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Reaction of 3-Amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxamides with Ninhydrin

V. V. Dotsenko[a,b,*], V. S. Muraviev[a,c], D. Yu. Lukina[a], V. D. Strelkov[a], N. A. Aksenov[b], I. V. Aksenova[b], G. D. Krapivin[d], and L. V. Dyadyuchenko[c]

[a] *Kuban State University, Krasnodar, 350040 Russia*
[b] *North Caucasus University, Stavropol, 355009 Russia*
[c] *All-Russian Research Institute of Biological Plant Protection, Krasnodar, 350039 Russia*
[d] *Kuban State Technological University, Krasnodar, 350072 Russia*
**e-mail: victor_dotsenko_@mail.ru*

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Abstract—The reaction of *N*-substituted amides of 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxylic acids with ninhydrin in the presence of catalytic amounts of sulfuric acid gave 1′-spiro[indene-2,2′-pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine]-1,3,4′(3′*H*)-triones. Structure of a number of key compounds was studied using 2D NMR spectroscopy; the bioavailability parameters of the obtained compounds *in silico* were calculated. In a laboratory experiment, a moderate antidote effect was revealed with respect to the 2,4-D herbicide for one compound.

Keywords: thieno[2,3-*b*]pyridines, Thorpe–Ziegler reaction, ninhydrin, heterocyclization, 2,4-D herbicide antidotes

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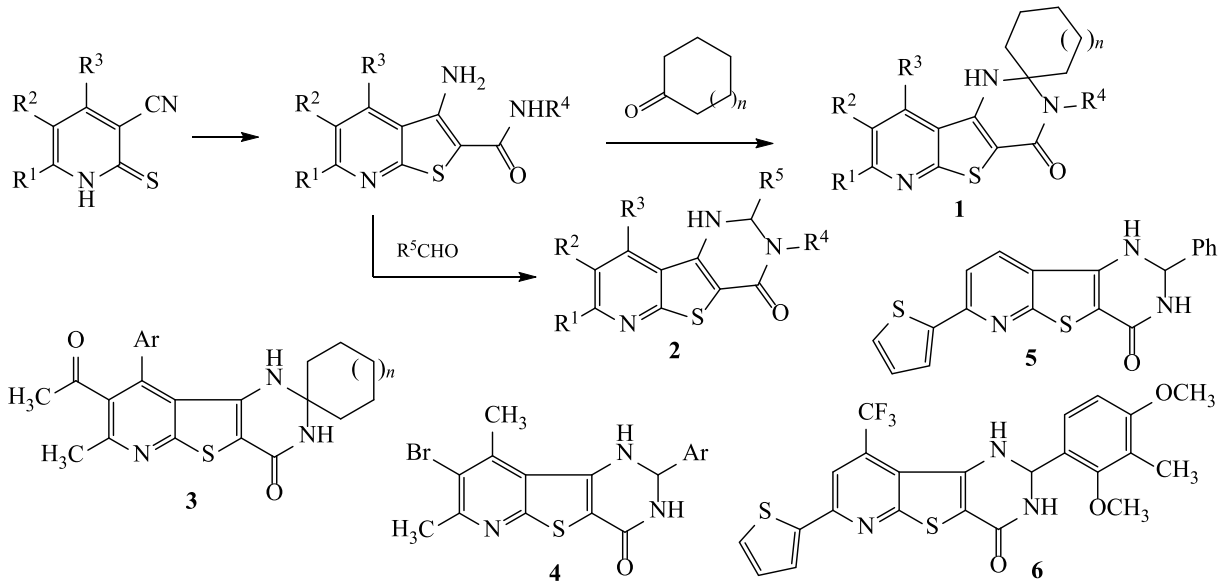
Compounds with thieno[2,3-*b*]pyridine fragment are of special interest due to a wide spectrum of biological activity (see reviews [1–7]). On the other hand, 3-aminothieno[2,3-*b*]pyridines obtained by the Thorpe–Ziegler reaction from 3-cyanopyridine-2(1*H*)-thiones [8–12] open the way to design various polycyclic systems. The latter, in turn, are also of interest as promising candidate substances for bioscreening [2–4].

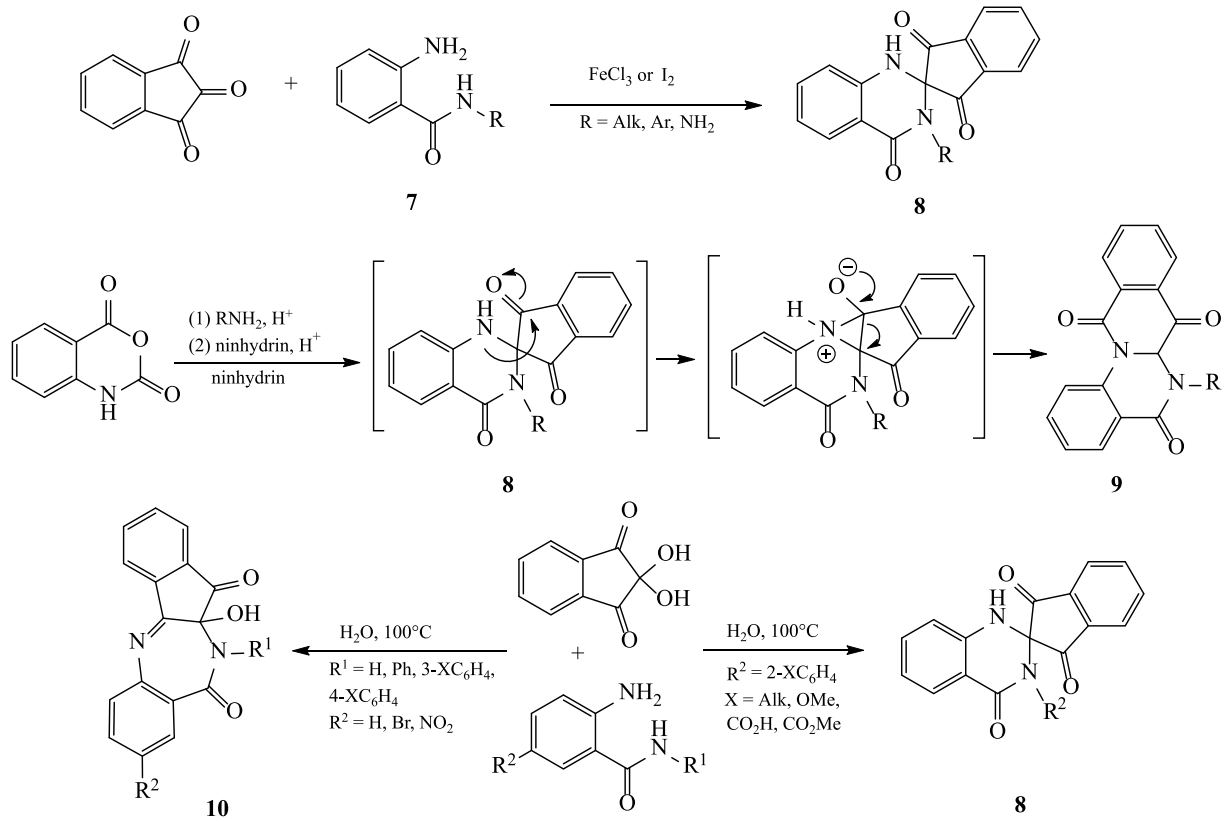
Amides of 3-aminothieno[2,3-*b*]pyridine-2-carboxylic acids are known to react readily with carbonyl compounds, aldehydes [13–27] or cyclic ketones [15–17, 22, 26, 28 –34], in boiling AcOH or toluene in the presence of catalytic amounts of acids to form pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine derivatives **1** and **2** (Scheme 1). Tricyclic compounds of this type exhibit various types of biological activity. Thus, compounds **3** [15] have an antibacterial effect; compounds **4** are inhibitors of pim-1 kinases with anti-cancer effects [24, 25]. Pyridothienopyrimidines **5** and **6** inhibit gluconeogenesis and are promising for the treatment of type 2 diabetes mellitus [35].

Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines are also of interest for agrochemistry. Thus, a number of compounds **2** have antidote activity against the herbicide 2,4-D [36] and growth-regulating effect [37]. Continuing studies in the synthesis of thieno[2,3-*b*]pyridine derivatives [38–48] and the potential of their use in agrochemical practice [49, 50], we examined the reactions of a number of 3-aminothieno[2,3-*b*]pyridine-2-carboxylic acids amides with ninhydrin as a highly reactive carbonyl compound (for a review of the chemistry of ninhydrin see [51, 52]). There are no data on reactions of thieno[2,3-*b*]pyridines with ninhydrin. At the same time, some examples of reactions of anthranylamides and related compounds with ninhydrin show that the reaction outcome substantially depends on the conditions and the substrate structure (Scheme 2). Thus, *ortho*-aminobenzamides **7** react with ninhydrin in the presence of catalytic amounts of Lewis acids ($FeCl_3$, CuBr, CuI) [53], iodine in boiling alcohol [54] or in ionic liquids [55] with the formation of the expected spiro derivatives of quinazoline **8**. However, according to other data, under conditions of heterogeneous acid catalysis (Fe_3O_4/SiO_2-Propyl-Pip-SO_3H in PEG-400 [56] or ZnO nanoparticles on a peptide nanofiber [57]), or when treating with HCl in boiling dioxane [58], a sequential reaction of isatoic anhydride with primary

Scheme 1.



Scheme 2.



amine and ninhydrin proceeds more deeply and leads to products of further transformation of spiroquinazoline intermediates **8**, isoquino[2,3-*a*]quinazoline-5,7,12-triones **9**, with yields of 60–92%. As was shown in [59], structure of the products of the catalyst-free reaction of anthranylamides with ninhydrin in boiling water depends on the substituent nature at the amide nitrogen atom: in the case of *ortho*-substituted anilides, quinazolines **8** were formed, while in the presence of other substituents formation of 11-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione **10** occurred.

Table 1. Main correlation in the $^{1}H–^{13}C$ HSQC and HMBC NMR spectra of 3-amino-4-(4-methoxyphenyl)-6-phenyl *N*-(*o*-tolyl)-thieno[2,3-*b*]pyridine-2-carboxamide **11b**[a]

δ_H, ppm	δ_C, ppm	
	$^{1}H–^{13}C$ HSQC	$^{1}H–^{13}C$ HMBC
2.22 s (3H, $ArCH_3$)	17.9* ($ArCH_3$)	130.2* (C^3, 2-MeC_6H_4NH), 134.1 (C^2, 2-MeC_6H_4NH), 136.3 (C^1, 2-MeC_6H_4NH)
3.85 s (3H, MeO)	55.3* (MeO)	159.9 (C^4, 4-$MeOC_6H_4$)
6.02 s (2H, NH_2)	–	98.0 (C^2), 121.1 (C^{3a})
7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$)	114.2* (C^3, C^5, 4-$MeOC_6H_4$)	114.2* (C^3, C^5, 4-$MeOC_6H_4$), 128.9* (C^2, C^6, 4-$MeOC_6H_4$), 159.9 (C^4, 4-$MeOC_6H_4$)
7.15-7.22 m (2H, H^4,H^5, 2-MeC_6H_4NH)	125.9*, 126.0* (C^4, C^5, 2-MeC_6H_4NH)	127.0* (C^6, 2-MeC_6H_4NH), 130.2* (C^3, 2-MeC_6H_4NH), 134.1 (C^2, 2-MeC_6H_4NH), 136.3 (C^1, 2-MeC_6H_4NH)
7.25 d. d (1H, H^3, 2-MeC_6H_4NH)	130.2* (C^3, 2-MeC_6H_4NH)	17.9* (Ar$\underline{C}H_3$), 125.9* ($C^{4/5}$, 2-MeC_6H_4NH), 126.0* ($C^{5/4}$, 2-MeC_6H_4NH), 136.3 (C^1, 2-MeC_6H_4NH)
7.29 d. d (1H, H^6, 2-MeC_6H_4NH)	127.0* (C^6, 2-MeC_6H_4NH)	134.1 (C^2, 2-MeC_6H_4NH), 125.9* ($C^{4/5}$, 2-MeC_6H_4NH), 126.0* ($C^{5/4}$, 2-MeC_6H_4NH)
7.49–7.55 m (5H, H^2,H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph)	128.9* (C^2, C^6, 4-$MeOC_6H_4$), 129.8* (C^4, Ph), 130.1* (C^3, C^5, Ph)	114.2* (C^3, C^5, 4-$MeOC_6H_4$), 127.1* (C^2, C^6, Ph), 128.5 (C^1, 4-$MeOC_6H_4$), 130.1* (C^3, C^5, Ph), 137.5 (C^1, Ph), 147.5 (C^4), 159.9 (C^4, 4-$MeOC_6H_4$)
7.75 s (1H, H^5)	118.5* (C^5)	121.1 (C^{3a}), 128.5 (C^1, 4-$MeOC_6H_4$), 137.5 (C^1, Ph), 147.5 (C^4), 155.7 (C^6)
8.22 d. d (2H, H^2, H^6, Ph)	127.1* (C^2, C^6, Ph)	127.1* (C^2, C^6, Ph), 129.8* (C^4, Ph), 130.1* (C^3, C^5, Ph), 155.7 (C^6)
9.25 s (CONH)	–	127.0* (C^6, 2-MeC_6H_4NH), 134.1 (C^2, 2-MeC_6H_4NH), 163.8 (CONH)

[a] Hereinafter, an asterisk denotes signals of carbon atoms that are in antiphase in the ^{13}C DEPTQ NMR spectrum (CH, CH_3).

The aim of this work was to reveal the conditions and directions of the raction of ninhydrin with 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxamides, which are structural analogues of anthranylamides, as well as the study of the possible biological activity of the products.

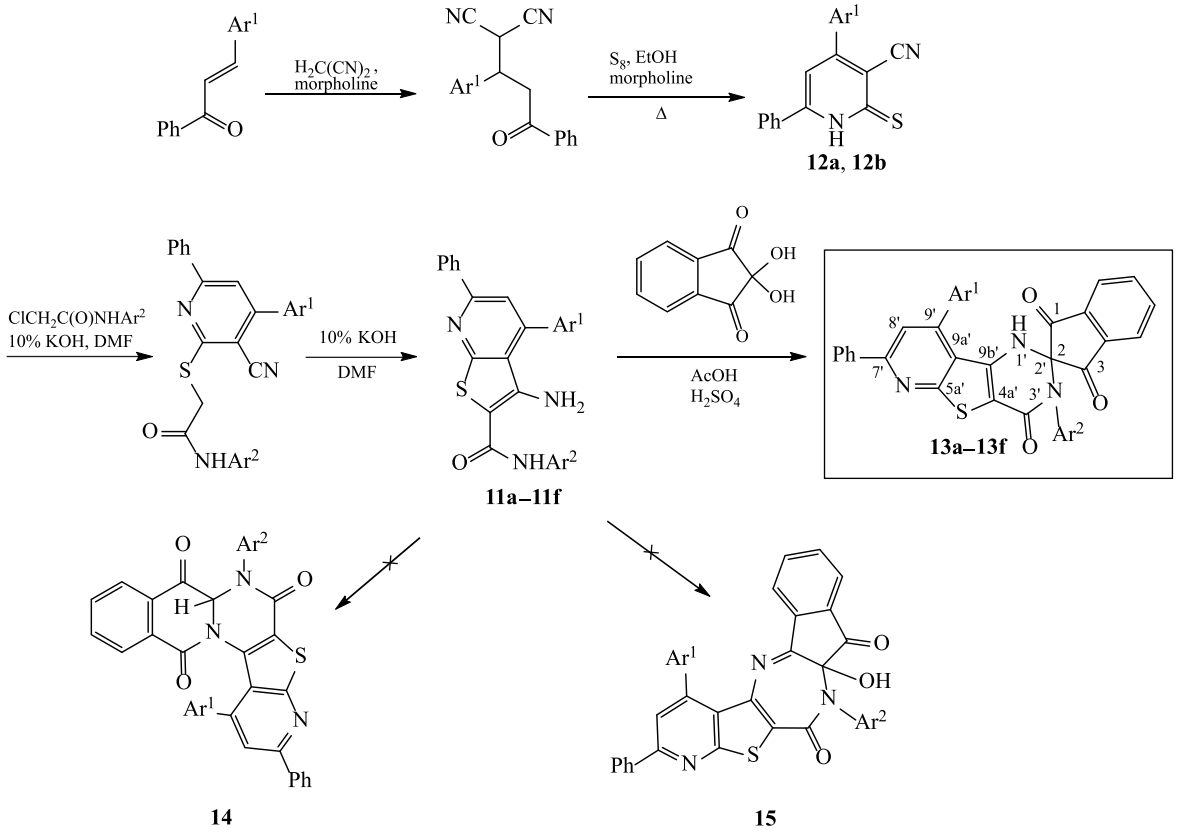
The starting 3-amino-4,6-diarylthieno[2,3-*b*]pyridine-2-carboxamides **11a–11f** were prepared by reacting 3-cyanopyridine-2(1*H*)-thiones **12a** and **12b** with *N*-substituted α-chloroacetanilides followed by cyclization of *S*-alkylation intermediates according to Thorpe–Ziegler mechanism (Scheme 3). Thiones **12** were obtained by a known procedure from the corresponding chalcone, malononitrile and sulfur [60–62]. Compounds **11** were not previously described in the literature; therefore, we have spectrally characterized them in detail, including two-dimensional NMR spectroscopy methods (Tables 1, 2).

