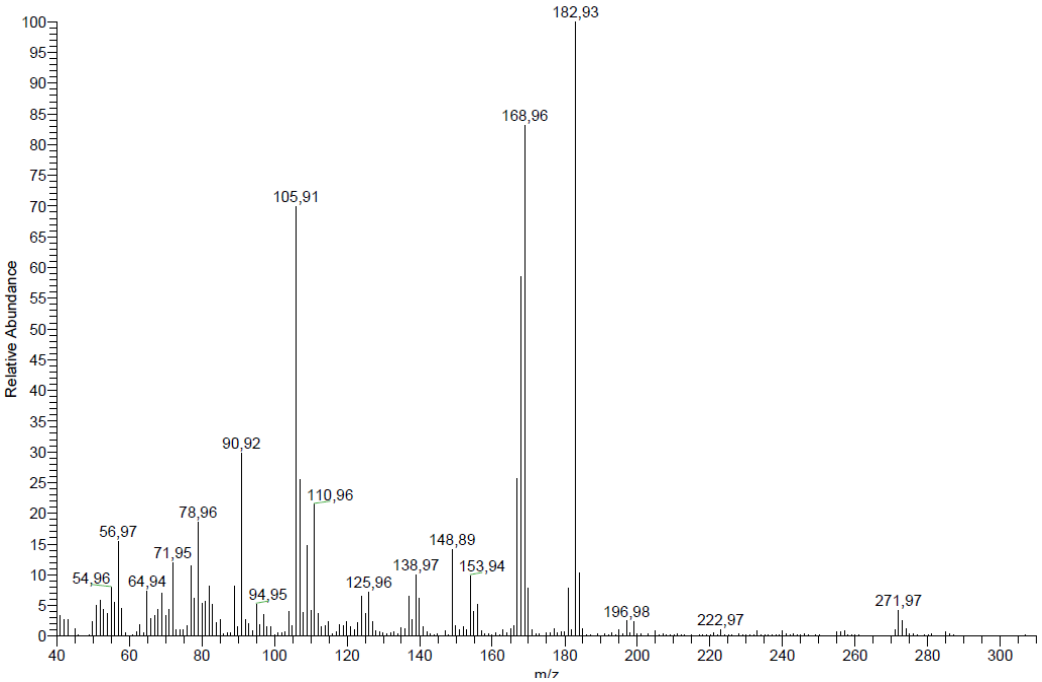
 ©ARKAT-USA, Inc.

MASS SPECTRA (EI, 70 eV)

6-Amino-2-methoxy-3-methyl-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2a)**

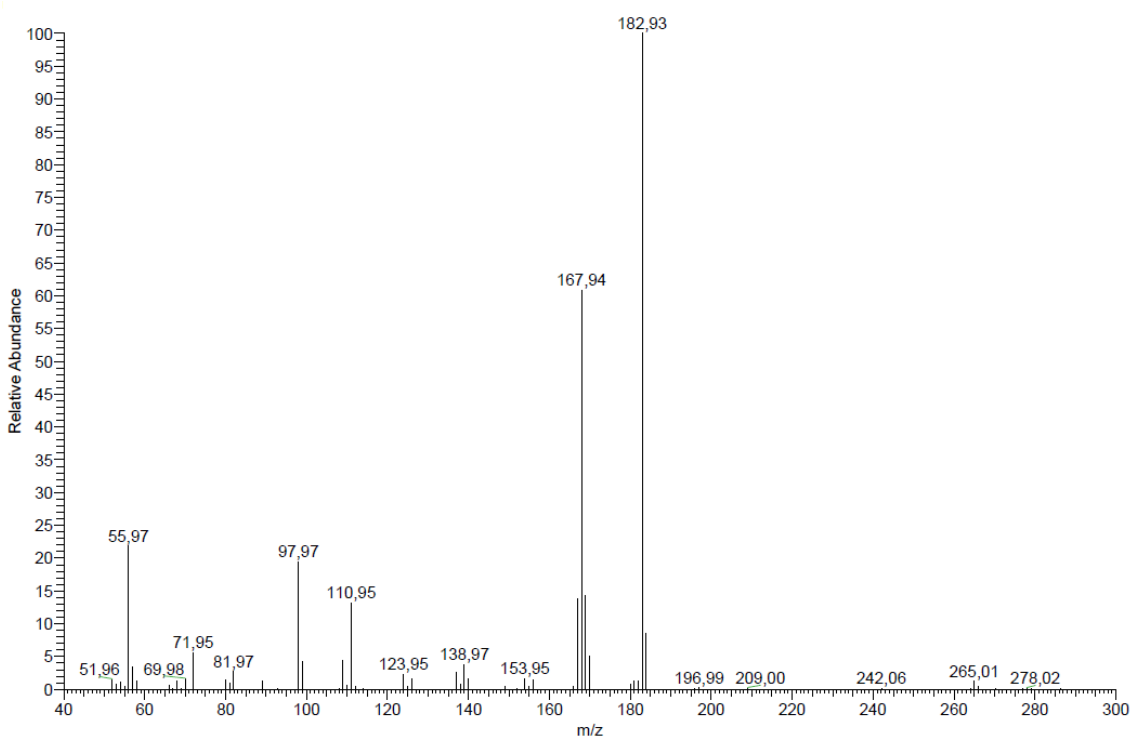


6-Amino-3-methyl-2-(methylthio)-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2b)**

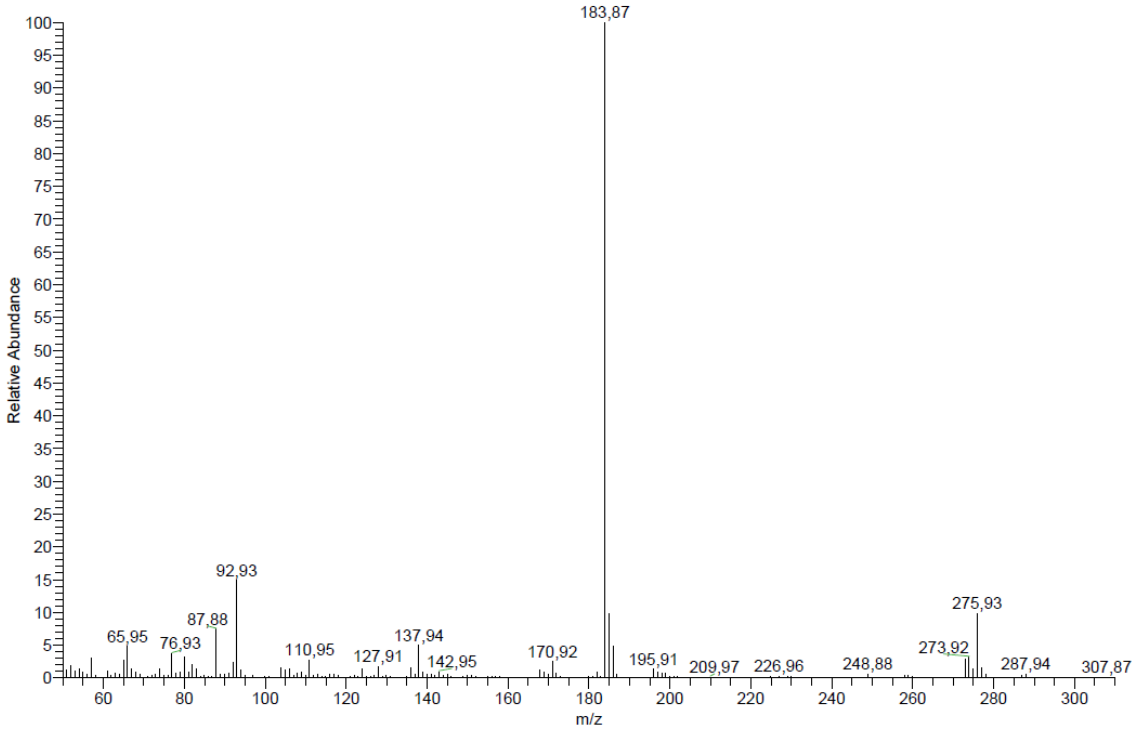


©ARKAT-USA, Inc.

