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Synthesis and antimicrobial study of new tetrazole, benzimidazole and N3-functionalized quinazolinone derivatives

Dina G. Sanad^{*,a}, Ahmed S.A. Youssef^b, Fatma A. El-Mariah^a and Heba E. Hashem^a

^aChemistry Department, Faculty of Women for Arts, Science and Education, Ain Shams University, Heliopolis, Cairo 11757, Egypt.

^bChemistry Department, Faculty of Science, Ain Shams University, Abasia, Cairo 11566, Egypt

Abstract:

Reactions of 4H-3,1-benzoxazin-4-one **3** with various nitrogen nucleophiles; sodium azide, hydroxylamine hydrochloride, ammonium acetate, and formamide afforded new N-heterocyclic compounds **4-7**. The synthesized quinazolinone derivative **7** was used as a useful building block for further synthesis of new series of N3-functionalized quinazolinone compounds **8-12**. The chemical structures of all synthesized heterocyclic compounds were deduced from their spectroscopic analyses. The antimicrobial activity of the new compounds was evaluated against several pathogenic microorganisms, and most of them showed remarkable activity comparable to the antibacterial Ciprofloxacin and antifungal Clotrimazole.

Keywords: Benzoxazinone, Quinazolinone, Benzimidazole, Tetrazole, Antimicrobial activity.

1. Introduction

Quinazolinone keleton is frequently encountered as a building block for hundreds of naturally occurring alkaloids [1,2]. Synthesis of quinazolinone heterocycles has broad importance in organic synthesis according to their extensive importance in medicinal chemistry because of their diverse pharmacological activities including antibacterial [3,4,46], antimalarial [5], antifungal [6-8,47], antihypertensive [9,10], antihistaminic [11], a local anesthetic [12], anti- Parkinson [13], cardiotoxic [14], anticancer [15-21], antiviral [22,23] and thymidylate synthase inhibitory activities [24]. Several simple and condensed quinazolines are also known to exhibit potent CNS activities as an analgesic [25], anti-inflammatory [26-28] and anti-

***Corresponding author:** Dina G. Sanad, Chemistry Department, Faculty of Women for Arts, Science and Education, Ain Shams University, Heliopolis, Cairo 11757, Egypt.

E-mail: dina.gamel@women.asu.edu.eg

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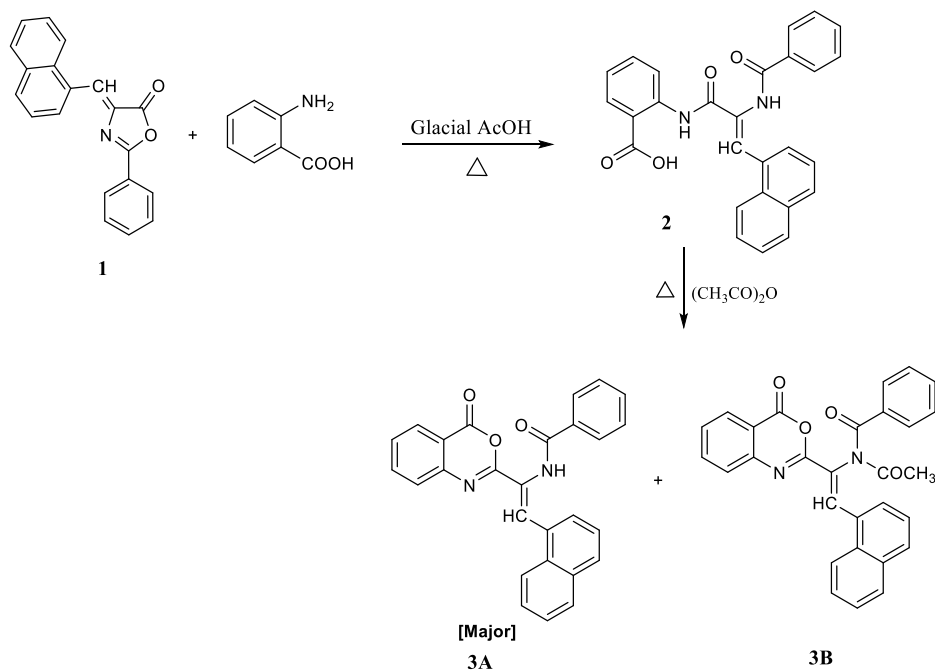
convulsant activities [29,30]. On the other hand, 4H-3,1-benzoxazinone is one of the most famous useful heterocyclic compounds. Antiphlogistic medicines are made from benzoxazinone compounds, and another molecule of this class is anthalexine, which is used as an antifungal and antibacterial agent. They are employed in a variety of industrial, research, and clinical purposes, just like other heterocyclic compounds [31-34,45].

One of the most important features of 4H-3,1-benzoxazinone compounds are their use as key starting compounds for the synthesis of different heterocyclic compounds. Based on this view, the present study aims to use benzoxazinone bearing naphthyl moiety for the synthesis of new N-3 functionalized quinazolinone compounds with anticipated biological activity.

2. Discussion:

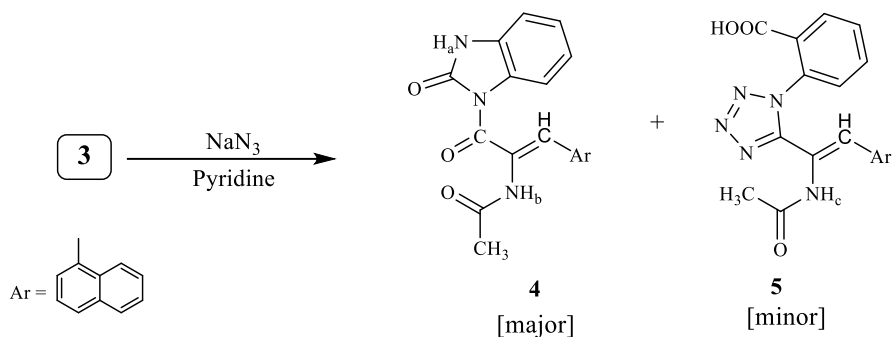
2.1. Chemistry:

Benzoxazine-4-one derivative **3** was prepared from the reaction of oxazol-5(4H)-one derivative **1** with anthranilic acid in boiling glacial acetic acid followed by refluxing in distilled acetic anhydride (Scheme 1). The IR spectrum of compound **3** showed a strong absorption band at 1764 cm^{-1} for C=O lactone. Further support for the assigned structure of benzoxazinone **3** was gained from its ^1H NMR spectrum which exhibited one broad singlet signal in the downfield region correlated with NH proton and one singlet signal in the up-field region for CH_3 protons. This is in accordance with its existence as a mixture of 3A and the N-acetylated by-product 3B in the ratio of 71:29 (Scheme 1). On the other hand, ^{13}C NMR spectrum showed a signal at $\delta\ 29.40$ ppm referring to the presence of CH_3 group, and other signals at $\delta\ 157.83$, 171.18 and 181.43 ppm for C=O groups.



