Access to Simplified Aza-Analogs of Grossularine from 4-Alkyl-7-Chloro-5-Methyl-1H-Imidazo[4,5-c][1,6]Naphthyridin-4(5H)-one

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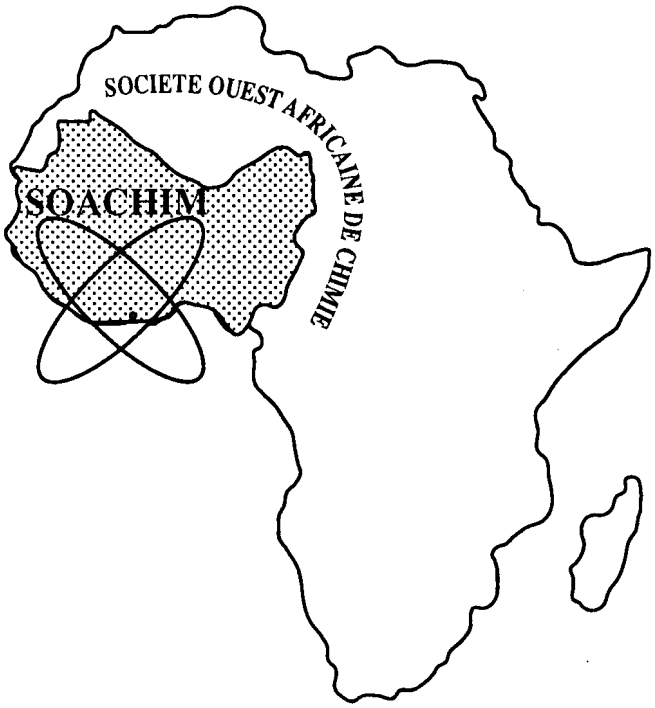

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Access to Simplified Aza-Analogs of Grossularine from 4-Alkyl-7-Chloro-5-Methyl-1H-Imidazo[4,5-c][1,6]Naphthyridin-4(5H)-one

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Abstract: Access to simplified aza-analogs of grossularine from 4-alkyl-7-chloro-5-methyl- 1H-imidazo[4,5-c][1,6] naphthyridin-4(5H)-one is reported. The strategy involves the preparation of a 7-halo imidazo[4,5-c][1,6] naphthyridine -4(5H)-one compound that undergoes functionalization using palladium-catalyzed cross-coupling reactions and SNAr reactions, resulting in disubstituted products. The desired products were obtained in moderate to good yields.

Keywords: Grossularine Aza-analogs, Suzuki-Miyaura cross-coupling, Nucleophilic aromatic substitution.

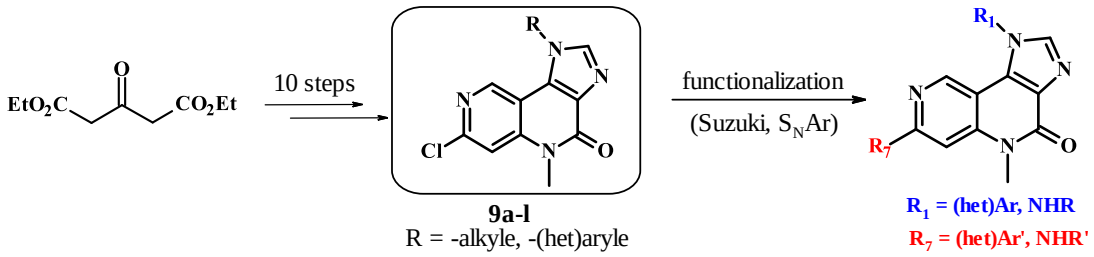

Figure 1. Target compounds.

Accès aux analogues aza simplifiés de la grossulaire à partir de la 4-alkyl-7-chloro-5-méthyl-1H-imidazo[4,5-c][1,6]naphtyridin-4(5H)-one

Résumé : L'accès à des analogues aza simplifiés de la grossularine à partir de la 4-alkyl-7-chloro-5-méthyl-1H-imidazo [4,5-c][1,6]naphtyridin-4(5H)-one est décrit. La stratégie repose sur la préparation d'un composé 7-halo-imidazo [4,5-c][1,6]naphtyridin-4(5H)-one qui subit une fonctionnalisation par des réactions de couplage croisé catalysées au palladium et des réactions SNAr, conduisant à des produits disubstitués. Les produits désirés ont été obtenus avec des rendements modérés à bons.

Mots clés : Aza analogues de la grossularine, couplage croisé de Suzuki-Miyaura, Substitution.Nucléophile Aromatique.

