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Synthesis of *N*-phenethylquinazolin-4-amines *via* silylation-amination mediated by hexamethyldisilazane

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ABSTRACT

N-phenethylquinazolin-4-amines have emerged as potential *Mycobacterium tuberculosis* cytochrome bd oxidase inhibitors and attractive scaffolds in tuberculosis drug discovery programs. The classical two-step strategy of chlorination-amination to synthesize such structures presents several operational issues accompanied by variable results. This work reports an efficient one-pot protocol to access *N*-phenethylquinazolin-4-amines *via* silylation-amination mediated by hexamethyldisilazane. The products were obtained with excellent yields (84–99%) under one-pot solvent-free conditions.

Introduction

Nitrogen-containing heterocycles such as quinazolines play a significant role in drug discovery and development [1]. Indeed, some clinically useful drugs **1**–**3** (Fig. 1) present the quinazoline scaffold with a variety of substituents [2,3]. In particular, the 4-position of the heterocycle has been extensively investigated over the decades, yielding many derivatives with diverse pharmacological activities [1,2]. Recently, a series of *N*-phenethylquinazolin-4-amines has been described as *Mycobacterium tuberculosis* cytochrome bd oxidase inhibitors [4]. The cytochrome *bd* oxidase is part of the respiratory terminal oxidase of the mycobacterial respiratory chain and has emerged as an important drug target in tuberculosis drug discovery campaigns [5].

A common strategy to synthesize 4-aminoquinazolines consists of chlorination at the 4-position of quinazolin-4(3*H*)-ones with the following amination through the S_NAr reaction (classical method) [6]. However, it involves critical drawbacks, such as *a*) the use of thionyl chloride or phosphorus oxychloride, which are hazardous and environmentally harmful chemicals [6,7]; *b*) the formation of quinazolin-4(3*H*)-one (*N*)-dimer as a side product under $POCl_3$ chlorination [7]; and *c*) the inherent chemical instability of 4-chloroquinazolines [8,9]. The instability of 4-chloroquinazoline derivatives is related to the heat sensitivity and high proneness to the hydrolysis reaction in the presence of water/moisture, reversing the chlorinated product to the quinazolin-4(3*H*)-one starting material. As an alternative to the classical method, hydroxy *N*-heterocycles, including tautomerazible quinazolin-4(3*H*)-ones, have been silylated by hexamethyldisilazane (HMDS) *in situ* and subsequently aminated [8,9]. This protocol would avoid the use of chlorination reagents and could provide the desired *N*-phenethylquinazolin-4-amines in a greener approach compared to existing methods.

As part of our ongoing program, we are interested in the development of alternative synthetic methodologies with improved efficiency and reduced environmental impact for obtaining novel antimycobacterial drug candidates [10]. The early stages of drug discovery (e.g., hit-to-lead optimization) are complex and time-consuming [11], and more efficient methods may boost access to antitubercular compounds. In addition, the pharmaceutical industry is one of the main waste generators among processing companies [12], so studying environmentally benign protocols should be a priority in early drug discovery programs. Therefore, based on the potential antitubercular

