Pak. j. sci. ind. res. Ser. A: phys. sci. 2018 **61A**(2) 66-73

Synthesis, Characterisation and Antimicrobial Evaluation of Some New Heterocyclic Compounds Using Citric Acid as a Synthon

Moayed Salim Al-Gwady, Salim Jasim Mohammed* and Attalla Mohammed Sheat
Department of Chemistry, College of Science, University of Mosul, Iraq

(received October 19, 2017; revised April 16, 2018; accepted April 23, 2018)

Abstract. In this paper several substituted 1,3,4-oxadiazoles, 1,2,4-traizoles and 1,3,4-thaiadiazoles were synthesised by Pechmann condensation from citric acid *via* reaction of α-naphthol with citric acid that gave an intermediate 2-(3-oxo-3H-benzo[f]chromen-1-yl) acetohydrazide. The structure of the new compounds were established on the basis of physical and spectral data. These compounds were tested for biological activities as antibacterial and antifungal agents and some of them showed a significance to moderate activity.

Keywords: citric acid, chromens, triazoles, oxadiazoles, thiadiazoles, biological activity

Introduction

Substituted chromens were synthesised owing to their biological activities as antibacterial, anticoagulant, vasodilatory and hypothermal (Khodairy *et al*., 2001; El-saghier *et al*., 1983; Okumur *et al*., 1962). Also substituted 1, 3, 4-oxadiazoles, 1, 2, 4-triazoles and 1, 3, 4-thaiadiazoles are well known to possess biological activities, and have important uses in the agricultural, medical and industrial applications. Some substituted 1, 3, 4-oxadiazoles possess various biological activities as antibacterial agent(Arvind *et al*., 2011), antifungal and anti-inflammatory agents (Nargunf *et al*., 1994; Dutta *et al*.,1986), while substituted 1,3,4-thiadiazoles show wide range of biological activities such as antifungal and antiviral (Vashi *et al*., 1996), antibacterial and antimicrobial (Mohan *et al*., 2005; 2000; Srivastava *et al*., 2000). The substituted 1,2,4-triazoles and their derivatives have attracted global interest because of their pharmacological and therapeutic properties such as have moderate antimicrobial activity (Mani *et al*., 2015), antifungal (Reginaldo *et al*., 2012), antitubercular activity (Dinesh *et al*., 2015), and some of triazoles exhibited potent inhibition against AChE and BChE (Gaochan *et al*., 2018).

It was found that the 1, 3, 4-oxadiazoles, 1, 2, 4-triazoles and 1, 3, 4-thaiadiazoles are typically formed by forming suitable esters which were converted to the corresponding acid hydrazides by their reaction with hydrazine hydrate in ethanol. Acid hydrazide is served as key intermediate for the synthesis of the target heterocyclic compounds where the interest of many researchers is in organic chemistry. Several procedures were reported for the synthesis of substituted 1,3,4-oxadiazoles, 1,2,4-triazoles and 1,3,4-thaiadiazoles and review of some chemical research by Kuldipsinh *et al*. (2017); Almasirad *et al*. (2011); Jitendra *et al*. (2010) and Mihaela *et al*. (2009).

Author for correspondence:
E-mail: dr_salimjasim@yahoo.com

Materials and Methods

Melting point were determined in open capillary type on Stuart melting point SMP30. The FTIR spectra were recorded on FTIR-600 Bio Tec. Engineering Management Co. Ltd. (UK) using KBr disk. Nuclear Magnetic Resonance (^{13}C & ^{1}H-NMR) spectra were recorded on Bruker DMX-500 NMR Spectrophotometer (300MHz); with TMS as internal standard, and DMSO-d_6 as solvents. UV spectra were recorded on Shimadzu UV/Vis using chloroform as a solvent.

2-(3-Oxo-3H-benzo[f]chromen-1-yl) acetic acid 1. (Manvar *et al*., 2008). A mixture of citric acid (l mol) and concentrated sulphuric acid (30 mL) was stirred for half an hour. Then the temperature was slowly raised during an interval of 15 min, soon the evolution of gas was reduced. Removed the flask from the bath, leave it aside until the reaction mixture became clear and free from carbon monoxide bubbles. Then cooled to (10 °C) in crushed ice. Then, α-naphthol (1 mol) was added drop wise and the reaction mixture was stirred at room temperature for about 48 h. The reaction mixture was then poured onto crushed ice, the solid precipitate was filtered off and dissolved in saturated sodium bicarbonate solution which on acidication and then recrystallization

from ethanol gave the title compound as a brown powder (Yield: 60%; m.p. 201-203 °C).

