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Convenient and versatile method of 8-amino-6-(2-R-thiazol-4-yl)-1,7-naphthyridines synthesis

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A B S T R A C T

On the base of 3-formylpicolinic acid by two successive heterocyclizations (the formation of a pyrone fragment by the cyclization of chloroacetone with the carboxyl and formyl groups; and the construction of the thiazole cycle through the bromination of the acetyl fragment and following interaction with thioamides), 6-(2-(phenyl/thiophen-2-yl)thiazole-4-yl)-8*H*-pyrano[3,4-*b*]pyridin-8-ones were obtained; and then the pyrone fragment was converted to pyridone by the action of ammonia under high pressure. When such 6-(2-R-thiazol-4-yl)-1,7-naphthyridin-8(7*H*)-ones reacted with triflic anhydride, *O*-sulfonylation of the pyridone fragment occurred, after that triflate group was easily substituted by secondary cyclic aliphatic amines. Thus, a number of new 8-amino-6-(2-R-thiazol-4-yl)-1,7-naphthyridines – previously inaccessible heterocyclic derivatives with promising biological activity – were obtained.

1. Introduction

Researchers' interest in a certain class of compounds is often caused by these substances' useful properties, and obviously, the last ones are the result of the character of the molecule structure. Therefore, in the design of new compounds, chemists may use the fragments of substances with already proven relationships between the structure and the application possibilities. One of the options for the basic structure modification is replacing certain fragments of the molecule with geometrically similar ones. An example of such a method of molecular modifying is the creation of aza-analogues of (hetero)aromatic systems.

Sometimes the synthesis of aza analogues is carried out to study how this modification affects the practically useful properties of the substance. For example, aza-analogues **1a,b** Pafuramidine (DB289) **1c** (**Fig. 1**) were obtained;[1] the initial drug was created for the treatment of the first stage of African sleeping sickness, but has not been put into practice because of kidney toxicity.[2]

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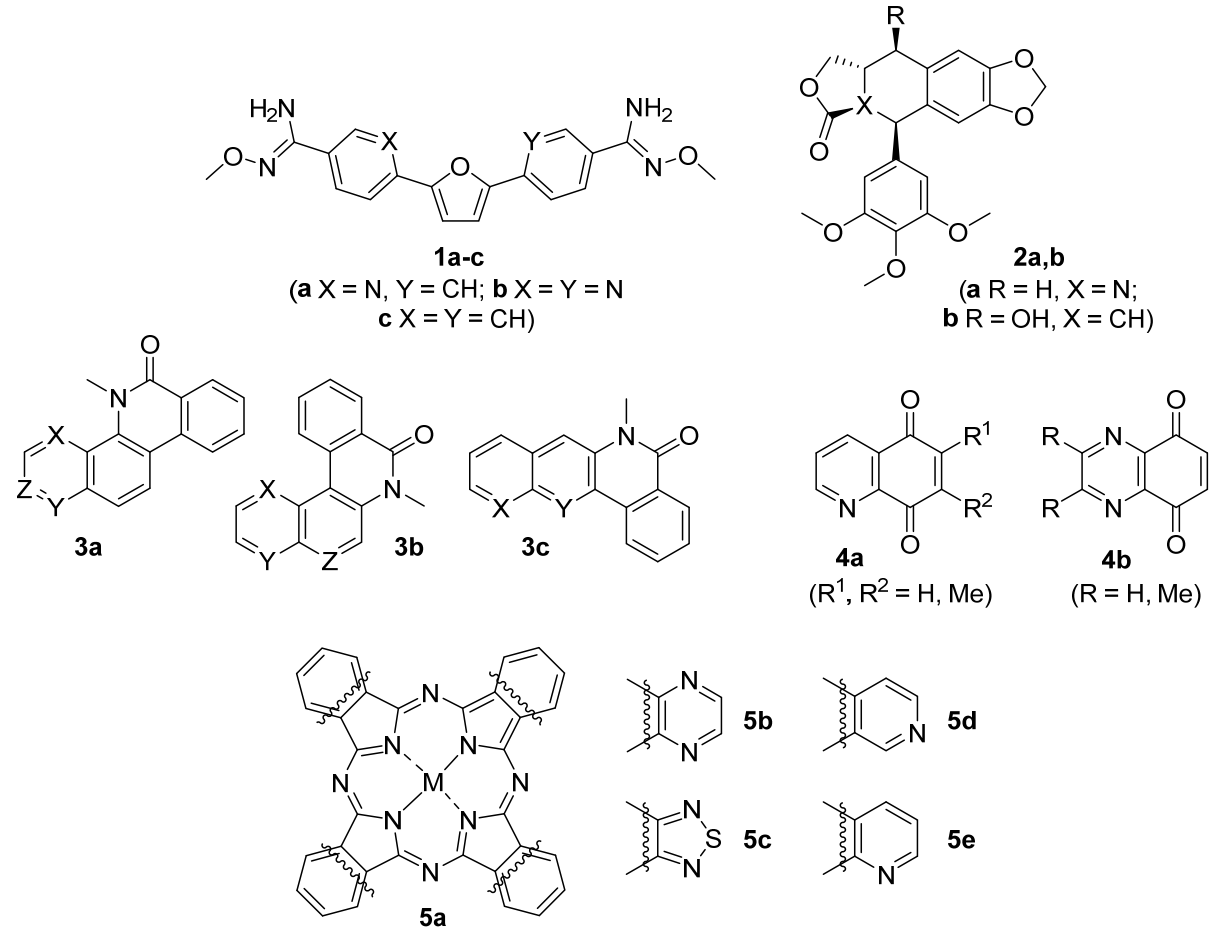
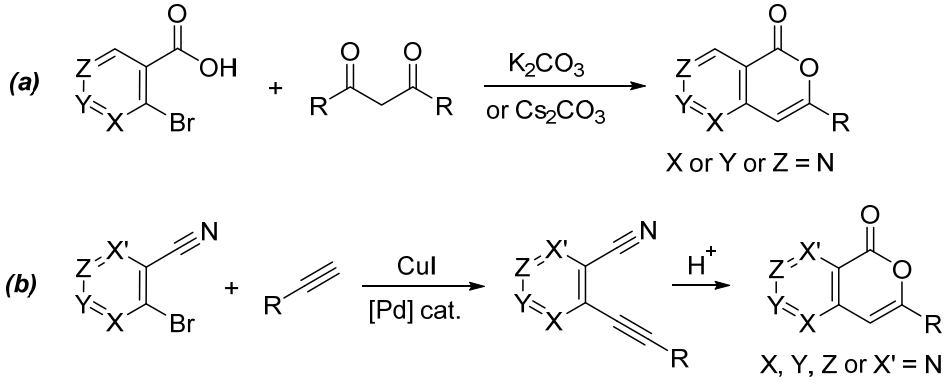


Fig. 1. Aza-analogues of bioactive (hetero)aromatic substances

Also, the literature data (**Fig. 1**) reported about the directed synthesis of substance **2a**[3] – aza-analogue of cytotoxic agent Podophyllotoxin **2b**; about obtaining a library of potentially cytotoxic aza-analogues **3**[4] of benzo[*c*]phenanthridine alkaloids; about the synthesis of aza-1,4-naphthoquinone **4a-c** (possible antimalarial activity);[5] and about obtaining of phthalocyanine photosensitizers aza-analogues (compounds **5b-e**),[6] etc.

