Substituted 4-(3-Cyanopyridin-2-ylthio)acetoacetates: New Convenient Reagents for the Synthesis of Heterocycles

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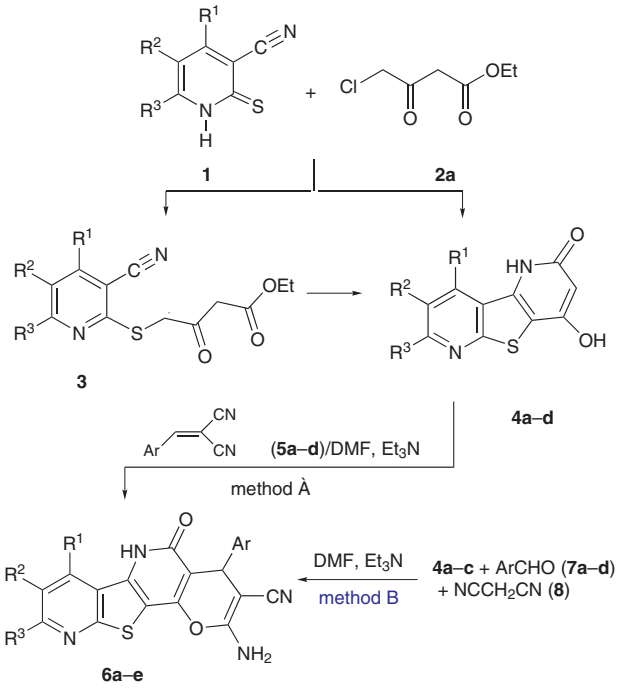
Abstract: Polyfunctional 4-(3-cyanopyridin-2-ylthio)acetoacetates were used in the synthesis of 4-hydroxy-1*H*-thieno[2,3-*b*:4,5-*b*]dipyridin-2-ones. The latter were used in reactions with arylidenemalononitriles or in three-component reactions with aldehydes and malononitrile to give 2-amino-4-aryl-3-cyano-5-oxo-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines. Utilizing 4-(3-cyanopyridin-2-ylthio)acetoacetates and arylidenemalononitriles or aldehydes and malononitrile, we developed a method for the synthesis of substituted 3-alkoxycarbonyl-6-amino-4-aryl-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans. Reactions of substituted 4-(3-cyanopyridin-2-ylthio)acetoacetates with hydrazine hydrate yielded substituted 3-hydroxypyrazoles, which were further used for the preparation of 6-amino-4-aryl-5-cyano-3-(pyrid-2-ylthiomethylene)-2,4-dihydropyrano[2,3-*c*]pyrazoles. Analogously, ethyl 4-(3-cyano-1,4-dihydropyridin-2-ylthio)acetoacetates were used for the synthesis of substituted 2-amino-4*H*-pyrans.

Key words: 2-amino-4*H*-pyrans, thienopyridines, 4-(3-cyanopyridin-2-ylthio)acetoacetates, pyranopyridines, multi-component reactions

We have previously reported that 4-(3-cyanopyridin-2-ylthio)acetoacetates (**3**) are convenient starting reagents for the syntheses of 4-hydroxy-1*H*-thieno[2,3-*b*:4,5-*b*]dipyridin-2-ones that are otherwise difficult to prepare.[1] Considering that compounds of type **3** contain several reaction centers, we decided to study the ability of these compounds to undergo a range of reactions in order to develop new routes to relatively inaccessible heterocycles, including new heterocyclic systems. Products of these reactions are of interest for several reasons, but mainly because of their similarity to the highly physiologically active hydroxy(oxo)pyridines[2,3] and 2-amino-4*H*-pyrans, which are licensed as drugs, pesticides, and other practically significant compounds.[4–8] It therefore seemed of practical interest to prepare substances containing simultaneously both pyridine and pyran rings.

Substituted 4-(3-cyanopyridin-2-ylthio)acetoacetates **3**, can be readily synthesized from 3-cyanopyridine-2(1*H*)-thiones **1** and 4-chloroacetates **2** and can be further transformed into 4-hydroxy-1*H*-thieno[2,3-*b*:4,5-*b*]dipyridin-2-ones **4** by successive Thorpe–Ziegler and Guareschi–Thorpe[1] intramolecular ring closures (Scheme 1).

We decided to use thienodipyridinones **4** and their hydrogenated analogues for the synthesis of annealated pyrans of type **6**, which represent a novel heterocyclic system.[9] Compounds **4**, similar to 4-hydroxyquinolin-2(1*H*)-one,[10,11] react as CH-acids with arylidenemalononitriles **5** in the presence of triethylamine or *N*-methylmorpholine in DMF to afford 2-amino-4-aryl-3-cyano-5,6-dihydro-5-oxo-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines **6a–e** (method A). Compounds **6a–d** were also obtained by three-component reaction of thienodipyridinones **4**, aromatic aldehydes **7**, and malononitrile **8** (method B) (Scheme 1).



Scheme 1 (**4a**) R^1 = Me, R^2 = H, R^3 = Me; (**4b**) R^1 = H, R^2 = H, R^3 = 4-$MeOC_6H_4$; (**4c**) R^1 = H, R^2-R^3 = $(CH_2)_5$; (**4d**) R^1 = H, R^2-R^3 = -$CH_2N(Me)CH_2CH_2$-; (**6a**) R^1 = Me, R^2 = H, R^3 = Me, Ar = 4-MeC_6H_4; (**6b**) R^1 = Me, R^2 = H, R^3 = Me, Ar = 3-C_5H_4N; (**6c**) R^1 = H, R^2 = H, R^3 = 4-$MeOC_6H_4$, Ar = 4-FC_6H_4; (**6d**) R^1 = H, R^2-R^3 = $(CH_2)_5$, Ar = 4-*i*-$PrOC_6H_4$; (**6e**) R^1 = H, R^2-R^3 = -$CH_2N(Me)CH_2CH_2$-, Ar = 4-F-C_6H_4; (**5a**, **7a**) Ar = 4-MeC_6H_4; (**5b**, **7b**) Ar = 3-C_5H_4N; (**5c**, **7c**) Ar = 4-FC_6H_4; (**5d**, **7d**) Ar = 4-*i*-$PrOC_6H_4$

The data of physicochemical analysis of pyranopyridothienopyridines **6** (Tables 1 and 2) indicate that the reactions leading to their formation are highly regioselective. Compounds **6** are high-melting microcrystals, which are stable under normal conditions, and poorly

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soluble in most of the organic solvents, excluding DMF and DMSO.

The ^{1}H NMR spectra of compounds **6a–e** show characteristic singlets of 4-H protons of the pyran ring at 4.43–4.71 ppm, and singlets of the NH_2 and NH protons at 7.09–7.25 ppm and 11.08–12.84 ppm, respectively. The IR spectra of compounds **6** are characterized by absorption bands of stretching vibrations of the nitrile group at 2184–2208 cm^{-1}, and by absorption bands of stretching vibrations (3164–3468 cm^{-1}) and bending vibrations (1632–1676 cm^{-1}) of the amino and amide groups. Similar IR and ^{1}H NMR spectra were previously observed for 2-amino-4-aryl-3-cyano-5,6-dihydro-5-oxo-4*H*-pyrano[3,2-*c*]quinoline[11] and other annelated 2-amino-4-aryl-3-cyano-4*H*-pyrans.[12–16]

These types of transformations were extended by us to include hydrogenated pyridinethiones (Scheme 2). Thus, 4-(1,4-dihydropyridin-2-ylthio)acetoacetates **10a–c** were obtained by the alkylation of morpholinium 1,4-dihydropyridinethiolates **9a–c** with ethyl chloroacetoacetate (**2a**) in ethanol. Compound **10a** was isolated as an amorphous substance, by precipitating a resinous residue from the solution with water, followed by extraction with diethyl ether.

The ^{1}H NMR spectra of compounds **10** (Tables 3 and 4) contain the characteristic singlets of NH and 4-H protons of the pyridine ring at 9.25–9.56 and 4.48–4.83 ppm, respectively. The signals of the methylene atoms were observed at 4.11–4.21 ppm (CH_2S) and at 3.65–3.75 ppm (CH_2O). Compounds **10b** and **10c** showed signals corresponding to the CONH protons at 8.97 ppm and 9.10 ppm, respectively. The IR spectra of compounds **10b** and **10c** showed absorption bands of the CN group at 2205 cm^{-1} and 2218 cm^{-1} and of the CO group in the region of 1730–1740 cm^{-1}.

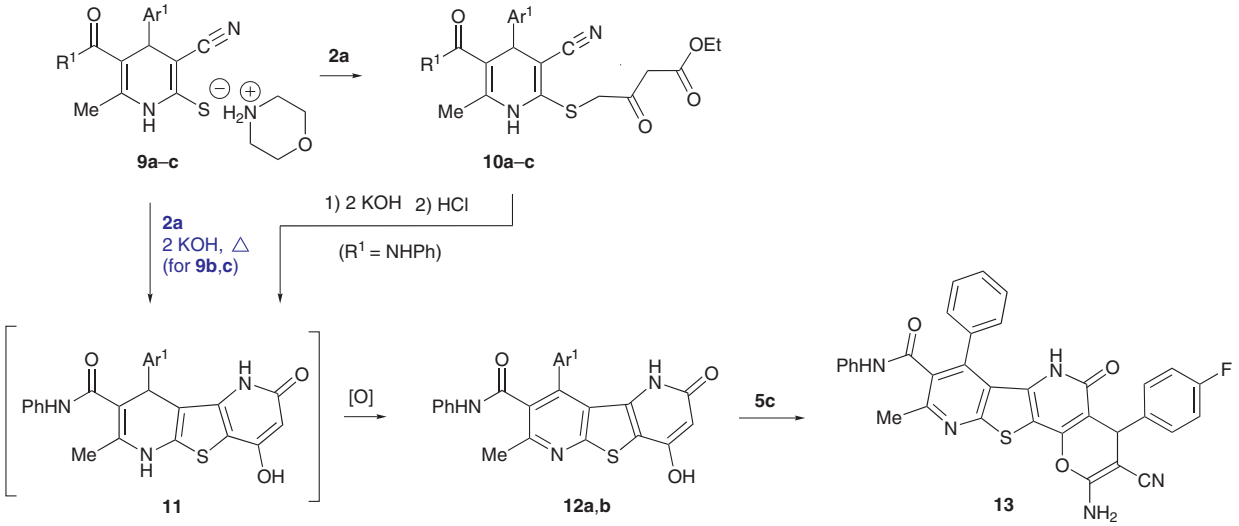
Esters **10** were used to prepare synthetically challenging 4-hydroxy-2-oxopyrido[2′,3′:4,5]thieno[2,3-*b*]pyridines.

Compounds **10b**,**c** were dissolved in hot ethanol, and a two-fold excess of base was added to the solution. The reaction mixture was then refluxed, cooled to room temperature and acidified with hydrochloric acid to precipitate compounds **12** which, according to the IR and ^{1}H NMR spectra, were formed in the reaction instead of the expected 4-hydroxy-1,2-dihydro-2-[2′,3′:4,5]thieno[2,3-*b*]pyridines **11** (Scheme 2).

