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Francis Giraud, Béatrice Josselin, Sandrine Ruchaud, Fabrice Anizon, Pascale Moreau. Synthesis of (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanone and derivatives. *Synthesis: Journal of Synthetic Organic Chemistry*, 2023, 55 (22), pp.3825-3832. 10.1055/a-2107-4571 . hal-04309294

HAL Id: hal-04309294

<https://hal.science/hal-04309294v1>

Submitted on 27 Nov 2023

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Synthesis of (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanone and derivatives.

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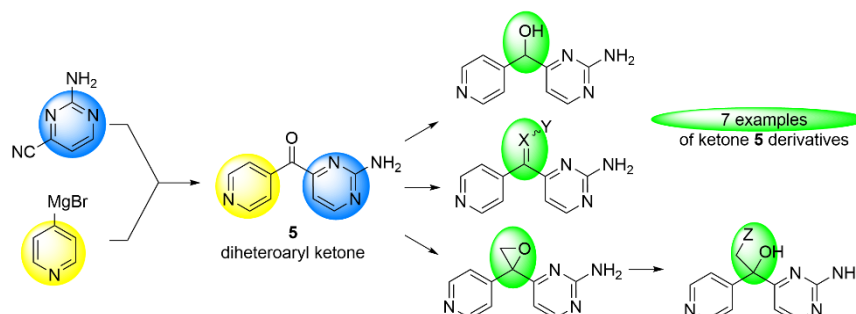
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Received:
 Accepted:
 Published online:
 DOI:

Abstract Pyrido[3,4-*g*]quinazoline was previously identified as a relevant scaffold for protein kinase inhibition. In order to assess if the planarity of this heterocyclic system was essential to the protein kinase inhibitory potency observed in this series, new compounds were synthesized and evaluated, in which the central cycle was opened to provide (pyridin-4-yl)(pyrimidin-4-yl)methane derivatives which were prepared from the corresponding ketone precursor. After preparing (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanone, derivatives were synthesized and evaluated toward a panel of protein kinases. The results demonstrated that the planar pyrido[3,4-*g*]quinazoline tricyclic system was mandatory to maintain the protein kinase inhibitory potency in this series.

Key words: Diheteroarylketone, Pyrido[3,4-*g*]quinazoline, (Pyrimidin-4-yl)(pyridin-4-yl)methanone, Grignard reagents, molecular shape, protein kinase inhibitors.

As part of our ongoing studies focused on the design and synthesis of new heteroaromatic compounds with potential protein kinases inhibitory potencies, we recently reported the identification of pyrido[3,4-*g*]quinazolines as nanomolar Cdc-like kinase 1 (CLK1) and Dual-specificity tyrosine-regulated kinase 1A (DYRK1A) inhibitors (Figure 1).^{1,2}

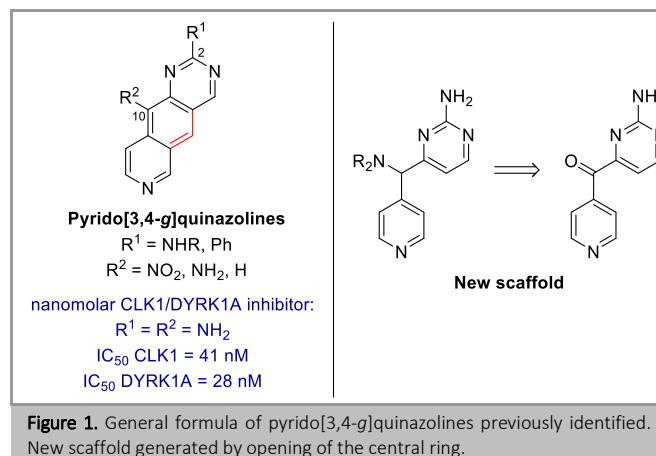
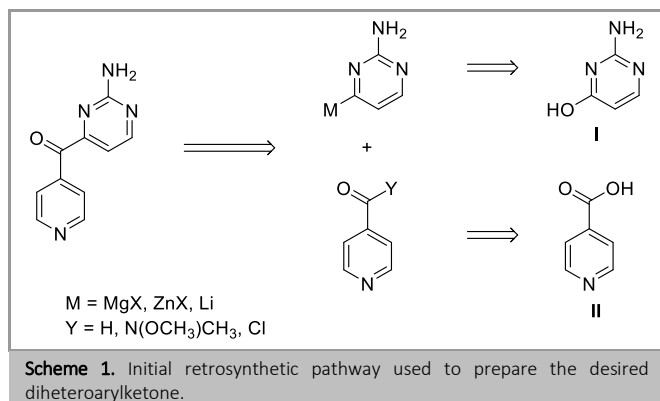


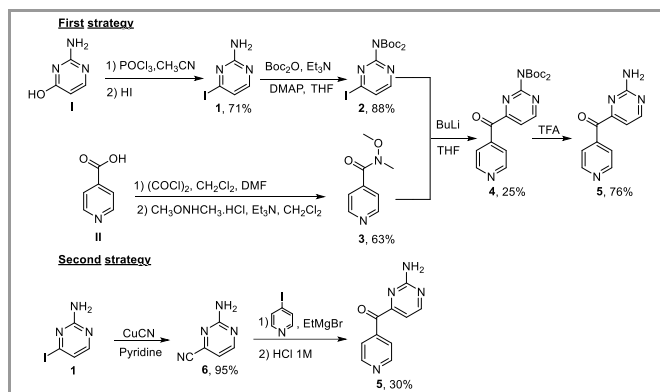
Figure 1. General formula of pyrido[3,4-*g*]quinazolines previously identified. New scaffold generated by opening of the central ring.