It was found that thienopyridines **11a–11f** do not react with ninhydrin in boiling AcOH or in the presence of HCl in boiling dioxane. However, the reaction proceeds easily with brief heating in ice-cold AcOH in the presence of catalytic amounts of conc. H_2SO_4. Structure of reaction products was studied using ^{13}C DEPTQ, $^{1}H–^{13}C$ HSQC, $^{1}H–^{13}C$ HMBC, $^{1}H–^{1}H$ COSY, NOESY NMR spectroscopy methods (Tables 3, 4). The reaction products were found to be uniquely correspond to 1′-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine]-1,3,4′(3′*H*)-triones **13a–13f**. According to the results of a detailed comparative analysis of the NMR spectra of the reaction products and compounds described in [53–59], possible alternative structures **14** and **15** were excluded from consideration.

It should be noted that, in our opinion, in [56–58], quite convincing evidence of the structure of compounds **9** is not presented. So, in these works there is no detailed discussion of the structural features of compounds **9**, there are no X-ray diffraction or 2D NMR spectroscopy data, the description of the spectra is lacking in detail and partially incorrect, and copies of the ^{1}H and ^{13}C NMR spectra presented cannot be unambiguously attributed to the claimed structures.

A signal at 76.9–77.1 ppm is found in the ^{13}C NMR spectra of the compounds **13a–13f**, which is consistent with the data from [58] (74.0–77.3 ppm for the putative

Scheme 3.



Ar^1 = 4-$MeOC_6H_4$ (**12a**), 4-BrC_6H_4 (**12b**); Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph (**11a**), 2-MeC_6H_4 (**11b**), 2-Me-5-ClC_6H_3 (**11c**), 2-$NO_2C_6H_4$ (**11d**), 2-Br-4-$NO_2C_6H_3$ (**11e**); Ar^1 = 4-BrC_6H_4, Ar^2 = 2-MeC_6H_4 (**11f**).

methine carbon signal $C^{6a}H$ in **9**). However, according to the results of the DEPTQ experiment, the signal at 76.9–77.1 ppm should be unambiguously attributed to the quaternary carbon atom, which excludes structure **14**. The obtained values of chemical shifts also correlate well with the data on the position of signals given in [53, 55] for spirocarbon atoms in the ^{13}C NMR spectra of spiroquinazolines **8** (68.7–74.2 ppm).

In the ^1H NMR spectrum of compound **13a**, a highly symmetric picture of the AA′BB′-system of four aromatic protons of the indane-1,3-dione fragment (7.89–8.00 ppm) is revealed. The ^{13}C NMR spectrum of compound **13a** contains signals of two carbons of carbonyl groups: the amide at 162.6 ppm and the ketone at 192.80 ppm. However, the spectra of the other thienopyridine derivatives **13b–13f** show some differences. Thus, in the ^1H NMR spectra of compounds **13b–13f**, the aromatic protons of the indane-1,3-dione fragment form a non-symmetrical set of three distinct multiplets, and three signals of carbonyl carbon atoms are detected in the ^{13}C NMR DEPTQ spectra: two carbon atoms of keto groups (189.8–190.9 and 191.0–193.0 ppm) and the amide carbon atom (162.4–162.7 ppm). Such a spectral picture does not correspond to structures **14** and **15**, but it correlates well with the spectra of spiroquinazolines **8** given by Devi and coauthors [59]. In our opinion, the non-symmetrical nature of the signals of the indane-1,3-dione fragment in the spectra of compounds **13b–13f** is due to non-valence contacts between a part of the atoms of the indanedione fragment and the *ortho*-substituents of the C(O)N-Ar fragment. In the ^1H NMR spectra of compounds **13**, a broadened singlet of NH protons is observed at 6.70–7.07 ppm. This signal in the ^1H–^{13}C NMR spectra of compound **13b** (Tables 3, 4) gives correlation cross peaks through 2–3 bonds with the signals of the 1,3-indanedione fragment [76.9–77.1 ($C^{2\prime}_{spiro}$), 190.7–190.9 and 192.9–193.0 (keto groups)], and with the signals of the thienopyridine core [108.7–110.1 ($C^{4a\prime}$), 120.5 ($C^{9a\prime}$)]. This also makes it possible to unambiguously exclude structures **14** and **15**

Table 2. Main correlation in the ^{1}H–^{1}H COSY and NOESY NMR spectra of 3-amino-4-(4-methoxyphenyl)-6-phenyl *N*-(*o*-tolyl)-thieno[2,3-*b*]pyridine-2-carboxamide **11b**

δ_H, ppm	δ_H, ppm	
	^{1}H–^{1}H COSY	^{1}H–^{1}H NOESY
2.22 s (3H, $ArCH_3$)	–	7.25 d. d (1H, H^3, 2-MeC_6H_4NH) 9.25 s (CONH)
3.85 s (3H, MeO)	–	7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$)
6.02 s (2H, NH_2)	–	9.25 s (CONH)
7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$)	7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph)	3.85 s (3H, MeO), 7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph)
7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH)	7.25 d. d (1H, H^3 2-MeC_6H_4NH), 7.29 d. d (1H, H^6, 2-MeC_6H_4NH)	7.25 d. d (1H, H^3, 2-MeC_6H_4NH), 7.29 d. d (1H, H^6, 2-MeC_6H_4NH)
7.25 d. d (1H, H^3, 2-MeC_6H_4NH)	7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH)	2.22 s (3H, $ArCH_3$), 7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH)
7.29 d. d (1H, H^6, 2-MeC_6H_4NH)	7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH)	7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH), 9.25 s (CONH)
7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph)	7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$), 8.22 d. d (2H, H^2, H^6, Ph)	6.02 s (2H, NH_2), 7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$), 7.75 s (1H, H^5) 8.22 d. d (2H, H^2, H^6, Ph)
7.75 s (1H, H^5)	–	8.22 d. d (2H, H^2, H^6, Ph)
8.22 d. d (2H, H^2, H^6, Ph)	7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph)	7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph), 7.75 s (1H, H^5)
9.25 s (CONH)	–	2.22 s (3H, $ArCH_3$), 6.02 s (2H, NH_2) 7.29 d. d (1H, H^6, 2-MeC_6H_4NH)

from consideration. The presence of absorption bands in the IR spectra of the obtained compounds corresponding to N–H bond vibrations (3193–3356 cm^{-1}), two ketone (1752–1755 and 1713–1722 cm^{-1}) and one amide (1657–1666 cm^{-1}) carbonyl groups confirms the structure of compounds **13**.

We studied the synthesized compounds as antidotes for the 2,4-D herbicide (2,4-dichlorophenoxyacetic acid) and as plant growth regulators. Of the series of compounds tested, only thienopyridine **13d** possesses moderate antidote activity (Table 5). At the same time, compound **13d** does not show any noticeable growth-regulating effect.

We also calculated the bioavailability parameters for compounds **13a–13f** *in silico*. The initial analysis of the structures for compliance with K. Lipinski rule [*c*Log*P* ≤ 5.0, molecular weight (MW) ≤ 500, TPSA ≤ 140 Å^2, the number of hydrogen bond acceptors ≤ 10, donors ≤ 5] [63–65] was done using the OSIRIS Property Explorer software [66]. The parameters *c*Log*P* [calculated logarithm of the partition coefficient between *n*-octanol and water log ($c_{octanol}/c_{water}$)], solubility (log *S*), topological polar surface area (TPSA), toxicological parameters such as risks of side effects (mutagenic, oncogenic, reproductive effects), similarities with known drugs (drug-likeness), as well as a general assessment of the pharmacological potential of the compound (drug score). The obtained calculated data are presented in Table 6. In general, they show low prospectivity of tested compounds from the point of view of bioscreening (the drug score parameter value is not higher than 0.11). In all cases *c*Log*P* >> 5.0, the values of log*S* and molecular weight of all compounds **13a–13f** also do not meet the criteria for oral bioavailability. As the calculation shows, compounds **13a–13f** have rather high TPSA values close to or even exceeding 140 Å^2, which indicates a probable low ability to penetrate through the cell membrane or blood-brain barrier. All compounds show a risk of potential effects on the reproductive system. At the same time, the calculation of the drug-likeness parameter gives unexpectedly high values for compounds **13a** and **13b**.

