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# New tetrahydroacridine hybrids with dichlorobenzoic acid moiety demonstrating multifunctional potential for the treatment of Alzheimer's disease

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# General procedure for the synthesis of 2a–2h

An aqueous solution of N-methylomorpholine was slowly added to a mixture of tetrahydrofuran (THF), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), 3,5-dichlorobenzoic acid. The reaction was carried out for about two hours in an ice bath. Then of diamine dissolved in THF was added to the mixture and the reaction continued at room temperature for 24 hours to yield the corresponding intermediates 2a–2h.

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]benzamide (2a)

Compound 2a was obtained from 1a and 3,5-dichlorobenzoic acid as standard procedure: 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.36 g, 2.07 mM), 3,5-dichlorobenzoic acid (0.40 g, 2.07 mM) and N-methylomorpholine (0.23 ml, 2.07 mM) were mixed. 1a compound (0.50 g, 2.07 mM) dissolved in THF (3 ml) was added. Compound 2a: yellow oil; 75.0% yield; FTIR (ATR) v ($cm^{-1}$): 748.9; 1236.7; 1316.8; 1449.0; 1563.8; 2937.8; 3252.9; $^1$H NMR (600 MHz, Methanol-d4) δ 8.48 (1H, d, J = 8.4 Hz, Ar), 7.87 (1H, t, J = 8.2 Hz, Ar), 7.75 (1H, d, J = 7.6 Hz, Ar), 7.67 (1H, t, J = 1.9 Hz, Ar), 7.61 – 7.65 (3H, m, Ar), 4.22 – 4.25 (2H, m, $CH_2$), 3.77 – 3.80 (2H, m, $CH_2$), 2.99 (2H, t, J = 6.2 Hz, $CH_2$), 2.78 (2H, t, J = 6.1 Hz, $CH_2$), 1.92 – 2.01 (4H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) (M+1) m/z: 215.9, 199.1, 172.2, 121.1; MS-HR (ESI): calcd. for $C_{22}H_{21}Cl_2N_3O$: 413.10617, found: 413.10588

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]benzamide (2b)

Compound 2b was obtained from 1b and 3,5-dichlorobenzoic acid as standard procedure: CDMT (0.34 g, 1.96 mM), 3,5-dichlorobenzoic acid (0.37 g, 1.96 mM) and N-methylomorpholine (0.22 ml, 1.96 mM) were mixed. 1b compound (0.50 g, 1.96 mM) dissolved in THF (3 ml) was added. Compound 2b: yellow oil; 70.0% yield; FTIR (ATR) v ($cm^{-1}$): 764.3; 1236.8; 1315.9; 1448.9; 1562.9; 2938.2; 3253.7; $^1$H NMR (600 MHz, Methanol-$d_4$) δ 8.40 (1H, d, J = 8.5 Hz, Ar), 7.84 (1H, t, J = 8.2 Hz, Ar), 7.74 (1H, d, J = 9.3 Hz, Ar), 7.67 (2H, d, J = 1.9 Hz, Ar), 7.65 (1H, t, J = 1.9 Hz, Ar), 7.56 (1H, t, J = 8.4 Hz, Ar), 4.07 (2H, t, J = 6.5 Hz, $CH_2$), 3.53 – 3.56 (2H, m, $CH_2$), 3.01 (2H, t, J = 6.0 Hz, $CH_2$), 2.77 (2H, t, J = 5.8 Hz, $CH_2$), 2.14 (2H, p, J = 6.5 Hz, $CH_2$), 1.94 – 2.01 (4H, m, $CH_2$), (protons of NH groups invisible); MS (ESI)(M+1) m/z: 230.0, 199.1, 172.9, 121.1; MS-HR (ESI): calcd. for $C_{23}H_{23}Cl_2N_3O$: 427.12182, found: 427.12128

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]benzamide (2c)

Compound 2c was obtained from 1c and 3,5-dichlorobenzoic acid as standard procedure: CDMT (0.33 g, 1.86 mM), 3,5-dichlorobenzoic acid (0.35 g, 1.86 mM) and N-methylomorpholine (0.20 ml, 1.86 mM) were mixed. 1c compound (0.50 g, 1.86 mM) dissolved in THF (3 ml) was added. Compound 2c: yellow oil; 68.0% yield; FTIR (ATR) v ($cm^{-1}$): 759.1; 1236.7; 1330.7; 1447.5; 1560.1; 2872.0; 3229.9; $^1$H NMR (600 MHz, Methanol-d4) δ 8.41 (1H, d, J = 8.6 Hz, Ar), 7.84 (1H, t, J = 8.1 Hz, Ar), 7.73 (1H, d, J = 7.9 Hz, Ar), 7.68 – 7.70 (2H, m, Ar), 7.65 (1H, t, J = 1.9 Hz, Ar), 7.58 (1H, t, J = 7.8 Hz, Ar), 4.04 (2H, t, J = 7.0 Hz, $CH_2$), 3.42 (2H, t, J = 6.7 Hz, $CH_2$), 3.01 (2H, t, J = 5.8 Hz, $CH_2$), 2.72 (2H, t, J = 5.6 Hz, $CH_2$), 1.90 – 2.00 (6H, m, $CH_2$), 1.77 (2H, p, J = 6.8 Hz, $CH_2$), (protons of NH groups invisible); MS (ESI)(M+1) m/z: 211.1, 199.1, 172.2, 121.1; MS-HR (ESI): calcd. for $C_{24}H_{25}Cl_2N_3O$: 441.13747, found: 441.13704

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]benzamide (2d)

Compound 2d was obtained from 1d and 3,5-dichlorobenzoic acid as standard procedure and gave compound 2d: CDMT (0.31 g, 1.76 mM), 3,5-dichlorobenzoic acid (0.34 g, 1.76 mM) and N-methylomorpholine (0.19 ml, 1.76 mM) were mixed. 1d compound (0.50 g, 1.76 mM) dissolved in THF (3 ml) was added. Compound 2d: yellow oil; 76.0% yield; FTIR (ATR) v ($cm^{-1}$): 767.3; 1236.8; 1330.9; 1451.0; 1559.1; 2967.2; $^1$H NMR (600 MHz, Methanol-d4) δ 8.41 (1H, d, J = 8.7 Hz, Ar), 7.85 (1H, t, J = 8.1 Hz, Ar), 7.73 – 7.76 (3H, m, Ar), 7.66 (1H, t, J = 1.9 Hz, Ar), 7.59 (1H, t, J = 8.4 Hz, Ar), 3.99 (2H, d, J = 7.1 Hz, $CH_2$), 3.41 (2H, t, J = 6.9 Hz, $CH_2$), 3.00 – 3.03 (2H, m, $CH_2$), 2.70 – 2.73 (2H, m, $CH_2$), 1.88 – 1.97 (6H, m, $CH_2$), 1.67 – 1.72 (2H, m, $CH_2$), 1.52 (2H, p, J = 7.7, 7.2 Hz, $CH_2$), (protons of NH groups invisible); MS (ESI) (M+1) m/z: 211.1, 199.1, 174.9, 121.1; MS-HR (ESI): calcd. for $C_{25}H_{27}Cl_2N_3O$: 455.15312, found: 455.15232

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) hexyl]benzamide (2e)

Compound 2e was obtained from 1e and 3,5-dichlorobenzoic acid as standard: CDMT (0.30 g, 1.68 mM), 3,5-dichlorobenzoic acid (0.32 g, 1.68 mM) and N-methylomorpholine (0.18 ml, 1.68 mM) were mixed. 1e compound (0.50 g, 1.68 mM) dissolved in THF (3 ml) was added. Compound 2e: yellow oil; 60.0% yield; FTIR (ATR) v ($cm^{-1}$): 767.3; 1236.6; 1331.9; 1452.9; 1559.1; 2947.6; 469,16877; $^1$H NMR (600 MHz, Methanol-d4) δ 8.40 (1H, d, J = 8.6 Hz, Ar), 7.85 (1H, t, J = 7.7 Hz, Ar), 7.75 – 7.78 (3H, m, Ar), 7.64 (1H, t, J = 1.9 Hz, Ar), 7.59 (1H, t, J = 8.3 Hz, Ar), 3.97 (2H, t, J = 3.6 Hz, $CH_2$), 3.38 – 3.40 (2H, m, $CH_2$), 3.03 (2H, t, J = 5.7 Hz, $CH_2$), 2.73 (2H, t, J = 5.4 Hz, $CH_2$), 1.96 – 2.01 (4H, m, $CH_2$), 1.87 (2H, p, J = 7.4 Hz, $CH_2$), 1.66 (2H, p, J = 7.1 Hz, $CH_2$), 1.43 – 1.55 (4H, m, $CH_2$), (protons of NH groups invisible); MS (ESI)(M+1) m/z: 211.1, 199.1, 172.9, 121.1; MS-HR (ESI): calcd. for $C_{26}H_{29}Cl_2N_3O$: 469.16877, found: 469.16750

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) heptyl]benzamide (2f)

Compound 2f was obtained from 1f and 3,5-dichlorobenzoic acid as standard procedure and gave compound 2f: CDMT (0.28 g, 1.61 mM), 3,5-dichlorobenzoic acid (0.31 g, 1.61 mM) and N-methylomorpholine (0.18 ml, 1.61 mM) were mixed. 1f compound (0.50 g, 1.61 mM) dissolved in THF (3 ml) was added. Compound 2f: yellow oil; 65.0% yield; FTIR (ATR) v ($cm^{-1}$): 752.9; 1241.8; 1330.3; 1457.0; 1563.8; 2930.7; 3274.7; $^1$H NMR (600 MHz, Methanol-d4) δ 8.39 (1H, d, J = 8.6 Hz, Ar), 7.85 (1H, t, J = 8.1 Hz, Ar), 7.76 – 7.78 (3H, m, Ar), 7.64 (1H, t, J = 1.9 Hz, Ar), 7.59 (1H, t, J = 8.4 Hz, Ar), 3.93 – 3.96 (2H, m, $CH_2$), 3.35 – 3.38 (2H, m, $CH_2$), 3.03 (2H, t, J = 5.8 Hz, $CH_2$), 2.72 (2H, t, J = 5.6 Hz, $CH_2$), 1.95 – 2.01 (4H, m, $CH_2$), 1.86 (2H, p, J = 7.6 Hz, $CH_2$), 1.63 (2H, p, J = 7.2 Hz, $CH_2$), 1.40 – 1.50 (6H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) (M+1) m/z: 211.1, 199.1, 172.9, 121.1; MS-HR (ESI): calcd. for $C_{27}H_{31}Cl_2N_3O$: 483.18442, found: 483.18357

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) octyl]benzamide (2g)