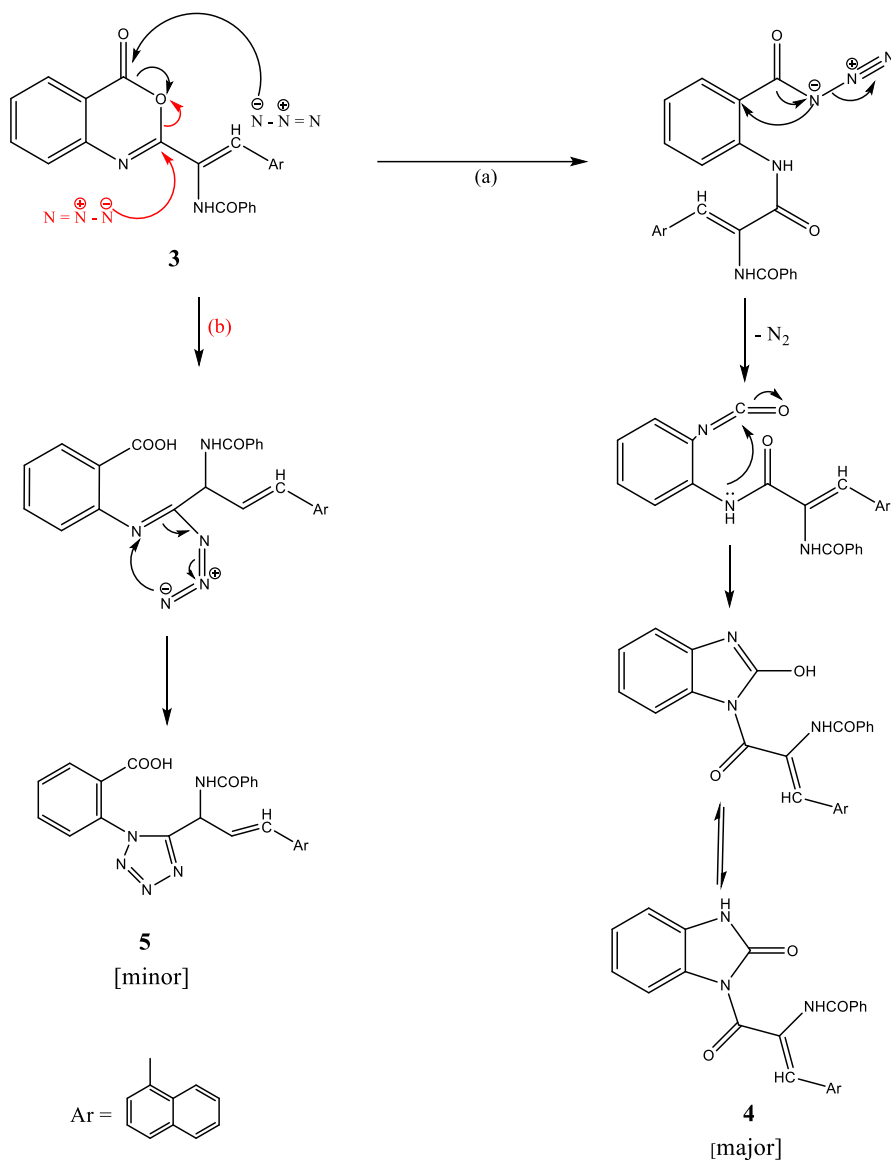
Scheme 1: Synthesis of 4H-3,1-benzoxazin-4-one **3**

Treatment of benzoxazinone derivative **3** with sodium azide in dry pyridine yielded a mixture of two compounds that was separated by fractional crystallization into benzimidazole **4** (major) and tetrazole **5** (minor) (Scheme 2) [35]. The structures of compounds **4** and **5** are substantiated from their spectral data. Their infrared spectra show absorption bands characteristic for OH, NH, C=O and C=N groups; further support for the suggested structures of compounds **4** and **5** is gained from the ^1H NMR spectrum which exhibited a broad singlet signal for OH proton at δ 13.72 ppm and three broad singlet signals at δ 9.74, 10.21 and 12.06 ppm for NH protons (cf. experimental).



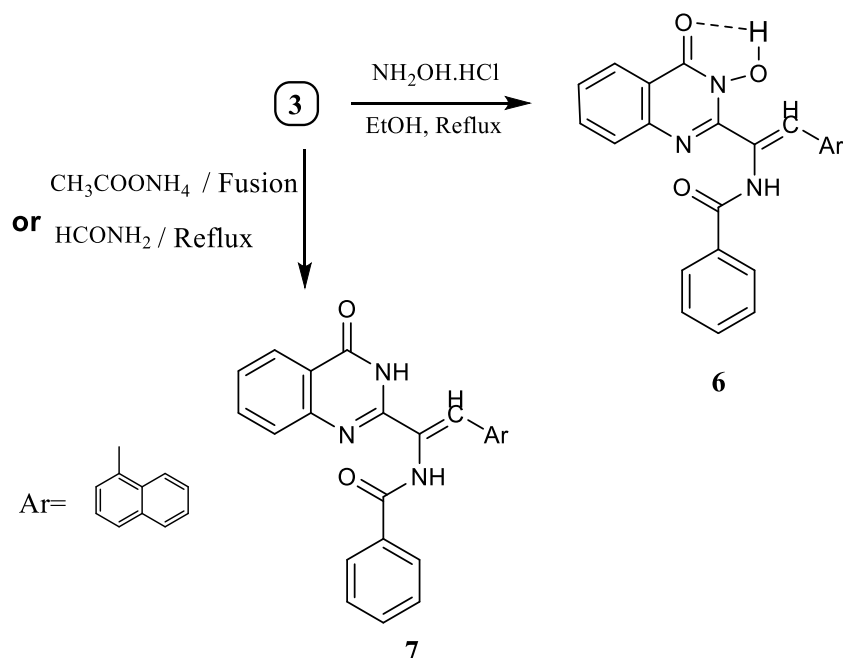
Scheme 2: Synthesis of benzimidazole and tetrazole derivatives **4** and **5**

Benzoxazinone ring has two active nucleophile sites attack, one at C2=O and the other at C=N, the addition reaction of the strong nucleophile azide to the benzoxazinone ring gave a mixture of compounds 4 and 5. The formation of compound 5 as a major product was expected to occur through the active 1,3- addition of sodium azide at the more active C=N site than the Ph-C=O site [33] as shown in (Scheme 3).



