One-Pot Synthesis of Quinazoline Derivatives Using Copper Nanocatalyst Stabilized on Graphene Oxide Functionalized by N1,N2-bis((Pyridine-2-yl)Methyl)Benzene-1,2-Diamine

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One-pot Synthesis of Quinazoline Derivatives Using Copper Nanocatalyst Stabilized on Graphene Oxide Functionalized by N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine

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Abstract

Having a biological property is just one of features of *N*-heterocycles. Another thing is to be dramatically well-designed. In other words, awe-inspiring combination of materials and the thing that really makes these materials just unique of its kind is nothing but its medical properties. That is why, majority of scientists are full of enthusiasm for synthesizing of these types of materials. In this article, we have reported five effective methods for synthesizing quinazoline, which is a immensely important group of *N*-heterocycles with using copper nanocatalyst stabilized on graphene oxide functionalized by N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine. Moreover, we have investigated the effects of substitutions connected to aldehydes, benzylamines and benzamides as a carbon source of quinazoline heterocyclic ring. Finally, we have assessed effects kinds of ammonium salts as a nitrogen source of quinazoline heterocyclic ring.

Keywords *N*-Heterocycle. Quinazoline, Graphene Oxide. Copper Nanocatalyst. N^1,N^2 -Bis((pyridine-2-yl)methyl)benzene-1,2-diamine.

1. Introduction

Nowadays, majority of people of all around the world especially undeveloped countries are really suffering from a lack of drug, particularly bacterial medicines. Most of drugs that is used to treat bacterial diseases contain nitrogen-rich heterocyclic rings. This way, designing and discovering novel ways to synthesize these types of heterocycles is very essential. Quinazolines are a category of nitrogen-containing heterocyclic compounds, using to treat

bacterial illnesses. Quinazolines have unique properties. For example, if thiophene is in position 2 of quinazoline structure, which gives to quinazoline the antibacterial property. Moreover, when benzene is in position of 4, that gives the inhibitory effect of modulating enzyme to quinazoline. But the most significant feature is here, in comparison with others, the simultaneous presence of thiophene and benzene, giving quinazoline both of mentioned properties (Figure 1).

FIGURE 1. The Structure of Quinazoline

Furthermore, the application and frequent presence of structure of quinazoline in immensely important drugs such as Prazosin, Gefitinib and Erlotinib that they are used as an anticancer drug (Figure 2) has led scientists to call this structure pharmaceutical skeleton. As a matter of fact, choosing this name describes the importance of its synthesis [1-10].

FIGURE 2. Quinazoline-based drugs

The fact that presence of catalyst in chemical reaction is important is obvious to all. Not only does it play a crucial role in increasing reaction yield but it also comes with a multitude number of benefits. Such as, decreasing time of reaction, promoting speed and so on. To opt for a catalyst, there are three necessary factors that must be considered. They are simply: green, green and of course green. Because unfortunately nowadays not many people place a high value on environment. The massive burden of protecting the environment is on the shoulders of chemists. Indeed some other options are also worth mentioning such as, high operating speed, high thermal resistance and so on. Trying to accomplish this worthwhile goal has led us to using chemical materials with biological properties. Graphene oxide is a good example of chemical materials with biological property. In other words, it is a green material. Actually, graphene oxide is a three-dimensional platform that destroy bacterias by covalent interaction with them in short time. The use graphene oxide in catalyst synthesis gives us hope that the catalyst's potential contact with the body will not cause any problems [17, 28, 38].

On the other hand, copper metal has attracted lots of attentions in the past few decades. Probably, this is because of toxicity low or the extraordinary the activities it has shown itself. Such as: the presence of copper in the body is essential to disable tyramine, anomalous diamagnetism behavior, high thermal resistance, biological properties and so on [32, 33, 35].

In this article, we have been able to produce a green catalyst with using a completely green method that have dealt with it in the following.

2. Experimental

General Information and Methods

All commercially available chemicals were purchased from Merck (Kenilworth, NJ) and Fluka (Buchs, Switzerland) companies and used without further purification unless otherwise stated. Infrared (IR) spectroscopy was conducted on a Perkin Elmer GX FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl_3 on Bruker Avance 400MHz FT spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm). Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Melting points were measured on a BUCHI 510 apparatus in open capillary tubes. Elemental analyses (C, H, N) were performed with a 4010 CHNS-O Analyzer.

Synthesis of N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine:

A mixture of benzene-1,2-diamine (6 mmol) and pyridine-2-carbaldehyde (12 mmol) was stirred in 25 mL of dry methanol under 60-80 °C for 12 h. Then, 24 mmol NaBH₄ was added to the reaction. After 12 h the reaction was completed then the reaction mixture was added 25 mL chloroform and 25 mL water. To purify, we created two phases of chloroform and water that product was dissolved in chloroform and impurities were dissolved in water. In this way they were separated each other.

Graphene oxide synthesis by Hummers method:

A mixture of natural graphite powder (5 g) and 115 mL H₂SO₄ (98%) was stirred for 30 min. Then, 2.5 g NaNO₃ was added to the reaction. To avoid agglomeration, it was stirred strongly. The reaction was transferred to the ice bath. 15 g of KMnO₄ and 50 mL of H₂O₂ (30%) were added to reaction. The mixture was stirred for 45 min and added 10 mL HCl (37%). Finally, separated by centrifugation.

