Synthesis of sterically hindered 3-(azolyl)pyridines

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Dedicated to Professor Alexander F. Pozharskii on his 70th birthday

Abstract
Sterically hindered 2,4-disubstituted 3-(1,2,4-oxadiazol-3-yl)-, 3-(imidazol-2-yl)- and 3-(thiazol-2-yl)pyridines were synthesized from the corresponding nicotinonitriles *via* amidoximes, amidines and thioamides, respectively. *N*-Alkyl- and *N*-arylamidines were prepared directly from nicotinonitriles using microwave technology. The series of 3-(azolyl)pyridines form a combinatorial library of heterocyclic derivatives of nicotinic acid and were examined by prognostic software PASS.

Keywords: Nicotinonitriles, 1,2,4-oxadiazoles, imidazoles, thiazoles, microwave irradiation

Introduction

One of the most promising strategies for searching for new pharmaceuticals and improving the properties of known ones is a replacement of metabolically unstable functional groups with bioisosteric five-membered heterocyclic rings.[1,2] The best-known azole that is used as a metabolism-resistant surrogate for the carboxylate group is 5-substituted tetrazole, since they both possess comparable acidity and size.[3] Nicotinic acid and its derivatives can be very often found among the carboxylic acids investigated with respect to such replacements.[2,4] Thus, 3-(5-tetrazolyl)pyridines were reported as a new class of lipolysis inhibitors[5] and bioisosteres of arecoline.[2]

At the same time, other azoles can also serve as the isosteric equivalents for labile functional groups in the derivatives of nicotinic acid. Thus, 3-(1,3,4-oxadiazol-2-yl)pyridines show antimicrobial and antifungal activity[6] and were tested as nonpeptidic inhibitors of human neutrophil elastase.[7] The corresponding derivatives of 1,2,4-oxadiazole displayed high affinity and efficacy as muscarinic agonists.[8] An antimycobacterial[9] as well as an anthelmintic[10] activity of pyridines substituted with 1,2,4-oxadiazoles as isosteres of nicotinic acid was described. 3-(Imidazol-2-yl)pyridines are known as inhibitors of xanthine oxidase,[11] nonsteroidal antiinflammatory agents,[12] potent and selective NPY5 receptor antagonists[13] as well as being tested as KDR kinase inhibitors.[14] 3-(Thiazol-2-yl)pyridines are known as inhibitors of superoxide production by human neutrophils,[15]

selective cyclooxygenase-2 inhibitors[16] and effective inhibitors of human cytochrome P-450 (CYP2A6), the major nicotine metabolizing enzyme;[17] they also displayed antifungal and antibacterial[18] as well as antitubercular activity;[19] besides, these compounds were used as building block for synthesis of berninamycinic acid[20] and heterocyclic core of micrococcin P1,[21] preparation of the central heterocyclic skeleton of antibiotic A10255,[22] macrocyclic antibiotic GE 2270 A[23] and other various thiostrepton-type macrocyclic antibiotics.[24] On the other hand, it was found that pyridine derivatives bearing a sterically hindered tetrazole unit at position 3 show some very interesting pharmacological properties.[25]

In view of above, it would be interesting to create a combinatorial library consisting of sterically hindered 3-(azolyl)pyridines **2**-**6** as derivatives of nicotinic acid (Figure 1). Such combinatorial library would be also of interest since only two examples of 2,4,5-trisubstituted 3-(azolyl)pyridines [namely, 3-(1,2,4-oxadiazol-3-yl)pyridines, structure **4**] were found in the literature.[26] It should be noted that these two compounds were identified as mixtures (purity 60%) prepared with low yields (25%).

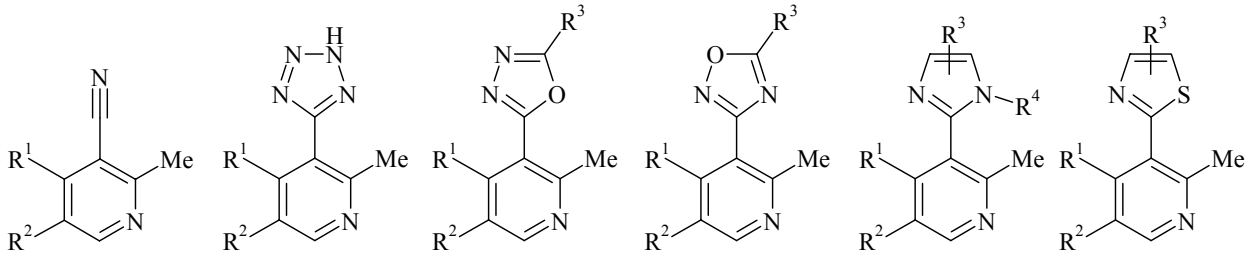
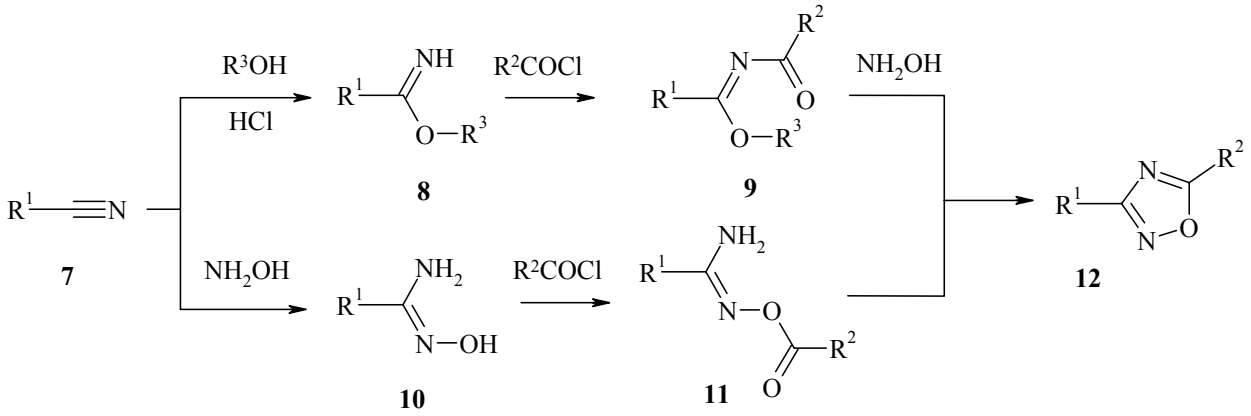


Figure 1. Nicotinonitriles **1** and 3-(azolyl)pyridines **2-6** as components of combinatorial library.

Recently, we have reported the microwave-assisted synthesis of 3-(5-tetrazolyl)pyridines **2** and their fused polycyclic derivatives from sterically hindered nicotinonitriles **1**.[27,28] The synthesis of 3-(1,3,4-oxadiazol-2-yl)pyridines **3** from the 3-(5-tetrazolyl)pyridines **2** was also described in one of these papers.[27] Herein, we wish to report the synthesis of 2,3,4-tri- and 2,3,4,5-tetrasubstituted pyridines bearing 1,2,4-oxadiazol-3-yl (**4**), imidazol-2-yl (**5**), and thiazol-2-yl (**6**) moieties at position 3 as well as methyl group at position 2. It should be noted that the 2,3-di- and 2,4,5-trisubstituted nicotinonitriles **1** had to be used as starting compounds common for the entire combinatorial library.

Results and Discussion

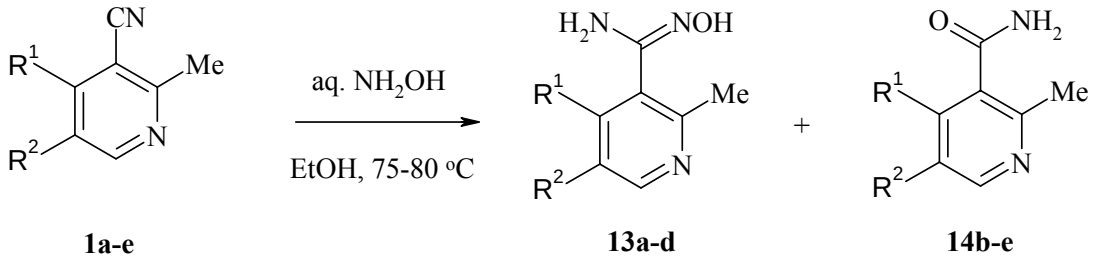
Two syntheses of 1,2,4-oxadiazoles **12** from nitriles **7** are widely known.[29] The first can be accomplished via the imidates **8**,[30] and the second approach is the condensation of amidoximes **10** with carboxylic acid derivatives (anhydrides, chlorides) followed by final ring closure (Scheme 1). The acylated intermediates **9**, **11** were mentioned as isolable compounds for both reaction routes.[29]



Scheme 1. Generalized synthesis of 1,2,4-oxadiazoles **12** from nitriles **7**.

It was insisted in many related publications that the both imidates **8** and amidoximes **10** can be easily prepared using facile procedures [9,10,30,31] including conditions of parallel synthesis.[8d,26,32] It should be noted that aromatic nitriles described in many of these papers had no substituents alongside of cyano group. However, all our attempts to prepare the imidates **8** from nicotinonitriles **1** failed. It was not surprising to us, since many reactions of nitrile groups are very susceptible to steric hindrance (for example, the Pinner reaction).[33] Further, the same result was obtained when we attempted to synthesize the amidoximes **10** from nicotinonitriles **1** using some conventional procedures (interaction of nitriles with $NH_2OH \cdot HCl$ in the presence of various bases). Indeed, a dependence of this reaction on sterical circumstances was also reported.[31d]

Now, we have found that the sterically hindered nicotinonitriles **1** can be converted into desired amidoximes **13** by long-continued heating with 50% aqueous solution of hydroxylamine (Scheme 2). The resultant amidoximes **13** were in many cases contaminated by corresponding amides **14** yields of which increased along with growth of volume of the substituent R^1 at position 4 (Table 1). Finally, amide **14e** turned out the sole reaction product for 4-*tert*-butylsubstituted nicotinonitrile **1e**. It was reported previously that such amide formation is a result of initial attack by the oxygen atom of hydroxylamine to cyano group but not due to hydrolysis of nitrile or amidoxime.[34] We found that the "amidoxime: amide" ratio did not depend on ratios of starting reagents as well as temperature and reaction time. Unfortunately, our attempts to improve the yields of amidoximes **13** as well as to reduce the reaction time using microwave conditions turned out also to be inefficient.

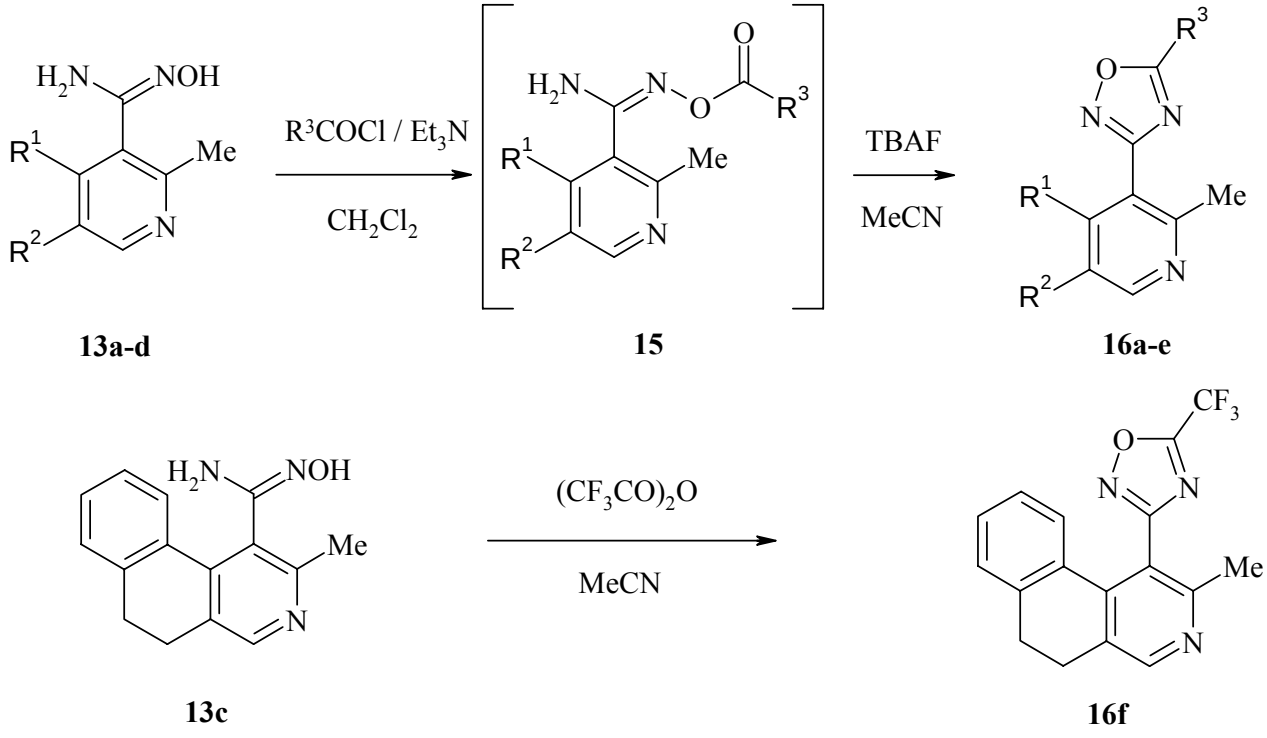


Scheme 2. Synthesis of sterically hindered amidoximes **13**.

