



Polyethylene glycol (PEG-400) as an efficient and recyclable reaction media for one-pot synthesis of simple and straight forward synthesis of 2,4-substituted quinazolines in catalyst free conditions

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ABSTRACT

Polyethylene glycol (PEG-400) was found to be an effective reaction medium for one-pot synthesis of quinazoline derivatives in good yields under mild reaction conditions. The use of PEG-400 is low, recyclable, and eco-friendly solvent.

Key words: One-pot synthesis Ammonium acetate, 2-Amino carbonyl compounds, 2,4-Disubstituted quinazolines, Catalyst-free conditions, Polyethylene glycol.

INTRODUCTION

Quinazoline and its derivatives are important compounds not only in organic synthesis but also in medicinal chemistry.¹ and these derivatives have attracted considerable interest because of their potential therapeutic properties as anticancer agents,² NF- κ B nuclear translocation inducers,³ ALK5 inhibitors,⁴ and cannabinoid-1 inverse agonists⁵. In particular quinazoline derivatives are potent inhibitors of Growth Factor Receptor (GFR) tyrosine kinases and have found clinical applications in Epidermal and Vascular Endothelial GFR targets (**Figure 1**)⁶⁻⁸. Among other pharmacological activities, such as antibacterial⁹, antidiabetic¹⁰, antihypertensive¹¹, antitumor^{12, 13}, anti-inflammatory¹⁴.

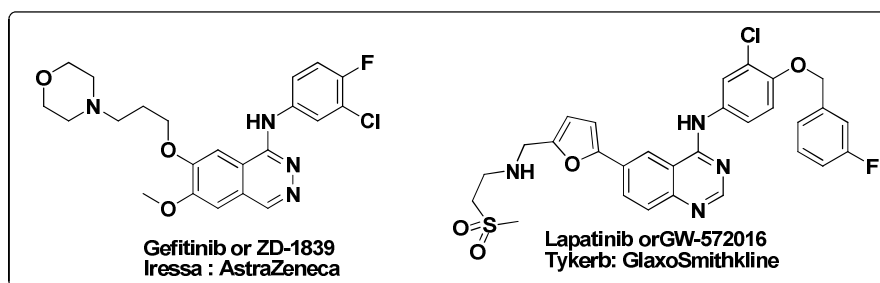
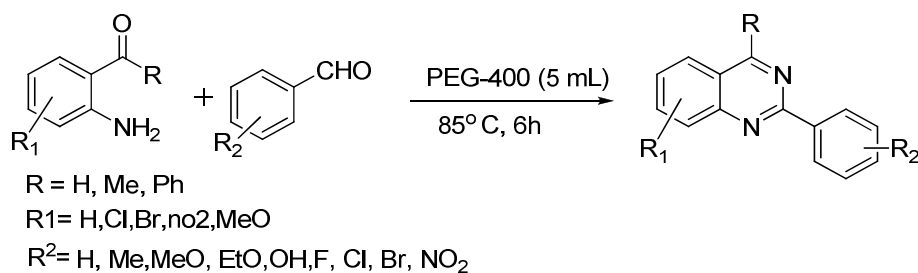


Figure 1

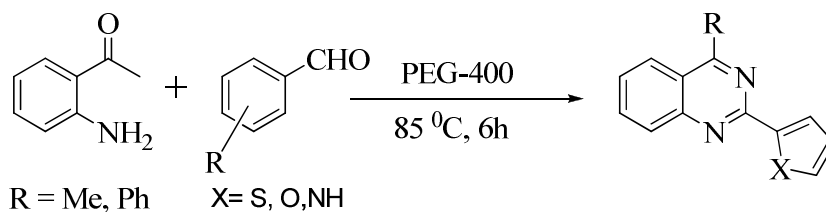
Therefore, there is sustained interest in developing simple and efficient methods for the synthesis various types of quinazolines. 2-Aminobenzonitriles, 2-halophenyl precursors, 2-nitrobenzoic acids or anthranilic acids as well as *N*-arylbenzamides are commonly used starting materials among those methods. Although several protocols have

been developed for the synthesis of quinazolines derivatives¹⁵⁻²¹, many of the methods are associated with various drawbacks, such as harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, and long reaction times and usage of expensive and moisture sensitive catalysts. Hence, there is a need for a rapid and efficient method for the synthesis of quinazolines derivatives under catalyst-free conditions.

