SAKARYA ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ DERGİSİ

Sakarya University Journal of Science
SAUJS

ISSN 1301-4048 e-ISSN 2147-835X Period Bimonthly Founded 1997 Publisher Sakarya University
http://www.saujs.sakarya.edu.tr/

Title: Synthesis and Structural Characterization of Novel 2-Aminomethyl Quinazolin-4(3H)-ones as Organic Building Blocks

Authors: Feyzi Sinan TOKALI

Recieved: 2022-03-09 00:00:00

Accepted: 2022-09-29 00:00:00

Article Type: Research Article

Volume: 26
Issue: 6
Month: December
Year: 2022
Pages: 1117-1130

How to cite
Feyzi Sinan TOKALI; (2022), Synthesis and Structural Characterization of Novel 2-Aminomethyl Quinazolin-4(3H)-ones as Organic Building Blocks. Sakarya University Journal of Science, 26(6), 1117-1130, DOI: 10.16984/saufenbilder.1085086
Access link
https://dergipark.org.tr/en/pub/saufenbilder/issue/74051/1085086

Sakarya University Journal of Science 26(6), 1117-1130, 2022

Synthesis and Structural Characterization of Novel 2-Aminomethyl Quinazolin-4(3*H*)-ones as Organic Building Blocks

Feyzi Sinan TOKALI*[1]

Abstract

Quinazoline and quinazolinone derivatives display an extensive application in organic and pharmaceutical chemistry, and they have been used as natural and synthetic materials for medicinal chemistry purposes. Here I reported an investigation of a new series of quinazolinone ring derivatives. In this context, starting from the methyl anthranilate, six quinazolinone derivatives (**4a-f**) with various aminomethyl moieties at position 2 were synthesized (89-80%). The structures of compounds **4a-f** were identified using FTIR and NMR Spectroscopy (^{1}H NMR - ^{13}C NMR). The data obtained from the all spectra clearly identify the structures of the compounds.

Keywords: Quinazoline, quinazolinone, synthesis, building blocks, NMR

1. INTRODUCTION

Heterocyclic compounds are very important building blocks in drug discovery studies. They are found in structure of many drugs as synthetic or natural products (Figure 1). Quinazolines and quinazolinones are some of the common chemical building blocks, which belong to the family of heterocyclic nitrogen compounds. Quinazolines are heterocyclic compounds that contain a fused pyrimidine and benzene ring in their structure. Quinazolinones are the saturated form of the quinazolines and classified according to the position of carbonyl group (2(1*H*), 4(3*H*), and 2,4(1*H*,3*H*) quinazolindiones). 4(3*H*) derivatives have attracted the attention of scientists due to their accessibility, ease of synthesis methods, easy availability of starting materials and their biological activities. This class of compounds that known natural and synthetic derivatives have investigated by many scientists for their antitumor [1, 2], anticancer [3-6], anti-inflammatory [7], antimicrobial [8-10], anticonvulsant [11, 12], antifungal [13], anticholinesterase [14, 15], anti-HIV [16], anti-diabetic [17, 18], dihydrofolate reductase inhibition [19], and kinase inhibition [20] properties. Quinazolinones are generally derived from the 2-position. Studies on quinazolinones with some alkyl [21-26] and aryl group [27-30] at the 2 position are frequently encountered in the literature. However, quinazolinones with an aminomethyl moiety at position 2 are rarely encountered. The ones synthesized from these compounds either do not have an experimental procedure or their structures have not been characterized [31].

* Corresponding author: feyzitokali@gmail.com
[1] Kafkas University
ORCID: https://orcid.org/0000-0001-5532-8802

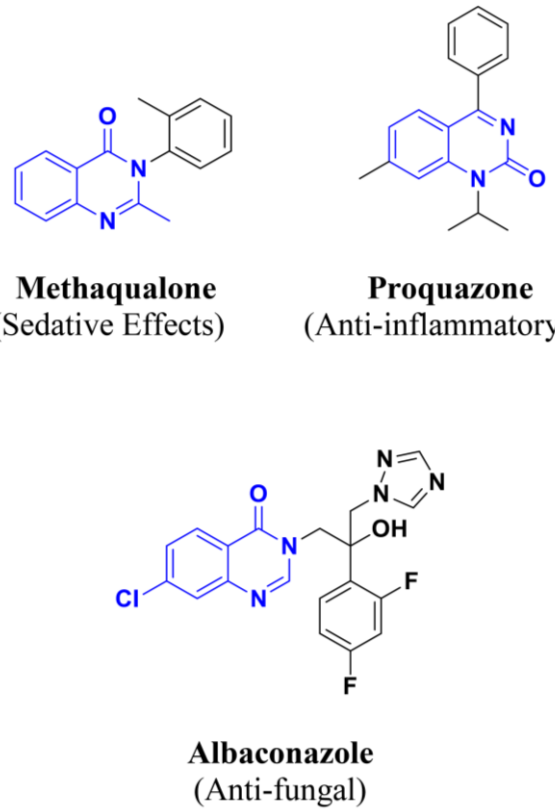

Figure 1 Some drugs containing quinazolinone ring

In this study, it was aimed to synthesize 2-aminomethyl derivatives of quinazolinones, which have great importance in organic, pharmaceutical, and medicinal chemistry for the scientist wants to study the biological activity of quinazolinone derivatives and to characterize their structures.

2. MATERIALS AND METHODS

2.1. Materials

The starting materials used in this synthesis study were purchased from various suppliers and used without any treatment. WRS-2A Meltingpoint Apparatus was used for determine melting points of the compounds. The FTIR spectra of the compounds were recorded using Alpha-P Bruker FTIR spectrophotometer. ^{1}H NMR spectras were recorded on Bruker (400 MHz) and ^{13}C NMR spectras were recorded on Bruker (100 MHz) spectrometer. Deuterated chloroform ($CDCl_3$) was used as solvent.

2.2. Methods

2.2.1. Synthesis of compounds 4a-f

Methyl-2-amino benzoate (methyl anthranilate) **(1)** (1,512 g, 10mmol) was dissolved in 20 mL dichloromethane. Sodium bicarbonate (1,68 g, 20mmol) was added to this solution and stirred for 20 minutes at 0-5°C. Chloroacetyl chloride (1,13 g, 10mmol) was added by dropwise and stirred for an hour at room temperature. After completion (checked by thin layer chromatography; PE:EtOAc – 9:1), the mixture was filtered off and the solvent was removed. *N*-chloroacetyl methyl anthranilate **(2)** (2,28 g, 10mmol) was added to a solution of secondary amine (10mmol) (primer amine for compound **3f**) and K_2CO_3 (2,07 g, 15mmol) in acetonitrile (30 mL) at room temperature. Potassium iodide (catalytic amount) was added and refluxed for an hour. After completion (checked by thin layer chromatography; PE:EtOAc – 7:3), the mixture was filtered off and the solvent was removed. The crude product **(3a-f)** (10mmol) was dissolved in absolute ethanol (20 mL) and $N_2H_4.H_2O$ (1,6 mL, 25mmol, w/w: 80%) was added. The solution was refluxed for 12 hours. After completion (checked by thin layer chromatography; PE:EtOAc – 1:1), 50% of solvent was removed and ether (20 mL) was added. Formed white crystals were filtered off. The crude products **(4a-f)** were recrystallized from ethanol:ether - 1:2 (Figure 2).

2.2.1.1. 2-(Morpholinomethyl)-3-amino-quinazolin-4(3*H*)-one (4a)

White crystals, yield 89% (2,32 g), mp: 126-128 °C. FTIR (cm^{-1}): ν_{max} 3312, 3262, 3070, 2953, 1662, 1598, 768. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*= 8.0 Hz, 1H, ArH), 7.64 – 7.62 (m, 2H, ArH), 7.42 (t, *J* = 7.3 Hz, 1H, ArH), 6.16 (brs, 2H, NH_2), 3.74

(s, 2H, N-CH_2), 3.63 (t, *J* = 4.0, 4H, CH_2-O-CH_2), 2.56 (t, *J* = 4.0, 4H, CH_2-N-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3 (C=O), 150.3 (N=C), 146.1, 133.9, 127.5, 126.9, 126.4, 120.0 (ArC), 66.9 (CH_2-O-CH_2), 61.9 (N-CH_2), 53.4 (CH_2-N-CH_2).

