ol000225e

Supporting Informations:

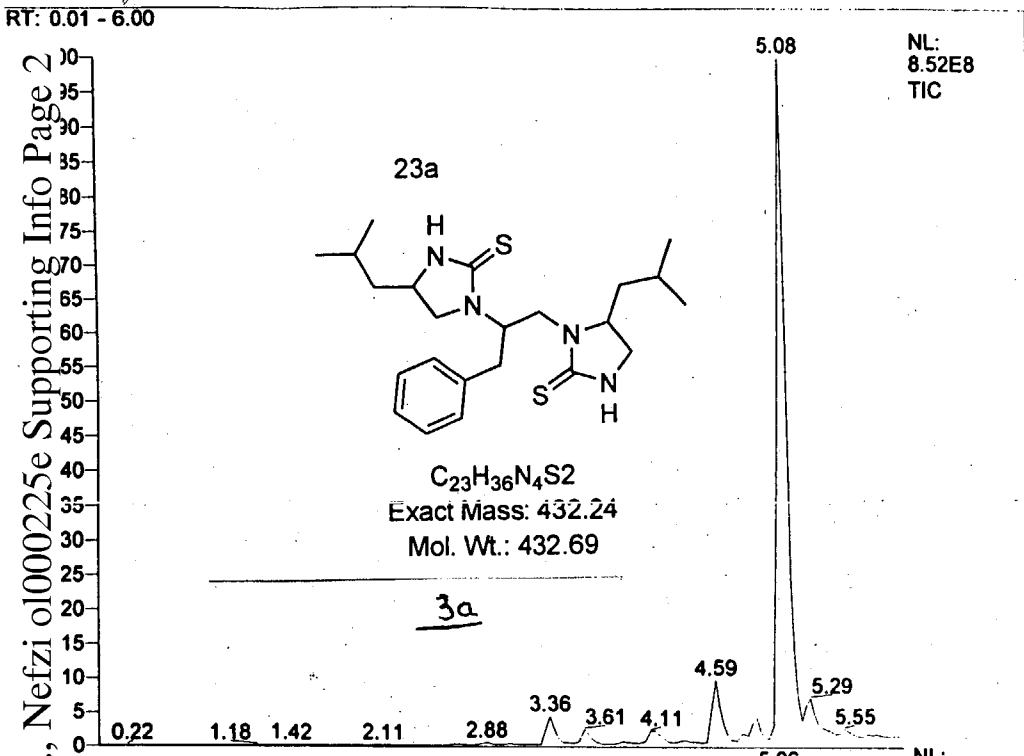
Experimental procedure:

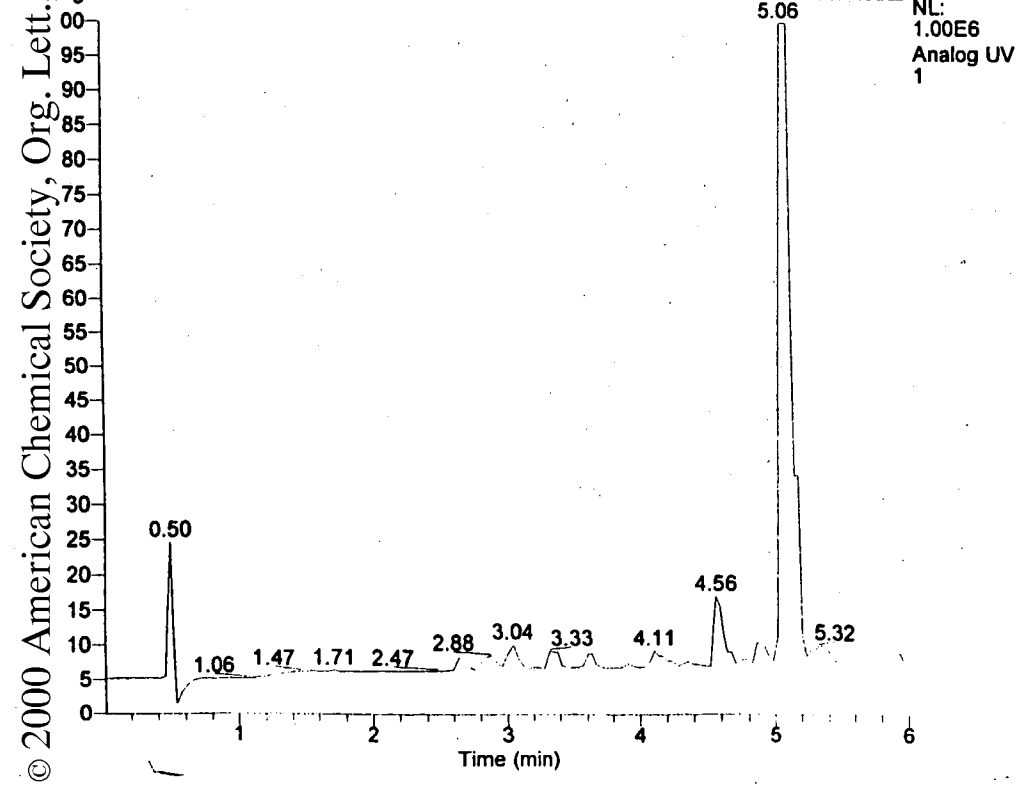
1) Tripeptide synthesis: 100 mg p-methylbenzydrylamine (MBHA) resin (0.1 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet. Reactions were carried out in 10 ml polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIPEA) in dichloromethane (DCM), the resin was washed with DCM. The first amino acid (Boc-Xaa-OH, 6eq) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 6eq) and diisopropylcarbodiimide (DIPCDI, 6eq) in anhydrous DMF for 60 min. Following removal of the Boc group with 55% TFA in DCM and washing with DCM (4x) neutralization with a solution of 5% DIEA in DCM (2X), the resin is washed with DCM (2x) and the second amino acid was coupled in the same conditions. Following Boc deprotection and washes and neutralization the third amino acid is coupled and the Boc group is then cleaved and the resin was neutralized in the same conditions as described before.

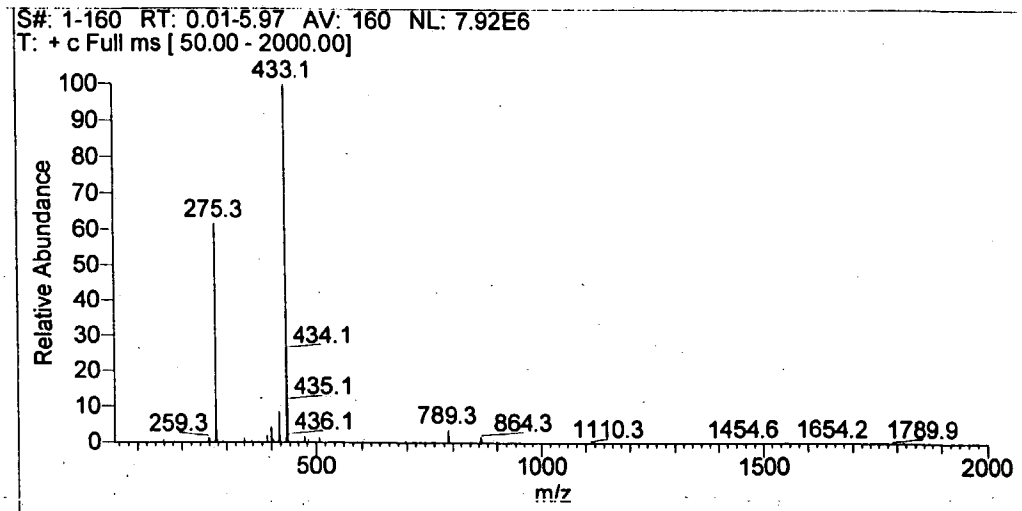
The completeness of amino acid coupling was verified using the ninhydrin test.

