Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

https://doi.org/10.36673/AJRCPS.2024.v12.i03.A12

DESIGNED SYNTHESIS AND BIO EVALUATION OF 2, 3-DISUBSTITUTED QUINAZOLIN-4-(3H)-ONES PROMOTED CAMPHOR SULFONIC ACID AS A CATALYST

Ch. Sudhakar[1], Anjum Aara[2], B. V. Durgarao[3], N. Krishnarao[4], Shaik Lakshman*[5]

[1]Department of Chemistry, SR and BGNR Government Arts and Science College (Autonomous), Khammam, Telangana, India.
[2*]Department of Chemistry, Government Degree College, Thorur, Mahabubabad, Telangana, India.
[3]Department of DFS (Chemistry), ONGC, RJY, Andhra Pradesh, India.
[4]Department of Organic Chemistry, PRISM P.G College, Visakhapatnam, India.
[5*]GSS, GITM (Deemed to be University), Visakhapatnam, India.

ABSTRACT

A straightforward, practical and economical process for producing quinazolin- 4-(3H)-ones derivatives is describe and a series of derivatives of the 2, 3-di-substituted quinazolin-4-(3H)-ones have been synthesized as a one pot synthesis of the reaction of 2-amino-N-phenyl benzamine and various substituted aromatic aldehyde in the presence of camphor sulfonic acid catalyst in a ethanol as solvent. The final derivatives can be characterized by ^{1}HNMR, ^{13}CNMR and Mass and besides the derivatives examined biological activity. No toxic organic solvents are used in the current procedure. Shortest reaction time, high product yields, easy work-up process and non-chromatographic product purification are only a few of this catalyst's encouraging reaction response characteristics.

KEYWORDS

2-amino-N-phenyl benzamide, Substituted aromatic aldehyde, CuI_2 2, 3-disubstituted quinazolin-4(3H)-ones and Antimicrobial activity.

Author for Correspondence:
Shaik Lakshman,
Department of Chemistry,
GSS, GITM (Deemed to be University),
Visakhapatnam, India.

Email: lshaik@gitaml.edu

INTRODUCTON

This class of compounds can be prepared in a variety of ways according to the literature. The most widely used method for producing quinazolin- 4-(3H)-ones is to employ various catalysts in one-pot multicomponent reactions (MCRs) where 2-amino-N-phenyl benzamine and various substituted aromatic aldehyde are exposed to an organic acid in a polar solvent. The synthesis of numerous

naturally occurring compounds and physiologically active molecules has been discovered to be facilitated by MCRs, making them an efficient synthetic tool. Compared to conventional synthetic methods, MCRs have shown to be noticeably more beneficial. This ensures good yields, great atom economy, low costs, shortened reaction times, less waste, energy and labor, ease of operation and avoidance of labor-intensive purification operations. MCR and the application of are crucial elements of the ideal green synthesis[1,2].

There has been a lot of interest in heterocyclic compounds' potential to close the knowledge gap between the biological and chemical sciences. These components are currently the focus of a lot of contemporary study being done all throughout the world. A survey of the literature indicates that the quinazolin- 4-(3H)-ones, different groups can be swapped to offer different functionalities. There exist number of pharmaceuticals that are sold commercially and contain the quinazolin- 4-(3H)-ones nucleus fall under different classes and have a range of therapeutic benefits, which has prompted the development of various techniques for combining this crucial component The study of organic and medicinal chemistry depends on primarily on heterocyclic compounds with nitrogen (N), a notable family of heterocyclic compounds has a variety of applications in the hunt for new compounds that are pharmacologically active.

Particularly, quinazolin- 4-(3H)-ones are six-membered heterocyclic with a N atom content that are extensively present in a variety of medicines and natural products and have important uses in pharmacology and medicine. Researchers and scientists are often intrigued by the wide variety of bioactivities of synthetic pathways. Using this method, it has been demonstrated that producing these bioactive heterocyclic in a single pot offers a viable and environmentally responsible solution. This method has a well-established effect on combinatorial chemistry, pharmaceuticals, catalysis, and drug development. Over the past few decades, there has been a significant increase in the manufacturing of multicomponent reactions that result in quinazolin- 4-(3H)-ones.

The quinazalones scaffold, as a privileged structure, has been used for the design and development of various therapeutic agents, including biologicalevaluation[3], Anti-microbial[4], anti-cancerandanti-tuberculosisactivities[5-7], antitumoragents[8], NF-κbinhibitors[9], antioxidant agents[10], Alzheimer's[11,12], Anti-inflammatory[13]. Recently, several quinazalones-based compounds have been reported as effective agents for the treatment of Alzheimer's diseases.

