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An Efficient Synthesis of a Variety of Substituted Pyridine-3-Thiols

Abstract

A practical and convenient method for the synthesis of pyridine-3-thiols using substituted 3-iodopyridines as starting compounds has been developed. Based on the use of thiobenzoic acid as a sulfur donor in a two-step procedure, this approach made it possible to synthesize a number of pyridine-3-thiols with F, Cl, Br, CH_3, OCH_3 substituents in various positions of the pyridine ring. The procedure presented gives high yields of the target products with a purity of 95 % and is suitable for the synthesis in tens of grams.

Keywords: pyridine; thiols; thiobenzoic acid; chromatography; hydrolysis

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Ефективний метод синтезу різноманітних заміщених піридин-3-тіолів

Анотація

Розроблено практичний і зручний метод синтезу піридин-3-тіолів із використанням як вихідних сполук заміщених 3-йодопіридинів. Цей підхід, заснований на використанні тіобензойної кислоти як донора сульфуру в межах двостадійної процедури, надав можливість синтезувати ряд піридин-3-тіолів із F, Cl, Br, CH_3, OCH_3 замісниками в різноманітних положеннях піридинового циклу. Зазначена процедура дозволяє одержати цільові продукти на масштабі десятків грам із високими виходами й чистотою 95 %.

Ключові слова: піридин; тіоли; тіобензойна кислота; хроматографія; гідроліз

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■ Introduction

Pyridine is a part of the body's oxidation systems and, in the form of nicotinic acid (vitamin B3), is a component of NAD^+ and $NADP^+$ (**Figure 1**) [1–3]. Pyridines are found in plants, for example, in alkaloids, such as nicotine. The latter is an important biological component and activator of nicotinic acetylcholine receptors (nAChRs); it plays a significant role in the formation of tobacco addiction [4, 5]. Anabasine, an alkaloid related to nicotine, is the major toxin of the Pacific hoplonemertine *Paranemertes peregrina*, which presumably uses the alkaloid for defense or to paralyze its prey [6].

The pyridine cycle is a pharmacophore of dihydropyridine calcium channel blockers [7]. Many other biologically active compounds with a pyridine cycle are known [8]. For example, huperzine A, an active Lycopodium alkaloid extracted

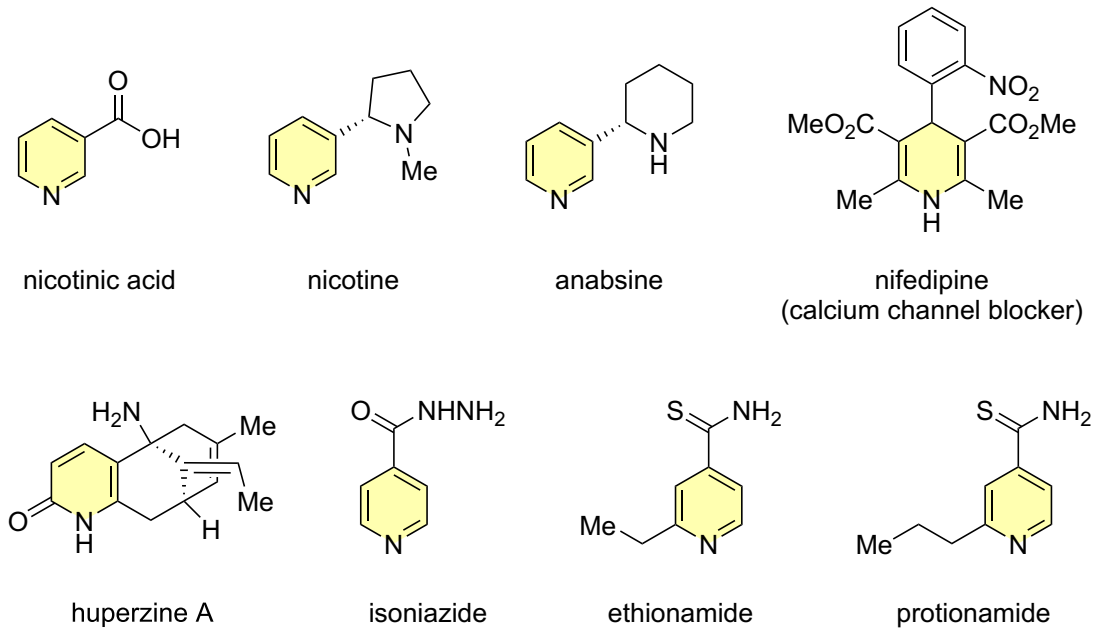

Figure 1. Natural pyridines and pyridine-containing medicines

from a traditional Chinese herb, is a potent, selective, and reversible acetylcholinesterase (AChE) inhibitor and has been widely used in China for the treatment of Alzheimer's disease [9].

