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ARTICLE

Iodine-promoted Radical Alkyl Sulfuration of Imidazopyridines with Dialkyl Azo Compounds and Elemental Sulfur

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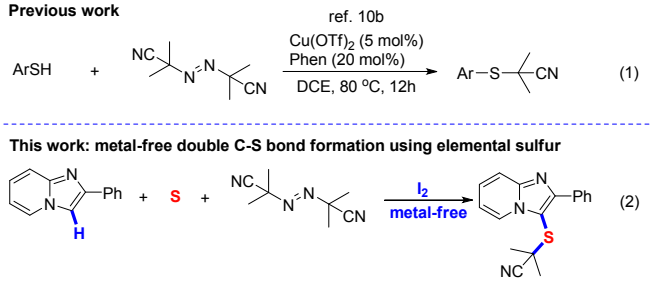
Yong-Chao Gao,[a] Zhuo-Bin Huang,[a] Li Xu,[a] Zhao-Dong Li,*[a] Zhi-Sheng Lai,[a] Ri-Yuan Tang*[ab]

Dialkyl azo compounds were found to be effective alkyl radical sources for direct alkyl sulfuration with imidazopyridines using elemental sulfur under metal-free conditions. Iodine, an inexpensive and mild reagent, could promote the alkyl sulfuration. A variety of quaternary cyanoalkyl radicals were successfully coupled with elemental sulfur. A subsequent C-H sulfuration of the imidazopyridines afforded a diverse array of imidazopyridine derivatives bearing cyanoalkylthio groups. The cyano group could be modified and further underwent condensation with 2-aminothiazole to afford an interesting heterocyclic amide. Control experiments showed that iodine could greatly suppress the self-coupling of cyanoalkyl radical, thus made the sulfuration proceeded smoothly.

Introduction

Elemental sulfur is an inexpensive, nontoxic, odourless, stable, and easily handled powder and is an ideal sulfur source for the synthesis of sulfur-containing compounds.[1] Coupling of two different molecules using elemental sulfur through a C–H sulfuration provides an economic and efficient route to a diverse range of sulfur-containing compounds. The direct sulfuration of drug skeletons using elemental sulfur enables access to biologically useful molecules.[2] Imidazopyridines are privileged scaffolds that have been widely used in medicinal chemistry.[3-5,7] The C-H sulfuration of an imidazopyridine backbone using elemental sulfur avoids the use of odorous and highly toxic thiols.[6-9] In recent years, an aryl sulfuration of imidazoheterocycles with elemental sulfur and aryl iodides or aryl boric acid, has been developed.[7] Recently, our group has also developed an oxidative radical dual C–H sulfuration of imidazopyridines with ethers or alkanes,[8] and a metal-free sulfuration with a diverse range of functionalized haloalkanes using elemental sulfur.[9] Although progress has been made, the C–H alkylthionation of imidazopyridines using elemental sulfur has not been widely reported. The development of new pharmaceutically useful alkyl reaction partners for the C–H sulfuration of imidazopyridines is greatly desired. We envisaged that dialkyl azo compounds (such as AIBN and related analogues) bearing different functional groups would be attractive reaction partners for such a transformation. AIBN is able to give cyanoalkyl [10] or cyano radicals,[11] which are useful species for chemical transformations. For example, Cheng and coauthors developed a copper-catalyzed cyanation of disulfides with AIBN. This provides an effective pathway for the preparation of thiocyanates.[11d] During the development of this work, Lei and coauthors reported an elegant method for the synthesis of alkylthionitrile derivatives via a copper-catalyzed radical coupling of aryl thiols with AIBN (Scheme 1, eqn 1).[10b] Compared with Lei's work, the coupling of cyanoalkyl radical with elemental sulfur and imidazopyridines is challenging because elemental sulfur is less reactive than thiol, and the cyanoalkyl radical readily undergoes a self-coupling reaction.[12] Thus, the self-coupling of the cyanoalkyl radical must be inhibited for selective cyanoalkyl sulfuration of imidazopyridines. We envisioned that iodine may capture the cyanoalkyl radical to form an iodide compound for next alkyl sulfuration[9] and may be able to accelerate the sulfuration.[5g] Based on these assumptions, we developed an iodine promoted alkylthionation of imidazopyridines with elemental sulfur and dialkyl azo compounds involving a radical process (Scheme 1, eqn 2).



Scheme 1. Sulfuration with dialkyl azo compounds.

Results and discussion

Our studies began with the three-component sulfuration of imidazopyridine **1a** with elemental sulfur and AIBN. Based on our

[a]Department of Applied Chemistry, College of Materials and Energy, South China Agricultural University, Guangzhou 510642, China. E-mail: rytang@scau.edu.cn
[b]Key Laboratory of Natural Pesticide & Chemical Biology, Ministry of Education, South China Agricultural University, Guangzhou 510642, China.
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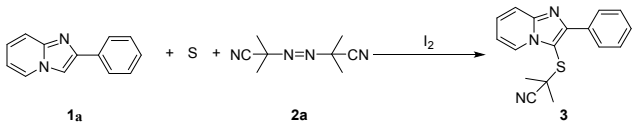
previous work,[5d, 5g] we envisioned that iodine may facilitate the cleavage of the S-S bond in S_8 to form a reactive sulfur species for the sulfuration of imidazopyridines. Thus, the reaction was carried out with two equivalents of iodine with different solvents (Table 1, entries 1-7). Solvents, such as DMF, NMP, DMSO, and dioxane, were not suitable (Table 1, entries 1-3 and 6). Reactions in DCE and toluene gave the desired product **3** in 12% and 17% yield, respectively (Table 1, entries 4 and 5). To our delight, CH_3CN was found to be the best solvent giving product **3** in 56% yield (Table 1, entry 7). In the absence of iodine, the reaction still proceeded in CH_3CN, but product **3** was obtained in only 18% yield (Table 1, entry 8). Next, the influence of the amount of iodine on the reaction was examined. The yield of product **3** decreased to 48% when 0.5 equivalents of iodine were used (Table 1, entry 9). The desired product was obtained in 76% yield in the presence of 1 equivalent of iodine (Table 1, entry 10), whereas the desired product **3** was obtained in 70% yield when the amount of iodine was increased to 1.5 equivalents (Table 1, entry 11). No reaction occurred at room temperature (Table 1, entry 12). Reaction at 100 °C gave the best yield of product. Deviation from a temperature of 100 °C led to a decrease in yield of **3** (Table 1, entries 13 and 14) and a 3-iodo-2-phenylimidazo[1,2-a]pyridine product was observed when the reaction was conducted at 80 °C. The product yield decreased to 54% in the presence of 0.5 equivalent of **2a** (Table 1, entry 15), whereas the product yield increased to 83% when using 2 equivalents of **2a** (Table 1, entry 16).

