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N-(2-Aminobenzoyl)benzotriazole Mediated Synthesis of 3-Acyl-2-alkyl(aryl)-4-hydroxyquinolines and 3-Acylamino-4(3*H*) quinazolinones

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Abstract: New methods have been developed for the synthesis of the substituted quinolines and quinazolinones derivatives by utilizing *N*-(2-aminobenzoyl)benzotriazoles under mild reaction conditions. 3-Acyl-2-alkyl(aryl)-4-hydroxyquinolines were obtained in modarete yields by the reaction of *N*-(2-aminobenzoyl)benzotriazoles and diketones in the presence of *tert*-BuOK. 3-Acylamino-4(3*H*) quinazolinones were obtained in good yields via *N*-(2-aminobenzoyl)benzotriazoles, orthoester and hyrazides in one-pot.

Key words: Covid-19, *N*-(2-Aminobenzoyl)benzotriazoles, benzotriazole, quinoline, quinazolinone

1. Introduction

N-Heterocyclic compounds are the most common skeletons in substances such as various synthetic drugs, bioactive natural products and pharmaceuticals. Due to their widespread application, these skeletons have long attracted great interest and facilitated the development of methods that will enable the synthesis of new biological activity molecules in medical chemistry [1]. Quinolinone and quinazolinone derivatives are important classes of nitrogenous heteroaromatic compounds that exhibit broad biological and pharmacological activity.

It has been reported that quinolinone derivatives [2] show several activities like antimicrobial [3], antiinflammatory, anticancer [4] and anticonvulsant [5]. Compounds with quinoline ring bearing acyl group in C3 position show important biological activity such as antiparasitic against Leishmania infantum [6], antitumor by inhibiting Hedgehog signalling pathway [7], antiviral against HIV-1 [8]. Moreover, chloroquine and hydroxychloroquine (Figure 1) which are quinoline derivatives used as an antimalarial drug; have been recently the subject of many in vitro and clinical studies for the treatment of Covid-19 [9–11].

Acyl-2-alkyl(aryl)-4-hydroxyquinolines having ketone groups in the C3 position were synthesized by various methods like; i) the reaction of aniline with acrylates [12], ii) the reaction of iodo aniline with α,β-unsaturated ketones [7], iii) the cyclization of aromatic enaminones formed by the reaction of iodobenzene with 4-substituted isoxazole by heating in an acidic medium [13] iv) the reaction of methyl-2-aminobenzoates with α,β-unsaturated ketones [14] v) the reaction of 2-aminobenzaldehyde with various alkynes [15], vi) the hydrolysis of the intermediate product formed by the reaction of 2-aminobenzonitrile with 1,3-diketones [16], vii) reaction of 2-[(benzylidine)amino]benzonitrile with various phosphorus ylides, viii) the reaction of 2-substituted benzoxazinon with 1,3-diketones in basic medium [17], ix) the reaction of isotoic anhydride with 1,3-diketones [18], x) Reaction of *o*-halogenobenzoyl chlorides and β-ketoenamines in basic (Et_3N or DBU) medium [19] xi) the thermolysis reaction of *N*-arylpyrrole-2,3-diones prepared by various methods at high temperatures [20], xii) the condensation reaction of *β*-amino-*α*-(*N*-arylimidoyl)crotonates in phosphoric acid [21] (Scheme 1).

There are many methods in the literature for the synthesis of 3-acyl-2-alkyl(aryl)-4-hydroxyquinoline; however these methods are associated with disadvantages such as harsh reaction conditions, long reaction steps, the use of expensive reagents, and the use of catalysts.

The quinazolinone ring is a heterocyclic compound formed by fusing benzene and pyrimidone [22]. It is the building block of about 200 alkaloids [23] isolated from different sources such as plants [24] and microorganisms [25]. Natural and synthetic quinazolinone are important for organic and medicinal chemistry owing to their effects such as anticancer [26] antimalarial [27], antifungal [28], antihyperlipidemic [29].

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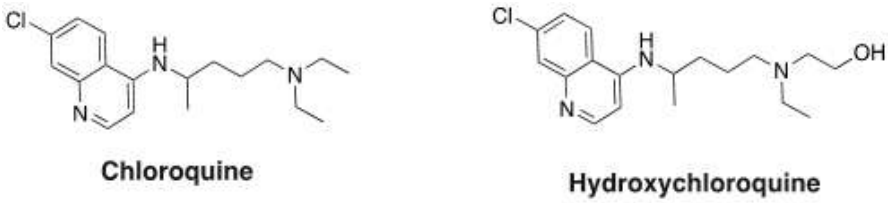
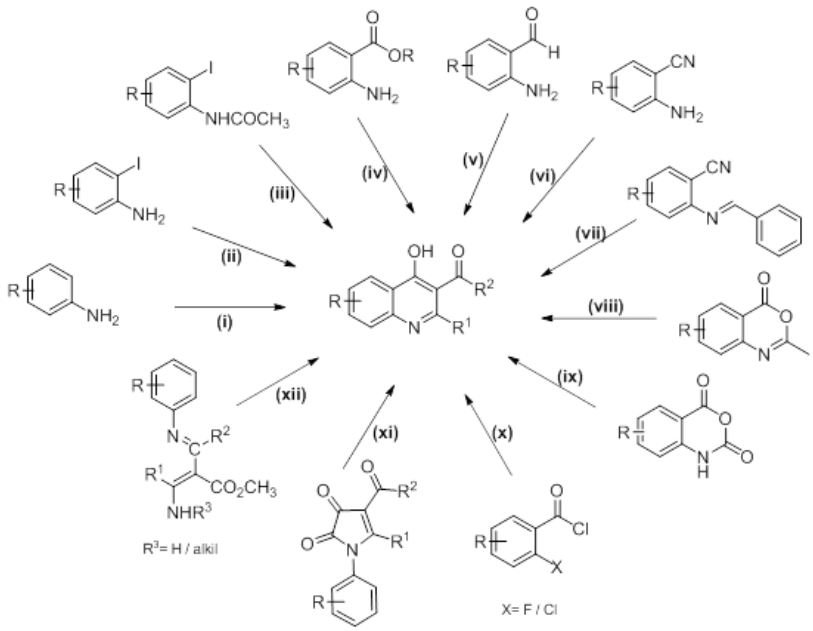


Figure 1. Chemical structures of chloroquine and hydroxychloroquine.



Scheme 1. Literature methods for preparing of 3-acyl-2-alkyl(aryl)-4-hydroxyquinoline.

In previous studies 3-acylamino-4(3*H*) quinazolinones were synthesized by; i) the reaction of anthranilic acid, acetic anhydride and primary amine in the presence of nano-TiO_2 [30], ii) the reaction of 3-amino-aryl/alkyl-4(3*H*) quinazolinone and an orthoester or acylchlorides in pyridine or benzene [31], iii) the reaction of benzoxazione and dicarboxylic acid dihydrazides [32], iv) adding acyl chloride to the intermediate product formed by heating methyl-2-amino benzoate with hydrazine [33] (Scheme 2).

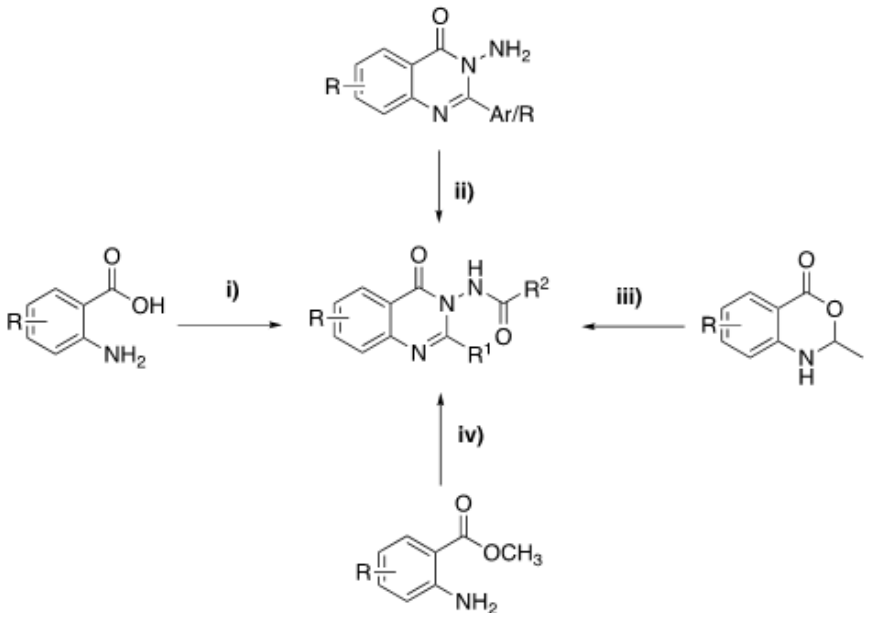
Although there are many methods in the literature for the synthesis of 3-acylamino-4(3*H*) quinazolinones, these methods have harsh reaction conditions, multiple reaction steps, and the use of catalysts. For this reason, mild reaction conditions are needed for the synthesis of these compounds.

N-(2-aminobenzoyl) benzotriazole compounds, which are derivatives of *N*-acyl benzotriazole, have many benefits such as being crystalline, dissolving in many organic solvents, not absorbing moisture, and being stable. Besides, these compounds are used as starting materials in the synthesis of anthranylesters and anthranylthioesters [34], anthranilamides [35] and some heterocyclic compounds [36–38].

2. Results and discussion

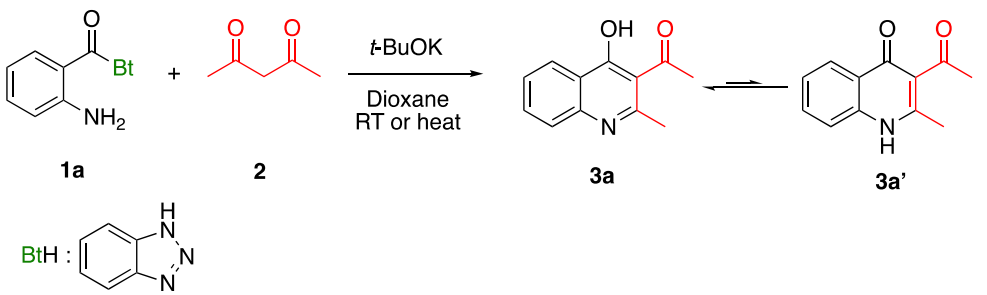
2.1. Preparation of 3-Acyl-2-alkyl(aryl)-4-hydroxyquinoline (3a-j)

N-(2-aminobenzoyl)benzotriazoles 1a–1j were prepared by the method in our previous study [35]. After *N*-(2-aminobenzoyl)benzotriazoles 1a–1j were synthesized, the synthesis of 3-acyl-2-alkyl(aryl)-4-hydroxyquinolines 3a–3j was started with the proposed method. First of all, the synthesis of 3-acyl-2-methyl-4-hydroxyquinoline 3a was tried under different reaction conditions to find the appropriate reaction conditions in the presence of *tert*-BuOK. This model reaction was tried in different solvents, at room temperature and under reflux conditions (Table 1). The highest yield for 3-acyl-2-methyl-4-hydroxyquinoline 3a was obtained when the reaction was performed in dioxane and heated. After the



Scheme 2. Literature methods for preparing of 3-acylamino-4(3*H*) quinazolinones.

Table 1. The effect of temperature and solvent on the model reaction.

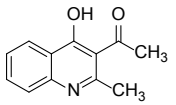
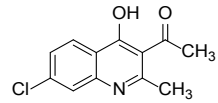
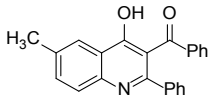
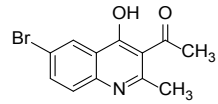
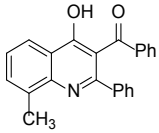
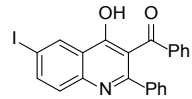
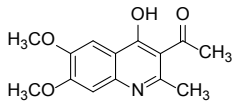
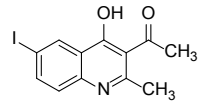
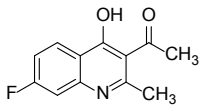
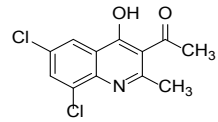
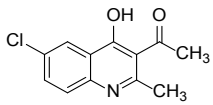
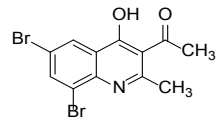


Solvent	Reaction conditions	% Yield (3a)
THF	R.T	24
THF	Reflux	39
DMF	R.T	44
DMF	Reflux	49
Dioxane	Reflux	59

reaction conditions were optimised, the synthesis of the other compounds in the series was carried out with 14%–59% yield (Table 2).

The structures of synthesized compounds were elucidated by ^{1}H, ^{13}C-NMR, HRMS and FTIR spectroscopy techniques. The characteristic singlet signal observed in downfield ^{1}H NMR spectrum is thought to belong to the -OH proton. Since these compounds contain a free acidic proton in their structure, they have two possible tautomeric structures having 4-hydroxyquinoline 3a and 4-oxoquinoline 3a'. The characteristic singlet peak observed in the range of 10.90–12.24 ppm is considered to belong to the OH or NH proton. In our previous study, ^{1}H-^{15}N HSQC experiment was performed to determine the OH and NH protons in quinolines with similar structures that we synthesized [32]. According to the results of the experiment, it was observed that the OH proton appeared at around 12 ppm, and the NH proton at around 9 ppm.

Table 2. 3-Acyl-2-alkyl(aryl)-4-hydroxyquinolines 3a–l.

Product	Structure	Yield % (Lit.)	Product	Structure	Yield % (Lit.)
3a		59 (51 [29])	**3g**		51 (39 [6])
3b		26 (88 [2])	**3h**		14 -
3c		22 (76 [30])	**3i**		27 -
3d		40 -	**3j**		44 (89 [31])
3e		55 -	**3k**		0 -
3f		40 -	**3l**		0 -

From the results of this NMR experiment, the characteristic singlet peak observed in the range of 10.90–12.24 ppm is thought to belong to the OH proton. When the ^{13}C-NMR spectra of the compounds were examined, the signals of the carbonyl carbons in the acyl group at position three were observed at 195.8–202.2 ppm.

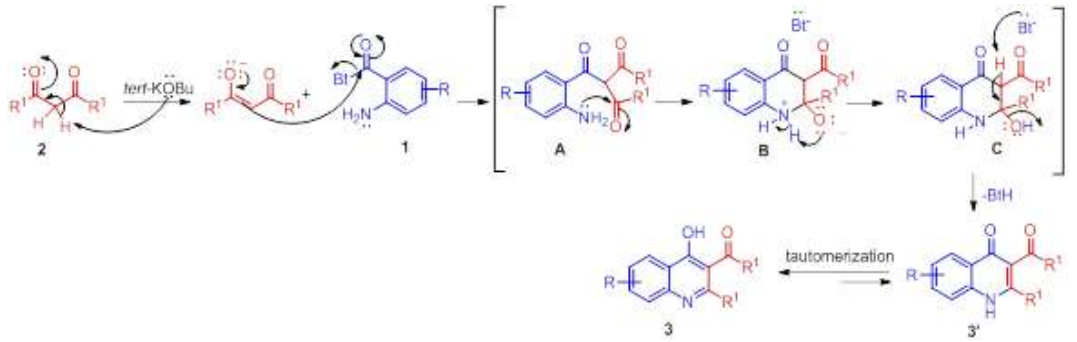
A possible reaction mechanism according to the formation of annulation product is proposed in Scheme 3. The reaction would be initiated by addition of the enol structure formed by the removal of the acidic hydrogen atom of the 1,3-dicarbonyl compound by *tert*-BuOK to *N*-(2-aminobenzoyl)benzotriazole. Then, the subsequent cyclization of formed intermediate A affords intermediate B and benzotriazolyl anion. The intermediate C is formed by proton exchange within the intermediate B itself. With the removal of the hydrogen atom in the C intermediate by the benzotriazolyl anion, the product 3′ is formed and the tautomerization of desired product produces the product 3.

The desired compounds in Table 3 were synthesized with moderate yields. The desired compounds 3k and 3l could not be obtained at the end of the reaction. Instead of these compounds, by-products 3kb and 3lb shown in the following the reaction mechanism (Scheme 4) were obtained. The structures of the by-products were elucidated with both ^{1}H-NMR and ^{13}C-NMR spectra. When the ^{1}H-NMR spectra of the by-products are examined, the absence of signals belonging to the acyl group and the absence of the signal belonging to the carbonyl group, which is observed around 200 ppm in the ^{13}C-NMR spectrum, supports the formation of by-products.

When the possible reaction mechanism for the obtained by-products 3kb and 3lb is examined, intermediate C is thought to be formed by the addition of the benzotriazolyl anion to the carbonyl group and then leaving as the *N*-acylbenzotriazolyl group as shown in Scheme 4.

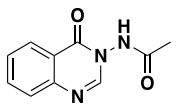
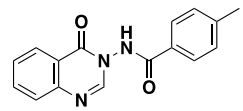
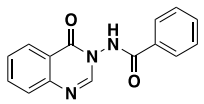
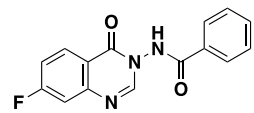
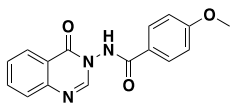
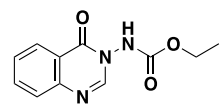
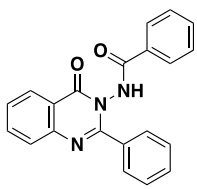
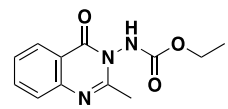
2.2. Preparation of 3-acylamino-4(3H) quinazolinones (6a–h)

3-Acylamino-4(3*H*) quinazolinones 6 were obtained in 34%–84% (Table 3) yield by refluxing *N*-(2-aminobenzoyl) benzotriazoles 1, orthoesters 4 and hydrazides 5 in dioxane for 18–20 h (Scheme 5).

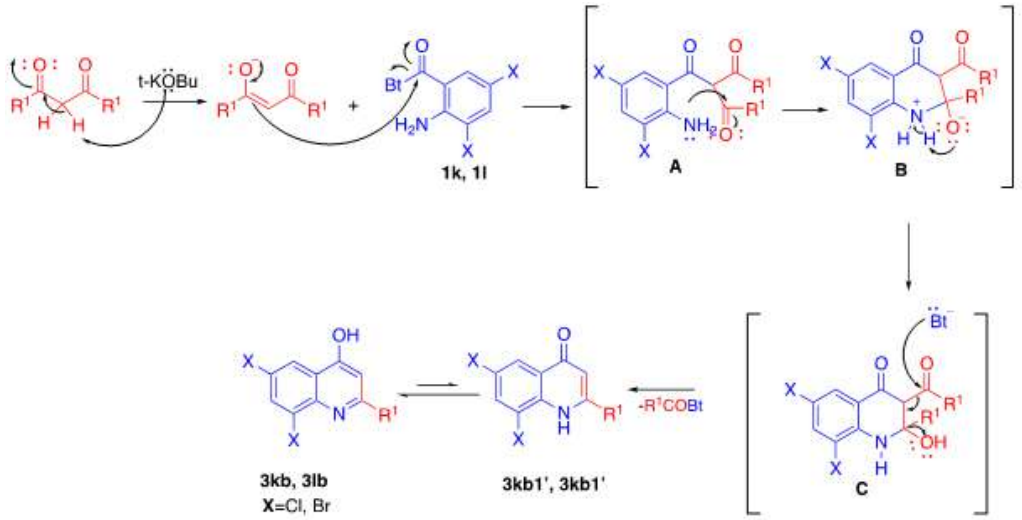


Scheme 3. Possible reaction mechanism for 3-acyl-2-alkyl(aryl)-4-hydroxyquinolines.

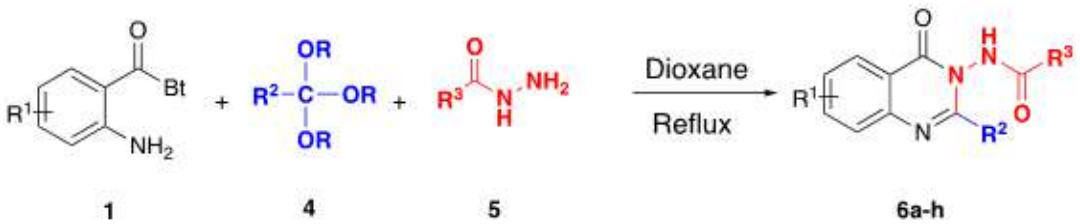
Table 3. 3-acylamino-4(3*H*) quinazolinones (6a–6h).

Product	Structure	Yield %(Lit.)	Product	Structure	Yield % (Lit.)
6a		64 (65 [32])	**6e**		34 -
6b		59 (52 [33])	**6f**		65 -
6c		35 -	**6g**		84 -
6d		53 (50) [39]	**6h**		73 (88) [40]

Structures of obtained products were idendified by ^{1}H NMR, ^{13}C NMR, HRMS and FTIR spectroscopy techniques. A characteristic singlet observed around 10 ppm in the ^{1}H NMR spectra was assigned to the hydrogen atom bound to nitrogen adjacent to N3. The hydrogen atom on C2 was observed between 8.23 ppm and 8.51 ppm (Supplemental information) For compounds 6d and 6h, no signal was observed around 8 ppm because of the substituent at the position 2. The ^{13}C NMR spectra of 6a–h showed new signals at 165.8–159.2 ppm as well as at 163.0–156.4 ppm, corresponding to carbonyl carbon at the position 4 and amidoyl (carbamoyl) carbon attached to the nitrogen at position 3 in the quinazoline ring, respectively. Moreover, HRMS and FTIR spectral data were also appropriately with the proposed structures. During



Scheme 4. Possible reaction mechanism for by-products.



Scheme 5. Method for the preparation of 3-acylamino-4(3*H*) quinazolinones.

the preparation of 3-acylamino-4(3*H*) quinazolinones 6a–6h, it was noticed that a by-products 6d′ and 6e' (Figure 2) formed with the expected products. The by-products 6d′ and 6e' were isolated by column chromatography in 36% and 78% yields respectively. The structures of the by-products shown in Figure 2 were elucidated by ^{1}H, ^{13}C NMR and HRMS.

A possible mechanism for the formation of 3-acylamino-4(3*H*) quinazolinones is proposed in Scheme 6. The reaction will be initiated by the addition of hydrazides to the carbonyl of the *N*-(2-aminobenzoyl)benzotriazoles. Intermediate B will be formed by removing the hydrogen atom of the benzotriazolyl group from the intermediate A formed. The product is formed as a result of the subsequent cyclization of intermediate D, which is formed as a result of the addition of intermediate B to the orthoester.

3. Experimental section

3.1. General information

NMR spectra of the synthesized products were recorded in DMSO-*d6* or $CDCl_3$, at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR (Agilent 4 DD2 400 MHz spectrometer). Melting points were determined with Mettler Toledo MP90 apparatus and were uncorrected. HRMS spectra were recorded with Shimadzuhybrid LC-MS-IT-TOF spectrometer. IR spectra were recorded with Perkin Elmer 100 FTIR. Necessary drying processes were applied to the solvents used during the synthesis and purification of the compounds.

3.2. General method for the synthesis of 3-Acyl-2-alkyl(aryl)-4-hydroxyquinoline (3a–3j)

Substituted *N*-(2-aminobenzoyl) benzotriazoles 1 (0.25 mmol) and 1,3-diketones 2 (0.25 mmol) were mixed in 5 mL of dioxane for 15 min. *tert*-BuOK 0.25 mmol) was added to the mixture and refluxed for 24 h. Reactions were monitored by thin layer chromatography (TLC) under UV light. After the reaction is complete, the solvent was removed under reduced pressure. The reaction mixture was purified by column chromatography with EtOAc/Hexane (1/1).

1-(4-Hydroxy-2-methylquinolin-3-yl)ethanone (3a)

Brown solid (30 mg, 59%), mp.: > 230 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.32 (s, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 11.90 (s, 1H). ^{13}C NMR (100

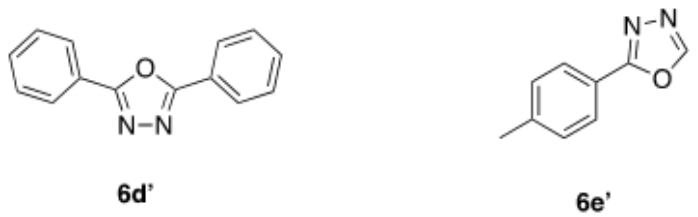
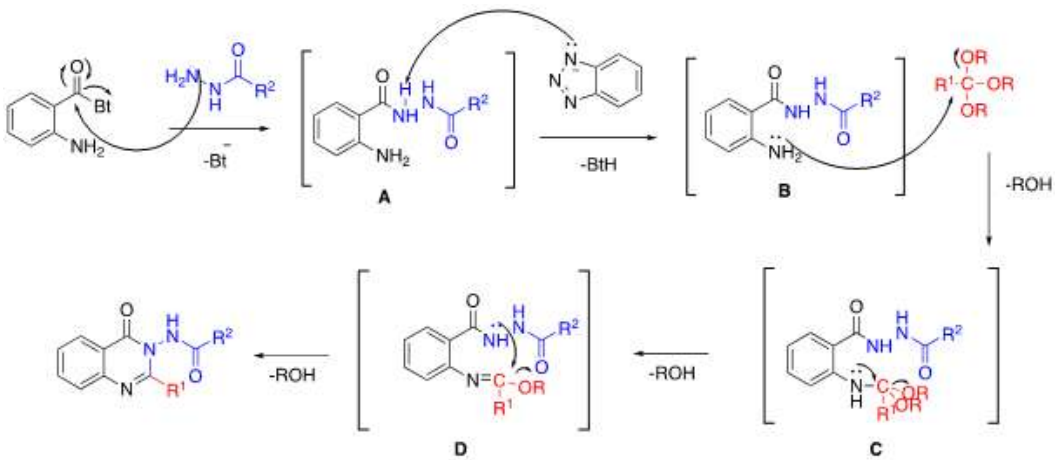


Figure 2. Chemical structures of by-products.



Scheme 6. Possible reaction mechanism for 3-acylamino-4(3*H*) quinazolinones.

MHz, DMSO-d_6): δ 19.4, 32.4, 118.4, 120.7, 124.5, 125.6, 125.8, 132.8, 139.2, 152.0, 175.8, 202.1. δ FTIR u_{max} (KBr): 757, 1348, 1511, 1550, 1673, 3020 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{11}NO_2$ 202.0863; found *m/z* 202.0858.

(4-Hydroxy-6-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3b)

White solid (22 mg, 26%), mp.: > 292 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H), 7.43–7.37 (m, 7H), 7.57–7.50 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 6.8 Hz, 2H), 7.86 (s, 1H), 12.05 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 119.2, 120.4, 124.5, 125.1, 128.9, 129.0, 129.1, 129.4, 130.4, 133.4, 133.8, 134.1, 134.3, 138.3, 138.4, 149.5, 175.3, 196.3. FTIR u_{max} (KBr): 694, 899, 1361, 1499, 1570, 1672, 2864 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{23}H_{17}NO_2$ 340.1332; found *m/z* 340.1332.

(4-Hydroxy-8-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3c)

Pale yellow solid (19 mg, 22%), mp.: > 290 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): 2.58 (s, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.40–7.34 (m, 5H), 7.44 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 10.90 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.2, 121.1, 123.2, 124.1, 125.5, 128.0, 128.6, 129.0, 129.3, 129.5, 130.2, 133.4, 133.9, 134.2, 138.2, 139.1, 150.2, 175.6, 196.1. FTIR u_{max} (KBr): 694, 899, 1361, 1499, 1570, 1672, 2864 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{23}H_{17}NO_2$ 340.1332; found *m/z* 340.1326.

1-(4-Hydroxy-6,7-dimethoxy-2-methylquinolin-3-yl)ethanone (3d)

Brown Solid (26 mg, 40%), mp. > 260 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): 2.37 (s, 3H), 2.47 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 7.16 (s, 1H), 7.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5, 32.5, 55.9, 56.2, 100.2, 104.8, 119.6, 119.8, 135.2, 147.3, 150.7, 153.4, 174.7, 202.2. FTIR u_{max} (KBr): 1202, 1235, 1427, 1586, 1658, 2964 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{14}H_{15}NO_4$ 262.1074; found *m/z* 262.1070.

1-(7-Fluoro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3e)

Pale Brown solid (30 mg, 55%), mp.: > 240 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 2.47 (s, 3H), 7.24–7.18 (m, 2H), 8.13 (d, *J* = 2.0 Hz, 1H), 11.97 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5, 32.4, 103.8, 113.2, 121.9, 129.0, 140.7, 152.5, 163.3, 165.8, 175.1, 201.9. FTIR u_{max} (KBr): 1161, 1353, 1515, 1636, 1674, 2874 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}FNO_2$ 220.0768; found *m/z* 220.0762.

1-(6-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3f)
Brown solid (23 mg, 39%), mp: > 250 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 2.47 (s, 3H), 7.62-7.53 (m, 2H), 7.99 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 32.5, 120.4, 122.7, 124.4, 127.6, 128.3, 132.0, 140.1, 154.0, 174.4, 202.0. FTIR u_{max} (KBr): 1259, 1509, 1685, 2905 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}ClNO_2$ 236.0473; found *m/z* 236.0475.

1-(7-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3g)
Pale yellow solid (30 mg, 51%), mp > 287 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 2.47 (s, 3H), 7.37 (dt, *J* = 8.5, 1.5 Hz, 1H), 7.53 (s, 1H), 8.08 (d, *J* = 8.8, 0.8 Hz, 1H), 12.04 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5, 32.4, 117.7, 121.2, 124.5, 124.8, 127.9, 137.3, 140.1, 152.5, 175.1, 201.8. FTIR u_{max} (KBr): 1350, 1505, 1686, 2911 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}ClNO_2$ 236.0473; found *m/z* 236.0463.

1-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)ethanone (3h)
White solid (10 mg, 14%), mp > 299 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 2.47 (s, 3H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.81 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 12.07 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5, 32.4, 117.1, 120.9, 121.1, 127.3, 127.7, 135.5, 138.2, 152.4, 174.4, 201.8. FTIR u_{max} (KBr): 1347, 1545, 2899 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}BrNO_2$ 279.9968; found *m/z* 279.9962.

