RESEARCH ARTICLE

Synthesis and Antioxidant Evaluation of Few Heterocyclic Derivatives

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ABSTRACT

A series of novel heterocyclic derivatives [A1-A7] have been synthesized by the alkylation reaction of the (SH, NH, OH) of various heterocyclic (oxadiazole, thiadiazole,4-hydroxy coumarin and benzothiazole) with chloro acetone or 2-bromoacetophenone. The resulting percentage yield of synthesized compound was relatively (69-85%). The producing compounds have been identified by infrared radiation (IR), proton nuclear magnetic resonance (^{1}H-NMR), Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy, and the quantities of various physical properties (melting point, crystal shape, and color). The synthesized derivatives were examined for their antioxidant activities.

Keywords: Antioxidant activity, Heterocyclic Compounds, Oxadiazole and Coumarin, Thiadiazole,

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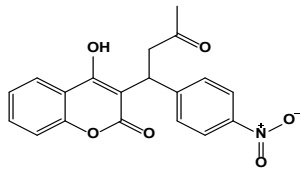
INTRODUCTION

The cyclic organic compounds that contain at least one atom of oxygen, nitrogen, and sulfur are called heterocyclic compounds-be aliphatic or aromatic.[1] Heterocyclic are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including anticancer, antifungal, antiviral, antidiabetic, and insecticidal agents.[2] Also, they have been frequently found as akey structural unit in medicinal chemistry and agriculture.[3] Thiadiazoles and oxadiazoles are heterocyclic compounds. Thiadiazoles are composed of a five-membered ring consisting of two nitrogen atoms and one sulfur atom, while oxadiazoles are also composed of a five-membered ring but contain one oxygen atom and two nitrogen atoms.[4,5] Oxadiazole and thiadiazoles occupied a wide place in the medical field, as the effectiveness of biologics as anti-bacterial, anti-inflammatory activities, antitumor, dyes and analytical reagents.[6]

Coumarin is one of the important classes that occupies a major position in the heterocyclic coumpound, where the fusion of the pyron ring with the benzene nucleus led to the emergence of this class.[7,8] Coumarin appears as a white crystalline powder with an aromatic smell like vanilla.[9] Coumarin derivatives have attracted a wide range of pharmaceutical action and biological functions. It is considered coumarin is one of the main oral anticoagulants, such as acenocoumarin.[10]



Acenocoumarol

EXPERIMENTAL

Chemicals

The primary substances were collected from companies of BDH and Sigma Aldrich.

Instruments

- Measurements degrees melting:- It has been measuring the degree of melting of the new compounds utilizing a device of the type/SMP31.
- The fourier transform infrared (FT-IR) spectra were recorded with KBr disk on "Perkin Elme,tensor27 Bruker" in the range (400–4000) cm^{-1}.
- Proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum were recorded on "a Bruker drug expert (DRX) system Al 500 MHz spectrometers" solvent d^{6}- DMSO with internal standard TMS in Higher School of chemistry /Sharif University and Tehran University, Iran.

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- Analytical (TLC) in the (3:7 or 4:6) ratio of ethyl acetate: hexane as the traveling phase was executed on plates (Merck 60 F254, 0.25 mm) silica gel.

Preparation of Compounds

Synthesis of Compound [A1-A3][11-12]

2-bromo-1-phenyl ethanone (0.199 g, 0.001mole) was added to mixture of (0.001 mole) (2- phenyl -1,3,4-oxadiazole -5-thiol, benzothiazole-2-thiol, 5-amino-1,3,4-thiadiazole-2-thiol) respectively, and (0.136 g, 0.001 mole) of sodium acetate in 25 mL ethanol. The resultant mixture was heated under reflux. The reaction's completion was monitored by using TLC [ethyl acetate: hexane (4:6)]. After that, the reaction mixture was left to cool. Then poured in ice, the precipitate was formed, filtered, washing with water. Recrystallized from methanol. Physical Properties are listed in Table 1.

Spectral Characterization of [A1]

IR (KBr), υ (cm^{-1}) :3300 (OH of phenol), 3059, 3032 (stretching vibration of C-H aromatic), 1676(stretching of C=O ketone), 1594(C=N stretching of the ring), 1185(stretching of C-O). ^{1}H- NMR data in ppm δ: 8.09–7.57 (m,10H, Aromatic protons), 5.19 (s,1H,SCH2CO) Figure 1.

^{13}C-NMR in ppm: δ 193.19 (C=O), 165.61- 163.79(C=N of oxadiazole ring), 135.56–123.46 (carbon of aromatic ring), 40.98 (S-CH2)[25], Figure 2.