Table 1. Screening of Optimal Conditions[a]



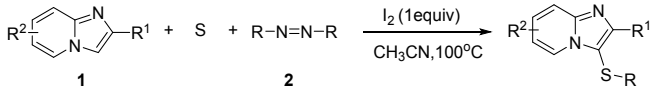
1a **2a** **3**

Entry	Iodine (equiv)	Solvent (ml)	Temp (°C)	Yield[b] (%)
1	I_2 (2)	DMF	100	0
2	I_2 (2)	NMP	100	0
3	I_2 (2)	DMSO	100	0
4	I_2 (2)	DCE	100	12
5	I_2 (2)	PhMe	100	17
6	I_2 (2)	Dioxane	100	Trace
7	I_2 (2)	CH_3CN	100	56
8	—	CH_3CN	100	18
9	I_2 (0.5)	CH_3CN	100	48
10	I_2 (1)	CH_3CN	100	76
11	I_2 (1.5)	CH_3CN	100	70
12	I_2 (1)	CH_3CN	rt	0
13	I_2 (1)	CH_3CN	80	Trace
14	I_2 (1)	CH_3CN	120	73
15[b]	I_2 (1)	CH_3CN	100	54
16[c]	I_2 (1)	CH_3CN	100	83

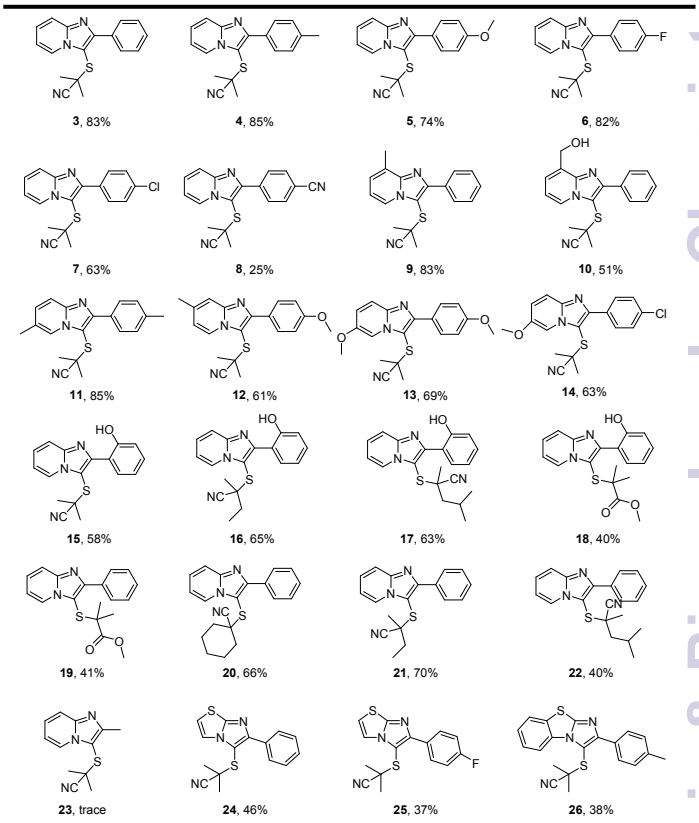
[a] Reaction conditions: **1a** (0.2 mmol), S (0.4 mmol, 2 equiv), **2a** (0.2 mmol, 1 equiv), solvent (1 mL), at 100 °C for 12 h. [b] **2a** (0.1 mmol, 0.5 equiv). [c] **2a** (0.4 mmol, 2 equiv).

With this metal-free C-H alkylthionation procedure in hand, the substrate scope was investigated (Table 2). Initially, a variety of 2-aryl imidazopyridines were subjected to reaction with AIBN (products **3–15**). Substituents on the benzene ring, including methyl, methoxy, fluoro, chloro, and cyano groups, were tolerated to give their corresponding products in moderate to good yields (products **4–8**). A substrate bearing a methyl group on the pyridine ring provided good reactivity, giving the corresponding product **9** in 85% yield. Interestingly, a hydroxyl group was also tolerated to afford product **10** in 51% yield. Disubstituted methyl, methoxy and chloro substrates were also amenable to the reaction conditions, giving the desired products **11**-**14** in moderate to good yields. 2-(imidazo[1,2-a]pyridin-2-yl)phenol is an excellent fluorescent molecule that is also suitable for such transformations.[13] Other AIBN analogues were also successfully reacted with 2-(imidazo[1,2-a]pyridin-2-yl)phenol.

Table 2. Reaction scope[a]



1 **2**



[a] Reaction conditions: **1** (0.2 mmol), **S** (0.4 mmol, 2 equiv), **2** (0.4mmol, 2 equiv), **I_2** (0.2 mmol, 1 equiv) in CH_3CN (1 mL) at 100 °C for 12 h.

To our delight, fluorescent molecules **15**-**18** could be prepared in moderate yields. It is worth noting that these fluorescent