(4-Hydroxy-6-iodo-2-phenylquinolin-3-yl)(phenyl)methanone (3i)
Brown solid (30 mg, 27%), mp.: > 301 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42–7.40 (m, 7H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 12.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 89.2, 121.1, 121.7, 126.9, 129.0, 129.1, 129.4, 130.6, 133.6, 133.7, 133.8, 138.1, 139.6, 140.9, 150.2, 174.1, 195.8. FTIR u_{max} (KBr): 581, 1345, 1667, 2798 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{22}H_{14}INO_2$ 452.0142; found *m/z* 452.0123.

1-(4-Hydroxy-6-iodo-2-methylquinolin-3-yl)ethanone (3j)
Brown solid (36 mg, 44%), mp.: > 301 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 2.46 (s, 3H), 7.33 (d, *J* = 8.4 Hz 1H), 7.93 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 12.07 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.6, 32.4, 89.2, 120.9, 121.0, 127.6, 134.0, 138.6, 140.8, 152.4, 174.3, 201.8. FTIR u_{max} (KBr): 1345, 1503, 1573, 1630, 2902 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}INO_2$ 327.9829; found *m/z* 327.9826.

6,8-Dichloro-2-methylquinolin-4-ol (3kb)
^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 6.01 (s, 1H), 7.94 (s, 2H), 10.95 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.3, 110.1, 123.1, 123.8, 127.1, 127.6, 131.8, 136.2, 152.1, 176.3. FTIR υmax (KBr): 529, 839, 1141, 1498, 1570, 1595, 1631, 2995 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{10}H_7Cl_2NO$ 227.9977 [M+H]$^+$, found, *m/z* 227.9972.

6,8-Dibromo-2-methylquinolin-4-ol (3lb)
^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 5.96 (s, 1H), 7.85 (s, 1H), 8.09 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 67.8, 111.1, 126.9, 129.1, 132.0, 132.1, 133.0, 145.9, 159.9, 167.4. FTIR υmax (KBr): 838, 1122, 1439, 1564, 1626, 3198 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{10}H_7Br_2NO$ 315.8967 [M+H]$^+$; found, *m/z* 315.8965.

1.1. General method for the synthesis of 3-acylamino-4(3H) quinazolinones (6a-h)
N-(2-aminobenzoyl) benzotriazole compounds 1 (0.25 mmol) were refluxed with orthoesters 4 (0.5 mmol) and hydrazides 5 (0.5 mmol) in 2 mL of dioxane for 18–20 h. The reactions were controlled by thin layer chromatography (TLC). At the end of the reaction, the solvent was vaporised under reduced pressure. The obtained residue was purified using column chromatography in EtOAc/Hexane mixtures (1:2 or 1:3).

***N*-(4-Oxoquinazolin-3(4*H*)-yl)acetamide (6a)**
Orange solid (32.3 mg, 64%); mp.: 199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H), 7.60–7.56 (m, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.89–7.85 (m, 1H), 8.16 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 8.23 (s, 1H), 11.26 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 122.4, 126.8, 127.9, 128.0, 135.4, 147.6, 149.4, 158.9, 169.9. FTIR u_{max} (KBr): 1473, 1502, 1667, 3270 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{10}H_9N_3O_2$ 204.0768; found *m/z* 204.0768.

***N*-(4-Oxoquinazolin-3(4*H*)-yl)benzamide (6b)**
White solid (38.8mg, 59%); mp.: 188–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68–7.55 (m, 4H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.92–7.88 (m, 1H), 7.98–7.96 (m, 2H), 8.19 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 8.43 (s, 1H), 11.86 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.4, 126.8, 128.0 128.1, 128.2, 129.2, 131.5, 133.3, 135.5, 147.7, 149.5, 159.0, 166.7. FTIR u_{max} (KBr): 1473, 1516, 1667, 3266 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{15}H_{11}N_3O_2$ 266.0924; found *m/z* 266.0914.

4-Methoxy-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6c)
Orange solid (25 mg, 35%); mp: 179–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (s, 3H), 6.87 (t, *J* = 4.2 Hz, 2H), 7.54–7.50 (m, 1H), 7.80–7.75 (m, 2H), 7.87 (t, *J* = 4.2 Hz, 2H), 8.12 (d, *J* =1.2 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 9.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 114.0, 121.9, 122.5, 127.0, 127.6, 127.8, 129.4, 129.8, 135.0, 147.1, 160.0, 163.4, 167.0. FTIR u_{max} (KBr): 1175, 1475, 1606, 1666, 3254 cm^{-1}. HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{13}N_3O_3$ 296.1030; found *m/z* 296.1024.

***N*-(4-Oxo-2-phenylquinazolin-3(4H)-yl)benzamide (6d)**
White solid (45 mg, 53%); mp.: 202–204 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 2H), 7.43 (t, *J* = 6.2 Hz, 4H), 7.55–7.50 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 3.2 Hz, 2H), 7.81 (d, *J* = 4 Hz, 2H), 8.29 (d, *J* = 8 Hz, 1H), 9.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.2, 127.1, 127.8, 128.0, 128.2, 128.3, 128.9, 129.1, 130.1, 131.6, 133.1, 133.8, 135.8, 147.1, 156.7, 160.1, 165.8. FTIR u_{max} (KBr): 1567, 1602, 1719, 3158 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{15}N_3O_2$ 342.1237; found *m/z* 342.1231.
2,5-diphenyl-1,3,4-oxadiazole (6d')
White solid (20 mg, 36%) mp.: 139–140 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 5.6 Hz, 6H), 8.15 (t, *J* = 3.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.9, 126.9, 129.1, 131.7, 164.6. FTIR u_{max} (KBr): 1069, 1268, 1446, 1485, 1547, 1605 cm^{-1} HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{10}N_2O$ 223.0866; found *m/z* 223.0864.
4-Methyl-*N*-(4-oxoquinazolin-3(4H)-yl)benzamide (6e)
White solid (24 mg, 34%); mp.: 202–204 °C. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 7.38 (d, *J* = 8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.92-7.87 (m, 3H), 8.19 (s, *J* = 6.8 Hz, 1H), 8.40 (s, 1H), 11.77 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ21.5, 122.4, 126.8, 128.0, 128.1, 128.3, 128.7, 129.7, 135.5, 143.4, 147.7, 149.6, 159.1, 166.6. FTIR u_{max} (KBr): 1478, 1497, 1613, 1664, 3242 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}N_3O_2$ 280.1081; found *m/z* 280.1071.
2-(p-Tolyl)-1,3,4-oxadiazole (6e')
Pale orange solid (31.1 mg, 78%); mp.: 85–86 °C. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8 Hz, 2H), 8.43 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 120.6, 127.0, 129.8, 142.6, 152.3, 164.9. FTIR u_{max} (KBr): 1067, 1102, 1497, 1611, 1927, 3126 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_9H_8N_2O$ 161.0709; found *m/z* 161.0686.
***N*-(7-Fluoro-4-oxoquinazolin-3(4*H*)-yl)benzamide (6f)**
White solid (46 mg, 65%); mp.: 189–191 °C. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.52-7.46 (m, 1H), 7.60–7.56 (m, 3H), 7.69–7.67 (m, 1H), 7.98 (d, *J* = 8 Hz, 2H), 8.26 (dd, *J* = 8.8 Hz, 6 Hz, 1H), 8.51 (s, 1H), 11.89 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 113,5, 116.8, 119.4, 127.9, 128.2, 129.1, 130.1, 131.4, 133.3, 150.0, 150.9, 158.3, 165.1, 166.7, 167.6. FTIR u_{max} (KBr): 856, 1446, 1482, 1609, 1667, 1716, 3213 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}FN_3O_2$ 284.0830; found *m/z* 284.0820.
Ethyl (4-oxoquinazolin-3(4*H*)-yl)carbamate (6g)
White solid (46.5 mg, 84%); mp.:179–181 °C. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.24 (t, *J* = 7.2 Hz, 3H), 4.19–4.13 (m, 2H), 7.61–7.57 (m, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.90-7.86 (m, 1H), 8.16 (dd, *J* = 8 Hz, 1.2 Hz, 1H), 8.35 (s, 1H), 10.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 62.3, 122.2, 126.8, 128.1, 128.2, 135.5, 147.6, 149.6, 156.4, 159.2. FTIR u_{max} (KBr): 1473, 1519, 1668, 1752, 2987, 3204 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_3O_3$ 234.0873; found *m/z* 234.0868.
Ethyl (2-methyl-4-oxoquinazolin-3(4*H*)-yl)carbamate (6h)
White solid (45 mg, 73%); mp.: 130–132 °C^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7 Hz, 3H), 2.41 (s, 3H), 4.19–4.13 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.85–7.81 (m, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 10.45 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ14.8, 21.6, 62.3, 120.9, 126.8, 127.3, 127.4, 135.5, 146.9, 156.1, 156.9, 159.7. FTIR u_{max} (KBr): 1471, 1610, 1663, 1754, 2990, 3217 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_3O_3$ 248.1030; found *m/z* 248.1035.

4. Conclusion

A novel method has been developed for the synthesis of 3-Acyl-2-alkyl(aryl)-4-hydroxyquinolines and 3-acylamino-4(3*H*) quinazolinones. Quinoline derivatives were synthesized in one step from the reaction of *N*-(2-aminobenzoyl) benzotriazoles, which are easy-handle starting materials with diketones. Quinazolinone derivatives were obtained with *N*-(2-aminobenzoyl)benzotriazoles, orthoesters, and hydrazides as three-components with generally high yields. In comparison with the other methods in the literature, the reactions were carried out in the absence of any catalyst under mild reaction conditions in one-pot.

References

[1] Khan I, Ibrar A, Ahmed W, Saeed A. Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue. European Journal of Medicinal Chemistry. 2015; 90: 124–169. https://doi.org/10.1016/j.ejmech.2014.10.084

[2] Dhiman P, Arora N, Thanikachalam PV, Monga V. Recent advances in the synthetic and medicinal perspective of quinolones: A review. Bioorganic Chemistry. 2019; 92: 103291. https://doi.org/10.1016/j.bioorg.2019.103291

[3] Hassanin HM, El Edfawy SM. Novel heterocyclic dertvatives of 2-quinolinone associated with antibacterial and antitumor potencies. Heterocycles. 2012; 85 (10): 2421–2436. https://doi.org/10.3987/COM-12-12523

[4] Upadhyay KD, Dodia NM, Khunt RC, Chaniara RS, Shah AK. Synthesis and Biological Screening of Pyrano [3,2- c] quinoline Analogues as Anti-inflammatory and Anticancer Agents. ACS Medicinal Chemistry Letters. 2018; 9 (3): 283–288. https://doi.org/10.1021/acsmedchemlett.7b00545

[5] Zhang HJ, Jin P, Wang SB, Li FN, Guan LP et al. Synthesis and Anticonvulsant Activity Evaluation of 4-Phenyl-[1,2,4]triazolo[4,3-a] quinazolin-5(4H)-one and Its Derivatives. Archiv der Pharmazie. 2015; 348 (8): 564–574. https://doi.org/10.1002/ardp.201500115

[6] Muscia GC, Bollini M, Carnevale JP, Bruno AM, Asís SE. Microwave-assisted Friedländer synthesis of quinolines derivatives as potential antiparasitic agents. Tetrahedron Letters. 2006; 47 (50): 8811–8815. https://doi.org/10.1016/j.tetlet.2006.10.073

[7] Alfonsi R, Botta B, Cacchi S. Design. Palladium-Catalyzed Synthesis, and Biological Investigation of 2-Substituted 3-Aroylquinolin-4(1H)-ones as Inhibitors of the Hedgehog Signaling Pathway. Journal of Medicinal Chemistry. 2017; 60 (4): 1469–1477. https://doi.org/10.1021/acs.jmedchem.6b01135

[8] Di Santo R, Costi R, Roux A, Artico M, Lavecchia A et al. Novel bifunctional quinolonyl diketo acid derivatives as HIV-1 integrase inhibitors: Design, synthesis, biological activities, and mechanism of action. Journal of Medicinal Chemistry. 2006; 49 (6): 1939–1945. https://doi.org/10.1021/jm0511583

[9] Gentile D, Fuochi V, Rescifina A, Furneri PM. New anti sars-cov-2 targets for quinoline derivatives chloroquine and hydroxychloroquine. International Journal of Molecular Sciences. 2020; 21 (16):1–16. https://doi.org/10.3390/ijms21165856

[10] Beura S, Chetti P. In-silico strategies for probing chloroquine based inhibitors against SARS-CoV-2. Journal of Biomolecular Structure and Dynamics. 2020; 0(0): 1–13. https://doi.org/10.1080/07391102.2020.1772111

[11] Rodríguez Martínez CE, Fernandes RM, Hawcutt DB, Sinha IP, Pacheco RL. Efficacy, safety and cost-effectiveness of hydroxychloroquine in children with COVID-19: A call for evidence. Acta Paediatrica, International Journal of Paediatrics. 2020; 109 (9):1711–1712. https://doi.org/10.1111/apa.15373

[12] Hu B, Jetter J, Kaufman D, Singaus R, Bernotas R et al Further modification on phenyl acetic acid based quinolines as liver X receptor modulators. Bioorganic and Medicinal Chemistry. 2007; 15 (10): 3321–3333. https://doi.org/10.1016/j.bmc.2007.03.013

[13] Jensen S, Torssell KB. Synthesis of 4-quinolone derivatives. Acta Chemica Scandinavica. 1995; 49: 53–56.

[14] Kang S, Park S, Kim KS, Song C, Lee Y. Copper-Catalyzed Aza-Michael Addition of 2-Aminobenzoate to β-Substituted α,β-Unsaturated Ketones: One-Pot Synthesis of 3-Carbonyl-2-Substituted Quinolin-4(1H)-ones. Journal of Organic Chemistry. 2018; 83 (5): 2694–2705. https://doi.org/10.1021/acs.joc.7b03162

[15] Khamarui S, Saima Y, Laha RM, Ghosh S, Maiti DK. Functionalised MnVI-nanoparticles: An advanced high-valent magnetic catalyst. Scientific Reports. 2015; 5: 46–48. https://doi.org/10.1038/srep08636

[16] Pérez Mayoral E, Musilová Z, Gil B, Marszalek B, Polozij M et al. Synthesis of quinolines via Friedländer reaction catalyzed by CuBTC metal-organic-framework. Dalton Transactions. 2012; 41 (14): 4036–4044. https://doi.org/10.1039/c2dt11978a

[17] El Hashash MA, Azab ME, Morsy JM. One-Pot Synthesis of Some Dynamic 2-Substituted Benzoxazinones and Their Corresponding Qinazolinones of Anticipated Biological Activity. Journal of Heterocyclic Chemistry. 2016; 53 (1): 95–101. https://doi.org/10.1002/jhet.2389

[18] Ma Y, Zhu Y, Zhang D, Meng Y, Tang T et al. Eco-friendly decarboxylative cyclization in water: Practical access to the anti-malarial 4-quinolones. Green Chemistry. 2019; 21 (3): 478–482. https://doi.org/10.1039/c8gc03570a

[19] Valès M, Lokshin V, Pépe G, Samat A, Guglielmetti R. Enaminones acylation: Competitive formation of quinolin-4-one and isoquinolin-1-one derivatives. Synthesis. 2001; 3 (16): 2419–2426. https://doi.org/10.1055/s-2001-18719

[20] Saripinar E, Karataş S. Synthesis and thermolysis of the 2,3-dihydro-1H-pyrole-2,3-diones, pseudopericyclic reactions of formyl(N-phenylimidoyl)ketene: Experimental data and PM3 calculations. Journal of Heterocyclic Chemistry. 2005; 42 (5): 787–796. https://doi.org/10.1002/jhet.5570420507

[21] Staskun B. A New Synthesis of 2-Aryl-3-acetyl-4-hydroxyquinolines Using Polyphosphoric Acid. Journal of Organic Chemistry. 1961; 26 (8): 2791–2794. https://doi.org/10.1021/jo01066a040

[22] Kshirsagar UA. Recent developments in the chemistry of quinazolinone alkaloids. Organic and Biomolecular Chemistry. 2015; 13 (36): 9336–9352. https://doi.org/10.1039/c5ob01379h

[23] Rohokale RS, Kshirsagar UA. Advanced Synthetic Strategies for Constructing Quinazolinone Scaffolds. Synthesis (Germany). 2016; 48 (9): 1253–1268. https://doi.org/10.1055/s-0035-1560413

[24] Ma ZZ, Hano Y, Nomura T, Chen YJ. Two new pyrroloquinazolinoquinoline alkaloids from Peganum nigellastrum. Heterocycles. 1997; 46: 541–546.

[25] Xu Z, Zhang Y, Fu H, Zhong H, Hong K et al. Antifungal quinazolinones from marine-derived Bacillus cereus and their preparation. Bioorganic and Medicinal Chemistry Letters. 2011; 21 (13): 4005–4007. https://doi.org/10.1016/j.bmcl.2011.05.002

[26] Gatadi S, Pulivendala G, Gour J, Malasala S, Bujji S et al. Synthesis and evaluation of new 4(3H)-Quinazolinone derivatives as potential anticancer agents. Journal of Molecular Structure. 2020; 1200: 127097. https://doi.org/10.1016/j.molstruc.2019.127097

[27] Zhu S, Wang J, Chandrashekar G, Smith E, Liu X et al. Synthesis and evaluation of 4-quinazolinone compounds as potential antimalarial agents. European Journal of Medicinal Chemistry. 2010; 45 (9): 3864–3869. https://doi.org/10.1016/j.ejmech.2010.05.040

[28] Zhang J, Liu J, Ma Y, Ren D, Cheng P et al. One-pot synthesis and antifungal activity against plant pathogens of quinazolinone derivatives containing an amide moiety. Bioorganic and Medicinal Chemistry Letters. 2016; 26 (9): 2273–2277. https://doi.org/10.1016/j.bmcl.2016.03.052

[29] Refaie FM, Esmat AY, Gawad SMA, Ibrahim AM, Mohamed MA. The antihyperlipidemic activities of 4(3H) quinazolinone and two halogenated derivatives in rats. Lipids in Health and Disease. 2005; 4: 1–11. https://doi.org/10.1186/1476-511X-4-22

[30] Khalafi Nezhad A, Haghighi SM, Purkhosrow A, Panahi F. An efficient one-pot access to quinazolinone derivatives using TiO_2 nanoparticles as catalyst: Synthesis and vasorelaxant activity evaluation. Synlett. 2012; 23 (6): 920–924. https://doi.org/10.1055/s-0031-1290610

[31] Khan MTH, Khan R, Wuxiuer Y, Arfan M, Ahmed M et al. Identification of novel quinazolin-4(3H)-ones as inhibitors of thermolysin, the prototype of the M4 family of proteinases. Bioorganic and Medicinal Chemistry. 2010; 18 (12): 4317–4327. https://doi.org/10.1016/j.bmc.2010.04.083

[32] Rambabu R, Kumar P, Venkateswararao J, Subbarao J. Synthesis, characterization and biological evaluation of certain new pyrazole derivatives. International Journal of Chemical Sciences. 2015; 13 (3): 1383–1392.

[33] Al Sehemi AG, Al Amri RSA, Irfan A. Characterization and density functional theory investigations of 3-monoacylaminoquinazolinone derivatives. Wuli Huaxue Xuebao/ Acta Physic-Chimica Sinica. 2013; 29 (1): 55–63. https://doi.org/10.3866/PKU.WHXB201210151

[34] Kökten Ş, Çelik I. A simple, mild, and practical method for the esterification and thioesterification of anthranilic acid utilizing N-(2-Aminobenzoyl) benzotriazole. Synthesis (Germany). 2013; 45 (18): 2551–2556. https://doi.org/10.1055/s-0033-1339469

[35] Kaniskan N, Kokten S, Celik I. A new protocol for the synthesis of primary, secondary and tertiary anthranilamides utilizing N-(2-aminoarylacyl)benzotriazoles. ARKIVOC (Gainesville, FL, United States). 2012; 2012 (8): 198–213. https://doi.org/10.3998/ark.5550190.0013.818

[36] Şenol İM, Çelik İ, Avan İ. One-pot synthesis of quinazolin-4(3H)-ones and 2,3-dihydroquinazolin-4(1H)-ones utilizing N-(2-aminobenzoyl)benzotriazoles. Turkish Journal of Chemistry. 2019; 43 (6): 1580–1596. https://doi.org/10.3906/kim-1906-50

[37] Çelik İ, Yıldız F. Synthesis of 4-hydroxyquinoline-2,3-dicarboxylates using N-(2-aminobenzoyl)benzotriazoles. Tetrahedron. 2017; 73 (27–28): 3878–3882. https://doi.org/10.1016/j.tet.2017.05.058

[38] Kökten Ş, Çelik I. N-(2-Aminobenzoyl)benzotriazole mediated and t-BuOK promoted synthesis of 2-substituted quinolone 3-carboxylates. Tetrahedron Letters. 2015; 56 (45): 6254–6256. https://doi.org/10.1016/j.tetlet.2015.09.109

[39] Vijayakumar K, Ahamed AJ. Synthesis and biological activities of some novel substituted quinazoline derivatives. *Pharma Chemi*ca. 2010;2(5):453–457.

[40] Legrand Louis NL. Heterocyclic sulfur compounds. XCV. Reaction of methyl or ethyl hydrazinecarboxylates with 3,1-benzothiazine-4-thiones and 3,1-benzothiazin-4-ones. *Bulletin de la Societe Chimique de France.* 1982;(5–6):II-133/II – 138.

Supplemental information

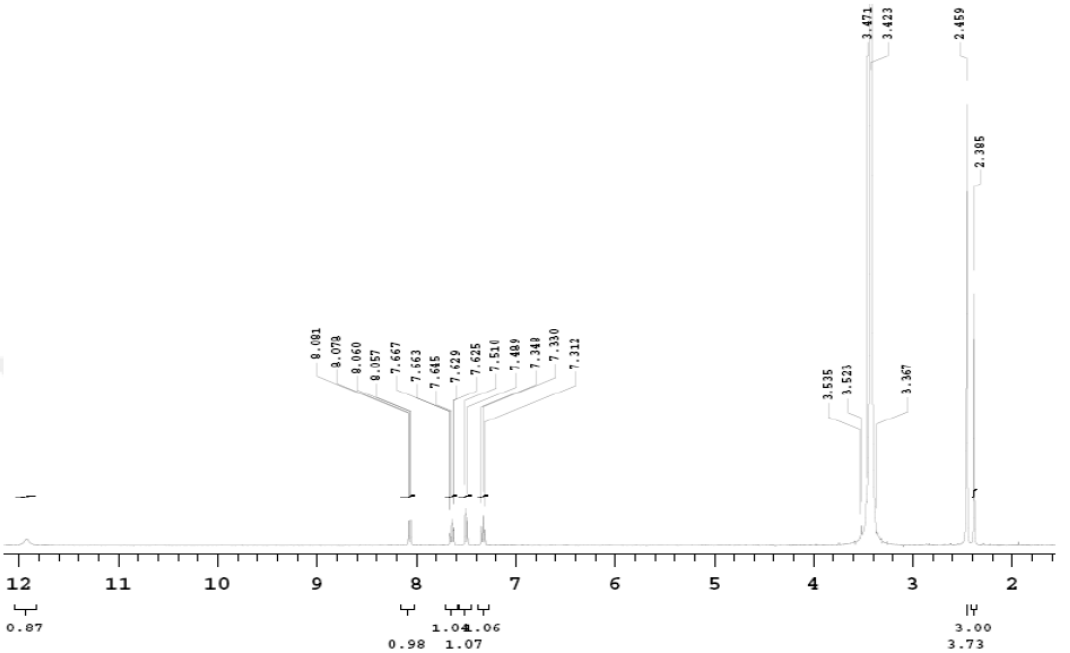


Figure S1. [1]H Spectrum of 1-(4-Hydroxy-2-methylquinolin-3-yl)ethanone 3a.

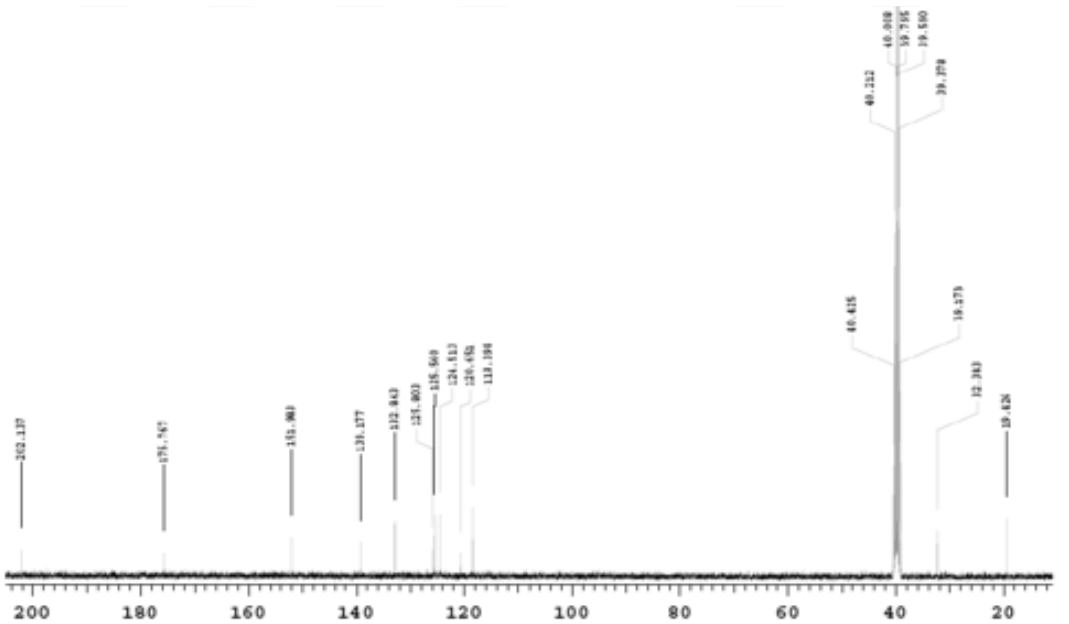


Figure S2. [13]C Spectrum of 1-(4-Hydroxy-2-methylquinolin-3-yl)ethanone 3a.

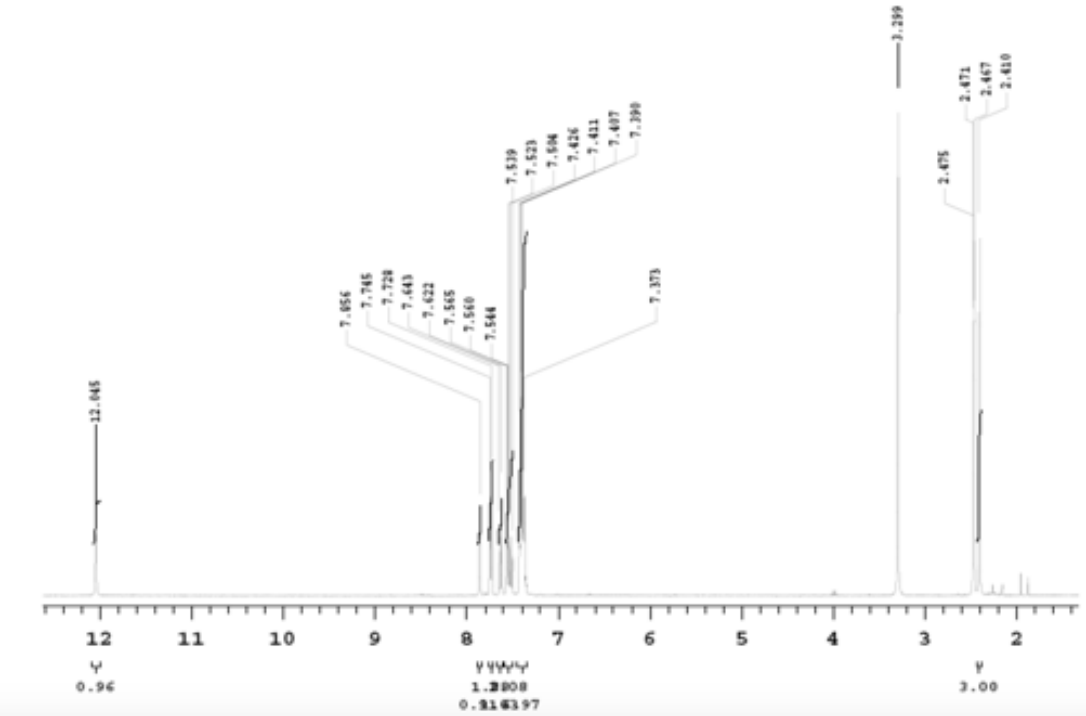


Figure S3. [1]H Spectrum of (4-Hydroxy-6-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3b).

