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SYNTHESIS OF SUBSTITUTED 4-OXO-3,4-DIHYDRO-THIENO[3,4-*d*]PYRIMIDINES AND COMPARISON OF THEIR PROPERTIES WITH THOSE OF POSITIONALLY ISOMERIC THIENOPYRIMIDINONES AND BENZO ISOSTERES

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2-Arylmethyl- and 2-arylmethyl-3-methyl-substituted 3,4-dihydrothieno[3,4-d]pyrimidin-4-ones were synthesized starting from 2-cyanomethylbenzoic acid and methyl 3-amino-4-thiophenecarbonate, obtained in situ from its hydrochloride by a new method which gives an increased yield of the desired products. The physicochemical properties and the biological potential of the compounds synthesized have been compared with analogous substituted 2,3-dimethylthieno[2,3-d][pyrimidinones, thieno[3,2-d]pyrimidinones, and their benzene isosteres. The differences associated with the position of the sulfur atom, are most clearly reflected in the electronic spectra. On the basis of calculated data, the transition from derivatives of 4-oxo-3,4-benzopyrimidines to their analogous thieno isosteres leads to changes in the profiles of their biological activities.

Keywords: isosteres, positionally isomers, derivatives of 4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidine, calculation of biological activity, cyclization.

In a continuation of our investigation of positionally isomeric thienopyrimidones [1] in this work we describe the synthesis of some substituted thieno[3,4-*d*]pyrimidin-4-one system (**A**) and compare the properties of these compounds with those of known analogous derivatives of the thieno[2,3-*d*]pyrimidin-4-one (**B**) and thieno[3,2-*d*]pyrimidin-4-one (**C**) systems and also their benzene isosteres of the quinazolin-4-one (**D**) system. Derivatives of system **A** have been studied far less than those of derivatives of systems **B** and **C.** According the date of Beilstein at the beginning of 2009 the number of references to compounds of series **A**, **B,** and **C** were in the ratio 1:100:40. However even the small number of publications indicates the wide pharmacological profile of derivatives of thieno[3,4-*d*]pyrimidin-4-one.

For example, substances are known which possess potential anticancer [2-4] and vasodilator [5] properties, and aldose inhibitors of aldose reductase [6]. The representatives of this series which are under

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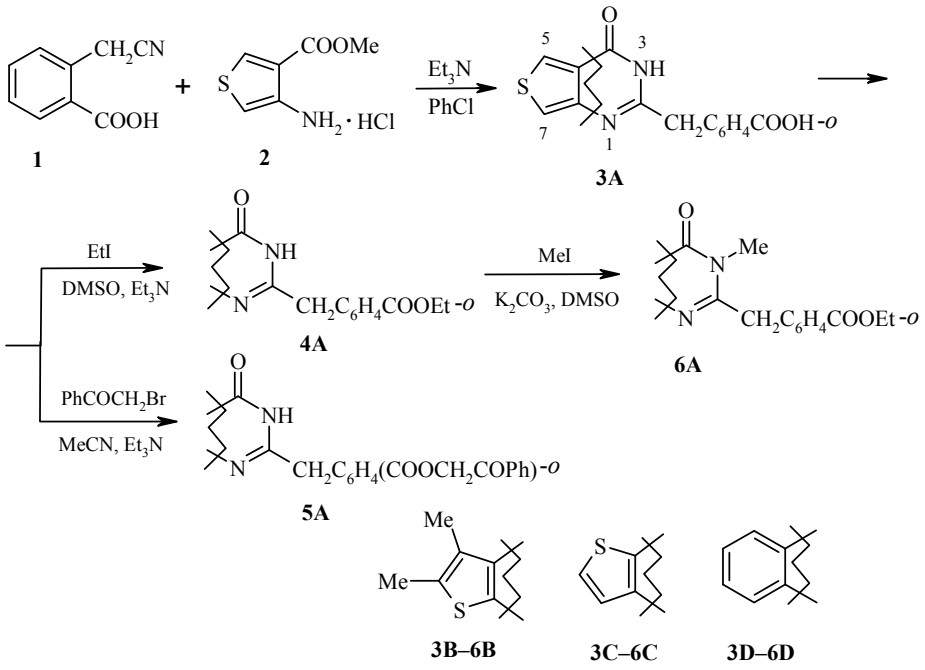
investigations for treatment of AIDS [7], H_2- [8] and H_1-histamine receptors [9] antagonists have reached the high level of pharmacological investigations. Derivatives of thieno[3,4-*d*]pyrimidin-4-one with benzyl or modified benzyl substituents in position 2 have not been described.