Annelated thienopyridines **12a** and **12b** were also synthesized in one step, without preliminary isolation of compounds **10**, by refluxing a mixture consisting of equimolar amounts of salt **9b**,**c** and **2a** in ethanol in the presence of a two-fold excess of base. Compounds **12a**,**b** are stable and poorly soluble in the majority of organic solvents.

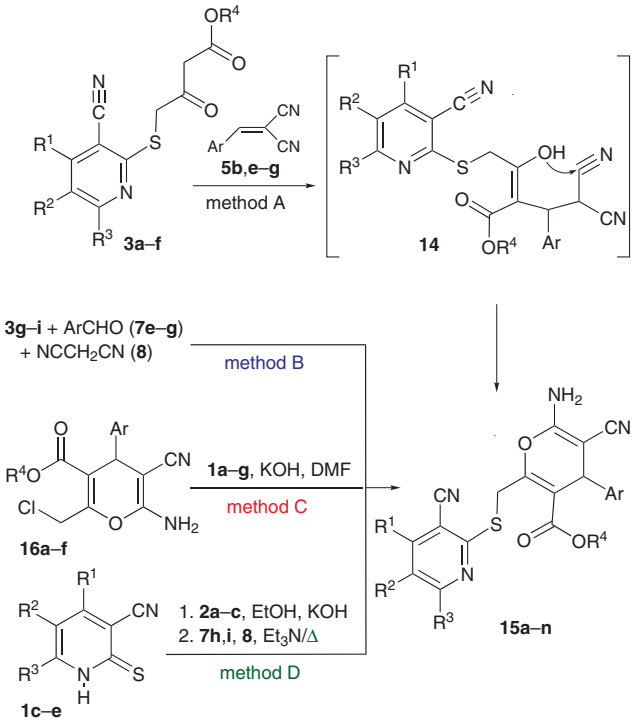
The IR spectra of compounds **12a**,**b** contain no signals from the CN groups, but do contain the characteristic signals of the NHCO and OH groups. The ^{1}H NMR spectra of these compounds show signals corresponding to the aryl protons and from the ArNH group (in regions 10.45 and 10.41 ppm). The signal from the 3-H proton of **12a** and **12b** was observed at 5.86 ppm and 6.19 ppm, respectively. The signal of the N^{1}H proton was observed at 12.05 ppm and 11.69 ppm, respectively, which is characteristic for pyridin-2(1*H*)-ones.[1] It proved difficult to assign the signal from the OH proton due to deuterium exchange that takes place in DMSO-d_6 and the poor solubility of **12** in other solvents used in ^{1}H NMR spectroscopy.

On heating in DMF in the presence of *N*-methylmorpholine, thienopyridine **12a** reacts with 4-fluorobenzylidenemalononitrile (**5c**) to form the tetracyclic-condensed system **13**. The IR spectrum of **13** contains the characteristic absorption band of the CN group at 2210 cm^{-1}, a broadened absorption band at 1640 cm^{-1} corresponding to bending vibrations of the NH_2 group, and an absorption band of the CO group at 1670 cm^{-1}. The ^{1}H NMR spectrum of **13** contains the characteristic signals from the NH_2 and NH protons at 7.53 ppm and 10.40 ppm, respectively.



Scheme 2 (**9a**, **10a**) R^1 = OMe, Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; (**9b**, **10b**) R^1 = NHC_6H_4, Ar^1 = Ph; (**9c**, **10c**) R^1 = NHC_6H_4, Ar^1 = 3-C_5H_4N; (**12a**) Ar^1 = Ph; (**12b**) Ar^1 = 3-C_6H_4N

Intermolecular reactions involving electrophilic and nucleophilic reactants with pyridinylthioacetoacetates **3** were also considered (Scheme 3).[9] The reaction of esters **3a–f** with arylidenemalononitriles **5b**,**e–g** occurs regioselectively only at one of the two available methylene-active groups (CH_2COOR group) and affords the substituted 2-amino-4*H*-pyrans **15a–f** (method A).



Scheme 3 (**1a**) $R^1 = R^2 = H$, $R^3 = Ph$; (**1b**) $R^1 = R^2 = H$, $R^3 = 4\text{-}C_5H_4N$; (**1c**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$; (**1d**) $R^1 = H$, $R^2 = Me$, $R^3 = Et$; (**1e**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$ (**1f**) $R^1 = H$, $R^2\text{-}R^3 = \text{-}CH_2N(Me)CH_2CH_2\text{-}$; (**1g**) $R^1 = 4\text{-}MeO\text{-}C_6H_4$, $R^2\text{-}R^3 = \text{-}CH_2CH(t\text{-}Bu)CH_2CH_2\text{-}$; (**2a**) $R^4 = Et$; (**2b**) $R^4 = Me$; (**2c**) $R^4 = i\text{-}Pr$; (**3a**) $R^1 = R^2 = H$, $R^3 = R^4 = Me$; (**3b**) $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Et$; (**3c**) $R^1 = R^2 = H$, $R^3 = 4\text{-}C_5H_4N$, $R^4 = Et$; (**3d**) $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = 2\text{-}C_4H_3S$, $R^4 = Et$; (**3e**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_3$, $R^4 = Me$; (**3f**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$, $R^4 = i\text{-}Pr$; (**3g**) $R^1 = Me$, $R^2 = H$, $R^3 = R^4 = Me$; (**3h**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_4$, $R^4 = i\text{-}Pr$; (**3i**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$, $R^4 = Et$; (**5b**) Ar = $3\text{-}C_5H_4N$; (**5e**) Ar = $2\text{-}ClC_6H_4$; (**5f**) Ar = $4\text{-}EtC_6H_4$; (**5g**) Ar = $4\text{-}C_5H_4N$; (**7c**) Ar = $4\text{-}FC_6H_4$; (**7e**) Ar = $2\text{-}FC_6H_4$; (**7f**) Ar = $4\text{-}NO_2C_6H_4$; (**7g**) Ar = $3\text{-}C_4H_3S$; (**7h**) Ar = $2\text{-}C_4H_3S$ (**7i**) Ar = $4\text{-}C_5H_4N$; (**15a**) $R^1 = R^2 = H$, $R^3 = R^4 = Me$, Ar = $2\text{-}ClC_6H_4$; (**15b**) $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Et$, Ar = $3\text{-}C_5H_4N$; (**15c**) $R^1 = R^2 = H$, $R^3 = 4\text{-}C_5H_4N$, $R^4 = Et$, Ar = $3\text{-}C_5H_4N$; (**15d**) $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = 2\text{-}C_4H_3S$, $R^4 = Et$, Ar = $3\text{-}C_5H_4N$; (**15e**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_3$, $R^4 = Me$, Ar = $4\text{-}EtC_6H_4$; (**15f**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$, $R^4 = i\text{-}Pr$, Ar = $4\text{-}C_5H_4N$; (**15g**) $R^1 = Me$, $R^2 = H$, $R^3 = R^4 = Me$, Ar = $2\text{-}FC_6H_4$; (**15h**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_4$, $R^4 = i\text{-}Pr$, Ar = $4\text{-}NO_2C_6H_4$; (**15i**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_5$, $R^4 = Et$, Ar = $3\text{-}C_4H_3S$; (**15j**); $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = Et$, Ar = $2\text{-}C_4H_3S$; (**15k**) $R^1 = H$, $R^2\text{-}R^3 = (CH_2)_6$, $R^4 = Me$, Ar = $4\text{-}C_5H_4N$; (**15l**) $R^1 = H$, $R^2\text{-}R^3 = \text{-}CH_2N(Me)CH_2CH_2\text{-}$, $R^4 = Me$, Ar = $4\text{-}FC_6H_4$; (**15m**) $R^1 = H$, $R^2\text{-}R^3 = \text{-}CH_2N(Me)CH_2CH_2\text{-}$, $R^4 = Et$, Ar = $4\text{-}ClC_6H_4$; (**15n**) $R^1 = 4\text{-}MeOC_6H_4$, $R^2\text{-}R^3 = \text{-}CH_2CH(t\text{-}Bu)CH_2CH_2\text{-}$, $R^4 = Et$, Ar = $2\text{-}C_4H_3S$; (**16a**) $R^4 = Et$, Ar = $3\text{-}C_5H_4N$; (**16b**) $R^4 = Et$, Ar = $3\text{-}C_4H_3S$; (**16c**) $R^4 = Et$, Ar = $2\text{-}C_4H_3S$; (**16d**) $R^4 = Me$, Ar = $4\text{-}C_5H_4N$; (**16e**) $R^4 = Me$, Ar = $4\text{-}FC_6H_4$; (**16f**) $R^4 = Et$, Ar = $4\text{-Cl-}C_6H_4$

In some cases, pyranopyridines **15g–i** were prepared using a simplified procedure without isolation of intermediates **5** by a three-component reaction of compounds **3g–i**, aromatic aldehydes **7e–g**, and malononitrile **8** in ethanol in the presence of bases (method B).

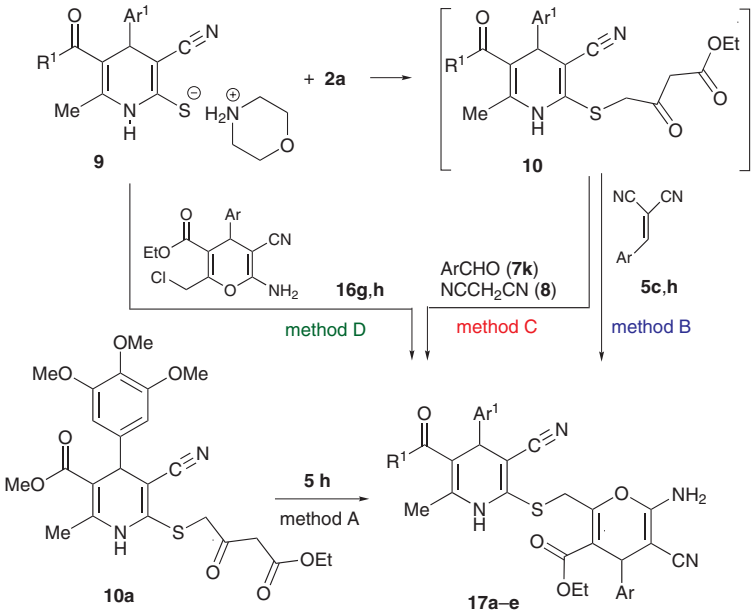
The structures of compounds **15** were also confirmed by a counter synthesis. The reaction of pyrans **16a–f** with the corresponding pyridine-2(1*H*)-thiones **1a–g** regioselectivly gave pyranopyridines **15b**,**c**,**i–n** (method C).

