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CSA-Catalyzed One-Pot Synthesis of 1, 2- Dihydroquinazolines

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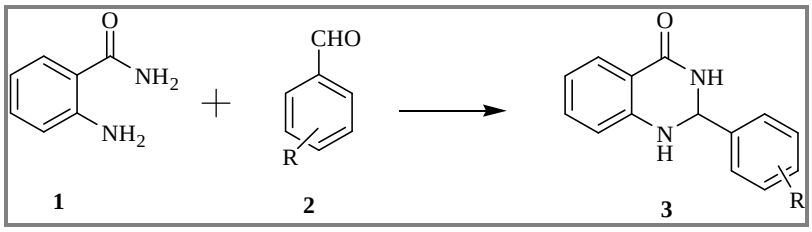
ABSTRACT

One-spot synthesis of 1, 2-dihydroquinazolines using substituted benzaldehydes and 2-aminobenzamide with camphor sulfonic acid as a catalyst tried in various solvents and finally achieved good yields in acetonitrile.

Graphical Abstract



CSA catalyzedone-pot synthesis of dihydroquinazolinones.

Keywords: 2-aminobenzamide, Substituted benzaldehydes, Camphor sulfonic acid, Acetonitrile.

INTRODUCTION

Nitrogen-containing polyheterocycles are ubiquitous structural motifs and exist in a wide range of bioactive natural products and biologically active molecules that can be intensively studied as drug candidates [**1**].

In 1988, Evans et al. introduced for the first time the concept of "privileged structures". They are useful tools in the field of drug discovery since they represent suitable lead compounds for diverse receptors and the rational optimization of such structures could provide new receptor modulators and potential drugs [**2**]. Medicinal chemists exploit the "privileged structures" to synthesize new libraries

of compounds based on a central scaffold and screen them against various receptors implicated in different pathways, in some cases yielding biologically active compounds. In this regard, the 2,3-Dihydroquinazolin-4(1*H*)-one core is emerging as a "privileged scaffold" and a variety of its derivatives, having diverse mechanism of action, are currently used for the treatment of various diseases [**3-8**].

A panel of marketed drugs with the 2, 3-Dihydroquinazolin-4(1*H*)-one core is shown in Fig.1.Besides these marketed drugs, a number of new 2, 3-Dihydroquinazolin-4(1*H*)-one derivatives have been designed that exhibit a wide range of pharmacological properties. Because of their importance, the synthesis of substituted 2, 3-Dihydroquinazolin-4(1*H*)-one derivatives has attracted much attention and different synthetic strategies have been developed. Since the classical protocols involved the use of toxic reagents and solvents in harsh reaction conditions, the evolution towards simple, clean, environmentally benign and high-yielding methods is gaining momentum (Figure 1).