Spectral Characterization of [A2]

IR (KBr), υ(cm^{-1}): 3050, 3002 (stretching of C-H aromatic), 1681 (stretching of C=O ketone), 1594(C=N stretching), 1577 (C=C stretching of aromatic ring) Figure 3. ^{1}H-NMR data in ppm :8.10- 7.34 (m, 9H, aromatic protons), 5.18 (s,2H,CH_2CO) Figure 4.

^{13}C- NMR data in ppmδ,193.41(C=O of ketone), 166.29 (C=N), 152.98-121.54 (C=C ring aromatic), 41.41(S-CH2) [32,33] Figure 5.

Spectral Characterization of [A3]

IR (KBr), υ(cm^{-1}): 3383-3259 (stretching of NH2), 3067(C-H aromatic),1694 (C=O of keton), 1654(N=N),1446 (stretching of N-N) Figure 6, ^{1}H-NMR data in ppm: δ 8.01-7.53(m,5H,ArH), 7.29 (s,2H, NH_2), 4.81(s,2H,CH_2CO) Figure 7.

Synthesis of Compound [A4].[13]

1,3,4-thiadiazole-2,5-dithiol (1.5 g, 0.001 mole) and sodium acetate trihydrate (2.72 g, 0.02 mole) dissolved in 20 mL of ethanol, then (1.5 mL, 0.02 mole) of chloroacetone was added. The resultant mixture is heated under reflux. The reaction was monitored by using TLC. After that, the solid product formed after cooling was collected and purified using ethanol. Physical Properties are listed in Table 1.

Spectral Characterization of [A4]

IR (KBr), υ(cm^{-1}): 2915,2880(C-H aliphatic), 1703 (stretching of C=O),1653 (C=N stretching of ring) Figure 8. ^{1}H NMR (500 MHz, dmso) δ data in ppm: 4.36(s,4H,S-CH_2-C=O) 3.34 (s,6H,C=O-CH_3)[28] Figure 9.

Synthesis of Compound [A5][14]

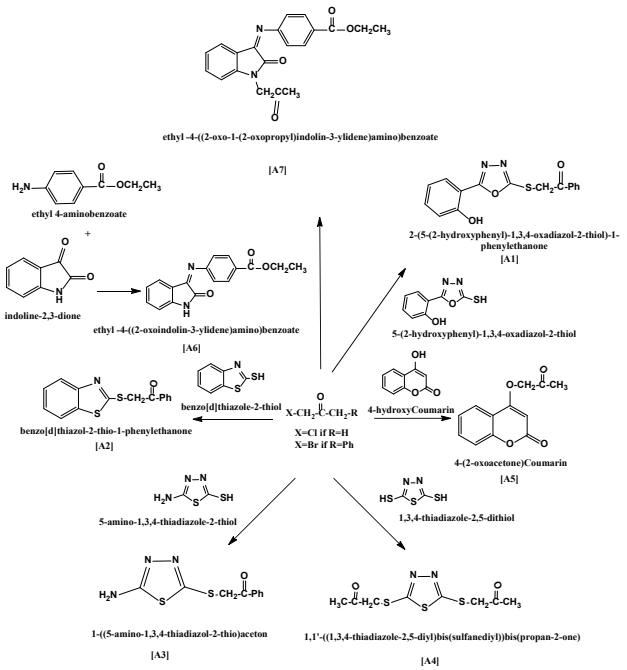
A mixture (1.62 g, 0.01-mole) of 4-hydroxy coumarin,(1.58g, 0.01-mole) of K_2CO_3 dissolved in 50 mL dry acetone, then (1mL,0.01 mole) of chloroacetone was added.The total mixture was heated in a water bath at 60°C for 24hours. The mixture was cooled, the precipitate was filtered, and it was recrystallized with ethanol physical properties are listed in Table 1.

Spectral Characterization of [A5]

IR (KBr), υ(cm^{-1}): 3065(stretching of C-H Aromatic ring), 2927-2958(C-H aliphatic),1747 (C=O of keton),1632 (O-C=O ester),1581(C=C aromatic). ^{1}H-NMR (500 MHz, DMSO) δ data in ppm 7.92- 7.50 (m,4H,ArH), 7.42(s,1H,C=CH lacton ring), 3.34(s,2H,CH_2), 2.25(s,3H,CH_3). Figure 10

Synthesis of Compound [A7]

The litiled compound [A6][ethyl-4-((2-oxoindoiln-3-ylidene) amino) benzoate was synthesized according to literature (Scheme 1)[15] from reaction indoline - 2,3-dione (0.149 g,0.001



Scheme 1: Synthesis of compound

Table 1: The physical Properties of Compounds.

