FULL PAPER

CuBr/Et_3N-Promoted Reactions of 2-Aminobenzamides and Isothiocyanates: Efficient Synthesis of Novel Quinazolin-4(3*H*)-ones

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A series of novel quinazolin-4(3*H*)-one derivatives were efficiently synthesized starting from isatoic anhydride. First, reaction of isatoic anhydride and amines in H_2O at room temperature afforded 2-aminobenzamides. Then, CuBr/Et_3N promoted reaction of 2-aminobenzamides and different aryl isothiocyanates in DMF at 80° afforded the title compounds in good yield.

Keywords: 2-Aminobenzamides, Heterocycles, Isatoic anhydride, Isothiocyanates, Quinazolin-4(3*H*)-ones.

Introduction

Quinazolin-4(3*H*)-ones are biologically important compounds due to their continued application in medicinal chemistry [1]. At this juncture, medicinal properties, such as antiulcer [2], anticancer [3], anti-inflammatory [4], anticonvulsant [5], hypolipidemic [6], antifungal [7], antiviral [8], and anti-coccidial [9], have been the center of attention for medicinal chemists. Therefore, several procedures have been reported for the synthesis of quinazolin-4(3*H*)-ones [10].

One of the classical methods for the construction of the quinazolinone ring is based on isatoic anhydride as a versatile starting material. It is known that its reaction with different amines gives 2-aminobenzamides as potent bident nucleophiles to react with a wide range of electrophiles [11]. In this regard, we have successfully developed efficient procedures for the preparation of quinazolinone using isatoic anhydride [12]. Literature survey reveals that 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-one derivatives have shown anti-inflammatory [13] and antibacterial [14] properties. Therefore, there is clearly demand for a general and user-friendly synthesis of this type of quinazolinones using readily available starting materials and reagents.

One of the common methods for the synthesis of 3-alkyl-2-(alkylamino)quinazolin-4(3*H*)-ones developed by *Ding et al.* [15a][15b] took advantage of the reaction of carbodiimides, obtained from aza-*Wittig* reactions between iminophosphorane and isocyanates, with amines. Subsequently, other methods were developed by the same group leading to the formation of 3,3′-disubstituted bis-2-arylaminoquinazolin-4(3*H*)-ones [15c]. At the same time, a solid-phase synthesis of 2-amino-4(3*H*)-quinazolinones was described by *Yang et al.* through the reaction of polymer-bound isothiourea with isatoic anhydride [11b]. Later, *Roberts et al.* [16] synthesized the target compounds *via* molybdenum-mediated cyclocarbonylation of 2-iodoaryl carbodiimides and amines. However, despite the merits of the reported procedures, existing drawbacks, such as the use of microwave irradiation, unavailable starting materials, and time consuming procedures, inspired us to develop an efficient and practical method for the preparation of novel 3-substituted 2-(arylamino)quinazolin-4(3*H*)-one derivatives **5** from isatoic anhydride (**1**) in good yields. The general approach has been depicted in *Scheme 1*. In connection with our interest in the synthesis of *N*-heterocycles [12][17], particularly using isatoic anhydride as a starting material, herein, we disclose a CuBr/Et_3N promoted synthesis of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-ones **5** *via* the reaction of 2-aminobenzamides **3** obtained from **1** and various amines **2**, with aryl isothiocyanates **4** (*Scheme 1*).

Results and Discussion

The sequence for the proposed reaction initiated by treating isatoic anhydride (**1**) with various amines **2** in H_2O at

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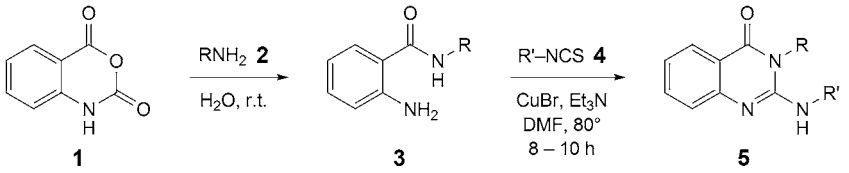
Scheme 1. Syntheses of 3-substituted 2-(arylamino)quinazolin-4*(3H)*-ones **5**.

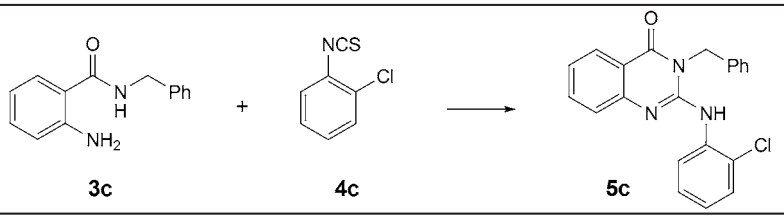


room temperature affording the related 2-aminobenzamides **3** [12][17]. All compounds **3** were easily prepared and used without further purifications. Next, to envisage all reaction details and conditions, we investigated the reaction of 2-amino-*N*-benzylbenzamide (**3c**) and 2-chlorophenyl isothiocyanate (**4c**) under different conditions to obtain the corresponding product **5a**. Some results are summarized in *Table 1*. For this purpose, literature review directed us to proficient desulfurizing agents, such as $HgCl_2$, which was successfully reported for guanidinylation of di-Boc-protected thioureas with amines [18][19], as well as synthesis of mono-, di-, and tri-substituted 5-aminotetrazoles *via* the nucleophilic attack of N_3^- on thioureas [20]. Also, molecular iodine (I_2) [21], DCC [22], and CuCl [23] were found to be efficient in various organic transformations including desulfurization step.

