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ARTICLE

Domino synthesis of pyrimido and imidazoquinazolinones

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Abstract

A simple method for the synthesis of *N*-alkyl-2-arylquinazolin-4-amines, methyl 4-((2-arylquinazolin-4-yl)amino) butanoates, 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones, and 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones has been described. It involves a simple reaction of *N*-(2-cyanophenyl)-substitutedbenzimidoyl chlorides with alkylamine, γ-aminobutyric acid, β-alanine, L-alanine, and glycine methyl esters hydrochloride in acetonitrile to afford the desired compounds after a series of instantaneous reactions that include Dimroth rearrangement. The reaction involves reflux for 12 hours, simple addition of reagents to an in situ generated benzimidoyl chloride, and simple workup, to form 21 examples of pure compounds in high yields. The active intermediate *N*-(2-cyanophenyl)-substitutedbenzimidoyl chlorides were formed by the reaction of *N*-(2-cyanophenyl)-substitutedbenzamides with thionyl chloride in a *one-pot* strategy. The alternative method described for this preparation deals with an exhausting multistep reactions starting from anthranilic acid.

1 | INTRODUCTION

Domino synthesis is a growing field in organic chemistry that execute the principles of sustainability (green chemistry). It involves the synthesis of complex structures by the addition of two or more active substrates and the formation or cleavage of two or more bonds in a single operation without isolation of intermediates, minimal time, maximum selectivity, and high atom economy.[1]

Imidoyl chloride[2] intermediates are used extensively in organic synthesis because of its increased reactivity. This reactivity is centered around the electrophilic and nucleophilic displacement and elimination of the chloride group. Imidoyl chloride is used in the synthesis of imidates, thioimidates, imidoyl cyanides, and imidoyl isothiocyanates by the reaction of imidoyl chloride with alcohols, thiols, amines, and thiocyanates.[2–6] Several named reactions Gattermann,[7] Vilsmeier-Haack reaction,[8] and Houben-Hoesch reaction[9] use imidoyl chloride to attack arenes and form aryl ketones by Freidal Craft acylation reaction. Also, imidoyl chloride is used in peptide synthesis via amidine intermediates.[10] The undo-use of imidoyl chorides could be due to the following obstacles: imidoyl chloride derivatives are prepared by the reaction of amides with chlorinating agents suffers from the formation of inactive iminium salts. Imidoyl chloride is very reactive and reacts easily with moisture. The chlorine atom of imidoyl chloride could be easily eliminated and leave it in the form of nitrile. Imidoyl chlorides having α-hydrogens could be easily isomerized. These complications make the attempts to isolate and store imidoyl chlorides for long period difficult; therefore, these compounds are prepared in situ without further purifications.

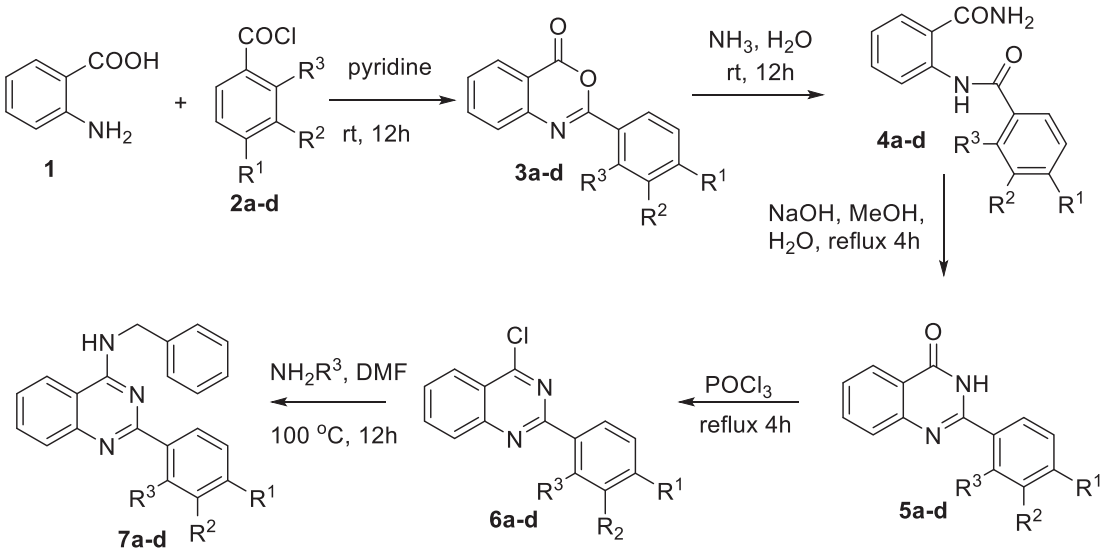
In continuation of our interest in the preparation of complex structures by Domino strategy, we found it interesting to prepare benzimidoyl chlorides as active intermediates and directly use these to prepare a series of *N*-alkyl 2-aryl quinazolin-4-amines, methyl 4-((2-arylquinazolin-4-yl)amino) butanoates, 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones, and 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones.

2 | DISCUSSION

The target compound *N*-alkyl 2-aryl quinazolin-4-amines could be easily prepared by the reaction of benzyl amine with chloroquinazoline in DMF for at 100°C for 12 hours. This is the most reliable classical method for this preparation; however, this method suffers from two aspects: first, amines used for this reaction should be of high boiling points such as benzyl amine (other amines normally of low boiling point did not give the desired product); second, we realize in Scheme 1 that this reliable method of preparation of chloroquinazoline from anthranilic acid occurs in a five-step sequential reactions and sixth step for the reaction with benzyl amines, Scheme 1.[11,12]

Following the main definition of domino reaction reveals synthesis of complex structures by the addition of two or more active substrates and the formation or cleavage of two or more bonds in a single operation without isolation of intermediates, minimal time, maximum selectivity, and high atom economy.[1] We found it interesting to prepare *N*-alkyl-2-arylquinazolin-4-amines **7a-d** and **10b** from the corresponding *N*-(2-cyanophenyl)-substitutedbenzamides **8a-d**. The reaction of *N*-(2-cyanophenyl)-substitutedbenzamides **8a-d** with thionyl chloride at 70°C for 8 hours afforded the in situ generated free benzimidoyl chlorides **9a-d** that was reacted in a one pot strategy with alkyl amines, benzyl amine, and allyl amine in acetonitrile (ACN) under reflux condition for 12 hours to afford the desired product in 51% to 70% yield, Scheme 2. The major advantages of this protocol are short reaction time, mild condition, simple work up, high yields, pure products based on *one-pot* domino reaction. We should note that the presence of unsubstituted benzamides or chloro-substituted benzamides **8a-d** were selected carefully to facilitate the Dimroth rearrangement and will be explained later.

