Таким чином, запропоновану методику визначення кислотності можна застосовувати. Слід провести ще детальніші дослідження для деяких функціональних груп і спробувати встановити системний характер похибки в розрахунку кислотності принаймні в однотипному ряду сполук. Є тенденція до заниження кислотності ароматичного типу сполук з аміногрупою. Отримано параметри, за якими можна буде розраховувати кислотність для модельних сполук.

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РАССЧЕТ pK_a ФЕНОЛОВ И ТИОЛОВ КАК МОДЕЛИ ДЛЯ ОЦЕНКИ КИСЛОТНОСТИ КАТАЛИЗАТОРОВ НА АКТИВОВИРОВАНОГО УГЛЯ

Для ряда тиолов и фенолов были рассчитаны pK_a с отклонением от их экспериментальных значений менее единицы. Апробированную методику можно применить для теоретической оценки кислотности катализаторов на активированном угле с привитыми на поверхности различными функциональными группами.

Ключевые слова: активированный уголь, кислотность, катализ.

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CALCULATION OF pK_a OF PHENOLS AND THIOLS AS A MODEL TO EVALUATE THE ACIDITY OF CATALYSTS ON ACTIVATED CHARCOAL

It was calculated a pK_a values for set of the phenols and thiols. The pK_a values don't deviate from its experimental values more than one unit. Tested method can be applied to theoretical predication of the acidity of activated charcoal catalyst with different functional groups on its surface.

Key words: activated charcoal, acidity, catalysis.

УДК 547.853.7

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SYNTHESIS OF 2,6-DIAMINO-5-HETARYLPYRIMIDINES AS POTENTIAL ANTIFOLATES

The ring transformation reactions of 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles with guanidine as 1,3-N,N-binucleophiles have been investigated. The method allows obtaining diaminopyrimidines, which have been of great interest in recent years due to their potent biological and pharmacological properties.

Key words: antifolate agents, diaminopyrimidines, 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles.

Introduction. Tetrahydrofolate cofactors are essential for the biosynthesis of purines, certain amino acids (serine, methionine), and thymidine. Most bacteria and plants produce these folate cofactors by de novo biosynthesis. Compounds that interfere with this pathway, antifolate agents, have found use in the clinic as antibacterials, antimalarials, and anticancer drugs [1].

Dihydrofolate reductase (DHFR) is an essential enzyme and plays a key role in the folate biosynthetic pathway. DHFR catalyzes the nicotinamide adenine dinucleotide phosphate (NADPH) dependent reduction of 7,8-dihydrofolate to tetrahydrofolate (THF). THF is then converted to 5,10-methylenetetrahydrofolate (5,10-CH_2THF) by serine hydroxymethyltransferase (SHMT) which supplies one-carbon unit from L-serine. 5,10-CH_2THF is a vital cofactor for the methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) monophosphate to 2'-deoxythymidine-5'-monophosphate (dTMP) catalyzed by thymidylate synthase (TS) [1, 2].

Inhibition of the folate cycle prevents biosynthesis of thymidine leading to inhibition of DNA biosynthesis and thus to inhibition of cell growth and proliferation. DHFR is an important target for drug development against cancer and a variety of infectious diseases caused by bacteria, protozoa, and fungi. DHFR inhibitors have been in clinical use for over 50 years as well-known anticancer, antibacterial, and antimalarial drugs, for example, methotrexate (MTX), trimethoprim (TMP), and pyrimethamine (PYR) (Fig. 1). In the past decade, an intensive search for more safer and potent compounds as

compared with available antifolates in the corresponding therapeutic areas have been undertaken [1–4].