In conclusion, the reaction of 3-amino-4,6-diaryl-thieno[2,3-*b*]pyridine-2-carboxamides with ninhydrin in the presence of catalytic amounts of sulfuric acid afforded new series of 1′-spiro[indene-2,2′-pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine]-1,3,4′(3′*H*)-triones, structure of which was unambiguous proved using 2D NMR spectroscopy methods. The analysis of bioavailability

Table 3. Main correlation in the ^{1}H–^{13}C HSQC and HMBC NMR spectra of 9′-(4-methoxyphenyl)-3′-(*o*-tolyl)-7′-phenyl-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine]-1,3,4′(3′*H*)-trione **13b**

δ_H, ppm	δ_C, ppm	
	^{1}H–^{13}C HSQC	^{1}H–^{13}C HMBC
2.23 s (2-$CH_3C_6H_4$)	18.0* (MeAr)	130.8* (C^3, 2-$CH_3C_6H_4$), 136.0 (C^1, 2-$CH_3C_6H_4$), 138.2 (C^2, 2-$CH_3C_6H_4$)
3.63 s (3H, MeO)	55.1* (MeO)	159.8 (C^4, 4-$MeOC_6H_4$)
6.58 d (1H, H^6, 2-$CH_3C_6H_4$)	127.7* (C^6, 2-$CH_3C_6H_4$)	128.5* (C^4, 2-$CH_3C_6H_4$), 136.0 (C^1, 2-$CH_3C_6H_4$), 138.2 (C^2, 2-$CH_3C_6H_4$)
6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$)	113.1* (C^3, C^5, 4-$MeOC_6H_4$)	113.1* (C^3, C^5, 4-$MeOC_6H_4$), 127.9 (C^1, 4-$MeOC_6H_4$), 159.8 (C^4, 4-$MeOC_6H_4$)
6.71 s (1H, NH)	–	76.9 ($C^{2'}_{spiro}$), 110.1 ($C^{4a'}$), 190.9 ($C{=}O_{ketone}$), 193.0 ($C{=}O_{ketone}$)
6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$)	126.5* (C^5, 2-$CH_3C_6H_4$)	130.8* (C^3, 2-$CH_3C_6H_4$), 136.0 (C^1, 2-$CH_3C_6H_4$)
7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)	128.5* (C^4, 2-$CH_3C_6H_4$)	126.5* (C^5, 2-$CH_3C_6H_4$), 127.7* (C^6, 2-$CH_3C_6H_4$), 138.2 (C^2, 2-$CH_3C_6H_4$)
7.21 d (1H, H^3, 2-$CH_3C_6H_4$)	130.8* (C^3, 2-$CH_3C_6H_4$)	18.0* (MeAr), 126.5* (C^5, 2-$CH_3C_6H_4$), 136.0 (C^1, 2-$CH_3C_6H_4$)
7.41 d (2H, H^2, H^6, 4-$MeOC_6H_4$)	131.1* (C^2, C^6, 4-$MeOC_6H_4$)	131.1* (C^2, C^6, 4-$MeOC_6H_4$), 147.7 ($C^{9'}$), 159.8 (C^4, 4-$MeOC_6H_4$)
7.50–7.55 m (3H, H^3–H^5, Ph)	128.9* (C^3, C^5, Ph), 129.9* (C^4, Ph)	127.3* (C^2, C^6, Ph), 128.9* (C^3, C^5, Ph), 129.9* (C^4, Ph), 137.5 (C^1, Ph)
7.78 d (1H, H-Ar)	123.8* (CH-Ar)	137.9* (CH, Ar), 139.5 (C, Ar), 190.9 ($C{=}O_{ketone}$)
7.86 s (1H, $H^{8'}$)	118.6* ($C^{8'}$)	120.8* ($C^{9a'}$), 127.9 (C^1, 4-$MeOC_6H_4$), 137.5 (C^1, Ph), 142.3 ($C^{9b'}$), 155.9 ($C^{7'}$)
7.97–8.00 m (1H, H-Ar)	137.2* (CH, Ar)	124.7* (CH, Ar), 139.5 (C, Ar)
8.10–8.11 m (2H, H-Ar)	124.7* (CH, Ar), 137.9* (CH, Ar)	123.8* (CH, Ar), 124.7* (CH, Ar), 137.2* (CH, Ar), 138.7 (C, Ar), 139.5 (C, Ar), 193.0 ($C{=}O_{ketone}$)
8.25 d. d (2H, H^2, H^6, Ph)	127.3* (C^2, C^6, Ph)	127.3* (C^2, C^6, Ph), 128.9* (C^3, C^5, Ph), 129.9* (C^4, Ph), 155.9 ($C^{7'}$)

parameters indicate a low pharmacological potential of the obtained compounds. At the same time, in the course of laboratory experiments, a moderate antidote activity was established with respect to the 2,4-D herbicide for one of the synthesized substances.

EXPERIMENTAL

NMR spectra for all compounds (except **11e**) were recorded on a Bruker Avance III HD 400MHz instrument [400.17 (^{1}H), 100.63 MHz (^{13}C)] from a DMSO-d_6 solution. Due to insufficient solubility in DMSO-d_6, the NMR spectra of compound **11e** were recorded from a $CDCl_3$–CF_3CO_2D solution on an Agilent 400/54 instrument (399.94 and 100.57 MHz, respectively). Residual solvent signals were used as a standard. IR spectra were recorded on a Bruker Vertex 70 Fourier transform IR spectrometer with an ATR attachment on a diamond crystal with a spectral resolution of ±4 cm^{-1}. Elemental analysis for C, H, N was carried out on a Carlo Erba 1106 instrument. Purity of the obtained compounds and the reaction progress were monitored by TLC on Sorbfil PTSX-AF-A plates (Imid LLC, Krasnodar), eluting with acetone–hexane mixture (1 : 1) and developing with iodine vapors or UV detector.

General procedure for the synthesis of 3-aminothieno[2,3-*b*]pyridine-2-carboxamides 11a–11f. To a suspension of 3.1 mmol of the corresponding 4-aryl-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile **12a** in 7–8 mL of DMF was added an aqueous 10% solution of KOH (d = 1.09 g/mL, 1.7 mL, 3.3 mmol). The resulting mixture was stirred while heating to dissolution, then 3.1 mmol of the corresponding α-chloroacetanilide in 2 mL of DMF was added to a solution through a paper filter. The mixture was stirred for 30 min, another 1.7 mL of a 10% aqueous KOH solution was added to the resulting suspension of the *S*-alkylation product, and the reaction mixture was brought to boiling with stirring, heated for 1–3 min, then cooled to room

Table 4. Main correlation in the ^{1}H–^{1}H COSY and NOESY NMR spectra of 9′-(4-methoxyphenyl)-3′-(*o*-tolyl)-7′-phenyl-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine]-1,3,4′(3′*H*)-trione **13b**

δ_H, ppm	δ_H, ppm	
	^{1}H–^{1}H COSY	^{1}H–^{1}H NOESY
2.23 s (2-$CH_3C_6H_4$)	–	7.21 d (1H, H^3, 2-$CH_3C_6H_4$)
3.63 s (3H, MeO)	–	6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$)
6.58 d (1H, H^6, 2-$CH_3C_6H_4$)	6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$)	6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$)
6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$)	7.41 d (2H, H^2, H^6, 4-$MeOC_6H_4$)	3.63 s (3H, MeO), 7.41 d (2H, H^2, H^6, 4-$MeOC_6H_4$)
6.71 s (1H, NH)	–	–
6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$)	6.58 d (1H, H^6, 2-$CH_3C_6H_4$), 7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)	6.58 d (1H, H^6, 2-$CH_3C_6H_4$), 7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)
7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)	6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$), 7.21 d (1H, H^3, 2-$CH_3C_6H_4$)	6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$), 7.21 d (1H, H^3, 2-$CH_3C_6H_4$)
7.21 d (1H, H^3, 2-$CH_3C_6H_4$)	7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)	2.23 s (2-$CH_3C_6H_4$), 7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$)
7.41 d (2H, H^2, H^6, 4-$MeOC_6H_4$)	6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$)	6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$)
7.50–7.55 m (3H, H^3–H^5, Ph)	8.25 d. d (2H, H^2, H^6, Ph)	8.25 d. d (2H, H^2, H^6, Ph)
7.78 d (1H, H-Ar)	7.97–8.00 m (1H, H-Ar)	7.97–8.00 m (1H, H-Ar)
7.86 s (1H, $H^{8'}$)	–	8.25 d. d (2H, H^2, H^6, Ph)
7.97–8.00 m (1H, H-Ar)	7.78 d (1H, H-Ar), 8.10–8.11 m (2H, H-Ar)	7.78 d (1H, H-Ar), 8.10–8.11 m (2H, H-Ar)
8.10–8.11 m (2H, H-Ar)	7.97–8.00 m (1H, H-Ar)	7.97–8.00 m (1H, H-Ar)
8.25 d. d (2H, H^2, H^6, Ph)	7.50–7.55 m (3H, H^3–H^5, Ph)	7.50–7.55 m (3H, H^3–H^5, Ph), 7.86 s (1H, $H^{8'}$)

temperature and diluted with an equal volume of 50% aqueous alcohol. After 24 h, the precipitate was filtered off, washed with 50% ethanol and petroleum ether. For analytical purposes, the sample was recrystallized from a suitable solvent (acetone, AcOH, DMF).