Undoubtedly, pyridine derivatives play a crucial role in the therapy of tuberculosis as drugs like isoniazid [10], ethionamide, and protionamide [11] are the derivatives of pyridine.

Pyridinethiols are of great importance as the parts of biologically active compounds (**Figure 2**). The introduction of pyridine-4-thiol fragment helped to obtain an effective dual inhibitor of cancer-related cysteine isopeptidase human ubiquitin-specific proteases 7 (**USP7**) and 47 (**USP47**). This is considered to have the potential as a cancer therapeutic, owing to the ability to stabilize the tumor suppressor p53 and to decrease DNA polymerase ϐ (Polϐ). Both of them have potential antitumor effects [12].

Newly developed selective galectin-3 inhibitors combining high affinity (nM) with oral bioavailability, which reduce the profibrotic gene expression in liver myofibroblasts and display the antifibrotic activity in CCl_4-induced liver fibrosis and bleomycin-induced lung fibrosis mouse models, also have 5-bromopyridine-3-thiol galactoside in their structure. Compound **GB1211** was selected as the clinical candidate. It is currently in phase IIa clinical trials as a potential therapy for liver cirrhosis and cancer [13].

Pyridine-4-thione is also a part of the fused systems of the effective and potent BRAF inhibitors bearing a novel pyridoimidazolone hinge-binding group. They showed beneficial therapeutic efficacy in mutant BRAF tumors, including melanoma. A thiopyridine derivative was found to be 4-fold more potent than sorafenib in inhibiting WM266.4 melanoma cell growth [14].

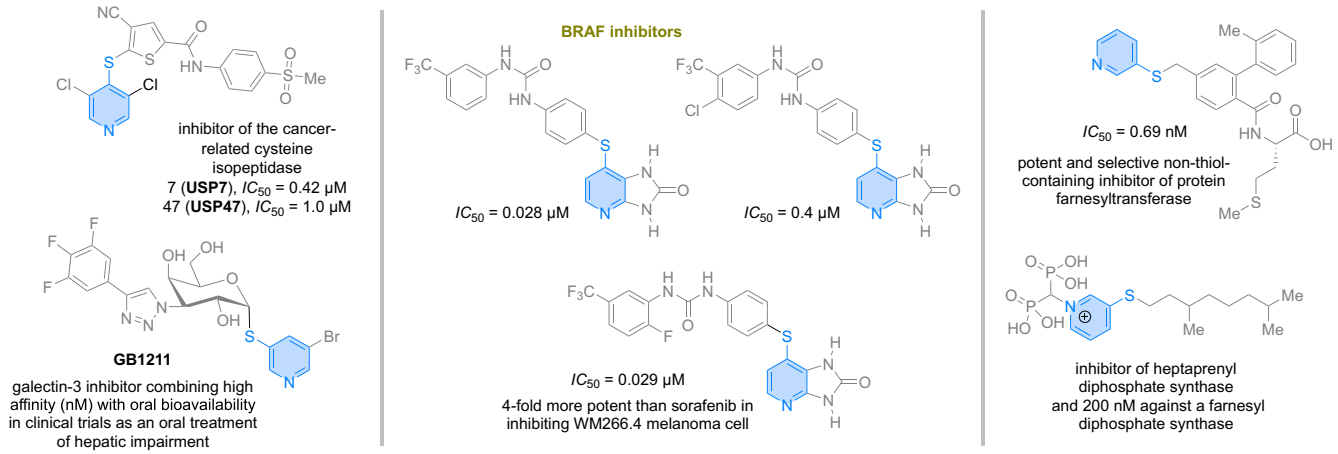

Figure 2. Biologically active compounds with a thiopyridine fragment

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The *o*-tolyl biphenyl core dramatically and unexpectedly enhanced the potency of other compounds as exemplified the activity of potent and selective non-thiol-containing inhibitors of protein farnesyltransferase playing an important role for the Ras protein posttranslational modifications, such as the farnesylation of a cysteine residue near the C-terminus by the enzyme farnesyltransferase (FTase). The inhibition of this enzyme will render Ras inactive and block the uncontrolled mitogenic signaling pathway [15].