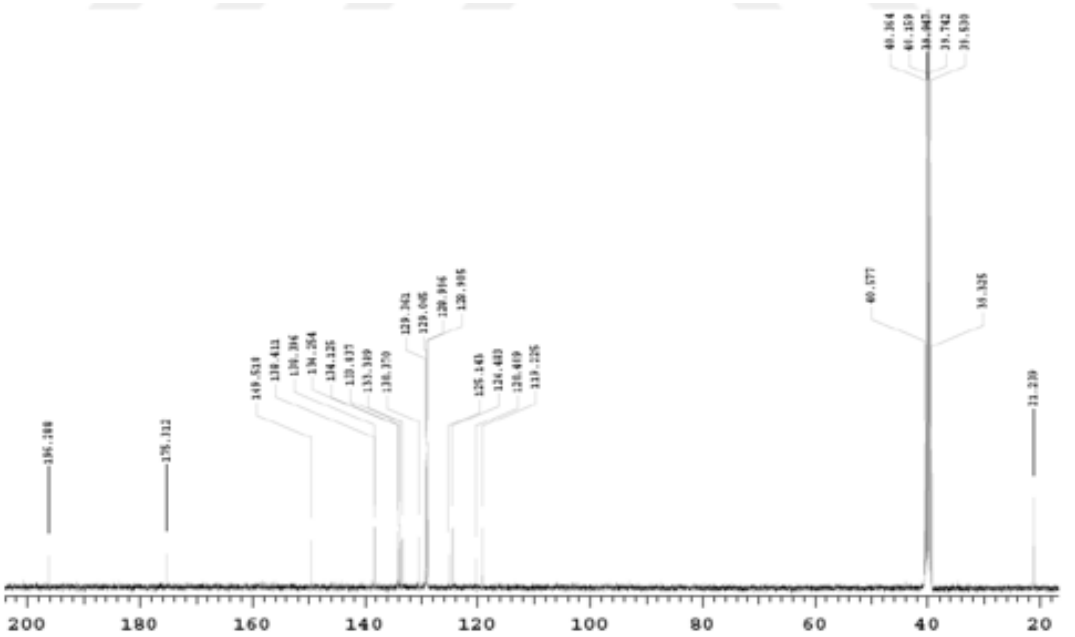


Figure S4. [13]C Spectrum of (4-Hydroxy-6-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3b)

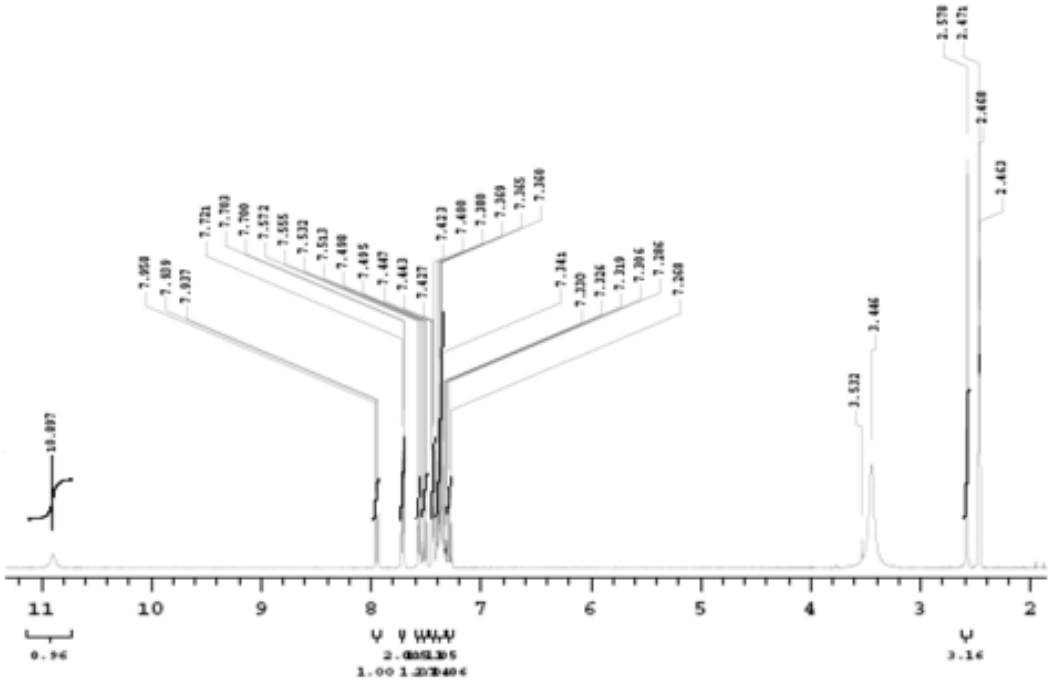


Figure S5. [1]H Spectrum of (4-Hydroxy-8-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3c).

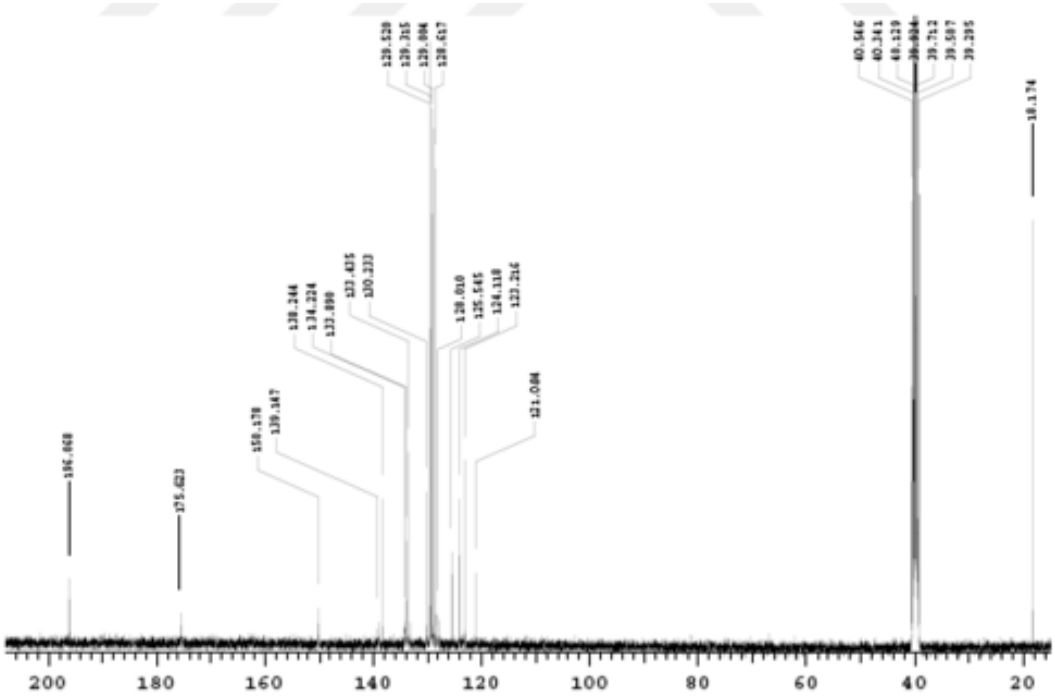


Figure S6. [13]C Spectrum of (4-Hydroxy-8-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3c).

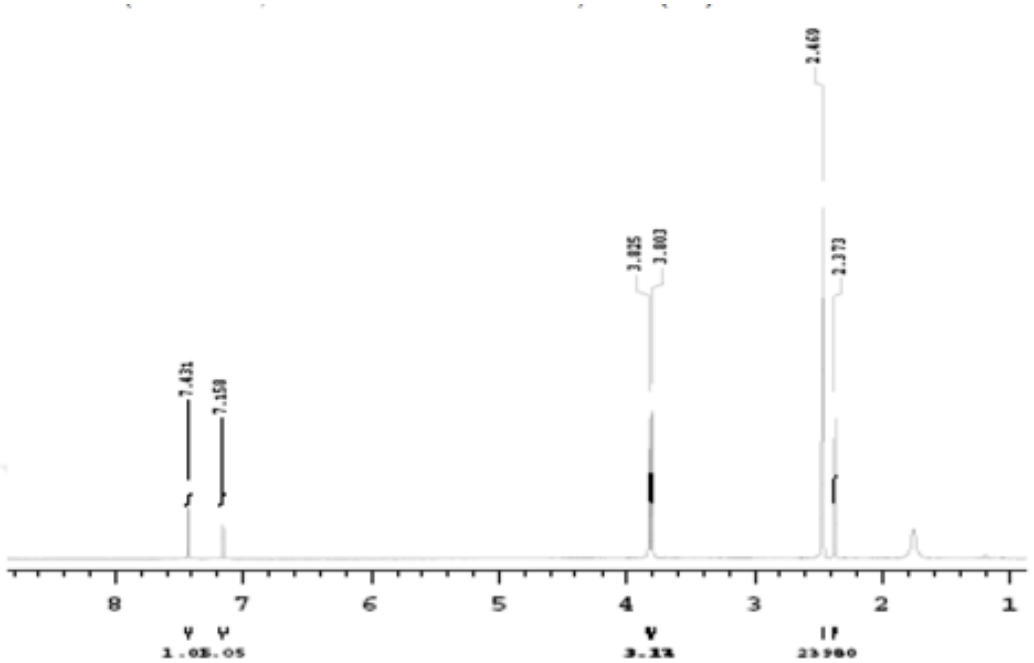


Figure S7. [1]H Spectrum of 1-(4-Hydroxy-6,7-dimethoxy-2-methylquinolin-3-yl)ethanone (3d).

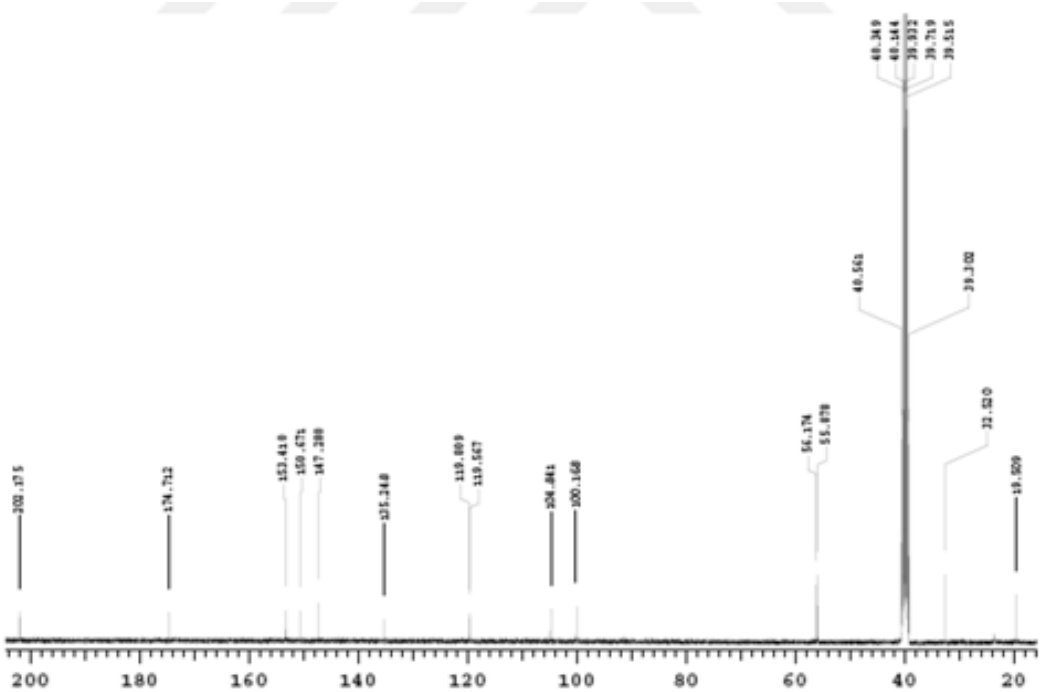


Figure S8. [13]C Spectrum of 1-(4-Hydroxy-6,7-dimethoxy-2-methylquinolin-3-yl)ethanone (3d).

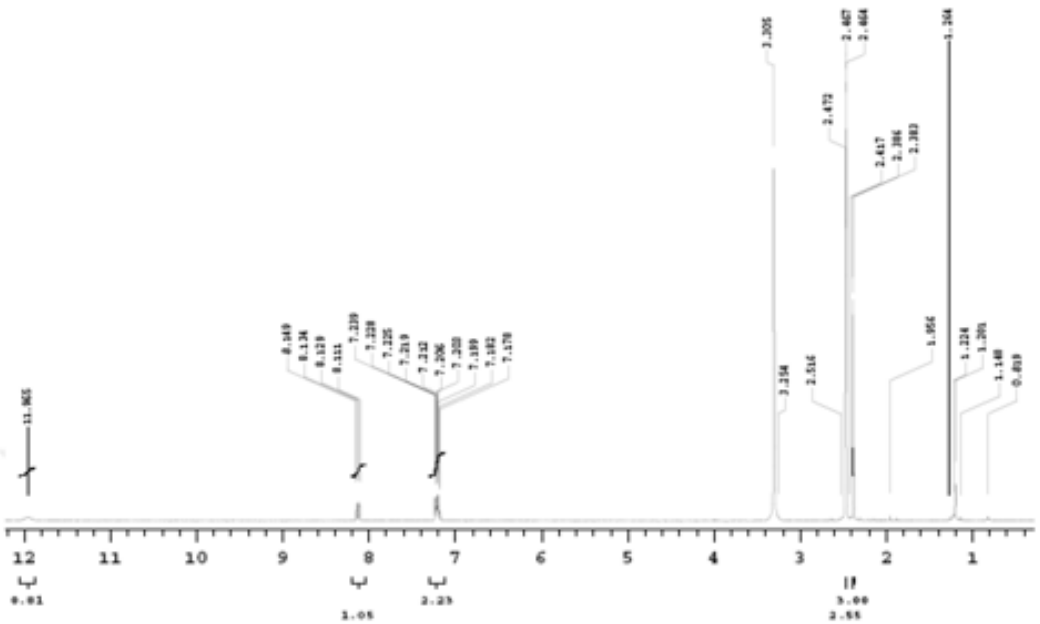


Figure S9. [1]H Spectrum of 1-(7-Fluoro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3e).

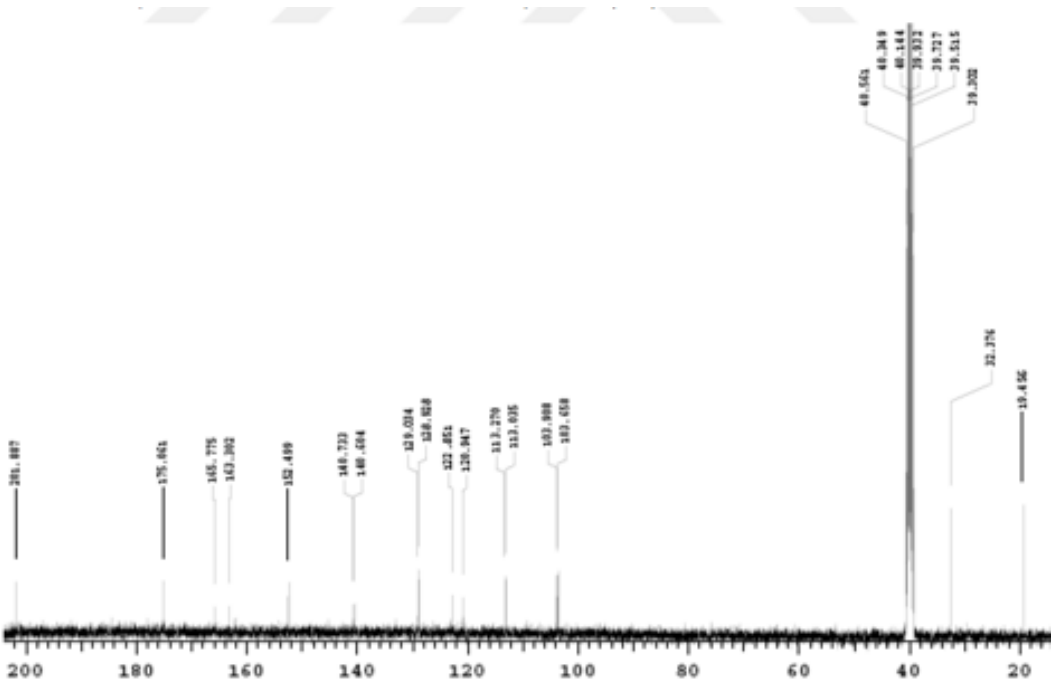


Figure S10. [13]C Spectrum of 1-(7-Fluoro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3e).

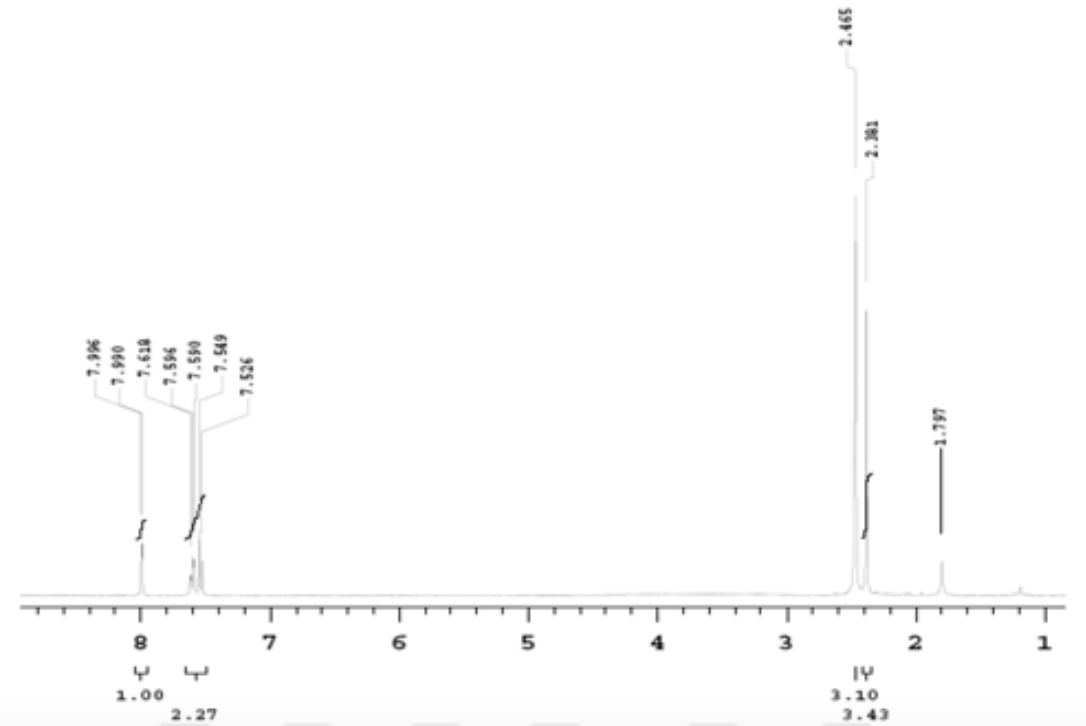


Figure S11. [1]H Spectrum of 1-(6-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3f).

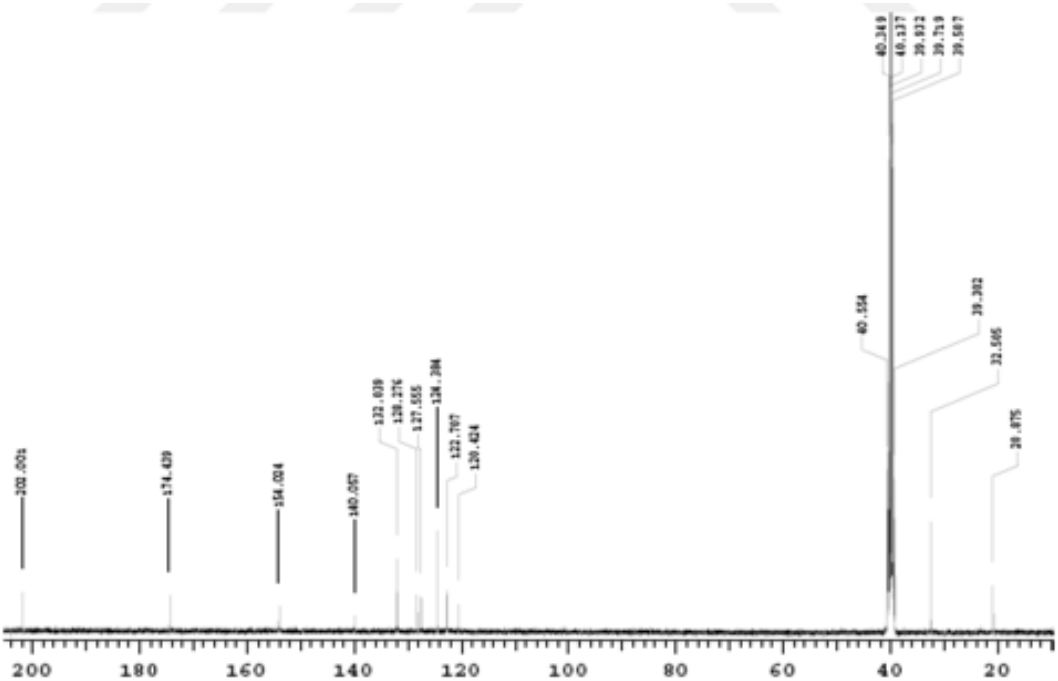


Figure S12. [13]C Spectrum of 1-(6-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3f).

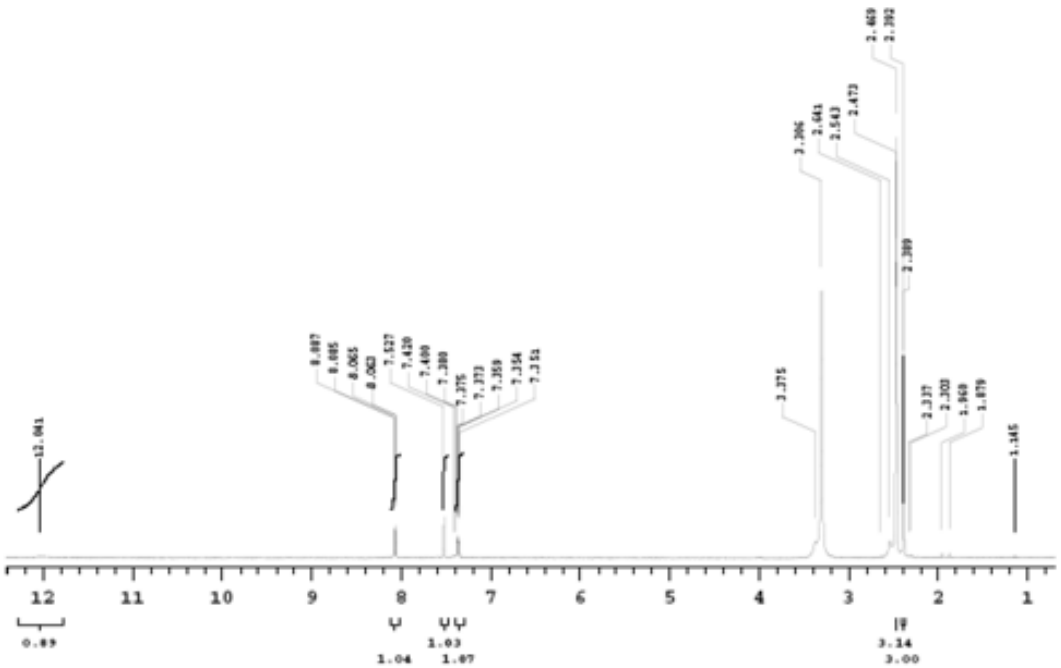


Figure S13. [1]H Spectrum of 1-(7-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3g).

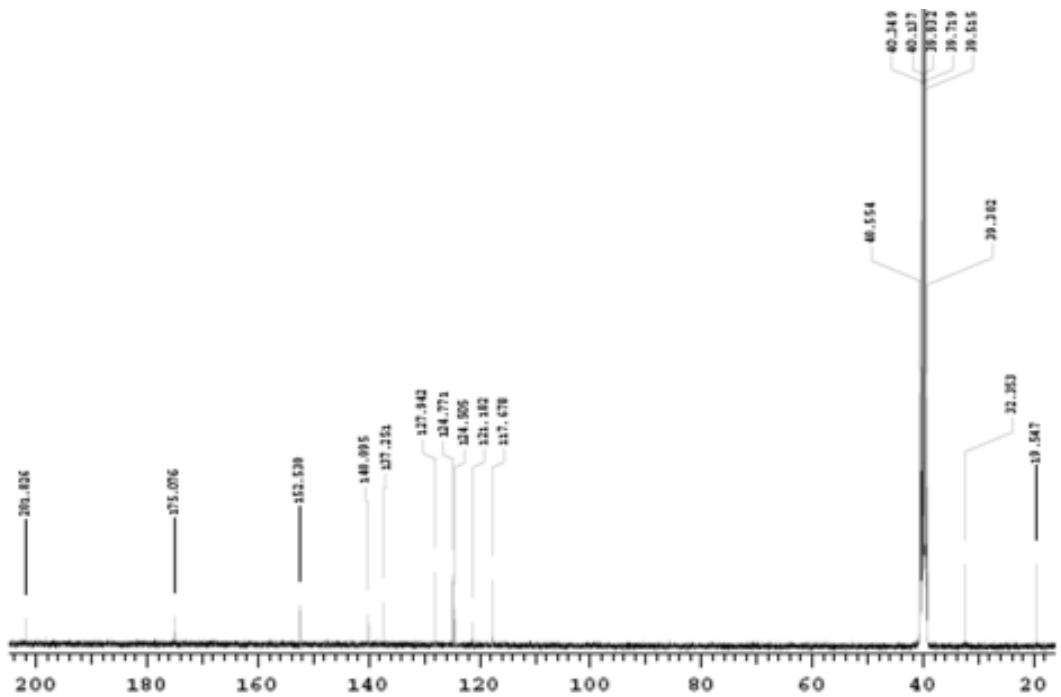


Figure S14. [13]C Spectrum of 1-(7-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3g).

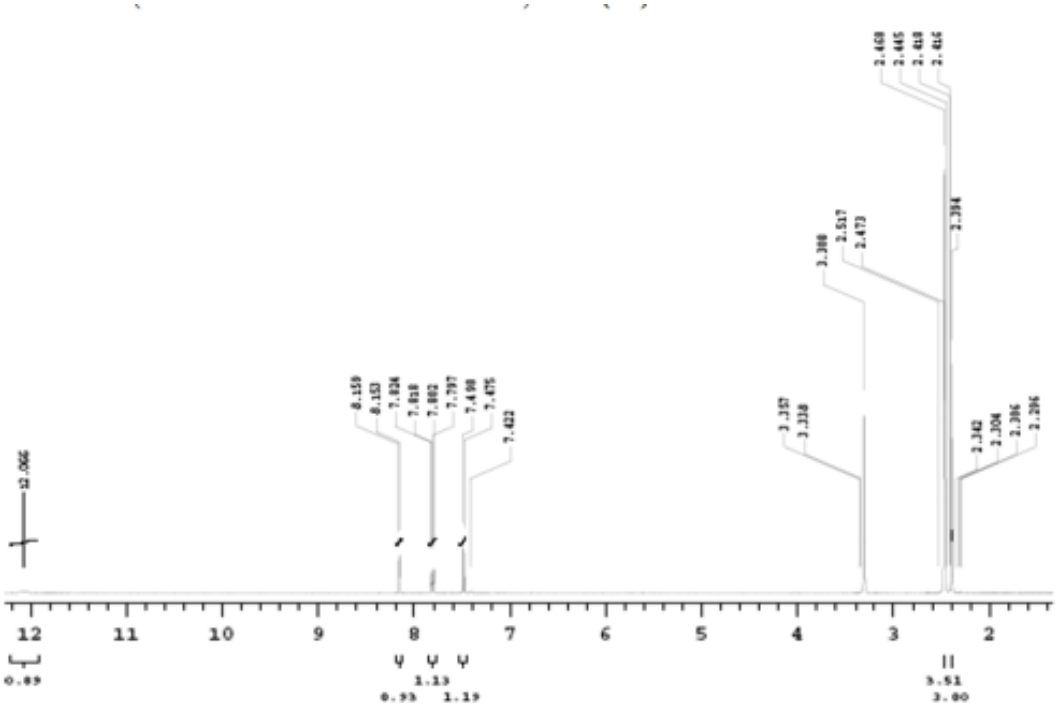


Figure S15. [1]H Spectrum of 1-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)ethanone (3h).

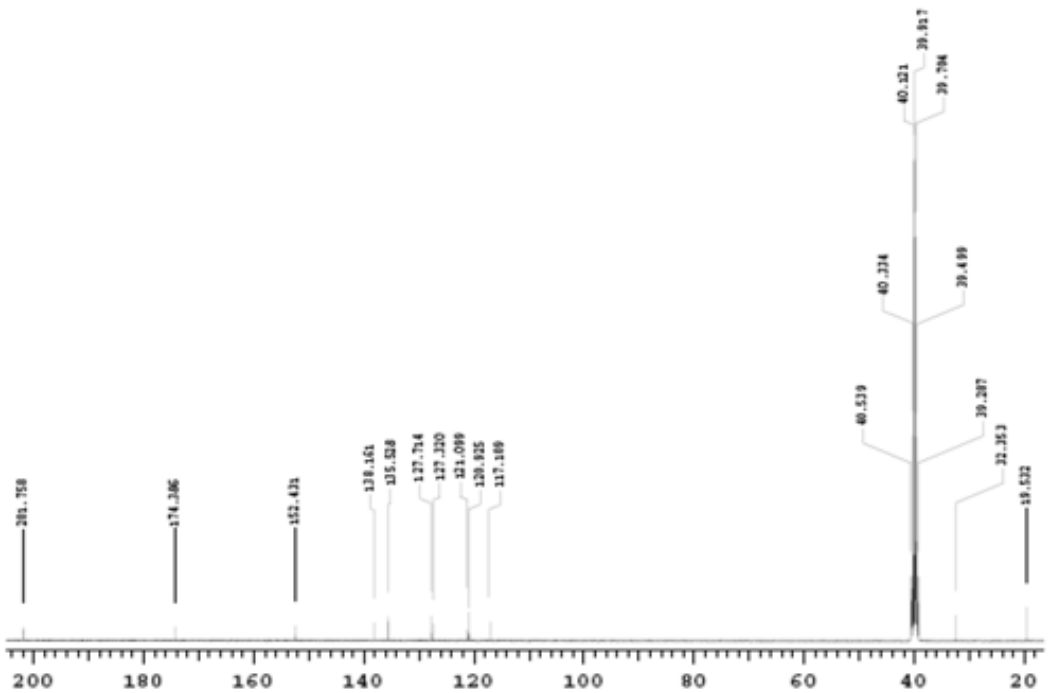


Figure S16. [13]C Spectrum of 1-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)ethanone (3h).

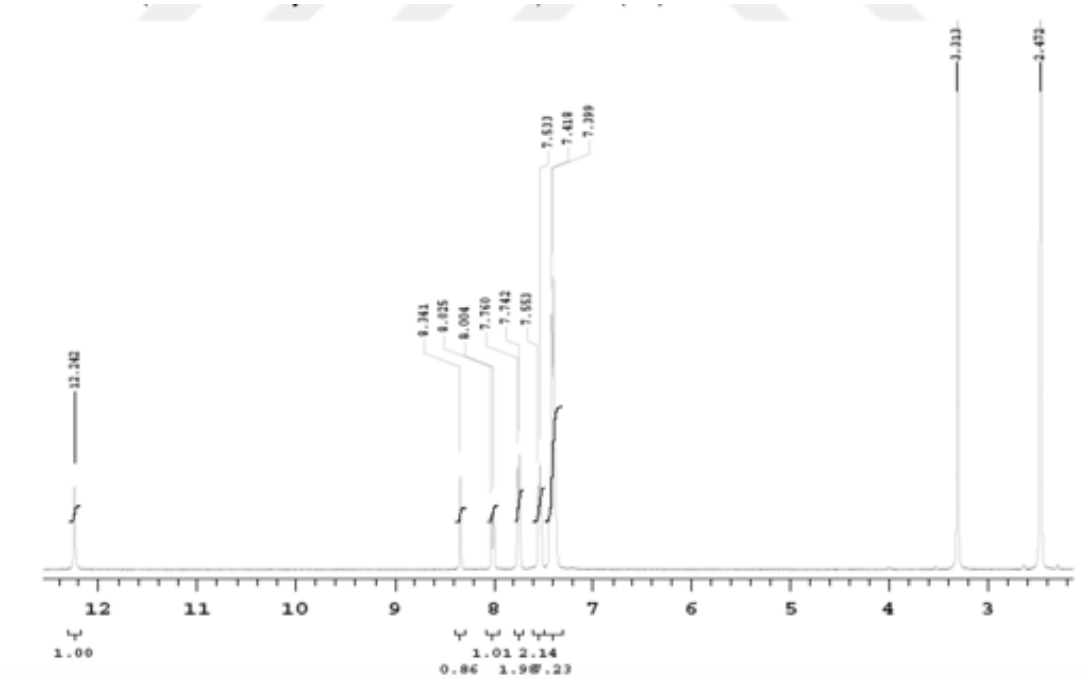


Figure S17.[1]H Spectrum of (4-Hydroxy-6-iodo-2-phenylquinolin-3-yl)(phenyl)methanone (3i).