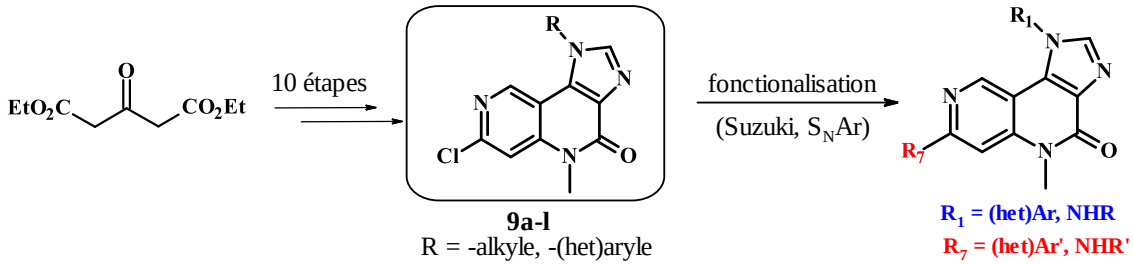

Figure 1: Composés cibles.

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1. Introduction

Metal-catalyzed cross-coupling reactions have emerged as powerful tools for functionalizing heterocyclic scaffolds, enabling the efficient formation of C–C and C–N bonds. Among them, the Suzuki-Miyaura cross-coupling reaction[1] and the Buchwald-Hartwig amination[2] have become highly suitable methods for developing bioactive molecules. These reactions, employing palladium or copper catalysts, are efficient approaches for synthesizing highly functionalized heterocycles[3]. As part of our ongoing interest in the synthesis of heterocyclic scaffolds using these methodologies[4], we have focused on developing synthetic strategies to access a wide variety of functionalized imidazo[4,5-c][1,6]naphthyridinones. Previous work has reported efficient syntheses of 3,7-disubstituted imidazo[4,5-c]quinolin-4-ones[5] and their applications as potential anticancer agents.[6], [7], [8] We now turn our attention to the imidazo[4,5-c][1,6]naphthyridin-4(5H)-one scaffold.

The 1,6-naphthyridinone family exhibits a wide range of biological properties. In particular, 3,7-disubstituted 1,6-naphthyridin-4(1H)-ones have been described as antibacterial agents[9], antivirals[10], and immunosuppressants[11]. To extend the functionalization of this heterocyclic core, we sought easy and reliable access to 1,7-disubstituted imidazo[4,5-c][1,6] naphthyridin-4(5H)-ones using cross-coupling and SNAr reactions (Figure 1). Here, we describe an efficient synthesis of a 7-halo imidazo[4,5-c][1,6] naphthyridin-4(5H)-one, enabling the preparation of 1,7-disubstituted imidazo[4,5-c][1,6] naphthyridin-4(5H)-ones of potential biological interest.

2. Materials and methods

All commercial reagents were used without further purification. All solvents were reagent or HPLC grade (MERCK). Analytical TLC was performed on silica gel 60 F254 plates. Column chromatography was carried out on silicagel Merck 60 (70-230 mesh ASTM) and Flash Chromatography Grace Reveleris X2™. LC/MS analyses were run on a Waters ACQUITY UPLC-MS system consisting of a Single Quadrupole Detector (SQD) Mass Spectrometer (MS) equipped with an Electrospray Ionization Interface (ESI) and a Photodiode Array detector (PDA). Microwave reactions were carried out on a CEM Discover SP monomode apparatus.

3. Results and discussion

Based on our previous work in the 1,6-naphthyridin-2(1H)-one series,[12] we developed a multi-step sequence to obtain compounds 11a–g (Scheme 1). We hypothesized that these key intermediates would readily undergo metal-catalyzed cross-coupling reactions and SNAr reactions. The synthesis begins with the preparation of 6-chloro-4-(methylamino)nicotinic acid (5). The first step involves the condensation of an equimolar amount of diethyl 3-oxopentanedioate (1) with triethyl orthoformate in acetic anhydride. The resulting intermediate is then cyclized by adding an aqueous ammonia solution to afford ester (2) in 87% yield.[13] In the second step, chlorination of (2) with phosphorus oxychloride at reflux yields compound (3), followed by regioselective aromatic nucleophilic substitution at position 4 with methylamine to give the monochlorinated derivative (4) in 96% yield. Compound (4) is then saponified with sodium hydroxide to obtain acid (5) in 99% yield. An intramolecular aminolysis of 6-chloro-4-(methylamino)nicotinic acid (5) in a mixture of acetic anhydride and acetic acid at 100 °C for 2 h affords 4-hydroxy-1,6-naphthyridin-2(1H)-one (6) in 60% yield. The reaction proceeds via amide formation, followed by cyclization in the presence of acetic acid. It is likely that the intramolecular C–C bond formation occurs through Claisen condensation of the acetamide and the mixed anhydride of the pyridine carboxylate, as per the proposed mechanism.[14]

