Synthesis of acylnaphthylamines and their applications in the formation of benzoquinazolines

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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, iPrCOCl 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

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**Introduction**

The quinazoline or quinazolinone skeleton is a building block of various alkaloids\(^1,2\) with diverse biological activities\(^3-5\) like for example *vasicine* and *vasicinone* (active compounds of *Justicia athtagoda*),\(^6-8\) 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,\(^13\) antiviral\(^14\) and antibacterial activity.\(^15,16\) Some of quinazoline derivatives have been approved as effective drugs against cancer,\(^17\) e.g. Gefitinib,\(^18,19\) Erlotinib\(^20\) or Ispinesib.\(^21\) Additionally, aryl- or alkyl-quinazolin-2(1H)-one derivatives are applied e.g. as nonsteroidal anti-inflammatory drugs\(^22\) (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 benzoquinazolone 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 \(^1\)BuLi 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, Ac\(_2\)O, AcOEt, PivCl and \(^1\)PrCOCl 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 Ac\(_2\)O, \(^b\) for the reaction of 4 with Ac\(_2\)O, \(^c\) for the reaction of 4 with \(^1\)PrCOCl.
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Temp. (°C)</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Products</th>
<th>Other products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcCl</td>
<td>-20</td>
<td>1</td>
<td>2a (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ac₂O</td>
<td>-20</td>
<td>1</td>
<td>2a (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ac₂O</td>
<td>-78</td>
<td>1</td>
<td>2a (45)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>AcN(OMe)Me</td>
<td>-20</td>
<td>1</td>
<td>2a (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PivCl</td>
<td>-20</td>
<td></td>
<td>2b (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PivCl</td>
<td>-78</td>
<td></td>
<td>2b (trace)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PivN(OMe)Me</td>
<td>-78</td>
<td>1</td>
<td>2b (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PivN(OMe)Me</td>
<td>-20</td>
<td>1</td>
<td>2b (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PivN(OMe)Me</td>
<td>0</td>
<td></td>
<td>2b (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>AcCl</td>
<td>-78</td>
<td></td>
<td>5a (45)</td>
<td></td>
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<tr>
<td>11</td>
<td>Ac₂O</td>
<td>-78</td>
<td>4</td>
<td>5a (55)</td>
<td>6 (8)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>12</td>
<td>AcOEt</td>
<td>-78</td>
<td>4</td>
<td>5a (10)</td>
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<tr>
<td>13</td>
<td>AcN(OMe)Me</td>
<td>-20</td>
<td></td>
<td>5a (trace)</td>
<td></td>
<td>7 (60)</td>
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<tr>
<td>14</td>
<td>iPrCOCl</td>
<td>-78</td>
<td></td>
<td>5b (20)</td>
<td></td>
<td>8 (5)</td>
</tr>
<tr>
<td>15</td>
<td>iPrCOCl</td>
<td>-20</td>
<td>4</td>
<td>5b (40)</td>
<td></td>
<td>8 (10)</td>
</tr>
<tr>
<td>16</td>
<td>iPrCON(OMe)Me</td>
<td>-20</td>
<td></td>
<td>5b (2)</td>
<td></td>
<td>7 (12)</td>
</tr>
</tbody>
</table>

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

*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 °C (2b (60%), 5b (40%), Table 1, entries 5, 15). When the reaction temperature was decreased from -20 °C to -78 °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 °C to about 5% (7, 8) at -78 °C (Table 1, entries 14, 15).

Weinreb amides are alternative acylating agents to classical ones. 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 (iPrCON(OMe)Me) in the reactions with naphthalene derivatives 1a or 4a. We noticed that bis-lithiated species 1a reacted with AcN(OMe)Me as well as PivN(OMe)Me at -20 °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, iPrCON(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).

