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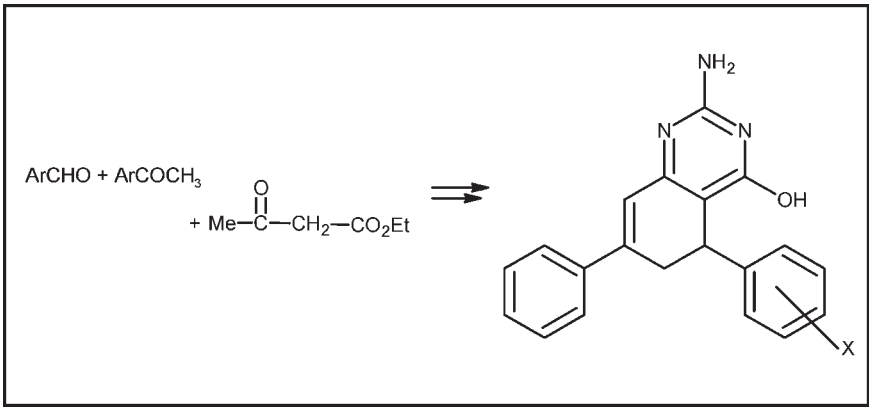

We report an efficient and new method of synthesis of 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols by the reaction of substituted cyclohexenones with guanidine hydrochloride in presence of NaOEt. The reactions are with 50–72% yield. All the synthesized compounds are characterized using IR, NMR and CHN analysis.

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INTRODUCTION

Quinazoline skeleton is an important pharmacophore that occurs frequently in medicinal chemistry literature [1]. Quinazolines are recently been the subject of deep investigation due to their diverse pharmacological properties such as analgesic, narcotic, antimalarial, sedative, hypoglycemic [2], anti-cancer [3] and anti-tubercular activities[4]. It has been reported that quinazolines act as potent [5] and highly selective inhibitors of epidermal growth factor receptor tyrosine kinase and have been employed as DNA binder [6]. Alkaloids with quinazoline ring system are known for natural compounds having a wide spectrum of biological effects. The biological activity of quinazolines strongly depends on the nature and the position of the substituents in the quinazoline ring. The 2-amino substituted quinazolines are reported as potential histamine antagonists [7]. This large interest in medicinal chemistry stimulated the development of new and more efficient synthesis of amino substituted heterocycles recently we have reported the synthesis and antibacterial activity of naphthyl and thienyl substituted 2-aminopyrimidines [8]. In continuation of synthesis of the biologically active heterocyclic compounds here we report a simple synthesis for 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols.

RESULTS AND DISCUSSION

Quinazolin-4-ols are synthesized in three steps (Scheme 1) starting from easily available acetophenone and benzaldehyde. Initialy, chalcones **1** were synthesized by Claisen-Schmidt condensation between benzaldehyde and acetophenone.

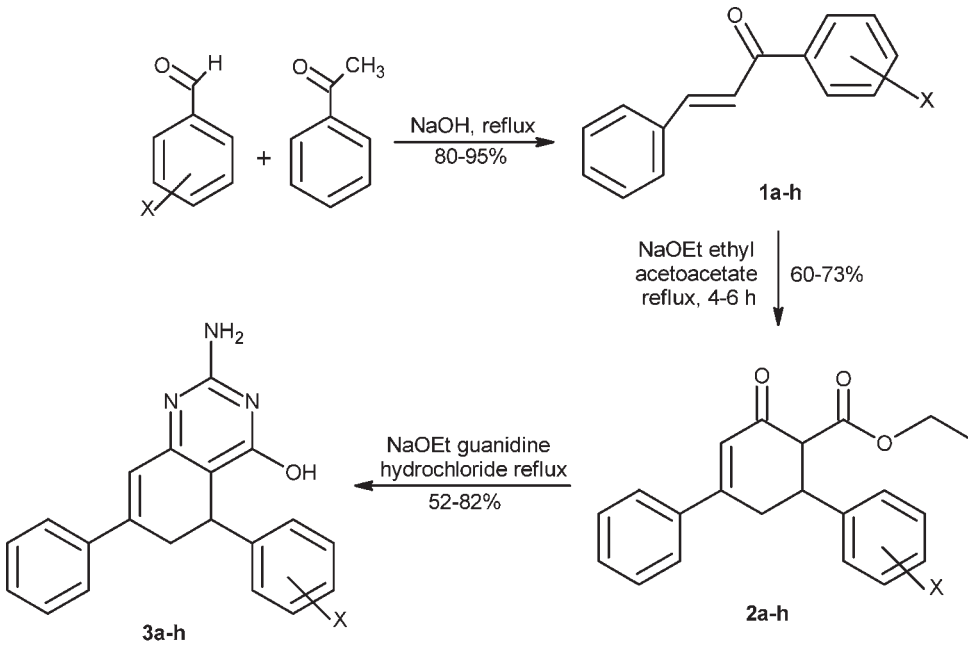
The chalcones on treatment with ethyl acetoacetate in the presence of sodium ethoxide gave carbethoxycyclohex-2-en-one derivatives **2.** The structure of the carbethoxycyclohex-2-en-one derivatives were conformed by comparing with their reported IR and melting points.

