Article

Modular Three-Component Synthesis of 4-Aminoquinolines via an Imidoylative Sonogashira/Cyclization Cascade

Jurriën W. Collet, Kelly Ackermans, Jeffrey Lambregts, Bert U. W. Maes, Romano V. A. Orru, and Eelco Ruijter

Just Accepted

Modular Three-Component Synthesis of 4-Aminoquinolines via an Imidoylative Sonogashira/Cyclization Cascade

Jurriën W. Collet,[†] Kelly Ackermans,[†] Jeffrey Lambregts,[†] Bert U.W. Maes,[‡] Romano V.A. Orru,[†,*] and Eelco Ruijter[†,*]

†Department of Chemistry and Pharmaceutical Sciences and Amsterdam Institute for Molecules, Medicines & Systems (AIMMS), Vrije Universiteit Amsterdam, De Boelelaan 1108, 1081 HZ Amsterdam, The Netherlands. E-mail: e.ruijter@vu.nl; r.v.a.orru@vu.nl   http://syborch.com/

‡Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
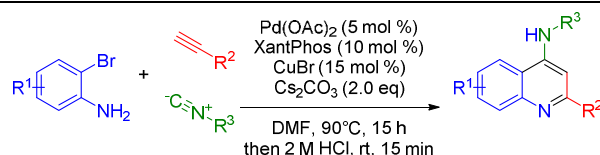
ABSTRACT:

We developed a one-pot, two-stage synthetic route to substituted 4-aminoquinolines involving an imidoylative Sonogashira coupling followed by acid-mediated cyclization. This three-component reaction affords pharmaceutically valuable 4-aminoquinolines in a one-pot procedure from readily available starting materials. The reaction tolerates various substituents on the arene as well as the use of secondary and even primary isocyanides. Additionally, the wide tolerance for functionalized isocyanides allows for the one-pot synthesis of various substituted chloroquine analogues as well as other medicinally relevant products.

Introduction

4-Aminoquinolines (4-AQs) have been widely investigated for their pharmaceutical potential, in particular their antimalarial properties.[1-5] Recently, B ring substituted (in particular 7-halo) 4-AQs were shown to display enhanced activities against highly resistant strains of *P. falciparum*.[6] Consequently, this scaffold is still of high interest for the development of novel antimalarials.[7] Additionally, chloroquine and amodiaquine (Fig. 1) have recently been flagged as leads against Ebola and Marburg viruses.[8,9] These known antimalarials also inhibit endosomal Toll-like receptors (TLRs).[10] Recently, other applications of 4-AQs have also been reported, as diversely substituted 4-AQs have been identified as promising antifilarials,[11] translocator protein biomarker ligands,[12] tuberculosis ATP synthase inhibitors,[13] and as nociceptin receptor antagonists.[14,15] Additionally, 4-AQs bearing 2-(hetero)aryl functionalities also show promise as non-nucleoside HIV-1 inhibitors.[16] Not surprisingly, there is great interest to efficiently access the 4-AQ core and over the past decades, several cascade reactions towards these medicinally valuable scaffolds have been developed (Scheme 1).[17-22] For example, 4-AQs can be obtained from the reaction of ynamides and nitrilium species, resulting from either arylation of nitriles[17] or dehydration of anilides.[18] The Cu(I)-catalyzed cyclization of imidoylacetylenes and sulfonyl azides affords 4-AQs as well.[19] A carbonylative Sonogashira reaction of 2-ethynylanilines with *in situ* amination at C4 also provides access to 4-AQs.[21] Finally, we recently showed that palladium-catalyzed oxidative isocyanide of *N*-aryl imines by double C-H activation also affords 4-AQs.[22] However, these methods rely on rather specialized starting materials[17-20] and/or afford the desired 4-AQs in disappointing yields.[18,22] Most diversity-oriented routes toward 4-AQs rely on the amination of 4-haloquinolines,[23,24] in turn derived from the corresponding 4-quinolones. Such multisubstituted quinolones (**2**) are generally difficult to synthesize by traditional condensation methods.[25-29] However, quinolones **2** are accessible via a carbonylative Sonogashira coupling (Scheme 2),
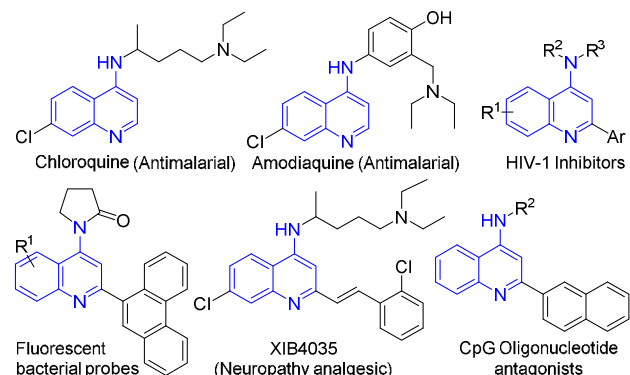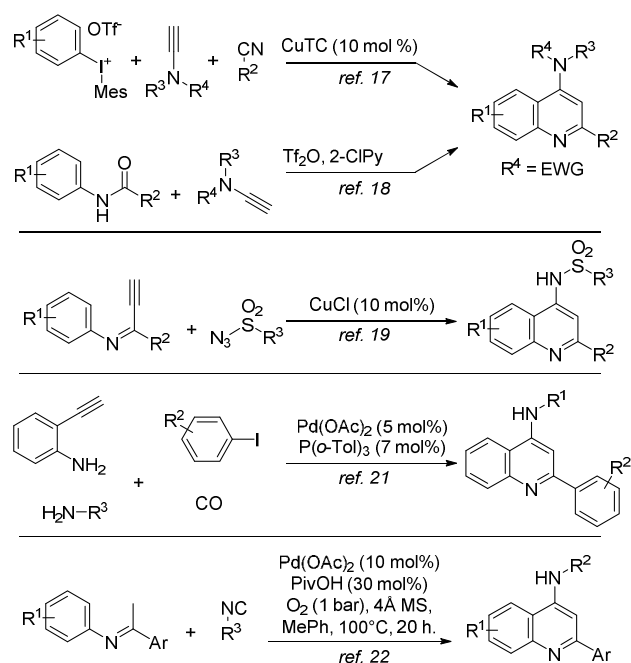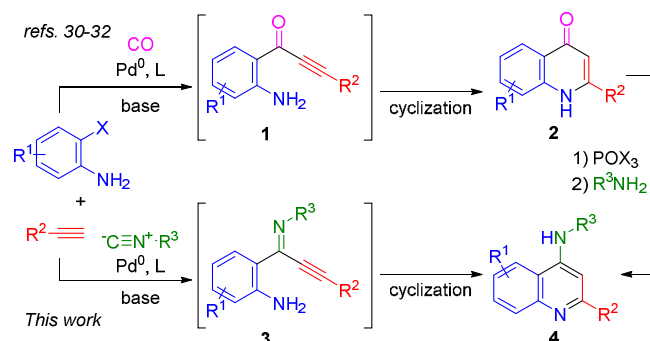

Figure 1. Examples of medicinally relevant 4-aminoquinolines.

Scheme 1. Previous routes to 4-aminoquinolines.

Scheme 2. Carbonylative and imidoylative Sonogashira coupling to 4-aminoquinolines.

using organic base to mediate the post-coupling cyclization (Scheme 2).[30-32] To the best of our knowledge, only one example of isocyanide insertion in a Sonogashira coupling has been reported, where the product ynimines are hydrolyzed *in situ* to the corresponding ynones.[33,34] Based on this, we envisioned a direct, one-pot synthesis of 4-AQs **4** via an imidoylative Sonogashira coupling and subsequent cycloaromatization (Scheme 2). Such an approach prevents the need for toxic CO gas, and avoids the two-step derivatization of quinolones **2**.