6-Amino-5-((cyclohexylamino)methyl)-2-methoxy-3-methylpyrimidin-4(3H)-one **(2c)**

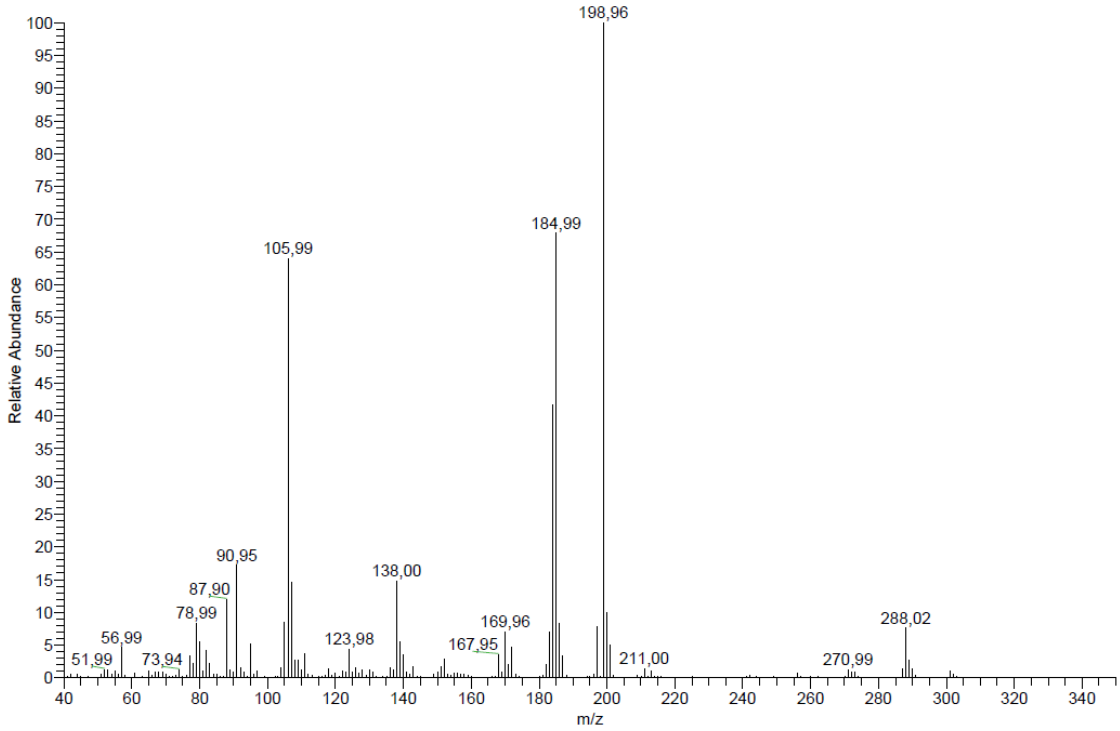


6-Amino-3-methyl-2-(methylthio)-5-((phenylamino)methyl)pyrimidin-4(3H)-one **(2d)**

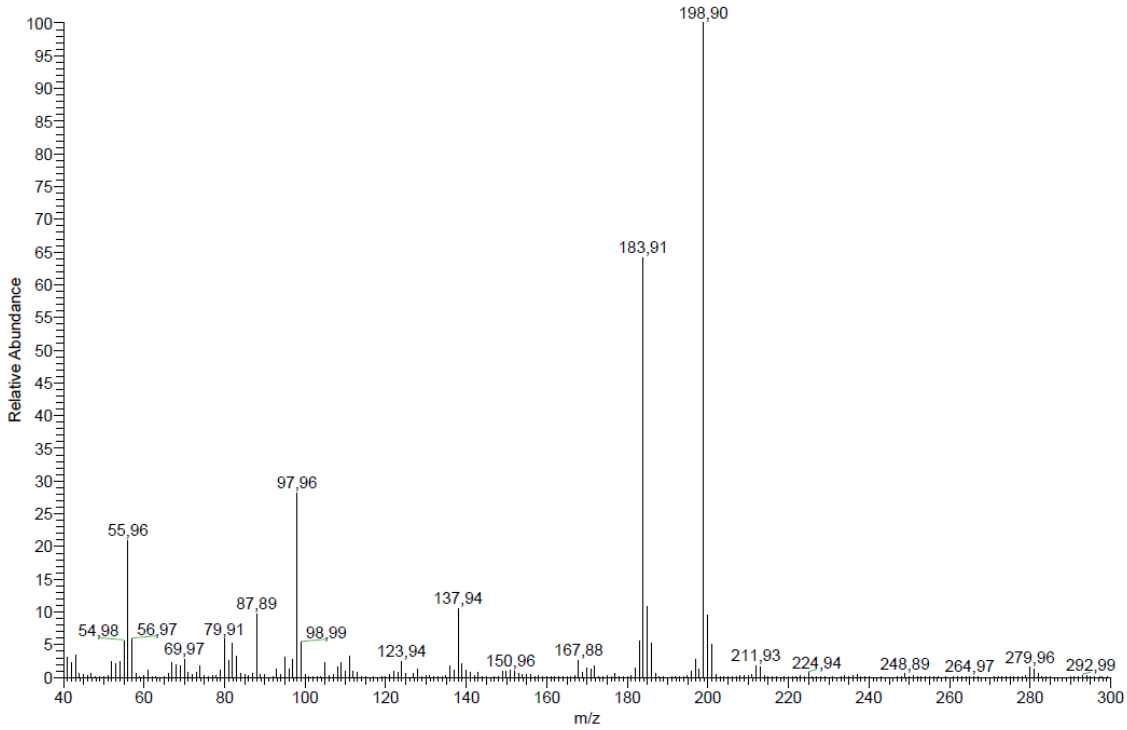


 ©ARKAT-USA, Inc.

6-Amino-5-((benzylamino)methyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one **(2e)**



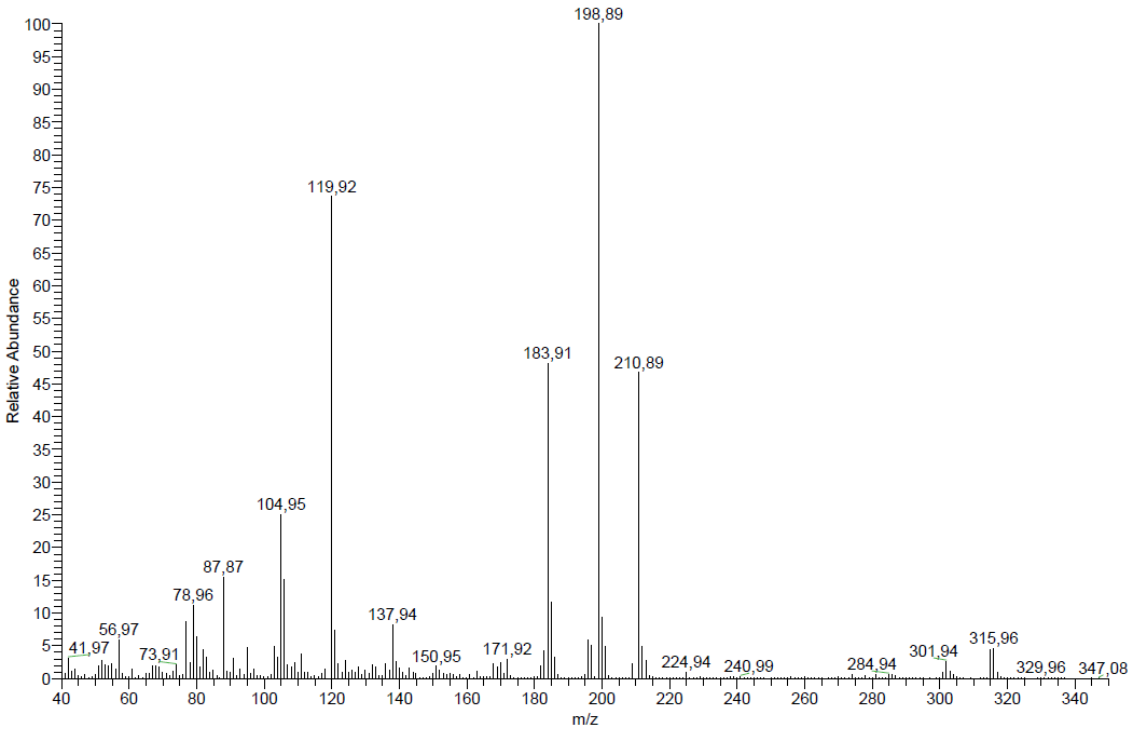
6-Amino-5-((cyclohexylamino)methyl)-3-methyl-2-(methylthio)pyramidin-4(3H)-one **(2f)**



