DOI 10.1007/s11094-015-1317-6
Pharmaceutical Chemistry Journal, Vol. 49, No. 8, November, 2015 (Russian Original Vol. 49, No. 8, August, 2015)

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF *N*-5-DIARYL-7-METHYL-3-OXO-2,3-DIHYDRO-5*H*-[1,3]THIAZOLO[3,2-*a*]PYRIMIDINE-6-CARBOXAMIDE HYDROCHLORIDES

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 49, No. 8, pp. 18 – 20, August, 2015.

Original article submitted September 4, 2014.

N,5-Diaryl-7-methyl-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochlorides were synthesized via the reaction of *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides with ethyl chloroacetate. Some of the synthesized compounds exhibited antimicrobial activity.

Keywords: *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides, ethyl chloroacetate, 5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxyamides, antimicrobial activity.

One of the most important problems in pharmaceutical chemistry is the design of highly effective and nontoxic drugs. The solution involves targeted synthesis and discovery of new biologically active compounds. In this respect, tetrahydropyrimidine-2(1*H*)-thiones, their derivatives, and condensed heterocycles based on them are some of the most promising classes of chemical compounds [1 – 7]. 5*H*-Thiazolo[3,2-*a*]pyrimidine derivatives are known to possess anti-inflammatory, antiparkinson, and antiherpes activity [8].

The synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines via the reaction of tetrahydropyrimidine-2(1*H*)-thione derivatives with α-halocarboxylate esters was reported [9].

We investigated the reaction of *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides with ethyl chloroacetate in order to prepare new heterocyclic compounds and study their antimicrobial activity. The reaction occurred upon storing the reagents at 120°C for 15-20 without a solvent and formed *N*,5-diaryl-7-methyl-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamides (**I**-**IX**) (Scheme 1).

Apparently, the first step involved nucleophilic substitution of the Cl atom in ethyl chloroacetate as a result of attack by the mercapto S atom formed via isomerization of the starting compound with subsequent intramolecular cyclization of the intermediate (i) (Scheme 2).

Compounds **I**-**IX** were yellow crystalline compounds that were soluble in DMF and DMSO and with heating in HOAc and EtOH and insoluble in H_2O, toluene, and benzene.

IR spectra of the thiazolopyrimidine hydrochlorides had a characteristic high-frequency absorption band in the range 1752 – 1768 cm^{-1} that belonged to thiazoline carbonyl stretching vibrations and bands due to amide stretching vibrations (1648 – 1688) and a C=C bond (1600 – 1624). The high-frequency shift of the lactam carbonyl absorption band was apparently explained by protonation of the neighboring N atom.

PMR spectra of **I**-**IX** showed resonances for aromatic protons and groups bonded to the aromatic ring in addition to resonances for 7-CH_3 protons at 1.80 – 2.28 ppm, a singlet for H-5 at 5.97 – 6.20, a singlet for the amide NH proton at 9.45 – 9.86, and doublets for methylene protons in the range 4.15 – 4.30.

^{13}C NMR spectra of **IX** included chemical shifts of C atoms that confirmed the proposed structure (see Experimental).

Thus, the observed reaction allowed 5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidine hydrochlorides with the *N*-arylamide

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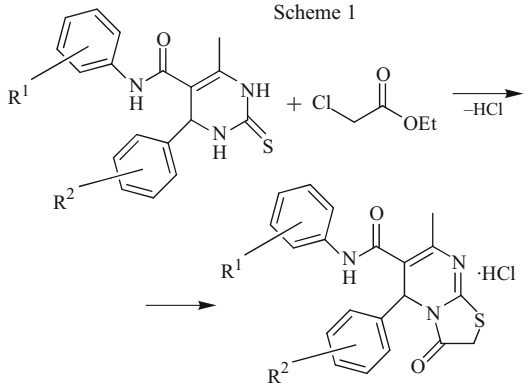
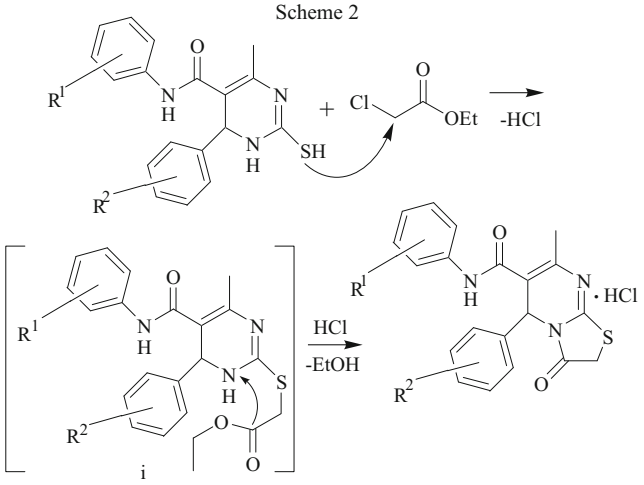
Scheme 1