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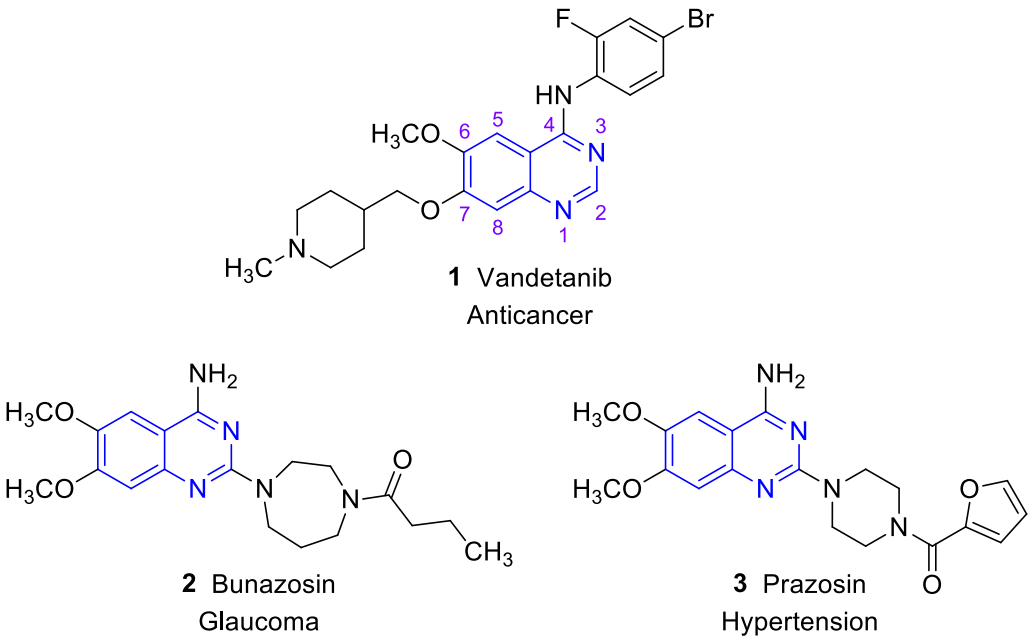
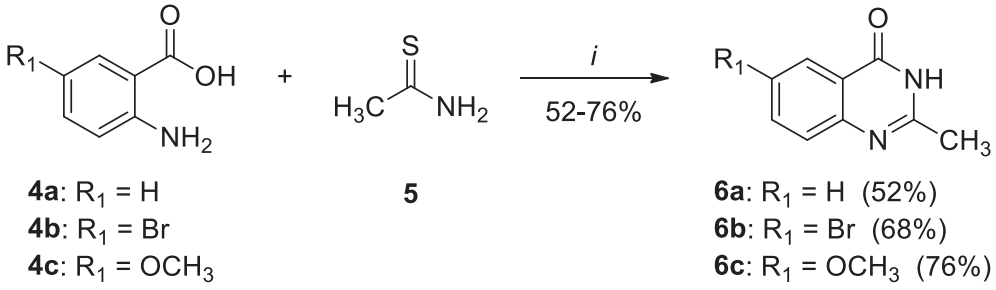


Fig. 1. Drugs containing the quinazoline core (highlighted in blue) and their clinical use. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Scheme 1. Synthesis of 2-methylquinazolin-4(3*H*)-ones (**6a-c**). Conditions: (*i*) = 150 °C, 2 h. Yields obtained from purified compounds.

utility of this chemical class, herein, a methodology to conveniently synthesize *N*-phenethylquinazolin-4-amines from quinazolin-4(3*H*)-ones and substituted phenethylamines mediated by HMDS was proposed.

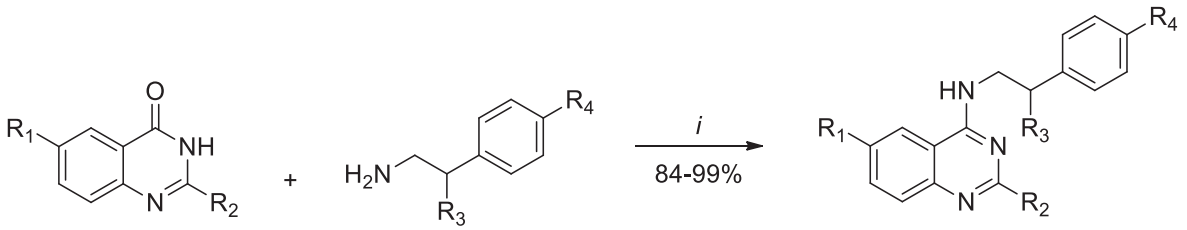
Results and discussion

The synthetic route involved two steps. First, substituted anthranilic acids **4a–c** were fused with thioacetamide **5**, giving rise to 6-substituted 2-methylquinazolin-4(3*H*)-ones **6a–c** with 52–76% yields (Scheme 1). Substituents at the 6-position (R_1) included hydrogen **6a**, electron-withdrawing **6b** (-Br), and electron-donating **6c** (–OCH_3) groups, allowing for the analysis of the applicability of the following step under different electron densities at the benzene moiety.