It was previously demonstrated that aminopyrimidine and pyridine moieties of the pyrido[3,4-*g*]quinazoline scaffold, as well as substituents at the 10-position, are critical for interactions with the targeted protein kinase.^{1,2} However, the pyridoquinazoline system possesses a planar structure which could lead to potential DNA intercalation. To limit the possible side effects due to this off-target activity, we hypothesized that opening the central pyridoquinazoline ring, while conserving aminopyrimidine, pyridine and 10-position moieties, could retain protein kinase inhibition (Figure 1). Thus, this structural modification would ultimately lead to (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanamines that could be prepared from the corresponding ketone precursor (Figure 1). Surprisingly, literature review showed not much nitrogen-containing diheteroarylketone syntheses whereas we found many reports on the preparation of these simple molecules in the carbocyclic series. Therefore, the preparation of these targeted molecules is of high interest not only for the medicinal chemistry purpose but also to enlarge chemical space diversity.

Starting from commercially available compounds **I** and **II**, the first strategy for (pyrimidin-4-yl)(pyridin-4-yl)methanone preparation was based on the condensation of a nucleophilic organometallic species with electrophilic aldehyde or carboxylic acid derivatives (Scheme 1).



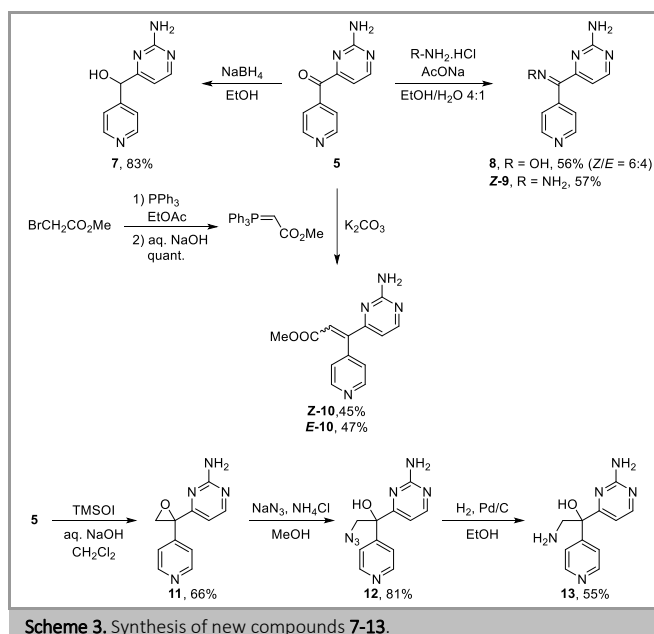
The preparation of starting materials **1–3** using reaction conditions adapted from the literature (see experimental section) were successful (Scheme 2). However, neither the Negishi cross-coupling (organozinc species + acyl chloride) in various conditions^{3–6} nor the addition of a Grignard reagent on a Weinreb amide⁷ afforded the desired compound. The only encouraging result was obtained from Weinreb amide **3**^{9,10} and organolithium derivative prepared from Boc-protected aminopyrimidine **2**⁸, leading to ketone **4** in 25% yield (Scheme 2). Protecting group cleavage in TFA provided **5** in 76% yield.



Numerous trials have been set up to optimize the preparation of **4**. From compounds **2** and **3**, changes in reaction conditions (temperature, stoichiometry, reagent addition order, use of *t*-BuLi) did not improve the yield. Thus, a second strategy based on the inversion of reactivity between both reaction partners was worked out. Nitrile intermediate **6** was prepared in 95% yield from **1** using CuCN in pyridine.¹¹ Compound **6** was then reacted with pyridin-4-ylmagnesium bromide prepared by iodine-magnesium exchange from 4-iodopyridine.¹² In these conditions, bis-heteroarylketone **5** was obtained in 30% yield, however without the need of the Boc-protection-deprotection sequence of the aminopyrimidine moiety (Scheme 2).

