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Exploring the 3-piperidin-4-yl-1*H*-indole scaffold as a novel antimalarial chemotype

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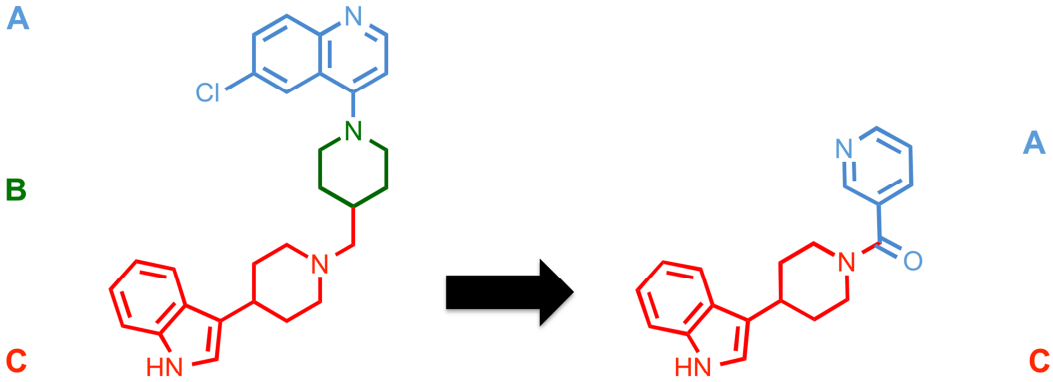

HTS hit (3) **10d**

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Title:

EXPLORING THE 3-PIPERIDIN-4-YL-1*H*-INDOLE SCAFFOLD AS A NOVEL ANTIMALARIAL CHEMOTYPE

Abstract:

A series of 3-piperidin-4-yl-1*H*-indoles with building block diversity was synthesized based on a hit derived from an HTS whole-cell screen against *Plasmodium falciparum.* Thirty-eight compounds were obtained following a three-step synthetic approach and evaluated for anti-parasitic activity. The SAR shows that 3-piperidin-4-yl-1*H*-indole is intolerant to most *N*-piperidinyl modifications. Nevertheless, we were able to identify a new compound (**10d**) with lead-like properties (MW = 305; cLogP = 2.42), showing antimalarial activity against drug-resistant and sensitive strains (EC_{50} values ~ 3 µM), selectivity for malaria parasite and no cross-resistance with chloroquine, thus representing a potential new chemotype for further optimization towards novel and affordable antimalarial drugs.

Keywords: antimalarial, drug lead, indole, reagent-based diversity

1. Introduction:

Malaria is one of the most life-threatening diseases, with almost one-third of the world's population at risk it represents a major public health problem due to its morbidity and mortality.[1, 2] An estimated 198 million cases led to nearly 584,000 deaths in 2013, 90% of which were reported in sub-Saharan Africa.[1] Malaria has a broad impact throughout tropical and subtropical areas of the globe, affecting indigenous populations as well as an increasing number of travelers [3-5]. According to the 2014 World Health Organization (WHO) Malaria Report, about 78% of deaths attributed to malaria occur in African

children under age of 5 [1]. In addition to the human cost of malaria, the economic burden of the disease is significant with a huge impact upon individual households due to lost wages and healthcare costs as well as detrimental affect on the national scale with about 40% of African health budgets spent on malaria every year [6].

Five *Plasmodium* species are known to infect humans and cause malaria: *P. vivax, P. ovale, P. malariae, P. knowlesi* and *P. falciparum* [7]. Of these species, *P. falciparum* is the most widespread in nearly all malaria endemic countries and is responsible for the majority of malaria mortality.[8]. The parasite has a complex life cycle, which involves alternate developmental stages within the human host and the female *Anopheles* mosquito [2, 9]. Within the human host, the asexual erythrocytic stage of the infection accounts for the clinical symptoms and constitutes the target for most chemotherapeutics used in the clinic, such as chloroquine (**1**) (**Figure 1**) and artemisin combination therapies (ACTs) [9-11].

The emergence of drug resistance has already rendered once-effective malaria treatments less reliable. Today, ACTs are the front line therapies for treatment of symptomatic malaria, however, we are at risk of losing their utility due to the emergence and spread of resistance [12-14]. The *Plasmodium* parasite has demonstrated an ability to evolve and adapt to every drug introduced thus far, and with this in mind, it is crucial that efforts are made to develop new analogues active against resistant strains, to identify new drugs, or even identify new therapeutic targets in the parasite [11, 15].

The strategies currently used for the development of novel antimalarial drugs include many approaches such as: the discovery of new active molecules from natural sources [16-23], repurposing of commercially available drugs, the development of hybrid compounds [24], and rational drug design with chemical modifications of existing antimalarials and hits [25-27], amongst others. Also, a great number of drug discovery and development programs from both public and private institutions, and public-private partnerships, using phenotypic screening with sensitive and resistant strains of *P. falciparum* have been pursued in the past recent years. Among them were large libraries from Novartis, St. Jude Children's Research Hospital and GlaxoSmithKline (GSK) [28, 29].

Joining these international efforts, we analyzed the recently disclosed Tres Cantos Antimalarial Set (TCAMS) from GSK to identify novel indole-based antimalarials as starting points for the development of next –generation antimalarial drugs. Indoles are an emerging antimalarial fragment present in several lead drug candidates with new mechanisms of action, such as the spiroindolone (**2**) [30-34] and aminoindoles classes [33, 35]. We were intrigued by TCMDC-134281 (**3**) (**Figure 1**), which emerged as a very potent antiplasmodial compound, with a reported EC_{50} of 34 nM against the chloroquine-sensitive

P. falciparum 3D7 strain. Additionally, compound **3** did not demonstrate measurable cytotoxicity as its EC_{50} against the human HepG2 hepatoma cell line was greater than 10 µM [28].

However, this compound showed poor drug-like properties and cross-resistance with chloroquine, possibly due to the presence of the 4-aminoquinolinyl fragment, which is the essential pharmacophore of chloroquine (CQ). To address these liabilities, we decided to remove one of the piperidin-4-yl fragments and to replace the 4-aminoquinoline fragment. This resulted in an overall reduction of the compound's LogP and MW and chemically differentiates the molecule from the 4-aminoquinoline antimalarials, which we hypothesized would overcome the observed cross-resistance with CQ. We herein report a structure-activity study aiming to explore the antimalarial potential of the 3-piperidin-4-yl-1*H*-indole scaffold (**Figure 1**). We synthesized three series of derivatives following a reagent-based diversity approach, in a total of 38 compounds, and assayed them against the multidrug resistant *P. falciparum* Dd2 strain at a fixed 5 µM concentration. The most potent derivatives were further profiled in dose-response against both *P. falciparum* drug-resistant (Dd2) and sensitive (3D7) strains to determine activity and parasite selectivity.

2. Results and Discussion:

2.1. Chemistry

We first resynthesized the original hit compound **3,** following a six-step synthesis, as shown in **scheme 1**. Starting with the condensation of the indole with N-benzyl-4-piperidone in the presence of a base, compound **4** was obtained in high yield (98%). Subsequent debenzylation with concurrent olefin reduction afforded the common intermediate 3-piperidin-4-yl-1H-indole (**5**) with 96% yield. Compound **5** was coupled with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid to give the amide intermediate **6** in moderate yield (60%). Reduction of the carbonyl group afforded compound 7, followed by Boc-deprotection to yield the amine compound **8**. Compound **3** was obtained by nucleophilic aromatic substitution of 4,6-dichloroquinoline with the amine intermediate **8** (**Scheme 1**).

The first series of derivatives was designed to explore the structure-activity relationship (SAR) of N-piperidinyl modifications. These compounds were obtained by reductive

amination[36] of the amine intermediate **5** with the corresponding aldehydes to give the title compounds **9a-s** (**Scheme 2**), with yields ranging from 25%-100% (**Table 1**). All but two derivatives from this series were obtained using commercially available aldehydes. Aldehydes **A** and **B**, used in the synthesis of compounds **9o** and **9n**, were previously obtained by reductive amination of terephthalaldehyde with piperidine or morpholine, respectively (**Scheme 2**).

We next synthesized a series of amide derivatives to assess the importance of the basic amine versus an amide linkage and resulting rotational hindrance. These compounds were synthesized by coupling the amine intermediate **5** with commercially available acid chlorides under standard Schotten Baumann conditions to afford the desired compounds **10a-f** (**Scheme 2**), in 25% to quantitative (Quant.) yields (**Table 1**). To access the derivatives **10g-j** (**Scheme 2**) in high yields we screened several coupling reagents and found PyBOP to give the best results (**Table 1**). Analogue **10j**, which consisted of the bis-amide compound with a benzyl linker, was synthesized by reacting excess of the amine intermediate **5** with terephthalic acid using PyBOP coupling conditions, with quantitative yield (**Scheme 2; Table 1**). Next we examined the importance of the 4-aminoquinoline fragment, the essential pharmacophore of chloroquinoline. We synthesized derivative **11**, which was obtained through a nucleophilic substitution between 4,6-dichloroquinoline and the amine intermediate **5 (Scheme 2; Table 1**).

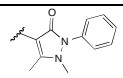
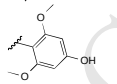
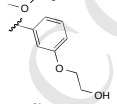
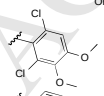
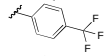
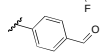
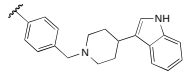
As a part of our SAR studies an additional series of derivatives was designed in order to maintain both the second piperidinyl group, as well as the amide linkages, while exploring the chemical variation at the terminal piperidinyl fragment. To synthesize this set of analogues the intermediate compound **6** was Boc-deprotected, followed by acylation of the free amine **12** with commercially available acid chlorides using standard Schotten Baumann conditions to obtain the desired compounds **13a-f** (**Scheme 3**), in 25% to quantitative yields (**Table 1**).

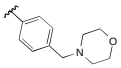
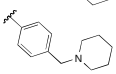
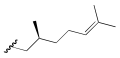
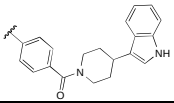
All synthesized compounds were purified by flash chromatography and the purity was assessed with HPLC-ELSD-MS prior to profiling for antiparasitic activity (purity was >90%). The structures of all compounds were confirmed by NMR spectroscopy using ^{1}H-NMR, ^{13}C-NMR and twodimensional experiments, including ^{1}H-^{1}H COSY, HMQC and HMBC (see details in Methods).

2.2. *In vitro* antimalarial activity

The synthesized derivatives were first evaluated at 5 µM fixed concentration for their growth inhibitory activity against the erythrocytic stage of the CQ-resistant *P. falciparum* strain Dd2 (**Table 1**). Lipophilicity of the synthesized indole compounds, expressed in terms of their partition coefficient values (clog *P*), molecular weight in g/mol and violations of Lipinski's rule of 5 (Ro5) were calculated in Instant JChem (Chemaxon) and considered as a preliminary test of the drug-likeness of the compounds (**Table 1**).

Table 1: Final step yield of synthesized compounds, their drug-like properties (MW, cLogP and compliance with "Lipinski's Rule of 5") and results from antimalarial activity screening.

Series	Compound	R	Yield (%)	MW (g/mol)	cLogP	Ro5 (≤2 violations)	% Inhibition at 5µM *P. falciparum* Dd2
	3	-	15	459.03	5.70	Yes	100
	5	-	96	200.28	2.18	Yes	<10
	8	-	Quant.	297.44	2.66	Yes	< 10
Amine	**9a**		79	400.52	3.41	Yes	<10
	9b		76	371.47	3.70	Yes	70
	9c		99	357.45	3.98	Yes	<10
	9d		55	346.49	5.16	Yes	16
	9e		53	290.40	4.28	Yes	15
	9f		55	304.43	4.80	Yes	11
	9g		42	366.45	3.47	Yes	<10
	9h		99	350.45	3.44	Yes	<10
	9i		60	419.34	5.18	Yes	<10
	9j		72	308.39	4.43	Yes	14
	9k		69	358.40	5.16	Yes	<10
	9l		25	318.41	4.00	Yes	20
	9m		30	502.69	6.60	Yes	100

Amine	**9n**		38	389.53	4.01	Yes	66
	9o		54	387.56	5.08	Yes	100
	9p		97	291.39	3.07	Yes	<10
	9q		65	296.43	4.20	Yes	<10
	9r		Quant.	296.45	4.67	Yes	<10
	9s		98	340.55	5.10	Yes	17
Amide	**10a**		55	304.39	3.64	Yes	<10
	10b		Quant.	364.44	3.33	Yes	<10
	10c		95	322.38	3.78	Yes	<10
	10d		25	305.37	2.42	Yes	100
	10e		66	310.41	3.55	Yes	<10
	10f		73	242.32	1.79	Yes	<10
	10g		60	305.37	2.42	Yes	14
	10h		95	305.37	2.81	Yes	<10
	10i		Quant.	306.36	1.59	Yes	<10
	10j		Quant.	530.66	5.31	Yes	80
	11	-	25	361.87	5.21	Yes	32
Bis-amide	**13a**		80	415.53	3.35	Yes	<10
	13b		75	475.58	3.04	Yes	10
	13c		75	433.52	3.50	Yes	<10
	13d		10	416.52	2.14	Yes	30
	13e		73	415.53	3.35	Yes	<10
	13f		40	475.58	3.04	Yes	10

Compounds inhibiting more than 95% of parasite growth at 5µM concentration were further profiled for dose-response to determine half maximal effective concentrations (EC_{50}) against CQ-resistant Dd2 and CQ-sensitive 3D7. The reference antimalarials chloroquine, atovaquone, amodiaquine and artesunate were included as controls and resulted in EC_{50}s in agreement with published results. The original hit molecule **3** and its simplified derivative **11** were also tested for comparison to the newly synthesized compounds (**Table 2**). Cytotoxicity (EC_{50}) of selected

compounds for human cells (HepG2) and selectivity index for CQ-resistant Dd2 (SI_{res}) and CQ-sensitive 3D7 strains (SI_{sen}) are reported in **Table 2**.

Table 2: *In vitro* antimalarial activity (EC_{50}) and cytotoxicity (EC_{50}) of selected compounds.

Compound	*P. falciparum* EC_{50} (μM) ±SD		HepG2 EC_{50} (μM) ±SD	Selectivity Index	
	Dd2	3D7		SI_{res} [a]	SI_{sen} [b]
3	0.94±0.51	0.24±0.08	3.86±0.50	4.10	16.08
9m	0.21±0.05	0.08±0.03	0.46±0.03	2.19	5.75
9o	2.91±0.35	1.35±0.45	n.d.	n.d.	n.d.
10d	2.95±0.30	3.80±0.50	12.80±0.28	4.33	3.37
11	5.01±1.50	6.30±1.50	4.24±0.21	0.85	0.67
Chloroquine	285±58[c]	23±1[c]	n.d.	n.d.	n.d.
Atovaquone	0.19±0.06[c]	0.35±0.14[c]	n.d.	n.d.	n.d.
Amodiaquine	12.30±4.21[c]	5.85±2.20[c]	n.d.	n.d.	n.d.
Artesunate	1.76±0.43[c]	1.97±0.29[c]	n.d.	n.d.	n.d.

[a] SI_{res} = EC_{50} HepG2 / IC_{50} *Pf*Dd2; [b] SI_{sen} = EC_{50} HepG2 / EC_{50} *Pf*3D7; n.d.= not determined; [c] EC_{50} values in nM; n.d.= not determined.

The hit compound **3** was resynthesized and tested against the Dd2 and 3D7 strains and exhibited an EC_{50} of 0.94 μM (Dd2) and 0.24 μM (3D7), which confirmed the previously observed cross-resistance with CQ (resistance index (RI) calculated as EC_{50} Dd2/EC_{50} 3D7 = 4). Interestingly, we found significantly decreased activity for this compound in our assay compared to that reported (EC_{50} 3D7 = 0.03 μM) [28]. This discrepancy in activities could be the consequence of different assays conditions, or possibly the result of inaccurate compound assay concentration, or presence of a biological active contaminent in the original HTS assay plates.

In a first approach to determine the requirement of each fragment of hit **3** for its antimalarial activity, we tested intermediates **5** and **8,** and concluded that the 4-amino-chloroquinoline moiety is essential for activity. Next, we investigated the requirement of the distal piperidinyl fragment

for the antimalarial activity of **3**. Removal of this fragment leads to a compound (**11**), which had substantially decreased antimalarial activity when compared to compound **3** (**Tables 1** and **2**).

We then further explored the 3-piperidin-4-yl-1*H*-indole scaffold. The effect of chemically diverse substituents linked to the N-piperidinyl group was investigated within the first series of amine derivatives (**9a-s**). Various aromatic fragments, including bicyclic (**9a-d**), monocyclic (**9e-l**) and mono heterocyclic (**9p-q**), as well as alkyl fragments (**9r-s**) were introduced in place of the 4-aminoquinoline. The results indicate that, with the exception of the N-acyl indole fragment (**9b**), none of the smaller fragments tested lead to compounds with anti-parasitic activity. However, the introduction of a second 3-piperidin-4-yl-1*H*-indole group linked through the *p*-position of the benzyl ring afforded a compound (**9m**) with significant antimalarial activity against both Dd2 and 3D7 strains of *P. falciparum* (EC_{50}s of 0.21 and 0.08 μM, respectively). Due to the increased lipophilic properties of **9m**, simplification of the latter benzyl substitution was investigated. The introduction of a basic piperidine group resulted in a compound (**9o**) with some antimalarial activity against both strains of *P. falciparum* (Dd2 EC_{50} = 2.91 and 3D7 EC_{50} = 1.35 μM), whereas the introduction of a less basic morpholine group decreases the activity (**9n**). Overall, the results indicate that in the amine series the antimalarial activity depends mostly on lipophilicity and the basic characteristics of the compounds, which may be a nonspecific antiproliferative effect as compound **9m** also showed an equivalent EC_{50} (0.46 μM) against the HepG2 cell line.

We next investigated the effect of an amide linkage in place of the basic amine, conferring rotational hindrance to the molecules, decreased basicity, as well as providing a hydrogen bond acceptor. A series of N-acyl substituted 3-piperidin-4-yl-1*H*-indoles with a wide variety of aromatic groups was synthesized. However, only one of the tested amide derivatives (**10a-j**) was active against Dd2. Compound **10d**, which was derived from N-acyl pyridin-3-yl substitution, demonstrated antimalarial activity (EC_{50} = 2.95 μM) comparable to analogue **9o**. Notably **10d** has a significantly improved cLogP compared to **9o** (2.42 *vs* 5.08). Moreover, **10d** did not show cross-resistance with CQ (RI = 1.3) and was modestly selective (4x) for *P. falciparum* over the tested human cell line (EC_{50} = 12.8 μM). Interestingly, the activity was highly susceptible to the substitution position of the pyridinyl moiety, with the N-acyl pyridine-4-yl (**10g**) and N-acyl pyridine-2-yl (**10h**) derivatives being inactive against the parasite, suggesting that the relative spatial disposition of the carbonyl group and the nitrogen atom is required for activity.

Comparison of the activity of bis-3-piperidin-4-yl-1*H*-indole compound **9m** and its bis-amide counterpart **10j**, suggests that the amide bond significantly reduces the antimalarial activity (**10j** with EC_{50} > 5 μM). To broaden our structure-activity relationship study we also examined a small series of analogues containing the 4-(piperidine-1-carbonyl)piperidin-1-yl) scaffold with structurally diverse N-acyl substituents (**13a-f**). No significant antimalarial activity was observed for the tested N-acyl derivatives, (**13a-f** with EC_{50} > 5 μM). Moreover, when comparing the N-acyl pyridin-3-yl substitution in the 3-piperidin-4-yl-1*H*-indole series (**10d**) to the same N-acyl substitution in the 4-(4-piperidine-1-carbonyl)piperidin-1-yl-1*H*-indole series (**13d**), the introduction of the second piperidinyl group results in loss of antimalarial activity.

3. Conclusion:

Despite efforts to protect the useful lifespan of frontline therapies, antimalarial drug resistance remains an ever-present threat. This challenge demands new drugs, preferably new chemotypes active against drug resistant parasites, with a good pharmacologic profile and affordable to endemic areas. Here we applied a rational fragment-based approach to design three related series of 3-piperidin-4-yl-1*H*-indoles around TCMDC-134281 (**3**), which was previously idenfied by GSK in a HTS campaign, to develop robust SAR and to validate this chemotype for further preclinical development. Altogether, 38 compounds were synthesized and evaluated for antimalarial activity. Compounds that demonstrate promising activity against the multidrug-resistant *P. falciparum* Dd2 strain were also tested in the 3D7 parasite strain and counterscreened in human HepG2 cells.

The SAR study revealed that the 4-aminoquinolinyl moiety present in hit **3** can be replaced by some smaller groups without significantly affecting activity. Compounds, which retained activity in spite of the absence of the chloroquine motif, demonstrate the potential of the 3-piperidin-4-yl-1*H*-indole scaffold as a new class of antimalarial drugs independent from the 4-aminoquinolines.

Our results suggest that the 3-piperidin-4-yl-1H-indole scaffold is very sensitive to most *N*-piperidinyl modifications. Out of the analogues synthesized, only three were active (**9m, 9o** and **10d**). While **9o** showed cross-resistance to chloroquine and **9m** was not selective in HepG2 cytotoxicity assays, the (4-(1H-indol-3-yl)piperidin-1-yl)(pyridin-3-yl)methanone (**10d**) showed *in vitro* antimalarial activity (EC_{50} values ~3 μM), no cross-resistance with chloroquine,

selectivity for the parasite, and lead-like properties (cLogP ≤ 3; MW ≤ 300). This represents a promising new antimalarial chemotype with a potential novel mechanism of action. Further medicinal chemistry efforts are underway to improve the potency of compound **10d** and disclose its antimalarial mechanism of action.

4. Experimental:

4.1. Chemistry

4.1.1. General

All chemicals were purchased from Chem-Impex International, Aldrich, Fluka, and Sigma- Aldrich Co. and used without further purification unless otherwise noted. All solvents for syntheses were anhydrous. Thin layer chromatography was performed with precoated aluminum-backed TLC plates obtained from VWR: Aluminum Oxide 60, Neutral F254 & Silica Gel 60, Neutral F254. Visualization of TLC plates was performed with ninhydrin, iodine, or an UVGL-25 Compact UV Lamp 254/365 UV (UVP 115V~60Hz/0.16 Amps). Purifications were performed on a Biotage Isolera 4 Purification System equipped with a 200-400 nm diode array detector. For flash purifications, Biotage SNAP Flash Chromatography Cartridges were used. Purity of compounds was determined by analytical LC-ELSD-MS performed on a Waters 2545 HPLC equipped with a 2998 diode array detector, a Waters 3100 ESI-MS module, using a XTerraMS C18 5 μm, 4.6 x 50 mm column at a flow rate of 5 mL/minute with a linear gradient (95% A: 5% B to 100% B with 90 seconds and 30 seconds hold at 100% B, solvent A = water + 0.1% formic acid, solvent B = acetonitrile + 0.1% formic acid). Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR spectra) were recorded on a Bruker Ascend^{TM} instrument at 400 and 101 MHz, respectively. Chemical shifts for protons are reported in parts per million (ppm) and are referenced to residual solvent peaks for DMSO (2.5 ppm), $CHCl_3$ (7.26 ppm), H_2O (4.79 ppm) and CH_3OH (3.31 ppm). Data is reported as follows: chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, q= quadruplet, m= multiplet, br=broad), coupling constants (Hz) and integration. Instant JChem was used for structure database management, search and prediction, Instant JChem 5.9.3, 2012, ChemAxon (http://www.chemaxon.com).

4.1.2. Synthesis

*3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (**4**)*

5 g (42.7 mmol) of indole were dissolved in isopropanol (50 mL). To this solution, potassium hydroxide (7.18 g, 128 mmol) in isopropanol (50 mL) was added, followed by the addition of 1-benzypiperidine-4-one (20 mL, 108 mmol) in isopropanol (50 mL). The reaction refluxed for 6h, after which it was cooled to room temperature. Solvent was removed under reduced pressure. The crude product was purified using flash chromatography using a gradient elution of Hexane/Ethyl Acetate. The desired product was obtained as a yellow solid (12.01 g, 98%).
ESI-MS: $C_{20}H_{20}N_2$, *m/z* calculated for $[M+H]^+$: 289.16, Found: 289.18.**^{1}H NMR** δ (MeOD) 7.84 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.31 (m, 6H), 7.28 (s, 1H), 7.14 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.20 (tt, *J* = 3.5, 1.5 Hz, 1H), 3.70 (s, 2H), 3.26 (m, 2H), 2.80 (t, *F* = 5.8 Hz, 2H), 2.67 (m, 2H); **^{13}C NMR** δ (MeOD) 138.8, 138.3, 131.7, 130.9, 129.4, 128.5, 126.4, 123.1, 122.5, 121.2, 120.4, 118.3, 117.7, 112.5, 63.8, 54.1, 51.1, 29.6.

*3-(piperidin-4-yl)-1H-indole (**5**)*

4 g (13.8 mmol) of compound **4** were dissolved in 10% acetic acid in ethyl acetate (160 mL). To this solution, 1.2 g of 10% palladium over activated carbon were added. The reaction was placed under 1 atm of H_2 (balloon) and stirred for 50 h, at r.t. Reaction mixture was filtered over Celite™ and washed with ethyl acetate followed by acetonitrile:water:methanol (1:1:1). Solvent was removed under reduced pressure and the crude product purified with flash chromatography using a gradient elution of ethyl acetate/acetonitrile:water:methanol (1:1:1) with 1% ammonium hydroxide to afford compound **5** as a yellow solid (2.66 g, 96%).
ESI-MS: $C_{13}H_{16}N_2$, *m/z* calculated for $[M+H]^+$: 201.13, Found: 201.42. **^{1}H NMR** δ (MeOD) 7.60 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.06 (s, 1H), 7.01 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 3.46 (dt, *J* = 12.8, 3.1 Hz, 2H), 3.22 – 3.06 (m, 3H), 2.23 (d, *J* = 12.3 Hz, 2H), 1.99 (m, 2H), 1.92 (s, NH); **^{13}C NMR** δ (MeOD) 136.9, 126.0, 121.1, 119.9, 118.3, 118.0, 117.9, 111.1, 44.2, 31.5, 29.7.

*tert-butyl 4-(4-(1H-indol-3-yl)piperidine-1-carbonyl)piperidine-1-carboxylate (**6**)*

To 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (1 g , 4.36 mmol) in acetonitrile (25 mL) was added compound **5** (873.2 mg, 4.36 mmol) in acetonitrile (25 mL), followed by N,N'-

dicyclohexylcarbodiimide (899.6 mg, 4.36 mmol) and 1-hydroxybenzotriazole (589.1 mg, 4.36 mmol). The reaction stirred at room temperature for 2 h. Suspension was filtered and solvent removed under reduced pressure. The crude product was purified using reverse phase flash chromatography using a gradient elution of water/acetonitrile to afford compound **6** as a white solid (1.08 g, 60%).

ESI-MS: $C_{24}H_{33}N_3O_3$, *m/z* calculated for $[M+H]^+$: 412.25, Found: 412.42. **^{1}H NMR** δ (MeOD) 7.61 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.9, 1.2 Hz, 1H), 7.08 – 6.99 (m, 2H), 4.69 (d, *J* = 13.2 Hz, 1H), 4.21 (d, *J* = 13.2 Hz, 1H), 4.15 (d, *J* = 13.4 Hz, 2H), 3.34-3.31 (m, 1H), 3.21-3.13 (tt, *J* = 12.8, 3.5 Hz, 1H), 2.97 (m, 2H), 2.85 (m, 2H), 2.21 (d, *J* = 12.9 Hz, 1H), 2.12 (d, *J* = 13.0 Hz, 1H), 1.79 – 1.60 (m, 6H), 1.50 (s, 9H); **^{13}C NMR** δ (MeOD) 173.7, 155.0, 136.9, 126.3, 120.9, 119.9, 119.8, 119.0, 118.1, 110.9, 79.7, 45.9, 42.5, 37.9, 33.7, 32.5, 28.2, 27.3.

*tert-butyl 4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (**7**)*

To a solution of **6** (100 mg, 0.24 mmol) in THF (3 mL) at -78°C was added DIBAL in THF (730 µL of 1M solution, 0.73 mmol). The reaction stirred at -78°C for 1 h and then quenched with MeOH followed by addition of 1M aq. sodium potassium tartrate. The reaction mixture stirred until clear and was extracted with ethyl acetate. Organic phase was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude product purified with flash chromatography using a gradient elution of ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford compound **7** as a beige solid (33.4 mg, 35%).

ESI-MS: $C_{24}H_{35}N_3O_2$, *m/z* calculated for $[M+H]^+$: 398.27, Found: 398.47. **^{1}H NMR** δ ($CDCl_3$) 8.05 (s, NH), 7.64 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.17 (ddd, *J* = 7.9, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 4.10 (d, *J* = 11.4 Hz, 2H), 2.99 (d, *J* = 11.5 Hz, 2H), 2.82 (m, 1H), 2.71 (t, *J* = 12.3 Hz, 2H), 2.23 (d, *J* = 6.9 Hz, 2H), 2.11 (td, *J* = 11.9, 1.9 Hz, 2H), 2.03 (d, *J* = 12.4 Hz, 2H), 1.87 – 1.64 (m, 5H), 1.46 (s, 9H), 1.11 (qd, *J* = 12.1, 3.4 Hz, 2H); **^{13}C NMR** δ ($CDCl_3$) 154.8, 136.2, 126.5, 121.7, 121.4, 119.5, 118.9, 118.8, 111.0, 79.0, 64.9, 54.8, 33.7, 33.4, 32.8, 30.8, 28.3, 28.2.

*3-(1-(piperidin-4-ylmethyl)piperidin-4-yl)-1H-indole (**8**)*

Compound **7** (30 mg, 0.075 mmol) was dissolved in a solution of 2M HCl in MeOH (3 mL) and stirred at room temperature for 20 min. The solvent was removed under reduced pressure and the crude product was purified by reverse phase flash chromatography using a gradient elution of water/acetonitrile to afford the desired product as a yellow solid (22.4 mg, qtt yield).
ESI-MS: $C_{19}H_{27}N_3$, *m/z* calculated for $[M+H]^+$: 298.22, Found: 298.45. **^{1}H NMR** δ (D_2O) 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.29 (dd, *J* = 8.2, 8.1 Hz, 1H), 7.25 (s, 1H), 7.20 (dd, *J* =8.2, 8.0 Hz, 1H), 3.71 (d, *J* = 12.5 Hz, 2H), 3.53 (d, *J* = 13.2 Hz, 2H), 3.24 – 3.05 (m, 7H), 2.32 (d, *J* = 12.9 Hz, 2H), 2.16 – 1.97 (m, 4H), 1.94 – 1.77 (m, 1H), 1.60 (q, *J* =11.9 Hz, 2H); **^{13}C NMR** δ (D_2O) 136.3, 125.4, 122.1, 121.3, 119.3, 118.7, 117.5, 112.1, 61.3, 53.7, 43.2, 30.5, 29.6, 28.7, 26.2.

*4-(4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)piperidin-1-yl)-6-chloroquinoline (**3**)*
To a solution of compound **8** (20 mg, 0.067 mmol) and DIPEA (35.21 μL, 0.202 mmol) in isopropanol (2 mL) was added 4,6-dichloroquinoline (19.80 mg, 0.10 mmol). The reaction mixture stirred under reflux for 56 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a gradient elution of ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford compound **3** as a beige oil (4.6 mg, 15%).
ESI-MS: $C_{28}H_{31}ClN_4$, *m/z* calculated for $[M+H]^+$: 459.22, Found: 459.37. **^{1}H NMR** δ (MeOD) 8.68 (d, *J* = 5.1 Hz, 1H), 8.46 (br, 1H), 8.06 (d, *J* = 2.3 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.73 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.11 (m, 3H), 7.05 (dd, *J* = 8.0, 7.9 Hz, 1H), 3.67-3.81 (m, 4H), 3.24-3.29 (m, 5H), 3.04 (t, *J* = 12.1 Hz, 2H), 2.37 (d, *J* = 13.4 Hz, 2H), 2.28-2.16 (m, 3H), 2.11 (d, *J* = 13.3 Hz, 2H), 1.79 (qd, *J* = 12.5, 3.7 Hz, 2H).

General Procedure A:
Aldehyde (1.5 eq.) and amine (1 eq.) were mixed in 1,2-dichloroethane, followed by addition of sodium triacetoxyborohydride (1.4 eq.). The reaction was stirred at room temperature under inert atmosphere for 4 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$, and the product was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford the desired product.

General Procedure B:

To a solution of acid chloride (1 eq.) in DCM (3 mL) was added a suspension of compound **5** (1.1 eq.) in sat. aq. $NaHCO_3$ (3 mL). The reaction mixture stirred vigorously at room temperature for 10 min. The organic phase was washed with HCl (aq., 10%), sat. aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford the desired product.

General Procedure C:

To a solution of acid chloride (1 eq.) in DCM (2 mL) was added a solution of compound **5** (1.1 eq.) and DIPEA (3 eq.) in DCM (2 mL). The reaction mixture stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford the desired product.

General Procedure D:

To a solution of carboxylic acid (1 eq.) in DCM (2 mL) was added a solution of compound **5** (1 eq.) and DIPEA (3 eq.) in DCM (2 mL) followed by PyBOP (1.1 eq.). The reaction mixture stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford the desired product.

4-(piperidin-1-ylmethyl)benzaldehyde

Reaction of terephthaldehyde (235.2 mg, 1.75 mmol), piperidine (100 mg, 1.17 mmol) and sodium triacetoxyborohydride (348.6 mg, 1.64 mmol) according to general procedure A, gave 166.25 mg (70 %) of desired aldehyde as a light yellow oil.

ESI-MS: $C_{13}H_{17}NO$, *m/z* calculated for $[M+H]^+$: 204.13, Found: 204.33.**^{1}H NMR** δ (MeOD) 10.01 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 3.64 (s, 2H), 2.52 – 2.46 (m, 4H), 1.70 – 1.60 (m, 4H), 1.53 – 1.49 (m, 2H); **^{13}C NMR** δ (MeOD) 192.4, 144.6, 135.8, 129.9, 129.3, 62.8, 54.1, 25.1, 23.7.

4-(morpholinomethyl)benzaldehyde

Reaction of terephthaldehyde (231.2 mg, 1.73 mmol), morpholine (100 mg, 1.15 mmol) and sodium triacetoxyborohydride (340.6 mg, 1.60 mmol) according to general procedure A, gave 136.80 mg (58 %) of desired aldehyde as a light yellow oil.

ESI-MS: $C_{12}H_{15}NO_2$, *m/z* calculated for $[M+H]^+$: 206.11, Found: 206.71. **^{1}H NMR** δ (MeOD) 10.01 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 3.77 – 3.71 (m, 4H), 3.65 (s, 2H), 2.55 – 2.48 (m, 4H); **^{13}C NMR** δ (MeOD) 192.4, 144.8, 135.8, 129.6, 125.7, 66.4, 62.4, 53.3.

*4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (**9a**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (32.4 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 28.4 mg (79 %) of desired compound as a yellow oil.

ESI-MS: $C_{25}H_{28}N_4O$, *m/z* calculated for $[M+H]^+$: 401.23, Found: 401.14.**^{1}H NMR** δ (MeOD) 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1H), 7.42 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.2, 1.2 Hz 1H), 7.04 (s, 1H), 7.00 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 3.53 (s, 2H), 3.26 (s, 3H), 3.22 (d, *J* = 10.5 Hz, 2H), 2.90 (m, 1H), 2.49 (t, *J* = 10.7 Hz, 2H), 2.43 (s, 3H), 2.11 (d, *J* = 12.6 Hz, 2H), 1.92 (qd, *J* = 12.1, 3.4 Hz, 2H); **^{13}C NMR** δ (MeOD) 166.0, 154.4, 136.9, 134.2, 129.2, 127.9, 126.4, 125.9, 120.8, 119.7, 119.4, 118.2, 117.9, 110.9, 101.4, 53.3, 49.3, 33.7, 32.9, 32.0, 10.0.

*1-(3-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)-1H-indol-1-yl)ethan-1-one (**9b**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 1-acetyl-1*H*-indole-3-carbaldehyde (28.1 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 25.3 mg (76 %) of desired amine as a beige solid.

ESI-MS: $C_{24}H_{25}N_3O$, *m/z* calculated for $[M+H]^+$: 372.21, Found: 372.41.**^{1}H NMR** δ ($CDCl_3$) 8.45 (d, *J* = 7.9 Hz, 1H), 8.01 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.28 (m, 4H), 7.17 (ddd, *J* = 8.4, 8.2, 1.2 Hz 1H), 7.10 (ddd, *J* = 8.4, 8.0, 1.0 Hz, 1H), 6.97 (d, *J*

= 2.1 Hz, 1H), 3.75 (s, 2H), 3.15 (d, *J* = 11.8 Hz, 2H), 2.87 (tt, *J* = 12.9, 3.6 Hz, 1H), 2.30 (td, *J* = 11.8, 2.1 Hz, 2H), 2.07 (d, *J* = 12.9 Hz, 2H), 1.88 (qd, *J* = 12.3, 3.6 Hz, 2H); **^{13}C NMR** δ (CDCl3) 169.0, 136.9, 136.4, 131.3, 127.1, 125.7, 124.8, 124.6, 123.9, 123.5, 122.4, 121.8, 120.1, 119.6, 117.0, 111.9, 111.7, 54.9, 54.0, 33.9, 33.4, 24.5.

*2-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)quinolin-8-ol (**9c**)*

Reaction of compound **5** (50 mg, 0.25 mmol), 8-hydroxyquinoline-2-carbaldehyde (64.8 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 92.6 mg (99 %) of desired amine as a light yellow oil.

ESI-MS: $C_{23}H_{23}N_3O$, *m/z* calculated for $[M+H]^+$: 358.18, Found: 358.20. **^{1}H NMR** δ (MeOD) 8.17 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.24 (m, 2H), 7.11 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.05 (ddd, *J* = 7.5, 6.9, 1.3 Hz, 1H), 7.01 (s, 1H), 6.96 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 4.22 (s, 2H), 3.28 – 3.25 (m, 2H), 2.97 (tt, *J* = 11.4, 4.1 Hz, 1H), 2.75 (td, *J* = 11.6, 1.6 Hz, 2H), 2.14 – 1.96 (m, 4H); **^{13}C NMR** δ (MeOD) 154.2, 153.7, 139.4, 138.5, 138.3, 129.6, 128.9, 127.7, 122.6, 122.4, 121.3, 119.9, 119.6, 119.0, 118.4, 112.54, 112.4, 63.6, 55.2, 33.5, 32.2.

*3-(1-(benzo[b]thiophen-3-ylmethyl)piperidin-4-yl)-1H-indole (**9d**)*

Reaction of compound **5** (50 mg, 0.25 mmol), benzo[*b*]thiophene-3-carbaldehyde (60.7 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 47.6 mg (55 %) of desired amine as a light yellow oil.

ESI-MS: $C_{22}H_{22}N_2S$, *m/z* calculated for $[M+H]^+$: 347.15, Found: 347.16. **^{1}H NMR** δ (DMSO) 10.77 (s, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.57 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.31 (m, 3H), 7.10 – 7.01 (m, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 3.77 (s, 2H), 3.00 (d, *J* = 11.2 Hz, 2H), 2.77 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.18 (t, *J* = 10.8 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.69 (qd, *J* = 12.3, 3.7 Hz, 2H); **^{13}C NMR** δ (DMSO) 139.9, 138.8, 136.4, 133.4, 126.3, 124.8, 124.3, 123.9, 122.8, 122.7, 120.8, 120.5, 119.6, 118.5, 118.0, 111.4, 56.2, 53.9, 33.1, 32.8.

*3-(1-benzylpiperidin-4-yl)-1H-indole (**9e**)*

Reaction of compound **5** (100 mg, 0.50 mmol), benzaldehyde (79.4 mg, 0.7 mmol) and sodium triacetoxyborohydride (118.6 mg, 0.75 mmol) according to general procedure A, gave 76.2 mg

(53 %) of desired amine as a dark yellow solid.

ESI-MS: $C_{20}H_{22}N_2$, *m/z* calculated for $[M+H]^+$: 291.18, Found: 291.12. **^{1}H NMR** δ (MeOD) 7.58 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.26 (m, 6H), 7.08 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.03 – 6.96 (m, 2H), 3.56 (s, 2H), 3.00 (d, *J* = 12.2 Hz, 2H), 2.80 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.18 (td, *J* = 12.2, 2.6 Hz, 2H), 2.02 – 1.96 (m, 2H), 1.84 (qd, *J* = 12.1, 3.3 Hz, 2H); **^{13}C NMR** δ (MeOD) 136.9, 132.8, 129.6, 128.0, 127.9, 127.1, 126.5, 120.8, 119.7, 118.4, 117.9, 110.9, 63.1, 53.8, 33.4, 32.3.

*3-(1-(2-methylbenzyl)piperidin-4-yl)-1H-indole (**9f**)*

Reaction of compound **5** (50 mg, 0.25 mmol), 2-methylbenzaldehyde (44.9 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 41.8 mg (55 %) of desired amine as a light orange solid.

ESI-MS: $C_{21}H_{24}N_2$, *m/z* calculated for $[M+H]^+$: 305.19, Found: 305.17. **^{1}H NMR** δ ($CDCl_3$) 8.15 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.22 – 7.13 (m, 4H), 7.09 (m, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 3.62 (s, 2H), 3.09 (d, *J* = 12.1 Hz, 2H), 2.87 (tt, *J* = 12.0, 3.8 Hz, 1H), 2.41 (s, 3H), 2.28 (td, *J* = 12.1, 2.6 Hz, 2H), 2.12 – 1.98 (m, 2H), 1.84 (qd, *J* = 12.2, 3.3 Hz, 2H); **^{13}C NMR** δ ($CDCl_3$) 137.7, 136.5, 130.5, 130.3, 130.3, 127.4, 126.8, 125.8, 121.9, 121.3, 119.9, 119.2, 119.1, 111.3, 60.7, 54.3, 33.5, 32.8, 19.6.

*4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)-3,5-dimethoxyphenol (**9g**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 4-hydroxy-2,6-dimethoxybenzaldehyde (27.3 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 13.6 mg (42 %) of desired amine as a yellow solid.

ESI-MS: $C_{22}H_{26}N_2O_3$, *m/z* calculated for $[M+H]^+$: 367.19, Found: 367.12.**^{1}H NMR** δ (DMSO) 10.91 (s, 1H), 10.12 (s, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.02 (m, 2H), 6.96 (m, 1H), 6.21 (s, 2H), 4.08 (s, 2H), 3.79 (s, 6H), 3.40 – 3.34 (m, 2H), 3.11 – 2.94 (m, 3H), 2.22 – 1.92 (m, 4H); **^{13}C NMR** δ (DMSO) 161.1, 160.1, 136.4, 125.8, 120.9, 120.8, 118.8, 118.2, 117.7, 111.5, 91.9, 55.8, 55.4, 51.9, 48.8, 43.5, 31.0, 30.7, 29.5, 29.0.

*2-(3-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)phenoxy)ethan-1-ol (**9h**)*

Reaction of compound **5** (50 mg, 0.25 mmol), 3-(2-hydroxyethoxy)benzaldehyde (62.3 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general

procedure A, gave 86.7 mg (99 %) of desired amine as an orange oil.
ESI-MS: $C_{22}H_{26}N_2O_2$, *m/z* calculated for $[M+H]^+$: 351.20, Found: 351.21.**^{1}H NMR** δ ($CDCl_3$) 8.36 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.27 (m, 1H), 7.19 – 7.12 (m, 2H), 7.08 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 6.97 (m, 2H), 6.87 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.13 (dd, *J* = 5.3, 4.0 Hz, 2H), 3.96 (dd, *J* = 5.3, 4.0 Hz, 2H), 3.71 (s, 2H), 3.15 (d, *J* = 11.5 Hz, 2H), 2.88 (tt, *J* = 11.4, 4.3 Hz, 1H), 2.36 (t, *J* = 10.9 Hz, 2H), 2.13 – 1.93 (m, 4H); **^{13}C NMR** δ ($CDCl_3$) 159.1, 136.5, 129.5, 126.6, 122.6, 121.9, 120.6, 120.1, 119.2, 119.0, 115.9, 114.4, 111.4, 69.4, 62.8, 61.5, 53.9, 33.1, 32.1.

*3-(1-(2,6-dichloro-3,4-dimethoxybenzyl)piperidin-4-yl)-1H-indole (**9i**)*
Reaction of compound **5** (50 mg, 0.25 mmol), 2,6-dichloro-3,4-dimethoxybenzaldehyde (87.6 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 62.9 mg (60 %) of desired amine as red solid.
ESI-MS: $C_{22}H_{24}Cl_2N_2O_2$, *m/z* calculated for $[M+H]^+$: 419.12, Found: 419.33. **^{1}H NMR** δ (DMSO) 10.74 (s, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 7.09 – 7.01 (m, 2H), 6.94 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.68 (s, 2H), 2.92 (d, *J* = 11.1 Hz, 2H), 2.77 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.35 (t, *J* = 11.1 Hz, 2H), 1.92 (d, *J* =13.7 Hz, 2H), 1.62 (qd, *J* = 12.2, 3.5 Hz, 2H); **^{13}C NMR** δ (DMSO) 152.6, 143.9, 136.3, 130.3, 130.2, 126.3, 120.7, 120.4, 119.5, 118.5, 117.9, 112.6, 111.4, 60.1, 56.5, 56.4, 53.7, 32.8.

*3-(1-(4-fluorobenzyl)piperidin-4-yl)-1H-indole (**9j**)*
Reaction of compound **5** (50 mg, 0.25 mmol), 4-fluorobenzaldehyde (46.4 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 55 mg (72 %) of desired amine as yellow oil.
ESI-MS: $C_{20}H_{21}FN_2$, *m/z* calculated for $[M+H]^+$: 309.17, Found: 309.09. **^{1}H NMR** δ (MeOD) 7.60 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.17 – 7.07 (m, 3H), 7.05 – 6.96 (m, 2H), 3.81 (s, 2H), 3.17 (d, *J* = 12.1 Hz, 2H), 2.94 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.51 (t, *J* = 11.1 Hz, 2H), 2.11 (d, *J* =12.9 Hz, 2H), 1.93 (qd, *J* = 12.1, 3.3 Hz, 2H); **^{13}C NMR** δ (MeOD) 164.1 (d, $^1J_{CF}$ = 245 Hz), 138.3, 133.3, 127.7, 122.3, 121.2, 120.3, 119.6, 119.5, 116.4, 116.2, 112.4, 62.6, 54.7, 34.0, 32.9.

*3-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-1H-indole (**9k**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 4-(trifluoromethyl)benzaldehyde (26.1 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 22.2 mg (69 %) of desired amine as a beige oil.

ESI-MS: $C_{21}H_{21}F_3N_2$, *m/z* calculated for $[M+H]^+$: 359.17, Found: 359.32. **^{1}H NMR** δ (MeOD) 7.72 – 7.55 (m, 5H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.03 (s, 1H), 7.00 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 3.72 (s, 2H), 3.06 (d, *J* = 12.3 Hz, 2H), 2.88 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.31 (td, *J* = 12.3, 2.5 Hz, 2H), 2.07 (m, 2H), 1.89 (qd, *J* = 12.3, 3.6 Hz, 2H); **^{13}C NMR** δ (MeOD) 143.3, 138.3, 131.3, 127.9, 126.2, 126.2, 126.1, 122.2, 121.1, 121.0, 119.6, 119.3, 112.3, 63.7, 55.3, 34.7, 33.8.

*4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)benzaldehyde (**9l**)*

Reaction of compound **5** (50 mg, 0.25 mmol), terephthaldehyde (50.3 mg, 0.37 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 19.9 mg (25 %) of desired amine as beige solid.

ESI-MS: $C_{21}H_{22}N_2O$, *m/z* calculated for $[M+H]^+$: 319.17, Found: 319.23. **^{1}H NMR** δ ($CDCl_3$) 10.00 (s, 1H), 8.07 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.18 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.97 (d, *J* = 1.2 Hz, 1H), 3.66 (s, 2H), 3.01 (d, *J* = 11.8 Hz, 2H), 2.86 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.23 (td, *J* = 11.8, 2.5 Hz, 2H), 2.05 (d, *J* = 13.9 Hz, 2H), 1.86 (qd, *J* = 11.9, 3.3 Hz, 2H); **^{13}C NMR** δ ($CDCl_3$) 191.9, 145.7, 136.2, 135.2, 129.6, 129.5, 126.8, 121.7, 121.1, 119.5, 118.9, 111.0, 62.9, 54.2, 33.2, 32.7.

*1,4-bis((4-(1H-indol-3-yl)piperidin-1-yl)methyl)benzene (**9m**)*

Reaction of compound **5** (50 mg, 0.25 mmol), terephthaldehyde (50.3 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 37.7 mg (30 %) of desired amine as beige solid.

ESI-MS: $C_{34}H_{38}N_4$, *m/z* calculated for $[M+H]^+$: 503.31, Found: 503.29. **^{1}H NMR** δ (DMSO) 10.74 (s, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.39 – 7.25 (m, 6H), 7.08 (s, 2H), 7.04 (dd, *J* = 7.5, 1.1 Hz, 2H), 6.94 (dd, *J* = 7.6, 1.2 Hz, 2H), 3.49 (s, 4H), 2.91 (d, *J* = 12.1 Hz, 4H), 2.75 (tt, *J* = 12.2, 3.8 Hz, 2H), 2.11 (td, *J* = 11.8, 2.5 Hz, 4H), 1.96 – 1.86 (m, 4H), 1.69 (qd, *J* = 12.0, 3.4 Hz, 4H);

^{13}C NMR δ (DMSO) 137.2, 136.3, 128.6, 126.3, 120.7, 120.5, 119.6, 118.5, 117.9, 111.4, 62.4, 53.8, 33.1, 32.8.

*4-(4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)benzyl)morpholine (**9n**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 4-(morpholinomethyl)benzaldehyde (30.8 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 14.8 mg (38 %) of desired amine as a beige solid.

ESI-MS: $C_{25}H_{31}N_3O$, *m/z* calculated for $[M+H]^+$: 390.25, Found: 390.17. **^{1}H NMR** δ ($CDCl_3$) 8.25 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.32 (m, 5H), 7.16 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.08 (ddd, *J* = 7.8, 7.1, 1.1 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 3.81 (s, 2H), 3.76 – 3.67 (m, 4H), 3.51 (s, 2H), 3.22 (d, *J* = 11.5 Hz, 2H), 2.90 (m, 1H), 2.52 – 2.37 (m, 6H), 2.10 – 2.06 (m, 4H); **^{13}C NMR** δ ($CDCl_3$) 136.5, 130.4, 130.3, 129.6, 129.6, 126.6, 122.1, 120.1, 119.3, 118.9, 111.5, 67.1, 63.2, 62.2, 53.7, 32.8, 31.7.

*3-(1-(4-(piperidin-1-ylmethyl)benzyl)piperidin-4-yl)-1H-indole (**9o**)*

Reaction of compound **5** (20 mg, 0.10 mmol), 4-(piperidin-1-ylmethyl)benzaldehyde (30.5 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 20.9 mg (54 %) of desired amine as a beige solid.

ESI-MS: $C_{26}H_{33}N_3$, *m/z* calculated for $[M+H]^+$: 388.27, Found: 388.43. **^{1}H NMR** δ ($CDCl_3$) 8.02 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.18 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 2H), 3.56 (s, 2H), 3.47 (s, 2H), 3.03 (d, *J* = 11.9 Hz, 2H), 2.84 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.45 – 2.31 (m, 4H), 2.17 (td, *J* = 11.9, 2.4 Hz, 2H), 2.08 – 1.98 (m, 2H), 1.83 (qd, *J* = 12.0, 3.5 Hz, 2H), 1.58 (m, 4H), 1.44 (m, 2H); **^{13}C NMR** δ ($CDCl_3$) 137.2, 137.1, 136.4, 129.1, 129.0, 126.7, 121.9, 121.7, 119.6, 119.0, 111.1, 63.7, 63.4, 54.5, 54.4, 33.5, 33.1, 25.9, 24.4.

*3-(1-(pyridin-4-ylmethyl)piperidin-4-yl)-1H-indole (**9p**)*

Reaction of compound **5** (50 mg, 0.25 mmol), isonicotinaldehyde (40.1 mg, 0.37 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 70.6 mg (97 %) of desired amine as orange oil.

ESI-MS: $C_{19}H_{21}N_3$, *m/z* calculated for $[M+H]^+$: 292.17, Found: 292.36.**^{1}H NMR** δ (MeOD) 8.49 (d, *J* = 6.0 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 6.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.08 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.02 – 6.92 (m, 2H), 3.63 (s, 2H), 3.01 (m, 2H), 2.84 (tt, *J* = 11.9, 3.9 Hz, 1H), 2.27 (t, *J* = 11.9 Hz, 2H), 2.04 (d, *J* = 13.8 Hz, 2H), 1.86 (qd, *J* = 12.0, 3.5 Hz, 2H); **^{13}C NMR** δ (MeOD) 150.0, 149.8, 149.7, 138.3, 127.9, 126.0, 122.7, 122.2, 121.1, 120.9, 119.7, 119.4, 112.3, 62.8, 55.4, 34.6, 33.8.

*3-(1-(thiophen-2-ylmethyl)piperidin-4-yl)-1H-indole (**9q**)*

Reaction of compound **5** (20 mg, 0.10 mmol), thiophene-2-carbaldehyde (16.8 mg, 0.15 mmol) and sodium triacetoxyborohydride (29.7 mg, 0.14 mmol) according to general procedure A, gave 19.24 mg (65 %) of desired amine as a light yellow oil.

ESI-MS: $C_{18}H_{20}N_2S$, *m/z* calculated for $[M+H]^+$: 297.13, Found: 297.37.**^{1}H NMR** δ ($CDCl_3$) 8.00 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 6.99 – 6.95 (m, 3H), 3.82 (s, 2H), 3.08 (d, *J* = 12.9 Hz, 2H), 2.84 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.24 (t, *J* = 11.8 Hz, 2H), 2.06 (d, *J* = 12.9 Hz, 2H), 1.86 (qd, *J* = 11.8, 3.3 Hz, 2H); **^{13}C NMR** δ ($CDCl_3$) 142.0, 136.8, 127.2, 126.9, 126.7, 125.4, 122.4, 121.9, 120.1, 119.6, 119.5, 111.6, 57.9, 54.4, 33.9, 33.4.

*3-(1-(cyclohexylmethyl)piperidin-4-yl)-1H-indole (**9r**)*

Reaction of compound **5** (50 mg, 0.25 mmol), (*S*)-3,7-dimethyloct-6-enal (42.1 mg, 0.375 mmol) and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 74.1 mg (qtt yield) of desired amine as orange oil.

