SYNTHESIS OF OXAZEPINO COMPOUND VIA ELECTROPHILIC CYCLIZATION AND EVALUATION OF THEIR BIOLOGICAL ACTIVITY

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Received 13.08.2024
Accepted 23.10.2024

Abstract: *In this research paper, we successfully synthesized some of E-1-(iodomethy-lene)-8-(aryl)-1,2,7,8-tetrahydro-9H benzo[6,7][1,4]oxazepino [4,5-a] quinazolin-9-one (compounds **3a-f**) through electrophilic cyclization of 3-aryl-2-(2-(prop-2-yn-1-yloxy) phenyl)-2,3-dihydroquinazolin-4(1H)-one derivatives (compounds **2a-f**) using iodine as an electrophilic source and potassium carbonate as a base in dichloromethane at room temperature in good yield. We optimized the best condition for this reaction with different electrophiles, bases, and solvents. (**2a-f**) were prepared from reaction of isatoic anhydride, amines and 2-(Prop-2-yn-1-yl oxy) benzaldehyde in mild condition. A confirmation of biological activity by docking shows that (3d) have highest binding affinity (-8.4) with shikimate kinase enzyme. Biological activity test agents selected bacteria gave that (2d & 3d) have highest inhibition zoom (27, 28 / mm) respectively. While (**2 c, 2 d**) showed middle activity against tested bacteria. In addition, (**2b, 3a**) failed to show any inhibition.*
Keywords: *Oxazepine, Dihydroquinazolinone, Docking, Shikimate kinase.*
DOI: 10.32737/2221-8688-2025-3-343-355

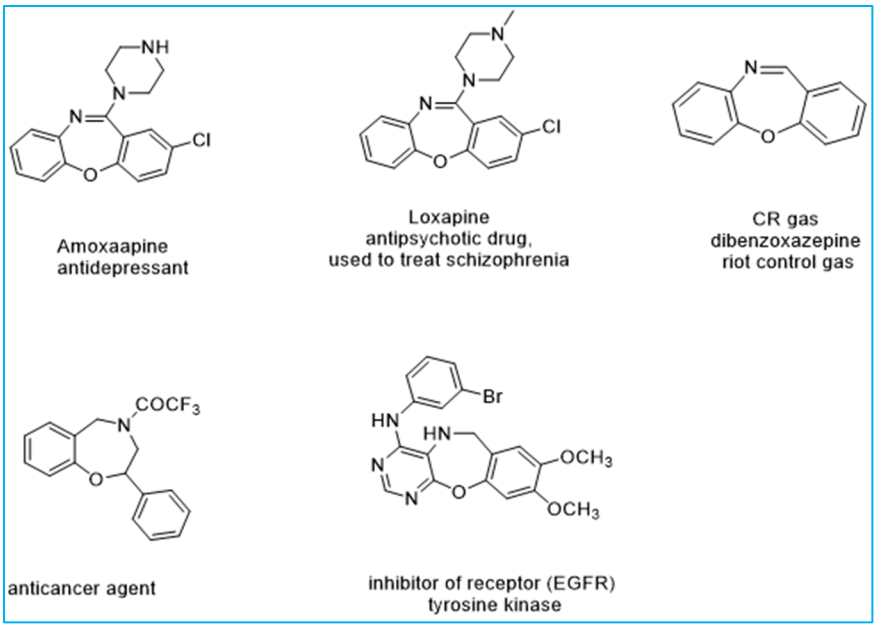
Introduction

Quinazolinone is a benzene ring fused with pyrimidinones, these compounds are important as a biologically active, natural product, veterinary products [1-3], pharmaceutical drugs, synthetic compounds, and agricultural chemicals [4-6]. 2,3-Dihydroquinazolin-4-(1H)-one compounds play a significant role in heterocyclic aromatic rings containing nitrogen due to their abundant pharmacological and biological activities. Compounds containing this structure have shown important biological activities, including analgesic, diuretics, anticancer, anticonvulsant, anti-defibrillator, antihistaminic, and many other activities [7]. Additionally, they include antifungal, antibacterial, antitumor, antidiabetic, and antihypertensive properties [8]. The biological activities of quinazolinones include antimalarial [9], anti-inflammatory [10-12], anticholinesterase [13], antihypertensive [14], antidiabetic [15], antipsychotic [16], dihydrofolate reductase inhibitors [17], dopamine agonist [18], and antimicrobial activities [19]. For example, tetracyclic quinazolinone is identified for its central nervous system inhibitory activity, and compound is a significant example of antitumoral drug. Benzoxazepines are between the important heterocycles a compound that exhibit numerous biological actions, including antipsychotic, anxiolytic, antidepressant, anticancer, analgesic, sedative, muscle relaxant, and antitubercular [20]. Particularly, the receptor protein (RIP1) kinase inhibitor shows an anticancer activity [21] Alzheimer's disease treated by indole-substituted benzoxazepine [22].

Researchers have developed various methods for preparing heterocyclic rings containing (O, N, S, Se) through electrophilic cyclization, which has broad applications in various fields of chemistry, including drug discovery, materials science, and bioorganic chemistry. This process involves attacking the electrophile on the C(sp) center of alkenes or alkynes. Importantly, the cyclization process occurs under mild reaction conditions and tolerates a wide range of functional groups. Heterocyclic rings containing halogens, and their derivatives are particularly important because the halogen atom plays an essential role

in the biological activity of the compound and is also used in structure development [23].