Carbethoxycyclohex-2-en-one derivatives **2** on treatment with guanidine hydrochloride in the presence of sodium ethoxide under go condensation reaction and gave 2-amino-5,6-dihydro-5,7-diarylquinazolin-4-ols (**3a–h**).

The structures of **3a–h** were elucidated by ^{1}H and ^{13}C NMR, mass spectral analysis and elemental analysis. In the ^{1}H NMR spectra, the characteristic chemical shift of the hydroxy protons of **3a–h** were found at $\delta = 10.76$–10.81 ppm as a broad singlet. The two amino protons were observed as a singlet at $\delta = 6.20$–6.42 ppm. The alkenic proton signal was observed at around 6.40 ppm.

To conclude, we have proposed an efficient method for the preparation of 2-amino-5,6-dihydro-5,7-diarylquinazoline-4-ols by reaction of guanidine hydrochloride

Scheme 1. Synthesis of 2-amino-5,6-dihydro-5,7-diarylquinazoline-4-ols.



Entry	X
a	-H
b	4-F
c	4-Cl
d	3-Br
e	4-Br
f	4-Me
g	4-OMe
h	3-NO_2

with carbethoxycyclohex-2-enone derivatives. These compounds are known pharmacophores in several structure based drug design approaches.

EXPERIMENTAL

Melting points are determined in open capillaries and are uncorrected. The NMR spectra were recorded on 300 MHz spectrometer in DMSO-d_6. Chemical shifts are expressed in parts per million using residual solvent proton and carbon as internal standards. The FT-IR spectra were recorded on NICOLET AVATAR 360-FTIR instrument by using KBr pellets. Elemental analyses were done on Vario EL. CHN elemental analyzer.

Preparation of chalcone (1a–h). About 0.5 g of sodium hydroxide was dissolved in 50 mL of water. A mixture of acetophenone (0.01 mole) and aromatic aldehyde (0.01 mole) in 50 mL of absolute ethanol was added. The mixture was stirred at room temperature for 3 h and allow to stand for overnight. The preceipitated solid was separated, washed with distilled water and recrystallized from hot ethanol. The products were confirmed from their reported IR spectra and melting points.

Ethyl-2-oxo-4,6-diarylcyclohex-2-en-carboxylate (2a-h). A mixture of chalcone (0.01 mole) (**1a-h**) and ethyl acetoacetate (0.01 mole) was dissolved in absolute ethanol (30 mL). Sodium ethoxide (2 g sodium in 60 mL ethanol) was added to the mixture and refluxed for the 5 h. The reaction mixture was kept aside for more than 1 h and the solid mass obtained was collected and recrystallized from ethanol. The products were confirmed from their reported IR spectra and melting points.

2-Amino-5,6-dihydro-5,7-diarylquinazolin-4-ols (3a–h). Appropriate diarylcyclohexenone (**2a–h**, 0.01 mole), guanidine hydrochloride (0.01 mole) and sodium ethoxide (2 g in 30 mL ethanol) were refluxed for 28–32 h. The reaction mixture was cooled to room temperature, poured into crushed ice and stirred. The separated product was purified using column chromatography (silica gel, 100–200 mesh, $CHCl_3$-EtOAc, 6:4). All the compounds were characterized using IR, ^1H and ^{13}C NMR and elemental analysis.

