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Synthesis, structure and cytotoxicity of novel tetrazolo[1′,5′-*c*]-fused 3-aza-A-homosteroids

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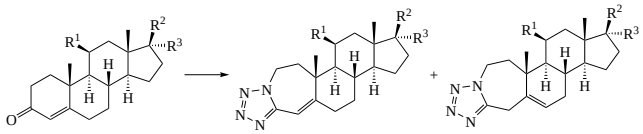
A series of new 1′*H*-tetrazolo[1′,5′-*c*]-fused 3-aza-A-homosteroids were synthesized by azidation of progesterone, testosterone and hydrocortisone acetate in the presence of silicon tetrachloride. According to NMR spectroscopy and X-ray analysis, two double bond positional isomers (double bond in ring A or in ring B) are formed in various ratios; according to quantum chemical calculations, their energies are close within 0.4 kcal mol^{-1}. Only low cytotoxic activity against Hep-2, MCF-7, HepG2, and Hek293 cell lines was determined *in vitro* for the compounds obtained.



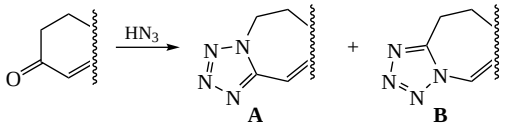
Keywords: azidation, tetrazoles, steroids, aza-A-homosteroids, isomerism, X-ray structures, M06-2X and MP2 calculations, cytotoxicity.

Steroids such as progestins (such as progesterone), androgens (such as testosterone), glucocorticoids (*e.g.* hydrocortisone) and some others are the specialized regulators of metabolism; they cover the activity of all organs and tissues of humans and animals. Natural steroids themselves are used as medicines, but they have some limitations in application while their synthetically modified derivatives turn out to be more effective. Among a wide variety of structural modifications of these natural molecules, a special attention is paid to the combination of a steroid skeleton with nitrogen heterocyclic fragment. Hybrid molecules containing azole or azine fragment linked or fused to ring D demonstrate biological activities, *e.g.*, galeterone and abiraterone are the medicines against prostate cancer.[1–4] Endocyclic azasteroids where nitrogen replaces one of carbon atoms in the steroid skeleton at positions 1–17, most often in rings A or D, are also known. Among others, effective therapeutics for benign prostatic hyperplasia finasteride and dutasteride can be mentioned.[5]

Tetrazole heterocycle, a well known drug-like fragment, occurs in structures of many drugs and drug candidates.[6,7] Tetrazole cycle is metabolically stable and is relatively low toxic bioisosteric analogue of cis-amide and carboxy groups. However, it is capable of forming different non-covalent interactions, for example, hydrogen bonds, which is important for interaction with enzymes.[8,9] Moreover, tetrazole derivatives, as a rule, do not exhibit pronounced acute toxicity which may be due to the fact that usually tetrazole cycle is not metabolized; the only reversible glycosylation is possible for NH tetrazoles.[10] Therefore, tetrazole ring linked or fused to steroid skeletons may be a challenge to obtain bioactive compounds with an improved pharmacokinetic profile, bioavailability and low side effects. As it was shown earlier, some tetrazole derivatives of steroids[11,12] and plant triterpenoids[13,14] exhibited significant antiviral and antiproliferative activity. However, still very few examples of such studies are known.

A possible access to a number of azasteroids of tetrazolo-A-homosteroid chemotype is the Schmidt azidation of 3-keto steroids in the presence of strong acids. During this reaction, two regioisomers **A** and **B** can in principle be formed (Scheme 1). We have found only two works[15,16] on this topic where general reasoning on steric hindrance with the UV spectral data gave assumption on preference for isomer **A**. Recently,[17] Škorić using this approach synthesized a series of C- and B-ring-fused tetrazoles based on cholic acid derivatives and studied their antiproliferative effect.

