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Efficient microwave-assisted two-step procedure for the synthesis of 1,3-disubstituted-imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones

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ABSTRACT

A general method has been developed for the synthesis of 1,3-disubstituted-imidazo[1,5-a]quinazolin-5-(4H)-ones. This process involves initial microwave-assisted quinazolinone formation between anthranilamide and various Boc- or acylamino acids, followed by intramolecular cyclodehydration under acidic conditions. In the case of 3-monosubstituted-imidazoquinazolinones, the procedure needs the formation of the formamide derivatives by deprotection and formylation of the Boc-intermediates.

1. Introduction

The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities.[1] The occurrence of the quinazolin-4-one core in various natural sources has generated interest of many groups on account of its useful biological properties. Among them, a wide range of five-membered ring containing nitrogen atoms based on fused [1,5- a]quinazolinones exhibit antiarthritic,[2] antihistaminic,[3] phosphodiesterase IV inhibitor[4] (**1**), PARP inhibitor[5] (**2**) and $GABA_A$ receptor ligand[6c] (**4**) activities (Fig. 1).

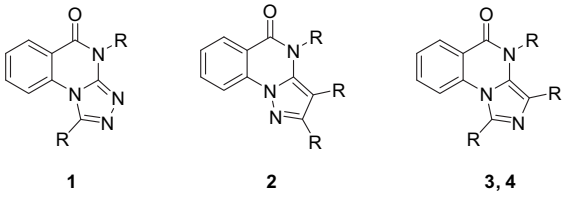
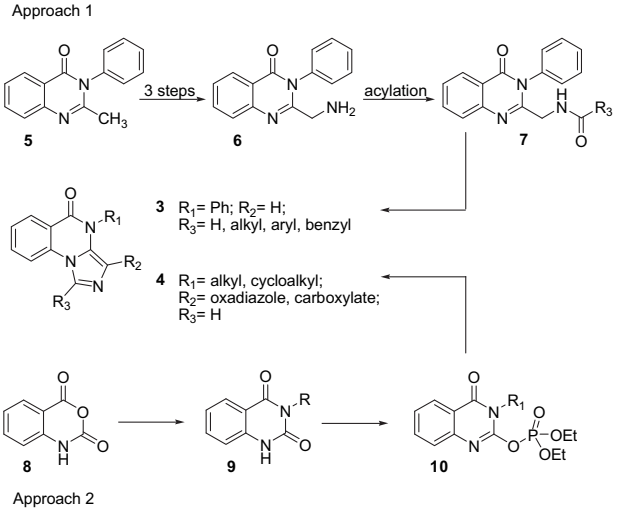


Figure 1. Structure of the 1,2-fused quinazolin-5-ones.

While structures **1** and **2** are well documented, only a few papers described the synthesis and the reactivity of heterocycles in which the quinazoline ring is fused with imidazole as imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones **3** and **4**. Thus far, two major synthetic strategies have been reported to access the core ring system **3** and **4** and these approaches are limited in that the nitrogen in position 4 was always substituted and the imidazole core monosubstituted (Scheme 1). Singh and Chaudhury[6a] reported the synthesis of



Scheme 1. Available approaches for the synthesis of Imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones.

aminomethyl derivative **6**, which could be converted into its *N*-carboxamide **7** for subsequent cyclization into imidazoquinazolone **3** (Approach 1), Scheme 1.

For this purpose, **6** was obtained from bromination of **5** by Gabriel synthesis followed by reaction with potassium phthalimide and hydrolysis with hydrazine hydrate. In the second approach,[6d] reaction of the desired quinazolin-2,4-diones **9**, synthesized from isatoic anhydride **8** and the corresponding amines, with sodium hydride followed by diethyl chlorophosphate, provided an intermediate enol phosphonate **10**. Without isolation, enol **10** was combined with the desired isocyanide and additional potassium

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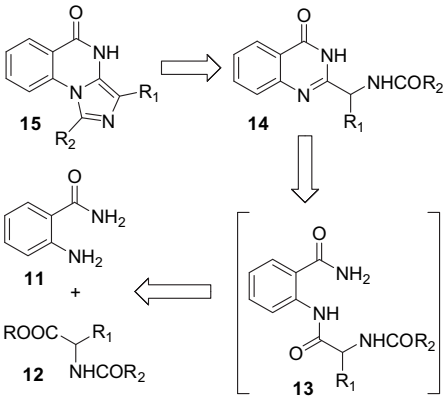
*tert*butoxide to provide the imidazo[1,5-*a*]quinazolin-5-(4*H*)-one **4** ring system. A general method for the synthesis of the 1,3-disubstituted-imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones **15** would be required in order to investigate this chemical space through the variation of the substituents on the imidazole core to include a diverse sampling of aliphatic, benzylic, and aromatic groups.