2.2.1.2. 2-[(4-Methylpiperazin-1-yl)methyl]-3-amino-quinazolin-4(3*H*)-one (4b)

White crystals, yield 80% (2,18 g), mp: 136-138 °C. FTIR (cm^{-1}): ν_{max} 3323, 3249, 3106, 2956, 1668, 1593, 776. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H, ArH), 7.81 – 7.65 (m, 2H, ArH), 7.49 (t, *J* = 6.3 Hz, 1H, ArH), 6.36 (brs, 2H, NH_2), 3.82 (s, 2H, N-CH_2), 2.67 (s, 4H, CH_2-N-CH_2), 2.44 (s, 4H, CH_2-N-CH_2), 2.29 (s, 3H, N-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C=O), 150.5 (N=C), 146.2, 133.8, 127.5, 126.8, 126.3, 120.0 (ArC), 61.5 (N-CH_2), 55.1(CH_2-N-CH_2) , 52.9 (CH_2-N-CH_2), 46.0 (N-CH_3).

2.2.1.3. 2-[(4-Phenylpiperazin-1-yl)methyl]-3-amino-quinazolin-4(3*H*)-one (4c)

White crystals, yield 85% (2,86 g), mp: 156-158 °C. FTIR (cm^{-1}): ν_{max} 3326, 3239, 3024, 2937, 1662, 1592, 771. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.7 Hz, 1H, ArH), 7.75 – 7.55 (m, 2H, ArH), 7.42 (t, *J* = 8.2 Hz, 1H, ArH), 7.18 (t, *J* = 8.0 Hz, 2H, ArH), 6.89 – 6.73 (m, 3H, ArH), 6.22 (brs, 2H, NH_2), 3.80 (s, 2H, N-CH_2), 3.11 (t, *J* = 4.0, 4H, CH_2-N-CH_2), 2.72 (t, *J* = 4.0, 4H, CH_2-N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C=O), 151.0 (ArC), 150.5 (N=C), 146.2, 133.9, 129.2, 127.5, 126.9, 126.4, 120.1, 120.0, 116.3 (ArC), 61.6 (N-CH_2), 53.1 (CH_2-N-CH_2), 49.3 (CH_2-N-CH_2).

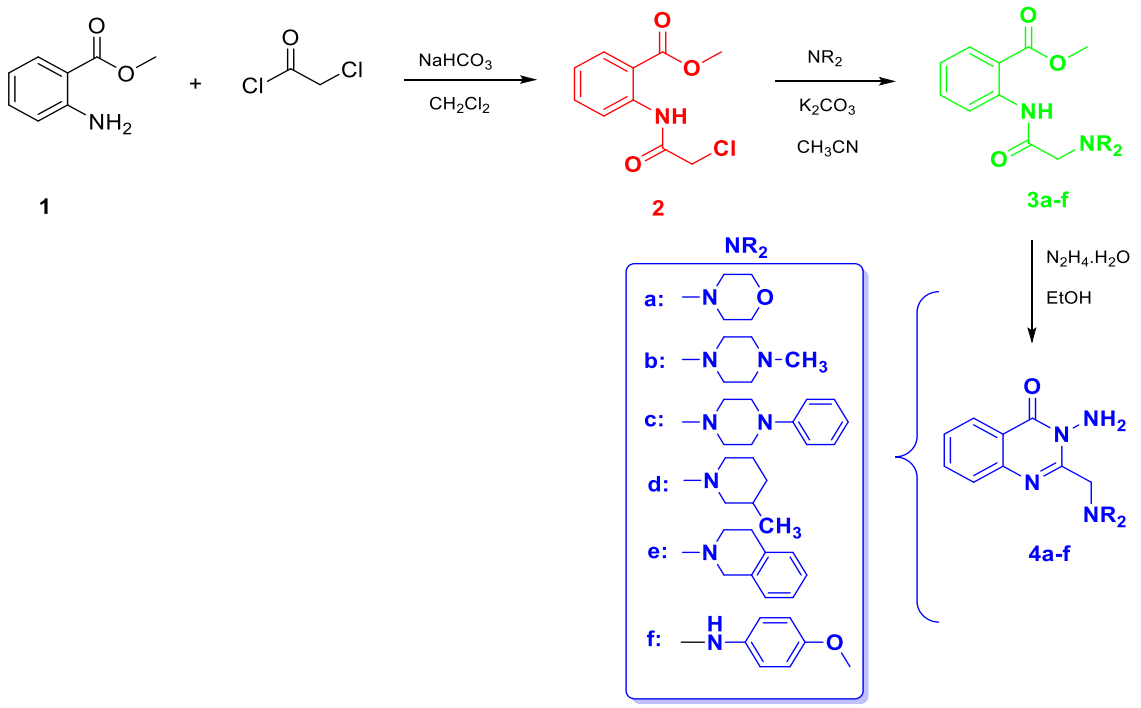

Figure 2 Synthesis of compounds **4a-f**

2.2.1.4. 2-[(3-Methylpiperidin-1-yl)methyl]-3-amino-quinazolin-4(3*H*)-one (4d)

White crystals, yield 80% (2,19 g), mp: 85-87 °C. FTIR (cm^{-1}): ν_{max} 3306, 3236, 2947, 1674, 1599, 779. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.6 Hz, 1H, ArH), 7.78 – 7.68 (m, 2H, ArH), 7.51 – 7.47 (m, 1H, ArH), 6.56 (brs, 2H, NH_2), 3.76 (s, 2H, N-CH_2), 2.83 (t, *J* = 12.0 Hz, 2H, N-CH_2), 2.15 (t, *J* = 10.1 Hz, 1H), 1.87 (t, *J* = 10.6 Hz, 1H), 1.74 – 1.57 (m, 3H), 1.52 – 1.48 (m, 1H) (Protons of piperidine ring), 1.00 –

0.88 (m, 1H, CH), 0.86 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C=O), 150.7 (N=C), 146.2, 133.6, 127.4, 126.7, 126.3, 120.0 (ArC), 62.3, 61.6, 53.8 (N-CH_2), 32.5 (CH_2), 31.4 (CH), 25.5 (CH_2), 19.4 (CH_3).

2.2.1.5. 2-[(3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl]-3-amino-quinazolin-4(3*H*)-one (4e)

White crystals, yield 89% (2,73 g), mp: 107-109 °C. FTIR (cm^{-1}): ν_{max} 3241, 3066, 2934, 1658, 1594, 757. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H, ArH), 7.66 (d, *J* = 3.6 Hz, 2H, ArH), 7.40 (m, 1H, ArH), 7.09 – 6.97 (m, 3H, ArH), 6.91 (d, *J* = 6.6 Hz, 1H, ArH), 6.26 (brs, 2H, NH_2), 3.89 (s, 2H, N-CH_2), 3.72 (s, 2H, N-CH_2), 2.84 (t, *J* = 4.0, 2H, CH_2), 2.82 (t, *J* = 4.0, 2H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1 (C=O), 150.6 (N=C), 146.2, 133.8, 133.7, 128.9, 127.5, 126.6, 126.4, 120.1 (ArC), 61.4, 55.7, 50.6 (N-CH_2), 29.1 (CH_2).

2.2.1.6.2-{[(4-Methoxyphenyl) amino]methyl}-3-amino-quinazolin-4(3*H*)-one (4f)

Beige solid, yield 87% (2,58 g), mp: 125-127 °C. FTIR (cm^{-1}): ν_{max} 3394, 3340, 3200, 3049, 2935, 1673, 1595, 771. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H, ArH), 7.65 – 7.57 (m, 2H, ArH), 7.34 (t, *J* = 7.3 Hz, 1H, ArH), 6.69 (m, 4H, ArH), 4.74 (brs, 3H, NH_2 and NH), 4.37 (s, 2H, N-CH_2), 3.64 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (C=O), 154.1 (ArC), 152.5 (N=C), 146.4, 141.4, 134.3, 127.3, 126.7, 126.4, 120.2, 114.9, 114.7 (ArC), 55.7 (OCH_3), 46.7 (NH-CH_2).

3. RESULTS AND DISCUSSION

3.1. Synthesis

In this study, six 2-aminomethyl quinazolin-4(3*H*)-one derivatives **(4a-f)** were synthesized with good purity and yields. (Figure 2). The reactants and the solvents used in this synthesis study were supplied from various suppliers and used without any treatment. Compounds **4a-f** were obtained starting from the methyl anthranilate **(1)** in three steps with good yields (89-80%). The purity of the all compounds synthesized in this study was checked using TLC. FTIR and NMR (^{1}H - ^{13}C) spectroscopies were applied for the characterization of the synthesized compounds.