3-Amino-4-(4-methoxyphenyl)-*N*,6-diphenylthieno[2,3-*b*]pyridine-2-carboxamide (11a). Yield 76%, mp 210°C, yellow powder. IR spectrum, ν, cm^{-1}: 3474, 3283 (N–H), 1657 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, MeO), 6.11 br. s (2H, NH_2), 7.05–7.09 m (1H, H^4 PhNH), 7.15 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 7.29–7.33 m (2H, H-Ar), 7.50–7.55 m (4H, H-Ar), 7.67 d (2H, H-Ar, ^3J = 7.6 Hz), 7.74 s (1H, H^5), 8.21 d (2H, H^2, H^6 Ph, ^3J = 7.9 Hz), 9.53 br. s (1H, CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.3 (MeO), 97.7* (C^2), 114.2 (C^3, C^5 4-$MeOC_6H_4$), 118.6 (C^5), 121.0* (C^{3a}), 121.3 (C^2, C^6, NHC_6H_5), 123.5 (C^4, NHC_6H_5), 127.1 (C^2, C^6, Ph), 128.4 (C^3, C^5, NHC_6H_5), 128.5* (C^1, 4-$MeOC_6H_4$), 128.9 (C^2, C^6, 4-$MeOC_6H_4$), 129.8 (C^4, Ph), 130.1 (C^3, C^5, Ph), 137.5* (C^1, Ph), 138.8* (C^1, NHPh), 146.8* (C^3), 147.5* (C^4), 155.8* (C^6), 159.9* (C^4, 4-$MeOC_6H_4$), 160.0* (C^{7a}), 163.8* (CONH). *Antiphase signals. Found, %: C 71.75; H 4.80; N 9.34. $C_{27}H_{21}N_3O_2S$. Calculated, %: C 71.82; H 4.69; N 9.31.

Table 5. Antidote activity of compound **13d**

Part	Antidote effect A at various concentrations,%			
	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Root	111	111	111	114
Stem	102	96	100	98

3-Amino-4-(4-methoxyphenyl)-6-phenyl-*N*-(*o*-tolyl)thieno[2,3-*b*]pyridine-2-carboxamide (11b). Yield 71%, mp 265°C, yellow powder. IR spectrum, ν, cm^{-1}: 3483, 3348, 3300 (N–H), 1684 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, $ArCH_3$), 3.85 s (3H, MeO), 6.02 br. s (2H, NH_2), 7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.8 Hz), 7.15–7.22 m (2H, H^4, H^5, 2-MeC_6H_4NH), 7.25 d. d (1H, H^3, 2-MeC_6H_4NH, ^3J = 7.2, ^4J = 1.5 Hz), 7.29 d. d (1H, H^6, 2-MeC_6H_4NH, ^3J = 7.8, ^4J = 1.5 Hz), 7.49–7.55 m (5H, H^2, H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph), 7.75 s (1H, H^5), 8.22 d. d (2H, H^2, H^6, Ph, ^3J = 8.0, ^4J = 1.7 Hz), 9.25 br. s (CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 17.9* ($ArCH_3$), 55.3* (MeO), 98.0 (C^2), 114.2*

Table 6. Toxicity risks and physico-chemical parameters of compounds **13a–13f** predicted by the OSIRIS Property Explorer software

Compound	Toxicity risks[a]				Physico-chemical parameters					
	A	B	C	D	*c*Log*P*	log*S*	MW	TPSA	drug likeness	drug score
13a	–	–	–	+	6.5	–10.6	593	116.8	3.43	0.109
13b	–	–	–	+	6.85	–10.9	607	116.8	3.01	0.101
13c	–	–	–	+	7.45	–11.6	641	116.8	2.38	0.090
13d	–	–	–	+	5.58	–11.1	638	162.6	–4.09	0.060
13e	–	–	–	+	6.31	–11.8	716	162.6	–5.51	0.048
13f	–	–	–	+	7.64	–11.8	655	107.6	0.89	0.077

[a] The "+" sign indicates a high risk of toxicity, "–"—the absence of toxicity; A—mutagenicity, B—carcinogenicity, C—irritant effect, D—reproductive effects.

(C^3, C^5, 4-$MeOC_6H_4$), 118.5* (C^5), 121.1 (C^{3a}), 125.9* ($C^{4/5}$, 2-MeC_6H_4NH), 126.0* ($C^{5/4}$, 2-MeC_6H_4NH), 127.0* (C^6, 2-MeC_6H_4NH), 127.1* (C^2, C^6, Ph), 128.5 (C^1, 4-$MeOC_6H_4$), 128.9* (C^2, C^6, 4-$MeOC_6H_4$), 129.8* (C^4, Ph), 130.1* (C^3, C^5, Ph), 130.2* (C^3, 2-MeC_6H_4NH), 134.1 (C^2, 2-MeC_6H_4NH), 136.3 (C^1, 2-MeC_6H_4NH), 137.5 (C^1, Ph), 146.3 (C^3), 147.5 (C^4), 155.7 (C^6), 159.9 (C^4, 4-$MeOC_6H_4$), 160.0 (C^{7a}), 163.8 (CONH). Found, %: C 72.20; H 5.09; N 9.05. $C_{28}H_{23}N_3O_2S$. Calculated, %: C 72.23; H 4.98; N 9.03.

3-Amino-*N*-(5-chloro-2-methylphenyl)-4-(4-methoxyphenyl)-6-phenylthieno[2,3-*b*]pyridine-2-carboxamide (11c). Yield 63%, mp 239°C, yellow powder. IR spectrum, ν, cm^{-1}: 3481, 3381, 3273 (N–H), 1653 (C=O). ^1H NMR spectrum, δ, ppm: 2.21 s (3H, $ArCH_3$), 3.85 s (3H, MeO), 6.04 br. s (2H, NH_2), 7.14 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.7 Hz), 7.20 d. d (1H, H^4 2-Me-5-ClC_6H_3NH, ^3J = 8.2, ^4J = 2.1 Hz), 7.28 d (1H, H^3, 2-Me-5-ClC_6H_3NH, ^3J = 8.2 Hz), 7.43 d (1H, H^6, 2-Me-5-ClC_6H_3NH, ^4J = 2.1 Hz), 7.48–7.55 m (5H, H^2,H^6, 4-$MeOC_6H_4$ + H^3–H^5, Ph), 7.75 s (1H, H^5), 8.22 br. d (2H, H^2,H^6, Ph, ^3J = 8.0 Hz), 9.29 br. s (CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 17.4* ($ArCH_3$), 55.3* (MeO), 97.7 (C^2), 114.3* (C^3, C^5, 4-$MeOC_6H_4$), 118.6* (C^5), 121.1 (C^{3a}), 125.5* (C^6, 2-Me-5-ClC_6H_3NH), 126.1* (C^4, 2-Me-5-ClC_6H_3NH), 127.1* (C^2, C^6, Ph), 128.5 (C^1, 4-$MeOC_6H_4$), 128.9* (C^2, C^6, 4-$MeOC_6H_4$), 129.7 (C^2, 2-Me-5-ClC_6H_3NH), 129.8* (C^4, Ph), 130.2* (C^3, C^5, Ph), 131.7* (C^3, 2-Me-5-ClC_6H_3NH), 132.7 (C^5, 2-Me-5-ClC_6H_3NH), 137.5 (C^1, Ph), 137.8 (C^1, 2-Me-5-ClC_6H_3NH), 146.7 (C^3), 147.6 (C^4), 155.8 (C^6), 159.9 (C^4, 4-$MeOC_6H_4$), 160.0 (C^{7a}), 163.8 (CONH). Found, %: C 67.20; H 4.50; N 8.38. $C_{28}H_{22}ClN_3O_2S$. Calculated, %: C 67.26; H 4.43; N 8.40.