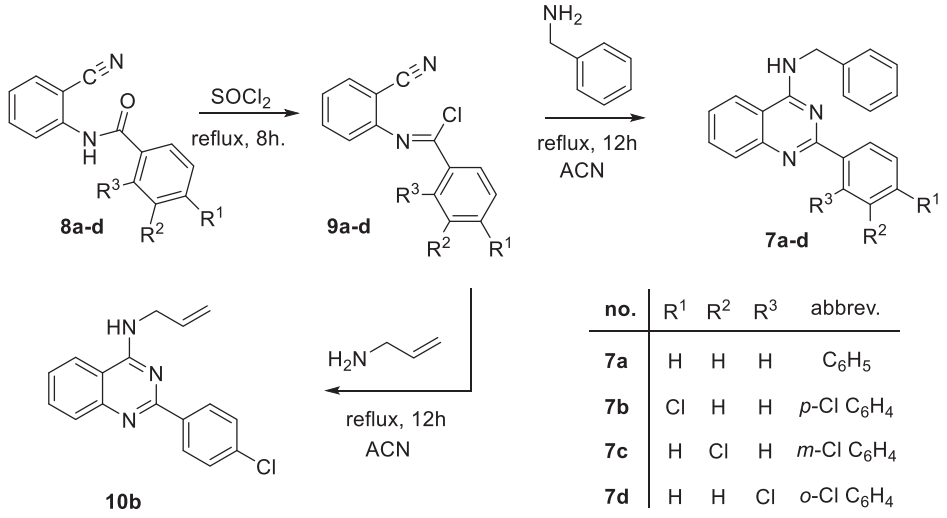
The identity of *N*-benzyl-2-arylquinazolin-4-amines **7a-d** is based on ^{1}H and ^{13}C NMR spectroscopy and physicochemical analysis beside equivocal synthesis using a classical method from 4-chloro-2-phenylquinazolines **6a-d**. Thus, the ^{1}H NMR spectrum of **7a** exhibits doublet, and broad singlet signals at δ 5.03 and 6.13 ppm are typically associated with CH_2 and NH groups. The doublet signal of CH_2 group confirms the Dimroth protocol and the location of benzyl substituent at position 4 of the quinazoline ring. The ^{1}H NMR spectrum of **7a** also exhibits doublet, doublet, multiplet, multiplet, and multiplet signals at δ 8.63, 7.99, 7.75 to 7.70, 7.54 to 7.48, and 7.42 to 7.34 ppm for 14 aromatic protons. The ^{13}C NMR spectrum of **7a** reveals signals at δ 159.3, 159.0, 150.1, 138.6, 135.7, 113.9, and 45.7 ppm associated with two C═N groups, four quaternary aromatic carbons, and CH_2 group, respectively.



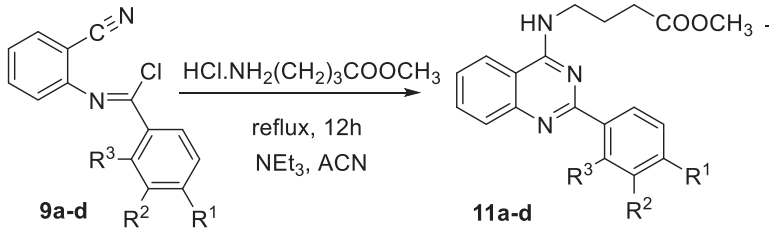
no.	R^1	R^2	R^3	abbrev.
7a	H	H	H	C_6H_5
7b	Cl	H	H	*p*-Cl C_6H_4
7c	H	Cl	H	*m*-Cl C_6H_4
7d	H	H	Cl	*o*-Cl C_6H_4

SCHEME 1 Classical preparation of *N*-benzyl-2-aryl-quinazolin-4-amines **7a-d**

SCHEME 2 Preparation of *N*-alkyl-2-aryl-quinazolin-4-amines **7a-d** and **10b** from *N*-(2-cyanophenyl)-substitutedbenzamides **8a-d** and **8b**, respectively



no.	R^1	R^2	R^3	abbrev.
7a	H	H	H	C_6H_5
7b	Cl	H	H	*p*-Cl C_6H_4
7c	H	Cl	H	*m*-Cl C_6H_4
7d	H	H	Cl	*o*-Cl C_6H_4



no.	R^1	R^2	R^3	abbrev.
11a	H	H	H	C_6H_5
11b	Cl	H	H	*p*-Cl C_6H_4
11c	H	Cl	H	*m*-Cl C_6H_4
11d	H	H	Cl	*o*-Cl C_6H_4

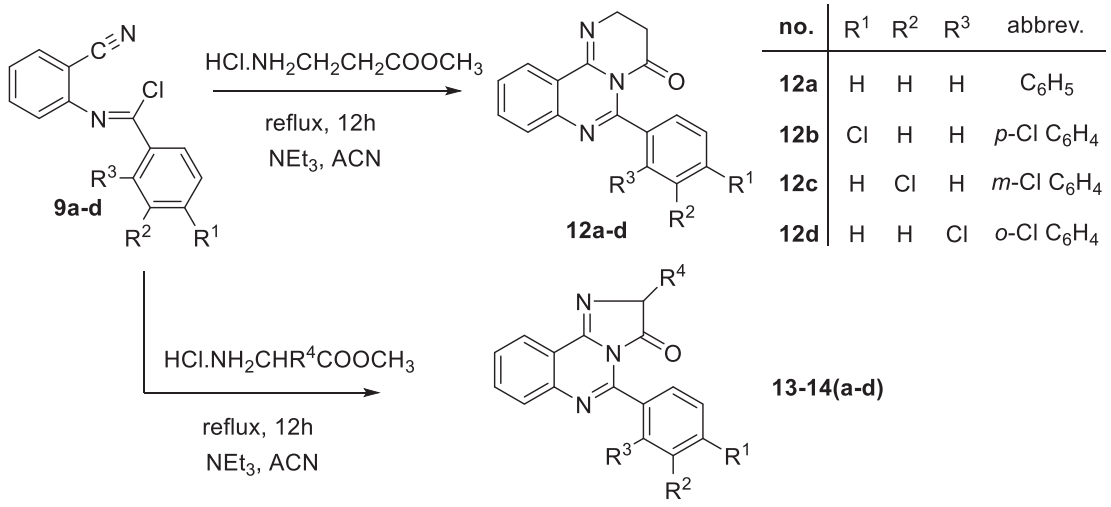
SCHEME 3 Preparation of methyl 4-((2-arylquinazolin-4-yl)amino) butanoates **11a-d**

Similarly, the reaction of the in situ generated benzimidoyl chlorides **9a-d** with γ-amino butyric acid methyl ester hydrochloride in the presence of triethyl amine in acetonitrile under reflux condition and gave methyl 4-((2-arylquinazolin-4-yl)amino) butanoates **11a-d** in high yields, Scheme 3.