Compound 2g was obtained from 1g and 3,5-dichlorobenzoic acid as standard procedure and gave compound 2g: 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (0.27 g, 1.54 mM), 3,5-dichlorobenzoic acid (0.29g, 1.54 mM) and N-methylomorpholine (0.17 ml, 1.54 mM) were mixed. 1g compound (0.50 g, 1.54 mM) dissolved in THF (3 ml) was added. Compound 2g: yellow oil; 60.0% yield; FTIR (ATR) v ($cm^{-1}$): 761.9; 1242.5; 1330.4; 1447.7; 1559.6; 2925.5; 3305.0; $^1$H NMR (600 MHz, Methanol-d4) δ 8.39 (1H, d, J = 8.6 Hz, Ar), 7.85 (1H, t, J = 8.1 Hz, Ar), 7.76 – 7.79 (3H, m, Ar), 7.64 (1H, t, J = 1.9 Hz, Ar), 7.59 (1H, t, J = 8.3 Hz, Ar), 3.94 (2H, t, J = 7.3 Hz, $CH_2$), 3.37 (2H, t, J = 7.1 Hz, $CH_2$), 3.03 (2H, t, J = 5.8 Hz, $CH_2$), 2.72 (2H, t, J = 5.3 Hz, $CH_2$), 1.96 – 2.01 (4H, m, $CH_2$), 1.84 (2H, p, J = 7.4 Hz, $CH_2$), 1.62 (2H, p, J = 7.1 Hz, $CH_2$), 1.37 – 1.48 (8H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) (M+1) m/z: 211.1, 199.1, 171.1, 121.1; MS-HR (ESI): calcd. for $C_{28}H_{33}Cl_2N_3O$: 497.20007, found: 497.19927

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) nonyl]benzamide (2h)

Compound 2h was obtained from 1h and 3,5-dichlorobenzoic acid as standard procedure and gave compound 2h: CDMT (0.26 g, 1.47 mM), 3,5-dichlorobenzoic acid (0.28g, 1.47 mM) and N-methylomorpholine (0.16 ml, 1.47 mM) were mixed. 1h compound (0.50 g, 1.47 mM) dissolved in THF (3 ml) was added. Compound 2h : yellow oil; 64.0% yield; FTIR (ATR) v ($cm^{-1}$): 755.7; 1282.1; 1355.5; 1497.4; 1562.1; 2925.1; 3273.4; $^1$H NMR (600 MHz, Methanol-d4) δ 8.30 (1H, d, J = 8.6 Hz, Ar), 7.74 – 7.79 (4H, m, Ar), 7.63 (1H, t, J = 1.9 Hz, Ar), 7.52 (1H, t, J = 8.3 Hz, Ar), 3.82 (2H, t, J = 7.2 Hz, $CH_2$), 3.35 – 3.38 (2H, m, $CH_2$), 3.03 (2H, d, J = 6.0 Hz, $CH_2$), 2.74 (2H, d, J = 5.7 Hz, $CH_2$), 1.95 – 1.99 (4H, m, $CH_2$), 1.78 (2H, p, J = 7.4 Hz, $CH_2$), 1.58 – 1.64 (2H, m, $CH_2$), 1.35 – 1.45 (10H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) (M+1) m/z: 211.1, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{29}H_{35}Cl_2N_3O$: 511.21572, found: 511.22220

# General Procedure for the Synthesis of Compounds 3a–3h

All new compounds were dissolved (2a-2h) in methanol and HCl/ether was added. After 24 h precipitates had formed and were isolated by filtration and dried. In this procedure, the 3a–3h compounds were obtained. Their physical and spectral data are listed below.

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]benzamide hydrochloride (3a)

Compound 3a: Yield: 40%; white solid; mp 238–240 ºC; FTIR (ATR) v ($cm^{-1}$): 759.8; 1246.0; 1317.2; 1456.7; 1562.7; 2939.4; 3204.1; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 13.52 (1H, s, Ar), 8.94 (1H, t, J = 5.5 Hz, Ar), 8.47 (1H, d, J = 8.6 Hz, Ar), 7.87 (1H, d, J = 7.2 Hz, Ar), 7.84 (1H, s, Ar), 7.83 (1H, s, Ar), 7.70 (1H, s, Ar), 7.60 (1H, t, J = 8.3 Hz, Ar), 4.09 (2H, q, J = 5.8 Hz, $CH_2$), 3.64 (2H, q, J = 5.8 Hz, $CH_2$), 2.96 (2H, t, J = 5.4 Hz, $CH_2$), 2.69 (2H, d, J = 5.4 Hz, 3H), 2.05 – 1.97 (m, 0H), 1.85 – 1.79 (m, 6H), (protons of NH groups invisible); MS (ESI) m/z: 215.9, 199.1, 172.9; MS-HR (ESI) calcd for $C_{22}H_{21}Cl_2N_3O$: 413.10617 (without HCl); found: 413.10649

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]benzamide hydrochloride (3b)

Compound 3b: Yield: 36%; white solid; mp 141–143 ºC; FTIR (ATR) v ($cm^{-1}$): 754.5; 1266.8; 1317.0; 1447.7; 1562.4; 2940.2; 3201.0; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.48 (s, 7H), 8.80 (t, J = 5.6 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.71 – 7.72 (2H, m, Ar), 7.48 (t, J = 8.3 Hz, 1H), 3.91 (2H, q, J = 6.4 Hz, $CH_2$), 3.29 – 3.32 (2H, m, $CH_2$), 2.88 – 2.94 (2H, m, $CH_2$), 2.57 – 2.64 (2H, m, $CH_2$), 1.96 (2H, p, J = 6.5 Hz, $CH_2$), 1.70 – 1.80 (4H, m, $CH_2$). ), (protons of NH groups invisible); MS (ESI) m/z: 430.1, 230.0, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{23}H_{23}Cl_2N_3O$: 427.12182 (without HCl); found: 427.12242

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]benzamide hydrochloride (3c)

Compound 3c: Yield: 35%; white solid; mp 114–116 ºC; FTIR (ATR) v ($cm^{-1}$): 758.6; 1230.1; 1317.3; 1456.2; 1576.4; 2879.5; 3202.5; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.35 (1H, s, HCl), 8.65 (1H, t, J = 5.5 Hz, Ar), 8.32 – 8.36 (1H, m, Ar), 7.79 – 7.82 (1H, m, Ar), 7.71 – 7.77 (3H, m, Ar), 7.51 (1H, t, J = 7.6 Hz, Ar), 3.85 (2H, q, J = 6.6 Hz, $CH_2$), 3.23 (2H, q, J = 6.6, 5.8 Hz, $CH_2$), 2.87 – 2.93 (2H, m, $CH_2$), 2.57 – 2.62 (2H, m, $CH_2$), 1.70 – 1.80 (6H, m, $CH_2$), 1.56 (2H, p, J = 6.7 Hz, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 444.1, 253.2, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{24}H_{25}Cl_2N_3O$: 441.13747 (without HCl); found: 441.13737

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]benzamide hydrochloride (3d)

Compound 3d: Yield: 43%; white solid; mp 88–90 ºC; FTIR (ATR) v ($cm^{-1}$): 760.6; 1238.8; 1338.9; 1456.2; 1607.9; 2880.4; 3200.3; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.44 (1H, s, HCl), 8.61 – 8.66 (1H, m, Ar), 8.33 – 8.37 (1H, m, Ar), 7.75 – 7.84 (4H, m, Ar), 7.52 (1H, t, J = 8.3 Hz, Ar), 3.82 (2H, q, J = 6.7 Hz, $CH_2$), 3.21 (2H, q, J = 6.5 Hz, $CH_2$), 2.89 – 2.95 (2H, m, $CH_2$), 2.56 – 2.62 (2H, m, $CH_2$), 1.68 – 1.79 (6H, m, $CH_2$), 1.50 (2H, p, J = 7.1 Hz, $CH_2$), 1.33 (2H, p, J = 7.6, 7.2 Hz, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 456,2, 267.2, 199.1, 1729; MS-HR (ESI): calcd. for $C_{25}H_{27}Cl_2N_3O$: 455.15312 (without HCl); found: 455.15203

## 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) hexyl]benzamide hydrochloride (3e)

Compound 3e: Yield: 45%; white solid; mp 86–87 ºC; FTIR (ATR) v ($cm^{-1}$): 762.5; 1275.1; 1313.8; 1457.2; 2873.5; 3206.1; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.52 (1H, s, HCl), 8.66 (1H, t, J = 5.5 Hz, Ar), 8.33 – 8.37 (1H, m, Ar), 7.79 – 7.83 (3H, m, Ar), 7.74 – 7.76 (1H, m, Ar), 7.51 – 7.55 (1H, m, Ar), 3.81 (2H, q, J = 6.6 Hz, $CH_2$), 3.19 (2H, q, J = 6.8 Hz, $CH_2$), 2.91 – 2.96 (2H, m, $CH_2$), 2.58 – 2.63 (2H, m, $CH_2$), 1.76 – 1.82 (4H, m, $CH_2$), 1.69 (2H, p, J = 7.1 Hz, $CH_2$), 1.47 (2H, p, J = 7.0 Hz, $CH_2$), 1.25 – 1.36 (4H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 430.9, 211.1, 199.1, 171.1; MS-HR (ESI): calcd. for $C_{26}H_{29}Cl_2N_3O$: 469.16877 (without HCl); found: 469.16943

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) heptyl]benzamide hydrochloride (3f)

Compound 3f: Yield: 38%; white solid; mp 82–83 ºC; FTIR (ATR) v ($cm^{-1}$): 757.5; 1242.8; 1323.3; 1456.2; 2896.4; 3204.3; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.61 (1H, s, HCl), 8.67 (1H, t, J = 5.6 Hz, Ar), 8.35 (1H, d, J = 8.7 Hz, Ar), 7.80 – 7.85 (3H, m, Ar), 7.75 (1H, t, J = 1.8 Hz, Ar), 7.53 (1H, t, J = 8.3 Hz, Ar), 3.80 (2H, q, J = 6.6 Hz, $CH_2$), 3.18 (2H, q, J = 6.7 Hz, $CH_2$), 2.92 – 2.97 (2H, m, $CH_2$), 2.57 – 2.62 (2H, m, $CH_2$), 1.75 – 1.80 (4H, m, $CH_2$), 1.71 – 1.64 (2H, m, $CH_2$), 1.45 (2H, p, J = 6.8 Hz, $CH_2$), 1.22 – 1.32 (6H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 430.9, 211.1, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{27}H_{31}Cl_2N_3O$: 483.18442 (without HCl); found: 483.18360

### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) octyl]benzamide hydrochloride (3g)