I – IV: R^2=3,4-$(CH_3O)_2$ (I), 3-F (II), 4-Cl (III), 4-CH_3 (IV), R^1=2-CH_3; V, VI: R^2=4-CH_3 (V), 2-F (VI), R^1=2,4-$(CH_3)_2$; VII – IX: R^2=4-CH_3O (VII), 4-C_2H_5O (VIII), 3-F (IX), R^1=2-Cl.

Scheme 2



pharmacophore in their structures to be prepared for the first time.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded in mineral oil on a Specord M-80 spectrophotometer. PMR and ^{13}C NMR spectra were recorded in DMSO-d_6 with TMS internal standard on a Bruker 300 spectrometer (operating frequency 300 and 75 MHz). Resonances of CH–, CH_2–, CH_3–, and quaternary C atoms were observed using a DEPT experiment. Mass spectra were obtained on a Finnigan MAT INCOS-50 instrument with ionization energy 70 eV. Elemental analyses were performed on a PerkinElmer 2400 instrument and agreed with those calculated. Melting points were measured on a Buchi M-565 apparatus.

***N*-(2-Methylphenyl)-5-(3,4-dimethoxyphenyl)-7-methyl-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (I) (general method).** A mixture of ethyl chloroacetate (3 mL, 35 mmol) and the appropriate tetrahydropyrimidine-2(1*H*)-thione (1.8 mmol) was heated for 20 min at 120°C. The resulting crystals were filtered off and rinsed with EtOH. Yield 0.55 g (64%). Yellow crystals, mp 234 – 236°C (EtOH). IR spectrum, ν, cm^{-1}: 1620 (C=C), 1688 (CON), 1768 (CO), 3296 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 1.92 (s, 3H, 7-CH_3), 2.24 (s, 3H, $\underline{CH_3}C_6H_4$), 3.76 and 3.77 (2s, 6H, CH_3O), 4.19 (d, 1H, J 11.4 Hz) and 4.23 (d, 1H, J 11.4 Hz, 2-CH_2), 5.77 (br.s, 1H, N^+H), 6.02 (c, 1H, H-5), 6.87 – 7.21 (m, 7H, $CH_3\underline{C_6H_4}$, $(CH_3O)_2\underline{C_6H_3}$), 9.56 (s, 1H, NH). $C_{23}H_{23}N_3O_4S \cdot HCl$.

7-Methyl-*N*-(2-methylphenyl)-5-(3-fluorophenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (II). Yield 0.53 g (68%). Yellow crystals, mp 224 – 226°C (EtOH). IR spectrum, ν, cm^{-1}: 1608 (C=C), 1648 (CON), 1752 (CO), 3296 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 1.86 (s, 3H, 7-CH_3), 2.28 (s, 3H, $\underline{CH_3}C_6H_4$), 4.19 (d, 1H, J 18.9 Hz) and 4.25 (d, 1H, J 18.9 Hz, 2-CH_2), 6.11 (c, 1H, H-5), 7.04 – 7.46 (m, 8H, $CH_3\underline{C_6H_4}$, FC_6H_4), 7.48 (br.s, 1H, N^+H), 9.68 (s, 1H, NH). $C_{21}H_{18}FN_3O_2S \cdot HCl$.