Table 1. Conditions and yields of amidoximes **13** and amides **14**

1, **13**, **14**	R^1	R^2	Yield **13** (%)	Yield **14** (%)	Reaction time (h)
a	- $(CH_2)_3$ -		39	0	7
b	- $(CH_2)_5$ -		48	5	80
c	- *o*-C_6H_4-$(CH_2)_2$ -		57	20	80
d	Ph	H	47	51	100
e	*t*-Bu	H	0	50	100

The target amidoximes **13a-d** were easily separated from the amides **14** with column chromatography or crystallization. A treatment of the amidoximes **13a-d** with aromatic and aliphatic acyl chlorides gave rise to O-acylated intermediates **15** (Scheme 3) one of them was isolated and purified for identification. The other *O*-acylamidoximes **15** were used as crude materials for further cyclization without an additional purification. The cyclization was carried out by action of tetra-*n*-butylammonium fluoride (TBAF) according to literature procedure.[35] Besides, the product **16f** was obtained in reaction of starting amidoxime **13c** with excess of trifluoroacetic anhydride as acylating and dehydrating reagent (i.e., without isolation of intermediate **15**).

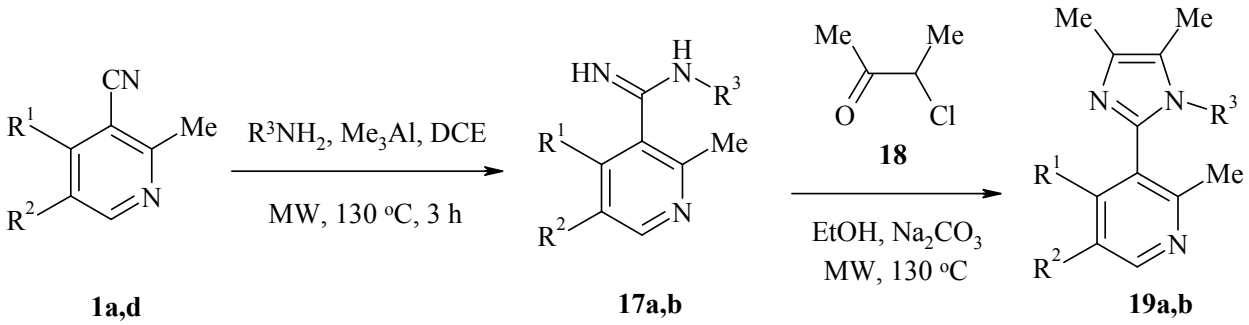


Scheme 3. Synthesis of sterically hindered 3-(1,2,4-oxadiazol-3-yl)pyridines **16**.

Table 2. Yields of 3-(1,2,4-oxadiazol-3-yl)pyridines **16** (relative to **13**)

13	16	R^1	R^2	R^3	Yield **16** (%)
a	**a**	- $(CH_2)_3$ -		Ph	69
b	**b**	- $(CH_2)_5$ -		4-O_2N-C_6H_4	78
c	**c**	- *o*-C_6H_4-$(CH_2)_2$ -		cyclopropyl	87
d	**d**	Ph	H	*t*-Bu	81
d	**e**	Ph	H	CO_2Me	46
c	**f**	- *o*-C_6H_4-$(CH_2)_2$ -		CF_3	98

The synthesis of sterically hindered 3-(imidazol-2-yl)pyridines **19a,b** and **22** utilized the condensation of amidines **17a**,**b** with α-haloketones **18, 20** (Schemes 4, 5). However, the conversion of nicotinonitriles **1** into amidines **17** as an initial step of this reaction presented severe difficulty. Most convenient synthesis of amidines from nitriles consist of two steps where a conversion of nitriles into imidates (the Pinner reaction) followed by reaction with amines yields the desired amidines.[36] Unfortunately, this approach turned out entirely unsuitable for sterically congested nicotinonitriles **1** (*vide supra*). After several unsuccessful efforts to reveal the conditions for direct reaction of the nicotinonitriles **1** with amines using anhydrous aluminium chloride,[37] lithium bis(trimethylsilyl)amide [38] and some other reagents,[12,39] trimethylaluminum was employed for this reaction.[40] However, very low yields of the amidines were achieved under the conditions described.[40] Therefore, we modified these conditions and found that the target amidines **17** can be successfully prepared from the nicotinonitriles **1** and amines in the presence of trimethylaluminum using microwave technology (MW) (Scheme 4).



1a,d **17a,b** **19a,b**

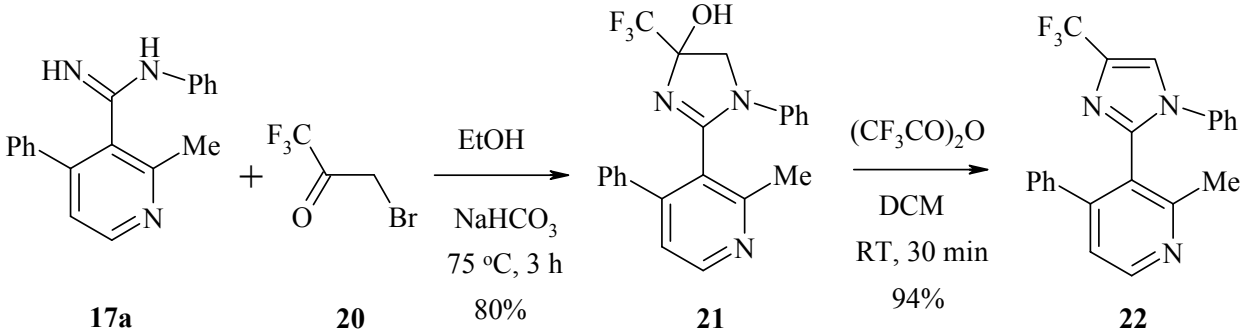
17a, $R^1 = R^3$ = Ph, R^2 = H, 82%
17b, R^1- R^2 = -$(CH_2)_3$-, R^3 = *n*-Pr, 66%

19a, $R^1 = R^3$ = Ph, R^2 = H, 6 h, 67%
19b, R^1- R^2 = -$(CH_2)_3$-, R^3 = *n*-Pr, 4 h, 92%

Scheme 4. Synthesis of sterically hindered 3-(imidazol-2-yl)pyridines **19a,b**.

The reactions of the amidines **17a**,**b** with 3-chlorobutan-2-one **18** were also carried out under microwave irradiation yielding directly the desired 3-(imidazol-2-yl)pyridines **19a,b** (Scheme 4). At the same time, simple refluxing of mixture of amidine **17a** with 3-bromo-1,1,1-trifluoroacetone **20** gave rise to hydroxy derivative **21** that was easily dehydrated with trifluoroacetic anhydride

(Scheme 5). Interestingly, the compound **21** existed as a mixture of two stereoisomers. The ^{1}H NMR spectrum of this product **21** was a superposition of two pictures in ratio 57:43 where a noncoincidence of chemical shifts was observed only for the resonances of methyl and methylene groups (see Experimental Section). It is obviously connected with difficulty of rotation at bond "pyridine-imidazoline" since further dehydration gave rise to the sole product **22**. The structure of the final 3-(imidazol-2-yl)pyridine **22** was confirmed by the assignment of ^{1}H and ^{13}C NMR spectra involving ^{1}H-^{13}C HSQC and HMBC experiments. The position of trifluoromethyl group at position 4 of imidazole ring was established by the cross-peaks in the 2D-^{1}H-^{13}C-HMBC spectra between 5-H in imidazole nucleus and 1-C in N-phenyl group as well as by interaction NOE in 2D-NOESY spectra between 5-H and *ortho*-protons of phenyl (Figure 2).



Scheme 5. Two-step conversion of amidine **17a**.

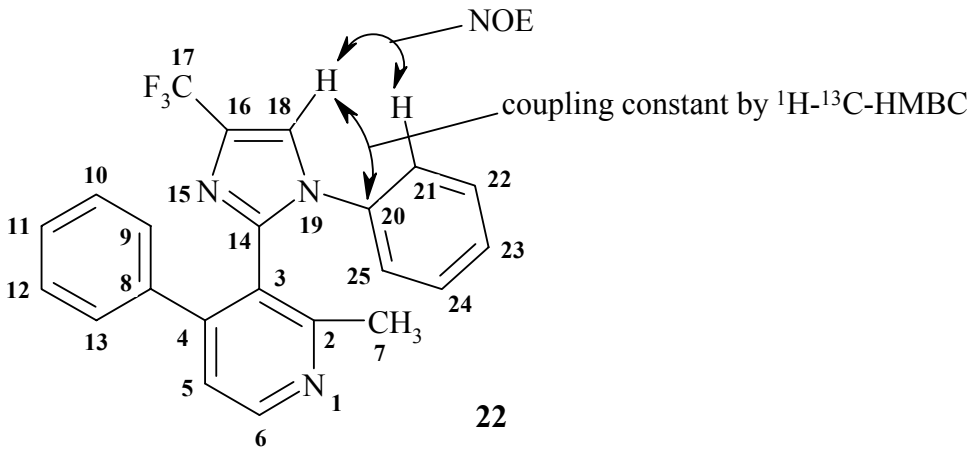
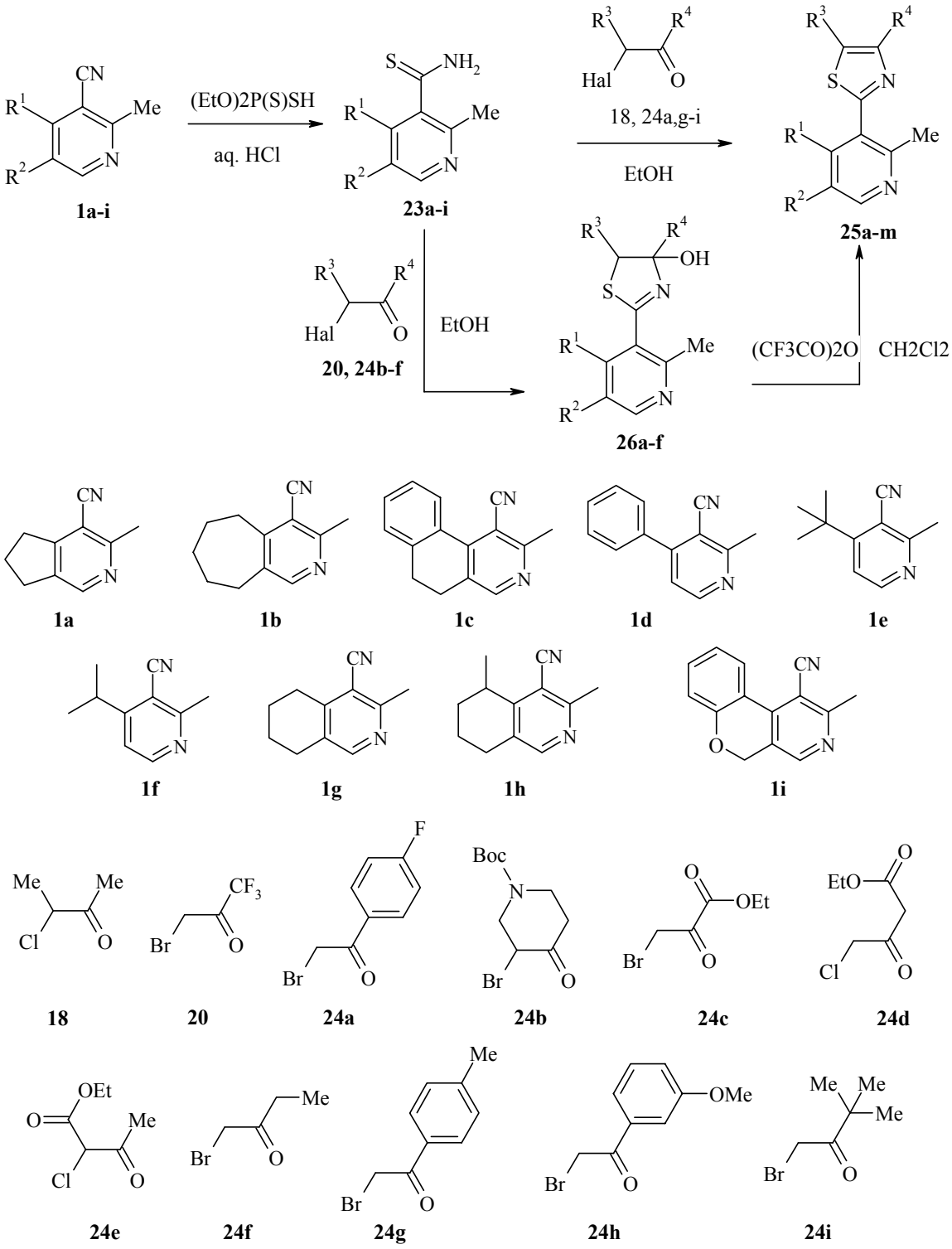


