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# Biological study on novel coumarinyl 1,3,4-oxadiazoles

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**Abstract:** Coumarinyl 1,3,4-oxadiazoles were synthesized from Schiff bases and acetic anhydride. All compounds were characterized by melting points and their structures confirmed by mass and $^{1}$H and $^{13}$C NMR spectrometry. These novel coumarinyl derivatives were subjected to antibacterial, antifungal, antaflatoxigenic, and antioxidant activity. Their activity varied depending on their structure, where 2-(3-acetyl-5-(((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,4-phenylene diacetate showed significant antioxidant and antibacterial activity on *B. subtilis*. 4-(3-Acetyl-5-(((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,2-phenylene diacetate was found to possess excellent antifungal and antiaflatoxigenic activity.

**Key words:** Coumarin, 1,3,4-oxadiazole, antibacterial, antifungal, antimycotoxigenic activity

## 1. Introduction

Oxadiazoles are heterocyclic compounds showing a wide range of biological activities and they have been explored by many researchers for decades. They can exist as four isomers, namely 1,2,4-oxadiazoles, 1,3,4-oxadiazoles, 1,2,3-oxadiazoles, and 1,2,5-oxadiazoles.[1,2] Due to their structural diversity their biological activities include antibacterial,[3,4] antitubercular, antifungal, cytotoxic, anticancer,[5,6] and many others. So far, our work has been based on the synthesis of 1,3,4-oxadiazoles, which are present in some well-known drugs like Furamizole (antibiotic), Raltegravir (antiretroviral), Zibotentan (anticancer), and tiodazosin and nesapidil (antihypertensive). Considering the synthesis of 1,3,4-oxadiazole derivatives, there are some common procedures for oxadiazole ring closure, depending on the starting compound. Dolman et al.[7] prepared 1,3,4-oxadiazoles by tosyl chloride/pyridine-mediated cyclization of thiosemicarbazides, Barbucenu et al.[8] reacted thiosemicarbazides with mercuric oxide in ethanol, while Narwade et al.[9] used $I_2$/KI in sodium hydroxide solution. Dobrota et al.[10] prepared heterocycles of this type by oxidative cyclization of hydrazines with an excess of Dess–Martin periodinane under mild conditions. Acetohydrazides were reacted with $CS_2$ in alkaline medium followed by acidic treatment.[11] 1,3,4-Oxadiazoles were also prepared by a reaction of different acylhydrazydes, aromatic acids, and phosphoryl chloride by Amir and Kumar[12] as well as by Khan and Akhtar.[13] Khan and Akhtar[13] performed a synthesis of oxadiazoles from acylhydrazide using cyanogen bromide, while Sharba et al.[14] reacted

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*N*-formyl acid hydrazide with phosphorous pentasulfide to obtain a 1,3,4-oxadiazole ring. A well-known and often employed procedure for their preparation is the cyclization of Schiff bases in excess of acetic anhydride [15–19] in the presence of chloramine T [13,20,21] or ceric ammonium nitrate (CAN). [22] Aside from conventional methods in their preparation, ultrasound irradiation [23] or one-pot reaction of aromatic hydrazides with aryl aldehydes in the presence of catalytic amount of molecular iodine can be employed by grinding technique. [24]

Nowadays, many bacteria have genetic ability to acquire resistance to conventional antibiotic drugs. [25] Side effects of overuse and misuse of antibiotics are also noticed, all harmful to vital organs and the immune system in general. There is a constant pursuit for new antibiotics in order to eliminate the infections caused by drug-resistant microbes. [26]

Our intention was to synthesize novel 1,3,4-oxadiazoles from coumarinyl Schiff bases and to investigate them in terms of their antibacterial, antifungal, and antiaflatoxigenic activity. The obtained data will give us a better insight into the structural activity relationship of these or similar compounds.

## 2. Results and discussion

Coumarinyl 1,3,4-oxadiazoles were synthesized from corresponding Schiff bases (Figure 1) and their structures were confirmed by $^{1}$H NMR, $^{13}$C NMR, and mass spectrometry.

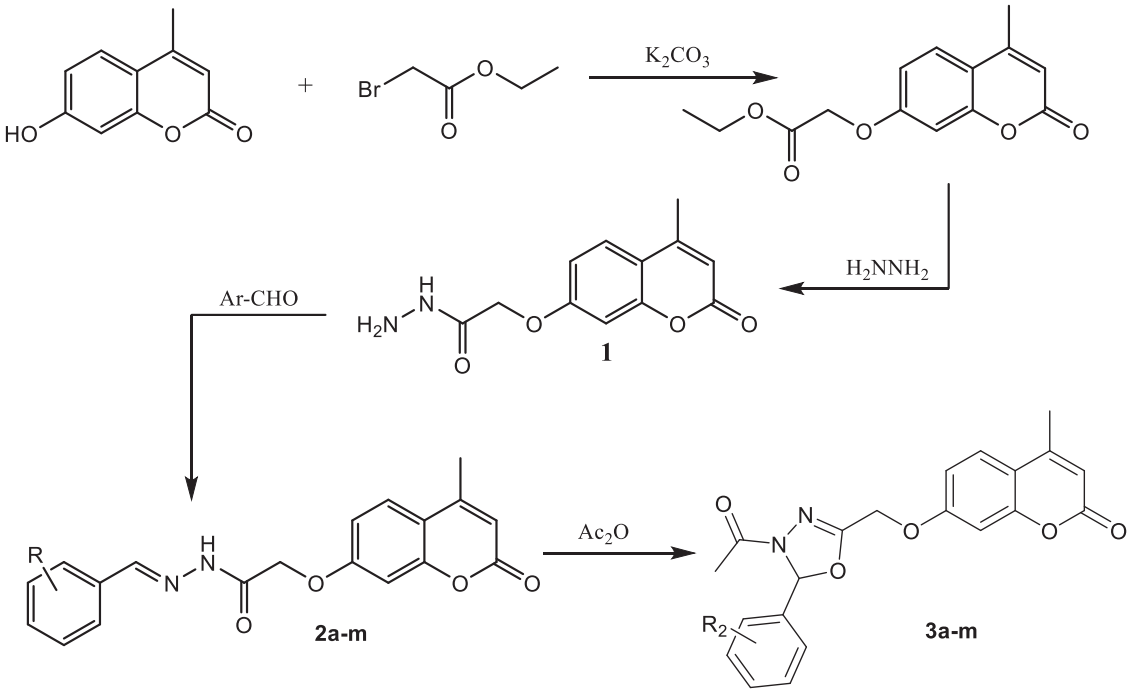



**Figure 1**. Synthetic route for coumarin derivatives.

The $^{1}$H NMR spectra show characteristic peaks for acetyl groups on the 1,3,4-oxadiazole ring (2.13–2.44 ppm), as well as typical shifts for aromatic protons (6.89–8.83 ppm) (see supplementary material for NMR spectra). Moreover, the coumarin core was characterized by the coumarinyl–$CH_3$ group in position C-4 (2.40 ppm), one proton in position C-3 (6.18–6.22 ppm), and aromatic protons (6–8 ppm). All 1,3,4-oxadiazole derivatives were synthesized from Schiff bases in excess of acetic anhydride, utilizing a very common

procedure.[16] A proposed mechanism, according to Desai et al.[17] is shown in Figure 2. All hydroxyl groups that were present in starting compounds were also acetylated. This was proven by $^1$H NMR shifts for protons of the –$COCH_3$ group (1.21–2.30 ppm), as well as mass spectra where peaks of molecular ions were in accordance with acetylated compounds. Our attempt was to synthesize 1,3,4-oxadiazoles from Schiff bases employing other protocols too, like grinding Schiff bases with molecular iodine,[24] or cyclization with chloramine T[21] or ceric ammonium nitrate.[27] However, although some authors describe them as very effective procedures, they were not suitable for our type of compounds. Low reactivity of Schiff bases towards these agents could be the reason for the low yields we obtained in our protocol. Nevertheless, since our goal was to investigate these compounds in terms of antimicrobial and antiaflatoxigenic activity, optimization of this synthetic route will be performed in our future work.

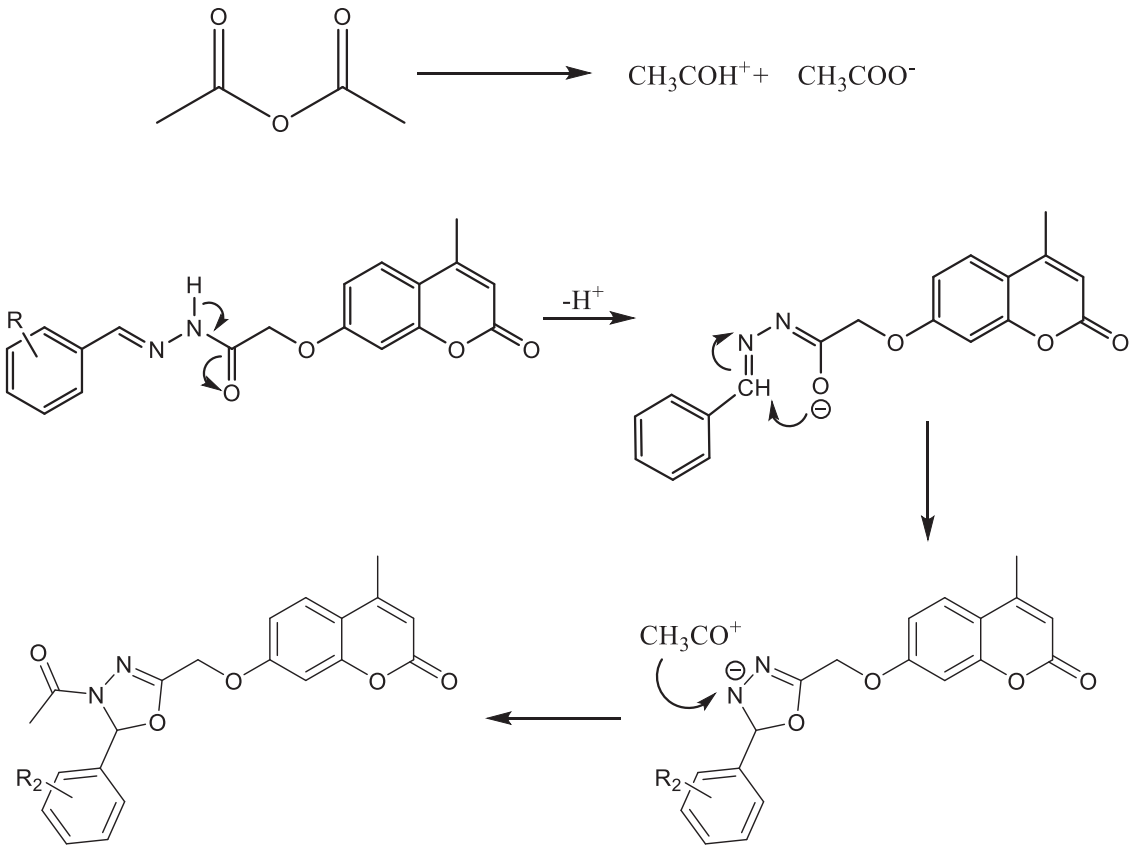



**Figure 2**. Proposed mechanism for conversion of **2** to **3**.

Antioxidant activity of synthesized compounds was performed with three different methods, each one of them showing antioxidant activity gained by different mechanisms. Antioxidant activity of 1,3,4-oxadiazole derivatives on DPPH$^\bullet$ (2,2-diphenyl-1-picrylhydrazyl) (Table 1) was very low, since all hydroxyl groups, which are usually responsible for high DPPH scavenging activity, were acetylated. Iron chelating activity was also low and not comparable to standard compound EDTA. When antioxidant activity was performed with the phosphomolybdenum method, where a different mechanism is employed, compounds like **3g** and **3h** showed significant antioxidant activity. These compounds also showed good antibacterial activity (Table 2) on *B. subtilis*, and **3h** excellent activity on antifungal (Table 3) and antiaflatoxigenic activity (at 125 $\mu$g/mL) (Table

4). Compounds **3d**, **3e**, and **3m** also showed very good antibacterial activity on *B. subtilis* and compound **3j** revealed good antifungal activity. Although the antifungal activity of our compounds was low, their antiaflatoxigenic activity was much higher. Compounds **3a**, **3d**, **3h**, and **3j** were excellent antiaflatoxigenic agents, depending on their concentration. All of these data indicate that the combination of 1,3,4-oxadiazole ring with coumarin core is a suitable system for achieving antimicrobial and antiaflatoxigenic activity, while new and more efficient methods could be investigated in order to obtain them more easily and in greater yields.

**Table 1**. Antioxidant activity of oxadiazoles determined by DPPH, iron chelating, and phosphomolybdenum method ($A_m$ – activity relative to ascorbic acid (AA) on a molar basis).

| Compound | DPPH scavenging (%) | $A_m$ | Iron chelatin activity (%) | $R_2$ |
|---|---|---|---|---|
| Ascorbic acid | 90.0 | 1 | - | - |
| EDTA | - | - | 97 | |
| **3a** | 0.2 | 0.86 | 0 | 2-$OCOCH_3$ |
| **3b** | 0 | 0.25 | 5.1 | 3-$OCOCH_3$ |
| **3c** | 0 | 0.87 | 2.0 | 4-$OCOCH_3$ |
| **3d** | 0 | 1.03 | 0 | 3-$OCH_3$ |
| **3e** | 0.3 | 0.95 | - | 4-$OCH_3$ |
| **3f** | 25 | 0.44 | 7.4 | 2,3-$(OCOCH_3)_2$ |
| **3g** | 1.3 | 1.73 | 7.2 | 2,5-$(OCOCH_3)_2$ |
| **3h** | 0 | 1.77 | 1.2 | 3,4-$(OCOCH_3)_2$ |
| **3i** | 3.2 | 0.76 | 0 | 2-Cl |
| **3j** | 1.3 | 0.66 | - | 2-Br |
| **3k** | 2.9 | 0.71 | - | 4-Br |
| **3l** | 0 | 0.87 | 0 | 2-F |
| **3m** | 0.4 | 0.81 | 0 | 3-F |

## 3. Experimental

### 3.1. General

All chemicals were of *p.a.* quality and purchased from commercial suppliers. Melting points were determined on a capillary melting point apparatus (Electrothermal, Rochford, Great Britain). NMR spectra were recorded on a Bruker Avance 300 MHz NMR Spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) at 293 K in DMSO-d6. The MS spectra were recorded on LCMS/MS API 2000 (Applied Biosystems/MDS SCIEX, CA, USA) using an electrospray ionization (ESI) source. The elemental analysis for C, H, and N was done on a PerkinElmer Analyzer 2400 Series II (PerkinElmer, Boston, MA, USA). The absorbance was measured on a UV visible spectrophotometer Helios $\gamma$, (ThermoSpectronic, Cambridge, UK). Mycelia growth was performed on a rotary shaker (KS 260 basic, IKA, Germany). Chromatographic analyses were performed in an Acquity UPLC H-Class system (Waters, Milford, MA, USA) using an Acquity BEH C18 column (2.1 $\times$ 100 mm, 1.7 $\mu$m) (Waters). MS/MS detection of aflatoxins was performed using a Xevo TQD tandem quadrupole mass spectrometer (Waters).