ESI-MS: $C_{20}H_{28}N_2$, *m/z* calculated for $[M+H]^+$: 298.23, Found: 298.20.**^{1}H NMR** δ ($CDCl_3$) 8.19 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 3.03 (d, *J* = 11.6 Hz, 2H), 2.83 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.21 (d, *J* = 6.9 Hz, 2H), 2.15 – 1.97 (m, 4H), 1.95 – 1.79 (m, 4H), 1.78 – 1.62 (m, 3H), 1.36 – 1.08 (m, 4H), 1.02 – 0.82 (m, 2H); **^{13}C NMR** δ ($CDCl_3$) 136.5, 126.8, 121.9, 121.6, 119.9, 119.2, 119.1, 111.3, 66.3, 55.1, 35.3, 33.7, 32.9, 32.3, 26.9, 26.3.

*3-(1-((S)-3,7-dimethyloct-6-en-1-yl)piperidin-4-yl)indoline (**9s**)*

Reaction of compound **5** (50 mg, 0.25 mmol), (*S*)-3,7-dimethyloct-6-enal (57.7 mg, 0.375 mmol)

and sodium triacetoxyborohydride (74.1 mg, 0.35 mmol) according to general procedure A, gave 83.4 mg (98 %) of desired amine as a dark orange oil.

ESI-MS: $C_{23}H_{36}N_2$, *m/z* calculated for $[M+H]^+$: 341.29, Found: 341.28. **^{1}H NMR** δ (DMSO) 10.75 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 5.01 (m, 1H), 2.94 (d, *J* = 9.3 Hz, 2H), 2.72 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.11 – 1.80 (m, 6H), 1.67 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.46 (m, 2H), 1.39 – 1.07 (m, 4H), 0.87 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** δ (DMSO) 136.4, 130.4, 126.3, 124.7, 120.7, 120.4, 119.7, 118.5, 117.9, 111.4, 58.8, 56.3, 54.3, 53.9, 36.7, 33.6, 33.3, 32.9, 30.2, 25.5, 24.9, 19.6, 17.5.

*(4-(1H-indol-3-yl)piperidin-1-yl)(phenyl)methanone (**10a**)*

Reaction of compound **5** (78.6 mg, 0.39 mmol) and benzoyl chloride (50 mg, 0.36 mmol) according to general procedure B, gave 59.9 mg (55 %) of desired amide as a beige solid.

ESI-MS: $C_{20}H_{20}N_2O$, *m/z* calculated for $[M+H]^+$: 305.16, Found: 305.13. **^{1}H NMR** δ (DMSO) 10.81 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.40 (m, 5H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.61 (br, 1H), 3.68 (br, 1H), 3.23 (br, 1H), 3.08 (tt, *J* = 3.4, 12.2 Hz, 1H), 2.95 (br, 1H), 2.15 – 1.80 (m, 2H), 1.68 – 1.58 (m, 2H); **^{13}C NMR** δ (DMSO) 169.4, 137.0, 136.8, 129.7, 128.9, 127.1, 126.6, 121.4, 121.3, 119.4, 118.9, 118.6, 111.9, 48.2, 42.6, 33.6.

*(4-(1H-indol-3-yl)piperidin-1-yl)(2,5-dimethoxyphenyl)methanone (**10b**)*

Reaction of compound **5** (54.9 mg, 0.27 mmol) and 2,5-dimethoxybenzoyl chloride (50 mg, 0.25 mmol) according to general procedure B, gave 91.04 mg (qtt yeild) of desired amide as a white solid.

ESI-MS: $C_{22}H_{24}N_2O_3$, *m/z* calculated for $[M+H]^+$: 365.18, Found: 365.16.**^{1}H NMR** δ ($CDCl_3$) 8.37 (s, NH), 7.62 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.51 (t, *J* = 2.3 Hz, 1H), 4.85 (br, 1H), 3.91 (br, 1H), 3.80 (s, 6H), 3.20 (br, 1H), 3.13 (tt, *J* = 11.8, 3.6 Hz, 1H), 2.98 (br, 1H), 2.18 (br, 1H), 2.06 (br, 1H), 1.82 (br, 1H), 1.66 (br, 1H); **^{13}C NMR** δ ($CDCl_3$) 170.1, 160.9, 138.3, 136.6, 126.4, 122.1, 120.2, 119.9, 119.3, 118.9, 111.5, 104.8, 101.6, 55.6, 48.4, 42.9, 33.9, 32.6, 29.8.

*(4-(1H-indol-3-yl)piperidin-1-yl)(4-fluorophenyl)methanone (**10c**)*

Reaction of compound **5** (69.6 mg, 0.35 mmol) and 4-fluorobenzoyl chloride (50 mg, 0.32 mmol) according to general procedure B, gave 97.9 mg (95%) of desired amide as a yellow oil. **ESI-MS:** $C_{20}H_{19}FN_2O$, *m/z* calculated for $[M+H]^+$: 323.15, Found: 323.33. **^{1}H NMR** δ (DMSO) 10.73 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.30 – 7.16 (m, 3H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 4.52 (br, 1H), 3.59 (br, 1H), 3.10 (br, 1H), 3.01 (tt, *J* = 11.8, 3.7 Hz, 1H), 2.91 (br, 1H), 1.91 (br, 2H), 1.57 (m, 2H); **^{13}C NMR** δ (DMSO) 168.5, 162.9 (d, $^1J_{CF}$ = 246 Hz), 136.8, 133.4, 129.8, 126.6, 121.3, 119.4, 118.9, 118.6, 115.9, 111.9, 48.4, 42.7, 33.6, 33.2, 29.5.

*(4-(1H-indol-3-yl)piperidin-1-yl)(pyridin-3-yl)methanone (**10d**)*

Reaction of compound **5** (78.1 mg, 0.39 mmol), nicotinoyl chloride (50 mg, 0.35 mmol) and DIPEA (182.9 µL, 1.05 mmol) according to general procedure C, gave 26.7 mg (25%) of desired amide as a beige solid.

ESI-MS: $C_{19}H_{19}N_3O$, *m/z* calculated for $[M+H]^+$: 306.15, Found: 306.38.**^{1}H NMR** δ ($CDCl_3$) 8.73 (d, *J* = 2.2 Hz, 1H), 8.68 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.46 (s, NH), 7.80 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.19 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 4.88 (br, 1H), 3.85 (br, 1H), 3.28 (br, 1H), 3.15 (tt, *J* = 11.9, 3.7 Hz, 1H), 3.01 (br, 1H), 2.20 (br, 1H), 2.08 (br, 1H), 1.83 (br, 1H), 1.70 (br, 1H); **^{13}C NMR** δ ($CDCl_3$) 167.8, 150.7, 147.9, 136.6, 135.0, 132.3, 126.4, 123.6, 122.2, 120.0, 119.9, 119.3, 118.9, 111.5, 48.6, 43.2, 33.8, 33.7, 32.5.

*(4-(1H-indol-3-yl)piperidin-1-yl)(thiophen-2-yl)methanone (**10e**)*

Reaction of compound **5** (76.1 mg, 0.38 mmol) and 2-thiophenecarbonyl chloride (50 mg, 0.35 mmol) according to general procedure B, gave 71.1 mg (66%) of desired amide as a beige solid. **ESI-MS:** $C_{18}H_{18}N_2OS$, *m/z* calculated for $[M+H]^+$: 311.11, Found: 311.29. **^{1}H NMR** δ ($CDCl_3$) 8.12 (s, NH), 7.64 (d, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.33 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.20 (ddd, *J* = 7.9, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 4.59 (br, 2H), 3.25 – 3.08 (m,

3H), 2.17 (br, 1H), 2.14 (br, 1H), 1.79 (m, 2H); **^{13}C NMR** δ ($CDCl_3$) 163.8, 137.7, 136.6, 128.7, 128.4, 126.8, 126.5, 122.3, 120.5, 119.9, 119.5, 119.0, 111.5, 34.0, 33.3, 29.9, 22.9, 14.3.

*1-(4-(1H-indol-3-yl)piperidin-1-yl)ethan-1-one (**10f**)*

Reaction of compound **5** (140.4 mg, 0.70 mmol) and acetyl chloride (50 mg, 0.64 mmol) according to general procedure B, gave 112.8 mg (73%) of desired amide as a yellow solid. **ESI-MS:** $C_{15}H_{18}N_2O$, *m/z* calculated for $[M+H]^+$: 243.14, Found: 243.37. **^{1}H NMR** δ ($CDCl_3$) 8.04 (s, NH), 7.63 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 4.77 (m, 1H), 3.92 (m, 1H), 3.26 (ddd, *J* = 13.4, 12.9, 2.7 Hz, 1H), 3.09 (tt, *J* = 11.8, 3.8 Hz, 1H), 2.75 (ddd, *J* = 13.4, 12.9, 2.9 Hz, 1H), 2.15 (s, 3H), 1.76 – 1.60 (m, 4H); **^{13}C NMR** δ ($CDCl_3$) 168.9, 136.4, 126.4, 122.2, 120.5, 119.7, 119.3, 118.9, 111.3, 47.1, 42.3, 33.8, 33.6, 32.3, 21.6.

*(4-(1H-indol-3-yl)piperidin-1-yl)(pyridin-4-yl)methanone (**10g**)*

Reaction of compound **5** (20 mg, 0.10 mmol), isonicotinic acid (12.3 mg, 0.10 mmol), DIPEA (52.3 µL, 0.3 mmol) and PyBOP (57.2 mg, 0.11 mmol) according to general procedure D, gave 18.30 mg (60 %) of desired amide as a yellow oil.

ESI-MS: $C_{19}H_{19}N_3O$, *m/z* calculated for $[M+H]^+$: 306.15, Found: 306.09.**^{1}H NMR** δ ($CDCl_3$) 8.71 (dd, *J* = 5.9, 1.6 Hz, 2H), 8.06 (s, NH), 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 5.9 Hz, 2H), 7.21 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 4.86 (d, *J* = 13.2 Hz, 1H), 3.74 (d, *J* = 15.9 Hz, 1H), 3.27 (td, *J* = 12.5, 2.3 Hz, 1H), 3.16 (tt, *J* = 3.7, 11.9 Hz, 1H), 3.0 (td, *J* = 12.9, 2.8 Hz, 1H), 2.23 (d, *J* = 13.3 Hz, 1H), 2.08 (d, *J* = 13.0 Hz, 1H), 1.84 (m, 1H), 1.63 (m, 1H); **^{13}C NMR** δ ($CDCl_3$) 167.5, 150.1, 143.9, 136.3, 126.1, 122.1, 120.9, 119.9, 119.5, 119.2, 118.7, 111.2, 48.0, 42.6, 33.6, 32.2, 29.5.

*(4-(1H-indol-3-yl)piperidin-1-yl)(pyridin-2-yl)methanone (**10h**)*

Reaction of compound **5** (20 mg, 0.10 mmol), picolinic acid (12.3 mg, 0.10 mmol), DIPEA (52.3 µL, 0.3 mmol) and PyBOP (57.2 mg, 0.11 mmol) according to general procedure D, gave 28.98 mg (95 %) of desired amide as a beige solid.

ESI-MS: $C_{19}H_{19}N_3O$, *m/z* calculated for $[M+H]^+$: 306.15, Found: 306.38.**^{1}H NMR** δ ($CDCl_3$) 8.71 (s, 2H), 8.22 (s, NH), 7.62 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.20 (ddd, *J* = 8.2, 7.1,

1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.86 (d, *J* = 12.8 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.27 (td, *J* = 12.7, 2.9 Hz, 1H), 3.15 (tt, *J* = 11.9, 3.7 Hz, 1H), 3.01 (td, *J* = 12.9, 2.7 Hz, 1H), 2.23 (d, *J* = 13.1 Hz, 1H), 2.08 (d, *J* = 13.0 Hz, 1H), 1.85 (m, 1H), 1.60 (m, 1H); **^{13}C NMR** δ ($CDCl_3$) 167.7, 150.3, 144.0, 136.4, 126.3, 122.2, 121.1, 119.9, 119.8, 119.3, 118.8, 111.4, 48.2, 42.8, 33.7, 33.6, 32.4.

*(4-(1H-indol-3-yl)piperidin-1-yl)(pyrazin-2-yl)methanone (**10i**)*

Reaction of compound **5** (20 mg, 0.10 mmol), pyrazine-2-carbonyl chloride (14.19 mg, 0.10 mmol), DIPEA (52.3 μL, 0.3 mmol) and PyBOP (57.2 mg, 0.11 mmol) according to general procedure D, gave 30.62 mg (qtt yield) of desired amide as a yellow solid.

ESI-MS: $C_{18}H_{18}N_4O$, *m/z* calculated for $[M+H]^+$: 307.15, Found: 307.38. **^{1}H NMR** δ ($CDCl_3$) 8.94 (d, *J* = 1.5 Hz, 1H), 8.63 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.10 (s, NH), 7.64 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 4.89 (d, *J* = 13.3 Hz, 1H), 4.05 (d, *J* = 13.5 Hz, 1H), 3.31 (td, *J* = 12.7, 2.8 Hz, 1H), 3.18 (tt, *J* = 11.8, 3.7 Hz, 1H), 3.04 (td, *J* = 12.9, 2.9 Hz, 1H), 2.23 (d, *J* = 13.2 Hz, 1H), 2.08 (d, *J* = 12.9 Hz, 1H), 1.95 – 1.76 (m, 2H); **^{13}C NMR** δ ($CDCl_3$) 165.7, 150.4, 145.7, 145.6, 143.2, 138.2, 126.8, 122.6, 120.7, 120.3, 119.8, 119.3, 111.8, 48.5, 43.8, 34.2, 33.9, 32.9.

*1,4-phenylenebis((4-(1H-indol-3-yl)piperidin-1-yl)methanone) (**10j**)*

Reaction of compound **5** (20 mg, 0.10 mmol), terephthalic acid (8.30 mg, 0.05 mmol), DIPEA (52.3 μL, 0.3 mmol) and PyBOP (57.2 mg, 0.11 mmol) according to general procedure D, gave 53.02 mg (qtt yield) of desired amide as a white solid.

ESI-MS: $C_{34}H_{34}N_4O_2$, *m/z* calculated for $[M+H]^+$: 531.27, Found: 531.45. **^{1}H NMR** δ (DMSO) 10.81 (s, 2H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.50 (s, 4H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 2.3 Hz, 2H), 7.05 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H), 6.96 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 2H), 4.61 (br, 2H), 3.70 (br, 2H), 3.26 (br, 2H), 3.09 (tt, *J* = 11.9, 3.6 Hz, 2H), 2.97 (br, 2H), 2.07 (br, 1H), 1.93 (br, 1H), 1.70 – 1.60 (m, 4H); **^{13}C NMR** δ (DMSO) 168.8, 137.8, 136.8, 127.3, 126.6, 121.4, 121.3, 119.4, 118.9, 118.6, 111.9, 49.1, 48.2, 33.6, 33.1, 14.4.

*4-(4-(1H-indol-3-yl)piperidin-1-yl)-6-chloroquinoline (**11**)*

To a solution of compound **5** (20 mg, 0.10 mmol) and DIPEA (52.3 µL, 0.3 mmol) in isopropanol (2 ml) was added 4,6-dichloroquinoline (19.80 mg, 0.10 mmol). The reaction mixture stirred under reflux for 56h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using a gradient elution of ethyl acetate/acetonitrile:water:methanol (1:1:1) to afford compound **11** as a yellow oil (9.05 mg, 25%).

ESI-MS: $C_{22}H_{20}ClN_3$, *m/z* calculated for $[M+H]^+$: 362.13, Found: 361.14. **^{1}H NMR** (DMSO) 10.89 (s, NH), 8.66 (d, *J* = 6.9 Hz, 1H), 8.22 – 8.09 (m, 2H), 8.02 (dd, *J* = 9.1, 1.3 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.08 (ddd, *J* = 7.8, 7.0, 1.3 Hz, 1H), 7.00 (m, 1H), 4.28 (d, *J* = 13.1 Hz, 2H), 3.70 (td, *J* = 12.8, 2.9 Hz, 2H), 3.29 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.20 (dd, *J* = 11.9, 2.0 Hz, 2H), 2.02 (qd, *J* = 12.9, 2.4 Hz, 2H); **^{13}C NMR** δ (DMSO) 159.5, 142.0, 138.5, 136.4, 133.5, 131.9, 130.3, 126.1, 125.3, 121.0, 120.9, 120.0, 118.6, 118.4, 118.2, 111.5, 106.2, 52.4, 32.4.

*(4-(1H-indol-3-yl)piperidin-1-yl)(piperidin-4-yl)methanone (**12**)*

Compound **6** (200 mg, 0.49 mmol) was dissolved in a solution of 2M HCl in MeOH (6 mL) and stirred at room temperature for 40 min. The solvent was removed under reduced pressure and the crude product was purified by reverse phase flash chromatography using a gradient elution of water/acetonitrile to afford the desired product as a yellow solid (151.2 mg, qtt yield).

ESI-MS: $C_{19}H_{25}N_3O$, *m/z* calculated for $[M+H]^+$: 312.20, Found: 312.41. **^{1}H NMR** δ (MeOD) 8.49 (s, NH), 7.59 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.10 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.04 (s, 1H), 7.01 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 4.66 (d, *J* = 13.3 Hz, 1H), 4.21 (d, *J* = 13.7 Hz, 1H), 3.49 (m, 2H), 3.39 (m, 1H), 3.24 – 3.08 (m, 4H), 2.87 (td, *J* = 12.9, 2.8 Hz, 1H), 2.21 (d, *J* = 13.1 Hz, 2H), 2.12 (d, *J* = 13.9 Hz, 2H), 2.07 – 1.86 (m, 4H), 1.70 (m, 2H); **^{13}C NMR** δ (MeOD) 173.7, 138.3, 127.7, 122.3, 121.2, 120.3, 119.5, 119.4, 112.3, 47.5, 44.4, 43.9, 36.7, 35.2, 34.9, 33.9, 26.8, 26.6, 25.9.

*(4-(1H-indol-3-yl)piperidin-1-yl)(1-benzoylpiperidin-4-yl)methanone (**13a**)*

Reaction of compound **12** (20 mg, 0.06 mmol) and benzoyl chloride (7.56 mg, 0.054 mmol) according to general procedure B, gave 22.4 mg (80 %) of desired product as a beige solid.

ESI-MS: $C_{26}H_{29}N_3O_2$, *m/z* calculated for $[M+H]^+$: 416.23, Found: 416.22. **^{1}H NMR** δ ($CDCl_3$) 8.66 (s, NH), 7.60 (m, 1H), 7.47 – 7.36 (m, 5H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.90 (s, 1H), 4.76 (m, 1H), 4.52 (br, 1H), 4.03 (m, 1H), 3.87 (br, 1H), 3.25 (t, *J* = 12.1 Hz, 2H), 3.09 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.96 – 2.70 (m, 5H), 2.23 – 2.05 (m, 2H), 1.92 – 1.80 (m, 2H), 1.74 – 1.59 (m, 2H); **^{13}C NMR** δ ($CDCl_3$) 172.6, 170.7, 136.6, 135.9, 133.1, 129.7, 128.6, 128.4, 126.9, 126.3, 121.9, 120.0, 119.8, 119.1, 118.8, 111.5, 51.9, 47.4, 46.3, 42.9, 42.0, 40.9, 38.4, 33.9, 32.5, 28.9.

*(4-(1H-indol-3-yl)piperidin-1-yl)(1-(3,5-dimethoxybenzoyl)piperidin-4-yl)methanone (**13b**)*
Reaction of compound **12** (20 mg, 0.06 mmol) and 3,5-dimethoxybenzoyl chloride (10.8 mg, 0.054 mmol) according to general procedure B, gave 19.24 mg (75 %) of desired product as a beige oil.
ESI-MS: $C_{28}H_{33}N_3O_4$, *m/z* calculated for $[M+H]^+$: 476.25, Found: 476.42. **^{1}H NMR** δ (MeOD) 7.61 (d, *J* = 8.2 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.61 (dd, *J* = 2.9, 2.3 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 4.70 (d, *J* = 13.6 Hz, 2H), 4.24 (d, *J* = 13.1 Hz, 1H), 3.84 (s, 6H), 3.80 (br, 1H), 3.30 – 3.07 (m, 3H), 3.01 (d, *J* = 11.6 Hz, 1H), 2.90 (m, 1H), 2.22 (d, *J* = 12.6 Hz, 1H), 2.14 (d, *J* = 12.6 Hz, 1H), 1.99 – 1.55 (m, 7H); **^{13}C NMR** δ (MeOD) 174.8, 172.1, 162.6, 138.9, 138.3, 127.7, 122.3, 121.2, 120.4, 119.5, 119.4, 112.3, 105.5, 102.5, 56.0, 47.4, 43.9, 39.3, 35.3, 35.1, 33.9.

*(4-(1H-indol-3-yl)piperidin-1-yl)(1-(4-fluorobenzoyl)piperidin-4-yl)methanone (**13c**)*
Reaction of compound **12** (20 mg, 0.06 mmol) and 4-fluorobenzoyl chloride (8.53 mg, 0.054 mmol) according to general procedure B, gave 17.54 mg (75 %) of desired product as a beige solid.
ESI-MS: $C_{26}H_{28}FN_3O_2$, *m/z* calculated for $[M+H]^+$: 434.22, Found: 434.23. **^{1}H NMR** δ ($CDCl_3$) 8.11 (s, NH), 7.62 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 7.5, 7.1 Hz, 1H), 7.14 – 7.06 (m, 3H), 6.95 (d, *J* = 2.4 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.67 (br, 1H), 4.03 (d, *J* = 12.4 Hz, 1H), 3.89 (br, 1H), 3.27 (t, *J* = 12.9 Hz, 1H), 3.12 (tt, *J* = 11.9, 3.7 Hz, 1H), 3.01 (br, 1H), 2.93 – 2.69 (m, 2H), 2.19 (d, *J* = 12.3 Hz, 1H), 2.12 (d, *J* = 12.9 Hz, 1H), 1.96 – 1.56 (m, 7H); **^{13}C NMR** δ ($CDCl_3$) 172.3, 169.6, 163.4 (d, $^1J_{CF}$ = 248 Hz), 136.4, 132.0,

129.2, 126.3, 122.2, 120.2, 119.7, 119.3, 118.8, 115.7, 115.5, 111.4, 46.2, 42.7, 40.9, 38.4, 33.9, 32.4.

*(4-(1H-indol-3-yl)piperidin-1-yl)(1-nicotinoylpiperidin-4-yl)methanone (**13d**)*

Reaction of compound **12** (20 mg, 0.06 mmol), nicotinoyl chloride (7.61 mg, 0.054 mmol) and DIPEA (52.3 μL, 0.16 mmol) according to general procedure C, gave 5.6 mg (25%) of desired product as a beige solid.

ESI-MS: $C_{25}H_{28}N_4O_2$, *m/z* calculated for $[M+H]^+$: 417.22, Found: 417.41. **^{1}H NMR** δ ($CDCl_3$) 8.73 – 8.60 (m, 2H), 8.23 (s, NH), 7.76 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.61 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.36 (m, 2H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.95 (d, *J* = 2.9 Hz, 1H), 4.78 (d, *J* = 12.9 Hz, 1H), 4.69 (br, 1H), 4.02 (d, *J* = 12.7 Hz, 1H), 3.79 (br, *J* = 1H), 3.28 (m, 1H), 3.12 (tt, *J* = 11.9, 3.8 Hz, 1H), 3.01 (br, 1H), 2.86 (td, *J* = 9.1, 4.6 Hz, 1H), 2.77 (t, *J* = 11.7 Hz, 1H), 2.19 (d, *J* = 12.4 Hz, 1H), 2.12 (d, *J* = 12.7 Hz, 1H), 1.95 – 1.79 (m, 3H), 1.77 – 1.58 (m, 4H); **^{13}C NMR** δ ($CDCl_3$) 172.1, 167.8, 150.7, 147.8, 136.5, 134.9, 131.9, 126.3, 123.5, 122.1, 120.1, 119.8, 119.3, 118.8, 111.4, 50.8, 46.2, 42.7, 38.2, 33.9, 32.4.

*(4-(1H-indol-3-yl)piperidin-1-yl)(1-(thiophene-2-carbonyl)piperidin-4-yl)methanone (**13e**)*

Reaction of compound **12** (20 mg, 0.06 mmol) and thiophene-2-carbonyl chloride (7.88 mg, 0.054 mmol) according to general procedure B, gave 16.6 mg (73 %) of desired product as a white solid.

ESI-MS: $C_{24}H_{27}N_3O_2S$, *m/z* calculated for $[M+H]^+$: 422.18, Found: 422.19. **^{1}H NMR** δ ($CDCl_3$) 8.19 (s, NH), 7.62 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 5.0 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 3.7 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.96 (s, 1H), 4.47 (d, *J* = 13.9 Hz, 2H), 3.18–3.01 (m, 4H), 2.91–2.84 (m, 2H), 2.16 (d, *J* = 12.2 Hz, 2H), 2.03–1.52 (m, 8H); **^{13}C NMR** δ ($CDCl_3$) 172.8, 164.2, 137.6, 136.9, 129.1, 128.9, 127.1, 126.8, 122.6, 120.6, 120.2, 119.7, 119.3, 111.8, 52.4, 41.4, 38.8, 34.3, 29.2, 28.7.

*1-(4-(4-(1H-indol-3-yl)piperidine-1-carbonyl)piperidin-1-yl)ethan-1-one (**13f**)*

Reaction of compound **12** (20 mg, 0.06 mmol) and acetyl chloride (4.21 mg, 0.054 mmol) according to general procedure B, gave 7.62 mg (40 %) of desired product as a white solid.

ESI-MS: $C_{21}H_{27}N_3O_2$, *m/z* calculated for $[M+H]^+$: 354.21, Found: 354.20. **^{1}H NMR** δ ($CDCl_3$) 8.15 (s, NH), 7.62 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.77 (d, *J* = 13.0 Hz, 1H), 4.60 (d, *J* = 13.2 Hz, 1H), 4.03 (d, *J* = 13.1 Hz, 1H), 3.90 (d, *J* = 13.5 Hz, 1H), 3.26 (t, *J* = 12.9 Hz, 1H), 3.17 – 3.08 (m, 2H), 2.88 – 2.66 (m, 2H), 2.24–2.16 (m, 2H), 2.10 (s, 3H), 1.91 (m, 1H), 1.83–1.56 (m, 6H); **^{13}C NMR** δ ($CDCl_3$) 172.9, 169.4, 136.9, 126.8, 122.6, 120.7, 120.2, 119.7, 119.3, 111.8, 49.6, 46.7, 46.3, 43.1, 41.5, 38.8, 34.4, 32.8, 26.1, 25.4, 21.9.

4.2. Biological Evaluation

4.2.1. *In vitro* Drug Sensitivity and EC_{50} Determination.

Drug assays were performed as previously described [37], with modifications for 384-well format. Briefly, synchronized ring-stage parasites were cultured in the presence of triplicate 12 point 2-fold serial dilutions of test compounds in 40 µl of RPMI-1640 (Sigma, USA) supplemented with 0.5% AlbuMAX® II (Gibco®, 11021-045) at 1.0% hematocrit and an initial parasitemia of 1.0% in black clear-bottom plates (Greiner Bio-one, 781090). Following a 72 hr incubation under standard culture conditions, SYBR Green I dye (Invitrogen, S7563) was added to a dilution of 1:5,000, and plates were stored at room temperature until fluorescence signal was read on a Spectramax M5 plate reader (Molecular Devices, ex 494 nm, em 530 nM). After background subtraction and normalization, EC_{50} values were calculated using a non-linear regression curve fit as implemented in the Mac OS X Prism 6.0c software package (GraphPad Software, Inc.).

4.2.2. *In vitro* Cytotoxicity to human cells.

HepG2 A16 human hepatic cell line viability was determined based on the MTT assay. An in vitro culture of HepG2 cells was maintained in standard culture conditions. Briefly, cells were seeded in a flat-bottomed 96-well tissue culture plate at a density of 1×10^4 cells/well and allowed to adhere overnight. After removing the medium, 200 μ L of fresh medium containing 7 ten-fold dilutions (100 μ M – 1 nM) of each compound were added, and a negative control was performed by adding 200 μ L of drug free medium. The plate was incubated for 24 h under standard culture conditions, medium was then substituted by fresh medium containing identical concentrations of the compounds, and the plates incubated another 24 h. At the end of the

incubation period (48 h), 20 μ L of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium (Sigma-Aldrich) (MTT; 5 mg/mL in PBS) was added to each well, wells were incubated for 3 h at standard culture conditions, supernatant was removed and 200 μL of acidified isopropanol was added to each well. Absorbance was read at 570 nm on a multi-mode microplate reader (Triad, Dynex Technologies), to produce a log dose-dependence curve. The EC_{50} was estimated for each compound by non-linear interpolation of the dose-dependence curve (GraphPad Software).

ASSOCIATED CONTENT

Supplementary Information: NMR spectra, including signals assignments for ^{1}H and ^{13}C of **10d**, ESI-MS spectra and HPLC-ELSD chromatograms of all compounds.

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ACKNOWLEDGMENT

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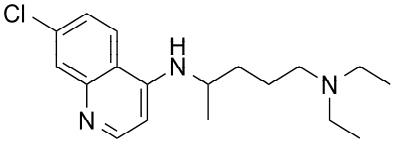
List of captions

Figure 1: Structures of (**1**), (**2**), TCMDC-134281 (**3**) and the indole-based explored scaffold.

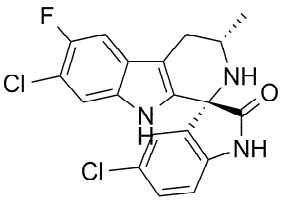
Scheme 1. Reagents and conditions: **a)** KOH, isopropanol, reflux, 6h, 98%; **b)** 10% Pd/C, 10% glacial acetic acid in ethyl acetate, H_2, 48h, r.t., 96%**; c)** DCC, HOBt, CH_3CN, 2h, r.t., 60%; **d)** DIBAL, THF, 1h, -78°C, 35%; **e)** 2M HCl/MeOH, 20 min, r.t., 99%; **f)** DIPEA, isopropanol, 56h, reflux, 15%.

Scheme 2. R fragments and yields are given in **Table 1**; Reagents and conditions: **a)** $NaBH(OAc)_3$, DCE, 1 h, r.t., 58-70 %; **b)** $NaBH(OAc)_3$, DCE, 4h, r.t. or $NaBH_3CN$, MeOH, Microwave at 100 °C, 20 min; **c)** DIPEA, isopropanol, 56 h, reflux, 25 %; **d)** DCM, aq. $NaHCO_3$, 10 min, r.t. or DIPEA, DCM, 30 min, r.t. or PyBOP, DIPEA, DCM, 0.5-1 h, r.t.

Scheme 3. R fragments and yields are listed in **Table 1**; Reagents and conditions: **a)** 2M HCl/MeOH, 40 min, r.t., quantitative yield; **b)** DCM, aq. $NaHCO_3$, 10 min, r.t.



Chloroquine (**1**)



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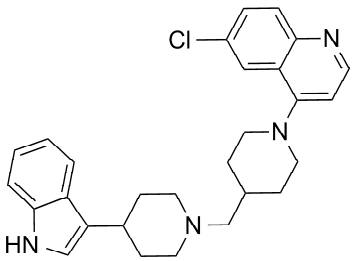

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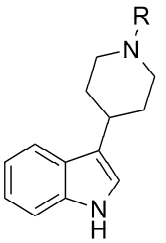

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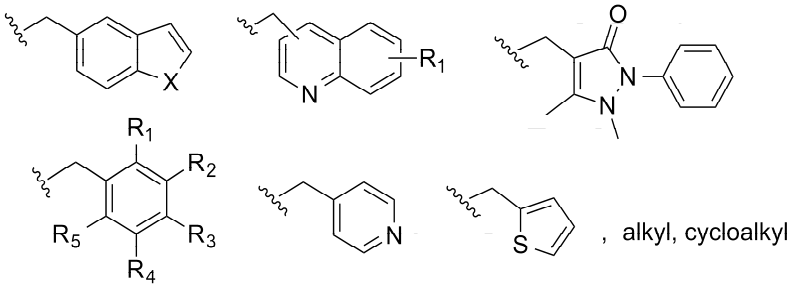
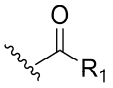
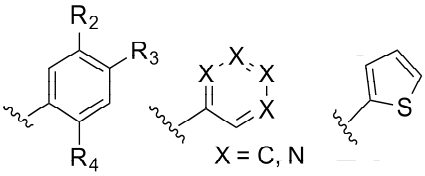
R = 

, alkyl, cycloalkyl

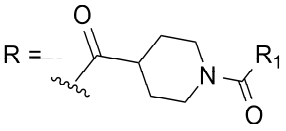
Amide series **(10a-k)**

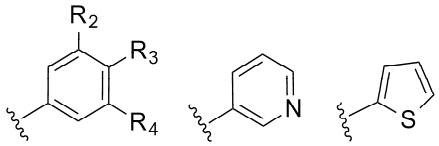
R = 

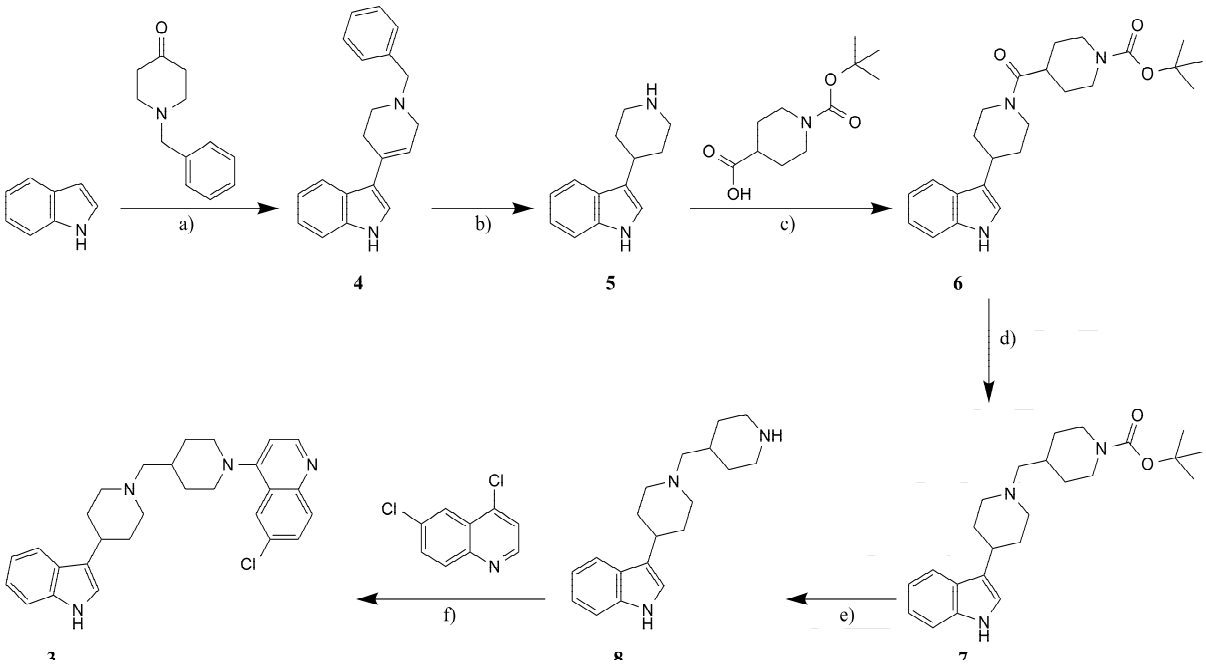
R_1 = Me, 

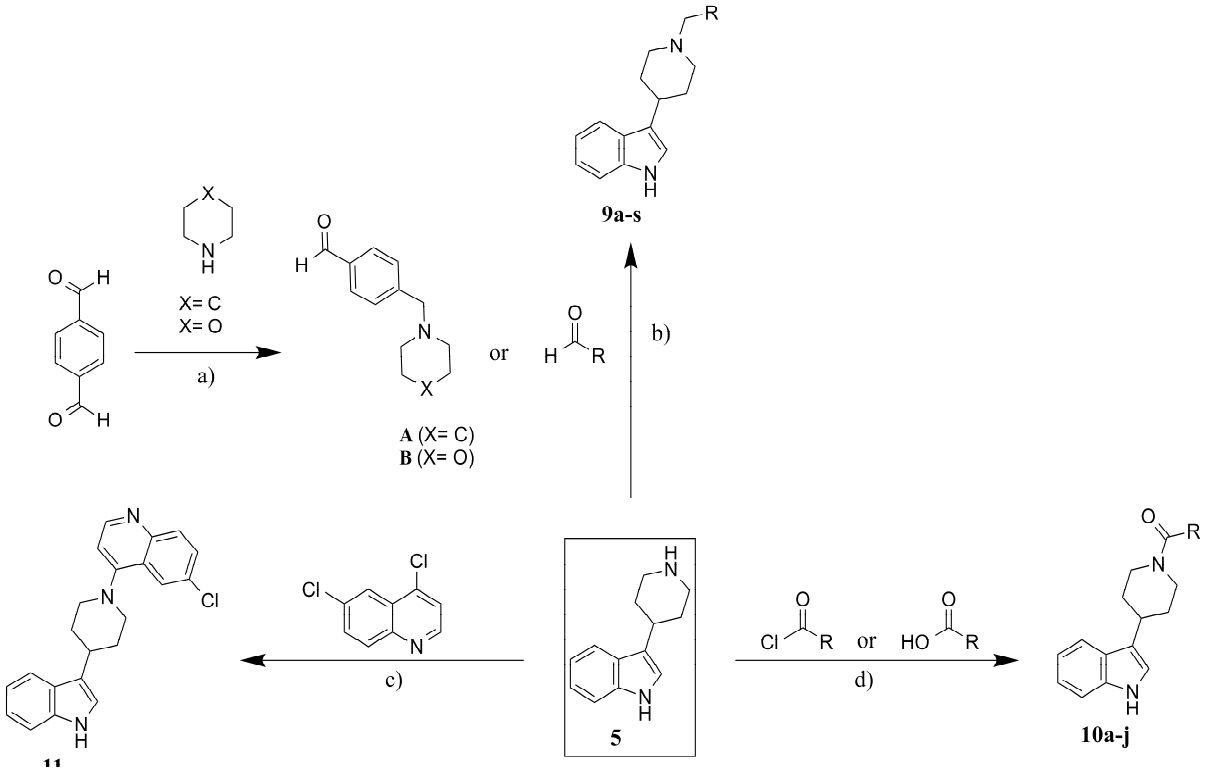
X = C, N

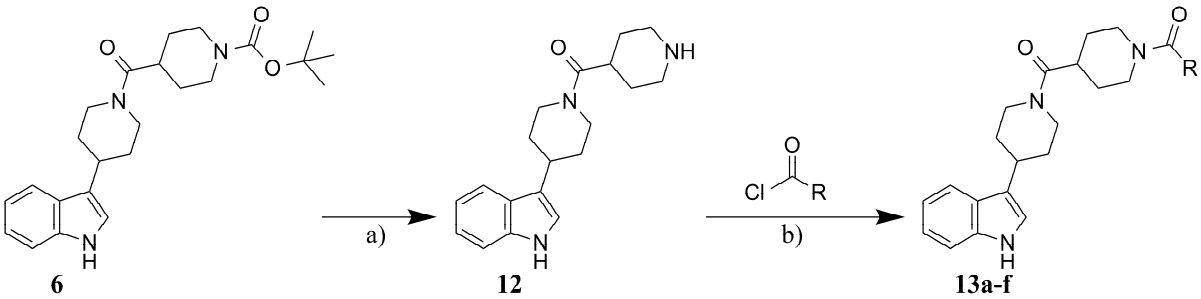
Bis-amide series **(13a-f)**

R = 

R_1 = Me, 







6 **12** **13a-f**

Highlights:

- A SAR library of new 3-piperidin-4-yl-1*H*-indole derivatives was synthesized.
- A succinct synthetic approach amenable to parallel combinatorial synthesis was developed.
- Activity against drug-sensitive and drug-resistant blood-stage *P. falciparum* was determined.
- Identification of a new compound (**10d**) with lead-like properties, antimalarial activity, selectivity and no cross-resistance with chloroquine.
- New chemotype independent from 4-aminoquinolines identified for further antimalarial drug development.

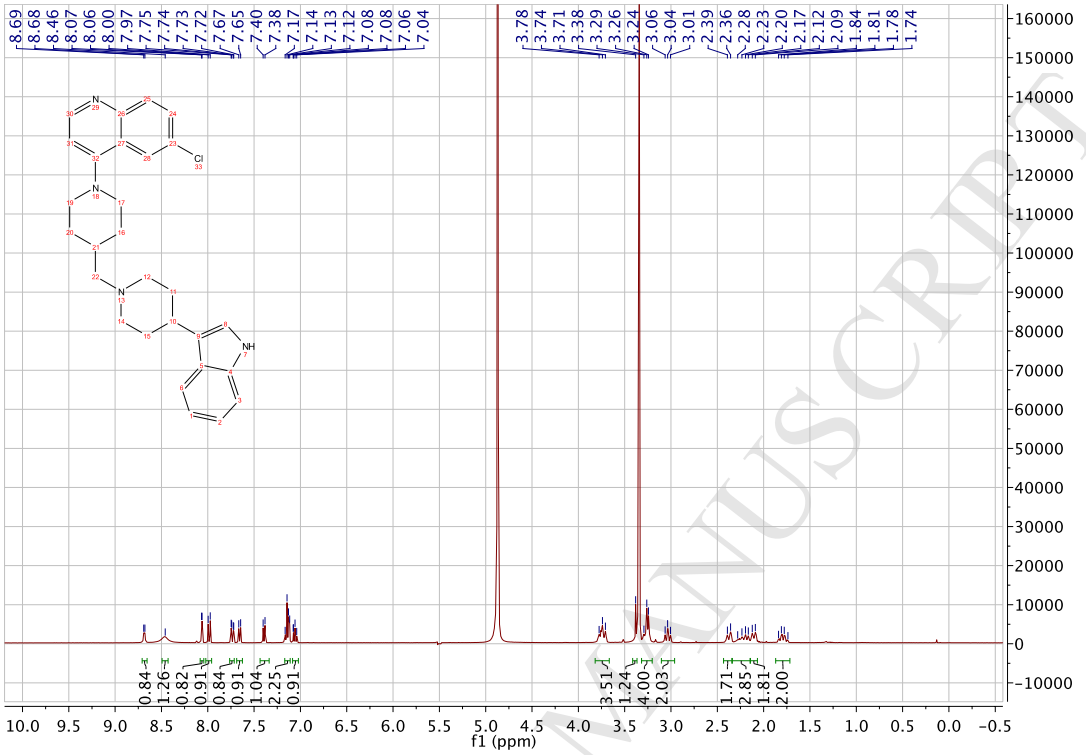
Supplementary Information

EXPLORING THE 3-PIPERIDIN-4-YL-1*H*-INDOLE SCAFFOLD AS A NOVEL ANTIMALARIAL CHEMOTYPE

Sofia A. Santos [a, b], Amanda K. Lukens [c, d], Lis Coelho [e], Fátima Nogueira [e], Dyann F. Wirth [c, d], Ralph Mazitschek [b, c, d], Rui Moreira [a], Alexandra Paulo [a]*

Compound 3

NMR



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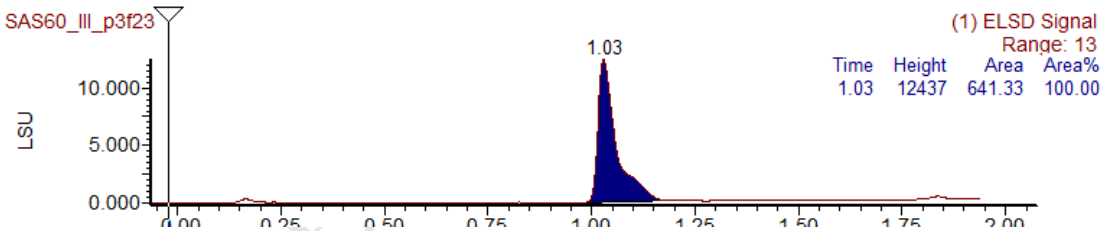

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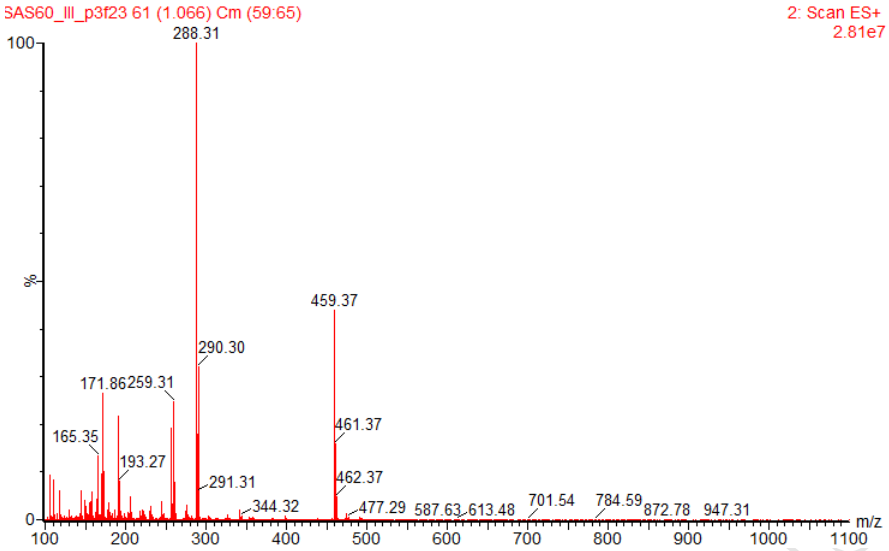
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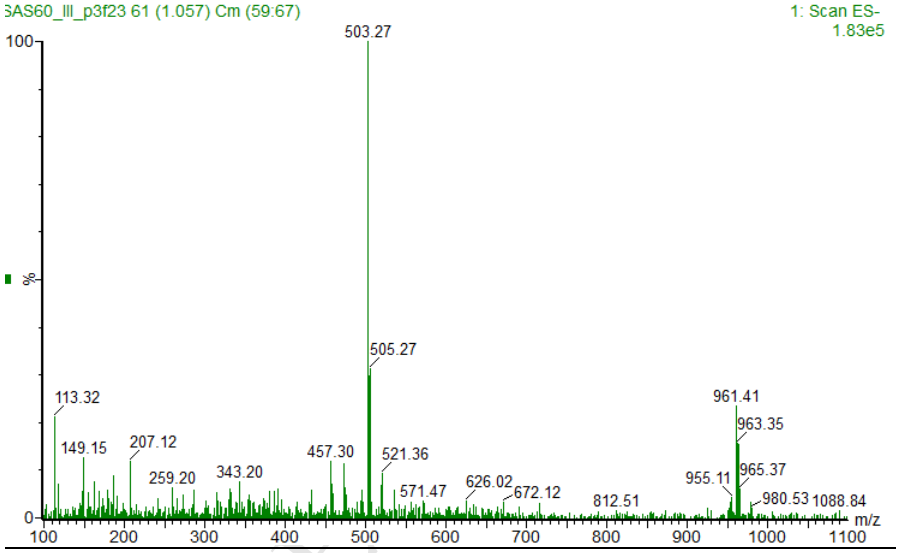
900
1000
1100

ES-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626.02
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955.11
965.37
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m/z
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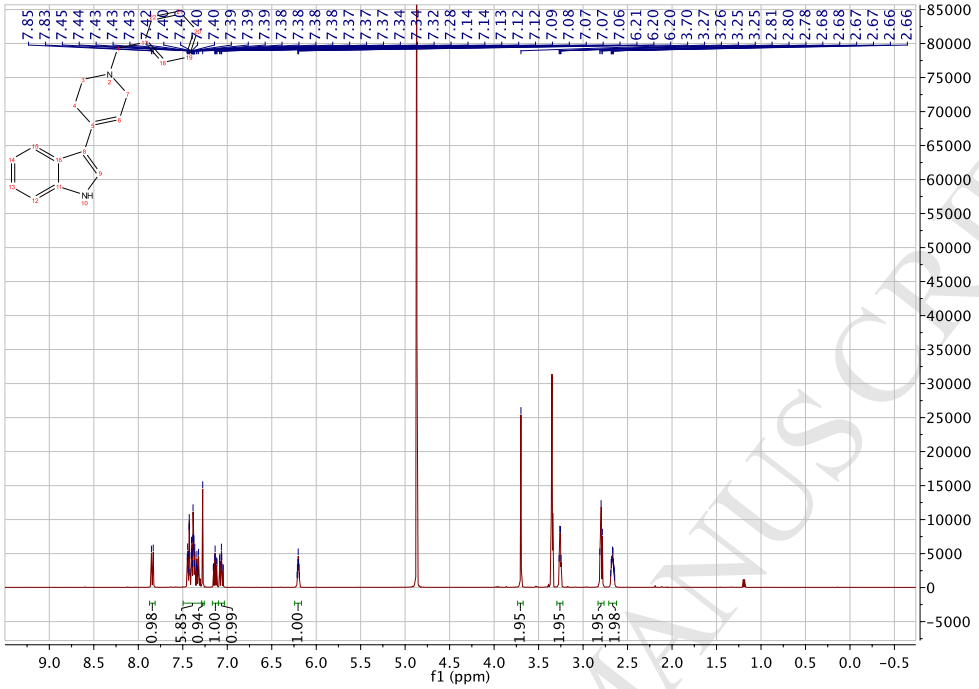
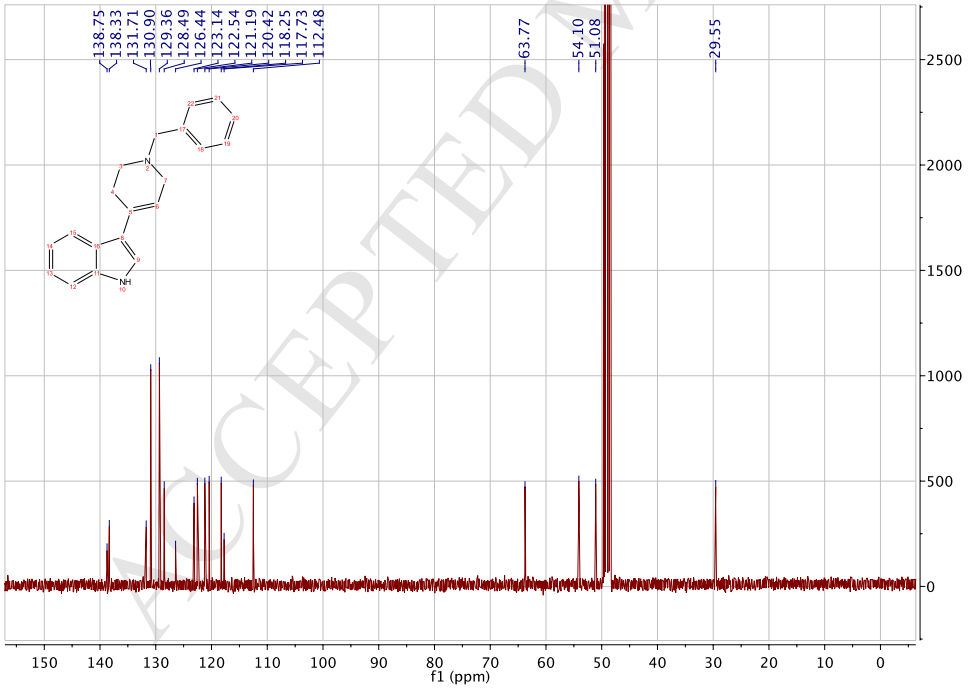
300
400
500
600
700
800
900
1000
1100

Compound 4

NMR





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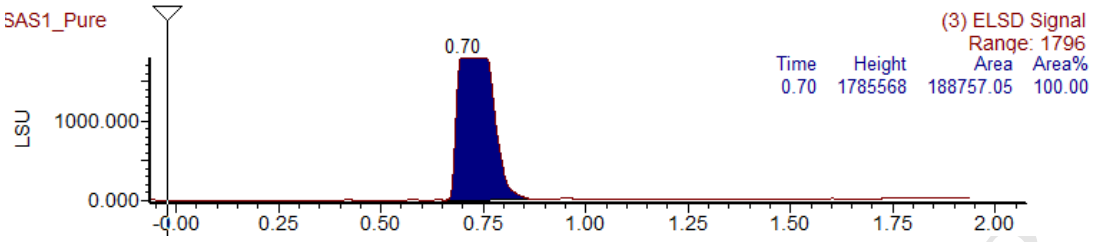
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LSU
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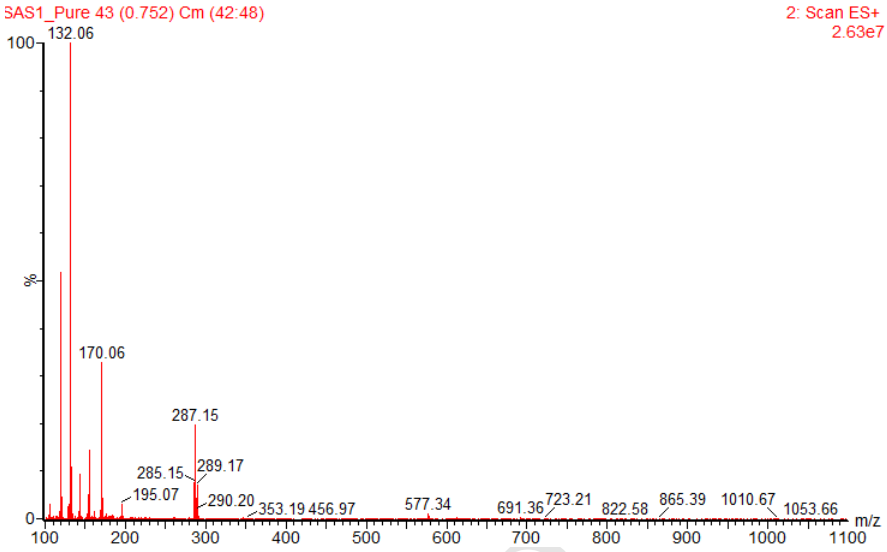
ES+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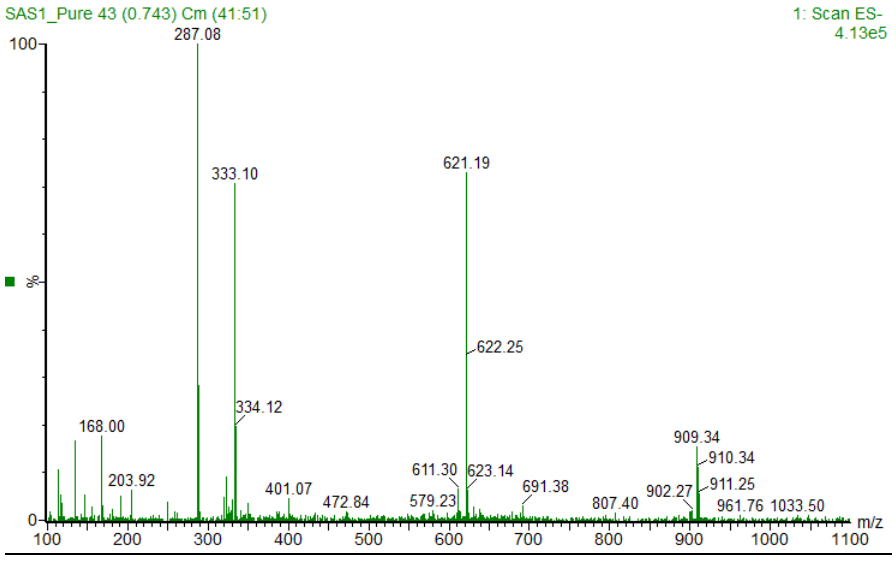
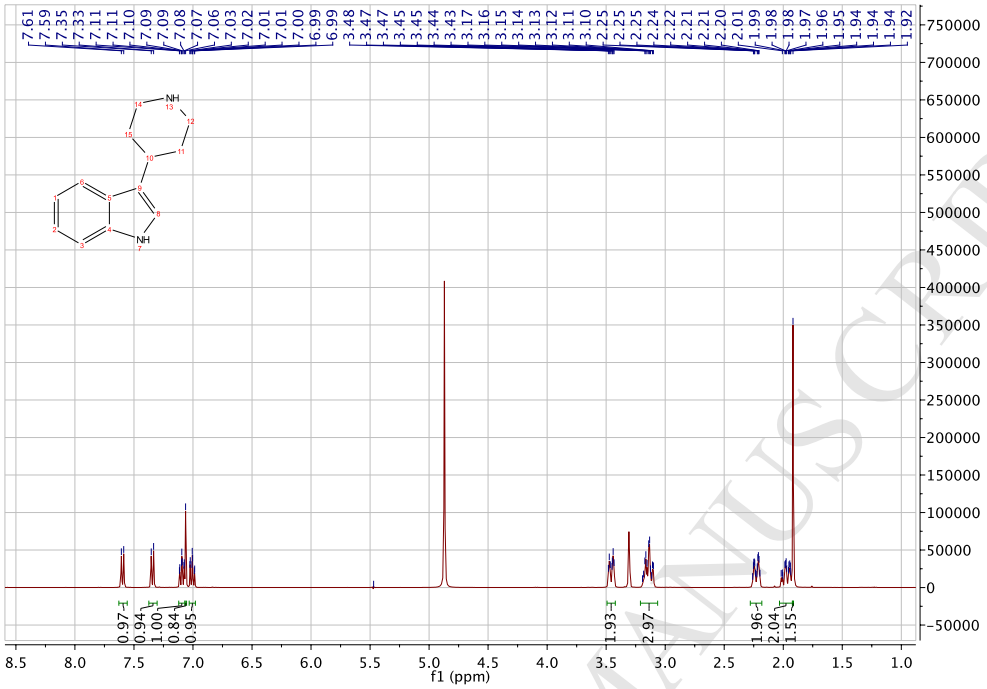
285.15
289.17
195.07
290.20
353.19 456.97
577.34
691.36
723.21
822.58
865.39
1010.67
1053.66
m/z
100 200 300 400 500 600 700 800 900 1000 1100