Taking into account that the formation of compounds **3** and **15** was highly regioselective, it was reasonable to assume that pyrans **15** could be synthesized by a simpler method without preliminary isolation and purification of pyridylthioacetoacetic esters **3** (method D). Esters **3** were generated by reaction of pyridinethiones **1c–e** and esters **2a–c** in ethanol (or methanol) in the presence of an equimolar amount of KOH, and then equimolar amounts of the corresponding aromatic aldehyde **7h**,**i** and malononitrile **8** and a catalytic amount of triethylamine were added to the reaction mixture to produce compounds **15**. Despite the moderate yields of compounds **15f**,**j**,**k** in method D (48–57%), this approach was found to be both the most convenient and the more economic route.

Generally, compounds **15** are colorless, crystalline substances, which are well soluble in most organic solvents. The ^1H NMR spectra of these compounds (Tables 5 and 6) contain the characteristic signals of the 4-H proton of the pyran ring at $\delta = 4.25–4.88$ ppm and protons of the amino group at $\delta = 6.63–7.00$ ppm. The methylene atoms of the CH_2S group were observed in the region of $\delta = 4.60–4.96$ ppm. Generally, signals from the methylene protons are present in the form of either a singlet or a doublet of doublets. For the latter, the spin-spin coupling constant ranges from 13.7–15.1 Hz.

The IR spectra of compounds **15** were characterized by two absorption bands of the nitrile groups of the pyran and pyridine rings at 2188–2204 cm^{-1} and 2216–2240 cm^{-1}, respectively. The absorption bands of the carbonyl group lie in a region of 1704–1728 cm^{-1}. The IR spectra of compounds **15** also show absorption bands of the amino group at 1668–1688 cm^{-1} for bending vibrations and as two or three (due to the formation of associates) bands at 3168–3472 cm^{-1} for stretching vibrations.

Similar transformations were carried out for hydrogenated pyridine derivatives (Scheme 4). In this case, the pyridine ring was not dehydrogenated, and 2-(6-amino-3-carbethoxy-5-cyano-4*H*-pyran-2-ylmethylenethio)-3-cyano-1,4-dihydropyridines **17** were obtained. For example, the reaction of ester **10a** with 4-methoxybenzylidenemalononitrile **5h** in ethanol in the presence of triethylamine gave compound **17a** (method A). Since isolation in the pure state and the work with resin-like esters **10** was difficult and decreased the yield of the target compounds, we generated esters **10** in the reaction mixture and then introduced them, without isolation, into the reaction with arylidenenemalononitriles **5c**,**h**. In this manner, com-



Scheme 4 (**5c**) Ar = 4-FC_6H_4; (**5h**) 4-$MeOC_6H_4$; (**7k**) Ar = 4-$MeOC_6H_4$; (**9a**) R^1 = OMe, Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; (**9d**) R^1 = OMe, Ar^1 = 3,4-$(MeO)_2C_6H_3$; (**9e**) R^1 = OEt, Ar^1 = 2-C_4H_3S; (**9f**) R^1 = OEt, Ar^1 = 4-$(MeO_2C)C_6H_4$; (**16g**) Ar = 4-$MeOC_6H_4$; (**16h**) Ar = 4-FC_6H_4; (**17a**) Ar = 4-$MeOC_6H_4$, R^1 = OMe, Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; (**17b**) Ar = 4-$MeOC_6H_4$, R^1 = OMe, Ar^1 = 3,4-$(MeO)_2C_6H_3$; (**17c**) Ar = 4-$MeOC_6H_4$, R^1 = OEt, Ar^1 = 2-C_4H_3S; (**17d**) Ar = 4-$MeOC_6H_4$, R^1 = OEt, Ar^1 = 4-$(MeO_2C)C_6H_4$; (**17e**) Ar = 4-F-C_6H_4, R^1 = OEt, Ar^1 = 2-C_4H_3S

pounds **17b**,**c**,**e** were obtained in good yields of ~70% (method B).

At the next stage this synthesis was simplified. After ester **10** was generated in the reaction mixture from salt **9e** (Ar^1 = 2-C_4H_3S) and ester **2a**, 4-methoxybenzaldehyde **7k**, malononitrile **8**, and triethylamine were added to the solution. After brief heating of the multi-component reaction mixture, compound **17c** was obtained in 57% yield (method C). Furthermore, the reaction of salts **9a**,**e**,**f** with pyrans **16g**,**h** was carried out in ethanol without catalysts to obtain compounds **17a**,**c**–**e** in 42–50% yield (method D).

The structures of compounds **17** were confirmed by the IR and ^{1}H NMR spectra (Tables 9 and 10). The IR spectra of compounds **17** contain the characteristic signals of the nitrile group of the pyran at 2202–2215 cm^{-1} and dihydropyridine at 2174–2195 cm^{-1}. The ^{1}H NMR spectra show signals of the 4-H proton of the pyran in a region of δ = 4.24–4.34 and 1,4-dihydropyridine at δ = 4.43–4.83 ppm, as well as the characteristic signals of the protons of the CH_2S methylene group as a doublet of doublets at δ = 4.00–4.70 ppm. Probably, this multiplicity is related to the hindered rotation of the pyran ring around the S–CH_2 bond. The ^{1}H NMR spectra also contain signals corresponding to the amino group at δ = 6.50–6.82 ppm along with signals of the NH proton at δ = 9.40–9.80 ppm.

The structure of compound **15a** was confirmed by X-ray diffraction analysis as 6-amino-4-(2-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-(3-cyano-6-methylpyridin-2-ylthiomethyl)-4*H*-pyran, the molecular structure of which is shown in Figure 1. In the 4*H*-pyran ring, the olefinic carbon atoms lie in one plane with an accuracy of 0.02 Å, and the O(1) and C(12) atoms deviate from this plane to the same side by 0.10 and 0.24 Å, respectively. In the basis molecule, the C(12) atom has the *R* configuration but molecules of compound **15a** are crystallized in the achiral space group $P2_1/n$. The structure of compound **15a** is layered and a projection along axis [100] is presented in Figure 2. Both hydrogen atoms of the amino group are involved in the formation of the N(3)–H(1)···O(3) (x + 1/2, –y + 1/2, z + 1/2) [N(3)–H(1) 0.85(3), H(1)···O(3) 2.01(3), N(3)···O(3) 2.806(3) Å, angle N(3)–H(1)···O(3) 155(2)°], N(3)–H(2)···N(4) (–x + 2, –y, –z + 1) [N(3)–H(2) 0.85(3), H(2)···N(4) 2.25(3), N(3)···N(4) 3.055(3) Å, angle N(3)–H(2)···N(4) 158(2)°] hydrogen bonds, which unify molecules **15a** to form layers parallel to the (1 0 –1) plane.

The presence of electrophilic carbonyl carbon atoms in the acetoacetic ester fragment together with nucleophilic centers in the molecule, prompted us to study their reaction with hydrazine, since 4-(3-cyanopyridin-2-ylthio)acetoacetates **3** have been recognized as convenient reagents for syntheses of substituted pyrazoles.[17] For example, the reaction of ester **3j** with hydrazine gives 2-(3-hydroxy-1*H*-pyrazolyl-5-methylthio)pyridine **18** (Scheme 5).

As pyrazoles are convenient reagents for the synthesis of 6-amino-5-cyano-2,4-dihydropyrano[2,3-*c*]pyrazoles,[10,13,14,17] we decided to apply this reaction to compound **18** in order to synthesize pyrano[2,3-*c*]pyrazoles **20a**,**b**. The reaction of pyrazole **18** with arylidenemalononitriles **5c**,**h** in ethanol in the presence of catalytic amounts of triethylamine yielded pyrazolopyrans **20a**,**b**. It is most probable that the reaction proceeds through the corresponding Michael adduct **19**, whose subsequent ring closure affords pyrano[2,3-*c*]pyrazoles **20**.

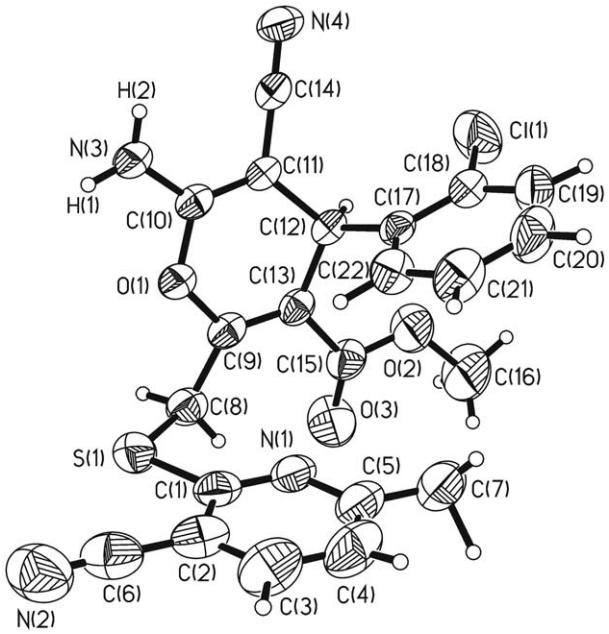


Figure 1 Molecular structure of 6-amino-4-(2-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-(3-cyano-6-methylpyridin-2-ylthiomethyl)-4*H*-pyran **(15a)**

The structures of pyranopyrazoles **20** were confirmed by spectroscopic methods. In addition to other characteristic proton signals, the ^{1}H NMR spectra of compounds **20a**,**b** contained singlets from the NH protons at 12.49 ppm and 12.44 ppm, the NH_2 group at 6.90 ppm and 6.83 ppm, as well as protons corresponding to the 4-H-pyran ring at 4.76 ppm and 4.67 ppm, respectively. The IR spectra of compounds **20a**,**b** showed two sets of absorption bands from the CN group of the pyridine and the pyran at 2224 cm^{-1}, 2232 cm^{-1} and 2184 cm^{-1}, 2188 cm^{-1}, respectively.