The compound with the antimicrobial activity against *Bacillus anthracis*, *Mycobacterium smegmatis*, *Bacillus subtilis,* and *Staphylococcus aureus* bearing pyridine-3-thione was reported. The compounds from this series target the biosynthesis of bacterial isoprenoids by inhibiting heptaprenyl diphosphate synthase and farnesyl diphosphate synthase at 200 nM [16].

Pyridine-2-thiol is a perfect ligand to stabilize the complexes with metals [17, 18].

The analysis of the screening compounds market revealed the urgent need for a variety of pyridine-3-thiols as building blocks. The analysis of the market using mathematical algorithms also clearly indicates a small number of blocks containing the SH group and the vacancy of this market segment [19].

■ Results and discussion

There are a number of approaches to the preparation of aromatic thiols that have been shown to be promising for the synthesis of pyridinethiols. The first reported method for obtaining pyridine-3-thiols was the reduction of the corresponding sulfonyl chloride [20]. In subsequent publications, the authors used more modern reduction methods, which made it possible to preserve a number of functional groups, such as the double bond or Boc protected amine [21, 22]. A number of researchers used pyridin-3-ol as a starting compound, which, when treated with dimethylthiocarbamoyl chloride, gave an *S*-aryl thiocarbamate, that could be further thermally rearranged into the corresponding *S*-aryl thiocarbamate according to the Newman–Kwart rearrangement [23]. It was shown that the hydrolysis of 3-pyridyl *S*-aryl thiocarbamate was a good way for the preparation of sodium salts of pyridine-3-thiol [15, 16]. Copper (II) sulfate catalyzed the interaction of 3-bromo pyridine with 1,2-ethandithiol was also reported as the one for preparing pyridine-3-thiol, which was alkylated *in situ* [24]. Some less convenient methods where the formation of disulfides was one of the by-processes were also reported [25].

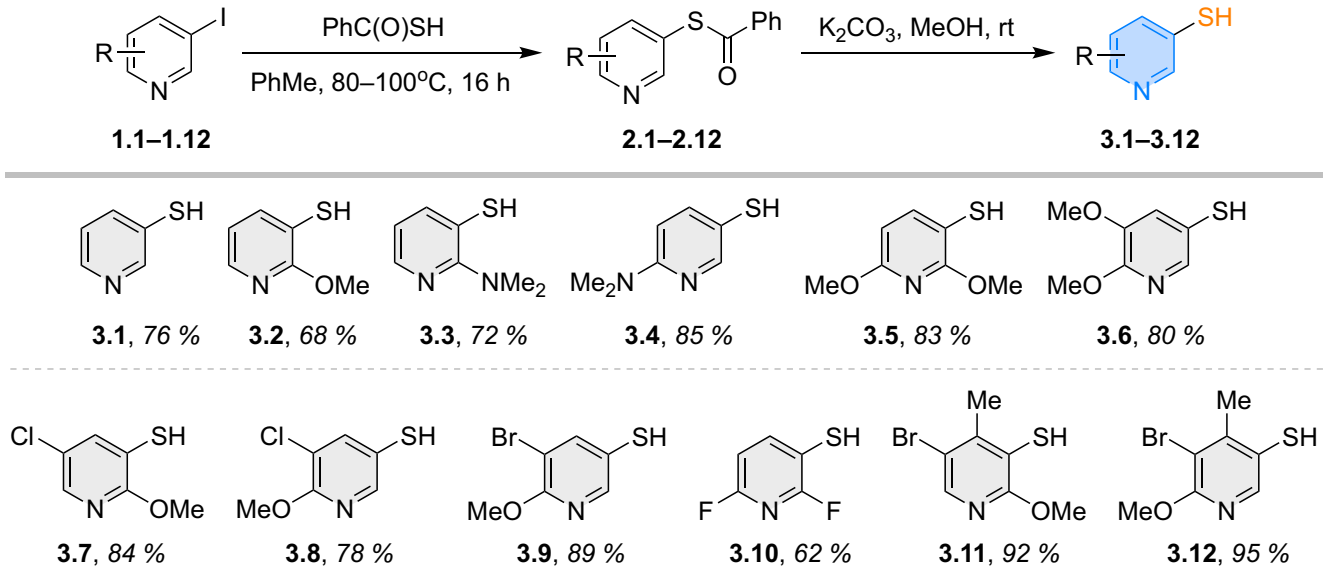
The analysis of the above methods has shown that most of them do not allow the isolation of pyridine-3-thiol with a purity of more than 95% and have not been studied on a wide variety of substituted pyridine derivatives. In recent years, the appearance of 3-iodopyridines in the market has led us to the idea of using them as starting compounds for the synthesis of corresponding thiols. Our attention was drawn to the possibility of the copper-catalyzed coupling of aryl iodides and thiobenzoic acid [26]. This reaction was previously carried out to form *S*-pyridin-3-yl benzenecarbothioate, which was subsequently used for the oxidative synthesis of the corresponding sulfochlorides [27].