Synthesis of graphene oxide functionalized by N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine:

A mixture of N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine (5 mmol) and ammonia (50 mL) was stirred in H₂O for 30 min. Then, 2 g of graphene oxide was added. The reaction was under a condition refluxed for 12 h. Finally, the product was washed with hot water and cold ethanol and transferred under the hood.

Copper immobilization on the graphene oxide functionalized by N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine:

A mixture of the graphene oxide functionalized by N^1,N^2 -bis((pyridine-2-yl)methyl)benzene-1,2-diamine (1 g) and Cu(CH₃COO)₂ (0.5 g) was stirred in EtOH under a condition refluxed for 10 h. Finally, it was washed several time with deionized water.

The typical procedure for the synthesis of 6-chloro-2-(4-(dimethylamino)phenyl)-4-phenylquinazoline (Table 7, entry 1):

A mixture of 4-(dimethylamino)benzaldehyde (1 mmol), 2-amino-5-chlorobenzophenone (1 mmol), ammonium acetate (1 mmol) and GO@N-Ligand-Cu (0.003 g) was stirred at 85 °C for the appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/n-hexane (1:6)], the chloroform was added to the reaction mixture and stirred for 10 min. Then added dissolved sodium bicarbonate dissolved. Next, the two-phase were separated and the product was obtained by evaporation of chloroform.

The typical procedure for the synthesis of 6-chloro-4-phenyl-2-(3,4,5-trimethoxyphenyl)quinazoline (Table 7, entry 2):

A mixture of (2-bromo-5-chlorophenyl)(phenyl)methanone (1 mmol), sodium azide (1 mmol), (3,4,5-trimethoxyphenyl)methanamine (1 mmol) and GO@N-Ligand-Cu (0.002 g) was stirred in DMSO (5 mL) at 30 °C for the appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/n-hexane (1:6)]. The chloroform was added to the reaction to stir for 10 min. Then, dissolved sodium bicarbonate added. Next, the two-phase were separated and the product was obtained by evaporation of chloroform.

The typical procedure for the synthesis of 6-chloro-4-phenyl-2-(2,4-dichlorophenyl)quinazoline (Table 7, entry 10):

A mixture of 2,4-dichlorobenzamide (1mmol), (2-bromo-5-chlorophenyl)(phenyl)methanamine (1 mmol), GO@N-Ligand-Cu (0.006 g) and K₂CO₃ (0.6 mmol) was stirred in 2-propanol solvent (5 mL) at 65 °C for appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/n-hexane (2:7)]. Then, it was purified by the method mentioned in Section 2.7.

The typical procedure for the synthesis of 6-chloro-2-(3-methoxyphenol)-4-phenylquinazoline (Table 7, entry 3):

A mixture of 2-(aminomethyl)-6-methoxyphenol (1 mmol), 2-amino-5-chlorobenzophenone (1 mmol) and GO@N-Ligand-Cu (0.005 g) was stirred under a O₂ atmosphere at 50 °C for the appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/n-hexane (2:6)]. Then, it was purified by the method mentioned in Section 2.7.

The typical procedure for the synthesis of 6-Chloro-2-(furan-2-yl)-4-phenylquinazoline (Table 7, entry 7):

A mixture of furan-2-carbaldehyde (1 mmol), 2-(amino(phenyl)methyl)-4-chlorobenzenamine (1 mmol) and GO@N-Ligand-Cu (0.005 g) was stirred at 75 °C for the appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/*n*-hexane (2:7)]. Then, it was purified by the method mentioned in Section 2.7.

Typical procedure for the preparation of bis-quinazoline (Scheme 8):

A mixture of 1-(3-phenoxypropoxy)benzaldehyde (1 mmol), 2-amino-5-chlorobenzophenone (2 mmol), ammonium acetate (2 mmol) and GO@N-Ligand-Cu (0.009 g) was stirred under 85 °C for the appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/toluene/*n*-hexane (1:2:9)]. Then, it was purified by the method mentioned in Section 2.7.

3. Results and Discussion

Our interest in the green design of the catalyst led us to synthesize copper nanocatalyst stabilized on graphene oxide functionalized by *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine (Scheme 1) [36].

Scheme 1. Copper nanocatalyst stabilized on graphene oxide functionalized by *N*¹,*N*²-bis((pyridine- 2-yl)methyl)benzene-1,2-diamine (GO@*N*-Ligand-Cu)

