



Synthesis of 2-Amino-5-aryl-5,6-dihydro-7-(naphthalen-2-yl) Quinazolin-4-ols

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Abstract

Quinazolines exhibit various biological activities. In the present investigation a series of new 2-amino-5-aryl-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ols are synthesized by the condensation of various naphthyl substituted cyclohexenones with guanidine in presence of NaOEt. All the synthesized compounds are characterized by various spectral techniques.

Keywords: Quinazoline, Aminoquinazoline, Quinazolinol, Aminopyrimidine

1. Introduction

Quinazoline and its derivatives are a class of heteroaromatic compounds that have drawn much attention because of their pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, tyrosine kinase inhibiting agents, antituberculars, antiparkinsons, antihelmintics, CNS depressant and they also show blood platelet anti-aggregating activity (Billker *et al.* 1998; Chen *et al.* 2001). Derivatives of aminoquinazolines are potent inhibitors of Growth Factor Receptor (GFR) tyrosine kinases and have found clinical applications in Epidermal and vascular Endothelial targets (Bridges *et al.* 1996; Wakeling *et al.* 2005).

In particular, Gefinitib (traded as Iressa, ZD1839) has been recognized as a tyrosine kinase inhibitor of the epidermal growth factor receptor and has been clinically used against cell lung cancer with ever increasing popularity. The quinazoline-dependent kinase (QDK) family of enzymes plays a vital role in the control of cell-cycle progression, particularly at cell-cycle check points. Aberrant cell cycle control, arising from tumour suppressor gene malfunction or oncogene activation, is associated with increase QDK/quinazoline activity in human tumours (Sherr, 1996; Malumbres & Barbacid, 2001).

As a consequence aminoquinazolines are very attractive target molecules in synthetic organic chemistry. Keeping in view the biological importance of the above mentioned heterocyclic compounds, and pursuing our research on pyrimidine derivatives (Chandrasekaran & Nagarajan, 2005; Ingarsal *et al.* 2007), we report herein the synthesis of 2-amino-5,6-dihydro-5-aryl-7-(naphthalen-2-yl)quinazolin-4-ols from ethyl 4-(naphthalen-2-yl)-2-oxo-6-aryl cyclohex-3-enecarboxylate. The synthesized compounds are characterized by various spectral techniques.

2. Results and discussion

The 2-aminoquinazolinols are synthesized in three steps (Scheme 1) starting from easily available 2-acetylnaphthalene and substituted benzaldehyde. The 2-naphthyl-3-arylpropen-2-en-1-ones, **3a-l** was obtained by treatment of 2-naphthylethanone with different aromatic aldehydes in presence of base. Naphthylethanone was prepared by acetylation of naphthalene in presence of anhydrous aluminium chloride. The reaction of compounds **3a-l** with ethyl acetoacetate in presence of sodium ethoxide gave ethyl 4-(naphthalen-2-yl)-2-oxo-6-aryl cyclohex-3-ene carboxylate. The target compounds 2-amino-5-aryl-5,6-dihydro-7-naphthylquinazolin-4-ols **5a-l** were obtained by treatment of **4a-l** with guanidine hydrochloride in presence of sodium ethoxide (Scheme 1). The products **5a-l** were purified by column chromatography (CHCl₃; MeOH; 4:1). Yield, melting point, reaction time and elemental analyses are mentioned in Table 1 and 2.

The IR spectra of the compounds **5a-l** displays characteristic absorption bands in the region of 3380, 2922, 1600, 1350, 1230. The ¹H NMR shows characteristic peaks for **5a** at 3.14 (d, 1H, J = 13.2 Hz), 3.16-3.29 (m, 1H), 4.26 (d, 1H, J =

6.8 Hz), 6.46 (s, NH₂), 7.08-8.05 (Ar-H); ¹³C NMR displays characteristics peaks around 33.8, 41.3, 113.7, 123.3, 136.2 and other signals for aromatic and *ipso* carbons.

3. Experimental

All chemicals were of analytical grade and solvents were distilled before use. Melting points were uncorrected and determined in open capillaries. The ¹H NMR and ¹³C NMR were recorded on Bruker Amx-500 spectrometer operating at 500 MHz using DMSO-*d*₆ as solvent. The FT-IR spectra were recorded on NICOLET AVATAR 360 FT-IR instrument by using KBr pellets. Elemental analysis were done on ELCHNO elemental analyzer.