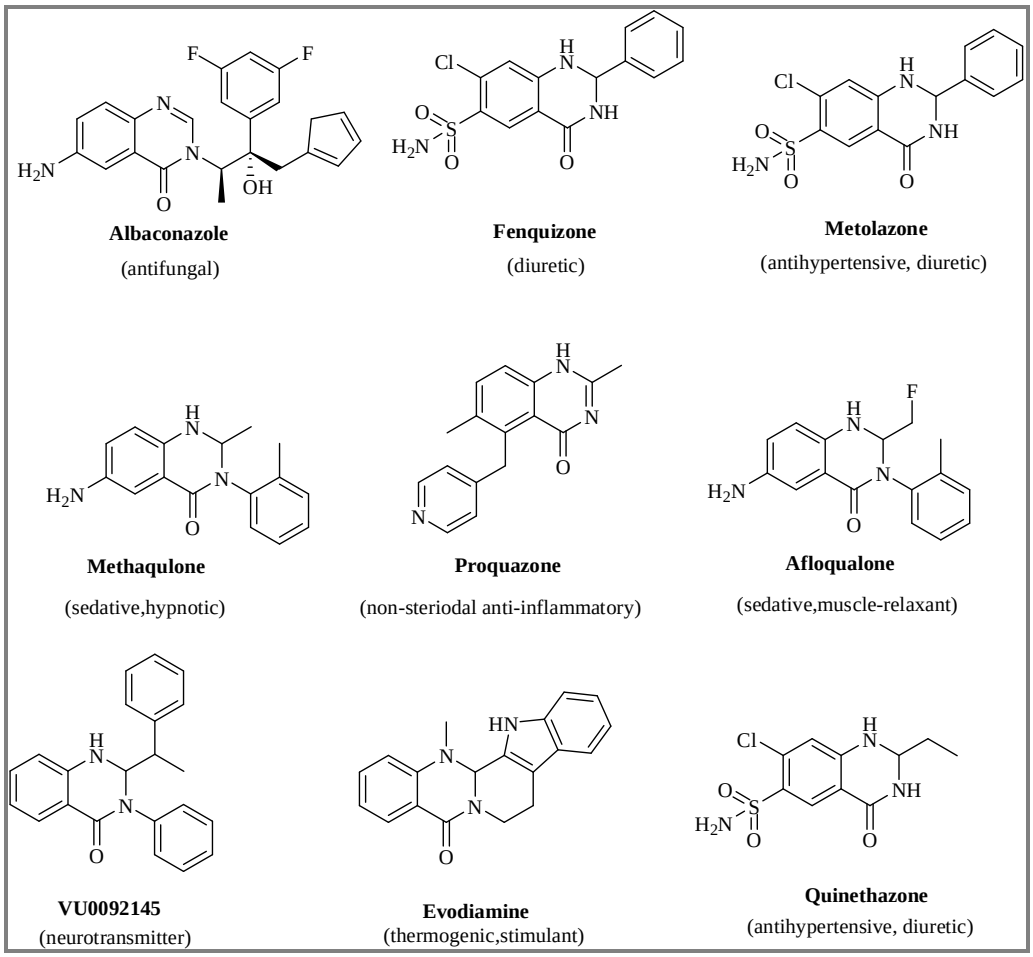
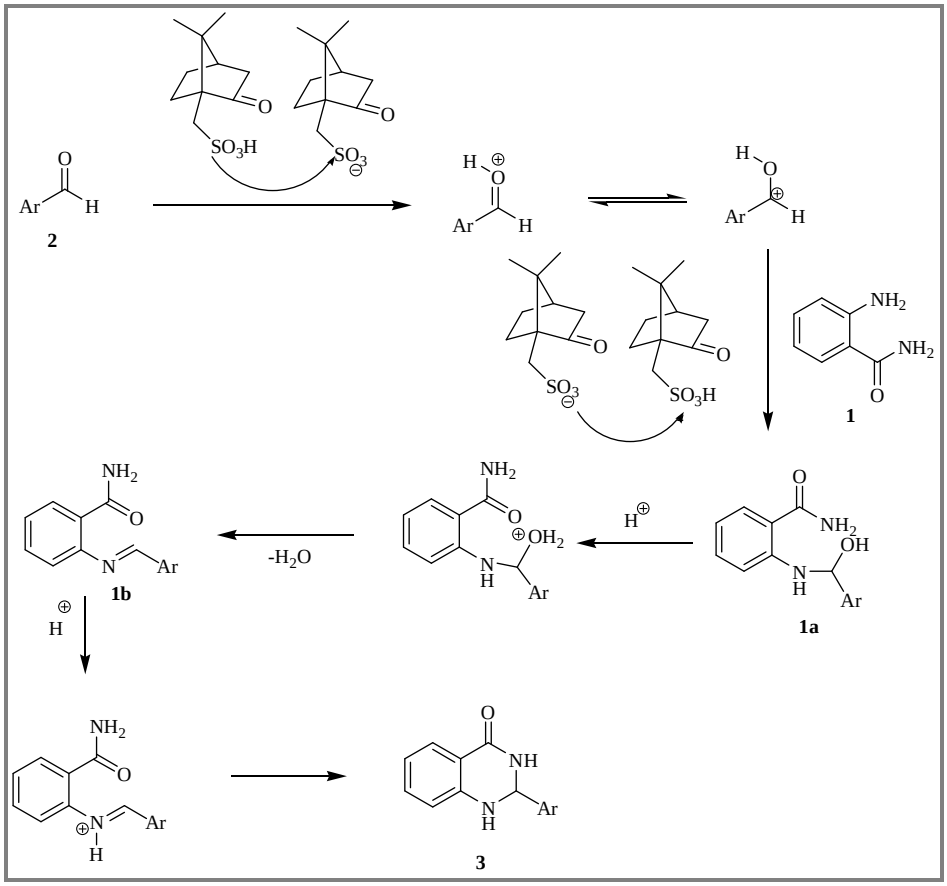


Figure 1. Marketed drugs with the 2, 3-Dihydroquinazolin-4(1H)-one core.

