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Synthesis, investigation of the new derivatives of dihydropyrimidines and determination of their biological activity

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ABSTRACT

We reported of synthesis and investigation of the new biologically active derivatives of dihydropyrimidines **2** and **3**. The investigation of structures of compounds by various experiments of NMR spectroscopy revealed the splitting of the signals to doublets and multiplets that confirms the presence of diastereomers in solution of compound **2** and the presence of diastereomers and tautomers in solution of compound **3**. The individual diastereomer of compound **3** has been isolated. Biological activity of the synthesized compounds was studied on various species of genus *Aspergillus* fungi.

1. Introduction

Dihydropyrimidines, as a class of organic compounds with a broad spectrum of biological activity, are widely used in medicine. The biological investigations of these various molecules via molecular manipulation showed such activities as antifungal [1], antiproliferative [1], antiviral [1], antitumor [2–7], antiinflammatory [8–10], antihypertensive [11–15], anti-HIV [16], antiepileptic [17], anti-malarial [18], antibacterial [19–22], antitubercular [23], miscellaneous [24–26], potassium [27–29] and calcium channel antagonist [30]. Among the derivatives of dihydropyrimidines that found their application in medicine we can mention the following drugs: batzelladine A and B [16], (S)-monastrol [2–7], (S)-enastron [2–7], mon-97 [2–7], (R)-fluorastrol [3], terazosin [25] and etc … Moreover, dihydropyrimidines SQ 32926, SQ 32547 which are aza-analogues of nifedipine, are promising targets for using them as oral antihypertensive agents [1]. Dihydropyrimidines, studied in Ref. [17], have similar structure to phenobarbital, thus have shown promising anti-epilepsy activity.

Dihydropyrimidines are obtained by various methods [31] and Biginelli reaction is a convenient one, due to the fact that it is a one-pot condensation reaction, and renewed exploration of the reaction conditions leads to obtaining of enantioenriched dihydropyrimidines [32]. Extraction of individual optical active compound is very important, especially if this compound is potent to be applied as a biologically active compound, because the presence of another enantiomer in drug leads to severe side effects [33–35]. Moreover, obtaining of individual enantiomer mostly is expensive in economic terms, because of using of special conditions and catalysts. According to above-mentioned, in some cases it is better to receive a mixture of diastereomers, which can be easily separated.

Considering the importance of dihydropyrimidines, we carried out Biginelli reaction and received new derivatives of dihydropyrimidines. Furthermore, we obtained a mixture of diastereomers and extracted individual diastereomer. The structures of obtained compounds were investigated by various methods, such as nuclear magnetic resonance (NMR), Fourier transform infrared spectroscopy (FT-IR) and elemental analysis. The biological activity of synthesized compounds was also studied against various species of genus *Aspergillus* fungi.

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2. Materials and methods

All chemicals, applied in the synthesis, were of analytical grade and used as received. K_2CO_3, dimethyl sulfoxide (DMSO), 1,2-dibromoethane, salicylaldehyde, CCl_4, urea, acetylacetone, thiourea, ethanol, NH_4Cl, acetic acid, benzaldehyde, acetone were purchased from Sigma-Aldrich (Taufkirchem, Germany).

The control of the reactions progress and the determination of the synthesized compounds purity were done by TLC on Sorbfil plates, iodine vapors were used as a developer. Elemental analysis was performed on the analyzer Carlo Erba 1108.

2.1. NMR spectra

The NMR experiments have been performed on a BRUKER FT NMR spectrometer AVANCE 300 (Bruker, Karlsruhe, Germany) (300 MHz for ^{1}H and 75 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ^{1}H are as follows: digital resolution = 0.23 Hz, SWH (spectral width in Hz) = 7530 Hz, TD (time domain) = 32 K, SI (Fourier transform **si**ze) = 16 K, 90° pulse-length = 10 μs, PL1 (power level for F1 channel) = 3 dB, ns (number of scans) = 1, ds (number of dummy scans) = 0, d1 (relaxation delay) = 1 s and for ^{13}C as follows: digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse-length = 9 μs, PL1 = 1.5 dB, ns = 100, ds = 2, d1 = 3 s.