Our next target was the application of this domino protocol to prepare a number of more complex structures; 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones **12a-d** and 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **13-14(a-d)**. Thus, the reaction of benzimidoyl chlorides **9a-d** with β-alanine methyl ester hydrochloride in the presence of triethylamine in acetonitrile under reflux condition and gave 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones **12a-d** (Scheme 4), while the reaction of benzimidoyl chlorides **9a-d** with glycine or L-alanine methyl ester hydrochloride in the presence of triethyl amine in acetonitrile under reflux condition gave 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-one **13a-d** and 5-aryl-2-methylimidazo[1,2-*c*]quinazolin-3(2*H*)-one **14a-d** in excellent yields (Scheme 4).

The identity of 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones **12a-d**, 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **13a-d**, and 5-aryl-2-methylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **14a-d** is based on ^{1}H and ^{13}C NMR spectroscopy and physicochemical analysis. Thus, the ^{1}H NMR spectrum of **12a** reveals two triplet signals at δ 4.21 and 2.71 ppm corresponding to two CH_2 groups. The ^{1}H NMR spectrum also exhibits doublet, triplet, doublet, and multiplet signals at δ 8.68, 7.85, 7.77, and 7.68-7.53 ppm for nine aromatic protons. The ^{1}H NMR spectrum of **12a** shows the absence of both: the ester methyl group and NH group that suggests the cyclization occurrence. The ^{13}C NMR spectrum of **12a** reveals signals at δ 175.4, 157.7153.1, 146.1, 133.8, 119.6, 46.7, and 29.7 ppm associated with C═O, 2C═N, three quaternary aromatic carbons, NCH_2 and CH_2CO, respectively.

The *one pot* domino reaction for the preparation of 5-phenylimidazo[1,2-*c*]quinazolin-3(2*H*)-one (**13a**) could be explained as follows: a first step addition of free glycine methyl ester to imidoyl group carbon and gave the methyl 2-[*N*-(2-cyanophenyl)benzimidamido] acetate I. Next, an intramolecular *N*-addition of the glycine residue NH at the nitrile group to produce methyl 2-(4-imino-2-phenylquinazolin-3(4*H*)-yl) acetate II. The subsequent Dimroth rearrangement via ring opening–ring closing type of mechanisms proceeds by free amino acid nucleophilic attack at C2 of the quinazoline ring and the consequent ring opening giving intermediate III. The aryl group at position 2 of intermediate II (phenyl group



no.	R^1	R^2	R^3	abbrev.
12a	H	H	H	C_6H_5
12b	Cl	H	H	*p*-Cl C_6H_4
12c	H	Cl	H	*m*-Cl C_6H_4
12d	H	H	Cl	*o*-Cl C_6H_4

no.	R^1	R^2	R^3	R^4	abbrev.	no.	R^1	R^2	R^3	R^4	abbrev.
13a	H	H	H	H	C_6H_5	**14a**	H	H	H	CH_3	C_6H_5
13b	Cl	H	H	H	*p*-Cl C_6H_4	**14b**	Cl	H	H	CH_3	*p*-Cl C_6H_4
13c	H	Cl	H	H	*m*-Cl C_6H_4	**14c**	H	Cl	H	CH_3	*m*-Cl C_6H_4
13d	H	H	Cl	H	*o*-Cl C_6H_4	**14d**	H	H	Cl	CH_3	*o*-Cl C_6H_4

SCHEME 4 Preparation of 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones **12a-d**, 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **13a-d**, and 5-aryl-2-methylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **14a-d**

or chlorophenyl groups) has the advantage to facilitate the previous Dimroth rearrangement; however, the presence of phenyl ring attached with electron donating group (MeO) specially at position 4 will decrease the electrophilicity of C2 of the quinazoline ring in intermediate II and prohibit the dimroth rearrangement. The following step is tautomerization together with amino-imino groups flipping and gave IV. Next, an amino group attacks at the amidine function group to give methyl [(2-phenylquinazolin-4-yl) amino] acetate V; this structure is formed in the case of benzyl amine and γ-amino butyric acid methyl ester hydrochloride reaction with benzimidoyl chlorides **9a-d** to afford **7a-d** and **11a-d**, respectively. The reaction continues and the intermediate V reveals NH group at position 3 of the quinazoline ring capable of attacking the amino acid ester group to finally give the expected product **13a** (Scheme 5). Similar Dimroth rearrangement results were obtained as reported in literature.[13–17]