2-Amino-5,6-dihydro-5,7-diphenylquinazolin-4-ol (3a). This compound was obtained as a yellow solid. mp 134–136°C; yield 72.5%; IR (KBr) ν cm^{-1} 3415 (N—H stretching), 2836 (C—H stretching), 1649 (C=C stretching) ^1H NMR (DMSO-d_6, 300 MHz), δ ppm 2.94 (d, 1H, J = 17.1 Hz), 3.12–3.22 (m, 1H), 4.21 (d, 1H, J = 7.5 Hz), 6.42 (s, NH_2), 6.46 (s, H-8), 7.09–7.49 (Ar-H), 10.76 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.3, 41.7, 110.1, 125.4, 125.9, 126.3, 126.9, 127.3, 127.8, 128.3, 128.5, 128.9, 129.1, 140.1, 145.2, 155.4, 161.5. Calc. for $C_{20}H_{17}N_3O$: C 76.17; H, 5.43; N, 13.32%. Observed were C, 76.12; H, 5.48; N, 13.48%.

2-Amino-5,6-dihydro-5-(4-flurophenyl)-7-phenylquinazolin-4-ol (3b). This compound was obtained as white solid. mp 217–219°C; yield 60.4%; IR (KBr) ν cm^{-1} 3336 (N—H

stretching), 2852 (C—H stretching), 1648 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.92 (d, 1H, J = 17.4 Hz), 3.21–3.11 (m, 1H), 4.21 (d, 1H, J = 8.1 Hz), 6.38 (s, NH_2), 6.44 (s, 1H), 7.00–7.50 (Ar-H), 10.76 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.2, C-6 (merged with DMSO), 115.3, 125.3, 125.5,125.9, 127.8, 128.9, 129.0, 129.1, 129.2, 129.3, 130.0, 130.2, 132.0, 132.1, 132.5, 139.5, 143.9, 155.3, 169.7. Calc. for $C_{20}H_{16}N_3O$ C, 72.06; H, 4.84; N, 12.61%; Observed were C, 72.02; H, 4.86; N, 12.59%.

2-Amino-5-(4-chlorophenyl)-5,6-dihydro-7-phenylquinazolin-4-ol (3c). This compound was obtained as white amorphous solid. mp 196–198°C; yield 70.1%; IR (KBr) ν cm^{-1} 3437 (N—H stretching), 2858 (C—H stretching), 1647 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.93 (d, 1H, J = 17.6 Hz), 3.75–3.14 (m, 1H), 4.29 (d, 1H, J = 8.4 Hz), 6.47 (s, NH_2), 6.54 (s. H-8), 7.13–7.51 (Ar-H), 10.78 (s, —OH). ^{13}C NMR (DMSO-d_6, 300 MHz) δ ppm 34.9, 43.1, 113.8, 120.1, 122.8, 125.2, 125.6, 126.4, 128.8, 129.9, 130.4, 130.5, 131.2, 137.2, 140.9, 159.1, 169.1. Calc. for $C_{20}H_{19}N_3ClO$ C, 68.67; H, 4.61; N, 12.01%; observed were C, 68.62; H, 4.64; N, 12.03%.

2-Amino-5-(3-bromophenyl)-5,6-dihydro-7-phenylquinazolin-4-ol (3d). This compound is obtained as brown solid. mp 226–229°C; yield 50.2%; IR (KBr) ν cm^{-1} 3464 (N—H stretching), 2920 (C—H stretching), 1638 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.97 (d, 1H, J = 17.2 Hz), 3.32–3.12 (m, 1H), 4.21 (d, 1H, J = 8.4 Hz), 6.41 (s, NH_2), 6.47 (s, H-8), 7.18–7.51 (Ar-H), 10.77 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.1, 41.5, 115.9, 121.0, 121.8, 123.9, 125.5, 125.9, 126.4, 127.8, 128.0, 129.2, 130.1, 139.4, 143.9, 147.9, 155.4, 170.9. Calc. for $C_{20}H_{16}N_3BrO$ C, 60.93; H, 4.09; N, 10.66%. Observed were C, 60.90; H, 4.05; N, 10.62%.