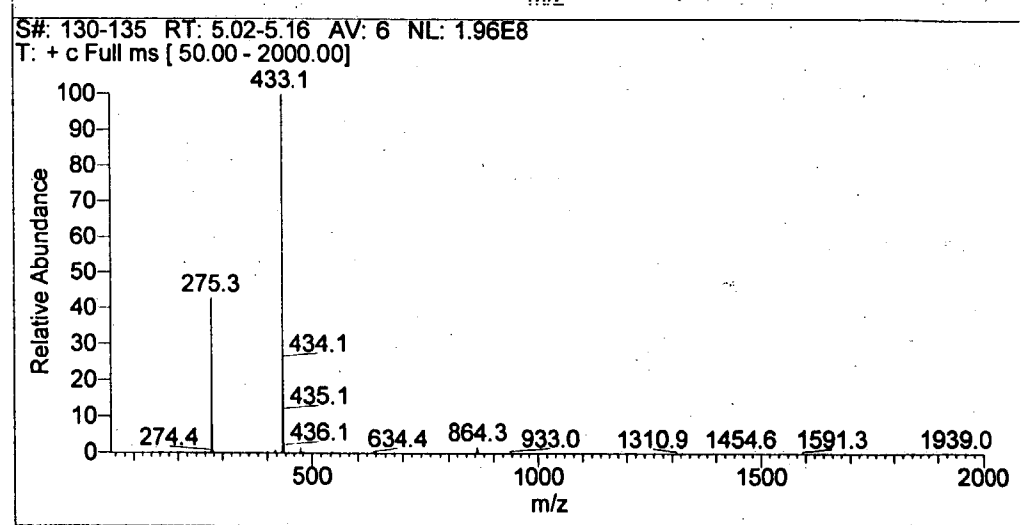
2) Exhaustive reduction of the amide groups: The resin was washed with DCM and dried under vacuum. The reduction was performed in 50 ml kimax tubes under nitrogen. The resin packet (1 meq resin, 100 mg of starting resin), and boric acid (15 fold excess over each amide bond) were added to each tube. Trimethyl borate (15-fold excess over each amide bond) was added, followed by 1M BH_3-THF (40-fold excess over each amide bond). The tubes were heated at 65°C for 72 h, followed by quenching with MeOH at room temperature. The resin was then washed with methanol (4x) and the borane disproportionated by treatment with piperidine at 65°C overnight. The resin was then washed with methanol (2x) and DMF (6x) and dried. The completeness of the reaction was verified by cleavage of controls and LC-MS analysis following cleavage.

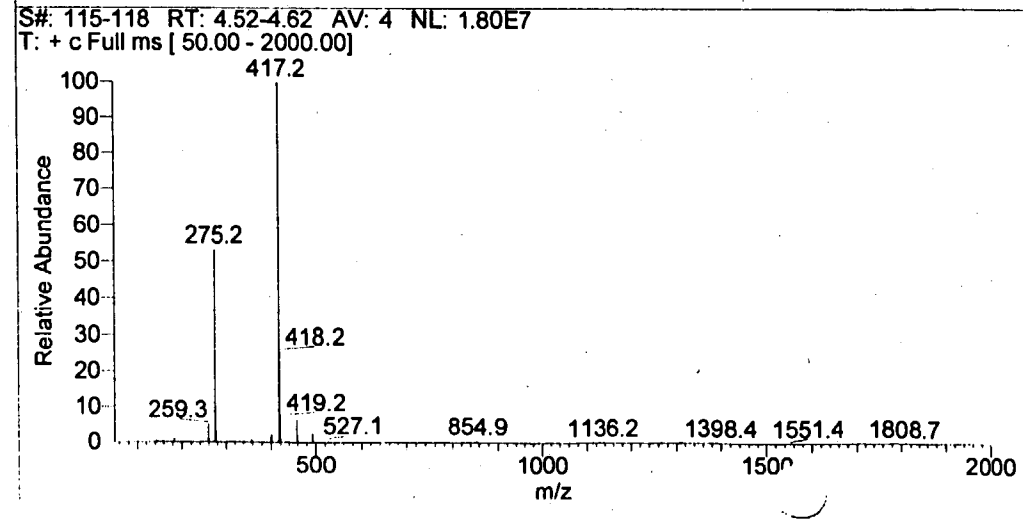
3) Treatment with thiocarbonyldiimidazole: The cyclization occurred following treatment of the resin-bound amines overnight with 5-fold excess of thiocarbonyldiimidazole (0.05 M) in anhydrous DCM. Following cleavage from the resin with anhydrous HF in the presence of anisole (95/5) at 0°C for 90 min, the desired product was extracted with acetonitrile/water (50:50) and lyophilized.

