

Synthesis of acyl naphthylamines and their applications in the formation of benzoquinazolines

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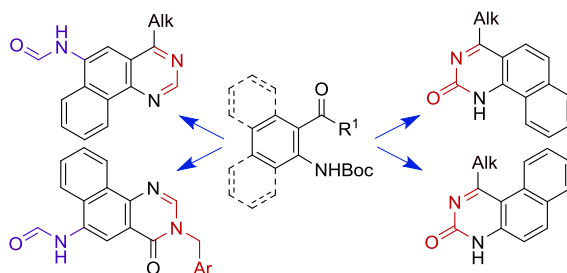
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Abstract

The synthesis of acyl *N*-Boc-1- and *N*-Boc-2-naphthylamines and their transformation into alkyl substituted benzoquinazolines and benzoquinazolinones through the reaction with formamide or potassium cyanate in the presence of ammonium acetate is described. Presented acyl derivatives were obtained from the reactions of the corresponding lithiated *N*-Boc naphthylamines with various acetylating agents like AcCl, Ac₂O, AcOEt, PivCl, *i*PrCOCl and also Wienreb amides. Biological screening of the potential cytotoxicity on the HT29 cell line and lymphocytes were demonstrated for some benzoquinazoline derivatives.



Keywords: Acylation, benzoquinazoline, benzoquinazolinone, Pd-coupling, Cu-coupling, cytotoxicity

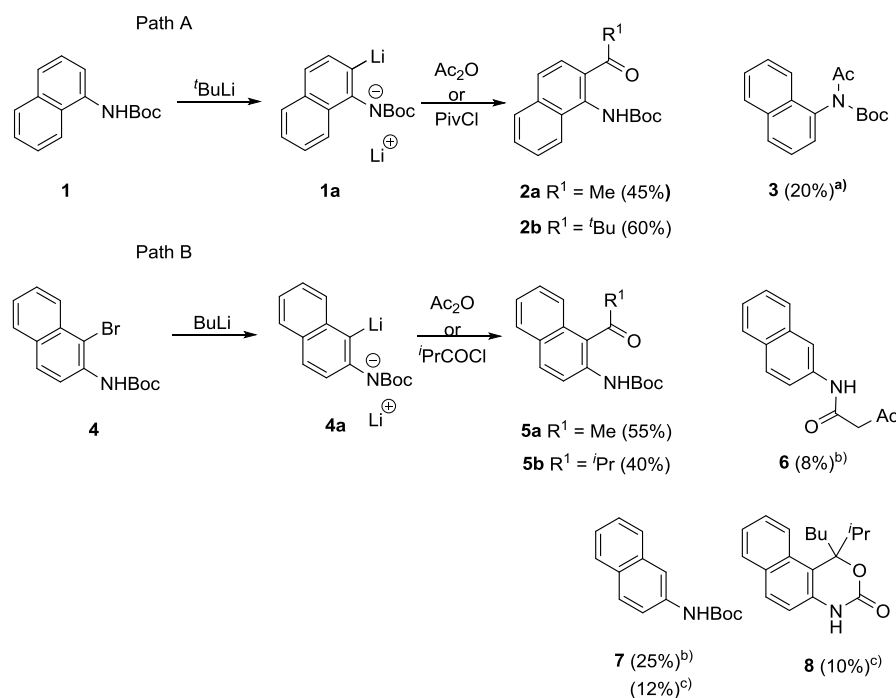
Introduction

The quinazoline or quinazolinone skeleton is a building block of various alkaloids^{1,2} with diverse biological activities³⁻⁵ like for example *vasicine* and *vasicinone* (active compounds of *Justicia athatoda*),⁶⁻⁸ asperlicins A-E (fungal metabolite components of *Aspergillus alliaceus*)^{9,10} or circumdatin H (from the fungus *Aspergillus ochraceus*).¹¹ It has been shown that e.g. asperlicin and its analogues can act as antagonists of neurotransmitter cholecystokinin (CCK).¹² Other quinazolinone alkaloids exhibit also anti-inflammatory,¹³ antiviral¹⁴ and antibacterial activity.^{15,16} Some of quinazoline derivatives have been approved as effective drugs against cancer,¹⁷ e.g. Gefitinib,^{18,19} Erlotinib²⁰ or Ispinesib.²¹ Additionally, aryl- or alkyl- quinazolin-2(1*H*)-one derivatives are applied e.g. as nonsteroidal anti-inflammatory drugs²² (Proquazone)²³ or in the treatment of cardiovascular diseases (Bemarinone).^{24,25}

In the present paper we focused on the synthesis of acyl-*N*-Boc-aminonaphthalenes and their application for the preparation of new alkylbenzoquinazolines, which constitute a continuation of our work in the field of benzoquinazoline derivatives chemistry and their potential cytotoxic activity.²⁶⁻²⁸

Results and Discussion

The synthesis of acyl-*N*-Boc-aminonaphthalenes **2a,b** and **5a,b** based on a two-stage procedure consisting of 1) in situ generation of lithium carbamates **1a** or **4a** using ^tBuLi or BuLi^{26,27} and then 2) their reaction with the selected acylating agents (Scheme 1). At the beginning of our investigations, the behavior of bis-metalated species **1a** and **4a** in the reaction with electrophiles like AcCl, Ac₂O, AcOEt, PivCl and ⁱPrCOCl was verified. The results are summarized in Table 1.



Scheme 1. Synthesis of ketones **2**, **5**. The reaction conditions ^{a)} for the reaction of **1** with Ac₂O, ^{b)} for the reaction of **4** with Ac₂O, ^{c)} for the reaction of **4** with ⁱPrCOCl.

The use of acetic anhydride for the acylation of **1** or **4** at -78 °C, turned out to be the most effective for **2a** (45%) and **5a** (55%), (Table 1, entries 3 and 11). When **1a** was treated with Ac₂O apart from **2a** also *N*-Ac, *N*-Boc derivative **3** was isolated from the post reaction mixture (Table 1, entry 3). Additionally, we have observed that an increase in the reaction temperature from -78 °C up to -20 °C, (Table 1, entry 2), resulted in a decrease in yield of **2a** (20%). Likewise ineffective was the use of acetyl chloride at -20 °C (**2a** was separated in only 10% yield, Table 1, entry 1). As can be seen in Table 1, treatment of bis-lithiated species **4a** with acetyl chloride at -78 °C gave **5a** (45%, entry 11), with comparable yield to that of acylation with Ac₂O (55%, entry 11) whereas ethyl acetate shown considerably less reactivity at this temperature (10%, entry 12).

Table 1. Optimization of conditions for the synthesis of acyl derivatives **2, 5**