3.2. Structural Characterization

In the FTIR spectra of compounds **4a-f**, the stretching bands of the NH_2 group were observed at 3340 – 3200 cm^{-1}. Aromatic and aliphatic C-H stretching bands were seen at 3106 – 3024 cm^{-1} and 2956 – 2934 cm^{-1}, respectively. The stretching bands of the C=O and C=N bonds were observed at 1674 – 1658 cm^{-1} and 1599 – 1592 cm^{-1}, respectively.

^{1}H NMR spectra of the compounds **4a-f** are seen in Figure 3-8. Peaks of the aromatic protons are seen at δ 8.29 – 6.69 ppm as a set of signals (multiplet, triplet or doublet) relative to their chemical environment. Peaks of the NH_2 protons at position 3 of the quinazolinone ring, are seen as a broad singlet at δ 6.56 – 6.16 ppm. For compound **4f**, peaks of the NH_2 protons and the NH proton at position 2 were overlapped and seen as a broad singlet at δ 4.74 ppm (Figure 8). The characteristic peaks of the aminomethyl protons (N-CH_2) were observed at δ 3.82 – 3.74 ppm. For compound **4f**, this peak was observed as a singlet at δ 4.37 ppm. Peaks of the aliphatic protons are seen at δ 3.63 – 0.88 ppm as a set of signals (multiplet, triplet, doublet or singlet) relative to their chemical environment. Finally, peaks of the OCH_3 protons (for compound **4f**) and CH_3 (for compound **4b**) are seen as a singlet at δ 3.64 ppm and δ 2.29 ppm, respectively (Figure 4 and 8). The spectroscopic data mentioned above are in accordance with the

structure of molecules and the data in the literature [16, 32].

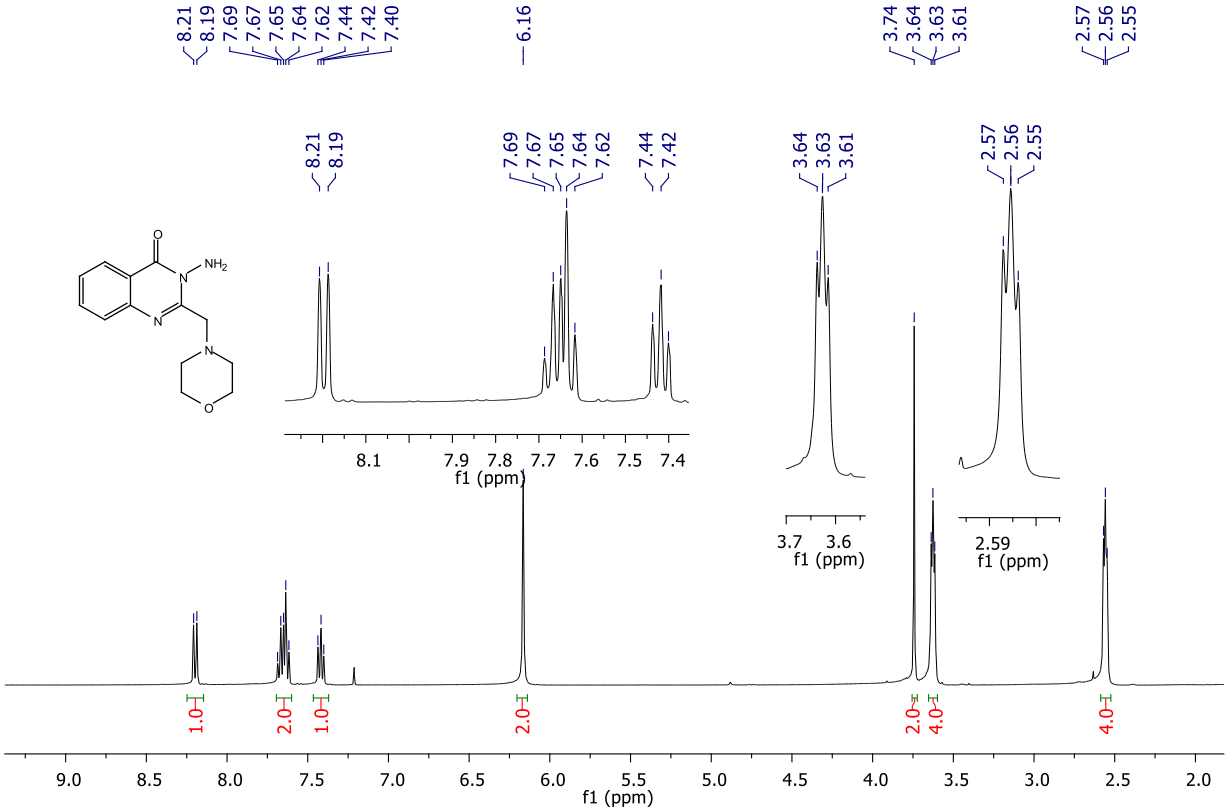

Figure 3 ^{1}H NMR (**4a**)

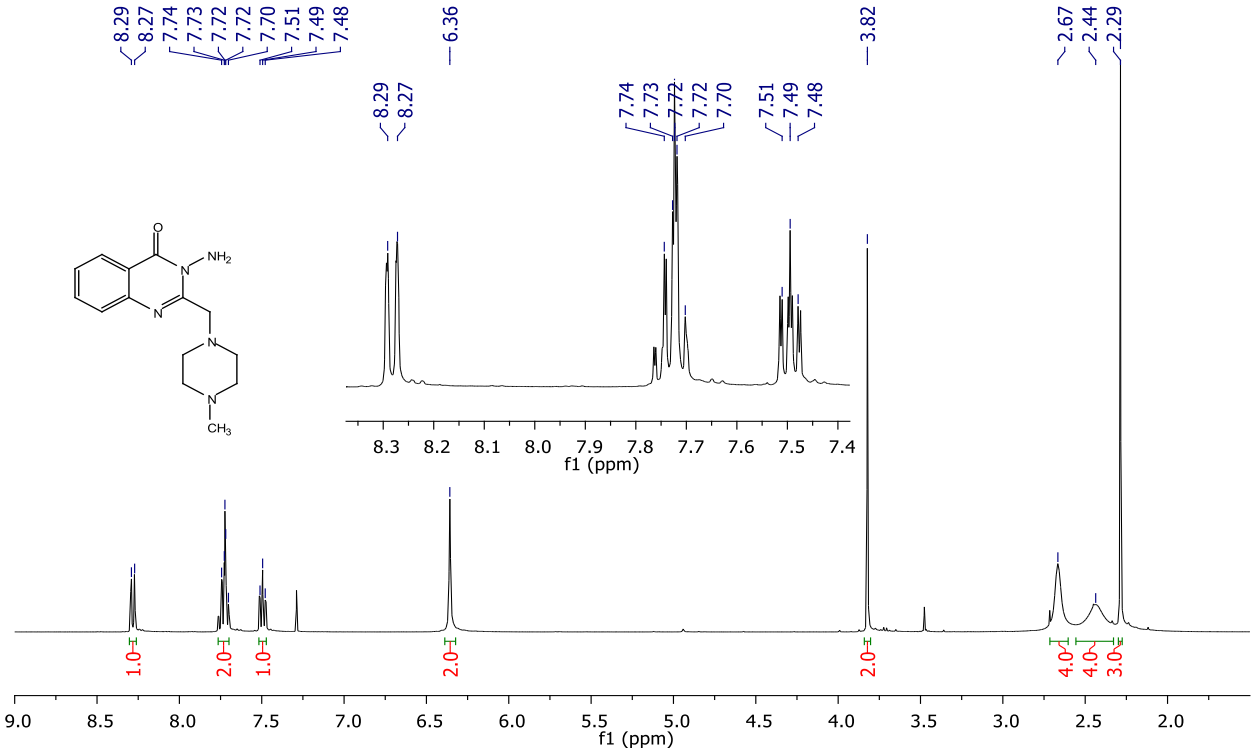

Figure 4 ^{1}H NMR (**4b**)

