Caffeinium Hydrogen Sulphate Catalysed Green Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones and Their Drug-likeness Studies as Antibacterial Agents

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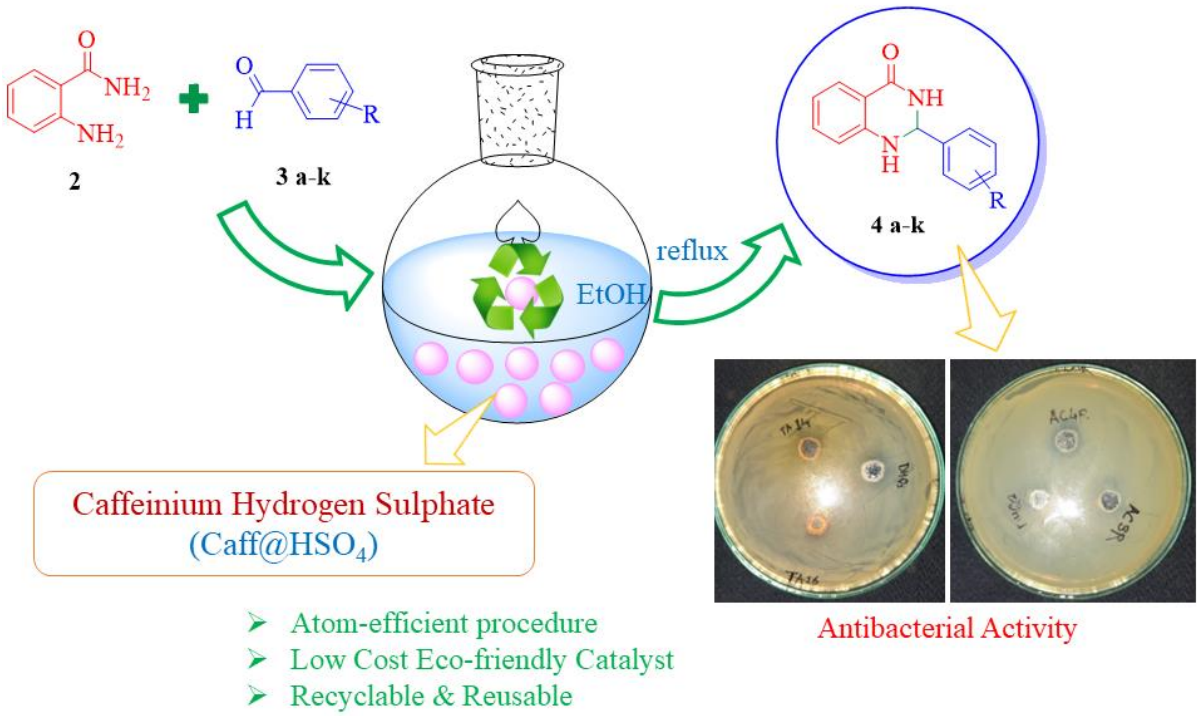
Graphical Abstract:



Caffeinium Hydrogen Sulphate Catalysed Green Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones and Their Drug-likeness Studies as Antibacterial Agents

Jayashree Kshirsagar[1,2], Wilson Chandane[3], Dipak Hiwarale[4], Mahesh Kukade[5,6], Bhaskar Tamhankar[6], Rajashri Salunkhe[3], Sunita Shirke[1]*

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***Abstract*:**

A novel environmentally benign synthetic protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones by using caffeinium hydrogen sulphate (Caff@HSO_4) as a solid acid catalyst has been developed. Caff@HSO_4 displayed excellent catalytic activity in the cylcocondensation of anthranilamide with aryl aldehydes affording good to high yields of products in ethanol as solvent. The synthesized 2,3-dihydroquinazolin-4(1H)-ones 4i and 4j displayed potential anti-bacterial activity against Staphylococcus aureus and Escherichia coli bacteria. Further, in agreement with the Lipinski rule of five, the synthesized 2,3-dihydroquinazolin-4(1H)-ones revealed drug-like properties.

***Keywords*:** *Green synthesis, 2,3-dihydroquinazolin-4(1H)-ones, caffeinium hydrogen sulphate, anti-bacterial agents*

INTRODUCTION

The current environmental issues have led to the increased demand for the development of eco-friendly green organic synthesis [1]. The green chemistry principles advocate the use of solid acid catalysts as a substitute for hazardous and polluting liquid mineral acids like nitric acid, hydrochloric acid and sulfuric acid [2]. Solid acids possess exceptional physicochemical properties such as low toxicity, high thermal and chemical stability, excellent selectivity and catalytic activity. Moreover, they are easy to prepare and can be effortlessly separated from the reaction mixture by simple filtration [3]. Owing to these distinguishing features solid acids have been applied in various organic transformations [4-6].

For decades, heterocyclic compounds have captivated attention in the field of medicinal chemistry for the development of numerous drugs and drug-like candidates [7-9]. Various nitrogen, oxygen and sulphur-containing heterocyclic compounds exhibit potential biological and pharmacological activities due to their unique physicochemical characteristics, such as lipophilicity, polarity and hydrogen bonding. [10, 11]. 2,3-Dihydroquinazolin-4(1*H*)-ones are privileged nitrogen heterocycles displaying wide-ranging biological and pharmacological activities such as anti-cancer, diuretic, anti-hypertensive, anti-bacterial, anti-microbial, anti-HIV, anti-tubercular, anti-fungal, ChE inhibitors and anti-convulsant. Several of these analogues are marketed as medicines, including Quinethazone, Afloqualone, Nolatrexed, Evodiamine, Albaconazole and Proquazone (Fig. 1) [12].

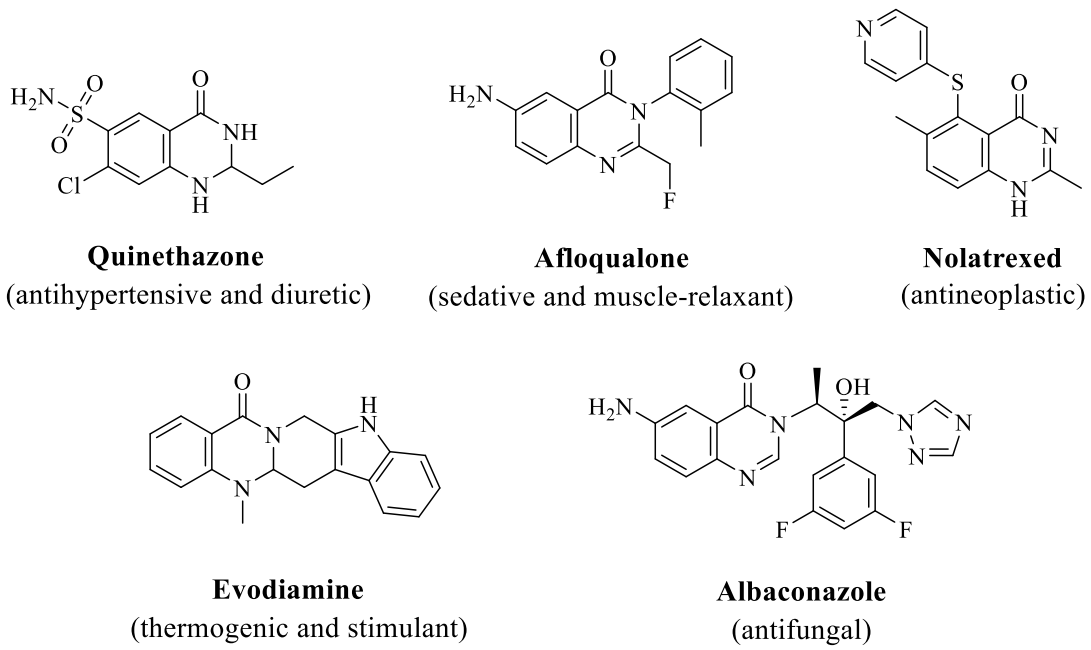
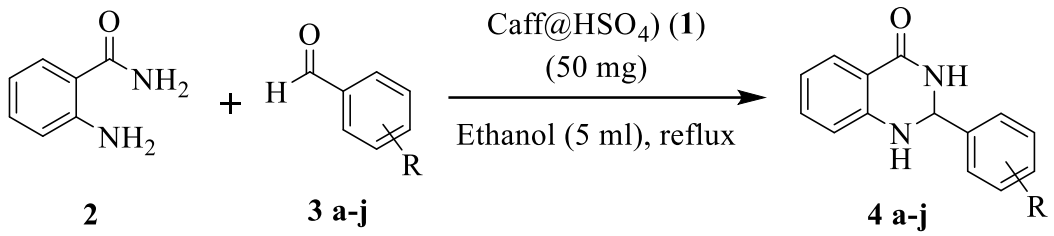


