CHAPTER 5

SYNTHESIS OF

4-(AMINOMETHYL)QUINOLIN-2(1*H*)-ONE

DERIVATIVES AS ANTI-CANCER AGENTS

5.1 Introduction

Over the past few decades with the advances in medicine, life expectancy of individuals has increased many folds, yet cancer is still most dreaded disease with highest mortality rate, ranked after the cardiovascular diseases. The biggest challenge faced by the health industry lies in the treatment of cancer. Cancer is curable if detected at an early stage or else it proves to be fatal. Uncontrolled cell differentiation and growth in any part of the body leads to cancer. From the medicinal chemistry point of view, the drug administered to patients suffering from cancer should cause selective induction of apoptosis in cancerous cells while leaving normal cells unaffected. Thus safe yet selective drug for the treatment of cancer is the need of the hour.

Various natural and synthetic molecules are reported to exhibit anti-cancer activity. Quinolones have promising pharmacological potential due to its drug-like properties and structural similarity to some specific targets and hence have gained importance. 2-Quinolone (carbostyril, 1-azacoumarin) are lactams whose derivatives are widely studied for their applications in the field of chemistry and biology. Joseph *et al* reported 3-aryl-2-quinolone derivatives as anti-tumor agents [1].

7-amino-4-methyl-2[1H]-quinolinone derivatives have been reported to act as antenna molecules which transfers the energy absorbed from the light to the lanthanide ions on the complex thereby rendering the complex fluorescent [2].

Substituted 4-aminomethyl-2[1H]-quinolone derivatives and various quinolone linked with coumarins via ether linkage have been studied for their anti-microbial and analgesic activities [3, 4].

Various 2-quinolone derivatives have been reported as inducible nitric oxide synthase (iNOS) inhibitors and potent anti-platelet agents [5, 6].

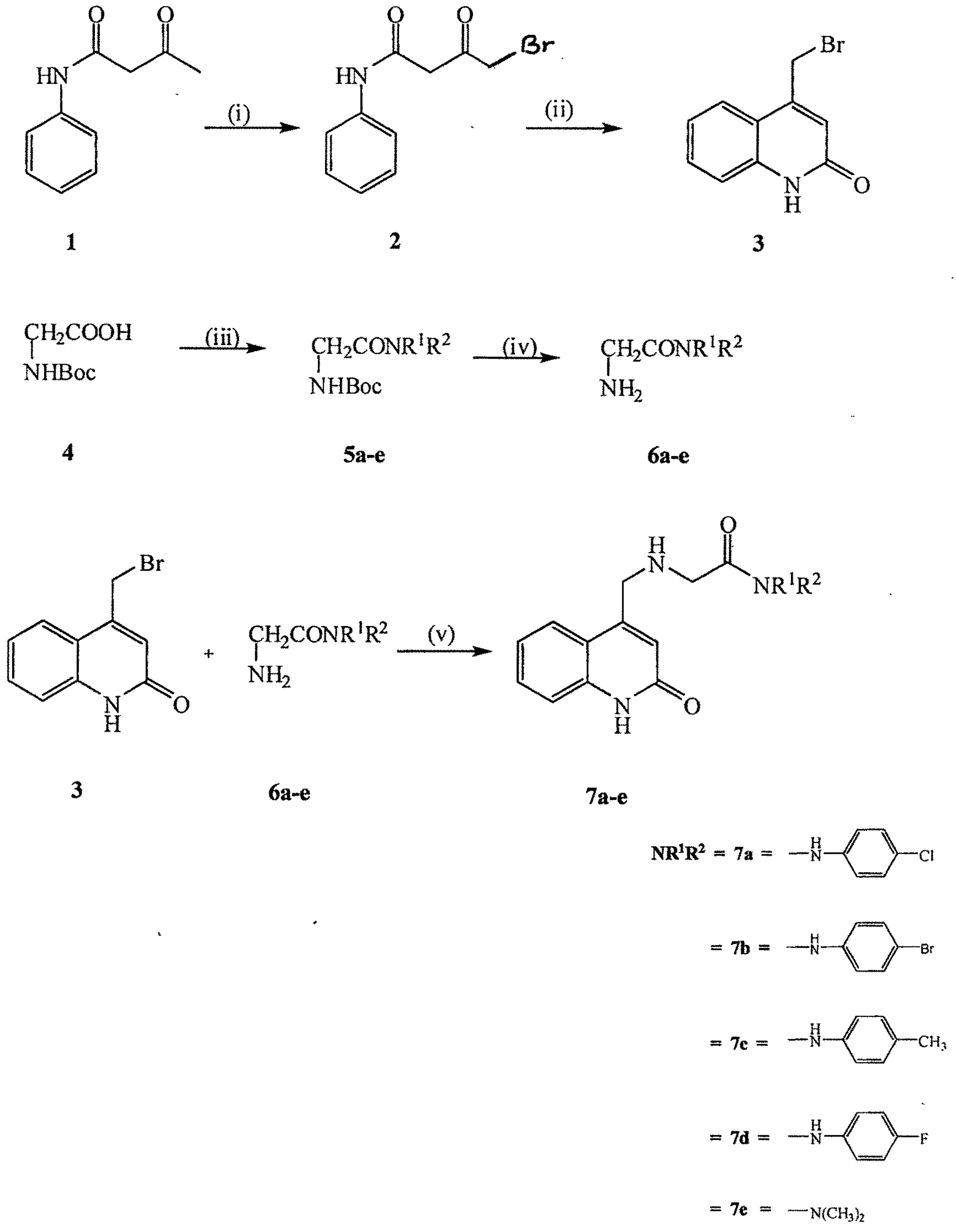
Recently, 7-amino-4-methyl-2[1H]-quinolinone derivatives have been reported to show anti-cancer activity [6, 7]. Present work has been designed for the synthesis of substituted 4-aminomethyl-2[1H]-quinolinone derivatives with application in the treatment of cancer. The molecules thus synthesized have been subjected to *in-vitro* anti-cancer activity of against A549 cell line

5.2 Results and Discussion

5.2.1 Chemistry

Bromination of acetoacetanilide **1** using bromine in glacial acetic acid gave bromoacetoacetanilide **2** which cyclizes on reaction with concentrated sulphuric acid (conc. H_2SO_4) to give 4-(bromomethyl)quinolin-2[1H]-one **3**. The structure of compound **3** was confirmed from its IR spectrum (Figure 5.2.1) which shows a strong band at 1653 cm^{-1} for the lactam carbonyl and its ^1H NMR spectrum (Figure 5.2.2) shows two singlets, one at δ 4.90 for the methylene protons at C-4 and another at δ 11.86 for the –NH lactam proton. Figure 5.2.3 and Figure 5.2.4 shows the ^{13}C NMR and ESI-MS spectra of **3** respectively. Presence of M^+ and $[M+2]^+$ peak if equal intensity confirms the presence of bromine in the structure of **3.**

Commercially available boc-protected glycine **4** was reacted with various amines in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), 4-dimethylaminopyridine (DMAP) to yield corresponding C-substituted amide derivatives of glycine **5a-e** as shown in Scheme 5.1.



Scheme 5.1: Reagents: (i) Br_2, CH_3COOH, I_2; (ii) conc.H_2SO_4; (iii) EDCI, HOBt, DMAP, various amines, DCM; (iv) 10% TFA in DCM; (v) $LiOH.H_2O$, DMF.

The IR spectrum of **5a** (Figure 5.3.1) shows two bands at 1681 and 1673 cm^{-1} for the amide carbonyl while in the ^{1}H NMR spectrum (Figure 5.3.2) a peak at δ 3.71 for the methylene protons of glycine and two doublets at δ 7.36 and 7.61 for the aromatic protons and molecular ion peak at *m/z* 307.0 [M+Na]$^+$ in the ESI-MS spectrum (Figure 5.3.4) confirms the formation of **5a** Figures 5.4.1 to 5.8.4 shows the IR, ^{1}H NMR, ^{13}C NMR and ESI-MS spectra of compounds **5b-f**. Deprotection of boc-protected glycine amides **5a-e** by trifluoroacetic acid (TFA) gave corresponding free bases **6a-e** which were not isolated and used for subsequent reaction after concentration. Further reaction of **3** with various free bases **6a-e** was carried out using various bases. Initially, organic bases like triethyl amine (TEA) and diisopropyl ethylamine (DIPEA) and later inorganic bases like potassium carbonate (K_2CO_3) were used from 3 to 10 equivalents and later effect on the progress of reaction by change of solvent, temperature were also experimented but all the reactions failed. Later, the reaction succeeded by use of a very strong inorganic base lithium hydroxide monohydrate and that too at room temperature. Thus by the use of strong base, gave the desired substituted 4-aminomethyl-2[1H]-quinolinone derivatives **7a-e** as shown in Scheme 5.1. The IR spectrum (Figure 5.9.1) of **7a** shows two strong bands at 3336 and 3260 cm^{-1} for –NH stretching vibrations of amide group and a strong band at 1660 cm^{-1} for the amide carbonyl group. The ^{1}H NMR spectrum (Figure 5.9.2) of **7a** shows two singlets at δ 2.9 and 3.9 for the –CH_2 groups, three singlets at δ 6.58, 9.90 and 11.60 indicates three –NH protons and the remaining aromatic protons were observed from δ 7.18-7.82 confirmed the structure of **7a.** Figures 5.9.3 and 5.9.4 shows the ^{13}C NMR and ESI-MS spectra of **7a**, thus confirms its formation.

An interesting observation under similar reaction conditions was disubstitution of the glycyl amino –NH_2 group by **3** thereby leading to formation of **7f** (Figure 5.1) which due to its poor solubility was not evaluated for its anti-cancer activity. The structure of **7f** was confirmed by its IR, spectrum (Figure 5.10.1) which shows bands at 3414 cm^{-1} for –NH of amide group and a strong band at 1659 cm^{-1} indicating lactam carbonyl group. The ^1H NMR spectrum (Figure 5.10.2) shows multiplet from δ 1.70-1.74 for four protons (C2-C3) and other multiplets at δ 3.15-3.50 for the remaining four protons (C1, C4) of the pyrrolidide group; a singlet δ 4.04 indicates the two sets of –CH_2 protons attached to the quinolinone system. And multiplets from δ 6.53 to 7.87 for the ten aromatic protons thus confirmed the formation of disubstituted product **7f**. Further, ESI-MS spectrum (Figure 5.10.4) of **7f** shows a peak at *m/z* 465 for $[M+Na]^+$ also supports the formation of **7f**.

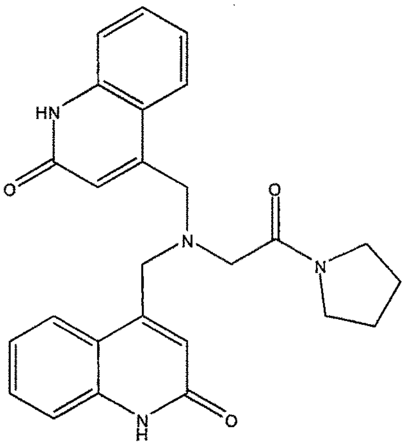


Figure 5.1: Structure of 4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene) diquinolin-2(1H)-one **7f**