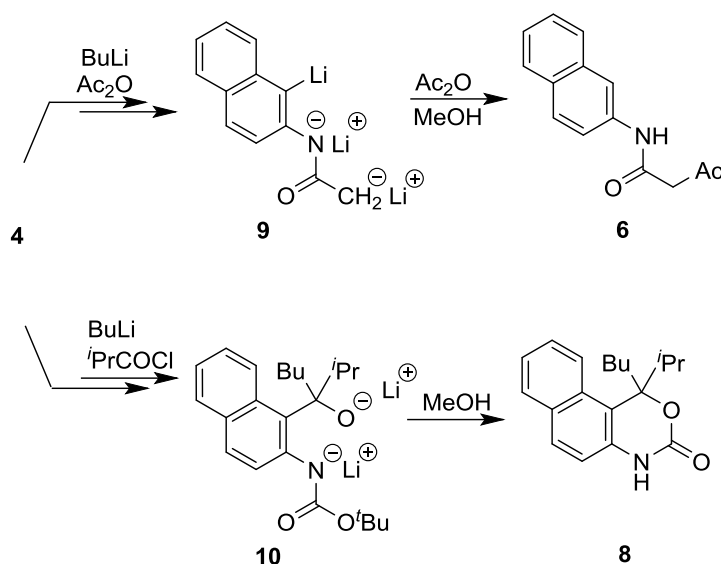
Entry	Electrophile	Temp. (°C)	Substrate	Yield (%) ^a		
				Products 2, 5	Other products	
1	AcCl	-20	1	2a (10)	–	
2	Ac ₂ O	-20		2a (20)	–	
3	Ac ₂ O	-78		2a (45)	3 (20)	
4	AcN(OMe)Me	-20		2a (30)	–	
5	PivCl	-20	1	2b (60)	–	
6	PivCl	-78		2b (trace)	–	
7	PivN(OMe)Me	-78		2b (0)	–	
8	PivN(OMe)Me	-20		2b (30)	–	
9	PivN(OMe)Me	0		2b (13)	–	
10	AcCl	-78		4	5a (45)	–
11	Ac ₂ O	-78			5a (55)	6 (8) 7 (25)
12	AcOEt	-78			5a (10)	–
13	AcN(OMe)Me	-20			5a (trace)	7 (60)
14	^{<i>i</i>} PrCOCl	-78	5b (20)		8 (5) 7 (5)	
15	^{<i>i</i>} PrCOCl	-20	5b (40)		8 (10) 7 (12)	
16	^{<i>i</i>} PrCON(OMe)Me	-20	5b (2)	–		

Reaction conditions: organolithium compound (2 hours, -20° C), 1 equiv. of electrophile (2 hours, temperature described in Table 1, entry 1-16).

^a Isolated yield

In case of the synthesis of acyl derivatives **2b**, **5b** the best results were achieved employing pivaloyl or 2-methylpropanoyl chloride at $-20\text{ }^{\circ}\text{C}$ (**2b** (60%), **5b** (40%), Table 1, entries 5, 15). When the reaction temperature was decreased from $-20\text{ }^{\circ}\text{C}$ to $-78\text{ }^{\circ}\text{C}$, yields of both acetyl derivatives **2b**, **5b** were lower (Table 1, entries 6, 14). Additionally, the decrease in the reaction temperature resulted also in reduced yields of side products **7**, **8** accompanying the formation of **5b**, from 12% (**7**), 10% (**8**) at $-20\text{ }^{\circ}\text{C}$ to about 5% (**7**, **8**) at $-78\text{ }^{\circ}\text{C}$ (Table 1, entries 14, 15).

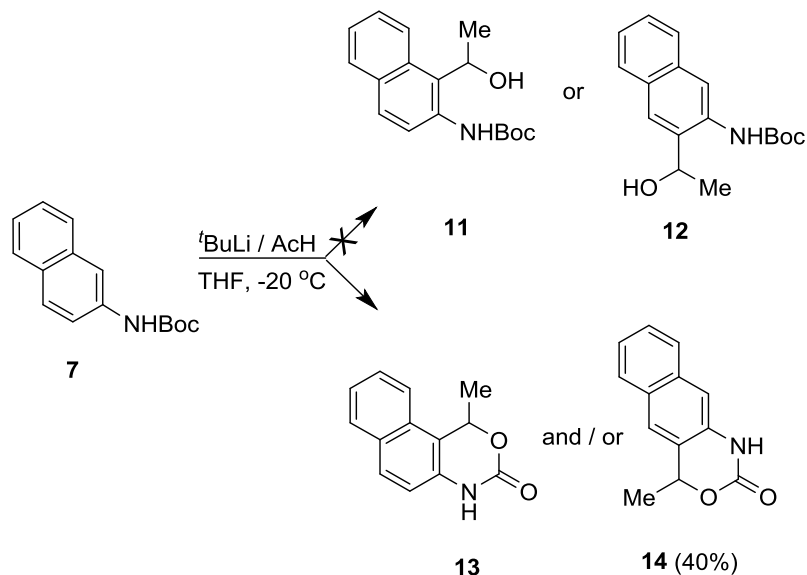
Weinreb amides are alternative acylating agents to classical ones.²⁹⁻³¹ On account of that fact, we decided to examine the effectiveness of *N*-methoxy-*N*-methylacetamide (AcN(OMe)Me), *N*-methoxy-*N*,2,2-trimethylpropanamide (PivN(OMe)Me) and *N*-methoxy-*N*,2-dimethylpropanamide (*i*PrCON(OMe)Me) in the reactions with naphthalene derivatives **1a** or **4a**.³² We noticed that bis-lithiated species **1a** reacted with AcN(OMe)Me as well as PivN(OMe)Me at $-20\text{ }^{\circ}\text{C}$ giving corresponding **2a** and **2b** in merely moderate 30% yield (Table 1, entries 4, 8). Surprisingly, the effectiveness of Weinreb amides (AcN(OMe)Me, *i*PrCON(OMe)Me) in the acylation of **4a** was very low and the desired products **5a,b** were formed in trace amounts (Table 1, entries 13, 16). Besides products **2** or **5** and mentioned above *N*-acetyl carbamate **3** (as an effect of the reaction of **1a** with Ac₂O, Table 1, entry 3), from the post reaction mixture some amounts of starting carbamates **1** or **4** (10-50%), ketoamide **6** (8%), *N*-Boc 2-naphthylamine **7** (5-60%) and naphtho[2,1-*d*][1,3]oxazin-3-one **8** (5-10%) were also isolated (confirmed by ¹H, ¹³C NMR, HRMS, Table 1, entries 11, 13-15). The formation of ketoamide **6**, appears to result from the *C*-acylation of lithiated *N*-(naphthalen-2-yl)acetamide **9** by Ac₂O, followed by quenching with methanol. The generation of **9** was most probably due to the ability of *N*-Boc-2-naphthylamine derivatives to cleave the Boc protecting group under basic conditions accompanied by *N*-acylation with Ac₂O (Scheme 2).²⁷



Scheme 2. Possible pathways for the formation of **6** and **8**.

This type of acetamide aldolization for the first time has been reported by Hauser and Gay.³³ They observed that acetanilide can be efficiently deprotonated by BuLi to produce the corresponding dianion, which is able to react with diverse electrophiles.³⁴ In turn, the formation of **8** seems to result from BuLi addition (excess of BuLi) to the carbonyl group of the emerging keto derivative which subsequently transforms into adduct **10** and finally to **8** via an intramolecular cyclization (Scheme 2).

We have observed the formation of systems similar to **8** in the reaction of the *bis*-lithium derivative generated from *N*-Boc-2-naphthylamine **7** (t BuLi/TMEDA) and acetaldehyde (Scheme 3). The ^1H NMR spectrum of the post reaction complex mixture indicated signals belonging to methyl-1,4-dihydronaphtho-1,3-oxazinones **13** and **14** (the ratio *ca.* 3:5, ^1H NMR) Ultimately, from the crude material only compound **14** was isolated in the pure form (40% yield).