Synthesis of hydrazide (**1**) was performed according to Šarkanj et al.[28] and synthesis of Schiff bases (**2**) was performed according to Molnar et al.[29] (Figure 1).

**Table 2**. Antibacterial activity of novel oxadiazoles on selected bacterial strains.

| | MIC (mg $mL^{-1}$) | | | |
|---|---|---|---|---|
| | G– | | G+ | |
| Compound | *Escherichia coli* | *Pseudomonas aeruginosa* | *Bacillus subtilis* | *Staphylococcus aureus* |
| AMKC | 0.001953125 | 0.001953125 | 0.001953125 | 0.001953125 |
| **3a** | 0.03125 | 0.015625 | 0.03125 | 0.015625 |
| **3b** | 0.03125 | 0.015625 | 0.03125 | 0.03125 |
| **3c** | 0.03125 | 0.015625 | 0.25 | 0.015625 |
| **3d** | 0.015625 | 0.015625 | 0.0078125 | 0.015625 |
| **3e** | 0.03125 | 0.015625 | 0.0078125 | 0.03125 |
| **3g** | 0.03125 | 0.015625 | 0.015625 | 0.03125 |
| **3h** | 0.03125 | 0.015625 | 0.0078125 | 0.015625 |
| **3i** | 0.03125 | 0.015625 | 0.03125 | 0.015625 |
| **3j** | 0.03125 | 0.015625 | 0.015625 | 0.03125 |
| **3k** | 0.03125 | 0.015625 | 0.03125 | 0.03125 |
| **3l** | 0.03125 | 0.015625 | 0.03125 | 0.015625 |
| **3m** | 0.03125 | 0.015625 | 0.0078125 | 0.03125 |

### 3.2. Synthesis of 1,3,4-oxadiazoles

A mixture of Schiff base and excess of acetic anhydride (10 mL) was refluxed for 1–4 h, and the reaction was monitored by TLC (benzene:acetone:acetic acid). The excess acetic anhydride was distilled off and residue was poured into ice-cold water. Upon formation of gummy/oily precipitate, the product was recrystallized from ethanol and filtered. Structures of all oxadiazole derivatives were confirmed by mass spectrometry, $^{1}$H and $^{13}$C NMR, and elemental analysis.

#### 3.2.1. *2-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate* (3a)

Yield (3%), mp 186–187 °C, Rf = 0.7: $C_6H_6$/acetone/AcOH (8:1:1). $^{1}$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.13 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 5.06 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.91 (1H, s, oxa), 6.93 (1H, d, coum-C6), 7.03 (1H, s, coum-C8), 7.22-7.55 (4H, m, arom), 7.62-7.67 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 11.3, 18.6, 21.2, 65.3, 65.7, 89.7, 102.0, 111.8, 112.8, 113.9, 124.4, 126.8, 128.1, 129.9, 131,7, 149.3, 153.8, 154.9, 157.3, 160., 161.5, 163.4, 169.3; MS $m/z$: 437.30 $[M + H]^+$, (M = 436.41); Anal. Calcd. For $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42; O, 25.66%; Found: C, 63.39; H, 4.29; N, 6.24%.

#### 3.2.2. *3-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate* (3b)

Yield (5%), mp 200–202 °C, Rf = 0.53: $C_6H_6$/acetone/AcOH (8:1:1). $^{1}$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.27 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 2.38 (s, 3H, $2CH_3$), 5.06 (s, 2H, $CH_2$), 6.22 (s, H, CH), 6.89 (1H, s, oxa), 6.98–7.01 (1H, d, coum-C6), 7.06 (1H, s, coum-C8), 7.26–7.65 (4H, m, arom), 7.90–7.96 (1H, d, coum-C5); $^{13}$C

**Table 3**. Antifungal activity of novel oxadiazoles determined on *Aspergillus flavus* NRRL 3251.

| Compound | Mycelia growth (g d.m.w.) | | | | | |
|---|---|---|---|---|---|---|
| | Tested concentration ($\mu$g mL$^{-1}$) | | | | | |
| | 500 | 250 | 125 | 62.5 | 31.25 | 15.625 |
| Control | 0.12460 ± 0.01382 | | | | | |
| **3a** | 0.14231 ± 0.00964 | 0.14569 ± 0.00531 | 0.15605 ± 0.01020 | 0.13103 ± 0.02134 | 0.13980 ± 0.01639 | 0.15866 ± 0.01702 |
| **3c** | 0.12901 ± 0.01934 | 0.12945 ± 0.00426 | 0.16145 ± 0.01312 | 0.10679 ± 0.01017 | 0.16774 ± 0.00216 | 0.13247 ± 0.00441 |
| **3d** | 0.11314 ± 0.01082 | 0.12323 ± 0.01584 | 0.13764 ± 0.00929 | 0.12543 ± 0.00615 | 0.12309 ± 0.01518 | 0.12379 ± 0.01086 |
| **3e** | 0.12121 ± 0.00756 | 0.14694 ± 0.00386 | 0.13857 ± 0.01666 | 0.13074 ± 0.00767 | 0.11518 ± 0.01461 | 0.14117 ± 0.01630 |
| **3g** | 0.12860 ± 0.00655 | 0.14488 ± 0.01650 | 0.13841 ± 0.00816 | * | 0.09636 ± 0.00151 | 0.09984 ± 0.01785 |
| **3h** | 0.11035 ± 0.01462 | 0.12716 ± 0.00896 | 0.07976 ± 0.5608 | 0.12344 ± 0.01081 | 0.14105 ± 0.01196 | 0.10667 ± 0.00195 |
| **3i** | 0.13439 ± 0.01007 | 0.14233 ± 0.01505 | 0.10512 ± 0.01409 | 0.13453 ± 0.00682 | 0.10582 ± 0.01112 | 0.13671 ± 0.00444 |
| **3j** | 0.12300 ± 0.00831 | * | 0.11907 ± 0.00460 | 0.09798 ± 0.01064 | 0.09659 ± 0.00371 | 0.09466 ± 0.01271 |
| **3l** | 0.13076 ± 0.01967 | 0.11580 ± 0.00473 | 0.07235 ± 0.00870 | 0.14706 ± 0.00931 | 0.11986 ± 0.01101 | 0.10731 ± 0.01605 |
| **3m** | 0.13916 ± 0.01907 | 0.14417 ± 0.00118 | 0.12579 ± 0.01665 | 0.09722 ± 0.01174 | 0.11423 ± 0.00756 | 0.12665 ± 0.01598 |
| | * *no data* | | | | | |

**Table 4**. Antiaflatoxigenic activity of novel oxadiazoles.

| Compound | Aflatoxin B1 production (ng $mL^{-1}$/g d.m.w.) | | | | | |
|---|---|---|---|---|---|---|
| | Tested concentration ($\mu$g $mL^{-1}$) | | | | | |
| | 500 | 250 | 125 | 62.5 | 31.25 | 15.625 |
| Control | 2193.10 ± 239.70 | | | | | |
| **3a** | 1124.79 ± 133.68 | 1119.75 ± 343.62 | 660.73 ± 136.67 | 291.27 ± 153.07 | 1429.59 ± 714.81 | 1091.38 ± 104.05 |
| **3c** | 1973.61 ± 344.15 | 1944.49 ± 1.88 | 819.62 ± 213.81 | 3431.55 ± 660.70 | 1096.46 ± 58.65 | 3000.24 ± 256.03 |
| **3d** | 760.04 ± 2.30 | 572.26 ± 107.99 | 91.15 ± 1.30 | 241.60 ± 85.91 | 313.48 ± 81.41 | 1293.54 ± 236.71 |
| **3e** | 1519.68 ± 84.25 | 1405.61 ± 64.07 | 2723.05 ± 200.31 | 2005.78 ± 92.67 | 2771.39 ± 229.61 | 2639.33 ± 388.87 |
| **3g** | 1638.10 ± 109.56 | 1125.51 ± 19.87 | 1205.11 ± 294.60 | * | 2307.26 ± 19.56 | 1686.60 ± 289.55 |
| **3h** | 2014.33 ± 392.27 | 1443.770 ± 54.46 | 52.82 ± 7.35 | 1731.56 ± 481.30 | 1165.20 ± 24.39 | 2108.40 ± 147.69 |
| **3i** | 5176.10 ± 778 | 3686.47 ± 672.38 | 3972.43 ± 774.39 | 1214.28 ± 68.94 | 2462.10 ± 498.19 | 2346.40 ± 383.42 |
| **3j** | 478.80 ± 158.51 | * | 88.48 ± 9.15 | 954.03 ± 14.98 | 1238.88 ± 199.4 | 609.45 ± 142.96 |
| **3l** | 2389.68 ± 1056.19 | 1639.34 ± 255.75 | 2151.48 ± 216.97 | 1026.68 ± 311.88 | 2200.24 ± 406.57 | 2671.61 ± 66.07 |
| **3m** | 2480.06 ± 315.11 | 1296.43 ± 27.14 | 2099.60 ± 394.25 | 1789.09 ± 683.41 | 3548.82 ± 231.40 | 752.18.18 ± 125.14 |
| | * *no data* | | | | | |

NMR (75 MHz, ppm, $(CD_3)_2SO$): 18.6, 26.3, 65.8, 68.7, 102.1, 111.8, 113.0, 114.4, 114.7, 119.6, 125.6, 126.8, 131.7, 135.7, 153.8, 155.1, 160.6, 161.5, 164.4, 164.9, 168.7, 171.3; MS $m/z$: 437.20 $[M + H]^+$, (M = 436.41); Anal. Calcd. For $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42; O, 25.66%; Found: C, 62.99; H, 4.29; N, 6.24%.

### 3.2.3. *4-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate* (3c)

Yield (13%), mp 193–194 °C, Rf = 0.89: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 1.88–2.27 (s, 3H, $CH_3$), 2.36–2.47 (s, 6H, $CH_3$), 5.39 (s, 2H, $CH_2$), 6.12 (s, H, CH), 6.93 (1H, s, oxa), 6.98–7.01 (1H, d, coum-C6), 7.05 (1H, s, coum-C8), 7.26–7.65 (4H, m, arom), 7.90 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 18.6, 21.4, 26.2, 65.3, 68.8, 102.1, 111.8, 113.0, 113.9, 116.3, 123.1, 126.8, 130.0, 130.8, 153.8, 155.1, 160.6, 161.5, 166.5, 168.4, 169.4, 171.2; MS $m/z$: 437.30 $[M + H]^+$, (M = 436.41); Anal. Calcd. For $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42; O, 25.66%; Found: C, 63.39; H, 4.51; N, 6.34%.

### 3.2.4. *7-((4-Acetyl-5-(3-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3d)

Yield (38%), mp 190–191 °C, Rf = 0.64: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, $(CD_3)_2SO$): 2.39–2.42(s, 6H, $CH_3$), 3.80 (s, 3H, $OCH_3$), 5.31 (s, 2H, $CH_2$), 6.22 (s, H, CH), 6.97 (1H, s, oxa), 7.01–7.04 (1H, d, coum-C6), 7.08 (1H, s, coum-C8), 7.15–7.46 (4H, m, arom), 7.65–7.74 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, DMSO-$d_6$): 18.6, 26.2, 55.7, 65.7, 68.8, 102.03, 111.8, 112.9, 113.1, 113.9, 118.7, 120.1, 121.8, 126.8, 126.9, 130.4, 134.6, 144.3, 153.8, 155.1, 160.0, 160.6, 161.5, 167.2, 168.4, 171.3; MS $m/z$: 409.10 $[M + H]^+$, (M = 408.41); Anal. Calcd. For $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86; O, 23.50%; Found: C, 64.39; H, 4.99; N, 6.74%.

### 3.2.5. *7-((4-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3e)

Yield (7%), mp 184–185 °C (lit.[30] 170 °C), Rf = 0.82: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.41(s, 6H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 5.31 (s, 2H, $CH_2$), 6.19 (s, H, CH), 6.89 (1H, s, oxa), 7.00–7.01 (1H, d, coum-C6), 7.05 (1H, s, coum-C8), 7.26–7.75 (4H, m, arom), 7.90–7.93 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 18.5, 25.9, 55.9, 68.9, 102.2, 111.8, 112.9, 114.1, 115.0, 125.8, 126.7, 130.8, 153.8, 155.1, 160.5, 161.6, 163.1, 167.5, 168.4, 171.2; MS $m/z$: 409.20 $[M + H]^+$, (M = 408.41); Anal. Calcd. For $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86; O, 23.50%; Found: C, 64.59; H, 4.69; N, 6.74%.

### 3.2.6. *3-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,2-phenylene diacetate* (3f)

Yield (2%), mp 109–110 °C, Rf = 0.55: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, $(CD_3)_2SO$): 2.08–2.13 (s, 3H, $CH_3$), 2.26–2.30 (s, 3H, $CH_3$), 2.36–2.41 (s, 6H, $CH_3$), 5.05 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.91 (1H, s, oxa), 6.93 (1H, d, coum-C6), 7.05 (1H, s, coum-C8), 7.33–7.46 (3H, m, arom), 7.62–7.65 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, DMSO-$d_6$): 11.3, 18.6, 20.9, 65.6, 88.2, 89.4, 101.9, 111.8, 112.8, 113.1, 113.9,126.3, 126.8, 127.1, 130.1, 141.2, 143.3, 153.8, 154.9, 157.4, 160.6, 161.5, 163.6, 168.2, 168.5; MS $m/z$:

495.30 [M + H]$^+$, (M = 494.46); Anal. Calcd. For $C_{25}H_{22}N_2O_9$: C, 60.73; H, 4.48; N, 5.67; O, 29.12%; Found: C, 60.40; H, 4.28; N, 5.24%.

