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

Francis Giraud*,a
Béatrice Josselin ${ }^{\text {b,c }}$ Sandrine Ruchaud ${ }^{\text {b }}$ Fabrice Anizon*,a Pascale Moreau*,a
${ }^{a}$ Université Clermont Auvergne, CNRS, Clermont Auvergne INP, ICCF, F-63000 Clermont-Ferrand, France.
${ }^{\text {b }}$ Sorbonne Université, CNRS, UMR8227, Integrative Biology of Marine Models Laboratory (LBI2M), Station Biologique de Roscoff, 29680 Roscoff, France
${ }^{\text {c }}$ Sorbonne Université, CNRS, FR2424, Plateforme de criblage KISSf (Kinase Inhibitor Specialized Screening facility), Station Biologique de Roscoff, 29680 Roscoff, France.

* indicates the main/corresponding author. Use another symbol to indicate equal contributions.
francis.giraud@uca.fr
fabrice.anizon@uca.fr
pascale.moreau@uca.fr


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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-
 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-4yl )(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 Cdclike 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-4yl )(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).


Scheme 1. Initial retrosynthetic pathway used to prepare the desired diheteroarylketone.

The preparation of starting materials $\mathbf{1 - 3}$ 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 amide ${ }^{7}$ afforded the desired compound. The only encouraging result was obtained from Weinreb amide $\mathbf{3}^{9,10}$ and organolithium derivative prepared from Boc-protected aminopyrimidine $\mathbf{2}^{8}$, leading to ketone 4 in 25\% yield (Scheme 2). Protecting group cleavage in TFA provided 5 in $76 \%$ yield.


Scheme 2. Synthesis of (2-aminopyrimidin-4-yl)(pyridin-4-yl)methanone 5.

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 iodinemagnesium 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 ammonia ${ }^{13}$,
ammonium acetate ${ }^{14}$ or benzylamines ${ }^{15,16}$ before reduction with $\mathrm{NaBH}_{4}$ did not afford expected amine derivatives. In these conditions, only the reduction product 7 (which could be prepared in $83 \%$ yield directly from $\mathbf{5}^{17}$ ) 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 $8\left(\mathrm{Mg} / \mathrm{HCOONH}_{4}{ }^{19}, \mathrm{Zn} / \mathrm{HCl} 2 \mathrm{M}^{20}\right)$ only resulted in recovered starting material or degradation. The attribution of ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR signals for each oxime isomer was performed using standard NMR experiments $\left({ }^{1} \mathrm{H}-{ }^{-1} \mathrm{H}\right.$ COSY, ${ }^{1} \mathrm{H}-{ }^{13} \mathrm{C}$ HSQC, ${ }^{1} \mathrm{H}-{ }^{13} \mathrm{C}$ HMBC). ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ 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 $\alpha-\operatorname{syn}-{ }^{13} \mathrm{C}$ of oximes are upshield shifted compared to $\alpha$-anti- ${ }^{13} \mathrm{C} .{ }^{21}$ Comparison of $\alpha-{ }^{13} \mathrm{C}$ chemical shifts for both isomers showed a similar behavior confirming the assignment. Indeed, pyridinyl $\alpha{ }^{-13} \mathrm{C}$ showed a chemical shift at $141.8 \mathrm{ppm}(\alpha$-anti) for the major $Z$-isomer, and $139,2 \mathrm{ppm}(\alpha-$ syn) for the minor $E$-isomer. Similarly, pyrimidinyl $\alpha-{ }^{13} \mathrm{C}$ was observed at $159.8 \mathrm{ppm}(\alpha-$-syn $)$ for the major $Z$-isomer and 161.7 ppm ( $\alpha$-anti) for the $E$-minor isomer. Additional assignment confirmation was provided by the calculation of ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR chemical shifts using Gaussian software, after geometry optimization calculations to produce the lowest-energy conformation for each isomer (Figure 2).


Scheme 3. Synthesis of new compounds 7-13.