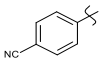
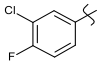
The nitration of 4-hydroxy-1,6-naphthyridin-2(1H)-one is performed at room temperature using a mixture of concentrated sulfuric acid and nitric acid in chloroform. This electrophilic aromatic substitution yields 3-nitro-1,6-naphthyridin-2(1H)-one (7) in 70% yield after 1 h.[15], [16] The conversion of the hydroxy group to chloride is achieved using phosphorus oxychloride for 3 h in the presence of triethylamine, affording 4,7-dichloro-1-methyl -3-nitro-1,6- naphthyridin-2(1H)-one (8) in 92% yield. The preferential aromatic nucleophilic substitution of the chlorine at position 4 by an

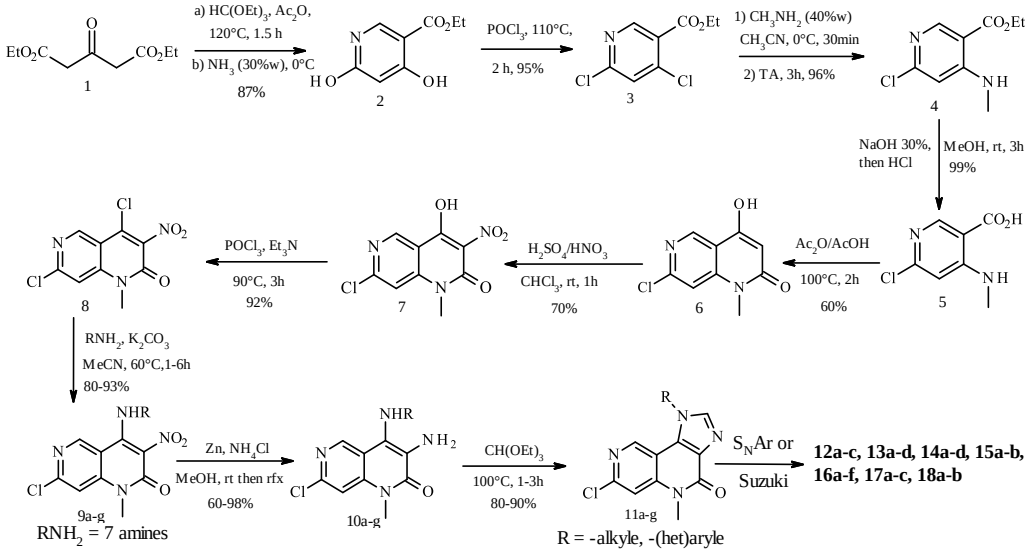
amine is facilitated by the nitro group at position 3. This reaction occurs at 60°C in the presence of a base, yielding the corresponding 4-alkylamino-3-nitro-1,6 -naphthyridin-2(1H)-ones in good yields[17] (Table 1).

The reduction of the nitro group is performed initially at room temperature and then at reflux in methanol in the presence of zinc and a saturated ammonium chloride solution.[18] The cyclization of the resulting diamine is carried out under reflux in triethyl orthoformate according to the proposed mechanism.[19] This reaction yields the tricyclic aza-simplified analogs of grossularine (11a–g), which are variously substituted at position 7 (Scheme 1).

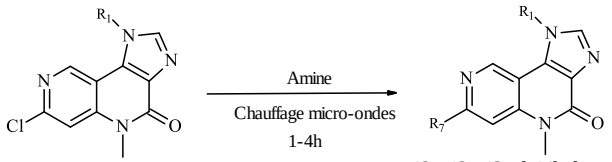
For the remaining functionalizations at position 7, we adopted the conditions reported by Dreyer et al.[20] This involves heating the products in a microwave at 130–165 °C in the presence of aromatic amines for 1 to 4 h. To enhance the solubility of our molecules and achieve greater structural diversity, we selected hydrophilic amines for this substitution. Although some amines required long reaction times, they afforded easily purified reaction mixtures with improved yields. Functionalization with n-propylamine required the addition of CuI to reach completion (Scheme 2, Table 2).

Table I: Access to compounds by cyclization according to procedure C.