The synthesized GO@*N*-Ligand-Cu was fully characterized by using various techniques such as FT-IR (Figure 3), Mass Spectroscopy (MS) (Figure 4), ¹H-NMR (Figure 5), Energy-dispersive X-ray spectroscopy (EDX) (Figure 6), X-Ray Diffraction (XRD) (Figures 7), Scanning Electron Microscopy (SEM) (Figure 8), DTG and DTA (Figure 9). Figure 3, FT-IR illustrates the different steps of catalyst synthesis, that spectrum a relevant to the synthesis of the *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine compound as the catalyst ligand. In this spectrum, single-branch N-H peak at 3405 cm⁻¹, aromatic C-H peak at 3053 cm⁻¹, aliphatic CH₂ peak at 2904 cm⁻¹, and peaks at 1573-1591 cm⁻¹ relevant to C=N can be seen. The b spectrum relevant to graphene oxide as the catalyst substrate includes the broad peak of the OH acid groups COOH at 2400-3500 cm⁻¹, the peak of the C=O groups COOH at 1712 cm⁻¹, the peak of the C-O-C group's epoxide at 1167-1229 cm⁻¹, in addition, two peaks at 846 cm⁻¹ and 820 cm⁻¹ also belong to the epoxide groups. Spectrum c relevant to step functionalization of the graphene oxide with *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine, which includes the broad peak of the OH acid groups COOH at 2400-3500 cm⁻¹, the peak of the C=O groups COOH at 1712 cm⁻¹, the peak of the C-O-C group's epoxide at 1155 cm⁻¹. The results obtained from this FT-IR show success in the synthesis of this compound. The d spectrum corresponds to the last phase of the catalyst synthesis which is after fixation copper, area 2400-3600 has been out of disorder and this indicates the copper coupling with the graphene oxide functional groups.

Figure 3. FT-IR spectra of a) *N*-Ligand, b) GO, c) GO@*N*-Ligand, and d) GO@*N*-Ligand-Cu

The Mass Spectroscopy of *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine is shown in Figure 4. The presence of molecular ion peak in 290 m/z is related to the combination of *N*-Ligand and peaks 78, 91, and 199 m/z which are related to cleavages during synthesis.

Figure 4. Mass Spectroscopy spectra of *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine (*N*-Ligand)

The ^1H -NMR (400 MHz, CDCl_3) spectra of *N*-Ligand is performed and investigated (Figure 5). The ^1H -NMR shows N-H peak at δ 4.06 (s, 1H), CH_2 peak at 4.86 (s, 2H) and other peak related to C-H aromatic as follows 6.10-6.12 (m, 2H), 6.19-6.21 (m, 2H), 6.52-6.53 (t, 2H), 6.67-6.69 (d, 2H), 6.87-6.69 (t, 2H) and 7.41-7.42 (d, 2H).

Figure 5. ^1H -NMR of N',N'' -bis((pyridine-2-yl)methyl)benzene-1,2-diamine (N -Ligand).

The elements present in the catalyst were investigated using the EDX technique (Figure 6). In this spectrum, O, N, Cu, C peaks were observed corresponding to the compounds of graphene oxide, *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine, copper, graphene oxide and *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine.

Figure 6. EDX of GO@*N*-Ligand-Cu

In XRD and SEM techniques, the size, shape and morphology of the catalyst were investigated. XRD relevant to graphene (spectrum a) and nanocatalyst (spectrum b) were investigated in Figure 7 and in the range of 2–90°. In spectrum, two peaks appear at $2\theta=25^\circ$, 45° corresponding to 100 and 200 graphene oxide crystal plates. In spectrum b, five peak numbers with values of 25° , 35° , 43° , 55° , 72° are seen that 25° and 35° peak corresponds to the graphene oxide and the 43° , 55° and 72° peak, relevant to the copper metal. In addition, the intensity of the peaks is weaker than of GO, indicating connecting copper to graphene oxide but the crystalline structure of graphene oxide remains.

Figure 7. XRD of a) GO and b) GO@N-Ligand-Cu

In another investigation, the scanning electron microscope (SEM) micrographs of the catalyst showed that the particles have not completely agglomerated. Moreover, particles of the catalyst were observed on a nanoscale (Figure 8).

Figure 8. SEM of GO@N-Ligand-Cu

Derivative thermal gravimetric (DTG) and differential thermal (DTA) of GO@N-Ligand-Cu was also investigated (Figure 9). Several degeneration stages observed for catalyst in the DTA pattern. The first weight loss is seen at 65 °C, which is estimated to be due to methanol solvent evaporation. The second weight loss occurs at temperatures of 90-100 °C, which may

be related to the evaporation of ethanol and water solvents. The third weight loss is observed at 325 to 320 °C, which is related to the degradation of the *N*¹,*N*²-bis((pyridine-2-yl)methyl)benzene-1,2-diamine compound and the graphene oxidized functional groups and the rest of the catalyst residues are degraded at the fourth weight loss at 410-500 °C. The obtained results indicate that the catalyst can be used up to 300 °C.

Figure 9. DTA and TGA of GO@*N*-Ligand-Cu

After the synthesis and full characterization of GO@*N*-Ligand-Cu, the catalyst was used to synthesize *N*-heterocycles compounds such as quinazolines and *bis*-quinazoline which will be discussed in the following.