As we found that (2-aminopyrimidin-4-yl)(pyridin-4yl)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. ${ }^{18} \mathrm{~A}$ crude mixture of $Z / E$ isomers was obtained, leading to $\boldsymbol{Z}$ - 9 in 57\% yield after column chromatography, as well as trace amount of $\boldsymbol{E - 9}$. Assignments
were performed by NMR from a mixture of both isomers. In the case of the $E$-isomer, ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}-\mathrm{NOESY}$ showed a correlation between hydrazone $\mathrm{NH}_{2}$, and a 3-pyridinyl proton. For the $Z$-isomer, weak NOE correlation was observed between hydrazone $\mathrm{NH}_{2}$ 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 upshield shift of $\alpha$-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 $\boldsymbol{Z}-10$ and $\boldsymbol{E - 1 0}$, respectively (Scheme 3). As above, ${ }^{1} \mathrm{H}-{ }^{1} \mathrm{H}$ 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 $\mathrm{LiAlH}_{4}$ in $\mathrm{THF}^{25}$ and compound $\mathbf{1 0}$ with magnesium turnings in MeOH. ${ }^{26}$ Nevertheless, no reduction of the $\mathrm{C}=\mathrm{C}$ 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 software ${ }^{27}$

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 713 were tested, as previously reported, ${ }^{31}$ toward 8 kinases (Haspin, CDK9/Cyclin T, GSK3 $\beta$, CK1 $\varepsilon$, CDK5/p25, Pim, CLK1 and DYRK1A). The percentage of residual kinase activity was evaluated in the presence of $10 \mu \mathrm{M}$ and $1 \mu \mathrm{M}$ 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 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 bisheteroaryl 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 ( v in $\mathrm{cm}^{-1}$ ). NMR spectra, performed on a Bruker AVANCE 400 III HD ( ${ }^{1} \mathrm{H}: 400 \mathrm{MHz},{ }^{13} \mathrm{C}: 101 \mathrm{MHz}$ ) or a Bruker AVANCE $500\left({ }^{1} \mathrm{H}: 500 \mathrm{MHz},{ }^{13} \mathrm{C}: 125 \mathrm{MHz}\right)$ 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, Universite Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40-63 $\mu \mathrm{m}$ 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 $\mathrm{mm} \times 250 \mathrm{~mm}, 5 \mathrm{~mm}$ ). Flow rate was $0.5 \mathrm{~mL} / \mathrm{min}$ and the analysis was performed at $25^{\circ} \mathrm{C}$ 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 $5: 95 \mathrm{~A} / \mathrm{B}$ 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 ${ }^{1} \mathrm{H}$ 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 $2(0.100 \mathrm{~g}, 0.239 \mathrm{mmol})$ and $\mathbf{3}(0.033 \mathrm{~g}, 0.196$ mmol ) in 3 mL of THF cooled to $-78^{\circ} \mathrm{C}$, was added $n$-BuLi $(0.265 \mathrm{~mL}, 1.6 \mathrm{M}$ solution in hexane). The reaction mixture was stirred for 4 h at $-78^{\circ} \mathrm{C}$ before a slow warm up to room temperature overnight. Water was added
before extraction with ethyl acetate. The combined organic phases were washed with a brine solution before drying over $\mathrm{MgSO}_{4}$ and evaporation under reduced pressure. The residue was purified by flash column chromatography using EtOAc/Pentane (3:7) to afford compound $4\left(R_{f}=\right.$ 0.25 ) in $25 \%$ yield ( $0.02 \mathrm{~g}, 0.050 \mathrm{mmol}$ ) as a green oil.

IR (ATR): 1753, 1722, 1535, 1412, $1245 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=9.21(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.83(\mathrm{~d}, J=6.0$ $\mathrm{Hz}, 1 \mathrm{H}$ ), $8.00(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.83(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.41(\mathrm{~s}, 18 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz 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), $83.6(2 \mathrm{C}), 27.9\left(6 \mathrm{CH}_{3}\right)$.
HRMS (ESI + ): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{25} \mathrm{~N}_{4} \mathrm{O}_{5}$ : 401.1819; found: 401.1812. $\mathrm{m} / \mathrm{z}\left[\mathrm{M}+\mathrm{CH}_{3} \mathrm{OH}+\mathrm{H}\right]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{29} \mathrm{~N}_{4} \mathrm{O}_{6}$ : 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 ( $0.026 \mathrm{~g}, 0.065$ $\mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(0.8 \mathrm{~mL})$ 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 $5\left(R_{f}=0.2\right)$ in $76 \%$ yield ( $0.010 \mathrm{~g}, 0.05 \mathrm{mmol}$ ) as a light green powder