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. They observed that acetanilide can be efficiently deprotonated by BuLi to produce the corresponding dianion, which is able to react with diverse electrophiles. 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 the 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 (\(^{1}\)BuLi/TMEDA) and acetaldehyde (Scheme 3). The \(^{1}\)H NMR spectrum of the post reaction complex mixture indicated signals belonging to methyl-1,4-dihydrornaphto-1,3-oxazinones 13 and 14 (the ratio ca. 3:5, \(^{1}\)H NMR) Ultimately, from the crude material only compound 14 was isolated in the pure form (40% yield).

\[ \begin{align*} \text{Scheme 3. Reaction of } N\text{-Boc-2-naphthylamine 7 with } ^{1}\text{BuLi / acetaldehyde.} \end{align*} \]

In the literature several strategies have been described for the construction of a quinazoline skeleton, e.g. using aromatic nitroaldehydes,\(^{35}\) imido amides\(^{36}\) 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 °C) of (acynaphthyl)carbamates 2a,b, 18 or their derivatives 15a, 19 with HCONH\(_2\)/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 HCONH\(_2\)/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.

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 HCONH2 and 2) cross coupling reaction with excess of formamide in the presence of PdCl2(PPh3)2 (30 mol%). Nonetheless, this way of synthesis did not give the expected product 21 (Scheme 5). The 1H NMR (DMSO-d6) spectrum of isolated compound did not show signals belonging to protons of the –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-arylf ormamidem derivative 21 existed as a mixture of two rotamers (≈ 2:1), favoring the Z form.
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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(4H)-ones 22 and benzo[h]quinazolin-2(1H)-ones 23 (Scheme 6). Heterocycles containing a quinazolin-2(1H)-one scaffold are a relatively little-studied class. Some studies reported that quinazolin-2(1H)-ones can be obtained by cyclization reactions using amino acetophenones or aminobenzonitriles. Our studies on the construction of benzoquinazolinone systems using N-Boc 1-naphthylamine derivatives 2a and 2b into lactams 23a (23%) and 23b (15%) was less efficient. $^1$H 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: $\text{I} \rightarrow \text{V} \rightarrow \text{VI} \rightarrow \text{VII} \rightarrow \text{II}$). On the other hand, the presence of AcONH$_4$, 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: $\text{I} \rightarrow \text{VIII} \rightarrow \text{IX} \rightarrow \text{II}$).
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; \(^{b}\) \(^{1}\)H NMR yield.

In the case of quinazolinones the lactam-lactim tautomerism is possible, wherein amide is the major form. Additionally, in quinazoline systems containing a methyl group at position 4 or 2, the tautomerism effect can extend to include the methylidene form. The spectroscopic analysis (\(^{1}\)H, \(^{13}\)C 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 methylidene form 24 increase till to \(\approx 14\%\). Compound 22b remained in this form. Crucial for the identification of tautomers 22a and 24 were the \(^{1}\)H 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 methylidene derivative 24. Also, methylidene proton signals (C=C\(\text{H}_2\)) 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 \(^{13}\)C NMR spectrum of a mixture of 22a \(\rightarrow\) 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. \(\approx 177-180.5\) ppm (C=N), \(\approx 158\) ppm (C=O))\(^{46,47,48}\) and the carbon atom signal of an alkyl group at 30.0 ppm (lit. \(\approx 22.9\) ppm).\(^{46,47,48}\) A similar image was observed in the \(^{13}\)C 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 methylidene carbon (C=CH\(_2\)) situated at 91.7 ppm (lit. \(\approx 84-88\) ppm) and C=CH\(_2\), C=O at 138.5 and 151.1 ppm (lit. \(\approx 150-159\) ppm), respectively.\(^{46,47,48}\) The comparison of \(^{13}\)C 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 \(^{13}\)C 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 $^{13}\text{C}$ 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 $^{13}\text{C}$ 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(3H)ones 26a,b$^{26,27}$ were subjected to the Cu(II) catalyzed formamidation$^4$ and Pd$_2$(dba)$_3$/Binap/Cs$_2$CO$_3$ 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. $^1$H 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 $\approx$ 3:1).