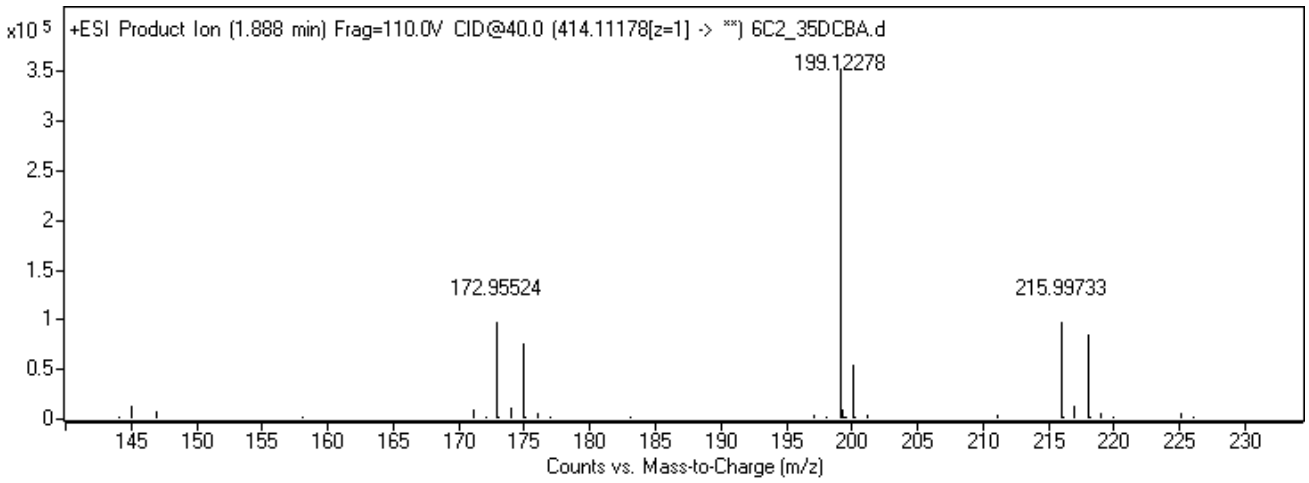
Compound 3g: Yield: 32%; white solid; mp 71–72 ºC; FTIR (ATR) v ($cm^{-1}$): 758.6; 1268.1; 1334.5; 1454.0; 2882.2; 3203.0; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.54 (1H, s, HCl), 8.66 (1H, t, J = 5.5 Hz, Ar), 8.35 (1H, d, J = 8.7 Hz, Ar), 7.80 – 7.83 (3H, m, Ar), 7.75 (1H, t, J = 1.9 Hz, Ar), 7.51 – 7.55 (1H, m, Ar), 3.80 (2H, q, J = 6.6 Hz, $CH_2$), 3.18 (2H, q, J = 6.7 Hz, $CH_2$), 2.92 – 2.96 (2H, m, $CH_2$), 2.58 – 2.62 (2H, m, $CH_2$), 1.77 – 1.80 (4H, m, $CH_2$), 1.68 (2H, p, J = 7.4 Hz, $CH_2$), 1.45 (2H, p, J = 6.5, 5.7 Hz, $CH_2$), 1.21 – 1.32 (8H. m, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 430.9, 211.1, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{28}H_{33}Cl_2N_3O$: 497.20007 (without HCl); found: 497.19920

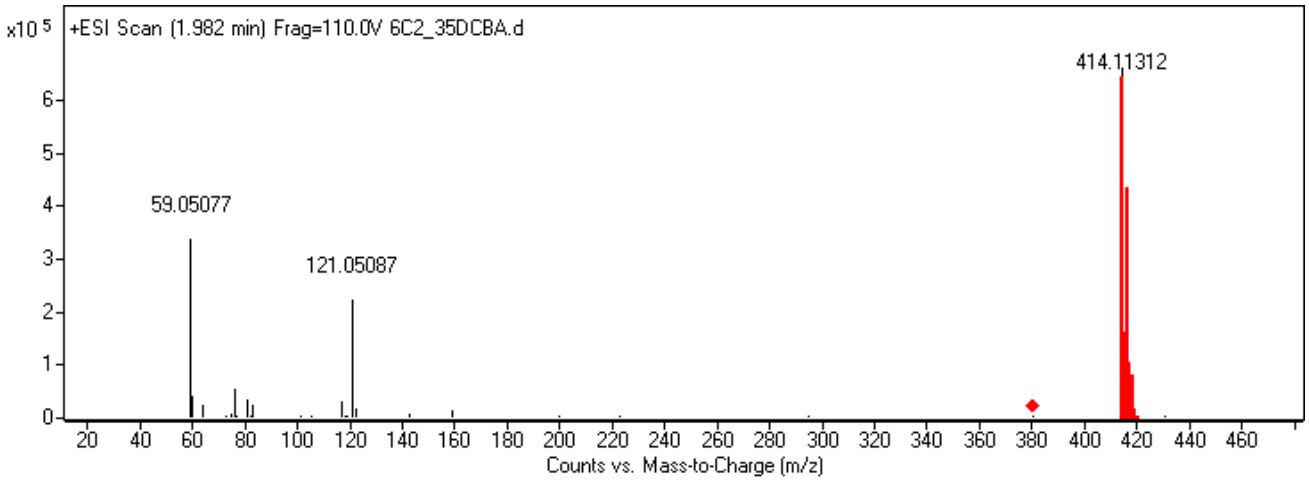
### 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) nonyl]benzamide hydrochloride (3h)

Compound 3h: Yield: 35%; white solid; mp 62–63 ºC; FTIR (ATR) v ($cm^{-1}$): 755.4; 1246.5; 1320.2; 1457.2; 2878.5; 3205.1; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.41 (1H, s, HCl), 8.64 (1H, t, J = 5.4 Hz, Ar), 8.32 – 8.36 (1H, m, Ar), 7.78 – 7.84 (3H, m, Ar), 7.75 (1H, t, J = 1.9 Hz, Ar), 7.53 (1H, t, J = 8.3 Hz, Ar), 3.80 (2H, q, J = 6.8 Hz, $CH_2$), 3.19 (2H, q, J = 6.9, 6.5 Hz, $CH_2$), 2.91 – 2.96 (2H, m, $CH_2$), 2.57 – 2.63 (2H, m, $CH_2$), 1.77 – 1.81 (4H, m, $CH_2$), 1.67 (2H, p, J = 7.5 Hz, $CH_2$), 1.44 (2H, p, J = 7.5, 6.9 Hz, $CH_2$), 1.20 – 1.31 (10H, m, $CH_2$), (protons of NH groups invisible); MS (ESI) m/z: 430.9, 211.1, 199.1, 172.9; MS-HR (ESI): calcd. for $C_{29}H_{35}Cl_2N_3O$: 511.21572 (without HCl); found: 511.2148