Results and Discussion

Our initial studies showed that such an imidoylative Sonogashira approach using **5**, **6a**, and **7a** afforded a range of products as a difficult to analyze mixture under typical conditions (Scheme 3). Most notably, with temperatures under 50°C or CuBr loadings approaching stoichiometric amounts, only the alkyne homocoupling product **10** was isolated. Additionally, SFC-MS analysis indicated that the use of *o*-iodoaniline promotes intramolecular Buchwald-Hartwig-type reactivity with double isocyanide insertion,

resulting in the formation of isatin diimine **11** (Scheme 3). If *o*-bromoaniline is employed, formation of **11** is suppressed to trace amounts, which is known for the synthesis of these isatinimines.[35] Surprisingly, these initial experiments revealed that the main product in all cases is the intermediate imidoylative Sonogashira product **8**, with only trace amounts of the desired cyclization product **9**. Direct formation of 4-AQs **9** from these previously underexplored ynimines **8** appears to be surprisingly difficult. Consequently, we focused our attention on the optimization of this cycloaromatization. Multiple cyclization conditions were investigated for the formation of aminoquinoline **9** from the proposed intermediate ynimine **8**. Neither strong nor weak bases proved effective in facilitating this cyclization (Table 1, entries 1-2). Weak acids (SiO$_2$, AcOH) were applied to activate the imine towards cyclization, but only afforded cyclization product **9a** in trace quantities (entries 3, 4). However, stronger acids like TFA (pK$_a$ = 0.23), phenylphosphinic acid (pK$_a$ = 1.85) and methanesulfonic acid (pK$_a$ = -1.9) rapidly afforded 4-amino-

Scheme 3. Initial Imidoylative Sonogashira studies towards 4-AQs and side products.
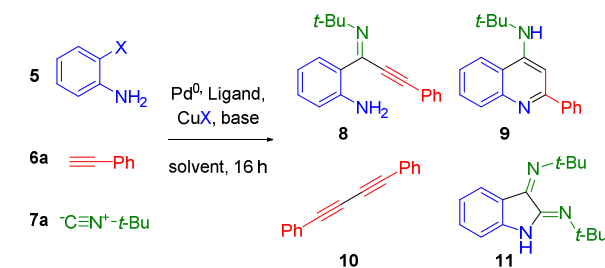
Table 1. Ynimine cyclization optimization.
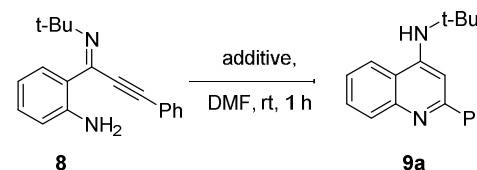
entry[a]	Additive (equiv.)	yield **9** (%)[b]
1	NaOEt (2.0)	n.r.
2	HNEt$_3$ (2.0)	n.r.
3[c]	SiO$_2$	trace
4	AcOH (4.0)	trace
5	**HCl in H$_2$O (4.0)**	**100**
6	HCl in MeOH (4.0)	96
7	HCl in dioxane (4.0)	99
8	TFA (4.0)	80
9	PhP(OH)$_2$ (4.0)	85
10	MeSO$_3$H (4.0)	100

[a] Conditions: ynimine **8** (0.55 mmol) in DMF (1 mL), additive, RT, 1 h. [b] Yield determined by NMR using an internal standard (1,3,5-trimethoxybenzene). [c] 0.150 g of SiO$_2$ was used. n.r. = no reaction, TFA = trifluoroacetic acid.

2

quinoline **9a**, even after short reaction times at ambient temperature (Table 1, entries 8-10). Interestingly, HCl also facilitated the cycloaromatization, even when employed as an aqueous solution. Curiously, acids with non-nucleophilic conjugate bases also afford aminoquinoline **9a** in high to quantitative yield (Table 1, entries 8, 10) implying either an intermolecular Michael/ Michael/retro-Michael mechanism,[30-32] or a direct intramolecular Michael reaction. Regardless, post-coupling addition of aqueous hydrochloric acid was selected as the optimal cyclization condition. While the addition of 1 M aqueous HCl readily facilitated cycloaromatization of **8** to **9a**, we opted for slightly harsher conditions (2 M aq. HCl (4 mL), 15 min., rt) for the *in situ* cyclization following the imidoylative Sonogashira reaction to account for excess Cs_2CO_3 as well as any residual starting materials. With the optimized cyclization protocol in hand, we turned our

Table 2. Optimization of the imidoylative Sonogashira/ cyclization conditions.[a]
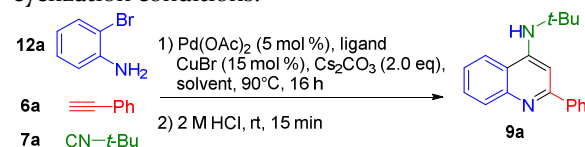
| entry	Pd source	ligand	solvent	**9a** (%)[b]
1[c]	Pd(PPh_3)_4	--	DMSO	--
2	Pd(PPh_3)_4	--	DMSO	61
3	Pd(PPh_3)_4	--	toluene	27
4	Pd(PPh_3)_4	--	dioxane	13
5	Pd(PPh_3)_4	--	DMF	70
6	Pd/C	--	DMF	--
7	Pd(OAc)_2	PPh_3	DMF	82
8	Pd(OAc)_2	Bu_3P	DMF	--
9	Pd(OAc)_2	DPEPhos	DMF	82
10	**Pd(OAc)_2**	**XantPhos**	**DMF**	**91**
11[d]	Pd(OAc)_2	XantPhos	DMF	--
12[e]	Pd(OAc)_2	XantPhos	DMF	56
13[f]	Pd(OAc)_2	XantPhos	DMF	--
14[g]	Pd(OAc)_2	XantPhos	DMF	31
15	Pd(OAc)_2	-	DMF	--
16	-	XantPhos	DMF	--

[a] Reaction conditions: 2-bromoaniline (**12a**, 0.5 mmol, 1 eq), phenylacetylene (**6a**, 1 mmol, 2 eq), *tert*-butyl isocyanide (**7a**, 0.625 mmol, 1.25 eq), catalyst (5 mol %), ligand (monodentate: 15 mol %, bidentate: 10 mol %), CuBr (15 mol %), Cs_2CO_3 (1 mmol, 2 eq) in solvent (3.0 mL) were stirred at 100° C for 16-20 h under N_2 atmosphere. [b] Yields determined by ^{1}H NMR analysis using 2,5-dimethylfuran as internal standard. [c] Reaction performed in the absence of CuBr. [d] KOtBu (2.0 eq.) employed as base. [e] K_2CO_3 (2.0 eq.) employed as base. [f] Et_3N (2.0 eq.) employed as base. [g] DBU (2.0 eq.) employed as base.

attention to the optimization of the imidoylative Sonogashira coupling. Using standard conditions (5 mol % Pd(PPh_3)_4, 15 mol % CuBr, 2.0 equiv. Cs_2CO_3, DMSO, 90 °C, 16 h) we obtained the desired 4-AQ **9a** in 61% yield (Table 1, entry 2). When the Cu(I)Br co-catalyst was omitted, only isatin diimine **11** was obtained (Table 2, entry 1). Subsequent solvent screening indicated that the transformation proceeds most efficiently in polar aprotic solvents, with DMF giving superior results (entries 2-5). As expected, a heterogeneous palladium catalyst (Pd/C) did not catalyze the reaction (entry 6). Switching from Pd(PPh_3)_4 to an *in situ* formed Pd° complex allowed for a ligand screening (entries 7-10). Interestingly, in addition to leading to the highest 4-AQ yield, the use of Xantphos as a ligand completely inhibited the formation of isatin diimine **11** (Table 1, entry 10). Changing the base from Cs_2CO_3 to other inorganic or organic bases (KOtBu, K_2CO_3, Et_3N, DBU) did not lead to an increase in yield (entries 11-14).