The authors [26] also showed the possibility of *S*-phenyl benzenecarbothioate cleavage with the formation of thiophenol under mild conditions (K_2CO_3, MeOH, rt). Thus, we decided to apply this approach and investigate it on a number of substituted 3-iodopyridines as the starting compounds.

As a result, we have found that the reaction of a number of 3-iodopyrimidines with thiobenzoic acid in the presence of phenanthroline and DIPEA as an organic base readily produces the corresponding *S*-pyridin-3-yl benzenecarbothioate. For more thorough purification, the residue was subjected to the flash chromatography using a gradient (toluene/hexane 1:1 to 100% toluene) on silica gel. This procedure turned out to be important for a significant increase in the yield of thiols in the next step.

Further cleavage of thiobenzoate was carried out in a 10-fold volume of methanol and using a 40% excess of a dry potassium carbonate at room temperature. For the purification of the target pyridine-3-thiol, the salt was dissolved in water, and non-polar impurities were extracted with methylene chloride. To isolate the product, the aqueous layer was acidified to pH 5, and the product was extracted with methylene chloride. To remove residual acid, the organic layer was washed with saturated sodium bicarbonate solution, dried, and evaporated. This isolation procedure allows obtaining a pure product **3** without additional operations (**Scheme**). The use of this procedure enabled the preparation of a variety of substituted pyridine-3-thiols in high yields.

In the spectra of compounds **3** obtained, a clear signal of the SH group is observed in the range of 2.89–4.29 ppm in $CDCl_3$ and at 4.73 ppm



Scheme. The synthesis of substituted pyridine-3-thiols

in DMSO-d_6 for 2,6-dimethoxypyridine-3-thiol **3.5**, indicating, together with the HRMS spectral data, the formation of pure compound **3** with a thione group without disulfide impurities.

■ Conclusions

An effective and practical two-step procedure for the preparation of pyridine-3-thiol starting from 3-iodopyridines has been developed. The scope of the iodo derivatives that could be used for the reaction has been studied, and as a result, 12 substituted pyridine-3-thiols have been obtained with a high yield.

■ Experimental part

All of the regents were taken from "Enamine" Ltd stock. Analytical TLC was performed using Polychrom SI F254 plates. The column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 AVANCE 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 AVANCE 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer; ^{19}F spectra were obtained on a Varian Unity Plus 400 (376 MHz) spectrometer. HRMS spectra were acquired with an Agilent 6200 Series TOF and 6500 Series Q-TOF LC/MS System.

The general procedure for the coupling step (compounds 2)

The reaction was carried out in a single-necked flask. To 0.1 mol of the corresponding 3-iodopyridine **1**, 150 mL of toluene was added, then 3.6 g of phenanthroline, 2 g of CuI, 30 mL of diisopropylethylamine and 14 mL of thiobenzoic acid were added while stirring. The flask was filled with argon. The reaction mixture was heated to 80–100 °C for 12–16 h. Then 150 ml of hexane was added to the cool reaction mixture. The reaction mixture was chromatographed on a 200 mL Schott funnel (50–60°C, 100–150 mL of silica gel) starting from the toluene/hexane 1:1 phase and pure toluene at the end furnishing thioesters **2**.