Figure 2. The resonance interactions in structure **22**.

Thioamides **23a-i** required for synthesis of the sterically hindered 3-(thiazol-2-yl)pyridines **25a-m** were prepared by reactions of starting nicotinonitriles **1a-i** with *O*,*O*-diethyldithiophosphoric acid (Scheme 6, Table 3). The latter and similar acids are known as effective reagents for conversion of various nitriles into thioamides in high yields under conditions sufficiently mild to preserve intact a

wide range of functional groups.[41] Some conventional methods (e.g., using ammonium sulfide [42]) for the transformation of nitriles into thioamides were initially tested but turned out insufficient.



Scheme 6. Synthesis of 3-(thiazol-2-yl)pyridines **25a-m** from nicotinonitriles **1a-i** and α–haloketones **18, 20, 24a-i**.

Table 3. Conditions and yields of thioamides **23a-i**

1, **23**	R^1	R^2	Yield **23** (%)	Recovered **1** (%)	Reaction time (h)
a	- $(CH_2)_3$ -		65	21	8
b	- $(CH_2)_5$ -		45	17	20
c	- *o*-C_6H_4-$(CH_2)_2$ -		62	-	100
d	Ph	H	85	10	8
e	*t*-Bu	H	39	59	100
f	*i*-Pr	H	68	30	40
g	- $(CH_2)_4$ -		60	25	20
h	-$CH(CH_3)(CH_2)_3$ -		66	18	14
i	- *o*-C_6H_4-OCH_2 -		44	-	40

It should be noted that the complete conversion of nitriles **1a-i** into amidines **23a-i** was not achieved in all the experiments even by long-term heating of reaction mixtures (up to 100 h). Some amount of a starting nitrile **1** remained and can be recovered in many cases (Table 3). Moreover, the conversion decreased if the temperature of reaction mixture was elevated to 100-120 ^oC. It can be explained by thermal decomposition of thioamides **23** to starting nitriles **1** and H_2S.[43] It is known also that a heating of thioamides with pyridine caused an analogous decomposition;[44] it is not improbable that a similar effect can have the starting cyanopyridines **1**. Unfortunately, our attempts to increase the conversion and improve the yields of the desired thioamides **23a-i** using microwave technology turned out unsuccessful.

Table 4. Yields of 3-(thiazol-2-)pyridines **25a-m**

Thio-amide	*α*-Halo-ketone	R^1	R^2	R^3	R^4	Yield **26** (%)	Yield **25** (%)
23a	**24a**	- $(CH_2)_3$ -		H	4-F-C_6H_4	-	86 (**25a**)
23a	**24b**	- $(CH_2)_3$ -		- $(CH_2)N(Boc)(CH_2)_2$ -		64 (**26a**)	52[a] (**25b**)
23b	**24a**	- $(CH_2)_5$ -		H	4-F-C_6H_4	-	99 (**25c**)
23c	**18**	- *o*-C_6H_4-$(CH_2)_2$ -		Me	Me	-	82 (**25d**)
23d	**20**	Ph	H	H	CF_3	90 (**26b**)	71[a] (**25e**)
23d	**24c**	Ph	H	H	CO_2Et	73 (**26c**)	83[a] (**25f**)
23d	**24d**	Ph	H	H	CH_2CO_2Et	100 (**26d**)	88[a] (**25g**)
23d	**24e**	Ph	H	CO_2Et	CH_3	72 (**26e**)	68[a] (**25h**)
23e	**24f**	*t*-Bu	H	H	Et	90 (**26f**)	71[a] (**25i**)
23f	**24g**	*i*-Pr	H	H	4-$CH_3C_6H_4$	-	90 (**25j**)
23g	**24g**	- $(CH_2)_4$ -		H	4-$CH_3C_6H_4$	-	80 (**25k**)
23h	**24h**	-$CH(CH_3)(CH_2)_3$ -		H	3-$CH_3OC_6H_4$	-	98 (**25l**)
23i	**24i**	- *o*-C_6H_4-OCH_2 -		H	*t*-Bu	-	46 (**25m**)

[a] Yields from the starting thioamides **23**.

The series of sterically hindered 3-(thiazol-2-yl)pyridines **25a-m** was synthesized by well-known reactions [45] of thioamides **23a-i** with α-haloketones **18**, **20**, **24a-i** (Scheme 8). The reactions were carried out in anhydrous ethanol to form hydrohalogenides of the target 3-(thiazol-2-yl)pyridines **25a-m** (Table 4). At the same time, intermediate alcohols **26a-f** were isolated in a number of cases (Scheme 8, Table 4). These alcohols **26a-f** were easily dehydrated by trifluoroacetic anhydride according to known procedures.[46]

Conclusions

In summary, we have developed procedures to convert a series of readily available sterically hindered nicotinonitriles into the corresponding 2,4-disubstituted 3-(1,2,4-oxadiazol-3-yl)-, 3-(thiazol-2-yl)- and 3-(imidazol-2-yl)pyridines. These compounds together with previously described 3-(5-tetrazolyl)pyridines [27] and 3-(1,3,4-oxadiazol-2-yl)pyridines [27] could constitute a basis for a potential combinatorial library. This entire library containing more than 200 compounds was tested by the computer software PASS (Prediction of Activity Spectra for Substances).[47] This program illustrates the predicted activity spectrum of a compound as probability of activity (P_a) and probability of inactivity (P_i). For example, it was predicted by the PASS that 3-(1,2,4-oxadiazol-3-yl)pyridines **16** can possess an antidepressant property, and anxiolytic activity for five of the tested six examples with P_a more than 70%. Our further investigations will be directed to the synthesis of the compounds with the potential activity predicted, and then to a pharmacological evaluation of the latter.

Experimental Section

General Procedures. Starting nicotinonitriles **1a-i** were prepared according to literature procedure.[48] All the acid chlorides, α-haloketones and other reagents are commercially available.
The reactions were monitored by TLC (aluminium sheets, silica gel 60 F_{254}, Merck). Merck Kieselgel 60 (230-400 mesh) was used for a column chromatography. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 (400.13 MHz) spectrometer equipped with a 5 mm inverse multinuclear gradient probehead in DMSO-d_6 or $CDCl_3$, and the chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard. ^{13}C NMR spectrum was recorded on the same instrument at 100.61 MHz using DMSO-d_6 as solvent. The assignments of signals in ^{1}H and ^{13}C NMR spectra were performed using HSQC, HMBC and NOESY experiments. Mass spectra were recorded in the course of LCMS measurements and were obtained by atmosphere pressure chemical ionization (APCI method, positive mode) on an 1100 LCMSD (Agilent Technologies) instrument. IR spectra were measured on an EQUINOX 55 Bruker spectrometer. Elemental analyses were carried out, using CARLO-ERBA 1106 and 1500 automatic elemental analyzers, by the Analytical Laboratory in the A.N. Nesmeyanov Institute of Organoelement Compounds (INEOS RAS, Vavilova str. 28, 119991, Moscow, Russia). Melting points were determined by open glass capillary method and were uncorrected. Milestone Ethos SYNTH (reactors MPR 600/12S and PRO-

24) and CEM Discover microwave labstations (both operating at 2450 MHz under continuous internal temperature control) were used for the experimental and scale-up reactions.

***N*-Hydroxy-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carboximidamide (13a).** Aqueous 50% solution of hydroxylamine (1.0 mL, 17 mmol) was added under stirring to the solution of 3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile **1a** (0.6 g, 3.8 mmol) in ethanol (20 mL). The mixture obtained was stirred at 75 °C for 7 h and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (35 mL). Precipitate formed was filtered off, dried and recrystallized from ethanol to give the titled product **13a** (0.28 g, 39%) as white powder; mp 114-116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94-2.07 (m, 2H, CH_2), 2.42 (s, 3H, Me), 2.78-2.93 (m, 4H, $2CH_2$), 5.78 (br s, 2H, NH_2), 8.28 (s, 1H, 6-H), 9.27 (s, 1H, OH). IR (film) ν 3506 (OH), 3290 (NH), 3168 (OH), 2916 (CH), 1620 (C=N) [49] cm^{-1}. APCI MS *m*/*z*: 192 $[M+H]^+$. Anal. Calcd for $C_{10}H_{13}N_3O$ (191.23): C, 62.81; H, 6.85; N, 21.97%. Found: C, 62.62; H, 7.01; N, 22.02%.

***N*-Hydroxy-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carboximidamide (13b).** Aqueous 50% solution of hydroxylamine (2.84 mL, 48.2 mmol) was added under stirring to the solution of 3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carbonitrile **1b** (2.0 g, 10.7 mmol) in ethanol (40 mL). The mixture was refluxed under stirring for 80 h and then evaporated to dryness. The residue was diluted with ethyl acetate (70 mL). Precipitate formed was filtered off, dried and recrystallized from ethanol to give the product **13b** (1.13 g, 48%) as white powder; mp 254-255 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44-1.64 (m, 4H, CH_2CH_2), 1.73-1.86 (m, 2H, CH_2), 2.38 (s, 3H, Me), 2.66-2.78 (m, 4H, CH_2CH_2), 5.83 (s, 2H, NH_2), 8.15 (s, 1H, 6-H), 9.23 (s, 1H, OH). IR (film) ν 3461 (OH), 3279 (NH), 3151 (OH), 2912 (CH), 1653 (C=N) cm^{-1}. APCI MS *m*/*z*: 220 $[M+H]^+$. Anal. Calcd for $C_{12}H_{17}N_3O$ (219.29): C, 65.73; H, 7.81; N, 19.16%. Found: C, 65.55; H, 7.68; N, 19.05%.

