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Original Article

ALUMINA CATALYST: SYNTHESIS OF NOVEL QUINAZOLINE DERIVATIVES AND THEIR SOLUBILITY INCREASES THROUGH INCLUSION WITH β-CYCLODEXTRIN

MOSSARAF HOSSAIN[1,2*], ASHIS KUMAR NANDA[1]

[1]Department of Chemistry, University of North Bengal, Darjeeling 734013, West Bengal, India, [2]Department of Chemistry, Siliguri College, Darjeeling 734001, West Bengal, India
Email: hossainmossaraf@gmail.com

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ABSTRACT

Objective: To synthesis a novel methodology of bioactive quinazoline derivatives under greener process to an excellent yields and increases their solubility via inclusion with β-cyclodextrin (CD).

Methods: Derivatives of quinazoline compounds were prepared by the mixture of 3-amino-2-phenylquinazolin-4(3H)-one, derived from 2-phenyl-4H-benzo[1,3]oxazin-4-one by refluxing with hydrazine, substituted aromatic aldehyde and alumina intimately in an agate mortar and pestle under solvent-free condition. Using various techniques for preparing inclusion complexes, kneaded method is the best method for encapsulation in host-guest complex chemistry. All compounds including inclusion complexes were characterised by spectral methods.

Results: Synthesized a series of novel quinazoline compounds under a very easier greener process with a commercially available reagent. However, their low bioavailability, due to low absorption and solubility, can limit their potential applications. CD was used to resolve this solubility problem. CD can easily accommodated the guest molecules to encapsulate inside its cavity due to interior the hydrophobic nature with a hydrophilic exterior part to form thermodynamically more stable molecular microcapsules, commonly name as host-guest complexes or inclusion complexes. In this sense, CD was utilized to enhance not only the solubility and bioavailability of these quinazoline compounds but also their antibacterial capacity. The formation of inclusion complex was thus confirmed by ultraviolet-visible spectroscopy (UV-VIS), Fourier Transform Infrared Spectrometry (FT-IR), differential scanning calorimetry (DSC) and solubility study technique.

Conclusion: Here we have successfully unfolded an eco-friendly methodology for the synthesis of derivatives of quinazoline and increased their solubility via host-guest inclusion technique. From the spectral analysis, it was concluded that the quinazoline compound is fully encapsulated inside the cavity of the CD.

Keywords: 3-amino-2-phenylquinazolin-4(3H)-one, Substituted aldehyde, Inclusion complex, β-Cyclodextrin, Solubility study

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INTRODUCTION

Quinazoline-4-(3H)-one moieties have gained wide-ranging research interest due to their broad spectrum range of biological activity. Quinazoline is an important studied moieties in medicinal field [1, 2]. At the beginning researches in the medicinal field started the febrifugine (3) discovery on the quinazoline scaffold which is a quinazolinone alkaloid, has immense anti-malarial activity from the plant aseru (dichroa febrifuge lour) [3, 4]. In addition, the anti-malarial activity [5], the derivatives of quinazoline demonstrate a broad range of biological activities including antibacterial [6, 7], anticancer [8, 9], antihypertensive [10], anti-inflammatory [11, 12], activities and so on (fig. 1). Even though their immense medicinal value to come out as successful drugs, water solubility, is one of the key factor [13].

