

Synthesis of 2, 3-Disubstituted Quinazolinones- 4-(3h)-Ones Promoted by Zr (NO₃)₂ as a Catalyst and Study of Antimicrobial Activity

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ABSTRACT:

A simple and efficient protocol is developed for the synthesis of series of the 2, 3-di-substituted quinazolin-4-(3H)-ones derivatives have been synthesized as a one pot synthesis of the reaction of 2-amino-N-phenyl benzamide and a various substituted aromatic aldehyde in the presence of Lewis acid catalyst Zr(NO₃)₂ as a catalyst in ethanol as a solvent. The final derivatives can be evaluated by ¹HNMR, ¹³CNMR & Mass and in addition of the derivatives evaluated by antimicrobial activity. This method provides several advantages such as high yield, shorter reaction time, mild reaction condition, operational simplicity, easy work-up procedure with environment friendly nature and purification of products by non-chromatographic methods has been developed

KEY WORDS:

2-amino-N-phenyl benzamide, substituted aromatic aldehyde, ZrOCl₂, 2,3-disubstituted quinazolin-4(3H)-ones, anti-microbial activity

1.INTRODUCTION:

The Quinazalones is a fused six membered heterocyclic compounds and is an important Class of Quinoline Alkaloids compounds. These are fused Benzene and Pyrimidine bicyclic compounds. These moieties have been described as privileged structures [1]. They provide different points of attachment for a diverse array of structural elements that can be used to target receptor agonists or antagonists [2]. Quinazolinones are the oxidized form of a Quinazalones Which are part of the Quinoline alkaloids. The compound processes oxygen atom and the Hydrogen on the Nitrogen (NH).

Quinazolinones are fused heterocyclic compounds which possesses two nitrogen's and one oxygen atom as a ketone position. These compounds are attracted to attention widespread due to the diverse range of pharmacological activities, e.g, Protein, Tyrosine kinase inhibitory,[3]. Cholecystokinin inhibitory [4], and Anti-inflammatory [5] and anti-allergy [6] properties and these compounds occupy a distinct and unique place in the field of medicinal chemistry. They have gained significant as a anti-malarial [7], anti-bacterial [8] and anticancer [9]. The first isolated quinazolinones alkaloid Febrifugine and its isomer Isofebrifugine exhibited antimalarial activity [10] and its halogenated derivative haloguginone used in veterinary medicine as a coccidiostat [11].

2,3-disubstituted-3H-Quinazoline-4-ones were considered to be an important chemical synthon possesses a veracity of biological effects including sedative-hypnotic [12]. Anti-anticonvulsant [13] and antitussive [14] activities. These compounds having Broad spectrum of activities there is a considerable interest which allows the generations of these compounds. In recent years, many researchers synthesis of these compounds can be synthesized rapidly.

2. METHODS AND MATERIAL:

2.1. EXPERIMENTAL SECTION:

All the chemical and synthetic grade reagents were procured from SD fine and Sigma Aldrich chemicals. The melting points of all newly synthesized compounds were determined in open capillary tube and are uncorrected. The ¹HNMR spectra (CDCl₃) were recorded on Broocker (400MHz) spectrometer using TMS as internal and also chemical

shift expressed in δ ppm. The molecular weight of synthesized compounds was estimated by LCMS spectrometer. Purity of all synthesized compounds was monitored by thin layer chromatography and iodine was used as visualizing agent.

2.2. GENERAL PROCEDURE:

ZrOCl₂ (0.05mmol) was added to a solution of 2-amino-N-phenylbenzamide (1.0 mmol) and substituted benzaldehyde (1.0 mmol) in ethanol. The reaction mixture was stirred about 5 at 70 °C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to RT. After cooling to room temperature, distilled water (5 ml) and EtOAc (3 ml) were added to the reaction mixture. The organic phase was separated and the aqueous phase was further extracted with EtOAc (3×3 ml). The organic layers were dried over anhydrous NaHCO₃, filtered through celite and concentrated. The residue was purified by recrystallization using ethanol affording the desired product. The pure product was well characterized by advanced spectral techniques like ¹H, ¹³C & mass data.