Procedure B: To a solution of 4-iodopyridine ( $1.014 \mathrm{~g}, 4.948 \mathrm{mmol}$ ) in 3 mL THF under argon was added slowly ethylmagnesium bromide ( 6.2 mL of a $0.8 \mathrm{~mol} / \mathrm{L}$ solution in THF, 4.948 mmol ). The suspension was stirred for 1 h at room temperature. In a second flask, a solution of compound $\mathbf{6}$ ( $148.6 \mathrm{mg}, 1.237 \mathrm{mmol}$ ) in 3 mL THF under argon was prepared. To this solution was slowly transferred the Grignard reagent and the reaction mixture was heated at $50^{\circ} \mathrm{C}$ overnight. After cooling, HCl 1 N solution (10 mL ) was added and stirring was continued for 30 min at room temperature. The reaction was poured on a saturated $\mathrm{NaHCO}_{3}$ 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 $\mathrm{MgSO}_{4}$ 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, $1233 \mathrm{~cm}^{-1}$.
Mp: $162-163{ }^{\circ} \mathrm{C}$ (decomposition)
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ): $\delta=8.81(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 8.56(\mathrm{~d}, J=4.8$ $\mathrm{Hz}, 1 \mathrm{H}), 7.83(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.04(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 7.02(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=193.0$ (CO), 163.1 (C), 160.5 (C), 141.8 (C), 160.7 (CH), 150.3 (2CH), 123.3 (2CH), 107.9 (CH).

HRMS (ESI+): $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{10} \mathrm{H}_{9} \mathrm{~N}_{4} \mathrm{O}$ : 201.0771; found: 201.0770 HPLC method B: purity $>96 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=5.33 \mathrm{~min}$.

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

To a solution of compound $\mathbf{1}(1.228 \mathrm{~g}, 5.556 \mathrm{mmol})$ in pyridine ( 14 mL ) at room temperature under argon was added copper cyanide ( $0.547 \mathrm{~g}, 6.112$ mmol ). The mixture was heated at $115^{\circ} \mathrm{C}$ 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 $\mathrm{MgSO}_{4}$ 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 $\mathrm{NaHCO}_{3}$ solution and large amount of water. After drying over $\mathrm{MgSO}_{4}$ and evaporation compound 6 ( $0.640 \mathrm{~g}, 5.328$ mmol ) was obtained in $95 \%$ yield as a yellow powder.
Experimental data were in accordance with literature. ${ }^{34}$

To a solution of compound $\mathbf{5}$ ( $30.9 \mathrm{mg}, 0.154 \mathrm{mmol}$ ) in 1 mL absolute EtOH at $0^{\circ} \mathrm{C}$ under argon was added sodium borohydride $(8.7 \mathrm{mg}, 0.231 \mathrm{mmol})$. The reaction mixture was warmed at room temperature and stirred for 75 min. Water and $\mathrm{NaHCO}_{3}$ 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 ( $26.2 \mathrm{mg}, 0.129$ mmol ) was isolated in $83 \%$ yield as a beige powder.
$R_{f}=0.10$ (EtOAc).
IR (ATR): 3363-2674, 1739, 1652, 1567, $1216 \mathrm{~cm}^{-1}$.
Mp: $125-126^{\circ} \mathrm{C}$
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $\mathrm{d}_{6}$ ): $\delta=8.50(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 8.21(\mathrm{~d}, J=4.8$ $\mathrm{Hz}, 1 \mathrm{H}), 7.38(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.74(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.58(\mathrm{br} \mathrm{s}, 2 \mathrm{H})$, $6.27(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.38(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, 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+): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{10} \mathrm{H}_{11} \mathrm{~N}_{4} \mathrm{O}$ : 203.0927; found: 203.0923.

