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Synthesis of Sultam Derivatives with Expected Biological Activity. 15^{\dagger}

S.H. Doss¹, V.B. Baghos², A.O. Abdelhamid²* and M.M.A. Halim¹

¹National Research Center, Giza, Egypt ²Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt E-mail: Abdou@main-scc.cairo.eun.eg

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Abstract: 4-(Trihydro-2H-1,2-thiazole-1,1-dioxide-2-yl)benzophenone (1), 4-(3,5-dimethyl-1`,2`-thiazine-1`,1`-dioxide-2-yl)benzophenone (2), and 4-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenone (6) were obtained from 4-aminobenzophenone and the appropriate reagents. Isomeric (*E*-) and (*Z*-) 2-Ethoxycarbonyl-4-phenyl-4-(4-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)phenyl-3-butenoic acids (11 and 12) and 2-carboxy-4(N-phenyl-thiocarbamoyl)-1-phenyl-6-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)naphthalene (16) were also synthesized.

Keywords: Sultam derivatives.

Introduction

Many sultam derivatives were found to possess valuable therapeutic properties such as; e.g., antitumor activity [1a] and anticonvulsive activity [1b,c]. In conjunction with our current research on sultam [2a] and on the Stobbe condensation [2b], we attempted to synthesize compounds expected to possess biological activity.

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Results and Discussion

4-Aminobenzophenone [3] was condensed with oxathiolan-2,2-dioxide, 4,6-dimethyl-1,2-oxathiin-2,2-dioxide, cyanoacetohydrazide and phenyl isothiocyanate to give the corresponding derivatives **1-4**, respectively. 4-(tetrahydro-2H-1,2-thiazin-1,1-dioxide-2-yl) benzophenone (**6**) was also prepared (*cf*. Scheme 1). The UV spectra of the sultamyl derivatives exhibited maximum absorption band at λ_{max} 235-254 nm (EtOH) assigned to the vibrational structure of the sultamyl group (n- π^*) transition [4]. Additional bands at λ_{max} 305-335 nm (EtOH) were present, also characteristic of the sultamyl group, but which were absent from the spectrum of the thiourea derivative.



Scheme 1.

Compound **6** reacted with cyanoacetohydrazide to give 4-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenonecyanoacetohydrazone (**7**). The structure of the latter product was elucidated on the basis of its elemental analysis and spectral data (*cf.* Experimental). Sultam derivatives **8-10** were obtained by the reaction of compound **7** with benzenediazonium chloride, benzaldehyde and salicylaldehyde, respectively (*cf.* Scheme 2). Structures **8-10** were confirmed on the basis of elemental analyses and spectral data (*cf.* Experimental).

Ketone **6** was condensed with diethyl succinate to give an oily half-ester (82%). The (*E*-) and (*Z*-) 3-ethoxycarbonyl-4-phenyl-4-(4-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)-3-butenoic acids were separated by fractional crystallization; the (*E*-) isomer was predominant. The relative ratio was estimated by the application of the spectrophotometric method [5], the ratio was almost the same as the ratio obtained by fractional crystallization (6:1).



Scheme 2.

The relative proportion of the two hemiesters obtained is determined by polar non-bonded interactions existing between the groups attached the carbonyl of the ketone and the carbanion. The predominance of the (E-) isomer is most likely probably due to the polar factor since repulsion between Ph and -COOR is expected to be less significant than that between Ar and -COOR. The polar factor i.e., repulsion between Ph and COOEt and between Ar and COOEt probably plays the more important role (See Figure 1).



Figure 1.

The conjugation of the lone pair of N in the sultam ring will increase electron density in the Ar group. Thus the (E-) Ar/-COOR configuration is expected to be predominant, as found experimentally. Evidence for the (E-) configuration of the hemiester was provided by its cyclization to the corresponding 1-phenylnaphthalene derivative **13** with the sultam ring in position 6. The structure of **13** was

proven by:

(a) analytical data;

(b) IR, ¹H-NMR and mass spectra (*cf.* Experimental and Table 1);

(c) No fragment of m/e 210 was obtained ($-\sqrt{-N}$, $C_{10}H_{12}O_2NS$); which is a reliable proof that the sultam ring is in position 6 of the 1-phenylnaphthalene and not in position 4'. Furthermore, the presence of five and not four adjacent hydrogen atoms [6] revealed the presence of an unsubstituted phenyl group (*cf.* mechanism [2b]).