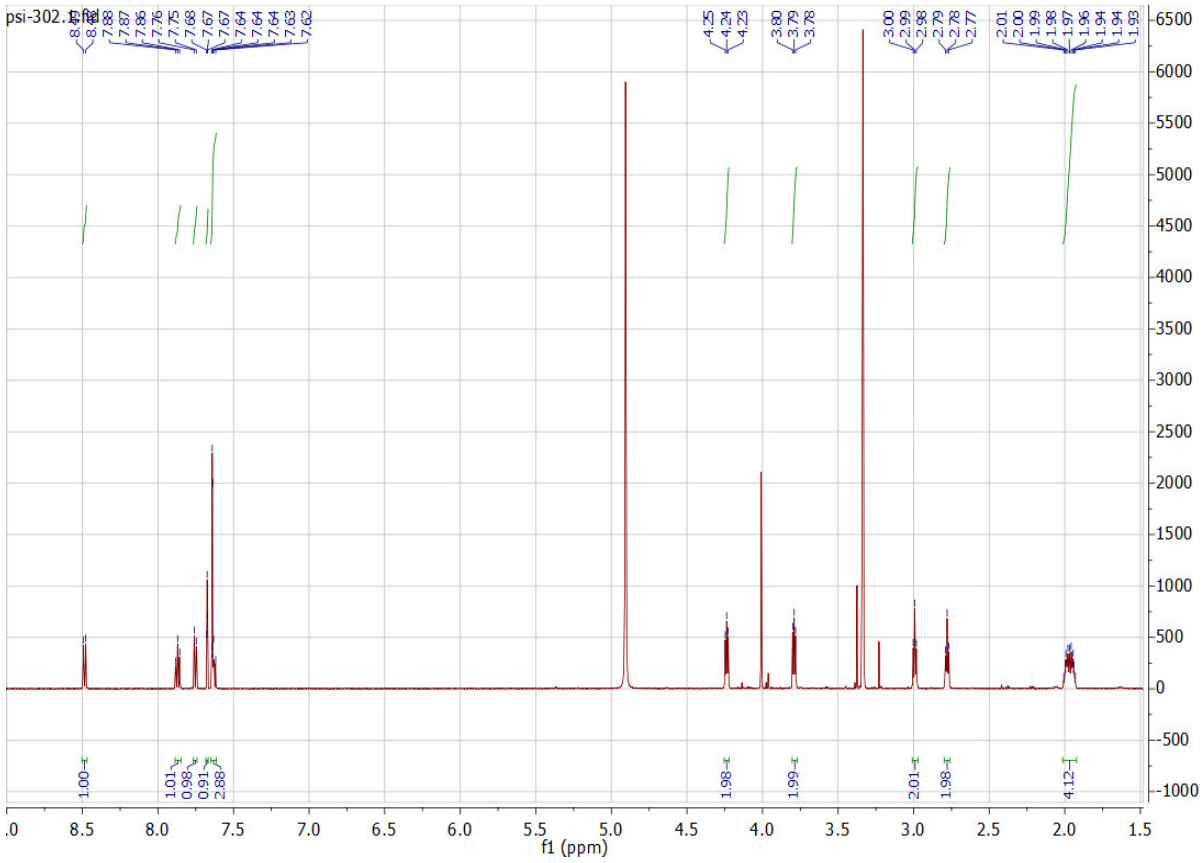
## Spectral Data

### MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]benzamide (2a)

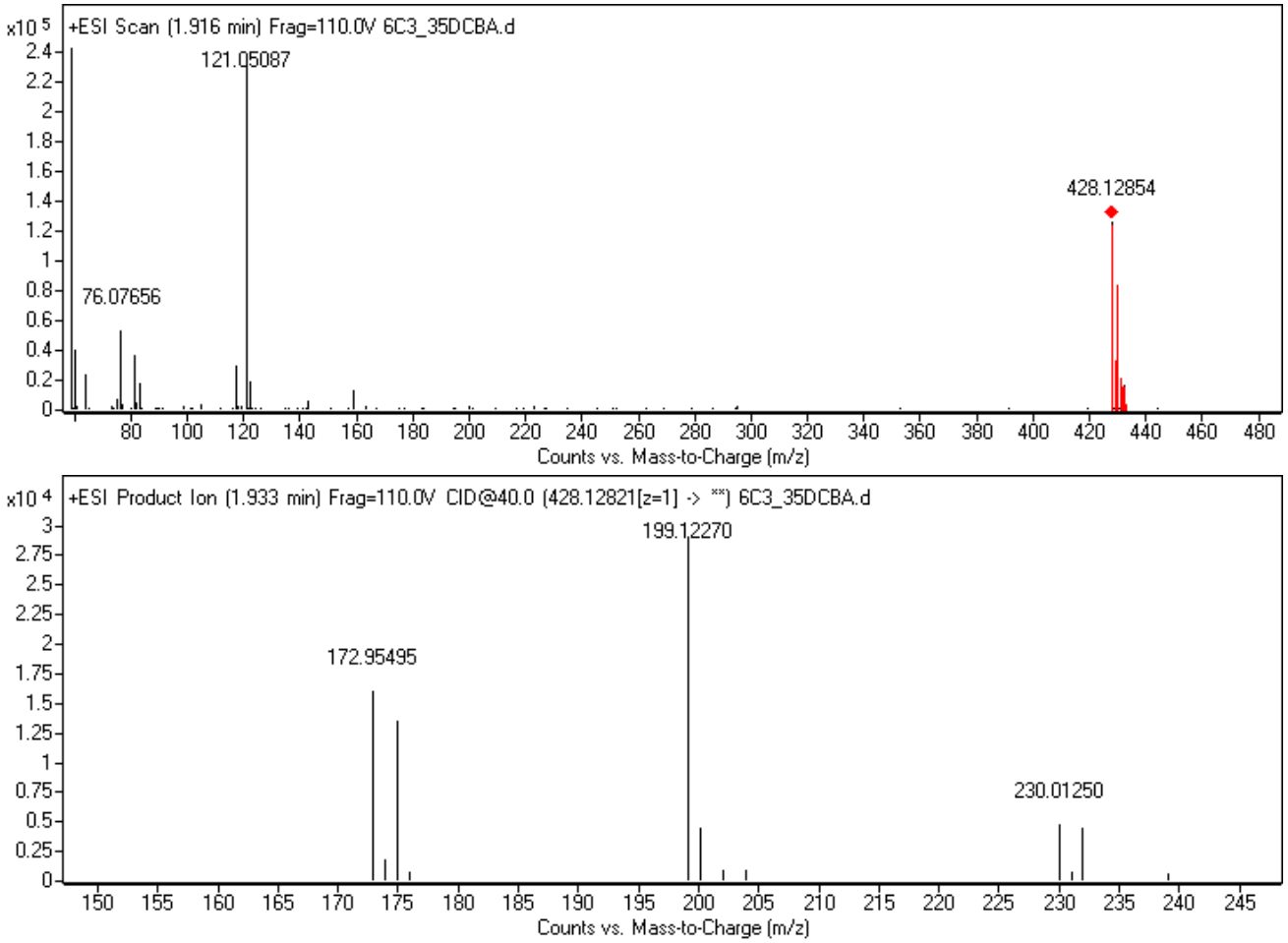




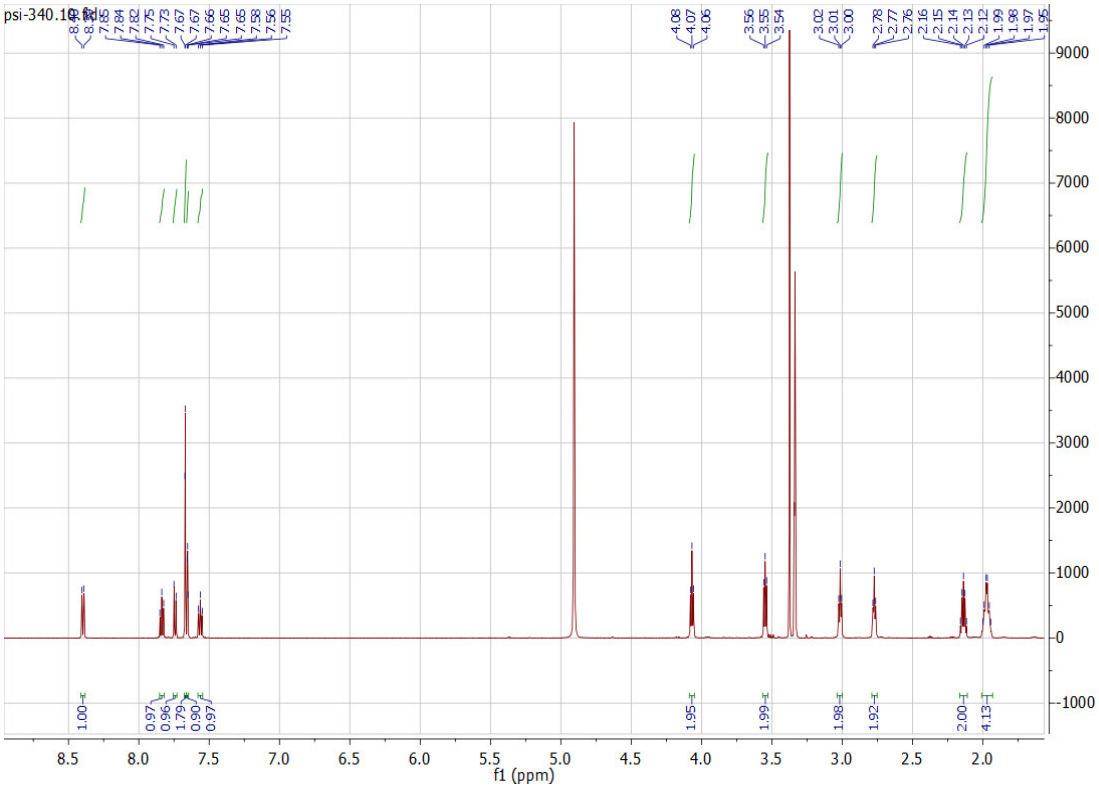

$^{1}$HNMR spectra for
3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)ethyl]benzamide (2a)



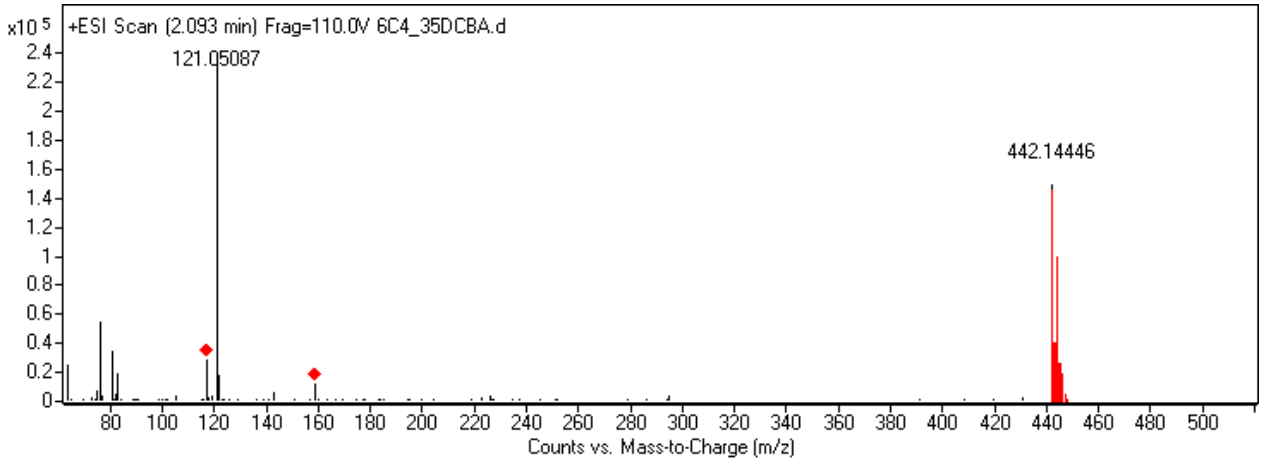
MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]benzamide (2b)

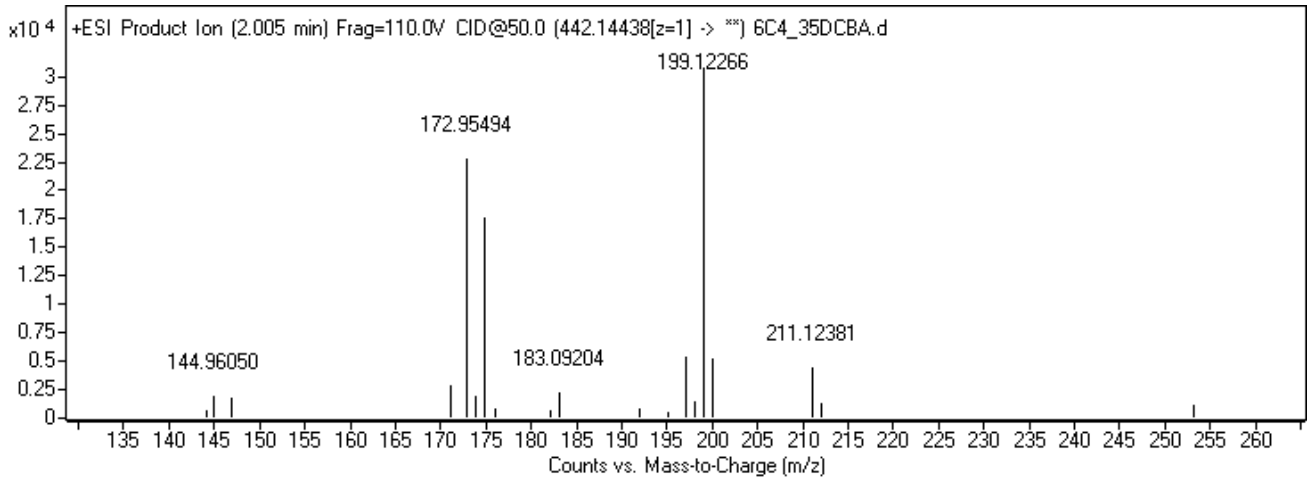


$^{1}$HNMR spectra for
3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)propyl]benzamide (2b)

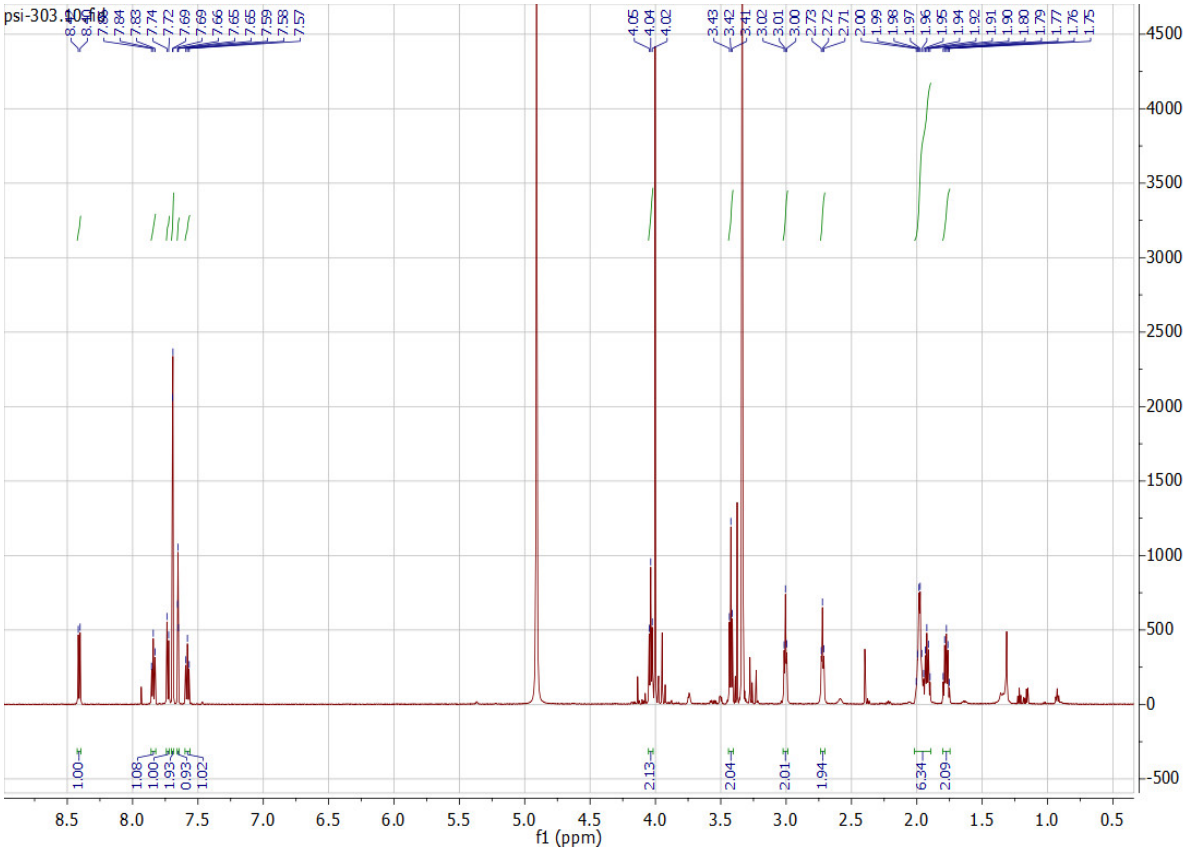


MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]benzamide (2c)