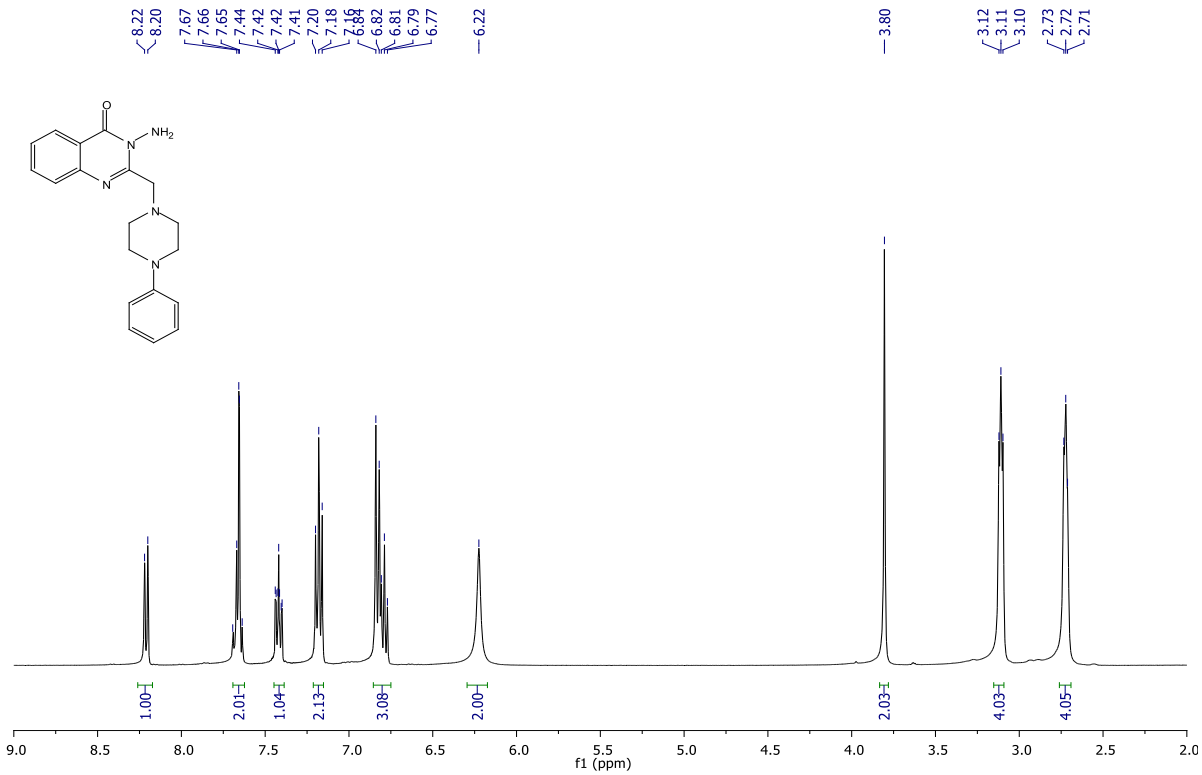

Figure 5 ^{1}H NMR (**4c**)

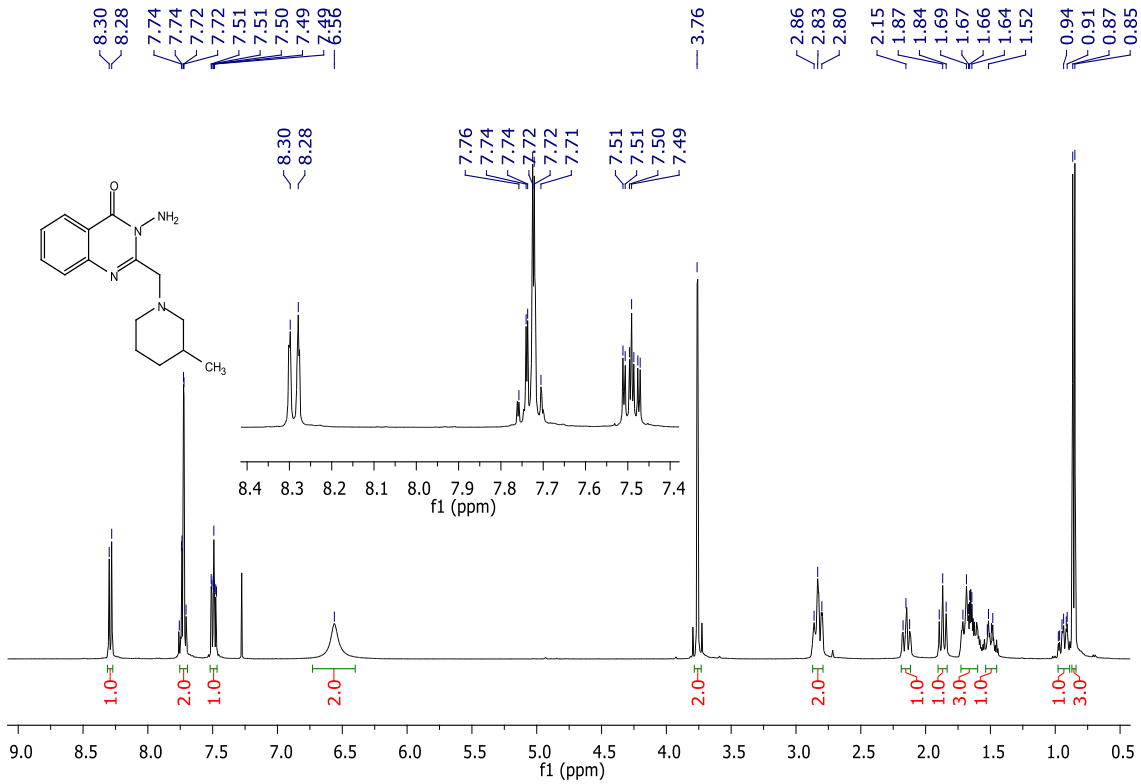

Figure 6 ^{1}H NMR (**4d**)

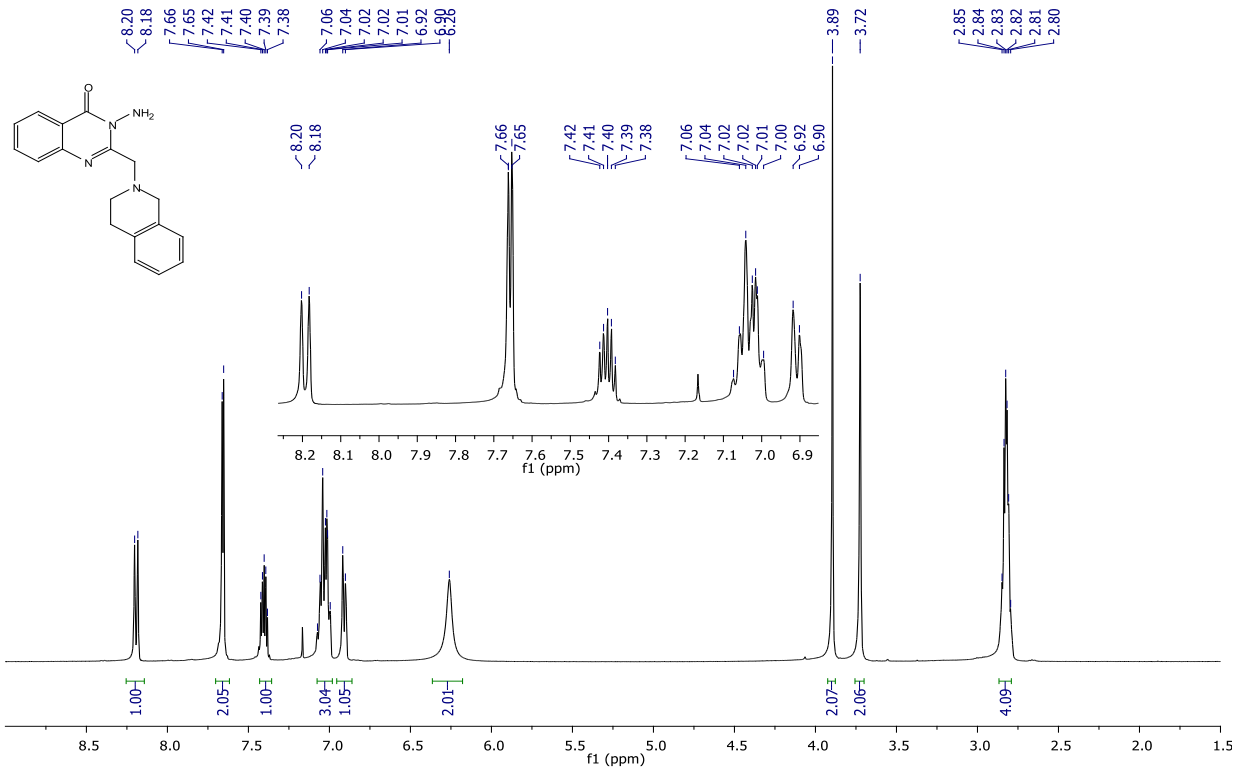

Figure 7 ^{1}H NMR (**4e**)