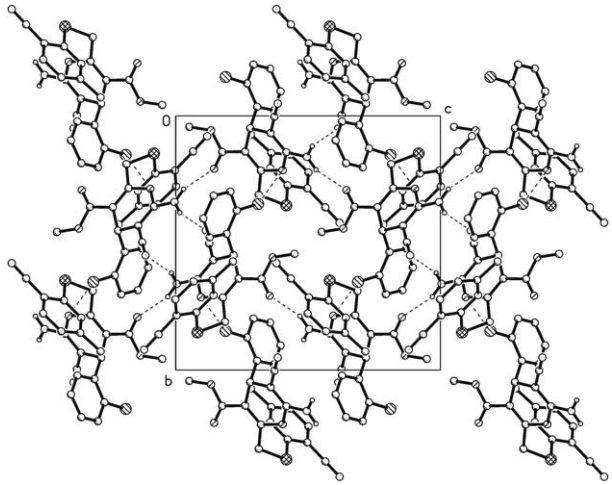
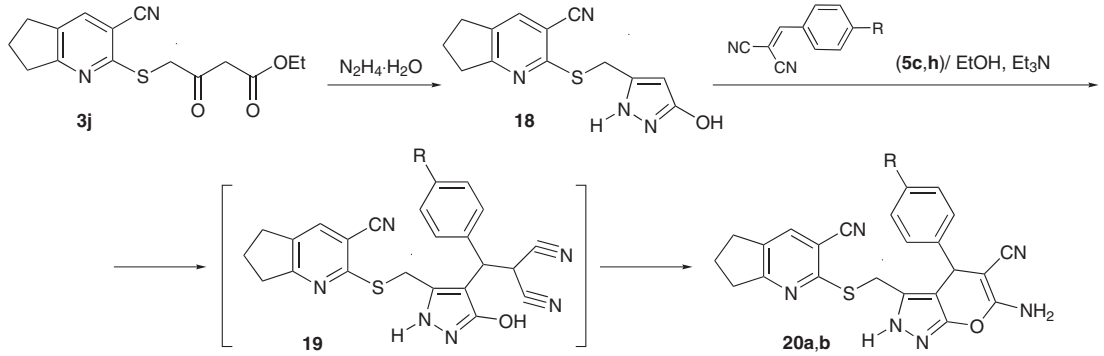


Figure 2 Projection of the structure of 6-amino-4-(2-chlorophenyl)-5-cyano-3-methoxycarbonyl-2-(3-cyano-6-methylpyridin-2-ylthiomethyl)-4*H*-pyran **(15a)** along axis [100]

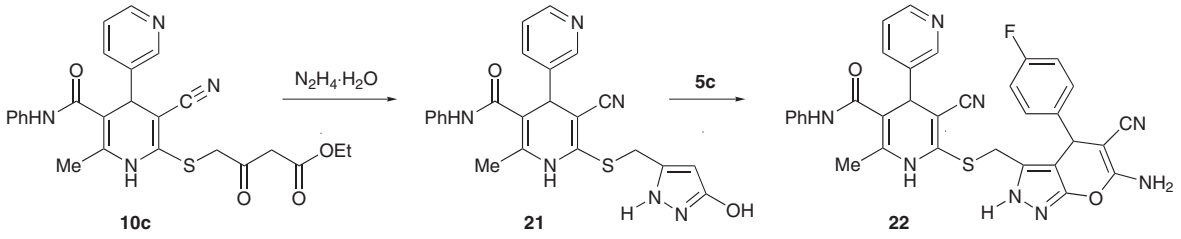
We also synthesized pyrano[2,3-*c*]pyrazole from hydrogenated pyridines (Scheme 6). The reaction of ester **10c** with hydrazine hydrate gave 2-(pyrazolyl-5-methylthio)-1,4-dihydropyridine **21**, which was used in a reaction with 4-fluorobenzylidenemalononitrile (**5c**) in ethanol in the presence of *N*-methylmorpholine to give the pyrazolopyran **22**.

In conclusion, we found that 3-cyanopyridinylthioacetoacetates **3** and **10**, containing several highly reactive centers are convenient reagents for the regioselective synthesis of functionally substituted heterocycles.

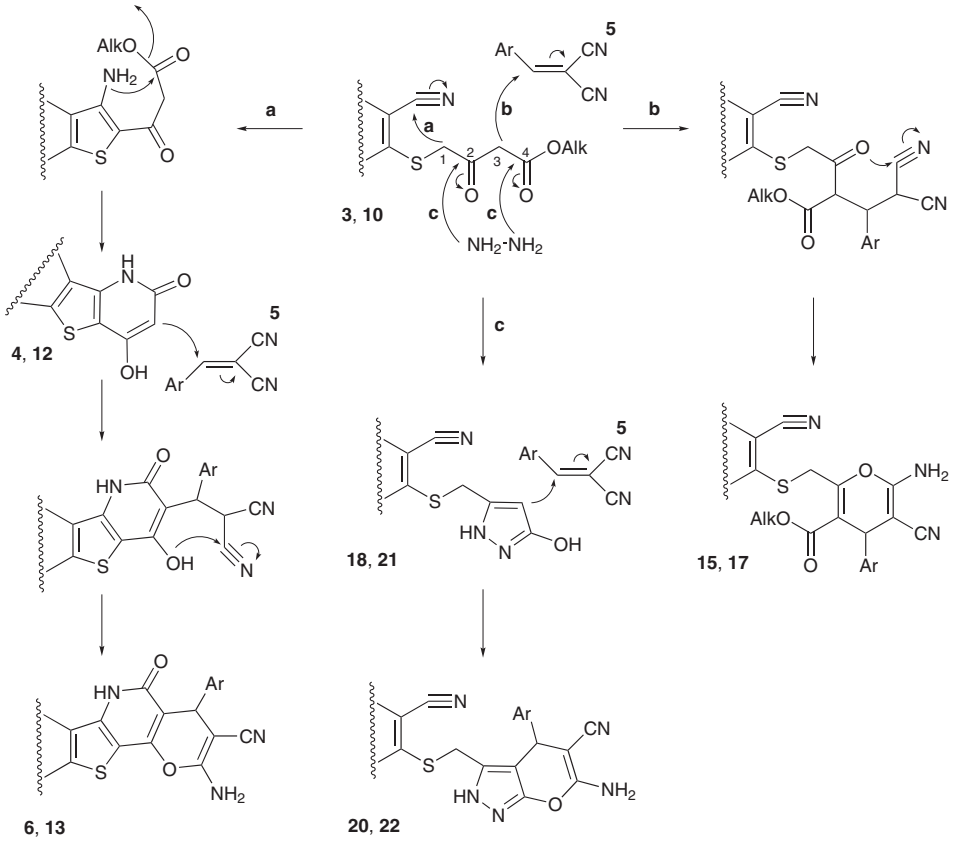
Nucleophilic properties of the molecules **3** and **10** are realized in two distinctive pathways (Scheme 7, pathways **a** and **b**). We found that either reaction pathway can occur,



Scheme 5 (**5c**, **20a**) R = F; (**5h**, **20b**) R = MeO



Scheme 6



Scheme 7

depending upon the sequence of the reagent addition and the reaction conditions. Thus, if a base and then arylidenemalononitriles **5** are added to esters **3** or **10**, the reaction leads to pyrans **6** or **13**, respectively (pathway **a**). But if esters **3** or **10** are first added to the unsaturated nitriles **5**, followed by catalytic base, the reaction takes pathway **b** and leads to pyrans **15** or **17**, respectively.

Finally, if esters **3** or **10** are first combined with hydrazine followed by subsequent nitrile **5** addition, then during the first step of the reaction, the esters realize their electrophilic properties (pathway **c**) to give pyrans **20** or **22** as final products.

Melting points were determined on a Kofler stage. Infrared spectra were obtained using a Perkin-Elmer 577 and Specord M82 instruments in KBr pellets at a concentration of 0.01 mol/L. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker WM-250 instrument (250 and 63 MHz, respectively) and Bruker AM-300 (300 MHz) instrument in DMSO-d_6 solutions. Mass spectra were obtained on a MAT INCOS-50 instrument (Finnigan) (ionizing energy 70 eV). Elemental analysis was carried out on a Perkin-Elmer CHN analyzer. The reactions' progress and composition were monitored by TLC on Silufol UV-254 plates (*n*-hexane–acetone, 5:3) and iodine vapor as a developer.

4-(3-cyanopyridin-2-ylthio)acetoacetates (**3**) and 4-hydroxy-1*H*-thieno[2,3-*b*:4,5-*b*′]dipyridin-2-ones (**4**) were synthesized using a described procedure.[1]

X-ray crystal data[18] for **15a**; Empirical formula $C_{19}H_{14}N_2O_2$; Crystal system = monoclinic; Space group $P2_1/n$; Unit cell dimensions a = 11.1247(8) Å, b = 13.7795(14) Å, c = 14.7256(13) Å, β = 103.40(2)°; V = 2195.9(3) A^3; ρ_{calcd} = 1.370 gcm^{-3}; Z = 4; Crystal size 0.4 × 0.4 × 0.4 mm; μ = 0.300 mm^{-1}; Reflections collected 8972. Independent reflections 5281; Collected at 23 °C on a Enraf Nonius CAD-4 diffractometer (MoK_α radiation, graphite monochromator, /2 scan mode to θ_{max} = 28°). Number of independent reflection with I>2σ(I) is 2902. The structure was solved by direct methods.[19] All hydrogen atoms were localized from the difference Fourier synthesis; refinement method anisotropic-isotropic (hydrogen atoms) least-squares. The final R factors were $R1$ = 0.0438, $wR2$ = 0.1186 (2902 independent reflections) and $R1$ = 0.1069, $wR2$ = 0.1431 (all reflections); Goodness-of-fit = 1.022. All calculations were performed using the SHELXL97 program.[20]

4-(3-Cyanopyridin-2-ylthio)acetoacetates (3)

The analytical data for compounds **3a**,**b**,**d**,**f–j** are presented in the references.[1,9]

Ethyl 4-[3-Cyano-6-(4-pyridyl)-pyridin-2-ylthio]acetoacetates (3c)

Yield: 59%; mp 141–142 °C.

IR (KBr): 1728, 1748 (CO), 2220 (CN) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.10 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$), 3.83 (s, 2 H, CH$_2$), 4.04 (q, J = 7.2 Hz, 2 H, CH$_3$CH_2), 4.47 (s, 2 H, SCH$_2$), 8.04 (m, 3 H, 5-H of pyridine, 2-H, 6-H of 4-C$_5$H$_4$N), 8.40 (d, J = 8.4 Hz, 1 H, 4-H of pyridine), 8.76 (d, J = 4.8 Hz, 2 H, 3-H, 5-H of 4-C$_5$H$_4$N).

Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.64; H, 4.23; N, 12.10.

Methyl 4-(3-Cyano-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-ylthio)acetoacetates (3e)
Yield: 85%; mp 109–110 °C.

IR (KBr): 1724, 1748 (CO), 2224 (CN) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.09 (m, 2 H, CH_2), 2.91 (m, 4 H, CH_2CH_2), 3.62 (s, 3 H, CH_3), 3.83 (s, 2 H, CH_2), 4.25 (s, 2 H, SCH_2), 8.02 (s, 1 H, 4-H).

Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 58.09; H, 4.74; N, 9.78.

2-Amino-4-aryl-3-cyano-5-oxo-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (6,13); General Procedure
*Method **A***: The arylidenemalononitrile **5** (0.01 mol) and Et_3N or *N*-methylmorpholine (0.1 mL) were added to a suspension of the corresponding compound **4**,**12a** (0.01 mol) in DMF. The reaction mixture was refluxed for 2–3 h (monitored by TLC), then concd HCl (1 mL) was added and the precipitate formed was filtered off and successively washed on the filter with H_2O (2 × 10 mL), EtOH (2 × 5 mL), and hexane (2 × 10 mL). All compounds **6** have mp>300 °C. The analytical data for compounds **6**,**13** are shown in Tables 1 and 2.

*Method **B***: Equimolar amounts (0.01 mol) of the corresponding aldehyde **7**, malononitrile **8**, and Et_3N were added to a suspension of the corresponding **4** (0.01 mol) in DMF and the reaction was conducted as described in method A.