1,4-Oxazepane consists of heterocyclic ring comprising seven atoms containing one nitrogen atom and one oxygen atom. They are multipurpose compounds exhibiting a wide range of biological activities. Although their known bi- and tri-cyclic counterparts, which contain a fused aryl ring, are synthetically prepared and they have not existed in nature [24]. Some oxazepanes are currently in medical use, such as the tetracyclic antidepressant amoxapine and loxapine, which is used to treat schizophrenia. Additionally, nitroxapine has been utilized. Moreover, dibenzoxepines have been employed as tear gas for riot control. There are still other drugs undergoing clinical trials for development as new medications, such as bicluzotan, for the treatment of acute stroke, and AZD7986, for the curing of chronic obstructive pulmonary disease (Scheme 1) [25].



Scheme1. Representative examples of some oxazepanes and their derivatives.

Experimental part

All chemicals were purchased from commercial companies such as Sigma Aldrich and Fluorochem and used without more purification. FTIR Shimadzu 8400, ^{1}HNMR 400MHz and ^{13}CNMR 100MHz with DMSO d^{6} are used to confirm the structure of prepared compounds. TLC 254nm from Merck are used to monitor the reactions. the biological activity carried out in the dep. of biology college of education for pure science Mosul University.

Synthesis of 2-(Prop-2-yn-1-yl oxy) benzaldehyde (1)

In a suitable round-bottom flask, (0.03 mole, 3.6 g) of salicylaldehyde is dissolved in (60 ml) of dimethylformamide. Then, was added (0.09 moles, 12.42 g) of potassium carbonate. The reaction mixture was refluxed with stirring for 30 minutes. After this period (0.036 mole, 5.1 ml) of propargyl bromide was added dropwise. the resulted mixture was refluxed with continuous stirring for about another 6 hours monitored with (TLC). Finally, the solid salt was removed, and the filtrate was poured to an ice-cold water. The precipitate filtrated then recrystallized using ethanol to get the final product [26].

Brown powder, yield (4.3 g, 84%), (m.p 62-64ºC); IR /cm^{-1}: 3269 (acetylene C-H), 2116 (triple bond), 1680 (carbonyl), 1263 (C-O bond). ^{1}H NMR (400 MHz, DMSO) δ ^{1}H NMR δ 10.43 (s, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 7.30 (s, 1H), 7.13 (s, 1H), 4.99 (d, J = 2.4 Hz, 2H), 2.58 (s, 1H); ^{13}C NMR δ 189.50, 159.96, 136.69, 128.37, 125.27, 122.02, 114.77, 79.53, 79.11, 56.91.

Synthesis of phenyl (2-(propynyloxy) phenyl) dihydroquinazolinone derivate- ives (2a-f).

In a suitable round-bottom flask, an equivalent mole (3 mmol, 0.48 g) of isatoic anhydride and (3 mmol) of aniline derivatives are placed along with (3 mmol, 0.48 g) of (1) in dioxane (30 ml) of. Then, the mixture stirred under reflux for about 7 hrs. monitored by (TLC). After this point, the reaction mixture is cooled to room temperature and poured into cold water to obtain the precipitate. The formed precipitate is filtered and recrystallized from ethanol [27].

3-(4-chlorophenyl) (2-(prop-2-yn-1-ylo- xy) phenyl) dihydroquinazolinone (2a)

Light yellow powder, yield in (76%), (m.p 100-102 ºC); IR / cm^{-1}:3219, 3069, 2111, 1725-1765, 1285, 1208, 818. ^{1}H NMR δ 7.89 (s, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.71 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.24 (s, 2H), 7.13 (s, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.55 (s, 1H), 4.99 (s, 2H), 4.95 (d, J = 2.4 Hz, 1H), 3.34 (s, 1H); ^{13}C NMR δ 160.37, 157.88, 156.60, 151.29, 147.59, 141.89, 137.42, 133.70, 130.65, 129.67, 129.50, 129.09 , 127.90, 127.21, 124.84, 124.00, 123.20, 122.08, 115.82, 114.31, 110.75, 79.40, 79.31, 61.67, 56.87.

3-(4-methoxyphenyl)(2-(propynyloxy) phenyl) dihydroquinazolinone (2b)

Dark green powder, yield in (73%), (m.p 187-189 ºC); IR /cm^{-1} : 3290, 2922, 2122,1643, 1292, 1214, 1160; ^{1}H NMR δ 7.76 (s, 1H), 7.74 (s, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 6.92 (s, 1H), 6.55 (s, 1H), 4.81 – 4.79 (m, 1H), 4.78 (s, 1H), 3.71 (s, 4H), 3.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 165.44 , 160.29 , 157.05, 149.55, 136.45, 136.32 , 132.57, 131.26, 130.77 129.95, 129.77, 125.17, 123.89, 120.33, 117.89, 117.42, 116.83, 116.67, 115.93, 82.10, 81.47, 71.08, 58.95, 58.12.

3-(4-nitrophenyl) (2-(propynyloxy) phenyl) dihydroquinazolinone (2c)

Light brown powder, yield in (80%), (m.p 129-131 ºC); IR / cm^{-1}: 3216, 3100, 2111, 1764, 1457, 1361, 1260, 1159. ^{1}H NMR δ 8.07 (s, 1H), 8.05 – 8.03 (m, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.75 – 7.73 (m, 1H), 7.60 (s, 1H), 7.41 (s, 1H), 7.38 (s, 1H), 7.28 – 7.25 (m, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.74 (s, 1H), 6.61 (d, 1H), 6.59 (s, 1H), 4.98 (d, J = 2.4 Hz, 2H), 3.35 (s, 1H). ^{13}C NMR δ 160.51, 158.90, 158.40, 147.73, 145.51, 142.03, 137.56, 134.61, 129.56, 128.01, 127.02, 125.66, 124.53, 124.14, 122.44, 122.29, 115.96, 114.54, 110.89, 79.56, 79.48, 79.45, 57.06.