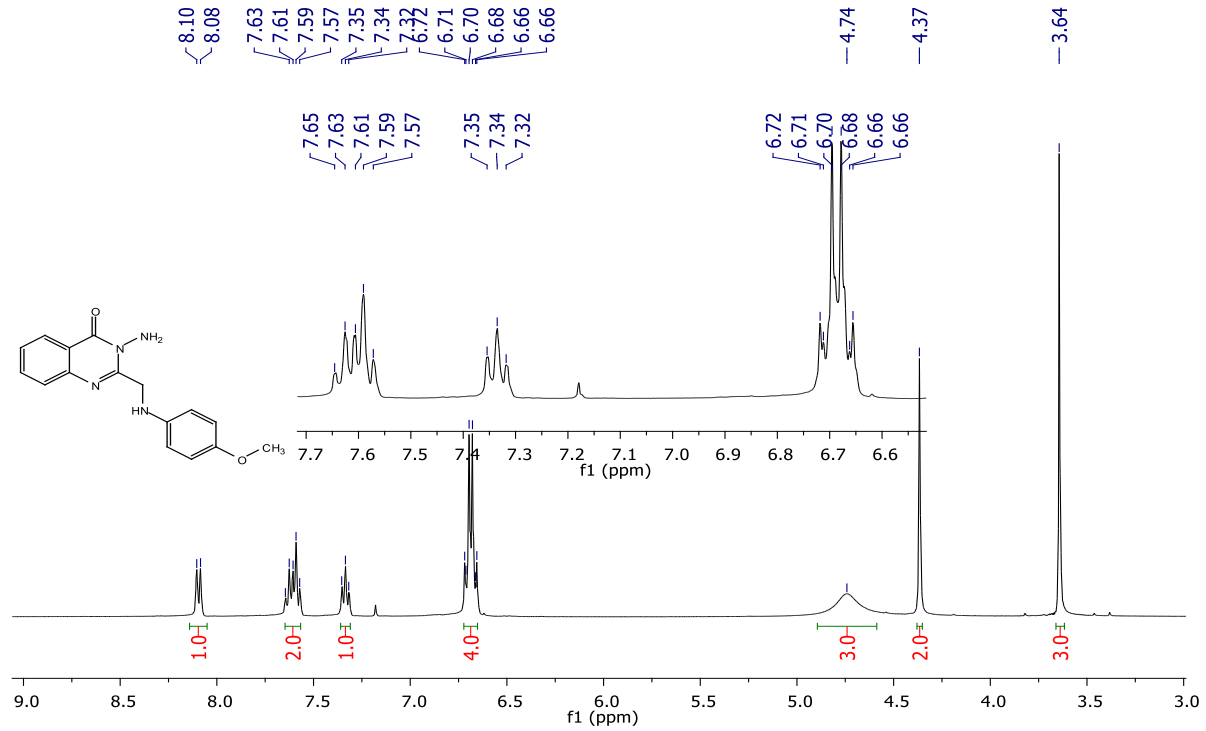

Figure 8 ^{1}H NMR (**4f**)

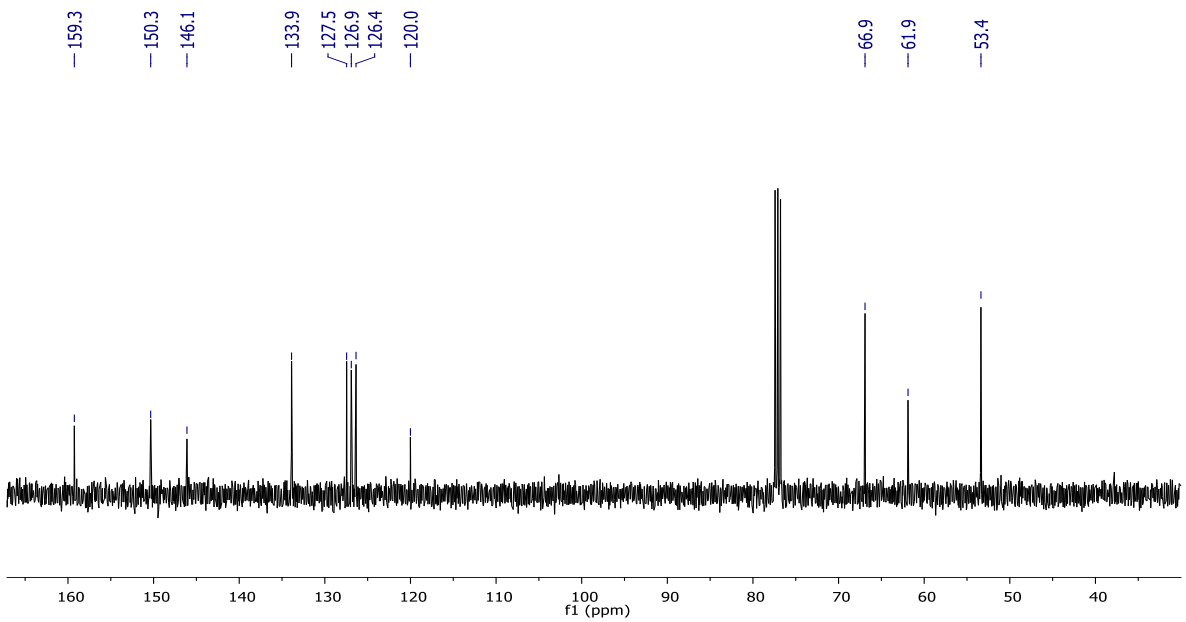

Figure 9 ^{13}C NMR (**4a**)

When the ^{13}C NMR spectra of the compounds **4a-f** were analysed (Figure 9-14), peaks of the carbonyl carbons (C4) are seen at δ 161.5 – 158.9 ppm. Peaks of carbons at the 2 position of quinazoline ring are observed at δ 152.5 – 150.3 ppm. Aromatic carbons are seen at δ 154.1 – 116.3 ppm. The characteristic peaks of the aminomethyl carbons (N-CH_2) were seen δ 61.9 – 61.4 ppm. For comound **4f**, this peak was observed at δ 46.7 ppm (Figure 14). For all compounds, peaks of the aliphatic carbons were seen at δ 66.9 – 19.4 ppm. Finally, for compound **4f**, peak of the OCH_3 carbon was observed at δ 55.7 ppm (Figure 14). The spectroscopic data mentioned above are in accordance with the structure of molecules and the data in the literature [16, 32].

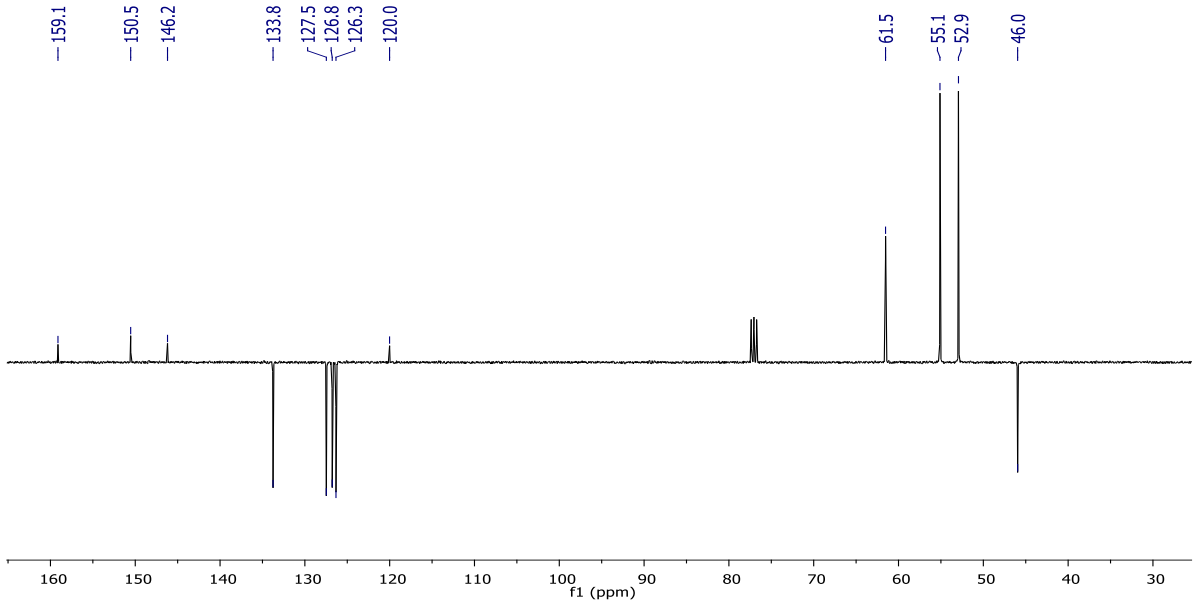

Figure 10 ^{13}C NMR (**4b**)