The general procedure for the hydrolysis step (thiols 3)

The resulting thiobenzoate **2** was added to methanol (1 g per 10 mL), then 40% excess of dry K_2CO_3 was added there. The hydrolysis took 1 h at 25°C. Then methanol was evaporated, and the residue was dissolved in the same amount of water. The amount of water was twice washed with dichloromethane, then acidified to pH 5 and extracted with dichloromethane. The dichloromethane extract was separated and washed with the aqueous sodium bicarbonate saturated solution. Then methylene chloride was evaporated leaving a residue of the pure product **3**.

Pyridine-3-thiol (**3.1**)

A yellow powder. Yield – 40 g (76%). M. p. 77–79°C dec. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.26 (1H, s, SH), 7.17 (1H, dd, J = 8.1, 4.7 Hz), 7.61 (1H, dt, J = 8.1, 2.0 Hz), 8.27–8.45 (1H, m), 8.52 (1H, d, J = 2.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 123.1, 127.8, 136.3, 146.3, 149.3. HRMS (ESI/TOF-Q), m/z: calcd for C_5H_5NS 111.0143, found 111.0143.

2-Methoxypyridine-3-thiol (**3.2**)

A yellow liquid. Yield – 25 g (68%). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.76 (1H, s, SH), 4.01

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(3H, s), 6.79 (1H, dd, J = 7.4, 4.9 Hz), 7.51 (1H, dd, J = 7.4, 1.7 Hz), 7.95 (1H, dd, J = 5.0, 1.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.5, 115.6, 116.6, 136.6, 142.7, 158.8. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_7NOS 141.0248, found 141.0246.

2-(Dimethylamino)pyridine-3-thiol (**3.3**)

A yellow liquid. Yield – 20.2 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.89 (7H, m, $2NCH_3$ + SH), 4.30 (1H, s), 6.84 (1H, ddd, J = 7.6, 4.7, 2.0 Hz), 7.55 (1H, dd, J = 7.7, 1.8 Hz), 8.10 (1H, dd, J = 4.8, 1.8 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 41.7, 118.1, 122.7, 138.1, 144.2, 160.1. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_{10}N_2S$ 154.0565, found 154.0563.

6-(dimethylamino)pyridine-3-thiol (**3.4**)

A yellow powder. Yield – 18 g (85%). M. p. 65–68°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.05 (7H, m, $2NCH_3$ + SH), 6.41 (1H, d, J = 8.8 Hz), 7.41–7.47 (1H, m), 8.18 (1H, d, J = 2.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 37.6, 105.4, 108.7, 141.3, 150.9, 157.9. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_{10}N_2S$ 154.0565, found 154.0562.

2,6-Dimethoxypyridine-3-thiol (**3.5**)

A yellow powder. Yield – 39 g (83%). M. p. 43–46°C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.82 (3H, d, J = 1.2 Hz), 3.90 (3H, d, J = 1.3 Hz), 4.73 (1H, s, SH), 6.35 (1H, dd, J = 8.1, 1.3 Hz), 7.62 (1H, dd, J = 8.1, 1.3 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 53.4, 54.0, 101.5, 101.8, 102.8, 141.8, 158.9, 161.6. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_9NO_2S$ 171.0354, found 171.0350.

5,6-Dimethoxypyridine-3-thiol (**3.6**)

A white powder. Yield – 41 g (80%). M. p. 38–42°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.29 (1H, s, SH), 3.84 (3H, d, J = 2.5 Hz), 3.97 (3H, d, J = 2.5 Hz), 7.02 (1H, t, J = 2.3 Hz), 7.70 (1H, d, J = 2.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.2, 55.2, 116.7, 120.3, 138.3, 143.3, 153.2. HRMS (ESI/TOF-Q), m/z: calcd for $C_7H_9NO_2S$ 171.0354, found 171.0352.

5-Chloro-2-methoxypyridine-3-thiol (**3.7**)

A gray powder. Yield – 43.8 g (84%). M. p. 48–52°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.82 (1H, s, SH), 3.98 (3H, s), 7.48 (1H, d, J = 2.3 Hz), 7.86 (1H, t, J = 2.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.9, 117.4, 123.5, 135.7, 140.7, 157.2. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6ClNOS 174.9859, found 174.9856.

5-Chloro-6-methoxypyridine-3-thiol (**3.8**)

A white powder. Yield – 39.8 g (78%). M. p. 53–58°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.30 (1H, s, SH), 3.99 (3H, s), 7.65 (1H, d, J = 2.2 Hz), 8.02 (1H, d, J = 2.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 53.9, 117.6, 117.8, 140.6, 146.0, 158.0. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6ClNOS 174.9859, found 174.9858.

