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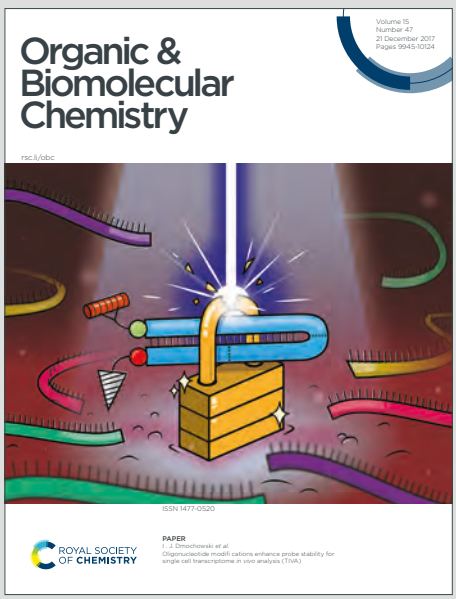




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# Modular and Divergent Synthesis of 2,*N*3-Disubstituted 4-Quinazolinones Facilitated by Regioselective *N*-Alkylation

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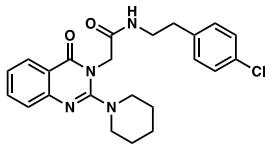
**ABSTRACT:** The synthesis of a biologically relevant 2-amino-*N*3-alkylamido 4-quinazolinone has been accomplished in four steps from commercially available materials using design principles from both modular and divergent synthesis. *N*3-alkylation of 2-chloro-4(3*H*)-quinazolinone using methyl bromoacetate, followed by C2-amination produced a suitable scaffold for introducing molecular diversity. Optimization of alkylation conditions afforded full regioselectivity, enabling exclusive access to the *N*-alkylated isomer. Subsequent C2-amination using piperidine, pyrrolidine, or diethylamine, followed by amide bond formation using variously substituted phenethylamines, generated fifteen unique 4-quinazolinones bearing C2-amino and *N*3-alkylamido substituents. These efforts highlight the reciprocal influence of C2 and *N*3 substitution on functionalization at either position, establish an effective synthetic pathway toward 2,*N*3-disubstituted 4-quinazolinones, and enable preliminary bioactivity studies while providing an experiential learning opportunity for undergraduate student researchers.

## INTRODUCTION

The synthesis of biologically relevant organic molecules has added much value to both the development of therapeutics and the expansion of synthetic knowledge.[1] Creation of libraries of structurally diverse compounds enables assessment of the influence of molecular structure on bioactivity[2] and inspires development of new strategies and reaction methodologies for maximizing molecular diversity and synthetic efficiency. Two common approaches toward compound library preparation include *modular synthesis*, in which simple molecular building blocks are combined interchangeably in a convergent fashion to rapidly access diverse structures,[3] and *divergent synthesis*, which involves efficiently preparing a central complex scaffold to be diversified at a later stage.[4] These strategies differ in approach toward generating complexity but share the common goal of creating a wide variety of targets.

The vast molecular space available for targets in these endeavors provides researchers with varying amounts of laboratory experience an opportunity to contribute to an overarching synthetic goal while maximizing individual impact by focusing on a specific subarea.[5] As a research group at a primarily undergraduate institution, we sought to design a project that would generate meaningful data while offering rich training opportunities for undergraduate students.[6] Several factors influenced our selection of a suitable target for compound library development: 1) biological activity and availability of collaborators for biological assessment and analysis, 2) accessibility to undergraduate researchers in terms of structural complexity and anticipated length of synthetic route, and 3) potential for facile structural modification.

Project design was facilitated by an institutional partnership with the not-for-profit organization Drugs for Neglected Diseases initiative (DNDi),[7] whose aim is to develop treatments for patients with neglected diseases. DNDi researchers identified a 2,*N*3-disubstituted 4-quinazolinone[8] (**1a**, Figure 1) that exhibits promising activity against the *T. cruzi* parasite that causes Chagas disease, a neglected tropic disease (NTD) endemic to Latin America that afflicts millions worldwide.[9] After an acute phase of infection where parasites proliferate in the bloodstream, the ensuing chronic phase can last decades and often results in damage to the heart and gastrointestinal system.[10] Left untreated, Chagas disease can prove fatal. Currently available treatments are limited to two drugs, nifurtimox and benznidazole, which both require lengthy treatment regimens, have undesirable toxicity, cause damaging side effects, and are effective only for the acute phase of infection if treatment begins early and is adhered to aggressively.[11]




***1a***
***DNDI0003243453***
***T. cruzi $IC_{50}$ = 2.1 $\mu$M***

**Figure 1.** Antiparasitic 2,*N*3-disubstituted quinazolinone **1a**.

Heterocycle-containing compounds are ubiquitous in drug molecules for the treatment of various NTDs caused by protozoan pathogens such as *T. cruzi*, *T. brucei*, and *Leishmania*.[12] Structures containing quinazoline[13] and