Fig. 1: Some important marketed medicines based on 2,3-dihydroquinazolin-4(1*H*)-one

Widespread biological applications of the substituted 2,3-dihydroquinazolin-4(1*H*)-ones have sparked intense interest in the development of numerous methods for their synthesis. Among these, the cyclocondensation of anthranilamide with aryl aldehydes is the most effective and popular method for producing 2,3-dihydroquinazolin-4(1*H*)-ones. For this purpose various catalysts such as strong Bronsted acids, Lewis acids, metal triflates,

ammonium salts [12], IL@MNP [13], tribromide ion supported on boehmite nanoparticles [14], $B(C_6F_5)_3$ [15], nano-ZrO_2-Al_2O_3 [16], urea/zinc chloride [17], Gr@SO_3H [18], Fe_3O_4@PEG-diaza crown ether@Ni [19], Fe_3O_4@PEG–Ni [20], ZnO nanomicelle [21], SBA-15@n-Pr-THAM-ZrO [22] and MCM-41-SPM-DMG-Cu(II) [23] have been utilized. Many of these systems have several drawbacks, including poor product yields, long reaction times, difficult reaction conditions, expensive catalysts and hazardous solvents. Given these restrictions, a novel heterogeneous catalyst that is effective, inexpensive and reusable must be employed to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones.

In this regard, we report herein, the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones *via* cyclocondensation of anthranilamide with aryl aldehydes using caffeinium hydrogen sulphate (Caff@HSO_4) as a solid acid catalyst (**Scheme 1**) and investigation of antibacterial activities of 2,3-dihydroquinazolin-4(1*H*)-ones along with their drug-likeness studies.



Scheme 1: Caffeinium hydrogen sulphate catalysed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

Experimental section

General remarks

All reactions were performed at atmospheric pressure in dried glassware. FT-IR spectra of samples were scanned as KBr discs (≈ 5% w/w) using Perkin-Elmer One FT-IR spectrophotometer. The thermal gravimetric analysis (TGA) was carried out with TA SDT Q600 V20.9 Build 20 in the presence of static air at a linear heating rate of 10 ºC/minute from 25 ºC to 1000 ºC. Elemental analyses were carried out in a Perkin-Elmer 2400. Using *d*-DMSO as a solvent and TMS as an internal standard, ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker AC (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR) spectrometer. A Shimadzu QP2010 GC-MS was used to record mass spectra. The MEL-TEMP capillary melting point equipment was used to determine the melting points, which are uncorrected. All chemicals were used as received without any further purification and were obtained from local suppliers.

Preparation of caffeinium hydrogen sulphate (Caff@HSO_4)

Caffeinium hydrogen sulphate (Caff@HSO_4) was prepared according to the procedure described in the literature [24]. Initially, 10 mmol of caffeine was mixed with 50 mL of chloroform with a constant stirring. To the resulting solution 10 mmol of 96 % H_2SO_4 was added dropwise over 30 minutes. Further, the reaction mixture was stirred for 2 hours and the

precipitate thus obtained was filtered, washed with acetone (3 x 10 mL) and dried in oven at 70 ºC for 2 hours to afford caffeinium hydrogen sulphate (Caff@HSO_4) (**1**). FT-IR (KBr, thin film): υ = 3385, 3046, 2999, 1704, 1658, 1227, 1139, 1014, 864 cm^{-1}; Elemental analysis observed: % C 33.04, % H 4.05, % N 19.23, % O 32.80, % S 10.88. Loading of sulfur = 4.08 mmol per gram of **1**.

General method for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones

To a solution anthranilamide (1 mmol) in ethanol (5 mL) was added aryl aldehyde (1 mmol) and caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) (50 mg) and the resulting mixture was refluxed. The completion of the reaction was monitored by thin layer chromatography (TLC). The hot reaction mixture was filtered to recover the insoluble Caff@HSO_4 (**1**). The compounds thus prepared were dried in vacuum and further purified by column chromatography using pet ether-EtOAc (8:2, v/v) solvent system over silica gel.

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one *(Table 3, product entry **4a**): White solid, M.P-215 °C (lit. 215-216°C); IR (KBr): υ = 3307, 3160, 3051, 2928, 1653, 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H, N**H**), 7.69-7.64 (m, 2H, Ar-**H**), 7.53-7.48 (m, 2H, Ar-**H**), 7.43-7.39 (m, 2H, Ar-**H**), 7.30-7.22 (m, 1H, Ar-**H**), 7.03 (s, 1H, N**H**), 6.78-6.71 (m, 2H, Ar-**H**), 6.14 (s, 1H, C-**H**); ^{13}C NMR (400 MHz, $CDCl_3$): 63.32 (Ar-**C**H), 114.44 (Ar-**C**), 115.21 (Ar-**C**), 117.55 (Ar-**C**), 127.38 (Ar-**C**), 128.57 (Ar-**C**), 129.51 (Ar-**C**), 131.15 (Ar-**C**), 132.24 (Ar-**C**), 147.13 (Ar-**C**), 163.88 (Ar-**C**=O); MS (EI): m/z 224 (M^+).*

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one *(Table 3, product entry **4b**): White solid, M.P-202 °C (lit. 202-203 °C), IR (KBr): υ = 3322, 3179, 3062, 2938, 1647, 16362 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 (s, 1H, N**H**), 7.67-7.63 (m, 2H, Ar-**H**), 7.51-7.47 (m, 1H, Ar-**H**), 7.41-6.37 (m, 2H, Ar-**H**), 7.27-7.23 (m, 1H, Ar-**H**), 6.99 (s, 1H, N**H**), 6.76-6.69 (m, 2H, Ar-**H**), 6.13 (s, 1H, C-**H**); ^{13}C NMR (100 MHz, DMSO-d_6): 63.65 (Ar-**C**H), 114.51 (Ar-**C**), 114.63 (Ar-**C**), 117.39 (Ar-**C**), 127.31 (Ar-**C**), 127.39 (Ar-**C**), 128.67 (Ar-**C**), 129.53 (Ar-**C**), 130.22 (Ar-**C**), 131.79 (Ar-**C**), 133.37 (Ar-**C**), 137.85 (Ar-**C**), 147.58 (Ar-**C**), 163.56 (Ar-**C**=O) ; MS (EI): m/z 260 $(M+2)^+$.*