### 3.2.7. *2-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,4-phenylene diacetate* (3g)

Yield (12%), mp 169–170 °C, Rf = 0.53: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.13 (s, 3H, $CH_3$), 2.28–2.39 (s, 9H, $3CH_3$), 5.07 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.91 (1H, s, oxa), 6.93 (1H, d, coum-C6), 7.02 (1H, s, coum-C8), 7.28–7.32 (3H, m, arom), 7.62–7.68 (1H, d, coum-C5), 7.90–7.96 (2H, m, arom); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 11.3, 18.6, 21.2, 65.7, 88.9, 102.0, 111.8, 112.8, 113.9, 113.9, 122.8, 125.18, 125.4, 126.8, 129.1, 146.6, 148.3, 153.8, 154.9, 157.4, 160.6, 161.5, 163.7, 169.3, 169.6; MS $m/z$: 495.30 [M + H]$^+$, (M = 494.46); Anal. Calcd. For $C_{25}H_{22}N_2O_9$: C, 60.73; H, 4.48; N, 5.67; O, 29.12%; Found: C, 60.79; H, 4.28; N, 5.24%.

### 3.2.8. *4-(3-Acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,2-phenylene diacetate* (3h)

Yield (31%), mp 136–137 °C, Rf = 0.53: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.13 (s, 3H, $CH_3$), 2.28–2.39 (s, 9H, $3CH_3$), 5.32 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.92–6.94 (1H, s, oxa), 7.01 (1H, d, coum-C6), 7.29 (1H, s, coum-C8), 7.32-7.44 (3H, m, arom), 7.62–7.68 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 11.3, 18.6, 21.2, 65.7, 68.8, 88.9, 102.0, 111.8,113.9, 120.7,122.8, 125.1, 126.8, 129.1, 146.6, 148.3, 153.8, 154.9, 157.4, 160.6, 161.5, 163.7, 169.3, 169.7, 171.13; MS $m/z$: 495.30 [M + H]$^+$, (M = 494.46); Anal. Calcd. For $C_{25}H_{22}N_2O_9$: C, 60.73; H, 4.48; N, 5.67; O, 29.12%; Found: C, 60.69; H, 4.39; N, 5.44%.

### 3.2.9. *7-((4-Acetyl-5-(2-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3i)

Yield (17%), mp 190–192 °C, Rf = 0.53: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.13 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 5.23 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.95 (1H, s, oxa), 6.96 (1H, d, coum-C6), 7.18 (1H, s, coum-C8), 7.42–7.57 (4H, m, arom), 7.63–7.67 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 11.4, 18.6, 65.8, 89.9, 102.0, 111.8, 112.9, 113.9, 126.8, 128.3, 129.6, 130.6, 132.3, 132.7, 132.9, 153.8, 154.9, 157.1, 160.6, 161.5, 164.0; MS $m/z$: 413.1 [M + H]$^+$, (M = 412.8); Anal. Calcd. For $C_{21}H_{17}ClN_2O_5$: C, 61.10; H, 4.15; Cl, 8.59; N, 6.79; O, 19.38%; Found: C, 62.19; H, 4.29; N, 6.64%.

### 3.2.10. *7-((4-Acetyl-5-(2-bromophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3j)

Yield (6%), mp 195–196 °C, Rf = 0.64: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.05–2.17 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 5.25 (s, 2H, $CH_2$), 6.22 (s, H, CH), 6.96 (1H, s, oxa), 6.98 (1H, d, coum-C6), 7.13 (1H, s, coum-C8), 7.33–7.48 (4H, m, arom), 7.64–7.73 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 11.4, 18.6, 65.3, 65.8, 91.7, 102.0, 111.8, 112.8, 112.9, 113.9, 122.4, 126.8, 126.9, 128.9, 129.5, 132.5, 133.8, 134.4, 153.8, 154.9, 157.0, 160.6, 161.5, 164.1; MS $m/z$: 459.1 [M + H]$^+$, (M = 457.3); Anal.

Calcd. For $C_{21}H_{17}BrN_2O_5$: C, 55.16; H, 3.75; Br, 17.47; N, 6.13; O, 17.49%; Found: C, 55.11; H, 3.49; N, 6.25%.

#### 3.2.11. *7-((4-Acetyl-5-(4-bromophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3k)

Yield (10%), mp 190 °C, Rf = 0.64: $CHCl_3$/MeOH (10:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.16 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 5.32 (s, 2H, $CH_2$), 6.18 (s, H, CH), 6.89 (1H, s, oxa), 6.93–6.95 (1H, d, coum-C6), 7.00 (1H, s, coum-C8), 7.42–7.73 (2H, m, arom), 7.81–7.82 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 17.9.6, 25.4, 68.5, 101.9, 111.4, 112.3, 113.7, 125.6, 126.2, 128.7, 130.1, 132.2, 153.0, 159.9, 161.1, 164.3, 168.2, 170.8; MS $m/z$: 458.20 $[M + H]^+$, (M = 457.3); Anal. Calcd. For $C_{21}H_{17}BrN_2O_5$: C, 55.16; H, 3.75; Br, 17.47; N, 6.13; O, 17.49%; Found: C, 55.20; H, 3.69; N, 6.19%.

#### 3.2.12. *7-((4-Acetyl-5-(2-fluorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3l)

Yield (92%), mp 180–183 °C, Rf = 0.86: $C_6H_6$/acetone/AcOH (8:1:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.39 (s, 3H, $OCH_3$), 2.43 (s, 3H, $CH_3$), 5.33 (s, 2H, $CH_2$), 6.21 (s, H, CH), 6.89 (1H, s, oxa), 6.93–6.95 (1H, d, coum-C6), 7.00 (1H, s, coum-C8), 7.42–7.73 (4H, m, arom), 7.81–7.82 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 18.6, 26.2, 68.8, 102.0, 111.7, 112.9, 113.9, 116.7, 120.8, 125.7, 126.8, 128.0, 134.9, 153.8, 155.1, 159.8, 160.6, 161.5, 163.7, 168.5, 171.3; MS $m/z$: 397.10 $[M + H]^+$, (M = 396.38); Anal. Calcd. For $C_{21}H_{17}FN_2O_5$: C, 63.63; H, 4.32; F, 4.79; N, 7.07; O, 20.18%; Found: C, 63.44; H, 4.49; N, 7.20%.

#### 3.2.13. *7-((4-Acetyl-5-(3-fluorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one* (3m)

Yield (46%), mp 150–151 °C, Rf = 0.65: $CHCl_3$/MeOH (10:1). $^1$H NMR (300 MHz, ppm, DMSO-$d_6$): 2.40 (s, 3H, $OCH_3$), 2.44 (s, 3H, $CH_3$), 5.36 (s, 2H, $CH_2$), 6.22 (s, H, CH), 6.96 (1H, s, oxa), 7.01–7.05 (1H, d, coum-C6), 7.09 (1H, s, coum-C8), 7.40–7.71 (4H, m, arom), 7.74–7.76 (1H, d, coum-C5); $^{13}$C NMR (75 MHz, ppm, $(CD_3)_2SO$): 18.6, 26.3, 68.7, 102.0, 111.7, 112.9, 113.9, 114.7, 119.3, 125.5, 126.8, 131.6,135.8, 153.8, 155.1, 160.6, 161.5, 164.4, 164.9, 168.6, 171.3; MS $m/z$: 397.10 $[M + H]^+$, (M = 396.38); Anal. Calcd. For $C_{21}H_{17}FN_2O_5$: C, 63.63; H, 4.32; F, 4.79; N, 7.07; O, 20.18%; Found: C, 63.56; H, 4.15; N, 7.24%.

### 3.3. DPPH scavenging activity assay

DMSO solution of the corresponding oxadiazole derivative (0.2 mM) was added to DMSO solution of DPPH radical (0.2 mM). The mixture was shaken and allowed to stand at room temperature. After 30 min the absorbance at 517 nm was determined and the scavenging activity was calculated. Ascorbic acid (AA) was used as a reference compound. All measurements were performed in triplicate.

### 3.4. Evaluation of antioxidant activity by phosphomolybdenum method

The antioxidant activity of tested coumarin derivatives was evaluated by the phosphomolybdenum method, according to the procedure described by Prieto et al.[31] The antioxidant activity was expressed relative to the antioxidant activity of the same concentration of AA.

### 3.5. Iron chelating activity

Iron chelating activity of the novel compounds was performed according to Čačić et al.[32] Briefly, solution of $FeCl_2$ (2 mM, 25 $\mu$L) was added to 2 mM solution of the desired compound followed by addition of ferrozine. After incubation at room temperature the absorbance was measured at 562 nm. EDTA was used as standard compound.

### 3.6. Antifungal and antiaflatoxigenic assay

Antifungal investigation was performed by submersed growing of *Aspergillus flavus* NRRL 3251 in aflatoxin-inducing YES media,[33] with the addition of coumarinyl 1,3,4-oxadiazoles to obtain final concentrations of 0, 15.625, 31.25, 62.5, 125, 250, and 500 mg $mL^{-1}$. Conidia suspension was prepared according to Šarkanj et al.[28] After incubation at 29 °C for 72 h, wet mycelia were separated and dry mycelia weight was determined. Separated culture filtrates were used for antiaflatoxigenic activity determination by the "dilute and shoot" method.[34] Chromatographic analyses were performed with a gradient elution consisting of eluent A (water with 0.1% formic acid) and eluent B (acetonitrile with 0.1% formic acid). Eluent A was held at 98% for the first 0.5 min, followed by a decrease to 10% in 4.0 min, held for 0.5 min at 10%, followed by an increase to 98% to 4.6 min, and equilibration for another 1.6 min, to give a total run time of 6 min. The flow rate was 0.5 mL $min^{-1}$ and the column temperature was 40 °C. The capillary voltage was 3.5 kV, the source temperature was 150 °C, and the desolvation gas temperature was 400 °C with a flow of 650 L $h^{-1}$. Instrument control, data acquiring, and processing were done by MassLynx and TargetLynx software (v. 4.1., Waters). Recovery was 92% for all aflatoxins. The limit of detection (LOD) was 0.15 ng $mL^{-1}$, and the limit of quantification (LOQ) was 0.5 ng $mL^{-1}$ for all aflatoxins.

### 3.7. Antibacterial assay

The antibacterial activities of coumarin derivatives were evaluated against four test bacteria strains as described in our previous work.[35] Briefly, two gram-positive *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* were investigated. The antibacterial activity was assessed by a modified broth microdilution method in terms of minimum inhibitory concentrations (MICs), defined as the lowest concentrations of a compound at which there was no visual turbidity due to microbial growth.[36] All assays were performed in duplicate.

## 4. Conclusions

We synthesized new coumarinyl derivatives bearing a 1,3,4-oxadiazole ring in their structure. This combination was proven to be an excellent tool for gaining some bioactive compounds, considering antibacterial, antifungal, and antiaflatoxigenic activity. Since some of the investigated compounds possess potent antibacterial and antiaflatoxigenic activity, structures of this type are a good base for the design and synthesis of some new and more efficient drugs. The results highlight these new coumarinyl derivatives as potential structures for further investigation on new antibacterial and antiaflatoxigenic drug candidates.