The cytotoxic activity of the tested quinazoline, quinazolinonene derivatives were evaluated against HT29 human colorectal adenocarcinoma cell line using the MTT test and additionally towards the normal human lymphocytes. The obtained IC\textsubscript{50} 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\textsuperscript{26,27} and also cisplatin\textsuperscript{49} were also added to Table 2.

### Table 2. IC\textsubscript{50} values of compounds 21, 27-33

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>IC\textsubscript{50} (\textmu M)</th>
<th>HT29</th>
<th>Lymphocytes</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>80.0</td>
<td>&gt;350</td>
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</tr>
<tr>
<td>2</td>
<td>27a</td>
<td>44.0</td>
<td>&gt;350</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>27b</td>
<td>80.0</td>
<td>&gt;350</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28a</td>
<td>16.7</td>
<td>279.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>28b</td>
<td>70.0</td>
<td>&gt;350</td>
<td></td>
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<tr>
<td>6</td>
<td>29\textsuperscript{27}</td>
<td>60.7</td>
<td>&gt;350</td>
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<tr>
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<td>532.5</td>
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<tr>
<td>9</td>
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<td>169.0</td>
<td>501.7</td>
<td></td>
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<tr>
<td>10</td>
<td>33\textsuperscript{26}</td>
<td>4.12</td>
<td>178.11</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Cisplatin\textsuperscript{49}</td>
<td>8.47</td>
<td>6.83</td>
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</tr>
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</table>

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 (IC\textsubscript{50} 16.7 \textmu M), formamido benzoquinazolinone 27a (IC\textsubscript{50} 44.0 \textmu M) and formamido benzoquinoline 29 (IC\textsubscript{50} 60.7 \textmu M), which exhibited the highest cytotoxicity against HT29 cell line. As it can be seen from Table 2, N-benzyl-benzoquinazolinone 28a (IC\textsubscript{50} 16.7 \textmu M) showed a greater toxicity than N-benzyl-benzoquinazolinone 30 (IC\textsubscript{50} 30.0 \textmu M) and N-dimethoxybenzyl derivative 28b (IC\textsubscript{50} 70.0 \textmu M). Regarding the activity of presented morpholine benzo[h]quinazolinones, compounds 28a, 28b were less active than methoxybenzyl derivative 33 (IC\textsubscript{50} 4.12 \textmu M). It might be suggested that cytotoxic activity for tested morpholine benzo[h]quinazolin-4(3H)-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, IC\textsubscript{50} 169.0 \textmu M) moiety, had an impact on the increase of activity (for 28b, IC\textsubscript{50} 70.0 \textmu M). However, the fluorophenylpiperazin-1-yl derivative 32 showed greater activity than their benzo[f]- analogue 31 (IC\textsubscript{50} 201.0 \textmu M).
Conclusions

We have presented a method to prepare of acynaphthalenecarbamates 2a,b, 5a,b as precursors in the synthesis of alkyl substituted benzo[j]quinazolin-3(4H)-ones 22a,b, benzo[h]quinazolin-2(1H)-ones 23a,b and also benzoquinazolines 16a,b, 20. New benzoquinazolinyln 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, 13C NMR spectra were recorded on a Bruker Advance III spectrometer at 600 MHz, 150 MHz respectively. The residual CDCl3 or DMSO-d6 signal was used for reference (CDCl3 at 7.26 ppm or DMSO-d6 at 2.54 ppm for 1H NMR and CDCl3 at 77.0 ppm or DMSO-d6 at 39.0 ppm for 13C 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 (Kiselgel 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 (tBuLi) 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 (Ac2O), ethyl acetate (AcOEt), pivaloyl chloride (PivCl), isobutyril chloride (PrCOCI), acetaldehyde (AcH), 1-naphthylamine, formamide, Boc2O, ethyl chloroformate, benzyl bromide (BnBr), 3,4-dimethoxybenzyl bromide (DMBBr), N-bromosuccinimide (NBS), CuSO4×5H2O, binap, Pd2dba3, PPh3PdCl2PPh3, acetic acid (AcOH 80%aq.), potassium cyanate (KOCN), ammonium acetate (AcONH4), 1,4-dioxane, THF, Et2O, 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 (AcN(OMe)Me), N-methoxy-N,2,2-trimethylpropanamide (PivN(OMe)Me), N-methoxy-N,2-dimethylpropanamide (PrCON(OMe)Me), 3-benzyl-6-bromobenzo[h]quinazolin-4(3H)-one (26a), 6-bromo-3-[(3,4-dimethoxyphenyl)methyl]benzo[h]quinazolin-4(3H)-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 Et2O (20 mL), at −20 °C, tBuLi 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 °C (for Ac₂O) or at −20 °C (for 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 Ac₂O at −78 °C from post-reaction mixture also substrate and compound 3 were isolated. On the other hand from reaction of 4 with Ac₂O and PrCOCl compounds 6, 7, 8 and a small amount of substrate were isolated.