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one *(Table 3, product entry **4c**): Yellow solid, M.P-192 °C (lit. 192-194 °C), IR (KBr): υ = 3297, 3170, 3038, 2940, 2859, 1649, 1613, 1522, 1468, 1352 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.35 (s, 1H, N**H**), 8.09 (t, J = 8.0 & 1.2 Hz, 2H, Ar-**H**), 7.84 (d, J = 7.6 Hz, 1H, Ar-**H**), 7.66 (t, 2H, J = 4.4 & 2.0 Hz, Ar-**H**), 7.50 (dd, 1H, J = 8.0 & 4.4 Hz, Ar-**H**), 7.17 (t, 1H, J = 7.2 & 8.0 Hz, Ar-**H**), 6.71-6.63 (m, 2H, Ar-**H**), 6.79 (s, 1H. N**H**), 5.85 (s, 1H, C-**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 66.05 (Ar-**C**H), 114.90 (Ar-**C**), 115.13 (Ar-**C**), 118.10 (Ar-**C**), 122.05 (Ar-**C**), 123.40 (Ar-**C**), 127.83 (Ar-**C**), 129.75 (Ar-**C**), 133.36 (Ar-**C**), 133.83 (Ar-**C**), 144.03 (Ar-**C**), 147.34 (Ar-**C**), 148.13 (Ar-**C**),164.39 (Ar-**C**=O); MS(ESI): m/z = 269(M^+).*

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one *(Table 3, product entry **4d**): Yellow solid, M.P-202°C (lit. 200-202°C); IR (KBr): υ = 3305, 3158, 3044, 2926, 2864, 1642, 1611, 1529, 1427, 1340 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H, N**H**), 8.01 (t, 3H, J =*

*8.1 & 8.4 Hz, Ar-**H**), 7.62-7.59 (m, 2H, Ar-**H**), 7.39-7.36 (m, 1H, N-**H**), 6.99 (s, 1H, N**H**), 6.70-6.60 (m, 2H, Ar-**H**), 5.72 (s, 1H, C**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 63.74 (Ar-**C**H), 114.25 (Ar-**C**), 115.11 (Ar-**C**), 117.35 (Ar-**C**), 126.34 (Ar-**C**), 127.50 (Ar-**C**), 128.04 (Ar-**C**), 131.89 (Ar-**C**), 147.38 (Ar-**C**), 147.72 (Ar-**C**), 163.02 (Ar-**C**=O); MS(ESI): m/z = 271(M^+).*

***2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4e**): White solid, M.P-216 °C (lit. 215-217 °C); IR (KBr): υ = 3309, 3178, 3064, 2918, 1652, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1H, N**H**), 7.64-7.60 (m, 2H, Ar-**H**), 7.48 (d, 2H, J = 8.4, Ar-**H**), 7.39 (d, 2H, J = 8.4, Ar-**H**), 7.35-7.31 (m, 1H, Ar-**H**), 7.02 (s, 1H, N**H**), 6.80-6.75 (m, 1H, Ar-**H**), 6.14 (s, 1H, C-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): 64.11 (Ar-**C**H), 114.48 (Ar-**C**), 115.29 (Ar-**C**), 117.78 (Ar-**C**), 127.44 (Ar-**C**), 128.05 (Ar-**C**), 129.44 (Ar-**C**), 131.52 (Ar-**C**), 133.14 (Ar-**C**),143.15 (Ar-**C**), 147.26 (Ar-**C**),163.60 (Ar-**C**=O); MS (EI): m/z 260 $(M+2)^+$.*

***2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4f**): White solid, M.P-176 °C (lit. 177-178 °C); IR (KBr): υ = 3430, 3320, 3188, 2940, 1682, 1604, 1478 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.15 (s, 1H, N-**H**), 7.61-7.59 (m, 1H, Ar-**H**), 7.42-7.39 (m, 2H, Ar-**H**), 7.25-7.21 (m, 1H, Ar-**H**), 6.98 (s, 1H, N-**H**), 6.95-6.92 (m, 2H, Ar-**H**), 6.73 (d, J = 8.0 Hz, 1H, Ar-**H**), 6.68-6.64 (m, 1H, Ar-**H**), 5.69 (s, 1H, C-**H**), 3.74 (s, 3H, -OC**H**$_3$); ^{13}C NMR (400 MHz, DMSO-d_6) δ = 55.13 (O-C**H**$_3$), 66.23 (Ar-**C**H), 113.59 (Ar-**C**), 113.96 (Ar-**C**), 114.35 (Ar-**C**), 114.95 (Ar-**C**), 117.02 (Ar-**C**), 127.28 (Ar-**C**), 128.12 (Ar-**C**), 133.17 (Ar-**C**), 133.45 (Ar-**C**), 147.93 (Ar-**C**), 159.38 (Ar-**C**), 163.62 (Ar-**C**=O); MS (ESI): m/z = 254 (M^+).*

***2-(4-Hydoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4g**): White solid, M.P-210 °C (lit. 210-212 °C), IR (KBr): υ = 3389, 3317, 3170, 3065, 2943, 1679, 1632 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.38 (s, 1H, Ar-O**H**), 8.10 (s, 1H, N**H**), 7.58 (d, J = 7.2 Hz, 1H, Ar-**H**), 7.27 (d, J = 8.0 Hz, 2H, Ar-**H**), 7.13 (t, J = 7.5 & 7.2 Hz, 1H, Ar-**H**), 7.01 (s, 1H, N**H**), 6.74-6.60 (m, 4H, Ar-**H**), 6.04 (s, 1H, C-**H**); ^{13}C NMR (100 MHz, DMSO-d_6)δ = 66.42 (Ar-**C**H), 114.37 (Ar-**C**), 115.06 (Ar-**C**), 115.59 (Ar-**C**), 118.28 (Ar-**C**), 127.32 (Ar-**C**), 128.45 (Ar-**C**), 133.60 (Ar-**C**), 134.47 (Ar-**C**), 147.22 (Ar-**C**) 159.20 (Ar-**C**), 163.23 (Ar-**C**=O); MS (ESI): m/z = 240 (M^+).*

***2-(p-Tolyl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4h**): White solid, M.P-233 °C (lit. 232-233 °C), IR (KBr): υ = 3304, 3183, 3052, 2934, 2853, 1921, 1653, 1600, 1500 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (s, 1H, N-**H**), 7.61-7.69 (m, 1H, Ar-**H**), 7.36 (d, 2H, J = 8.0 Hz, Ar-**H**), 7.25-7.17 (m, 3H, Ar-**H**), 7.02 (s, 1H, N-**H**), 6.73 (d, 1H, J = 8.0 Hz, Ar-**H**), 6.68-6.64 (m, 1H, Ar-**H**), 5.70 (s, 1H, C-**H**), 2.29 (s, 3H, C**H**$_3$); ^{13}C NMR (400 MHz, DMSO-d_6) δ = 20.66 (-C**H**$_3$), 66.31 (Ar-**C**H), 114.35 (Ar-**C**), 114.95 (Ar-**C**), 117.00 (Ar-**C**), 126.71 (Ar-**C**), 127.27 (Ar-**C**), 128.75(Ar-**C**), 133.19 (Ar-**C**), 137.65 (Ar-**C**), 138.64 (Ar-**C**), 147.84 (Ar-**C**), 163.57 (Ar-**C**=O); MS(ESI): m/z = 238(M^+).*