Cyclization of the predominant (*E*-) hemiester (**11**) using sodium acetate and acetic anhydride [7] gave 4-acetoxy-2-ethoxycarbonyl-1-phenyl-6-(tetrahydro-1,2-thiazin-1,1-dioxide-2-yl)-naphthalene (**13**). Compound **13** was hydrolyzed with aqueous sodium hydroxide (8%) to give the phenolic acid **14**. The latter acid was either treated with phenyl isothiocyanate in benzene to give **16** or methylated to give methoxy ester **15**. The latter was hydrolyzed with sodium hydroxide (2N) to give 2-carboxy-4-methoxy-1-phenyl-6-(tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)naphthalene (**17**) (cf. Scheme 3).

Saponification of the (*E*-) hemiester **11** with 2N sodium hydroxide (at 50-60^oC) gave the dibasic acid **18** in 87% yield. Use more of concentrated alkali or alcoholic alkali was not successful. This may be due to the destruction of sultam ring. The dibasic acid was converted by refluxing with acetic anhydride to the corresponding cyclic anhydride which exhibited the expected carbonyl coupling bands (1830 and 1780 cm⁻¹) [4,6].

Biological testing of all reported compounds, in particular for antitumor and antiepileptic activity, is currently under way and results will be published elsewhere.

Experimental

General

All melting points were determined on a Electrothermal melting point apparatus and are uncorrected. IR spectra (KBr disks) were recorded on a Beckman IR 4220 spectrophotometer. ¹H-NMR spectra were recorded on a Varian EM 390-90 MHz. spectrometer and chemical shifts are expressed in δ (ppm) units using TMS as internal reference. Electronic absorption spectra were recorded in ethanol solutions a Shimadzu graphic printer Pr-1 spectrophotometer. Mass spectra were recorded using a GCMS-QP 1000 EX Shimadzu spectrometer. The Microanalytical units of Cairo University and of the National Research Center performed elemental analyses.

4-(Trihydro-2H-1,2-thiazole-1,1-dioxide-2-yl)benzophenone (1)

4-Aminobenzophenone (1.97g, 0.01 mol) was fused with oxathiolan-2,2-dioxide (1.2 g, 0.01 mol) at 90-100°C in oil bath for one hour. The reaction mixture changed to yellow, then brownish oil, which solidified. This solid was washed with hydrochloric acid and then with water. Yield 69%. Compound **1** had mp. 230-32°C (methanol), Found for C₁₆H₁₅NO₃S (301.36): C, 63.51; H, 4.80; N, 4.80 and S, 10.10. Calcd.: C, 63.77; H, 5.01; N, 4.65; S, 10.63. ¹H NMR: 1.7 (m, 2H, CH₂CH₂SO₂), 2.6 (t, 2H, NCH₂), 3.2 (t, 2H, CH₂SO₂) and 7.4-7.7 (m, 9H, ArH's)[8]. UV: λ_{max} 218 (log ε = 4.47), 285 (log ε = 4.32) and 332 (log ε = 4.90) nm ; IR (cm⁻¹) 1648 (CO), 1157 (SO₂), 1317 (SO₂ asym.), 1283 (sultam band) and 738-705 (5 phenylic adjacent H atoms).

4-(3,5-Dimethyl-1',2'-thiazine-1',1'-dioxide-2-yl)benzophenone (2)

4-Aminobenzophenone (1.97 g, 0.01 mol) was fused with 4,6-dimethyl-1,2-oxathiin-2,2-dioxide (1.6g, 0.01 mol) at 110°C for one hour in an oil bath. The solid formed was washed with dil. hydrochloric acid and then with water. Yield: 35%. Compound **2** had mp. 185-86°C (methanol), Found for $C_{19}H_{17}NO_3S$ (339.41): C, 66.80; H, 5.00; N, 3.90; S, 9.50. Calcd.: C, 67.23; H, 5.40; N, 4.12; S, 9.44. UV λ_{max} 245 (log $\varepsilon = 4.00$) and 334 (log $\varepsilon = 4.03$); IR (cm⁻¹) 1658 (CO), 1581 (conjugated double bond of the sultam ring), 1280 (sultam ring).