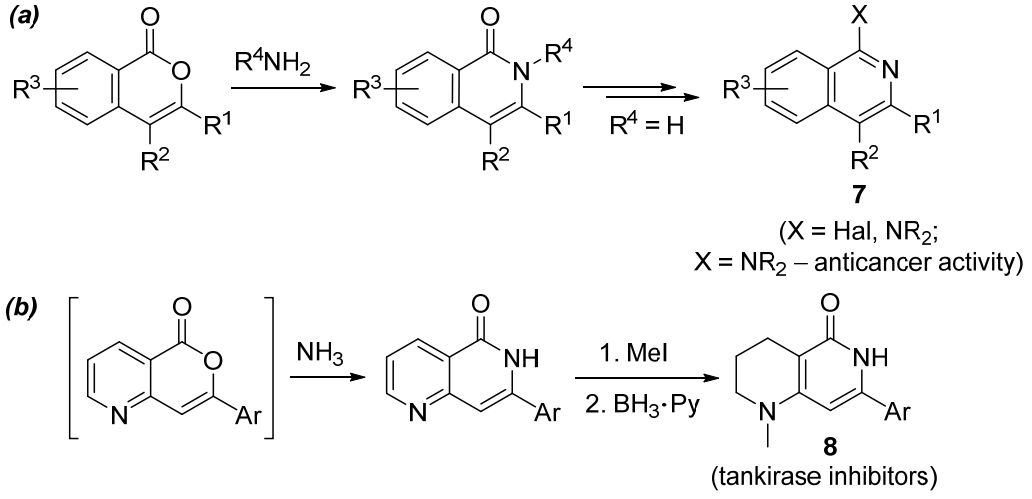
Not only the biological characteristics of (hetero)aromatic cycles aza-analogues creation may be interesting; the synthesis of such compounds is often uneasy task for researchers. The method of aza-analogues obtaining can be radically different from the scheme of synthesis of the original molecule;[7] but sometimes, the similar principles can be used for construction of the aza-analogue and the initial structure.



Scheme 1. The main strategies for the azaisocoumarins synthesis

Thus, the strategies for the synthesis of the currently known rare isocoumarins aza-analogues are very close to the methods of isocoumarins obtaining, such as condensation of *ortho*-halogen substituted (het)aromatic carboxylic acids and symmetric 1,3-diketones (**Scheme 1a**);[8] or metal-catalyzed coupling of similar acids or their derivatives and terminal alkynes with subsequent cyclization (**Scheme 1b**).[8–11]

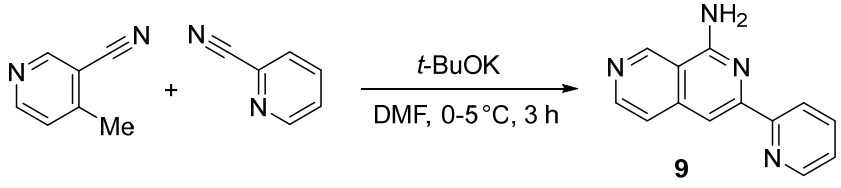
It's well known that isocoumarins can be used in the synthesis of isoquinoline derivatives.[12] In particular, we have recently obtained functionalized isoquinolines (**Scheme 2a**) based on 3-hetarylisocoumarins, which were synthesized from 3-(2-bromoacetyl)isocoumarin.[13] The most interesting among these products were 1-aminoisoquinolines **7**, because they demonstrated anti-cancer activity, unlike their precursors. This fact gives a reason to use this synthetic approach (**Scheme 2a**) for the transformation of azaisocoumarins with a heterocyclic substituent into appropriate naphthyridones. At least, in the literature[8] there is an example of bioactive naphthyridone derivatives **8** synthesis from the azaisocoumarins (**Scheme 2b**).



Scheme 2. Recyclization of (aza)isocoumarins as a method of bioactive compounds obtaining

Therefore, the aim of our work was to implement the following synthetic sequence: bromination of the acetyl fragment of 3-acetylazaisocoumarin, creation of the heterocyclic substituent in position 3 of azaisocoumarin due to the interaction of bromoacetyl group with the corresponding binucleophile, recyclization of lactone under the action of ammonia, conversion of naphthyridinone to aminonaphthyridine.

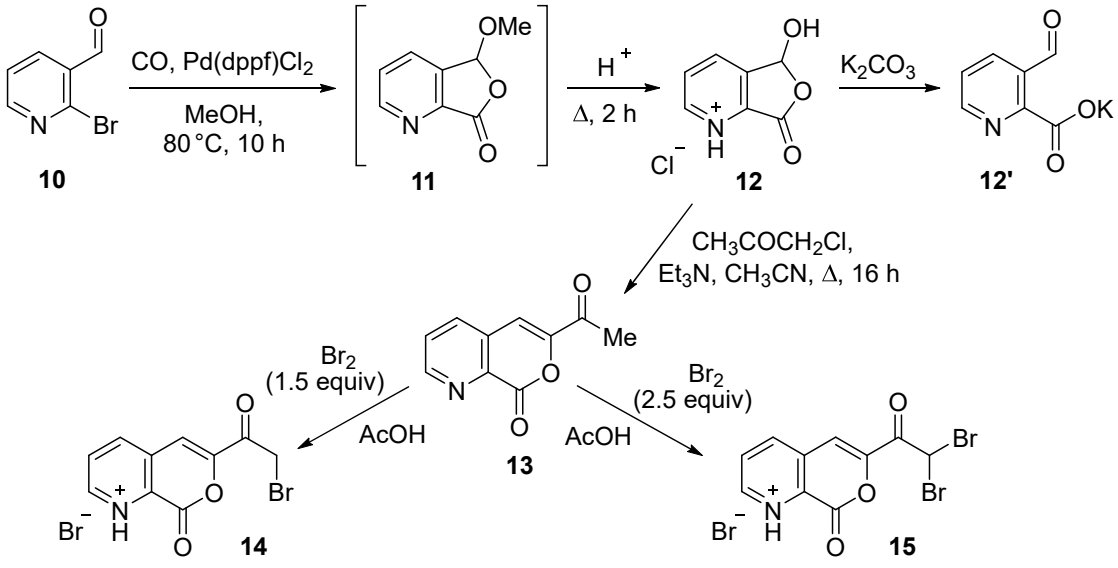
In addition, this strategy of hetaryl substituted aminonaphthyridine creation can make such interesting heterocycles more numerous and diverse. Now this group is limited only to pyridine substituted derivatives with promising biological activity such as compound **9** (**Scheme 3**),[14,15] but their synthesis can't provide enough variability.