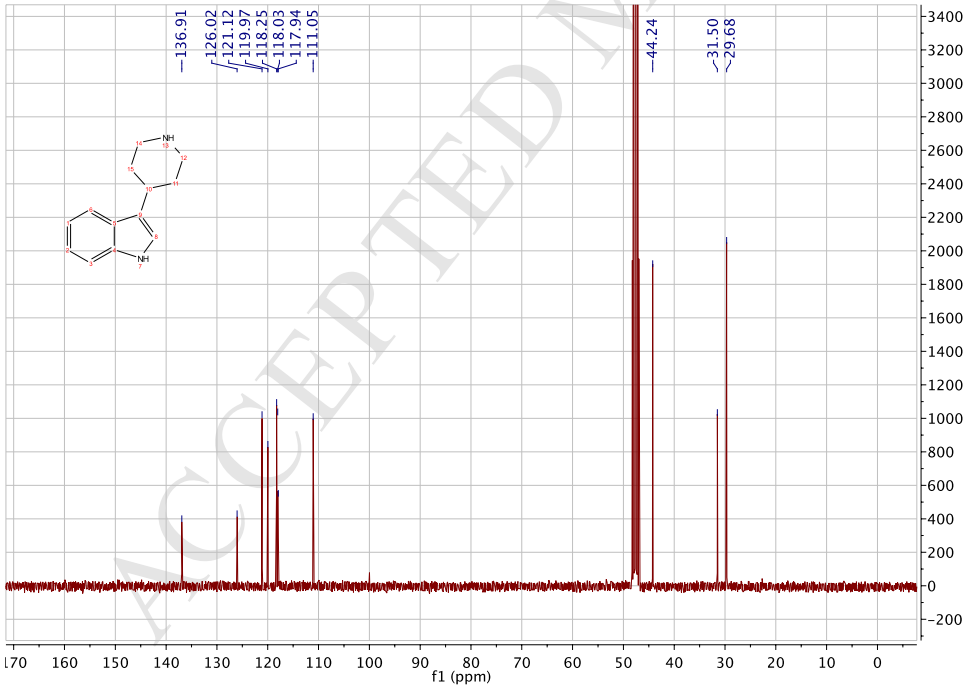
ES-


SAS1_Pure 43 (0.743) Cm (41:51)
1: Scan ES-
4.13e5
100
%
0
287.08
333.10
621.19
622.25
334.12
168.00
203.92
401.07
472.84
611.30
623.14
579.23
691.38
807.40
909.34
910.34
902.27
911.25
961.76 1033.50
m/z
100 200 300 400 500 600 700 800 900 1000 1100

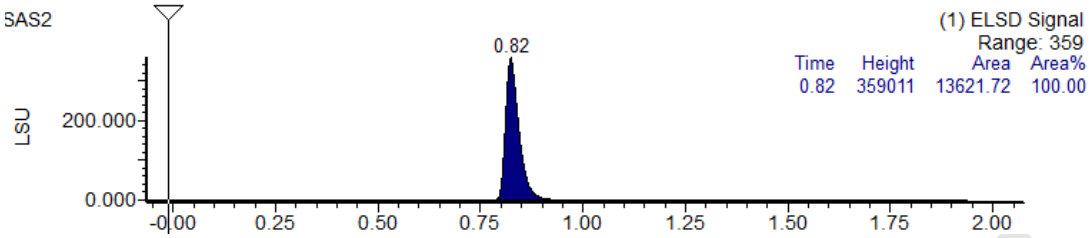
Compound 5

NMR

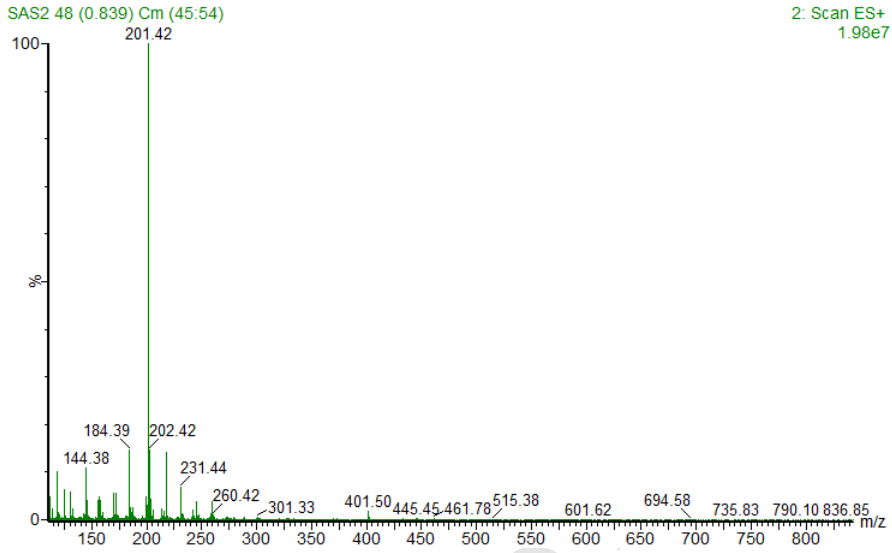




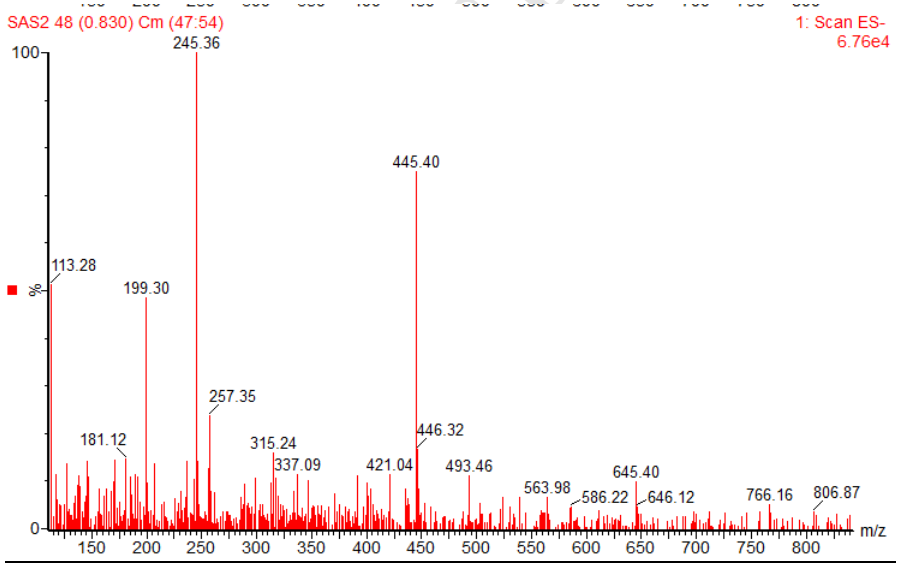
ELSD


SAS2
(1) ELSD Signal
Range: 359
Time Height Area Area%
0.82 359011 13621.72 100.00
0.82
LSU
200.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

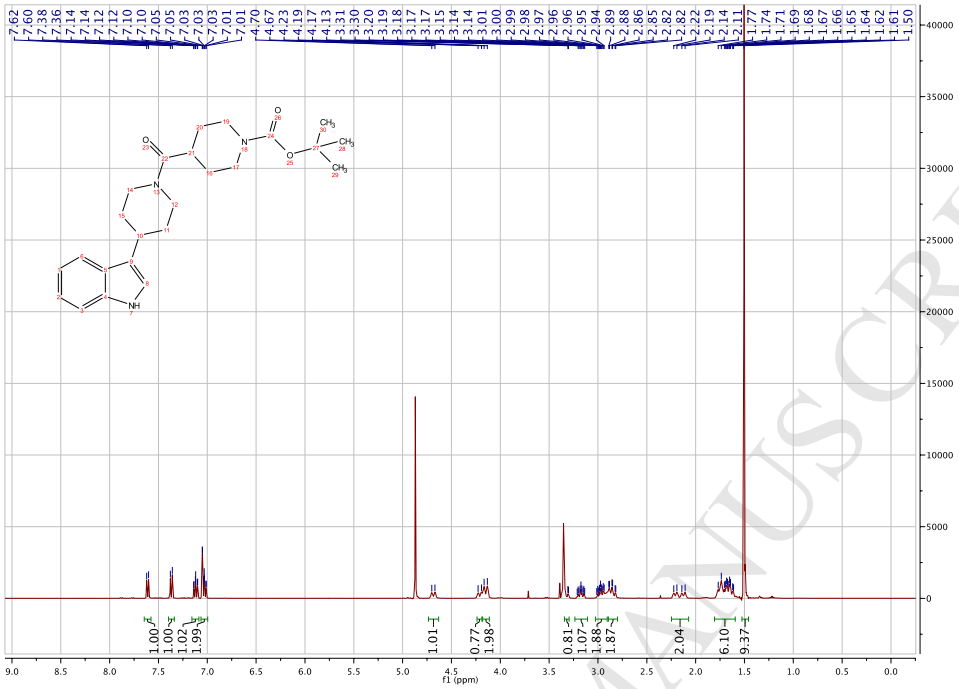

SAS2 48 (0.839) Cm (45:54)
2: Scan ES+
1.98e7
201.42
100
%
0
184.39
202.42
144.38
231.44
260.42
301.33
401.50
445.45
461.78
515.38
601.62
694.58
735.83
790.10
836.85
150 200 250 300 350 400 450 500 550 600 650 700 750 800
m/z

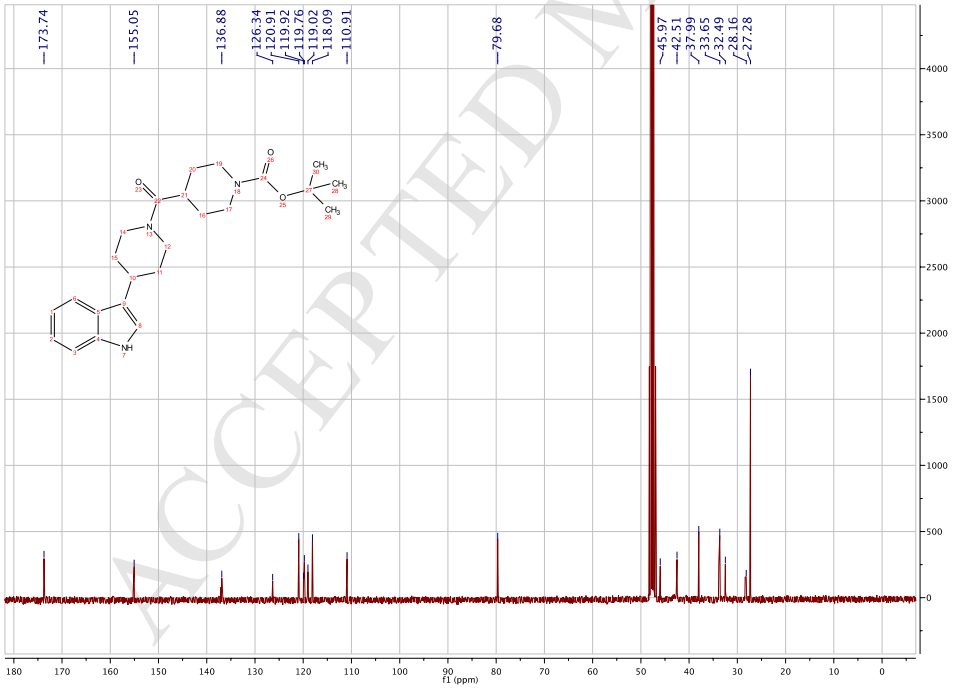
ES-


SAS2 48 (0.830) Cm (47:54)
1: Scan ES-
6.76e4
245.36
100
%
0
445.40
113.28
199.30
257.35
181.12
315.24
337.09
421.04
446.32
493.46
563.98
586.22
645.40
646.12
766.16
806.87
150 200 250 300 350 400 450 500 550 600 650 700 750 800
m/z

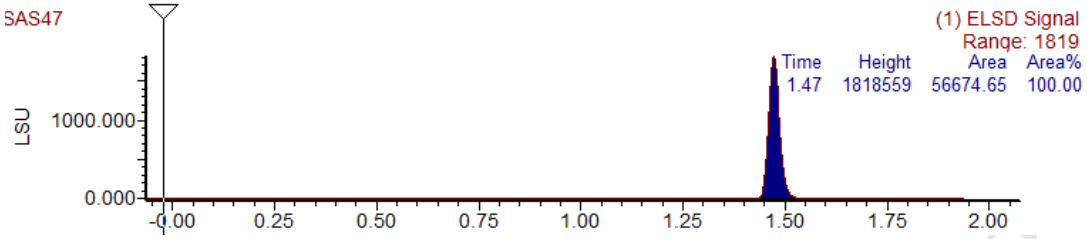
Compound 6

NMR

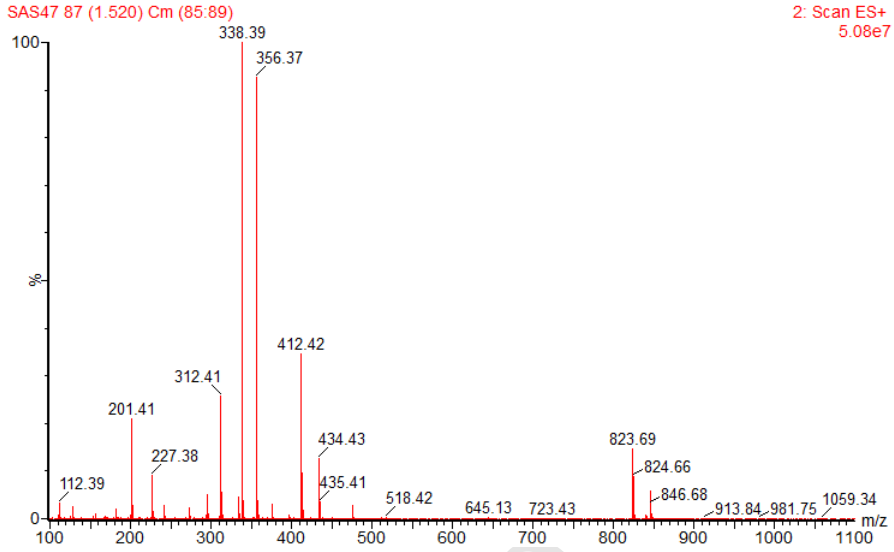




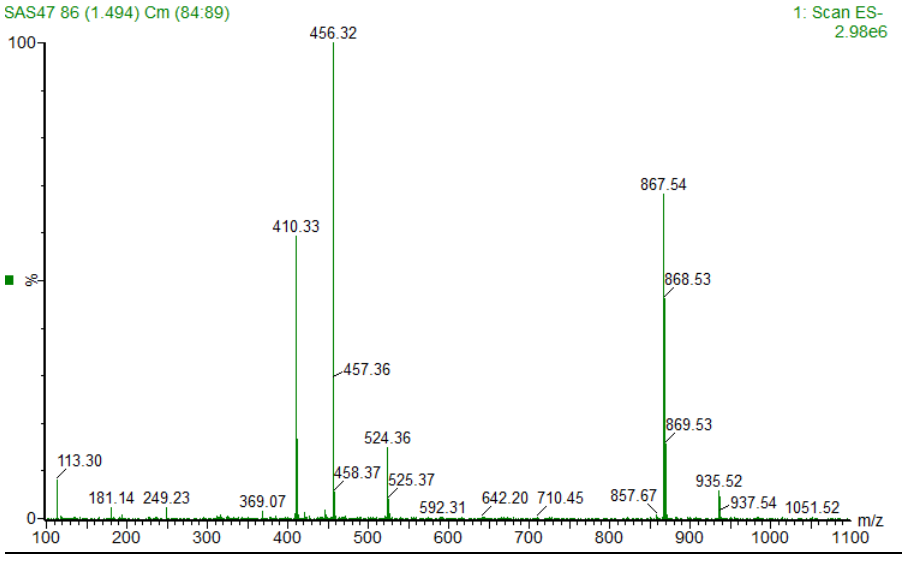
ELSD


SAS47
(1) ELSD Signal
Range: 1819
Time Height Area Area%
1.47 1818559 56674.65 100.00
LSU
1000.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

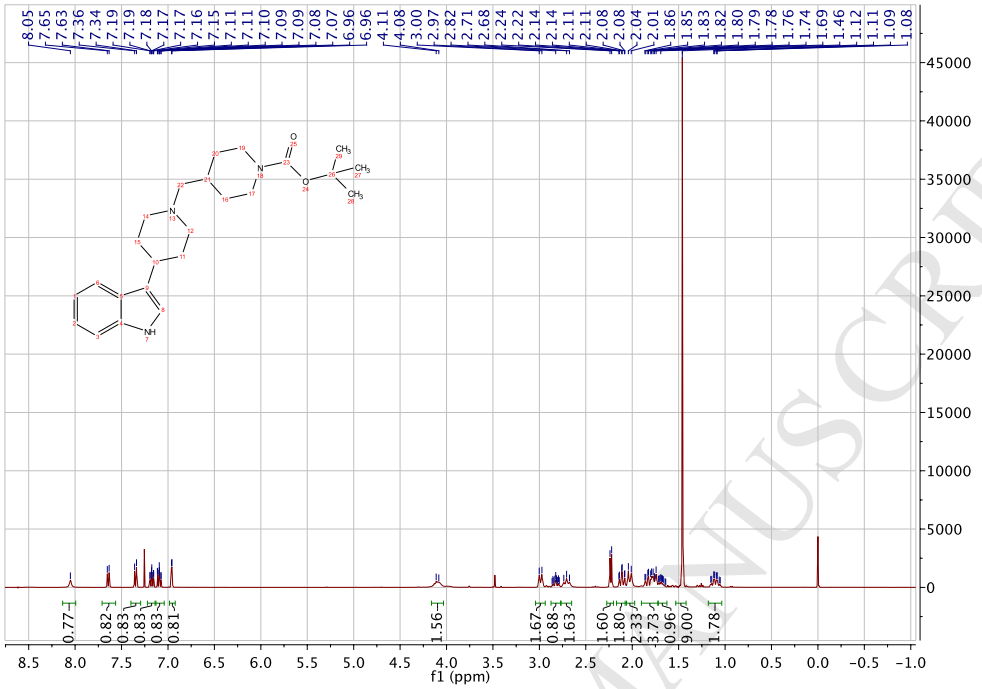

SAS47 87 (1.520) Cm (85:89)
2: Scan ES+
5.08e7
100
%
0
338.39
356.37
412.42
312.41
201.41
227.38
112.39
434.43
435.41
518.42
645.13
723.43
823.69
824.66
846.68
913.84
981.75
1059.34
100 200 300 400 500 600 700 800 900 1000 1100
m/z

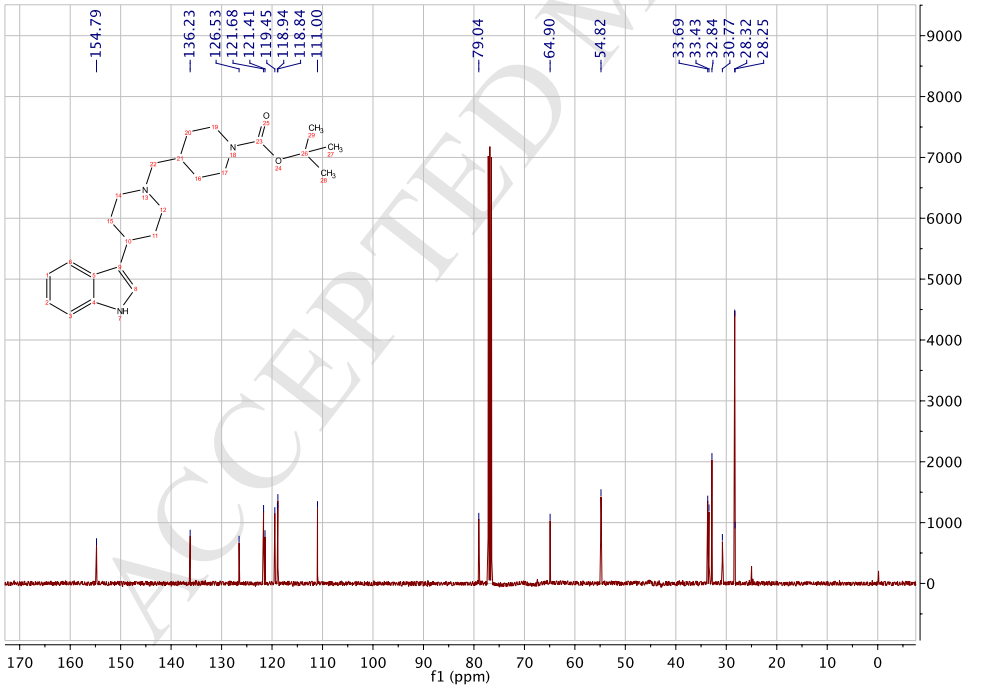
ES-


SAS47 86 (1.494) Cm (84:89)
1: Scan ES-
2.98e6
100
%
0
456.32
867.54
410.33
868.53
457.36
869.53
524.36
458.37
525.37
113.30
181.14
249.23
369.07
592.31
642.20
710.45
857.67
935.52
937.54
1051.52
100 200 300 400 500 600 700 800 900 1000 1100
m/z

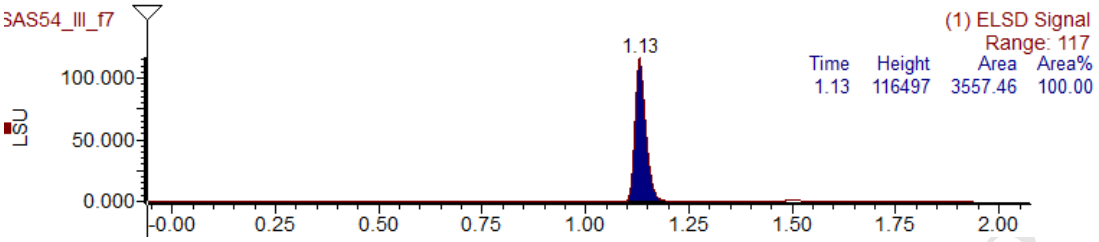
Compound 7

NMR

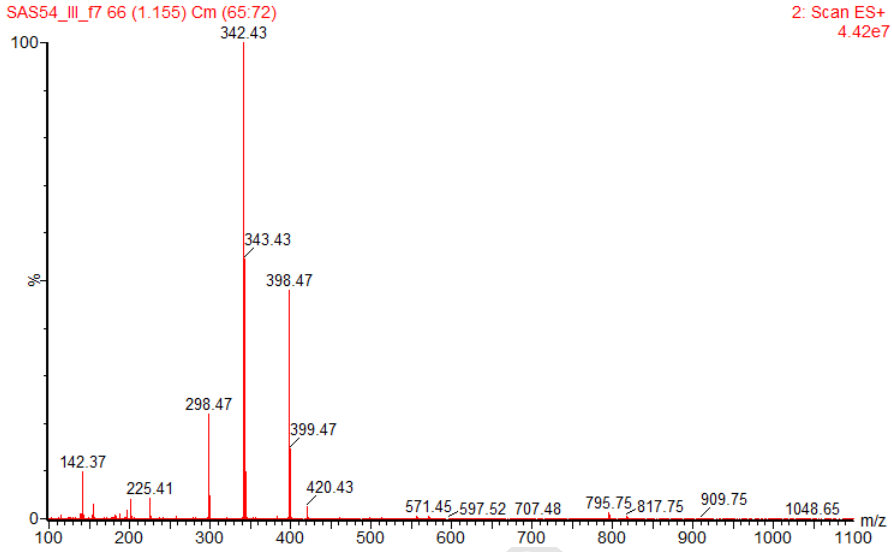




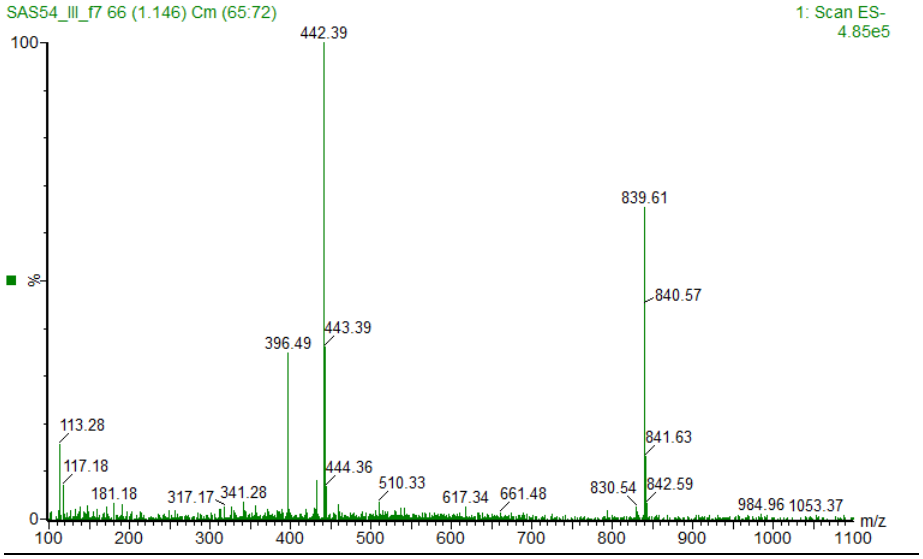
ELSD


SAS54_III_f7
(1) ELSD Signal
Range: 117
Time Height Area Area%
1.13 116497 3557.46 100.00
1.13
LSU
100.000
50.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

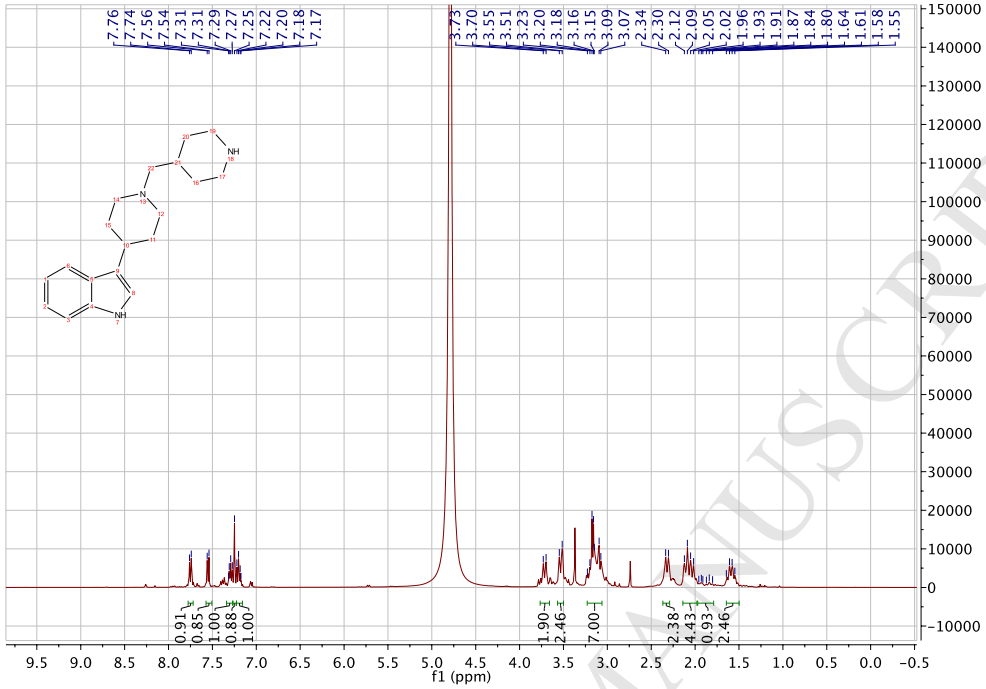

SAS54_III_f7 66 (1.155) Cm (65:72)
2: Scan ES+
4.42e7
342.43
343.43
398.47
298.47
399.47
142.37
225.41
420.43
571.45 597.52 707.48
795.75 817.75
909.75
1048.65
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

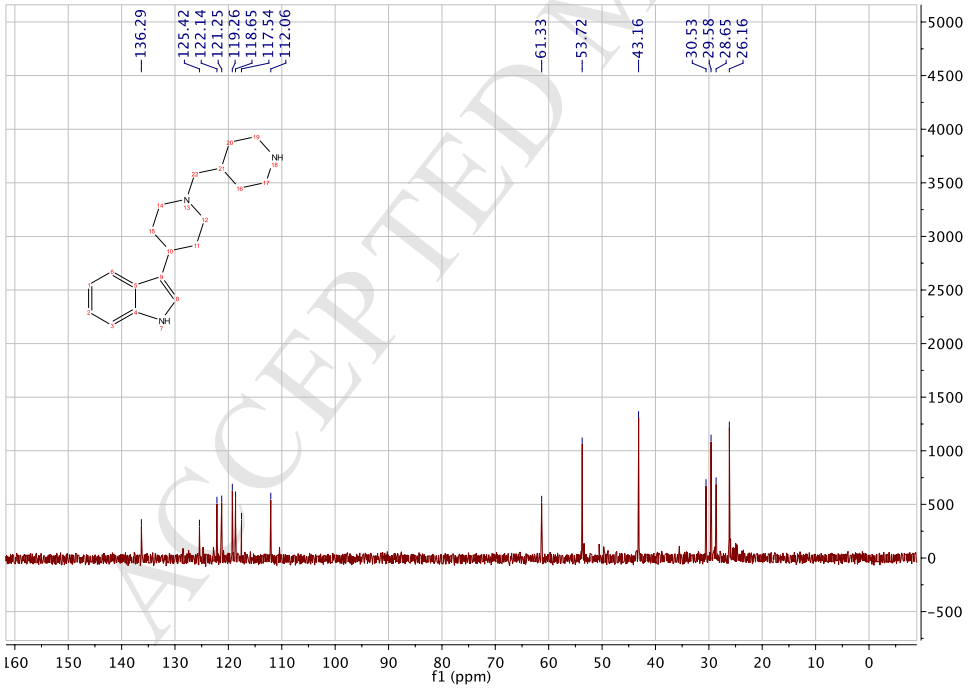
ES-


SAS54_III_f7 66 (1.146) Cm (65:72)
1: Scan ES-
4.85e5
442.39
839.61
840.57
443.39
396.49
113.28
841.63
117.18
444.36
510.33
181.18
317.17 341.28
617.34 661.48
830.54
842.59
984.96 1053.37
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

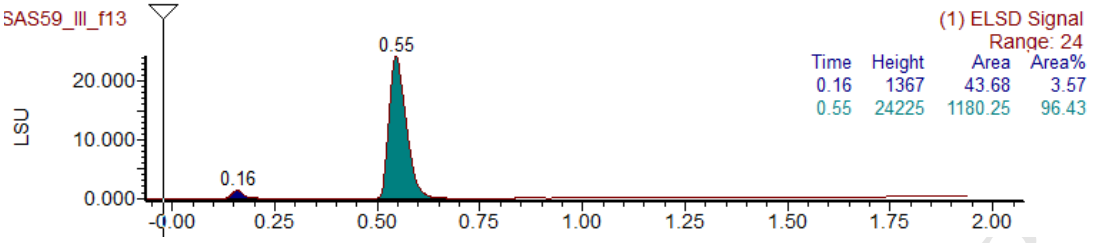
Compound 8

NMR

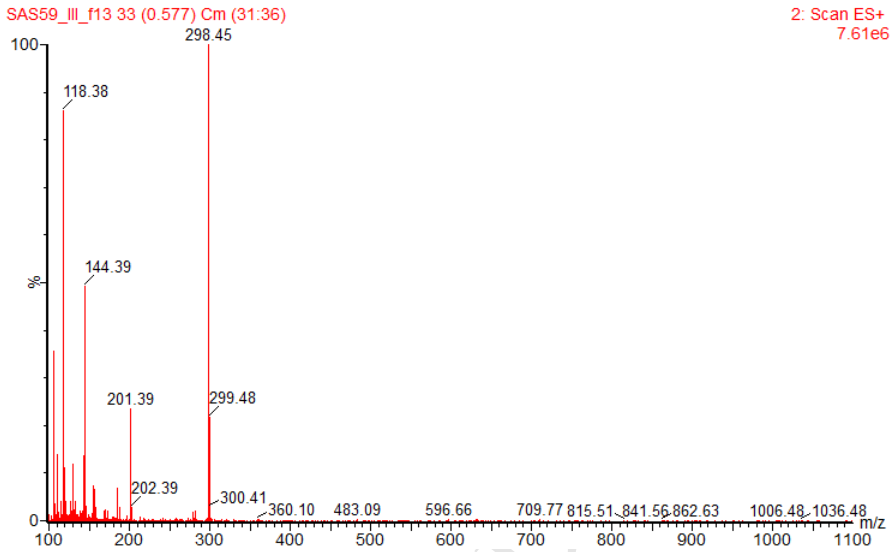




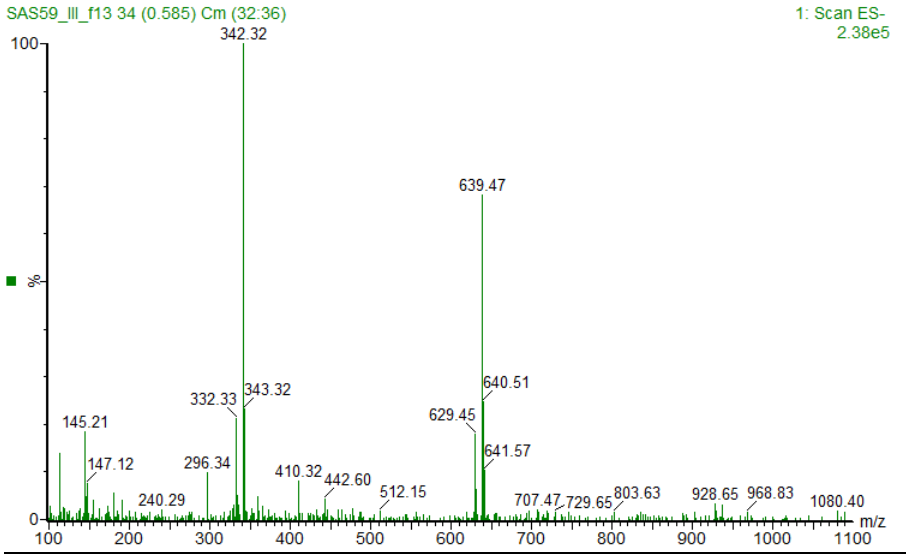
ELSD


SAS59_III_f13
(1) ELSD Signal
Range: 24
Time Height Area Area%
0.16 1367 43.68 3.57
0.55 24225 1180.25 96.43
LSU
20.000
10.000
0.000
0.16
0.55
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

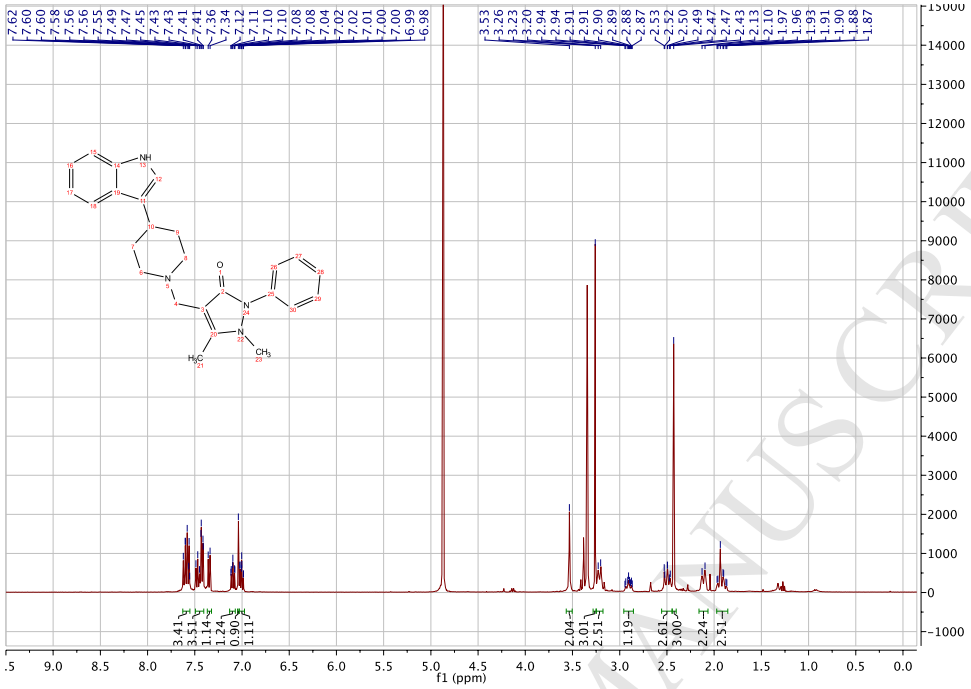

SAS59_III_f13 33 (0.577) Cm (31:36)
2: Scan ES+
7.61e6
100
%
0
298.45
118.38
144.39
201.39
299.48
202.39
300.41
360.10
483.09
596.66
709.77
815.51
841.56
862.63
1006.48
1036.48
100 200 300 400 500 600 700 800 900 1000 1100
m/z

ES-

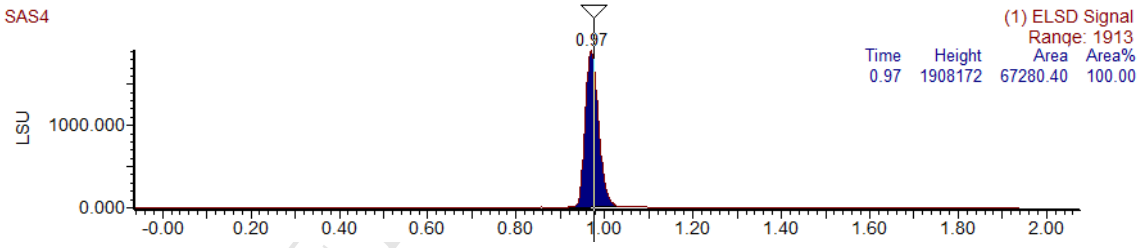

SAS59_III_f13 34 (0.585) Cm (32:36)
1: Scan ES-
2.38e5
100
%
0
342.32
639.47
640.51
343.32
332.33
629.45
145.21
641.57
147.12
296.34
410.32
442.60
512.15
240.29
707.47
729.65
803.63
928.65
968.83
1080.40
100 200 300 400 500 600 700 800 900 1000 1100
m/z

Compound 9a

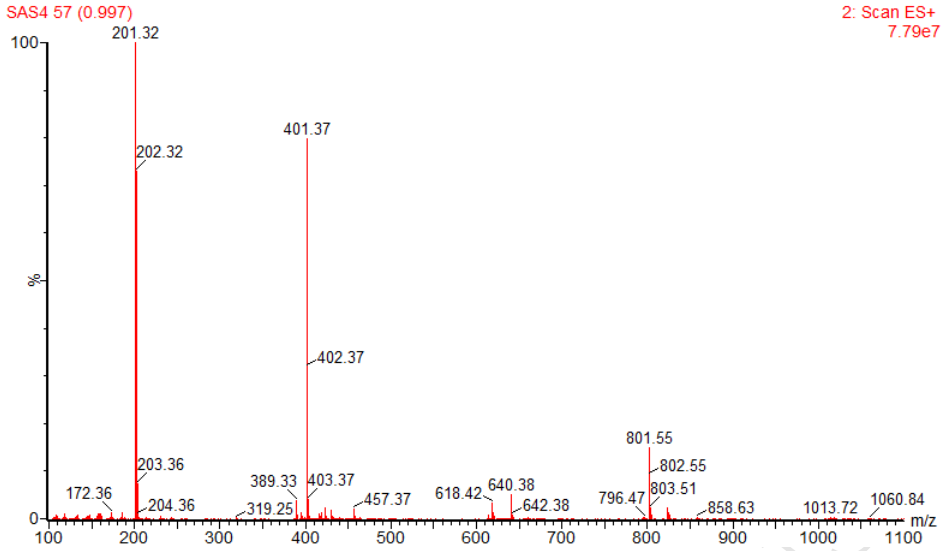
NMR



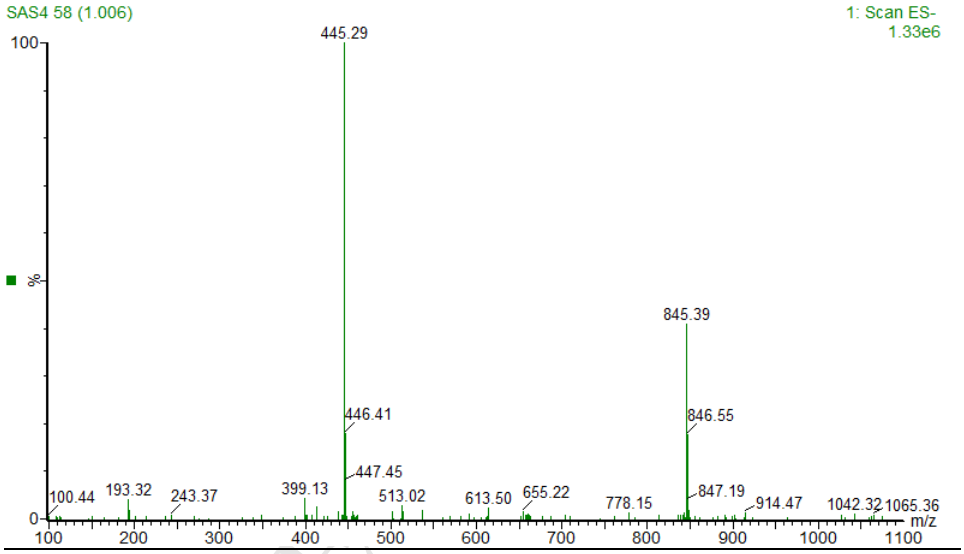
ELSD



ES+

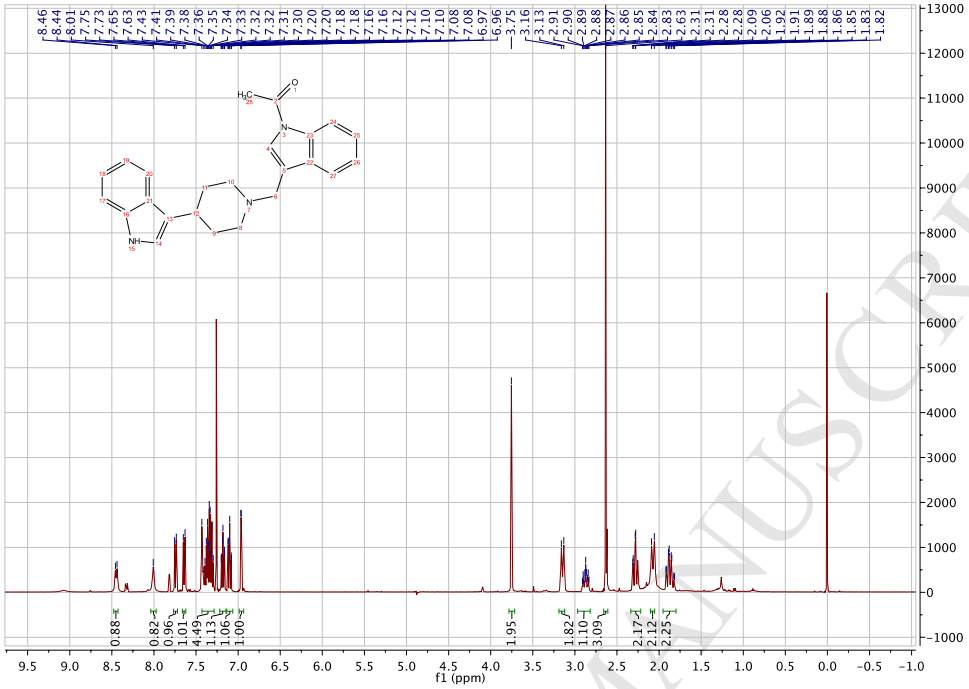

SAS4 57 (0.997)
2: Scan ES+
7.79e7
100
%
0
201.32
202.32
401.37
402.37
203.36
172.36
204.36
389.33
403.37
319.25
457.37
618.42
640.38
642.38
796.47
801.55
802.55
803.51
858.63
1013.72
1060.84
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

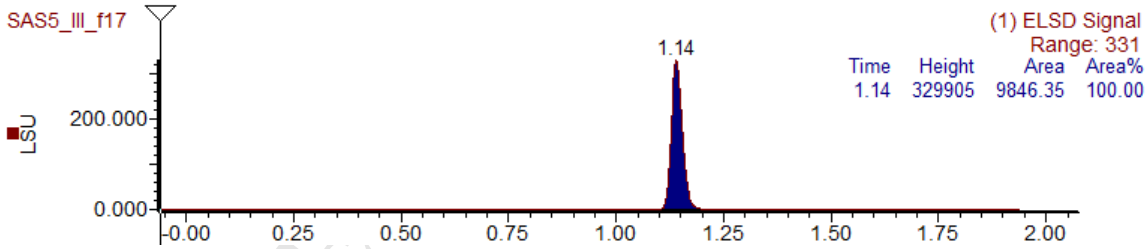

SAS4 58 (1.006)
1: Scan ES-
1.33e6
100
%
0
445.29
446.41
447.45
100.44
193.32
243.37
399.13
513.02
613.50
655.22
778.15
845.39
846.55
847.19
914.47
1042.32
1065.36
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 9b

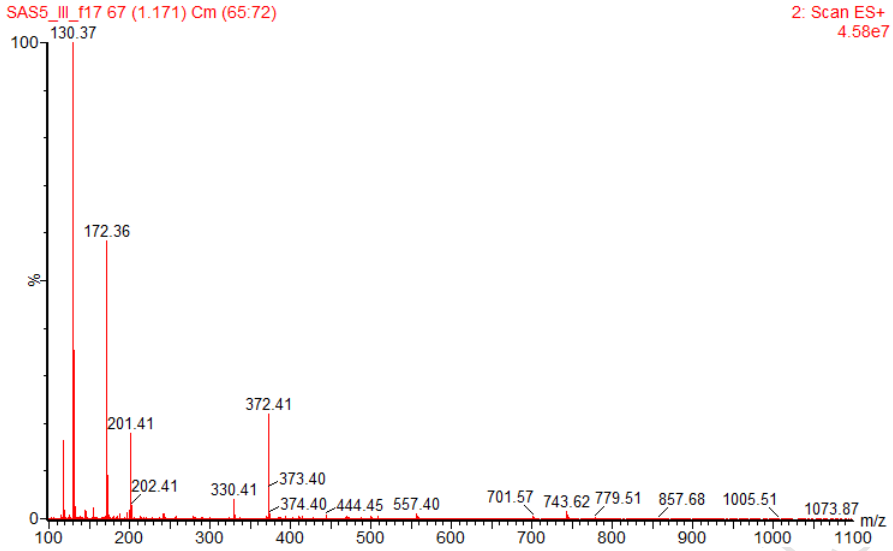
NMR



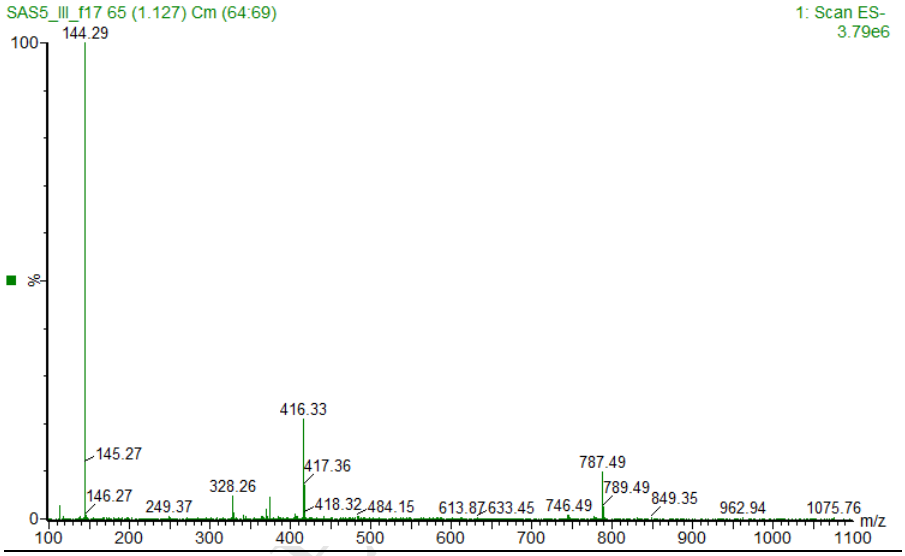
ELSD



ES+

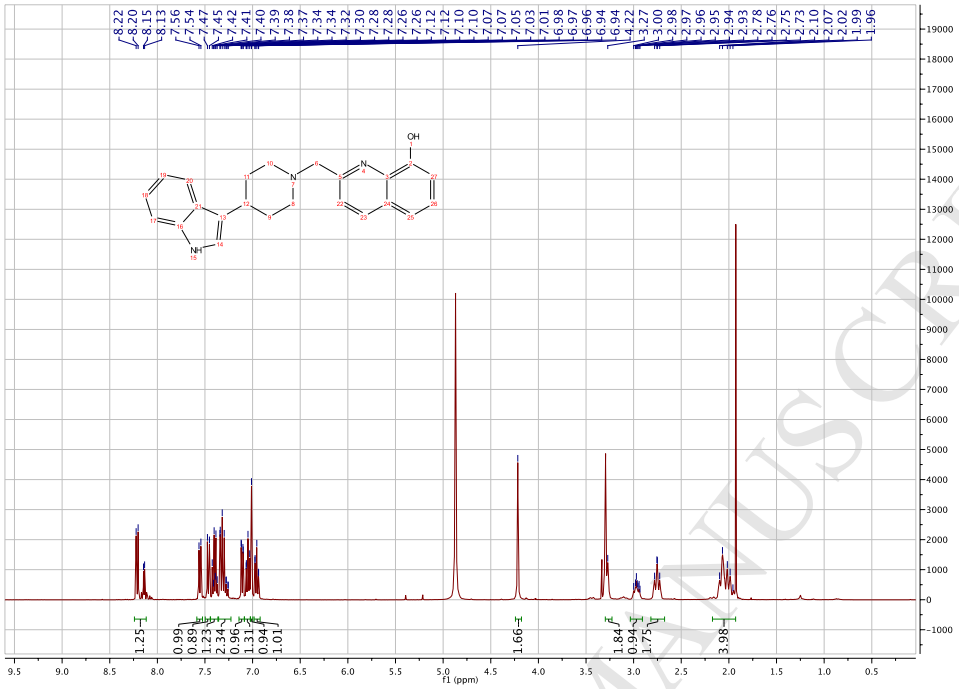

SAS5_III_f17 67 (1.171) Cm (65:72)
2: Scan ES+
4.58e7
100
%
0
130.37
172.36
201.41
202.41
330.41
372.41
373.40
374.40
444.45
557.40
701.57
743.62
779.51
857.68
1005.51
1073.87
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

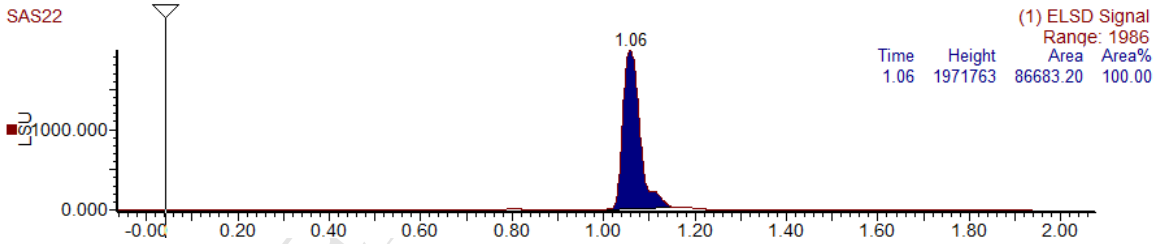

SAS5_III_f17 65 (1.127) Cm (64:69)
1: Scan ES-
3.79e6
100
%
0
144.29
145.27
146.27
249.37
328.26
416.33
417.36
418.32
484.15
613.87
633.45
746.49
787.49
789.49
849.35
962.94
1075.76
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 9c