7-Methyl-*N*-(2-methylphenyl)-5-(4-chlorophenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (III). Yield 0.48 g (59%). Yellow crystals, mp 250 – 252°C (EtOH). PMR spectrum ^1H, δ, ppm (J, Hz): 1.82 (s, 3H, 7-CH_3), 2.19 (s, 3H, $\underline{CH_3}C_6H_4$), 4.15 (d, 1H, J 17.6 Hz) and 4.32 (d, 1H, J 17.6 Hz, 2-CH_2), 5.97 (c, 1H, H-5), 6.87 – 7.43 (m, 8H, $CH_3\underline{C_6H_4}$, ClC_6H_4), 7.52 (br.s, 1H, N^+H), 9.51 (s, 1H, NH). $C_{21}H_{18}ClN_3O_2S \cdot HCl$.

7-Methyl-*N*-(2-methylphenyl)-5-(4-methylphenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (IV). Yield 0.42 g (55%). Yellow crystals, mp 216 – 218°C (EtOH). PMR spectrum ^1H, δ, ppm (J, Hz): 1.91 (s, 3H, 7-CH_3), 2.23 and 2.32 (2s, 6H, $2\underline{CH_3}C_6H_4$), 4.15 (d, 1H, J 11.4 Hz) and 4.22 (d, 1H, J 11.4 Hz, 2-CH_2), 6.04 (c, 1H, H-5), 7.05 – 7.57 (m, 8H,

TABLE 1. Antimicrobial Activity of **I-IX**

Compound	MIC, μg/mL	
	Staphylocoñcus aureus	*Escherichia coli*
I	500	1000
II	500	1000
III	500	500
IV	500	500
V	1000	1000
VI	500	1000
VII	500	500
VIII	1000	1000
IX	500	1000
Chloramine B	500	250
Dioxidine	62.5 – 1000	3.9 – 62.5

2$CH_3\underline{C_6H_4}$), 7.76 (br.s, 1H, N^+H), 9.81 (s, 1H, NH). $C_{22}H_{21}N_3O_2S \cdot HCl$.

7-Methyl-*N*-(2,4-dimethylphenyl)-5-(4-methylphenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (V). Yield 0.46 g (58%). Yellow crystals, mp 214 – 216°C (EtOH). IR spectrum, ν, cm^{-1}: 1604 (C=C), 1672 (CON), 1760 (CO), 3392 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 1.86 (s, 3H, 7-CH_3), 2.24, 2.32, 2.59 (3s, 9H, $(\underline{CH_3})_2C_6H_3$+$\underline{CH_3}C_6H_4$), 4.22 (d, 1H, J 18.9 Hz) and 4.25 (d, 1H, J 18.9 Hz, 2-CH_2), 6.03 (c, 1H, H-5), 6.96 – 7.49 (m, 7H, $CH_3\underline{C_6H_4}$, $(CH_3)_2\underline{C_6H_3}$), 7.55 (br.s, 1H, N^+H), 9.48 (s, 1H, NH). $C_{23}H_{23}N_3O_2S \cdot HCl$.

7-Methyl-*N*-(2,4-dimethylphenyl)-5-(2-fluorophenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (VI). Yield 0.50 g (62%). Yellow crystals, mp 214 – 216°C (EtOH). PMR spectrum ^1H, δ, ppm (J, Hz): 1.80 (s, 3H, 7-CH_3), 2.10 and 2.20 (2s, 6H, $(\underline{CH_3})_2C_6H_3$), 4.15 (d, 1H, J 18.9 Hz) and 4.25 (d, 1H, J 18.9 Hz, 2-CH_2), 6.20 (c, 1H, H-5), 6.90 – 7.50 (m, 7H, $F\underline{C_6H_4}$, $(CH_3)_2\underline{C_6H_3}$), 7.61 (br.s, 1H, N^+H), 9.45 (s, 1H, NH). Mass spectrum (70 eV), *m/z* (I_{rel}, %): 409 $[M\text{-}HCl]^+$ (11), 289 $[M\text{-}(CH_3)_2C_6H_3NH]^+$ (100), 120 $[(CH_3)_2C_6H_3NH]^+$ (30), 77 $[Ph]^+$ (26), 36 $[HCl]^+$ (53). $C_{22}H_{20}FN_3O_2S \cdot HCl$.