Entry	R_7	Heating time	Yield (%)
9a		2 h	90
9b	H	72 h	90
9c		2 h	94
9d	CH_3	2 h	80
9e		1 h	80
9f		1 h	53
9g		2 h	91



Scheme 1. Synthesis of 4-alkyl-7-chloro-5-methyl-1*H*-imidazo[4,5-*c*][1,6]naphthyridin-4 (5*H*)–one **9a-g.**

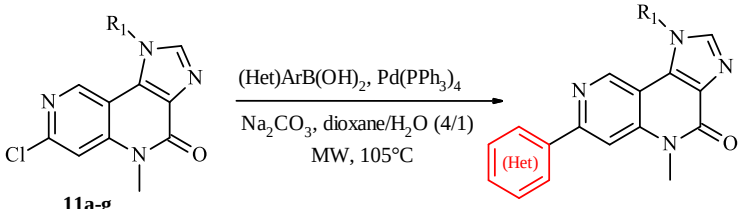


11a-g **12a, 12c, 13c-d, 14b-d, 15a-b, 16e-f, 17a-b, 18a-b**

Scheme 2: Functionalization of position 7 by SNAr**.**

Another approach we explored for functionalization at position 7 was the Suzuki coupling [1], which enables the synthesis of biaryl compounds through carbon–carbon bond formation. This coupling involves a halogenated derivative, a boronic acid, a base, and a palladium(0) complex. The reaction tolerates a wide variety of functional groups, generally provides good yields with high selectivity, requires only small amounts of catalyst, and can be conducted in various solvents at different temperatures.[21]

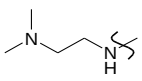
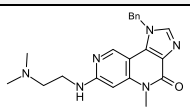
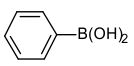
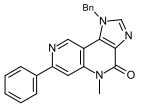
The 7-arylation of the halogenated derivatives was performed according to the conditions described by Wu et al. for 4-alkyl-7-chloro-5-methyl-1H-imidazo[4,5-c][1,6]naphthyridin-4 (5H)-ones.[22] It involves a boronic acid, tetrakis(triphenylphosphine)palladium as the catalyst, and sodium carbonate as the base. A first coupling test of phenylboronic acid with compound (11a) using $Pd(PPh_3)_4$ as the catalyst and Na_2CO_3 as the base in a 1,4-dioxane/H_2O (4:1) mixture was heated at 105 °C for 1 h in the microwave, resulting in 100% conversion (by LC-MS) to product (12b), which was easily purified by silica gel chromatography. We therefore adopted these conditions for subsequent Suzuki-Miyaura couplings. In general, the variation of substituents (R_1) on the imidazole had no influence on the coupling success. Thus, aromatic or aliphatic substituents, as well as donor groups (e.g., methoxy in 14a), did not affect the reactivity of the boronic acids. However, electron-withdrawing groups (halogens, e.g., in 19c) led to failures or reduced yields. This yield reduction could be explained by difficulties in handling these compounds, particularly their solubility. Compounds unsubstituted on the imidazole (13a, 13b), which were hydrophilic, required prolonged reaction times (2 h) as well as freeze-drying and reverse-phase chromatography. By varying the phenylboronic acids and starting compounds, 9 original imidazo[4,5-c][1,6]naphthyridine-4(5H)-ones, variously substituted at positions 7 and R_1, were isolated using the previously described reaction conditions (Scheme 3, Table 3).

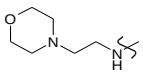
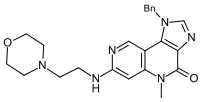
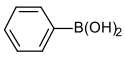
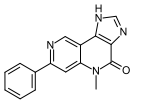
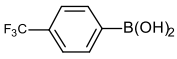
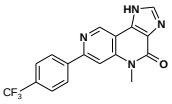
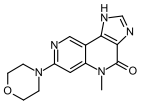
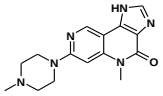
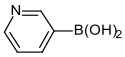
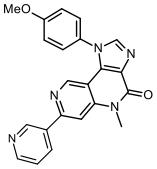
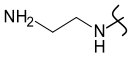
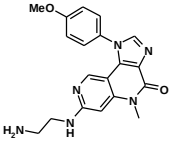
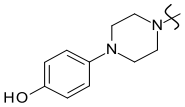
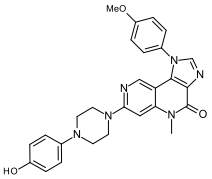
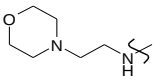
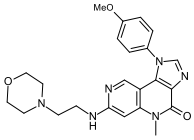
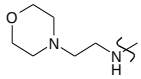
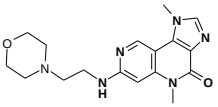
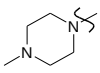
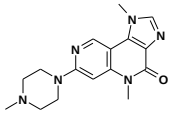
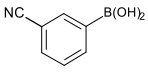
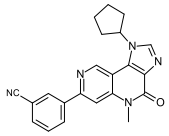
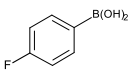
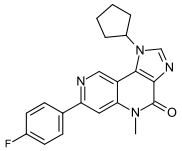