Mechanism: A possible mechanism for the formation of products is shown in below. The addition of nucleophiles to the aldehydes is promoted by protonation of the carbonyl group with the aid of CSA and enhancing the electrophilicity of this moiety. The proton from CSA is donated to the oxygen atom of the aldehyde. Therefore, it is proposed that, at first, the reaction starts through nucleophilic attack of the amino group in 2-aminobenzamide at the activated carbonyl group in arylaldehyde by CSA. It seems that the reaction proceeds through intermediate (1a), such that, after dehydration, the imine intermediate is produced. Then, the intermediate (1b) undergoes protonation and heterocyclization to furnish the corresponding 2, 3-dihydroquinazolin-4(1*H*)-ones (3).



MATERIALS AND METHODS

All reactions were carried out in oven-dried glassware (120°C) under an atmosphere of nitrogen unless as indicated otherwise. Ethyl acetate and hexanes from Merck Inc. were dried and distilled from CaH_2.

Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycleultra pure silica gel (particle size 40–63 µm, 230–400 mesh). The Infrared (IR) spectra were measured on a Perkin–Elmer model spectrum one B spectrophotometer. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; and w, weak. Proton NMR spectra were obtained on a Varian Mercury-400 (400 MHz) spectrometer by use of chloroform-*d* ($CDCl_3$) and acetone-d_6 (CD_3COCD_3) as solvents. Proton NMR chemical shifts were referenced to residual protonated solvents (δ7.24 and 2.05 ppm for chloroform and acetone, respectively). Carbon-13 NMR spectra were obtained on a Varian Mercury-400 (100 MHz) spectrometer by used of chloroform-*d* as the solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz). High-resolution mass spectra were obtained by means of a JEOL JMS-700 mass spectrometer. A Perkin-Elmer 241 polarimeter with a sodium lamp was used for determination of specific rotations at room temperature. Melting points were obtained with a Fargo MP-2D melting point apparatus.

General procedure for the synthesis of dihydroquinazolinones: A mixture of substituted aldehyde (**2**) (1 mmol), 2-aminobenzamide (**1**) (1 mmol) and CSA catalyst (5 mol%) was taken in acetonitrile (10 ml) and reaction mixture was stirred at room temperature till the completion of the reaction (monitored by TLC). After completion, the reaction mixture was diluted with water (3 mL) and filtered. The

obtained crude product was purified by recrystallization from diethyl ether/n-hexane (1 mL: 10 mL). All compounds were characterized by NMR, IR and mass spectral data.

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3a): White solid; mp: 201-203°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.42-7.51 (m, 4H), 7.24 (t, J = 8.4 Hz, 1H), 7.13 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.72(s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.51, 147.66, 140.68, 133.41, 132.98, 128.79, 128.32, 127.37, 117.32, 114.95, 114.48, 65.77 ppm.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3b): Pale yellow solid; mp: 310-312°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.53 (s, 1H), 8.23 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.34 (s, 1H), 7.26 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 5.91 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.34, 149.35, 147.46, 147.27, 133.62, 128.07, 127.45, 123.63, 117.51, 114.91, 114.53, 65.22 ppm.

2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3c): White solid; mp: 211-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 (s, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.23 (t, J = 7.6Hz, 1H), 7.11 (s, 1H), 6.90-7.01 (m, 3H), 6.73 (d, J = 8.4 Hz, 1H), 6.66 (t, J = 6.8 Hz, 1H), 5.68 (s, 1H), 3.73 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.76, 148.98, 148.57, 148.08, 133.54, 133.25, 127.35, 119.22, 117.15, 115.07, 114.45, 111.21, 110.58, 66.55, 55.46 ppm.

4-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (3d): White solid; mp: 249-255°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.47 (s, 1H), 7.87 (d, J = 6.8 Hz, 2H), 7.65 (d, J = 7.6Hz, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.21-7.27 (m, 2H), 6.75 (d, J = 7.6 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.35, 147.35, 133.57, 132.44, 127.71, 127.41, 118.68, 117.44, 114.90, 114.52, 111.07, 66.52 ppm.

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e): Pale yellow solid; mp: 210-212°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (s, 1H), 8.35 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.35 (s, 1H), 7.26 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 5.92 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.38, 147.71, 147.33, 144.30, 133.64, 133.41, 130.08, 127.43, 123.32, 121.60, 117.56, 114.94, 114.61, 65.17 ppm.