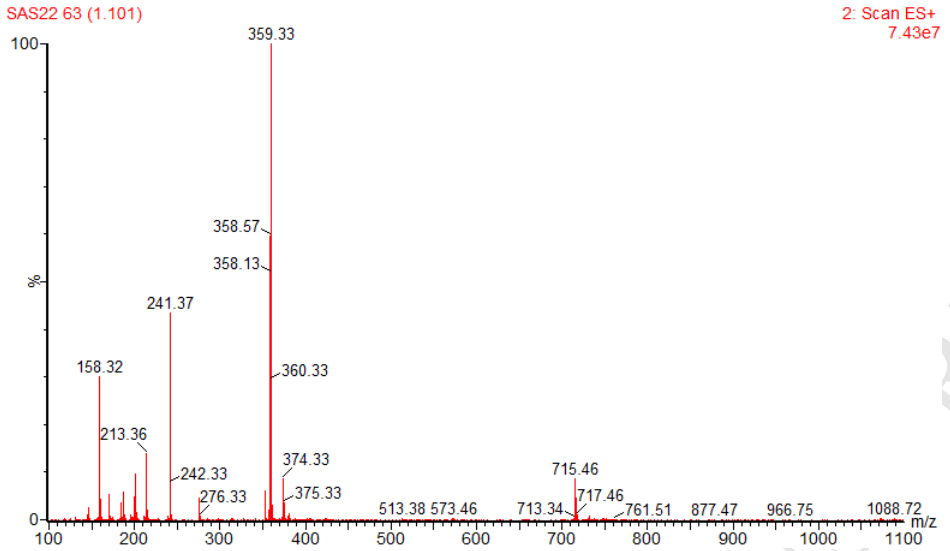
NMR



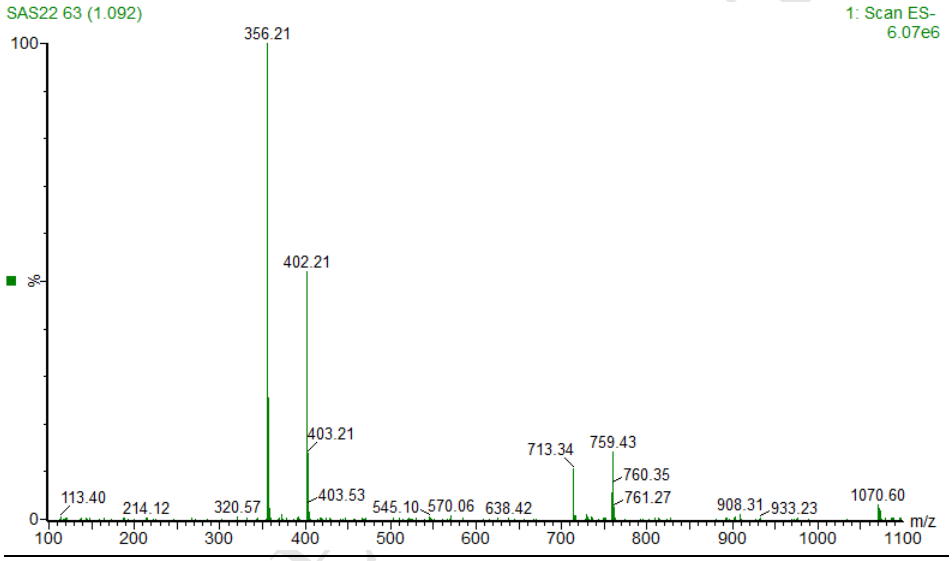
ELSD



ES+

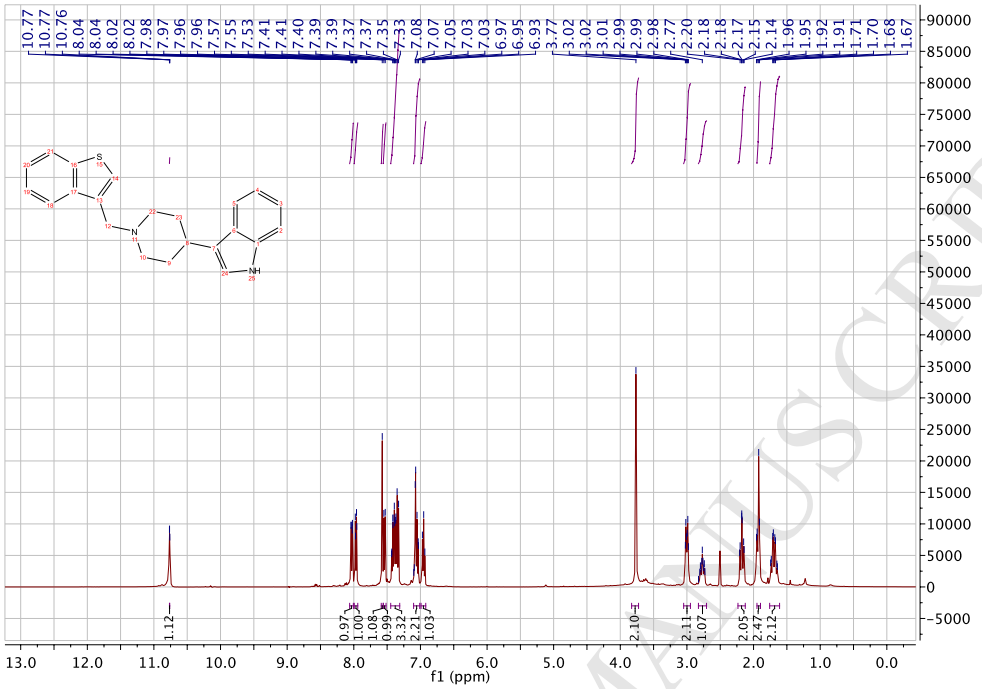

SAS22 63 (1.101)
2: Scan ES+
7.43e7
100
%
0
359.33
358.57
358.13
241.37
158.32
360.33
213.36
242.33
374.33
276.33
375.33
715.46
717.46
513.38 573.46
713.34
761.51
877.47
966.75
1088.72
100 200 300 400 500 600 700 800 900 1000 1100
m/z

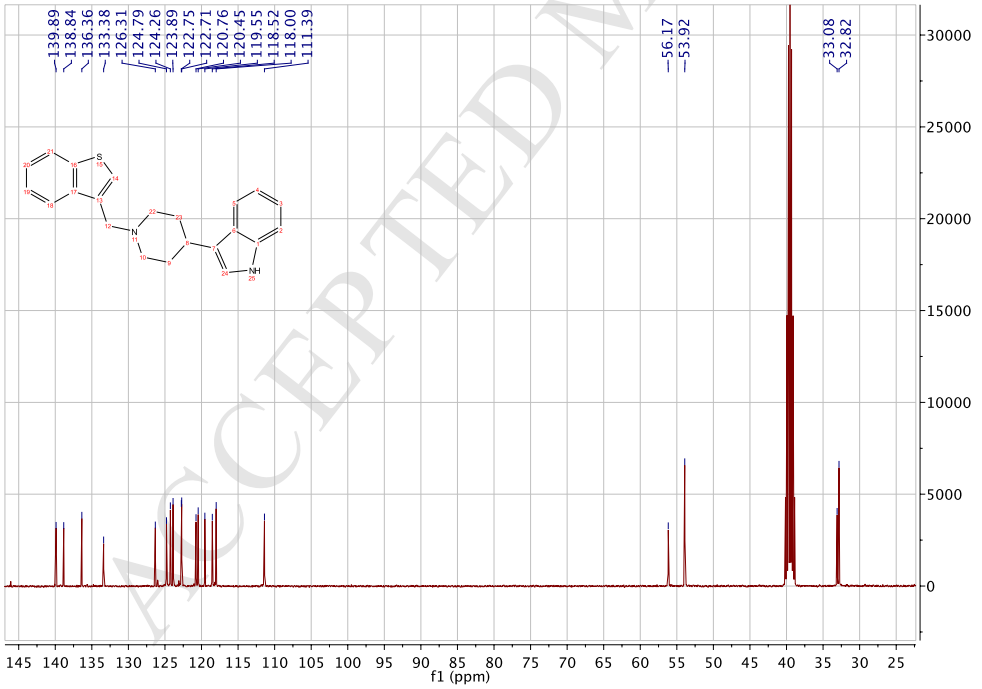
ES-


SAS22 63 (1.092)
1: Scan ES-
6.07e6
100
%
0
356.21
402.21
403.21
403.53
759.43
713.34
760.35
761.27
113.40
214.12
320.57
545.10
570.06
638.42
908.31
933.23
1070.60
100 200 300 400 500 600 700 800 900 1000 1100
m/z

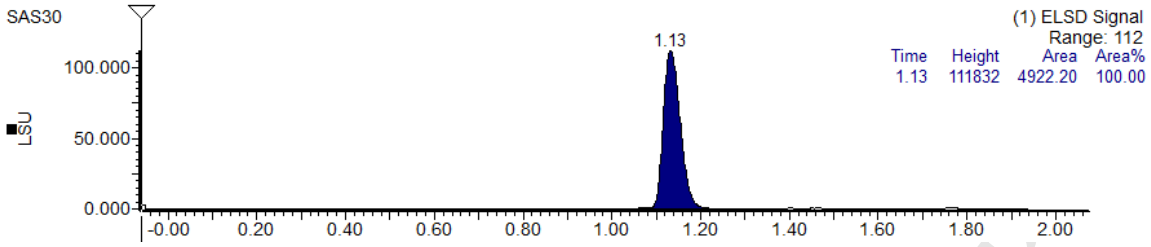
Compound 9d

NMR

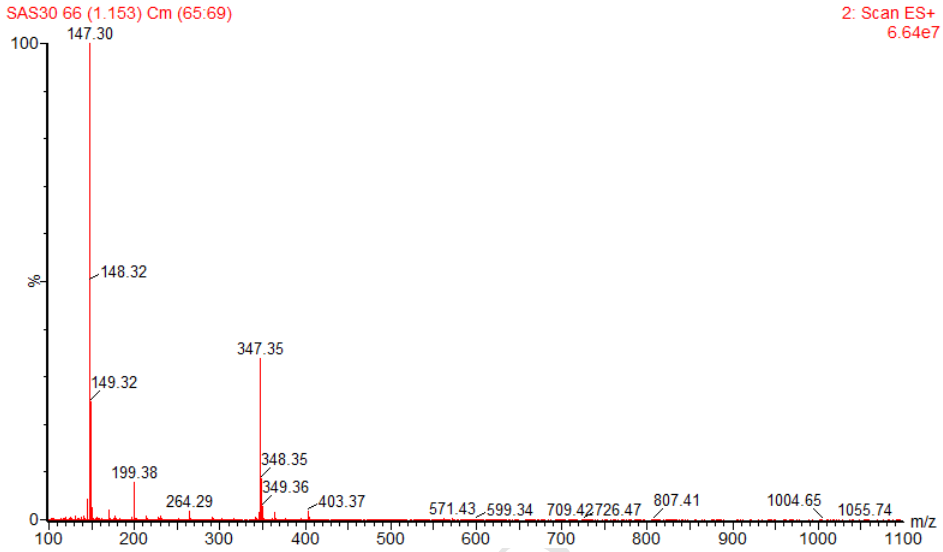




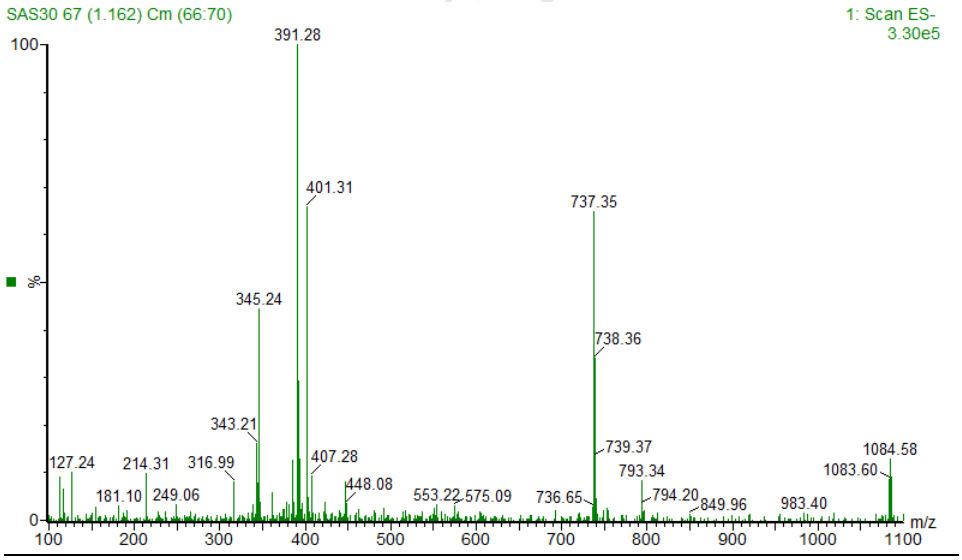
ELSD


SAS30
(1) ELSD Signal
Range: 112
Time Height Area Area%
1.13 111832 4922.20 100.00
1.13
LSU
100.000
50.000
0.000
-0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00

ES+

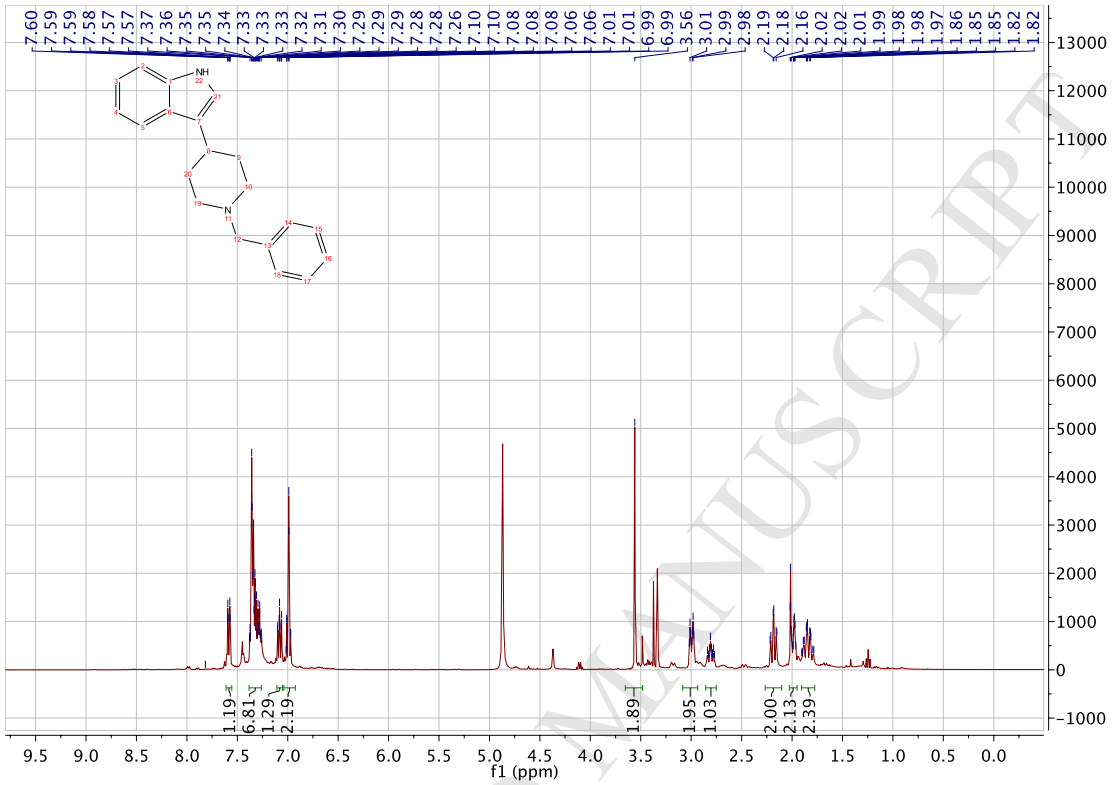

SAS30 66 (1.153) Cm (65:69)
2: Scan ES+
6.64e7
147.30
148.32
149.32
199.38
264.29
347.35
348.35
349.36
403.37
571.43 599.34 709.42 726.47
807.41
1004.65
1055.74
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

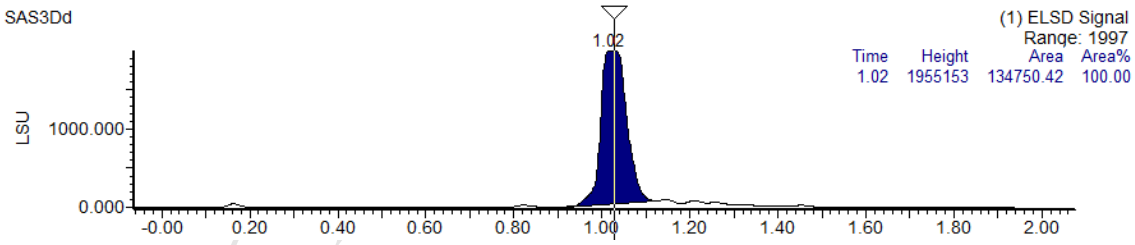

SAS30 67 (1.162) Cm (66:70)
1: Scan ES-
3.30e5
391.28
401.31
737.35
345.24
738.36
343.21
739.37
1084.58
1083.60
793.34
127.24 214.31 316.99
407.28
448.08
181.10 249.06
553.22 575.09
736.65
794.20
849.96
983.40
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 9e

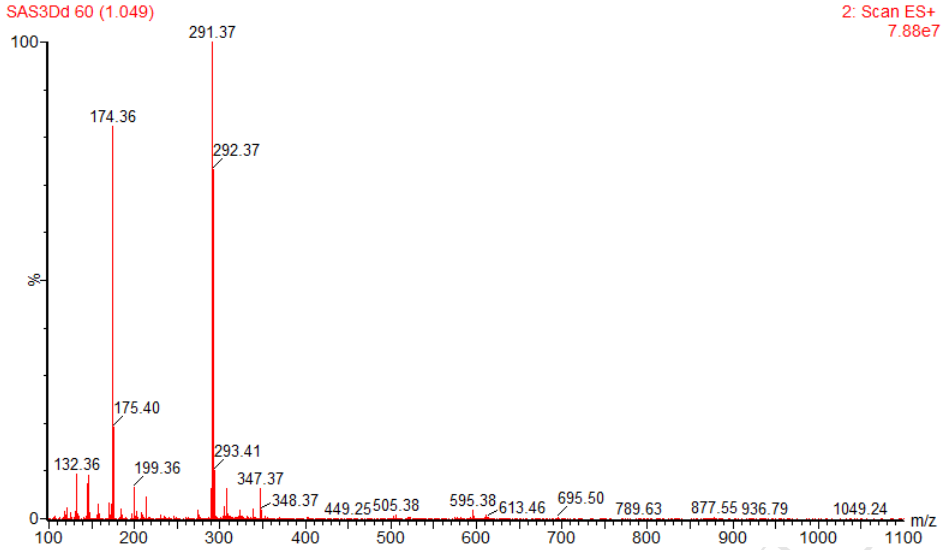
NMR



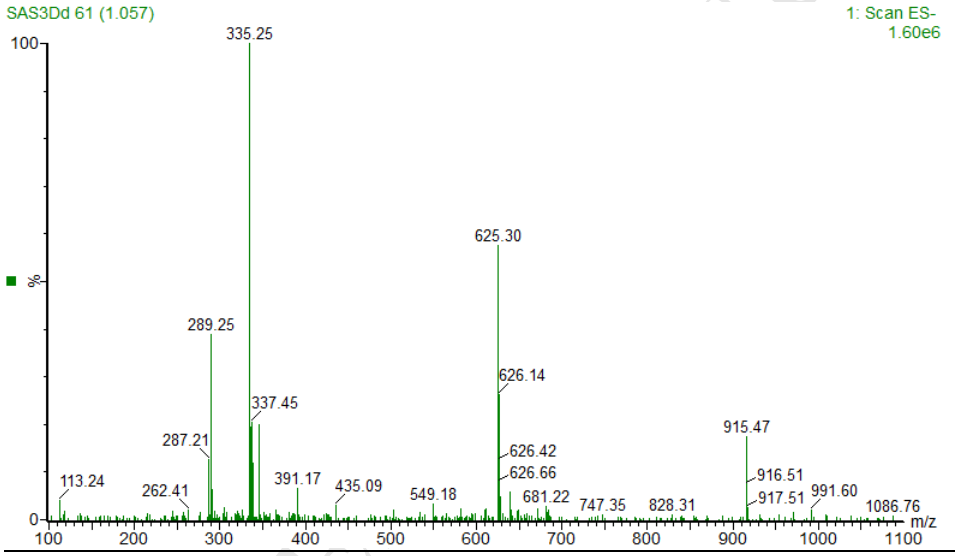
ELSD



ES+

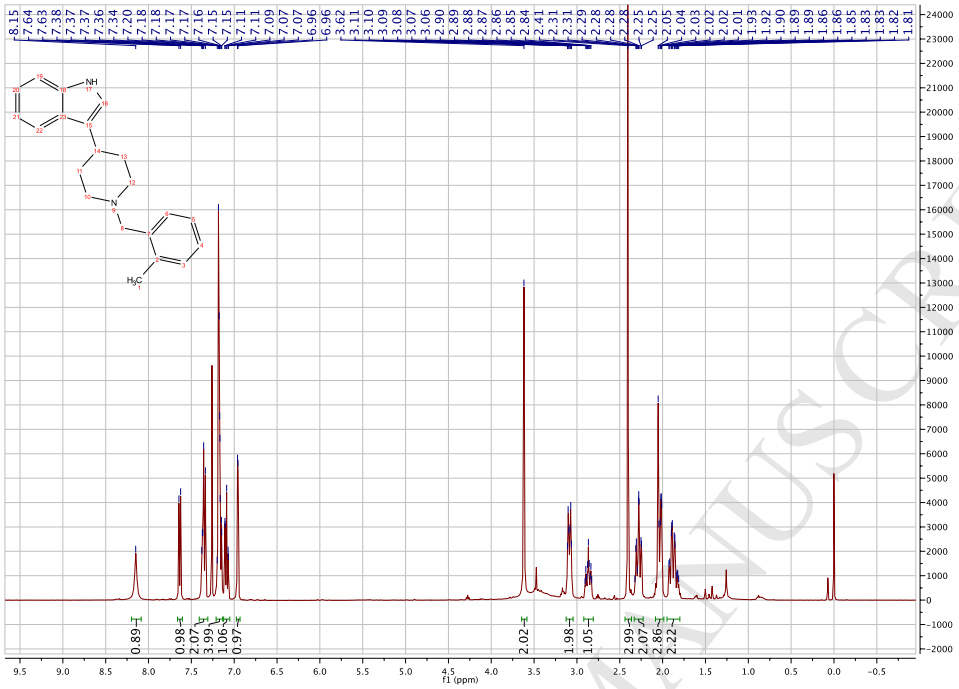

SAS3Dd 60 (1.049)
2: Scan ES+
7.88e7
100
%
0
291.37
174.36
292.37
175.40
293.41
132.36
199.36
347.37
348.37
449.25
505.38
595.38
613.46
695.50
789.63
877.55
936.79
1049.24
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

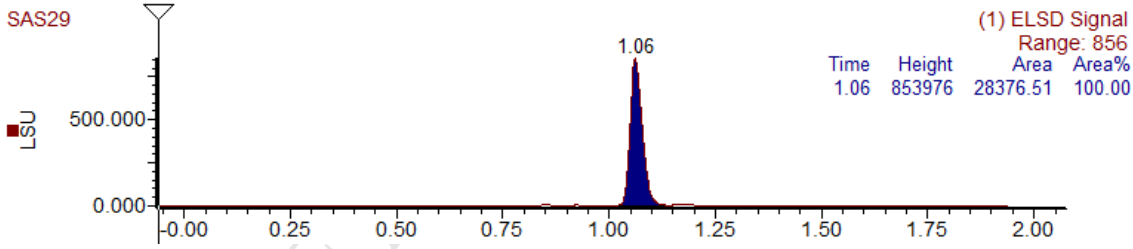

SAS3Dd 61 (1.057)
1: Scan ES-
1.60e6
100
%
0
335.25
625.30
289.25
626.14
337.45
915.47
287.21
626.42
626.66
916.51
917.51
991.60
113.24
262.41
391.17
435.09
549.18
681.22
747.35
828.31
1086.76
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 9f

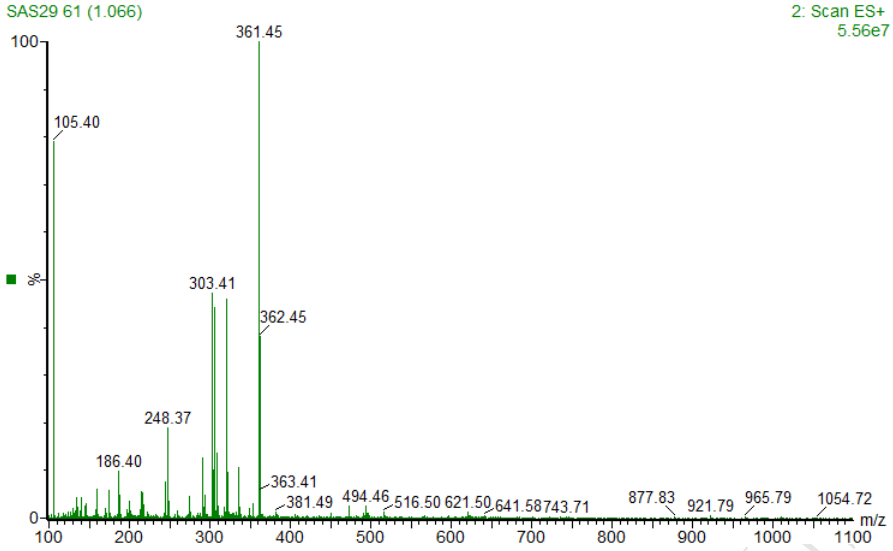
NMR



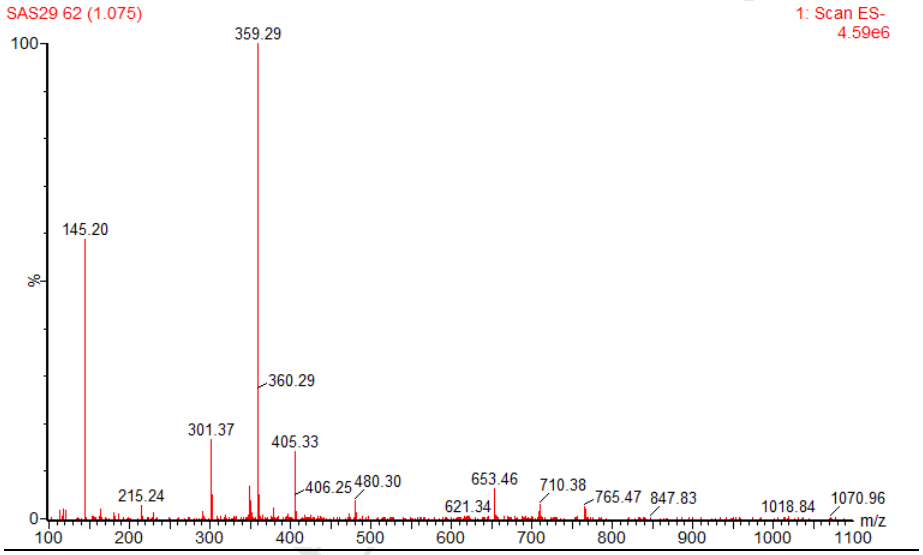
ELSD



ES+

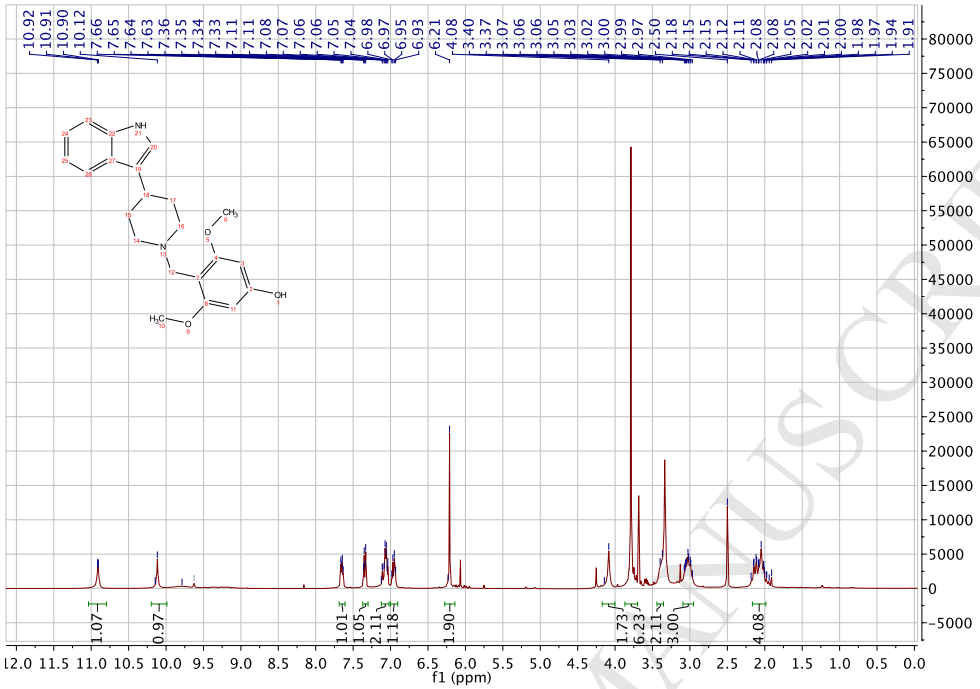

SAS29 61 (1.066)
2: Scan ES+
5.56e7
100
%
0
361.45
105.40
303.41
362.45
248.37
186.40
363.41
381.49
494.46
516.50
621.50
641.58
743.71
877.83
921.79
965.79
1054.72
100
200
300
400
500
600
700
800
900
1000
1100
m/z

ES-

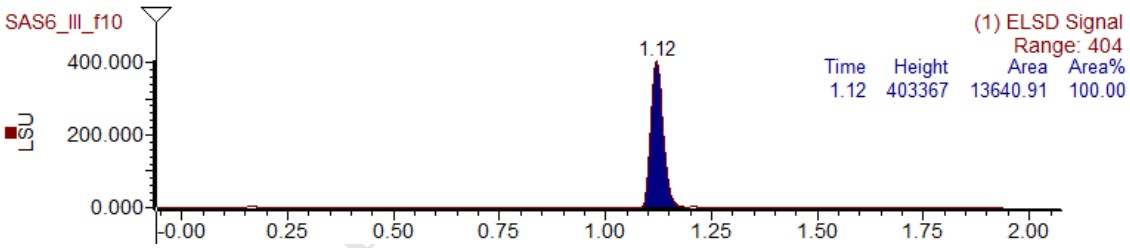

SAS29 62 (1.075)
1: Scan ES-
4.59e6
100
%
0
359.29
145.20
360.29
301.37
405.33
215.24
406.25
480.30
653.46
621.34
710.38
765.47
847.83
1018.84
1070.96
100
200
300
400
500
600
700
800
900
1000
1100
m/z

Compound 9g

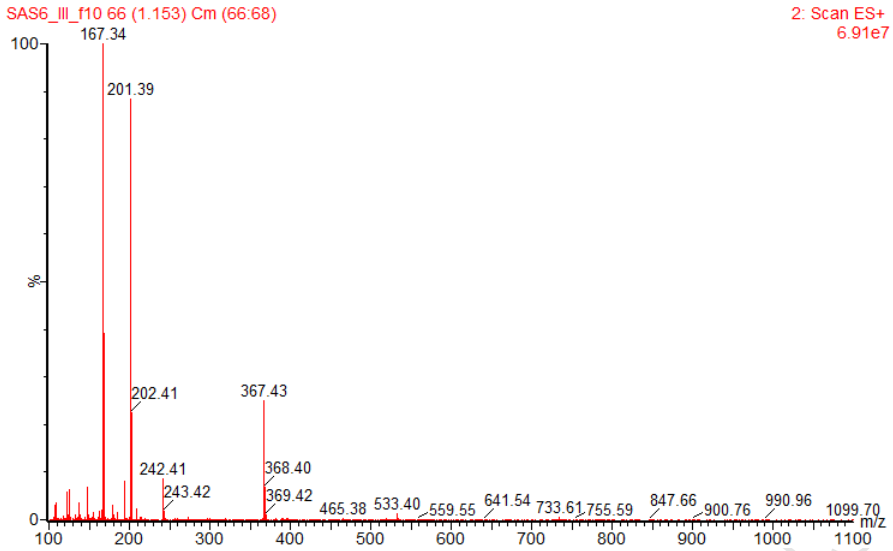
NMR



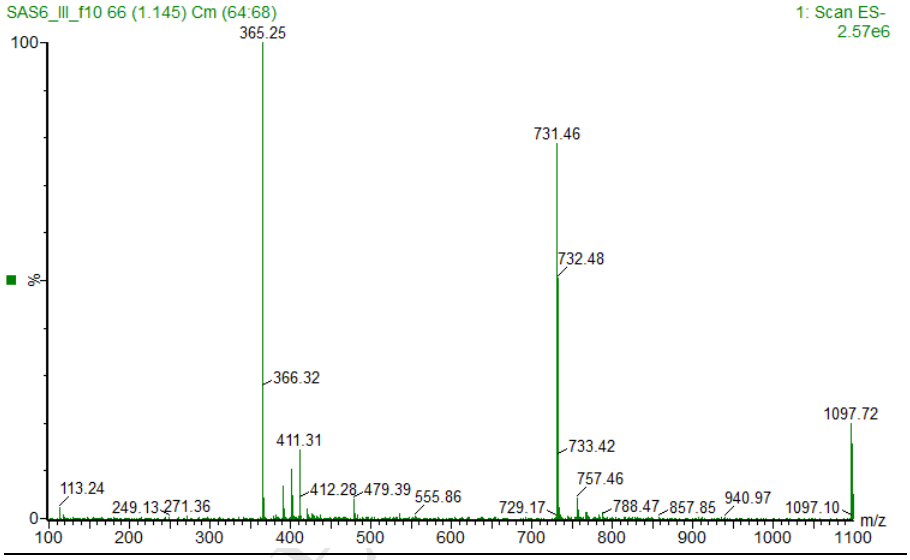
ELSD



ES+

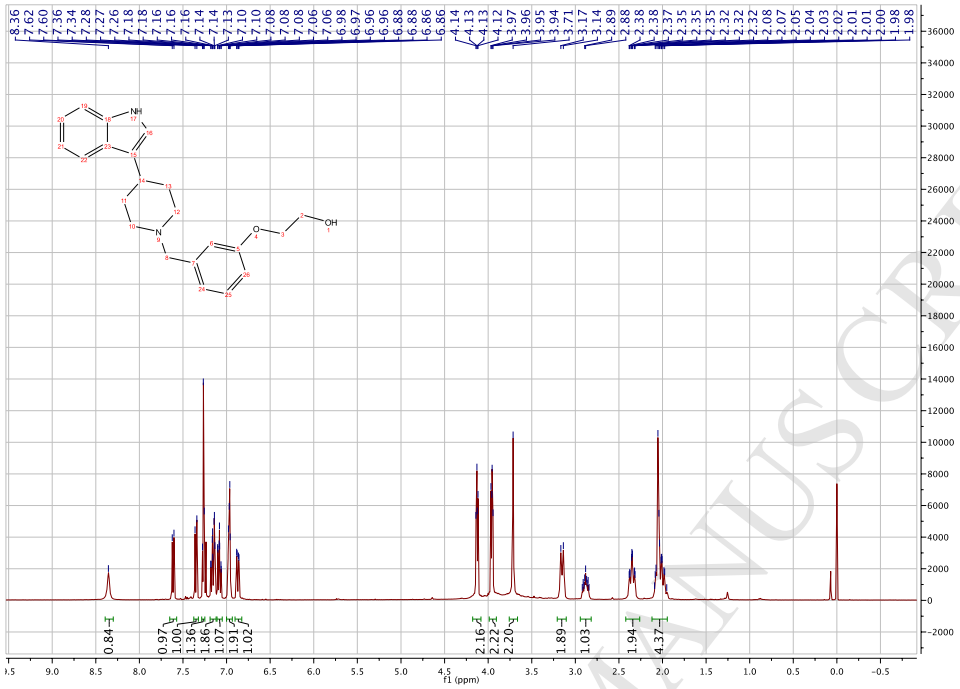

SAS6_III_f10 66 (1.153) Cm (66:68)
2: Scan ES+
6.91e7
100
%
0
167.34
201.39
202.41
367.43
242.41
368.40
243.42
369.42
465.38
533.40
559.55
641.54
733.61
755.59
847.66
900.76
990.96
1099.70
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

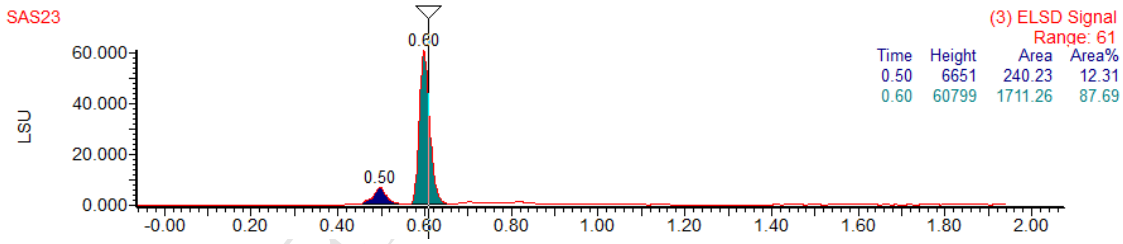

SAS6_III_f10 66 (1.145) Cm (64:68)
1: Scan ES-
2.57e6
100
%
0
365.25
731.46
732.48
366.32
1097.72
411.31
733.42
757.46
113.24
249.13
271.36
412.28
479.39
555.86
729.17
788.47
857.85
940.97
1097.10
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 9h

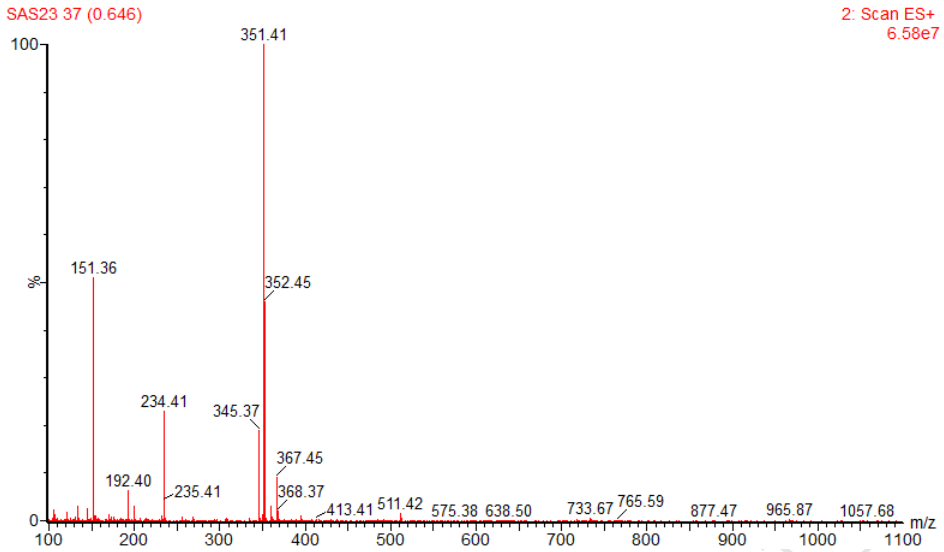
NMR



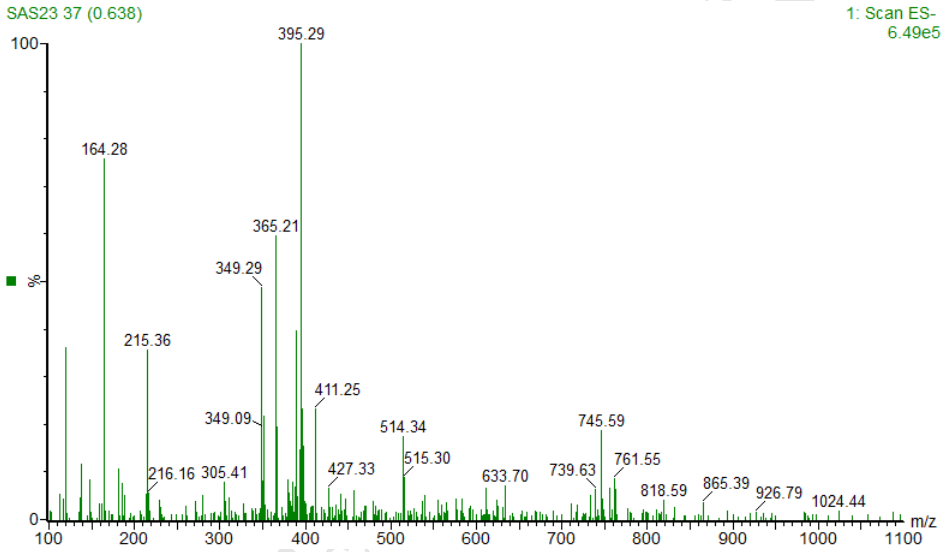
ELSD



ES+

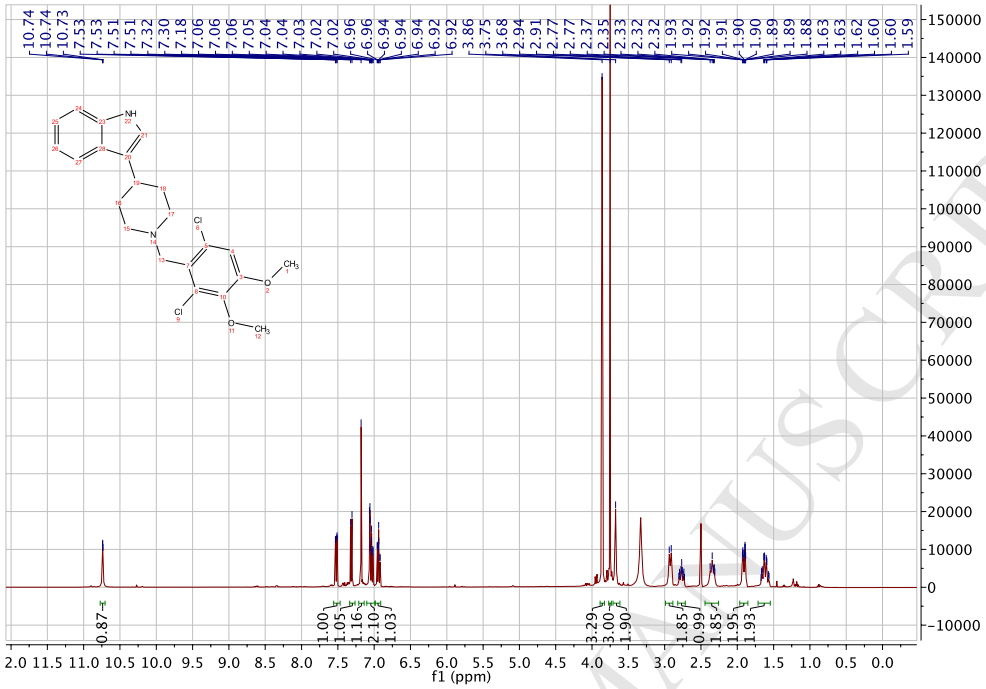

SAS23 37 (0.646)
2: Scan ES+
6.58e7
100
%
0
351.41
151.36
352.45
234.41
345.37
367.45
192.40
235.41
368.37
413.41
511.42
575.38
638.50
733.67
765.59
877.47
965.87
1057.68
m/z
100
200
300
400
500
600
700
800
900
1000
1100

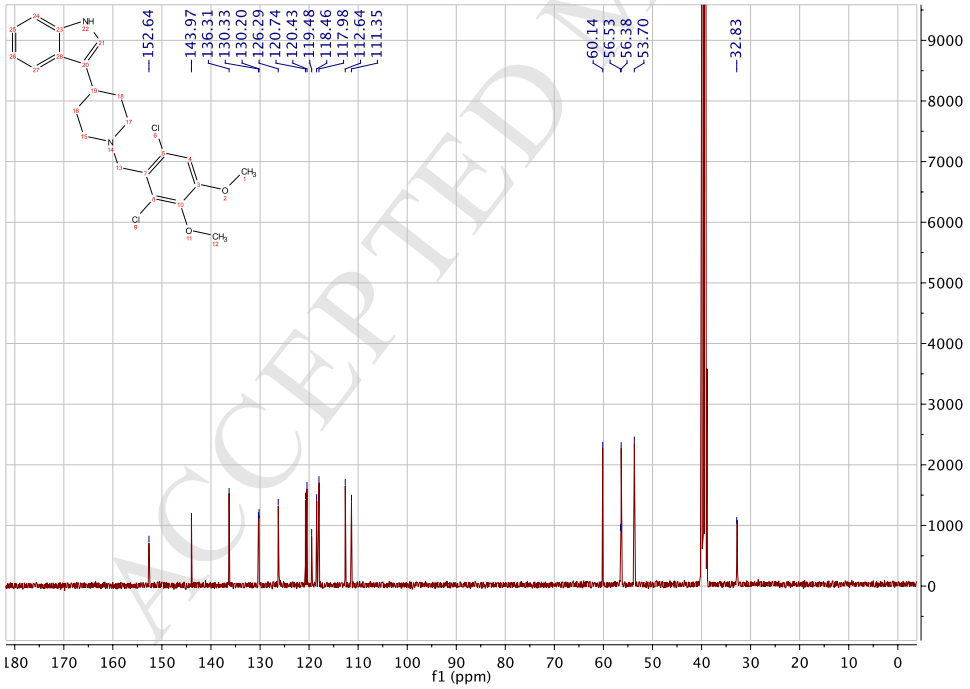
ES-


SAS23 37 (0.638)
1: Scan ES-
6.49e5
100
%
0
395.29
164.28
365.21
349.29
215.36
411.25
349.09
514.34
745.59
515.30
761.55
216.16
305.41
427.33
633.70
739.63
818.59
865.39
926.79
1024.44
m/z
100
200
300
400
500
600
700
800
900
1000
1100

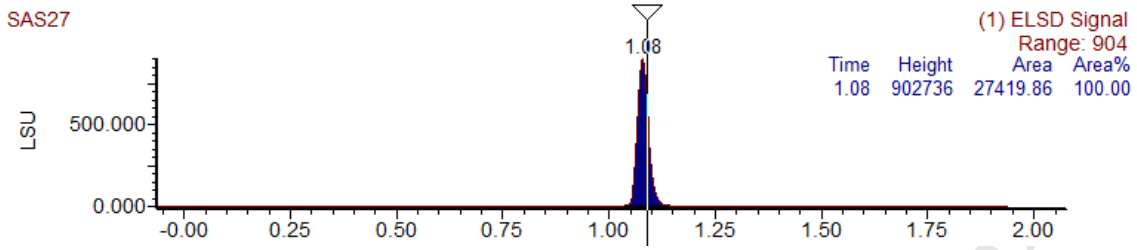
Compound 9i

NMR

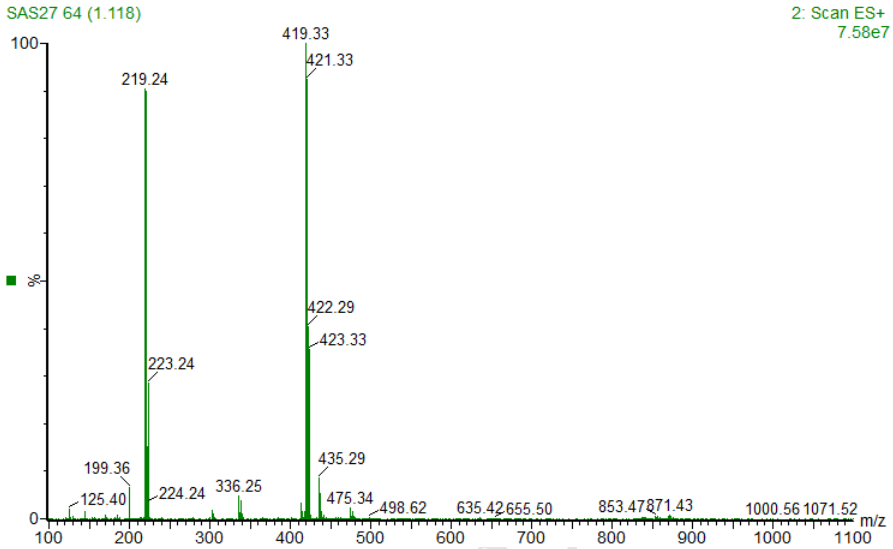




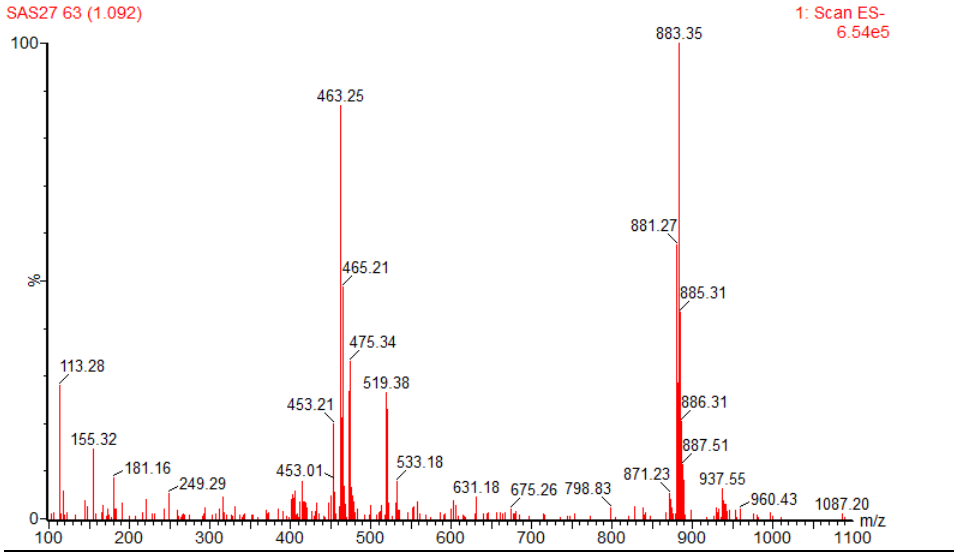
ELSD


SAS27
(1) ELSD Signal
Range: 904
Time Height Area Area%
1.08 902736 27419.86 100.00
1.08
LSU
500.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

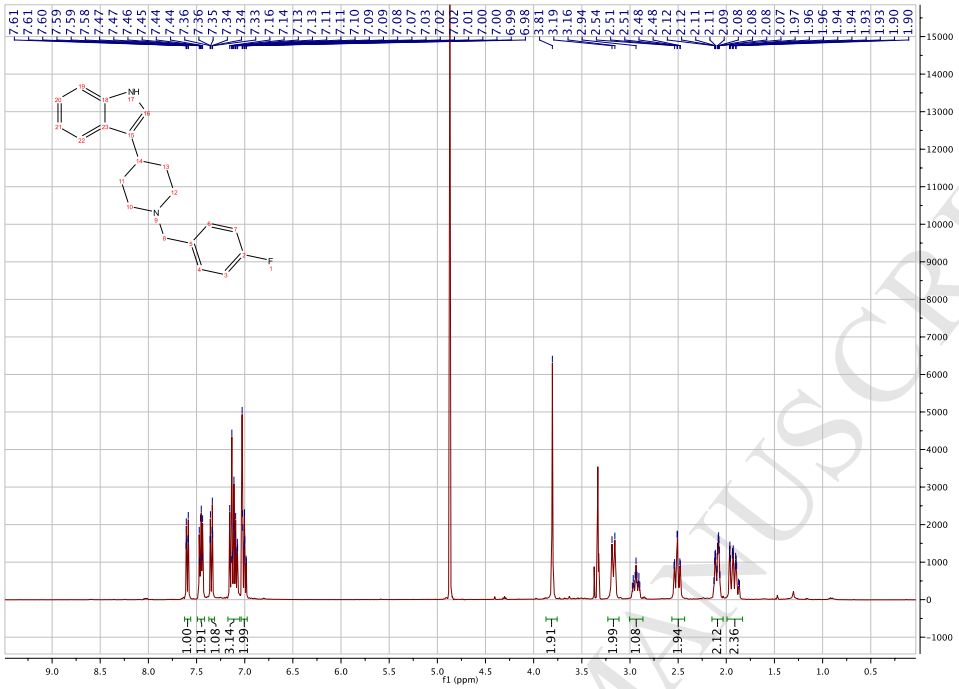

SAS27 64 (1.118)
2: Scan ES+
7.58e7
100
%
0
419.33
421.33
219.24
422.29
423.33
223.24
435.29
199.36
125.40
224.24
336.25
475.34
498.62
635.42 655.50
853.47 871.43
1000.56 1071.52
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

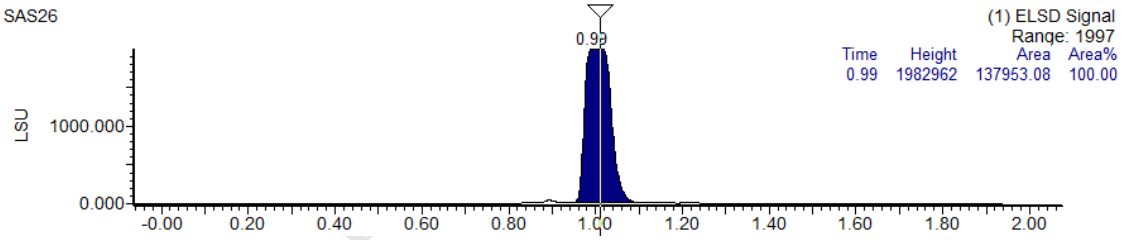

SAS27 63 (1.092)
1: Scan ES-
6.54e5
100
%
0
883.35
463.25
881.27
465.21
885.31
475.34
113.28
519.38
453.21
886.31
155.32
887.51
181.16
533.18
453.01
871.23
937.55
249.29
631.18
675.26
798.83
960.43
1087.20
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 9j