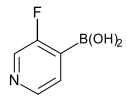
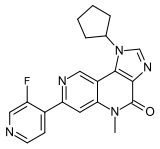
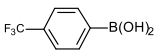
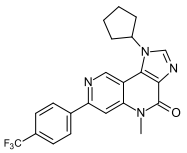
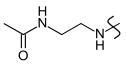
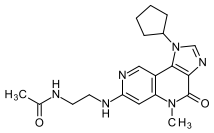
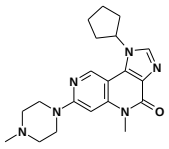
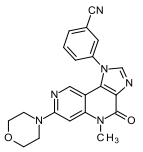
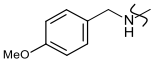
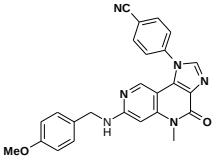
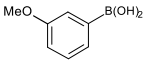
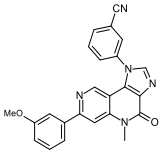
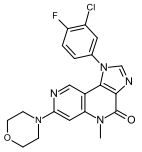
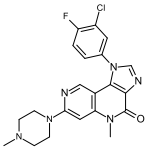
11a-g **12b, 13a-b, 14a, 15a-d, 16c**

Scheme 3: Functionalization of position 7 by Suzuki method.

Table II. Microwave-promoted C-7 functionalization of 4-alkyl-7-chloro-5-methyl-1*H* -imidazo [4,5-*c*] [1,6]naphthyridin-4(5*H*)-ones through Suzuki or S_NAr reactions.

Entry	Starting material	Type of reaction[a,b]	Reactant	Product	Time*	Yield (%)[a]
1	**11a**	S_NAr[a]			2h	**12a** (45)
2	**11a**	Suzuki			1h	**12b** (94)

Entry	Starting material	Type of reaction[a,b]	Reactant	Product	Time*	Yield (%)[a]
3	**11a**	S_NAr			1 h	**12c** (40)
4	**11b**	Suzuki			2 h	**13a** (51)
5	**11b**	Suzuki			2 h	**13b** (51)
6	**11b**	S_NAr			3 h	**13c** (13)
7	**11b**	S_NAr			1 h	**13d** (28)
8	**11c**	Suzuki			1 h	**14a** (92)
9	**11c**	S_NAr[b]			6h*	**14b** (69)
10	**11c**	S_NAr			4h	**14c** (31)
11	**11c**	S_NAr			2h	**14d** (63)
12	**11d**	S_NAr			2h	**15a** (44)
13	**11d**	S_NAr			1h	**15b** (43)
14	**11e**	Suzuki			1h	**15a** (35)
15	**11e**	Suzuki			1h	**16b** (38)

Entry	Starting material	Type of reaction[a,b]	Reactant	Product	Time*	Yield (%)[a]
16	**11e**	Suzuki			1h	**16c** (42)
17	**11e**	Suzuki			1h	**16d** (41)
18	**11e**	S_NAr[a]			1h	**16e** (38)
15	**11e**	S_NAr			1h	**16f** (39)
19	**11f**	S_NAr			1h	**17a** (23)
20	**11f**	S_NAr			1h	**17b** (74)
21	**11f**	Suzuki			1h	**17c** (39)
22	**11g**	S_NAr			1h	**18a** (36)
23	**11g**	S_NAr			1h	**18b** (48)

[a]Addition of CuI
[b*]N-BOC-1,2-diaminoethane (2 steps

EXPERIMENTAL

All commercial reagents were used without further purification. All solvents were reagent or HPLC grade. Analytical TLC was performed on silica gel 60 F254 plates. Column chromatography was carried out on silicagel Merck 60 (70-230 mesh ASTM) and Flash Chromatography Grace Reveleris X2™. Yields refer to chromatographically and spectroscopically pure compounds. Melting points were determined on an Electrothermal IA 9000 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IRAffinity-1 IR-FT spectrophotometer equipped with a MIRacle 10 accessory ATR. ^{1}H and ^{13}C NMR

spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Bruker AVANCE 400 MHz spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants (*J*) are given in hertz (Hz). Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, appt = apparent triplet, m = massif, mt = multiplet, q = quartet, br s = broad singlet. LC/MS analyses were run on a Waters ACQUITY UPLC-MS system consisting of a Single Quadrupole Detector (SQD) Mass Spectrometer (MS) equipped with an Electrospray Ionization Interface (ESI) and a Photodiode Array detector (PDA). Microwave reactions were carried out on a CEM Discover SP monomode apparatus.

Procedure A: Typical procedure for S_NAr of amines: 9a-g.