Scheme 3. Synthesis of 1-amino-3-(pyridine-2-yl)-2,7-naphthyridine

2. Results and Discussion

Like the previous 3-acetylisocoumarin synthesis, our strategy of its aza-analogues obtaining was based on the formylpyridinecarboxylic acids using. Such precursors aren't inexpensive; so we started with more synthetic available isomer – 3-formylpicolinic acid. The last one may be synthesized by Pd-catalyzed carbonylation of 2-bromonicotinaldehyde (**10**). The product of this reaction – acetal **11** – was formed after 16 h treatment with CO in hydrothermal autoclave (**Scheme 4**). After removing the solvent, the resulting solid contained nearly 85 % of substance **11**, which could be easily identified by the typical signal of acetal CH fragment in ^{1}H NMR spectra: 5.78 ppm. The crude product **11** without purification was hydrolysed in acidic aqua medium, and the 3-formylpicolinic acid (**12**) was obtained with 56 % yield in two steps. It should be noted, that earlier oxidation of 8-hydroxyquinoline[17] and reducing of pyridine-2,3-dicarboxylic acidanhydride[14] were used for substance **12** obtaining; so carbonylation as a synthesis of 3-formylpicolinic acid is a good alternative to previous known methods.



Scheme 4. Synthesis of 6-acetyl-8*H*-pyrano[3,4-*b*]pyridin-8-one and its bromination

While the analytical pure compound **12** in NMR spectra was registered only as cyclic hemiacetal (**Fig. 2**), in the crude product spectrum a little amount of non-cyclic form can be observed. The sample of pure potassium salt **12'** (**Scheme 4**) was prepared by solving the compound **12** in water with the equivalent amount of K_2CO_3, and further water evaporation.

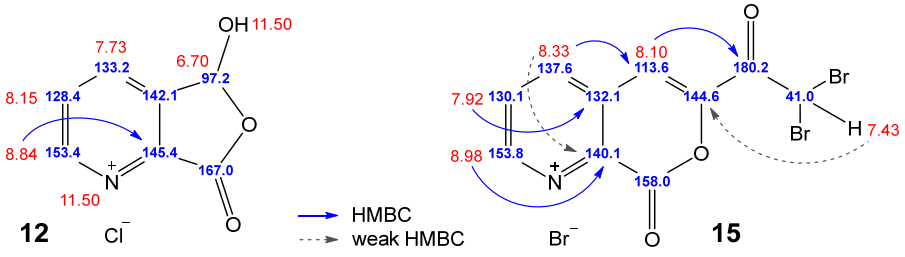
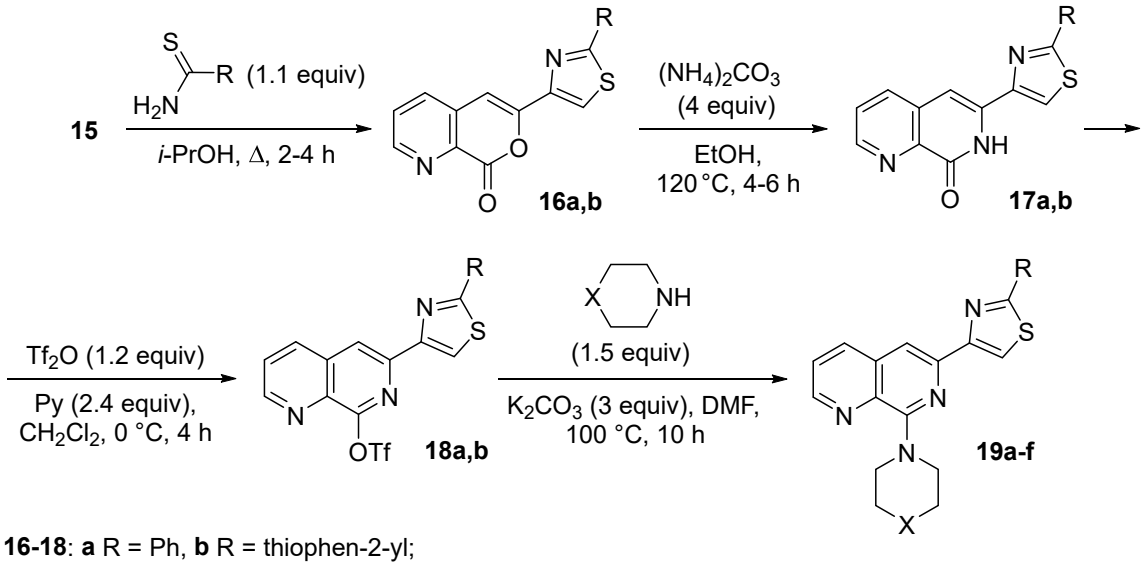


Fig. 2. ^{1}H NMR (red) and ^{13}C NMR (blue) data of compounds **12, 15** (δ, ppm)

For the reaction of substance **12** with chloroacetone, we used the procedure which had been early adapted by us for convenient 3-acetylisocoumarin syntheses[18]. This condensation without difficult operations gave enough yield for the target product **13** (**Scheme 4**). But the bromination of 6-acetyl-8*H*-pyrano[3,4-*b*]pyridin-8-one (**13**) wasn't so easy and needed an thoroughnessin the realization of the procedure because of the possible formation of two products. To obtain separate mono- **14** and dibromoderivative **15** (**Scheme 4**), 1.5 and 2.5 equiv, respectively, of the bromine must be slowly added to a hot solution of ketone **13** (see also Experimental section). Another serious problem was instability of monobromoderivative **14** in high concentrated solution and in isolated form. That is why only its ^{1}H NMR spectrum was recorded; correct ^{13}C NMR spectrum, and elemental analysis data couldn't be registered. ^{1}H NMR and LC/MS spectra recorded immediately after the extraction of the substance and corresponded to the structure; but in a more concentrated solution, when ^{13}C NMR spectrum was recorded, the additional signals were detected, and over time, their share only increased, in spite of what solvent was used ($CDCl_3$, DMSO-d_6, CF_3CO_2D). Small crystals of substance **14**, which were isolated as a result of synthetic procedures (see Experimental section), significantly changed their form and colour within 1-2 days. Such a sample could still be used in some synthetic manipulations with a satisfactory result, but its quality was not enough to establish characteristics like elemental analysis.