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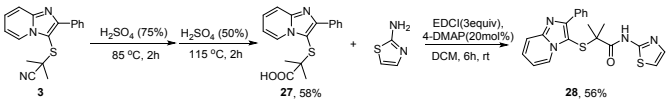
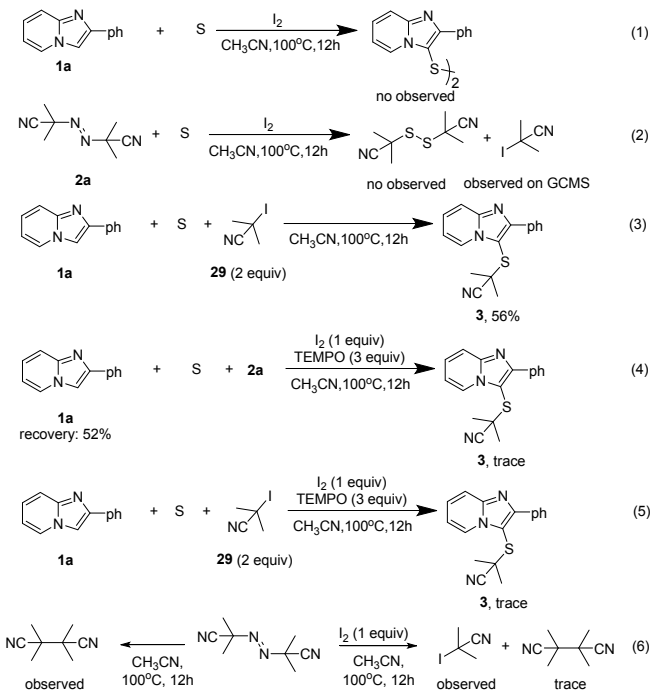
molecules bearing a cyano or an ester group can be subjected to further transformations. Next, other AIBN analogues were also subjected to reaction with 2-phenyl imidazopyridine and their corresponding products **19**-**22** were obtained in moderate yields. Although the cyanocyclohexyl group is sterically demanding, reaction with the corresponding dialkyl azo compound afforded product **20** in 66% yield. However, 2-methyl imidazopyridine did not react successfully with this compound possibly due to the conjugative effect of the benzene ring being important for such transformations. Imidazothiazoles were also employed under the optimal reaction conditions, but their reactivity proved to be lower than that of the imidazopyridines (products **24**-**26**). An electron-withdrawing group (e.g. cyano or nitro) on the pyridine ring would greatly suppress the reaction, and only a trace amount of product was observed.

Next, further modification of the cyano group of product **3** was conducted. The hydrolysis of compound **3** was carried out to afford the carboxylic acid **27** in 58% yield. The condensation of compound **27** with 2-aminothiazole gave amide **28** in 56% yield (scheme 2). Compound **28**, which possesses an imidazopyridine and a thiazole motif, is of great interest in medicinal chemistry.



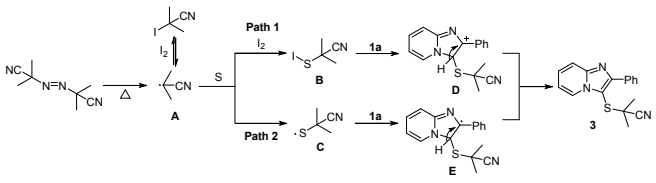
Scheme 2 Modification of the cyano group.



Scheme 3 Control experiments.

In order to elucidate the reaction mechanism, the control experiments shown in Scheme 3 were conducted. In the presence of iodine, the reaction of imidazopyridine **1a** with elemental sulfur did not produce the corresponding heterocyclic disulfide, suggesting that elemental sulfur may firstly react with AIBN (Eqn 1). The reaction of AIBN with elemental sulfur did not produce the corresponding cyanoalkyl disulfide, only 2-iodo-2-methylpropanenitrile **29** was observed according to GC-MS. We speculated that 2-iodo-2-methylpropanenitrile may be a reaction intermediate (Eqn 2). The reaction still proceeded in the absence of iodine when 2-iodo-2-methylpropanenitrile **29** was used in place of AIBN, giving product **3** in 56% yield (Eqn 3). AIBN is a good radical initiator and the reaction may proceed via a radical process. To confirm this hypothesis, 3 equivalents of 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO, a radical trapping agent) were added to the reaction. Both of the reactions using AIBN and 2-iodo-2-methylpropanenitrile were completely suppressed (Eqns 4 and 5). These results demonstrate that both AIBN and 2-iodo-2-methylpropanenitrile release a cyanoalkyl radical at high temperature. To elucidate the role of iodine in the reaction, the transformation of AIBN in the presence/absence of iodine at elevated temperature, was studied (Eqn 6). In the absence of iodine, AIBN was transformed into 2,2,3,3-tetramethylsuccinonitrile. In the presence of iodine, only a trace amount of 2,2,3,3-tetramethylsuccinonitrile was observed according to GC-MS, and 2-iodo-2-methylpropanenitrile was formed. These results suggest that iodine is able to inhibit the self-coupling of the cyanoalkyl radical, and the newly formed 2-iodo-2-methylpropanenitrile acts as a relay radical intermediate for the sulfuration.

Based on our results and previous reports concerning C-H alkylthionation using elemental sulfur,[8,9] possible reaction mechanisms have been proposed (Scheme 4). When heated, AIBN decomposes to the cyanoalkyl radical **A,** which can react with iodine to form 2-iodo-2-methylpropanenitrile. This process is reversible at elevated temperature. The subsequent transformation may proceed via one of two pathways: Intermediate **A** may react with sulphur and iodine to afford an active species **B**, which then undergoes an electrophilic addition with imidazopyridine to form a carbenium ion **D**. Finally, the carbenium ion **D** undergoes hydrogen elimination to afford the desired product **3** (Path 1). Alternatively, radical **A** may react with sulphur to form a cyanoalkyl sulfur radical **C,** which then undergoes a radical addition with imidazopyridine to form a radical **E.** A subsequent hydrogen elimination gives product **3** (Path 2). Both the carbenium ion **D** and radical **E** can be stabilized by the conjugative effect of the benzene ring.



Scheme 4 Possible reaction mechanisms.

Conclusion

In summary, a metal-free iodine promoted alkylthionation reaction of imidazopyridines and dialkyl azo compounds using elemental sulfur has been developed. Iodine was able to inhibit the self-coupling of the cyanoalkyl radical, and the 2-iodo-2-methylpropanenitrile intermediate formed in-situ acts as a relay cyanoalkyl radical allow for efficient transformation. In the presence of iodine, a variety of vulcanized imidazopyridines were successfully synthesized, which are difficult to prepare via other means involving odorous thiols. We believe that these imidazoheterocycles bearing cyanoalkylthio groups are of great interest to medicinal chemists.

Experimental

General remarks

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-Ⅲ 600 instrument (600MHz for ^{1}H, 151 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts for ^{1}H and ^{13}C NMR were referred to internal Me_4Si (0 ppm) as the standard. The following abbreviations (or combinations thereof) were used to explain chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants (*J*) in hertz (Hz). IR spectra were measured on a Nicolet IS10. Mass spectra were measured on an Agilent GC-MS-5975C Plus spectrometer (EI). LCMS (ESI) analysis was measured on an AB Sciex API3200. HRMS (ESI) analysis was measured on a Thermo Scientific LTQ Orbitrap XL.