4,7-Dichloro-1-methyl-3-nitro-1,6-naphthyridin-2(1*H*)-one (7) (1.5 g, 5.5 mmol) was dissolved in acetonitrile (100 mL) and the appropriate amine: benzylamine (600 µL, 5.5 mmol), propylamine (450 µL, 5.5 mmol), ammonia (128 µL, 5.5 mmol), 4-methoxybenzylamine (680 mg, 5.5 mmol), methylamine (190 µL, 5.5 mmol), cyclopentylamine (635 µL, 9.15 mmol), cyclohexylamine (630 µL, 5.5 mmol), cyclobutylamine.HCl (592 mg, 5.5 mmol), 4-(2-aminoethyl)morpholine (722 µL, 5.5 mmol), *N*,*N*-dimethylethylenediamine (604 µL, 5.5 mmol), 4-aminobenzonitrile (650 µL, 5.5 mmol), 3-chloro-4-fluoroaniline (800 mg, 5.5 mmol). Potassium carbonate (760 mg, 5.5 mmol) was added in one portion, and the whole was heated at 60°C for 1-16 h. Most of the solvent was evaporated and the residue was acidified with HCl 2 N to pH 6. The precipitate was collected by filtration to afford expected compounds.

Procedure B: Typical procedure for Reduction of Nitro Groups: 10 a-g.

To a solution of 4-alkylamino-7-chloro-1-methyl-3-nitro-1,6-naphthyridin-2(1*H*)-one (1.7 g, 4.9 mmol) in methanol (100 mL) at room temperature, saturated ammonium chloride solution (12 mL) and zinc dust (1.4 mg, 22.05 mmol) were added sequentially. After stirring 30 minutes at room temperature, additional zinc dust (1.4 mg, 22.05 mmol) was added and the reaction mixture was refluxed for 1 h. The reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure. The residue was suspended into EtOAc (200 mL) and washed with NaOH 1 N. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (dichloromethane) to give expected compounds.

Procedure C: Typical procedure for Cyclisation of : 11 a-g.

A solution of 4-alkylamino-3-amino-7-chloro-1-methyl-1,6-naphthyridin-2(1*H*)-one (1g) in triethyl orthoformate (50 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was suspended into $CHCl_3$ (200 mL) washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (dichloromethane) to give expected compounds.

Procedure E: Typical procedure for S_NAr using aliphatic amines under microwave irradiation: 12a, 12c, 13c-d, 14b-d, 15a-b, 16e-f, 17a-b, 18a-b

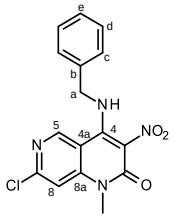
In a 10 mL vessel were added the 1-alkyl-7-chloro-5-methyl-1,5-dihydro-4*H*-imidazo[4,5-*c*] [1,6]naphthyridin-4-one (100 mg, 0.31 mmol) and the appropriate aliphatic amine: 2-(morpholin-4-yl)ethanamine (2.2 mL, 17.05 mmol), *N*,*N*-dimethylethylenediamine (440 µL, 4.03 mmol), 1-(2-hydroxyethyl)piperazine (2 mL, 17.05 mmol), 1-methylpiperazine (1.2 mL, 17.05 mmol), morpholine (1.5 mL, 17.05 mmol), 1-(4-hydroxyphenyl)piperazine (718 mg, 4.03 mmol), 1-(4-methoxyphenyl)piperazine (775 mg, 4.03 mmol), 1-benzylpiperazine (2.9 mL, 17.05 mmol). The tube was sealed, and the reaction mixture was heated under microwave irradiation at 130 to 170 °C for 1 h. After cooling, water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography or triturated with diisopropyl ether to provide expected compounds.

Procedure D: Typical procedure for Suzuki–Miyaura cross-coupling: 12b, 13a-b, 14a, 15a-d, 16c

In a 10 mL vessel were added the 1-alkyl-7-chloro-5-methyl-1,5-dihydro-4*H*-imidazo [4,5-*c*][1,6] naphthyridin-4-one (100 mg, 0.31 mmol) in a 1,4-dioxane/water mixture (4/1,5 mL), the appropriate boron reagent (41 mg, 0.34 mmol), Na_2CO_3 (82 mg, 0.78 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol). The tube was sealed and then heated under microwave heating at 105 °C for 1 h. After cooling, water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography or triturated with diisopropyl ether to provide expected compounds.

4-Benzylamino-7-chloro-1-methyl-3-nitro-1,6-naphthyridin-2(1*H*)-one 9a

According to the general *procedure A*, compound **9a** was obtained by reaction between benzylamine (600 mL, 5.5 mmol), K_2CO_3 (759 mg, 5.5 mmol) and compound **8** (1.5 g, 5.5 mmol). Compound **9a** (1.8 g, 93% yield) was obtained after filtration as a yellow powder.