These synthetic troubles motivated us to choose in the further stage the maximal convenient binucleophile for heterocyclization. Early,[13,18] good results were reached in Hantzsch reaction of 3-(2-bromoacetyl)isocoumarin with thioamides, and the series of 3-(2-R-thiazol-4-yl)isocoumarins were obtained. α-Bromoketones are well known substrates for Hantzsch thiazole synthesis. But it is also known that α,α-dibromoketones can react with thioamides to give the same thiazoles.[19,20] And 6-(2-R-thiazol-4-yl)-8*H*-pyrano[3,4-*b*]pyridin-8-ones **16a,b** were really synthesized by us on the base of dibromoderivative **15** (**Scheme 5**); fortunately, isolation of the last one in spectral pure form (**Fig. 2**) in significant quantities wasn't difficult, unlike monobromoderivative **14**.



16-18: **a** R = Ph, **b** R = thiophen-2-yl;
19: **a** R = Ph, X = NMe, **b** R = Ph, X = O, **c** R = Ph, X = S,
d R = thiophen-2-yl, X = NMe, **e** R = thiophen-2-yl, X = O, **f** R = thiophen-2-yl, X = S

Scheme 5. Synthesis of 6-(2-R-thiazol-4-yl)-8*H*-pyrano[3,4-*b*]pyridin-8-ones and their recyclization to 8-oxy(amino)-6-(thiazol-4-yl)-1,7-naphthyridines

Recyclization of the pyrone core of substances **16a,b** into pyridinone took place in ethanol solution with heating and high pressure due to the excess of $(NH_4)_2CO_3$ (an ammonia equivalent) action; and the naphthyridones **17a,b** were formed with a high purity.

For transformation of naphthyridones **17a,b** into target naphthyridines, the triflates **18a,b** were obtained by the triflic anhydride action (**Scheme 5**). The triflate residue was easily substituted with the alicyclic secondary amine (*N*-methylpiperazine, morpholine, thiomorpholine) in DMF solution and K_2CO_3 as a base. First we planned to convert naphthyridones **17a,b** into 8-chloro-1,7-naphthyridines by $POCl_3$ action in order to substitute Chlorine atom by the amine, as in work[13] for isoquinolones was done; but unfortunately $POCl_3$caused the substances **17a,b** destruction. So, triflates **18a,b** were the best substrates for 8-amino-6-hetaryl-1,7-naphthyridines **19a,b** obtaining.

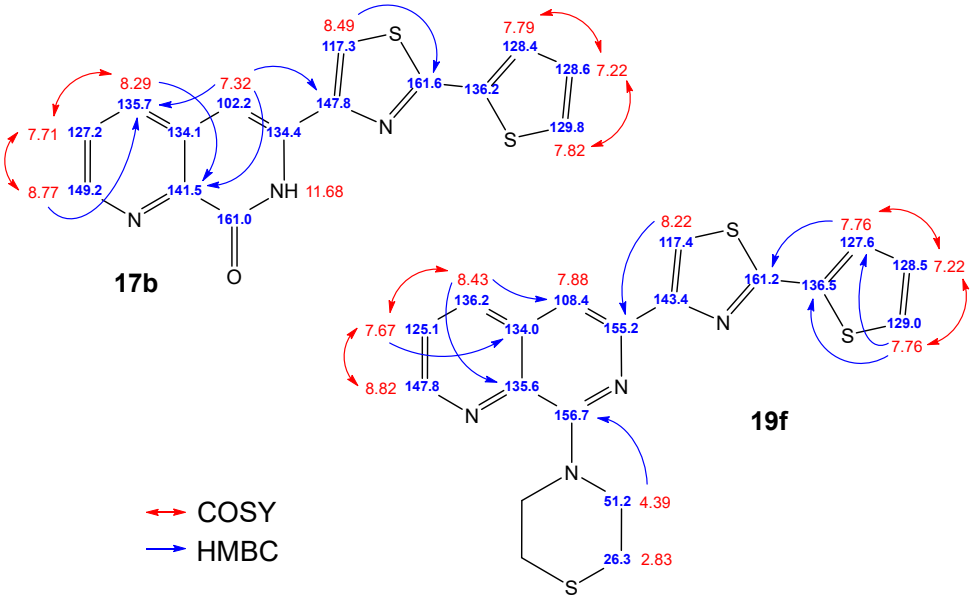


Fig. 3. ^{1}H NMR (red) and ^{13}C NMR (blue) data of compounds **17b, 19f** (δ, ppm)

This methodology of 6-hetaryl-1,7-naphthyridines synthesis can be used subsequently for the synthesis of other similar compounds, so, unambiguous recognition of the signals in NMR spectra might be helpful in practical analysis of the

products. For identification of all the signals in ^{1}H and ^{13}C NMR spectra of naphthyridone **17b** (halfway product) and naphthyridine **19f** (finished product), a number of correlation techniques (COSY, HSQC, HMBC) were used (**Fig. 3**).

It is noteworthy, that naphthyridines **18a,b**, because of the presence of aliphatic amine residue, have high solubility in organic solvents (EtOAc, toluene) and also in diluted aqueous acid; such properties should be suitable for further biological investigation.

3. Conclusions

Thus, the product of dibromination of the acetyl fragment in 6th position of 8*H*-pyrano[3,4-*b*]pyridin-8-one position has indeed proven to be a convenient and productive precursor for the synthesis of new heterocyclic naphthyridone derivatives: using the dibromoacetyl group, a 2-R-thiazole-4-yl substituent was easily added to pyranopyridine, then, under the ammonia action, the pyranopyridine cycle was converted to 1,7-naphthyridine with oxo- and amino groups in position 8. During the variation of substituents in the thiazol cycle and the residues of cyclic secondary amines in position 8 1,7-naphthyridine, no difficulties or limitations were observed. Furthermore, the dibromoacetyl group may be used for not only the thiazole cycle, but also for the synthesis of other heterocycles, therefore, it makes possible to create an extremely large variety of 8-amino-6-hetaryl-1,7-naphthyridines to study the prospects for their practical use.

Acknowledgements

We would like to thank *Enamine* Ltd for the material and technical support, and the "European Chemistry School for Ukrainians" (https://ecpsfu.org/) for new scientific ideas.

