DOI 10.1007/s11094-015-1336-3
Pharmaceutical Chemistry Journal, Vol. 49, No. 9, December, 2015 (Russian Original Vol. 49, No. 9, September, 2015)

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF THIETANYLPYRIMIDIN-2,4(1*H*,3*H*)-DIONE ACETANILIDES AND ACETYLHYDRAZONES

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 49, No. 9, pp. 28 – 31, September, 2015.

Original article submitted November 15, 2013.

Alkylation of 6-methyl-1-(thietan-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione with chloroacetanilides yielded N-acetanilide derivatives. Interaction of 2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)acetohydrazide with carbonyl compounds was used to synthesize arylaldehyde and ketone N-acetylhydrazones. The antimicrobial and antifungal activities of the compounds synthesized here were studied.

Keywords: thietane, pyrimidin-2,4-(1*H*,3*H*)-dione, N-acetanilides, N-acetylhydrazones, *E, Z* isomerism, antimicrobial and antifungal activity.

The problem of creating new antibacterial substances remains relevant because of the appearance of new infections, genetic transformations of known pathogens leading to the development of resistant strains of microorganisms, and the need to decrease the side effects of many known antibacterial agents [1]. The molecular structures of most antibacterial substances contain acylamide or azomethine fragments, which are responsible for antimicrobial activity or influence the width of the antibacterial spectrum of action [2]. The aims of the present work were to synthesize acetanilides and acetylhydrazones based on pyrimidin-2,4(1*H*,3*H*)-dione containing a thetane ring and to study their antimicrobial and antifungal activities.

6-Methyl-1-(thietan-3-yl)pyrimidin-2,4(1*H*,3*H*)-dione (I) was synthesized by thiirane-thietane regrouping on interaction of equimolar quantities of 6-methylpyrimidin-2,4(1*H*,3*H*)-dione and 2-chloromethylthiirane in water in the presence of a basic component [3]. Alkylation of pyrimidinedione I with chloroacetanilide in acetonitrile in the presence of a 1.5-fold molar excess of potassium carbonate with boiling of the reaction mix for 7 h produced acetanilides II – V (Scheme 1).

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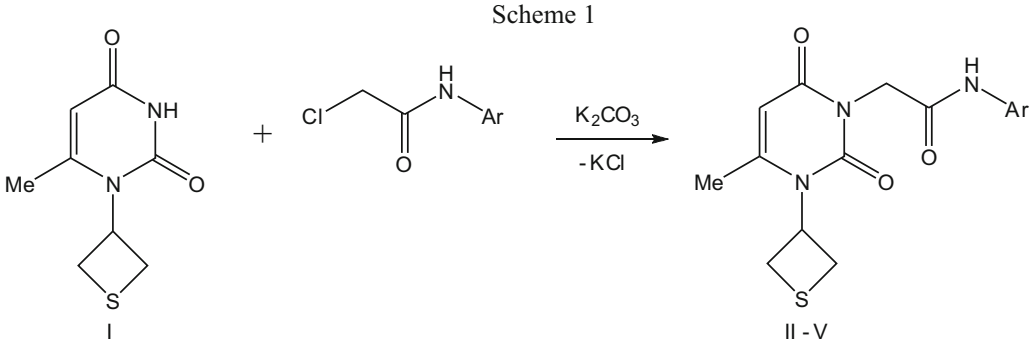
Scheme 1



Ar = Ph-4-Me (II); Ph-3-Me (III); Ph-2,6-Cl_2 (IV); Ph-4-SO_2NH_2 (V).

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)acetohydrazide (VI) was prepared by boiling compound I with monochloroacetic acid ethyl ester in acetone in the presence of potassium carbonate followed by interaction of the resulting ester with hydrazine hydrate [4]. Condensation of hydrazide VI with arylaldehydes, acetone, or acetophenone derivatives in ethanol medium without acid catalysts led to the formation of N-acetylhydrazones VII – XII.