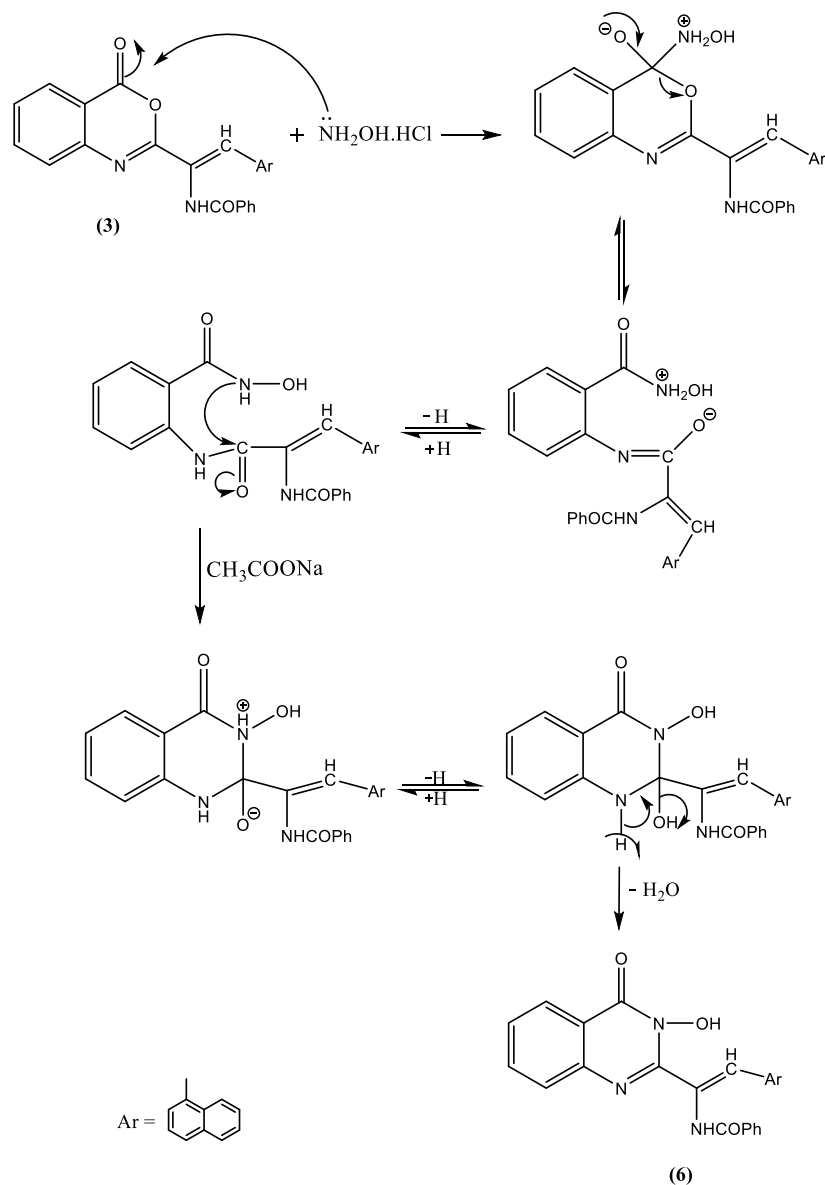
Scheme 3: Synthesis of benzimidazole **4** and tetrazole derivatives **5**

The reaction of benzoxazinone **3** with hydroxylamine hydrochloride in dry ethanol and in the presence of a catalytic amount of freshly fused sodium acetate produced the N-hydroxy quinazolinone derivative **6** [36].



Scheme 4: Synthesis of quinazolinone derivatives **6** and **7**.

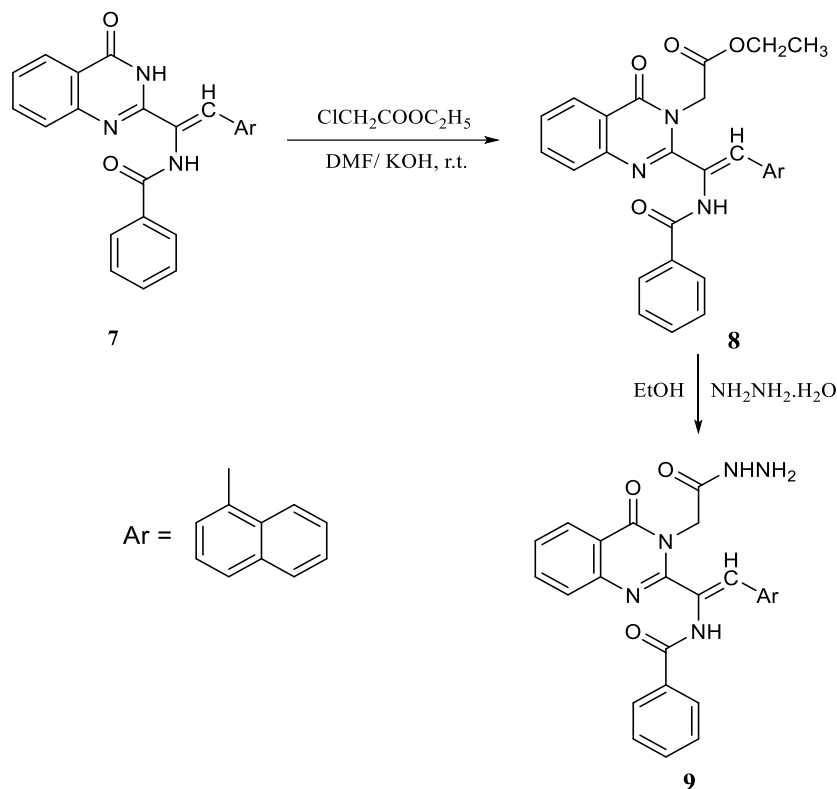
On the other hand, the treatment of benzoxazinone **3** with formamide or ammonium acetate afforded the quinazolinone derivative **7** (Scheme 4) [37,38]. The spectroscopic analyses of compounds **6** and **7** agreed with their suggested structures (cf. experimental). The formation of compound **6** was expected to occur by ring opening reaction of benzoxazinone ring at carbonyl group followed by ring closer to the most stable quinazolinone derivative instead of further addition at $\text{CH}=\text{CHAr}$ (Scheme 5). The lower absorption frequency of quinazolinone carbonyl at 1586 cm^{-1} is in accordance with existence of compound **6** as the chelated form shown (Scheme 4).



Scheme 5: Suggested mechanism for the formation of compound **6**.

Quinazolinone compound **7** is used as a useful building block for the synthesis of some new series of quinazolinone derivatives with anticipated biological activities. Thus, the reaction of compound **7** with ethyl chloroacetate in dimethylformamide and a catalytic amount of potassium hydroxide at room temperature gave quinazolinone derivatives **8**. Refluxing

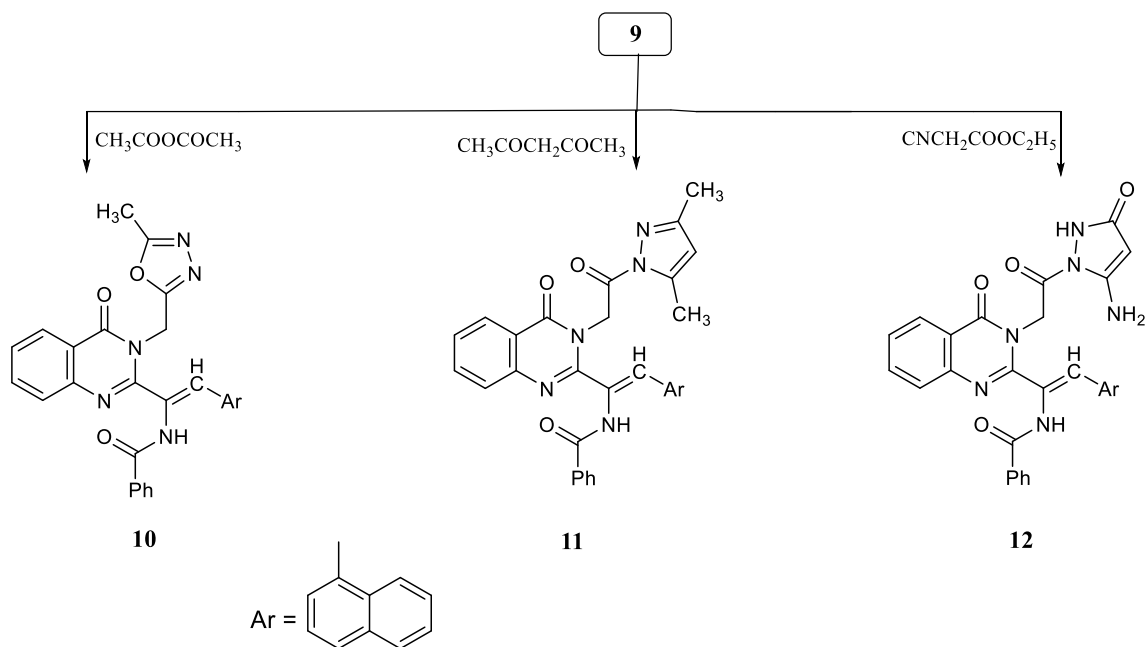
compound **8** with hydrazine hydrate in ethanol afforded the corresponding hydrazone derivative **9** (Scheme 6). The structures of compounds **8** and **9** are deduced from their spectral data.