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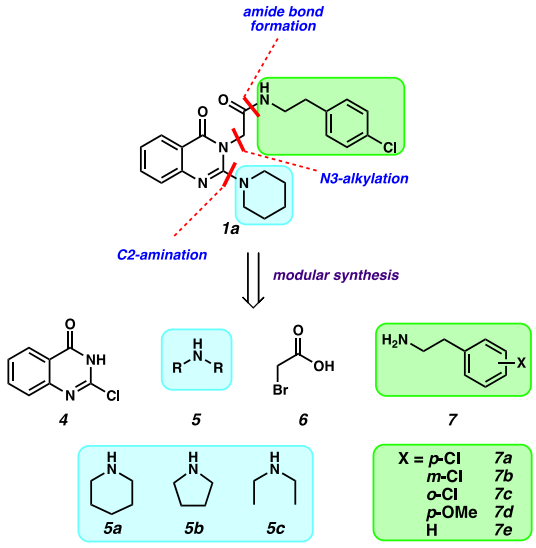
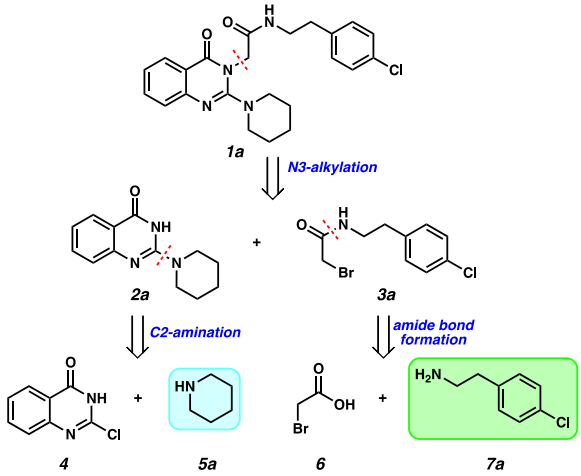
quinazolinedione[14] frameworks have recently shown promising activity against *T. cruzi* in particular. We aimed to develop a robust synthesis of **1a**, which would be used to create a small library of structural derivatives with systematically varied amine and amide moieties to explore the structure–activity relationship. We recognized that **1a** could be assembled in a modular fashion from molecular building blocks **4**–**7** through a sequence of three synthetic transformations: C2-amination, *N*3-alkylation, and amide bond formation (Scheme 1). Variation of the amine (**5**) and phenethylamine (**7**) building blocks (highlighted in blue and green, respectively) would enable access to various analogs of **1a**. Amines with varying degrees of flexibility and steric bulk such as piperidine (**5a**), pyrrolidine (**5b**), and diethylamine (**5c**), would be installed to probe the effect of conformational restraint.[15] The influence of substituent identity (Cl vs. OMe) and placement (ortho, meta, para) in the pendent aromatic ring of the amide moiety would also be explored using phenethylamine reagents **7a**–**e**.[16]




**Scheme 1.** Modular synthetic approach toward **1a**.

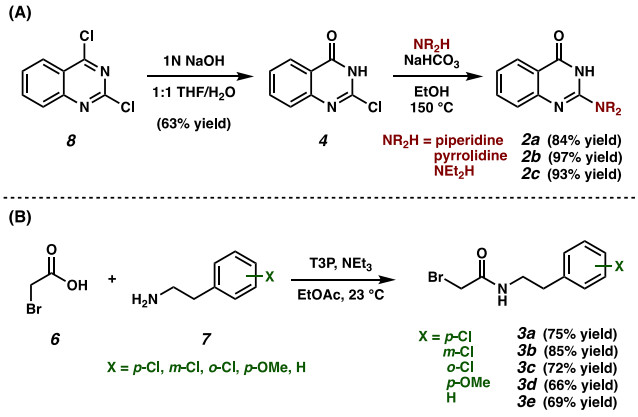
## RESULTS AND DISCUSSION

**Initial Synthetic Approach.** The initial synthetic approach toward **1a** was designed collaboratively with the Open Synthesis Network (OSN), a DNDi project which offers undergraduate students opportunities to engage with synthetic research on schedules amenable to typical time commitments of college students.[17] Considering the importance of efficiently generating molecular complexity and diversity in modular synthesis,[3] we devised a convergent strategy toward assembling **1a** from building blocks **4**–**7**. We envisioned accessing **1a** through *N*3-alkylation of C2-aminated quinazolinone scaffold **2a** using bromoamide **3a** (Scheme 2). Aminated quinazolinone **2a** would be prepared through amination of 2-chloro-4(3*H*)-quinazolinone (**4**) using piperidine (**5a**), and bromoamide **3a** would be synthesized through amide coupling of bromoacetic acid (**6**) with 4-chlorophenethylamine (**7a**). Exchanging piperidine (**5a**) for pyrrolidine (**5b**) or diethylamine (**5c**) and interchanging 4-chlorophenethylamine (**7a**) with a variant bearing *o*-Cl, *m*-Cl, or *p*-OMe substitution (**7b**–**7d**) or unsubstituted phenethylamine (**7e**) would introduce the desired molecular diversity. This strategy would employ building blocks of similar size and complexity and thus offered a reasonable starting point for our efforts.




**Scheme 2.** Initial convergent synthetic approach toward **1a**, with building blocks to be varied highlighted in blue and green.

Implementation of this plan began with basic hydrolysis of 2,4-dichloroquinazoline (**8**), which furnished 2-chloroquinazolinone **4** in moderate yield. Heating **4** in the presence of piperidine and sodium bicarbonate effected the desired amination, forming aminated quinazolinone **2a** in good yield. The procedure was repeated using pyrrolidine and diethylamine, generating quinazolinones **2b** and **2c** in robust yields (Scheme 3A). Bromoamide **3a** was synthesized readily via T3P coupling of bromoacetic acid with 4-chlorophenethylamine.[18] This approach was subsequently used to prepare additional phenethylamine-derived bromoamides containing variously substituted aryl groups in good yields (**3a**–**e**, Scheme 3B).