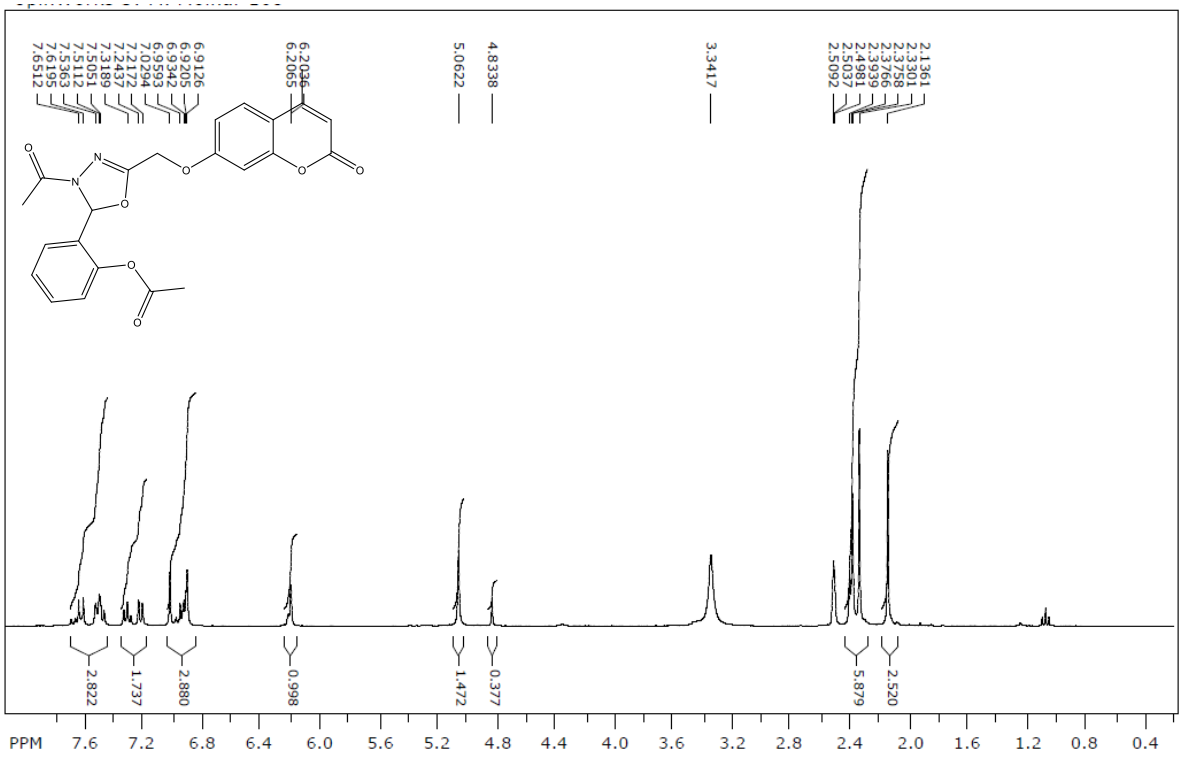
## References

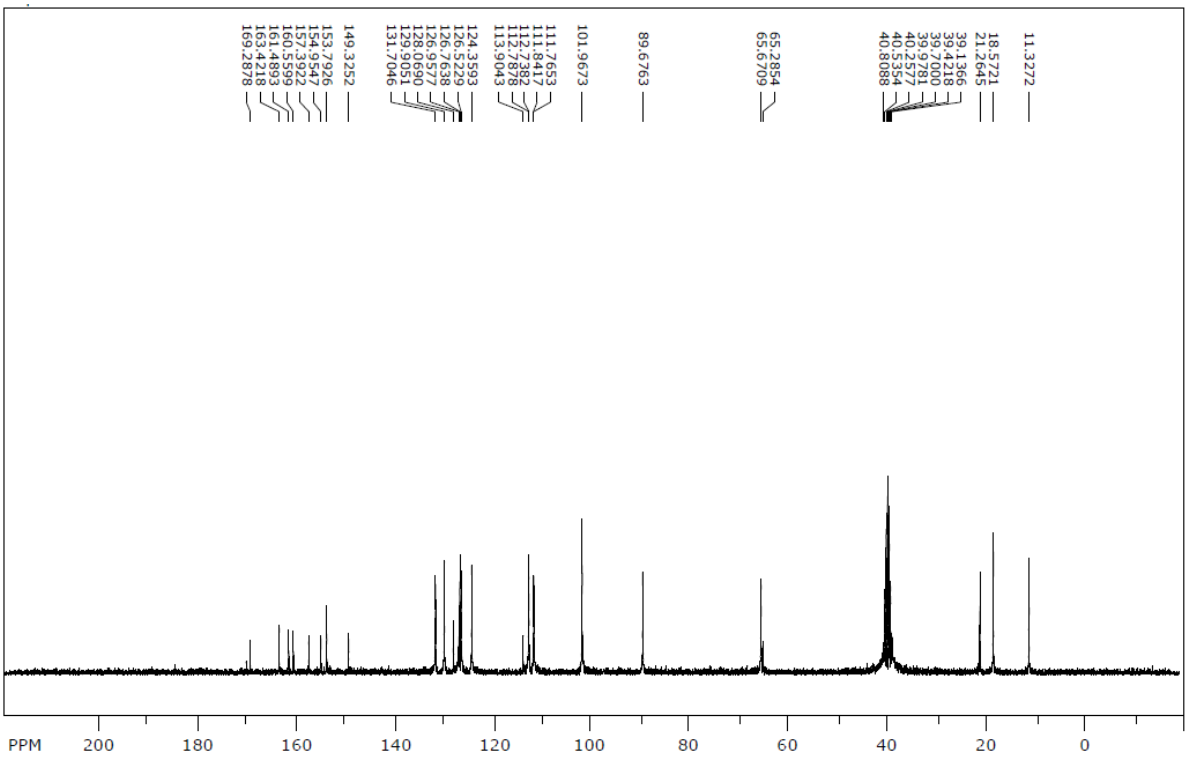
1. Bhatia, S.; Gupta, M. *J. Chem. Pharm. Res.* **2011**, *3*, 137-147.
2. de Oliveira, C. S.; Lira, B. F.; Barbosa-Filho, J. M.; Lorenzo, J. G. F.; de Athayde-Filho, P. F. *Molecules* **2012**, *17*, 10192-10231.
3. Raval, P. J.; Tarunkumar, A. N.; Dhaval, J. M.; Kruti, M. N.; Nilesh, P. H. *J. Saudi Chem. Soc.* **2014**, *18*, 101-106.

4. Spink, E.; Ding, D.; Peng, Z.; Boudreau, M. A.; Leemans, E.; Lastochkin, E.; Song, W.; Lichtenwalter, K.; O'Daniel, P. I.; Testero, S. A.; et al. J. Med. Chem. **2015**, *58*, 1380-1389.
5. Chen, C. J.; Song, B. A.; Yang, S.; Xu, G. F.; Bhadury, P. S.; Jin, L. H.; Hu, D. Y.; Li, Q. Z.; Liu, F.; Xue, W.; Lu, P.; et al. *Bioorg. Med. Chem.* **2007**, *15*, 3981-3989.
6. Zhang, K.; Wang, P.; Xuan, L. N.; Fu, X.; Fen, J.; Sha, L.; Liu, Y.; Chen, B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5154-5156.
7. Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2006**, *71*, 9548-9551.
8. Barbucenu, S. F.; Bancescu, G.; Cretu, O. D.; Draghici, C.; Bancescu, A.; Radu-Popescu, M. *Rev. Chem. (Bucuresti)* **2010**, *61*, 140-145.
9. Narwade, S. K.; Halnor, V. B.; Dalvi, N. R.; Gill, C. H.; Karale, B. K. *Ind. J. Chem.* **2006**, *45B*, 2776-2780.
10. Dobrota, C.; Paraschivescu, C. C.; Dumitru, I.; Matache, M.; Baciu, I.; Ruţă, L. L. *Tetrahedron Lett.* **2009**, *50*, 1886-1888.
11. Misra, U.; Hitkari, A.; Saxena, A. K.; Gurtu, S.; Shanker, K. *Eur. J. Med. Chem.* **1996**, *31*, 629-634.
12. Amir, M.; Kumar, S. *Acta Pharm.* **2007**, *57*, 31-45.
13. Khan, M. S. Y.; Akhtar, M. *Ind. J. Chem.* **2003**, *42B*, 900-904.
14. Sharba, A.; Al-Bayati, R.; Aouad, M.; Rezki, N. *Molecules* **2005**, *10*, 1161-1168.
15. Bhat, M. A.; Siddiqui, N.; Khan, S. A. *Acta Pol. Pharm. Drug Res.* **2008**, *65*, 235-239.
16. Fuloria, N. K.; Singh, V.; Shaharyar, M.; Ali, M. *Molecules* **2009**, *14*, 1898-1903.
17. Deasi, N. C.; Dodiya, A. M. *Arab. J. Chem.* **2016**, *9*, S379-S387.
18. Aanandhi, M. V.; Mansoori, M. H.; Shanmugapriya, S.; George, S.; Shanmugasundaram, P. *Res. J. Pharm. Biol. Chem. Sci.* **2010**, *1*, 1083-1090.
19. Chawla, R.; Arora, A.; Parameswaran, M. K.; Chandersharma, P.; Michael, S., Ravi, T. K. *Acta Pol. Pharm. Drug Res.* **2010**, *67*, 247-253.
20. Jedlovska, E.; Leško, J. *Synth. Commun.* **1994**, *24*, 1879-1885.
21. Cin, G. T.; Verep, G.; Topel, S. D.; Ciger, V. *Chem. Heterocyclic Comp.* **2013**, *49*, 1061-1067.
22. Pudota, P. T.; Purohit, R. S. M.; Pujar, G. V. *J. App. Chem. Res.* **2013**, *7*, 7-18.
23. Dabholkar, V. V.; Gavande, R. P. *Rasayan J. Chem.* **2010**, *3*, 655-659.
24. Kumar, A.; Makrandi, J. K. *Green Chem. Lett. Rev.* **2011**, *4*, 87-89.
25. Cohen, M. L. *Science* **1992**, *257*, 1050-1055.
26. Giamarellou, H. *Expert Rev. Anti. Infect. Ther.* **2006**, *4*, 601-618.
27. Behalo, M. S. *RSC Adv.* **2016**, *6*, 103132-103136.
28. Šarkanj, B.; Molnar, M.; Čačić, M.; Gille, L. *Food Chem.* **2013**, *139*, 488-495.
29. Molnar, M.; Šarkanj, B.; Čačić, M.; Gille, L.; Strelec, I. *Der Pharma Chem.* **2016**, *6*, 313-320.
30. Eid, A. I.; Ragab, F. A.; El-Ansary, S. L.; El-Gazayerly, S. M.; Mourad, F. E. *Arch. Pharm. (Wienheim).* **1994**, *327*, 211-213.
31. Prieto, P.; Pineda, M.; Aguilar, M. *Anal. Biochem.* **1999**, *269*, 337-341.
32. Čačić, M.; Pavić, V.; Molnar, M.; Šarkanj, B.; Has-Schon, E. *Molecules* **2014**, *19*, 1163-1177.
33. Chanda, A.; Roze, L. V.; Kang, S.; Artymovich, K. A.; Hicks, G. R.; Raikhel, N. V.; Calvo, A. M.; Linz, J. E. *Proc. Natl. Acad. Sci. USA*. **2009**, *106*, 19533-19538.
34. Kovač, T.; Kovač, M.; Strelec, I.; Nevistić, A.; Molnar, M. *Arh. Hig. Rada Toksikol.* **2017**, *68*, 9-15.
35. Molnar, M.; Pavić, V.; Šarkanj, B.; Čačić, M.; Vuković, D.; Klenkar, J. *Heterocyc. Commun.* **2017** doi: 10.1515/hc-2016-0078
36. Gu, W.; Wang, S. *Eur. J. Med. Chem.* **2010**, *45*, 4692-4696.

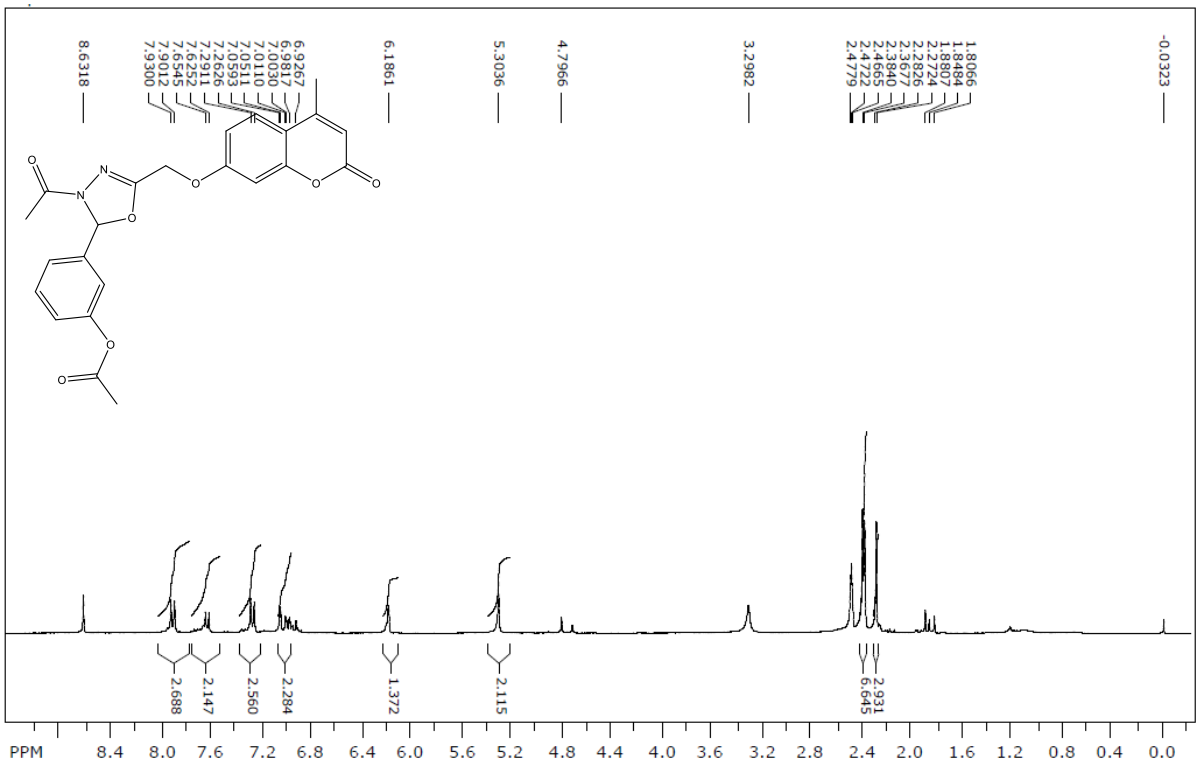
**Supplementary material**

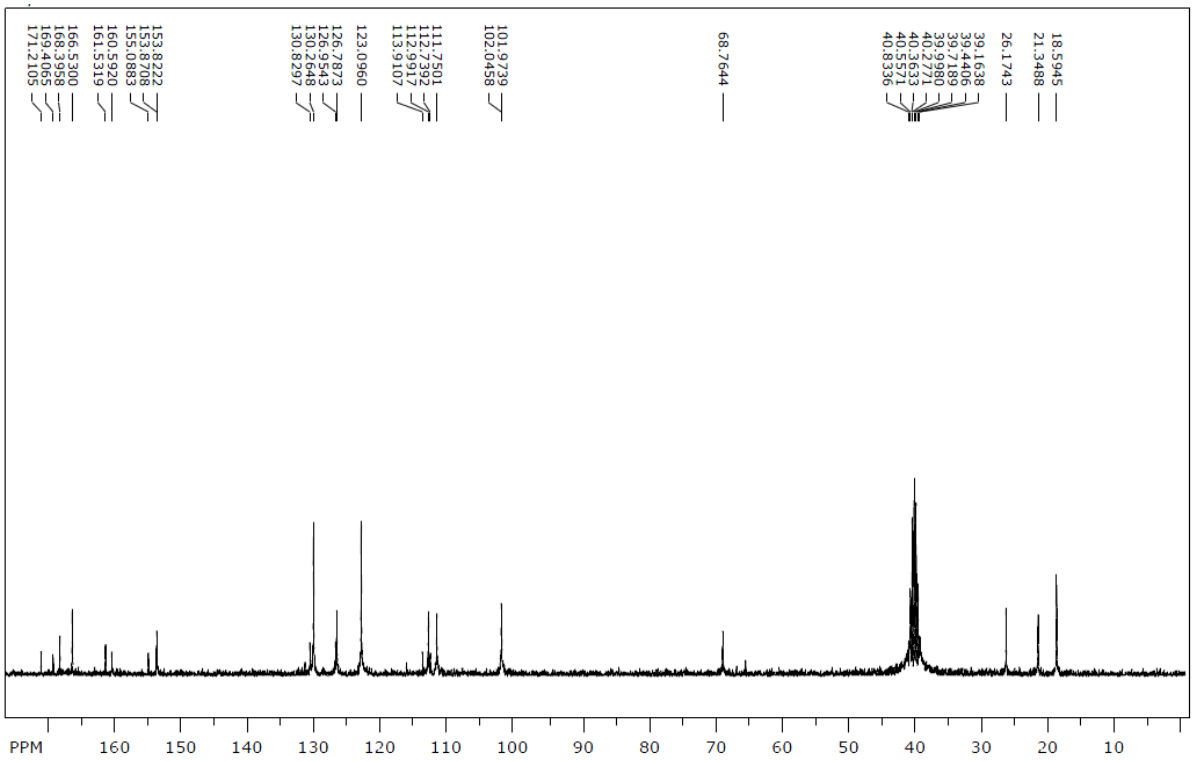
***2-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate (3a)***