Preparation of 1-(1-naphthyl)ethanone (2)

A mixture of 41.9g (38 mL, 0.53 mol) of acetyl chloride and 100 mL of carbon tetrachloride was taken in a one-litre three necked flask. The flask was equipped with condenser carrying a guard tube and a dropping funnel. About 70g (0.52 mol) of powdered dry AlCl₃ was added slowly to the vigorously stirred mixture. The mixture was cooled to 20°C and a solution of naphthalene (32g, 0.25 mol) in 100 mL of CCl₄ was added for 90 minutes from the dropping funnel. The hydrogen chloride was evolved. After the completion of the addition, the mixture was warmed to 30°C for 30 minutes. The resulting mixture was decomposed with ice and concentrated hydrochloric acid. The product was separated and the crude was distilled under reduced pressure b.p 165°C/15 mm Hg.

Preparation of naphthyl chalcones (3a-l)

2-Acetylnaphthalene (0.01 mole) was dissolved in ethanol and added to a solution containing NaOH (0.5g) aromatic aldehyde (0.01 mole). The mixture was refluxed for about 2 hours. The resulting mixture was poured into cold water. The product was further purified by recrystallisation from EtOH.

General procedure for the synthesis of ethyl 4-(naphthalen-2-yl)-2-oxo-6-arylcyclohex-3-ene carboxylate (4a-l)

A mixture of chalcone **3a-l** (0.01 mole) and sodium ethoxide (2 g sodium in 60 ml ethanol) with freshly distilled ethyl acetoacetate (0.01 mole) was dissolved in absolute ethanol (30 ml) and refluxed for eight hours. The reaction mixture was kept aside for more than one hour and the yellow solid mass obtained was collected and recrystallized from ethanol. All the compounds were characterized with IR and NMR spectroscopy.

2-Amino-5-aryl- 5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ols (5a-l)

Appropriate cyclohexenones (**4a-l**, 0.01 mole) and guanidine hydrochloride (0.01 mole) in the presence of sodium ethoxide (2 g in 30 ml ethanol) were refluxed for 16-23 hours. The reaction mixture was cooled to room temperature and poured into crushed ice and stirred well. The separated product was purified using column chromatography silica gel, CHCl₃-MeOH, 4:1. All the compounds were characterized using IR, ¹H, ¹³C NMR and elemental analysis.

2-Amino-5,6-dihydro-7-(naphthalen-2-yl)-5-phenylquinazolin-4-ol (**5a**): Yellow Solid; IR (KBr) (ν_{max} , cm⁻¹): 3380, 1600, 2922, 1230, 1350; ¹H NMR δ = (ppm) 3.14 (d, 1H, H-6, J = 13.2 Hz) 3.16-3.29 (m, 1H, H-6), 4.26 (d, 1H, H-5, J = 6.8 Hz), 6.46 (s, NH₂), 6.73 (s, H8), 7.08-8.05 (Ar-H), 10.90 (s, -OH); ¹³C NMR δ = 33.8, 41.3, 113.9, 123.3, 123.5, 123.9, 124.5, 125.8, 126.0, 126.4, 126.9, 127.3, 128.3, 130.9, 132.2, 132.9, 136.2, 136.7, 143.0, 144.6, 154.2, 162.3.

2-Amino-5-(4-chlorophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5b**): White solid; IR (KBr) (ν_{max} , cm⁻¹): 3328, 1647, 3057, 1247, 751; ¹H NMR δ = (ppm) 3.14 (d, 1H, H-6, J = 13.3Hz), 3.23-3.30 (m, 1H, H-6); 4.26 (d, 1H, H-5, J = 6.7 Hz), 6.47 (s, NH₂), 6.73 (s, H8), 7.03-8.07 (Ar-H), 10.90 (-OH); ¹³C NMR δ = 33.8, 41.3, 113.2, 123.3, 123.6, 123.9, 124.5, 125.8, 126.0, 126.2, 126.9, 127.3, 128.0, 128.3, 130.9, 132.2, 132.7, 132.9, 136.2, 136.7, 143.0, 144.6, 154.2, 162.3.

2-Amino-5,6-dihydro-7-naphthyl-5-p-tolylquinazolin-4-ol (**5c**): Brownish yellow solid; IR (KBr) (ν_{max} , cm⁻¹): 3376, 1654, 3057, 1227, 1342; ¹H NMR δ = (ppm) 2.16 (-CH₃), 3.10 (d, 1H, H-6, J = 13.2 Hz), 3.20-3.29 (m, 1H, H-6), 4.21 (d, 1H, H-5, J = 6.8 Hz), 6.50 (s, NH₂), 6.71 (s, 8H), 6.96-8.05 (Ar-H), 10.96 (-OH); ¹³C NMR δ = 20.4 (-CH₃) 33.6, 113.6, 120.2, 123.3, 124.0, 124.5, 125.8, 126.2, 126.5, 126.7, 126.9, 127.7, 128.3, 128.5, 130.7, 132.7, 132.8, 134.9 and C-6 merged with DMSO signal.