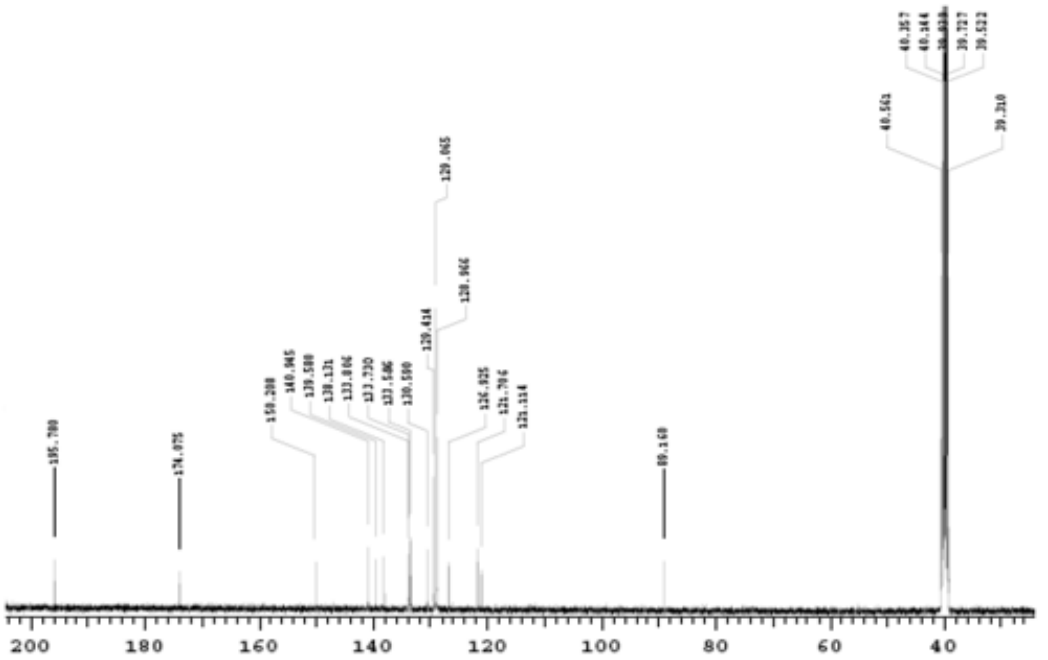


Figure S18.[13]C Spectrum of (4-Hydroxy-6-iodo-2-phenylquinolin-3-yl)(phenyl)methanone (3i).

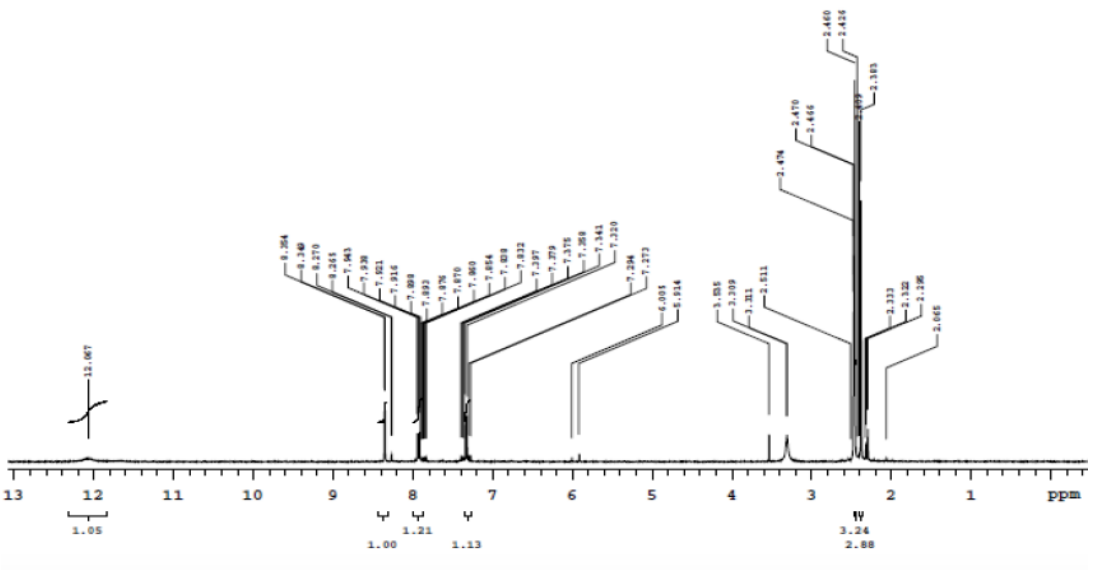


Figure S19. [1]H Spectrum of 1-(4-Hydroxy-6-iodo-2-methylquinolin-3-yl)ethanone (3j).

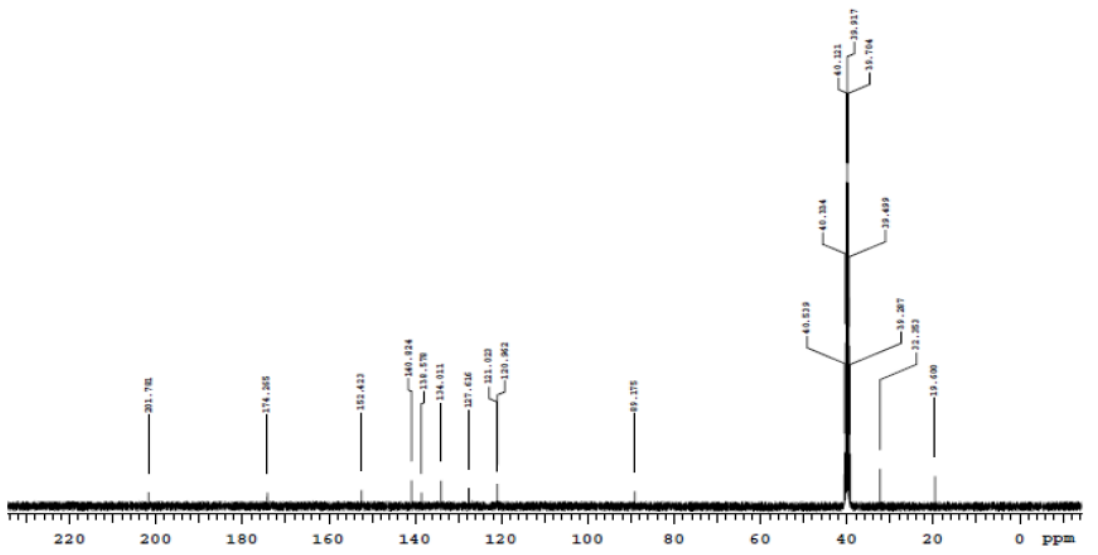


Figure S20. [13]C Spectrum of 1-(4-Hydroxy-6-iodo-2-methylquinolin-3-yl)ethanone (3j).

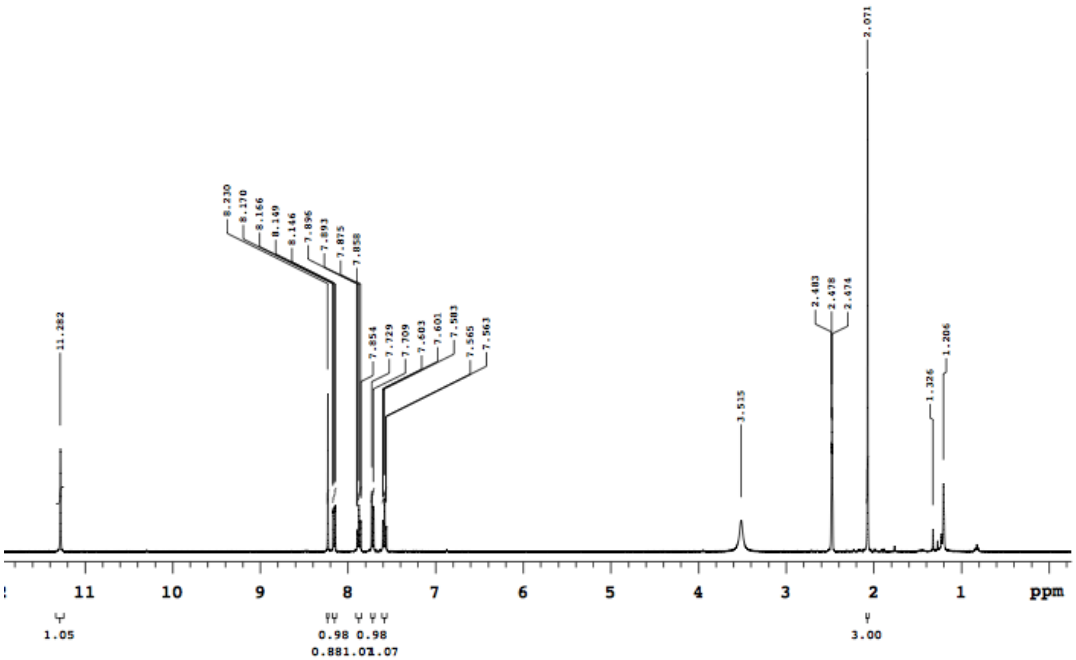


Figure S21. [1]H Spectrum of *N*-(4-Oxoquinazolin-3(4*H*)-yl)acetamide (6a).

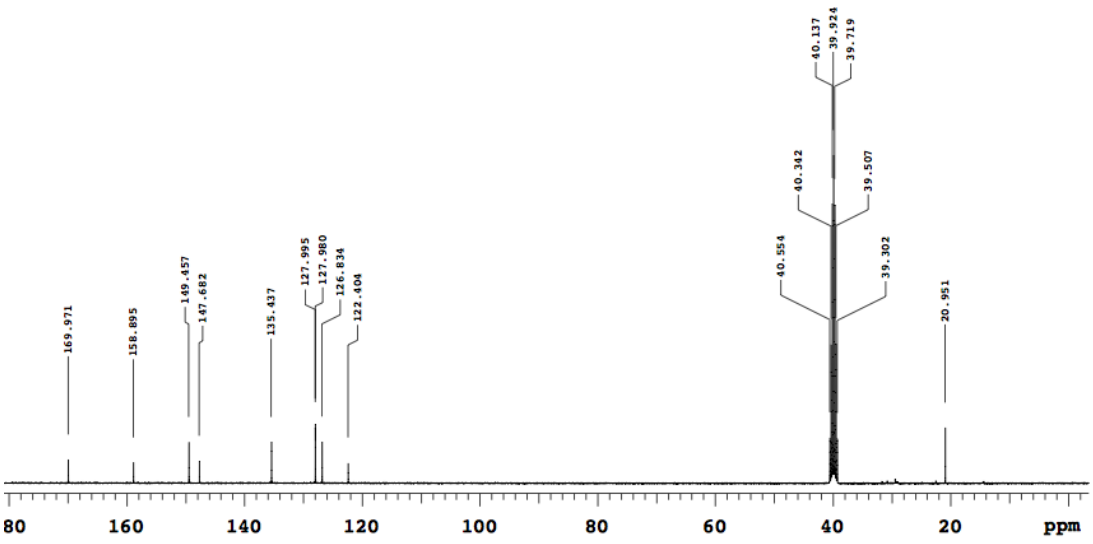


Figure S22. [13]C Spectrum of *N*-(4-Oxoquinazolin-3(4*H*)-yl)acetamide (6a).

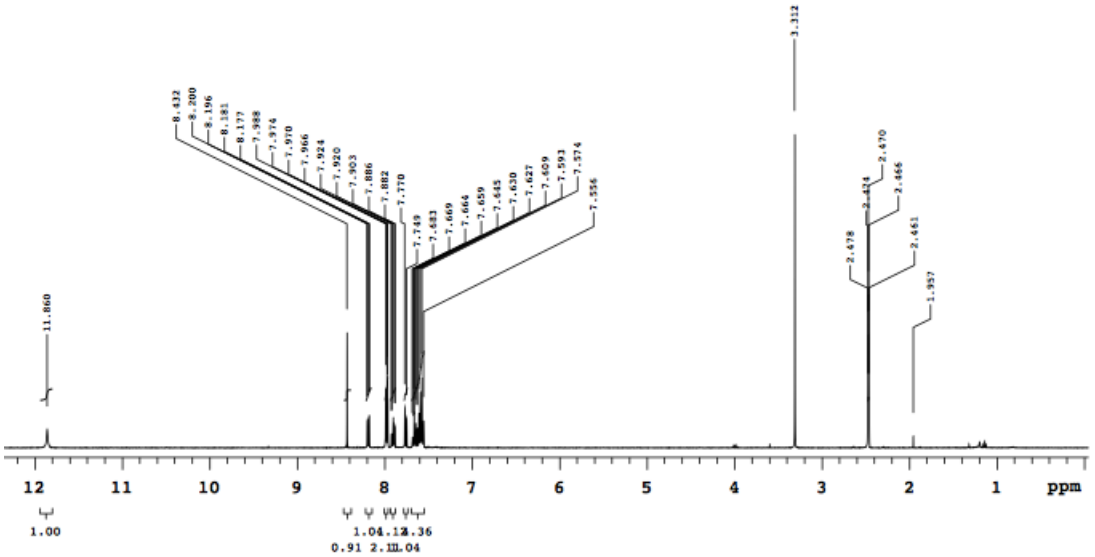


Figure S23. [1]H Spectrum of *N*-(4-Oxoquinazolin-3(4*H*)-yl)benzamide (6b).

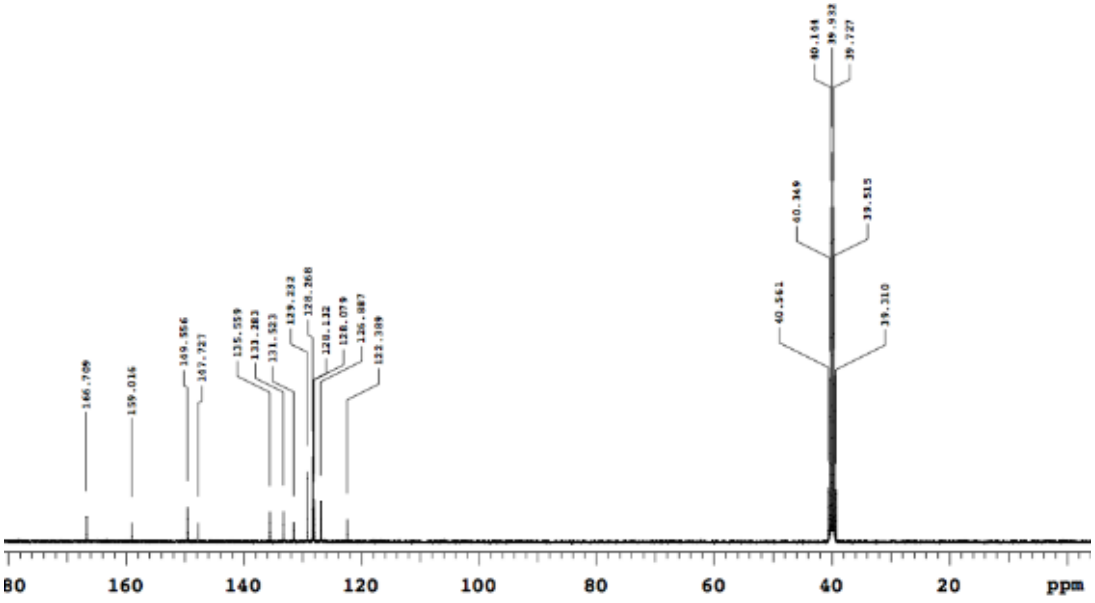


Figure S24. [13]C Spectrum of *N*-(4-Oxoquinazolin-3(4*H*)-yl)benzamide (6b).

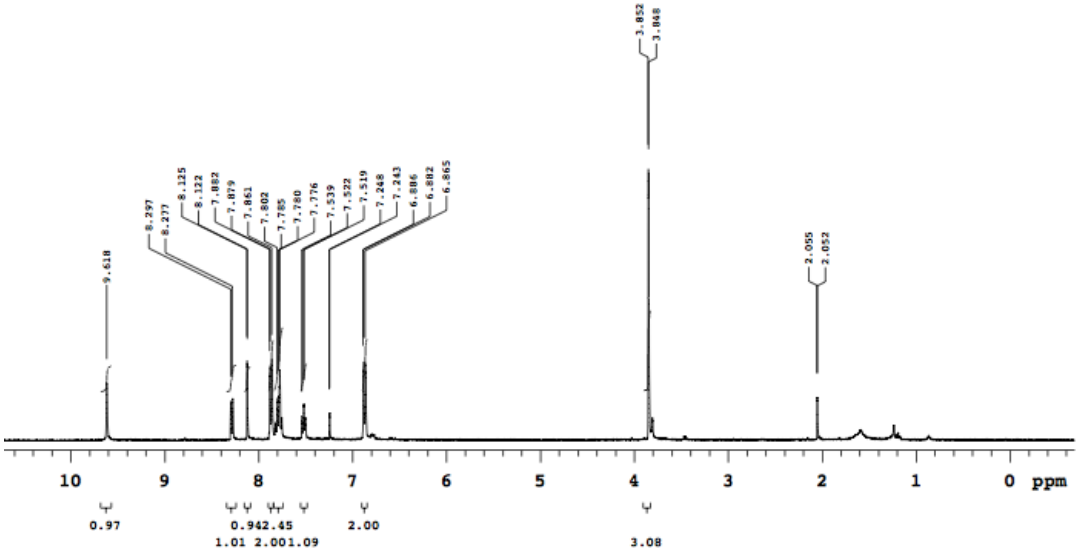


Figure S25. [1]H Spectrum of 4-Methoxy-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6c).

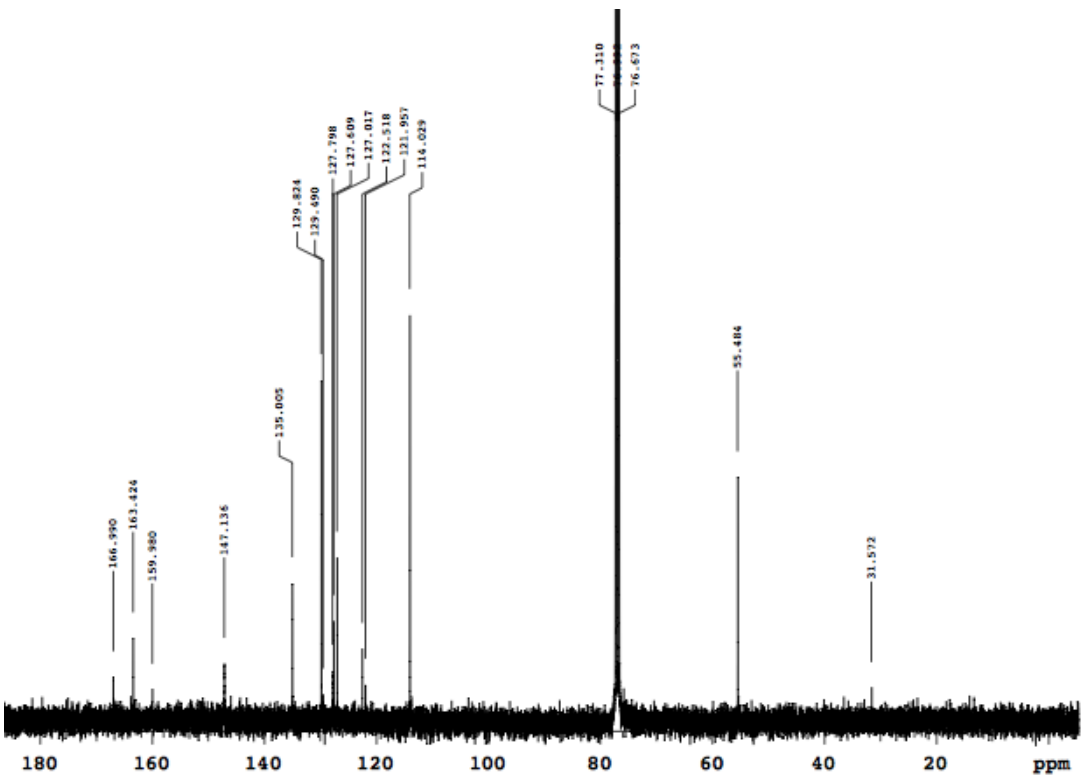


Figure S26. [13]C Spectrum of 4-Methoxy-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6c).

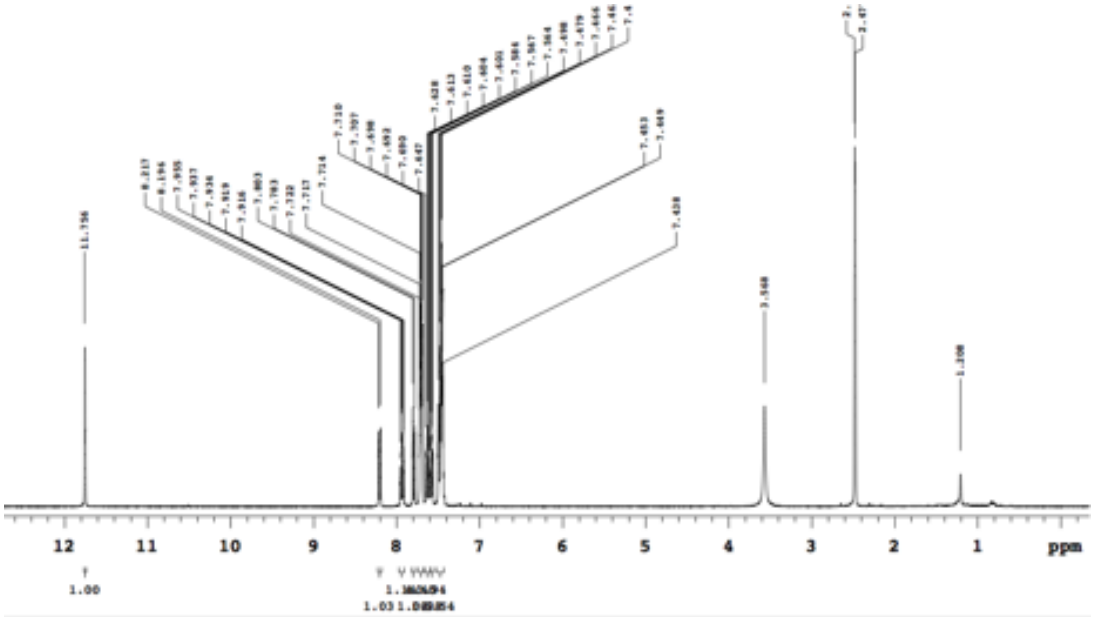
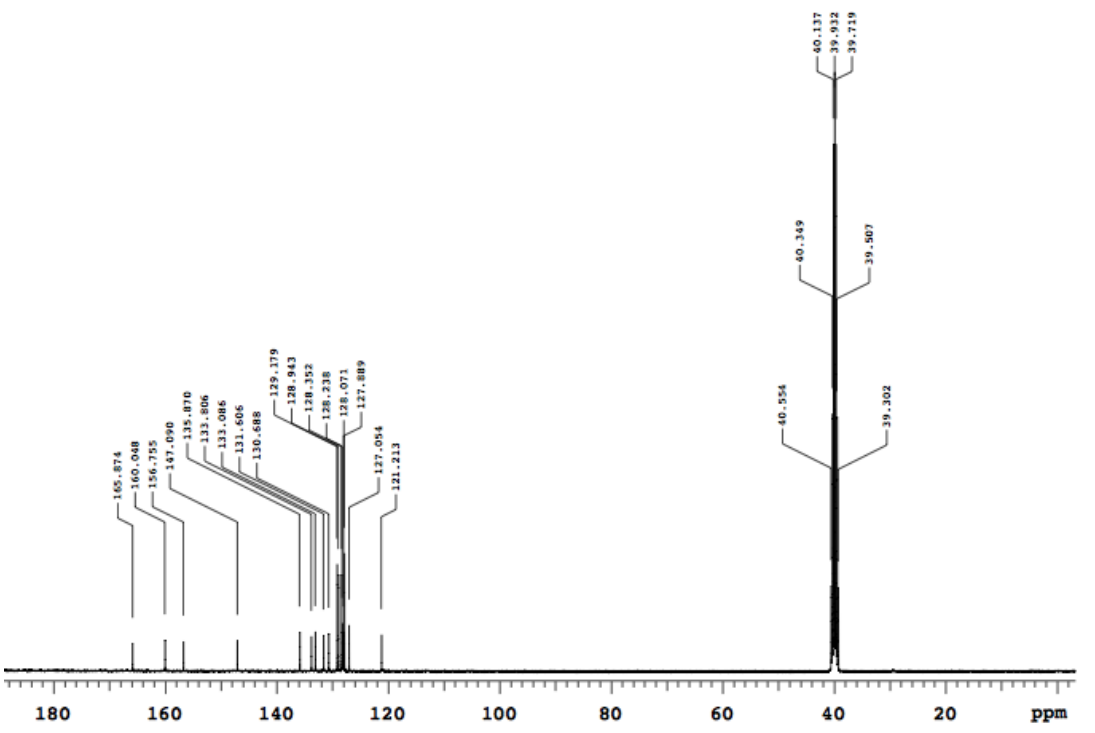


Figure S27. ^{1}H Spectrum of *N*-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)benzamide (6d).



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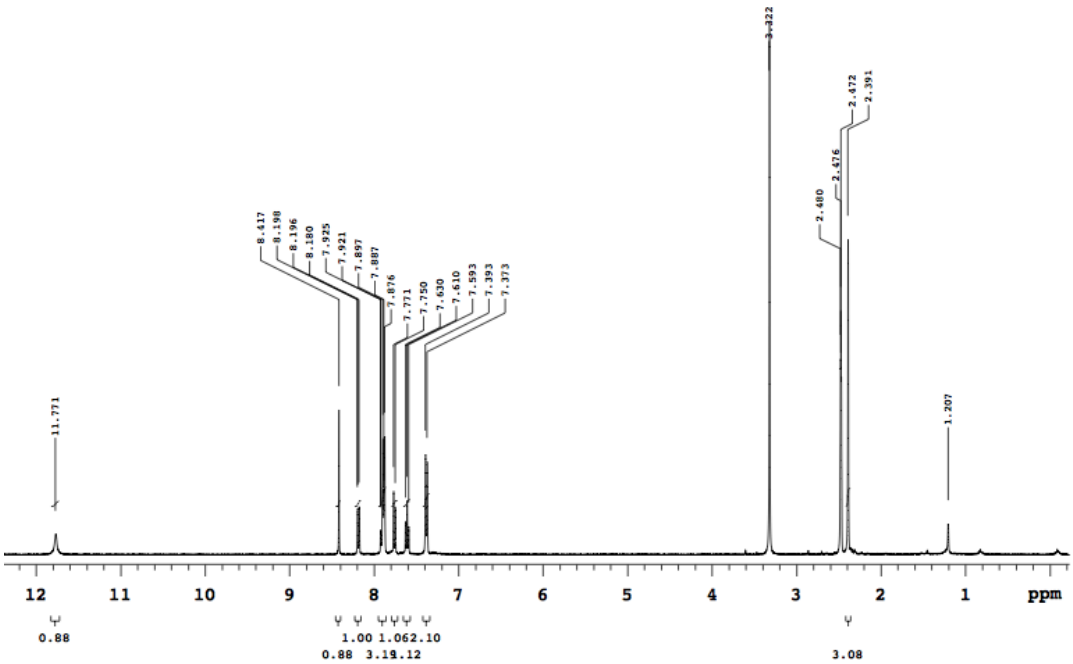
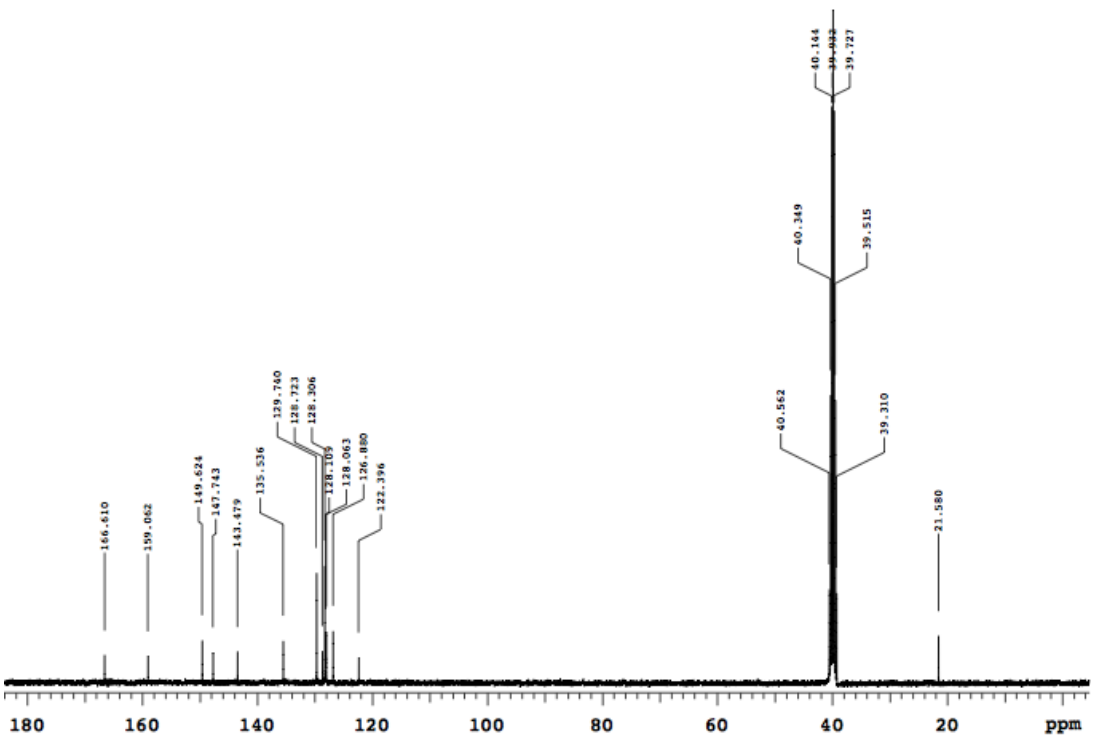


Figure S29. [1]H Spectrum of 4-Methyl-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6e).



