Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis and evaluation of novel Ellipticines as potential anti-cancer agents

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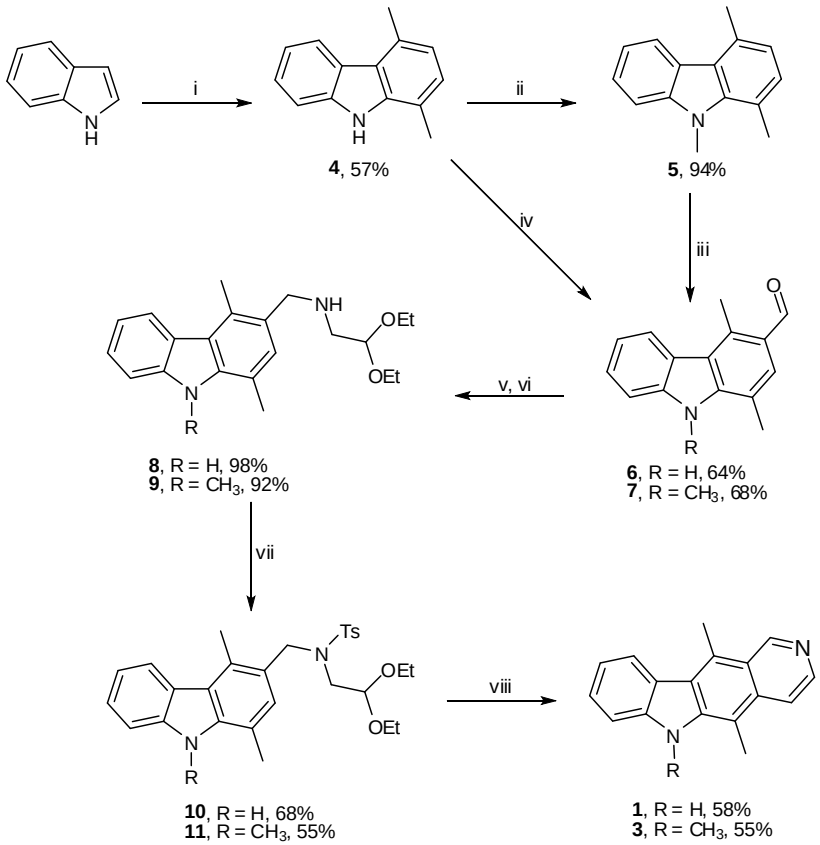
Supplementary Information

1. **Synthesis of ellipticine (1) and 6-methylellipticine 3**
2. **NMR data**
3. **LCMS data**

1. Synthesis of ellipticine (1) and 6-methylellipticine 3

The formylation reactions of 1,4-dimethyl-9*H*-carbazole (**4**) and 1,4,9-trimethylcarbazole (**5**) were key steps in the synthesis of sufficient quantities of ellipticine (**1**) and 6-methylellipticine **3** to complete our proposed biological evaluations. The Vilsmeier-Haack reaction described by Murakami ($POCl_3$, DMF, 100 °C) was found to be the most efficient for the formylation of 1,4,9-trimethylcarbazole (**5,** towards 6-methylellipticine **3**).[12,13] Application of our modified Vilsmeier-Haack reaction facilitated the production of 3-formyl-1,4-dimethylcarbazole (**6**, a key precursor towards the synthesis of ellipticine **1**, Scheme 1) in increased yields.[14] Regardless of the formylation method employed, both 3-formylcarbazoles **6** and **7** were found to be contaminated with an undesired 6-formylcarbazole isomer by-product. As a result of identical R_f value, removal of the undesired 6-formyl isomers from the 3-formyl compounds by column chromatography was not an option. Multiple recrystallisations were carried out to enable purification of compounds **6** and **7** with a subsequent yield reduction. Highest overall yields were obtained when the isomeric mixtures were carried through the synthetic route whereby recrystallization of tosylamides **10** and **11** afforded the 3-isomer as the sole product. From 3-formylcarbazoles **6** and **7**, the route to ellipticine proceeds *via* a modified Pomeranz-Fritsch approach in which amines **8** and **9**, formed *via* reductive amination, were subsequently tosylated. Ellipticine (**1**) and 6-methylellipticine **3** were obtained in moderate yields by heating the respective tosyl amines **10** and **11** in acidic conditions (Scheme 1).



Scheme 1. Reagents and Conditions. (*i*) 2,5-hexanedione, *p*-TsOH (cat.), EtOH, reflux for 2h; (*ii*) NaH, MeI, DMF, r.t. overnight; (*iii*) $POCl_3$, DMF, 100 °C for 6 h; (*iv*) $POCl_3$, DMF, C_6H_5Cl, reflux for 6.5 h; (*v*) amino-acetaldehyde diethylacetal, 110 °C for 2 h ; (*vi*) PtO_2, H_2, EtOH, r.t, 50 psi for 3 d (**8**) or $NaBH_4$, MeOH, r.t for 2 h (**9**); (*vii*) *p*-TsCl, pyridine, r.t for 3 d (**10**) or *p*-TsCl, K_2CO_3, THF.H_2O (1:2), r.t. for 1.5 h (**11**); (*viii*) HCl, dioxane, reflux for 2.5 h.

2. NMR Data

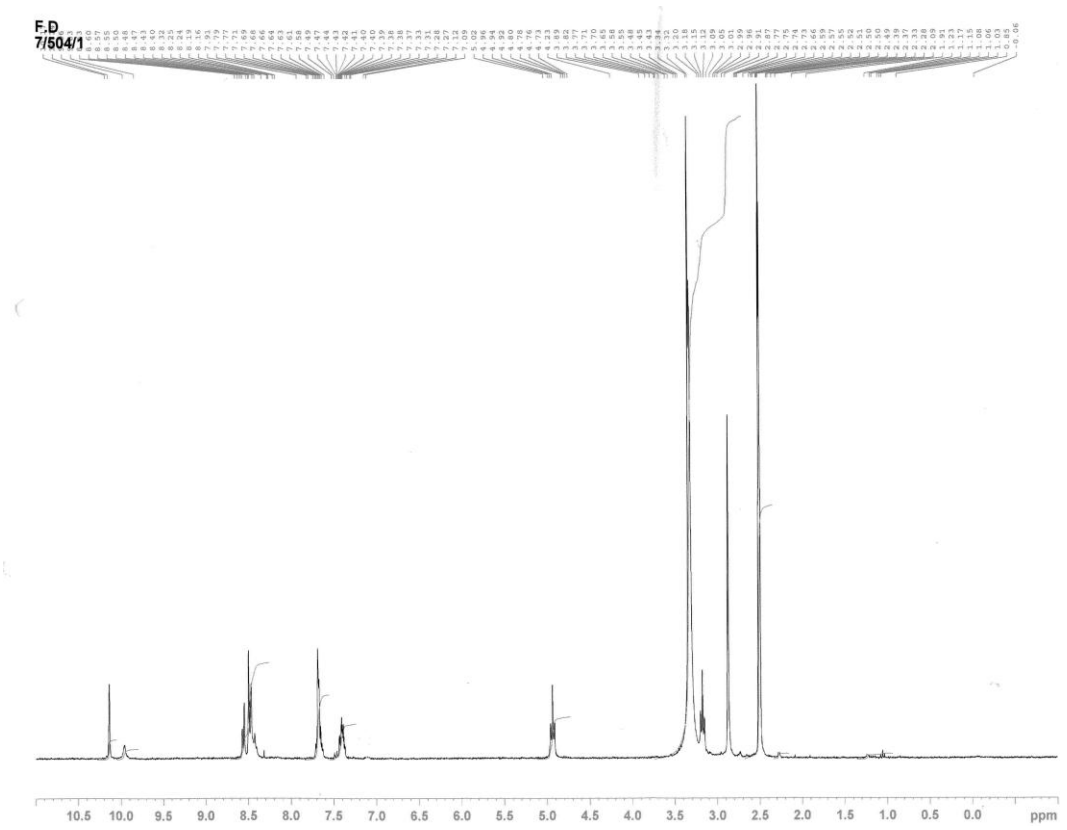


Figure 1 ^{1}H NMR of N^{2}-(2′-Carboxyethyl)-ellipticinium bromide (12)