4. Experimental

4.1. General Methods

All reagents and solvents were purchased from Aldrich and used as received. The reaction progress was monitored by the TLC method on Silica gel 60 F_{254} Merck; the eluent was $CHCl_3$–methanol 9:1. NMR spectra of obtained products were recorded at Varian Unity Plus 400 spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C), Bruker 170 spectrometer (500 MHz for ^{1}H and 126 MHz for ^{13}C), and Agilent ProPulse 600 spectrometer (600 MHz for ^{1}H, 151 MHz for ^{13}C); chemical shifts are reported in ppm with solvent residual signal used as an internal standard (^{1}H, ^{13}C). Melting points were measured on an automated melting point System Opti Melt. Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry NAS of Ukraine.

Chromatomass spectra (MS) were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC/MS mass selective detector allowing a fast switching of the positive/negative ionization modes (chemical ionization).

4.2. Synthetic Procedures and Spectral Data

*4.2.1. 5-Hydroxyfuro[3,4-b]pyridin-7(5H)-one hydrochloride (**12**).* To a solution of 2-bromonicotinaldehyde (**10**) (74.40 g, 0.4 mol) in methanol (1 L) $Pd(dppf)Cl_2$(10.24 g, 0.014 mol, 3.5 mol %) was added and the reaction mixture was stirred in CO atmosphere (70 bar) at 110 °C for 16 h. After the reaction finished, the solvent was evaporated under reduced pressure, and EtOAc (2.5 L) was added to the residue; the mixture was heated and filtered from the non-soluble residue, the solvent was evaporated under reduced pressure, earning the crude product **11**. The compound **11** without purification was suspended in water (0.5 L) and concentrated HCl (170 mL, 2 mol, 5 equiv) was added. The reaction mixture was stirred at 80 °C for 4 h. After the reaction finished, the solvent was evaporated under reduced pressure, and the residue was treated by MeCN (250 mL), and filtered off. Then another portion of hot MeCN (250 mL) was added to the solid, the mixture was heated with stirring for 2-3 min to dissolve the by-products, and then the solid of pure product **12** was filtered off. Yield 56 %. Mp 115-116 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 8.89 (d, J = 4.7 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H), 7.76 (dd, J = 7.8, 4.7 Hz, 1H), 6.71 (s, 1H); OH exchanged with H_2O. ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 167.0, 153.4, 145.4, 142.1, 133.2, 128.4, 97.2. LCMS, *m/z*: 150.2 $[M\text{-}HCl\text{-}1]^-$. Anal. Calcd for $C_7H_6ClO_3$: C, 44.82; H, 3.22; Cl 18.90; N, 7.47 %. Found: C, 44.93; H, 3.24; Cl 18.91; N, 7.49 %.

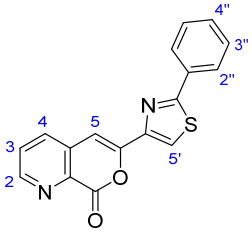
*Potassium 3-formylpicolinate(**12'**).* To a suspension of compound **12** (0.30 g, 2 mmol) in water (10 mL) K_2CO_3 (0.28 g, 2 mmol, 1 equiv) was added, and the mixture was stirred up to obtain a clear solution. The water was evaporated under reduced pressure; the solid residue was filtered off, washed by methanol and dried, gettingthe target salt with an almost quantitative yield. Mp 248-249 °C. ^{1}H NMR (500 MHz, D_2O), δ, ppm: 10.31 (s, 1H, CH=O), 8.59 (dd, J = 4.8, 1.8 Hz, 1H, H-6), 7.91 (dd, J = 7.8, 1.8 Hz, 1H, H-4), 7.32 (dd, J = 7.8, 4.8 Hz, 1H, H-5). ^{13}C NMR (126 MHz, D_2O), δ, ppm: 193.5, 172.7, 157.2, 152.4, 137.9, 127.2, 124.0.

*4.2.2. 6-Acetyl-8H-pyrano[3,4-b]pyridin-8-one (**13**).* To a solution of compound **12** (30.0 g, 0.2 mol) in MeCN (500 mL) chloroacetone (20.4 mL, 0.24 mol, 1.2 equiv) and Et_3N (67.0 mL, 0.48 mol, 2.4 equiv) were added; and the mixture was refluxed with stirring for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue was dissolved into boiling EtOAc. This solution was filtered twice through a silicagel layer to purify from tar admixtures, and the solvent was evaporated under reduced pressure to about 100 mL. The mixture was carefully stirred until ahomogeneous suspension was formed, the solid residue was filtered off. Yield 68 %. Mp 179-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.98 (d, J = 4.5 Hz, 1H, H-2), 8.00 (d, J = 8.0 Hz, 1H, H-4), 7.71 (dd, J = 8.0, 4.5 Hz, 1H, H-3), 7.35 (s, 1H, H-5), 2.58 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 191.8, 158.6, 153.0, 150.0, 140.1, 136.3, 132.3, 129.1, 107.0, 26.2. LCMS, *m/z*: 190.0 $[M+1]^+$. Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40 %. Found: C, 63.34; H, 3.62; N, 7.45 %.

*4.2.3. 6-(2-Bromoacetyl)-8H-pyrano[3,4-b]pyridin-8-one hydrobromide (**14**).* To a solution of compound **13** (9.46 g, 0.05 mol) in AcOH (200 mL) concentrated hydrobromic acid (11.4 mL, 0.1 mol, 2 equiv) was added. The mixture was heated to 70 °C, and the solution of bromine (3.9 mL, 0.075 mol, 1.5 equiv) in AcOH (50 mL) was slowly added into the stirred mixture. After bromine was added, the mixture was stirred at 70 °C for 0.5 h; then the solvent was completely removed by evaporation under reduced pressure. The product involved an initial compound admixture, so it was dissolved into a large volume of boiling $CHCl_3$ (about 1 L for 1 g), and filtered from non-solving admixtures; then the solvent was evaporated under reduced pressure. Yield 48 %. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 8.99 (dd, J = 4.5, 1.6 Hz, 1H, H-2), 8.34 (dd, J = 8.1, 1.6 Hz, 1H, H-4), 7.93 (dd, J = 8.1, 4.5 Hz, 1H, H-3), 7.90 (s, 1H, H-5), 4.80 (s, 2H, CH_2). LCMS, *m/z*: 268 $[M–Br]^+$.