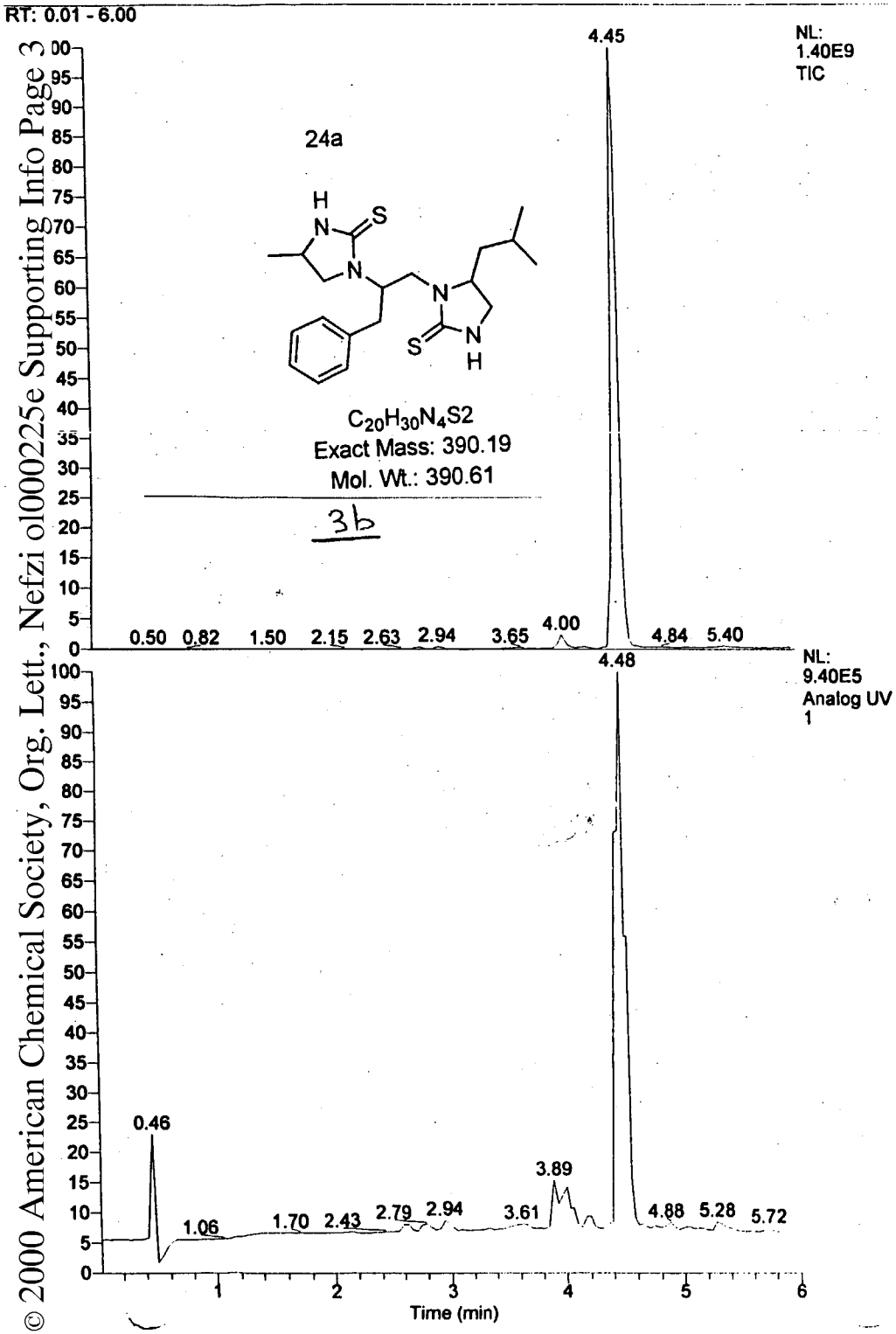


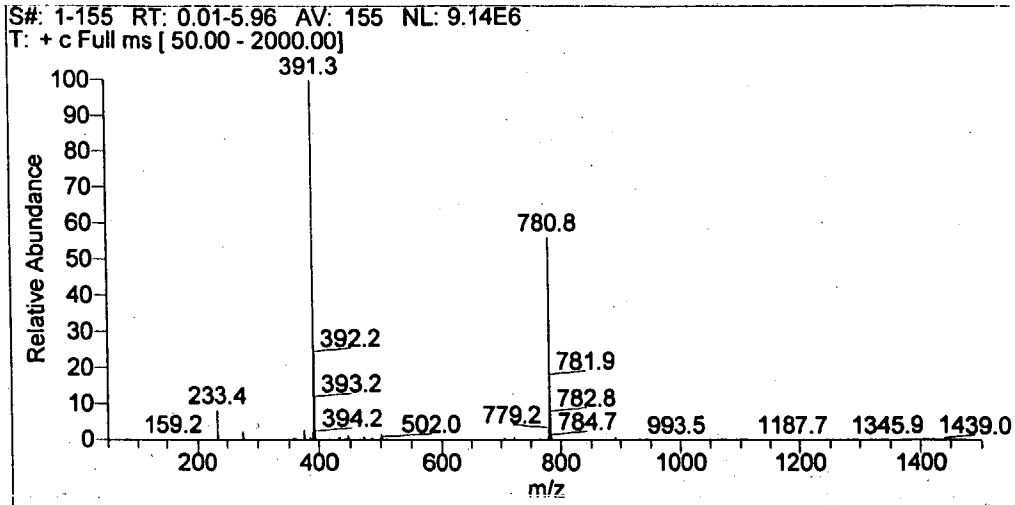


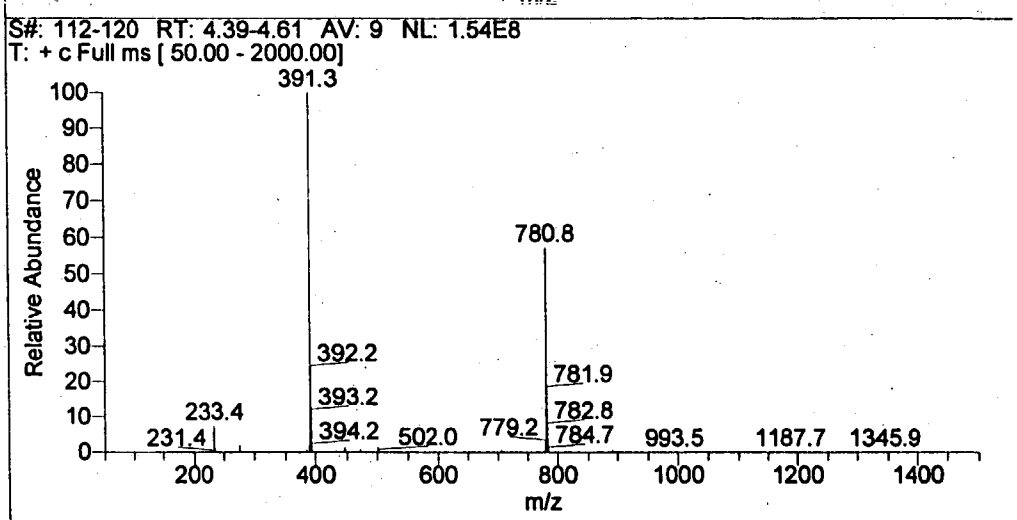


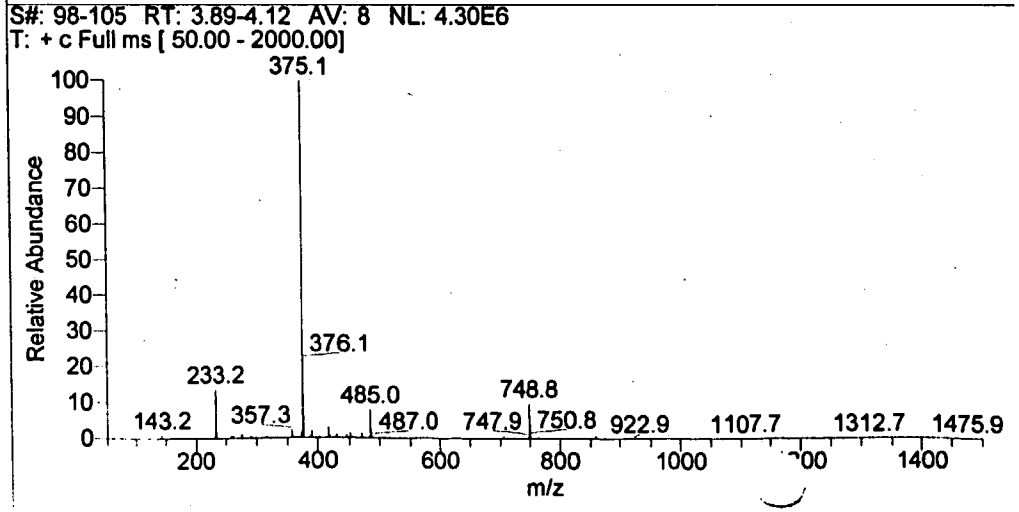








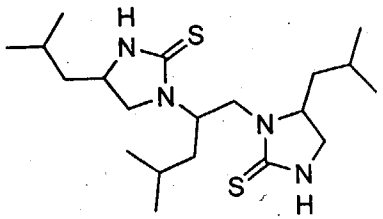




RT: 0.02 - 6.02

NL: 2.94E9 TIC

25a



$C_{20}H_{38}N_4S_2$

Exact Mass: 398.25

Mol. Wt.: 398.67

3c

NL: 1.00E6 Analog UV 1

Time (min)

