Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 89 (11) S386–S422 (2024) *Supplementary material*

SUPPLEMENTARY MATERIAL TO

Synthesis and *in silico* ADMET evaluation of new thiazole and thiazolidine-4-one derivatives as non-ulcerogenic analgesic and anti-inflammatory agents

MANSUR NASSIRI KOOPAEI[1], MAHSHID MONAVARI[2], NASIM VOUSOOGHI[3,4], SADAF MOSHIRABADI[5], MOHAMMAD JAVAD ASSARZADEH[5], MOHSEN AMINI[1,6] and ALI ALMASIRAD[5]*

[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran, [3]Department of Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran, [4]Research Center for Cognitive and Behavioral Sciences, Tehran University of Medical Sciences, Tehran, Iran, [5]Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran and [6]Pharmaceutical Sciences Research Center (PSRC), The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

J. Serb. Chem. Soc. 89 (11) (2024) 1411–1422

Synthesis of (2-phenoxybenzylidene)thiosemicarbazide ***(7)***

The yield was 1.0 g (69%), mp 203–205ºC (EtOH); IR (KBr): νcm^{-1}, 3426, 3264 (NH_2 NH), 3165 (CH, aromatic, alkene), 1606 (C=N), 1365 (C=S). ^{1}H NMR (DMSO-d_6, 400MHz): 11.41 (bs, 1H, NH), 8.36 (s, 1H, CH=N), 8.20 (d, J=8.0Hz, 1H, aromatic), 7.95 (bs, 2H, NH_2), 7.45-6.93(m, 8H, aromatic).

Synthesis of (2-phenoxybenzylidene)-2-(4-phenylthiazol-2-yl)hydrazine ***(8)***

Yield (51%), IR (KBr): νcm^{-1}, 3298 (NH), 3165 (CH, aromatic, alkene), 1686 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 12.20 (bs, 1H, NH), 8.31 (s, 1H, CH=N), 7.95 (d, J=7.6Hz, 1H, aromatic), 7.84 (d, J=8.4Hz, 2H, aromatic), 7.43-7.38 (m, 4H, aromatic), 7.33 (s, 1H, thiazole), 7.31-7.13 (m, 4H, aromatic), 7.01 (d, J=8.0Hz, 2H, aromatic), 6.94 (d, J=8.0Hz, 1H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 168.49, 157.62, 154.47, 136.28, 131.22, 130.60, 129.52, 129.05, 128.00, 126.38, 126.07, 125.99, 124.87, 123.86, 120.22, 118.40, 118.30, 104.25. MS: m/z (%) 371 (M^+, 29), 356 (6), 328 (4), 269 (15), 198 (71), 181 (100), 168 (29), 152 (17), 134 (35), 77 (93),

51(44).Anal. Calcd. for $C_{22}H_{17}N_3OS$: C, 71.15; H, 4.58; N, 11.32. Found: C, 71.20; H, 4.63; N, 11.27.

* Corresponding author. E-mail: almasirad.a@iaups.ac.ir

2-(2-(2-phenoxybenzylidene)hydrazinyl)thiazol-4(5H)-one ***(9)***

The yield was 1.0 g (71%), mp 214–218ºC (EtOH); IR (KBr): νcm^{-1}, 3441 (NH), 3052 (CH, aromatic, alkene), 1712(C=O), 1641(C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 11.95 (bs, 1H, NH), 8.48 (s, 1H, CH=N), 7.99 (d, 1H, *J*=7.2Hz, aromatic), 7.50-6.97 (m, 8H, aromatic), 3.85 (s, 2H, CH_2, thiazolone). Anal. Calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.73; H, 4.18; N, 13.50. Found: C, 61.68; H, 4.14; N, 13.54.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(benzylidene)thiazol-4(5H)-one ***(10a)***

Yield (42%), IR (KBr): νcm^{-1}, 3411 (NH), 3059 (CH aromatic, alkene), 1719 (C=O), 1643 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 12.61 (bs, 1H, NH), 8.67, 8.53 (s, 1H, CH=N, E/Z isomers, 23% & 67%), 7.85-7.01 (m, 15H, aromatic, alkene). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 168.59, 157.81, 134.45, 134.21, 131.38, 130.70, 130.64, 130.30, 130.14, 129.70, 129.34, 129.12, 128.38, 124.96, 124.31, 124.10, 123.92, 118.95, 118.31. MS: m/z (%) 399 (M^+, 9), 307 (95), 230 (38), 219 (8), 197 (18), 181 (35), 134 (100), 104 (12), 90 (40), 77 (22), 51 (14). Anal. Calcd. for $C_{23}H_{17}N_3O_2S$: C, 69.17; H, 4.26; N, 10.52. Found: C, 69.23; H, 4.31; N, 10.45.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-fluorophenyl)thiazol-4(5H)-one ***(10b)***

Yield (50%), IR (KBr): νcm^{-1}, 3444 (NH), 1716 (C=O), 1641 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 8.59, 8.52 (s, 1H, CH=N, E/Z isomers, 55% & 45%) 8.09-6.95 (m, 15H, =CH alkene, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 161.88, 157.63, 155.59, 133.09, 132.66, 132.59, 130.69, 130.63, 127.74, 125.72, 124.90, 124.77, 124.32, 123.93, 120.40, 118.96, 118.32, 118.22, 116.89, 116.71, 116.55, 116.37. MS: m/z (%) 417 (M^+, 2), 397 (3), 343 (10), 323 (6), 311 (18), 237 (78), 218 (17), 197 (90), 181 (100), 152 (34), 141 (22), 123 (42), 108 (68), 95 (37), 77 (40), 51 (28). Anal. Calcd. for $C_{23}H_{16}N_3FO_2S$: C, 66.18; H, 3.83; N, 10.07. Found: C, 66.24; H, 3.77; N, 10.02.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-chlorobenzylidene)thiazol-4(5H)-one ***(10c)***

Yield (51%), IR (KBr): νcm^{-1}, 3420 (NH), 3031 (CH aromatic, alkene), 1717 (C=O), 1643 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 8.62, 8.53 (s, 1H, CH=N, E/Z isomers, 54% & 46%), 8.08 (dd, *J*=9.2Hz, J=2.0Hz, 1H, aromatic), 7.85 (d, *J*=8.4Hz, 2H, aromatic), 7.72-7.06 (m,9H, aromatic, alkene), 7.01 (d, *J*=8.4Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 167.89, 157.56, 155.71, 152.61, 134.75, 133.22, 132.96, 131.93, 130.63, 129.99, 129.73, 129.44, 128.20, 127.79, 125.53, 124.84, 123.97, 120.30, 118.38. MS: m/z (%) 433 (M^+, 9), 375 (25), 340 (22), 324 (17), 255 (22), 197 (44), 181 (100), 168 (62), 152 (21), 139 (90), 124 (25), 111 (56), 77 (38), 51 (22). Anal. Calcd. for $C_{23}H_{16}N_3ClO_2S$: C, 63.66; H, 3.69; N, 9.68. Found: C, 63.69; H, 3.75; N, 9.61.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-Bromobenzylidene)thiazol-4(5H)-one ***(10d)***

Yield (67%), IR (KBr): νcm^{-1}, 3422 (NH), 3031 (CH aromatic, alkene), 1716 (C=O), 1645 (C=N). ^{1}H NMR DMSO-d_6, 400MHz): 12.65 (bs, 1H, NH), 8.53 (s, 1H, CH=N), 8.07-6.96 (m, 14H, =CH alkene, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 167.00, 156.89, 133.53, 133.29, 132.70, 132.40, 132.12, 130.72, 130.65, 130.22, 129.47, 128.38, 124.97, 124.94, 124.79, 124.38, 123.64, 119.43, 119.01. MS: m/z (%) 479 (M^++2, 5), 477 (M^+, 5), 392 (21), 311 (11), 297 (32), 284 (22), 254 (22), 213 (75), 211 (75), 196 (94), 181 (100), 165 (37), 152 (40), 133 (25), 115 (23), 89 (85), 77 (84). Anal. Calcd. for $C_{23}H_{16}N_3BrO_2S$: C, 57.74; H, 3.34; N, 8.78. Found: C, 57.69; H, 3.37; N, 8.82.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(2-hydroxybenzylidene)thiazol-4(5H)-one ***(10e)***

Yield (45%), IR (KBr): νcm^{-1}, 3419 (OH,NH), 3031 (=CH aromatic, alkene), 1712 (C=O), 1630 (C=N). ^{1}H NMR (DMSO-d$_6$, 400MHz): 12.85 (bs, 1H, NH), 10.79 (s, 1H, OH), 8.74, 8.61 (s, 1H, CH=N, E/Z isomers, 65% & 35%), 7.80 (d, *J*=7.71, 1H, aromatic), 7.72-7.63(m, 2H, aromatic), 7.53-7.02 (m, 11H, =CH aromatic, alkene), 6.96 (d, 1H, *J*=8.0Hz, aromatic). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ= 163.72, 158.31, 156.85, 155.84, 133.08, 132.28, 130.73, 130.65, 129.99, 129.38, 127.83, 127.53, 124.81, 124.41, 123.98, 123.45, 120.07, 119.43, 119.03, 118.36, 116.86. MS: m/z (%) 415 (M$^+$, 8), 398 (6), 322 (11), 255 (13), 196 (21), 181 (100), 165 (37), 152 (14), 121 (30), 77 (60), 51 (30). Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.50; H, 4.09; N, 10.12. Found: C, 66.56; H, 4.04; N, 10.15.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-hydroxybenzylidene)thiazol-4(5H)-one ***(10f)***

Yield (50%), IR (KBr): νcm^{-1}, 3354 (OH, NH), 3025 (=C.H aromatic, alkene) 1710 (C=O), 1636 (C=N). ^{1}H NMR (DMSO-d$_6$, 400MHz): 12.55 (bs, 1H, NH), 10.08 (bs, 1H,OH), 8.61 (s, 1H, CH=N), 8.38 (d, 1H, *J*=6.4Hz, aromatic), 8.06-6.75 (m, 10H, aromatic), 7.57 (s, 1H, alkene), 6.87 (d, J=8.8Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ= 165.89, 159.80, 157.65, 155.58, 133.10, 132.59, 130.69, 130.63, 129.96, 127.84, 124.94, 124.31, 123.92, 120.43, 118.94, 118.31, 116.72, 116.25, 116.17. MS: m/z (%) 415 (M$^+$, 62), 398 (16), 339 (37), 322 (100), 225 (9), 196 (25), 181 (96), 165 (14), 150 (71), 121 (25), 77 (26), 51 (12). Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.50; H, 4.09; N, 10.12. Found: C, 66.47; H, 4.06; N, 10.09.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-methylbenzylidene)thiazol-4(5H)-one ***(10g)***

Yield (50%), IR (KBr): νcm^{-1}, 3438 (NH), 3027 (=CH aromatic, alkene), 1712 (C=O), 1642 (C=N). ^{1}H NMR (DMSO-d$_6$, 400MHz): 12.55 (bs, 1H, NH), 8.54, 8.44 (s, 1H, CH=N, E/Z isomers, 41% & 35%), 8.08 (d, 1H, *J*=8Hz, aromatic), 7.78-6.99 (m, 13H, , aromatic, alkene), 2.36 (s, 3H, CH3). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ= 165.23, 157.76, 155.31, 141.20, 140.00, 132.73, 131.91, 131.65, 130.62, 130.28, 130.24, 130.17, 129.93, 128.30, 124.99, 123.82, 118.82, 118.73, 118.18, 21.53. MS: m/z (%) 413 (M$^+$, 66), 398 (12), 337 (42), 320 (100), 255 (10), 196 (19), 181 (92), 148 (62), 119 (19), 77 (21), 51 (10). Anal. Calcd. for $C_{24}H_{19}N_3O_2S$: C, 69.73; H, 4.60; N, 10.16. Found: C, 69.680; H, 4.65; N, 10.11.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-methoxybenzylidene)thiazol-4(5H)-one ***(10h)***

Yield (71%), IR (KBr): νcm^{-1}, 3430 (NH), 3040 (=C.H aromatic, alkene), 1712 (C=O), 1624 (C=N). ^{1}H NMR (DMSO-d$_6$, 400MHz): 12.50 (bs, 1H, NH), 8.60, 8.45 (s, 1H, CH=N, E/Z isomers, 70% & 30%), 8.11-6.96 (m, 14H, aromatic, alkene), 3.83 (s, 3H, CH3). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ= 162.01, 160.88, 157.47, 155.62, 132.24, 130.70, 130.63, 130.11, 129.26, 127.02, 126.64, 124.33, 123.94, 120.64, 120.39, 118.95, 118.33, 115.27, 114.84, 55.82. MS: m/z (%) 429 (M$^+$, 80), 398 (35), 367 (60), 336 (100), 225 (10), 203 (15), 196 (12), 181 (87), 164 (55), 152 (45), 121 (25), 77 (35), 51 (16). Anal. Calcd. for $C_{24}H_{19}N_3O_3S$: C, 67.13; H, 4.42; N, 9.79. Found: C, 67.17; H, 4.38; N, 9.74.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-thiomethylbenzylidene)thiazol-4(5H)-one ***(10i)***

Yield (62%), IR (KBr): νcm^{-1}, 3416 (NH), 3050 (CH aromatic.alkene), 1711 (C=O), 1644 (C=N). ^{1}H NMR DMSO-d$_6$, 400MHz): 12.55 (bs, 1H, NH), 8.61, 8.49 (s, 1H, CH=N,E/Z isomers, 51% & 49%), 8.09 (d, 1H, *J*=7.6Hz, aromatic), 7.78-6.95 (m, 13H, aromatic, alkene), 2.53 (s, 3H, CH3). ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ= 162.01, 160.88, 157.47, 155.62, 132.24, 130.70, 130.63, 130.11, 127.02, 126.64, 124.92, 124.33, 123.94, 120.64, 120.39, 118.95, 118.33, 115.27, 114.84, 55.82. MS: m/z (%) 445 (M$^+$, 9%), 353 (44),

197 (63), 181 (100), 139 (68), 123 (29), 51 (81). Anal. Calcd. for $C_{24}H_{19}N_3O_2S_2$: C, 64.71; H, 4.26; N, 9.43. Found: C ,64.67; H, 4.29; N, 9.47.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(4-nitrobenzylidene)thiazol-4(5H)-one ***(10j)***

Yield (47%), IR (KBr): νcm^{-1}, 3429 (NH), 3106, 3064 (CH aromatic, alkene), 1720 (C=O), 1645 (C=N), 1513, 1342 (NO_2). ^{1}H NMR (DMSO-d_6, 400MHz): 8.61 (s, 1H, CH=N), 8.36 (d, *J*=8.0Hz, 2H, aromatic), 8.08 (d, *J*=8.4Hz, 1H, aromatic), 7.90 (d, *J*=8.0Hz, 2H, aromatic), 7.65 (s, 1H, alkene), 7.61-7.13 (m, 6H, aromatic), 7.07 (d, J=8Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 166.86, 157.62, 155.59, 147.24, 140.99, 133.08, 131.03, 130.81, 130.64, 128.83, 127.67, 125.75, 124.87, 124.68, 124.61, 124.50, 123.94, 120.38, 118.34. MS: m/z (%) 444 (M^+, 36), 397 (15), 351 (92), 305 (12), 275 (8), 196 (37), 181 (100), 149 (20), 135 (15), 89 (42), 77 (28), 51 (12). Anal. Calcd. for $C_{23}H_{16}N_4O_4S$: C, 62.16; H, 3.60; N, 12.61. Found: C, 62.21; H, 3.64; N, 12.64.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-((furan-2-yl)methylene)thiazol-4(5H)-one ***(10k)***

Yield (37%), IR (KBr): νcm^{-1}, 3423 (NH), 1709 (C=O), 1623 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 12.45 (bs, 1H, NH), 8.6, 8.32 (s, 1H, CH=N, E/Z isomer, 29% & 71%), 8.08 (s, 1H, Furan), 7.94 (s, 1H, aromatic), 7.53-6.93 (m, 9H, aromatic, alkene), 6.74 (s, 1H, furan), 6.68 (s, 1H, furan). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 167.68, 157.59, 155.65, 150.30, 149.59, 147.18, 146.67, 133.15, 130.64, 125.65, 124.92, 123.97, 119.69, 118.35, 117.53, 117.07, 116.25, 113.74, 112.93. MS: m/z (%) 389 (M^+, 22), 296 (17), 287 (62), 196 (7), 181 (35), 153 (11), 124 (100), 121 (10), 96 (35), 80 (20), 70 (13), 52 (29). Anal.Calcd.for $C_{21}H_{15}N_3O_3S$: C, 64.78; H, 3.85; N, 10.79. Found: C, 64.72; H, 3.79; N, 10.74.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-((pyridine-2-yl)methylene)thiazol-4(5H)-one ***(10l)***

Yield (36%), IR (KBr): νcm^{-1}, 3421 (NH), 3055 (CH aromatic, alkene), 1721 (C=O), 1638 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 12.45 (bs, 1H, NH), 8.83 (d, 1H, *J*=4.8Hz, Pyridin), 8.61, 8.43 (s, 1H, CH=N, E/Z isomers, 68% & 32%), 8.06 (m, 1H, pyridin), 7.93 (m, 2H, pyridin), 7.81 (d, *J*=7.2Hz, 1H, aromatic), 7.66 (s, 1H, alkene), 7.55-7.13 (m, 6H, aromatic), 7.02 (d, *J*=8.0Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 168.08, 157.60, 155.63, 152.56, 152.37, 149.77, 137.73, 133.09, 130.64, 128.17, 127.67, 127.63, 126.26, 125.73, 124.91, 123.96, 123.77, 120.35, 119.69, 118.34. MS: m/z (%) 400 (M^+, 38), 307 (100), 269 (8), 204 (41), 196 (28), 181 (95), 161 (20), 152 (15), 135 (73), 115 (8), 77 (30), 51 (21). Anal. Calcd. for $C_{22}H_{16}N_4O_2S$: C, 66.00; H, 4.00; N, 14.00. Found: C,66.07; H, 4.05; N, 13.97.