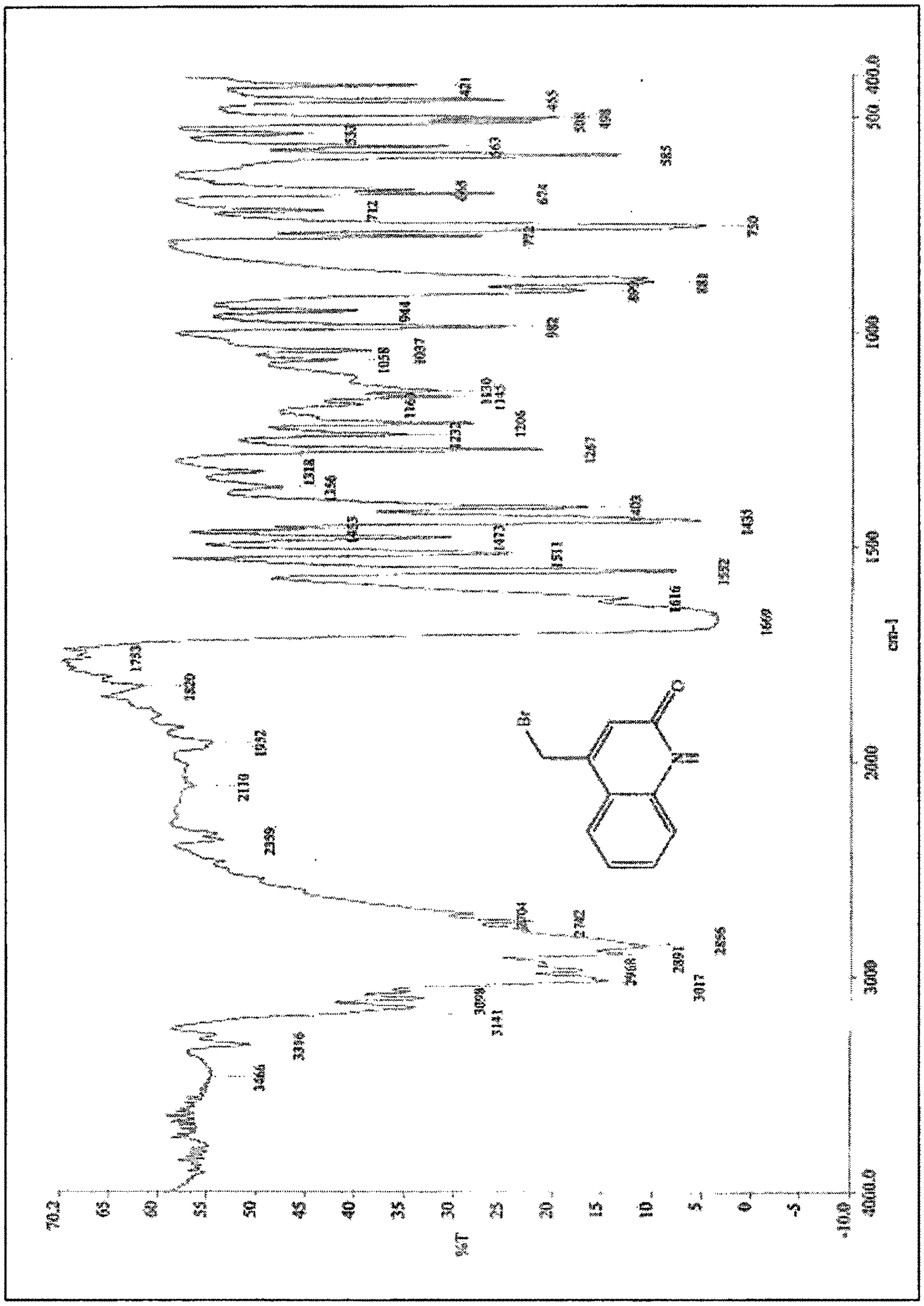


Figure 5.2.1: IR spectrum of 4-(bromomethyl)quinolin-2(1H)-one **3**

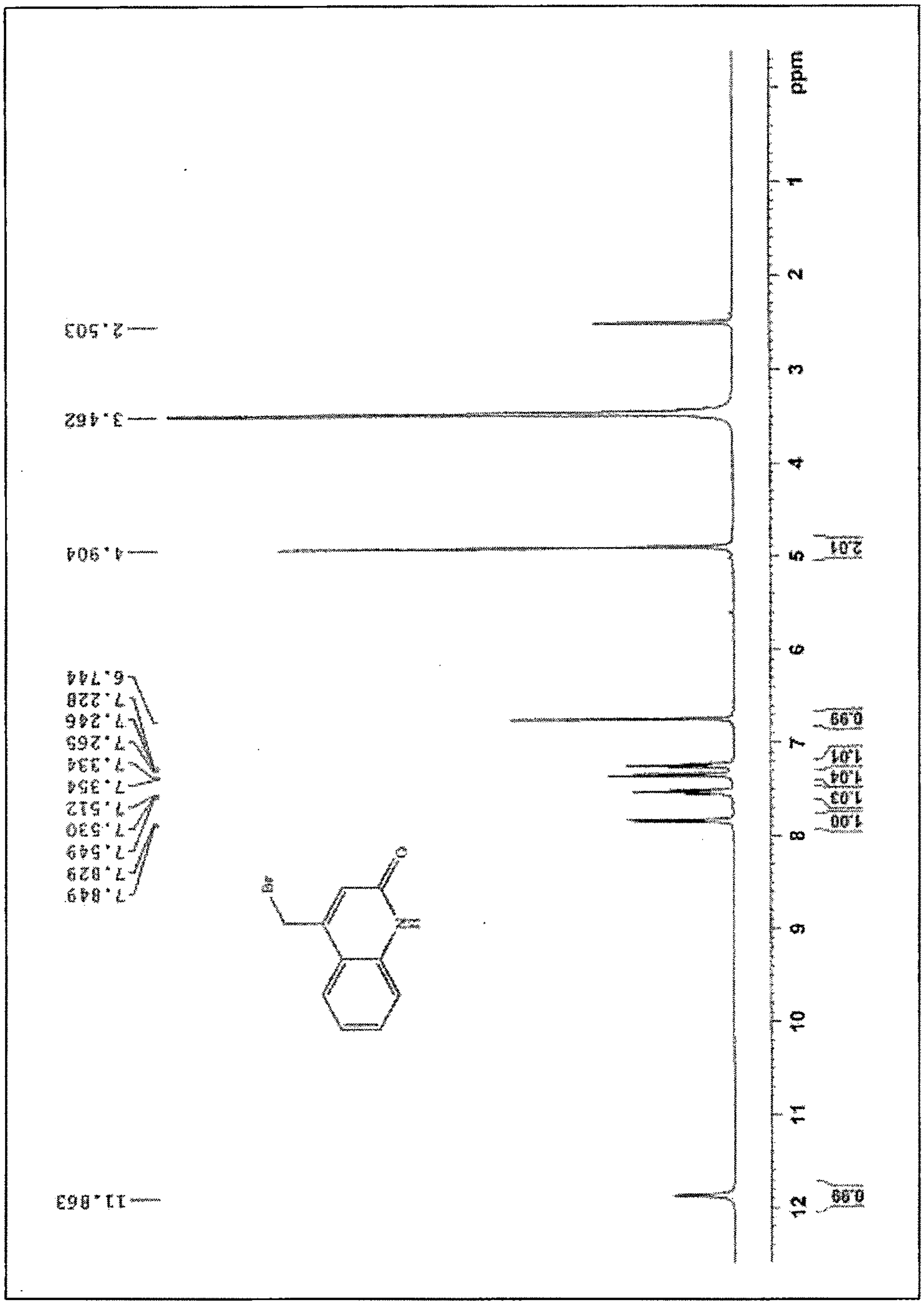


Figure 5.2.2: ^{1}H NMR spectrum of 4-(bromomethyl)quinolin-2(1H)-one **3**

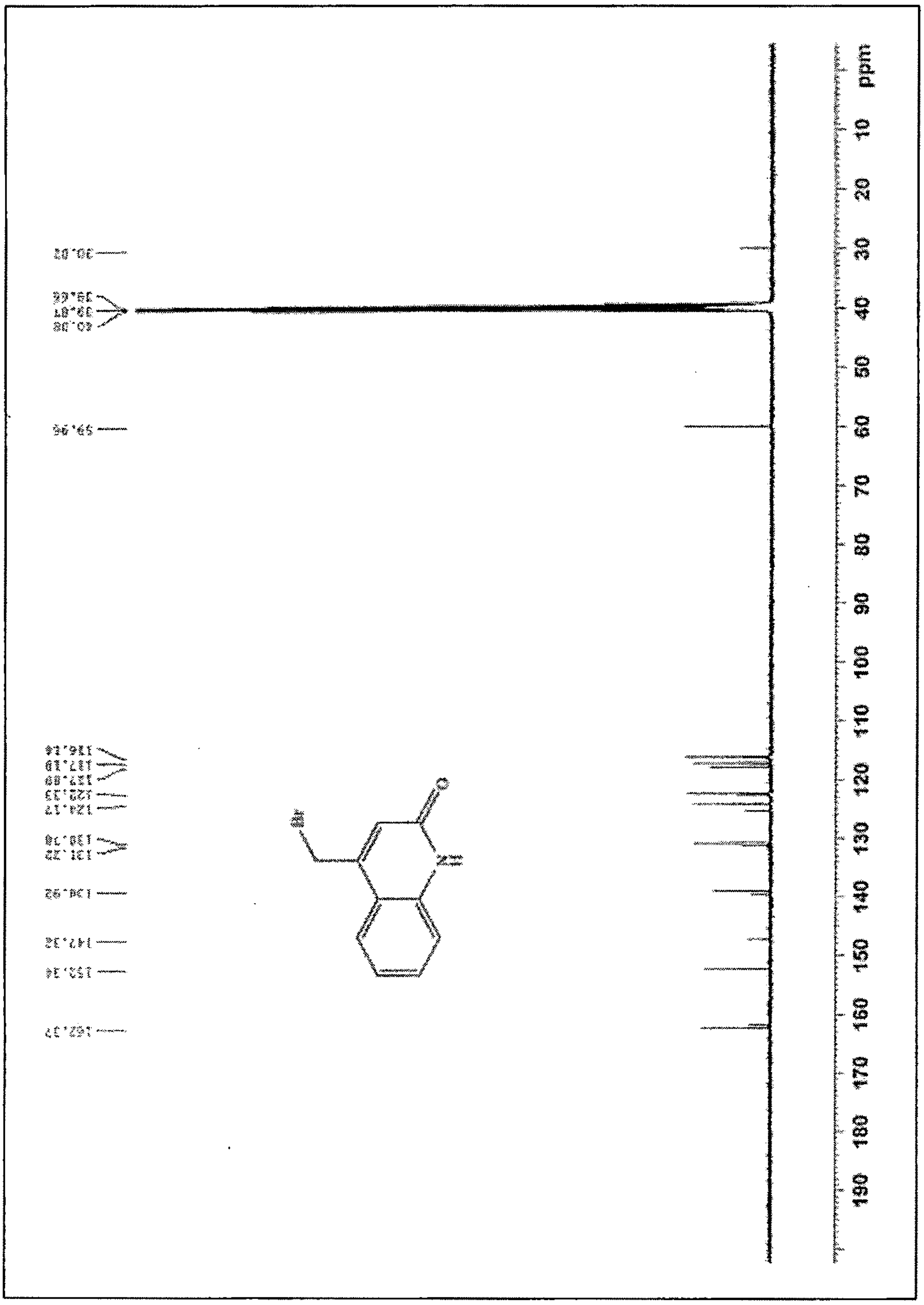


Figure 5.2.3: ^{13}C NMR spectrum of 4-(bromomethyl)quinolin-2(1H)-one **3**

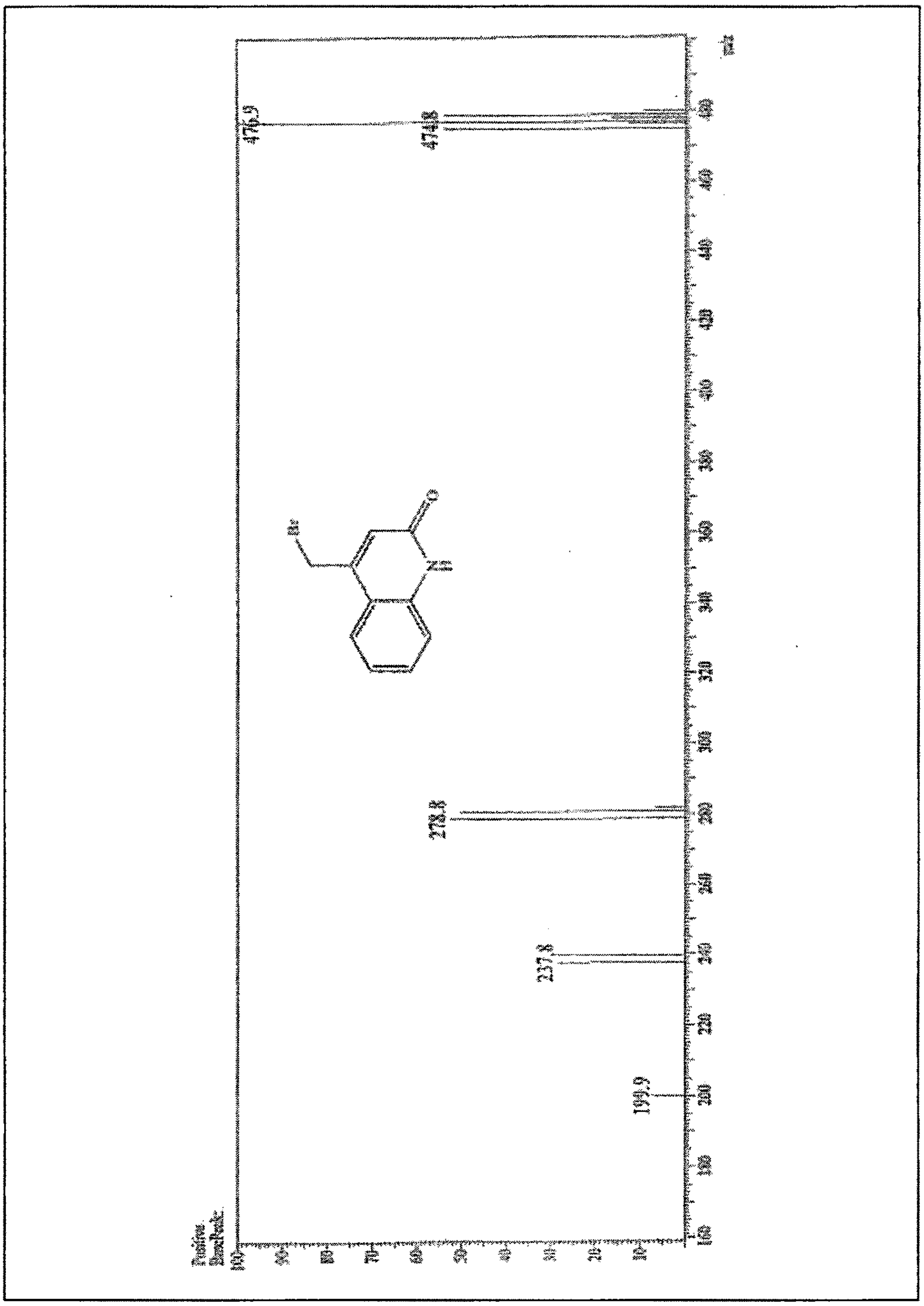


Figure 5.2.4: ESI-MS spectrum of 4-(bromomethyl)quinolin-2(1H)-one **3**

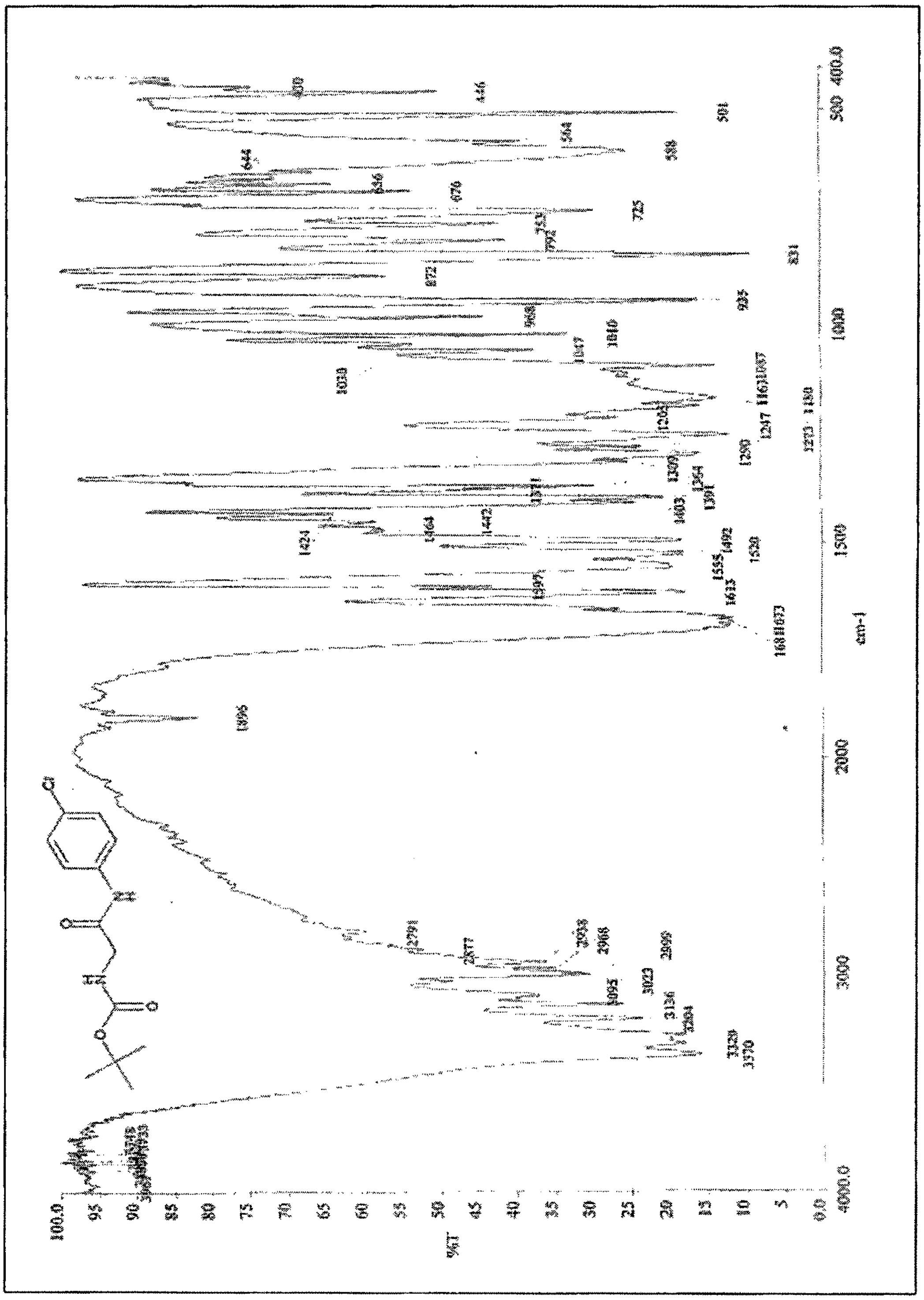


Figure 5.3.1: IR spectrum of *tert*-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate

5a

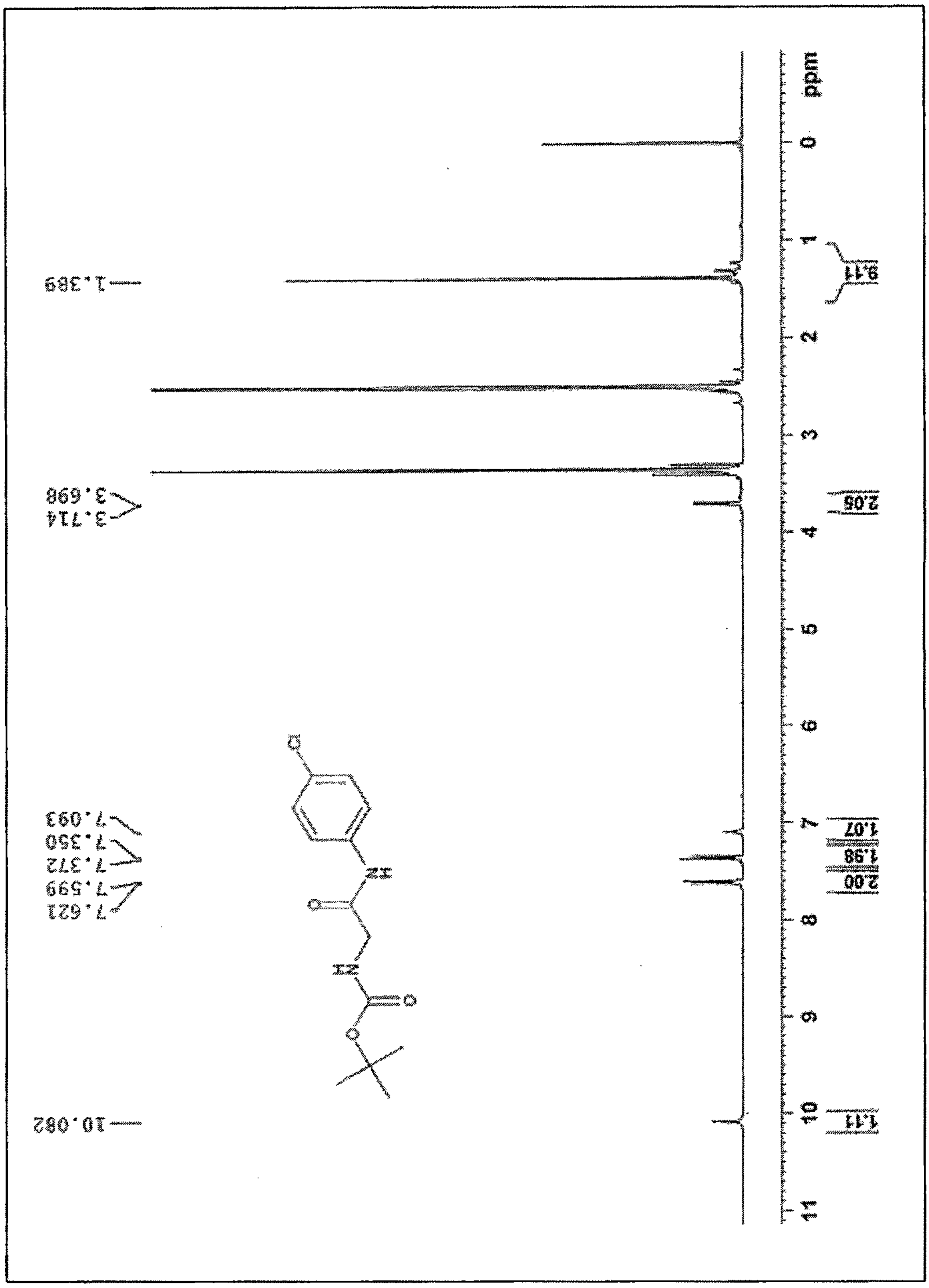


Figure 5.3.2: ^{1}H NMR spectrum of *tert*-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate **5a**

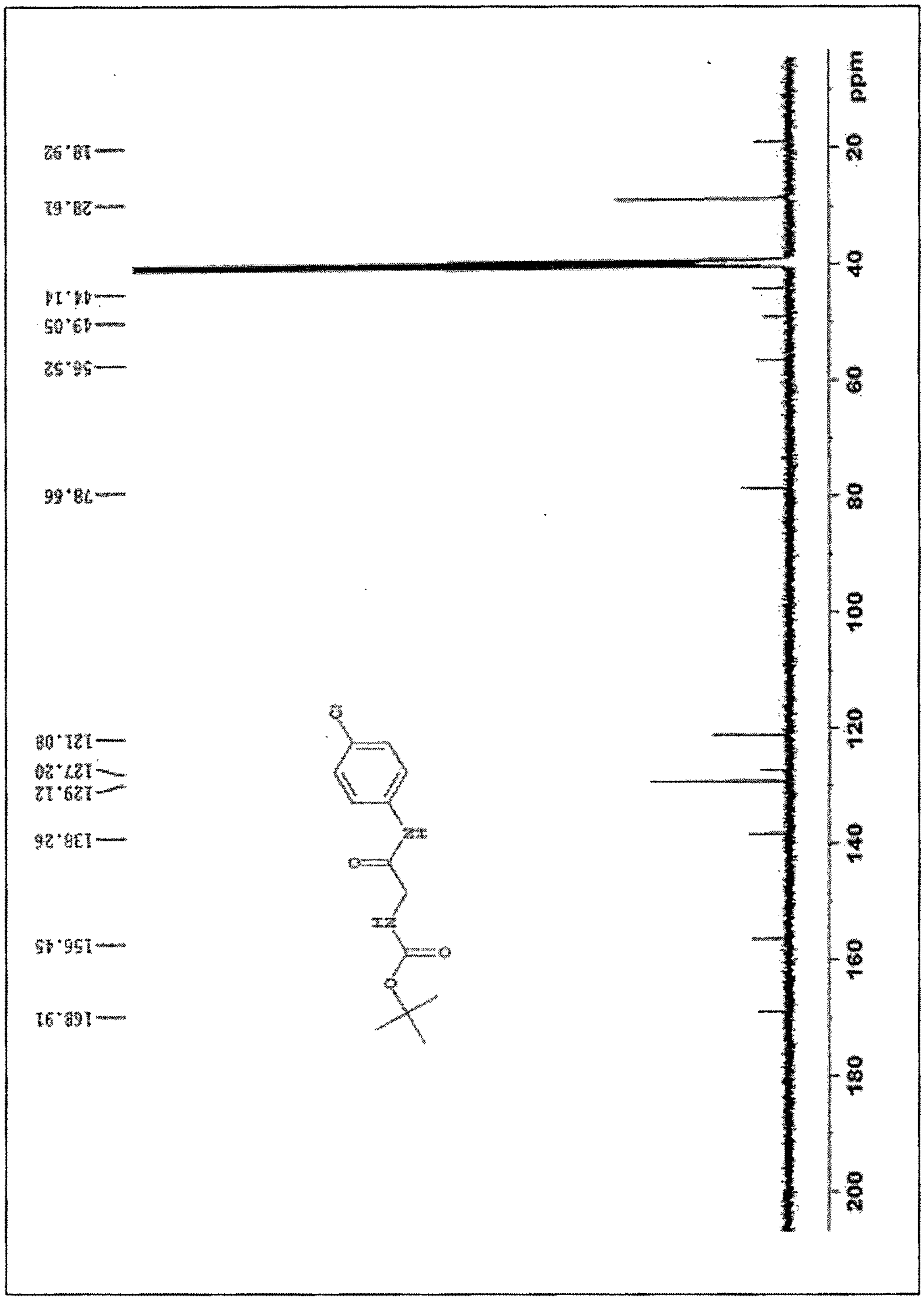


Figure 5.3.3: ^{13}C NMR spectrum of *tert*-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate **5a**

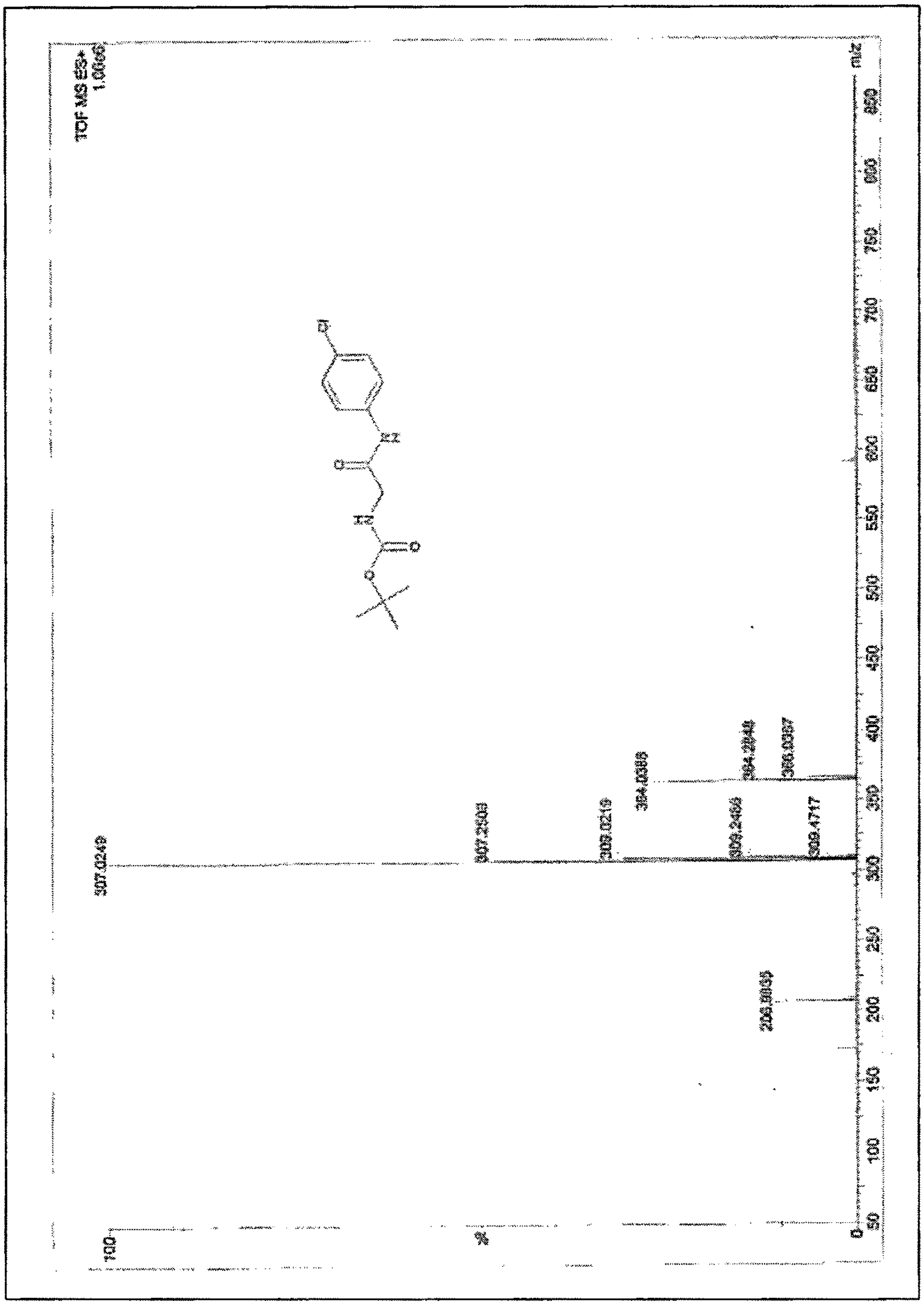


Figure 5.3.4: ESI-MS spectrum of *tert*-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate **5a**