2-Amino-5-(3-chlorophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5d**): Yellow Solid; IR (KBr) (ν_{max} , cm⁻¹): 3372, 1654, 3063, 1287, 1408, 746; ¹H NMR δ = (ppm) 3.17 (d, 1H, H-6, J = 13.2 Hz), 3.23-3.25 (m, 1H, H-6), 4.26 (d, 1H, H-5, J = 6.8 Hz), 6.41 (s, NH₂), 6.73 (s, 8H), 7.09-8.08 (Ar-H), 10.72 (-OH); ¹³C NMR δ = 35.3, 43.7, 113.5, 123.5, 123.9, 124.4, 126.5, 126.6, 126.9, 127.3, 127.4, 128.0, 129.0, 132.8, 133.5, 135.1, 135.7, 140.8, 154.7, 163.1.

2-Amino-5-(2-chlorophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5e**): Yellow Solid; IR (KBr) (ν_{max} , cm⁻¹): 3341, 1646, 3052, 1247, 1414, 749; ¹H NMR δ = (ppm) 3.10 (d, 1H, H-6, J = 13.2 Hz), 3.18-3.20 (m, 1H, H-6), 4.20 (d, 1H, H-5, J = 6.8 Hz), 6.46 (s, NH₂), 6.73 (s, 8H), 6.72-8.07 (Ar-H), 10.90 (-OH); ¹³C NMR δ = 32.3, 113.2, 123.2, 123.6, 124.4, 126.5, 126.8, 127.4, 127.5, 127.8, 128.1, 128.2, 128.3, 129.2, 129.5, 132.2, 132.4, 132.7, 1330, 136.3, 140.2, 142.5, 155.1, 162.2.

2-Amino-5,6-dihydro-7-naphthyl-5-(3-nitrophenyl)quinazolin-4-ol (**5f**): Brownish Solid; IR (KBr) (ν_{max} , cm⁻¹): 3398,

1651, 3057, 1216, 1375, 1498; ^1H NMR = (ppm) 3.12 (d, 1H, H-6, J = 13.6 Hz), 3.22-3.29 (m, 1H, H-6), 4.25 (d, 1H, H-5, J = 6.8 Hz), 6.67 (s, NH_2), 6.73 (s, 8H), 7.18-8.07 (Ar-H), 10.92 (-OH); ^{13}C NMR = 33.4, 113.6, 123.3, 123.8, 124.6, 125.9, 126.4, 124.5, 127.8, 128.1, 129.4, 129.8, 130.2, 130.9, 132.9, 136.0, 143.0, 144.0, 155.2, 162.4.

2-Amino-5,6-dihydro-7-naphthyl-5-(4-nitrophenyl)quinazolin-4-ol (**5g**): Yellow Solid; IR (KBr) (cm^{-1}): 3358, 1661, 3052, 1281, 1344, 1514; ^1H NMR = (ppm) 3.10 (d, 1H, H-6, J = 13.6 Hz), 3.22-3.24 (m, 1H, H-6); 4.25 (d, 1H, H-5, J = 6.8 Hz), 6.41 (s, NH_2), 6.73 (s, 8H), 7.24-8.06 (Ar-H), 10.82 (-OH); ^{13}C NMR = 33.2, 113.8, 123.3, 123.8, 124.6, 125.9, 126.2, 126.4, 126.5, 127.3, 127.8, 128.1, 128.4, 129.2, 130.2, 130.9, 136.0, 143.0, 144.0, 155., 162.4, C-6 merged with DMSO.

2-Amino-5-(4-methoxyphenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5h**): Brownish Solid; IR (KBr) (cm^{-1}): 3339, 1650, 3056, 1247, 1298; ^1H NMR = (ppm) 2.26 (CH_3) 3.10 (d, 1H, H-6, J = 13.6), 3.24-3.19 (m, 1H, H-6), 4.21 (d, 1H, H-5, J = 6.6 Hz), 6.38 (s, NH_2), 6.73 (s, 8H), 6.96-8.05 (Ar-H), 10.69 (-OH); ^{13}C NMR = 20.7 (- OCH_3), 33.6, 106.8, 123.3, 123.4, 123.9, 124.4, 126.4, 126.5, 126.8, 127.3, 127.8, 128.0, 128.3, 128.5, 132.7, 132.9, 134.8, 141.5, 142.9, 154.9, 162.5, C-6 merged with DMSO.