The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, ethyl acetate) to afford the starting nitrile **1b** (0.3 g, 15%), amidoxime **13b** (0.12 g, 5%) and **3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carboxamide (14b).** (0.11 g, 5%) as white solid; mp 172-173 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47-1.61 (m, 4H, CH_2CH_2), 1.73-1.84 (m, 2H, CH_2), 2.38 (s, 3H, Me), 2.65-2.78 (m, 4H, CH_2CH_2), 7.56 and 9.23 (both br. s, 1H and 1H, NH_2), 8.14 (s, 1H, 6-H). IR (film) ν 3451 (NH), 2908 (CH), 1642 (C=O) cm^{-1}. APCI MS *m*/*z*: 205 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}N_2O$ (204.27): C, 70.56; H, 7.90; N, 13.71%. Found: C, 70.33; H, 8.00; N, 13.80%.

***N*-Hydroxy-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carboximidamide (13c).** Aqueous 50% solution of hydroxylamine (2.4 mL, 41 mmol) was added under stirring to the solution of 2-methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carbonitrile **1c** (2.0 g, 9.1 mmol) in ethanol (40 mL). The mixture obtained was refluxed under stirring for 80 h and then evaporated to dryness. The residue was chromatographed (silica gel, chloroform/methanol 95:5) to give the product **13c** (1.31 g, 57%) as pale-yellow solid; mp 256-257 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, Me), 2.64-2.85 (m, 4H, CH_2CH_2), 6.03 (s, 2H, NH_2), 7.19-7.37 (m, 3H, C_6H_4), 8.14 (d, 1H, *J* 7.8 Hz, C_6H_4), 8.38 (s, 1H, 6-H), 9.28 (s, 1H, OH). IR (film) ν 3489 (OH), 3386 (NH), 3179 (OH), 2938 (CH), 1653 (C=N) cm^{-1}. APCI MS *m*/*z*: 254 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}N_3O$ (253.31): C,

71.13; H, 5.97; N, 16.59%. Found: C, 71.11; H, 5.93; N, 16.42%. Another product isolated from chromatography column was identified as **2-methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carboxamide (14c)** (0.44 g, 20%), white powder; mp 203-205 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, Me), 2.65-2.85 (m, 4H, CH_2CH_2), 7.25-7.37 (m, 3H, C_6H_4), 7.67 and 7.93 (both br. s, 1H and 1H, NH_2), 8.05 (d, 1H, *J* 7.8 Hz, C_6H_4), 8.37 (s, 1H, 6-H). IR (film) *v* 3366 (NH), 2947 (CH), 1659 (C=O) cm^{-1}. APCI MS *m*/*z*: 239 $[M+H]^+$. Anal. Calcd for $C_{15}H_{14}N_2O$ (238.29): C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.51; H, 5.76; N, 11.65%.

***N*-Hydroxy-2-methyl-4-phenylpyridine-3-carboximidamide (13d).** Aqueous 50% solution of hydroxylamine (2.7 mL, 46 mmol) was added under stirring to the solution of 2-methyl-4-phenylnicotinonitrile **1d** (2.0 g, 10.3 mmol) in ethanol (40 mL). The mixture obtained was refluxed under stirring for 100 h and then evaporated to dryness. The residue was chromatographed (silica gel, chloroform/methanol 94:6) to give the product **13d** (1.10 g, 47%) as pale-yellow powder; mp 206-207 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, Me), 5.90 (s, 2H, NH_2), 7.21 (d, 1H, *J* 5.0 Hz, 5-H), 7.34-7.44 (m, 3H, Ph), 7.52-7.57 (m, 2H, Ph), 8.48 (d, 1H, *J* 5.0 Hz, 6-H), 9.17 (s, 1H, OH). IR (film) *v* 3451 (OH), 3297 (NH), 3178 (OH), 1666 (C=N) cm^{-1}. APCI MS *m*/*z*: 228 $[M+H]^+$. Anal. Calcd for $C_{13}H_{13}N_3O$ (227.27): C, 68.71; H, 5.77; N, 18.49%. Found: C, 68.56; H, 5.61; N, 18.35%. Another product isolated from chromatography column was identified as **2-methyl-4-phenylnicotinamide (14d)** (1.12 g, 51%), white powder; mp 174-176 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, Me), 7.22 (d, 1H, *J* 5.1 Hz, 5-H), 7.37-7.57 (m, 5H, Ph), 7.49 and 7.82 (both s, 1H and 1H, NH_2), 8.48 (d, 1H, *J* 5.1 Hz, 6-H). IR (film) *v* 3306 (NH), 1698 (C=O) cm^{-1}. APCI MS *m*/*z*: 213 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}N_2O$ (212.25): C, 73.57; H, 5.70; N, 13.20%. Found: C, 73.59; H, 5.73; N, 13.28%.

4-*tert*-Butyl-2-methylnicotinamide (14e). Aqueous 50% solution of hydroxylamine (2.36 mL, 40 mmol) was added under stirring to the solution of 4-*tert*-butyl-2-methylnicotinonitrile **1e** (2.0 g, 11.5 mmol) in ethanol (40 mL). The mixture obtained was refluxed under stirring for 100 h and then evaporated to dryness. The residue was chromatographed (silica gel, ethyl acetate) to give the starting nitrile **1e** (0.9 g, 45%) and the titled product **14e** (1.10 g, 50% in regard to the initial amount of **1e**, or 91% taking into account the conversion level) as white powder; mp 164-165 °C (from EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H, *t*-Bu), 2.45 (s, 3H, Me), 7.24 (d, 1H, *J* 5.4 Hz, 5-H), 7.62 and 7.92 (both br. s, 1H and 1H, NH_2), 8.31 (d, 1H, *J* 5.4 Hz, 6-H). IR (film) *v* 3471 (NH), 2970 (CH), 1686 (C=O) cm^{-1}. APCI MS *m*/*z*: 193 $[M+H]^+$. Anal. Calcd for $C_{11}H_{16}N_2O$ (192.26): C, 68.72; H, 8.39; N, 14.57%. Found: C, 68.51; H, 8.29; N, 14.68%.

3-Methyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (16a). Benzoyl chloride (0.25 g, 0.21 mL, 1.8 mmol) was added dropwise at 0 °C to cooled solution of *N*-hydroxy-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carboximidamide **13a** (0.28 g, 1.46 mmol) and triethylamine (0.3 g, 0.42 mL, 3.0 mmol) in anhydrous dichloromethane (4 mL) under stirring. The reaction mixture was then stirred at room temperature for 14 h and poured into saturated aqueous solution of $NaHCO_3$ (50 mL). The product was extracted with ethyl acetate (6 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, chloroform/methanol 9:1) to furnish the intermediate **15** [***N*-(benzoyloxy)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carboximidamide**] (R^3 = Ph)

(0.38 g, 88%) as pale-brown crystal solid; mp 185-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99-2.10 (m, 2H, CH_2), 2.51 (s, 3H, Me), 2.88-2.97 (m, 4H, $2CH_2$), 7.00 (s, 2H, NH_2), 7.50-7.57 (m, 2H, Ph), 7.63-7.69 (m, 1H, Ph), 8.15-8.20 (m, 2H, Ph), 8.38 (s, 1H, 6-H).

The intermediate **15** was then suspended in anhydrous acetonitrile (2 mL), and tetra-*n*-butylammonium fluoride trihydrate (TBAF) (0.46 g, 1.46 mmol) was added to the suspension. The reaction mixture was stirred at room temperature for 12 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to give the product **16a** (0.28 g, 69% in regard to the starting **13a**) as light gray crystal solid; mp 75-76 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01-2.11 (m, 2H, CH_2), 2.63 (s, 3H, Me), 2.97 (t, 2H, *J* 7.5 Hz, CH_2), 3.05 (t, 2H, *J* 7.5 Hz, CH_2), 7.64-7.70 (m, 2H, Ph), 7.71-7.78 (m, 1H, Ph), 8.16-8.21 (m, 2H, Ph), 8.49 (s, 1H, 6-H). APCI MS *m*/*z*: 278 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.47; H, 5.49; N, 15.04%.

3-Methyl-4-[5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl]-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (16b). 4-Nitrobenzoyl chloride (0.186 g, 1.0 mmol) was added to solution of the precursor **13b** (0.20 g, 0.91 mmol) and triethylamine (0.15 g, 0.21 mL, 1.5 mmol) in anhydrous dichloromethane (2 mL) under stirring. The reaction mixture was stirred at room temperature for 10 h then poured into saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted with ethyl acetate (7 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was suspended in anhydrous acetonitrile (2 mL), and TBAF (0.32 g, 1.00 mmol) was added to the suspension. The reaction mixture was stirred at room temperature for 3 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate 1:1) to give the product **16b** (0.25 g, 78%) as pale-yellow crystal solid; mp 104-106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.48-1.65 (m, 4H, CH_2CH_2), 1.75-1.84 (m, 2H, CH_2), 2.33 (s, 3H, Me), 2.59-2.65 (m, 2H, CH_2), 2.82-2.89 (m, 2H, CH_2), 8.38 (s, 1H, 6-H), 8.41-8.50 (m, 4H, C_6H_4). APCI MS *m*/*z*: 351 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_4O_3$ (350.38): C, 65.13; H, 5.18; N, 15.99%. Found: C, 65.11; H, 5.23; N, 15.89%.

1-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline (16c). Cyclopropanecarbonyl chloride (0.125 g, 1.2 mmol) was added at 0 °C to solution of the intermediate **13c** (0.25 g, 1.0 mmol) and triethylamine (0.15 g, 0.21 mL, 1.5 mmol) in anhydrous dichloromethane (2 mL) under stirring. The reaction mixture was stirred at room temperature for 10 h then poured into saturated aqueous solution of $NaHCO_3$ (10 mL). The product was extracted with ethyl acetate (4 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was suspended in anhydrous acetonitrile (2 mL), and TBAF (0.32 g, 1.00 mmol) was added to the suspension. The reaction mixture was stirred at room temperature for 10 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to give the product **16c** (0.26 g, 87%) as dark-brown oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10-1.16 (m, 2H, cyclopropyl), 1.27-1.34 (m, 2H, cyclopropyl), 2.32 (s, 3H, Me), 2.41-2.48 (m, 1H, cyclopropyl), 2.74-2.84 (m, 4H, CH_2CH_2), 6.80 (dd, 1H, *J* 7.9, 1.2 Hz, C_6H_4), 7.10 (ddd, 1H, *J* 7.9, 1.3 Hz, C_6H_4), 7.28 (ddd, 1H, *J* 7.5, 1.2 Hz, C_6H_4), 7.35 (dd, 1H, *J* 7.4, 1.3 Hz, C_6H_4), 8.56 (s, 1H, 6-H). APCI MS *m*/*z*: 304 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}N_3O$ (303.37): C, 75.23; H, 5.65; N, 13.85%. Found: C, 75.20; H, 5.54; N, 13.75%.

3-(5-*tert*-Butyl-1,2,4-oxadiazol-3-yl)-2-methyl-4-phenylpyridine (16d). Pivaloyl chloride (0.11 g, 0.93 mmol) was added at 0 °C to solution of *N*-hydroxy-2-methyl-4-phenylpyridine-3-carboximidamide **13d** (0.20 g, 0.88 mmol) and triethylamine (0.1 g, 0.14 mL, 0.97 mmol) in anhydrous dichloromethane (2 mL) under stirring. The reaction mixture was stirred at room temperature for 3 h then poured into saturated aqueous solution of $NaHCO_3$ (5 mL). The product was extracted with ethyl acetate (4 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was suspended in anhydrous acetonitrile (3 mL), and TBAF (0.28 g, 0.88 mmol) was added to the suspension. The reaction mixture was stirred at room temperature for 10 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to give the product **16d** (0.21 g, 81%) as yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (s, 9H, *t*-Bu), 2.42 (s, 3H, Me), 7.15-7.20 (m, 2H, Ph), 7.32-7.35 (m, 3H, Ph), 7.41 (d, 1H, *J* 5.1 Hz, 5-H), 8.68 (d, 1H, *J* 5.1 Hz, 6-H). APCI MS *m*/*z*: 294 $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}N_3O$ (293.37): C, 73.70; H, 6.53; N, 14.32%. Found: C, 73.58; H, 6.51; N, 14.14%.