*2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-((pyridine-3-yl)methylene)thiazol-4(5H)-one (****10m)***

Yield (42%), IR (KBr): νcm^{-1}, 3430 (NH), 1718 (C=O), 1636 (C=N). ^{1}H NMR (DMSO-d_6, 400MHz): 8.96, 8.87 (s, 1H, CH=N, E/Z isomers, 15% & 85%), 8.69 (m, 2H, Pyridine), 8.23 (d, 1H,*J*=8.0Hz, pyridin), 8.11-7.15 (m, 9H, aromatic, pyridine, alkene), 7.01 (d, J=8.0Hz, 2H, aromatic). ^{13}C NMR (125 MHz, DMSO-d_6): δ= 168.21, 157.61, 155.66, 151.68, 150.36, 136.30, 134.78, 133.26, 130.76, 130.64, 127.91, 125.96, 125.55, 124.96, 124.83, 124.18, 123.95, 120.40, 119.70, 118.34. MS: m/z (%) 400 (M^+, 50), 307 (100), 280 (7), 218 (8), 196 (23), 181 (94), 162 (15), 152 (12), 135 (50), 91 (18), 77 (21), 51 (15). Anal. Calcd. for $C_{22}H_{16}N_4O_2S$: C, 66.00; H, 4.00; N, 14.00. Found: C,66.03; H, 4.06; N, 14.05.

2-(2-(2-phenoxybenzylidene)hydrazinyl)-5-(2-phenoxybenzylidene)thiazol-4(5H)-one ***(10n)***

Yield (50%), IR (KBr): νcm^{-1}, 3419 (NH), 3032 (CH aromatic, alkene), 1716 (C=O), 1638 (C=N). ^{1}H NMR DMSO-d_6, 400MHz): 8.60, 8.51 (s, 1H, CH=N, E/Z isomers, 28% & 72%), 8.06 (d, 1H, *J*=7.2Hz, aromatic), 7.76-6.96 (m, 18H, aromatic, alkene).^{13}C NMR (125

MHz, DMSO-d_6): δ= 169.97, 157.63, 156.94, 155.78, 155.61, 133.15, 132.03, 130.70, 130.64, 129.46, 127.77, 125.68, 125.59, 124.94, 124.79, 124.34, 123.94, 120.41, 119.45, 118.97, 118.32,. MS: m/z (%) 491 (M^+, 8), 398 (25), 311 (16), 218 (31), 196 (25), 181 (100), 165 (15), 119 (12), 77 (25). Anal. Calcd. for $C_{29}H_{21}N_3O_3S$: C, 70.87; H, 4.27; N, 8.55. Found: C, 70.83; H, 4.29; N, 8.51.

Pharmacological evaluations

Male NMRI mice weighing 20–25 g and male Wistar rats (100–150 g) (Pasteur Institute of Iran) were used for analgesic activity evaluation by abdominal constriction test. Mefenamic acid was prescribed (30 mg/kg) and target compounds were injected in an equal molar ratio to 30 mg/kg of reference drug, 30 min after the animals were injected ip with acetic acid (0.6 %, 0.1 ml/10 g). All the procedures, statistical analysis and calculation of inhibition percent were performed conforming to our previously expressed research.[1] Wistar male rats were used in carrageenan-induced rat paw edema test and the selected doses were similar to the writing test and other situations, estimation of increment in paw volume and statistical analysis were done similarly as reported earlier (Table III). [2, 3]

The results were expressed as the mean±SEM of 6 animals per group. The data were statistically analyzed by one-way analysis of variance (ANOVA) followed by Tukey multicomparison test. Differences with $P<0.05$ between experimental groups were considered statistically significant. In ulcerogenic test, suspension of indomethacin, 60 mg/kg and compounds in an equal molar ratio to indomethacin dose, in 0.5 % aqueous sodium carboxymethyl cellulose as vehicle, were administered orally to test animals. The control group animals received the same volumes of dosing vehicle.

Insilico ADMET Evaluation

Lipinski's rule of five important parameters for oral absorption of synthesized compounds states that the molecular weight of the target compound should be ≤ 500. The number of hydrogen bond donors should be ≤ 5 and the number of hydrogen bond acceptors should be ≤ 10. The topological polar surface area should be ≤ 140. The number of rotatable bonds should be ≤ 10. If a compound violates two aforesaid rules, it will lead to poor oral absorption.[4]

For determining drug-likeness, a fragment list was created by shredding 3300 traded drugs as well as 15000 commercially available chemicals of Fluka company yielding a complete list of all available fragments. The occurrence frequency of every one of the fragments was determined within the collection of traded drugs and within the supposedly non-drug-like collection of Fluka compounds. While 80% of the traded drugs have a positive drug-likeness value, the big majority of Fluka chemicals account for a negative value. The drug-score combines drug-likeness, clogp, clogs, molecular weight, and toxicity risks in one functional value that might be used to judge the compound's overall potential to qualify for a drug.[5]

Another tool for assessing the ADMET properties of compounds is a comprehensive platform called admetSAR3.0, which is utilized for search, prediction, and optimization purposes. Within the search module, there are over 370,000 high-quality experimental ADMET data entries available, covering 104,652 unique compounds. Moreover, it includes a chemical structure similarity search function to aid in comparison. In the prediction module, admetSAR3.0 covers an expanded range of endpoints, including 119 ADMET-related endpoints across five categories: basic properties, ADME properties, human health toxicities, environmental risk assessment, and cosmetic risk assessment. Within the optimization

module, it optimizes ADMET properties via scaffold hopping and transformation rules. In ADMETopt, more than 50,000 distinct scaffolds from the ChEMBL and Enamine databases assist in matching similar scaffolds. Finally, the updated interface of admetSAR3.0 represents users with succinct result presentations along with practical assistance. [6]

Table S-I: The significant pharmacokinetic parameters for acceptable oral bioavailability of the synthesized compounds **8**, **10a-10n**

Compound	MW[a] (g/mol)	NROTB[b]	HBA[c]	HBD[d]	TPSA[e] (Å^2)	ClogP[f]	GI absorption	LV[g]
8	371.45	6	3	1	74.75	5.01	High	0
10a	399.46	6	4	1	88.35	4.55	High	0
10b	417.46	6	5	1	88.35	4.80	High	0
10c	433.91	6	4	1	88.35	5.01	High	0
10d	478.36	6	4	1	88.35	5.09	High	1
10e	415.46	6	5	2	108.58	4.02	High	0
10f	415.46	6	5	2	108.58	4.08	High	0
10g	413.49	6	4	1	88.35	4.83	High	0
10h	429.49	7	5	1	97.58	4.49	High	0
10i	445.56	7	4	1	113.65	5.04	Low	0
10j	444.47	7	6	2	138.01	2.74	Low	0
10k	389.43	6	5	1	101.49	3.90	High	0
10l	400.45	6	5	1	101.24	3.84	High	0
10m	400.45	6	5	1	101.24	3.84	High	0
10n	491.56	8	5	1	97.58	5.73	Low	1

[a]Molecular weight; [b]Number of rotatable bonds; [c]Number of hydrogen bond acceptors; [d]Number of hydrogen bond donors; [e]Topological polar surface area; [f] Consensus log $P_{o/w}$ (logarithm of partition coefficient of compound between n-octanol and water); [g]Lipinski's violation

Table S-II: The toxicity risks, drug-likeness, and drug-score of target compounds **8**, **10a-10n**

Compound	Toxicity Risks[1]				Drug-Likeness	Drug-Score
	M[2]	**T[3]**	**I[4]**	**R[5]**		
8	-	+	-	-	4.54	0.16
10a	-	-	-	-	3.92	0.36
10b	-	-	-	-	4.01	0.34
10c	-	-	-	-	5.67	0.3
10d	-	-	-	-	3.04	0.27
10e	-	-	-	-	5.13	0.38
10f	-	-	-	+	5.14	0.23
10g	-	-	-	-	3.56	0.33
10h	-	-	-	-	5.16	0.35
10i	-	-	-	-	5.1	0.3
10j	-	-	-	-	-5.25	0.19
10k	+	-	-	-	4.69	0.25
10l	-	-	-	-	5.03	0.44
10m	-	-	-	-	5.48	0.44
10n	-	-	-	-	5.04	0.23

[1]Ranked according to (-) no risk, (±) medium risk, (+) high risk; M[2], Mutagenic; T[3], Tumorigenic; I[4], Irritant; R[5], Reproductive effective.

Table S-III: Human oral bioavailability and toxicity risks of target compounds **8**, **10a-10n**

Compound	Human oral bioavailability	Toxicity Risks[1]			
		Carcinogenicity	Skin irritation	Reproductive toxicity	Respiratory toxicity
8	Low	+	-	-	-
10a	High	-	-	-	-
10b	High	-	-	+	-
10c	High	-	-	+	-
10d	High	-	-	+	-
10e	High	-	-	+	-
10f	High	-	-	+	-
10g	Low	-	-	-	-
10h	Low	-	-	-	-
10i	High	-	-	+	-
10j	High	-	-	+	-
10k	High	-	-	-	-
10l	High	-	-	+	-
10m	Low	-	-	-	-
10n	Low	-	-	+	-

[1]Ranked according to (-) low risk and (+) high risk.

REFERENCES

1. A. Almasirad, R. Hosseini, H. Jalalizadeh, Z. Rahimi-Moghaddam, N. Abaeian, M. Janafrooz, M. Abbaspour, V. Ziaee, A. Dalvandi, A. Shafiee, *Biol. Pharma. Bull.* **29** (2006) 1180 (https://doi.org/10.1248/bpb.29.1180)

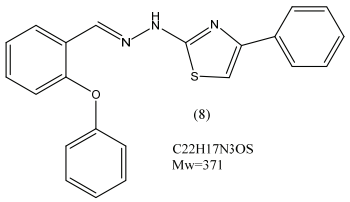
2. A. Rineh, N. Mahmoodi, M. Abdollahi, A. Foroumadi, M. Sorkhi, A. Shafiee, *Arch. Pharm. Chem. Life. Sci.* **340** (2007) 409 (https://doi.org/10.1002/ardp.200700045)

3. A. Almasirad, M. Nassiri Koopaei, A. Shafiee, N. Nassiri-Koopaei, M. J. Assarzadeh, A. Tabei, M. Ghadimi, *J. Pharm. Health. Sci***. 1** (2013) 137 (https://sid.ir/paper/188761/en)

4. M. Faizi, R. Jahani, S. A. Ebadi, S. A. Tabatabai, E. Rezaee, M. Lotfaliei, M. Amini, A. Almasirad, *EXCLI. J.* **16** (2017) 52 (https://doi.org/10.17179/excli2016-692)

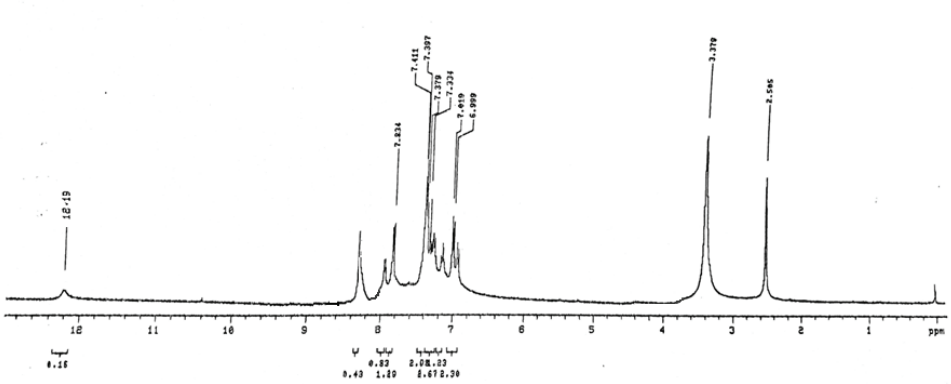
5. https://www.organic-chemistry.org/prog/peo/

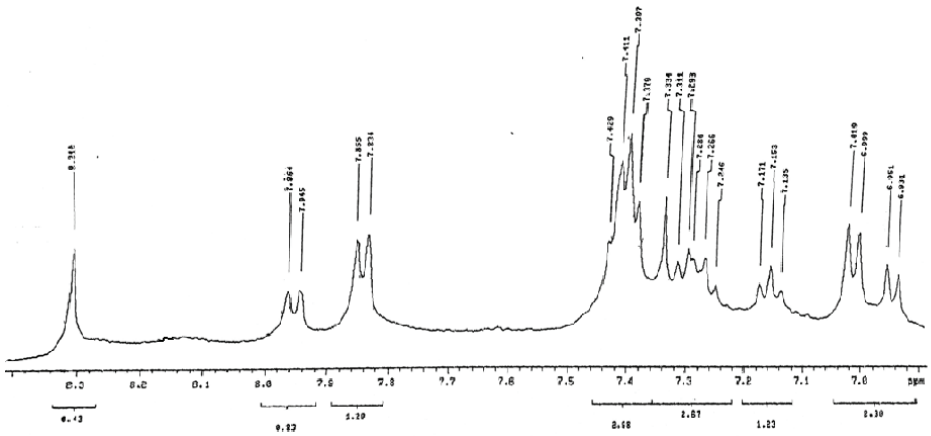
6. Gu Y . Gu, Z. Yu, Y. Wang, L. Chen, C. Lou, C. Yang, W. Li, G. Liu, Y . Tang, *Nucleic Acids Res*. **22** (2024) gkae298 (https://doi.org/10.1093/nar/gkae298).