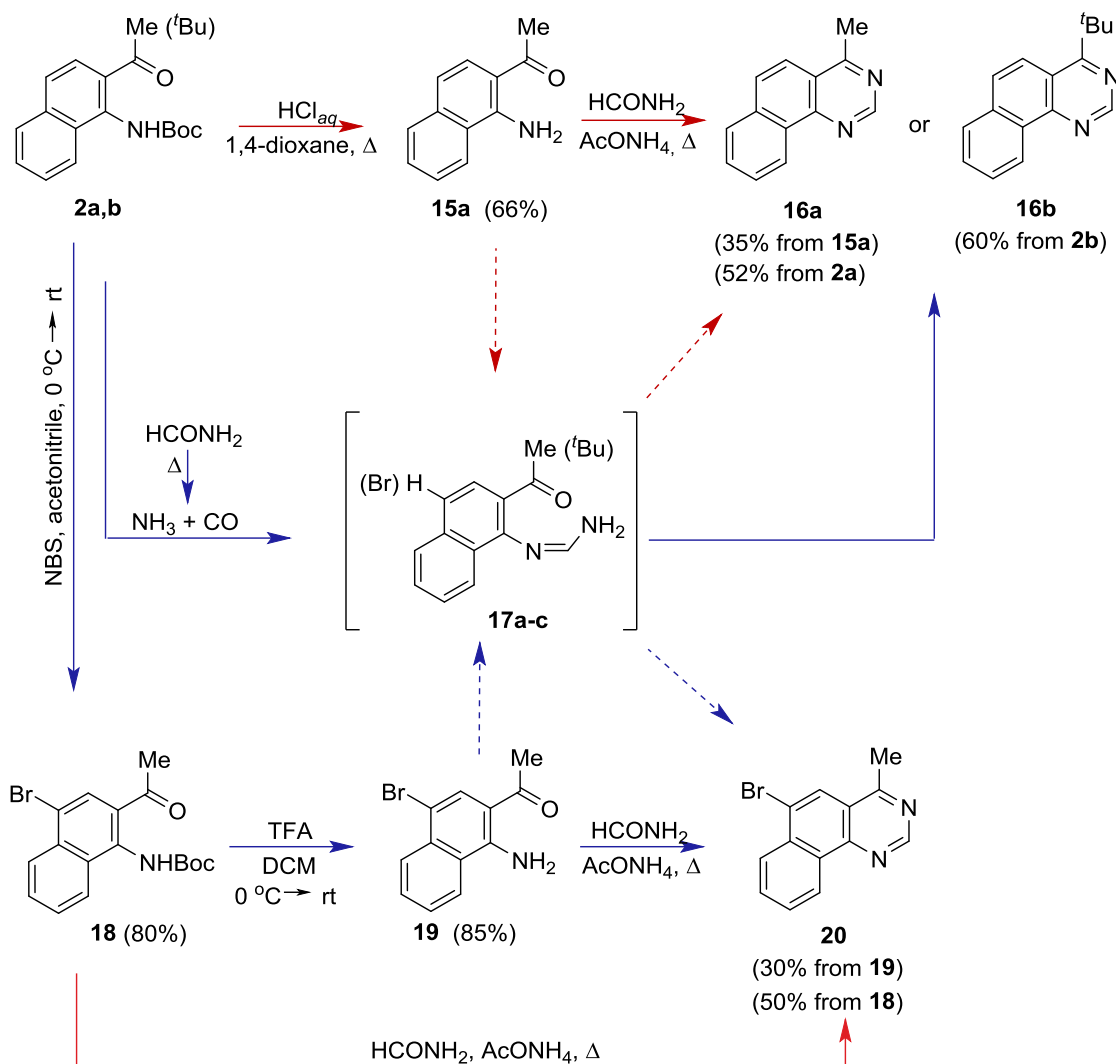


Schemat 3. Reaction of *N*-Boc-2-naphthylamine **7** with t BuLi / acetaldehyde.

In the literature several strategies have been described for the construction of a quinazoline skeleton, e.g. using aromatic nitroaldehydes,³⁵ imido amides³⁶ or amines,^{37,38} as substrates. There are some procedures for the preparation of functionalized benzoquinazolines from naphthylamine derivatives like e.g. amidines (reactions with DMFA)³⁹ or anilides (reactions with ammonium formate).³⁸ However, there are few examples of the synthesis of benzoquinazoline systems with simple alkyl substituents.^{38,40,41}

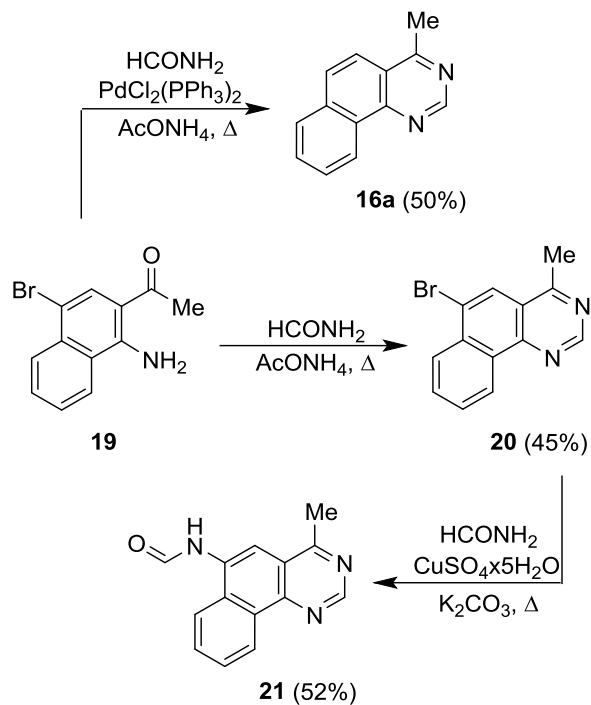
In this work alkylbenzoquinazoline derivatives were synthesized by the thermal condensation ($170\text{ }^\circ\text{C}$) of (acylnaphthyl)carbamates **2a,b**, **18** or their derivatives **15a**, **19** with $\text{HCONH}_2/\text{AcONH}_4$ (Scheme 4). Transformation of aminoketones **15a**, **19** provided the desired products **16a**, **20** in moderate yields (35%, 30%, respectively). Much better results were obtained from the direct reaction of *N*-Boc derivatives **2a**, **2b** or **18** with formamide/ AcONH_4 . The corresponding alkylbenzoquinazolines **16a,b** and **20** were obtained in 50-60% yields. Attempts to modify the reaction conditions for *N*-Boc derivatives, e.g. by the replacement of ammonium acetate by formic acid or the use only of formamide, led to a substantial decrease in yield (e.g. **16a**, 10-20% by use of $\text{HCONH}_2/\text{HCOOH}$ or 25-35% *via* reaction with HCONH_2).

In our opinion, the formation of quinazolines **16a,b** and **20** from ketones (**2a,b** and **18**, Scheme 4) by condensation with formamide runs through the formation of arylamidine type intermediate **17a** and then the ring closure reaction with a subsequent elimination of water. This can be supported by the fact that the *N*-Boc derivatives **2a,b** and **18** during the reaction with formamide, underwent deprotection to their parent ketoamines (isolated yields 6-15%) in any case.



Scheme 4. Synthesis of benzoquinazolines **16**, **20** from acyl derivatives of *N*-Boc-1-naphthylamine **2**.