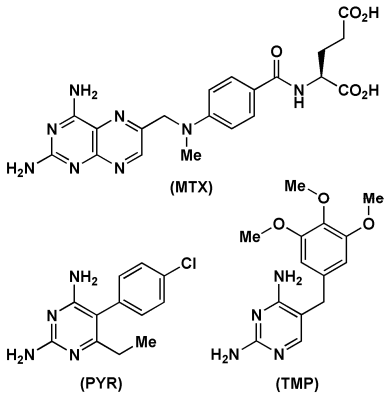


Fig. 1. Antifolates

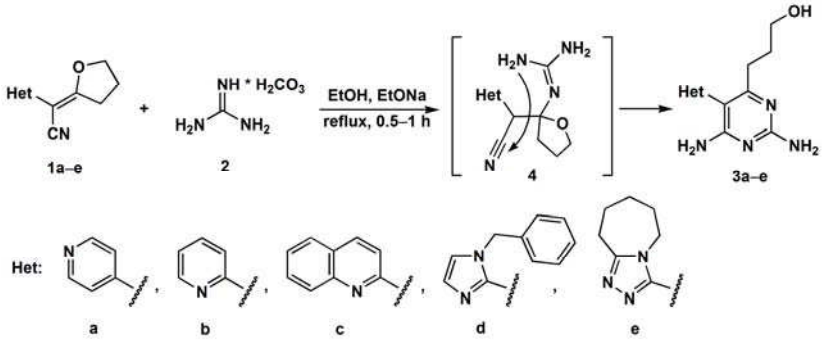
All DHFR inhibitors exhibiting IC_{50}'s in the micromolar range or less contain the 2,6-diaminopyrimidine pharmacophore. The pharmaceutical with aromatic, aliphatic and saturated heterocyclic moieties in the fifth position of the 2,6-diaminopyrimidines are well-known. Therefore it would be interesting to prepare the 2,6-diamino-5-hetarylpyrimidine derivatives as bioisosteric replacements.

Results and discussion. A general synthetic pathway for the preparation of 2,6-diaminopyrimidine scaffold consists of condensing enol ethers of β-ketonitriles with guanidine [2].

2-Hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles **1** represent versatile building blocks in the synthetic chemistry on account of their 3-functionalized acrylonitriles fragment incorporated into unsaturated heterocyclic ring which can react with *N*-nucleophiles by a ring transformation. In this process the nucleophilic substitution of the bridged heteroatom causes a disconnection of the starting ring giving a ω-hydroxyalkyl side chain [5, 6]. Nitriles **1** have already been utilized as cyclic 1,3-dicarbonyl heteroanalogs in the synthesis of ω-hydroxyalkylheterocycles [7].

In this context, in the present work we have employed the 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles **1** as 1,3-bielectrophilic synthon containing the heterocyclic moiety in the synthesis of 2,6-diamino-5-hetarylpyrimidines **3**. The reaction of nitriles **1a-e** with guanidine carbonate **2** in the presence of sodium ethoxide gave rise to desired 3-[2,6-diamino-5-hetaryl-4-pyrimidinyl]-1-propanols **3a-e**.

The reaction has been suggested to proceed through the intermediate formation of Michael's adduct **4** with the subsequent disclosing tetrahydrofuranyliden ring and the intramolecular interaction of the spatially close amino and cyano groups that leads to pyrimidine derivatives **3**:



Thus, the final heterocyclic ring is formed by condensation while the starting saturated ring system discloses to give the ω-substituted side chain [8, 9].

The structures of the cyclization products **3a-e** were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

The absence of nitrile group absorption band in IR spectra evidently indicated the ring closure. The amino groups stretching vibrations are located at 3337–3103 cm^{-1}. ^{1}H NMR spectra reveal two singlets of amino groups at 5.7-6.2 ppm and $A_2M_2X_2$ spin system of the hydroxypropyl side chain at 1.5-3.3 ppm. The signal of OH proton is observed at 4.3-5.0 ppm. It is noteworthy that signals of the 2,3-CH_2 methylene protons of compound **3e** as well as Ph-CH_2 methylene protons of compound **3d** are observed in ^{1}H NMR spectrum as multipletes owing to their diastereotopicity (Fig. 2).

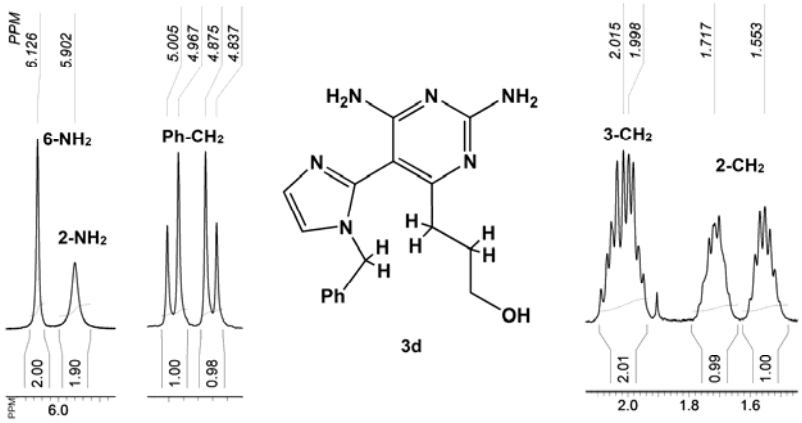


Fig. 2. ^{1}H NMR data of compound 3d

Conclusion. Present investigation has resulted in the efficient synthesis of biologically relevant compounds – 2,6-diamino-5-hetarylpyrimidines. Biological evaluation of compounds obtained as inhibitors of DHFR is currently in progress.