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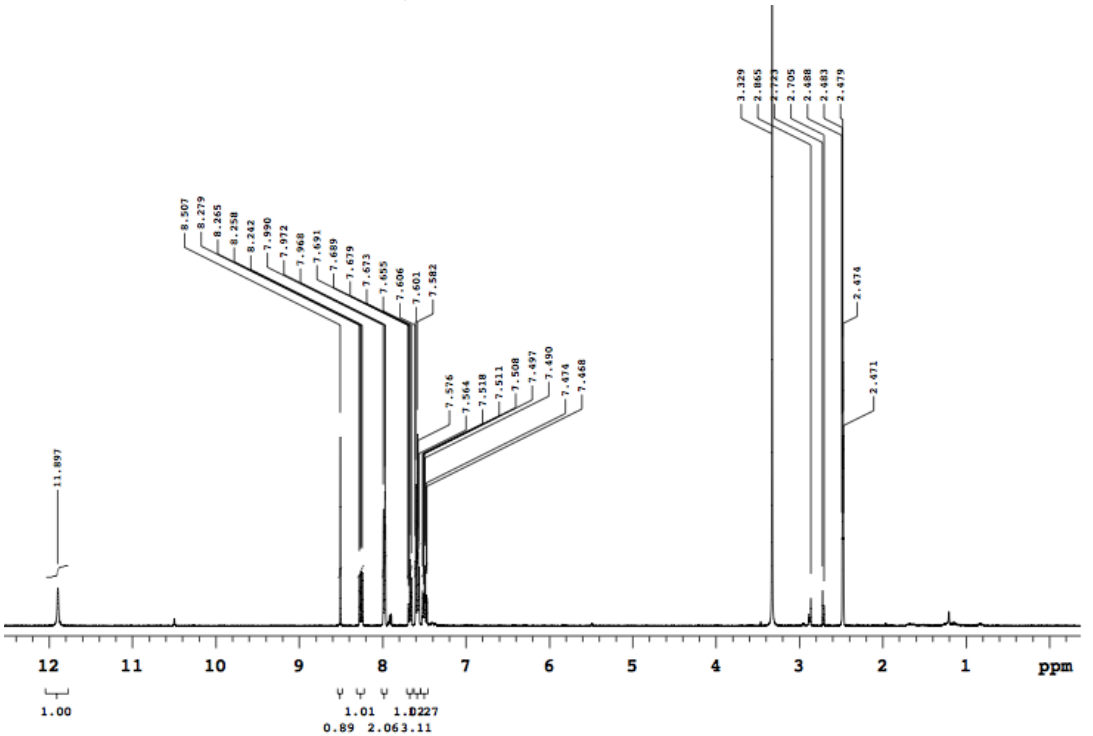


Figure S31. [1]H Spectrum of *N*-(7-Fluoro-4-oxoquinazolin-3(4*H*)-yl)benzamide (6f).

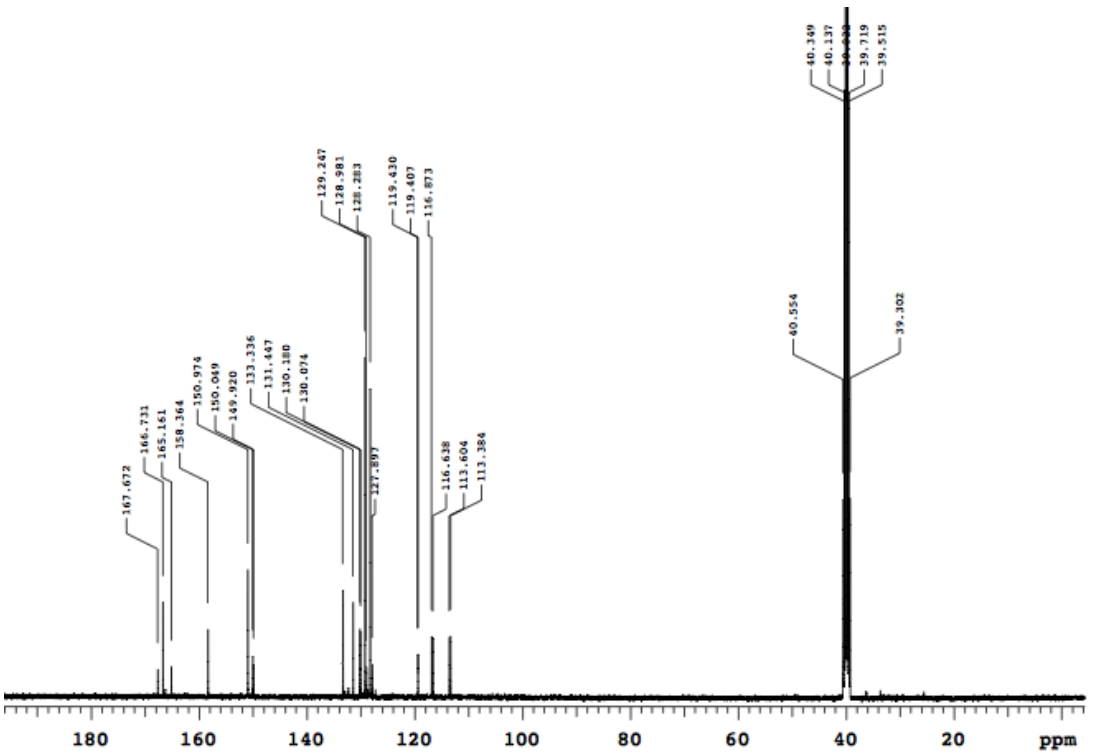


Figure S32. [1]H Spectrum of *N*-(7-Fluoro-4-oxoquinazolin-3(4*H*)-yl)benzamide (6f).

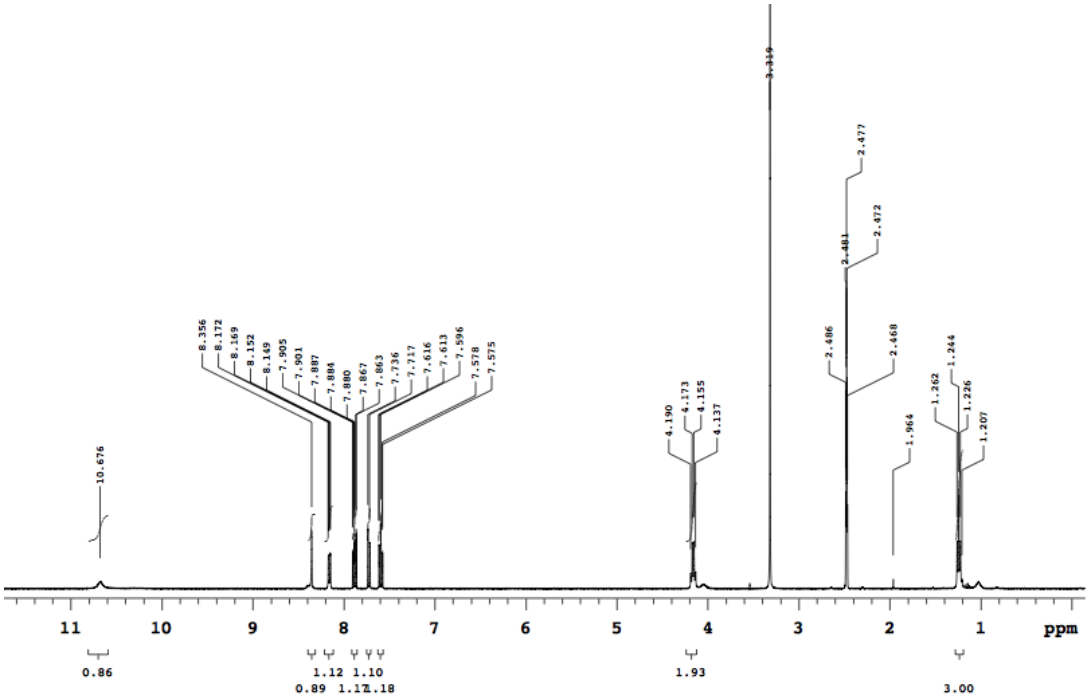
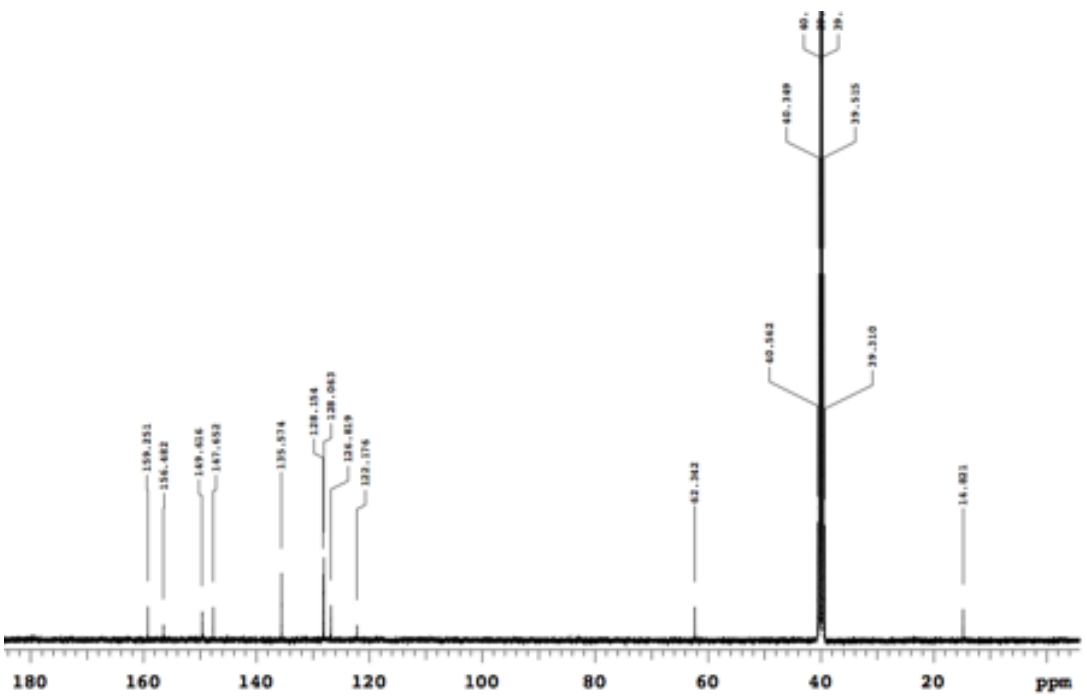


Figure S33. [1]H Spectrum of Ethyl (4-oxoquinazolin-3(4*H*)-yl)carbamate (6g).



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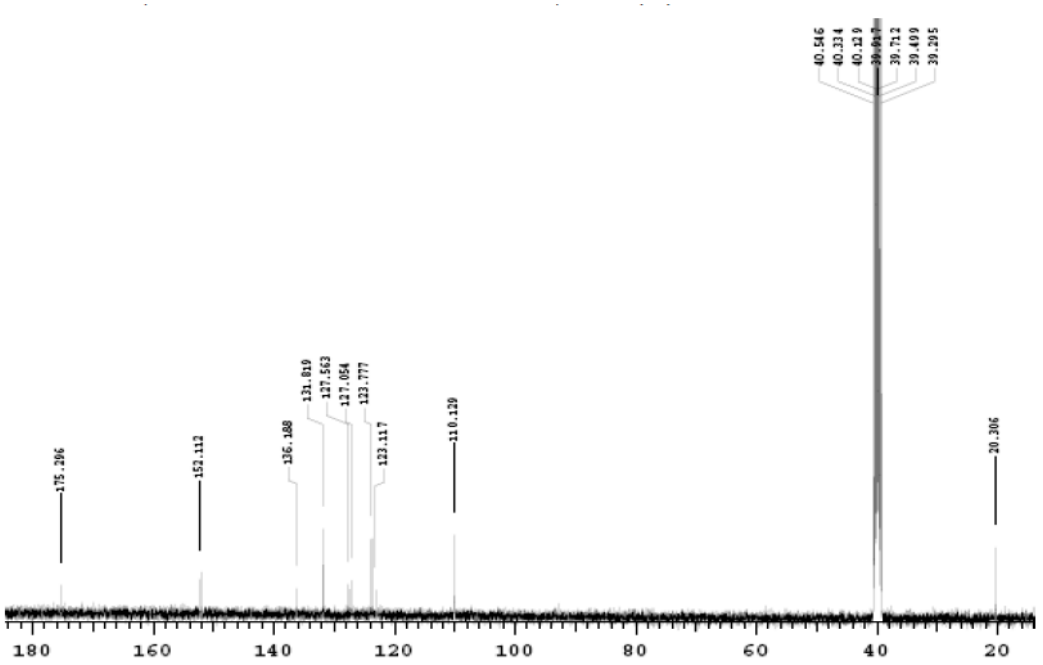

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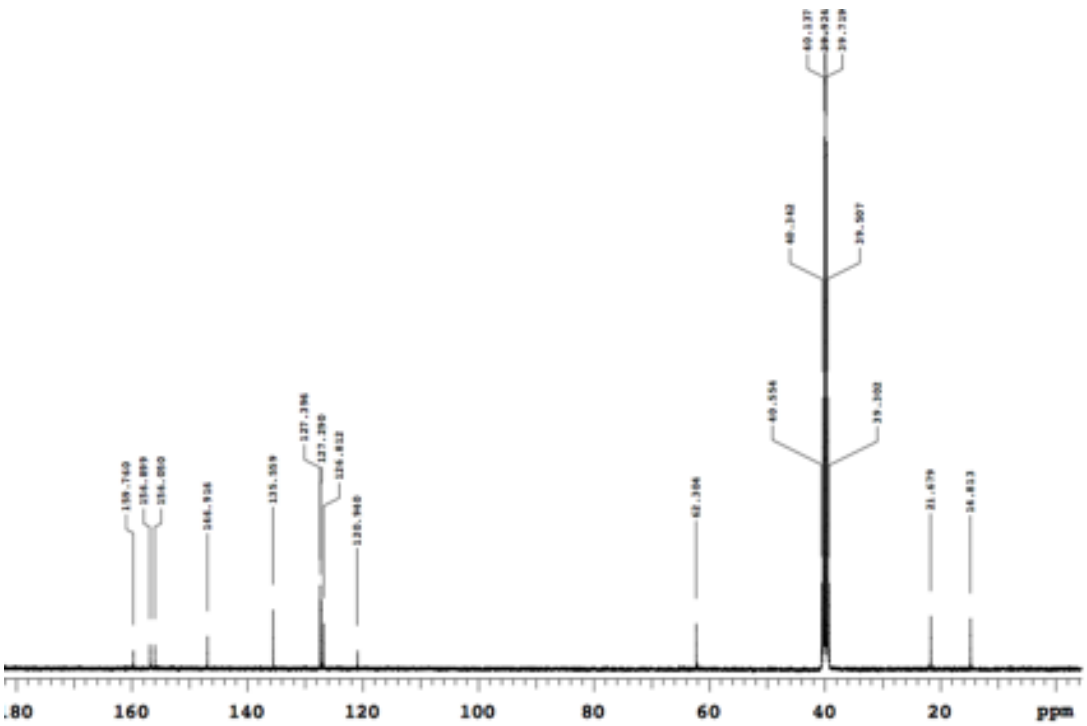


Figure S36.[13]C Spectrum of Ethyl (2-methyl-4-oxoquinazolin-3(4*H*)-yl)carbamate (6h).

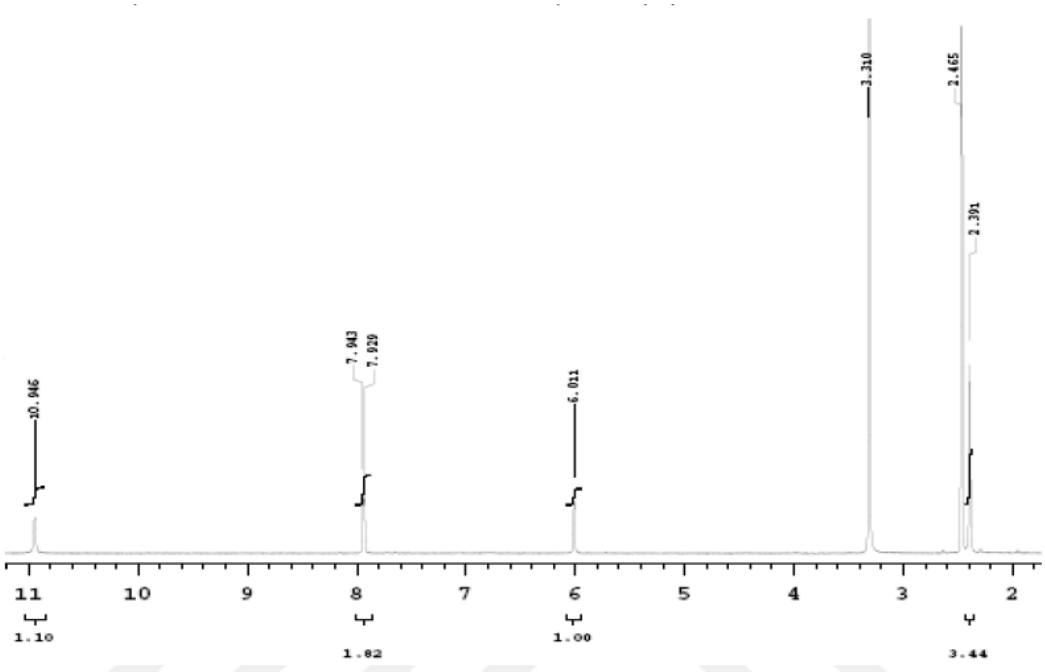


Figure S37. [1]H Spectrum of 6,8-dichloro-2-methylquinolin-4-ol (3kb).

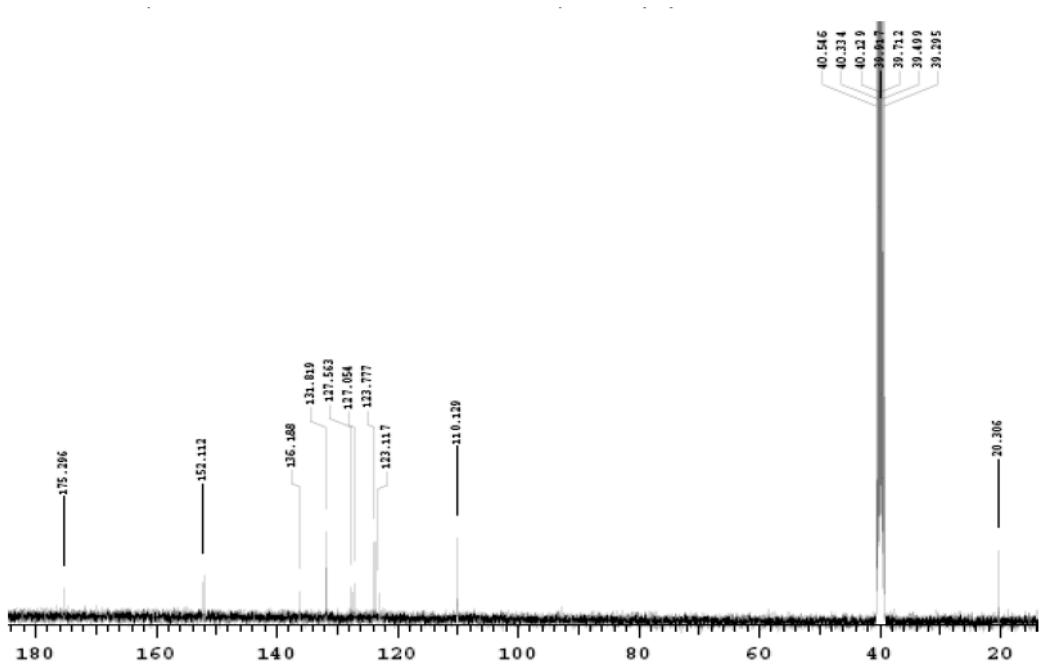


Figure S38. [13]C Spectrum of 6,8-dichloro-2-methylquinolin-4-ol (3kb).

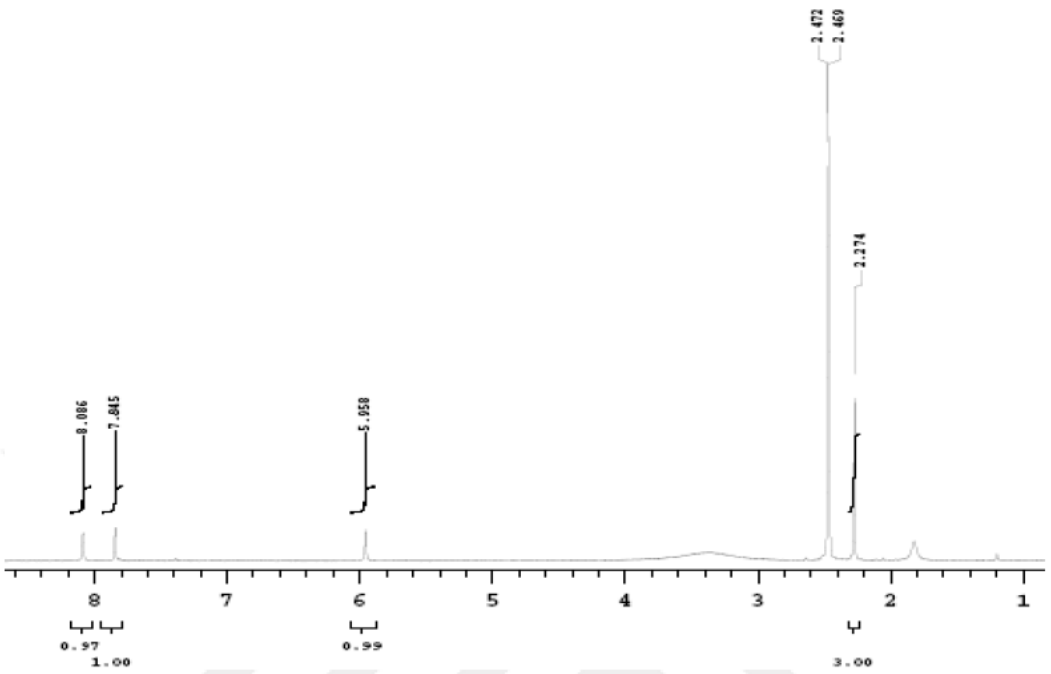


Figure S39. [1]H Spectrum of 6,8-dibromo-2-methylquinolin-4-ol (3lb).

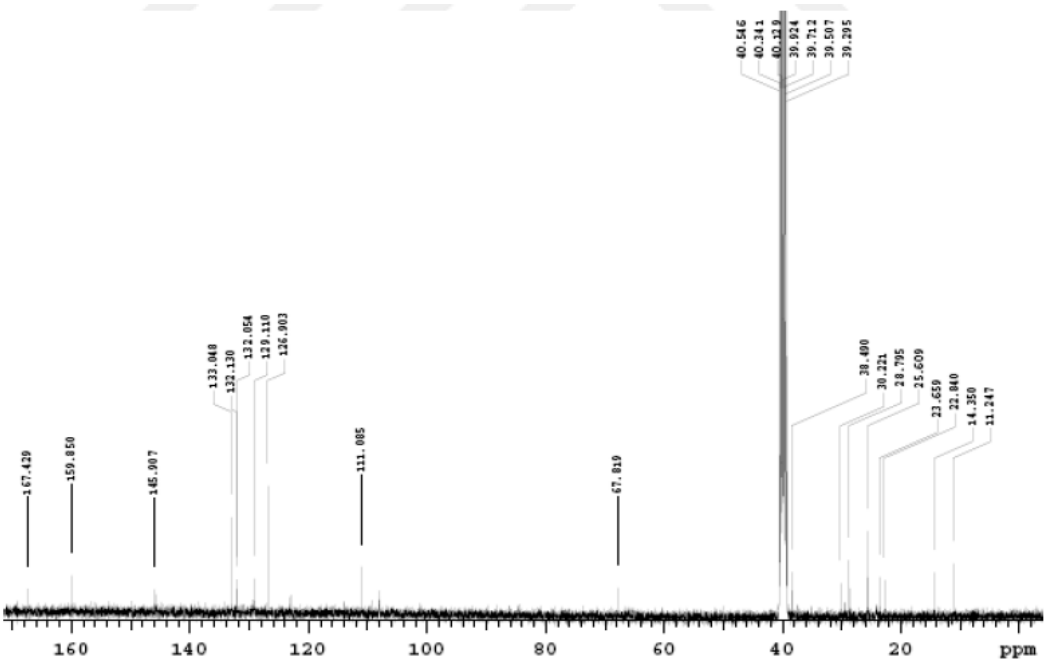


Figure S40. [13]C Spectrum of 6,8-dibromo-2-methylquinolin-4-ol (3lb).

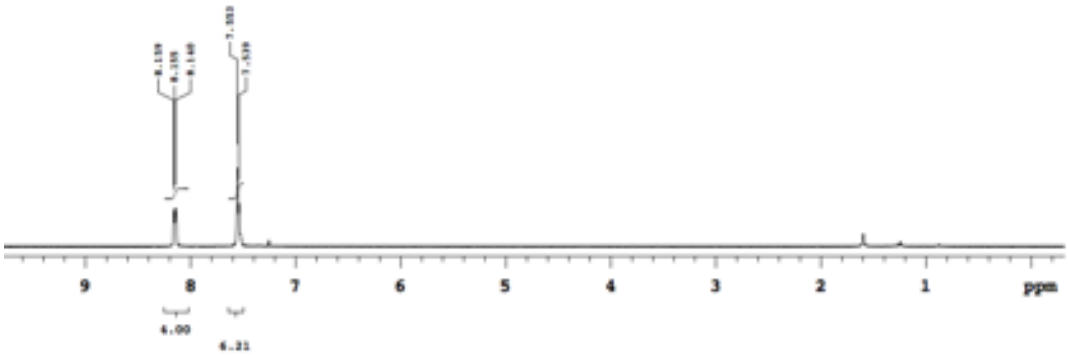


Figure S41. [1]H Spectrum of 2,5-diphenyl-1,3,4-oxadiazole (6d').

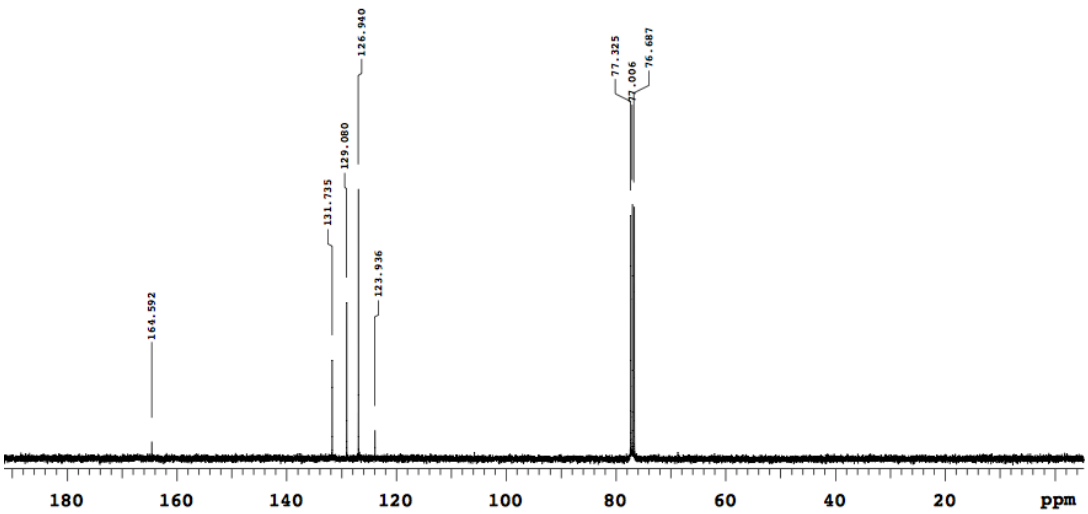


Figure S42. [13]C Spectrum of 2,5-diphenyl-1,3,4-oxadiazole (6d').

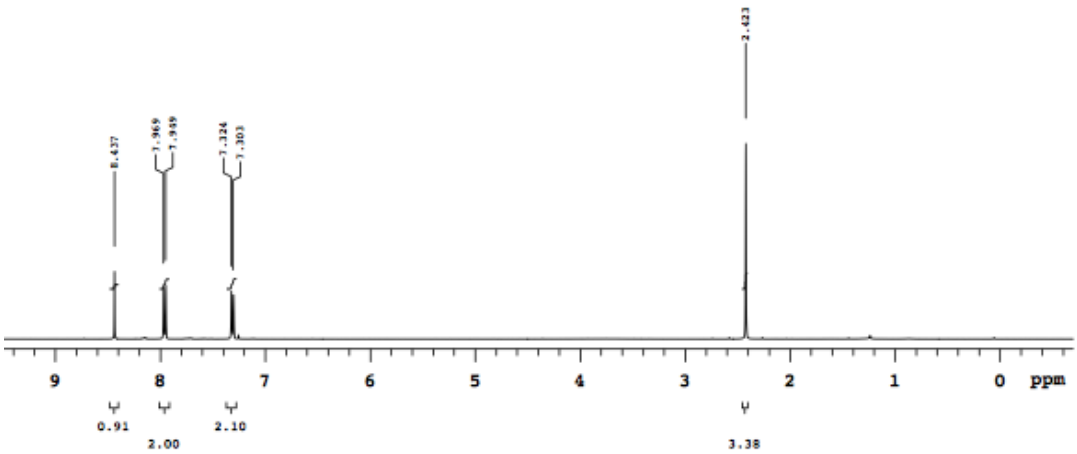


Figure S43. [1]H Spectrum of 2-(*p*-Tolyl)-1,3,4-oxadiazole (6e').