4-Aminobenzophenone cyanoacetohydrazone (3)

To a mixture of 4-aminobenzophenone (1.97g, 0.01 mol) and cyanoacetohydrazide [8] (0.99g, 0.01 mol) in ethanol (50 mL), 3 drops of hydrochloric acid are added. The mixture was left at room temperature for 72 hrs. Yield: 99%. Compound **3** had mp., 145-46°C. Found for $C_{16}H_{14}N_4O$ (278.31): C, 69.10; H, 5.10; N, 20.04. Calcd.: C, 69.05, H, 5.07; N, 20.13. ¹H NMR: 3.8 (s, 2H, NH₂), 4.2 (d, 2H, CH₂CN), 6.5-7.6 (m, 9H, ArH's) and 9.6 (s, 1H, NH). IR (cm⁻¹), 3460, 3375 (NH₂), 2260 (CN), 1687 (CONH), 1140 (SO₂), 1322 (SO₂ asym).

4-(Phenyl thioureido)benzophenone (4)

A mixture of 4-aminobenzophenone (1.97g, 0.01 mol), phenyl isothiocyanate (1.35g, 0.01 mol) and triethylamine (3 drops) in benzene (50 mL) was refluxed for 5 hrs. The solvent was evaporated under vacuum to give an oily residue. It was triturated with light petroleum (60-80°C) to afford a solid. Yield: 45%. Compound **4** had mp. 156-57°C (benzene-acetone). Found for C₂₀H₁₆N₂OS (332.426): C, 72.50; H, 4.50; N, 8.00; S, 9.20. Calcd.: 72.26; H, 4.85; N, 8.42; S, 9.64. (UV λ_{max} 217, 274 nm (log ϵ = 4.16 and 4.06, respectively). IR (cm⁻¹), 3322-3029 (NH), 1690 (CO), 1253-1023 (CS).

4-(Tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenone (6)

4-chloro-1-butanesulfonyl chloride (0.01 mol) was added dropwise at room temperature over 0.5 hr to a stirred solution of 4-aminobenzophenone (1.97g, 0.01 mol) in benzene (20 mL) and pyridine (3 mL) to give 4-benzoyl-4-chlorobutanesulfonanilide (5). Compound 5 had mp., 105-106°C (benzene-petroleum ether). Found for $C_{17}H_{18}CINO_3$ (351.85): C, 58.30; H, 5.20; N, 3.92; S, 9.00. Calcd.: C, 58.03; H, 5.12; N; 3.98; S, 9.11. Its 2,4-DNP derivative, mp. 233-34°C (acetic acid, 60%). Found for $C_{23}H_{22}CIN_5O_6S$ (531.98): C, 52.00; H, 4.10; N, 13.20; S, 6.00. Calcd.: C, 51.93; H, 4.16; N, 13.16; S, 6.03.

A solution of **5** was warmed at 40-50°C for 3 hrs with sodium hydroxide (2N) to give **6** [4]. Yield: 63%, mp. 136-37°C (benzene). Found for $C_{17}H_{17}NO_3S$ (315.39): C, 64.70; H, 5.30; N, 4.40; S, 9.90. Calcd., C, 64.74; H, 5.43; N, 4.44; S, 10.15. ¹H NMR: 1.8 (m, 2H, <u>CH₂CH₂SO₂), 2.3 (m, 2H</u>,

SO₂CH₂CH₂CH₂, 3.2 (t, 2H, SO₂CH₂), 3.8 (t, 2H, NCH₂) and 7.2-7.7 (m, 9H, ArH's. IR (cm⁻¹), 1690 (CO), 1325 (SO₂N), 1280 (sultam) and 770-700 (five adjacent hydrogen atoms). UV λ_{max} 235, 305nm (log ϵ = 4.68 and 4.89, respectively). Its DNP had mp. 275-76°C (acetic acid). Found for C₂₃H₂₁N₅O₆S (495.52); C, 56.10; H, 4.40; N, 13.60; S, 6.20. Calcd.: C, 55.75; H, 4.26; N, 14.19; S, 6.67.