2-(2-(prop-2-yn-1-yloxy)phenyl)-3-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (2d)

Brown powder yield in (77%), (m.p 96-98 ºC); FT-IR / cm^{-1}: 3287, 2921, 2118, 1737, 1292, 1158, 1019.^{1}H NMR δ 7.51 (s, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.25 (s, 1H), 7.23 (d, J = 2.2 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 4.96 (d, J = 2.4 Hz, 2H), 4.80 (s, 2H), 3.70 (s, 3H), 2.54 (s, 1H), 2.51 – 2.49 (m, 1H); ^{13}C NMR δ 158.24 , 157.71, 157.42, 154.46, 153.48, 146.96, 145.10, 133.85, 133.73, 130.28, 129.69, 128.18, 127.19, 122.86, 122.31, 121.89, 121.30, 117.75, 114.15, 79.50, 78.85, 56.69, 55.52, 36.11.

3-(4-bromophenyl)(2-(propynyloxy) phenyl)dihydroquinazolinone (2e)

Greenish brown powder, yield in (81%), (m.p 123-125 ºC); IR / cm^{-1}: 3237, 2937, 2112, 1729, 1286, 1207, 926;^{1}H NMR (400 MHz, DMSO) δ 7.75 (s, 1H), 7.59 – 7.49 (m, 2H), 7.36 – 7.27 (m, 3H), 7.23 (s, 1H), 7.17 (s, 1H), 6.93 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.77 (s, 1H), 6.69 (s, 1H), 5.49 (s, 1H), 5.02 – 4.89 (m, 2H), 4.58 (s, 1H); ^{13}C NMR δ 163.81, 157.17, 145.47, 135.82, 135.56, 132.13, 131.92, 131.00, 129.50, 128.80, 128.41, 128.41, 128.33, 123.43, 123.04, 122.38, 119.66, 118.97, 115.34, 113.92, 80.00, 78.79, 62.07, 59.70.

3-(3-nitrophenyl)(2-(propynyloxy) phenyl)dihydro-quinazolinone (2f)

Light yellow powder, yield in (79%), (m.p 103-105 ºC); IR /cm^{-1}:3216, 3070, 2111, 1764, 1479, 1234, 1208; ^{1}H NMR δ 8.39 (s, 1H), 8.01 (s, 1H), 7.80 (s, 1H), 7.68 (s, 1H), 7.57 (s, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 6.97 (d, J = 4.0 Hz, 2H), 6.88 (s, 1H), 6.87 (s, 1H), 6.44 (s, 1H), 5.02 – 4.71 (m, 2H), 2.33 (s, 1H); ^{13}C NMR δ 163.81, 157.17, 149.66, 145.47, 139.68, 135.82, 131.00, 130.81, 130.12, 129.50, 128.43, 123.43, 123.04, 122.67, 122.38, 120.31, 118.97, 115.34, 113.92, 80.00, 78.79, 62.07, 59.70.

Synthesis of E-1-(iodomethylene)-8-phenyl tetrahydrobenzo oxazepino quinazolinone derivatives (3a-f)

In a suitable round-bottom flask, (0.0023 mol) of one of the compounds (2a), (0.0046 mol, 0.63 g) potassium carbonate in 15 mL

dichloromethane, and is add (0.0046 mol, 0.58 g) of iodine. The mixture was stirred at room temperature for 7 hours until the total starting material disappeared as determined by thin-layer chromatography (TLC), the reaction was quenched by saturated aqueous sodium thiosulfate (10 mL) and water (10 mL). The resulting solution was extracted using ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude product was purified using flash column chromatography (toluene/ethyl acetate). [28]

E-8-(4-chlorophenyl)-1-(iodomethylene) tetrahydro benzo oxazepino quinazolin- one (3a)

yellowish brown powder, yield in (84%), (m.p 228-230 ºC); IR /cm^{-1}: 2962, 1683, 1488, 1454, 1258, 1010; ^{1}H NMR δ 7.71 (s, 1H), 7.69 (s, 2H), 7.56 – 7.55 (m, 1H), 7.50 (s, 1H), 7.41 – 7.41 (m, J = 1.0 Hz, 1H), 7.39 (s, 2H), 7.39 (s, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.8 Hz, 1H), 5.41 (s, 1H), 5.33 (s, 1H), 5.29 (s, 2H), 4.65 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 164.49, 160.71, 157.71, 156.90 , 151.32, 147.58, 136.86, 134.44, 134.02, 133.06, 131.65, 129.86, 124.85, 123.71, 123.20, 123.18, 119.73, 117.13, 115.66, 115.19, 114.44, 99.60, 65.76.

E-1-(iodomethylene)-8-(4-methoxyphen- yl) tetrahydro benzo oxazepino quinazo- linone (3b)

Dark brown powder, yield in (78%), (m.p 186-188 ºC); IR / cm^{-1}: 2958, 1650, 1608, 1441, 1397, 1109; ^{1}H NMR δ 7.91 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.27 (s, 1H), 7.17 (s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.74 (s, 1H), 6.59 (s, 1H), 4.68 (d, J = 2.4 Hz, 1H), 4.56 (s, 1H), 3.70 – 3.68 (m, 1H); ^{13}C NMR δ 161.89, 159.18, 154.33, 147.85, 135.24, 131.03, 130.11, 127.86, 127.73, 126.93, 125.69, 121.36, 121.32, 120.92, 113.84, 113.68, 112.14, 98.74, 86.90, 79.68, 55.68.