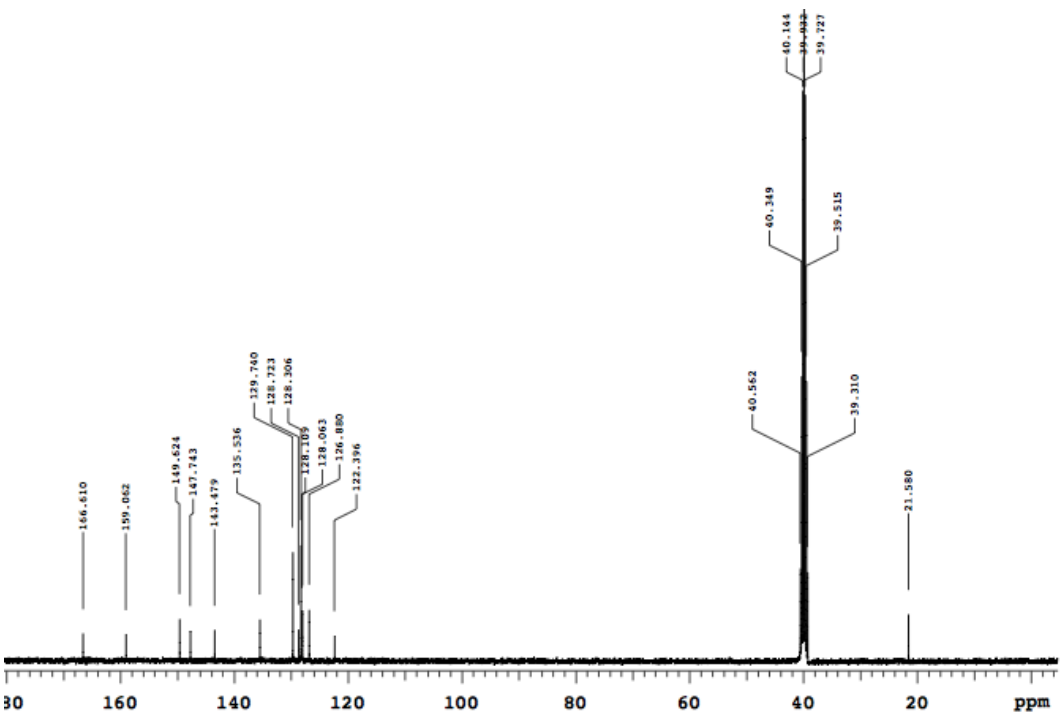


Figure S44. [13]C Spectrum of 2-(*p*-Tolyl)-1,3,4-oxadiazole (6e').

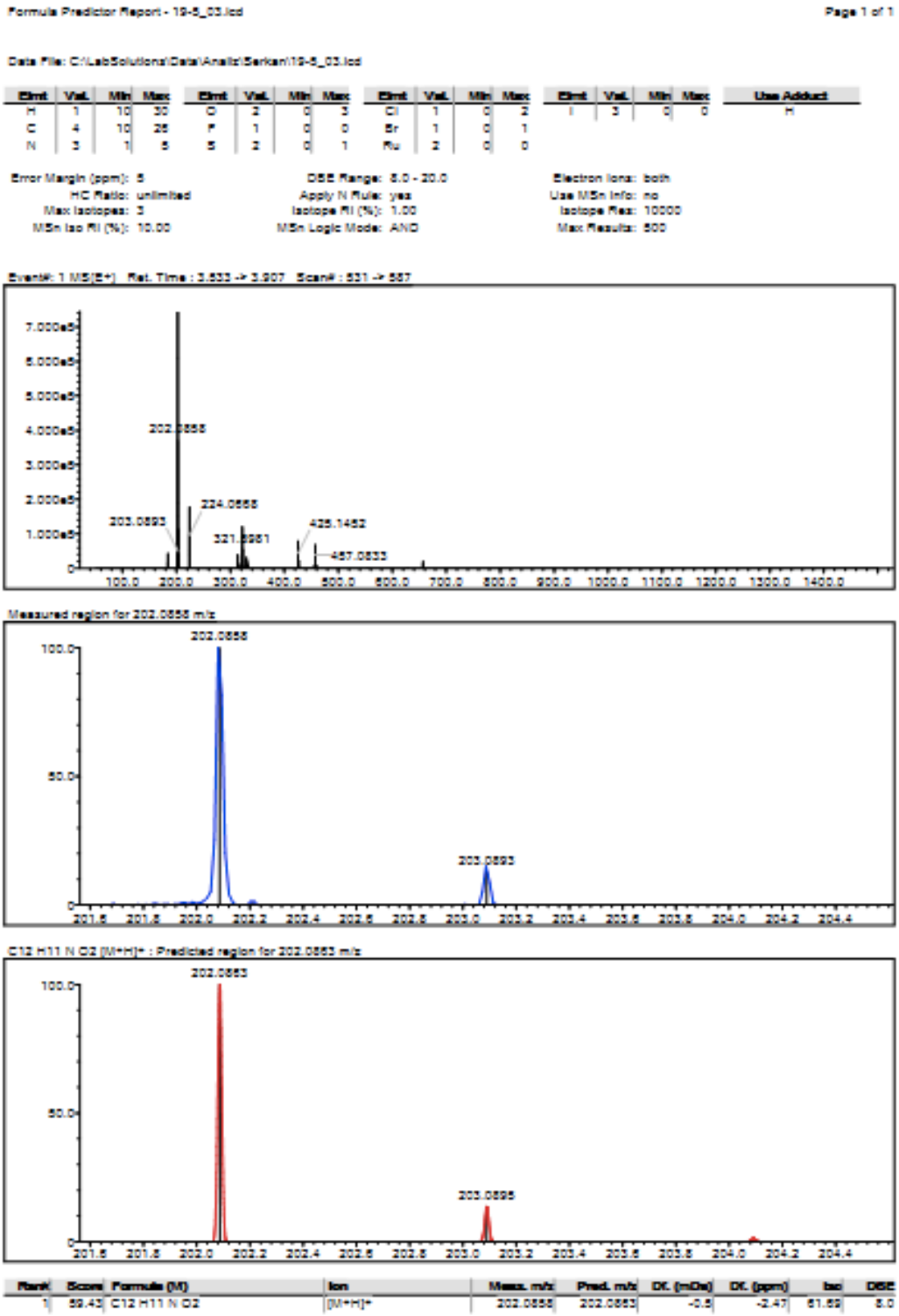


Figure S45. HRMS Spectrum of 1-(4-Hydroxy-2-methylquinolin-3-yl)ethanone (3a).

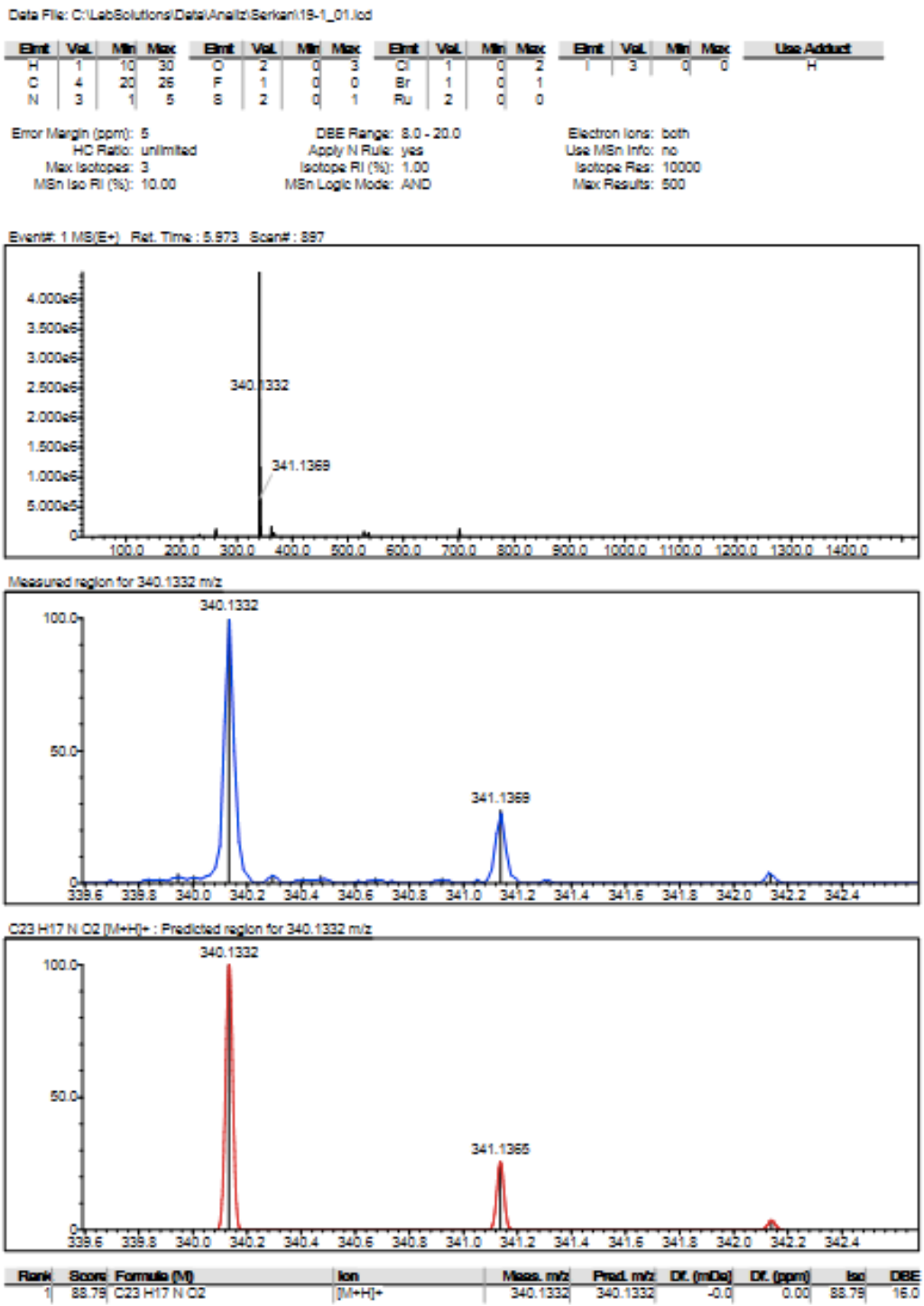


Figure S46. HRMS Spectrum of (4-Hydroxy-6-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3b).

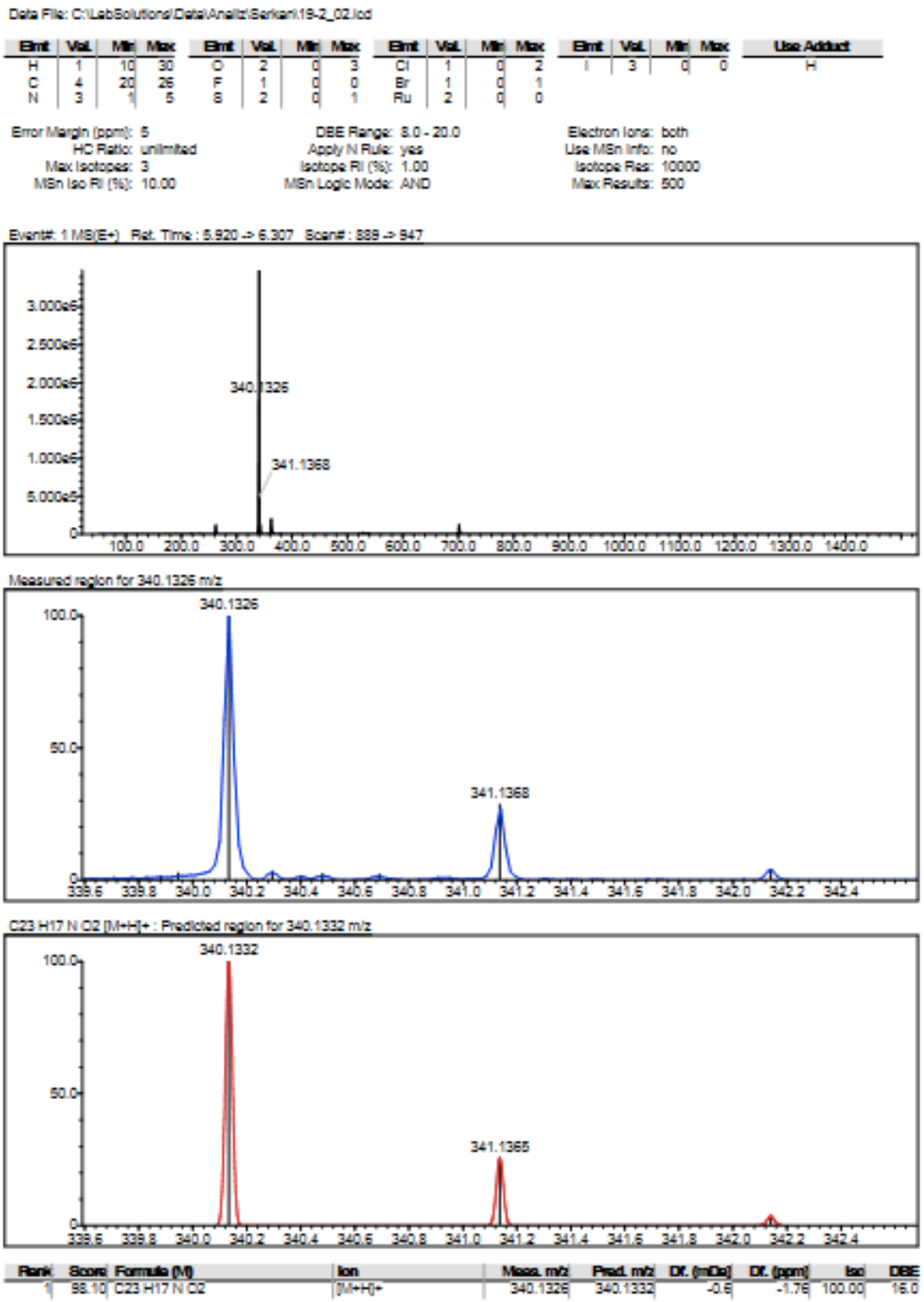


Figure S47. HRMS Spectrum of (4-Hydroxy-8-methyl-2-phenylquinolin-3-yl)(phenyl)methanone (3c).

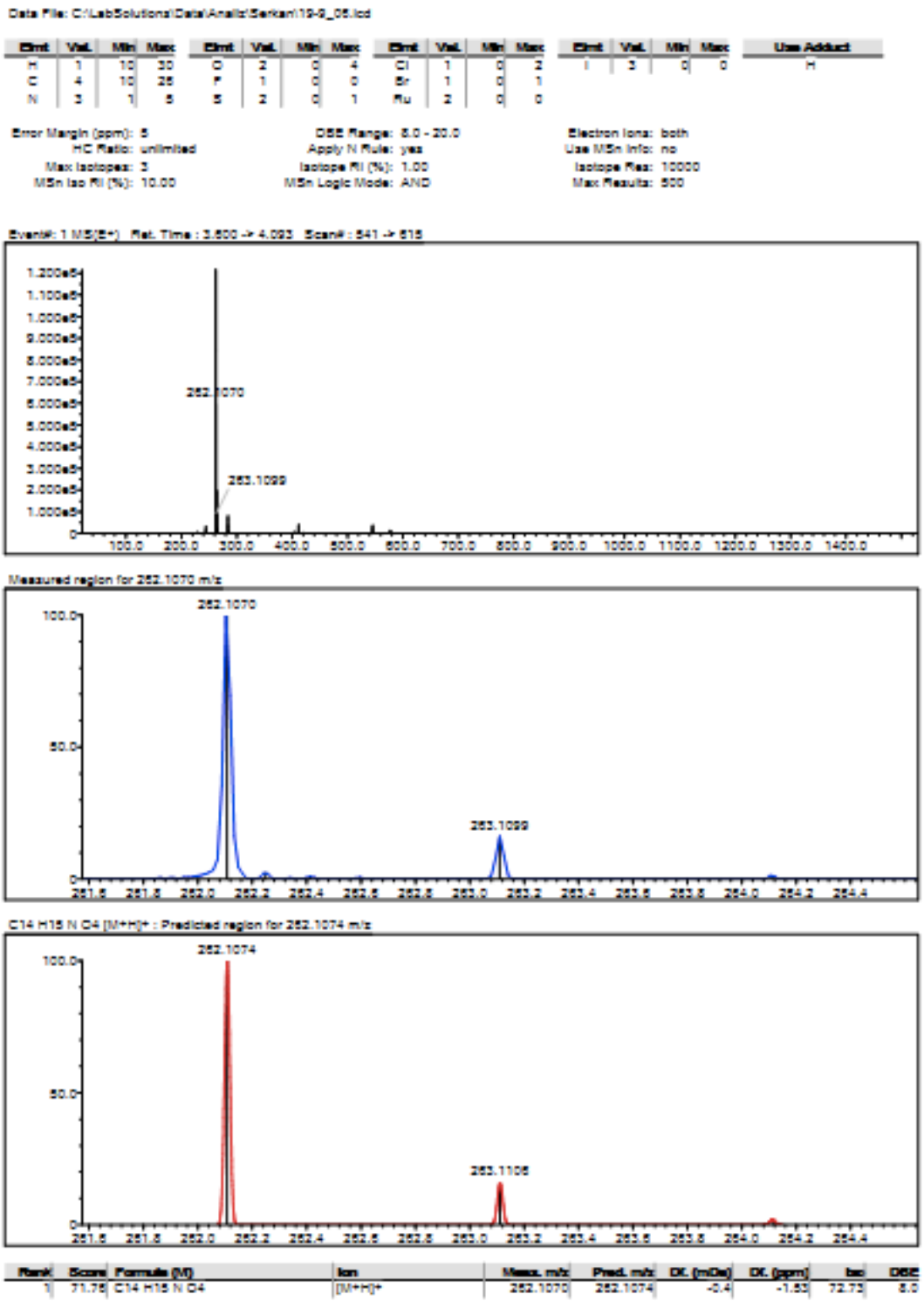
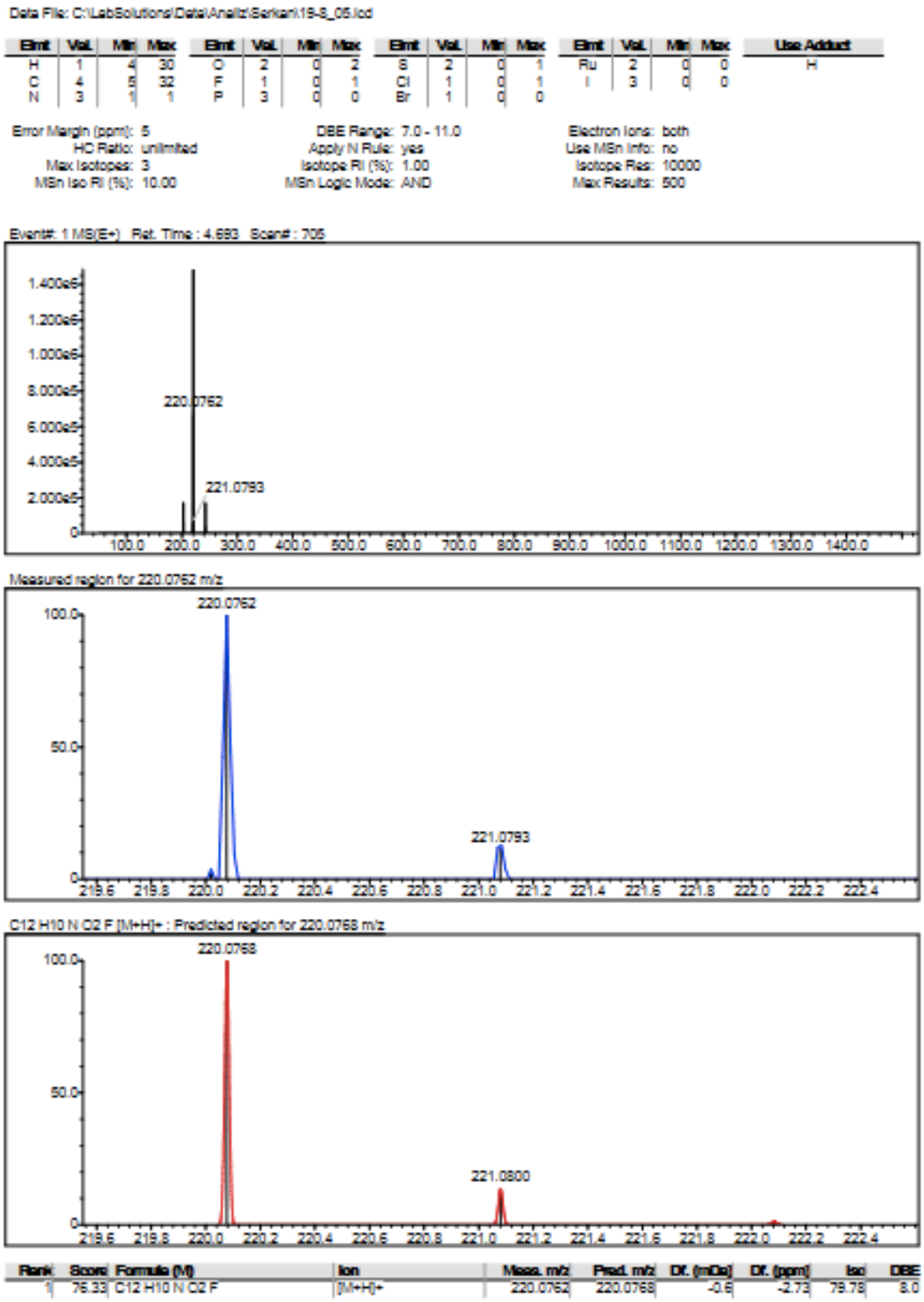


Figure S48. HRMS Spectrum of 1-(4-Hydroxy-6,7-dimethoxy-2-methylquinolin-3-yl)ethanone (3d).



Rank	Score	Formula (M)	Ion	Mass. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	76.33	C12 H10 N O2 F	[M+H]+	220.0762	220.0768	-0.6	-2.73	79.78	8.0

Figure S49. HRMS Spectrum of 1-(7-Fluoro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3e).

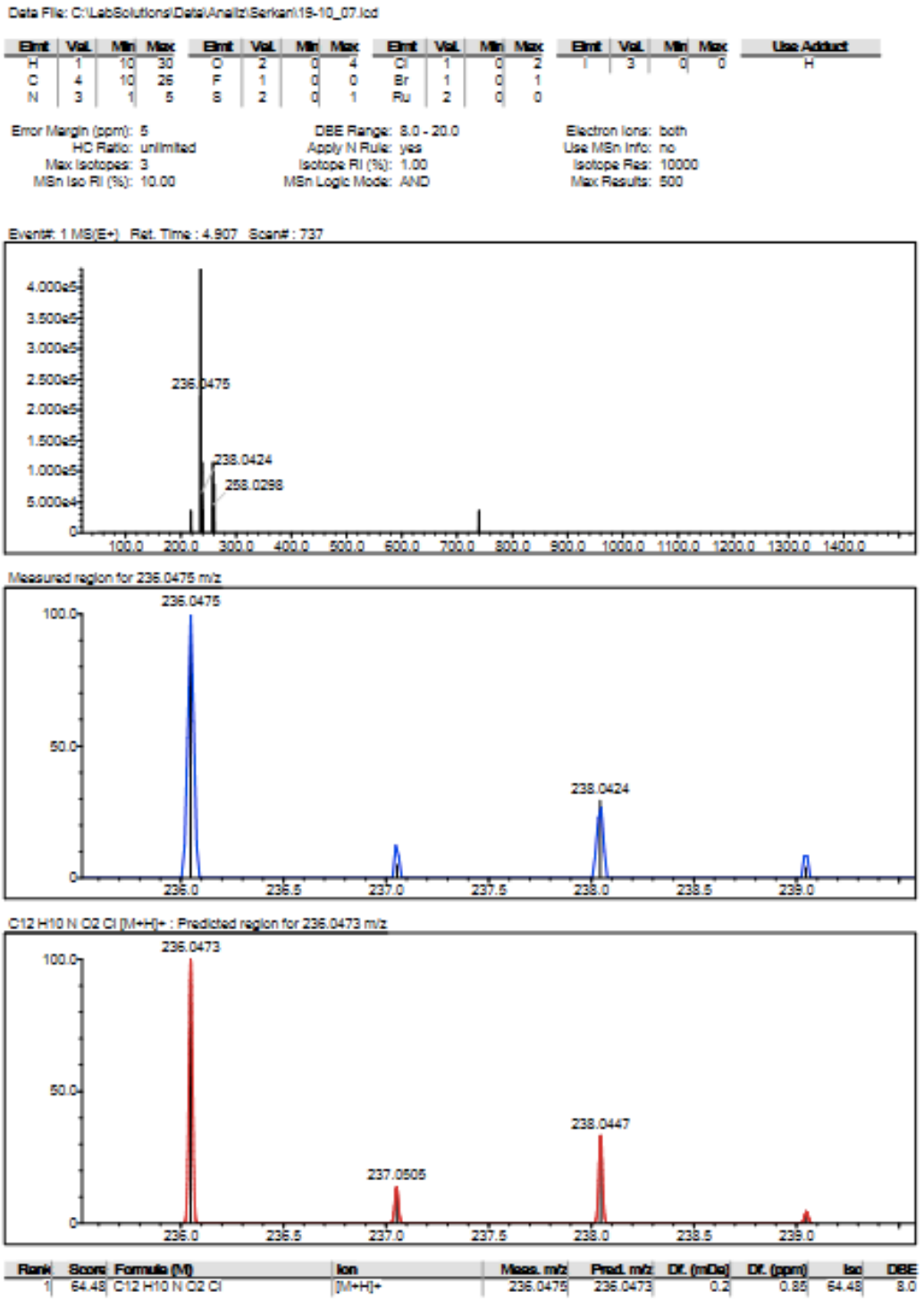


Figure S50. HRMS Spectrum of 1-(6-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3f).

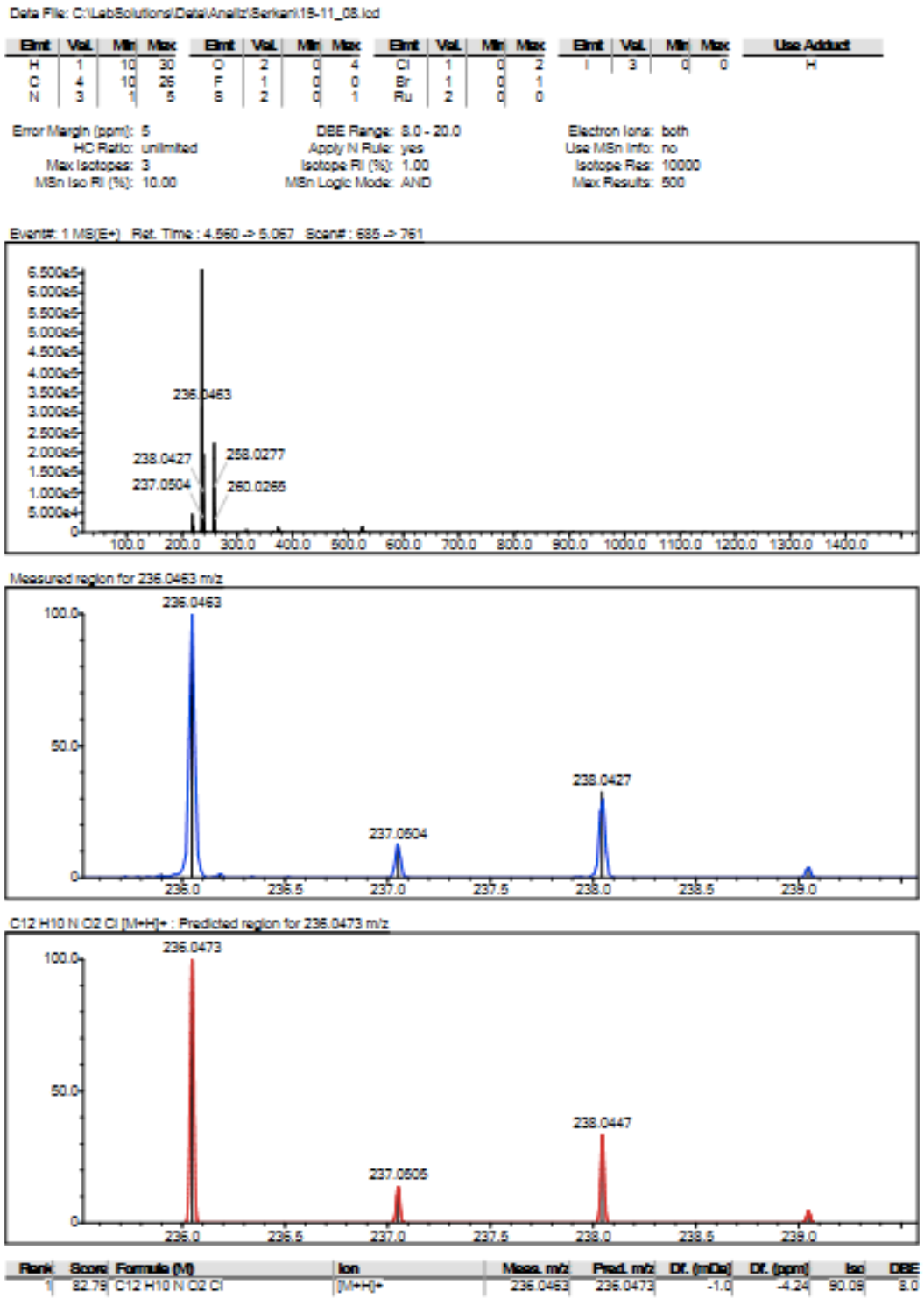


Figure S51. HRMS Spectrum of 1-(7-Chloro-4-hydroxy-2-methylquinolin-3-yl)ethanone (3g).