tert-Butyl (2-acetynaphthalen-1-yl)carbamate (2a). Light yellow solid, yield 45%, 270 mg, mp 150–152 °C; Rf (Hex/AcOEt 5:1) = 0.22. FTIR (KBr, v max cm⁻¹) 3257, 3055, 3003, 2979, 2928, 1709, 1689. ¹H NMR (CDCl₃): δ 9.26 (1 H, s, NH) 8.07 (1 H, d, J 8.4 Hz, Ar–H), 7.82 (1 H, d, J 8.4 Hz, Ar–H), 7.78 (1 H, d, J 8.6 Hz, Ar–H), 7.70 (1 H, d, J 8.7 Hz, Ar–H), 7.56 (2 H, m, Ar–H), 7.21 (3 H, s, Me), 1.52 (9 H, s, Boc–Me). ¹³C NMR (CDCl₃): 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 C₁₁H₁₃NO₃: 186.1438; found [M+H]+: 186.1441.

tert-Butyl (1-acetynaphthalen-2-yl)carbamate (5a). Beige solid, yield 55%, 243 mg, mp 119–121°C; Rf (Hex/AcOEt 5:1) 0.55. FTIR (KBr, v max cm⁻¹) 3274, 3103, 3066, 3002, 2978, 2929, 1711, 1687. ¹H NMR (CDCl₃): δ 8.31 (1 H, s, NH), 8.26 (1 H, d, J 9.1 Hz, Ar–H), 7.87 (1 H, d, J 9.1 Hz, Ar–H), 7.82 (1 H, d, J 8.1 Hz, Ar–H), 7.76 (1 H, d, J 8.5 Hz, Ar–H), 7.54–7.49 (1 H, m, Ar–H), 7.46–7.41 (1 H, m, Ar–H), 2.69 (3 H, s, Me), 1.53 (9 H, s, Boc–Me). ¹³C NMR (CDCl₃): 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 C₁₁H₁₃NO₃: 186.1438; found [M+H]+: 186.1435.

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 °C, TMEDA (2.2 equiv.) and next 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 °C, 6.5 equiv. of acetaldehyde was added dropwise and whole was further stirred at −20 °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 204–206 °C; Rf (Hex/AcOEt 4:3) = 0.34. FTIR (KBr, v max cm⁻¹) 3432, 1713, 1296. ¹H NMR (CDCl₃): δ 9.54 (1 H, 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 (1 H, 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 (1 H, s, Ar–H), 5.67 (1H, qd, J 6.6, 1.2 Hz, CH), 1.84 (3H, d, J 6.6 Hz, Me). ¹³C NMR (CDCl₃): 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 C₁₃H₁₂NO₂: 214.0863; found [M+H]+: 214.0866.