With compound **5** in hands, we planned to prepare (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanamine derivatives by reductive amination reaction. Treatment by ammonia¹³,

ammonium acetate¹⁴ or benzylamines^{15,16} before reduction with NaBH₄ did not afford expected amine derivatives. In these conditions, only the reduction product **7** (which could be prepared in 83% yield directly from **5**¹⁷) was isolated (Scheme 3), indicating difficulties to generate the intermediate imine. Next, we expected to synthesize the primary amine *via* the oxime. Thus, oxime **8** was prepared from **5** and hydroxylamine hydrochloride in 56% yield as a *Z/E* 6:4 mixture.¹⁸ However, attempts to reduce **8** (Mg/HCOONH₄¹⁹, Zn/HCl 2M²⁰) only resulted in recovered starting material or degradation. The attribution of ¹H and ¹³C NMR signals for each oxime isomer was performed using standard NMR experiments (¹H-¹H COSY, ¹H-¹³C HSQC, ¹H-¹³C HMBC). ¹H-¹H NOESY experiment was also recorded in order to assign signals to the correct isomer. For the two isomers, weak NOE correlations were observed between hydroxyl group and both heterocycles. Strongest correlation was observed with the 3-pyridinyl proton for the minor isomer, and with the 5-pyrimidinyl proton for the major isomer, suggesting *E* and *Z* configuration, respectively (Figure 2). In addition, it was previously shown that α -syn-¹³C of oximes are upfield shifted compared to α -anti-¹³C.²¹ Comparison of α -¹³C chemical shifts for both isomers showed a similar behavior confirming the assignment. Indeed, pyridinyl α -¹³C showed a chemical shift at 141.8 ppm (α -anti) for the major *Z*-isomer, and 139.2 ppm (α -syn) for the minor *E*-isomer. Similarly, pyrimidinyl α -¹³C was observed at 159.8 ppm (α -syn) for the major *Z*-isomer and 161.7 ppm (α -anti) for the *E*-minor isomer. Additional assignment confirmation was provided by the calculation of ¹H and ¹³C NMR chemical shifts using Gaussian software, after geometry optimization calculations to produce the lowest-energy conformation for each isomer (Figure 2).



As we found that (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanamines could not be obtained, we sought to extend our chemical library. Thus, hydrazone **9** was first prepared from **5** with hydrazine hydrochloride in similar condition than those used for the synthesis of oxime **8**.¹⁸ A crude mixture of *Z/E* isomers was obtained, leading to **Z-9** in 57% yield after column chromatography, as well as trace amount of *E-9*. Assignments

were performed by NMR from a mixture of both isomers. In the case of the *E*-isomer, ^1H - ^1H -NOESY showed a correlation between hydrazone NH_2 , and a 3-pyridinyl proton. For the *Z*-isomer, weak NOE correlation was observed between hydrazone NH_2 and both 3-pyridinyl and 5-pyrimidinyl protons moieties, the effect being weaker on the side of the pyridine moiety. However, a strong effect was observed between 3-pyridinyl and 5-pyrimidinyl protons, which is consistent with the structure obtained by molecular modeling (Figure 2C). As for oximes **8**, the upfield shift of α -syn chemical shifts was observed^{22,23} (Figures 2C, 2D), confirming the assignment, also supported by NMR chemical shift calculations.

Finally, a Wittig reaction was performed in the presence of potassium carbonate using **5** and a phosphorus ylide prepared quantitatively from methyl 2-bromoacetate.²⁴ Again, the two *Z* and *E* diastereoisomers were obtained and isolated by column chromatography leading to 45% and 47% yields of isolated **Z-10** and **E-10**, respectively (Scheme 3). As above, ^1H - ^1H NOESY experiments were performed to determine the alkene configuration. Distinct NOE effect was observed between the alkene proton and the 3-pyridinyl position for the *Z* isomer, and the 5-pyrimidinyl proton for the *E* isomer (Figure 2E, 2F). In the latter case, this proximity between protons was not confirmed by the structure obtained by molecular modeling, indicating a different conformation. However, the assignment was confirmed by chemical shift calculations.

To extend our chemical library, compound **9** was mixed with LiAlH_4 in THF²⁵ and compound **10** with magnesium turnings in MeOH.²⁶ Nevertheless, no reduction of the C=C double bonds was observed, starting materials were recovered. This might be explained by steric hindrance induced by both heteroaryl rings.

carbon; assignment was done with the help of NMR calculation. The images were produced using UCSF Chimera software²⁷.

Lastly, compound **5** was engaged in a Johnson-Corey-Chaykovsky epoxidation reaction in the presence of trimethylsulfoxonium iodide (TMSOI) to give **11** in 66% yield (Scheme 3).²⁸ Epoxide opening with sodium azide led to compound **12** in 81% yield.²⁹ Then, **12** was converted to the corresponding primary amine **13** under catalytic hydrogenation conditions (Scheme 3).³⁰

Finally, in order to measure the importance of the planar tricyclic system in the inhibition of protein kinases, compounds **5** and **7-13** were tested, as previously reported,³¹ toward 8 kinases (Haspin, CDK9/Cyclin T, GSK3 β , CK1 ϵ , CDK5/p25, Pim, CLK1 and DYRK1A). The percentage of residual kinase activity was evaluated in the presence of 10 μM and 1 μM compound concentrations. The results obtained showed that none of the tested compounds exhibited potent inhibitory potency toward the kinases tested.