5-Bromo-6-methoxypyridine-3-thiol (**3.9**)

A white powder. Yield – 41.5 g (89%). M. p. 49–53°C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.30 (1H, s, SH), 3.98 (3H, s), 7.82 (1H, d, J = 2.2 Hz), 8.06 (1H, d, J = 2.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 54.1, 106.4, 117.9, 143.9, 146.8, 158.7. HRMS (ESI/TOF-Q), m/z: calcd for C_6H_6BrNOS 218.9353, found 218.9353.

2,6-Difluoropyridine-3-thiol (**3.10**)

A yellow powder. Yield – 25 g (62%). M. p. 39–44°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.56 (1H, s, SH), 6.80 (1H, dd, J = 8.2, 3.0 Hz), 7.69–7.85 (1H, m). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -72.31, -66.11. ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 106.3 (dd, J = 35.3, 5.9 Hz), 109.7 (dd, J = 34.1, 6.2 Hz), 144.6 (dd, J = 7.3, 3.2 Hz), 155.9 (dd, J = 14.0, 3.2 Hz), 158.8 (dd, J = 242.3, 13 Hz), 159.4 (dd, J = 246.3, 12 Hz). HRMS (ESI/TOF-Q) m/z: calcd for C_5H_3FNS 146.9954, found 146.9955.

5-Bromo-2-methoxy-4-methylpyridine-3-thiol (**3.11**)

A white powder. Yield – 45.3 g (92%). M. p. 63–65°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.42 (3H, s), 4.02 (3H, s), 4.29 (1H, s, SH), 8.03 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 20.0, 54.0, 114.9, 117.5, 142.2, 143.5, 157.0. HRMS (ESI/TOF-Q), m/z: calcd for C_7H_8BrNOS 232.9510, found 232.9506.

6-methoxy-5-Bromo-4-methylpyridine-3-thiol (**3.12**)

A white powder. Yield – 44.5 g (90%). M. p. 65–67°C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.52 (3H, s), 3.16 (3H, s), 3.97 (1H, s, SH), 8.04 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 21.2, 54.1, 109.3, 118.9, 146.0, 149.0, 159.1. HRMS (ESI/TOF-Q), m/z: calcd for C_7H_8BrNOS 232.9510, found 232.9506.

References

1. Ahmed, I. A. Major Dietary Interventions for the Management of Liver Disease. In *Dietary Interventions in Liver Disease*; Elsevier, 2019; pp 205–212. https://doi.org/10.1016/B978-0-12-814466-4.00017-3.
2. Nakhaee, S.; Mehrpour, O. Niacin. In *Encyclopedia of Toxicology*; Elsevier, 2024; pp 755–761. https://doi.org/10.1016/B978-0-12-824315-2.00113-5.
3. Sledge, C. L.; Morgan, B. W. Niacin. In *Encyclopedia of Toxicology*; Elsevier, 2014; pp 504–505. https://doi.org/10.1016/B978-0-12-386454-3.00760-0.
4. Wittenberg, R. E.; Wolfman, S. L.; De Biasi, M.; Dani, J. A. Nicotinic Acetylcholine Receptors and Nicotine Addiction: A Brief Introduction. *Neuropharmacology* **2020**, *177*, 108256. https://doi.org/10.1016/j.neuropharm.2020.108256.