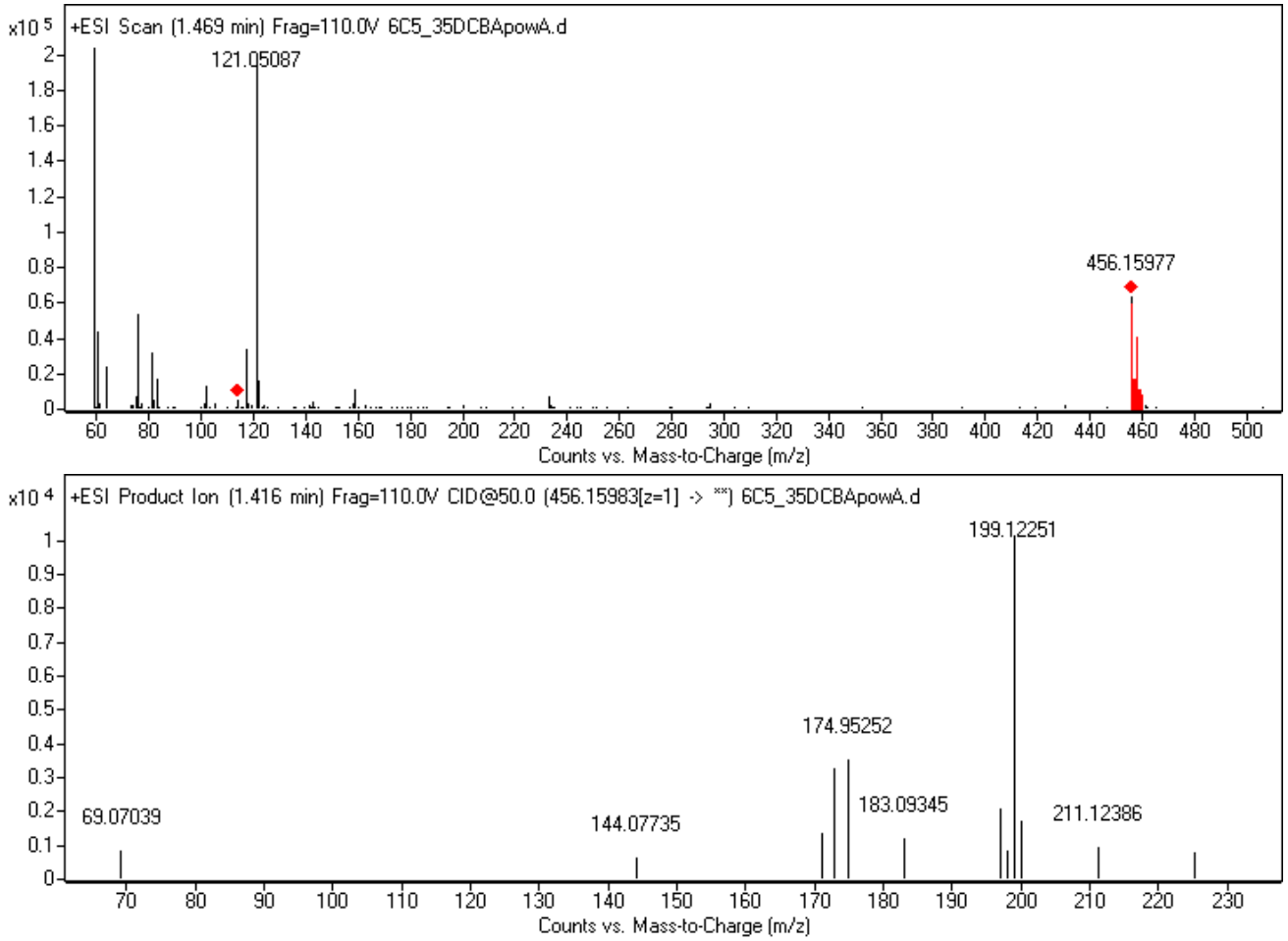


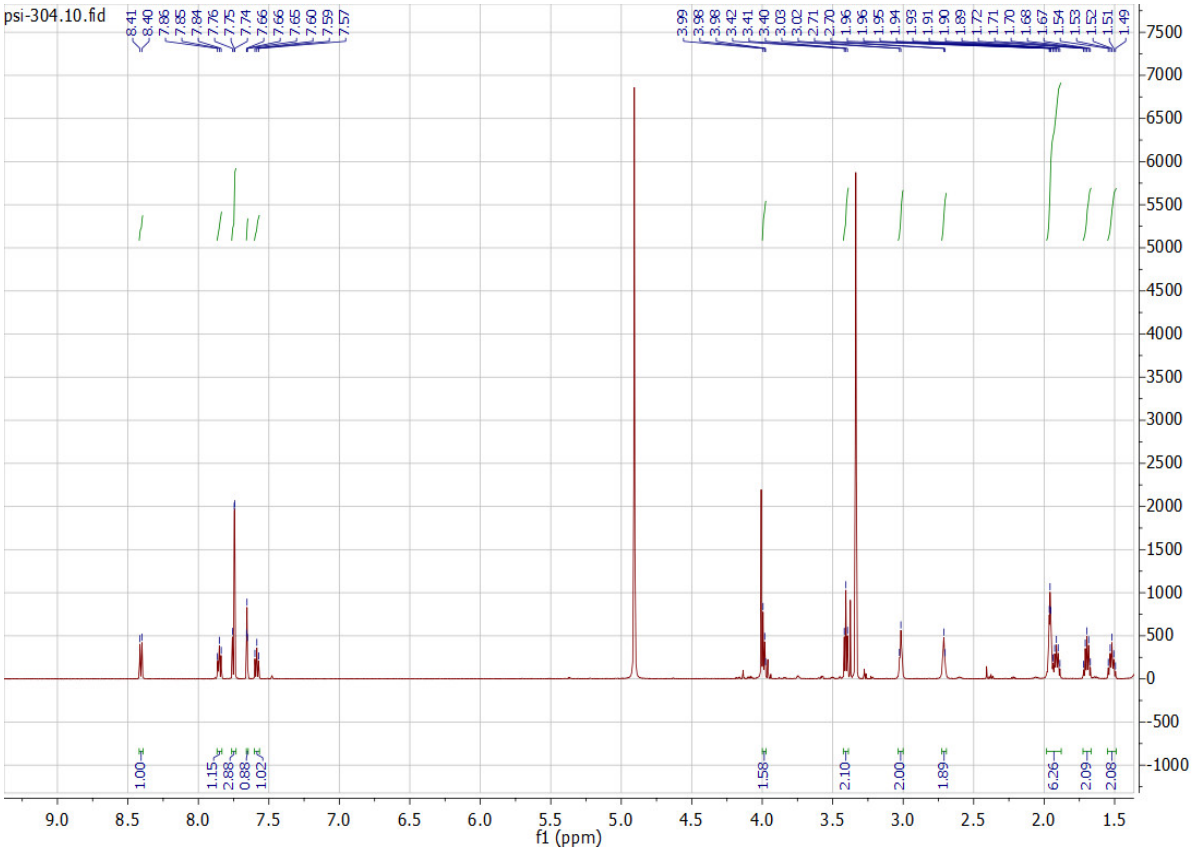
$^{1}$HNMR spectra for
3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)butyl]benzamide (2c)



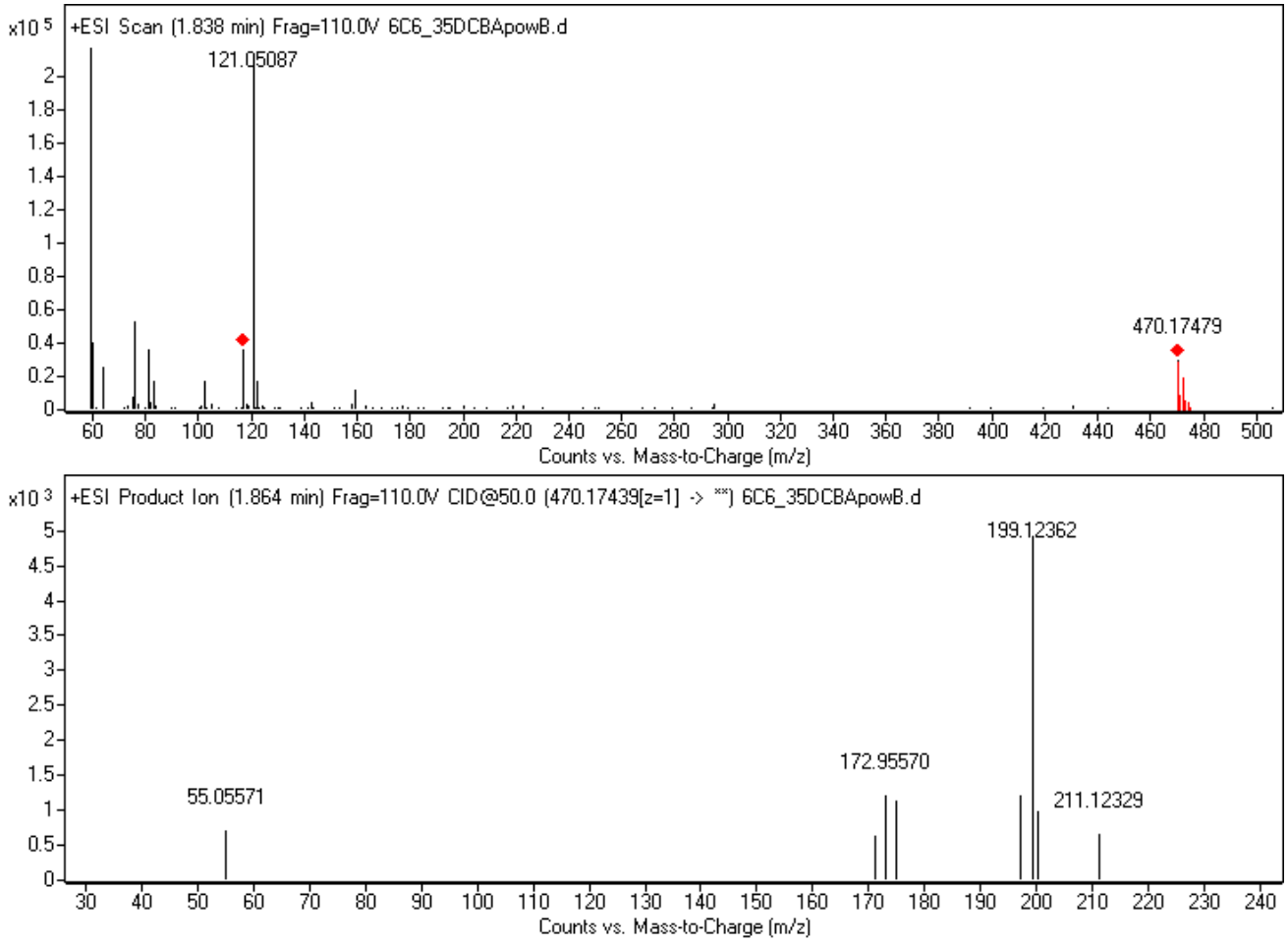
MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]benzamide (2d)