The structures of the resulting compounds were confirmed by spectral methods (IR, ^{1}H and ^{13}C NMR) and elemental analysis data (Table 1). Acetanilides II – V were characterized by *E, Z* isomerism due to inhibited rotation around the amide bond, the conformational equilibrium of which depended on, apart from the nature of the solvent, a number of spatial and electronic factors determining the structure and interactions of all its components: the acylamino group, the aromatic nucleus, and the thietanpyrimidine fragment [5].

Analysis of the ^{1}H NMR spectrum of II showed that in DMSO-d_6 it is present as a mixture of the *E* and *Z* conformers, as evidenced by the doubling of the signals from the pyrimidin-2,4(1*H*,3*H*)-dione fragment protons, the N^3-CH_2CO group, the methyl group, and the NH group of the *p*-toluidine residue. By analogy with published data [6], the chemical shifts of the CH_2CO and NH protons of the *E* isomer showed a weakfield shift compared with the signals of the *Z* conformer. The *E* isomer was dominant, and its content as calculated from the integral intensities of proton singlets from the CH_2CO and NH groups, was 90%. The ^{1}H NMR spectrum of acetanilide IV, containing the 2,6-dichloroaryl fragment, contained one set of resonance signals, coming from the *E* conformer.

Acetylhydrazones VII – XII can exist as four stereoisomeric forms or mixtures of several of these due to the *E*, *Z* geometric isomerism with respect to the C=N bond of the hydrazone residue and *E*′,*Z*′ conformational isomerism due to the inhibited rotation around the hydrazide C-N bond. It should be noted that *Z* isomerism of arylhydrazones, including thietanpyrimidinylacetohydrazones, is due to inhibition of rotation around the N-N bond, which is prevented by steric hindrances, such that they exist only as the *E* conformer relative to the N-N bond [7]. The presence of two sets of resonance signals in the ^{1}H NMR spectra of compounds IX – XI shows that acetylhydrazones IX – XI in DMSO-d_6 exists as a mixture of two stereoisomers. The structure of the present acetylhydrazones was studied by synthesizing acylhydrazones of the symmetrically substituted ketone (X) in which geometrical isomerism was degenerate and signal doubling in the ^{1}H NMR spectrum taken in DMSO-d_6 could only be due to inhibited rotation around the hydrazide C-N bond [8, 9]. Signals from CH_2CO and NH group protons from the *Z*′ conformer of acetylhydrazone X showed strongfield displacement compared with the corresponding signals of the *E*′ conformer [6, 7, 9]. Analysis of the spectrum of compound X and published data [7 – 9] led to the conclusion that acetylhydrazones IX and XI in DMSO-d_6 exist as a mixture of two amide forms of the $E_{C=N}$ isomer with dominance of the *EE*′ conformer. The ratio of isomers calculated from integral intensity values, was: 15% (*EZ*′):85% (*EE*′) for compound IX, 25% (*EZ*′):75% (*EE*′) for compound X, and 21% (*EZ*′):79% (*EE*′) for compound XI.

The IR spectra of acetanilides II – V and acetylhydrazones VII – XII showed intense splitting of absorption bands in the range 1737 – 1572 cm^{-1}, typical of stretch vibrations of the C=O, C=N, and C=C bonds, and in the range 1456 – 1383 cm^{-1}, typical of stretch vibrations of the C-N bond of the pyrimidine fragment and the acetyl residue [10]. We note that the IR spectra of acetanilides II – V showed single intense absorption bands at 1551 – 1513 cm^{-1}, relating to the "amide II" band of the CO-NH of the acetyl grouping, while the absorption frequencies of this grouping in the spectra of acetylhydrazones VII – XII showed low-frequency displacement and overlapped with the bands from the stretch vibrations of C-N bonds. IR spectral data also confirmed that compounds VII – XII exist in crystals as mixtures of two conformers, as evidenced by the presence of two absorption bands in the region of the stretch vibrations of the N-H bond of the amide or hydrazone fragments [8]. Acetanilides III – V exist only in a single amide form, as stretch vibrations of the N-H bond corresponded to a single absorption band: 3292 cm^{-1} (III), 3209 cm^{-1} (IV), and 3091 cm^{-1} (V) [8].

