SYNTHESIS AND CYTOTOXIC ACTIVITY OF DERIVATIVES OF 6Z-ACETYL METHYLENE-PENICILLANIC ACID tert-BUTYL ESTER

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The sulfoxide of 6Z-[2-(methoxyimino)propylidene]penicillanic acid tert-butyl ester and the sulfones of 6Z-[2-(hydroxyimino-, methoxyimino-, benzoyloxyimino-, 2-bromo- and 4-bromobenzyloxyimino)-propylidene]penicillanic acid in the syn and anti forms have been synthesized by the condensation of the sulfoxide and sulfone of 6Z-acetylmethylenepenicillanic acid tert-butyl ester with hydroxylamine, methoxyamine, benzoyloxyamine, 2-bromo- and 4-bromobenzyloxyamines. The syn and anti isomers of 3Z-(2-methoxyiminopropylidene)-4R-(benzothiazolyl-2-dithio)-2-oxazetidinyl-1R-(2-propenyl)acetic acid tert-butyl ester were obtained by opening of the thiazolidine ring in 6Z-[2-(methoxyimino)propylidene]-1-oxopenicillanic acid tert-butyl ester with 2-mercaptobenzothiazole. The 3Z-(2-methoxyiminopropylidene)-4R-(methylsulfonyl)-2-oxazetidinyl-1-(2-propylidene)acetic acid tert-butyl ester was synthesized by the interaction of 1,8-diazabicyclo[5.4.0]undec-7-ene and methyl iodide with 6Z-[2-(methoxyimino)propylidene]-1,1-dioxopenicillanic acid tert-butyl ester. A dependence of the cytotoxic effect in relation to cancer and normal cells in vitro on the structure of the substituent in position 6 and the syn and anti isomerism of the oxyimino group was established for the synthesized compounds.

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It was established by us previously that condensation of the acetylmethylene group in 7Z-acetymethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid tert-butyl ester with hydroxylamine or arylmethoxamines leads to the preparation of hydroxy- and arylmethoxyimino derivatives of cephem 1 in the syn

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and anti isomeric forms, characterized by the presence of selective cytotoxic properties in relation to cancer cells [1]. In continuing this investigation it seemed expedient to synthesize and subject to cytotoxic screening similarly modified penams and also their derivatives with cleavage of the S(1)–C(2) bond.

For this purpose the sulfoxide and sulfone of 6Z-acetylmethylenepenicillanic acid tert-butyl ester 2a,b, synthesized by us previously in [2], were treated with the hydrochlorides of hydroxylamine 3a, methoxyamine 3b, and benzoxoamines 3c-e. These reactions were carried out at room temperature in methanol in the presence of sodium acetate. The condensation products 4 and 5a-e were formed as mixtures of syn and anti isomers, in the case of 4 and 5a they were separated into individual isomers with the aid of column chromatography.

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\begin{align*}
3,5 \text{ a } R = H, & \quad b \ R = Me, \quad c \ R = PhCH_2, \quad d \ R = 2-BrC_6H_4CH_2, \quad e \ R = 4-BrC_6H_4CH_2; \\
2 \text{ a } n = 1, & \quad b \ n = 2
\end{align*}
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The syn and anti configurations of the oxyimino fragments in compounds 4 and 5a-e were identified with the aid of \(^1\)H NMR spectroscopy based on the results of an analysis of the Overhauser effect for analogously modified cephalosporins [1]. According to this the spectra of the syn isomers of 4, 5a-e are characterized by a low field displacement of the signal of the H-8 proton in comparison with the analogous shift in the anti isomers of 4, 5a-e.

The oxyiminopropylidene structure of the substituent in position 6 of the obtained compounds does not prevent the execution of reactions directed at cleavage of the S(1)–C(2) bond of the penam nucleus in them. The sulfoxide of 6Z-[2-(methoxyimino)propylidene]penicillanic acid tert-butyl ester (4) was converted with the aid of 2-mercaptobenzothiazole (6) into 3Z-(2-methoxyiminopropylidene)-4R-(benzothiazolyl-2-dithio)-2-oxo-azetidinyl-1R-(2-propenyl)acetic acid tert-butyl ester (7) as syn and anti isomers.