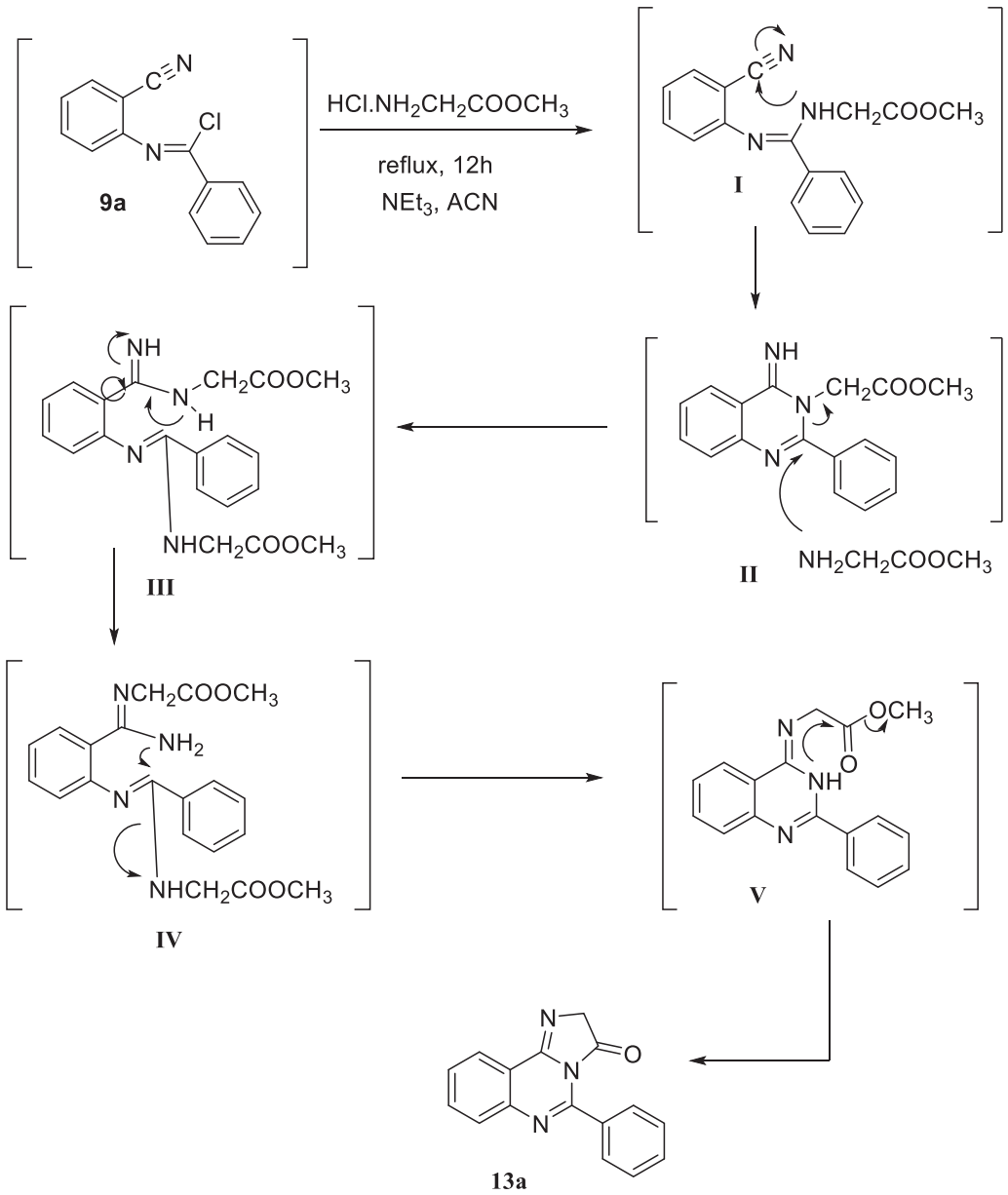
3 | EXPERIMENTAL SECTION

3.1 | General procedures

Solvents were purified and dried by standard procedures. The boiling range of the petroleum ether used was 40°C to 60°C for thin-layer chromatography (TLC) silica gel 60 F_{254} plastic plates (E. Merck, layer thickness, 0.2 mm) were used, detected by UV absorption. The solvent system used was ethyl acetate- pet ether 3:1. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus, and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 75.5 MHz, respectively, on a Bruker AC 400 in $CDCl_3$ and DMSO-d_6 solution with tetramethylsilane as an internal standard. The NMR analyses were performed at the Chemistry Department, Sohag University, Sohag, Egypt. The starting substituted *N*-(2-cyanophenyl)benzamides **8a-d** were prepared according to the reported method.[18] Also, starting compounds **1-6** were prepared according to reported literature.[11,12]

3.1.1 | General procedures for preparation of 4-chloro-2-aryl-3,4-dihydroquinazolines 6a-d

Phosphoryl chloride (30 mL) was added to quinazolin-4-one derivatives **5a-d** (20 mmol); the reaction mixture was stirred at 5°C for 0.5 hour and then refluxed for 6 hours. The reaction mixture was evaporated under reduced pressure, cooled, and dissolved in 20 mL of



SCHEME 5 Rational preparation of 5-phenylimidazo[1,2-*c*]quinazolin-3(2*H*)-one **13a**

methylene chloride. The methylene chloride solution was washed several times with ice-cold ammonia solution 5% (20 mL) then dried over sodium sulfate. The methylene chloride solution was filtered, evaporated, and gave chloroquinazoline derivatives **6a-d** in a pure state and was used without further purification.[11,12]

3.1.2 | General procedure for the preparation of *N*-alkyl-2-arylquinazolin-4-amines 7a-d and 10b

Method A

A mixture of 4-chloro-2-aryl-3,4-dihydro-quinazolines **6a-d** (1.0 mmol) and the appropriate amine, benzyl amine or allyl amine, were dissolved in DMF and were heated at 100°C for 12 hours. The reaction mixture was cooled and poured over H_2O to give thick white precipitate from the crude product. The reaction mixture was filtered and was crystallized from ethanol to give *N*-alkyl-2-arylquinazolin-4-amine **7a-d** in good yield.

Method B

A mixture of substituted *N*-(2-cyanophenyl) benzamides **8a-d** (1.0 mmol) and thionyl chloride (10 mL) was heated at 70°C for 8 hours. The thionyl chloride was removed under reduced pressure, and the residue was heated at 120°C under reduced pressure (50 mmHg) for 4 extra hours to give a yellowish oil of substituted *N*-(2-cyanophenyl) benzimidoyl chlorides **9a-d**, which

was not further purified. The crude oil was cooled and dissolved in dry acetonitrile; to this, acetonitrile solution was added to the appropriate amine (2.0 mmol), benzyl amine or allyl amine. The reaction mixture was refluxed for 12 hours, and the acetonitrile solvent was evaporated under reduced pressure. The crude product was crystallized from ethanol to give the pure product **7a-d** and **10b** in excellent yields.

N-Benzyl-2-phenylquinazolin-4-amine (7a)

Method A: 0.24 g, yield 78%; Method B: 0.20 g, yield 65%. White crystals, mp 156°C to 157°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.63 (2H, d, *J* = 8.0, ArH); 7.99 (1H, d, *J* = 8.0, ArH); 7.75-7.70 (2H, m, ArH); 7.54-7.48 (5H, m, ArH); 7.42-7.34 (4H, m, ArH); 6.13 (1H, bs, NH); 5.03 (2H, d, *J* = 6.0, NHC$\underline{H}_2$). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 159.3 (C═N); 159.0 (C═N); 150.1 (C_q); 138.6 (C_q); 135.7 (C_q); 132.7 (CH_{Ar}); 131.5 (CH_{Ar}); 129.6 (CH_{Ar}); 128.5 (CH_{Ar}); 128.2 (CH_{Ar}); 128.1 (CH_{Ar}); 127.9 (CH_{Ar}); 127.4 (CH_{Ar}); 125.6 (CH_{Ar}); 120.4 (CH_{Ar}); 113.9 (C_q); 45.7 (NH$\underline{C}H_2$). Anal. calcd. for $C_{21}H_{17}N_3$ (311.4): C, 81.00; H, 5.50; N, 13.49. Found: C, 80.85; H, 5.47; N, 13.32.