In the present work, 1′*H*-tetrazolo[1′,5′-*c*]-fused 3-aza-A-homosteroids were synthesized by azidation of progesterone,



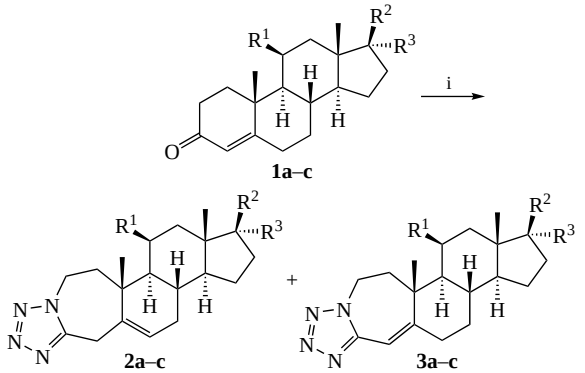
Scheme 1

testosterone, and hydrocortisone acetate. The compounds obtained were characterized by 1D and 2D NMR spectroscopy and high-resolution mass spectrometry as well as X-ray analysis (see Online Supplementary Materials for details). Double bond positional isomerism has been discussed by means of experimental and theoretical [M06-2X/6-31+G(d,p), MP2/6-311++G(d,p)] methods. Cytotoxicity of the compounds against Hep-2, MCF-7, HepG2, and Hek293 cancer cell lines has been studied.

To prepare the target tetrazolo-fused 3-aza-A-homosteroids, initial 3-keto steroids **1a–c** were treated with the azidation agent formed *in situ* from sodium azide and silicon tetrachloride in dioxane under mild conditions (Scheme 2). Under these conditions, various mixed silicon azides-chlorides $Si(N_3)_nCl_{4-n}$ can act as azidation agents.[18] The reaction obviously proceeds according to a mechanism similar to that of the Schmidt reaction (see Scheme 1). During the process, mixed silicon azides-chlorides react with the 3-positioned keto group of the steroid ring A to form germinal C,C-diazido intermediates which, in turn, would generate nitrene species upon losing a nitrogen molecule, rearrange into imidoyl azide and finally cyclize into tetrazole. Apparently, silicon chloride serves as an acidic activator of the keto group. In our case, the use of dioxane as a solvent allowed for a marked improvement in the yield of the target reaction products, but with longer reaction times (at higher temperatures or with the use of acetonitrile as the reaction medium, amount of impurities would significantly increase).

It should be noted that the possibility of tetrazole preparation from ketones using various acid activators is not unknown. However, among various reagents, relatively soft silicon tetrachloride/sodium azide system is well-recognized.[18] The use of stronger acids would cause the destruction of the steroidal skeleton. Apparently for this reason, even in this system, we observed a large number of impurities and the products could only be separated by thorough chromatographic purification.

As noted earlier, two isomers of types **A** or **B** can be formed during the reaction (see Scheme 1). In our case according to the LC-HRMS data, two compounds with the same molecular weight were actually formed. In the IR spectra, no absorption band for the carbonyl group (C^3=O) at 1661 cm^{-1} in these compounds was observed. NMR spectroscopy revealed a mixture



a $R^1 = R^3 = H$, $R^2 = OH$
b $R^1 = R^3 = H$, $R^2 = Ac$
c $R^1 = R^3 = OH$, $R^2 = C(O)CH_2OAc$

Scheme 2 *Reagents and conditions*: i, NaN_3, $SiCl_4$, 1,4-dioxane, room temperature, 10 days.

of two isomers **2** and **3** differing in the position of the double bond in ring A or B of the steroid skeleton (see Scheme 2). Such double bond positional isomerization of steroids in acids has been documented earlier.[19] In view of position of nitrogen atom in the newly formed aza-A-ring, both isomers **2**,**3** belong to **A** type (see Scheme 1).

Characteristic signals of the C^2H_2 and C*H*=C protons of both isomers **2** and **3** are present in the ^{1}H NMR spectrum of the reaction mixture. However, only the dominant isomer could be isolated from the reaction mixture by liquid chromatography, namely, compounds **2a**, **2b** and **3c**. Their structures were determined by 1D and 2D NMR spectroscopy and X-ray analysis. In the case of tetrazolo-A-homo derivatives **2a**,**b** with localization of the double bond in ring B (at positions 5,6 of the steroid skeleton), characteristic signals are present in the ^{1}H NMR spectra at δ_H 5.71 dd (1H, C^6H_1), 3.81 d (1H, C^4H_α), 3.58 d (1H, C^4H_β) and 5.68 dd (1H, C^6H_1), 3.77 d (1H, C^4H_α), 3.56 d (1H, C^4H_β) ppm, respectively. In their ^{13}C NMR spectra characteristic signals were observed at δ_C 136 (C^5) and 129 (C^6). In contrast, for a tetrazole derivative of hydrocortisone **3c** with the double bond in ring A (positions 4,5 of the steroid skeleton), the characteristic signals of α,β-unsaturated 3-ketimino moiety were observed at δ_H 5.68 s (1H, C^4H_1), 2.69–2.57 m (1H, C^6H) , 2.40–2.28 m (2H, C^1H, C^6H) ppm, as well as δ_C 103.1 (C^4) and 162.9 (C^5). The presence of tetrazole fragment in the final structures is confirmed by the signal for the carbon atom of the heterocycle at δ_C 154 for compounds **2a**,**b** and at δ_C 151 ppm for compound **3c**. In the ^{1}H NMR spectra of the studied compounds, one can note a certain downfield shift of the signals of α- and β-oriented hydrogens at C^2 carbon when the double bond is localized in ring A (4.63 C^2H_α and 4.31 C^2H_β ppm) compared to the double bond isomer where it is localized in ring B (4.53 C^2H_α and 4.11 C^2H_β ppm).