E-1-(iodomethylene)-8-(4-nitrophenyl) tetrahydro benzo oxazepino quinazolin- one (3c)

Dark brown powder, yield in (80%), (m.p 235-237ºC); IR /cm^{-1}: 2964, 1692, 1611, 1148, 1395; ^{1}H NMR δ 8.30 (m, 2H), 8.00 (m, 1H), 7.93 (s, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.13 (s, 1H), 7.04 (s, 1H), 7.02 (s, 1H), 6.73 (s, 2H), 6.59 (s, 1H), 6.57 (s, 1H), 6.49 (s, 1H), 5.09 (s, 1H), 4.23 (d, 2H); ^{13}C NMR δ 162.81, 156.24, 155.32, 153.19, 137.36, 136.07, 134.45, 131.07, 128.60, 126.89, 126.60, 126.60, 125.56, 122.12 117.02, 115.19, 114.88, 112.87, 98.89, 87.62, 79.69 .

E-1-(iodomethylene)-8-(p-tolyl) tetra- hydro benzo oxazepino quinazolinone (3d)

Dark grey powder, yield in (83%), (m.p 211-213 ºC); IR /cm^{-1}: 2922, 1726, 1671, 1455, 1404, 813;^{1}H NMR δ 7.80 (s, 1H), 7.33 (s, 1H), 7.30 – 7.27 (m, 1H), 7.21 (s, 1H), 7.21 – 7.19 (m, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 6.96 (s, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 6.39 (s, 1H), 5.81 (s, 1H), 4.60 (s, 1H), 4.57 (s, 1H), 2.30 (m, 1H); ^{13}C NMR δ 163.15, 158.28, 146.73, 138.40, 136.54, 135.63, 134.12, 132.56, 131.21,129.68, 127.72, 127.13, 125.04, 124.93, 123.15, 122.52, 121.84, 115.31, 96.66, 67.21, 21.13.

E-8-(4-bromophenyl)-1-(iodomethylene) tetrahydro benzo oxazepino quinazolin- one (3e)

Dark brown powder, yield in (82%), (m.p 221-223 ºC); IR / cm^{-1}: 2922, 1735, 1601, 1489, 1456, 1245, 754;^{1}H NMR δ 7.80 (s, 1H), 7.55 – 7.43 (m, 2H), 7.33 (s, 1H), 7.26 – 7.17 (m, 3H), 7.10 (s, 1H), 6.96 (d, J = 5.0 Hz, 2H), 6.89 (s, 1H), 6.80 (s, 1H), 6.39 (s, 1H), 5.84 (s, 1H), 4.62 (d, J = 15.0 Hz, 2H); ^{13}C NMR δ 163.15, 158.28, 146.73, 138.40, 135.18, 134.12, 132.56, 132.43, 129.68, 127.72, 127.13, 125.04, 123.15, 122.52, 121.84, 119.19, 115.31, 96.66, 67.21.

E-1-(iodomethylene)-8-(3-nitrophenyl) tetrahydro benzo oxazepino quinazolin- one (3f)

Brown powder, yield in (77%), (m.p 214-216 ºC); IR / cm^{-1}): 2925, 1644, 1611, 1478, 1448, 1238;^{1}H NMR δ 8.34 (s, 1H), 7.95 (d, J = 67.2 Hz, 2H), 7.72 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 7.14 (s, 1H), 7.06 (s, 1H), 6.87 (d, J = 19.4 Hz, 2H), 6.77 (s, 1H), 6.61 (s, 1H), 6.39 (s, 1H), 5.84 (s, 1H), 4.62 (d, J = 15.0 Hz, 2H); ^{13}C NMR δ 163.15, 158.28, 150.05, 146.73, 139.35, 138.40, 134.12, 132.56, 131.15, 130.12, 129.68, 127.72, 127.13, 125.04, 123.15, 122.59, 121.84, 120.58, 115.31, 96.66, 67.2.

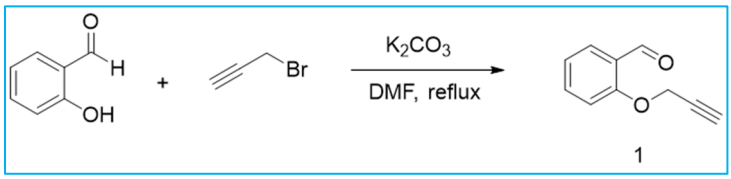
Biological activity. The prepared organic compounds 1, 2(a-f), 3(a-f) were tested in the laboratory for their antimicrobial activity against different types of bacteria using the agar diffusion method, agar medium for bacteria [29]. The prepared organic compounds were inspected to evaluate their antibacterial ability against four different types of strains of bacteria,

including Gram-positive bacteria such as *Staphylococcus* (Gram +ive) as well as Gram-negative bacteria such as *Escherichia coli* (Gram -ive), *Klebsiella pneumoniae* (Gram -ive), *Pseudomonas* (Gram -ive), pathogenic bacteria using ampicillin 25 mg/ml and Ciprofloxacin (15mg/ml) as reference compounds. These bacteria were chosen due to their importance in the medical field and their involvement in various diseases, as well as their differing nature of resistance to different drugs and antibiotics. The prepared organic compounds were dissolved in dimethyl sulfoxide solvent at concentrations of 10, 50, and 100 micrograms/ml. After preparing the agar and broth medium, the sterilized agar medium poured into sterilized p. dishes in a sterile environment. After pouring, p. dishes kept at room temperature for 15-30 minutes until the medium was absorbed. Initially, the Petri dishes were wiped with bacteria, then wells were made in the Petri dishes using a cork borer and all samples including the reference compound were placed. Petri dishes were then incubated at 37 degrees Celsius for 24 hours, and the inhibition area was measured in millimeters by reading the diameters of the inhibition zone using a standard scale. Results are shown in Table 2 [30, 31].