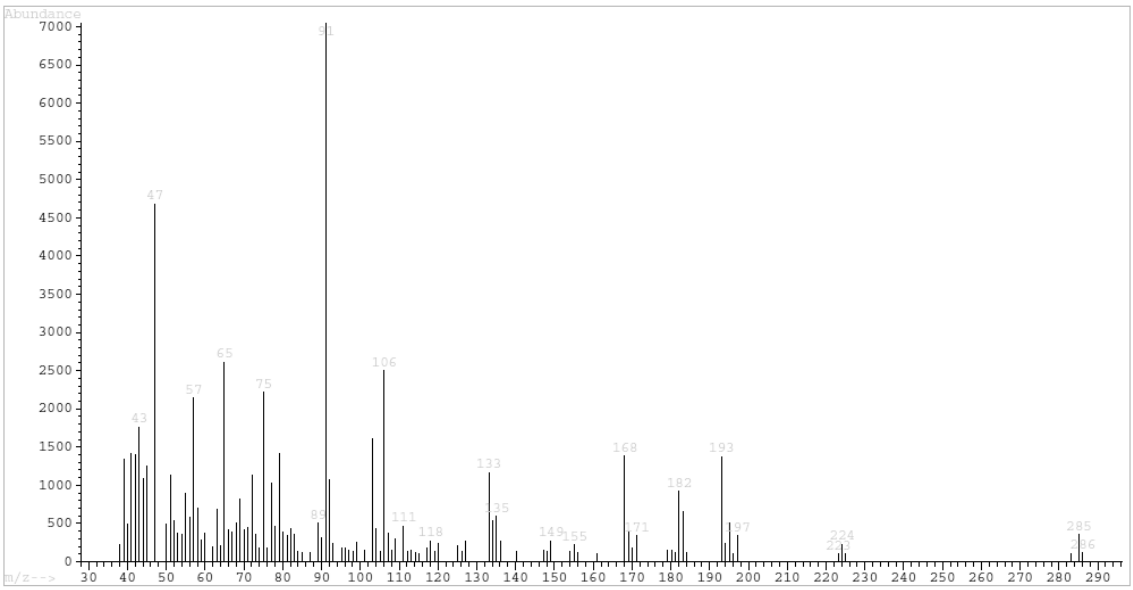
 ©ARKAT-USA, Inc.

(R)-6-Amino-3-methyl-2-methylthio-5-{[(1-phenylethyl)amino]methyl}pyrimidin-4(3*H*)-one **(2g)**

(*S*)-6-Amino-3-methyl-2-methylthio-5-{[(1-phenylethyl)amino]methyl}pyrimidin-4(3*H*)-one **(2g')**

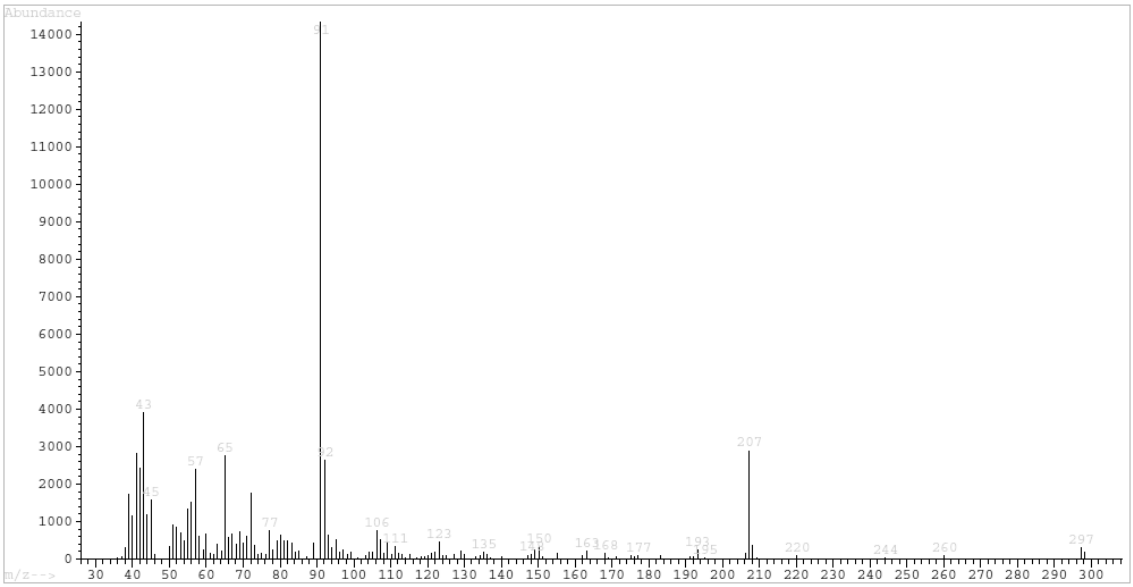


6-Benzyl-2-methoxy-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3a)**

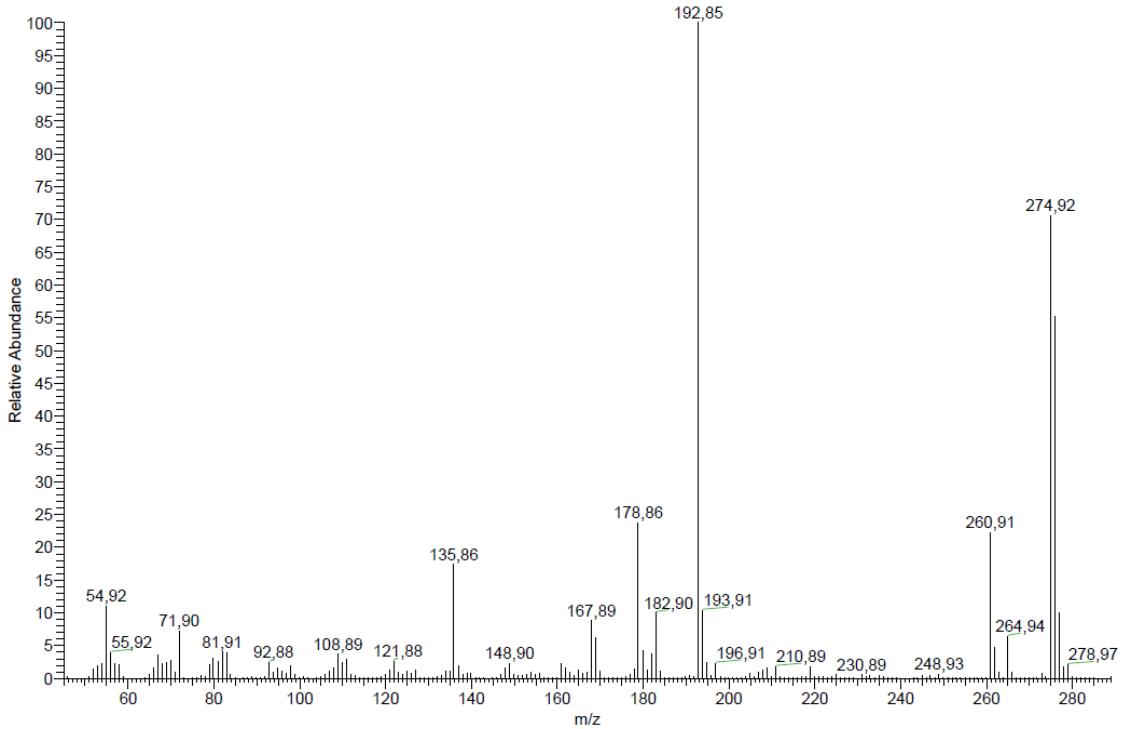


©ARKAT-USA, Inc.