3-Amino-4-(4-methoxyphenyl)-*N*-(2-nitrophenyl)-6-phenylthieno[2,3-*b*]pyridine-2-carboxamide (11d). Yield 58%, mp 192–193°C, yellow orange powder. IR spectrum, ν, cm^{-1}: 3467, 3330 (N–H), 1646 (C=O), 1585 (NO_2, as), 1340 (NO_2, s). ^1H NMR spectrum, δ, ppm: 3.85 s (3H, MeO), 6.15 br. s (2H, NH_2), 7.15 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.8 Hz), 7.30–7.34 m (1H, H^4, 2-$NO_2C_6H_4NH$), 7.49–7.56 m (5H, H-Ar), 7.69–7.73 m (1H, H-Ar), 7.78 s (1H, H^5), 8.00–8.04 m (2H, H-Ar), 8.23 d. d (2H, H^2,H^6, Ph, ^3J = 8.1, ^4J = 1.5 Hz), 10.29 br. s (CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.3* (MeO), 114.3* (C^3, C^5, 4-$MeOC_6H_4$), 117.0 (C^2), 118.7* (C^5), 121.0 (C^{3a}), 124.96* ($C^{4/6}$, 2-$NO_2C_6H_4NH$), 125.04* ($C^{6/4}$, 2-$NO_2C_6H_4NH$), 127.2* (C^2, C^6, Ph), 128.3 (C^1, 4-$MeOC_6H_4$), 128.9* (C^2, C^6, 4-$MeOC_6H_4$), 129.8* ($C^{3/5}$, 2-$NO_2C_6H_4NH$), 129.9* (C^4, Ph), 130.1* (C^3, C^5, Ph), 134.3* ($C^{5/3}$, 2-$NO_2C_6H_4NH$), 137.4 (C^1, 2-$NO_2C_6H_4NH$), 137.6 (C^1, Ph), 141.2 (C^2, 2-$NO_2C_6H_4NH$), 147.9 (C^4), 154.4 (C^3), 156.2 (C^6), 160.0 (C^4, 4-$MeOC_6H_4$), 160.1 (C^{7a}), 163.7 (CONH). Found, %: C 65.22; H 4.20; N 11.34. $C_{27}H_{20}N_4O_4S$. Calculated, %: C 65.31; H 4.06; N 11.28.

3-Amino-*N*-(2-bromo-4-nitrophenyl)4-(4-methoxyphenyl)-6-phenylthieno[2,3-*b*]pyridine-2-carboxamide (11e). Yield 52%, mp 252°C, yellow orange powder. IR spectrum, ν, cm^{-1}: 3483, 3350, 3323 (N–H), 1651 (C=O), 1584 (NO_2, as), 1344 (NO_2, s). ^1H NMR spectrum, δ, ppm: 4.00 s (3H, MeO), 7.25 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 7.61 d (2H, H^2, H^6, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 7.66–7.70 m (2H, H-Ph), 7.74–7.77 m (1H, H-Ph), 7.87 s (1H, H^5), 7.95 d (2H, H^2,H^6, Ph, ^3J = 7.5 Hz), 8.26–8.27 m (2H, H^6, H^5, ArNH), 8.54 br. s (1H, H^3, ArNH). Signals of NH and NH_2 protons do not appear due to deutero exchange with CF_3CO_2D. ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.6 (MeO), 97.2 (C^2), 115.4 (CBr), 115.6 (C^3, C^5, 4-$MeOC_6H_4$), 122.1 (C^5), 122.6 ($C^{5/6}$, ArNH), 123.9 ($C^{6/5}$, ArNH), 125.17 (C^{3a}), 125.23 (C^1, 4-$MeOC_6H_4$), 127.8 (C^2, C^6, Ph), 128.4

(C^1, Ph), 129.4 (C^3, ArNH), 130.0 (C^2, C^6, 4-$MeOC_6H_4$), 130.4 (C^3, C^5, Ph), 134.0 (C^4, Ph), 140.5 (CNO_2), 144.2 (C^1, ArNH), 148.1 (C^3), 151.3 (C^{7a}), 153.3 (C^6), 157.5 (C^4), 162.3 (C^4, 4-$MeOC_6H_4$), 163.2 (CONH). Found, %: C 56.22; H 3.45; N 9.66. $C_{27}H_{19}BrN_4O_4S$. Calculated, %: C 56.36; H 3.33; N 9.74.

3-Amino-4-(4-bromophenyl)-6-phenyl-*N*-(*o*-tolyl)-thieno[2,3-*b*]pyridine-2-carboxamide (11f). Yield 43%, mp 208°C, yellow powder. IR spectrum, ν, cm^{-1}: 3473, 3390, 3325 (N–H), 1634 (C=O). ^1H NMR spectrum, δ, ppm: 2.22 s (3H, $ArCH_3$), 5.98 br. s (2H, NH_2), 7.16–7.30 m (4H, H-Ar), 7.51–7.57 m (5H, H-Ar), 7.78 d (2H, H-Ar, ^3J = 8.1 Hz), 7.80 s (1H, H^5), 8.22 d (2H, H^2, H^6, Ph, ^3J = 8.0 Hz), 9.30 br. s (CONH). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 17.9 ($ArCH_3$), 98.7* (C^2), 118.3 (C^5), 120.8* (C^{3a}), 122.8* (CBr), 125.95 ($C^{4/5}$, 2-MeC_6H_4NH), 126.0 ($C^{5/4}$, 2-MeC_6H_4NH), 127.0 (C^6, 2-MeC_6H_4NH), 127.1 (C^2, C^6, Ph), 128.9 (2CH, Ar), 129.9 (C^4, Ph), 130.2 (C^3, 2-MeC_6H_4NH), 131.0 (2CH, Ar), 131.6 (2CH, Ar), 134.2* (C^2, 2-MeC_6H_4NH), 135.7* (C^1, 4-BrC_6H_4), 136.3* (C^1, 2-MeC_6H_4NH), 137.4* (C^1, Ph), 146.2* (C^3), 146.4* (C^4), 155.7* (C^6), 159.9* (C^{7a}), 163.8* (CONH). Found, %: C 63.02; H 4.06; N 8.14. $C_{27}H_{20}BrN_3OS$. Calculated, %: C 63.04; H 3.92; N 8.17.

General procedure for the synthesis 3′,7′,9′-triaryl-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine]-1,3,4′(3′*H*)-triones 13a–13f. To a suspension of 0.3 g of the starting thienopyridine **11a**–**11f** in 5 mL of glacial AcOH were added 2–3 drops of conc. sulfuric acid. The mixture was refluxed, and then an equimolar amount of ninhydrin was added. The resulting black solution was boiled for 3–5 min. After cooling to room temperature, the mixture was poured into 20 mL of cold water and kept for 24 h. The precipitate was filtered off, washed with water and recrystallized from EtOH.

9′-(4-Methoxyphenyl)-3′,7′-diphenyl-1′*H*-spiro-[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyri-midine]-1,3,4′(3′*H*)-trione (13a). Yield 51%, mp 211°C, yellow powder. IR spectrum, ν, cm^{-1}: 3300 (N–H), 1753, 1720, 1659 (3 C=O). ^1H NMR spectrum, δ, ppm: 3.64 s (3H, MeO), 6.69 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 6.72 s (1H, NH), 6.93 d (2H, H^2, H^6, Ph–N, ^3J = 7.0 Hz), 7.14–7.23 m (3H, H^3–H^5, Ph–N), 7.44 d (2H, H^2, H^6, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 7.50–7.56 m (3H, H^3–H^5, Ph), 7.86 s (1H, $H^{8\prime}$), 7.89–8.00 m (4H, H-Ar, AA′BB′-system), 8.25 d (2H, H^2, H^6, Ph, ^3J = 8.1 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.1* (MeO), 77.0 ($C^{2\prime}{}_{spiro}$), 108.5 ($C^{4a\prime}$), 113.3* (C^3, C^5, 4-$MeOC_6H_4$), 118.6* ($C^{8\prime}$), 120.5* ($C^{9a\prime}$), 124.1* (2CH, Ar), 127.3* (2CH, Ar), 128.0 (C^1, 4-$MeOC_6H_4$), 128.3* (C^4H, Ph–N), 128.9* (2CH, Ar), 129.0* (2CH, Ar), 129.6* (2CH, Ar), 130.0* (C^4H, Ph), 131.1* (2CH, Ar), 136.4 (Ar), 137.46 (Ar), 137.49* (2CH, Ar), 139.1 (Ar), 142.4 ($C^{9b\prime}$), 147.7 ($C^{9\prime}$), 155.7 ($C^{7\prime}$), 159.9 (C^4, 4-$MeOC_6H_4$), 160.2* ($C^{5a\prime}$), 162.6 ($C{=}O_{amide}$), 192.8 ($C{=}O_{ketone}$). Found, %: C 72.90; H 4.09; N 6.98. $C_{36}H_{23}N_3O_4S$. Calculated, %: C 72.83; H 3.91; N 7.08.