Methyl 3-(2-methyl-4-phenylpyridin-3-yl)-1,2,4-oxadiazole-5-carboxylate (16e). Methyl oxalyl chloride (0.113 g, 0.92 mmol) was added at 0 °C to solution of *N*-hydroxy-2-methyl-4-phenylpyridine-3-carboximidamide **13d** (0.20 g, 0.88 mmol) and triethylamine (0.1 g, 0.14 mL, 0.97 mmol) in anhydrous dichloromethane (2 mL) under stirring. The reaction mixture was stirred at room temperature for 12 h then poured into saturated aqueous solution of $NaHCO_3$ (5 mL). The product was extracted with ethyl acetate (4 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was suspended in anhydrous acetonitrile (3 mL), and TBAF (0.28 g, 0.88 mmol) was added to the suspension. The reaction mixture was stirred at room temperature for 10 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to give the product **16e** (0.12 g, 46%) as pale-yellow solid; mp 114-117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H, Me), 3.96 (s, 3H, MeO), 7.15-7.22 (m, 2H, Ph), 7.32-7.39 (m, 3H, Ph), 7.44 (d, 1H, *J* 5.0 Hz, 5-H), 8.72 (d, 1H, *J* 5.0 Hz, 6-H). APCI MS *m*/*z*: 296 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}N_3O_3$ (295.30): C, 65.08; H, 4.44; N, 14.23%. Found: C, 65.11; H, 4.47; N, 14.13%.

2-Methyl-1-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-5,6-dihydrobenzo[*f*]isoquinoline (16f). Trifluoroacetic anhydride (0.25 g, 0.17 mL, 1.2 mmol) was added dropwise to solution of *N*-hydroxy-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carboximidamide **13c** (0.10 g, 0.4 mmol) in anhydrous acetonitrile (2 mL) under stirring. The reaction mixture was stirred at room temperature for 12 h then diluted with saturated aqueous solution of $NaHCO_3$ (5 mL). The product was extracted with ethyl acetate (4 × 5 mL), and the extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to give the product **16f** (0.13 g, 98%) as white solid; mp 105-106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 3H, Me), 2.76-2.87 (m, 4H, CH_2CH_2), 6.66 (dd, 1H, *J* 7.9, 1.2 Hz, C_6H_4), 7.10 (ddd, 1H, *J* 7.9, 1.3 Hz, C_6H_4), 7.30 (ddd, 1H, *J* 7.4, 1.2 Hz, C_6H_4), 7.38 (dd, 1H, *J* 7.4, 1.3 Hz, C_6H_4), 8.64 (s, 1H, 6-H). APCI MS *m*/*z*: 332 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}F_3N_3O$ (331.30): C, 61.63; H, 3.65; F, 17.20; N, 12.68%. Found: C, 61.67; H, 3.64; F, 17.09; N, 12.64%.

2-Methyl-*N*,4-diphenylpyridine-3-carboximidamide hydrochloride (17a). 2M solution of trimethylaluminum in toluene (10 mL, 20 mmol) was slowly added dropwise to solution of aniline (1.4 g, 15 mmol) in anhydrous dichloroethane (10 mL) under stirring at 0 °C in inert atmosphere (argon). The mixture was stirred at room temperature for 30 min then solution of 2-methyl-4-phenylnicotinonitrile **1d** (1.94 g, 10 mmol) in anhydrous dichloroethane (10 mL) was added under stirring. The reaction mixture formed was subjected to microwave irradiation at 130 °C for 3 h then cooled to room temperature and carefully treated with methanol (100 mL). The jelly-like precipitate was filtered off through Celite and washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, chloroform/methanol in gradient 0 to 30%) to give the viscous unstable oil that was identified as hydrochloride. For that, the oily compound was dissolved in anhydrous dioxane (15 mL), and 4M solution of HCl in dioxane (7.5 mL, 3 eq.) was added under stirring. The precipitate formed was filtered off, washed with anhydrous ether and dried in vacuum at room temperature to afford the titled compound **17a** (2.65 g, 82%) as pale-yellow solid; mp 214-216 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.82 (s, 3H, Me), 7.09-7.14 (m, 2H, Ph), 7.35-7.65 (m, 8H, Ph), 7.71 (d, 1H, *J* 5.4 Hz, 5-H), 8.87 (d, 1H, *J* 5.4 Hz, 6-H), 9.36 (br. s, 1H, NH), 10.44 (br. s, 1H, NH), 12.69 (br. s, 1H, NH). IR (film) *v* 3424 (NH), 3247 (=NH), 1631 (C=N) cm^{-1}. APCI MS *m*/*z*: 288 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}ClN_3$ (323.83): C, 70.47; H, 5.60; Cl, 10.95; N, 12.98%. Found: C, 70.33; H, 5.61; Cl, 11.02; N, 12.79%.

3-Methyl-*N*-propyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carboximidamide dihydrochloride (17b). Obtained analogously to previous amidine from 3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile **1a** and propylamine, yield 66%, colorless solid; mp 207-209 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97 (t, 3H, *J* 7.0 Hz, $CH_2CH_2\mathit{CH_3}$), 1.61-1.72 (m, 2H, $CH_2\mathit{CH_2}CH_3$), 2.10-2.21 (m, 2H, CH_2 of carbocycle), 2.67 (s, 3H, 2-Me), 3.01-3.10 (m, 4H, CH_2CH_2 of carbocycle), 3.44 (dt, 2H, *J* 7.0 Hz, $\mathit{CH_2}CH_2CH_3$), 8.71 (s, 1H, 6-H), 9.75 (br. s, 1H, NH), 9.96 (br. s, 1H, NH), 10.56 (br. s, 1H, NH). IR (film) *v* 3553 (NH), 3466 (=NH), 2985 (CH), 1684 (C=N) cm^{-1}. APCI MS *m*/*z*: 218 $[M+H]^+$. Anal. Calcd for $C_{13}H_{21}Cl_2N_3$ (290.24): C, 53.80; H, 7.29; Cl, 24.43; N, 14.48%. Found: C, 53.73; H, 7.30; Cl, 24.35; N, 14.40%.

3-(4,5-Dimethyl-1-phenyl-1*H*-imidazol-2-yl)-2-methyl-4-phenylpyridine (19a). Sodium carbonate (0.74 g, 7.0 mmol) then 3-chlorobutan-2-one **18** (0.37 g, 3.5 mmol) were added to solution of amidine **17a** (free base) (0.50 g, 1.74 mmol) in anhydrous ethanol (10 mL). The resulting mixture was subjected to microwave irradiation at 130 °C for 3 h. Additional amount of 3-chlorobutan-2-one (0.37 g, 3.5 mmol) was added to the mixture, and the microwave irradiation was continued under the same conditions for 3 h. The reaction mass was cooled, filtered and concentrated under reduced pressure. The residue was chromatographed (silica gel, chloroform/methanol 95:5) to give the product **19a** (0.40 g, 67%) as pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 3H, Me), 2.32 (s, 3H, Me), 2.65 (s, 3H, Me), 6.11-6.21 (m, 2H, Ph), 6.82-6.87 (m, 2H, Ph), 6.93 (d, 1H, *J* 5.1 Hz, 5-H), 6.98-7.04 (m, 2H, Ph), 7.09-7.15 (m, 1H, Ph), 7.16-7.22 (m, 2H, Ph), 7.24-7.30 (m, 1H, Ph), 8.44 (d, 1H, *J* 5.1 Hz, 6-H). APCI MS *m*/*z*: 340 $[M+H]^+$. Anal. Calcd for $C_{23}H_{21}N_3$ (339.44): C, 81.39; H, 6.24; N, 12.38%. Found: C, 81.25; H, 6.08; N, 12.31%.

4-(4,5-Dimethyl-1-propyl-1*H*-imidazol-2-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (19b). Prepared analogously from amidine **17b** (free base) and 3-chlorobutan-2-one **18**; glassy

mass; yield 0.57 g (92%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.66 (t, 3H, J 7.3 Hz, $CH_2CH_2CH_3$), 1.31-1.42 (m, 2H, $CH_2CH_2CH_3$), 1.94-2.03 (m, 2H, CH_2 of carbocycle), 2.08 (s, 3H, 2-Me), 2.16 (s, 3H, Me), 2.18 (s, 3H, Me), 2.46-2.56 (m, 1H, CH_2 of carbocycle), 2.58-2.68 (m, 1H, CH_2 of carbocycle), 2.92 (d, 2H, J 7.3 Hz, CH_2 of carbocycle), 3.52 (t, 2H, J 7.1 Hz, $CH_2CH_2CH_3$), 8.37 (s, 1H, 6-H). APCI MS m/z: 270 $[M+H]^+$. Anal. Calcd for $C_{17}H_{23}N_3$ (269.39): C, 75.80; H, 8.61; N, 15.60%. Found: C, 76.03; H, 8.80; N, 15.41%.

2-Methyl-4-phenyl-3-[1-phenyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl]pyridine (22). A mixture of 2-methyl-*N*,4-diphenylpyridine-3-carboximidamide **17a** (0.5 g, 1.74 mmol), $NaHCO_3$ (0.3 g, 3.6 mmol) and 3-bromo-1,1,1-trifluoroacetone **20** (0.69 g, 3.6 mmol) in anhydrous ethanol (10 mL) was heated under stirring at 75 °C for 3 h then cooled and filtered. The filtrate was concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 50 to 100%) to furnish intermediate **2-(2-methyl-4-phenylpyridin-3-yl)-1-phenyl-4-(trifluoromethyl)-4,5-dihydro-1*H*-imidazol-4-ol (21)** (0.55 g, 80%), mp 94-95 °C. The ^{1}H NMR spectrum was a superposition of two ones: (**a**), 57%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (s, 3H, Me), 3.21-3.60 (br. s, 1H, OH), 3.68 (d, 1H, J 12.0 Hz, CH_2), 3.96 (d, 1H, J 12.0 Hz, CH_2), 6.21-6.26 (m, 2H, Ph), 6.89-7.03 (m, 4H, Ph), 7.12-7.41 (m, 5H, Ph, 5-H), 8.59 (d, 1H, J 5.1 Hz, 6-H); (**b**), 43%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (s, 3H, Me), 3.20-3.59 (br. s, 1H, OH), 3.79 (d, 1H, J 12.0 Hz, CH_2), 4.02 (d, 1H, J 12.0 Hz, CH_2), 6.21-6.26 (m, 2H, Ph), 6.89-7.03 (m, 4H, Ph), 7.12-7.41 (m, 5H, Ph, 5-H), 8.58 (d, 1H, J 5.1 Hz, 6-H). The intermediate alcohol **21** (0.48 g, 1.2 mmol) was dissolved in anhydrous dichloromethane (10 mL), and trifluoroacetic anhydride (2 mL) was added to the solution. The reaction mixture was stirred at room temperature for 30 min then evaporated to dryness. The residue was mixed with saturated aqueous solution of $NaHCO_3$ (10 mL) then treated with ethyl acetate (4 × 10 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 30 to 50%) to afford the product **22** (0.43 g, 94%) as pale-yellow solid; mp 133-134 °C (from Et_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, Me), 6.45 (d, 2H, J 7.3 Hz, Ph), 6.68 (d, 2H, J 7.3 Hz, Ph), 7.13-7.35 (m, 6H, Ph), 7.18 (d, 1H, J 5.2 Hz, 5-H), 8.13 (s, 1H, CH of imidazole ring), 8.78 (d, 1H, J 5.2 Hz, 6-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.2 (7-C), 121.5 (5-C), 121.9 (17-C), 122.0 (18-C), 122.7 (3-C), 124.1 (21-C, 25-C), 127.9 (9-C, 13-C), 128.2 (11-C), 128.3 (23-C), 128.4 (10-C, 12-C), 129.0 (22-C, 24-C), 130.6 (16-C), 135.2 (20-C), 137.2 (4-C), 144.3 (14-C), 149.3 (8-C), 150.3 (6-C), 158.8 (2-C) (atom numbering see Figure 2). APCI MS m/z: 380 $[M+H]^+$. Anal. Calcd for $C_{22}H_{16}F_3N_3$ (379.39): C, 69.65; H, 4.25; F, 15.02; N, 11.08%. Found: C, 69.70; H, 4.43; F, 15.06; N, 11.00%.