Comp.No	*M.P°C*	*Yield%*	*Rf*	*Crystal Color and shape*	*Rec. Solvent*
A1	162	77	0.58	White needle crystal	Ethanol
A2	116	84	0.66	White yellowish needle crystal	Ethanol
A3	184	82	0.7	White powder	Ethanol
A4	98–100	76	0.4	White powder	Ethanol
A5	155	69	0.85	White powder	Ethanol
A6	235–233	68	0.34	Orange powder	Ethanol
A7	168–165	70	0.37	Orange powder	Ethanol

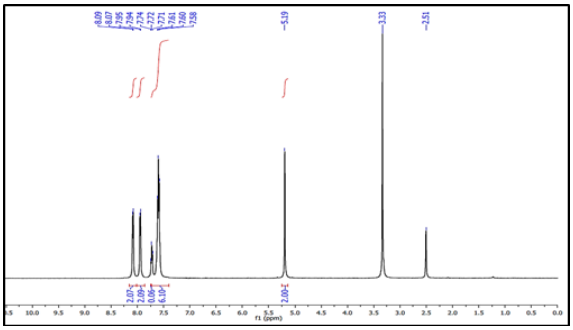


Figure 1: ^{1}H-NMR spectrum of A1

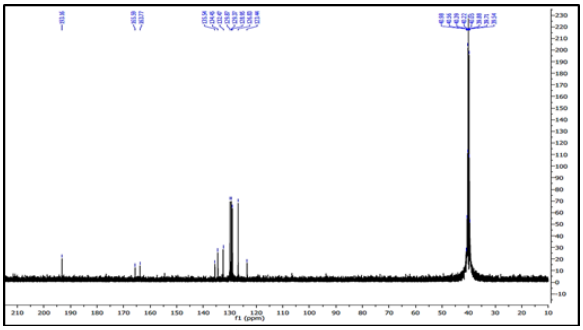


Figure 2: ^{13}C-NMR spectrum of A1

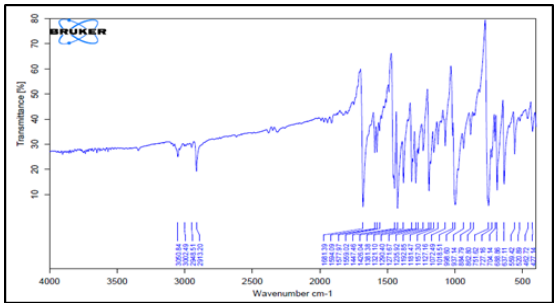


Figure 3:IR spectrum of A2

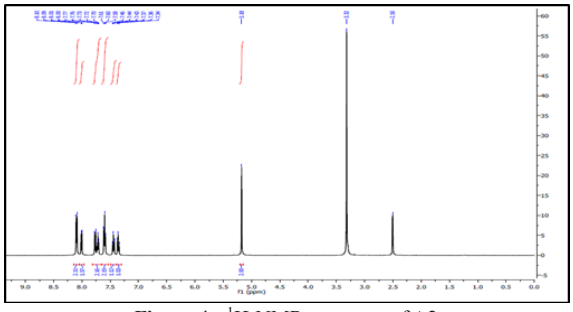


Figure 4:: ^{1}H-NMR spectrum of A2

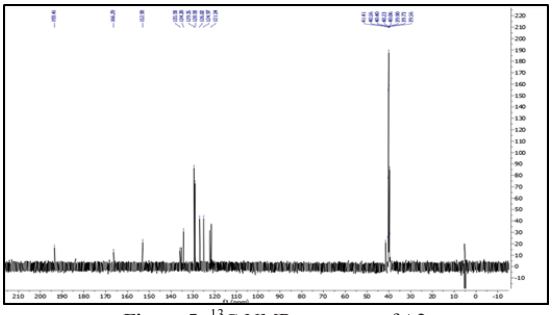


Figure 5: ^{13}C-NMR spectrum of A2

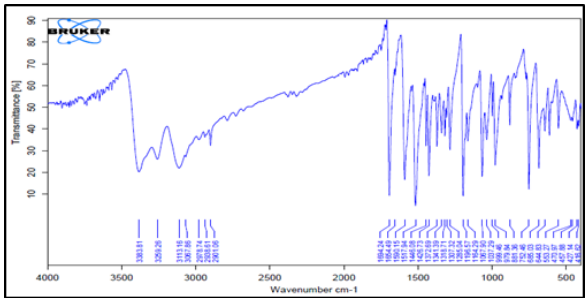


Figure 6: IR spectrum of A3

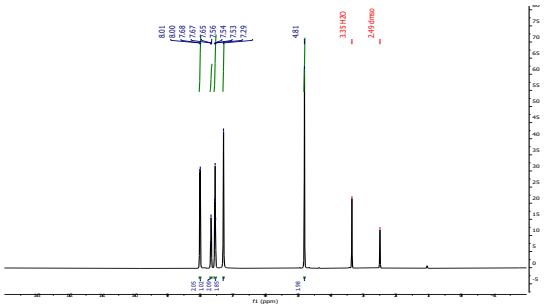


Figure 7: ^{1}H-NMR spectrum of A3

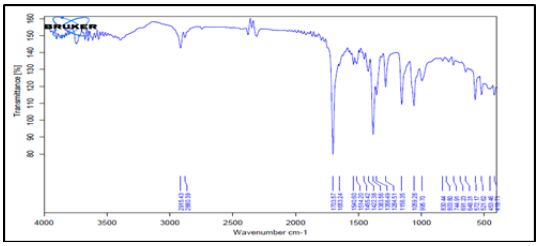


Figure 8: IR spectrum of A4

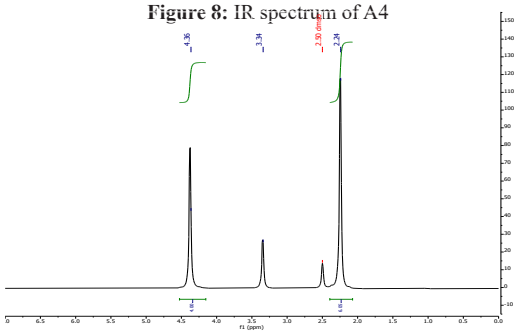