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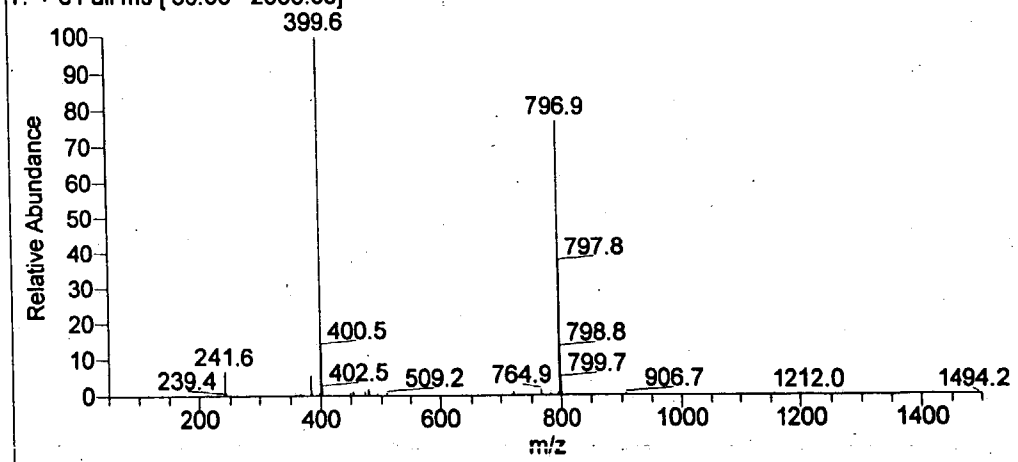
T: + c Full ms [50.00 - 2000.00]



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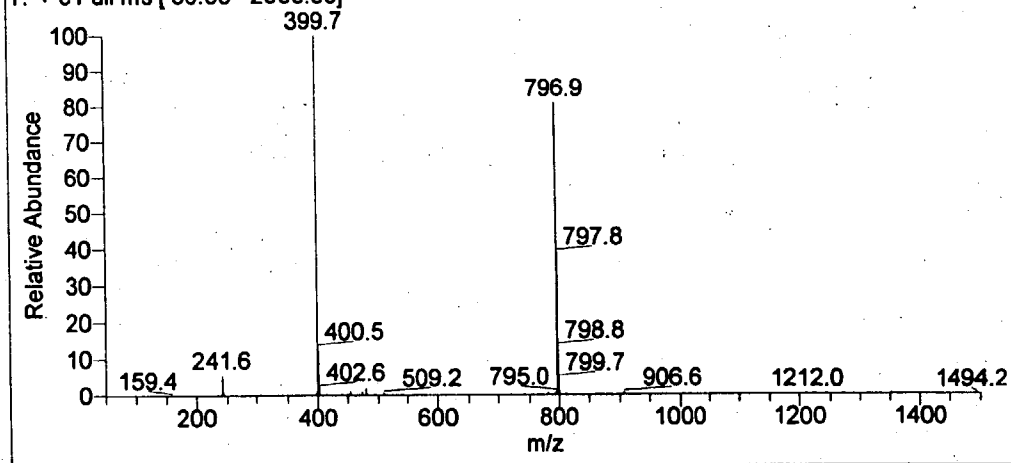
T: + c Full ms [50.00 - 2000.00]