History

In 1869 Griess prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline, by the reaction of cyanogens with anthranilic acid. The bicyclic product was called bicyanoamido benzoyl and used this name until 1885 [13]. The preparation of the quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel in 1903. The name was proposed by Widge. Other names such as phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine, and 1,3-diazanaphthaline have occasionally been used [13-17]. In recent years, different strategies have been proposed for the synthesis of quinazoline. In 2015, Ghorbani-Vaghei et al. the quinazoline derivatives were synthesized using TBBDA and PBBS catalysts [8]. Deshmukh et al. in 2018 were able to synthesize quinazoline derivatives using benzylamine, ammonium

acetate and 2-aminobenzylalcohol [2]. The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected in the reactions of quinazoline. The properties of substitute quinazolines depend largely on the nature of the substituents, whether they are in the pyrimidine ring or in the benzene ring, and whether or not complete conjugation is present in the pyrimidine ring [17]. In this paper, five green and efficient methods for the synthesis of quinazoline using two-component reactions and tri-component reactions in the presence of GO@N-Ligand-Cu as a useful catalyst are reported (Scheme 2).

scheme 2. Synthesis of quinazoline derivatives

As the first part of our research in organic synthesis catalyzed by GO@N-Ligand-Cu, we report an efficient and green strategy for the synthesis of quinazoline *via* tri-component reaction and one-pot from 2-amino-5-chlorobenzophenone, ammonium salts and aldehyde derivatives under a solvent-free condition at 85 °C (Scheme 2, reaction 1). Initial efforts have been focused on optimizing a condition for the synthesis 6-chloro-2-(4-(dimethylamino)phenyl)-4-phenylquinazoline of 4-(dimethylamino)benzaldehyde, 2-amino-5-chlorobenzophenone and ammonium acetate as a model reaction under different conditions. We investigated kinds of solvents and a solvent-free condition with a wide variety of temperatures and different amounts of catalyst for the model reaction. The results showed that 0.003 g of GO@N-Ligand-Cu catalyst under a solvent-free condition at 85 °C could have the highest reaction rate and highest product yield (Table 1, entry 1, 12 min, 91%).

Table 1. Reaction time and yield in different conditions

Entery	Solvent	Amount of catalyst [GO@N-Ligand-Cu (g)]	Temperature (°C)	Time (min)	Yield (%) ^b
1	Solvent-free	0.003	85	12	91
2	Solvent-free	0.001	85	55	79
3	Solvent-free	0.004	85	25	67
4	Solvent-free	0.005	85	33	60
5	Solvent-free	0.006	85	35	55
6	Solvent-free	0.007	85	60	43
7	Solvent-free	0.008	85	21	40
8	Solvent-free	0.006	95	21	87
9	Solvent-free	0.006	105	25	83
10	Solvent-free	0.006	75	18	85
11	Solvent-free	0.006	65	60	54
12	Solvent-free	0.006	55	180	47
13	C ₂ H ₅ OH	0.006	90	480	32
14	H ₂ O	0.006	100	430	30
15	C ₂ H ₅ OH/H ₂ O	0.006	95	540	33
16	CHCl ₃	0.006	67	540	47

17	CH ₃ COCH ₃	0.006	50	540	32
18	C ₆ H ₅ Cl	0.006	120	300	87
19	C ₆ H ₅ I	0.006	120	300	43
20	C ₄ H ₈ O ₂	0.006	85	600	10
21	C ₆ H ₅ CH ₃	0.006	110	1440	5

^a **Reaction condition:** 4-(dimethylamino)benzaldehyde (1 mmol), 2-amino-5-cholorobenzophenone (1 mmol) and ammonium acetate (1 mmol), 85°C and GO@N-Ligand-Cu (0.003) (Reaction 1, scheme 2). ^bIsolated yield.

To determine the scope and generality of this protocol, we examined the types of ammonium salts as a nitrogen source and the types of aldehydes as a carbon source. Under a optimum condition, several ammonium halides were tested (NH₄X, X= I, Br, Cl) which among them ammonium iodide had the best yield while the ammonium bromide had little yield. Seems to the larger volume of iodide causes crystal defect and makes it easier to break or since iodide has less electronegativity than bromide, it settles negative charge less quickly gains ammonium's protons. Then, ammonium acetate was used. The reaction yield was increased in the presence of ammonium acetate (Table 2, entry 5). That may be related to the amount of energy needed to separate ammonia from the salt system or due to the production of stable acetic acid from ammonium acetate, the pH of the system decreases and the presence of H⁺ in the reaction medium activates the carbonyl group.

The use of ammonium acetate in the reaction was preferred to other ones due to its high efficiency, low toxicity and easy separation.

Table 2. Optimizatin of the reaction condition^a

Entry	*N*	Yield (%)
1	NH ₄ I	68
2	NH ₄ Br	Trace
3	NH ₄ Cl	Trace
4	NH ₄ HCO ₃	5
5	NH ₄ OAc	91

^a**Reaction Condition:** 4-(dimethylamino)benzaldehyde (1 mmol), 2-amino-5-cholorobenzophenone (1 mmol) and ammonium acetate (1 mmol), 85 °C and GO@N-Ligand-Cu (0.003 g).

In another study, the effect and positions of electron releasing substituents and electron-withdrawing substituents attached to the aldehydes were investigated as carbon source. The highest yield was obtained as the electron releasing substituents were attached to the aldehyde in the para position (Table 4, entries 1 and 4, reaction 1). The reaction yield was relatively high in the ortho position (Table 4, entry 12, reaction 1). Of course, the ortho positions may be due to spatial hindrance, that is less yield than the para position. As the substitutions were in the meta positions, it had no effect on reaction efficiency (Table 4, entries 5 and 13, reaction 1). However, substitutions of electron-withdrawing in para and ortho positions did not any affect on the efficiency of reaction (Table 4, entries 6 and 10). The reaction yield is reduced if they are in the meta position (Table 4, entry 9, reaction 1). In scheme 3 we propose a mechanism for the conversion of 2-amino-5-chlorobenzophenone, ammonium acetate and aldehyde to quinazoline.