4-(Tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenonecyanoacetohydrazone (7)

Prepared from **6** in a similar fashion as above, yield 75%. Mp. 122-23°C (ethanol). Found for $C_{20}H_{20}N_4O_3S$ (396.47): C, 60.50; H, 5.10; N, 14.00; S, 8.20. Calcd.: C, 60.59; H, 5.08; N, 14.13, S, 8.08. ¹H NMR: 1.8 (m, 2H, SO₂CH₂CH₂), 2.3 (m, 2H, SO₂CH₂CH₂CH₂), 3.2 (t, SO₂CH₂), 3.8 (t, N<u>CH₂</u>), 7.4-7.7 (m, 9H, ArH's), 9.3 (s, 1H, NHCO).

(a) The hydrazone derivative **7** (0.01 mol) was coupled with benzenediazonium chloride (0.01 mol) to give **8**, yield at room temperature 64%, mp. 130-31°C (acetic acid). Found for $C_{26}H_{24}N_6O_3S$ (500.58): C, 61.40; H, 4.80; N, 16.80; S, 6.40. Calcd.: C, 61.38; H, 4.83; N, 16.78; S, 6.40. IR (cm⁻¹), 2152 (CN), 1648 (CONH) and 1280 (sultam).

(b) To hydrazone derivative **7** (0.01 mol), benzaldehyde (0.01 mol) in ethanol (20 mL) and 2 drops of piperidine were added. The mixture was refluxed for 30 minutes on a water bath. After cooling, the solid was collected and crystallized to give **9** (73.5%), mp. 230-31°C (ethanol). Found for $C_{26}H_{24}N_4O_3S$ (472.57): C, 66.30; H, 5.10; N, 11.70; S, 6.40. Calcd.: C, 66.08; H, 5.12; N, 11.85; S, 6.76. IR (cm⁻¹), 2152 (CN), 1648 (CONH) and 1280 (sultam).

(c) To hydrazone derivative **7** (0.01 mol), salicylaldehyde (0.01 mol) in ethanolic sodium ethoxide solution [prepared from sodium metal (1.1 g-atom) in ethanol (20 mL)] was added. The mixture was refluxed for 2 hrs., then cooled. The reaction mixture was acidified with hydrochloric acid to give **10**, yield 55%, mp. 243-44°C (ethanol). Found for $C_{27}H_{23}N_3O_5S$ (501.56): C, 64.50; H, 4.60; N, 8.80, S, 6.70. Calcd.: C, 64.65; H, 4.62; N, 8.38; S, 6.39. IR (cm⁻¹) 3446 (NH), 1700, 1648 (two CO) and 1282 (sultam).

3-Ethoxycarbonyl-4-phenyl-4-(4'-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)phenyl-3-butenoic acids (11 and 12)

To a cooled stirred mixture of ketone **6** (0.01 mol) and diethyl succinate (0.02 mol) in <u>t</u>-butanol (15 mL), potassium <u>t</u>-butoxide was added dropwise [prepared from 1.2 g-atom potassium and <u>t</u>-butanol (50 mL)]. After 72 hrs, the reaction mixture was heated at 65-70°C for one hour, then worked up as usual [2b] to give an acidic brown viscous oily product (yield ~ 7.3g, 82%). The (*E*-) (**11**) and (*Z*-) (**12**) isomeric hemiesters were separated by fractional crystallization.

Compound **11** had mp. 144-45°C (benzene-acetone). Found for $C_{23}H_{25}NO_6S$ (443.52): C, 62.00; H, 5.50; N, 3.30; S, 7.60. Calcd.: C, 62.28; H, 5.64; N, 3.16; S, 7.23. IR (cm⁻¹), 3300-2600 (γ OH), 1700-1620 (CO), 1270 (sultam).

Compound **12** had m.p. 108-109°C (benzene). Found for C₂₃H₂₅NO₆S (443.52): C, 62.40; H, 5.50;

N, 3.30; S, 7.50. Calcd.: C, 62.28; H, 5.64, N, 3.16; S, 7.23. IR (cm⁻¹), 3600-2500 (OH), 1700-1640 (CO), 1280 (sultam).