**Scheme 3.** Preparation of (A) aminated quinazolinones **2a**–**c** and (B) bromoamides **3a**–**e.**

With the desired aminated quinazolinones (**2a**–**c**) and bromoamides (**3a**–**e**) in hand, we were poised to assemble target disubstituted quinazolinone **1a** via *N*3-substitution in accordance with our synthetic strategy. We anticipated that regioselective alkylation of the N/O ambident nucleophile might prove challenging based on prior studies documenting the sensitivity of quinazolinone alkylation to C2 substitution.[19,20] Although a standard set of conditions to reliably favor one site of reactivity has yet to be established, several reports suggest that employing potassium carbonate as the base and DMF as the

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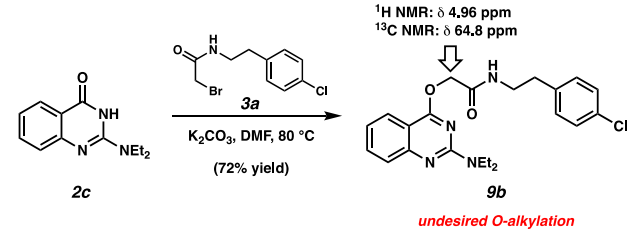
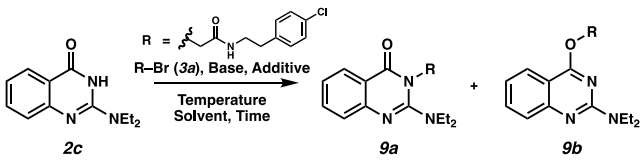
solvent would promote the desired *N*-alkylation.[18,21] Under these conditions, treatment of aminated quinazolinone **2c** with bromoamide **3a** proceeded with good conversion, but we suspected that the major product was *O*-alkylation adduct **9b** based on resonances observed at δ 4.96 ppm in the $^{1}$H NMR spectrum and δ 64.8 ppm in the $^{13}$C NMR spectrum, indicative of the newly attached $CH_2$ moiety (Scheme 4). Reports by Bates[22] and Pour[23] indicate that the *N*-alkylation products of quinazolin-4(3*H*)-ones display $CH_2$ $^{13}$C NMR signals in the δ 45–55 ppm range whereas *O*-alkylation products typically appear in the δ 65–75 ppm range. Disappointingly, *O*-alkylation prevailed under various conditions expected to promote *N*-alkylation (Table 1).[24,25,26]




**Scheme 4.** Undesired *O*-alkylation of quinazolinone **2c**.



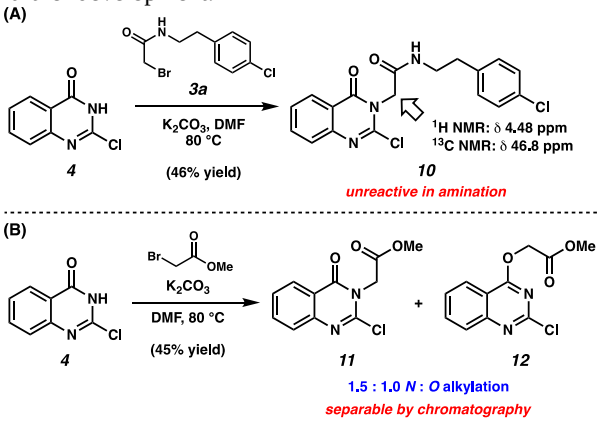

| Entry | Base | Additive | Solvent | Temperature | Time | Result |
|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | None | DMF | 80 °C | 22 h | 72% yield of ***9b*** |
| 2 | $K_2CO_3$ | None | DMF | 35 °C | 17 h | 86% yield of ***9b*** |
| 3 | NaH | LiBr | 4:1 DME/DMF | 65 °C | 16 h | Mostly ***9b***[a] |
| 4 | NaH | KI | 4:1 DME/DMF | 65 °C | 17 h | Mostly ***9b***[a] |
| 5 | $K_2CO_3$ | LiBr, TBAB | 10:1 PhMe/$H_2O$ | 80 °C | 1 h | Mostly ***9b***[a] |
| 6 | $K_2CO_3$ | CsF, TBAB | 10:1 PhMe/$H_2O$ | 80 °C | 1 h | Mostly ***9b***[a] |

[a] Based on TLC and $^{1}$H NMR

**Table 1.** Exploration of conditions for alkylation of **2c**.

**Revised Synthetic Strategy.** We hypothesized that the observed undesired regioselectivity stemmed from unfavorable steric interactions between bromoamide **3a** and the diethylamine moiety in quinazolinone **2c**, as sterics at the C2 position have been reported to affect alkylation regioselectivity in similar quinazolinone systems, especially with larger electrophiles.[20] Furthermore, prior work by Hori[19] suggests that the electron-donating nature of the C2 amine substituent may also promote *O*-alkylation. To explore this possibility, we modified our approach toward functionalizing the quinazolinone core to introduce C2 amination *after* *N*3-alkylation in the synthetic sequence. When C2-chlorinated quinazolinone **4** and bromoamide **3a** were subjected to the original alkylation conditions ($K_2CO_3$, DMF, 80 °C), the reaction proceeded with the desired regioselectivity, preferentially generating *N*-alkylated product **10**, which displayed a $CH_2$ $^{1}$H NMR resonance at δ 4.48 ppm and a $^{13}$C NMR resonance at δ 46.8 ppm, as expected of the *N*-alkylated compound (Scheme 5A). This result corroborated our hypothesis about the influence of sterics and electronics on the regioselectivity of alkylation, as the C2-chloro substituent in **4** represents a smaller and less electron-donating group than the C2-diethylamino moiety in **2c**. A small amount of *O*-alkylated product was observed in the $^{1}$H NMR spectrum of the crude product mixture, but it was separable from desired *N*-alkylated product **10** by column chromatography.