Scheme 4. Alkyne and o-bromoaniline variation.[a]
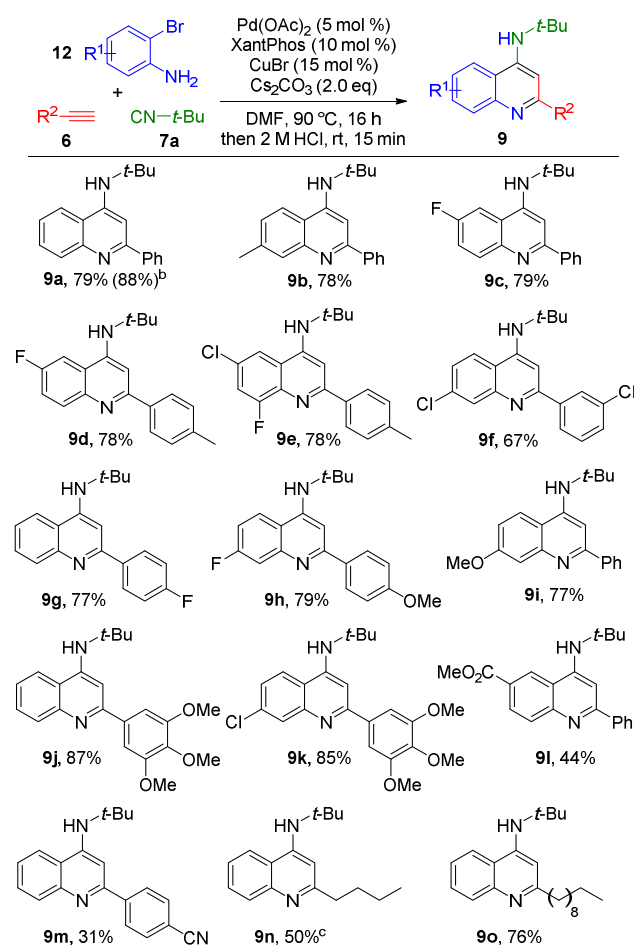
[a] Conditions: *o*-Bromoaniline (**12**, 1.0 mmol), *tert*-butyl isocyanide (**7a**, 1.25 mmol), alkyne (**6**, 2.0 mmol), Pd(OAc)_2 (0.05 mmol), Xantphos (0.1 mmol), CuBr (0.15 mmol), Cs_2CO_3 (2.0 mmol) in DMF (8.0 mL). [b] Reaction performed on 10.0 mmol scale. [c] Closed vial, 5.0 mmol of 1-hexyne.

Finally, as anticipated, **9a** was not formed when either the palladium source or the ligand was omitted (entries 15, 16).

With the optimized reaction conditions in hand, we set out to explore the compatibility of diversely substituted *o*-bromoanilines and terminal alkynes with our three-component reaction (Scheme 4). The reaction proved compatible with neutral and moderately electron-donating substituents (**9a,b**). The use of halo-substituted *o*-bromoanilines did not lead to lower yields (**9c-g**). Decoration of the *o*-bromoaniline or the arylalkyne with electron-donating functionalities afforded the substituted 4-AQs in high yields (**9h-k**). However, *o*-bromoanilines bearing electron-withdrawing substituents displayed lower compatibility with the three-component cascade protocol. When 3-bromo-4-aminobenzoate was used, the corresponding aminoquinoline **9l** was isolated in lower yield. Similar results were observed for **9m**, where the introduction of an additional distal electron acceptor on the opposite side of the ynimine renders the alkyne susceptible to 5-*exo-dig* cyclization. This cyclization to an aza-aurone side product most likely accounts for the diminished yields, as it does not require external acid activation and can therefore take place during the reaction. Additionally, it is possible that withdrawing electron density through substituent effects renders ynimines **8** more susceptible to hydrolysis during the cyclization stage. Gratifyingly, the developed conditions proved to tolerate aliphatic alkynes as well, as demonstrated by the isolation of **9n** and **9o**, with somewhat lower yield for **9n** as a result of the volatility of 1-hexyne.

Interestingly, this palladium-catalyzed imidoylative Sonogashira coupling displayed high tolerance with regard to the isocyanide input (Scheme 5). Secondary isocyanides, which are known to undergo double insertion more readily under palladium catalysis,[36,37] proved fully compatible with this protocol (**9p-r**). Satisfyingly, even primary isocyanide insertion afforded aminoquinoline **9s** in acceptable yield. The use of bromoanilines and arylalkynes bearing electron-withdrawing substituents afforded the corresponding products in lower yields, in accordance with earlier results (**9t-u**). Unfortunately, the use of 4-methoxyphenyl isocyanide did not afford isolable quantities of the corresponding 4-arylaminoquinoline **9v**. We then investigated the utility of our method in the synthesis of pharmaceutically relevant 4-AQs. The use of readily accessible *N,N*-diethyl-4-isocyanopentan-1-amine provided access to a variety of chloroquine analogues (**9w-9y**) in high yields. Similarly, the use of the isocyanide derived from the known vasoconstrictor octodrine[38] afforded **9aa** in good yield. Analogues of this highly fluorescent 2-naphthyl-4-AQ have been identified as potent immunostumulatory CpG-oligonucleotide antagonists.[39,40] Furthermore, the use of 2-bromo-5-fluoroaniline, combined with *N,N*-diethyl-4-isocyano-pentan-1-amine and cyclohexylacetylene furnishes 4-amino-2-cyclohexyl-7-fluoroquinoline (**9z**). Structures of this type have been

described as promising antileishmanials.[41] Finally, ethyl 4-isocyanopiperidine-1-carboxylate can be used to construct **9ab** in 68% yield, providing a handle for further functionalization of these medicinally valuable scaffolds.

Scheme 5. Isocyanide variation.[a]
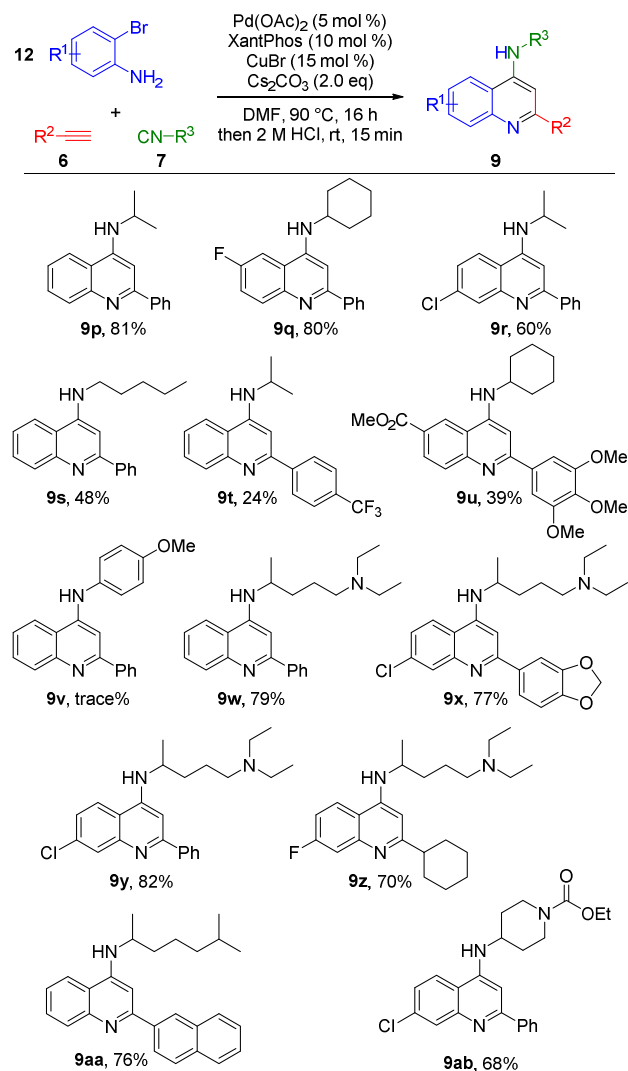
[a] Conditions: *o*-Bromoaniline (1.0 mmol), isocyanide (1.75 mmol), alkyne (2.0 mmol), Pd(OAc)$_2$ (0.05 mmol), Xantphos (0.1 mmol), CuBr (0.15 mmol), Cs$_2$CO$_3$ (2.0 mmol) in DMF (8.0 mL).

In conclusion, we have developed an novel one- pot imidoylative Sonogashira cross-coupling/acid-mediated cyclization toward 4-aminoquinolines. The devised methodology is highly compatible with electronically diverse *o*-bromoanilines, arylalkynes and aliphatic alkynes, although electron-withdrawing substituents on either arene lead to lower yields. The transformation is compatible with tertiary, secondary, and even primary aliphatic isocyanides. Additionally, using functionalized alkyl isocyanides, this method can be used to directly synthesize 2-substituted 4-aminoquinolines of high medicinal relevance.