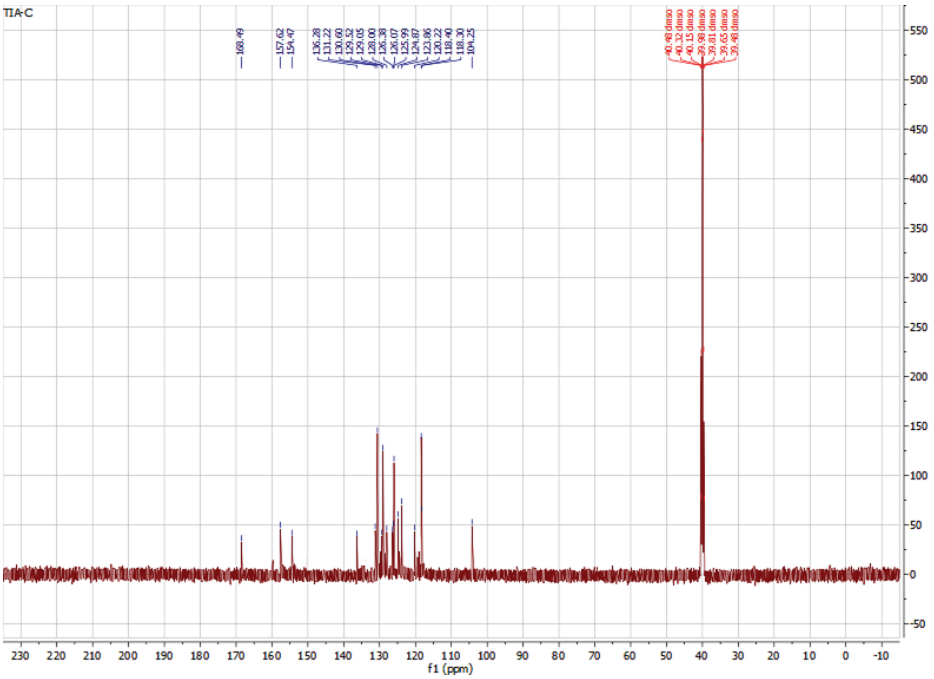


(8)

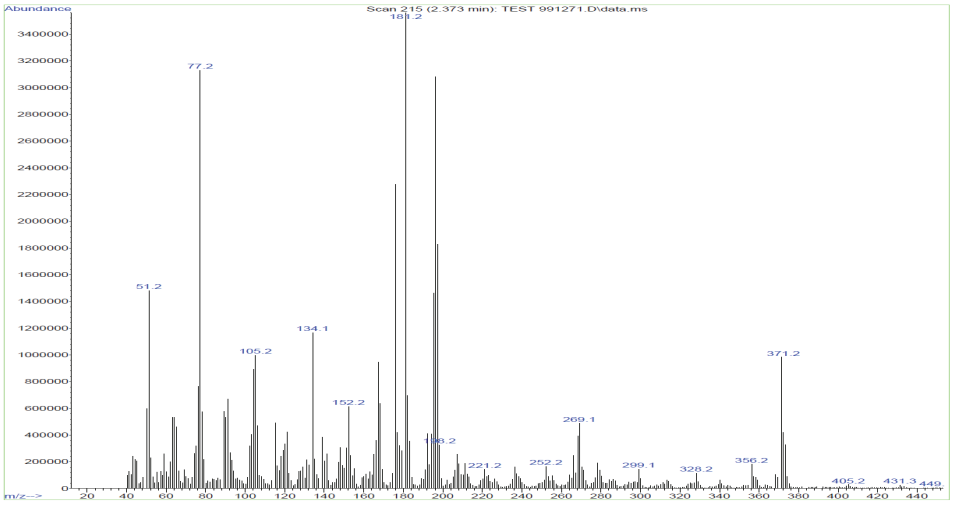
C22H17N3OS
Mw=371

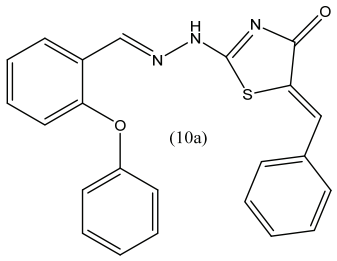






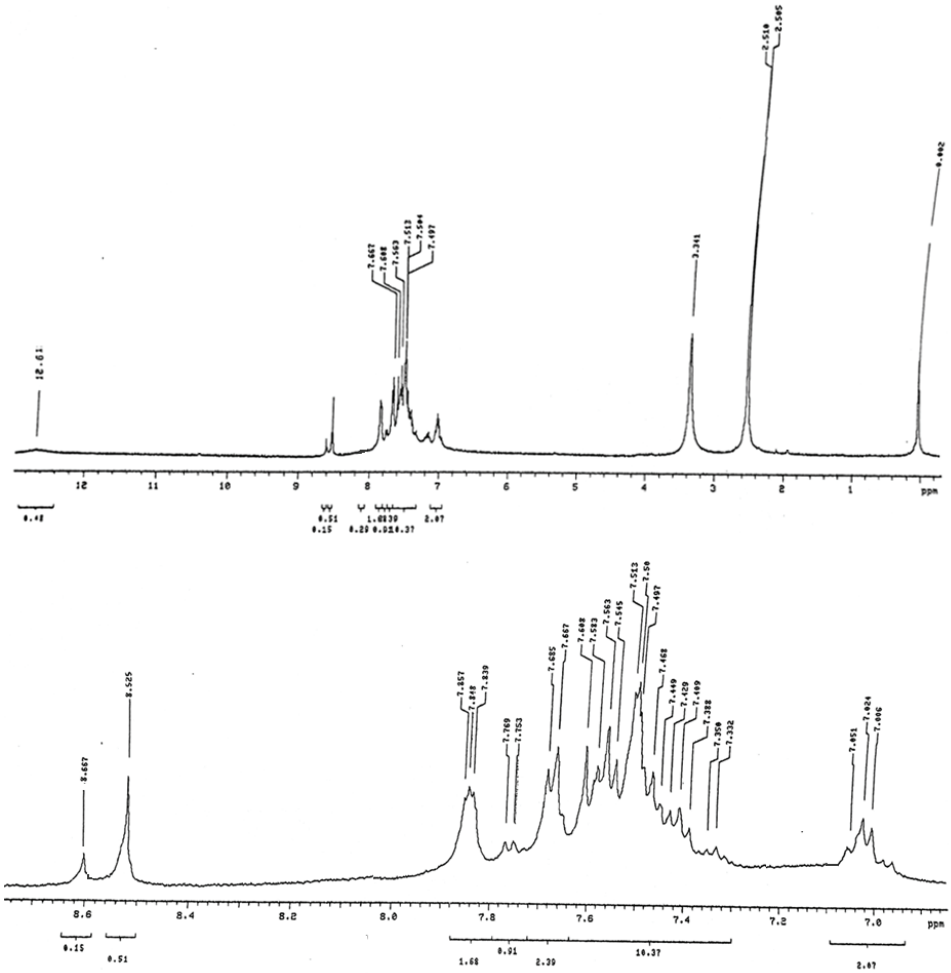
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991271.D
Operator :
Acquired : 23 Jul 2007 22:08 using AcqMethod test.M
Instrument : MSD
Sample Name: Thia
Misc Info :
Vial Number: 1

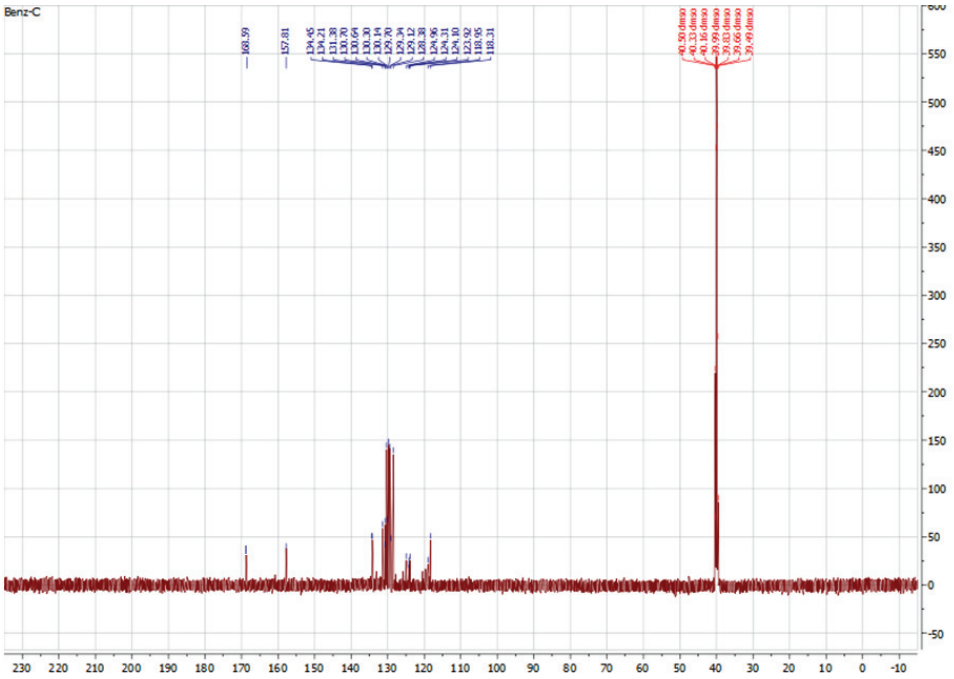




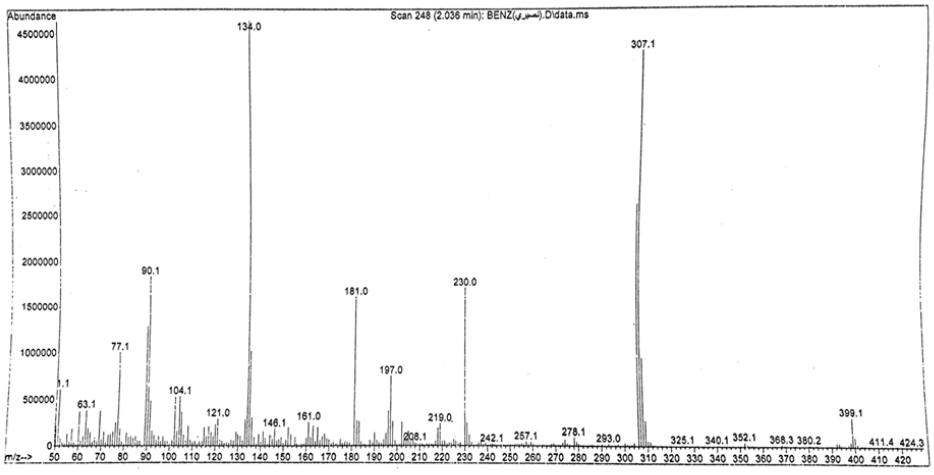
(10a)

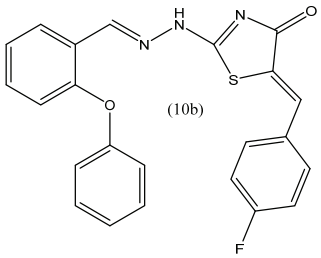
C23H17N3O2S
Mw=399





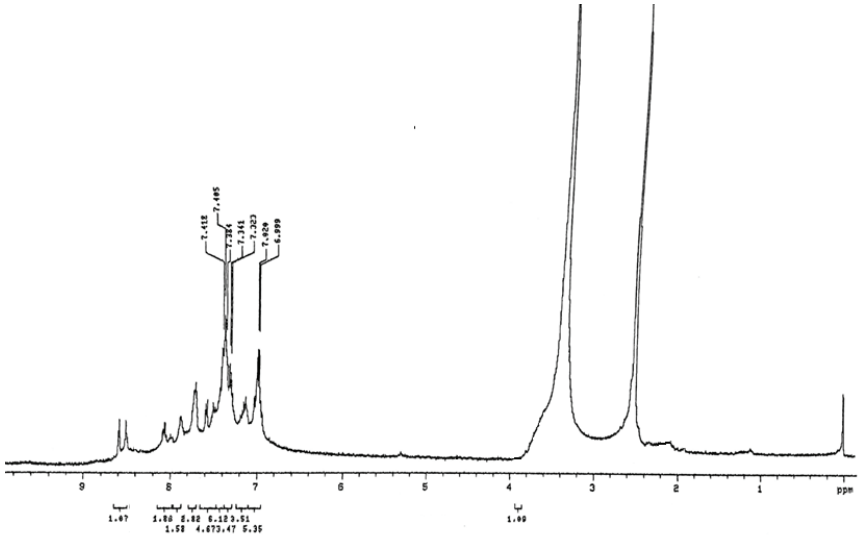
File :C:\msdchem\3\DATA\BENZ(صحیح).D
Operator : ahoupal
Acquired : 13 Dec 2010 13:20 using AcqMethod test dp.M
Instrument : MSD Direct Probe
Sample Name: benz
Misc Info :
Vial Number: 1

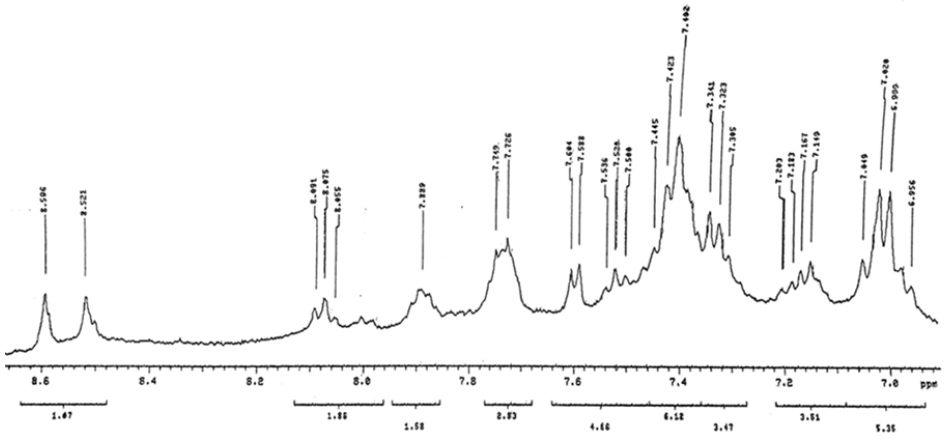


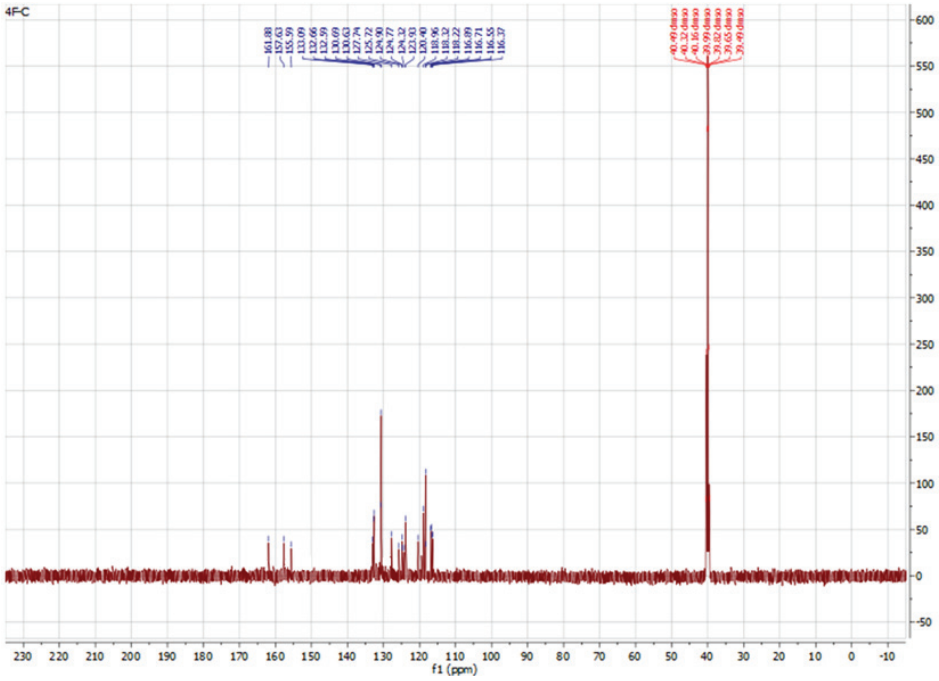


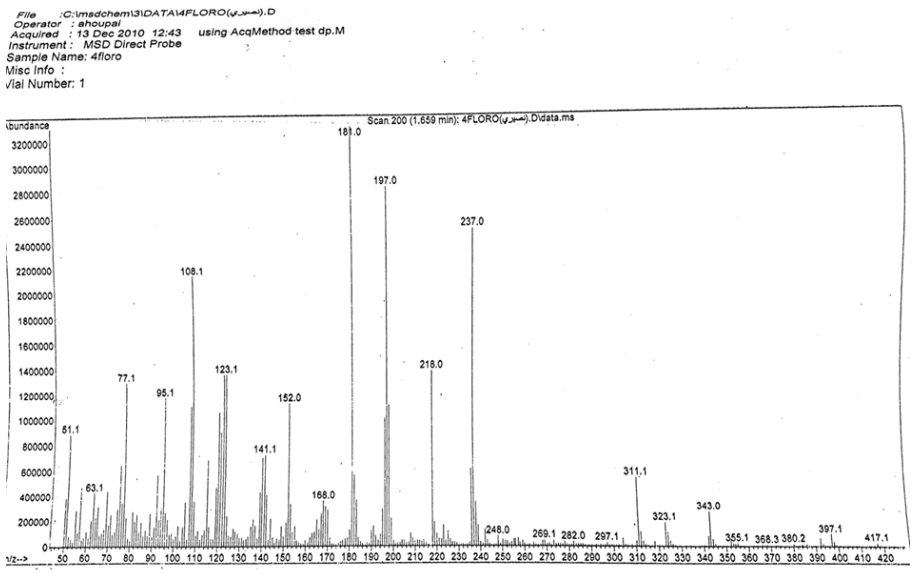
(10b)