6-Benzyl-2-methoxy-3,7-dimethyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3b)**

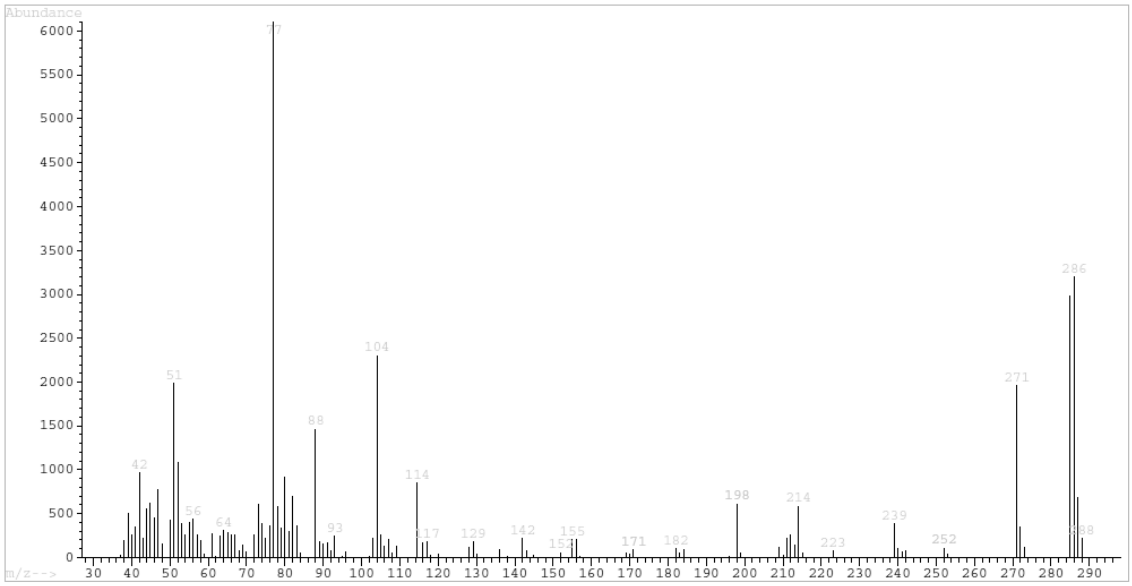


6-Cyclohexyl-2-methoxy-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3c)**

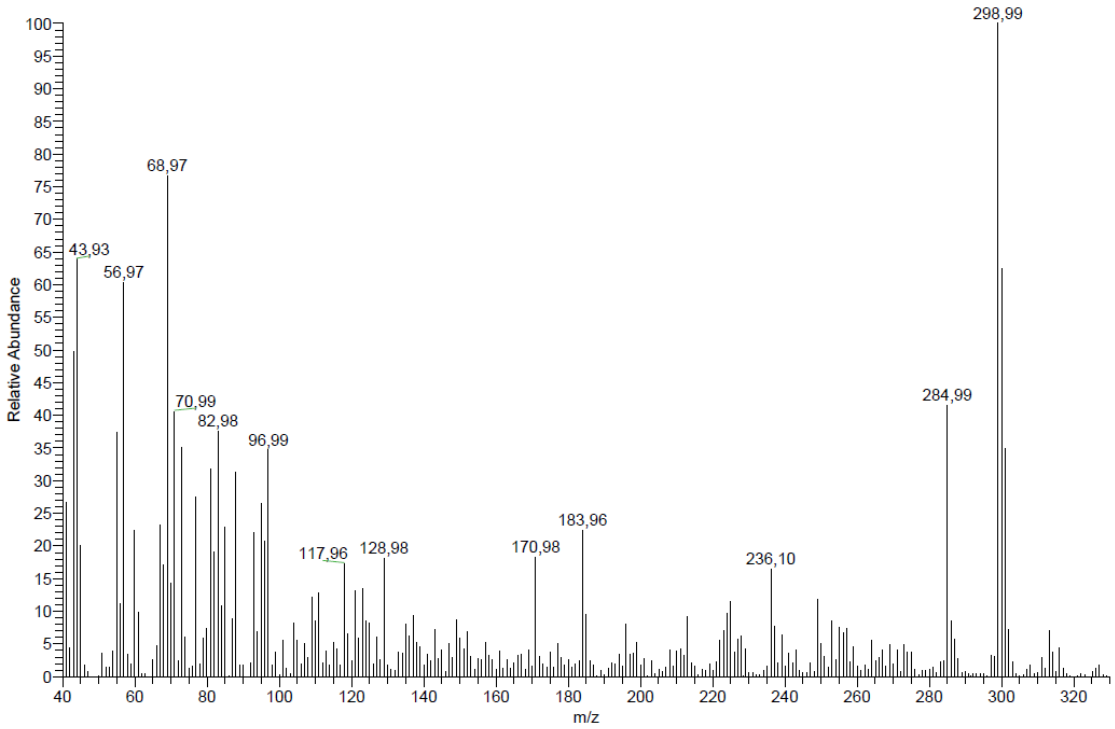


 ©ARKAT-USA, Inc.

3-Methyl-2-(methylthio)-6-phenyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3d)**

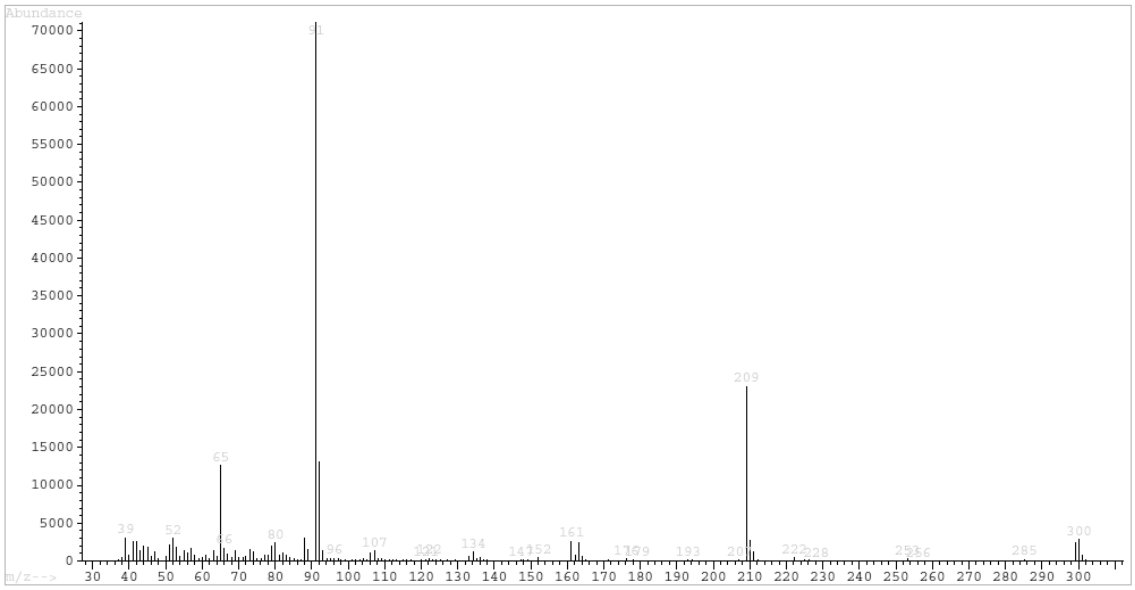


3,7-Dimethyl-2-(methylthio)-6-phenyl-5,6-dihydropyrimido-[4,5-d]pyrimidin-4(3H)-one **(3e)**