In recent years, polyethylene glycol (PEG) has emerged as a powerful phase transfer catalyst and is utilized in many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations²². This inspired us to focus on the aspect of the synthesis of biologically active quinazolines derivatives under catalyst free conditions by using PEG as an eco-friendly and recyclable medium. Herein we report the synthesis of quinazolines derivatives by using PEG-400 as a recyclable medium without adding any organic solvent and catalyst. To the best of our knowledge there are no reports for the synthesis of quinazolines derivatives by using PEG-400 as a reaction medium under catalyst-free conditions (**Scheme 1**).



Scheme 1



Scheme 1

EXPERIMENTAL SECTION

In general, all the reactions were clean affording the 2,4-substituted quinazolinederivatives in high yields under the above conditions. Both electron rich and electron-deficient aldehyde derivatives gave the desired products (Table 1 and 2). The structures of all the products were determined from their spectral (IR, ¹H NMR, ¹³C NMR and ESI-MS) data and also by direct comparison with authentic samples.^[23]

The generality of this reaction was investigated with substituted aldehydes and 2-amino acetophenone/2-amino benzophenones and the results are presented in Table 1 and 2. A variety of aldehydes underwent smooth condensation with 2-amino acetophenone/2-amino benzophenones in PEG-400 at 85 °C to provide a diversified 2,4-substituted quinazolinederivatives (Table 1 and 2).

General procedure for the synthesis of 2, 4 - Substitutedquinazolines in polyethylene glycol-400:

To a flask containing the 2-amino acetophenone/2-amino benzophenones (1 mmol) in water (20mL), aldehydes (1.25 equiv.) and NH₄OAc (0.77 g, 10 mmol) were added. The mixture was magnetically stirred at 85 °C until reaction was complete (as monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethylacetate (25 mL). The extract was further washed with water and saturated brine solution, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give 2,4-substituted quinazolines in 25-77 % yields. (Scheme 1 and 2)

The characteristic data of compounds are given below.

Compound (1, Table 1): 4 - Methyl - 2 - phenylquinazoline: Brown. Yield: 62%. M.p.: 72-75 °C. ¹H NMR (500 MHz, CDCl₃, δ, ppm): 8.65-8.60 (m, 2H, ArH), 8.05 (m, 2H, ArH), 7.483-7.39 (m, 5H, ArH), 2.99 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 168.6, 162.2, 150.46, 139.9, 138.8, 133.7, 130.6, 129.5, 128.5, 128.6, 126.8, 124.6, 123.8, 122.5, 21.9. MS (ESI, m/z): 221 [M+H]⁺.

Compound (4, Table 1): 6,7 - Dimethoxy - 4 - methyl - 2 - phenylquinazoline: Light yellow. Yield: 59%. M.p.: 132-134 °C. ¹H NMR (300MHz, CDCl₃, δ, ppm): 8.57-8.53 (m, 2H, ArH), 7.48-7.45 (m, 3H, ArH), 7.33 (s, 1H, ArH), 7.15 (s, 1H, ArH), 4.09 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 2.90 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 164.6, 155.7, 149.8, 149.6, 147.9, 139.3, 138.5, 130.3, 128.9, 128.5, 128.5, 127.9, 107.6, 102.5, 56.6, 55.9, 21.9. MS(ESI, m/z): 281 [M+H]⁺.

Compound (5, Table 1): 6 - Chloro - 2 - phenylquinazoline: Light yellows. Yield: 60%. M.p.: 200-204 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 9.39 (s, 1H, ArH), 8.65-8.59 (m, 2H, ArH), 8.2 (m, 1H, ArH), 7.89 (m, 1H, ArH), 7.84-7.82 (m, 1H, ArH), 7.53-7.49 (m, 3H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 159.9, 149.5, 137.6, 135.5, 132.9, 130.9, 130.5, 128.66, 128.63, 125.8, 123.9. MS (ESI): m/z 241 [M+H]⁺.