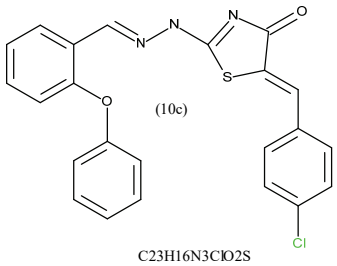
C23H16N3FO2S
Mw=417





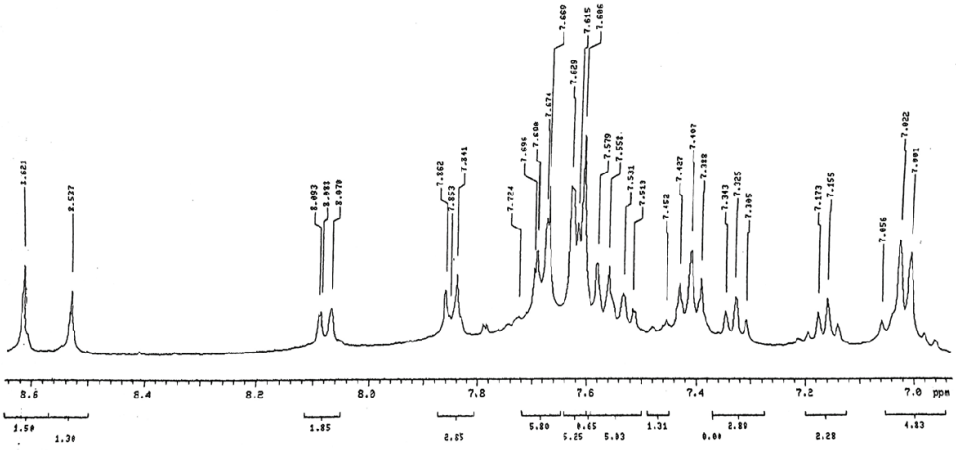


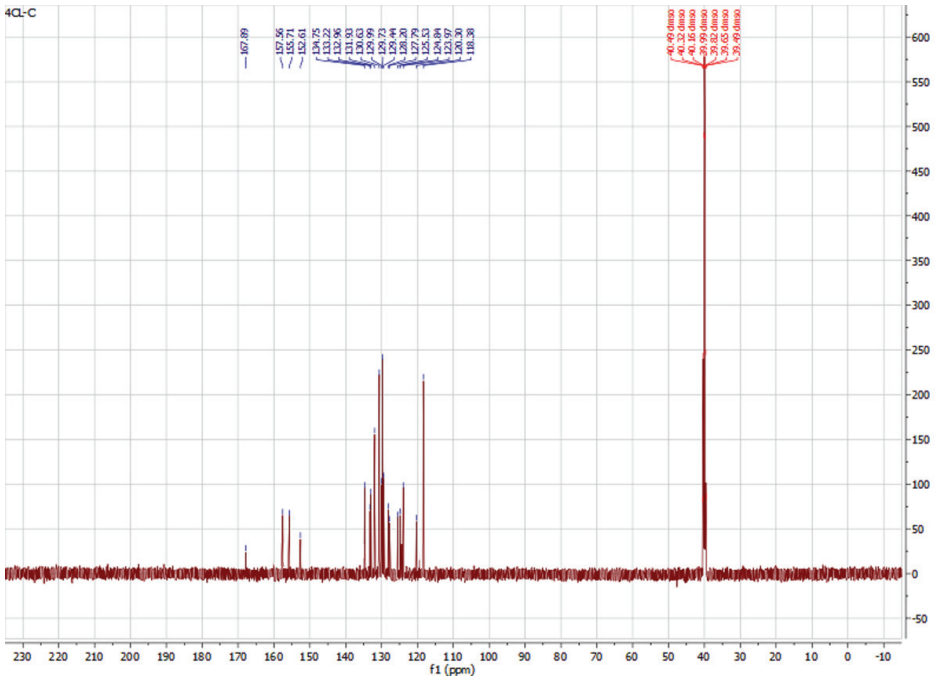


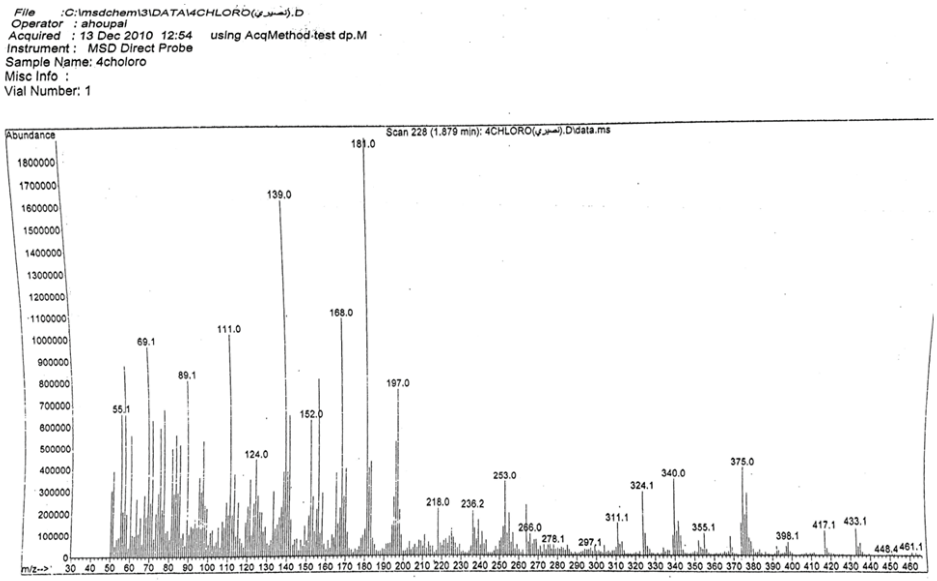


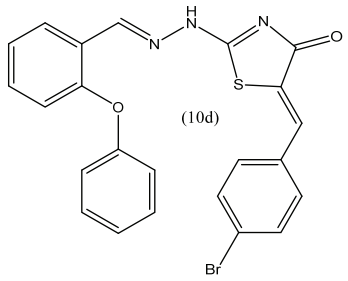
(10c)

C23H16N3ClO2S
Mw=433.5



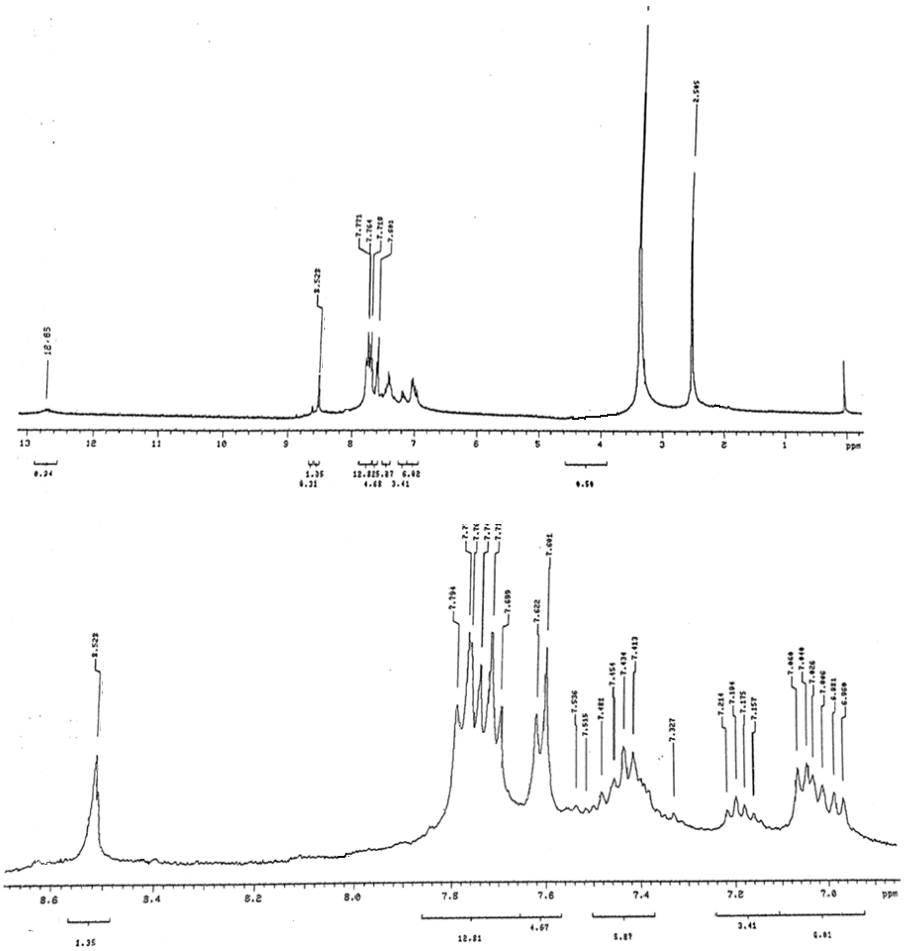


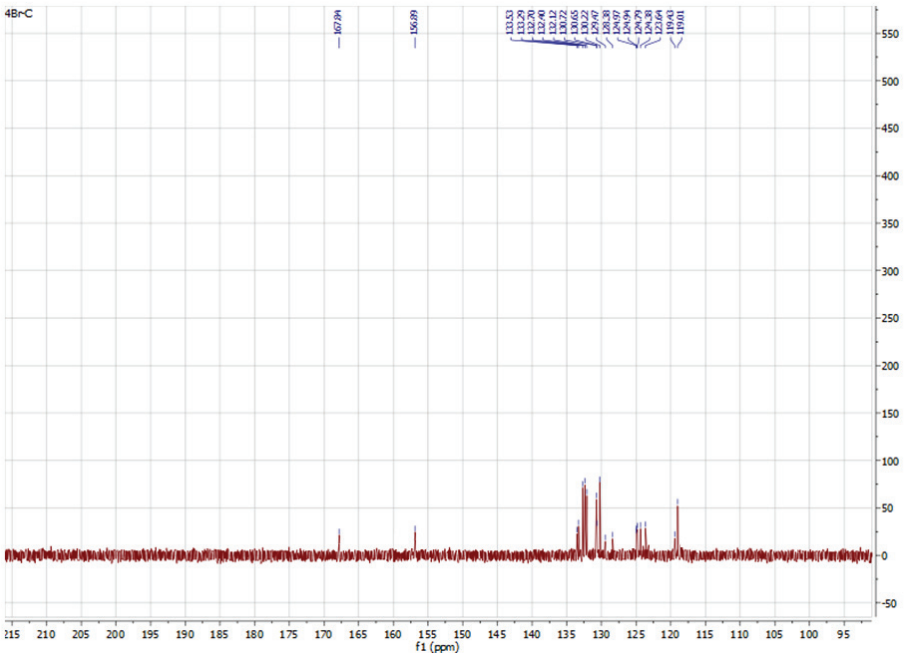


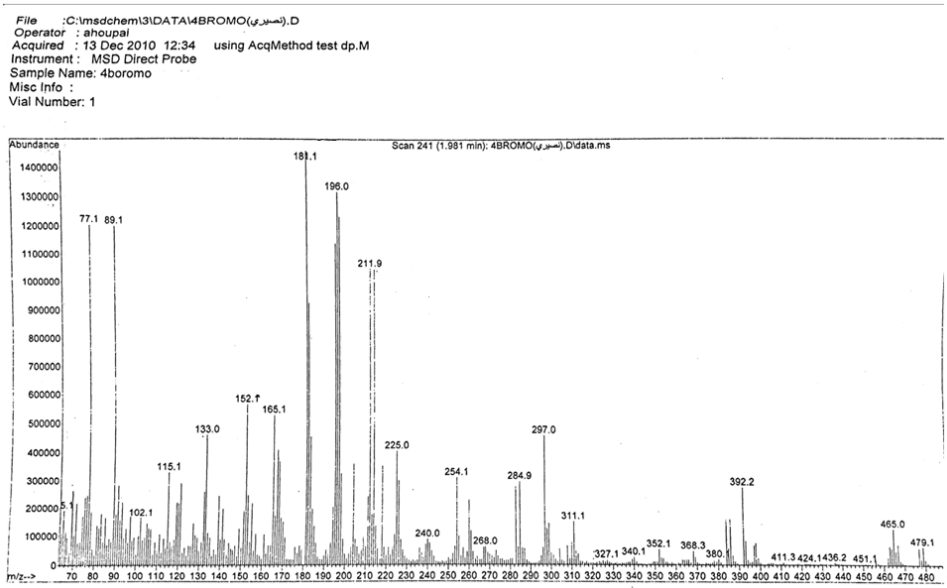


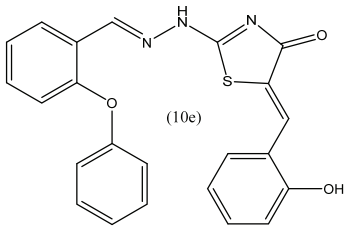
(10d)

C23H16N3BrO2S
Mw=478



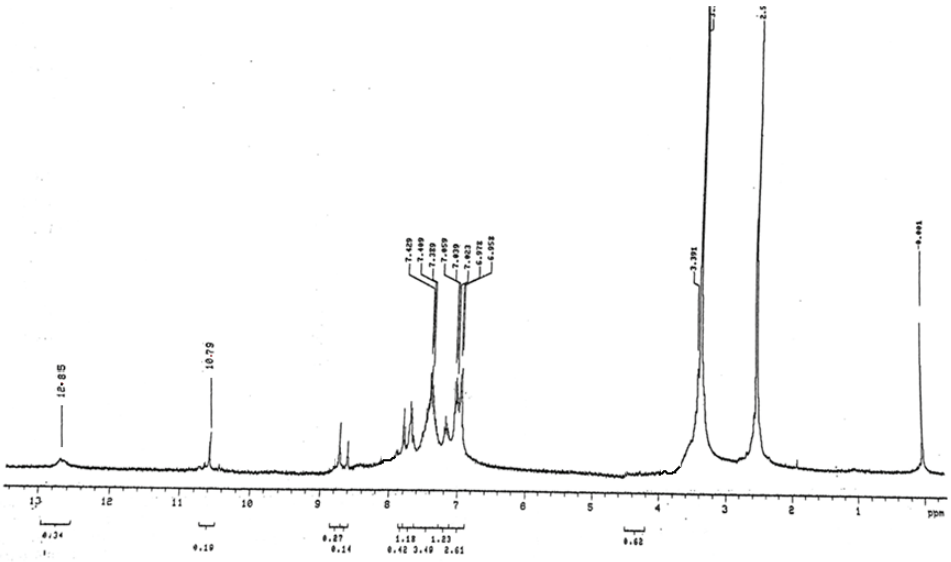


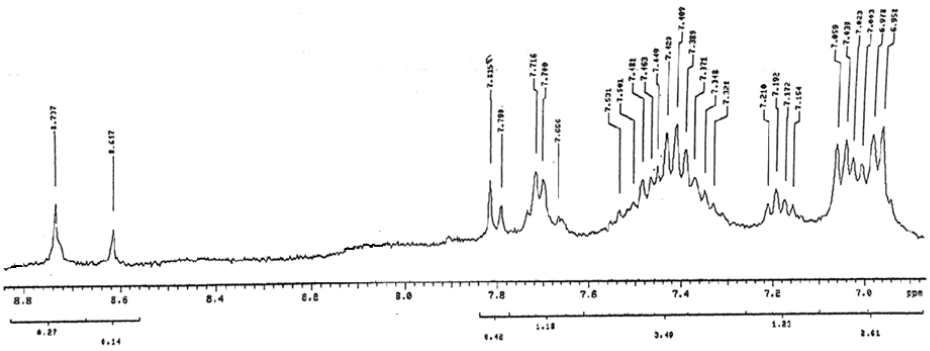


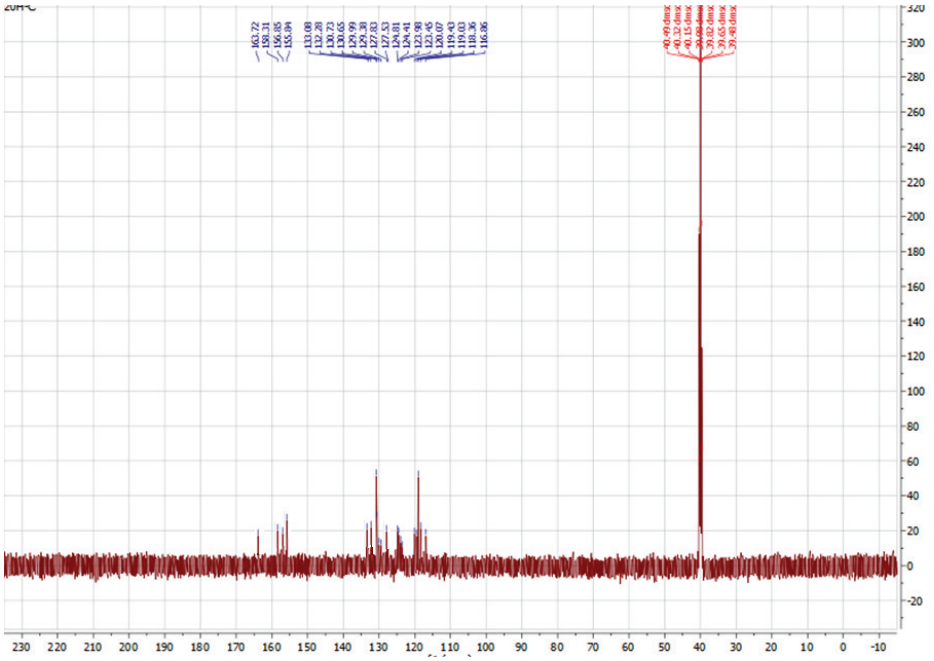


(10e)