As can be seen in *Table 1*, CuBr, CuI, I_2, $HgCl_2$, and DCC were examined. Our results revealed that $HgCl_2$ and CuBr were more thiophilic than the other reagents and promoted the desulfurization/cyclization reaction efficiently. Obviously, CuBr was the best choice due to the mercury toxicity, although $HgCl_2$ gave a slightly better yield (Entries 4 and 10, *Table 1*). The model reaction (*Table 1*) was investigated in the presence of various amounts of CuBr as well as different temperatures. It should be noted that the presence of a base was crucial, and Et_3N was selected as the efficient base. Also, 0.5 equiv. of CuBr was enough to give good results. The optimized ratio of **3c**/**4c**/CuBr/Et_3N 2:2:1:1 led to 3-benzyl-2-((2-chlorophenyl)amino)quinazolin-4(3*H*)-one (**5c**) in 78% yield. Also, various organic solvents, such as DMF, CH_2Cl_2, toluene, and EtOH, were examined and DMF was found to be the most effective medium. Subsequently, using the optimized conditions, we successfully prepared a series of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-ones **5** (*Table 2*). Interestingly, various isothiocyanates **4** containing electron-donating (MeO) and electron-withdrawing (Cl and F) groups in their *ortho*- or *para*-positions reacted efficiently with different 2-aminobenzamides **3** to give the related quinazolinones **5**.

The reaction sequences for the formation of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-ones **5** could be explained according to the literature [21] as shown in *Scheme 2*. Initially, reaction of 2-aminobenzamide derivative **3** and isothiocyanate **4** led to the intermediate **6**, which was desulfurized and gave carbodiimide **7**. The latter undergoes cyclization reaction to afford the corresponding product **5**. It may be supposed that the

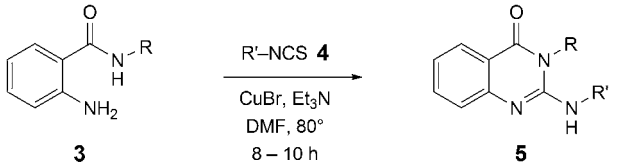
Table 1. Optimization of reaction conditions for the synthesis of **5c**[a])



Entry	Reagent	Solvent	Temperature	Base	Yield [%][b])
1	–	DMF	80°	–	0
2	CuBr	DMF	r.t.	–	0
3	CuBr	DMF	80°	–	15
4	CuBr	DMF	80°	Et_3N	78
5	CuBr	CH_2Cl_2	80°	Et_3N	10
6	CuBr	Toluene	80°	Et_3N	45
7	CuBr	EtOH	80°	Et_3N	60
8	I_2	DMF	80°	Et_3N	10
9	DCC	DMF	80°	Et_3N	Trace
10	CuI	DMF	80°	Et_3N	55
11	$HgCl_2$	DMF	80°	Et_3N	85

[a]) The model reaction was conducted using **3c** (2 mmol) and **4c** (2 mmol) in a solvent (5 ml) in the presence of a selected reagent (1 mmol) for 8 h. [b]) Yield of isolated product.

Table 2. Synthesis of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-ones **5**[a])



3 **5**

Entry	R	R′	Product	Yield [%][b])
1	Ph	2-Me–C_6H_4	**5a**	75
2	Ph	4-Me–C_6H_4	**5b**	70
3	Bn	2-Cl–C_6H_4	**5c**	78
4	4-Me–$C_6H_4CH_2$	Ph	**5d**	75
5	4-MeO–$C_6H_4CH_2$	2-Cl–C_6H_4	**5e**	79
6	2-Cl–$C_6H_4CH_2$	4-MeO–C_6H_4	**5f**	76
7	2-Cl–$C_6H_4CH_2$	2-Cl–C_6H_4	**5g**	89
8	2-Cl–$C_6H_4CH_2$	4-F–C_6H_4	**5h**	75
9	2-Cl–$C_6H_4CH_2$	Me	**5i**	75
10	4-Cl–$C_6H_4CH_2$	Ph	**5j**	73
11	4-Cl–$C_6H_4CH_2$	4-F–C_6H_4	**5k**	78
12	4-Cl–$C_6H_4CH_2$	Me	**5l**	77
13	Furan-2-ylmethyl	2-F–C_6H_4	**5m**	72
14	Furan-2-ylmethyl	2-Cl–C_6H_4	**5n**	88
15	CH_2=$CHCH_2$	2-Cl–C_6H_4	**5o**	75
16	^{i}Pr	Ph	**5p**	79

[a]) Compounds **3** were prepared from the reaction of commercially available starting materials, isatoic anhydride (**1**) and amines **2**. [b]) Yields of isolated products were calculated based on the organic starting materials.

formation of 2-thioxoquinazolinone derivatives **8** from the reaction of compounds **3** and **4** was involved in the reaction mechanism (*Scheme 3*) as reported [24]. For this purpose, reaction of **8** and different amines **2** was investigated in the presence of various desulfurizing agents. It was found that no desired product was obtained confirming the fact that this route is not possible.

Conclusion

In summary, we have developed a practical procedure for the synthesis of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-one derivatives *via* CuBr/Et_3N-promoted reaction of various 2-aminobenzamides and isothiocyanates in DMF at 80°. It should be noted that starting materials possessing electron-donating or electron-withdrawing groups underwent the reaction to give the corresponding products in good yields.