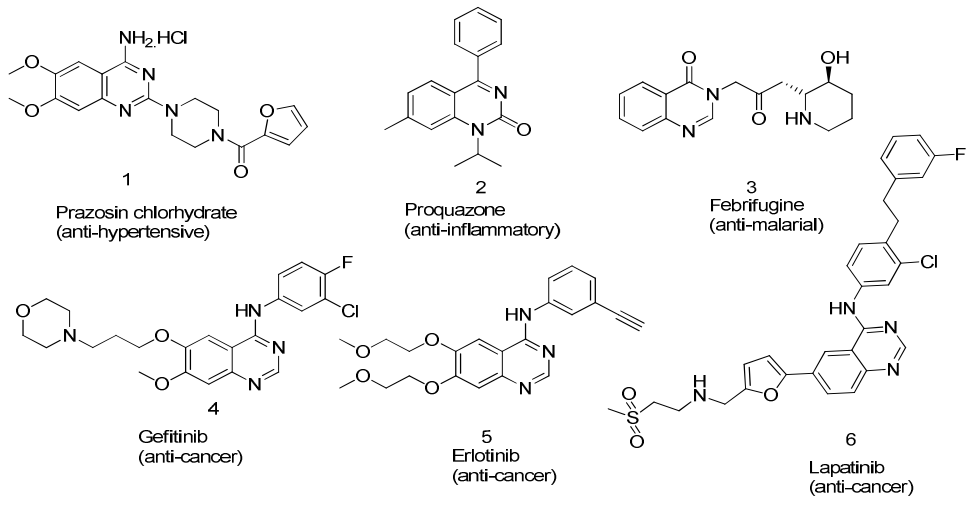


Fig. 1: Representative some bioactive molecules containing quinazoline scaffold

In 2007, this work reported [14], from our laboratory under refluxing condition in ethanol solution to formation of a substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one and reported their anti-bacterial activity with quantitative structure-activity relationship (QSAR) studies. Now furthermore investigating a new methodology, we have synthesized this series of bioactive quinazoline moieties in a very easier greener technique under solvent-free protocol at 50 °C for 20 min using alumina as a catalyst that enhances the electrophilicity character of the carbonyl of respective aldehyde up to the product formation 90% (fig. 2). But one drawback of these series of compounds is fully water-insoluble, despite their immense medicinal property to come out as profitable drugs. Water solubility is part of the key factors to enhance the biological activity [15]. Here we tried to solve this problem through inclusion with β-cyclodextrin. Cyclodextrins (CDs) are homochiral, cyclic oligosaccharides belonging the family of 6, 7, or 8 member α-1, 4-linkage D-glucopyranose units (namely α, β, and γ cyclodextrins), fully water-soluble and have cavity sizes ranging from 0.49 to 0.79 nm [16, 19]. Most recently, this technique of complexion with cyclodextrins has been repeatedly applied in the preparation of oral bioavailability [20, 22]. In this technique, some drugs expand shelf life [23] to a certain extent, and furthermore, it contributes to control drug release rate, progressed organoleptic properties and maximized tolerance in gastrointestinal [24]. Thus, increased drugs solubility plays a very significant role in the absorption, which in due course affects its bioavailability [25]. Therefore it is very important to develop protocols to improve the efficiency of complexation of drug-cyclodextrins.

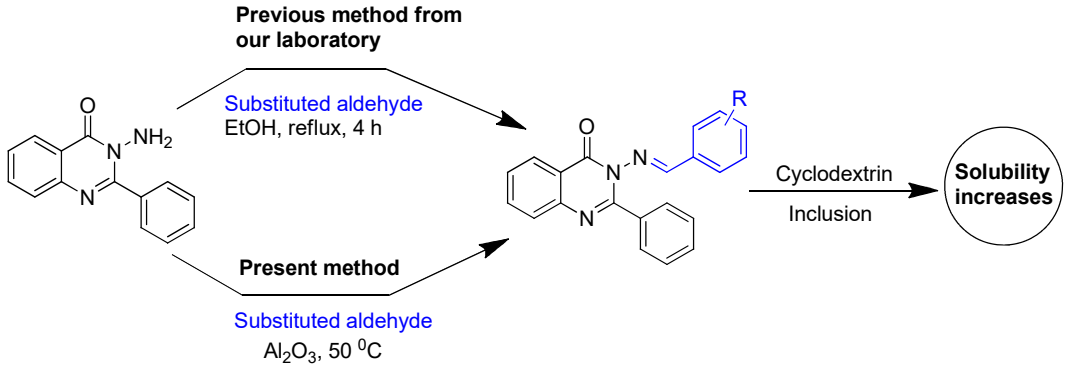


Fig. 2: Synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina as a catalyst

MATERIALS AND METHODS

The commercially available all reagents used here such as anthranilic acid, benzoyl chloride, pyridine, hydrazine, substituted aldehydes, cyclodextrin needed for molecules and ligand synthesis were used further without purification from the suppliers. Other reagents used throughout this work were purchased from the different companies sigma-aldrich, acros, thomas and baker, merck and were used as received except otherwise stated. Employed glassware was proceeding to reaction flame-dried or oven and cooled.

Characterization of the compounds and inclusion complexes

Nuclear magnetic resonance (NMR) spectroscopy

^{1}H-NMR (300 MHz) spectra and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) unit relative to reference as tetramethylsilane (TMS, δ 0.00 ppm). Coupling patterns are reflected in the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Solvents are varied in each case.

Ultraviolet-visible spectroscopy

UV-VIS spectra were recorded on a JASCO V-530 Jasco, Tokyo, Japan spectrophotometer at room temperature in the wavelength range 200–800 nm. The water solution of the complex was prepared with constant stirring and filtered the solution. UV spectra were recorded by using the filtered solution.

Fourier transform infrared (FT-IR) spectroscopy

Infrared (IR) spectra were recorded on a Schimadzu FTIR-8300 spectrometer in the 4000–400 cm^{-1} region as in nujol. Only respective absorption bands are informed. Absorption is given in unit, wave numbers (cm^{-1}); abbreviations: strong = s, medium = m, weak = w, broad = b.

Differential scanning calorimetry (DSC)

DSC studies were recorded in a Perkin Elmer Pyris 6. Temperature heating range and heating rate were done in the 30-250 °C and 5-10 °C per min. 2-5 mg of sample was packed in aluminium pans.

Mass spectroscopy

The electron-spray mass spectra were taken on a MICROMASS QUATTRO II triple quadrupole mass spectrometer. FAB MS analyses were taken on a Jeol SX 102/Da-600 mass spectrometer. Data system using Argon/Xenon (6 kv, 10 mA) as the FAB gas. 10 kV was the accelerating voltage and spectra were made at room temperature.

Thin-layer chromatography (TLC)

TLC was performed for the compound, CD and inclusion compound using the eluent [ethyl acetate: butanol (5:4 v/v)] on TLC silica gel 60 F_{254}, Merck.

Melting points (MP)

MP was recorded in open glass capillaries using concentrated sulphuric acid bath and are uncorrected.