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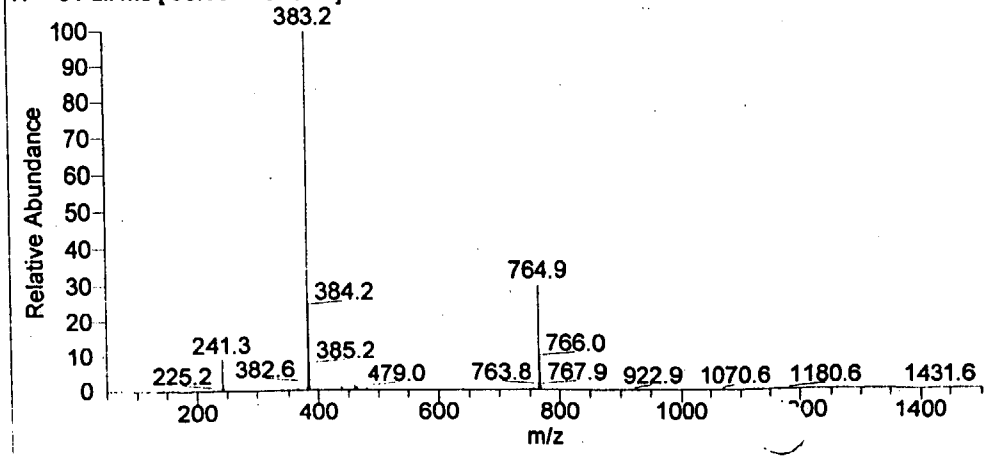
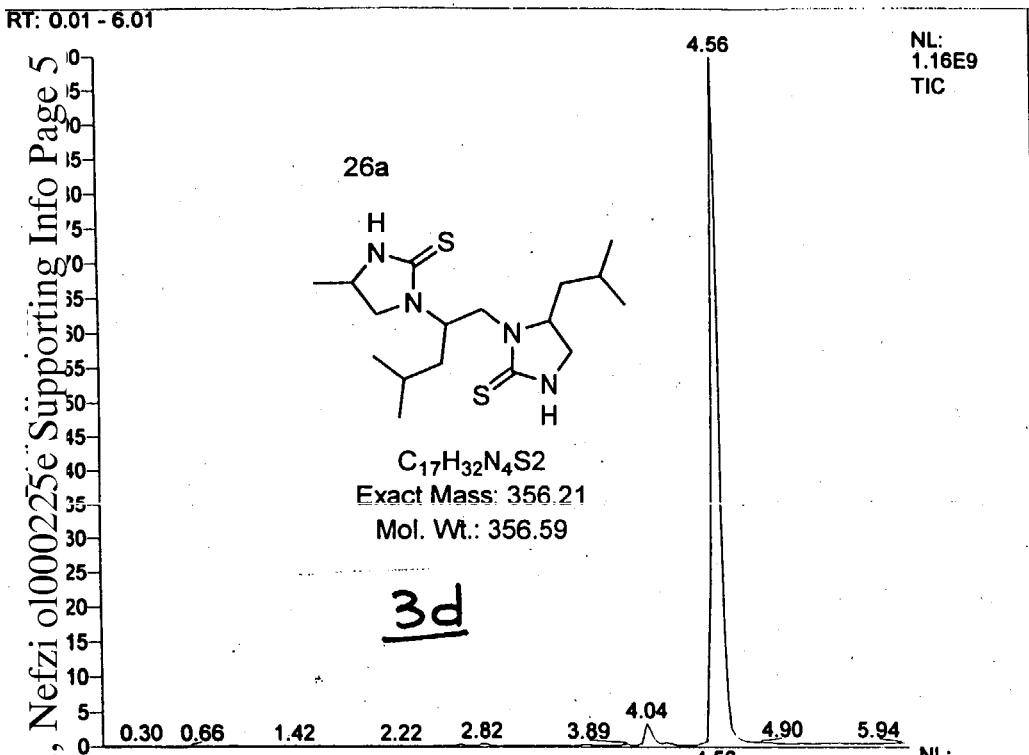
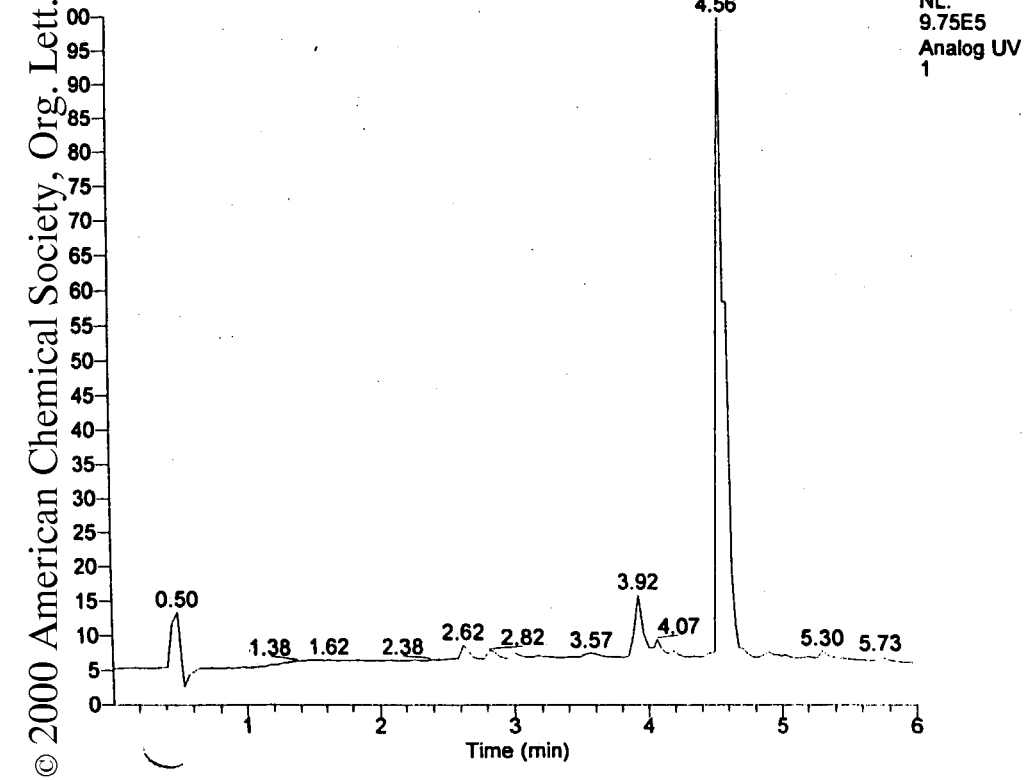
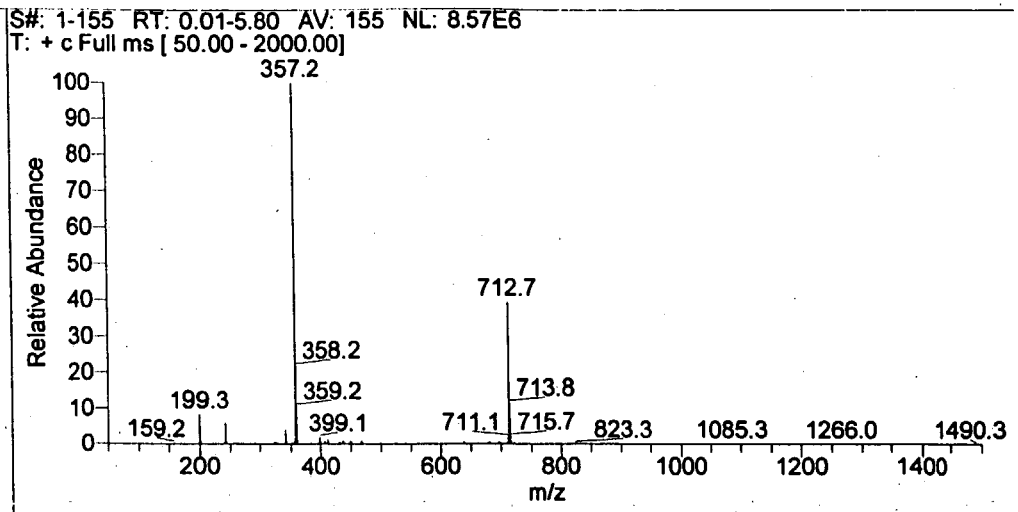
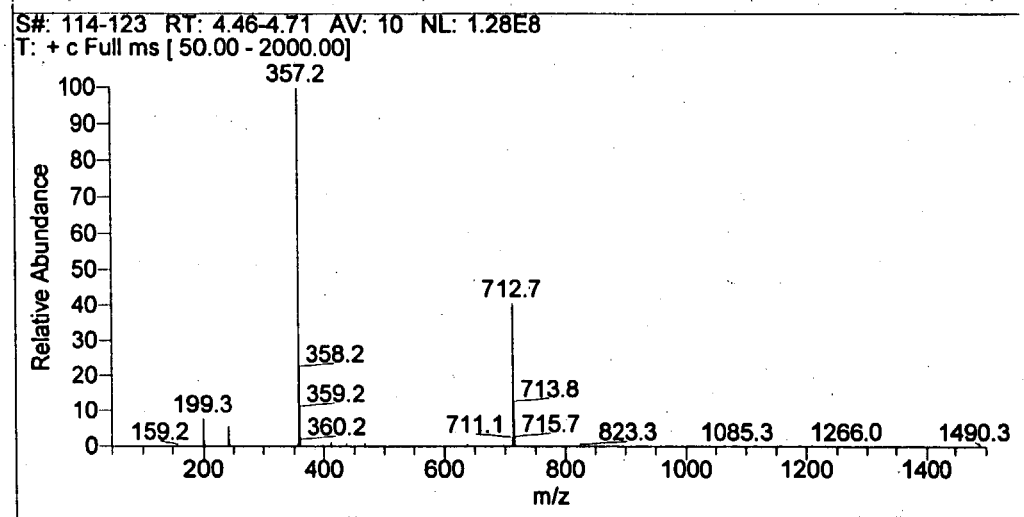
T: + c Full ms [50.00 - 2000.00]

