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Synthesis of 2, 3-Disubstituted Quinazolinones- 4-(3h)-Ones Promoted by Tio_2 as a Catalyst and Study of Antimicrobial Activity

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ABSTRACT:

The synthesis of a series of 2, 3-di-substituted quinazolin-4-(3H)-ones derivatives has been accomplished in a single pot by reacting 2-amino-N-phenyl benzamide with a variety of substituted aromatic aldehydes while using ethanol as a solvent and TiO_2 a Lewis acid catalyst. This process is straightforward and effective. In addition to the derivatives assessed by antibacterial activity, the final derivatives can be assessed by ^{1}HNMR, ^{13}CNMR, and mass. This approach offers a number of benefits, including a high yield, a quick reaction time, mild reaction conditions, ease of operation, an easy work-up process that is environmentally benign, and the development of non-chromatographic methods for product purification.

KEY WORDS:

2-amino-N-phenyl benzamide, substituted aromaticaldehyde, TiO_2,2,3-disubstituted quinazolin-4(3H)-ones, anti-microbial activity

1. INTRODUCTION:

The Quinazalones is a combination of six membered heterocyclic moieties and is an important molecule of Quinoline Alkaloids compounds. These are fusion of benzene and Pyrimidine nucleus compounds. These moieties have been explained as privileged structures of Quinazalones [1].They provide various points of attachment for a diverse array of structural elements that will be used to target receptor agonists or antagonists [2]. Quinazolinones are the oxidized form of a Quinazalones that part of the Quinoline alkaloids. The compound was containing oxygen atom and the Hydrogen on the Nitrogen.

Quinazolinones are fused heterocyclic compounds which possesses two nitrogen and one oxygen atom as a ketone position. These compounds are attracted to attention broad range area 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] activity and this moiety occupy distinct and unique place in the field of medicinal chemistry. They have acquired significant as antimalarial [7], anti-bacterial [8] and anticancer [9]. The first isolated quinazolinones alkaloid Febrifugine and its isomer Isofebrifugine showed antimalarial activity [10] and its halogenated derivative haloguginone used in veterinary medicine as a coccidiostat [11].

The 2,3-disubstituted-3H-Quinazoline-4-ones were considered to be a significant chemical synthon which was possessed a different 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, synthetic grade reagents were purchased from Sigma Aldrich chemicals. The melting points of all prepared compounds were estimate in open capillary tube and are uncorrected. The ^{1}HNMR and ^{13}CNMR 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 newly synthesized derivatives was estimated by LCMS spectrometer. The purity of all prepared derivatives was checked by thin layer chromatography and iodine was used as visualizing agent.

2.2. GENERAL PROCEDURE:

TiO_2 (0.06mmol) was added to a solution of 2-amino-N-phenylbenzamide (1.0 mol) and substituted benzaldehyde (1.0 mol) in ethanol. The reaction mixture was stirred about 4 hours at 70 ^{0}c. After completion of the all reactants as identified 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 layer was separated and the aqueous phase was further extracted with EtOAc. The organic layers were dried over anhydrous Na_2SO_4, 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 & mass data.

CHARACTERISATION TITLED DERVATIVES:

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

Yellow compound ; Yeild-80%, Mp: 174-176^{0}c,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.246 (d, J = 8.8Hz, 1H, Ar-H), 7.562 (d,J=8.0Hz, 1H, Ar-H), 7.514-7.224 (m, 6H, Ar-H), 7.200-7.012 (m 4H, Ar-H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 164.78, 154.14, 148.81, 136.65, 134.80, 131.06, 129.87, 129.21, 128.84, 128.54, 128.31, 127.74, 127.13, 126.03, 121.54, LCMS(m/z); 299.54 (M+H);Molecular Formulae : $C_{20}H_{14}N_2O$: Elemental analysis : calculated : C- 80.52,H- 4.73 N- 9.39 ; Obtained ; C- 80.47 , H- 4.71, N- 9.45.

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

Pale yellow solid , Yeild-90%, Mp: 190-192^{0}c,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.354 (s, 1H, -OH), 8.201 (s, 1H,Ar-H), 7.917-7.803 (m, 3H, Ar-H), 7.725-7.687 (m, 1H,Ar-H), 7.592 (d, J = 8.0 Hz, 1H,Ar-H), 7.514-7.484(m, 1H,Ar-H), 7.354-7.161 (m, 6H,Ar-H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 167.51, 162.92, 160.48, 148.51, 138.29, 132.20, 130.04, 130.08, 129.56, 128.77, 128.36, 127.55, 124.14, 122.18, 120.22. LCMS (m/z): 315.87 (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.