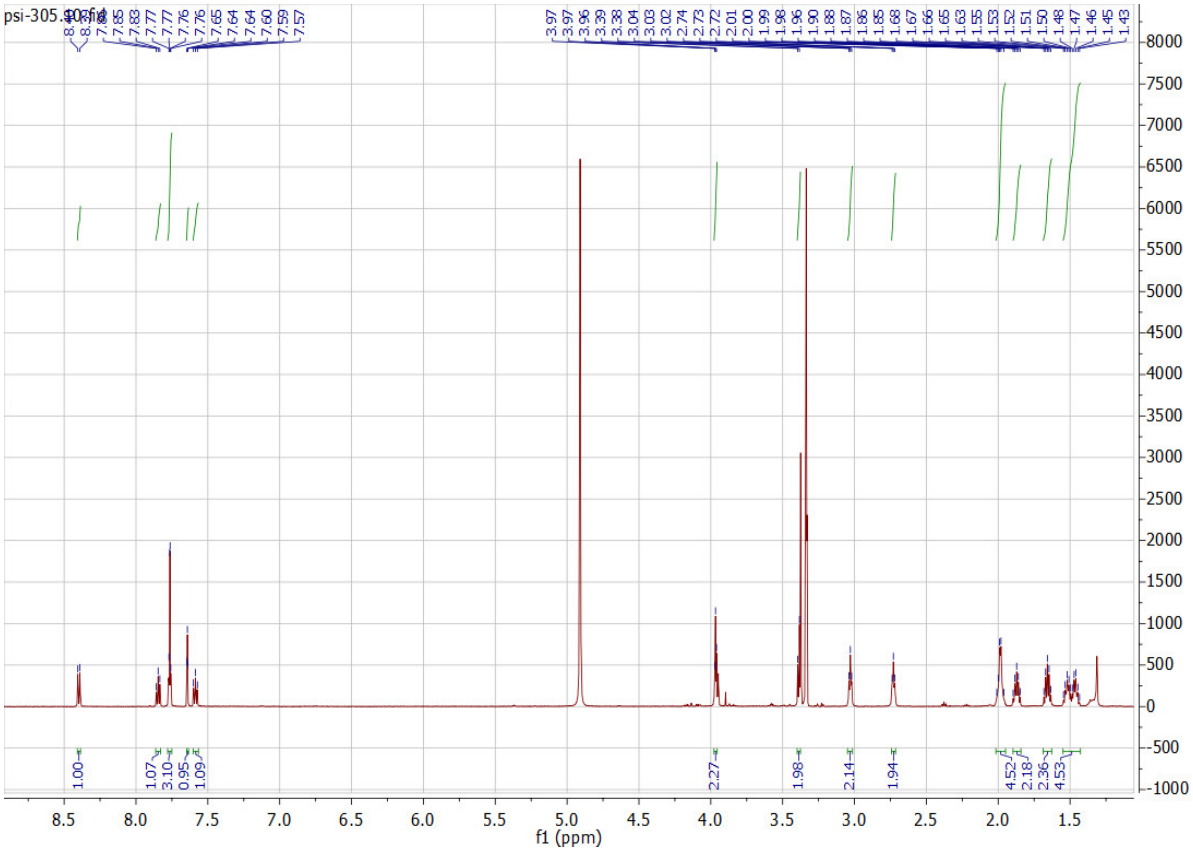
$^{1}$HNMR spectra for
3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino)pentyl]benzamide (2d)



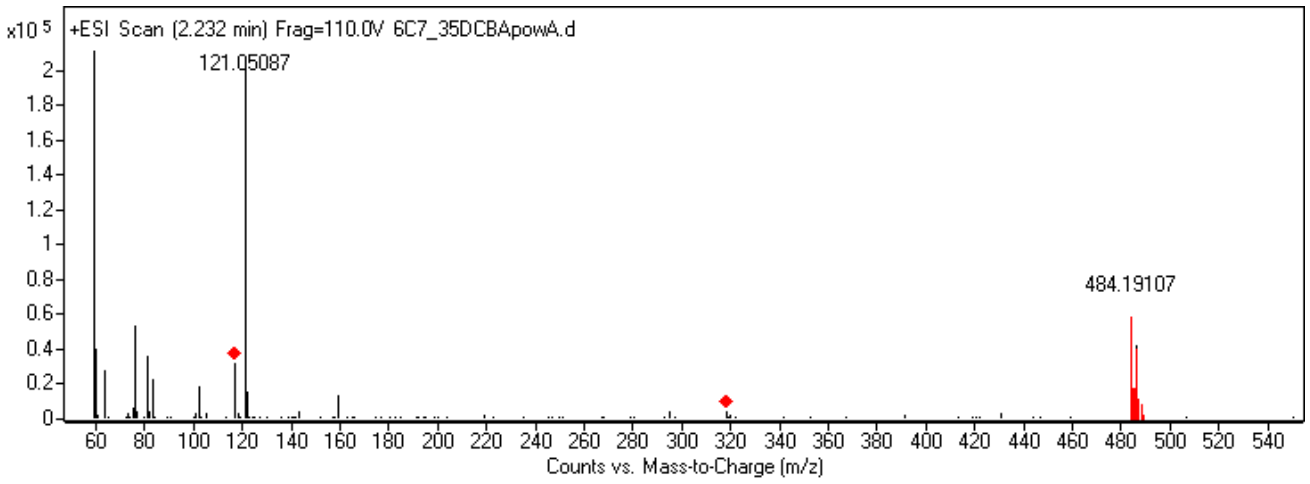
MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) hexyl]benzamide (2e)

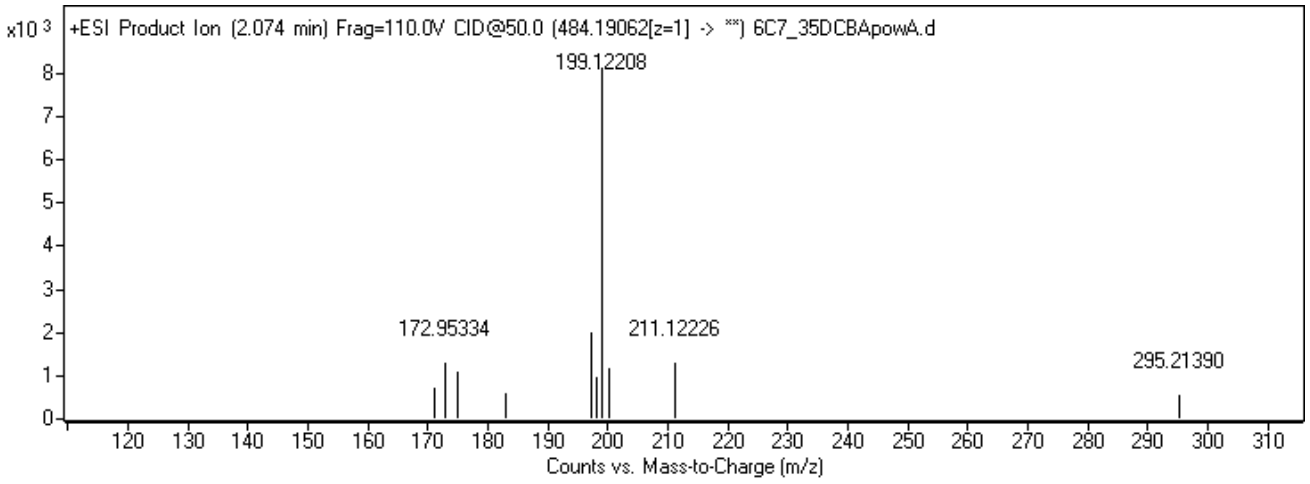


[1]HNMR spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) hexyl]benzamide (2e)

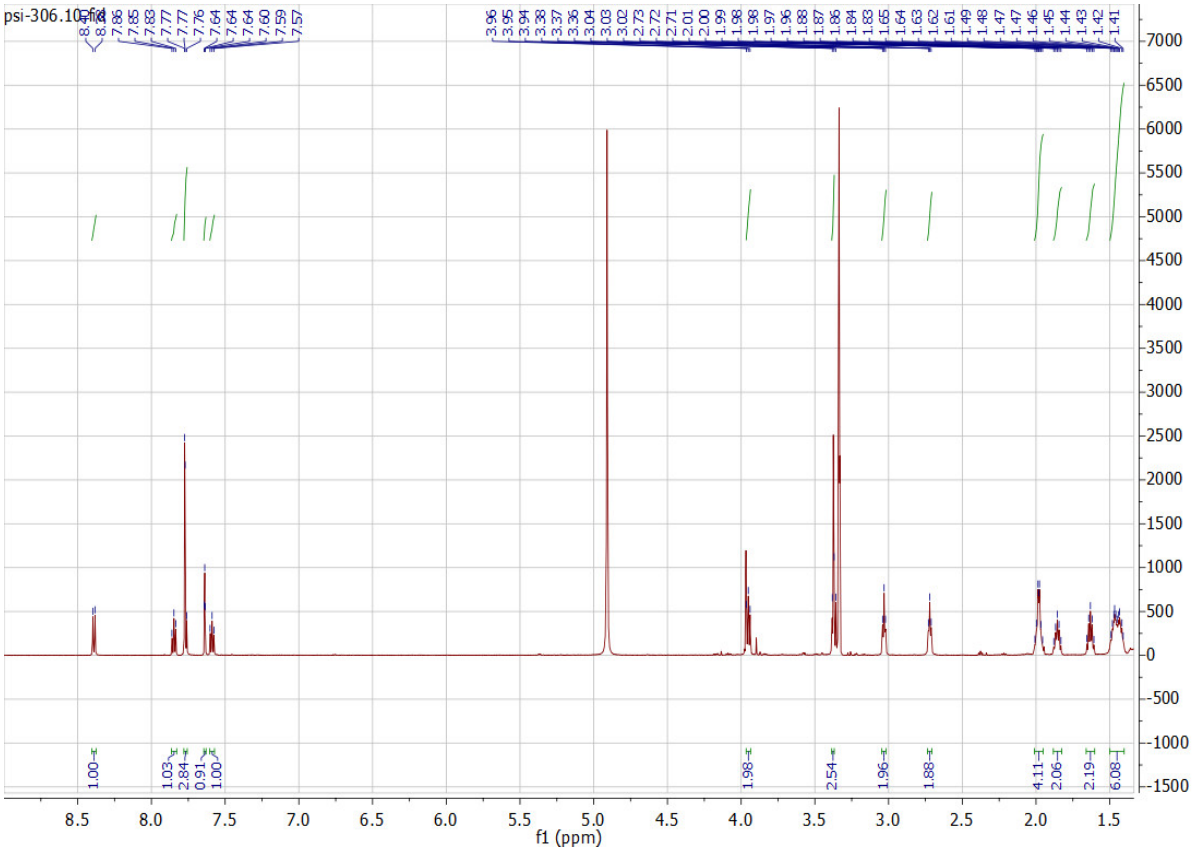


MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) heptyl]benzamide (2f)