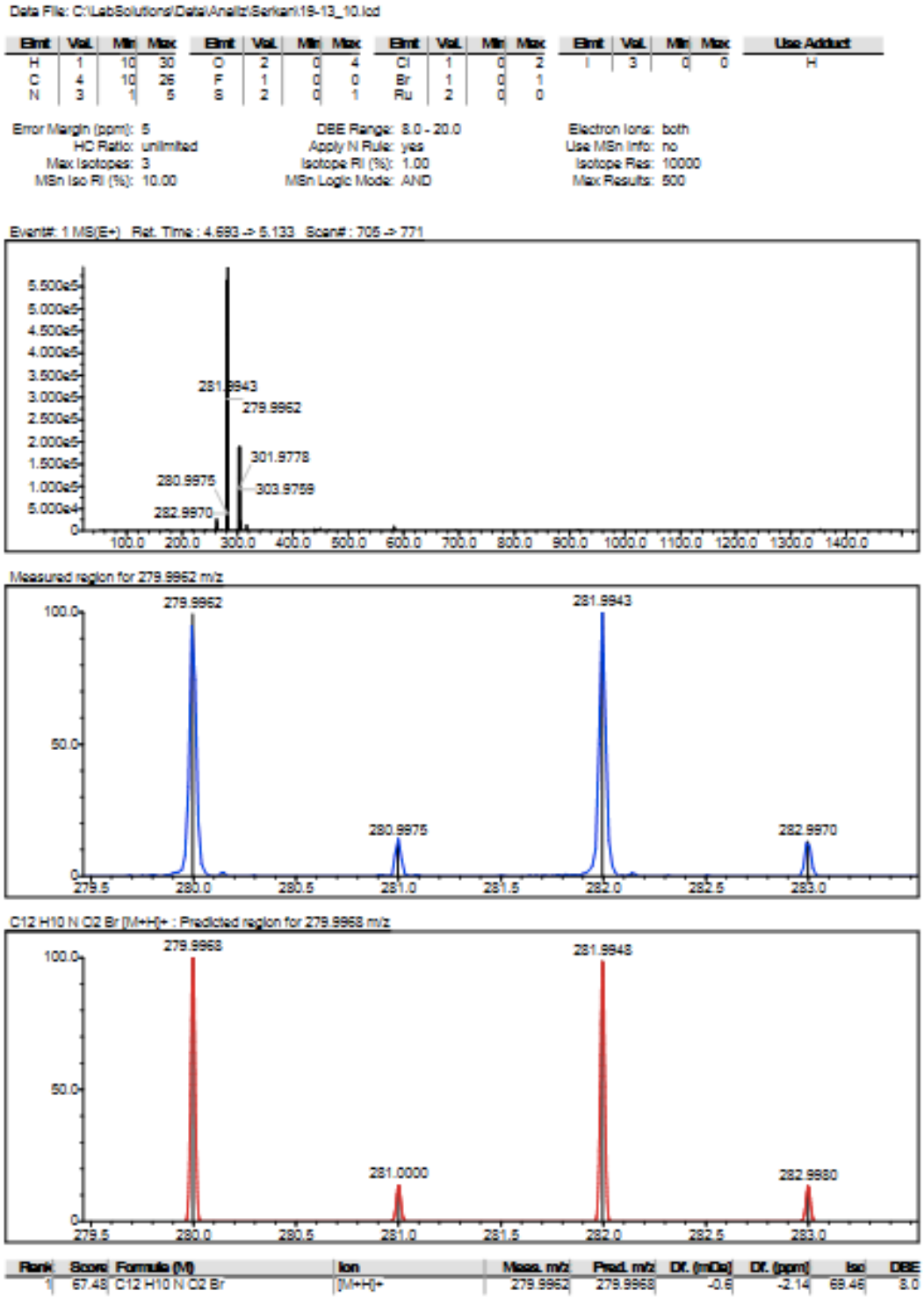


Figure S52. HRMS Spectrum of 1-(6-Bromo-4-hydroxy-2-methylquinolin-3-yl)ethanone (3h).

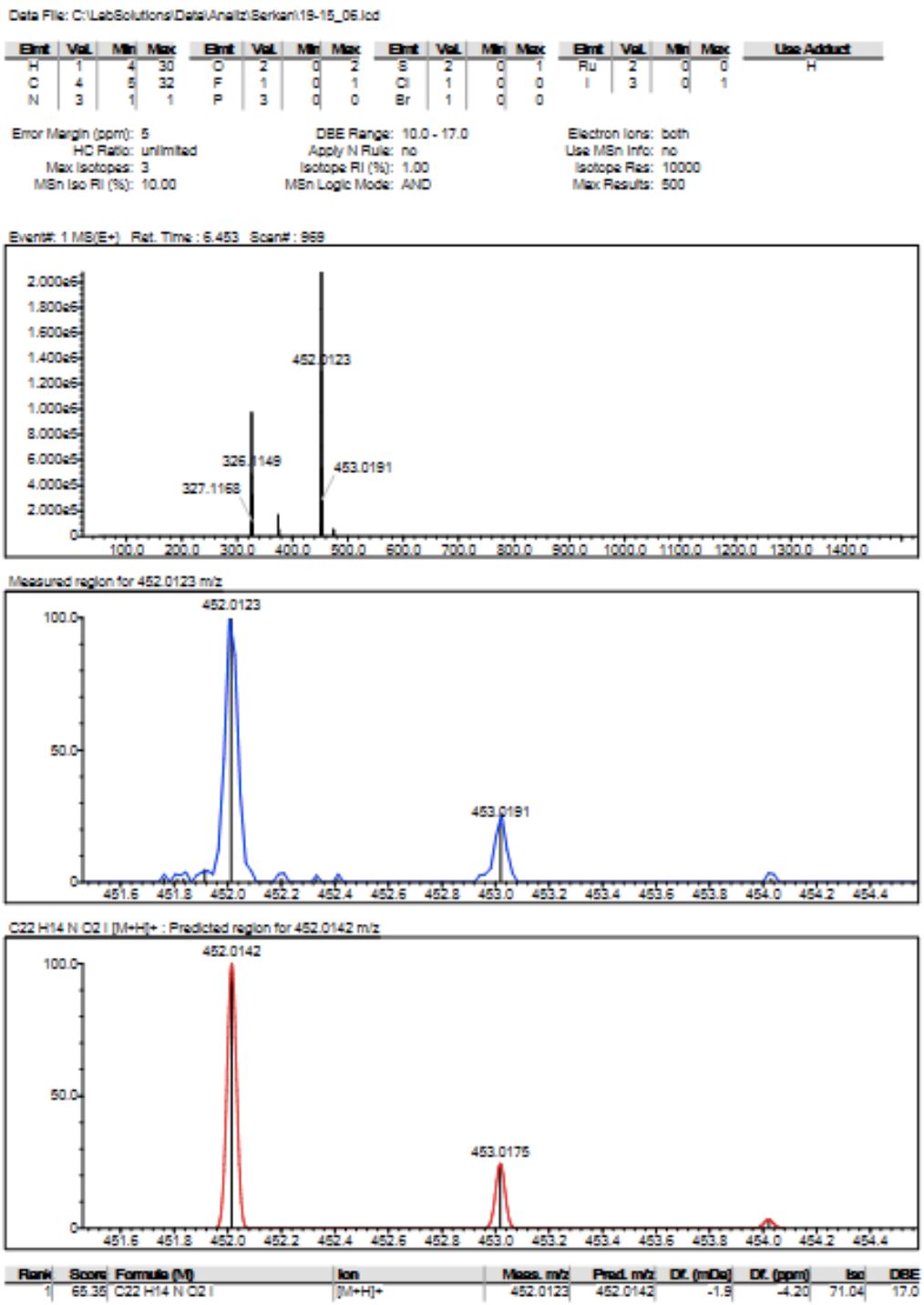


Figure S53. HRMS Spectrum of (4-Hydroxy-6-iodo-2-phenylquinolin-3-yl)(phenyl)methanone (3i).

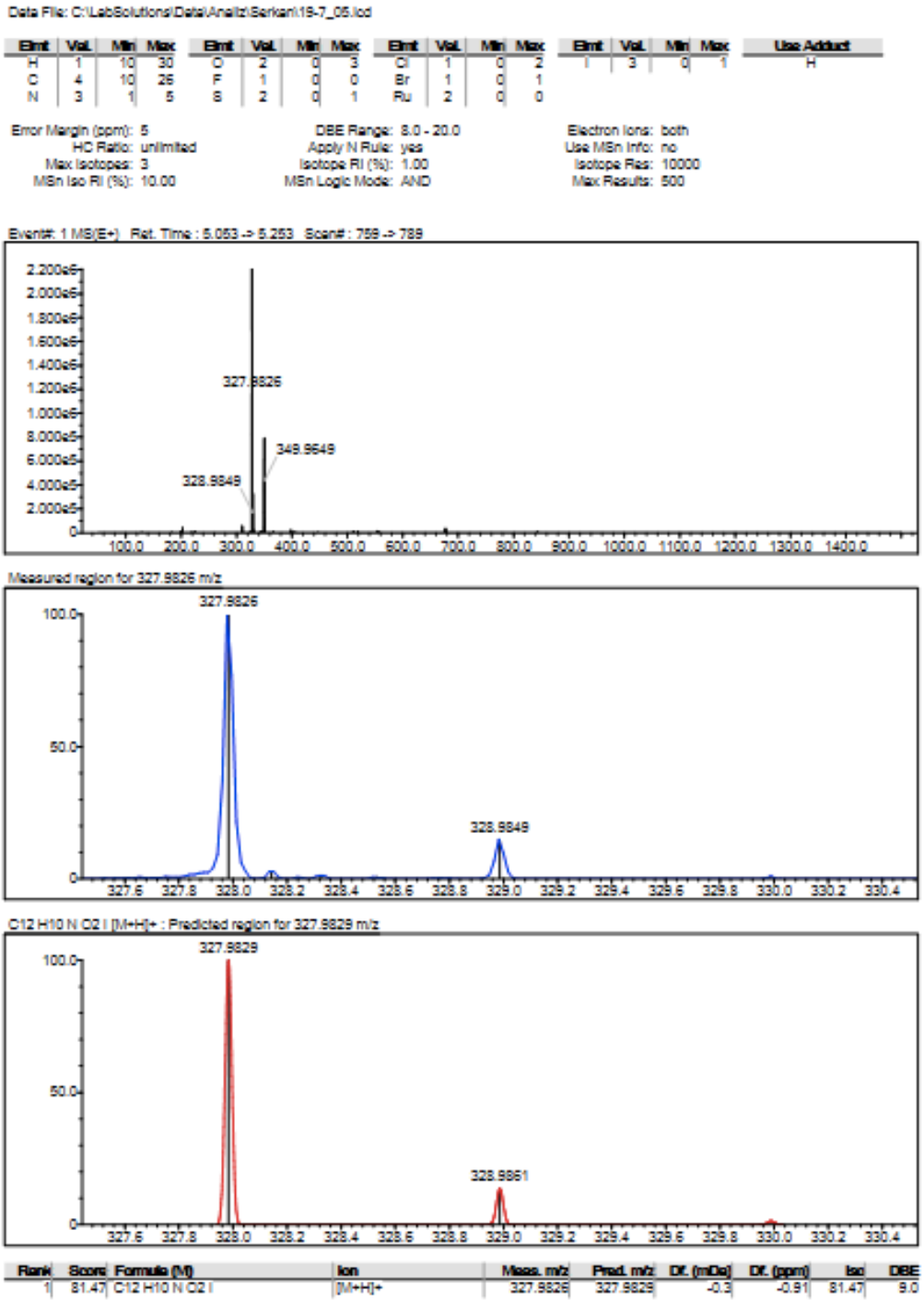


Figure S54. HRMS Spectrum of 1-(4-Hydroxy-6-iodo-2-methylquinolin-3-yl)ethanone (3j).

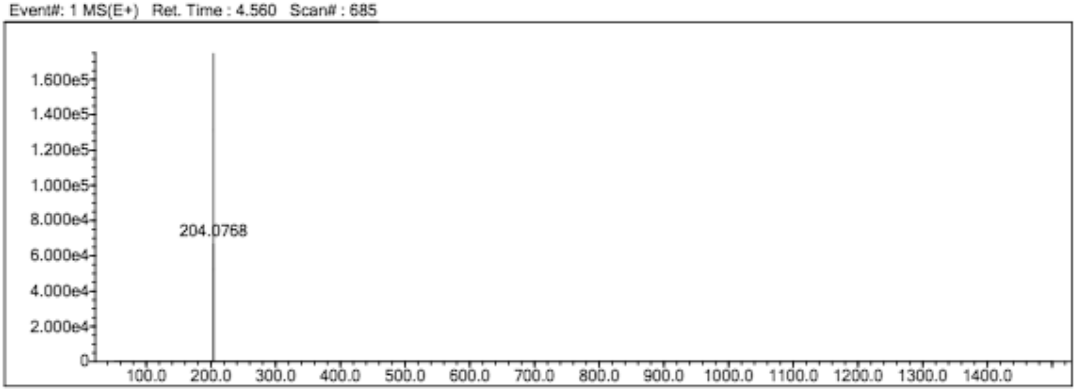
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

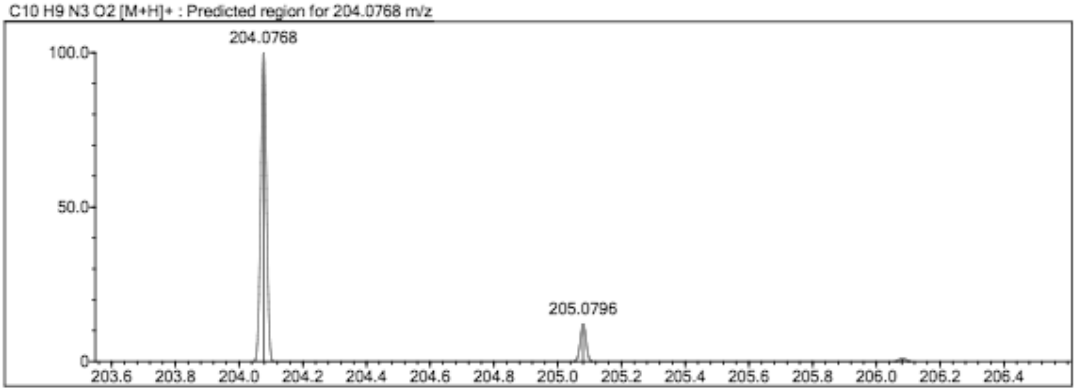
Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

Event#: 1 MS(E+) Ret. Time : 4.560 Scan# : 685



Measured region for 204.0768 m/z

C10 H9 N3 O2 [M+H]+ : Predicted region for 204.0768 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	0.00	C10 H9 N3 O2	[M+H]+	204.0768	204.0768	0.0	0.00	0.00	8.0

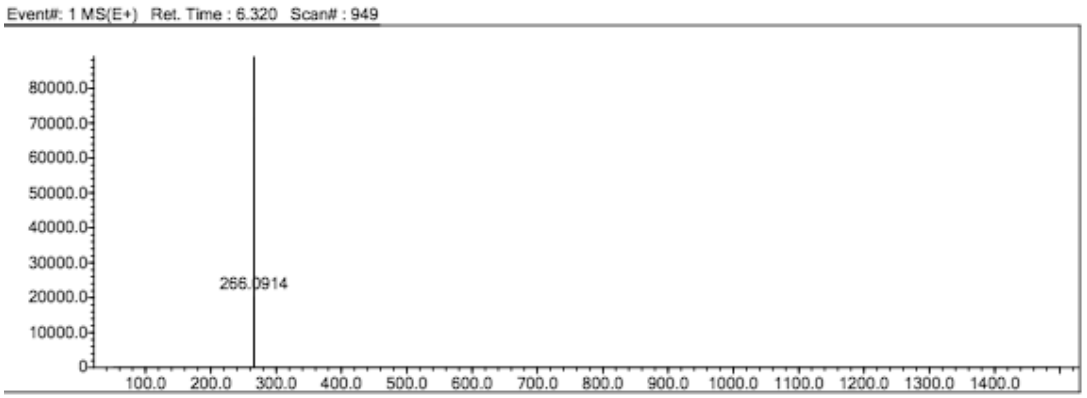
Figure S55. HRMS Spectrum *of N*-(4-Oxoquinazolin-3(4*H*)-yl)acetamide (6a).

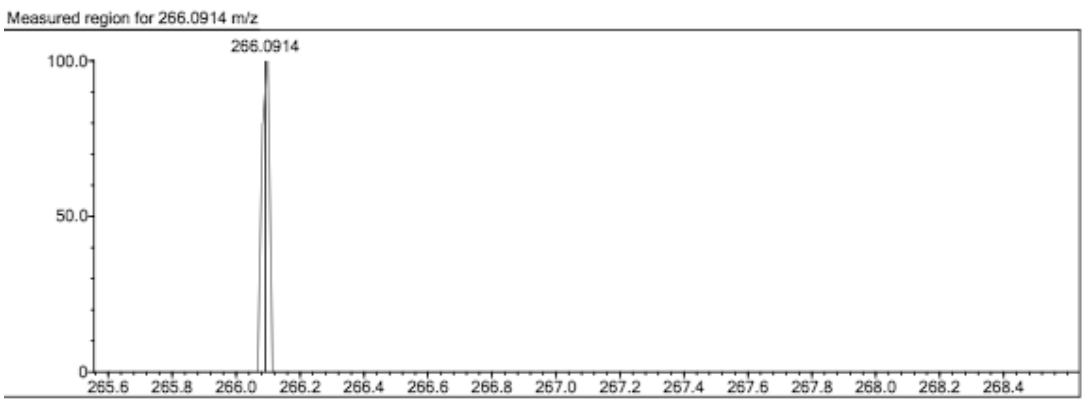
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

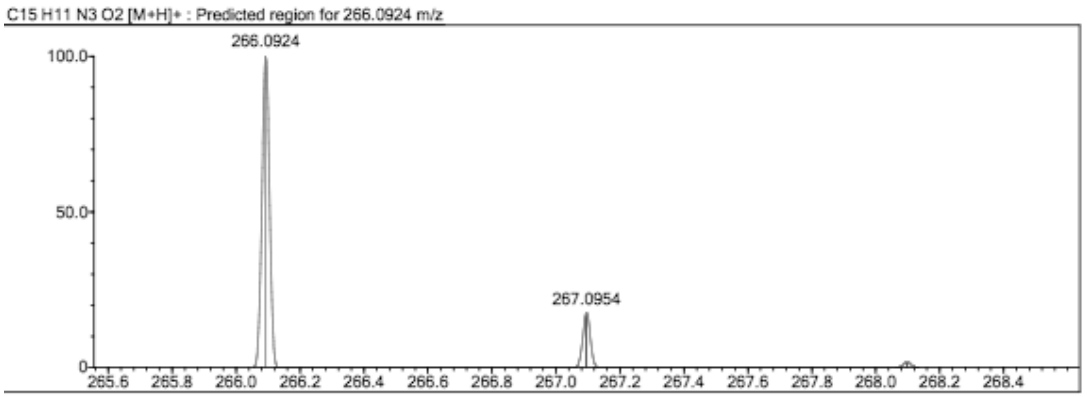
Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500







Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	0.00	C15 H11 N3 O2	[M+H]+	266.0914	266.0924	-1.0	-3.76	0.00	12.0

Figure S56. HRMS Spectrum of *N*-(4-Oxoquinazolin-3(4*H*)-yl)benzamide (6b).

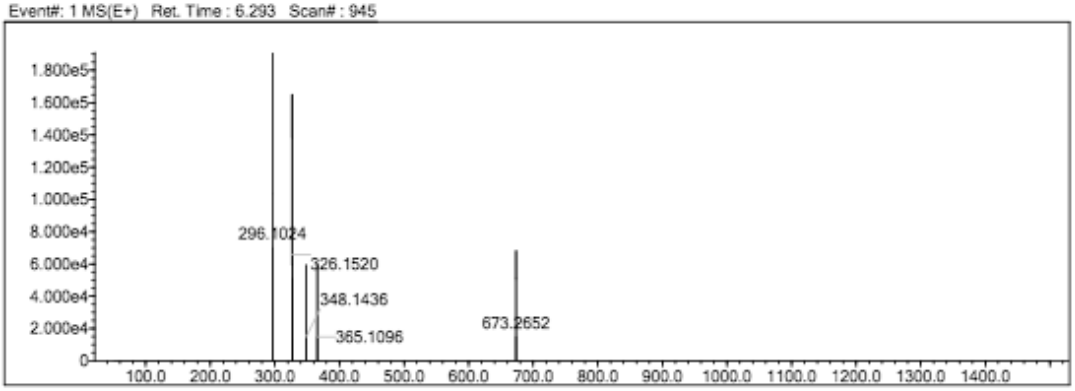
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	0	Cl	1	0	2	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

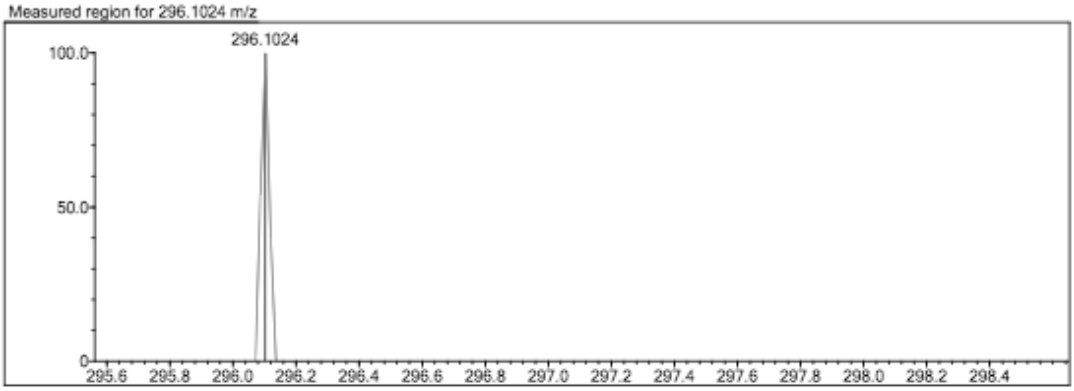
DBE Range: 5.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

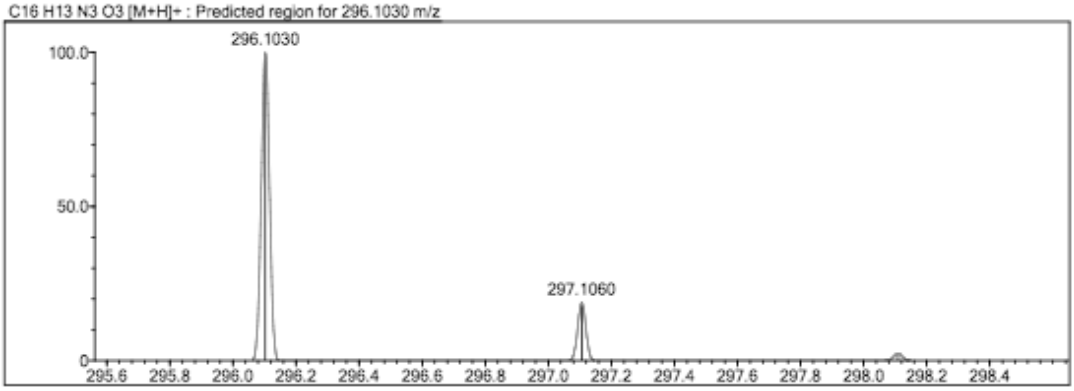
Event#: 1 MS(E+) Ret. Time : 6.293 Scan# : 945



Measured region for 296.1024 m/z



C16 H13 N3 O3 [M+H]+ : Predicted region for 296.1030 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	0.00	C16 H13 N3 O3	[M+H]+	296.1024	296.1030	-0.6	-2.03	0.00	12.0

Figure S57. HRMS Spectrum of 4-Methoxy-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6c).

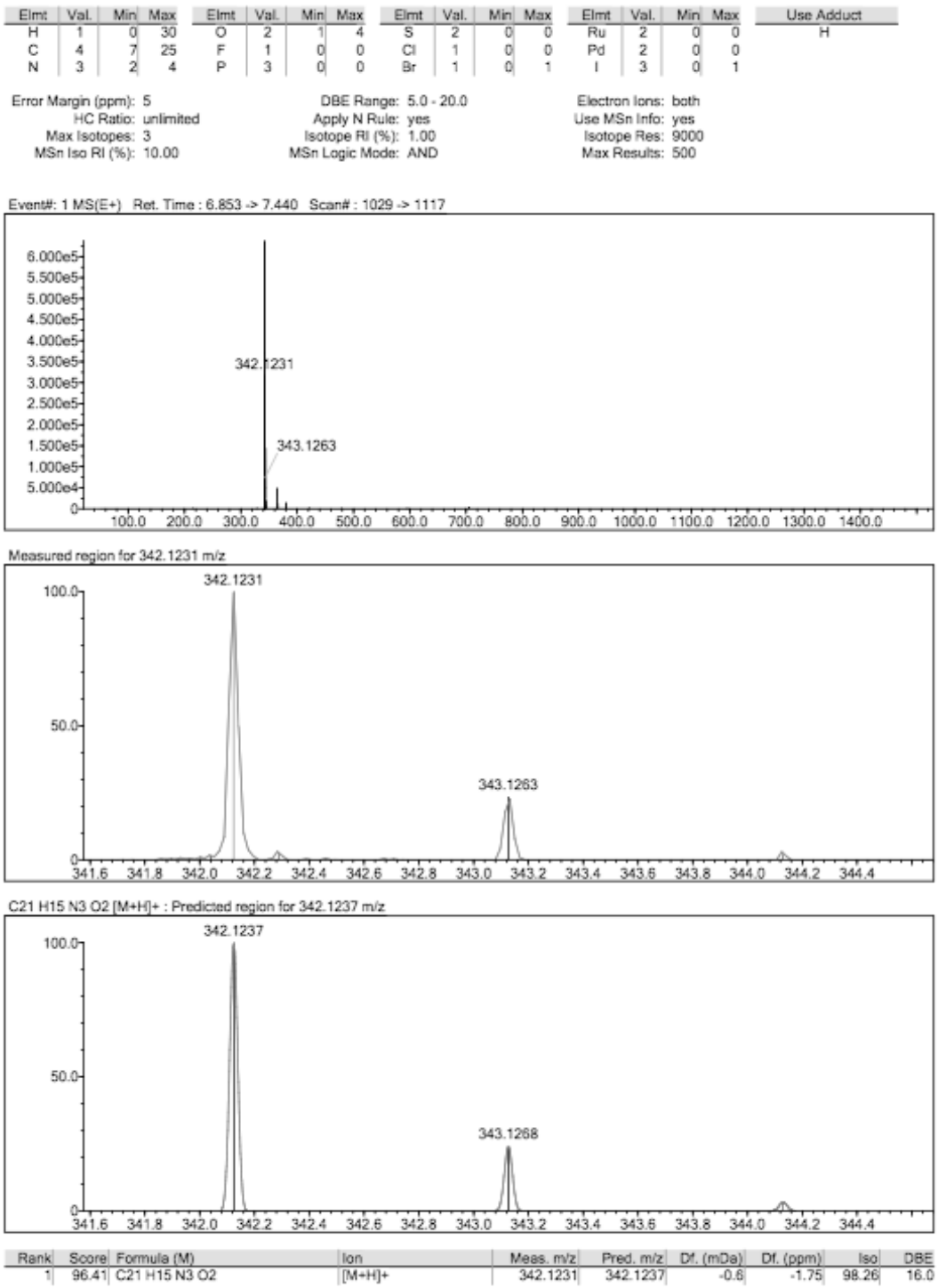


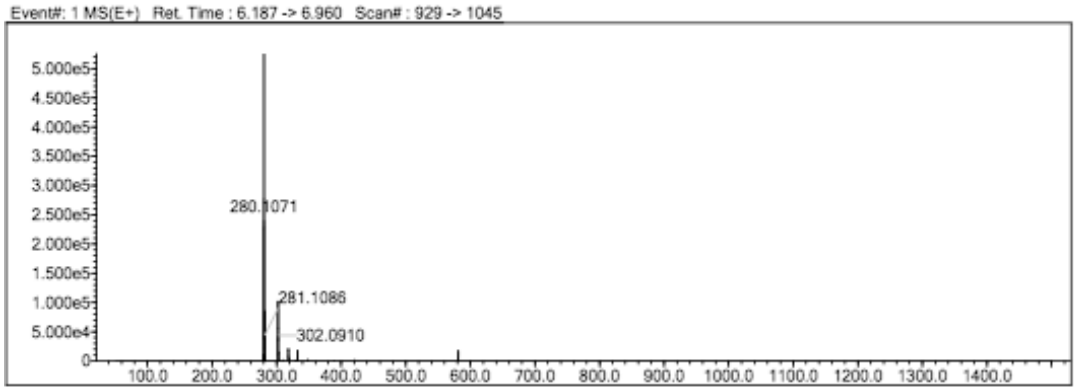
Figure S58. HRMS Spectrum of *N*-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)benzamide (6d).