Results and discussion

For synthesized of heterocyclic compounds containing nitrogen and oxygen atoms with biological activity, the necessary conditions were initially developed for the synthesis of 2-(Prop-2-yn-1-yl oxy) benzaldehyde (Scheme 2), where salicylaldehyde and propargyl bromide were taken as starting materials.

The synthesis was carried out by reacting salicylaldehyde with propargyl bromide in dimethylformamide in the presence of potassium carbonate and refluxed it with a yield of 85%.



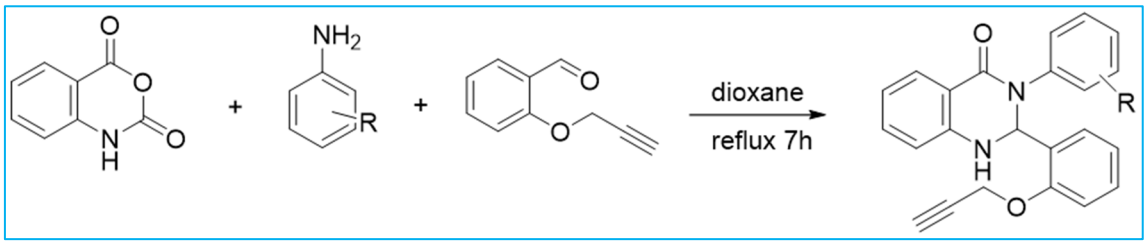
Scheme 2. Synthesis of 2-(propynyloxy) benzaldehyde

Structure of the prepared compound was determined based on the spectral analysis data of infrared spectroscopy, ^{1}HNMR, ^{13}C.

The infrared spectra of compound (1) show absorption bands of stretching vibrations of the C≡CH bond in the region of 3269 cm^{-1} and the C≡C bond in the region of 2116 cm^{-1}. Absorption bands are present for the C=O group in the region of 1680 and 1661 cm^{-1}, in addition to stretching vibrations of the C-O-C bond in the region of (1263 and 1285) cm^{-1} in the infrared spectra. The ^{1}HNMR spectrum of compound (1) contains the following distinctive signals: a singlet signal belongs to acetylene proton at δ 2.58 ppm, also the two protons of the carbon linked to oxygen gave singlet signal at δ 4.99 ppm, chemical shifts for aromatic ring protons between δ (7.21-7.79) ppm, while the hydrogen atom in the aldehyde group appears at δ 10.43 ppm as a singlet signal [32].

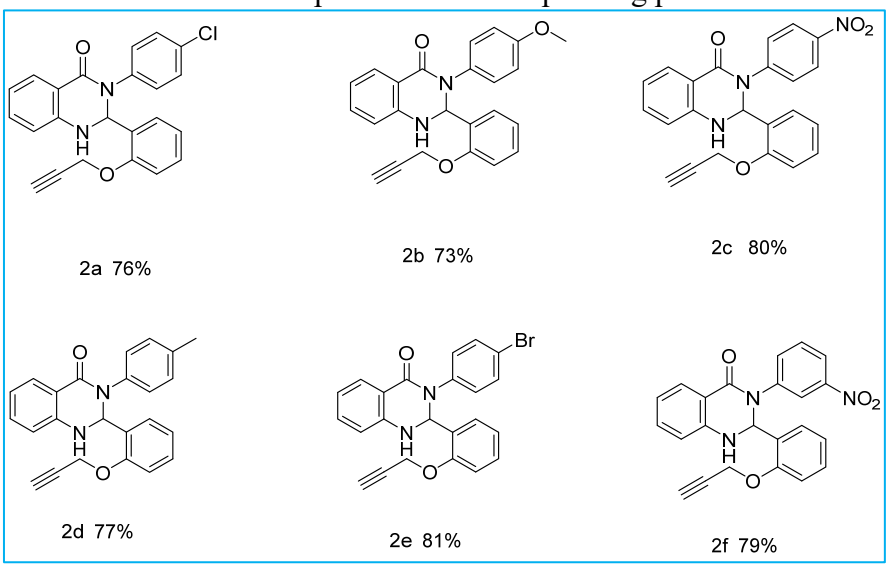
In the ^{13}C NMR spectrum of compound (1), the carbon atom of the carbonyl group was observed at δ 189.50 ppm. The signals in the range of δ (114.77-159.96) ppm correspond to the aromatic ring carbon atoms. The carbon atoms of the acetylene group give signals at δ (79.53 – 79.11) ppm. The signal at δ 56.91 ppm can be attributed to the carbon atom in the -OCH_2- group.

After the Synthesis of 2-(prop-2-yn-1-yl oxy) benzaldehyde (1), and due to our interest in developing multicomponent reactions, triple-component condensation reactions were conducted in a single vessel between compound (1) and isatoic anhydride along with one of the aniline substituents to form derivatives of 2,3-dihydroquinazolin-4-(1H)-one (a-f) (Scheme 3).



Scheme 3. Synthesis of 2,3-dihydroquinazolin-4-(1H)-one

The synthesis was carried out through the reaction of equivalent mole of isatoic anhydride, benzaldehyde, and aniline derivative presence of dioxane as a solvent. Upon conducting the reaction under reflux conditions, the yield of the corresponding product was excellent.



Scheme 4. Derivatives of 2,3-dihydroquinazolin-4-(1H)-one

All substituted 2,3-dihydroquinazolin-4(1H)-ones compounds were characterized based on the spectral analysis data of infrared, ^{1}H and ^{13}C NMR. In the infrared spectrum, absorption bands of the acetylene group C≡CH observed at 3068 cm^{-1}, and the C≡C bond appears at 2111 cm^{-1}. There are absorption bands for the C=O group in the range of 1725 and 1765 cm^{-1}, in addition to the stretching vibrations of the N-H group observed at 3210 cm^{-1}, C-N vibrations in the region of 1285 cm-1, the stretching vibration band of the C-O-C bond is observed at 1208 cm^{-1}, and the stretching vibration band of the C-Cl bond is seen in the region of 818 cm^{-1} [33].