Typical experimental procedure for the alkyl sulfuration of imidazopyridines: To a 15-mL tube with a Teflon cap, equipped with a magnetic stirring bar was charged with **1a** (0.2 mol), S_8 (0.4 mmol), AIBN (0.4 mmol) in MeCN (0.5 mL). The reaction mixture was stirred at 100 °C for 12 hours. After the reaction finished, the mixture was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether / ethyl acetate) to afford the desired product.

Experimental procedure for the synthesis of compound 27: To a 50-mL flask with a reflux condensing tube, equipped with a magnetic stirring bar was charged with compound **3** (1 mmol) and H_2SO_4 (5 mL, 75%), the reaction mixture was stirred at 85 °C for 3 hours. Water (2.5 g) was then added to the reaction mixture, and the reaction was stirred at 115°C for 2 hours. After the reaction finished, the mixture was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether / ethyl acetate) to afford the desired product **27**.

Experimental procedure for the synthesis of compound 28: To a 25-mL flask with a rubber stopper, equipped with a magnetic stirring bar was charged with compound **27** (1 mmol), thiazol-2-amine (2 mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (3 mmol), 4-Dimethylaminopyridine (4-DMAP) (0.2 mmol), and DCM (5 mL) were added. The reaction mixture was stirred at room temperature for 6 hours. After the reaction was completed, the solvent was removed under vacuo. The residue was dissolved in ethyl acetate and washed with water and then brine, dried over Na_2SO_4, filtered and concentrated under vacuo. The resulting residue was purified by flash column chromatography using hexanes and EtOAc as the eluent.

Analytical data for products

2-methyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)propanenitrile (3): yield (48.7 mg, 83%); Yellow solid, mp 124.8 – 126.4 °C; v_{max}/cm^{-1} 2985, 2233 (CN), 1463, 1381, 706, 697; δH (600 MHz; $CDCl_3$; Me_4Si) 8.81 (1H, d, *J* = 6.8 Hz, *Ar*), 8.18 (2H, d, *J* = 7.3 Hz, *Ar*), 7.68 (1H, d, *J* = 9.0 Hz, *Ar*), 7.46 (2H, t, *J* = 7.4 Hz, *Ar*), 7.39 (1H , t, *J* = 7.4 Hz, *Ar*), 7.36 (1H, t, *J* = 7.5 Hz, *Ar*), 6.96 (1H, t, *J* = 6.6 Hz, *Ar*), 1.62 (3H, s, *Me*), 1.29 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 153.6, 147.7, 133.5, 129.0, 128.7, 128.3, 127.5, 125.4, 122.9, 117.8, 113.0, 106.0, 41.5, 27.3, 27.1; HRMS (ESI) m/z calcd for $C_{17}H_{16}N_3S^+$ (M+H)$^+$ 294.10594, found 294.10620.

2-methyl-2-((2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)thio)propanenitrile (4): yield (52.2 mg, 85%); Yellow solid, mp 157.4 – 159.7 °C; v_{max}/cm^{-1} 2973, 2861, 2228 (CN), 1460, 1362, 828; δH (600 MHz; $CDCl_3$; Me_4Si) 8.80 (1H, d, *J* = 6.8 Hz, *Ar*), 8.10 (2H, d, *J* = 7.4 Hz, Ar), 7.67 (1H, d, *J* = 8.9 Hz, *Ar*), 7.34 (1H, t, *J* = 7.8 Hz, *Ar*), 7.27 (2H, d, *J* = 7.6 Hz,*Ar*), 6.94 (1H, t, *J* = 6.8 Hz, *Ar*), 2.41 (3H, s, Me), 1.62 (3H, s, Me), 1.30 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 153.6, 147.7, 138.6, 130.6, 129.1, 128.8, 127.5, 125.4, 123.0, 117.6, 112.9, 105.6, 41.5, 27.4, 27.03, 21.4; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3S^+$ (M+H)$^+$ 308.12159, found 308.12178.

2-((2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (5): yield (47.8 mg, 74%); Yellow solid, mp 119.1 – 120.3 °C; v_{max}/cm^{-1} 2970, 2854, 2225 (CN), 1457, 1387, 805; δH (600 MHz; $CDCl_3$; Me_4Si) 8.79 (1H, d, *J* = 6.8 Hz, *Ar*), 8.16 (2H, d, *J* = 8.8 Hz, *Ar*), 7.66 (1H, d, *J* = 8.9 Hz, *Ar*), 7.37 – 7.31 (1H, m, *Ar*), 6.99 (2H, d, *J* = 8.8 Hz, *Ar*), 6.94 (1H, t, *J* = 6.8 Hz, *Ar*), 3.86 (3H, s, O*Me*), 1.63 (3H, s, *Me*), 1.31 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 160.1, 153.3, 147.6, 130.3, 127.5, 126.0, 125.4, 123.0, 117.5, 113.8, 112.9, 105.2, 55.3, 41.5, 27.4, 27.2; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3OS^+$ (M+H)$^+$ 324.11651, found 324.11682.

2-((2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (6): yield (51.0 mg, 82%); Yellow solid, mp 129.2 – 131.3 °C; v_{max}/cm^{-1} 2228 (CN), 1461, 1390, 1391, 1003, 840; δH (600 MHz; $CDCl_3$; Me_4Si) 8.79 (1H, d, *J* = 6.9 Hz, *Ar*), 8.22 – 8.15 (2H , m,), 7.66 (1H, d, *J* = 9.0 Hz, *Ar*), 7.40 – 7.33 (1H ,m, *Ar*), 7.17 – 7.11 (2H, m, *Ar*), 6.96 (1H, td, *J* = 6.8, 1.0 Hz, *Ar*), 1.62 (3H, s, *Me*), 1.31 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 163.1(d, $J_{C\text{-}F}$ = 248.9 Hz, 1C), 162.3, 152.5, 147.7, 130.8 (d, $J_{C\text{-}F}$ = 8.2 Hz, 1C), 129.6 (d, $J_{C\text{-}F}$ = 3.5 Hz, 1C) 127.7, 125.4, 122.7, 117.7, 115.5 (d, $J_{C\text{-}F}$ = 21.4 Hz, 1C), 113.2, 105.8, 41.7, 27.4, 27.0; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN_3S^+$ (M+H)$^+$ 312.09652, found 312.09680.