The ^{13}C NMR spectra of compounds III and VIII also confirmed formation of anilide- and ylidenehydrazide derivatives of thietanpyrimidinylacetic acid: signals from pyrimidin-2,4(1*H*,3*H*)-dione and thietane carbon atoms were seen in the characteristic positions [11], along with signals at 47.25 (III) and 45.69 (VIII) ppm from the $\underline{C}H_2CO$ atom and weakfield signals at 165.54 (III) and 168.24 (VIII) ppm from the $CH_2\underline{C}O$ atom of the acetic acid residue. Signals in the range 110.78 – 138.41 ppm came from carbon atoms in the aryl fragments of compounds III and VIII.

EXPERIMENTAL CHEMICAL SECTION

IR spectra were recorded on an Infralyum FT-02 instrument in KBr disks. ^{13}C and ^{1}H NMR spectra were taken on a Bruker AM-300 instrument (300.13 MHz for ^{1}H; 75.47 MHz for ^{13}C). Internal standards were provided by signals from solvent DMSO-d_6. The identities of the compounds synthesized here were confirmed by TLC on Silufix plates developed in systems consisting of acetone and acetonitrile (1:1) (II, IV, V), acetone, acetonitrile, and hexane (2:2:1) (III), and ethanol (VII – XII). Plates were developed in UV light and iodine vapor in a moist box. Elemental analysis data were consistent with calculated values.

Compound I was synthesized as described in [3], chloroacetanilides as described in [12], and hydrazide VI as described in [4].

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)-N-(4-methylphenyl)acetamide (II). A

suspension of 0.99 g (5 mmol) of compound I and 1.04 g (7.5 mmol) of calcinated ground potassium carbonate in 30 ml of acetonitrile was boiled for 30 min; 1.01 g (5.5 mmol) of 2-chloro-N-(*p*-tolyl)acetamide was added and boiling was continued to 7 h. The reaction mix was cooled, and the precipitate was collected by filtration and washed on the filter with acetonitrile. The filtrate was evaporated to dryness at reduced pressure. The dry residue was recrystallized form ethanol. The IR spectrum, ν_{max}, cm^{-1}, was: 1431, 1456, 1513 (C–N), 1604, 1670 (C=C, C=O, C4=O), 1708 (C2=O), 3272 (NH). The ^{1}H NMR spectrum, ppm, was: 2.12(*Z*), 2.18(*E*) (s, 3H, 6-CH_3), 2.25(*E*), 2.35(*Z*), (s, 3H, 4_{arom}-CH_3), 3.08 – 3.13 (m, 2H, S$(CH)_2$), 4.15 – 4.21 (m, 2H, S$(CH)_2$), 4.38(*Z*), 4.64(*E*) (s, 2H, 3-CH_2), 5.63(*E*), 5.68(*Z*) (s, 1H, 5-CH), 6.03 – 6.09 (m, 1H, NCH), 7.13(*E*), 7.33(*Z*) (d, J 8.1 Hz, arom. H, 2H), 7.46 (d, J 8.1 Hz, arom. H. 2H), 9.94(*Z*), 10.26(*E*) (broad s, 1H, NH).

Compounds III – V were prepared using a method analogous to that used for compound II.