4

Experimental section

General information. Chemicals were purchased from Sigma Aldrich or Fluorochem and were used without purification. Solvents were purchased from VWR Chemicals (CH_2Cl_2), or Sigma Aldrich (toluene, dioxane, DMSO) and used without purification, unless stated otherwise. Dry solvents were dried over an Inert PS-MD-5 Solvent Purification System, equipped with an activated alumina/copper wire column. ^{1}H NMR measurements were acquired on a Bruker Avance 300 (300.13 MHz) or Bruker Avance 500 (500.23 MHz) spectrometer. ^{13}C NMR measurements were acquired on a Bruker Avance 500 (125.78 MHz) spectrometer. Chemical shifts are reported in ppm downfield of tetramethylsilane, and are corrected according to solvent. Mass analysis was performed using a Bruker MicrOTOF-Q instrument on a positive ion polarity mode for ESI (Electrospray Ionization). Capillary charge: 4000V. Melting points were measured using a Büchi M-565 melting point apparatus. SiO_2 column chromatography was performed using Merck Silica Gel C60 (particle size 40-60 μm). TLC chromatography was performed on Merck Silica Gel C60 F254 plates (silica coat on aluminum support). All isolated yields are corrected for present impurities (if present)

General procedure 1 for the synthesis of 4-*tert*-butylaminoquinolines from bromoanilines, alkynes and *tert*-butyl isocyanide. A solution of $Pd(OAc)_2$ (0.011 g, 0.05 mmol) and Xantphos (0.058 g, 0.10 mmol) in dry DMF (8 mL) was stirred for 20 min at RT under N_2 atmosphere, forming a yellow suspension. To this mixture were added consecutively Cs_2CO_3 (0.651 g, 2.0 mmol), *o*-bromoaniline (1.0 mmol), *tert*-butyl isocyanide (0.141 mL, 1.25 mmol), CuBr (0.021 g, 0.15 mmol) and alkyne (2.0 mmol). The resulting mixture was stirred 90°C for 16 h. Hereafter, the reaction was allowed to cool to RT, after which 4 mL 2 M HCl was added and stirred for 15 min. The mixture was diluted with CH_2Cl_2, filtered over a pad of diatomaceous earth, and washed with 1 M HCl and sat. $NaHCO_3$, before being dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification was performed by column chromatography (gradient, cHex:EtOAc:Et$_3$N 19:1:0.01 – 1:1:0.01, unless stated otherwise) to afford the pure 4-aminoquinoline derivative.

General procedure 2 for the synthesis of 4-aminoquinolines from bromoanilines, alkynes and isocyanides. A solution of $Pd(OAc)_2$ (0.011 g, 0.05 mmol) and Xantphos (0.058 g, 0.10 mmol) in dry DMF (8 mL) was stirred for 20 min at RT under N_2 atmosphere, forming a yellow suspension. To this mixture were added consecutively Cs_2CO_3 (0.651 g, 2.0 mmol), *o*-bromoaniline (1.0 mmol), isocyanide (1.75 mmol), CuBr (0.021 g, 0.15 mmol) and alkyne (2.0 mmol). The resulting mixture was stirred 90°C for 16 h. Hereafter, the reaction was allowed to cool to RT, after which 4 mL 2 M HCl was added and stirred for 15 min. The mixture was diluted with CH_2Cl_2, filtered over a pad of diatomaceous earth, and washed with 1 M HCl and sat. $NaHCO_3$, before being dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification was performed by column chromatography (gradient, cHex:EtOAc:Et$_3$N 19:1:0.01 – 1:1:0.01, unless stated otherwise) to afford the pure 4-aminoquinoline derivative.

N-(tert-butyl)-2-phenylquinolin-4-amine (9a) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.234 g, 79%); R$_F$ = 0.19 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 139 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.10-8.03 (m, 3H), 7.68 (dd, J = 1.5, 8.5 Hz, 1H), 7.63 (ddd, J = 1.5, 7.0, 8.5, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.47-7.38 (m, 2H), 7.12 (s, 1H), 5.03 (bs, 1H), 1.60 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 157.9, 148.8, 148.3, 141.2, 130.5, 129.0, 128.8, 128.6, 127.5, 124.3, 118.9, 118.5, 99.1, 51.5, 29.4; HRMS (ESI): m/z calcd for $C_{19}H_{21}N_2^+$ [M+H]$^+$ 277.1695, found: 277.1707.

N-(tert-butyl)-7-methyl-2-phenylquinolin-4-amine (9b) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.237 g, 78%); R$_F$ = 0.33 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 134 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.05 (dd, J = 1.5, 7.5 Hz, 2H), 7.85 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.47-7.40 (m, 1H), 7.23 (dd, J = 7.5, 8.5 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 4.99 (bs, 1H), 2.52 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 157.9, 149.0, 148.3, 141.3, 139.0, 129.7, 128.7, 128.6, 127.5, 126.4, 118.6, 116.4, 98.7, 51.4, 29.4, 21.5; HRMS (ESI): m/z calcd for $C_{20}H_{23}N_2^+$ [M+H]+291.1851, found: 291.1854.

N-(tert-butyl)-6-fluoro-2-phenylquinolin-4-amine (9c) Synthesized in accordance with general procedure 1. Isolated as a light brown solid (0.232 g, 79%); R$_F$ = 0.44 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 163 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.14-8.06 (m, 3H), 7.54 (t, J = 7.5 Hz, 2H), 7.50-7.44 (m, 1H), 7.48-7.37 (m, 1H), 7.36 (dd, J = 2.5, 10.0 Hz, 1H), 7.17 (s, 1H), 4.79 (bs, 1H), 1.57 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.5 (d, J = 245.0 Hz), 157.3 (d, J = 2.5 Hz), 147.9 (d, J = 4.5 Hz), 145.8, 140.9, 132.8 (d, J = 8.5 Hz), 128.8, 128.6, 127.4, 118.9 (d, J = 8.0 Hz), 118.6 (d, J = 24.5 Hz), 103.3 (d, J = 23.0 Hz), 99.4, 51.6, 29.3; HRMS (ESI): m/z calcd for $C_{19}H_{20}N_2F^+$ [M+H]$^+$ 295.1601, found: 295.1604.

N-(tert-butyl)-6-fluoro-2-(p-tolyl)quinolin-4-amine (9d) Synthesized in accordance with general procedure 1. Isolated as a light brown solid (0.241 g, 78%); R$_F$ = 0.43 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 155 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.04 (dd, J = 5.5, 9.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.42-7.36 (m, 1H), 7.34-7.27 (m, 3H), 7.12 (s, 1H), 4.74 (bs, 1H), 2.43 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.5 (d, J = 245.0 Hz), 157.3 (d, J = 2.5 Hz), 147.8 (d, J = 5.0 Hz), 145.8, 138.8, 138.0, 132.7 (d, J = 8.5 Hz), 129.4, 127.3, 118.9 (d, J = 8.0 Hz), 118.5 (d, J = 25.0 Hz), 103.3 (d, J = 23.0 Hz), 99.3, 51.5, 29.3, 21.3; HRMS (ESI): m/z calcd for $C_{20}H_{22}N_2F^+$ [M+H]$^+$ 309.1757, found: 309.1769.

5

N-(tert-butyl)-6-chloro-8-fluoro-2-(p-tolyl)quinolin-4-amine (9e) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.253 g, 78%); R_F = 0.69 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 166-167 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.42 (s, 1H), 7.34-7.28 (m, 3H), 7.17 (s, 1H), 4.86 (s, 0H), 2.42 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.8, 157.8 (d, J = 18.5 Hz), 147.3 (d, J = 3.5 Hz), 138.4 (d, J = 235.5 Hz), 138.2 (d, J = 11.0 Hz), 129.4, 128.5 (d, J = 11.0 Hz), 127.37, 120.6 (d, J = 3.5 Hz), 114.7 (d, J = 23.0 Hz), 114.4 (d, J = 4.5 Hz), 100.1, 51.8, 29.3, 21.4; HRMS (ESI): m/z calcd for C$_{20}$H$_{21}$N$_2$ClF$^+$ [M+H]$^+$ 343.1368, found: 343.1376.

N-(tert-butyl)-7-chloro-2-(3-chlorophenyl)quinolin-4-amine (9f) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.231 g, 67%); R_F = 0.58 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 51-54 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.08-7.98 (m, 2H), 7.89 (d, J = 6.5 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.47-7.39 (m, 2H), 7.34 (d, J = 9.0 Hz, 1H), 7.04 (s, 1H), 5.03 (bs, 1H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 157.3, 149.5, 148.6, 142.5, 135.0, 134.7, 129.9, 129.3, 129.0, 127.6, 125.5, 125.2, 120.5, 117.0, 98.9, 51.7, 29.3; HRMS (ESI): m/z calcd for C$_{19}$H$_{19}$N$_2$Cl$_2^+$ [M+H]$^+$ 345.0917, found: 345.0925.