2-((2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (7): yield (41.2 mg, 63%); Yellow solid, mp 152.1 – 153.5°C; v_{max}/cm^{-1} 2978, 2931, 2228 (CN), 1454, 1371,837, 611; δH (600 MHz; $CDCl_3$; Me_4Si) 8.80 (1H, d, *J* = 6.8 Hz, *Ar*), 8.16 (2H ,d, *J* = 7.4 Hz, *Ar*), 7.67 (1H, d, *J* = 8.9 Hz, *Ar*), 7.44 (2H, d, *J* = 7.4Hz, *Ar*), 7.37 (1H, t, *J* = 7.8 Hz, *Ar*), 6.98 (1H, t, *J* = 6.8 Hz, *Ar*), 1.64 (3H, s, *Me*), 1.32 (3H,s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 152.2, 147.7, 134.7, 132.0, 130.2, 128.6, 127.8, 125.4, 122.7, 117.8, 113.2,

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106.1, 41.7, 27.3; HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN_3S^+$ $(M+H)^+$ 328.06697, found 328.06723.

4-(3-((2-cyanopropan-2-yl)thio)imidazo[1,2-a]pyridin-2-yl)benzonitrile (8): yield (15.9 mg, 25%); Yellow oil; v_{max}/cm^{-1} 2925, 2854, 2227 (CN), 1463, 1342, 850; δH (600 MHz; $CDCl_3$; Me_4Si) 8.77 (1H, d, *J* = 6.8 Hz, *Ar*), 8.35 (2H, d, *J* = 8.3 Hz, *Ar*), 7.73 (2H ,d, *J* = 8.2 Hz, *Ar*), 7.68 (1H, d, *J* = 9.0 Hz, *Ar*), 7.38 (1H, t, *J* = 7.9 Hz, *Ar*), 6.99 (1H, t, *J* = 6.8 Hz, *Ar*), 1.62 (3H, s, *Me*), 1.33 (3H, s, *Me*); δC (151 MHz; CDCl3; Me4Si) 151.0, 147.8, 138.0, 132.1, 129.4, 128.2, 125.4, 122.3, 118.8, 118.00, 113.7, 112.1, 107.2, 42.0, 27.3; HRMS (ESI) m/z calcd for C_{18} $H_{15}N_4S^+$ $(M+H)^+$ 319.10119, found 319.10153.

2-methyl-2-((8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)thio)propanenitrile (9): yield (51.0 mg, 83%); White solid, mp 91.1 – 92.8 °C; v_{max}/cm^{-1} 2974, 2759, 2225 (CN), 1471, 1386, 706; δH (600 MHz; $CDCl_3$; Me_4Si) 8.67 (1H, d, *J* = 6.8 Hz, *Ar*), 8.15 (2H , d, *J* = 7.2 Hz, *Ar*), 7.46 (2H, t, *J* = 7.6 Hz, *Ar*), 7.38 (1H, t, *J* = 7.4 Hz, *Ar*), 7.15 (1H, d, *J* = 6.9 Hz, *Ar*), 6.88 (1H, t, *J* = 6.9 Hz, *Ar*), 2.68 (3H, s, *Ar-Me*), 1.60 (3H, s, *Me*), 1.27 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 153.2, 148.0, 133.8, 129.2, 128.5, 128.3, 127.7, 126.2, 123.2, 122.9, 113.0, 106.2, 41.5, 27.4, 27.2, 16.7; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3S^+$ $(M+H)^+$ 308.12159, found 308.12183.

2-((8-(hydroxymethyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (10): yield (33.0 mg, 51%); Yellow solid, mp 137.2 – 137.9 °C; v_{max}/cm^{-1} 3430 (OH), 2978, 2930, 2863, 2225 (CN), 1462, 1487, 1355, 706; δH (600 MHz; $CDCl_3$; Me_4Si) 8.7 (1H, d, *J* = 6.8, *Ar*), 8.16 (2H, d, *J* = 7.2 Hz, *Ar*), 7.44 (2H, t, *J* = 7.5 Hz, *Ar*), 7.38 (1H, t, *J* = 7.3 Hz, *Ar*), 7.26 (1H, d, *J* = 6.7 Hz, *Ar*), 6.92 (1H, t, *J* = 6.9 Hz, *Ar*), 5.06 (2H, s, CH_2), 4.47 (1H , s, *OH*), 1.61 (3H, s, *Me*), 1.29 (3H , s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 152.7, 146.5, 133.2, 129.9, 129.0, 128.8, 128.4, 124.4, 122.8, 113.1, 106.5, 62.0, 41.6, 27.2; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3OS^+$ $(M+H)^+$ 324.11651, found 324.11673.

2-methyl-2-((6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)thio)propanenitrile (11): yield (54.6 mg, 85%); Yellow solid, mp 165.3 – 166.3 °C; v_{max}/cm^{-1} 2978, 2864, 2225 (CN), 1457, 1390, 814, 706; δH (600 MHz; $CDCl_3$; Me_4Si) 8.59 (1H, s, *Ar*), 8.09 (2H, d, *J* = 7.4 Hz, *Ar*), 7.57 (1H, d, *J* = 9.0 Hz, *Ar*), 7.26 (2H, d, *J* = 7.7 Hz, *Ar*), 7.19 (1H, d, *J* = 9.1 Hz, *Ar*), 2.41 (6H, s, *Ar-Me*), 1.63 (3H, s, *Me*), 1.30 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 153.3, 146.6, 138.5, 130.7, 130.5, 129.0, 128.8, 123.2, 123.0, 122.8, 116.9, 105.2, 41.4, 27.2, 21.4, 18.4; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3S^+$ $(M+H)^+$ 322.13724, found 322.13742.

2-((2-(4-methoxyphenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (12): yield (41.1 mg, 61%); Yellow solid, mp 130.8 – 131.9 °C; v_{max}/cm^{-1} 2974, 2238 (CN), 1462, 1368, 783; δH (600 MHz; $CDCl_3$; Me_4Si) 8.63 (1H, d, *J* = 6.9 Hz, *Ar*), 8.14 (2H, d, *J* = 8.5 Hz, *Ar*), 7.39 (1H, s, *Ar*), 6.97 (2H, d, *J* = 8.5 Hz, *Ar*), 6.75 (1H, d, *J* = 7.0 Hz, *Ar*), 3.85 (3H, s, *OMe*), 2.42 (3H, s, *Ar-Me*), 1.61 (3H, s, *Me*), 1.29 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 159.9, 153.2, 148.0, 138.7, 130.2, 126.2, 124.5, 123.1, 116.0, 115.4, 113.7, 104.4, 55.3, 41.5, 27.4, 26.9, 21.4; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3OS^+$ $(M+H)^+$ 338.13216, found 338.13254.