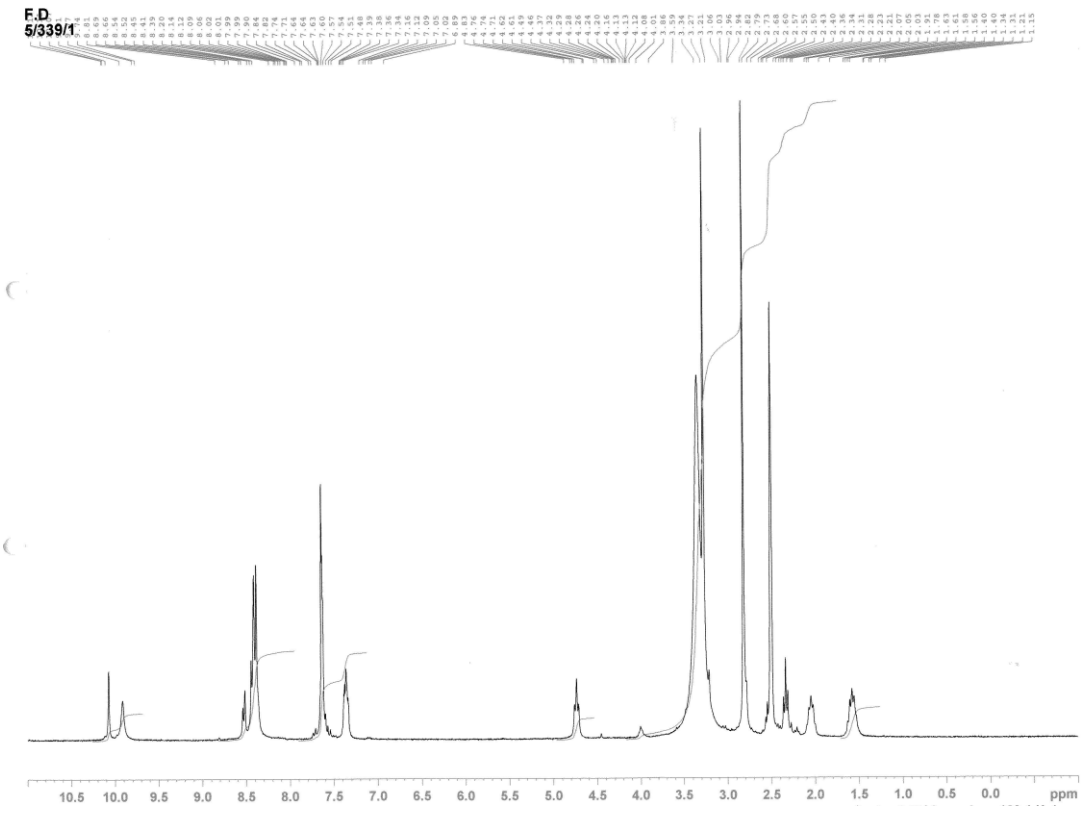


Figure 2 ^{1}H NMR of N^{2}-(4′-Carboxybutyl)-ellipticinium bromide (13)

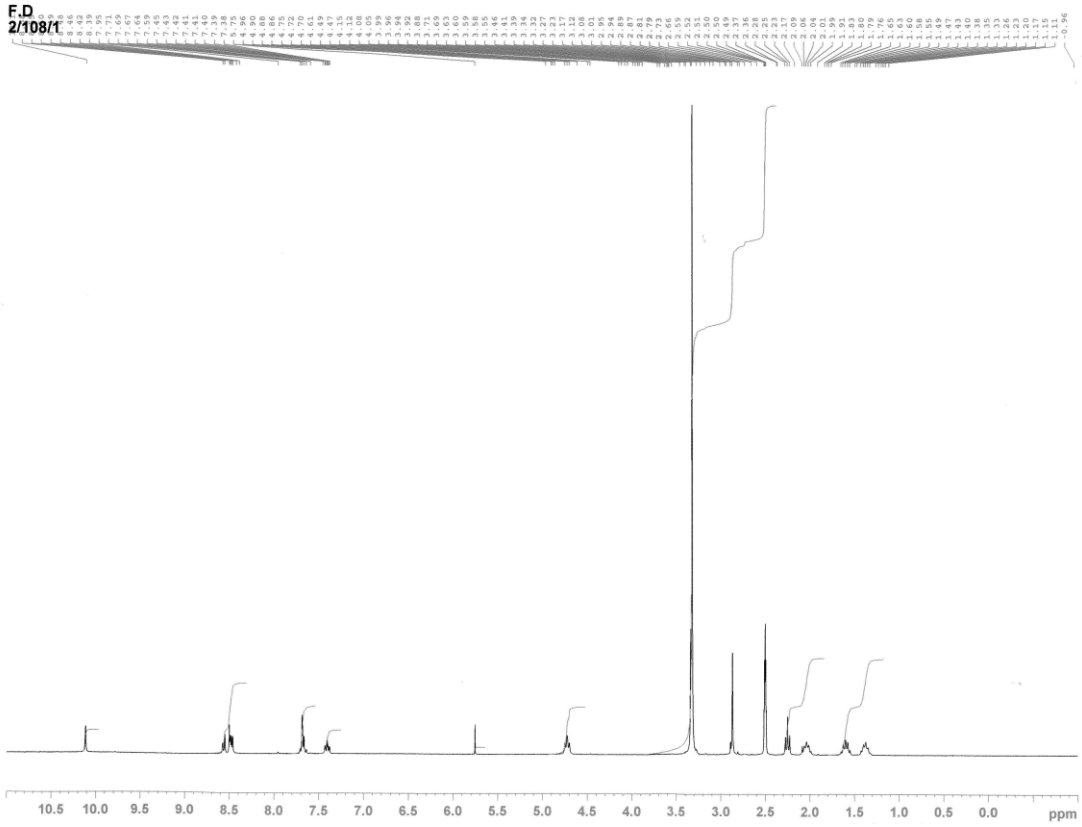


Figure 3 ^{1}**H NMR of** N^{2}**-(5′-Carboxypentyl)-ellipticinium bromide (14)**