Methyl 2-(3-oxo-3H-benzo[f]chromen-1-yl) acetate 2. (Manvar *et al*., 2008). The 2-(3-oxo-3H-benzo[f] chromen-1-yl) acetic acid **1** (1 mol) was dissolved in methanol (30 mL), and a few drops of sulphuric acid were added. The reaction mixture was refluxed for 3 h. After completion of the reaction, the solvent was evaporated and the resulting reaction mixture was extracted with ethyl acetate, washed with sodium bicarbonate and the solvent was removed in vacuum to give the compound **2** as a brown powder (Yield: 67%; m.p.: 112-114 °C).

2-(3-Oxo-3H-benzo[f]chromen-1yl)acetohydrazide 3. (Manvar *et al*., 2008). A mixture of (0.1 mol) ester **2**, 86% hydrazine hydrate (10 mL) and methanol (40 mL) was refluxed with continuous stirring for about 3 h. After completion of the reaction, the reaction mixture was poured onto crushed ice, the separated solid product was filtered off, recrystallized from ethanol which furnished 2-(3-oxo-3H-benzo[f]chromen-1-yl) acetohydrazide **3** as a pale brown powder (Yield: 92%:m.p.: 119-120 °C).

1-((5-Mercapto-1,3,4-oxadiazol-2-yl)methyl)-3H-benzo[f]chromen-3-one 4. (Selvakumar *et al*., 2011) Hydrazide **3** (0.05 mol) was dissolved in potassium hydroxide solution (0.56 g/100 mL ethanol). To this solution carbon disulphide (6 mL, 0.1 mol) was added with shaking. The reaction mixture was refluxed for 24 h until the liberation of hydrogen sulphide was ceased. The solvent was evaporated under reduced pressure and the residue was poured into crushed ice; and acidified with dilute hydrochloride acid. The precipitate was filtered off and recrystallized from methanol which gave the compound **4** as a pale yellow powder (Yield: 42%; m.p. :132-134 °C).

Potassium2-(2-(3-oxo-3H-benzo[f]chromen-1-yl) acetyl)hydrazine-1-carbodithioate 5. (Yadav *et al*., 2016). Acid hydrazide **3** (0.05 mol) was dissolved in potassium hydroxide solution (0.56 g/100 mL ethanol). To this solution carbon disulphide (6 mL, 0.1 mol) was added with shaking, then continuously stirred for 24 h. The solvent was evaporated under reduced pressure and the residue was poured into crushed ice; and acidified with dilute hydrochloride acid. The precipitate was filtered off and recrystallized from methanol which gave the compound **5** as a pale yellow powder (Yield: 42%; m.p.: 132-134 °C).

1-((4-Amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)-3H-benzo[f]chromen-3-one 6. *Method-I*. (Almasirad *et al*., 2007). To a suspension of compound **4** (0.14 mol) in ethanol (5 mL), hydrazine hydrate (0.28 mL) was added. The reaction mixture was refluxed for 24 h. After completion of the reaction, the reaction mixture was cooled and acidified with cold aqueous (3N) hydrochloric acid. The mixture was extracted with ether and the organic layer was washed with cold water dried over anhyd. sodium sulphate, filtered off, and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol which furnished the compound **6** as a brown powder (Yield: 55%; m.p. :240-242 °C).

***Method-II*.** (Yusra *et al*., 2015). A suspension of salt **5** (0.01 mol), hydrazine hydrate (0.02 mol) and water (50 mL) were refluxed for 6 h. The colour of the reaction mixture changed to green. The reaction mixture was cooled to room temperature: a brown solid was precipitated out by adding cold water (50 mL) followed by acidification with concentrated HCl. The precipitate was filtered off: washed with cold water, recrystallized from ethanol which furnished the desired compound **6** as a brown powder (Yield: 48%; m.p. :240-242 °C).