Regrettably, subsequent efforts to aminate **10** were unsuccessful under various conditions,[27] returning only unreacted starting material. Predicting that sterics might again be responsible for the observed lack of reactivity, we revised the synthetic route once more. To address the steric issue while maintaining the desired alkylation regioselectivity, we designed an alkylation of quinazolinone **4** using a less bulky electrophile containing a functional handle that could later be converted into the target amide functionality. We were pleased to find that alkylation of **4** with methyl bromoacetate in the presence of potassium carbonate in DMF proceeded smoothly with moderate regioselectivity for the desired *N*-alkylated product (**11**, Scheme 5B). Significantly, *N*-alkylation and *O*-alkylation products **11** and **12** were readily separable by column chromatography, suggesting that this approach may be suitable for further development.




**Scheme 5.** Successful *N*-alkylation of **4** using (A) bromoamide **3a** or (B) methyl bromoacetate.

With purified **11** in hand, we were prepared to assess its amenability toward C2-amination. Although C2-amination had previously been achieved on substrate **4** in ethanol (Scheme 3A), these conditions resulted in transesterification of the methyl ester in **11**. Due to the moderate solubility of **11** in methanol, we adopted a 1:1 methanol/ethyl acetate solvent system for C2-amination of **11**. Gratifyingly, treatment of **11** with piperidine and sodium bicarbonate using these conditions afforded C2-amino quinazolinone **13a** in good yield (Scheme 6). Base-mediated hydrolysis of the methyl ester proceeded smoothly, although the resulting carboxylic acid proved challenging to isolate after aqueous work-up due to its high water-solubility. We circumvented this issue by conducting a one-pot hydrolysis–amidation: upon full conversion of **13a** and subsequent acidification, all solvent was removed and T3P coupling reagent and 4-chlorophenethylamine were added directly to the flask and stirred in ethyl acetate. This procedure furnished target 2,*N*3-disubstituted quinazolinone **1a** in modest yield.

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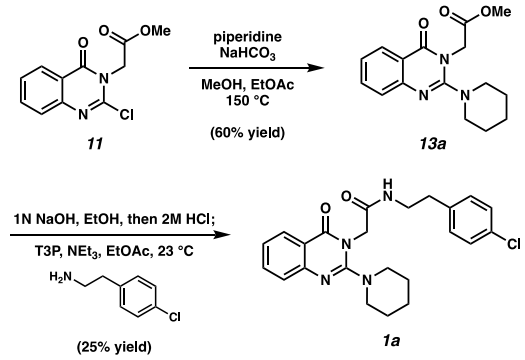
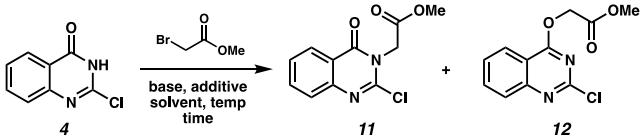



**Scheme 6.** Synthesis of bioactive 2,*N*3-disubstituted quinazolinone **1a** via alkylation product **11**.

**Synthetic Optimization.** Having confirmed the viability of the new synthetic route, we began optimization efforts, focusing first on the alkylation of quinazolinone **4**. In the revised synthesis, *N*3-alkylated quinazolinone **11** represents the initial branching point for introducing molecular diversity and thus plays the role of a central diversification scaffold, as employed in divergent synthesis. As such, robust production of **11** would be critical for assembling the compound library, which represents a limitless number of targets. We were especially interested in improving the regioselectivity of alkylation, as the loss of 40% of product mass to undesired *O*-alkylation constituted a significant setback in synthetic efficiency.

After examination of various bases, solvent systems, and temperatures, we discovered that the regioselectivity remained relatively constant at 1.5 : 1.0 *N*-alkylation (**11**) : *O*-alkylation (**12**) product when potassium carbonate was employed as the base with DMF as the solvent, regardless of additives, temperature, or reaction time (Table 2, Entries 1–4). Decreasing solvent polarity and using a phase transfer catalyst improved regioselectivity slightly (Entries 5–6).[25] Use of sodium hydride as the base in the presence of lithium bromide using 4:1 DME/DMF as the solvent system significantly improved regioselectivity (Entries 7–8).[24] Interestingly, elimination of DMF entirely from the reaction conditions led to formation of **11** as the sole product (Entry 9), and the lithium bromide additive was, in fact, not necessary for *N*-alkylation (Entry 10). This differs from previous work demonstrating the importance of a lithium counterion for *N*-alkylation of 6-substituted 2-pyridones, which necessitated use of DMF as a co-solvent.[24] Possibly, the additional fused aromatic ring in the quinazolinone system creates a "softer" nucleophile better matched by the sodium counterion.[28] The use of pure DME without the more polar DMF co-solvent permits greater ion clustering, thus promoting reactivity at the "softer" nitrogen nucleophile.[29] We were pleased to discover that the less hazardous base sodium carbonate was as effective as sodium hydride and a reaction time of only 1.5 hours was required for full conversion (Entry 11). Potassium carbonate was also a competent base for this transformation, but *O*-alkylation product **12** comprised 5% of the crude product mixture (Entry 12), highlighting the importance of the sodium counterion for achieving *N*-alkylation.