3-Methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbothioamide (23a). 3-Methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile **1a** (0.79 g, 5 mmol) was suspended in water (3 mL), and conc. HCl (1 mL, 10 mmol) then *O*,*O*-diethyl dithiophosphate (1.86 g, 1.68 mL, 10 mmol) were successively added dropwise to the suspension under stirring at room temperature. The resulting mixture was stirred at 80 °C for 8 h (TLC monitoring, silica gel, ethyl acetate). The reaction mixture was then cooled to room temperature and slowly poured into stirred saturated aqueous solution of $NaHCO_3$ (30 mL). The mixture was extracted with ethyl acetate (4 × 25 mL), and the extract was washed with brine (10 mL), dried over $MgSO_4$ and evaporated at 60 °C/20 Torr.

The residue was recrystallized from ethyl acetate to give the product **23a** (0.62 g, 65%) as pale-brown powder; mp 220 °C (subliming); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97-2.07 (m, 2H, CH_2), 2.42 (s, 3H, Me), 2.81 (t, 2H, *J* 7.5 Hz, CH_2), 2.88 (t, 2H, *J* 7.5 Hz, CH_2), 8.24 (s, 1H, 6-H), 9.61 and 10.07 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3204 (NH), 2991 (CH), 1181 (C=S) cm^{-1}. APCI MS *m*/*z*: 193 $[M+H]^+$. Anal. Calcd for $C_{10}H_{12}N_2S$ (192.28): C, 62.47; H, 6.29; N, 14.57; S, 16.68%. Found: C, 62.45; H, 6.38; N, 14.45; S, 16.69%.

The mother liquid after recrystallization was chromatographed (silica gel, ethyl acetate) to afford the starting nitrile **1a** (0.17 g, 21%).

3-Methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carbothioamide (23b). Prepared analogously from 3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carbonitrile **1b** (0.93 g, 5 mmol); reaction time 20 h; the crude product was chromatographed (silica gel, hexane/ethyl acetate in gradient 50 to 100%) to give the starting nitrile **1b** (0.16 g, 17%) and the target product **23b** (0.49 g, 45%) as pale-yellow powder; mp 238-239 °C (from EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46-1.65 (m, 4H, CH_2CH_2), 1.74-1.85 (m, 2H, CH_2), 2.39 (s, 3H, Me), 2.68-2.78 (m, 4H, $2CH_2$), 8.11 (s, 1H, 6-H), 9.66 and 10.12 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3209 (NH), 2937 (CH), 1162 (C=S) cm^{-1}. APCI MS *m*/*z*: 221 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}N_2S$ (220.34): C, 65.41; H, 7.32; N, 12.71; S, 14.55%. Found: C, 65.52; H, 7.41; N, 12.58; S, 14.40%.

2-Methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carbothioamide (23c). Prepared analogously from 2-methyl-5,6-dihydrobenzo[*f*]isoquinoline-1-carbonitrile **1c** (1.10 g, 5 mmol); additional amount of *O*,*O*-diethyl dithiophosphate (0.93 g, 0.84 mL, 5 mmol) was added to reaction mixture after heating at 80 °C for 95 h, and the resulting mixture was additionally heated under the same conditions for 5 h. The crude mass after work-up was recrystallized from ethyl acetate to furnish the pure product **23c** (0.79 g, 62%) as pale-yellow crystal solid; mp 225-227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, Me), 2.64-2.80 (m, 4H, CH_2CH_2), 7.21-7.35 (m, 3H, C_6H_4), 8.33 (s, 1H, 6-H), 8.35-8.41 (m, 1H, C_6H_4), 9.93 and 10.29 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3396 (NH), 2946 (CH), 1159 (C=S) cm^{-1}. APCI MS *m*/*z*: 255 $[M+H]^+$. Anal. Calcd for $C_{15}H_{14}N_2S$ (254.36): C, 70.83; H, 5.55; N, 11.01; S, 12.61%. Found: C, 70.83; H, 5.43; N, 11.10; S, 12.46%.

2-Methyl-4-phenylpyridine-3-carbothioamide (23d). Prepared analogously to thioamide **23a** from 2-methyl-4-phenylnicotinonitrile **1d** (0.97 g, 5 mmol); the crude product was recrystallized from ethyl acetate to give the product **23d** (0.97 g, 85%) as yellow powder; mp 199-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (s, 3H, Me), 7.15 (d, 1H, *J* 5.0 Hz, 5-H), 7.36-7.45 (m, 3H, Ph), 7.48-7.54 (m, 2H, Ph), 8.43 (d, 1H, *J* 5.0 Hz, 6-H), 9.76 and 10.03 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3097 (NH), 1110 (C=S) cm^{-1}. APCI MS *m*/*z*: 229 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}N_2S$ (228.32): C, 68.39; H, 5.30; N, 12.27; S, 14.04%. Found: C, 68.19; H, 5.38; N, 12.29; S, 14.02%. The starting nitrile **1d** (0.09 g, 10%) was isolated from the mother liquid.

4-*tert*-Butyl-2-methylpyridine-3-carbothioamide (23e). Prepared analogously to thioamide **23c** from 4-*tert*-butyl-2-methylnicotinonitrile **1e** (0.88 g, 5 mmol); the crude product was chromatographed (silica gel, hexane/ethyl acetate in gradient 50 to 100%) to give the starting nitrile **1e** (0.52 g, 59%) and the product **23e** (0.41 g, 39%) as white crystal solid; mp 196-197 °C (from benzene); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (s, 9H, *t*-Bu), 2.48 (s, 3H, Me), 7.28 (d, 1H, *J* 5.6 Hz, 5-H), 8.27 (d, 1H, *J* 5.6 Hz, 6-H), 9.80 and 10.21 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3225

(NH), 2969 (CH), 1195 (C=S) cm^{-1}. APCI MS *m*/*z*: 209 $[M+H]^+$. Anal. Calcd for $C_{11}H_{16}N_2S$ (208.33): C, 63.42; H, 7.74; N, 13.45; S, 15.39%. Found: C, 63.48; H, 7.73; N, 13.33; S, 15.50%.

4-Isopropyl-2-methylpyridine-3-carbothioamide (23f). Prepared analogously to thioamide **23a** from 4-isopropyl-2-methylnicotinonitrile **1f** (0.80 g, 5 mmol); the crude product obtained after heating at 80 °C for 40 h was recrystallized from ethyl acetate to give the product **23f** (0.66 g, 68%) as pale-yellow powder; mp 197-198 °C (from EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (d, 6H, *J* 6.8 Hz, CH(*CH*$_3$)$_2$), 2.44 (s, 3H, Me), 3.03-3.16 (septet, 1H, *J* 6.8 Hz, *CH*(CH$_3$)$_2$), 7.20 (d, 1H, *J* 5.4 Hz, 5-H), 8.31 (d, 1H, *J* 5.4 Hz, 6-H), 9.71 and 10.19 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3298 (NH), 2972 (CH), 1101 (C=S) cm^{-1}. APCI MS *m*/*z*: 195 $[M+H]^+$. Anal. Calcd for $C_{10}H_{14}N_2S$ (194.30): C, 61.82; H, 7.26; N, 14.42; S, 16.50%. Found: C, 61.80; H, 7.24; N, 14.43; S, 16.53%. The starting nitrile **1f** (0.24 g, 30%) was isolated from the mother liquid.

3-Methyl-5,6,7,8-tetrahydroisoquinoline-4-carbothioamide (23g). Prepared analogously to thioamide **23a** from 3-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile **1g** (0.86 g, 5 mmol); the crude product obtained after heating at 80 °C for 20 h was recrystallized from ethyl acetate to give the product **23g** (0.62 g, 60%) as pink powder; mp 235-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63-1.77 (m, 4H, CH_2CH_2), 2.37 (s, 3H, Me), 2.50-2.59 (m, 1H, CH_2), 2.65-2.73 (m, 2H, CH_2), 2.78-2.89 (m, 1H, CH_2), 8.09 (s, 1H, 6-H), 9.61 and 10.14 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3215 (NH), 2939 (CH), 1188 (C=S) cm^{-1}. APCI MS *m*/*z*: 207 $[M+H]^+$. Anal. Calcd for $C_{11}H_{14}N_2S$ (206.31): C, 64.04; H, 6.84; N, 13.58; S, 15.54%. Found: C, 63.98; H, 6.82; N, 13.34; S, 15.68%. The starting nitrile **1g** (0.21 g, 25%) was isolated from the mother liquid.

3,5-Dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbothioamide (23h). Prepared analogously to thioamide **23c** from 3,5-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile **1h** (0.93 g, 5 mmol); additional amount of *O*,*O*-diethyl dithiophosphate (0.93 g, 0.84 mL, 5 mmol) was added to reaction mixture after heating at 80 °C for 10 h, and the resulting mixture was additionally heated under the same conditions for 4 h. The crude mass after work-up was chromatographed (silica gel, hexane/ethyl acetate in gradient 50 to 100%) to furnish the starting nitrile **1h** (0.17 g, 18%) and the titled product **23h** (0.73 g, 66%) as pale-yellow crystal solid, mp 205-207 °C (from EtOH). The NMR spectrum of the product **23h** was a superposition of two spectra corresponding to two rotamers: (**a**), 66%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (d, 3H, *J* 7.1 Hz, CH-*CH*$_3$), 1.60-1.95 (m, 4H, CH*CH*$_2$*CH*$_2$), 2.37 (s, 3H, 2-Me), 2.56-2.70 (m, 1H, CH_2), 2.72-2.86 (m, 1H, CH_2), 3.50-3.61 (m, 1H, *CH*-CH$_3$), 8.10 (s, 1H, 6-H), 9.76 and 10.20 (both br. s, 1H and 1H, NH_2); (**b**), 34%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, 3H, *J* 7.1 Hz, CH-*CH*$_3$), 1.60-1.95 (m, 4H, CH*CH*$_2$*CH*$_2$), 2.40 (s, 3H, 2-Me), 2.56-2.70 (m, 1H, CH_2), 2.72-2.86 (m, 1H, CH_2), 2.99-3.08 (m, 1H, *CH*-CH$_3$), 8.10 (s, 1H, 6-H), 9.57 and 10.13 (both br. s, 1H and 1H, NH_2). IR (film) *v* 3267 (NH), 2942 (CH), 1179 (C=S) cm^{-1}. APCI MS *m*/*z*: 221 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}N_2S$ (220.34): C, 65.41; H, 7.32; N, 12.71; S, 14.55%. Found: C, 65.37; H, 7.29; N, 12.81; S, 14.55%.

2-Methyl-5*H*-chromeno[3,4-*c*]pyridine-1-carbothioamide (23i). Prepared analogously to thioamide **23c** from 2-methyl-5*H*-chromeno[3,4-*c*]pyridine-1-carbonitrile **1i** (1.11 g, 5 mmol); additional amount of *O*,*O*-diethyl dithiophosphate (0.93 g, 0.84 mL, 5 mmol) was added to reaction mixture after heating at 80 °C for 30 h, and the resulting mixture was additionally heated under the same conditions for 10 h. The crude mass after work-up was recrystallized from ethyl acetate to

give the product **23i** (0.56 g, 44%) as pink-yellow crystal solid; mp 293-294 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, 2-Me), 5.06 (s, 2H, CH_2), 7.03-7.08 (m, 2H, C_6H_4), 7.34-7.40 (m, 1H, C_6H_4), 8.36 (s, 1H, 6-H), 8.36-8.40 (m, 1H, C_6H_4), 10.03 and 10.41 (both br. s, 1H and 1H, NH_2). IR (film) ν 3386 (NH), 3037 (CH), 1159 (C=S) cm^{-1}. APCI MS *m*/*z*: 257 $[M+H]^+$. Anal. Calcd for $C_{14}H_{12}N_2OS$ (256.33): C, 65.60; H, 4.72; N, 10.93; S, 12.51%. Found: C, 65.46; H, 4.69; N, 11.10; S, 12.46%.