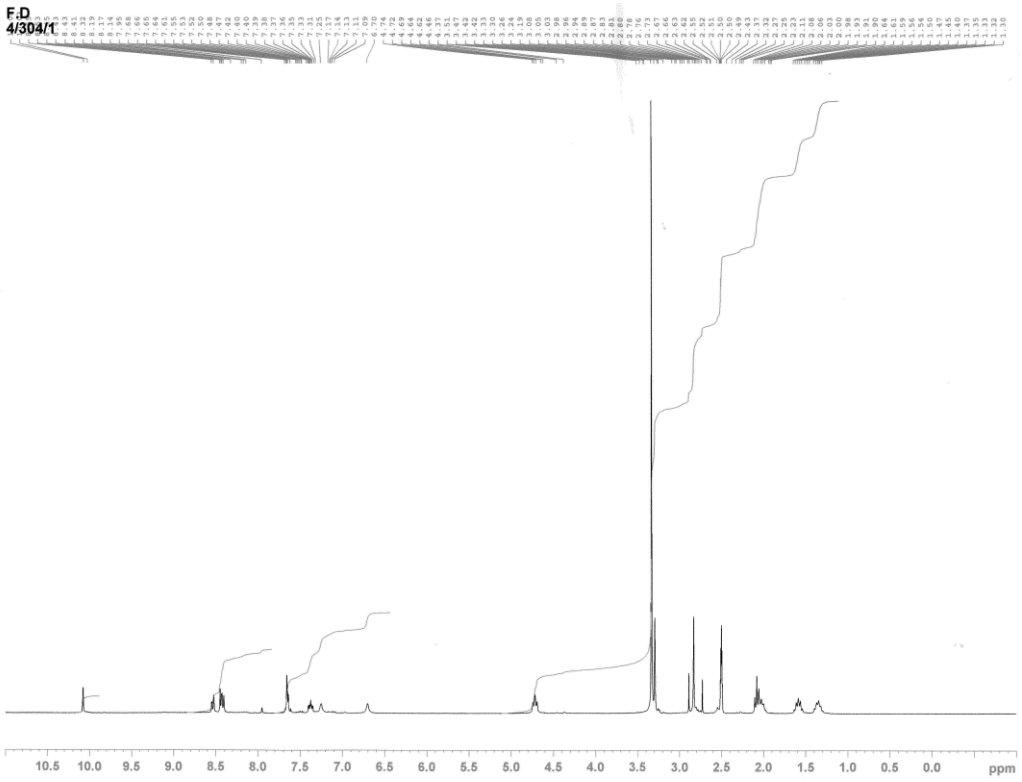


Figure 4 ^{1}**H NMR of** N^{2}**-(5′-Carboxyaminopentyl)-ellipticinium bromide (15)**

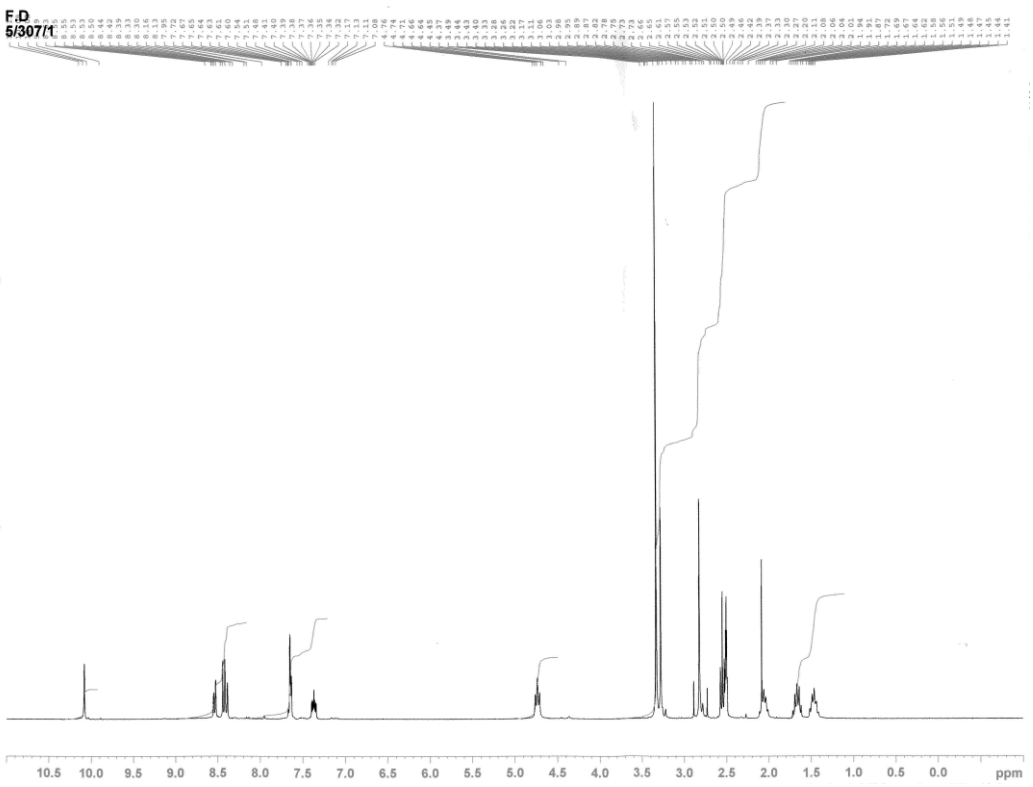


Figure 5 **^{1}H NMR of N^{2}-(5′-Cyanopentyl)-ellipticinium bromide (16)**

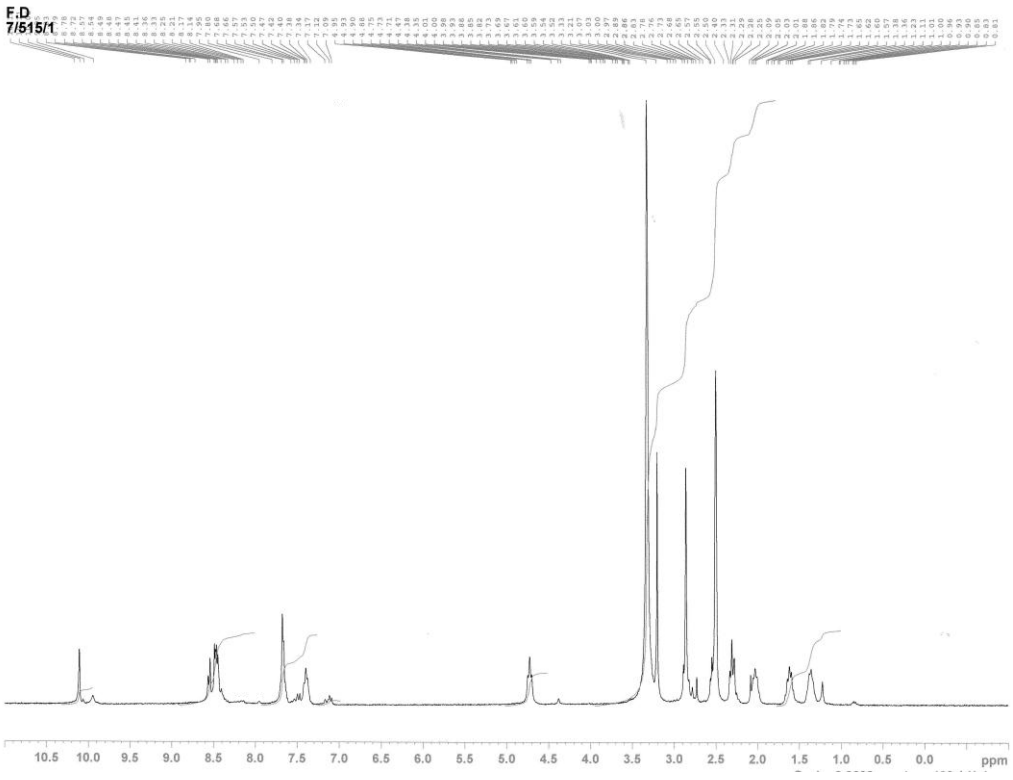


Figure 6 **^{1}H NMR of N^{2}-(5′-Hexanoylmethylsuphonamide)-ellipticinium bromide (17)**