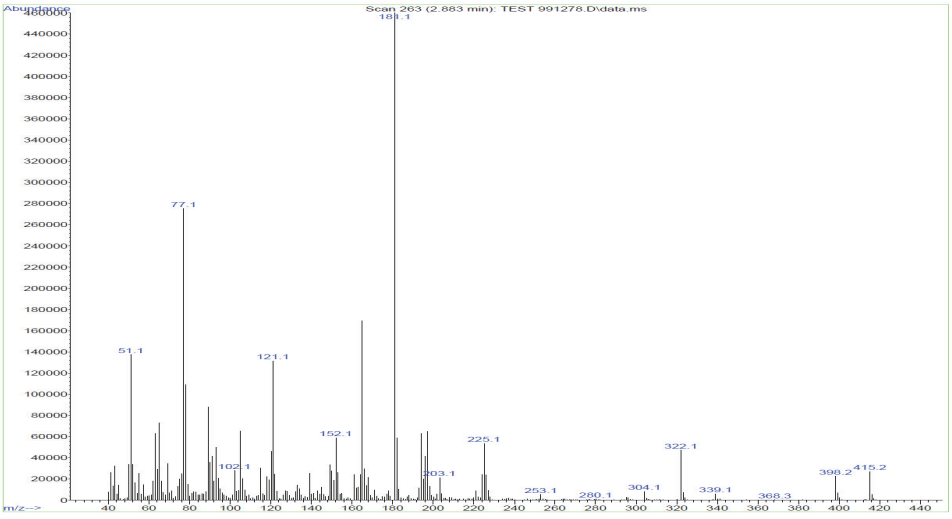
C23H17N3O3S
Mw=415

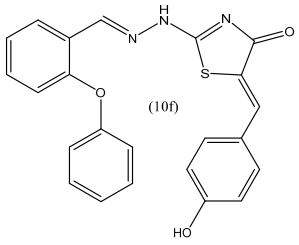






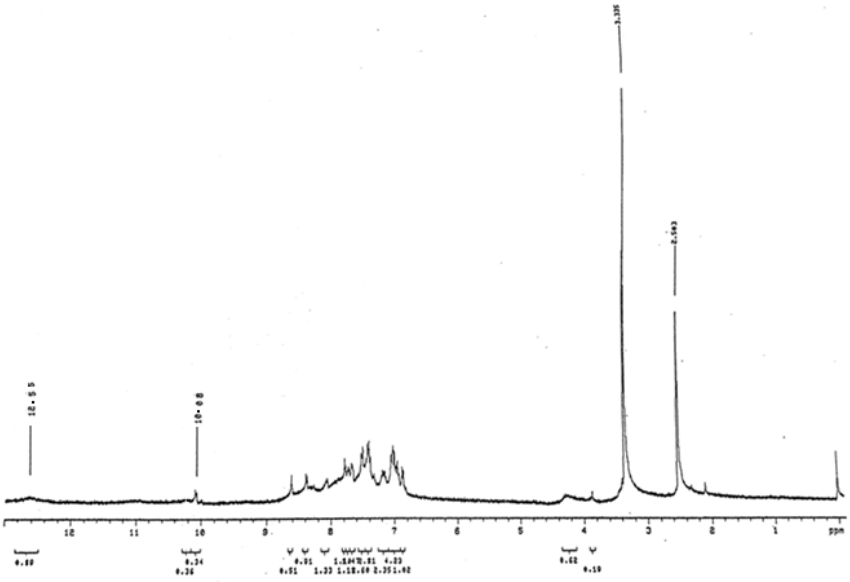
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991278.D
Operator :
Acquired : 23 Jul 2007 23:25 using AcqMethod test.M
Instrument : MSD
Sample Name: 2OH
Misc Info :
Vial Number: 1

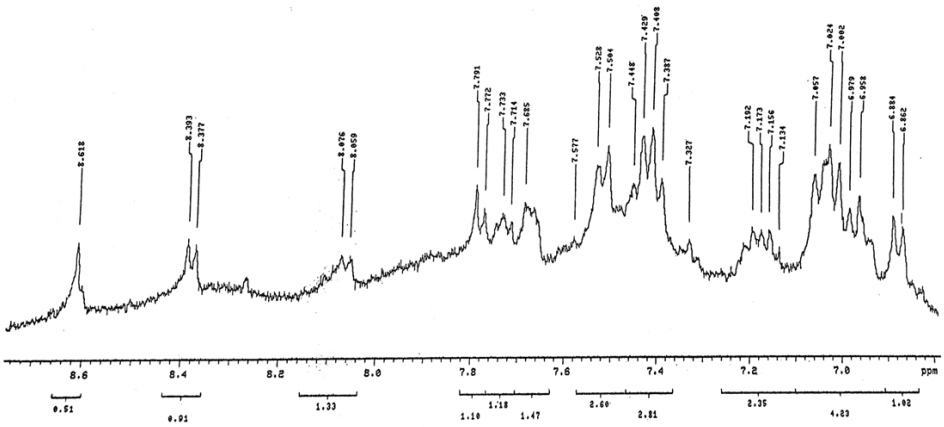


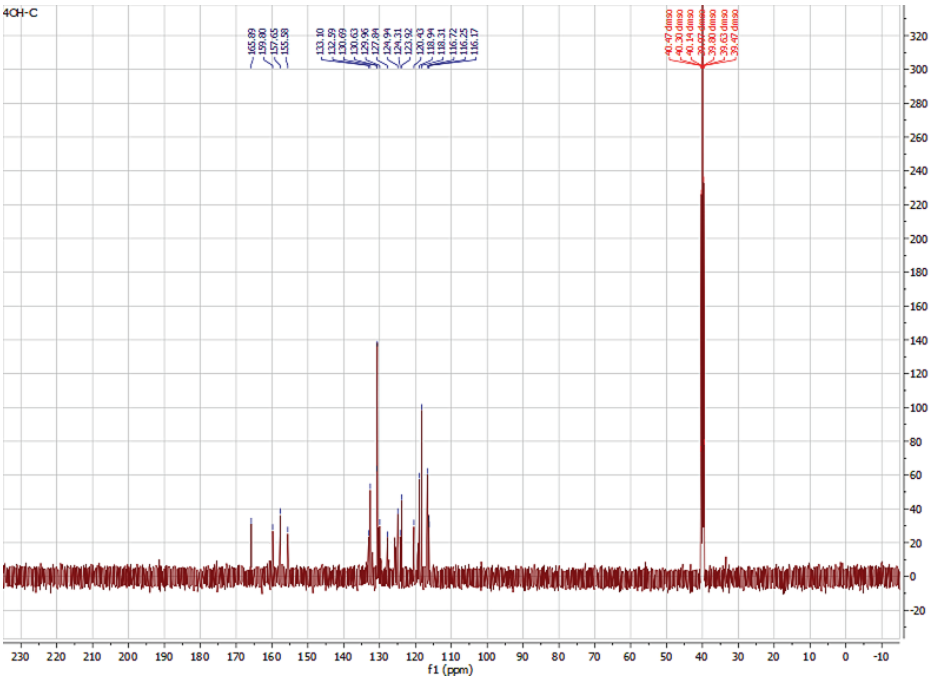


(10f)

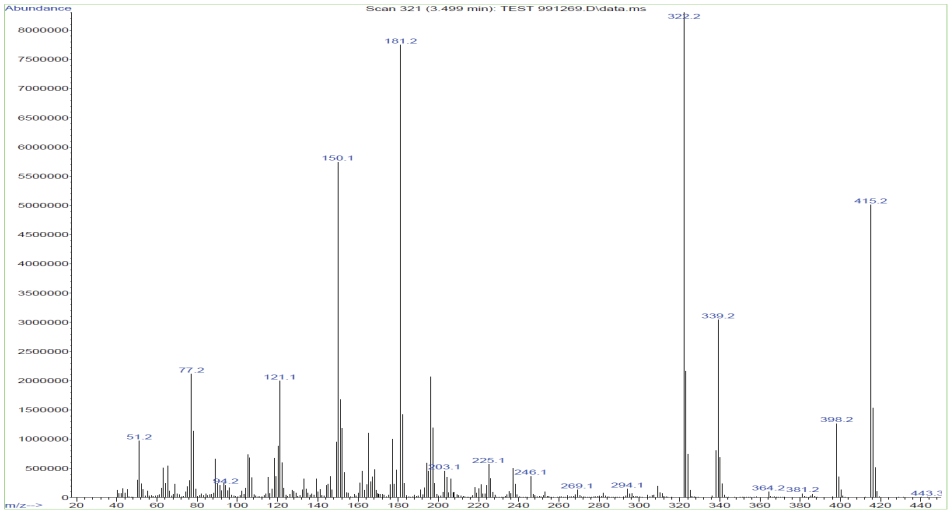
C23H17N3O3S
Mw=415

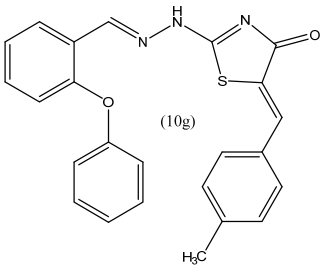






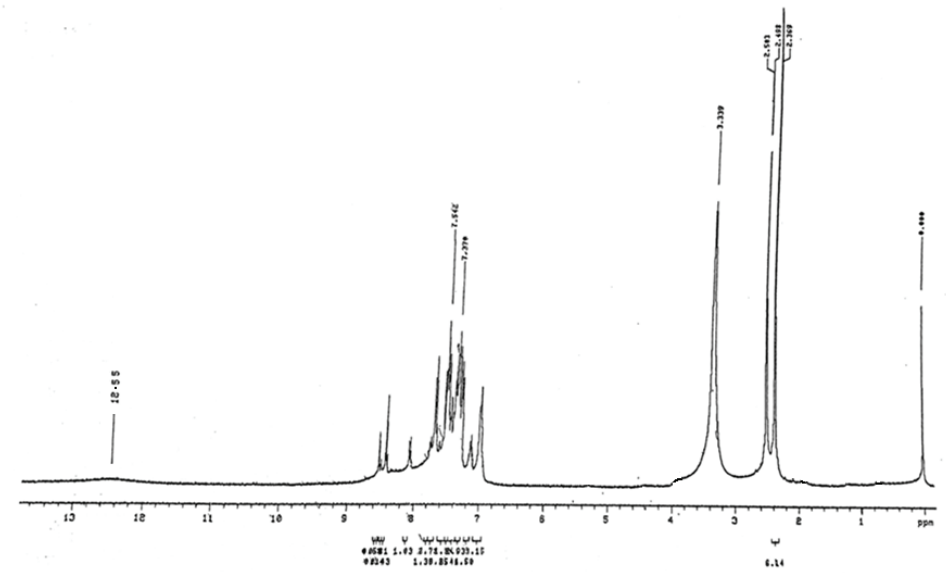
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991269.D
Operator :
Acquired : 23 Jul 2007 21:41 using AcqMethod test.M
Instrument : MSD
Sample Name: 4OH
Misc Info :
Vial Number: 1

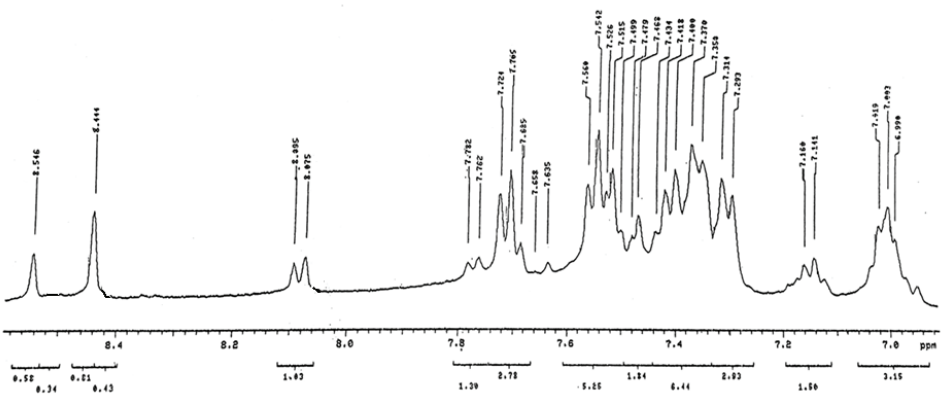


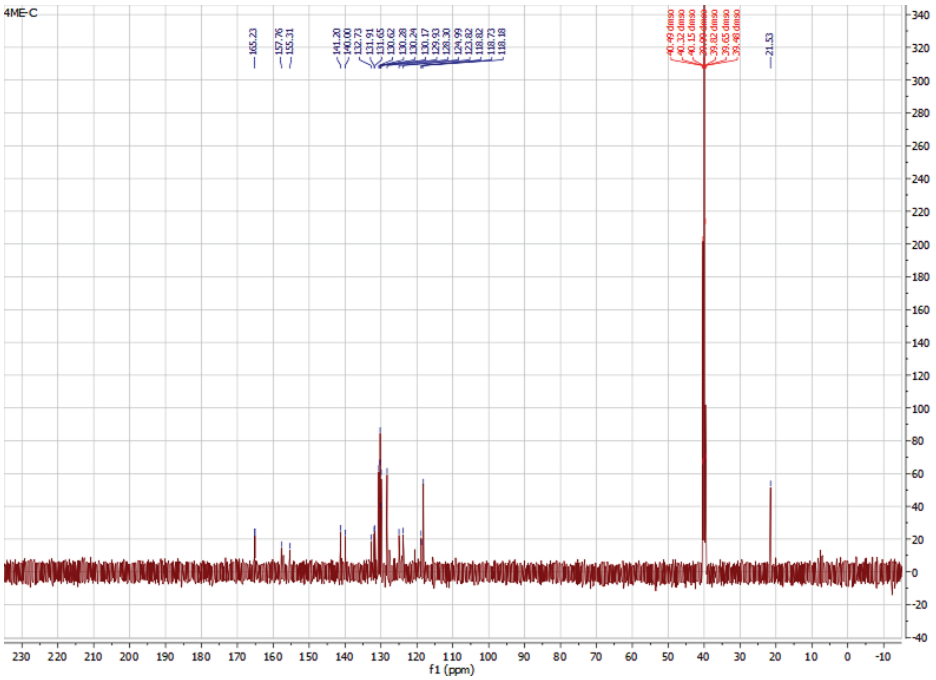


(10g)