Ethyl 4-(4-Aryl-3-cyano-6-methyl-1,4-dihydropyridin-2-ylthio)acetoacetates (10); General Procedure
Ethyl 4-chloroacetoacetate (**2a**) (1.4 mL, 0.01 mol) was added to a stirred solution of the corresponding salt **9** (0.01 mol) in EtOH (15–20 mL), and stirring was continued at 40–45 °C for 0.5–1 h. The mixture was quenched with H_2O (5 mL), and the resulting solution was kept for 1–3 h in the refrigerator. The precipitate formed was filtered off and washed with H_2O (2 × 5 mL), EtOH (2 × 5 mL), and hexane (2 × 10 mL). In the case of compound **10a**, the formed residue was separated, washed with H_2O (2 × 10 mL), and extracted with Et_2O (2 × 15 mL). The organic layer was then evaporated under reduced pressure to give the final product in pure state. The analytical data for compounds **10** are presented in Tables 3 and 4.

4-Hydroxy-1*H*-thieno[2,3-*b*:4,5-*b*]dipyridin-2-ones (12); General Procedure
*Method **A***: The corresponding ester **10b**,**c** (0.01 mol) was dissolved on heating in EtOH (30 mL) and a solution of KOH (1.12 g) in EtOH (20 mL) was added to the resulting solution. The reaction mixture was boiled for 5 min then, after cooling to r.t., it was acidified with concd. HCl (3 mL) to pH 2. The precipitate formed was filtered off, and successively washed on the filter with H_2O (2 × 10 mL), EtOH (2 × 5 mL), and hexane (2 × 10 mL).

*Method **B***: Ethyl 4-chloroacetoacetate (**2a**) (1.4 mL, 0.01 mol) was added to a suspension of the corresponding salt **9b**,**c** (0.01 mol) in EtOH (20 mL), and the reaction mixture was heated until the starting materials dissolved. A soln of aq KOH (10%, 1.12 mL) was added, and the mixture was stirred for 0.5 h under reflux. After cooling to r.t., the reaction mixture was acidified with concd. HCl (3 mL). The precipitate formed was filtered off, and successively washed with H_2O (2 × 5 mL), EtOH (2 × 5 mL), and hexane (2 × 10 mL).

4-Hydroxy-7-methyl-2-oxo-9-phenyl-1,2-dihydrothieno[2,3-*b*:4,5-*b*′]dipyridine-8-carboxylic Acid Phenylamide (12a)
Yield: 3.5 g (82%) by method A and 2.7 g (64%) by method B; mp >300 °C.

IR (KBr): 1600–1650 (CO), 3370, 3050 (CONH, OH) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.70 (s, 3 H, CH_3), 5.86 (s, 1 H, 3-H), 6.95–7.69 (10 H, m, 2 × C_6H_5), 10.45 (s, 1 H, N*H*C_6H_5), 12.05 (s, 1 H, N^{1}H).

Anal. Calcd for $C_{24}H_{17}N_3O_3S$: C, 67.43; H, 4.01; N, 9.83. Found: C, 67.22; H, 4.18; N, 9.74.

4-Hydroxy-7-methyl-2-oxo-9-(pyridin-3-yl)-1,2-dihydrothieno[2,3-*b*;4,5-*b*′]dipyridine-8-carboxylic Acid Phenylamide (12b)
Yield: 2.44 g (57%) by method A and 2.1 g (48%) by method B; mp >300 °C.

IR (KBr): 1600–1651 (CO), 3400, 3340, 3040 (CONH, OH) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.71 (s, 3 H, CH_3), 6.19 (s, 1 H, 3-H), 7.00–8.70 (m, 9 H, C_6H_5, 3-C_5H_4N), 10.41 (s, 1 H, N*H*C_6H_5), 11.69 (s, 1 H, N^{1}H).

Anal. Calcd for $C_{23}H_{16}N_4O_3S$: C, 64.48; H, 3.76; N, 13.08. Found: C, 64.50; H, 3.89; N, 12.92.

3-Alkoxycarbonyl-6-amino-4-aryl-5-cyano-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans (15); General Procedure
*Method **A***: The corresponding arylidenemalononitrile **5** (0.01 mol) and Et_3N (0.1 mL) were added to a stirred suspension of the corresponding ester **3** (0.01 mol) in EtOH or MeOH (15–20 mL), and the mixture was boiled for 3–5 min. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the mixture was left overnight. The precipitate formed was filtered off and washed on the filter with cold EtOH (2 × 5 mL) and hexane (2 × 7 mL).

*Method **B***: Aldehyde **7** (0.01 mol), malononitrile **8** (0.66 g, 0.01 mol), and Et_3N (0.1 mL) were added to a stirred suspension of the corresponding ester **3** (0.01 mol) in EtOH or MeOH (15–20 mL), and the reaction mixture was boiled for 5–10 min. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the resulting mixture was left overnight. The precipitate formed was filtered off and washed on the filter with cold EtOH (2 × 5 mL) and hexane (2 × 7 mL).

*Method **C***: Pyran **16** (0.01 mol) was added to a stirred suspension of the corresponding pyridinethione **1** (0.01 mol) in EtOH or MeOH (15–20 mL), and the mixture was stirred at 40–45 °C for 0.5–1 h. After cooling to r.t., the solution was quenched with H_2O (5 mL), and left overnight. The precipitate formed was filtered off and washed on the filter with cold EtOH (2 × 5 mL) and hexane (2 × 7 mL).

*Method **D***: The ester of 4-chloroacetoacetic acid **2** (0.042 mol) was added to a stirred suspension of the corresponding pyridinethione **1** (0.004 mol) in EtOH or MeOH (15–20 mL), and stirring was continued at 40–45 °C for 10–15 min. To the resulting solution was added aldehyde **7** (0.0043 mol), malononitrile **8** (0.28 g, 0.0043 mol), and Et_3N (0.1 mL), and the mixture was boiled for 3–5 min. After cooling to r.t., the solution was quenched with H_2O (5 mL) and left overnight. The precipitate of compound **15** was filtered off and washed on the filter with cold EtOH (2 × 5 mL) and hexane (2 × 7 mL). Compounds **15** were recrystallized from EtOH or MeOH. The analytical data for compounds **15** are shown in Tables 5 and 6.

5-Alkoxycarbonyl-2-amino-4-aryl-6-chloromethylene-3-cyano-1*H*-pyrans (16); General Procedure
Et_3N (0.1 mL) was added to a suspension of ester **2a**,**b** (0.01 mol), aldehyde **7** (0.01 mol), and malononitrile **8** (0.66 g, 0.01 mol) in EtOH or MeOH (15–20 mL). The reaction mixture was boiled for 5–7 min and left at r.t. for 10–12 h. The precipitate formed was filtered off and washed on the filter with EtOH (2 × 3 mL) and hexane (2 × 5 mL). Compounds **16** were recrystallized from EtOH or MeOH. The analytical data for compounds **16** are presented in Tables 7 and 8.

2-(6-Amino-4-aryl-5-cyano-3-ethoxycarbonyl-4*H*-pyran-2-ylmethylthio)-4-aryl-3-cyano-6-methyl-1,4-dihydropyridine (17)

*Method **A***: 4-Methoxybenzylidenemalononitrile **5h** (0.01 mol) and Et_3N (0.1 mL) were added to a stirred suspension of the ester **10a** (0.01 mol) in EtOH (15 mL), and the mixture was boiled for 5 min. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the mixture was left overnight. The formed precipitate was filtered off and washed on the filter with cold EtOH (2 × 3 mL) and hexane (2 × 5 mL).

*Method **B***: Ethyl 4-chloroacetoacetate (**2a**) (1.4 g, 0.01 mol) was added to a stirred suspension of the corresponding salt **9** (0.01 mol) in EtOH (15–20 mL), and stirring was continued at 40–45 °C for 10–15 min. The corresponding arylidenemalononitrile **5c**,**h** (0.01 mol) and Et_3N (0.1 mL) were added to the solution, and the reaction mixture was boiled for 3–5 min. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the mixture was left overnight. The precipitate formed was filtered off and washed on the filter with cold EtOH (2 × 3 mL) and hexane (2 × 5 mL).

*Method **C***: Ethyl 4-chloroacetoacetate (**2a**) (1.4 mL, 0.01 mol) was added to a stirred suspension of the salt **9e** (3.93 g, 0.01 mol) in EtOH (15–20 mL), and stirring was continued at 40–45 °C for 10–15 min. Aldehyde **7k** (1.24 mL, 0.01 mol), malononitrile (**8**) (0.66 g, 0.01 mol), and Et_3N (0.1 mL) were added to the solution, and the reaction mixture was boiled for 3–5 min. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the mixture was left overnight. The precipitate of compound **17c** formed was filtered off and washed on the filter with cold EtOH (2 × 3 mL) and hexane (2 × 5 mL).

*Method **D***: The corresponding pyran **16g**,**h** (0.01 mol) was added to a stirred suspension of the corresponding salt **9a**,**e**,**f** (0.01 mol) in EtOH (15–20 mL). The mixture was stirred at 40–45 °C for 0.5–1 h. After cooling to r.t., the solution was quenched with H_2O (5 mL), and the mixture was left overnight. The precipitate formed was filtered off and washed on the filter with cold EtOH (2 × 3 mL) and hexane (2 × 5 mL). Compounds **17** were recrystallized from EtOH. The analytical data for compounds **17** are shown in Tables 9 and 10.

3-Cyano-2-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (18)

Hydrazine hydrate (0.5 mL) was added to a solution of ester **3j** (1.52 g, 0.005 mol) in EtOH (15 mL). The reaction mixture was boiled for 1–2 min and left overnight at r.t.. The precipitate formed was filtered off and washed with H_2O (2 × 5 mL), EtOH (2 × 3 mL), and hexane (2 × 5 mL).

Yield: 88% (1.19 g); slightly yellow powder; mp 257–258 °C.

IR (KBr): 2216 (CN), 3344 (NH) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.10 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 4.38 (s, 2 H, CH_2S), 5.39 (s, 1 H, 4-H of pyrazole), 8.02 (s, 1 H, 4-H of pyridine), 11.36 (s, 1 H, NH).

Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.42; H, 4.53; N, 20.66.

6-Amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles (20); General Procedure

A mixture of pyrazolylmethylthiopyridine **18** (0.55 g, 0.002 mol), the corresponding arylidenemalononitrile **5c**,**h** (0.002 mol), and Et_3N (0.1 mL) in EtOH (20 mL) was boiled for 10 min, and then kept overnight at r.t.. The precipitate formed was filtered off, washed on the filter with EtOH (2 × 3 mL) and hexane (2 × 5 mL), and recrystallized from 1,4-dioxane or EtOH.

6-Amino-5-cyano-3-(3-cyano-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-ylthio)methyl)-4-(4-fluorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole (20a)

Yield: 0.56 g (63%); mp 231–232 °C.