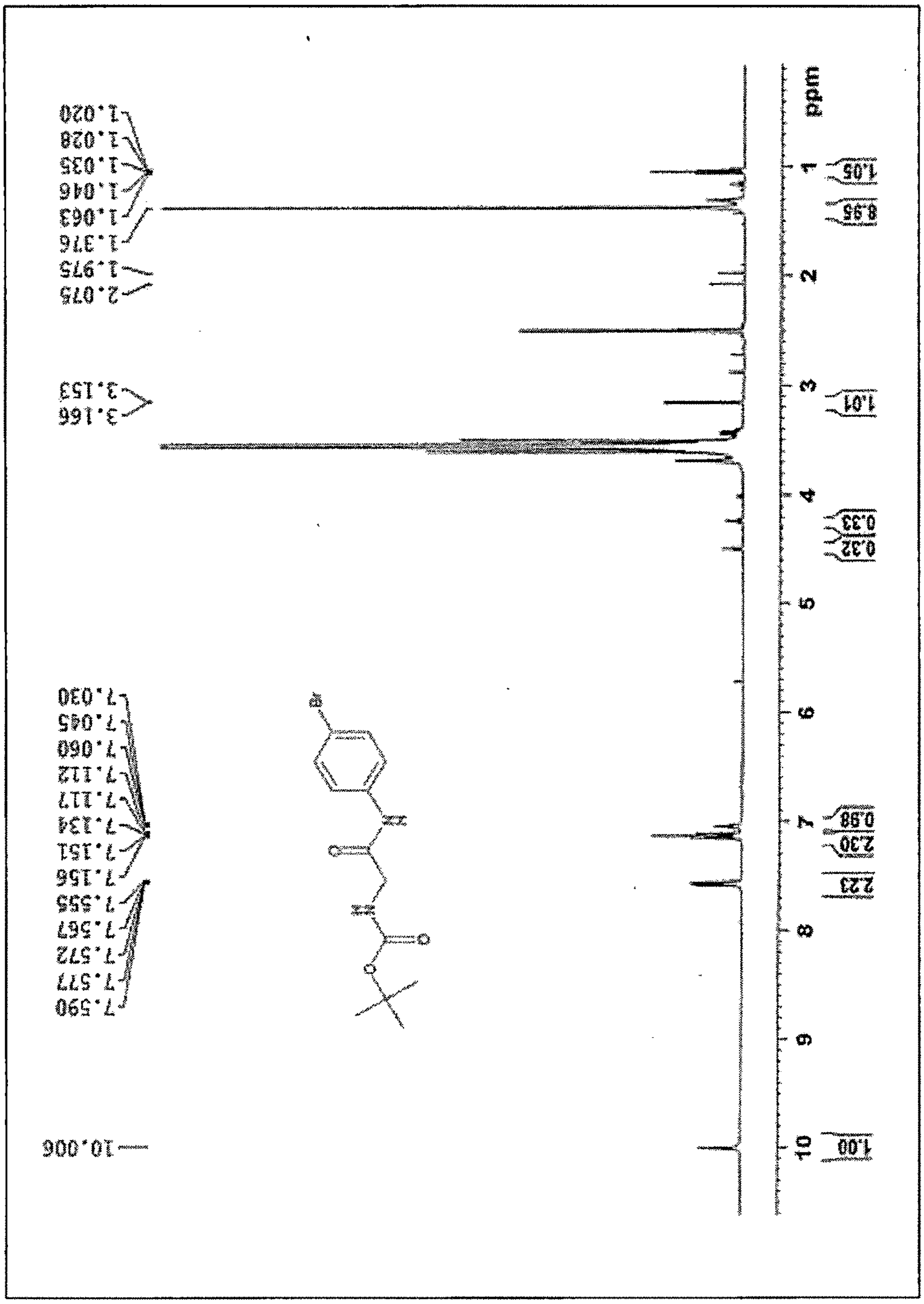


Figure 5.4.2: ^{1}H NMR spectrum of *tert*-butyl 2-(4-bromophenylamino)-2-oxoethylcarbamate **5b**

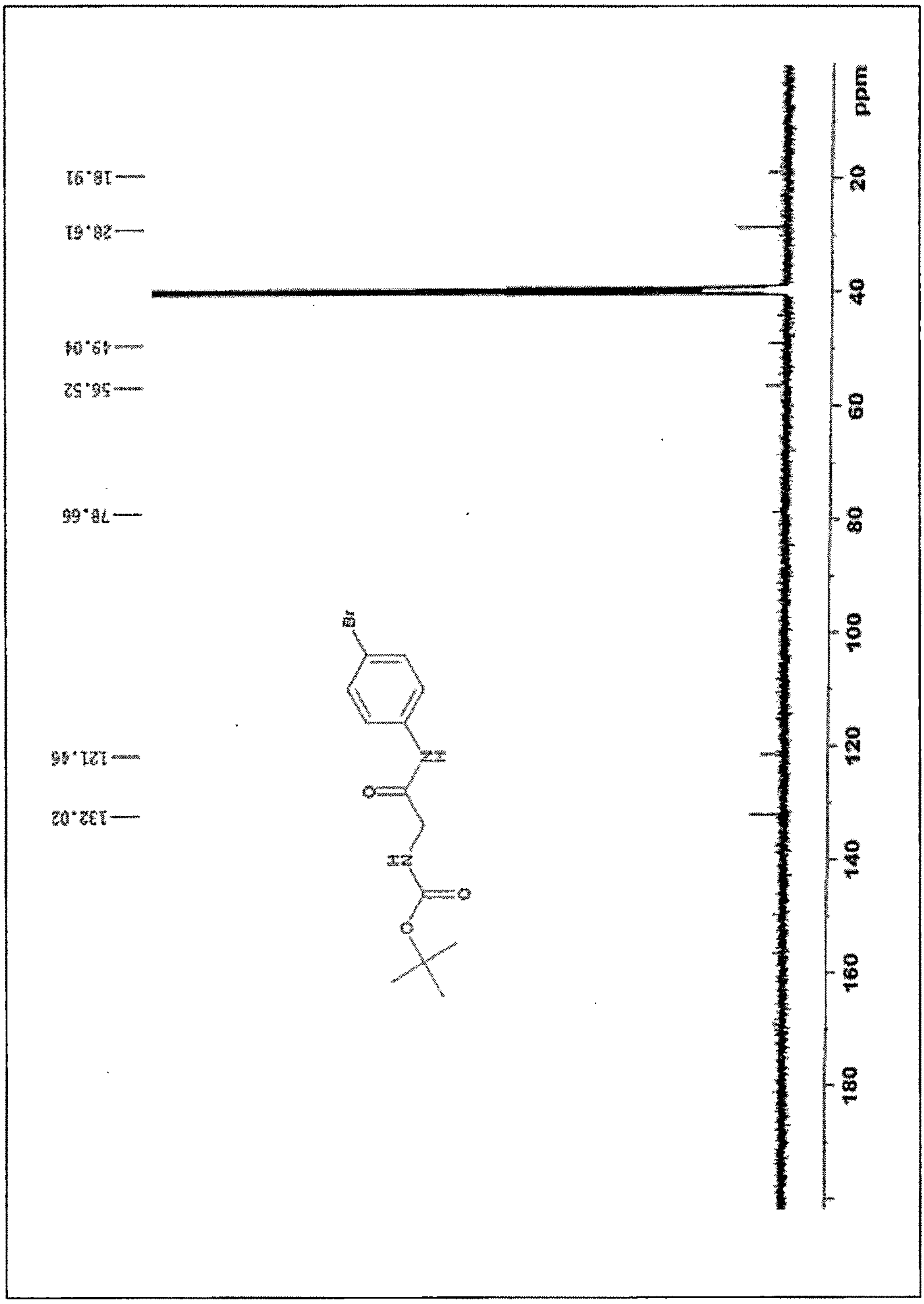


Figure 5.4.3: ^{13}C NMR spectrum of *tert*-butyl 2-(4-bromophenylamino)-2-oxoethylcarbamate **5b**

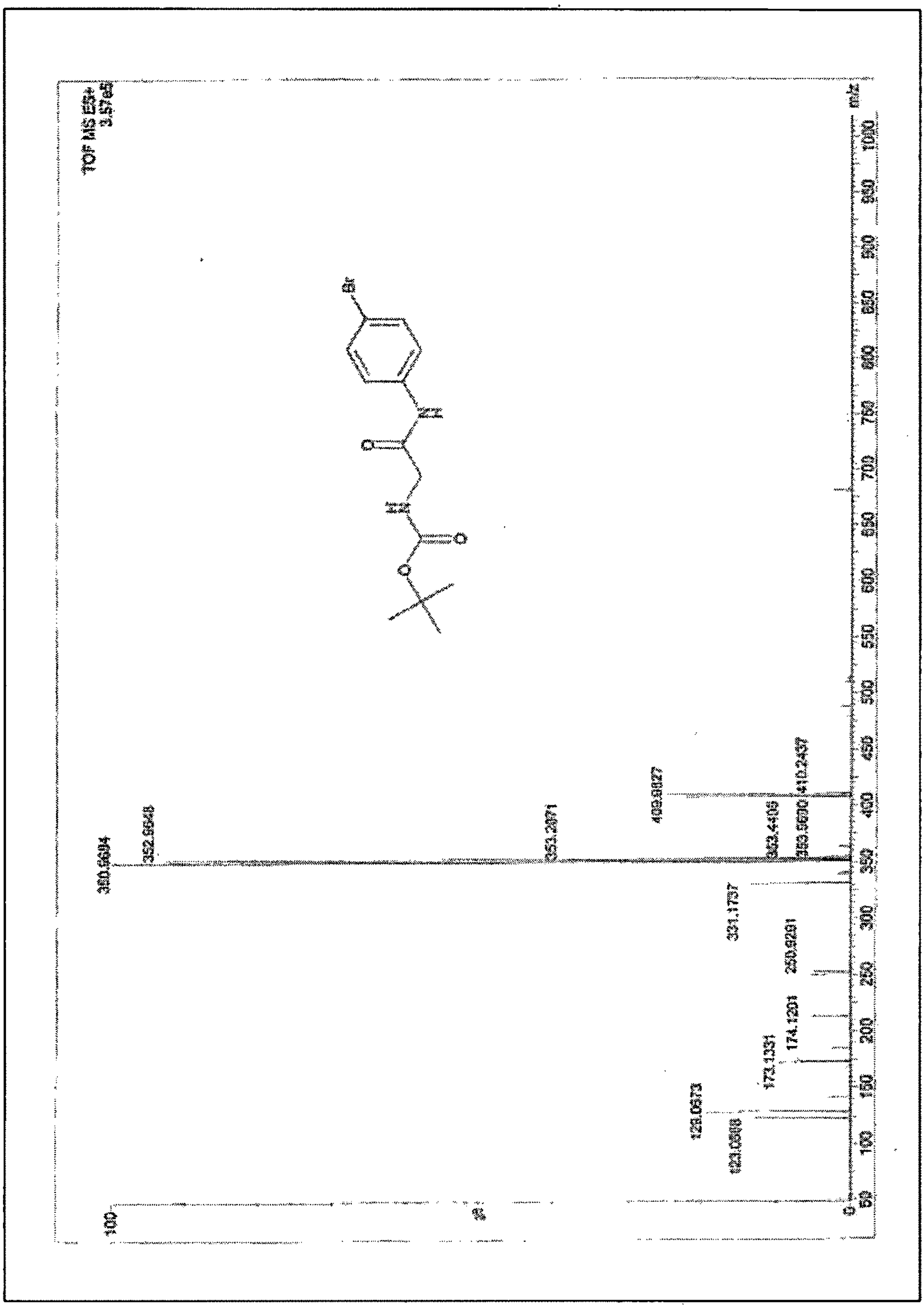


Figure 5.4.4: ESI-MS spectrum of *tert*-butyl 2-(4-bromophenylamino)-2-oxoethylcarbamate **5b**

Figure 5.5.1: IR spectrum of *tert*-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate **5c**

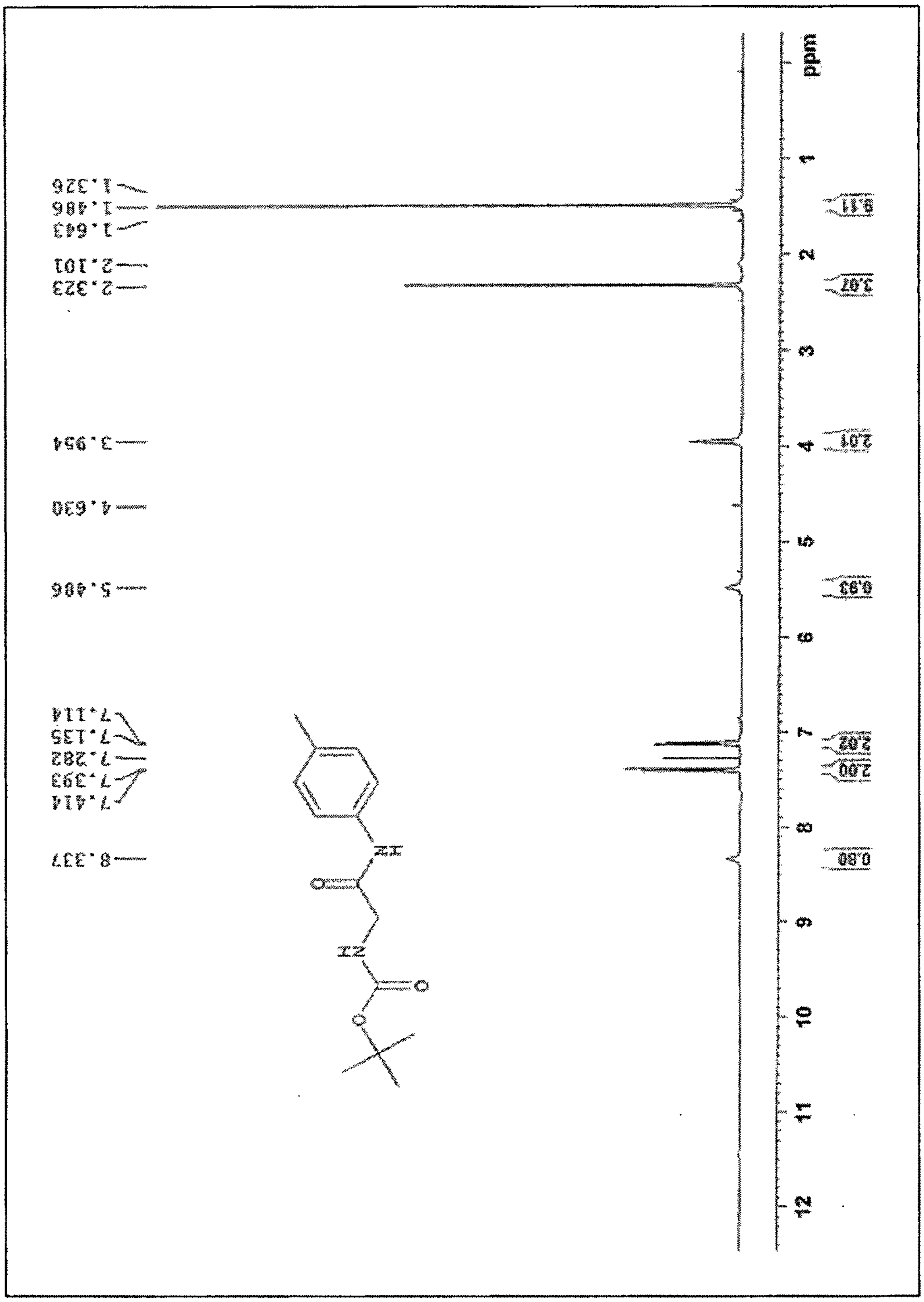


Figure 5.5.2: ^{1}H NMR spectrum of *tert*-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate **5c**

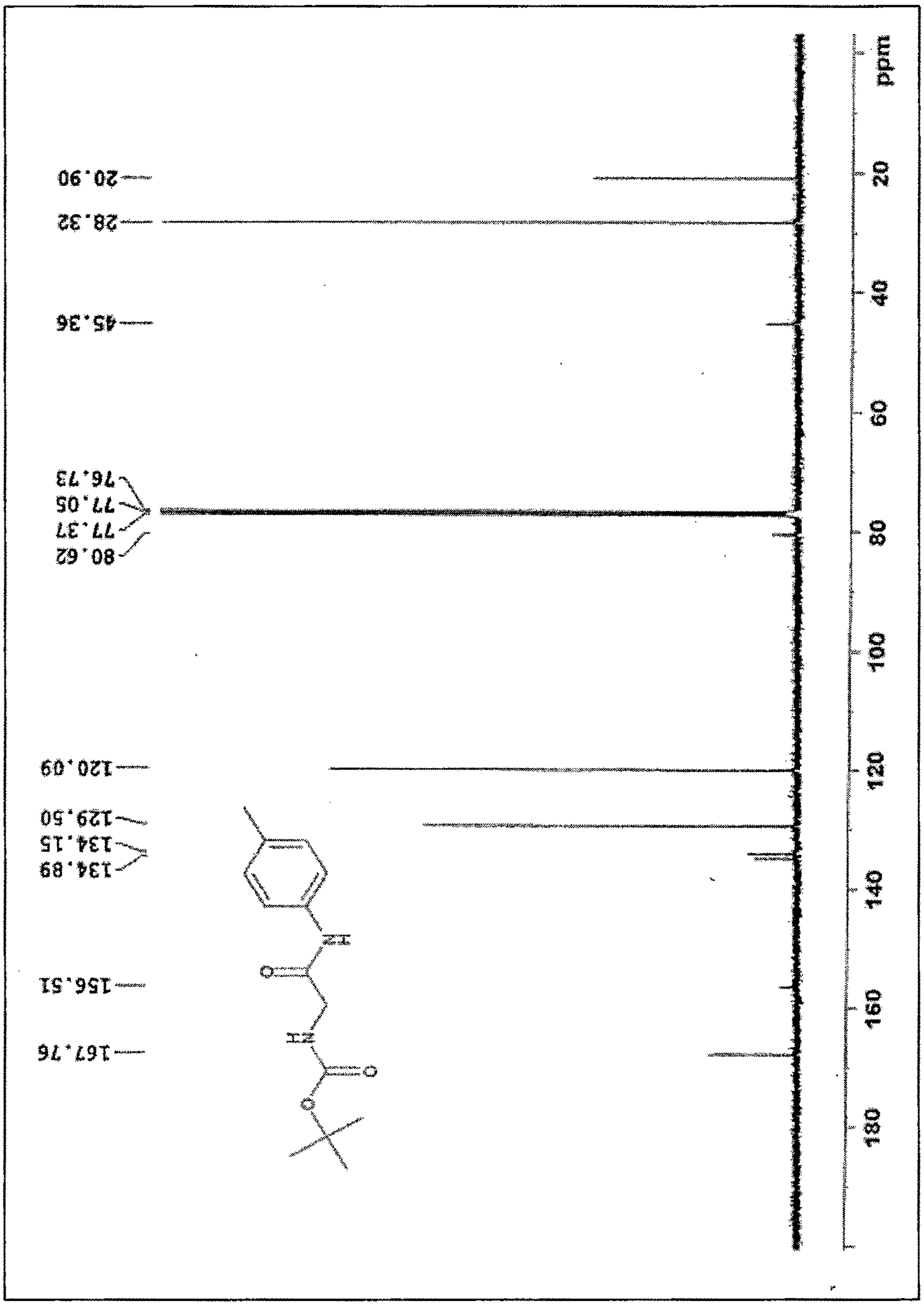


Figure 5.5.3: ^{13}C NMR spectrum of *tert*-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate **5c**