Experimental. Melting points were determined by using a Kofler-type hot stage microscope (Boetius VEB Analytik) and are corrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Mercury-400

spectrometer in DMSO-d_6. Chemical shifts (δ) were given in ppm downfield from the internal standard TMS. The J values were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz on the same instruments in DMSO-d_6. The IR spectra were obtained with a FTIR Spectrometer Perkin Elmer BX II with KBr pellets. Elemental analyses were performed on a CHNOS elementar vario MICRO Cube analyzer. The reaction progress was monitored by TLC on Silufol UV-254 silica gel plates using $CHCl_3$-MeOH (9:1) system as the eluent. 2-Hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles **1a-e** were prepared according to the procedure published earlier [10].

General Procedure for the Preparation of 3-[2,6-diamino-5-(2-hetaryl)-4-pyrimidinyl]-1-propanols 3a-e. To a stirred solution of sodium (0.09 g, 4 mmole) in anhyd ethanol (5 mL) the corresponding amidine **2** (4 mmole) and 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitrile **1** (2 mmole) were added. The reaction mixture was refluxed for 0.5-1 h and ethanol was then evaporated in vacuo. The residue was triturated with H_2O, acidified with HCl to pH = 7, filtered off and recrystallized from appropriate solvent.

3-[2,6-Diamino-5-(4-pyridinyl)-4-pyrimidinyl]-1-propanol (3a). Colorless microcrystals (from ethanol); mp 273-274ºC; yield: 0.43 g (88 %); IR (KBr): 3424, 3330, 3209, 3126, 1574, 1073 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.65 (m, 2H, 2-CH_2), 2.20 (t, J = 7.8 Hz, 2H, 3-CH_2), 3.31 (t, J = 6.2 Hz, 2H, 1-CH_2), 4.28 (br s, 1H, OH), 5.74 (br s, 2H, 2-NH_2), 5.98 (s, 2H, 6-NH_2), 7.19 (dd, J = 4.2, 1.6 Hz, 2H, 3,5-H_{Het}), 8.56 (dd, J = 4.2, 1.6 Hz, 2H, 2,6-H_{Het}); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.50, 31.96, 61.12, 105.17, 126.51, 145.04, 150.50, 162.03, 162.64, 165.77; Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.63; H, 6.41; N, 28.44.

3-[2,6-Diamino-5-(2-pyridinyl)-4-pyrimidinyl]-1-propanol (3b). Colorless microcrystals (from ethanol); mp 171-172ºC; yield: 0.45 g (92 %); IR (KBr): 3437, 3321, 3170, 3103, 1569, 1068 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.70 (m, 2H, 2-CH_2), 2.34 (t, J = 7.8 Hz, 2H, 3-CH_2), 3.31 (t, J = 6.2 Hz, 2H, 1-CH_2), 4.42 (s, 1H, OH), 5.79 (s, 2H, 2-NH_2), 5.95 (s, 2H, 6-NH_2), 7.23 (m, $^3J_{5,4}$ = 7.5, $^3J_{5,6}$ = 4.9, $^4J_{5,3}$ = 1.0 Hz, 1H, 5-H_{Het}), 7.30 (m, $^3J_{3,4}$ = 7.8, $^4J_{3,5}$ = 1.0, $^5J_{3,6}$ = 0.8 Hz, 1H, 3-H_{Het}), 7.77 (m, $^3J_{4,3}$ = 7.8, $^3J_{4,5}$ = 7.5, $^4J_{4,6}$ = 1.8 Hz, 1H, 4-H_{Het}), 8.58 (m, $^3J_{6,5}$ = 4.9, $^4J_{6,4}$ = 1.8, $^5J_{6,3}$ = 0.8 Hz, 1H, 6-H_{Het}); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.61, 32.00, 61.17, 107.05, 122.06, 126.37, 137.26, 149.80, 156.34, 162.36, 162.67, 166.59; Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.95; H, 6.05; N, 28.62.

3-[2,6-Diamino-5-(2-quinolinyl)-4-pyrimidinyl]-1-propanol (3c). Colorless microcrystals (from ethanol); mp 196-197ºC; yield: 0.55 g (93 %); IR (KBr): 3391, 3312, 3150, 1645, 1550, 1439 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.76 (m, 2H, 2-CH_2), 2.43 (t, J = 7.3 Hz, 2H, 3-CH_2), 3.34 (t, J = 6.3 Hz, 2H, 1-CH_2), 4.52 (br s, 1H, OH), 5.87 (s, 2H, 2-NH_2), 6.20 (s, 2H, 6-NH_2), 7.48 (d, J = 8.3 Hz, 1H, 3-H_{Het}), 7.54 (t, J = 7.8 Hz, 1H, 7-H_{Het}), 7.70 (d, J = 7.8 Hz, 1H, 6-H_{Het}), 7.91 (d, J = 7.8 Hz, 1H, 5-H_{Het}), 7.98 (d, J = 7.8 Hz, 1H, 8-H_{Het}), 8.28 (d, J = 8.3 Hz, 1H, 4-H_{Het}); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.68, 31.83, 60.99, 106.95, 124.47, 126.34, 126.54, 127.90, 128.86, 129.61, 136.52, 147.71, 157.07, 162.12, 162.63, 166.90; Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.25; H, 5.88; N, 23.59.