HPLC method B: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=5.24 \mathrm{~min}$.

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

To a solution of compound $\mathbf{5}$ ( $42.7 \mathrm{mg}, 0.213 \mathrm{mmol}$ ) in $3 \mathrm{~mL} \mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}$ 4:1 at room temperature were successively added hydroxylamine hydrochloride ( $23.7 \mathrm{mg}, 0.341 \mathrm{mmol}$ ) and sodium acetate ( $34.9 \mathrm{mg}, 0.426$ mmol ). The mixture was stirred at $100{ }^{\circ} \mathrm{C}$ 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 ( $26.0 \mathrm{mg}, 0.121 \mathrm{mmol}$ ) in $56 \%$ yield as a white powder. 6:4 Z/E mixture was observed by ${ }^{1}$ H NMR.
$R_{f}=0.15$ (EtOAc).
IR (ATR): 3471-2993, 1562, 1451, $1226 \mathrm{~cm}^{-1}$.
$\mathrm{Mp}>250^{\circ} \mathrm{C}$
Z-8 isomer. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=12.11$ (br s, 1 H ), 8.57 ( $\mathrm{d}, \mathrm{J}=$ $5.2 \mathrm{~Hz}, 2 \mathrm{H}), 8.35(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.81(\mathrm{br} \mathrm{s}, 2$ H), $6.68(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=163.8$ (C), 159.8 (C), 151.7 (C), 141.8 (C), 158.7 (CH), 149.9 (2CH), 120.7 (2CH), 110.5 (CH).
$\boldsymbol{E}-\mathbf{8}$ isomer. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{DMSO}-\mathrm{d}_{6}$ ): $\delta=12.20(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.63(\mathrm{~d}, \mathrm{~J}=$ $4.4 \mathrm{~Hz}, 2 \mathrm{H}), 8.27(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.31(\mathrm{~d}, J=5.6 \mathrm{~Hz}, 2 \mathrm{H}), 6.98(\mathrm{~d}, J=5.2$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 6.60 (br s, 2 H$).{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO-d $\mathrm{d}_{6}$ : $\delta=163.3$ (C), 161.7 (C), 152.9 (C), 139.7 (C), 158.5 (CH), 149.2 (2CH), 124.1 (2CH), 106.3 (CH).

HRMS (ESI+): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{~N}_{5} \mathrm{O}$ : 216.0880; found: 216.0878.

HPLC method B: purity $>99 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=6.55 \mathrm{~min}$.
(E/Z)-(2-Aminopyrimidin-4-yl)(pyridin-4-yl)methanone hydrazone (9)

To a solution of compound $\mathbf{5}$ ( $74.5 \mathrm{mg}, 0.372 \mathrm{mmol}$ ) in $7 \mathrm{~mL} \mathrm{EtOH} / \mathrm{H}_{2} \mathrm{O}$ 4:1 at room temperature were successively added hydrazine monohydrochloride ( $40.8 \mathrm{mg}, 0.595 \mathrm{mmol}$ ) and sodium acetate $(61.0 \mathrm{mg}$, 0.744 mmol ). The mixture was stirred at $100^{\circ} \mathrm{C}$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to $\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 88: 12$ as eluent afforded compound $\boldsymbol{Z}$ - 9 ( $46.1 \mathrm{mg}, 0.215 \mathrm{mmol}$ ) in $57 \%$ yield as a white powder.
$R_{f}=0.20$ and $R_{f}=0.32(E t O A c / \mathrm{MeOH} 9: 1)$.
IR (ATR): 3400-2615, 1641, 1575, 1547, 1448, $1411 \mathrm{~cm}^{-1}$.
Mp: 206-208 ${ }^{\circ} \mathrm{C}$ (decomposition)