In conclusion, we studied the synthetic route to (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanone and derivatives. Despite of the simplicity of their structure, the preparation of these compounds is poorly documented in the literature compared to the one of their analogues from the carbocyclic series. The preparation and biological evaluation of bis-heteroaryl ketone **5** and analogues **7-13** highlighted the need of a planar polycyclic moiety in the pyridoquinazoline series to inhibit the tested kinases.

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Procedures

Starting materials were obtained from commercial suppliers and used without further purification. IR spectra were recorded on a PerkinElmer Spectrum 65 FT-IR spectrometer (ν in cm^{-1}). NMR spectra, performed on a Bruker AVANCE 400 III HD (^1H : 400 MHz, ^{13}C : 101 MHz) or a Bruker AVANCE 500 (^1H : 500 MHz, ^{13}C : 125 MHz) are reported in ppm using the solvent residual peak as an internal standard; the following abbreviations are used: singlet (s), doublet (d), broad signal (br s). Coupling constants are expressed in Hertz. High resolution mass spectra were determined on a high-resolution Waters Micro Q-ToF or Thermo Scientific Q Exactive Q-Orbitrap apparatus (UCA START, Université Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40-63 μm silica gel. Reactions were monitored by TLC using fluorescent silica gel plates (60 F254 from Macherey Nagel). Melting points were measured on a Stuart SMP3 apparatus and are uncorrected. The purity of compounds **5** and **7-13** was established by HPLC analysis using a VWR Hitachi chromatograph with DAD detector and a Macherey Nagel Nucleodur gravity column (4.6 mm x 250 mm, 5 mm). Flow rate was 0.5 mL/min and the analysis was performed at 25 $^\circ\text{C}$ at 240 nm as detection wavelength for each compound. Solvents were (A) water/0.1% trifluoroacetic acid, (B) acetonitrile. Two methods were designed: method A was a gradient 5:95 A/B for 5 min to 95:5 A/B in 45 min whereas method B was an isocratic mode using 90/10 water/acetonitrile.

Derivatives **1-3** were prepared following literature procedures without any modifications. Their structures were proved by ^1H NMR spectral analysis and were in accordance with reported data.^{9,10,32-35}

Di-*tert*-butyl [4-(pyridine-4-carbonyl)pyrimidin-2-yl]imidodicarbonate (**4**)

To a solution of compounds **2** (0.100 g, 0.239 mmol) and **3** (0.033 g, 0.196 mmol) in 3 mL of THF cooled to -78°C , was added *n*-BuLi (0.265 mL, 1.6 M solution in hexane). The reaction mixture was stirred for 4 h at -78°C before a slow warm up to room temperature overnight. Water was added

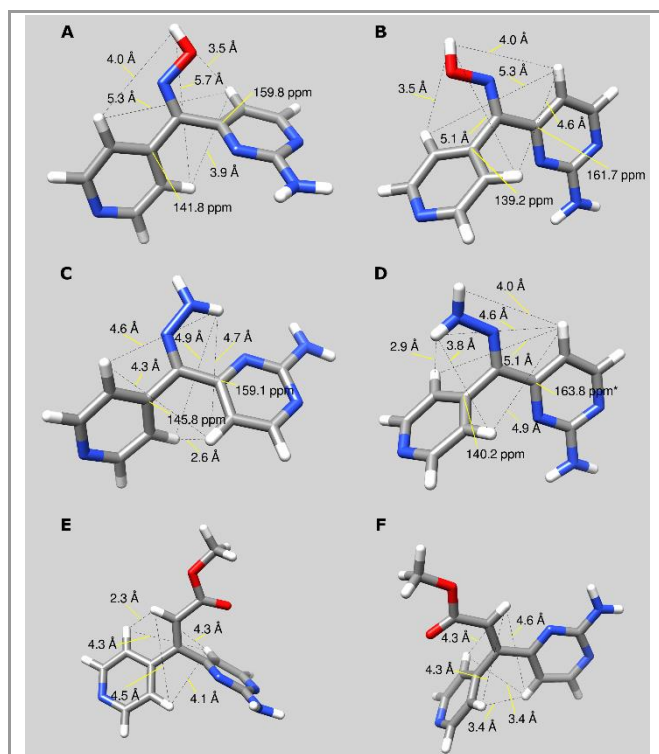


Figure 2. Modeling of *Z*- (left) and *E*-isomer (right) of oxime **8** (A, B), hydrazone **9** (C, D) and methyl ester **10** (E, F). Relevant distances (dashed lines) and experimental NMR chemical shifts of α -syn and α -anti ^{13}C are indicated.

* uncertain assignment: 2D NMR experiments did not allow to attribute this

before extraction with ethyl acetate. The combined organic phases were washed with a brine solution before drying over MgSO_4 and evaporation under reduced pressure. The residue was purified by flash column chromatography using EtOAc/Pentane (3:7) to afford compound **4** ($R_f = 0.25$) in 25% yield (0.02 g, 0.050 mmol) as a green oil.