2. Results and discussion

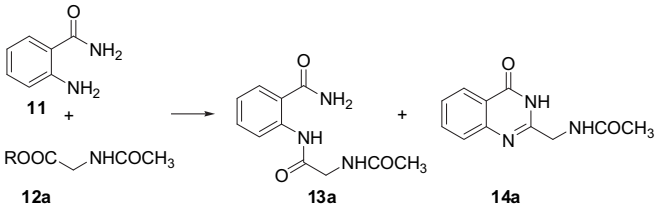
A number of microwave-assisted methods have been recently reported for the synthesis of 2-substituted quinazolin-4-(3*H*)-one analogs by the use of anthranilic acid,[7] anthranilamide,[8] isatoic anhydride,[9] and 3,1-benzoxazinones[10] as appropriate precursors. Our approach in the retrosynthetic strategy (Scheme 2) was investigated with **14** as a key-intermediate, which could be formed via transannular cyclization of intermediate diamide **13**. The diamide **13** may be accessed in situ from readily available anthranilamide **11** and *N*-acylamino acids derivatives **12**. Three microwave assisted procedures for the preparation of quinazolinone **14a** were investigated. The first involved treatment of anthranilamide **11** and *N*-acetylglycine **12a** with HOBT and EDCI[11] using various combinations of solvent/power irradiation/temperature (Table 1). The best result (entry 5) was obtained with 2 equiv of **12a** in acetonitrile under microwave irradiation at 120 °C for 20 min. Previous published synthetic studies[12] toward making imidazo-[1,5-*a*]pyrimidin-4(l*H*)-ones have utilized ethyl *N*-acylamino esters in the presence of sodium ethoxide in refluxing ethanol.



Scheme 2. Retrosynthetic strategy of **15**.

These conditions were then applied and optimized (entry 6 and 7) to the microwave-assisted synthesis of **14a** in 60% yield. An improved procedure for the *N*-acylation of amine derivatives involved treatment with a mixed anhydride,[13] prepared in situ from the corresponding carboxylic acid, isobutyl chloroformate, and *N*-methylmorpholine.[14] Isobutyl chloroformate was then added dropwise to a cold (−15 °C) mixture of *N*-acetyl-glycine **12a** and methylmorpholine in THF followed by addition of anthranilamide then heating upon microwave irradiation at 120 °C for 20 min (entry 8). These conditions led to 80% yield formation of quinazolinone **14a** and diamide **13a** in the proportion of, respectively 55 and 45%.[15] Under the final optimized microwave conditions, reaction of anthranilamide (1 equiv) with isobutoxycarbonyl *N*-acetylglycinate (1 equiv) in THF at 120 °C for 20 min, followed by addition of 2 N sodium ethoxide solution in ethanol (2 equiv) and microwave irradiation at 120 °C for 10 min to complete cyclization reaction afforded the desired quinazolinone **14a** in 80% yield (entry 9). Under conventional thermal heating conditions, longer reaction times are necessary, which would lead to significant decomposition of isobutoxycarbonylamino ester and supply weaker yield of the desired quinazolinone.

Table 1
Investigation of the microwave-assisted synthesis of Quinazolinone **14a**[a]



Entry	R (**12a**, equiv)	Conditions[b]	Yield[c] (products)
1	H (1)	**A**, DMF, 80 °C, 10 min	10% (**13a**+**14a**)
2	H (1)	**A**, DMF, 80 °C, 20 min	15% (**13a**+**14a**)
3	H (1)	**A**, THF/H_2O, 120 °C, 20 min	18% (**13a**+**14a**)
4	H (2)	**A**, THF/H_2O, 120 °C, 20 min	28% (**13a**+**14a**)
5	H (2)	**A**, CH_3CN, 120 °C, 20 min	50% (**14a**)
6	Et (3)	**B** (2 equiv), 120 °C, 20 min	50% (**14a**)
7	Et (5)	**B** (3 equiv), 120 °C, 20 min	60% (**14a**)
8	H (1)	**C**, 120 °C, 20 min	80% (**13a**+**14a**)
9	H (1)	**C**, 120 °C, 20 min, then *2 N NaOEt*/EtOH (2 equiv), 120 °C, 10 min	80% (**14a**)

[a] All reactions were carried out on a 1 mmol scale of anthranilamide in sealed vials under pressure in a CEM Discover® apparatus.
[b] A: HOBT (1 equiv), EDCI (1 equiv); B: *2 N NaOEt*, EtOH; C: isobutyl chloroformate (1 equiv), *N*-methylmorpholine (1 equiv), THF, −15 °C to room temperature, then anthranilamide (1 equiv).
[c] Isolated yield.

Heating quinazolinone **14a** in xylene in the presence of polyphosphoric acid[16,17] (PPA) for 12 h at 120 °C led to a mixture of the desired 3-methyl- imidazo[1,5-*a*]quinazolin-5-(4*H*)-one **15a** and starting material in weak yield. Under microwave irradiation,[18] the reaction occurred at atmospheric pressure for 15 min at 120 °C and afforded only the desired compound **15a** in 85% yield. These optimized conditions were then applied to the synthesis of a range of imidazo[1,5-*a*]quinazolin-5-(4*H*)-one derivatives as shown in Table 2. No alternative cyclization to nitrogen at position 3 of the quinazolinone core occurred and the structures of some compounds were unequivocally determined by NMR spectra, including steady state NOE measurements. In the case of 3-monosubstituted-imidazoquinazolinones **15c**,**g**,**k**,**o**, the procedure needs the formation of the formamide derivatives by deprotection with trifluoroacetic acid and formylation with ethyl formate[19] of the corresponding Boc-intermediates **14b**,**f**,**j**,**n**.