N-(tert-butyl)-2-(4-fluorophenyl)quinolin-4-amine (9g) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.252 g, 77%); R_F = 0.33 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 138 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.09-8.01 (m, 3H), 7.68 (d, J = 8.5 Hz, 1H), 7.67-7.60 (m, 1H), 7.44-7.37 (m, 1H), 7.19 (t, J = 8.5 Hz, 2H), 7.06 (s, 1H), 5.05 (bs, 1H), 1.60 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 163.4 (d, J = 248.0 Hz), 156.8, 148.8, 148.4, 137.3 (d, J = 3.0 Hz), 130.4, 129.2 (d, J = 8.5 Hz), 129.1, 124.4, 118.9, 118.4, 115.5 (d, J = 21.5 Hz), 98.7; HRMS (ESI): m/z calcd for C$_{19}$H$_{20}$N$_2$F$^+$ [M+H]$^+$ 295.1601, found: 295.1601.

N-(tert-butyl)-7-fluoro-2-(4-methoxyphenyl)quinolin-4-amine (9h) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.257 g, 79%); R_F = 0.38 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 47-49 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.11-7.99 (m, 2H), 7.78-7.57 (m, 2H), 7.13 (t, J = 8.5 Hz, 1H), 7.08-6.93 (m, 3H), 4.97 (bs, 1H), 3.88 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 163.0 (d, J = 248.0), 160.5, 158.5, 150.3 (d, J = 12 Hz), 148.4, 133.3, 128.8, 121.1 (d, J = 10.0 Hz), 114.0, 113.7 (d, J = 19.5), 113.6 (d, J = 25.0 Hz), 98.3, 55.4, 51.6, 29.4); HRMS (ESI): m/z calcd for C$_{20}$H$_{22}$N$_2$FO$^+$ [M+H]$^+$ 325.1706, found: 325.1723.

N-(tert-butyl)-7-methoxy-2-phenylquinolin-4-amine (9i) Synthesized in accordance with general procedure 1. Isolated as a bright yellow solid (0.236 g, 77%); R_F = 0.29 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 56-61 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.06 (m, 2H), 7.57 (d, J = 9.0, 1H), 7.54-7.47 (m, 2H), 7.46-7.41 (m, 2H), 7.04 (dd, J = 2.5, 9.0 Hz, 1H), 7.02 s, 1H), 4.96 (bs, 1H), 3.94 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 160.2, 158.4, 150.7, 148.5, 141.3, 128.7, 128.6, 127.4, 120.2, 116.7, 112.9, 108.6, 98.2, 55.4,

51.5, 29.4; HRMS (ESI): m/z calcd for C$_{20}$H$_{23}$N$_2$O$^+$ [M+H]$^+$ 307.1800, found: 307.1788.

N-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)quinolin-4-amine (9j) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.319 g, 87%); R_F = 0.10 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 67-69 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.06 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.26 (s, 2H), 7.03 (s, 1H), 5.06 (bs, 1H), 3.99 (s, 6H), 3.90 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 157.8, 153.3, 184.6, 148.6, 148.4, 138.9, 130.3, 129.1, 124.4, 118.9, 118.4, 104.9, 99.1, 60.3, 56.2, 51.5, 29.4; HRMS (ESI): m/z calcd for C$_{22}$H$_{27}$N$_2$O$_3^+$ [M+H]$^+$ 367.2010, found: 367.2026.

N-(tert-butyl)-7-chloro-2-(3,4,5-trimethoxyphenyl)quinolin-4-amine (9k) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.328 g, 82%); R_F = 0.28 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 68-70 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.03 (s, 1H), 7.60 (dd, J = 2.0, 9.0 Hz, 1H), 7.33 (dt, J = 2.0, 9.0 Hz, 1H), 7.25 (d, J = 1.5 Hz, 2H), 7.02 (d, J = 1.5 Hz, 1H), 5.00 (bs, 1H), 3.98 (s, 6H), 3.91 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.7, 153.3, 149.5, 148.4, 139.1, 136.6, 134.9, 129.2, 124.9, 120.5, 116.9, 104.8, 99.2, 60.9, 56.3, 51.7, 29.3; HRMS (ESI): m/z calcd for C$_{22}$H$_{26}$N$_2$O$_3$Cl$^+$ [M+H]$^+$ 401.1621, found: 401.1634.

Methyl 4-(tert-butylamino)-2-phenylquinoline-6-carboxylate (9l) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.147 g, 44%); R_F = 0.38 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 131-134 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.49 (s, 1H), 8.19 (dd, J = 2.0, 8.5 Hz, 1H), 8.11-8.02 (m, 3H), 7.56-7.49 (m, 2H), 7.49-7.45 (m, 1H), 7.15 (s, 1H), 5.27 (bs, 1H), 3.99 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 167.0, 159.8, 151.3, 149.4, 140.7, 130.5, 129.3, 128.7, 128.6, 127.6, 125.2, 122.5, 117.7, 99.5, 52.3, 51.9, 29.3; HRMS (ESI): m/z calcd for C$_{21}$H$_{23}$N$_2$O$_2^+$ [M+H]$^+$ 335.1749, found: 335.1759.

4-(4-(tert-butylamino)quinolin-2-yl)benzonitrile (9m) Synthesized in accordance with general procedure 1. Isolated as a yellow solid (0.090 g, 31%); R_F = 0.33 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 79-81 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.18 (d, J = 8.5 Hz, 2H), 8.04 (dd, J = 1.5, 8.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.70 (dd, J = 1.5, 8.5 Hz, 1H), 7.66 (ddd, J = 1.5, 7.0, 8.5 Hz, 1H), 7.45 (ddd, J = 1.5, 7.0, 8.5 Hz, 1H), 7.09 (s, 1H), 5.13 (bs, 1H), 1.61 (s, 9H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 155.6, 148.7, 145.4, 132.5, 130.6, 129.4, 128.1, 125.1, 119.0, 118.9, 118.6, 112.2, 98.7, 51.7, 29.3; HRMS (ESI): m/z calcd for C$_{20}$H$_{20}$N$_3^+$ [M+H]$^+$ 302.1648, found: 302.1656.

N-(tert-butyl)-2-butylquinolin-4-amine (9n) Synthesized in accordance with general procedure 1. Isolated as a brown solid (0.129 g, 50%); R_F = 0.53 (EtOAc: Et$_3$N 100:1); M.p.: 68-70 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 7.91 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.59-7.53 (m, 1H), 7.35 (ddd, J = 1.0, 7.0, 8.5 Hz, 1H), 6.57 (s, 1H), 4.91 (bs, 1H), 2.87-2.79 (m, 2H), 1.81-1.72 (m, 2H), 1.54 (s, 9H), 1.51-1.40

6

(m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 163.0, 148.4, 147.8, 129.5, 128.7, 123.7, 118.8, 118.1, 100.8, 51.4, 39.6, 32.4, 29.3, 22.7, 14.1; HRMS (ESI): m/z calcd for C$_{17}$H$_{25}$N$_2$$^+$ [M+H]$^+$ 257.2007, found: 257.2023.

N-(tert-butyl)-2-decylquinolin-4-amine (9o) Synthesized in accordance with general procedure 1. Isolated as a red-brown wax (0.255 g, 75%); R$_F$ = 0.62 (EtOAc:Et$_3$N 100:1); ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 7.92 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.56 (ddd, J = 1.5, 7.0, 8.5 Hz, 1H), 7.34 (t, J = 1.5, 7.5, 7.0 Hz, 1H), 6.57 (s, 1H), 4.91 (bs, 1H), 2.82 (t, J = 8.0 Hz, 2H), 1.78 (p, J = 8.0 Hz, 2H), 1.53 (s, 9H), 1.46-1.38 (m, 2H), 1.38-1.32 (m, 2H), 1.31-1.21 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 163.0, 148.4, 147.8, 129.5, 128.6, 123.7, 118.8, 118.1, 100.8, 51.3, 39.9, 31.9, 30.2, 29.62, 29.58, 29.56, 29.3, 29.2, 22.6, 14.1; HRMS (ESI): m/z calcd for C$_{23}$H$_{37}$N$_2$$^+$ [M+H]$^+$ 341.2943, found: 341.2965.