N-Benzyl-2-(4-chlorophenyl)quinazolin-4-amine (7b)

Method A: 0.24 g, yield 69%; Method B: 0.19 g, yield 56%. White crystals, mp 150°C to 152°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.55 (2H, d, *J* = 8.0, ArH); 7.95 (1H, d, *J* = 8.0, ArH); 7.76 (1H, t, *J* = 8.0, ArH); 7.70 (1H, d, *J* = 8.0, ArH); 7.49-7.33 (8H, m, ArH); 5.99 (1H, bs, NH); 5.02 (2H, d, *J* = 6.0, NHC$\underline{H}_2$). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 159.4 (C═N); 159.2 (C═N); 150.6 (C_q); 138.6 (C_q); 136.2 (C_q); 132.7 (CH_{Ar}); 129.8 (CH_{Ar}); 129.0 (CH_{Ar}); 128.9 (CH_{Ar}); 128.4 (CH_{Ar}); 128.0 (CH_{Ar}); 127.4 (CH_{Ar}); 125.6 (CH_{Ar}); 120.4 (CH_{Ar}); 113.6 (C_q); 45.4 (NH$\underline{C}H_2$). Anal. calcd. for $C_{21}H_{16}ClN_3$ (345.8): C, 72.93; H, 4.66; N, 12.15. Found: C, 72.81; H, 4.62; N, 12.13.

N-Benzyl-2-(3-chlorophenyl)quinazolin-4-amine (7c)

Method A: 0.17 g, yield 49%; Method B: 0.24 g, yield 70%. White crystals, mp 115°C to 116°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.60 (1H, s, ArH); 8.49 (1H, d, *J* = 8.0, ArH); 7.98 (1H, d, *J* = 8.0, ArH); 7.77-7.71 (2H, m, ArH); 7.49-7.35 (8H, m, ArH); 6.16 (1H, bs, NH); 4.99 (2H, d, *J* = 6.0, NHC$\underline{H}_2$). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 159.5 (C═N); 159.1 (C═N); 149.9 (C_q); 140.4 (C_q); 138.4 (C_q); 134.4 (C_q); 132.8 (CH_{Ar}); 130.2 (CH_{Ar}); 129.5 (CH_{Ar}); 128.9 (CH_{Ar}); 128.6 (CH_{Ar}); 128.1 (CH_{Ar}); 127.7 (CH_{Ar}); 126.6 (CH_{Ar}); 125.9 (CH_{Ar}); 120.7 (CH_{Ar}); 113.6 (C_q); 45.5 (NH$\underline{C}H_2$). Anal. calcd. for $C_{21}H_{16}ClN_3$ (345.8): C, 72.93; H, 4.66; N, 12.15. Found: C, 72.71; H, 4.54; N, 12.01.

N-Benzyl-2-(2-chlorophenyl)quinazolin-4-amine (7d)

Method A: 0.13 g, yield 39%; Method B: 0.18 g, yield 51%. White crystals, mp 116-117°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.51 (1H, s, ArH); 7.97 (1H, d, *J* = 8.0, ArH); 7.78 (1H, t, *J* = 8.0, ArH); 7.71 (1H, d, *J* = 8.0, ArH); 7.51-7.30 (9H, m, ArH); 6.03 (1H, bs, NH); 5.02 (2H, d, *J* = 6.0, NHC$\underline{H}_2$). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 160.8 (C═N); 159.5 (C═N); 147.6 (C_q); 138.2 (C_q); 133.3 (C_q); 132.9 (CH_{Ar}); 131.6 (CH_{Ar}); 130.5 (CH_{Ar}); 130.3 (CH_{Ar}); 128.7 (CH_{Ar}); 128.3 (CH_{Ar}); 127.6 (CH_{Ar}); 126.9 (CH_{Ar}); 126.6 (CH_{Ar}); 121.6 (CH_{Ar}); 113.0 (C_q); 45.4 (NH$\underline{C}H_2$). Anal. calcd. for $C_{21}H_{16}ClN_3$ (345.8): C, 72.93; H, 4.66; N, 12.15. Found: C, 72.88; H, 4.62; N, 12.02.

N-Allyl-2-(4-chlorophenyl)quinazolin-4-amine (10b)

Method A: 0.25 g, yield 72%; Method B: 0.23 g, yield 69%. White crystals, mp 101°C to 102°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.60 (1H, d, *J* = 8.0, ArH); 8.56 (1H, d, *J* = 8.0, ArH); 7.91 (1H, d, *J* = 8.0, ArH); 7.72 (1H, d, *J* = 8.0, ArH); 7.67 (1H, t, *J* = 8.0, ArH); 7.53 (1H, d, *J* = 8.0, ArH); 7.45 (1H, d, *J* = 8.0, ArH); 7.40 (1H, t, *J* = 8.0, ArH); 7.25 (1H, bs, NH); 6.15-6.07 (1H, m, CH); 5.39 (1H, d, *J* = 16.0, CH_2); 5.28 (1H, d, *J* = 12.0, CH_2); 4.48-4.46 (2H, m, NHC$\underline{H}_2$). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 164.4 (C═N); 159.6 (C═N); 140.5 (C_q); 139.1 (C_q); 134.9 (CH); 132.2 (CH_{Ar}); 130.4 (C_q); 129.4 (CH_{Ar}); 128.9 (CH_{Ar}); 128.6 (CH_{Ar}); 124.5 (CH_{Ar}); 121.2 (CH_{Ar}); 117.7 (CH_2); 116.4 (C_q); 44.2 (NH$\underline{C}H_2$). Anal. calcd. for $C_{17}H_{14}ClN_3$ (295.8): C, 69.04; H, 4.77; N, 14.21. Found: C, 68.86; H, 4.53; N, 14.18.

3.1.3 | General procedure for the preparation of methyl 4-((2-arylquinazolin-4-yl)amino) butanoates 11a-d

A mixture of substituted *N*-(2-cyanophenyl) benzamides **8a-d** (1.0 mmol) and thionyl chloride (10 mL) was heated at 70°C for 8 hours. The thionyl chloride was removed under reduced pressure, and the residue was heated at 120°C under reduced pressure (50 mmHg) for 4 extra hours to give a yellowish oil of substituted *N*-(2-cyanophenyl) benzimidoyl chlorides **9a-d**. The crude oil was cooled and dissolved in dry acetonitrile; to this, acetonitrile solution was added to a solution of γ-aminobutyric acid methyl ester hydrochloride (1.0 mmol) and triethyl ethylamine (2.0 mmol) in acetonirile. The reaction mixture was refluxed for 12 hours, and the acetonitrile solvent was evaporated under reduced pressure. The crude product was crystalized from ethanol to give the pure methyl 4-((2-arylquinazolin-4-yl)amino) butanoates **11a-d**.