Starting from 2-cyanomethylbenzoic acid (**1**) and methyl 3-amino-4-thiophenecarboxylate we have synthesized compounds of types **3-6** of system **A** (series **A**) by the scheme shown below – these are analogs of the derivatives of systems **B**, **C**, and **D** which we prepared previously: **3B-6B**, **3C-6C** [1], and **3D-6D** [10, 11]. In connection with the known instability of the amino ester starting material [12], the latter was obtained *in situ* from its hydrochloride **2** by adding to the reaction mixture the calculated amount of Et_3N. The proposed new method allowed the yield of product **3A** to increase to 90%.



1 **2** **3A** **4A** **6A** **5A** **3B–6B** **3C–6C** **3D–6D**

For the others the conditions for obtaining derivatives **3-6** of series **A** were analogous to those we described previously for the synthesis of compounds **3-6** of series **B-D** [1, 10, 11].

Acid **3A** is a colorless finely crystalline substance which, like its analogs **3B-3D**, has amphoteric properties: it dissolves both in 2 N base solution and partially in 2 N HCl. The melting points of these acids fall in the following order: **3C** > **3D** > **3B** ≈ **3A**. A different sequence is observed for the ethyl esters **4A-4D**: **4B** > **4D** > **4C** > **4A**, which is retained for the phenacyl esters **5A-5D**, and for the products of alkylation of the esters **4** – methyl-substituted **6A-6D**. So among the compounds compared, derivatives of series **A** are the most readily melted. Differences in chemical behavior and also in yields for the positional isomers **3-5** for series **A-C** were not noted.

Table 1. IR Spectra of the Compounds Synthesized

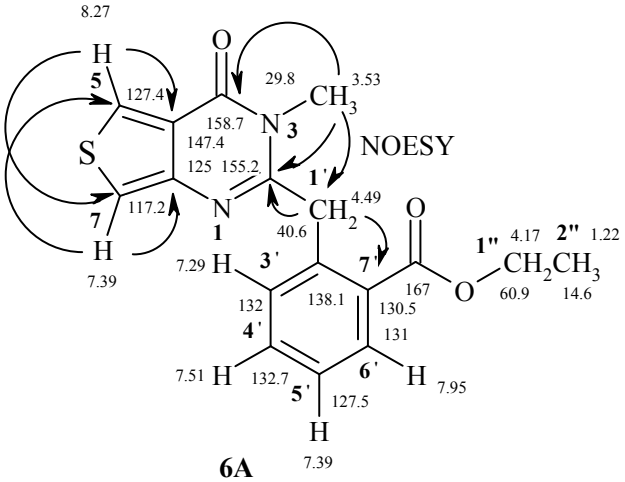
Compound	ν, cm^{-1}					
	O–C	C(=O)–OH	C=N	C(4)=O	C_6H_4C=O	PhC=O
3A	1254	—	1620	1682		—
4A	1262	1077	1608	1681	1712	—
5A	1280	1128	1625	1669	1692	1724
6A	1267	1082	1598	1686		—

The structure of compound **6A** was established on the basis of its spectral characteristics. It is known [13] that alkylation of the well studied thienopyrimidin-4-ones is possible both at atoms N(1), N(3), and the oxygen atom. We excluded the structure of the O-methylated product on the basis of analysis of the IR and ^{1}H NMR spectra (Tables 1 and 2 respectively).