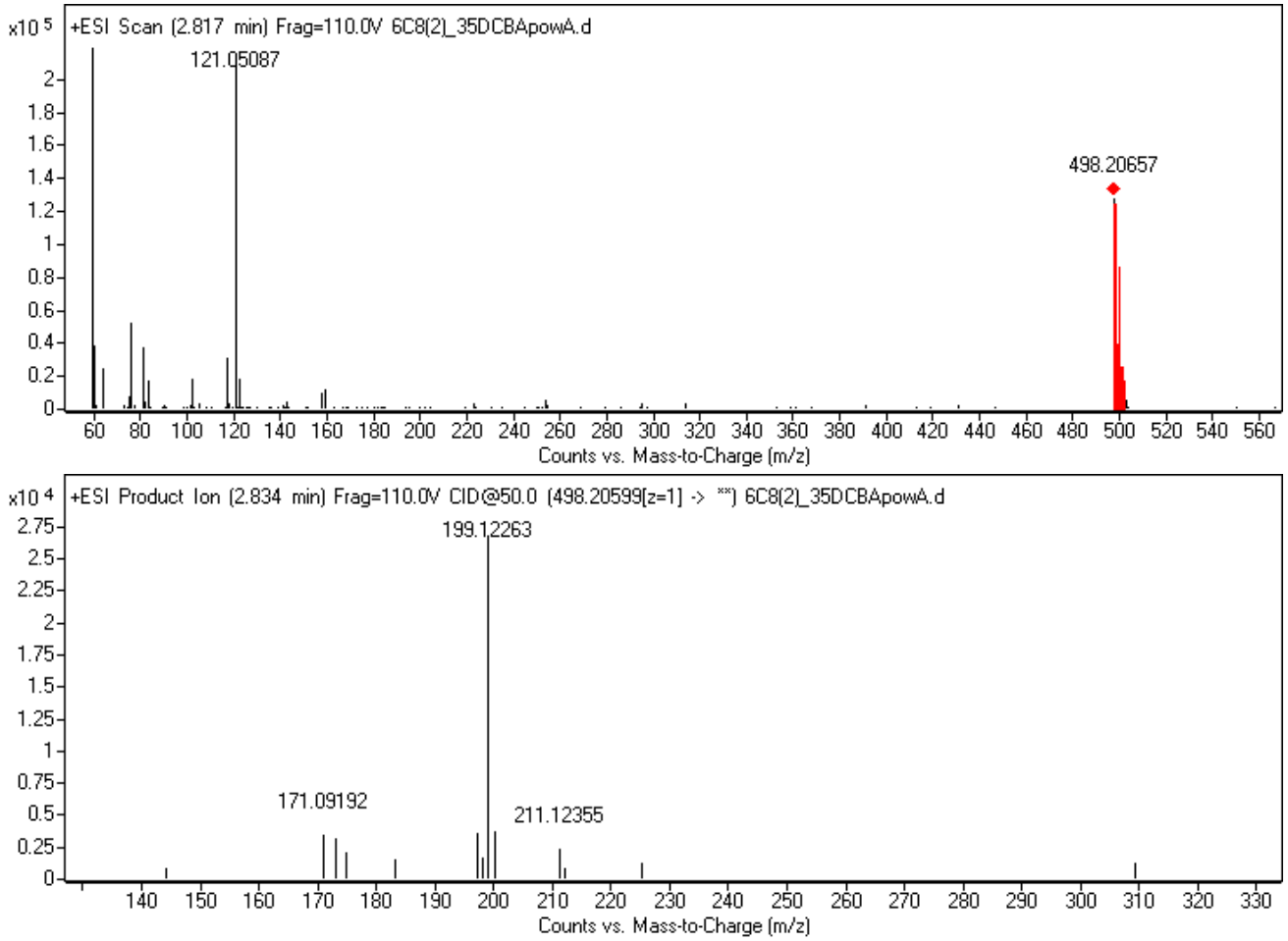


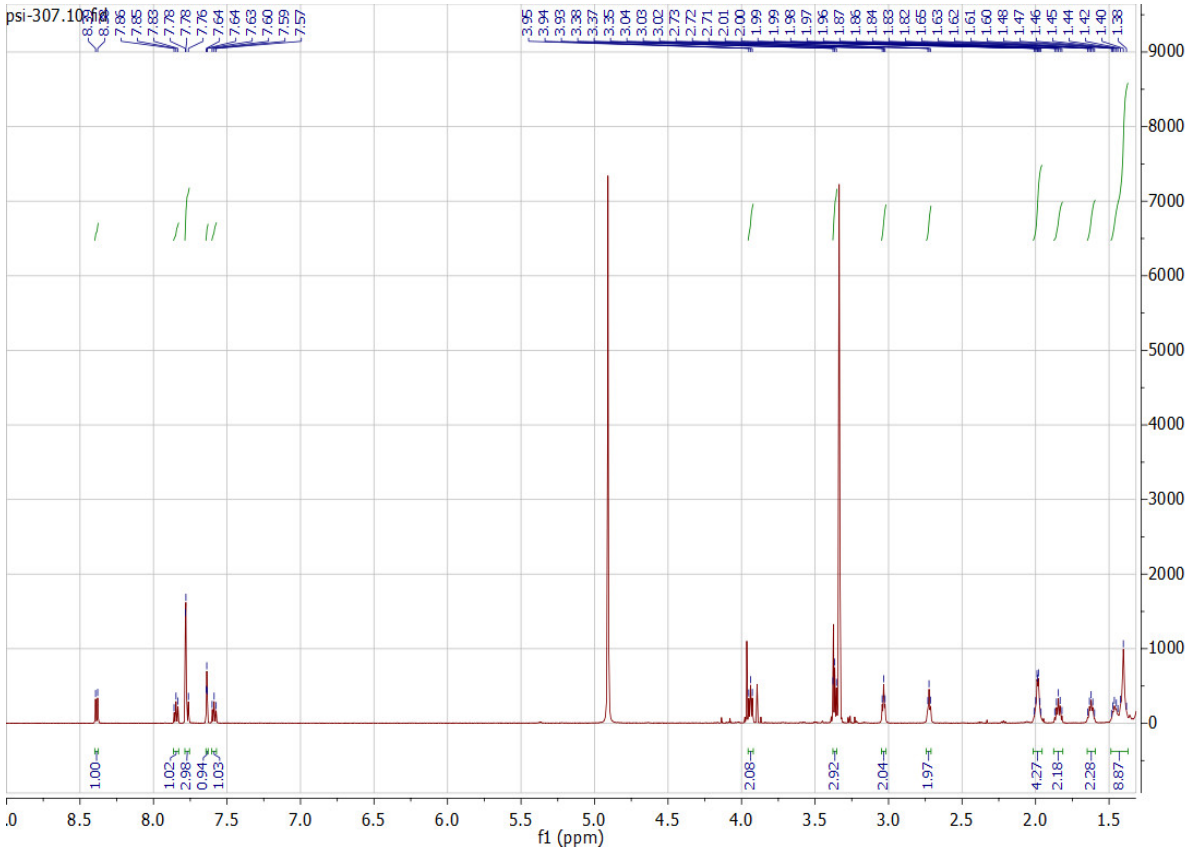
[1]HNMR spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) heptyl]benzamide (2f)



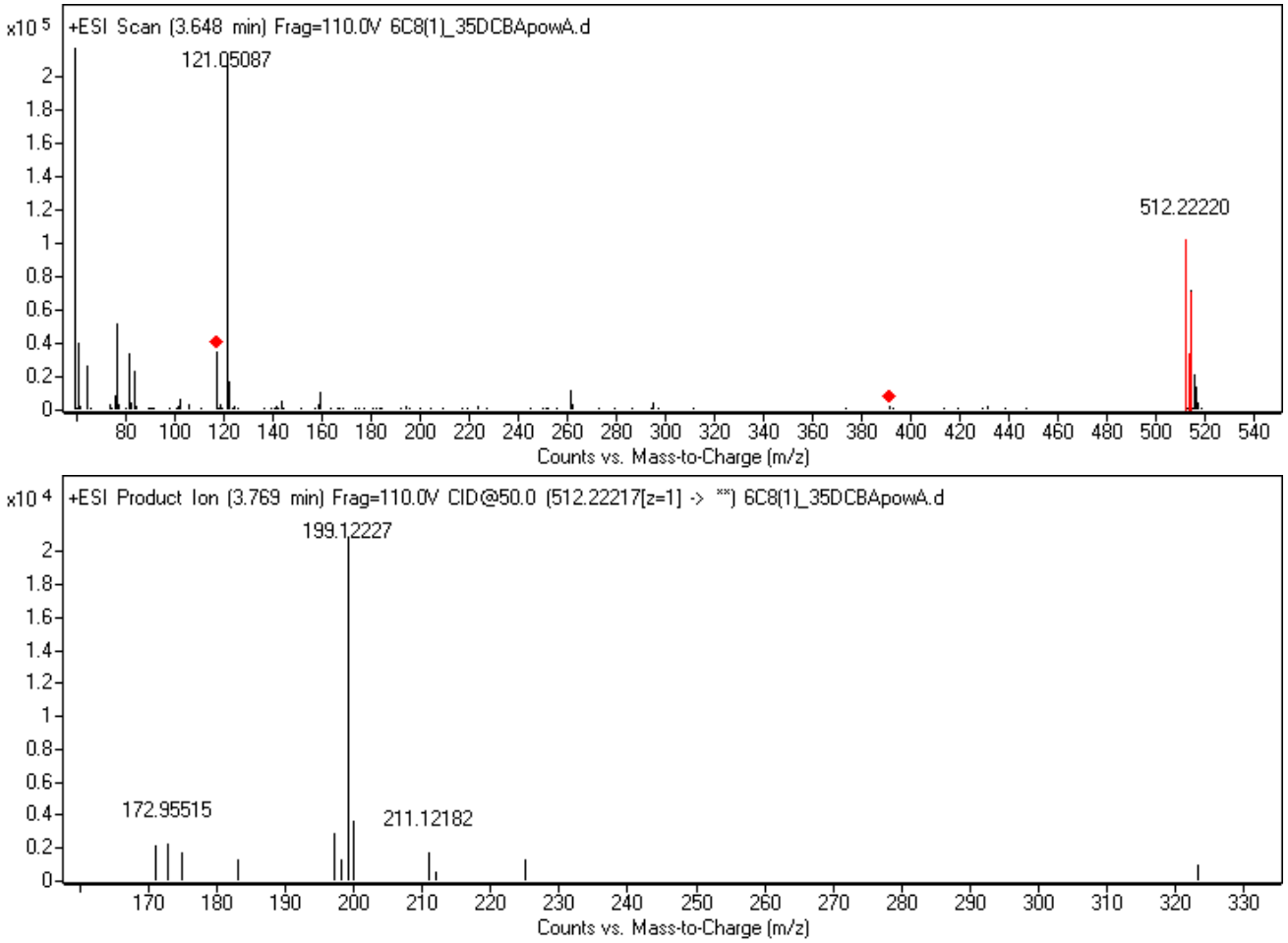
MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) octyl]benzamide (2g)