***2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4i**): White solid, M.P-192 °C (lit. 191-193 °C), IR (KBr): υ = 3448, 2930, 2857, 1647, 1432, 1365 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.41 (s, 1H, N-**H**), 7.62-7.60 (m, 1H, Ar-**H**), 7.45-7.43 (m, 1H,*

*Ar-**H**), 7.27-7.23 (m, 2H, Ar-**H**), 7.10 (d, 1H, J = 3.2 Hz, Ar-**H**), 6.98-6.96 (m, 1H, Ar-**H**), 6.76 (s, 1H, N**H**), 6.74-6.68 (m, 1H, Ar-**H**), 6.01 (s, 1H, C-**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 62.50 (Ar-**C**H), 114.64 (Ar-**C**), 115.07 (Ar-**C**), 117.45 (Ar-**C**), 125.60 (Ar-**C**), 125.79 (Ar-**C**), 126.39 (Ar-**C**), 127.25 (Ar-**C**), 133.30 (Ar-**C**), 146.41 (Ar-**C**), 147.16 (Ar-**C**), 163.04 (Ar-**C**=O); MS(ESI): m/z = 230(M^+).*

***2-(Pyridin-4-yl)-2,3-dihydroquinazolin-4(1H)-one** (Table 3, product entry **4j**): White solid, M.P-168 °C (lit. 166-167 °C), IR (KBr): υ = 2930, 2854, 1687, 1452 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.69 (s, 1H, N-**H**), 8.22-8.19 (m, 1H, Ar-**H**), 7.26-7.23 (m, 1H, Ar-**H**), 7.19-7.17 (m, 2H, Ar-**H**), 7.10-7.08 (m, 2H, Ar-**H**), 6.92-6.90 (m, 1H, Ar-**H**), 6.80 (s, 1H, N-**H**), 6.68-6.64 (m, 1H, Ar-H), 6.02 (s, 1H, C**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 63.15 (Ar-**C**H), 114.92 (Ar-**C**), 115.24 (Ar-**C**), 118.46 (Ar-**C**), 125.17 (Ar-**C**), 131.69 (Ar-**C**), 138.28 (Ar-**C**), 146.12 (Ar-**C**), 148.44 (Ar-**C**), 149.58 (Ar-**C**), 163.07 (Ar-**C**=O); MS(ESI): m/z = 255 (M^+).*

Anti-microbial activity

Agar well diffusion technique is the most common technique employed for the evaluation of anti-microbial activity [25, 26]. In this technique a volume of the microbial inoculum is dispersed throughout the entire agar surface to inoculate the agar plate surface. Next, a volume (20-100 µL) of the antimicrobial agent or extract solution is put into the well by aseptically drilling a hole with a diameter of 6 to 8 mm using a sterile cork borer or tip. The test microorganism is then placed on an appropriate agar plate, and the incubation process is continued. The anti-microbial agent spreads across the agar media and stops the tested microbial strain from growing.

Drug-likeness prediction

Lipinski's Rule of Five was used to predict the drug-likeness properties of the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones. The rule was developed to establish ground criteria for drug-likeness of new molecular entities. The drug-likeness of the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones was estimated by employing a free web server http://www.swissadme.ch.

Results and Discussion

Caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) was prepared by adding conc. H_2SO_4 to a solution of caffeine in chloroform. A white solid thus obtained on drying in oven at 70 ºC afforded the desired caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) which was characterized by FT-IR, ^{1}H and ^{13}C-NMR spectroscopy, elemental and thermogravimetric analysis. The prepared Caff@HSO_4 displayed high solubility in water due to its ionic nature but was immiscible with organic solvents.

FTIR spectrum of caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) (Fig. 2) displayed a broad band at 3385 cm^{-1} which was ascribed to the stretching vibration of N-H group. The characteristic bands observed at 1227 and 1139 cm^{-1} were assigned to the asymmetric and

symmetric stretching frequencies of O=S=O and O-S-O bonds while the bending vibrations were observed at 1014 and 864 cm^{-1} indicating the presence of HSO_4^- species.

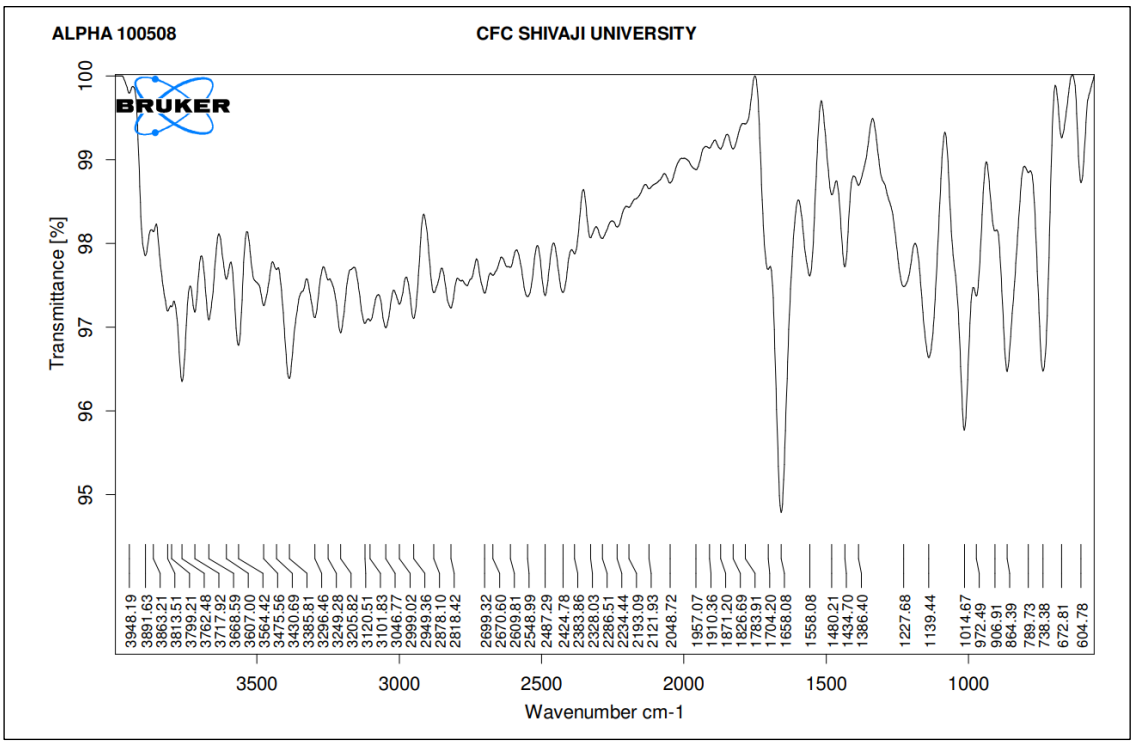


Fig. 2: FT-IR spectra of Caff@HSO_4 (**1**)

^1H and ^{13}C-NMR spectra of the caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) was recorded to confirm the structural integrity of caffeine scaffold. The ^1H-NMR spectrum of Caff@HSO_4 (**1**) (Fig. 3) revealed a singlet at 7.799 ppm ascribed to nitrogen atom present at position 9. Moreover, ^1H-NMR spectrum displayed peaks similar to caffeine. The ^{13}C-NMR spectrum of Caff@HSO_4 (**1**) (Fig. 4) also revealed the same peak pattern as that of caffeine.