Preparation of 1-((5-amino-1,3,4-thiadiazol-2-yl) methyl)-3H-benzo[f]chromen-3-one 7. (Harika and Sudha, 2014). Thiosemicarbazide (0.025 mol) was suspended in a 1,4-dioxane (25 mL) and stirrers with the addition of 2-(3-oxo-3H-benzo[f]chromen-1-yl)acetic acid **1** (0.03 mol). The poly phosphoric acid was added at 0-5 °C. The reaction mixture was heated at 80-85 °C for about 6 h and then, left to room temperature. The solvent was evaporated; poured into crushed ice (50 mL) with vigorous stirring. Then, the reaction mixture was basified to pH-9 by the addition of 40% NaOH solution. The precipitate was filtered off: washed with cold water to remove all coloured impurities which gave the compound **7** as a pale yellow colour (Yield: 94%; m.p.:167-169 °C).

1-((5-((Substitutedbenzylidene)amino)-1,3,4-thiadiazol-2-yl)methyl)-3H-benzo[f]chromen-3-one8a-f. (Harika and Sudha, 2014): To (0.1 mol) of compound **7** in ethanol (25 mL), added benzaldehyde or substituted benzaldehyde (0.5 mol) and acetic anhydride (0.5 mL). The reaction mixture was refluxed for 10 h. The reaction mixture was cooled and poured with stirring onto crushed ice contained in a 500 mL beaker. The solid product was filtered off and dried,

recrystallized from suitable solvent to give the compounds **8a-f**. The physical and spectral data are listed in Tables 1 and 4, respectively.

2-((5-((3-Oxo-3H-benzo[f]chromen-1-yl)methyl)-1,3,4-thiadiazol-2-yl)imino)indolin-3-one 8 g. To a solution of compound **7** (0.1 mol) in ethanol (25 mL), added isatine (0.5 mol) and acetic anhydride (0.5 mL). The reaction mixture was refluxed for 12 h. After completion of the reaction, the reaction was cooled, poured with stirring onto crushed ice contained in a (500 mL) beaker. The solid product was filtered, dried and recrystallized from ethanol to give the compound **8g** as a pale yellow (Yield: 72%); m.p.: 160-162 °C).

Results and Discussion

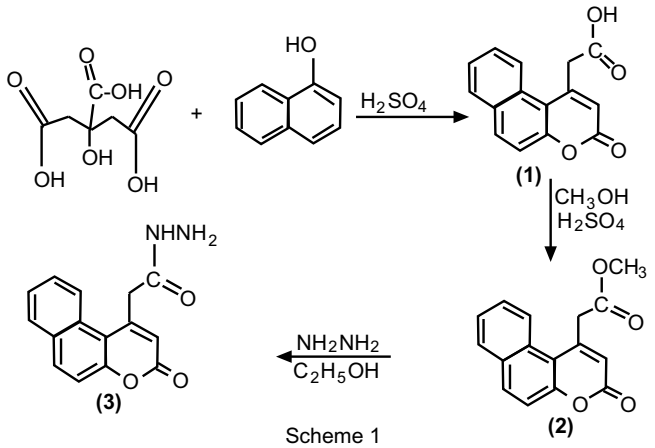
The synthesis of many heterocyclic system containing substituted 1,3,4-oxadiazoles,1,2,4-triazoles, 1,3,4-thaiadiazoles and 1,2,4-triazoles ring were achieved from reaction of citric acid with α-naphthol to give 2-(3-oxo-3H-benzo[f]chromen-1-yl) acetic acid **1** which on treatment with methanol, in the presence of few drops of sulphuric acid give ester **2** which were converted to the corresponding acid hydrazides **3** by their reaction with hydrazine hydrate in ethanol. The synthetic procedures adopted are illustrated in Scheme 1.

The IR spectra for compounds **1-3** showed characteristic absorption peak in the range of (1645-1692 cm^{-1}) stretching for (C=O), at (1714-1726 cm^{-1}) stretching group due to (C=O) group of lactones' ring. The ^{1}H-NMR spectrum for compounds (**1-3**) showed significant peaks as the following singlet in the range (2.79-2.95 ppm) for (CH_2) group, (6.32-6.45 ppm) due to (CH) group in the ring, also the aromatic part showed multiplet peaks in the range (7.18-8.22ppm). While ^{13}C-NMR spectra showed peaks for the carbon signal appeared at δ values as shown in Table 2. The UV spectra showed absorption peaks at λ_{max} in the range (309-398 nm), (242-276 nm) due to ($n \rightarrow \pi^*$) and ($\pi > \pi^*$) electronic transitions, respectively.