N-isopropyl-2-phenylquinolin-4-amine (9p) Synthesized in accordance with general procedure 2. Isolated as a red-brown solid (0.216 g, 81%); R$_F$ = 0.16 (cHex:EtOAc:Et$_3$N 4:1:0.05); M.p.: 176 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.12 (m, 3H), 7.72 (d, J = 8.5 Hz, 1H), 7.68-7.61 (m, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.48-7.38 (m, 2H), 6.89 (s, 1H), 4.87 (bd, J = 7.0 Hz, 1H), 4.04-3.92 (m, 1H), 1.40 (dd, J = 1.5, 6.5 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.4, 149.0, 148.7, 141.1, 130.3, 129.1, 128.7, 128.5, 127.5, 124.2, 119.0, 117.8, 97.0, 43.9, 22.5; HRMS (ESI): m/z calcd for C$_{18}$H$_{19}$N$_2$$^+$ [M+H]$^+$ 263.1539, found: 263.1556.

N-cyclohexyl-6-fluoro-2-phenylquinolin-4-amine (9q) Synthesized in accordance with general procedure 2. Isolated as a yellow solid (0.229 g, 80%); R$_F$ = 0.50 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 146-149 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.09-8.06 (m, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.0, 2H), 7.47-7.37 (m, 2H), 7.34 (dd, J = 2.0, 10.0, 1H), 6.86 (s, 1H), 4.71 (bd, J = 7.5 Hz, 1H), 3.66-3.56 (m, 1H), 2.20 (dd, J = 4.0, 13.0, 2H), 1.89-1.81 (m, 2H), 1.76-1.70 (m, 1H), 1.53-1.44 (m, 2H), 1.42-1.30 (m, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.5 (d, J = 245.0), 157.9 (d, J = 2.5 Hz), 148.6 (d, J = 5.0 Hz), 145.7, 140.8, 132.5 (d, J = 8.5 Hz), 128.9, 128.6, 127.5, 118.8 (d, J = 25.0 Hz), 118.2 (d, J = 8.0 Hz), 103.4 (d, J = 23.0 Hz), 97.3, 51.3, 32.8, 25.7, 24.8; HRMS (ESI): m/z calcd for C$_{21}$H$_{22}$N$_2$F$^+$ [M+H]$^+$ 321.1757, found: 321.1776.

7-chloro-N-isopropyl-2-phenylquinolin-4-amine (9r) Synthesized in accordance with general procedure 2. Isolated as a yellow solid (0.175 g, 60%); R$_F$ = 0.47 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 147-148 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.11-8.00 (m, 3H), 7.65 (d, J = 9.0 Hz, 1H), 7.53-7.48 (m, 2H), 7.47-7.43 (m, 1H), 7.34 (dd, J = 2.0, 9.0 Hz, 1H), 6.85 (s, 1H), 4.88 (bs, 1H), 4.04-3.91 (m, 1H), 1.40 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.3, 149.4, 149.2, 140.5, 135.0, 129.1, 129.0, 128.6, 127.5, 124.9, 120.6, 116.2, 97.2, 44.1, 22.5; HRMS (ESI): m/z calcd for C$_{18}$H$_{18}$N$_2$Cl$^+$ [M+H]$^+$ 297.1150, found: 297.1163.

N-pentyl-2-phenylquinolin-4-amine (9s) Synthesized in accordance with general procedure 2. Isolated as a red-brown wax (0.131 g, 48 %); R$_F$ = 0.35 (cHex:EtOAC:Et$_3$N 4:1:0.01); ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.14-8.06 (m, 3H), 7.72 (d, J = 8.5 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H)m 7.51 (t, J = 7.5 Hz, 2H), 7.47-7.38 (m, 2H), 6.86 (s, 1H), 5.00 (bt, J = 5.0 Hz, 1H), 3.36 (q, J = 6.5 Hz, 2H), 1.79 (p, J = 7.5 Hz, 2H), 1.53-1.37 (m, 4H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.4, 150.1, 148.6, 141.0, 130.2, 129.1, 128.8, 128.5, 127.5, 124.3, 119.0, 117.8, 96.6, 43.2, 29.3 28.6, 22.4, 14.0; HRMS (ESI): m/z calcd for C$_{20}$H$_{23}$N$_2$$^+$ [M+H]$^+$ 291.1851, found: 291.1846.

N-isopropyl-2-(4-(trifluoromethyl)phenyl)quinolin-4-amine (9t) Synthesized in accordance with general procedure 2. Isolated as a yellow solid (0.074 g, 24%); R$_F$ = 0.39 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 60-63 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.18 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.5 Hz, 1H), 7.79-7.70 (m, 3H), 7.67 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 6.86 (s, 1H), 4.93 (bd, J = 7.0 Hz, 1H), 4.05-3.96 (m, 1H), 1.41 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 156.8, 149.3, 148.7, 144.4, 130.6 (q, J = 32.5 Hz), 130.4, 129.4, 127.8, 125.5 (q, J = 4.0 Hz), 124.8, 124.3 (q, J = 271.5 Hz), 119.0, 117.9, 96.8, 40.0, 22.5; HRMS (ESI): m/z calcd for C$_{19}$H$_{18}$N$_2$F$_3$$^+$ [M+H]$^+$ 331.1413, found: 331.1429.

Methyl 4-(cyclohexylamino)-2-(3,4,5-trimethoxyphenyl) quinoline-6-carboxylate (9u) Synthesized in accordance with general procedure 2. Isolated as a dark yellow solid (0.167 g, 39%); R$_F$ = 0.13 (cHex:EtOAc:Et$_3$N 4:1:0.01); M.p.: 141-143 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.52 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 2.0, 9.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.27 (s, 2H), 6.80 (s, 1H), 5.19 (bd, J = 7.0 Hz, 4.11-3.95 (m, 9H), 3.91 (s, 3H), 3.63 (dtt, J = 3.5, 7.0, 10.0 Hz, 1H), 2.24-2.17 (m, 2H), 1.97-1.82 (m, 2H), 1.81-1.68 (m, 2H), 1.52-1.37 (m, 4H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 167.0, 160.3, 153.3, 151.1, 149.9, 139.3, 136.5, 130.2, 128.8, 125.1, 122.7, 117.0, 105.1, 97.1, 60.9, 56.3, 52.3, 51.5, 32.7, 25.6, 24.9; HRMS (ESI): m/z calcd for C$_{26}$H$_{31}$N$_2$O$_5$$^+$ [M+H]$^+$ 451.2220, found: 451.2236.

N1,N1-diethyl-N4-(2-phenylquinolin-4-yl)pentane-1,4-diamine (9w) Synthesized in accordance with general procedure 2. Isolated as a red-brown wax (0.287 g, 79%); R$_F$ = 0.09 (EtOAc:Et$_3$N 100:1); ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.09-8.02 (m, 3H), 7.76 (d, J = 8.0 Hz, 1H), 7.67-7.60 (m, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.47-7.37 (m, 2H), 6.86 (s, 1H), 5.18 (bd, J = 7.5 Hz, 1H), 3.90-3.80 (m, 1H), 2.57 (q, J = 7.0 Hz, 4H), 2.50 (t, J = 7.0 Hz, 2H), 1.85-1.75 (m, 1H), 1.73-1.63 (m, 2H), 1.37 (d, J = 6.5 H, 3H), 1.03 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.5, 149.3, 148.8, 141.2, 130.3, 129.1, 128.7, 128.6, 127.5, 124.2, 119.2, 117.9, 96.9, 52.6, 48.2, 46.8, 34.7, 23.8, 20.4, 11.4; HRMS (ESI): m/z calcd for C$_{24}$H$_{32}$N$_3$$^+$ [M+H]$^+$ 362.2584, found: 362.2595.

N4-(3-(benzo[d][1,3]dioxol-5-yl)-6-chloronaphthalen-1-yl)-N1,N1-diethylpentane-1,4-diamine (9x) Synthesized in accordance with general procedure 2. Isolated as a yellow-

7

brown solid (0.327 g, 78 %); R_F = 0.15 (EtOAc:Et$_3$N 99:1); M.p.: 48-50 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.01 (s, 2H), 5.25 (bd, *J* = 7.0 Hz, 1H), 3.79 (hept, *J* = 6.5 Hz, 1H), 2.53 (q, *J* = 7.0 Hz, 4H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.81-1.65 (m, 2H), 1.65-1.59 (m, 2H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.6, 149.5, 149.3, 148.5, 148.0, 135.1, 134.8, 128.9, 124.4, 121.5, 120.9, 116.3, 108.2, 107.9, 101.2, 96.5, 52.4, 48.2, 46.7, 34.5, 23.8, 20.2, 11.3; HRMS (ESI): m/z calcd for C$_{25}$H$_{31}$N$_3$O$_2$Cl$^+$ [M+H]$^+$ 440.2093, found: 440.2092.