3. Conclusion

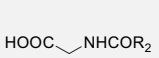
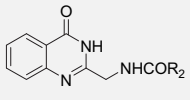
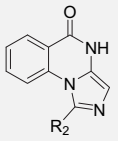
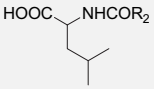
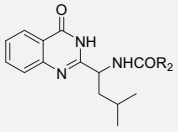
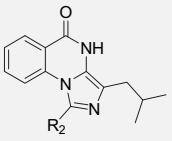
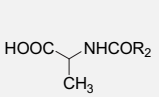
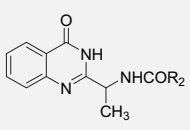
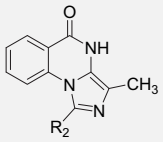
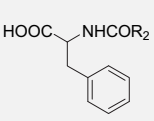
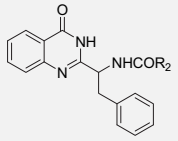
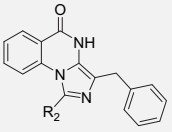
In conclusion, we have developed a novel and highly efficient two-step procedure promoted by microwave irradiation for the synthesis of imidazo[1,5-*a*]quinazolin-5-(4*H*)-one derivatives (15) from anthranilamide and various Boc- or acylamino acids, followed by intramolecular cyclodehydration under acidic conditions. These results demonstrate the value of microwave-assisted chemistry not only to provide increased yields and shortened reaction times, but also to expand the accessible chemical space by generating products, which are difficult to obtain in usual thermal conditions. This method has now been adapted to the synthesis of diverse screening libraries of related imidazoquinazolinones, which can be employed as intermediates in the synthesis of expected bioactive compounds and will be published in due course.

4. Experimental

4.1. General experimental information

All reagents and solvents were purchased and used without further purification. Melting points were determined on a BÜCHI

Table 2
Microwave-assisted synthesis[a] of quinazolinones **14a–p**[b] and cyclodehydration to **15a–p**[c]

Entry	Amino acid **12**	**14** (yield,[d] %)	**15** (yield,[d] %)	Entry	Amino acid **12**	**14** (yield,[d] %)	**15** (yield,[d] %)
							
1	R_2=CH_3	14a (80)	15a (85)	9	R_2=CH_3	14i (79)	15i (87)
2	OtBu	14b (65)		10	OtBu	14j (73)	
3	H	14c (76)	15c (81)	11	H	14k (73)	15k (79)
4	Ph	14d (81)	15d (79)	12	Ph	14l (71)	15l (92)
							
5	R_2=CH_3	14e (72)	15e (74)	13	R_2=CH_3	14m (82)	15m (78)
6	OtBu	14f (76)		14	OtBu	14n (87)	
7	H	14g (69)	15g (95)	15	H	14o (77)	15o (81)
8	Ph	14h (76)	15h (93)	16	Ph	14p (88)	15p (80)

[a] Microwave irradiation was performed in a CEM Discover® apparatus.
[b] All reactions were carried out in sealed vials under pressure with isobutyl chloroformate (2 mmol), *N*-methylmorpholine (2 mmol), *N*-acylamino acid derivative (2 mmol), anthranilamide (2 mmol) and *NaOEt*/EtOH (4 mmol).
[c] The cyclodehydration occurred at atmospheric pressure at 120 °C within 15 min.
[d] Isolated yield after recrystallization from ethanol.

B-540 apparatus and are uncorrected. Mass spectra were performed on a Finnigan MAT SSQ 710 Advantage spectrometer and were recorded in the ES+ mode. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 P and 2D NMR spectra on a Bruker DPX 300. Elemental analyses were performed by C.N.R.S-Vernaison, and were in agreement with the calculated values within ±0,4%. Microwave experiments were carried out under pressure (0–20 bar, tubes of 15 mL, sealed with a septum) or at atmospheric pressure in a glass vessel prolonged by a condenser, using a focused microwave reactor (CEM Discover™). The temperature content of the reaction mixture is monitored using calibrated infrared sensor mounted under the sealed vial or the glass vessel. The target temperature was reached with a ramp of 2 min and the microwave power stay constant to hold the mixture at this temperature. The time of the reaction does not include the ramp period.

4.2. General procedure for synthesis of 2-*N*-acylaminoalkyl-quinazolin-4-(3*H*)-ones 14a,b,d–f,h–j,l–n,p

In a sealed reaction vial, isobutyl chloroformate (2 mmol) was added to a cold (−15 °C) solution of *N*-acylamino acid derivative **12** (2 mmol) and *N*-methylmorpholine (2 mmol) in THF (10 mL) and the mixture was stirred at −15 °C for 30 min. Anthranilamide (2 mmol) was then added and the sealed vial was irradiated in the microwave for 20 min at 120 °C (power of 100 W). After cooling the mixture to room temperature, a solution of *2 N NaOEt* in ethanol (2 mL) was added and the resulting mixture was heated in the microwave at 120 °C for 10 min (power of 100 W). After evaporation under reduced pressure, the resulting residue was hydrolyzed, acidified with aqueous 1 N HCl solution untill precipitation and recrystallized from EtOH.