In the ^{1}H NMR spectrum, the acetylene proton appeared at δ 3.34 ppm, while the NH proton was observed at δ 4.95 ppm. OCH_2 protons were observed at 4.99 ppm, whereas the appearance of the CH proton attached to the nitrogen atoms was at δ 6.53 ppm. The chemical shift of the aromatic ring protons was observed between δ 6.98-7.89 ppm.

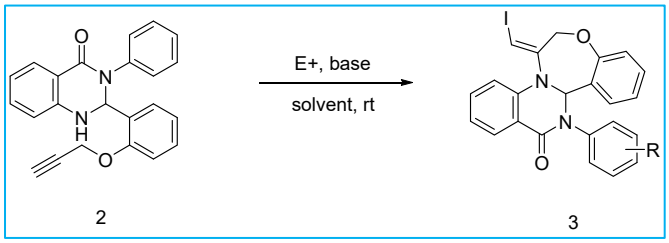
In the ^{13}C NMR spectrum, resonance signals for the acetylene carbons were observed at 79.31-79.46 ppm. The carbon atom located between the two nitrogen atoms gave a signal at 61.67 ppm, while the carbon atom of amid group appeared in the range of 160.37 ppm. The carbon atom in the -OCH_2- group was observed in the range of 56.87 ppm. Signals in the range of 110.75-157.88 ppm correspond to aromatic ring carbons.

Optimization of the reaction conditions:

Initially, the primary reactions aimed to find an electrophilic source capable of promoting the cyclization of compounds (2). When we started using iodine as the electrophilic source, it was done by examining the reaction of compound (2) with iodine in DCM and using potassium bicarbonate, sodium bicarbonate as a base in this reaction. Compound (3a) obtained yields of 20% and 30% respectively (Table 1, Entries 1 and 2 respectively).

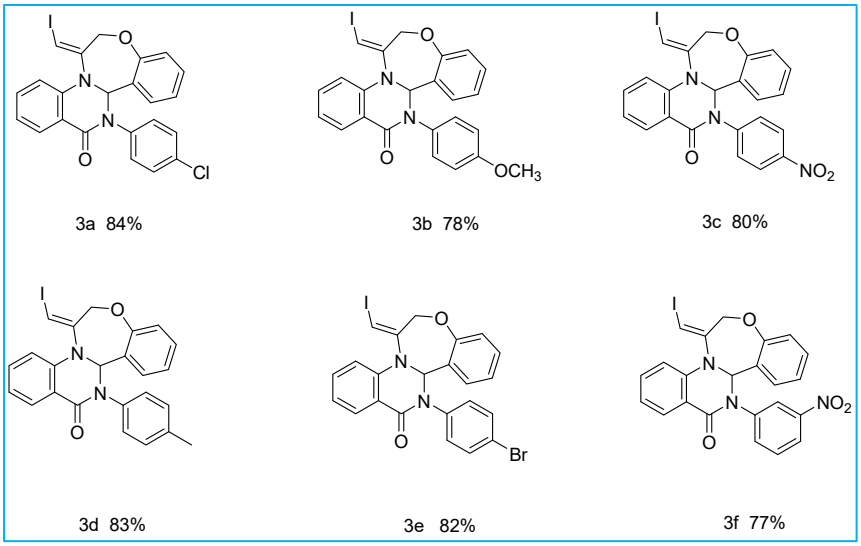
Table 1. Optimizationof the Reaction Conditions

Entry	Solvent	E^+	Base	Yield (%)
1	DCM	I_2	$KHCO_3$	**20**
2	DCM	I_2	$NaHCO_3$	**25**
3	DCM	I_2	K_2CO_3	**84**
4	DCM	I_2	Na_2CO_3	**40**
5	CH_3CN	I_2	K_2CO_3	**trace**
6	THF	I_2	K_2CO_3	**trace**
7	DCM	ICl	K_2CO_3	**25**
8	DCM	NIS	K_2CO_3	**33**
9	DCM	Br	K_2CO_3	**28**
10	DCM	*t*-BuOK	K_2CO_3	**trace**



We tested other bases such as K_2CO_3 and Na_2CO_3 and found that K_2CO_3 is the best base for preparing compound 3a with a yield of 84% (Table 1, Entries 3 and 4 respectively). Other solvents, such as acetonitrile and tetrahydrofuran, were unable to improve the results (Table 1, Entries 5 and 6 respectively). Additionally, while using electrophilic iodine present in the reagents, such as ICl and NIS, yielded products, the yields were lower than those obtained using I_2 (Table 1, Entries 7 and 8 respectively). We also studied the cyclization using the electrophile bromine; however, potassium tert-butoxide did not perform well, leading to the recovery of compound (2a) (Table 1, Entries 9 and 10).

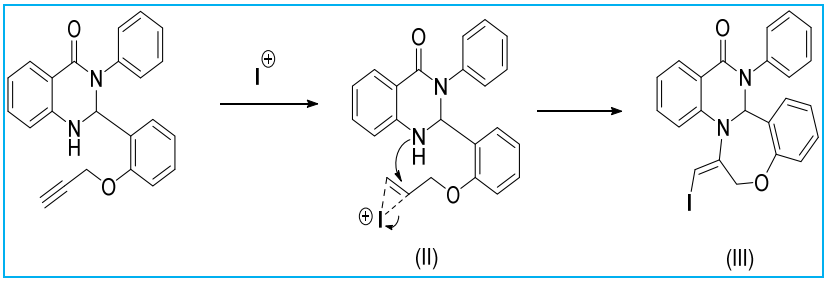
With the optimal conditions, we found that the formation of non-homogeneous ring compounds using iodine as the electrophile and potassium carbonate as the base in DCM is the best. The results were summarized in Scheme 5.