N4-(7-chloro-2-phenylquinolin-4-yl)-N1,N1-diethylpentane-1,4-diamine (9y) Synthesized in accordance with general procedure 2. Isolated as a red-brown wax (0.326 g, 82%); R_F = 0.14 (EtOAc: Et$_3$N 99:1); ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.08-8.02 (m, 3H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 2H), 7.48-7.40 (m, 1H), 7.33 (dd, *J* = 2.0, 9.0 Hz, 1H), 6.85 (s, 1H), 5.29 (bd, *J* = 7.0 Hz, 1H), 3.82 (hept, *J* = 6.5, 1H), 2.54 (q, *J* = 7.0 Hz, 4H), 2.47 (t, *J* = 7.0 Hz, 2H), 1.83-1.74 (m, 1H), 1.74-1.60 (m, 3H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.01 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 159.4, 149.6, 149.5, 140.7, 134.9, 129.1, 129.0, 128.6, 127.5, 124.7, 120.9, 116.4, 97.1, 52.5, 48.3, 46.8, 34.6, 23.8, 20.3, 11.3; HRMS (ESI): m/z calcd for C$_{24}$H$_{31}$N$_3$Cl$^+$ [M+H]$^+$ 396.2195, found: 396.2213.

N4-(2-cyclohexyl-7-fluoroquinolin-4-yl)-N1,N1-diethylpentane-1,4-diamine (9z) Synthesized in accordance with general procedure 2. Isolated as a red-brown wax (0.268 g, 70 %); R_F = 0.14 (EtOAc: Et$_3$N 99:1); ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 7.71-7.64 (m, 1H), 7.53 (dt, *J* = 2.0, 10.5 Hz, 1H), 7.06 (t, *J* = 8.5 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 5.16 (bd, *J* = 7.0 Hz, 1H), 3.72 (p, *J* = 6.5 Hz, 1H), 2.72 (td, *J* = 3.0, 12.0 Hz, 1H), 2.52 (q, *J* = 7.0 Hz, 4H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.01-1.94 (m, 2H), 1.87-1.81 (m, 2H), 1.77-1.69 (m, 2H), 1.65-1.50 (m, 5H), 1.42 (q, *J* = 11.5 Hz, 2H), 1.34-1.24 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.00 (td, *J* = 2.0, 7.0, 6H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 168.7, 162.9 (d, *J* = 247.5 Hz), 149.6 (d, *J* = 12.5 Hz), 149.3, 121.5 (d, *J* = 10.5 Hz), 114.8, 113.1 (d, *J* = 25.0 Hz), 112.8 (d, *J* = 20.0 Hz), 96.3, 52.5, 48.0, 47.9, 46.7, 34.5, 32.89, 32.86, 26.5, 26.0, 23.7, 20.2, 11.2; HRMS (ESI): m/z calcd for C$_{24}$H$_{37}$N$_3$F$^+$ [M+H]$^+$ 386.2958, found: 386.2970.

N-(6-methylheptan-2-yl)-2-(naphthalen-2-yl)quinolin-4-amine (9aa) Synthesized in accordance with general procedure 2. Isolated as a red-brown solid (0.294 g, 77 %); R_F = 0.26 (cHex:EtOAc: Et$_3$N 4:1:0.01); M.p.: 128-129 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.57-8.53 (m, 1H), 8.26 (dd, *J* = 2.8, 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.01-7.98 m, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.92-7.87 (m, 1H), 7.76-7.72 (m, 1H), 7.67 (ddd, *J* = 1.5, 7.0, 8.5 Hz, 1H), 7.54-7.49 (m, 2H), 7.44 (ddd, *J* = 1.5, 7.0, 8.5 Hz, 1M), 7.01 (s, 1H), 4.90 (bd, *J* = 7.5 Hz, 1H), 3.89 (hept, *J* = 6.5 Hz, 1H), 1.81-1.73 (m, 1H), 1.70-1.53 (m, 3H), 1.53-1.44 (m, 2H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.30-1.24 (m, 2H), 0.90 (d, *J* = 1.5 Hz, 3H), 0.89 (d, *J* =

1.5 Hz, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): δ 158.2, 149.4, 148.8, 138.3, 133.7, 133.4, 130.3, 129.3, 128.7, 128.2, 127.7, 126.9, 126.4, 126.1, 125.4, 124.4, 119.0, 117.9, 97.0, 48.3, 38.9, 37.1, 27.9, 24.0, 22.60, 22.58, 20.4; HRMS (ESI): m/z calcd for C$_{27}$H$_{31}$N$_2$$^+$ [M+H]$^+$ 383.2475, found: 383.2490.

Ethyl 4-((7-chloro-2-phenylquinolin-4-yl)amino)piperidine-1-carboxylate (9ab) Synthesized in accordance with general procedure 2. Isolated as a yellow-orange solid (0.277 g, 68%); R_F = 0.11 (cHex:EtOAc: Et$_3$N 4:1:0.01); M.p.: 186-187 °C; ^{1}H NMR (500.23 MHz, CDCl$_3$): δ 8.07 (d, *J* = 2.0 Hz, 1H), 8.05-8.03 (m, 1H), 8.03-8.01 (m, 1H), 7.65 d, *J* = 9.0 Hz, 1H), 7.68-7.62 (m, 2H), 7.50-7.42 (m, 1H), 7.35 (dd, *J* = 2.0, 9.0 Hz, 1H), 6.85 (s, 1H), 4.95 (bs, 1H), 4.32-4.25 m, 2H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.80 (tdt, *J* = 4.0, 7.5, 10.5 Hz, 1H), 3.08 (t, *J* = 12.5 Hz, 2H), 2.28-2.14 (m, 2H), 1.64-1.48 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.97 MHz, CDCl$_3$): 159.3, 155.4, 148.7, 140.3, 135.3, 129.3, 129.1, 128.7, 127.6, 125.2, 120.6, 116.2, 97.2, 61.6, 49.7, 42.6, 31.7, 14.7; HRMS (ESI): m/z calcd for C$_{23}$H$_{25}$N$_3$O$_2$Cl$^+$ [M+H]$^+$ 410.1625, found: 410.1630.

N,N-diethyl-4-isocyanopentan-1-amine (7w) A solution of *N1,N1*-diethylpentane-1,4-diamine (3.87 mL, 20 mmol) in ethyl formate (4.82 mL, 60 mmol) was refluxed for 16 h., after which the solvent was removed *in vacuo*. To a solution of the crude product (3.00 g, 16.1 mmol) in dry CH$_2$Cl$_2$ (80 mL) was added DIPEA (7.01 mL, 40.25 mmol) and cooled to -40°C. Triphosgene (1.67 g, 5.64 mmol) was added portionwise, after which the mixture was allowed to warm to 0°C, and stirred for 2h. The crude product was poured in water (80 mL), and the organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo* to afford the title compound as a pale yellow liquid (2.370 g, 88%); R_F = 0.11 (EtOAc:MeOH:Et$_3$N 9:1:0.09); ^{1}H NMR (500.23 MHz, CDCl3): δ 3.71-3.59 (m, 1H), 2.52 (q, *J* = 7.0 Hz, 4H), 2.44 (t, *J* = 7.0 Hz, 2H), 1.70-1.52 (m, 4H), 1.37 (dt, J_{HN} = 2.0 Hz, J_{HH} = 7.0 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C (125.97 MHz, CDCl$_3$): δ 154.2 (t, $J_{C(sp)N}$ = 5.0 Hz), 52.0, 50.3 (t, $J_{C(sp3)N}$ = 5.5 Hz), 46.8, 34.8, 23.3, 21.8, 11.6; HRMS (ESI): m/z calcd for C$_{10}$H$_{21}$N$_2$$^+$ [M+H]$^+$ 169.1695, found: 169.1705.