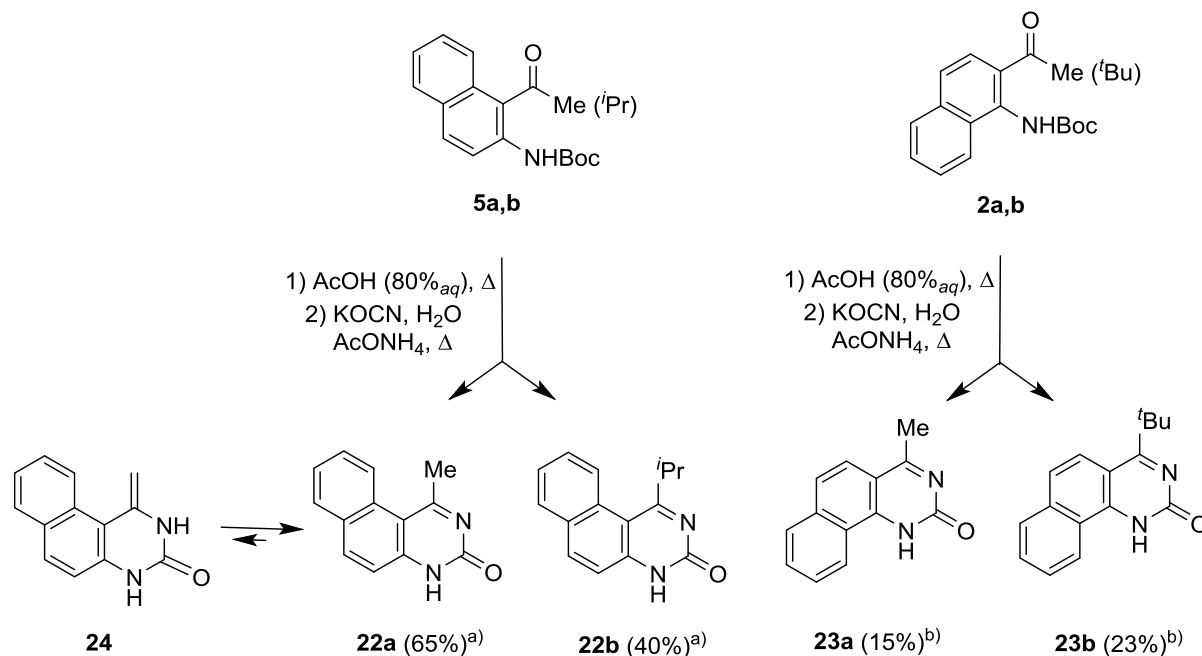
Next, we employed naphthalene ketone **19** in the synthesis of formamido quinazoline **21** via the one-pot type reaction comprising 1) condensation of amine **19** with HCONH_2 and 2) cross coupling reaction with excess of formamide in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (30 mol%). Nonetheless, this way of synthesis did not give the expected product **21** (Scheme 5). The ^1H NMR ($\text{DMSO}-d_6$) spectrum of isolated compound did not show signals belonging to protons of the $-\text{NHCHO}$ group at position 6 of benzoquinazoline skeleton. The obtained spectrum was identical to the one observed for compound **16a**. Thereby, in the course of this reaction the β -hydride elimination dominated in the last stage of the catalytic cycle and in consequence led to the formation of **16a** (50%) instead **21**. Finally, the target product **21** was obtained by the Cu(II) mediated coupling reaction⁴² of quinazoline **20** with an excess of formamide with access to air (52%, Scheme 5). The spectroscopic analysis indicated that *N*-arylformamide derivative **21** existed as a mixture of two rotamers ($\approx 2:1$), favoring the *Z* form.



Scheme 5. The formamidation reaction of benzoquinazoline derivatives **19**, **20**.

The second part of the presented work concerned the investigation of the behavior of acyl derivatives **2** or/and **5** in the synthesis of benzo[*f*]quinazolin-3(4*H*)-ones **22** and benzo[*h*]quinazolin-2(1*H*)-ones **23** (Scheme 6). Heterocycles containing a quinazolin-2(1*H*)-one scaffold are a relatively little-studied class. Some studies reported that quinazolin-2(1*H*)-ones can be obtained by cyclization reactions using amino acetophenones^{25,43,44} or aminobenzonitriles.⁴⁵ Our studies on the construction of benzoquinazolinone systems using *N*-Boc 2-naphthylamine derivatives showed that, when a solution of **5a** in acetic acid was treated with a large excess of potassium cyanate, the methylbenzoquinazolinone (**22a**) can be produced in a satisfactory yield (50%, Scheme 6). In addition, when ammonium acetate was added to the reaction mixture, the yield of lactam **22a** increased up to 65%. In accordance with this methodology, when the isopropyl derivative **5b** was treated with a mixture of KOCN, AcONH₄ the desired product **22b** was obtained in 40% yield (Scheme 6).

The transformation of *N*-Boc 1-naphthylamine derivatives **2a** and **2b** into lactams **23a** (23%) and **23b** (15%) was less efficient. ¹H NMR spectra of post reaction mixtures, showed that the main ingredients were the starting carbamates **2**. Furthermore, proton signals for the aminoketone generated by Boc group cleavage from **2b** were also observed. The analysis of obtained results gives a ground for conclusion that the conversion of acyl carbamates **2** or **5** into corresponding benzoquinazolinones **22**, **23** runs through the acidic deprotection of the amino group, as the first step and then condensation of the resulting ketoamine with potassium cyanate giving finally benzoquinazolinones (*see supplementary material*, Scheme S1, Path A: **I**→**V**→**VI**→**VII**→**II**). On the other hand, the presence of AcONH₄, which can act as a source of nitrogen (ammonium) implies the possibility to include the alternative pathway by the formation of an imidoyl derivative **VIII** (*see supplementary material*, Scheme S1, Path B: **I**→**VIII**→**IX**→**II**).

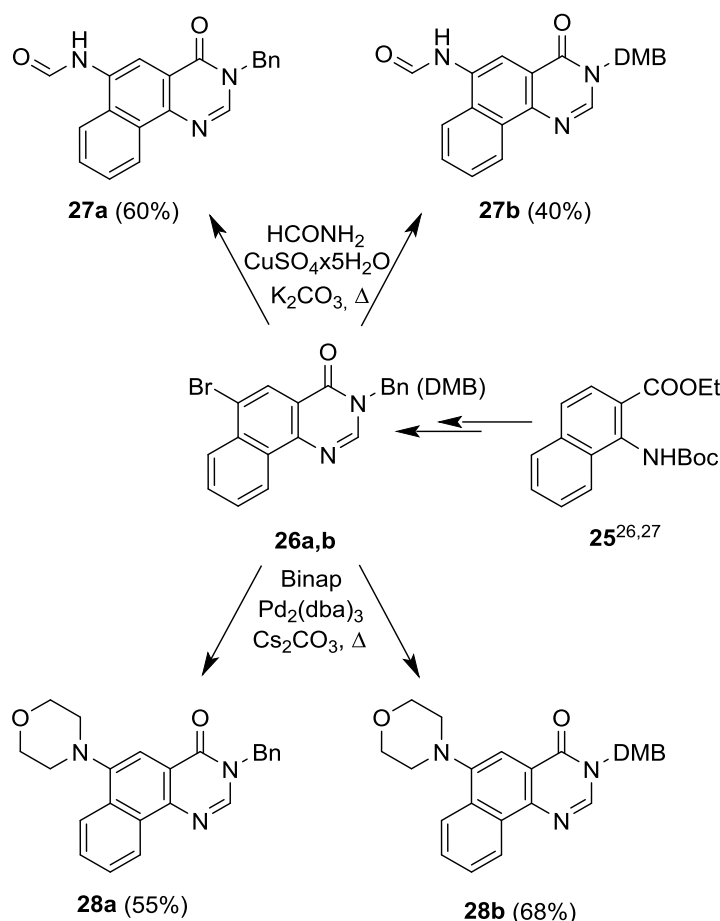


Scheme 6. The synthesis of alkyl 4-alkylbenzo[*h*]quinazolin-2(1*H*)-ones **22** and 1-alkylbenzo [*f*]quinazolin-3(4*H*)-ones **23**; ^{a)} isolated yield; ^{b)} ¹H NMR yield.