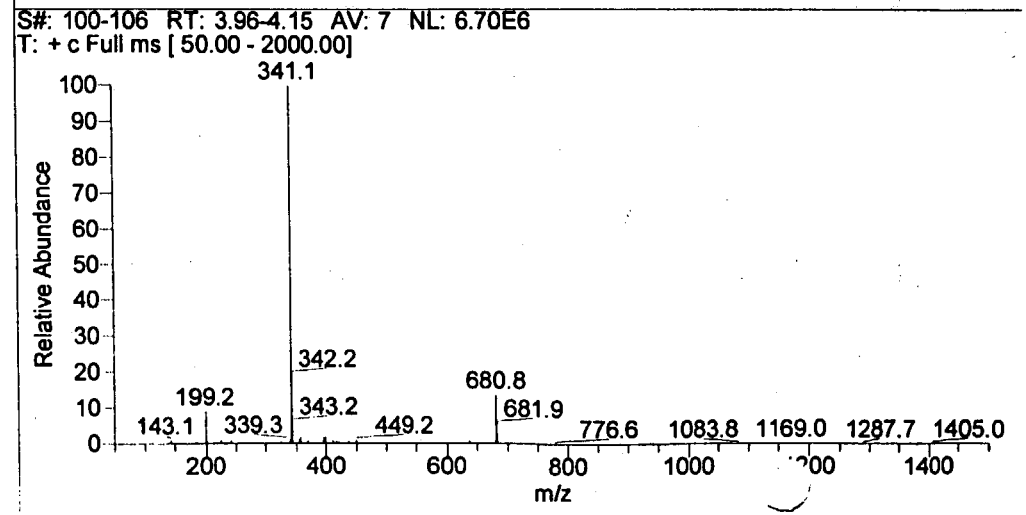












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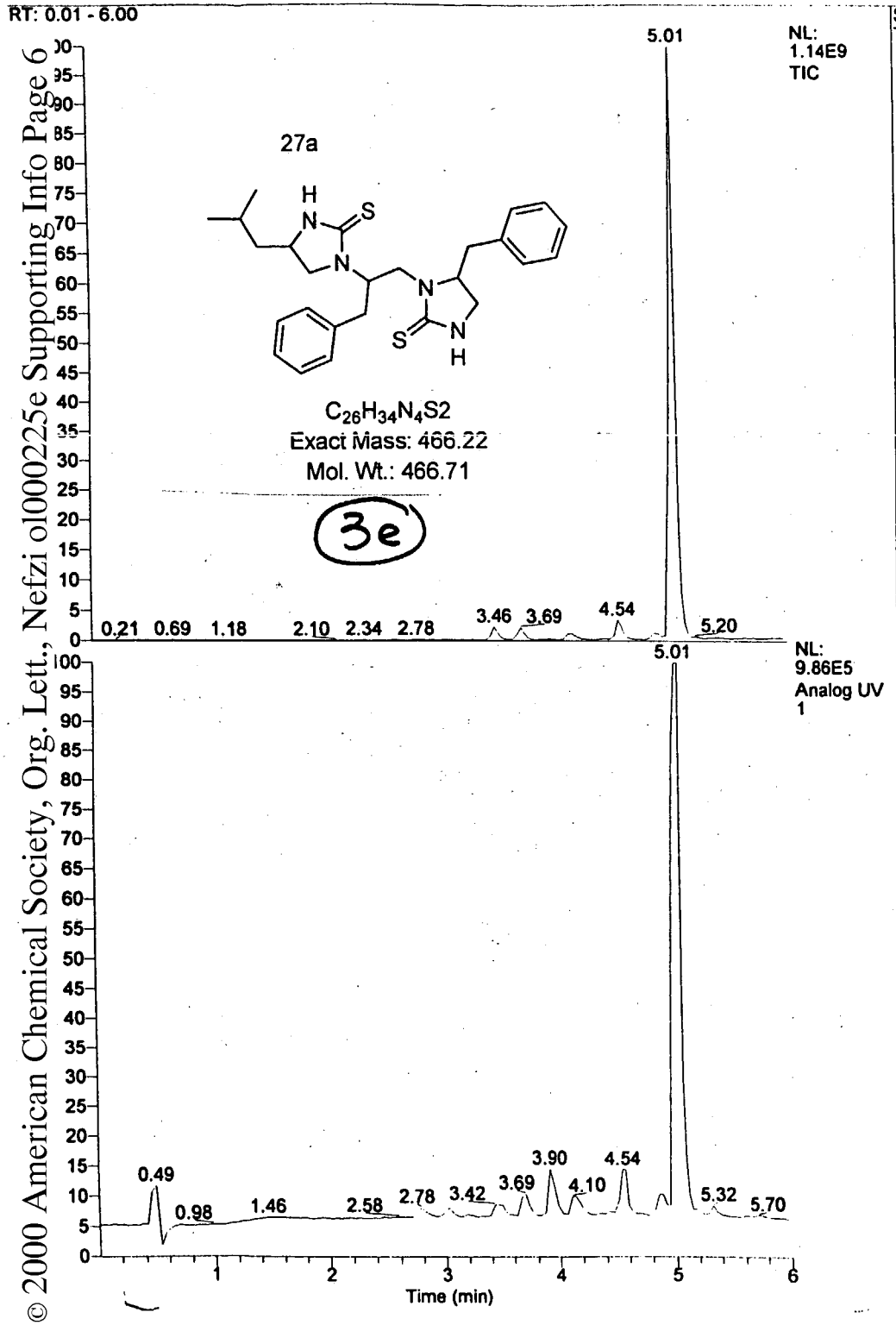