*4.2.4. 6-(2,2-Dibromoacetyl)-8H-pyrano[3,4-b]pyridin-8-onehydrobromide (**15**).*To a solution of compound **13** (9.46 g, 0.05 mol) in AcOH (200 mL) concentrated hydrobromic acid (11.4 mL, 0.1 mol, 2 equiv) was added. The mixture was heated to 70 °C, and the solution of bromine (6.5 mL, 0.125 mol, 2.5 equiv) in AcOH (50 mL) was slowly added into the stirred mixture. After bromine was added, the mixture was stirred at 70 °C for 0.5 h; then the mixture was cooled to room temperature, the precipitate was filtered off, washed by AcOH, and recrystallized from AcOH. Yield 77 %. Mp 159-160 °C. ^{1}H NMR (600 MHz, DMSO-d_6), δ, ppm: 8.98 (dd, J = 4.5, 1.6 Hz, 1H, H-2), 8.33 (dd, J = 8.0, 1.6 Hz, 1H, H-4), 8.10 (s, 1H, H-5), 7.92 (dd, J = 8.0, 4.5 Hz, 1H, H-3), 7.43 (s, 1H, $CHBr_2$). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 180.2, 158.0, 153.8, 144.6, 140.1, 137.6, 132.1, 130.1, 113.6, 41.0. LCMS, *m/z*: 345.8 $[M\text{-}HBr\text{-}1]^-$. Anal. Calcd for $C_{10}H_6Br_3NO_3$: C, 28.07; H, 1.41; Br, 56.02; N, 3.27 %. Found: C, 28.31; H, 1.38; Br, 55.88; N, 3.30 %.

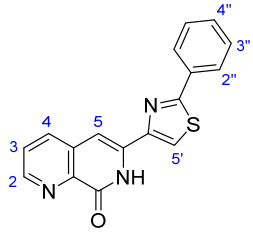
*4.2.6. 6-(2-R-Thiazol-4-yl)-8H-pyrano[3,4-b]pyridin-8-ones **16a,b** Synthesis.* To a solution of hydrobromideof dibromoketone **15** (4.28 g, 0.01 mol) in *i*-PrOH (30 mL) corresponding thioamide (0.0105 mol) was added, and the mixture was refluxed with stirring for 4-6 h. After the mixture was cooled to the room temperature, the precipitate was filtered off, washed by water and recrystallized from *i*-PrOH.



*6-(2-Phenylthiazol-4-yl)-8H-pyrano[3,4-b]pyridin-8-one (**16a**).*Yield 86 %. Mp 267-268 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 8.84 (d, J = 4.4 Hz, 1H, H-2), 8.28 (d, J = 8.1 Hz, 1H, H-4), 8.25 (s, 1H, H-5'), 8.09 – 8.03 (m, 2H, H-2",6"), 7.84 (dd, J = 8.1, 4.4 Hz, 1H, H-3), 7.60 – 7.55 (m, 4H, H-5,3"–5"). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 168.4, 158.7, 150.7, 149.0, 147.5, 137.5, 135.1, 134.2, 132.3, 130.9, 129.3 × 2, 129.2, 126.4 × 2, 119.5, 101.8. LCMS, *m/z*: 307.2 $[M+1]^+$. Anal. Calcd for $C_{17}H_{10}N_2O_2S$: C, 66.65; H, 3.29; N, 9.14; S, 10.47 %. Found: C, 66.63; H, 3.31; N, 9.18; S, 10.49 %.

*6-(2-(Thiophen-2-yl)thiazol-4-yl)-8H-pyrano[3,4-b]pyridin-8-one(**16b**).*Yield 75 %. Mp 273-274 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 8.83 (d, J = 4.0 Hz, 1H, H-2), 8.28 (d, J = 8.1 Hz, 1H, H-4), 8.14 (s, 1H, H-5'), 7.84 – 7.74 (m, 3H, H-3,3",5"), 7.45 (s, 1H, H-5), 7.22 (t, J = 4.2 Hz, 1H, H-4"). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 162.4, 158.7, 150.7, 148.8, 147.0, 137.6, 135.6, 135.3, 134.2, 129.9, 129.2, 128.6 × 2, 119.0, 101.8. LCMS, *m/z*: 313.0 $[M+1]^+$. Anal. Calcd for $C_{15}H_8N_2O_2S_2$: C, 57.68; H, 2.58; N, 8.97; S, 20.53 %. Found: C, 57.45; H, 2.54; N, 9.04; S, 20.30 %.

*4.2.7. 6-(2-R-Thiazol-4-yl)-1,7-naphthyridin-8(7H)-ones **17a,b** Synthesis.* A mixture of *8H*-pyrano[3,4-*b*]pyridin-8-one **16** (7.5 mmol) and $(NH_4)_2CO_3$ (2.90 g, 0.03 mol, 4 equiv) in *i*-PrOH (30 mL) was stirred at 120 °C in a hydrothermal autoclave for 4-6 h. When the mixture was cooled, the precipitate was formed; then it was filtered off, washed with H_2O, and purified by crystallization from EtOH–DMF, 1:1.

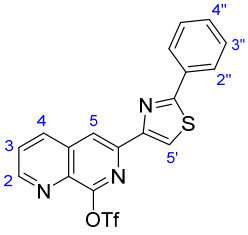


*6-(2-Phenylthiazol-4-yl)-1,7-naphthyridin-8(7H)-one (**17a**).*Yield 84 %. Mp 270-271 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 11.65 (br. s, 1H, NH), 8.78 (dd, J = 4.4, 1.7 Hz, 1H, H-2), 8.57 (s, 1H, H-5'), 8.25 (dd, J = 8.0, 1.7 Hz, 1H, H-4), 8.11-8.07 (m, 2H, H-2",6"), 7.71 (dd, J = 8.0, 4.4 Hz, 1H, H-3), 7.59-7.52 (m, 3H, H-3"-5"), 7.44 (s, 1H, H-5). ^{13}C NMR (126 MHz, CF_3CO_2D), δ, ppm: 176.7, 157.3, 147.6, 144.6, 138.9, 136.0, 135.9, 132.0, 131.3, 130.6, 130.3 × 2, 127.8 × 2, 124.6, 123.1, 106.1. LCMS, *m/z*: 305.0 $[M+1]^+$. Anal. Calcd for $C_{17}H_{11}N_3OS$: C, 66.87; H, 3.63; N, 13.76; S, 10.50 %. Found: C, 66.71; H, 3.61; N, 13.82 %.

*6-(2-(Thiophen-2-yl)thiazol-4-yl)-1,7-naphthyridin-8(7H)-one (**17b**).*Yield 81 %. Mp 275-276 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 11.68 (s, 1H, NH), 8.77 (d, J = 4.3 Hz, 1H, H-2), 8.49 (s, 1H, H-5'), 8.29 (d, J = 8.0 Hz, 1H, H-4), 7.82 (d, J = 5.0 Hz, 1H, H-5"), 7.79 (d, J = 3.8

Hz, 1H, H-3"), 7.71 (dd, *J* = 8.0, 4.3 Hz, 1H, H-3), 7.32 (s, 1H, H-5), 7.22 (br. t, *J* = 4.4 Hz, 1H, H-4"). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 161.6, 161.0, 149.2, 147.8, 141.5, 135.7, 135.5, 134.4, 134.1, 129.8, 128.6, 128.4, 127.2, 117.3, 102.2. LCMS, *m/z*: 312.0 $[M+1]^+$. Anal. Calcd for $C_{15}H_9N_3OS_2$: C, 57.86; H, 2.91; N, 13.50; S, 20.59 %. Found: C, 57.77; H, 2.93; N, 13.54 %.