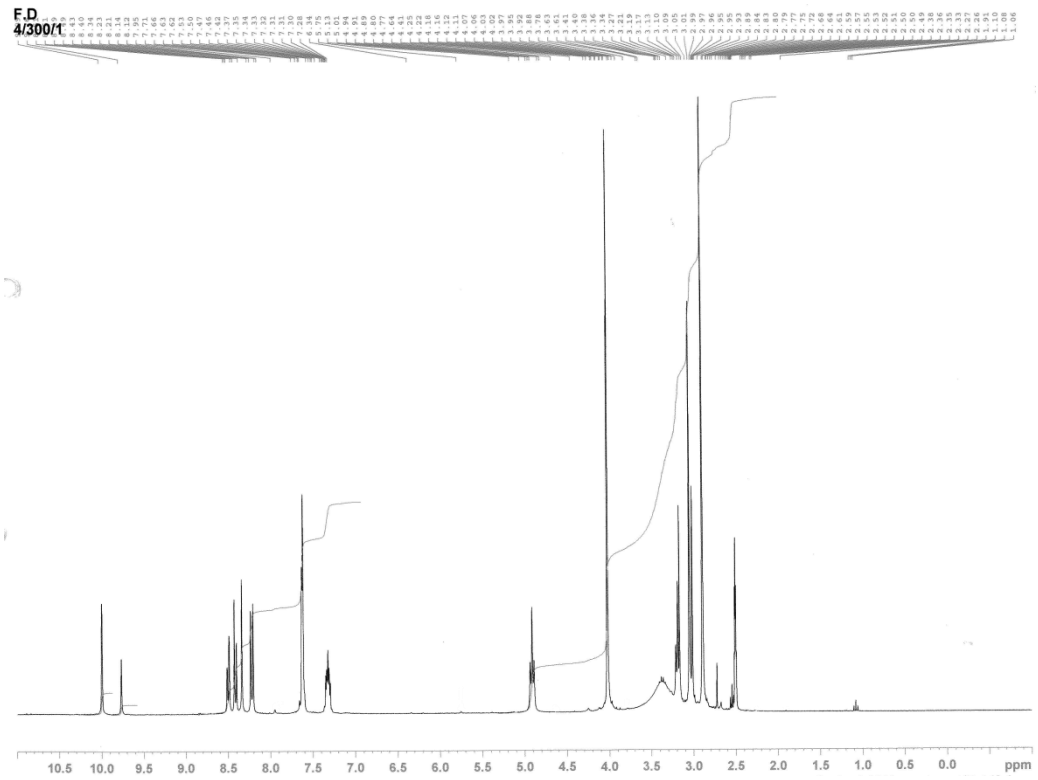


Figure 7 **^{1}H NMR of N^{2}-(2′-Carboxyethyl)-6-methylellipticinium bromide (18)**

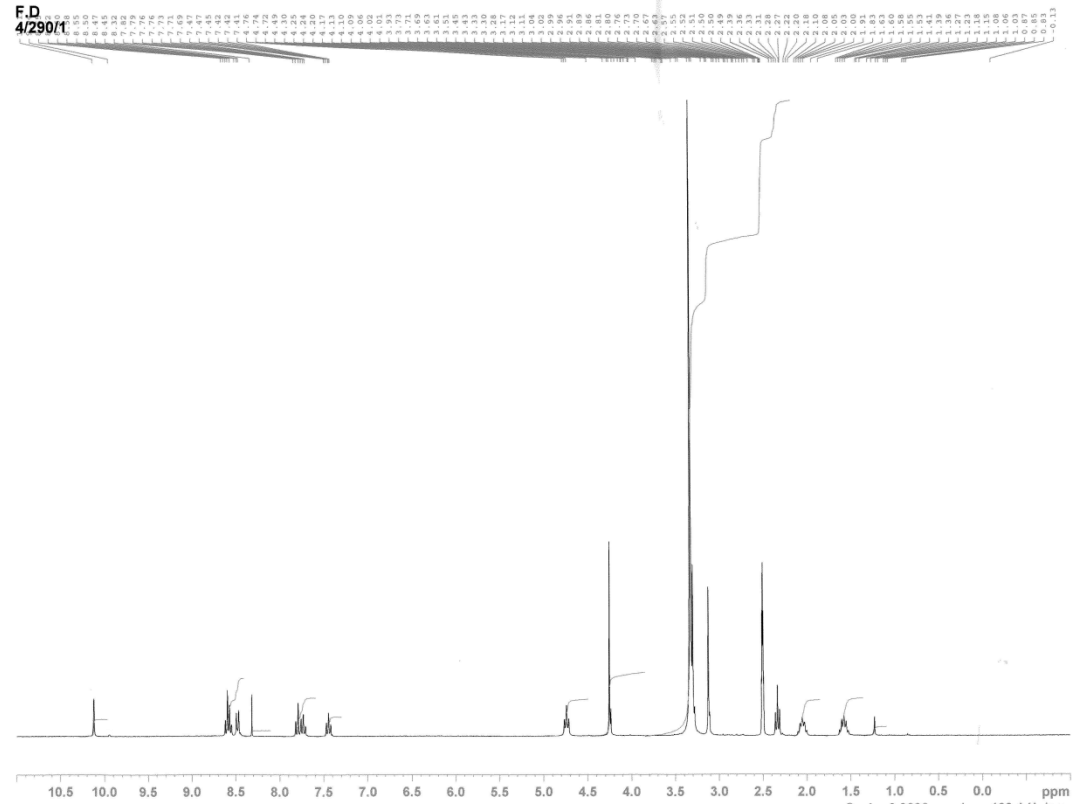


Figure 8 **^{1}H NMR of N^{2}-(4′-Carboxybutyl)-6-methylellipticinium bromide (19)**