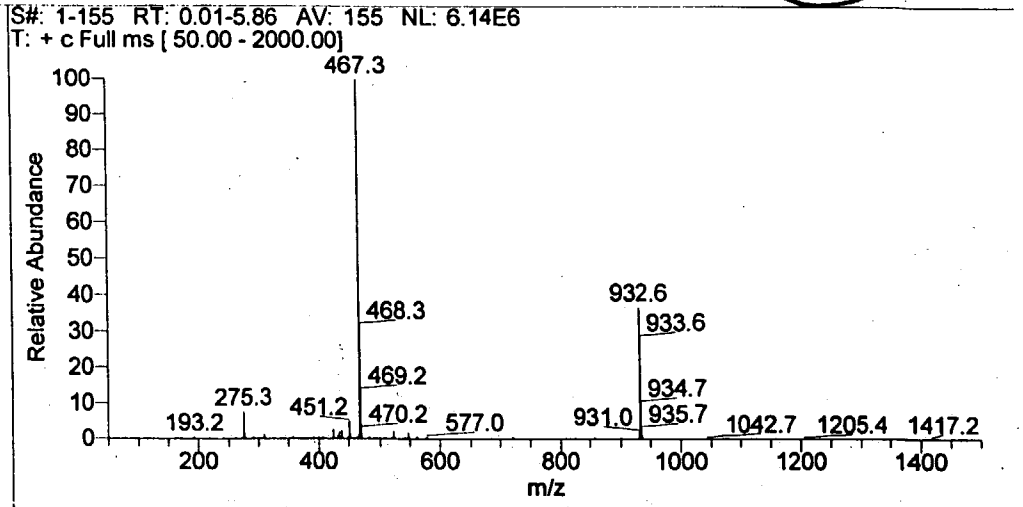

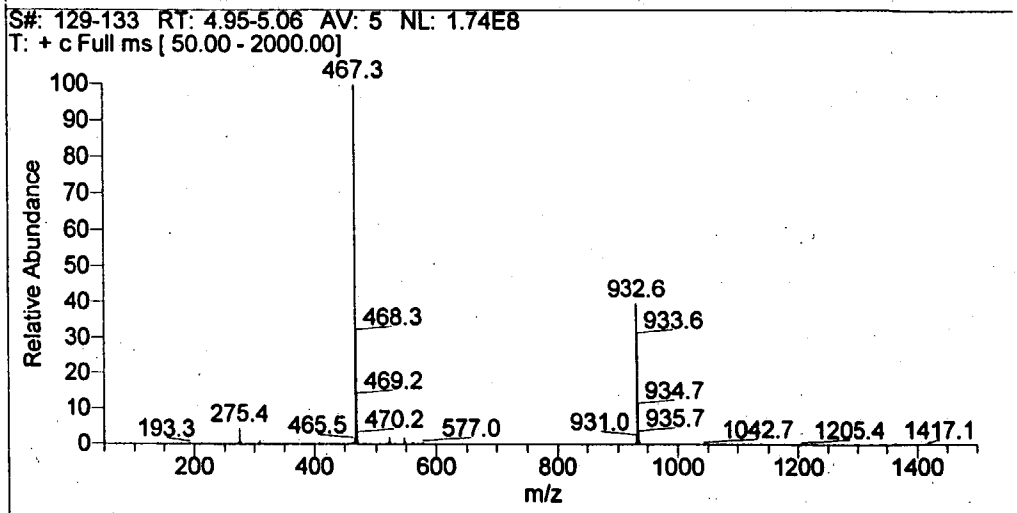

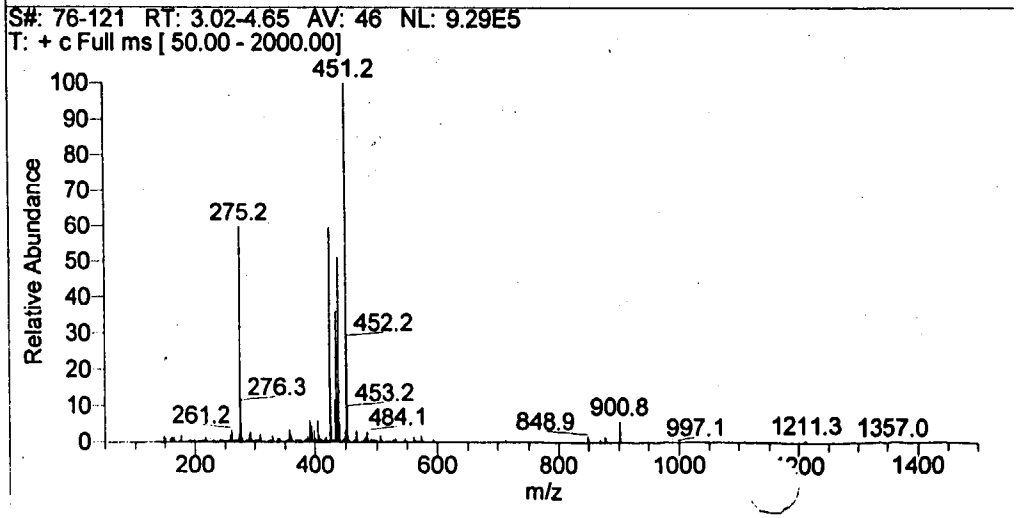

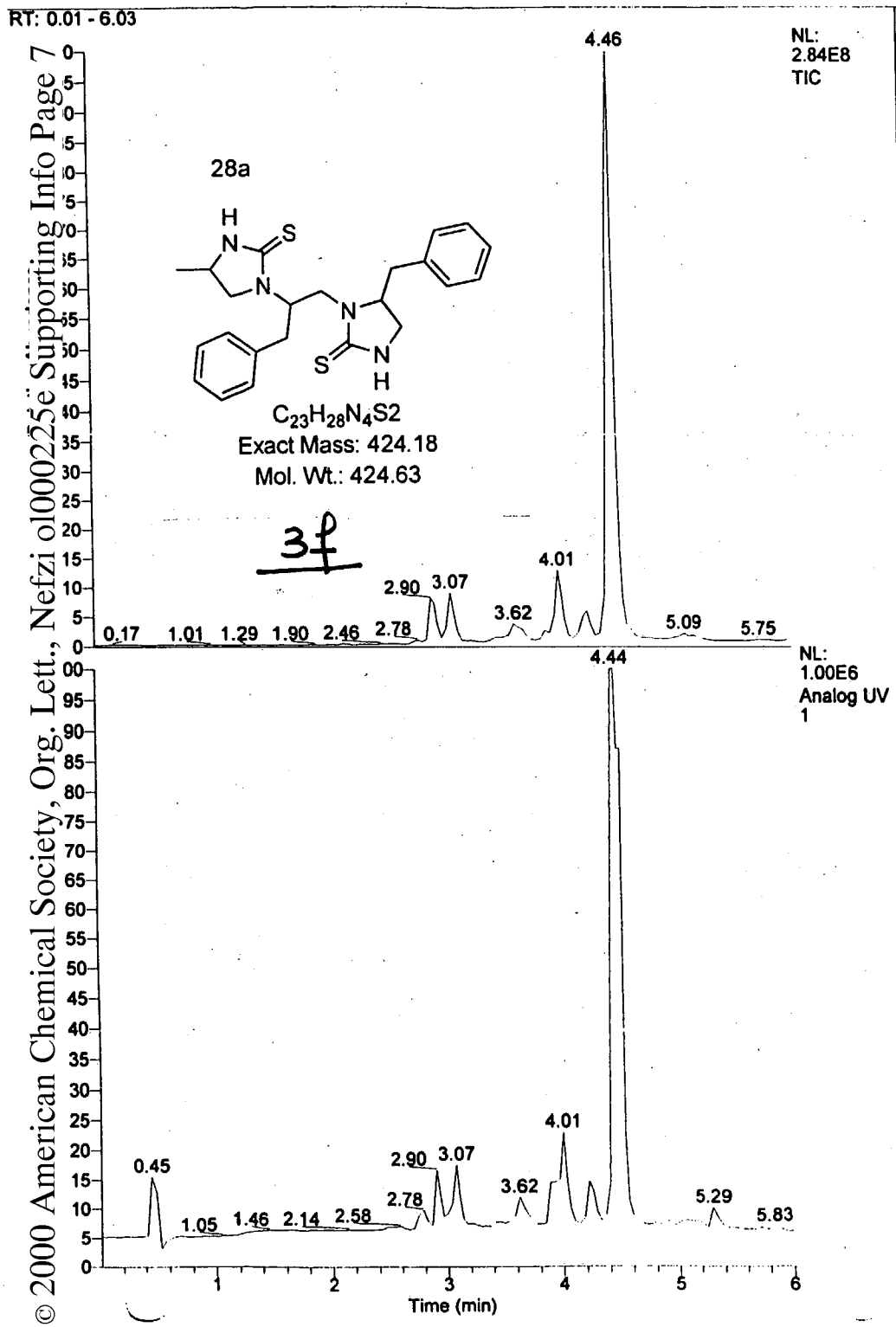

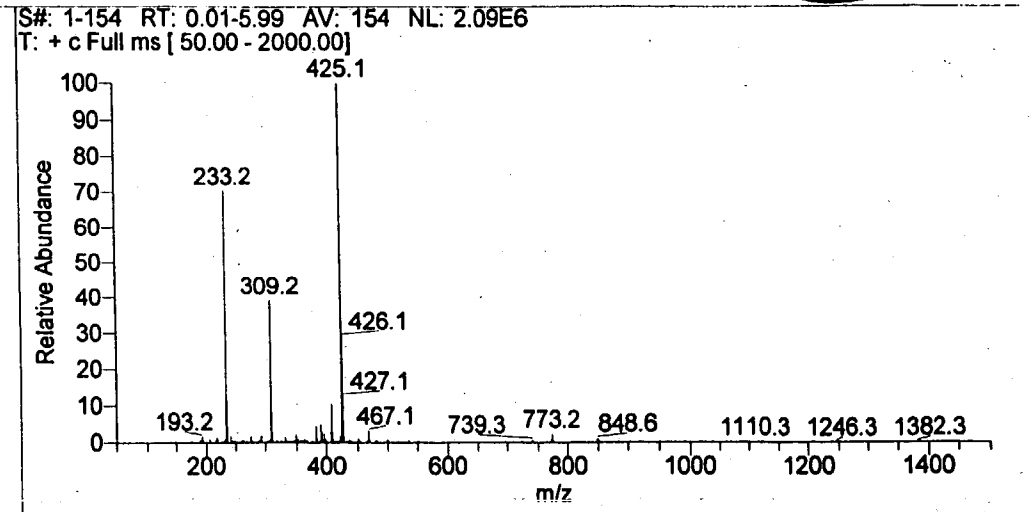