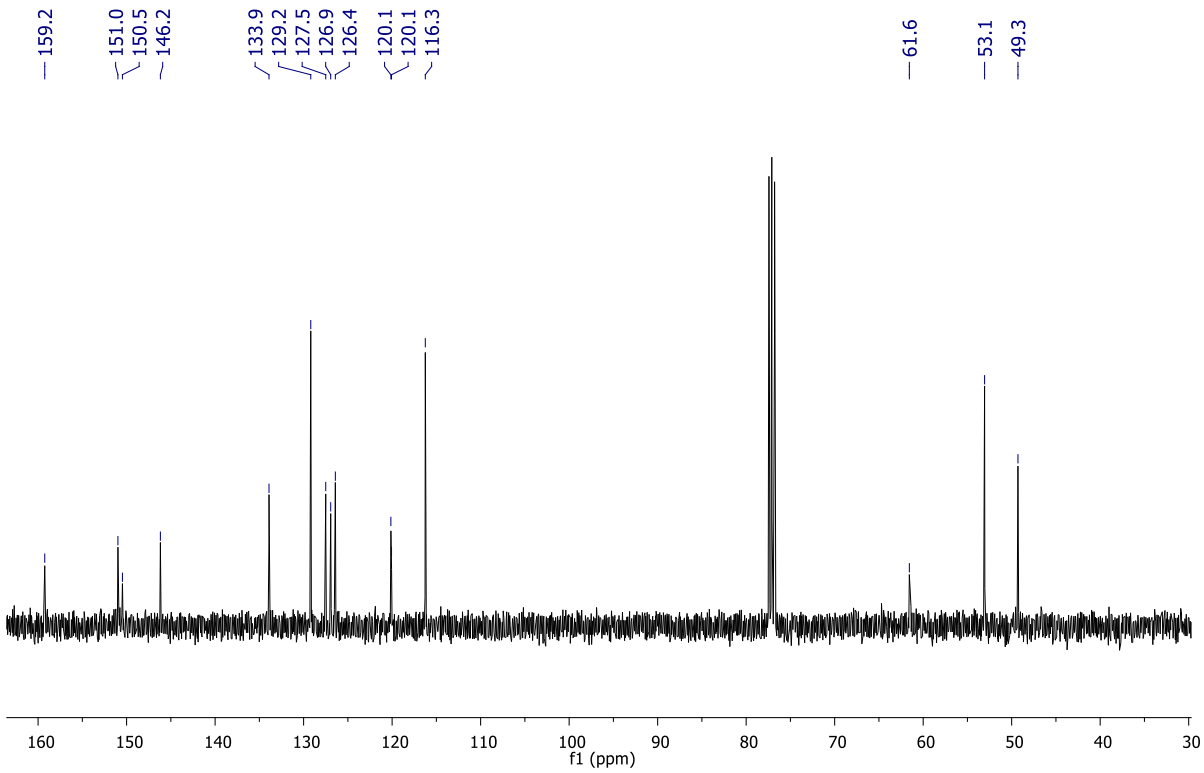

Figure 11 ^{13}C NMR (**4c**)

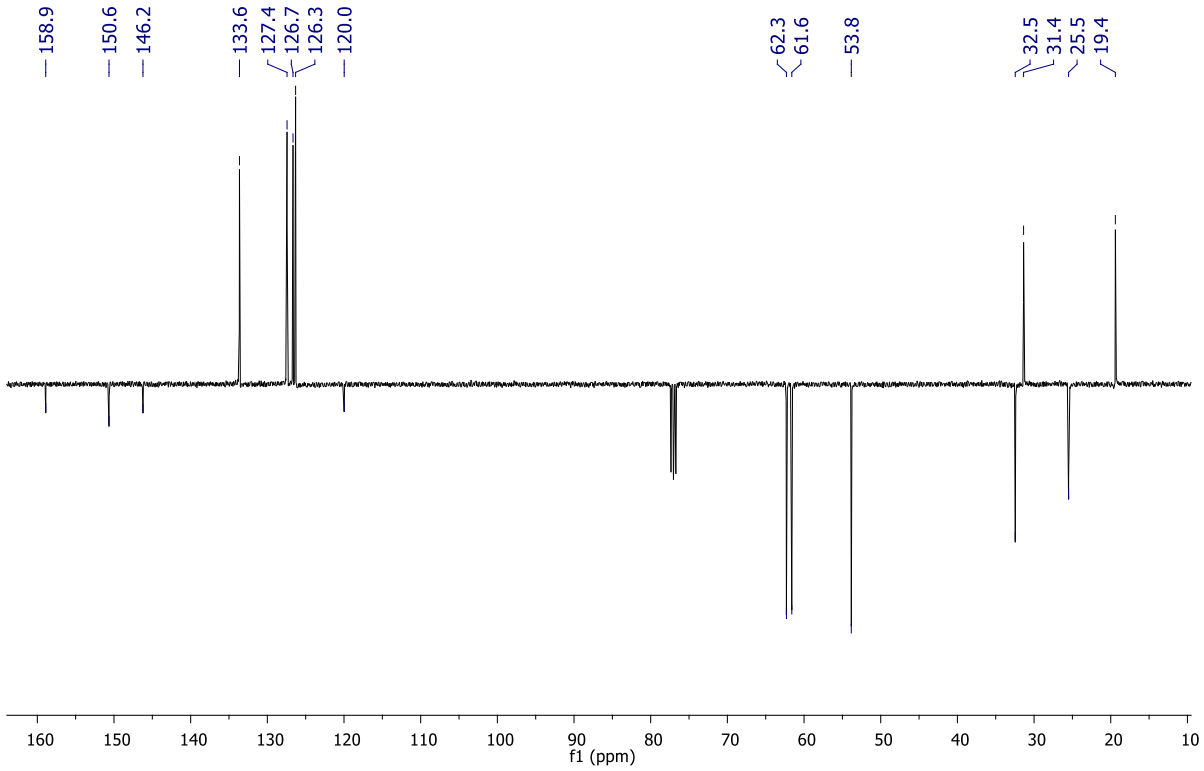

Figure 12 ^{13}C NMR (**4d**)