IR (ATR): 1753, 1722, 1535, 1412, 1245 cm^{-1} .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 9.21$ (d, $J = 5.2$ Hz, 2 H), 8.83 (d, $J = 6.0$ Hz, 1 H), 8.00 (d, $J = 4.8$ Hz, 2 H), 7.83 (d, $J = 6.0$ Hz, 1 H), 1.41 (s, 18 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): $\delta = 190.8$ (CO), 150.3 (2 CO), 160.7 (C), 157.0 (C), 140.9 (C), 161.9 (CH), 150.2 (2CH), 123.4 (2CH), 118.1 (CH), 83.6 (2C), 27.9 (6 CH_3).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_5$: 401.1819; found: 401.1812. m/z $[\text{M}+\text{CH}_3\text{OH}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}_6$: 433.2087; found: 433.2075.

(2-Aminopyrimidin-4-yl)(pyridin-4-yl)methanone (**5**)

Procedure A: TFA (0.2 mL) was added to a solution of **4** (0.026 g, 0.065 mmol) in CH_2Cl_2 (0.8 mL) under argon. The reaction mixture was stirred for 30 min before evaporation and purification by flash column chromatography using EtOAc/Pentane (8:2) to give **5** ($R_f = 0.2$) in 76% yield (0.010 g, 0.05 mmol) as a light green powder.

Procedure B: To a solution of 4-iodopyridine (1.014 g, 4.948 mmol) in 3 mL THF under argon was added slowly ethylmagnesium bromide (6.2 mL of a 0.8 mol/L solution in THF, 4.948 mmol). The suspension was stirred for 1 h at room temperature. In a second flask, a solution of compound **6** (148.6 mg, 1.237 mmol) in 3 mL THF under argon was prepared. To this solution was slowly transferred the Grignard reagent and the reaction mixture was heated at 50 °C overnight. After cooling, HCl 1N solution (10 mL) was added and stirring was continued for 30 min at room temperature. The reaction was poured on a saturated NaHCO_3 aqueous solution to adjust the pH value to 8. Product was extracted with EtOAc, combined organic phases were washed with water and brine, dried over MgSO_4 and concentrated. Purification by flash chromatography using EtOAc/cyclohexane 2:1 then pure EtOAc and finally a gradient from 1 to 2% of MeOH in EtOAc afforded pure compound **5** in 30% yield (75.7 mg, 0.378 mmol) as a yellow powder.

$R_f = 0.35$ (EtOAc).

IR (ATR): 3446-2512, 1689, 1634, 1557, 1402, 1233 cm^{-1} .

Mp: 162-163 °C (decomposition)

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.81$ (d, $J = 6.0$ Hz, 2 H), 8.56 (d, $J = 4.8$ Hz, 1 H), 7.83 (d, $J = 6.0$ Hz, 2 H), 7.04 (br s, 2 H), 7.02 (d, $J = 4.8$ Hz, 1 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): $\delta = 193.0$ (CO), 163.1 (C), 160.5 (C), 141.8 (C), 160.7 (CH), 150.3 (2CH), 123.3 (2CH), 107.9 (CH).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{N}_4\text{O}$: 201.0771; found: 201.0770.

HPLC method B: purity > 96%, $\lambda = 240$ nm, $t_R = 5.33$ min.

2-Aminopyrimidine-4-carbonitrile (**6**)

To a solution of compound **1** (1.228 g, 5.556 mmol) in pyridine (14 mL) at room temperature under argon was added copper cyanide (0.547 g, 6.112 mmol). The mixture was heated at 115 °C overnight before cooling and filtration over Celite pad. Washings with EtOAc (400 mL) and acetone (200 mL) afforded an organic phase which was concentrated to 200 mL. The residue was washed with water and brine, dried over MgSO_4 and evaporated to dryness. First a purification by flash column chromatography using Cyclohexane/acetone 1:1 to 1:2 was performed but the product was contaminated with pyridinium salts. It was taken up with EtOAc and washed with NaHCO_3 solution and large amount of water. After drying over MgSO_4 and evaporation compound **6** (0.640 g, 5.328 mmol) was obtained in 95% yield as a yellow powder.

Experimental data were in accordance with literature.³⁴

(±)-(2-Aminopyrimidin-4-yl)(pyridin-4-yl)methanol (**7**)

To a solution of compound **5** (30.9 mg, 0.154 mmol) in 1 mL absolute EtOH at 0 °C under argon was added sodium borohydride (8.7 mg, 0.231 mmol). The reaction mixture was warmed at room temperature and stirred for 75 min. Water and NaHCO_3 solution were added and the product was extracted with EtOAc. Combined organic phases were dried over MgSO_4 , evaporated and purified by flash column chromatography using EtOAc/MeOH gradient from 1% to 10%. Pure compound **7** (26.2 mg, 0.129 mmol) was isolated in 83% yield as a beige powder.

$R_f = 0.10$ (EtOAc).

IR (ATR): 3363-2674, 1739, 1652, 1567, 1216 cm^{-1} .