2-((6-methoxy-2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile(13): yield (48.7 mg, 69%); Yellow solid, mp 152.5 – 153.7 °C; v_{max}/cm^{-1} 2977, 2835, 2225 (CN), 1465, 1350, 821; δH (600 MHz; $CDCl_3$; Me_4Si) 8.56 (1H, d, *J* = 7.5 Hz, *Ar*), 8.15 (2H, d, *J* = 8.8 Hz, *Ar*), 6.97 (2H, d, *J* = 8.8 Hz, *Ar*), 6.93 (1H, d, *J* = 2.3 Hz, *Ar*), 6.63 (1H, dd, *J* = 7.5, 2.5 Hz, *Ar*), 3.88 (3H, s, *OMe*), 3.86 (3H, s, *OMe*), 1.61 (3H, s, *Me*), 1.30 (3H, s, *Me*). δC (151 MHz; $CDCl_3$; Me_4Si) 160.0, 159.9, 153.2, 149.2, 130.0, 126.1, 125.7, 123.0, 113.7, 107.5, 103.7, 95.1, 55.7, 55.3, 41.6, 27.4, 26.8; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_2S^+$ $(M+H)^+$ 354.12707, found 354.12753.

2-((2-(4-chlorophenyl)-6-methoxyimidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (14): yield (45.0 mg, 63%);Yellow solid, mp 177.7 – 178.3 °C; v_{max}/cm^{-1} 2985, 2223 (CN), 1454, 1368, 757, 688; δH (600 MHz; $CDCl_3$; Me_4Si) 8.55 (1H, d, *J* = 7.5 Hz, *Ar*), 8.14 (2H, d, *J* = 7.7 Hz, *Ar*), 7.41 (2H, d, *J* = 8.2 Hz, *Ar*), 6.92 (1H, s, *Ar*), 6.65 (1H, d, *J* = 7.4 Hz, *Ar*), 3.88 (3H, s, *OMe*), 1.61 (3H, s, *Me*), 1.30 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 160.2, 152.1, 149.3, 134.5, 132.1, 130.0, 128.5, 125.8, 122.8, 108.0, 104.7, 95.2, 55.7, 41.7, 27.4, 26.9; HRMS (ESI) m/z calcd for C_{18} $H_{17}ClN_3OS^+$ $(M+H)^+$ 358.07754, found 358.07788.

2-((2-(-hydroxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanenitrile (15): yield (35.9 mg, 58%); Yellow solid, mp 138.6 – 139.1°C; v_{max}/cm^{-1} 3438 (OH), 2964, 2851, 2233 (CN), 1455, 1385, 757; δH (600 MHz; $CDCl_3$; Me_4Si) 12.91 (1H, s, *OH*), 8.89 (1H, d, *J* = 6.9 Hz, *Ar*), 8.71 (1H, dd, *J* = 7.9, 1.2 Hz, *Ar*), 7.64 (1H, d, *J* = 8.9 Hz, *Ar*), 7.45 – 7.42 (1H, m, *Ar*), 7.31 – 7.27 (1H, m, *Ar*), 7.07 – 7.02 (2H, m, *Ar*), 6.90 (1H, t, *J* = 7.6 Hz, *Ar*), 1.73 (3H, s, *Me*), 1.46 (3H, s, *Me*) ; δC (151 MHz; $CDCl_3$; Me_4Si) 158.6, 151.1, 145.4, 131.0, 128.5, 128.1, 125.3, 122.8, 118.4, 118.1, 116.8, 115.9, 113.7, 104.9, 41.9, 27.5, 27.1; HRMS (ESI) m/z calcd for $C_{17}H_{16}N$ $_3OS^+$ $(M+H)^+$ 310.10086, found 310.10114.

2-((2-(2-hydroxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylbutanenitrile (16): yield (42.0 mg, 65%); A mixture of conformational isomerism. Yellow solid, mp 103.7 – 104.2°C; v_{max}/cm^{-1} 3451 (OH), 2976, 2938, 2855, 2229 (CN), 1451, 1390, 757; δH (600 MHz; $CDCl_3$; Me_4Si) 12.92 (1H, s, *OH*), 8.89 (1H, d, *J* = 6.1 Hz, *Ar*), 8.70 (1H, t, *J* = 8.5 Hz, *Ar*), 7.63 (1H, d, *J* = 8.9 Hz, *Ar*), 7.43 (1H, t, *J* = 7.8 Hz, *Ar*), 7.29 (1H, t, *J* = 7.5 Hz, *Ar*), 7.07 – 7.03 (2H, m, *Ar*), 6.90 (1H, q, *J* = 7.5 Hz, *Ar*), 2.07 – 1.77 (2H, q, CH_2), 1.63/1.38 (3H, s, *Me*), 1.27/0.95 (3H, t, *J* = 7.3 Hz, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 158.6, 151.1, 145.3, 130.9, 128.5, 128.2, 128.1, 125.3, 122.0, 121.7, 118.5, 118.4, 118.0, 116.7, 115.9, 113.7, 104.6, 104.4, 47.5, 47.2, 32.8, 33.2, 25.0, 23.8,10.0, 9.6; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3OS^+$ $(M+H)^+$ 324.11651, found 324.11676.

2-((2-(2-hydroxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2,4-dimethylpentanenitrile (17): yield (44.2 mg, 63%); A mixture of conformational isomerism. Yellow oil; v_{max}/cm^{-1} 3630 (OH), 2957, 2925, 2854, 2226 (CN), 1456, 1390, 757; δH (600 MHz; $CDCl_3$; Me_4Si) 12.89 (1H, s, *OH*), 8.92–8.85 (1H, m, *Ar*), 8.70 – 8.68 (1H, m, *Ar*), 7.63 (1H, d, *J* = 8.8 Hz, *Ar*), 7.42 (1H, t, *J* = 7.9 Hz, *Ar*), 7.29 (1H, t, *J* = 7.7 Hz, *Ar*), 7.09 – 7.01 (2H, m, *Ar*), 6.92 – 6.88 (1H, m, *Ar*), 2.09 (1H, m, *CH*), 1.92/1.79 (2H, dd, *J* = 6.1 Hz, CH_2), 1.64/1.41 (3H, s, *Me*), 1.12/0.84 (6H, d, *J* = 6.7 Hz, *2Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 158.6, 158.4, 151.2, 151.1, 145.3, 130.9, 128.5, 128.3, 128.1, 125.4, 125.1, 122.7, 122.2, 118.5, 118.3, 118.0, 117.8, 116.7, 116.6, 115.9, 113.6, 104.6, 48.1, 47.9, 46.1, 45.7, 26.2, 26.0, 25.4, 23.8, 23.6; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_3OS^+$ $(M+H)^+$ 352.14781, found 352.14819.