It was shown previously that alkylation at atom N(1) led to a shift of the carbonyl stretching vibration to 1630 cm^{-1}, whereas the alternative alkylation at atom N(3) led to a shift to 1655-1660 cm^{-1} [11]. In the infrared spectrum of compound **6A** the band discussed was found at 1686 cm^{-1} (see Table 1). Since the possible 1-methyl- and 3-methyl-substituted compounds have identical structural fragments the spectra for the ^{1}H and ^{13}C do not permit a conclusion on the direction of alkylation. Therefore we obtained two-dimensional NMR spectra for product **6A** with homonuclear (COSY, NOESY) and heteronuclear ^{1}H-^{13}C correlations across one (HMQC) or 2-3 bonds (HMBC). In the NOESY spectrum there is only a single cross peak between the signals of the protons of the NCH_3 and CH_3 groups which completely confirms the structure of **6A**: on alkylation at N(1) a cross peak with the signal of proton H-7 also would appears.

A basic indicator for the structure of **6A** is the correlation signal of the protons of the NCH_3 group at 3.53 ppm with the signal of the carbon atom of either the carbonyl group (C(4)=O) or COOEt) at 158.7 ppm. Such a correlation is impossible for the group $N(1)CH_3$ since the carbon atoms of the C=O groups are more than three chemical bonds away. The HMQC, HMBC, and NOESY correlations are cited in Table 3. The signals of the protons of the benzene ring can be assigned if it is assumed that the protons of the phenyl group neighboring the COOEt substituent correspond to the chemical shift 7.95 ppm. The assignments of the remaining signals of the spin systems then follow from the COSY correlation.

The ^{1}H NMR spectral data for all the synthesized compounds **3-6** of series **A** are cited in Table 2. Comparison with the known spectral data of the **3-6** analogs of series **B**, **C** [1] and **D** [10, 11] shows that change in the position of the S atom and its replacement by the CH=CH unit affects the chemical shifts of the signal of proton H-3 and the signals of the protons of the 2-CH_3 and 3-CH_3 groups: in all the compounds of series **A** these signals are found at a stronger field, and the signals of their analogs in series **C** are at a weaker field. However these differences are not very large and the most notable for the signals of the NH group was no more than 0.65 ppm.



6A

HMQC and HMBC Correlation spectra for compound 6A.
Signals are assigned for all carbon atoms, the arrows show the most important HMBC correlations, on which all the assignments are based.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	4-Oxothieno[3,4-*d*]pyrimidin-2-yl			2-$CH_2C_6H_4COOR$					
					C_6H_4				
	H-3/3-CH_3 (s)	H-5 (1H, d, ^3J = 3.5)	H-7 (1H)	CH_2 (2H, s)	H-3' (1H, d, ^3J = 7.5)	H-4' (1H, t, ^3J = 7.5)	H-5' (1H, t, ^3J = 7.5)	H-6' (1H, d, ^3J = 7.5)	R
3A	11.71 (1H)	8.38	7.54 (d, ^3J = 3.5)	4.25	7.35	7.38	7.51	7.89	—*
4A	11.77 (1H)	8.41	7.56 (m)	4.25	7.42 (2H, m)		7.56-7.88 (2H, m)		4.16 (2H, q, ^3J = 7.5, CH_2); 1.16 (3H, t, ^3J = 7.5, CH_3)
5A	11.74 (1H)	8.40	7.57 (m)	4.28	7.45	7.70	7.49	8.07	5.67 (2H, s, CH_2); 7.98 (2H, d, ^3J = 7.5, *o*-H Ph); 7.63 (1H, t, ^3J = 7.5, *p*-H Ph); 7.57 (3H, m, H Ar)
6A	3.54 (3H)	8.27	7.39 (d, ^3J = 3.5)	4.49	7.29	7.51	7.39	7.95	4.17 (2H, q, ^3J = 7.5, CH_2); 1.22 (3H, t, ^3J = 7.5, CH_3)

* The signal is not seen because of water impurity in the DMSO.