Scheme 6: Synthesis of quinazolinones **8** and **9**

The infrared spectrum of compound **8** showed an absorption band at 1729 cm^{-1} for C=O ester. Further evidence is gained from its proton nuclear magnetic resonance analysis spectrum ($^1\text{HNMR}$) which exhibited signals for protons of CH_3CH_2 , CH_2 in the up-field region as well as a broad singlet signal for NH proton in the down field region. The infrared spectrum (IR) of compound **9** showed absorption bands at 3455 , 3309 , and 3193 cm^{-1} for NH and NH_2 , and the $^1\text{HNMR}$ spectrum displayed signals at δ 3.88, 4.13, and 10.20 ppm for CH_2 , NH_2 and NH groups, respectively.

Compound **9** is used for the synthesis of N-3- heterocyclic functionalized quinazolinone derivatives through its reaction with acetic anhydride, acetylacetone or ethyl cyanoacetate in refluxing ethanol (Scheme 7) [39]. The structures of compounds **10-12** are deduced from their spectral data (cf. experimental).



Scheme 7: Synthesis of N-3 functionalized quinazolinone **10-12**.

2.2. Biological evaluation:

2.2.1. Antimicrobial activity

All new synthesized compounds [**3-12**] were screened for their in vitro anti-microbial activity against a panel of two Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213 and *Bacillus subtilis* ATCC 6633), two Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) and two fungi (*Candida albicans* ATCC 10231 and *Aspergillus flavus* ATCC 46283) using the disc diffusion method [40]. The antibacterial activity of Ciprofloxacin and Clotrimazole was also recorded as a common standard antibiotic and antifungal, respectively. The results of this study were recorded as the average inhibition zones diameter (mm) and summarized in **Table 1**.

Table 1

Antimicrobial studies for the synthesized compounds measured as inhibition zone diameter (mm) and % activity index

Comp. No.	<i>E. coli</i>		<i>Pseudomonas aeruginosa</i>		<i>S. aureus</i>		<i>Bacillus subtilis</i>		<i>C. Albicans</i>		<i>A. flavus</i>	
	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
3	NA	----	2	8.7	4	16.7	NA	----	3	11.1	4	16
4	21	80.7	16	69.5	18	75.0	17	73.9	23	85.1	20	80.0
5	19	73.0	18	78.2	22	91.6	15	65.2	17	62.9	16	64.0
6	9	34.6	5	21.7	6	25.0	7	30.4	11	40.7	8	32.0
8	20	76.9	17	73.9	21	87.5	18	78.2	22	81.4	19	76.0
9	24	92.3	19	82.6	20	83.3	21	91.3	25	92.5	22	88.0
10	18	69.2	15	65.2	16	66.6	19	82.6	14	51.8	12	48.0
11	16	61.5	13	56.5	15	62.5	14	60.8	12	44.4	11	44.0
12	17	65.3	14	60.8	19	79.1	16	69.5	18	66.6	23	92.0
Cip.	26	100	23	100	24	100	23	100	NA	----	NA	----
Col.	NA	----	NA	----	NA	----	NA	----	27	100	25	100

NA: no activity, Cip.: Ciprofloxacin; Col.: Clotrimazole

From the result of this study, it was found that compounds **4**, **8** and **9** revealed strong antimicrobial activities against all tested bacterial and the fungal strains. Compounds **5**, **10**, **11**, and **12** exhibit moderate antimicrobial activity. While compound **6** has weak antimicrobial. On the other hand, it was noticed that the starting benzoxazinone compound **3** showed no antibacterial activity and weak antifungal activity.

2.2.2. Structural Activity relationship SAR:

From this study, it was revealed that the new synthesized compounds have higher antimicrobial activity compared to the started benzoxazinone **3**. The highest activity of compounds **4**, **8** and **9** may be related to the presence of the benzimidazole, carboxylate and carbohydrazide groups, respectively. On the other hand, new quinazolinone functionalized N-3 heterocyclic compounds **10**, **11**, and **12** showed an effective antimicrobial activity against all

bacteria and fungi strains, may be due to the formation of oxadiazole, pyrazolone ring system (cf. Figure 1) [35,41,42].

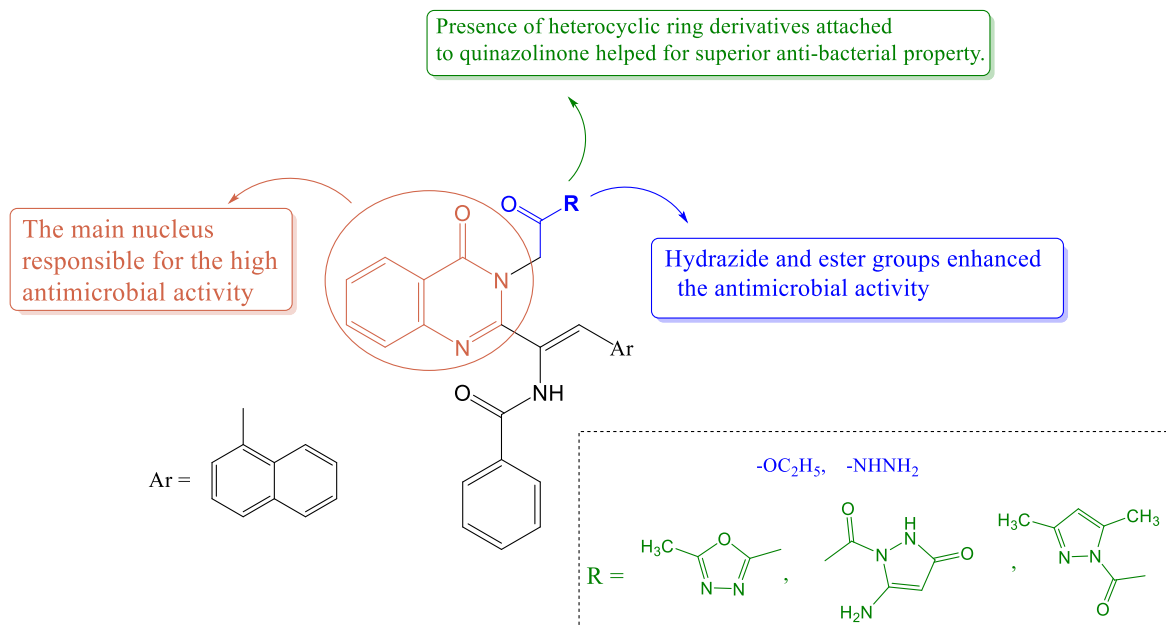


Figure 1: Structure activity relationship SAR of the new synthesized compounds

3. Experimental:

3.1. Chemical Methodology:

All melting points are uncorrected and measured on a Gallenkamp electric melting point apparatus. The infrared spectra were carried out using potassium bromide disks on a Fourier transform infrared (FTIR) Thermo Electron Nicolet 7600 (USA) infrared spectrometer at the central laboratory of faculty of science Ain shams University. ^1H NMR and ^{13}C NMR spectra were run at 300 and 75 MHz on a GEMINI 300 BB NMR spectrometer at the central laboratory of faculty of pharmacy, Ain shams University. The mass spectra operating at 70 eV on Shimadzu GCMS-QP-1000EX mass spectrometer at the Regional center for Mycology and Biotechnology of Al-Azhar University. All reaction progresses were monitored by the thin layer chromatography on Merck Kiesel gel 60 F254 aluminum backed plates, and the spots

were detected by Ultraviolet irradiation (UV) at 254-365 nm. Antimicrobial activity was studied at Pharmacology Department, Faculty of Pharmacy, Mansoura University. 4-(Naphthalen-1-ylmethylene)-2-phenyloxazol-5(4H)-one **1** was synthesized according to the method outlined in the literatures [43,44].