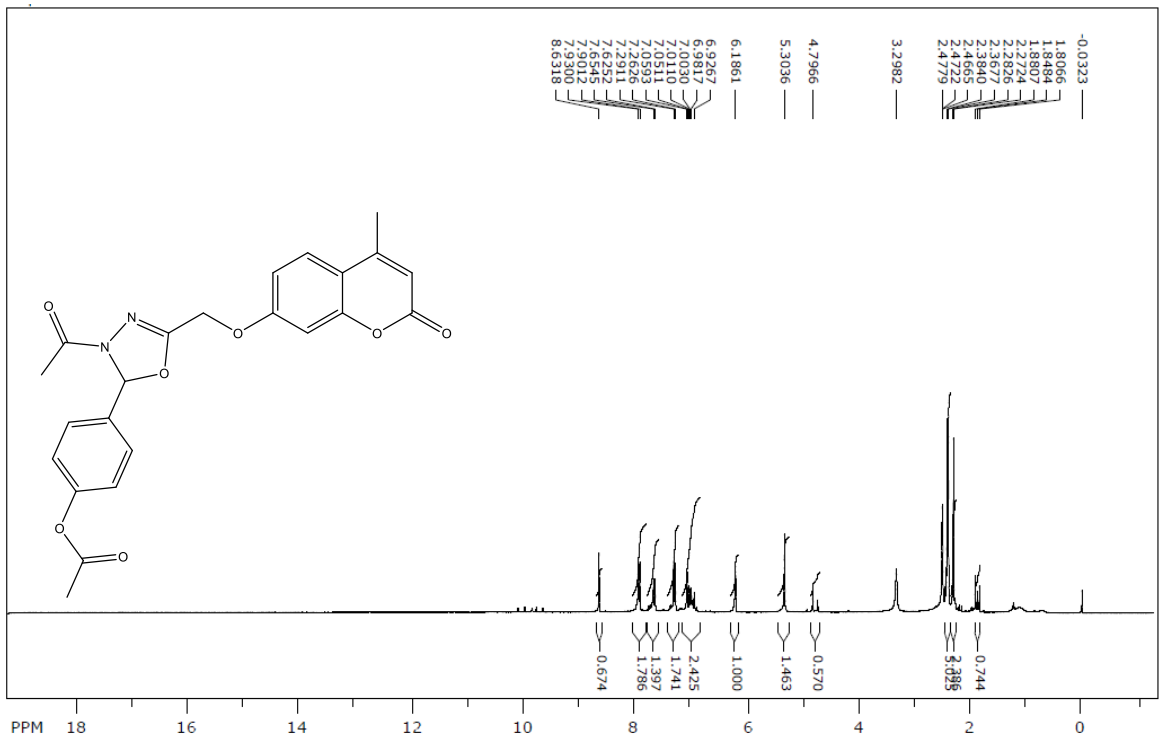



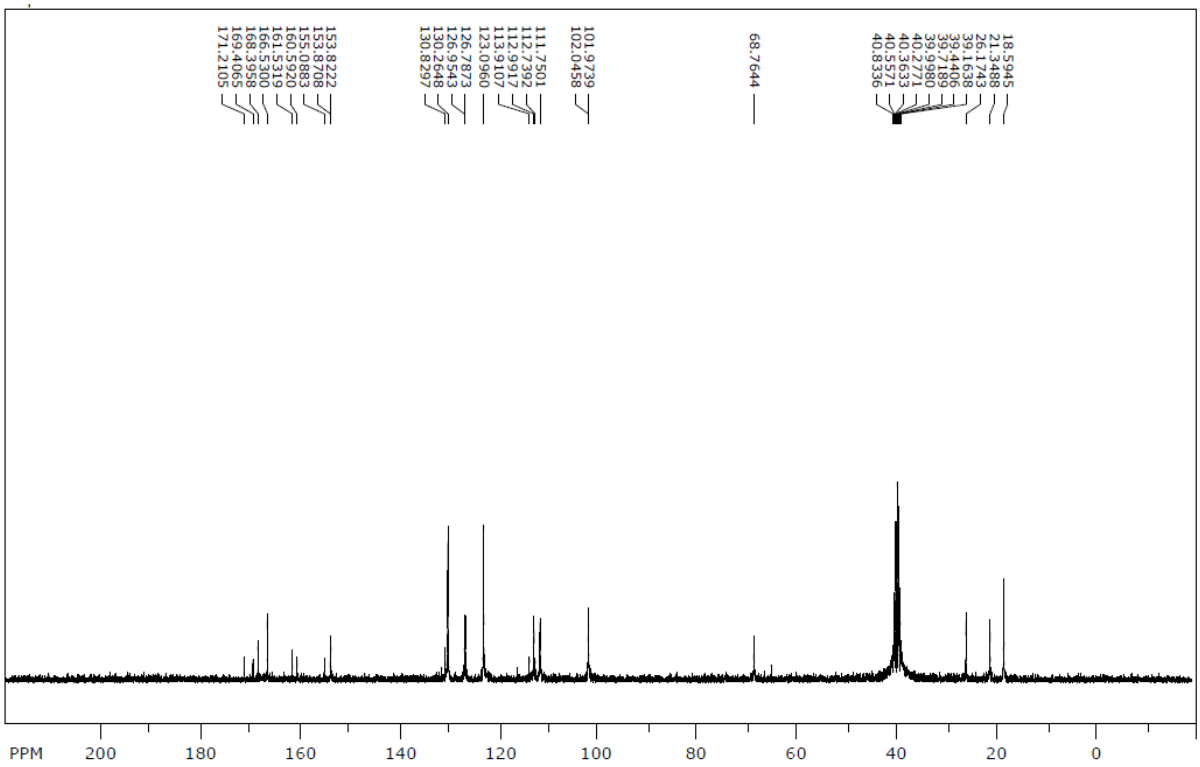
***3-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate*** **(3b)**



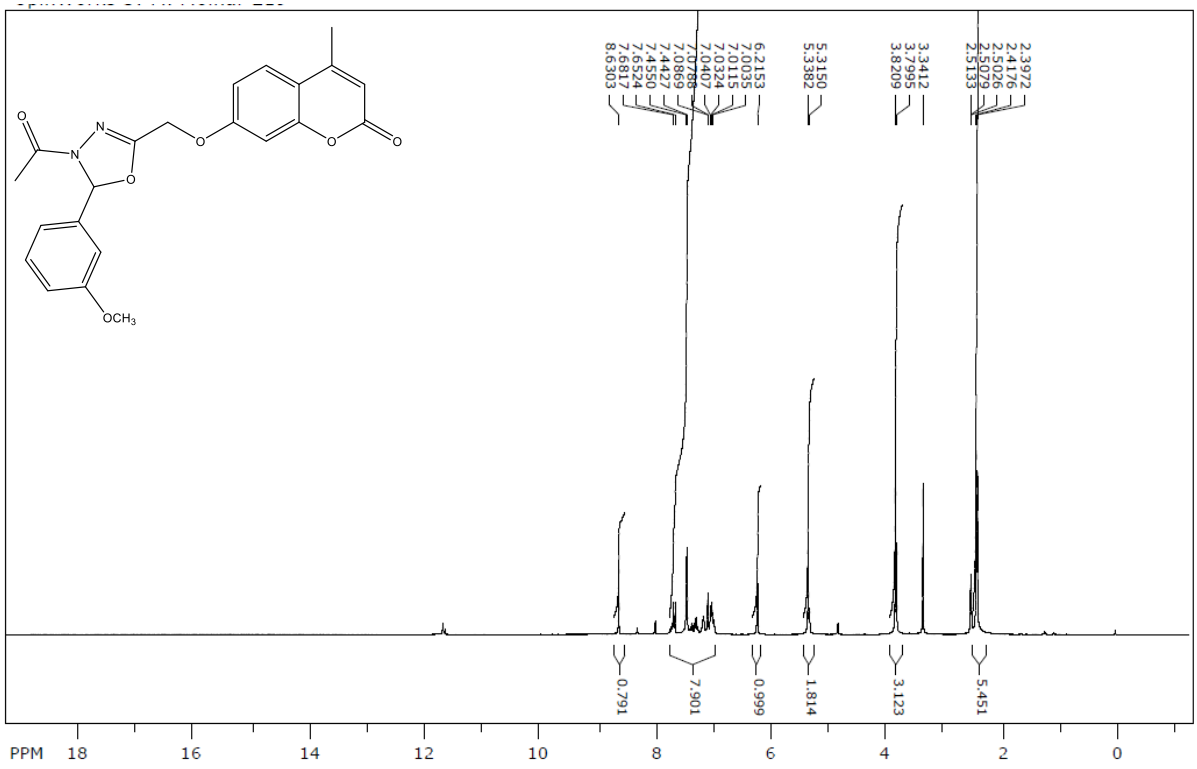



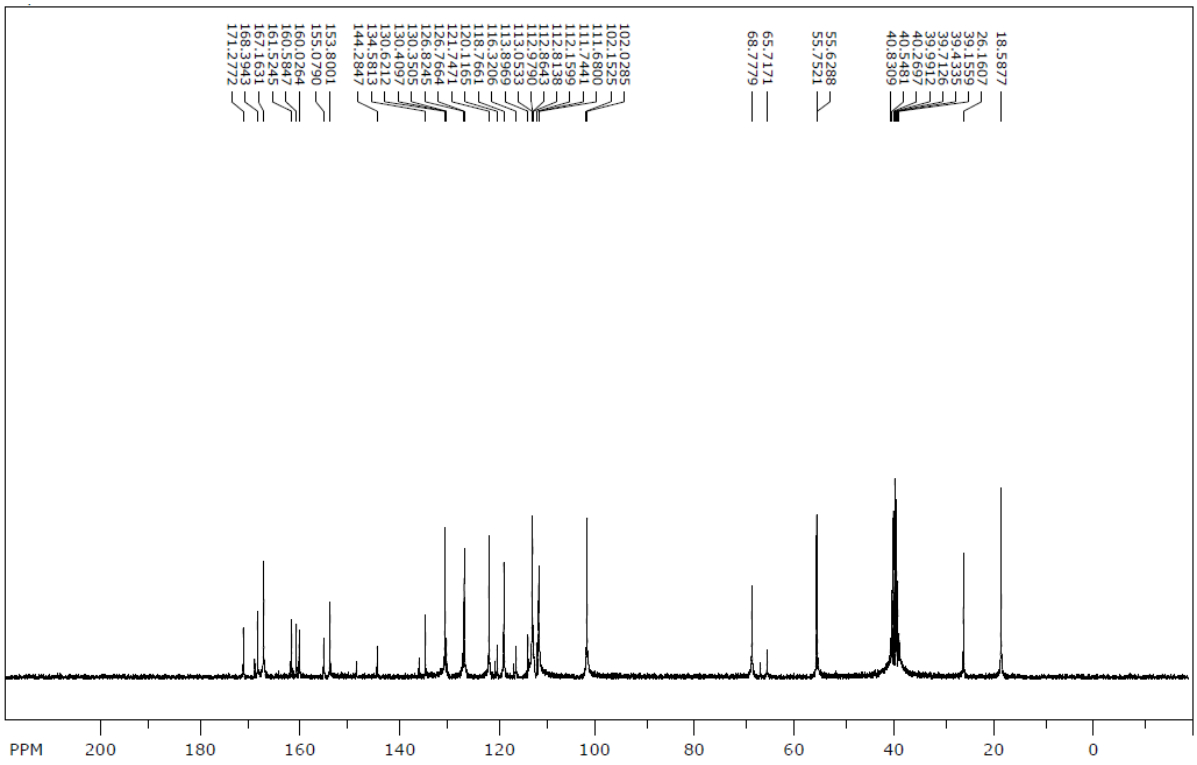
***4-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate(3c)***



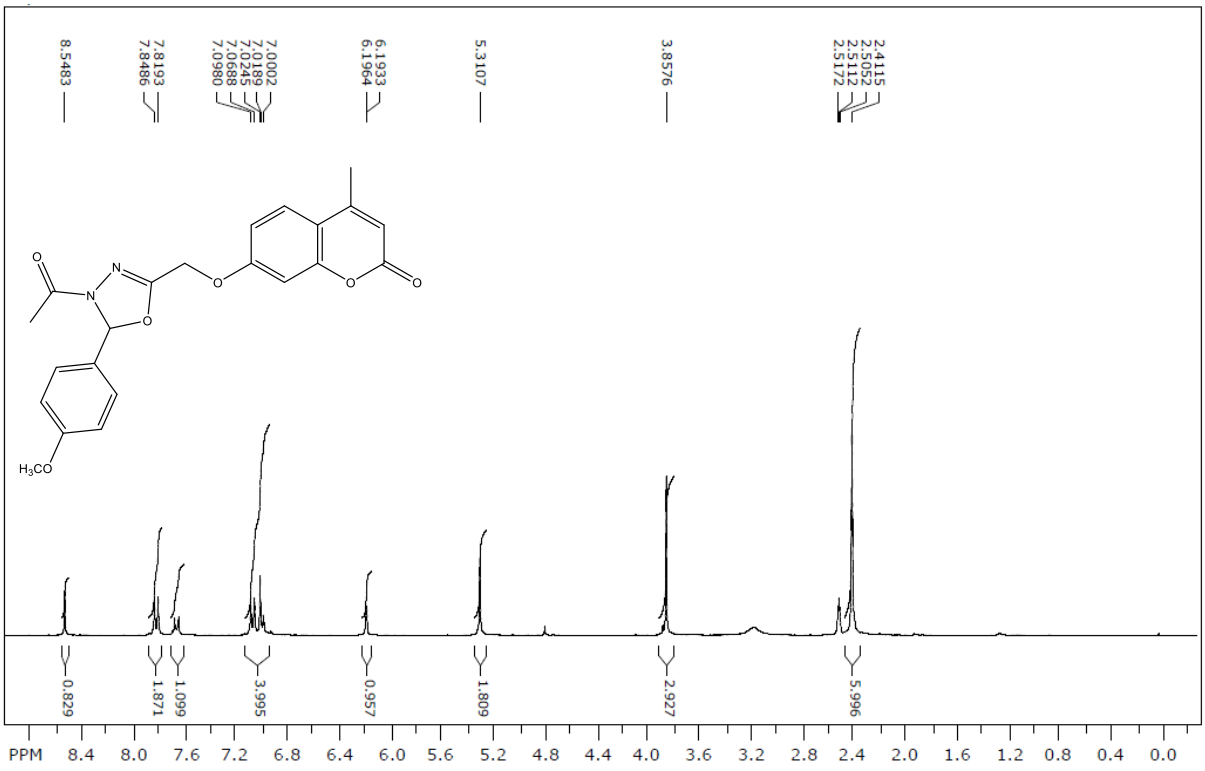



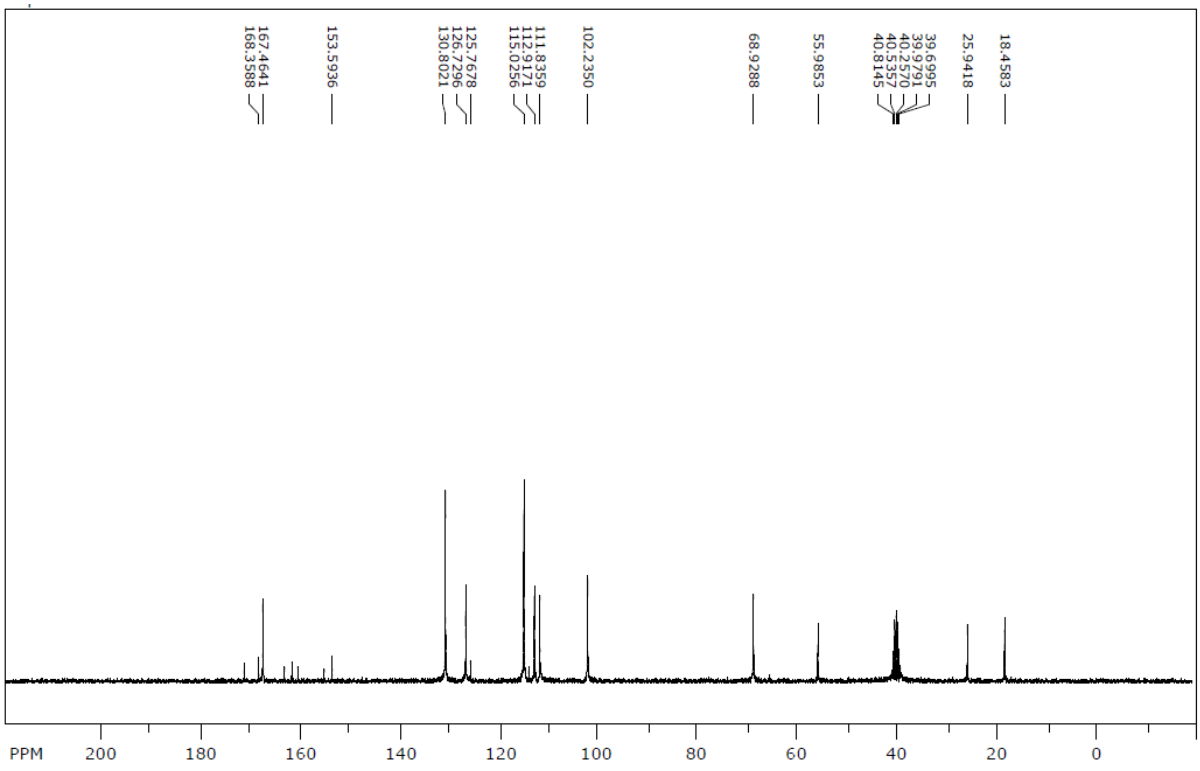
***7-((4-acetyl-5-(3-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3d)***