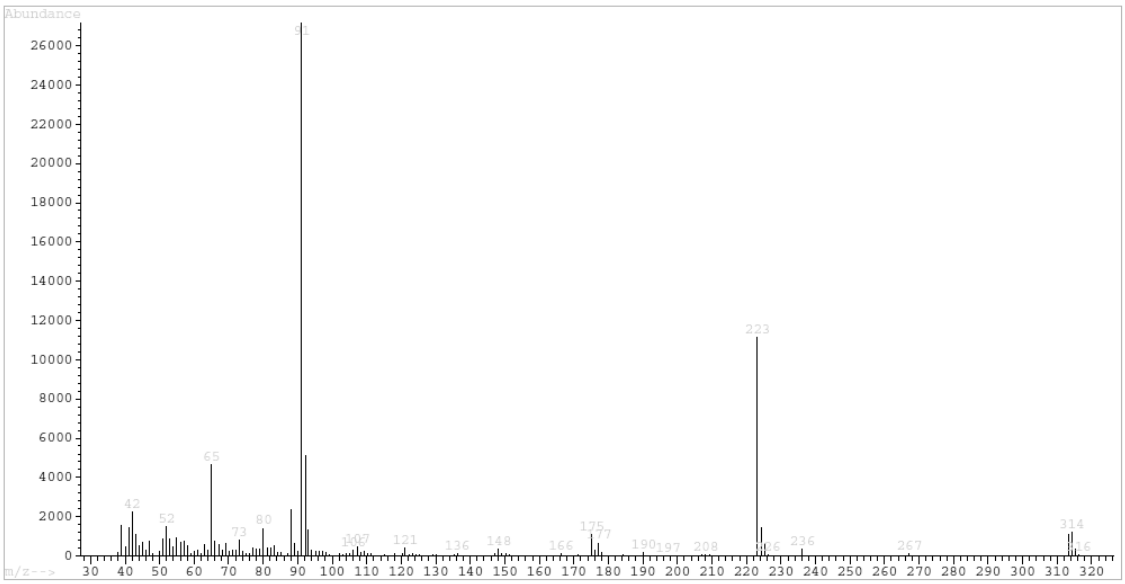


 ©ARKAT-USA, Inc.

6-Benzyl-3-methyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3f)**

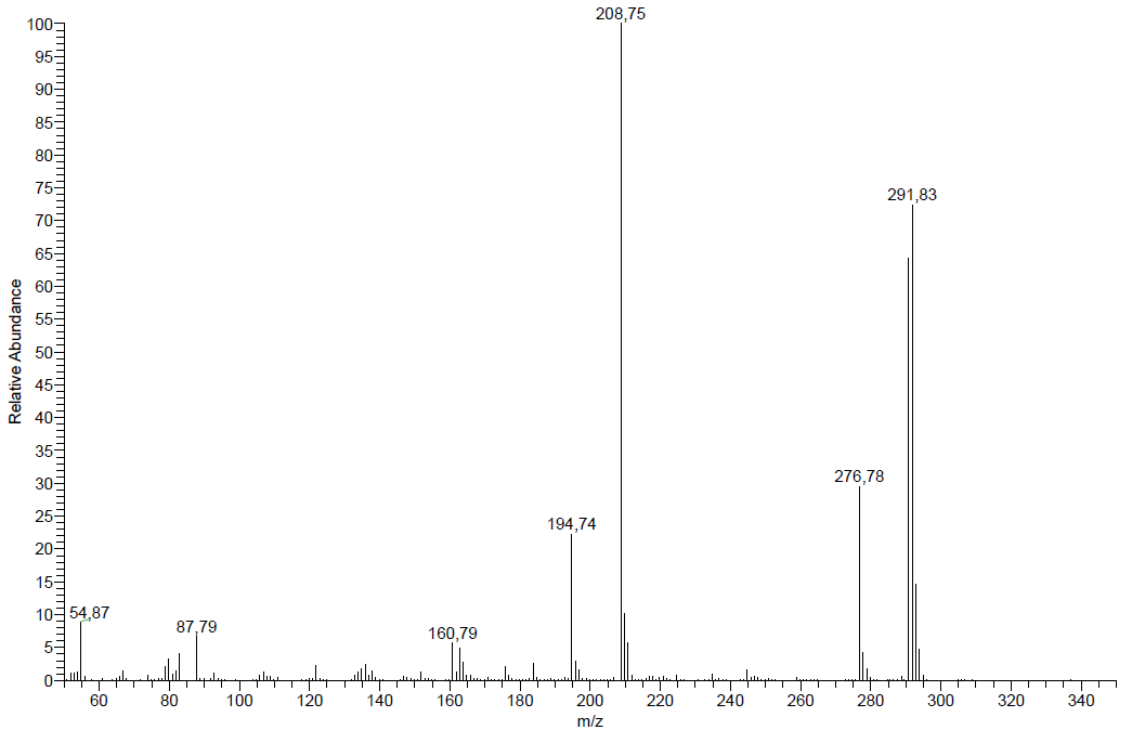


6-Benzyl-3,7-dimethyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3g)**

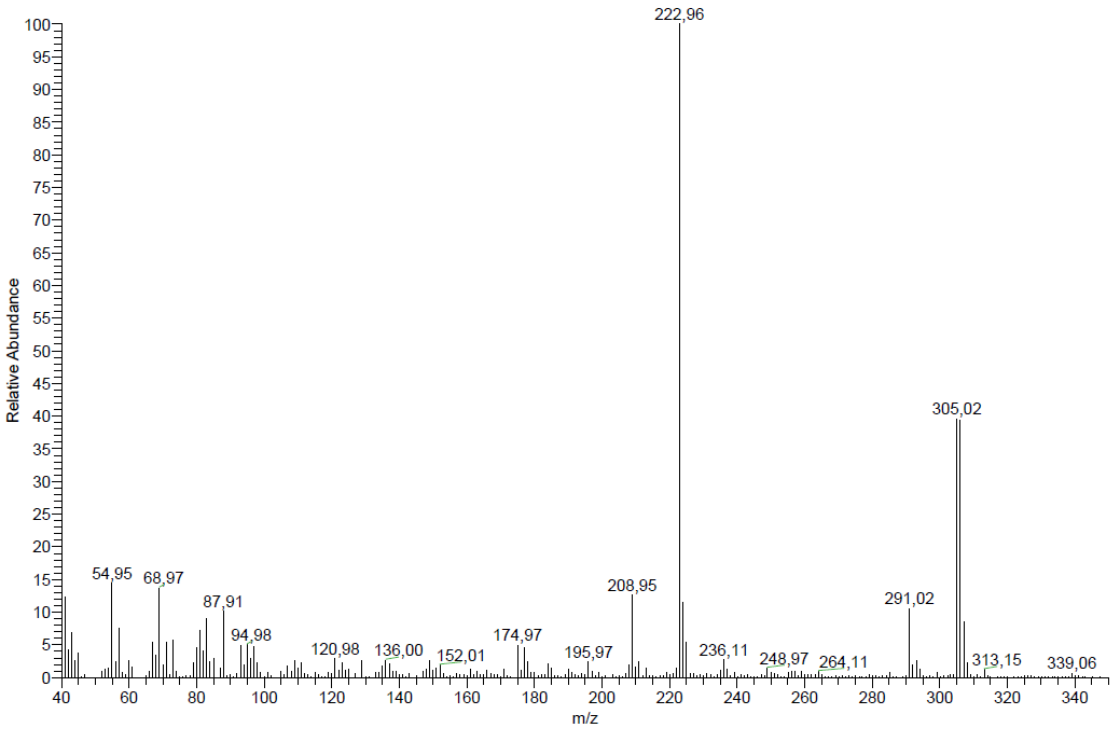


 ©ARKAT-USA, Inc.