Mp: 125-126 °C

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.50$ (d, $J = 6.0$ Hz, 2 H), 8.21 (d, $J = 4.8$ Hz, 1 H), 7.38 (d, $J = 6.0$ Hz, 2 H), 6.74 (d, $J = 4.8$ Hz, 1 H), 6.58 (br s, 2 H), 6.27 (d, $J = 4.4$ Hz, 1 H), 5.38 (d, $J = 4.4$ Hz, 1 H).

^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): $\delta = 171.7$ (C), 163.0 (C), 151.6 (C), 158.8 (CH), 149.4 (2CH), 121.6 (2CH), 105.9 (CH), 73.7 (CH-OH).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}$: 203.0927; found: 203.0923.

HPLC method B: purity > 95%, $\lambda = 240$ nm, $t_R = 5.24$ min.

(E/Z)-(2-Aminopyrimidin-4-yl)(pyridin-4-yl)methanone oxime (**8**)

To a solution of compound **5** (42.7 mg, 0.213 mmol) in 3 mL EtOH/ H_2O 4:1 at room temperature were successively added hydroxylamine hydrochloride (23.7 mg, 0.341 mmol) and sodium acetate (34.9 mg, 0.426 mmol). The mixture was stirred at 100 °C overnight, cooled and evaporated to dryness. Ethanol was added in 5 portions (10 mL each) and evaporated to remove water. Purification by flash column chromatography using EtOAc/MeOH 98:2 as eluent afforded compound **8** (26.0 mg, 0.121 mmol) in 56% yield as a white powder. 6:4 Z/E mixture was observed by ^1H NMR.

$R_f = 0.15$ (EtOAc).

IR (ATR): 3471-2993, 1562, 1451, 1226 cm^{-1} .

Mp > 250 °C

Z-8 isomer. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 12.11$ (br s, 1 H), 8.57 (d, $J = 5.2$ Hz, 2 H), 8.35 (d, $J = 5.2$ Hz, 1 H), 7.36 (d, $J = 6.0$ Hz, 2 H), 6.81 (br s, 2 H), 6.68 (d, $J = 5.2$ Hz, 1 H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): $\delta = 163.8$ (C), 159.8 (C), 151.7 (C), 141.8 (C), 158.7 (CH), 149.9 (2CH), 120.7 (2CH), 110.5 (CH).

E-8 isomer. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 12.20$ (br s, 1 H), 8.63 (d, $J = 4.4$ Hz, 2 H), 8.27 (d, $J = 5.2$ Hz, 1 H), 7.31 (d, $J = 5.6$ Hz, 2 H), 6.98 (d, $J = 5.2$ Hz, 1 H), 6.60 (br s, 2 H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): $\delta = 163.3$ (C), 161.7 (C), 152.9 (C), 139.7 (C), 158.5 (CH), 149.2 (2CH), 124.1 (2CH), 106.3 (CH).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{N}_5\text{O}$: 216.0880; found: 216.0878.

HPLC method B: purity > 99%, $\lambda = 240$ nm, $t_R = 6.55$ min.

(E/Z)-(2-Aminopyrimidin-4-yl)(pyridin-4-yl)methanone hydrazone (**9**)

To a solution of compound **5** (74.5 mg, 0.372 mmol) in 7 mL EtOH/ H_2O 4:1 at room temperature were successively added hydrazine monohydrochloride (40.8 mg, 0.595 mmol) and sodium acetate (61.0 mg, 0.744 mmol). The mixture was stirred at 100 °C overnight, cooled and evaporated to dryness. Ethanol was added in 5 portions (10 mL each) and evaporated to remove water. Purification by flash column chromatography using CH_2Cl_2 to $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 88:12 as eluent afforded compound **Z-9** (46.1 mg, 0.215 mmol) in 57% yield as a white powder.

$R_f = 0.20$ and $R_f = 0.32$ (EtOAc/MeOH 9:1).

IR (ATR): 3400-2615, 1641, 1575, 1547, 1448, 1411 cm^{-1} .

Mp: 206-208 °C (decomposition)

Z-9 isomer. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 9.21 (br s, 2 H), 8.49 (d, J = 6.0 Hz, 2 H), 8.31 (d, J = 5.2 Hz, 1 H), 7.34 (d, J = 4.8 Hz, 2 H), 6.88 (br s, 2 H), 6.34 (d, J = 5.2 Hz, 1 H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ = 163.1 (C), 159.1 (C), 145.8 (C), 133.1 (C), 159.5 (CH), 149.4 (2CH), 121.6 (2CH), 108.3 (CH).

E-9 isomer (spectra measured from a ~75:25 *Z/E* mixture). $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.67 (d, J = 6.0 Hz, 2 H), 8.10 (d, J = 5.6 Hz, 1 H), 7.29 (br s, 2 H), 7.22 (d, J = 4.4 Hz, 2 H), 6.99 (d, J = 5.6 Hz, 1 H), 6.27 (br s, 2 H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): 163.8 (C), 163.1 (C), 157.0 (CH), 150.1 (2CH), 140.2 (C), 138.4 (C), 124.6 (2CH), 104.4 (CH).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{N}_6$: 215.1039; found: 215.1040.