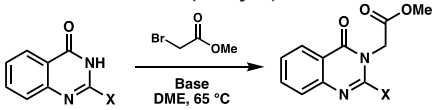

| Entry | Base | Additive | Solvent | Temperature | Time | *11* : *12* [a] |
|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | None | DMF | 25 / 50 / 80 °C | 12 h | 1.5 : 1.0 |
| 2 | $K_2CO_3$ | None | DMF | 80 °C | 2 h | 1.5 : 1.0 |
| 3 | $K_2CO_3$ | LiBr | DMF | 23 °C | 12 h | 1.5 : 1.0 |
| 4 | $K_2CO_3$ | CsF | DMF | 23 °C | 12 h | 1.5 : 1.0 |
| 5 | $K_2CO_3$ | LiBr, TBAB | 10:1 PhMe/$H_2O$ | 110 °C | 1 h | 2.6 : 1.0 |
| 6 | $K_2CO_3$ | CsF, TBAB | 10:1 PhMe/$H_2O$ | 110 °C | 1 h | 2.5 : 1.0 |
| 7 | NaH | LiBr | 4:1 DME/DMF | 65 °C | 6 h | 4.9 : 1.0 |
| 8 | NaH | LiBr | 4:1 DME/DMF | 65 °C | 19 h | 3.8 : 1.0 |
| 9 | NaH | LiBr | DME | 65 °C | 6 h | Only *11* |
| 10 | NaH | None | DME | 65 °C | 6 h | Only *11* |
| 11 | $Na_2CO_3$ | None | DME | 65 °C | 1.5 h | Only *11* |
| 12 | $K_2CO_3$ | None | DME | 65 °C | 1.5 h | 19.3 : 1.0 |

[a] Determined by $^1$H NMR of crude mixture

**Table 2.** Optimization of conditions for *N*3-alkylation of **4.**

Overall, the optimized conditions using sodium carbonate as the base and DME as the solvent (Entry 11) furnished *N*-alkylation product **11** as the sole isomer in quantitative yield with no need for purification beyond aqueous work-up. Successful optimization of this reaction significantly improved synthetic efficiency and scalability, enabling rapid access to multigram quantities of central diversification scaffold **11**. Furthermore, the replacement of sodium hydride with sodium carbonate and the decreased reaction time rendered this procedure more accessible to undergraduate researchers.

This protocol was successfully applied to the *N*-alkylation of 4-hydroxyquinazoline (**14**) and 2-methylquinazolin-4(3*H*)-one (**15**) to afford *N*-alkylated products **16** and **17**, respectively (Table 3). These substrates were less reactive than **4**, typically requiring longer reaction times for appreciable conversion,[30] but for both substrates no evidence of *O*-alkylation was observed. Bearing no C2 substituent, substrate **14** reacted fully after 24 hours, producing *N*-alkylated compound **16** in quantitative yield without need for purification (Entry 2). C2-methylated substrate **15** never reached full conversion, even after 48 hours, underscoring the sensitivity of alkylation to C2 substitution in 4-quinazolinones (Entries 3–4). We predicted that a stronger base may be necessary for deprotonation of **15** in the absence of the electron-withdrawing C2-chloro substituent. Indeed, reaction of **15** with sodium hydride and methyl bromoacetate in DME furnished *N*-alkylated product **17** in 68% yield after 1.5 hours (Entry 5).




| Entry | X | Substrate | Product | Base | Time | Yield[a] |
|---|---|---|---|---|---|---|
| 1 | Cl | *4* | *11* | $Na_2CO_3$ | 1.5 h | 99% |
| 2 | H | *14* | *16* | $Na_2CO_3$ | 24 h | 99% |
| 3 | $CH_3$ | *15* | *17* | $Na_2CO_3$ | 24 h | 49%[b] |
| 4 | $CH_3$ | *15* | *17* | $Na_2CO_3$ | 48 h | 67%[b] |
| 5 | $CH_3$ | *15* | *17* | NaH | 1.5 h | 68%[b] |

[a] Isolated yield; [b] Remaining mass balance is unreacted starting material.

**Table 3.** Alkylation of 4-quinazolinones **4**, **14**, and **15** using optimized conditions.

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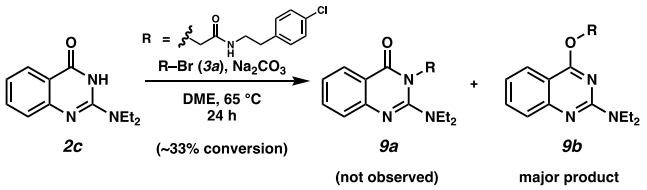
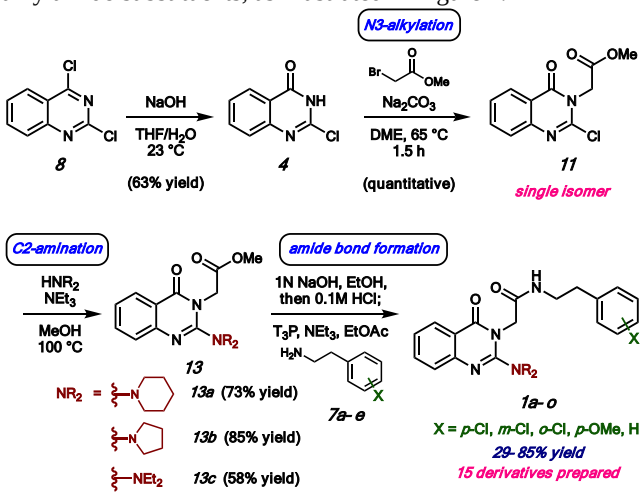
To assess whether the optimized alkylation conditions would enable successful *N*3-alkylation of C2-aminated 4-quinazolinones, as attempted in our previous synthetic route (Scheme 2), we treated 2-amino-4-quinazolinone **2c** with sodium carbonate and bromoamide **3a** in DME. After 24 hours at 65 °C, we observed only partial conversion and preferential formation of *O*-alkylated product **9b** via TLC and $^1$H NMR (Scheme 7). This outcome mirrored our previous efforts (Table 1) and reaffirmed our earlier finding that the bulky, electron-donating C2-diethylamino substituent cannot be installed before *N*3-alkylation.