COSY: pulse program = *cosygpdf*, digital resolution = 1.97 Hz, SWH = 2610, TD = 1 K, SI = 512, 90° pulse-length = 10 μs, PL1 = 3 dB, ns = 4, ds = 16, d1 = 1 s.

ROESY: pulse program = *roesyph*, digital resolution = 1.49 Hz, SWH = 3063 Hz, TD = 2 K, SI = 512 K, 90° pulse-length = 10 μs, PL1 = 3 dB, ns = 16, ds = 4, d1 = 2 s.

The NMR-grade DMSO-d_6 (99.7%, containing 0.3% H_2O) was used for the solutions of **1**, **2**, **3**, **4** and **5**. TopSpin plot editor was used to edit the 2D NMR contour plots.

2.2. IR spectra

FTIR spectra were recorded on a Varian 3600 FTIR spectrophotometer in KBr tablets. The spectrum was taken in the range of 4000–400 cm^{-1} at room temperature.

2.2.1. Synthesis of 2.2′-(ethane-1.2-diylbis(oxy)) dibenzaldehyde (*1*)

To a solution of 38.3 mmol of salicylaldehyde in 20 ml DMSO were added 19.8 mmol of 1,2-dibromoethane and 37.7 mmol of K_2CO_3. The reaction mixture was heated on a water bath for 3.5 h. Subsequently, it was cooled with ice. The precipitate was filtered, washed with distilled water, dried and afterwards washed with CCl_4; yield is 80%, M. p. 116–118 °C.

^{1}H NMR spectrum of compound **1**: (DMSO-d_6, δ, ppm), 4.6 s (4H, 2OCH$_2$), 7–7.8 m (8H, Ar), 10.3 s (2H, COH).

^{13}C NMR spectrum of compound **1**: (DMSO-d_6, δ, ppm), 68 (2OCH$_2$), 115 (2CH, Ar), 121 (2CH, Ar), 125 (2C, Ar), 128 (2CH, Ar), 138 (2CH, Ar), 161 (2C, Ar), 190 (2COH).

Found, %: C 71.04; H 5.11. $C_{16}H_{14}O_4$. Calculated, %: C 71.11; H 5.19.

2.2.2. Synthesis of 4.4′-(2.2′-(ethane-1.2-diylbis(oxy)bis(2.1-phenylene))bis(5-ace-tyl-6-methyl-3.4-dihydropyrimidin-2(1H)-one) (*2*)

To a solution of 2 mmol of 2.2'-(ethane-1.2-diylbis(oxy)) dibenzaldehyde in 50 ml of ethanol were added 35 mmol of urea, 17 mmol of acetylacetone and 4 ml of ice acetic acid. The reaction mixture was heated on a water bath for 9 h. Subsequently, it was cooled with ice. The precipitate was filtered, washed with distilled water and dried; yield is 90%, M. p. 347–350 °C.

^{1}H NMR spectrum of compound **2**: (DMSO-d_6, δ, ppm), 1.9 (6H, 2CH$_3$), 2.3 (6H, 2CH$_3$), 4.5 (4H, 2OCH$_2$), 5.6 (2H, 2CH), 6.9–7.3 (12H, 2Ar+2NH), 9.1 (2H, 2NH).

^{13}C NMR spectrum of compound **2**: (DMSO-d_6, δ, ppm), 19 (2CH$_3$), 30 (2CH$_3$), 49 (2OCH$_2$), 67 (2CH), 108 (2C), 112 (2C), 121 (2CH, Ar), 128 (2CH, Ar), 129 (2CH, Ar), 131 (2CH, Ar), 149 (2C), 153 (2C, Ar), 157 (2CO), 195 (2CO).

Found, %: C 64.81; H 5.71; N 10.71. $C_{28}H_{30}N_4O_6$. Calculated, %: C 64.86; H 5.79; N 10.81.

