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SYNTHESIS OF 2, 3-DISUBSTITUTED QUINAZOLINONES- 4-(3H)-ONES PROMOTED BY ZROCL$_2$ 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 as a catalyst in ethanol as a solvent. The final derivatives can be evaluated by ^{1}HNMR, ^{13}CNMR and 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.

KEYWORDS

2-amino-N-phenyl benzamide, Substituted aromatic aldehyde, $ZrOCl_2$, 2, 3-disubstituted quinazolin-4(3H)-ones and Anti-microbial activity.

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INTRODUCTON

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.

METHODS AND MATERIAL

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 ^{1}HNMR spectra ($CDCl_3$) 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.

General procedure

$ZrOCl_2$ (0.05mmol) was added to a solution of 2-amino-N-phenylbenzamide (1.0mmol) and substituted benzaldehyde (1.0mmol) in ethanol. The reaction mixture was stirred about 5 at 70^{o}C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to RT. After cooling to room temperature, distilled water (5ml) and EtOAc (3ml) were added to the reaction mixture. The organic phase was separated and the aqueous phase was further extracted with EtOAc (3×3ml). The organic layers were dried over anhydrous $NaHCO_3$, 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 ^{1}H, ^{13}C and mass data.

CHARACTERISATION TITLED DERVATIVES

2, 3-diphenylquinazolin-4(3H)-ones (3a)

Pale yellow compound; Yeild-85%, Mp: 178-180^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{20}H_{14}N_2O$: Elemental analysis: calculated: C- 80.52, H- 4.73 N- 9.39; Obtained; C- 80.45, H- 4.72, N- 9.45.

2-(4-hydroxyphenyl)-3-phenyl-quinazolin-4(3H)-one (3b)

White solid, Yeild-91%, Mp: 191-193^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{20}H_{14}N_2O_2$: Elemental analysis: calculated: C- 76.42, H- 4.49 N- 8.91; Obtained; C- 76.35, H- 4.48, N- 8.97.

2-(4-methoxyphenyl)-3-phenyl-quinazolin-4(3H)-one (3c)

White solid, Yeild-93%, Mp: 164-166^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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,OCH_3, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{21}H_{16}N_2O_2$; Elemental analysis: calculated: C- 76.81, H- 4.91 N- 8.53; Obtained; C- 76.75, H- 4.90, N- 8.60.

2-(4-methyl)-3-phenyl-quinazolin-4(3H)-one (3d)

White solid; Yeild-90%, Mp: 178-180^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{21}H_{15}N_2O$; Elemental analysis: calculated: C- 80.75, H- 5.16 N- 8.97; Obtained; C- 80.70, H- 5.15, N- 9.06.

2-(4-chlorophenyl)-3-phenyl-quinazolin-4(3H)-one (3e)

Pale yellow solid; Yeild-88%, Mp: 194-196^{o}C, ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 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). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{20}H_{13}ClN_2O$; Elemental analysis: Calculated: C- 72.18, H- 3.94 N- 8.42; Obtained; C- 72.10, H- 3.92, N- 8.50

2-(4-bromophenyl)-3-phenyl-quinazolin-4(3H)-one (3f)

Pale red: Yeild-89%, Mp: 167-169^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 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: $C_{20}H_{13}BrN_2O$; Elemental analysis: Calculated: C- 63.68, H- 3.47 N- 7.43; Obtained; C- 63.60, H- 3.46, N- 7.50.

2-(4-nitrophenyl)-3-phenyl-quinazolin-4(3H)-one (3g)

White solid; Yeild-87%, Mp: 225-227^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 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).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 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: $C_{20}H_{13}N_3O_3$; Elemental analysis: Calculated: C- 69.97, H- 3.82, N- 12.24; Obtained; C- 69.91, H- 3.80, N- 12.31.

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 46^{o}C and inoculated with test organism (20ml of sub culture medium/100ml of the assay medium) 30ml of inoculated media distributed into petri dishes. Four cups (8mm 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 0.1ml of test solution and 0.1ml of standard solution (100µg/ml, 250µg/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 37^{o}C in one day and zone of inhibition were measured and results are presented in Table No.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 5 µL of fungal suspension, fluconazole is a standard drug and zone of inhibition were measured and results are presented in Table No.5.

RESULTS AND DISCUSSION

Chemistry

The synthetic approach to the titled compounds is given in the Scheme No.1. The starting materials 2-amino-N-phenylbenzamide reacts with substituted aromatic aldehyde in the presence of $ZrOCl_2$ in ethanol as solvent at reflux scaffold desired compounds such as 2, 3-disubstituted quinazolin-4(3H)-ones. The reaction condition controlled and pick up the reaction by Lews acid catalyst at reflux. The advantages of the catalyst, an accelerated the rate of reaction, high yield developed the by this catalyst, short reaction time and the scope this catalyst commercially available, easy work up and also nontoxic nature.

In this reaction, optimization of the various catalysts, temperature, solvent as well as loaded catalyst applied and the result exhibited and given below. There are different transition metal oxide catalyst were applied during this reaction at constant temperature. The entry “1” and entry “5” are most effective catalyst but generation of product very poor, such as 50% and 62% respectively. The entry “2” and entry “3” are most effective catalyst but effect of product very moderate, such as 65% and 58% respectively. The entry “4” is powerful Lews acid catalyst that is produced excellent yield is “93.

The amount of catalyst is very most significant role play during in this reaction; 1mmole amount of the catalyst was utilized in starting, acquired traces amount of product and gradually developing upto 5mmol amount of the catalyst during the reaction. Hence, maximum amount yield obtained (93). Further, amount of the catalyst increased up to entry “5” and get no improvement as shown Table No.2.