Scheme 3. Proposed mechanism for the synthesis quinazoline by the use of GO@N-Ligand-Cu *via* method 1 (Reaction 1 in Scheme 2)

According to this mechanism, GO@N-Ligand-Cu nanocatalyst act as Lewis acid, and by receiving the electron pair of the carbonyl aldehyde group activates it, that gives the formation of the intermediate compound **a**. Then, by the entrance of amine, the intermediate compound **b** is formed. In continuation, the catalyst activates the carbonyl group intermediate **b**, and forms the intermediate **c**. In the next step, by the attack of ammonia to the activated carbonyl formed intermediate **d**, which by an intramolecular reaction and oxidation is formed the quinazoline [8].

Another advantage of this catalyst is to reuse. After completion of the reaction, by adding 10 mL of chloroform to the reaction mixture, the catalyst was separated from the product that it was used after washing and drying in the reaction model. Copper nanocatalyst can be used five times in a row without losing of activity (Figure 10).

Figure 10. Recycling and reuse of atalyst GO@N-Ligand-Cu

As the second part of our research in this paper, in another efficient strategy, we were able to synthesize quinazoline derivatives *via* a tri-component reaction of (2-bromo-5-chlorophenyl)(phenyl)methanone, benzylamine derivatives and sodium azide (Scheme 2, reaction 2). Initially, the reaction of (2-bromo-5-chlorophenyl)(phenyl)methanone, sodium azide and (3,4,5-trimethoxyphenyl)methanamine was evaluated as a simple model substrate in the presence of solvents, a solvent-free condition, at a wide variety of temperatures, different amounts of GO@N-Ligand-Cu catalyst under different atmosphere conditions to reaction optimization. It was found the reaction is completed in DMSO solvent after 14 min at 30 °C under O₂ a atmosphere and 0.002 g of the catalyst with a 94% yield (Tbale 3).

Table 3. Reaction time and yield in different conditions^a.

Entery	Solvent	Amount of catalyst [GO@N-Ligand-Cu (g)]	Temperature (°C)	Time (min)	Yield (%) ^b
1	DMSO	0.002	30	14	94
2	DMSO	0.002	40	14	93
3	DMSO	0.002	50	14	93
4	DMSO	0.002	60	16	92
5	DMSO	0.002	75	20	89
6	DMSO	0.002	100	35	70
7	DMSO	0.004	30	15	85
8	DMSO	0.006	30	19	60
9	DMSO	0.008	30	45	47
10	Chlorobenzene	0.002	30	14	87
11	Iodobenzene	0.002	30	55	40
12	Toluene	0.002	30	5 (h)	30
13	EtOH	0.002	30	2 (h)	54
14	H ₂ O	0.002	30	3 (h)	58
15	EtOH/H ₂ O	0.002	30	3 (h)	73
16	Chloroform	0.002	30	6 (h)	23
17	Acetone	0.002	30	4 (h)	45
18	Ethyl acetate	0.002	30	10 (h)	16
19	DMSO	0.002	30	10 (h0	trace

^a**Reaction conditions:** (2-bromo-5-chlorophenyl)(phenyl)methanone (1 mmmol), sodium azide(1 mmmol) and (3,4,5-trimethoxyphenyl)methanamine (1 mmmol), 30°C, GO@N-Ligand-Cu (0.002) and under O₂ atmosphere (Reaction 2, scheme). ^b**Isolated yield.**^cUnder nitrogen atmosphere

Then, we examined the effect of substituents attached to benzylamine. It was found benzylamines containing electron releasing substituents in the para position had the highest yield (Table 4, entry 2, reaction 2). It may be due to their resonance state at the ring formation stage that it helps protons exit radically. Furthermore, benzyls containing electron-withdrawing substituents were tested too. Electron-withdrawing substituents in the meta position results in lower reaction yield but other situations (para and ortho) had a little impact on reaction yield (Compare entry 9 with entries 10 and 16 in Table 4, reaction 2).

Table 4. Synthesis of quinazoline derivatives in the presence of GO@*N*-Ligand-Cu

Entry	Product	Reaction1	Reaction2	Reaction3	Reaction4	Reaction5
	M.p	Time (min)	Time (min)	Time (min)	Time (min)	Time (min)
		& Yield(%)	&Yield(%)	& Yield(%)	&Yield(%)	&Yield(%)
1	162-164	12/91	31/89	170/57	22/89	40/90
2	164-166	17/87	30/94	100/65	24/86	42/90
3	249-251	26/80	19/82	110/63	20/90	47/85
4	190-191	25/86	33/85	32/71	30/80	60/75
5	182-184	45/70	38/66	20/79	53/71	63/72
6	186-187	30/75	40/78	10/85	93/64	80/64

7

26/72

35/74

85/68

26/83

35/93

195-197

8

28/70

36/69

50/73

32/78

45/88

223-224

9

50/63

55/70

15/80

170/55

120/58

178-180

10

33/74

43/73

8/87

120/60

90/60

161-162

11

28/79

34/80

91/64

27/84

48/80

156-158

12

23/86

31/88

150/59

25/85

54/78

13

32/75

37/74

54/72

50/70

60/70

14

35/73

39/67

30/74

35/75

64/78

217-218

15		26/73	44/72	25/50	60/65	58/69
16		40/65	46/74	15/83	62/61	75/67

194-196

The proposed mechanism to the synthesis of quinazoline derivatives by the use of (2-bromo-5-chlorophenyl)(phenyl)methanone, sodium azide and benzylamine derivatives in the presence of GO@N-Ligand-Cu is illustrated in Scheme 4.