5. Xiao, C.; Zhou, C.; Jiang, J.; Yin, C. Neural Circuits and Nicotinic Acetylcholine Receptors Mediate the Cholinergic Regulation of Midbrain Dopaminergic Neurons and Nicotine Dependence. *Acta Pharmacol. Sin.* **2020**, *41* (1), 1–9. https://doi.org/10.1038/s41401-019-0299-4.
6. *Experimental and Clinical Neurotoxicology*, 2nd ed.; Spencer, P. S., Schaumburg, H. H., Ludolph, A. C., Eds.; Oxford University Press: New York, 2023.
7. Wang, J.-G.; Kario, K.; Lau, T.; Wei, Y. Q.; Park, C. G.; Kim, C. H.; Huang, J.; Zhang, W.; Li, Y.; Yan, P.; Hu, D. Use of Dihydropyridine Calcium Channel Blockers in the Management of Hypertension in Eastern Asians: A Scientific Statement from the Asian Pacific Heart Association. *Hypertens. Res.* **2011**, *34* (4), 423–430. https://doi.org/10.1038/hr.2010.259.
8. Ling, Y.; Hao, Z.-Y.; Liang, D.; Zhang, C.-L.; Liu, Y.-F.; Wang, Y. The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design. *DDDT* **2021**, *15*, 4289–4338. https://doi.org/10.2147/DDDT.S329547.
9. Zhang, H. New Insights into Huperzine A for the Treatment of Alzheimer's Disease. *Acta Pharmacol. Sin.* **2012**, *33* (9), 1170–1175. https://doi.org/10.1038/aps.2012.128.
10. Huaman, M. A.; Sterling, T. R. Treatment of Latent Tuberculosis Infection – An Update. *Clinics in Chest Medicine* **2019**, *40* (4), 839–848. https://doi.org/10.1016/j.ccm.2019.07.008.
11. Thee, S.; Garcia-Prats, A. J.; Donald, P. R.; Hesseling, A. C.; Schaaf, H. S. A Review of the Use of Ethionamide and Prothionamide in Childhood Tuberculosis. *Tuberculosis* **2016**, *97*, 126–136. https://doi.org/10.1016/j.tube.2015.09.007.
12. Weinstock, J.; Wu, J.; Cao, P.; Kingsbury, W. D.; McDermott, J. L.; Kodrasov, M. P.; McKelvey, D. M.; Suresh Kumar, K. G.; Goldenberg, S. J.; Mattern, M. R.; Nicholson, B. Selective Dual Inhibitors of the Cancer-Related Deubiquitylating Proteases USP7 and USP47. *ACS Med. Chem. Lett.* **2012**, *3* (10), 789–792. https://doi.org/10.1021/ml200276j.
13. Zetterberg, F. R.; MacKinnon, A.; Brimert, T.; Gravelle, L.; Johnsson, R. E.; Kahl-Knutson, B.; Leffler, H.; Nilsson, U. J.; Pedersen, A.; Peterson, K.; Roper, J. A.; Schambye, H.; Slack, R. J.; Tantawi, S. Discovery and Optimization of the First Highly Effective and Orally Available Galectin-3 Inhibitors for Treatment of Fibrotic Disease. *J. Med. Chem.* **2022**, *65* (19), 12626–12638. https://doi.org/10.1021/acs.jmedchem.2c00660.
14. Niculescu-Duvaz, D.; Gaulon, C.; Dijkstra, H. P.; Niculescu-Duvaz, I.; Zambon, A.; Ménard, D.; Suijkerbuijk, B. M. J. M.; Nourry, A.; Davies, L.; Manne, H.; Friedlos, F.; Ogilvie, L.; Hedley, D.; Whittaker, S.; Kirk, R.; Gill, A.; Taylor, R. D.; Raynaud, F. I.; Moreno-Farre, J.; Marais, R.; Springer, C. J. Pyridoimidazolones as Novel Potent Inhibitors of V-Raf Murine Sarcoma Viral Oncogene Homologue B1 (BRAF). *J. Med. Chem.* **2009**, *52* (8), 2255–2264. https://doi.org/10.1021/jm801509w.
15. Augeri, D. J.; O'Connor, S. J.; Janowick, D.; Szczepankiewicz, B.; Sullivan, G.; Larsen, J.; Kalvin, D.; Cohen, J.; Devine, E.; Zhang, H.; Cherian, S.; Saeed, B.; Ng, S.-C.; Rosenberg, S. Potent and Selective Non-Cysteine-Containing Inhibitors of Protein Farnesyltransferase. *J. Med. Chem.* **1998**, *41* (22), 4288–4300. https://doi.org/10.1021/jm980298s.