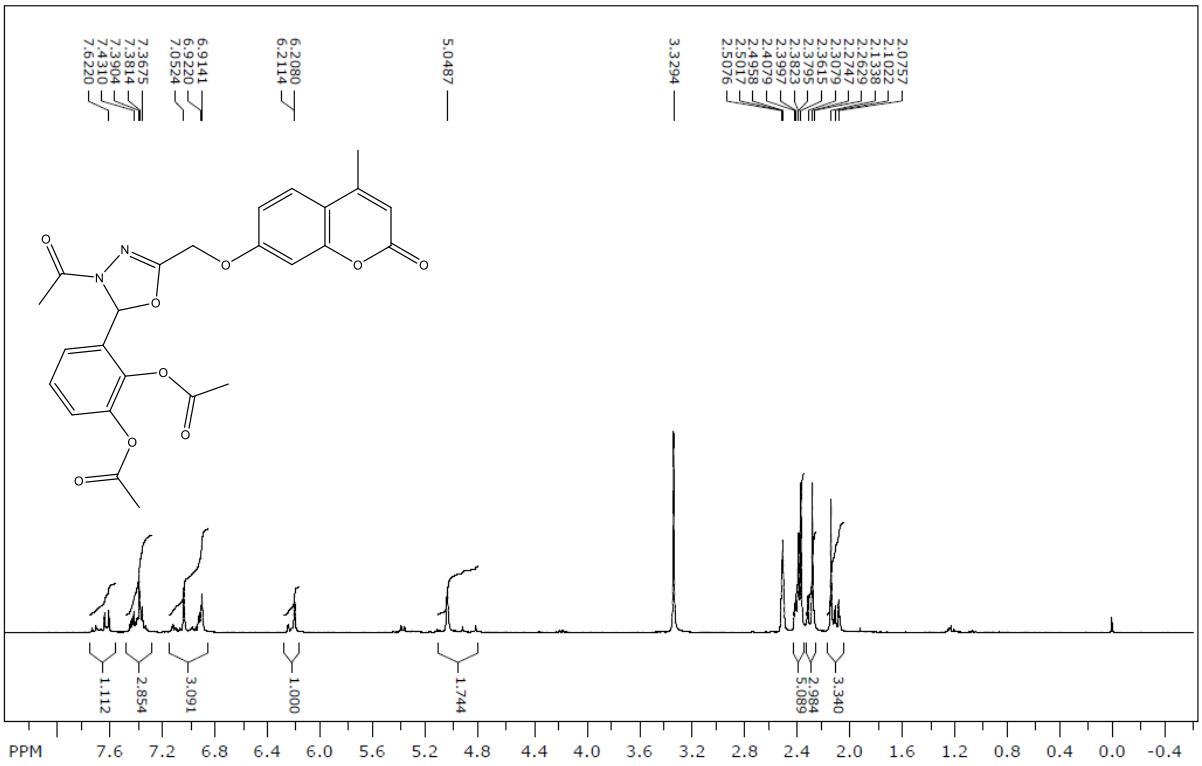



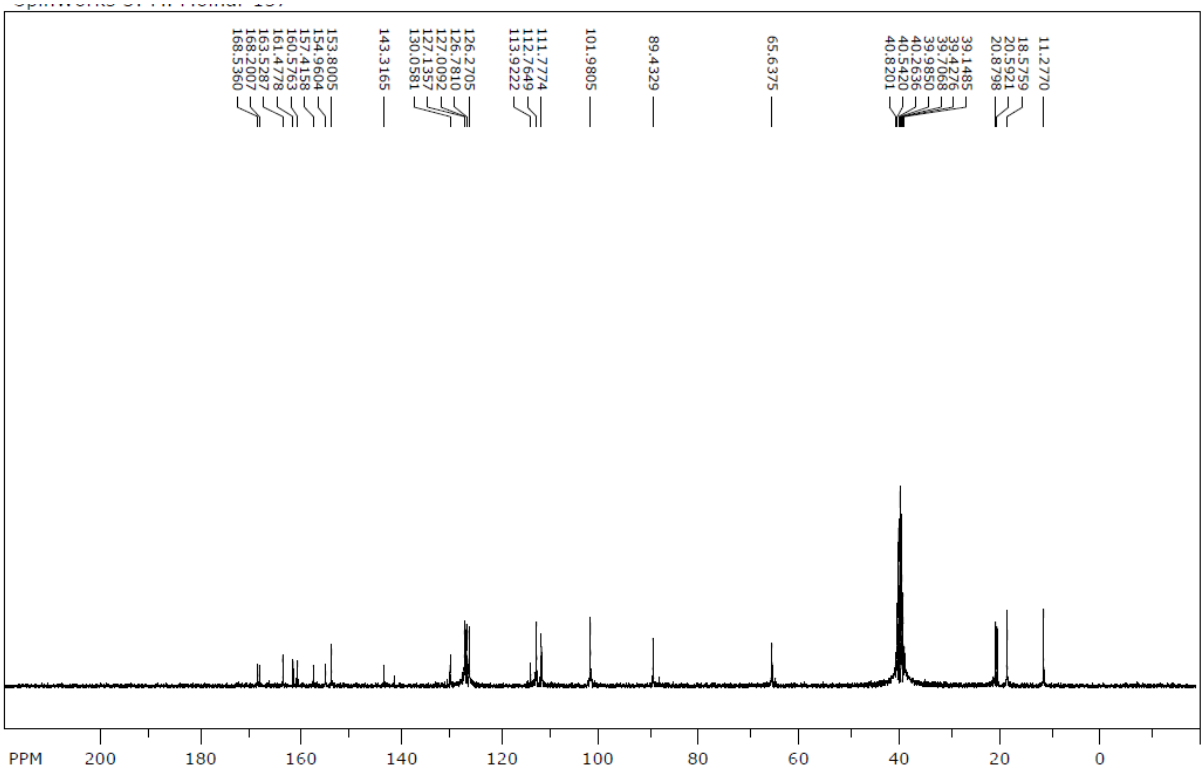
***7-((4-acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3e)***



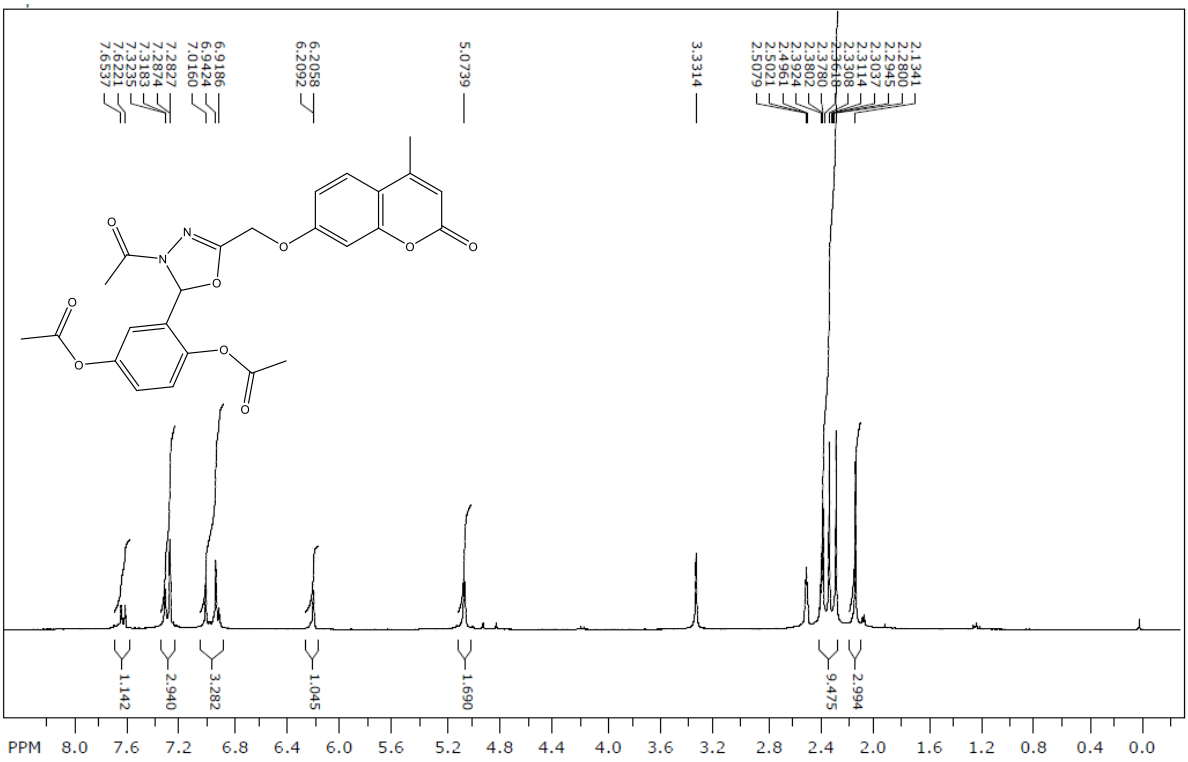



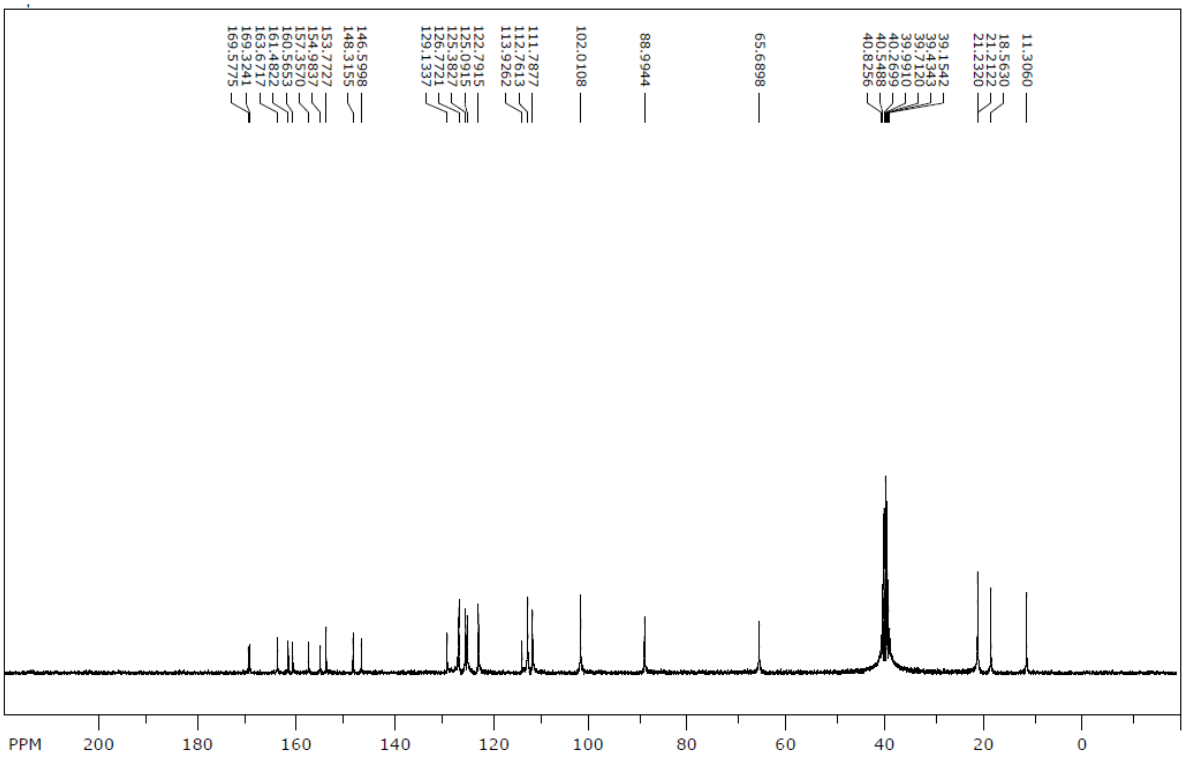
***3-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,2-phenylene diacetate (3f)***