methyl 2-((2-(2-hydroxyphenyl)imidazo[1,2-a]pyridin-3-yl)thio)-2-methylpropanoate (18) : yield (27.4 mg, 40%); Orange solid, mp 120.2 – 121.4 °C; v_{max}/cm^{-1} 3437 (OH), 2983, 1729, 1454, 1383, 695; δH (600 MHz; $CDCl_3$; Me_4Si) 13.00 (1H, s, *OH*), 8.79 (1H,

d, *J* = 8.0 Hz, *Ar*), 8.59 (1H, d, *J* = 6.9 Hz, *Ar*), 7.62 (1H, d, *J* = 8.9 Hz, *Ar*), 7.38 (1H, t, *J* = 7.9 Hz, *Ar*), 7.28 (1H, s, *Ar*), 7.04 (1H, d, *J* = 8.2 Hz, *Ar*), 6.98 (1H, t, *J* = 6.8 Hz, *Ar*), 6.91 (1H, t, *J* = 7.5 Hz, *Ar*), 3.24 (3H, s, *Me*), 1.48 (3H, s, *Me*), 1.41 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 173.5, 158.4, 150.2, 144.6, 130.5, 128.2, 127.4, 124.7, 118.5, 117.7, 116.6, 116.4, 113.2, 107.2, 54.0, 52.2, 25.6, 25.1; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_3S^+$ $(M+H)^+$ 343.11109, found 343.11142.

methyl 2-methyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)propanoate (19): yield (26.7 mg, 41%); White solid, mp 82.3 – 84.7 °C; v_{max}/cm^{-1} 2965, 2852, 1725 (CO), 1463, 1380, 701, 692; δH (600 MHz; $CDCl_3$; Me_4Si) 8.50 (1H, d, *J* = 6.9 Hz, *Ar*), 8.25 (2H, d, *J* = 7.2 Hz, *Ar*), 7.65 (1H, d, *J* = 8.9 Hz, *Ar*), 7.44 (2H, t, *J* = 7.7 Hz, *Ar*), 7.35 (1H, t, *J* = 7.4 Hz, *Ar*), 7.30 – 7.27 (1H, m, *Ar*), 6.91 – 6.87 (1H, m, *Ar*), 3.16 (3H, s, *Me*), 1.33 (6H, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 173.7, 152.5, 147.0, 133.9, 128.9, 128.4, 128.3, 126.6, 124.9, 117.6, 112.6, 108.1, 53.6, 52.1, 25.2; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_2S^+$ $(M+H)^+$ 327.11617, found 327.11646.

1-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)cyclohexane-1-carbonitrile (20): yield (44.0 mg, 66%); White solid, mp 159.5 – 160.1 °C; v_{max}/cm^{-1} 2932, 2854, 2227 (CN), 1462, 702, 693; δH (600 MHz; $CDCl_3$; Me_4Si) 8.82 (1H, d, *J* = 6.9 Hz, *Ar*), 8.17 (2H, d, *J* = 7.6 Hz, *Ar*), 7.67 (1H, d, *J* = 9.0 Hz, *Ar*), 7.46 (2H, t, *J* = 7.7 Hz, *Ar*), 7.39 (1H, t, *J* = 7.4 Hz, *Ar*), 7.34 (1H, t, *J* = 7.7 Hz, *Ar*), 6.95 (1H, t, *J* = 6.1 Hz, *Ar*), 2.38 – 1.55 (8H, m, CH_2), 1.24 – 1.06 (2H, m, CH_2); δC (151 MHz; $CDCl_3$; Me_4Si) 153.6, 147.7, 133.6, 129.1, 128.6, 128.3, 127.4, 125.6, 121.5, 117.7, 112.9, 105.0, 48.1, 36.0, 24.5, 23.2; HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3S^+$ $(M+H)^+$ 334.13724, found 334.13742.

2-methyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)butanenitrile (21): yield (43.0 mg, 70%); Cyan oil; v_{max}/cm^{-1} 2973, 2924, 2852, 2228 (CN), 1489, 1463, 1385, 695; δH (600 MHz; $CDCl_3$; Me_4Si) 8.78 (1H, d, *J* = 6.8 Hz, *Ar*), 8.15 (2H, d, *J* = 7.6 Hz, *Ar*), 7.65 (1H, d, *J* = 8.9 Hz, *Ar*), 7.43 (2H, t, *J* = 7.6 Hz, *Ar*), 7.36 (1H, t, *J* = 7.4 Hz, *Ar*), 7.31 (1H, t, *J* = 7.9 Hz, *Ar*), 6.92 (1H, t, *J* = 6.8 Hz, *Ar*), 1.92 – 1.43/1.22 – 0.69 (8H, m, *CH_2, 2Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 153.8, 147.7, 133.5, 129.1, 128.6, 128.3, 127.5, 125.5, 122.0, 117.7, 113.0, 105.6, 47.1, 32.7, 25.0, 9.8; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3S^+$ $(M+H)^+$ 308.12159, found 308.12186.

2,4-dimethyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)pentanenitrile (22): yield (26.8 mg, 40%); Brown oil; v_{max}/cm^{-1} 2944, 2884, 2859, 2274 (CN), 1479, 1384, 724; δH (600 MHz; $CDCl_3$; Me_4Si) 8.78 (1H, s, *Ar*), 8.13 (2H, d, *J* = 7.6 Hz, *Ar*), 7.63 (1H, d, *J* = 8.9 Hz, *Ar*), 7.42 (2H, t, *J* = 7.5 Hz, *Ar*), 7.35 (1H, t, *J* = 7.2 Hz, *Ar*), 7.31 – 7.26 (1H, m, *Ar*), 6.93 – 6.86 (1H, m, *Ar*), 2.08–0.66 (12H, m, CH, CH_2, $3CH_3$); δC (151 MHz; $CDCl_3$; Me_4Si) 153.8, 147.7, 133.6, 129.1, 128.6, 128.3, 127.5, 125.6, 122.7, 117.7, 113.0, 105.7, 47.8, 45.3, 26.0, 25.1, 23.7, 23.6; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_3S^+$ $(M+H)^+$ 336.15289, found 336.15308.