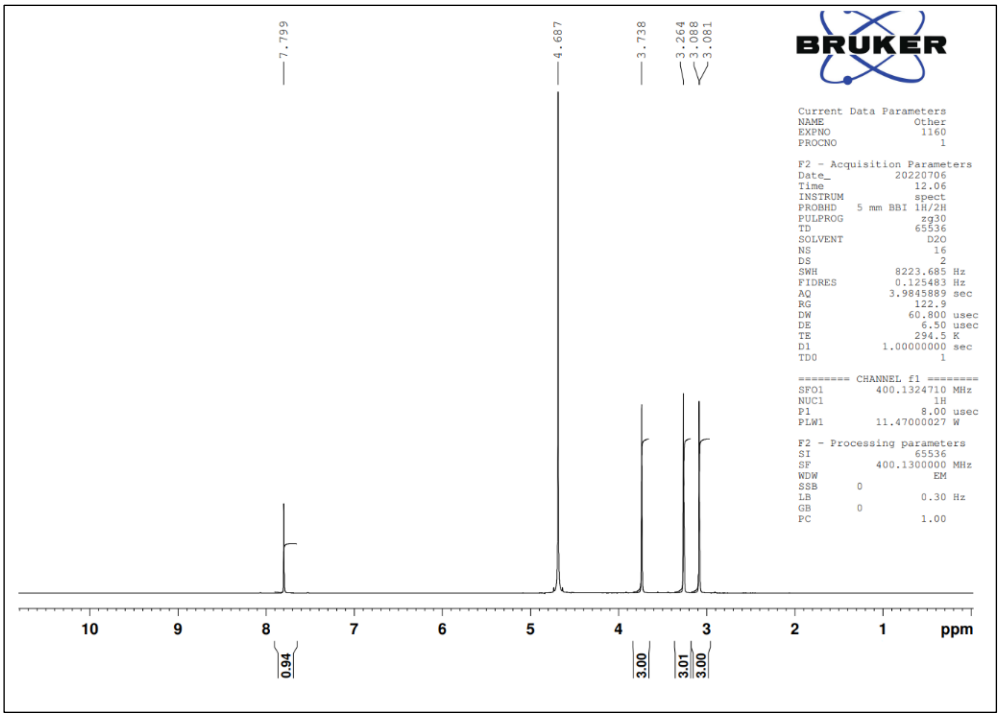


Fig. 3: ^{1}H-NMR spectrum of Caff@HSO_4 (**1**)

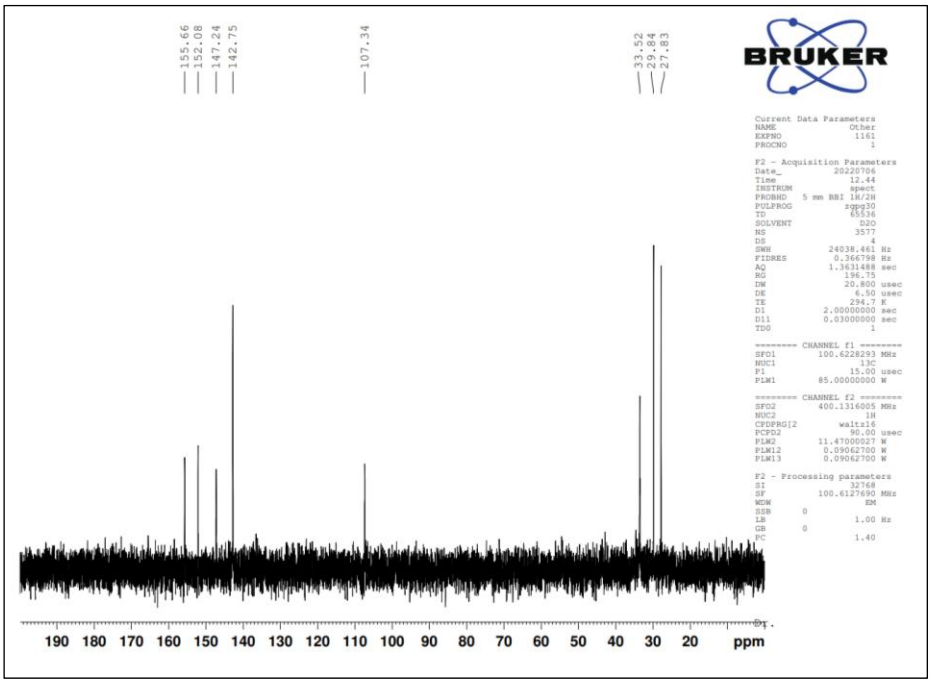


Fig. 4: ^{13}C-NMR spectrum of Caff@HSO_4 (**1**)

Thermogravimetric analysis (TGA) of caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) was carried out at 25-1000 ºC with a heating rate of 10 ºC/minute. Thermal degradation graph of **1** (Fig. 5) displayed a two-step weight loss. The first weight loss of 75% up to 105 ºC is due to the loss of surface adsorbed water. A major weight loss of 94.25% up to 400 ºC is attributed to the decomposition of the catalyst.

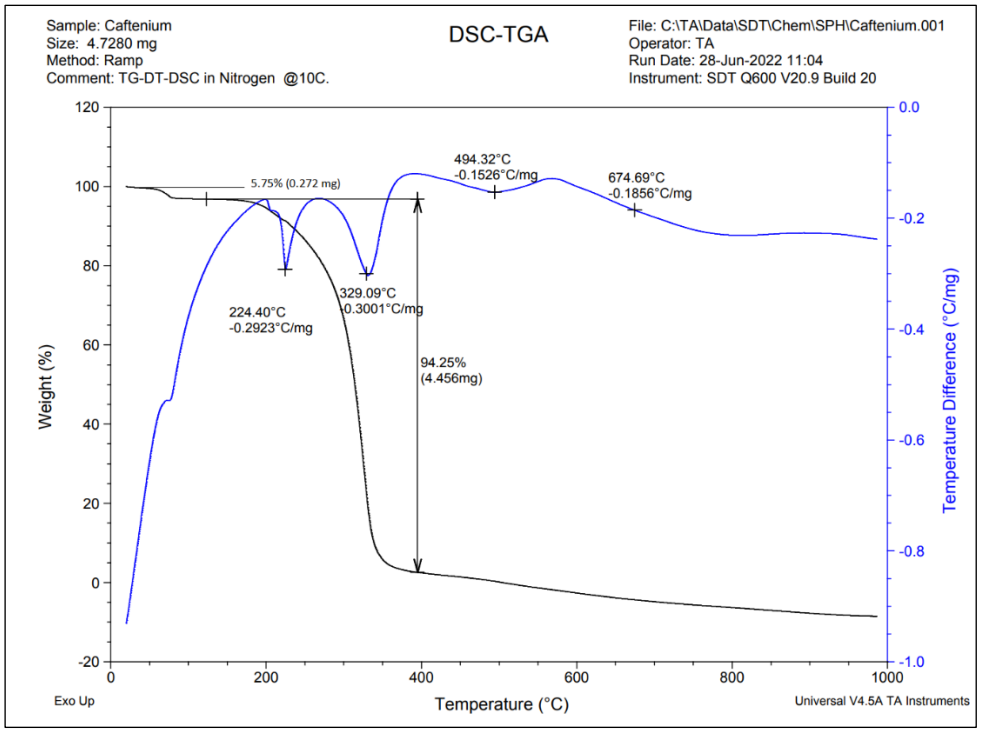
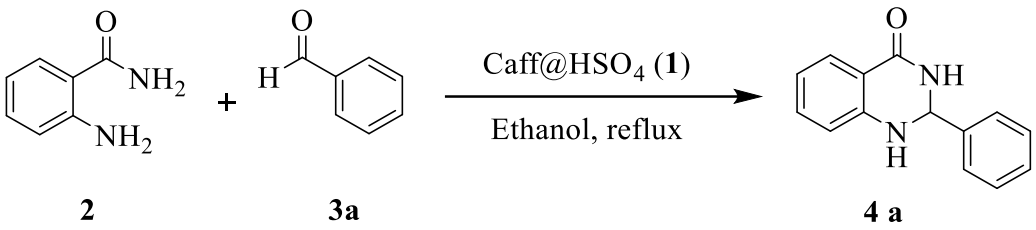