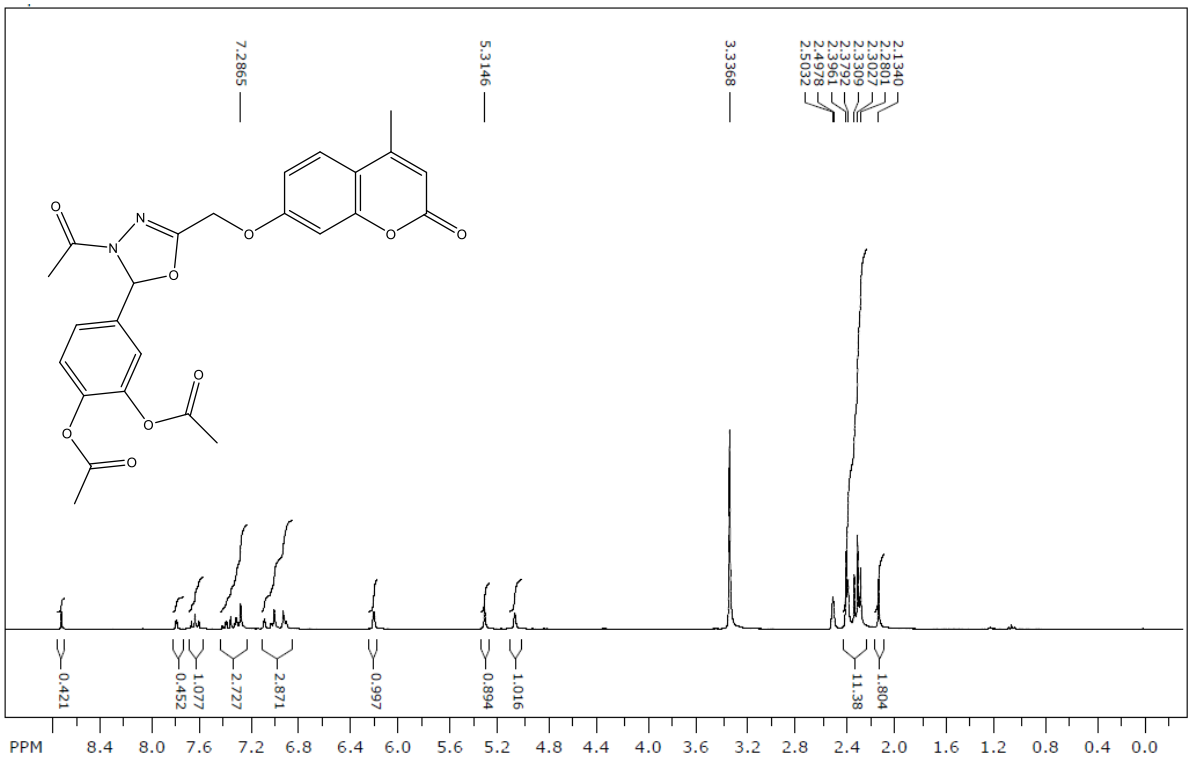



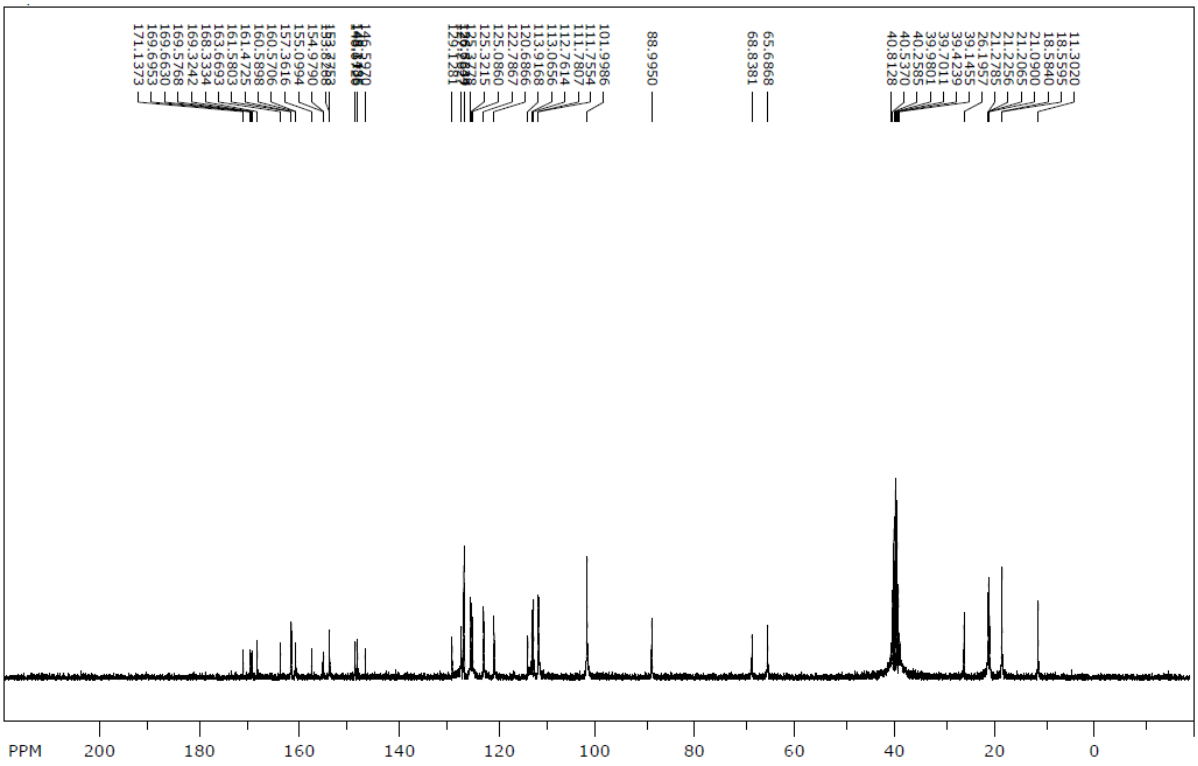
***2-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,4-phenylene diacetate (3g)***



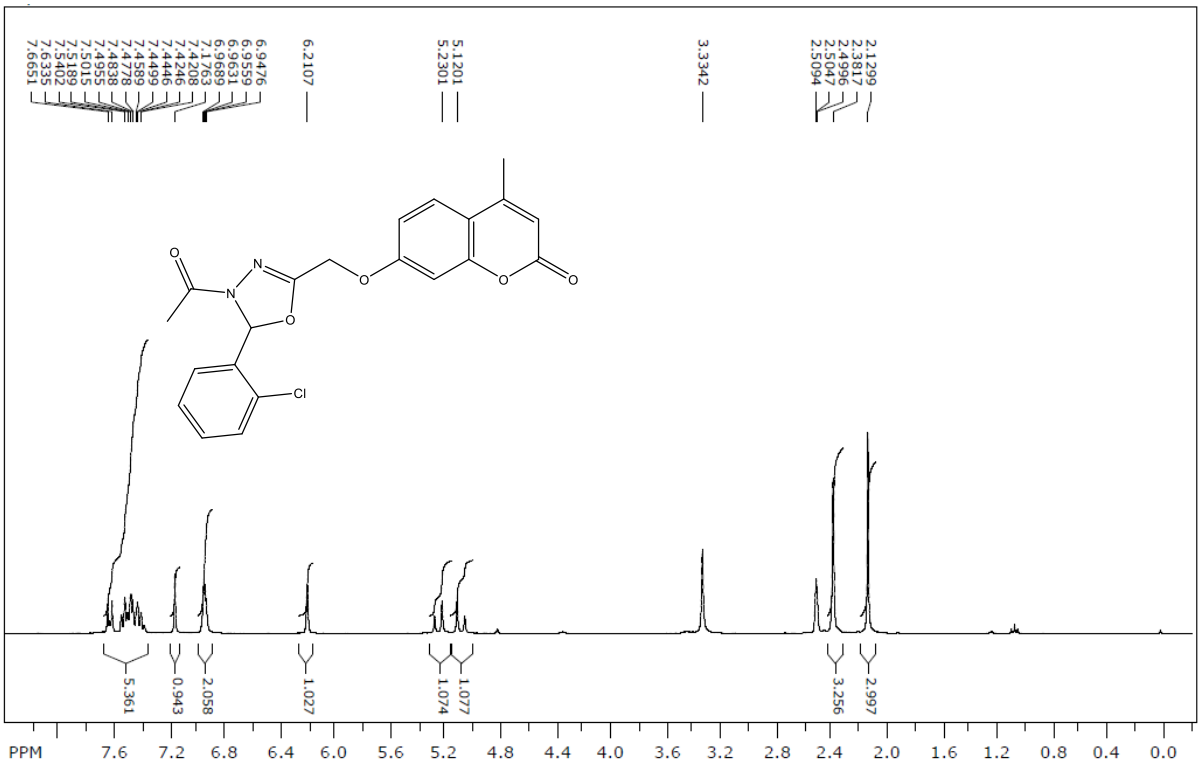



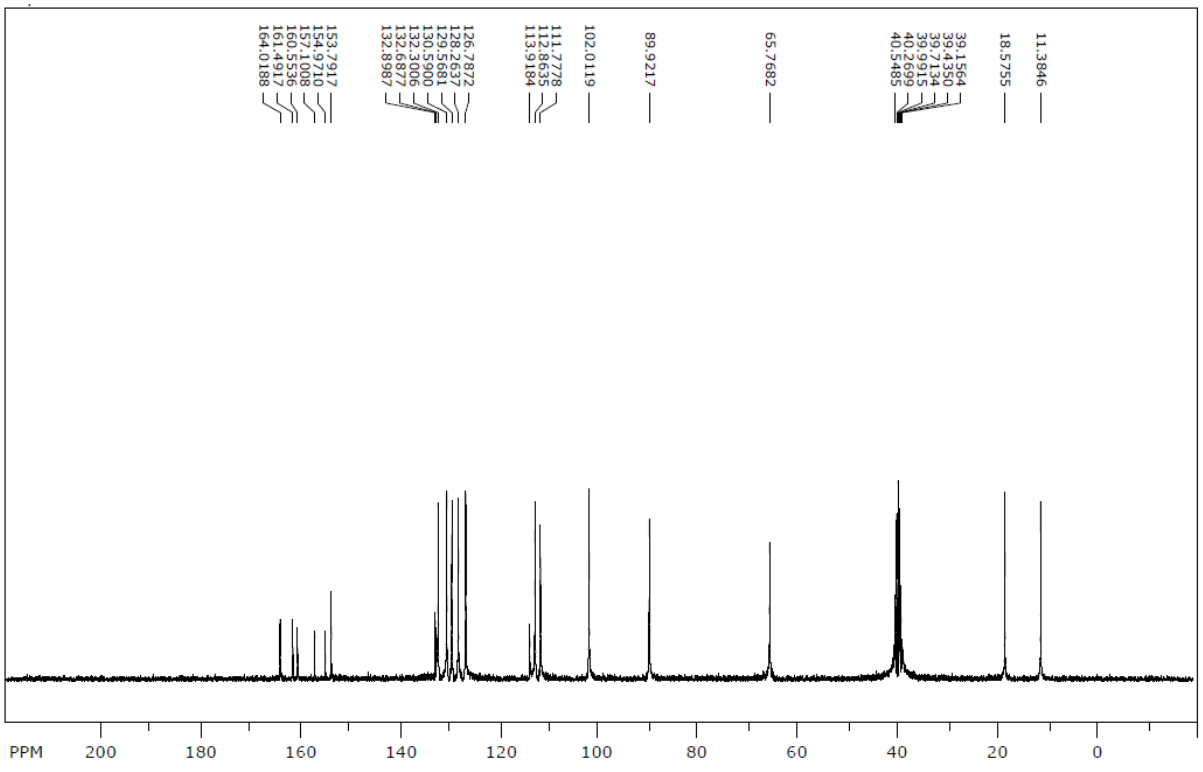
***4-(3-acetyl-5-(((4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1,2-phenylene diacetate (3h)***