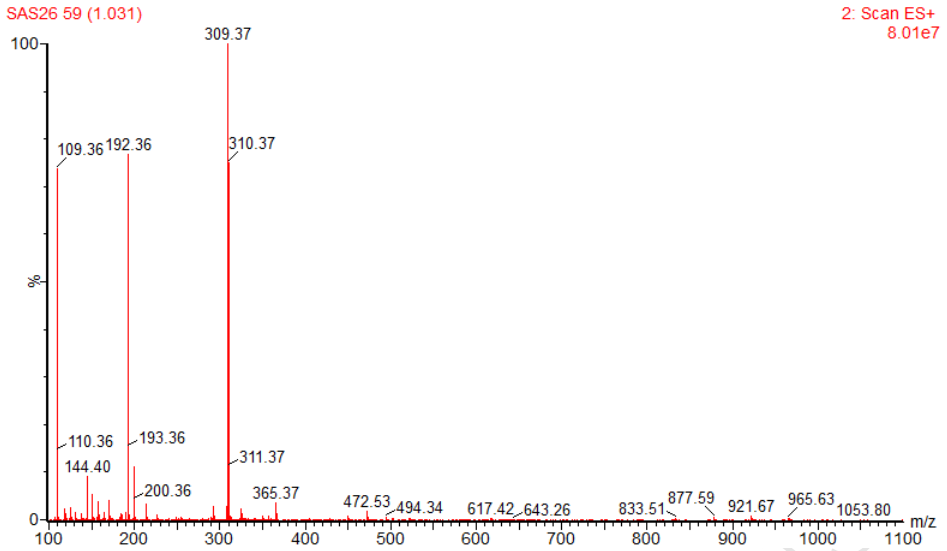
NMR



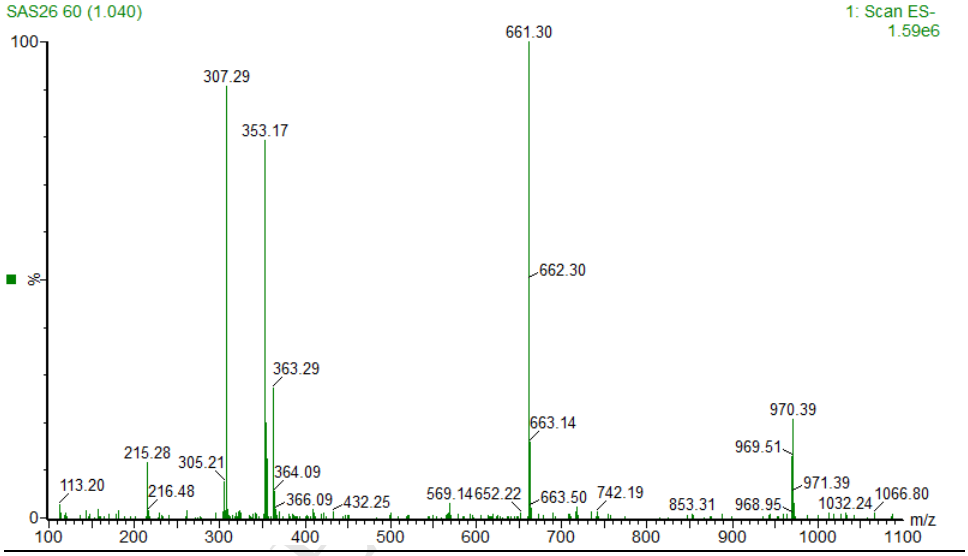
ELSD



ES+

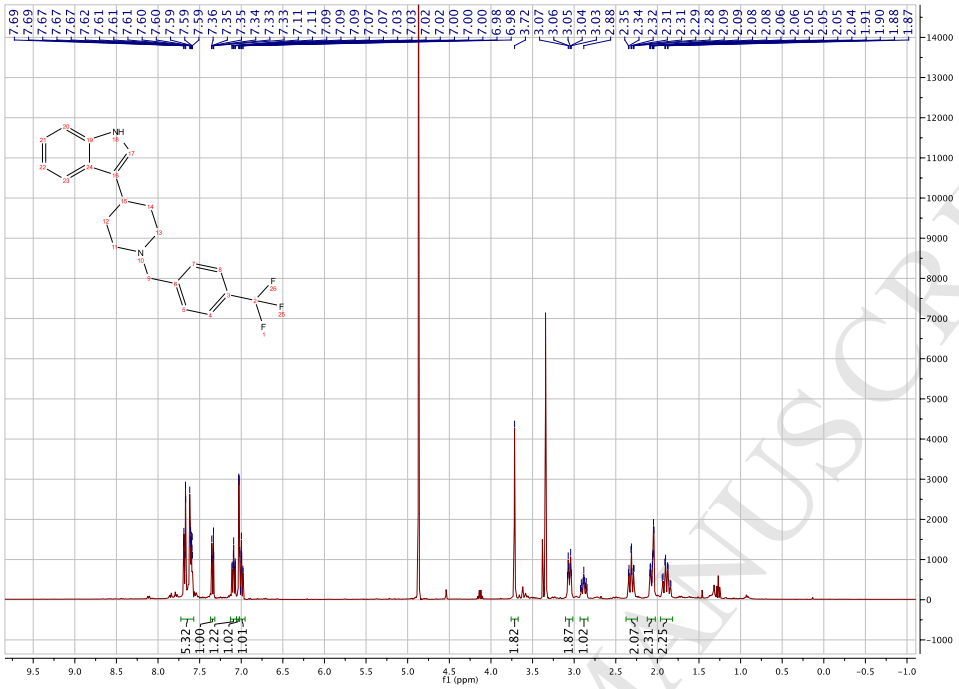

SAS26 59 (1.031)
2: Scan ES+
8.01e7
100
%
0
309.37
109.36
192.36
310.37
110.36
193.36
144.40
311.37
200.36
365.37
472.53
494.34
617.42
643.26
833.51
877.59
921.67
965.63
1053.80
100
200
300
400
500
600
700
800
900
1000
1100
m/z

ES-

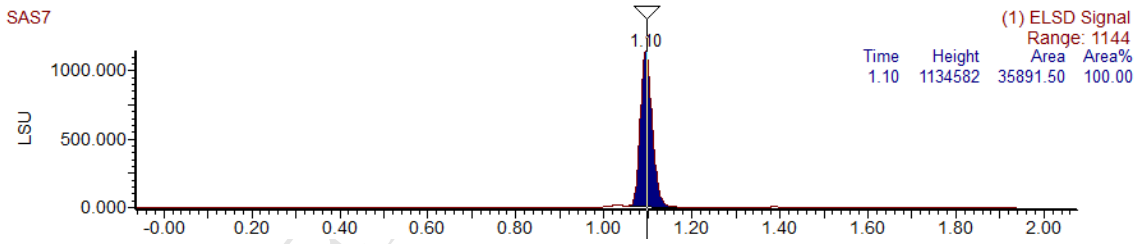

SAS26 60 (1.040)
1: Scan ES-
1.59e6
100
%
0
661.30
307.29
353.17
662.30
363.29
663.14
970.39
969.51
215.28
305.21
364.09
971.39
113.20
216.48
366.09
432.25
569.14
652.22
663.50
742.19
853.31
968.95
1032.24
1066.80
100
200
300
400
500
600
700
800
900
1000
1100
m/z

Compound 9k

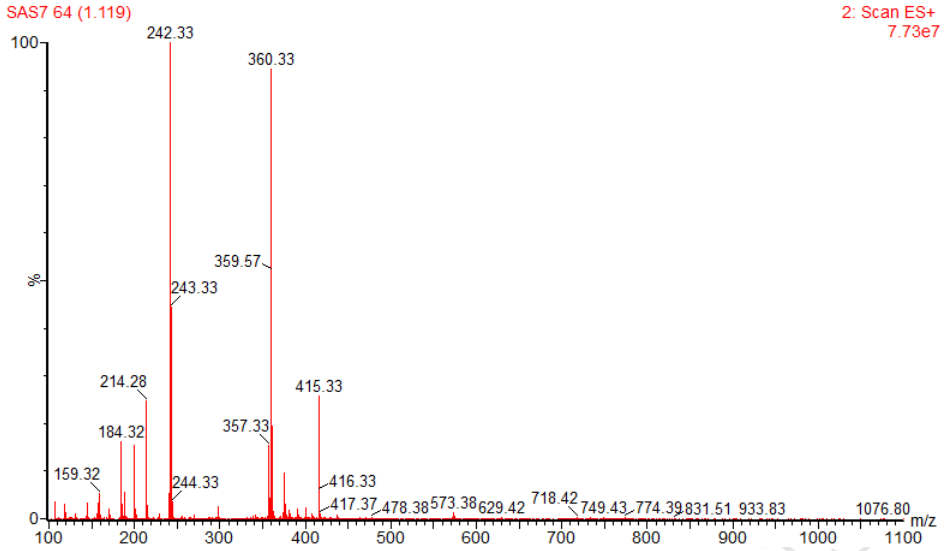
NMR



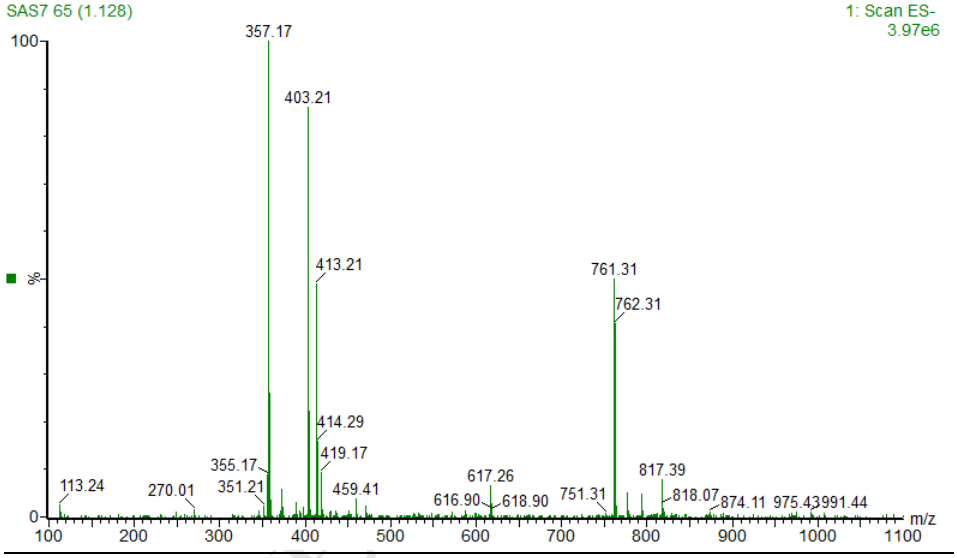
ELSD



ES+

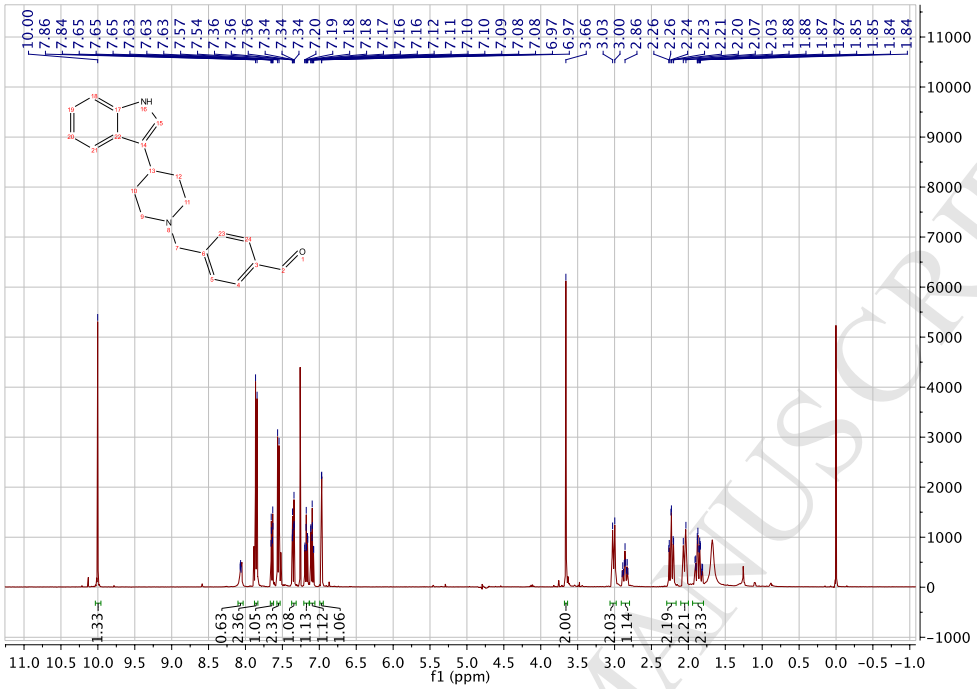

SAS7 64 (1.119)
2: Scan ES+
7.73e7
242.33
360.33
359.57
243.33
214.28
415.33
184.32
357.33
159.32
244.33
416.33
417.37
478.38
573.38
629.42
718.42
749.43
774.39
831.51
933.83
1076.80
%
m/z

ES-

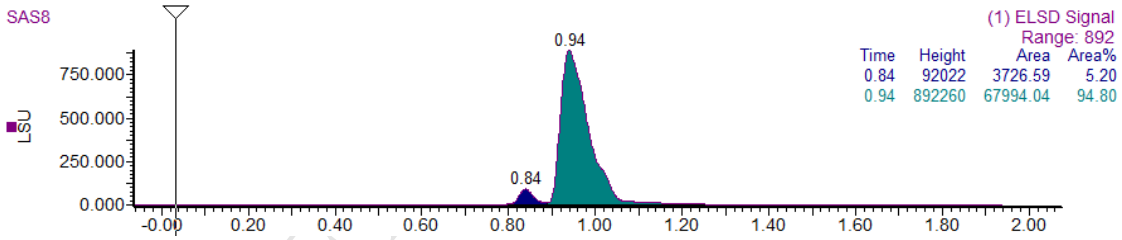

SAS7 65 (1.128)
1: Scan ES-
3.97e6
357.17
403.21
413.21
761.31
762.31
414.29
419.17
355.17
351.21
617.26
817.39
113.24
270.01
459.41
616.90
618.90
751.31
818.07
874.11
975.43
991.44
%
m/z

Compound 9l

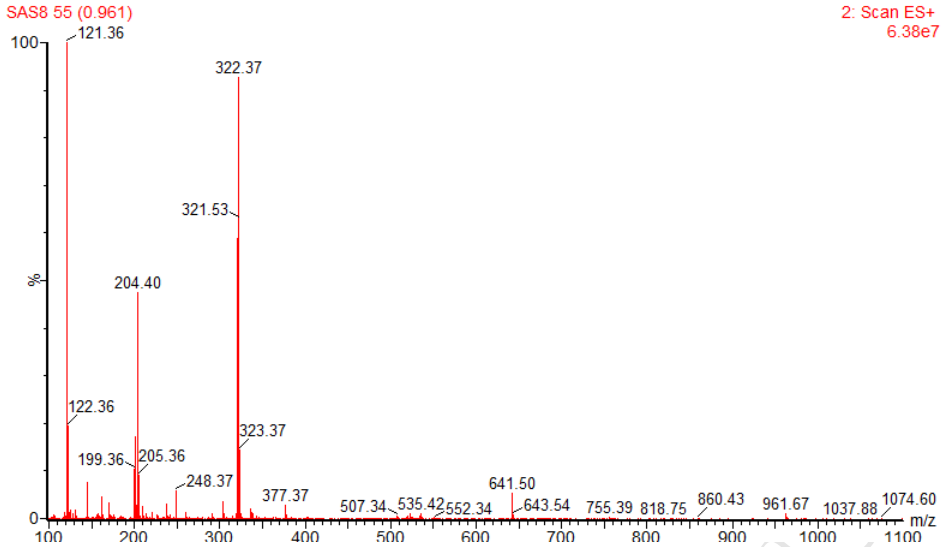
NMR



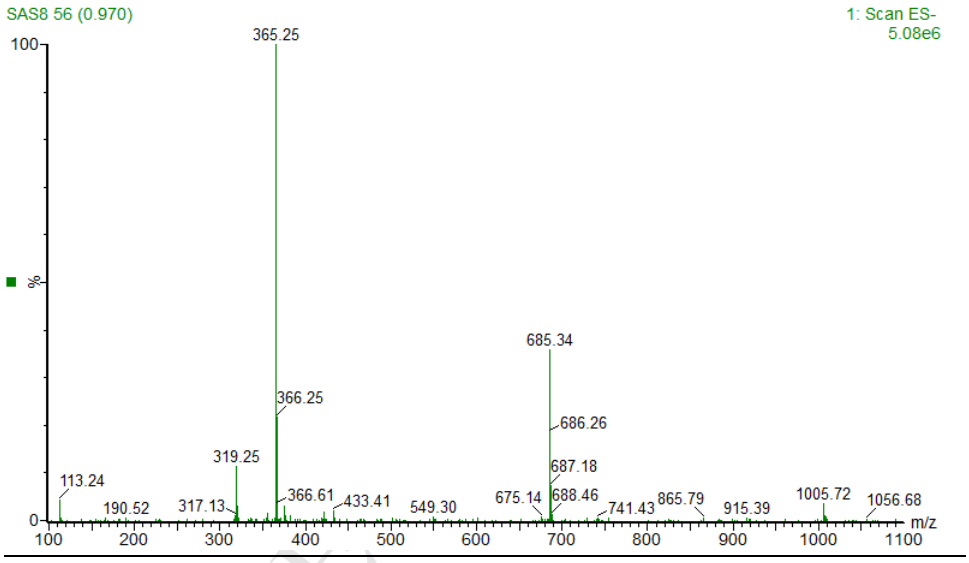
ELSD



ES+

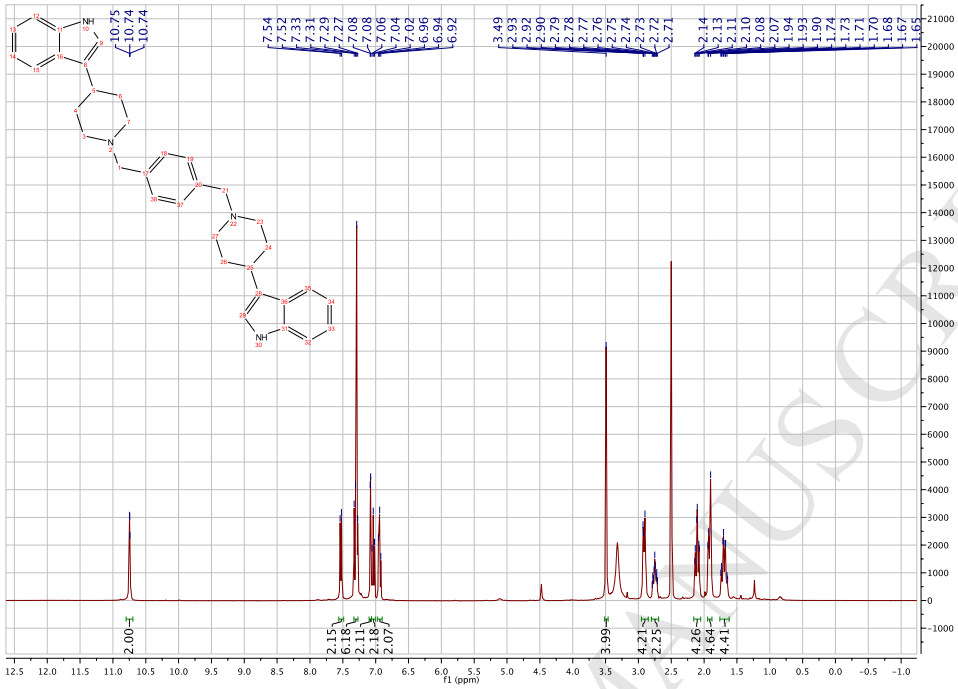

SAS8 55 (0.961)
2: Scan ES+
6.38e7
100
%
0
121.36
322.37
321.53
204.40
122.36
323.37
199.36
205.36
248.37
377.37
507.34
535.42
552.34
641.50
643.54
755.39
818.75
860.43
961.67
1037.88
1074.60
m/z
100
200
300
400
500
600
700
800
900
1000
1100

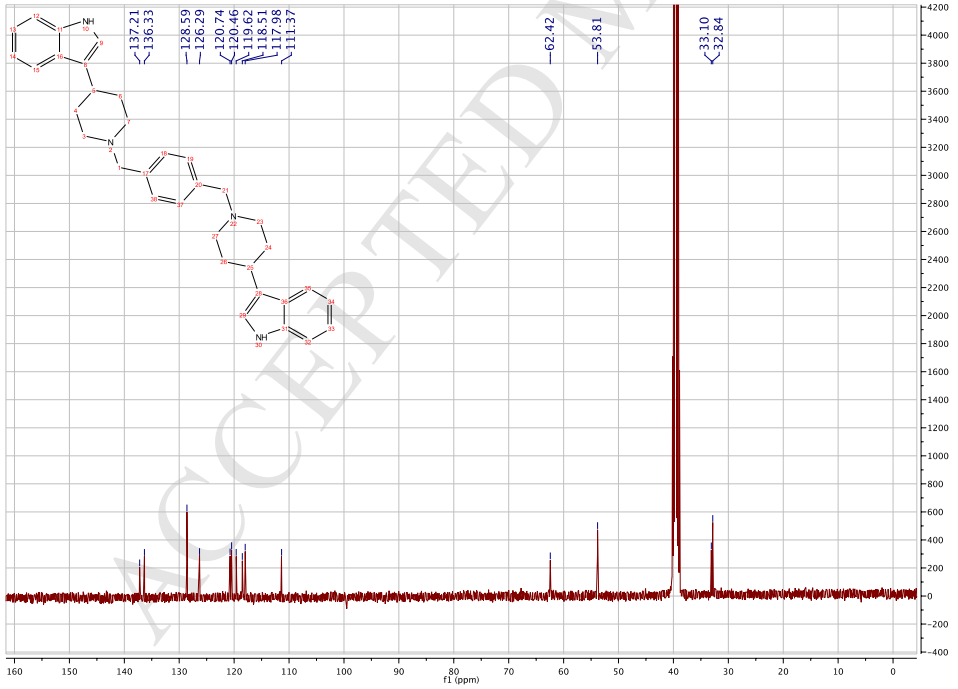
ES-


SAS8 56 (0.970)
1: Scan ES-
5.08e6
100
%
0
365.25
685.34
366.25
686.26
319.25
687.18
113.24
190.52
317.13
366.61
433.41
549.30
675.14
688.46
741.43
865.79
915.39
1005.72
1056.68
m/z
100
200
300
400
500
600
700
800
900
1000
1100

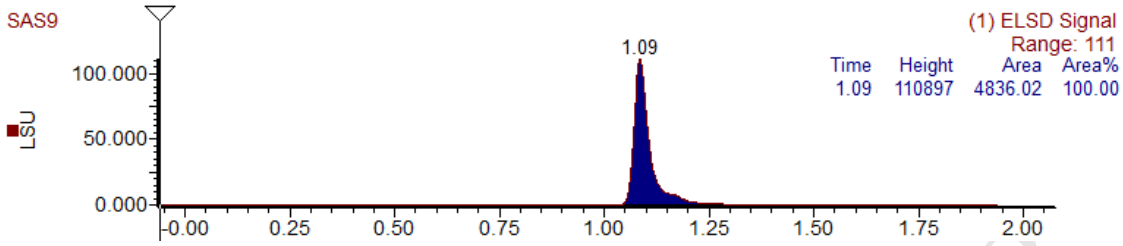
Compound 9m

NMR

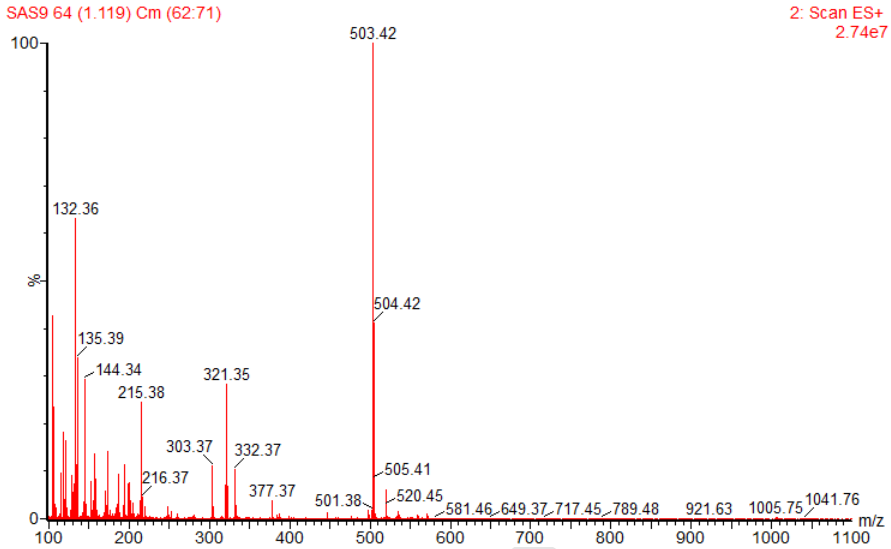




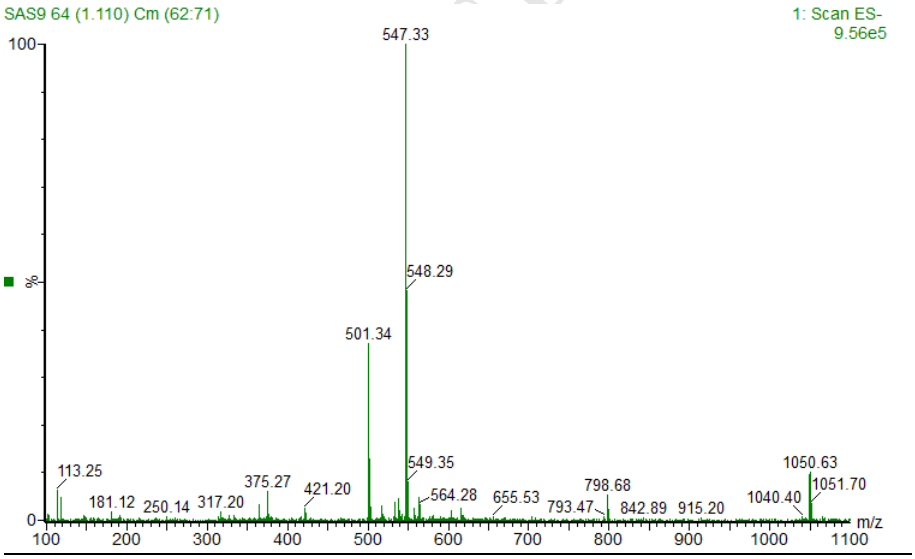
ELSD


SAS9
(1) ELSD Signal
Range: 111
Time Height Area Area%
1.09 110897 4836.02 100.00
1.09
LSU
100.000
50.000
0.000
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

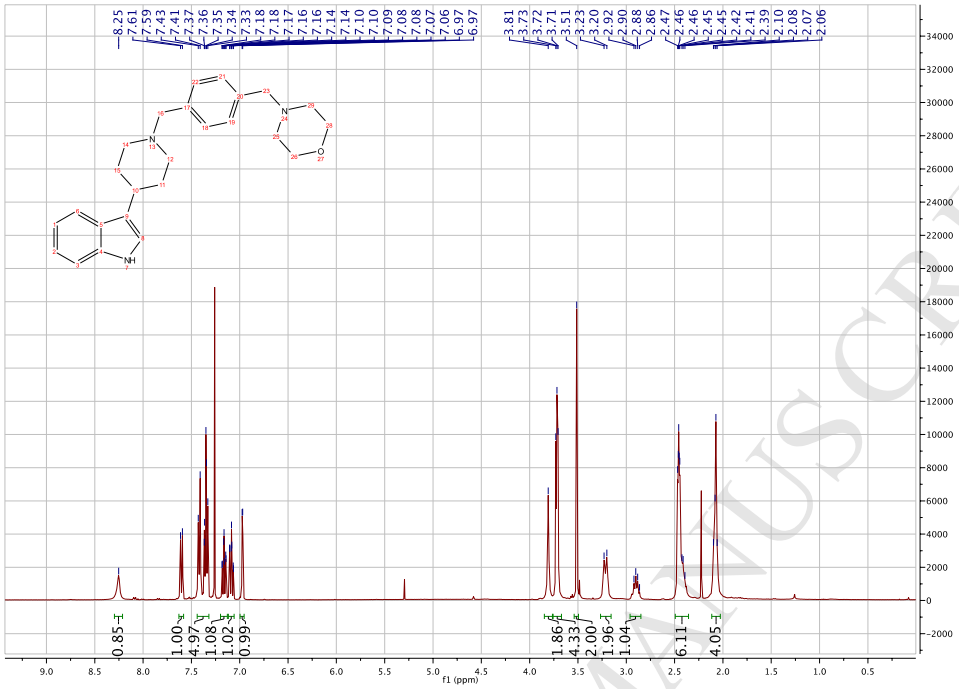

SAS9 64 (1.119) Cm (62:71)
2: Scan ES+
2.74e7
503.42
132.36
504.42
135.39
144.34
215.38
321.35
303.37
332.37
216.37
505.41
377.37
520.45
501.38
581.46
649.37
717.45
789.48
921.63
1005.75
1041.76
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

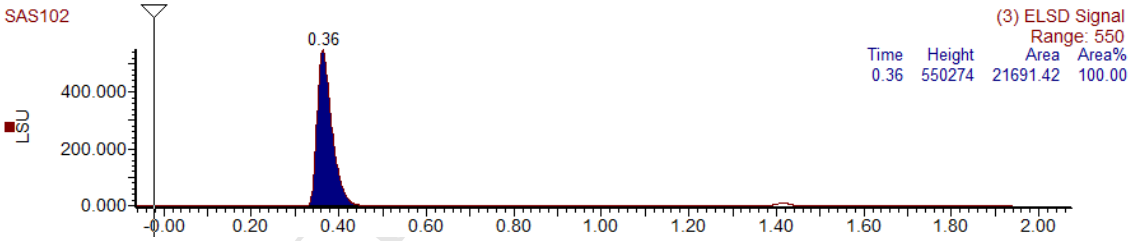

SAS9 64 (1.110) Cm (62:71)
1: Scan ES-
9.56e5
547.33
548.29
501.34
549.35
1050.63
1051.70
113.25
375.27
421.20
181.12
250.14
317.20
564.28
655.53
798.68
793.47
842.89
915.20
1040.40
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 9n

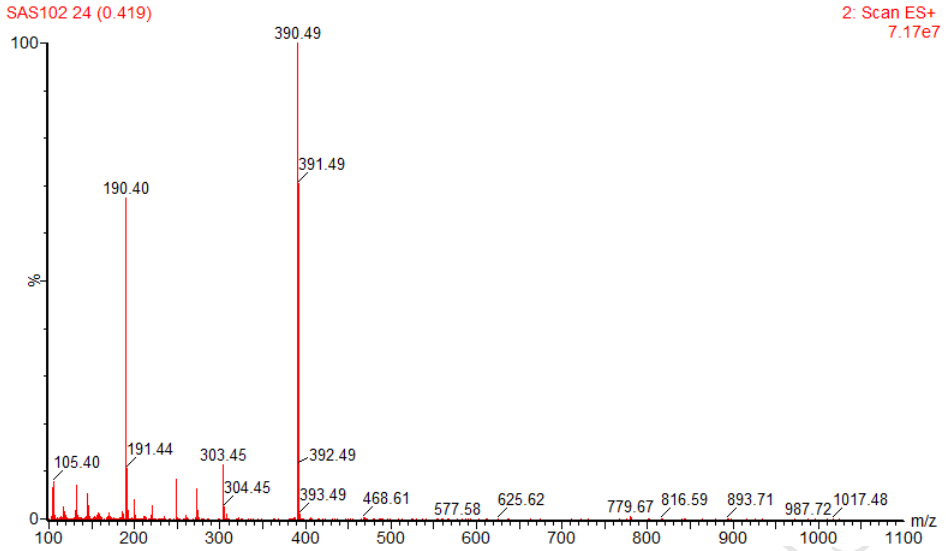
NMR



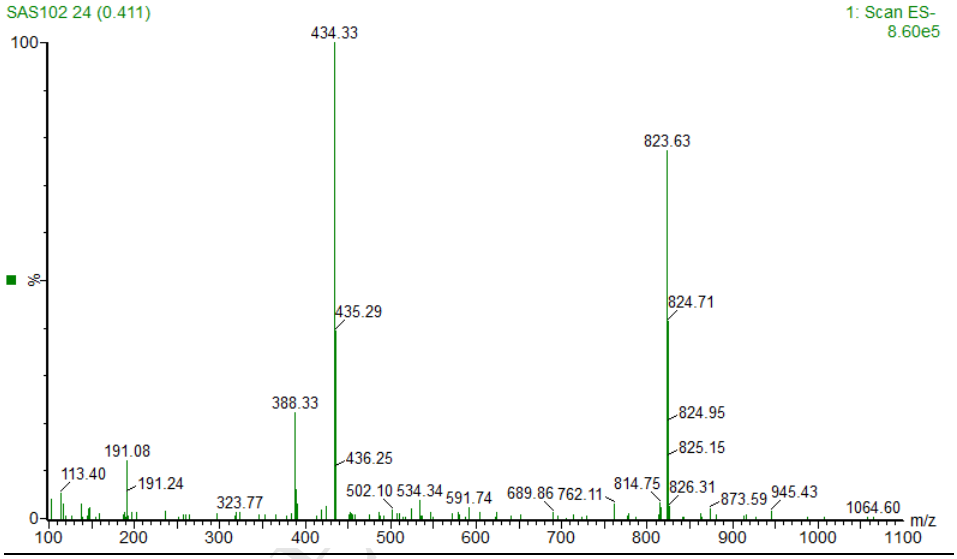
ELSD



ES+

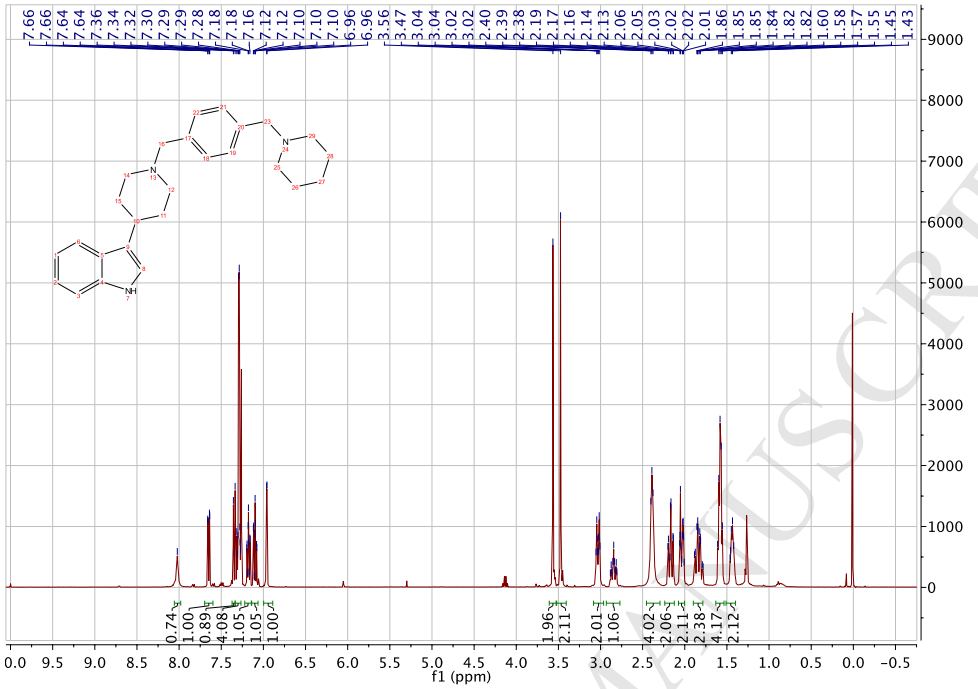

SAS102 24 (0.419)
2: Scan ES+
7.17e7
100
%
0
390.49
391.49
190.40
105.40
191.44
303.45
304.45
392.49
393.49
468.61
577.58
625.62
779.67
816.59
893.71
987.72
1017.48
100
200
300
400
500
600
700
800
900
1000
1100
m/z

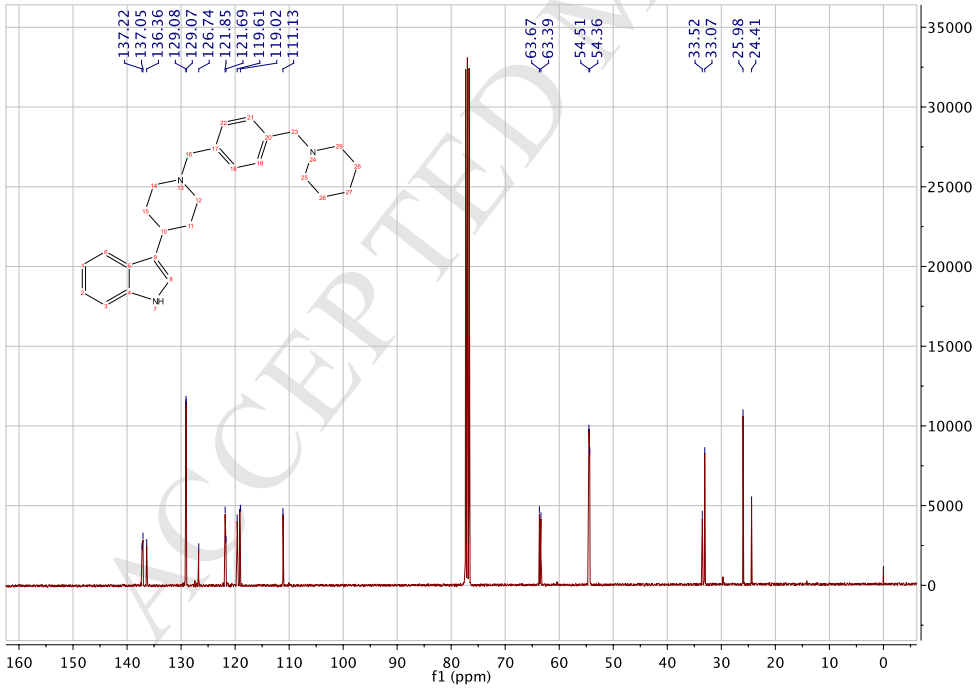
ES-


SAS102 24 (0.411)
1: Scan ES-
8.60e5
100
%
0
434.33
823.63
435.29
824.71
388.33
824.95
825.15
191.08
436.25
113.40
191.24
323.77
502.10
534.34
591.74
689.86
762.11
814.75
826.31
873.59
945.43
1064.60
100
200
300
400
500
600
700
800
900
1000
1100
m/z

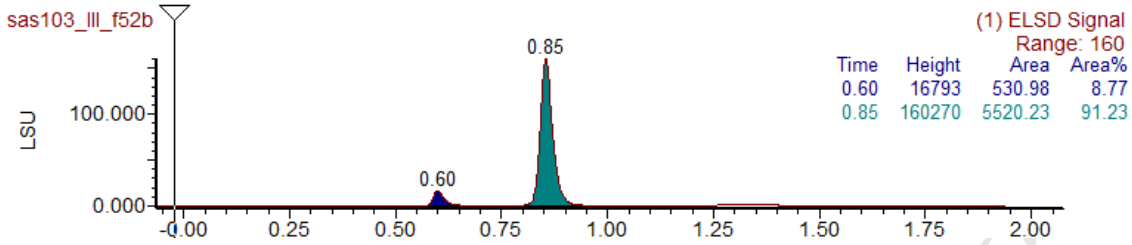
Compound 9o

NMR

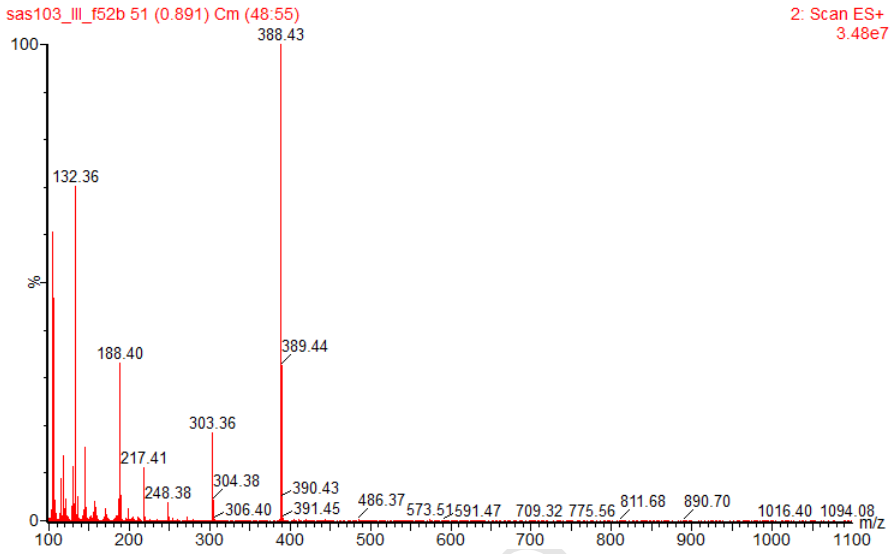




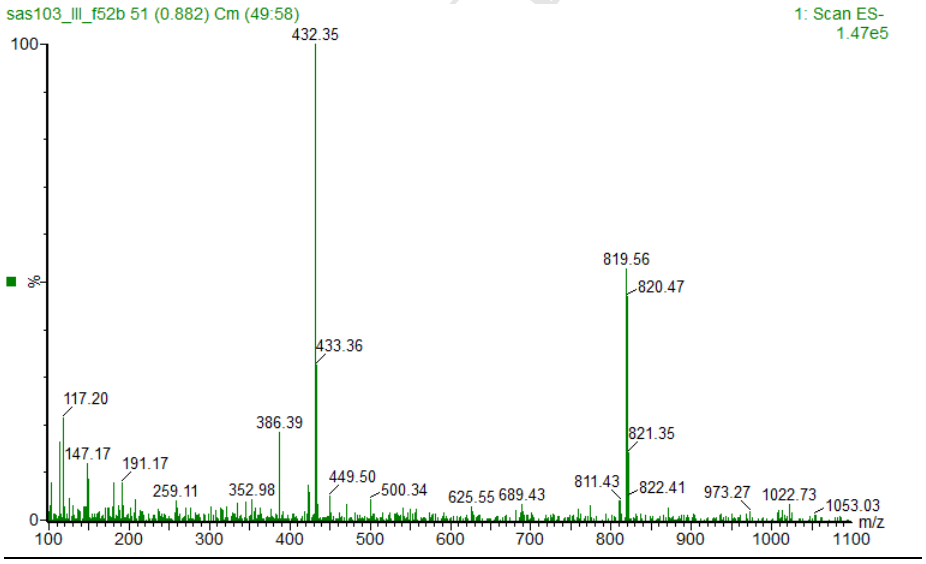
ELSD


sas103_lll_f52b
(1) ELSD Signal
Range: 160
Time Height Area Area%
0.60 16793 530.98 8.77
0.85 160270 5520.23 91.23
LSU
100.000
0.000
0.60
0.85
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

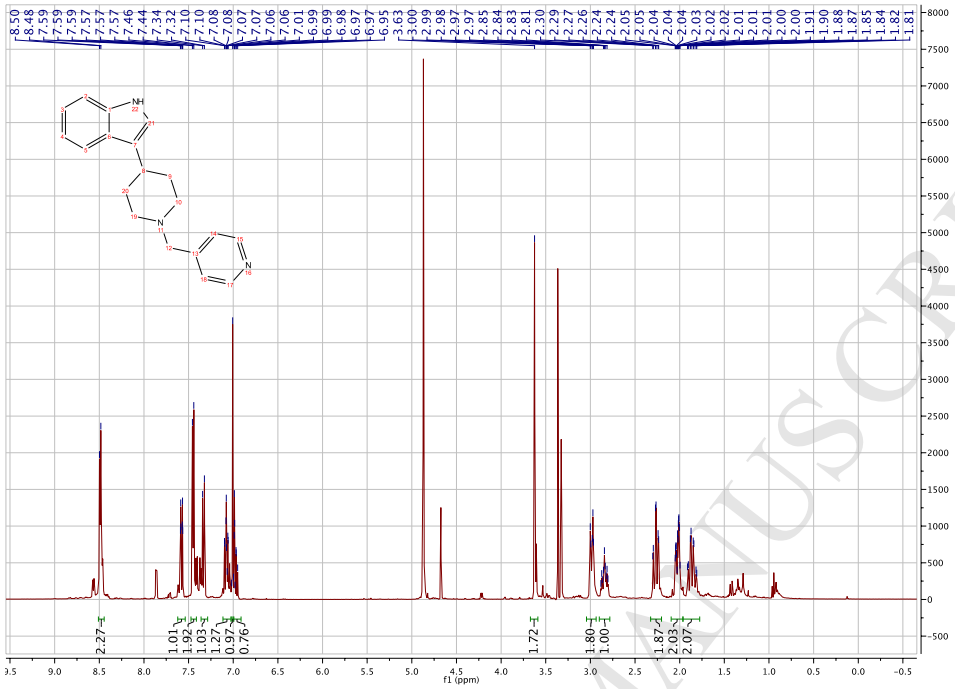

sas103_lll_f52b 51 (0.891) Cm (48:55)
2: Scan ES+
3.48e7
%
388.43
132.36
188.40
389.44
303.36
217.41
304.38
248.38
390.43
306.40
391.45
486.37
573.51 591.47 709.32 775.56
811.68
890.70
1016.40 1094.08
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

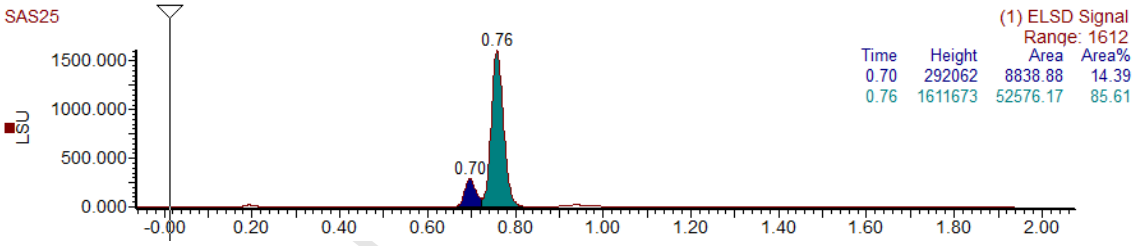

sas103_lll_f52b 51 (0.882) Cm (49:58)
1: Scan ES-
1.47e5
%
432.35
819.56
820.47
433.36
117.20
386.39
821.35
147.17
191.17
449.50
259.11
352.98
500.34
625.55 689.43
811.43
822.41
973.27
1022.73
1053.03
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 9p

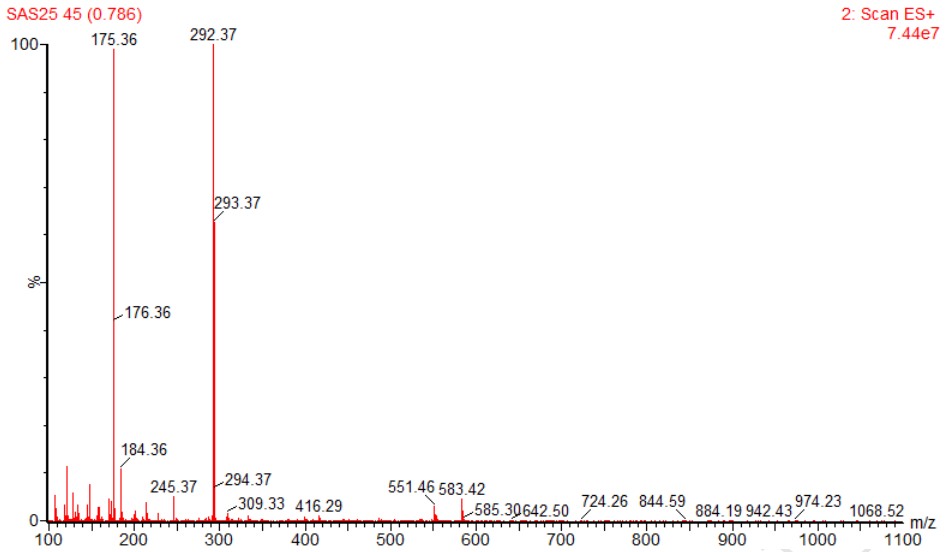
NMR



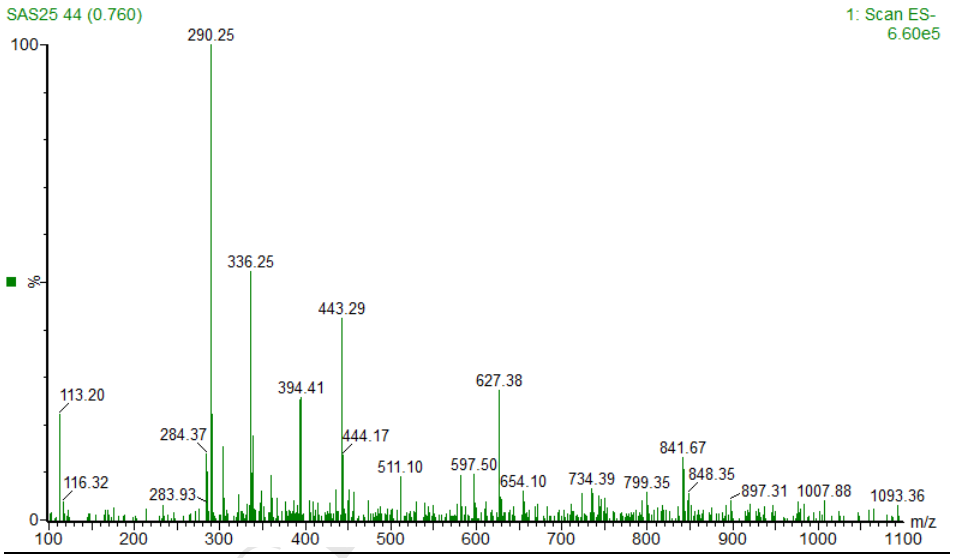
ELSD



ES+

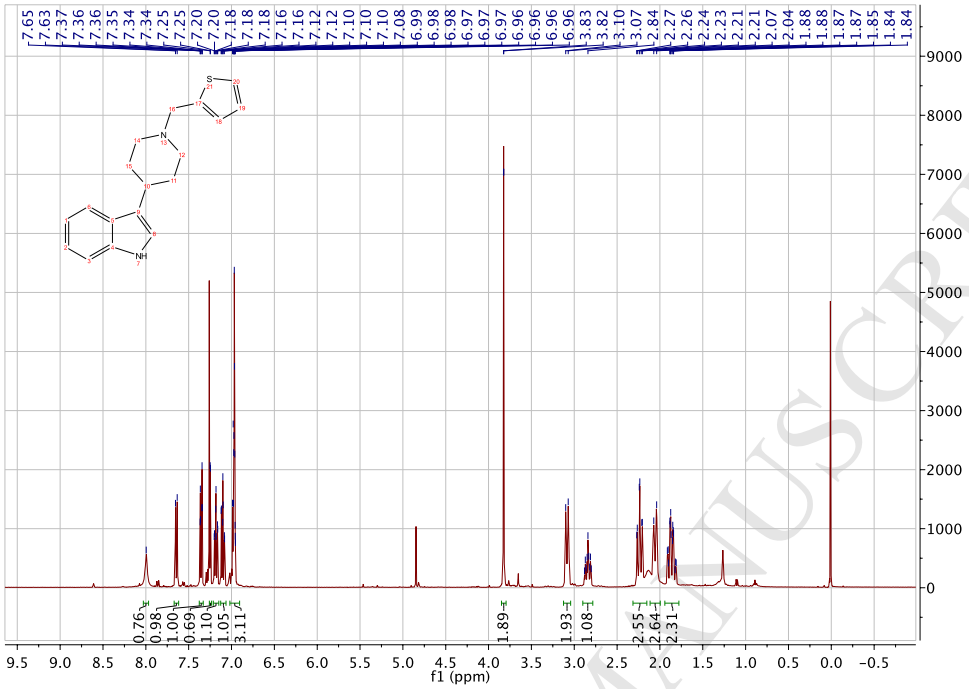

SAS25 45 (0.786)
2: Scan ES+
7.44e7
100
%
0
175.36
292.37
293.37
176.36
184.36
245.37
294.37
309.33
416.29
551.46
583.42
585.30
642.50
724.26
844.59
884.19
942.43
974.23
1068.52
100
200
300
400
500
600
700
800
900
1000
1100
m/z

ES-

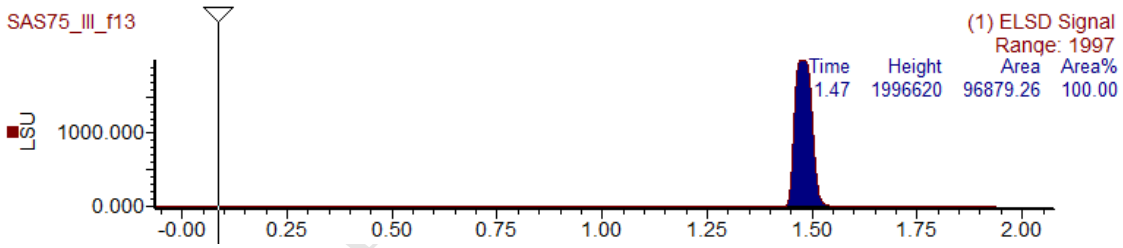

SAS25 44 (0.760)
1: Scan ES-
6.60e5
100
%
0
290.25
336.25
443.29
113.20
394.41
627.38
284.37
444.17
841.67
511.10
597.50
116.32
654.10
734.39
799.35
848.35
283.93
897.31
1007.88
1093.36
100
200
300
400
500
600
700
800
900
1000
1100
m/z