Scheme 4. Proposed mechanism for the synthesis quinazoline by the use of GO@N-Ligand-Cu *via* method 2 (Reaction 2 in Scheme 2)

Firstly, carbonyl is activated by GO@N-Ligand-Cu and intermediate (I) is formed. By the arrival of benzylamine and the loss of one molecule of water, intermediate (II) is formed. By acidic proton exit radically in the presence of atmospheric oxygen, radical ions are created. Then, by the entry of sodium azide and copper coupling, intermediate (III) is formed. In the next step, by the use of cyclization, loss of N₂, and H⁺ from IV, the product is produced [37].

Our interest in quinazoline synthesis *via* different methods led us to synthesize quinazoline by the use of another useful method (Scheme 2, reaction 3). Based on this method, quinazoline was obtained *via* a two-component reaction and one-pot of benzamide derivatives and (2-bromo-5-chlorophenyl)(phenyl)methanamine. In order to obtain a optimal condition, reaction of 2,4-dichlorobenzamide and (2-bromo-5-chlorophenyl)(phenyl)methanamine were investigated as a model reaction at a wide variety of temperatures, types of solvents, different amount of catalyst and different bases. After doing experiments, it was found to increase yield to 87% in the presence of 0.006 g of GO@N-Ligand-Cu, 2-propanol solvent and K₂CO₃ (0.06 mmol) (Table 5, entry 1). Therefore, 0.006 g of nanocatalyst was sufficient to complete the reaction, of course a higher amount of catalyst does not increase yield (Table 5, entries 18, 19 and 20). Investigation of various solvents, such as, EtOH, DMSO, DMF, H₂O, iodobenzene and chlorobenzene in the presence of 0.006 g of catalyst at a temperature range of 50-115 ° C showed these solvents reverse the reaction and decrease yield of reaction (6 h & 50%, 5 h & 35%, 10 h & 28%, 4 h & 58%, 10 h & 20% and 5 h 45%, Table 5). The reaction was completed under a solvent-free condition at 24 h with a 9% yield (Table 5, entry 21).

Table 5. Reaction time and yield in various conditions^a.

Entery	Solvent	Amount of catalyst [GO@N-Ligand-Cu (g)]	Temperature (°C)	Base	Yield(%) ^b /Time(min)
1	2-Propanol	0.006	65	K ₂ CO ₃	87/8
2	2-Propanol	0.006	50	K ₂ CO ₃	67/30
3	2-Propanol	0.006	75	K ₂ CO ₃	73/20
4	2-Propanol	0.006	95	K ₂ CO ₃	69/25
5	2-Propanol	0.006	115	K ₂ CO ₃	68/30
6	DMSO	0.006	65	K ₂ CO ₃	35/5 (h)

7	DMF	0.006	65	K ₂ CO ₃	28/10 (h)
8	EtOH	0.006	65	K ₂ CO ₃	50/6 (h)
9	H ₂ O	0.006	65	K ₂ CO ₃	58/4 (h)
10	H ₂ O/EtOH	0.006	65	K ₂ CO ₃	70/2 (h)
11	2-Propanol	0.006	65	K ₃ PO ₄	46/1 (h)
12	2-Propanol	0.006	65	Cs ₂ CO ₃	15/4 (h)
13	Chlorobenzene	0.006	65	K ₂ CO ₃	45/5 (h)
14	Iodobenzene	0.006	65	K ₂ CO ₃	20/10 (h)
15	2-Propanol	0.002	65	K ₂ CO ₃	37/35
16	2-Propanol	0.003	65	K ₂ CO ₃	49/30
17	2-Propanol	0.005	65	K ₂ CO ₃	70/15
18	2-Propanol	0.007	65	K ₂ CO ₃	68/20
19	2-Propanol	0.008	65	K ₂ CO ₃	59/30
20	2-Propanol	0.009	65	K ₂ CO ₃	37/1 (h)
21	Solvent-free	0.006	65	K ₂ CO ₃	9/24 (h)

^a**Reaction condition:** 2,4-dichlorobenzamide (1 mmol) and (2-bromo-5-chlorophenyl)(phenyl)methanamine (1 mmol), 65 °C, GO@N-Ligand-Cu (0.006 g) and K₂CO₃ (0.6 mmol) (**Reaction 3**, scheme 2). ^bIsolated yield.

After optimizing the condition, different amides were used. Although amides containing electron-withdrawing substituents at para and ortho positions increased the reaction yield (Table 4, entries 6, 10 and 16, reaction 3), electron releasing substituents reduced the reaction yields (Table 4, entries 1 and 2). The results are summarized in Table 4. Scheme 5 presents a proposed mechanism for quinazoline synthesis.