Spatial NOE interactions of ring A protons in the reaction products were determined form the NOESY experiment (Figure 1). In this case, it was assumed that in ^{1}H NMR spectrum the signals of the ring B protons for initial steroids **1a–c** and the reaction products **2a**, **2b** and **3c** are not significantly different.

The X-ray diffraction data for compounds **2a**, **2b** and **3c** is given in Figures 2–4 and Tables S1–S7 (see Online Supplementary Materials).† The positions of the double bond either in ring A (**2a**,**b**) or in ring B (**3c**) of the steroid skeleton is thus confirmed. The tetrazole cycle in all cases are fused with the steroid core to give 3-aza-A-homo derivatives (isomer type **A**, see Scheme 1). The tetrazole cycle is highly planar with bond

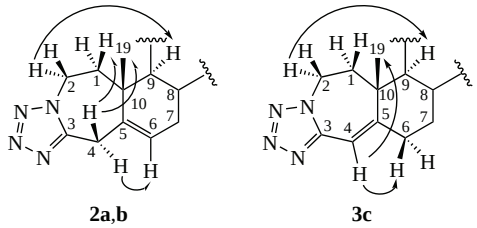


Figure 1 NOE interactions in double bond positional isomers **2a**, **2b** and **3c**.

† Crystals of compounds **2a**, **2b**, and **3c** were grown from distilled samples by slow solution evaporation.

Crystal data for **2a**. $C_{19}H_{28}N_4O$, M = 328.45, monoclinic, space group $P2_1$, 100 K, a = 6.19730(10), b = 12.7562(3) and c = 10.9121(3) Å, β = 98.905(2)°, Z = 2, V = 852.25(3) Å^3, d_{calc} = 1.280 g cm^{-3}, $F(000)$ = 356. Colorless prism-shaped single crystal with dimensions 0.11 × 0.26 × 0.29 mm was selected and intensities of 7687 reflections were measured using a Rigaku Oxford Diffraction 'XtaLAB Supernova' (ω scans, sealed tube, λ[CuKα] = 1.54184 Å, μ = 0.639 mm^{-1}, $2\theta_{max}$ = 148.458°). After merging of equivalents and absorption correction, 3427 independent reflections (R_{int} = 0.0373) were used for the

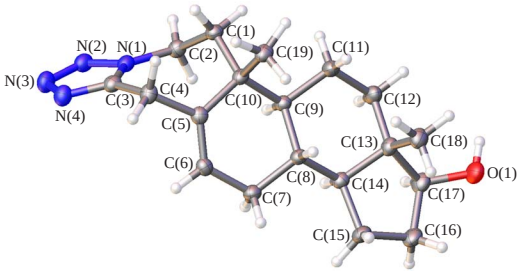


Figure 2 Molecular structure of compound **2a** (the probability of thermal ellipsoids is 50%).