2-(3-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3f): White solid; mp: 185-188°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (s, 1H), 7.22-7.58 (m, 7H), 6.67-6.74 (m, 2H), 5.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.45, 147.53, 144.39, 133.50, 132.99, 130.33, 128.29, 127.39, 126.78, 125.44, 117.35, 114.90, 114.49, 65.56 ppm.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3g): White solid; mp: 203-205°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.50-7.54 (m, 2H), 7.19-7.25 (m, 3H), 7.10 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.63, 163.36, 160.93, 147.85, 137.78, 133.41, 129.04, 127.40, 117.30, 115.24, 115.03, 65.96 ppm.

2-(3-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3h): White solid; mp: 266-268°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.39 (s, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.16-7.42 (m, 6H), 6.66-6.75 (m, 2H), 5.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.49, 160.84, 147.58, 144.79, 133.46, 130.44, 127.39, 122.81, 117.33, 115.27, 114.94, 114.49, 113.36, 65.61 ppm.

2-(2-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3i): White solid; mp: 195-198°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.25 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.37-7.42 (m, 1H), 7.19-7.26 (m, 3H), 7.05 (s, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.69 (t, J = 7.6 Hz, 1H), 6.04 (s, 1H)

ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.60, 160.95, 158.50, 147.68, 133.42, 130.59, 128.44, 127.37, 124.47, 117.34, 115.55, 114.68, 114.45, 60.84 ppm.

2-(4-Ethylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3j): White solid; mp: 209-211°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.38-7.40 (m, 2H), 7.20-7.24 (m, 3H), 7.05 (s, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 5.70 (s, 1H), 2.58 (q, 2H), 1.14 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.18, 148.48, 144.68, 139.40, 133.80, 128.23, 127.87, 127.46, 117.59, 115.49, 114.91, 66.99, 28.43, 16.28 ppm.

2-(*p*-Tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (3k): White solid; mp: 231-233°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 6.9 Hz, 2H), 7.16-7.24 (m, 3H), 7.05 (s, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 5.69 (s, 1H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.69, 147.95, 138.65, 137.75, 132.28, 128.82, 127.36, 126.83, 117.09, 115.01, 114.43, 66.40, 20.75 ppm.

2-(4-(tert-Butyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3l): White solid; mp: 219-221°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 8.3 Hz, 4H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.92-6.85 (m, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 5.86 (s, 1H), 5.78(bs, 1H, NH), 4.38 (bs, 1H, NH), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.68, 151.03, 147.99, 138.60, 133.27, 127.37, 126.72, 125.12, 117.06, 114.96, 114.36, 66.47, 34.35, 31.12 ppm.

2-(2,6-Difluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3m): White solid; mp: 209-212°C; IR (υ_{max}/cm^{-1}, KBr): 3462, 3387, 2932, 2887, 1673, 1623, 1489; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, 7.6 Hz, 1H), 7.45-7.37 (m, 2H), 7.03-6.88 (m, 3H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.49 (s, 1H), 5.97 (bs, 1H, NH), 4.45 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.03, 162.07, 159.58, 147.51, 133.24, 131.07, 127.17, 116.94, 114.19, 113.81, 112.23, 58.54 ppm. HRMS (ES): Calcd 261.0834, found 261.0849; Anal. calcd for $C_{14}H_{10}F_2N_2O$: C, 64.61; H, 3.87; N, 10.76: found: C, 64.81; H, 3.67; N, 10.96.

2-(2,4-Dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3n): White solid; mp: 182-184°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 7.36-7.28 (m, 1H), 6.88 (t, *J* = 7.63 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.29 (s, 2H), 4.64 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.54, 147.53, 136.96, 133.95, 133.54, 132.92, 130.18, 128.99, 127.70, 127.40, 117.64, 114.66, 114.62, 63.33 ppm.

2-(2,6-Dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3o): White solid; mp: 167-170°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 (bs, 1H, NH), 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* =7.6 Hz, 2H), 7.45 -7.38 (m, 1H), 7.24-7.18 (m, 1H), 7.00 (bs, 1H, NH), 6.75 (s, 1H), 6.66-6.57 (m,2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.80, 147.86, 135.40, 133.53, 133.34, 131.00, 129.79, 127.22, 116.53, 113.60, 113.36 ppm.

2-(2,4-Dimethylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3p): White solid; mp: 161-163°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.41 (d, *J* = 7.6Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.02-7.04 (m, 2H), 6.80 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 5.93 (s, 1H), 2.37 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.09, 148.60, 137.66, 135.92, 135.09, 133.17, 131.27, 127.47, 126.42, 117.15, 114.93, 114.47, 64.54, 20.66, 18.73 ppm.