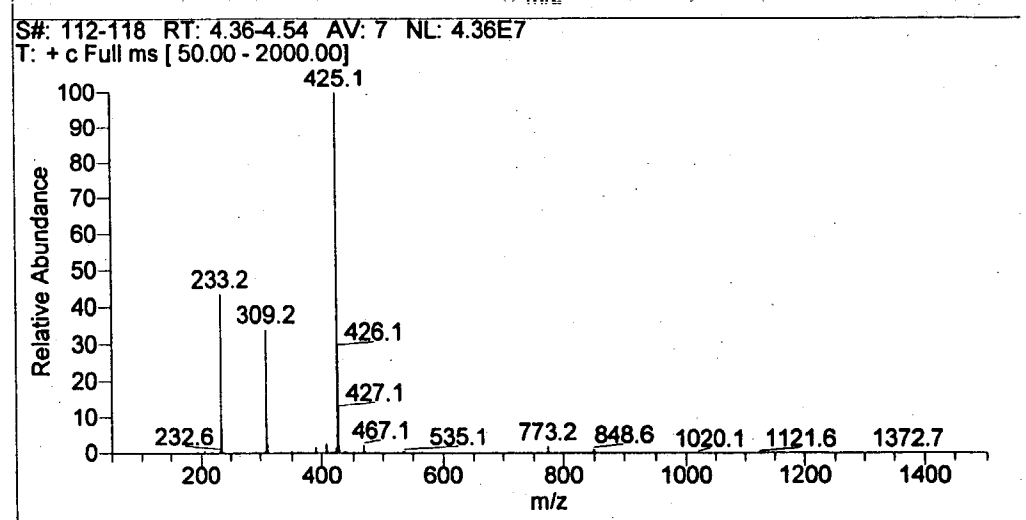

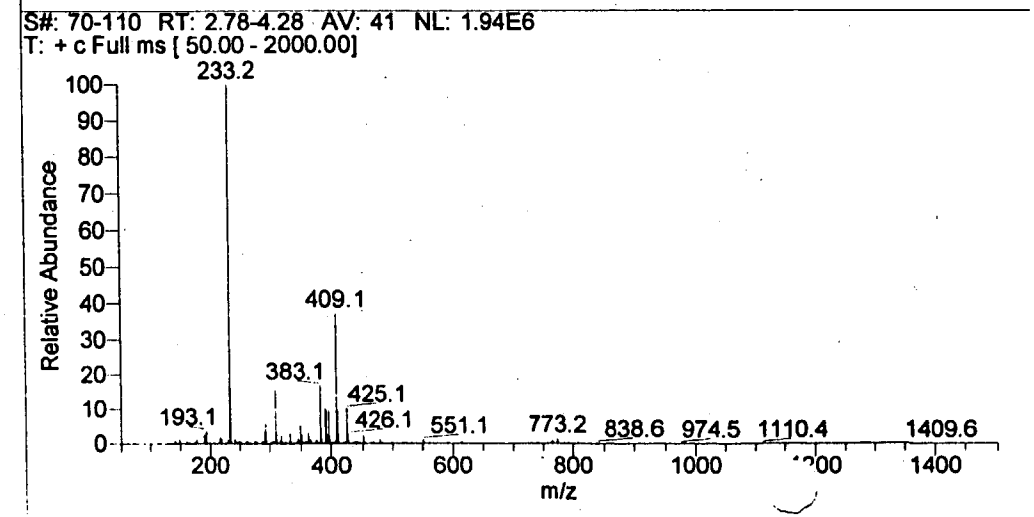

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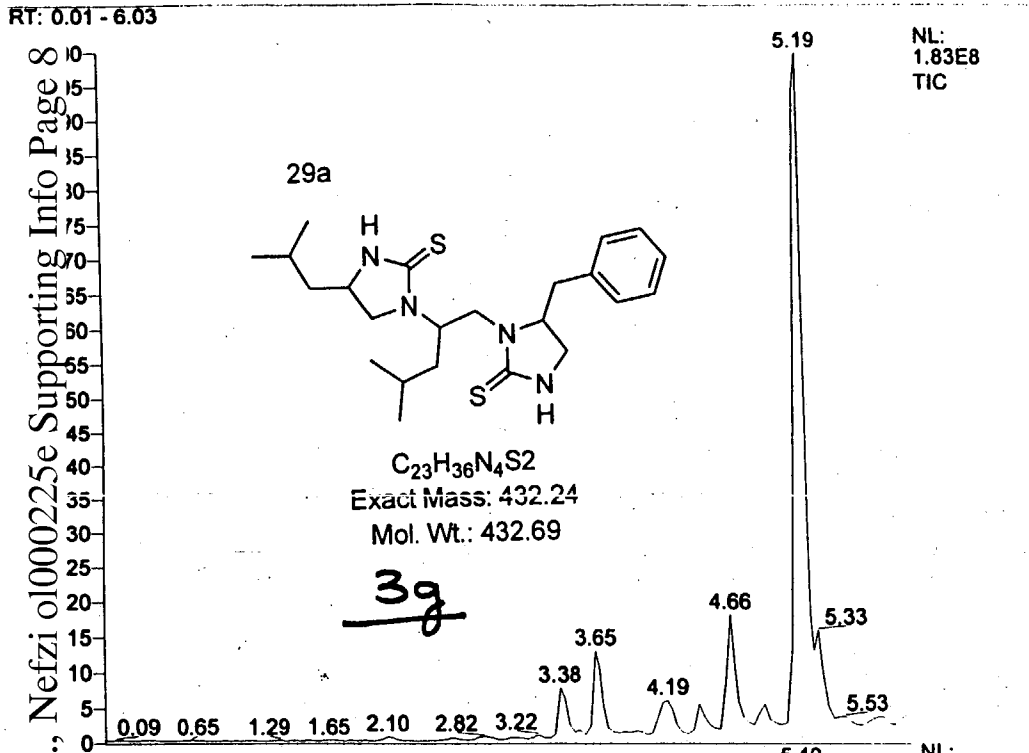

29a

$C_{23}H_{36}N_4S_2$

Exact Mass: 432.24

Mol. Wt.: 432.69