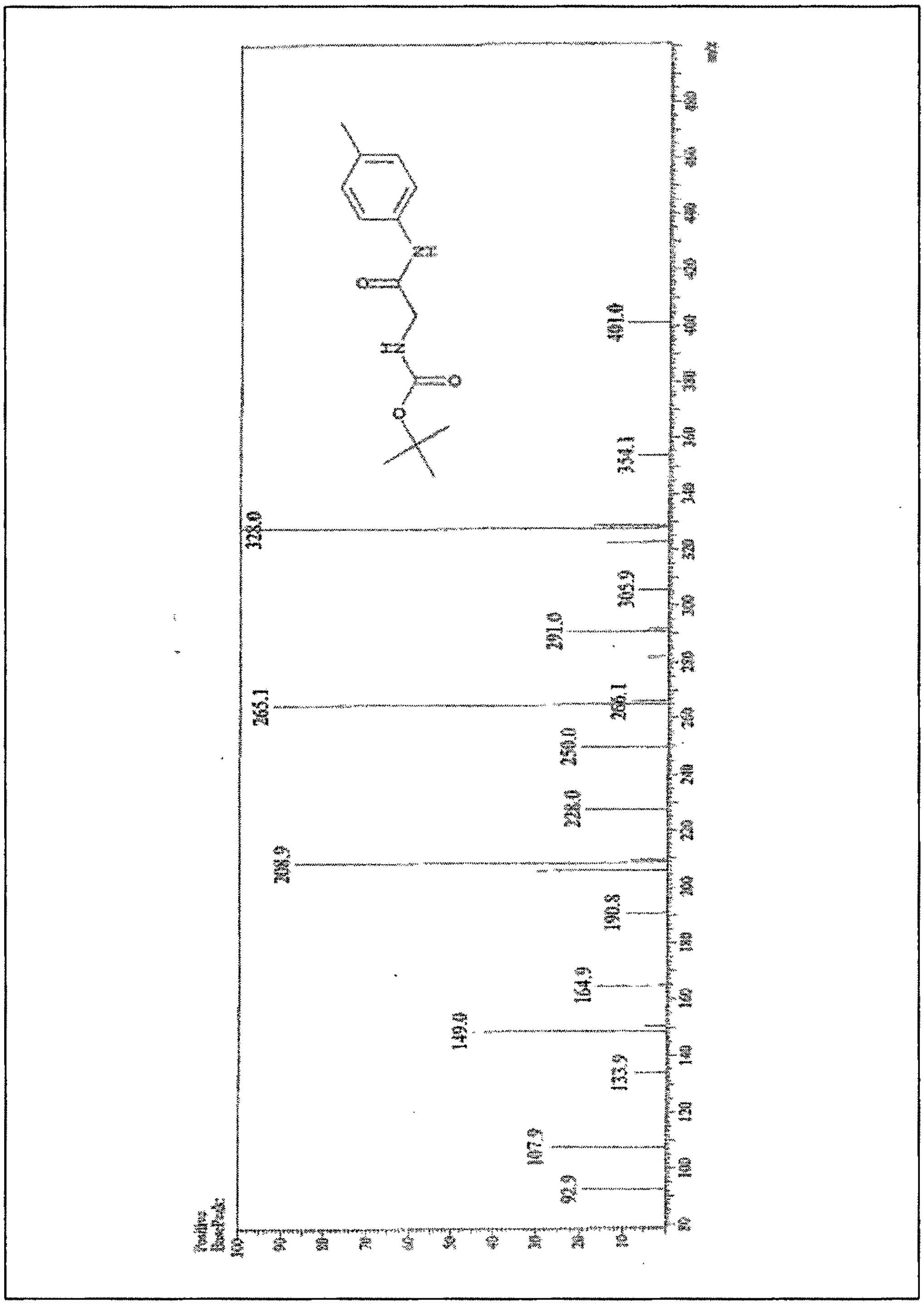


Figure 5.5.4: ESI-MS spectrum of *tert*-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate **5c**

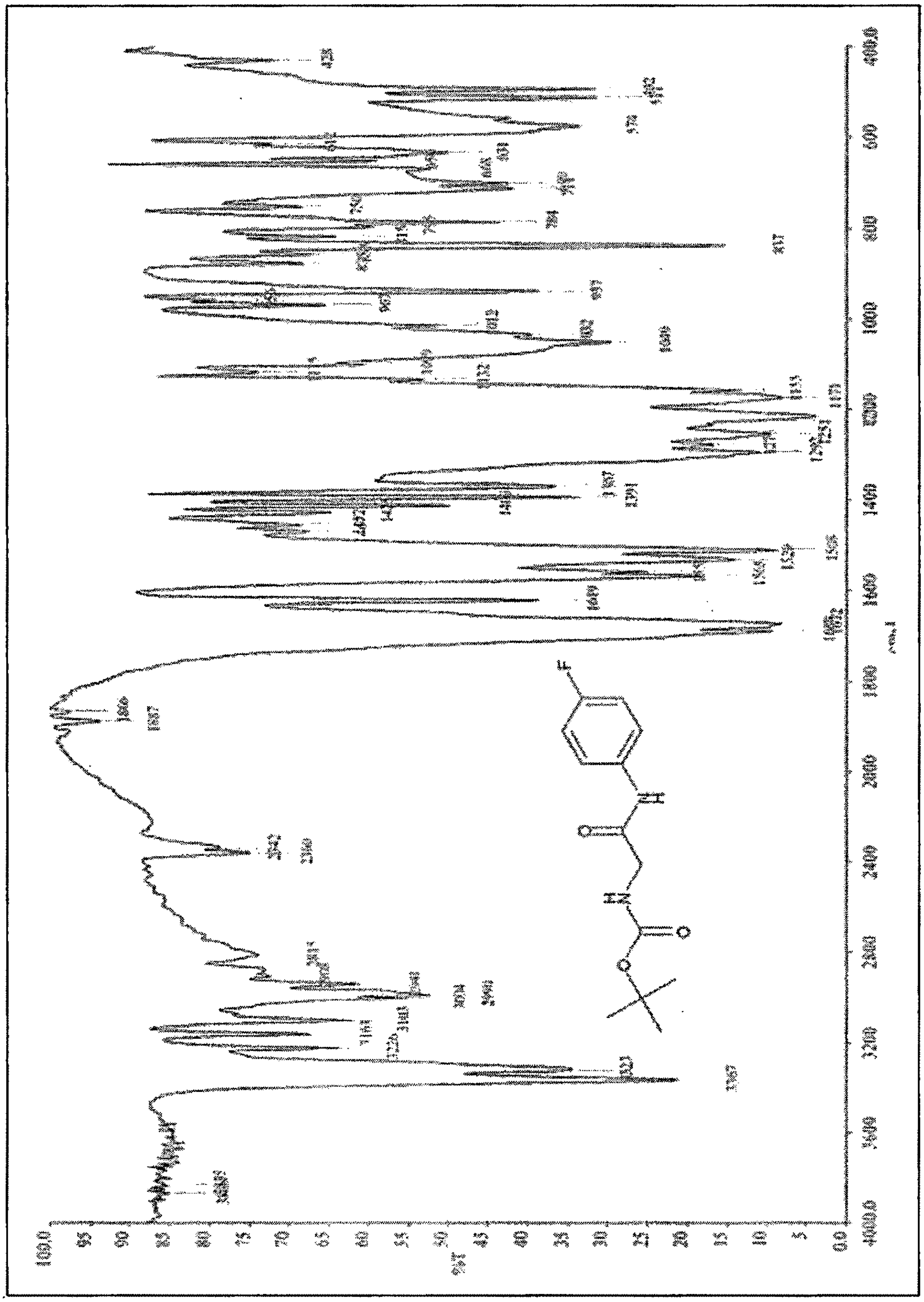


Figure 5.6.1: IR spectrum of *tert*-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate **5d**

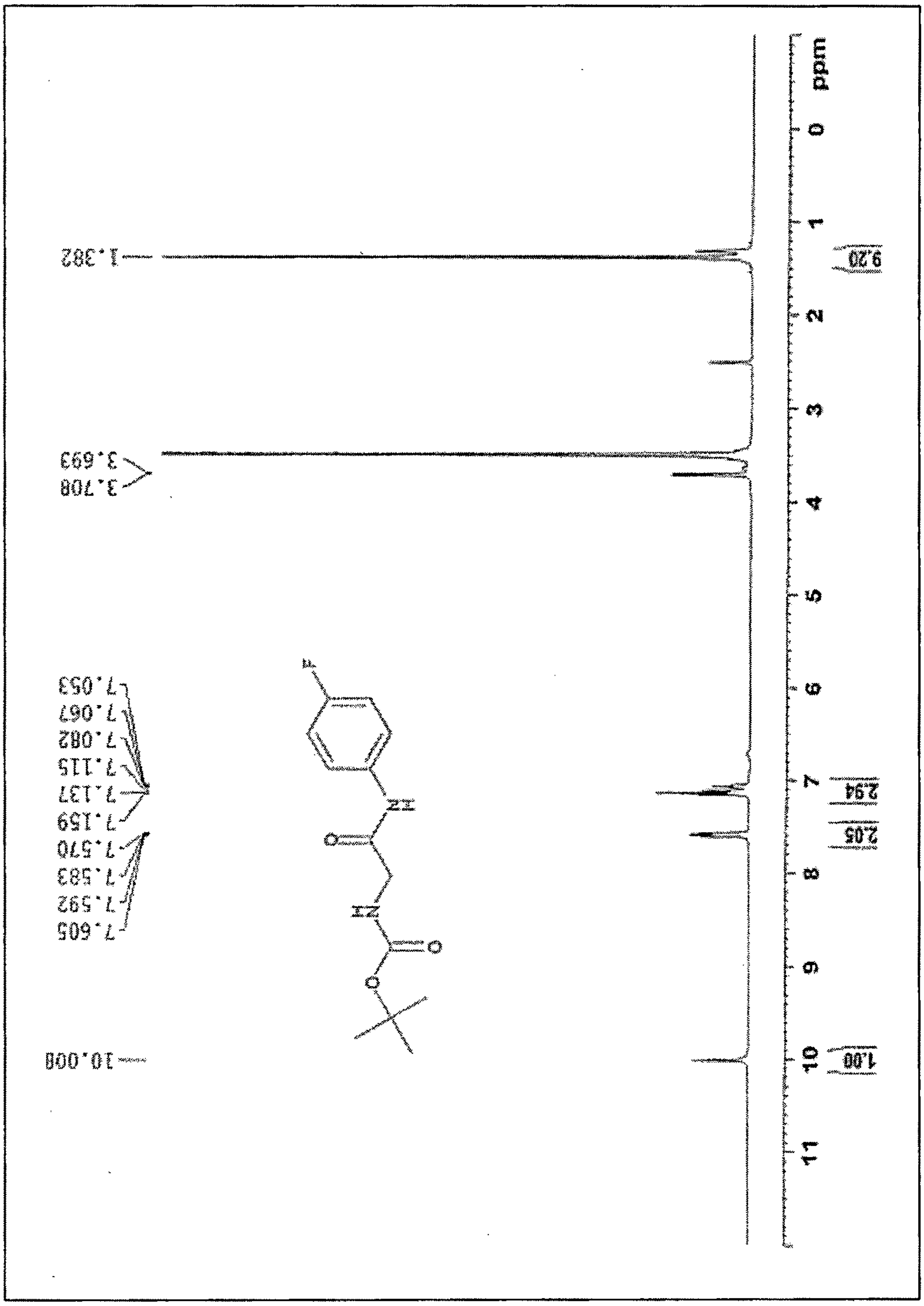


Figure 5.6.2: ^{1}H NMR spectrum of *tert*-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate **5d**

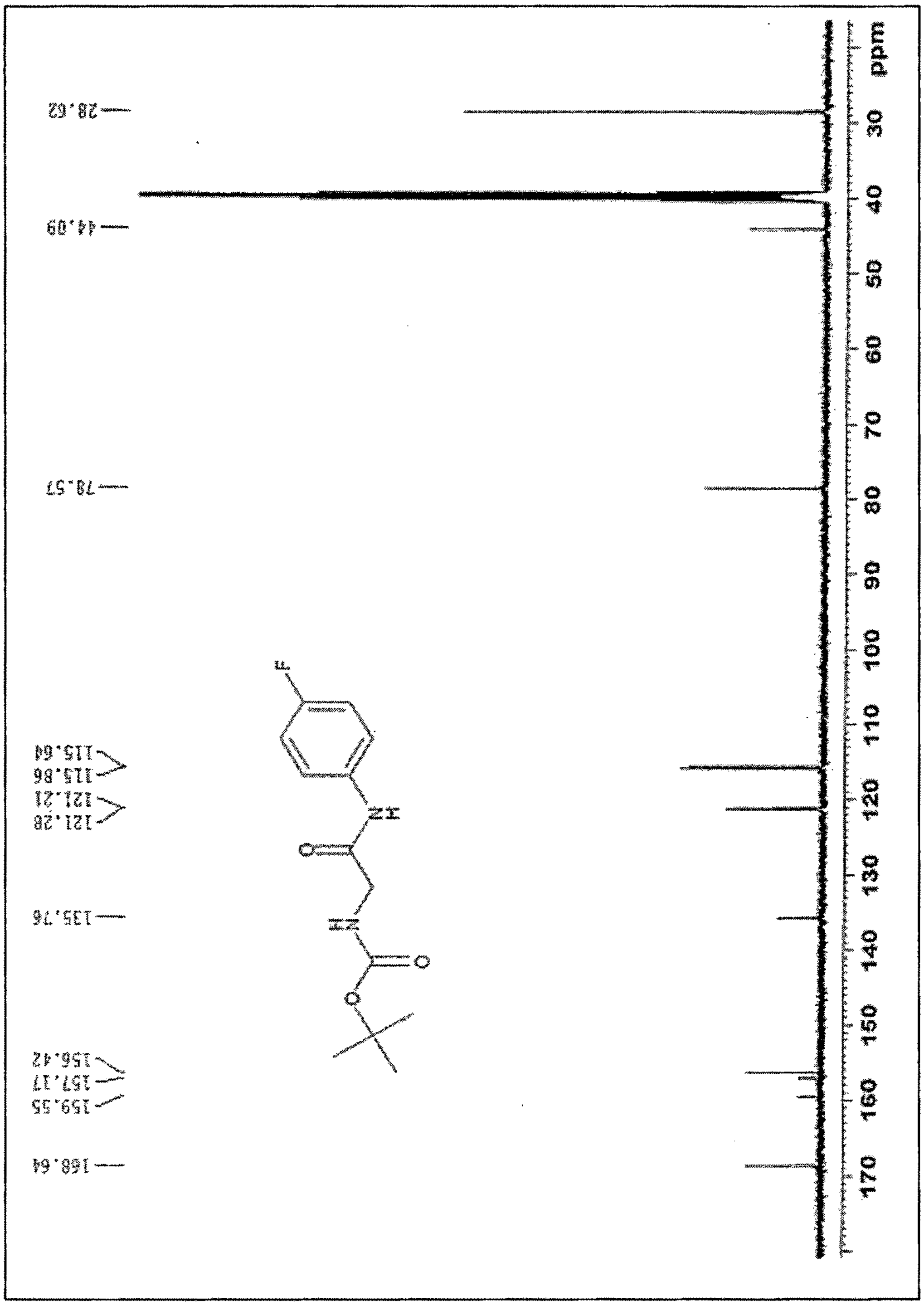


Figure 5.6.3: ^{13}C NMR spectrum of *tert*-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate **5d**

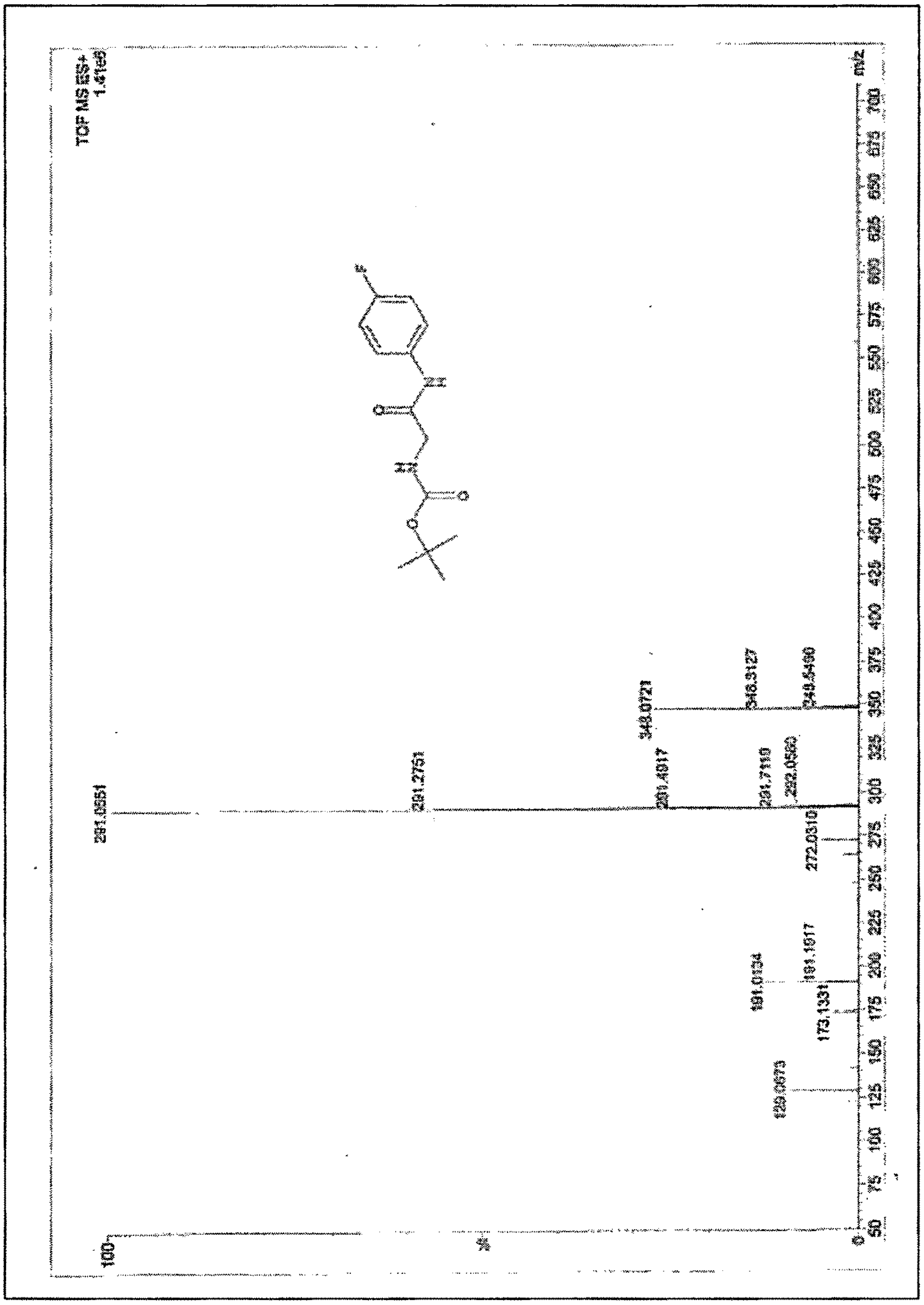


Figure 5.6.4: ESI-MS spectrum of *tert*-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate **5d**