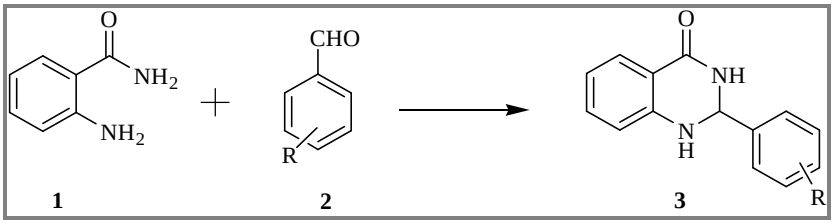
2-(2-(Trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one(3q): White solid; mp: 173-176°C; IR (υ_{max}/cm^{-1}, KBr): 3276, 2923, 2852, 2367, 1663, 1488, 1313, 1121; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.75-7.80 (m, 2H), 7.60-7.66 (m, 2H), 7.27 (t, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 6.72-6.76 (m, 2H), 6.04 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.55, 148.08, 138.70, 133.47, 132.98, 129.82, 129.52, 127.46, 126.60, 125.31, 122.73, 117.77, 114.71, 114.54, 63.22 ppm; HRMS (ES): Calcd 293.0896, found 293.0902; Anal. calcd for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.59: found: C, 61.84; H, 3.69; N, 9.68.

2-(4-(Trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3r): White solid; mp: 193-195°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.44 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6Hz, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 8.0 Hz, 2H), 6.74 (d, J = 8.4 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.85 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.44, 147.50, 146.42, 133.52, 129.01, 128.71, 127.69, 127.40, 125.36, 117.38, 114.92, 114.49, 65.70 ppm.

2-(2,6-Dimethylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3s): White solid; mp: 174-178°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.09 (s, 2H), 6.82 (s, 1H), 6.67-6.74 (m, 2H), 5.95 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.99, 148.65, 137.60, 134.73, 133.54, 130.95, 130.23, 129.38, 127.81, 117.48, 116.83, 115.26, 114.73, 114.16, 64.89, 64.51 ppm.

RESULTS AND DISCUSSION

In order to optimize the reaction, a model reaction was performed with 2-aminobenzamide (**1**) with substituted benzaldehyde (**2**) using 10 mol% of CSA catalyst (Scheme 1) in various solvents at room temperature as shown in Table 1. Desired products were obtained in poor to moderate yield in the presence of water, DMF, DMSO, toluene and THF (Table 1, entries 1,4,5,7 and 9). While, in case of MeOH, EtOH, DCM and 1,4-dioxne (Table 1, entries 2, 3, 6 and 10) the product was obtained in 80 – 95% yield. Interestingly, the progress of reaction was improved in the presence of acetonitrile as a solvent at room temperature to afford the product 98% yield (Table 1, entry 8). Thus, the optimization of the reaction conditions showed that 10 mol% of CSA catalyst in acetonitrile as a solvent at room temperature was best to afford dihydroquinazolinones in excellent yields shown in scheme 1.



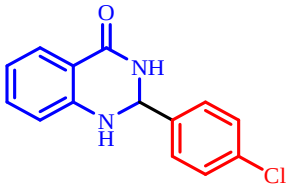
Scheme 1. CSA catalyzedone-pot synthesis of dihydroquinazolinones.

Table 1. Reaction condition: 2-aminobenzamide (1 mmol), benzaldehyde (1 mmol), solvent (1.5 mL), CSA (5 mol %), [a]Isolated yield.

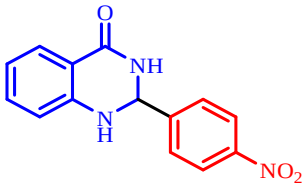
Entry	Solvent	Temp. (^{o}C)	Time (min)	Yield of 3[a] (%)
1	H_2O	Room tem.	30	65
2	MeOH	Room tem.	10	80
3	EtOH	Room tem.	10	95
4	DMF	Room tem.	30	50
5	DMSO	Room tem.	30	45
6	DCM	Room tem.	10	80
7	Toluene	Room tem.	30	55
8	**Acetonitrile**	Room tem.	**5**	**98**
9	THF	Room tem.	30	55
10	1,4-dioxane	Room tem.	10	90

With these interesting results in our hand, we investigated the substrate scope of the present method with various aromatic aldehydes and 2-aminobenzamide as shown in table 2. Almost all the derivatives were formed in excellent yields.