HPLC method B: purity > 95%, λ = 240 nm, t_{R} = 6.74 min.

(E)- and (Z)-Methyl 3-(2-aminopyrimidin-4-yl)-3-(pyridin-4-yl)prop-2-enoate (10)

To a solution of [(methoxycarbonyl)methylene]triphenylphosphorane prepared following the same procedure as described²⁴ (41.8 mg, 0.125 mmol) in 1 mL CH_2Cl_2 at room temperature was added potassium carbonate (34.6 mg, 0.250 mmol). The suspension was stirred for 10 min at this temperature and compound **5** (30 mg, 0.150 mmol) was finally added in one portion as a solid. The reaction mixture was stirred for 4 h, diluted with NaHCO_3 solution. The product was extracted with CH_2Cl_2 and combined organic layers were dried over MgSO_4 and evaporated. Purification by flash column chromatography using EtOAc/MeOH 98:2 to 95:5 gradient as eluent afforded 1st isomer of compound **E-10** (15.1 mg, 0.059 mmol) in 47% yield as a beige powder and later the 2nd isomer of compound **Z-10** (14.5 mg, 0.056 mmol) in 45% yield as a colorless oil.

Characterization data for **E-10**:

R_f = 0.12 (EtOAc).

IR (ATR): 3437-2790, 1709, 1639, 1545, 1431, 1413, 1269 cm^{-1} .

Mp: 121-122 °C (decomposition)

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.61 (d, J = 6.0 Hz, 2 H), 8.27 (d, J = 5.2 Hz, 1 H), 7.23 (d, J = 6.0 Hz, 2 H), 7.15 (s, 1 H), 6.82 (br s, 2 H), 6.16 (d, J = 4.8 Hz, 1 H), 3.55 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ = 165.0 (C), 163.3 (C), 161.7 (C), 149.7 (C), 144.4 (C), 160.1 (CH), 149.3 (2CH), 123.7 (2CH), 121.4 (CH), 108.8 (CH), 51.5 (CH_3).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2$: 257.1033; found: 257.1031.

HPLC method A: purity > 95%, λ = 240 nm, t_{R} = 16.99 min.

Characterization data for **Z-10**:

R_f = 0.08 (EtOAc).

IR (ATR): 3529-2831, 1721, 1623, 1549, 1456, 1278 cm^{-1} .

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.60 (d, J = 6.4 Hz, 2 H), 8.28 (d, J = 4.8 Hz, 1 H), 7.35 (d, J = 6.4 Hz, 2 H), 6.74 (s, 1 H), 6.73 (br s, 2 H), 6.50 (d, J = 4.8 Hz, 1 H), 3.60 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ = 165.0 (C), 164.4 (C), 163.5 (C), 149.2 (C), 144.5 (C), 158.4 (CH), 150.2 (2CH), 121.8 (2CH), 121.4 (CH), 109.7 (CH), 51.5 (CH_3).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2$: 257.1033; found: 257.1034.

HPLC method A: purity > 95%, λ = 240 nm, t_{R} = 16.71 min.

(±)-4-[2-(Pyridin-4-yl)oxiran-2-yl]pyrimidin-2-amine (11)

To a solution of compound **5** (50.2 mg, 0.251 mmol) in 1.5 mL CH_2Cl_2 at room temperature were added trimethylsulfoxonium iodide (110.4 mg, 0.501 mmol) and a freshly prepared sodium hydroxide solution (100 mg,

2.507 mmol of solid NaOH dissolved in 0.5 mL of water). The reaction mixture was refluxed overnight. Brine was added and the product was extracted with CH_2Cl_2 , combined organic layers were dried over MgSO_4 and evaporated. Purification by flash column chromatography using EtOAc/MeOH 98:2 to 96:4 gradient as eluent afforded compound **11** (35.6 mg, 0.166 mmol) in 66% yield as a beige powder.

R_f = 0.10 (EtOAc).

IR (ATR): 3421-2831, 1636, 1566, 1477, 1408 cm^{-1} .

Mp: 146-147 °C (decomposition)

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.58 (d, J = 4.4 Hz, 2 H), 8.28 (d, J = 5.2 Hz, 1 H), 7.43 (d, J = 4.4 Hz, 2 H), 6.77 (br s, 2 H), 6.58 (d, J = 5.2 Hz, 1 H), 3.40 (d, J = 5.6 Hz, 1 H), 3.26 (d, J = 5.2 Hz, 1 H).

$^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ = 165.7 (C), 163.2 (C), 146.2 (C), 159.5 (CH), 149.6 (2CH), 122.2 (2CH), 106.8 (CH), 59.7 (C-O), 55.2 (CH_2).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{N}_4\text{O}$: 215.0927; found: 215.0923.

HPLC method B: purity > 97%, λ = 240 nm, t_{R} = 6.39 min.