Figure 9: ^{1}H-NMR spectrum of A4

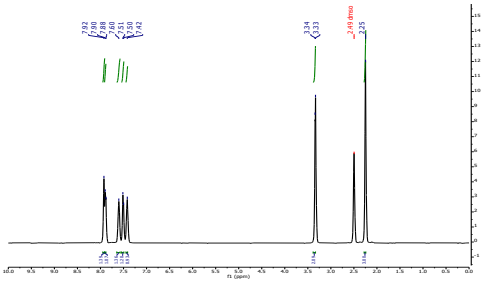


Figure 10: ^{1}H-NMR spectrum of A5

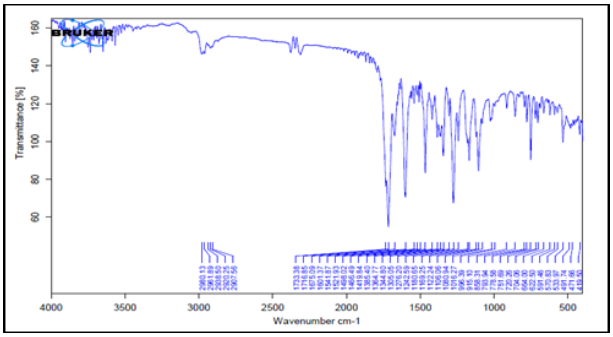


Figure11: IR spectrum of A7

mole) with (0.165, 0.001 mole) of ethyl-4-amino benzoate.The physical properties are registered in Table 1. Then compound [A7][16] was synthesis by mix (0.965 g, 0.001 mole) of compound [A6] with (0.138 g,0.001 mole) potassium carbonate in 25 mL dry acetone. Then (0.4 mL, 0.005 mole) of chloro acetone. The reactant mixture was heated under reflux for 30 hours. TLC determines the end time of the reaction. The orange precipitate formed after cooling, filtered, dried, and recrystallized from ethanol. Physical properties are listed in Table 1.

Spectral Characterization of [A7]

IR (KBr), υ(cm^{-1}): 1733 (C=O of ester), 1716 (C=O of ketone), 1675 (C=O of amide). (Figure 11), ^{1}H NMR (500 MHz, dmso) data in ppm δ: 8.07- 6.81 (m, 8H, ArH),4.79(s, 2H, N-CH_2-C=O), 4.35- 4.31 (q, 2H, O-CH_2-CH_3), 2.27 (s, 3H, CH_3-C=O), 1.35- 1.33 (t, 3H, CH_2-CH_3).