7-Methyl-*N*-(2-chlorophenyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (VII). Yield 0.59 g (71%). Yellow crystals, mp 217 – 219°C (EtOH). IR spectrum, ν, cm^{-1}: 1624 (C=C), 1676 (CON), 1760 (CO), 3368 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 2.23 (s, 3H, 7-CH_3), 3.69 (s, 3H, CH_3O), 4.18 (d, 1H, J 18.3 Hz) and 4.32 (d, 1H, J 18.3 Hz, 2-CH_2), 5.97 (c, 1H, H-5), 6.80 – 7.41 (m, 8H, ClC_6H_4, $CH_3O\underline{C_6H_4}$), 8.12 (br.s, 1H, N^+H), 9.73 (s, 1H, NH). Mass spectrum (70 eV), *m/z* (I_{rel}, %): 427 $[M]^+$ (11), 273 $[M\text{-}C_6H_4ClNHCO]^+$ (11), 301 $[M\text{-}C_6H_4ClNH]^+$ (100), 36 $[HCl]^+$ (21). $C_{21}H_{18}ClN_3O_3S \cdot HCl$.

7-Methyl-*N*-(2-chlorophenyl)-5-(4-ethoxyphenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (VIII). Yield 0.52 g (61%). Yellow crystals, mp 213 – 215°C (EtOH). IR spectrum, ν, cm^{-1}: 1600 (C=C), 1676 (CON), 1752 (CO), 3296 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 1.34 (t, 3H, $\underline{CH_3}CH_2O$, J 7.2 Hz), 4.05 (q, 2H, $CH_3\underline{CH_2}O$, J 7.2 Hz), 2.28 (s, 3H, 7-CH_3), 4.24 (d, 1H, J 18.3 Hz) and 4.30 (d, 1H, J 18.3 Hz, 2-CH_2), 6.07 (c, 1H, H-5), 6.93 – 7.52 (m, 8H, ClC_6H_4, $C_2H_5O\underline{C_6H_4}$), 6.20 (br.s, 1H, N^+H), 9.82 (s, 1H, NH). $C_{22}H_{20}ClN_3O_3S \cdot HCl$.

7-Methyl-*N*-(2-chlorophenyl)-5-(3-fluorophenyl)-3-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide hydrochloride (IX). Yield 0.58 g (78%). Yellow crystals, mp 215 – 217°C (EtOH). IR spectrum, ν, cm^{-1}:1604 (C=C), 1680 (CON), 1750 (CO), 3289 (N^+H). PMR spectrum ^1H, δ, ppm (J, Hz): 2.31 (s, 3H, 7-CH_3), 4.29 (d, 1H, J 18.0 Hz) and 4.36 (d, 1H, J 18.0 Hz, 2-CH_2), 6.14 (c, 1H, H-5), 7.20 – 7.51 (m, 8H, ClC_6H_4, $F\underline{C_6H_4}$), 8.65 (br.s, 1H, N^+H), 9.98 (s, 1H, NH). PMR spectrum ^{13}C (300 MHz, DMSO-d_6), δ, ppm: 19.02 (7-CH_3), 39.60 (2-CH_2), 56.37 (5-CH), 112.86 (C-6), 127.51, 127.68, 127.95, 129.01, 129.67, 130.74, 130.85 (C Ph), 140.99 (C-7), 164.08 (NHCO), 170.92 (C-3). $C_{20}H_{15}FN_3O_2S \cdot HCl$.

EXPERIMENTAL BIOLOGICAL PART

Antimicrobial activity was determined by the sequential dilution method of the test compound in meat-peptone broth (MPB) and was studied against pharmacopoeial strains *Staphylococcus aureus* ATCC 6538-P and *Escherichia coli* ATCC 25922. The bacterial load was 250,000 microbe cells per mL of growth liquid. Test results were assessed 18 – 20 h after storing control and test samples in a thermostat at 36 – 37°C. Growth of bacterial cultures or its inhibition due to the bacteriostatic action of the compounds was noted. The active dose was taken as the minimum inhibiting concentration (MIC) (μg/mL) that inhibited growth of the bacterial cultures.

The antimicrobial activity of the nine compounds was studied.

It was found that **I-IX** exhibited weak antimicrobial activity (Table 1).

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