6-Cyclohexyl-3-methyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3h)**

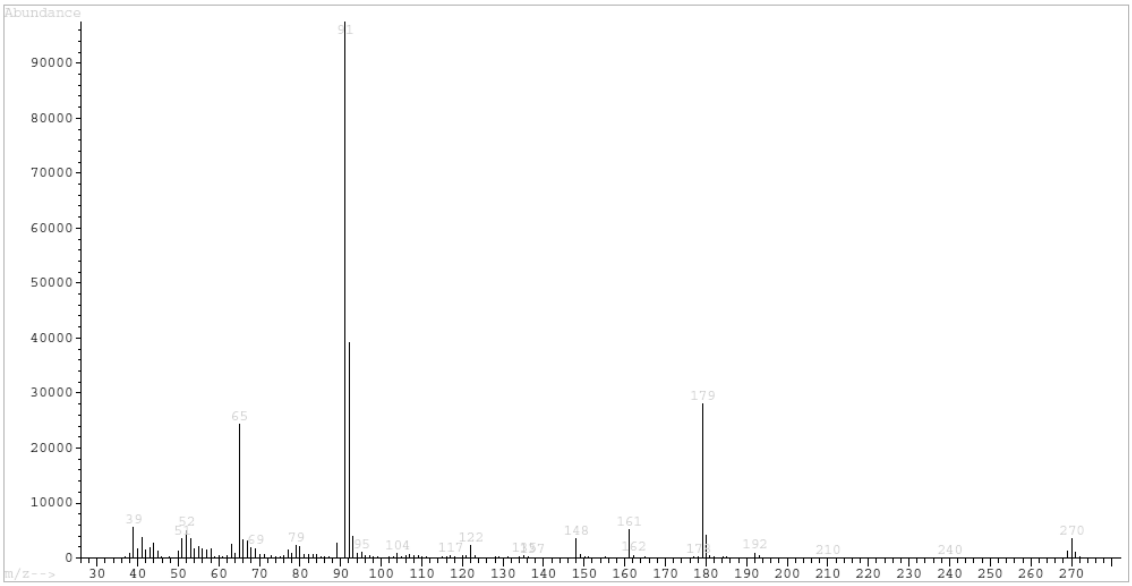


6-Cyclohexyl-3,7-dimethyl-2-(methylthio)-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one **(3i)**

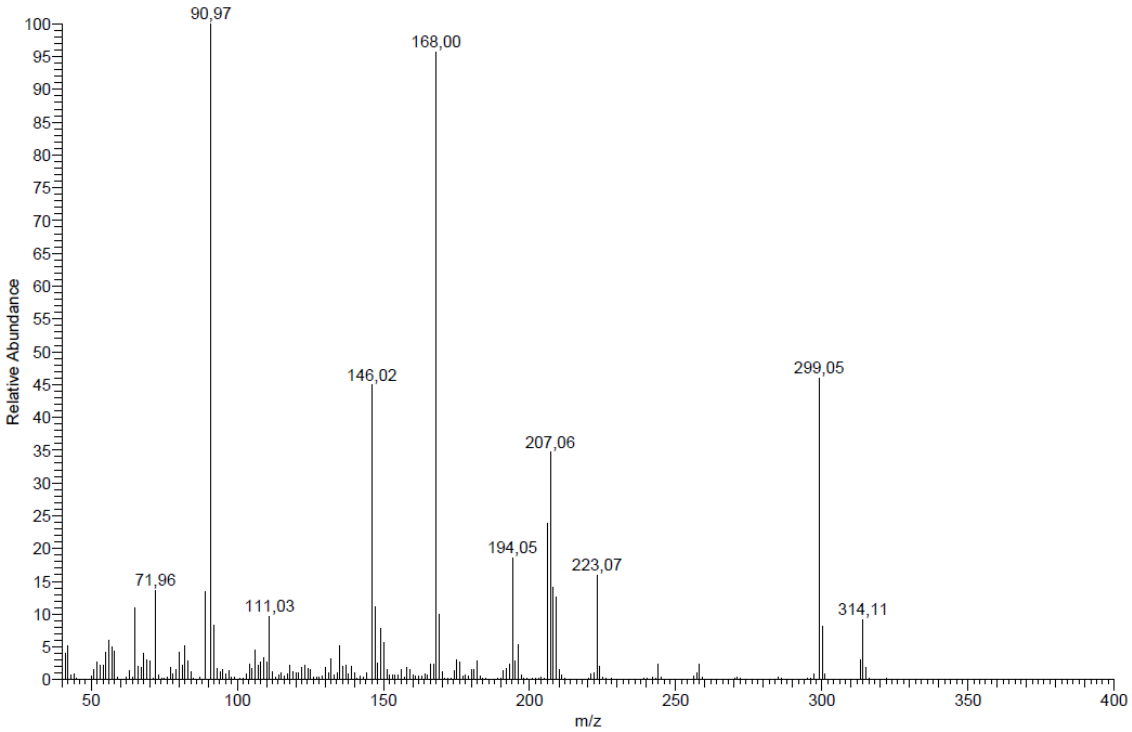


 ©ARKAT-USA, Inc.

6-Benzyl-3-methyl-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione **(3j)**

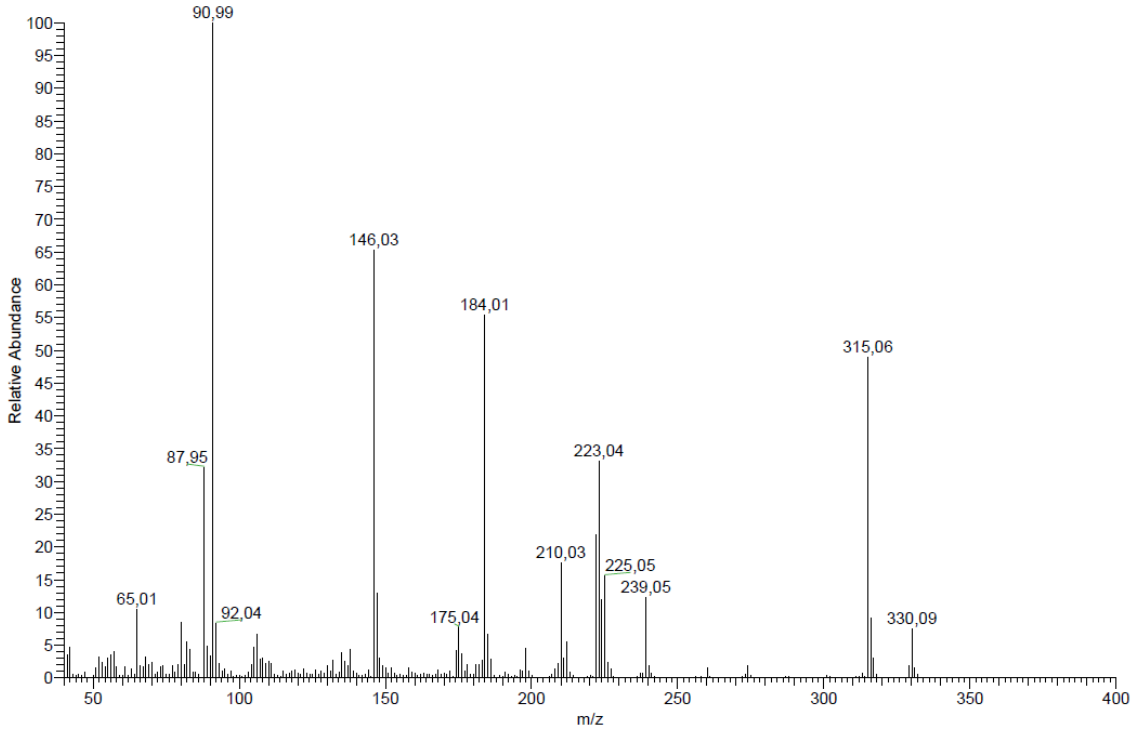


6-Benzyl-3,7,7-trimethyl-2-methoxy-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4a)**