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)-N-(3-methylphenyl)acetamide (II). This was recrystallized from propan-2-ol. The IR spectrum, ν_{max}, cm^{-1}, was: 1434, 1537 (C–N), 1657, 1663 (C=C, C=O, C4=O), 1707 (C2=O), 3292 (NH). The ^{13}C spectrum, δ, ppm, was: 19.27 (6-CH_3), 21.10 ($\underline{C}H_3C3_{arom}$), 31.40 ($C2'_{thietane}$, $C4'_{thietane}$), 46.98 ($C3'_{thietane}$), 47.25 (3-CH_2), 100.19 (C5), 116.27 ($C6_{arom}$), 119.64 ($C2_{arom}$), 124.23 ($C4_{arom}$), 128.63 ($C5_{arom}$), 138.04 ($C3_{arom}$), 138.41 ($C1_{arom}$), 151.62 (C6), 153.84 (C2), 161.23 (C4), 165.54 (3-CH_2-$\underline{C}$=O).

N-(2,6-Dichlorophenyl)-2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)acetamide (IV). This was recrystallized from a mixture of DMF and water (1:1). The IR spectrum, ν_{max}, cm^{-1}: 1437, 1455, 1551 (C–N), 1572, 1649, 1661 (C=C, C=O, C4=O), 1697 (C2=O), 3209 (NH). The ^{1}H NMR spectrum, δ, ppm, was: 2.23 (s, 3H, 6-CH_3), 3.08 – 3.14 (m, 2H, S$(CH)_2$), 4.17 – 4.23 (m, 2H, S$(CH)_2$), 4.76 (s, 2H, 3-CH_2), 5.70 (s, 1H, 5-CH), 6.05 – 6.11 (m, 1H, NCH), 7.37 (t, J 8.1 Hz, arom. H, 1H),7.56 (d, J 8.0 Hz, arom. H, 2H), 10.30 (broad s, 1H, NH).

N-[4-(Aminosulfonyl)phenyl]-2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)acetamide (V). The reaction mix was filtered without cooling. Substance was recrystallized from acetonitrile. The IR spectrum, ν_{max}, cm^{-1}, was: 1172, 1373 (SO_2), 1418, 1521 (C–N), 1607, 1647, 1688 (C=C, C=O, C4=O), 1737 (C2=O), 3091, 3285 (NH, NH_2).

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)-N′-[(3-nitrophenyl)methylen]acetohydrazide (VII). A solution of 0.54 g (2 mmol) of hydrazide VI in 15 ml of ethanol was supplemented with 0.36 g (2.4 mmol) of 3-nitrobenzaldehyde and the mixture was boiled for 3 h and cooled. The resulting precipitate was collected by filtration, washed with ethanol, and dried (from a mixture of ethanol and water, 1:1). The IR spectrum, ν_{max}, cm^{-1}, was: 1341 (NO_2), 1409, 1433 (C–N), 1527 (NO_2), 1650, 1661, 1681 (C=C, C=N, C=O, C4=O), 1703 (C2=O), 3098, 3237 (NH).

Compounds VIII, IX, XI, and XII were prepared as described for compound VII.

N′-[(1*E*)-(5-Bromo-2-hydroxyphenyl)methylen]-2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1-(2*H*)-yl)acetohydrazide (VIII). This compound was recrystallized from propan-2-ol. The IR spectrum, ν_{max}, cm^{-1}, was: 1273 (C-O), 1383, 1418, 1477 (C–N), 1623 (C=C), 1653, 1670 (C=N, C=O, C4=O), 1706 (C2=O), 3078, 3224 (NH, OH). The ^{13}C NMR spectrum, δ, ppm, was: 19.10 (6-CH_3),31.40 ($C2'_{thietane}$, $C4'_{thietane}$), 45.69 (3-CH_2), 46.95 ($C3'_{thietane}$), 100.11 (C5), 110.78 ($C5_{arom}$), 118.39 ($C3_{arom}$), 122.38($C1_{arom}$), 127.59 ($C6_{arom}$), 133.52 ($C4_{arom}$), 139.54 (N=CH), 151.58 ($C2_{arom}$), 153.95 (C6), 155.60 (C2), 161.17 (C4), 168.24 (3-CH_2-$\underline{C}$=O).