In the present work reported the one pot multicomponent synthesis of 2, 3-disubstituted quinazolin 4-(3H)-ones promoted camphor sulfonic acid as a catalyst .This compounds were obtained by the reaction of 2-amino-N-phenyl benzamine and various substituted aromatic aldehyde in the presence of camphor sulfonic acid catalyst as catalyst ethanol in a solvent and also evaluation od antimicrobial activity against the various bacterial strains and also fungal strains. The excellent yield was obtained during the synthesis.

EXPERIMENTAL METHODS

Merck and Sigma Aldrich chemicals provided all of the synthetic grade and chemical reagents. All newly-derived melting points were measured in an open capillary tube without correction. On a Broker (400MHz) spectrometer, the ^{1}HNMR spectra ($CDCl_3$) were acquired with TMS as the internal standard and the chemical shift indicated in δ ppm. Using an LCMS spectrometer, the molecular weight of the produced molecules was calculated. Iodine was utilized as a visualizing agent while thin layer chromatography was used to check the purity of all produced chemicals.

GENERAL PROCEDURE

Camphorsuphonic acid (1.0mmol) were added to a solution of 2-amino-N-phenylbenzamide (1.0mmol) and aryl aldehyde (1.0mmol) in ethanol. The reaction mixture was stirred about 5h at 75^{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 (5 ml) and EtOAc (3ml) were added to the reaction mixture. The organic phase was separated and the aqueous phase

was further extracted with EtOAc (2×5ml). The organic layers were dried over anhydrous Na_2So_4, filtered through celite and concentrated. The residue was purified by silica gel chromatography using a mixture of hexane and EtOAc as eluents affording the desired product. The pure product was well characterized by advanced spectral techniques like ^1H, ^{13}C and mass data. The Characterization of derivatives was interpreted and explained below

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

Yellow solid; Yield -81%, MP: 178-179^oC, ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.284 (1H, d, J = 8.0Hz), 7.789, 7.333 (m, 7H), 7.254-7.156 (m 2H), 7.128-7.014 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δppm: 165.04, 158.38, 145.56, 138.60, 135.55, 132.76, 130.44, 129.87, 128.92, 128.53, 128.03, 127.45, 126.19, 125.11, 118.85, LCMS: m/z 299.24.

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

Yellow solid; Yield -90%, MP: 185-187^oC, ^1H NMR (400 MHz, $CDCl_3$) δppm: 9.645 (s, 1H), 8.274 (s, 1H), 7.944-7.787 (m, 3H), 7.718-7.675 (m, 1H), 7.549 (d, J = 6.8 Hz, 1H), 7.441 (d, J = 5.8 Hz, 1H), 7.250-7.026 (m, 6H). ^{13}CNMR (100 MHz, $CDCl_3$) δppm: 168.06, 162.95, 160.15, 148.10, 139.02, 132.44, 130.51, 130.20, 129.63, 128.73, 128.14, 126.56, 123.22, 122.63, 120.59. LC MS: (m/z): 315.36.

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

Yellow solid; Yield -88%, M.p: 189-191^oC, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.358 (d, J = 12.4 Hz, 1H), 7.882-7.680 (m, 2H), 7.484(s, 1H), 7.434-7.271 (m, 5H), 7.254 (d, J = 7.6 Hz, 2H), 6.875(d, J = 4.8 Hz, 2H), 3.670 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.34, 159.75, 153.19, 148.06, 136.89, 133.08, 130.01, 129.57, 129.12, 128.65, 127.77, 127.24, 126.94, 125.67, 119.28, 113.52, 55.75, LC MS: m/z 329.16.

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

Pale yellow solid; Yield -86%, M.p: 194-196^oC, ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.286 (d, J = 7.2Hz, 1H), 7.881 (s, 1H), 7.545 (s, 1H), 7.436-7.293 (m, 3H), 7.270 (d, J =10.4Hz, 2H), 7.165 (d, J = 5.2 Hz, 2H), 7.048(d, J = 7.2 Hz, 2H), 1.825 (s 3H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 164.05, 154.78, 146.05, 139.55, 136.05, 134.18, 132.16, 130.25, 129.86, 129.14, 128.91, 128.54, 127.67, 127.09, 126.39, 120.11, 21.04. LC MS: m/z 313.54.

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

Yellow solid; Yield -87%, M.p: 179-181^oC, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.325 (d, J = 8.4 Hz, 1H), 7.853 (s, 1H), 7.714 (m, 1H), 7.535-7.286 (m, 6H), 7.242-7.014(m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.24, 156.65, 147.78, 140.80, 138.29, 135.33, 133.85, 131.09, 129.77, 129.22, 128.78, 128.33, 127.57, 127.18, 126.90, 121.75; LCMS(m/z): 335.78.