Compound (7, Table 1): 8 - Methyl - 6 - phenyl - [1, 3] dioxolo [4, 5 - g] quinazoline: Brown. Yield: 61%. M.p.: 133-136 °C. ¹H NMR (500MHz, CDCl₃, δ, ppm): 8.55 (m, 1H, ArH), 7.52-7.48 (m, 4H, ArH), 7.31 (s, 1H, ArH), 7.32 (s, 1H, ArH), 6.09 (s, 2H, OCH₂O), 2.94 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 165.3, 159.4, 153.6, 149.9, 147.9, 138.6, 130.9, 129.9, 128.6, 128.5, 128.3, 119.9, 105.8, 101.9, 100.5, 22.10. MS (ESI, m/z): 265 [M+H]⁺.

Compound (8, Table 1): 2,4 - Diphenylquinazoline: Yellow. Yield: 63%. M.p.: 117-119 °C. ¹H NMR (500 MHz, CDCl₃, δ, ppm): 8.75(m, 2H, ArH), 8.18-8.19 (m, 2H, ArH), 7.95-7.85 (m, 3H, ArH), 7.65-7.49 (m, 7H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 168.5, 160.5, 152.5, 138.5, 137.9, 133.5, 130.8, 130.9, 129.8, 129.5, 128.8, 128.5, 126.9, 121.8. MS (ESI, m/z): 283 [M+H]⁺.

Compound (9, Table 1): 6 - Chloro - 2,4 - diphenylquinazoline: Yellow. Yield: 67%. M.p.: 201-204 °C. ¹H NMR (500 MHz, CDCl₃, δ, ppm): 8.69-8.65 (m, 2H, ArH), 8.09-8.08 (m, 2H, ArH), 7.89-7.79 (m, 3H, ArH), 7.65-7.59 (m, 3H, ArH), 7.55-7.49 (m, 3H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 167.8, 160.9, 151.6, 138.4, 137.9, 134.8, 133.2, 131.8, 131.2, 130.8, 129.3, 129.3, 129.3, 126.8. MS(ESI, m/z): 317 [M+H]⁺.

Compound (10, Table 1): 6 - Chloro - 4 - (2 - chlorophenyl) - 2 - phenylquinazoline: Grey. Yield: 65%. M.p.: 210-212 °C. ¹H NMR (500 MHz, CDCl₃, δ, ppm): 8.65-8.67 (m, 2H, ArH), 8.08 (m, 1H, ArH), 7.79-7.85 (m, 1H, ArH), 7.63-7.48 (m, 8H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 167.8, 160.6, 151.5, 138.2, 137.9, 134.6, 133.2, 131.7, 131.6, 130.7, 129.6, 129.2, 128.8, 126.2. MS (ESI, m/z): 351 [M+H]⁺.

Compound (11, Table 1): 7 - Bromo - 2,4 - diphenylquinazoline: Yellow. Yield: 62%. M.p.: 136-139 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.65-8.69 (m, 2H, ArH), 8.15 (m, 1H, ArH), 8.06 (m, 1H, ArH), 7.88-7.89 (m, 1H, ArH), 7.71-7.72 (m, 4H, ArH), 7.48-7.56 (m, 4H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 167.3, 160.5, 152.5, 138.3, 136.9, 133.9, 131.9, 130.9, 129.8, 128.6, 127.5, 126.9, 124.6, 121.4. MS (ESI, m/z): 361 [M+H]⁺.