N′-2-(2-Furyl)ethylidene]-2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)acetohydrazide (IX). This compound was recrystallized from propan-2-ol. The IR spectrum, ν_{max}, cm^{-1}, was: 1398, 1420, 1448.1463 (C–N, $C=C_{fur}$), 1626, 1661 (C=C, C=N, C=O, C4=O), 1716 (C2=O), 3121, 3196 (NH). The ^{1}H NMR spectrum, δ, ppm, was: 2.15 (*EE*′), 2.18(*EZ*′) (s, 3H, 6-CH_3), 3.08 – 3.14 (m, 2H, S$(CH)_2$), 4.15 – 4.21 (m, 2H, S$(CH)_2$), 4.57 (*EZ*′), 4.94(*EE*′) (s, 2H, 3-CH_2), 5.68 (s, 1H, 5-CH), 6.00 – 6.12 (m, 1H, NCH), 6.63 – 6.65 (m, arom. H, 1H),6.93 (d, J 3.3 Hz, arom. H, 1H), 7.83 – 7.86 (m, arom. H, 1H), 7.93(*EE*′), 8.09 (*EZ*′) (s, 1H, N=CH), 11.34 (*EZ*′), 11.70 (*EE*′) (broad s, 1H, NH).

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)-N′-(1-methylethylidene)acetohydrazide (X). A solution of 0.54 g (2 mmol) of hydrazide III in 15 ml of ethanol was supplemented with 1.16 g (20 mmol) of acetone and the mixture was boiled for 3 h and cooled. The resulting precipitate was collected by filtration, washed with ethanol, and dried (from propan-2-ol). The IR spectrum, ν_{max}, cm^{-1}, was: 1399, 1409, 1442 (C–N), 1624, 1663 (C=C, C=N, C=O, C4=O), 1718 (C2=O), 3091, 3197 (NH). The ^{1}H NMR spectrum, δ, ppm, was: 1.89 (s, 3H, CH_3), 1.94 (*Z*′), 1.96(*E*′) (s, 3H, CH_3), 2.12 (*E*′), 2.14(*Z*′) (s, 3H, 6-CH_3), 3.08 – 3.13 (m, 2H, S$(CH)_2$), 4.14 – 4.20 (m, 2H, S$(CH)_2$), 4.76 (*Z*′), 4.86 (*E*′) (s, 2H, 3-CH_2), 5.67 (s, 1H, 5-CH), 6.01 – 6.10 (m, 1H, NCH), 10.41 (*Z*′), 10.57 (*E*′) (broad s, 1H, NH).

2-(4-Methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)-N′-(1-(4-nitrophenyl)ethylidene)acetohydriazide (XI). This compound was recrystallized from ethanol. The IR spectrum, ν_{max}, cm^{-1}, was: 1346 (NO_2), 1391, 1411, 1444 (C–N), 1518 (NO_2), 1627, 1662 (C=C, C=N, C=O, C4=O), 1718 (C2=O), 3081, 3192 (NH). The ^{1}H NMR spectrum, δ, ppm, was:, 2.18 (*EE*′), 2.20 (*EZ*′) (s, 3H, 6-CH_3), 2.21 (*EE*′), 2.25 (*EZ*′) (s, 3H, N=C-CH_3),

TABLE 1. Properties of the compounds Synthesized Here

Compound	Yield, %	mp, °C	R_f	Atomic formula
II	90	220 – 221	0.67	$C_{17}H_{19}N_3O_3S$
III	96	211 – 213	0.90	$C_{17}H_{19}N_3O_3S$
IV	82	226 – 228	0.85	$C_{16}H_{15}Cl_2N_3O_3S$
V	51	210 – 212	0.87	$C_{16}H_{18}N_4O_5S_2$
VII	67	194 – 196	0.60	$C_{17}H_{17}N_5O_5S$
VIII	59	176 – 178	0.65	$C_{17}H_{17}BrN_4O_4S$
IX	68	226 – 227 degraded	0.79	$C_{15}H_{16}N_4O_4S$
X	55	232 – 234	0.66	$C_{13}H_{18}N_4O_3S$
XI	83	238 – 240	0.71	$C_{18}H_{19}N_5O_5S$
XII	57	187 – 189	0.78	$C_{18}H_{20}N_4O_5S$