Scheme 5. Proposed mechanism for the synthesis quinazoline by the use of GO@N-Ligand-Cu and *via* method 3 (Reaction 3 in Scheme 2)

According to the mechanism proposed, in the first step carbonyl group of amide activated by catalyst (Intermediate **I**). Then, (2-bromo-5-chlorophenyl)(phenyl)methanamine compound attacks the carbonyl group and form intermediate **II**. By coupling copper is formed intermediate **III**. In the next, by cyclization (Intermediate **IV**) and oxidation is formed quinazoline [38].

In addition to the strategies mentioned, we were able to synthesize quinazoline through another green method, that is a two-component reaction and one-pot of 2-amino-5-chlorobenzophenone and benzylamine derivatives (Scheme 2, Reaction 4). During optimization of reaction condition, including temperature, the amount of catalyst and solvents, reaction of 2-amino-5-chlorobenzophenone with 2-(aminomethyl)-6-methoxyphenol were used as the model substrate. As shown in Table 6, the reaction had the highest yield at 50 °C, 0.005 g of GO@N-Ligand-Cu in a solvent-free condition and a O₂ atmosphere (Entry 1).

Table 6. Reaction time and yield in various conditions^a.

Entry	Solvent	Amount of catalyst [GO@N-Ligand-Cu (g)]	Temperature (°C)	Time (min)	Yield (%)
1	Solvent-free	0.005	50	20	90
2	Solvent-free	0.004	50	40	87
3	Solvent-free	0.003	50	50	80
4	Solvent-free	0.002	50	1 (h)	60
5	Solvent-free	0.001	50	4 (h)	35
6	Solvent-free	0.006	50	30	85
7	Solvent-free	0.007	50	45	75
8	Solvent-free	0.008	50	2 (h)	64
9	Solvent-free	0.005	40	40	80
10	Solvent-free	0.005	30	1 (h)	71
11	Solvent-free	0.005	60	25	89
12	Solvent-free	0.005	70	33	86
13	Solvent-free	0.005	80	50	74
14	EtOH	0.005	50	40	75
15	H ₂ O	0.005	50	56	67
16	H ₂ O/EtOH	0.005	50	58	72
17	Chlorobenzene	0.005	50	30	84
18	Iodobenzene	0.005	50	1 (h)	56
19	DMSO	0.005	50	38	69
20	Solvent-free	0.005	50	5 (h)	Trace ^c
21	Solvent-free	-	50	24 (h)	5

^a**Reaction condition:** 2-amino-5-chlorobenzophenone (1 mmol) and 2-(aminomethyl)-6-methoxyphenol (1 mmol), 50 °C, GO@N-Ligand-Cu (0.005 g) and a oxygen atmosphere (**Reaction 4**, scheme 2). ^bIsolated yield.

^cUnder a nitrogen atmosphere.

A bunch of benzylamines were tested that benzylamine containing electron releasing substituents exhibited the best activity (compare entries 3,10, 15 and 16 in Table 4). We observed to produce a trace amount of the product in the absence of copper nanocatalyst (Table 6, entry 21). We tested a solvent-free condition and many kinds of solvents. It turned out that a solvent-free condition had the highest yield (compare entries 1 and 14-19 in Table 6). The yield decreased when the temperature of reaction was lowered (compare entries 9 and 10 in Table 6). The results are summarized in Tables 4 and 6. A possible mechanism for the synthesis of quinazoline derivatives is proposed in Scheme 6 according to the results above.

Scheme 6. Proposed mechanism for the synthesis quinazoline by the use of GO@N-Ligand-Cu *via* method 4 (Reaction 4 in Scheme

Firstly, the group of carbonyl of 2-amino-5-chlorobenzophenone is activated by the GO@N-Ligand-Cu catalyst and forms intermediate **i**. In the next, after attack of amine, the intermediate **ii** is formed. Finally, through cyclization, proton loss (intermediate **iv**) and oxidation quinazoline is produced [39].

Part of our ongoing efforts in the lab for developing new chemical methods for quinazoline synthesis lead to the discovery of a new method was for quinazoline synthesis. To our knowledge, it is the first time that quinazoline is synthesized in this way. In this method,

quinazoline was synthesized by the one-pot and two-component reaction of 2-(amino(phenyl)methyl)-4-chlorobenzeneamine and aldehyde derivatives in the presence of GO@N-Ligand-Cu nanocatalysts (Scheme 2, reaction 5). After checking the effects solvent, temperature, the amount of catalyst and a solvent-free condition in this reaction, we found that the reaction of furan-2-carbaldehyde and 2-(amino(phenyl)methyl)-4-chlorobenzeneamine at 75 °C, a solvent-free condition and 0.005 g of catalyst has a yield 93% (Table 7, entry 1).

Table 7. Reaction time and yield in various conditions^a.

Entry	Solvent	Amount of catalyst	Temperature (°C)	Time (min)	Yield(%) ^b
		[GO@N-Ligand-Cu (g)]			
1	Solvent-free	0.005	75	35	93
2	Solvent-free	0.005	90	30	91
3	Solvent-free	0.005	115	33	90
4	Solvent-free	0.005	50	37	87
5	Solvent-free	0.005	40	45	80
6	Solvent-free	0.006	75	37	86
7	Solvent-free	0.007	75	40	82
8	Solvent-free	0.008	75	55	57
9	Solvent-free	0.004	75	50	81
10	Solvent-free	0.002	75	3 (h)	53
11	EtOH	0.005	75	45	75
12	H ₂ O	0.005	75	2 (h)	40
13	Ethanol/H ₂ O	0.005	75	1 (h)	50
14	Chlofrom	0.005	75	40	76
15	Acetone	0.005	75	35	78

16	Chlorobenzene	0.005	75	35	83
17	Iodobenzene	0.005	75	1 (h)	32
18	Ethyl acetate	0.005	75	5 (h)	18
19	Toluene	0.005	75	24 (h)	15

^a**Reaction condition:** furan-2-carbaldehyde (1 mmol) and 2-(amino(phenyl)methyl)-4-chlorobenzenamine (1 mmol), 75°C and GO@*N*-Ligand-Cu (0.005 g) (Reaction 5, scheme 2). ^bIsolated yield.