9′-(4-Methoxyphenyl)-7′-phenyl-3′-(*o*-tolyl)-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine]-1,3,4′(3′*H*)-trione (13b). Yield 56%, mp 208°C, yellow powder. IR spectrum, ν, cm^{-1}: 3263 (N–H), 1753, 1713, 1661 (3C=O). ^1H NMR spectrum, δ, ppm: 2.23 s (2-C**H**$_3C_6H_4$), 3.63 s (3H, MeO), 6.58 d (1H, H^6, 2-$CH_3C_6H_4$, ^3J = 7.6 Hz), 6.64 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 6.71 s (1H, NH), 6.89–6.93 m (1H, H^5, 2-$CH_3C_6H_4$), 7.10–7.13 m (1H, H^4, 2-$CH_3C_6H_4$), 7.21 d (1H, H^3, 2-$CH_3C_6H_4$, ^3J = 7.3 Hz), 7.41 d (2H, H^2, H^6, 4-$MeOC_6H_4$, ^3J = 8.6 Hz), 7.50–7.55 m (3H, H^3–H^5, Ph), 7.78 d (1H, H-Ar, ^3J = 7.7 Hz), 7.86 s (1H, $H^{8\prime}$), 7.97–8.00 m (1H, H-Ar), 8.10–8.11 m (2H, H-Ar), 8.25 d. d (2H, H^2,H^6, Ph, ^3J = 8.1, ^4J = 1.7 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 18.0* (MeAr), 55.1* (MeO), 76.9 ($C^{2\prime}{}_{spiro}$), 110.1 ($C^{4a\prime}$), 113.1* (C^3, C^5, 4-$MeOC_6H_4$), 118.6* ($C^{8\prime}$), 120.8* ($C^{9a\prime}$), 123.8* (CH, Ar), 124.7* (CH, Ar), 126.5* (C^5, 2-$CH_3C_6H_4$), 127.3* (C^2, C^6, Ph), 127.7* (C^6, 2-$CH_3C_6H_4$), 127.9 (C^1, 4-$MeOC_6H_4$), 128.5* (C^4, 2-$CH_3C_6H_4$), 128.9* (C^3, C^5, Ph), 129.9* (C^4, Ph), 130.8* (C^3, 2-$CH_3C_6H_4$), 131.1* (C^2, C^6, 4-$MeOC_6H_4$), 136.0 (C^2, 2-$CH_3C_6H_4$), 137.2* (CH, Ar), 137.5 (C^1, Ph), 137.9* (CH, Ar), 138.2 (C^1, 2-$CH_3C_6H_4$), 138.7 (Ar), 139.5 (Ar), 142.3 ($C^{9b\prime}$), 147.7 ($C^{9\prime}$), 155.9 ($C^{7\prime}$), 159.1 ($C^{5a\prime}$), 159.8 (C^4, 4-$MeOC_6H_4$), 162.5 ($C{=}O_{amide}$), 190.9 ($C{=}O_{ketone}$), 193.0 ($C{=}O_{ketone}$). Found, %: C 73.10; H 4.23; N 6.89. $C_{37}H_{25}N_3O_4S$. Calculated, %: C 73.13; H 4.15; N 6.91.

3′-(5-Chloro-2-methylphenyl)-9′-(4-methoxy-phenyl)-7′-phenyl-1′*H*-spiro[indene-2,2′-pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine]1,3,4′(3′*H*)-trione (13c). Yield 62%, mp 203°C, yellow powder. IR spectrum, ν, cm^{-1}: 3242 (N–H), 1755, 1715, 1661 (3 C=O). ^1H NMR spectrum, δ, ppm: 2.20 s (2-C**H**$_3C_6H_4$), 3.65 s (3H, MeO), 6.57 d (1H, H^6, 2-CH_3-5-ClC_6H_3, ^4J = 1.8 Hz), 6.69 d (2H, H^3, H^5, 4-$MeOC_6H_4$, ^3J = 8.5 Hz), 6.79 s (1H, NH), 7.21 d. d (1H, H^4, 2-CH_3-5-ClC_6H_3, ^3J = 8.3, ^4J = 1.8 Hz), 7.26 d (1H, H^3, 2-CH_3-5-ClC_6H_3, ^3J = 8.3 Hz), 7.44 d (2H, H^2, H^6, 4-$MeOC_6H_4$, ^3J = 8.5 Hz), 7.50–7.56 m (3H, H^3–H^5, Ph), 7.80 d (1H, H-Ar,

^3J = 7.7 Hz), 7.87 s (1H, H$^{8'}$), 7.98–8.02 m (1H, H-Ar), 8.11–8.13 m (2H, H-Ar), 8.26 d (2H, H^2,H^6, Ph, ^3J = 8.0 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 17.5* (MeAr), 55.1* (MeO), 77.1 (C$^{2'}{}_{spiro}$), 108.7 (C$^{4a'}$), 113.3* (C^3, C^5, 4-MeOC$_6$H$_4$), 118.6* (C$^{8'}$), 120.5 (C$^{9a'}$), 123.9* (CH, Ar), 124.6* (CH, Ar), 127.3* (C^2, C^6, Ph), 127.9 (C^1, 4-MeOC$_6$H$_4$), 128.2* (C^6, 2-CH$_3$C$_6$H$_4$), 128.6* (C^4, 2-CH$_3$C$_6$H$_4$), 128.9* (C^3, C^5, Ph), 129.9 (C^5, 2-CH$_3$C$_6$H$_4$), 130.0* (C^4, Ph), 131.1* (C^2, C^6, 4-MeOC$_6$H$_4$), 132.3* (C^3, 2-CH$_3$C$_6$H$_4$), 137.1 (C^2, 2-CH$_3$C$_6$H$_4$), 137.3* (CH, Ar), 137.4 (C^1, Ph), 137.7 (C^1, 2-CH$_3$C$_6$H$_4$), 138.0* (CH, Ar), 138.8 (Ar), 139.6 (Ar), 142.9 (C$^{9b'}$), 147.8 (C$^{9'}$), 156.1 (C$^{7'}$), 159.1 (C$^{5a'}$), 159.9 (C^4, 4-MeOC$_6$H$_4$), 162.6 (C=O$_{amide}$), 190.7 (C=O$_{ketone}$), 192.9 (C=O$_{ketone}$). Found, %: C 69.16; H 3.89; N 6.52. $C_{37}H_{24}ClN_3O_4S$. Calculated, %: C 69.21; H 3.77; N 6.54.

9′-(4-Methoxyphenyl)-3′-(2-nitrophenyl)-7′-phenyl-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine]1,3,4′(3′*H*)-trione (13d). Yield 60%, mp 160°C, yellow powder. IR spectrum, ν, cm^{-1}: 3356 (N–H), 1753, 1722, 1665 (3C=O), 1531 (NO$_2$, as), 1354 (NO$_2$, s). ^{1}H NMR spectrum, δ, ppm: 3.62 s (3H, MeO), 6.56 d (2H, H^3, H^5, 4-MeOC$_6$H$_4$, ^3J = 8.6 Hz), 7.00 s (1H, NH), 7.06 d. d (1H, H^6, 2-NO$_2$C$_6$H$_4$, ^3J = 7.7, ^4J = 1.3 Hz), 7.36 d (2H, H^2, H^6, 4-MeOC$_6$H$_4$, ^3J = 8.6 Hz), 7.50–7.57 m (5H, H-Ar), 7.84–7.86 m (1H, H-Ar), 7.86 s (1H, H$^{8'}$), 8.01–8.04 m (2H, H-Ar), 8.10–8.11 m (2H, H-Ar), 8.25 d. d (2H, H^2,H^6, Ph, ^3J = 8.2, ^4J = 1.7 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.1* (MeO), 77.4 (C$^{2'}{}_{spiro}$), 109.5 (C$^{4a'}$), 113.0* (C^3, C^5, 4-MeOC$_6$H$_4$), 118.7* (C$^{8'}$), 120.6 (C$^{9a'}$), 124.3* (CH, Ar), 124.8* (CH, Ar), 125.6* (CH, Ar), 127.4* (C^2, C^6 Ph), 127.8 (C^1, 4-MeOC$_6$H$_4$), 128.9* (C^3, C^5, Ph), 129.9* (C^4, Ph), 130.0 * (CH, Ar), 130.15* (CH, Ar), 130.2 (C^2, 2-NO$_2$C$_6$H$_4$), 131.1* (C^2, C^6, 4-MeOC$_6$H$_4$), 134.6* (CH, Ar), 137.38* (CH, Ar), 137.41 (C^1, Ph), 138.0* (CH, Ar), 138.4 (Ar), 139.3 (Ar), 142.8 (C$^{9b'}$), 147.2 (C$^{9'}$), 148.0 (C^1, 2-NO$_2$C$_6$H$_4$), 156.3 (C$^{7'}$), 159.4 (C$^{5a'}$), 159.8 (C^4, 4-MeOC$_6$H$_4$), 162.7 (C=O$_{amide}$), 190.3 (C=O$_{ketone}$), 191.2 (C=O$_{ketone}$). Found, %: C 67.60; H 3.59; N 8.92. $C_{36}H_{22}N_4O_6S$. Calculated, %: C 67.70; H 3.47; N 8.77.