**Scheme 7.** Alkylation of **2c** using optimized conditions.

Having thoroughly explored the *N*3-alkylation reaction, we turned our attention to optimizing the remainder of the synthesis. C2-amination of *N*-alkylated scaffold **11** generally proceeded smoothly in good yield. We found that use of triethylamine as the base instead of sodium bicarbonate improved the solubility of **11** without loss of yield, enabling elimination of the ethyl acetate co-solvent. Additionally, under these conditions a lower reaction temperature of 100 °C proved effective, further streamlining logistics for C2-amination and providing ready access to C2-aminated scaffolds **13a**–**c** (Scheme 8). The subsequent low-yielding hydrolysis–amidation sequence required further optimization for reliable preparation of target derivatives **1a**–**o**. Yields were improved by using a more dilute acid during the acidic work-up (0.1 M HCl instead of 2 M HCl) following basic hydrolysis of the methyl ester. Subsequent T3P coupling with phenethylamine reagents **7a**–**e** using the one-pot method previously described afforded 2,3-disubstituted 4-quinazolinones **1a**–**o** in moderate to good yields.

The overall optimized synthetic route to **1a**–**o** is summarized in Scheme 8. This four-step sequence begins with base-mediated hydrolysis of commercially available 2,4-dichloroquinazolinone (**8**) to generate quinazolinone **4**. Selective *N*3-alkylation of **4** with methyl bromoacetate can be achieved in quantitative yield using sodium carbonate in DME. The resulting methyl ester (**11**) requires no purification and readily undergoes C2-amination using piperidine, pyrrolidine, or diethylamine in good yields. Each aminated product (**13a**–**c**) undergoes a one-pot ester hydrolysis and subsequent T3P coupling with variously substituted phenethylamine reagents to afford the target disubstituted quinazolinones **1a**–**o**. Ultimately, this strategy enabled access to fifteen unique disubstituted quinazolinones with varying combinations of 2-amino and *N*3-alkylamido substituents, as illustrated in Figure 2.




**Scheme 8.** Optimized synthetic route toward 2,*N*3-disubstituted quinazolinones **1a–o**.

Notably, this synthesis adopts a more linear approach compared to the original convergent strategy. While this adjustment was necessitated by the precise sequencing required for successful *N*3-alkylation, C2-amination, and amide bond formation, this synthetic route is ultimately more conducive to compound library preparation. Creating a central diversification scaffold (**11**) streamlines subsequent installation of the amine and phenethylamine building blocks. Leveraging principles of both modular and divergent synthesis,[31] this approach offers a systematic blueprint for assembling 2-amino-*N*3-alkylamido 4-quinazolinones.

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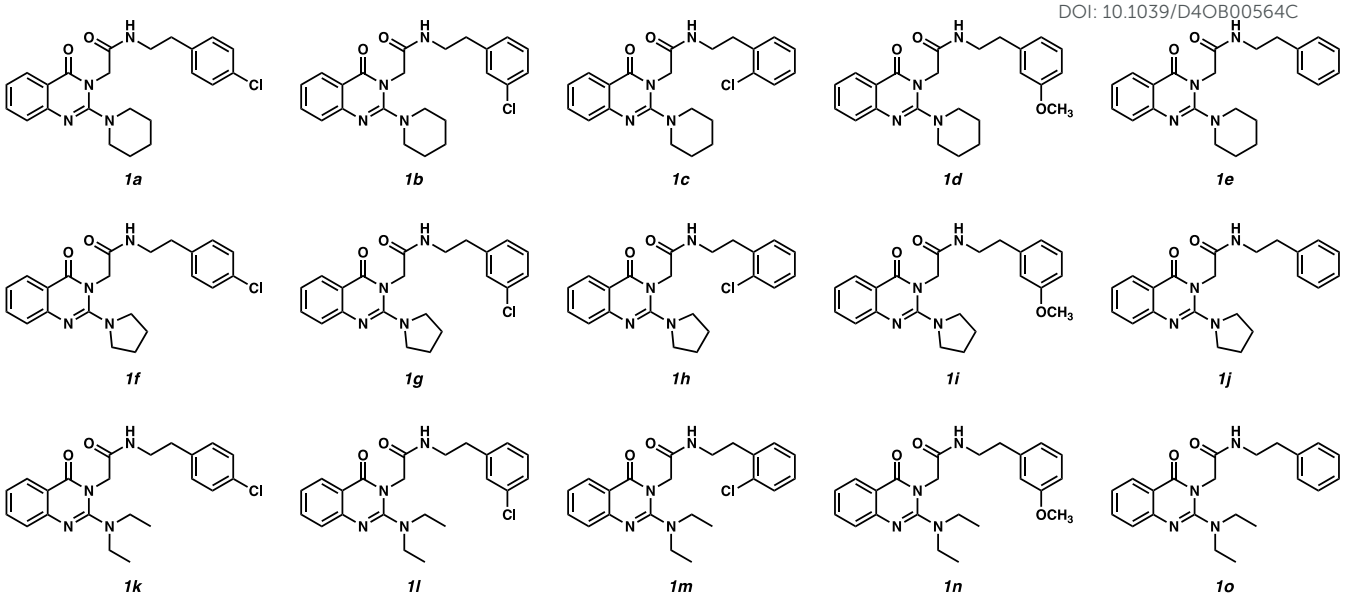