2-(2-Benzamido-3-(naphthalen-1-yl)acrylamido)benzoic acid (**2**).

A mixture of **1** (0.01 mol) and anthranilic acid (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure and the residue was poured onto ice water. The solid formed was filtered off and recrystallized from ethanol to give compound **2**. (Yield 55%); yellow crystals; m.p. 232-234°C; IR (KBr) (ν , cm^{-1}): 3424 (OH), 3308, 3223 (NH), 3059 (CH_{arom}), 1713, 1671, 1654 (CO); ^1H NMR (DMSO- d_6) δ : 7.17-8.90 (m, 17H, [ArH + CH=]), 10.23 (br.s, 1H, NHCOPh, exchangeable), 12.29 (br.s, 1H, ArNHCO, exchangeable), 13.61 (br.s, 1H, OH, exchangeable); MS (70 eV) m/z (%): 436 (M^+ , 36), 359 (21), 322 (49), 164 (50), 120 (25), 94 (54), 83 (34), 44 (7).

N-(2-(naphthalen-1-yl)-1-(4-oxo-4H-benzo[d][3,1]oxazin-2-yl)vinyl) benzamide (**3A**) and N-acetyl-N-(2-(naphthalen-1-yl)-1-(4-oxo-4H-benzo[d][3,1]oxazin-2-yl)vinyl)benzamide (**3B**).

A solution of **2** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 3 h. the solvent was evaporated, and the residue was treated with ice water. The solid obtained was filtered off and recrystallized from methanol. (Yield 58%); yellow crystals; m.p. 156-158°C; IR (KBr) (ν , cm^{-1}): 3385 (NH), 3058 (CH_{arom}), 2924, 2854 (CH_{alkyl}), 1764, 1707, 1694 (CO), 1632 (C=N); ^1H NMR (DMSO- d_6) δ : 7.17-8.37 (m, 24H, [ArH + CH=]), **For (3A)**: 10.30 (br.s, 1H, NH, exchangeable); **For (3B)**: 2.29 (s, 3H, COCH_3); ^{13}C NMR (DMSO- d_6) δ : 29.40 (CH_3), 129.32, 129.56 (CH=C), 131.16-139.41 (22Ar-C), 157.83 (N=C-O), 160.61, 171.18, 181.43 (C=O) ; MS (70 eV) m/z (%): 460 (M^+ , 17), 418 (M^+ , 100), 417 (16), 297 (2), 146 (1), 105 (24), 77 (12).

Reaction of 2-(naphthalen-1-yl)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)benzamide 3 with sodium azide.

An equimolar mixture of **3** (0.01 mol) and sodium azide (0.01 mol) in dry pyridine (20 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residue was poured onto ice/HCl. The solid obtained was filtered off, dried and was separated through fractional crystallization to afford compound **4** from petroleum ether (60-80) °C and compound **5** from ethanol.

1-(Naphthalen-1-yl)-3-oxo-3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)prop-1-en-2-yl)acetamide (4).

m.p.: 135 °C, yellow crystals (from petroleum ether 60-80 °C), yield (36%); IR (KBr)(v, cm⁻¹): 3233 (NH), 3056 (CH_{arom}), 2935 (CH_{alkyl}), 1701, 1669 (C=O), 1601 (C=N); ¹HNMR (DMSO-d₆) δ: 1.95 (s, 3H, CH₃), 7.15-8.87 (m, 12H, [ArH + CH=]), 9.74 (br.s, 1H, NH_a, exchangeable), 12.06 (br.s, 1H, NH_b, exchangeable), MS (70 eV) m/z (%): 371 (M⁺,3), 356 (53), 340 (1), 162 (10).

2-(5-(1-Acetamido-2-(naphthalen-1-yl)vinyl)-1H-tetrazol-1-yl)benzoic acid (5).

m.p.: 215 °C, white crystals (from ethanol), (yield 18%); IR (KBr)(v, cm⁻¹): 3418 (OH), 3214 (NH), 3058 (CH_{arom}), 2924 (CH_{alkyl}), 1673 (C=O), 1604 (C=N); ¹HNMR (DMSO-d₆) δ: 1.95 (s, 3H, CH₃), 7.15-8.87 (m, 12H, [ArH + CH=]), 10.21 (br.s, 1H, NH_c, exchangeable), 13.72 (br.s, 1H, OH, exchangeable), MS (70 eV) m/z (%): 399 (M⁺,2), 354 (14), 332 (6), 141 (8).

1-(3-Hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(naphthalen-1-yl)vinyl benzamide 6.

A mixture of **3** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in ethanol (15 ml) and freshly fused sodium acetate (0.3 gm) was heated under reflux for 6 h. The excess of solvent was evaporated, and the residue was poured onto ice water. The solid product was filtered off, dried and recrystallized to give **6**, (69% yield), yellow crystals (ethanol), m.p. 185°C ; IR (KBr) (v, cm⁻¹): 3430 (OH), 3219 (NH), 3061 (CH_{arom}), 2945(CH_{alkyl}), 1630, 1586 (C=O), 1564 (C=N); ¹HNMR (DMSO-d₆) δ: 7.09-8.35 (m, 17H, [ArH + CH=]), 10.20 (br.s,

1H, NH, exchangeable), 11.15 (br.s, 1H, OH, exchangeable); MS(70 eV) m/z (%): 433 (M⁺,27), 409 (72), 342 (100), 112 (36), 70 (9).

2-(Naphthalen-1-yl)-1-(4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)benzamide (7).

Method A: A mixture of **3** (0.01 mol) and ammonium acetate (0.01) was fused on sand bath at 158°C for 1 h. The reaction mixture was left to cool at room temperature and then treated with ice water. The formed solid was filtered off and recrystallized to give compound **7**. (Yield 62%); deep red crystals (ethanol); m.p. 220°C. IR (KBr)(v, cm⁻¹): 3326, 3244 (NH), 3060 (CH_{arom}), 1680, 1625 (C=O), 1600 (C=N); ¹HNMR (DMSO-*d*₆) δ: 7.39-7.92 (m, 17H, [ArH + CH=]), 8.68, 8.66 (2br.s, 2H, 2NH, exchangeable); MS (70 eV) m/z (%): 417 (M⁺,36), 340 (48), 298 (29), 290 (18), 141 (28).

Method B: A solution of benzoxazinone **3** (0.01 mol) in formamide (20 ml) was heated under reflux for 3 h. The solvent was distilled off under reduced pressure, and the residue was poured onto ice water. The solid obtained was filtered off and recrystallized from dilute ethanol to give product which was identical (m.p., m.m.p and TLC) with compound **7**.