Z-9 isomer. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=9.21$ (br s, 2 H ), 8.49 (d, $J=$ $6.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.31(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.34(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.88(\mathrm{br} \mathrm{s}, 2$ H), $6.34(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $\mathrm{d}_{6}$ ): $\delta=163.1$ (C), 159.1 (C), 145.8 (C), 133.1 (C), 159.5 (CH), 149.4 (2CH), 121.6 (2CH), 108.3 (CH).
$\boldsymbol{E}-9$ isomer (spectra measured from a $\sim 75: 25 \mathrm{Z} / E$ mixture). ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ): $\delta=8.67(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 8.10(\mathrm{~d}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.29$ (br s, 2 H ), 7.22 (d, $J=4.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $6.99(\mathrm{~d}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.27(\mathrm{br} \mathrm{s}, 2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO-d $\mathrm{d}_{6}$ ): 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+): $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{10} \mathrm{H}_{11} \mathrm{~N}_{6}$ : 215.1039; found: 215.1040. HPLC method B: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=6.74 \mathrm{~min}$.
(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 described ${ }^{24}$ ( $41.8 \mathrm{mg}, 0.125$ mmol ) in $1 \mathrm{~mL} \mathrm{CH} \mathrm{Cl}_{2}$ at room temperature was added potassium carbonate ( $34.6 \mathrm{mg}, 0.250 \mathrm{mmol}$ ). The suspension was stirred for 10 min at this temperature and compound $\mathbf{5}(30 \mathrm{mg}, 0.150 \mathrm{mmol})$ was finally added in one portion as a solid. The reaction mixture was stirred for 4 h , diluted with $\mathrm{NaHCO}_{3}$ solution. The product was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and combined organic layers were dried over $\mathrm{MgSO}_{4}$ and evaporated. Purification by flash column chromatography using EtOAc/MeOH 98:2 to 95:5 gradient as eluent afforded $1^{\text {st }}$ isomer of compound $\boldsymbol{E}-\mathbf{1 0}(15.1 \mathrm{mg}$, $0.059 \mathrm{mmol})$ in $47 \%$ yield as a beige powder and later the $2^{\text {nd }}$ isomer of compound $\boldsymbol{Z}$-10 ( $14.5 \mathrm{mg}, 0.056 \mathrm{mmol}$ ) in $45 \%$ yield as a colorless oil. Characterization data for $\mathbf{E - 1 0}$ :
$R_{f}=0.12$ (EtOAc).
IR (ATR): 3437-2790, 1709, 1639, 1545, 1431, 1413, $1269 \mathrm{~cm}^{-1}$.
Mp: 121-122 ${ }^{\circ} \mathrm{C}$ (decomposition)
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=8.61(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.27(\mathrm{~d}, J=5.2$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 7.23 (d, $J=6.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.15 ( $\mathrm{s}, 1 \mathrm{H}), 6.82(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 6.16(\mathrm{~d}, J=$ $4.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.55 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ): $\delta=165.0$ (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), $51.5\left(\mathrm{CH}_{3}\right)$.

HRMS (ESI + ): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{13} \mathrm{H}_{13} \mathrm{~N}_{4} \mathrm{O}_{2}$ : 257.1033; found: 257.1031.

HPLC method A: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=16.99 \mathrm{~min}$.
Characterization data for Z-10:
$R_{f}=0.08$ (EtOAc).
IR (ATR): 3529-2831, 1721, 1623, 1549, 1456, $1278 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ): $\delta=8.60(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.28(\mathrm{~d}, J=4.8$ $\mathrm{Hz}, 1 \mathrm{H}$ ), $7.35(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.74(\mathrm{~s}, 1 \mathrm{H}), 6.73(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 6.50(\mathrm{~d}, J=$ $4.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.60 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO-d $\mathrm{d}_{\text {) }}$ : $\delta=165.0$ (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), $51.5\left(\mathrm{CH}_{3}\right)$.

HRMS (ESI+): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{13} \mathrm{H}_{13} \mathrm{~N}_{4} \mathrm{O}_{2}$ : 257.1033; found: 257.1034.

HPLC method A: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=16.71 \mathrm{~min}$.