Methyl 4-((2-phenylquinazolin-4-yl)amino) butanoate (11a)

0.20 g, yield 63%. Whitish oil. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.60 (2H, d, *J* = 8.0, ArH); 8.03 (1H, d, *J* = 8.0, ArH); 7.85 (1H, d, *J* = 8.0, ArH); 7.72 (1H, t, *J* = 8.0, ArH); 7.57-7.49 (3H, m, ArH); 7.42 (1H, t, *J* = 8.0, ArH); 6.77 (1H, bs, NH); 3.90 (2H, q, *J* = 6.0, NHC$\underline{H}_2$); 3.68 (3H, s, OCH_3); 2.56 (2H, t, *J* = 6.0, CH_2CO); 2.21-2.14 (2H, m, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 174.4 (C═O); 159.9 (C═N); 159.7 (C═N); 147.7 (C_q); 137.0 (C_q); 133.1 (CH_{Ar}); 130.9 (CH_{Ar}); 128.7 (CH_{Ar}); 128.4 (CH_{Ar}); 126.7 (CH_{Ar}); 126.0 (CH_{Ar}); 121.6 (CH_{Ar}); 113.4 (C_q); 51.8 (OCH_3); 41.2 (NH$\underline{C}H_2$); 31.9 ($\underline{C}H_2CO$); 24.1 (CH_2). Anal. calcd. for $C_{19}H_{19}N_3O_2$ (321.4): C, 71.01; H, 5.96; N, 13.08. Found: C, 70.83; H, 5.87; N, 13.01.

Methyl 4-((2-(4-chlorophenyl)quinazolin-4-yl)amino) butanoate (11b)

0.27 g, yield 75%. White crystals, mp 110°C to 112°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.57 (2H, d, *J* = 8.0, ArH); 7.98 (1H, d, *J* = 8.0, ArH); 7.81-7.63 (2H, m, ArH); 7.58-7.50 (3H, m, ArH); 6.56 (1H, bs, NH); 3.82 (2H, q, *J* = 6.0, NHC$\underline{H}_2$); 3.66 (3H, s, OCH_3); 2.51 (2H, t, *J* = 6.0, CH_2CO); 2.16-2.08 (2H, m, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 174.4 (C═O); 159.6 (C═N); 159.2 (C═N); 149.0 (C_q); 134.4 (C_q); 132.9 (CH_{Ar}); 130.3 (CH_{Ar}); 129.5 (CH_{Ar}); 128.6 (CH_{Ar}); 127.9 (CH_{Ar}); 126.7 (CH_{Ar}); 126.0 (CH_{Ar}); 114.1 (C_q); 52.0 (OCH_3); 43.3 (NH$\underline{C}H_2$); 30.5 ($\underline{C}H_2CO$); 22.5 (CH_2). Anal. calcd. for $C_{19}H_{18}ClN_3O_2$ (355.8): C, 64.14; H, 5.10; N, 11.81. Found: C, 63.93; H, 4.92; N, 11.76.

Methyl 4-((2-(3-chlorophenyl)quinazolin-4-yl)amino) butanoate (11c)

0.30 g, yield 84%. White crystals, mp 95°C to 96°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.57 (1H, s, ArH); 8.48 (1H, d, *J* = 8.0, ArH); 7.95 (1H, d, *J* = 8.0, ArH); 7.78 (1H, d, *J* = 8.0, ArH); 7.73 (1H, t, *J* = 8.0, ArH); 7.46-7.40 (3H, m, ArH); 6.52 (1H, bs, NH); 3.85 (2H, q, *J* = 6.0, NHC$\underline{H}_2$); 3.69 (3H, s, OCH_3); 2.56 (2H, t, *J* = 6.0, CH_2CO); 2.17-2.12 (2H, m, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 174.6 (C═O); 159.8 (C═N); 158.8 (C═N); 149.0 (C_q); 140.0 (C_q); 134.4.0 (C_q); 132.9 (CH_{Ar}); 130.3 (CH_{Ar}); 129.5 (CH_{Ar}); 128.6 (CH_{Ar}); 127.9 (CH_{Ar}); 126.7 (CH_{Ar}); 126.0 (CH_{Ar}); 121.1 (CH_{Ar}); 113.7 (C_q); 51.8 (OCH_3); 41.3 (NH$\underline{C}H_2$); 32.0 ($\underline{C}H_2CO$); 24.0 (CH_2). Anal. calcd. for $C_{19}H_{18}ClN_3O_2$ (355.8): C, 64.14; H, 5.10; N, 11.81. Found: C, 63.95; H, 4.84; N, 11.63.

Methyl 4-((2-(2-chlorophenyl)quinazolin-4-yl)amino) butanoate (11d)

0.22 g, yield 62%. White crystals, mp 150°C to 151°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.54 (1H, d, *J* = 8.0, ArH); 7.96 (1H, d, *J* = 8.0, ArH); 7.75 (1H, d, *J* = 8.0, ArH); 7.71 (1H, t, *J* = 8.0, ArH); 7.49-7.39 (4H, m, ArH); 6.61 (1H, bs, NH); 3.89 (2H, q, *J* = 6.0, NHC$\underline{H}_2$); 3.61 (3H, s, OCH_3); 2.54 (2H, t, *J* = 6.0, CH_2CO); 2.16-2.09 (2H, m, CH_2). Anal. calcd. for $C_{19}H_{18}ClN_3O_2$ (355.8): C, 64.14; H, 5.10; N, 11.81. Found: C, 64.03; H, 5.07; N, 11.63.

3.1.4 | General procedure for the preparation of 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones 12a-d

Compounds 6-aryl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones **12a-d** were prepared according to the prescribed method for the preparation of methyl 4-((2-arylquinazolin-4-yl)amino) butanoates **11a-d** using β-alanine methyl ester hydrochloride instead of γ-aminobutyric acid methyl ester hydrochloride.

*6-Phenyl-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-one (12a)*

0.16 g, yield 58%. White crystals, mp 230°C to 231°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.68 (1H, d, *J* = 8.0, ArH); 7.85 (1H, t, *J* = 8.0, ArH); 7.77 (1H, d, *J* = 8.0, ArH); 7.68-7.53 (6H, m, ArH); 4.21 (2H, q, *J* = 6.0, NCH_2); 2.71 (2H, q, *J* = 6.0, CH_2CO). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 175.4 (C═O); 157.7 (C═N); 153.1 (C═N); 146.1 (C_q); 135.5 (CH_{Ar}); 133.8 (C_q); 130.7 (CH_{Ar}); 129.2 (CH_{Ar}); 128.3 (CH_{Ar}); 128.1 (CH_{Ar}); 127.5 (CH_{Ar}); 127.3 (CH_{Ar}); 119.6 (C_q); 46.7 (N$\underline{C}H_2$); 29.7 ($\underline{C}H_2CO$). Anal. calcd. for $C_{17}H_{13}N_3O$ (275.3): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.05; H, 4.76; N, 15.18.