(±)-1-(2-Aminopyrimidin-4-yl)-2-azido-1-(pyridin-4-yl)ethan-1-ol (12)

To a solution of compound **11** (49 mg, 0.229 mmol) in 2 mL MeOH at room temperature were added sodium azide (44.6 mg, 0.686 mmol), ammonium chloride (27.6 mg, 0.517 mmol). The reaction mixture was refluxed overnight. Water was added and the product was extracted with CH_2Cl_2 , combined organic layers were washed with brine, dried over MgSO_4 and evaporated. Purification by flash column chromatography using EtOAc/MeOH 90:10 as eluent afforded compound **12** (47.9 mg, 0.186 mmol) in 81% yield as a beige powder.

R_f = 0.70 (EtOAc/MeOH 90:10).

IR (ATR): 3493, 3397-2550, 2099, 1630, 1571, 1468, 1223 cm^{-1} .

Mp: 149-150 °C

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.52 (d, J = 4.8 Hz, 2 H), 8.22 (d, J = 5.2 Hz, 1 H), 7.52 (d, J = 4.8 Hz, 2 H), 6.82 (d, J = 5.2 Hz, 1 H), 6.68 (br s, 2 H), 6.59 (s, 1 H), 4.05 (d, J = 12.4 Hz, 1 H), 3.89 (d, J = 12.4 Hz, 1 H).

$^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ = 171.0 (C), 162.8 (C), 151.7 (C), 159.1 (CH), 151.7 (2CH), 120.8 (2CH), 106.2 (CH), 77.6 (C-OH), 57.9 (CH_2).

HRMS (ESI+): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{N}_7\text{O}$: 258.1098; found: 258.1094.

HPLC method B: purity > 95%, λ = 240 nm, t_{R} = 6.55 min.

(±)-2-Amino-1-(2-aminopyrimidin-4-yl)-1-(pyridin-4-yl)ethan-1-ol (13)

To a solution of compound **12** (23.8 mg, 0.092 mmol) in 1 mL EtOH at room temperature was added palladium on charcoal (2.5 mg). The reaction mixture was placed under 1 atm H_2 and stirred at room temperature for 4 h. It was filtered through a short pad of Celite (Pasteur pipette) and washed with EtOH. The filtrate was evaporated and CH_2Cl_2 was added in three portions to remove solvent residues. Purification by reverse phase C18 column chromatography using $\text{H}_2\text{O}/\text{MeOH}$ gradient from 98:2 to 5:95 as eluent afforded compound **13** (11.8 mg, 0.051 mmol) in 55% yield as a white foam.

R_f = 0.20 (EtOAc/MeOH 1:1).

IR (ATR): 3467-2840, 1633, 1557, 1456, 1261 cm^{-1} .

Mp: 76-77 °C

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ = 8.48 (d, J = 6.0 Hz, 2 H), 8.17 (d, J = 5.2 Hz, 1 H), 7.51 (d, J = 4.8 Hz, 2 H), 6.80 (d, J = 5.2 Hz, 1 H), 6.62 (br s, 2 H), 5.96 (br s, 1 H), 3.35 (d, J = 13.6 Hz, 1 H), 3.02 (d, J = 13.6 Hz, 1 H). The NH_2

signal corresponding to the aminomethyl group was not visible on the spectrum.

¹³C NMR (101 MHz, DMSO-*d*₆): δ = 172.6 (C), 163.0 (C), 153.4 (C), 158.9 (CH), 149.4 (2CH), 121.2 (2CH), 107.1 (CH), 77.9 (C-OH), 50.8 (CH₂).

HRMS (ESI+): *m/z* [M+H]⁺ calcd for C₁₁H₁₄N₅O: 232.1193; found: 232.1189.

HPLC method B: purity > 95%, λ = 240 nm, t_R = 5.58 min.

Molecular Modeling

Structures were optimized using Gaussian 16 software³⁶ using DFT (density functional theory) method using B3LYP hybrid functional. Optimized geometries were obtained by relaxed potential energy surface scans with 6-31g basis set. Lower-energy structures were optimized in gas phase (B3LYP/6-31g+(d,p)) and vibrational frequencies were computed to check the absence of imaginary frequency. Gauge-Independent Atomic Orbital (GIAO) method was used for the calculation of NMR shielding tensors using the Gaussian 16 default solvation model (IEFPCM, DMSO), using mPW1PW91 functional and 6-311+G(d,p) or 6-311+G(2d,p) basis sets. Isotropic shield tensors were converted into δ chemical shifts using scaling factors reported by G.K. Pierens (with 6-311+G(2d,p) basis set).³⁷ Agreement between experimental and calculated NMR data was determined with the aid of DP4+ probability (using 6-311+G(d,p) basis set).³⁸⁻⁴⁰

Funding Information

This research was financed by the French government IDEX-ISITE initiative 16-IDEX-0001 (CAP 20-25) (Projet Emergence). We are also grateful to the Mésocentre Clermont Auvergne University for providing computing resources. The authors (FG, FA, PM) also thank WeylChem InnoTec (Frankfurt, Germany) for financial support.

Acknowledgment

The authors thank to Aurélie Job for HPLC analysis.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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