**Figure 2.** 2-Amino-*N*3-alkylamido 4-quinazolinones synthesized for biological testing.

**Preliminary Biological Studies.** Biological evaluation of 2,*N*3-disubstituted quinazolinones **1a**–**o** was carried out by DNDi collaborators at the University of Antwerp. Preliminary results indicate that compounds **1b**–**o** do not exhibit significant potency against the *T. cruzi, T. brucei, or L. infantum* parasites compared to the initial screening hit **1a**, suggesting a possible structure activity cliff in this series. Nevertheless, there remain opportunities for further evaluation of these compounds against additional disease agents and design of further targets based on these preliminary results. Moreover, as new discoveries are made, the synthetic strategy described here can be applied toward the preparation of 2,*N*3-disubstituted 4-quinazolinones far beyond those prepared in this study. We plan to report these findings in due course.

## CONCLUSION

In summary, we have prepared fifteen unique 2,*N*3-disubstituted 4-quinazolinones in four steps from commercially available materials. Synthetic success was predicated on two key accomplishments: 1) determining an effective sequence for C2-amination, *N*3-alkylation, and amide bond formation; and 2) optimizing *N*3-alkylation to promote the desired regioselectivity. Installation of the C2-amino substituent proved sensitive to the identity of the *N*3-substituent, and regioselectivity of *N*3-alkylation was similarly influenced by C2 substituent identity. We ultimately found that *N*3-alkylation of the quinazolinone core using an electrophile sterically unencumbered enough to permit subsequent C2-amination followed by amide bond formation enabled access to the target bioactive quinazolinone (**1a**). Additionally, the development of a highly effective protocol for regioselective *N*-alkylation of 2-chloro-4(3*H*)-quinazolinone (**4**) facilitated the preparation of central diversification scaffold **11**, thus expediting synthesis of 2-amino-*N*3-alkylamido-4-quinazolinones **1a**–**o**.

Overall, these findings showcase the synergistic application of modular and divergent synthetic approaches in the preparation of diverse molecular targets. Our efforts have generated a small library of compounds for further elaboration and biological testing and provided an experiential learning experience in multistep organic synthesis for undergraduate students. Preliminary biological studies indicate potential for further investigation and design of new targets. We anticipate that the synthetic insights gleaned from these endeavors will provide useful guidance to other researchers in this area of study.

## EXPERIMENTAL SECTION

**General Procedure A:** Preparation of aminated quinzolinones **2a–c**.

To a suspension of quinazolinone **4** (100.0 mg, 0.55 mmol, 1.0 equiv) and sodium bicarbonate (231.0 mg, 2.75 mmol, 5.0 equiv) in ethanol (2 mL) at 23 °C was added amine (1.66 mmol, 3.0 equiv). The flask was sealed (via Kontes valve) and the resulting mixture was stirred and heated in an oil bath to 150 °C. After 6 hours, the reaction mixture was filtered over Celite and concentrated. The crude residue was purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford the aminated quinazolinone as a white solid.

**General Procedure B:** Preparation of Bromoamides **3a**–**e**.

To a solution of bromoacetic acid (4.46 g, 32.1 mmol, 1.0 equiv) in ethyl acetate (40 mL) at 0 °C was added 1-propanephosphonic acid cyclic anhydride (50 wt % in ethyl acetate, 30.7 mL, 48.2 mmol, 1.5 equiv). While stirring the resulting mixture, a solution of substituted phenethylamine (32.1 mmol, 1.0 equiv) and triethylamine (8.96 mL, 64.3 mmol, 2.0 equiv) in ethyl acetate (20 mL) was added, and the reaction was allowed to warm up gradually overnight. The reaction mixture was washed with $H_2O$ (2 x 30 mL), and brine (30 mL), and the organic layer was dried over $Na_2SO_4$. After filtration and concentration, the crude material was purified by silica gel column chromatography (25% → 30% → 50% ethyl acetate in hexanes).

**General Procedure C:** Quinazolinone alkylation in DME using Methyl Bromoacetate and Sodium Carbonate.

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To a solution of quinazolinone **4**, **14**, or **15** (0.30 mmol, 1.0 equiv) in DME (3.0 mL) was added sodium carbonate (0.315 mmol, 1.05 equiv) at 23 °C. After stirring for 10 minutes, methyl bromoacetate (0.057 mL, 0.60 mmol, 2.0 equiv) was added dropwise, and the reaction flask was sealed and heated in an oil bath to 65 °C. After 1.5 hours, the reaction was removed from heat and poured into brine (10 mL) after 25 minutes, then extracted with ethyl acetate (6 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford *N*-alkylated product **11**, **16**, or **17**.

**General Procedure D:** Preparation of 2-Amino-*N*3-Alkyl Quinazolinones **13a**–**c**.

To a solution of methyl ester **11** (200 mg, 0.792 mmol, 1.0 equiv) in methanol (8.0 mL) at 23 °C was added amine **5a**, **5b**, or **5c** (2.38 mmol, 3.0 equiv) and triethylamine (0.55 mL, 3.16 mmol, 5.0 equiv) sequentially. The flask was sealed (via Kontes valve) and the resulting mixture was stirred and heated in an oil bath to 100 °C. After 90 minutes, the reaction mixture was removed from heat, filtered over Celite, and concentrated. The crude residue was purified by silica gel column chromatography (25% ethyl acetate in hexanes) to afford aminoquinazolinone **13a**, **13b**, or **13c** as a white solid.