IR (KBr): 2184, 2224 (CN, pyrane, pyridine), 1644 (δ), 3288, 3406 (NH, NH_2) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.11 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 4.10 (d, *J* = 14.7 Hz, 1 H, SCH_2), 4.18 (d, *J* = 14.7 Hz, 1 H, SCH_2), 4.76 (s, 1 H, 4-H of pyrane), 6.90 (s, 2 H, NH_2), 7.03 (m, 2 H, 3-H, 5-H of 4-F-C_6H_4), 7.15 (m, 2 H, 2-H, 4-H of 4-F-C_6H_4), 7.98 (s, 1 H, 4-H of pyridine), 12.49 (s, 1 H, NH of pyrazole).

Anal. Calcd for $C_{23}H_{17}FN_6OS$: C, 62.15; H, 3.86; N, 18.91. Found: C, 62.27; H, 3.71; N, 18.74.

6-Amino-5-cyano-3-(3-cyano-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-ylthio)methyl)-4-(4-methoxyphenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole (20b)

Yield: 0.62 g (68%); mp 245–247 °C.

IR (KBr): 2188, 2232 (CN, pyrane, pyridine), 1632 (δ), 3288, 3320, 3432 (NH, NH_2) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.12 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 3.03 (m, 2 H, CH_2), 3.84 (s, 3 H, CH_3O), 4.08 (d, *J* = 14.0 Hz, 1 H, SCH_2), 4.16 (d, *J* = 14.0 Hz, 1 H, SCH_2), 4.67 (s, 1 H, 4-H of pyrane), 6.78 (d, *J* = 8.5 Hz, 2 H,3-H, 5-H of 4-CH_3O-C_6H_4), 6.83 (s, 2 H, NH_2), 7.04 (d, *J* = 8.5 Hz, 2 H, 2-H, 6-H of 4-CH_3O-C_6H_4), 7.99 (s, 1 H, 4-H of pyridine), 12.44 (s, 1 H, NH of pyrazole).

Anal. Calcd for $C_{24}H_{20}N_6O_2S$: C, 63.14; H, 4.42; N, 18.41. Found: C, 63.29; H, 4.53; N, 18.31.

5-Cyano-6-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)-2-methyl-3-(*N*-phenylcarbamoyl)-4-(pyrid-3-yl)-1,4-dihydropyridine (21)

Hydrazine hydrate (0.5 mL) was added to a solution of ester **10c** (2.37 g, 0.005 mol) in EtOH (30 mL). The reaction mixture was boiled for 1–2 min and left overnight. The precipitate formed was filtered off and washed on the filter with H_2O (2 × 5 mL), EtOH (2 × 3 mL), and hexane (2 × 5 mL).

Yield: 1.53 g (69%); colorless powder; mp 185–187 °C.

IR (KBr): 2210 (CN), 1658 (δ, CO), 3300, 3460 (NH) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.11 (s, 3 H, CH_3), 4.14 (s, 2 H, SCH_2), 4.82 (s, 1 H, 4-H of pyridine), 5.39 (s, 1 H, 4-H of pyrazole), 7.00 (t, *J* = 7.1 Hz, 1 H, C_6H_5), 7.23 (t *J* = 7.1 Hz, 2 H, C_6H_5), 7.36 (m, 1 H, 5-H of 3-C_5H_4N), 7.50 (d, *J* = 7.1 Hz, 3 H, C_6H_5, 6-H of 3-C_5H_4N), 8.37 (s, 1 H, 2-H of 3-C_5H_4N,), 8.42 (d, *J* = 3.2 Hz, 1 H, 4-H of 3-C_5H_4N), 9.32 (br s, 1 H, NH), 9.64 (s, 1 H, NH of pyrazole), 11.56 (br s, 1 H, NH of pyridine).

Anal. Calcd for $C_{23}H_{20}N_6O_2S$: C, 62.15; H, 4.54; N, 18.91. Found: C, 62.27; H, 4.31; N, 19.01.

6-{6-Amino-5-cyano-4-(4-fluorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazol-3-ylthiomethyl}-5-cyano-2-methyl-4-(pyrid-3-yl)-1,4-dihydropyridine (22)

A mixture of the corresponding pyrazolylmethylthiopyridine **21** (0.89 g, 0.002 mol), 4-fluorobenzylidenemalononitrile (**5c**) (0.34 g, 0.002 mol), and *N*-methylmorpholine (0.1 mL) was refluxed in EtOH (20 mL) for 10 min. After 24 h, the precipitate formed was filtered off, washed with EtOH (2 × 3 mL) and hexane (2 × 3 mL), and recrystallized from 1,4-dioxane.

Yield 0.60 g (49%); mp 198–200 °C.

IR (KBr): 1638 (δ, NH_2), 1710 (CO), 2192, 2200 (CN), 3440 (NH) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.08 (s, 3 H, CH_3), 4.15 (d, J = 14.7 Hz, 1 H, SCH_2), 4.35 (d, J = 14.7 Hz, 1 H, SCH_2), 4.80 (s, 1 H, 4-H of pyridine), 4.89 (m, 1 H, 4-H of pyran), 6.73–7.67 and 8.40 (m, 15 H, C_6H_5, 4-F-C_6H_4, 3-C_5H_4N, NH_2), 9.01 (s, 1 H, NH), 9.67 (s, 1 H, NH of pyrazole), 12.48 (s, 1 H, NH of pyridine).

Anal. Calcd for $C_{33}H_{25}FN_8O_2S$: C, 64.27; H, 4.09; N, 18.17. Found: C, 64.03; H, 4.17; N, 18.29.

Table 1 2-Amino-4-aryl-3-cyano-5-oxo-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (**6**, **13**)

Compound	Yield (%) (method)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})	
			C	H	N	CN	CONH, NH_2
6a	77 (A), 71 (B)	$C_{23}H_{18}N_4O_2S$	66.87 66.65	4.59 4.38	13.80 13.52	2208	1632 (δ), 1672, 3184, 3284, 3420
6b	84 (A), 80(B)	$C_{21}H_{15}N_5O_2S$	62.74 62.83	3.52 3.77	17.33 17.45	2184	1664 (δ), 3320, 3356, 3408
6c	92 (A), 73 (B)	$C_{27}H_{17}FN_4O_3S$	65.50 65.31	3.52 3.45	11.40 11.28	2200	1640 (δ), 1676, 3192, 3324, 3412
6d	84 (A), 78 (B)	$C_{28}H_{26}N_4O_3S$	67.21 67.45	5.18 5.26	11.03 11.24	2188	1640 (δ), 1676, 3164, 3316, 3440
6e	72 (A)	$C_{24}H_{18}FN_5O_2S$	62.51 62.73	3.71 3.95	15.02 15.24	2200	1636 (δ), 1668, 3168, 3300, 3468
13[a]	39 (A)	$C_{34}H_{23}FN_5O_3S$	68.10 67.99	4.03 3.86	11.38 11.66	2210	1640 (δ), 1670, 3130, 3300, 3370

[a] Mp 230–231 °C.

Table 2 2-Amino-4-aryl-3-cyano-5-oxo-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (**6**, **13**)

Compound	^{1}H NMR δ [DMSO-d_6, J (Hz)]						
	R^1	R^2	R^3	Ar	4-H (1 H, s)	NH_2 (2 H, s)	NH (1 H, s)
6a[a]	2.58 (3 H, s)	7.20 (1 H, s)	2.89 (3 H, s)	2.25 (3 H, s, CH_3), 7.06–7.17 (4 H, m)	4.58	7.09	11.08
6b[b]	2.58 (3 H, s)	7.20 (1 H, s)	2.88 (3 H, s)	7.32 (1 H, t, J = 3.9), 7.59 (1 H, d, J = 4.7), 8.43 (1 H, d, J = 7.8), 8.51 (1 H, s)	4.71	7.25	11.17
6c	8.74 (1 H, d, J = 8.1)	8.11 (1 H, d, J = 8.1)	3.86 (3 H, s, OCH_3), 7.24[c] (2 H, d, J = 8.1), 8.18 (2 H, d, J = 8.1)	7.11[c] (2 H, m), 7.32[c] (2 H, m)	4.55	7.11[c]	12.84
6d[d]	8.44 (1 H, s)	1.67 (4 H, m), 1.86 (2 H, m), 2.89 (2 H, m), 3.12 (2 H, m)		1.23 (3 H, d, CH_3, J = 2.7), 1.24 (3 H, d, CH_3, J = 2.7), 4.53 (1 H, m, CHO), 6.82 (2 H, d, J = 8.1), 7.97 (2 H, d, J = 9.5)	4.43	7.23	12.81
6e	8.48 (1 H, s)	2.71 (3 H, s, N-CH_3), 2.52[e] (2 H, m), 3.25 (2 H, m), 4.15 (2 H, s)		7.11 (m, 2 H), 7.30 (m, 2 H)	4.54	7.24	12.77
13	7.04–7.57[c] (5 H, m)	7.04–7.57[c] (5 H, m, C_6H_5), 10.40 (1 H, s, NH)	2.72 (3 H, s)	7.04–7.57[c] (4 H, m)	4.44	7.53[c]	7.95

[a] ^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.95, 20.54, 23.77, 36.38, 58.41, 100.40, 119.65, 121.91, 122.13, 127.15, 127.26, 127.37, 128.69, 128.80, 128.91, 135.71, 141.54, 144.98, 150.96, 158.00, 158.60, 159.67, 160.28.

[b] ^{13}C NMR(63 MHz, DMSO-d_6): δ = 18.67, 23.52, 34.42, 57.41, 102.65, 109.41, 118.98, 121.70, 121.84, 122.36, 123.31, 134.74, 139.48, 144.78, 147.60, 148.59, 150.94, 157.92, 158.61, 159.67, 160.23.

[c] The signal is overlapped with the signal of another fragment.

[d] MS (EI, 70 eV): m/z (%) = 432 (14) [M – $NCCH_2CN$]$^+$, 389 (52), 373 (5), 363 (8), 286 (20), 170 (39).

[e] The signal is overlapped with the signal for the protons of DMSO.

Table 3 Ethyl 4-(4-Aryl-3-cyano-6-methyl-1,4-dihydropyridin-2-ylthio)acetoacetates (**10**)

Compound	Mp (°C)	Yield (%)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})	
				C	H	N	CN	CO, NH
10a	–[a]	60	$C_{24}H_{28}N_2O_8S$	57.05 57.13	5.89 5.59	5.34 5.55		
10b	146–147	73	$C_{26}H_{25}N_3O_4S$	65.42 65.67	5.38 5.30	8.70 8.84	2205	1740 (δ), 1720 (δ), 1645 (δ,CONH), 3290, 3320
10c	149–150	67	$C_{25}H_{24}N_4O_4S$	62.91 63.01	5.22 5.08	11.51 11.76	2218	1730 (δ), 1710 (δ), 1628 (δ,CONH), 3360

[a] Amorphous substance.