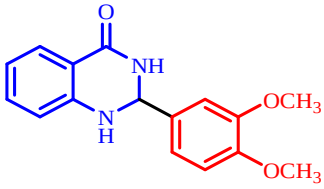
Table 2. Synthesis of substituted 2, 3-Dihydroquinazolin-4(1H)-one derivatives



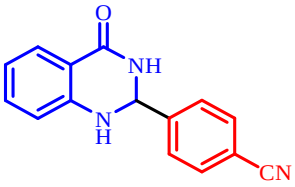
3a, 5 min, 98 %



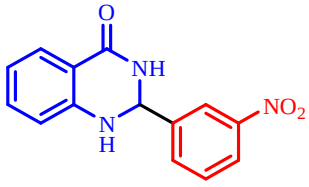
3b, 10 min, 95%



3c, 8 min, 96%



3d, 10 min, 92%



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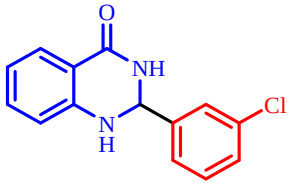

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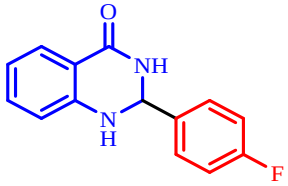
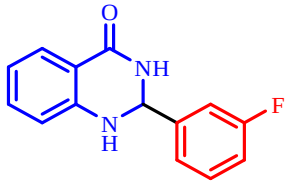
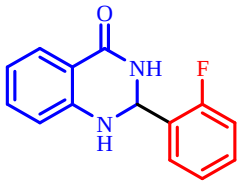


3g, 8 min, 92%



3h, 9 min, 91%



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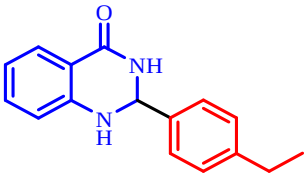

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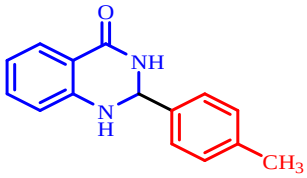

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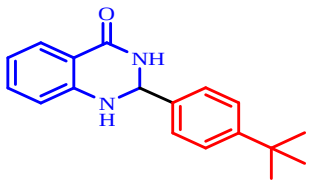

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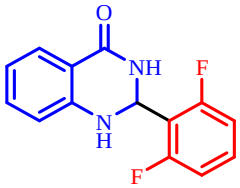

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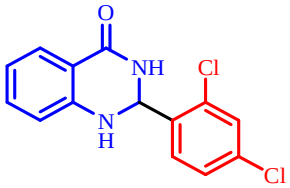

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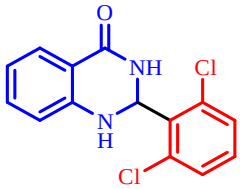

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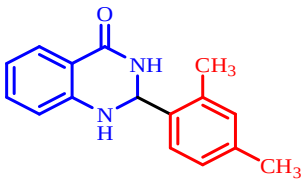

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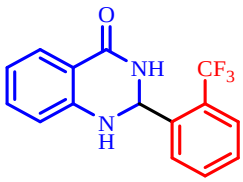

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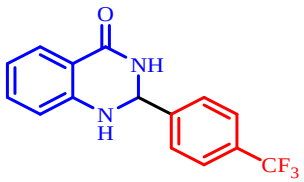

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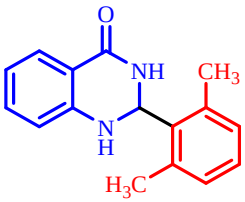

3s, 10 min, 93%

APPLICATION

New heterocyclic moieties and related 2, 3-dihydroquinazolin-4(1*H*)-one derivatives have been developed by this method to provide simple, efficient, high yield and convenient one pot techniques.

CONCLUSION

In summary, a series of 2, 3-dihydroquinazolin-4(1*H*)-one derivatives (**3a–3s**) were synthesized by using 5 mol% CSA as catalyst. The protocol demonstrated a concise, efficient, mild, and facile condition favouring short reaction times and safe experimental procedures, and is easy and safe to handle for large scale synthesis without the use of column chromatography for purification of the final products.

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