FTIR spectrum is given in Fig. S23. The bands at 3383 cm^{-1} and 3232 cm^{-1} correspond to stretching vibrations of NH groups. The intense bands at 1697 cm^{-1} and 1598 cm^{-1} correspond to stretching vibrations of C=O groups. The peaks within the range 1487–1325 cm^{-1} are corresponding to stretching vibrations of C–C in aromatic ring. The peaks within the range 1111–1062 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1234 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH$_2$ group.

2.2.3. Synthesis of 1-[4-[2-[2-[2-(5-acetyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-pyrimidinyl)phenoxy]ethoxy]phenyl]-1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyri-midinyl]ethanone (*3*)

To a solution of 2 mmol of 2.2'-(ethane-1.2-diylbis(oxy)) dibenzaldehyde in 20 ml of ethanol were added 34 mmol of thiourea, 17 mmol of acetylacetone and 2 mmol of NH_4Cl. The reaction mixture was heated on a water bath for 1.5 h. Subsequently, it was cooled with ice. The precipitate was filtered, washed with distilled water and dried; yield is 91%, M. p. 270–272 °C. Extraction of individual diastereomer was implemented by dissolving in acetone, in which it doesn't dissolve.

^{1}H NMR spectrum of compound **3**: (DMSO-d_6, δ, ppm), 1.9 (6H, 2CH$_3$), 2.2 (6H, 2CH$_3$), 4.4 (4H, 2OCH$_2$), 5.6 (2H, 2CH), 6.9–7.3 (10H, 2Ar), 9.3 (2H, 2NH), 10.2 (2H, 2NH), 13.4 (1H, SH).

^{13}C NMR spectrum of compound **3**: (DMSO-d_6, δ, ppm), 18.3 (2CH$_3$), 30 (2CH$_3$), 49.8 (2OCH$_2$), 66 (2CH), 109.3 (2C), 113 (2C), 121 (2CH, Ar), 128 (2CH, Ar), 129 (2CH, Ar), 131 (2CH, Ar), 145 (2C), 156 (2C, Ar), 174 (2CS), 195 (2CO).

Found, %: C 61.01; H 5.37; N 10.08; S 11.52. $C_{28}H_{30}N_4S_2O_4$. Calculated, %: C 61.09; H 5.45; N 10.18; S 11.63.

FTIR spectrum is given in Fig. S24. The bands at 3399 cm^{-1} and 3196 cm^{-1} correspond to stretching vibrations of NH groups. The intense bands at 1677 cm^{-1} correspond to stretching vibrations of C=O group and 1187 cm^{-1} correspond to stretching vibrations of C=S group. The peaks within the range 1598–1285 cm^{-1} are corresponding to stretching vibrations of C–C in aromatic ring. The peaks within the range 1125–1052 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1237 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH$_2$ group.

2.2.4. Synthesis of 5-acetyl-6-methyl-4-phenyl-3.4-dihydropyrimidin-2(1H)-one (*4*) and 1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-il)ethanone (*5*) was implemented as described in literature [36,37]

^{1}H NMR spectrum of compound **4**: (DMSO-d_6, δ, ppm), 2 s (3H, CH$_3$), 2.3 s (3H, CH$_3$), 5.2 s (1H, CH), 7–7.5 m (5H, Ar), 7.8 s (1H, NH), 9.1 s (1H, NH).

^{13}C NMR spectrum of compound **4**: (DMSO-d_6, δ, ppm), 19 (CH$_3$), 30 (CH$_3$), 55 (CH), 110 (C), 127 (2CH, Ar), 128 (CH, Ar), 129 (2CH, Ar), 145 (C), 148 (C, Ar), 153 (CO), 194 (CO).

Found, %: C 67.74; H 6.01; N 12.1. $C_{13}H_{14}N_2O_2$. Calculated, %: C 67.83; H 6.09; N 12.17.

^{1}H NMR spectrum of compound **5**: (DMSO-d_6, δ, ppm), 2.1 s (3H,