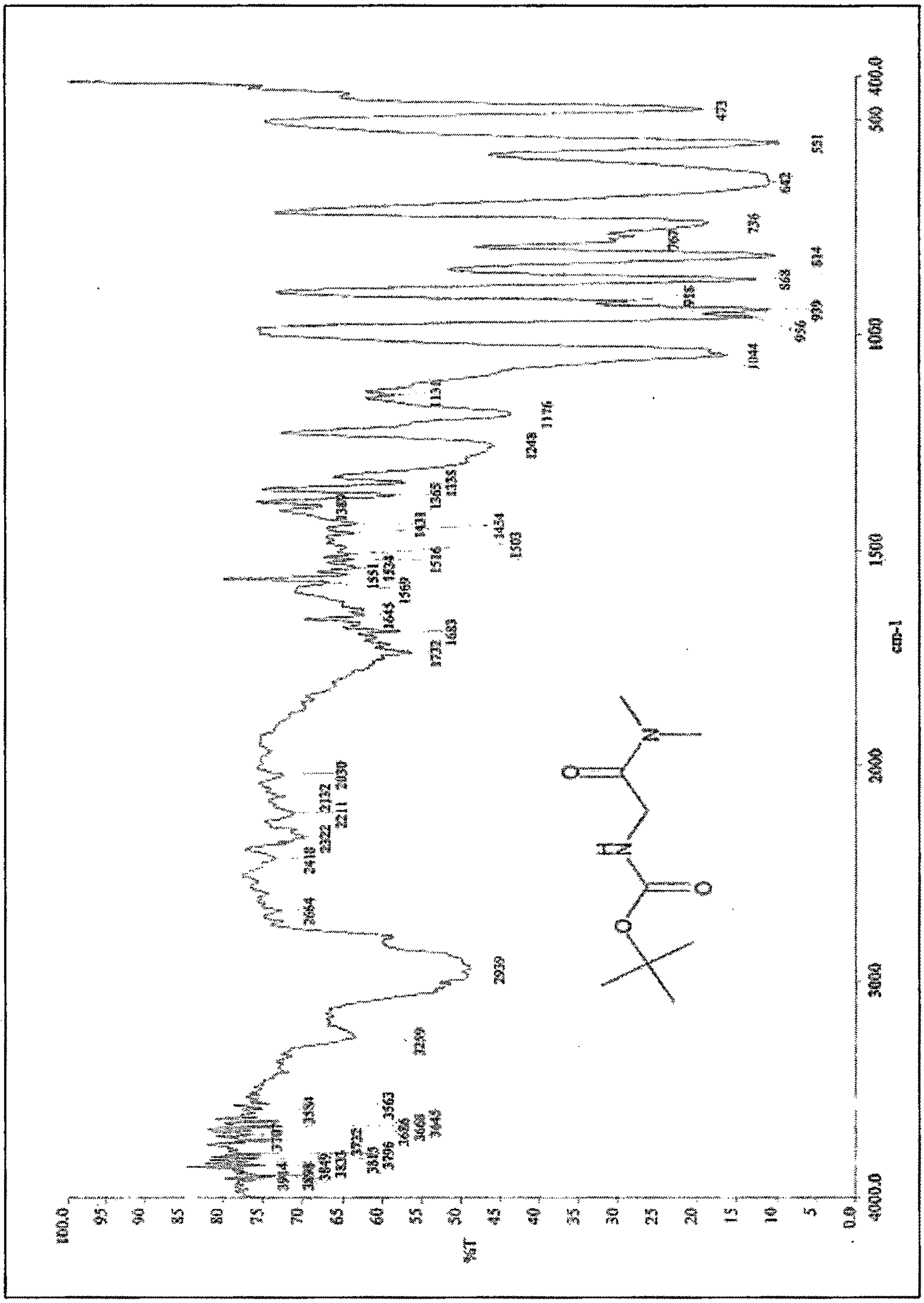


Figure 5.7.1: IR spectrum of *tert*-butyl 2-(dimethylamino)-2-oxoethylcarbamate **5e**

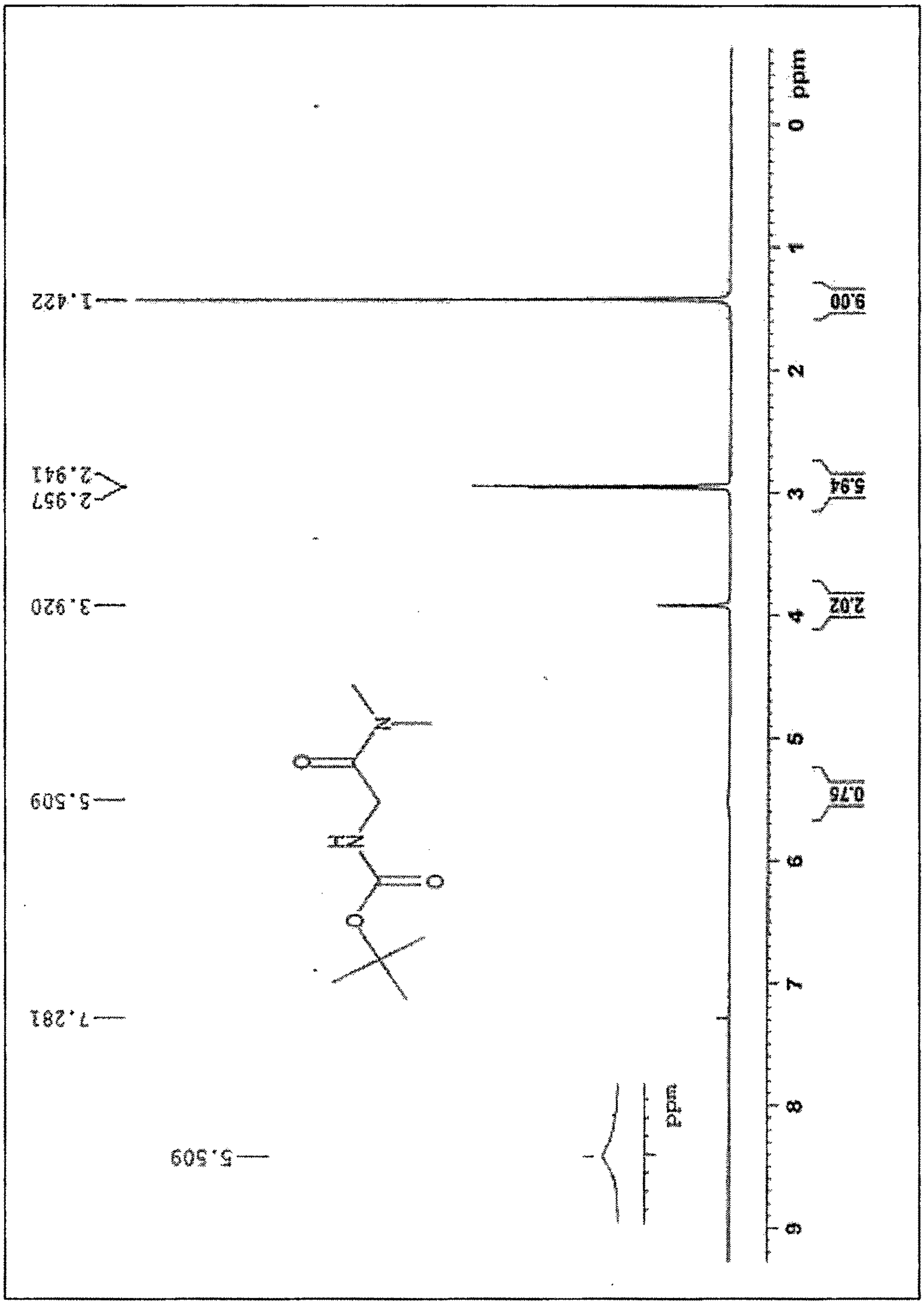


Figure 5.7.2: ^{1}H NMR spectrum of *tert*-butyl 2-(dimethylamino)-2-oxoethylcarbamate **5e**

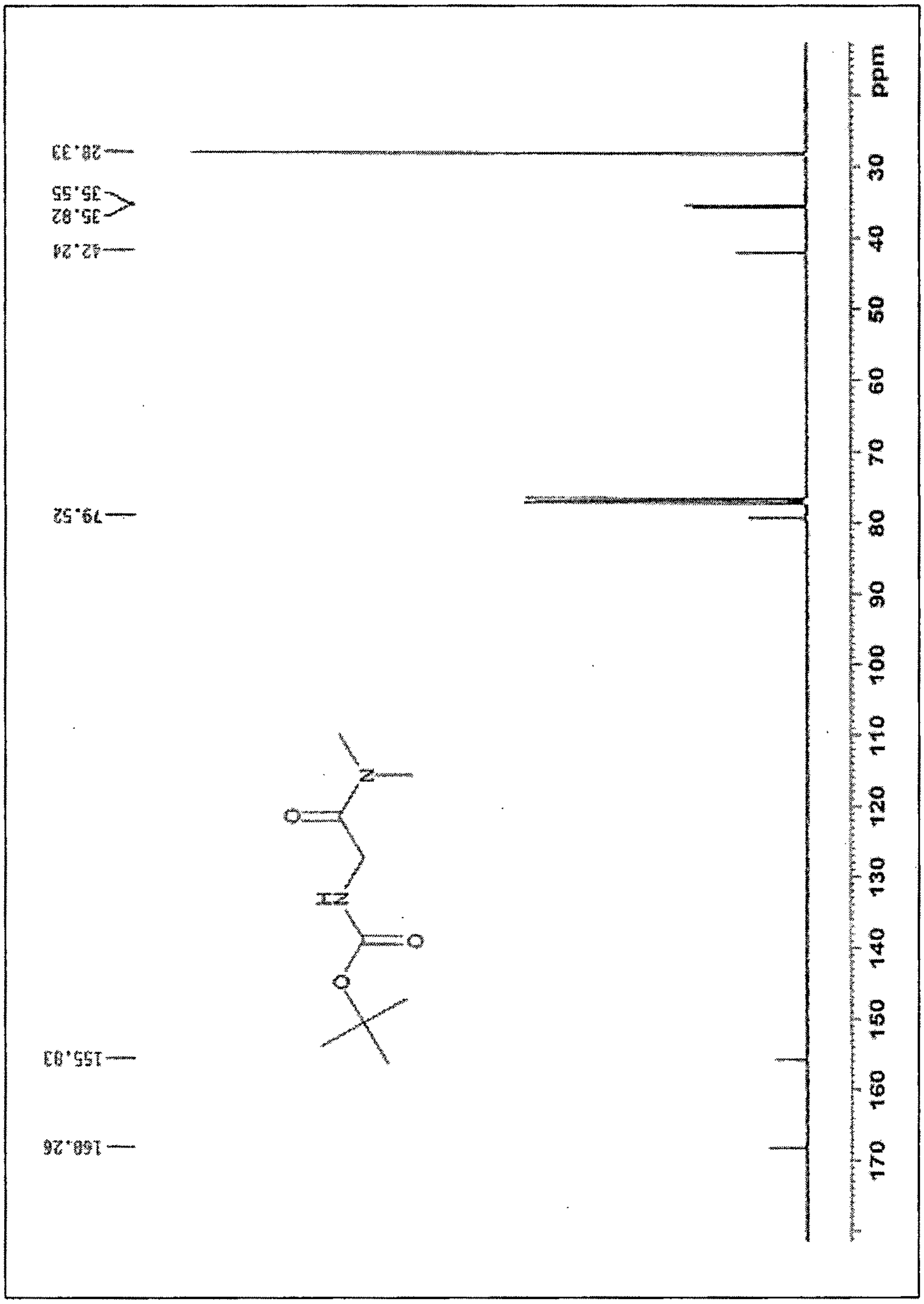


Figure 5.7.3: ^{13}C NMR spectrum of *tert*-butyl 2-(dimethylamino)-2-oxoethylcarbamate **5e**

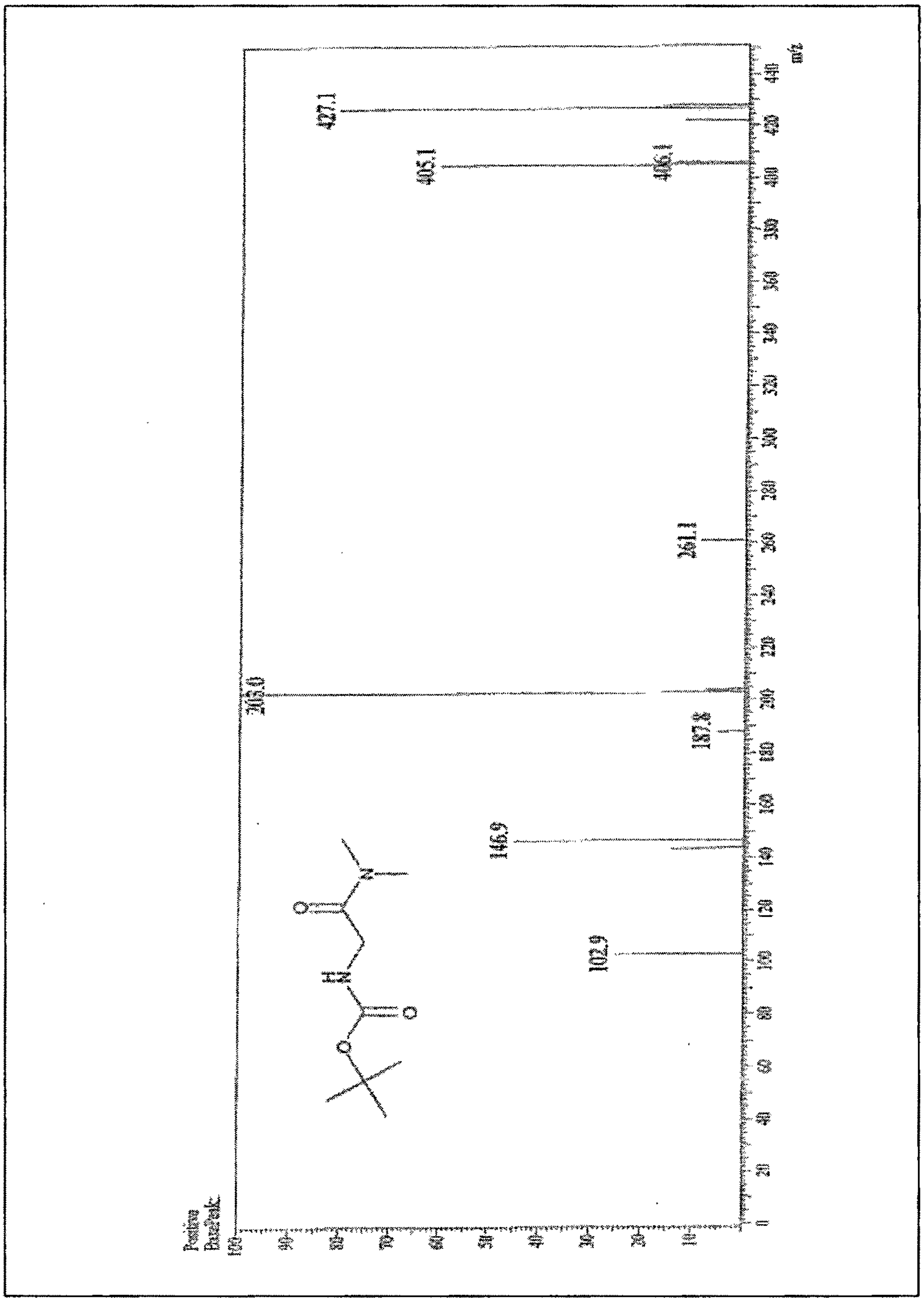


Figure 5.7.4: ESI-MS spectrum of *tert*-butyl 2-(dimethylamino)-2-oxoethylcarbamate **5e**

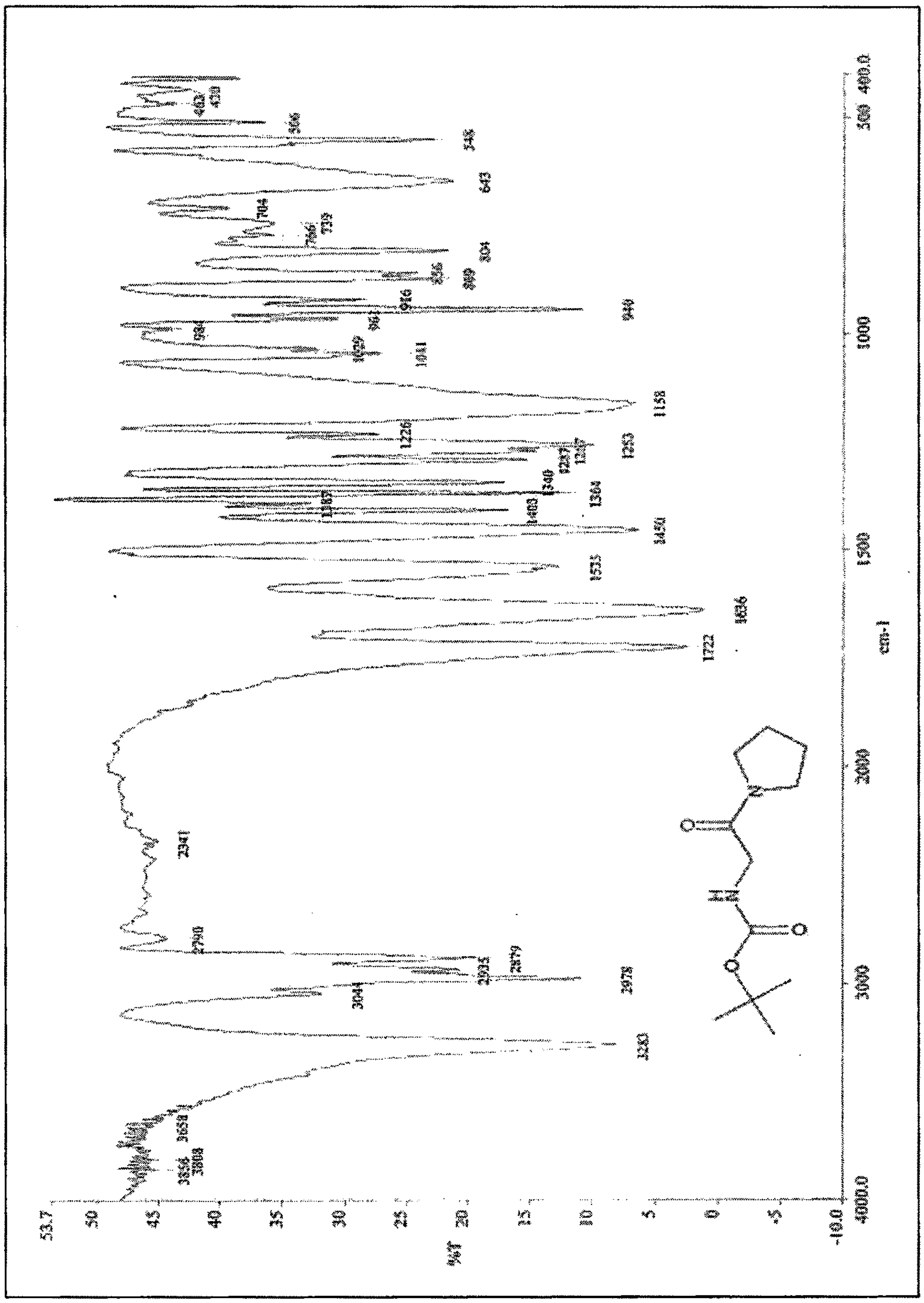


Figure 5.8.1: IR spectrum of *tert*-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate **5f**