2-Amino-5-(4-bromophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5i**): Yellow crystalline Solid; IR (KBr) (cm^{-1}): 3335, 1645, 3057, 1230, 1350, 557; ^1H NMR = (ppm) 3.12-3.24 (m, 1H, H-6), 3.15 (d, 1H, H-6, J = 13.6 Hz), 4.23 (d, 1H, H-5, J = 6.8 Hz), 6.44 (s, NH_2), 6.73 (s, 8H), 7.12-8.32 (Ar-H), 10.75 (-OH); ^{13}C NMR = 113.1, 123.0, 124.9, 125.2, 125.5, 126.1, 126.5, 127.9, 128.6, 129.8, 130.2, 132.7, 133.2, 136.0, 141.3, 143.8, 144.1, 144.6, 152.9, 160.3. C-5 and C-6 merged with DMSO signal.

2-Amino-5-(4-fluorophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5j**): White solid; IR (KBr) (cm^{-1}): 3346, 1652, 3052, 1384, 1090; ^1H NMR = (ppm) 3.15 (d, 1H, H-6, J = 13.2 Hz), 3.22-3.52 (m, 1H, H-6), 4.24 (d, 1H, H-5, J = 6.8 Hz), 6.50 (s, NH_2), 6.73 (s, 8H), 7.19-8.09 (Ar-H), 11.10 (-OH); ^{13}C NMR = 33.6, 113.8, 123.4, 124.5, 126.2, 126.6, 127.3, 127.7, 128.0, 128.2, 128.3, 128.8, 130.7, 132.7, 132.9, 136.3, 136.6, 136.9, 142.9, 152.0, 162.4 and C-6 merged with DMSO signal.

2-Amino-5-(3-bromophenyl)-5,6-dihydro-7-(naphthalen-2-yl)quinazolin-4-ol (**5k**): Brown solid; IR (KBr) (cm^{-1}): 3378, 1631, 3056, 1215, 1380, 620; ^1H NMR = (ppm) 2.98 (d, 1H, H-6, J = 13.2 Hz), 3.23-3.31 (m, 1H, H-6), 4.65 (d, 1H, H-5, J = 6.6 Hz), 6.47 (s, NH_2), 6.77 (s, 8H), 6.96-7.97 (Ar-H), 10.79 (-OH); ^{13}C NMR = 33.5, 113.4, 123.3, 123.4, 123.6, 124.6, 124.9, 125.9, 126.2, 126.4, 126.5, 126.9, 127.3, 127.7, 127.9, 128.1, 128.2, 128.4, 128.7, 130.3, 130.6, 131.1, 132.2, 132.8, 133.6, 133.6, 143.0, 143.5, 154.2, 158.0 and C-6 merged DMSO signal.

2-Amino-5,6-dihydro-7-naphthyl-5-(2-nitrophenyl)quinazolin-4-ol (**5l**): Yellowish red crystal; IR (KBr) (cm^{-1}): 3367, 1652, 2922, 1269; ^1H NMR = (ppm) 3.18 (d, 1H, H-6, J = 13.3 Hz), 3.22-3.27 (m, 1H, H-6), 4.26 (d, 1H, H-5, J = 6.7 Hz), 6.46 (s, NH_2), 6.74 (s, 8H), 6.46-8.05 (Ar-H), 10.90 (-OH); ^{13}C NMR = 113.5, 123.7, 128.2, 129.3, 129.5, 129.9, 130.9, 141.3, 146.9, 149.9, 153.6, 155.6, 158.1 and C-5 and C-6 merged with DMSO signal.