Fig. 5: TGA of Caff@HSO_4 (**1**)

Next, we investigated the catalytic efficiency of caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) as a solid acid catalyst in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by a cyclocondensation of anthranilamide with various aryl aldehydes. A reaction between anthranilamide (**2**) and benzaldehyde (**3a**) was selected as a model reaction to optimize the reaction conditions (**Scheme 2**).

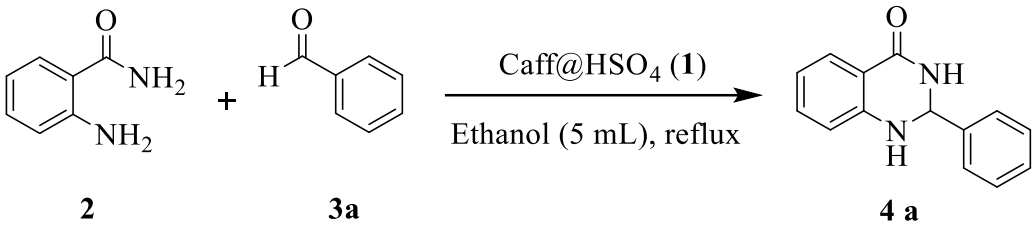


2 **3a** **4 a**

Scheme 2: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using caffeinium hydrogen sulphate (Caff@HSO_4) (**1**)

In the beginning, different amounts of **1** were used to study the effect of catalyst quantity on the model reaction (Table 1). It was observed that 50 mg catalyst quantity gave the maximum yield (93%) of the corresponding product **4a** in minimum time (Table 1, entry 5). A further increase the amount of catalyst showed no substantial increase in the yield of product. Therefore, for further optimization experiments, 50 mg of the catalyst quantity was used.

Table 1 Optimization of catalyst quantity in synthesis of 2,3-dihydroquinazolin-4-(1*H*)-ones[a]



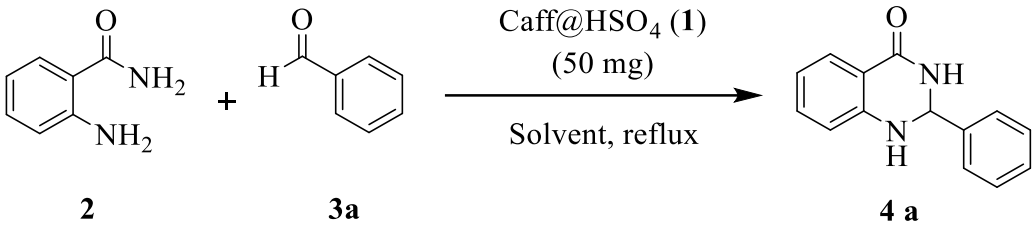
2 **3a** **4 a**

Entry	Catalyst (mg)	Time (min)	Yield[b] (%)
1.	10	75	45
2.	20	60	53
3.	30	40	69
4.	40	25	82
5.	**50**	**15**	**93**
6.	100	11	94
7.	150	9	95
8.	200	9	95

[a]Reaction condition: anthranilamide (1 mmol), benzaldehyde (1 mmol), ethanol (5 mL)
[b]Isolated yields after chromatography

For the optimization of solvent various solvents such as acetonitrile, THF, DMF, DCM, toluene, water and ethanol were tested (Table 2). Among all solvents tested, ethanol gave excellent yield (93%) of the corresponding product **4a** in short reaction time (Table 2, entry 7). As compared to ethanol other solvents gave poor yields.

Table 2 Optimization of solvent in synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[a]



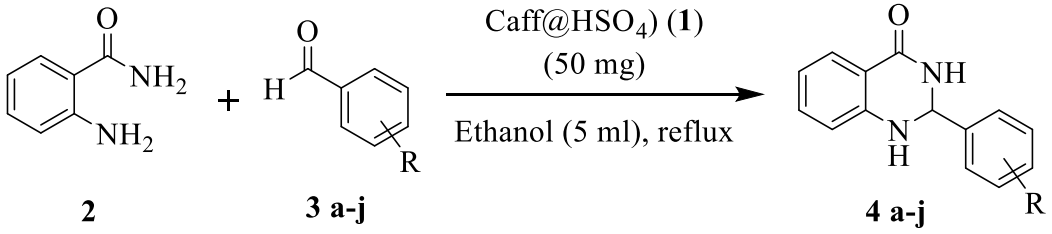
2 **3a** **4 a**

Entry	Solvent	Time (min)	Yield[b] (%)
1.	Water	240	49
2.	DMF	180	87
3.	Acetonitrile	120	68
4.	THF	50	85
5.	DCM	40	74
6.	Toluene	35	81
7.	**Ethanol**	**15**	**93**

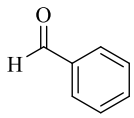
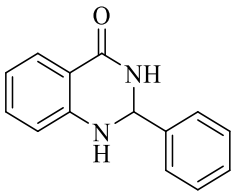
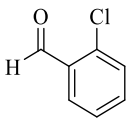
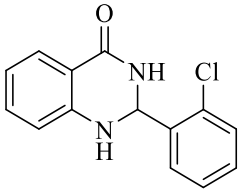
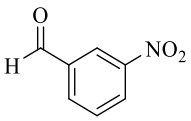
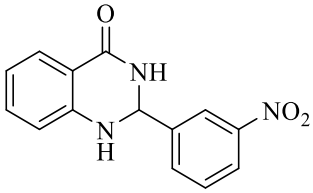
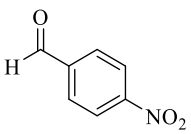
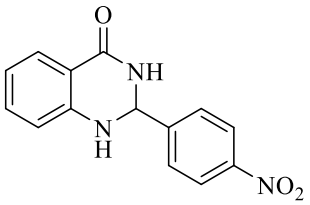
[a]Reaction condition: anthranilamide (1 mmol), benzaldehyde (1 mmol), solvent (5 mL)
[b]Isolated yields after chromatography