*4.2.1. 2-N-Acetylaminomethyl-quinazolin-4-(3H)-one (**14a**).* Anthranilamide was reacted with *N*-acetylglycine to obtain **14a** as a white solid in 80% yield: mp 267–270 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.92 (s, 3H), 4.22 (d, *J*=5.7 Hz, 2H), 7.49 (t, *J*=7.1 Hz 1H), 7.62 (d, *J*=8.1 Hz, 1H), 7.80 (t, *J*=7.1 Hz, 1H), 8.10 (d, *J*=7.9 Hz, 1H), 8.39 (t, *J*=5.7 Hz, 1H), 12.17 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=23.0, 42.0, 121.6, 126.3, 126.8, 127.3, 134.9, 148.9, 155.0, 161.9, 170.4; MS *m*/*z* 218.22 (M+H); Calcd for $C_{11}H_{13}N_3O_2$: C 60.26%; H 5.98%; N 19.17%, found: C 60.45%; H 5.74%; N 19.23%.

*4.2.2. 2-N-Terbutoxycarbonylaminomethyl-quinazolin-4-(3H)-one (**14b**).* Anthranilamide was reacted with *N*-Boc-glycine to obtain **14b** as a white solid in 65% yield: mp 208–210 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.40 (s, 9H), 4.08 (m, 2H), 7.18 (t, *J*=5.50 Hz, 1H), 7.48 (t, *J*=7.60 Hz, 1H), 7.60 (d, *J*=7.9 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 11.83 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=28.6, 43.1, 78.8, 121.6, 126.3, 126.7, 127.3, 134.9, 149.0, 155.2, 156.2, 162.0; MS *m*/*z* 276.30 (M+H); Calcd for $C_{14}H_{19}N_3O_3$: C 60.63%; H 6.91%; N 15.15%, found: C 60.87%; H 6.76%; N 15.27%.

*4.2.3. 2-N-Benzoylaminomethyl-quinazolin-4-(3H)-one (**14d**).* Anthranilamide was reacted with hippuric acid to obtain **14d** as a white solid in 81% yield: mp 279–281 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=4.42 (d, *J*=5.6, 2H), 7.45–7.60 (m, 5H), 7.77 (t, *J*=7.5 Hz, 1H), 7.92 (d, *J*=7.7 Hz, 2H), 8.08 (d, *J*=8.0 Hz, 1H), 9.03 (t, *J*=5.6, 1H), 12.27 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=42.7,121.6,126.3,126.7,127.3,127.8,128.8,131.9,134.3,134.8, 149.0,155.2,162.2,167.1; MS *m*/*z* 280.29 (M+H); Calcd for $C_{16}H_{15}N_3O_2$: C 68.31%; H 5.37%; N 14.94%, found: C 68.62%; H 5.25%; N 15.03%.

*4.2.4. 2-[1-(N-Acetylamino)ethyl]-quinazolin-4-(3H)-one (**14e**).* Anthranilamide was reacted with *N*-acetylalanine to obtain **14e** as a white solid in 72% yield: mp 254–256 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.38 (d, *J*=7.15, 3H), 1.87 (s, 3H), 4.72 (m, 1H), 7.48 (t, *J*=7.5, 1H), 7.61 (d, *J*=8.0, 1H), 7.78 (t, *J*=7.55, 1H), 8.08 (d, *J*=8.0, 1H), 8.32 (d, *J*=7.05, 1H), 12.16 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=19.7, 23.0, 48.2, 121.6, 126.3, 126.8, 127.4, 134.9, 149.1, 159.0, 162.1, 169.8; MS *m*/*z* 232.25 (M+H); Calcd

for $C_{12}H_{15}N_3O_2$: C 61.79%; H 6.48%; N 18.01%, found: C 61.95%; H 6.29%; N 18.37%.

*4.2.5. 2-[1-(N-Terbutoxycarbonylamino)ethyl]-quinazolin-4-(3H)-one (**14f**).* Anthranilamide was reacted with *N*-Boc-alanine to obtain **14f** as a white solid in 76% yield: mp 218–220 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.36 (m, 12H), 4.47 (m, 1H), 7.19 (d, *J*=7.5 Hz, 1H), 7.48 (t, *J*=7.3 Hz, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.78 (t, *J*=7.3 Hz, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 12.08 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=19.8, 28.6, 49.7, 78.7, 121.5, 126.2, 126.8, 127.4, 134.9, 149.0, 155.5, 159.2, 162.2; MS *m*/*z* 290.32 (M+H); Calcd for $C_{15}H_{21}N_3O_3$: C 61.84%; H 7.27%; N 14.42%, found: C 62.04%; H 7.17%; N 14.56%.

*4.2.6. 2-[1-(N-Benzoylamino)ethyl]-quinazolin-4-(3H)-one (**14h**).* Anthranilamide was reacted with *N*-Benzoylalanine to obtain **14h** as a white solid in 76% yield: mp 260–262 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.55 (d, *J*=7.05, 3H), 4.95 (m, 1H), 7.45–7.62 (m, 5H), 7.78 (t, *J*=7.3, 1H), 7.93 (d, *J*=8.10, 2H), 8.10 (d, *J*=8.0, 1H), 8.81 (d, *J*=6.90, 1H), 12.31 (m, 1H); MS *m*/*z* 294.32 (M+H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=19.4, 49.2, 121.6, 126.3, 126.8, 127.5, 128.0, 128.7, 131.9, 134.3, 134.9, 149.0, 159.0, 162.2, 166.7; MS *m*/*z* 294.32 (M+H); Calcd for $C_{17}H_{15}N_3O_2$: C 69.61%; H 5.15%; N 14.33%, found: C 69.84%; H 5.08%; N 14.46%.