Compound (12, Table 1): 6 - Nitro - 2, 4 - diphenylquinazoline: Brown. Yield: 25%. M.p.: 214-218 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 9.05 (s, 1H, ArH), 8.75-8.77 (m, 2H, ArH), 8.25 (m, 1H, ArH), 7.92-7.95 (m, 2H, ArH), 7.66-7.68 (m, 3H, ArH), 7.53-7.55 (m, 3H, ArH), 7.25 (s, 1H, ArH). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 124.2, 126.9, 167.6, 160.9, 150.9, 132.8, 131.9, 131.5, 130.9, 130.5, 129.5, 129.3, 128.8. MS (ESI, m/z): 328 [M+H]⁺.

Compound (1, Table 2): 4 - Methyl - 2 - p - tolylquinazoline: Brown. Yield: 60%. M.p.: 80-85 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.53 (m, 2H, ArH), 8.01 (m, 2H, ArH), 7.88-7.79 (m, 1H, ArH), 7.55-7.49 (m, 1H, ArH), 7.33-7.23 (m, 2H, ArH), 2.99 (s, 3H, CH₃), 2.45 (s, 3H, CH₃). ESI-MS: 235 [M+H]⁺.

Compound (2, Table 2): 4 - Methyl - 2 - (naphthalen - 1 - yl) quinazoline: Yield: 64%. M.p.: 92-95 °C. ¹H NMR (500 MHz, CDCl₃, δ, ppm): 8.88 (m, 1H, ArH), 8.09-7.89 (m, 6H, ArH), 7.56-7.49 (m, 4H, ArH), 3.05 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 167.8, 159.9, 149.9, 135.5, 134.6, 134.2, 133.5, 129.6, 128.8, 128.8, 128.5, 127.6, 127.6, 127.5, 126.5, 126.5, 125.5, 125.5, 124.8, 122.8, 122.5, 21.8. MS (ESI, m/z): 271 [M+H]⁺.

Compound (3, Table 2): 2 - (4 - Chlorophenyl) - 4 - methylquinazoline: Brown. Yield: 69%. M.p.: 64-67 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.59 (m, 2H, ArH), 7.98-7.99 (m, 2H, ArH), 7.88-7.79 (m, 1H, ArH), 7.52-7.45 (m, 3H, ArH), 2.92 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 168.5, 158.9, 150.5, 136.6, 136.5, 133.6, 129.9, 128.9, 128.8, 126.9, 124.9, 123.9, 122.9, 21.8. MS (ESI, m/z): 255 [M+H]⁺.

Compound (4, Table 2): 4 - Methyl - 2 - (4 - nitrophenyl) quinazoline: Brown. Yield: 74%. M.p.: 151-153 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.85 (m, 2H, ArH), 8.37 (m, 2H, ArH), 8.12-8.09 (m, 2H, ArH), 7.98-7.89 (m, 1H, ArH), 7.69-7.62 (m, 1H, ArH), 3.05 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 133.9, 129.8, 129.5, 127.9, 125.5, 123.8, 22.7. MS (ESI, m/z): 266 [M+H]⁺.

Compound (5, Table 2): 2 - (4 - Methoxyphenyl) - 4 - methylquinazoline: Brown. Yield: 58%. M.p.: 67-71 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.57 (m, 2H, ArH), 8.05-7.98 (m, 2H, ArH), 7.85-7.76 (m, 2H, ArH), 7.53-7.47 (m, 1H, ArH), 6.98 (m, 1H, ArH), 3.89 (s, 3H, OCH₃), 2.99 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 167.5, 161.8, 160.2, 150.8, 133.5, 130.9, 130.5, 129.5, 128.9, 126.5, 124.9, 124.5, 124.2, 122.8, 115.5, 113.9, 55.2, 22.3. MS (ESI): m/z 251 [M+H]⁺.

Compound (6, Table 2): 2 - (4 - Ethoxyphenyl) - 4 - methylquinazoline (:Grey. Yield: 55%. M.p.: 75-79 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.55 (m, 2H, ArH), 8.00 (m, 2H, ArH), 7.79 (m, 1H, ArH), 7.49 (m, 1H, ArH), 6.95 (m, 2H, ArH), 4.15 (q, J = 6.5, 2H, CH₂), 2.99 (s, 3H, CH₃), 1.48 (t, J = 6.8, 3H, CH₃). MS (ESI, m/z): 265 [M+H]⁺.