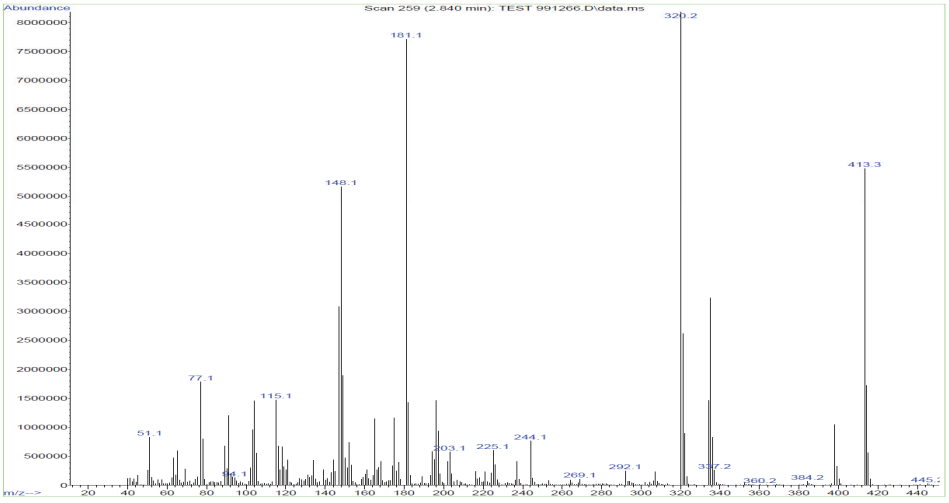
C24H19N3O2S
Mw=413

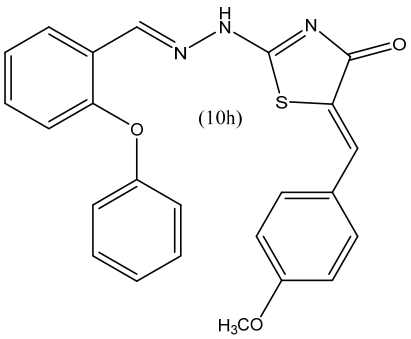






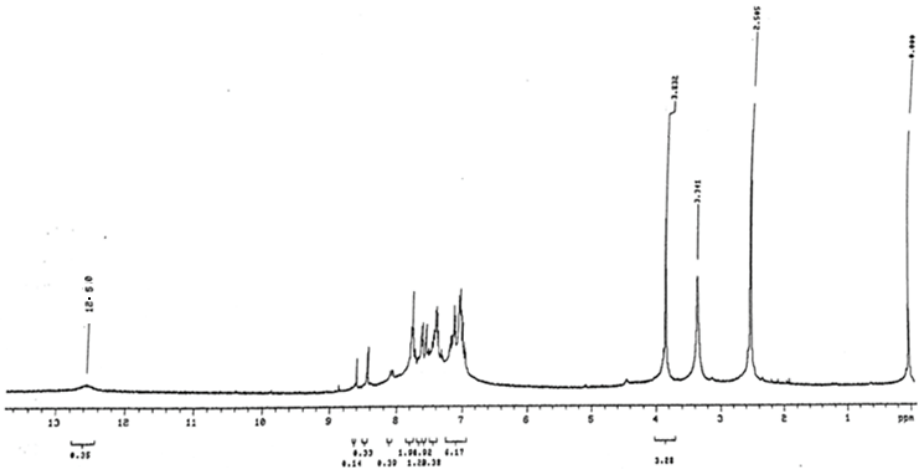
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991266.D
Operator :
Acquired : 23 Jul 2007 21:03 using AcqMethod test.M
Instrument : MSD
Sample Name: 4CH3
Misc Info :
Vial Number: 1

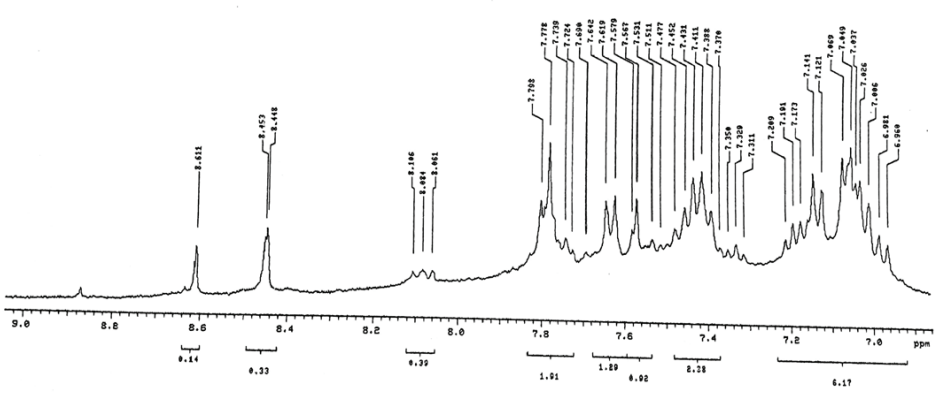


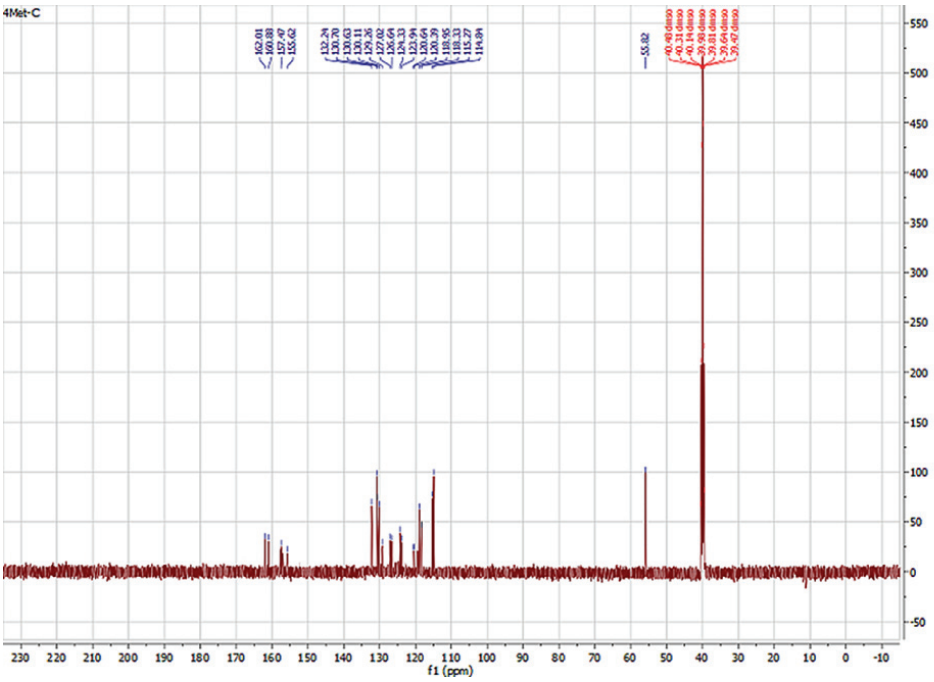


(10h)

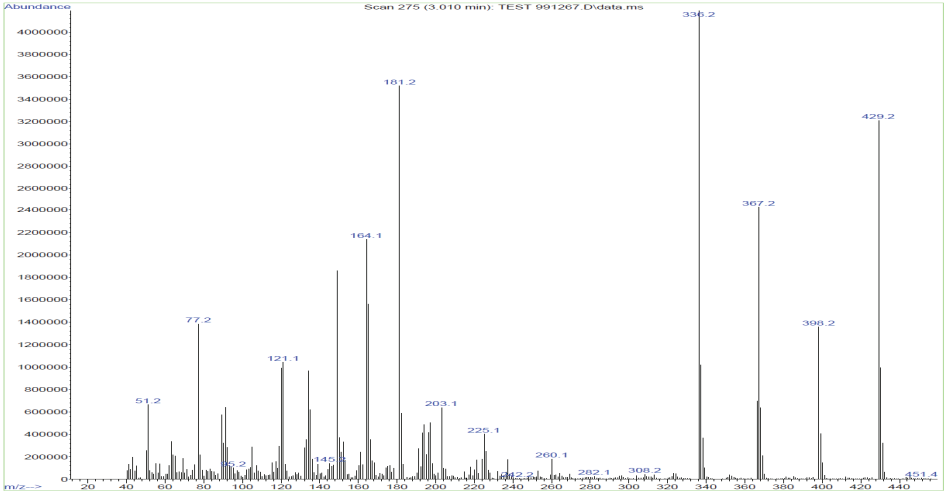
$C_{24}H_{19}N_3O_3S$
MW: 429.49

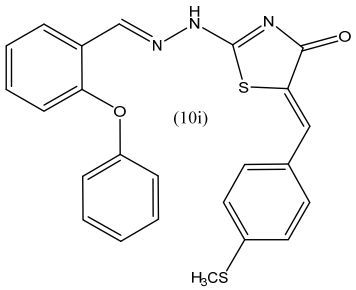






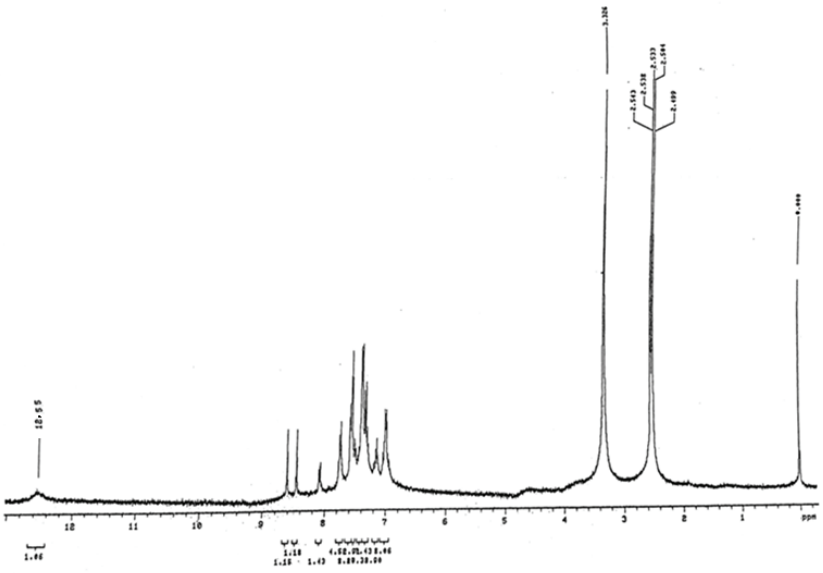
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991267.D
Operator :
Acquired : 23 Jul 2007 21:15 using AcqMethod test.M
Instrument : MSD
Sample Name: 4OCH3
Misc Info :
Vial Number: 1

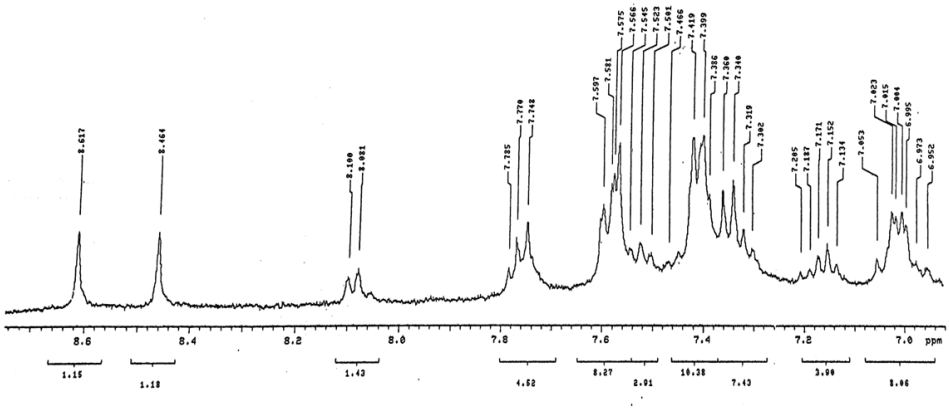


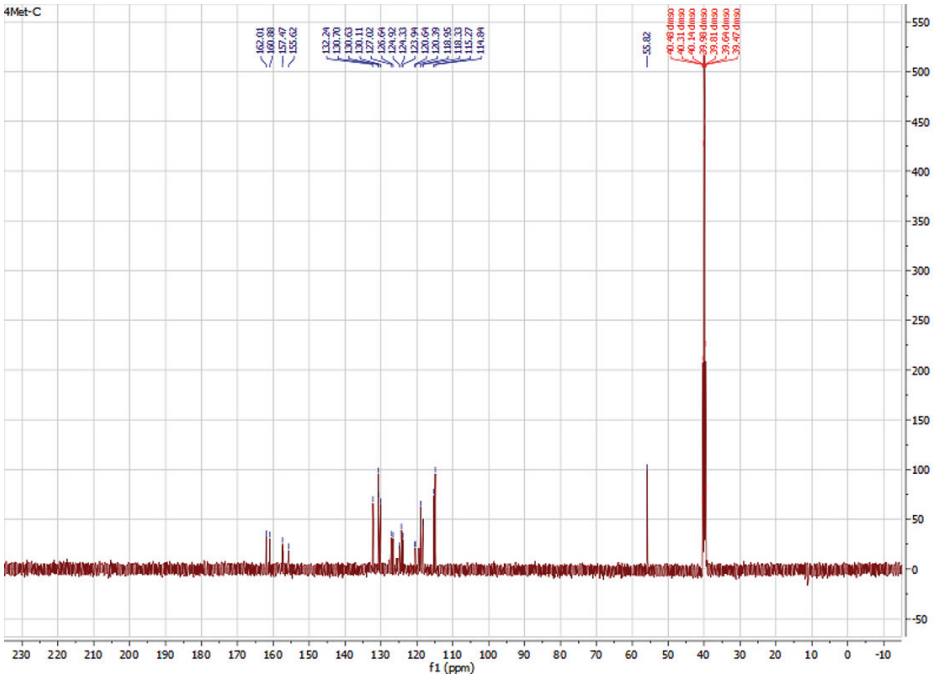


(10i)

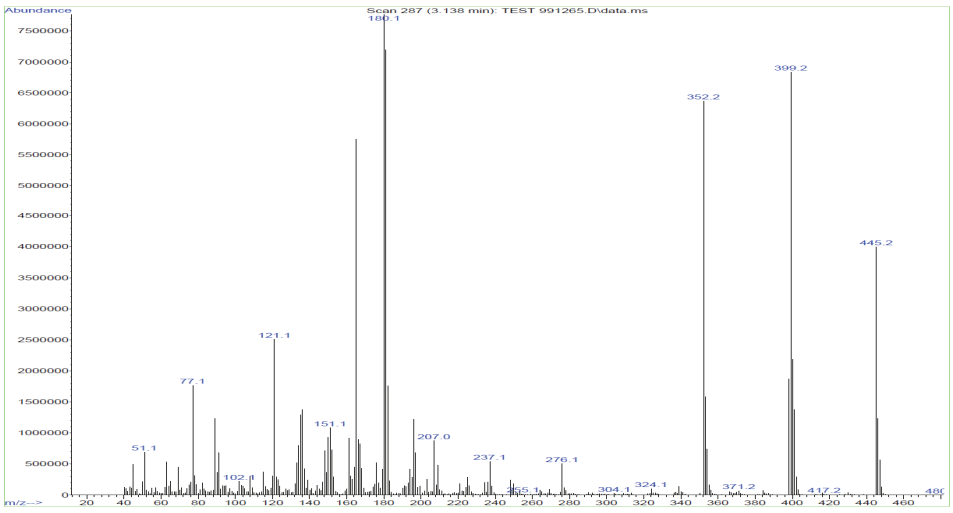
C24H19N3O2S2
Mw=445

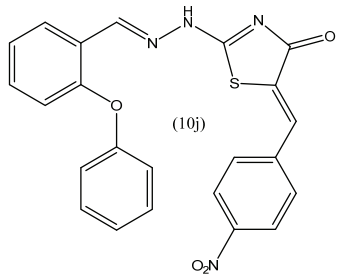






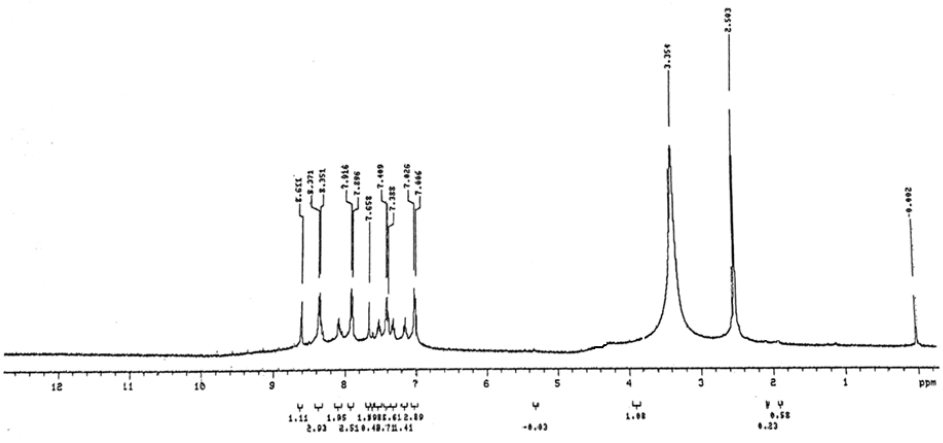
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991265.D
Operator :
Acquired : 23 Jul 2007 20:50 using AcqMethod test.M
Instrument : MSD
Sample Name: 4SCH3
Misc Info :
Vial Number: 1