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

Reddish brown solid: Yield -87%, MP: 192-194^oC, ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.315 (d, J = 8.0 Hz, 1H), 7.914-7.687 (m, 2H), 7.585 (s, 1H), 7.492-7.324 (m, 5H), 7.234-7.215 (m, 2H), 7.131-7.013 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 165.35, 157.27, 148.93, 138.34, 136.54, 134.60, 132.07, 130.65, 129.75, 129.21, 128.44, 127.94, 127.32, 126.34, 123.07, 121.15. LC MS (m/z): 378.39.

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

Yellow solid; Yield -85%, MP: 202-204^oC, ^1H NMR (400 MHz, $CDCl_3$) δppm: 8.245 (d, J = 9.2 Hz, 1H) 1H), 7.810 (d, J = 6.8 Hz, 1H), 7.704-7.417 (m, 5H), 7.312 (d, J = 12.8 Hz, 1H), 7.247 (m, 1H), 7.048 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 168.78, 165.08, 162.17, 146.18, 139.28, 135.47, 133.09, 130.69, 129.12, 128.51, 127.58, 126.06, 124.08, 122.18, 120.24, 118.14. LCMS (m/z): 343.45.

4-(4-oxo-3-phenyl-3, 4-dihydroquinazolin-2-yl) benzonitrile (3h)

Pale Yellow solid; Yield -86%, MP: 187-189^oC, ^1H NMR (400 MHz, CDCl3) δppm: 8.147 (d, J = 9.6 Hz, 1H), 7.825 (d, J = 7.6 Hz, 1H), 7.754-7.401 (m, 5H), 7.334 (d, J = 12.4 Hz, 1H), 7.235 (m, 1H), 7.078 (d, J = 8.0 Hz, 2H).^{13}C NMR (100 MHz, CDCl3) δppm: 169.27, 164.65, 161.58, 145.68, 140.27, 136.04, 132.14, 130.06, 128.95, 128.44,

127.66, 126.14, 124.09, 122.25, 120.65, 118.29. LCMS (m/z): 324.02(M+H).

4-(4-oxo-3-phenyl-3, 4-dihydroquinazolin-2-yl) benzoic acid (3i)

Pale red solid; Yield -85%, MP-196-198^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 11.258(s,1H), 8.354 (d, J = 7.2 Hz, 1H), 7.901 (d, J = 5.6 Hz, 1H), 7.714-7.368 (m, 5H), 7.294 (d, J = 11.2 Hz, 1H), 7.257 (m, 1H), 7.114 (d, J = 8.8 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 178.25, 166.14, 162.61, 158.58, 146.16, 140.02, 134.54, 132.01, 130.11, 128.90, 128.2, 127.60, 126.56, 124.22, 122.58, 120.15, 119.29. LCMS (m/z): 342.45(M+).

RESULTS AND DISCUSSION

In an initial endeavor, the emergent procedure followed by one-pot two-component synthesis of titled compounds by the reaction of substituted aryl aldehydes, 2-amino-N-phenyl benzamine under thermal condition in water with camphor sulphonic acid in catalyst in acetonitrile (Scheme -1). To developed the yield and optimize the reaction conditions, the same reaction were carried out in the presence of various amounts of camphor sulphonic acid under similar conditions. In all reactions, the conditions were optimized for 100% conversion.

The reaction condition of these derivatives was optimized at various catalyst, different amount of the catalyst and different solvent are used. The maximum yield of the compounds was obtained in presence of protic acid camphorsulphonic acid (CSA) catalyst than oxidative related catalyst such as Silicasuported sulphonic acid (SSA), Methanesulphonic acid(MSA),-toluene Sulphonic acid(PTSA), camphorsulphonic acid (CSA) and Trichlorosalicylic acid (TCSA) (Table No.1) whereas different amount of catalyst utilized during the reaction below.

The various solvents were used during the reaction that were evaluated (DMF, Isopropanol acetonitrile, ethanol, methanol, cyclohexane) in the model reaction. It was found to be the best medium for the reaction, with 90% product yield and was therefore used as the solvent for subsequent reactions on the merits of higher yield, green nature and easy work-up.

A significant enhancement of the desired compounds was represented as shown Table No.3, the yield of 3c being developed to 90%. The amount of the catalyst applied during the synthesis and effect of the yield of the products as well as rate of reaction done. As shown the Table No.3, the identified improvement of the product by the variation of the loaded catalyst. The maximum amounts of the catalyst could not improve the results. Although, use of 4.0mmol% CSA allowed the reaction time to be decreased to 1h, the yield unexpectedly decreased to 35%as shown Table No.3.