*6-(3-Chlorophenyl)-2,3-dihydro-4*H*-pyrimido[1,2-*c*] quinazolin-4-one (12b)*

0.23 g, yield 74%. White crystals, mp 178°C to 179°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.65 (1H, d, *J* = 8.0, ArH); 7.84 (1H, t, *J* = 8.0, ArH); 7.74 (1H, d, *J* = 8.0, ArH); 7.60-7.52 (5H, m, ArH); 4.21 (2H, q, *J* = 6.0, NCH_2); 2.71 (2H, q, *J* = 6.0, CH_2CO). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 175.2 (C═O); 157.6 (C═N); 152.1 (C_q); 145.9 (C_q); 137.2 (C_q); 135.5 (CH_{Ar}); 132.1 (C_q); 129.6 (CH_{Ar}); 129.5 (CH_{Ar}); 128.5 (CH_{Ar}); 127.5 (CH_{Ar}); 127.3 (CH_{Ar}); 119.6 (C_q); 46.7 (N$\underline{C}H_2$); 29.7 ($\underline{C}H_2CO$). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.83; H, 3.87; N, 13.46.

*6-(3-Chlorophenyl)-2,3-dihydro-4*H*-pyrimido[1,2-*c*] quinazolin-4-one (12c)*

0.22 g, yield 70%. White crystals, mp 210°C to 211°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.64 (1H, d, *J* = 8.0, ArH); 7.84 (1H, t, *J* = 8.0, ArH); 7.74 (1H, d,

J = 8.0, ArH); 7.64 (1H, s, J = 8.0, ArH); 7.60-7.46 (4H, m, ArH); 4.21 (2H, q, J = 6.0, NCH_2); 2.72 (2H, q, J = 6.0, CH_2CO). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.78; H, 3.83; N, 13.45.

6-(2-Chlorophenyl)-2,3-dihydro-4H-pyrimido[1,2-c] quinazolin-4-one (12d)

0.17 g, yield 56%. White crystals, mp 178°C to 179°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.66 (1H, d, J = 8.0, ArH); 7.85 (1H, t, J = 8.0, ArH); 7.72 (1H, d, J = 8.0, ArH); 7.61 (1H, d, J = 8.0, ArH); 7.63-7.52 (4H, m, ArH); 4.21 (2H, q, J = 6.0, NCH_2); 2.73 (2H, q, J = 6.0, CH_2CO). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.79; H, 3.83; N, 13.41.

3.1.5 | General procedure for the preparation of 5-aryl-2-substitutedimidazo[1,2-*c*]quinazolin-3(2*H*)-ones 13a-d and 14a-d

Compounds 5-arylimidazo[1,2-*c*]quinazolin-3(2*H*)-ones **13a-d** and 5-aryl-2-methyl imidazo[1,2-*c*]quinazolin-3(2*H*)-ones **14a-d** were prepared according to the prescribed method for the preparation of methyl 4-((2-arylquinazolin-4-yl)amino) butanoates **11a-d** using glycine methyl ester hydrochloride or L-alanine methyl ester hydrochloride, respectively instead of γ-aminobutyric acid methyl ester hydrochloride.

5-Phenylimidazo[1,2-c]quinazolin-3(2H)-one (13a)

0.22 g, yield 86%. White crystals, mp 236°C to 237°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.47 (1H, d, J = 8.0, ArH); 7.93 (1H, t, J = 8.0, ArH); 7.89 (1H, d, J = 8.0, ArH); 7.75 (2H, d, J = 8.0, ArH); 7.68-7.61 (4H, m, ArH); 4.56 (2H, s, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 185.7 (C═O); 171.2 (C═N); 159.3(C═N); 150.1 (C_q); 147.0 (CH_{Ar}); 136.5 (C_q); 133.8 (CH_{Ar}); 133.1 (CH_{Ar}); 131.0 (CH_{Ar}); 129.5 (CH_{Ar}); 128.0 (CH_{Ar}); 127.2 (CH_{Ar}); 125.8 (CH_{Ar}); 115.4 (C_q); 52.8 (CH_2). Anal. calcd. for $C_{16}H_{11}N_3O$ (261.3): C, 73.55; H, 4.24; N, 16.08. Found: C, 73.44; H, 4.15; N, 15.86.

5-(4-Chlorophenyl)imidazo[1,2-c]quinazolin-3(2H)-one (13b)

0.22 g, yield 74%. White crystals, mp 206°C to 207°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.46 (1H, d, J = 8.0, ArH); 7.93 (1H, t, J = 8.0, ArH); 7.87 (1H, d, J = 8.0, ArH); 7.74 (2H, d, J = 8.0, ArH); 7.64 (1H, t, J = 8.0, ArH); 7.59 (2H, d, J = 8.0, ArH); 4.55 (2H, s, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 186.6 (C═O); 171.0 (C═N); 159.8 (C═N); 150.5(C_q); 145.4 (CH_{Ar}); 136.3 (C_q); 133.4 (C_q); 133.1 (CH_{Ar}); 131.7 (CH_{Ar}); 129.5 (CH_{Ar}); 128.6 (CH_{Ar}); 127.5 (CH_{Ar}); 125.5 (CH_{Ar}); 115.2 (C_q); 53.5 (CH_2). Anal. calcd. for $C_{16}H_{10}ClN_3O$ (295.7): C, 64.98; H, 3.41; N, 14.21. Found: C, 64.82; H, 3.38; N, 14.04.

5-(3-Chlorophenyl)imidazo[1,2-c]quinazolin-3(2H)-one (13c)

0.18 g, yield 62%. White crystals, mp 214°C to 215°C. ^{1}H NMR spectrum, (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 8.27 (1H, d, J = 8.0, ArH); 8.02 (1H, t, J = 8.0, ArH); 7.94 (1H, s, ArH); 7.85 (2H, t, J = 8.0, ArH); 7.75-7.69 (2H, m, ArH); 7.62 (1H, t, J = 8.0, ArH); 4.71(2H, s, CH_2). ^{13}C NMR spectrum, (75.0 MHz, DMSO-d_6), δ, ppm: 185.1 (C═O); 171.3 (C═N); 150.2 (C═N); 147.3 (C_q); 136.8 (CH_{Ar}); 135.7 (C_q); 133.8 (C_q); 131.3 (CH_{Ar}); 131.1 (CH_{Ar}); 128.8 (CH_{Ar}); 128.3 (CH_{Ar}); 127.6 (CH_{Ar}); 127.1 (CH_{Ar}); 115.8 (C_q); 53.9 ($N\underline{C}H_2$). Anal. calcd. for $C_{16}H_{10}ClN_3O$ (295.7): C, 64.98; H, 3.41; N, 14.21. Found: C, 64.82; H, 3.29; N, 14.06.