Next, the first attempts to synthesize the *N*-phenethylquinazolin-4-amines **11a–11d** (Table 1) were performed by using similar conditions to other already described methods [13]. However, under this protocol, only compounds **11a** and **11d** were obtained with the total consumption of starting materials (**6a** and **6d**). Afterwards, different conditions and proportions between the reactants and HMDS were evaluated. Equivalent proportions of phenethylamine and HMDS were increased until the optimal ratio of 1:3:3 (quinazolin-4(3*H*)one:phenethylamine:HMDS) was reached under solvent-free conditions. While the HMDS produces soluble silylated intermediates, an excess of amine improves the starting material solubilization, serving as a reaction medium for the subsequent amination reaction [14]. It is important to mention that HMDS-mediated reactions have required the presence of ammonium sulfate ($(NH_4)_2SO_4$) as a catalyst depending on the reactivity of the heterocyclic system [14]. In our study, the amount of $(NH_4)_2SO_4$ was fixed at 10 mol%. Thus, under this protocol, *N*-phenethylquinazolin-4-amines **11a–d** and **12a–d** were obtained after heating at 125 °C for 24 h with 84–99% yields (Table 1). By contrast, derivatives bearing 4-chlorophenethyl (**13a–d**) and bulky 2,2-diphenylethyl (**14a–d**) groups required 48 h for the complete conversion of the reactants into the respective products (Table 1). *N*-Phenethylquinazolin-4-amines **13a–d** and **14a–d** were obtained after stirring at 125 °C for 48 h with 89–98% yields (Table 1).

We speculate that the volatility of **9** (b.p. = 60–65 °C) could be related to the reaction times necessary to obtain the chlorinated-structures **13a–d** (Table 1). As the vapor pressure is lower for reactant **9**, its elevated presence in the gas phase may reduce the conversion rate. Regarding amine **10**, in silico simulations revealed that the extra phenyl ring increases the molecular volume by 54.8% (225.9 Å) compared with phenethylamine (**7**) (145.9 Å) (**Supporting information**). Thus, a plausible explanation for the longer reaction time for obtaining **14a–d** may be the steric hindrance between the additional phenyl ring and the *O*-trimethylsilyl group during the amination step (Fig. 2). These steric difficulties should demand specific conformations for an effective amination process. All these insights must be taken into account in the decision-making process when using this methodology to design

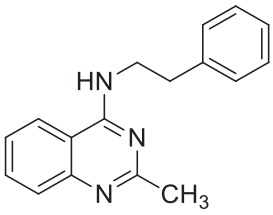
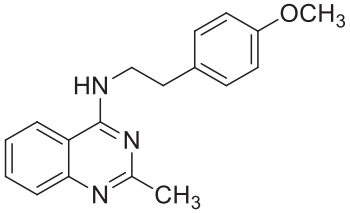
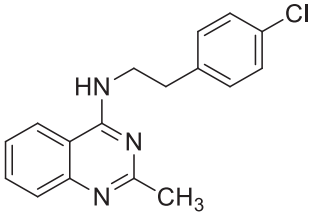
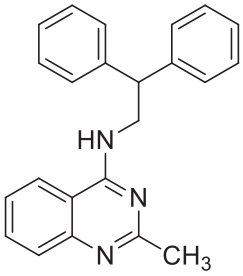
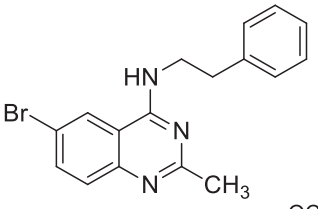
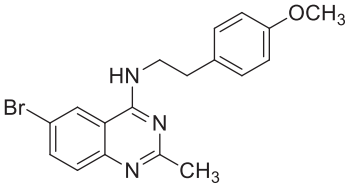
Table 1
Substrate scope and products.