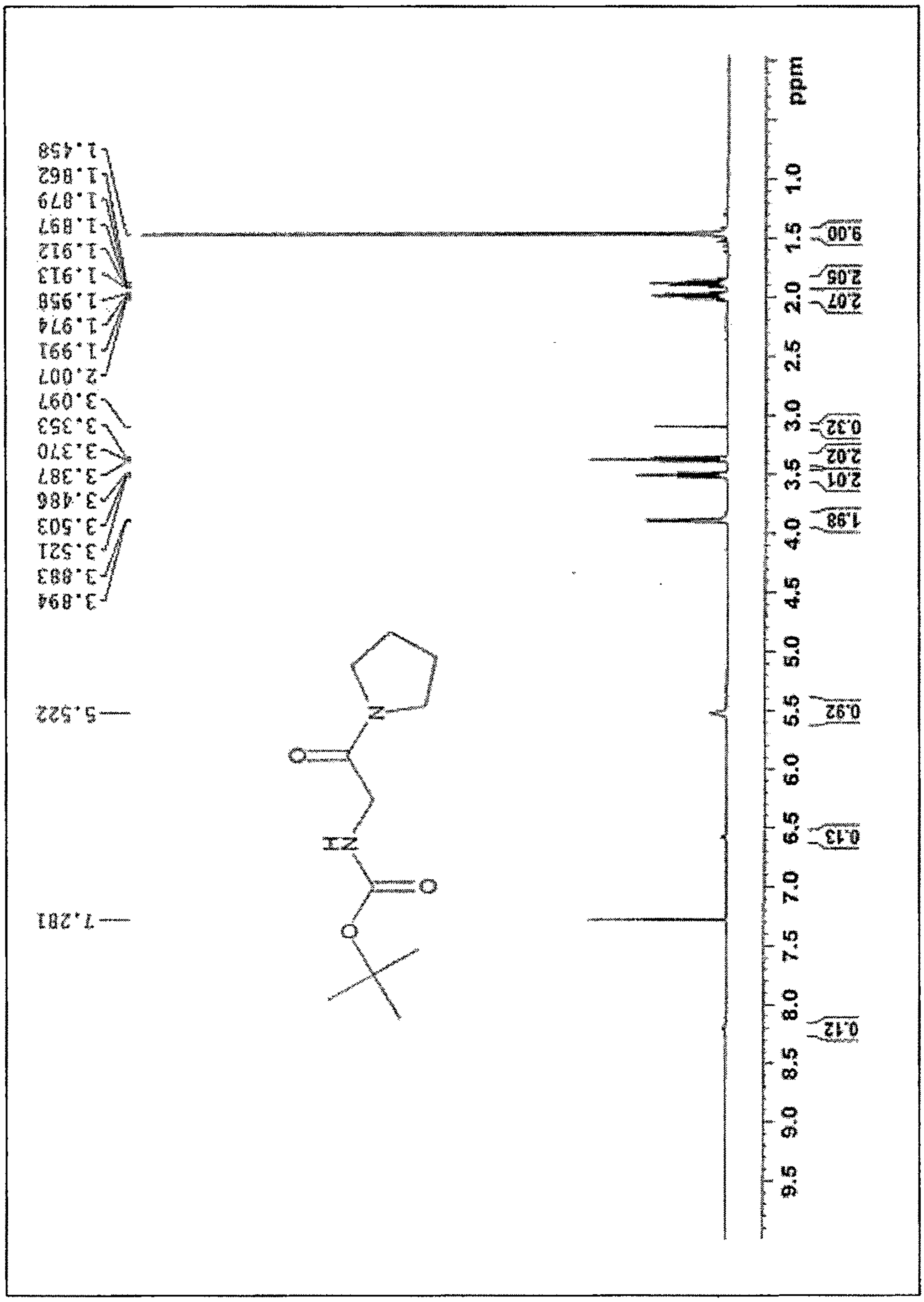


Figure 5.8.2: ^{1}H NMR spectrum of *tert*-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate **5f**

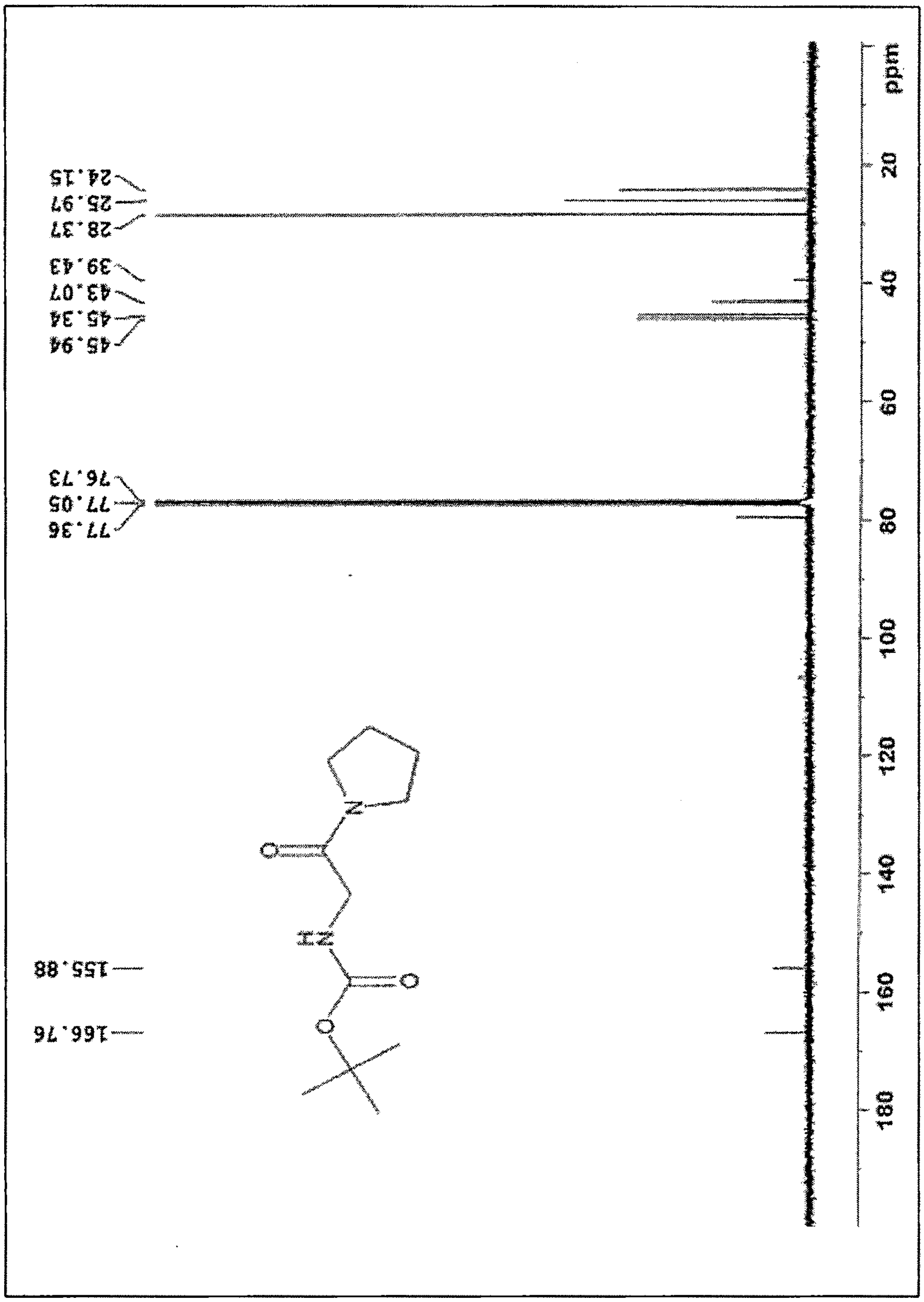


Figure 5.8.3: ^{13}C NMR spectrum of *tert*-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate **5f**

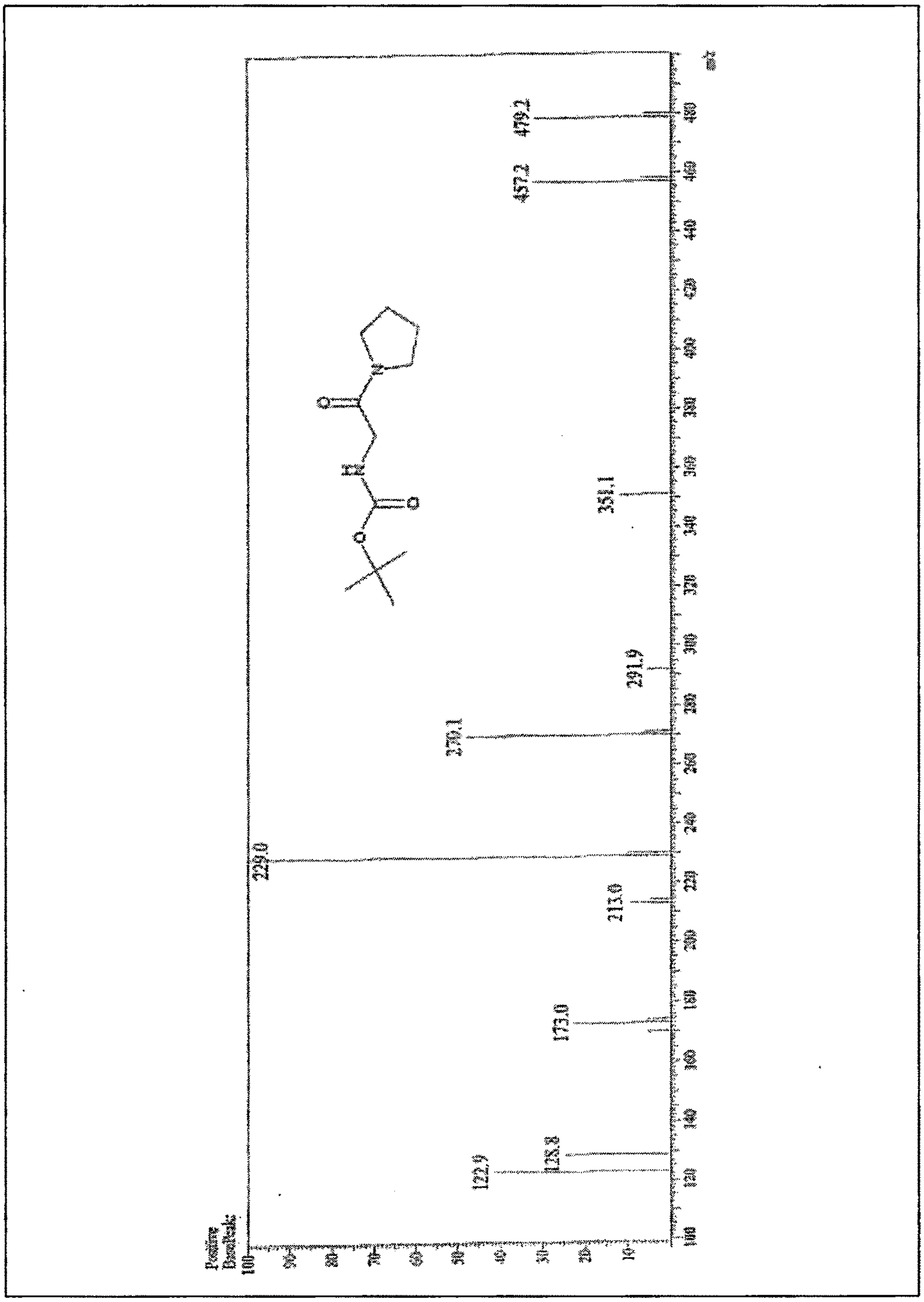


Figure 5.8.4: ESI-MS spectrum of *tert*-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate **5f**

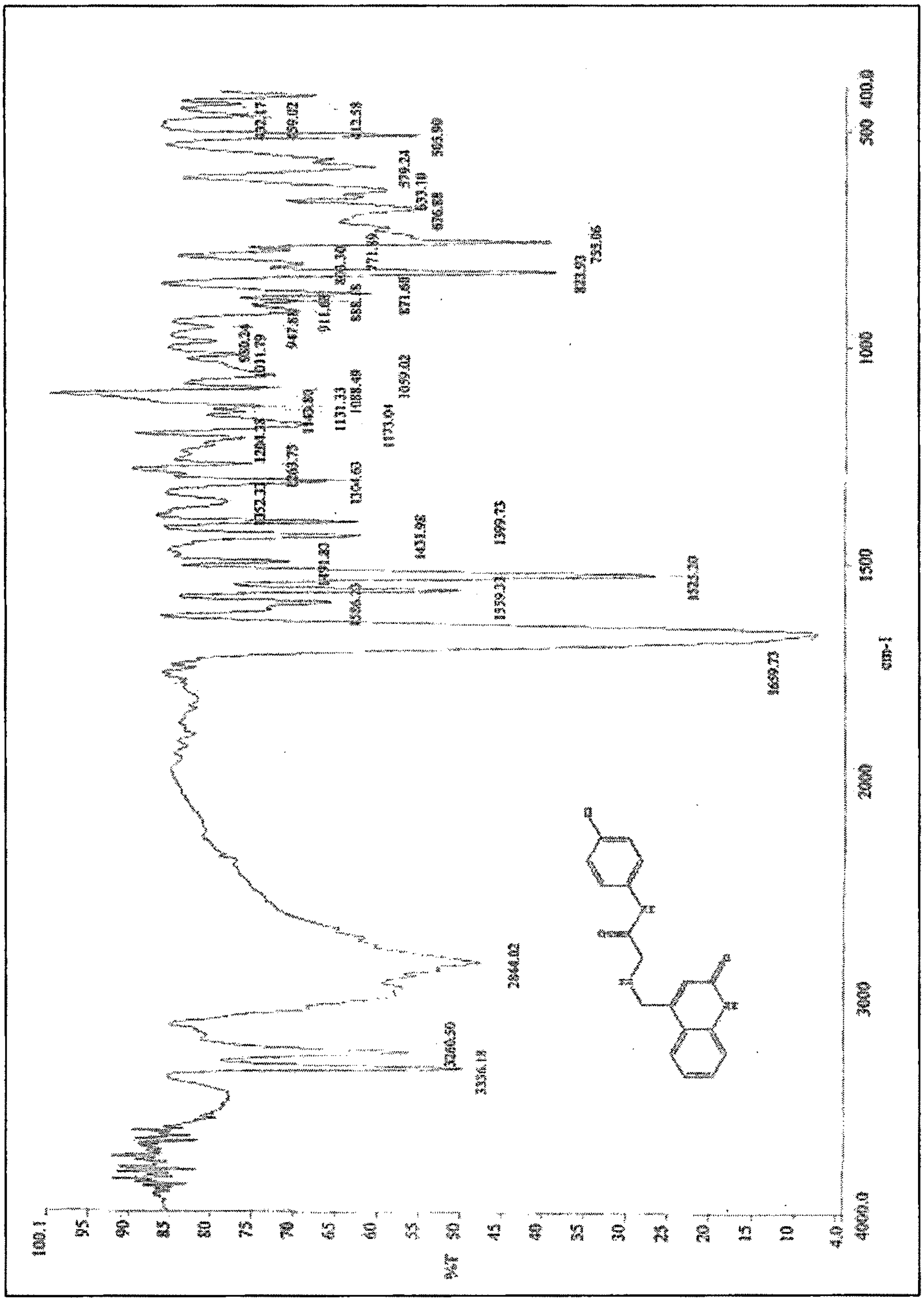


Figure 5.9.1: IR spectrum of N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide **7a**

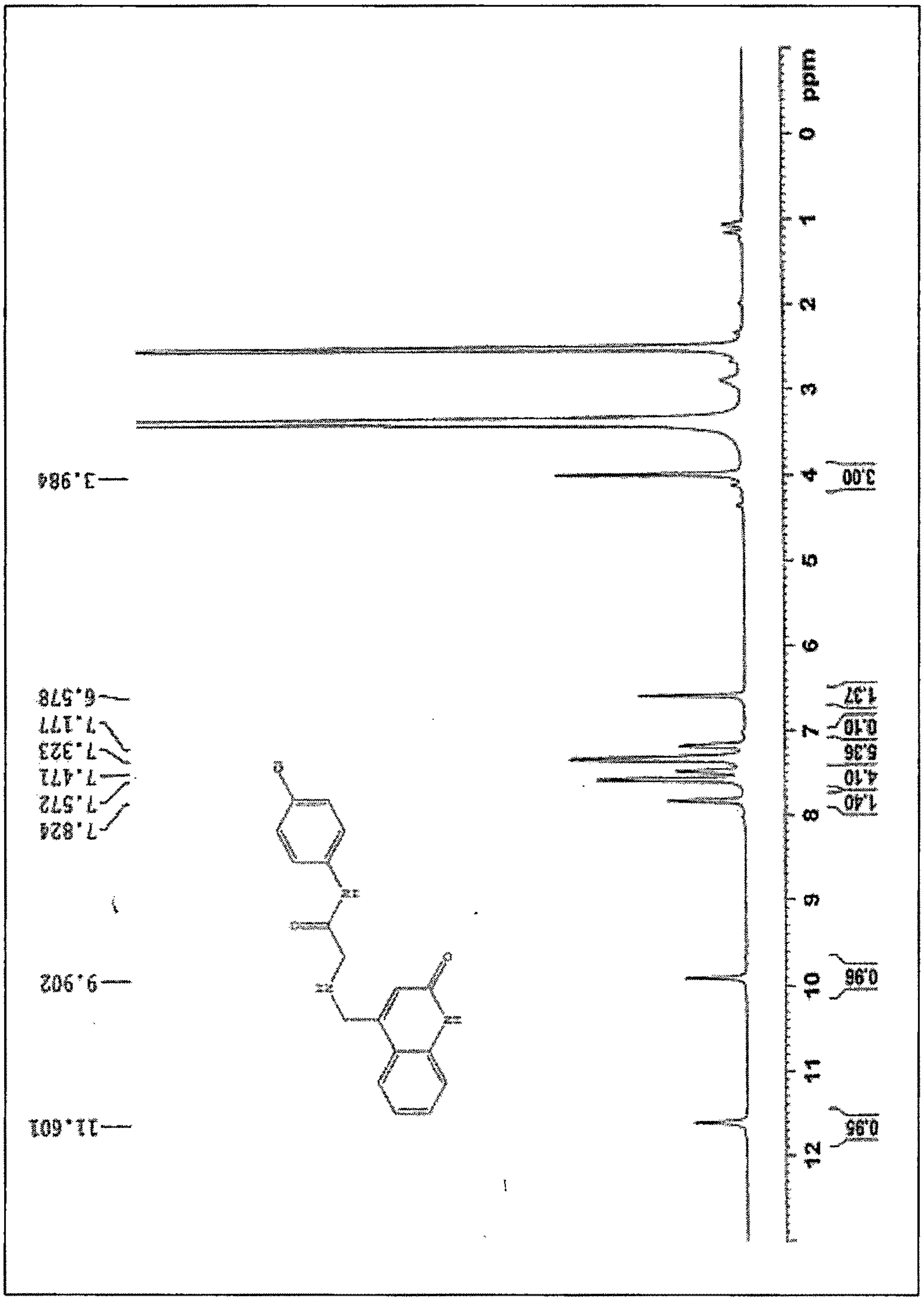


Figure 5.9.2: ^{1}H NMR spectrum of N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide **7a**

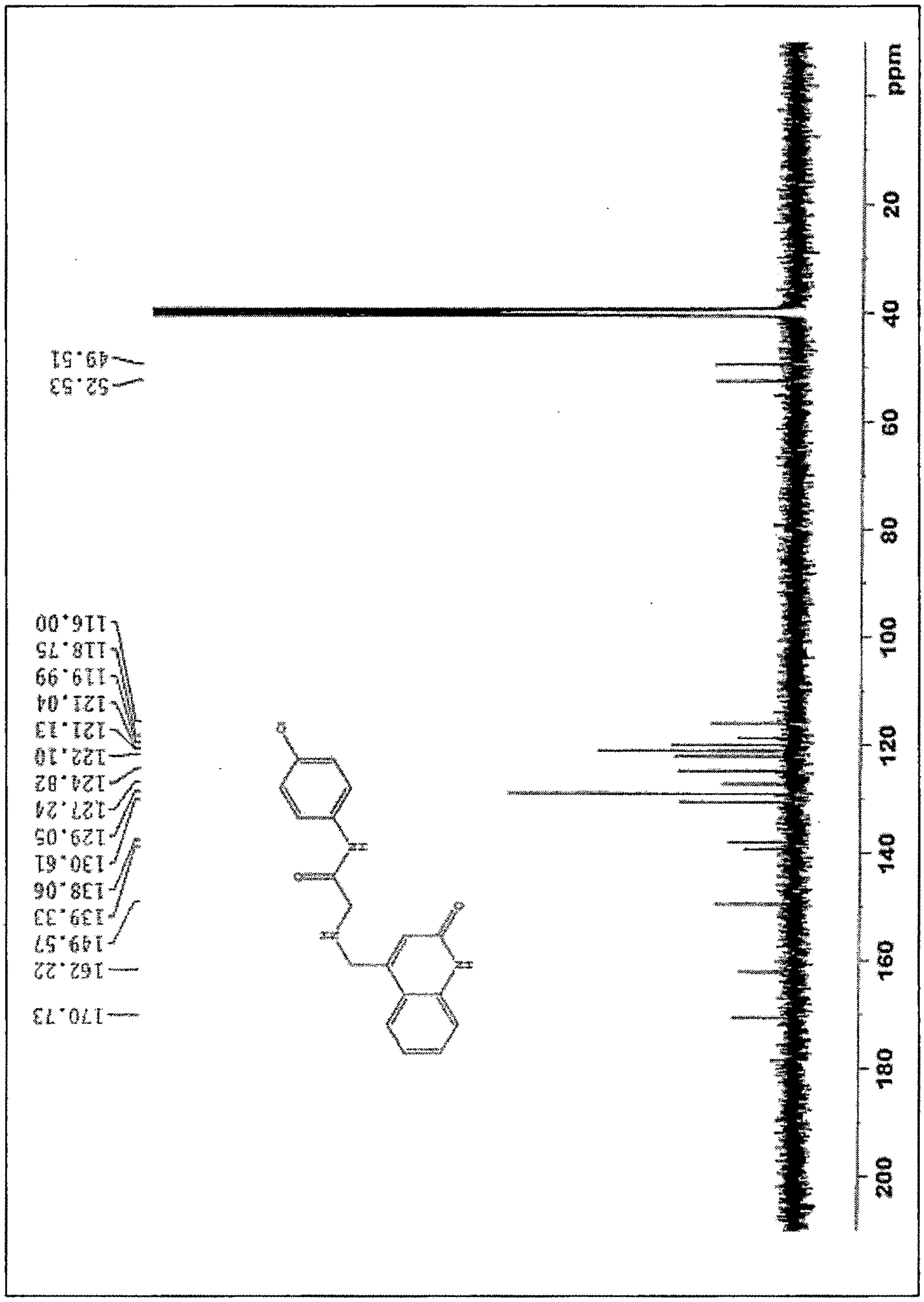


Figure 5.9.3: ^{13}C NMR spectrum of N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide **7a**