CHARACTERISATION TITLED DERIVATIVES:

2.2.1.2, 3-diphenylquinazolin-4(3H)-ones (3a):

Pale yellow compound ; Yeild-85%, Mp: 214-216⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.258 (d, J = 8.0Hz, 1H, Ar-H), 7.565 (d, J=8.8Hz, 1H, Ar-H), 7.413-7.276 (m, 6H, Ar-H), 7.223-7.185 (m 2H, Ar-H), 7.156-7.014 (m, 2H, Ar-H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 163.78, 156.02, 147.85, 136.33, 134.89, 132.68, 129.78, 129.04, 128.92, 128.75, 128.32, 127.56, 127.09, 126.35, 120.16, LCMS(m/z); 299.36 (M+H); Molecular Formulae : C₂₀H₁₄N₂O: Elemental analysis : calculated : C- 80.52, H- 4.73 N- 9.39 ; Obtained ; C- 80.45 , H- 4.72, N- 9.45.

2.2.2.2-(4-hydroxyphenyl)-3-phenyl-quinazolin-4(3H)-one (3b):

White solid , Yeild-91%, Mp: 234-236⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.245 (s, 1H, -OH), 8.129 (s, 1H, Ar-H), 7.953-7.827 (m, 3H, Ar-H), 7.718-7.675 (m, 1H, Ar-H), 7.542 (d, J = 8.8 Hz, 1H, Ar-H), 7.444-7.401 (m, 1H, Ar-H), 7.158-7.061 (m, 6H, Ar-H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.54, 162.95, 160.49, 148.58, 138.27, 132.29, 130.94, 130.02, 129.55, 128.67, 128.24, 127.05, 124.25, 122.11, 120.54. LCMS (m/z): 315.36 (M+H). Molecular Formulae: C₂₀H₁₄N₂O₂: Elemental analysis: calculated: C- 76.42, H- 4.49 N- 8.91; Obtained; C- 76.35, H- 4.48, N- 8.97.

2.2.3.2-(4-methoxyphenyl)-3-phenyl-quinazolin-4(3H)-one (3c):

White solid , Yeild-92%, Mp: 221-223⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.354 (d, J = 8.0 Hz, 1H), 7.882-7.780 (m, 2H, Ar-H), 7.487 (s, 1H, Ar-H), 7.334-7.276 (m, 5H, Ar-H), 7.242 (d, J = 7.6 Hz, 2H, Ar-H), 6.756 (d, J = 8.4 Hz, 2H, Ar-H), 3.724 (s, OCH₃, 3H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 164.03, 161.78, 153.58, 148.28, 138.28, 132.87, 130.58, 129.58, 129.08, 128.12, 127.97, 127.57, 126.90, 126.25, 120.80, 113.58, 55.71; LCMS(m/z): 329.56 (M+H); Molecular Formulae: C₂₁H₁₆N₂O₂; Elemental analysis: calculated: C- 76.81, H- 4.91 N- 8.53; Obtained; C- 76.75, H- 4.90, N- 8.60.

2.2.4.2-(4-methyl)-3-phenyl-quinazolin-4(3H)-one (3d):

White solid; Yeild-90%, Mp: 231-233⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.368 (d, J = 7.2Hz, 1H, Ar-H), 7.880 (s, 1H, Ar-H), 7.575 (s, 1H, Ar-H), 7.396-7.308 (m, 3H, Ar-H), 7.278 (d, J = 8.0Hz, 2H, Ar-H), 7.167 (d, J = 8.8 Hz, 2H, Ar-H), 7.047 (d, J = 7.2 Hz, 2H, Ar-H), 2.125 (s 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 161.87, 156.75, 146.15, 138.25, 136.05, 134.08, 132.16, 129.78, 129.25, 129.02, 128.77, 128.38, 127.84, 127.32, 126.91, 122.26, 21.47. LC MS: m/z 313.74 (M+H); Molecular Formulae: C₂₁H₁₅N₂O; Elemental analysis: calculated: C- 80.75, H- 5.16 N- 8.97; Obtained; C- 80.70, H- 5.15, N- 9.06.