Determination of the relative ratio of the two (E-) and (Z-) hemiesters by electronic absorption spectroscopy [5]

Values for E_{obs}/E_1 were plotted vs. the values for E_{2s}/E_1 where E_{obs} is the observed optical density of the mixture and E_1 and E_2 are the optical densities of the hemiesters **11** and **12** respectively, at the same wavelength. A straight line was obtained from which the ratio of 5.9/1 was calculated. This is almost the same ratio as that obtained experimentally by fractional crystallization.

Cyclization of the (E-) hemiester

A mixture of the (*E*-) hemiester (1 mol) fused sodium acetate (1.2 mol) and acetic anhydride (30 mL/ 1g sodium acetate) was left overnight with occasional shaking at room temperature. The temperature was gradually raised to 70-80°C for 3hrs. The neutral cyclized product **13** was isolated and had mp. 122-23°C (ethanol). Found for $C_{25}H_{25}NO_6S.H_2O$ (485.56): C, 62.00; H, 5.40; N, 3.00; S, 6.80. Calcd.: C, 61.84; H, 5.19; N, 2.88; S, 6.61. Mass spectrum, m/e = 485 and ¹H NMR: 1.2 (t, 3H, CH₃CH₂O), 1.8 (m, 2H, SO₂CH₂CH₂), 2.3 (m, 2H, CH₂(CH₂)₂SO₂, 3.2 (t, 2H, SO₂CH₂), 3.5 (t, 2H, NCH₂), and 7.0-7.8 (m, 9H, ArH's)⁹. IR (cm⁻¹), 1760 (CO), 1290 (sultam ring), 740-700 (five adjacent hydrogen atoms).

Conversion of the acetoxy ester 13 into methoxy acid 17

The acetoxy ester was hydrolysed with 2N sodium hydroxide on water-bath (70 - 80°C) for two hrs. The hydroxy acid **14** (1 mol) was methylated by refluxing for 10 hrs with dimethyl sulphate (5 mol) and potassium carbonate (6 mol) in dry acetone. The methoxy ester was hydrolyzed to the corresponding acid by warming for 3 hrs with 8% sodium hydroxide, followed by cooling and acidification.

Compound **14** had mp. 225-26°C (acetic acid). Found for $C_{21}H_{19}NO_5S$ (397.45): C, 63.20; H, 5.10; N, 3.40; S, 7.70. Calcd.: C, 63.47; H, 4.81; N, 3.52; S, 8.06.

Compound **15** had mp. 167-68° (methanol). Found for C₂₃H₂₃NO₅S (425.50): C, 64.70; H, 5.00; N, 3.60, S, 7.90. Calcd.: C, 64.92; H, 5.44; N, 3.29; S, 7.52.

Compound **17** had mp., 120-21°C (acetic acid). Found for $C_{22}H_{21}NO_5S$ (411.48): C, 63.90; H, 5.30; N, 3.40; S, 7.60. Calcd.: C, 64.23; H, 5.14; N, 3.40; S, 7.78. IR (cm⁻¹), 1725 (CO), 1295 (sultam) and 740-700 (five adjacent hydrogen atoms).

2-Carboxy-4(N-phenylthiocarbamoyl)-1-phenyl-6-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)naphthalene (16)

A mixture of hydroxynaphthoic acid derivative 14 (0.01 mol), phenyl isothiocyanate (0.01 mol) and

3 drops of triethylamine in dry benzene (30 mL) was refluxed for 5 hrs. The benzene was evaporated under reduced pressure to give yellow solid **16**, yield 71%. It had mp. 133-34°C (benzene-acetone). Found for $C_{28}H_{24}N_2O_5S_2$ (532.64): 62.90; H, 4.90; N, 5.40; S, 11.90. Calcd.: C, 63.14; H, 4.54; N, 5.26; S, 12.01. IR (cm⁻¹), 3247-2800 (OH), 1725(CO), 1290 (sultam) and 744-701 (five adjacent hydrogen atoms).