5-(2-Chlorophenyl)imidazo[1,2-c]quinazolin-3(2H)-one (13d)

0.18 g, yield 60%. White crystals, mp 181°C to 182°C. ^{1}H NMR spectrum, (400 MHz, DMSO), δ, ppm (J, Hz): 8.32 (1H, d, J = 8.0, ArH); 8.05 (1H, t, J = 8.0, ArH); 7.86 (1H, d, J = 8.0, ArH); 7.79-7.56 (5H, m, ArH); 4.38 (2H, s, CH_2). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 183.8 (C═O); 171.1 (C═N); 148.7 (C_q); 147.2 (C_q); 136.5 (CH_{Ar});; 132.4 (CH_{Ar}); 131.9 (C_q); 130.4 (CH_{Ar}); 129.8 (CH_{Ar}); 128.8 (CH_{Ar}); 128.4 (CH_{Ar}); 128.0 (CH_{Ar}); 127.6 (CH_{Ar}); 122.8 (CH_{Ar}); 115.8 (C_q); 51.9 ($N\underline{C}H_2$). Anal. calcd. for $C_{16}H_{10}ClN_3O$ (295.7): C, 64.98; H, 3.41; N, 14.21. Found: C, 64.65; H, 3.29; N, 14.03.

2-Methyl-5-phenylimidazo[1,2-c]quinazolin-3(2H)-one (14a)

0.13 g, yield 49%. White crystals, mp 230°C to 231°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.40 (1H, d, J = 8.0, ArH); 7.90-7.81 (2H, m, ArH); 7.75-7.73 (2H, m, ArH); 7.63-7.56 (4H, m, ArH); 4.79 (1H, q, J = 6.0, CH); 1.17 (3H, d, J = 6.0, CH_3). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 188.0 (C═O); 170.8 (C═N); 159.0 (C═N); 150.8 (C_q); 147.3 (CH_{Ar}); 136.5 (C_q); 134.1 (CH_{Ar}); 133.3 (CH_{Ar}); 131.3 (CH_{Ar}); 129.4 (CH_{Ar}); 128.4 (CH_{Ar}); 127.6 (CH_{Ar}); 126.4 (CH_{Ar}); 115.6 (C_q); 59.9 (CH); 16.5 (CH_3). Anal. calcd. for $C_{17}H_{13}N_3O$ (275.3): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.11; H, 4.64; N, 15.17.

5-(4-Chlorophenyl)-2-methylimidazo[1,2-c]quinazolin-3 (2H)-one (14b)

0.22 g, yield 71%. White crystals, mp 225°C to 226°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.57 (1H, d, J = 8.0, ArH); 7.96 (1H, t, J = 8.0, ArH); 7.89 (1H, d, J = 8.0, ArH); 7.76 (2H, d, J = 8.0, ArH); 7.67 (1H, t,

J = 8.0, ArH); 7.61 (2H, d, J = 8.0, ArH); 4.92 (1H, q, J = 6.0, CH); 1.27 (3H, d, J = 6.0, CH_3). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 187.5 (C═O); 171.6 (C═N); 160.2 (C═N); 150.5 (C_q); 145.1 (CH_{Ar}); 135.6 (C_q); 133.1 (C_q); 133.6 (CH_{Ar}); 130.4 (CH_{Ar}); 129.5 (CH_{Ar}); 128.2 (CH_{Ar}); 127.9 (CH_{Ar}); 125.3 (CH_{Ar}); 115.6 (C_q); 59.6 (CH); 16.2 (CH_3). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.87; H, 3.73; N, 13.48.

5-(3-Chlorophenyl)-2-methylimidazo[1,2-c]quinazolin-3(2H)-one (14c)

0.27 g, yield 86%. White crystals, mp 240°C to 241°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.52 (1H, d, J = 8.0, ArH); 7.95 (1H, t, J = 8.0, ArH); 7.88 (1H, d, J = 8.0, ArH); 7.78 (1H, s, ArH); 7.68-7.61 (3H, m, ArH); 7.56 (1H, t, J = 8.0, ArH); 4.84 (1H, q, J = 6.0, CH); 1.25 (3H, d, J = 6.0, CH_3). ^{13}C NMR spectrum, (75.0 MHz, DMSO-d_6), δ, ppm: 185.3 (C═O); 170.9 (C═N); 150.2 (C═N); 147.3 (C_q); 136.7 (CH_{Ar}); 135.3 (C_q); 133.2 (C_q); 131.3 (CH_{Ar}); 131.0 (CH_{Ar}); 128.9 (CH_{Ar}); 128.6 (CH_{Ar}); 127.7 (CH_{Ar}); 126.8 (CH_{Ar}); 115.5 (C_q); 59.4 (CH); 16.9 (CH_3). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.74; H, 3.79; N, 13.42.

5-(2-Chlorophenyl)-2-methylimidazo[1,2-c]quinazolin-3(2H)-one (14d)

0.15 g, yield 48%. White crystals, mp 150°C to 151°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.49 (1H, d, J = 8.0, ArH); 8.10 (1H, t, J = 8.0, ArH); 8.00-7.88 (2H, m, ArH); 7.76-7.66 (3H, m, ArH); 7.33 (1H, t, J = 8.0, ArH); 5.03 (1H, q, J = 6.0, CH); 1.29 (3H, d, J = 6.0, CH_3). ^{13}C NMR spectrum, (75.0 MHz, $CDCl_3$), δ, ppm: 184.6 (C═O); 170.4 (C═N); 147.3 (C_q); 147.7 (C_q); 137.0 (CH_{Ar});; 132.9 (CH_{Ar}); 131.3 (C_q); 130.7 (CH_{Ar}); 129.6 (CH_{Ar}); 128.9 (CH_{Ar}); 128.5 (CH_{Ar}); 128.0 (CH_{Ar}); 127.2 (CH_{Ar}); 123.1 (CH_{Ar}); 115.5 (C_q); 59.0 (CH); 16.7 (CH_3). Anal. calcd. for $C_{17}H_{12}ClN_3O$ (309.8): C, 65.92; H, 3.91; N, 13.57. Found: C, 65.82; H, 3.86; N, 13.44.

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