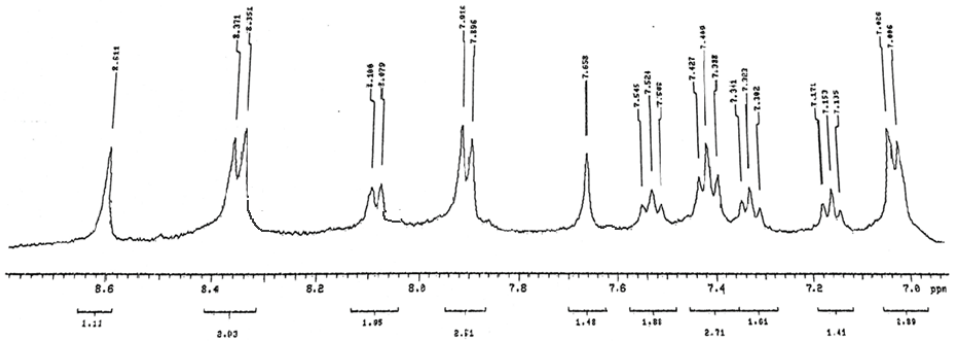


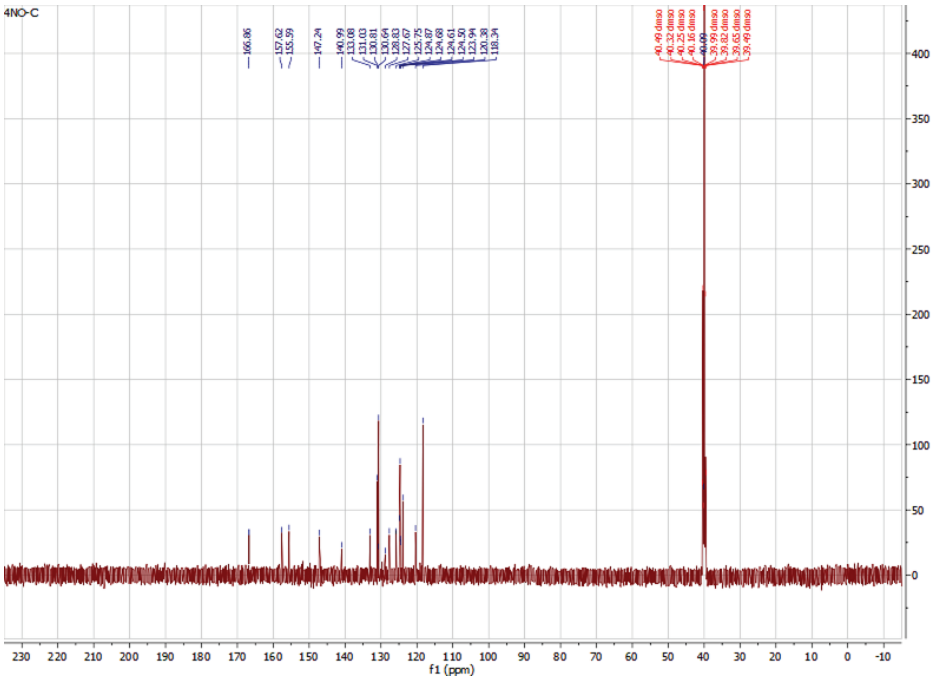


(10j)

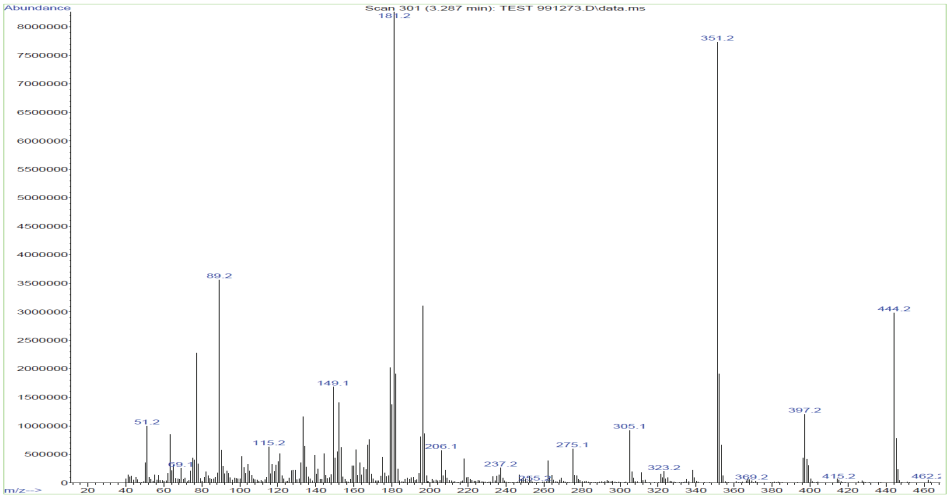
C23H16N4O4S
Mw=444

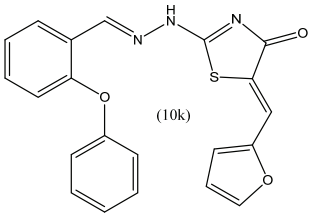






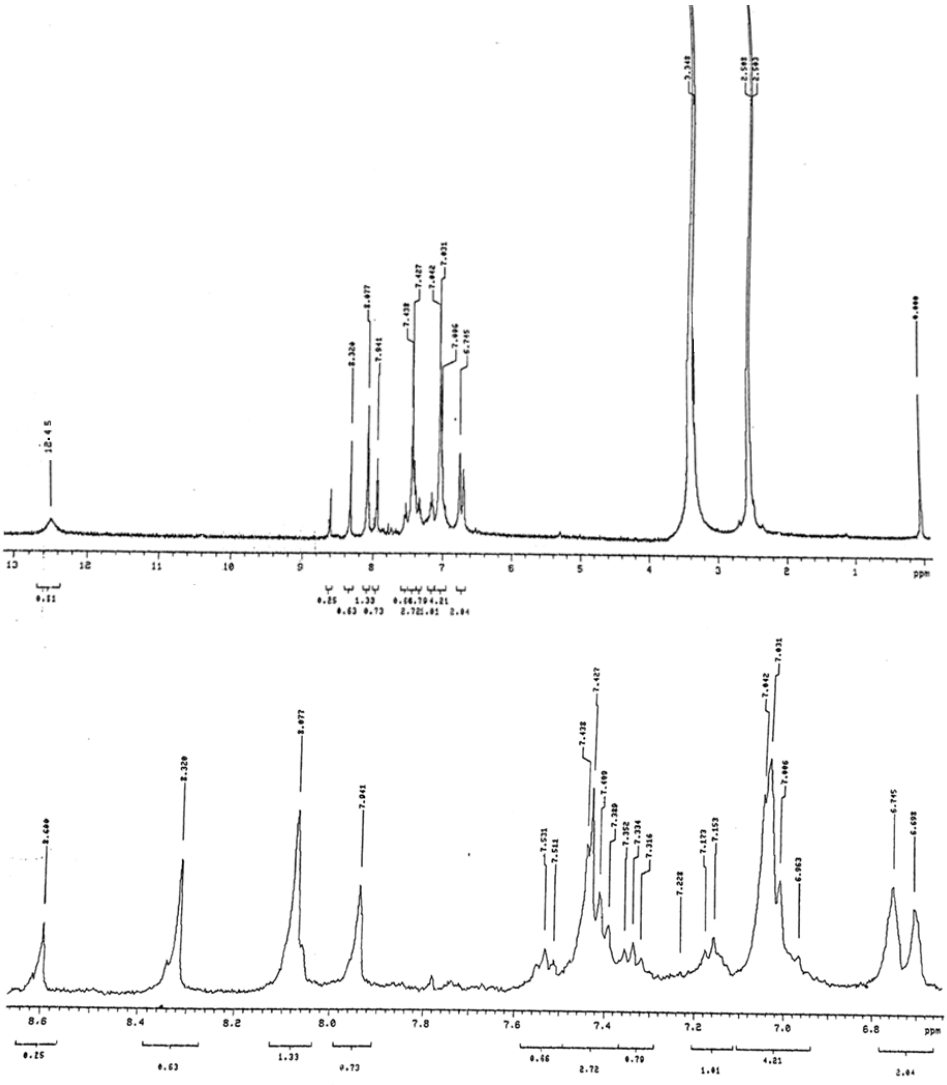
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991273.D
Operator :
Acquired : 23 Jul 2007 22:31 using AcqMethod test.M
Instrument : MSD
Sample Name: 4NO2
Misc Info :
Vial Number: 1

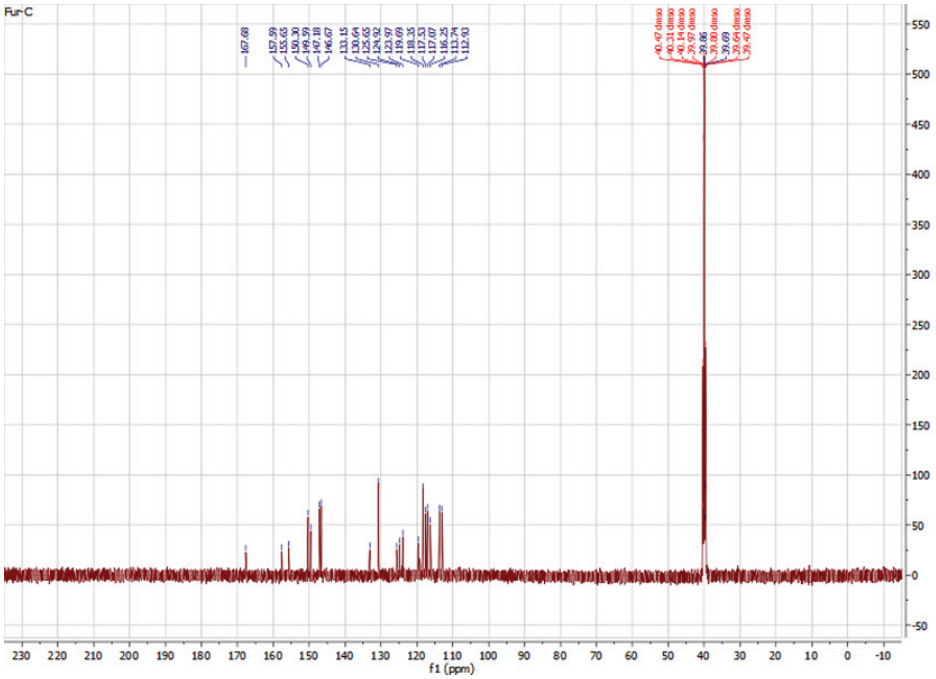




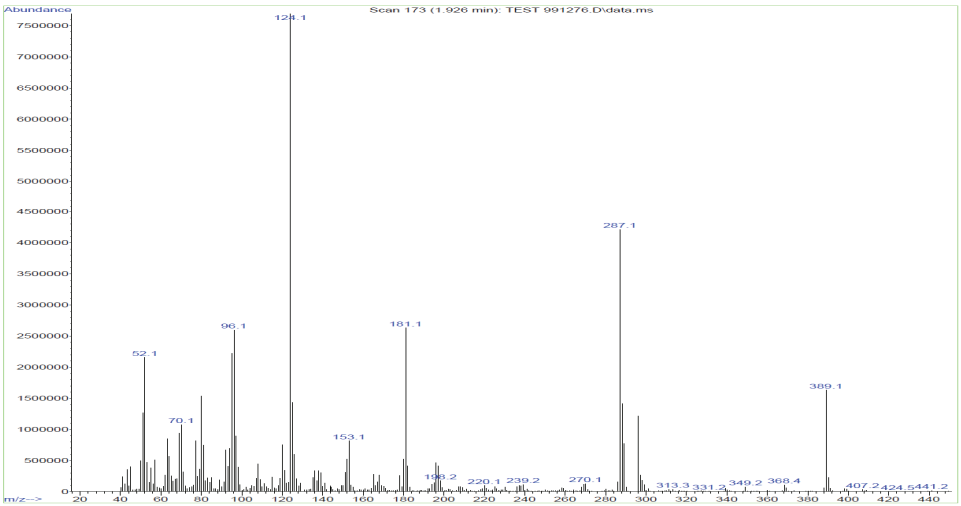
(10k)

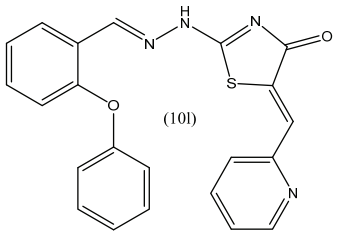
C21H15N3O3S
Mw=389





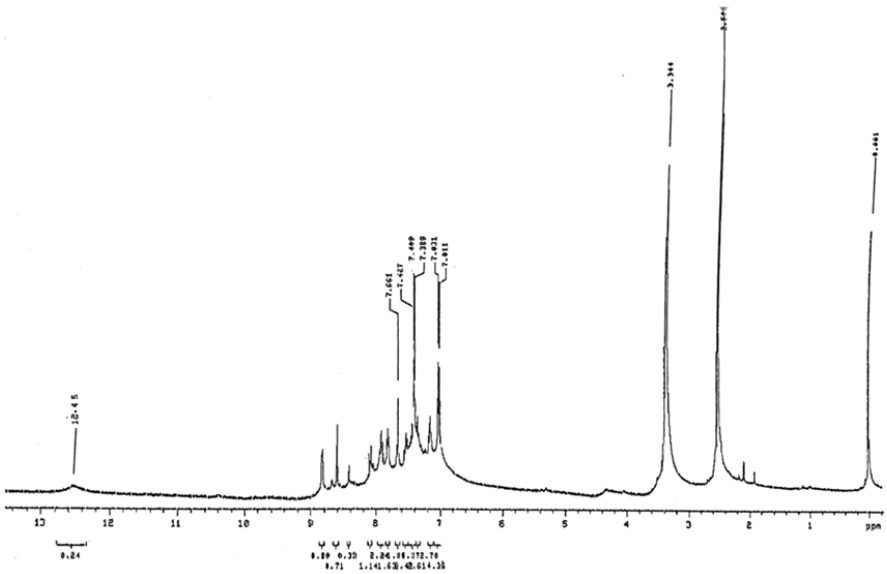
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991276.D
Operator :
Acquired : 23 Jul 2007 23:05 using AcqMethod test.M
Instrument : MSD
Sample Name: Fur
Misc Info :
Vial Number: 1