2-methyl-2-((6-phenylimidazo[2,1-b]thiazol-5-yl)thio)propanenitrile (24): yield (27.5 mg, 46%);Yellow solid , mp 104.9 – 106.0 °C; v_{max}/cm^{-1} 2925, 2854, 2230 (CN), 1465,1369, 789 ; δH (600 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* = 7.8 Hz, *Ar*), 7.84 (1H, d, *J* = 4.4 Hz, *Ar*), 7.42 (2H, t, *J* = 7.5 Hz, *Ar*), 7.35 (1H, t, *J* = 7.3 Hz, *Ar*), 6.91 (1H, d, *J* = 4.4 Hz, *Ar*), 1.48 (6H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 154.9, 152.6, 133.5, 128.3, 128.3, 128.2, 123.0, 119.3, 112.9, 107.1, 41.6, 26.9; HRMS (ESI) m/z calcd for $C_{15}H_{14}N_3S_2^+$ $(M+H)^+$ 300.06237, found 300.06265.

2-((6-(4-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)thio)-2-methylpropanenitrile (25): yield (23.5 mg, 37%);Yellow solid, mp 136.7 – 137.5°C; v_{max}/cm^{-1} 2925, 2853, 2229 (CN), 1458, 1335, 1291 , 708, 684; δH (600 MHz; $CDCl_3$; Me_4Si) 8.12 – 8.06 (2H, m, *Ar*), 7.80 (1H, d, *J* = 4.5 Hz, *Ar*), 7.13 – 7.07 (2H, m, *Ar*), 6.90 (1H, d, *J* = 4.5 Hz, *Ar*), 1.48 (6H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 161.3 (d, $J_{C\text{-}F}$ = 249.1 Hz, 1C), 153.9, 152.7, 130.1 (d, $J_{C\text{-}F}$ = 7.6 Hz, 1C), 122.8, 119.2, 115.3 (d, $J_{C\text{-}F}$ = 21.1 Hz, 1C), 113.0, 106.9, 41.8, 27.0; HRMS (ESI) m/z calcd for $C_{15}H_{13}FN_3S_2^+$ $(M+H)^+$ 318.05294, found 318.05331.

2-methyl-2-((2-(p-tolyl)benzo[d]imidazo[2,1-b]thiazol-3-yl)thio)propanenitrile (26): yield (27.6 mg, 38%);Yellow solid, mp 127.1 – 128.2 °C; v_{max}/cm^{-1} 2922, 2852, 2229 (CN), 1479, 1368, 810 , 800; δH (600 MHz; $CDCl_3$; Me_4Si) 8.72 (1H, d, *J* = 8.3 Hz, *Ar*), 8.01 (2H, d, *J* = 8.2 Hz, *Ar*), 7.70 (1H, d, *J* = 7.7 Hz, *Ar*), 7.50 (1H, t, *J* = 7.8 Hz, *Ar*), 7.37 (1H, t, *J* = 7.4 Hz, *Ar*), 7.24 (2H, d, *J* = 8.0 Hz, *Ar*), 2.40 (3H, s, *Me*), 1.61 (3H, s, *Me*), 1.35 (3H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 156.1, 151.8, 138.4, 133.8, 130.5, 130.0, 129.1, 128.5, 126.2, 125.1, 124.1, 121.7, 115.0, 108.9, 42.9, 27.3, 21.4; HRMS (ESI) m/z calcd for $C_{20}H_{18}N_3S_2^+$ $(M+H)^+$ 364.09367, found 364.09393.

2-methyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)propanoic acid (27): yield (181.0 mg, 58%); Yellow solid, mp 207.1 – 208.8 °C; v_{max}/cm^{-1} 2993, 2919, 1704 (COOH), 1471, 1384, 1442, 708; δH (600 MHz; DMSO; Me_4Si) 12.70 (1H, s, *COOH*), 8.62 (1H, dt, *J* = 6.8, 1.2 Hz, *Ar*), 8.34 – 8.23 (2H, m, *Ar*), 7.67 (1H, d, *J* = 8.9 Hz, *Ar*), 7.47 (2H, t, *J* = 7.6 Hz, *Ar*), 7.44 – 7.41 (1H, m, *Ar*), 7.41 – 7.36 (1H, m, *Ar*), 7.05 (1H, td, *J* = 6.8, 1.2 Hz, *Ar*), 1.24 (6H, d, *J* = 118.8 Hz, *Me*); δC (151 MHz; DMSO; Me_4Si) 174.9, 151.4, 146.8, 134.3, 128.7, 128.7, 128.6, 127.7, 125.8, 117.5, 113.4, 108.0, 54.0, 25.6; HRMS (ESI) m/z calcd for $C_{17}H_{17}N_2O_2S^+$ $(M+H)^+$ 313.10052, found 313.10086.

2-methyl-2-((2-phenylimidazo[1,2-a]pyridin-3-yl)thio)-N-(thiazol-2-yl)propanamide (28): yield (220.7 mg, 56%);White solid, mp 221.9 – 223.0 °C; v_{max}/cm^{-1} 3435 (NH), 2974, 2930, 1463, 1384, 708, 694; δH (600 MHz; $CDCl_3$; Me_4Si) 9.16 (1H, s, *NH*), 8.42 (1H, d, *J* = 6.8 Hz, *Ar*), 8.11 (2H, d, *J* = 7.6 Hz, *Ar*), 7.61 (1H, d, *J* = 8.9 Hz, *Ar*), 7.32 (3H, t, *J* = 7.7 Hz, *Ar*), 7.22 (2H, q, *J* = 7.1 Hz, *Ar*), 6.89 (1H, d, *J* = 2.8 Hz, *Ar*), 6.70 (1H, t, *J* = 6.8 Hz, *Ar*), 1.47 (6H, s, *Me*); δC (151 MHz; $CDCl_3$; Me_4Si) 170.6, 153.1, 147.3, 137.1, 133.3, 129.9, 128.8, 128.3, 128.2, 126.8, 124.7, 117.7, 113.8, 112.9, 106.9, 54.5, 25.0; HRMS (ESI) m/z calcd for $C_{20}H_{19}N_4OS_2^+$ $(M+H)^+$ 395.09948, found 395.09967.

Conflicts of interest

"There are no conflicts to declare".

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Notes and references

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