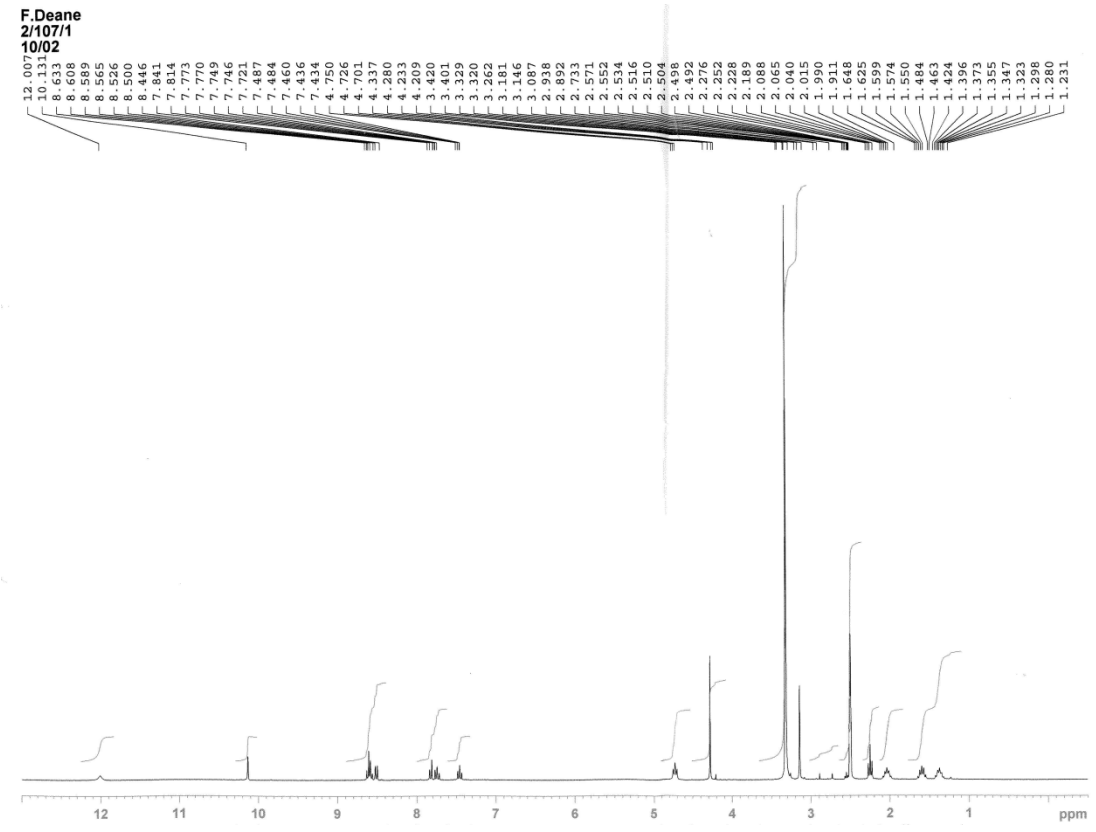


Figure 9 ^{1}**H NMR of** N^{2}**-(5′-Carboxypentyl)-6-methylellipticinium bromide (20)**

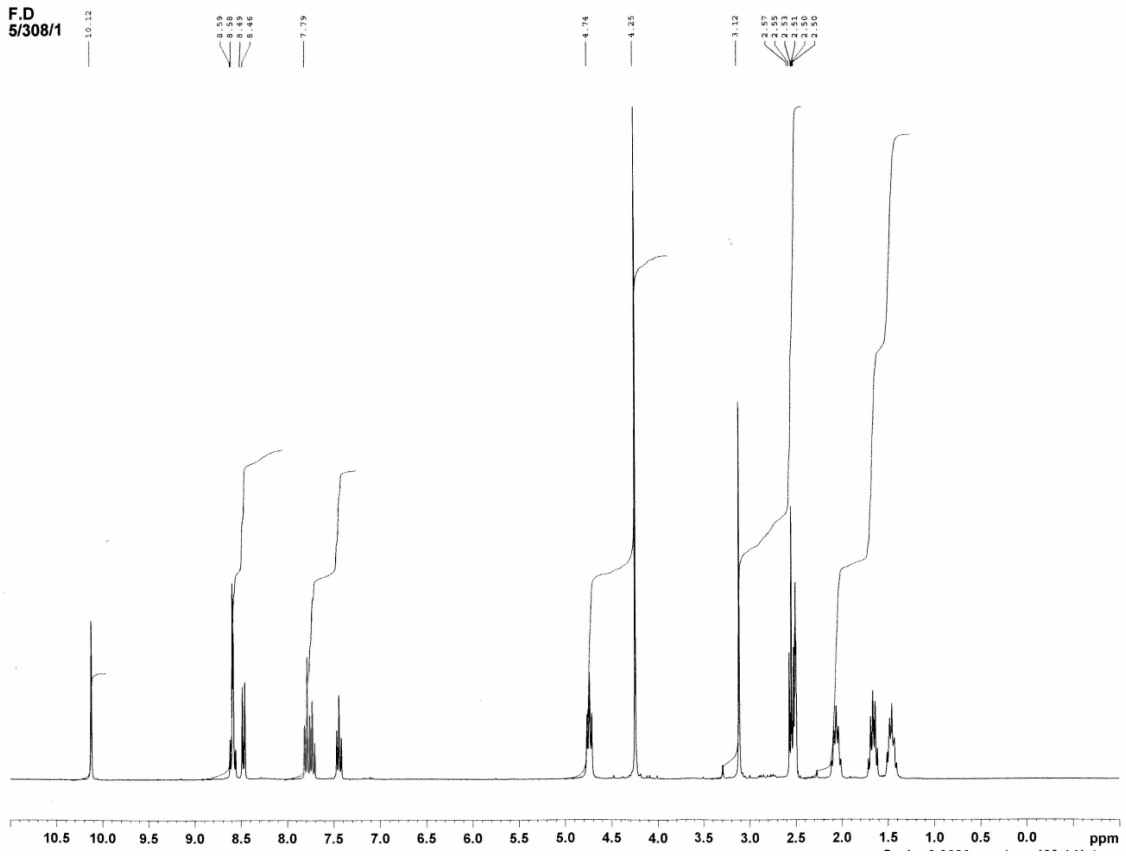


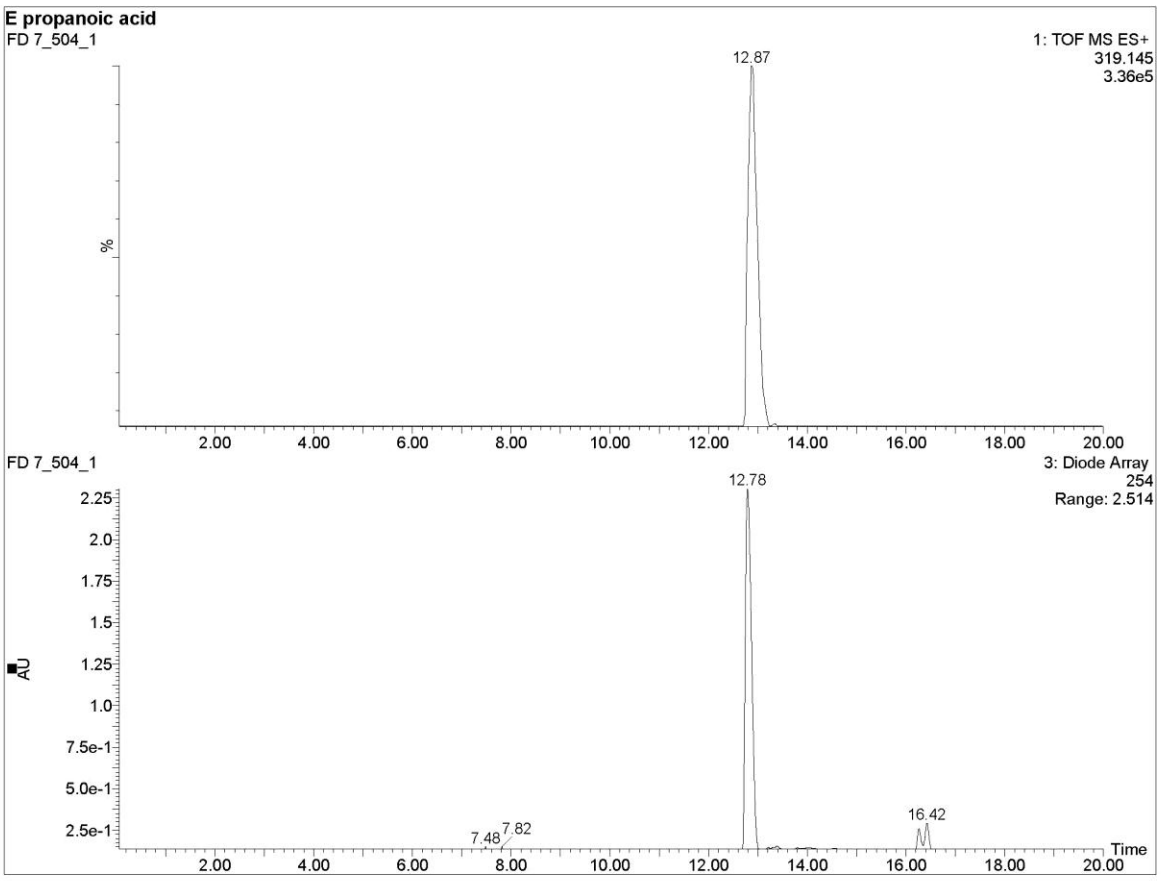
Figure 10 ^{1}**H NMR of** N^{2}**-(5′-Cyanopentyl)-6-methylellipticinium bromide (22)**
(peak at 3.30ppm under water suppression)