Compound 9q

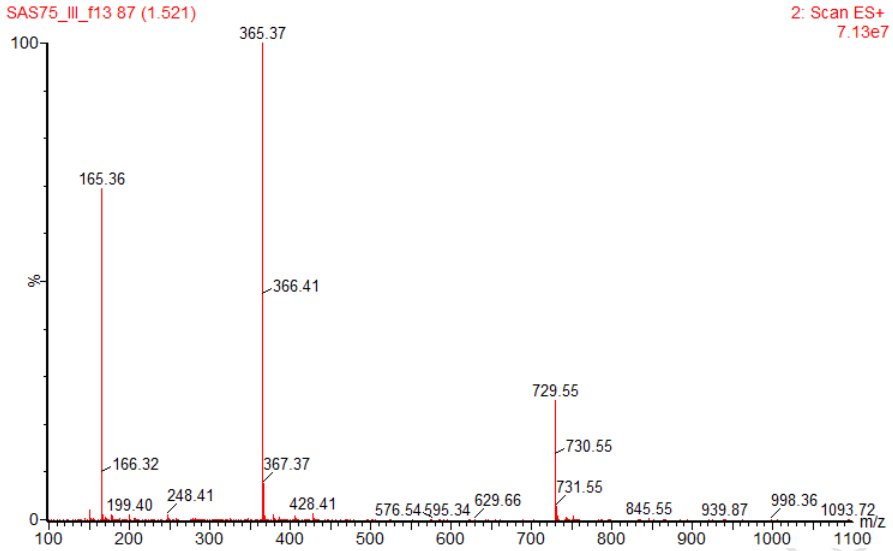
NMR



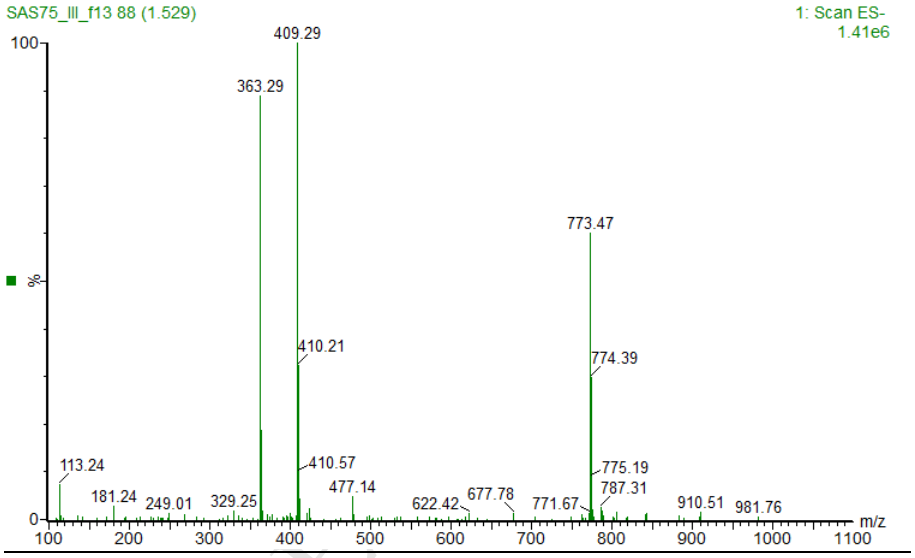
ELSD



ES+

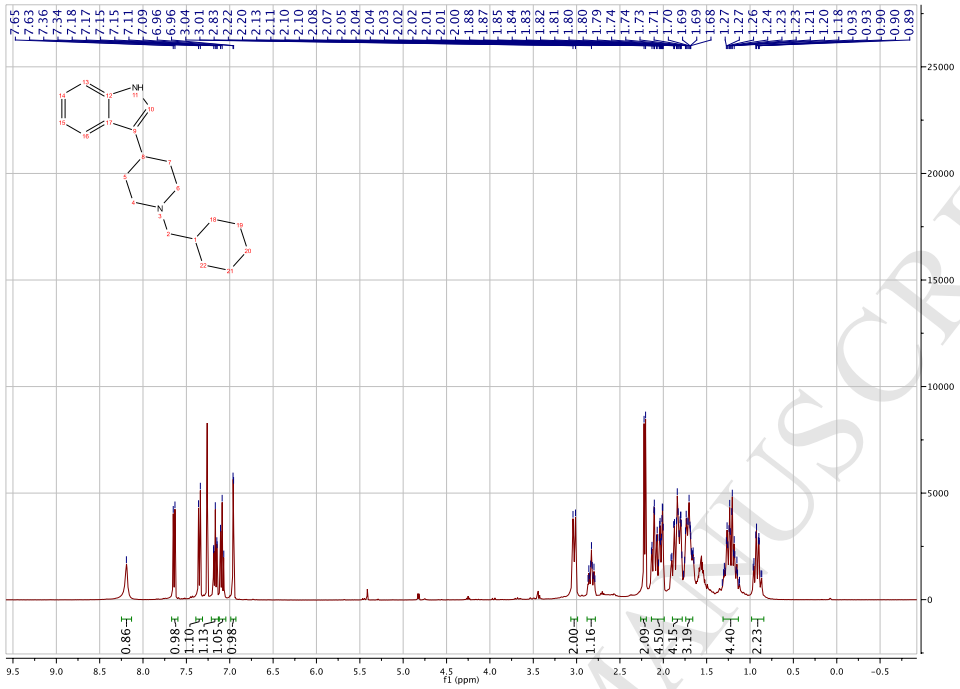

SAS75_III_f13 87 (1.521)
2: Scan ES+
7.13e7
365.37
165.36
366.41
729.55
730.55
166.32
367.37
731.55
199.40
248.41
428.41
576.54
595.34
629.66
845.55
939.87
998.36
1093.72
%
m/z

ES-

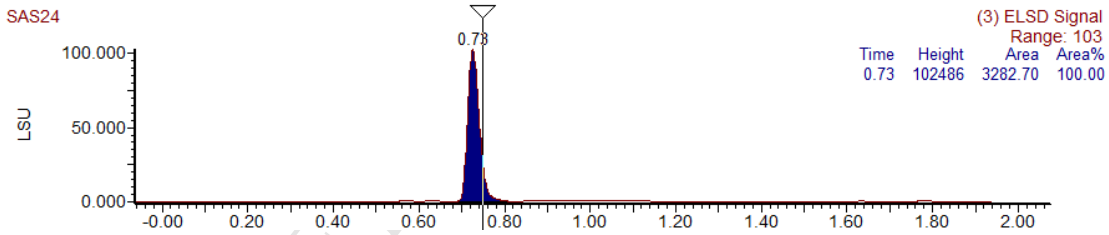

SAS75_III_f13 88 (1.529)
1: Scan ES-
1.41e6
409.29
363.29
773.47
410.21
774.39
113.24
410.57
775.19
477.14
787.31
181.24
249.01
329.25
622.42
677.78
771.67
910.51
981.76
%
m/z

Compound 9r

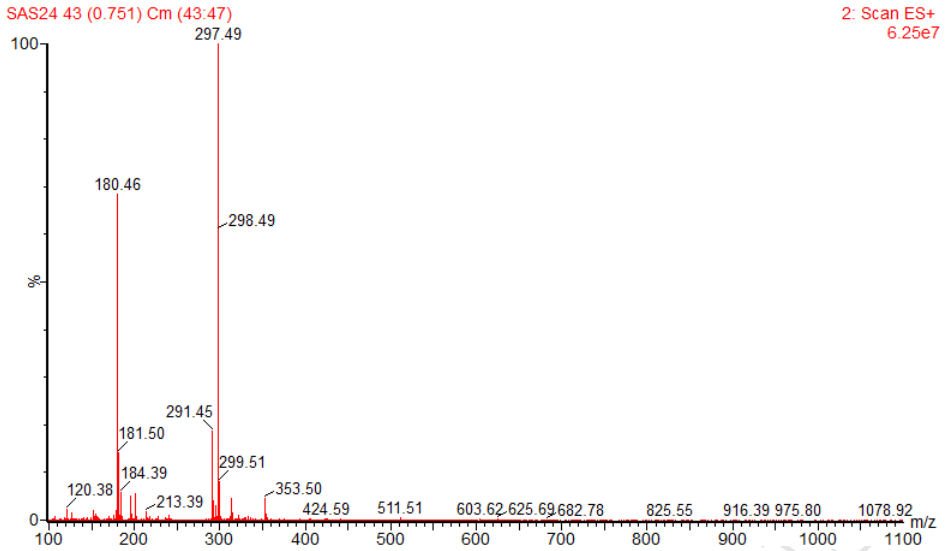
NMR



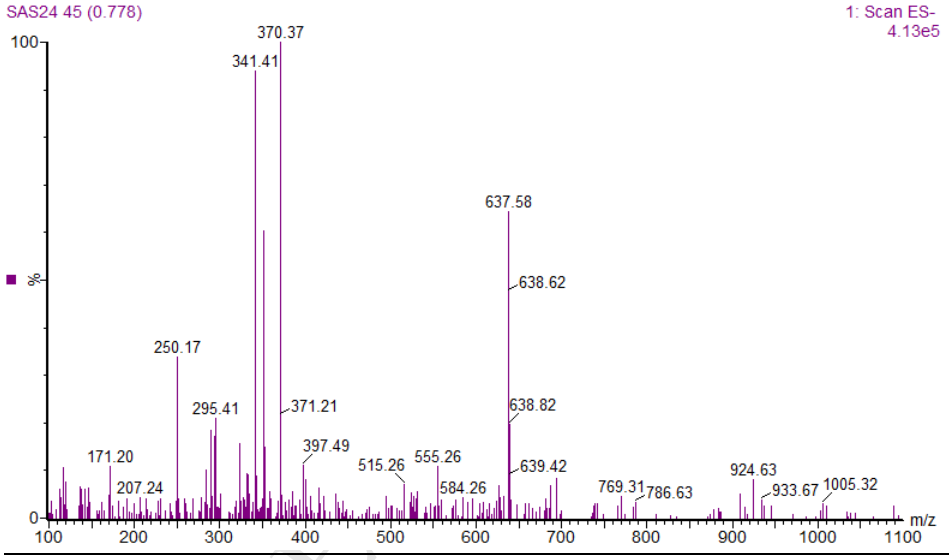
ELSD



ES+

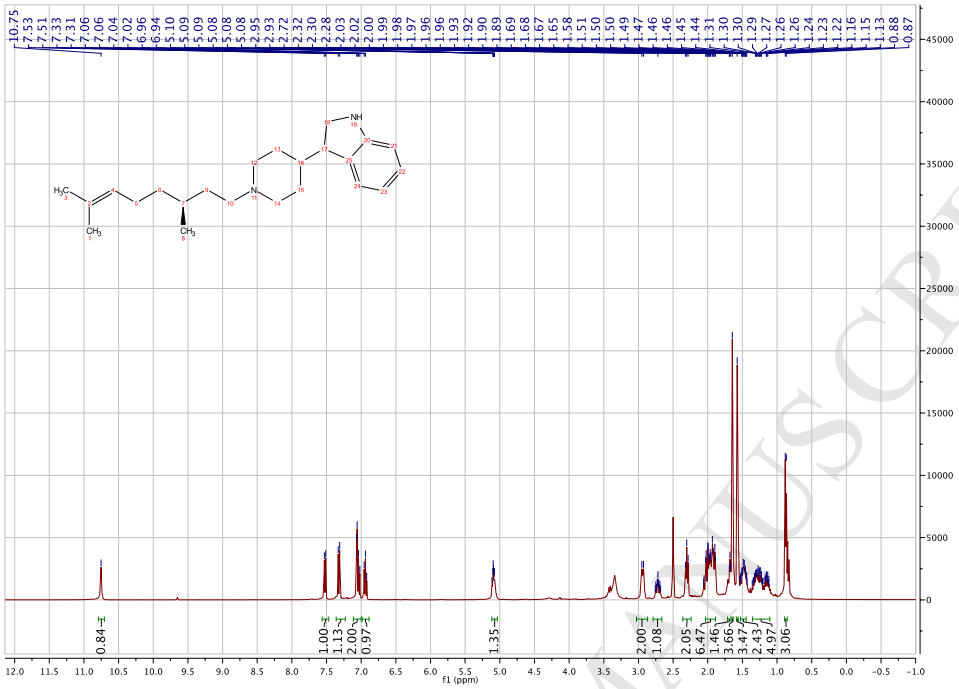

SAS24 43 (0.751) Cm (43:47)
2: Scan ES+
6.25e7
297.49
180.46
298.49
291.45
181.50
299.51
184.39
120.38
213.39
353.50
424.59
511.51
603.62
625.69
682.78
825.55
916.39
975.80
1078.92
%
m/z

ES-

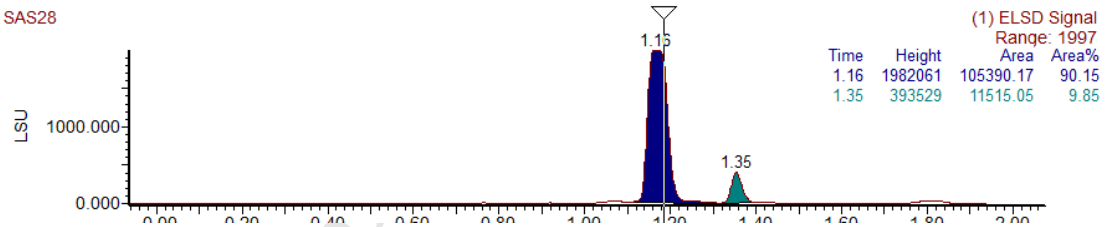

SAS24 45 (0.778)
1: Scan ES-
4.13e5
370.37
341.41
637.58
638.62
250.17
295.41
371.21
638.82
397.49
171.20
515.26
555.26
639.42
207.24
584.26
769.31
786.63
924.63
933.67
1005.32
%
m/z

Compound 9s

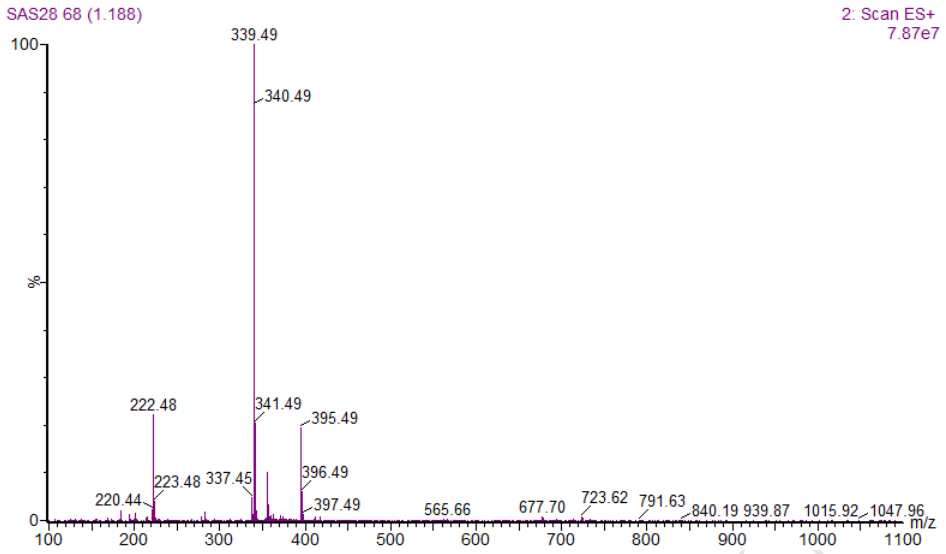
NMR



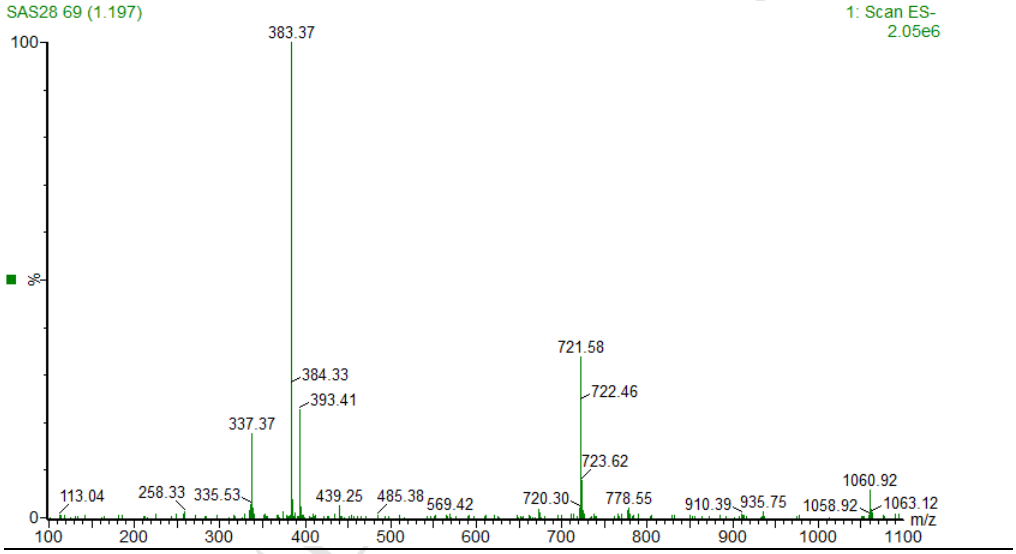
ELSD



ES+

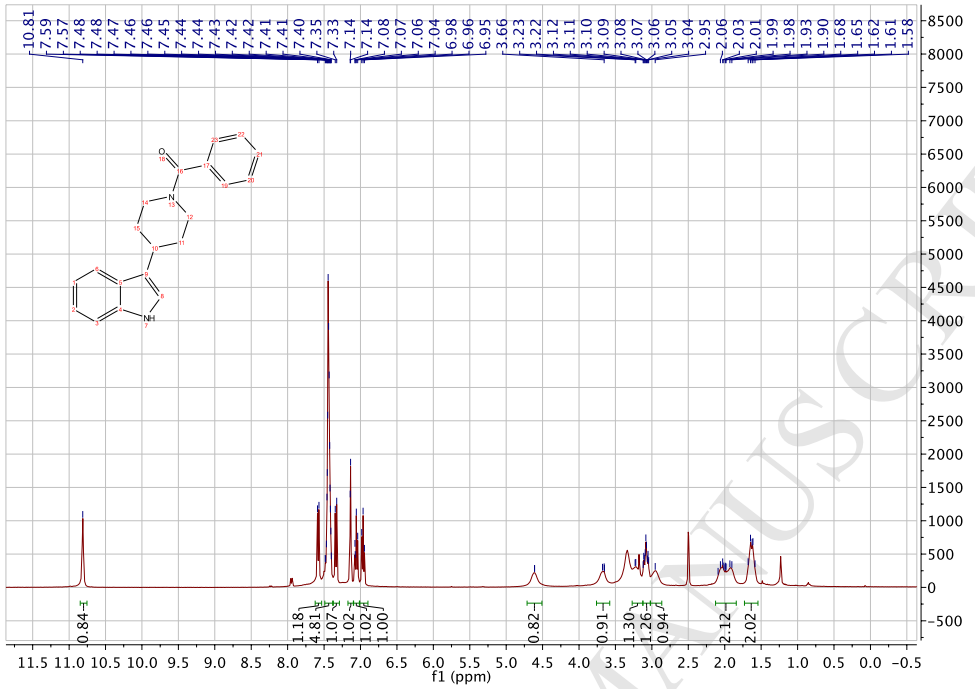

SAS28 68 (1.188)
2: Scan ES+
7.87e7
100
%
0
339.49
340.49
222.48
341.49
395.49
396.49
223.48
337.45
397.49
220.44
565.66
677.70
723.62
791.63
840.19
939.87
1015.92
1047.96
m/z
100
200
300
400
500
600
700
800
900
1000
1100

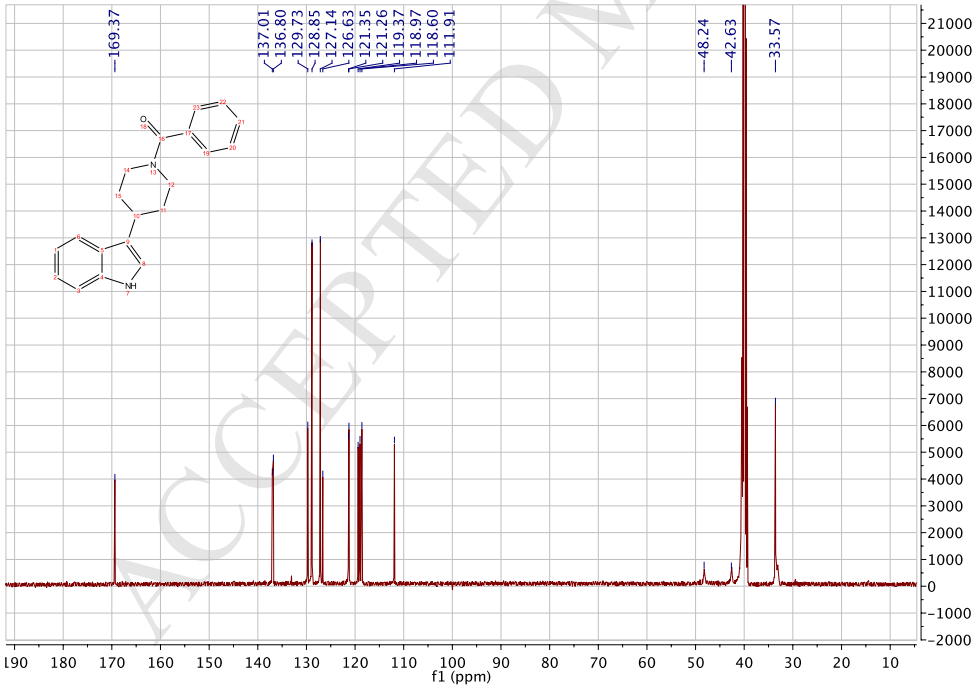
ES-


SAS28 69 (1.197)
1: Scan ES-
2.05e6
100
%
0
383.37
721.58
384.33
722.46
393.41
337.37
723.62
1060.92
113.04
258.33
335.53
439.25
485.38
569.42
720.30
778.55
910.39
935.75
1058.92
1063.12
m/z
100
200
300
400
500
600
700
800
900
1000
1100

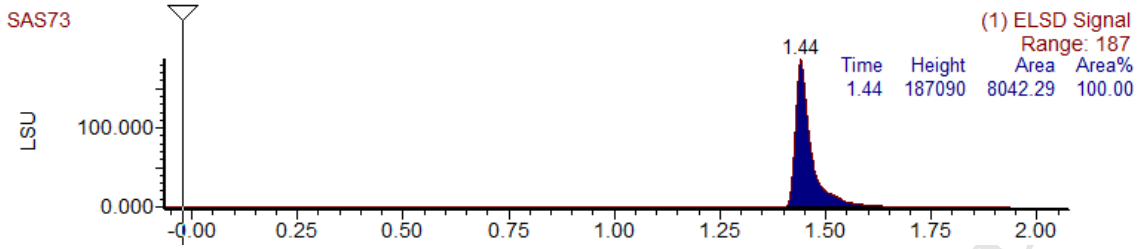
Compound 10a

NMR

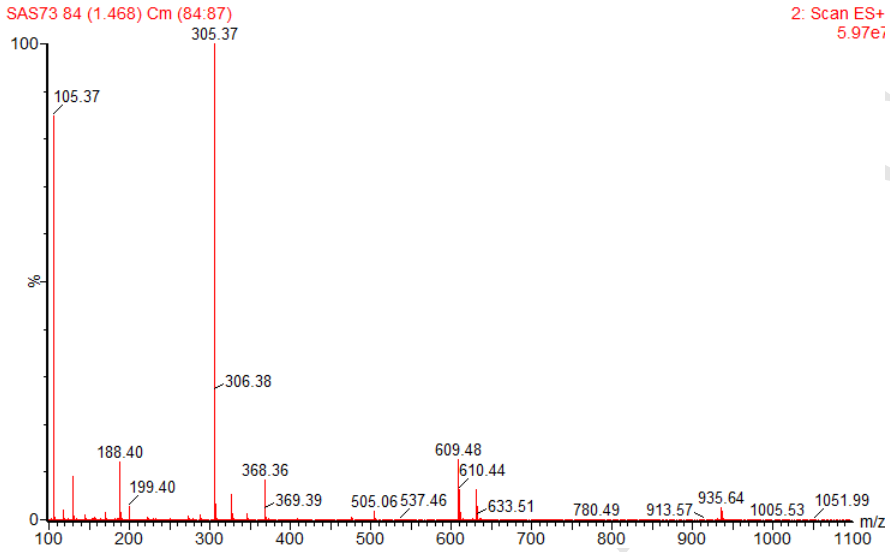




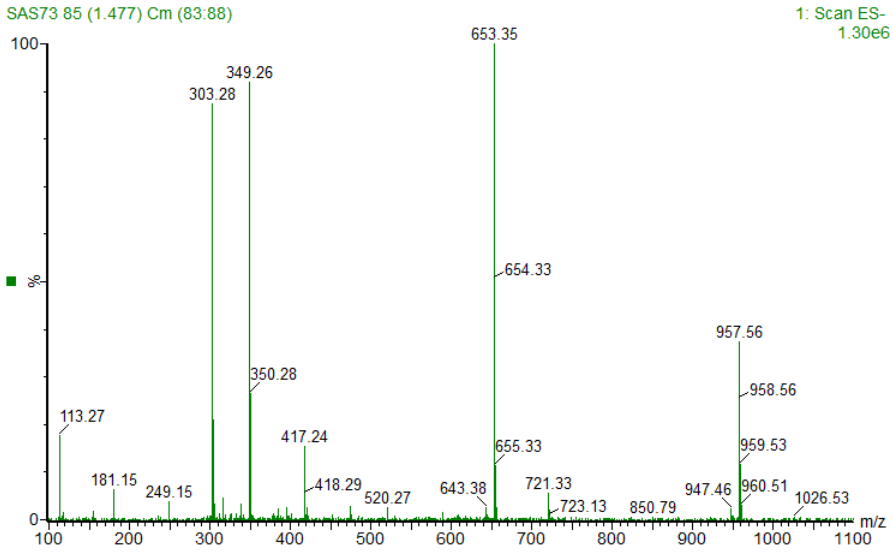
ELSD


SAS73
(1) ELSD Signal
Range: 187
Time Height Area Area%
1.44 187090 8042.29 100.00
1.44
LSU
100.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

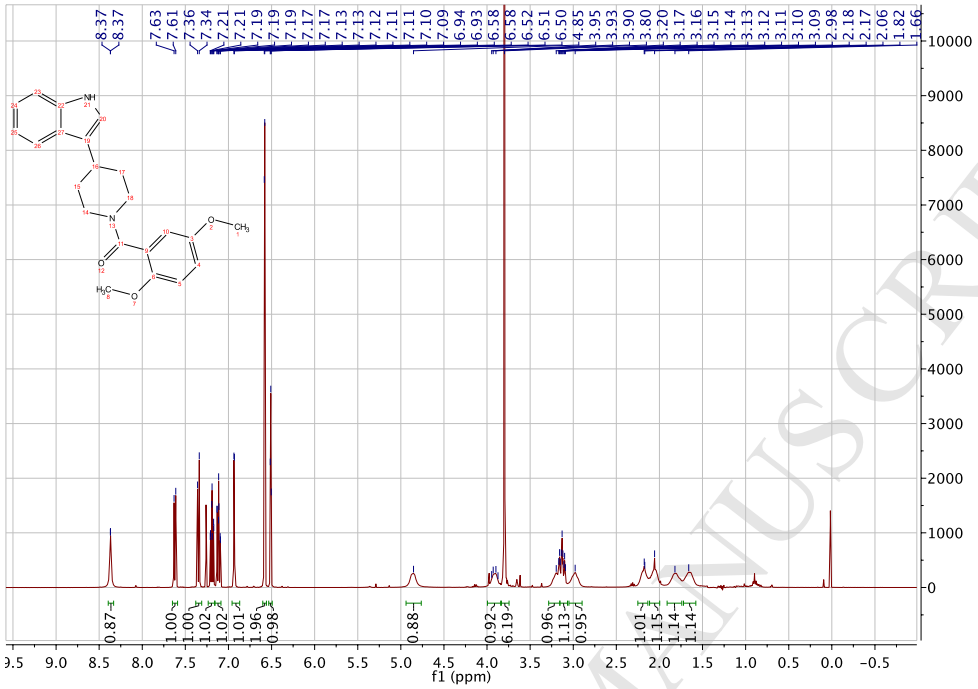

SAS73 84 (1.468) Cm (84:87)
2: Scan ES+
5.97e7
305.37
105.37
306.38
188.40
199.40
368.36
369.39
505.06
537.46
609.48
610.44
633.51
780.49
913.57
935.64
1005.53
1051.99
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

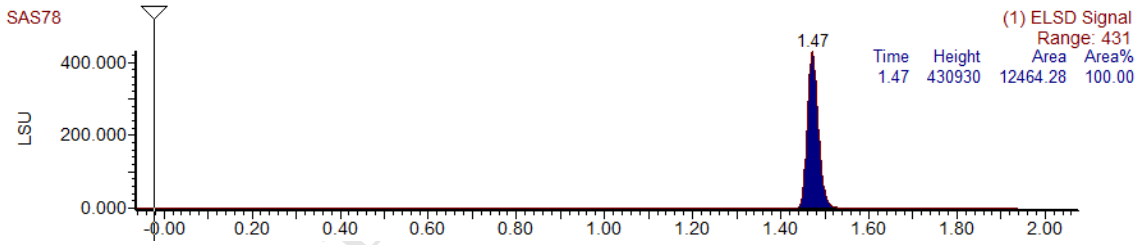

SAS73 85 (1.477) Cm (83:88)
1: Scan ES-
1.30e6
653.35
349.26
303.28
654.33
957.56
350.28
958.56
113.27
417.24
655.33
959.53
181.15
249.15
418.29
520.27
643.38
721.33
723.13
850.79
947.46
960.51
1026.53
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 10b

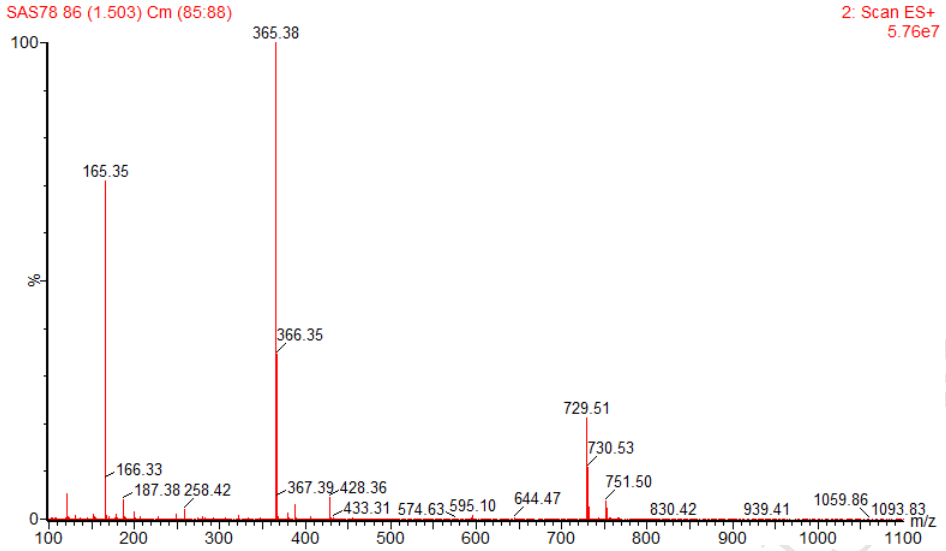
NMR



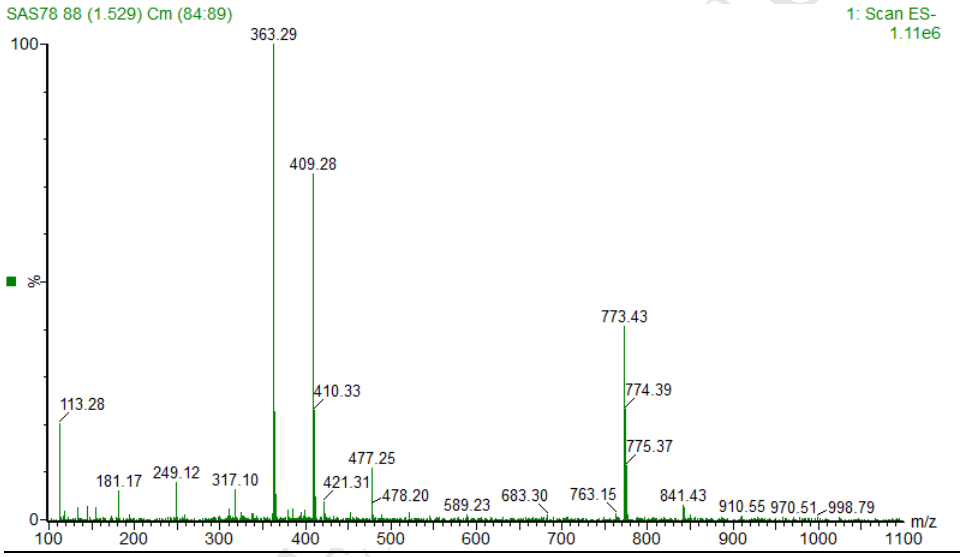
ELSD



ES+

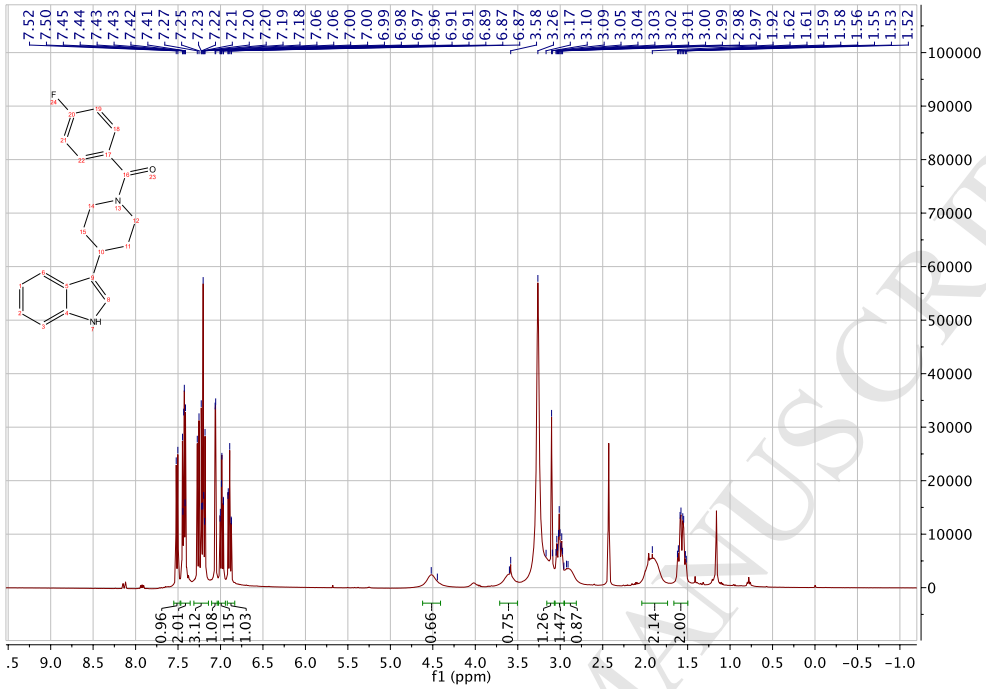

SAS78 86 (1.503) Cm (85:88)
2: Scan ES+
5.76e7
365.38
165.35
366.35
729.51
730.53
166.33
751.50
187.38
258.42
367.39
428.36
433.31
574.63
595.10
644.47
830.42
939.41
1059.86
1093.83
%
m/z

ES-

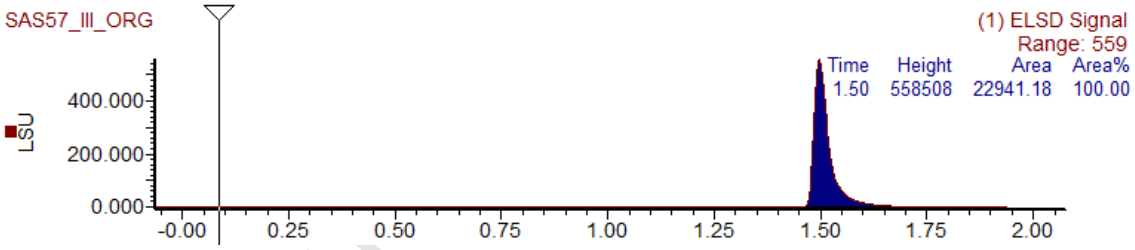

SAS78 88 (1.529) Cm (84:89)
1: Scan ES-
1.11e6
363.29
409.28
773.43
410.33
774.39
113.28
775.37
477.25
181.17
249.12
317.10
421.31
478.20
589.23
683.30
763.15
841.43
910.55
970.51
998.79
%
m/z

Compound 10c

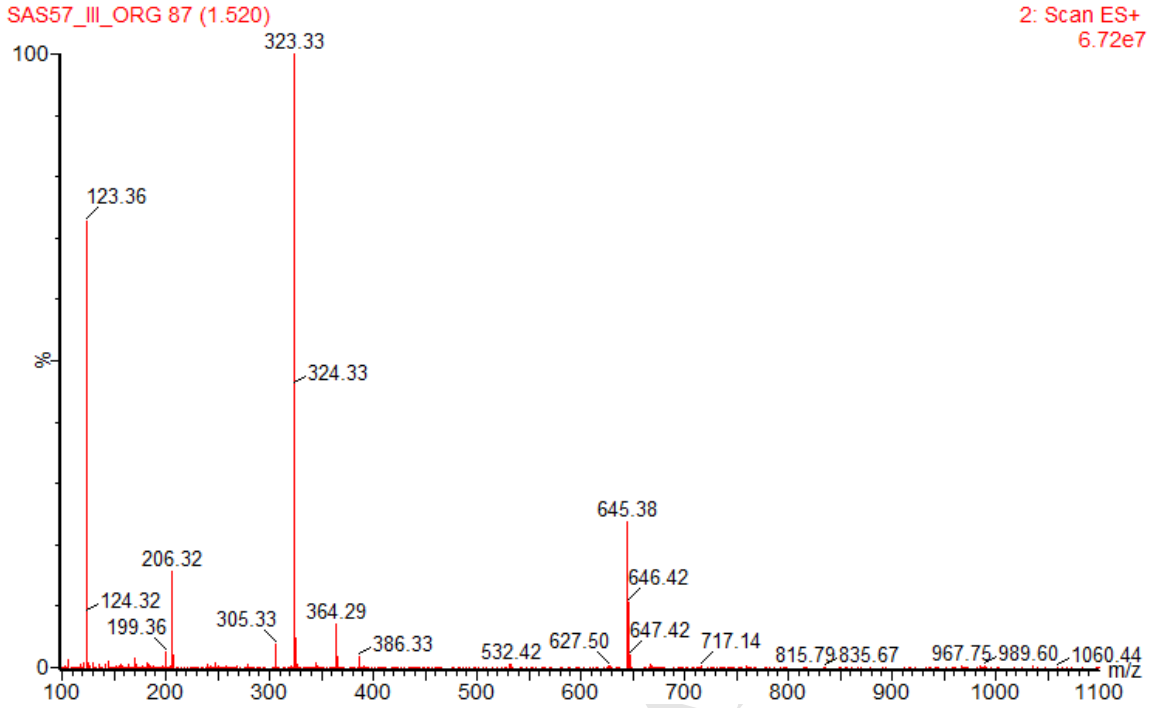
NMR



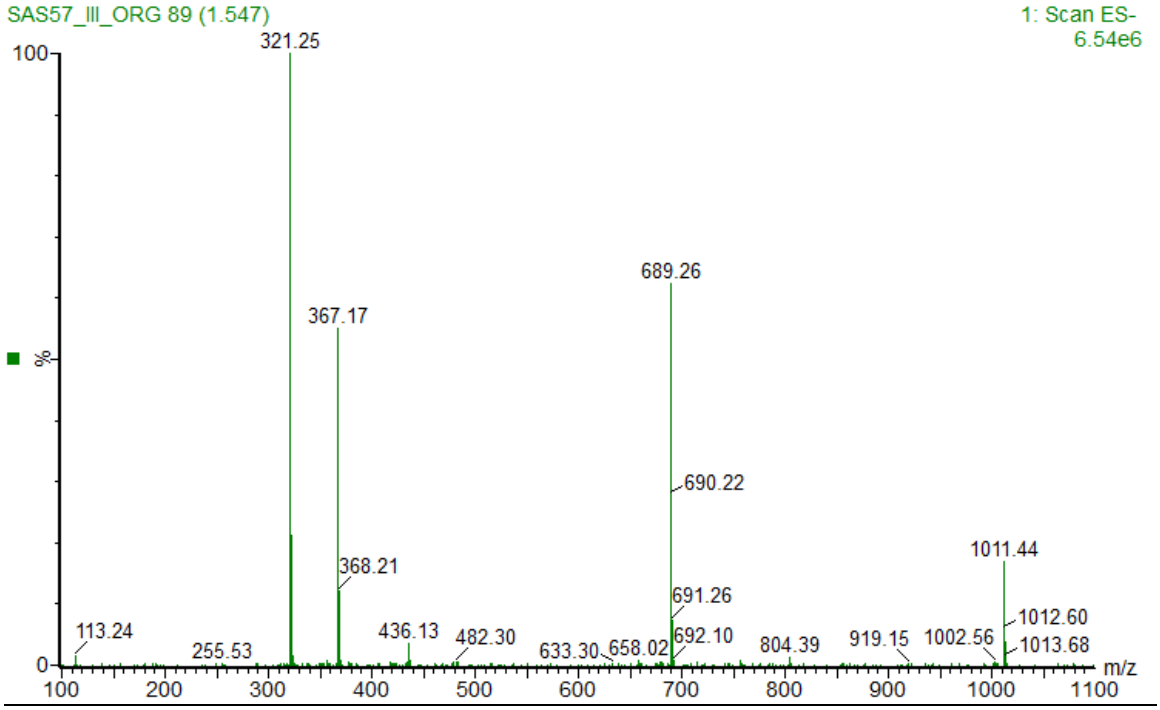
ELSD



ES+


SAS57_III_ORG 87 (1.520)
2: Scan ES+
6.72e7
100
%
0
323.33
123.36
324.33
645.38
206.32
646.42
124.32
199.36
305.33
364.29
647.42
386.33
532.42
627.50
717.14
815.79
835.67
967.75
989.60
1060.44
m/z
100
200
300
400
500
600
700
800
900
1000
1100

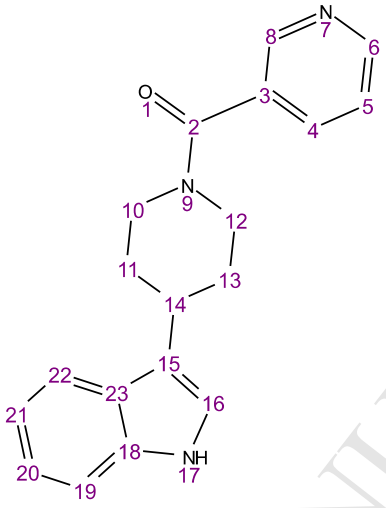
ES-

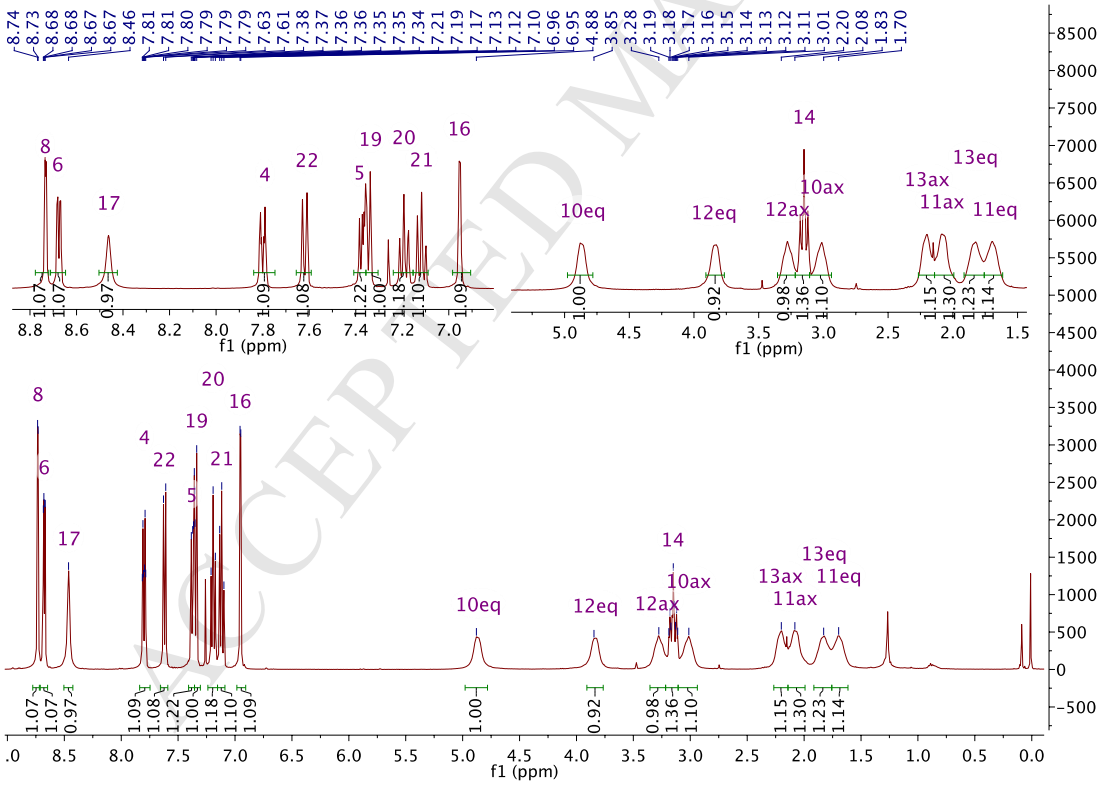

SAS57_III_ORG 89 (1.547)
1: Scan ES-
6.54e6
100
%
0
321.25
689.26
367.17
690.22
1011.44
368.21
691.26
1012.60
113.24
255.53
436.13
482.30
633.30
658.02
692.10
804.39
919.15
1002.56
1013.68
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 10d

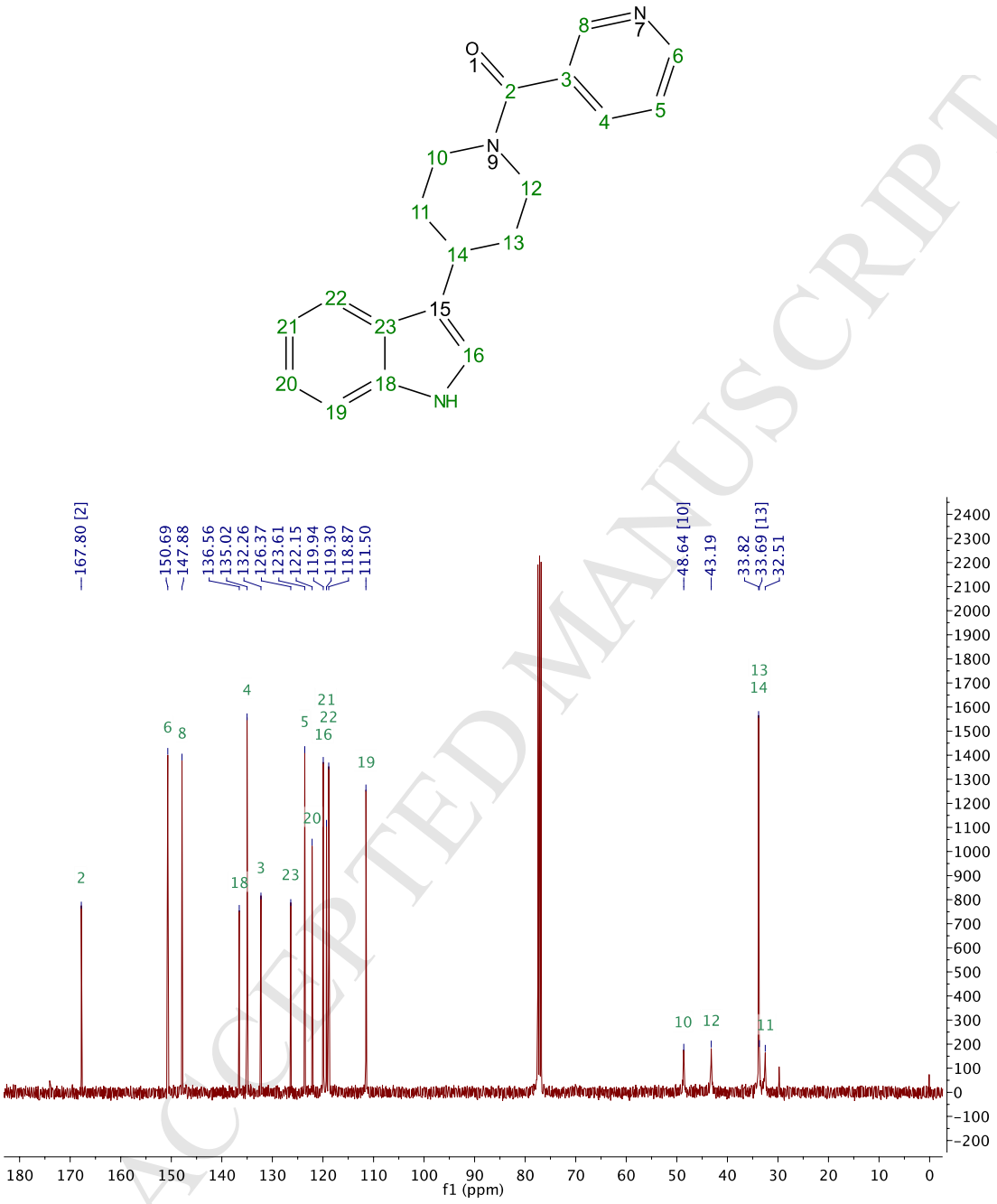
NMR

1H-NMR

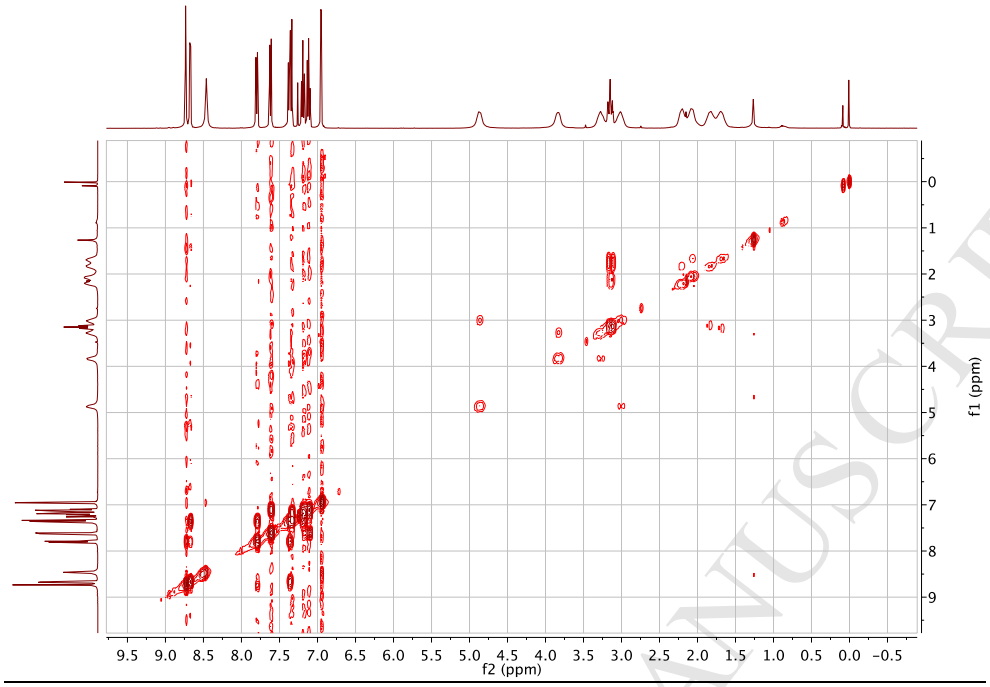


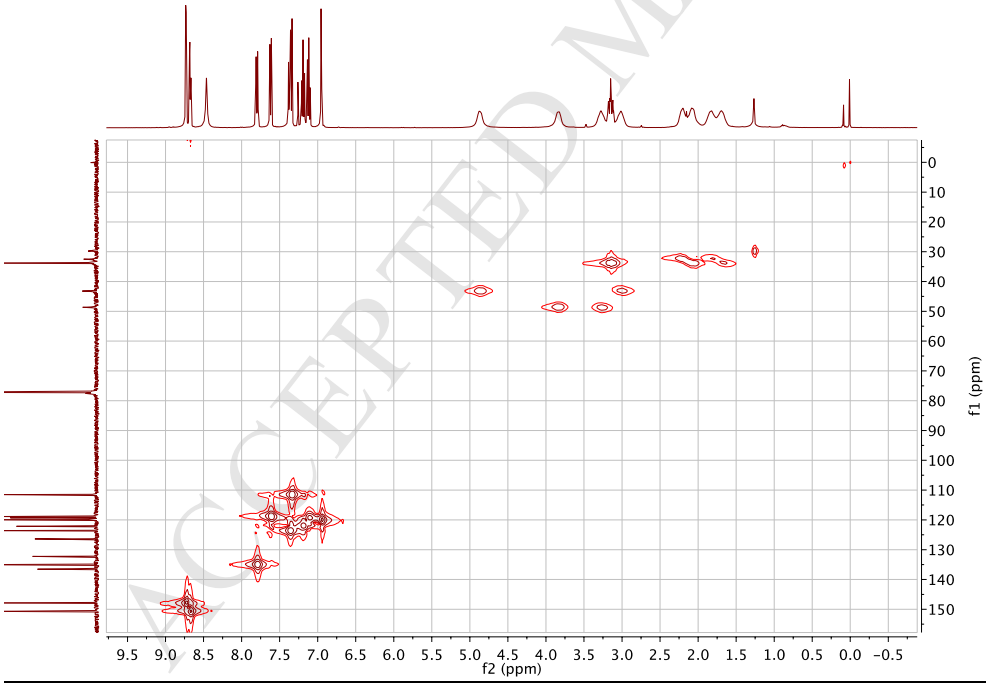


13C-NMR

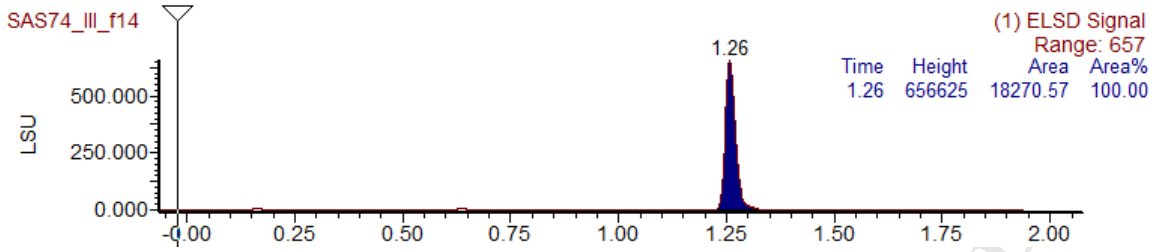


COSY and HMQC

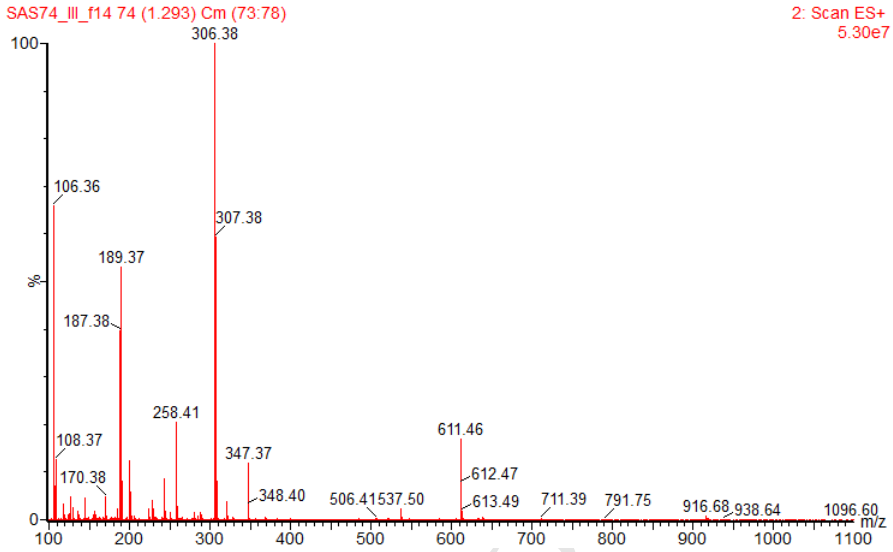




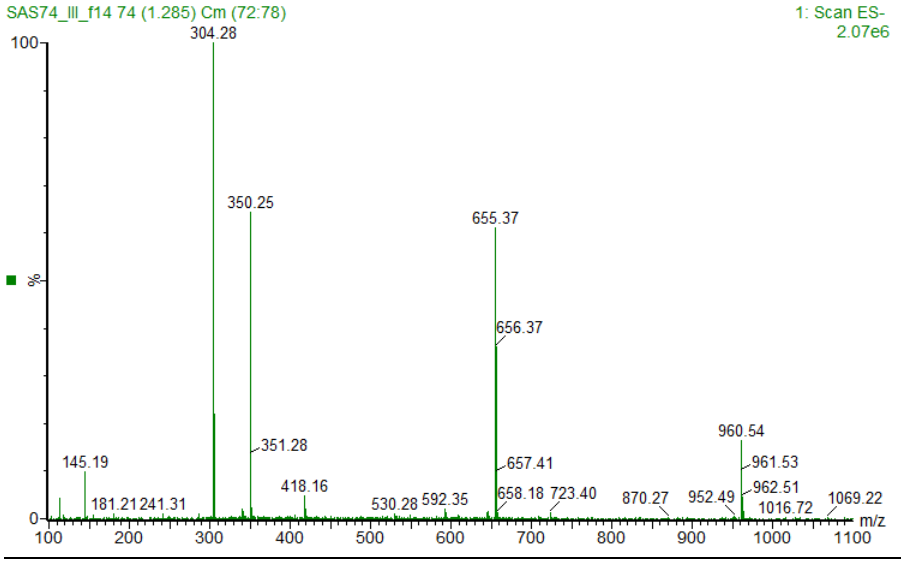
ELSD


SAS74_III_f14
(1) ELSD Signal
Range: 657
Time Height Area Area%
1.26 656625 18270.57 100.00
1.26
LSU
500.000
250.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