*4.2.7. 2-[1-(N-Acetylamino)-3-methylbutyl]-quinazolin-4-(3H)-one (**14i**).* Anthranilamide was reacted with *N*-acetylleucine to obtain **14i** as a white solid in 79% yield: mp 213–215 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.90 (m, 6H), 1.63 (m, 3H), 1.88 (s, 3H), 4.75 (m, 1H), 7.48 (t, *J*=7.1 Hz 1H), 7.61 (d, *J*=7.6 Hz, 1H), 7.79 (t, *J*=7.1 Hz, 1H), 8.09 (d, *J*=7.6 Hz, 1H), 8.28 (d, *J*=7.9 Hz, 1H), 12.26 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=21.9, 22.9, 23.4, 24.8, 42.4, 51.0, 121.5, 126.2, 126.7, 127.3, 134.8, 149.1, 159.0, 162.1, 169.9; MS *m*/*z* 274.33 (M+H); Calcd for $C_{15}H_{19}N_3O_2$: C 65.91%; H 7.01%; N 15.37%, found: C 66.13%; H 6.95%; N 15.52%.

*4.2.8. 2-[1-(N-Terbutoxycarbonylamino)-3-methylbutyl]-quinazolin-4-(3H)-one (**14j**).* Anthranilamide was reacted with *N*-Boc-leucine to obtain **14j** as a white solid in 73% yield: mp 178–180 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.89 (m, 6H), 1.35 (s, 9H), 1.58 (m, 3H), 4.48 (m, 1H), 7.13 (d, *J*=8.2 Hz, 1H), 7.47 (t, *J*=7.6 Hz 1H), 7.60 (d, *J*=8.1 Hz, 1H), 7.78 (t, *J*=7.6 Hz, 1H), 8.08 (d, *J*=8.1 Hz, 1H), 12.15 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=21.9, 23.3, 24.9, 28.6, 42.4, 52.8, 87.7, 121.5, 126.2, 126.7, 127.4, 134.9, 155.7, 159.0, 162.2; MS *m*/*z* 332.41 (M+H); Calcd for $C_{18}H_{25}N_3O_3$: C 65.23%; H 7.60%; N 12.68%, found: C 65.49%; H 7.51%; N 12.83%.

*4.2.9. 2-[1-(N-Benzoylamino)-3-methylbutyl]-quinazolin-4-(3H)-one (**14l**).* Anthranilamide was reacted with *N*-Benzoylleucine to obtain **14l** as a white solid in 71% yield: mp 240–242 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.92 (m, 6H), 1.70 (m, 2H), 1.92 (m, 1H), 5.0 (m, 1H), 7.42–7.60 (m, 5H), 7.75 (t, *J*=7.6, 1H), 7.93 (d, *J*=7.4, 2H), 8.08 (d, *J*=7.8, 1H), 8.85 (d, *J*=7.6, 1H), 12.39 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=21.9, 23.4, 25.1, 42.2, 52.3, 121.6, 126.3, 126.5, 127.2, 128.0, 128.7, 131.9, 134.4, 134.6, 149.2, 159.7, 163.2, 166.8; MS *m*/*z* 336.39 (M+H); Calcd for $C_{20}H_{21}N_3O_2$: C 71.62%; H 6.31%; N 12.53%, found: C 71.90%; H 6.22%; N 12.65%.

*4.2.10. 2-[1-(N-Acetylamino)-2-phenylethyl]-quinazolin-4-(3H)-one (**14m**).* Anthranilamide was reacted with *N*-acetylphenylalanine to obtain **14m** as a white solid in 82% yield: mp 256–258 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.80 (m, 3H), 2.92 (m, 1H), 3.15 (m, 1H), 4.92 (m, 1H), 7.15–7.35 (m, 5H), 7.49 (t, *J*=7.5 Hz, 1H), 7.64 (d, *J*=8.1 Hz, 1H), 7.80 (t, *J*=7.5 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 8.48 (d, *J*=7.8 Hz, 1H), 12.37 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=22.9, 54.1, 121.6, 126.3, 126.8, 126.9, 128.6, 129.7, 135.0, 138.1, 149.1, 158.2, 162.1, 169.9; MS *m*/*z* 308.34 (M+H); Calcd for $C_{18}H_{17}N_3O_2$: C 70.34%; H 5.58%; N 13.67%, found: C 70.56%; H 5.47%; N 13.78%.

*4.2.11. 2-[1-(N-Terbutoxycarbonylamino)-2-phenylethyl]-quinazolin-4-(3H)-one (**14n**).* Anthranilamide was reacted with *N*-Boc-phenylalanine to obtain **14n** as a white solid in 87% yield: mp 211–213 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.28 (m, 9H), 2.91 (m, 1H), 3.10 (m, 1H), 4.63 (m, 1H), 7.15–7.37 (m, 6H), 7.49 (t, *J*=7.5 Hz, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.80 (t, *J*=7.5 Hz, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 12.36 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=28.6, 55.9, 78.7, 121.6, 126.3, 126.8, 127.3, 128.5, 129.8, 134.9, 138.2, 155.8, 162.2; MS *m*/*z* 366.42 (M+H); Calcd for $C_{21}H_{23}N_3O_3$: C 69.02%; H 6.34%; N 11.50%, found: C 69.18%; H 6.24%; N 11.65%.