Scheme 5. Structures and yields of the compound of cyclization.

From the previously mentioned notes, it appears from the provided data (Table 1, Entry 3) that when compound 2a (0.0023 mol) reacted with (0.0046 mol) of I_2, with (0.0046 mol) of K_2CO_3 in (20 ml) CH_2Cl_2 at room temperature for 7 hours, the structure of compounds (3a-f)

was confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The proposed mechanism included linking of iodine with alkyne bonds gave (II) followed by an intramolecular cyclization (Scheme 6).



Scheme 6. The proposed mechanism of linking of iodine with alkyne bonds

Taking 3a as an example, in the infrared spectrum, absorption bands of the C-H stretching vibrations attached to the double bond appear in the region 2922 cm^{-1}. The C=C bond stretching vibrations are observed in the region 1601 cm^{-1}. Additionally, absorption bands corresponding to the C=O stretching vibrations are seen 1735 cm^{-1}. Vibrations corresponding to the stretching of the C-N group are observed at 1489 and 1456 cm-1, while absorption bands of the CO bond appear 1245 cm^{-1}. Furthermore, absorption bands for the C-Cl bond vibrations are observed in the region 754 cm^{-1}. In the (^{1}HNMR) spectrum , we notice the disappearance of protons acetylene and NH protons, and the appearance of protons of the -CH_2 group attached to oxygen in the oxazepino ring at (4.64 and 4.66) δ (ppm), and the appearance of the CH proton attached to the C=C group at δ 5.29 ppm, and while the appearance of the CH proton attached to the two nitrogen atoms is at δ 6.25 ppm, The chemical shift of the aromatic ring protons occurs between δ (7.71- 6.94) ppm. In the ^{13}CNMR spectrum, the disappearance of resonance signals of acetylene carbon atoms was observed, and the appearance of a resonance signal of the carbon linked to the -OCH_2- group in the oxazepino ring at 65.77 ppm was observed. Carbon atom of the C=C group was observed in the region at 96.60 ppm. The signals in the range of 114.44-160.71 ppm are attributed to the carbon atoms of the aromatic ring. The signal at 164.49 ppm can be attributed to the carbon linked to the carbonyl.

Antibacterial activity. From Table (2), the results of the biological activity indicate that some of the organic compounds prepared in the laboratory can inhibit the bacteria used. It was observed that with an increase in the concentration of the substance, the diameter of inhibition (the diameter of the area free from bacterial growth) increases. Compounds (3a, 2b) were found to be inactive towards the types of bacteria used compared to the rest of the compounds. Meanwhile, compounds (3f, 3d, 2f, 2e, 2d) showed moderate activity against *Klebsiella*, *Escherichia coli*, and *Staphylococcus*. All the synthesized compounds (1, 2a-f, 3a-f) were proved inactive against Pseudomonas providing no significant results. Compound 3d at a concentration of 100µg/ml was found potent antibacterial against *Klebsiella*, *Escherichia coli*, and *Staphylococcus* showing good inhibitory action.

Table 2. Antibacterial activity screening data of the synthetic compound

Comp.	***Klebsiella*** ZI/mm			***Escherichia coli*** ZI/mm			***Staphylococcus*** ZI/mm			***Pseudomonas*** ZI/mm		
	10 µg/ml	**50 µg/ml**	**100 µg/ml**	**10 µg/ml**	**50 µg/ml**	**100 µg/ml**	**10 µg/ml**	**50 µg/ml**	**100 µg/ml**	**10 µg/ml**	**50 µg/ml**	**100 µg/ml**
1	9	11	11	9	13	16	0	9	12	0	0	0

2a	12	14	16	10	14	17	0	14	16	0	0	0
2b	0	0	0	0	0	0	0	0	0	0	0	0
2c	14	18	22	0	12	12	8	11	16	0	0	0
2d	13	17	23	16	21	24	12	17	18	0	0	0
2e	9	16	16	12	15	15	13	15	19	0	0	0
2f	11	17	19	14	18	20	11	14	18	0	0	0
3a	0	0	0	0	0	0	0	0	0	0	0	0
3b	0	10	10	9	10	13	0	0	0	0	0	0
3c	11	17	22	0	0	0	0	0	0	0	0	0
3d	15	24	28	19	23	25	16	22	27	0	0	0
3e	0	14	19	0	0	0	0	0	0	0	0	0
3f	9	9	9	8	9	9	9	12	16	0	0	0
Control (DMSO)	0	0	0	0	0	0	0	0	0	0	0	0
Amoxicillin	25			–			25			–		
Ciproflox acin				15			–			15		

Note: 20 mm or above = highest inhibition, 15-20 mm = average inhibition, less than 15 mm. weak.

Docking Study. A docking experiment was carried out using online server CB-dock2 [34] which can be accessed via https://cadd.labshare.cn/cb-dock2/php/index.php. The protein target was shikimate kinase enzyme of Escherichia coli (pdb ID: 1KAG and the substrate of enzyme namely shikimate as control according to method of Al-Khayyat [35]. Study was conducted to find inhibitors of shikimate kinase enzyme in *Mycobacterium tuberculosis* using Autodock vina as docking tool.[36] Six compounds were selected having binding affinities ranged from − 3.5 to − 8.1 kcal/mol from 298 compounds. The best one was (E)-1-(iodomethylene)-8-p-tolyl)-1,2,7b,8-tetrahydro-9H benzo[1,4]oxazepino[4,5-a]quinazolin-9-one with -8.1 kcal/ mol as docking score. Table 2 show results of docking experiments with hydrogen bonding and hydrophobic interactions involved. Interactions were visualized using LigPlot software [37].