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Experimental Part

General

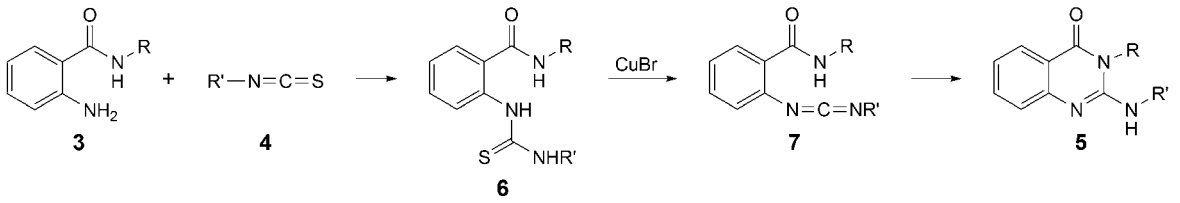
M.p.: *Kofler* hot stage apparatus; uncorrected. IR Spectra: *Nicolet Magna FTIR* 550 spectrophotometer (*Nicolet Instrument Corp*., Madison, WI, USA; in KBr); $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker FT-400* (Germany); δ in ppm rel. to Me_4Si as internal standard, J in Hz. Elemental analysis: *VarioEL* CHNS mode (*Elementar Analysensystem GmbH*, Hanau Germany).

*Syntheses of 3-Substituted 2-(Arylamino)quinazolin-4(3*H*)-ones* **5**

General Procedure

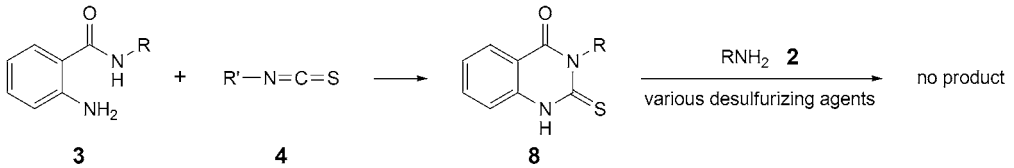
All 2-aminobenzamide derivatives **3** were prepared through the reaction of equiv. amounts of isatoic anhydride (**1**) and an appropriate amine **2** in H_2O at room temperature for 2 – 5 h [11][12]. After completion of the reaction, the precipitated product was filtered off, dried at 60°, and used for further reaction without any

Scheme 2. Reaction sequences for the construction of 3-substituted 2-(arylamino)quinazolin-4(3*H*)-ones **5**.



3 **4** **6** **7** **5**

Scheme 3. Reaction of 2-thioxoquinazolinone derivatives **8** and amines **2**.



3 **4** **8**

purification. A mixture of 2-aminobenzamide **3** (2 mmol), an isothiocyanate derivative **4** (2 mmol), CuBr (1 mmol), and Et_3N (1 mmol) in DMF (5 ml) was heated at 80° for 8 – 10 h. After completion of the reaction (checked by TLC), the mixture was filtered off through a bed of Celite and washed with AcOEt. Then, H_2O (20 ml) was added to the filtrate, it was extracted with AcOEt (3 × 15), and dried (Na_2SO_4). The solvent was then removed under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel and petroleum ether (PE)/AcOEt (5:1) as eluent. All products were recrystallized from PE/AcOEt (1:1) to give pure products **5**.

2-[(2-Methylphenyl)amino]-3-phenylquinazolin-4(3*H*)-one (**5a**). Yield: 0.24 g (75%). White crystals. M.p. 255 – 257°. IR: 3452, 2950, 2825 1635, 1475. ^{1}H-NMR: 2.00 (*s*, Me); 6.99 (*s*, NH); 7.08 (*t*, *J* = 7.5, 1 H, H–C(6)); 7.18 – 7.19 (*m*, 3 H, H–C(4′), H–C(5′), H–C(6′)); 7.25 (*d*, *J* = 8.0, 1 H, H–C(3′)); 7.53 – 7.63 (*m*, 7 H, Ph, H–C(7), H–C(8)); 7.97 (*d*, *J* = 7.5, 1 H, H–C(5)). ^{13}C-NMR: 17.3; 117.3; 122.5; 124.8; 125.1; 125.6; 125.9; 126.4; 129.2; 129.4; 130.0; 130.1; 132.4; 134.4; 134.9; 136.8; 148.2; 148.9; 161.6. Anal. calc. for $C_{21}H_{17}N_3O$ (327.14): C 77.04, H 5.23, N 12.84, found: C 77.21, H 5.34, N 12.73.

2-[(4-Methylphenyl)amino]-3-phenylquinazolin-4(3*H*)-one (**5b**). Yield: 0.23 g (70%). White crystals. M.p. 251 – 253°. IR: 3452, 2955, 2850, 1632, 1474. ^{1}H-NMR: 2.27 (*s*, Me); 6.99 (*s*, NH); 7.09 (*d*, *J* = 8.0, 2 H, H–C(3′), H(5′)); 7.21 (*t*, *J* = 7.5, 1 H, H–C(6)); 7.35 (*d*, *J* = 8.0, 2 H, H–C(2′), H–C(6′)); 7.47 – 7.66 (*m*, 7 H, Ph, H–C(7), H–C(8)); 7.96 (*d*, *J* = 7.5, 1 H, H–C(5)). ^{13}C-NMR: 20.3; 117.8; 122.7; 123.0; 124.9; 126.4; 128.5; 129.0; 129.3; 129.9; 132.7; 134.4; 134.7; 136.0; 148.1; 148.6; 161.7. Anal. calc. for $C_{21}H_{17}N_3O$ (327.14): C 77.04, H 5.23, N 12.84, found: C 76.91, H 5.32, N 12.96.