Ethyl 2 (2-(1-benzamido-2-(naphthalen-1-yl)vinyl)-4-oxoquinazolin-3(4H)-yl)acetate (8).

A solution of quinazolinone **7** (0.01 mol) in dimethylformamide (10 ml) and a catalytic amount of potassium hydroxide (0.3 gm) was stirred at room temperature for 1 h;(0.01 mol) of ethyl chloroacetate was added dropwise, then the reaction mixture was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residue was treated with cold water. The formed product was filtered off and recrystallized from (petroleum ether (60-80°C) to give **8**. (Yield 75%); brown crystals; m. p. 145°C. IR (KBr) cm⁻¹: 3268 (NH), 3057 (CH_{arom}), 2980, 2929 (CH_{alkyl}), 1729, 1668 (C=O), 1604 (C=N); ¹HNMR (DMSO-*d*₆) δ: 0.89 (t, 3H, CH₃), 4.14 (s, 2H, CH₂), 4.49 (q, 2H, OCH₂), 6.83-8.24 (m, 17H, [ArH + CH=]), 10.7 (br.s, 1H, NH, exchangeable); MS (70 eV) m/z (%): 503 (M⁺,12), 474 (35), 459 (10), 376 (7), 233 (2).

1-(3-(2-Hydrazinyl-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(naphthalen-1-yl)vinylbenzamide (9).

A mixture of **8** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (20 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residue was treated with crushed ice. The obtained product was filtered off and recrystallized from ethanol to afford **9**. (Yield 65%); white crystals (ethanol); m.p. 175°C. IR (KBr) cm^{-1} : 3455, 3309 (NH_2), 3193 (NH), 3061 (CH_{arom}), 2958, 2856 (CH_{alkyl}), 1671, 1654 (C=O), 1578 (C=N); $^1\text{HNMR}$ (DMSO- d_6) δ : 3.88 (s, 2H, CH_2), 4.13 (br.s, 2H, NH_2 , exchangeable), 7.04-8.21 (m, 17H, [$\text{ArH} + \text{CH}=\text{}$]), 8.89 (br.s, 1H, NHNH_2 , exchangeable), 10.20 (br.s, 1H, NHCOPh , exchangeable); MS (70 eV) m/z (%): 489 (M^+ ,11), 430 (27), 365 (30), 277 (34), 144 (33).

2-(Naphthalen-1-yl)-1-(3-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-4-oxo-3,4-dihydroquinazolin-2-yl)vinylbenzamide (10).

A solution of hydrazide **9** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residue was poured onto ice water. The formed solid product was filtered off and recrystallized from methanol to give compound **10**. (Yield 58%); brown crystals; m.p. 152°C. IR (KBr) cm^{-1} : 3309 (NH), 3052 (CH_{arom}), 2966, 2920 (CH_{alkyl}), 1689 (C=O), 1600 (C=N); $^1\text{HNMR}$ (DMSO- d_6) δ : 2.19 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.50-8.32 (m, 17H, [$\text{ArH} + \text{CH}=\text{}$]), 10.2 (br.s, 1H, NH, exchangeable); MS (70 eV) m/z (%): 513 (M^+ ,10), 374 (18), 250 (15), 140 (14), 77 (100).

2-(Naphthalen-1-yl)-1-(3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)vinylbenzamide (11).

A mixture of hydrazide **9** (0.01 mol) and acetylacetone (0.01 mol) in ethanol (20 ml) was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the residue was treated with cold water. The obtained product was filtered off and recrystallized to give **11**. (Yield 55%); white crystals (diluted ethanol); m.p.210°C. IR (KBr) cm^{-1} : 3288 (NH), 3072 (CH_{arom}), 2990, 2924 (CH_{alkyl}), 1669 (C=O), 1605 (C=N); $^1\text{HNMR}$ (DMSO- d_6) δ : 1.99 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 6.92-7.55 (m, 17H, [$\text{ArH} + \text{CH}=\text{}$]), 10.7

(br.s, 1H, NH, exchangeable); MS (70 eV) m/z (%): 553 (M⁺,43), 538 (16), 523 (100), 157 (28), 144 (36).

1-(3-(2-(5-Amino-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(naphthalen-1-yl)vinyl)benzamide (12).

A mixture of hydrazide **9** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 12 h. The solvent was distilled off under reduced pressure, and the residue was treated with cold water. The solid product formed was filtered off and recrystallized from diluted ethanol to give **12**. (Yield 56%); brown crystals (dilute ethanol); m.p. 265°C. IR (KBr) cm⁻¹ : 3377, 3285, 3230 (NH₂), 3105 (NH), 3050 (CH_{arom}), 2922 (CH_{alkyl}), 1700 (C=O_{pyrazol}), 1675 (C=O_{Quinazolinone}), 1602 (C=N), 1594 (C=C); ¹HNMR (DMSO-d₆) δ: 4.61 (s, 2H, CH₂CO), 5.42 (br.s, 2H, NH₂, exchangeable), 6.99 (s, H, CHCO_{pyrazol}), 7.10-7.94 (m, 17H, [ArH + CH=]), 9.59 (br.s, 1H, NHCOPh, exchangeable), 10.6 (br.s, 1H, NNH_{pyrazol}, exchangeable); MS (70 eV) m/z (%): 556 (M⁺,26), 480 (99), 346 (18), 323 (35), 289 (52).

3.2. Biological Activity:

3.2.1 Antimicrobial study:

The in vitro antimicrobial assay was performed for the synthesized compounds against a panel of two Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), two Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and two fungi (*Candida albicans*, *Aspergillus flavus*). Each of these compounds was dissolved in DMSO and solution of the concentration 1 mg /ml were prepared separately paper discs of Whatman filter paper were prepared with standard size (5cm) were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the complex solution were places aseptically in the petri dishes containing nutrient agar media (agar 20g + beef extract 3g + peptone 5g) seeded with *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus flavus*. The petri dishes were incubated at 36°C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial

activity of a common standard antibiotic Ciprofloxacin and antifungal Clotrimazole was also recorded using the same procedure as above at the same concentration and solvents.

Conclusion:

A new series of potent heterocyclic compounds, tetrazole, benzimidazole, and quinazolinone derivatives was synthesized from benzoxazinone compound bearing naphthyl group. The chemical structures of the new synthesized compounds were elucidated through their spectroscopic analysis. All synthesized compounds were screened for antimicrobial activity against different pathogenic bacterial and fungal strains, and most of them showed moderate to high antimicrobial activity. Compounds **4**, **8**, and **9** showed remarkable activity against all strains for promising bioactive drugs in the future study.

Declaration of Competing Interest

Authors have declared no conflict of interest for publication of this work.