6a: R_1 = H ; R_2 = CH_3
6b: R_1 = Br ; R_2 = CH_3
6c: R_1 = OCH_3 ; R_2 = CH_3
6d: R_1 = R_2 = H

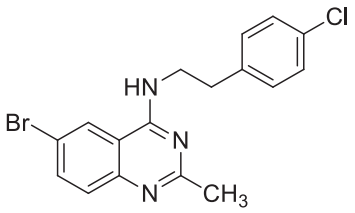
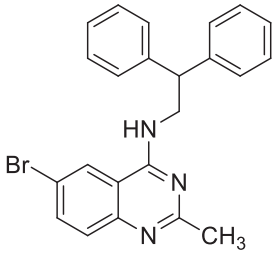
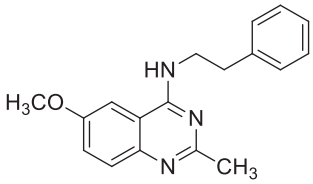
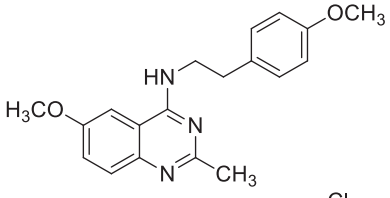
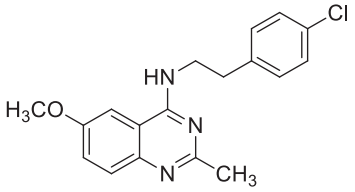
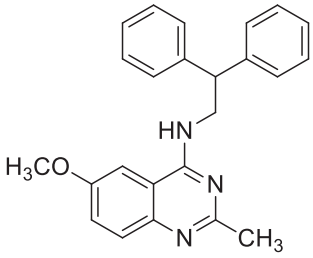
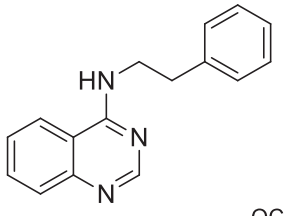
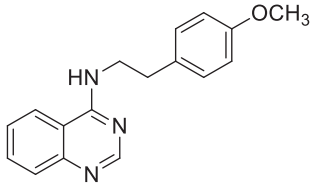
7: R_3 = R_4 = H
8: R_3 = H ; R_4 = OCH_3
9: R_3 = H ; R_4 = Cl
10: R_3 = Ph ; R_4 = H

11a - 14a: R_1 = H ; R_2 = CH_3
11b - 14b: R_1 = Br ; R_2 = CH_3
11c - 14c: R_1 = OCH_3 ; R_2 = CH_3
11d - 14d: R_1 = R_2 = H

Entry	Product	Time (h)	Yield (%)
11a		24	85
12a		24	84
13a*		48	97
14a*		48	89
11b		24	91
12b		24	96

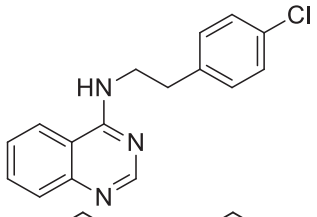
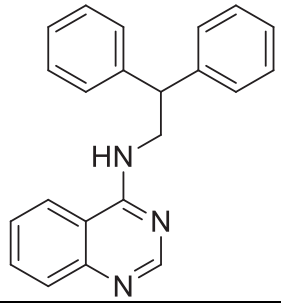
(*continued on next page*)

Table 1 (*continued*)

Entry	Product	Time (h)	Yield (%)
13b*		48	96
14b*		48	92
11c		24	99
12c		24	96
13c*		48	96
14c*		48	92
11d		24	99
12d		24	96

(*continued on next page*)

Table 1 (*continued*)

Entry	Product	Time (h)	Yield (%)
13d*		48	98
14d*		48	95

Reagents and conditions: (*i*) = HMDS, $(NH_4)_2SO_4$, 125 °C, 24–48 h. Quinazolin-4(3*H*)one:phenethylamine:HMDS:$(NH_4)_2SO_4$ = 1:3:3:0.1. *The reaction was performed in a Schlenk flask.