BIOLOGICAL ACTIVITIES

Antibacterial and antifungal activities

The desired derivatives were examined for their *in-vitro* antibacterial and antifungal activities following micro broth dilution method. The *in vitro* antibacterial activity was examined against gram-positive (*B. subtilis and S.aureus*) and gram-negative (*E.coli and P.aeruginosa*) microorganisms. The *in vitro* antifungal activity was evaluated against *A.Niger* and *C.albicans* microorganisms. The standard drugs were used for this study were Streptomycin and Ketonozole for antibacterial as well as antifungal screening. The standard strains used for screening of antibacterial and antifungal activities were commercially purchased from the Culture collection and geneank (MTCC), Chandigarh, India. Mueller Hinton Broth was used as a nutrient medium for bacteria and Sabouraud dextrose Broth for fungal growth. Inoculums size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. The stock solution (2000µg/mL) of the compounds under investigation and standard drugs were prepared by successive two fold dilution.

In the preliminary examination 500, 250 and 100µg/mL concentrations of the compounds were used. The compounds found to be active in this primary screening were further examination. In secondary screening, 200, 100, 50 and 25µg/mL concentrations were used. The inoculated wells were incubated overnight at 37°C in a humid

atmosphere. The highest dilution showing complete inhibition was considered as a minimum inhibition concentration (MIC). The MIC values revealed that the synthesized compounds showed moderate to good inhibition. The compounds "3e and3f exhibited good excellent activities against bacterial strains. The MIC values of antifungal activity shown that compound 3c and 3b exhibited good activity against all fungal strain. Antimicrobial activity of compounds (3a-3i) is listed in Table No.4.

Table No.1: The effect of catalyst for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	SSA	8	59
2	MSA	5	70
3	PTSA	10	68
4	CSA	7	78
5	TCSA	3	90

Table No.2: The effect of solvent for preparation of titled derivatives

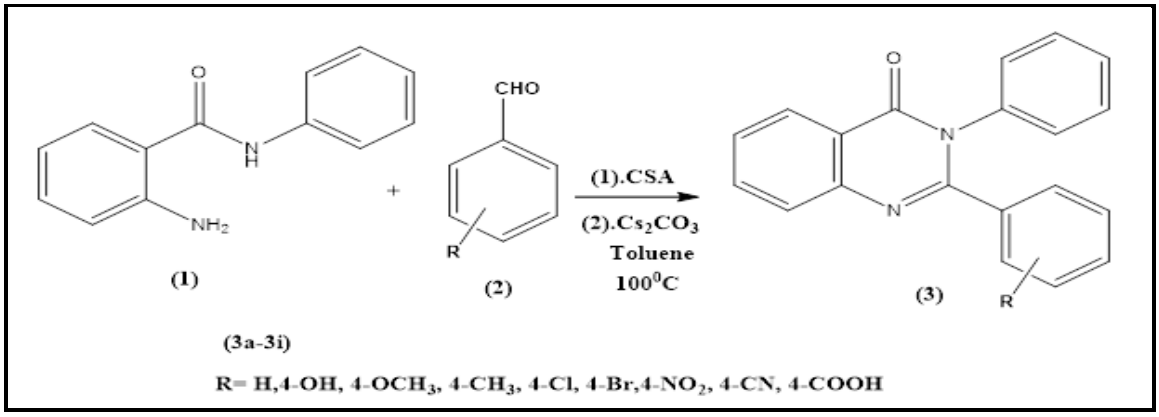
Entry	Catalyst	Time (hrs.)	Yield (%)
1	DMF	5	51
2	IPA	5	72
3	CH_3CN	5	65
4	EtOH	5	90
5	MeOH	5	69

Table No.3: The effect of loaded for preparation of titled

Entry	Amount catalyst (mmol)	Time (hrs)	Yield (%)
1	1.0	5	20
2	2.0	5	35
3	4.0	5	90
4	6.0	5	90
5	2.5	3	75

Table No.4: Antimicrobial activity of compounds (3a-3i)

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
Strains	***B. subtilis***	***S. aureus***	***P. aeruginosa***	***E. coli***	***A. Niger***	***C. Albicans***
3a	06	05	08	07	05	05
3b	17	16	18	17	13	14
3c	18	16	18	14	13	14
3d	17	16	17	15	15	17
3e	22	22	20	20	18	18
3f	20	21	21	22	17	18
3g	10	12	10	13	10	09
3h	08	08	06	06	08	09
3i	06	08	10	08	07	09
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
DMSO						



Scheme No.1

CONCLUSION

We have developed a new, easy, an efficient process for synthesis of 2, 3-disubstituted quinazolinones- 4-(3H)-ones derivatives via one-pot two component condensation of substituted aromatic aldehyde and 2-amino-N-phenyl benzamine in ethanol medium with camphorsulphonic acid as an efficient catalyst. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives. In additionally, an excellent effect of antimicrobial potent activity of desired compounds was evaluated.

ACKNOWLEDGEMENT

Authors are very thankful to PRISM PG and DG College and they were for providing all the necessary facilities.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Shaik Lakshman *et al*. Designed synthesis and bio evaluation of 2, 3-disubstituted quinazolin-4-(3h)-ones promoted camphor sulfonic acid as a catalyst, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 12(3), 2024, 100-106.