3.09 – 3.14 (m, 2H, $S(CH)_2$), 4.16 – 4.21 (m, 2H, $S(CH)_2$), 4.84 (*EZ*′), 4.96 (*EE*′) (s, 2H, 3-CH_2), 5.69 (s, 1H, 5-CH), 6.04 – 6.12 (m, 1H, NCH), 7.95 – 8.11 (m, arom. H, 2H), 8.15 – 8.28 (m, arom. H, 2H), 10.54 (*EZ*′), 10.73 (*EE*′) (broad s, 1H, NH).

N′-[1-(2, 5-Dihydroxyphenyl)ethylidene]-2-(4-methyl-2,6-dioxo-3-thietan-3-yl-3,6-dihydropyrimidin-1(2*H*)-yl)acetohydriazide (XII). This compound was recrystallized from a mixture of ethanol and water (1:2). The IR spectrum, ν_{max}, cm^{-1}, was: 1273 (C–O), 1425, 1455, 1487 (C–N), 1624 (C=C), 1654, 1671 (C=N, C=O, C4=O), 1713 (C2=O), 2955, 3071, 3205 (NH, OH).

EXPERIMENTAL BIOLOGICAL SECTION

The antimicrobial and antifungal activities of 6-methylpyrimidin-2,4(1*H*,3*H*)-dione (methyluracil, OOO Polisintez, Russia) and compounds I – XII were assessed using the agar diffusion method and two-fold serial dilutions in meat peptone broth (MPB) pH 7.2 – 7.4 [13]. Test cultures were microbial strains deposited at the Tarasevich State Science Research Institute of Standardization and Control of Medical Biological Preparations, Russian Ministry of Health at the Department of Microbiology, Virology, and Immunology, Bashkir State Medical Institute: *Staph. aureus*, *E. coli*, *P. vulgaris*, *Kl. pneumoniae*, *C. diversus*, *Ent. aerogenes*, *Ps. aeruginosa*, and *E. cloacae*, and the lower fungus *C. albicans.* Initial dilutions were prepared by dissolving 100 mg of study compound in 1 ml of DMSO followed by dilution with MPB to the working concentration of 10 mg/ml. The microbial inoculum consisted of 2×10^6 cells in 1 ml of nutrient medium. Inocula were incubated at 37°C for 72 h and at 25°C for 48 h, after which the presence, suppression, or absence of test culture growth was assessed visually.

Screening showed that 6-methylpyrimidin-2,4(1*H*,3*H*)-dione and compounds I – VII and IX – XI at a concentration of 10,000 μg/ml did not suppress the growth of the microbial test strains; these compounds included acetanilide V, in which the anilide-containing component is streptocid. Acetylhydrazone VIII, with a hydroxyl group in the ylidene fragment, showed weak antimicrobial activity (MIC 2500 μg/ml) against Gram-negative test cultures, while acetylhydrazone XII (MIC 625 μg/ml), containing an aryl substituent with two hydroxy groups, had both antimicrobial and against Gram-positive and Gram-negative test cultures and antifungal activity against lower fungi.

These data identify some degree of relationship between the structure of thietanpyrimidines and activity, as introduction of a thetane ring into the pyrimindin-2,4(1*H*,3*H*)-dione molecule does not produce antimicrobial or antifungal activity, as with introduction of arylamide and arylylidene substituents. However, the presence of a hydroxy group in the aromatic ring of the ylidene fragment leads to inhibition of the viability of the test cultures. It should also be noted that the thietanpyrimidine fragment does not retain the antimicrobial activity of the sulfanilamide agent streptocid (MIC 250 μg/ml against most microbial strains) [14]**.**

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