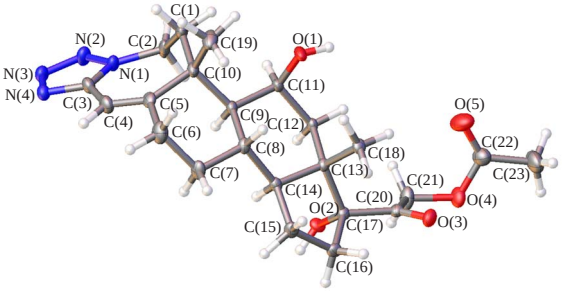


Figure 4 Molecular structure of compound **3c** (the probability of thermal ellipsoids is 50%).

lengths characteristic of 1*H*-tetrazoles.[26] For compound **3c**, the C^{tetr}–C^4 bond length is 1.455 Å which is somewhat less than the usual single carbon–carbon bond, as well as a similar bond in compounds **2a**,**b** (1.499 Å). This indicates the presence of a weak π–π-conjugation between the tetrazole ring and the double bond in steroid ring A, which additionally stabilizes isomer **3**. In general, it should be noted that among compounds **2a**,**b** and **3c** the geometry of steroid skeleton (except for ring A)

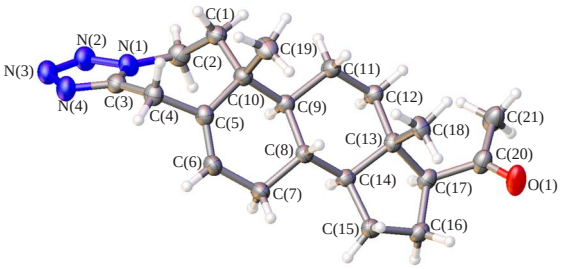


Figure 3 Molecular structure of compound **2b** (the probability of thermal ellipsoids is 50%).

corresponds to that of the initial natural substrates **1a**–**c**. Orientation of the tetrazolyl moiety relative to the steroid cores is the same in all cases.

Taking into account that during the azidation of 3-keto steroids the formation of two isomers differing in the localization of double bond is possible, a comparison of their relative energies would be quite demonstrative. Thus, the energies of tetrazolyl derivative of all tetrazolo steroids **2a**–**c** and **3a**–**c** were calculated using the quantum-chemical methods (Table S8). Both methods M06-2X/6-31+G(d,p) and MP2/6-311++G(d,p) agree that compound **2b** is more energetically favorable than **3b** although the difference was just within 0.4 kcal mol^{-1}. In the case of testosterone derivatives **2a**, **3a**, the M06-2X/6-31+G(d,p) method agrees with the previous case, while the MP2 method shows a slightly different picture, namely, the differences in the stability of these tautomers are almost negligible. However, for the hydrocortisone derivatives **2c** and **3c**, localization of the double bond in ring A of the steroid skeleton becomes more preferred according to the results obtained by both methods. The calculations are in principle consistent with experimental data on the composition of isomers obtained from ^{1}H NMR spectra of their mixtures isolated from the reaction masses.

It can be assumed that some additional stabilization of forms **3a**–**c** is achieved due to the conjugation between the multiple bond in ring A and the aromatic tetrazole ring. However, this stabilization is not so strong. In general, the relative stability of a particular isomer might be determined by energy of whole system including all possible intramolecular interactions.

Tetrazole derivatives are known to exhibit various types of biological activity.[6,7] Here, the effect of compounds **2a**,**b** and **3c** on viability of Hep2, MCF-7, HepG2 and Hek293 cells was examined in the presence of different concentrations of tested aza steroids dissolved in DMSO. The cytotoxicity studies were carried out using dual staining with Hoechst 33342 and propidium iodide (PI) with differentiation of cells into live, dead and apoptotic. The IC_{50} was calculated from curves constructed by plotting cell survival (%) *versus* drug concentration (μM). Obtained IC_{50} values are summarized in Table S9.

The data presented in Table S9 and Figure S26 show that compounds **2a**,**b** and **3c** are non-toxic against MCF-7, HepG2 and Hek293 cell lines in the 1–50 μM concentration range. Compound **2a** exhibits dose-dependent cytotoxicity only on Hep2 cell line, while compounds **2b** and **3c** do not cause cytotoxic effect on these cells. Exposure of Hep2 cells to **2a** with 25 and 50 μM concentrations for 48 h initiates cell death: the percentage of cells developing morphological changes in the nuclei characteristic of apoptosis is high (25 and 60%, respectively), while the maximal percentage of dead cells is 2.5% at the highest tested concentration. The IC_{50} value for **2a** is 42.9 ± 2.7 μM against Hep2 cells. However, activity of clinically approved drug carboplatin is 2.5 times higher on this cell line (IC_{50} = 16.8 ± 0.2 μM).

structure solution and refinement. Final *R* factors: R_1 = 0.0396 [3270 reflections with $I > 2\sigma(I)$], wR_2 = 0.1056 (all reflections), GOF = 1.060.