3-Benzyl-2-[(2-chlorophenyl)amino]quinazolin-4(3*H*)-one (**5c**). Yield: 0.28 g (78%). White crystals. M.p. 195 – 197°. IR: 3458, 2968, 1632, 1474. ^{1}H-NMR: 5.54 (*s*, 2 H, CH_2); 6.92 (br. *s*, NH); 7.01 (*td*, *J* = 7.5, 1.2, 1 H, H–C(6)); 7.30 – 7.38 (*m*, 8 H, Ph, H–C(4′), H–C(5′), H–C(6′)); 7.43 (*d*, *J* = 7.5, 1 H, H–C(8)); 7.67 (*t*, *J* = 7.5, 1 H, H–C(7)); 8.28 (*d*, *J* = 7.5, 1 H, H–C(5)); 8.44 (*d*, *J* = 8.4, 1 H, H–C(3′)). ^{13}C-NMR: 45.4; 122.5; 123.5; 124.3; 125.7; 126.8; 127.3; 127.4; 127.7; 128.2; 128.6; 129.1; 129.4; 134.3; 134.6; 135.2; 146.7; 147.8; 163.0. Anal. calc. for $C_{21}H_{16}ClN_3O$ (361.10): C 69.71, H 4.46, N 11.61, found: C 69.48, H 4.20, N 11.73.

3-(4-Methylbenzyl)-2-(phenylamino)quinazolin-4(3*H*)-one (**5d**). Yield: 0.25 g (75%). White crystals. M.p. 140 – 141°. IR: 3309, 2950, 1653, 1608, 1471. ^{1}H-NMR: 2.39 (*s*, Me); 5.45 (*s*, 2 H, CH_2); 6.53 (br. *s*, NH); 6.95 (*t*, *J* = 7.6, 1 H, H–C(6)); 7.25 (*d*, *J* = 8.0, 2 H, H–C(3′), H–C(5′)); 7.28 – 7.35 (*m*, 5 H, Ph); 7.39 (*d*, 2 H, *J* = 8.0, H–C(2′), H–C(6′)); 7.49 (*d*, *J* = 7.6, 1 H, H–C(8)); 7.66 (*t*, *J* = 7.6, 1 H, H–C(7)); 8.27 (*d*, *J* = 7.6, 1 H, H–C(5)). ^{13}C-NMR: 21.2; 45.1; 118.0; 120.8; 123.7; 123.8; 125.7; 126.8; 127.3; 128.9; 130.4; 131.9; 134.5; 138.3; 138.6; 147.2; 148.3; 163.0. Anal. calc. for $C_{22}H_{19}N_3O$ (341.15): C 77.40, H 5.61, N 12.31, found: C 77.68, H 5.47, N 12.54.

2-[(2-Chlorophenyl)amino]-3-(4-methoxybenzyl)quinazolin-4(3*H*)-one (**5e**). Yield: 0.30 g (79%). Off-white crystals. M.p. 155 – 157°. IR: 3437, 2834, 1672, 1602, 1541. ^{1}H-NMR: 3.79 (*s*, MeO); 5.46 (*s*, 2 H, CH_2); 6.91 (*d*, *J* = 8.4, 2 H, H–C(3′), H–C(5′)); 7.02 (br. *s*, NH); 7.30 – 7.50 (*m*, 6 H, H–C(6), H–C(2′), H–C(6′), H–C(4″), H–C(5″), H–C(6″)); 7.48 (*d*, *J* = 8.0, 1 H, H–C(8)); 7.58 (*t*, *J* = 8.0, 1 H, H–C(7)); 8.27 (*d*, *J* = 8.0, 1 H, H–C(5)); 8.44 (*d*, *J* = 8.4, 1 H, H–C(3″)). ^{13}C-NMR: 45.0; 55.4; 113.6; 114.8; 118.3; 122.5; 123.5; 123.9; 124.2; 125.7; 126.1; 127.3; 127.4; 128.2; 128.6; 134.6; 146.8; 147.8; 159.8; 163.0. Anal. calc. for $C_{22}H_{18}ClN_3O_2$ (391.11): C 67.43, H 4.63, N 10.72, found: C 67.21, H 4.47, N 10.54.

3-(2-Chlorobenzyl)-2-[(4-methoxyphenyl)amino]quinazolin-4(3*H*)-one (**5f**). Yield: 0.29 g (76%). Off-white crystals. M.p. 174 – 175°. IR: 3473, 284, 1684, 1632, 1571. ^{1}H-NMR: 3.92 (*s*, MeO); 5.40 (*s*, 2 H, CH_2); 6.60 (*d*, *J* = 7.7, 1 H, H–C(3″), H–C(5″)); 6.65 (*s*, NH); 6.93 (*d*, *J* = 7.9, 1 H, H–C(6)); 7.32 – 7.39 (*m*, 4 H, H–C(2″), H–C(6″), H–C(4′), H–C(6′)); 7.48 – 7.51 (*m*, 2 H, H–C(8), H–C(5′)); 7.63 (*t*, *J* = 7.9, 1 H, H–C(7)); 7.84 (*d*, *J* = 7.9, 1 H, H–C(5)); 8.00 (*d*, *J* = 7.1, 1 H, H–C(3′)). ^{13}C-NMR: 43.8; 55.9; 114.0; 114.8; 118.3; 123.2; 125.9; 126.0; 127.0; 127.4; 128.5; 129.1; 130.7; 130.9; 134.5; 134.9; 146.8; 147.8; 158.7; 162.8. Anal. calc. for $C_{22}H_{18}ClN_3O_2$ (391.11): C 67.43, H 4.63, N 10.72, found: C 67.78, H 4.70, N 10.84.