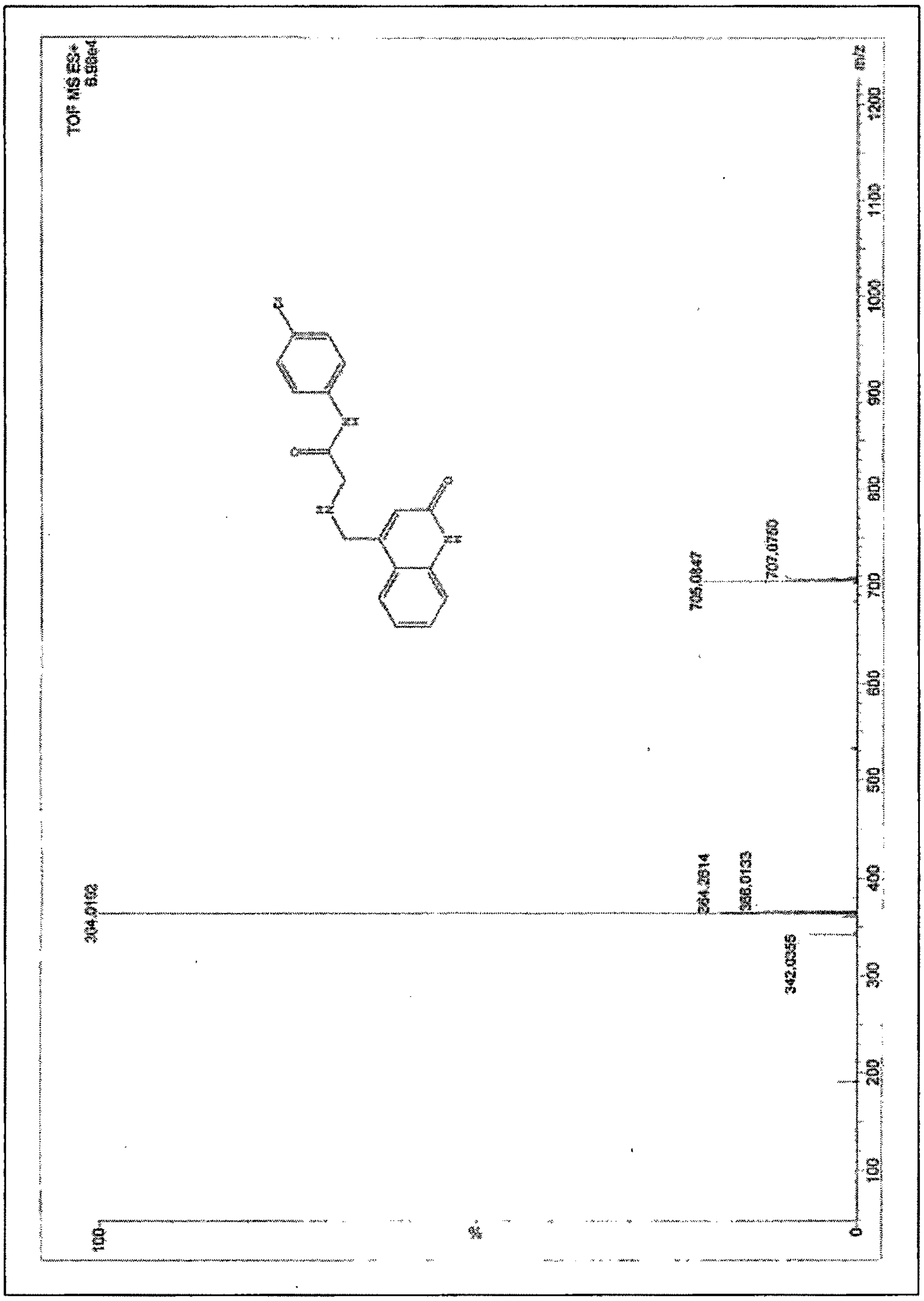


Figure 5.9.4: ESI-MS spectrum of N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide **7a**

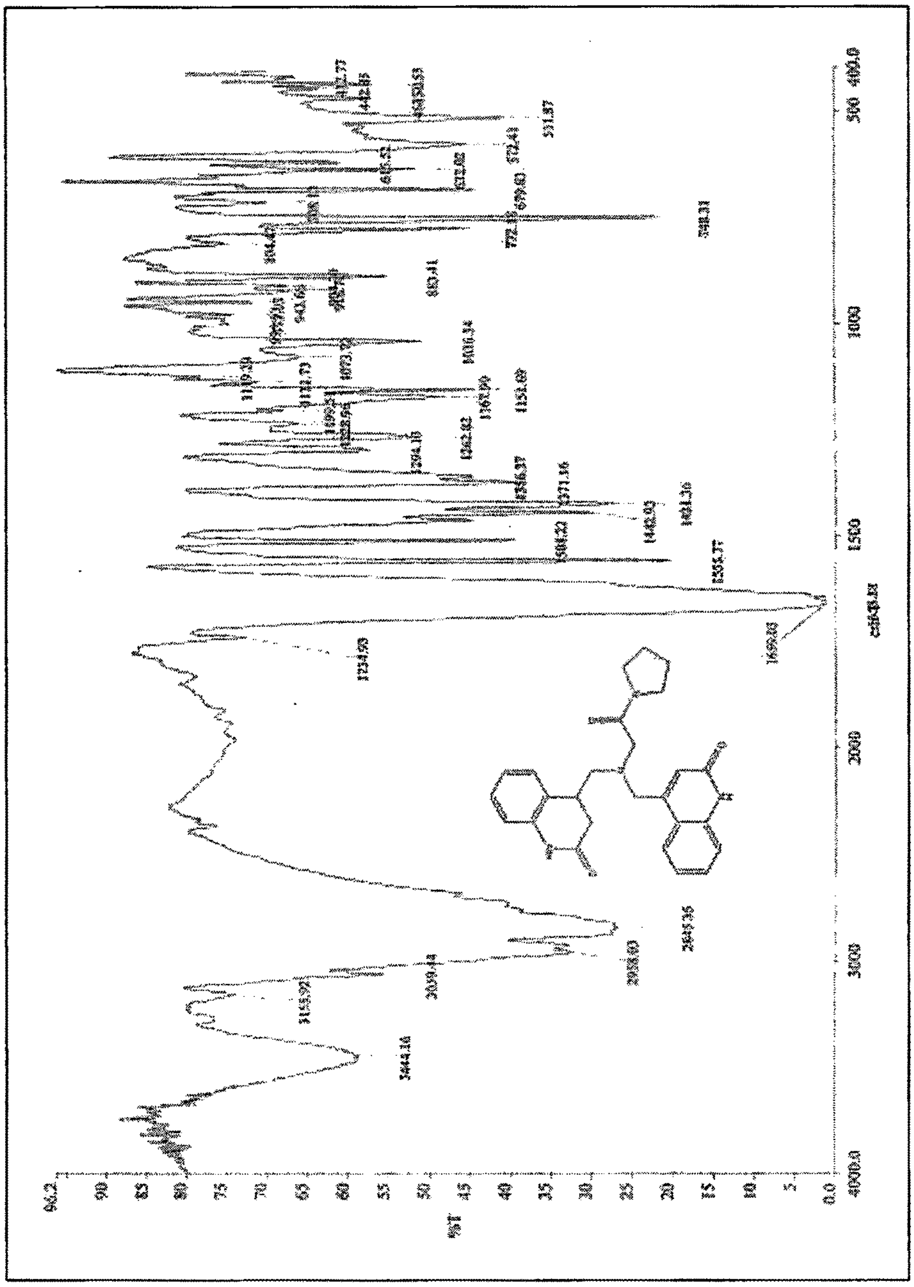


Figure 5.10.1: IR spectrum of 4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one **7f**

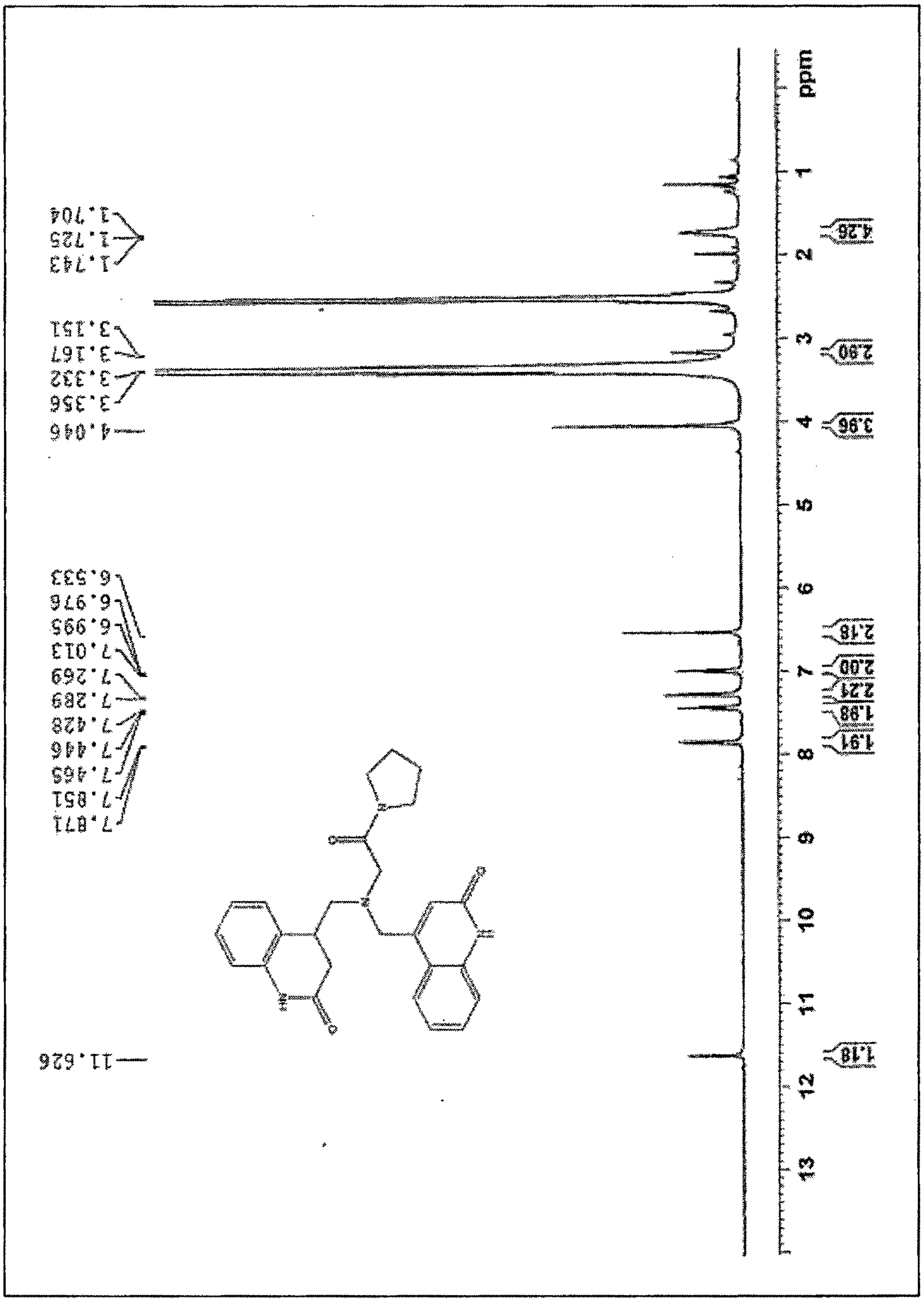


Figure 5.10.2: ^{1}H NMR spectrum of 4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one **7f**

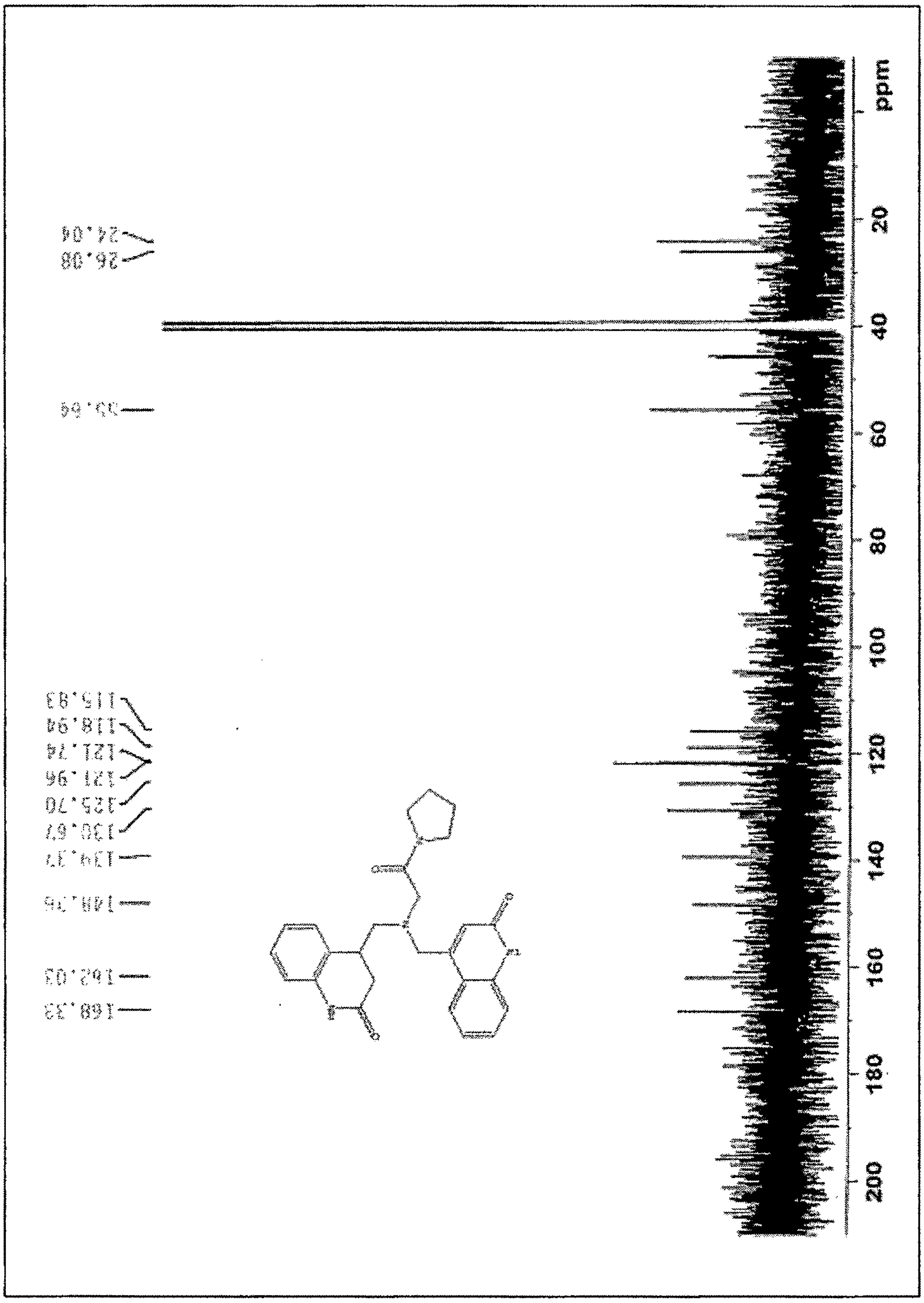


Figure 5.10.3: ^{13}C NMR spectrum of 4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one **7f**

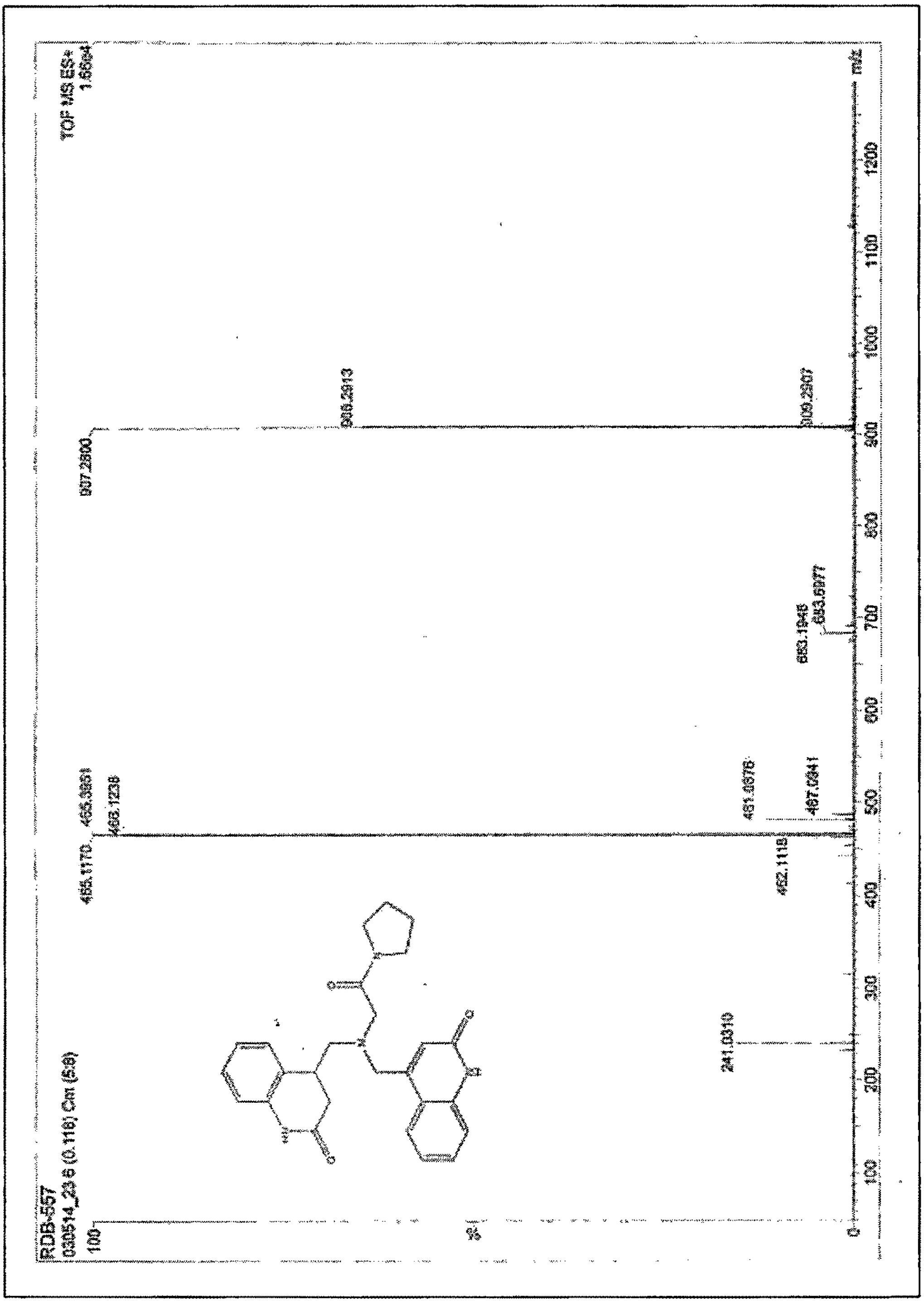
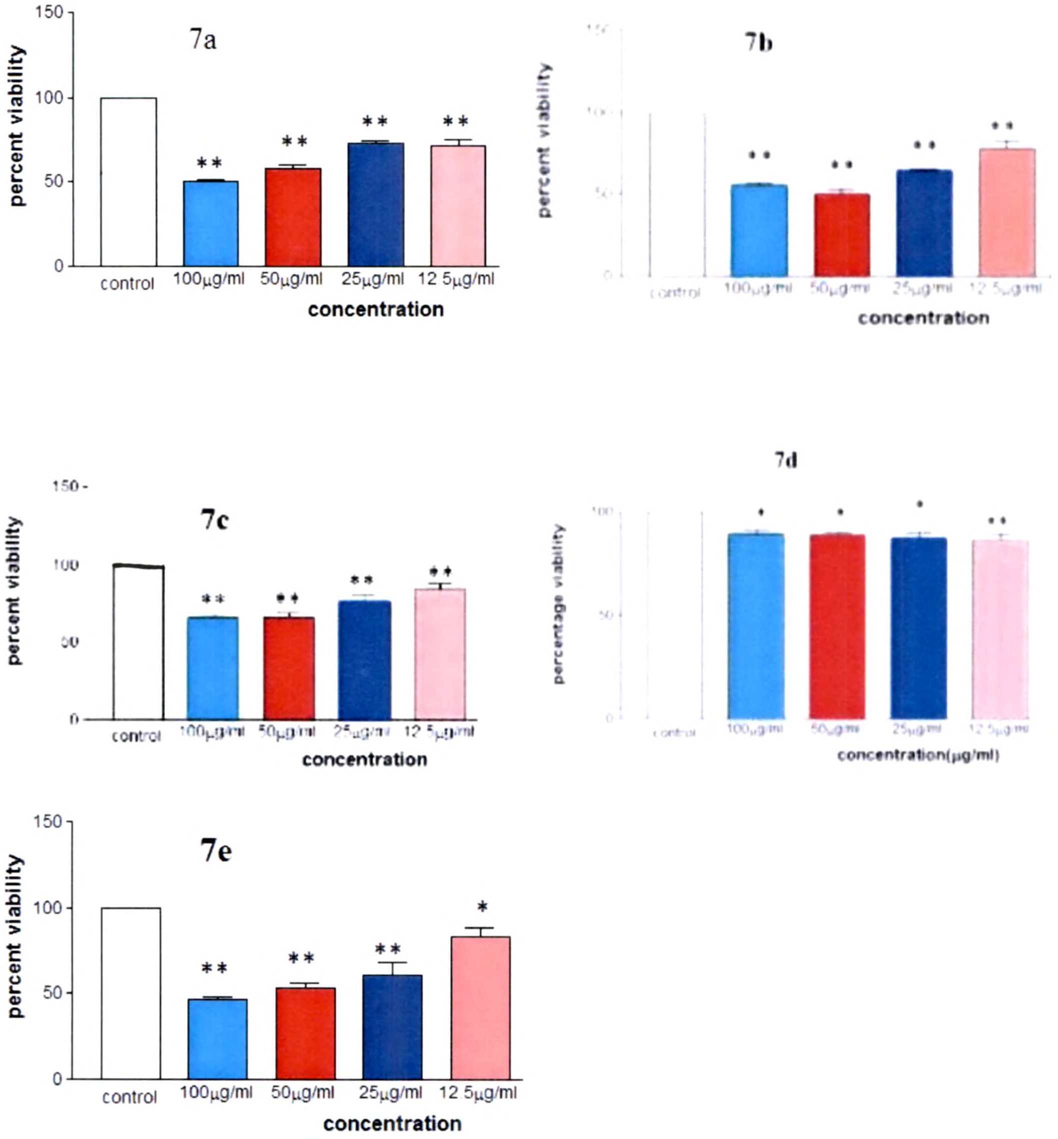