Crystal data for **2b**. $C_{21}H_{30}N_4O$, M = 354.49, orthorhombic, space group $P2_12_12_1$, 100 K, a = 7.63990(10), b = 11.4831(2) and c = 21.3820(3) Å, Z = 4, V = 1875.84(5) $Å^3$, d_{calc} = 1.255 g cm^{-3}, $F(000)$ = 768. Colorless prism-shaped single crystal with dimensions 0.21 × 0.24 × 0.33 mm was selected and intensities of 12453 reflections were measured using a Rigaku Oxford Diffraction 'XtaLAB Supernova' (ω scans, sealed tube, λ[CuKα] = 1.54184 Å, μ = 0.619 mm^{-1}, $2\theta_{max}$ = 147.914°). After merging of equivalents and absorption correction, 3772 independent reflections (R_{int} = 0.0349) were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0448 [3561 reflections with $I > 2\sigma(I)$], wR_2 = 0.1227 (all reflections), GOF = 1.042.

Crystal data for **3c**. $C_{23}H_{32}N_4O_5$, M = 444.52, orthorhombic, space group $P2_12_12_1$, 100 K, a = 7.72085(11), b = 14.1374(2) and c = 20.5233(2) Å, Z = 4, V = 2240.18(5) $Å^3$, d_{calc} = 1.318 g cm^{-3}, $F(000)$ = 952. Colorless prism-shaped single crystal with dimensions 0.25 × 0.3 × 0.5 mm was selected and intensities of 26864 reflections were measured using an Agilent Technologies (Oxford Diffraction) 'Xcalibur' (ω scans, sealed tube, λ[MoKα] = 0.71073 Å, μ = 0.094 mm^{-1}, $2\theta_{max}$ = 54.998°). After merging of equivalents and absorption correction, 5136 independent reflections (R_{int} = 0.0288) were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0377 [4832 reflections with $I > 2\sigma(I)$], wR_2 = 0.0970 (all reflections), GOF = 1.042.

The structure was solved by direct method and refined by full-matrix technique against F^2 in anisotropic approximation. The positions of hydrogen atoms in methyl and methylene groups were calculated geometrically and refined in rigid body approximation. All calculations were carried out with Superflip[20–22] and SHELXT[23] (structures solution) and SHELXL[24] program (structure refinement). Molecular graphics was drawn using OLEX2[25] program.

CCDC 1938454 **(2a)**, 1938453 **(2b)** and 1936462 **(3c)** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

The study shows that among compounds **2a**,**b** and **3c**, only **2a** has dose-dependent toxicity against Hep-2 cells. Though it kills cancer cells less effectively than medically approved carboplatin, the complex induces apoptosis in cancer cells. Agents that block or destroy tumor cell proliferation by inducing apoptosis are considered as promising antitumor mediators.[27] In addition, compound **2a** has a highly specific cytotoxicity toward Hep2 human larynx carcinoma cells. Selectivity of tetrazole containing steroid derivatives to a particular tumor and non-tumor cell lines has been described in earlier studies.[12,17,28] In particular, some of D-homo fused steroidal tetrazoles from androstane and estratriene 16,17-seco-16-cyano-17-mesyloxy derivatives caused cell death of MCF-7 and PC3 cells, while no activity was observed against HeLa, HT-29 and MRC-5 cells in the studied concentration range (up to 100 μl).

In conclusion, the azidation of 3-keto steroids in the presence of silicon tetrachloride leads to mixtures of isomers of 3-aza-A-homo-tetrazole-fused derivatives which differ in the position of the double bond: in ring A or ring B of the steroid skeleton in comparable quantities. Geometry of the steroid skeleton (except ring A) corresponds to the initial natural steroids and an orientation of the tetrazolyl moiety relative to the steroid rings is the same in all cases. According to the results of theoretical calculations, the differences in the energy of these isomers are quite insignificant. For isomer containing a double bond in ring A, a weak π–π-conjugation between the tetrazole ring and the multiple bond is observed. According to the results of biological tests, only for compound **2a** there is a weak, but highly specific cytotoxicity towards Hep2 human larynx carcinoma cells and this compound induces apoptosis in the cancer cells. Studies of the biological properties of such compounds are advisable to continue.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.011.

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