Table 4 Ethyl 4-(4-Aryl-3-cyano-6-methyl-1,4-dihydropyridin-2-ylthio)acetoacetates (**10**)

Compound	^{1}H NMR δ [DMSO-d_6, J (Hz)]							
	R^1	CH_2CO (2 H, s)	6-CH_3 (3 H, s)	OC_2H_5	Ar	4-H (1 H, s)	SCH_2 (2 H, s)	NH (1 H, s)
10a	3.59 (3 H, s)	3.65	3.32	1.25 (3 H, t, J = 7.2), 4.11 (2 H, q, J = 7.2)[a]	3.59 (3 H, s, CH_3O), 3.70 (3 H, s, CH_3O), 3.78 (3 H, s, CH_3O), 6.39 (2 H, s)	4.48	4.11[a]	9.25
10b	8.97 (1 H, s, NH), 6.95–7.55,[b] (5 H, m, C_6H_5)	3.75	2.08	1.22 (3 H, t, J = 7.1), 4.10 (2 H, q, J = 7.1)	6.95–7.55 (m, 5 H, C_6H_5)[b]	4.79	4.20 (d, J = 3.9)	9.56
10c	9.09 (1 H, s, NH), 7.00–7.49,[b] (5 H, m, C_6H_5)	3.74	2.07	1.20 (3 H, t, J = 7.1), 4.12 (2 H, m)	7.36 (1 H, dd, J = 5.2, J = 7.8),[b] 7.60 (1 H, d, J = 7.8), 8.42 (1 H, s), 8.45 (1 H, m)	4.82	4.20 (d, J = 3.9)	9.65

[a] The signals of the protons of the methylene groups are overlapped.
[b] The signals of the protons of the aryl substituents are overlapped.

Table 5 3-Alkoxycarbonyl-6-amino-4-aryl-5-cyano-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans (**15**)

Compound	Mp (°C)	Yield (%) (method)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})		
				C	H	N	CN	C=O	NH_2
15a	209–211	77 (A)	$C_{22}H_{17}ClN_4O_3S$	58.61 58.34	3.84 3.78	12.01 12.37	2196, 2220	1712	1672 (δ), 3196, 3328, 3416
15b	116–118	67 (A), 58 (C)	$C_{27}H_{21}N_5O_3S$	65.32 65.44	4.23 4.27	14.03 14.13	2200, 2228	1716	1680 (δ), 3168, 3316, 3344
15c	157–158	60 (A), 54 (C)	$C_{26}H_{23}N_6O_3S$	62.64 62.89	3.89 4.06	16.73 16.92	2200, 2224	1712	1676 (δ), 3124, 3296, 3352
15d	160–162	59 (A)	$C_{31}H_{22}ClN_5O_3S_2$	61.01 60.83	3.45 3.62	11.23 11.44	2196, 2220	1724	1684 (δ), 3180, 3328, 3452
15e	164–165	87 (A)	$C_{26}H_{24}N_4O_3S$	66.28 66.08	5.20 5.12	12.02 11.86	2188, 2224	1716	1684 (δ), 3160, 3312, 3384
15f	174–175	67 (A), 48 (D)	$C_{27}H_{27}N_5O_3S$	64.33 64.65	5.26 5.43	13.58 13.96	2196, 2240	1728	1676 (δ), 3172, 3320, 3380
15g	203–204	77 (B)	$C_{23}H_{19}FN_4O_3S$	61.14 61.32	4.11 4.25	12.19 12.44	2204, 2224	1724	1680 (δ), 3192, 3316, 3388
15h	187–188	42 (B)	$C_{27}H_{25}N_5O_5S$	60.79 61.00	4.61 4.74	12.91 13.17	2196, 2228	1712	1684 (δ), 3180, 3324, 3472
15i	111–112	65 (B), 74 (C)	$C_{25}H_{24}N_4O_3S_2$	60.55 60.95	4.72 4.91	11.13 11.37	2188, 2220	1704	1668 (δ), 3188, 3316, 3384

Table 5 3-Alkoxycarbonyl-6-amino-4-aryl-5-cyano-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans (**15**) (continued)

Compound	Mp (°C)	Yield (%) (method)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})		
15j	173–175	89 (C), 57 (D)	$C_{23}H_{22}N_4O_3S_2$	59.07 59.21	4.58 4.75	11.80 12.01	2204, 2216	1720	1688 (δ), 3184, 3316, 3460
15k	146–147	79 (C), 57 (D)	$C_{26}H_{25}N_5O_3S$	63.80 64.05	4.89 5.17	14.04 14.36	2196, 2228	1716	1676 (δ), 3176, 3300, 3404
15l	122–123	51 (C)	$C_{25}H_{22}FN_5O_3S$	60.82 61.09	4.26 4.51	14.04 14.25	2200, 2228	1716	1684 (δ), 3348, 3472
15m	162–163	54 (C)	$C_{26}H_{24}ClN_5O_3S$	59.62 59.82	4.52 4.63	13.04 13.42	2196, 2228	1716	1680 (δ), 3360, 3428
15n	212–214	60 (C)	$C_{35}H_{36}N_4O_4S_2$	65.95 65.60	5.43 5.66	8.34 8.74	2200, 2223	1716	1680 (δ), 3196, 3324, 3392

Table 6 3-Alkoxycarbonyl-6-amino-4-aryl-5-cyano-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans (**15**)

Compound	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]							
	R^1	R^2	R^3	R^4	Ar	NH_2 (2H, s)	4-H (1H, s)	SCH_2 (2H)
15a	8.11 (1 H, d, *J* = 7.5)	7.21 (1 H, d, *J* = 7.5)[a]	2.42 (3 H, s)	3.54 (3 H, s)	7.08 (1 H, m), 7.21 (2 H, m),[a] 7.38 (1 H, d, *J* = 6.2)	6.92	4.88	4.72 (s)
15b	8.20 (1 H, d, *J* = 8.1)	7.85 (1 H, d, *J* = 8.1)	7.49 (3 H, m), 8.14 (2 H, m)	1.10 (3 H, t, *J* = 7.5), 4.00 (2 H, q, *J* = 7.5)	7.25 (1 H, m), 7.52 (1 H, m), 8.40 (2 H, m)	6.81	4.42	4.83, 4.96 (both d of 1H, *J* = 13.7)
15c	8.31 (1 H, d, *J* = 8.3)	8.00 (1 H, d, *J* = 8.3)	8.06 (2 H, d, *J* = 5.3), 8.70 (2 H, d, *J* = 5.3)	1.08 (3 H, t, *J* = 7.4), 4.02 (2 H, q, *J* = 7.4)	7.25 (1 H, dd, *J* = 3.9, *J* = 7.9), 7.51 (1 H, d, *J* = 7.9), 8.40 (2 H, m)	6.78	4.41	4.84, 4.96 (both d of 1H, *J* = 13.8)
15d	7.67 (2 H, q, *J* = 8.3), 7.78 (2 H, q, *J* = 8.3)	7.91 (1 H, s)	7.26 (1 H, t, *J* = 4.4), 7.82 (1 H, d, *J* = 4.4), 8.11 (1H, d, *J* = 4.4)	1.03 (3 H, t, *J* = 7.2), 4.02 (2 H, q, *J* = 7.2)	7.35 (1 H, dd, *J* = 6.1, *J* = 8.3), 7.57 (1 H, d, *J* = 8.3), 8.42 (1 H, s), 8.45 (1 H, d, *J* = 6.1)	6.94	4.47	4.77, 4.89 (both d of 1H, *J* = 14.3)
15e	8.02 (1 H, s)	2.03 (2 H, m), 2.71–2.92 (4 H, m)		3.60 (3 H, s)	1.16 (3 H, t, *J* = 7.2), 2.56 (2 H, q, *J* = 7.2), 6.97 (1 H, d, *J* = 7.9), 7.08 (1 H, d, *J* = 7.9)	6.84	4.25	4.65 (s)
15f	7.96 (1 H, s)	1.57 (4 H, m), 1.80 (2 H, m), 2.77 (2 H, m), 2.93 (2 H, m)		0.92 (3 H, d, *J* = 5.9), 1.14 (3 H, d, *J* = 5.9), 4.84 (1 H, m)	7.12 (2 H, d, *J* = 5.9), 8.47 (2 H, d, *J* = 5.9)	6.94	4.36	4.71 (s)
15g	2.34 (3 H, s)	7.11 (1 H, s)	2.42 (3 H, s)	3.57 (3 H, s)	7.06–7.30 (4 H, m)	6.97	4.62	4.64, 4.75 (both d of 1H, *J* = 14.5)
15h	7.83 (1 H, s)	1.76 (4 H, m), 2.70 (4 H, m)		0.97 (3 H, d, *J* = 6.3), 1.19 (3 H, d, *J* = 6.3), 4.88 (1 H, m)	7.37 (2 H, d, *J* = 8.7), 8.12 (2 H, d, *J* = 8.7)	6.87	4.46	4.62, 4.73 (both d of 1H, *J* = 13.8)
15i	7.95 (1 H, s)	1.55 (4 H, m), 1.79 (2 H, m), 2.77 (m, 2 H), 2.94 (2 H, m)		1.12 (3 H, t, *J* = 7.2), 4.06 (2 H, q, *J* = 7.2)	6.8 (1 H, d, *J* = 4.6), 7.1 (1 H, d, *J* = 1.3), 7.4 (1 H, dd, *J* = 4.6, *J* = 1.3)	6.88	4.44	4.60, 4.73 (both d on 1H, *J* = 14.4)
15j	7.95 (1 H, s)	2.27 (3 H, s)	1.21 (3 H, t, *J* = 8.4), 2.78 (2 H, q, *J* = 8.4)	1.15 (3 H, t, *J* = 7.2), 4.12 (2 H, q, *J* = 7.2)	6.84 (1 H, d, *J* = 2.7), 6.94 (1 H, dd, *J* = 2.7, *J* = 4.9), 7.46 (1 H, d, *J* = 4.9)	6.90	4.69	4.62, 4.75 (both d of 1H, *J* = 13.7)

Table 6 3-Alkoxycarbonyl-6-amino-4-aryl-5-cyano-2-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans (**15**) (continued)

Compound	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]						
	R^1	R^2	R^3	R^4	Ar	NH_2 (2H, s)	4-H (1H, s)	SCH_2 (2H)
15k	7.84 (1 H, s)	1.36 (4 H, m), 1.68 (4 H, m), 2.76 (2 H, m), 2.86 (2 H, m)		3.60 (3 H, s)	7.00 (2 H, m), 7.14 (2 H, m)	6.63	4.34	4.62, 4.75 (both d of 1H, *J* = 14.3)
15l	7.95 (1 H, s)	2.37 (3 H, s), 2.65–2.91 (4 H, m), 3.50 (2 H, s)		3.59 (3 H, s)	7.12 (4 H, m)	6.85	4.33	4.65 (s)
15m	7.95 (1 H, s)	2.36 (3 H, s), 2.61–2.90 (4 H, m), 3.48 (2 H, s)		1.06 (3 H, t, *J* = 7.2), 4.04 (2 H, q, *J* = 7.2)	7.06 (2 H, d, *J* = 7.7), 7.31 (2 H, d, *J* = 7.7)	6.89	4.33	4.60, 4.70 (both d of 1H, *J* = 13.8)
15n	3.84 (3 H, s), 7.09 (2 H, d, *J* = 9.2), 7.31 (2 H, d, *J* = 9.2)	0.8 (9 H, s), 1.34, 1.95, 2.22, 2.40, 2.89 (7 H, m)		1.17 (3 H, t, *J* = 6.8), 4.16 (2 H, q, *J* = 6.8)	6.83 (1 H, d, *J* = 3.9), 6.92 (1 H, dd, *J* = 3.9, *J* = 4.5), 7.35 (1 H, d, *J* = 4.5)	7.00	4.69	4.62, 4.72 (both d of 1H, *J* = 15.1)

[a] The signal is overlapped with the signal of another fragment.