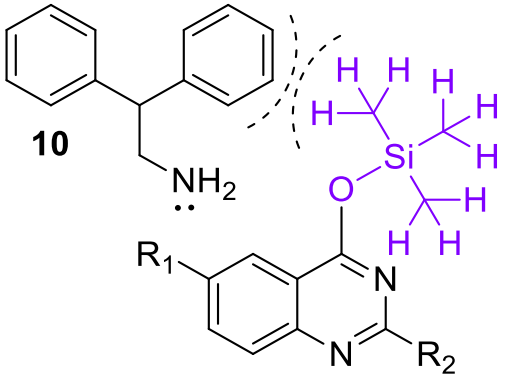


Fig. 2. Proposed steric hindrance between 2,2-diphenylethylamine (**10**) and *O*-trimethylsilyl group (highlighted in lilac) during the amination step.

Table 2
Comparison between yields obtained by the classical method using chlorinating reagents with the silylation-amination approach described in this work.

Entry	Substituent (R_4)	Yield (%) [4]	Yield (%) [this work]
11d	H	28	99
12d	OMe	43	96
13d	Cl	20	98

novel *N*-phenethylquinazolin-4-amines.

It is noteworthy that the yields of *N*-phenethylquinazolin-4-amines **11a**–**14d** (Table 1) were obtained after purification of the products by column chromatography without a previous reaction work-up. The differences observed in the yields seem to be related to the purification procedures rather than the electronic and steric effects from methylquinazolin-4(3*H*)-ones **6a**–**c** and phenethylamines **7**–**10**. After column chromatography, the relative purity of compounds **11a**–**14d** was > 98% based on HPLC experiments. Additionally, all synthesized molecules showed spectroscopic and spectrometric data confirming the proposed structures (Supporting information).

Finally, the comparison between the efficiency of the classic method [4] with the HMDS-mediated approach showed the superiority of the yields of this one-pot solvent-free protocol (Table 2). The yields of the *N*-phenethylquinazolin-4-amines **11d**, **12d**, and **13d** were at least 53% higher using the greener approach (Table 1). Clearly, the present protocol represents a convenient alternative to synthesizing these compounds compared to the existing methodologies.

In summary, we have synthesized a series of *N*-phenethylquinazolin-4-amines *via* the silylation-amination procedure, evidencing its improved efficiency over the classical chlorination-amination method. The methodology tolerated quinazolin-4(3*H*)-ones and phenethylamines with distinct electronic and steric features. However, further studies are still needed to verify the influence of substituents at different positions of quinazolin-4(3*H*)-one and phenethylamine rings. Furthermore, the simplicity of execution, excellent yields (84–99%), purity of products (>98%), and reduced number of reaction steps (one-pot) make this greener protocol highly attractive. It is noteworthy that some examples of *N*-phenethylquinazolin-4-amines with inhibitory potential against *Mycobacterium tuberculosis* cytochrome *bd* oxidase have already been reported, including the hit compound **11d**. Therefore, this methodology can be used to obtain a wide series of *N*-phenethylquinazolin-4-amines with possible antimycobacterial applicability accompanied by reduced environmental, operational, and financial costs when compared to existing protocols.

CRediT authorship contribution statement

Guilherme Arraché Gonçalves: Conceptualization, Methodology, Investigation, Writing – original draft. **Flávio Castro do Nascimento:** Methodology, Investigation. **Sidnei Moura e Silva:** Resources. **Cristiano Valim Bizarro:** Writing – review & editing, Funding acquisition. **Luiz Augusto Basso:** Writing – review & editing, Funding acquisition. **Pablo Machado:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100539.

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