3. LCMS data

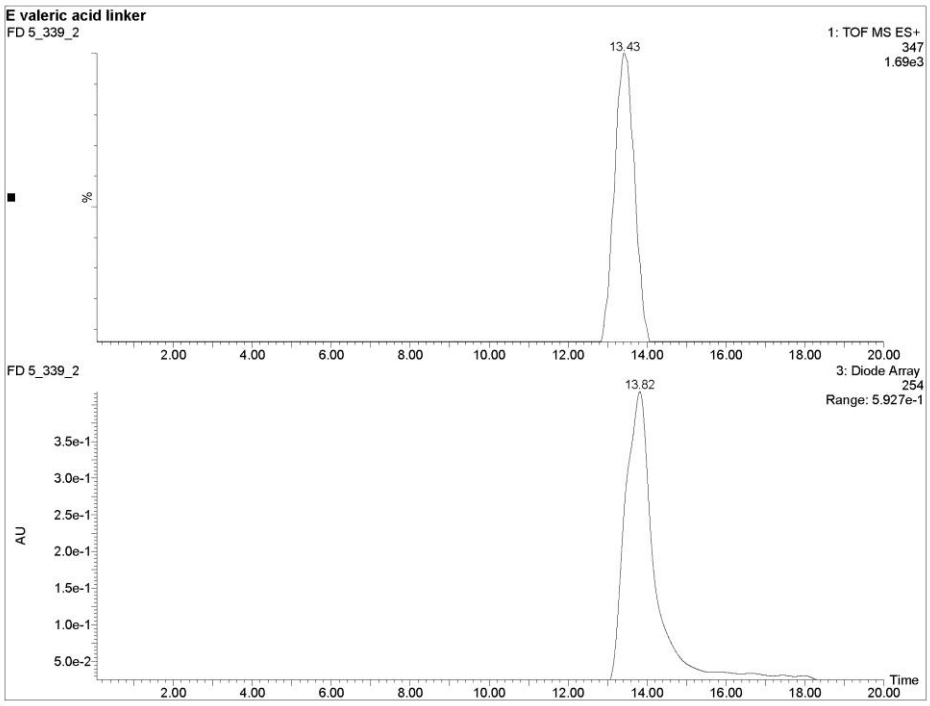
LCMS data

Conditions: LCMS conditions: Samples were analysed for purity via LCMS using a Waters Alliance 2695 HPLC, Waters 996 photodiode array detector and a Waters LCT Premier TOF mass spectrometer (instrument number KD 160). The samples were injected onto a Waters Atlantis T3 column (150 x 4.6mm, 5um particle size) using acetonitrile (+0.1% HCOOH) and water (+0.1% HCOOH) as mobile phase over a 20 minute run time at a flow rate of 0.5 mL/min. The HPLC conditions are as follows: (gradient method) 0mins 10% ACN, 2mins 10% ACN, 18mins 90% ACN, 19mins 10% ACN, 20mins 10% ACN. Results are presented from the absorbance at 254nm and the molecular ion responsible for each sample.

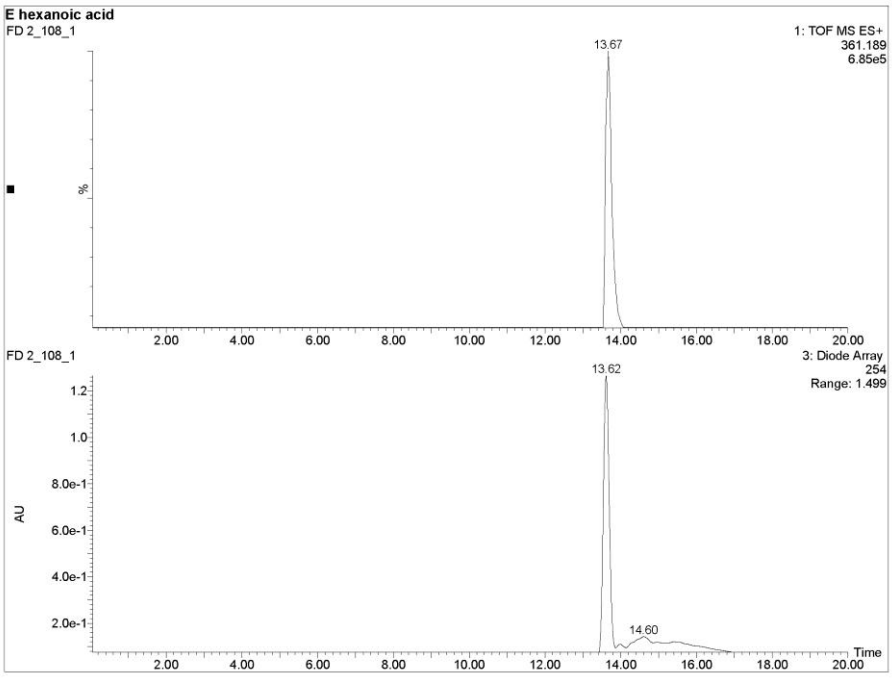
Compound 12 ***N*^{2}-(2′-Carboxyethyl)-ellipticinium bromide**