ethyl 4-isocyanopiperidine-1-carboxylate (7ab) Ethyl 4-aminopiperidine-1-carboxylate (4.03 mL, 29.0 mmol) was refluxed in ethyl formate (7.01 mL, 87.1 mmol) for 16 h., after which the solvent was removed *in vacuo*. To a solution of the crude formamide (3.10 g, 15.5 mmol) in dry CH$_2$Cl$_2$ (45 mL) was added Et$_3$N (4.32 mL, 31 mmol). The solution was cooled to -40 °C, after which triphosgene (1.61 g, 5.52 mmol) was added portionwise. The resulting mixture was slowly warmed to room temperature, and stirred for 3 h. Hereafter, the reaction was quenched with ice-water (50 mL), and the resulting biphasic system was separated. The organic layer was washed with 1 M HCl, saturated NaHCO$_3$, and water, dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*, affording the target isocyanide as a pale yellow oil. (2.471 g, 88 %); R_F = 0.16 (cHex:EtOAc: Et$_3$N 4:1:0.01); ^{1}H NMR (500.23 MHz, CDCl3): δ 4.12 (q, *J* =

7.0 Hz, 2H), 3.89-3.81 (m, 1H), 3.60 (ddd, J = 3.5, 8.0, 14.0 Hz, 2H), 3.54-3.44 (m, 1H), 1.93-1.83 M, 2H), 1.83-1.75 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H); [13]C (125.97 MHz, CDCl$_3$): 156.2 (t, J = 5.0 Hz), 155.2, 61.6, 49.3 (t, J = 6.0 Hz), 40.0, 31.2, 14.6; HRMS (ESI): m/z calcd for $C_9H_{14}N_2O_2Na^+$ [M+Na]$^+$ 205.0944, found: 205.0955.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

* E. Ruijter: e.ruijter@vu.nl *R.V.A. Orru: r.v.a.orru@vu.nl

Author Contributions

The manuscript was written through contributions of all authors.

ORCID

Bert U. W. Maes: 0000-0003-0431-7606
Eelco Ruijter: 0000-0002-1105-3947

Notes

The authors declare no competing financial interest.

Acknowledgements

References

(1) Fidock, D. A. *Nature* **2010**, *465*, 297.
(2) Ridley, R. G. *Nature* **2002**, *415*, 686.
(3) Wellems, T. E. *Nature* **1992**, *355*, 108.
(4) Gregson, A.; Plowe, C. V. *Pharmacol. Rev.* **2005**, *57*, 117.
(5) Goulopoulou, S.; McCarthy, C. G.; Webb, R. C. *Pharmacol. Rev.* **2015**, *68*, 142.
(6) Madrid, P. B.; Sherrill, J.; Liou, A. P.; Weisman, J. L.; DeRisi, J. L.; Guy, R. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1015.
(7) Miller, L. H.; Ackerman, H. C.; Su, X.-z.; Wellems, T. E. *Nat. Med.* **2013**, *19*, 156.
(8) Gignoux, E.; Azman, A. S.; de Smet, M.; Azuma, P.; Massaquoi, M.; Job, D.; Tiffany, A.; Petrucci, R.; Sterk, E.; Potet, J.; Suzuki, M.; Kurth, A.; Cannas, A.; Bocquin, A.; Strecker, T.; Logue, C.; Pottage, T.; Yue, C.; Cabrol, J.-C.; Serafini, M.; Ciglenecki, I. *New Engl. J. Med.* **2016**, *374*, 23.
(9) Madrid, P. B.; Chopra, S.; Manger, I. D.; Gilfillan, L.; Keepers, T. R.; Shurtleff, A. C.; Green, C. E.; Iyer, L. V.; Dilks, H. H.; Davey, R. A.; Kolokoltsov, A. A.; Carrion, R., Jr.; Patterson, J. L.; Bavari, S.; Panchal, R. G.; Warren, T. K.; Wells, J. B.; Moos, W. H.; Burke, R. L.; Tanga, M. J. *PLoS One* **2013**, *8*, e60579.
(10) Kužnik, A.; Benčina, M.; Švajger, U.; Jeras, M.; Rozman, B.; Jerala, R. *J. Immunol.* **2011**, *186*, 4794.
(11) Tewari, S.; Chauhan, P. M. S.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1409.

(12) Brouwer, C.; Jenko, K.; Zoghbi, S. S.; Innis, R. B.; Pike, V. W. *J. Med. Chem.* **2014**, *57*, 6240.
(13) Singh, S.; Roy, K. K.; Khan, S. R.; Kashyap, V. K.; Sharma, A.; Jaiswal, S.; Sharma, S. K.; Krishnan, M. Y.; Chaturvedi, V.; Lal, J.; Sinha, S.; Dasgupta, A.; Srivastava, R.; Saxena, A. K. *Bioorg. Med. Chem.* **2015**, *23*, 742.
(14) Shinkai, H.; Ito, T.; Iida, T.; Kitao, Y.; Yamada, H.; Uchida, I. *J. Med. Chem.* **2000**, *43*, 4667.
(15) Sestili, I.; Borioni, A.; Mustazza, C.; Rodomonte, A.; Turchetto, L.; Sbraccia, M.; Riitano, D.; Del Giudice, M. R. *Eur. J. Med. Chem.* **2004**, *39*, 1047.
(16) Kireev, D. B.; Chrétien, J. R.; Raevsky, O. A. *Eur. J. Med. Chem.* **1995**, *30*, 395.
(17) Oh, K. H.; Kim, J. G.; Park, J. K. *Org. Lett.* **2017**, *19*, 3994.
(18) Wezeman, T.; Zhong, S.; Nieger, M.; Bräse, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 3823.
(19) Li, Y.; Zhang, L.; Zhang, L.; Wu, Y.; Gong, Y. *Org. Biomol. Chem.* **2013**, *11*, 7267.
(20) Dhanapal, R.; Perumal, P. T.; Damodiran, M.; Ramprasath, C.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6494.
(21) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454.
(22) Vlaar, T.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem. Heterocycl. Compd.* **2013**, *49*, 902.
(23) Tsai, J.-Y.; Chang, C.-S.; Huang, Y.-F.; Chen, H.-S.; Lin, S.-K.; Wong, F. F.; Huang, L.-J.; Kuo, S.-C. *Tetrahedron* **2008**, *64*, 11751.
(24) Ren, J.; Zhao, J.; Zhou, Y.-S.; Liu, X.-H.; Chen, X.; Hu, K. *Med. Chem. Res.* **2013**, *22*, 2855.
(25) Tollari, S.; Cenini, S.; Ragaini, F.; Cassar, L. *J. Chem. Soc., Chem. Commun.* **1994**, *15*, 1741.
(26) Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-S.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 1126.
(27) Sun, F.; Zhao, X.; Shi, D. *Tetrahedron Lett.* **2011**, *52*, 5633.
(28) Carta, D.; Bortolozzi, R.; Hamel, E.; Basso, G.; Moro, S.; Viola, G.; Ferlin, M. G. *J. Med. Chem.* **2015**, *58*, 7991.
(29) Strekowski, L.; Say, M.; Henary, M.; Ruiz, P.; Manzel, L.; Macfarlane, D. E.; Bojarski, A. J. *J. Med. Chem.* **2003**, *46*, 1242.
(30) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *32*, 237.
(31) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773.
(32) Åkerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464.
(33) Tang, T.; Fei, X.-D.; Ge, Z.-Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem.* **2013**, *78*, 3170.
(34) Kosugi, M.; Ogata, T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, *15*, 1197.
(35) Pan, Y.-Y.; Wu, Y.-N.; Chen, Z.-Z.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. *J. Org. Chem.* **2015**, *80*, 5764.
(36) Whitby, R. J.; Saluste, C. G.; Furber, M. *Org. Biomol. Chem.* **2004**, *2*, 1974.
(37) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem. Int. Ed.* **2012**, *51*, 13058.
(38) Craciunescu, D. G.; Doadrio, A.; Furlani, A.; Scarcia, V. *Chem. Biol. Interact.* **1982**, *42*, 153.
(39) Manzel, L.; Strekowski, L.; Ismail, F. M. D.; Smith, J. C.; Macfarlane, D. E. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 1337.

9

(40) Strekowski, L.; Zegrocka, O.; Henary, M.; Say, M.; Mokrosz, M. J.; Kotecka, B. M.; Manzel, L.; Macfarlane, D. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1819.
(41) Herrera, L.; Stephens, D. E.; D'Avila, A.; George, K. G.; Arman, H.; Zhang, Y.; Perry, G.; Lleonart, R.; Larionov, O. V.; Fernandez, P. L. *Org. Biomol. Chem.* **2016**, *14*, 7053.