Oxadiazole **4** was obtained by the reaction of acid hydrazide (Almasirad *et al*., 2011) with carbon disulphide in alkaline medium under reflux conditions. The mechanism of the reaction was accomplished by nucleophilic attack of nitrogen of hydrazide at the carbon atom of carbon disulphide to form the salts which undergoes intra nucleophilic attack of the oxygen of the carbonyl group on the carbon of C=S group followed by elimination of hydrogen sulphide to afford 1-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-3H-benzo[f]chromen-3-one **4** (Ajllo *et al*., 1972). While the same reaction under the stirring at room temperature gave different potassium 2-(2-(3-oxo-3H-benzo[f]chromen-yl)acetyl) hydrazine-1-carbodithioate **5**, which were converted to triazole **6** by reacting with hydrazine hydrate. Traizole **6** was obtained. Also, given by reaction of oxadiazole **4** with hydrazine hydrate as shown in Scheme 2.

Table 1. Physical data for compounds **8a-f**

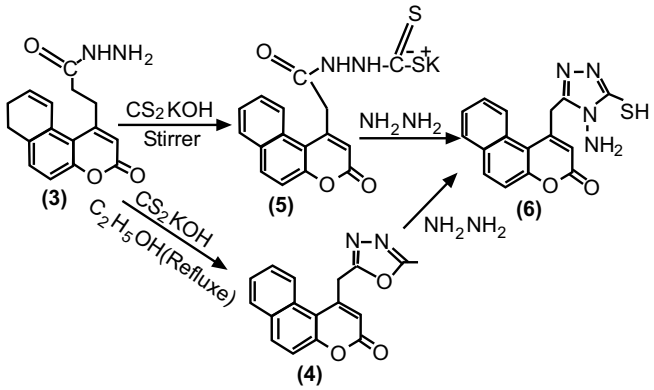
Comp. no.	R	M.P. (°C)	Yield (%)	Colour	Cryst. solvent
a	H	185-187	39	Yellow	Ethanol
b	2-OH	153-155	42	Brown	Methanol
c	4-CH_3	186-188	49	Brown	Ethanol
d	4-OCH_3	197-199	60	Pale yellow	Acetone
e	2-CO_2H	181-183	55	Brown	Methanol
f	CH=CH	184-186	35	Yellow	Ethanol



Scheme 1

The IR spectra for compounds **4-6** showed characteristic absorption peak in the range of (1646-1658 cm^{-1}) stretching for (C=N), at (2332-2336 cm^{-1}) due to (SH) group and at (1709-1718 cm^{-1}) stretching group for (C=O) group of lactones' ring. The ^{1}H-NMR spectrum for compounds **4-6** showed significant peaks as the following singlet in the range (2.68-3.24 ppm) due to (CH_2) group,(6,25-6.39 ppm) to (CH) group in the ring, while the aromatic part showed multiplet in the range (7.14-8.29 ppm), also the protons of (SH) group were appeared in the range (13.35-12.93 ppm). ^{13}C-NMR spectra showed peaks for the carbon signal appeared at δ values as shown in Table 2-3. The UV spectra showed absorption peaks at λ_{max} (374-386 nm), (228-248 nm) for ($n \rightarrow \pi^*$) and ($\pi \rightarrow \pi^*$) electronic transitions, respectively.

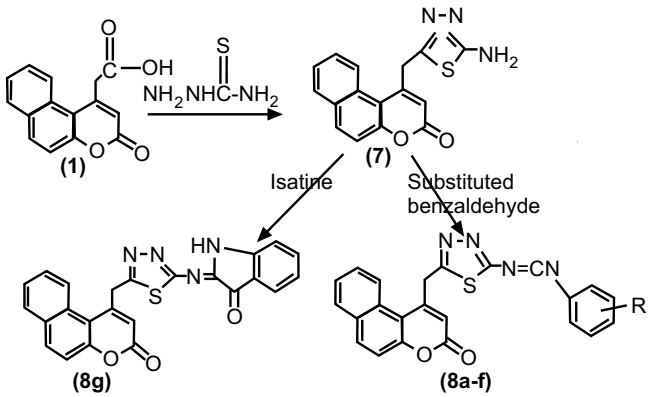
Newly synthesised compounds **8a-f** were characterised by the physical properties shown in Table 1. The synthetic strategy for the synthesis of imines **8a-g** has been described in the Scheme 3, involves reaction of acid hydrazide **1** with thiosemicarbazide to give first on a product it is 1-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-3H-benzo[f]chromen-3-one **7**, which is considered as starting material for the synthesis of imines **8a-f** and **8g** by its reaction with substituted aldehydes or isatin as shown in Scheme 3. Thus treatment of thaidiazole **7** with substituted benzaldehyde and isatin gave the compounds **8a-f** and **8g**, respectively.