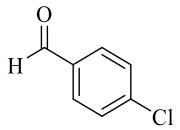
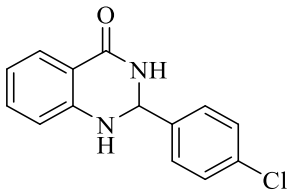
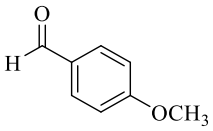
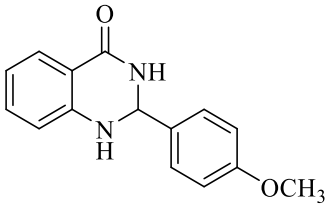
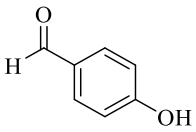
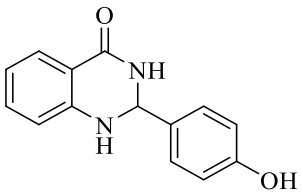
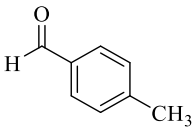
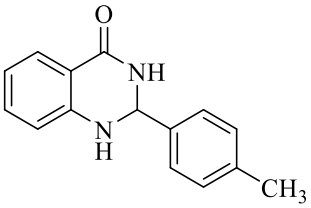
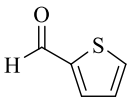
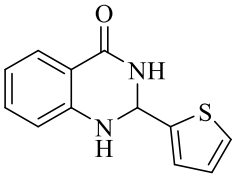
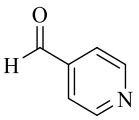
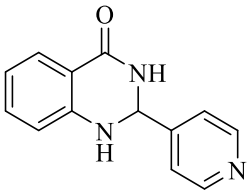
After optimization of the reaction conditions, the general applicability of protocol was explored by reacting anthranilamide (**2**) with various of *o*-, *m*- and *p*-substituted aromatic aldehydes (**3a-j**) (Table 3). Notably, anthranilamide reacted efficiently with both electron-rich and electron-deficient aromatic aldehydes to afford the desired compounds in good to high yields. (Table 3, entry **4a-j**). Furthermore, heterocyclic aromatic aldehydes like thiophene-2-carbaldehyde (Table 3, entry **3i**) and pyridine-4-aldehyde (Table 3, entry **3j**) gave the corresponding products in good yields (Table 3, entries **4i** and **4j**, 76-79%).

Table 3 Caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones[a]



2 **3 a-j** **4 a-j**

Entry	Aldehyde (3)	Product (4)	Time (Min)	Yield[b] (%)
a.			15	93
b.			20	89
c.			15	92
d.			15	94

e.			15	88
f.			20	87
g.			25	85
h.			20	91
i.			25	76
j.			25	79

[a]Reaction conditions: anthranilamide (1 mmol), aldehydes (1 mmol), ethanol (5 mL), caffeinium hydrogen sulphate (Caff@HSO_4) (**1**) (50 mg)
[b]Isolated yields after chromatography

Anti-microbial activity

Among the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones compounds **4i** and **4j** were tested for their *in vitro* anti-microbial activity against standard strains of the Gram-positive bacteria (*Staphylococcus aureus* ATCC 19433) and the Gram-negative bacteria (*Escherichia coli* ATCC 25922). The primary screening was carried out using the agar well diffusion technique. With the use of a sterile cork borer or tip, a hole measuring 6 to 8 mm in diameter is made aseptically and a volume (20 to 100 µL) of the ant-imicrobial agent or extract solution is then injected into the well at the necessary concentration. The test microorganism is then placed on an appropriate agar plate and the incubation process is continued. The anti-microbial compound

penetrates the agar gel and prevents the growth of the tested microbiological strain (Fig. 6). The results of anti-microbial activity have been summarized in the table 4. The results indicated that compound **4i** displayed medium antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, while compound **4j** exhibited strong antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*.

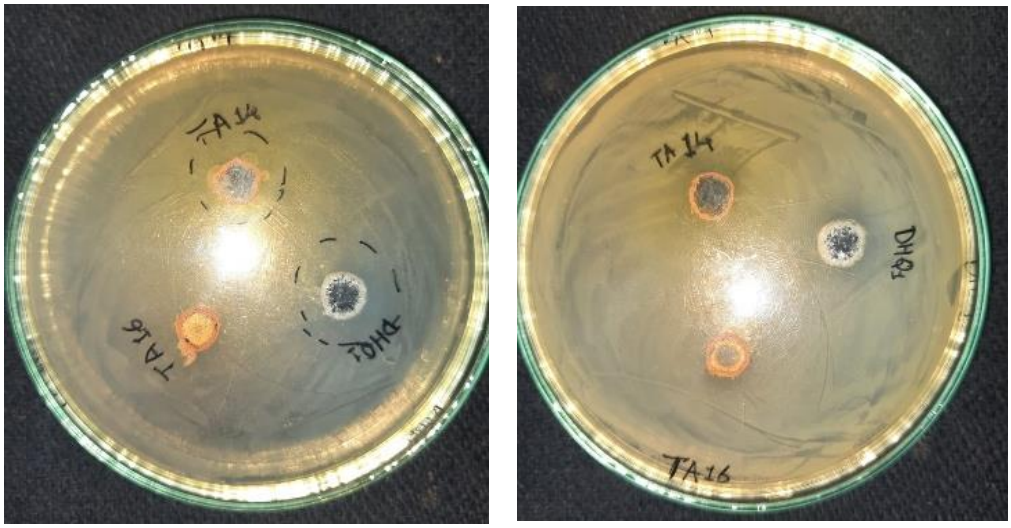


Fig. 6: Zone of inhibition

Table 4: Antimicrobial activity of compounds **4i** and **4j**

Compound	Microorganism	Zone of inhibition (mm)	Activity
4i	*Staphylococcus aureus*	0.4	Medium
	Escherichia coli	0.4	Medium
4j	*Staphylococcus aureus*	0.5	Strong
	Escherichia coli	0.5	Strong

Drug-likeness prediction

Molecular descriptors and drug-likeliness characteristics of synthesized 2,3-dihydroquinazolin-4(1*H*)-ones based on the Lipinski Rule of Five were examined using the SwissADME server [24]. When developing new drugs, pharmaceutical chemists use Lipinski's rule of five to determine the oral bioavailability of potential lead or therapeutic compounds. A molecule wouldn't be orally active, according to Lipinski's Rule of Five, if it didn't satisfy two or more of the five requirements. Table 5 displays the drug-like properties of synthesized 2,3-dihydroquinazolin-4(1*H*)-ones.

Table 5 Drug-likeness properties of synthesized of 2,3-dihydroquinazolin-4(1*H*)-ones

Compound	Mol. Wt. (g/mol)	Rotatable bonds	HBA	HBD	LogP	Molar Refractivity	Log K_p (cm/s)	TPSA (Å²)
4a	224.26	1	1	2	1.97	73.16	-6.45	41.13
4b	258.70	1	1	2	2.11	78.17	-6.22	41.13
4c	269.26	2	3	2	1.52	81.98	-6.85	86.95
4d	269.26	2	3	2	1.57	81.98	-6.85	86.95
4e	258.70	1	1	2	2.06	78.17	-6.22	41.13
4f	254.28	2	2	2	2.12	79.65	-6.66	50.36
4g	240.26	1	2	3	1.48	75.18	-6.81	61.36
4h	238.28	1	1	2	2.10	78.13	-6.28	41.13
4i	230.29	1	1	2	1.98	71.04	-6.07	69.37
4j	225.25	1	2	2	1.53	70.95	-7.22	54.02
Lipinski rule	≤500	-	<10	<10	<5	40-130	-	-

HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor

Fascinatingly, all synthesized 2,3-dihydroquinazolin-4(1*H*)-ones revealed molecular weights between 224 and 269 (< 500). According to the Lipinski rule, the transportation, distribution and absorption of low molecular weight drug molecules (≤ 500) is easier than high molecular weight drug molecules. The number of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) in the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones were found between 1 to 2 and 1 to 3, respectively. The lipophilicity (logP values) and total polar surface area (TPSA values) are significant variables for estimating the oral bioavailability of drug molecules. Lower the value of logP higher is the rate of absorption. The synthesized 2,3-dihydroquinazolin-4(1*H*)-ones displayed the logP value between 1.48 to 2.12 and the TPSA values less than 140, indicating good gastrointestinal absorption [27]. Additionally, the logKp for skin permeability is within an acceptable range [28]. Since all synthesized 2,3-dihydroquinazolin-4(1*H*)-ones fulfilled Lipinski's criteria, the data suggested that they all had drug-like characteristics.