3-(2-Chlorobenzyl)-2-[(2-chlorophenyl)amino]quinazolin-4(3*H*)-one (**5g**). Yield: 0.35 g (89%). White crystals. M.p. 188 – 190°. IR: 3225, 3058, 1692, 1644, 1467. ^{1}H-NMR: 5.63 (*s*, 2 H, CH_2); 6.80 (br. *s*, NH); 7.02 (*t*, *J* = 7.5, 1 H, H–C(6)); 7.10 (*d*, *J* = 7.0, 1 H, H–C(6″)); 7.21 – 7.41 (*m*, 5 H, H–C(4′), H–C(5′), H–C(6′), H–C(4″), H–C(5″)); 7.67 – 7.71 (*m*, 2 H, H–C(8), H–C(3″)); 7.69 (*t*, *J* = 7.5, 1 H, H–C(7)); 8.26 (*d*, *J* = 7.5, 1 H, H–C(5)); 8.49 (*d*, *J* = 8.1, 1 H, H–C(3′)). ^{13}C-NMR: 42.9; 113.9; 118.0; 122.4; 123.6; 124.1; 124.3; 125.8; 126.8; 127.3; 127.4; 127.8; 129.0; 129.6; 130.1; 131.4; 133.0; 134.8; 146.2; 147.9; 162.8. Anal. calc. for $C_{21}H_{15}Cl_2N_3O$ (395.06): C 63.65, H 3.82, N 10.60, found: C 63.49, H 3.64, N 10.48.

3-(2-Chlorobenzyl)-2-[(4-fluorophenyl)amino]quinazolin-4(3*H*)-one (**5h**). Yield: 0.28 g (75%). White crystals. M.p. 203 – 205°. IR: 3450, 2960, 1630, 1470. ^{1}H-NMR: 5.54 (*s*, 2 H, CH_2); 7.15 – 7.18 (*m*, 4 H, NH, H–C(6), H–C(3″), H–C(5″)); 7.24 – 7.30 (*m*, 4 H, H–C(4′), H–C(5′), H–C(2″), H–C(6″)); 7.39 (*d*, *J* = 7.0, 1 H, H–C(6′)); 7.54 – 7.55 (*m*, 2 H, H–C(8), H–C(3′)); 7.64 (*t*, *J* = 7.0, 1 H, H–C(7)); 8.00 (*d*, *J* = 7.0, 1 H, H–C(5)). ^{13}C-NMR: 43.0; 114.9 (*d*, J_{C-F} = 22.5); 117.1; 123.0; 124.7 (*d*, J_{C-F} = 8.1); 124.9; 126.3; 128.4; 129.1; 129.7; 129.8; 131.5; 131.7; 134.5; 135.2 (*d*, J_{C-F} = 21.1); 148.0; 148.1; 159.5 (*d*, J_{C-F} = 245.0); 162.0. Anal. calc. for $C_{21}H_{15}ClFN_3O$ (379.09): C 66.41, H 3.98, N 11.06, found: C 66.58, H 4.15, N 10.91.

3-(2-Chlorobenzyl)-2-(methylamino)quinazolin-4(3*H*)-one (**5i**). Yield: 0.22 g (75%). White crystals. M.p. 172 – 174°. IR: 3455, 2955, 1635, 1470. ^{1}H-NMR: 2.81 (*s*, Me); 4.72 (*s*, 2 H, CH_2); 7.05 (*s*, NH); 7.06 (*t*, *J* = 7.0, 1 H, H–C(6)); 7.29 (*t*, *J* = 7.5, 1 H, H–C(5′)); 7.36 (*t*,

J = 7.5, 1 H, H–C(4′)); 7.43 – 7.50 (*m*, 2 H, H–C(8), H–C(6′)); 7.53 (*t*, J = 7.0, 1 H, H–C(7)); 7.67 (*d*, J = 7.5, 1 H, H–C(3′)); 7.93 (*d*, J = 7.0, 1 H, H–C(5)). ^{13}C-NMR: 27.3; 46.4; 115.6; 122.5; 123.2; 125.4; 127.1; 128.1; 128.8; 129.3; 132.1; 133.1; 137.6; 145.7; 147.6; 152.8. Anal. calc. for $C_{16}H_{14}ClN_3O$ (299.08): C 64.11, H 4.71, N 14.02, found: C 64.28, H 4.59, N 13.92.

3-(4-Chlorobenzyl)-2-(phenylamino)quinazolin-4(3*H*)-one (**5j**). Yield: 0.26 g (73%). White crystals. M.p. 169 – 170°. IR: 3399, 2968, 1673, 1608. ^{1}H-NMR: (*s*, 2 H, CH_2); 6.40 (br. *s*, NH); 7.10 (*td*, J = 7.7, 1.4, 1 H, H–C(6)); 7.28 – 7.36 (*m*, 6 H, Ph, H–C(2′), H–C(6′)); 7.49 – 7.53 (*m*, 4 H, Ph, H–C(3′), H–C(5′)); 7.67 (*td*, J = 7.7, 1.4, 1 H, H–C(7)); 8.25 (*dd*, J = 7.7, 1.4, 1 H, H–C(5)). ^{13}C-NMR: 41.7; 121.1; 123.8; 124.0; 125.7; 127.3; 128.2; 128.5; 128.9; 129.8; 129.9; 132.2; 134.7; 138.0; 146.4; 148.2; 163.0. MS: 363 ($M + 2^{+\cdot}$), 361 ($M^{+\cdot}$), 326, 236, 125, 77. Anal. calc. for $C_{21}H_{16}ClN_3O$ (361.10): C 69.71, H 4.46, N 11.61, found: C 69.58, H 4.69, N 11.78.