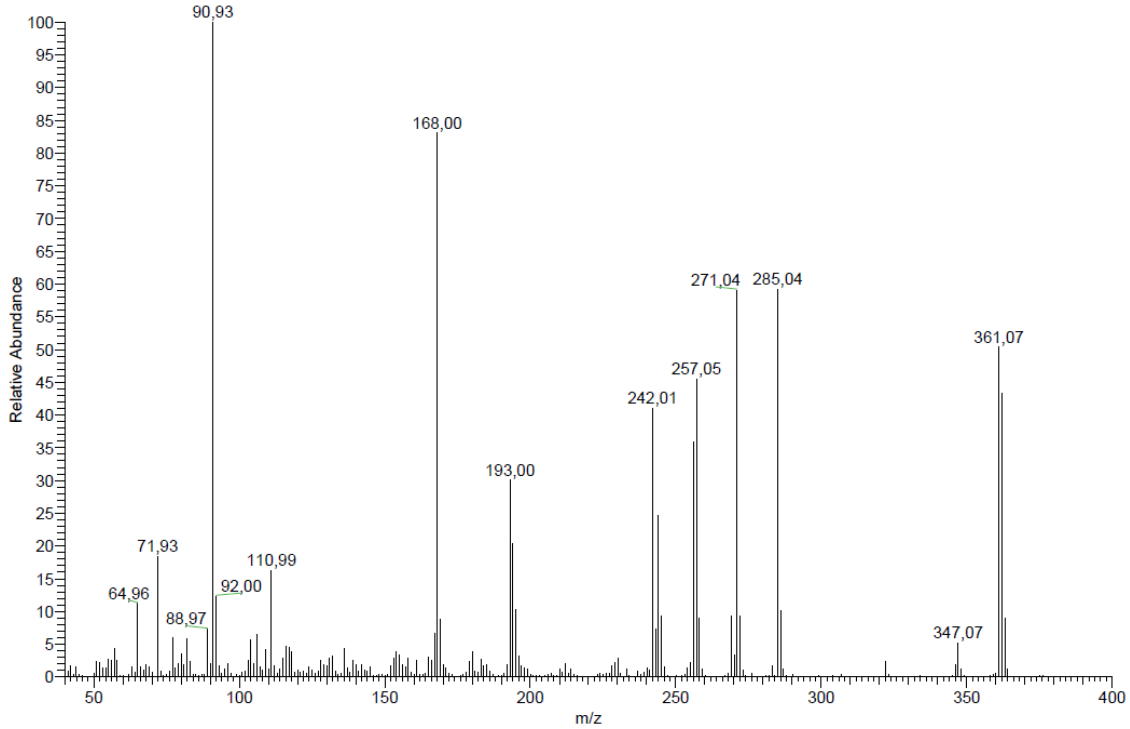


 ©ARKAT-USA, Inc.

6-Benzyl-3,7,7-trimethyl-2-(methylthio)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4b)**

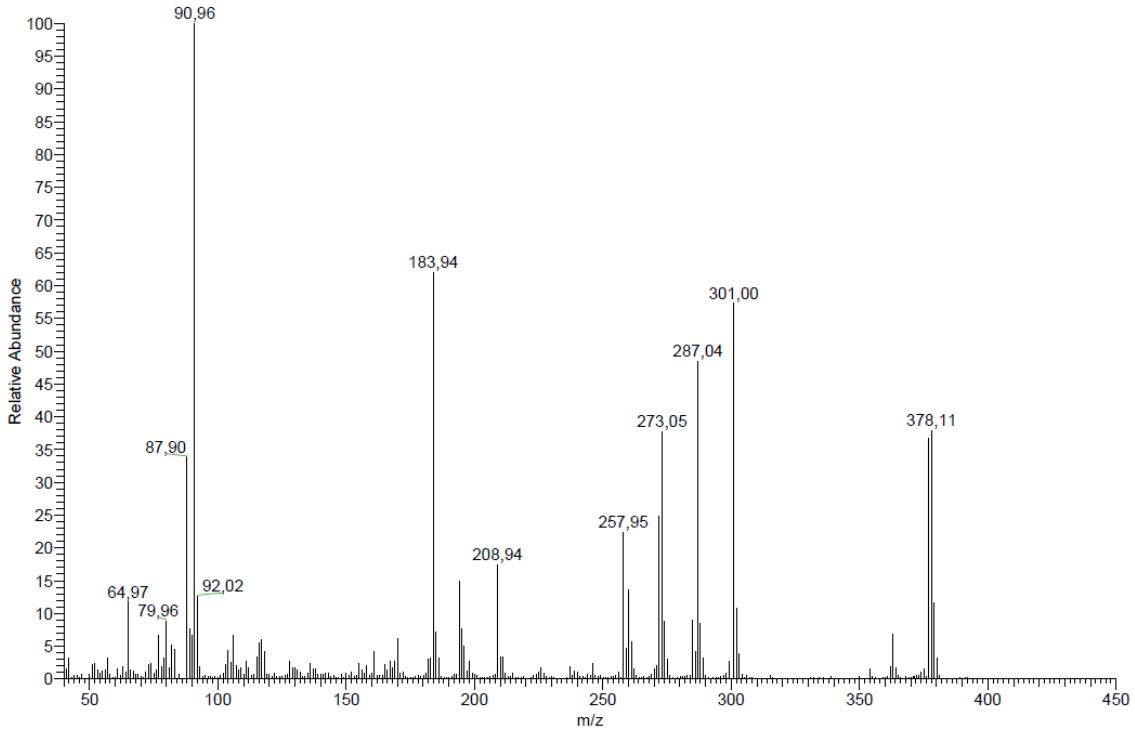


6-Benzyl-3-methyl-2-methoxy-7-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4c)**