References

- [1] T. Gupta, A. Rohilla, A. Pathak, M.J. Akhtar, M.R. Haider, M.S. Yar, Current perspectives on quinazolines with potent biological activities: A review, *Synth. Commun.* 48: (2018) 1099–1127.
- [2] M. Komar, M. Molnar, M. Jukić, L. Glavaš-obrovac, *Green Chemistry Letters and Reviews* Green chemistry approach to the synthesis of 3- substituted-quinazolin-4 (3H)-ones and biological evaluation 4: (2020) 93–101.
- [3] S. Gatadi, T.V. Lakshmi, S. Nanduri, *European Journal of Medicinal Chemistry* 4 (3 H) - Quinazolinone derivatives : Promising antibacterial drug leads, *Eur. J. Med. Chem.* 170: (2019) 157–172.
- [4] A. Jabar Kh. Atia, S. S. Al-Mufreij, *Synthesis and Antibacterial Activities of New 3-Amino-2-Methyl-Quinazolin-4 (3H)-One Derivatives*, *Am. J. Chem.* 2: (2012) 150–156.
- [5] M. Mishra, V.K. Mishra, P. Senger, A.K. Pathak, S.K. Kashaw, *Exploring QSAR studies on 4-substituted quinazoline derivatives as antimalarial compounds for the development of predictive models*, *Med. Chem. Res.* 23: (2014) 1397–1405.
- [6] J. Zhang, J. Liu, Y. Ma, D. Ren, P. Cheng, J. Zhao, F. Zhang, Y. Yao, *Bioorganic & Medicinal Chemistry Letters* One-pot synthesis and antifungal activity against plant pathogens of quinazolinone derivatives containing an amide moiety, *Bioorg. Med. Chem. Lett.* 26: (2016) 2273–2277.

- [7] D.S.A. Haneen, R.S. Gouhar, H.E. Hashem, A.S.A. Youssef, Synthesis and reactions of 4H-3,1-benzoxazin-4-one derivative bearing pyrazolyl moiety as antimicrobial and antioxidant agents, *Synth. Commun.* 49: (2019) 2840–2855.
- [8] A. Nath, A. Kumer, F. Zaben, W. Khan, Investigating the binding affinity , molecular dynamics , and ADMET properties of 2 , 3-dihydrobenzofuran derivatives as an inhibitor of fungi , bacteria , and virus protein, *Beni-Suef Univ. J. Basic Appl. Sci. Res.* 10: (2021) 1–13.
- [9] V. Alagarsamy, U.S. Pathak, Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-ones, *Bioorganic Med. Chem.* 15: (2007) 3457–3462.
- [10] V. Alagarsamy, K. Chitra, G. Saravanan, V.R. Solomon, M.T. Sulthana, B. Narendhar, An overview of quinazolines: Pharmacological significance and recent developments, *Eur. J. Med. Chem.* 151: (2018) 628–685.
- [11] S. Kumar, U. Yadava, A. Upadhyay, M.L. Sharma, Bioorganic Chemistry Synthesis , biological evaluation and molecular docking studies of novel quinazolinones as antitubercular and antimicrobial agents, *Bioorg. Chem.* 108: (2021) 104611.
- [12] A.A.M. Abdel-Aziz, L.A. Abou-Zeid, K.E.H. Eltahir, R.R. Ayyad, M.A.A. El-Sayed, A.S. El-Azab, Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4(3 H)-quinazolinones, *European Journal of Medicinal Chemistry* 121: (2016) 410-421.
- [13] K.P. Rakesh, H.K. Kumara, B.J. Ullas, J. Shivakumara, D.C. Gowda, Bioorganic Chemistry Amino acids conjugated quinazolinone-Schiff's bases as potential antimicrobial agents Synthesis , SAR and molecular docking studies, *Bioorg. Chem.* 90: (2019) 103093.
- [14] A. Sharaf, S. Shaban, R. Ahmed, A.E. Elkhabiry, S. Ibrahim, E. Tantawy, E. Sayed, Synthesis and biological evaluation of some 3 H -quinazolin-4-one derivatives, *Journal of the Iranian Chemical Society* 19.1: (2022) 291-302.
- [15] S. Kumar, J.C. Aghara, A.T. Alex, J.M. Aranjani, Novel Quinolone Substituted Quinazolin-4 (3H) -Ones as Anti-Inflammatory , Anticancer Agents : Synthesis and Biological Screening, *Indian Journal of Pharmaceutical Education and Research* 52: (2018) 1-9.
- [16] M.T. Elsaadi, N.H. Amin, S.S. Zaki, H.M. Abdel-Rahman, Synthesis, docking and biological evaluation of 2,4-disubstituted quinazolines with multi-target activities as anti-cancer and antimicrobial agents, *Egypt. J. Chem.* 63: (2020) 3721–3734.
- [17] P. Sivaguru, K. Parameswaran, A. Lalitha, Antioxidant , anticancer and electrochemical redox properties of new bis (2 , 3-dihydroquinazolin-4 (1 H) -one) derivatives, *Mol. Divers.* 21: (2017) 611–620.
- [18] G.S. Hassan, H.H. Georgey, N.A. Ibrahim, S.S. Zaki, Synthesis of novel substituted quinazoline and quinazolin-4 (3 H) -one derivatives of expected antitumor activity, *Der Pharma Chemica* 7: (2015)106-119.

- [19] N.J.P. Subhashini, L. Jilla, P.K. Kolluri, Novel Benzosuberone-quinazolinone Derivatives : Synthesis and Antitumour Activity 90: (2020) 1960–1967.
- [20] A. Aboelmagd, E.M.S. Salem, I.A.I. Ali, M.S. Gomaa, Synthesis of quinazolindionyl amino acid and dipeptide derivatives as possible antitumour agents, *Arkivoc.* 20: (2019)1-16.
- [21] M.H. Hekal, F.S.M. Abu El-Azm, S.R. Atta-Allah, Ecofriendly and highly efficient microwave-induced synthesis of novel quinazolinone-undecyl hybrids with in vitro antitumor activity, *Synth. Commun.* 49: (2019) 2630–2641.
- [22] S.Y. Abbas, K.A.M. El-Bayouki, W.M. Basyouni, E.A. Mostafa, New series of 4(3H)-quinazolinone derivatives: syntheses and evaluation of antitumor and antiviral activities, *Med. Chem. Res.* 27: (2018) 571–582.
- [23] K. Vijayakumar, A.J. Ahamed, G. Thiruneelakandan, Synthesis , Antimicrobial , and Anti-HIV1 Activity of Quinazoline-4 (3H) -one Derivatives, *Hindawi Publishing Corporation Journal of Applied Chemistry* 5: (2013) 7–12.
- [24] D.R. Patel, K.C. Patel, Synthesis , characterization and in vitro antimicrobial screening of some new MCT reactive dyes bearing nitro quinazolinone moiety, *J. Saudi Chem. Soc.*19: (2015) 347–359.
- [25] S. Lakshmanan, D. Govindaraj, N. Ramalakshmi, S.A. Antony, Synthesis, molecular docking, DFT calculations and cytotoxicity activity of benzo[g]quinazoline derivatives in choline chloride-urea, *J. Mol. Struct.* 1150: (2017) 88–95.
- [26] A.P. Keche, V.M. Kamble, Synthesis and anti-inflammatory and antimicrobial activities of some novel urea , thiourea and sulphonamide functionalities, *Arab. J. Chem.* 12: (2019) 1522–1531.
- [27] M.A.E. El-hashash, E. Azab, A.E. Faty, Synthesis , Antimicrobial and Anti-inflammatory Activity of Some New Benzoxazinone and Quinazolinone Candidates, *Chem. Pharm. Bull. Pharm. Bull.* 64: (2016) 263–271.
- [28] A. Mokal, Synthesis and Evaluation of Antimicrobial Activities of New 1, 2, 4-Triazole Derivatives, *International Journal of Applied Chemistry*, 7: (2020) 1–5.
- [29] M. Ibrahim, K. El-adl, A.A. Al-karmalawy, Design , synthesis , molecular docking and anticonvulsant evaluation of novel 6-iodo-2-phenyl- 3-substituted-quinazolin-4 (3 H) -ones, *Bull. Fac. Pharmacy, Cairo Univ.* 53: (2015) 101–116.
- [30] A. Rajasekaran, V. Rajamanickam, S. Darlinquine, Synthesis of some new thioxoquinazolinone derivatives and a study on their anticonvulsant and antimicrobial activities, *European Review for Medical and Pharmacological Sciences*, 6: (2013) 95–104.
- [31] M. Shariat and S. Abdollahi, “Synthesis of benzoxazinone derivatives: A new route to 2-(N-phthaloylmethyl)-4H-3,1-benzoxazin-4-one,” *Molecules* 9: (2004) 705–712.
- [32] M. A. A. S. U. Sarkar, A. Nath, A. Kumer, C. Mallik, F. Akter, and A. Ali, “Synthesis, molecular docking screening, ADMET and dynamics studies of synthesized 4-(4-methoxyphenyl)-