3′-(2-Bromo-4-nitrophenyl)-9′-(4-methoxyphenyl)-7′-phenyl-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine]1,3,4′(3′*H*)-trione (13e). Yield 75%, mp 156°C, yellow powder. IR spectrum, ν, cm^{-1}: 3356 (N–H), 1753, 1720, 1666 (C=O), 1528 (NO$_2$, as), 1346 (NO$_2$, s). ^{1}H NMR spectrum, δ, ppm: 3.61 s (3H, MeO), 6.56 d (2H, H^3, H^5, 4-MeOC$_6$H$_4$, ^3J = 8.6 Hz), 7.07 s (1H, NH), 7.06 d (1H, H^6, 2-Br-4-NO$_2$C$_6$H$_3$, ^3J = 8.6 Hz), 7.37 d (2H, H^3, H^5, 4-MeOC$_6$H$_4$, ^3J = 8.6 Hz), 7.50–7.56 m (3H, H^3–H^5, Ph), 7.87 s (1H, H$^{8'}$), 7.89 d (1H, H-Ar, ^3J = 7.7 Hz), 8.03–8.06 m (2H, H-Ar), 8.14–8.15 m (2H, H-Ar), 8.25 d. d (2H, H^2,H^6, Ph, ^3J = 8.2, ^4J = 1.8 Hz), 8.44 d (1H, H^3, 2-Br-4-NO$_2$C$_6$H$_3$, ^4J = 2.7 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 55.1* (MeO), 77.4 (C$^{2'}{}_{spiro}$), 109.4 (C$^{4a'}$), 113.0* (C^3, C^5, 4-MeOC$_6$H$_4$), 118.7* (C$^{8'}$), 120.6 (C$^{9a'}$), 123.8* (CH,Ar), 124.5* (CH, Ar), 125.0* (CH, Ar), 126.5 (CBr), 127.4* (C^2, C^6, Ph), 127.8 (C^1, 4-MeOC$_6$H$_4$), 127.9* (CH, Ar), 128.9* (C^3, C^5, Ph), 130.1* (C^4, Ph), 130.8* (CH, Ar), 131.1* (C^2, C^6, 4-MeOC$_6$H$_4$), 137.4 (C^1, Ph), 137.5* (CH, Ar), 138.1* (CH, Ar), 138.5 (Ar), 139.4 (Ar), 142.6 (Ar), 142.8 (C$^{9b'}$), 147.2 (C$^{9'}$), 148.1 (C Ar), 156.3 (C$^{7'}$), 158.5 (C$^{5a'}$), 159.8 (C^4, 4-MeOC$_6$H$_4$), 162.7 (C=O$_{amide}$), 189.8 (C=O$_{ketone}$), 191.0 (C=O$_{ketone}$). Found, %: C 60.21; H 3.09; N 7.89. $C_{36}H_{21}BrN_4O_6S$. Calculated, %: C 60.26; H 2.95; N 7.81.

9′-(4-Bromophenyl)-7′-phenyl-3′-(*o*-tolyl)-1′*H*-spiro[indene-2,2′-pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidine]-1,3,4′(3′*H*)-trione (13f). Yield 72%, mp 163°C, yellow powder. IR spectrum, ν, cm^{-1}: 3193 (N–H), 1752, 1717, 1657 (3 C=O). ^{1}H NMR spectrum, δ, ppm: 2.23 s (2-C**H**$_3$C$_6$H$_4$), 6.59 d (1H, H^6, 2-CH$_3$C$_6$H$_4$, ^3J = 7.6 Hz), 6.70 s (1H, NH), 6.89–6.93 m (1H, H^5, 2-CH$_3$C$_6$H$_4$), 7.10–7.14 m (1H, H^4, 2-CH$_3$C$_6$H$_4$), 7.22 d (1H, H^3, 2-CH$_3$C$_6$H$_4$, ^3J = 7.7 Hz), 7.25 d (2H, 4-BrC$_6$H$_4$, ^3J = 8.6 Hz), 7.40 d (2H, 4-BrC$_6$H$_4$, ^3J = 8.6 Hz), 7.50–7.55 m (3H, H^3–H^5, Ph), 7.79 d (1H, H-Ar, ^3J = 7.7 Hz), 7.92 s (1H, H$^{8'}$), 7.97–8.02 m (1H, H-Ar), 8.11–8.12 m (2H, H-Ar), 8.26 d. d (2H, H^2, H^6, Ph, ^3J = 8.1, ^4J = 1.6 Hz). ^{13}C NMR spectrum (DEPTQ), δ_C, ppm: 18.0* (MeAr), 76.9 (C$^{2'}{}_{spiro}$), 111.1 (C$^{4a'}$), 118.7* (C$^{8'}$), 120.7* (C$^{9a'}$), 122.5 (CBr), 123.8* (CH, Ar), 124.7* (CH, Ar), 126.5* (C^5, 2-CH$_3$C$_6$H$_4$), 127.3* (C^2, C^6, Ph), 127.6* (C^6, 2-CH$_3$C$_6$H$_4$), 128.5* (C^4, 2-CH$_3$C$_6$H$_4$), 128.9* (C^3, C^5, Ph), 130.1* (C^4, Ph), 130.4* (C^3, C^5, 4-BrC$_6$H$_4$), 130.8* (C^3, 2-CH$_3$C$_6$H$_4$), 131.7* (C^2, C^6, 4-BrC$_6$H$_4$), 134.8 (C^1, 4-BrC$_6$H$_4$), 136.0 (C^2, 2-CH$_3$C$_6$H$_4$), 137.2* (CH, Ar), 137.3 (C^1, Ph), 137.9* (CH, Ar), 138.2 (C^1, 2-CH$_3$C$_6$H$_4$), 138.7 (Ar), 139.4 (Ar), 141.9 (C$^{9b'}$), 146.6 (C$^{9'}$), 156.1 (C$^{7'}$), 159.0 (C$^{5a'}$), 162.4 (C=O$_{amide}$), 190.9 (C=O$_{ketone}$), 192.9 (C=O$_{ketone}$). Found, %: C 65.80; H 3.51; N 6.39. $C_{36}H_{22}BrN_3O_3S$. Calculated, %: C 65.86; H 3.38; N 6.40.

A study of the effectiveness of compounds as antidotes 2,4-D was carried out on sunflower seedlings at the All-Russian Research Institute of Biological Plant Protection (Krasnodar) using the roll method according

to the procedure reported in [67, 68]. The protective (antidote) effect was determined by increasing the length of the hypocotyl and root in the herbicide + antidote experiment relative to the indicated values in the case of seed treatment with only 2,4-D [variant "herbicide" (standard)]. The experimental data were statistically processed using Student's t-test at $p = 0.95$. The antidote effect (%) was calculated by the formula (1).

$$A = (L_o/L_e)\times 100, \quad (1)$$

where A—antidote effect, L_o—the length of the organ (mm) in the experimental group of seedlings (in the "herbicide + antidote" experiment); L_e—organ length (mm) in a group of seedlings treated with a 2,4-D standard.

The growth regulator activity was studied using solutions of the studied compounds of various concentrations (10^{-2}–10^{-5}%). The effect was evaluated by increasing the length of the stem and root in the group of seedlings treated with substances relative to the indicated values in the control group.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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