TABLE 3. Results of Homonuclear (NOESY) and Heteronuclear (HMBC and HMQC) Correlation Experiments for Compound **6A**

Atom position (see diagram)	δ, ppm	HMQC	HMBC	NOESY
5	8.27	127.4	117.2; 125.0; 147.4; 158.7	–
6'	7.95	131.0	132.7; 138.1; 167.0	7.39
7, 5'	7.39	117.2; 127.5	125.0 (сл); 127.4; 130.5; 132.0; 147.4 (сл)	7.51; 7.95
4'	7.51	132.7	131.0; 132.0; 138.1	7.29; 7.39
3'	7.29	132.0	40.6; 127.5; 130.5; 132.7; 167.0 (сл)	4.49; 7.51
3	3.53	29.8	155.2; 158.7	4.49
1'	4.49	40.6	130.5; 132; 138.1; 155.2; 167.0 (sl)	3.53; 7.29
1"	4.17	60.9	14.6; 167.0	1.22
2"	1.22	14.6	60.9	4.17

The IR spectra of the compared compounds **3-6** of series **A-D** are similar (see Table 1 and [1, 10, 11]). For all of the esters **4-6** both intense "ester bands" of the C–O–C stretching vibration in the 1075-1128 range and carbonyl bands in the 1260-1280 cm^{-1} range. In the spectra of acids **3** of series **A, B, D** and the esters **6** of series **A** and **D** the absorptions of the C(4)=O and COOEt groups are observed as a single broad band.

Esters **4** of series **A-C** have intense absorptions in the UV region 220-315 nm. A notable difference in their electronic spectra (see Table 4 and [1, 10]) is the position of the long wavelength maxima of the absorption of the positional isomers **A**, **B** (313 and 312 respectively) and **4C** (293 nm).The shift of these maxima (similar in intensity) relative to the less intense absorption maximum of the isostere **4D** should be noted: bathochromic (~8-9 nm) in the case of compounds **4A**, **4B** and hypsochromic (~ 11 nm) for compound **4C**. The spectra of the acids **3A-D** differ only in intensity from the spectra of their ethyl esters **4A-D**. Alkylation at atom N(3) also does not change the electron density distribution which is reflected in the similar spectra of the esters **6** of series **A-D**.

To elucidate the biological potentials of the substances synthesized with the help of the PASS programs (Prediction of Activity Spectra for Substances) [14-16] an estimate of the spectra of their biological activity was produced. The basis for the choice of the active compounds was the position in a multilevel estimate of the surrounding atoms and a comparison of the calculated 2D descriptors with a choice of either high activity or an absence of activity. The find results of the program are presented as a probability of the appearance of activity (p_a) or inactivity (p_i) as parts of the unit. For each compound the spectrum of more than 3000 types of activities was estimated, a threshold for activity was chosen $p_a > 0.8$, $p_i < 0.2$. From the analysis of the results of the calculations (see Table 5) it was unexpectedly shown that none of the compounds **3-6** of series **B** fell within the limits chosen. According to the predictive data, on transition from derivatives of series **D** to their thiophene isosteres a change in the profile of biological activity occurs.

TABLE 4. Electronic Spectra of Esters **4** of series **A-D**

λ_{max}, nm (log ε)			
A	**B** [1]	**C** [1]	**D** [10]
235 (4.72)	220 (4.68)	236 (4.81)	230 (4.80)
266 (4.24)	260 (4.27)	265 (4.25)	266 (4.22)
313 (4.30)	312 (4.41)	293 (4.40)	304 (3.94)

TABLE 5. Results of Estimates of Biological Activity of the Compounds Synthesized According to the PASS Program

Compound	Probable type of biological activity	p_a
3A	Agonist of dopamine D_4-receptor	0.808
3C	Agonist of dopamine D_4-receptor	0.858
	Antiischemic (cerebral)	0.836
	Antiischemic	0.831
3D	Inhibitor of arylalkylacylamidazes	0.809
4A,**D**, **6A**	Inhibitor of (4S)-limonene synthetase	0.814-0.853
4C	Agonist of dopamine D_4-receptor	0.840
	Antiischemic (cerebral)	0.830
	Antiischemic	0.826
	Inhibitor of (4S)-limonene synthetase	0.803
5C	Antiischemic	0.835
	Agonist of dopamine D_4-receptor	0.822
6C	Agonist of dopamine D_4-receptor	0.838
	Inhibitor of (4S)-limonene synthetase	0.807