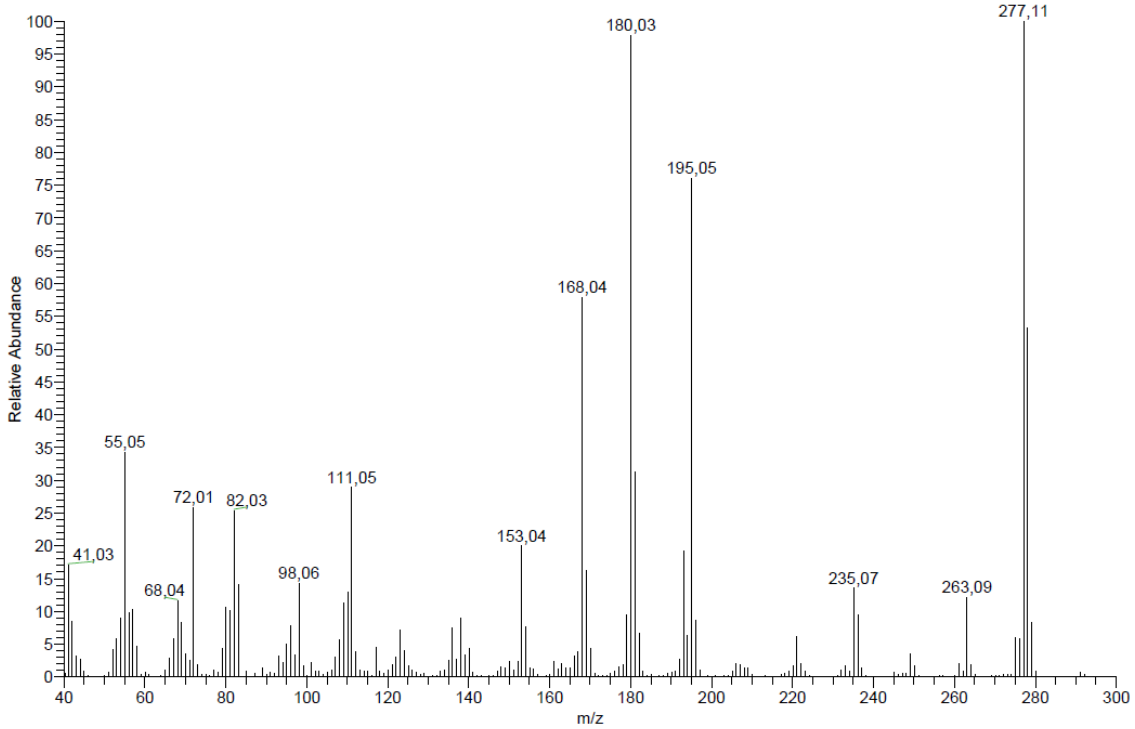


 ©ARKAT-USA, Inc.

6-Benzyl-3-methyl-2-(methylthio)-7-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4d)**

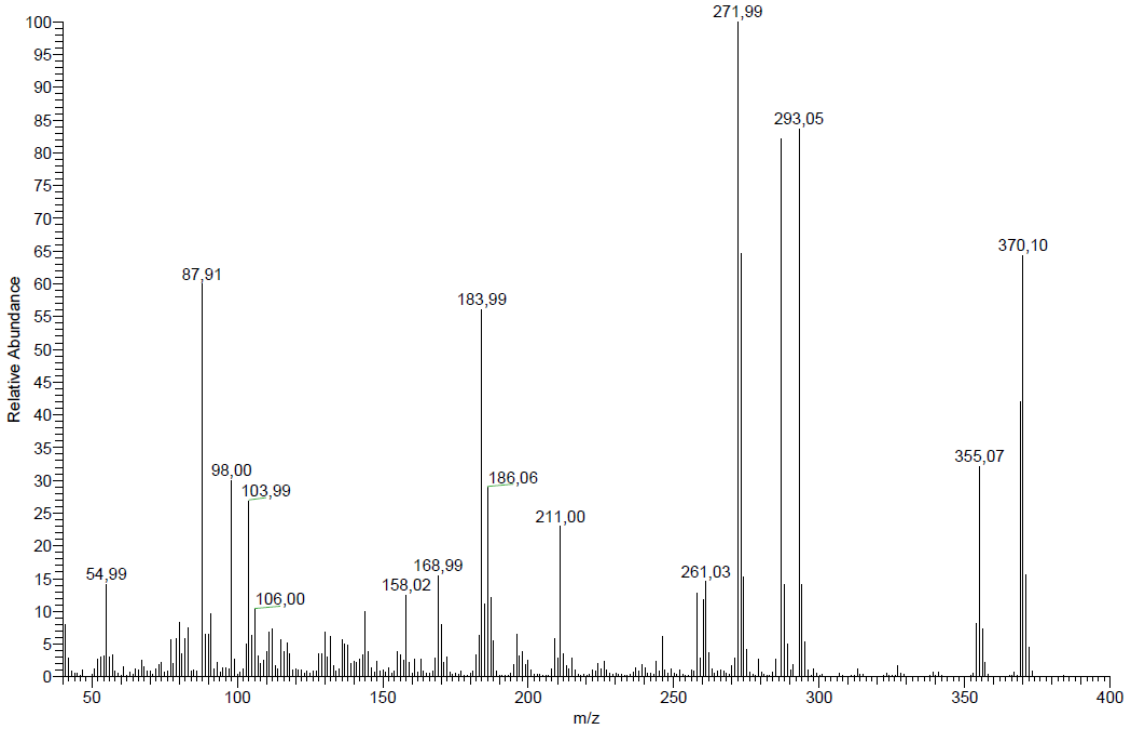


6-Cyclohexyl-3-methyl-2-methoxy-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4e)**



 ©ARKAT-USA, Inc.

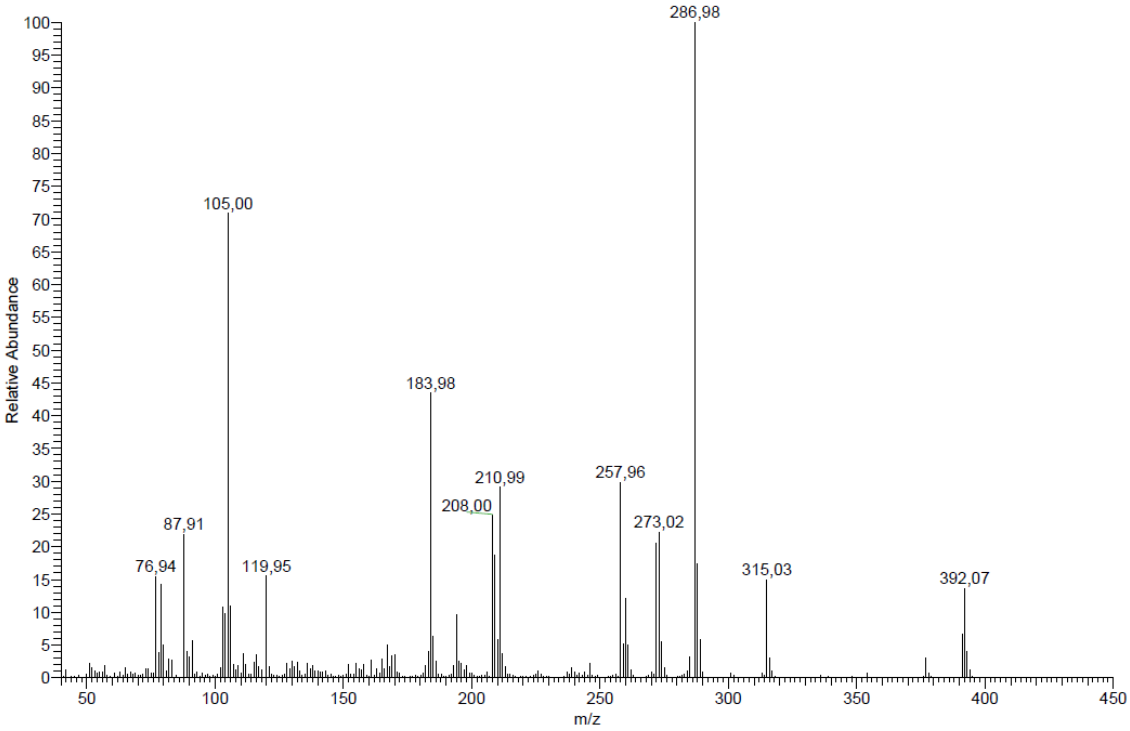
6-Cyclohexyl-3-methyl-2-(methylthio)-7-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4f)**



 ©ARKAT-USA, Inc.

3-Methyl-2-(methylthio)-7(R)-phenyl-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4g$_1$)** / *3-Methyl-2-(methylthio)-7(S)-phenyl-6-[(S)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one* **(4g$_4$)**

3-Methyl-2-(methylthio)-7(S)-phenyl-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one **(4g$_2$)**/*3-methyl-2-(methylthio)-7(R)-phenyl-6-[(S)-1-phenylethyl]-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-4(3H)-one* **(4g$_3$)**



 ©ARKAT-USA, Inc.