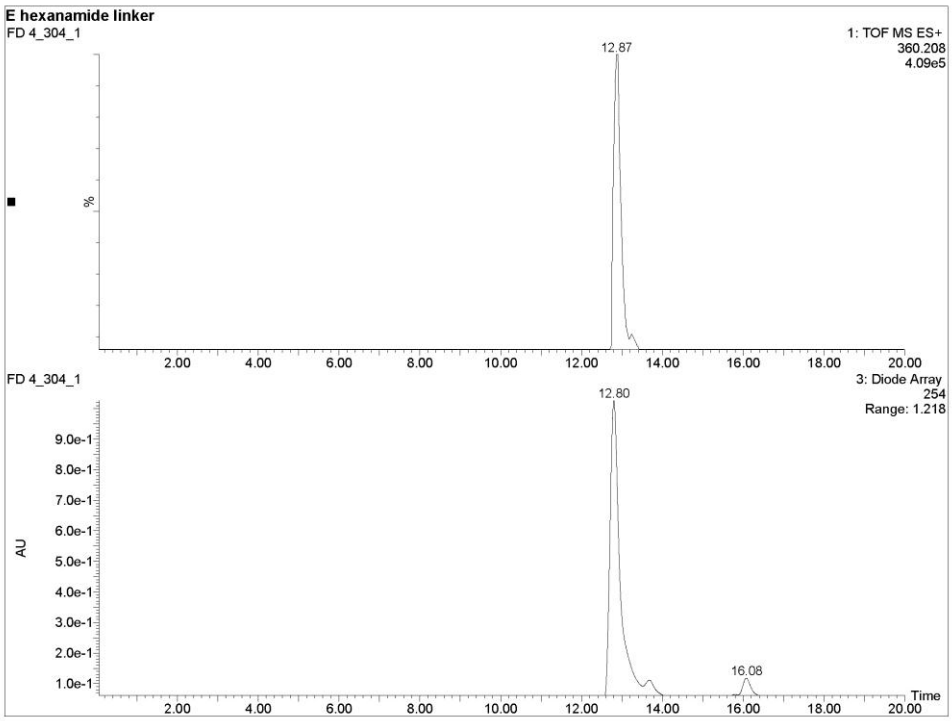
Compound 13 N^2-(4′-Carboxybutyl)-ellipticinium bromide



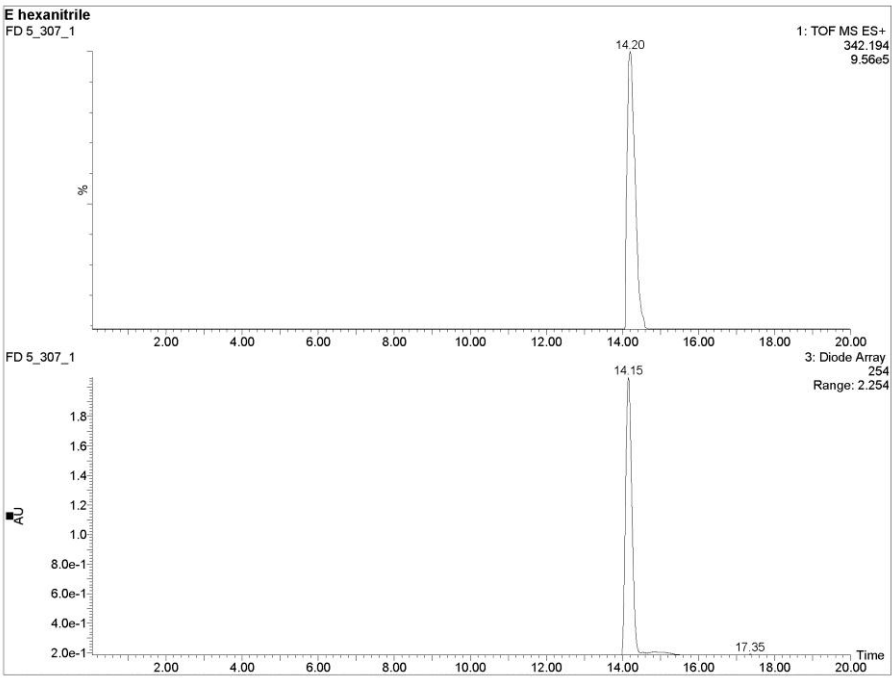
Compound 14 N^2-(5′-Carboxypentyl)-ellipticinium bromide



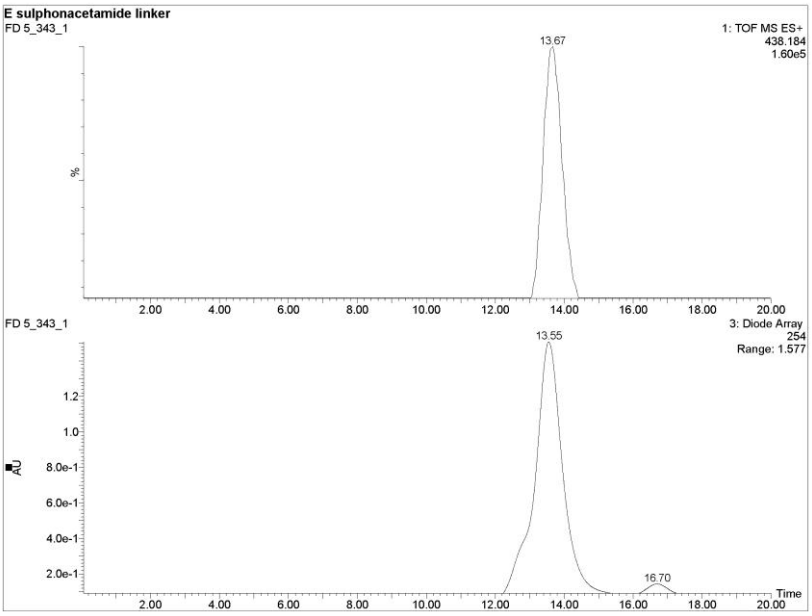
Compound 15 N^2-(5′-Carboxyaminopentyl)-ellipticinium bromide



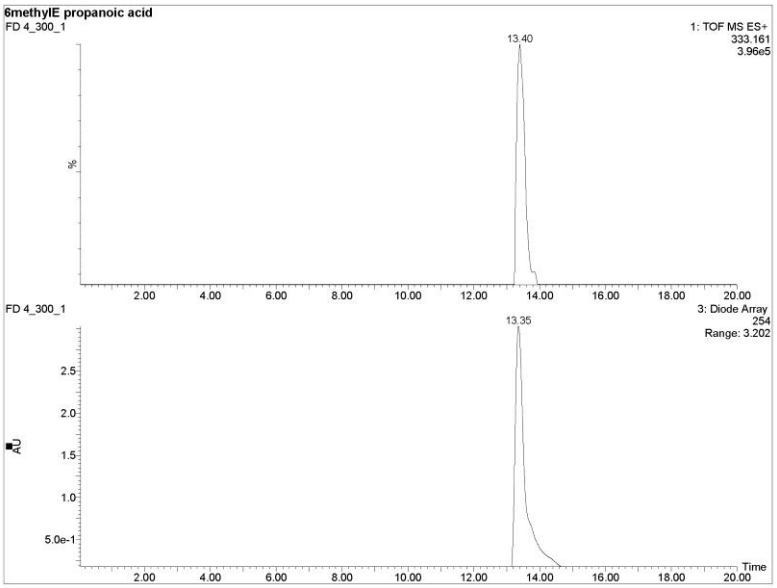
Compound 16 N^2-(5′-Cyanopentyl)-ellipticinium bromide