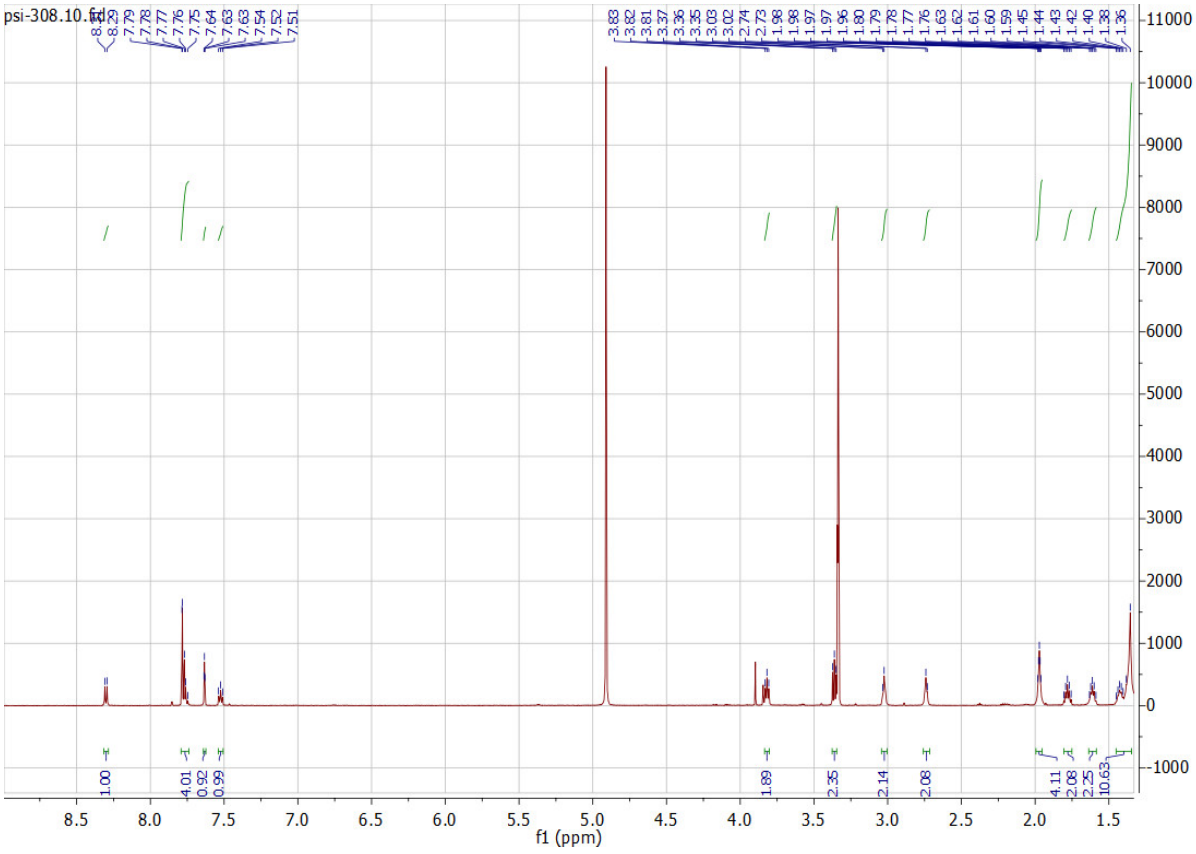
$^{1}$HNMR spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) octyl]benzamide (2g)



MS spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) nonyl]benzamide (2h)



[1]HNMR spectra for 3,5-dichloro-N-[2-(1,2,3,4-tetrahydroacridin-9-ylamino) nonyl]benzamide (2h)



# Molecular Modeling - figures with binding modes of selected compounds

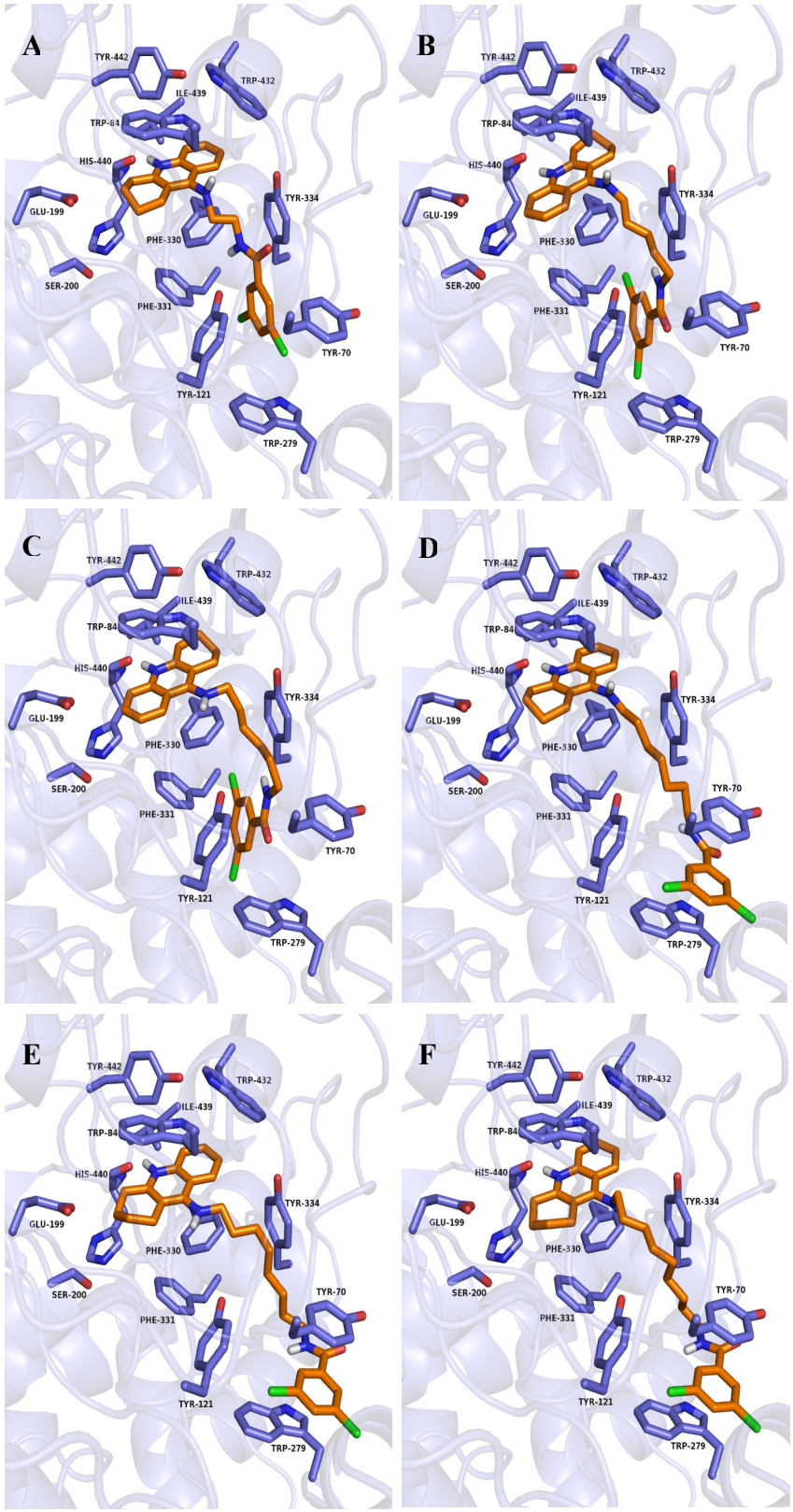



**Figure 1S.** Binding mode of compound **3a (A), 3d (B), 3e (C), 3f (D), 3g (E)** and **3h (F)** within acetylcholinesterase.

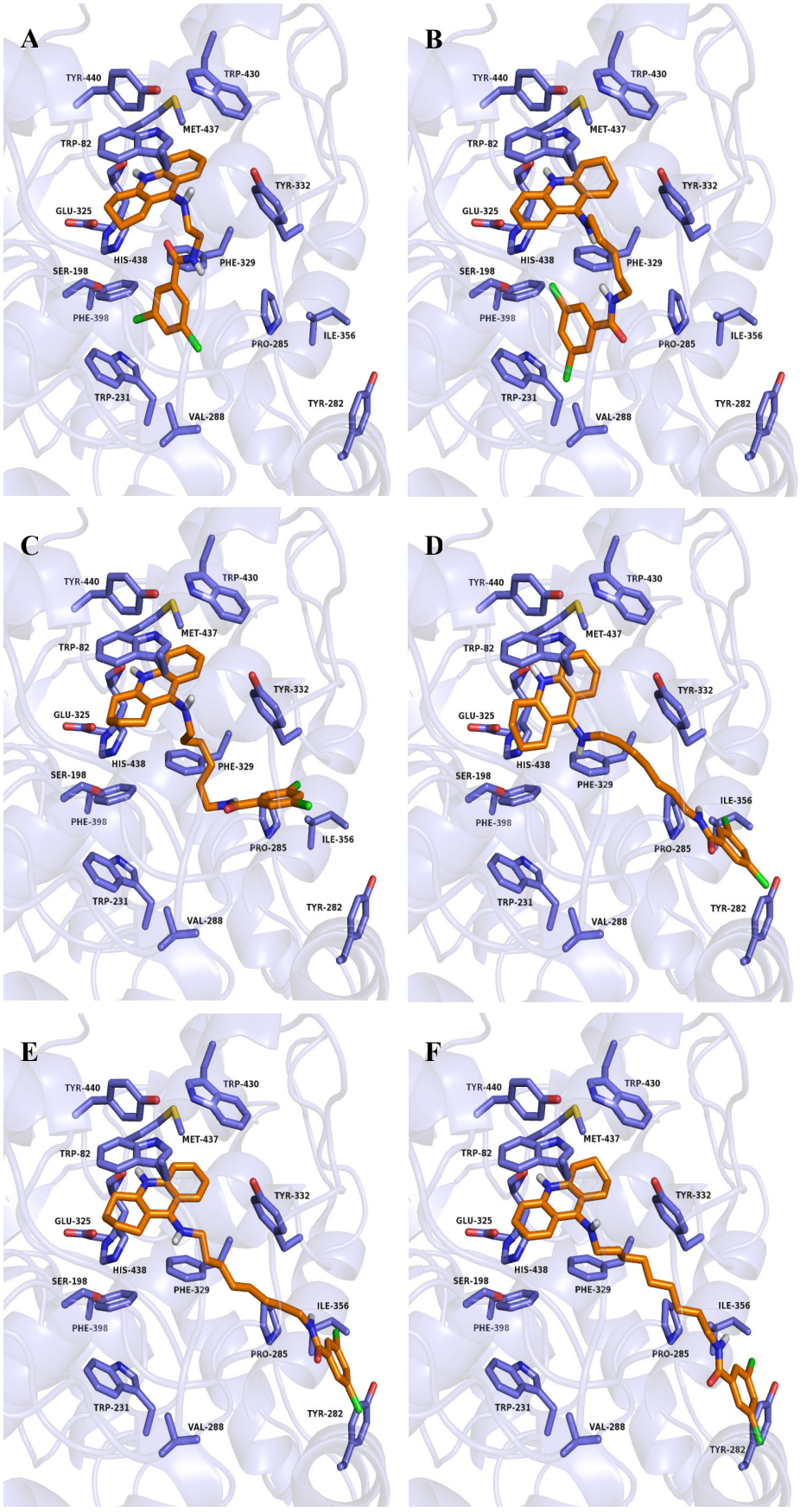



**Figure 2S.** Binding mode of compound **3a (A), 3d (B), 3e (C), 3f (D), 3g (E)** and **3h (F)** within butyrylcholinesterase.