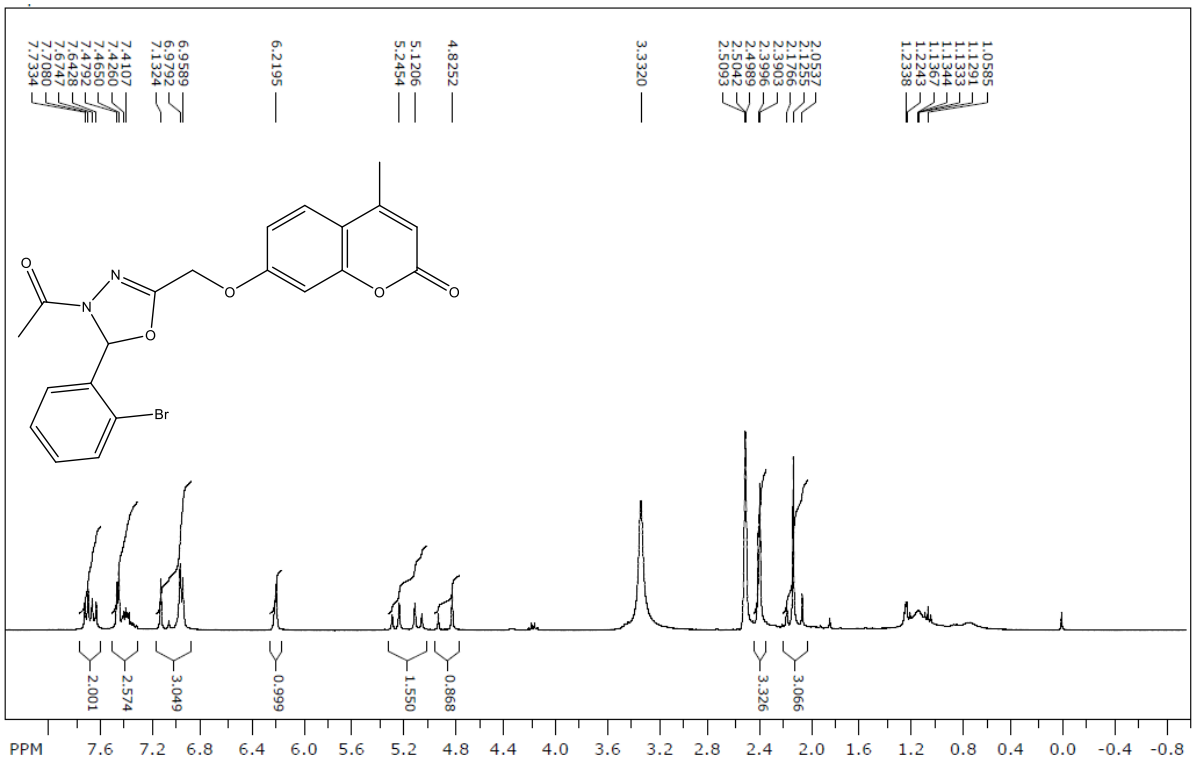



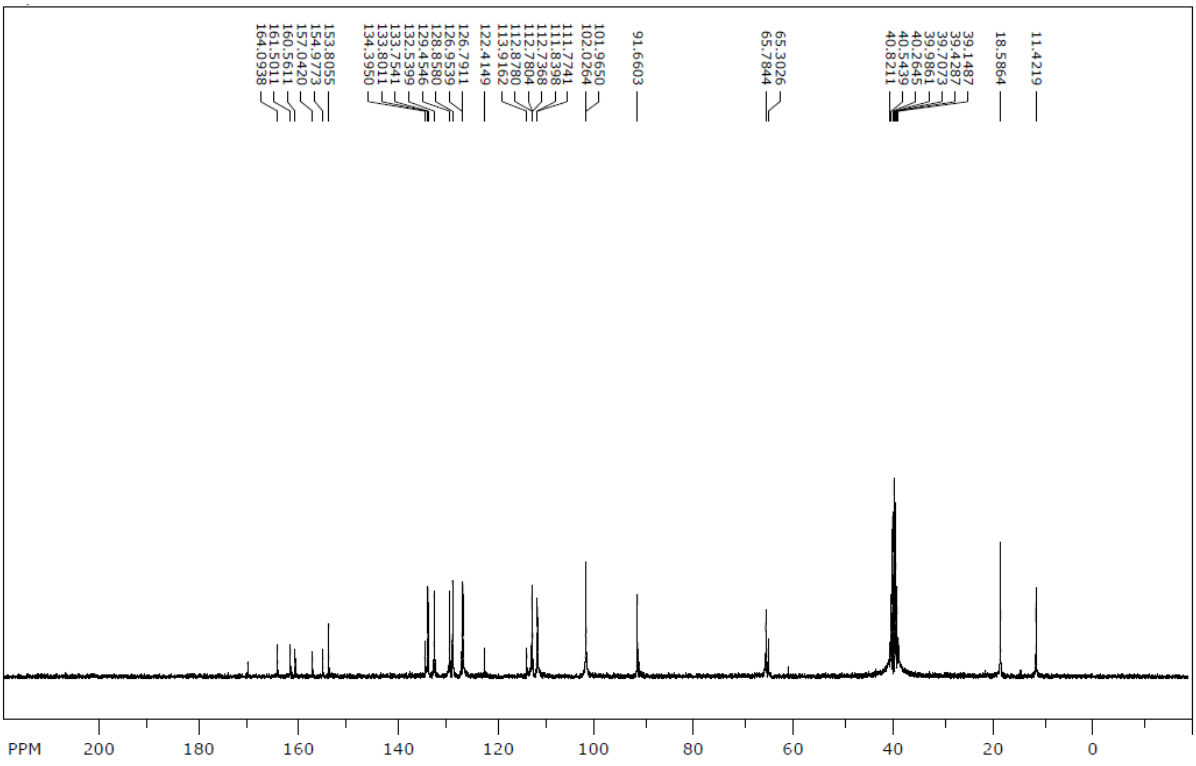
***7-((4-acetyl-5-(2-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3i)***



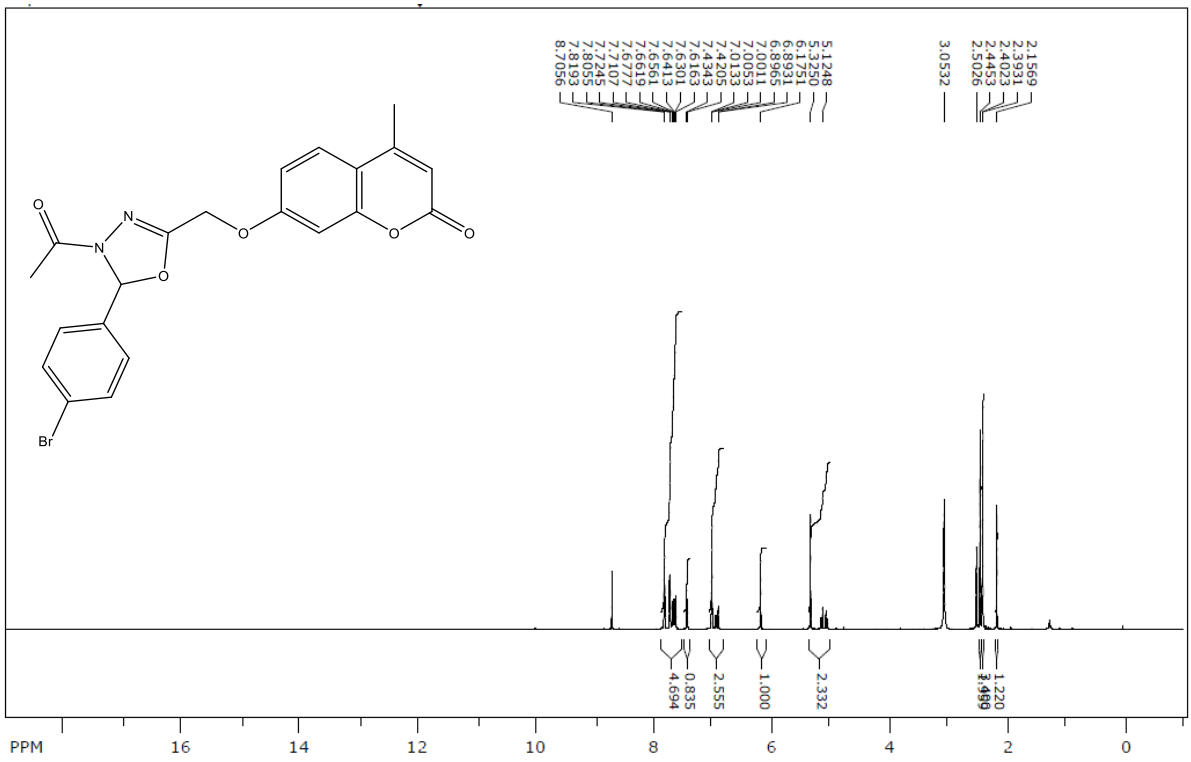



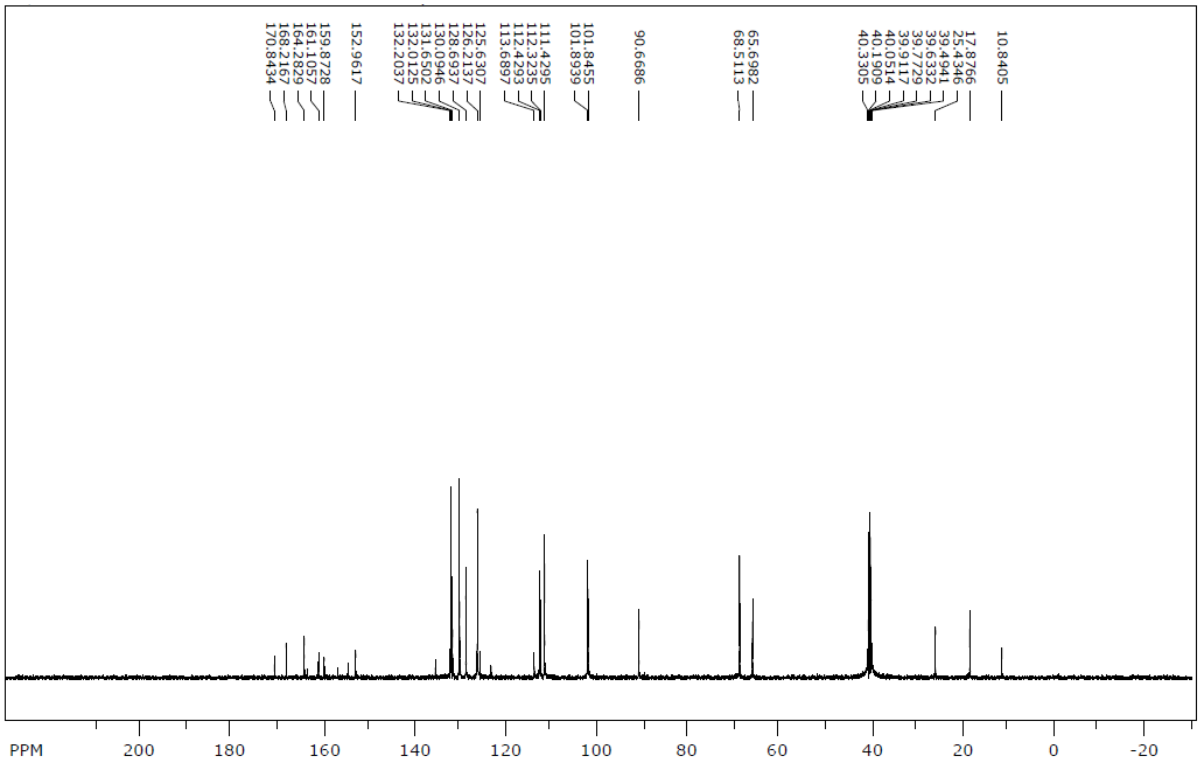
***7-((4-acetyl-5-(2-bromophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3j)***



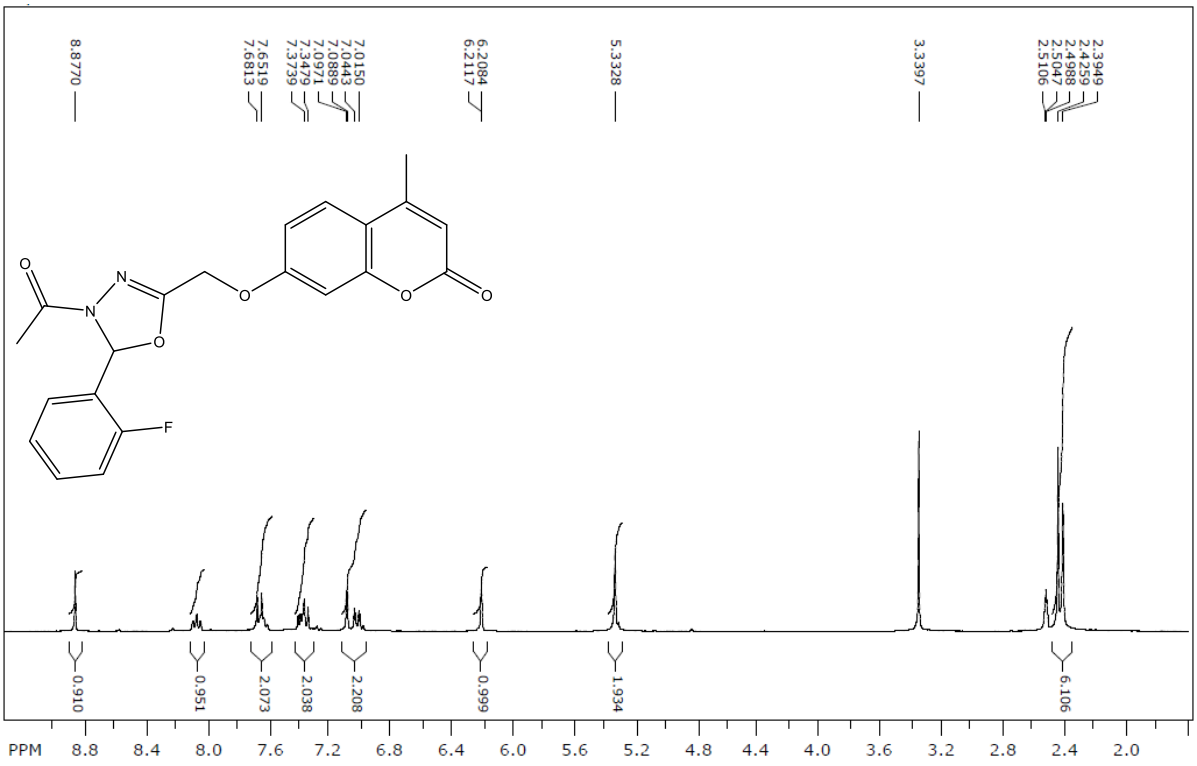



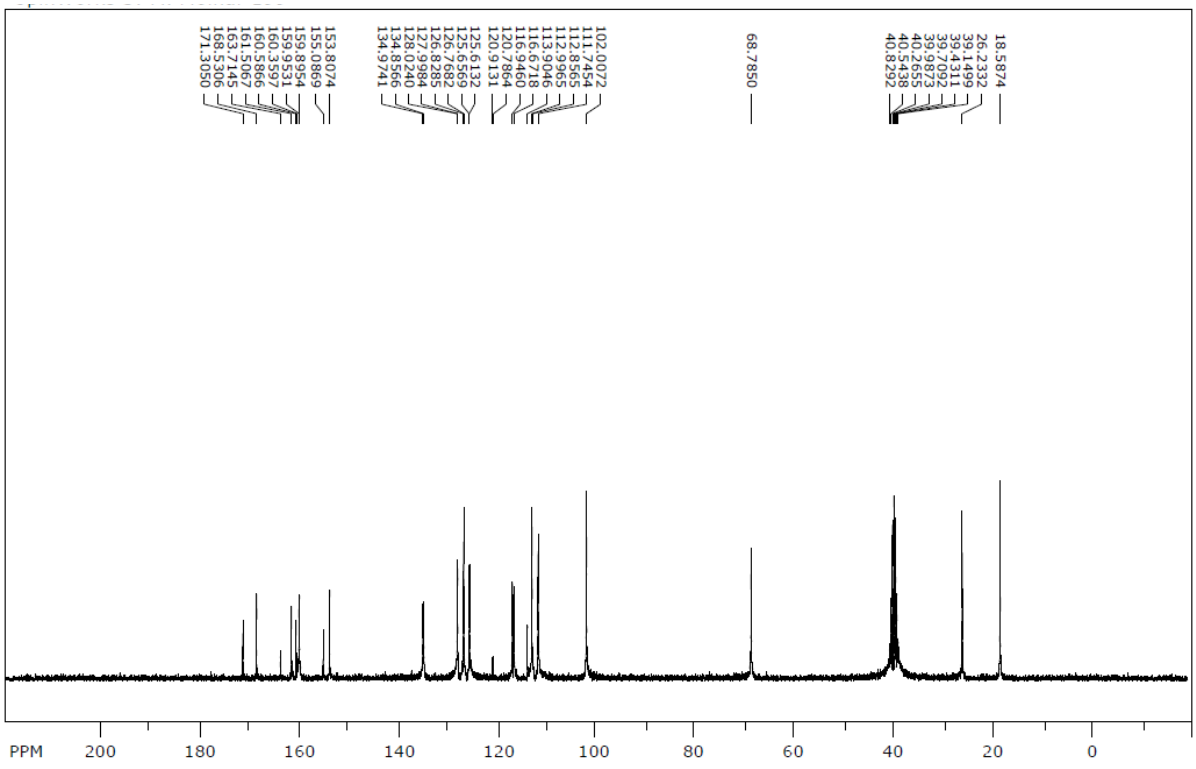
***7-((4-acetyl-5-(4-bromophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3k)***



***7-((4-acetyl-5-(2-fluorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3l)***



***7-((4-acetyl-5-(3-fluorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (3m)***