Following the above catalyst effected during the reaction method, we proceeded to the evaluated of solvent effects using a different of solvents, including H_2O, CH_3CN, EtOH, MeOH and MDC. Our observations are identified that the good reaction conditions are those if without the use of solvents and also the completion of the reaction as well as for the yield of the desired product compared than those obtained in any of the solvents investigated (Table No.3).

In order to study the catalytic performance of transition metal oxychloride $ZrOCl_2$, substituted aromatic aldehydes were first chosen for the reaction with 2-amino-N-phenylbenzamide. Even though at higher temperatures, the reaction conditions were developed to synthesis titled compounds and an efficiently in a solvent-free situation with a catalytic quantity of $ZrOCl_2$. As a result, we introduced reaction catalyst to a range of solvents and conducted reactions at varying temperatures (Table No.4). We were able to attain 93% of the product yield in the ethanol system through experiments.

Biological activity

We observed that the bacterial activity of compound 3a-3g, mostly electron withdrawing group of compound viz; 3a and 3f exhibited low active potent while electron donating group of compounds 3b, 3c, 3f exhibited moderate active potent. The compound 3e and 3f exhibited good active potential due to halogen group present in the compound. We also observed the Antifungal Activity of compound (3a-3g) exhibited different activity compound 5c showed good activity and rate of the compound showed low to moderate activity.

Table No.1: Comparison among the various catalyst synthesis of titled compound (3d)

Entry	Catalyst	Time (h)	Yield (%)
1	TiO_2	8	50
2	CuO	6	65
3	$ZnCl_2$	10	58
4	$ZrOCl_2$	3	93
5	$FeCl_3$	9	62

Table No.2: Optimization amount of the catalyst (ZrOCl2) for synthesis of derivatives (3d)

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	0.5	3	traces
2	1.0	3	40
3	2.5	3	65
4	5	3	93
5	10	3	93

Table No.3: The effect of the solvent for synthesis of compound (3d)

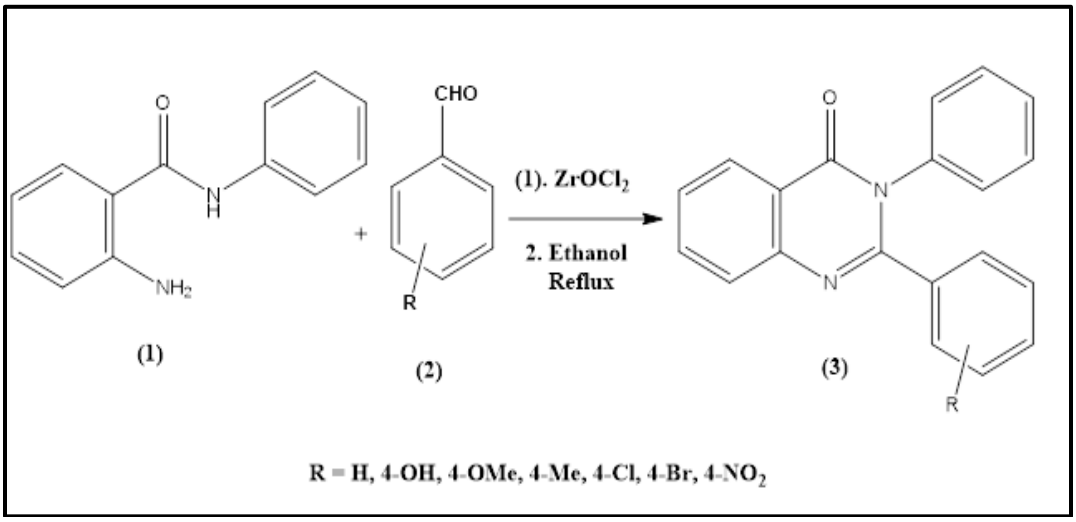
Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	H_2O	3	15
2	MeOH	3	45
3	EtOH	3	93
4	DMF	3	55
5	MDC	3	63

Table No.4: The effect of the Temperature for synthesis of compound (3d)

Entry	Temperature (^oC)	Time (h)	Yield (%)
1	Below RT	3	20
2	RT	3	39
3	80	3	92
4	90	3	85
5	110	3	80

Table No.5: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	***E.coli***	***S. typhi***	***B.substills***	***A. niger***	***C. albicans***
1	3a	05	07	08	03	04	05
2	3b	14	16	15	13	10	11
3	3c	18	19	18	18	12	14
4	3d	15	14	15	12	10	11
5	3e	21	22	17	18	16	17
6	3f	19	21	20	20	15	16
7	3g	12	10	11	09	07	07
8	streptomycin	25	25	22	22	NA	NA
9	fluconazole	NA	NA	NA	NA	20	20
10	DMSO	---	----	---	---	---	---



Scheme No.1

CONCLUSION

In summary, a one-pot, one-step, multicomponent reaction involving 2-amino-N-phenylbenzamide, substituted aromatic aldehydes, in the presence of $ZrOCl_2$ under solvent as ethanol conditions has been improved to obtained a series of titled derivatives. This protocol is easy to follow, quick, convenient and environmentally friendly. This method works well for synthesizing 2, 3-diphenylquinazolin-4(3H)-ones. Outstanding characteristics of this protocol include high to excellent yields, high reaction rates, the avoidance of toxic organic solvents, operational simplicity, simple catalyst separation and recycling, large-scale synthetic applicability, the formation of water as green waste, excellent atom economy, high reaction mass efficiency and low E-factor. In addition to the derivatives 3e and 3f exhibited excellent activity against bacterial as well as fungal strains. The rest of the derivatives showed moderate activity against activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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