16. Malwal, S. R.; Chen, L.; Hicks, H.; Qu, F.; Liu, W.; Shillo, A.; Law, W. X.; Zhang, J.; Chandnani, N.; Han, X.; Zheng, Y.; Chen, C.-C.; Guo, R.-T.; AbdelKhalek, A.; Seleem, M. N.; Oldfield, E. Discovery of Lipophilic Bisphosphonates That Target Bacterial Cell Wall and Quinone Biosynthesis. *J. Med. Chem.* **2019**, *62* (5), 2564–2581. https://doi.org/10.1021/acs.jmedchem.8b01878.
17. Campillo, D.; Belío, Ú.; Martín, A. New Pt→M (M = Ag or Tl) Complexes Based on Anionic Cyclometalated Pt(ii) Complexes. *Dalton Trans.* **2019**, *48* (10), 3270–3283. https://doi.org/10.1039/C9DT00121B.
18. Fortuño, C.; Martín, A.; Mastrorilli, P.; Latronico, M.; Petrelli, V.; Todisco, S. Stable Mixed-Valence Diphenylphosphanido Bridged Platinum(II)–Platinum(IV) Complexes. *Dalton Trans.* **2020**, *49* (15), 4935–4955. https://doi.org/10.1039/D0DT00712A.
19. Zabolotna, Y.; Volochnyuk, D. M.; Ryabukhin, S. V.; Horvath, D.; Gavrilenko, K. S.; Marcou, G.; Moroz, Y. S.; Oksiuta, O.; Varnek, A. A Close-up Look at the Chemical Space of Commercially Available Building Blocks for Medicinal Chemistry. *J. Chem. Inf. Model.* **2022**, *62* (9), 2171–2185. https://doi.org/10.1021/acs.jcim.1c00811.
20. Fürst, H.; Heltzig, M.; Göbel, W. Beitrag Zur Darstellung Des Pyridin-3-sulfochlorids Und Des Pyridin-3-thiols. *J. Prakt. Chem.* **1967**, *36* (3–4), 160–164. https://doi.org/10.1002/prac.19670360306.
21. El-Aal, H. A. K. A.; Khalaf, A. A. Design and Diversity-Oriented Synthesis of Benzo- and Pyrido-Annulated Medium-Sized N,S-Heterocycles via Thio-Michael and Friedel-Crafts Approaches. *Arkivoc* **2019**, *2019* (6), 212–227. https://doi.org/10.24820/ark.5550190.p011.048.
22. St. Jean, D. J.; Ashton, K. S.; Bartberger, M. D.; Chen, J.; Chmait, S.; Cupples, R.; Galbreath, E.; Helmering, J.; Hong, F.-T.; Jordan, S. R.; Liu, L.; Kunz, R. K.; Michelsen, K.; Nishimura, N.; Pennington, L. D.; Poon, S. F.; Reid, D.; Sivits, G.; Stec, M. M.; Tadesse, S.; Tamayo, N.; Van, G.; Yang, K. C.; Zhang, J.; Norman, M. H.; Fotsch, C.; Lloyd, D. J.; Hale, C. Small Molecule Disruptors of the Glucokinase–Glucokinase Regulatory Protein Interaction: 2. Leveraging Structure-Based Drug Design to Identify Analogues with Improved Pharmacokinetic Profiles. *J. Med. Chem.* **2014**, *57* (2), 325–338. https://doi.org/10.1021/jm4016747.
23. Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31* (12), 3980–3984. https://doi.org/10.1021/jo01350a023.
24. Liu, Y.; Kim, J.; Seo, H.; Park, S.; Chae, J. Copper(II)-Catalyzed Single-Step Synthesis of Aryl Thiols from Aryl Halides and 1,2-Ethanedithiol. *Adv. Synth. Catal.* **2015**, *357* (10), 2205–2212. https://doi.org/10.1002/adsc.201400941.
25. Maślankiewicz, A.; Marciniec, K.; Pawlowski, M.; Zajdel, P. From Haloquinolines and Halopyridines to Quinoline- and Pyridinesulfonyl Chlorides and Sulfonamides. *Heterocycles* **2007**, *71* (9), 1975. https://doi.org/10.3987/COM-07-11088.
26. Sawada, N.; Itoh, T.; Yasuda, N. Efficient Copper-Catalyzed Coupling of Aryl Iodides and Thiobenzoic Acid. *Tetrahedron Lett.* **2006**, *47* (37), 6595–6597. https://doi.org/10.1016/j.tetlet.2006.07.008.
27. Ho, D. K. H.; Chan, L.; Hooper, A.; Brennan, P. E. A General and Mild Two-Step Procedure for the Synthesis of Aryl and Heteroaryl Sulfonamides from the Corresponding Iodides. *Tetrahedron Lett.* **2011**, *52* (7), 820–823. https://doi.org/10.1016/j.tetlet.2010.12.050.

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