General procedure for substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina as a catalyst

Mixture of 3-amino-2-phenylquinazolin-4(3H)-one (1 mmol), substituted aromatic aldehyde (1 mmol) and alumina (4 equiv w. r. t. stating substance) were mixed intimately in an agate mortar and pestle for a period of 20-30 min under solvent-free condition. Then the mixture was heated in an oil bath at 50 °C. To this mixture, a few ml of water were added, filtered and dried the mass in an oven until to dryness. Then dried mass was dissolved in ethanol and collects the filtrate and evaporation of the solvent afforded the residue as a pure product. Purity of the product was checked by TLC on a TLC plate.

3-{[(2-hydroxyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one[2a]: Yield 75%. m. p. 233 °C. IR ν (cm^{-1}) (nujol): 3200-3100, 1681, 1604, 1467. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 6.69-8.36 (^{13}H, m, Ar-H), 9.19 (1H, s, H-C=N), 9.99 (OH, H-bonded), ^{13}C NMR δ ppm $CDCl_3$ (TMS): 116.4, 117.5, 119.7, 121.5, 127.3, 127.4, 128.0, 128.9, 130.3, 132.5, 133.3, 134.2, 134.8, 146.4, 153.6, 159.1, 159.7, 164.7. Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.45; N, 12.31; found: C, 74.10; H, 4.45; N, 12.28. FAB MS (m/z): 342 (M+1).

3-{[(4-methoxyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one [2b]: Yield 80%. m. p. 210 °C. IR ν (cm^{-1}) (nujol): 1679, 1602, 1448, 1494, 1257, 1170. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 3.84 (3H, s,-OCH_3), 7.37-8.36 (13H, m, Ar-H), 8.87 (1H, s, H-C=N-N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 55.4, 114.3, 121.5, 125.9, 126.9, 127.3, 127.7, 127.9, 129.9, 129.9, 130.7, 134.4, 134.7, 146.5, 159.4, 163.0, 164.0, 166.5. Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35, H, 4.82, N, 11.82; found: C, 74.40, H, 4.90, N, 11.78. FAB MS (m/z): 356 (M+1).

3-{[(4-fluorophenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one [2c]: Yield 90%. m. p. >200 °C. IR ν (cm^{-1}) (nujol): 1674, 1614, 1593, 1554, 1537, 1469, 1373, 1184. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 7.10-8.70 (13H, m, Ar-H), 9.04 (1H, s, H-C=N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 166.3, 164.8, 153.9, 153.9, 146.6, 134.5, 134.1, 131.0, 130.9, 130.5, 129.3, 128.9, 127.7, 127.2, 126.8, 121.5, 116.3. Anal. Calcd. for $C_{21}H_{14}N_3OF$: C, 73.46, H, 4.11, N, 12.24; found: C, 73.50, H, 4.10, N, 12.18. FAB MS (m/z): 344 (M+1).

3-{[4-dimethylaminophenyl) methylene] amino}-2-phenyl-quinazolin-4(3H)-one [2d]: Yield 75%. m. p. 240 °C. IR ν (cm^{-1}) (nujol): 1681, 1589, 1556, 1508, 1456, 1375, 1328, 1313. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 3.04 (-N-CH3), 6.68-8.70 (13H, m, Ar-H), 8.67 (1H, s, H-C=N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 187.6, 159.8, 154.0, 153.0, 146.7, 134.8, 134.1, 130.7, 129.7, 129.3, 127.9, 127.7, 127.2, 126.8, 121.6, 120.3, 111.5, 40.1. Anal. Calcd. for $C_{23}H_{20}N_4O$: C, 74.98, H, 5.47, N, 15.2; found: C, 74.99, H, 5.50, N, 15.13. FAB MS (m/z): 344 (M+1).

3-{[4-chloroyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one [2e]: Yield 85%. m. p. 196 °C. IR ν (cm^{-1}) (nujol): 1679, 1591, 1554, 1377. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 7.37-8.36 (13H, m, Ar-H), 9.10 (1H, s, H-C=N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 121.5, 127.1, 127.3, 127.9, 127.9, 129.2, 129.8, 129.9, 130.0, 131.7, 134.4, 134.8, 138.5, 146.5, 154.0, 159.2, 164.4. Anal. Calcd. for $C_{21}H_{14}N_3OCl$: C, 70.10; H, 3.92; N, 11.68; found: C, 70.20; H, 4.10; N, 11.62. FAB MS (m/z): 360 (M+1).

3-{[3-methoxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2f]: Yield 82%. m. p. 234 °C. IR ν (cm^{-1}) (nujol): 1679, 1575, 1465, 1367, 1317, 1276. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 3.74 (3H, s,-OCH_3), 7.30-8.37 (13H, m, Ar-H), 9.09 (1H, s, H-C=N-N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 111.7, 119.1, 121.7, 121.8, 122.3, 127.0, 127.3, 127.9, 128.1, 128.2, 129.8, 134.2, 134.5, 134.9, 146.5, 154.1, 159.3, 159.9, 165.5. Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.28; N, 11.82; found: C, 74.45; H, 4.35; N, 11.78. FAB MS (m/z): 356 (M+1).