3-(4-Chlorobenzyl)-2-[(4-fluorophenyl)amino]quinazolin-4(3*H*)-one (**5k**). Yield: 0.28 g (78%). White crystals. M.p. 214 – 216°. IR: 3450, 2960, 1630, 1470. ^{1}H-NMR: 5.55 (*s*, 2 H, CH_2); 6.86 (br. *s*, NH); 7.14 – 7.18 (*m*, 3 H, H–C(6), H–C(3″), H–C(5″)); 7.21 – 7.39 (*m*, 6 H, H–C(2′), H–C(3′), H–C(5′), H–C(6′), H–C(2″), H–C(6″)); 7.55 – 7.63 (*m*, 2 H, H–C(7), H–C(8)); 8.01 (*d*, J = 8.0, 1 H, H–C(5)). ^{13}C-NMR: 43.0; 115.1 (*d*, J_{C-F} = 31.2); 117.1; 123.0; 123.4 (*d*, J_{C-F} = 12.5); 124.8 (*d*, J_{C-F} = 7.5); 124.9; 126.5; 128.0; 128.4; 129.5; 131.8; 134.4; 135.3; 148.0 (*d*, J_{C-F} = 22.5); 158.5 (*d*, J_{C-F} = 238.7); 162.0. Anal. calc. for $C_{21}H_{15}ClFN_3O$ (379.09): C 66.41, H 3.98, N 11.06, found: C 66.58, H 4.21, N 11.20.

3-(4-Chlorobenzyl)-2-(methylamino)quinazolin-4(3*H*)-one (**5l**). Yield: 0.23 g (77%). White crystals. M.p. 170 – 172°. IR: 3425, 2960, 1635, 1465. ^{1}H-NMR: 2.82 (*s*, Me); 4.65 (*s*, 2 H, CH_2); 7.02 – 7.07 (*m*, 2 H, NH, H–C(6)); 7.38 (*d*, J = 8.5, 2 H, H–C(2′), H–C(6′)); 7.42 (*d*, J = 7.5, 1 H, H–C(8)); 7.44 (*d*, J = 8.5 Hz, 2 H, H–C(3′), H–C(5′)); 7.54 (*t*, J = 7.5, 1 H, H–C(7)); 7.90 (*dd*, J = 7.5, 1.0, 1 H, H–C(5)). ^{13}C-NMR: 27.3; 48.0; 115.6; 122.5; 123.2; 125.4; 128.1; 129.3; 130.9; 133.0; 139.3; 145.7; 147.3; 152.9. Anal. calc. for $C_{16}H_{14}ClN_3O$ (299.08): C 64.11, H 4.71, N 14.02, found: C 64.20, H 4.88, N 14.17.

2-[(2-Fluorophenyl)amino]-3-(furan-2-ylmethyl)quinazolin-4(3*H*)-one (**5m**). Yield: 0.24 g (72%). White crystals. M.p. 192 – 194°. IR: 3473, 1687, 1665, 1589. ^{1}H-NMR: 5.44 (*s*, 2 H, CH_2); 6.62 (*d*, J = 3.1, 1 H, furan); 6.44 (*dd*, J = 3.1, 1.9, 1 H, furan); 7.08 (br. *s*, NH); 7.16 (*ddd*, J = 11.0, 8.1, 1.5, 1 H, H–C(3′)); 7.22 (*t*, J = 8.0, 1 H, H–C(6)); 7.31 (*td*, J = 8.1, 1.5, 1 H, H–C(5′)); 7.47 – 7.49 (*m*, 2 H, H–C(8), furan); 7.66 – 7.63 (*m*, 2 H, H–C(7), H–C(6′)); 8.21 (*dd*, J = 8.0, 1.2, 1 H, H–C(5)); 8.40 (*td*, J = 8.1, 1.5, 1 H, H–C(4′)). ^{13}C-NMR: 38.3; 110.3; 111.1; 114.9 (*d*, J_{C-F} = 19.1); 118.3; 122.6; 123.6 (*d*, J_{C-F} = 7.3); 124.1; 124.3; 124.9; 125.7; 127.1; 134.5; 143.0; 146.6; 147.7; 148.6; 153.3 (*d*, J_{C-F} = 230.3); 162.3. Anal. calc. for $C_{19}H_{14}FN_3O_2$ (335.11): C 68.05, H 4.21, N 12.53, found: C 67.87, H 4.49, N 12.78.

2-[(2-Chlorophenyl)amino]-3-(furan-2-ylmethyl)quinazolin-4(3*H*)-one (**5n**).Yield: 0.30 g (88%). Off-white crystals. M.p. 183 – 184°. IR: 3473, 3123, 1693, 1635, 1574. ^{1}H-NMR: 5.46 (*s*, 2 H, CH_2); 6.42 (*dd*, J = 3.0, 1.8, 1 H, furan); 6.60 (*d*, J = 3.0, 1 H, furan); 7.08 (*td*, J = 7.7, 1.5, 1 H, H–C(6)); 7.31 (*td*, J = 8.0, 1.4, 1 H, H–C(4′)); 7.35 (*td*, J = 8.0, 1.4, 1 H, H–C(5′)); 7.43 (*dd*, J = 8.0, 1.4, 1 H, H–C(6′)); 7.45 (*dd*, J = 1.8, 0.6, 1 H, furan); 7.47 (*dd*, J = 7.7, 1.5, 1 H, H–C(8)); 7.65 (*td*, J = 7.7, 1.5, 1 H, H–C(7)); 7.71 (s, NH); 8.22 (*dd*, J = 7.7, 1.5, 1 H, H–C(5)); 8.36 (*dd*, J = 8.0, 1.4, 1 H, H–C(3′)). ^{13}C-NMR: 38.7; 110.0; 111.0; 118.3; 122.7; 124.0; 124.3; 125.7; 127.1; 127.3; 129.3; 134.5; 135.5; 141.7; 142.9; 146.6; 147.5; 148.4; 162.4. Anal. calc. for $C_{19}H_{14}ClN_3O_2$ (351.08): C 64.87, H 4.01, N 11.94, found: C 64.71, H 3.87, N 12.21.