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

White compound , Yeild-94%, M.p: 187-189^{0}c,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.324 (d, J = 8.2 Hz, 1H), 7.941-7.880 (m, 2H,Ar-H), 7624(s, 1H,Ar-H), 7.514-7.295 (m, 5H,Ar-H), 7.256 (d, J = 7.2 Hz, 2H,Ar-H), 7.075(d, J = 8.0 Hz, 2H,Ar-H), 3.714 (s,OCH_3, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 165.03, 160.78, 154.58, 147.28, 137.28, 131.87, 130.54, 129.66, 129.04, 128.44, 127.90, 127.07, 126.91, 126.12, 121.80, 112.58, 54.71;LCMS(m/z): 329.13 (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.

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

Pale brown solid; Yeild-89%, M.p: 171-173^{0}c, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.326 (d, J = 7.6Hz, 1H,Ar-H), 7.891 (s, 1H,Ar-H), 7.624 (s, 1H,Ar-H), 7.541-7.348 (m, 3H,Ar-H), 7.332 (d, J =8.8Hz, 2H,Ar-H), 7.262 (d, J = 8.4 Hz, 2H,Ar-H), 7.078 (d, J = 7.6 Hz, 2H,Ar-H), 2.025 (s 3H.CH3).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 162.87, 155.75, 147.15, 139.25, 135.05, 133.08, 131.16, 129.71, 129.22, 129.04, 128.87, 128.34, 127.85, 127.31, 126.51, 122.66, 21.41.LC MS: m/z 313.26(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.

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

Pale yellow solid; Yeild-87%, Mp: 193-195^{0}c,^{1}HNMR (400 MHz, $CDCl_3$) δppm: 8.278 (d, J = 8.4 Hz, 1H,Ar-H), 7.874-7.857(m,1H,Ar-H), 7.558 (m, 1H,Ar-H), 7.517-7.296 (m, 6H,Ar-H), 7.246-7.044(m, 4H,Ar-H).^{13}C NMR (100 MHz, $CDCl_3$)δppm: 165.78, 158.36, 149.78, 137.08, 136.74, 133.74, 131.17, 129.91, 129.45, 129.22, 128.78, 128.36, 127.58, 127.05, 126.44, 121.77. LCMS (m/z):334.78(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

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

Red solid : Yeild-87%, M.p: 187-189^{0}c,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.304 (d, J = 8.8 Hz, 1H,Ar-H), 7.887-7.712(m,2H,Ar-H),7.554 (m, 1H,Ar-H), 7.492-7.312(m, 5H,Ar-H), 7.287-7.214 (m,2H,Ar-H), 7.182-7.077(m, 2H,Ar-H).^{13}CNMR(100MHz,$CDCl_3$)δppm: 166.58, 157.08, 144.91, 138.05, 137.25, 133.06, 131.17, 131.06, 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

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

Yellow solid ; Yeild-85%, M.p: 201-203^{0}c,^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.254 (s, 1H,Ar-H), 7.807 (s, 1H,Ar-H), 7.678-7.417 (m, 5H,Ar-H),7.367 (d, J = 8.4 Hz, 1H,Ar-H), 7.240 (s, 1H,Ar-H), 7.081 (d, J = 9.0 Hz, 2H,Ar-H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 168.51, 164.67, 163.56, 143.40, 139.84, 135.50, 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.

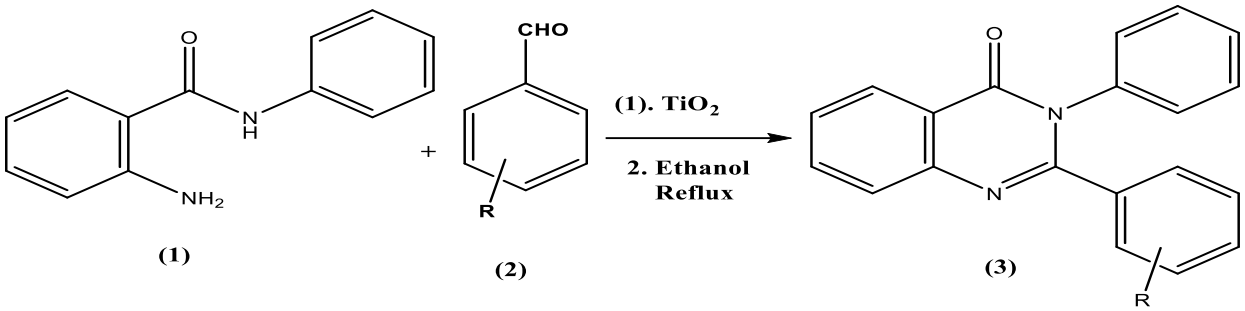
3. ANTI BACTERIAL ACTIVITY:

The antimicrobial activities of all the tested compounds (3**a-3g)** were examined against gram (-Ve) microorganisms such as E.coli, P.aerugenosa and gram positive microorganism such as S.aureus, B.substill strains referred to Streptomycin as standard drug 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 and it represented Table-5

ANTI-FUGAL ACTIVITY:

The tested compounds **(3a-3g)** were examined for their anti-fungal activity against aspergillus Niger, canadida albicans and Aspergillus flavus were using agar well diffusion assays. The sterile molten potato dextrose agar (PDA) medium was inoculated with 50µL 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:



(1) (2) (3)

R = H, 4-OH, 4-OMe, 4-Me, 4-Cl, 4-Br, 4-NO_2

(Scheme-1)

4.1. CHEMISTRY:

In this investigation**, t**he synthetic approach of the desired derivatives is given in the scheme -1. The starting materials 2-amino-N-phenylbenzamide was treated with substituted aromatic aldehyde in the presence of TiO_2 in ethanol as solvent at reflux scaffold titled derivatives such as 2, 3-disubstituted quinazolin-4(3H)-ones, The reaction condition was controlled and start the reaction by Lews acid catalyst as TiO_2 at reflux. The scope and advantages of this catalyst, the enhancement rate of reaction, excellent yield progressed the by this catalyst, short reaction time and the scope this catalyst commercially available, easy work up and also nontoxic nature.

In this reaction, an optimization of the different catalysts, temperature, solvent as well as amount of catalyst applied and the result exhibited and given below. There are various transition metal oxide catalyst were applied during this reaction at constant temperature. The entry "4" gave 71%. The entry "2" and entry "3" are most effective catalyst but effect of product very moderate, such as 64% and 57% respectively. The entry "1" is powerful Lews acid catalyst that is produced excellent yield is "94%".

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

Entry	Catalyst	Time (h)	Yield (%)
1	TiO_2	5	94
2	CuO	5	64
3	$ZnCl_2$	5	57
4	$ZrOCl_2$	5	71

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 (94). Further, amount of the catalyst increased up to entry "5" and get no improvement as shown Table-2.

Table-2: Optimization amount of the catalyst (ZrOCl2) for synthesis of derivatives (3d):

Entry	Catalyst (mol)	Time (h)	Yield (%)
1	0.5	3	traces
2	1.0	3	41
3	2.5	3	62
4	5	3	94
5	10	3	94

It noticed that Following the above catalyst impact during the reaction method, we followed to the evaluated of solvent effects applying a several 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-3).

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

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	H_2O	3	21
2	MeOH	3	49
3	EtOH	3	94
4	DMF	3	54
5	MDC	3	68

In order to investigate the catalytic performed of transition metal oxychloride TiO_2, substituted aromatic aldehydes were first applied for the reaction with 2-amino-N-phenylbenzamide. Even though at higher temperatures, the reaction conditions were improved to synthesis titled compounds and an efficiently in a solvent-free situation with a catalytic quantity of TiO_2. As a result, we introduced reaction catalyst to a range of solvents and conducted reactions at changed temperatures (Table-4). We were able to attain 94% of the product yield in the ethanol system through experiments.

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

Entry	Temperature (^{0}C)	Time (h)	Yield (%)
1	Below RT	3	20
2	RT	3	39
3	80	3	94
4	90	3	85
5	110	3	80

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	04	08	07	05	05	06
3b	15	16	15	14	11	10
3c	19	18	17	19	13	15
3d	16	16	14	13	11	12
3e	20	21	22	21	17	18
3f	19	21	20	20	15	16
3g	12	10	11	09	07	07
streptomycin	25	25	22	22	NA	NA
fluconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

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

5. CONCLUSION:

In summary, a one-pot, multicomponent reaction was involving 2-amino-N-phenylbenzamide, substituted aromatic aldehydes, in the presence of TiO_2 under solvent as ethanol conditions has been improved to obtain a series of titled derivatives. This protocol is easy to follow, quick, convenient and 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

6 AKOWNLDEMENT:

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