*4.2.12. 2-[1-(N-Benzoylamino)-2-phenylethyl]-quinazolin -4-(3H)-one (**14p**).* Anthranilamide was reacted with *N*-benzoylphenylalanine to obtain **14p** as a white solid in 88% yield: mp 274–276 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=3.22 (m, 2H), 5.14 (m, 1H), 7.17 (t, *J*=7.2 Hz, 1H), 7.27 (t, *J*=7.1 Hz, 2H), 7.43–7.53 (m, 6H), 7.61 (d, *J*=7.8 Hz, 1H), 7.80 (m, 3H), 8.11 (d, *J*=7.8 Hz, 1H), 8.94 (d, *J*=7.7 Hz, 1H), 12.51 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=38.8, 55.0, 121.7, 126.3, 126.9, 127.4, 127.9, 128.6, 128.7, 129.8, 131.9, 134.2, 134.9, 138.4, 149.0, 158.0, 162.1, 166.9; MS *m*/*z* 370.41 (M+H); Calcd for $C_{23}H_{19}N_3O_2$: C 74.78%; H 5.18%; N 11.37%, found: C 74.87%; H 5.10%; N 11.51%.

4.3. General procedure for synthesis of 2-*N*-formylaminoalkyl-quinazolin-4-(3*H*)-ones 14c,g,k,o

A mixture of the appropriate Boc-derivative **14b**,**f**,**j**,**n** (1 mmol) and trifluoroacetic acid (2,5 mL) in CH_2Cl_2 (20 mL) was stirred for 2 h at reflux. After evaporation of the solvent, triethylamine (2 mL) and ethyl formate (10 mL) were added and the reaction mixture was refluxed overnight. Trituration of the residue, obtained after evaporation under vacuum, with water provided a white powder, which was recrystallized from EtOH.

*4.3.1. 2-N-Formylaminomethyl-quinazolin-4-(3H)-one (**14c**).* **14c** was obtained as a white solid (76%): mp 263–265 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=4.28 (d, *J*=5.9 Hz, 2H), 7.49 (t, *J*=7.3 Hz 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.79 (t, *J*=7.3 Hz, 1H), 8.09 (d, *J*=7.7 Hz, 1H), 8.17 (s, 1H), 8.50 (m, 1H), 12.18 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=121.6, 126.3, 126.8, 127.2, 134.9, 148.8, 154.3, 162.0, 162.5; MS *m*/*z* 204.19 (M+H); Calcd for $C_{10}H_{11}N_3O_2$: C 58.53%; H 5.40%; N 20.48%, found: C 58.79%; H 5.35%; N 20.53%.

*4.3.2. 2-[1-(N-Formylamino)ethyl]-quinazolin-4-(3H)-one (**14g**).* **14g** was obtained as a white solid (69%): mp 239–241 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=1.40 (d, *J*=6.8 Hz, 3H), 4.81 (m, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 8.07 (m, 2H), 8.59 (d, *J*=6.7 Hz, 1H), 12.27 (m, 1H); ^{13}C NMR (75 MHz) δ=20.0, 46.7, 121.6, 126.3, 126.9, 127.4, 134.9, 148.9, 158.2, 161.4, 162.0; MS *m*/*z* 218.22 (M+H); Calcd for $C_{11}H_{11}N_3O_2$: C 60.82%; H 5.10%; N 19.34%, found: C 60.93%; H 5.04%; N 19.47%.

*4.3.3. 2-[1-(N-Formylamino)-3-methylbutyl]-quinazolin-4-(3H)-one (**14k**).* **14k** was obtained as a white solid (73%): mp 214–216 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.89 (m, 6H), 1.35 (s, 9H), 1.64 (m, 3H), 4.84 (m, 1H), 7.48 (t, *J*=7.5 Hz 1H), 7.61 (d, *J*=8.1 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 8.09 (m, 2H), 8.52 (d, *J*=8.3 Hz, 1H), 12.36 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=21.9, 23.4, 24.8, 42.6, 49.5, 121.5, 126.3, 126.8, 127.3, 134.9, 149.1, 158.4, 161.6, 162.1; MS

m/*z* 260.30 (M+H); Calcd for $C_{14}H_{17}N_3O_2$: C 64.85%; H 6.61%; N 16.21%, found: C 65.01%; H 6.53%; N 16.41%.

*4.3.4. 2-[1-(N-Formylamino)-2-phenylethyl]-quinazolin-4-(3H)-one (**14o**).* **14o** was obtained as a white solid (77%): mp 214–215 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.94 (m, 1H), 3.19 (m, 1H), 5.04 (m, 1H), 7.28 (m, 5H), 7.50 (m, 1H), 7.64 (m, 1H), 7.81 (m, 1H), 7.99 (m, 1H), 8.10 (m, 1H), 8.69 (m, 1H), 12.47 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=52.5, 121.6, 126.3, 127.0, 127.4, 128.6, 129.1, 129.8, 129.9, 135.0, 137.7, 148.9, 157.4, 161.6, 162.0; MS *m*/*z* 294.32 (M+H); Calcd for $C_{17}H_{15}N_3O_2$: C 69.61%; H 5.15%; N 14.33%, found: C 69.80%; H 5.09%; N 14.44%.