3-Allyl-2-[(2-chlorophenyl)amino]quinazolin-4(3*H*)-one (**5o**). Yield: 0.23 g (75%). White crystals. M.p. 170 – 172 °. IR: 3399, 3090, 2996, 1673, 1576. ^{1}H-NMR: 4.95 – 4.96 (*m*, 2 H, =CH_2); 5.49 (*s*, 2 H, CH_2); 6.08 (*ddt*, J = 17.5, 10.2, 5.0, 1 H, CH); 7.06 (*td*, J = 7.5, 1.4, 1 H, H–C(6)); 7.19 (br. *s*, NH); 7.30 (*t*, J = 8.0, 1 H, H–C(4′)); 7.33 (*d*, J = 8.0, 1 H, H–C(5′)); 7.41 (*d*, J = 8.0, 1 H, H–C(6′)); 7.49 (*d*, J = 7.5, 1 H, H–C(8)); 7.66 (*t*, J = 7.5, 1 H, H–C(7)); 8.21 (*d*, J = 7.5, 1 H, H–C(5)); 8.53 (*d*, J = 8.0, 1 H, H–C(3′)). ^{13}C-NMR: 44.3; 118.2; 118.8; 122.3; 123.6; 123.9; 124.2; 125.6; 127.2; 127.5; 129.1; 131.2; 134.5; 135.2; 146.6; 147.6; 162.2. MS: 313 ($M + 2^{+\cdot}$), 311 ($M^{+\cdot}$), 296, 276, 236. Anal. calc. for $C_{17}H_{14}ClN_3O$ (311.08): C 65.49, H 4.53, N 13.48, found: C 65.69, H 4.28, N 13.67.

3-(1-Methylethyl)-2-(phenylamino)quinazolin-4(3*H*)-one (**5p**) [15b]. Yield: 0.22 g (79%). White crystals. M.p. 139 – 140°. IR: 3224, 2965, 2928, 1687, 1629, 1468. ^{1}H-NMR: 1.53 (*d*, J = 6.8, 6 H, Me); 5.51 – 5.53 (*m*, 1 H, CH); 6.83 (br. *s*, NH); 7.00 – 7.27 (*m*, 6 H, Ph, H–C(6)); 7.45 (*d*, J = 7.8, 1 H, H–C(8)); 7.40 (*t*, J = 7.8, 1 H, H–C(7)); 7.91 (*d*, J = 7.8, 1 H, H–C(5)). ^{13}C-NMR: 20.3; 46.2; 122.1; 122.3; 124.3; 124.8; 125.0; 127.5; 128.3; 128.8; 129.2; 130.7; 149.2; 162.8. Anal. calc. for $C_{17}H_{17}N_3O$ (279.14): C 73.10, H 6.13, N 15.04, found: C 72.83, H 5.90, N 15.28.

REFERENCES

[1] I. Khan, A. Ibrar, N. Abbas, A. Saeed, *Eur. J. Med. Chem.* **2014**, *76*, 193.

[2] K. Terashima, H. Shimamura, A. Kawase, Y. Tanaka, T. Tanimura, T. Kamisaki, Y. Ishizuka, M. Sato, *Chem. Pharm. Bull.* **1995**, *43*, 2021.

[3] S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding, R.-T. Li, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915.

[4] B. A. Rather, T. Raj, A. Reddy, M. P. S. Ishar, S. Sivakumar, P. Paneerselvam, *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 108.

[5] J. F. Wolfe, T. L. Rathman, M. C. Sleevi, J. A. Campbell, T. D. Greenwood, *J. Med. Chem.* **1990**, *33*, 161.

[6] Y. Kurogi, Y. Inoue, K. Tsutsumi, S. Nakamura, K. Nagao, H. Yohsitsugu, Y. Tsuda, *J. Med. Chem.* **1996**, *39*, 1433.

[7] J. Bartroli, E. Turmo, M. Algueró, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos, J. Gracía-Rafanell, J. Forn, *J. Med. Chem.* **1998**, *41*, 1869.

[8] Z. Wang, M. Wang, X. Yao, Y. Li, J. Tan, L. Wang, W. Qiao, Y. Geng, Y. Liu, Q. Wang, *Eur. J. Med. Chem.* **2012**, *53*, 275.