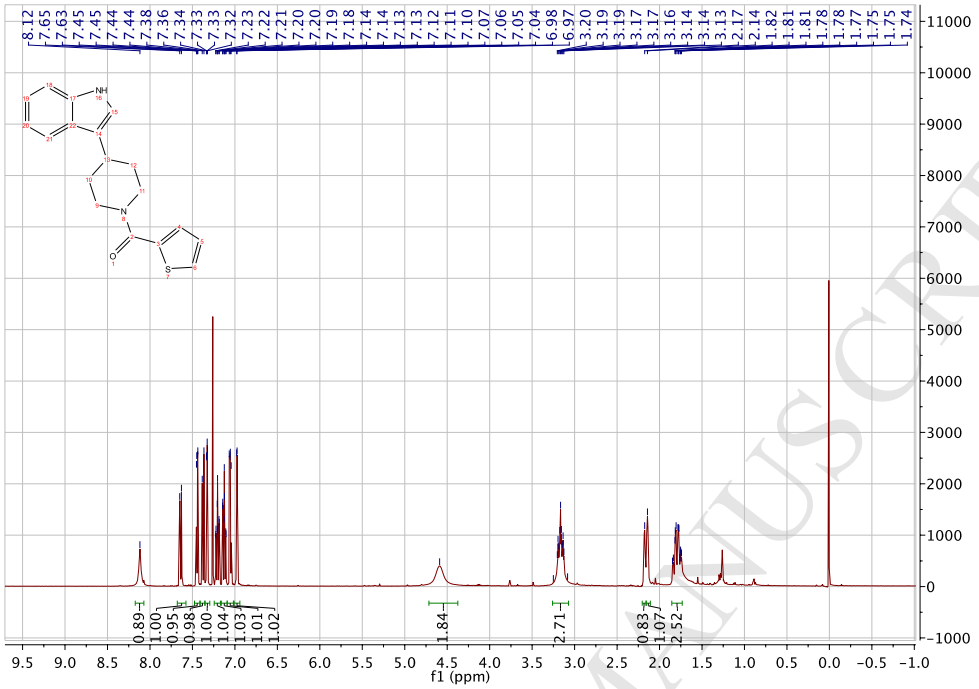

SAS74_III_f14 74 (1.293) Cm (73:78)
2: Scan ES+
5.30e7
306.38
106.36
307.38
189.37
187.38
258.41
108.37
347.37
170.38
348.40
506.41537.50
611.46
612.47
613.49
711.39
791.75
916.68
938.64
1096.60
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

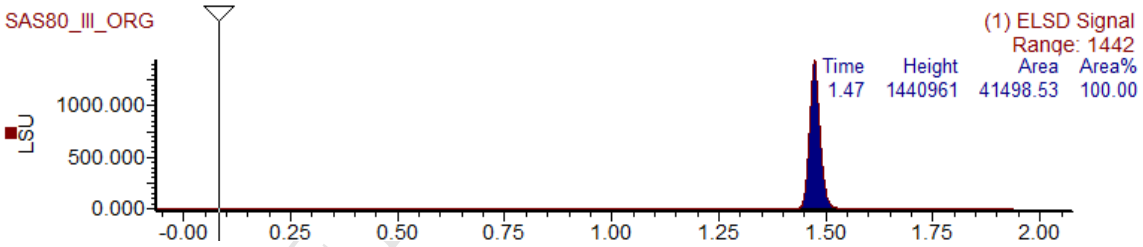

SAS74_III_f14 74 (1.285) Cm (72:78)
1: Scan ES-
2.07e6
304.28
350.25
655.37
656.37
351.28
960.54
145.19
657.41
961.53
418.16
962.51
181.21241.31
530.28 592.35
658.18 723.40
870.27
952.49
1016.72
1069.22
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 10e

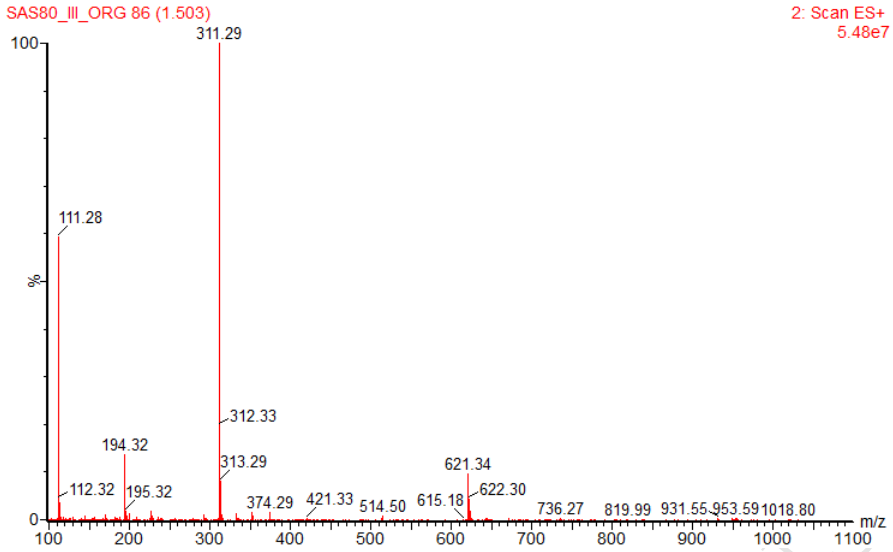
NMR



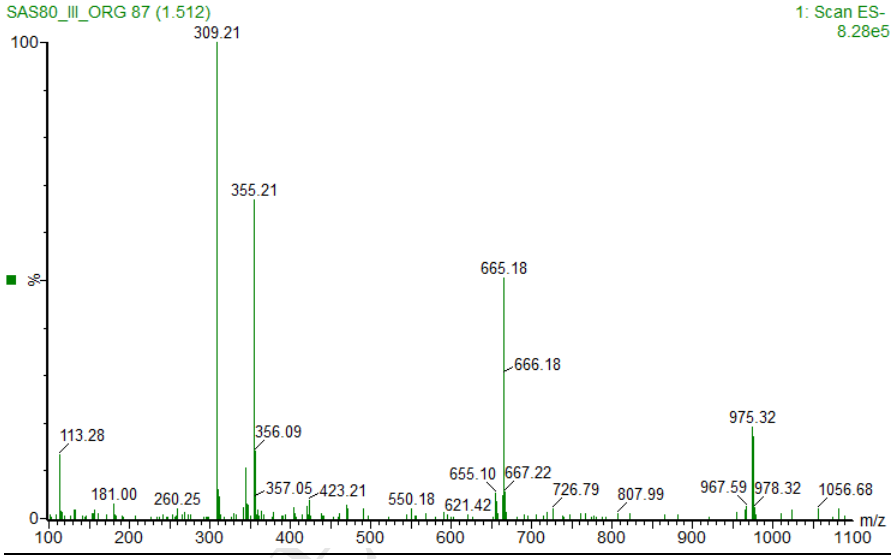
ELSD



ES+

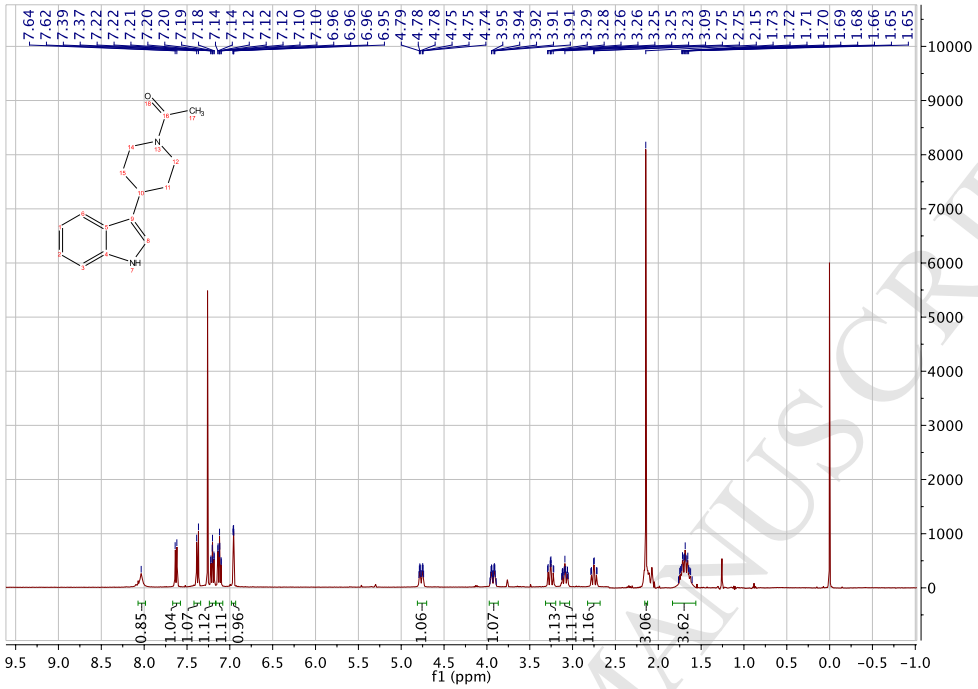

SAS80_III_ORG 86 (1.503)
2: Scan ES+
5.48e7
311.29
111.28
312.33
194.32
313.29
621.34
112.32
195.32
622.30
374.29
421.33
514.50
615.18
736.27
819.99
931.55
953.59
1018.80
%
m/z

ES-

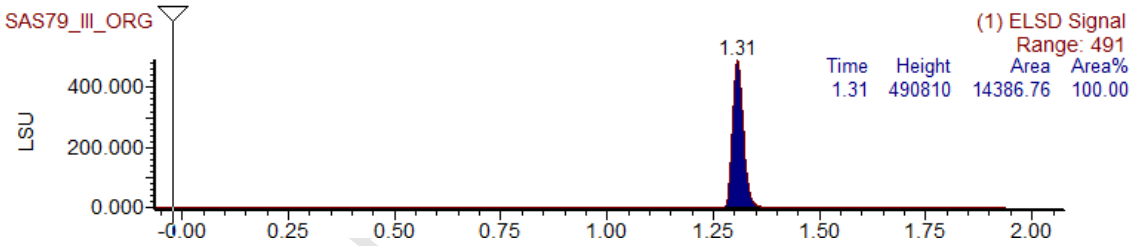

SAS80_III_ORG 87 (1.512)
1: Scan ES-
8.28e5
309.21
355.21
665.18
666.18
975.32
113.28
356.09
655.10
667.22
181.00
260.25
357.05
423.21
550.18
621.42
726.79
807.99
967.59
978.32
1056.68
%
m/z

Compound 10f

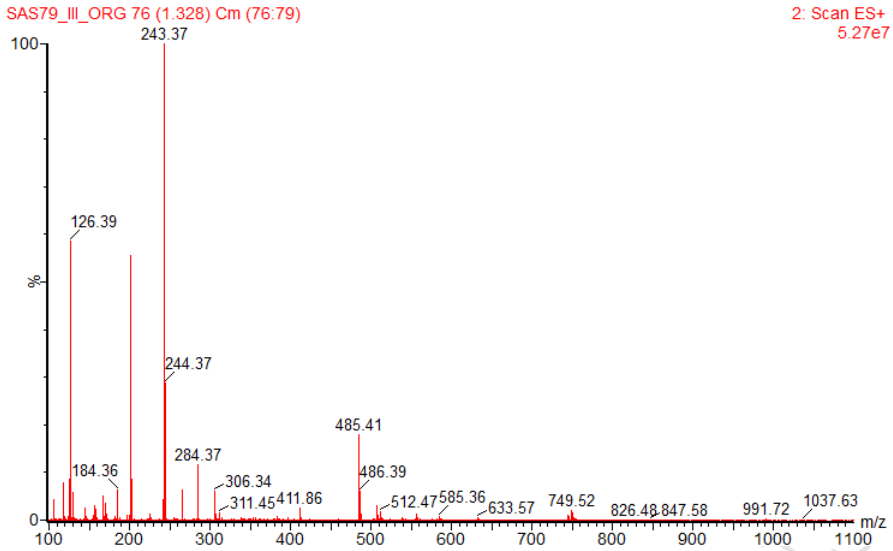
NMR



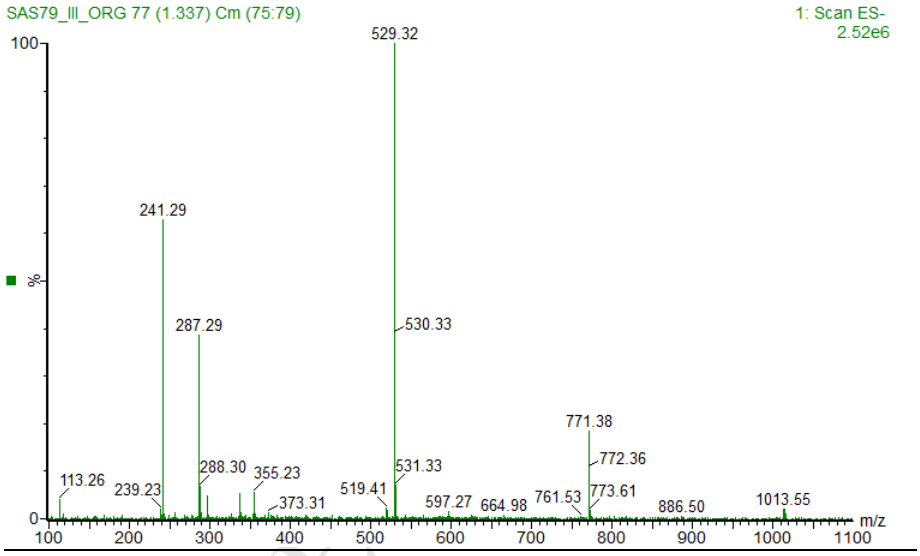
ELSD



ES+

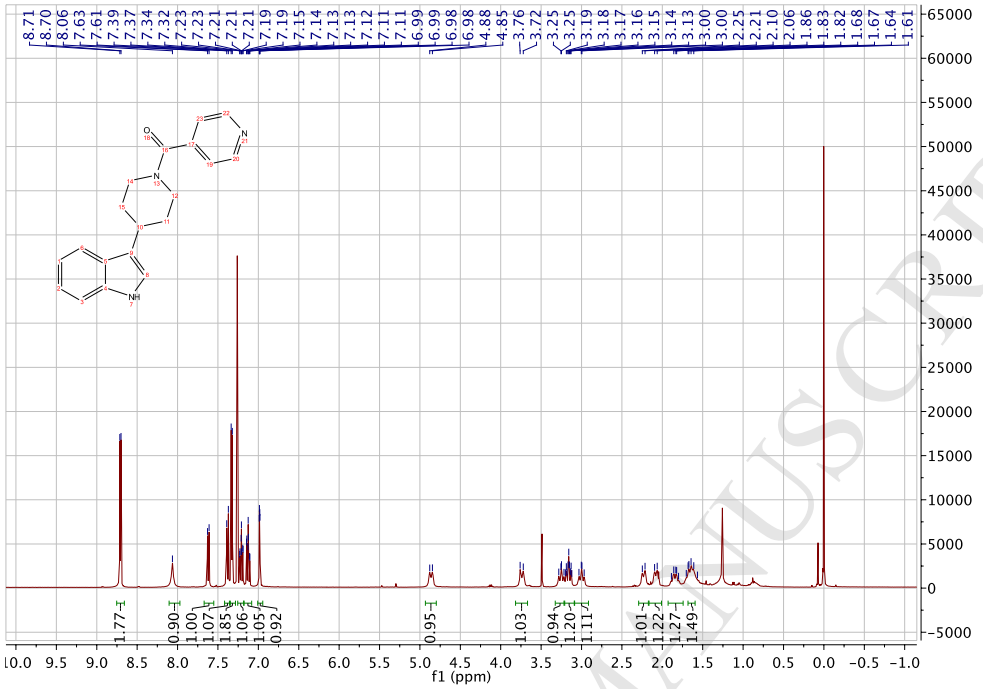

SAS79_III_ORG 76 (1.328) Cm (76:79)
2: Scan ES+
5.27e7
100
%
0
243.37
126.39
244.37
485.41
284.37
184.36
306.34
311.45
411.86
486.39
512.47
585.36
633.57
749.52
826.48
847.58
991.72
1037.63
100
200
300
400
500
600
700
800
900
1000
1100
m/z

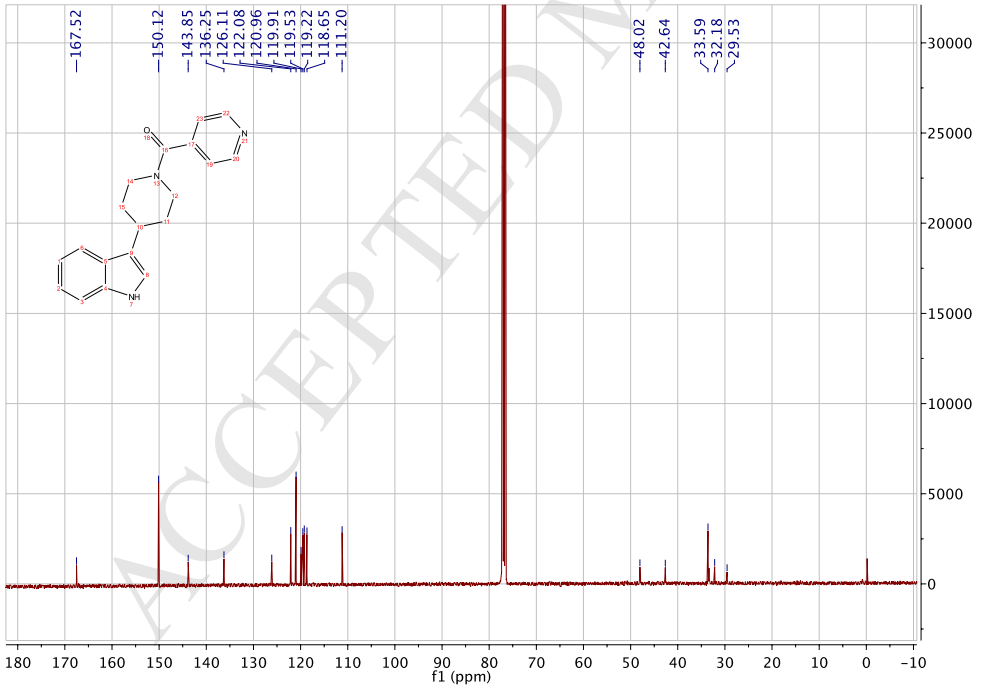
ES-


SAS79_III_ORG 77 (1.337) Cm (75:79)
1: Scan ES-
2.52e6
100
%
0
529.32
241.29
287.29
530.33
771.38
772.36
113.26
239.23
288.30
355.23
531.33
519.41
373.31
597.27
664.98
761.53
773.61
886.50
1013.55
100
200
300
400
500
600
700
800
900
1000
1100
m/z

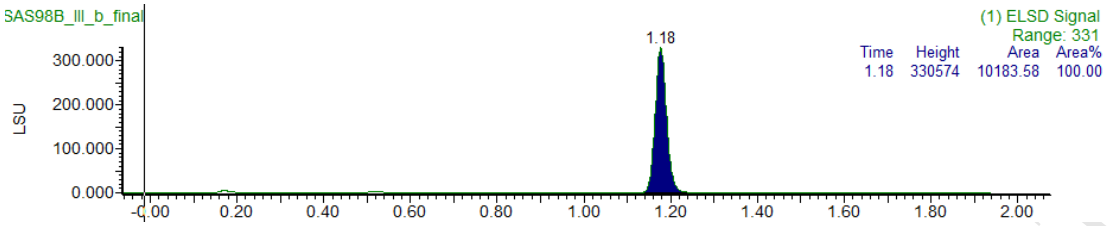
Compound 10g

NMR

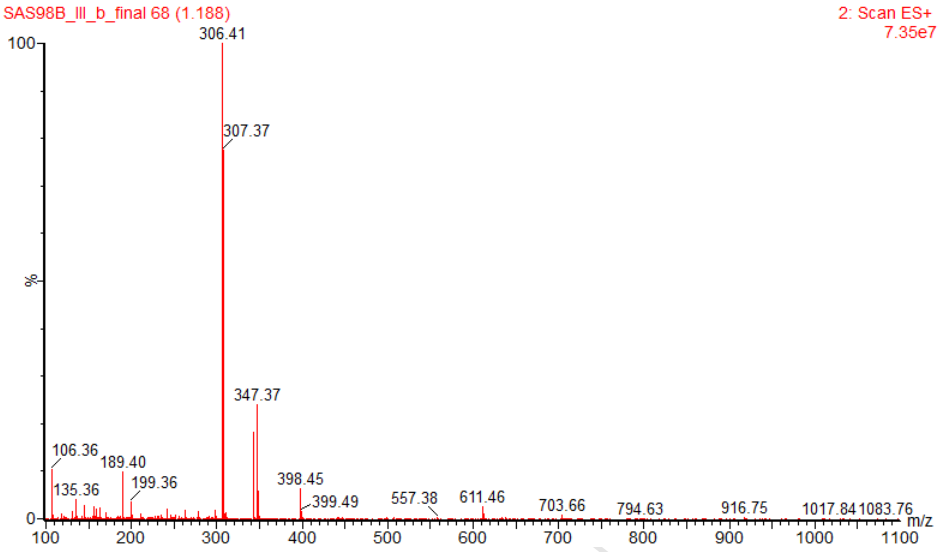




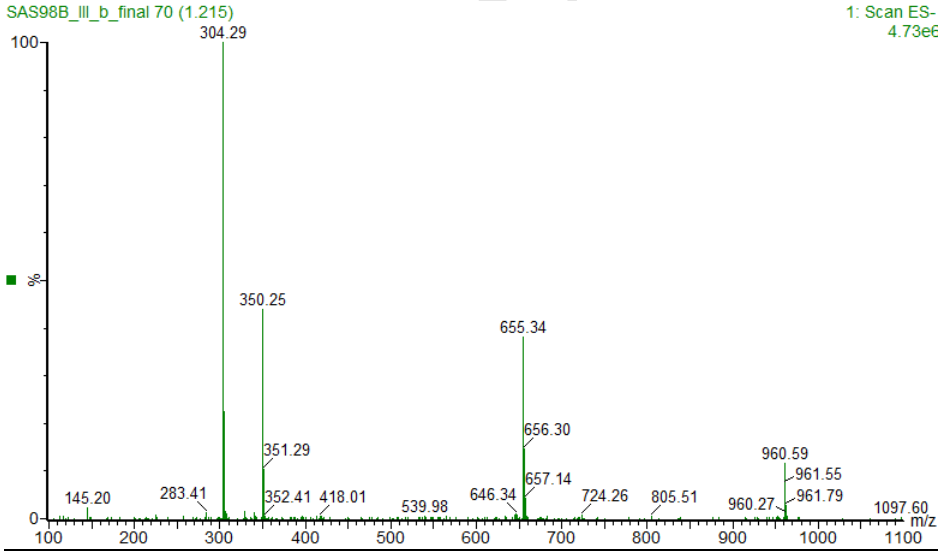
ELSD


SAS98B_III_b_final
(1) ELSD Signal
Range: 331
Time Height Area Area%
1.18 330574 10183.58 100.00
1.18
LSU
300.000
200.000
100.000
0.000
0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00

ES+

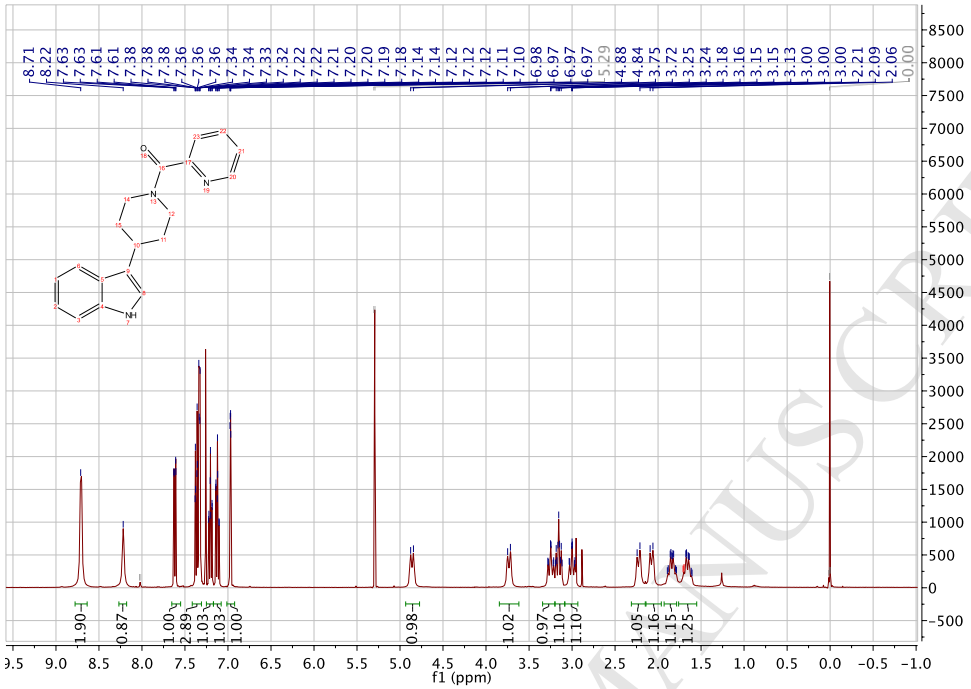

SAS98B_III_b_final 68 (1.188)
2: Scan ES+
7.35e7
306.41
307.37
347.37
106.36
189.40
135.36
199.36
398.45
399.49
557.38
611.46
703.66
794.63
916.75
1017.84
1083.76
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

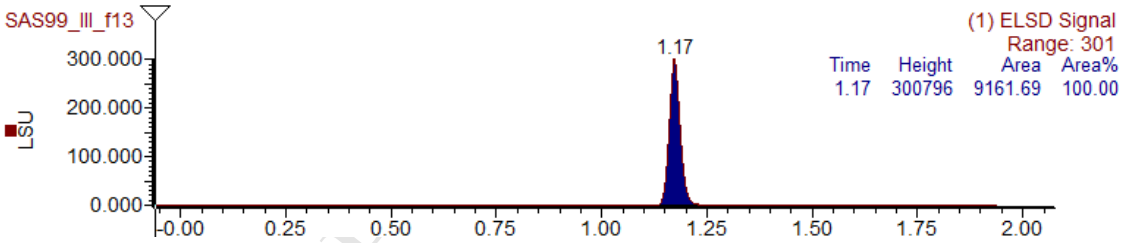

SAS98B_III_b_final 70 (1.215)
1: Scan ES-
304.29
350.25
655.34
656.30
351.29
960.59
961.55
657.14
961.79
145.20
283.41
352.41
418.01
539.98
646.34
724.26
805.51
960.27
1097.60
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 10h

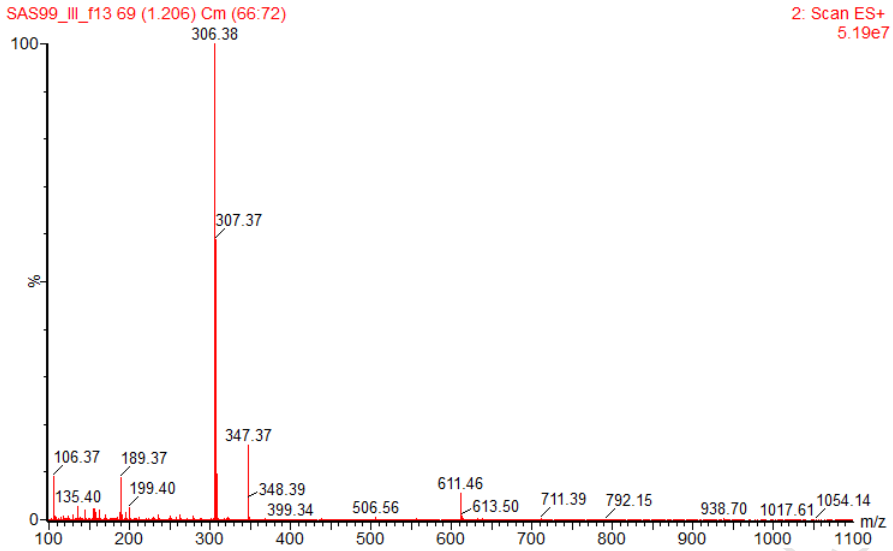
NMR



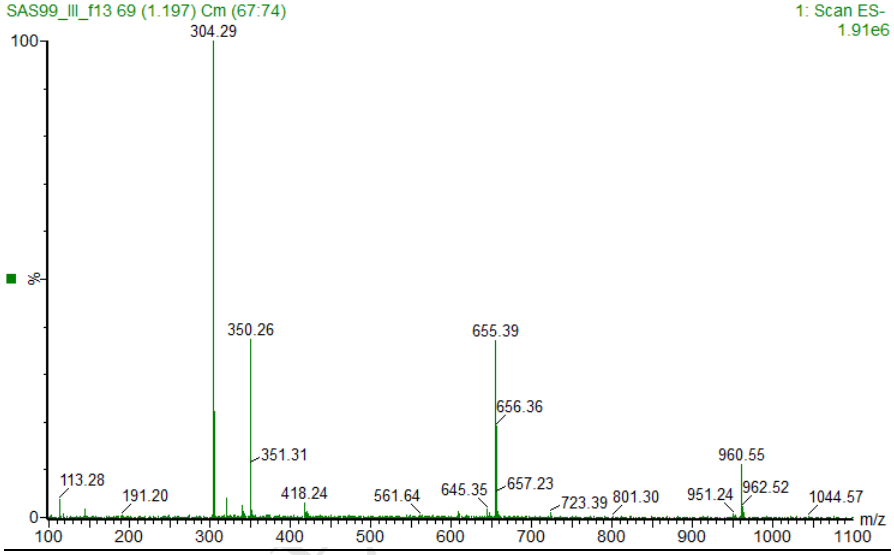
ELSD



ES+

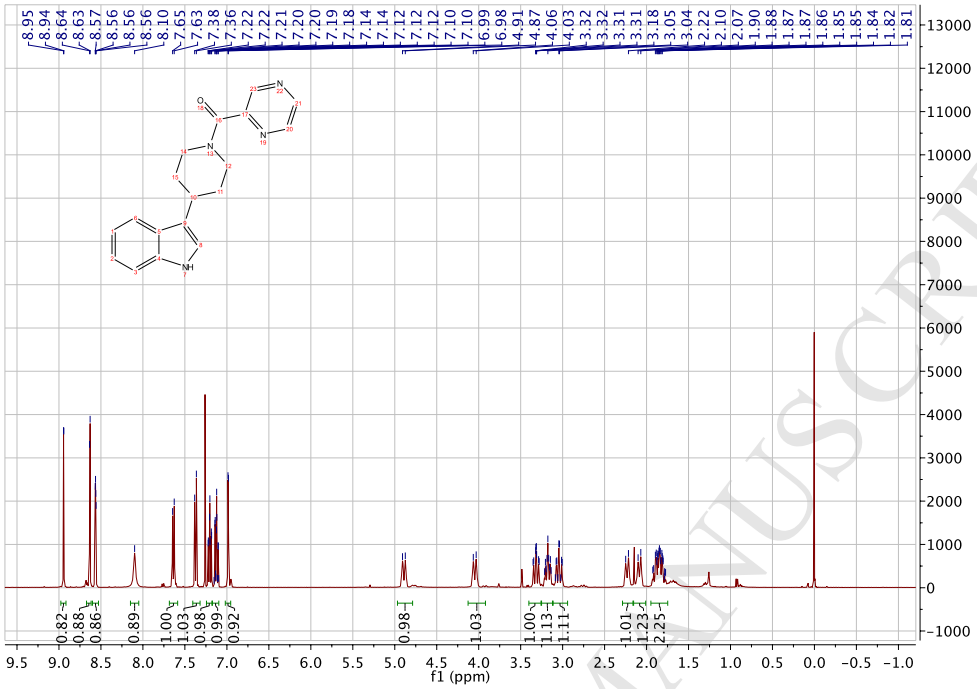

SAS99_III_f13 69 (1.206) Cm (66:72)
2: Scan ES+
5.19e7
306.38
307.37
347.37
106.37
189.37
135.40
199.40
348.39
399.34
506.56
611.46
613.50
711.39
792.15
938.70
1017.61
1054.14
%
m/z

ES-

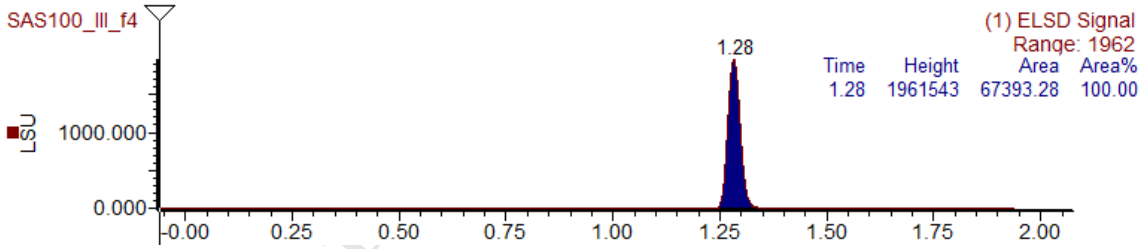

SAS99_III_f13 69 (1.197) Cm (67:74)
1: Scan ES-
1.91e6
304.29
350.26
655.39
656.36
351.31
960.55
113.28
191.20
418.24
561.64
645.35
657.23
723.39
801.30
951.24
962.52
1044.57
%
m/z

Compound 10i

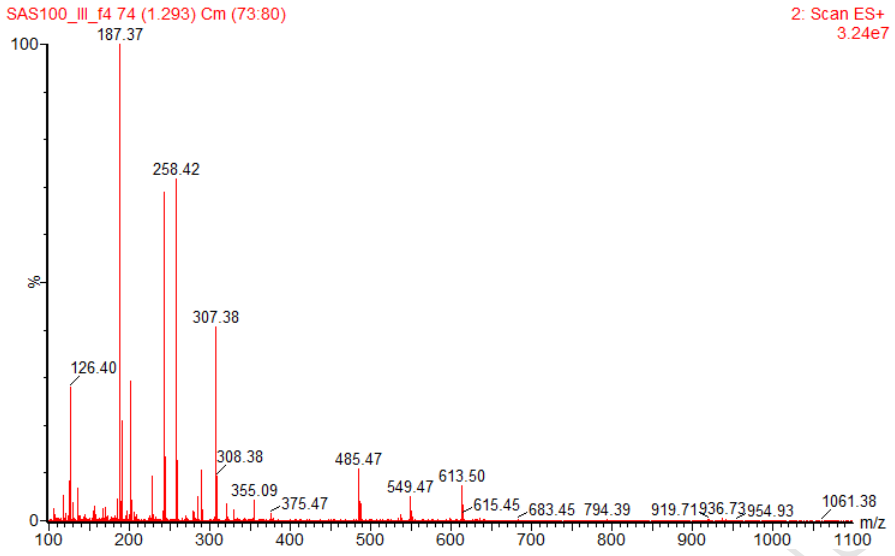
NMR



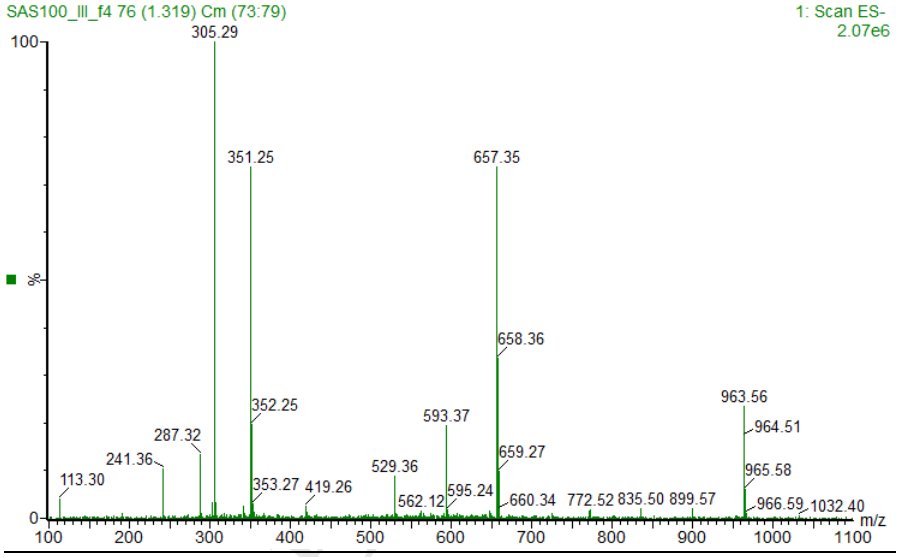
ELSD



ES+

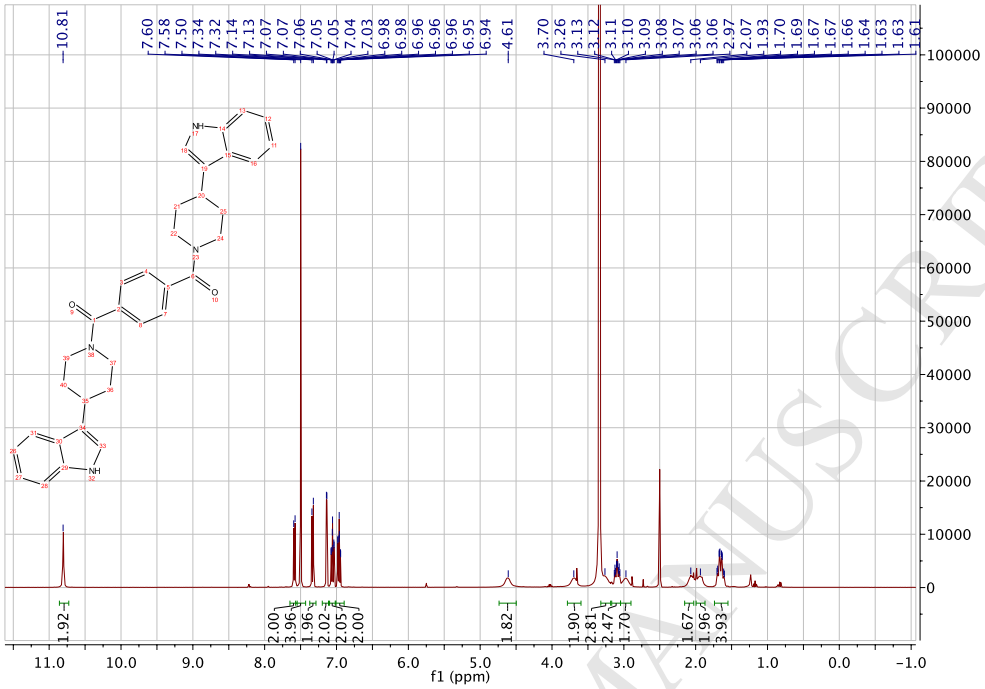

SAS100_III_f4 74 (1.293) Cm (73:80)
2: Scan ES+
3.24e7
187.37
258.42
307.38
126.40
308.38
485.47
355.09
549.47
613.50
375.47
615.45
683.45
794.39
919.71
936.73
954.93
1061.38
m/z

ES-

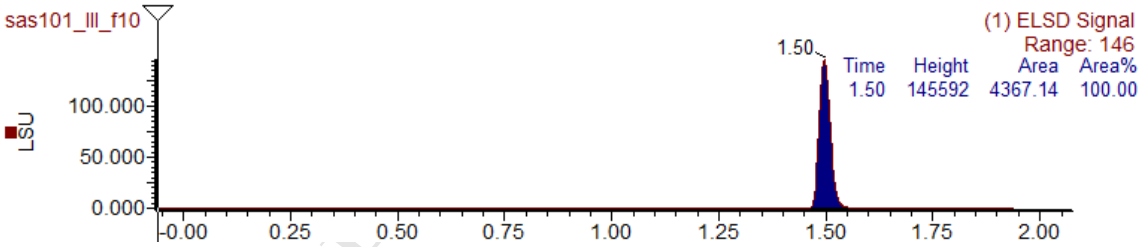

SAS100_III_f4 76 (1.319) Cm (73:79)
1: Scan ES-
2.07e6
305.29
351.25
657.35
658.36
352.25
963.56
593.37
964.51
287.32
659.27
241.36
529.36
965.58
113.30
353.27
419.26
595.24
562.12
660.34
772.52
835.50
899.57
966.59
1032.40
m/z

Compound 10j

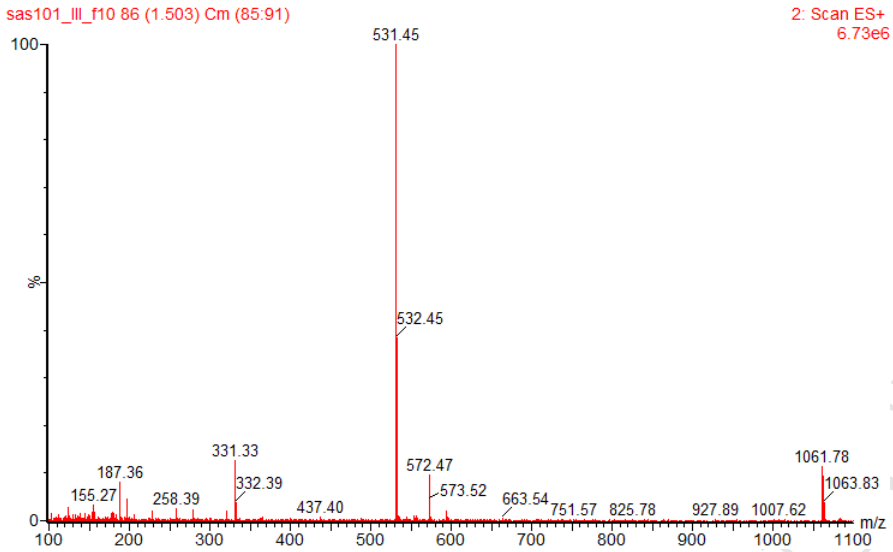
NMR



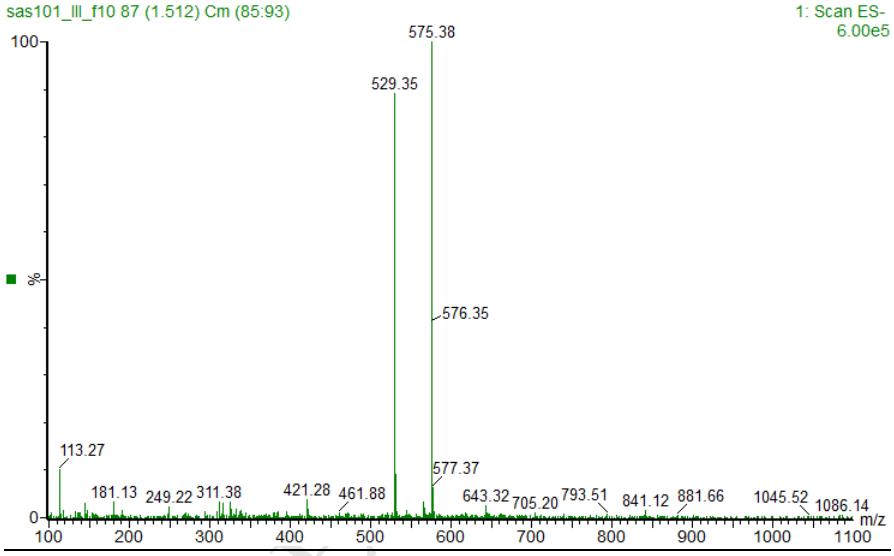
ELSD



ES+

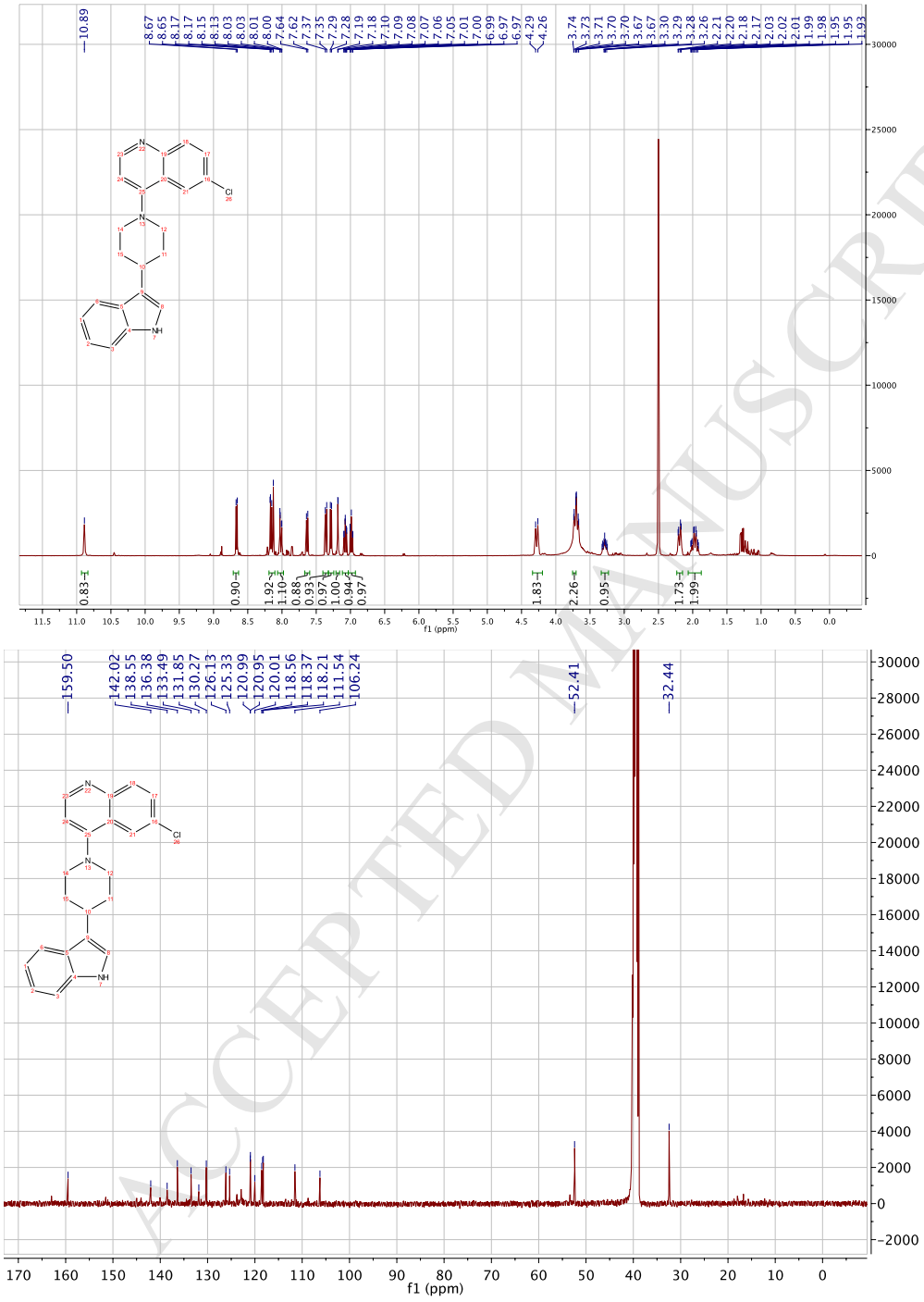

sas101_lll_f10 86 (1.503) Cm (85:91)
2: Scan ES+
6.73e6
100
%
0
531.45
532.45
331.33
187.36
155.27
258.39
332.39
437.40
572.47
573.52
663.54
751.57
825.78
927.89
1007.62
1061.78
1063.83
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

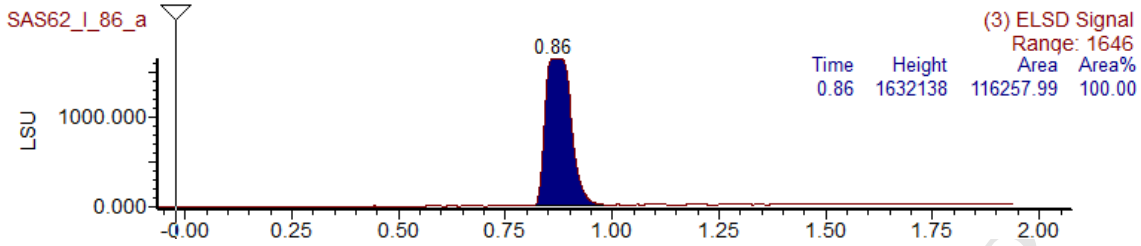

sas101_lll_f10 87 (1.512) Cm (85:93)
1: Scan ES-
6.00e5
100
%
0
575.38
529.35
576.35
113.27
181.13
249.22
311.38
421.28
461.88
577.37
643.32
705.20
793.51
841.12
881.66
1045.52
1086.14
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 11

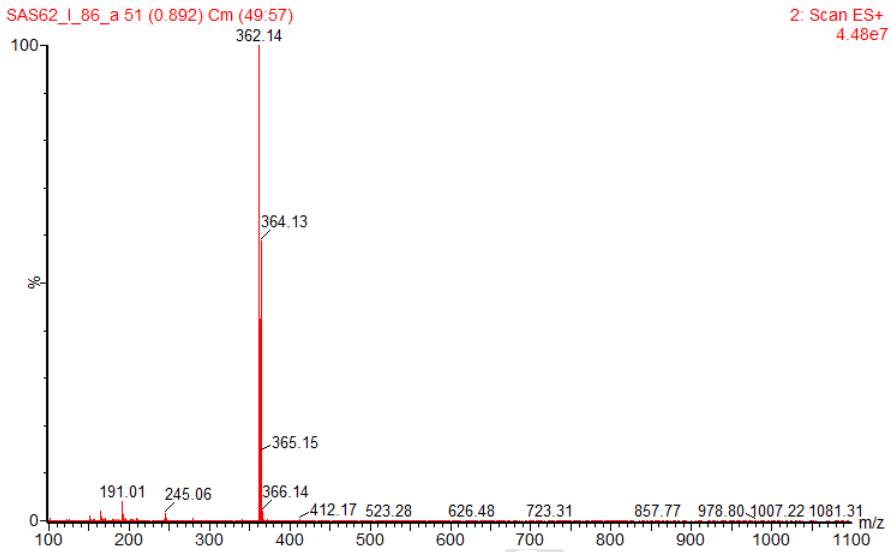
NMR



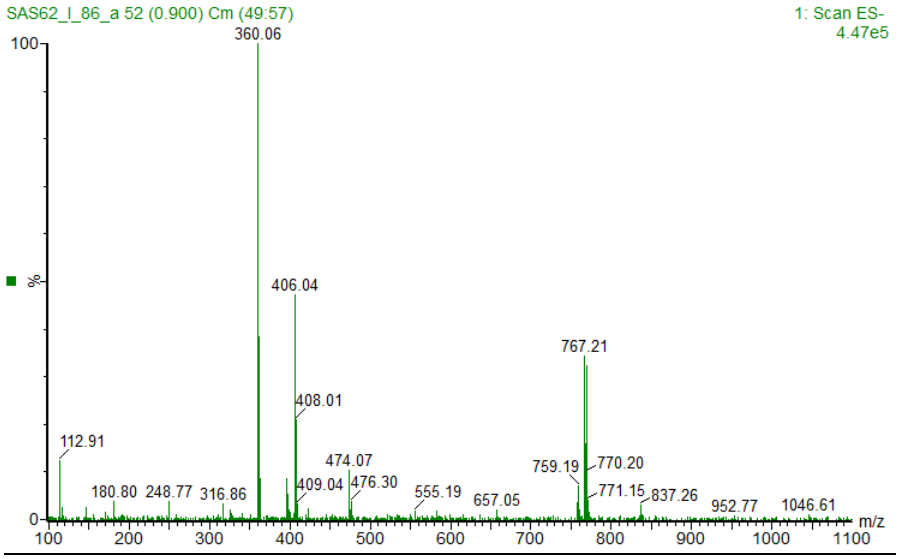
ELSD


SAS62_I_86_a
(3) ELSD Signal
Range: 1646
Time Height Area Area%
0.86 1632138 116257.99 100.00
0.86
LSU
1000.000
0.000
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

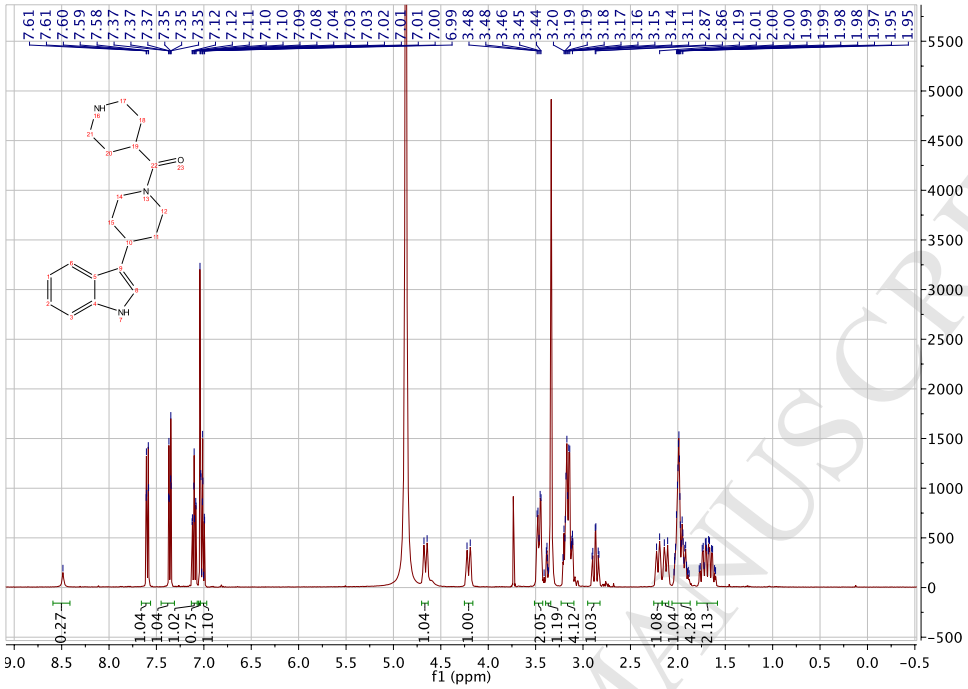

SAS62_I_86_a 51 (0.892) Cm (49:57)
2: Scan ES+
4.48e7
362.14
364.13
365.15
366.14
191.01
245.06
412.17
523.28
626.48
723.31
857.77
978.80
1007.22
1081.31
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