4.4. General procedure for synthesis of imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones 15a–p

A mixture of the appropriate acylaminoquinazolinone derivative **14** (1 mmol) and PPA (3 g/mmol) in xylene (5 mL) was heated at 120 °C under microwave irradiation at atmospheric pressure for 15 min (power of 20 W). The xylene was decanted and the remaining gum was washed twice with petroleum ether and dissolved in water. The aqueous solution was filtrated and dropwise addition of 30% NaOH led to precipitation of the product, which was removed by filtration and recrystallized in EtOH.

*4.4.1. 1-Methylimidazo[1,5-a]quinazolin-5-(4H)-one (**15a**).* **15a** was obtained as a beige solid (85%): mp 200–202 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.77 (s, 3H), 6.38 (s, 1H), 7.50 (t, *J*=7.3 Hz, 1H), 7.84 (t, *J*=7.3 Hz, 1H), 8.04 (d, *J*=8.4 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 11.79 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=18.8, 105.3, 116.6, 117.9, 125.8, 129.1, 130.3, 134.9, 136.4, 136.5, 157.8; MS *m*/*z* 200.21 (M+H); Calcd for $C_{11}H_9N_3O$: C 66.32%; H 4.55%; N 21.09%, found: C 66.48%; H 4.49%; N 21.17%.

*4.4.2. Imidazo[1,5-a]quinazolin-5-(4H)-one (**15c**).* **15c** was obtained as a beige solid (81%): mp 240–242 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=6.52 (s, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.84 (t, *J*=7.5 Hz, 1H), 8.12 (d, *J*=7.9 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 8.53 (s, 1H), 11.84 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=107.6, 115.6, 117.1, 126.4, 126.5, 129.0, 129.7, 135.1, 158.2; MS *m*/*z* 186.18 (M+H); Calcd for $C_{10}H_7N_3O$: C 64.86%; H 3.81%; N 22.69%, found: C 65.02%; H 3.73%; N 22.75%.

*4.4.3. 1-Phenylimidazo[1,5-a]quinazolin-5-(4H)-one (**15d**).* **15d** was obtained as a yellow solid (79%): mp 258–260 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ 6.65 (s, 1H), 7.12 (d, *J*=8.3 Hz, 1H), 7.42 (t, *J*=7.8 Hz, 1H), 7.49–7.61 (m, 6H), 8.16 (d, *J*=7.9 Hz, 1H), 11.96 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ 107.3, 116.5, 118.3, 126.2, 129.3, 129.4, 129.9, 131.3, 133.3, 134.1, 136.1, 138.5, 158.0; MS *m*/*z* 262.27 (M+H); Calcd for $C_{16}H_{11}N_3O$: C 73.55%; H 4.24%; N 16.08%, found: C 73.72%; H 4.16%; N 16.19%.

*4.4.4. 1,3-Dimethylimidazo[1,5-a]quinazolin-5-(4H)-one (**15e**).* **15e** was obtained as a yellow solid (74%): mp 286–288 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.15 (s, 3H), 2.74 (s, 3H), 7.48 (t, *J*=7.4 Hz, 1H), 7.82 (t, *J*=7.4, 1H), 7.99 (d, *J*=8.2, 1H), 8.18 (dd, *J*=7.9, 1.7, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=11.5, 18.7, 112.5, 116.4, 117.7, 125.2, 125.5, 129.2, 134.9, 135.1, 136.6, 158.2; MS *m*/*z* 214.25 (M+H); Calcd for $C_{12}H_{11}N_3O$: C 67.59%; H 5.20%; N 19.71%, found: C 67.74%; H 5.11%; N 19.90%.

*4.4.5. 3-Methylimidazo[1,5-a]quinazolin-5-(4H)-one (**15g**).* **15g** was obtained as a beige solid (95%): mp 220–222 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.18 (s, 3H), 7.45 (t, *J*=7.8 Hz, 1H), 7.81 (t, *J*=7.6 Hz, 1H), 8.11 (m, 2H), 8.44 (s, 1H), 11.70 (m, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=11.7, 115.1, 115.3, 116.9, 125.0, 125.2, 126.1, 129.0, 135.1, 135.3, 158.5; MS *m*/*z* 200.21 (M+H); Calcd for $C_{11}H_9N_3O$: C 66.32%; H 4.55%; N 21.09%, found: C 66.50%; H 4.45%; N 21.21%.

*4.4.6. 3-Methyl-1-phenylimidazo[1,5-a]quinazolin-5-(4H)-one (**15h**).* **15h** was obtained as a yellow solid (93%): mp 227–229 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.23 (s, 3H), 7.09 (d, *J*=8.4 Hz, 1H), 7.38 (t, *J*=7.8 Hz, 1H), 7.46–7.58 (m, 6H), 8.14 (d, *J*=7.7 Hz, 1H), 11.85 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=11.6,114.7, 116.3,118.1,125.9,126.5,127.9,128.7,129.3,129.8,133.3,134.0,136.2,137.3, 158.4; MS *m*/*z* 276.30 (M+H); Calcd for $C_{17}H_{13}N_3O$: C 74.17%; H 4.76%; N 15.26%, found: C 74.32%; H 4.66%; N 15.40%.