Scheme 2

Table 2. Spectral data for compounds (**1-3**)

Comp. no.	U.V. $CHCl_3$ λ_{max} nm ($\pi \rightarrow \pi^*$) $n \rightarrow \pi^*$	FTIR (KBr) γcm^{-1} C=O lactone ring	C=O	Other	^{1}H-NMR δ (ppm) DMSO-d_6	^{13}C-NMR (δ, ppm) DMSO-d_6
1.	(266) 377	1724	1692	3345 OH-	2.95(bs,2H,CH_2), 6.42(s,1H, HC), 7.24-8.22(m,6H,ArH), 12.31(s,1H,OH)	37.2,112.6,115.8,116.8,122.612,6.4, 126.9,128.5,128.8,130.2,13,1.9155.7, 160.9,171.3
2.	(276) 398	1726	1685	-	3.65(s,3H,CH_3), 2.85(bs,2H,CH_2), 6.35(s,1H, HC), 7.18-8.17(m,6H,ArH),	34.9,51.8,115.7,116,6,122.4,12,3.5, 126.9,128.4,128.8,130.2,13,2.1, 150.6,161.1,168.3
3.	(242) 309	1714	1645	3228, NH 3365,NH_2	2.79 (bs,2H,CH_2), 6.32(s,1H, HC),7.36-8.18 (m,6H,ArH),9.14(s,1H,NH), 4.28(d,2H,NH_2)	45.7,112.7,115.6,116.4,122.5,126.7, 128.3,128.8,130.2,131.9,151.2,144.1, 161.1,170,4



Scheme 3

The IR spectra for compound **7** showed the following frequencies: 3100-3300 cm^{-1} and 1560-1590 cm^{-1} due to NH stretching and bending respectively, 1595-1600 cm^{-1} for C=N stretching and 1723 cm^{-1} due to (C=O) group of lactones' ring, also ^{1}H-NMR spectrum for this compound distinguish the appearance characteristic absorption peak in as the following singlet in 3.24 ppm due to (CH_2) group,at 6.37 ppm for (CH) and doublet at 6.91 ppm due to (NH_2) group, while the aromatic part showed multiplet in the range (7.34-8.19 ppm). The ^{13}C-NMR spectrum showed peaks for the carbon signal appeared at δ values as shown in the following signal: 45.19, 115.8, 116, 4, 122.2, 123.8, 126.3, 128.1, 128.7, 130.4, 131.4, 150.4, 155.3, 161.21, 168.3, 169.8.

The IR spectra for imine compounds **8a-g** showed characteristic absorption peak in the range of (1588-1638 cm^{-1}) stretching for (C=N), at (1695-1722 cm^{-1}) stretching group for (C=O) group of lactones' ring. The ^{1}H-NMR spectra for compounds **8a-g** showed signi-ficant peaks as the following singlet in the range (2.71-3.25 ppm) for (CH_2) group, (6,22-6.39 ppm) due to (CH) group in the ring, also at the range (8.71-9.1 ppm) as singlet peak due to (CH=N) group. Which are characterised by the compounds **8a-f**, while aromatic parts showed two types where multiple peaks were found at range (7.49-7.83 ppm). Return to the aromatic part which represents substituted aldehydes while the other aromatic part showed multiplet in the range (7.12-8.21 ppm) due to protons of chromens

Table 3. Spectral data for compounds (**4-6**)

Comp. no.	U.V. $CHCl_3$ λ_{max} nm ($\pi \rightarrow \pi^*$) $n \rightarrow \pi^*$	FTIR (KBr) γcm^{-1} C=O lactone ring	SH	C=N	^{1}H-NMR δ (ppm) DMSO-d_6	^{13}C-NMR (δ, ppm) DMSO-d_6
4.	(228) 374	1718	2336	1646	3.24(bs,2H,CH_2), 6.25(s,1H, HC),7.34-8.09 (m,6H,ArH),13.35(s,1H,SH)	37.2,112.6,115.8,116.8,122.612,6.4, 126.9,128.5,128.8,130.2,13,1.9155.7, 160.9,171.3
5.	(248) 379	1709	-	-	2.68(bs,2H,CH_2), 6.39(s,1H, HC),7.14-8.21 11.05(s,1H,NH)	45.9,115.6,116,4,122.2,123.8,126.4, 128.1,128.7,130.4,131.8,150.4, (m,6H,ArH),7.71(s,1H,NH), 155.4,161.1,169.8,203.5.
6.	(236) 386	1712	2332	1658	3.19(bs,2H,CH_2),6.26 (s,1H, HC),7.33-8.14 (m,6H,ArH).4.8(d,2H,NH_2), 12.93(s,1H,SH).	34.2,112.5,115.4,116.1,122.4,126.3, 128.6,128.8,130.3,131.7,150.2, 154.1,160.1

ring. ^{13}C-NMR spectra showed good peaks for the carbon signal appeared at δ values as shown in Table 4.