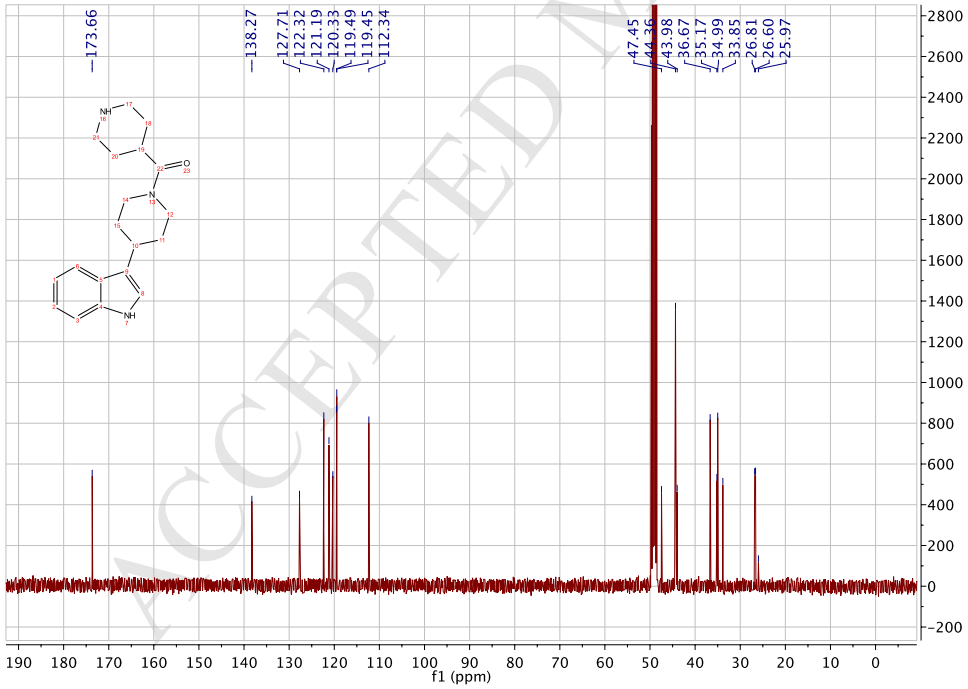
ES-


SAS62_I_86_a 52 (0.900) Cm (49:57)
1: Scan ES-
4.47e5
360.06
406.04
408.01
767.21
112.91
474.07
409.04
476.30
555.19
657.05
759.19
770.20
771.15
837.26
952.77
1046.61
180.80
248.77
316.86
%
m/z
100 200 300 400 500 600 700 800 900 1000 1100

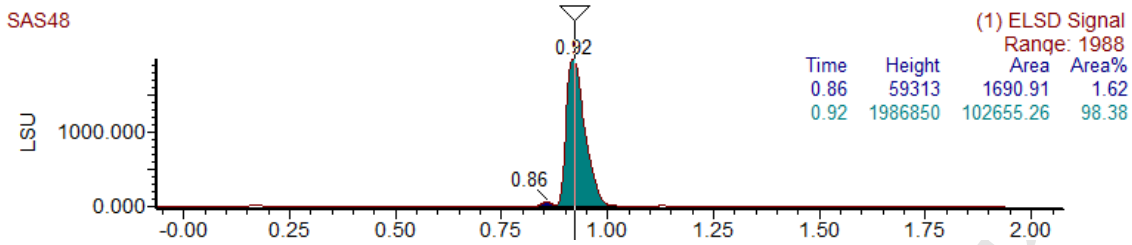
Compound 12

NMR

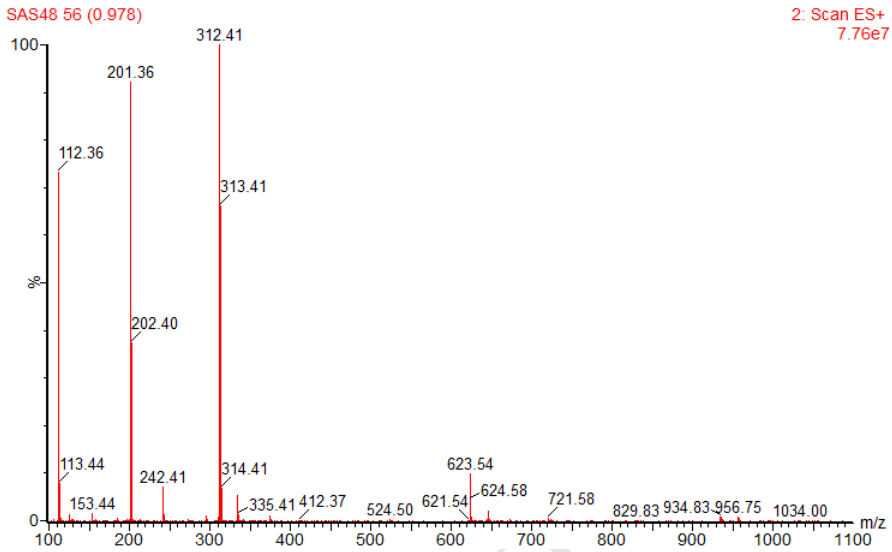




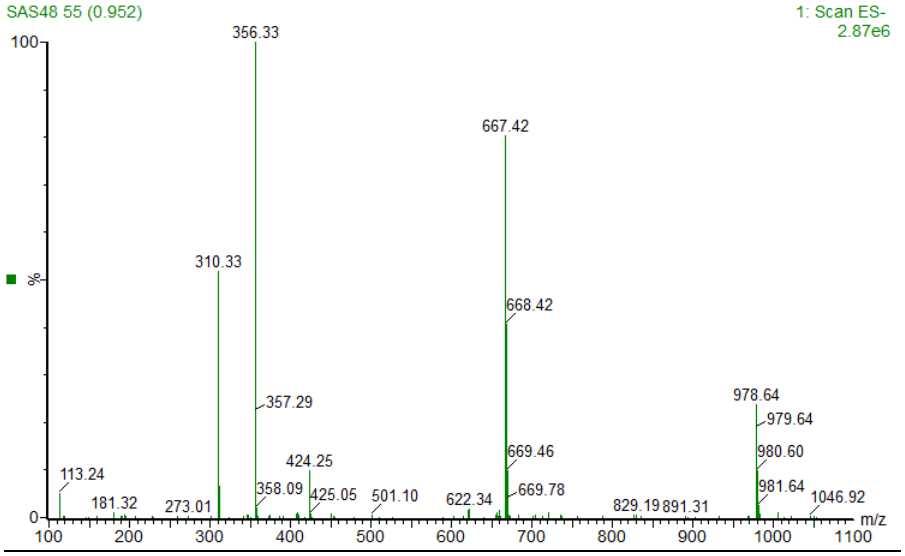
ELSD


SAS48
(1) ELSD Signal
Range: 1988
Time Height Area Area%
0.86 59313 1690.91 1.62
0.92 1986850 102655.26 98.38
LSU
1000.000
0.000
0.92
0.86
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

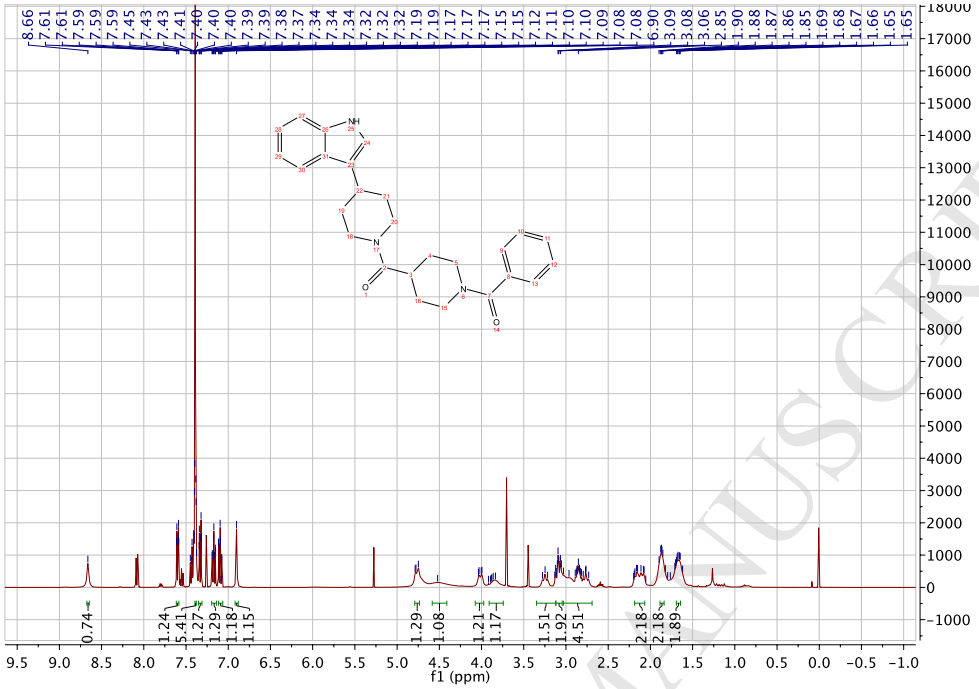

SAS48 56 (0.978)
2: Scan ES+
7.76e7
100
%
0
312.41
201.36
112.36
313.41
202.40
113.44
242.41
314.41
153.44
335.41
412.37
524.50
621.54
623.54
624.58
721.58
829.83
934.83
956.75
1034.00
m/z
100 200 300 400 500 600 700 800 900 1000 1100

ES-

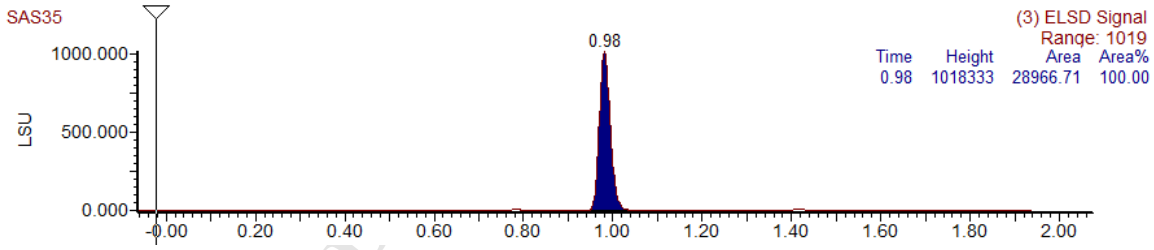

SAS48 55 (0.952)
1: Scan ES-
2.87e6
100
%
0
356.33
667.42
310.33
668.42
357.29
978.64
979.64
424.25
669.46
980.60
113.24
358.09
425.05
501.10
622.34
669.78
981.64
181.32
273.01
829.19
891.31
1046.92
m/z
100 200 300 400 500 600 700 800 900 1000 1100

Compound 13a

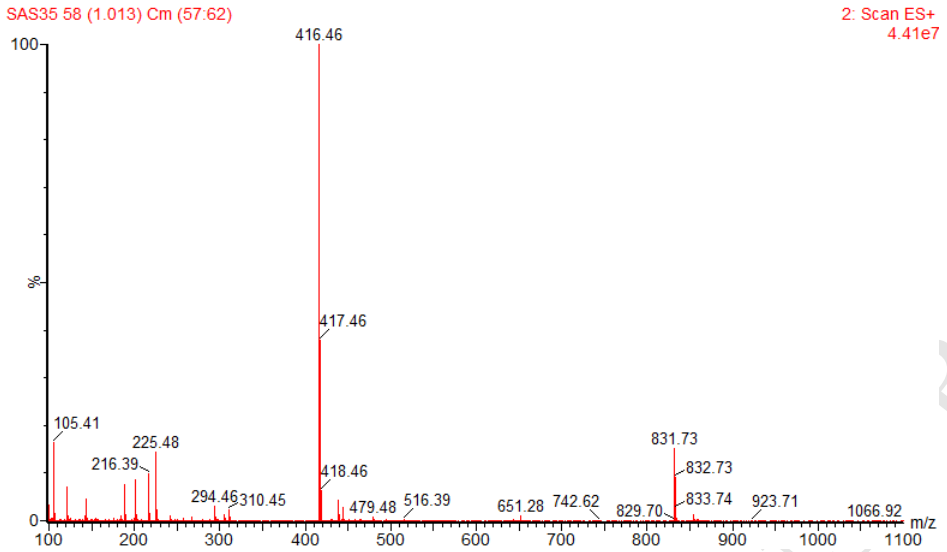
NMR



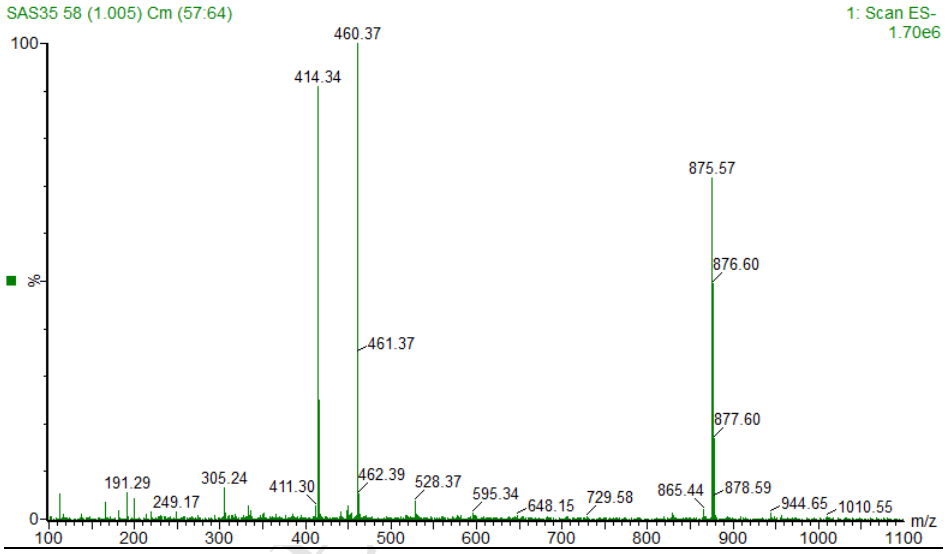
ELSD



ES+

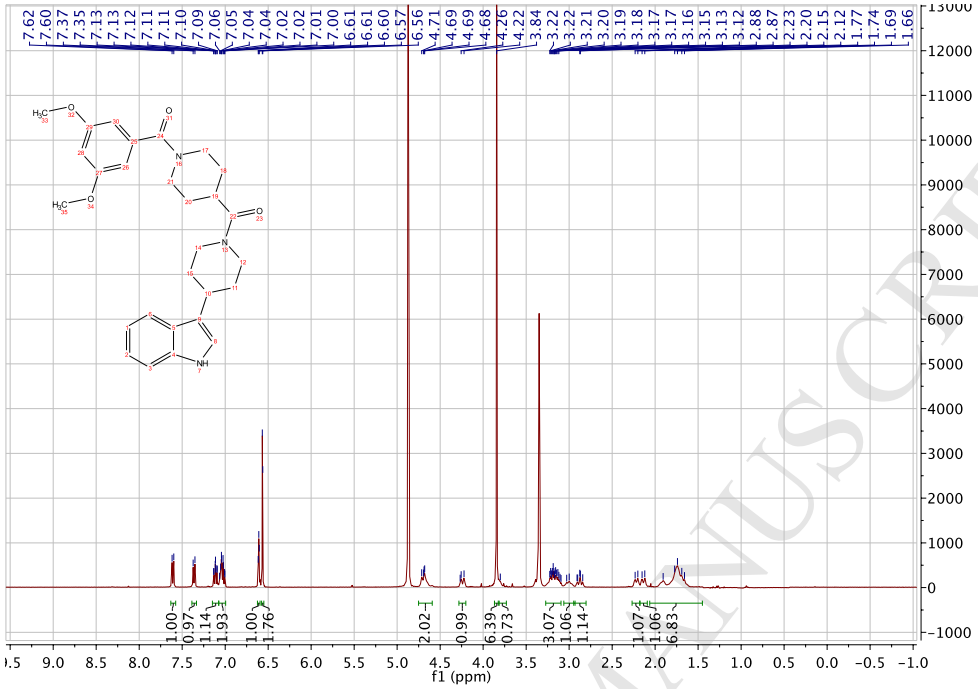

SAS35 58 (1.013) Cm (57:62)
2: Scan ES+
4.41e7
100
%
0
416.46
417.46
105.41
225.48
216.39
418.46
294.46
310.45
479.48
516.39
651.28
742.62
829.70
831.73
832.73
833.74
923.71
1066.92
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-

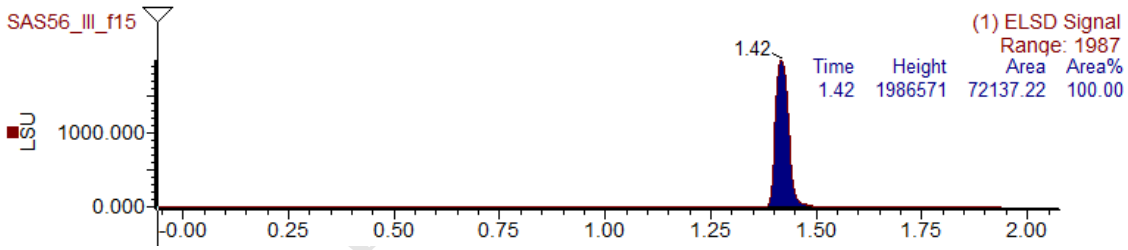

SAS35 58 (1.005) Cm (57:64)
1: Scan ES-
1.70e6
100
%
0
460.37
414.34
875.57
876.60
461.37
877.60
191.29
249.17
305.24
411.30
462.39
528.37
595.34
648.15
729.58
865.44
878.59
944.65
1010.55
m/z
100
200
300
400
500
600
700
800
900
1000
1100

Compound 13b

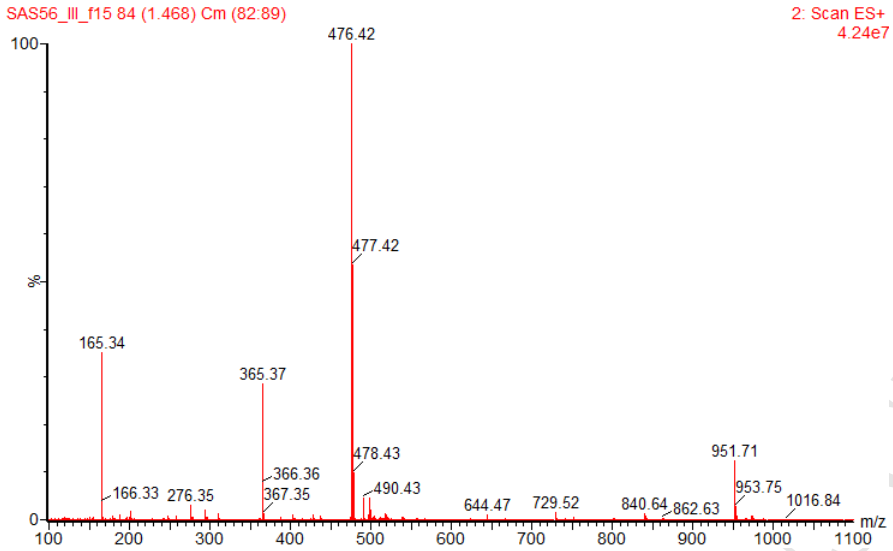
NMR



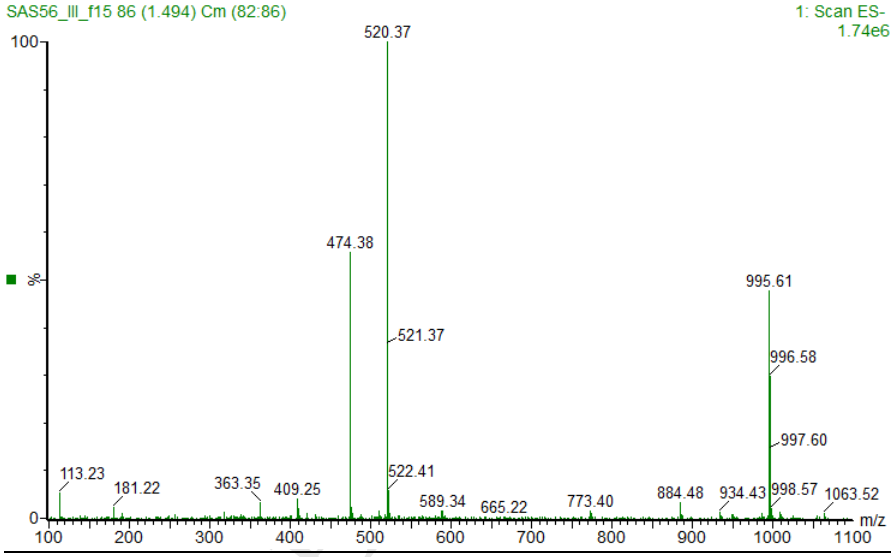
ELSD



ES+

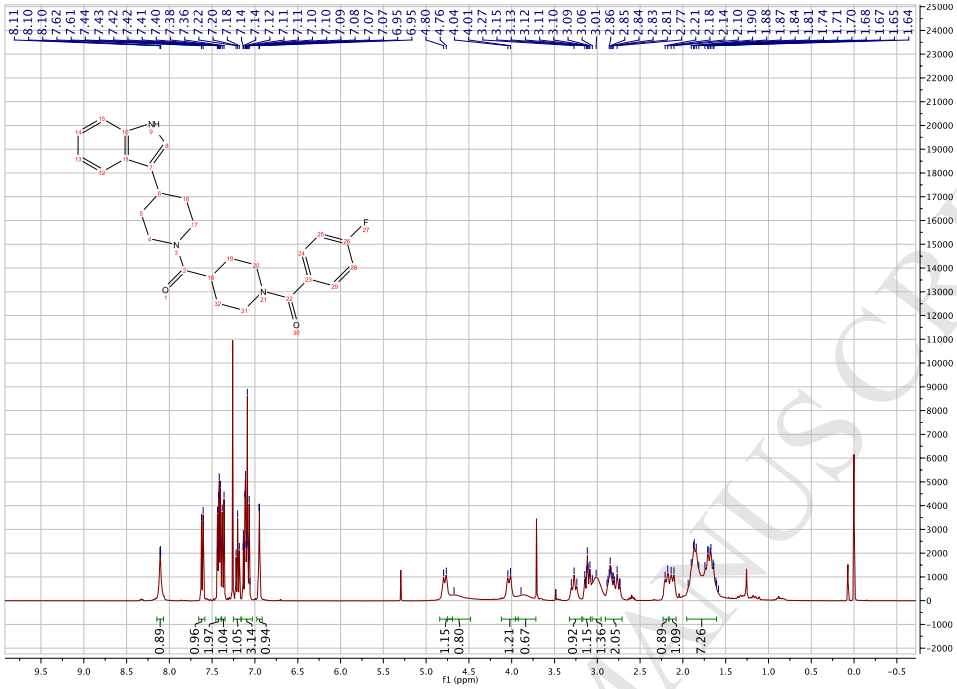

SAS56_III_f15 84 (1.468) Cm (82:89)
2: Scan ES+
4.24e7
100
%
0
476.42
477.42
165.34
365.37
478.43
951.71
366.36
953.75
166.33
276.35
367.35
490.43
1016.84
644.47
729.52
840.64
862.63
m/z
100
200
300
400
500
600
700
800
900
1000
1100

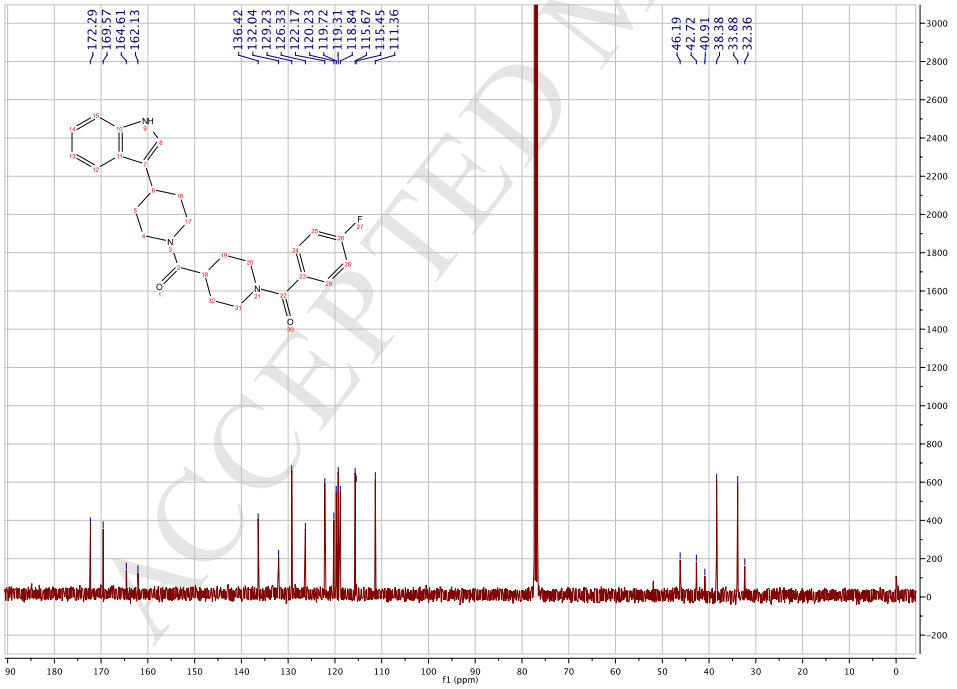
ES-


SAS56_III_f15 86 (1.494) Cm (82:86)
1: Scan ES-
1.74e6
100
%
0
520.37
474.38
995.61
521.37
996.58
997.60
113.23
522.41
181.22
363.35
409.25
589.34
665.22
773.40
884.48
934.43
998.57
1063.52
m/z
100
200
300
400
500
600
700
800
900
1000
1100

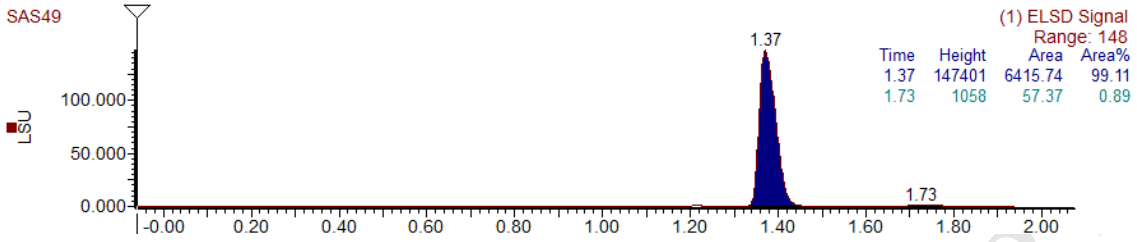
Compound 13c

NMR

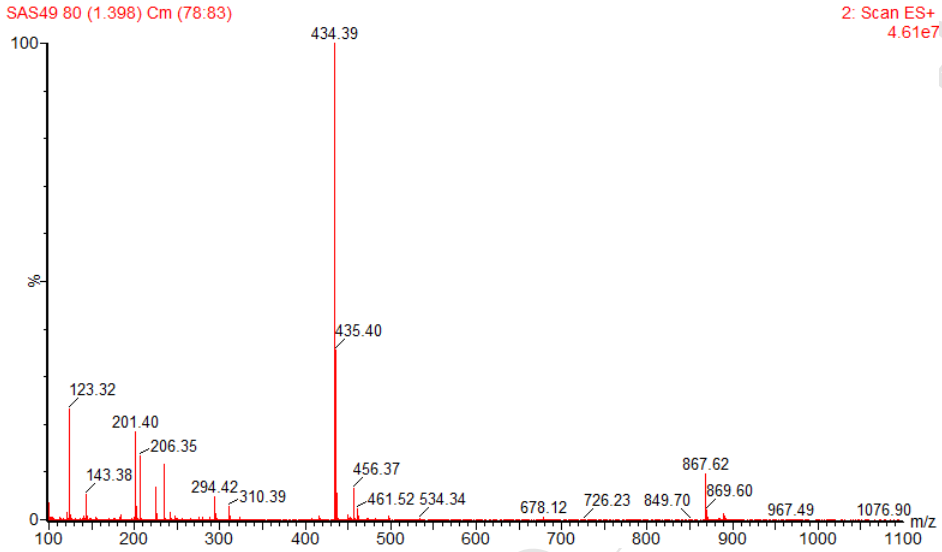




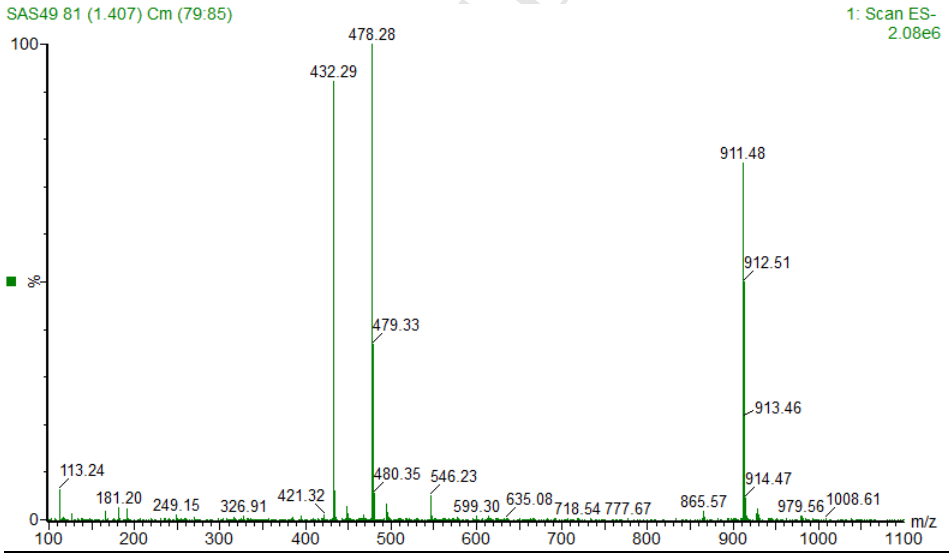
ELSD


SAS49
(1) ELSD Signal
Range: 148
Time Height Area Area%
1.37 147401 6415.74 99.11
1.73 1058 57.37 0.89
LSU
100.000
50.000
0.000
1.37
1.73
-0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00

ES+

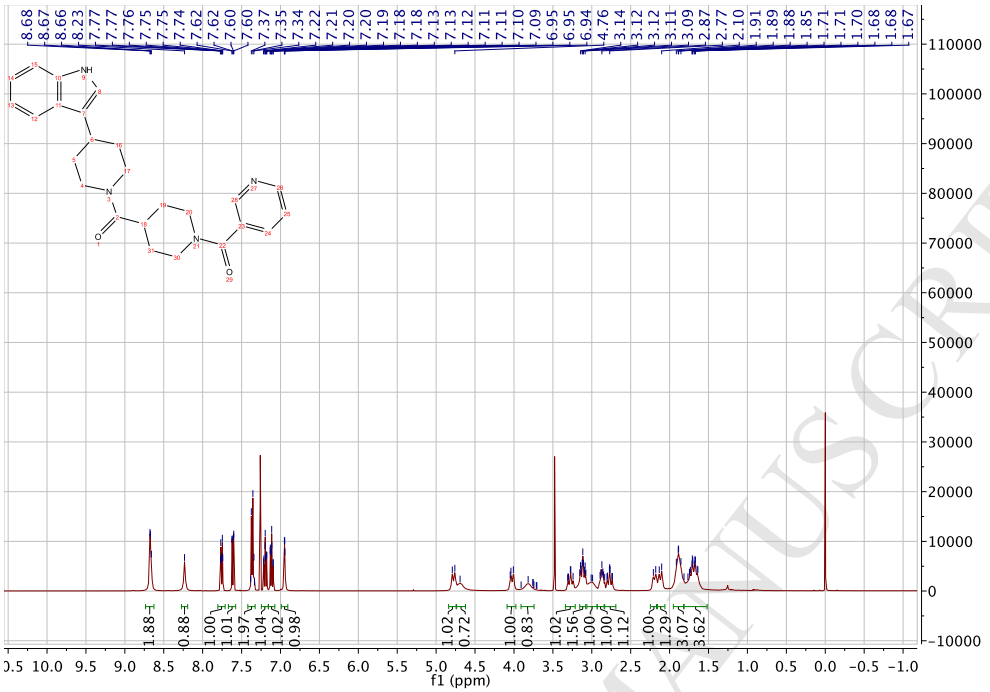

SAS49 80 (1.398) Cm (78:83)
2: Scan ES+
4.61e7
100
%
0
434.39
435.40
123.32
201.40
206.35
143.38
294.42
310.39
456.37
461.52 534.34
678.12
726.23
849.70
867.62
869.60
967.49
1076.90
m/z
100 200 300 400 500 600 700 800 900 1000 1100

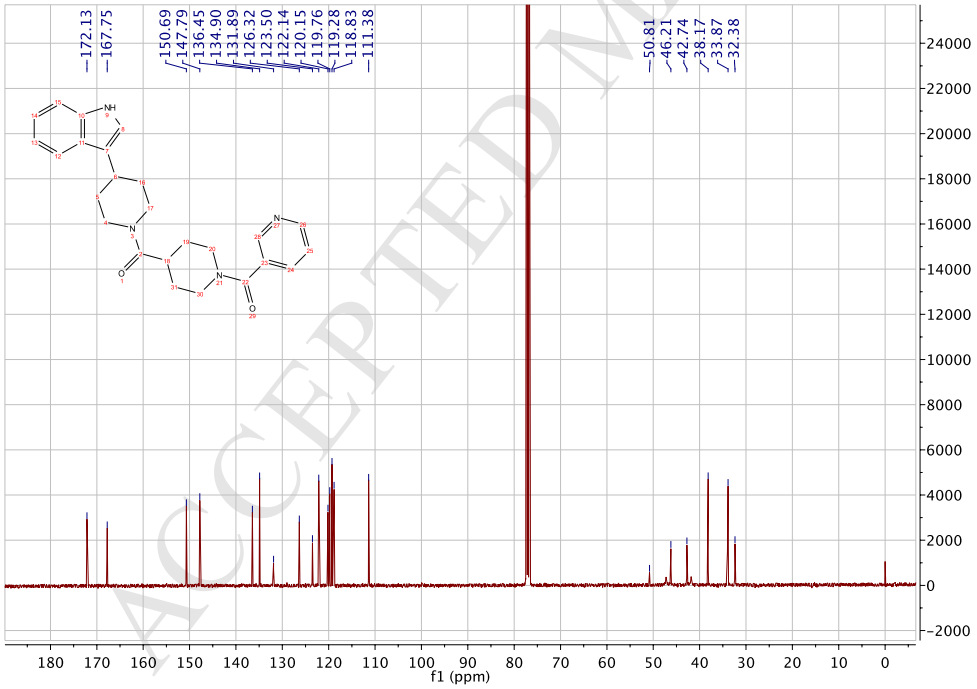
ES-


SAS49 81 (1.407) Cm (79:85)
1: Scan ES-
2.08e6
100
%
0
478.28
432.29
911.48
912.51
479.33
913.46
914.47
113.24
181.20
249.15
326.91
421.32
480.35
546.23
599.30
635.08
718.54 777.67
865.57
979.56
1008.61
m/z
100 200 300 400 500 600 700 800 900 1000 1100

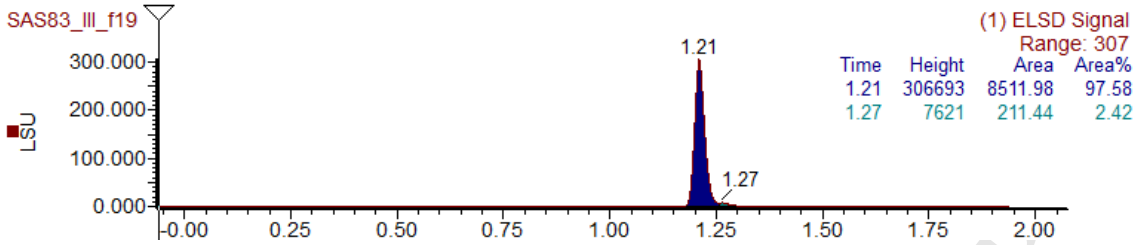
Compound 13d

NMR

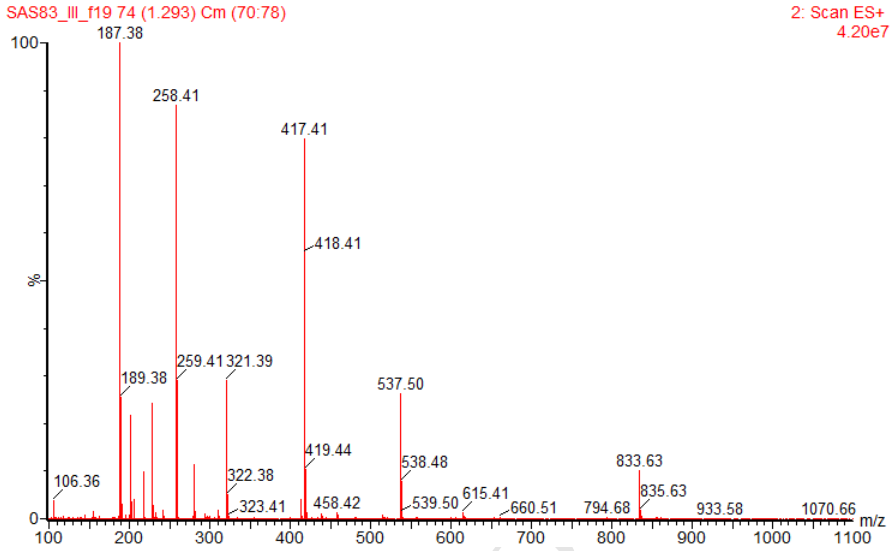




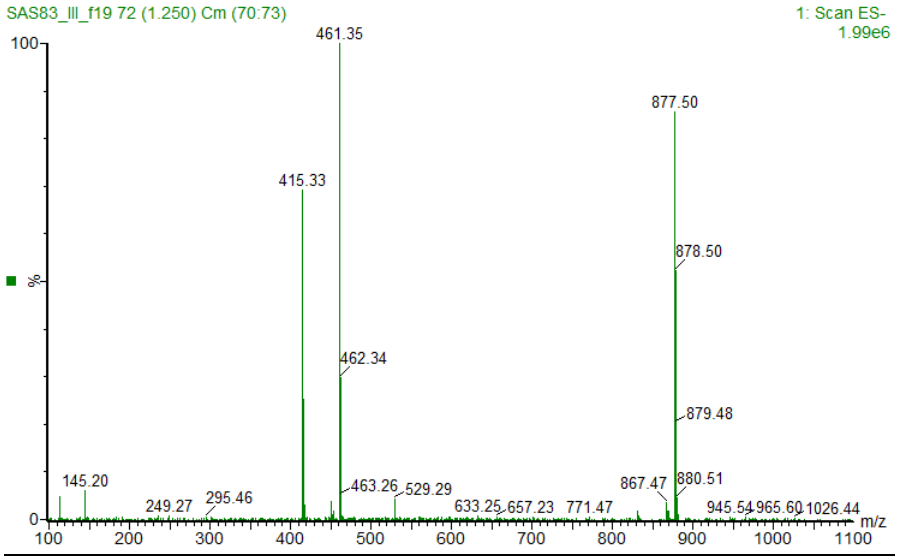
ELSD


SAS83_III_f19
(1) ELSD Signal
Range: 307
Time Height Area Area%
1.21 306693 8511.98 97.58
1.27 7621 211.44 2.42
LSU
300.000
200.000
100.000
0.000
1.21
1.27
-0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

ES+

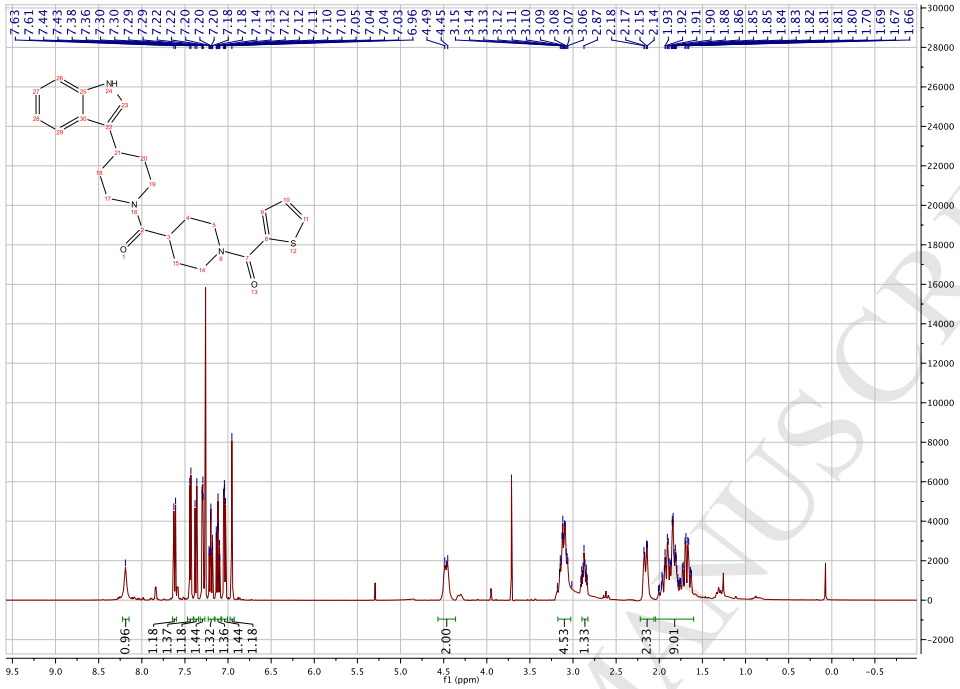

SAS83_III_f19 74 (1.293) Cm (70:78)
2: Scan ES+
4.20e7
100
%
0
187.38
258.41
417.41
418.41
189.38
259.41
321.39
537.50
419.44
538.48
833.63
106.36
322.38
323.41
458.42
539.50
615.41
660.51
794.68
835.63
933.58
1070.66
100 200 300 400 500 600 700 800 900 1000 1100
m/z

ES-

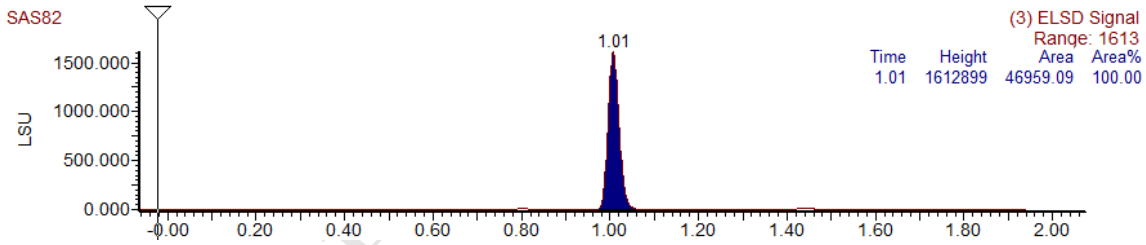

SAS83_III_f19 72 (1.250) Cm (70:73)
1: Scan ES-
1.99e6
100
%
0
461.35
877.50
415.33
878.50
462.34
879.48
145.20
249.27
295.46
463.26
529.29
633.25
657.23
771.47
867.47
880.51
945.54
965.60
1026.44
100 200 300 400 500 600 700 800 900 1000 1100
m/z

Compound 13e

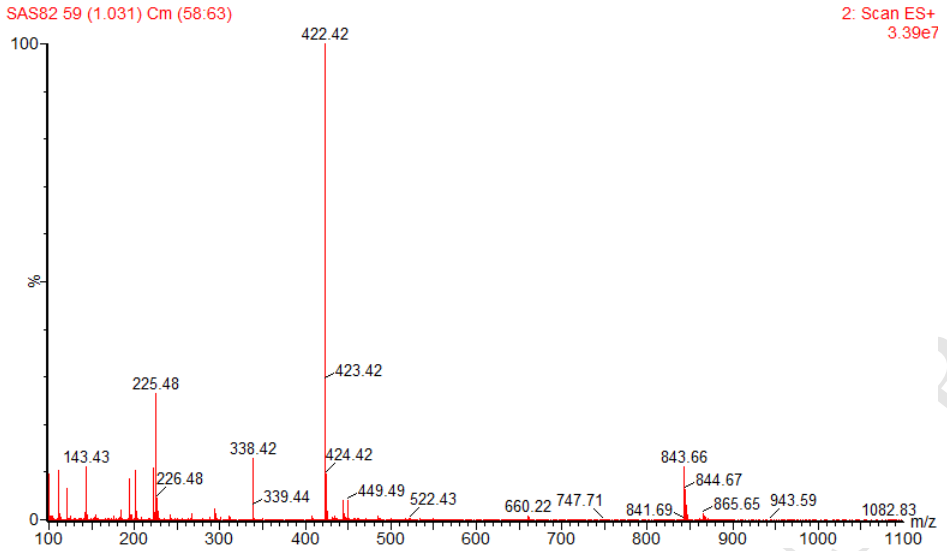
NMR



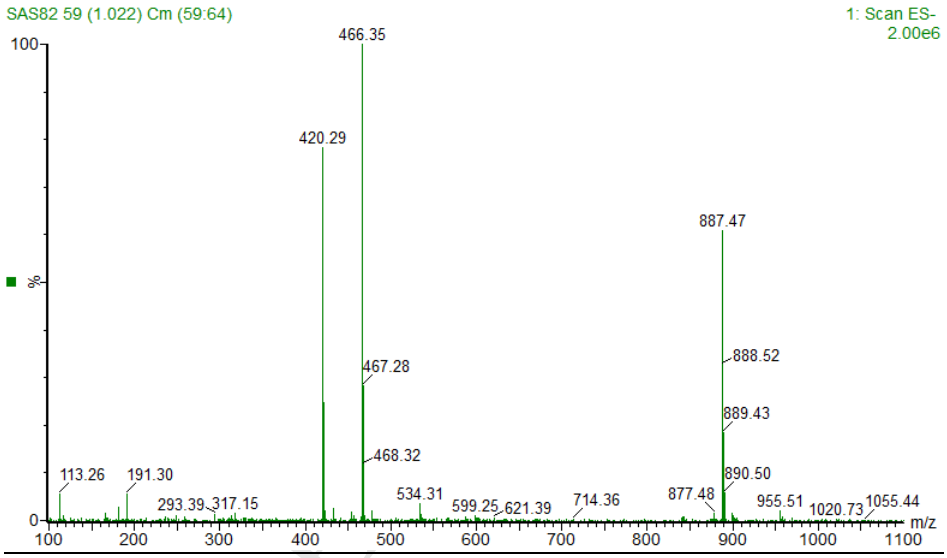
ELSD



ES+

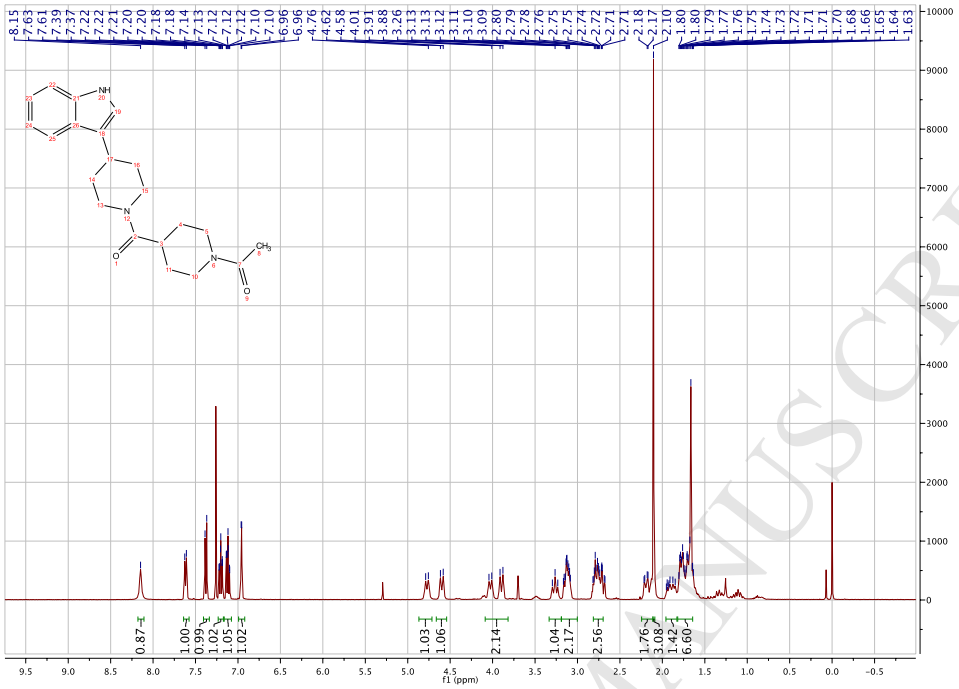

SAS82 59 (1.031) Cm (58:63)
2: Scan ES+
3.39e7
100
%
0
422.42
423.42
225.48
143.43
338.42
424.42
226.48
339.44
449.49
522.43
660.22
747.71
841.69
843.66
844.67
865.65
943.59
1082.83
100
200
300
400
500
600
700
800
900
1000
1100
m/z

ES-

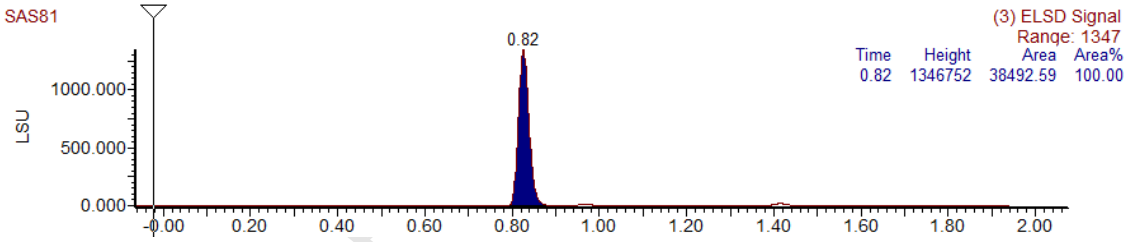

SAS82 59 (1.022) Cm (59:64)
1: Scan ES-
2.00e6
100
%
0
466.35
420.29
887.47
888.52
467.28
889.43
468.32
890.50
113.26
191.30
293.39
317.15
534.31
599.25
621.39
714.36
877.48
955.51
1020.73
1055.44
100
200
300
400
500
600
700
800
900
1000
1100
m/z

Compound 13f

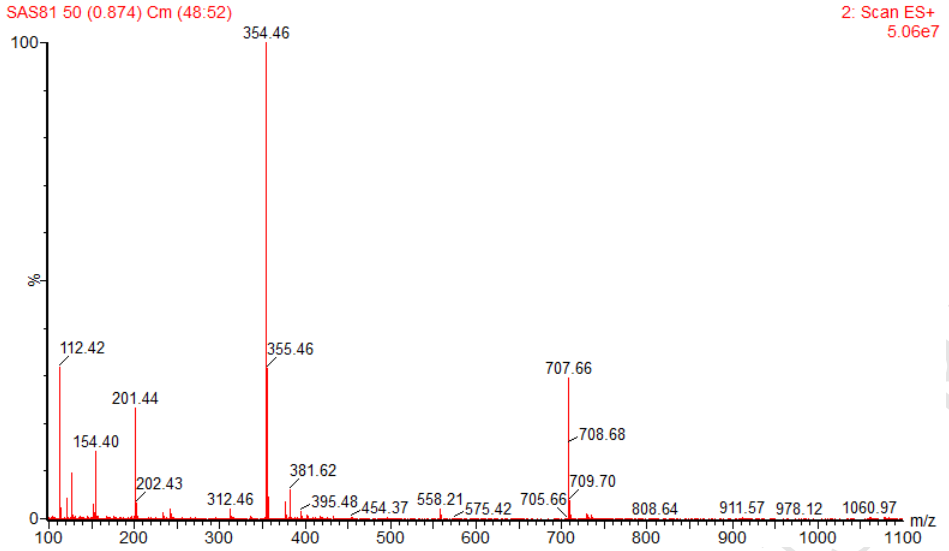
NMR



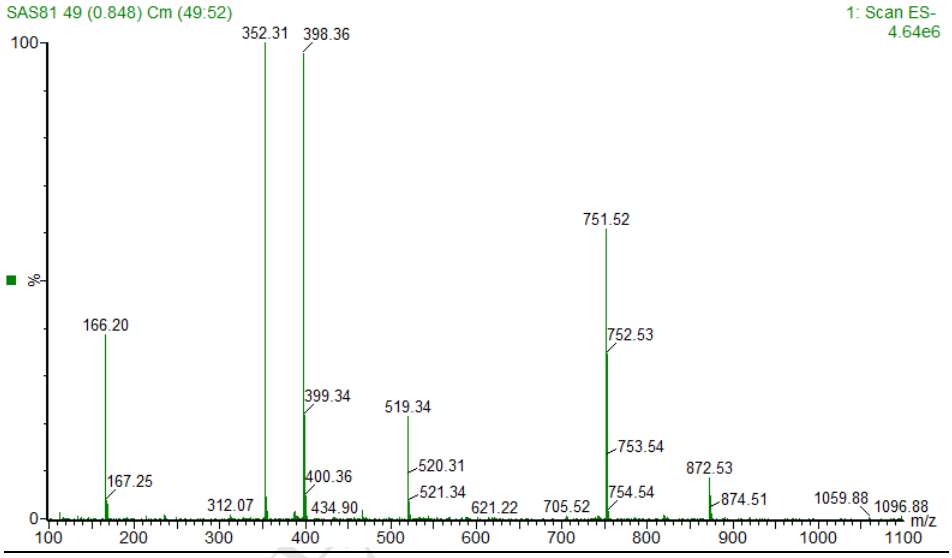
ELSD



ES+


SAS81 50 (0.874) Cm (48:52)
2: Scan ES+
5.06e7
100
%
0
354.46
112.42
355.46
707.66
201.44
708.68
154.40
381.62
709.70
202.43
312.46
395.48
454.37
558.21
575.42
705.66
808.64
911.57
978.12
1060.97
m/z
100
200
300
400
500
600
700
800
900
1000
1100

ES-


SAS81 49 (0.848) Cm (49:52)
1: Scan ES-
4.64e6
100
%
0
352.31
398.36
751.52
166.20
752.53
399.34
519.34
753.54
520.31
872.53
167.25
400.36
521.34
754.54
312.07
434.90
621.22
705.52
874.51
1059.88
1096.88
m/z
100
200
300
400
500
600
700
800
900
1000
1100