3-{[(4-hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2g]: Yield 80%. m. p. 233 °C. IR ν (cm^{-1}) (nujol): 3307, 3213, 1668, 1645, 1604, 1554, 1375, 1338. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 5.03 (-OH), 7.42-8.29 (13H, m, Ar-H), 9.16 (1H, s, H-C=N-N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 110.0, 120.1, 126.6, 127.0, 127.8, 128.2, 129.2, 130.3, 133.9, 134.5, 134.5, 143.1, 149.0, 149.9, 155.0, 161.5. Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; found: C, 73.99; H, 4.49; N, 12.30. FAB MS (m/z): 342 (M+1).

3-{[(4-hydroxy-3-methoxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2h]: Yield 70%. m. p. >240 °C. IR ν (cm^{-1}) (nujol): 3305, 3215, 1749, 1712, 1664, 1575, 1467, 1377. ^{1}H NMR δ ppm $CDCl_3$ (TMS): 3.81 (3H, s,-OCH_3), 5.03 (-OH), 6.92-8.30 (12H, m, Ar-H), 8.90 (1H, s, H-C=N-N); ^{13}C NMR δ ppm $CDCl_3$ (TMS): 55.9, 108.7, 114.5, 125.4, 126.4, 126.6, 127.0, 127.3, 127.8, 128.2, 129.3, 129.9, 130.3, 134.5, 143.2, 146.7, 147.3, 154.4, 159.8. Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31; found: C, 71.25; H, 4.65; N, 11.26. FAB MS (m/z): 372 (M+1).

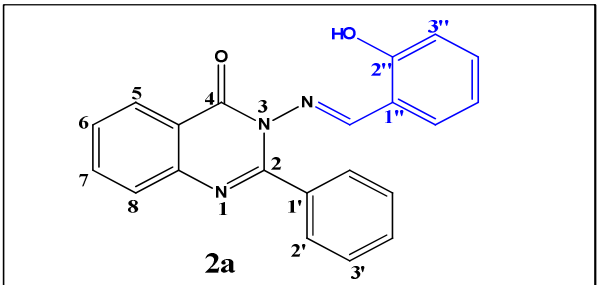
3-{[(3-nitrophenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2i]: Yield 85%. m. p. 248 °C. IR ν (cm^{-1}) (nujol): 1674, 1641, 1500, 1456, 1344. ^{1}H NMR δ ppm ($CDCl_3$+DMSO-d6) (TMS): 7.22-8.54 (12H, m, Ar-H), 9.58 (1H, s, Ar-H), 8.59 (1H, s, H-C=N); ^{13}C NMR δ ppm (TMS) ($CDCl_3$+DMSO-d6): 118.3, 120.6, 122.3, 122.3, 126.9, 127.3, 127.9, 128.1, 128.9, 130.0, 131.5, 132.4, 133.5, 134.0, 139.8, 161.6, 164.9, 165.5. Anal. Calcd. for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.84; N, 15.15; found: C, 68.15; H, 3.81; N, 15.13. FAB MS (m/z): 371 (M+1).

3-{[(pheny)lmethylene]amino}-2-phenylquinazolin-4(3H)-one [2j]: Yield 83%. m. p.196 °C. IR ν (cm^{-1}) (nujol): 1662, 1647, 1645, 1556, 1454. ^{1}H NMR δ ppm ($CDCl_3$+DMSO-d6) (TMS): 6.98-8.62 (14H, m, Ar-H), 8.47 (1H, s, H-C=N); ^{13}C NMR δ ppm ($CDCl_3$+DMSO-d6) (TMS): 119.8, 121.6, 122.8, 127.5, 127.7, 127.8, 128.7, 128.8, 130.6, 132.1, 132.7, 133.6, 134.3, 139.8, 15.0, 165.8, 166.0. Anal. Calcd. for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91; found: C, 77.54; H, 4.71; N, 12.85. FAB MS (m/z): 326 (M+1).

Inclusion technique

Formation of complexes

In this portion, the complex is formed by the kneaded protocol and is characterized by UV, IR, DSC, and solubility study technique. It is examined that the effects of complex formation by β-CD showing improvement solubility of the compound in an aqueous medium. We developed different protocols for the complex formation and screened the most suitable protocol of its preparation. We worked only with compound 2a for complexation.



(*E*)-3-((2-hydroxybenzylidene)amino)-2-phenylquinazolin-4(3*H*)-one

Preparation of physical mixture (PM)

The physical mixture of the compound 3-{[(2-hydroxyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one and β-CD [1:1 molar ratio] were prepared by mixing simultaneously in a mortar and pestle [26].

Complex formation by kneading method (KN)

To the best of our knowledge to design the most excellent formulation of inclusion complexes, a little volume of warm water was mixed with β-CD to make a slurry and then reserved at 50 °C for 12 h. The slurry was observed for 12 h with infrequent mauling. After 12 h, an equivalent amount of the 3-{[(2-hydroxyphenyl) methylene] amino}-2-phenyl-quinazolin-4(3H)-one and the β-CD was mixed by triturating in a mortar and pestle with a small volume of water-ethanol mixture to form a slurry. The slurry was grinded for 45 min and dried at 50 °C. The dried mass was sieved through 100-micron mesh [27, 28].