## ( $\mathbf{\pm}$ )-4-[2-(Pyridin-4-yl)oxiran-2-yl]pyrimidin-2-amine (11)

To a solution of compound $\mathbf{5}(50.2 \mathrm{mg}, 0.251 \mathrm{mmol})$ in $1.5 \mathrm{mLCH}_{2} \mathrm{Cl}_{2}$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, combined organic layers were dried over $\mathrm{MgSO}_{4}$ and evaporated. Purification by flash column chromatography using EtOAc/MeOH 98:2 to 96:4 gradient as eluent afforded compound 11 (35.6 $\mathrm{mg}, 0.166 \mathrm{mmol}$ ) in $66 \%$ yield as a beige powder.
$R_{f}=0.10$ ( EtOAc ).
IR (ATR): 3421-2831, 1636, 1566, 1477, $1408 \mathrm{~cm}^{-1}$.
Mp: 146-147 ${ }^{\circ} \mathrm{C}$ (decomposition)
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ): $\delta=8.58(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.28(\mathrm{~d}, J=5.2$ $\mathrm{Hz}, 1 \mathrm{H}), 7.43(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.77(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 6.58(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H})$, $3.40(\mathrm{~d}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.26(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $\mathrm{d}_{6}$ ): $\delta=165.7$ (C), 163.2 (C), 146.2 (C), 159.5 $(\mathrm{CH}), 149.6(2 \mathrm{CH}), 122.2(2 \mathrm{CH}), 106.8(\mathrm{CH}), 59.7(\mathrm{C}-0), 55.2\left(\mathrm{CH}_{2}\right)$.

HRMS (ESI+): $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{~N}_{4} \mathrm{O}: ~ 215.0927$; found: 215.0923.

HPLC method B: purity $>97 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=6.39 \mathrm{~min}$.

## ( $\pm$ )-1-(2-Aminopyrimidin-4-yl)-2-azido-1-(pyridin-4-yl)ethan-1-ol (12)

To a solution of compound $\mathbf{1 1}(49 \mathrm{mg}, 0.229 \mathrm{mmol})$ in 2 mL MeOH at room temperature were added sodium azide ( $44.6 \mathrm{mg}, 0.686 \mathrm{mmol}$ ), ammonium chloride ( $27.6 \mathrm{mg}, 0.517 \mathrm{mmol}$ ). The reaction mixture was refluxed overnight. Water was added and the product was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, combined organic layers were washed with brine, dried over $\mathrm{MgSO}_{4}$ 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, $1223 \mathrm{~cm}^{-1}$.
Mp: $149-150{ }^{\circ} \mathrm{C}$
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ): $\delta=8.52(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.22(\mathrm{~d}, J=5.2$ $\mathrm{Hz}, 1 \mathrm{H}), 7.52(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.82(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.68(\mathrm{br} \mathrm{s}, 2 \mathrm{H})$, $6.59(\mathrm{~s}, 1 \mathrm{H}), 4.05(\mathrm{~d}, \mathrm{~J}=12.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.89(\mathrm{~d}, J=12.4 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $\mathrm{d}_{6}$ ): $\delta=171.0$ (C), 162.8 (C), 151.7 (C), 159.1 (CH), 151.7 (2CH), $120.8(2 \mathrm{CH}), 106.2(\mathrm{CH}), 77.6(\mathrm{C}-\mathrm{OH}), 57.9\left(\mathrm{CH}_{2}\right)$.

HRMS (ESI+): m/z [M+H]+ calcd for $\mathrm{C}_{11} \mathrm{H}_{12} \mathrm{~N} 7 \mathrm{O}: 258.1098$; found: 258.1094.

HPLC method B: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=6.55 \mathrm{~min}$.