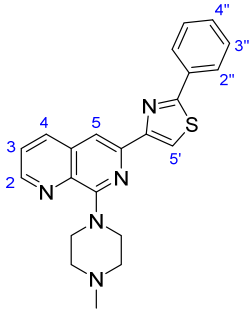
4.2.8. 6-(2-R-Thiazol-4-yl)-1,7-naphthyridin-8-yl trifluoromethanesulfonates ***18a,b*** *Synthesis.* To a solution of 1,7-naphthyridin-8(7*H*)-one**17**(5 mmol)CH_2Cl_2 (25 mL) at 0 °C triflic anhydride (1.1 mL, 6.0 mmol, 1.2 equiv) and pyridine (0.96 mL, 12 mmol, 2.4 equiv) were added. The mixture was stirred at 0 °C for 4 h, then H_2O (25 mL) and CH_2Cl_2 (25 mL) were added; the organic layer was separate, dried with Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The solid residue was suspended in MTBE (25 mL) and the spectrally pure product was filtered off. Additionally, it can be purified by crystallization from a small amount of EtOAc.



*6-(2-Phenylthiazol-4-yl)-1,7-naphthyridin-8-yl trifluoromethanesulfonate (****18a****).*Yield 92 %. Mp 168-169 °C. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 9.20 (d, *J* = 4.0 Hz, 1H, H-2), 8.89 (s, 1H, H-5), 8.79 (d, *J* = 8.4 Hz, 1H, H-4), 8.30 (s, 1H, 5'), 8.12 (d, *J* = 7.2 Hz, 2H, H-2",6"), 8.01 (dd, *J* = 8.4, 4.0 Hz, 1H, H-3), 7.62 – 3.31 (m, 3H, H-3"-5"). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 168.5, 153.8, 152.7, 151.4, 143.3, 136.1, 136.1, 134.0, 132.6, 130.7, 129.3 × 2, 127.6, 126.3× 2, 119.8, 118.9; the Carbon of CF_3 group not identified. ^{19}F NMR (376 MHz, DMSO-d_6), *δ*, ppm: -73.63. LCMS, *m/z*: 438.0 $[M+1]^+$. Anal. Calcd for $C_{18}H_{10}F_3N_3O_3S_2$: C, 49.43; H, 2.30; F, 13.03; N, 9.61; S, 14.66 %. Found: C, 49.25; H, 2.32; N, 9.63; S, 14.67 %.

*6-(2-(Thiophen-2-yl)thiazol-4-yl)-1,7-naphthyridin-8-yl trifluoromethanesulfonate(****18b****).*Yield 88 %. Mp 202-203 °C. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 9.19 (dd, *J* = 4.2, 1.6 Hz, 1H, H-2), 8.83 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 8.74 (s, 1H, H-5), 8.23 (s, 1H, H-5'), 7.99 (dd, *J* = 8.4, 4.2 Hz, 1H, H-3), 7.84-7.81 (m, 2H, H-3",5"), 7.24 (dd, *J* = 5.0, 3.7 Hz, 1H, H-4"). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 162.4, 153.9, 152.2, 151.5, 143.0, 136.3, 136.2, 136.0, 134.0, 129.6, 128.6, 128.3, 127.7, 119.4, 118.8; the Carbon of CF_3 group not identified. ^{19}F NMR (376 MHz, DMSO-d_6), *δ*, ppm: -73.64. LCMS, *m/z*: 443.8 $[M+1]^+$. Anal. Calcd for $C_{16}H_8F_3N_3O_3S_3$: C, 43.34; H, 1.82; F, 12.85; N, 9.48; S, 21.69 %. Found: C, 43.43; H, 1.84; N, 9.54; S, 21.72 %.

4.2.9. 4-(8-Dialkylamino-1,7-naphthyridin-6-yl)-2-R-thiazoles ***19a-e*** *Synthesis.*To a solution of triflate **18** (2.5 mmol) in DMF (10 mL) corresponding amine (1-methylpiperazine or morpholine or thiomorpholine, 3.75 mmol, 1.5 equiv) and K_2CO_3 (1.04 g, 7.5 mmol, 3 equiv) were added, and the resulting mixture was heated with stirring at 100 °C for 10 h. The hot reaction mixture was filtered from inorganic residue, and the solvent was evaporated. EtOAc (25 mL) was added to the residue; the mixture was heated and filtered from the residue. The clear solution was kept at -10 °C until colourless or yellowish crystals were formed, which were filtered off, washed with cold EtOAc to get a spectrally pure product. The filtrate after crystallization still contained a significant portion of the target product, thus the solvent was evaporated and the residue was recrystallized from EtOAc (10 mL).



*4-(8-(4-Methylpiperazin-1-yl)-1,7-naphthyridin-6-yl)-2-phenylthiazole (****19a****).*Yield 74 %. Mp 118-119 °C. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 8.83 (dd, *J* = 4.2, 1.6 Hz, 1H, H-2), 8.40 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 8.30 (s, 1H, H-5), 8.08 (d, *J* = 6.6 Hz, 2H, H-2",6"), 8.00 (s, 1H, H-5'), 7.68 (dd, *J* = 8.4, 4.2 Hz, 1H, H-3), 7.61-7.50 (m, 3H, H-3"-5"), 4.13-4.06 (m, 4H, 2 NCH_2), 2.56 (t, *J* = 4.8 Hz, 4H, 2 NCH_2), 2.26 (s, 3H, NCH_3). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 167.3, 157.1, 155.9, 147.7, 143.7, 136.0, 135.8, 134.0, 133.0, 130.4, 129.3× 2, 126.2× 2, 125.0, 117.9, 108.5, 54.9× 2, 48.4× 2, 45.9. LCMS, *m/z*: 388.0 $[M+1]^+$. Anal. Calcd for $C_{22}H_{21}N_5S$: C, 68.19; H, 5.46; N, 18.07; S, 8.27 %. Found: C, 68.42; H, 5.50; N, 8.12 %; S, 8.27 %.