*4.4.7. 3-Isobutyl-1-methylimidazo[1,5-a]quinazolin-5-(4H)-one (**15i**).* **15i** was obtained as a beige solid (87%): mp 266–268 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.87 (d, *J*=6.7 Hz, 6H), 1.85 (m, 1H), 2.42 (d, *J*=7.0 Hz, 2H), 2.74 (s, 3H), 7.47 (t, *J*=7.5 Hz, 1H), 7.81 (t, *J*=7.5 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 11.64 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=18.8, 22.6, 28.9, 34.0, 116.4, 116.8, 117.8, 125.5, 125.7, 129.1, 134.9, 135.2, 136.8, 158.2; MS *m*/*z* 256.31 (M+H); Calcd for $C_{15}H_{17}N_3O$: C 70.56%; H 6.71%; N 16.46%, found: C 70.71%; H 6.54%; N 16.57%.

*4.4.8. 3-Isobutylimidazo[1,5-a]quinazolin-5-(4H)-one (**15k**).* **15k** was obtained as a beige solid (79%): mp 257–259 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.88 (d, *J*=6.6 Hz, 6H), 1.88 (m, 1H), 2.48 (m, 2H), 7.46 (t, *J*=7.5 Hz, 1H), 7.82 (t, *J*=7.5 Hz, 1H), 8.12 (m, 2H), 8.46 (s, 1H), 11.74 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=22.5, 29.0, 34.3, 115.4, 116.9, 119.3, 125.3, 126.1, 129.0, 135.1, 135.3, 158.6; MS *m*/*z* 242.28 (M+H); Calcd for $C_{14}H_{15}N_3O$: C 69.69%; H 6.27%; N 17.41%, found: C 69.82%; H 6.12%; N 17.53%.

*4.4.9. 3-Isobutyl-1-phenyllimidazo[1,5-a]quinazolin-5-(4H)-one (**15l**).* **15l** was obtained as a yellow solid (92%): mp 283–285 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=0.91 (d, *J*=6.6 Hz, 6H), 1.92 (m, 1H), 2.52 (d, *J*=7.1 Hz, 2H), 7.12 (d, *J*=8.3 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.47–7.59 (m, 6H), 8.14 (d, *J*=7.9 Hz, 1H), 11.81 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=22.7, 28.9, 34.1, 116.4, 118.1, 119.0, 125.9, 126.9, 129.3, 129.7, 129.9, 133.4, 134.1, 136.3, 137.5, 158.7; MS *m*/*z* 318.38 (M+H); Calcd for $C_{20}H_{19}N_3O$: C 75.69%; H 6.03%; N 13.24%, found: C 75.87%; H 5.98%; N 13.31%.

*4.4.10. 3-Benzyl-1-methylimidazo[1,5-a]quinazolin-5-(4H)-one (**15m**).* **15m** was obtained as a white solid (78%): mp 200–202 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=2.73 (s, 3H), 3.92 (s, 2H), 7.14 (m, 1H), 7.24 (m, 4H), 7.48 (t, *J*=7.9 Hz, 1H), 7.82 (t, *J*=7.5 Hz, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 8.18 (d, *J*=7.7 Hz, 1H), 11.91 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=18.8, 31.1, 116.2, 116.5, 117.7, 125.6, 126.1, 128.5, 128.9, 129.2, 135.0, 135.8, 136.4, 141.4, 158.4; MS *m*/*z* 290.33 (M+H); Calcd for $C_{18}H_{15}N_3O$: C 74.72%; H 5.23%; N 14.52%, found: C 74.90%; H 5.15%; N 14.71%.

*4.4.11. 3-Benzylimidazo[1,5-a]quinazolin-5-(4H)-one (**15o**).* **15o** was obtained as a beige solid (81%): mp 274–276 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=3.97 (s, 2H), 7.14 (m, 1H), 7.26 (m, 4H), 7.46 (t, *J*=7.4 Hz, 1H), 7.81 (t, *J*=7.3 Hz, 1H), 8.12 (m, 2H), 8.48 (s, 1H), 11.96 (s, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C) δ=31.4, 115.4, 117.0, 118.8, 125.3, 125.8, 126.1, 126.2, 128.6, 128.9, 129.0, 135.1, 135.2, 141.3, 158.6; MS *m*/*z* 276.30 (M+H); Calcd for $C_{17}H_{13}N_3O$: C 74.17%; H 4.76%; N 15.26%, found: C 74.41%; H 4.65%; N 15.39%.

*4.4.12. 3-Benzyl-1-phenylimidazo[1,5-a]quinazolin-5-(4H)-one (**15p**).* **15p** was obtained as a yellow solid (80%): mp 270–272 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C) δ=4.02 (s, 2H), 7.14 (m, 2H), 7.26 (t, *J*=7.3 Hz, 2H), 7.32 (d, *J*=7.8 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 1H), 7.48–7.58 (m, 6H), 8.16 (d, *J*=7.9 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (75 MHz,

[D_6]DMSO, 25 °C) δ=31.2, 116.4, 118.2, 126.0, 126.2, 126.8, 128.6, 129.0, 129.3, 129.9, 133.2, 134.1, 136.2, 137.9, 141.1, 158.6; MS *m*/*z* 352.40 (M+H); Calcd for $C_{23}H_{17}N_3O$: C 78.61%; H 4.88%; N 11.96%, found: C 78.78%; H 4.81%; N 12.05%.

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