2.2.5.2-(4-chlorophenyl)-3-phenyl-quinazolin-4(3H)-one(3e):

Pale yellow solid; Yeild-88%, Mp: 241-243⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.258 (d, J = 8.8 Hz, 1H, Ar-H), 7.884-7.847 (m, 1H, Ar-H), 7.558-7.555 (m, 1H, Ar-H), 7.487-7.276 (m, 6H, Ar-H), 7.247-7.014 (m, 4H, Ar-H). ¹³C NMR

(100 MHz, CDCl₃) δ ppm: 164.78, 159.36, 148.78, 136.08, 134.74, 132.74, 130.17, 129.97, 129.66, 129.02, 128.66, 128.25, 127.85, 127.15, 126.58, 122.73. LCMS (m/z):334.56(M⁺); Molecular Formulae: C₂₀H₁₃ClN₂O; Elemental analysis: Calculated: C- 72.18, H- 3.94 N- 8.42; Obtained; C- 72.10, H- 3.92, N- 8.50

2.2.6.2-(4-bromophenyl)-3-phenyl-quinazolin-4(3H)-one (3f):

Pale red : Yeild-89%, Mp: 217-219⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.314 (d, J = 8.0 Hz, 1H,Ar-H), 7.844-7.687(m,2H,Ar-H),7.558-7.515 (m, 1H,Ar-H), 7.392-7.324(m, 5H,Ar-H), 7.247-7.201 (m, 2H,Ar-H), 7.162-7.013(m, 2H,Ar-H). ¹³CNMR(100MHz,CDCl₃) δ ppm: 164.58, 156.08, 145.91, 139.05, 136.25, 134.06, 132.17, 131.66, 129.85, 129.22, 128.68, 128.27, 127.44, 126.04, 123.55, 121.20. LC MS (m/z): 378.56.(M+H); Molecular Formulae: C₂₀H₁₃BrN₂O; Elemental analysis: Calculated: C- 63.68, H- 3.47 N- 7.43; Obtained; C- 63.60, H- 3.46, N- 7.50

2.2.3.72-(4-nitrophenyl)-3-phenyl-quinazolin-4(3H)-one (3g):

Pale solid ; Yeild-87%, Mp: 226-227⁰c, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.312 (s, 1H,Ar-H), 7.815 (s, 1H,Ar-H), 7.667-7.497 (m, 5H,Ar-H),7.467 (d, J = 8.0 Hz, 1H,Ar-H), 7.247-7.223 (m, 1H,Ar-H), 7.081 (d, J = 9.2 Hz, 2H,Ar-H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 168.57, 164.65, 163.58, 143.48, 139.84, 135.58, 132.09, 129.55, 128.68, 128.15, 127.67, 126.56, 123.58, 121.85, 120.78, 120.25. LCMS (m/z):344.26 (M+H). Molecular Formulae: C₂₀H₁₃N₃O₃; Elemental analysis: Calculated: C- 69.97, H- 3.82, N- 12.24; Obtained; C- 69.91, H- 3.80, N- 12.31.

3.ANTI BACTERIAL ACTIVITY:

The antimicrobial activities of all the newly synthesized compounds (**3a-3g**) were evaluated against gram negative microorganisms such as E.coli, P.aerugenosa and gram positive microorganism such as S.aureus, B.substills strains using streptomycin as a reference by the cup plate technique as explained by Hugo and Russe (**15**).In this technique the test solutions was placed in contact with agar, which was already inoculated with test organism. After incubation, zones of inhibition were observed. The test solution may be placed in a small cup sealed to the agar surface in a well cut from the agar with a sterile cork borer or applied in the form of impregnated disc of filter papers.