8-methyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one and quinazolinone derivatives,” J. Mol. Struct 2:(2021) 130953.

[33] M. A. E.-A. El-Hashash, M. E. Azab, R. A. E.-A. Faty, and A. E.-G. E. Amr, “Synthesis, Antimicrobial and Anti-inflammatory Activity of Some New Benzoxazinone and Quinazolinone Candidates,” Chem. Pharm. Bull. Pharm. Bull., 64: (2015) 263–271.

[34] S. Y. Abbas, K. A. M. El-Bayouki, W. M. Basyouni, and E. A. Mostafa, “New series of 4(3H)-quinazolinone derivatives: syntheses and evaluation of antitumor and antiviral activities,” Med. Chem. Res., 27: (2018) 571–582.

[35] M.A. El-hashash, S.A. Rizk, Behaviour of 4-(4-acetylamino-phenyl)-4-oxobut-2-enoic acid towards nucleophiles and synthesis of various N-heterocycles, European Chemical Bulletin, 2: (2013) 456–460.

[36] E. Jafari, G. Khodarahmi, F. Hassanzadeh, G. Hakimelahi, F. Tsai, Synthesis of some new tricyclic 4 (3H)-quinazolinone derivatives. Research in Pharmaceutical Sciences, 7: (2012) 93–100.

[37] R.S.M. Ismail, N.S.M. Ismail, S. Abuserii, D.A. Abou, E. Ella, Future Journal of Pharmaceutical Sciences Recent advances in 4-aminoquinazoline based scaffold derivatives targeting EGFR kinases as anticancer agents, Futur. J. Pharm. Sci. 2: (2016) 9–19.

[38] Y.A. El-badry, Synthesis of bioactive quinazolin-4 (3 H) -one derivatives via microwave activation tailored by phase-transfer catalysis, [Acta Pharmaceutica Sinica B](#) (APSB) 70: (2020) 161–178.

[39] H.E. Hashem, A.E. Amr, E.S. Nossier, E.A. Elsayed, and E.M. Azmy, Synthesis, Antimicrobial Activity and Molecular Docking of Novel Thiourea Derivatives Tagged with Thiadiazole, Imidazole and Triazine Moieties as Potential DNA Gyrase and Topoisomerase IV Inhibitors, Molecules. 25: (2020) 1–18.

[40] A.S.A. Youssef, M.M. Hemdan, F.A. El-Mariah, H.E. Hashem, Synthesis of Some Quinazolinone Derivatives Functionalized with N-3 Heterocyclic Side Chain, J. Heterocycl. Chem. 55: (2018) 1626–1633.

[41] Y. Kaddouri, F. Abridach, E.B. Yousfi, M. El Kodadi, R. Touzani, New thiazole, pyridine and pyrazole derivatives as antioxidant candidates: synthesis, DFT calculations and molecular docking study, Heliyon. 6: (2020) 1-9.

[42] E.P. and D.H.-L. Evangelos Mavridis, Eleftherios Bermperoglou, 5-(4 H)-Oxazolones and Their Benzamides as Potential Bioactive Small Molecules, Molecules. 25.14: (2020) 3173.

[43] B. Sha, L. Hadian, A.R. Khosropour, RSC Advances An innovation for development of Erlenmeyer Plochl reaction and synthesis of AT-130 analogous, a new application of continuous-flow method †, RSC Adv. 6: (2016) 19861–19866.

[44] H.E.Hashem and A.M. Abo-Bakr, Synthesis of Some New 1,2,4-Triazine and 1,2,5-Oxadiazine Derivatives with Antimicrobial Activity, Heteroat. Chem.23: (2019) 1–7.

[45] H. Mahmoud, A. Alazaly, H. H. Monir, H. S. Abdel-samad, and A. A. Abdel-shafi, "Spectroscopic Studies on the inclusion complex formation between 2,4-dihydroxyquinoline and cyclodextrin derivatives," *Journal of Scientific Research in Science* 36: (2019) 442–452.

[46] A. H. Ahmed, Z. M. H. Kheiralla, and A. A. M, "Cellular Cytotoxicity and Epigenetic Alteration in RP1 and RASSF1A Genes as Response for Anticancer Capabilities of Some Probiotic Bacteria in Breast Cancer." *Journal of Scientific Research in Science* 38: (2021) 1-15.

[47] E. G. Elabbasy, A. A. Hussain, S. M. Ashour, and S. Y. Ibrahim, "Antifungal activity of *Streptomyces canescens* MH7 isolated from mangrove sediment against some dermatophytes." *Journal of Scientific Research in Science* 38: (2021) 36-59.

الملخص العربي

تحضير و دراسة النشاط المضادات للميكروبات لمشتقات جديدة من تيترازول، بينزيميدازول، و

كينازولينون ذات رابطة متصلة من الوضع ن 3

دينا جميل سند¹ - احمد سعيد احمد يوسف² - فاطمة عبدالرحمن المارية¹ - هبة الله عزت هاشم¹

¹ قسم الكيمياء - كلية البنات للأداب والعلوم والتربية - جامعة عين شمس - مصر الجديدة - القاهرة - جمهورية مصر العربية

² قسم الكيمياء - كلية العلوم - جامعة عين شمس - العباسية - القاهرة - جمهورية مصر العربية

الملخص العربي

عند تفاعل (4H)-بينزو[3,1]-اوكسازين-4-ون (3) مع مجموعة متنوعة من مركبات النيتروجين نيوكليوفيل: أزيد الصوديوم، كلوريد هيدروكسيل أمين، أسيتات الامونيوم، و فورماميد فإنه يعطي مركبات ن-غير متجانسة الحلقة جديدة (4-7). و من ثم تم استخدام مشتق الكينازولينون (7) كمادة اساسية لتحضير سلسلة من مشتقات الكينازولينون الجديدة ذات رابطة متصلة من الوضع ن 3 (8-12). قد تم اثبات التركيب البنائي للمركبات الجديدة المحضرة اعتمادا على التحليل الطيفي لها. قد تم دراسة التأثير البيولوجي للمركبات الجديدة المحضرة ضد بعض من الكائنات الحية الدقيقة المسببة للأمراض، و قد وجد ان غالبية المركبات الجديدة المحضرة لها تأثير بيولوجي ملحوظ مقارنة سيبروفلوكساسين المضاد للبكتيريا و كلوتريمازول المضاد للفطريات.