*4-(6-(2-Phenylthiazol-4-yl)-1,7-naphthyridin-8-yl)morpholine (****19b****).*Yield 85 %. Mp 168-169 °C. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 8.83 (d, *J* = 4.2 Hz, 1H, H-2), 8.41 (d, *J* = 8.4 Hz, 1H, H-4), 8.30 (s, 1H, H-5), 8.08 (d, *J* = 7.8 Hz, 2H, H-2",6"), 8.03 (s, 1H, H-5'), 7.69 (dd, *J* = 8.4, 4.2 Hz, 1H, H-3), 7.59-7.51 (m, 3H, H-3"-5"), 4.12-4.04 (m, 4H, 2 CH_2), 3.89-3.82 (m, 4H, 2 CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 167.3, 157.0, 155.8, 147.9, 143.6, 136.1, 135.7, 133.9, 133.0, 130.4, 129.3 × 2, 126.2 × 2, 125.1, 118.0, 108.8, 66.3 × 2, 49.2 × 2. LCMS, *m/z*: 375.2 $[M+1]^+$. Anal. Calcd for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96; S, 8.56 %. Found: C, 67.18; H, 4.83; N, 14.99; S, 8.58 %.

*4-(6-(2-Phenylthiazol-4-yl)-1,7-naphthyridin-8-yl)thiomorpholine (****19c****).*Yield 91 %. Mp 142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6), *δ*, ppm: 8.82 (d, *J* = 4.2 Hz, 1H, H-2), 8.40 (d, *J* = 8.2 Hz, 1H, H-4), 8.28 (s, 1H, H-5), 8.08 (d, *J* = 7.0 Hz, 2H, H-2",6"), 8.00 (s, 1H, H-5'), 7.68 (dd, *J* = 8.2, 4.2 Hz, 1H, H-3), 7.60-7.51 (m, 3H, H-3"-5"), 4.40 (t, *J* = 4.8 Hz, 4H, 2 CH_2), 2.87 – 2.80 (t, *J* = 4.8 Hz, 4H, 2 CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), *δ*, ppm: 167.3, 156.7, 155.8, 147.8, 143.7, 136.1, 135.6, 134.1, 133.0, 130.5, 129.3× 2, 126.2× 2, 125.1, 117.9, 108.5, 51.3× 2, 26.3× 2. LCMS, *m/z*: 391.2 $[M+1]^+$. Anal. Calcd for $C_{21}H_{18}N_4S_2$: C, 64.59; H, 4.65; N, 14.35; S, 16.42 %. Found: C, 64.55; H, 4.67; N, 14.31; S, 16.46 %.

*4-(8-(4-Methylpiperazin-1-yl)-1,7-naphthyridin-6-yl)-2-(thiophen-2-yl)thiazole(**19d**).* Yield 65 %. Mp 123-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 8.82 (dd, J = 4.2, 1.8 Hz, 1H, H-2), 8.42 (dd, J = 8.4, 1.8 Hz, 1H, H-4), 8.23 (s, 1H, H-5), 7.86 (s, 1H, H-5'), 7.78 (dd, J = 5.0, 1.0 Hz, 1H, H-3"), 7.75 (dd, J = 3.7, 1.0 Hz, 1H, H-5"), 7.67 (dd, J = 8.4, 4.2 Hz, 1H, 1H, H-3), 7.22 (dd, J = 5.0, 3.7 Hz, 1H, H-4"), 4.09 (t, J = 5.4 Hz, 4H, 2 NCH_2), 2.55 (t, J = 4.9 Hz, 4H, 2 NCH_2), 2.26 (s, 3H, NCH_3). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 161.2, 157.1, 155.3, 147.8, 143.4, 136.5, 136.1, 135.7, 133.9, 129.0, 128.5, 127.6, 125.0, 117.4, 108.3, 54.9 × 2, 48.4 × 2, 45.9. LCMS, *m/z*: 394.2 $[M+1]^+$. Anal. Calcd for $C_{20}H_{19}N_5S_2$: C, 61.04; H, 4.87; N, 17.80; S, 16.29 %. Found: C, 60.94; H, 4.87; N, 17.83; S, 16.38 %.

*4-(6-(2-(Thiophen-2-yl)thiazol-4-yl)-1,7-naphthyridin-8-yl)morpholine(**19e**).* Yield 78 %. Mp 169-170 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 8.83 (dd, J = 4.2, 1.8 Hz, 1H, H-2), 8.45 (dd, J = 8.2, 1.8 Hz, 1H, H-4), 8.25 (s, 1H, H-5), 7.91 (s, 1H, H-5'), 7.78 (d, J = 4.9 Hz, 1H, H-3"), 7.76 (d, J = 3.9 Hz, 1H, H-5"), 7.68 (dd, J = 8.2, 4.2 Hz, 1H, H-3), 7.21 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H, H-4"), 4.12 – 4.03 (t, J = 4.8 Hz, 4H, 2 NCH_2), 3.85 (t, J = 4.8 Hz, 4H, 2 NCH_2). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 161.3, 157.0, 155.2, 147.9, 143.3, 136.5, 136.2, 135.7, 133.9, 129.1, 128.5, 127.6, 125.1, 117.5, 108.7, 66.3× 2, 49.2× 2. LCMS, *m/z*: 381.0 $[M+1]^+$. Anal. Calcd for $C_{19}H_{16}N_4OS_2$: C, 59.98; H, 4.24; N, 14.73; S, 16.85 %. Found: C, 59.84; H, 4.22; N, 14.78; S, 16.90 %.

*4-(6-(2-(Thiophen-2-yl)thiazol-4-yl)-1,7-naphthyridin-8-yl)thiomorpholine(**19f**).* Yield 86 %. Mp 183-184 °C. ^{1}H NMR (600 MHz, DMSO-d_6), δ, ppm: 8.82 (d, J = 4.1 Hz, 1H, H-2), 8.43 (d, J = 8.2 Hz, 1H, H-4), 8.22 (s, 1H, H-5), 7.88 (s, 1H, H-5'), 7.78 (d, J = 4.9 Hz, 1H, H-3"), 7.76 (d, J = 3.6 Hz, 1H, H-5"), 7.67 (dd, J = 8.2, 4.1 Hz, 1H, H-3), 7.22 (t, J = 4.2 Hz, 1H, H-4"), 4.42-4.37 (m, 4H, 2 CH_2), 2.83 (t, J = 4.9 Hz, 4H, 2 CH_2). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 161.2, 156.7, 155.2, 147.8, 143.4, 136.5, 136.2, 135.6, 134.0, 129.0, 128.5, 127.6, 125.1, 117.4, 108.4, 51.2× 2, 26.3× 2. LCMS, *m/z*: 397.2 $[M+1]^+$. Anal. Calcd for $C_{19}H_{16}N_4S_3$: C, 57.55; H, 4.07; N, 14.13; S, 24.25 %. Found: C, 57.33; H, 4.04; N, 14.17; S, 24.33 %.

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