In the case of quinazolinones the lactam-lactim tautomerism is possible, wherein amide is the major form. Additionally, in quinazolinone systems containing a methyl group at position 4 or 2, the tautomerism effect can extend to include the methylenic form. The spectroscopic analysis (¹H, ¹³C NMR) of compounds **22a,b** showed that methylquinazolinone **22a** in DMSO-*d*₆ solution exist in equilibrium with its tautomeric form **24** (Scheme 6) (see supplementary material, Fig. S1). The series of spectra recorded within 7 days demonstrated that the concentration of the methylenic form **24** increase till to ≈14%. Compound **22b** remained in this form. Crucial for the identification of tautomers **22a** and **24** were the ¹H NMR signals of the NH protons observed as a broad singlet at 12.11 ppm for the lactam form **22a** (at 12.06 ppm for **22b**) and as two singlets at 9.94 and 9.48 ppm for methylenic derivative **24**. Also, methylenic proton signals (C=CH₂) of **24** observed as two singlets at 4.86 and 4.74 ppm as well as a singlet of methyl protons of **22a** at 3.04 ppm, had the essential diagnostic value. By contrast, in the interpretation of ¹³C NMR spectrum of a mixture of **22a** ⇌ **24** the significant role is played by the resonance signals for C=N and C=O carbon atoms of **22a** located at 174.0 and 154.1 ppm, respectively (lit. ≈ 177-180.5 ppm (C=N), ≈ 158 ppm (C=O))^{46,47,48} and the carbon atom signal of an alkyl group at 30.0 ppm (lit. ≈ 22.9 ppm).^{46,47,48} A similar image was observed in the ¹³C NMR spectrum of compound **22b**. The corresponding carbon atom signals of C=N and C=O moiety were located at 181.7 and 154.4 ppm, respectively. For the identification of compound type **24**, useful were also signals of the methylenic carbon (C=CH₂) situated at 91.7 ppm (lit. ≈ 84-88 ppm) and C=CH₂, C=O at 138.5 and 151.1 ppm (lit. ≈ 150-159 ppm), respectively.^{46,47,48} The comparison of ¹³C NMR spectroscopic data for both quinazolinones **22a** and **22b** with carbon chemical shifts was calculated using GIAO method at the B3LYP/6-311++G(d,p) level of theory in DMSO-*d*₆ solution (IEF-PCM implicit solvation model) and allowed to signals identify and next their assignment to the corresponding carbon atoms (see supplementary material, Table S1). The calculated ¹³C NMR shifts of atoms C4a-C10b of the naphthalene system **22b**, as was shown in Table S1 (entries 4, 7, 10-12, 14, 17, 18, 21, 23) were located in the range 117.7-151.6 ppm and they have been

assigned to ten experimental signals observed in NMR spectrum at 144.8, 136.8, 129.9, 129.8, 128.8, 128.4, 125.1, 124.8, 116.3 and 109.4 ppm. In the case of **22a** chemical shifts of carbon atoms C4a-C10b indicated similar values. Slightly greater differences were visible for C=N (C1) and C=O (C3) carbons. The comparison between theoretical and experimental ^{13}C NMR shifts for C1 and C3 carbon atoms were as follows: signals of **22b** were found at 193.5 and 181.7 ppm for C=N, and at 161.1 and 154.4 ppm for C=O, while for **22a** at 185.8 and 174.0 ppm, and at 160.4 and 154.1 ppm, respectively. The calculated ^{13}C NMR shift values correlated well with their experimental counterparts with the correlation coefficient (r^2) of 0.9992 (**22a**), 0.9996 (**22b**) and 0.9913 (**24**).

In our previous work we demonstrated that a morpholine substituent attached to the benzo[*h*]quinazolinone scaffold can be responsible for increased cytotoxicity properties. In the last part of this work 3-substituted-6-bromobenzo[*h*]quinazolin-4(3*H*)ones **26a,b**^{26,27} were subjected to the Cu(II) catalyzed formamidation⁴² and Pd₂(dba)₃/Binap/Cs₂CO₃ catalyzed Buchwald-Hartwig amination reaction (Scheme 7). According this, target formamides **27a,b** were obtained in 60% and 40% yield, respectively, in turn the morpholine products **28a,b** were isolated in 55% and 68% yields. ¹H NMR spectra of the new formamides **27** possess a double set of resonance signals, which points out that compounds **27a** and **27b**, similarly as **21** exist in two rotameric forms in DMSO-*d*₆ solution, and the *cis* form is dominant (*cis:trans* ≈ 3:1).

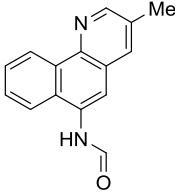
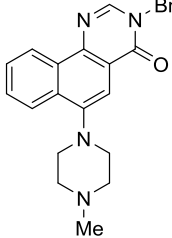
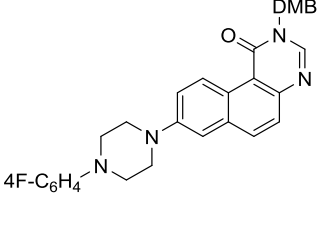
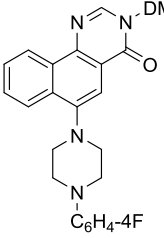
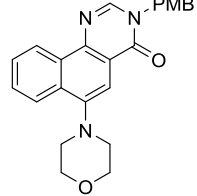


Scheme 7. The formamidation reaction of benzoquinazolinone derivatives **26**.

The cytotoxic activity of the tested quinazoline, quinazolinone derivatives were evaluated against HT29 human colorectal adenocarcinoma cell line using the MTT test and additionally towards the normal human lymphocytes. The obtained IC₅₀ values were collected in Table 2. In addition, in order to interpret more fully the results obtained, the cytotoxicity values of compounds **30-33**, evaluated in our earlier papers^{26,27} and also cisplatin⁴⁹ were also added to Table 2.

Table 2. IC₅₀ values of compounds **21**, **27-33**

Entry	Compound	IC ₅₀ (μM)	
		HT29	Lymphocytes
1	21	80.0	>350
2	27a	44.0	>350
3	27b	80.0	>350
4	28a	16.7	279.0
5	28b	70.0	>350
6	29 ²⁷	60.7	>350
7	30 ²⁷	30.0	49.0
8	31 ²⁷	201.0	532.5
9	32 ²⁷	169.0	501.7
10	33 ²⁶	4.12	178.11
11	Cisplatin ⁴⁹	8.47	6.83

				
29	30	31	32	33

The tested new synthesized derivatives **21**, **27**, **28** showed different activity. Out of these compounds the most interesting results were obtained for morpholine benzoquinazolinone **28a** (IC₅₀ 16.7 μM), formamido benzoquinazolinone **27a** (IC₅₀ 44.0 μM) and formamido benzoquinoline **29** (IC₅₀ 60.7 μM), which exhibited the highest cytotoxicity against HT29 cell line. As it can be seen from Table 2, *N*-benzyl-benzoquinazolinone **28a** (IC₅₀ 16.7 μM) showed a greater toxicity than *N*-benzyl-benzoquinazolinone **30** (IC₅₀ 30.0 μM) and *N*-dimethoxybenzyl derivative **28b** (IC₅₀ 70.0 μM). Regarding the activity of presented morpholine benzo[*h*]quinazolinones, compounds **28a**, **28b** were less active than methoxybenzyl derivative **33** (IC₅₀ 4.12 μM). It might be suggested that cytotoxic activity for tested morpholine benzo[*h*]quinazolin-4(3*H*)-ones was dependent on the substituent at the lactam nitrogen atom and the trend of increasing antitumor activity for these compounds was PMB>Bn>DMB. Generally, the introduction of the morpholine moiety into the 3,4-dimethoxybenzyl benzoquinazolinone skeleton in return of the 4-(4-fluorophenyl)piperazin-1-yl (for **32**, IC₅₀ 169.0 μM) moiety, had an impact on the increase of activity (for **28b**, IC₅₀ 70.0 μM). However, the fluorophenylpiperazin-1-yl derivative **32** showed greater activity than their benzo[*f*]-analogue **31** (IC₅₀ 201.0 μM).

Conclusions

We have presented a method to prepare of acylnaphthalenecarbamates **2a,b**, **5a,b** as precursors in the synthesis of alkyl substituted benzo[*f*]quinazolin-3(4*H*)-ones **22a,b**, benzo[*h*]quinazolin-2(1*H*)-ones **23a,b** and also benzoquinazolines **16a,b**, **20**. New benzoquinazolinyll formamides **21**, **28a,b** achieved *via* copper catalyzed coupling reaction can constitute a suitable starting point for further modifications.