Figure 5.10.4: ESI-MS spectrum of 4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one **7f**

5.2.2 Biological activity

Cytotoxicity assay

For testing cytotoxicity potential of test compounds 7a-e, MTT assay was performed. In a 96 well plate A549 cells were plated (104 cells ⁄ well in 100 μL of medium) in their exponential growth phase , the cells were incubated for 24 hr. Test compounds were prepared in 1% DMSO at 2 fold concentration (12.5, 25.0, 50.0 and 100.0 μg/mL) and cells were exposed to different concentration of test compounds. Post incubation media was removed and cell were incubated with 100 μL MTT reagent (1 mg⁄mL) at 37 °C for 160 min. DMSO (100 μL) was used to solubilize formazan, produced by only viable cells. Plate was placed on micro-vibrator for 5 min to assist solublization; absorbance at 540nm was read by microplate reader. Percentage cytotoxicity was calculated against control (media with DMSO only) for test compounds **7a-e.** The results are shown in Figure 5.10.



Data expressed as mean ± S.E.M. for n=3. ### P<0.001 compared with control (DMSO), **and *P<0.05, **P<0.01, ***P<0.001 and ns = not significant compared.**

Figure 5.10: MTT assay of compounds **7a-e**.

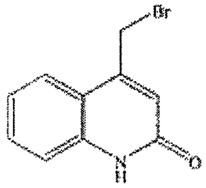
5.3 Conclusion

From the MTT assay it can be concluded that amongst the test compounds **7a-e**, *para*-substituted aniline derivatives showed good cytotoxicity of which *p*-bromo aniline derivative **7b** is the most toxic while the aliphatic dimethyl amine derivative **7e** is the most potent anti-cancer agent in the series.

5.4 Experimental

Reagent grade chemicals and solvents were purchased from commercial supplier and used after purification. TLC was performed on silica gel F254 plates (Merck). Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX 1 spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 400 spectrometer (400 MHz) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. *J* values are in Hz. Mass of the compounds were determined by ESI-MS, using a Shimadzu LCMS 2020 apparatus. All reactions were carried out under nitrogen condition.

General method for the preparation of 4-(bromomethyl)quinolin-2(1H)-one 3:



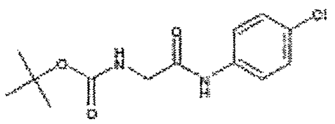
To a solution of acetoacetanilide **1** (0.056 mmol) in glacial acetic acid (10 mL) containing catalytic amount of iodine, bromine (0.056 mmol) in glacial acetic acid (30 mL) was added at 0-5 °C, over a period of 30 minutes and then the reaction mixture was stirred at room temperature till the completion of reaction as monitored on TLC. On completion of reaction, it was poured onto crushed ice and the solid thus separated was filtered and washed with cold water several times and dried to yield 3-oxo-3-(phenylamino)propanoyl bromide **2**. A solution of compound **2** (1 g) in conc. H_2SO_4 (2 mL) on heating at 90-100 °C for 2 hours, poured into crushed ice, gave crude product which on recrystallization from absolute ethanol gave, off-white fluffy mass of 4-(bromomethyl)quinolin-2(1H)-one **3**.

Yield: 65%; off-white solid; m.p.: 258-260 °C [Lit. 258-260 °C]; IR (KBr): 3316, 3141,3098, 3017, 2968, 2891, 2856, 2742, 1669, 1616, 1552, 1511, 1473, 1435, 1403, 1267, 1206, 1145, 1130, 982, 899, 881, 750, 585 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.90 (s, 2H), 6.74 (s, 1H), 7.24 (t, 1H, J = 7.6 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.84 (d, 1H, J = 8.0 Hz), 11.86 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 59.96, 116.14, 117.19, 117.89, 122.33, 124.17, 130.78, 131.22, 138.92, 147.32, 152.34, 162.37; $C_{10}H_8BrNO$; ESI-MS: *m/z* 237.8 $[M]^+$ and 239.8 $[M+2]^+$.

General procedure for the preparation of compounds 5a-f:

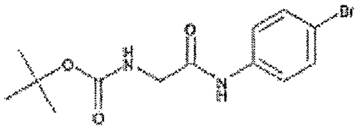
A mixture of boc-glycine **4** (1.11 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.67 mmol) (EDCI), 1-hydroxybenzotriazole (1.11 mmol) (HOBt), 4-dimethylaminopyridine (1.34mmol) (DMAP) and amine (1^0 and 2^0) (1.22 mmol) in dichloromethane (50 mL) (DCM) was stirred at room temperature for 16 hours. The reaction was monitored using TLC. On completion of the reaction, it was washed with water (2X20 mL), brine (1X10 mL), dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to give the crude product which was then purified by column chromatography using silica gel, employing methanol in dichloromethane (5:95) as eluent to yield desired product as white solid **5a-f**.

tert-butyl 2-(4-chlorophenylamino)-2-oxoethylcarbamate 5a:



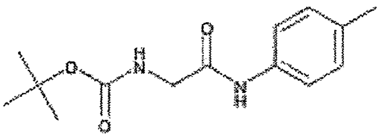
Yield: 70%; white solid; m.p.: 182-184 °C; IR (KBr): 3370, 3320, 3204, 3136, 2999, 2968, 2938, 1681, 1673, 1613, 1555, 1520, 1492, 1403, 1391, 1290, 1247, 1180, 1163, 1087, 935, 831, 725 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (s, 9H), 3.71 (d, 2H, *J* = 6.4 Hz), 7.09 (br s, 1H), 7.36 (d, 2H, *J* = 8.8 Hz), 7.61 (d, 2H, *J* = 8.8 Hz), 10.08 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 18.92, 28.61, 44.14, 49.05, 56.52, 78.66, 121.08, 127.20, 129.12, 138.26, 156.45, 168.91; $C_{13}H_{17}ClN_2O_3$; ESI-MS: *m/z* 307.0 [M+Na]$^+$.

tert-butyl 2-(4-bromophenylamino)-2-oxoethylcarbamate 5b:



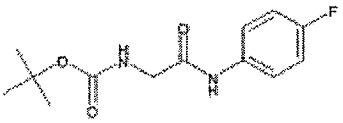
Yield : 75%; white solid; m.p.: 172-174 °C; IR (KBr) : 3372, 3320, 3281, 3204, 3134, 2996, 1678, 1611, 1545, 1523, 1491, 1391, 1290, 1246, 1180, 827 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (m, 2H), 7.03-7.06 (m, 1H), 7.11-7.16 (m, 2H), 7.56-7.59 (m, 2H), 10.01 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 18.92, 28.62, 44.07, 49.05, 56.52, 78.64, 115.65, 115.87, 121.25, 121.33, 135.70, 156.44, 168.65; $C_{13}H_{17}BrN_2O_3$; ESI-MS : *m/z* 350.9 [M+Na]$^+$.

tert-butyl 2-oxo-2-(p-tolylamino)ethylcarbamate 5c:



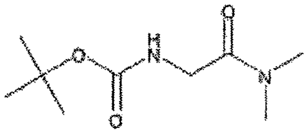
Yield: 55%; white solid; m.p.: 156-158 °C; IR (KBr): 3379, 3319, 3208, 3141, 2987, 2971, 2936, 1690, 1674, 1612, 1549, 1525, 1393, 1316, 1289, 1250, 1170, 935, 821, 729, 580, 505 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 2.22 (s, 3H), 3.95 (br s, 2H), 5.49 (br s, 1h), 7.12 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz), 8.34 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.90, 28.32, 45.36, 80.62, 120.09, 129.50, 134.15, 134.89, 156.51, 167.76; $C_{14}H_{20}N_2O_3$; ESI-MS: *m/z* 265.1 $[M+H]^+$.

tert-butyl 2-(4-fluorophenylamino)-2-oxoethylcarbamate 5d:



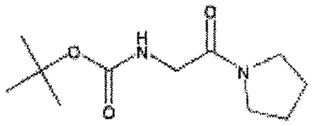
Yield: 69%; white solid; m.p.: 166-164 °C; IR (KBr): 3367, 3323, 3226, 3163, 3103, 3004, 2990, 2941, 1688, 1672, 1619, 1565, 1529, 1508, 1391, 1367, 1292, 1251, 1171, 1155, 1049, 837 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (s, 9H), 3.70 (d, 2H, J = 6.0 Hz), 7.05-7.08 (m, 1H), 7.12-7.16 (m, 2H), 7.57-7.61 (m, 2H), 10.01 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 28.62, 44.09, 78.57, 115.64, 115.86, 121.21, 121.28, 135.76, 156.42, 157.17, 159.55, 168.64; $C_{13}H_{17}FN_2O_3$; ESI-MS: *m/z* 291 $[M+Na]^+$.

tert-butyl 2-(dimethylamino)-2-oxoethylcarbamate 5e:



Yield: 50%; white solid; m.p.: 66-68 °C; IR (KBr): 3563, 3259, 2939, 1569, 1732, 1683, 1645, 1569, 1551, 1534, 1503, 1454, 1431, 1365, 1335, 1248, 1176, 1044, 956, 939, 868, 814, 736, 642, 551 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.42 (s, 9H), 2.94 (s, 3H), 2.96 (s, 3H), , 3.92 (s, 2H), 5.51 (s, 1H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 28.33, 35.55, 35.82, 42.24, 79.52, 155.83, 168.26; $C_9H_{18}N_2O_3$; ESI-MS: *m/z* 203.0 [M+H]$^+$.

tert-butyl 2-oxo-2-(pyrrolidin-1-yl)ethylcarbamate 5f:

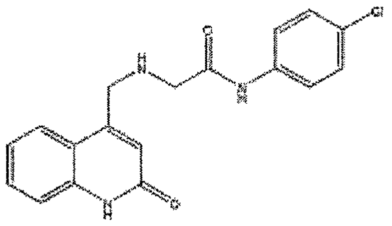


Yield: 45%; viscous liquid; IR (KBr): 3283, 3044, 2978, 2935, 2879, 1722, 1636, 1535, 1450, 1403, 1364, 1340, 1287, 1267, 1253, 1226, 1158, 1041, 940, 869, 856, 804, 766, 643, 548 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.46 (s, 9H), 1.86-1.91 (m, 2H), 1.96-2.01 (m, 2H), 3.37 (t, 2H, J = 6.8 Hz), 3.50 (t, 2H, J = 6.8 Hz), 3.89 (d, 2H, J = 4.4 Hz), 5.52 (br s, 1H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 24.15, 25.97, 28.37, 39.43, 43.07, 45.34, 45.94, 155.88, 166.76; $C_{11}H_{20}N_2O_3$; ESI-MS: *m/z* 229.0 [M+H]$^+$.

General procedure for preparation of compounds 7a-e:

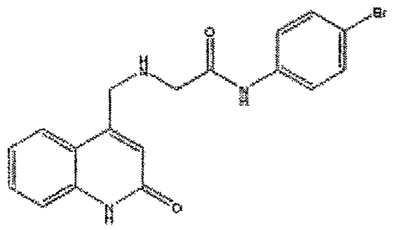
Compounds **5a-e** were deprotected by stirring it in a solution of 10% trifluoroacetic acid (TFA) in dichloromethane (DCM). On deprotection of amine, the solvent was evaporated under reduced pressure to give corresponding free base **6a-e** (1.1 mmol), to which a solution of compound **3** (1.0 mmol) in dimethyl formamide (DMF) was added followed by lithium hydroxide mono hydrate (2.0 mmol) and the resulting mixture was stirred at room temperature till completion of reaction, as monitored on TLC. On completion of reaction, it was poured onto crushed ice and the solid filtered, dried and recrystallized from absolute ethanol to yield product **7a-e**.

N-(4-chlorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide 7a:



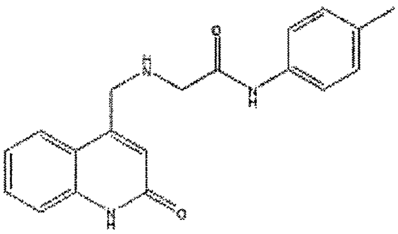
Yield: 25%; white solid; m.p.: 246-248 °C; IR (KBr): 3336, 3260, 2844, 1660, 1559, 1525, 1432, 1400, 1305, 1173, 1059, 871, 824, 755, 676, 506 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.8-3.0 (m, 2H), 3.98 (s, 2H), 6.58 (s, 1H), 7.18-7.82 (m, 10H), 9.90 (s, 1H), 11.60 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$): δ 49.51, 52.53, 1116.00, 118.75, 119.99, 121.04, 121.13, 122.10, 124.82, 127.24, 129.05, 130.61, 138.06, 139.33, 149.57, 162.22, 170.73; $C_{18}H_{16}ClN_3O_2$; ESI-MS: *m/z* 364 [M+Na]$^+$.

N-(4-bromophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide 7b:



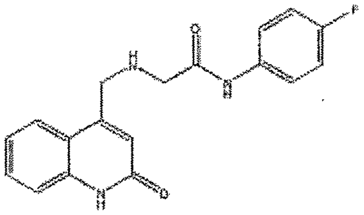
Yield: 15%; white solid; m.p.: 260 °C (decomposes); IR (KBr): 3338, 3250, 2854, 1666, 1531, 1435, 1314, 1072, 892, 818, 751cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ; ^{13}C NMR (400 MHz, DMSO-d_6): δ 2.8-3.0 (m, 2H), 3.98 (s, 2H), 6.58 (s, 1H), 7.07-7.93 (m, 8H), 9.72 (s, 1H), 11.67 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 49.54, 52.57, 116.01, 118.76, 120.00, 121.15, 122.11, 124.82, 127.25, 129.05, 130.61, 138.07, 139.34, 149.57, 162.23, 170.74; $C_{18}H_{16}BrN_3O_2$; ESI-MS: *m/z* 407.9 [M+Na]$^+$.

2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)-N-p-tolylacetamide 7c:



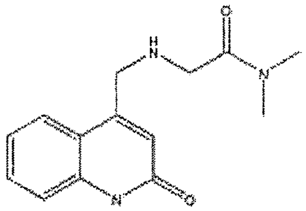
Yield: 25%; white solid; m.p.: 240-242 °C; IR (KBr): 3337, 3248, 3000, 2852, 1668, 1661, 1559, 1532, 1436, 1408, 1355, 1316, 1206, 1133, 914, 892, 817, 752, 674 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 2H), 3.99 (s, 2H), 6.58 (s, 1H), 7.07-7.91 (m, 9H), 9.71 (s, 1H), 11.67 (s, 1H); $C_{19}H_{19}N_3O_2$; ESI-MS: *m/z* 344 [M+Na]$^+$.

N-(4-fluorophenyl)-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide 7d:



Yield: 35%; white solid; m.p.: 220 °C (decomposes); IR (KBr): 3265, 1671, 1614, 1559, 1509, 1468, 1407, 1295, 1216, 1155, 958, 836, 754, 689 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.5 (s, 2H), 3.97 (s, 2H), 6.58 (s, 1H), 7.06-7.84 (m, 10H), 9.92 (s, 1H), 11.75 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 26.04, 49.50, 115.55, 115.77, 116.06, 118.76, 119.93, 121.34, 121.42, 122.12, 124.79, 130.60, 135.59, 139.32, 149.62, 157.21, 162.29, 170.53, 174.95; $C_{18}H_{16}FN_3O_2$; ESI-MS: *m/z* 364 $[M+K]^+$.

N,N-dimethyl-2-((2-oxo-1,2-dihydroquinolin-4-yl)methylamino)acetamide 7e:



Yield : 25%; yellow solid; m.p. : 200 °C (decomposes); IR (KBr) : 3260, 2849, 1655, 1557, 1408, 748 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 6H), 4.24 (br s, 2H), 4.49 (br s, 2H), 6.53 (s, 1H), 7.00-7.82 (m, 4H), 11.67 (s, 1H); $C_{14}H_{17}N_3O_2$; ESI-MS : *m/z* 282 $[M+Na]^+$.

4,4'-(2-oxo-2-(pyrrolidin-1-yl)ethylazanediyl)bis(methylene)diquinolin-2(1H)-one 7f

Yield : 28%; off-white solid; m.p. : 230 °C (decomposes); IR (KBr) : 3444, 2958, 2845, 1735, 1659, 1556, 1501, 1443, 1421, 1356, 1294, 1262, 1168, 1151, 1036, 941, 883, 772, 679, 632, 572 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.70-1.74 (m, 4H), 3.15-3.50 (m, 4H), 4.04 (s, 4H), 6.53 (s, 1H), 6.98-7.87 (m, 8H), 11.62 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$): 24.04, 26.08, 45.34, 45.94, 55.64, 115.83, 118.94, 121.74, 121.96, 125.70, 130.67, 139.37, 148.36, 162.03, 168.33; $C_{26}H_{26}N_4O_3$; ESI-MS : *m/z* 465.11 [M+Na]$^+$.

5.5 References

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