4-[4-(4-Fluorophenyl)-1,3-thiazol-2-yl]-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine hydrobromide (25a). The mixture of thioamide **23a** (0.10 g, 0.52 mmol), 2-bromo-1-(4-fluorophenyl)ethanone **24a** (0.12 g, 0.55 mmol) and anhydrous ethanol (1 mL) was stirred at 75 °C for 1 h then cooled. The precipitate was filtered off, washed with ethyl acetate (2 mL), and dried to afford the product **25a** (0.175 g, 86%) as pale-gray solid; mp 139-140 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13-2.23 (m, 2H, CH_2), 2.80 (s, 3H, 2-Me), 3.14 (t, 2H, *J* 7.6 Hz, CH_2), 3.24 (t, 2H, *J* 7.6 Hz, CH_2), 7.29-7.37 (m, 2H, C_6H_4), 8.05-8.12 (m, 2H, C_6H_4), 8.51 (s, 1H, CH of thiazole ring), 8.76 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 311 $[M+H]^+$. Anal. Calcd for $C_{18}H_{16}BrFN_2S$ (391.31): C, 55.25; H, 4.12; Br, 20.42; N, 7.16; S, 8.19%. Found: C, 55.17; H, 4.05; Br, 20.37; N, 7.11; S, 8.35%.

***tert*-Butyl 2-(3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-4-yl)-6,7-dihydro[1,3]thiazolo-[5,4-*c*]pyridine-5(4*H*)-carboxylate (25b).** The mixture of thioamide **23a** (0.10 g, 0.52 mmol), *tert*-butyl 3-bromo-4-oxopiperidine-1-carboxylate **24b** (0.15 g, 0.55 mmol), $NaHCO_3$ (0.087 g, 1.04 mmol), and anhydrous ethanol (2 mL) was stirred at 70 °C for 24 h then cooled, diluted with ethyl acetate (10 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, ethyl acetate) to give the intermediate alcohol **26a** (0.13 g, 64%) as pale-yellow solid that was used for next step without an additional purification; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (s, 9H, *t*-Bu), 1.95-2.12 (m, 4H, CH_2CH_2), 2.45 (s, 3H, 2-Me), 2.81-2.92 (m, 4H, CH_2CH_2), 3.15-3.40 (m, 2H, CH_2), 3.59-3.77 (m, 2H, CH_2), 3.88-3.95 (m, 1H, CH), 6.52 (s, 1H, OH), 8.34 (s, 1H, 6-H). The alcohol **26a** was dissolved in anhydrous dichloromethane (3 mL), and trifluoroacetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The residue was dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL), and the product was extracted with ethyl acetate (3 × 5 mL). The extract was dried over $MgSO_4$ and evaporated to give the titled product **25b** (0.10 g, 52%, for two steps) as pale-yellow glassy mass; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H, *t*-Bu), 2.03-2.14 (m, 2H, CH_2), 2.55 (s, 3H, 2-Me), 2.90 (t, 2H, *J* 7.6 Hz, CH_2), 2.96 (t, 2H, *J* 7.6 Hz, CH_2), 2.99 (t, 2H, *J* 5.6 Hz, CH_2), 3.82 (t, 2H, *J* 5.6 Hz, CH_2), 4.72 (s, 2H, CH_2), 8.38 (s, 1H, 6-H). APCI MS *m*/*z*: 372 $[M+H]^+$, 316 $[M - t\text{-Bu} + H]^+$, 272 $[M - Boc + H]^+$. Anal. Calcd for $C_{20}H_{25}N_3O_2S$ (371.51): C, 64.66; H, 6.78; N, 11.31; S, 8.63%. Found: C, 64.77; H, 6.63; N, 11.05; S, 8.42%.

4-[4-(4-Fluorophenyl)-1,3-thiazol-2-yl]-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]-pyridine (25c). The mixture of thioamide **23b** (0.10 g, 0.45 mmol), 2-bromo-1-(4-fluorophenyl)ethanone **24a** (0.103 g, 0.47 mmol) and anhydrous ethanol (1 mL) was stirred at 75 °C for 1 h then cooled, diluted with ethyl acetate (5 mL) and washed with saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Combined organic solutions were washed with brine (10 mL), dried over $MgSO_4$, and evaporated at 60 °C/20 Torr to afford the

product **25c** (0.15 g, 99%) as yellow glassy mass; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44-1.54 (m, 2H, CH_2), 1.55-1.64 (m, 2H, CH_2), 1.73-1.83 (m, 2H, CH_2), 2.55 (s, 3H, 2-Me), 2.51-2.58 (m, 2H, CH_2), 2.78-2.86 (m, 2H, CH_2), 7.25-7.32 (m, 2H, C_6H_4), 8.01-8.07 (m, 2H, C_6H_4), 8.31 (s, 1H, CH of thiazole ring), 8.33 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 339 $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}FN_2S$ (338.45): C, 70.98; H, 5.66; F, 5.61; N, 8.28; S, 9.47%. Found: C, 71.07; H, 5.88; F, 5.42; N, 7.99; S, 9.29%.

1-(4,5-Dimethyl-1,3-thiazol-2-yl)-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline (25d). The mixture of thioamide **23c** (0.20 g, 0.8 mmol), 3-chlorobutan-2-one **18** (0.104 g, 0.98 mmol) and anhydrous ethanol (2 mL) was subjected to microwave irradiation at 100 ^{o}C for 4 h. Additional 3-chlorobutan-2-one **18** (0.104 g, 0.98 mmol) was added, and the microwave irradiation was continued at 100 ^{o}C for 4 h. The reaction mixture was then concentrated under reduced pressure, and the residue was dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL). The mixture was extracted with ethyl acetate (3 × 5 mL); the extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed (silica gel, hexane/ethyl acetate 7:3) to give the product **25d** (0.15 g, 99%) as dark-brown oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H, Me), 2.38 (s, 6H, 2Me), 2.72-2.83 (m, 4H, CH_2CH_2), 6.89 (dd, 1H, *J* 7.7, 1.2 Hz, C_6H_4), 7.00 (ddd, 1H, *J* 7.7, 1.5 Hz, C_6H_4), 7.22 (ddd, 1H, *J* 7.7, 1.2 Hz, C_6H_4), 7.32 (dd, 1H, *J* 7.7, 1.5 Hz, C_6H_4), 8.48 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 307 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2S$ (306.43): C, 74.47; H, 5.92; N, 9.14; S, 10.46%. Found: C, 74.31; H, 5.98; N, 9.05; S, 10.22%.

2-Methyl-4-phenyl-3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridine (25e). The mixture of thioamide **23d** (0.10 g, 0.44 mmol), 3-bromo-1,1,1-trifluoroacetone **20** (0.092 g, 0.48 mmol) and anhydrous ethanol (1 mL) was stirred at 70 ^{o}C for 48 h then evaporated to dryness to afford the intermediate alcohol **26b** (hydrobromide) (0.166 g, 90%), that was used for next step without an additional purification; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.67 (s, 3H, Me), 3.47 (d, 1H, *J* 13.1 Hz, CH_2), 3.63 (d, 1H, *J* 13.1 Hz, CH_2), 7.44-7.56 (m, 5H, Ph), 7.79 (d, 1H, *J* 5.9 Hz, 5-H), 7.88 (br. s, 2H, OH, HBr), 8.86 (d, 1H, *J* 5.9 Hz, 6-H). The intermediate **26b** was dissolved in anhydrous dichloromethane (5 mL), and trifluoroacetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature for 24 h and then diluted with saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL); the extract was dried over $MgSO_4$ and evaporated to yield the target product **25e** (0.10 g, 71% for two steps) as white crystal solid; mp 99-101 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H, Me), 7.14-7.21 (m, 2H, Ph), 7.29-7.35 (m, 3H, Ph), 7.40 (d, 1H, *J* 5.1 Hz, 5-H), 8.56 (s, 1H, CH of thiazole ring), 8.66 (d, 1H, *J* 5.1 Hz, 6-H). APCI MS *m*/*z*: 321 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}F_3N_2S$ (320.34): C, 59.99; H, 3.46; F, 17.79; N, 8.74; S, 10.01%. Found: C, 60.07; H, 3.49; F, 17.60; N, 8.79; S, 9.96%.

Ethyl 2-(2-methyl-4-phenylpyridin-3-yl)-1,3-thiazole-4-carboxylate (25f). The mixture of thioamide **23d** (0.10 g, 0.44 mmol), ethyl bromopyruvate **24c** (0.094 g, 0.48 mmol), and anhydrous ethanol (1 mL) was stirred at 70 ^{o}C for 80 h. Additional ethyl bromopyruvate **24c** (0.094 g, 0.48 mmol) as well as $NaHCO_3$ (0.11 g) were added to the mixture that was stirred at 70 ^{o}C for 4 h then concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate 3:1) to give the target 3-(thiazol-2-yl)pyridine **25f** (0.018 g, 13%) and intermediate alcohol **26c** (0.11 g, 73%) that was used for next step without an additional purification; ^{1}H NMR (400

MHz, $CDCl_3$) δ 1.35 (t, 3H, *J* 7.2 Hz, CH_2CH_3), 2.68 (s, 3H, Me), 3.40 (d, 1H, *J* 12.1 Hz, S-CH_2), 3.86 (d, 1H, *J* 12.1 Hz, S-CH_2), 4.29 (br. s, 1H, OH), 4.33 (q, 2H, *J* 7.2 Hz, CH_2CH_3), 7.21 (d, 1H, *J* 5.2 Hz, 5-H), 7.37-7.43 (m, 3H, Ph), 7.44-7.50 (m, 2H, Ph), 8.57 (d, 1H, *J* 5.2 Hz, 6-H). The alcohol **26c** was dissolved in anhydrous dichloromethane (2 mL), and trifluoroacetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate 3:1) to give the desired product **25f** (0.1 g); the total yield was 0.118 g (83% for two steps), pale-yellow crystal solid; mp 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 2.54 (s, 3H, Me), 4.46 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 7.18-7.30 (m, 5H, Ph), 7.28 (d, 1H, *J* 6.1 Hz, 5-H), 8.16 (s, 1H, CH of thiazole ring), 8.62 (d, 1H, *J* 6.1 Hz, 6-H). APCI MS *m*/*z*: 325 $[M+H]^+$. Anal. Calcd for $C_{18}H_{16}N_2O_2S$ (324.40): C, 66.65; H, 4.97; N, 8.64; S, 9.88%. Found: C, 66.71; H, 5.01; N, 8.44; S, 10.02%.

Ethyl [2-(2-methyl-4-phenylpyridin-3-yl)-1,3-thiazol-4-yl]acetate (25g). The mixture of thioamide **23d** (0.20 g, 0.88 mmol), ethyl 4-chloro-3-oxobutanoate **24d** (0.16 g, 0.97 mmol), $NaHCO_3$ (0.15 g, 1.76 mmol), and anhydrous ethanol (2 mL) was stirred at 75 °C for 3 h then cooled, diluted with ethyl acetate (10 mL) and filtered. The filtrate was concentrated under reduced pressure to give the intermediate alcohol **26d** (0.32 g, 100%, with impurities) as pale-yellow oil that was used for next step without an additional purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* 7.3 Hz, CH_2CH_3), 2.67 (s, 3H, Me), 2.73 (s, 1H, CH_2), 2.74 (s, 1H, CH_2), 3.30 (d, 1H, *J* 12.0 Hz, S-CH_2), 3.41 (d, 1H, *J* 12.0 Hz, S-CH_2), 4.23 (q, 2H, *J* 7.3 Hz, CH_2CH_3), 4.89 (br. s, 1H, OH), 7.17 (d, 1H, *J* 5.1 Hz, 5-H), 7.38-7.46 (m, 5H, Ph), 8.56 (d, 1H, *J* 5.1 Hz, 6-H). The alcohol **26d** was dissolved in anhydrous dichloromethane (2 mL), and trifluoroacetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature for 12 h and evaporated to dryness. The residue was dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL), and the solution was treated with ethyl acetate (3 × 5 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate 7:3) to give the product **25g** (0.26 g, 88%) as brown solid; mp 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J* 7.2 Hz, CH_2CH_3), 2.52 (s, 3H, Me), 3.87 (s, 2H, CH_2), 4.21 (q, 2H, *J* 7.2 Hz, CH_2CH_3), 7.17 (s, 1H, CH of thiazole ring), 7.18-7.22 (m, 2H, Ph), 7.23 (d, 1H, *J* 5.3 Hz, 5-H), 7.24-7.29 (m, 3H, Ph), 8.60 (d, 1H, *J* 5.3 Hz, 6-H). APCI MS *m*/*z*: 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_2S$ (338.43): C, 67.43; H, 5.36; N, 8.28; S, 9.47%. Found: C, 67.34; H, 5.36; N, 8.24; S, 9.41%.