**General Procedure E:** Hydrolysis–Amidation to Prepare Target Derivatives **1a**–**o**.

To a solution of aminoquinazolinone **13** (0.05 mmol, 1.0 equiv) in ethanol (5 mL) was added a 1N solution of NaOH (0.3 mL, 0.3 mmol, 5.0 equiv). The resulting mixture was stirred vigorously at 23 °C. When TLC analysis showed complete conversion of **13** (typically after 24 hours), the reaction flask was cooled to 0 °C in an ice bath, and 0.1M HCl was added dropwise to adjust the pH to 4–5. The solvents were then removed under reduced pressure at 37 °C, and the resulting white solid was diluted with ethyl acetate (3 mL) and cooled to 0 °C. To this suspension was added 1-propanephosphonic acid cyclic anhydride (50 wt % in ethyl acetate, 0.05 mL, 0.16 mmol, 3.0 equiv). While stirring the resulting mixture, a solution of substituted phenethylamine (0.11 mmol, 2.0 equiv) and triethylamine (0.03 mL, 0.22 mmol, 4.0 equiv) in ethyl acetate (2 mL) was added, and the reaction was allowed to warm up gradually overnight. The reaction mixture was washed with $H_2O$ (2 x 10 mL), and brine (10 mL), and the organic layer was dried over $Na_2SO_4$. After filtration and concentration, the crude material was purified by silica gel column chromatography (ethyl acetate/hexanes).

**Compound 11.** White solid, 125 mg, 45% yield from 200 mg of **4**; mp 99.9–101.7 °C (from EtOAc/hex); $R_f$ = 0.68 (50% ethyl acetate in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.78 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 5.06 (s, 2H), 3.81 (s, 3H); $^{13}$C NMR ($CDCl_3$, 126 MHz) δ 167.4, 161.7, 146.6, 143.9, 135.5, 127.9, 127.6, 127.1, 120.0, 53.0, 47.0; IR (Neat Film) 3231, 1635, 1603, 1555, 1503, 1472, 1460, 1357, 1280, 1194, 907, 732 cm$^{-1}$; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{10}ClN_2O_3$ $[M+H]^+$: 253.0380, found 253.0377.

**Compound 13a.** White solid; 173 mg, 73% yield; mp 86.0–87.5 °C (from EtOAc/hex). $R_f$ = 0.72 (50% ethyl acetate in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.65 (ddd, *J* = 7.7, 7.1, 1.6 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.32 (ddd, *J* = 7.5, 7.1, 1.2 Hz, 1H), 4.80 (s, 2H), 3.77 (s, 3H), 3.11–3.05 (m, 4H), 1.70–1.63 (m, 4H), 1.63–1.56 (m, 2H). $^{13}$C NMR ($CDCl_3$, 126 MHz) δ 168.9, 163.7, 155.6, 147.7, 134.5, 127.1, 126.5, 125.4, 119.4, 52.6, 51.5, 45.9, 25.5, 24.2; IR (Neat Film) 2938, 2351, 1751, 1680, 1587, 1567, 1472, 1439, 1383, 1333, 1207, 1183, 1102, 986, 858, 771, 710 cm$^{-1}$; HRMS (ESI+) *m/z* calc'd for $C_{16}H_{20}N_3O_3$ $[M+H]^+$: 302.1505, found 302.1513.

**Compound 1a.** White solid, 26 mg, 86% yield from 21 mg (0.070 mmol) of **13a**; mp 177.2–180.1 °C (from EtOAc/hex). $R_f$ = 0.45 (50% hexanes in ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.69 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.21–7.15 (m, 2H), 7.12–7.06 (m, 2H), 6.47 (s, 1H), 4.65 (s, 2H), 3.53 (td, *J* = 7.0, 5.9 Hz, 2H), 3.13 – 3.08 (m, 4H), 2.79 (t, *J* = 7.0 Hz, 2H), 1.74–1.67 (m, 4H), 1.66–1.59 (m, 2H); $^{13}$C NMR ($CDCl_3$, 126 MHz) δ 168.1, 164.9, 155.8, 147.9, 137.2, 134.9, 132.5, 130.2, 128.8, 126.9, 126.5, 125.4, 119.1, 51.7, 49.5, 40.8, 35.1, 25.7, 24.3; IR (Neat Film) 2959, 2929, 2873, 2960, 1719, 1462, 1408, 1380, 1265, 1247, 1115, 1101, 1019, 874, 729 cm$^{-1}$; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{26}ClN_4O_2$ $[M+H]^+$: 425.1744, found 425.1756.

## SUPPORTING INFORMATION

The Supporting Information is available on the RSC Publications website and contains NMR spectra of all new compounds (PDF).

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K. E. K. – conceptualization, data curation, funding acquisition, investigation, resources, supervision, project administration, visualization, writing original draft, review & editing; J. R. C., A. J. P., G. C. H., C. J. M., M. F. F., K. M. – investigation, data curation, validation; B. P. – conceptualization.

### Conflicts of Interest

The authors declare no conflicts of interest.

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30. For both substrates **14** and **15**, minimal conversion was observed by TLC after 1.5 hours. Working up the reactions at this time generated 0–2% yield of *N*-alkylated product and mostly returned starting material.
31. For another recent example of a combined modular and divergent synthesis, see: Tian, G.; Zhang, Y.-C.; Qin, C.; Wang, J. A modular and divergent approach for the total synthesis of *Elaeocarpus* alkaloids. *Org. Chem. Front.* **2023**, *10*, 68–73.