Compound (7, Table 2): 2 - (4 - Methylquinazolin - 2 - yl)phenol: Brown. Yield: 52%. M.p.: 208-210 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 9.45 (s, 1H, OH), 8.45 (m, 2H, ArH), 8.08 (m, 1H, ArH), 7.95-7.81 (m, 2H, ArH), 7.56 (m, 1H, ArH), 6.87 (m, 2H, ArH), 2.98 (s, 3H, CH₃). MS (ESI, m/z): 237 [M+H]⁺.

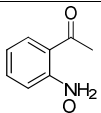
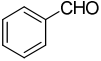
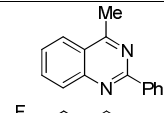
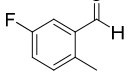
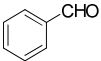
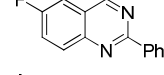
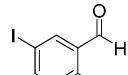
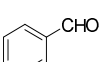
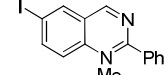
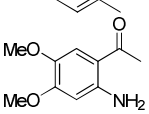
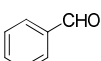
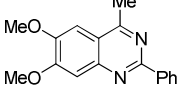
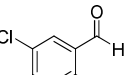
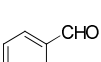
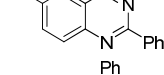
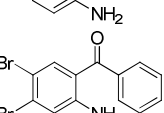
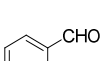
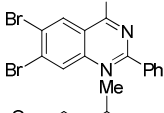
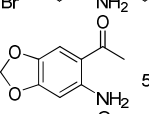
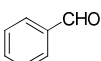
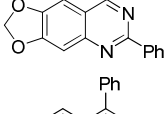
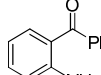
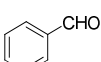
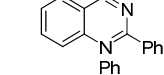
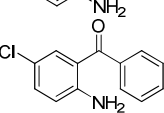
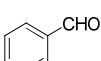
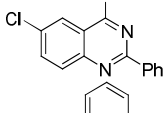
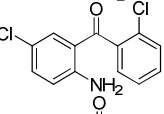
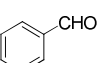
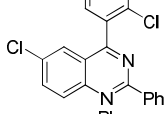
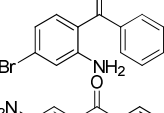
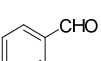
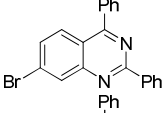
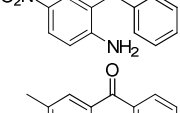
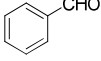
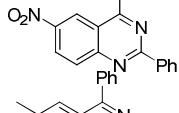
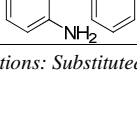
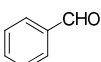
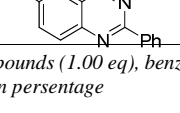
Compound (8, Table 2): 2 - Methoxy - 5 - (4 - methylquinazolin - 2 - yl)phenol: Brown. Yield: 58%. M.p.: 198-200 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.26 (m, 1H, ArH), 8.18 (s, 1H, OH), 8.00 (m, 2H, ArH), 7.85-7.78 (m, 1H, ArH), 7.55-7.49 (m, 1H, ArH), 6.99 (m, 1H, ArH), 6.85-6.78 (m, 1H, ArH), 4.09 (s, 3H, OCH₃), 2.98 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 134.9, 133.5, 130.9, 129.2, 127.8, 126.3, 122.9, 121.2, 117.6, 115.8, 114.7, 110.9, 56.2, 21.9. MS (ESI, m/z): 267 [M+H]⁺.

Compound (9, Table 2): 4 - Methyl - 2 - (3,4,5 - trimethoxyphenyl)quinazoline: Brown. Yield: 57%. M.p.: 140-142 °C. ¹H NMR (300 MHz, CDCl₃, δ, ppm): 8.06-8.05 (m, 2H, ArH), 7.92 (s, 2H, ArH), 7.87-7.79 (m, 1H, ArH), 7.58-7.56 (m, 1H, ArH), 4.05 (s, 6H, OCH₃), 3.95 (s, 3H, OCH₃), 3.05 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃, δ, ppm): 153.5, 150.6, 133.5, 129.3, 126.8, 124.9, 105.9, 62.8, 56.5, 22.0. MS (ESI, m/z): 311 [M+H]⁺.