Bromo carbamate 18. To a solution of the appropriate carbamate 2a (0.86 mmol) in acetonitrile (10 mL) at 0 °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 (= 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 161–163 °C; Rf (Hex/AcOEt 10:1) = 0.20. FTIR (KBr, v max cm⁻¹) 3279, 3002, 2964, 2924, 2854, 1723, 1681. ¹H NMR (CDCl₃): δ 9.09 (1 H, s, NH), 8.22 (1 H, d, J 8.4 Hz, Ar–H), 8.11–8.05 (2 H, m, Ar–H), 7.72–7.66 (1 H, m, Ar–H), 7.63–7.56 (1 H, m, Ar–H), 2.70 (3H, s, Me), 1.51 (9 H, s, Boc–Me). ¹³C NMR (CDCl₃): 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 C₁₃H₁₃BrNO₃: 364.0543; found [M+H]+: 364.0541.

Procedure for the preparation of aminoketone 15a. To a mixture of HClq (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 50–60 °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 ketone 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 reduced 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; Rf (Hex/AcOEt 5:1) = 0.32. FTIR (KBr, νmax 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 C₇₁H₁₁BrNO: 264.0019; found [M+H]+: 264.0016.

Synthesis of benzoquinazolinones 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 (3×10 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. A crude residue 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 (3×10 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; Rf (DCM/AcOEt 10:1) = 0.16. FTIR (KBr, νmax 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; Rf (acetone/MeOH/Hex 2:1:1) = 0.76. \textsuperscript{1}H NMR (DMSO-\textit{d}_6): \( \delta \) 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 C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O: 211.0866; found [M+H]\textsuperscript{+}: 211.0870.

Mixture of 1-methylbenzo[f]quinazolin-3(4H)-one (22a) and 1-methyliden-1,4-dihydrobenzo[f]quinazolin-3(2H)-one (24) in ratio 1:0.16.* FTIR (KBr, \( v_{\text{max}} \) cm\(^{-1}\)) 3437, 3003, 2973, 2858, 2822, 2753, 1663, 1621. \textsuperscript{1}H NMR (DMSO-\textit{d}_6): \( \delta \) 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\textsubscript{2}*), 4.74 (1H, s, CH\textsubscript{2}*), 3.04 (3H, s, Me). \textsuperscript{13}C NMR (DMSO-\textit{d}_6): \( \delta \) 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) CuSO\textsubscript{4}x5H\textsubscript{2}O (0.68 mmol) and K\textsubscript{2}CO\textsubscript{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\textsubscript{4} and concentrated in vacuo. The residue was next subjected to flash chromatography to afford the pure product 21 or 27.

\textbf{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; Rf (AcOEt/DCM 5:1) = 0.38. FTIR (KBr, \( v_{\text{max}} \) cm\(^{-1}\)) 3223, 3075, 1719. \textsuperscript{1}H NMR (DMSO-\textit{d}_6): \( \delta \) 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). \textsuperscript{13}C NMR (DMSO-\textit{d}_6): \( \delta \) 165.8, 164.3, 160.9, 158.5, 153.8, 153.7, 146.2, 135.9, 132.0, 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 C\textsubscript{14}H\textsubscript{12}N\textsubscript{2}O: 238.0975; found [M+H]\textsuperscript{+}: 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 Pd\textsubscript{2}(dba\textsubscript{3}) (0.062 mmol), Binap (0.62 mmol) and freshly distilled toluene (4 mL). The vessel was evacuated and backfilled with argon, which was repeated 3 times. After that Cs\textsubscript{2}CO\textsubscript{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; Rf (DCM/AcOEt 1:1) = 0.72. FTIR (KBr, \( v_{\text{max}} \) cm\(^{-1}\)) 3081, 3066, 3032, 2968, 2917, 2915, 2889, 2853, 2826, 1678. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \( \delta \) 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\textsubscript{2}), 4.04–3.96 (4H, m, Morf), 3.25–3.11 (4H, m, Morf). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \( \delta \) 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 C\textsubscript{23}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}: 372.1707; found [M+H]\textsuperscript{+}: 372.1702.
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Supplementary Material

Copies of selected $^1$H 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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