Complex formation by co-evaporation method (COE)

The aqueous solution of β-CD was mixed with an alcoholic solution of 3-{[(2-hydroxyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one. Then the mixture was stirred for 1 h and was evaporated to dryness at 45 °C. The dried mass was crushed and sieved through 100 micron mesh [29].

Complex formation by freeze-drying method (FD)

The physical mixtures (PM) were taken in 500 ml double distilled water and stirred for 5 d. The resulting suspension was freeze-dried and freeze-dried complex. Thus formed was crushed and sieved through 100 micron mesh [30, 31].

Preparation of different water solution

In distilled water (5 ml), β-CD (34 mg) solubilized to form clear solution, the physical mixture [3.34 mg said compound+17 mg β-CD (3 mmol: 3 mmol)] made a turbid suspension and the complex [3.34 mg said compound+17 mg β-CD (3 mmol: 3 mmol)] was made to be faintly turbid as shown in fig. 6 (A, B, and C respectively).

RESULTS AND DISCUSSION

The initial reactant, 3-amino-2-phenylquinazolin-4(3H)-one (1) was synthesized in our laboratory following a method reported earlier. The reactants 3-amino-2-phenylquinazolin-4(3H)-one and substituted aldehyde were thoroughly mixed in an agate mortar and

pestle in presence of alumina at room temperature. Thereafter, the mixture was transferred to a round bottom flask and heated at 50 °C for 20-30 min. The corresponding product was isolated following by standard washing techniques [32].

All the compounds were characterized by NMR, FT-IR and Mass spectrometry. In the study of optimization, a model reaction was performed for the formation of 2j. The reaction was optimized with regards to the amounts of the lewis acid, temperature and the time for the reaction which has been summarized in table 1.

To investigate the reaction optimization, initially, an equivalent mixture of the 3-amino-2-phenyl quinazolin-4(3H)-one and benzaldehyde at room temperature (RT) for 20 min but TLC plate did not exhibit any new spot. Thereafter, the temperature was increased to 50 °C, wherein 30% conversion was obtained. (table 1, entry 2). For further rationalization we used alumina (2 equiv w. r. t substrates) as a catalyst at the same temperature condition, wherein, the conversion is about 60% (table 1, entry 3). Gradual increase in concentration of alumina up to 4 equivalents of alumina w. r. t substrates, keeping other experimental conditions identical, resulted in corresponding increase in product, i.e., 83%. Thereafter, the further increase in alumina did not respond with hike in product yield. Therefore, the reaction was optimized with 4 equivalents of alumina w. r. t substrates at 50 °C for 20 min (table 1, entry 5).

Table 1: Optimized table for formation of 3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina as a catalyst

Entry	Alumina (equiv)	Time (min)	Temp (°C)	Yield (%)
1	_	20	RT	no reaction
2	_	20	50	30
3	2	20	50	60
4	3	20	50	77
5	4	20	50	83
6	5	20	50	83