Saponification of the (E-) hemiester to the corresponding dibasic acid 18 and anhydride 19

The (<u>*E*-</u>) hemiester (0.1 mol) was left in NaOH (2N, 50 mL) for about 72 hrs., then kept 60-80°C for one hour. The dibasic acid **18** was refluxed with a mixture of acetic anhydride (7 mL) and acetyl chloride (5 mL) on a sand bath for 30 minutes, to give the corresponding anhydride (**19**).

Compound **18** had mp., 175-76°C (benzene-acetone). Found for $C_{21}H_{21}NO_6S$ (415.47): C, 60.20; H, 5.10; N, 3.90; S, 7.20. Calcd.: 60.72; H, 5.08; N, 3.37; S, 7.85. ¹H NMR: 1.7 (m, 2H, CH₂CH₂SO₂), 2.3 (m, 2H, CH₂(CH₂)2SO₂), 3.2 (t, 2H, SO₂CH₂), 3.5 (t, 2H, NCH₂), 7.1-7.4 (m, 9H, ArH's) and 12.5 (s, 2H, (COOH)₂. IR (cm⁻¹), 3446-2500 (γ OH), 1720-1656 (CO), 1276 (sultam), 745-707 (five adjacent hydrogen atoms).

Compound **19** had mp. 137-38°C (benzene-peteroleum ether). Found for $C_{21}H_{19}NO_5S$ (397.45): C, 63.20; H, 5.00; N, 3.90; S, 8.30. Calcd.: C, 63.46; H, 4.81; N, 3.52; S, 8.07. IR (cm⁻¹), 1840,1780 (CO-O-CO), 1280 (sultam ring) and 750-700 (five adjacent hydrogen atoms).

Table 1. Mass spectra of compounds 1, 3, 6, 11, 12 and 13.

- 1 301 (20, $C_{16}H_{15}NSO_3^+$); 224 (12, $C_{10}H_{10}NSO_3^+$); 197 (100, $C_9H_{10}NSO_2^{+1}$); 180 (5, $C_{13}H_9O^{+1}$); 120 (8, $C_3H_6NSO_2^+$); 77 (16, $C_6H_5^+$).
- **3** 278 (100, $C_{16}H_{14}ON_4^+$); 238(21.69, $C_{14}H_{12}ON_3^+$); 210(37.08, $C_{13}H_{12}N_3^+$), 180 (29.44, $C_{13}H_{10}N^+$); 119 (1.87, $C_7H_5ON^+$); 77 (16.64, $C_6H_5^+$).
- **6** 315 (100, $C_{17}H_{17}NSO_3^+$; 238 (47.13, $C_{11}H_{12}NSO_3^+$); 210(14.93 $C_{10}H_{12}NSO_2^+$); 132 (19, $C_9H_{10}N^+$); 105 (19, $C_7H_5O^+$); 77(16, $C_6H_5^+$).
- 11 443 (12.1, $C_{23}H_{25}NSO_6^+$); 339 (33.6, $C_{22}H_{25}NSO_4^{+1}$); 379 (1.8, $C_{23}H_{25}NO_4^+$); 365 (14.4, $C_{22}H_{23}NO_4^+$); 325 (100, $C_{19}H_{18}NO_4^{+1}$); 308 (7.9, $C_{19}H_{16}O_4^+$); 144 (1.6, $C_6H_8O_4^+$); 134 (0.7, $C_4H_8NSO_2^+$); 77 (1.5, $C_6H_5^+$).
- **12** 443 (12.80, $C_{23}H_{25}NSO_6^+$); 325 (100, $C_{19}H_{18}O_4N^{+1}$); 308 (13.4, $C_{19}H_{16}O_4^+$); 139 (5.2, $C_6H_2O_4^{+1}$); 134 (3.4, $C_4H_8NSO_2^+$); 77(7.9, $C_6H_5^+$).
- **13** 485 (100, $C_{25}H_{25}NSO_{6}H_{2}O^{+}$); 467 (5, $C_{25}H_{25}NSO_{6}^{+}$); 404 (5, $C_{25}H_{25}NO_{4}^{+1}$); 361 (5, $C_{23}H_{22}NO^{+1}$).

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Samples Availability: Available from the authors.

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