Experimental Section

General. Melting points were determined on a Boetius hot stage apparatus and were uncorrected. ^1H , ^{13}C NMR spectra were recorded on a Bruker Advance III spectrometer at 600 MHz, 150 MHz respectively. The residual CDCl_3 or $\text{DMSO-}d_6$ signal was used for reference (CDCl_3 at 7.26 ppm or $\text{DMSO-}d_6$ at 2.54 ppm for ^1H NMR and CDCl_3 at 77.0 ppm or $\text{DMSO-}d_6$ at 39.0 ppm for ^{13}C NMR). IR spectra were recorded on a Nexus FT-IR spectrometer. LC/HRMS analyses were performed using an Agilent Technologies HPLC 1290 coupled to an Agilent Technologies 6550 Accurate Mass Q-TOF LC-MS mass spectrometer equipped with a JetStream Technology ion source housed in the Department of Pathophysiology, Medical University of Lublin, Poland. Internal mass calibration was enabled, reference ions of m/z 121.0509 and 922.0098 were used. The analytical thin layer chromatography tests (TLC) were carried out on Sigma Aldrich (Supelco) silica gel plates (Kieselgel 60 F254, layer thickness 0.2 mm) and the spots were visualized using UV lamp. The flash column chromatography purifications were performed on Fluka silica gel (Silica gel 60, 0.040-0.063 mm).

Butyllithium (BuLi) solution in hexanes (Aldrich), *tert*-butyllithium ($^t\text{BuLi}$) solution in pentane (Aldrich) were each time titrated before use.²⁶ All reactions with organolithium and organopalladium compounds were performed under an argon atmosphere using standard Schlenk technique. Diethyl ether, THF and 1,4-dioxane were distilled from sodium benzophenone ketyl prior to use. Commercially available solvents and reagents: acetyl chloride (AcCl), acetic anhydride (Ac_2O), ethyl acetate (AcOEt), pivaloyl chloride (PivCl), isobutyryl chloride ($^i\text{PrCOCl}$), acetaldehyde (AcH), 1-naphthylamine, formamide, Boc_2O , ethyl chloroformate, benzyl bromide (BnBr), 3,4-dimethoxybenzyl bromide (DMBBBr), *N*-bromosuccinimide (NBS), $\text{CuSO}_4 \times 5\text{H}_2\text{O}$, binap, $\text{Pd}_2(\text{dba})_3$, $\text{PPh}_3\text{PdCl}_2\text{PPh}_3$, acetic acid (AcOH 80%_{aq}), potassium cyanate (KOCN), ammonium acetate (AcONH_4), 1,4-dioxane, THF, Et_2O , acetonitrile were purchased from Sigma–Aldrich, Flucka or POCh and were used without further purification.

N-Boc-1-naphthylamine (**2**), *N*-Boc-1-bromo-2-naphthylamine (**4**), *N*-Boc-2-naphthylamine (**8**), *N*-methoxy-*N*-methylacetamid ($\text{AcN}(\text{OMe})\text{Me}$), *N*-methoxy-*N*,2,2-trimethylpropanamide ($\text{PivN}(\text{OMe})\text{Me}$), *N*-methoxy-*N*,2-dimethylpropanamide ($^i\text{PrCON}(\text{OMe})\text{Me}$), 3-benzyl-6-bromobenzo[*h*]quinazolin-4(3*H*)-one (**26a**), 6-bromo-3-[(3,4-dimethoxyphenyl)methyl]benzo[*h*]quinazolin-4(3*H*)-one (**26b**), *N*-(3-methylbenzo[*h*]quinolin-6-yl)formamide (**29**) were prepared by a procedure similar to that in the literature.^{26,27,32}

General procedure for the preparation of compounds 2,5. Under argon, to a solution of *N*-Boc-1-naphthylamine (**1**) or *N*-Boc-1-bromo-2-naphthylamine (**4**) (2.1 mmol) in dry Et_2O (20 mL), at $-20\text{ }^\circ\text{C}$, $^t\text{BuLi}$ solution in pentane or BuLi solution in hexanes (2.2 equiv.) was added dropwise. The reaction mixture was

stirred at this temperature for 2 hours. After this time, 1 equiv. of electrophile at $-78\text{ }^{\circ}\text{C}$ (for Ac_2O) or at $-20\text{ }^{\circ}\text{C}$ (for $^i\text{PrCOCl}$ or PivCl) was added dropwise and whole was further stirred at appropriate temperature for next 2 hours. Next, to the reaction mixture 20 mL of methanol was added. Evaporation of solvents and purifications of the crude residue by flash chromatography gave the desired product **2** or **5**. In the case of the reaction of **1** with Ac_2O at $-78\text{ }^{\circ}\text{C}$ from post-reaction mixture also substrate and compound **3** were isolated. On the other hand from reaction of **4** with Ac_2O and $^i\text{PrCOCl}$ compounds **6**, **7**, **8** and a small amount of substrate were isolated.

tert-Butyl (2-acetylnaphthalen-1-yl)carbamate (2a). Light yellow solid, yield 45%, 270 mg, mp $150\text{--}152\text{ }^{\circ}\text{C}$; R_f (Hex/ AcOEt 5:1) = 0.22. FTIR (KBr, ν_{max} , cm^{-1}) 3257, 3055, 3003, 2979, 2928, 1709, 1689. ^1H NMR (CDCl_3): δ 9.26 (1H, s, NH), 8.07 (1H, d, J 8.4 Hz, Ar-H), 7.82 (1H, d, J 8.4 Hz, Ar-H), 7.78 (1H, d, J 8.6 Hz, Ar-H), 7.70 (1H, d, J 8.7 Hz, Ar-H), 7.56 (2H, m, Ar-H), 2.71 (3H, s, Me), 1.52 (9H, s, Boc-Me). ^{13}C NMR (CDCl_3): δ 202.0, 154.5, 136.6, 136.1, 129.1, 128.6, 127.9, 126.7, 126.7, 126.4, 125.5, 125.1, 81.0, 29.6, 28.4. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3$: 286.1438; found $[\text{M}+\text{H}]^+$: 286.1441.

tert-Butyl (1-acetylnaphthalen-2-yl)carbamate (5a). Beige solid, yield 55%, 243 mg, mp $119\text{--}121\text{ }^{\circ}\text{C}$; R_f (Hex/ AcOEt 5:1) 0.55. FTIR (KBr, ν_{max} , cm^{-1}) 3274, 3103, 3066, 3002, 2978, 2929, 1711, 1687. ^1H NMR (CDCl_3): δ 8.31 (1H, s, NH), 8.26 (1H, d, J 9.1 Hz, Ar-H), 7.87 (1H, d, J 9.1 Hz, Ar-H), 7.82 (1H, d, J 8.1 Hz, Ar-H), 7.76 (1H, d, J 8.5 Hz, Ar-H), 7.54–7.49 (1H, m, Ar-H), 7.46–7.41 (1H, m, Ar-H), 2.69 (3H, s, Me), 1.53 (9H, s, Boc-Me). ^{13}C NMR (CDCl_3): δ 206.0, 153.2, 134.7, 132.0, 130.3, 130.2, 128.8, 127.4, 125.1, 124.7, 120.8, 81.2, 33.0, 28.5. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3$: 286.1438; found $[\text{M}+\text{H}]^+$: 286.1435.