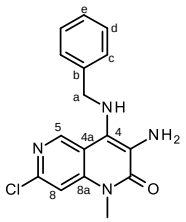
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (s, 1H, H_5), 8.52 (t, ^3J = 6.0 Hz, 1H, NH), 7.64 (s, 1H, H_8), 7.38-7.31 (m, 5H, $H_{c\text{-}e}$), 4.43 (d, ^3J = 6.0 Hz, 2H, H_a), 3.52 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 155.86 (C=O), 152.79 (C_{8a}), 147.01 (C_4), 145.61 (C_5), 141.93 (C_7), 137.35 (C_3), 128.44 ($2C_c$), 127.46 (C_b), 126.90 ($2C_d$), 122.66 (C_e), 110.37 (C_{4a}), 109.06 (C_8), 46.66 (C_a), 29.34 (NCH_3).

IR, ν (cm^{-1}): 3287 (νN-H), 3099 (νC-H_{ar}), 1603 (νC=O), 1568 (νC=C), 1470 and 1543 (νC-NO_2), 696 (νC-Cl).

MS (ESI), m/z (%): 345.07 (100) $[M+H]^+$, 347.7 (40) $[M+H+2]^+$.

3-Amino-4-benzylamino-7-chloro-1-methyl-1,6-naphthyridin-2(1*H*)-one 10aAccording to the general *procedure B*, compound **10a** was obtained by reaction between compound **9a** (3.90 g, 11.3 mmol), saturated NH_4Cl (15 mL) and zinc dust (6.6 g, 4.5 + 4.5 equiv.) in methanol (100 mL). Purification by silica gel chromatography (dichloromethane) gave **10a** (3.25 g, 92% yield) as a white powder.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H, H_5), 7.57 (s, 1H, H_8), 7.47-7.21 (m, 5H, $H_{c\text{-}e}$), 5.41 (t, ^3J = 7.6 Hz, 1H, NH), 5.15 (s, 2H, H_a), 4.33 (s, 2H, NH_2), 3.66 (s, 3H, NCH_3).

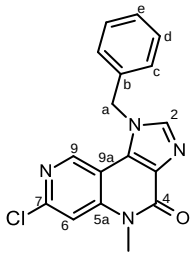
^{13}C NMR (100 MHz, DMSO-d_6): δ 158.41 (C=O), 145.78 (C_{8a}), 143.66 (C_4), 140.27 (C_5), 140.06 (C_7), 128.13 ($2C_c$), 127.65 ($2C_d$), 126.82 (C_b), 126.27 (C_e), 125.45 (C_3), 114.72 (C_{4a}), 107.87 (C_8), 49.20 (C_a), 29.49 (NCH_3).

IR, ν (cm^{-1}): 3460 (νN-H), 3096 (νC-H_{ar}), 1628 (νC=O), 1574 (νC=C), 698 (νC-Cl).

MS (ESI), m/z (%): 315.09 (100) $[M+H]^+$, 317.09 (40) $[M+H+2]^+$.

1-Benzyl-7-chloro-5-methyl-1*H*-imidazo[4,5-*c*][1,6]naphthyridin-4(5*H*)-one 11a

According to the general *procedure C*, compound **11a** was obtained by refluxing compound **10a** (1.10 g, 3.5 mmol) in triethyl orthoformate (30 mL) for 2 h. The crude product was purified by silica gel chromatography (dichloromethane) to give **11a** (1.02 g, 92% yield) as a white powder.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H, H_9), 8.46 (s, 1H, H_2), 7.67 (s, 1H, H_6), 7.41-7.13 (m, 5H, $H_{c\text{-}e}$), 5.97 (s, 2H, H_a), 3.68 (s, 3H, NCH_3).

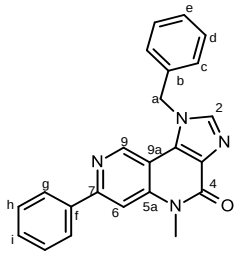
^{13}C NMR (100 MHz, DMSO-d_6): δ 157.03 (C=O), 148.79 (C_{5a}), 145.04 (C_7), 144.41 (C_9), 143.34 (C_2), 135.68 (C_{4c}), 132.48 (C_{5c}), 130.31 (C_b), 129.03 ($2C_c$), 127.85 (C_e), 126.00 ($2C_d$), 109.74 (C_{9a}), 108.53 (C_6), 49.76 (C_a), 29.23 (NCH_3).

IR, ν (cm^{-1}): 3356 (νN-H), 1575 (νC=O), 1441 (νC=C), 671 (νC-Cl).

MS (ESI), m/z (%): 325.08 (100) $[M+H]^+$, 327.08 (40) $[M+H+2]^+$.