## ( $\pm$ )-2-Amino-1-(2-aminopyrimidin-4-yl)-1-(pyridin-4-yl)ethan-1-ol (13)

To a solution of compound 12 ( $23.8 \mathrm{mg}, 0.092 \mathrm{mmol}$ ) in 1 mL EtOH at room temperature was added palladium on charcoal ( 2.5 mg ). The reaction mixture was placed under $1 \mathrm{~atm} \mathrm{H}_{2}$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added in three portions to remove solvent residues. Purification by reverse phase C18 column chromatography using $\mathrm{H}_{2} \mathrm{O} / \mathrm{MeOH}$ gradient from 98:2 to 5:95 as eluent afforded compound $\mathbf{1 3}$ ( $11.8 \mathrm{mg}, 0.051 \mathrm{mmol}$ ) in $55 \%$ yield as a white foam.
$R_{f}=0.20$ (EtOAc/MeOH 1:1).
IR (ATR): 3467-2840, 1633, 1557, 1456, $1261 \mathrm{~cm}^{-1}$.
Mp: $76-77^{\circ} \mathrm{C}$
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ): $\delta=8.48(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), $8.17(\mathrm{~d}, J=5.2$ $\mathrm{Hz}, 1 \mathrm{H}), 7.51(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.80(\mathrm{~d}, J=5.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.62(\mathrm{br} \mathrm{s}, 2 \mathrm{H})$, 5.96 (br s, 1 H$), 3.35(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.02(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H})$. The $\mathrm{NH}_{2}$
signal corresponding to the aminomethyl group was not visible on the spectrum.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ): $\delta=172.6$ (C), 163.0 (C), 153.4 (C), 158.9 $(\mathrm{CH}), 149.4(2 \mathrm{CH}), 121.2(2 \mathrm{CH}), 107.1(\mathrm{CH}), 77.9(\mathrm{C}-\mathrm{OH}), 50.8\left(\mathrm{CH}_{2}\right)$.
HRMS (ESI+): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{~N}_{5} \mathrm{O}$ : 232.1193; found: 232.1189.

HPLC method B: purity $>95 \%, \lambda=240 \mathrm{~nm}, \mathrm{t}_{\mathrm{R}}=5.58 \mathrm{~min}$.

## Molecular Modeling

Structures were optimized using Gaussian 16 software ${ }^{36}$ using DFT (density functional theory) method using B3LYP hybrid functional. Optimized geometries were obtained by relaxed potential energy surface scans with $6-31 \mathrm{~g}$ 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. GaugeIndependent 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 $311+G(2 d, p)$ basis sets. Isotropic shield tensors were converted into $\delta$ chemical shifts using scaling factors reported by G.K. Pierens (with 6 $311+G(2 d, p)$ 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). ${ }^{38-40}$

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## 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.