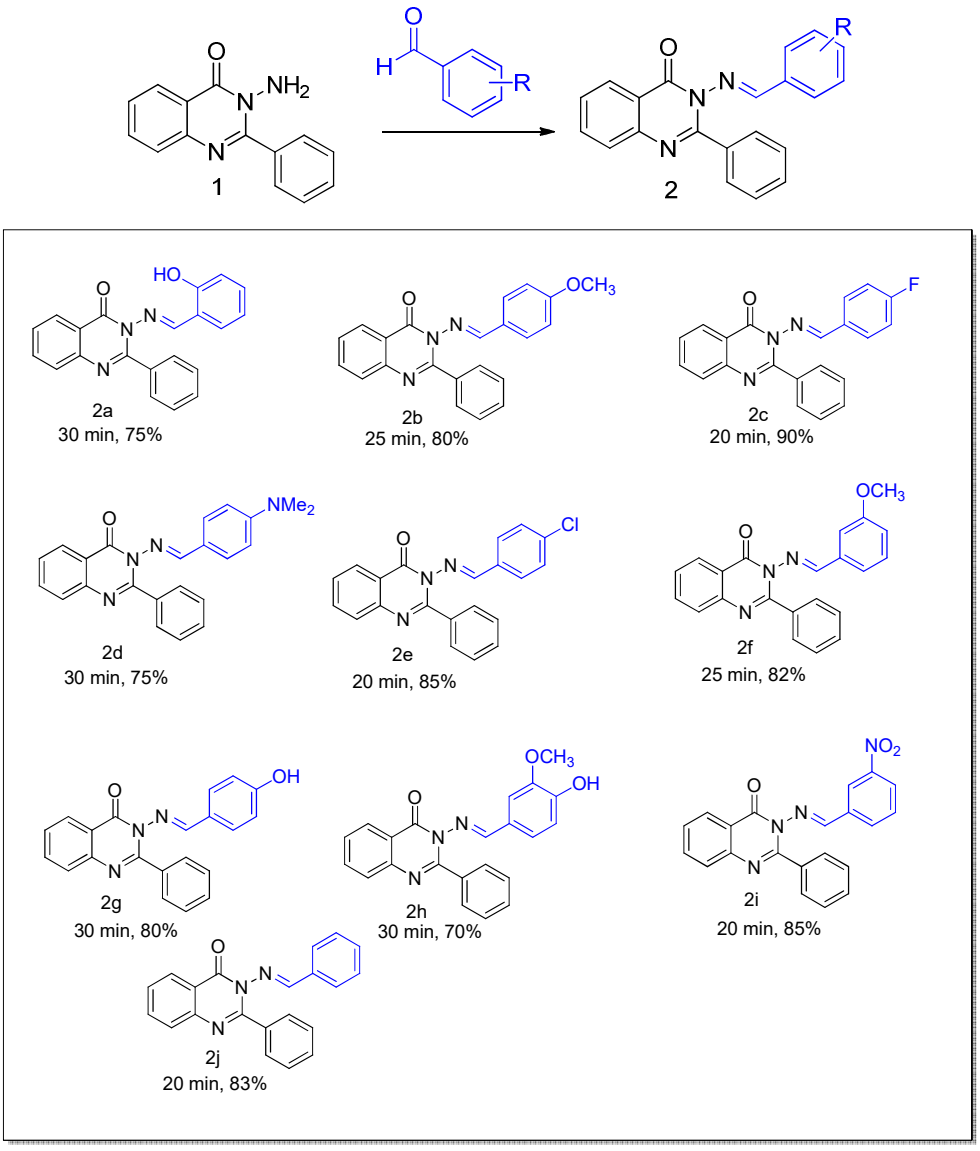


Fig. 3: Substrate scope of alumina catalyst substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one

For more insight on the diversity of the catalyst, the reaction was studied with different substrates varying in the nature of the substituent, i.e., electron withdrawing and electron donating (fig. 3) at optimised condition [33]. Both types of the substituent responded appreciably in this reaction condition. In the case of electron withdrawing substituent such as-F,-Cl,-NO_2 etc., the conversion of the reaction is high. This is largely due to the increasing electrophilicity of the carbonyl carbon of the corresponding aldehyde. When 4-fluorobenzaldehyde reacts with 3-amino-2-phenylquinazolin-4(3H)-one (1:1), conversion occurs up to 90% (fig. 3, entry 2c) due to the very high electronegativity of fluorine atom which withdraws electron through inductive effect directly, thereby increaseing the electrophilicity at the carbonyl carbon leading to the improved reaction yield. In case of-Cl (85%, fig. 3, entry 2e) and-NO_2 (85%, fig. 3, entry 2i), yields are slightly lower as compared to-F because-Cl showed the low inductive effect while the nitro group present in meta position do not participate in resonance effect. For similar reasons, in the case of the electron donating substituent such as-OCH_3,-NMe_2,-OH, product conversion is slightly reduced due to increase in the electron availability in the carbonyl carbon of aldehyde group. When these groups are directly connected in the ortho or para position w. r. t aldehyde group, conversion of the desired products yields excellent to moderate. When in the meta position, product conversion is enhanced up to 82% (fig. 3, entry 2f). Very interestingly, when the reaction takes place only with benzaldehyde that is no substituent are incorporated in the aryl ring still product conversion 83% (fig. 3, entry 2j) since aryl ring shows both inductive as well as resonance effect. For this behaviour, it converted the reaction yield up to 83% in between donating and withdrawing substituent.

Mechanism

Using alumina as a catalyst not only enhances the carbonyl character through electrophilicity but also acts as a powerful desiccant that improved the reaction towards the forward direction by forcing dehydration to produce the desired product (fig. 4). Alumina bind with carbonyl to activate the central facilitate the nucleophilic attack of the formation of intermediate (3). Finally a molecule of water eliminated from the system to give the desired Product (2).

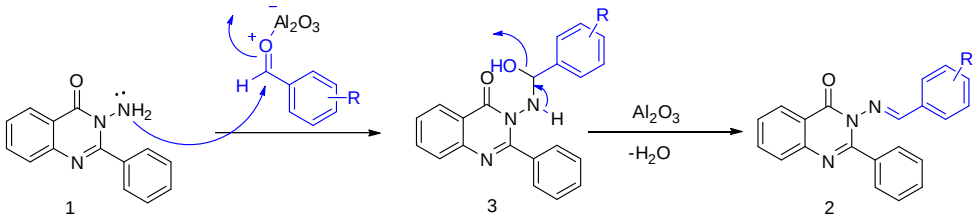


Fig. 4: Plausible mechanisms for solvent-free synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina

UV-VIS spectroscopic study

From the absorption spectra, the corresponding absorbance of the compound was varied due to the formation of the complex as showed in fig. 5. In the complex formed through physical mixtures without the addition of water are very slow as compared to the complex formed from the kneading method which contained water during crushing. The study demonstrates that the dissolution rate of 3-{[(2-hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one was increased to such an extent by using kneading method for complex formation as compared to other methods.