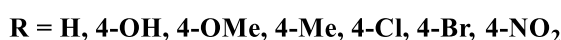
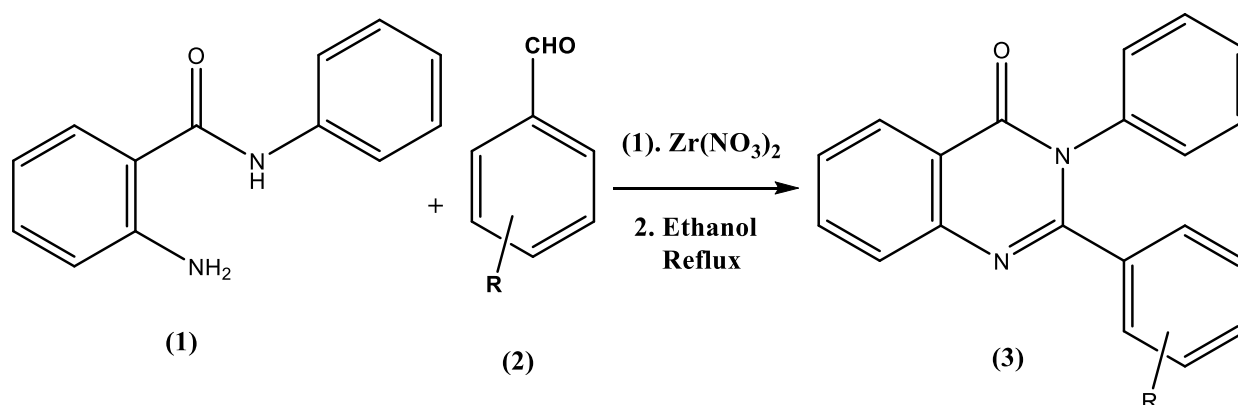
Preparation of Media Petri dishes:

Conical flask with medium was cooled to 46⁰c and inoculated with test organism (20 ml of sub culture medium/100 ml of the assay medium) 30 ml of inoculated media distributed into petri dishes. Four cups (8 mm diameter) per plate were made by using a sterile cork borer. The whole operation was carried out under the laminar flow especially. Cups were filled with 0.1 ml of test solution and 0.1 ml of standard solution (100 μ g/ml, 250 μ g/ml) and blank (DMSO) were placed in each cups separately under aseptic condition. Then the petri dishes uniform diffusion of drug into the agar medium. All the petri dishes were then incubated at the 37⁰c in one day and zone of inhibition were measured and results are presented in Table -5.

ANTI-FUGAL ACTIVITY:

The newly synthesized compounds (**3a-3g**) were screened for their anti-fungal activity against aspergillus Niger, canadida albicans and Aspergillus flavus using agar well diffusion assays. Sterile molten potato dextrose agar (PDA) medium was inoculated with 50 μ L of fungal suspension, fluconazole is a standard drug and zone of inhibition were measured and results are presented in **Table-5**.

4.RESULT AND DISCUSSION:



(Scheme-1)

4.1. CHEMISTRY:

Scheme 1 provides the synthesis method for the named chemicals. In the presence of $Zr(NO_3)_2$, the starting material 2-amino-N-phenylbenzamide combines with substituted aromatic aldehyde in ethanol as a solvent at reflux to produce desirable compounds like 2,3-disubstituted quinazolin-4(3H)-ones. The Lewis acid catalyst at reflux controlled the reaction conditions and picked up the reaction. The catalyst's benefits include an increased rate of reaction, a high yield produced by it, a quick reaction time, its commercial availability, ease of workup, and its nontoxic nature.

Optimization of the different catalysts, temperature, solvent, and loaded catalyst was used in this reaction, and the outcome is shown and provided below. During this reaction, several transition metal oxide catalysts were used at a constant temperature. The catalysts listed in entries "1" and "5" are the most effective, however their product generation is quite low—51% and 61%, respectively. The catalysts listed in entries "2" and "3" are the most efficient, but their product effects are only moderate—68% and 55%, respectively. The strong Lewis acid catalyst in entry "4" yields an exceptional yield of "92."