Table 3. Molecular docking results of the compounds against shikimate kinase enzyme

Compound	Docking score (Kcal/mol)	Hydrogen bonds	Hydrophobic interactions
Shikimate	-6.5	Asp^{34}, Asp^{36}, Ala^{15}, Ser^{18}, lys^{17}, Gly^{16}, Gly^{14}	Pro^{121}

3d	-8.1	Leu^{123}	Lys^{17}, Ser^{18}, Asp^{36}, Pro^{121}, thr^{114}, His^{124}, Met^{13}, Thr^{127}, Leu^{122}
3b	-7.8	Thr^{19}, Ser^{18}	Gly^{16}, Thr^{114}, Ala79, Asp^{34}, Lys^{17}, Pro^{121}, Met^{13}, Gly^{14}, Leu^{122}
3f	-3.5	Arg^{22}, Ser^{18}, Asp^{34}, Lys^{17}, Gly^{16}, Gly^{14}, Ala^{15}	----
3c	Error		
3a	-7.9	Gly^{16}, Lys^{17}	Asp^{34}, Ser^{18}, Pro^{121}, $Asp36$, Gly^{14}, Thr^{114}
3e	-7.9	Gly^{16}, Lys^{17}	Asp^{34}, Ser^{18}, Asp^{36}, Pro^{121}, Thr^{114}, Gly^{14}

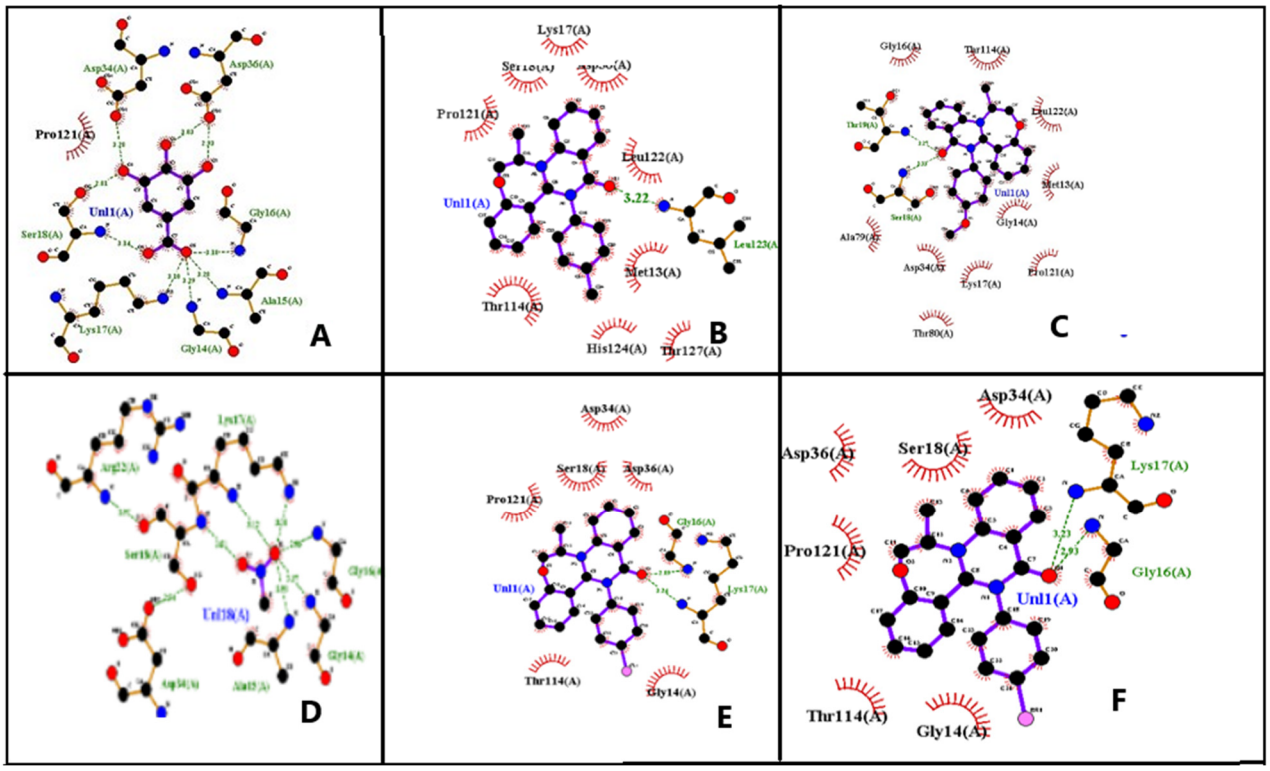


Fig. 1. Shikimate kinase interactive with **(A), (B), (C), (D) (E), (F)**

Conclusion

The synthetic tactic which was described in this paper shows the importance of intramolecular alkyne cyclization for the creation of attractive heterocyclic systems. An efficient synthesis of E-1-(iodomethylene)-8-phenyl-1,2,7b,8-tetrahydro-9H-benzo[6,7][1,4]oxazepino[4,5-a]quinazolin-9-one derivatives from 3-phenyl-2-(2-(prop-2-yn-1-yloxy) phenyl)-2,3-dihydroquinazolin-4(1H)-one derivatives has been advanced under mild reaction conditions.

Acknowledgement

The authors would like to acknowledge university of Mosul/college of education for pure science. In addition, we present our thanks to Mr. Mohammed Zaghlool al-Khayyat for his efforts in docking study.

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