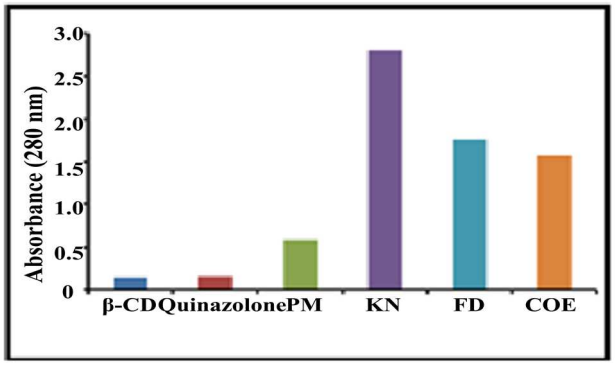


Fig. 5: Efficiency of diverse methods for the complex formation

Thereafter, the crushing time for the complex preparation was varied as: 0 min, 20 min, 30 min, 40 min, 60 min. The mixture of β-CD and compounds (1:1) was added in each preparation. It may be emphasized that crushing time has an important role in the complex formation. With increasing crushing time there is a pronounced increase in absorbance of the reaction mixture. Beyond 40 min of crushing, an absorbance of the drug with β-CD showed a plateau which indicated that the optimum condition (fig. 6). Therefore, the optimized kneading time was found to be 40 min. No such high absorption was observed for the quinazolone and CD in the range 270-300 nm, while a high absorption was found for the inclusion complex in 270-300 nm region. Moreover, from this UV spectrum, it can be concluded that there must be an inclusion complex [34, 35].

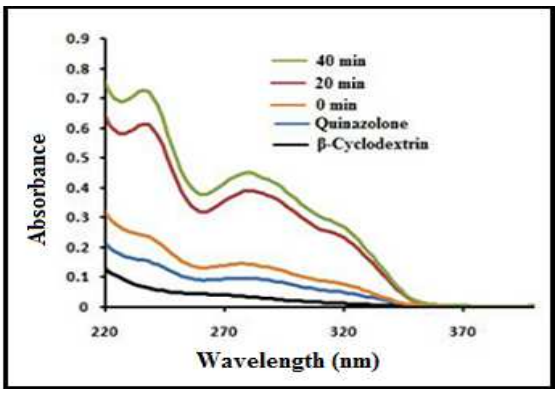


Fig. 6: UV spectrum of complex formation in various crushing time

Infrared studies

The IR spectrum of β-CD, 3-{[(2-hydroxyphenyl) methylene] amino}-2-phenylquinazolin-4(3H)-one (2a), physical mixture (1:1 molar ratios) as well as the complex formation under kneaded method are shown in below (fig. 7). In the drug-loaded compound, the essential bands are carbonyl (-C=O), imine (-C=N), amine (-C-N), aromatic-C-H (stretching and out of a plane, bent), alcoholic-OH (H-bonding) and aromatic-C=C group. Analysis of the IR spectrum of both a physical mixture and inclusion complexes are observed in a changing frequency or hidden or lower the intensity of the spectrum band.

The spectrum of 2a showed a separate peak in the ~1651 cm^{-1}, indicating the presence of carbonyl group which ranges at 1700-1650 cm^{-1}. The band in ~1604 cm^{-1}regions was assigned to imine (-C=N), the band in ~1280 $cm^{-1}$was represented to amine vibration band (-C-N), aromatic-C=C skeleton vibrations band was observed in ~1530 cm^{-1},

the bands at ~758 and ~702 cm^{-1} were corresponded to the out of plane and bending vibration of aromatic-C-H. Moreover, the aromatic-CH stretching band region which appear at 3064 cm^{-1} are shifted towards shorter wave number. The band was also observed in ~3216 cm^{-1} to the represent-OH group which showed some disappearance (due to H-bonding, the normally-OH band appears at 3400-3600 cm^{-1} regions). In the case of β-CD, a broadband was appeared at ~3300 cm^{-1} could be alloted to the numerous hydrogen bonds (fig. 7).

The spectrum of PM was the simple mixture of 2a and β-CD, several characteristic bands of 2a and the typical broadband of β-CD at ~3300 cm^{-1} were straightforwardly found, indicating that 2a and β-CD were independently belonged to each other without any interaction. But for the inclusion complex, the characteristic bands of 2a were completely disappeared. The shape, intensity, shift or disappearance of these bands varied dramatically for the complex as compared to those for pure drug and physical mixture. These pointed out that the bending and vibrating of the guest molecule, [3-{[(2-hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one], 2a, was restricted owing to the formation of a complex, suggesting a new structure was fig. out and the guest molecule was entirely inserted into the internal hole of β-CD [36, 37].