Biological activity. All the synthesised compounds were screened for *in vitro* antibacterial and antifungal activity by adopting the disc diffusion method. For antibacterial studies the microorganisms employed were *Esherichia coli*, *Staphylococcus aureus*, *Micrococcus*, *Pseudomonas*, *Bacillus* 11 and *Bacillus* 12. While for antifungal, *Microsporum gypseum*, *Microsporum destortum* and *Trichophyton rubrum* were used as microorganisms. Both antimicrobial studies were

Table 4. Spectral data for compounds (**8a-g**)

Comp. no.	U.V. $CHCl_3$ λ_{max} nm ($\pi \rightarrow \pi^*$) $n \rightarrow \pi^*$	FTIR (KBr) γcm^{-1} C=O	C=N	ArCH	^{1}H-NMR δ (ppm) DMSO-d_6	^{13}C-NMR (δ, ppm) DMSO-d_6
a	(297) 359	1703	1611	3058	3.15(bs,2H,CH_2),6.32 (s,1H,HC),7.65-7.78 (m,4H,ArH),7.26-8.12 (m,6H,ArH),9.07 (s,1H,CH=N)	36.8,112.4,115.8,116.8,122.7,126.2, 126.9,128.5,128.4,130.5,131.9,155.7, 160.9,160.5,161.3,167.9,168.5
b	(301) 369	1711	1633	3054	2.85(bs,2H,CH_2),6.35 (s,1H,HC),7.62-7.73 (m,4H,ArH),7.12-8.20 (m,6H,ArH),9.1 (s,1H,CH=N),11.2(s,1H,OH)	39.7,112.4,117,6,120.4,121.7,126.2, 128.1,128.8,131.3,132.2,150.3, 168.2,161.1,168.3
c	(287) 388	1695	1597	3062	2.45(s,3H,CH_3),2.75 (bs,2H,CH_2),6.37 (s,1H,HC),7.49-7.71 (m,4H,ArH),7.36-8.18 (m,6H,ArH),8,86(s,1H,CH=N)	45..4,112.7,115.6,116.4,122.5,126.7, 128.3,128.8,130.2,131.9,151.1, 160.3,160.7,161.4,168.2
d	(276) 391	1722	1608	3065	3.82(s,3H,OCH_3),2.71 (bs,2H,CH_2),6.31 (s,1H,HC),7.54-7.68 (m,4H,ArH),7.32-8.16 (m,6H,ArH),8,96(s,1H,CH=N)	39.5,55.7,112.1,114.5,115.6,116.7, 122.4,123.9,126.7,128.5128.7,130.2, 130.5,131.3,132.4,150.3,150.4, 160.5,160.9,162.4,168.4.
e	(304) 412	1705	1594	2073	3.23(bs,2H,CH_2),6.39 (s,1H,HC),7.61-7.77 (m,4H,ArH),7.23-8.19 (m,6H,ArH),8.99(s,1H,CH=N), 13.15(s,1H,OH)	39.2,112.8,115,6,116.2,120.6,121.7, 126.8,128.1,128.8,131.3,132.2,150.3, 155.8,168.2,161.1,167.3,168.2
f	(298) 365	1721	1638	3053	2.88(bs,2H,CH_2),6.25 (s,1H,HC),6.85(s,1H,=CH)6.93 (s1H,CH-triazole),7.24 (s,IH,-CH=)7.52-7.83 (m,4H,ArH),7.14-8.21 (m,6H,ArH),8.71(s,1H,CH=N)	41.1,113.4,117.1,118.9,122.3,126.8, 128.1,128.8,131.3,132.3,150.3,155.5, 68.2,160.7,167.6,168.2.,170.6
g	(258) 366	1698	1588	3059	3.25(bs,2H,CH_2),6.22 (s,1H, HC),6.92-7.74 (m,4H,ArH of isatin ring) 7.29-8.17(m,6H,ArH),10.75 (s1H,NH)	39.9,112.2.112.6,114.1,115.2,116.7, 122.4,123.6,124.2,126.3,128.4,128.8, 130.2,131.4,135.5,150.5,151.7,155.5, 156.4,160.7,168.3,187.4