After this reaction optimization, we studied the various aldehyde derivatives that its results are summarized in Table 4. The aldehydes containing the electron releasing substituents were most effective, especially if they were in the para position (compre entries 1,2,3 with 9 and 10, reaction 5 in the Table 4). Whereas the aldehydes containing the electron-withdrawing substituents were less yield. The mechanism proposed for this reaction is shown in Scheme 7.

Scheme 7. Proposed mechanism for the synthesis quinazoline by the use of GO@*N*-Ligand-Cu via method 5 (Reaction 5 in Scheme)

First, GO@*N*-Ligand-Cu activate the carbonyl group and forms the intermediate A. Then, amine attacks to carbonyl and creates intermediate B. In the next step, it is achieved by amine attack, ring formation and loss of proton [39].

In another study, to understand the effect of the components used in catalyst synthesis, such as, *N*-Ligand, GO, GO@*N*-Ligand, *N*-Ligand-Cu and GO@Cu were used separately as catalysts under a optimal condition of the model reactions. The results showed that *N*-Ligand causes thermal stability, retention of graphene sheets to prevent deposition and increases the number of copper atoms used in the manufacture of catalyst. Also, the presence of graphene oxide in the structure of the catalyst as a substrate improves the dispersion of copper metal on the graphene and prevents their accumulation. On the other hand, metal-free catalyst (GO@*N*-Ligand) due to reduced catalytic activity in reaction and poisoning by intermediate compounds convinced us to use metal. The results are summarized in Table 8.

Table 8. Model reaction under different catalysts

Entry	Catalyst	Yield (%) Reaction 1	Yield (%) Reaction 2	Yield (%) Reaction 3	Yield (%) Reaction 4	Yield (%) Reaction 5
1	-	9	-	-	8	6
2	<i>N</i> -Ligand	9	-	-	8	6
3	GO	22	-	-	25	7
5	GO/Cu	46	58	44	57	35
6	<i>N</i> -Ligand/Cu	15	23	20	19	10
7	GO@ <i>N</i> -Ligand-Cu	91	94	87	90	93

Bis-Quinazoline

Nitrogen-rich heterocyclic compounds represent a unique class of chemicals with special properties and have been modified to design novel pharmaceutically active compounds. *Bis*-quinazoline is considered a premium structure in pharmaceutical chemistry. Since they have several active centers, they have a high affinity to connect to pathogens. That is why, Their

mechanism of action is extraordinary. Given this feature, the trend of using *bis*-quinazoline in the structure of drugs has been increasing in recent years. Figure 11 is an example of the structure of *bis*-quinazoline used in most sedatives.

Figure 11. 1-(7-nitroquinazoline)-4-(3-(1-methylpiperidin-4-yl)propyl)piperidine

So far various methods have been reported to synthesize them, each having disadvantages such as solvent utilization, reaction time, low yield and so on. In this paper, we reported a green effective method for their synthesis (Scheme 8). In which using a one-step reaction of (2-amino-5-chlorophenyl)benzophenone and 1-(3-phenoxypropoxy)benzaldehyde in the presence of 0.009 g nanocatalysts at 85 °C and a solvent-free condition *bis*-quinazoline was achieved.

Scheme 8. Synthesis of *bis*-quinazoline.

The proposed mechanism for the synthesis of *bis*-quinazoline is presented in Scheme 9. The compound 1-(3-phenoxypropoxy)benzaldehyde has two carbonyl groups, that are activated by the catalyst copper atoms simultaneously (intermediate 1). In the following, amine groups of 2-amino-5-chlorobenzophenone attack to activated carbonyls (intermediate

2). Next, carbonyls of intermediate 2 are activated by the catalyst. Then, ammonia attacks the activated carbonyls and forms the intermediate 3. Finally, it is obtained *bis*-quinazoline by the intramolecular reaction and oxidation [8].

Scheme 9. Proposed mechanism for the synthesis *bis*-quinazoline using GO@N-Ligand-Cu

4. Conclusion

There have been many attempts over the past few decades to synthesize *N*-heterocycles. Every year, different ways of synthesizing them are offered around the world. In this article, we have synthesized a couple of green protocols for the synthesis of biological derivatives of quinazoline and bis-quinazoline. The main advantages of these methods are outlined as very simple, reliable, applicable, easy reaction workup, easy recyclability, and reusability of the catalyst. The synthesized catalyst and products were characterized by FE-SEM, MASS, H-NMR, C-NMR, TGA, XRD and FT-IR techniques. We have developed successfully a new approach toward the synthesis of quinazoline and *bis*-quinazoline.

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