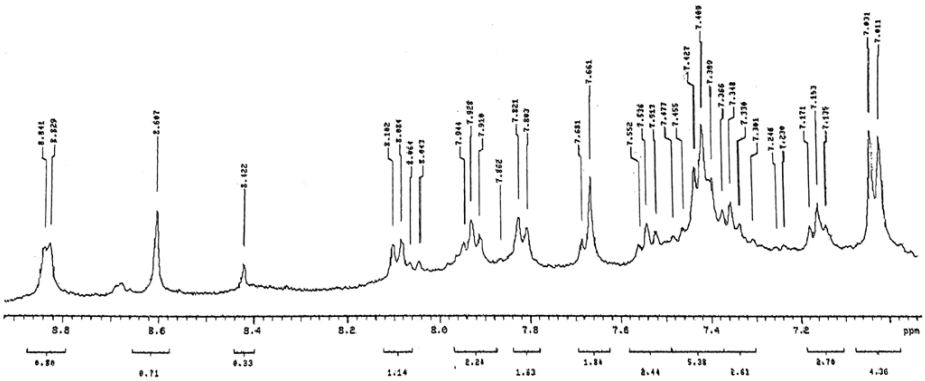


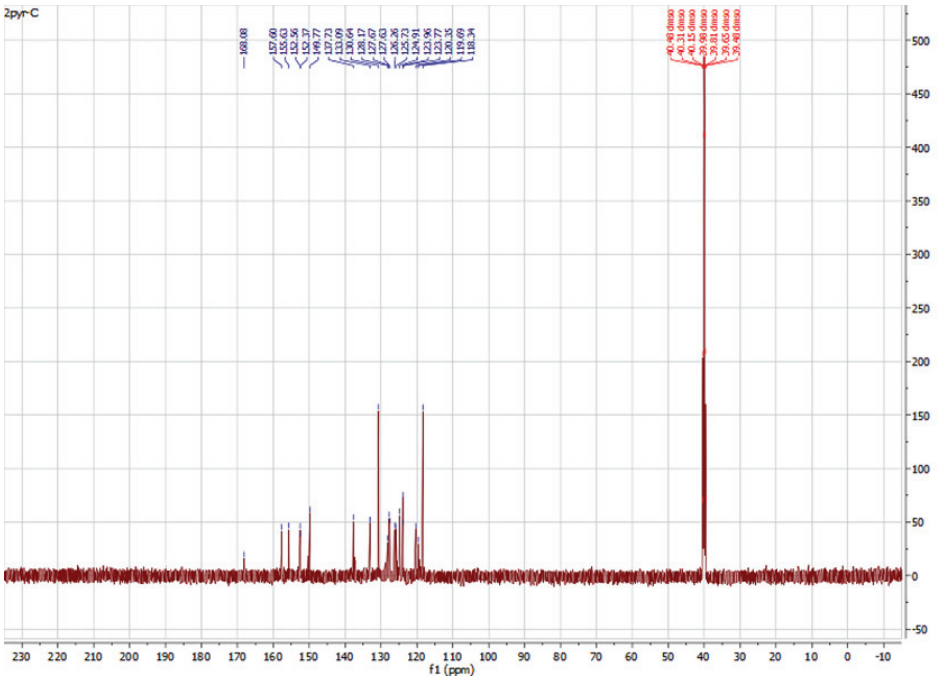


(10l)

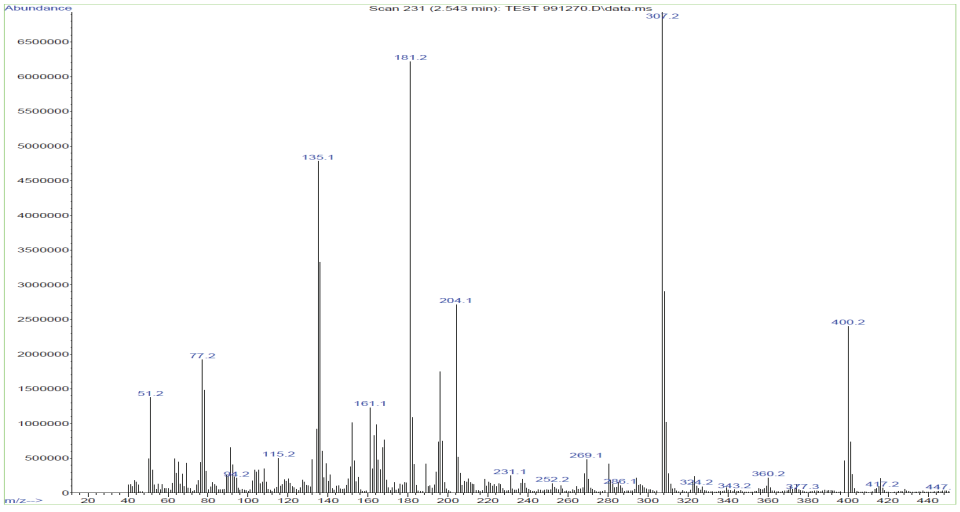
C22H16N4O2S
Mw=400

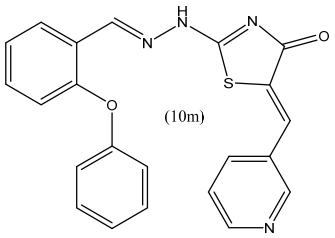






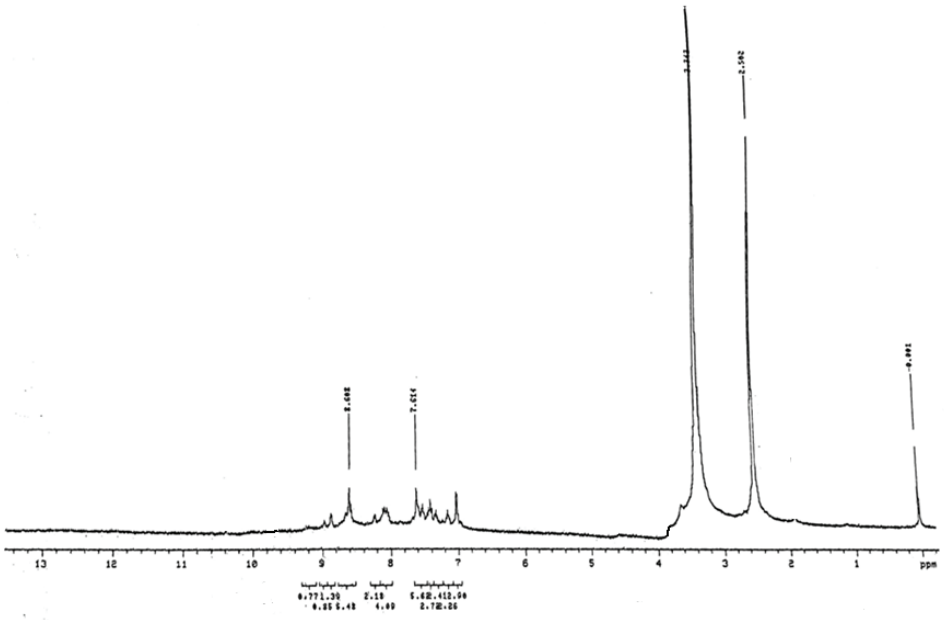
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991270.D
Operator :
Acquired : 23 Jul 2007 21:57 using AcqMethod test.M
Instrument : MSD
Sample Name: 2Pyr
Misc Info :
Vial Number: 1

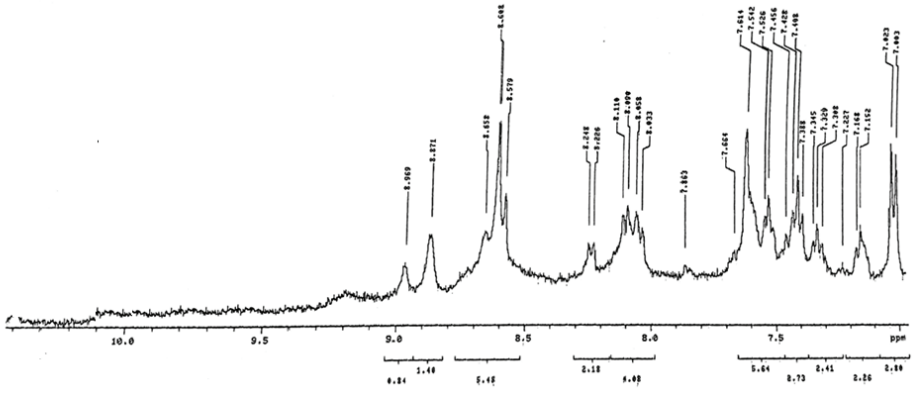


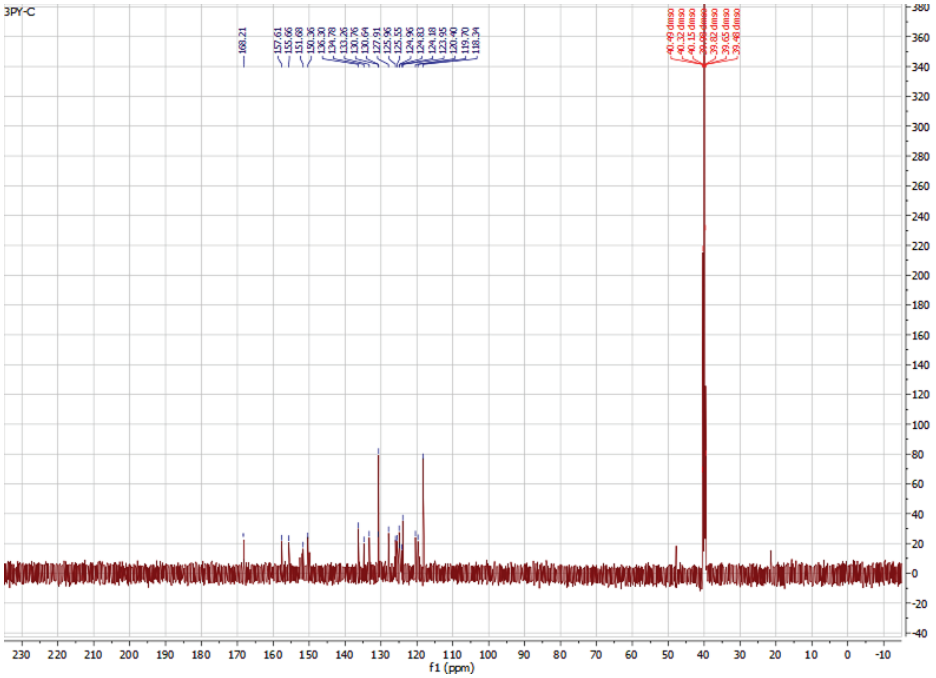


(10m)

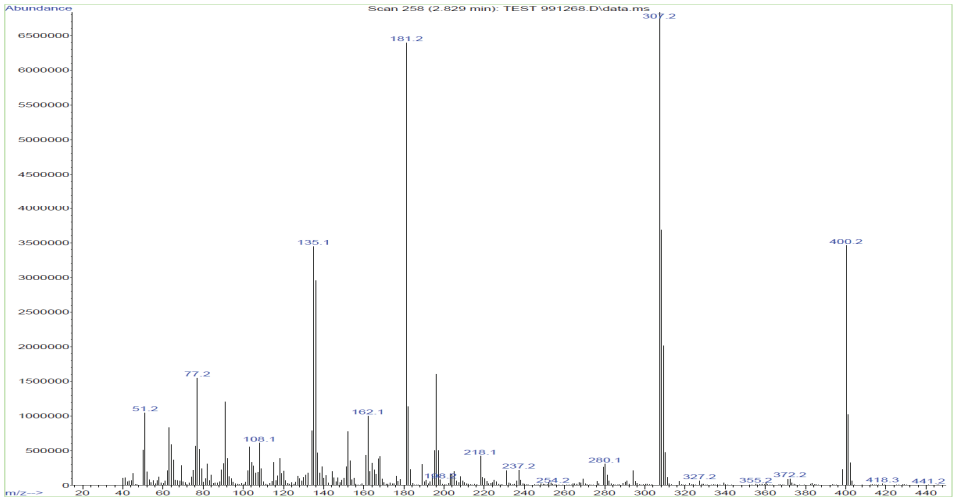
C22H16N4O2S
Mw=400

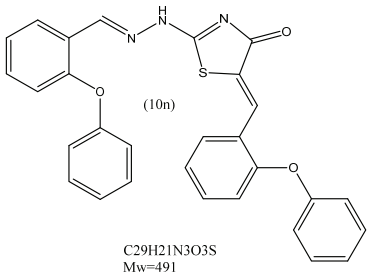






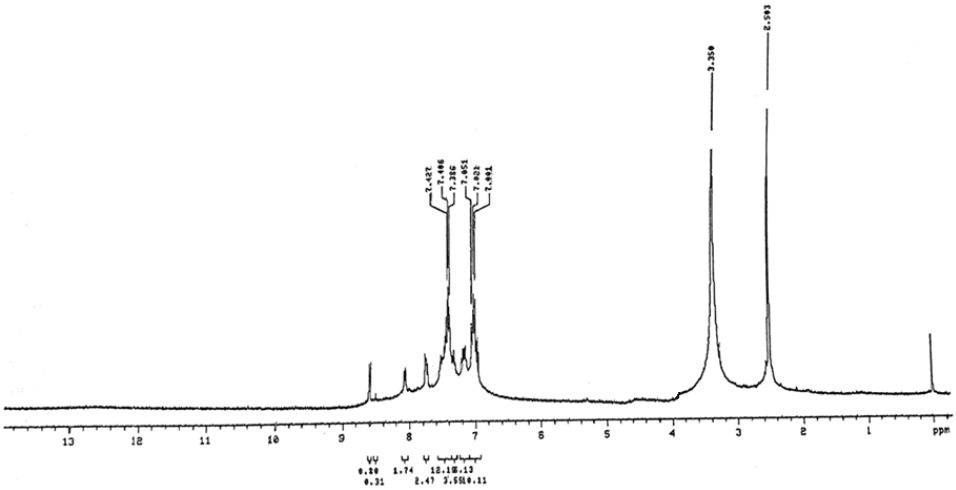
File :C:\MSDCHEM\3\DATA\Snapshot\TEST 991268.D
Operator :
Acquired : 23 Jul 2007 21:28 using AcqMethod test.M
Instrument : MSD
Sample Name: 3Pyr
Misc Info :
Vial Number: 1

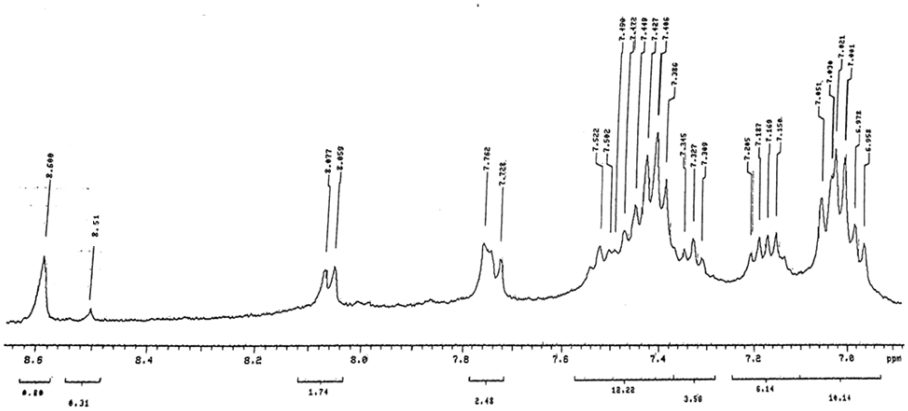


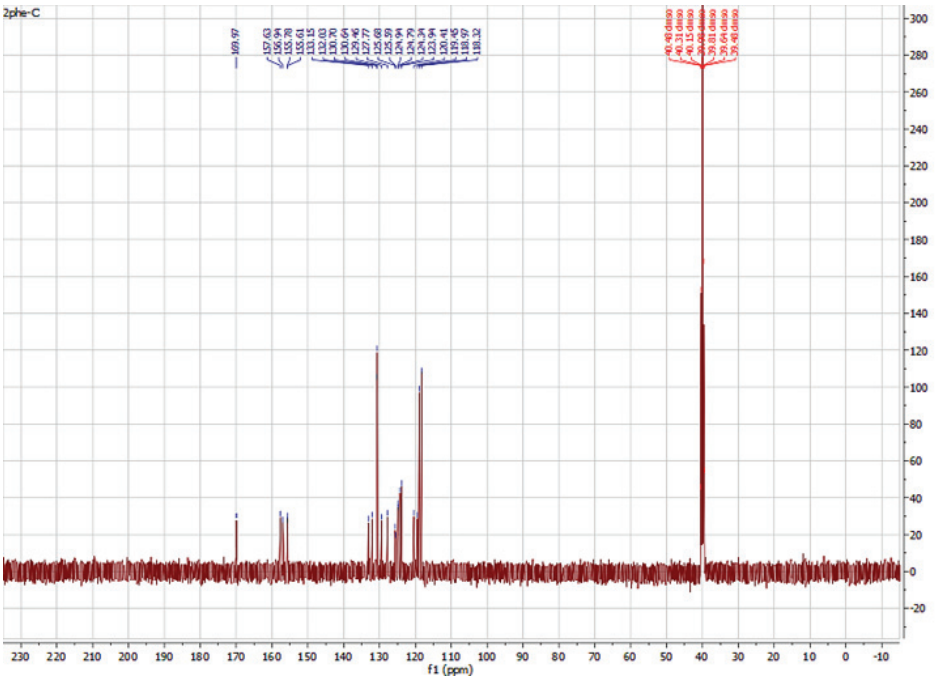


(10n)

C29H21N3O3S
Mw=491







File :C:\msdchem\3\DATA\2PHENOXY(تصویری).D
Operator : ahoupai
Acquired : 13 Dec 2010 13:03 using AcqMethod test dp.M
Instrument : MSD Direct Probe
Sample Name: 2phenoxy
Misc Info :
Vial Number: 1