Conclusion

In summary, we have developed a green procedure for the efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by cyclocondensation of anthranilamide with various aromatic aldehydes employing caffeinium hydrogen sulphate (Caff@HSO_4) as a solid acid catalyst. The use of green solvent, high yields of products and short reaction time are the salient features of the present protocol. Additionally, among the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones

4i and 4j exhibited excellent anti-bacterial activity against *Staphylococcus aureus* and *Escherichia coli* bacteria, while all derivatives possessed drug-like characteristics as evaluated on the basis of Lipinski Rule of Five.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Spectra of some represnetative compounds:

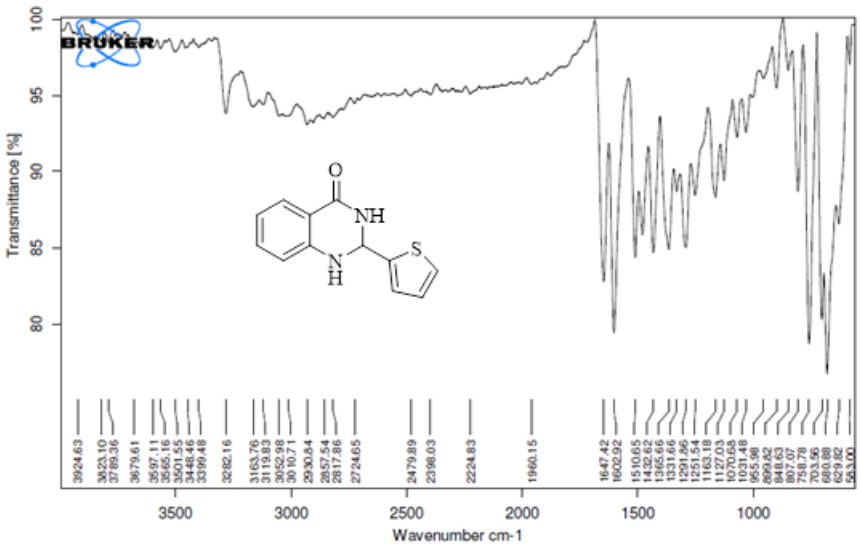

Fig. 7. IR spectrum of 2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**4i**)

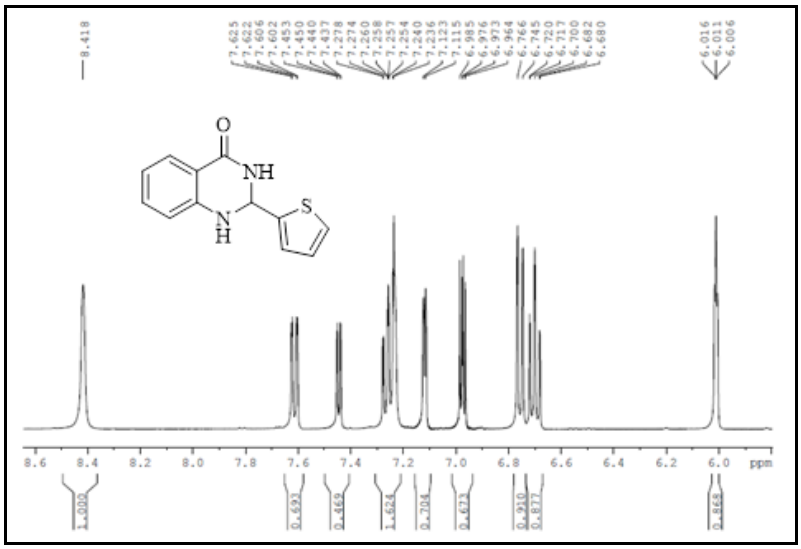

Fig. 8. ^{1}H NMR spectrum of 2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**4i**)

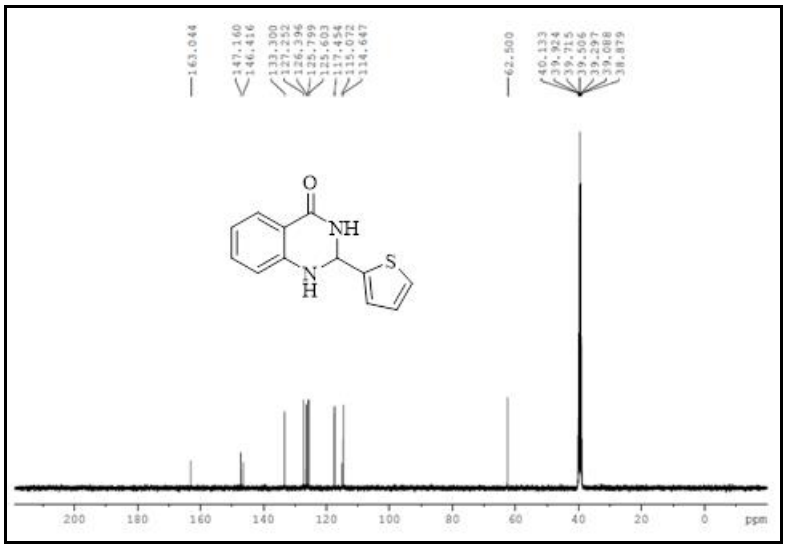

Fig. 9. ^{13}C NMR spectrum of 2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**4i**)

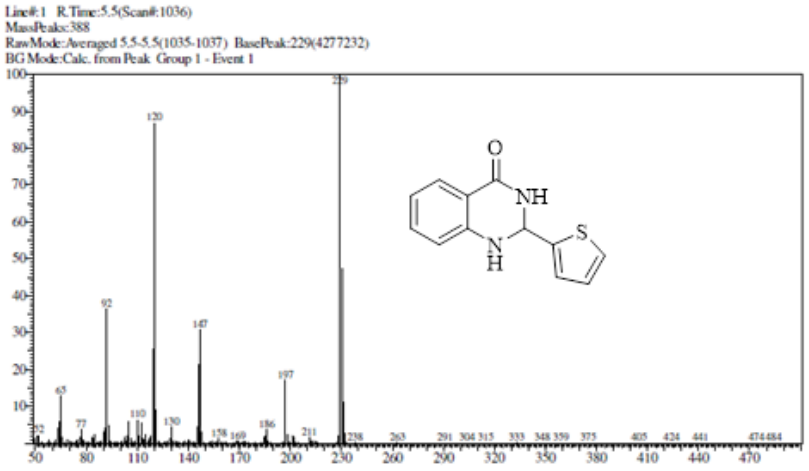

Fig. 10. Mass spectrum of 2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (**4i**)