2-Amino-5-(4-bromophenyl)-5-dihydro-7-phenylquinazolin-4-ol (3e). This compound was obtained as a yellowish brown colour solid. mp 184–186°C; yield 55.1%; IR (KBr) ν cm^{-1} 3377 (N—H stretching), 2853 (C—H stretching), 1630 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 2.89 (d, 1H, J = 17.7 Hz), 3.21–3.11 (m, 1H), 4.19 (d, 1H, J = 8.4 Hz), 6.42 (s, NH_2), 6.47 (s, H—), 7.13–7.49 (Ar-H), 10.83 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.4, C-6 (merged with DMSO), 113.9, 125.4, 125.9, 126.0, 127.1, 127.7, 128.3, 128.4, 128.9, 129.0, 129.3, 129.4, 129.5, 139.7, 144.0, 155.2, 170.0. Calc. for $C_{20}H_{16}N_3BrO$ C, 50.93; H, 4.09; N, 10.66%, observed were C, 50.89; H, 4.10; N, 10.59%.

2-Amino-5,6-dihydro-5-(4-methylphenyl)-7-phenylquinazolin-4-ol (3f). This compound was obtained as brownish red colour solid. mp 174–178°C; yield 45.7%; IR (KBr) ν cm^{-1} 3331 (N—H stretching), 2852 (C—H stretching), 1644 (C=C stretching) ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ ppm 1.23 (s, 3H, —CH_3), 2.91 (d, 1H, J = 17.4 Hz), 3.19–3.09 (m, 1H), 4.16 (d, 1H, J = 8.1 Hz), 6.35 (s, —NH_2), 6.41 (s, 1H), 6.99–7.49 (Ar-H), 10.71, (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 15.1, 32.8, 40.8, 116.1, 125.0, 125.3, 125.4, 125.9, 126.0, 127.1, 127.3, 127.7, 128.9, 129.0, 129.1, 129.2, 129.5, 131.5, 135.2, 136.2, 139.5, 140.2, 142.2, 155.2, 168.4. Calc. for $C_{21}H_{19}N_3O$ C, 76.57; H, 5.81; N, 12.76%; observed were C, 76.52; H, 5.79; N, 12.69%.

2-Amino-5,6-dihydro-5-(4-methoxyphenyl)-7-phenylquinazolin-4-ol (3g). This compound was obtained as yellow crystalline solid. mp 204–206°C; yield 65.3%; IR (KBr) ν cm^{-1} 3371 (N—H stretching), 2852 (C—H stretching), 1645 (C=C stretching) ^{1}H NMR (DMSO-d_6 300 MHz) 2.08 (s, 3H, —OCH_3), 2.90 (d, 1H, J = 17.1 Hz), 3.34–3.08 (m, 1H), 4.16 (d, 1H, J = 8.1 Hz), 6.44 (s, NH_2), 6.53 (s, H-8), 7.08–7.49 (Ar-H), 10.79 (s, OH). ^{13}C NMR (DMSO-d_6 75 MHz) 35.5, 40.8, 60.5, 110.8, 123.3, 126.8, 126.9, 128.8, 129.3, 130.1, 131.0, 132.1, 159.7, 169.6. Calc. for $C_{21}H_{19}N_3O_2$ C, 73.03; H, 5.54; N, 12.17%; observed were C, 73.10; H, 5.61; N, 12.15%.

2-Amino-5,6-dihydro-5-(3-nitrophenyl)-7-phenylquinazolin-4-ol (3h). This compound was obtained as brownish yellow solid. mp 262–265°C; yield 65.3%; IR (KBr) ν cm^{-1} 3448 (N—H stretching), 2923 C—H stretching, 1653 (C=C stretching) ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 3.01 (d. 1H, J = 17.4 Hz), 3.18–3.32 (m, 1H), 4.37 (d, 1H, J = 8.1 Hz), 6.45 (s, NH_2), 6.51 (s, 1H), 7.35–7.54 (Ar-H), 10.85 (s, —OH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 34.4, C-6 (merged with DMSO), 113.5, 125.4, 125.9, 128.8, 129.2, 129.7, 131.4, 131.6, 139.5, 143.9, 144.0, 144.5, 155.5, 166.6. Calc. for $C_{20}H_{16}N_4O_3$ C, 66.66; H, 4.48; N, 15.55%; observed were C, 66.62; H, 4.45; N, 15.50%.

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