1-Benzyl-5-methyl-7-phenyl-1*H*-imidazo[4,5-*c*][1,6]naphthyridin-4(5*H*)-one 12b

According to the general *procedure D*, compound **12b** was obtained by reaction between compound **11a** (100 mg, 0.31 mmol) (4:1, 5 mL), phenylboronic acid (40.2 mg, 0.33 mmol), Na_2CO_3 (79,42 mg, 0.75 mmol) and $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) in a 1,4-dioxane/water mixture. Purification by silica gel chromatography (mixtures of dichloromethane/methanol of increasing polarity) afforded **12b** (103 mg, 94% yield) as a yellow powder.



^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 1H, H_9), 8.44 (s, 1H, H_2), 7.97 (s, 1H, H_6), 7.66-7.16 (m, 10H, H_{b-i}), 6.02 (s, 2H, H_a), 3.83 (s, 3H, NCH_3).

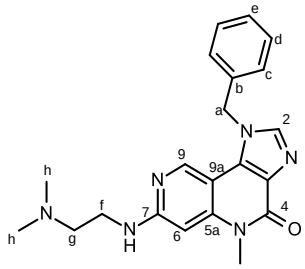
^{13}C NMR (100 MHz, DMSO-d_6): δ 157.36 (C=O), 154.43 (C_{5a}), 144.76 (C_7), 143.61 (C_9), 143.21 (C_2), 138.23 (C_{4c}), 139.02 (C_{5c}), 134.2 (C_b), 132.47 (C_f), 129.95 ($2C_c$, $2C_g$), 129.31 (C_e, C_i), 126.90 ($2C_d$, $2C_h$), 107.86 (C_{9a}), 106.13 (C_6), 49.48 (C_a), 29.04 (NCH_3).

IR, ν (cm^{-1}): 3080 (νC-H_{ar}), 2851(νC-H_{aliph}), 1666 (νC=O), 1543 (νC=C).

MS (ESI), m/z (%): 367.43 (100) $[M+H]^+$.

1-Benzyl-7-((2-(dimethylamino)ethyl)amino)-5-methyl-1*H*-imidazo[4,5-*c*][1,6]naphthyridin-4(5*H*)-one (12a)

According to the general *procedure E*, compound **12a** was obtained by reaction between compound **11a** (100 mg, 0.31 mmol), *N*,*N*-dimethylethylenediamine (0.44 mL, 4.03 mmol) and CuI (0.51 equiv.) in NMP (2 mL). Purification by silica gel chromatography (mixtures of dichloromethane/methanol of increasing polarity) afforded **12a** (52.4 mg, 45% yield) as a yellow powder.



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H, H_9), 8.21 (s, 1H, H_2), 7.41-7.10 (m, 5H, H_{c-e}), 6.91 (br s, 1H, NH), 6.46 (s, 1H, H_6), 5.85 (s, 2H, CH_{2a}), 3.65 (s, 3H, NCH_3), 3.49-3.43 (m, 2H, H_f), 2.70 (t, ^3J = 6.0 Hz, 2H, H_g), 2.42 (s, 6H, H_h).

^{13}C NMR (100 MHz, DMSO-d_6): δ 158.08 (C=O), 157.65 (C_{5a}), 144.31 (C_7), 143.04 (C_9), 142.92 (C_2), 136.24 (C_{4c}), 132.27 (C_{5c}), 128.94 ($2C_c$), 128.88 (C_b), 127.63 (C_e), 125.97 ($2C_d$), 101.08 (C_{9a}), 97.73 (C_6), 57.17 (C_g), 49.48 (C_a), 43.98 (C_f), 37.66 (NCH_3), 28.98 ($2C_h$),

IR, ν (cm^{-1}): 3337 (νN-H), 3101 (νC-H_{ar}), 2937 (νC-H_{aliph}), 1665 (νC=O), 1564 (νC=C).

MS (ESI), m/z (%): 377.08 (100) $[M+H]^+$.

4. Acknowledgements

The authors gratefully acknowledge support of this project by the IICiMed-EA1155 (Nantes University) and the University of Sciences, Techniques and Technologies of Bamako (Mali).

5. Conclusion

This methodological approach allowed us to synthesize some original final compounds, variously substituted with very heterogeneous yields.

Activity tests carried out on a panel of 7 kinases (Haspin, CLK1, DYRK1A, CDK5, CDK9, GSK3α/β and CK1) did not reveal any "hit" compounds. However, the study of the residual kinase activity on the kinases involved shows the emergence of interesting inhibitory activities allowing us to consider some optimization studies. In addition, it is also planned to increase the panel of kinases since

the number and nature of those that have been the subject of the biological studies of our work are far from being representative of the human kinome.

6. References

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