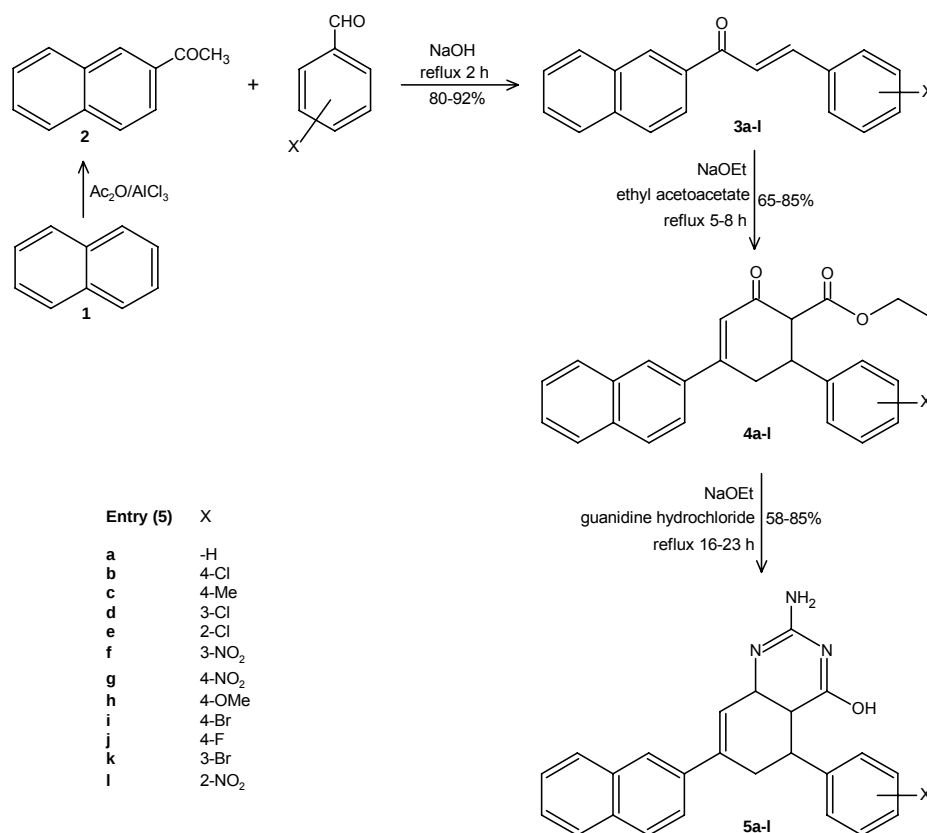
Acknowledgements

We thank NMR Research Centre, Indian Institute of Science, Bangalore for NMR spectral measurements and S.S. is grateful to the Cavinkare Research Centre, Chennai for Research Fellowship.

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Scheme 1

Table 1. The molecular formula, yield, melting point and reaction time

Entry	Molecular formula	Yield (%)	Melting point (°C)	Time (h)
5a	C ₂₄ H ₁₉ N ₃ O	90	189-192	22
5b	C ₂₄ H ₁₈ ClN ₃ O	82	184-186	20
5c	C ₂₅ H ₂₁ N ₃ O	60	184-187	18
5d	C ₂₄ H ₁₈ ClN ₃ O	55	192-195	17
5e	C ₂₄ H ₁₈ ClN ₃ O	65	186-189	21
5f	C ₂₄ H ₁₈ N ₄ O ₃	72	199-202	23
5g	C ₂₄ H ₁₈ N ₄ O ₃	85	192-194	20
5h	C ₂₅ H ₂₁ N ₃ O ₂	91	187-190	18.5
5i	C ₂₄ H ₁₈ BrN ₃ O	55	182-184	16
5j	C ₂₄ H ₁₈ FN ₃ O	45	212-215	18
5k	C ₂₄ H ₁₈ BrN ₃ O	50	202-204	21
5l	C ₂₄ H ₁₈ N ₄ O ₃	72	198-204	23

Table 2. Elemental composition and molecular weight

Entry	Molecular weight	Elemental analysis					
		C	C*	H	H*	N	N*
5a	365.43	78.61	78.86	5.94	5.22	10.93	11.52
5b	399.87	72.99	72.08	4.32	4.56	10.01	10.50
5c	379.45	79.32	79.12	5.44	5.60	11.91	11.06
5d	399.87	72.22	72.10	4.67	4.52	10.87	10.53
5e	399.87	72.44	72.12	4.01	4.53	10.07	10.52
5f	410.42	70.65	70.25	4.03	4.41	13.04	13.64
5g	410.42	70.89	70.22	4.87	4.40	13.15	13.66
5h	395.45	75.02	75.91	5.65	5.37	10.02	10.62
5i	444.32	64.00	64.85	4.44	4.09	9.88	9.43
5j	383.42	75.87	75.11	4.04	4.78	9.79	9.45
5k	444.32	64.02	64.89	4.43	4.05	9.96	9.45
5l	410.42	70.90	70.25	4.87	4.41	13.15	13.64

* Calculated value