Ethyl 4-methyl-2-(2-methyl-4-phenylpyridin-3-yl)-1,3-thiazole-5-carboxylate (25h). The mixture of thioamide **23d** (0.111 g, 0.49 mmol), ethyl 2-chloro-3-oxobutanoate **24e** (0.084 g, 0.51 mmol), and anhydrous ethanol (1 mL) was stirred at 50 °C for 50 h then concentrated under reduced pressure to afford hydrochloride of the intermediate alcohol **26e** (0.14 g, 72%) as yellow solid that was used for next step without an additional purification (^{1}H NMR spectra in DMSO-d_6 was an intricate superposition of two spectra for two diastereomers). The alcohol **26e** was dissolved in anhydrous dichloromethane (3 mL), and trifluoroacetic anhydride (0.5 mL) was added. The reaction mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL), and the solution was extracted with ethyl acetate (3 x 5 mL). The extract was dried over $MgSO_4$ and concentrated under reduced

pressure. The residue was chromatographed (silica gel, hexane/ethyl acetate 3:1) to give the desired product **25h** (0.112 g, 68%) as pale-yellow powder; mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 2.52 (s, 3H, Me), 2.76 (s, 3H, Me), 4.28 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 7.17-7.24 (m, 3H, Ph), 7.27-7.31 (m, 2H, Ph), 7.29 (d, 1H, *J* 5.1 Hz, 5-H), 8.61 (d, 1H, *J* 5.1 Hz, 6-H). APCI MS *m*/*z*: 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_2S$ (338.43): C, 67.43; H, 5.36; N, 8.28; S, 9.47%. Found: C, 67.39; H, 5.47; N, 8.31; S, 9.64%.

4-*tert*-Butyl-3-(4-ethyl-1,3-thiazol-2-yl)-2-methylpyridine (25i)

Method A. The mixture of 4-*tert*-butyl-2-methylpyridine-3-carbothioamide **23e** (0.11 g, 0.49 mmol), 1-bromobutan-2-one **24f** (0.09 g, 0.59 mmol), and anhydrous ethanol (1 mL) was stirred at room temperature for 24 h then concentrated at 60 °C/20 Torr. The residue was mixed with ethyl acetate (5 mL). The precipitate was filtered off, washed with ether and dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL), and the solution was extracted with ethyl acetate (3 × 5 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the intermediate alcohol **26f** (0.13 g, 90%) as pale-yellow oil that was used for next step without an additional purification; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (t, 3H, *J* 7.0 Hz, CH_2CH_3), 1.40 (s, 9H, *t*-Bu), 1.90 (q, 2H, *J* 7.0 Hz, CH_2CH_3), 2.45 (s, 3H, Me), 3.22-3.38 (m, 1H, S-CH_2), 3.44-3.59 (m, 1H, S-CH_2), 6.06 (br. s, 1H, OH), 7.31 (d, 1H, *J* 5.4 Hz, 5-H), 8.38 (d, 1H, *J* 5.4 Hz, 6-H). The alcohol **26f** was dissolved in anhydrous 1,2-dichloroethane (5 mL), and trifluoroacetic anhydride (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was dissolved in saturated aqueous solution of $NaHCO_3$ (5 mL), and the solution was extracted with ethyl acetate (3 × 10 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the titled product **25i** (0.098 g, 71%) as pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H, *t*-Bu), 1.34 (t, 3H, *J* 7.3 Hz, CH_2CH_3), 2.24 (s, 3H, Me), 2.88 (q, 2H, *J* 7.3 Hz, CH_2CH_3), 7.07 (s, 1H, CH of thiazole ring), 7.28 (d, 1H, *J* 5.6 Hz, 5-H), 7.44 (d, 1H, *J* 5.6 Hz, 6-H). APCI MS *m*/*z*: 261 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}N_2S$ (260.40): C, 69.19; H, 7.74; N, 10.76; S, 12.31%. Found: C, 69.24; H, 7.83; N, 10.59; S, 12.22%.

Method B. The mixture of 4-*tert*-butyl-2-methylpyridine-3-carbothioamide **23e** (0.1 g, 0.48 mmol), 1-bromobutan-2-one **24f** (0.09 g, 0.59 mmol), and anhydrous ethanol (1 mL) was stirred at 75 °C for 5 h then concentrated at 60 °C/20 Torr. The residue was mixed with ethyl acetate (5 mL). The precipitate was filtered off, washed with ether and dried to give the target product (hydrobromide) **25i** (0.095 g, 58%) as pale-yellow solid; mp 175-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (s, 9H, *t*-Bu), 1.26 (t, 3H, *J* 7.3 Hz, CH_2CH_3), 2.33 (s, 3H, Me), 2.82 (q, 2H, *J* 7.3 Hz, CH_2CH_3), 7.67 (s, 1H, CH of thiazole ring), 8.05 (d, 1H, *J* 5.6 Hz, 5-H), 8.83 (d, 1H, *J* 5.6 Hz, 6-H). APCI MS *m*/*z*: 261 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}N_2S \times 1.1HBr$ (349.41): C, 51.56; H, 6.09; Br, 25.16; N, 8.02; S, 9.18%. Found: C, 51.33; H, 6.22; Br, 24.93; N, 7.87; S, 8.97%.

4-Isopropyl-2-methyl-3-[4-(4-methylphenyl)-1,3-thiazol-2-yl]pyridine hydrobromide (25j). The mixture of 4-isopropyl-2-methylpyridine-3-carbothioamide **23f** (0.1 g, 0.52 mmol), 4-methylphenacyl bromide **24g** (0.115 g, 0.54 mmol), and anhydrous ethanol (1 mL) was stirred at 75 °C for 80 min then concentrated at 60 °C/20 Torr. The residue was mixed with ethyl acetate (5 mL). The precipitate was filtered off, washed with ether and dried to give the target product **25j** (0.18 g, 90%) as white crystal solid; mp 186-187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (d, 6H, *J* 6.8

Hz, CH*(CH$_3$)$_2$*), 2.35 (s, 3H, Me), 2.50 (s, 3H, Me), 2.81-2.90 (m, 1H, *CH*(CH$_3$)$_2$), 7.28 (d, 2H, *J* 8.0 Hz, C$_6$H$_4$), 7.89 (d, 2H, *J* 8.0 Hz, C$_6$H$_4$), 8.00 (d, 1H, *J* 6.1 Hz, 5-H), 8.42 (s, 1H, CH of thiazole ring), 8.87 (d, 1H, *J* 6.1 Hz, 6-H). APCI MS *m*/*z*: 309 [M+H]$^+$. Anal. Calcd for $C_{19}H_{21}BrN_2S$ (389.36): C, 58.61; H, 5.44; Br, 20.52; N, 7.19; S, 8.24%. Found: C, 58.54; H, 5.41; Br, 20.39; N, 7.11; S, 8.17%.

3-Methyl-4-[4-(4-methylphenyl)-1,3-thiazol-2-yl]-5,6,7,8-tetrahydroisoquinoline hydrobromide (25k). Prepared analogously from 3-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbothioamide **23g** (0.1 g, 0.49 mmol) and 4-methylphenacyl bromide **24g** (0.11 g, 0.51 mmol). Yield 0.156 g (80%); white crystal solid; mp 277-278 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 1.68-1.82 (m, 4H, CH$_2$CH$_2$), 2.35 (s, 3H, Me), 2.47 (s, 3H, Me), 2.62-2.72 (m, 2H, CH$_2$), 2.87-2.97 (m, 2H, CH$_2$), 7.28 (d, 2H, *J* 8.1 Hz, C$_6$H$_4$), 7.88 (d, 2H, *J* 8.1 Hz, C$_6$H$_4$), 8.41 (s, 1H, CH of thiazole ring), 8.72 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 321 [M+H]$^+$. Anal. Calcd for $C_{20}H_{21}BrN_2S$ (401.37): C, 59.85; H, 5.27; Br, 19.91; N, 6.98; S, 7.99%. Found: C, 59.92; H, 5.31; Br, 19.79; N, 7.04; S, 7.90%.

4-[4-(3-Methoxyphenyl)-1,3-thiazol-2-yl]-3,5-dimethyl-5,6,7,8-tetrahydroisoquinoline hydrobromide (25l). Prepared analogously from 3,5-dimethyl-5,6,7,8-tetrahydroisoquinoline-4-carbothioamide **23h** (0.1 g, 0.45 mmol) and 3-methoxylphenacyl bromide **24h** (0.11 g, 0.48 mmol), heating at 70 °C for 2 h. Yield 0.192 g (98%); white crystal solid; mp 235-236 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 1.06 (d, 3H, *J* 7.3 Hz, CH-*CH*$_3$), 1.64-1.94 (m, 4H, CH$_2$CH$_2$), 2.45 (s, 3H, Me), 2.80-2.94 (m, 1H, *CH*-CH$_3$), 3.00-3.21 (m, 2H, CH$_2$), 3.82 (s, 3H, OMe), 6.97 (ddd, 1H, *J* 8.2, 2.7, 1.0 Hz, 4-H, C$_6$H$_4$), 7.39 (dd, 1H, *J* 8.2, 7.8 Hz, 5-H, C$_6$H$_4$), 7.55 (dd, 1H, *J* 2.7, 1.0 Hz, 2-H, C$_6$H$_4$), 7.59 (ddd, 1H, *J* 7.8, 1.0, 1.0 Hz, 6-H, C$_6$H$_4$), 8.56 (s, 1H, CH of thiazole ring), 8.76 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 351 [M+H]$^+$. Anal. Calcd for $C_{21}H_{23}BrN_2OS$ (431.40): C, 58.47; H, 5.37; Br, 18.52; N, 6.49; S, 7.43%. Found: C, 58.50; H, 5.40; Br, 18.43; N, 6.36; S, 7.25%.

1-(4-*tert*-Butyl-1,3-thiazol-2-yl)-2-methyl-5*H*-chromeno[3,4-*c*]pyridine (25m). The mixture of 2-methyl-5*H*-chromeno[3,4-*c*]pyridine-1-carbothioamide **23i** (0.10 g, 0.39 mmol), 1-bromo-3,3-dimethylbutan-2-one **24i** (0.077 g, 0.43 mmol) and anhydrous ethanol (1 mL) was stirred at 70 °C for 1 h then concentrated under reduced pressure. The residue was diluted in saturated aqueous solution of NaHCO$_3$ (5 mL). The mixture was extracted with ethyl acetate (3 × 5 mL). The extract was dried over MgSO$_4$ and evaporated at 60 °C/20 Torr. The residue was chromatographed (silica gel, hexane/ethyl acetate 7:3) to give the target product **25m** (0.06 g, 46%) as pale-yellow glassy mass; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 1.37 (s, 9H, *t*-Bu), 2.30 (s, 3H, Me), 5.13 (s, 2H, CH$_2$), 6.50 (dd, 1H, *J* 8.1, 1.5 Hz, C$_6$H$_4$), 6.72 (ddd, 1H, *J* 8.1, 7.3, 1.2 Hz, C$_6$H$_4$), 7.05 (dd, 1H, *J* 8.1, 1.2 Hz, C$_6$H$_4$), 7.27 (ddd, 1H, *J* 8.1, 7.3, 1.5 Hz, C$_6$H$_4$), 7.54 (s, 1H, CH of thiazole ring), 8.54 (s, 1H, CH of pyridine ring). APCI MS *m*/*z*: 337 [M+H]$^+$. Anal. Calcd for $C_{20}H_{20}N_2OS$ (336.46): C, 71.40; H, 5.99; N, 8.33; S, 9.53%. Found: C, 71.31; H, 5.98; N, 8.29; S, 9.35%.

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