Antioxidant Action

When the free radical production rate exceeds oxidative stress, a harmful process is produced that can damage cell structures, including fats, proteins, and DNA.[20] Therefore, defense mechanisms that dismantle and stabilize free radicals protect all creatures from any free radical attack. Antioxidants are compounds that prevent oxidative cell damage by neutralizing free radicals.[21] DPPH radical scavenging movement (RSA) assessment is used as a standard to examine the capacity of the antioxidant activity in many previous studies. It is a fast method to show the radical scavenging activity of the synthesized compounds. The free radical scavenging special effects of all the prepared compounds using the 2,2-diphenylpicrylhydrazyl (DPPH) radical were calculated with various concentrations (1000, 500,250) ppm. The solvent was methanol: Dimethyl sulfoxide (DMSO) (50:50), mixed with of a freshly prepared (0.004 gm) DPPH methanol: DMSO solution. The reaction solution was kept in the dark at 25°C. The absorbance was recorded with a spectrophotometer UV at 517 nm. Ascorbic acid was used as a positive control. Radical scavenging activity was expressed as the inhibition percentage of free radicals by the sample and was calculated using the following formula:

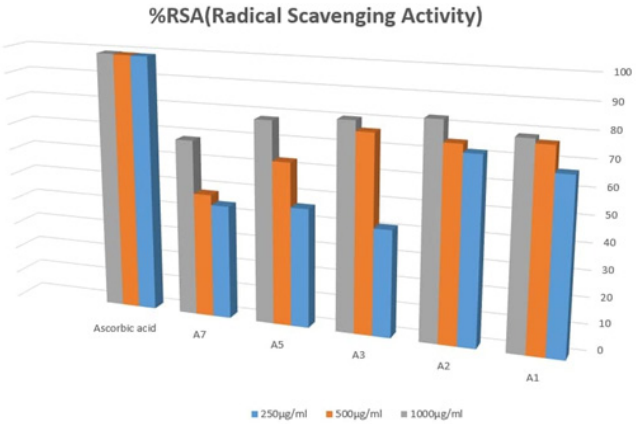
$$\text{DPPH radical scavenging activity (\%)} = \frac{Abs\ control - Abs\ sample}{Abs\ control} \times 100$$

Where

Abs Control = absorbance of DPPH radical + methanol : DMSO (50:50)

Table 2: Antioxidant activity of compound by DPPH

Compound	Scavenging Effect(%)		
	250 µg/mL	500 µg/mL	1000 µg/mL
A1	66.8	76.5	78.2
A2	71.4	74.5	82.6
A3	41.09	76.2	80.1
A5	45.9	62.8	77.9
A7	43.9	47.7	68.05
Ascorbic acid	98.6	98.7	98.9



Figuge 12: Antioxidant activity of compound by DPPH using ascorbic acid

Abs Sample = absorbance of DPPH radical + sample [test sample / standard]

RESULTS AND DISCUSSION.

Initially, compounds [A1, A2, A3] were obtained by the reaction of the (5-Amino-1,3,4-thiadiazole-2-thiol, 2- phenyl -1,3,4-oxadiazole -5-thiol,1,3-benzothiazole-2-thiol) with 2-bromoaceto phenone in the presence of sodium acetate trihydrate of catalys in ethanol. The FT-IR spectra of synthesized compounds illustrated by the appear) of significant bands at (1676, 1680, 1694) cm^{-1}, respectively of stretching vibration of C=O of ketone.disappears (2550–2570) cm^{-1} which refer to the vibration of (SH) group, on the other side the ^{1}H-NMR spectrum of compounds [A1, A2, A3] illustrated signals at (5.19, 5.18, 4.81) ppm of two proton refer to (S-CH_2). The ^{13}C-NMR spectrum showed important signals at ppm for (C=O) ketone groups.

The compounds [A4-A5] have been synthesized by heating (1,3,4-thiadiazole -2,5-dithiol, 4- hydroxy coumarin) with chloroacetone in 20 mL of ethanol. The FT-IR spectrum of compound [A4-A5] shows the appearance of an absorption band at (2915-2880, 2927-2958) cm^{-1} (C-H aliphatic),

(1703,1747)cm-1 (stretching C=O of ketone), and disappears band of SH compound [A4]and band indicated to stretching of OH in the 4-hydroxy coumarin.[22]

The compound [A7] showed absorption bands new at 1716 cm^{-1} (C=O of ketone), and disappears band of NH at 3179 cm^{-1}.^{1}H-NMR spectrum illustrated signals at 4.79 (s, 2H, N-CH_2-C=O).

The free radical scavenging activity of the compound was carrid out in the presence of the stable free radical DPPH using ascorbic acid (Figure 12).

CONCLUSION

The producing compounds have been identified by infrared radiation (IR), proton nuclear magnetic resonance (^{1}H-NMR), carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy, and the quantities of various physical properties (melting point, crystal shape, and color). The synthesized derivatives were examined for their antioxidant activities.

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