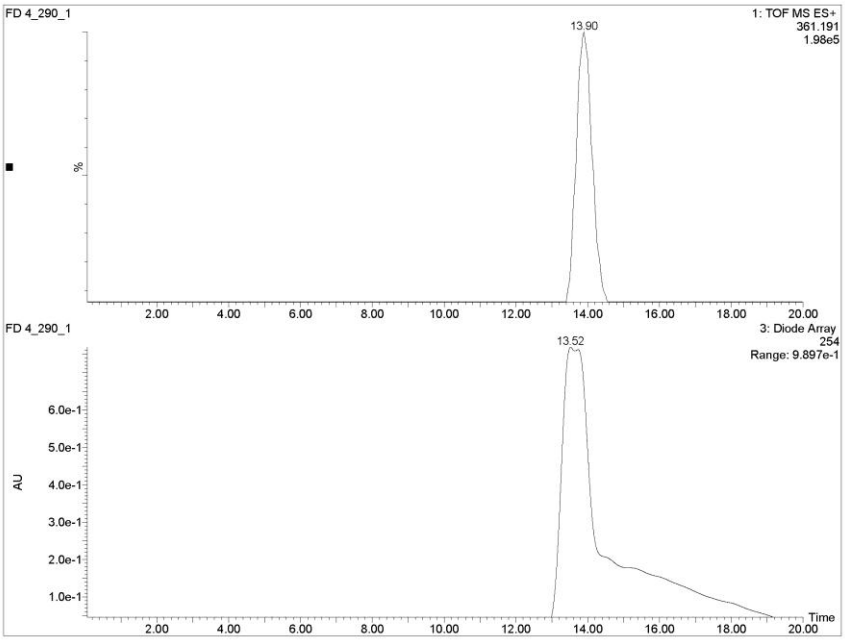
Compound 17 N^2-(5′-Hexanoylmethylsuphonamide)-ellipticinium bromide



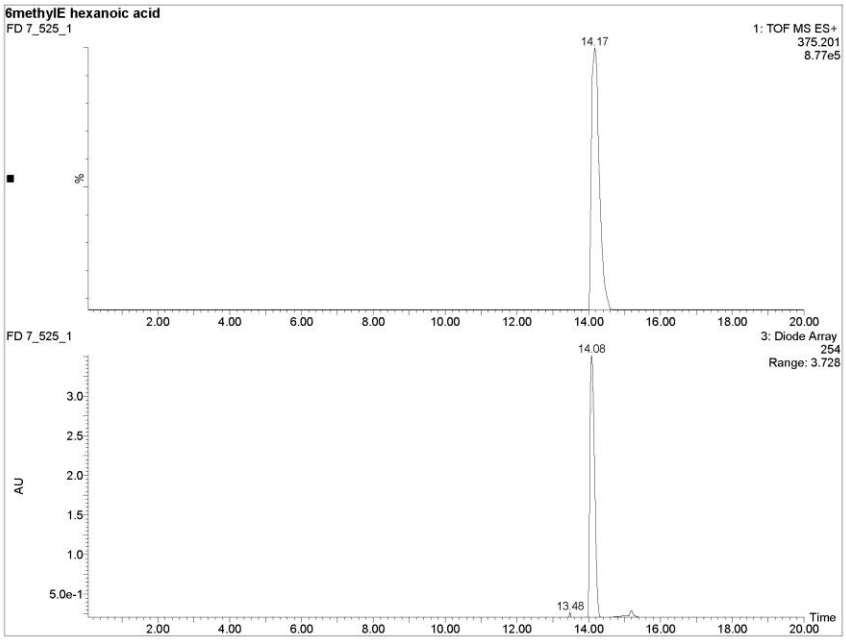
Compound 18 N^2-(2′-Carboxyethyl)-6-methylellipticinium bromide



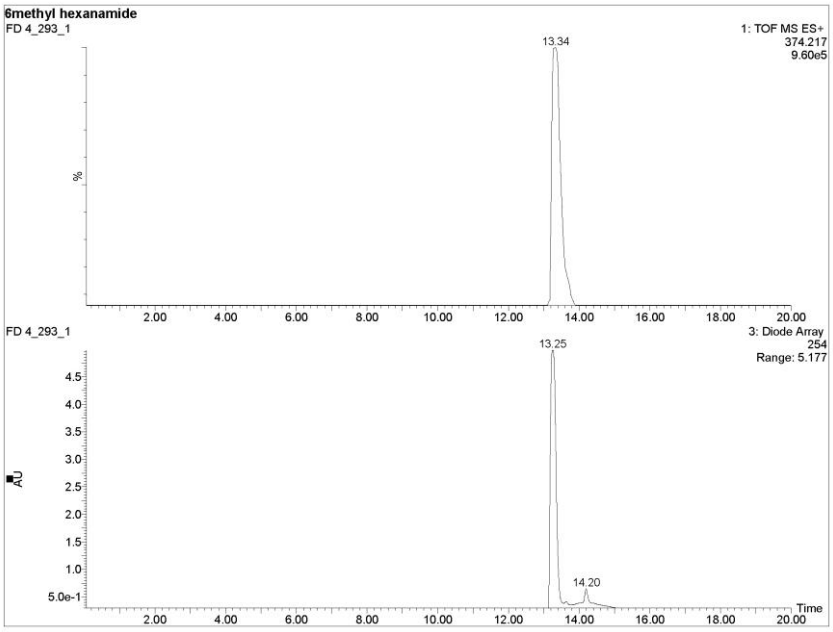
Compound 19 N^2-(4′-Carboxybutyl)-6-methylellipticinium bromide



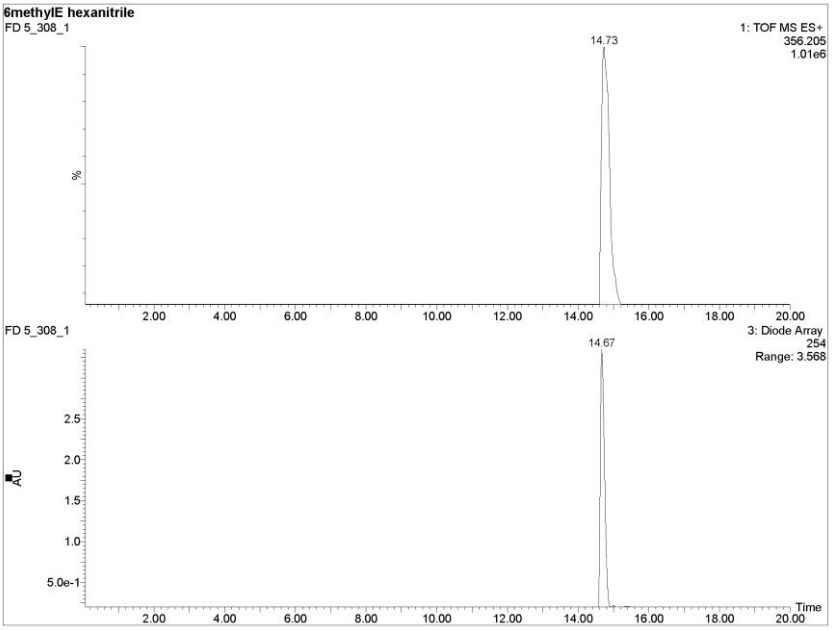
Compound 20 N^2-(5′-Carboxypentyl)-6-methylellipticinium bromide



Compound 21 N^2-(5′-Carboxyaminopentyl)-6-methyllipticinium bromide



Compound 22 N^2-(5′-Cyanopentyl)-6-methyllipticinium bromide



Compound 23 N^2-(5′-Hexanoylmethylsulphonamide)-6-methyllipticinium bromide