Table –1: Comparison among the various catalyst synthesis of titled compound (3d):

Entry	Catalyst	Time (h)	Yield (%)
1	TiO ₂	4	51
2	CuO	4	68
3	ZnCl ₂	4	55
4	Zr (NO ₃) ₂	4	92
5	FeCl ₃	4	61

The most important factor in this reaction is the amount of catalyst used; 1 mmole of catalyst was used to start the reaction, obtained traces of product, and gradually developed up to 5 mmol of catalyst during the reaction. Thus, the highest yield was reached (92). Additionally, as Table 2 illustrates, the catalyst amount increased up to entry "5" without any improvement.

Table-2: Optimization amount of the catalyst ($Zr(NO_3)_2$) for synthesis of derivatives (3d):

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	1.0	4	traces
2	2.0	4	45
3	3.0	4	68

4	4.0	4	92
5	5.0	4	92

After the catalyst mentioned above was used in the reaction process, we used a variety of solvents, such as H₂O, CH₃CN, EtOH, MeOH, and MDC, to assess the solvent effects. According to our observations, the best reaction conditions are those in which solvents are not used, the reaction is completed, and the yield of the intended product is higher than that of any of the solvents examined (Table 3).

Table-3: The effect of the solvent for synthesis of compound (3d):

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	H ₂ O	3	15
2	MeOH	3	45
3	EtOH	3	93
4	DMF	3	55
5	MDC	3	63

Substituted aromatic aldehydes were initially selected for the reaction with 2-amino-N-phenylbenzamide in order to investigate the catalytic performance of transition metal oxychloride of Zr(NO₃)₂. With a catalytic amount of Zr(NO₃)₂, the reaction conditions were devised to efficiently synthesize named compounds at higher temperatures without the need for a solvent. Consequently, we conducted reactions at different temperatures and added reaction catalyst to a variety of solvents (Table 4). Through trials, we were able to achieve 92% of the product yield in the ethanol system

Table-4: The effect of the Temperature for synthesis of compound (3d):

Entry	Temperature (°C)	Time (h)	Yield (%)
1	Below RT	4	25
2	RT	4	38
3	80	4	92
4	90	4	82
5	110	4	78

4.2. BIOLOGICAL ACTIVITY:

Table-5: Antimicrobial activity screening activity synthesized scaffold:

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
3a	06	08	10	05	08	07
3b	15	17	17	14	12	10
3c	19	18	17	18	14	15
3d	16	14	17	14	11	12
3e	20	21	18	20	18	15
3f	20	22	21	20	17	15
3g	10	12	12	08	06	08
streptomycin	27	27	25	25	NA	NA
fluconazole	NA	NA	NA	NA	20	20
DMSO	---	---	---	---	---	---

The bacterial activity of compounds 3a–3g was found to be low for the electron-withdrawing group (compounds 3a and 3f) and moderate for the electron-donating group (compounds 3b, 3c, and 3f). Because compounds 3e and 3f included halogen groups, they showed exceptional active potential. Additionally, we noticed that the antifungal activity of compounds (3a–3g) varied; compound 3c demonstrated good action, while the compound's rate revealed low to moderate activity.

5. CONCLUSION:

In conclusion, a series of named derivatives have been produced by improving a one-pot, one-step, multicomponent process comprising 2-amino-N-phenylbenzamide, substituted aromatic aldehydes, and $\text{Zr}(\text{NO}_3)_2$ under solvent conditions like ethanol. This procedure is quick, simple, practical, and eco-friendly. For the synthesis of 2, 3-diphenylquinazolin-4(3H)-ones, this technique is effective. High to excellent yields, high reaction rates, avoidance of hazardous organic solvents, ease of operation, straightforward catalyst separation and recycling, large-scale synthetic applicability, the production of water as green waste, excellent atom economy, high reaction mass efficiency, and low E-factor are some of this protocol's notable features. Furthermore, derivatives 3e and 3f shown exceptional efficacy against both bacterial and fungal strains. In contrast to activity, the remaining derivatives displayed modest activity.

6 AKOWNLDEMENT:

The Authors are grateful to management of PRISM PG&DG College for providing facility to project work.

7.REFERENCES

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