Table 7 5-Alkoxycarbonyl-2-amino-4-aryl-6-chloromethylene-3-cyano-1*H*-pyrans (**16**)

Compound	Mp (°C)	Yield (%)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})		
				C	H	N	CN	CO	NH_2
16a	184–186	94	$C_{15}H_{14}ClN_3O_3$	56.17 56.35	4.22 4.41	12.84 13.14	2200	1724	1684 (δ), 3352, 3304
16b	178–179	68	$C_{14}H_{13}ClN_2O_3S$	51.40 51.77	3.83 4.03	8.39 8.63	2196	1696	1676 (δ), 3404, 3332
16c	175–177	84	$C_{14}H_{13}ClN_2O_3S$	52.01 51.77	4.40 4.03	8.85 8.63	2192	1696	1676 (δ), 3408, 3328
16d	118–119	53	$C_{14}H_{12}ClN_3O_3$	55.37 55.00	3.81 3.96	13.42 13.74	2196	1728	1672 (δ), 3368, 3320
16e	177–178	43	$C_{15}H_{12}ClFN_2O_3$	55.64 55.83	3.54 3.75	8.39 8.68	2196	1708	1680 (δ), 3420, 3336
16f	152–154	90	$C_{16}H_{14}Cl_2N_2O_3$	54.35 54.41	3.83 4.00	7.70 7.93	2196	1700	1680 (δ), 3408, 3332
16g	150–151	93	$C_{17}H_{17}ClN_2O_4$	58.26 58.54	4.71 4.91	7.97 8.03	2196	1704	1680 (δ), 3416, 3328
16h	153–155	98	$C_{16}H_{14}ClFN_2O_3$	56.90 57.07	4.04 4.19	8.09 8.32	2188	1696	1676 (δ), 3412, 3332

Table 8 5-Alkoxycarbonyl-2-amino-4-aryl-6-chloromethylene-3-cyano-1*H*-pyrans (**16**)

Compound	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]				
	CH_2Cl (2 H, s)	NH_2 (2 H, s)	R^4	4-H (1 H, s)	Ar
16a	4.67, 4.78 (both d of 1 H, *J* = 11.4)	7.00	1.08 (3 H, t, *J* = 7.3), 4.06 (2 H, q, *J* = 7.3)	4.47	7.48 (1 H, m), 7.57 (1 H, d, *J* = 7.8), 8.41 (1 H, s), 8.46 (1 H, d, *J* = 4.3)
16b	4.63, 4.73 (both d of 1 H, *J* = 13.6)	6.87[a]	1.14 (3 H, t, *J* = 7.2), 4.11 (2 H, q, *J* = 7.2)	4.52	6.90 (1 H, m),[a] 7.18 (1 H, d, *J* = 3.6), 7.46 (1 H, m)
16c	4.68	7.01	1.18 (3 H, t, *J* = 7.1), 4.14 (2 H, q, *J* = 7.1)	4.73	6.87 (1 H, d, *J* = 2.9), 6.96 (1 H, dd, *J* = 2.9, *J* = 7.1), 7.49 (1 H, d, *J* = 7.1)

Table 8 5-Alkoxycarbonyl-2-amino-4-aryl-6-chloromethylene-3-cyano-1*H*-pyrans (**16**) (continued)

Compound	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]				
	CH_2Cl (2 H, s)	NH_2 (2 H, s)	R^4	4-H (1 H, s)	Ar
16d	4.69, 4.78 (both d of 1 H, *J* = 11.8)	7.09	3.60 (3 H, s)	4.47	7.27 (2 H, d, *J* = 5.3), 8.58 (2 H, d, *J* = 5.3)
16e	4.67, 4.72 (both d of 1 H, *J* = 11.8)	6.96	3.60 (3 H, s)	4.10	7.18 (4 H, m)
16f	4.67, 4.76 (both d of 1 H, *J* = 12.9)	7.04	1.07 (3 H, t, *J* = 7.1), 4.04 (2 H, q, *J* = 7.1)	4.40	7.19 (2 H, d, *J* = 7.1), 7.40 (2 H, d, *J* = 7.1)
16g	4.70	6.84	1.10 (3 H, t, *J* = 7.2), 4.05 (2 H, q, *J* = 7.2)	4.33	3.74 (3 H, s, OCH_3), 6.89 (2 H, d, J = 7.8), 7.08 (2 H, d, J = 7.8)
16h	4.67, 4.75 (both d of 1 H, *J* = 12.9)	7.02	1.07 (3 H, t, *J* = 7.1), 4.04 (2 H, q, *J* = 7.1)	4.40	7.15–7.21 (4 H, m)

[a] The signal is overlapped with the signal of another fragment.

Table 9 2-(6-Amino-4-aryl-5-cyano-3-ethoxycarbonyl-4*H*-pyran-2-ylmethylthio)-4-aryl-3-cyano-6-methyl-1,4-dihydropyridine (**17**)

Compound	Mp (°C)	Yield (%) (method)	Molecular formula	Found/Calculated (%)			IR (cm^{-1})		
				C	H	N	CN (pyridine, pyrane)	CO, NH	NH_2 (δ)
17a	210–211	69 (A) 50 (D)	$C_{35}H_{36}N_4O_9S$	60.92 61.04	5.34 5.27	8.24 8.13	2195, 2215	1675, 1690, 3320	1600
17b	190–191	72 (B)	$C_{34}H_{34}N_4O_8S$	61.77 61.99	5.13 5.20	8.42 8.51	2183, 2203	1640, 1720, 3315	1625
17c	227–228	71 (B) 57 (C) 45 (D)	$C_{31}H_{30}N_4O_6S_2$	60.29 60.18	4.94 4.89	8.85 9.06	2178, 2215	1675, 1705, 3380	1608
17d	118–120	42 (D)	$C_{35}H_{34}N_4O_8S$	62.50 62.68	5.00 5.11	8.47 8.35	2176, 2216	3352-2952, 1696, 1656	1616
17e	151–152	69 (B) 46 (D)	$C_{30}H_{27}FN_4O_5S_2$	59.31 59.39	4.53 4.49	3.41 3.13	2174, 2202	1665, 1705, 3420	1605

Table 10 2-(6-Amino-4-aryl-5-cyano-3-ethoxycarbonyl-4*H*-pyran-2-ylmethylthio)-4-aryl-3-cyano-6-methyl-1,4-dihydropyridine (**17**)

	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]									
Compound	R^1	OC_2H_5	6-CH_3 (3 H, s)	SCH_2 (2 H, s)	4-H pyrane (1 H, s)	4-H pyridine (1 H, s)	Ar	Ar^1	NH_2 (2 H, s)	NH (1 H, s)
17a	3.56 (3 H, s)	1.07 (3 H, t, *J* = 7.2), 4.00 (2 H, m)[a]	2.28	4.00 (1 H, m),[a] 4.60 (1 H, d, *J* = 14.4)	4.26	4.46	6.81 (2 H, d, *J* = 8.3), 7.09 (2 H, d, *J* = 8.3), 3.89 (3 H, s, CH_3O)	6.98 (2 H, s), 3.76 (9 H, s, 3 CH_3O)	6.54	9.45
17b	3.52 (3 H, s)	1.07 (3 H, t, *J* = 7.1), 3.97 (2 H, m)	2.27	4.04, 4.58 (both d of 1 H, *J* = 14.3)	4.25	4.42	6.77 (2 H, d, *J* = 8.4),[a] 7.05 (2 H, d, *J* = 8.4), 3.71 (3 H, s, CH_3O)	6.64 (1 H, m), 6.72 (1 H, d, *J* = 7.2), 6.78 (1 H, s),[a] 3.74 (3 H, s, CH_3O), 3.75 (3 H, s, CH_3O)	6.61	9.40
17c	1.14 3 H, t, *J* = 7,1), 4.00 (2 H, m)[a]	1.00 (3 H, t, *J* = 7.4), 4.00 (2 H, m)[a]	2.36	4.00 (1 H, m),[a] 4.70 (1 H, d, *J* = 14.2)	4.25	4.80	6.78 (2 H, d, *J* = 8.4), 7.10 (2 H, d, *J* = 8.4), 3.72 (3 H, s, CH_3O)	6.82 (1 H, d, *J* = 3.2),[b] 6.93 (1 H, dd, *J* = 3.2, 4.0), 7.35 (1 H, d, *J* = 4.0)	6.82[b]	9.80

Table 10 2-(6-Amino-4-aryl-5-cyano-3-ethoxycarbonyl-4*H*-pyran-2-ylmethylthio)-4-aryl-3-cyano-6-methyl-1,4-dihydropyridine (**17**) (continued)

	^{1}H NMR δ [DMSO-d_6, *J* (Hz)]									
Compound	R[1]	OC_2H_5	6-CH_3 (3 H, s)	SCH_2 (2 H, s)	4-H pyrane (1 H, s)	4-H pyridine (1 H, s)	Ar	Ar[1]	NH_2 (2 H, s)	NH (1 H, s)
17d	1.08 (3 H, t, *J* = 7.2),[a] 3.95 (2 H m)[b]	1.08 (3 H, t, *J* = 7.2),[a] 3.95 (2 H, m)[b]	2.32 (d, *J* = 11. 5)	4.07 (1 H, m), 4.50 (1 H, m)	4.27 (d, *J* = 12.4)	4.62 (d, *J* = 12.4)	6.77 (2 H, d, *J* = 8.5), 7.08 (2 H, d, *J* = 8.5), 3.73 (3 H, d, *J* = 5.9, CH_3O)	7.28 (2 H, d, *J* = 7.3), 7.88 (2 H, d, *J* = 7.3), 3.86 (3 H, d, *J* = 3.2, CH_3OOC)	6.51 (d, *J* = 15. 8)	9.46 (d, *J* = 10. 5)
17e	1.20 (3 H, t, *J* = 7.5), 4.02 (2 H, m)[a]	1.06 (3 H, t, *J* = 7.2), 4.02 (2 H, m)[a]	2.27	4.63 (1 H, d, *J* = 14.3), 4.05 (1 H, m)[a]	4.33	4.81	7.02 (2 H, t, *J* = 8.7), 7.22 (2 H, m)[b]	6.81 (1 H, d, *J* = 3.1), 6.90 (1 H, t, *J* = 3.7), 7.22 (1 H, m)[b]	6.50	9.58

[a,b] The signal is overlapped with the signal of another fragment.

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