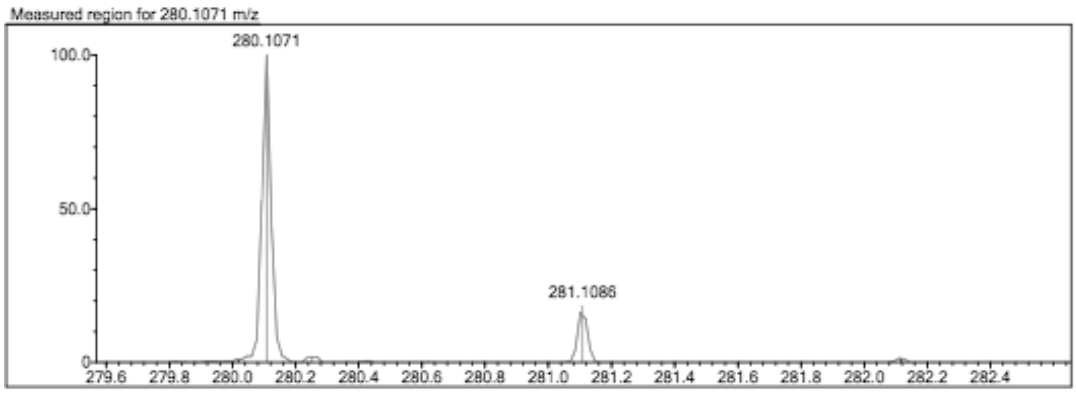
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	1	Cl	1	0	0	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

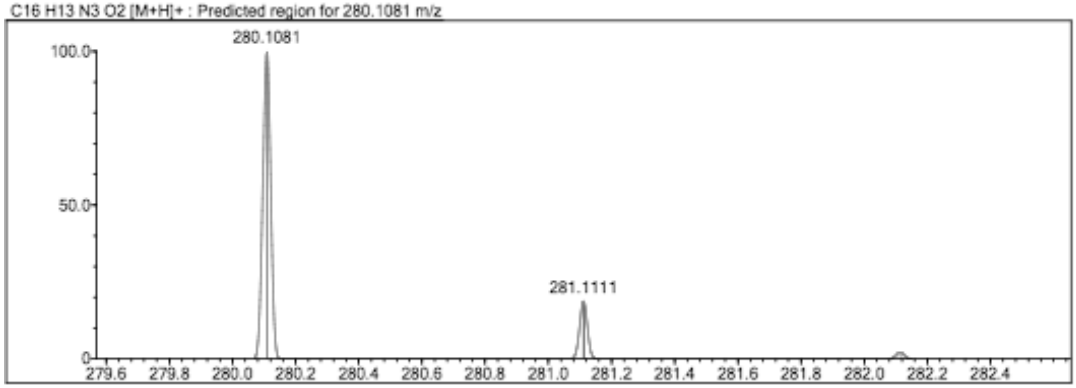
Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500





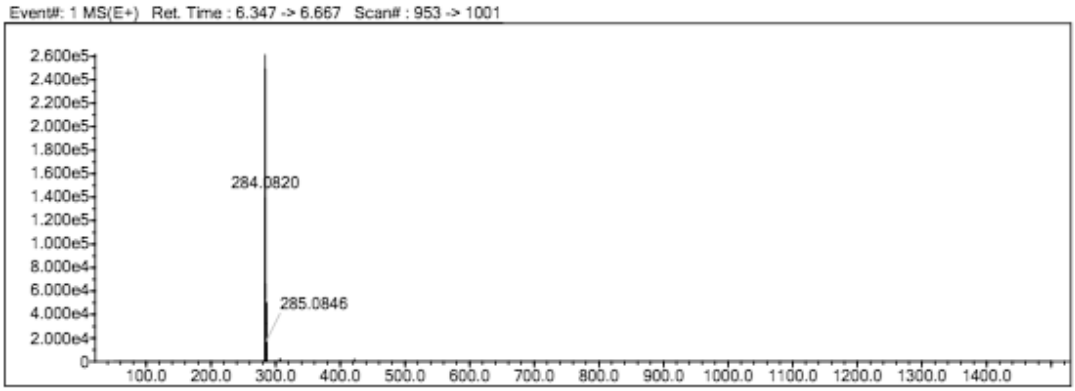


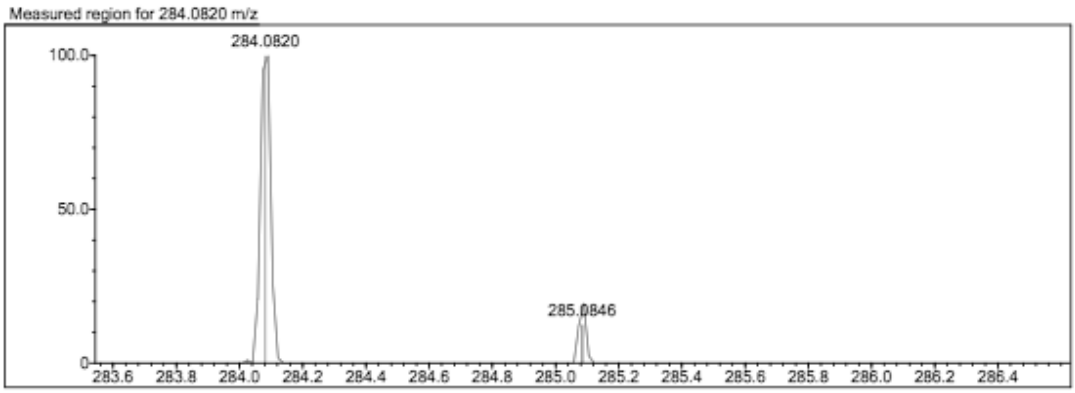
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	89.94	C16 H13 N3 O2	[M+H]+	280.1071	280.1081	-1.0	-3.57	96.12	12.0

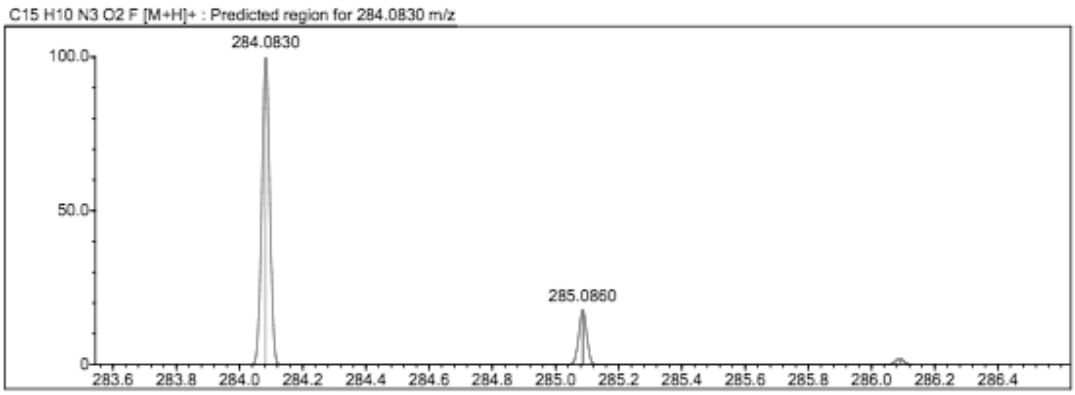
Figure S59. HRMS Spectrum of 4-Methyl-*N*-(4-oxoquinazolin-3(4*H*)-yl)benzamide (6e).

Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	1	Cl	1	0	0	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

Error Margin (ppm):	5	DBE Range:	5.0 - 15.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	yes
Max Isotopes:	3	Isotope RI (%):	1.00	Isotope Res:	9000
MSn Iso RI (%):	10.00	MSn Logic Mode:	AND	Max Results:	500







Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	93.70	C15 H10 N3 O2 F	[M+H]+	284.0820	284.0830	-1.0	-3.52	100.00	12.0

Figure S60. HRMS Spectrum of *N*-(7-Fluoro-4-oxoquinazolin-3(4*H*)-yl)benzamide (6f).

Elmt	Val.	Min	Max
H	1	0	30
C	4	7	25
N	3	2	4

Elmt	Val.	Min	Max
O	2	1	4
F	1	0	1
P	3	0	0

Elmt	Val.	Min	Max
S	2	0	0
Cl	1	0	0
Br	1	0	1

Elmt	Val.	Min	Max
Ru	2	0	0
Pd	2	0	0
I	3	0	1

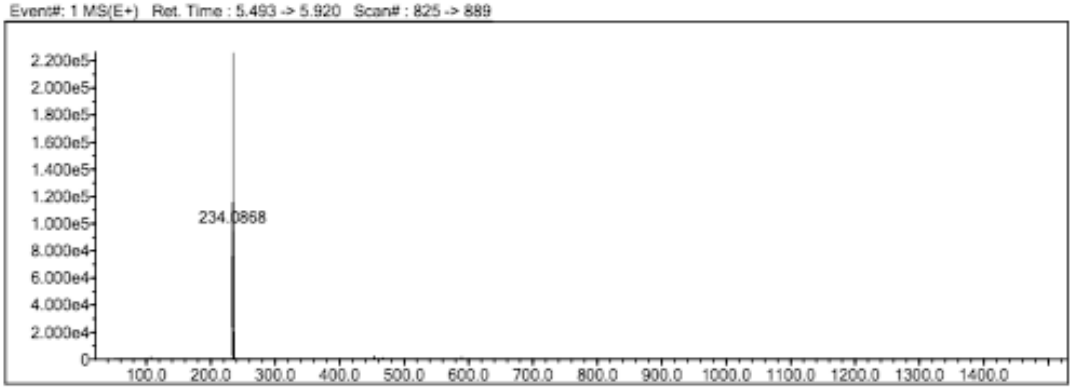
Use Adduct
H

Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

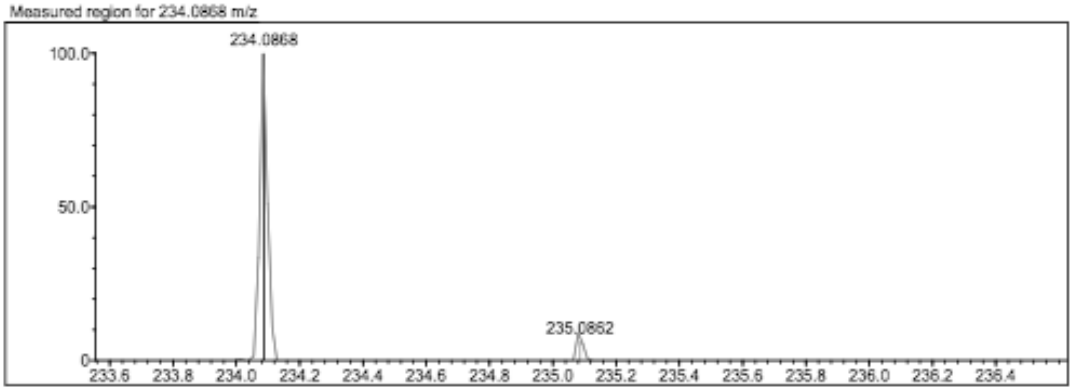
DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

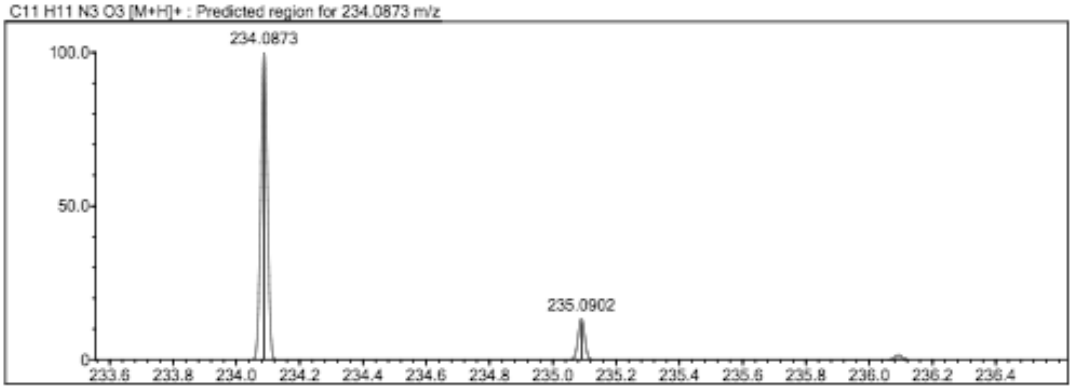
Event#: 1 MS(E+) Ret. Time : 5.493 -> 5.920 Scan# : 825 -> 889



Measured region for 234.0868 m/z



C11 H11 N3 O3 [M+H]+ : Predicted region for 234.0873 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	35.96	C11 H11 N3 O3	[M+H]+	234.0868	234.0873	-0.5	-2.14	37.01	8.0

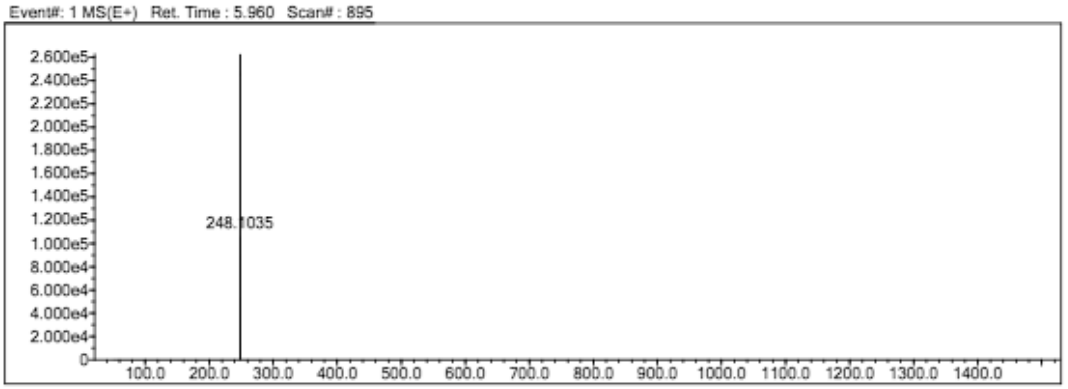
Figure S61. HRMS Spectrum of Ethyl (4-oxoquinazolin-3(4*H*)-yl)carbamate (6g).

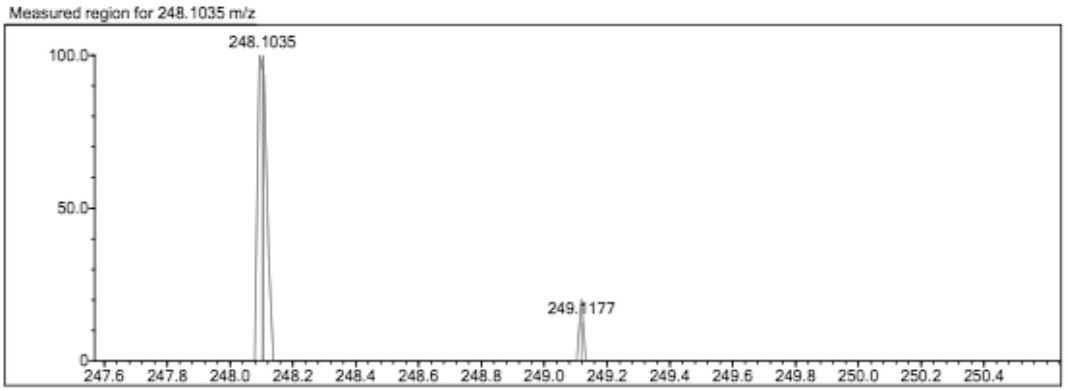
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	1	4	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	1	Cl	1	0	0	Pd	2	0	0	
N	3	2	4	P	3	0	0	Br	1	0	1	I	3	0	1	

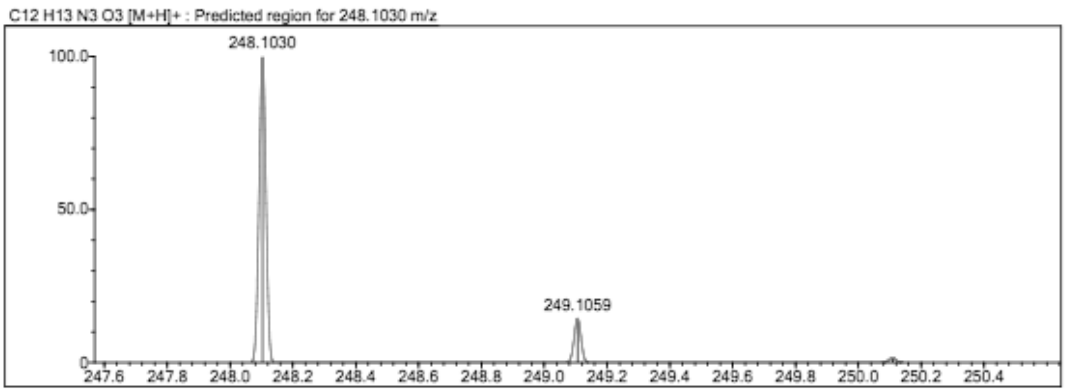
Error Margin (ppm): 15
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

DBE Range: 5.0 - 15.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500







Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	23.73	C12 H13 N3 O3	[M+H]+	248.1035	248.1030	0.5	2.02	24.35	8.0

Figure S62. HRMS Spectrum of Ethyl (2-methyl-4-oxoquinazolin-3(4*H*)-yl)carbamate (6h).

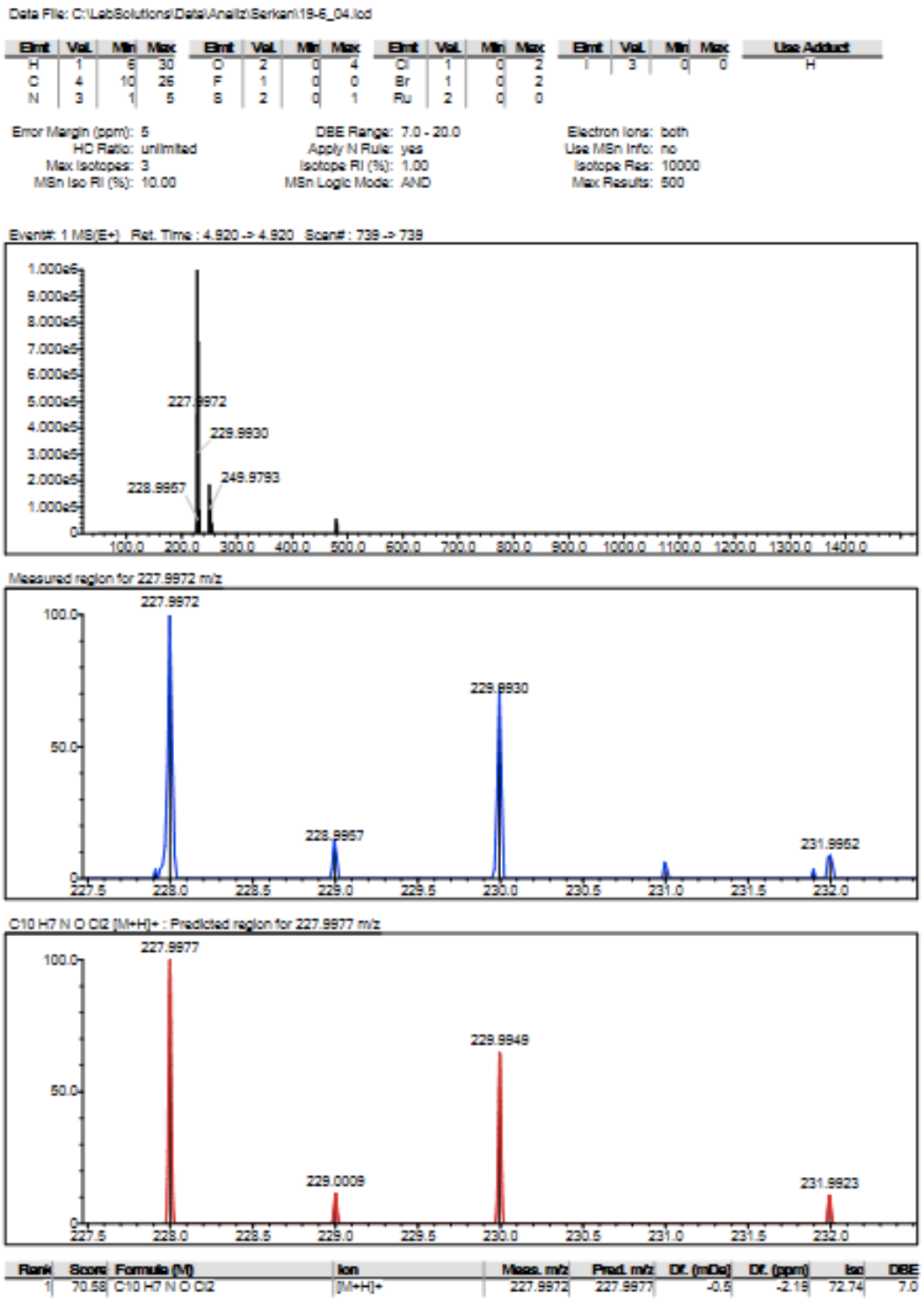


Figure S63. HRMS Spectrum of 6,8-dichloro-2-methylquinolin-4-ol (3kb).

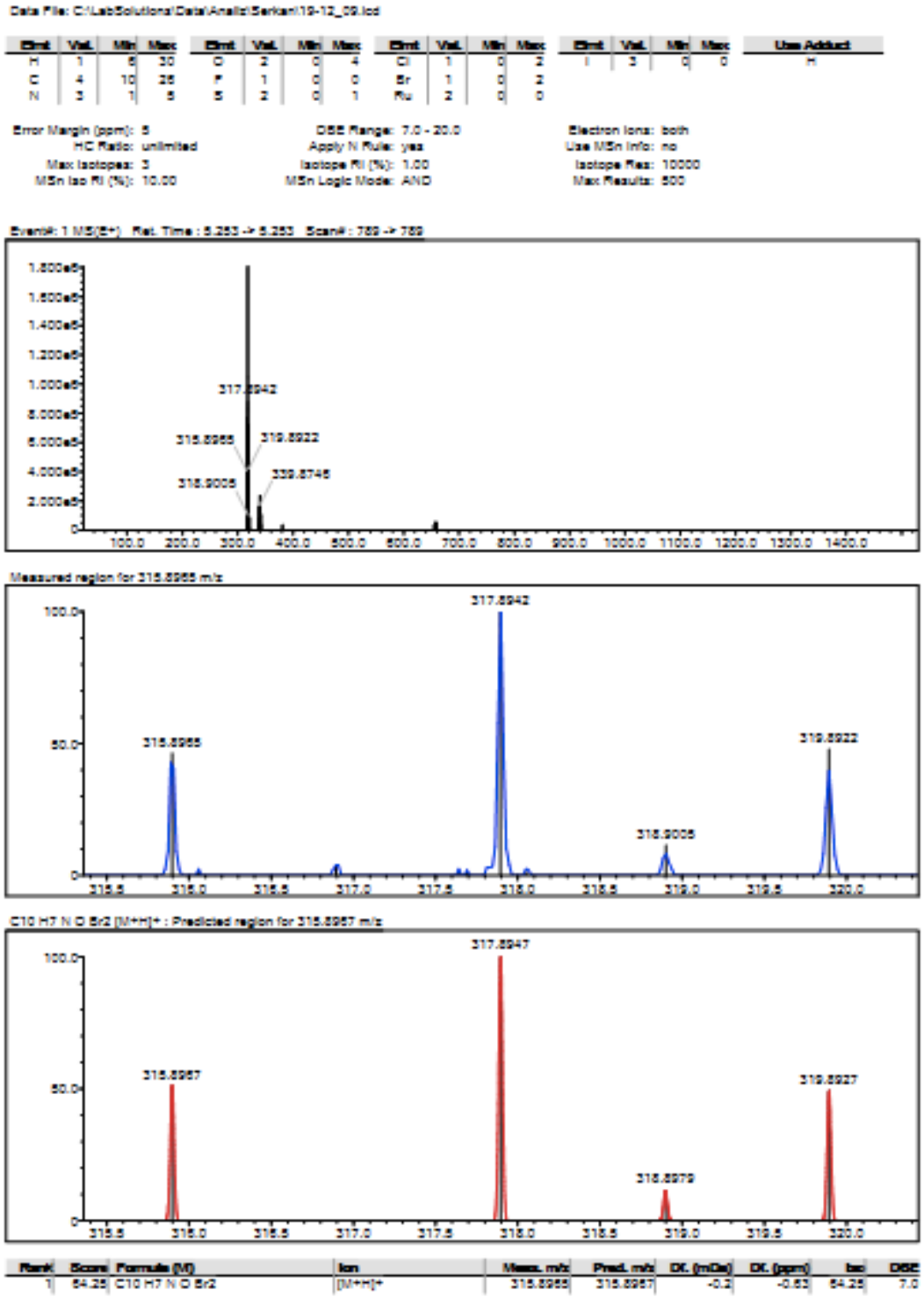


Figure S64. HRMS Spectrum of 6,8-dibromo-2-methylquinolin-4-ol (3lb).

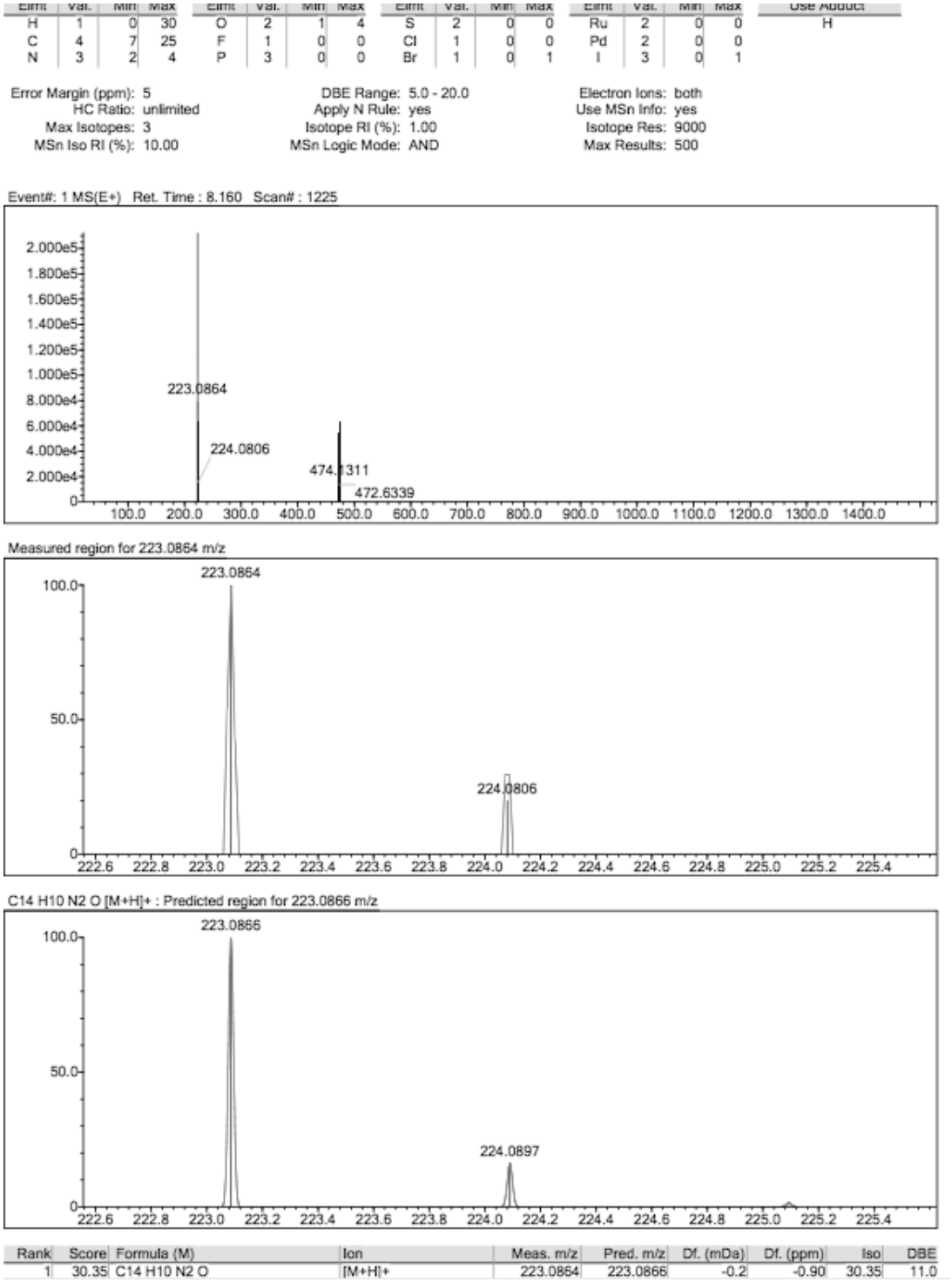


Figure S65. HRMS Spectrum of 2,5-diphenyl-1,3,4-oxadiazole (6d').

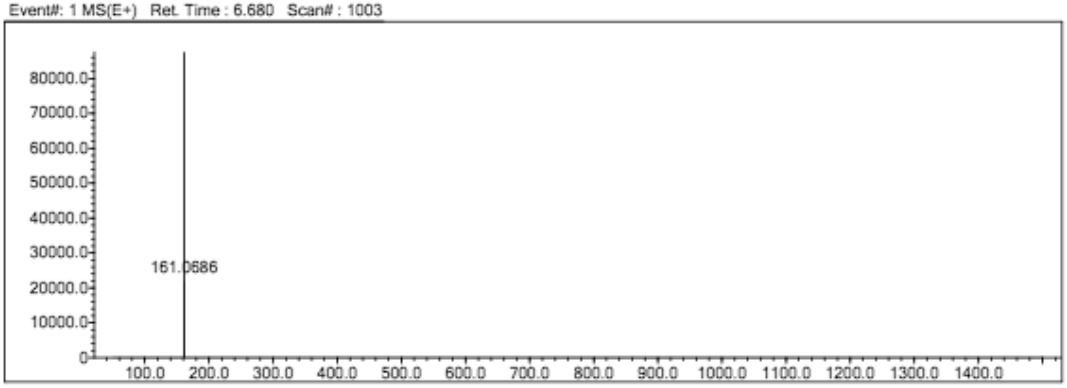
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	30	O	2	0	5	S	2	0	0	Ru	2	0	0	H
C	4	7	25	F	1	0	0	Cl	1	0	0	Pd	2	0	0	
N	3	1	4	P	3	0	0	Br	1	0	2	I	3	0	0	

Error Margin (ppm): 20
HC Ratio: unlimited
Max Isotopes: 3
MSn Iso RI (%): 10.00

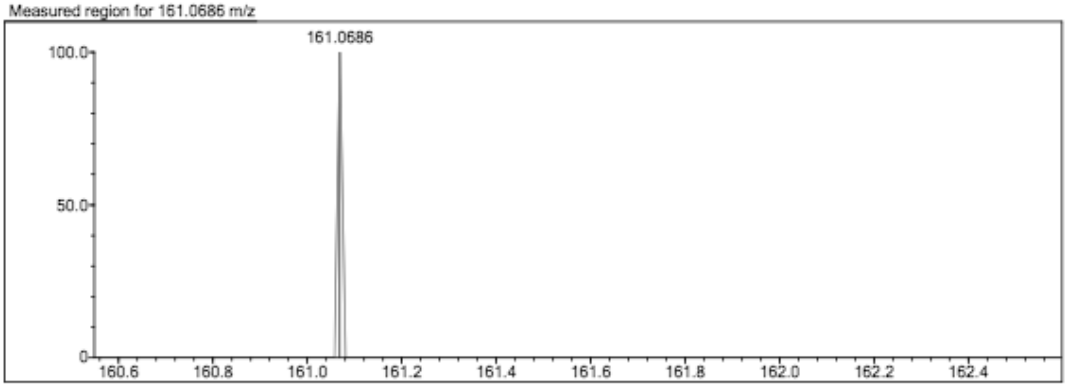
DBE Range: 0.0 - 20.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 9000
Max Results: 500

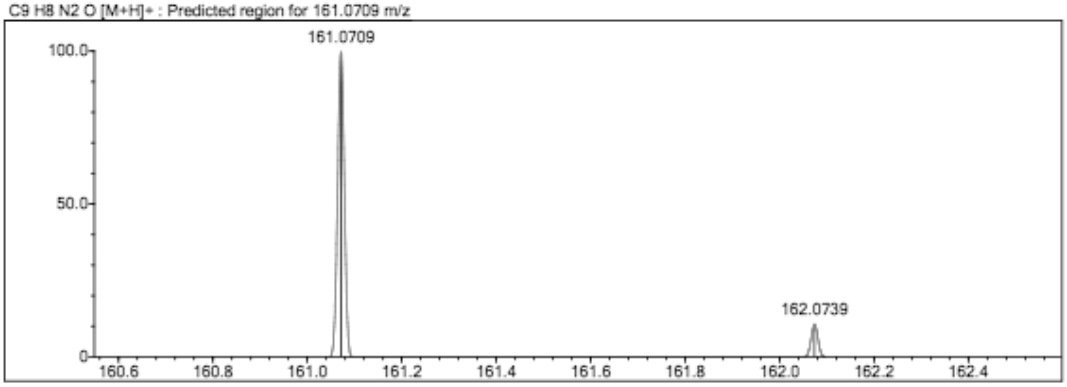
Event#: 1 MS(E+) Ret. Time : 6.680 Scan# : 1003



Measured region for 161.0686 m/z



C9 H8 N2 O [M+H]+ : Predicted region for 161.0709 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	7.84	C9 H8 N2 O	[M+H]+	161.0686	161.0709	-2.3	-14.28	27.44	7.0

Figure S66. HRMS Spectrum of 2-(*p*-Tolyl)-1,3,4-oxadiazole (6e').