4-Methyl-1,4-dihydro-2H-naphtho[2,3-d][1,3]oxazin-2-one (14). Under argon, to a solution of *N*-Boc-2-naphthylamine (**8**) (4.11 mmol) in dry THF (20 mL), at $-20\text{ }^{\circ}\text{C}$, TMEDA (2.2 equiv.) and next $^t\text{BuLi}$ solution in pentane (2.2 equiv.) was added dropwise. The reaction mixture was stirred at this temperature for 2 hours. After this time, at $-20\text{ }^{\circ}\text{C}$, 6.5 equiv. of acetaldehyde was added dropwise and whole was further stirred at $-20\text{ }^{\circ}\text{C}$ for next 1 hour. Next, to the reaction mixture 20 mL of methanol was added. Evaporation of solvents and purification of the crude residue by flash chromatography gave **14**. White solid, yield 40%, 350 mg, mp $204\text{--}206\text{ }^{\circ}\text{C}$; R_f (Hex/ AcOEt 4:3) = 0.34. FTIR (KBr, ν_{max} , cm^{-1}) 3432, 1713, 1296. ^1H NMR (CDCl_3): δ 9.54 (1H, s, NH), 7.77 (1H, dd, J 8.1, 0.4 Hz, Ar-H), 7.73 (1H, dd, J 8.1, 0.4 Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.46 (1H, ddd, J 8.1, 6.9, 1.2 Hz, Ar-H), 7.39 (1H, ddd, J 8.1, 6.8, 1.2 Hz, Ar-H), 7.28 (1H, s, Ar-H), 5.67 (1H, qd, J 6.6, 1.2 Hz, CH), 1.84 (3H, d, J 6.6 Hz, Me). ^{13}C NMR (CDCl_3): δ 154.1, 133.9, 133.1, 130.3, 128.1, 127.2, 127.0, 125.1, 124.0, 123.3, 110.3, 75.9, 20.4. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2$: 214.0863; found $[\text{M}+\text{H}]^+$: 214.0866.

Bromo carbamate 18. To a solution of the appropriate carbamate **2a** (0.86 mmol) in acetonitrile (10 mL) at $0\text{ }^{\circ}\text{C}$, a solution of NBS (1.3 mmol) in acetonitrile (10 mL) was added dropwise. Next, the resulting mixture was allowed to warm to ambient temperature. The reaction was continued under these conditions until TLC analysis of the reaction mixture indicated the absence of starting material **2a** (\approx 3-6 hours). After the reaction was completed, acetonitrile was removed under reduced pressure and the bromo derivative **18** was separated by flash chromatography. Beige solid, yield 80%, 251 mg, mp $161\text{--}163\text{ }^{\circ}\text{C}$; R_f (Hex/ AcOEt 10:1) = 0.20. FTIR (KBr, ν_{max} , cm^{-1}) 3279, 3002, 2964, 2924, 2854, 1723, 1681. ^1H NMR (CDCl_3): δ 9.09 (1H, s, NH), 8.22 (1H, d, J 8.4 Hz, Ar-H), 8.11–8.05 (2H, m, Ar-H), 7.72–7.66 (1H, m, Ar-H), 7.63–7.56 (1H, m, Ar-H), 2.70 (3H, s, Me), 1.51 (9H, s, Boc-Me). ^{13}C NMR (CDCl_3): δ 200.7, 154.3, 136.3, 134.4, 130.3, 130.0, 128.9, 127.4, 127.2, 127.1, 122.7, 119.6, 81.4, 29.5, 28.4. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{BrNO}_3$: 364.0543; found $[\text{M}+\text{H}]^+$: 364.0541.

Procedure for the preparation of aminoketone 15a. To a mixture of HCl_{aq} (0.5 M) and 1,4-dioxane in the ratio 2:3 (v/v), at room temperature ketone **2a** (0.48 mmol) was added. The resulting mixture was then heated at $50\text{--}60\text{ }^{\circ}\text{C}$ (oil bath) for about 3-4 hours, until TLC analysis of the reaction mixture indicated the absence of

starting material **2a**. After the reaction was completed, all the volatile materials were removed under reduced pressure and water (5-10 mL) was added to residue. The mixture was adjusted to pH 8-10 with saturated NaHCO₃ and then extracted with chloroform (3×20 mL). The combined extracts were dried over MgSO₄, concentrated under reduced pressure. A crude residue was subjected to column chromatography to give amine **15a**.

Procedure for the preparation of amino ketone 19. To the solution of *N*-Boc-amino keton **18** (0.88 mmol) in DCM (4.8 mL) at 0 °C, TFA (8.8 mmol, 0.67 mL) was added. The resulting mixture was allowed to warm to ambient temperature and stirring in these conditions until the completion of reaction (TLC analysis). After this time, all the volatile materials were removed under reduced pressure and to residue water (5 mL) was added. The whole lot was adjusted to pH=8-10 (saturated solution of NaHCO₃) and next extracted with DCM (3×20 mL). The combined extracts were dried over MgSO₄ and concentrated under reduce pressure. The crude residue was purified via flash chromatography to give the appropriate amine **19**. Yellow solid, yield 85%, 198 mg, mp 134–136 °C; R_f (Hex/AcOEt 5:1) = 0.32. FTIR (KBr, ν_{max}, cm⁻¹) 3439, 3288, 3027, 3000, 1634, 1602. ¹H NMR (CDCl₃): δ 8.15 (1H, d, *J* 8.4 Hz, Ar–H), 7.97 (1H, s, Ar–H), 7.91 (1H, d, *J* 8.4 Hz, Ar–H), 7.72–7.48 (4H, m, NH₂, Ar–H), 2.64 (3H, s, Me). ¹³C NMR (CDCl₃): δ=199.4, 148.8, 134.5, 131.0, 130.2, 128.1, 126.3, 124.7, 122.2, 112.5, 107.7, 28.5. HRMS (ESI) *m/z* calcd for C₁₂H₁₁BrNO: 264.0019; found [M+H]⁺: 264.0016.

Synthesis of benzoquinazolines **16**, **20**

Method A (from amino ketones) and Method B (from carbamates). To a mixture of amino ketone (*Method A*) **15a** or **19** (0.31 mmol) or carbamate (*Method B*) **2a** or **2b** or **18** (0.31 mmol) in 10 mL of formamide, MeCOONH₄ (0.52 mmol) was added. The whole mixture was stirred and heated at 170 °C (oil bath). After completion of the reaction, as indicated by TLC (7-15 hours), the resulting solution was cooled to room temperature and 40 mL of water was added. Then mixture was extracted with chloroform (3x10 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. A crude residues was purified by column chromatography to afford products **16a**, **16b**, **20**.

Method C (β-hydrogen elimination). To a mixture of amino ketone **19** (0.38 mmol) in 10 mL of formamide, MeCOONH₄ (0.66 mmol), PPh₃PdCl₂PPh₃ (0.11 mmol) was added. The whole mixture was stirred and heated at 160 °C (oil bath) with 3Å molecular sieves. After completion of the reaction, as indicated by TLC (25 hours), the resulting solution was cooled to room temperature and 40 mL of water was added. Then mixture was extracted with chloroform (3x10 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. A crude residue was purified by column chromatography to afford product **16a**. Light yellow solid, yield: 35% (*Method A*), 21 mg, 52% (*Method B*), 31 mg, 55% (*Method C*), 41 mg, mp 136–138 °C; R_f (DCM/AcOEt 10:1) = 0.16. FTIR (KBr, ν_{max}, cm⁻¹) 3070, 3042, 2925, 2854, 1621. ¹H NMR (CDCl₃): δ 9.32 (1H, s, Ar–H), 9.30–9.26 (1H, m, Ar–H), 7.95–7.87 (3H, m, Ar–H), 7.82–7.75 (2H, m, Ar–H), 2.99 (3H, s, Me). ¹³C NMR (CDCl₃): δ 166.5, 154.8, 149.9, 135.2, 130.6, 130.1, 128.7, 128.0, 127.8, 125.2, 122.3, 121.1, 22.1. HRMS (ESI) *m/z* calcd for C₁₃H₁₁BN₂: 195.0917; found [M+H]⁺: 195.0914.