3-[2,6-Diamino-5-(1-benzyl-1H-imidazol-2-yl)-4-pyrimidinyl]-1-propanol (3d). Colorless microcrystals (from ethanol); mp 162-163ºC; yield: 0.48 g (74 %); IR (KBr): 3446, 3337, 3089, 1648, 1579, 1053 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.55 (m, 1H, 2^a-CH_2), 1.71 (m, 1H, 2^b-CH_2), 1.89-2.00 (m, 2H, 3-CH_2), 3.29 (m, 2H, 1-CH_2), 4.83 (d, J = 15.3 Hz, 1H, CH_2^a-Ph), 4.96 (d, J = 15.3 Hz, 1H, CH_2^b-Ph), 5.05 (br s, 1H, OH), 5.90 (br s, 2H, 2-NH_2), 6.12 (s, 2H, 6-NH_2), 7.00 (d, J = 1.2 Hz, 1H, 5-H_{Het}), 7.05 (d, J = 7.6 Hz, 2H, 2,6-H_{Ph}), 7.11 (d, J = 1.2 Hz, 1H, 4-H_{Het}), 7.24 (m, 3H, 3,4,5-H_{Ph}); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.42, 31.48, 49.76, 60.62, 96.50, 121.48, 127.80, 127.98, 128.63, 128.96, 137.71, 143.07, 163.26, 163.43, 169.38; Anal. Calcd for $C_{17}H_{20}N_6O$: C, 62.95; H, 6.21; N, 25.91. Found: C, 63.07; H, 6.36; N, 25.89.

3-(2,6-Diamino-5-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)pyrimidin-4-yl)propan-1-ol (3e). Colorless microcrystals (from ethanol); mp 294-295ºC; yield: 0.51 g (84 %); IR (KBr): 3407, 3336, 3187, 2941, 1636, 1576 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.54-1.77 (m, 8H, 6,7,8,9-$(CH_2)_{Het}$), 2.06 (m, 1H, 2^a-CH_2), 2.18 (m, 1H, 2^b-CH_2), 2.82-2.96 (m, 2H, 3-CH_2), 3.28 (t, J = 6.6 Hz, 2H, 1-CH_2), 3.63 (m, 2H, 5-$(CH_2)_{Het}$), 4.50 (s, 1H, OH), 5.98 (s, 2H, 2-NH_2), 6.13 (s, 2H, 6-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.24, 26.78, 28.07, 30.49, 31.47, 31.70, 44.89, 60.62, 92.64, 150.16, 157.10, 163.33, 163.58, 169.71; Anal. Calcd for $C_{14}H_{21}N_7O$: C, 55.43; H, 6.98; N, 32.32. Found: C, 55.57; H, 6.82; N, 32.19.

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СИНТЕЗ 2,6-ДІАМІНО-5-ГЕТАРИЛПІРИМІДИНІВ ЯК ПОТЕНЦІЙНИХ АНТИФОЛАТІВ

Досліджено реакцію трансформації циклу 2-гетарил-2-(тетрагідро-2-фураніліден)ацетонітрилів під дією гуанідину в якості 1,3-N,N-бінуклеофілу. Метод дозволяє отримувати похідні діамінопіримідинів, що становить значний інтерес в останні роки з огляду на їх потужні біологічні та фармакологічні властивості.

Ключові слова: антифолатні агенти, діамінопіримідини, 2-гетарил-2-(тетрагідро-2-фураніліден)ацетонітрили.

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СИНТЕЗ 2,6-ДИАМИНО-5-ГЕТАРИЛПИРИМИДИНОВ В КАЧЕСТВЕ ПОТЕНЦИАЛЬНЫХ АНТИФОЛАТОВ

Исследованы реакции трансформации цикла 2-гетарил-2-(тетрагидро-2-фуранилиден)ацетонитрилов под действием гуанидина в качестве 1,3-N,N-бинуклеофила. Метод позволяет получать производные диаминопиримидинов, что представляет значительный интерес в последние годы благодаря наличию у последних высокой биологической и фармакологической активности.

Ключевые слова: антифолатные агенты, диаминопиримидины, 2-гетарил-2-(тетрагидро-2-фуранилиден)ацетонитрилы.