## References

(1) Tazarki, H.; Zeinyeh, W.; Esvan, Y. J.; Knapp, S.; Chatterjee, D.; Schröder, M.; Joerger, A. C.; Khiari, J.; Josselin, B.; Baratte, B.; Bach, S.; Ruchaud, S.; Anizon, F.; Giraud, F.; Moreau, P. Eur. J. Med. Chem. 2019, 166, 304.
(2) Esvan, Y. J.; Zeinyeh, W.; Boibessot, T.; Nauton, L.; Théry, V.; Knapp, S.; Chaikuad, A.; Meijer, L.; Anizon, F.; Giraud, F.; Moreau, P. Eur. J. Med. Chem. 2016, 118, 170.
(3) Jung. H.-S.; Kim, S.-H. Tetrahedron Lett. 2015, 56, 1004.
(4) Yu, L.; Ren, L.; Chen, T.; Yi, R.; Wu, Y.; Guo, R. Org. Prep. Proced. Int. 2012, 44, 169.
(5) Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T. B.; Yang, Z.; Lei, A. Org. Lett. 2008, 10, 2661.
(6) Linke, S.; Manolikakès, S. M.; Auffrant, A.; Gosmini, C. Synthesis 2018, 50, 2595.
(7) Bejugam M., Hosahalli S., Mahalingam N. WO2014125426, 2014.
(8) Singh, K.; Singh,K.; Balzarini, J. Eur. J. Med. Chem. 2013, 67, 428.
(9) Peixoto, P. A.; Boulangé, A. Leleu, S.; Franck, X. Eur. J. Org. Chem 2013, 3316.
(10) Delaine, T.; Bernardes-Génisson, V.; Meunier, B.; Bernadou, J. J. Org. Chem. 2007, 72, 675.
(11) Thomann A., Brengel C., Börger C., Kail D., Steinbach A., Empting M., Hartmann R.W. ChemMedChem 2016, 11, 2522
(12) Doláková P., Masojídková M., Holy A. Heterocycles 2007, 71, 1107.
(13) Emerson W.S. Org. React. 1948, 4, 174.
(14) Dong L., Aleem S., Fink C.A. Tetrahedron Lett. 2010, 51, 5210.
(15) Chandrasekhar S., Reddy C.R., Ahmed M. Synlett 2000, 11, 1655.
(16) Takeru M., Nadja E.N., Baudoin O. Ang. Chem. Int. Ed. 2022, 61, e202116101.
(17) Yang Y., Gao X., Zeng X., Han J., Xu B. Chem. Eur. J. 2021, 27, 1297.
(18) Patra T., Das M., Daniliuc C.G., Glorius F. Nature Catalysis 2021, 4, 54
(19) Abiraj K., Gowda D.C. Synth. Comm. 2004, 34, 599.
(20) Poschalko A., Welzig S., Treu M., Nerdinger S., Mereiter K., Jordis U. Tetrahedron 2002, 58, 1513.
(21) Hawkes, G. E.; Herwig, K.; Roberts J. D. J. Org. Chem. 1974, 39, 1017.
(22) Fraser, R. R.; Dhawan, K. L.; Taymaz, K. Org. Magn. Res. 1978, 11, 269.
(23) Bunnell, C. A.; Fuchs, P. L. J. Org. Chem. 1977, 42, 2614.
(24) Nyhlen J., Eriksson L., Bäckvall J.-E. Chirality 2008, 20, 47.
(25) Cohen, S. G.; Wang, C. H. J. Am. Chem. Soc. 1955, 77, 2457.
(26) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. Tetrahedron Lett. 1987, 28, 5287.
(27) Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. J. Comput. Chem. 2004, 25, 1605.
(28) Corey E.J., Chaykovsky M., J. Am. Chem. Soc. 1965, 87, 1353.
(29) Kempf D.J., De Lara E., Stein H.H., Cohen J., Plattner J.J. J. Med. Chem. 1987, 30, 1978.
(30) Reitz A.B., Tuman R.W., Marchione C.S., Jordan Jr. A.D., Bowden C.R., Maryanoff B.E. J. Med. Chem. 1989, 32, 2110.
(31) Zeinyeh, W.; Esvan, Y. J.; Josselin, B.; Defois, M.; Baratte, B.; Knapp, S.; Chaikuad, A.; Anizon, F.; Giraud, F.; Ruchaud, S.; Moreau P. Eur. J. Med Chem. 2022, 236, 114369.
(32) Zehnder, L.; Bennett, M.; Meng, J.; Huang, B.; Ninkovic, S.; Wang, F.; Braganza, J.; Tatlock, J.; Jewell, T.; Zhou, J. Z.; Burke, B.; Wang, J. Maegley, K.; Mehta, P. P.; Yin, M.-J.; Gajiwala, K. S.; Hickey, M. J. Yamazaki, S.; Smith, E.; Kang, P.; Sistla, A.; Dovalsantos, E.; Gehring M. R.; Kania, R.; Wythes, M.; Kung, P.-P.J. Med. Chem. 2011, 54, 3368 Minakawa, N.; Kojima, N.; Hikishima, S.; Sasaki, T.; Kiyosue, A.; Atsumi, N.; Ueno, Y.; Matsuda, A. J. Am. Chem. Soc. 2003, 125, 9970. Reichelt, A.; Bailis, J. M.; Bartberger, M. D.; Yao, G.; Shu, H.; Kaller, M R.; Allen, J. G.; Weidner, M. F.; Keegan, K. S.; Dao, J. H. Eur. J. Med Chem. 2014, 80, 364.
(35) Walker, S. R.; Czyz, M. L.; Morris, J. C. Org. Lett. 2014, 16, 708.

Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N. Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.
(37) Pierens, G. K. J. Comput. Chem. 2014, 35, 1388.
(38) Grimblat, N.; Zanardi, M. M.; Sarotti, A. M. J. Org. Chem. 2015, 80, 24, 12526.
(39) Marcarino, M. O.; Cicetti, S.; Zanardi, M. M.; Sarotti, A. M. Nat. Prod. Rep. 2022, 39, 58.
(40) Cortés, I; Sarotti, A. M. Org. Biomol. Chem. 2023, 21, 2935.