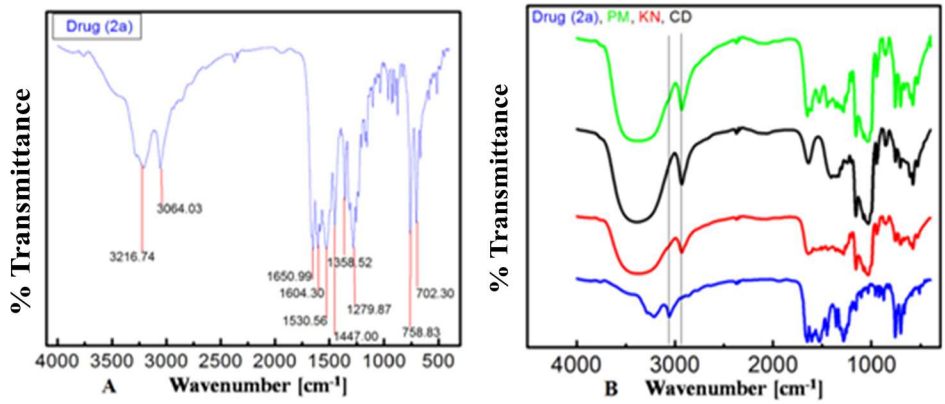


Fig. 7: IR spectrum of A) drug (2a) and B) drug (2a), cyclodextrin (CD), physical mixtiure (PM) and complex (KN), [blue line= drug; red line= complex; black line= CD; green line= PM]

Differential scanning calorimetry studies

DSC is a very helpful technique to find inclusion complexes. When guest molecules were entirely or partly inserted into the cavity portion of CD, their sublimation, boiling and melting points would all shift to a lower temperature or intencity towards lower or even vanished [38, 39]. The DSC thermograms of drug (2a), CD, physical mixtures (1:1) and complex (1:1) are shown in fig 8. Drug was characterized by a single, sharp melting endotherm at 234.6 °C (ΔH= 88.71 J/g) in the time of DSC analysis and a broad endothermic thermogram of CD are observed at a maximum around 97 °C respectively, mainly due to release of a molecule of water, encapsulated into β-CD cavity during heating. In the case of complex, the drug endotherm almost disappeared along with a shift to 231.6 °C and the peak which arises from CD are shifted to 104 °C approximately, which was indicated to be caused by inclusion complex of the drug molecules in the cavity inside of CD to substitute a fraction of molecules of water [40]. Peak intencity was reduced but not as that of complex and temperature shifted to lower in case of a physical mixture. On the basis of above outcomes, it was indicated that 2a-β-CD was successfully made with the hydrophobic parts of the drug molecule being incorporated inside the cavity of β-CD to form the inclusion complex, commonly called 'host-guest' complex [41].

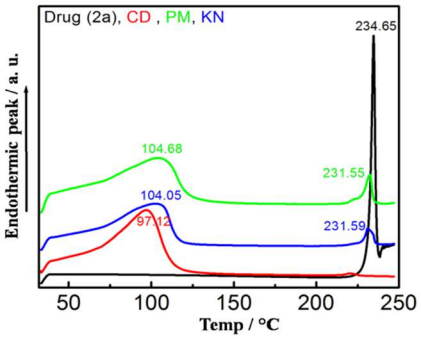


Fig. 8: DSC thermograms of drug (2a), cyclodextrin (CD), physical mixture (PM) and complex (KN). [mentioned with respective colour]

Solubility studies

Inclusion complexes made by different protocols were primarily illustrated by the degree of transparency of the drug of the solution prepared in water. In fig. 9. it may be seen that solubility of the complex was increased as compared to the physical mixture [42]. This transparency indicated that there exists interaction between host and guest molecule. A comparative study was done on silica-gel plates (TLC) using the eluent [ethyl acetate: butanol (5:4 v/v)]. Spots of β-CD and the compound were observable with slight trailing off spot of the compound for the physical mixture (PM) while in the complex a concentrated bulk trailing was examined with faint spot compared of the free compound. The appearance of the faint trailing spot indicated that of the slow diffusion of the compound in the TLC study in the used eluent. This further corroborates the reported study that the molecule, 2a, must be encapsulated inside the cavity of β-CD through 'host-guest' complexation.

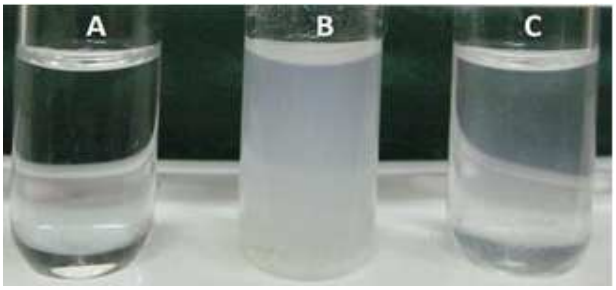


Fig. 9: Water solution of A) β-CD. B) physical mixture. C) complex

CONCLUSION

In summary, we have developed a new synthetic route for the synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using a greener reagent in a very short span under solvent-free condition with excellent yield. In the reported back all these compounds are biologically active but low solubility in the

water medium. Herein we have tried to develop the solubility in an aqueous medium of this synthesized molecule. Finally, we have unfolded the solubility problem through inclusion with β-cyclodextrin. For preparing a complex with β-cyclodextrin to increase solubility, the kneaded method is the best method among the all other mentioned method. The bioavailability of the drug molecule has been found to be high which promises potential pharmaceutical application.

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AUTHORS CONTRIBUTIONS

MH, AKN: Conceived the idea and designed the experiments. MH: Performed the synthetic methodology, inclusion technique and wrote the article. MH, AKN: Analysed the UV, IR, DSC data. Final manuscript is prepared with approval of both authors. MH: Revised the Manuscript.

CONFLICT OF INTERESTS

The authors declare no competing interests

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