EXPERIMENTAL

IR spectra (KBr tablets) were recorded with a Perkin-Elmer Spectrum BX instrument, UV spectra of $5 \cdot 10^{-5}$ M DMF solutions were recorded with a Perkin-Elmer Lambda 20 UV-Vis spectrometer. ^{1}H and ^{13}C NMR spectra of the compounds synthesized, two-dimensional ^{1}H NMR spectroscopy, and also HMQC and HMBC heteronuclear correlation spectra were recorded with a Varian Mercury 400 (400 and 100 MHz) instrument. All two-dimensional experiments were carried with gradient selection of the beneficial signals. The mixing time of the impulse sequences corresponded to $^1J_{CH}$ = 140.0 and $^{2\text{-}3}J_{CH}$ = 8.0 Hz. The quantity of increments in the COSY and HMQC spectra was 128, and in the HMBC spectra was 400. The ^{1}H NMR spectra of the remaining compounds were measured with a Bruker Avance DRX 500 (500 MHz). In all cases the solvent was DMSO-d_6 and the internal standard was TMS. The individuality of the compounds synthesized was confirmed with an Agilent 1100 series mass-chromatograph with an Agilent LC/MSD SL selective detector. Samples were introduced in a trifluoroacetic acid matrix, an ionization was by EI. Melting points were measured in Pyrex capillaries in a Thiele apparatus and were corrected.

The hydrochloride of the amino ester **2** was prepared using method [2].

2-(4-Oxo-3,4-dihydrothieno[3,4-*d*]pyrimidin-2-yl)methylbenzoic Acid (3A). To a suspension of hydrochloride **2** (20 mmol) in chlorobenzene (5ml) were added successively triethylamine (3 ml, 40 mmol), then with stirring 2-cyanomethylbenzoic acid (1.61 g, 10 mmol). The mixture was boiled for 10 min. After evaporating the solvent in vacuum 1,4-dioxane (40 ml) was added to the residue and the suspension was boiled for 2 h. After cooling, the precipitate was filtered off and washed with diethyl ether to give compound **3A**, 2.57 g (90%); mp 270-271°C (DMF). Mass spectrum, *m/z*: 287 [M^++1]. Found, %: C 58.75; H 3.50; N 9.80; S 11.22. $C_{14}H_{10}N_2O_3S$. Calculated, %: C 58.73; H 3.52; N 9.78; S 11.20.

Esters 4-6 of series **A** were prepared by the method of paper [1].

Ethyl 2-(4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidin-2-yl)methylbenzoate (4A) was obtained from the reaction of EtI with acid **3A**. Yield 85%; mp 85-86°C (DMF). Mass spectrum, *m/z*: 315 [M^++1]. Found, %: C 61.15; H 4.50; N 8.89; S 10.19. $C_{16}H_{14}N_2O_3S$. Calculated, %: C 61.13; H 4.49; N 8.91; S 10.20.

2-Oxo-2-phenyl 2-(4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidin-2-yl)methylbenzoate (5A) was obtained from acid **3A** and phenacyl bromide. Yield 92%; mp 200-201°C (DMF). Mass spectrum, *m/z*: 405 [M^++1]. Found: %: C 68.00; H 4.12; N 7.25; S 8.29. $C_{22}H_{16}N_2O_3S$. Calculated, %: C 68.03; H 4.15; N 7.21; S 8.25.

Ethyl 2-(3-Methyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimidin-2-yl)methylbenzoate (6A) was obtained from ester **4A** and MeI. Yield 85%; mp 115-116°C (DMF). Mass spectrum, *m/z*: 329 [M^++1]. Found, %: C 62.16; H 4.88; N 8.52; S 9.78. $C_{17}H_{16}N_2O_3S$. Calculated, %: C 62.18; H 4.91; N 8.53; S 9.76.

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