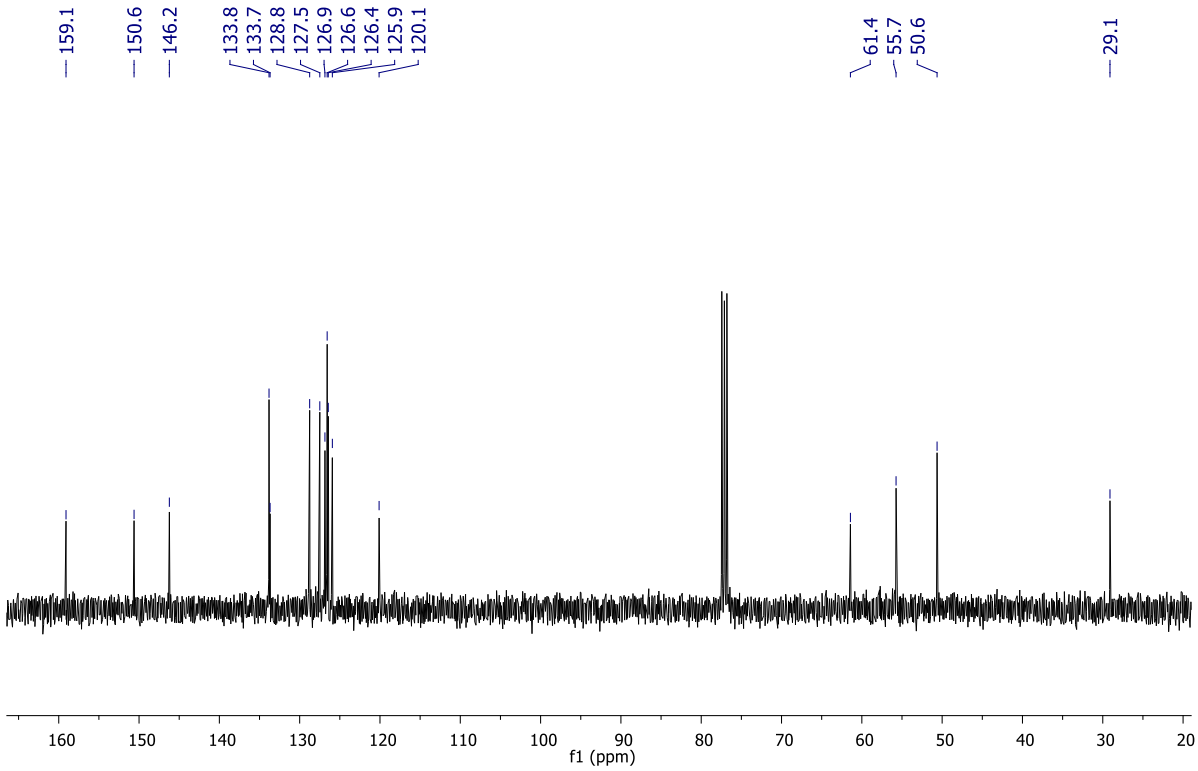

Figure 13 ^{13}C NMR (**4e**)

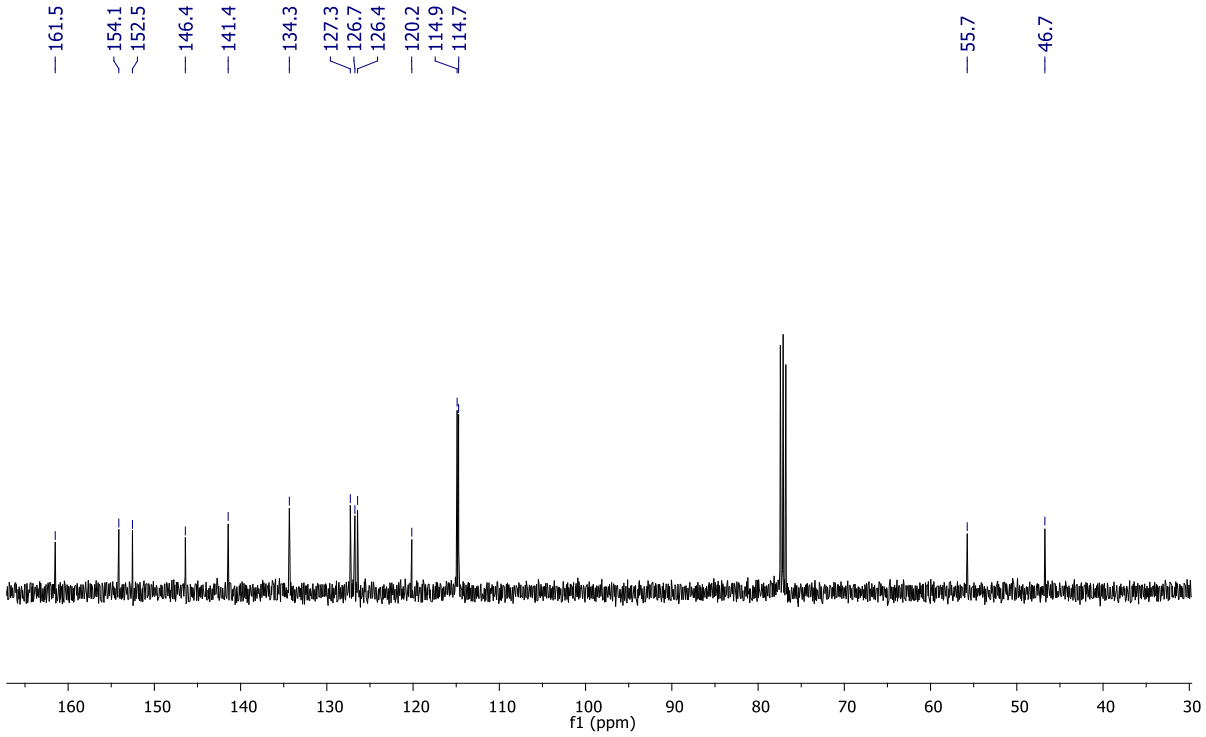

Figure 14 ^{13}C NMR (**4f**)

4. CONCLUSION

In this study, the synthesis of new members of quinazolin-4(3*H*)-ones with aminomethyl moiety at 2 positions were carried out, successfully (according to the data from the spectra). The structures of the compounds were identified and some physical properties were determined. New ligands or building blocks have been

synthesized for scientists interested in the chemical and pharmaceutical properties of quinazolines. Because these molecules contain an aminomethyl group in their structure, they behave like Mannich Bases, which have many uses in various fields of chemistry [33]. In addition, it is possible to synthesize many new molecules by easily derivatizing the molecules over the free NH_2 at the 3 position. NH_2 group at the 3 position of the ring has the character of aromatic primary amine in chemical reactions. Therefore, Schiff Bases with aldehydes, amides with acyl chlorides, and sulfonamide derivatives with sulfonyl chlorides can be easily synthesized. These classes of compounds are mentioned because they are frequently used in pharmaceutical chemistry, medicinal chemistry and biochemistry. Because the molecules have a polar aminomethyl group in their structure, their solubility is quite good in polar solvents (including hot water). Molecules are compounds that can be stored at room temperature and are not affected by heat, light and moisture. Therefore, the molecules are excellent ligands for scientists who want to study the pharmaceutical properties of quinazolinones and their derivatives.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the author.

The Declaration of Ethics Committee Approval

This study does not require ethics committee permission or any special permission.

The Declaration of Research and Publication Ethics

The author of the paper declares that he complies with the scientific, ethical, and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, he declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

REFERENCES

[1] R. J. Abdel-Jalil, H. M. Aldoqum, M. T. Ayoub, W. Voelter, "Synthesis and Antitumor Activity of 2-aryl-7-fluoro-6-(4-methyl-1-piperazinyl)-4(3H)-quinazolinones," Heterocycles-Sendai Institute Heterocyclic Chemistry, vol.65, pp.2061-2070, 2005.

[2] A. S. El-Azab, K. E. El-Tahir, "Design and Synthesis of Novel 7-Aminoquinazoline Derivatives: Antitumor and Anticonvulsant Activities," Bioorganic and Medicinal Chemistry Letters, vol.22, pp.1879-1885, 2012.

[3] V. M. Sharma, P. Prasanna, K. A. Seshu, B. Renuka, C. L. Rao, G. S. Kumar, C. P. Narasimhulu, P. A. Babu, R. Puranik, D. Subramanyam, "Novel Indolo [2, 1-b] quinazoline Analogues as Cytostatic Agents: Synthesis, Biological Evaluation and Structure–activity Relationship," Bioorganic and Medicinal Chemistry Letters, vol.12 pp.2303-2307, 2002.

[4] H. J. Park, Y-S. Kim, J. S. Kim, E-J. Lee, Y-J. Yi, H. J. Hwang, M-E. Suh, C-K. Ryu, S. K. Lee, "6-Arylamino-7-chloro-quinazoline-5,8-diones as Novel Cytotoxic and DNA Topoisomerase Inhibitory Agents," Bioorganic and Medicinal Chemistry Letters, vol.14, pp.3385-3388, 2004.

[5] Z. Ma, Y. Hano, T. Nomura, Y. Chen, "Novel Quinazoline–quinoline Qlkaloids with Cytotoxic and DNA Topoisomerase II Inhibitory Activities," Bioorganic and Medicinal

Chemistry Letters, vol.14, pp.1193-1196, 2004.

[6] N. Malecki, P. Carato, B. T. Rigo, J-F. Goossens, R. Houssin, C. Bailly, J-P, Hénichart, "Synthesis of Condensed Quinolines and Quinazolines as DNA Ligands," Bioorganic and Medicinal Chemistry, vol.12 pp.641-647, 2004.