Synthesis of benzoquinazolinones **22, **23**.** A solution of the appropriate carbamate **2a** or **2b** or **5a** or **5b** (0.52 mmol) in 5 mL of 80% acetic acid was stirred at 130 °C (oil bath) for 2 hours. Then KOCN (4.44 mmol) and MeCOONH₄ (9.86 mmol) in water (1-2 mL) was added to the mixture. After 30 min. next portion of KOCN (8.86 mmol) and MeCOONH₄ (9.86 mmol) in water (1-2 mL) was added. The resulting mixture was further heated at 130 °C (oil bath) for 2.5 hours. After that to the stirring mixture the last portion of KOCN (2.7 mmol) and MeCOONH₄ (9.1 mmol) in water (1-2 mL) was added. The reaction mixture was held at this conditions for next 3 hours. After cooling, 40 mL water was added. The precipitated solid was filtered and purified by flash chromatography.

1-Methylbenzo[f]quinazolin-3(4H)-one (22a). Gray solid, yield 65%, 72 mg, mp decomposition above 280 °C; R_f (acetone/MeOH/Hex 2:1:1) = 0.76. $^1\text{H NMR}$ (DMSO- d_6): δ 12.11 (1H, s, NH), 8.60 (1H, d, J 8.7 Hz, Ar-H), 8.21 (1H, d, J 8.9 Hz, Ar-H), 8.01 (1H, d, J 7.9 Hz, Ar-H), 7.78–7.71 (1H, m, Ar-H), 7.62–7.55 (1H, m, Ar-H), 7.43 (1H, d, J 8.9 Hz, Ar-H), 3.04 (3H, s, Me). HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}$: 211.0866; found $[\text{M}+\text{H}]^+$: 211.0870.

Mixture of 1-methylbenzo[f]quinazolin-3(4H)-one (22a) and 1-methylidene-1,4-dihydrobenzo[f]quinazolin-3(2H)-one (24) in ratio 1:0.16*. FTIR (KBr, ν_{max} , cm^{-1}) 3437, 3003, 2973, 2858, 2822, 2753, 1663, 1621. $^1\text{H NMR}$ (DMSO- d_6): δ 12.11 (1H, br s, NH), 9.94 (1H, s, NH*), 9.58 (1H, s, NH*), 8.60 (1H, d, J 8.7 Hz, Ar-H), 8.44 (1H, d, J 8.6 Hz, Ar-H*), 8.21 (1H, d, J 8.9 Hz, Ar-H), 8.01 (1H, dd, J 7.9, 1.2 Hz, Ar-H), 7.85 (1H, d, J 8.2 Hz, Ar-H*), 7.82 (1H, d, J 8.7 Hz, Ar-H*), 7.78–7.71 (1H, m, J 8.5, 7.0, 1.4 Hz, Ar-H), 7.62–7.55 (1H, m, Ar-H), 7.54–7.50 (1H, m, Ar-H*), 7.43 (1H, d, J 8.9 Hz, Ar-H), 7.40–7.35 (1H, m, J 7.4 Hz, Ar-H*), 7.12 (1H, d, J 8.7 Hz, Ar-H*), 4.86 (1H, s, CH_2^*), 4.74 (1H, s, CH_2^*), 3.04 (3H, s, Me). $^{13}\text{C NMR}$ (DMSO- d_6): δ 174.0, 154.1, 151.1, 144.8, 138.4, 138.5, 136.9, 136.7, 130.8, 129.8, 129.7, 129.2, 128.9, 128.7, 127.5, 125.0, 124.9, 123.8, 123.1, 116.3, 115.8, 110.2, 110.2, 91.7, 30.0.

Preparation of 21 or 27 via copper-mediated N-formamidation. To the bromo derivative **20** or **26** (0.27 mmol) suspended in formamide (15 mL) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.68 mmol) and K_2CO_3 (1.35 mmol) was added. Whole mixture was heated with magnetic stirring at 150 °C (oil bath) for about 15-25 hours. After completion the reaction, as indicated by TLC the mixture was cooled and poured into crushed ice with water (20-30 mL). After 30 min. mixture was extracted with DCM. The combined extracts were dried over MgSO_4 and concentrated in vacuo. The residue was next subjected to flash chromatography to afford the pure product **21** or **27**.

N-(4-Methylbenzo[h]quinazolin-6-yl)formamide (21). Mixture of rotamers 2:1*, light yellow solid, yield 47%, 30 mg, mp 299–301 °C; R_f (AcOEt/DCM 5:1) = 0.38. FTIR (KBr, ν_{max} , cm^{-1}) 3223, 3075, 1719. $^1\text{H NMR}$ (DMSO- d_6): δ 10.71 (1H, s, NH*), 10.59 (1H, s, NH), 9.32–9.20 (3H, m, 2Ar-H, Ar-H*), 8.83 (1H, d, J 9.4 Hz, CHO*), 8.68 (1H, s, Ar-H), 8.62 (1H, s, CHO), 8.37 (1H, d, J 8.3 Hz, Ar-H), 8.32 (1H, d, J 8.1 Hz, Ar-H*), 8.01–7.91 (2H, m, Ar-H, Ar-H*), 7.91–7.86 (3H, m, Ar-H, 2Ar-H*), 2.96 (3H, s, Me*), 2.90 (3H, s, Me). $^{13}\text{C NMR}$ (DMSO- d_6): δ 165.8, 164.3, 160.9, 158.5, 153.8, 153.7, 146.2, 135.9, 132.3, 130.3, 130.2, 129.8, 128.8, 128.2, 127.9, 124.9, 123.1, 122.1, 121.5, 111.8, 111.4, 21.8, 21.6. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{12}\text{N}_3\text{O}$: 238.0975; found $[\text{M}+\text{H}]^+$: 238.0974.

Preparation of benzoquinazolinone derivatives 28 via Pd cross-coupling reaction. An oven dried resealable Schlenk flask which was equipped with a magnetic stirring bar was charged with $\text{Pd}_2(\text{dba})_3$ (0.062 mmol), Binap (0.062 mmol) and freshly distilled toluene (4 mL). The vessel was evacuated and backfilled with argon, which was repeated of 3 times. After that Cs_2CO_3 (0.62 mmol), bromo derivative **28a** or **28b** (0.42 mmol) dissolved in toluene (6 mL) and morpholine (1.2 mmol) was added. The whole mixture was stirred and heated at 100 °C (oil bath) for 30 hours. After this time the reaction mixture was cooled and diluted with chloroform (5 mL). The solid was filtered off, washed with chloroform (2 mL) and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography.

3-Benzyl-6-(morpholin-4-yl)benzo[h]quinazolin-4(3H)-one (28a). White solid, yield: 55%, 86 mg, mp 165–166 °C; R_f (DCM/AcOEt 1:1) = 0.72. FTIR (KBr, ν_{max} , cm^{-1}) 3081, 3066, 3032, 2968, 2917, 2915, 2889, 2853, 2826, 1678. $^1\text{H NMR}$ (CDCl_3): δ 8.99 (1H, d, J 8.2 Hz, Ar-H), 8.28 (1H, d, J 8.2 Hz, Ar-H), 8.25 (1H, s, Ar-H), 7.80 (1H, s, Ar-H), 7.74–7.66 (2H, m, Ar-H), 7.43–7.27 (5H, m, Bn), 5.28 (2H, s, CH_2), 4.04–3.96 (4H, m, Morf), 3.25–3.11 (4H, m, Morf). $^{13}\text{C NMR}$ (CDCl_3): δ 161.2, 149.3, 145.2, 143.7, 135.9, 132.1, 131.5, 129.2, 129.0, 128.5, 128.3, 127.2, 125.7, 123.8, 119.2, 109.5, 67.5, 53.6, 50.1. HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_2$: 372.1707; found $[\text{M}+\text{H}]^+$: 372.1702.

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Supplementary Material

Copies of selected ^1H and ^{13}C NMR spectra of new compounds, Biology section information (general), Computational details and additional compounds characterization data, Schemes, Tables, Figures can be found in supplementary material in the online version of this article.

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