assessed by a minimum inhibitory concentration. From the obtained data, it is evident that compounds **8a** and **8d** possess a very good activity against bacteria strains like *E. coli* and *Staphylococcus* and the compounds **8e**, **8f** and **8g** possess almost a significant activity against all fungi tested at 1 mg/mL and 2 mg/mL. The remaining compounds showed a moderate activity against other bacteria and fungi tested.

Conclusion

From the experiment it was concluded that the synthesis of 1,3,4-oxadiazoles, 1,2,4-triazoles and 1,3,4-thaiadiazoles were prepared on safe and simplicity with a good product yields, and some of them showed a good significance to moderate activity as antibacterial and antifungal agents.

Acknowledgement

We are grateful to Department of Chemistry, College of Science, Mosul University, for the facilities given to perform this work. Thanks are also due to Dr. Maha A. Al-Rejaboo, Department of Biology, College of Science, University of Mosul for the biological assays.

References

Ajllo, E., Migliara, O., Sprio, V. 1972. New syntheses of condensed heterocycles from isoxazole derivatives. III.*s*-Triazolo[4,3-*b*]pyridazine. *Journal of Heterocyclic Chemistry*, **9:** 1169-1170.

Almasirad, A., Shafiee, A., Abdollahi, M., Noeparast, A., Shahrokhinejad, N., Vousooghi, N., Tabatabai, S.A., Khorasani, R. 2011. Synthesis and analgesic activity of new 1,3,4-oxadiazoles and 1,2,4-triazoles. *Medicinal Chemistry Research*, **20:** 435-442.

Almasirad, A., Vousooghi, N., Tabatabai, S.A., Kebriaeezadeh, A., Shafiee, A. 2007. Synthesis anticonvulsant and muscle relaxant activities of substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole 1,2,4-triazole. *Acta Chimica Slovenica*, **54:** 317-327.

Arvind, K.S.,Vinay, K., Deepmala, Y. 2011. Biological activities of 2,5-disubstituted – 1, 3, 4-oxadiazoles. *International Journal of Pharmaceutical Science and Research*, **2:** 135-147.

Dinesh, R.G., Anand, A.J., Anil, M.S., Jighani, P.M. 2015. Synthesis and biological screening of 1, 2, 4-trizole derivatives. *Indian Journal of Chemistry*, **54B:** 556-564.

Dutta, M.M., Goswami, B.N., Kataky, J.C. 1986. Studies on biologically active heterocycles. Part-I, synthesis and antifungal activity of some new aroyl hydrazones and 2,5-disubstituted-1,3,4-oxadiazoles. *Journal of Heterocyclic Chemistry*, **23:** 793.

El-saghier, A.M.M., Al-afaleq, E.I., Mouli, R.B., Reddy, Y.D. 1983. Synthetic reactions of coumarin-3-(4-aminosulfonyl-carboanlide derivatives with active methylene compounds. *Indian Journal of Chemistry*, **2B:** 176.

Gaochan, W., Yun, G.D.K., Boshi, H., Zhipeng, H., Huiqing, L., Vasanthanathan, P., Peng, Z., Xinyong, L. 2018. Design, synthesis and biological evaluation of tacrine-1,2,3-triazole derivatives as potent cholinesterase inhibitors. *Chemical Communications*, **9:** 149-159.

Harika, M.S., Sudha, B.N. 2014. Synthesis & characterization of N-thiadiazolyl thiazolidinone derivatives. *International Journal of Research in Pharmaceutical Sciences*, **4:** 13-16.

Jitendra, K.G., Rakesh, Y., Rupesh, D., Pramod, K.S. 2010. Recent advancements in the synthesis and pharmacological evaluation of substituted 1, 3, 4-thiadiazole derivatives. *International Journal of PharmTech Research*, **2:** 1493-1507.

Khodairy, A. 2001. Synthesis of some new heterocyclic compounds from benzopyrano [2,3-c]pyrazol-3-one derivatives. *Synthetic Communications*, **31:** 2697-2712.