[9] P. Panneerselvam, B. A. Rather, D. R. S. Reddy, N. R. Kumar, *Eur. J. Med. Chem.* **2009**, *44*, 2328.
[10] D. A. Patil, P. O. Patil, P. K. Deshmukh, G. B. Patil, B. D. Shewale, D. D. Patil, S. G. Gattani, *Res. J. Pharm. Technol.* **2010**, *3*, 979; N. Montazeri, K. Rad-Moghadam, *Phosphorus, Sulfur Silicon Relat. Elem*. **2004**, *179*, 2533; S. -L. Wang, K. Yang, C. -S. Yao, X. -S. Wang, *Asian J. Chem*. **2012**, *24*, 5361; H. B. Jalani, A. N. Pandya, D. H. Pandya, J. A. Sharma, V. Sudarsanam, K. K. Vasu, *Tetrahedron Lett*. **2012**, *53*, 4062; A. V. Lygin, A. de Meijere, *Org. Lett*. **2009**, *11*, 389; D. Gravier, J.-P. Dupin, F. Casadebaig, G. Hou, M. Boisseau, H. Bernard, *Pharmazie* **1992**, *47*, 91; F. A. Cabrera-Rivera, C. Ortíz-Nava, J. Escalante, J. M. Hernández-Pérez, M. Hô, *Synlett* **2012**, *23*, 1057; D. Ranganathan, R. Rathi, K. Keshavan, W. P. Singh, *Tetrahedron* **1986**, *42*, 4873; T. Kametani, C. Van Loc, T. Higa, M. Koizumi, M. Ihara, K. Fukumoto, *J. Am. Chem. Soc*. **1977**, *99*, 2306; M. Wang, Z. G. Song, T. T. Zhang, *Chin. Chem. Lett*. **2010**, *21*, 1167; G. U. Baig, M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2765.
[11] a) A. Gopalsamy, H. Yang, *J. Comb. Chem.* **2000**, *2*, 378; b) R.-Y. Yang, A. Kaplan, *Tetrahedron Lett*. **2000**, *41*, 7005; c) R. Iemura, M. Hori, T. Saito, H. Ohtaka, *Chem. Pharm. Bull*. **1989**, *37*, 2723; d) J. Reisch, C. O. Usifoh, J. O. Oluwadiya, *Monatsh. Chem*. **1992**, *123*, 247; e) M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary, A. A. Mohammadi, *Tetrahedron Lett*. **2005**, *46*, 6123; f) K. S. Kumar, P. M. Kumar, K. A. Kumar, M. Sreenivasulu, A. A. Jafar, D. Rambabu, G. R. Krishna, C. M. Reddy, R. Kapavarapu, K. Shivakumar, K. K. Priya, K. V. L. Parsa, M. Pal, *Chem. Commun*. **2011**, *47*, 5010.
[12] M. Asadi, M. Ebrahimi, M. Mahdavi, M. Saeedi, P. R. Ranjbar, F. Yazdani, A. Shafiee, A. Foroumadi, *Synth. Commun.* **2013**, *43*, 2385; S. Farzipour, M. Saeedi, M. Mahdavi, H. Yavari, M. Mirzahekmati, N. Ghaemi, A. Foroumadi, A. Shafiee, *Synth. Commun*. **2014**, *44*, 481; M. Asadi, S. Masoomi, S. M. Ebrahimi, M. Mahdavi, M. Saeedi, A. Shafiee, A. Foroumadi, *Monatsh. Chem*. **2014**, *145*, 497; S. Nahavandian, S. Allameh, M. Saeedi, S. Ansari, M. Mahdavi, A. Foroumadi, A. Shafiee, *Helv. Chim. Acta* **2015**, *98*, 1028; M. Mahdavi, K. Pedrood, M. Safavi, M. Saeedi, M. Pordeli, S. K. Ardestani, S. Emami, M. Adib, A. Foroumadi, A. Shafiee, *Eur. J. Med. Chem*. **2015**, *95*, 492.
[13] V. Alagarsamy, V. R. Solomon, S. Murugesan, *Arzneimittelforschung* **2008**, *58*, 174; V. Alagarsamy, S. Meena, K. V. Ramaseshu, V. R. Solomon, T. D. A. Kumar, K. Thirumurugan, *Chem. Biol. Drug Des*. **2007**, *70*, 254.
[14] X. Wang, J. Yin, L. Shi, G. Zhang, B. Song, *Eur. J. Med. Chem.* **2014**, *77*, 65.
[15] a) M.-W. Ding, G.-P. Zeng, T.-J. Wu, *Synth. Commun.* **2000**, *30*, 1599; b) Y. Liang, M.-W. Ding, Z.-J. Liu, X.-P. Liu, *Synth. Commun*. **2003**, *33*, 2843; c) X.-H. Yang, M.-H. Wu, S.-F. Sun, J.-L. Xie, M.-W. Ding, Q.-H. Xia, *J. Heterocycl. Chem*. **2008**, *45*, 1365.
[16] B. Roberts, D. Liptrot, T. Luker, M. J. Stocks, C. Barber, N. Webb, R. Dods, B. Martin, *Tetrahedron Lett.* **2011**, *52*, 3793.
[17] M. Saeedi, M. Mahdavi, A. Foroumadi, A. Shafiee, *Tetrahedron* **2013**, *69*, 3506; M. Mahdavi, N. Foroughi, M. Saeedi, M. Karimi, H. Alinezhad, A. Foroumadi, A. Shafiee, T. Akbarzadeh, *Synlett* **2014**, *25*, 385; M. Mahdavi, M. Asadi, M. Saeedi, Z. Rezaei, H. Moghbel, A. Foroumadi, A. Shafiee, *Synlett* **2012**, *23*, 2521.
[18] K. S. Kim, L. Qian, *Tetrahedron Lett.* **1993**, *34*, 7677.
[19] C. Levallet, J. Lerpiniere, Y. S. Ko, *Tetrahedron* **1997**, *53*, 5291.
[20] R. A. Batey, D. A. Powell, *Org. Lett.* **2000**, *2*, 3237.
[21] R. Yella, N. Khatun, S. K. Rout, B. K. Patel, *Org. Biomol. Chem.* **2011**, *9*, 3235.
[22] A.-M. M. E. Omar, N. S. Habib, O. M. Aboulwafa, *Synthesis* **1977**, 864.
[23] X.-J. Wang, L. Zhang, Y. Xu, D. Krishnamurthy, C. H. Senanayake, *Tetrahedron Lett.* **2004**, *45*, 7167.
[24] S. Allameh, M. M. Heravi, M. M. Hashemi, F. F. Bamoharram, *Chin. Chem. Lett.* **2011**, *22*, 131.

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