[7] E. Manivannan, S. Chaturvedi, "Analogue-based Design, Synthesis and Molecular Docking Analysis of 2,3-Diaryl Quinazolinones as Non-ulcerogenic Anti-inflammatory Agents," Bioorganic and Medicinal Chemistry, vol.19, pp.4520-4528, 2011.

[8] A. Gangjee, O. O. Adair, M. Pagley, S. F. Queener, "N9-substituted 2,4-diaminoquinazolines: Synthesis and Biological Evaluation of Lipophilic Inhibitors of Pneumocystis Carinii and Toxoplasma Gondii Dihydrofolate Reductase," Journal of Medicinal Chemistry, vol.51, pp.6195-6200, 2008.

[9] J. Chevalier, A. Mahamoud, M. Baitiche, E. Adam, M. Viveiros, A. Smarandache, A. Militaru, M. L. Pascu, L. Amaral, J-M, Pagès, "Quinazoline Derivatives are Efficient Chemosensitizers of Antibiotic Activity in Enterobacter Aerogenes, Klebsiella Pneumoniae and Pseudomonas Aeruginosa Resistant Strains," International Journal of Antimicrobial Agents, vol.36, pp.164-168, 2010.

[10] A. Mahamoud, J. Chevalier, M. Baitiche, E. Adam, J-M, Pages, "An Alkylaminoquinazoline Restores Antibiotic Activity in Gram-negative Resistant Isolates," Microbiology, vol.157, pp.566-571, 2011.

[11] K. Bajaj, V. K. Srivastava, A. Kumar, "Newer Substituted Benzoxazepinyl quinazolinones as Potent Antipsychotic and Anticonvulsant Agents," ArzneimittelForschung, vol.53, pp.480-485, 2003.

[12] M. Amir, I. Ali, M. Z. Hassan, "Design and Synthesis of Some New Quinazolin-4-(3H)-ones as Anticonvulsant and Antidepressant Agents," Archives of Pharmacal Research, vol.36, pp.61-68, 2013.

[13] M. Shivananda, B. S. Holla, "Antifungal Activity Studies of Some Quinazolinone Derivatives," Journal of Chemical and Pharmaceutical Research, vol.3, pp.83-86, 2011.

[14] M. Decker, "Novel Inhibitors of Acetyl and Butyrylcholinesterase Derived from the Alkaloids Dehydroevodiamine and Rutaecarpine," European Journal of Medicinal Chemistry, vol.40, pp.305-313, 2005.

[15] F. S. Tokalı, P. Taslimi, İ. H. Demircioğlu, M. Karaman, M. S. Gültekin, K. Şendil, İ. Gülçin, "Design, Synthesis, Molecular Docking, and Some Metabolic Enzyme Inhibition Properties of Novel Quinazolinone Derivatives," Archiv der Pharmazie (Weinheim, Germany), vol.354, no.5, pp.2000455, 2021.

[16] A. Gürsoy, N. Karalı, "Synthesis and Primary Cytotoxicity Evaluation of 3-[[(3-Phenyl-4(3H)-quinazolinone-2-yl) mercaptoacetyl] hydrazono]-1H-2-indolinones," European Journal of Medicinal Chemistry, vol.38, pp.633-643, 2003.

[17] M. S. Malamas, J. Millen, "Quinazolineacetic Acids and Related Analogs as Aldose Reductase

Inhibitors," Journal of Medicinal Chemistry, vol.34 pp.1492-1503, 1991.

[18] F. S. Tokalı, Y. Demir, İ. H. Demircioğlu, C. Türkeş, E. Kalay, K. Şendil, Ş. Beydemir, "Synthesis, *in silico* docking study and biological evaluation of novel library sulfonates containing quinazolin-4(3*H*)-one derivatives as potential aldose reductase inhibitors," Drug Development Research, vol.83, no.3, pp.586-604 2022.

[19] A. Gangjee, M. Kothare, R. L. Kisliuk, "The Synthesis of Novel Nonclassical Reversed Bridge Quinazoline Antifolates as Inhibitors of Thymidylate Synthase," Journal of Heterocyclic Chemistry, vol.37, pp.1097-1102, 2000.

[20] R-D. Li, X. Zhang, Q-Y. Li, Z-M. Ge, R-T. Li, "Novel EGFR Inhibitors Prepared by Combination of Dithiocarbamic Acid Esters and 4-Anilinoquinazolines," Bioorganic and Medicinal Chemistry Letters, vol.21, pp.3637-3640, 2011.

[21] J. P. Patil, S. V. Amrutkar, M. S. Ranawat, "Microwave Assisted Synthesis of Quinazolinone Using Different Bases," Journal of Pharmaceutical Sciences and Research, vol.1, no.3, pp.52-54, 2009.

[22] S. G. Davies, K. B. Ling, R. M. Roberts, A. J. Russell, J. E. Thomson, P. A. Woods, "The Stereodivergent Aziridination of Allylic Carbamates, Amides and Sulfonamides," Tetrahedron, vol.66, no.34, pp.6806-6813, 2010.

[23] A. M. F. Eissa, A. M. El-Metwally, M. A. El-Hashash, A. M. F. El-Gohary, "Synthesis and Biological Evaluation of Some New 2-Propyl-4(3H)-quinazolinone Derivatives as Anti-bacteria," Journal of the Korean Chemical Society, vol.52, no.3, pp.328-337, 2008.

[24] A. F. M. Fahmy, M. A. El-Hashash, M. M. Habashy, S. A. El-Wannise, "Some Reactions of 2-Isopropyl-[4H]-3,1-benzoxazin-4-one," Revue Roumaine de Chimie, vol.23, no.11-12, pp.1567-1573, 1978.

[25] V. Alagarsamy, V. Rajasolomon, R. Meena, K. V. Ramseshu, "Synthesis and Analgesic, Anti-inflammatory and Antibacterial Activities of Some Novel 3-substituted 2-butylquinazolin-4(3H)-ones," Biological & Pharmaceutical Bulletin, vol.28, no.6, pp.1091-1094, 2005.

[26] M. A. El-Sherbeny, "Synthesis, Antitumor Activity, and Anti-HIV-1 Testing of Certain Heterocyclic Systems Containing an Adamantane Nucleus," Archiv der Pharmazie (Weinheim, Germany), vol.333, no.10, pp.323-328, 2000.

[27] P. Kumar, B. Shrivastava, S. N. Pandeya, J. P. Stables, "Design, Synthesis and Potential 6 Hz Psychomotor Seizure Test Activity of Some Novel 2-(Substituted)-3-{[substituted]amino}quinazolin-4(3H)-one," European Journal of Medicinal Chemistry, vol.46, no.4, pp.1006-1018, 2011.

[28] C. K. Reddy, P. S. N. Reddy, C. V. Ratnam, "A New Synthesis of 2-Aryl-3,4-dihydro-5H-1,3,4-benzotriazepin-5-ones," Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry, vol.24B, no.9, pp.902-904, 1985.

[29] H. Patel, R. Pawara, S. Surana, "Resolving the Mystery of Ring Opening in the Synthesis of Benzo[d][1, 3]oxazin-4-one and

Quinazolin-4(3H)-one," Letters in Organic Chemistry, vol.16, no.11, pp.898-905, 2019.

[30] L. M. Deck, S. D. Turner, J. A. Deck, E. P. Papadopoulos, " Synthesis of Derivatives of Thiophene Using Methyl 2-isothiocyanatobenzoate," Journal of Heterocyclic Chemistry, vol.38, no.2, pp.343-347, 2001.

[31] F. Sauter, P. Stanetty, U. Jordis, "New 3-Aminoquinazolinones," Archiv der Pharmazie (Weinheim, Germany), vol.310, no.8, pp.680-682, 1977.

[32] F. S. Tokalı, P. Taslimi, İ. H. Demircioğlu, K. Şendil, B. Tüzün, İ. Gülçin, "Novel Phenolic Mannich Base Derivatives: Synthesis, Bioactivity, Molecular Docking, and ADME-Tox Studies," Journal of the Iranian Chemical Society, vol.19, pp.563–577, 2022.

[33] G. Roman, "Mannich bases in medicinal chemistry and drug design," European Journal of Medicinal Chemistry, vol. 89, pp. 743 – 816, 2015.