Kuldipsinh, P.B., Kuntal, S.M., Manjunath, D.G. 2017. Design, synthesis and antimicrobial activities of some novel 1,3,4-thiadiazole, 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole. *Journal of Saudi Chemical Society*, **21:** 535-543.

Laskowski, S.C., Clinton, R.O. 1950. Coumarins. II. Derivatives of coumarin-3- and -4- acetic acids. *Journal of American Chemical Society*, **72:** 3987-3991.

Mani, P., Mahesh, P., Praveen, C., Murthy, Y.L.N. 2015. Synthesis of novel 1,2,4-triazoles and their evaluation of 5-LOX inhibition and antimicrobial activity. *Der Pharma Chemica*, **7:** 116-120.

Manvar, A., Malde, A., Verma, J., Vijay, V., Arun, M., Kuldip, U., Hrishikesh, A., Evans, C., Anamik, S. 2008. Synthesis, anti-tubercular activity and 3D-QSAR study of coumarin- 4-acetic acid benzylidene hydrazides. *European Journal of Medicinal Chemistry*, **43:** 2395-2403.

Mihaela, M., Valeriu, S., Lenuta, P., Marcel, P., Jacques, D., Ristian, P. 2009. Synthesis and biological activity

of some new 1,3,4-thiadiazole and 1,2,4-triazole compounds containing a phenylalanine moiety. *Molecules*, **14:** 2621-2631.

Mohan, J., Anupama, R. 2005. Condensed bridgehead nitrogen heterocyclic systems: Synthesis and bio-activity of imidazo[2,1-b]-1,3,4-thiadiazol [(2,3-c]-s-triazoles and s-triazolo[3,4-b]-1,3,4- thiadiazol [(3,2-b]-imidazo[4,5-b]quinoxaline. *Indian Journal of Heterocyclic Chemistry*, **15:** 77-78.

Mohan, J., Anupama, R. 2000. Condensed bridgehead nitrogen heterocyclic systems: synthesis and bioactivity of s-triazolo [3,4-b] [1,3,4] thiadiazoles, s-triazolo [3,4-b] [1,3,4] thiadiazines and s-triazolo [3′,4′: 2,3]-thiadiazino [5,6-b] quinoxaline. *Indian Journal of Heterocyclic Chemistry*, **10:** 1-4.

Nargunf, L.V., Reddy, G.R., Harriprasad. 1994. Inflammatory activity of substituted 1,3,4-oxadiazoles. *Journal of Pharmaceutical Sciences*, **83:** 246-248.

Okumura, K., Ashino, K., Okuda, T. 1962. Synthesis and antibacterial activity of some new fused chromenes. *Yakugaku Zasshi*, **81:** 1482.

Reginaldo, G., Lima-Neto, I., Nery, N.M., Cavalcante, Rajendra, M., Srivastava, Francisco, J.B., Mendonça Junior, Almir, G., Wanderley, Rejane, P., Neves, Janaína, V.dos, Anjos. 2012. Synthesis of 1,2,3-triazole derivatives and *in-vitro* antifungal evaluation on candida strains. *Molecules*, **17:** 5882-5889.

Selvakumar, K., Anandarajagopal, K., Rajamanickam, V., Ajaykumar, T.V, Jesindha, B. 2011. 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thione derivatives: synthesis, characterization and antimicrobial evaluation. *International Journal of Pharmaceutical Science Review and Research*, **6:** 64-67.

Srivastava, S.D., Guru, N. 2000. Synthesis and antimicrobial activities of some new pyrazolothiadizoles and their azetidinones. *Journal of Indian Chemical Society*, **77:** 400.

Vashi, B.S., Mehta, D.S., Shah, V.H. 1999. Synthesis of 2,5-disubstituted-1,3,4-oxadiazole,1,3,4-thiadiazole derivatives potential antimicrobial agents. *Indian Journal of Chemistry*, **35B:** 111-115.

Yadav, D., Bodke, S., Biradar, A., Kenchappa, R. 2016. Synthesis, characterization and biological evaluation of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole and 3,6-diphenyl[1,2,4]triazole[3,4] [1,3,4]thiadiazole derivatives. *Indian Journal of Advances in Chemical Science*, **4:** 269-275.

Yusra, H., Alaraji, Jawad, K., Shneine, Ahmad, N., Ahmed, A.A. 2015. Synthesis, characterization, and antibacterial activity of new Schiff's basses with 1,2,4-triazole moiety. *Journal of Science*, **5:** 293-299.