RESULTS AND DISCUSSION

In search of developing a new and catalyst-free method for quinazoline derivatives, a model reaction was carried out in aqueous medium taking 2-amino acetophenone, benzaldehyde and NH₄OAC as substrates. After maintenance for 15 hrs at 100 °C, the desired quinazoline was isolated with 62% of yield. In our thorough investigation, reaction time and temperature were optimized at 4 hours and 75 °C respectively. Studying various experimental conditions we varied the amount of aldehydes (1-1.5 equiv) and NH₄OAC (10 to 25 equiv). The results show that 20 equiv of NH₄OAC is favorable to the reaction with 1.25 equiv of aldehyde. Later, in a trial to enhance the product yield, we examined the reaction in different organic solvents such as EtoAc, Toluene, Acetonitrile, MeoH, Isopropanol, Dichloromethane and PEG-400. However, water remained the best solvent among the solvents tested. In toluene no product was obtained. Acetonitrile, Isopropanol, and methanol resulted in trace amounts of quinazoline with so many byproducts. Low yields were obtained in case of EtoAc, Dichloromethane and PEG-400.

Table 1. Synthesis of quinazolines from various 2-aminoarylcarbonyl compounds in presence of PEG-400

Entry	Substrate	Benzaldehyde	Product	Time(h)	Yield ^b
1				9	67
2				9	68
3				8	66
4				8	69
5				7	60
6				8	62
7				8	61
8				6	72
9				7	70
10				7	65
11				8	62
12				12	45
13				12	58

Reaction conditions: Substituted 2-aminocarbonyl compounds (1.00 eq), benzaldehyde (1.25) in PEG-400 at 85 °C.
^bYields in percentage

We next explored the substrate scope with a variety of 2- amino carbonyl compounds. The formation of quinazolines all in moderate to good yields (Fig. 1) showed that the reaction tolerates a good range of functionality in the 2-amino carbonyls. Cl, Br, OMe, NO₂ were tolerated in 2-amino carbonyls. To probe the sensitivity of the reaction to substituents at the 4-position of the quinazoline, we extended our investigation to aldehydes. When electron-withdrawing groups, such as chloro, fluoro-, and nitro-, were introduced to the phenyl ring of benzaldehyde, good results were obtained (Table, entries 6-8). Whereas the introduction of electron-donating groups, such as OMe, OEt as well as hydroxyl to the phenyl ring of benzaldehyde, the yields decreased further (Table, entries 4 and 5).The reaction tolerates OMe, OEt as well as hydroxyl functional groups of aldehydes. A

wide range of substrates, including electron rich and/or electron deficient substituents (Table, entries 4 and 5) in addition to heterocyclic aldehydes (Table 2, entries 10-16) were compatible with this method.

Aliphatic aldehydes propanal, butanal, hexanal, octanal and cyclohexane carboxaldehyde were also examined. Hexanal, cyclohexane carboxaldehyde resulted in respected dihydroquinazolines as products. Rest of the aliphatic aldehydes remained inactive in the present condition.

Table 2. Synthesis of quinazolines from various benzaldehydes

Entry	2-Aminoacetophenone	Aldehyde	Product	Time (h)	Yield ^b
1				8	60
2				8	64
3				7	72
4				7	69
5				6	74
6				8	58
7				9	55
8				8	52
9				8	57
10				8	60
11				8	60

^a Reaction conditions: 2-aminoacetophenone (1.0 eq), substituted benzaldehyde (1.25eq) in PEG-400, 85 °C
^b Yields in percentage

CONCLUSION

In conclusion, we have developed an eco-friendly synthesis of 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one derivatives by using PEG-400 as a recyclable reaction medium without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of this protocol.

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